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MW-assisted synthesis of eight new 6-nitrilmethyl pyrrolo[3,4-*b*]pyridin-5-ones via a domino process: *aza* Diels-Alder / *N*-acylation / aromatization†

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† Presented at the 22th International Electronic Conference on Synthetic Organic Chemistry.

Academic editor: Julio A. Seijas

Abstract: An efficient MW-assisted synthesis of eight new 6-nitrilmethyl-pyrrolo[3,4-*b*]pyridin-5-ones via a domino process: *aza* Diels-Alder / *N*-acylation / aromatization (dehydration-decarboxylation) from their corresponding 2-aminonitrile-oxazoles and maleic anhydride is described. The use of MW as heat source and scandium (III) triflate as catalyst to promote the cycloaddition process was crucial to construct these polyfunctionalized products in very good yields (51–79%) considering both, their molecular complexity, and that only one domino-type experimental procedure was required for their synthesis. It is worthy to note that all herein reported products have not been synthesized nor isolated anywhere. However, they can be of high interest for synthetic and medicinal chemistry community because the pyrrolo[3,4-*b*]pyridin-5-one is the structural core of various bioactive compounds. In the same context, it can be considered as a privileged aza-analogue of the isoindolin-1-one, which in turn is the core of numerous anticancer agents.

Keywords: Multicomponent reactions; Ugi-three component reactions; Pyrrolo[3,4-*b*]pyridin-5-ones; Domino processes; *aza* Diels-Alder Cycloadditions; *N*-acylations; Aromatization processes.

1. Introduction

The fused-type polyheterocyclic pyrrolo[3,4-*b*]pyridin-5-one system **1** is the structural core of various synthetic products showing interesting biological properties, such as the antiepileptic **2** [1] and the antihypoglycemic **3** [2] agents. Besides, the polyheterocyclic framework **1** is considered as a privileged aza-analogue of the isoindolin-1-one system **4** [3]. In the same context, some natural products of high interest in medicinal chemistry such as the (±)-Nuevamine (**5**) [4], (±)-Lennoxamine (**6**) [5] and the Magallanesine (**7**) [6] are structurally based on the isoindolin-1-one moiety, **Figure 1**. Thus, the aim of this communication is to describe an efficient MW-assisted synthesis of the eight new 6-nitrilmethyl-pyrrolo[3,4-*b*]pyridin-5-ones **8a-h** via a domino process: *aza* Diels-Alder / *N*-acylation / aromatization (dehydration-decarboxylation) from their corresponding 2-aminonitrile-oxazoles and maleic anhydride. Most of the reported methods to assemble pyrrolo[3,4-*b*]pyridin-5-one based architectures involve multistep strategies as well as the use of harsh conditions. As example, the

synthetic methodology reported by Devasthale *et al.* [2]. However, various Multicomponent Reaction (MCRs) based synthetic strategies toward series of novel pyrrolo[3,4-*b*]pyridin-5-one containing polyheterocycles have been reported in the last decade by us [7–14], as an integral part of our ongoing research program. It is important to note that MCRs are highly convergent one pot processes in which three or more reagents are combined sequentially to assemble complex products [15], like polyheterocycles [16], eventually in good yields, obeying most of the green chemistry principles [17].

