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Synthesis of Highly Substituted Imidazole Uracil Containing Molecules via Ugi-4CR and Passerini-3CR

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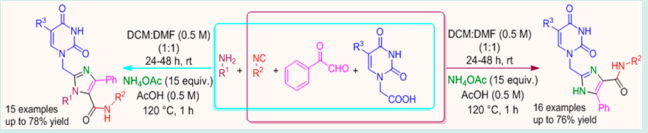
Supporting Information

ABSTRACT: The synthesis of uracil/thymine containing tetra/trisubstituted imidazole derivatives was demonstrated using Ugi/Passerini-reaction followed by a postcyclization reaction sequence. The approach enables the one-pot facile construction of diverse compounds in moderate to excellent yields (47−82%). The 5-fluorouracil and 5-methyluracil moieties afford potentially bioactive molecules with drug-like properties. These scaffolds are currently being utilized in the screening deck of the European Lead Factory.



KEYWORDS: *Ugi-4CR, Passerini-3CR, uracil/thymine, imidazole, one-pot*

Uracil (U), thymine (T), and their corresponding derivatives are highly important fragments in bioactive molecules including drugs and cofactors, for example, 5-fluorouracil and 5-mercaptouracil which are important anticancer agents.[1] In the protein databank there are multiple examples of U and T binding in a highly specific way to different receptors.[2] The CO−NH−CO moiety of T and U binds exclusively, employing all hydrogen bond donor and acceptor atoms (Figure 1). Additionally, the U/T binding site in receptors is mostly very narrow, accommodating the flat six-membered ring tightly and deeply buried. Thus, the heterocyclic U/T comprise a strong anchoring motif and can be used as starting point for the design of U/T mimics which can potentially alter the biological activity of the receptor. Such anchoring motifs (hydrophobic amino acids in protein interface epitopes) have already been successfully used for the design of potent protein−protein interaction small molecular weight antagonists.[3] To leverage nucleobase anchors in drug discovery, fast and efficient access to organic non-nucleotide derivatives is essential and currently not given.

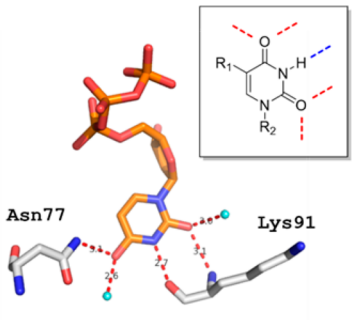


Figure 1. Thymine and uracil are important anchoring moieties toward protein receptors displaying a distinct universal hydrogen bonding network. Above: schematic hydrogen bonding network of U derivatives with hydrogen bond donors and acceptors shown as blue and red dotted lines, respectively. Below: *Mycobacterium tuberculosis* dUTPase complexed with dUTP (PDB ID 1SMC) as an archetypical nucleobase receptor interaction.

Therefore, we propose here the usage of privileged nucleobase building blocks derived from U and T in multicomponent reactions to synthesize nucleobase derivatives in a highly general and efficient way. As a first example, we are grafting the nucleobases U and T onto flat heterocyclic five-membered oxazole and imidazole heterocycles connected by a methylene moiety to allow for sufficient conformational flexibility and drug-like properties. The vast majority of the synthetic routes toward imidazole synthesis focuses on the synthesis of disubstituted imidazole rings.[4,5] The van Leusen three component imidazole synthesis (vL-3CR) is a common and convenient synthetic strategy; however, is limited to tosylmethyl isocyanide (TosMIC) or its derivatives.[6] In recent years there has been a tremendous development in literature for disubstituted imidazoles via multistep ring closing methods which are limited in scope and require harsh conditions.[4] However, synthesizing tri- and tetra-substituted imidazoles having a specific substitution pattern can be challenging. Importantly, uracil containing, tetra-substituted imidazoles are particularly difficult to obtain. In this context, multi component reactions (MCRs) are recognized as valuable tools to decorate the complex molecules in short and mild process.[7] Practically isocyanide based multicomponent reactions (IMCRs) (Ugi and Passerini) are highly convergent processes which have a great impact in pharmaceutical and drug

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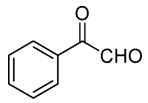
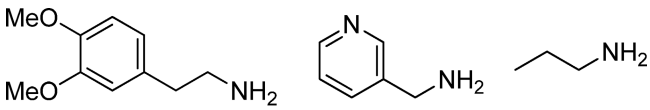
discovery research.[8] Hence, the synthesis of imidazole scaffold by Ugi- and Passerini-reactions could be an interesting subject to study and explore through IMCRs.

