NITENPYRAM DETECTION BY A CARBON QUANTUM DOTS-BASED SENSOR AND MOLECULAR MODIFICATION USING 3D-QSAR MODELING

by

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Abstract

Due to the high demand for agricultural products, pesticides have been widely used to protect crops from potential diseases. Recently, some pesticides have been categorized as harmful emerging contaminants found in natural water, soil, and agricultural products, leading to toxicity for human beings. Therefore, monitoring and controlling their existence in the environment is essential. Carbon quantum dots-based optical sensors are a promising candidate for selective detection of pesticides at low concentrations because of their high sensitivity, selectivity, and fast procedure. In the first part of this study, a hybrid fluorescent sensor based on nitrogen-doped carbon quantum dots (N-CQDs) and silica gel was developed for quantitative detection of nitenpyram, a toxic neonicotinoid existing in the aquatic environment. The prepared N-CQDs@SiO_2 sensor exhibited remarkable sensing selectivity and sensitivity towards nitenpyram among the four tested pesticides. A prominent fluorescence quenching of N-CQDs@SiO_2 at 445 nm was observed in the presence of nitenpyram with a linear response range of 0–300.0 mg/L and an estimated detection limit of 2.6 mg/L. The excellent sensing selectivity could be attributed to a good affinity between N-CQDs and nitenpyram through hydrogen bonding and π–π interaction, which provokes an auto-absorption of excitation/emission light (IFE) for fluorescence quenching.

The design of nitenpyram derivatives with improved environmental properties and functionality and enhanced sensing capacity is a critical way to control the harmfulness of the pesticide. In the second part of this study, 3D-QSAR modeling was adopted to obtain nitenpyram derivatives with improved environmental properties (i.e., biodegradability and bioaccumulation capacity). The functionality of these derivatives as pesticides was further investigated by evaluating their toxicity to pests. Based on the modeling results, the nitenpyram derivatives with higher biodegradability, lower bioaccumulation capacity, and better functionality were selected. They were then examined for their interaction with N-CQDs through molecular docking. The nitenpyram derivative showing a better interaction toward N-CQDs would result in improved sensing and detection. Integrating 3D-QSAR modeling and molecular docking successfully facilitated the design of environmentally friendly nitenpyram derivatives and CQDs-based detection of these products.

General Summary

Pesticides are a group of chemicals used in agriculture and can be found in water, soil and food as toxic contaminants. In this work, the detection of nitenpyram pesticide has been presented by using a carbon quantum dots-based optical sensor to monitor its existence in water samples. The as-prepared sensor showed excellent selectivity and sensitivity toward nitenpyram in aquatic samples. Molecular modification has been also applied to introduce new structures with improved environmental properties and functionality using a modeling tool. The sensing capacity of these compounds was then evaluated by investigating their interaction with the sensor. These theoretical results help introduce derivatives with improved sensing capacity and reduced associated environmental risks.

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List of Abbreviations and Symbols

AChR	Acetylcholine receptors
ATZ	Atrazine
BAF	Bioaccumulation factor
BCF	Bioconcentration factor
CL	Chemiluminescence
CoMFA	Comparative molecular fields analysis
CoMSIA	Comparative molecular similarity indices analysis
CQDs	Carbon quantum dots
ECL	Electrochemiluminescence
EPI	Environmental performance index
FRET	Forster resonance energy transfer
FTIR	Fourier transform infrared spectroscopy
GC	Gas chromatography
HOMO	Highest Occupied Molecular Orbital
HPLC	High-performance liquid chromatography
HR-TEM	High-resolution transmission electron microscopy.
HSA	Human serum albumin
IMD	Imidacloprid
IEF	Inner filter effect
LGA	Lamarckian genetic algorithm
LOD	Limit of detection

LUMO	Lowest unoccupied molecular orbital
MIP	Molecularly imprinted polymer
MOF	Metal-organic frameworks
N-CQDs	Nitrogen-doped carbon quantum dots
NTP	Nitenpyram
pLC_{50}	Phototoxic median lethal concentration
PET	Photoinduced electron transfer
QDs	Quantum dots
QSAR	Quantitative structure-activity relationship
QY	quantum yield
TMX	Thiamethoxam
UV-Vis	Ultraviolet-visible
UV-DRS	UV–Vis diffuse reflectance spectra (DRS)
XPS	X-ray photoelectron spectroscopy

Chapter 1 Introduction

1.1 Background

Pesticides are a group of organic chemicals used in agriculture to protect products from potential diseases. Organophosphorous, carbamate, and neonicotinoid are the three most important groups of pesticides. Neonicotinoids including acetamiprid, thiacloprid, nitenpyram, imidacloprid, clothianidin, thiamethoxam, and dinotefuran constitute a major class of pesticides that are widely used in agriculture to protect crops from pests.[1] Neonicotinoids have significant toxicity to insects but low toxicity to mammals, birds, and other higher organisms.[2, 3] However, there is evidence that chronic exposure to these compounds can induce biological effects in mammalian experimental models and may also affect human health.[1–4] Neonicotinoids are water-soluble and persistent so they could accumulate in the environment over time.[5] Studies have shown that between 80 and 90% of neonicotinoids are transported from agricultural fields into the surface and groundwater.[5–7] This raises a concern that these compounds may contaminate natural sources of drinking water. It is therefore important to monitor and control their existence in the environment.

Currently, traditional analytical techniques such as gas chromatography (GC), GC-mass spectrometry (GC-MS), high-performance liquid chromatography (HPLC), and HPLC-MS are available to detect pesticides in contaminated samples. Still, they are costly, time-consuming, and need sample preparation.[8] Therefore, finding substituted ways to offer more rapidity, simplicity, accuracy, and even in-situ detection of pesticides are highly preferred. Among the different rapid sensing techniques, fluorescence-based sensing offers advantages in terms of high selectivity, ultra sensitivity, rapid response time, and low cost.[9, 10] A fluorescent chemosensor is a molecular system in which the physicochemical properties change upon interaction with an analyte, so that a change in fluorescence is produced.[10] Nowadays, the development and application of fluorescence chemosensors for monitoring environmental pollutants have attracted increasing attention.

Nanomaterials have been the subject of intense and extensive research in developing various fluorescence sensing tools due to their remarkable structural and functional attributes.[11] Carbon quantum dots (CQDs) are promising findings from the carbonaceous nanomaterials family with unique fluorescence properties. CQDs are zero-dimensional (< 10 nm) carbon nanomaterials with high nitrogen/oxygen contents and consist of graphitic and turbostratic carbon combinations in various volumetric ratios. They are easy to synthesize, non-toxic, biocompatible, and inexpensive.[12] Thus, in recent years, they have gained more attention due to the wide range of offered applications as sensors, bioimaging tools, drug delivers, and catalysis. [13-16]

CQD immobilization in solid-state is a good practice to prevent fluorescence quenching of CQDs due to aggregation and have more active sites, and in some cases, to offer advantages of solid matrixes.[17] As a sensor, the interaction of CQDs with analytes leads to fluorescence change (intensity or wavelength) of CQDs, which is utilized for detecting various analytes. Since pesticide compounds may have specific interactions with the functional groups located on the surface of CQDs, they may show turn-on or turn-off effects in the presence of CQDs as an optical sensor. Although CQDs-based fluorescent chemosensors have been reported for detecting several neonicotinoids,[18-20] the uncertainty of the exact fluorescence mechanisms of CQDs and the difficulty in finding the recognitions elements remain significant challenges. More research efforts should be dedicated to developing neonicotinoid-specific detection using CQDs-based fluorescent sensors.

Apart from monitoring and removing pesticides, it would also be worth improving their properties by substituting them with other structures that show better properties and functionality. Three-dimensional quantitative structure-activity relationships (3D-QSAR) modeling, an important in-silico tool in drug design and discovery, permits correlations between the actual molecular structures and their behavior in biological systems.[21] In recent years, 3D-QSAR modeling found broader applications in different areas, such as guiding the synthesis of environmentally friendly materials, investigating and predicting environmental behaviors of chemicals, and assessing risks of contamiants.[21, 22] It is a powerful tool for both scientists and engineers to make predictions of designed compounds before chemical synthesis and novel analogs.

Introducing new structures with improved properties for environmental pollutants is one of the capabilities of 3D-QSAR modeling. Biodegradability and bioaccumulation are two critical characteristics of organic contaminants for evaluating their environmental impacts. Biodegradability denotes the ability of an organic matter to decompose after interactions with microorganisms.[23] Whereas bioaccumulation refers to accumulating a substance, especially a contaminant in a living organism over time.[24] Molecular structures leading to high biodegradability and low bioaccumulation potential are desired in the 3D-QSAR studies.

Meanwhile, it is of great interest to propose improved derivatives with better sensing capacity so that they can be detected more accurately. Molecular docking, a theoretical method applied in different areas to predict the affinity of molecules can be applied to find the sensing capacity of newly defined derivatives by investigating any interaction between target molecules and the CQD sensor.

1.2 Research Objectives

To the best of our knowledge, the detection of pesticides as a large group of organic chemicals, especially nitenpyram using CQDs-based sensors has not been studied broadly. Also, the design of nitenpyram derivatives to obtain neonicotinoid pesticides with improved environmental properties, functionality, and sensing capacity has not been tackled. Therefore, this thesis tried to address the research gaps from two perspectives.

The first research objective is to fabricate CQDs-based optical sensor for selective detection of nitenpyram in water samples. Further, the thesis tackles the design of nitenpyram derivatives with improved environmental properties and functionality using 3D-QSAR modeling. Molucular docking is then adopted to determine the newly designed derivatives to be sensed by CQDs more efficiently. The research outputs would provide a feasible method to detect nitenpyram from water samples and design nitenpyram structures to facilitate its sensing and environmental impact reduction.

1.3 Structure of the Thesis

This thesis includes five chapters. After an introduction presented in Chapter 1, a thorough literature review regarding CQDs and their application as an optical sensor and molecular modeling tools and their applications in finding new chemical structures was conducted and presented in Chapter 2. Chapter 3 stated the synthesis and characterization of a CQDs-based optical sensor and its application to detect nitenpyram selectively. Both CQDs and CQDs@SiO_2 were comprehensively characterized. Sensing selectivity and mechanisms were further discussed based on the obtained experimental results. Chapter 4 presented 3D-QSAR modeling (CoMFA and CoMSIA models) using SYBYL X2.0 software for designing nitenpyram derivatives with improved environmental properties and functionality. Molecular docking was then used to determine the selected derivatives with improved sensing capacity toward CQDs. Chapter 5 summarizes the key findings of the thesis and provides recommendations for future works.

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Chapter 2 Literature Review

2.1 Introduction

To comply with the environmental standards and policies, detection and control of pesticides are of great interest. Quantification of pesticides present in the environment can be conducted through different analytical methods. In-situ monitoring using optical sensors is a promising and reliable approach, but with limited studies currently. In addition, manipulation of pesticide structures to propose new compounds with improved environmental, functional, and sensory properties is another attitude. Both ways aim to facilitate the detection and control of pesticides in the ecological systems. In this chapter, the overall knowledge related to pesticide detection using optical sensors and modification of the chemical structure of pesticides was presented.

2.2 Pesticides in the Environment

Pesticides are a large group of organic chemicals that are used to protect crops from pests. They are categorized into four subclasses: insecticides, herbicides, rodents, and fungicides.[1] No one can ignore the importance of pesticides in the agriculture industry. However, the use of pesticides has two sides: they can increase the production of crops while causing toxicity to the environment and non-target organisms.[2] Normally, they are designed and prepared to fight against specific pests with minimum effects on other insects and non-target species. Still, in many cases, current pesticides show diverse environmental impacts. Their accumulation in crops or transportation through the air, water, and soil makes them a source of pollution in the environment. The toxicity of pesticides as water-soluble organic pollutants and their accumulation and resistance to biodegradation are challenging subjects to environmental scientists.[1, 2]

Neonicotinoids have been a widespread group of insecticides in almost 120 counties worldwide since the 1980s. Neonicotinoids devoted 24% of total world insecticide consumption in 2007. They are divided into three categories, chloropyridinyl compounds (imidacloprid, nitenpyram, acetamiprid, thiacloprid), chlorothiazolyl compounds (thiamethoxam, clothianidine), and tetrahydrofuryl compounds (dinotefuran). [1-4]

Neonicotinoids have widely occurred in the environment, with residues found in different areas, including cultivated fields, air, rivers, oceans, and urban ecological systems. Adsorption and accumulation of neonicotinoids in the soil would alter the ecological structure of the earth in which small creatures such as earthworms live.[5] The neonicotinoid residue may spread around in the form of dust. These particles can cause death in bees flying after inhaling. They also can find a way to reach water resources. The transfer of neonicotinoids into aquatic ecosystems may cause danger for the sensitive organisms living in water bodies and human health. [6] Neonicotinoids have been detected in the urine samples of people without any history of working with pesticides.[7] Actions must be taken to monitor these pesticides further and reduce their associated environmental risks.

Nitenpyram is a rapid-acting neonicotinoid product that can affect neuronal nicotinic acetylcholine receptors (nAChRs) of the nervous system in insects and pests. The toxic part of neonicotinoids is the pyridine ring (carbon and nitrogen) in their structure with bounded chlorin. It has a high solubility in water (i.e., 34 g/L), can absorb from all parts of plants, and is highly demanding to fight insect pests.[4] Although it is recognized as an effective pesticide in agriculture and even in veterinary medicine, several side effects have been reported to non-target organisms regarding the applying nitenpyram. Due to the high solubility of nitenpyram in water, the chance of its exitance in water resources is high. Nitenpyram has shown an impact on the DNA of Zebrafish by oxidative damage.[8] In addition, a relation between the existence of nitenpyram and a decrease in the population of honeybees[9] as well as nitenpyram existence in biological samples of humans was proved. The findings show its accumulation in the body leads to toxicity to living beings.[10]

Considering the side effect of pesticides, detection of their presence in the environment is vital. Optical sensors such as CQDs-based compounds are promising and reliable candidates to help pesticide detection in pollutant samples. To mitigate the danger of pesticides in the environment, rather than detection, it would be a good practice to improve their environmental properties and offer more environmentally friendly compounds.

