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Regioselective synthesis, stereochemical structure, spectroscopic characterization and geometry optimization of dispiro[3*H*-indole-3, 2′-pyrrolidine-3′,3″-piperidines]

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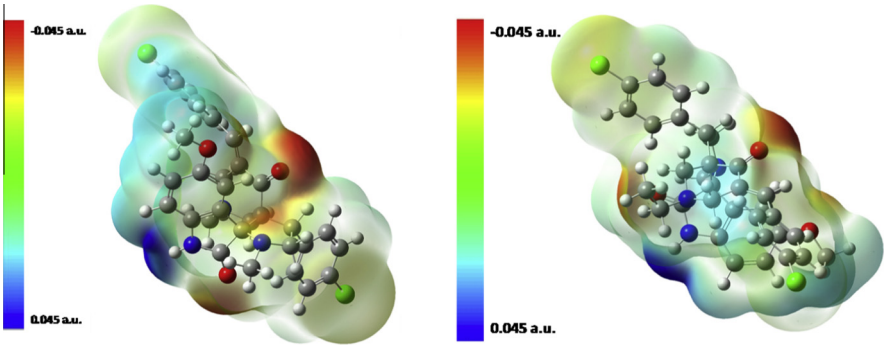
HIGHLIGHTS

- Dispiro-indole containing compounds were prepared in a regioselective manner.
- Single crystal X-ray identify the stereochemical configuration of the structures.
- MEP were calculated at B3LYP/6-31G(d,p) level of theory.
- FMOs exhibit large energy gap between HOMO and LUMO orbitals.

GRAPHICAL ABSTRACT



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ABSTRACT

In this work, two dispiro[3*H*-indole-3,2′-pyrrolidine-3′,3″-piperidines], $C_{31}H_{29}Cl_2N_3O_3$ (**4a**) and $C_{32}H_{31}Cl_2N_3O_3$ (**4b**), have been synthesized and characterized by IR, ^{1}H NMR, ^{13}C NMR, ^{1}H ^{1}H COSY, ^{1}H ^{13}C HSQC and single crystal X-ray diffraction. Both compounds were found to be crystallized in the triclinic space group $P\bar{1}$ with $Z = 2$. Molecules of the crystalline structure of **4a** are linked with intermolecular C—H···O and N—H···O hydrogen bonding. Meanwhile, an intermolecular N—H···O hydrogen bonding was recognized in the crystalline structure of **4b**. Molecular mechanics force field (MM^+), followed by either semi-empirical AM1 or PM3, has been used to calculate the optimized geometrical parameters for the two compounds. The determined theoretical geometry parameters were found to be in a good agreement with the parameters obtained using X-ray studies. Moreover, the Molecular Electrostatic Potential (MEP) of both compounds have been calculated at B3LYP/6-31G(d,p) level of theory exhibiting that, the most electrophilic site of the synthesized compounds, is the piperidone O3 atom however, the most nucleophilic site is the indolyl N2. Additionally, the Frontier Molecular Orbitals (FMOs) **4a** and **4b** have been determined by the same technique exhibiting large energy gap between HOMO and LUMO orbitals (3.40, 3.43 eV for **4a** and **4b**, respectively), inferring good stability, high excitation energies and large chemical hardness of these molecules.

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Introduction

Azomethine ylides are reactive 1,3-dipoles that are used intensively in [3 + 2]-cycloaddition reactions for construction of five-membered nitrogen-containing heterocycles. Azomethine ylides readily react with various dipolarophiles to give the corresponding pyrrole analogues [1]. Several synthetic targets, that have attracted attention in the last two decades, possess spiropyrrolidine-oxindole structural motif. This framework forms a core structure of many alkaloid and natural products exhibiting potent biological and/or pharmacological properties [2–9]. Examples of the naturally isolated spiropyrrolidine-oxindoles are coerulescine, which is the simplest analogue found in nature, with local anesthetic properties [10]. Horsfiline isolated from *Horsfieldia superb* [11] and elacomine found in *Elaeagnus commutate* [12] are used as indigenous medicines. Mitraphylline, isolated from *Uncaria tomentosa*, possess potent antitumor properties against human brain cancer cell lines, neuroblastoma SKN-BE(2) and malignant glioma GAMG [13]. More examples are provided by spirotryprostatins A and B, isolated from the fermentation broth of *Aspergillus fumigatus* that were shown to completely inhibit the G2/M progression of cell division in mammalian tsFT210 cells [14,15].