Initially, the Ugi four-component reaction (U-4CR) of phenylglyoxal **1**{*1*}, 3,4-dimethoxyphenethylamine **2**{*1*}, cyclohexyl isocyanide **3**{*1*}, and uracil derived acetic acid **4**{*1*} in methanol (1.0 M) furnished the corresponding product in poor yields even after 48 h. After a thorough investigation, it was found that a mixture of DCM/DMF (1:1) was the appropriate combination for this Ugi-reaction to yield up to 90% within 48 h. After completion of the Ugi reaction, we aimed to convert the Ugi products to the corresponding tetra-substituted imidazoles using an excess of NH_4OAc (15 equiv) in acetic acid at 120 °C for 1 h, which afforded the desired product in 75% yield. Next, we investigated the U-4CR and the postcyclization reaction in a one pot-sequence. The optimized conditions can be described as, the use of 1.0 equiv of isocyanide **3**{*1*} relative to the aldehyde **1**{*1*} (1.0 mmol), amine **2**{*1*} (1.0 mmol), and **4**{*1*} (1.0 mmol) in DCM:DMF (1:1) at 25 °C for 48 h. After quick filtration and evaporation of the solvents, the resulting crude material was treated with NH_4OAc (15 equiv) in AcOH at 120 °C for 1 h furnishing the desired product **6**{*1,1,1,1*} in 60% overall yield.



1{1}

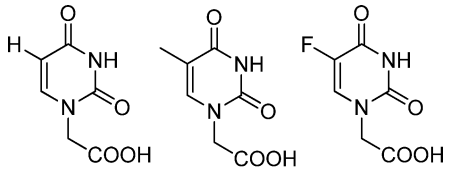
Figure 2. Chemset **1** consisting of phenyl glyoxal.



2{1} **2**{2} **2**{3}

Figure 3. Chemset **2** consisting of amines.

All isocyanides afforded the corresponding imidazoles in good yields (Table 1). Interestingly, even the bulky adamantine **3**{*10*} and camphor **3**{*9*} derived isocyanides reacted nicely. The U4CR and post cyclization reaction worked with all aliphatic and aliphatic-aromatic amines resulting in a variety of tetra-substituted imidazoles in good to excellent overall yields (Table 1). Products **6**{*1,1,8,3*} (57%) and **6**{*1,1,8,2*} (47%) obtained from 5-fluorouracil and 5-methyluracil acetic acids respectively are interesting analogs of the marketed drugs Retrovir and Tegafur obtained in just two synthetic steps. Both tri- and tetra-substituted imidazole libraries reported within the



4{1} **4**{2} **4**{3}

Figure 5. Chemset **4** consisting of acids.

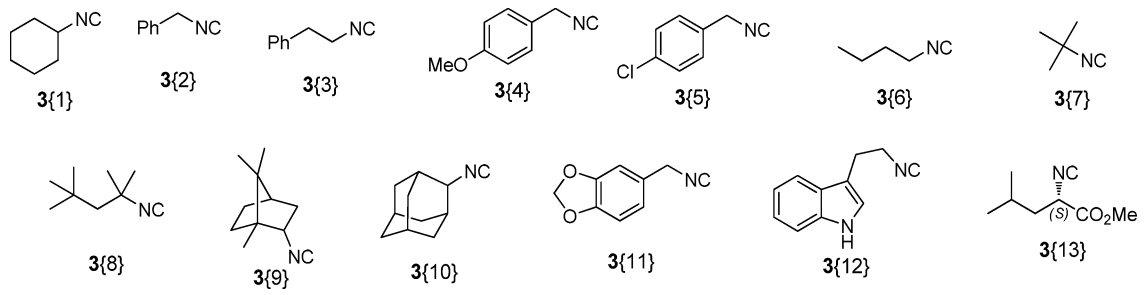
paper have average values of Molecular Weight (MW), logP, Hydrogen Bond Donors (HBD) and Hydrogen Bond Acceptors (HBA) that follow the Lipinski rule of 5 suggesting a possible drug likeness that can be further explored (see SI).