2.3 CQDs-Based Fluorescent Sensor

Carbon quantum dots (CQDs), a new member of the QD family introduced in 2004, are quasispherical, non-toxic (or less toxic), water-soluble, highly fluorescent nanomaterial with specific properties and applications in different areas. They may comprise other atoms besides carbon, such as nitrogen, oxygen, sulfur, and phosphorus. The most outstanding characteristic of CQDs is the tunable emission and excitation properties with high quantum yield (QY). [11, 12]

To prepare CQDs, starting chemicals might be selected from different sources of organic molecules and natural products or bioresources. Based on a desirable application of CQDs, the surface can also be modified or functionalized to tune the properties. CQDs are zero-dimension carbon nanoparticles (less than 10 nm).[13-15]

Generally, carbon quantum dots can be obtained from two major methods of synthesis: top-down and bottom-top. Top-down methods mainly covert macromolecules into the carbon sources, then carbonize them to form CQDs. However, in bottom-up procedures, small carbon-based molecules are polymerized to form CQDs. The bottom-up synthesis methods are more flexible and include hydrothermal, solvothermal, and microwave methods.[16] Hydrothermal is the most popular method to prepare CQDs due to its simplicity. Also, the CQD particles produced in this method are almost uniform and show a high quantum yield. In a typical hydrothermal method, small organic molecules are dissolved in water and transferred to a Teflon-lined stainless steel autoclave to conduct the reaction at a relatively high temperature. Citric acid and ethylene diamine as carbon and nitrogen sources dissolved in water are examples of starting solutions to fabricate CQDs in a hydrothermal method.[17] Solvothermal procedure is also used in the same way as other solvents. An example of CQD synthesis using a solvothermal method is to apply citric acid and urea as starting substances and N, N-dimethylformamide (DMF) as a solvent. The product of this reaction was reported as a CQD with orange emission.[16] Ultrasonic is another may of CQDs fabrication in which the required energy to conduct the reaction is provided during ultrasonication. Dissolving glucose in water and adding NaOH followed by introducing an ultrasonic wave for 4-5 hr is a reported method for CQD preparation. In this case, ultrasonic energy can help agitate reactants and provide a high level of energy to break the carbon bonds to have physical and chemical transformations.[18] Using and engineering different ways for CQD synthesis can provide the product with different molecular structures and will emit light at different wavelengths.[16]

Several functional groups such as hydroxyl, epoxy, carbonyl, and carboxyl positioned on the carbon core make them water-soluble, easy to functionalize with other species, and enhance the optical properties. The most crucial atom in the CQD structure rather than carbon is oxygen. The amount of oxygen highly depends on the precursors and the synthesis method. Nitrogen and sulfur are other elements that can be dopped in the CQDs structure to provide a specific application. In general, the structure of CQDs is carbon atoms with sp^2/sp^3 hybridization and oxygen/nitrogen-based groups or polymeric aggregations.[19, 20]

2.3.1 Fluorescent properties of CQDs

CQDs are fluorescent nanomaterials with different functional groups bearing quantum effects and tunable photoluminescent properties. The fluorescence originates when the surfaces of CQDs are exposed to UV-light irradiation. By exposure of CQDs to UV light, electrons on the surface can be excited into higher energy states, and when electrons fall back to their ground state, a color photon is emitted. The emission spectrum is broad and wavelength-dependent, meaning that the PL emission peak position and intensity depend on the excitation wavelength. It is suggested that this property is because of the wide size distribution and different surface chemistry.[21] CQDs show optical absorption at around 280 and 350 nm. The peak around 240 nm corresponds to a pi–pi* transition of the aromatic C-C bond, and that at 350 nm corresponds to an n–pi* transition of the C-O bond. CQDs can be synthesized in different procedures to produce different colors and properties. N-CQDs are nitrogen-riched CQDs emitting blue light under UV-light irradiation that can be obtained from a hydrothermal method. To have an N-CQDs, besides a carbon source, using a nitrogen source is also required. [18]

As the surface of CQDs is surrounded by different functional groups, CQDs can interact with analytes and hydrogen bonds, π-π interactions, and electron transfer between donor and acceptor groups may happen.[22] Meanwhile, functionalization and heteroatom doping are generally accepted as two strategies to enhance the fluorescence properties and improve active sites to interact with an analyte subjected to sensing. For instance, adding an amino-functional group on the surface of CQDs not only produces CQDs with an increase in PL emission at higher quantum yields but also makes CQDs more interactive through hydrogen bonds with organic compounds bearing functional groups containing nitrogen or oxygen, and as a result, selective sensing can occur. Heteroatom doping is another practical way to tune the fluorescent properties of CQDs. Any change in the properties is due to electronic, chemical, and surface modification. Both metal and non-metal elements with different valances can change the CQD's properties.[22]

2.3.2 CQDs -immobilized on solid films or polymers

Utilizing bare CQDs in different applications may cause a low performance due to instability and self-quenching due to aggregation. Thus, combining and stabilizing CQDs on solid films is recommended to overcome the shortcomings of bare CQDs and profit from other advantages of solid matrixes. CQDs can be attached to the matrix through interactions such as electrostatic, hydrogen, and covalent or non-covalent bonds.[23]A brief review of the CQD-based composite materials loaded on solid phases, including metal-organic frameworks, molecularly imprinted polymers, and other solid surfaces, are presented in this section.

Metal-organic frameworks (MOFs) are a group of porous structures with outstanding properties, such as tunable structures with high surface area. They comprise metal ions coordinated to the organic framework. Sensing is one of the applications of MOFs. Since metal ions and the organic part of MOF can emit light, they can be used to enhance the emission of a second incorporated compound. However, using non-fluorescence MOFs is also favorable for scientists in the sensor area.[24]

The introduction of CQDs-MOFs composites is a new approach to fluorescence sensors. Besides of fluorescence properties of MOFs, they can be applied to prevent CQDs from aggregation and self-quenching. Encapsulation into MOFs is an effective strategy to reduce the collision, which may cause adhesion of the CQD particles together.[25]

To design and prepare a composite of CQDs and MOF bearing optical properties of both CQDs and MOF, the pore size of MOF and the CQDs particle size should be focused on to introduce the optimum conditions and offer a more efficient sensor. Several methods of combining CQDs and MOF have been presented. They include one-step synthesis, “bottle around ship” which is the encapsulation of CQDs into the cavities of MOFs during the synthesis of MOF, and “ship in bottle” in which CQDs are immobilized into the pores of pre-synthesized MOF owing to intermolecular forces.[24]

In this regard, a composite of blue CQDs-ZIF-8 could be prepared by encapsulating CQDs into the ZIF-8 to detect trace amounts of Cu^{2+} ions in wastewater samples. The sensing procedure is the strong and preferred adsorption of Cu^{2+} into the MOFs and then selectively detection through CQDs. When the ZIF-8 framework collects the Cu^{2+} ions from the water sample, the chance of detection becomes higher so that CQDs can sense ions more efficiently with amplified signals. The mechanism of detection attributes to the interaction between Cu^{2+} ions and amino groups located on the surface of CQDs, resulting in the complex formation and quenching of CQDs’ fluorescence by inner filter effect (IFE) mechanism.[25]

Another example of encapsulation of CQDs in MOF is the work carried out by Wang et al. A fluorescence-based sensor was fabricated from blue fluorescence nitrogen and cobalt (II) co-doped carbon quantum dots encapsulated in europium metal-organic to detect Cr (VI). The sensor worked based on the dual emission of both CQDs and MOF with high stability in water. By adding Cr (VI) the fluorescence intensity of the sensor decreased in a static quenching mechanism through IFE in both laboratory tests and real water samples. Here, Eu metal-organic framework can be considered as a host for CQDs and a media to collect the analyte from the water sample and, as a result, enhance the sensitivity of the sensor. It is also a supportive medium to provide a uniform dispersion of CQD particles and avoid aggregation and self-quenching.[26]

Molecularly imprinted polymer (MIP) is a new technique to apply highly stable polymers, including recognition sites that are made during in situ copolymerization process of monomers around a template. Scientists have found that combining MIPs with optical transducers can improve the sensing mechanism. Therefore, MIP-based fluorescence sensors have been used for sensitive and selective detection of a wide range of analytes due to their ability to enhance separation efficacy. Precipitation polymerization, bulk polymerization, suspension polymerization, and sol-gel polymerization are the most popular methods to produce MIPs with a higher focus on sol-gel.[27,28]

CQDs coated with molecularly imprinted polymers (MIPs) were synthesized by Ensafi et al. as an optical sensor to detect promethazine hydrochloride (PrHy), a type of antihistamine medicine. The surface covering of CQDs with MIP matrix and producing recognition sites of PrHy were performed in a sol-gel polymerization procedure. When the analyte is added to the sensor, the fluorescence intensity is quenched due to attaching PrHy to the recognition sites in the matrix. Here, the mechanism of detection is charge transfer. This method resulted in improved selectivity of CQDs toward the desired analyte.[29]

Rather than MOFs and MIPs incorporated with CQDs to utilize as sensors, CQDs can be combined with various porous materials such as zeolites, carbonaceous porous materials, porous graphitic carbon nitride (g-C_3N_4), mesoporous SiO_2, natural polymers, and porous metallic compounds. These composites can be prepared in situ during the synthesis of CQDs or by mixing the prepared CQDs with the precursors of porous materials. They are used in different areas such as optics, biomedicine, sensing, electrochemistry, and photocatalysis.[23] A few examples of these composites will be presented briefly as follows.

Due to zeolites' uniform and stable structure, these materials are good candidates to host functional guests like CQDs. Zeolitic composite of CQDs and then applying them as a light-emitting and temperature sensor are two research studies done recently.[30, 31]

The incorporation of CQDs and carbonaceous materials such as activated carbon, graphene, and carbon nanospheres is a framework to benefit the electrochemical property of carbon in the composites. The combination of CQDs and graphene aerogel is an example reported in a photocatalysis application. g-C_3N_4 – CQDs is another combination that is applied for photocatalytic degradation.[32]

SiO_2 with a large surface area is another matrix to load CQDs. The composite can be prepared by mixing CQDs with the SiO_2 precursors and template and then eliminating the template. One application of such a composite is to adsorb uranium.[33]

Metallic compounds such as metal oxides, transition-metal, hydroxides, and metal borides are used as carriers of embedded CQDs and prepared via mixing CQDs and porous metallic compounds. CQDs/TiO_2, CQDs/p-$InVO_4$ as two photocatalysts, and CQDs/ alumina as a fluorescent material with two characteristic emission peaks are a couple of instances in this scope.[34-36]

Immobilizing CQDs onto natural polymers such as chitosan and using the resultant composite as a sensor to detect metal ions is another example of CQDs composite as a sensor.[37] The porous structures can also be used in the detection of gaseous materials at low concentrations by enriching the structure with the gas molecules. The detection of acetic acid gas, which is conducted through silica/CQDs composite, is based on this fact. The results showed an enhanced fluorescent response and improved detection sensitivity.[38]

2.3.3 CQDs as fluorescent sensors for pesticides detection

Fluorescent sensors are one of the most used due to their high sensitivity and simplicity. Their applications range from environmental pollutants control to biomedical diagnosis. One advantage of these sensors is the possibility of fluorescence change by the naked eye in many cases. Semiconductor carbon materials, metal nanoparticles, and fluorescence dyes are a couple of examples of fluorescence-based sensors. When coupling a fluorescence element to a recognition unit is the case, it is crucial to choose the right combination based on the desired “turn off”, “turn on”, or “ratiometric” signal.[22]

Today, it is important to prepare highly sensitive sensors for pesticide detection to protect the environment, control food safety, and prevent disease.[39] The sensing of pesticides through bare CQDs will be discussed in detail in the following sections.

Detection of organic compounds can be directly performed through optical sensors like carbon quantum dots (CQDs) as these chemicals may have specific interactions with the functional groups located on the CQDs surface and cause turn-on or turn-off effects. Pesticides are a large group of organic chemicals associated with several active sites to make bonds or interact with functional groups of CQDs. If a type of pesticide interacts sensitively with the CQDs, it would be considered as an acceptable optical sensor. It is also essential to have a good selectivity toward a targeted pesticide when other pesticides also exist. Therefore, a good sensing system is one with high sensitivity and selectivity simultaneously.[40] Researchers in this area try to find more efficient sensors with less complication for pesticide detection. For instance, in a study by Shakerbeygi et al. [41], bare CQDs with no further coupling was introduced as an optical sensor to detect diazinon, a pesticide from the organophosphorus family. They showed that by increasing the concentration of the target chemical, the quenching effect would increase. The results have also proved the selectivity of the sensor in the presence of other pesticides as an important factor in the evaluation of any sensor and reported that there is no significant or adverse effect for diazinon detection related to the presence of other chemicals. To show the ability of bare CQDs to detect pesticides, another study was reported by a group of researchers presenting the fluorescence turn-on and turn-off sensing of pesticides by CQDs.[42] They investigated five pesticides from different classes, including atrazine (from the triazine group), chlorpyrifos (from the organophosphorus group), imidacloprid (from the neonicotinoid group), lindane (from the organophosphorus group), and tetradifon (from sulfone group) that may exist in wastewater. All these chemicals showed a significant effect on CQD fluorescence intensity (turn-on or turn-off) due to possible molecular interaction between active functional groups of CQDs and target molecules, leading to fluorescence change of CQDs. To inspect the selectivity and examine the sensing capability of CQDs towards the different pesticides, the fluorescence spectrum of the CQDs in the presence of the target pesticides was also investigated. The results revealed that all the pesticides could quench the fluorescence intensity of the CQDs except imidacloprid. Therefore, the synthesized CQDs can be used as a selective turn-on sensor for imidacloprid detection and a turn-off sensing method for tetradifon which has a higher quenching effect than other pesticides. These studies show that in these cases, bare CQDs can be introduced as a selective and sensitive sensor to detect a targeted pesticide without adding any other elements.[42] However, it is not always the case. In many other studies, researchers showed that bare CQDs could not sense pesticides with high accuracy and making a complicated system to provide a reliable sensor is desired. Also, bare CQDs, in some cases, show fluorescence leakage that might result in sensor instability.[40]

2.3.4 Mechanisms of CQDs-based fluorescence sensing

Generally, sensing happens when CQDs interact with an analyte resulting in signal response. Dipole-dipole interactions and charge transfer are two known interactions between CQDs and a specific analyte. When QDs are applied as sensors, the detection is generally based on the sensitivity of their fluorescence to the surface state of the nanoparticles. Therefore, chemical or physical interaction with a target molecule may cause an increase or a decrease in photoluminescence intensity.[43]

Based on CQDs – analyte interaction, different mechanisms of detection are proposed. FRET, IEF, and PET are three effective mechanisms that were discussed in details in the following sections.

- **FRET mechanism**

Forster Resonance Energy Transfer (FRET) is an energy transfer mechanism between CQDs and a target molecule. This mechanism is based on energy transfer from a donor, CQDs, and an acceptor. This non-radiative energy transfer happens through dipole-dipole interaction. The main criterium which should be met to have FRET is the overlapping of the UV-vis spectrum of analyte and the emission spectrum of CQDs. Also, the distance between CQDs and quencher would be 10 Å – 100 Å, and the lifetime of CQDs in the presence of the analyte molecule must show a change.[18, 44]

One example in this regard is the work conducted by Xu et al. They prepared amino-functionalized CQDs to detect trypsin. Their turn-on sensor was worked based on the FRET mechanism. The proposed sensing system comprises three elements of peptides, gold nanoparticles, and amino-functionalized CQDs. Peptide molecules were first immobilized on the surface of AuNPs. By adding trypsin to the mixture, peptides are hydrolyzed, and the product of the reaction now interacts with AuNPs and makes them aggregated, which decreases the probability of the electrostatic interaction between AuNPs and CQDs, leading to the recovery of fluorescence emitted by CQDs. The as-prepared sensor showed a sensitive and selective behavior toward trypsin with a LOD of 0.84 ng / mL.[45]

- **IEF mechanism**

If the UV-absorption spectrum of an analyte overlaps with the excitation and/or emission spectrum of CQDs, the inner filter effect (IEF) may occur. IFE is a kind of energy conversion model in spectra-fluorometry, which results from the absorption of the excitation and/or emission light by the absorber in the detection system. IFE does not require electron or energy transfer. The IFE can still occur if the distance between the CQDs and the analyte is more than 10 nm. To have an IFE-based sensor, a few conditions should be provided: (1) The absorption spectrum of the analyte should show an overlap with the excitation and/or the emission spectrum of CQDs, (2) The absorption of the absorber should exhibit a sensitive response to the variation of the analyte concentration, (3) The fluorescence of CQDs should be independent on the analyte, and (4) The absorption and fluorescence features of the selected absorber and fluorescent should be free from the influence of external factors.[43]

The detection of Cu^{2+} by branched poly(ethylenimine)-functionalized carbon quantum dots (BPEI-CQDs) has occurred through an IFE mechanism. The surface of CQDs has enough amino groups to interact with metal ions. In this sensing system, the amino groups of the BPEI-CQDs capture the ions, and a complex of cupric amine forms on the surface of CQDs. This complex may cause a significant quenching of CQD fluorescence, which is proved by the exhibition of specific UV/vis absorption of cupric amine.[46]

- **PET mechanism**

The third mechanism for quenching is photoinduced electron transfer (PET). PET is based on the formation of a complex between the electron donor and the electron acceptor by a charge transfer between photoexcited and ground-state molecules. In PET, the excited fluorophore can be considered as either the electron donor or acceptor. Here, the donor structure is the one that donates an electron to an acceptor. In PET, the terms donor and acceptor do not identify which species is initially in the excited state. PET quenching can also occur by electron transfer from the excited fluorophore to the quencher. The quenching mechanism shows a decrease in the lifetime of CQDs and an energy gap of LUMO/HUMO or LUMO/LUMO between the CQDs and the quencher.[47]

Luo et al. presented a sensor of β-cyclodextrin functionalized S, N-doped CQDs to detect testosterone selectively. The mechanism governed in this system is competitive guest-host PET to monitor the concentration of analyte in water. As the functionalized CQDs are hydrophobic, by adding (ferrocenylmethyl) trimethylammonium iodide (Fc^{+}) to the system, Fc enters into the cavity of CQDs. So, the distance between the iron core of Fc^{+} and the surface of the CDs decreases. As a result, the photo-induced excited electron transfers to the empty orbitals of Fc$^{+,}$ and the fluorescent intensity of β-cyclodextrin functionalized S, and N-doped CQDs decreases. When testosterone is added, Fc^{+} in the β-CQDs will be replaced by testosterone and produce a new β-CQD-testosterone complex leading to the fluorescence recovery of CQDs.[48]

