

Article

Exploring Regio- and Stereoselectivity in [3+2] Cycloaddition: Molecular Electron Density Theory Approach for Novel Spirooxindole-Based Benzimidazole with Pyridine Spacer

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Abstract: A new ethylene derivative was synthesized as a precursor for the [3+2] cycloaddition (32CA) reaction to access a novel spirooxindole embodied with benzimidazole with a pyridine spacer. The chalcone derivatives **3a–j** is obtained with condensation of the acetyl derivative with aryl aldehydes. The one-pot multi-component reaction of the ethylene derivative, 5-Cl-isatin, and octahydroindole-2-carboxylic acid enables the construction of a highly functionalized quaternary center spirooxindole scaffold in a high chemical yield. A study using the Molecular Electron Density Theory (MEDT) explains the complete regio- and stereoselectivity of the reaction, resulting in the exclusive formation of the ortho/endo-cycloadduct under kinetic control. The low activation Gibbs free energy is the result of the supernucleophilic character of the in situ-generated azomethine ylide and the strong electrophilic character of the ethylene derivatives.

Keywords: [3+2] cycloaddition reaction; spirooxindole; MEDT (Molecular Electron Density Theory)



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1. Introduction

The skeleton of a spirooxindole core structure is present in many natural alkaloids and attracts many synthetic chemists because this privileged structure plays an important role in drug discovery and medication enhancement [1–5]. There are diverse synthetic tools that are accessible and reproducible for the construction of chiral spirooxindole frameworks with pharmacological relevant targets [6–10]. Spirooxindoles are a prominent class of compounds that possess many medication targets including treatment of cancer [11–15], anti-inflammatory [16], SARS-CoV-2 [17,18], anti-diabetics [19–21], and others [22–27]. This rigid spirocyclic scaffold has an outstanding ability for the physicochemical properties' improvement compared to other mono-cyclic structures [28]. Therefore, the construction of spirooxindoles based on chiral quaternary centers has attracted significant attention from many researchers and remains a challenging task.

Several synthetic approaches have the ability to access spirooxindoles; among them are the use of nano-catalysis [29], organocatalyst oxidative annulations [30–33], microwave irradiations [34], sonochemical strategy [35], NHC (N-Heterocyclic carbene) catalyst-mediated [3+2] cycloaddition annulation [36], and transition metal catalysts [37,38] (e.g., Ru, Rh, Pd, etc.) that require a specific olefin or indolinone-based alkene moiety in the precursor structure. A mild condition, facile, and eco-friendly approach to compose the spirooxindoles are still required to a great extent.

The one-pot multi-component [3+2] cycloaddition (32CA) reaction is among the most versatile eco-friendly and atom-economy strategies that enable the synthesis of spirooxindole-based chiral functionality. Many spirooxindole molecules were developed

based on this approach and were discovered to be competitive and highly effective for their valuable anti-disease pharmacological potential.

Azomethine ylides (AYs) are highly reactive intermediates in 32CA reactions, resulting in the formation of diverse hetero/carbocyclic molecules, particularly spirooxindoles and others [39,40]. These three-atom components (TACs) have been extensively studied and explored in many total syntheses of biologically active natural as well as synthetic products from 32CA reactions. Recent Molecular Electron Density Theory (MEDT) [41] studies of the chemical reactivity of these TACs suggested that these organic species may present *pseudodiradical*, *pseudo(mono)radical*, carbenoid, and even zwitterionic natures depending on the substitution, and consequently, the term of “1,3-dipole” is not justified for these reactions [42].

In this work, we designed a new olefin for the 32CA reaction, which is crucial for accessing the desired spirooxindoles. The mechanism of the 32CA reaction is studied from the perspective of MEDT.

2. Materials and Methods

2.1. Synthesis of Chalcones (3a–j) and Spiro-Compounds (6a–j)

2.1.1. Synthesis of Chalcones (3a–j)

The arylaldehyde derivative **2a–j** (2 mmol) was added to ketone derivative **1** (0.5 g, 2 mmol) in an ethanol solution of potassium hydroxide (40 mmol of potassium hydroxide in 40 mL of ethanol). The reaction mixture was subsequently stirred at room temperature for 12 h and neutralized with a solution of 30% acetic acid, leading to a precipitate. It was filtered, dried, and recrystallized in EtOH to give compounds **3a–j**.

(*E*)-1-(6-(1*H*-Benzo[d]imidazol-2-yl)-2-methylpyridin-3-yl)-3-(4-methoxyphenyl)prop-2-en-1-one **3a**

¹H-NMR (DMSO-*d*₆, 400 MHz) δ 13.03 (¹H, NH, s), 8.28 (¹H, Py-H, d, *J* = 8.1 Hz), 8.20 (¹H, Py-H, d, *J* = 8.1 Hz), 7.79 (²H, ArH, d, *J* = 8.8 Hz), 7.74 (¹H, ArH, d, *J* = 8.1 Hz), 7.61 (¹H, ArH, d, *J* = 7.3 Hz), 7.56 (¹H, =CH, d, *J* = 16.1 Hz), 7.35 (¹H, COCH, d, *J* = 16.1 Hz), 7.26 (²H, ArH, m), 7.01 (²H, ArH, d, *J* = 8.8 Hz), 3.81 (³H, OCH₃, s), 2.71 (³H, CH₃, s); ¹³C-NMR (DMSO-*d*₆, 100 MHz) δ 194.1, 162.3, 156.9, 150.7, 149.4, 146.6, 144.6, 138.01, 135.6, 135.0, 131.6, 127.5, 124.0, 122.7, 120.0, 119.1, 115.1, 112.9, 56.0, 24.0; Anal. for C₂₃H₁₉N₃O₂: Calcd: C, 74.78; H, 5.18; N, 11.37; Found: C, 75.15; H, 4.89; N, 11.14.

1-(6-(1*H*-Benzo[d]imidazol-2-yl)-2-methylpyridin-3-yl)-3-mesitylprop-2-en-1-one **3b**

¹H-NMR (DMSO-*d*₆, 500 MHz) δ 12.99 (¹H, NH, s), 8.22 (¹H, Py-H, d, *J* = 8.0 Hz), 8.15 (¹H, Py-H, d, *J* = 8.0 Hz), 7.68 (¹H, ArH, d, *J* = 7.9 Hz), 7.64 (¹H, =CH, d, *J* = 16.4 Hz), 7.56 (¹H, ArH, d, *J* = 7.9 Hz), 7.23 (¹H, ArH, t, *J* = 7.5 Hz), 7.18 (¹H, ArH, t, *J* = 7.5 Hz), 6.92 (¹H, COCH, d, *J* = 16.4 Hz), 6.89 (²H, ArH, s), 2.70 (³H, CH₃, s), 2.28 (⁶H, CH₃, s), 2.19 (³H, CH₃, s); ¹³C-NMR (DMSO-*d*₆, 126 MHz) δ 194.1, 165.4, 157.4, 149.5, 144.6, 139.3, 138.2, 137.6, 135.8, 134.5, 131.0, 129.7, 124.0, 122.7, 120.0, 119.0, 112.9, 23.8, 20.3; Anal. for C₂₅H₂₃N₃O: Calcd: C, 78.71; H, 6.08; N, 11.02; Found: C, 78.75; H, 6.05; N, 11.07.

