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MCR-based C1 heteroannulations

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Abstract

C1 chemistry has a central role in efficiently utilizing single-carbon-molecules contributing significantly to sustainability, innovation and economic growth across various sectors. In this study, we present an efficient and rapid method for synthesizing a variety of heteropyrimidones using cyanoacetamide-based multicomponent reaction (MCR) chemistry. By employing the abundant and inexpensive formamide as a C1 feedstock under neat conditions, we were able to efficiently access substituted thieno-, quinolino- and indolo-pyrimidones in a one-pot process. A single crystal structure has been obtained revealing certain geometrical features.

Keywords

Multicomponent reactions; cyanoacetamide; pyrimidone; Gewald; 2-amino heterocycles

Introduction

The term “net-zero carbon” is becoming increasingly common as we consider a future marked by rising global temperatures and severe weather patterns, a result of human-induced greenhouse gas emissions. The principle of net zero revolves around the idea of using Earth’s carbon resources at a rate that does not exceed their natural replenishment. In other words, it’s about maintaining equilibrium between the greenhouse gases emitted into the atmosphere and those that are removed, essentially balancing carbon emissions with their sequestration. In 2015, the United Nations introduced the “Sustainable Development Goals (SDGs) from which the 7th goal focuses on ensuring access to affordable, renewable, and clean energy [1]. Moreover, the European Union has committed to ambitious environmental targets as part of the European Green Deal [2]. Very recently, Cefic, Europe’s leading chemical industry association, published a manifesto outlining how the industry could remain competitive while still becoming climate-neutral by 2050. Moreover, U.S. Securities and Exchange Commission (SEC) proposed a rule that would require publicly traded companies to disclose, amongst other things, the amount of greenhouse gases they emit [3]. It is already estimated that the financial burden of failing to reduce emissions is estimated to be about six times greater than the investment required to keep global warming below 2°C [4].

Advancements in C1 chemistry stand as pivotal methods in achieving this equilibrium as shifting towards a net-zero carbon future is essential for synthetic methods [5]. Therefore, advancing C1 chemistry remains a crucial endeavor for our group [6]. In most of the cases, in the synthetic organic chemistry arsenal, C1 compounds are installed by CO, CO_2, HCO_2H, CH_3OH and CH_4 mostly due to the their presence in greenhouse emissions [7]. Although abundant and inexpensive, their

valorization still remains problematic due to their thermodynamic stability and chemical inertness [8–16]. Multicomponent reaction (MCRs) chemistry is a type of a convergent chemistry characterized for its diversity, complexity and efficiency. MCRs are compatible in C1 chemistry, due to in general, great tolerance of the different functional groups. They have mostly employed in the synthesis of oxazolidinones and oxazinanones (NAOs) utilizing CO_2 and CO [6,17–21]. In addition, CDI-based heteroannulations via MCRs have been reported, giving access to drug like scaffolds [22–25]. However, their employment in the C1 efforts should and can be even more enhanced.

Here, we would like to point out the employment of formamide ($HCONH_2$) as alternative relevant building block in C1 chemistry using specific, suitably functionalized MCR-based scaffolds as versatile, synthetic hubs towards privileged scaffolds and high-end chemicals. The reactivity of formamide has been widely explored over the years in heterocyclic chemistry but it has only recently started to being established as C1 feedstock [26]. Its high polarity and dielectric constant (miscible with water)[27] with the ability to solubilize a wide range of reagents, from salts to polymers, proteins and saccharides renders formamide an excellent C1 building block [26]. Thus, our target under the frame of C1 chemistry is to provide a straightforward access to the privileged scaffolds of fused heteropyrimidones, which demonstrate a broad range of biological activities [28–35], including emissive nucleoside analogues [36–38]. Moreover, they have been found in a variety of commercially available drugs (Figure 1).

