

Multicomponent Synthesis of the New Compound 2-Benzyl-6-(3-((7-chloroquinolin-4-yl)amino)propyl)-3-morpholino-7-(4-pyridin-2-yl)phenyl)-6,7-dihidro-5H-pyrrolo[3,4-*b*]pyridin-5-one [†]

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Abstract

The combination of multicomponent reactions with post-transformation processes is a powerful strategy for the rapid synthesis of structurally complex polyheterocycles. Herein, we describe the preparation of the novel compound 2-benzyl-6-(3-((7-chloroquinolin-4-yl)amino)propyl)-3-morpholino-7-(4-(pyridin-2-yl)phenyl)-6,7-dihidro-5H-pyrrolo[3,4-*b*]pyridin-5-one via a sequence that combines an Ugi-Zhu reaction with a cascade process (*aza*-Diels–Alder/*N*-acylation/aromatization) under microwave irradiation in chlorobenzene using ytterbium (III) triflate (Yb(OTf)₃) as the catalyst. The method provided the target polyheterocycle in 75% yield and 85% atom economy. Structural characterization was performed by 1D (¹H and ¹³C) and 2D (COSY, HSQC and HMBC) NMR spectroscopy, and the molecular mass was confirmed by high-resolution mass spectrometry (HRMS). These results illustrate the effectiveness of MCR as powerful synthetic tools for expanding chemical diversity.

Keywords: multicomponent reactions; Ugi-Zhu reaction; MW-assisted reactions; quinoline

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1. Introduction

Multicomponent reactions (MCRs) are convergent processes that allow for the creation of complex molecules with high atom economy, utilizing three or more components [1]. These reactions are particularly appealing because, with the careful selection of starting components, it is possible to incorporate multiple privileged chemical structures important in both medicinal chemistry and materials science. This one significantly expands the potential applications of the compounds synthesized through these methods. A notable example is the synthesis of polyheterocycles featuring a pyrrolo[3,4-*b*]pyridin-5-one core, which is an *aza*-analogue of the isoindolin-2-one, a well-established privileged structure in medicinal chemistry [2]. The pyrrolo[3,4-*b*]pyridin-5-one core can be assembled through a one-pot process involving an Ugi-Zhu reaction (UZ-3CR) coupled to a cascade sequence that includes a *N*-acylation, an *aza*-Diels–Alder cycloaddition, and an

aromatization [3]. Compounds derived from this method have shown considerable biological activity as well as luminescent properties (Figure 1) [4–8]. In this work, we describe the synthesis and characterization of a new polyheterocyclic compound containing the pyrrolo[3,4-*b*]pyridin-5-one core. This compound incorporates the privileged structures of quinoline and 2-phenylpyridine, with the latter being particularly relevant for applications in materials science [9].

