Research Article

Synthesis of New (*E*)-2-(1*H*-Indole-3-ylcarbonyl)-3-heteroaryl-acrylonitriles via Microwave-Assisted Knoevenagel Condensation

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Given the broad spectrum of biological uses of heteroaryl-acrylonitrile derivatives, it is necessary to find simple methods to synthesize and diversify this family of compounds. We report a stereoselective synthesis of a series of new (*E*)-2-(1*H*-indole-3-ylcarbonyl)-3-heteroaryl-acrylonitriles (**3a–3i**) obtained from 3-(cyanoacetyl)indole and heteroaryl-aldehydes under microwave-assisted Knoevenagel reaction at 300 W of potency and 100°C. The desired derivatives (**3a–3i**) were obtained with variable yields (30–94%) and time reactions (8–90 min). All the heteroaryl-acrylonitriles were characterized by physicoanalytical techniques such IR, ¹H, ¹³C NMR, and electrospray mass spectrometry.

1. Introduction

Knoevenagel condensation reaction has been widely used for the formation of new olefinic scaffolds [1]. Since the first report of Knoevenagel [2], methylene active compound has been one of the most useful synthetic methods to prepare α , β -unsaturated systems [3–6] like alkenes with structural diversity and 3-aryl-2-heteroaryl-acrylonitriles [7–12]. The latter are known to have interesting biological properties, including antibacterial and cytotoxic agents [13], compounds with antifungal and antitumor activity [11], antitubercular activity [14], antioxidant compounds [15], tubulin inhibitors [16], and inhibitors of kinase-3 [JNK-3] [17], as well as fluorescent probes for the detection of intracellular thiols [18], DNA detection [19] and chemosensory for detecting cations [20], and others [21–24].

Recent studies from Parveen et al. [25] and our laboratory [12] show evidence about the applications of heteroaryl-acrylonitriles as a new generation of acetylcholinesterase inhibitors (AChEIs). However, the design, facile, and eco-friendly synthesis of a wide library of new acrylonitrile derivatives coupled with a variety of heterocycles scaffolds

could help to elucidate the main molecular features that contribute to the bioactivity of this family of compounds as AChEIs.

For the other hand, heterocyclic scaffolds like quinoline, isoxazole, pyrazole, imidazole, pyridine, pyrimidine, and indole moieties, among others, have special interest within the scope of medicinal chemistry due their versatile reactivity to design synthetic hybrids with potential biological activities [26–35]. Indeed, indole derivatives have been one of the scaffolds more studied to date in the chemistry of heterocyclic compounds, especially, due to their potent pharmacological properties as natural derivatives [36]. Indole nucleus are found in terrestrial plants [37, 38], marine organism [36, 39, 40], and fungi [39] which makes them have a wide range of biological properties, such as antimalarial [41], analgesics [42], nonnucleoside inhibitors of hepatitis C virus [43], inhibitors of human cytosolic phospholipase A₂ α [34], anti-fungal, and antimycobacterial [44], anticarcinogenic [45–47], antitubulin agents [48], protein kinases inhibitors [49, 50], antioxidants, and scavengers [51, 52]. Whereby the indolic derivatives are privileged structures to design and synthesize new library of heteroaryl-acrylonitrile compounds, in this

sense, the 3-(cyanoacetyl)indole is a methylene active compound that has been reported as a versatile building block to prepare a wide variety of functionalized alkenes via Knoevenagel reaction [7, 8, 53].

Among the dynamic and emerging synthetic tools widely used in organic synthesis (OS) and medicinal chemistry, microwave irradiation (MWI) [54] reactions are considered as efficient, fast, and green chemistry procedures [55–59]. This technique has several advantages over classical step-by-step synthetic routes (linear or convergent) not only from atom-economy and eco-friendly perspective but also by the operational simplicity of these procedures that offer a variety of carbon-hetero atom bonds formation [60, 61]. Furthermore, this technique provides highest speed reaction and rapid increase in reaction temperature; it is specific and does not require contact between the power source and the reaction vessel [62]. This methodology also increases the rate of reaction and the diversity of the compounds produced [63–65].