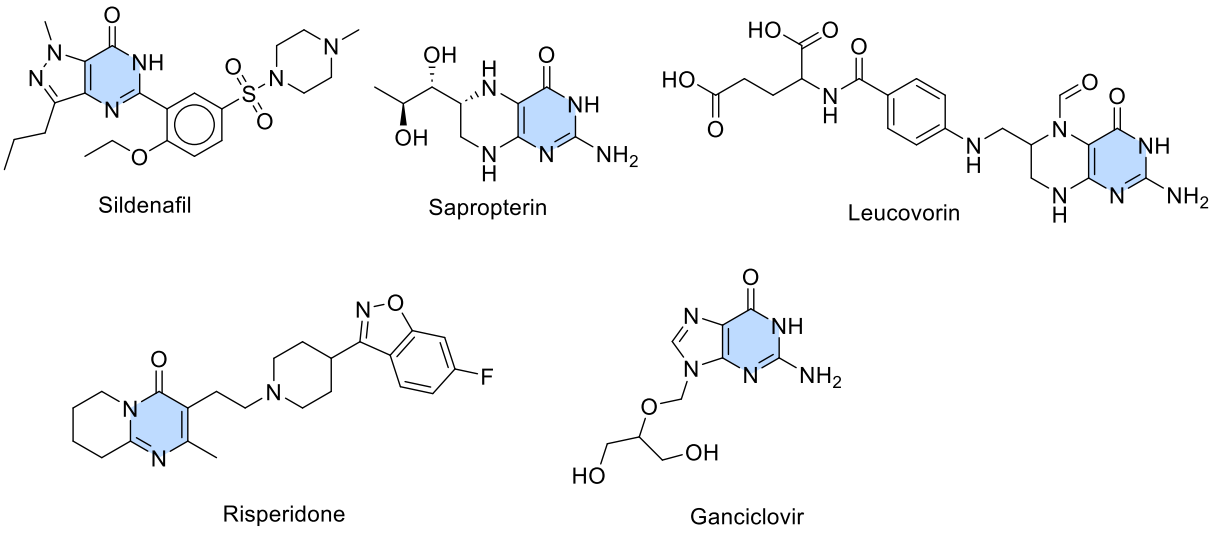
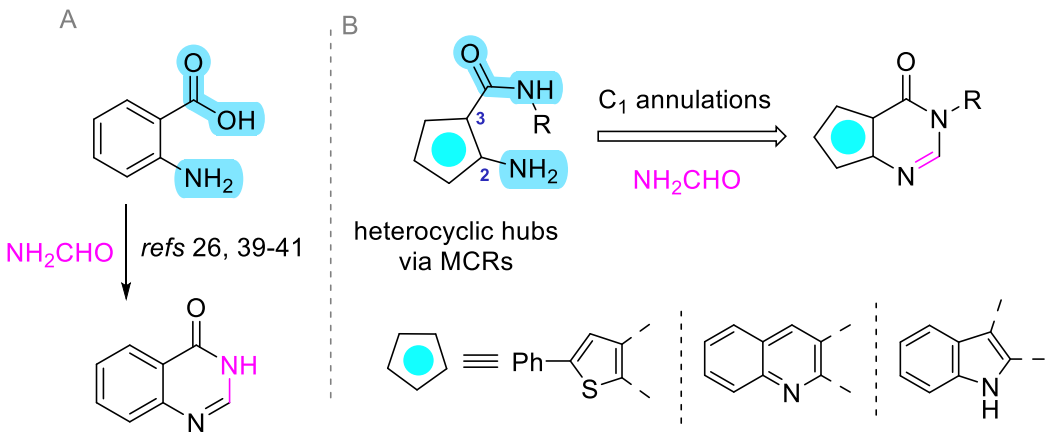


Figure 1. Heteropyrimidones in the drug discovery realm; Blockbuster drugs that are based on the privileged scaffold of pyrimidone.