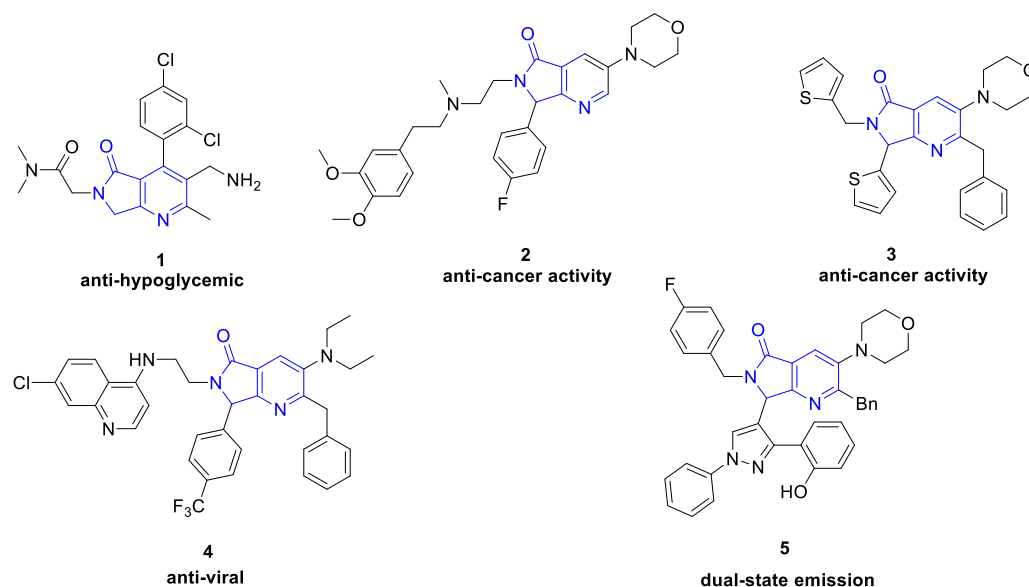


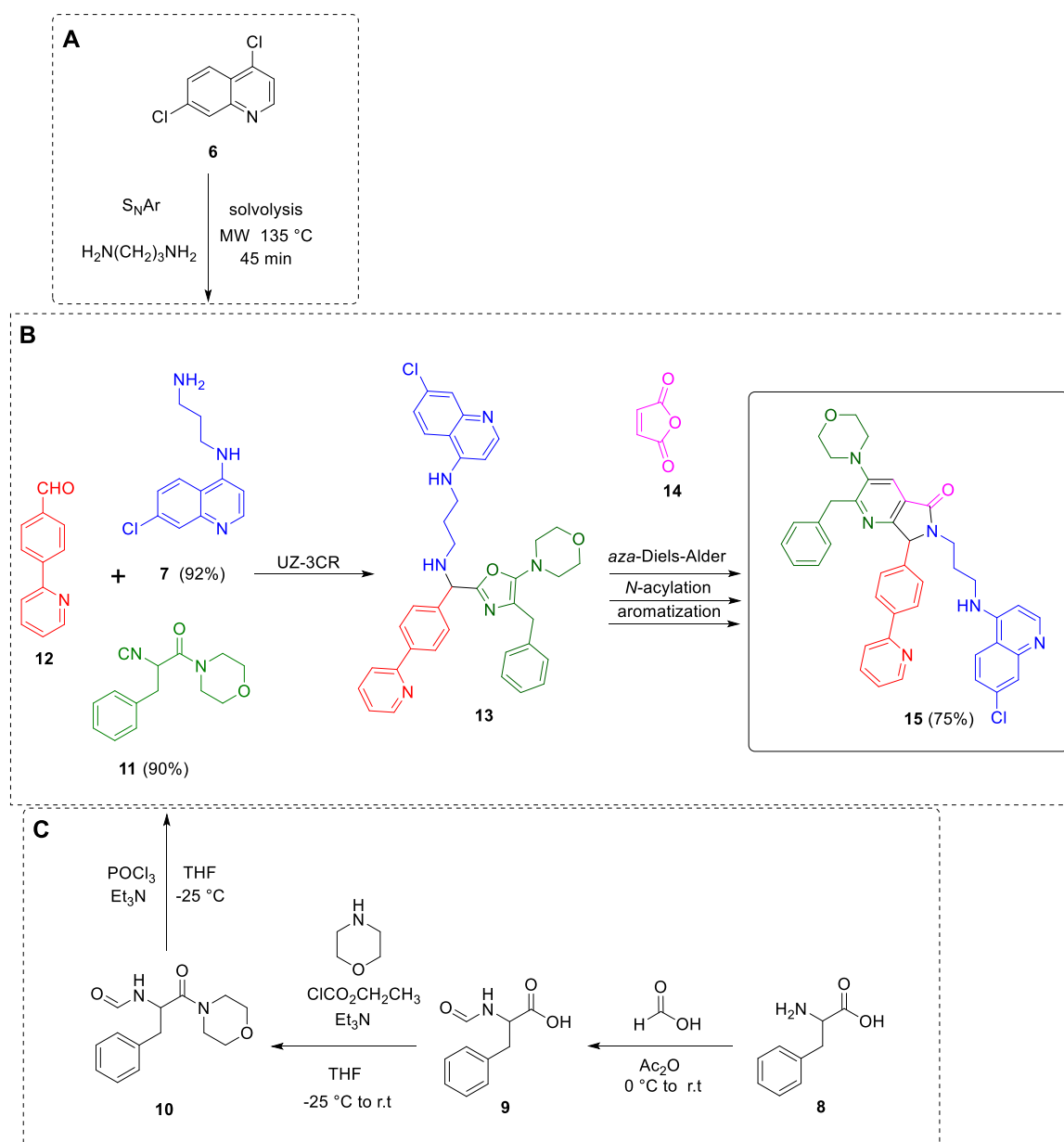
Figure 1. Polyheterocycles based on the pyrrolo[3,4-*b*] pyridin-5-one core with biological and luminescent properties.

2. Results and Discussion

In order to access to the desired polyheterocycle, the initial step involved the synthesis of two key components: the aminoquinoline **7** and the α -isocyanoacetamide **11**. The 4-(2-pyridyl)benzaldehyde **12** was used as a commercially available reagent without needing purifications.

The aminoquinoline **7** was obtained via a nucleophilic aromatic substitution (S_NAr) on 4,7-dichloroquinoline **6**, employing propane-1,3-diamine as the nucleophile, under solvent-free conditions and microwave irradiation (135 °C, 100 W). Under these conditions, the desired product was obtained in 92% yield (Scheme 1A).

The α -isocyanoacetamide **11** was synthesized from racemic phenylalanine **8** through a three-step sequence involving a formylation, a peptide coupling, and an Ugi-type dehydration. This synthetic route was adapted from the protocol reported by Bienaymé and coworkers, affording the target compound in an overall yield of 90% (Scheme 1C) [10].