In this paper, we report a stereoselective synthesis of a new library of (*E*)-2-(1*H*-indole-3-ylcarbonyl)-3-heteroaryl-acrylonitriles (**3a–i**) obtained by equimolar amounts of 3-(cyanoacetyl)indole (**1**) and heteroaryl-aldehydes (**2a–i**) microwave-assisted Knoevenagel condensation using ethanol as solvent-catalyzer, 300 W and 100°C. Under these conditions, a series of new (*E*)-2-(1*H*-indole-3-ylcarbonyl)-3-hetero-aryl-acrylonitriles were obtained in excellent purities and variable time and yields (Scheme 1).

2. Material and Methods

2.1. General. The reagents, all aromatic aldehydes, and solvents used for the reactions and recrystallization were of analytical grade and were acquired commercially from Sigma-Aldrich and Merck.

Microwave-assisted irradiation was used for the reactions and performed one-pot reaction in a focused microwave reactor (CEM Discover™), with maximum power of 300 W at a controlled temperature of 100°C for 8–90 minutes, respectively. The reaction progress was monitored using thin layer chromatography on PF254 TLC aluminum sheets from Merck and visualization of the spots by UV light. Melting points were recorded on a Buchi apparatus and were uncorrected. They were expressed as degree Celsius (°C). IR spectra (KBr pellets, 500–4000 cm⁻¹) were recorded on a Thermo Nicolet NEXUS 670 FT-IR spectrophotometer.

High-resolution electrospray ionisation mass spectrometry (ESI-MS) analyses were conducted in a high-resolution hybrid quadrupole (Q) and orthogonal time-of-flight (TOF) mass spectrometer (Waters/Micromass Q-TOF micro, Manchester, UK) with a constant nebulizer temperature of 100°C. The experiments were carried out in positive ion mode, and the cone and extractor potentials were set at 10 V, with a scan range of *m/z* 100–600. The MS product ions were analyzed with a high-resolution orthogonal TOF analyzer. The samples were infused directly into the ESI source via a syringe pump at flow rates of 5 mL min⁻¹, via the instrument's injection valve.

Nuclear magnetic resonance spectra (¹H-NMR and ¹³C-NMR) were measured on a Bruker Ultrashield-400

spectrometer (400 MHz ¹H-NMR and 100 MHz ¹³C-NMR), in diluted solutions of DMSO-*d*₆ using TMS as an internal standard. *J* values are reported in Hz; chemical shifts are reported in ppm (δ) relative to the solvent peak (residual DMSO in DMSO-*d*₆ at 2.59 ppm for protons and 39.38–40.62 ppm for ¹³C). Signals were designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; and m, multiplet.

2.2. Synthesis: General Procedure for the Synthesis of (*E*)-2-(1*H*-Indole-3-ylcarbonyl)-3-heteroaryl-acrylonitriles. The starting compound 3-(cyanoacetyl)indole was prepared according to the procedure described by Slätt et al. [66].

A mixture of 3-(cyanoacetyl)indole **1** (1 mmol) and heteroaryl-aldehydes **2a–i** (1 mmol) in ethanol 0.5 mL was irradiated at 300 W and 100°C for 8–90 min, respectively. After completion of the reaction, the mixture was allowed to cool to room temperature and collected by filtration. The solid products were isolated by crystallization of the reaction mixture from ethanol and washed with a cool mixture of hexane/ethanol (7:3, 3 × 4 mL) to give the corresponding compounds. The solid products obtained were purified by flash column chromatography performed with Silica gel (60–120 mesh) and/or recrystallization using a mixture of petroleum ether and ethyl acetate (7:3 and 6:4) or dichloromethane (CH₂Cl₂) as an eluent to afford pure heteroaryl-acrylonitriles (**3a–i**).