2.4 Molecular Modification of Pesticides

To address the issues attributed to the harmful nature of pesticides in the environment, one can recommend other structures of these chemicals and modifying pesticides associated with improved environmental characteristics to substitute the current pesticides. For instance, synthesizing cis-configured neonicotinoids and seeing their biological function is an approach. Although it is accepted that trans-configuration is generally more stable than cis isomers, the biological activity and toxicity of cis and trans configuration of neonicotinoids are different. In some cases, cis isomers show higher activity against pesticides-resistant insects through other binding models than trans configurations.[49] Another approach to improve the properties of pesticides is to replace the problematic groups with safer ones.[50]

It is a general idea to evaluate the pesticide's functionality and investigate their potential diverse effects on the environment in advance and then release them to the market. Therefore, any proposed structure should be examined first. To save time and costs, new compounds can be firstly designed theoretically, and then the results applied before experimental tests and structure synthesis. To do this, a reliable molecular modeling tool is required to define and introduce novel structures. Quantitative structure-activity relationship (QSAR) modeling is an acceptable approach in this scope. Low cost, fast, replicability, and high efficiency are a couple of advantages of QSAR models.[51]

2.4.1 QSAR-based pesticides modification

QSAR is a popular computational method applied in different scopes of science. There are two ways (i.e., 2D and 3D) in QSAR modeling. 2D-QSAR includes geometric and topological parameters, while in 3D-QSAR spatial factors are also considered. The main purpose of QSAR models is to correlate biological activities defined in pharmaceuticals, toxicants, or environmental contaminants in a molecular framework by analyzing and detecting the influential items for a targeted property.[52] 3D-QSAR modeling can be conducted using two models of comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) analysis to introduce the counter maps around a target molecule and determine the potential positions on the structure to be substituted by other groups.[51] The outcome of the models can then apply for further research considerations when the experimental data are limited or unavailable. One can use QSAR and provide models to introduce novel structures and predict the desired property for them in the food, pharmaceutical, and agricultural industries. A good QSAR model is the one with high reliability to validate and then predict properties for new compounds.[52]

In agriculture, QSAR modeling can be conducted to predict the toxic function and other environmental properties of pesticides and insecticides used to protect plants before experimental tests. It offers a pre-investigation and provides quick and detailed information about the design of the compounds. It is utilized to introduce reliable and safer chemical structures to apply as pesticides in agriculture, and collecting data in this regard can help evaluate the current chemicals and provide proper scenarios to release better products to use in agriculture. It is also beneficial to assess the ecotoxicological properties of pesticides and comply with the standards.[53]

Applying QSAR to build a predictive model for toxicity is very popular and studied broadly. The model can be applied to estimate the toxicity of a variety of chemicals in the absence of experimental data on toxicity. To do this, models are developed using a training set of structures with known toxicity with the assumption of a relationship between chemical structure and toxicity.[52] However, other factors rather than toxicity can also be studied in QSAR. Furthermore, a group of pesticides can be evaluated in QSAR for risk assessment purposes.[54] Here, those studies focused on QSAR applications in the pesticide modification need to be presented.

As mentioned, risk assessment can be performed from the results of a QSAR modeling. A group of researchers used a genetic algorithm and multi-linear regression to see the influence of different descriptors on toxicity using 289 molecules. They showed the lipophilic groups might have a positive effect on toxicity by increasing permeability and accumulation in organisms, while all the electro-topological states showed a negative contribution. The proposed model can help determine the toxicity of pesticides and provide a sufficient dataset of pesticides structures to run a risk assessment study.[54]

To check the effect of hydrophobicity, electronic and structural properties of pesticides on their functionality, a QSAR model was developed to predict pesticide bioavailability in terms of membrane permeability as a proper descriptor for oral human absorption of pesticides. They found the permeability coefficient an excellent descriptor for predicting human oral absorption. The results of this study can be applied to filter and choose new pesticides with improved properties. This group of researchers also studied the membrane accumulation parameter as another effective element rather than bioconcentration in the design of pesticides.[55] A series of sulfone compounds was introduced and synthesized based on the results obtained from QSAR models and examined toward a bacterial disease in rice. The new structures showed improved antibacterial functionality, and the authors proposed one structure among all that can be substituted as a potential antibacterial compound in the future.[56]

One application of QSAR in the pesticides field is to investigate the ecotoxicity of those products released after the degradation or transformation of pesticides. In this way, the toxicity of the identified products toward a type of algae and fish was predicted, and the most toxic products were determined. These results can provide deep knowledge of applying different pesticides and their consequences on the environment.[57]

In another study, attachment of a few pesticides, including acetamiprid, nitenpyram, and related compounds to the receptor biomolecule of nAChR in houseflies and their binding activity were investigated in 3D-QSAR models and compared to imidacloprid as a cyclic compound. A comprehensive survey involving atoms, cycles, and functional groups has been conducted to see their effects on binding to the target receptor. The results proved the significantly less steric effect in imidacloprid compared to other structures with no cycle in their chemical structures.[58]

The ecological effect of pesticides was also studied through molecular modeling. A QSAR model using a large set of data (311 organic pesticides) was built to predict the acute toxicity of pesticides toward rainbow trout fish. The authors discussed the mathematical parameters of the model, such as the ideality index of correlation which is the main parameter of this approach and defined as the predictive potential of the QSAR models. The available structures were randomly distributed in the active training set (25 %), passive training set (25 %), calibration set (25 %), and validation set (25 %). This model provided a good range of statistical parameters and was proposed to be used for the prediction of new compounds and corresponding toxicities.[53]

Synthesis of a group of new structures of neonicotinoid possessing nitro methylene using the results of a QSAR modeling was conducted by Tian et al. and then tested for bioassay functionality. Their results showed good insecticidal activity for some structures against a specific insect. A quantitative relation for the bioactivity of structures was also determined.[59] Zhao et al. established a QSAR model to design new neonicotinoid pesticides which had improved selective toxicity by choosing a target molecule with high toxicity. They found that a few new neonicotinoid derivatives have low adverse effects on the environment and human body with higher toxicity effects on pests and grubs so that they can substitute the current neonicotinoid pesticides.[60]

A 3D-QSAR model was established with CoMSIA by Zhao et al. to study the effect of substituting current sites with new groups into the neonicotinoid on the bioconcentration factor of novel structures. They found 105 novel compounds with reduced bioconcentration factor (BCF) and almost the same toxicity. Homology modeling was also used to study the interaction between new structures and AChR using molecular docking to find the best structures in terms of bi-directional selective effects on pests and bees.[61]

A 3D-QSAR model was also established based on the molecular structures and the toxicity (pLC_{50}) of neonicotinoid insecticides to show the bi-directional selective toxic effects and drug resistance using molecular docking. From the results, different sites of a target molecule were specified to be replaced by other groups to increase the pLC_{50} values. 37 new structures were introduced, and eventually, one showed the best bi-directional selective toxicity and resistance-inducing effects on pests and bees and was selected as a new insecticide.[62]

2.4.2 Molecular docking-based pesticides studies

Molecular docking is a popular theoretical method applied in several areas, from drug design to biosensors studies. Generally, molecular docking would offer three main functions: pose prediction, virtual screening, and binding affinity estimation in different areas of science.[63] Molecular docking can predict binding modes and affinities of small molecules toward a receptor. However, the most useful application of molecular docking would be found in biomolecular studies. The basis of docking in the biomolecule area is to conduct molecular modeling studies to find any interaction between biomolecules and target molecules such as drugs.[64] In the environmental field, molecular docking would help to check the mechanism of toxicity function of pollutants such as pesticides through the study of pollutant-protein interaction. In addition, it can be conducted to find the biodegradation mechanism of a target contaminant.[65] One of the main applications of molecular docking in the pesticides field, especially neonicotinoid, is to investigate the receptor-binding cavity of all AChRs and pesticide molecules which have been conducted in several works.[61, 66, 67] Normally, molecular docking is used for macromolecules on one side and a small molecule on the other. Although the interaction between CQDs and biomolecules such as human serum albumin (HSA) has been investigated,[68] to the best of our knowledge, the interaction between CQDs and smaller molecules has not been studied yet. As CQDs are moderate size molecules but much larger than nitenpyram, applying molecular docking to study the binding affinity of pesticides such as nitenpyram and its derivatives with CQDs can be performed.

2.5 Summary

In this chapter, an overview of pesticide detection and modification has been presented. Applying CQDs-based optical sensors is a promising approach to detecting pesticides. Furthermore, modification of pesticides' molecular structures via computational modeling such as QSAR is another method to introduce new alternatives and mitigate the harmfulness of pesticides in the environment. Considering the available pieces of research performed in the field of pesticide detection using optical sensors or structural modification of pesticides, it is concluded that the detection of pesticides, especially nitenpyram, has not been studied broadly. Furthermore, applying CQDs as a sensor in pesticide quantification is generally limited. The design of new nitenpyram-based derivatives is also rare. Since the in-situ detection of pesticides is of great interest in environmental studies, examining the molecular interaction of new derivatives with optical sensors such as CQDs-based sensors is also valuable to select those structures with enhanced sensing capacity toward a sound sensor that is not released in the literature to the best of our knowledge.

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Chapter 3 Selective detection of nitenpyram pesticide by silica-supported carbon quantum dots

3.1 Introduction

Carbon quantum dots (CQDs)-based fluorescent sensors are promising alternatives to the conventional geotechnical instrumentation techniques in environmental detection (e.g., heavy metal ions, organic pollutants) and biological fluorescence imaging due to attractive properties of tunable fluorescence, high stability, good biocompatibility, low toxicity, and simple synthesis.[1-6] Despite not being extensively studied, CQDs-based fluorescent sensors for selective sensing of neonitinnoids were reported by several research groups.[7–10] CQDs synthesized from gelatin were used as fluorescence sensors to detect five pesticides (imidacloprid, atrazine, chlorpyrifos, lindane and tetradifon).[7] The prepared CQDs displayed different binding characteristics with pesticides, resulting in a turn-on effect (30.0% increase) of fluorescence in the presence of imidacloprid, and a turn-off effect (35.0% quenching) of fluorescence in the presence of tetradifon.[8] Gao et al. reported a N-(aminobutyl)-N-(ethylisoluminol) functionalized CQDs sensor for the fluorescence sensing of thiamethoxam, flubendiamide, dimethoate, dipterex, and chlorpyrifos.[9] 15% and 8% of fluorescence quenching were observed when the sensor was in contact with chlorpyrifos and thiamethoxam, respectively. More recently, a dual-emission ratiometric fluorescent probe of sulfur-doped CQDs and CuNCs hybrid was introduced for sensitive and selective detection of dinotefuran. The as-prepared sensor demonstrated excellent selectivity and analytical performance of dinotefuran with a limit of detection (LOD) of 7.04 μM.[10]

Results from the reported studies reflect that the selectivity and sensitivity of CQDs-based fluorescent chemosensors highly depend on the type of binding and binding constants between analytes and CQDs. However, the uncertainty of the exact fluorescence mechanisms of CQDs and the difficulty in finding the recognitions elements are significant challenges in the design and application of CQDs-based fluorescent sensors. In addition, poor selectivity and low sensitivity of CQDs-based sensors are still a big hurdle to overcome. More research and creative endeavors are needed to develop neonicotinoid-specific detection using CQDs-based fluorescent sensors with high selectivity and sensitivity.

In this study, a turn-off silica supported CQDs sensor was fabricated for the selective and sensitive detection of nitenpyram (NTP), a neonicotinoid pesticide still being used commercially. Silica gel was selected as the immobilization carrier for CQDs in this work due to its protective characteristics of the porous structure, low cost and non-toxicity.[11] The as-prepared sensor was characterized by the Fourier transform infrared (FTIR) spectroscopy, high-resolution transmission electron microscopy (HR-TEM) and X-ray photoelectron spectroscopy (XPS). Its fluorescence responses to several pesticide molecules were investigated and the results indicated that the prepared sensor showed very good sensing selectivity and sensitivity to nitenpyram through the mechanisms of IFE.

3.2 Materials and Methods

3.2.1 Materials

Anhydrous citric acid (99.5%) and ethylenediamine (99%) from Fisher Scientific, as well as ACS grade anhydrous ethanol from Greenfield were used to synthesize nitrogen-doped CQDs (N-CQDs). Tetraethoxysilane (TEOS, 99%), LUDOX-HS 40 colloidal silica, and all pesticides (analytical standard) including nitenpyram (NTP), imidacloprid (IMD), thiamethoxam (TMX) and atrazine (ATZ) were purchased from Sigma. These chemicals were used as received without further purification. If not particularly indicated, all solutions were prepared with deionized (DI) water from a Milli-Q water purification system.

3.2.2 Preparation of the N-CQDs@SiO_2 fluorescent sensor

The synthesis of N-CQDs was performed by hydrothermal/solvothermal method. Briefly, 0.965 g of ethylenediamine and 0.84 g of citric acid were mixed with 20.0 ml of ethnol-H_2O solution (1:3 v/v) in a Teflon-lined autoclave at room temperature and then transferred into the oven at 200 ˚C for 3.0 h. The resultant products were allowed to cool down at room temperature. The obtained solution was then centrifuged at 4000 rpm for 0.5 h and filtered through 0.22 μm membrane filters to remove any large particles. Unreacted chemicals were also removed using a dialysis (molecular weight cutoff of 500 Da) process for 24 h, and the solid N-CQDs were collected after freeze-drying. Fig. 3.1 shows the synthesis autoclave and the resultant CQDs under daylight.

To immobilize N-CQDs onto the silica gel, 5.0 mL of tetraethoxysilane (TEOS) solution was mixed with 5.0 mL of colloidal silica LUDOX-HS 40 in acidic conditions (pH 2.0) adjusted by adding drops of HCl. The mixture was then neutralized by adding NaOH solution to pH 7.0.[12] In the next step, N-CQDs@SiO_2 gel was prepared by mixing 10.0 mL of the as-prepared silica solution with 8.0 mL of the N-CQDs solution (1 mg/mL). The mixture was ultrasound for 1.0 h and stirred overnight. The resultant solution can be used as the sensor.

Figure 3.1 a) Stainless steel autoclave, b) N-CQDs solution before dilution under daylight

3.2.3 Characterization

The as-prepared N-CQDs and N-CQDs@SiO_2 sensor were characterized using various apparatus. The FTIR spectra were obtained from a Bruker Tensor II FTIR spectrometer (Bruker, Germany) over a range from 400 to 4000 cm^{-1}. The HR-TEM images of N-CQDs were taken on a FEI Titan 80-300 HB electron microscope (FEI, USA). XPS measurements were performed using a XPS-PHI 5000 VPIII (ULPAC-PHI Inc., Japan) with peak positions being recalibrated by shifting C 1s peak to 284.8 eV. The fluorescence excitation and emission spectra of the N-CQDs@SiO_2 sensor with and without analytes, were obtained from a PTI-Quanta Master spectrofluorometer (Photon Technology International Inc., USA). UV-Vis and UV-Vis diffuse reflectance spectroscopy (DRS) analyses were performed using Varian Cary 100 Bio and U-3900H Spectrophotometers, respectively. The cyclic voltammogram of CQDs was also conducted in a solution of Bu_4NPF_6 (0.1 M) in DMF as the supporting electrolyte using a standard three-electrode system (BASi Epsilon potentiostat) which consists of glassy carbon as the working electrode, a platinum wire as the counter electrode and Ag/AgCl as the reference electrode. The de-oxygenation was done by using nitrogen flow to remove dissolved oxygen in the solution.