Results and Discussion

Design and strategy

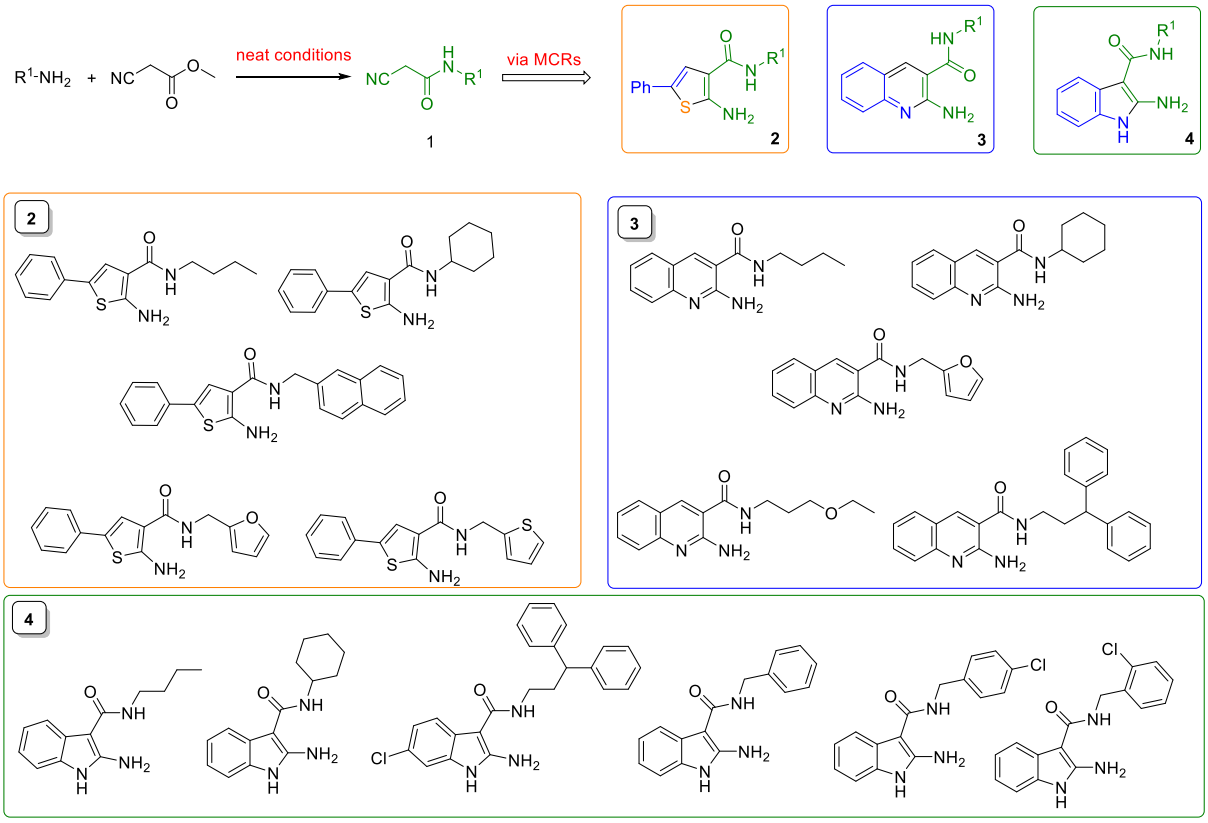
We envisioned applying the Niementowski quinazoline synthesis[26,39–41] (Scheme 1,A) by employing three different heterocyclic systems as precursors, which have an orthogonally installed amino group and a disubstituted amide group at the 2- and 3-position, respectively and react them with formamide (Scheme 1,B). Those synthetic hubs can be rapidly accessed by cyanoacetamide-based MCRs, which is a very interesting type of reactions giving access to privileged cores, utilized numerous times in medchem campaigns as hits, leads and eventually even drugs, such as 2-amino-thiophenes, -quinolines and -indoles [42–45].



Scheme 1. The strategy towards the targeted adducts; (A) The Niementowski quinazoline synthesis utilizing anthranilic acids. (B) Access to heteropyrimidones by exploiting suitably substituted MCR-based heterocycles with formamide as the C1 source.

Exploitation

The synthesis of the key building blocks of cyanoacetamides was our primary objective. In a parallel setup, a variety of primary amines was reacted with methyl cyanoacetate[46] giving rise to the corresponding cyanoacetamides **1** (Scheme 2). Subsequently, they were reacted accordingly to yield a variety of the targeted 2-aminothiophenes **2** via a Gewald three-component reaction (GW-3CR) [42], 2-aminoquinolines **3** [43] and 2-aminoindoles **4** [45]. Our focus was to create a representative library of building blocks with great diversity and complexity, different shape and chemical space coverage. Thus, we have employed aliphatic and (hetero)aromatic, bulky and linear amines with different substitution pattern. The compounds **2-4** were purified by recrystallization and employed as such in a one-pot procedure (Scheme 2).

