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Theoretical and experimental investigations on molecular structure of 7-Chloro-9-phenyl-2,3-dihydroacridin-4(1*H*)-one with cytotoxic studies

Rajendran Satheeshkumar [a], Ramasamy Shankar [b], Werner Kaminsky [c], Sivalingam Kalaiselvi [d], Viswanadha Vijaya Padma [d], Karnam Jayarampillai Rajendra Prasad [a, *]

[a] Department of Chemistry, Bharathiar University, Coimbatore 641 046, Tamil Nadu, India
[b] Department of Physics, Bharathiar University, Coimbatore 641 046, Tamil Nadu, India
[c] Department of Chemistry, University of Washington, Seattle, WA 98195, USA
[d] Department of Biotechnology, Bharathiar University, Coimbatore 641 046, Tamil Nadu, India

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ABSTRACT

7-Chloro-9-phenyl-2,3-dihydroacridin-4(1*H*)-one (**3**) is synthesized from 2-amino-5-chlorobenzophenone (**1**) and 1,2-cyclohexanedione (**2**) in the presence of catalyst $InCl_3$. FT-IR, FT-Raman and FT-NMR spectra of **molecule 3** have been recorded and the structure was confirmed by single crystal X-ray diffraction. $CDCl_3$ and DMSO-d_6 FT-NMR spectra and ^1H and ^{13}C NMR chemical shifts have been measured in molecule **3** and calculated at the B3LYP/6-311G (d,p) and MO6-2x/6-311G (d,p) levels of theory. Similarly calculated vibrational frequencies were found in good agreement with experimental findings. The optimized geometry of molecule **3** was compared with experimental XRD values. DFT calculations of the molecular electrostatic potential (MEP) and HOMO - LUMO frontier orbitals identified chemically active sites of molecule **3** responsible for its bioactivity. The title compound, **3** exhibits higher cytotoxicity in Human breast cancer cells (MCF-7) compared to human lung adenocarcinoma cells (A549).

1. Introduction

Nitrogen containing heterocyclic compounds featuring an acridone scaffold is important to organic chemistry, because of a wide variety of biological properties and functions [1]. Acridones in particular are naturally occurring alkaloids which can be considered as aza-analogs of xanthones [2]. Acridone derivatives, known since the 19th century, were first used as pigments and in dyes. They are regarded as potent fluorescent, intercalating, antitumor [3] and anticancer agents [4]. Promising biological and pharmacological activity shown by some acridine derivatives emphasizes the importance for developing new acridine-based poly cyclic heterocycle syntheses, as there are many known naturally occurring acridone derivatives with significant biological activity such as anti-bacterial [5], anti-HIV [6], antimalarial [7], or functioning as DNA-binding agents [8]. The synthesis of reactive methylenes with *o*-aminoarylketones mostly follows the Friedländer synthesis procedure [9]. Extending on this, one would envisage elaborating poly cyclic quinoline compounds into the Friedländer reaction, taking account of a broad substrate scope to synthesize different derivatives of quinolines from 2-aminoarylketones. This way, quinoline derivatives have been prepared by condensation of 2-aminoarylketones with carbonyl compounds possessing a reactive methylene group, followed by cyclodehydration [10]. To this day it is still considered the most useful method for preparing such compounds, we recently [11] reported cyclic condensed process.

Quantum chemical methods offer powerful tools for chemo-structural studies. Therefore, structural parameters, Molecular

* Corresponding author. Department of Chemistry, Bharathiar University, Coimbatore 641 046, Tamil Nadu, India. Tel.: +91 422 2422311; fax: +91 422 2422387.
E-mail address: prasad_125@yahoo.com (K.J. Rajendra Prasad).

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electrostatic potential, HOMO–LUMO, and vibrational frequencies, studied by DFT methods, will assist in the understanding of molecular properties [12]. Here we present results of a detailed investigation of the synthesis and structural characterization of 7-chloro-9-phenyl-2,3-dihydroacridin-4(1*H*)-one using single crystal X-ray diffraction, FT-IR, FT-Raman, FT-NMR spectroscopy and quantum chemical methods [13]. Calculations of molecular electrostatic potential (MEP) and molecular orbitals (HOMO and LUMO) were performed using density functional theory at B3LYP/6-311G (d,p) and MO6-2x/6-311G (d,p) levels of theory.

7-Chloro-9-phenyl-2,3-dihydroacridin-4(1*H*)-one (**3**) was synthesized from 2-amino-5-chlorobenzophenone (**1**) and 1,2-cyclohexanedione (**2**) in presence of $InCl_3$ as a catalyst. Molecular structure, vibrational properties and chemical shifts of molecule **3** were examined experimentally and theoretically. The biological activity of molecule **3** and its cytotoxicity in vitro was evaluated by a (MTT) assay [14].