The present work describes synthesis of novel spiropyrrolidine-oxindole analogs utilizing a facile regioselective technique (Fig. 1). The compounds **4a** and **4b** have been characterized by using single-crystal X-ray diffraction, IR and NMR. Essential chemical information such as the molecular geometry, bond distances and angles and the packing of the molecules in the crystal have been discussed. Absolute-configuration determination is a fine detail of crystal-structure determination, which depends on being able to identify small diffraction intensity differences between two crystal-structure models of opposite chirality [16]. The present work also includes geometry optimization of the synthesized compounds utilizing different computational chemistry techniques (AM1 and PM3). This allows comparison of the experimental and theoretical data, providing useful understanding of the bases of these techniques. The properties of structural geometry, molecular electrostatic potential and frontier orbitals have been, also, studied.

Experimental

*Synthesis and crystallization of the **4a** and **4b***

The starting compounds (**1a** and **1b)** were prepared according to the previously reported procedures [17,18]. A mixture of equimolar amounts of the appropriate 3*E*,5*E*-1-alkyl-3,5-bis[(4-chlorophenyl)methylidene]-4-piperidones **1a, 4b** (5 mmol), 5-methoxyisatin and sarcosine in absolute ethanol (25 ml) was boiled under reflux for 12 h (TLC monitoring). The separated solid was collected and crystallized from *n*-butanol affording the corresponding **4a** and **4b**.

The melting points of **4a** and **4b** were measured in open capillary tubes on a digital Stuart SMP3 melting point apparatus. The IR spectra (KBr) were recorded using a JASCO 6100 FT-IR spectrophotometer in the range of 4000–400 cm^{-1} region. The ^1H- and ^{13}C-nuclear magnetic resonance (NMR) spectra were recorded on a JEOL AS 500 (^1H: 500, ^{13}C: 125 MHz) spectrometer. 2D-NMR spectra, including ^1H, ^1H-COSY and HSQC were recorded on a Bruker Ascend 400/R (^1H: 400, ^{13}C: 100 MHz) spectrometer.

Spectroscopic and physical properties of the synthesized compounds

*4′-(4-Chlorophenyl)-5″-[(4-chlorophenyl)methylidene]-1′,1″-dimethyl-5-methoxy-dispiro [3H-indole-3,2′-pyrrolidine-3′,3″-piperidine]-2(1H), 4″-dione (**4a**)*