(*E*)-1-(6-(1*H*-Benzo[d]imidazol-2-yl)-2-methylpyridin-3-yl)-3-(*p*-tolyl)prop-2-en-1-one **3c**

¹H-NMR (DMSO-*d*₆, 400 MHz) δ 12.64 (¹H, NH, s), 8.30 (¹H, Py-H, d, *J* = 8.0 Hz), 8.23 (¹H, Py-H, d, *J* = 8.0 Hz), 7.72 (²H, ArH, d, *J* = 7.9 Hz), 7.69–7.65 (²H, ArH, m), 7.58 (¹H, =CH, d, *J* = 16.0 Hz), 7.45 (¹H, COCH, d, *J* = 16.0 Hz), 7.29–7.22 (⁴H, ArH, m), 2.72 (³H, CH₃, s), 2.33 (³H, CH₃, s); ¹³C-NMR (DMSO-*d*₆, 101 MHz) δ 194.0, 158.1, 155.4, 152.2, 150.1, 146.5, 140.9, 138.2, 134.6, 133.0, 130.8, 129.9, 125.8, 122.6, 120.0, 118.9, 24.1, 21.5; Anal. for C₂₃H₁₉N₃O: Calcd: C, 78.16; H, 5.42; N, 11.89; Found: C, 78.21; H, 5.37; N, 11.85.

1-(6-(1*H*-Benzo[d]imidazol-2-yl)-2-methylpyridin-3-yl)-3-(*m*-tolyl)prop-2-en-1-one **3d**

¹H-NMR (DMSO-*d*₆, 500 MHz) δ 13.00 (¹H, NH, s), 8.25 (¹H, Py-H, d, *J* = 8.1 Hz), 8.21 (¹H, Py-H, d, *J* = 8.1 Hz), 7.63 (¹H, ArH, d, *J* = 2.0 Hz), 7.57 (²H, ArH, d, *J* = 7.8 Hz), 7.53 (¹H, =CH, d, *J* = 16.0 Hz), 7.45 (¹H, COCH, d, *J* = 16.0 Hz), 7.30 (¹H, ArH, t, *J* = 7.6 Hz), 7.24 (²H, ArH, d, *J* = 7.8 Hz), 7.22–7.18 (²H, ArH, m), 2.69 (³H, CH₃, s), 2.30 (³H, CH₃, s);

^{13}C -NMR (DMSO- d_6 , 126 MHz) δ 194.0, 157.2, 150.6, 149.5, 146.5, 138.8, 138.2, 136.7, 135.8, 134.8, 134.6, 132.25, 129.9, 129.4, 127.9, 126.8, 126.1, 123.7, 122.7, 119.1, 112.9, 24.1, 21.4; Anal. for $\text{C}_{23}\text{H}_{19}\text{N}_3\text{O}$; Calcd: C, 78.16; H, 5.42; N, 11.89; Found: C, 78.20; H, 5.36; N, 11.86.

(*E*)-1-(6-(1*H*-Benzo[*d*]imidazol-2-yl)-2-methylpyridin-3-yl)-3-(4-nitrophenyl)prop-2-en-1-one **3e**

^1H -NMR (DMSO- d_6 , 400 MHz) δ 12.85 (^1H , NH, s), 8.35 (^1H , Py-H, d, J = 8.1 Hz), 8.30 (^1H , Py-H, d, J = 8.1 Hz), 8.25 (^1H , ArH, d, J = 8.1 Hz), 8.10 (^2H , ArH, d, J = 8.8 Hz), 7.79–7.58 (^4H , ArH, CH=CH, m), 7.34–7.17 (^3H , ArH, m), 2.76 (^3H , CH_3 , s); ^{13}C -NMR (DMSO- d_6 , 101 MHz) δ 200.2, 157.8, 150.5, 149.8, 138.7, 133.9, 130.5, 123.4, 119.1, 24.5; Anal. for $\text{C}_{22}\text{H}_{16}\text{N}_4\text{O}_3$; Calcd: C, 68.74; H, 4.20; N, 14.58; Found: C, 68.12; H, 4.01; N, 13.98.

(*E*)-1-(6-(1*H*-Benzo[*d*]imidazol-2-yl)-2-methylpyridin-3-yl)-3-(4-chlorophenyl)prop-2-en-1-one **3f**

^1H -NMR (DMSO- d_6 , 400 MHz) δ 12.71 (^1H , NH, s), 8.53 (^1H , Py-H, d, J = 8.1 Hz), 8.37 (^1H , Py-H, d, J = 8.1 Hz), 8.14–8.05 (^2H , ArH, m), 8.02–7.96 (^1H , ArH, m), 7.91 (^2H , ArH, d, J = 8.1 Hz), 7.83 (^1H , ArH, d, J = 6.6 Hz), 7.70 (^2H , ArH, d, J = 7.3 Hz), 7.42 (^1H , ArH, d, J = 4.4 Hz), 7.38 (^1H , ArH, d, J = 4.4 Hz), 2.74 (^3H , CH_3 , s); ^{13}C -NMR (DMSO- d_6 , 101 MHz) δ 193.8, 157.4, 150.6, 149.67, 144.7, 138.4, 136.1, 135.4, 134.4, 133.9, 131.2, 129.9, 128.8, 126.0, 123.2, 119.2, 23.9; Anal. for $\text{C}_{22}\text{H}_{16}\text{ClN}_3\text{O}$; Calcd: C, 70.68; H, 4.31; N, 11.24; Found: C, 71.21; H, 4.13; N, 11.91.

(*E*)-1-(6-(1*H*-Benzo[*d*]imidazol-2-yl)-2-methylpyridin-3-yl)-3-(4-bromophenyl)prop-2-en-1-one **3g**

^1H -NMR (DMSO- d_6 , 400 MHz) δ 13.04 (^1H , NH, s), 8.42 (^1H , Py-H, d, J = 8.1 Hz), 8.27 (^1H , Py-H, d, J = 8.1 Hz), 7.73 (^2H , d, J = 8.1 Hz), 7.64 (^1H , d, J = 8.8 Hz), 7.61–7.55 (^3H , m), 7.41 (^1H , d, J = 5.9 Hz), 7.26 (^3H , m), 2.60 (^3H , CH_3 , s); ^{13}C -NMR (DMSO- d_6 , 101 MHz) δ 193.8, 157.3, 150.5, 149.6, 144.8, 138.4, 136.3, 134.4, 134.2, 132.8, 132.5, 131.8, 131.4, 126.9, 124.9, 122.7, 120.0, 119.0, 112.9, 24.2; Anal. for $\text{C}_{22}\text{H}_{16}\text{BrN}_3\text{O}$; Calcd: C, 63.17; H, 3.86; N, 10.05; Found: C, 63.85; H, 3.74; N, 10.12.

(*E*)-1-(6-(1*H*-Benzo[*d*]imidazol-2-yl)-2-methylpyridin-3-yl)-3-(3-fluorophenyl)prop-2-en-1-one **3h**

^1H -NMR (400 MHz, DMSO- d_6) δ 12.91 (^1H , NH, s), 8.50 (^1H , Py-H, d, J = 8.1 Hz), 8.39 (^1H , Py-H, d, J = 8.1 Hz), 8.27 (^1H , ArH, d, J = 7.3 Hz), 8.00 (^1H , d, J = 8.1 Hz), 7.79 (^2H , d, J = 9.5 Hz), 7.54–7.43 (^3H , m), 7.31 (^2H , d, J = 8.1 Hz), 6.79 (^1H , s), 2.75 (^3H , CH_3 , s); ^{13}C -NMR (DMSO- d_6 , 101 MHz) δ 193.78, 164.9, 159.0, 157.5, 150.6, 150.2, 150.1, 149.7, 144.7, 138.5, 137.4, 136.1, 134.3, 127.5, 126.5, 125.2, 119.1, 112.7, 25.0; Anal. for $\text{C}_{22}\text{H}_{16}\text{FN}_3\text{O}$; Calcd: C, 73.94; H, 4.51; N, 11.76; Found: C, 73.19; H, 4.23; N, 11.44.