2.2.1. (*E*)-2-(1*H*-Indole-3-ylcarbonyl)-3-(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl)-acrylonitrile (3a**).** Yellow solid. Yield 30%. mp 196–198°C. IR (KBr, cm⁻¹): 3214 (NH), 3107, 3047, 2927, 2209 (CN), 1710 (C=O), 1634, 1596, 1518, 1433, 1231, 1136, 999, 827, 759. ¹H-NMR (400 MHz, DMSO-*d*₆): δ ppm 12.31 (s, 1H, NH_{Indole}), 8.45 (d, 1H, H2'_{Indole}, *J* = 2.7 Hz), 8.20 (d, 1H, H4'_{Indole}, *J* = 6.6 Hz), 8.05 (s, 1H, H-C=olefinic), 7.60 (d, 4H, CH_{o-m-phenyl}, *J* = 5.4 Hz), 7.57 (s, 1H, CH_{p-phenyl}), 7.55 (d, 1H, H7'_{Indole}, *J* = 6.6 Hz), 7.31–7.25 (m, 2H, H5'-H6'_{Indole}), 2.46 (s, 3H, CH₃); ¹³C-NMR (100 MHz, DMSO-*d*₆): δ ppm 183.91, 150.59, 149.26, 142.34, 136.85, 136.34, 135.66, 135.26, 134.14, 132.43, 129.20 (2), 128.40, 125.27 (2), 124.88, 123.07, 122.13, 120.79, 116.60, 112.17, 13.04. HRMS (ESI), calcd.: C₂₂H₁₅ClN₄O [M+H]⁺ *m/z*: 387.0934; [M+K]⁺ *m/z*: 425.1917, found: [M+H]⁺ *m/z*: 387.2427; [M+K]⁺ *m/z*: 425.0022.

2.2.2. (*E*)-2-(1*H*-Indole-3-ylcarbonyl)-3-(1-methyl-1*H*-imidazol-2-yl)-acrylonitrile (3b**).** Ivory solid. Yield 71%. mp 160–163°C. IR (KBr, cm⁻¹): 3290 (NH), 2956, 2917, 2855, 2210 (CN), 1776 (C=O), 1631, 1513, 1419, 1370, 1321, 1237, 1129, 1011, 899, 774. ¹H-NMR (400 MHz, DMSO-*d*₆): δ ppm 12.24 (s, 1H, NH_{Indole}), 8.54 (s, 1H, H2'_{Indole}), 8.20 (d, 1H, H4'_{Indole}, *J* = 6.9 Hz), 7.97 (s, 1H, H-C=olefinic), 7.54 (m, 2H, H7'_{Indole}, H4_{Imidazole}), 7.35 (s, 1H, H5_{Imidazole}), 7.30–7.23 (m, 2H, H5'-H6'_{Indole}), 3.83 (s, 3H, N-CH₃); ¹³C-NMR (100 MHz, DMSO-*d*₆): δ ppm 181.85, 141.06, 137.11, 136.08, 135.47, 131.88, 127.15, 126.74, 123.98, 122.81, 121.93, 117.78, 114.34, 112.91, 109.35, 33.33. HRMS (ESI), calcd.: C₁₆H₁₂N₄O [M]⁺ *m/z*: 276.1000; [M+H]⁺ *m/z*: 277.1000; [M+Na]⁺ *m/z*:

SCHEME 1: Microwave-assisted Knoevenagel reaction of novel (*E*)-2-(1*H*-indole-3-ylcarbonyl)-3-hetero-aryl-acrylonitriles **3a-i**.

299.0897; $[M+K]^+$ m/z : 315.1983, found: $[M]^+$ m/z : 276.8098; $[M+H]^+$ m/z : 277.8231; $[M+Na]^+$ m/z : 299.7046; $[M+K]^+$ m/z : 315.3912.