Obtained from reaction of **1a**, **2** and **3**. Yellow crystals. M.p.: 233–235 °C. Yield: 78%. Anal. Calcd. for $C_{31}H_{29}Cl_2N_3O_3$ (562.50): C, 66.19; H, 5.20; N, 7.47. Found: C, 66.11; H, 5.09; N, 7.63. IR: ν_{max}/cm^{-1} 3166 (NH), 1685 (C═O), 1593, 1487. ^1H NMR ($CDCl_3$): δ 1.67 (d, 1H, upfield H of piperidinyl H_2C-2″, J = 12.25 Hz), 2.03 (s, 3H, piperidinyl NCH_3), 2.15 (s, 3H, pyrrolidinyl NCH_3), 2.92 (d, 1H, upfield H of piperidinyl H_2C-6″, J = 14.55 Hz), 3.24 (d, 1H, downfield H of piperidinyl H_2C-2″, J = 12.25 Hz), 3.28–3.32 (m, 2H, downfield H of piperidinyl H_2C-6″ + upfield H of pyrrolidinyl H_2C-5′), 3.78 (s, 3H, OCH_3), 3.88 (t, 1H, downfield H of pyrrolidinyl H_2C-5′, J = 9.93 Hz), 4.76 (dd, 1H, pyrrolidinyl HC-4′, J = 6.90, 10.70 Hz), 6.53-7.33 (m, 12H, 11 arom. H + olefinic CH), 8.14 (s, 1H, NH). ^{13}C NMR "on-resonance & DEPT" (DMSO-d_6): δ 34.7 (pyrrolidinyl NCH_3), 44.9 (piperidinyl NCH_3), 45.1 (pyrrolidinyl HC-4′), 55.8 (OCH_3), 56.5 (piperidinyl H_2C-6″), 57.1 (pyrrolidinyl H_2C-5′), 57.6 (piperidinyl H_2C-2″), 65.3 [spiro C-3′ (C-3″)], 75.8 [spiro C-3 (C-2′)], 109.6, 114.0, 114.1, 128.5, 128.8, 129.1, 131.4, 132.0, 133.7, 134.2, 134.5, 135.6, 137.3, 137.9, 154.7 (arom. C + olefinic C), 177.0 [indolyl C═O (C-2)], 198.3 [piperidinyl C═O (C-4″)].

*4′-(4-Chlorophenyl)-5″-[(4-chlorophenyl)methylidene]-1″-ethyl-5-methoxy-1′-methyl-dispiro[3H-indole-3,2′-pyrrolidine-3′, 3″-piperidine]-2(1H),4″-dione (**4b**)*

Obtained from reaction of **1b**, **2** and **3**. Pale yellow crystals. M.p.: 220–222 °C. Yield: 78%. Anal. Calcd. for $C_{32}H_{31}Cl_2N_3O_3$ (576.53): C, 66.67; H, 5.42; N, 7.29. Found: C, 66.84; H, 5.54; N, 7.35. IR: ν_{max}/cm^{-1} 3166 (NH), 1684 (C═O), 1588, 1487 (C═C). ^1H NMR ($CDCl_3$): δ 0.79 (t, 3H, piperidinyl NCH_2CH_3, J = 6.90 Hz), 1.74 (d, 1H, upfield H of piperidinyl H_2C-2″, J = 12.20 Hz), 2.12–2.16 (m, 4H, pyrrolidinyl NCH_3 + upfield H of piperidinyl NCH_2CH_3), 2.34–2.38 (m, 1H, downfield H of piperidinyl NCH_2CH_3), 2.85 (d, 1H, upfield H of piperidinyl H_2C-6″, J = 14.50 Hz), 3.22 (d,

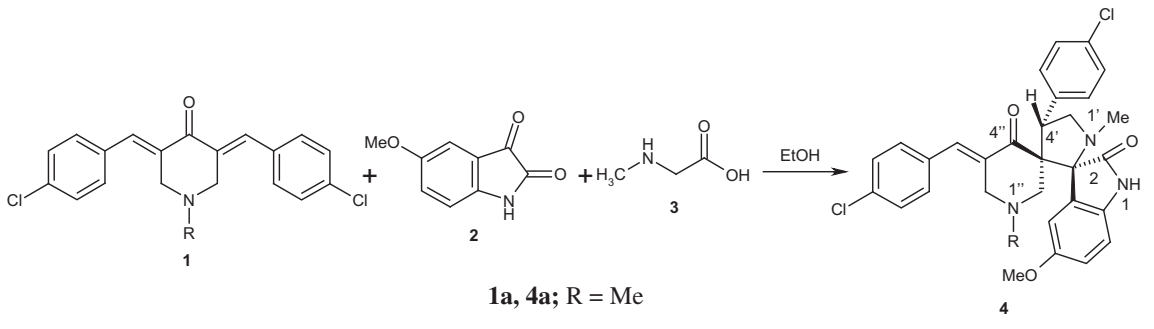

Fig. 1. Synthetic route towards dispiro[3*H*-indole-3,2′-pyrrolidine-3′,3″-piperidines].