2. Materials and methods

2.1. General

Melting point (M.p., uncorrected, (°C)) was determined on a Mettler FP 51 apparatus (Mettler Instruments, Switzerland). Microanalysis was performed on a Vario EL III model CHNS analyzer (Vario, Germany). All reagents were purchased from Sigma Aldrich. Unless otherwise specified, other reagents were obtained from commercial suppliers. The purity of the product was tested by TLC with plates coated with silica gel-G using petroleum ether and ethyl acetate in the ratio of 1:1 as developing solvents.

2.2. Synthesis

2.2.1. General procedure for synthesis of 9-phenyl-3,4-dihydroacridin-1(2H)-one (3)

2-amino-5-chlorobenzophenone (**1,** 1 mmol) and 1,2-cyclohexanedione (**2,** 1.2 mmol) were dissolved in ethanol and reacted with $InCl_3$ as a catalyst. The completion of the reaction was monitored by TLC. The obtained solid was filtered and washed with water, extracted with EtOAc, and dried over anhydrous magnesium sulphate. Evaporation of the solvent was followed by purification via column chromatography over silica gel using petroleum ether: ethyl acetate (95:5) as eluent to yield 7-chloro-9-phenyl-2,3-dihydroacridin-4(1*H*)-one (**3**).

2.3. FT-IR, FT-Raman and NMR analysis

A Nicolet Avatar Model FT-IR spectrophotometer was used to record the IR spectrum using KBr pellet (4000–400 cm^{-1}). Raman spectrum was collected with a JY-1058 Raman spectrometer (3000–50 cm^{-1}). ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker AV 400 (400 MHz (^1H) and 100 MHz (^{13}C)) spectrometers using tetramethylsilane (TMS) as an internal reference. The chemical shifts are expressed in parts per million (ppm). Coupling constants (*J*) are reported in hertz (Hz).

2.4. Thermal analysis

Simultaneous TG-DTA studies were carried out on a PYRIS-DIAMOND thermal analyzer in air using platinum cups as sample holder with 5–10 mg of the samples at the heating rate of 10 °C/min up to 700 °C.

2.5. X-ray single crystal analysis

X-ray diffraction measurements were performed on a Bruker-Nonius FR590 Kappa CCD diffractometer at 130 K using monochromatic Mo Kα radiation. Further details are given below.

2.6. DFT computational analysis

The geometry of molecule **3**, in the ground state, was optimized via density functional method, including Beck's three parameters nonlocal–exchange functional with the correlation functional of Lee–Yang–Parr (B3LYP) as well as Minnesota functional MO6-2x, using the 6-311G (d,p) basis sets [15]. The vibrational frequency calculations have been performed at the same levels of theory. The absence of imaginary frequencies for the optimized geometry of molecule **3** indicates proper conversion of the model calculations.

2.7. In vitro cytotoxicity assay

The in vitro cytotoxicity assay (IC_{50}) was performed on the in Human breast cancer cell line (MCF-7) and human lung adenocarcinoma cell line (A549) by standard 3-(4,5-dimethylthiazol-2'-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Cells were placed in 96-well microassay culture plates (1×10^4 cells per well in 100 μL DMEM) and grown overnight at 37 °C in a 5% CO_2 incubator. Compounds tested were dissolved in DMSO and diluted with Dulbeccos Modified Eagles Medium (DMEM) to the required concentrations prior to use (200 μL/well). The plates were incubated at 37 °C in a 5% CO_2 incubator for 24 h. All measurements were made in triplicate and the medium, containing no test complexes, served as the control. After 24 h, 20 μL of MTT (5 mg/mL) in phosphate buffered saline (PBS) was added to each well and incubated at 37 °C for 4 h. The medium with MTT was then flicked off and the formazan crystals that had formed were solubilized in 200 μL of DMSO and the absorbance at 570 nm was measured using a microplate reader. The % cell inhibition was determined using the following formula,

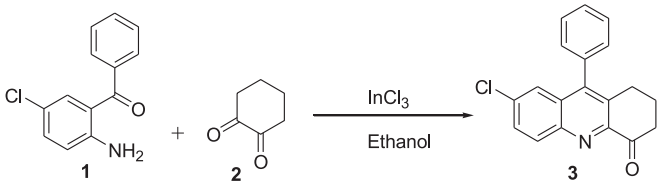
% Cell inhibition = 100 − Abs (sample) /Abs (control) x 100

The IC_{50} values were calculated from the graph plotted between % cell inhibition and concentration.

3. Results and discussion

3.1. Chemistry

The reaction of 2-amino-5-chlorobenzophenone (**1**) and 1,2-cyclohexanedione (**2**) in presence of $InCl_3$ as a catalyst in ethanol to afforded a yellow solid (**3**) in 89% yield (Scheme 1). Elemental analysis of compound **3**: calculated C, 74.15; H, 4.58; N, 4.55; found C, 74.07; H, 4.49; N, 4.62; M.p. 252–254 °C. **3** were further confirmed by FT-IR, FT-Raman, FT-NMR spectra and Thermal analysis as well as single crystal XRD.



Scheme 1. Synthesis of 7-Chloro-9-phenyl-2,3-dihydroacridin-4(1*H*)-one (**3**).