(*E*)-1-(6-(1*H*-Benzo[*d*]imidazol-2-yl)-2-methylpyridin-3-yl)-3-(4-fluorophenyl)prop-2-en-1-one **3i**

^1H -NMR (DMSO- d_6 , 400 MHz) δ 13.06 (^1H , NH, s), 8.30 (^1H , Py-H, d, J = 8.1 Hz), 8.26 (^1H , Py-H, d, J = 8.1 Hz), 7.92 (^2H , ArH, dd, J = 8.8, 5.1 Hz), 7.74 (^1H , ArH, d, J = 9.5 Hz), 7.63 (^1H , ArH, d, J = 7.3 Hz), 7.49 (^1H , CH=, d, J = 16.1 Hz), 7.34 (^1H , =CH, d, J = 16.1 Hz), 7.27 (^4H , ArH, m), 2.73 (^3H , CH_3 , s); ^{13}C -NMR (DMSO- d_6 , 101 MHz) δ 193.9, 165.4, 163.0, 157.3, 150.6, 149.6, 145.1, 144.6, 138.3, 135.6, 134.6, 132.5, 131.6, 126.2, 124.0, 122.6, 120.0, 119.1, 116.6, 115.3, 112.0, 24.2; Anal. for $\text{C}_{22}\text{H}_{16}\text{FN}_3\text{O}$; Calcd: C, 73.94; H, 4.51; N, 11.76; Found: C, 73.29; H, 4.31; N, 11.84.

(*E*)-1-(6-(1*H*-Benzo[*d*]imidazol-2-yl)-2-methylpyridin-3-yl)-3-phenylprop-2-en-1-one **3j**

^1H -NMR (DMSO- d_6 , 400 MHz) δ 13.07 (^1H , NH, s), 8.30 (^1H , Py-H, d, J = 8.1 Hz), 8.26 (^1H , Py-H, d, J = 8.1 Hz), 7.86–7.81 (^2H , ArH, m), 7.75 (^1H , ArH, d, J = 8.1 Hz), 7.65–7.59 (^2H , ArH, =CH $^{(\beta)}$, m), 7.52 (^1H , =CH $^{(\alpha)}$, d, J = 16.1 Hz), 7.45 (^2H , ArH, d, J = 5.9 Hz), 7.29–7.21 (^3H , ArH, m), 2.74 (^3H , CH_3 , s); ^{13}C -NMR (DMSO- d_6 , 101 MHz) δ 194.1, 157.3, 150.6, 149.56, 146.4, 144.6, 138.3, 135.6, 134.9, 134.6, 131.6, 129.6, 129.5, 128.8, 126.3, 124.1, 122.7, 120.1, 119.1, 112.9, 24.2; Anal. for $\text{C}_{22}\text{H}_{17}\text{N}_3\text{O}$; Calcd: C, 77.86; H, 5.05; N, 12.38; Found: C, 77.81; H, 5.09; N, 12.42.

2.1.2. Synthesis of Spiro-Oxindole Derivatives (6a–j)

Enones **3a–j** (0.5 mmol), 5-chloro isatin (91 mg, 0.5 mmol), and octahydroindole-2-carboxylic acid (84.62 mg, 0.5 mmol) were dissolved in 20 mL of dry MeOH in a 100 mL round-bottom flask. Then, the reaction mixture was heated for 3 h at 60–65 °C. After the reaction was completed, as monitored with thin-layer chromatography (TLC), the desired spiro-oxindole derivatives **6a–j** was purified by flash column chromatography by using n-hexane/ethyl acetate (4:2).

Spiro-oxindole derivative **6a**

¹H-NMR (DMSO-*d*₆, 400 MHz) δ 12.94 (s, ¹H, NH), 10.12 (s, ¹H, NH), 8.11 (m, ²H, Py-H), 7.73 (d, *J* = 7.3 Hz, ¹H, ArH), 7.56 (d, *J* = 8.1 Hz, ¹H, ArH), 7.54–7.50 (m, ²H, ArH), 7.49 (s, ¹H, ArH), 7.33–7.17 (m, ³H, ArH), 6.89 (dd, *J* = 7.0, 4.8 Hz, ²H, ArH), 6.55 (d, *J* = 8.8 Hz, ¹H, ArH), 5.06 (d, *J* = 11.7 Hz, ¹H, COCH), 4.06–3.91 (m, 1H), 3.84 (t, *J* = 11.0 Hz, ¹H), 3.72 (s, ³H, OCH₃), 3.53–3.37 (m, ¹H, aliphatic-H), 3.15–2.96 (m, ¹H, aliphatic-H), 2.08 (dt, *J* = 11.0, 5.5 Hz, ¹H, aliphatic-H), 2.03–1.90 (m, ¹H, aliphatic-H), 1.85 (s, ³H, CH₃), 1.59–1.41 (m, ³H, aliphatic-H), 1.37–1.22 (m, ²H, aliphatic-H), 0.90–0.66 (m, ³H, aliphatic-H); ¹³C-NMR (DMSO-*d*₆, 101 MHz) δ 198.4, 179.8, 158.6, 157.9, 150.3, 149.8, 144.5, 141.5, 138.8, 135.5, 132.0, 131.8, 130.7, 130.2, 129.2, 128.2, 126.3, 126.1, 124.2, 122.8, 120.0, 118.5, 114.4, 112.9, 111.8, 71.4, 65.8, 57.2, 56.6, 55.6, 51.4, 41.7, 36.7, 28.1, 27.9, 24.9, 24.7, 22.8, 21.6, 19.8, 19.1; Anal. for C₃₉H₃₆ClN₅O₃; Calcd: C, 71.17; H, 5.51; N, 10.64; Found: C, 70.95; H, 4.12; N, 11.24.

Spiro-oxindole derivative **6b**

¹H-NMR (DMSO-*d*₆, 500 MHz) δ 12.88 (s, ¹H, NH), 10.17 (s, ¹H, NH), 8.06 (d, *J* = 8.1 Hz, ¹H, Py-H), 7.71 (d, *J* = 8.1 Hz, ¹H, Py-H), 7.68 (d, *J* = 7.9 Hz, ¹H, ArH), 7.51 (d, *J* = 7.2 Hz, ¹H, ArH), 7.25–7.17 (m, ⁴H, ArH), 6.79 (d, *J* = 16.4 Hz, ²H, ArH), 6.49 (d, *J* = 8.2 Hz, ¹H, ArH), 5.43 (d, *J* = 12.1 Hz, ¹H, COCH), 4.42–4.33 (m, ¹H), 4.21–4.13 (m, ¹H), 3.01 (d, *J* = 4.5 Hz, ¹H, aliphatic-H), 2.68 (s, ³H, CH₃), 2.63 (s, ³H, CH₃), 2.12 (s, ³H, CH₃), 2.08 (q, *J* = 5.7 Hz, ¹H, aliphatic-H), 1.86 (s, ³H, CH₃), 1.76 (dd, *J* = 15.3, 11.8 Hz, ¹H, aliphatic-H), 1.52 (dd, *J* = 10.8, 5.9 Hz, ²H, aliphatic-H), 1.48–1.40 (m, ²H, aliphatic-H), 1.29–1.21 (m, ²H, aliphatic-H), 0.95–0.89 (m, ¹H, aliphatic-H), 0.85–0.80 (m, ¹H, aliphatic-H), 0.74 (d, *J* = 12.7 Hz, ¹H, aliphatic-H); ¹³C-NMR (DMSO-*d*₆, 126 MHz) δ 199.0, 179.9, 161.5, 158.0, 150.1, 149.8, 144.4, 141.6, 138.6, 138.4, 135.9, 135.7, 135.5, 131.8, 131.7, 130.2, 130.0, 129.8, 127.6, 126.5, 126.1, 124.2, 123.5, 122.8, 120.0, 118.6, 112.9, 112.0, 71.9, 67.8, 64.6, 57.3, 47.4, 41.8, 38.1, 28.3, 27.6, 27.3, 24.7, 23.0, 22.3, 21.7, 20.8, 19.9; Anal. for C₄₁H₄₀ClN₅O₂; Calcd: C, 73.47; H, 6.02; N, 10.45; Found: C, 73.42; H, 6.07; N, 10.40.