3.2.4 Fluorescent sensing of NTP

The stock solution of NTP was prepared by dissolving it into DI water with a final concentration of 480.0 mg/L. NTP solutions with different concentrations (5.0–300.0 mg/L) were prepared by diluting the stock solution into DI water. The typical procedures for fluorescence measurement include a) mixing 2.0 mL of N-CQDs@SiO_2 solution completely with 2.0 mL NTP solutions in a quartz cuvette; and b) recording the fluorescence emission spectra at an excitation wavelength of 360 nm (λ_{ex}=360nm). The selectivity of the N-CQDs@SiO_2 sensor toward NTP was evaluated by adding three other pesticides solutions instead of NTP in a similar way. In order to verify the influence of other pesticide molecules on the selectivity of the sensor towards NTP, the fluorescence spectrum of N-CQDs@SiO$_2$ in the presence of the mixed solution of the four pesticides was also examined. All experiments were performed at room temperature.

pH effect on the fluorescence intensity of N-CQDs@SiO$_2$ and its sensing of NTP was studied by varying the pH values (pH 2.0–9.0) of the N-CQDs@SiO$_2$ solution. The fluorescence intensity at 445 nm (λ_{em} = 445 nm) was measured at λ_{ex}=360 nm in the absence and presence of NTP by adding 100.0 µL of 480.0 mg/L NTP solution into the N-CQDs@SiO$_2$ solution.

3.2.5 Detection of NTP in natural water samples

Natural water samples including surface water, ground water and soil leachate were collected from a local waste management facility (St. John's, Canada). The natural water samples were first centrifuged for 15 min at 4000 rpm to remove the large particles and suspended soil and then filtered using a 0.22 µM membrane. After that, NTP natural water solutions with different concentrations of NTP were prepared. Fluorescence quenching of the N-CQDs@SiO$_2$ sensor by NTP natural water solutions was measured using the same method as that for NTP DI water solutions.

3.3 Results and Discussion

3.3.1 Characterization of N-CQDs and N-CQDs@SiO$_2$

Fig. 3.2 shows the HR-TEM images of the synthesized N-CQDs, which indicate that the particle sizes of N-CQDs were predominantly in the range of 5 – 10 nm, and they were essentially spherical in nature. Partial self-passivation could lead to variation in sizes however a distinct spherical morphology was maintained throughout. Surface functional groups of N-CQDs was clarified from the FTIR spectra (Fig. 3.3), which suggested that N-CQDs were comprised of –OH and –NH groups (broad peaks in 3500-3100 cm^{-1}), C=N (1651 cm^{-1}), aromatic C=C (1538 cm^{-1}), and carboxyl group with characteristic peaks of C=O at 1699 cm^{-1} and C–O at 1050 cm^{-1}, respectively. The results show good agreement with those reported in the open literature for N-CQDs prepared with similar carbon and nitrogen precursors.[13-15]

XPS is an important chemical characterization technique for CQDs, which provides detailed information on the elemental composition and the bond properties of the atoms that make up the CQDs. XPS survey spectrum shows that the as-prepared N-CQDs are mainly composed of three elements of C, O and N (Fig. 3.4a). In the high-resolution spectrum of C 1s (Fig. 3.4b), three deconvoluted BE peaks at 284.8, 286.04, 287.42 eV could be assigned to the sp^2 C (C=C/C–C), the oxidized C (C–O and C=O) and sp^3 bonded C (C–N), respectively.[16] Three deconvoluted BE peaks at 399.63, 400.97 eV corresponding to pyridinic N (C–N–C), pyrrolic N (C–N) and amino N (N–H) were observed for N 1s from Fig. 3.4c.[16, 17] The two peaks of the O 1s spectrum (Fig. 3.4d) at 531.18 and 532.21 eV are attributed to the C=O and C–O groups respectively.[15, 18]

To scrutinize the optical properties of N-CQDs, UV−Vis absorption and the fluorescence excitation and emission spectra of N-CQDs were investigated. It was seen from Fig. 3.5 that the as-prepared N-CQDs have a broad absorption peak at 239 nm, which could be identified to the $\pi-\pi^*$ transition of the aromatic sp^2 (C=C) bonds. N-CQDs also have an obvious absorption peak at 345 nm, which is due to the $n-\pi^*$ transition of the C=O bond.[19] The fluorescence spectra reveal that the N-CQDs have optimal excitation and emission wavelengths at 360 and 445 nm. The inset of Fig. 3.5 shows the picture of N-CQDs under UV light (395 nm) irradiation in bright blue color.

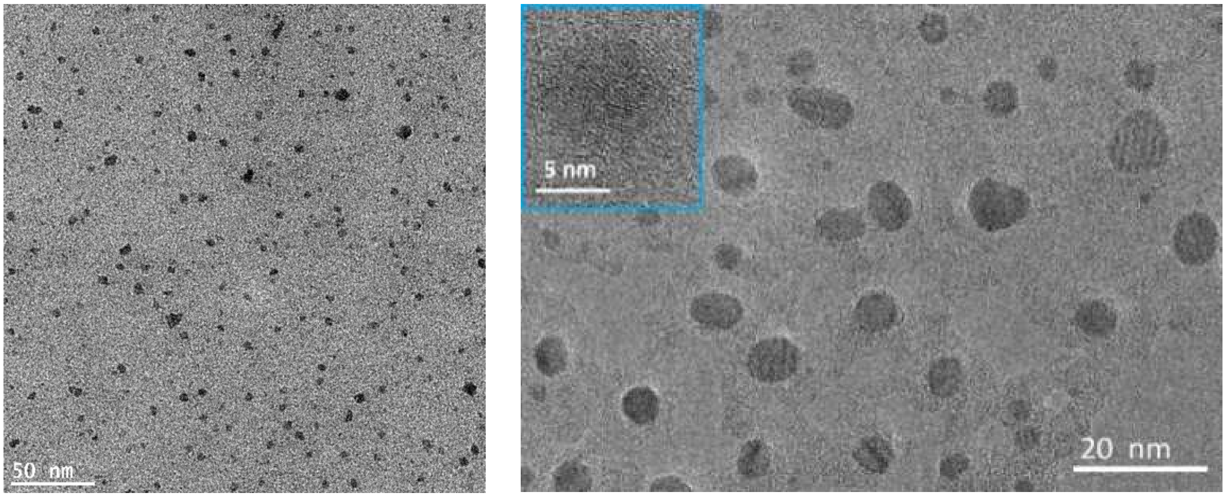

Figure 3.2 HR-TEM image of N-CQDs

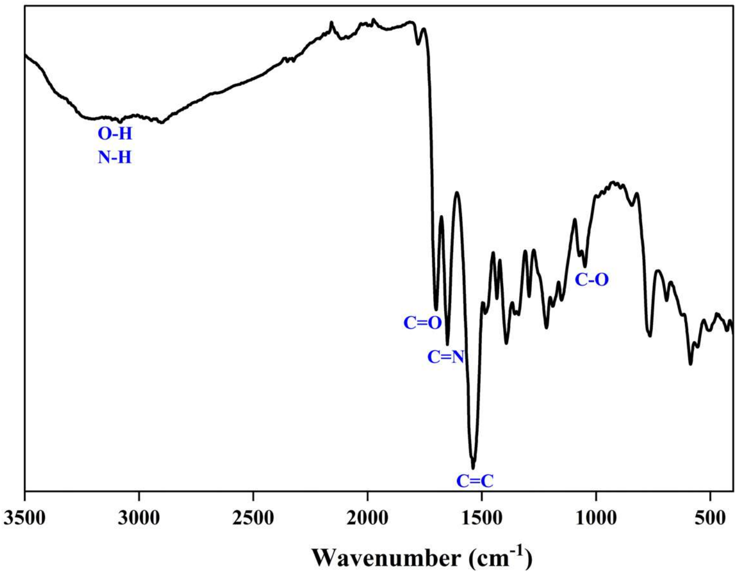

Figure 3.3 FTIR spectrum of N-CQDs

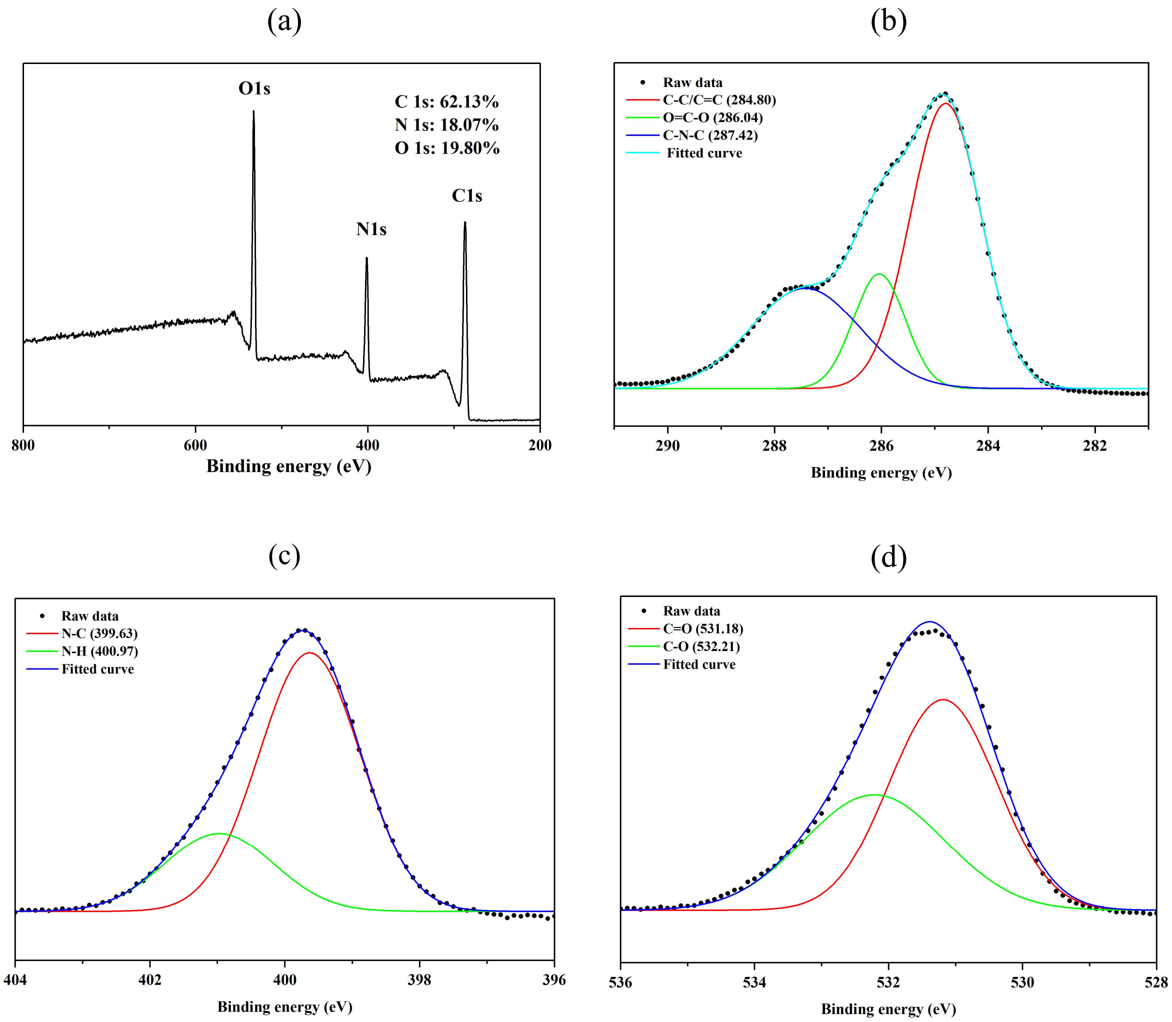

Figure 3.4 a) Survey XPS spectrum of N-CQDs, b) high-resolution XPS spectra of C 1s, c) N 1s, d) O 1s

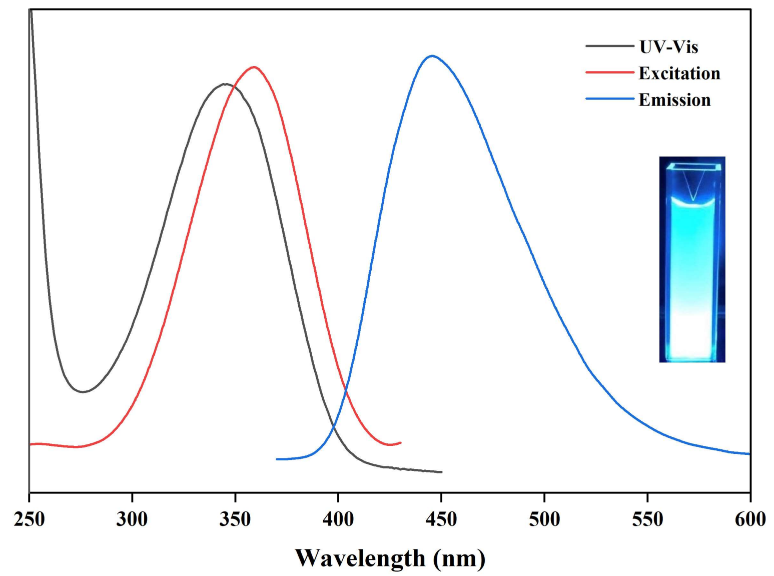

Figure 3.5 UV-Vis absorbance and fluorescence excitation/emission spectra of N-CQDs@SiO_2

FT-IR and XPS analyses were performed for the surface functionality and composition of N-CQDs@SiO_2 composite either. From the IR spectrum of N-CQDs@SiO_2 illustrated in Fig. 3.6, the presence of vital vibrational modes referring to the Si–O–Si groups was observed from typical transmittance bands at 451 and 794 cm^{-1}, as well as a very prominent band in the range of 1000–1250 cm^{-1}.[20] XPS survey spectrum shown in Fig. 3.7 confirmed that the atomic levels of elements Si and O are tens-fold higher than those of C and N in the composite gel. However, N-CQDs@SiO_2 gel demonstrated very similar UV−Vis absorption and the fluorescence excitation and emission spectra (Fig. 3.8) as those of N-CQDs.

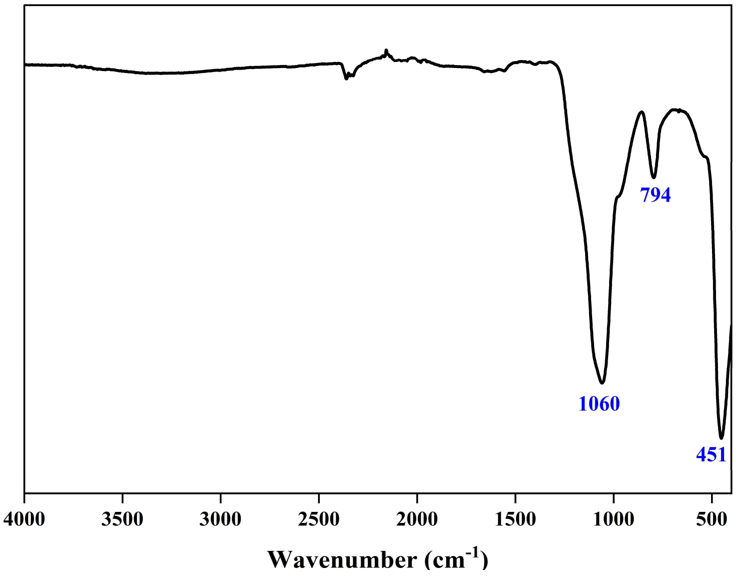

Figure 3.6 FTIR spectrum of N-CQDs@SiO_2

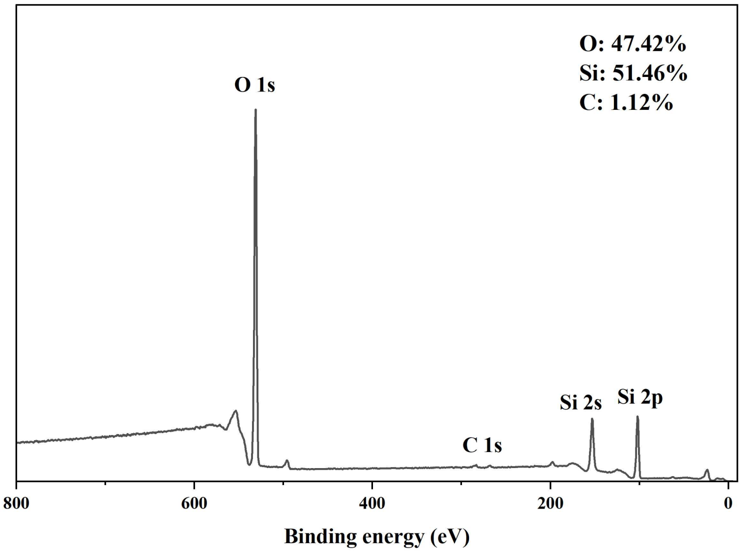

Figure 3.7 Survey XPS spectra of N-CQDs@SiO_2

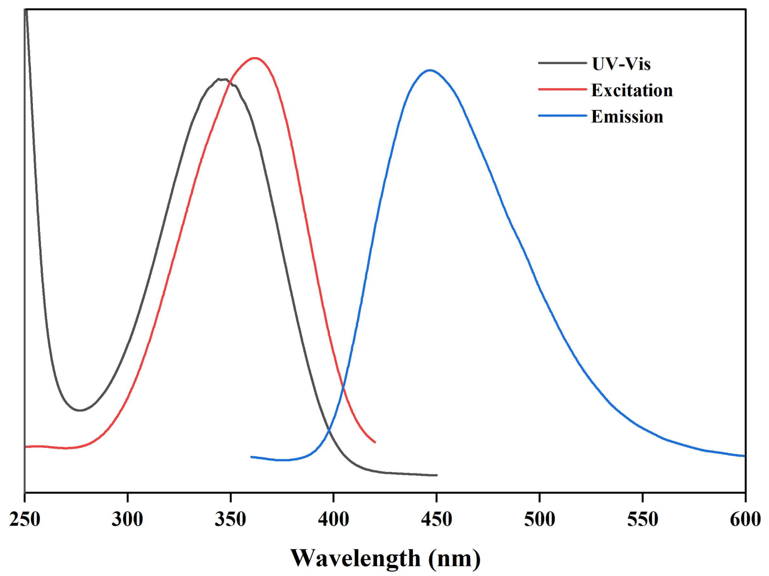

Figure 3.8 UV-Vis absorbance and fluorescence excitation/emission spectra of N-CQDs@SiO_2