After the successful synthesis of the tetra-substituted imidazoles, we planned to synthesize oxazoles by employing the Passerini reaction as an initial step. The above optimized reaction conditions were used in the Passerini reaction as well followed by the cyclization reaction sequence. Phenylglyoxal, cyclohexyl isocyanide and uracil derived acetic acid were reacted in DCM:DMF (1:1) for 48 h. The crude mixtures were treated with NH_4OAc (15 equiv) in AcOH at 120 °C for 1 h.

After careful elucidation of the X-ray structures of compounds **8**{*1,9,1*} and **8**{*1,11,1*}, we concluded that the free NH-imidazole was formed instead of the expected trisubstituted oxazole. The formation of the imidazole instead of the oxazole can be attributed to the excess of ammonia used during the reaction. A proposed mechanism involves the initial formation of the oxazole followed by the nucleophilic attack of ammonia at the C2. Subsequently the oxazole ring opens through the intermediacy of an amidine at C-2 and a ketone at C-5 followed by dehydration which leads to the unexpected free NH-imidazole (Scheme 1). The postcyclization step of the Passerini products was also performed with 1.0 equiv of NH_4OAc in AcOH at 120 °C, but still the formation of imidazole along with oxazole (22% and 16% yield respectively) and incomplete starting material was observed, even after 12 h of reaction time. With these results in hand, we decided to investigate the synthesis of a library of *NH*-imidazoles.

The structures exhibit interesting hydrogen bonding patterns. In **8**{*1,9,1*}, the Uracil undergoes a bifurcated hydrogen bonding to the Uracil of a neighboring molecule. Moreover, a hydrogen bond from the imidazole NH to a DMSO solvent molecule is formed. In **8**{*1,11,1*}, a hydrogen bonding between the imidazole NH to the U-CO of a neighboring molecule is formed.

In general, the free *NH*-imidazoles were obtained in good yields regardless of their steric and electronic properties. First, a wide variety of aliphatic and aliphatic-aromatic isocyanides were reacted with phenylglyoxal **1**{*1*} and uracil derived acetic acid in



3{1} **3**{2} **3**{3} **3**{4} **3**{5} **3**{6} **3**{7} **3**{8} **3**{9} **3**{10} **3**{11} **3**{12} **3**{13}

Figure 4. Chemset **3** consisting of isocyanides.

