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Synthesis and structural studies of acyl hydrazone derivatives having tetrahydrocarbazole moiety

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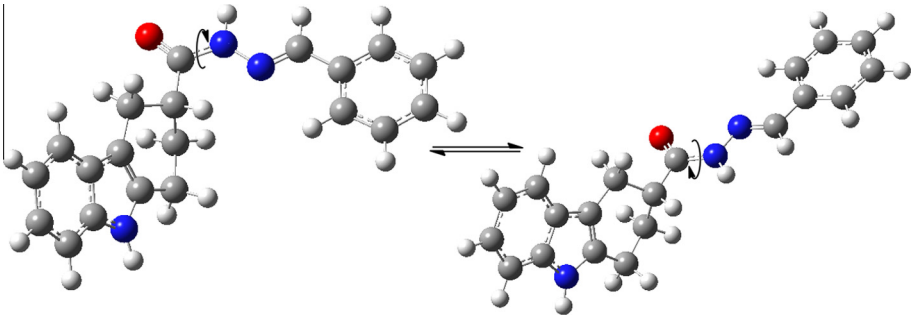
HIGHLIGHTS

- 17 new acyl hydrazone compounds having tetrahydrocarbazole moiety were synthesized.
- Structures and physical properties of the hybrid compounds were elucidated.
- Conformational analysis were made by means of DFT calculations.

GRAPHICAL ABSTRACT



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ABSTRACT

Seventeen new compounds having tetrahydrocarbazole moiety were synthesized by condensation of tetrahydrocarbazole hydrazide with aromatic aldehydes. The structures and physical properties of these hybrid compounds were elucidated by IR, ^{1}H NMR, APT-NMR and mass spectroscopy. In addition, to gain more insight into conformational structures and energetics of the compounds, DFT calculations at B3LYP/6-311++G(d,p) level in DMSO were performed on a selected compound from the series.

Introduction

Tetrahydrocarbazoles are wellknown chemical intermediates used in the synthesis of many natural alkaloids [1], hydrogen bond sensitive fluorescent probes [2], luminogenic molecules [3], potential materials for on-board organic hydrogen storage compounds [4], and synthetic biologically active compounds [5,6]. Some of the tetrahydrocarbazole derivatives are also found to exhibit antibacterial [7–9], anti-HPV activities [10,11] and cytotoxic activity against human cancer cells [12].

Acyl hydrazone derivatives are another molecular template to generate biologically active compounds. They are reported for their antibacterial, antifungal [13–15], anticonvulsant [16–18], anti-inflammatory [19,20], antimalarial [21] and antituberculosis activities [22–25]. Moreover, these compounds can be used as suitable ligands for the development of coordination compounds because of their potential ability to coordinate several metal ions [26,27]. They are also key reagents for the synthesis of various nitrogen containing derivatives [28–30]. Because of their widespread

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applications, substituted acyl hydrazones have been subjected to quite a large number of synthetic [31–33], X-ray structure determination [34,35] and quantum chemical studies [36,37]. Although significant progress has been made with these studies in understanding their structures, some points still remain unanswered; such as conformational pathways and energetics between experimentally suggested conformational structures.

In this study, on the basis of the biological activity profiles of tetrahydrocarbazoles and acyl hydrazones, we were hybridized these two ring systems into one unit. In the characterization of these new compounds, besides the spectroscopic methods, DFT quantum chemical calculations were also used to answer the questions about the conformational properties of these compounds, and experimental and theoretical results were compared.

Experimental section

All chemicals were from Aldrich Chemical Co. Melting points were measured in sealed tubes using electrothermal digital melting point apparatus and are uncorrected. IR spectra (KBr) were recorded on a thermoscientific Nicolet iS10 spectrometer. APT-NMR and ^{1}H NMR spectra were obtained by a Bruker instrument DPX-400, 400 MHz High Performance Digital FT-NMR Spectrometer using DMSO-d_6. All chemical shift values were recorded in δ (ppm). Chemical shift (δ) values of rotameric hydrogens whenever identified are presented within the parenthesis by assigning an asterisk (*) along with that of the other form. The purity of the compounds was controlled by thin layer chromatography on silica-gel-coated aluminium sheets.