2.2.3. (*E*)-2-(1*H*-Indole-3-ylcarbonyl)-3-(1*H*-imidazol-2-yl)-acrylonitrile (3c**).** Brilliant ochre solid. Yield 85%. mp 207–209°C. IR (KBr, cm^{-1}): 3329 (NH), 2959, 2910, 2844, 2210 (CN), 1800 (C=O), 1638, 1516, 1429, 1412, 1321, 1175, 1129, 1011, 767, 746. ^1H -NMR (400 MHz, $\text{DMSO}-d_6$): δ ppm 12.18 (s, 1H, $\text{NH}_{\text{Indole}}$), 9.74 (s, 1H, $\text{NH}_{\text{Imidazole}}$), 8.43 (s, 1H, $\text{H}2'_{\text{Indole}}$), 8.18 (d, 1H, $\text{H}4'_{\text{Indole}}$, $J = 7.1$ Hz), 8.14 (s, 1H, $\text{H}-\text{C}=\text{olefinic}$), 8.01 (s, 1H $\text{H}5_{\text{Imidazole}}$), 8.06 (s, 1H $\text{H}4_{\text{Imidazole}}$), 7.53 (d, 1H, $\text{H}7'_{\text{Indole}}$, $J = 8.1$ Hz), 7.28–7.21 (m, 2H, $\text{H}5'-\text{H}6'_{\text{Indole}}$); ^{13}C -NMR (100 MHz, $\text{DMSO}-d_6$): δ ppm 182.52, 145.15, 138.89, 136.81, 134.86, 127.13, 126.68, 123.73, 122.91, 122.52, 121.87, 118.87, 114.25, 112.78, 105.74. HRMS (ESI), calcd.: $\text{C}_{15}\text{H}_{10}\text{N}_4\text{O}$ $[M]^+$ m/z : 262.0900; $[M+Na]^+$ m/z : 285.0797, found: $[M]^+$ m/z : 262.8657; $[M+Na]^+$ m/z : 285.2617.

2.2.4. (*E*)-2-(1*H*-Indole-3-ylcarbonyl)-3-(*tert*-butyl-4-phenylpiperazine-1-carboxyl)-acrylonitrile (3d**).** Yellow solid. Yield 74%. mp 200–203°C. IR (KBr, cm^{-1}): 3227 (NH), 2975, 2854, 2363, 2334, 2208 (CN), 1701 (C=O), 1599, 1516, 1436, 1366, 1245, 1163, 1003, 914, 824, 749, 645. ^1H -NMR (400 MHz, $\text{DMSO}-d_6$): δ ppm 12.14 (s, 1H, $\text{NH}_{\text{Indole}}$), 8.40 (s, 1H, $\text{H}2'_{\text{Indole}}$), 8.16 (d, 1H, $\text{H}4'_{\text{Indole}}$, $J = 7.8$ Hz), 8.11 (s, 1H, $\text{H}-\text{C}=\text{olefinic}$), 7.99 (d, 2H, $\text{H}2, \text{H}6_{\text{phenyl}}$, $J = 9.1$ Hz), 7.52 (d, 1H, $\text{H}7'_{\text{Indole}}$, $J = 7.3$ Hz), 7.28–7.21 (m, 2H, $\text{H}5'-\text{H}6'_{\text{Indole}}$), 7.06 (d, 2H, $\text{H}3, \text{H}5_{\text{phenyl}}$, $J = 9.0$ Hz), 3.43 (s, 8H, $(-\text{CH}_2)_6_{\text{piperazine}}$), 1.41 (s, 9H, $-\text{CH}_3$); ^{13}C -NMR (100 MHz, $\text{DMSO}-d_6$): δ ppm 181.48, 153.81, 153.10, 152.33, 136.43, 134.49, 133.04 (2), 126.32, 123.26, 122.06, 121.43, 121.19, 119.44, 113.90, 113.65, 112.33 (2), 104.14, 79.11, 46.01 (2), 40.13, 38.87, 28.03 (3). HRMS (ESI), calcd.: $\text{C}_{27}\text{H}_{28}\text{N}_4\text{O}_3$ $[M+H]^+$ m/z : 358.1477, $[M+Na]^+$ m/z : 380.1374, found: $[M+H]^+$ m/z : 358.4130, $[M+Na]^+$ m/z : 380.4027.

