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ORIGINAL ARTICLE

Selective synthesis, structural studies and antitumor evaluation of some novel unsymmetrical 1-hetaryl-4-(2-chloroquinolin-3-yl)azines

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Abstract A series of novel unsymmetrical 1-hetaryl-4-(2-chloroquinolin-3-yl) azines **4**–**9** was selectively synthesized in a three-step procedure starting from acetanilide (**1**). The molecular structures of **4**–**9** were established by elemental analyses, spectral data, hybrid density functional theory (DFT) and time-dependent density functional theory (TD-DFT) calculations. Molecular conformation analysis for compounds **4**–**9**, performed using DFT calculations utilizing the energy functional 3-Parameter (Exchange), Lee, Yang and Parr (B3LYP) and the full-electron basis set Density Gauss double-zeta with polarization functions (DGDZVP), on the synthesized azines considering the torsion angles (θ_1, θ_2, θ_3) revealed 8 plausible conformers for each compound. Electronic and thermodynamic properties including the dipole moment and the thermodynamic energy values of the Frontier occupied and virtual molecular orbitals, HOMO and LUMO, respectively, were calculated for the most stable conformer for each compound. Furthermore, TD-DFT calculations coupled with the polarizable conductor calculation model (PCM), performed on the most stable conformers in DMF to account for the solvent effect, revealed that the optical properties including λ_{max} and oscillator strength performed on the most stable conformers were in excellent agreement with the experimental λ_{max} and molar extinction coefficient, which clearly validate the most stable molecular conformers identified for compounds **4**–**9**. Comparison of the biological results to the calculated electronic and thermodynamic properties showed that the cytotoxicity is dependent on the low-lying

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E_{LUMO} because compound **8** has the lowest E_{LUMO} value and exhibited the greatest antitumor activity.

1. Introduction

Azines, 2,3-diazabuta-1,3-dienes (commonly known as bis-Schiff bases), are a class of compounds that undergo a wide variety of chemical processes and have been used as potential substrates for crisscross cycloaddition reactions [1]. The two imine bonds that make up the azine moiety can be considered as polar acceptor groups oriented in opposite directions because they are joined by an N-N bond [2]. The presence of an azine bridge between two conjugated systems prevents electron delocalization occurring between the two systems, and azines are therefore considered to be conjugation stoppers [3]. Azines are versatile intermediate in heterocyclic synthesis [4], and are useful in the generation of conducting materials [5]. Some heterocyclic azines showed an excellent anti-leukemia activity [6] and act as fluorescent brightening agents and photosensitizers [7]. Azines were also developed for use as ion-selective optical sensors [8].

On the other hand, the diverse pharmacological properties of quinoline and their derivatives attracted worldwide attention in the last few decades because of their wide occurrence in natural products, and drugs [9]. Literature survey revealed that five-to-six membered heterocyclic compounds bearing a quinoline ring in a linear fashion were found to possess antimicrobial and anticancer activities [10,11].

Although symmetrical azines are readily synthesized by the reaction of hydrazine with an excess of an aldehydes or ketones, the preparation of their unsymmetrical azines is more challenging [12]. Among the different published procedures for the synthesis of unsymmetrical azines, a two-step procedure is reported which involves (i) preparation of aldimines/ketimines by condensation of hydrazine with aldehydes or ketones, (ii) reaction of the resulting aldimines or ketimines with other carbonyl derivatives [13–15]. Recently, Safari et al. [16] reported the one-step synthesis of unsymmetrical azines *via* condensation of aromatic aldehyde derivatives with hydrazine sulfate in triethylamine and absolute ethanol solution.

Gaining deep insights into the structure–property and/or structure–activity relationship of unsymmetrical azine analogs **4–9** presented in this study for conducting material, anti-leukemia or photosensitizers require obtaining the correct molecular geometry, which is the critical first step in predicting electronic, optical and thermodynamic properties and establishing structure–activity/property relationships. With the aforementioned in mind, one of the key objectives in this study was to identify the most stable conformer (equilibrium molecular geometry) for each compound, using DFT calculations, of the synthesized unsymmetrical azines **4–9** and validate that by comparing the calculated optical properties including λ_{max} and oscillator strength, obtained from TD-DFT calculations, to the experimental λ_{max} and molar extinction coefficient.