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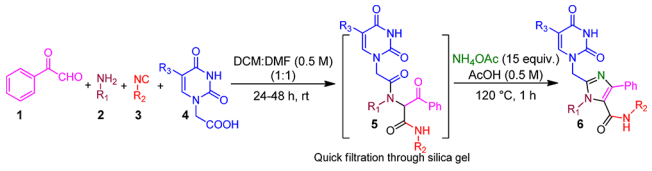
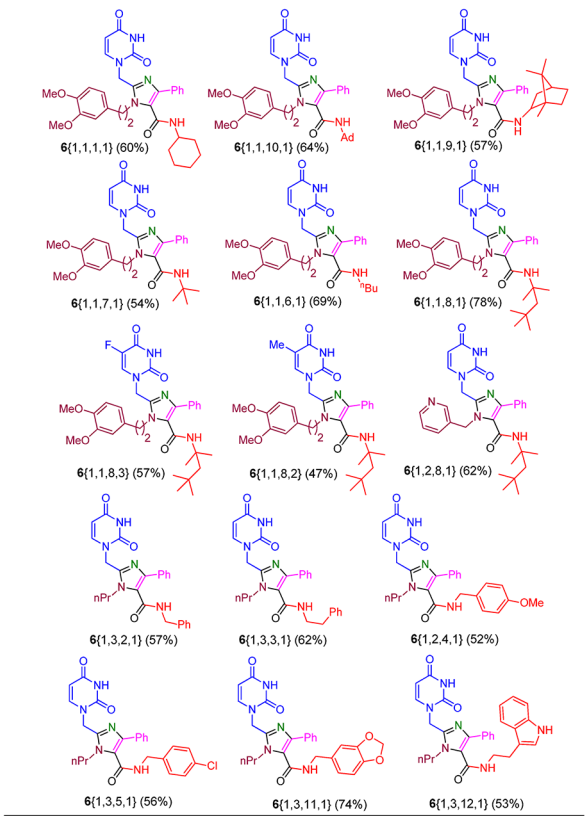
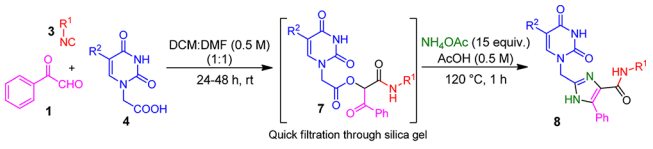
Table 1. Synthesis of Tetra-Substituted Imidazoles 6[a,b]

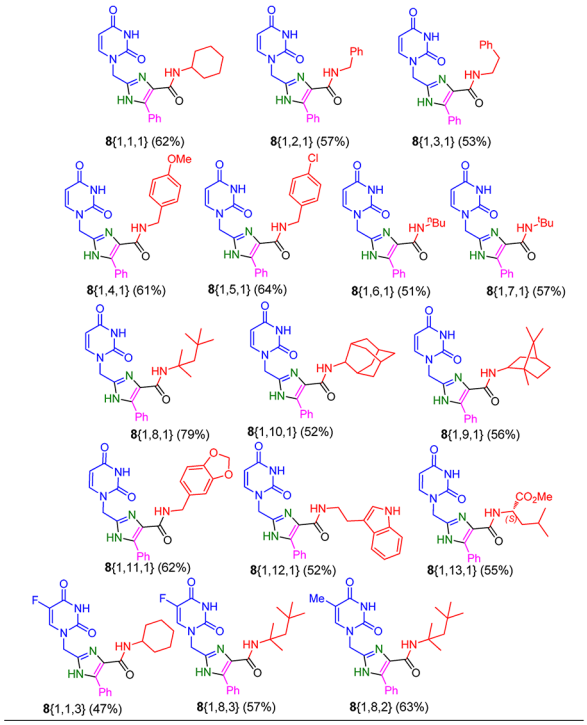




[a]Reactions were carried out in DCM:DMF (1:1) (0.5 M) with 1.0 equiv of **3** relative to the aldehyde **1** (1.0 mmol), amine **2** (1.0 mmol), and acid **4** (1.0 mmol) at 25 °C for 24−48 h. After a simple filtration, resulting crude mixture was treated with NH_4OAc (15 equiv) in AcOH (0.5 M) at 120 °C for 1 h. [b]Yield refers to the purified products.

Table 2. Synthesis of Tri-Substituted NH-Imidazoles 8[a,b]





[a]Reactions were carried out in DCM:DMF (1:1) (0.5 M) with 1.0 equiv of **3** relative to the aldehyde **1** (1.0 mmol) and isocyanide **3** (1.0 mmol) at 25 °C for 24−48 h. After one quick filtration, resulting crude products were treated with NH_4OAc (15 equiv) in AcOH (0.5 M) at 120 °C for 1 h. [b]Yield refers to the column-purified products.