2.2.5. (*E*)-2-(1*H*-Indole-3-ylcarbonyl)-3-(5-(4-fluorophenyl)isoxazol-3-yl)-acrylonitrile (3e**).** Light yellow solid. Yield 94%. mp 233–235°C. IR (KBr, cm^{-1}): 3413 (NH), 3173, 2957, 2916, 2851, 2352, 2215 (CN), 1734 (C=O), 1593, 1574, 1485, 1423, 1315, 1232, 1174, 1002, 830, 793. ^1H -NMR (400 MHz, $\text{DMSO}-d_6$): δ ppm 12.42 (s, 1H, $\text{NH}_{\text{Indole}}$), 8.53 (d, 1H, $\text{H}2'_{\text{Indole}}$, $J = 2.0$ Hz), 8.19 (d, 1H, $\text{H}4'_{\text{Indole}}$, $J = 7.8$ Hz), 8.10 (s, 1H, $\text{H}-\text{C}=\text{olefinic}$), 8.05 (dd, 2H, $-\text{CH}_{\text{O-phenyl}}$, $J_1 = 8.9$ Hz, $J_2 = 5.3$ Hz), 7.56 (d, 1H, $\text{H}7'_{\text{Indole}}$, $J = 6.9$ Hz), 7.51 (s, 1H, $\text{H}4''_{\text{isoxazole}}$), 7.43 (t, 2H, $-\text{CH}_{\text{m-phenyl}}$, $J = 8.9$ Hz), 7.33–7.26 (m, 2H, $\text{H}5'-\text{H}6'_{\text{Indole}}$); ^{13}C -NMR (100 MHz, $\text{DMSO}-d_6$): δ ppm 179.60,

163.47, 158.99, 156.41, 152.04, 138.60, 136.13, 130.36, 129.93 (2), 128.17, 127.55, 127.48, 124.73, 123.60, 117.44, 116.39 (2), 116.11, 112.49, 93.46. HRMS (ESI), calcd.: $\text{C}_{21}\text{H}_{12}\text{FN}_3\text{O}_2$ $[M+H]^+$ m/z : 358.0947, found: $[M+H]^+$ m/z : 358.6270.

2.2.6. (*E*)-2-(1*H*-Indole-3-ylcarbonyl)-3-(5-phenylisoxazol-3-yl)-acrylonitrile (3f**).** Fluorescent yellow solid. Yield 86%. mp 255–257°C. IR (cm^{-1}): 3249 (NH), 2920, 2839, 2349, 2214 (CN), 1750 (C=O), 1628, 1571, 1509, 1433, 1237, 1171, 1153, 1020, 872, 755. ^1H -NMR (400 MHz, $\text{DMSO}-d_6$): δ ppm 12.41 (s, 1H, $\text{NH}_{\text{Indole}}$), 8.54 (d, 1H, $\text{H}2'_{\text{Indole}}$, $J = 2.2$ Hz), 8.21–8.18 (m, 1H, $\text{H}4'_{\text{Indole}}$), 8.11 (s, 1H, $\text{H}-\text{C}=\text{olefinic}$), 7.96 (dd, 2H, $-\text{CH}_{\text{O-phenyl}}$, $J_1 = 7.5$, $J_2 = 2.1$ Hz), 7.61–7.55 (m, 4H, $\text{H}7'_{\text{Indole}}$, $(-\text{CH})_{\text{m,p-phenyl}}$), 7.51 (s, 1H, $\text{H}_{\text{isoxazole}}$), 7.33–7.27 (m, 2H, $\text{H}5', \text{H}6'_{\text{Indole}}$). ^{13}C -NMR (100 MHz, $\text{DMSO}-d_6$): δ ppm 180.36, 171.14, 158.73, 138.50, 137.50, 137.35, 131.59, 129.95 (2), 126.50, 126.38 (3), 124.33, 123.21, 121.84, 117.97, 116.50, 113.83, 113.13, 100.25. HRMS (ESI), calcd.: $\text{C}_{21}\text{H}_{13}\text{N}_3\text{O}_2$ $[M]^+$ m/z : 339.1008; $[M+H]^+$ m/z : 340.1041, found: $[M]^+$ m/z : 339.6259; $[M+H]^+$ m/z : 340.7304.