In the light of the above mentioned finding, we report herein the synthesis, antitumor evaluation of some novel unsymmetrical 1-hetaryl-4-(2-chloroquinolin-3-yl) azines (**4–9**) and a comprehensive DFT study of plausible conformers and identifying the most stable conformer for each compound followed by TD-DFT calculations to predict the optical properties.

2. Experimental

Melting points were determined on digital Gallen-Kamp MFB-595 instrument using open capillary tubes and are uncorrected. UV–Vis spectra were recorded on Shimadzu UV-1800 spectrophotometer. IR spectra were recorded on Shimadzu FTIR 440 spectrometer using KBr pellets. Mass spectra were performed on Shimadzu Qp-2010 plus mass spectrometer at 70 eV. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker model 500 MHz Ultra Shield NMR spectrometer in DMSO-d_6 using tetramethylsilane (TMS) as an internal standard; chemical shifts are reported as δ_{ppm} units. The elemental analyses were done at the Microanalytical Center, Cairo University, Cairo, Egypt. 2-Chloroquinoline-3-carbaldehyde (**2**) [17], 2-chloroquinoline-3-carbaldehyde hydrazone (**3**) [10], 1-(piperdin-1-ylmethyl)indoline-2,3-dione, and 1-(morpholinomethyl)indoline-2,3-dione [18] were prepared according to the literature procedures.

2.1. General procedure for the synthesis of unsymmetrical azines 4–9

A mixture of compound **2** (2.05 g, 0.01 mol) and appropriate heterocyclic aldehydes or ketones (0.01 mol) in ethanol 30 mL was refluxed for 4 h. The reaction mixture was allowed to cool down to room temperature and the solid formed was filtered, washed with ethanol, dried, and recrystallized from a mixture of EtOH/DMF (2:1) to afford azines **4–9**.

2.1.1. 2-Chloroquinoline-3-carbaldehyde [(1E)-2-furylmethylene]hydrazone (4)

Yellow powder, Yield (64%), mp > 300 °C; IR (KBr) ν_{max}/cm^{-1}: 3095 (CH-Ar), 1614 (C=N), 1583 (C=C, conjugated), 1049 (C-O), 774 (C-Cl); ^{1}H-NMR (DMSO-d_6): δ_{ppm} = 7.24 (t, J = 4 Quinoline-H$_7$), 8.04 (Hz, 1H, Furan-H$_4$), 7.71 (t, J = 7 Hz, 1H, Quinoline-H$_6$), 7.75 (d, J = 5 Hz, 1H, Furan-H$_3$), 7.90 (d, J = 5 Hz, 1H, Furan-H$_5$), 7.94 (t, J = 7 Hz, 1H, Quinoline-H$_7$), 7.98 (d, J = 8 Hz, 1H, Quinoline-H$_8$), 8.23 (d, J = 8 Hz, 1H, Quinoline-H$_5$), 8.96 (s, 1H, Quinoline-H$_4$), 8.98 (s, 1H, CH=N), 9.06 (s, 1H, CH=N); ^{13}C-NMR (DMSO-d_6): δ_{ppm} = 125.5 (Quinoline-C$_{4a}$), 126.7 (Quinoline-C$_6$), 127.6 (Furan-C$_5$), 127.9 (Quinoline-C$_3$), 128.5 (Furan-C$_4$), 129.7 (Furan-C$_3$), 132.0 (Quinoline-C$_8$), 132.7 (Quinoline-C$_5$), 134.7 (Quinoline-C$_4$), 136.9 (Quinoline-C$_7$), 138.2 (Furan-C$_2$), 147.7 (Quinoline-C$_{8a}$), 149.0 (Quinoline-C$_2$), 156.7 (Furan-CH=N), 157.6 (Quinoline-CH=N). MS m/z (%): 283 (M$^+$, 1.8), 244 (1.3), 217 (1.4), 216 (7.6), 204 (1.5), 198 (4.0), 162 (14.1), 81 (9.7), 80 (100.0); Anal. Calcd. for $C_{15}H_{10}ClN_3O$ (283.71): C, 63.50; H, 3.55; N, 14.81%, Found: C, 63.47; H, 3.48; N, 14.78%.

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