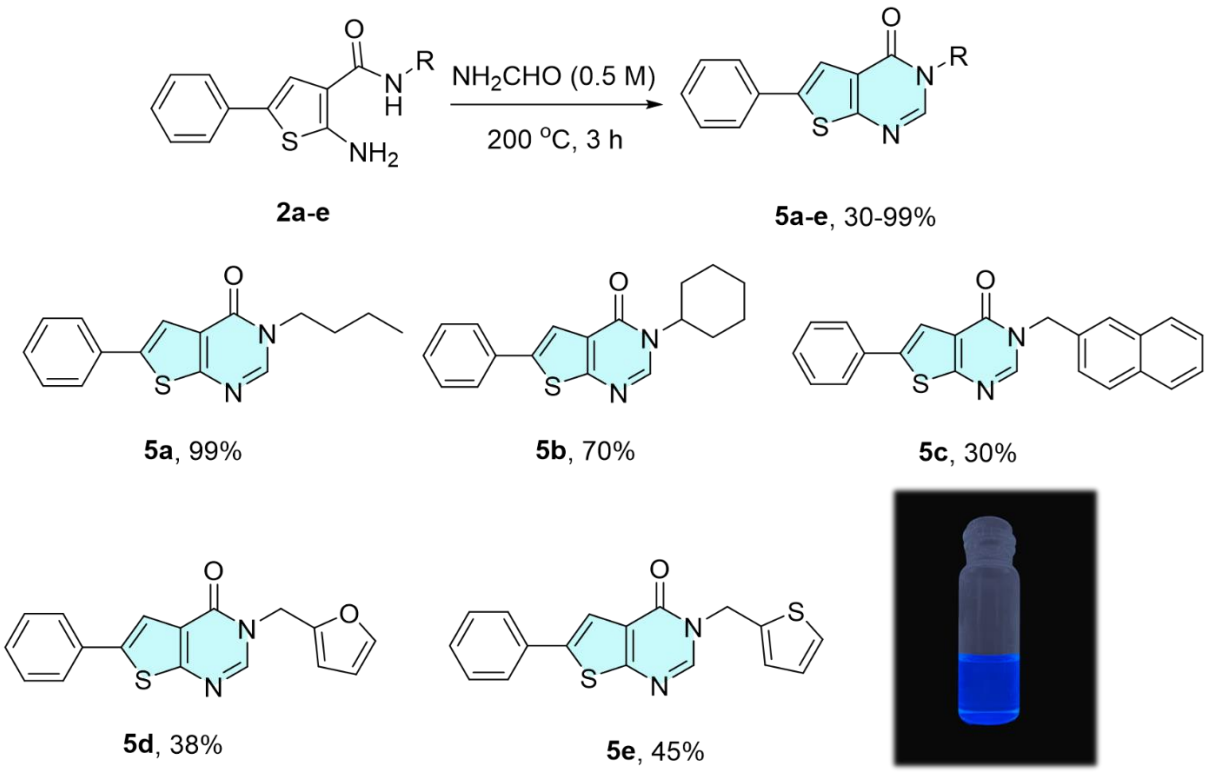


Scheme 2. Access to the key building blocks **2**, **3** and **4** by employing three different non-isocyanide based MCRs. Diversity and complexity are the essential features of our starting material deck.

To our great delight, the corresponding **2**-**4** heterocycles have been successfully subjected with refluxing formamide under neat conditions, yielding instantly the desired thienopyrimidones **5a-e**, quinolinopyrimidones **6a-e** and indolopyrimidones **7a-e**, respectively (Schemes 3-5). In accordance with the reported mechanism [41], after the initial formylation of the amino group at the 2-position, an intramolecular nucleophilic attack by the NH of the amide group is followed yielding to the pyrimidone annulation. This is observed for the first time and completes the reported heteroannulation landscape utilizing the Niementowski reaction [26]. The reactions in general present a quite broad scope, as a great range of cyanoacetamides is compatible. The synthesis is efficient and rapid as the final adducts are being isolated only by precipitation. In

addition, the reactions were performed in a parallel setup using custom-made metal blocks.