2.2.7. (*E*)-2-(1*H*-Indole-3-ylcarbonyl)-3-(5-(4-nitrophenyl)furan-2-yl)-acrylonitrile (3g**).** Orange solid. Yield 74%. mp 323–325°C. IR (KBr, cm^{-1}): 3218 (NH), 2952, 2915, 2363, 2246, 2211 (CN), 1684 (C=O), 1638, 1598, 1514, 1456, 1427, 1327, 1236, 1155, 1038, 853, 750. ^1H -NMR (400 MHz, $\text{DMSO}-d_6$): δ ppm 12.28 (s, 1H, $\text{NH}_{\text{Indole}}$), 8.52 (s, 1H, $\text{H}2'_{\text{Indole}}$), 8.38 (dd, 2H, $\text{H}_{\text{O-phenyl}}$, $J_1 = 9.1$, $J_2 = 2.3$ Hz), 8.20–8.17 (m, 2H, $\text{H}_{\text{m-phenyl}}$), 8.15 (s, 1H, $\text{H}-\text{C}=\text{olefinic}$), 7.70–7.65 (m, 2H, $\text{H}4'_{\text{Indole}}, \text{H}3_{\text{furan}}$), 7.57–7.53 (m, 2H, $\text{H}7'_{\text{Indole}}, \text{H}4_{\text{furan}}$), 7.31–7.23 (m, 2H, $\text{H}5'-\text{H}6'_{\text{Indole}}$). ^{13}C -NMR (100 MHz, $\text{DMSO}-d_6$): δ ppm 180.66, 155.63, 150.22, 147.68, 137.11, 137.04, 135.82, 134.85, 126.69, 125.96 (2), 125.49, 125.11 (2), 124.04, 122.86, 121.95, 118.67, 114.27, 113.83, 112.96, 107.24. HRMS (ESI), calcd.: $\text{C}_{22}\text{H}_{13}\text{N}_3\text{O}_4$ $[M]^+$ m/z : 383.0906; $[M+K]^+$ m/z : 423.1923, found: $[M]^+$ m/z : 383.4413; $[M+K]^+$ m/z : 423.1823.

2.2.8. (*E*)-2-(1*H*-Indole-3-ylcarbonyl)-3-(5-(4-chlorophenyl)furan-2-yl)-acrylonitrile (3h**).** Ochre solid. Yield 65%. mp 278–280°C. IR (KBr, cm^{-1}): 3343 (NH), 2957, 2918, 2856, 2204 (CN), 1727 (C=O), 1617, 1510, 1458, 1436, 1279, 1122, 1075, 794, 743. ^1H -NMR (400 MHz, $\text{DMSO}-d_6$): δ ppm 12.28 (s, 1H, $\text{NH}_{\text{Indole}}$), 8.52 (s, 1H, $\text{H}2'_{\text{Indole}}$), 8.21 (d, 1H, $\text{H}4'_{\text{Indole}}$, $J = 6.6$ Hz), 8.12 (s, 1H, $\text{H}-\text{C}=\text{olefinic}$), 7.98 (d, 2H, $\text{CH}_{\text{O-chlorophenyl}}$, $J = 8.6$ Hz), 7.64 (d, 2H, $\text{CH}_{\text{m-chlorophenyl}}$, $J = 8.6$ Hz), 7.56 (s, 1H, $\text{H}7'_{\text{Indole}}$), 7.54 (d, 1H, $\text{H}4_{\text{furan}}$, $J = 3.7$ Hz), 7.45 (d, 1H, $\text{H}3_{\text{furan}}$, $J = 3.7$ Hz), 7.31–7.24 (m, 2H, $\text{H}5'-\text{H}6'_{\text{Indole}}$); ^{13}C -NMR (100 MHz, $\text{DMSO}-d_6$): δ ppm 183.88, 150.59, 149.26,

SCHEME 2: Plausible mechanism of Knoevenagel condensation by microwave-assisted irradiation.