2,3,4,9-Tetrahydro-1H-carbazole-3-carbohydrazide 2; synthetic procedure

A solution of the ethyl-2,3,4,9-tetrahydro-1*H*-carbazole-3-carboxylate (**1**) (15.0 g, 61.7 mmol) in 100 ml ethanol was refluxed with hydrazine hydrate (50.0 mL) for 15 h. After it was cooled to room temperature, solvent was removed by rotary evaporator. The residue was treated with water. The solid separated was filtered and dried to give the desired product **2**.

*2,3,4,9-Tetrahydro-1H-carbazole-3-carbohydrazide (**2**)*

White solid, yield 74%, mp 197–198 °C. IR (ν_{max}): 3380 (N—H), 3297 (N—H), 3052 (C—H), 2920 (C—H), 2853 (C—H), 1643 (C=O), 1611 (N—H), 1524 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 1.82–1.92 (m, 1H, CH), 1.99–2.01 (m, 1H, CH), 2.67–2.80 (m, 4H, $2CH_2$), 4.24 (s, 2H, NH_2), 6.92 (t, 1H, ArH, J = 7.02 Hz), 6.99 (t, 1H, ArH, J = 7.20 Hz), 7.25 (d, 1H, ArH, J = 7.91 Hz), 7.34 (d, 1H, ArH, J = 7.60 Hz), 9.12 (s, 1H, NH_{amide}), 10.69 (s, 1H, NH_{indole}) APT-NMR (100 MHz, DMSO): δ = 22.7, 24.7, 26.7, 39.8, 107.5, 111.1, 117.6, 118.6, 120.7, 127.5, 134.1, 136.3, 175.0 (C=O). HRMS m/z calcd for $C_{13}H_{16}N_3O$ $[M+H]^+$ 230.1293; found 230.1295.

*Acyl hydrazones **3**–**18**; general synthetic procedure*

To a stirred solution of 2,3,4,9-tetrahydro-1*H*-carbazole-3-carbohydrazide (**2**) (0.5 g, 2.2 mmol) in ethanol (15 mL), various aldehydes (2.2 mmol) was added, after which the mixture was heated at 90–95 °C until completion of the reaction (TLC monitoring). The mixture was cooled to room temperature and the solvent was removed by rotary evaporator. The residue was treated with water. The solid separated was filtered and dried to give the desired products **3**–**18**.

*N′-benzylidene-2,3,4,9-tetrahydro-1H-carbazole-3-carbohydrazide (**3**)*

White solid, yield 90%, mp 246–248 °C. IR (ν_{max}): 3334 (N—H), 3195 (N—H), 3057 (C—H), 2920 (C—H), 2853 (C—H), 1629 (C=O), 1603 (C=N), 1564 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 1.88–1.96 (m, 1H, CH), 2.12–2.15 (m, 1H, CH), 2.71–2.95 (m, 4H, $2CH_2$), 3.58–3.62 (m, 1H, CH), 6.9–7.72 (m, 9H, ArH), 8.24 (8.05*, s, 1H, =CH), 10.74 (10.73*, s, 1H, NH_{indole}), 11.51 (11.34*, s, 1H, NH). APT-NMR (100 MHz, DMSO): δ = 22.2, 22.3, 23.5, 24.2, 25.6, 26.2, 36.8, 40.0, 106.8, 107.1, 110.6, 117.2, 118.1, 118.1, 120.2, 120.2, 126.6, 127.0, 127.0, 127.1, 128.8, 128.8, 129.6, 129.9, 133.6, 133.8, 134.3, 134.3, 135.9, 142.7, 146.2, 171.5, 176.8. HRMS m/z calcd for $C_{20}H_{20}N_3O$ $[M+H]^+$ 318.1606; found 318.1616.