3.3.2 pH effect on fluorescent sensing of NTP

The fluorescence intensity of N-CQDs@SiO_2 in the absence and presence of NTP was studied and the results are presented in Fig. 3.9. The fluorescence emission spectra of the prepared sensor exhibited pH-dependent characterization, with strong fluorescence emission under neutral/alkaline conditions and relatively weak fluorescence emission under acidic conditions. This phenomenon is related to the deprotonation and protonation of acidic and basic groups (on N-CQDs) in ground or excited states, which could change the property and the rate of transition processes, and finally affect the fluorescence intensity of N-CQDs@SiO_2.[21] The fluorescence quenching effect of N-CQDs@SiO_2 by NTP varies with pH either, with the optimum quenching effect observed at pH 7.0, indicating that the molecular interaction between NTP with N-CQDs@SiO_2 is the strongest at pH 7.0. Thus pH 7.0 was chosen in the further experiments.

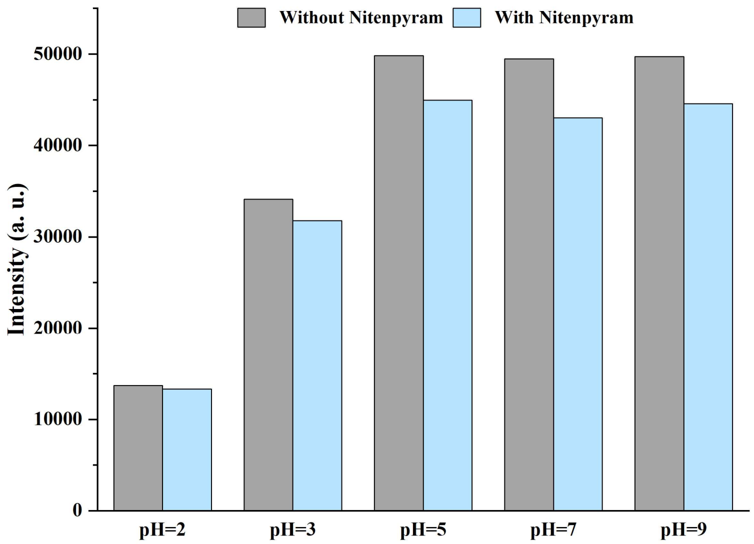

Figure 3.9 pH effect on the fluorescence intensity and sensitivity of N-CQDs@SiO_2

3.3.3 Fluorescent sensing of NTP by N-CQDs@SiO_2

The fluorescence spectra of N-CQDs@SiO_2 solution in the absence and presence of NTP obtained at excitation of 360 nm have been presented in Fig. 3.10a in a concentration range of 0–300.0 mg/L. It is obvious that the fluorescence intensity of N-CQDs@SiO_2 keeps decreasing with the increase of NTP concentration without any blue- or red-shift. Fig. 3.10b shows a linear relationship between fluorescence intensity change of the N-CQDs@SiO_2 sensor and concentrations of NTP over the range of 5.0–300.0 mg/L, which can be described by Stern-Volmer correlation in Eq. (1),

$$F_0/F = 1 + K_{SV}c \tag{3−1}$$

where F_0 and F are the fluorescence intensity of N-CQDs@SiO_2 in the absence and presence of NTP respectively, K_{sv} is the Stern–Volmer quenching constant and c is the concentration of NTP (mg/L). By this linear correlation, the K_{SV} value is calculated to be 3.6 L/g with a correlation coefficient, R^2, of 0.997. Using the linear calibration curve at lower concentrations and the standard deviation of intercept, the LOD of the prepared sensor is 2.6 mg/L with a signal-to-noise ratio of 3.3[22] showing the lowest reliable concentration of the analyte that can be measured in this detection method which is acceptable compared to the other methods applied for the detection of nitenpyram with more complications.[23, 24]

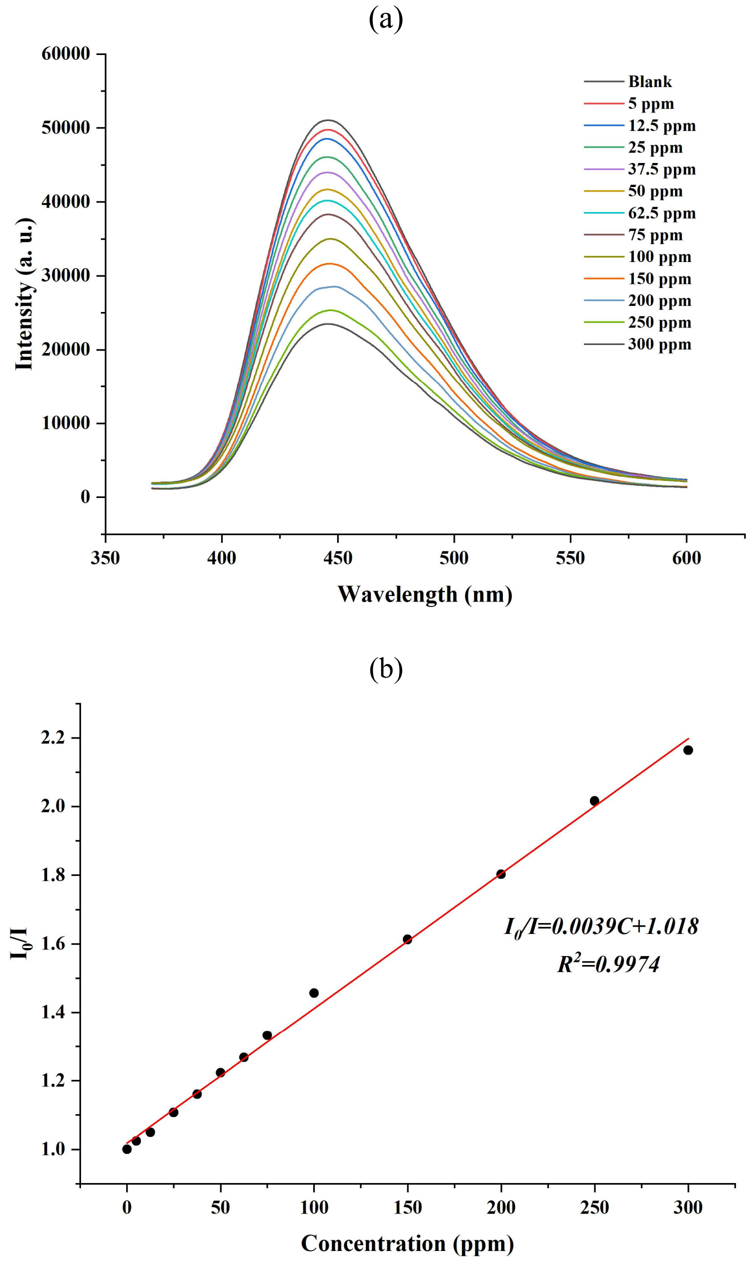

Figure 3.10 a) Fluorescence emission spectra of N-CQDs@SiO$_2$ at different concentrations of NTP, b) linear correlation of FL intensity variation versus the concentration of NTP

The binding constant (K_a) of NTP to the N-CQDs@SiO$_2$ sensor could be determined using the below equation:[25]

$$\frac{1}{\Delta F}=\frac{1}{\Delta F_{\max}}+\frac{1}{\Delta F_{\max}K_a}\left(\frac{1}{c}\right) \tag{3−2}$$

In Eq. (2), ΔF (F_0-F) is the change of fluorescence intensity of the N-CQDs@SiO_2 in the presence of NTP; $\Delta F_{\max}$ is the maximal change of fluorescence intensity; and c is the concentration of NTP solution. By linear regression of $1/\Delta F$ versus $1/c$ based on Eq. (2) over the concentration range of 5.0–300.0 mg/L, the K_a value of 7.36 L/g has been obtained, which indicates rather strong binding affinity between NTP and N-CQDs@SiO_2.

3.3.4 Selective sensing of NTP and its mechanism

The sensing selectivity of the as-prepared N-CQDs@SiO_2 was studied by mixing the N-CQDs@SiO_2 gel with individual pesticide solutions (e.g., NTP, IMD, TMX and ATZ) at three concentration levels. As seen from Fig. 3.11, significant fluorescence quenching of the N-CQDs@SiO_2 occurred after being immersed to 25.0, 100.0 and 250.0 mg/L NTP solutions, leading to 9.7%-50% reduction in the fluorescence intensity. Because of the similar chemical structures of AMD and NTP, AMD could also quench the fluorescence of N-CQDs@SiO_2 by 5.5%-12% at concentrations of 100.0 and 250.0 mg/L, which are significantly lower than those by NTP at the same concentration levels. However, the N-CQDs@SiO_2 sensor had no distinctive fluorescent response to TMX and ATZ among the four compounds.

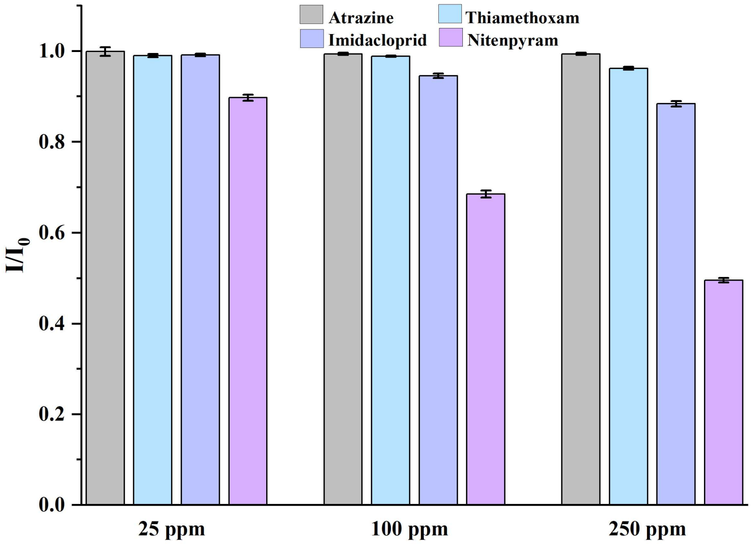

Figure 3.11 Fluorescence quenching of N-CQDs@SiO_2 by various pesticides at different concentrations

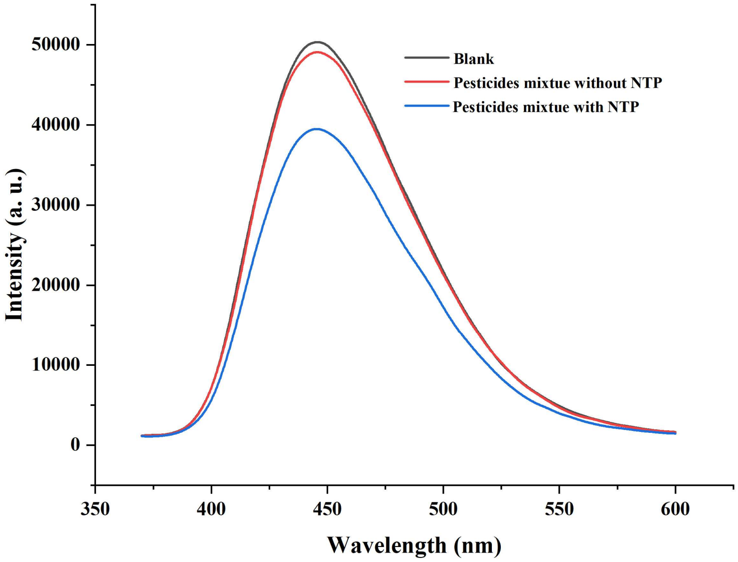

Figure 3.12 Fluorescence emission spectra of N-CQDs@SiO_2 in the presence of pesticide mixtures (DI water as solvent for all pesticide solutions with concentration of each for 200 mg/L)

Fig. 3.12 shows the selectivity of N-CQDs@SiO_2 toward NTP when other compounds were also present in the solution. Remarkable quenching effect of the sensor was induced by the mixture solution with NTP. Whereas other coexisting interference molecules showed negligible influences on the fluorescence response of N-CQDs@SiO$_2$. This selectivity can be better explained by the different binding affinities of pesticide molecules to N-CQDs. Among the four tested compounds, NTP shows the highest binding affinity to N-CQDs through the interactions of hydrogen bonding between nitro-groups of NTP and functional groups (e.g., COOH, –NH$_2$ and –OH) of N-CQDs and π–π stacking between the pyridine ring of NTP and aromatic heterocyclic carbon core of the N-CQDs.[14, 26] (Fig. 3.13).

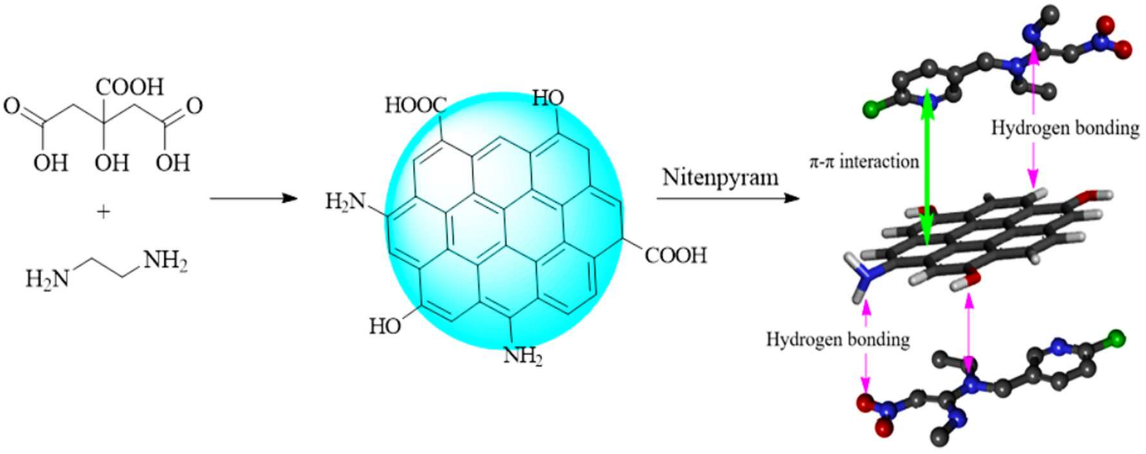

Figure 3.13 Molecular interactions between NTP and N-CQDs@SiO$_2$

To clarify the sensing mechanism, the UV–Vis absorption spectrum of NTP and other pesticides, and fluorescence excitation and emission spectra of the N-CQDs@SiO$_2$ were measured and compared in Fig. 3.14a. As seen from Fig. 3.14a, the absorption spectrum of NTP does not overlap with the fluorescence emission spectrum of N-CQDs@SiO$_2$, suggesting that the quenched emission of N-CQDs@SiO$_2$ in the presence of NTP is not due to the mechanism of FRET. However, the UV–Vis absorption spectrum of NTP overlaps with the excitation band of the N-CQDS@SiO$_2$ sensor, suggesting that fluorescence quenching may relate to IFE. In addition, to check the validity of PET mechanism, the HOMO and LUMO energy levels of the N-CQDs were determined through the measurement of the redox potential from cyclic voltammetry (E_{red}=-0.65 eV) and the band gap energy obtained from UV-DRS analysis (E_g = 2.15 eV) of N-CQDs (Fig. 3.14b, c&d) based on the following equations:[27]

$$E_{LUMO} = -\left(E_{red} + 4.4\right) \tag{3−3}$$

$$E_{HOMO} = E_{LUMO} - E_g \tag{3−4}$$

The LUMO and HOMO levels of N-CQDs were found to be -3.75 eV and -5.90 eV respectively, whereas the LUMO level of NTP based on the reported research is -1.55 eV.[28] Photoexcited electrons in the N-CQDs are not energetically allowed to transfer to the LUMO of NTP, thereby ruling out the PET between N-CQDs and NTP (Fig. 3.14e). Such analysis suggests IFE is the major mechanism responsible for the fluorescence quenching of N-CQDs by NTP.