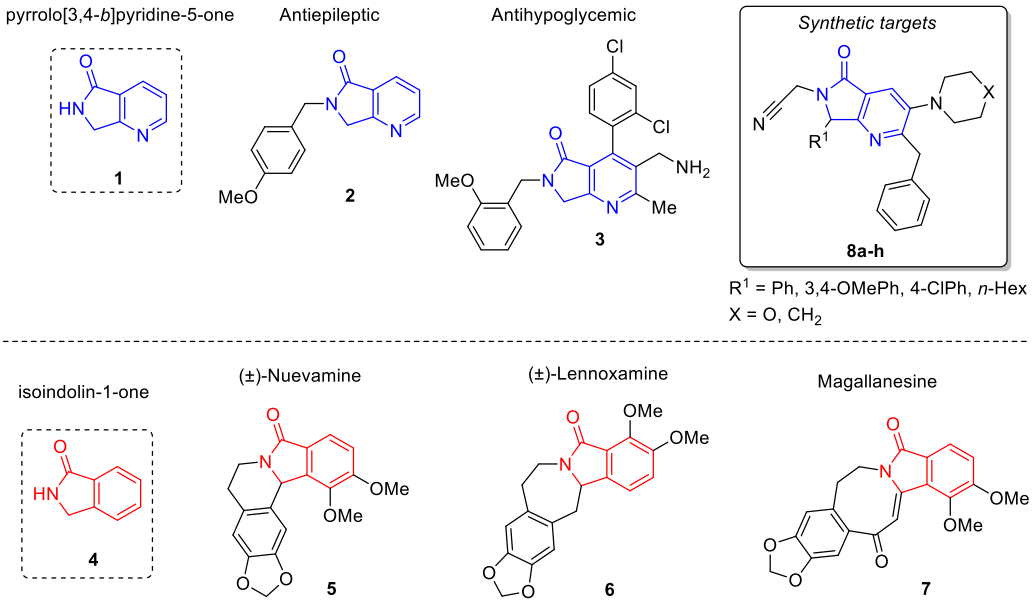
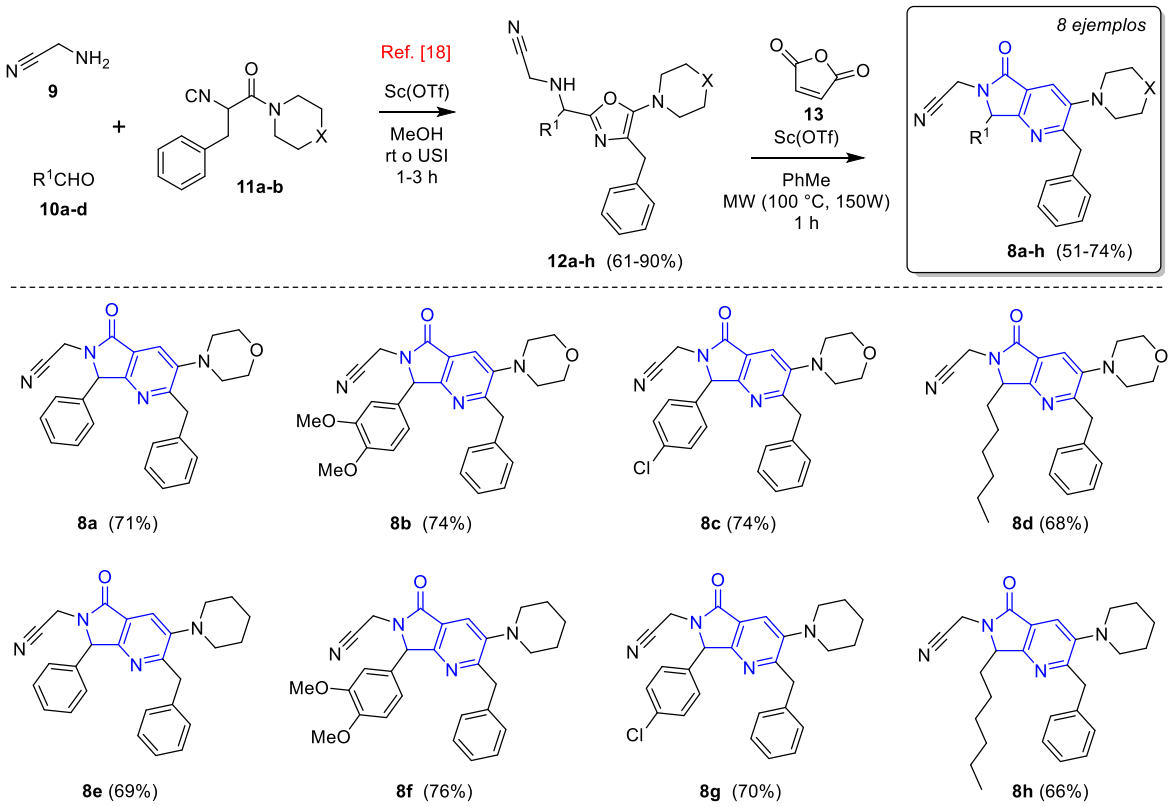


Figure 1. pyrrolo[3,4-*b*]pyridin-5-ones and isoindolin-1-ones of interest.