142.28, 136.82, 136.34, 135.66, 135.26, 132.43, 129.20 (2), 125.20 (2), 124.88, 123.07, 122.27, 122.09, 120.79, 116.56, 114.22, 113.79, 112.19. HRMS (ESI), calcd.: $C_{22}H_{15}ClN_4O$ $[M+H]^+$ m/z : 372.0666; $[M+Na]^+$ m/z : 395.0563; $[M+K]^+$ m/z : 411.1649, found: $[M+H]^+$ m/z : 373.4272; $[M+Na]^+$ m/z : 395.1320; $[M+K]^+$ m/z : 411.2668.

2.2.9. (E)-2-(1H-Indole-3-ylcarbonyl)-3-(4-oxo-4H-chromen-3-yl)-acrylonitrile (3i). Ochre solid. Yield 83%. mp 272–274°C. IR (KBr, cm^{-1}): 3450 (NH), 2959, 2924, 2856, 2365 (CN), 1731 (C=O), 1649, 1460, 1379, 1283, 1183, 1073, 880, 738. 1H -NMR (400 MHz, $DMSO-d_6$): δ ppm 12.33 (s, 1H, NH_{Indole}), 9.20 (d, 1H, $J = 1.0$ Hz $C10_{chromone}$), 8.41 (d, 1H, $J = 3.2$, $H2_{indole}$), 8.19–8.15 (m, 2H, $H4'_{indole}$, $C6_{chromone}$), 8.13 (s, 1H, $H-C=olefinic$), 7.92–7.88 (m, 1H, $C4_{chromone}$), 7.77 (d, 1H, $J = 8.1$ Hz, $C3_{chromone}$), 7.60–7.55 (m, 2H, $H7'_{indole}$, $C5_{chromone}$), 7.32–7.26 (m, 2H, $H5'$, $H6'_{indole}$). ^{13}C -NMR (100 MHz, $DMSO-d_6$): δ ppm 180.32, 174.08, 158.20, 153.78, 143.37, 136.65, 136.36, 136.17, 135.79, 125.98, 124.69, 123.67, 122.66, 121.35, 120.50, 118.55, 117.87, 116.93, 113.56, 113.11, 112.54. HRMS (ESI), calcd.: $C_{21}H_{12}N_2O_3$ $[M]^+$ m/z : 340.0848; $[M+Na]^+$ m/z : 362.0745; $[M+K]^+$ m/z : 378.0848, found: $[M]^+$ m/z : 339.6259; $[M+Na]^+$ m/z : 361.3391; $[M+K]^+$ m/z : 377.2256.

3. Results and Discussion

We report here the synthesis of (E)-2-(1H-indole-3-ylcarbonyl)-3-heteroaryl-acrylonitriles (**3a–i**), via microwave-assisted Knoevenagel condensation reaction. The reaction was carried out using 3-(cyanoacetyl)indole (**1**) as a precursor with different heteroaryl-aldehydes (**2a–i**) in ethanol, as shown in Scheme 1 and Table 1.

Under these optimal conditions the Knoevenagel reaction may follow through the cyanoacetyl system present in the cyanoacetylindole (**1**), a methylene-activated system used as a versatile nucleophile in Knoevenagel reaction to obtain acrylonitriles derivatives [7, 66, 67], influenced by the participation of ethanol as acid ($pK_a = 15.9$), that deprotonated, will produce ethoxide ion, as strong base, and by the presence

of different heteroaryl-aldehydes (**2a–i**) with the electron-withdrawing and electron-releasing substituents.

The possible mechanism is illustrated in Scheme 2. Start with a nucleophilic attack of enol form of starting compound **1** to aldehyde **2**, generating a zwitterionic intermediate, and finally a dehydration step to afford compounds **3a–i**.

