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Molecular docking, molecular modeling, vibrational and biological studies of some new heterocyclic α-aminophosphonates

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ABSTRACT

A new diphenyl (aryl) (Ǹ-quinazolin-4-yl-hydrazino) methylphosphonates **3a**–**3d** was synthesized via anhydrous zinc chloride catalyzed Kabachnic-Fields reaction. The structure of the synthesized compounds was confirmed by elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR, ^{31}P NMR and MS spectral data. The synthesized compounds showed significant antimicrobial and also remarkable cytotoxicity anticancer activities against breast carcinoma cell line (MCF7). The quantum chemical calculations were performed using density functional theory (DFT) to study the effect of the changes of molecular and electronic structures on the biological activity of the investigated compounds. Also, NBO and theoretical FT-IR were calculated. The experimental results were validated by molecular docking simulation of compound **3b** in the active pocket of the enzyme. The important binding interactions with the key residues in the active site were revealed. A good correlation was found between the quantum chemical parameters and experimental data.

1. Introduction

Quinazoline nucleus is an essential building block, which can be found in a huge number of natural products as well as synthetic derivatives [1]. From the chemistry point of view, quinazoline can be considered as a benzopyrimidine heterocyclic fused ring. 4-Aminoquinazoline derivatives, an important class of heterocyclic compounds [2], which showed the broad variety of biological activity profiles, e.g. anticancer [3–5], antimalarial [6], antimicrobial [7], and antiviral activities [8,9], and many others. In addition, these derivatives can act as selective inhibitors of tyrosine kinase [10,11]. α-Aminophosphonates had an attention in the recent years because of their structural analogy to the corresponding α-amino acids as well as heterocyclic phosphonates [12], such as α-aminophosphonates based on quinazoline, which have a wide range of biological activity [13]. In addition, α-aminophosphonates have the broad application due to their antimicrobial [14], antioxidant [15], anticancer [16], antiviral [17], and anti-HIV [18], herbicides [19], pharmaceutical agents [20] and enzyme inhibitors [21]. Hence, several approaches [22] have been developed for the synthesis of α-amino phosphonates. The main pathway is Kabachnic–Fields three-component reactions, in which a carbonyl, an amine and a di- or trialkyl phosphite react in a single-pot [23]. These reactions were carried out as straightforward one-pot procedures without any catalyst [24], but in most cases, they were performed using catalysts [25].

Recently, the field of computer-aided drug design (CADD) enhanced our understanding of complex biological processes and protein-ligand interactions. CADD can predict experimental results with a reasonable accuracy and reduced time, cost and equipment. CADD continuously enhances the progress of drug discovery and refinement of therapeutic agents with many successful examples. Computational drug design has been widely used in the pharmaceutical industry to either identify new compounds or optimize lead compounds that show significant inhibitory activity against a target biological receptor [26]. The density functional theory (DFT) showed a great accuracy in reproducing the experimental values for the geometry, dipole moment, vibrational frequency, chemical shifts, non-linear optical effects, Natural bond orbital (NBO) analysis, molecular electrostatic potential, frontier molecular orbitals and thermodynamic properties, etc. [27–29].

Due to various types of biological activity found in quinazoline derivatives, the aims of this work is synthesizing some new α-aminophosphonates containing quinazoline moiety using Kabachnic-Fields three components reaction of carbonyl compounds, amine and triphenylphosphite in the presence of anhydrous zinc chloride catalyst

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and then studying their antimicrobial activities and in vitro anticancer activities against breast carcinoma cell line (MCF7). Also, density functional theory (DFT) was studied to examine the effect of the molecular and electronic structure changes on the biological activity of the investigated compounds and compare the theoretical data with the experimental ones.

2. Computational Details

2.1. Quantum Chemical Methods

Calculation of structural parameters, geometry optimization, vibrational frequencies of the investigated new compounds was carried out with Gaussian 09 program package [30] using Lee–Yang–Parr nonlocal correlation functional (B3LYP) [31–33] with 6-31G + (d) basis set. Quantum-chemical descriptors obtained from the DFT calculations were used to explain the correlation between the biological activity of the α-aminophosphonates and their molecular structures. The concepts of these parameters are related to each other [34–37].