2. Results and Discussion

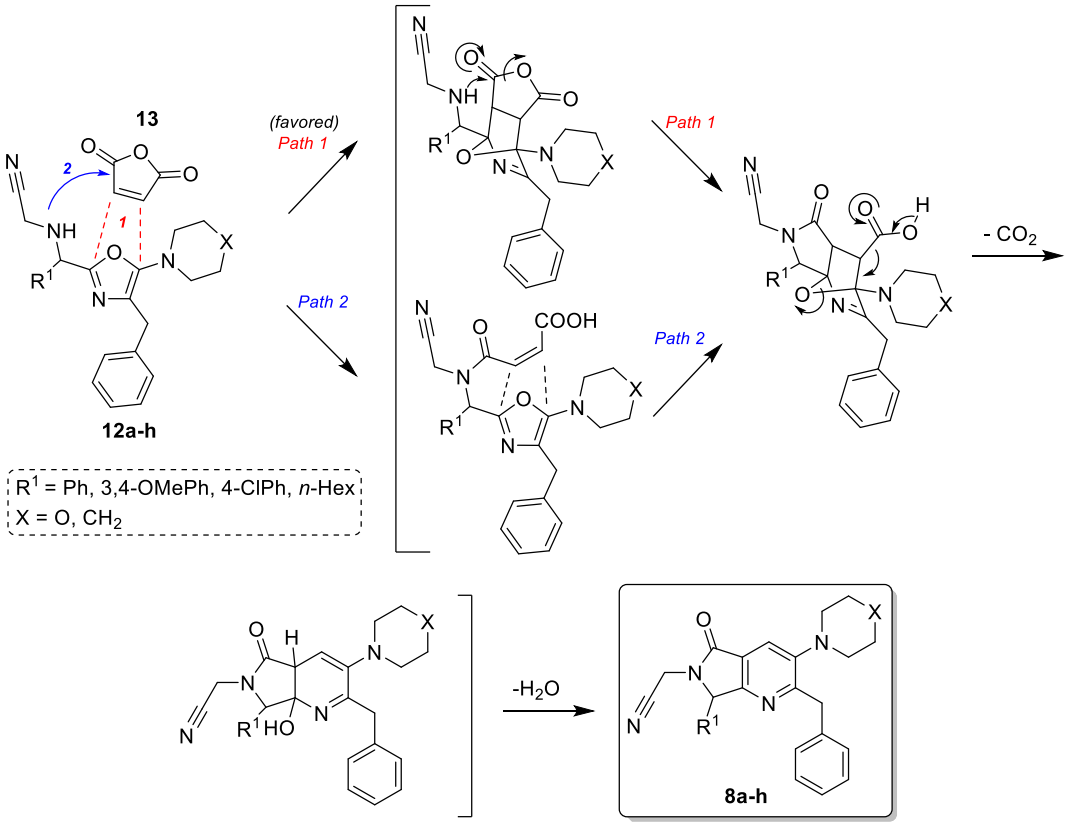
In 2017 at the 21st international ECSOC, we reported an ultrasound-assisted synthesis of the eight new and highly functionalized 2-aminonitrile oxazoles **12a-h** via an Ugi-3CR by combining the aminoacetonitrile (**9**) with the corresponding aldehydes **10a-d** and the chain-ring tautomerizable isocyanides **11a-b** in MeOH as the solvent, **scheme 1**. Now, we combined just the oxazole-based compounds **12a-h** with maleic anhydride (**13**) to synthesize the corresponding eight new 6-nitrilmethyl-pyrrolo[3,4-*b*]pyridin-5-ones **8a-h** via a domino process : *aza* Diels-Alder / *N*-acylation / aromatization (dehydration-decarboxylation), **scheme 1**. Then, choosing the 2-aminonitrile oxazole **12a** as starting reagent, we screened the acid catalyst, heat source, temperature, solvent and the concentration to find the optimal reaction parameters toward the new 6-nitrilmethyl-pyrrolo[3,4-*b*]pyridin-5-one **8a**. Thus, after various attempts, the use of scandium (III) triflate as the catalyst (3% mol), toluene as the solvent [0.3 M], microwaves as heat source at 100 °C and 150 W of power, gave the best yield for the product **8a** (71%). So, by using these optimal conditions, the other analogues **8b-h** were synthesized successfully in closer yields (66–76%) with respect to the product **8a** (71%). As seen, the substrate scope was studied by using aromatic aldehydes with electron-releasing and electron-withdrawing groups (R^1 = Ph, 3,4-OMePh, 4-ClPh), as well as with an aliphatic substituent (R^1 = *n*-Hex), **scheme 1**. The best yield was observed for the analogues **8b** (74%, R^1 = 3,4-OMePh; X = O) and **8f** (76%, R^1 = 3,4-OMePh; X = CH_2), while the lowest yield was observed for the alkylic analogues, **8d** (68%, R^1 = *n*-Hex; X = O) and **8h** (66%, R^1 = *n*-Hex; X = CH_2). This behavior is attributed to a little difference in the stereoelectronic nature between aromatic and aliphatic substituents, favorable to aromatic ones. This observation matches also with our previous report [18], **scheme 1**.