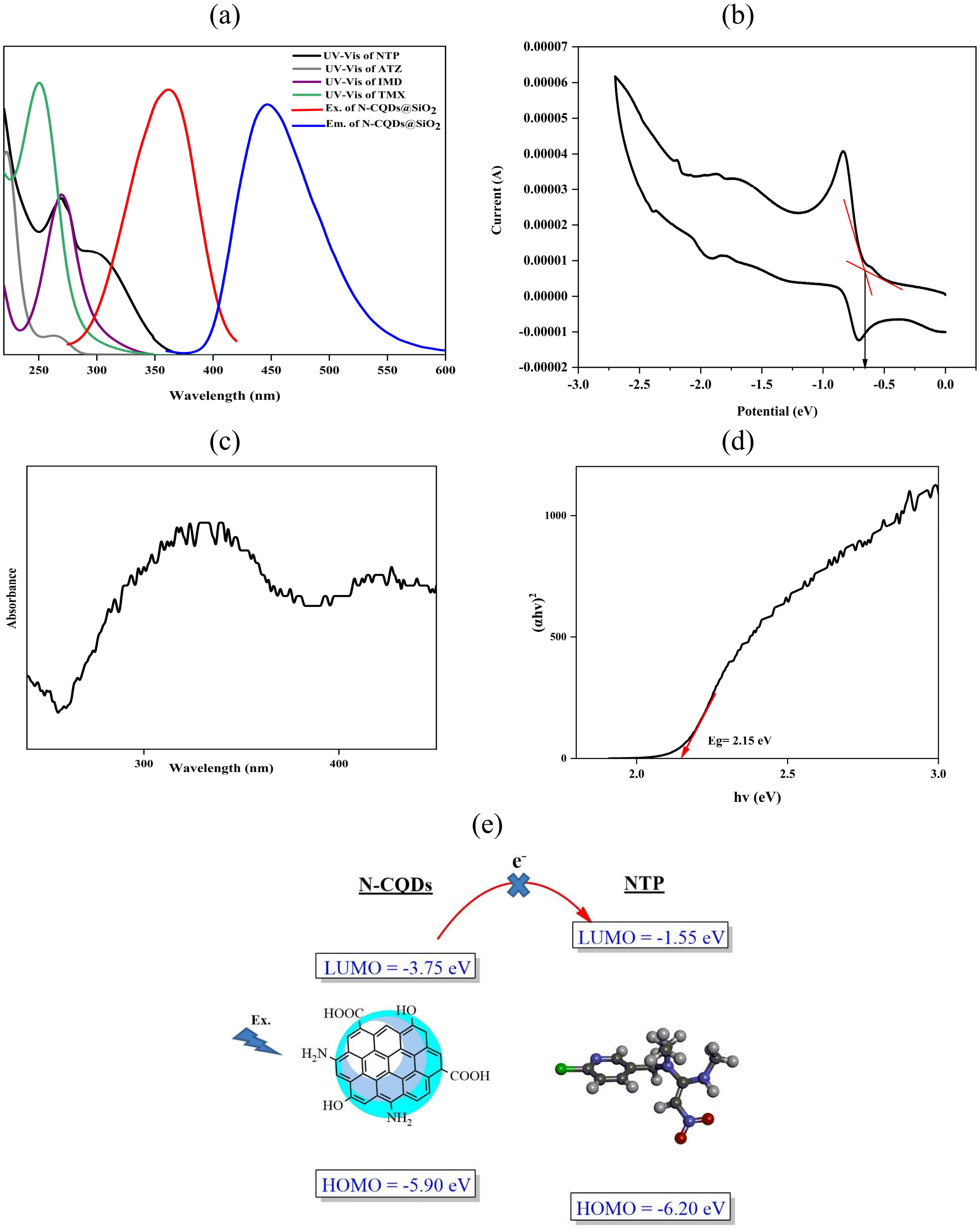

Figure 3.14 a) Comparison of UV-vis absorbance of all pesticides and fluorescence excitation/emission spectra of N-CQDs@SiO_2, b) Cyclic voltammetry of N-CQDs, c) UV-DRS spectrum of N-CQDs, d) Band gap energy from UV-DRS data, e) LUMO and HOMO of N-CQDs and NTP

To check the selectivity toward nitenpyram based on IFE mechanism, the UV-Vis spectra of all three pesticides rather than nitenpyram were also collected in Fig. 3.14a. As it is obvious from the graphs ATZ and TMX do not show overlapping with the excitation spectrum of CQDs@SiO$_2$ and only IMD shows a small overlapping which is consistent with the experimental results obtained for the selectivity.

3.3.5 Fluorescence sensing of NTP in natural water samples

To check the validity of the method proposed and the ability of the current sensor for the detection of NTP from real water samples, DI water was replaced with three different natural water samples. The results of recovery are presented in Table 3.1. All recovery percentages are in an acceptable range showing the capability of as-prepared sensor in measuring the NTP level in different water samples.

Table 3.1 Detection of NTP from natural water samples

Sample	c_{spiked}, **mg/L**	c_{meas}, **mg/L**	**% Recovery**
Surface water	20.0	21.79	108.9
	40.0	38.94	97.4
	60.0	62.43	104.0
Groundwater	20.0	19.44	97.2
	40.0	40.55	101.4
	60.0	61.43	102.4
Soil leachate	20.0	20.18	100.9
	40.0	41.06	102.6
	60.0	61.81	103.0

3.4 Summary

In this work, a novel CQDs-based fluorescent sensor (N-CQDs@SiO$_2$) was prepared and applied for the selective detection of nitenpyram (NTP), a pesticide from neonicotinoid class which may present in soil and water. Characterization of the synthesized sensor was performed through FT-

IR, HRTEM and XPS analyzers to prove the desired chemical structure and particles size. The as-prepared sensor demonstrated remarkable analytical performance over the NTP concentration range of 5.0 to 300.0 mg/L with a low LOD of 2.6 mg/L. This sensor showed excellent selectivity toward NTP in the presence of other pesticides. The excellent selectivity of N-CQDs@SiO_2 to NTP was attributed to the good affinity between N-CQDs and NTP through hydrogen bonding and π–π interactions and the fluorescent response was under the mechanism of IFE. Additionally, the capability of the prepared sensor in quantifying the NTP levels in real water samples was also tested and the results showed acceptable recovery values.

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Chapter 4 Design of Environmentally Friendly Derivatives of Nitenpyram with Improved Sensing Capacity

4.1 Introduction

Pesticides are a group of organic chemicals used in agriculture to protect products from potential diseases by combating pests. Despite their toxicity to the environment and human health, which may come from water or food, these chemicals cannot be neglected in agricultural production. Some pesticides are considered harmful emerging contaminants in the environment that can be found in natural water, soil, and agricultural products.[1] Neonicotinoid is a class of pesticides that are used broadly to protect crops from threatening insects due to their high effectiveness on the target pests. These chemicals are water-soluble and long-lasting compounds and can quickly diffuse and stay in wastewater and soil. Studies have shown that between 80 and 90% of neonicotinoids are transported from agricultural fields into the surface and groundwater and may transfer and accumulate into the human body.[2]

Nitenpyram is a well-known and efficient pesticide from the neonicotinoid class that is highly popular in agricultural uses and has been commercially available since 1991. The function of nitenpyram is to mimic neural transmitters' action and then disable the central nervous system of pests.[3, 4] Nitenpyram dissolves in water readily. Nitenpyram is a pyridine-based compound that is dangerous to humans, wildlife, and microorganisms. A comprehensive study proved the existence of seven neonicotinoid pesticides, including nitenpyram, in the biological sample of individuals without any history of working with these pesticides showing the accumulation of neonicotinoids in human tissues.[5] Furthermore, nitenpyram has a resistant chemical structure that takes a relatively long time to be degraded. Persistent chemical structures with toxic properties that remain in soil or water for a long time can cause adverse effects on the non-target ecosystem.[6] Therefore, introducing less-resistant pesticides with satisfied functionality and more environmentally friendly structures to substitute nitenpyram would address this issue.

Moreover, due to the severe impact of nitenpyram on the environment, it is necessary to wisely control and monitor the existence of pesticides in the environment by using a reliable quantitative detection method. Currently, traditional analytical techniques such as GC, GC-MS, HPLC, and HPLC-MS are available to detect and measure the level of existence of nitenpyram in soil or water samples; however, they are costly, time-consuming, and need sample preparation. [7] Considering all these drawbacks, scientists are focusing on finding alternative ways to offer more simplicity and accuracy compared to traditional analyzers in recent years. Fluorescence-based sensors are one of the most exciting tools with remarkable properties which can specify them as proper candidates for pollutants detection in water. CQDs are promising findings in this area owing to their unique properties to apply as an optical sensor to detect nitenpyram at very low concentrations.[7-9]

The primary approach to sensing nitenpyram through CQDs is to make any possible interaction between nitenpyram and CQDs structure. Although these two compounds already have shown interactions leading to a quenching effect on CQDs (Chapter 3), compared to other chemicals, these interactions are not too much because nitenpyram has a stable and non-reactive structure. Therefore, any nitenpyram structure modification that may result in better interaction with CQDs will modify and increase the sensing capacity.

Quantitative structure-activity relationship (QSAR) is a computational modeling method to find a reliable relationship between the structural properties of chemical compounds and a given property. QSAR can be applied in different areas. One of the most valuable scopes is defining new structures and predicting unmeasured properties. This way, one can also determine possible improvements for the newly synthesized compounds. Thus, QSAR is a powerful tool to present potential compounds before synthesis in the lab to introduce any other derivatives of nitenpyram. QSAR can provide a theoretical basis for further experimental studies and accelerate the development of new structures.[10, 11]

In this regard, several studies focusing on modifying pesticides have been carried out to introduce new structures or improve their environmental properties. For instance, a group of researchers tried to design and synthesize Nitro methylene neonicotinoids with specific chemical structures using the results of QSAR modeling and examined their derivatives for biological activities.[12] Increased Multi-directional selective toxicity of a neonicotinoid pesticide is another work conducted by Zhao et al.[13] to introduce and test several new compounds through QSAR modeling and molecular docking. They showed enhanced toxicity of new structures on pests and reduced impact on non-target organisms proving the selective toxicities on the farmland ecosystems. Using a QSAR modeling, the design of a group of environmentally friendly neonicotinoid insecticides with a selective toxic effect on pests and, meanwhile, lower bioconcentration was studied by the same group.[14] Via homology modeling and molecular docking, they revealed that a few of their derivatives had bi-directional selectivity with more significant effects on pests and lower impact on bees. They also investigated the resistance along with bi-directional selective toxicity for a group of neonicotinoids through QSAR and molecular docking analysis and introduced the best structure with high toxicity and low resistance inducing to pests and low toxicity and high resistance in the bee population.[15] According to the literature, recommendations of new nitenpyram derivatives with improved environmental properties such as bioaccumulation and biodegradation capacities have not been covered to date.

In general, investigation of possible interactions between N-CQDs and other molecules to find sensing capacity has been studied experimentally, but the theoretical research is still limited. To determine the interaction between N-CQDs and new derivatives, molecular docking can be used. Molecular docking is a computational method applied to predict noncovalent binding between molecules.[16] It has been involved in several areas, from drug design to biosensors studies. The basis of docking in the biomolecule area is to conduct molecular modeling studies to find any interaction between biomolecules and target molecules such as pesticides. Typically, this molecular modeling is used for macromolecules on one side and a small molecule on the other side. Although the interaction between CQDs and biomolecules such as human serum albumin (HSA) has been investigated,[17] to the best of our knowledge, the interactions between CQDs and pesticides have not been studied yet. As CQDs are moderate size molecules but much larger than nitenpyram, we applied molecular docking for the first time to study the binding affinity of nitenpyram derivatives and N-CQDs.

This work aims to design nitenpyram derivatives with (1) improved environmental properties (i.e., higher biodegradation and lower bioaccumulation capacity) by developing 3D-QSAR models, (2) increased functionality by evaluating their toxicity toward pests, and (3) better sensing capacity by investigating the interaction between the selected derivatives and N-CQDs using molecular docking. The research outputs would provide reliable methods for molecular modification of nitenpyram and beyond. The findings would also facilitate monitoring pesticides in the aquatic systems and reducing their associated environmental risks.

4.2 Methodologies

In this study, the molecular modification of nitenpyram was achieved by integrating 3D-QSAR modeling with molecular docking and by evaluating and estimating the environmental properties, functionality, and sensing capacity of the derivatives.

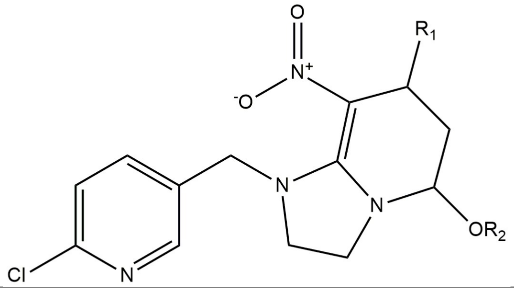
Two 3D-QSAR models were established to provide new sets of derivative structures with improved environmental properties (i.e., biodegradation and bioaccumulation capacity). The biodegradability was evaluated using a time course of ultimate biodegradation. The lower the time, the higher the biodegradability of the derivative. The bioaccumulation capacity was assessed using the bioaccumulation factor (BAF). The higher the BAF value, the higher the bioaccumulation of the derivative. After 3D-QSAR modeling, derivatives with higher biodegradability and lower bioaccumulation capacity were obtained. Their functionality as pesticides was further evaluated using their toxicity toward pests which were calculated from a pre-built model found in the literature.[14] The sensing capacity of the selected derivatives was then examined by evaluating the interactions between those chemicals and N-CQDs through molecular docking. The higher the docking score, the higher its interaction with N-CQDs, and the better the sensing capacity of a derivative in terms of N-CQDs-based optical sensors. The detailed methodologies are stated below.

4.2.1 3D-QSAR modeling aided design of nitenpyram derivatives with improved environmental properties and functionality

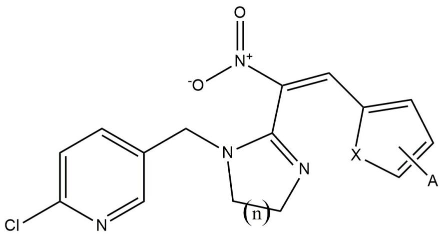
4.2.1.1 Construction of the 3D-QSAR model to introduce structures with improved biodegradability

The 3D-QSAR model was established through SYBYL X-2.0 software (Tripos Assoc., St Louis, MO, USA). To develop the model, a set of molecules with some similarities with nitenpyram is needed. For this purpose, 36 molecules were taken from literature[13, 14,] and divided into 29 structures to form the training set and 7 as the test set for model validation. The division of structures is normally based on the presence of almost 80% of the whole set in the training set.[18] The structural parameters are independent variables, and the values of ultimate biodegradation time are the dependent variables for building comparative molecular fields analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) models to introduce new structures and then predict the biodegradability. All molecular structures were drawn and optimized in SYBYL X-2.0 software. The optimization was performed using Tripos Force Field in Powell's method with the maximum number of optimizations of 10,000 and energy convergence gradient for energy gradient of 0.005 kJ/mol with Gasteiger-Hückel charges. Ultimate biodegradation values as the indicator to reflect the biodegradation capacity were obtained from EPI Suite software (EPIWEB 4.1) and listed with their corresponding structures in Table 4.1. The lower the time of biodegradation, the higher the biodegradation capacity.