2.2. Molecular Docking Protocol

The docking study was carried out on Hp-pc (Hp pavilion dv6 Notebook pc) with AMD Phenom (TM) II N930 Quad-Core processor 2.00 GHz and RAM is 4.00 GB. Docking simulation was done using molecular operating environment (MOE) software [38]. MOE has core technology for simulations of small organics and macromolecules. Simulations are an important tool to validate ligand pose geometries, stability and the generation of macromolecule conformations for docking, protein engineering, etc. The crystal structure of cathepsin D obtained from the protein data bank (PDB: 4OBZ, 2.9 Å) was selected as a receptor for docking study. The validation was done for docking methodology by re-docking the co-crystallized ligand and it was carried out successfully with RMSD <1 Å.

3. Experimental

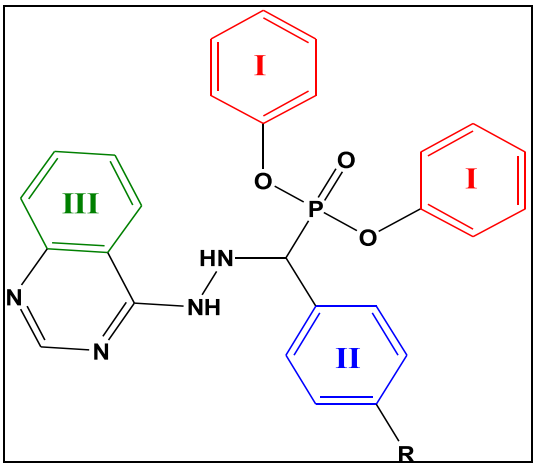
3.1. General Experimental

Melting points were determined by the open capillary method using an Electrothermal MEL-TEMP II apparatus and were reported uncorrected. Elemental analyses (C, H and N) were carried out at the Micro-analytical Center of Cairo Univ., Giza, Egypt. FT-IR spectra were recorded on a Perkin–Elmer1430 Spectrophotometer using KBr disk technique. ^{1}H NMR spectra were measured at Cairo University, Cairo, Egypt on a Bucher AC300 spectrometer operating at 300 MHz. The spectra were recorded in dimethyl sulphoxide DMSO d_6, and chemical shifts δ were reported in parts per million (ppm) relative to TMS. El-Mass spectra for compounds were recorded on a mass spectrometer model 7070 at energy 70 e VV at Cairo University, Cairo, Egypt.

All samples were examined by analytical thin layer chromatography (TLC), which is performed on EM silica gel F254 sheet (0.2 mm).

3.2. Synthesis of Diphenyl (Aryl) (Ǹ-Quinazolin-4-yl-Hydrazino) Methyl Phosphonates 3a–3d

To a stirred solution of 4-hydrazino-quinazoline **1** (0.01 mol, 1.6 g) and different aldehydes (0.012 mol) in dry dichloromethane CH_2Cl_2 (5 mL), triphenylphosphite (0.01 mol, 3.6 ml) and anhydrous zinc chloride $ZnCl_2$ (10 mol%) were added. The reaction mixture was stirred at room temperature (49–54 h) until completion of the reaction as indicated by TLC. Then CH_2Cl_2 was evaporated and the α-aminophosphonates were precipitated using methanol. The precipitate was filtered off affords new α-aminophosphonates in very good yield.