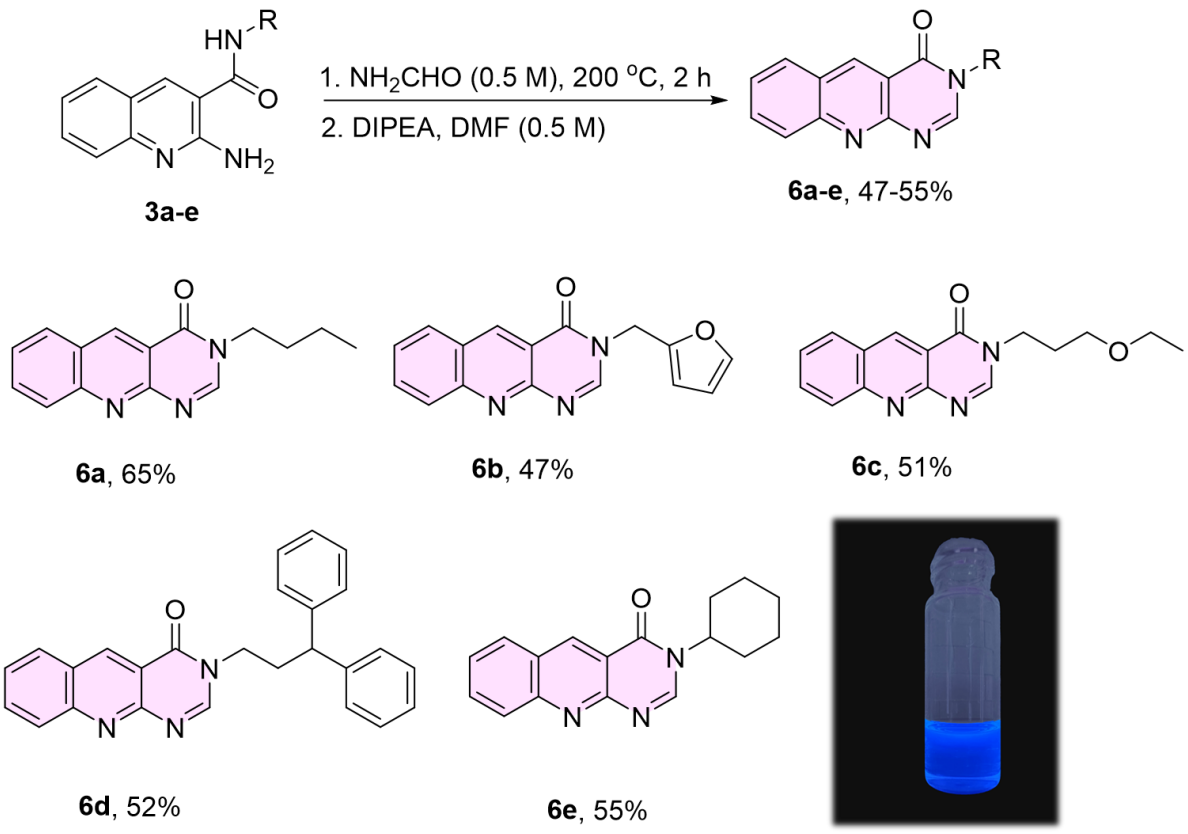
Specifically, thienopyrimidine and thienopyrimidone derivatives exhibit a range of biological activities, i.e. analgesics, anti-inflammatory, antihypertensive and many more (DB06889, DB07397, DB08777) [47–56]. Thienopyrimidone derivatives have also been described by other Gewald-based MCRs in past, but the reported diversity was quite low.[57–60] The reaction of the **2** with formamide is performed in only 3 h (Scheme 3) yielding the *N*-substituted thienopyrimidones **5a-e** in 30-99% total yield with aliphatic and (hetero)aromatic substituents as well.



Scheme 3. Synthesis of *N*-substituted thienopyrimidones **5a-e** by the GW-3CR employing 2-aminothiophenes **2a-e** and formamide as C1 source. A characteristic fluorescence for compound **5a** is reported (DMSO, 365 nm).