We observed under the above-described synthesis conditions that in general the compounds were relatively easy purified and obtained at a high purity degree compared when the basic nonnucleophilic triethylamine catalyst was used, which gave a greater amount of by-products (data not shown). The compounds **3b–i** showed high yields (65–94%), except the compound **3a** which has the 5-chloro-3,4-dimethyl-1-phenyl-1H-pyrazoles as substituent and had a moderate yield (30%). Reaction times had a more varied behavior, from a few minutes as observed for compounds **3b** and **3i** (8 and 20 min, resp.) up to 90 minutes in the case of compound **3h**. This long reaction times obtained in this synthesis behavior could be due to the low solubility of 3-cyanoacetylindole in ethanol and low reactivity of 5-(4-chlorophenyl)furan-2-yl-aldehyde. The rest of the compounds showed reaction times between 30 and 60 min (Table 1).

All compounds were purified and characterized based on their spectra of IR, 1H -NMR, ^{13}C -NMR, and mass spectrometry. The entire carbon skeleton was assigned by ^{13}C -NMR spectra. Notice that all the compounds synthesized retain signals similar to the cyanoacetylindole skeleton, similar to those reported previously [68, 69], differing only in the corresponding to the heteroaryl substituents. The double bond of carbon (C2–C3) leads to chemical shifts (δ ; ppm) in values of 93.46–112.54 to C2 and 135.47–143.37 to C3, the signal of CN in values of 113.65 to 116.60, and a typical CN absorption in the IR spectrum (ν ; 2,400–2,200 cm^{-1}). In addition, fully consistent with the previously reported structures, a ketone signal in values of 179.60–183.88 ppm in the ^{13}C -NMR spectrum as well as a typical ketone absorption in the IR spectrum (ν ; 1,650–1,550 cm^{-1}) was observed.

In all cases, the analysis of 1H -NMR in $DMSO-d_6$ included a NH indole resonance in values of 12.21–10.93 ppm,

TABLE 1: Products of Knoevenagel condensation: structures and reaction parameters.

<div> </div>				
Compound	R	mp. (°C)	Reaction time (min)	Yield (%) ^a
3a	<div> </div>	196–198	30	30
3b	<div> </div>	160–163	8	71
3c	<div> </div>	207–209	25	85
3d	<div> </div>	200–203	35	74
3e	<div> </div>	233–235	55	94
3f	<div> </div>	255–257	30	86
3g	<div> </div>	323–325	50	74
3h	<div> </div>	278–280	90	65
3i	<div> </div>	272–274	20	83

^aIsolated yields.

as well as a typical NH absorption in the IR spectrum (ν ; 3,400–3,300 cm^{-1}).

All the new derivatives also revealed a singlet between 8.14 and 7.71 ppm for a single olefinic proton consistent with the formation of a single isomer *E* or *Z*.

However, the configuration of the double bond of acrylonitrile could not be established by NMR methods. Previous studies have shown that depending on the type of substituent at the position 3 of acrylonitrile, as the use of catalysts, it is possible to induce the formation of the *E* isomer [70, 71] or

Z [11, 25]. In our work, the product obtained was assigned as *E* isomer, assuming it as the thermodynamically more stable isomer. As previously reported with products of similar structural characteristics which also showed preference for the *E* isomer [8, 10, 53, 71, 72].

4. Conclusion

In summary, we reported an eco-efficient MWI method for the synthesis of (*E*)-2-(1*H*-indole-3-ylcarbonyl)-3-heteroaryl-acrylonitriles by Knoevenagel condensation of cyanoacetylindole and heteroaryl-aldehydes, in the presence of minimum amount of ethanol as a solvent. The promising points of the presented methodology are efficiency, generality, high yield, relatively short reaction time, low cost, cleaner reaction profile, simplicity, and ease of product isolation. We feel that this economically viable procedure will prove to be a better alternative and green protocol for the synthesis of (*E*)-2-(1*H*-indole-3-ylcarbonyl)-3-heteroaryl-acrylonitriles as compared to the conventional method. These new derivatives may be beneficially used as precursors for biologically active cyanoacetylindole-acrylonitriles in medicinal chemistry research. Further structure-activity relationship studies aiming at developing pharmaceutical candidates and testing the pharmacological activity of these compounds are in progress.

Disclosure

The statements made herein are solely the responsibility of the authors.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

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