Diphenyl (aryl) (Ǹ-quinazolin-4-yl-hydrazino) methyl phosphonates **3a–3d.**

3.2.1. Diphenyl (Phenyl) (Ǹ-Quinazolin-4-yl-Hydrazino) methyl phosphonates 3a, Reaction time: 49 h, m.p. 287–289 °C, yield: 81%

The structure of compound **3a** was confirmed by:

- Correct analytical data for $C_{27}H_{23}N_4O_3P$ (482) Calculated: C, 67.21; H, 4.77; N, 11.61%. Found: C, 67.43; H, 4.95; N, 11.84%.
- FT-IR (KBr) υ/cm^{-1}: 3442 (NH), 3186 (NH), 3068 (CH_{Ar}), 2926 ($CH_{Aliph.}$), 1652 (C═C), 1611 (C═N), 1445 (C—C_{Ar}), 1279 (P═O), 1028 (P—O—C), 756 (P—CH).
- ^{1}HNMR (DMSO) δ: 5.63 (s, 1H, CHP), 5.68 (s, 1H, NH $_{\text{aliphatic hydrazino}}$), 6.65–7.18 (m, 10H, 2 Ph-O (**I**)), (7.527–7.64, m, 5H, Ar (**II**)), 7.74–7.99 (m, 4H, Ar-H, quinazoline protons (**III**)), 8.41 (s, 1H, N-CH-N $_{\text{quinazoline}}$), 8.68 (s, 1H, NH $_{\text{aromatic hydrazino}}$).

3.2.2. Diphenyl (3-Nitrophenyl) (Ǹ-Quinazolin-4-yl-Hydrazino) Methyl Phosphonates 3b, Reaction Time: 50 h, m.p. 308–310 °C, yield: 94%

The structure of compound **3b** was confirmed by:

- Correct analytical data for $C_{27}H_{22}N_5O_5P$ (527) Calculated: C, 61.48; H, 4.20; N, 13.28%. Found: C, 61.76; H, 4.46; N, 13.57%.
- FT-IR (KBr) υ/cm^{-1}: 3452 (NH), 3207 (NH), 3082 (CH_{Ar}), 2981 ($CH_{Aliph.}$), 1645 (C═C), 1589 (C═N), 1486 (C═C_{Ar}), 1233 (P═O), 1020 (P—O—C), 755 (P—CH).
- 3439, 2956, 1678, 1626, 1468, 1246, 1020, 769.
- ^{1}HNMR (DMSO) δ: 5.62 (s, 1H, CHP), 5.78 (s, 1H, NH $_{\text{aliphatic hydrazino}}$), 6.72–7.57 (m, 10H, 2 Ph-O (**I**)), 7.59–7.85 (m, 4H, Ar (**II**)), 7.96–8.31 (m, 4H, Ar—H, quinazoline protons (**III**)), 8.42 (s, 1H, CH $_{\text{quinazoline}}$), 8.64 (s, 1H, NH $_{\text{aromatic hydrazino}}$).
- The ^{13}C NMR (DMSO) δ: 152.67, 151.49 (C═N $_{\text{imine}}$), 150.50 (C—N) quinazoline ring, 148.31 (C-NO_2), 69.84 (P—CH $_{\text{aliphatic}}$), 145.97, 145.49 (C—O—Ph), 134.60, 134.09, 133.84, 130.43, 130.29, 129.82, 129.22, 127.55, 126.92, 125.72, 124.69, 124.24, 124.04, 123.67, 120.87, 119.77, 115.69 (C $_{\text{Aromatic}}$).
- The ^{31}P NMR (DMSO): δ 14.23.
- MS spectra showed molecular ion peak (M^+) at m/z = 527 (9.71), 466 (6.05), 283 (24.08), 191 (23.49), 130 (47.60), 121 (46.28), 93 (28.94), 55 (100).

3.2.3. Diphenyl (4-Hydroxyphenyl) (Ǹ-Quinazolin-4-yl-Hydrazino) Methyl Phosphonates 3c, Reaction Time: 54 H, 319–321 °C, Yield: 90%

The structure of compound **3c** was confirmed by:

- Correct analytical data for $C_{27}H_{23}N_4O_4P$ (498) Calculated: C, 65.06; H, 4.62; N, 11.24%. Found: C, 65.32; H, 4.83; N, 11.37%.