Quinoline derivatives are prevalent in nature and many exhibit a range of biological activities, including antimalarial, antitumor, anthelmintic, antibacterial, antiasthmatic, and antiplatelet effects [61–63]. In particular quinolinopyrimidine and pyrimidone

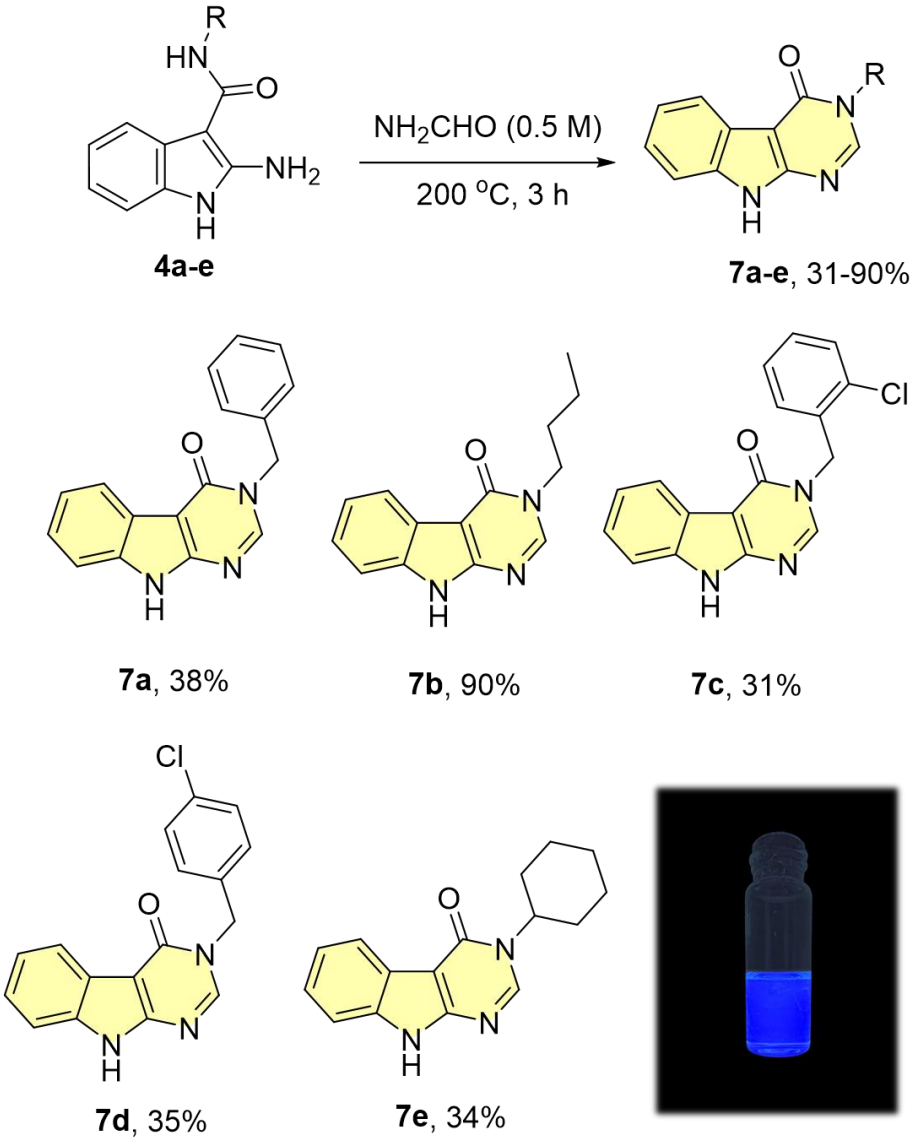
derivatives have attracted a great interest due to their biological profile.[64–69] After some optimization, we found out that the reaction conditions towards the targeted adducts were quite more drastic compared with **5** as basic conditions found to be necessary in order for the reaction to be completed. Additional treatment with *N*,*N*-diisopropylethylamine (DIPEA)/DMF afforded the corresponding substituted quinolinopyrimidones **6a-e** in 47-55% total yield in 12-16 h with a series of aliphatic and aromatic substituents (Scheme 4).



Scheme 4. Synthesis of *N*-substituted qunolinopyrimidones **6a-e** by the 2-amino indoles **3a-e** and formamide as C1 source. A characteristic fluorescence for compound **6c** is reported (DMSO, 365 nm).

Pyrimidines and pyrimidone-bearing indole derivatives are crucial in organic chemistry because of their extensive use as bioactive compounds with a wide array of significant biological activities (DB03074, DB03304, DB08131) [70–72]. In a similar

fashion, substituted indolopyrimidone derivatives **7a-e** have been obtained in 3 h under heating with formamide in 31-90% total yield (Scheme 5).