Scheme 1. Synthesis of pyrrolo[3,4-*b*]pyridin-5-ones (substrate scope).

With respect to the reaction mechanisms, the synthesis of the 2-aminonitrile oxazoles **12a-h** via Ugi-3CR was reported in our previous work [18]. However, the conversion of **12a-h** into **8a-h** can take two possible pathways, as it was discussed in a mechanistic study from DFT-based calculations published in 2016 also by us [19], from similar structural polyheterocyclic systems. Thus the 2-aminonitrile oxazoles **12a-h** may react with the maleic anhydride **13** via a domino sequence 1: intermolecular *aza* Diels-Alder cycloaddition / intramolecular *N*-acylation / aromatization (dehydration-decarboxylation) or sequence 2: intermolecular *N*-acylation / intramolecular *aza* Diels-Alder cycloaddition / aromatization (dehydration-decarboxylation), **scheme 2**. Thus, based on the structural similarities to the polyheterocycles studied then, we assume that the most plausible path way for the synthesis of our current products is the domino sequence 1.

Finally, all the products were characterized by their physicochemical properties, as well as by the classical spectroscopic techniques (*See the experimental part for further details)*. The product **8a** was chosen to discuss succinctly its ^{1}H and ^{13}C NMR spectra, **figure 2**. Thus, with respect to the ^{1}H NMR key signals, it is worth of highlighting a couple of singlets, on of them at 7.90 ppm, attributed to the C-H of pyridine ring, while the other key peak appears at 5.62 ppm, attributed to the C-H from its pyrrolodin-5-one ring, **figure 2a**. The latter discussed signal is the most important among all because that C-H is in which all the components converge. Besides, with respect to the ^{13}C NMR key signals, there is a peak at 166.5 ppm attributed to the carbonyl from its pyrrolodin-5-one system, **figure 2b**. This signal indicates that the γ-lactam was created in the synthetic process, **figure 2b**.



Scheme 2. Plausible reaction mechanism.