Table 4.1 Molecular structures of the dataset used in biodegradation models

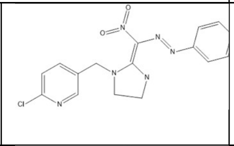
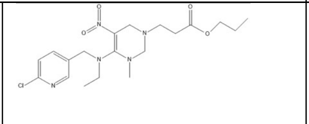
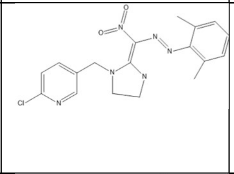
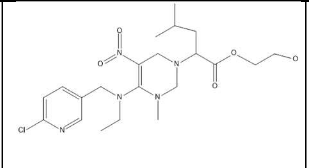
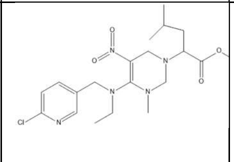
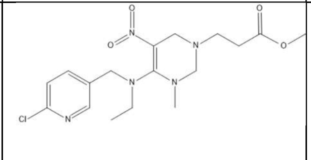


Compound	**R_1**	**R_2**	**Biodegradation (time, month)**
1	Me	H	1.711
2	Me	Me	1.511
3	Me	Et	1.480
4	Me	n-Pr	1.449
5	Me	C_2H_4Cl	1.231
6	Et	H	1.680
7	Me	i-Pr	1.449
8	Et	Et	1.449
9	Et	n-Pr	1.418
10	Et	i-Pr	1.418
11	H	H	1.742
12	H	Me	1.542
13[a]	H	Et	1.511
14	H	n-Pr	1.480
15	H	Bn	1.396
16	-	Nitenpyram	1.9498



Compound	**n**	**X**	**A**	**Biodegradation (time, month)**
17	0	O	-	2.043
18[a]	0	O	5-Me	1.937
19[a]	0	O	5-Et	1.906
20	0	O	4,5-(Me)$_2$	1.831
21[a]	0	O	5-CH$_2$OH	2.136
22	0	O	5-Br	1.732
23	0	O	5-NO$_2$	1.774
24	0	S	-	2.007
25	0	S	5-Me	1.901
26	0	NH	-	2.045
27	1	O	-	2.012
28	1	O	5-Cl	1.729
29	1	S	-	1.976
30	1	S	5-Me	1.870

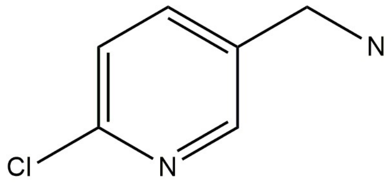
Other structures in biodegradation sets

Compound		**Biodegradation (time, month)**	**Compound**		**Biodegradation (time, month)**
31[a]		1.446	**34**		1.523
32		1.137	**35**[a]		1.275
33		1.182	**36**[a]		1.368

[a] denotes any compound in the test set

Molecular structures alignment toward 3D-QSAR modeling

Molecular alignment is the first and most crucial step toward 3D-QSAR modeling. In this work, all structures were aligned on the common core proposed by distil approach available in SYBYL. Nitenpyram was selected as the template structure. The common cores from distil for the biodegradation dataset are shown in Scheme 4.1.



Scheme 4.1 The common core structure for the biodegradation set

CoMFA and CoMSIA studies to obtain derivatives with improved biodegradability

The CoMFA and CoMSIA models were performed to evaluate steric and electrostatic fields (from CoMFA) and electrostatic, steric, hydrophobic, hydrogen bond donor, and acceptor fields (from CoMSIA) using the same training and test sets.

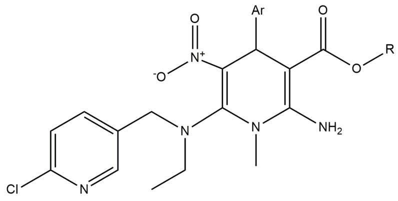
All corresponding values of biodegradation of the structures were entered into the training table. Then the models' parameters were calculated automatically by Autofill using SYBYL for both CoMFA and CoMSIA. After completion of the table, partial least-squares regression analysis was applied to find the relationships between the structures and biodegradation values for both models separately. First, we used the leave-one-out method to cross-validate the training set compounds and determined the values of q^2 and n. Next, a non-cross-validation analysis was conducted to obtain r^2, F, and the standard error of estimation (SEE) values. If these values meet the criteria, then the values of the standard error of prediction (SEP) and r^2 for the test set will be obtained.

Since this model's objective is to improve nitenpyram's environmental properties, this molecule was selected as the target molecule to put in the model results.

4.2.1.2 Construction of the 3D-QSAR model to introduce structures with improved bioaccumulation

To build a QSAR model for reflecting the bioaccumulation factor (BAF), a set of 26 molecules were taken from literature[19] and divided into 20 structures in the training set and the rest to form the test set for model validation. Other steps are pretty similar to the one performed in the biodegradation case. Table 4.2 shows the structures used for the construction of bioaccumulation models, and the common core is presented in Scheme 4.2.

Table 4.2 Structures for the construction of bioaccumulation models

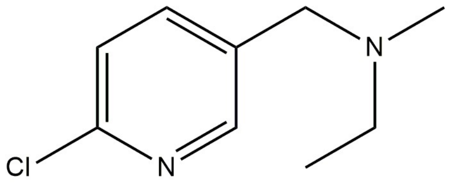


Compound	**R**	**Ar**	**BAF (concentration, g/kg)**
1	Me	3-F-C_6H_4	4.027
2	Me	4-F-C_6H_4	4.027
3	Me	2,4-di-Cl-C_6H_3	6.683
4	Me	3,4-di-Cl-C_6H_3	6.683
5	Me	4-CH_3–C_6H_4	12.410
6	Me	2-CH_3O–C_6H_4	3.828
7	Et	4-Cl–C_6H_4	6.622
8	Pr	C_6H_5	6.546
9	Pr	2-F–C_6H_4	6.637
10	Pr	3-F– C_6H_4	6.637
11	Pr	4-F– C_6H_4	6.637
12	Pr	2-Cl– C_6H_4	12.531
13	Pr	3-Cl– C_6H_4	12.531
14	Pr	4-Cl– C_6H_4	12.531
15	Pr	2,4-di-Cl-C_6H_3	12.560
16	Pr	3,4-di-Cl-C_6H_3	12.560
17	Pr	4-Br–C_6H_4	12.589
18	Pr	2-CH_3O–C_6H_4	6.591
19	Pr	4-CH_3O–C_6H_4	6.591
20	Pr	4-CH_3–C_6H_4	12.502

Other structures in bioaccumulation sets from biodegradation sets

Compound*	**BAF** (g/kg)	**Compound**	**BAF** (g/kg)
21^a(comp. 4)	2.767	**24^a (comp.10)**	4.571
22^a (comp. 5)	2.198	**25^a (comp.21)**	1.972
23^a (comp.8)	2.767	**26^a (comp.34)**	6.109

^{a} denotes any compound in the test set



Scheme 4. 2 Common core structure for bioaccumulation set

4.2.1.3 3D-QSAR modeling aided selection of nitenpyram derivatives with improved functionality as pesticides

When all derivative structures with improved environmental properties were obtained, their functionality as pesticides was investigated by evaluating their toxicity towards pests. The acceptable structures should show enhanced or at least the same toxicity to pests to prove their functionality. To perform this concept, a pre-built 3D-QSAR model from the literature was used[14] to calculate pLC_{50} (-log (LC_{50}) as an indicator to reflect the toxicity of a derivative to pests and thus its functionality. The evaluated derivatives were the selected compounds with higher biodegradability and lower bioaccumulation capacity.

4.2.2 Molecular docking aided selection of nitenpyram derivatives with improved sensing capacity

After finding novel structures with improved environmental properties (i.e., biodegradation and bioaccumulation capacities) and better functionality, the interaction between carbon quantum dots and the selected derivatives was studied through molecular docking via AutoDock 4.2 to achieve improved sensing capacity in the rigid macromolecule using Lamarckian Genetic Algorithm (LGA), with 200 GA runs and 25000 000 energy evaluations. Other parameters were left as default. The obtained results were analyzed through AutoDockTools-1.5.6 for cluster analysis using a root mean square deviation (RMSD $\leq$ 2 Å).[20] Better interaction with carbon quantum dotes may provide higher sensing capacity and a more reliable quenching effect on this optical sensor.

4.3 Results and Discussion

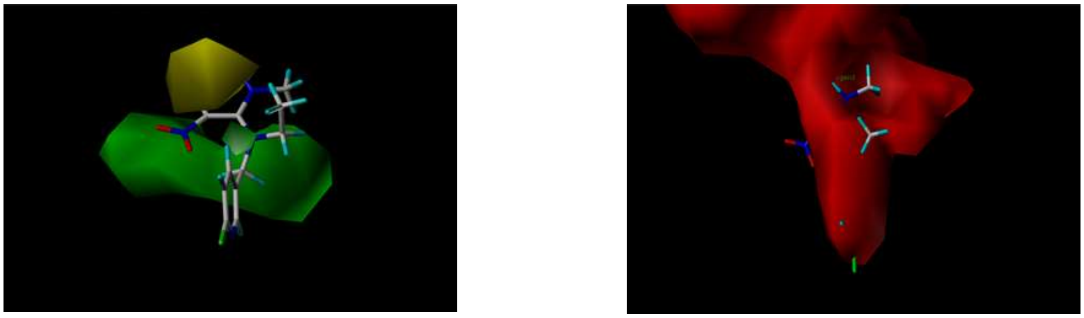
4.3.1 Performance evaluation of the constructed 3D-QSAR models

QSAR modeling presents desired parameters showing the ability of CoMSIA and CoMFA models to introduce new derivative structures with modified properties. The results of biodegradation models and corresponding parameters can be found in Table 4.3:

Table 4.3 Results of CoMFA and CoMSIA of biodegradation modeling

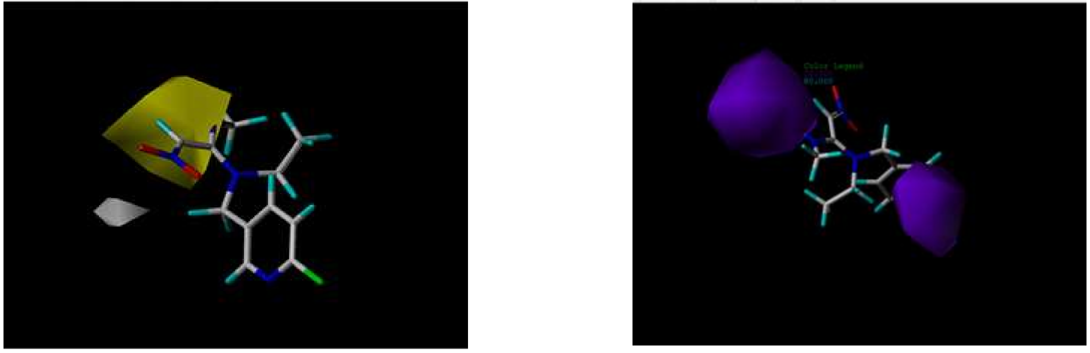
Model	**$q^2 > 0.5$**	**SEE**	**$r^2 \sim 1$**	**F-value**	**$(r^2 - q^2)/r^2 < 0.25$**	**SEP**	**r^2 (Pred.) >0.6**
CoMFA	0.743	0.032	0.988	453.37	0.247	0.214	0.680
CoMSIA	0.761	0.022	0.995	554.09	0.235	0.223	0.651

As seen in Table 4.3, all parameters meet the criteria defined for a good model.[21] Therefore, we can rely on these results to find contour maps around the target molecule. As the contours from CoMFA are far from the molecule area, the contour maps of nitenpyram for biodegradation from only the CoMSIA model are presented in Fig. 4.1.



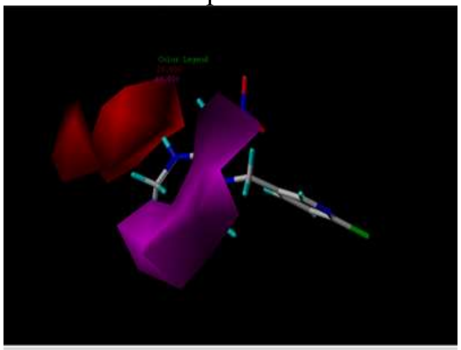
Steric field

Electrostatic field



Hydrophobic field

Donor field

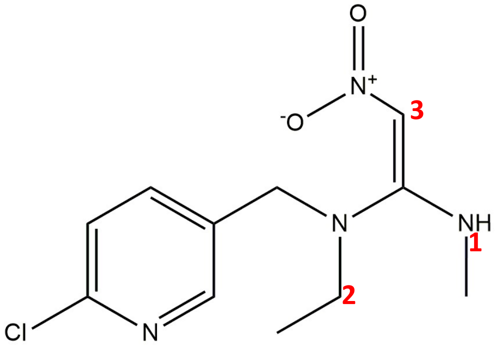


Acceptor field

Figure 4.1 Contour maps around nitenpyram in the biodegradation model

Each color illustrates a possible substitution in the structure of nitenpyram. For example, the yellow color in the steric field shows if a bulky group is substituted, the focused property can be decreased.[13] According to the contour maps, to improve the biodegradability by lowering the time required for the biodegradation process, the following positions can be replaced by other functional groups: The yellow region, which is a steric field, is distributed at positions 1 and 3 in Scheme 4.3

and can be substituted by bulky groups to enhance biodegradability. The red region is distributed at position 1 and can be substituted by electrostatic groups to increase biodegradability. The purple region is distributed at position 1 and can be substituted by donor groups to improve biodegradability. The dark red region is distributed at position 1 and can be substituted by acceptor groups to have a lower required time of biodegradation.

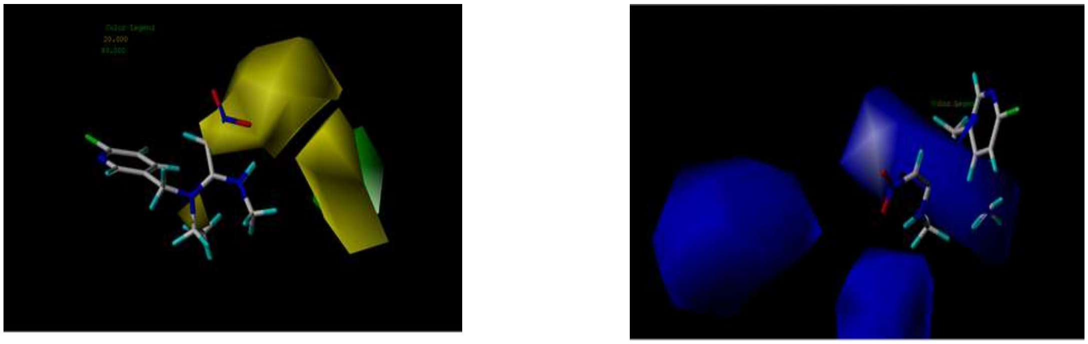


Scheme 4.3 Nitenpyram structure

Table 4.4 represents the results of the bioaccumulation model: same as biodegradation, and as is shown in the table, all parameters meet the criteria defined for a good model except r^2 for the prediction set of the CoMFA model, which must be higher than 0.6. Thus, we can ignore it and only use the results of CoMSIA as a more comprehensive model in this case and rely on CoMSIA results to find contour maps around the target molecule.