Spiro-oxindole derivative **6c**

¹H-NMR (DMSO-*d*₆, 500 MHz) δ 12.90 (s, ¹H, NH), 10.07 (s, ¹H, NH), 8.09–8.04 (m, ²H, Py-H), 7.65 (ddd, *J* = 29.4, 5.9, 3.3 Hz, ¹H, ArH), 7.53 (s, ¹H, ArH), 7.48 (d, *J* = 2.3 Hz, ¹H, ArH), 7.42 (d, *J* = 8.2 Hz, ²H, ArH), 7.24 (dd, *J* = 8.3, 2.2 Hz, ¹H, ArH), 7.23–7.17 (m, ²H, ArH), 7.09 (d, *J* = 8.1 Hz, ²H, ArH), 6.51 (d, *J* = 8.2 Hz, ¹H, ArH), 5.05 (d, *J* = 11.8 Hz, ¹H, COCH), 3.95–3.89 (m, ¹H), 3.85–3.79 (m, ¹H), 3.02 (d, *J* = 4.3 Hz, ¹H, aliphatic-H), 2.22 (s, ³H, CH₃), 2.03 (ddd, *J* = 9.3, 5.6, 3.6 Hz, ¹H, aliphatic-H), 1.95–1.90 (m, ¹H, aliphatic-H), 1.80 (s, ³H, CH₃), 1.49–1.44 (m, ²H, aliphatic-H), 1.41–1.37 (m, ¹H, aliphatic-H), 1.25 (dd, *J* = 9.6, 3.6 Hz, ²H, aliphatic-H), 0.96–0.89 (m, ¹H, aliphatic-H), 0.87–0.77 (m, ²H, aliphatic-H), 0.67 (d, *J* = 10.5 Hz, ¹H, aliphatic-H); ¹³C-NMR (DMSO-*d*₆, 126 MHz) δ 198.3, 179.7, 172.6, 157.8, 150.2, 149.8, 141.5, 138.8, 136.9, 136.2, 132.0, 130.2, 129.6, 128.0, 126.3, 126.1, 118.5, 111.8, 71.4, 71.3, 65.6, 57.1, 51.7, 41.8, 36.6, 29.5, 28.1, 27.8, 24.9, 22.7, 21.6, 21.2, 19.7, 14.5; Anal. for C₃₉H₃₆ClN₅O₂; Calcd: C, 72.94; H, 5.65; N, 10.91; Found: C, 72.22; H, 5.14; N, 11.10.

Spiro-oxindole derivative **6d**

¹H-NMR (DMSO-*d*₆, 500 MHz) δ 12.90 (s, ¹H, NH), 10.07 (s, ¹H, NH), 8.10 (d, *J* = 8.1 Hz, ¹H, PyH), 8.06 (d, *J* = 8.1 Hz, ¹H, PyH), 7.68 (d, *J* = 8.0 Hz, ¹H, ArH), 7.52 (d, *J* = 7.6 Hz, ¹H, ArH), 7.38 (t, *J* = 2.0 Hz, ¹H, ArH), 7.33 (d, *J* = 7.9 Hz, ¹H, ArH), 7.24 (dd, *J* = 8.4, 2.2 Hz, ²H, ArH), 7.18 (m, ³H, ArH), 6.98 (d, *J* = 8.8 Hz, ¹H, ArH), 6.50 (d, *J* = 8.2 Hz, ¹H,

ArH), 5.07 (d, $J = 12.0$ Hz, ^1H , COCH), 3.97–3.92 (m, ^1H), 3.84–3.80 (m, ^1H), 3.02 (d, $J = 4.3$ Hz, ^1H , aliphatic-H), 2.28 (s, ^3H , CH_3), 2.07–2.04 (m, ^1H , aliphatic-H), 1.93 (td, $J = 5.9, 5.1, 2.2$ Hz, ^1H , aliphatic-H), 1.80 (s, ^3H , CH_3), 1.47 (dd, $J = 11.7, 6.5$ Hz, ^2H , aliphatic-H), 1.39 (d, $J = 5.1$ Hz, ^1H , aliphatic-H), 1.27–1.21 (m, ^3H , aliphatic-H), 0.93 (dt, $J = 13.0, 3.2$ Hz, ^1H , aliphatic-H), 0.84–0.81 (m, ^1H , aliphatic-H), 0.68 (d, $J = 10.8$ Hz, ^1H , aliphatic-H); ^{13}C -NMR (DMSO- d_6 , 126 MHz) δ 198.4, 179.7, 157.9, 150.2, 149.8, 144.5, 141.4, 139.9, 138.9, 138.1, 135.5, 131.9, 130.2, 128.8, 128.8, 128.0, 127.8, 126.3, 126.1, 125.2, 122.75, 120.0, 118.4, 112.9, 111.8, 71.33, 65.7, 57.2, 52.1, 41.8, 36., 34.02, 29.5, 28.1, 27.8, 24.9, 22.7, 21.6, 19.7, 18.0; Anal. for $\text{C}_{39}\text{H}_{36}\text{ClN}_5\text{O}_2$; Calcd: C, 72.94; H, 5.65; N, 10.91; Found: C, 72.92; H, 5.61; N, 10.89.

Spiro-oxindole derivative 6e

^1H -NMR (DMSO- d_6 , 400 MHz) δ 12.96 (s, ^1H , NH), 10.16 (s, ^1H , NH), 8.24 (d, $J = 8.1$ Hz, ^1H , Py-H), 8.20 (d, $J = 8.8$ Hz, ^2H , ArH), 8.12 (d, $J = 8.1$ Hz, ^1H , Py-H), 7.96 (d, $J = 8.1$ Hz, ^2H , ArH), 7.73 (d, $J = 7.3$ Hz, ^1H , ArH), 7.65 (s, ^1H , ArH), 7.57 (d, $J = 7.3$ Hz, ^1H , ArH), 7.26 (m, ^3H , ArH), 6.55 (d, $J = 8.1$ Hz, ^1H , ArH), 5.26 (d, $J = 11.7$ Hz, ^1H , COCH), 4.14 (t, $J = 11.0$ Hz, ^1H), 4.02 (d, $J = 7.3$ Hz, ^1H), 3.07 (d, $J = 3.7$ Hz, ^1H , aliphatic-H), 2.12–2.01 (m, ^2H , aliphatic-H), 1.84 (s, ^3H , CH_3), 1.48 (dd, $J = 11.4, 6.2$ Hz, ^2H , aliphatic-H), 1.42 (dd, $J = 8.4, 4.8$ Hz, ^1H , aliphatic-H), 1.33–1.23 (m, ^2H , aliphatic-H), 1.10–1.04 (m, ^1H , aliphatic-H), 1.01–0.93 (m, ^1H , aliphatic-H), 0.86 (d, $J = 12.5$ Hz, ^1H , aliphatic-H), 0.72 (d, $J = 11.7$ Hz, ^1H , aliphatic-H); ^{13}C -NMR (DMSO- d_6 , 101 MHz) δ 198.3, 179.5, 157.9, 150.2, 149.9, 148.4, 147.0, 144.5, 141.5, 138.8, 135.5, 131.7, 129.8, 129.8, 127.7, 126.3, 126.1, 124.1, 124.0, 123.2, 120.6, 118.0, 113.0, 111.9, 71.3, 57.2, 51.9, 46.0, 41.7, 38.7, 35.9, 28.0, 24.9, 19.8; Anal. for $\text{C}_{38}\text{H}_{33}\text{ClN}_6\text{O}_4$; Calcd: C, 67.80; H, 4.94; N, 12.48; Found: C, 68.10; H, 4.21; N, 12.16.