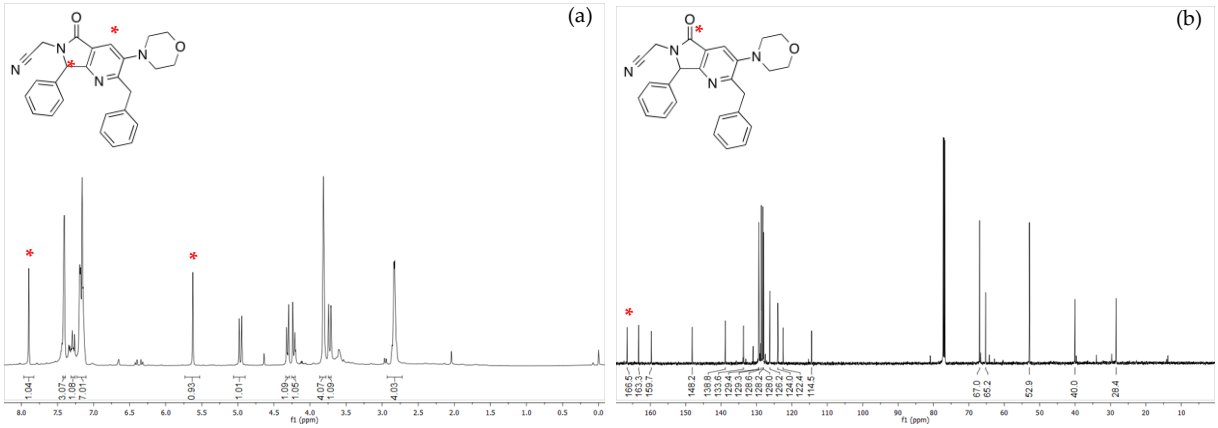


Figure 2. (a) ^{1}H NMR spectrum of the compound **8a**, (b) ^{13}C NMR spectrum of the compound **8a**.

3. Conclusions

The synthetic strategy herein described allowed a rapid preparation of eight new 6-aminonitril pyrrolo[3,4-*b*]pyridin-5-ones in good yields (66–76%) considering the molecular complexity of the final products, that only one domino-type one pot process was required for the synthesis, and that the products are polyfunctionalized, which in turn can be exploited for further reactions, for example, the nitrile group can be converted easily into a tetrazole ring via a Huisgen-type [3+2] dipolar cycloaddition. This kind of compounds are being synthesized and the results will be communicated soon.

4. Experimental Section

4.1 General information, instrumentation, and chemicals

^{1}H and ^{13}C NMR spectra were acquired on either, Bruker Advance III spectrometers (500 or 400 MHz). The solvent used was deuterated chloroform ($CDCl_3$). Chemical shifts are reported in parts per million (δ/ppm). Internal reference for 1H NMR spectra is respect to TMS at 0.0 ppm. Internal reference for ^{13}C NMR spectra is respect to $CDCl_3$ at 77.0 ppm. Coupling constants are reported in Hertz (*J*/Hz). Multiplicities of the signals are reported using the standard abbreviations: singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). NMR spectra were analyzed using the MestreNova software version 10.0.1-14719. IR spectra were acquired on a Perkin Elmer 100 spectrometer. The absorbance peaks are reported in reciprocal centimeters (υ_{max}/cm^{-1}). Microwave assisted reactions were performed on a CEM Discover™ Synthesis Unit in close vessel mode. Reaction progress was monitored by TLC on precoated Silica-gel 60 F_{254} plates and the spots were visualized under UV light at 254 or 365 nm. Mixtures of hexane with ethyl acetate (AcOEt) were used to run TLC and for measuring retention factors (R_f). Flash column chromatography was performed using silica gel (230-400 mesh) and mixtures of hexane with AcOEt in different proportions (v/v) as mobile phase. All starting materials were purchased from Sigma-Aldrich and were used without further purification. Chemical names and drawings were obtained using the ChemBioDraw Ultra 13.0.2.3020 software package. The purity for all the synthesized products (up to 99%) was assessed by NMR.

4.2 Synthesis and characterization of the pyrrolo[3,4-*b*]pyridin-6-yl-acetonitriles **8a-h**

General procedure (GP): the corresponding 2-aminonitrile oxazoles **12a-h** (1.0 equiv.), maleic anhydride (**13**) (2.0 equiv.) and $Sc(OTf)_3$ (3% mol) were placed in a 10 mL sealed CEM Discover™ microwave reaction tube and diluted in 1.0 mL of dry toluene. Then, the mixture was irradiated (MW, 100 °C, 150 W) for 60 min, and the solvent was removed to dryness under reduced pressure. The crude was dissolved in CH_2Cl_2 (5.0 mL) and washed with aqueous $NaHCO_3$ (3 × 25 mL) and brine (3 × 25 mL). The organic layer was dried with Na_2SO_4, filtered and the solvent was removed to dryness under vacuum. The residue was purified by silica-gel chromatoflash using mixtures of hexanes–EtOAc (*v*/*v*) in different proportions to afford the corresponding 6-aminonitril pyrrolo[3,4-*b*]pyridin-5-ones (**8a-h**).