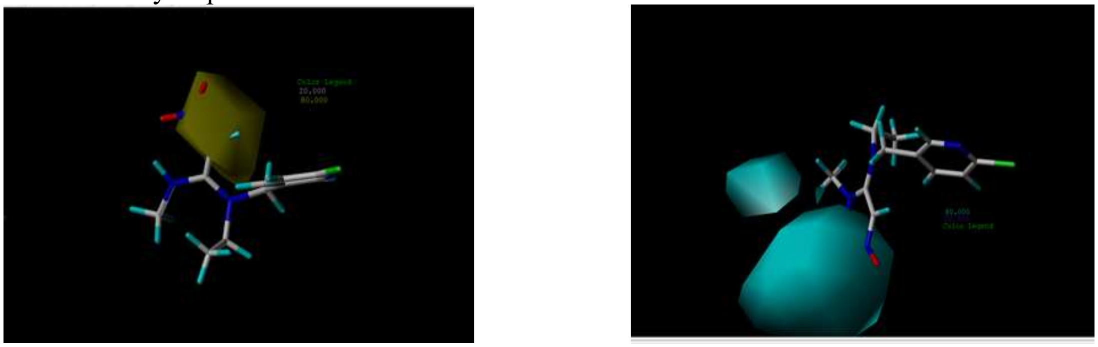
Table 4.4. Results of CoMFA and CoMSIA of bioaccumulation modeling

Model	**q^2 >0.5**	**SEE**	**r^2~1**	**F-value**	**(r^2- q^2)/ r^2 <0.25**	**SEP**	**r^2 (Pred.)>0.6**
CoMFA	0.777	0.669	0.975	171.869	0.203	1.272	0.502
CoMSIA	0.769	0.417	0.992	270.19	0.224	0.978	0.706



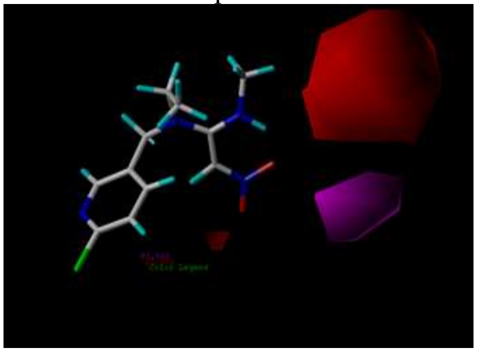
Steric field

Electrostatic field



Hydrophobic field

Donor field



Acceptor field

Figure 4.2 Contour maps around nitenpyram for bioaccumulation model

According to the contour maps shown in Fig. 4.2, to reduce the bioaccumulation capacity, the following positions can be replaced. The yellow region, which is a steric field, is distributed at positions 2 and 3 and can be substituted by bulky groups to reduce bioaccumulation.

4.3.2 Environmentally friendly nitenpyram derivatives obtained through 3D-QSAR modeling

To find different derivatives of nitenpyram, several functional groups are substituted at the designated sites in the nitenpyram structure. Since nitenpyram is a small molecule, only three positions are found to be replaced with other functional groups. Therefore, in this case, we combine both results of biodegradation and bioaccumulation contours to have a relatively large table of derivatives and then choose the best ones. The groups chosen to put and replace at three sites are as follows: NO_2, OH, COOH, Cl, Br, I, CHO, SO_2, SO_3H, SH, CO, OCH_3, C_2H_2, C_2H_4, NH_2, NO. Table 4.5 presents the environmental values of derivatives with better biodegradability values and lower or very close bioaccumulation factors compared to nitenpyram (values less than 1.95 month for biodegradation and less than or close to 0.897 g/kg for bioaccumulation).

Table 4.5. Environmental values of proposed derivatives

Compound	**Biodegradation (time, month)**	**% Improvement**	**Bioaccumulation (concentration, g/kg)**	**% Improvement**
Derivative-1	1.8337	5.95	0.8932	0.46
Derivative-2	1.6383	15.97	0.8969	0.05
Derivative-3	1.5676	19.60	0.8930	0.49
Derivative-4	1.7248	11.54	0.8930	0.49
Derivative-5	1.6097	17.44	0.8936	0.42
Derivative-6	1.4598	25.13	0.9009	-0.39
Derivative-7	1.5637	19.80	0.9027	-0.59
Derivative-8	1.4309	26.61	0.9181	-2.30
Derivative-9	1.6695	14.37	0.8934	0.4
Derivative-10	1.6341	16.19	0.8957	0.19
Derivative-11	1.6450	15.63	0.8951	0.25
Derivative-12	1.6781	13.93	0.9066	-1.02
Derivative-13	1.6201	16.91	0.8932	0.47
Derivative-14	1.8537	4.93	0.8932	0.46
Derivative-15	1.6582	14.95	0.8945	0.32
Derivative-16	1.5875	18.58	0.8934	0.44
Derivative-17	1.7448	10.51	0.8930	0.49
Derivative-18	1.4798	24.10	0.8977	-0.03
Derivative-19	1.5837	18.77	0.8967	0.08
Derivative-20	1.4509	25.58	0.9028	-0.60
Derivative-21	1.6895	13.35	0.8941	0.36
Derivative-22	1.2594	35.41	0.9070	-1.06
Derivative-23	1.6689	14.40	0.9001	-0.30
Derivative-24	1.4170	27.32	0.8956	0.20
Derivative-25	1.8900	3.06	0.9095	-1.34
Derivative-26	1.8480	5.22	0.8934	0.44
Derivative-27	1.8502	5.11	0.8931	0.48
Derivative-28	1.8851	3.32	0.8963	0.12
Derivative-29	1.5071	22.70	0.9090	-1.29
Nitenpyram	1.9498	-	0.8974	-

To investigate the functionality of new structures as pesticides, those selected structures in the previous step were tested to provide the toxicity values toward pests as presented in Table 4.6. These values show higher functionality of new structures in almost all compounds compared to nitenpyram.

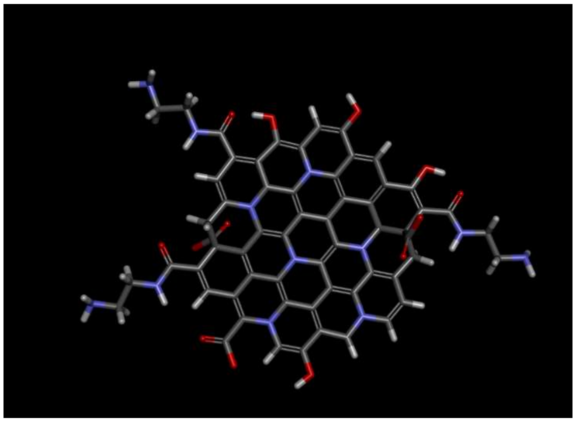
Table 4.6 Toxicity values toward pests

Compound	Toxicity (pLC_{50})	%Improvement
Derivative-1	8.278	21.41
Derivative-2	8.055	18.14
Derivative-3	7.368	8.06
Derivative-4	7.750	13.67
Derivative-5	8.340	22.32
Derivative-6	8.188	20.09
Derivative-7	8.461	24.09
Derivative-8	8.376	22.85
Derivative-9	8.174	19.88
Derivative-10	6.726	-1.34
Derivative-11	9.070	33.03
Derivative-12	7.608	11.58
Derivative-13	8.071	18.37
Derivative-14	7.992	17.22
Derivative-15	7.985	17.11
Derivative-16	7.996	17.27
Derivative-17	7.738	13.49
Derivative-18	7.877	15.53
Derivative-19	8.032	17.80
Derivative-20	8.155	19.60
Derivative-21	7.915	16.08
Derivative-22	7.048	3.37
Derivative-23	7.087	3.94
Derivative-24	6.730	-1.29
Derivative-25	7.324	7.42
Derivative-26	7.329	7.49
Derivative-27	7.408	8.65
Derivative-28	6.866	0.70
Derivative-29	6.905	1.27
Nitenpyram	6.818	-

4.3.3 Nitenpyram derivatives with improved sensing capacity obtained through molecular docking

From the data obtained for biodegradation, bioaccumulation, and functionality, in the last step, 13 structures with improved values of the as-mentioned parameters were selected to investigate the affinity with N-CQDs. The affinity values of N-CQDs and each derivative compound have been evaluated to find the best derivatives which can show better interaction with N-CQDs compared with nitenpyram using Molecular docking.

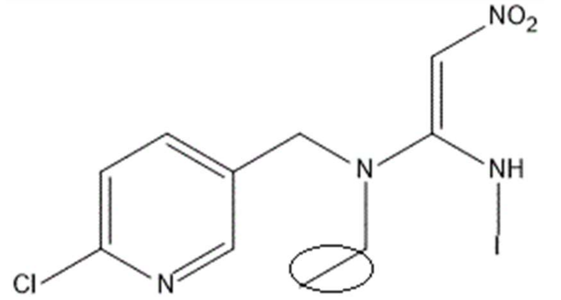
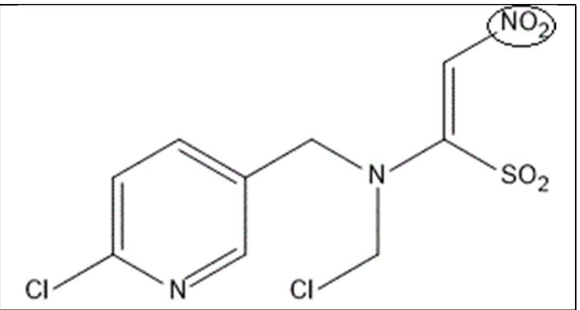
The structure selected for N-CQDs is Scheme 4.4, which is drawn in GaussView 5 and optimized at [B3LYP combined to 6-31+G(d,p)] in Gaussian 09. As CQDs do not have a proven molecular structure yet, this structure was proposed based on the synthesis precursors and the results of different analyses presented in this work and those reported in the literature.[22-24]



Scheme 4.4 Proposed structure of N-CQDs

Table 4.7 shows the affinity scores between N-CQD structure and each derivative which are the highest score values among all modes.

Table 4.7 The selected derivatives to interact with N-CQDs

<table>
<tr><td colspan="3"> </td><td colspan="3"> </td></tr>
<tr><th>Compound</th><th>Group</th><th>Score</th><th>Compound</th><th>Group</th><th>Score</th></tr>
<tr><td>Derivative-1</td><td>OH</td><td>7.48</td><td>Derivative-13</td><td>NO_2</td><td>7.35</td></tr>
<tr><td>Derivative-2</td><td>SH</td><td>6.97</td><td>Derivative-16</td><td>SO_2</td><td>6.74</td></tr>
<tr><td>Derivative-3</td><td>SO_2</td><td>7.05</td><td>Derivative-18</td><td>Cl</td><td>6.60</td></tr>
<tr><td>Derivative-5</td><td>NO_2</td><td>5.50</td><td>Derivative-19</td><td>Br</td><td>5.69</td></tr>
<tr><td>Derivative-6</td><td>Cl</td><td>7.10</td><td>Derivative-20</td><td>I</td><td>7.50</td></tr>
<tr><td>Derivative-7</td><td>Br</td><td>7.64</td><td>Derivative-21</td><td>CO</td><td>6.66</td></tr>
<tr><td>Derivative-11</td><td>NO</td><td>6.27</td><td>Nitenpyram</td><td>-</td><td>5.48</td></tr>
</table>

The results show higher docking scores between selected structures and N-CQDs. Compared to the chemical structure of nitenpyram which has alkyl groups in position 2 and the tail of position1, replacing more active functional groups can enhance the chance of possible interactions with active sites on the surface of N-CQDs. For instance, replacing the alkyl group with OH can improve the likelihood of hydrogen bonding of derivatives with the COOH group of N-CQDs. [25, 26] Also, any structure with an OH group can make a hydrogen bond with the OH group presented on the N-CQDs.Meanwhile, the interaction between halogens and N-CQDs has been studied by other researchers to show the quenching effect of Cl, Br, and I ions on N-CQDs. These elements are heavy atoms that exhibit the quenching-lead interaction with N-CQDs in molecular dyes.[27, 28] It is also expected a possible quenching of fluorescence intensity by NO_2 because of the interaction of electron-donating amine groups on the surface of N-CQDs and the electron-withdrawing NO_2 group of the new derivatives[21]. Strong electron absorption of NO_2 makes it difficult for the electrons in the N-CQDs core to be excited, leading to fluorescence quenching. [29]

NO can also interact with functional groups of N-CQDs and quench the fluorescence as a detection method reported previously. [30] SO_2 and amine groups on the quantum dots can have hydrogen bonds. As SO_2 does have oxygen atoms with lone pair electrons, it would be able to form a hydrogen bond with a molecule that has O—H and N—H bonds. The hydrogen in SH can also interact with carbon rings to weaken hydrogen-pi bonding.

Additionally, OH, SH, SO_2, halogens, and NO_2 are all polar functional groups, while methyl is a non-polar group. Since polarity can increase the solubility in water, the structures with such groups can show better biodegradability due to higher bioavailability. Also, higher soluble chemicals have a lower potential to accumulate in live cells.[31]

4.4 Summary

In this chapter, 3D-QSAR modeling has been adopted as a tool to obtain derivatives of the nitenpyram pesticides with improved environmental properties as well as proper functionality. Biodegradability, bioaccumulation factor, and toxicity to pests were evaluated to screen derivatives structures. Both CoMFA and CoMSIA models were applied. However, the results of CoMSIA are more reliable and comprehensive. The positions on the nitenpyram that can be replaced were determined from the contour maps of QSAR modeling and substituted by other functional groups. The properties and function of new structures were then calculated using EPI and QSAR model prediction. From the results, 13 compounds with higher biodegradability, lower bioaccumulation capacity, and better functionality were selected. In the next step, the interaction between N-CQDs and these selected structures was investigated through molecular docking. Derivatives with higher affinity scores indicated better interactions toward N-CQDs, resulting in improved sensing and detection capacity.

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Chapter 5 Conclusions and Recommendations

5.1 Conclusions

In this study, N-CQDs were synthesized from citric acid and ethylenediamine in a hydrothermal/solvothermal method. The prepared N-CQDs were fully characterized using FTIR, TEM, XRD, and XPS. Then, CQDs were immobilized on a silica gel support to be stabilized. The as-prepared N-CQDs@SiO_2 sensor was used to detect nitenpyram, a pesticide from the neonicotinoid family which is widely used in agriculture. The selectivity of the sensor in the presence of other pesticides, including imidacloprid, atrazine, and thiamethoxam, was also investigated. The results showed excellent selectivity and sensitivity toward nitenpyram through the IFE mechanism. In addition, the results demonstrated the capability of the prepared sensor in quantifying the nitenpyram levels in real water samples with acceptable recovery values.

To improve the sensing capacity of CQDs, new nitenpyram derivatives with improved environmental properties (i.e., biodegradation and bioaccumulation capacity) were designed by developing two 3D-QSAR models. The functionality of all obtained derivatives as pesticides were further examined by evaluating their toxicity toward pests. Among 300 obtained derivatives, 13 compounds with higher biodegradation, lower bioaccumulation capacity, and better functionality were selected. The sensing capacity of these compounds was then assessed by investigating their interaction with N-CQDs using molecular docking. The results helped identify the derivatives with improved sensing capacity toward CQDs. The research outputs would provide reliable methods for molecular modification of nitenpyram and beyond. The findings would also facilitate monitoring pesticides in the aquatic systems and reducing their associated environmental risks.

5.2 Recommendations for future work

A couple of items are recommended to improve the current study and any desired works in the future. In developing CQDs-based optical sensor, the sensitivity of the current sensor needs to be improved and the following suggestions can be conducted:

- Further purification of bare CQDs to eliminate any possible interference of impurities in the sensing mechanism. HPLC is a proper apparatus to apply for CQD purification due to its high capabilities.
- Applying other supports such as molecularly imprinted polymer structures for CQDs incorporation to improve the detection sensitivity.
- Functionalization of CQDs to add more interactive functional groups with pesticides to make stronger interaction between nitenpyram and CQDs and provide a higher quenching effect.
- Investigation of selectivity in the presence of other possible chemical structures and ions available in wastewater samples.
- Degradation of nitenpyram in a photocatalytic reaction by using CQDs as a catalyst.

In terms of presenting new structures rather than nitenpyram, the following recommendations can be followed:

- Docking study to check the function of the new structures on the target enzyme.
- Study the effect of new structures on non-target organisms and the bi-directional toxic effect.
- Analyzing molecular interactions using other approaches such as Gaussian and comparing the results with the ones obtained from molecular docking.