Spiro-oxindole derivative 6f

^1H -NMR (DMSO- d_6 , 400 MHz) δ 12.94 (s, ^1H , NH), 10.12 (s, ^1H , NH), 8.17 (d, $J = 8.1$ Hz, ^1H , Py-H), 8.10 (d, $J = 8.1$ Hz, ^1H , Py-H), 7.73 (d, $J = 7.3$ Hz, ^1H , ArH), 7.65 (d, $J = 8.1$ Hz, ^2H , ArH), 7.58–7.54 (m, ^3H , ArH), 7.50 (s, ^1H , ArH), 7.28 (d, $J = 8.1$ Hz, ^3H , ArH), 6.54 (d, $J = 8.1$ Hz, ^1H , ArH), 5.12 (d, $J = 11.7$ Hz, ^1H , COCH), 4.01–3.95 (m, ^2H), 3.06 (d, $J = 3.7$ Hz, ^1H , aliphatic-H), 2.11–2.08 (m, ^1H , aliphatic-H), 1.98 (d, $J = 9.5$ Hz, ^1H , aliphatic-H), 1.83 (s, ^3H , CH_3), 1.51 (d, $J = 6.6$ Hz, ^2H , aliphatic-H), 1.27 (d, $J = 9.5$ Hz, ^2H , aliphatic-H), 1.05 (d, $J = 5.9$ Hz, ^1H , aliphatic-H), 0.97 (d, $J = 13.2$ Hz, ^2H , aliphatic-H), 0.84 (d, $J = 3.7$ Hz, ^1H , aliphatic-H), 0.71 (d, $J = 12.5$ Hz, ^1H , aliphatic-H); Anal. for $\text{C}_{38}\text{H}_{33}\text{Cl}_2\text{N}_5\text{O}_2$; Calcd: C, 68.88; H, 5.02; N, 10.57; Found: C, 68.12; H, 4.93; N, 11.05.

Spiro-oxindole derivative 6g

^1H -NMR (CDCl_3 , 500 MHz) δ 8.82 (s, ^1H , NH), 8.18 (d, $J = 7.3$ Hz, ^1H), 7.76 (s, ^1H , NH), 7.58 (s, ^2H), 7.46 (d, $J = 8.4$ Hz, ^2H), 7.40 (d, $J = 8.4$ Hz, ^2H), 7.31 (d, $J = 8.6$ Hz, ^1H), 7.26 (dd, $J = 6.1, 2.9$ Hz, ^2H), 7.22 (d, $J = 2.1$ Hz, ^1H), 7.19 (d, $J = 8.9$ Hz, ^1H), 6.58 (d, $J = 8.6$ Hz, ^1H), 4.96 (d, $J = 10.9$ Hz, ^1H , COCH), 4.32–4.23 (m, ^1H), 3.69 (t, $J = 10.7$ Hz, ^1H), 3.08 (d, $J = 4.0$ Hz, ^1H), 1.95 (s, ^3H , CH_3), 1.73 (td, $J = 12.0, 6.1$ Hz, ^2H), 1.55 (d, $J = 7.2$ Hz, ^1H), 1.53 (d, $J = 6.9$ Hz, ^1H), 1.42–1.35 (m, ^2H), 1.27 (d, $J = 4.9$ Hz, ^1H), 1.01 (dd, $J = 29.6, 14.0$ Hz, ^2H), 0.93–0.89 (m, ^1H), 0.80 (d, $J = 15.9$ Hz, ^1H); ^{13}C -NMR (CDCl_3 , 126 MHz) δ 197.4, 180.9, 159.3, 139.5, 138.1, 132.0, 130.0, 129.7, 127.9, 127.7, 125.9, 124.2, 121.1, 118.4, 111.7, 71.73, 71.01, 66.99, 57.6, 52.8, 41.9, 37.7, 31.0, 29.8, 29.5, 28.3, 27.64, 24.7, 23.0, 19.7; Anal. for $\text{C}_{38}\text{H}_{33}\text{BrClN}_5\text{O}_2$; Calcd: C, 64.55; H, 4.70; N, 9.90; Found: C, 64.78; H, 4.80; N, 10.15.

Spiro-oxindole derivative 6h

^1H -NMR (CDCl_3 , 500 MHz) δ 8.91 (s, ^1H , NH), 8.11 (d, $J = 7.7$ Hz, ^1H), 7.73 (s, ^1H , NH), 7.59 (d, $J = 14.0$ Hz, ^2H), 7.32–7.27 (m, ^3H), 7.27 (d, $J = 4.7$ Hz, ^1H), 7.21 (d, $J = 2.3$ Hz, ^2H), 7.16 (dd, $J = 8.2, 2.2$ Hz, ^2H), 6.93–6.90 (m, ^1H), 6.54 (d, $J = 8.7$ Hz, ^1H), 4.96 (d, $J = 11.6$ Hz, ^1H , COCH), 4.31–4.25 (m, ^1H), 4.23–4.15 (m, ^1H), 3.08 (d, $J = 4.6$ Hz, ^1H), 1.96 (s, ^3H , CH_3), 1.79–1.72 (m, ^3H), 1.66–1.61 (m, ^2H), 1.57 (d, $J = 3.0$ Hz, ^1H), 1.09–1.05 (m, ^1H), 1.02–0.97 (m, ^1H), 0.93 (d, $J = 7.2$ Hz, ^2H), 0.84 (d, $J = 3.0$ Hz, ^1H); ^{13}C -NMR (CDCl_3 , 126 MHz) δ 197.0, 183.4, 161.1, 149.2, 144.4, 139.0, 129.9, 127.2, 125.7, 123.7, 119.0, 115.4, 111.1, 72.0, 71.8, 71.0,

57.6, 46.4, 41.9, 41.0, 37.7, 32.2, 29.3, 28.5, 28.3, 27.8, 27.6, 26.5, 24.4, 24.0, 23.1, 20.9, 19.8, 17.7, 17.6, 17.38, 14.73; Anal. for $C_{38}H_{33}ClFN_5O_2$; Calcd: C, 70.64; H, 5.15; N, 10.84; Found: C, 71.02; H, 4.93; N, 11.14.

Spiro-oxindole derivative **6i**

1H NMR (DMSO- d_6 , 500 MHz) δ 12.90 (s, 1H , NH), 10.07 (s, 1H , NH), 8.13 (d, J = 8.2 Hz, 1H , Py-H), 8.06 (d, J = 8.2 Hz, 1H , Py-H), 7.68 (d, J = 7.8 Hz, 1H , ArH), 7.61 (dd, J = 9.0, 5.5 Hz, 2H , ArH), 7.52 (d, J = 9.1 Hz, 2H , ArH), 7.26–7.22 (m, 2H , ArH), 7.18 (td, J = 7.6, 7.2, 1.5 Hz, 1H , ArH), 7.13–7.08 (m, 2H , ArH), 6.50 (d, J = 8.2 Hz, 1H , ArH), 5.08 (d, J = 11.8 Hz, 1H , COCH), 3.94–3.86 (m, 2H), 3.01 (s, 1H), 2.05 (q, J = 4.7 Hz, 1H), 1.96–1.92 (m, 1H), 1.79 (s, 3H , CH_3), 1.48–1.43 (m, 2H), 1.29–1.17 (m, 4H), 1.13 (t, J = 7.1 Hz, 1H), 1.06–1.02 (m, 1H), 0.67 (d, J = 13.0 Hz, 1H); ^{13}C -NMR (DMSO- d_6 , 126 MHz) δ 198.4, 179.6, 162.6, 160.7, 157.9, 150.2, 149.8, 144.4, 141.5, 138.9, 136.1, 135.5, 131.9, 130.2, 130.1, 130.0, 128.0, 126.2, 126.1, 124.1, 122.8, 120.0, 118.4, 115.7, 115.5, 112.9, 111.8, 71.3, 71.3, 65.6, 57.1, 51.2, 41.8, 36.3, 31.5, 28.1, 27.8, 24.9, 22.7, 22.6, 19.7, 14.6, 14.5; Anal. for $C_{38}H_{33}ClFN_5O_2$; Calcd: C, 70.64; H, 5.15; N, 10.84; Found: C, 70.60; H, 5.11; N, 10.89.