Scheme 5. Synthesis of *N*-substituted indolopyrimidones **7a-e** by the 2-aminoindoles **4a-e** and formamide as C1 source. A characteristic fluorescence for compound **7b** is reported (DMSO, 365 nm).

In support of the proposed scaffold **7a**, we were able to solve its crystal structure (Figure 2). An intermolecular bifurcated hydrogen bond network of 2.0 Å is revealed demonstrating the potential of those derivatives in drug and material discovery.

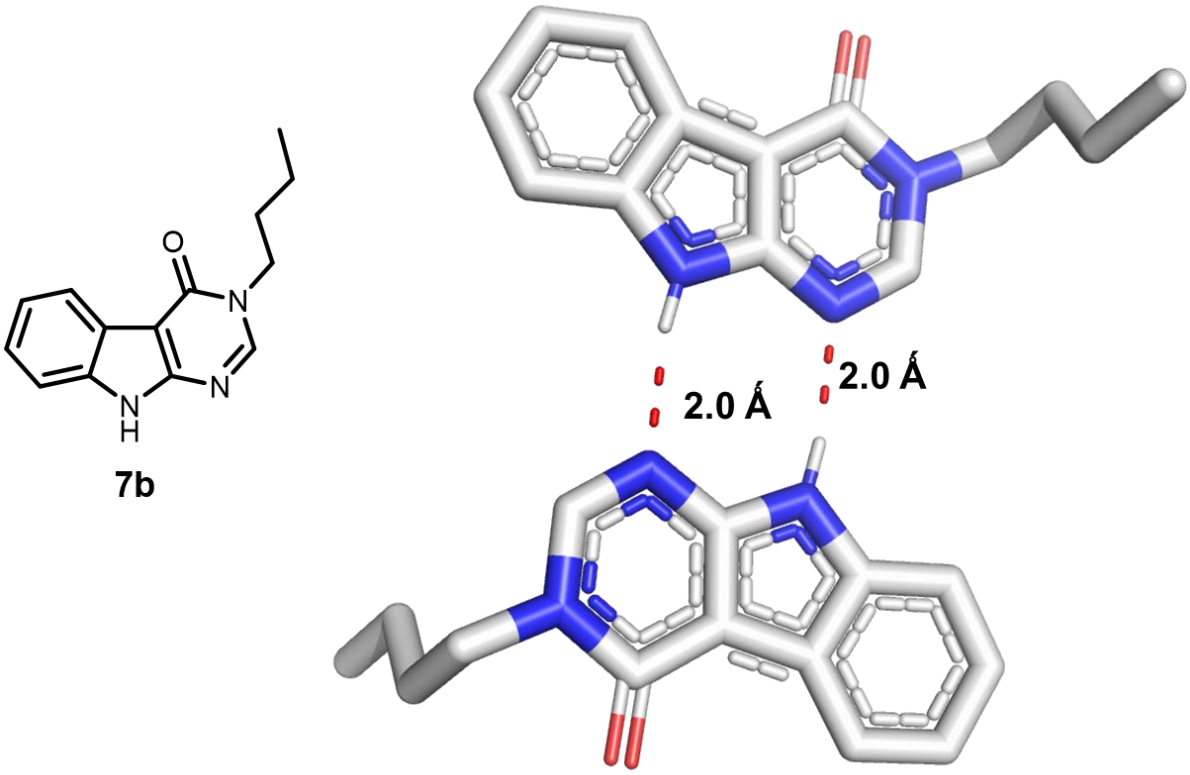


Figure 2. Molecular geometry observed in the crystal structure of compound **7b** (CCDC 2376493)

Conclusion

In conclusion, we successfully integrated the Niementowski quinazoline synthesis with the non-isocyanide-based MCR chemistry within the context of C1 chemistry, thereby expanding and enhancing its repertoire. We have obtained 15 diverse substituted heteropyrimidones employing privileged scaffolds as thiophenes, quinolines and indoles in a rapid and one-pot fashion in a parallel setup.

Supporting Information

Supporting Information: experimental methods, procedures, analytical data and exemplary copies of NMR spectra of novel compounds and single crystal x-ray structure determination methods.

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