*N′-(2-chlorobenzylidene)-2,3,4,9-tetrahydro-1H-carbazole-3-carbohydrazide (**4**)*

White solid, yield 81%, mp 217–219 °C. IR (ν_{max}): 3393 (N—H), 3177 (N—H), 3009 (C—H), 2943 (C—H), 2844 (C—H), 1647 (C=O), 1594 (C=N) cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 1.88–1.96 (m, 1H, CH), 2.13–2.16 (m, 1H, CH), 2.68–2.95 (m, 4H, $2CH_2$), 3.61 (m, 1H, CH), 6.92–8.00 (m, 8H, ArH), 8.64 (8.45*, s, 1H, =CH), 10.74 (10.74*, s, 1H, NH_{indole}), 11.74 (11.54*, s, 1H, NH). APT-NMR (100 MHz, DMSO): δ = 22.2, 22.3, 23.5, 24.2, 25.6, 26.7, 36.8, 40.2, 106.8, 107.1, 110.6, 117.2, 118.2, 120.2, 120.3, 126.5, 126.8, 127.1, 127.2, 127.5, 129.8, 130.9, 131.2, 131.6, 132.9, 133.1, 133.6, 133.8, 136.0, 138.8, 142.2, 171.8, 177.0. HRMS m/z calcd for $C_{20}H_{19}ClN_3O$ $[M+H]^+$ 352.1216; found 352.1227.

*N′-(3-chlorobenzylidene)-2,3,4,9-tetrahydro-1H-carbazole-3-carbohydrazide (**5**)*

White solid, yield 92%, mp 222–224 °C. IR (ν_{max}): 3331 (N—H), 3188 (N—H), 3054 (C—H), 2928 (C—H), 2845 (C—H), 1634 (C=O), 1561 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 1.85–1.98 (m, 1H, CH), 2.12–2.16 (m, 1H, CH), 2.68–2.94 (m, 4H, $2CH_2$), 3.57–3.63 (m, 1H, CH), 6.90–7.77 (m, 8H, ArH), 8.22 (8.03*, s, 1H, =CH), 10.75 (10.74*, s, 1H, NH_{indole}), 11.65 (11.46*, s, 1H, NH). APT-NMR (100 MHz, DMSO): δ = 22.6, 22.7, 23.9, 24.6, 26.1, 26.6, 37.2, 40.5, 107.2, 107.5, 111.1, 117.6, 118.6, 118.6, 120.7, 120.7, 125.7, 126.1, 126.5, 126.7, 127.5, 127.6 129.8, 130.0, 131.2, 131.2, 134.1, 134.3, 136.4, 137.1, 137.2, 141.6, 145.0, 172.2, 177.4. HRMS m/z calcd for $C_{20}H_{19}ClN_3O$ $[M+H]^+$ 352.1216; found 352.1234.

*N′-(4-chlorobenzylidene)-2,3,4,9-tetrahydro-1H-carbazole-3-carbohydrazide (**6**)*

White solid, yield 93%, mp 231–232 °C. IR (ν_{max}): 3418 (N—H), 3323(N—H), 3196 (N—H), 3058 (C—H), 2925 (C—H), 2843 (C—H), 1651 (C=O), 1594 (C=N), 1548 cm^{-1}. ^{1}H NMR (400 MHz, DMSO): δ = 1.87–1.97 (m, 1H, CH), 2.11–2.14 (m, 1H, CH), 2.68–2.94 (m, 4H, $2CH_2$), 3.56–3.62 (m, 1H, CH), 6.90–7.75 (m, 8H, ArH), 8.23 (8.04*, s, 1H, =CH), 10.75 (10.74*, s, 1H, NH_{indole}), 11.58 (11.41*, s, 1H, NH). APT-NMR (100 MHz, DMSO): δ = 22.1, 22.2, 23.5, 24.1, 25.5, 26.1, 36.7, 40.0, 106.7, 107.0, 110.6, 117.1, 117.2, 118.1, 118.1, 120.2, 120.2, 127.0, 127.1, 128.2 128.6, 128.9, 133.2, 133.3, 133.6, 133.8, 134.0, 134.3, 135.9, 141.4, 144.8, 171.6, 176.8. HRMS m/z calcd for $C_{20}H_{19}ClN_3O$ $[M+H]^+$ 352.1216; found 352.1232.

*N′-(2-bromobenzylidene)-2,3,4,9-tetrahydro-1H-carbazole-3-carbohydrazide (**7**)*

White solid, yield 95%, mp 219–221 °C. IR (ν_{max}): 3393 (N—H), 3179 (N—H), 3010 (C—H), 2940 (C—H), 2845 (C—H), 1645 (C=O), 1592 (C=N), 1564 cm^{-1}. ^{1}H NMR (400 MHz, DMSO):