Scheme 1. (A) Synthetic route to aminoquinoline **7**, (B) Synthetic route to α -isocyanoacetamide, (C) Synthetic route to access pyrrolo[3,4-*b*]pyridin-5-one.

Once all components were ready, the Ugi–Zhu three-component reaction was performed. Therefore, 4-(2-pyridyl)benzaldehyde **12** was reacted with *N*¹-(7-chloroquinolin-4-yl)propane-1,3-diamine **7** in chlorobenzene under microwave irradiation at 80 °C and 100 W. After 25 min., thin-layer chromatography (TLC) analysis confirmed the complete consumption of the aldehyde **12**. Next, ytterbium triflate (Yb(OTf)₃) was added as an imine activator (Table 1, entry 1). The reaction mixture was irradiated at 65 °C and 100 W. After this step, 2-isocyano-1-morpholino-3-phenylpropan-1-one **11** was introduced, and the mixture was heated again to 80 °C at 100 W for 30 min. This process yielded the corresponding 5-aminooxazole **13**, as confirmed by TLC analysis. At this point, maleic anhydride **14** was added, which was reacted with the 5-aminooxazole **13** at 80 °C under microwave irradiation at 100 W for 25 min, initiating a cascade process that involved an *aza*-Diels–Alder cycloaddition coupled to a *N*-acylation and a subsequent aromatization through a tandem decarboxylation / dehydration process, ultimately resulting in the formation of the pyrrolo[3,4-*b*]pyridin-5-one **15** with an overall 51% yield (Scheme 1B).

To enhance the overall yield, the effect of using various loadings of ytterbium triflate was evaluated (Table 1, entry 2). The presence of nitrogen atoms in both aminoquinoline and the aldehyde may lead to undesired coordination with the ytterbium center. This one could interfere with its interaction with the imine intermediate and negatively affect the subsequent *aza* Diels–Alder cycloaddition. It is important to note that ytterbium has been shown to facilitate this type of cycloadditions [11]. Under these conditions, the highest yield was achieved with a loading of 10 mol% of Yb(OTf)₃ (Table 1, entry 3). Increasing the catalyst loading beyond this amount did not result in any significant improvement (Table 1, entry 4).

Table 1. Variation of the amount of ytterbium triflate.

Entry	% mol Yb(OTf) ₃	Yield (%) ^a
1	5%	51
2	7%	64
3	10%	75
4	12%	74

^a Yields measured after the purification of the compound **15**.

The synthesized polyheterocycle **15** was thoroughly characterized using nuclear magnetic resonance spectroscopy (¹H, ¹³C, COSY, HMBC, and HSQC), and its molecular weight was confirmed through high-resolution mass spectrometry (HRMS). See the [ESM](#) file for further details and to access to all copies of all spectra. This novel compound is anticipated to demonstrate promising biological activity and luminescent properties.

3. Experimental Section

3.1. General Information, Instrumentation and Chemicals

Hydrogen-1 (¹H) and Carbon-13 (¹³C) Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Avance III 500 MHz spectrometer, using deuterated chloroform (CDCl₃) as the solvent. Chemical shifts (δ) are reported in parts per million (ppm) relative to the internal standard tetramethylsilane (TMS). Coupling constants (*J*) are expressed in Hertz (Hz), and signal multiplicities are described using the conventional abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). NMR data were processed and analyzed using MestReNova software (version 14.2.0-26256). Reaction progress was monitored by thin-layer chromatography (TLC) on plastic plates pre-coated with silica gel F₂₅₄, with spot visualization under UV light at 254 nm and 360 nm. Flash column chromatography was carried out on silica gel (230–400 mesh), employing mixtures of hexanes and ethyl acetate as the eluent system. These solvent mixtures were also used for TLC development and for determination of retention factors (*R_f*). All chemicals and reagents were obtained from Sigma-Aldrich and used as received, without further purification. Chemical structures were generated using ChemDraw Professional software (version 15.0.0.106, PerkinElmer Informatics, Cambridge, MA, USA).

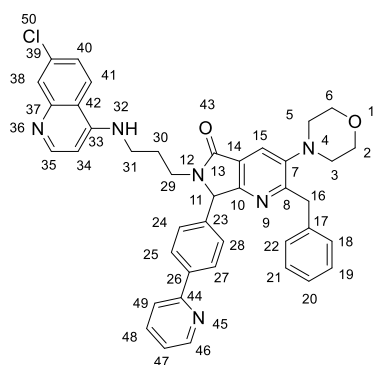
3.2. General Procedure

In a 10 mL microwave reactor tube (CEM Discover system) equipped with magnetic stirring, 2.0 mL of anhydrous chlorobenzene (PhCl) was added, followed by the addition of 1 mmol (1 equiv.) of 4-(2-pyridyl)benzaldehyde and 1 mmol (1 equiv.) of *N*¹-(7-chloroquinolin-4-yl)propane-1,3-diamine. The reaction mixture was heated under microwave irradiation at 80 °C and 100 W for 25 min. Subsequently, 0.1 mmol (0.1 equiv.) of ytterbium triflate (Yb(OTf)₃) was added, and the mixture was subjected to microwave heating at 65 °C and 100 W for 5 min. Then, 1.2 mmol (1.2 equiv.) of 2-isocyano-1-morpholino-3-