2-(2-Benzyl-3-morpholino-5-oxo-7-phenyl-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)acetonitrile (**8a**)

According to GP: 2-aminonitrile oxazole (**12a**) (136.0 mg, 0.303 mmol), maleic anhydride (59.4 mg, 0.606 mmol) and scandium triflate (4.5 mg, 0.009 mmol) were reacted together in toluene (1.0 mL) to afford the pyrrolo[3,4-*b*]pyridin-6-yl-acetonitrile **8a** (109.0 mg, 71%) as a yellow gum; R_f = 0.25 (hexane-AcOEt = 3:2 *v*/*v*); FT-IR (ATR) υ_{max}/cm^{-1} 1702 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.90 (s, 1H) 7.43–7.39 (m, 3H), 7.31–7.26 (m, 1H), 7.23–7.10 (m, 7H), 5.62 (s, 1H), 4.96 (d, *J* = 17.5 Hz, 1H), 4.31 (d, *J* = 13.9 Hz, 1H), 4.23 (d, *J* = 13.8 Hz, 1H), 3.88–3.78 (m, 4H), 3.73 (d, *J* = 17.5 Hz, 1H), 2.93–2.72 (m, 4H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 166.5, 163.3, 159.7, 148.2, 138.8, 133.6, 129.4, 129.3, 128.6, 128.2, 128.0, 126.2, 124.0, 122.4, 114.5, 67.0, 65.2, 52.9, 40.0, 28.4 ppm.

2-(2-Benzyl-7-(3,4-dimethoxyphenyl)-3-morpholino-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)acetonitrile (**8b**)

According to the GP: 2-aminonitrile oxazole **12b** (94.0 mg, 0.242 mmol), maleic anhydride (47.0 mg, 0.483 mmol) and scandium triflate (3.5 mg, 0.007 mmol) were reacted together in toluene (1.0 mL) to afford the pyrrolo[3,4-*b*]pyridin-6-yl-acetonitrile **8b** (73.0 mg, 74%) as a yellow gum; R_f = 0.11 (hexanes-AcOEt = 3:2 v/v); FT-IR (ATR) υ_{max}/cm^{-1} 1709 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.92 (s,

1H), 7.24–7.21 (m, 1H), 7.14–7.04 (m, 1H), 6.83–6.79 (m, 1H), 6.76–6.72 (m, 1H), 6.33 (s, 1H), 5.59 (s, 1H), 4.85 (d, *J* = 17.3 Hz, 1H), 4.31–4.23 (s, 2H), 3.82 (s, 3H), 3.78–3.74 (m, 4H), 3.72 (s, 3H), 3.67 (d, *J* = 17.1 Hz, 1H) 2.91–2.65 (m, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 166.1, 162.9, 158.7, 150.0, 149.8, 148.4, 138.8, 135.5, 134.6, 128.8, 128.2, 126.3, 121.1, 114.6, 111.6, 110.6, 67.1, 65.0, 56.1, 56.0, 54.5 , 39.7, 28.5 ppm.

2-(2-Benzyl-7-(4-chlorophenyl)-3-morpholino-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)acetonitrile (**8c**)

According to GP: 2-aminonitrile oxazole **12c** (101.0 mg, 0.239 mmol), maleic anhydride (46.8 mg, 0.477 mmol) and scandium triflate (3.5 mg, 0.007 mmol) were reacted together in toluene (1.0 mL) to afford the pyrrolo[3,4-*b*]pyridin-6-yl-acetonitrile **8c** (81.0 mg, 74%) as a white solid; R_f = 0.21 (hexane-AcOEt = 3:2 v/v); m.p. 168-171 °C; FT-IR (ATR) υ_{max}/cm^{-1} 1699 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.88 (s, 1H), 7.42–7.37 (m, 2H), 7.31–7.26 (m, 1H), 7.20–7.13 (m, 6H), 5.59 (s, 1H), 4.98 (d, *J* = 17.6 Hz, 1H), 4.31 (d, *J* = 13.9 Hz, 1H), 4.22 (d, *J* = 13.9 Hz, 1H), 3.88–2.78 (m, 4H), 3.74 (d, *J* = 17.3 Hz, 1H), 3.01–2.65 (m, 4H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 166.5, 163.5, 159.3, 148.4, 138.8, 135.5, 132.3, 129.7, 129.4, 128.7, 128.3, 126.4, 124.0, 122.3, 114.4, 67.1, 64.6, 53.0, 40.1, 28.5 ppm.