Spiro-oxindole derivative **6j**

1H -NMR (DMSO- d_6 , 400 MHz) δ 13.00 (s, 1H , NH), 10.18 (s, 1H , NH), 8.17 (d, J = 8.1 Hz, 1H , Py-H), 8.14 (d, J = 8.1 Hz, 1H , Py-H), 7.74 (d, J = 8.1 Hz, 1H , ArH), 7.63–7.54 (m, 4H , ArH), 7.39–7.17 (m, 6H , ArH), 6.57 (d, J = 8.1 Hz, 1H , ArH), 5.16 (d, J = 11.7 Hz, 1H , COCH), 4.06–3.97 (m, 1H), 3.92 (t, J = 10.6 Hz, 1H), 3.08 (d, J = 3.7 Hz, 1H), 2.06 (dt, J = 11.0, 5.9 Hz, 1H), 1.97 (q, J = 6.6, 5.9 Hz, 1H), 1.87 (s, 3H , CH_3), 1.55–1.39 (m, 3H), 1.38–1.24 (m, 2H), 1.10–1.02 (m, 1H), 0.91 (dt, J = 38.8, 13.9 Hz, 2H), 0.73 (d, J = 11.7 Hz, 1H); ^{13}C -NMR (DMSO- d_6 , 101 MHz) δ 198.4, 179.8, 158.0, 150.3, 149.9, 144.5, 141.5, 140.0, 138.9, 135.5, 132.0, 130.2, 129.0, 128.2, 128.0, 127.2, 126.3, 126.2, 124.2, 122., 120.1, 118.5, 112.9, 111.9, 71.5, 71.4, 65.7, 57.2, 52.2, 41.8, 36.7, 28.1, 27.8, 25.0, 22.8, 19.8; Anal. for $C_{38}H_{34}ClN_5O_2$; Calcd: C, 72.66; H, 5.46; N, 11.15; Found: C, 72.57; H, 5.42; N, 11.19.

2.2. Computational Protocol

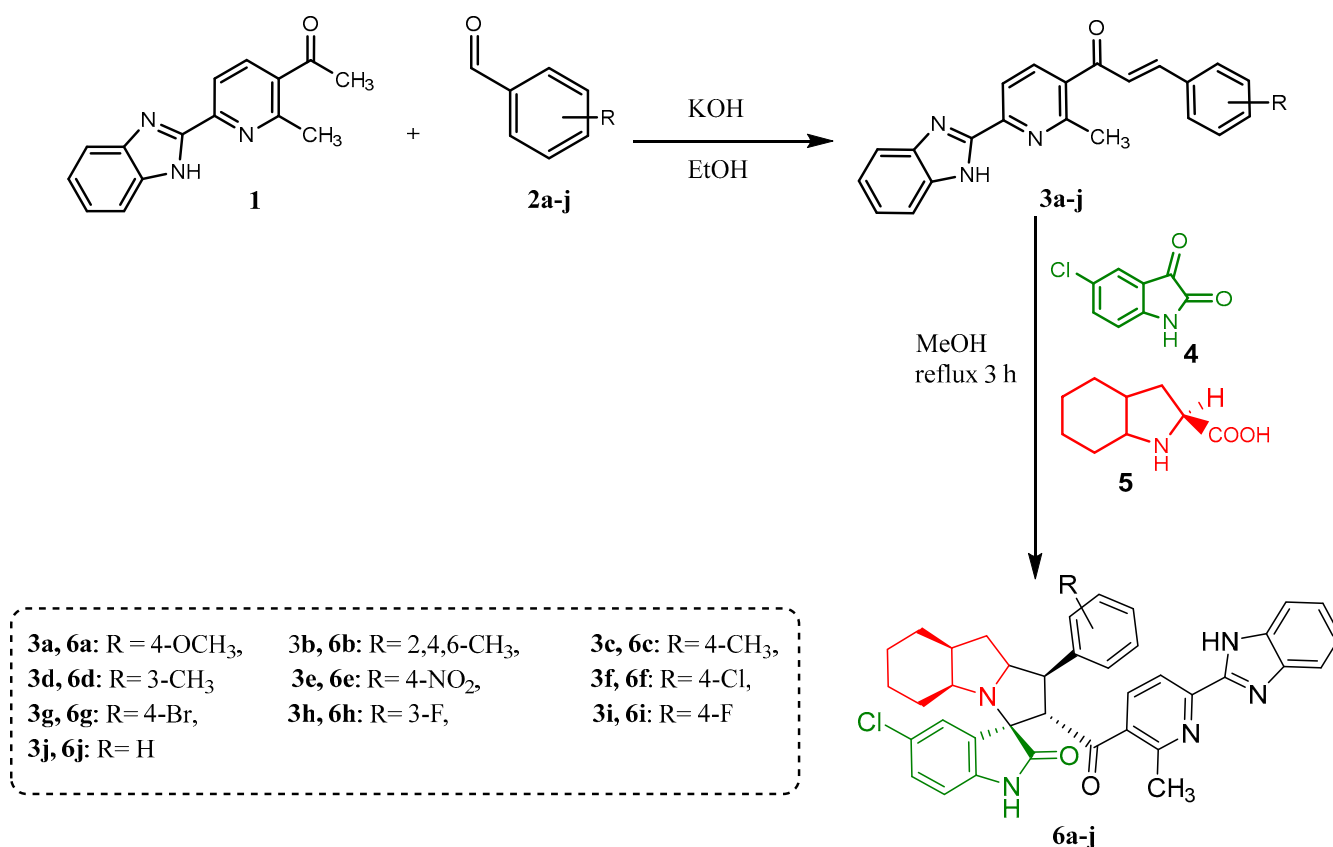
“The ω B97X-D [43] functional, together with the standard 6-311G (d,p) [44] basis set, was used throughout this MEDT study. Solvent effects of methanol were taken into account by full optimization of the gas-phase structures at the same computational level using the polarizable continuum model (PCM) [45,46] in the framework of the self-consistent reaction field (SCRF) [47–49]. The global electron density transfer (GEDT) [50] values were computed using the equation $GEDT(f) = \sum q_f$, where q is the natural charges [51,52] of the atoms belonging to one of the two frameworks (f) at the TS geometries. Global and local Conceptual DFT (CDFT) indices [53,54] were calculated using the equations given in reference [54]. The Gaussian 16 suite of programs was used to perform the calculations [55]. Molecular geometries were visualized using the GaussView program” [56].

3. Results and Discussion

3.1. Experimental Characterization

A variety of chalcones were prepared using acetyl derivative **1** previously reported by our research group [57] followed by the [3+2] cycloaddition reactions to obtain the desired spiro-compounds **6a–j**. The general synthetic strategy for the formation of the desired compounds is shown in Scheme 1. Chalcones **3a–j** were synthesized from 1-(6-(1*H*-benzo[d]imidazole-2-yl)-2-methylpyridin-3-yl)ethan-1-one **1**. This ketone was then condensed with aryl aldehyde derivatives (**2a–j**) using the Claisen–Schmidt reaction. The neutralization of the reaction mixture with dilute acetic acid followed by recrystallization gave compounds **3a–j** with yields ranging between 65 and 95%. The structures of the final products were confirmed on the basis of spectral studies. IR, 1H -NMR, ^{13}C -NMR, and an elemental analysis were used to characterize all the newly synthesized compounds. The IR spectrum of (*E*)-1-(6-(1*H*-benzo[d]imidazole-2-yl)-2-methylpyridin-3-yl)-3-(4-methoxyphenyl)prop-2-en-1-one (**3a**) showed a strong absorption band at

3428 cm^{-1} corresponding to benzimidazole NH. A sharp absorption at 1592 cm^{-1} corresponds to carbonyl stretching. The ^1H -NMR spectrum showed a singlet peak at δ 13.03 ppm, which was assigned to benzimidazole NH. The two doublet peaks at δ 8.28 and 8.20 ppm correspond to pyridine CH/CH. The doublet peaks for α,β -unsaturated protons appear at δ 7.56 (CH_β)/7.35 (CH_α) ppm, and the singlet peak at δ 3.81 ppm corresponds to the protons of the methoxy group (OCH_3). The ^{13}C -NMR spectrum showed a peak at δ 194.10 ppm, which was assigned to the carbonyl group ($\text{C}=\text{O}$), while all other peaks for carbons are observed in their expected region, which supported its structure.