phenylpropan-1-one was added, and the reaction was continued at 80 °C and 100 W for an additional 30 min. Finally, 1.2 mmol (1.2 equiv.) of maleic anhydride was introduced, and the mixture was heated once again at 80 °C and 100 W for 30 min. Upon completion of the reaction, the crude mixture was transferred to a 100 mL separatory funnel, followed by the addition of 15 mL of saturated K₂CO₃ solution and 15 mL of ethyl acetate (EtOAc). The organic layer was separated, and liquid–liquid extractions were performed. The organic phase was evaporated to dryness under reduced pressure. The crude product was purified by column chromatography using silica gel as the stationary phase and mixtures of hexane and ethyl acetate as eluents. Final purification was carried out by preparative chromatography, also using silica-gel as the stationary phase and a hexane/ethyl acetate mixture (3:2 v/v) as the eluent. A slightly yellow solid 0.51 g was obtained.

3.3. Spectral Data

2-benzyl-6-(3-((7-chloroquinolin-4-yl)amino)propyl)-3-morpholino-7-(4-(pyridin-2-yl)phenyl)-6,7-dihydro-5H-pyrrolo[3,4-*b*]pyridin-5-one



¹H NMR (500 MHz, CDCl₃): δ 8.69 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H, H-46), 8.45 (d, *J* = 5.4 Hz, 1H, H-35), 8.00–7.96 (m, 3H, H-41, H-27, H-25), 7.93 (s, 1H, H-15), 7.91 (d, *J* = 2.4 Hz, 1H, H-38), 7.78–7.74 (m, 1H, H-48), 7.72–7.69 (m, 1H, H-49), 7.37 (dd, *J* = 8.9, 2.2 Hz, 1H, H-40), 7.27–7.23 (m, 3H, H-47, H-28, H-24), 7.18–7.11 (m, 5H, H-22, H-21, H-20, H-19, H-18), 6.59 (t, *J* = 6.5 Hz, 1H, H-32), 6.32 (d, *J* = 5.5 Hz, 1H, H-34), 5.30 (s, 1H, H-11), 4.33 (d, *J* = 13.9 Hz, 1H, H-16), 4.20 (d, *J* = 13.9 Hz, 1H, H-16'), 3.95–3.87 (m, 1H, H-29), 3.82 (t, *J* = 4.6 Hz, 3H, H-6, H-2), 3.51–3.41 (m, 1H, H-31), 3.40–3.30 (m, 1H, H-31'), 3.30–3.22 (m, 1H, H-29'), 2.93–2.47 (m, 4H, H-5, H-3), 1.84–1.66 (m, 2H, H-30); ¹³C NMR (125 MHz, CDCl₃): δ 168.5 (C-13), 162.6 (C-10), 160.1 (C-8), 156.5 (C-44), 151.8 (C-35), 149.8 (C-46), 149.7 (C-37, C-33), 149.3 (C-7), 148.1 (C-26), 140.2 (C-42), 139.1 (C-17), 136.8 (C-48), 135.8 (C-23), 134.8 (C-39), 128.7 (C-15), 128.5 (C-38), 128.4 (C-20, C-14), 128.2 (C-28, C-24), 127.6 (C-27, C-25), 126.2 (C-22, C-18), 125.3 (C-40), 123.7 (C-41), 122.5 (C-47), 121.8 (C-21, C-19), 120.5 (C-49), 117.6 (C-42), 98.4 (C-34), 67.1 (C-6, C-2), 65.9 (C-11), 53.0 (C-5, C-3), 40.1 (C-16), 39.0 (C-31), 37.9 (C-29), 26.0 (C-30); HRMS (ESI⁺): *m/z* calcd for C₄₁H₃₇ClN₆O₂ [M + H]⁺ 681.2735, found 681.2739.

4. Conclusions

The MCR/cascade methodology allowed the synthesis of a structurally complex polycyclic heterocycle containing a couple of biologically relevant and luminescent fragments in just 90 min. This process required only a single step for purification and isolation. Remarkably, 85% of the atoms from the starting materials were incorporated into the final product, while two molecules of H₂O and one CO₂ were produced as by-products.

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and editing; A.I.-J., funding acquisition, conceptualization, and writing-review and editing. All authors have read and agreed to the published version of the manuscript.

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