2-(2-Benzyl-7-hexyl-3-morpholino-5-oxo-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)acetonitrile (**8d**)

According to GP: 2-aminonitrile oxazole **12d** (110.0 mg, 0.277 mmol), maleic anhydride (54.4 mg, 0.555 mmol) and scandium triflate (4.1 mg, 0.008 mmol) were reacted together in toluene (1.0 mL) to afford the pyrrolo[3,4-*b*]pyridin-6-yl-acetonitrile **8d** (81.0 mg, 68%) as a brown gum; R_f = 0.25 (hexane-AcOEt = 3:2 v/v); FT-IR (ATR) υ_{max}/cm^{-1} 1701 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.88 (s, 1H), 7.30–7.18 (m, 5H), 4.85 (d, *J* = 16.3 Hz, 1H), 4.80–4.59 (m, 1H), 4.56–4.42 (m, 1H), 4.42–4.29 (m, 1H), 4.23 (d, *J* = 13.1 Hz, 1H), 3.92–3.76 (m, 4H), 3.03–2.70 (m, 4H), 2.46–2.27 (m, 1H), 2.10–1.87 (m, 1H), 1.35–1.04 (m, 8H), 0.84 (t, *J* = 6.75 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 166.5, 162.2, 159.1, 148.2, 138.9, 128.9, 128.4, 126.5, 124.5, 123.6, 114.6, 67.1, 61.2, 53.1, 38.8, 31.5, 29.4, 29.0, 28.7, 22.7, 22.5, 14.0 ppm.

2-(2-Benzyl-5-oxo-7-phenyl-3-(piperidin-1-yl)-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)acetonitrile (**8e**)

According to GP: 2-aminonitrile oxazole **12e** (236.0 mg, 0.610 mmol), maleic anhydride (119.7 mg, 1.220 mmol) and scandium triflate (9.0 mg, 0.018 mmol) were reacted together in toluene (1.0 mL) to afford the pyrrolo[3,4-*b*]pyridin-6-yl-acetonitrile **8e** (180.0 mg, 69%) as a pale yellow gum; R_f = 0.61 (hexane-AcOEt = 3:2 v/v); FT-IR (ATR) υ_{max}/cm^{-1} 1704 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.82 (s, 1H), 7.39–7.30 (m, 3H), 7.21–7.04 (m, 7H), 5.57 (s, 1H), 4.89 (d, *J* = 16.8 Hz, 1H), 4.42–4.07 (m, 2H), 3.65 (d, *J* = 17.3 Hz, 1H), 2.95–2.46 (m, 4H), 1.85–1.56 (m, 4H), 1.56–1.48 (m, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 166.5, 163.1, 158.9, 149.3, 138.9, 133.7, 129.5, 129.4, 129.0, 128.3, 128.2, 126.3, 124.1, 122.6, 114.5, 65.4, 54.6, 40.0, 28.6, 26.2, 23.8 ppm.

2-(2-Benzyl-7-(3,4-dimethoxyphenyl)-5-oxo-3-(piperidin-1-yl)-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)acetonitrile (**8f**)

According to GP: 2-aminonitrile-oxazoles **12f** (227.0 mg, 0.508 mmol), maleic anhydride (99.7 mg, 1.02 mmol) and scandium triflate (7.5 mg, 0.015 mmol) were reacted together in toluene (1.0 mL) to afford the pyrrolo[3,4-*b*]pyridin-6-yl-acetonitrile **8f** (187.0 mg, 76%) as a brown gum; R_f = 0.28 (hexane-AcOEt = 3:2 v/v); FT-IR (ATR) υ_{max}/cm^{-1} 1715 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.82 (s, 1H), 7.22–7.19 (m, 1H), 7.19–7.14 (m, 2H), 7.10–7.06 (m, 2H), 6.83–6.80 (m, 1H), 6.77–6.71 (m, 1H), 6.50 (s,