Scheme 1. Synthesis of chalcones (**3a–j**) and spiro-compounds (**6a–j**).

The synthesis of spiro-derivatives (**6a–j**) from the three-component reaction was achieved via a 32CA protocol (Scheme 1). The reaction of enones (**3a–j**) with 5-chloro isatin, and octahydroindole-2-carboxylic acid, was carried out at 60 $^\circ\text{C}$ in MeOH for 3 h to produce the target compounds in good to moderate yields. The structure of the synthesized spiro-compounds was confirmed through spectroscopic analyses. For instance, the IR spectrum for (**3a**) showed specific signals for the functional groups such as 3436 cm^{-1} for NH and 1729 cm^{-1} and 1690 cm^{-1} for the two carbonyl groups ($\text{C}=\text{O}$). The ^1H -NMR data for compound (**3a**) confirm its structure; the peaks at δ 12.94 and 10.12 ppm refer to NH in benzimidazole and isatin, respectively, in the region of 8.11 until 6.55 ppm related to aromatic protons; the one at δ 3.72 ppm belongs to the methoxy group, while those from 5.06 to 0.66 ppm indicate the aliphatic protons. The ^{13}C -NMR spectrum also supports the proposed structure. The two peaks at δ 198.41 and 179.79 ppm were assigned to carbonyl groups ($\text{C}=\text{O}$), and a spiro-carbon peak appears at δ 71.38 ppm, while all other peaks for carbons are observed in their expected region.

3.2. MEDT Study of the 32CA Reaction between AY 7 and Ethylene 3j

In order to understand the experimental outcomes, the 32CA reaction between AY 7 and ethylene **3j** is theoretically studied in this section within the MEDT [41].

3.2.1. Analysis of Conceptual DFT (CDFT) Reactivity Indicators

The reactivity indicators defined within the CDFT [53,54] have demonstrated to be useful tools to predict and understand reactivity in polar reactions [58]. The global reactivity indices, namely, the electronic chemical potential μ , chemical hardness η , electrophilicity ω , and nucleophilicity N , for AY 7 and ethylene 3j are gathered in Table 1.

Table 1. ω B97X-D/6-311G (d,p) electronic chemical potential μ , chemical hardness η , electrophilicity ω , and nucleophilicity N indices, in eV, of AY 7 and ethylene 3j.

	μ	η	ω	N
Ethylene 3j	−4.41	7.11	1.36	3.43
AY 7	−3.15	6.96	0.71	4.77

The electronic chemical potential μ [59] of AY 7, $\mu = -3.15$ eV, is higher than that of ethylene 3j, $\mu = -4.41$ eV, indicating that in a polar 32CA reaction, the GEDT [50] will take place from AY 7, acting as a nucleophile, to ethylene 3j, acting as an electrophile. Thus, the studied 32CA reaction is classified as of a forward electron density flux (FEDF) [60].

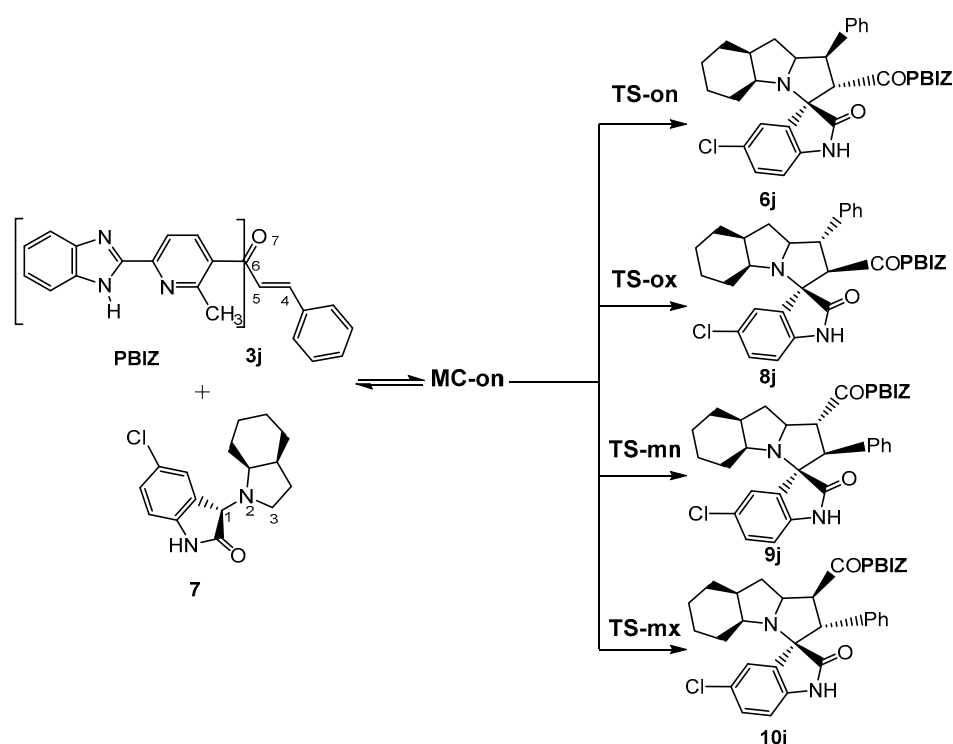
AY 7 has an electrophilicity ω index [61] of 0.71 eV, which allows for classifying it as a moderate electrophile based on the electrophilicity scale [54,62], and a nucleophilicity N index [63] of 4.77 eV, which allows for categorizing it as a strong nucleophile based on the nucleophilicity scale [54,62]. The very strong nucleophilic character of AY 7, higher than 4.0 eV, indicates that it is a supernucleophile [58,62]. On the other hand, ethylene 3j has electrophilicity ω and nucleophilicity N indices of 1.36 and 3.43 eV, respectively, thus being classified as a strong electrophile and as a moderate nucleophile.

The supernucleophilic character of AY 7 together with the strong electrophilic character of ethylene 3j suggest that the present 32CA reaction of FEDF will be highly polar [58], which is known to enhance reaction rates.

3.2.2. Study of the Competitive Reaction Paths

Owing to the non-symmetry of the reagents, the 32CA reaction between AY 7 and ethylene 3j can take place along two *ortho/meta*-regioisomeric reaction paths and two *endo/exo*-stereoisomeric paths (see Scheme 2). Note that as the octahydroindole substituent of AY 7 hinders one of its two diastereoisomeric faces, only the less hindered approach has been studied. The Gibbs free energy profiles corresponding to the four competitive reaction paths are represented in Figure 1, while full thermodynamic data are given in Table S1 in the Supplementary Material.

The stationary points located in the four reaction paths show that this 32CA reaction follows a one-step mechanism. For each channel, a molecular complex (MC) strongly stabilized by weak intermolecular interactions between the two reagents was found. Given the thermodynamic equilibrium between them, only the most stable one, **MC-on**, was considered the energy reference to obtain relative energies. Formation of this MC is exergonic by 5.3 kcal·mol^{−1} (see Figure 2). Considering the presence of **MC-on**, the activation Gibbs free energies of the selected isomeric paths range between 15.0 (**TS-on**) and 19.4 (**TS-mx**) kcal·mol^{−1}, while reaction Gibbs free energies are found between −17.8 (**10j**) and −23.9 (**6j**) kcal·mol^{−1}. The high exergonic characteristic of the reaction indicates that it is irreversible under the experimental conditions and, therefore, the product of a kinetic control will be obtained. In this sense, the Eyring–Polanyi kinetics equation [64] yields a product percentage relation of 97 (**6j**):0.7 (**8j**):2.2 (**9j**):0.1 (**10j**), indicating that the reaction is completely *ortho/endo*-selective via **TS-on**, leading to **6j** exclusively. These results are fully consistent with the experimental data.



Scheme 2. The reaction of AY 7 with ethylene derivative 3j by cycloaddition reaction (32CA); A competitive reaction paths.

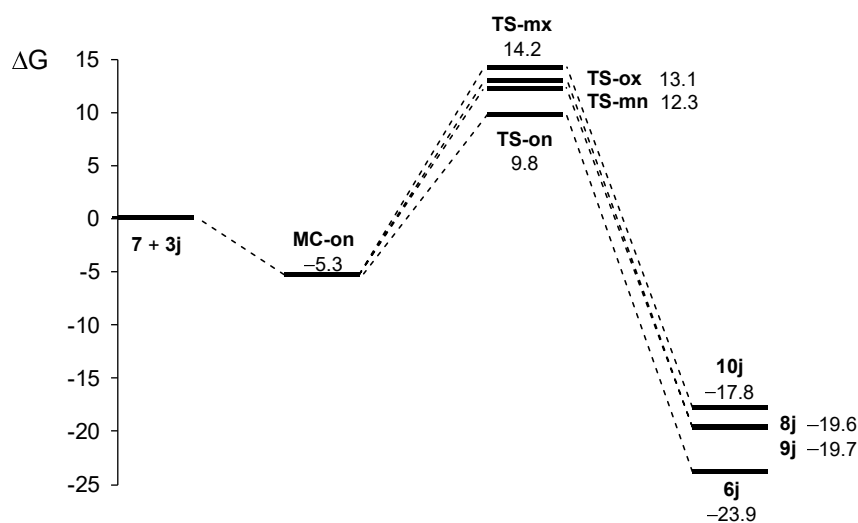


Figure 1. ω B97X-D/6-311G (d,p) Gibbs free energy profile, in kcal·mol⁻¹, for the 32CA reaction of AY 7 with ethylene 3j in methanol at 60 °C.

The optimized geometries of the four TSs in methanol are displayed in Figure 2. The C3(1)–C4 and C1(3)–C5 distances at the four TSs indicate that, except for the most unfavorable **TS-mx**, the other three TSs correspond to asynchronous C–C single bond formation processes in which the shorter C–C distance involves the most electrophilic β -conjugated C4 carbon of ethylene 3j. The most favorable **TS-on**, with C3–C4 and C1–C5 distances of 2.068 and 2.731 Å, respectively, is the most asynchronous one. An analysis of the intrinsic reaction coordinate (IRC) path [65] from the highly asynchronous **TS-on** towards **CA-on** indicates that the formation of the second C1–C5 single bond begins when the first C3–C4 single bond is completely formed (see Figure S1 in Supplementary Material). Consequently, the present 32CA reaction takes place through a non-concerted *two-stage one-step* mechanism [66].

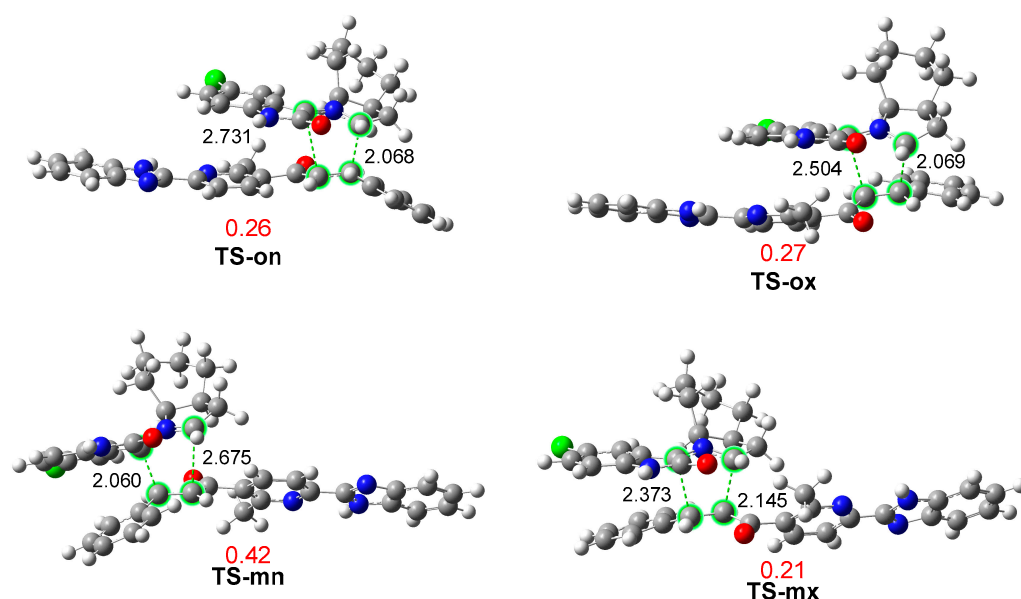


Figure 2. ω B97X-D/6-311G (d,p) optimized geometries in methanol of the TSs involved in the 32CA reaction of AY 7 with ethylene 3j. Distances are expressed in angstroms, Å, while GEDT values, in red, are given in average number of electrons, e.

Finally, an analysis of GEDT [50] at the most favorable **TS-on** allows quantifying the polar characteristic of this 32CA reaction. GEDT values lower than 0.05 e correspond to non-polar processes, while values higher than 0.20 e characterize polar processes. The GEDT values at the four TSs are given in Figure 2. The GEDT at **TS-on** is 0.26 e. This high value, which is a consequence of the supernucleophilic character of AY 7 and the strong electrophilic character of ethylene 3j (see Table 1), corroborates the highly polar character of this 32CA reaction, which accounts for its low activation Gibbs free energy of $15.0 \text{ kcal}\cdot\text{mol}^{-1}$ via **TS-on**. The direction of the flux of the electron density, from AY 7 to ethylene 3j, consolidates the classification of this 32CA reaction as FEDF [60], as predicted with the analysis of the CDFT indicators.

4. Conclusions

A new series of spirooxindoles based on benzimidazole with a pyridine spacer was synthesized in a high yield via a 32CA reaction approach using a wide range of reagents with varying substitutions. The desired compounds were obtained with full regio- and stereoselectivity, as confirmed by the Molecular Electronic Density Theory (MEDT) study of the 32CA reaction, with reagents containing the simplest substitution ($R = H$) as a case study reference.

The activation Gibbs free energy of the reaction via the most favorable **TS-on** is $15.0 \text{ kcal}\cdot\text{mol}^{-1}$ —the reaction being strongly exergonic with $23.9 \text{ kcal}\cdot\text{mol}^{-1}$. The MEDT study accounts for the total *ortho/endo*-selectivity, as **TS-on** is 3.3 and $2.5 \text{ kcal}\cdot\text{mol}^{-1}$ lower in energy than the corresponding *exo*- and *meta*-TSs, respectively. No diastereoisomer of the final products is detected, due to the presence of the octahydroindole substituent at AY 7, which hinders one of its two diastereoisomeric faces. The low energy barrier of the wide range of reactions reported herein is the result of the supernucleophilic character of the reactive AY 7 generated in situ and the strong electrophilic character of the α,β -unsaturated carbonyl compounds, which render these 32CA reactions of FEDF highly polar. This favors bond formation through a non-concerted *two-stage one-step* mechanism in which the first single bond formation involves the hexahydroindole carbon of AY 7 and the β -conjugated carbon of ethylene derivative 3j.

Given the well-known pharmacological applications of spirocyclic compounds, the new products reported herein could be useful for drug discovery application, which will be considered in the near future by our research group.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/cryst13071085/s1>, IUPAC name for the spiro-oxindole derivatives; Table S1: Full thermodynamic data. Figure S1: IRC of the most favorable *endo/exo*-reaction path via **TS-on**. Cartesian coordinates, electronic energies, and imaginary frequencies of the stationary points involved in the 32CA reaction of AY 7 with ethylene derivative 3j.

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