1H), 5.52 (s, 1H), 4.86 (d, *J* = 17.4 Hz, 1H), 4.29 (d, *J* = 13.7 Hz, 1H), 4.24 (d, *J* = 13.8 Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 3.67 (d, *J* = 17.6 Hz, 1H), 2.88–2.67 (m, 4H), 1.75–1.62 (m, 4H), 1.56–1.51 (m, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 166.1, 162.9, 158.7, 150.0, 149.8, 148.4, 138.8, 135.5, 134.6, 128.8, 128.2, 126.3, 121.1, 114.6, 111.6, 110.6, 65.0, 56.1, 56.0, 54.5 , 39.7, 28.4, 26.1, 23.7 ppm.

2-(2-Benzyl-7-(4-chlorophenyl)-5-oxo-3-(piperidin-1-yl)-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)aceto nitrile (**8g**)

According to GP: 2-aminonitrile oxazoles **12g** (245.0 mg, 0.582 mmol), maleic anhydride (114.1 mg, 1.16 mmol) and scandium triflate (8.5 mg, 0.017 mmol) were reacted together in toluene (1.0 mL) to afford the pyrrolo[3,4-*b*]pyridin-6-yl-acetonitrile **8g** (188.0 mg, 70%) as a yellow gum; R_f = 0.61 (hexane-AcOEt = 3:2 v/v); FT-IR (ATR) υ_{max}/cm^{-1} 1707 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.77 (s, 1H), 7.33–7.28 (m, 2H), 7.15–7.03 (m, 7H), 5.51 (s, 1H), 4.88 (d, *J* = 17.5 Hz, 1H), 4.24 (d, *J* = 13.4 Hz, 1H), 4.14 (d, *J* = 13.5 Hz, 1H), 3.66 (d, *J* = 17.4 Hz, 1H), 2.88–2.63 (m, 4H), 1.77–1.63 (m, 4H), 1.54–1.49 ppm (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 166.5, 163.4, 158.4, 138.9, 135.4, 132.5, 129.6, 129.5, 128.9, 128.2, 127.5, 126.3, 123.6, 114.4, 64.5, 54.3, 28.5, 26.2, 23.8 ppm.

2-(2-benzyl-7-hexyl-5-oxo-3-(piperidin-1-yl)-5,7-dihydro-6*H*-pyrrolo[3,4-*b*]pyridin-6-yl)acetonitrile (**8h**)

According to GP: 2-aminonitrile oxazole **12h** (137.0 mg, 0.347 mmol), maleic anhydride (68.1 mg, 0.694 mmol) and scandium triflate (5.1 mg, 0.010 mmol) were reacted together in toluene (1.0 mL) to afford the pyrrolo[3,4-*b*]pyridin-6-yl-acetonitrile **8h** (149.5 mg, 66%) as a brown gum; R_f = 0.64 (hexane-AcOEt = 3:2 v/v); FT-IR (ATR) υ_{max}/cm^{-1} 1720 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.82 (s, 1H), 7.39–7.29 (m, 3H), 7.22–7.04 (m, 7H), 5.57 (s, 1H), 4.89 (d, *J* = 16.9 Hz, 1H), 4.42–4.07 (m, 2H), 3.65 (d, *J* = 17.7 Hz, 1H), 2.96–2.46 (m, 4H), 1.85–1.57 (m, 4H), 1.57–1.49 (m, 2H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$, 25 °C): δ 173.0, 166.6, 158.8, 134.8, 134.2, 130.9, 129.1, 128.8, 128.7, 127.4, 115.8, 60.5, 39.3, 34.8, 31.7, 29.3, 28.8, 28.7, 25.0, 24.8, 24.3, 22.6, 14.0 ppm.

Author Contributions: All authors contributed equally to this work.

Acknowledgments: M.A.R.G. (707974/585367) and S.G.P. (636753/573230) thank CONACYT for their scholarships. A.I.-J. acknowledges QI-DQ-CBI-UAMI for his visiting professor position (40966) and PRODEP-SEP for financial support (12413143). E.G.-Z. thanks CONACyT-México (CB-2014-236879) for financial support. R.G.-M- thanks CONACYT-México (CB-2016-285622) for her project.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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The samples of the products **8a-h** are available from the authors.