DCM:DMF (1:1) followed by an excess of NH_4OAc (15 equiv) and treatment in acetic acid at 120 °C for 1 h, providing the desired free NH-imidazoles **8** in very good yield. On the other hand, indole and amino acid derived isocyanides were also valid substrates in the Passerini/cyclization sequence (**8**{*1,12,1*} and **8**{*1,13,1*}). 5-Fluoro and 5-methyl uracil acetic acids along with phenylglyoxal and isocyanides also furnished the expected trisubstituted imidazoles (**8**{*1,1,3*}, **8**{*1,8,3*}, and **8**{*1,8,2*}) in 47%, 57%, and 63% yields, respectively.

Imidazole rings are the second most common five-membered aromatic nitrogen heterocycles U.S. FDA approved drugs.[9a] The imidazole ring is considered to be an attractive isostere of a triazole, oxazole, pyrazole, thiazole, and tetrazole because of its capability to coordinate with a variety of inorganic metal ions, as well as biological molecules in the human body. In this report, along with the imidazole ring, we have grafted an attractive extra uracil part and based on the interesting scaffold properties they are now part of the screening decks of the European Lead Factory (ELF).[9b] In summary, we have described a novel method for the synthesis of Uracil containing tetra- and trisubstituted imidazoles. This simple and mild procedure is a valuable addition to MCR chemistry and expands its unique scaffold diversity. Work is ongoing to identify biological targets for our compound libraries and will be reported in due course.

EXPERIMENTAL PROCEDURES

Nuclear magnetic resonance spectra were recorded on a Bruker Avance 500 spectrometer {^{1}H NMR (500 MHz), ^{13}C NMR (126 MHz)}. Chemical shifts for ^{1}H NMR were reported as δ values and coupling constants were in hertz (Hz). The following abbreviations were used for spin multiplicity: s = singlet, br s = broad singlet, d = doublet, t = triplet, q = quartet, quin = quintet, dd = double of doublets, ddd = double of doublet of doublets, m = multiplet. Chemical shifts for ^{13}C NMR were reported in ppm relative to the solvent peak. Thin layer chromatography was performed on Fluka precoated silica gel plates (0.20 mm thick, particle size 25 μm). Flash chromatography was performed on a Teledyne ISCO Combiflash Rf, using RediSep Rf Normal-phase Silica Flash Columns (Silica Gel 60 Å, 230−400 mesh) and on a Reveleris X2 Flash Chromatography, using Grace Reveleris Silica flash cartridges (12 g). Reagents were available from commercial suppliers (Sigma-Aldrich, ABCR, Acros, and AK Scientific) and used without any purification unless otherwise noted. All microwave irradiation reactions were carried out in a Biotage Initiator Microwave Synthesizer. Electrospray ionization mass

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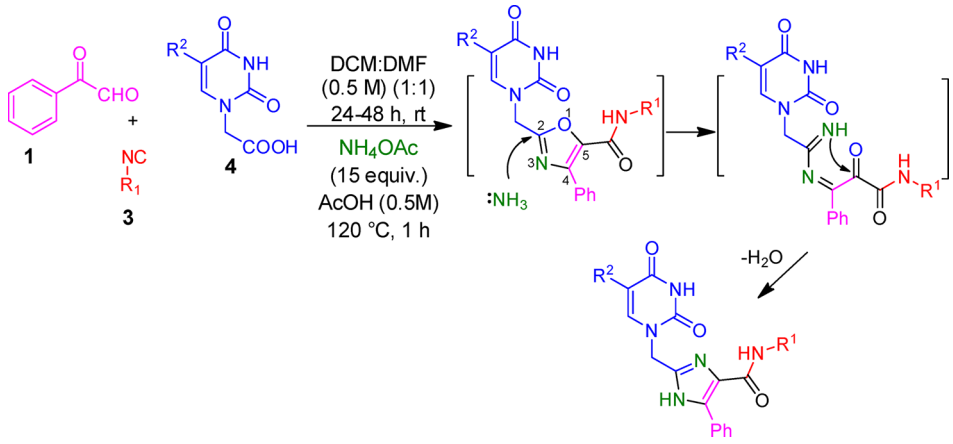
Scheme 1. Proposed Reaction Mechanism for Free NH-Imidazole Formation



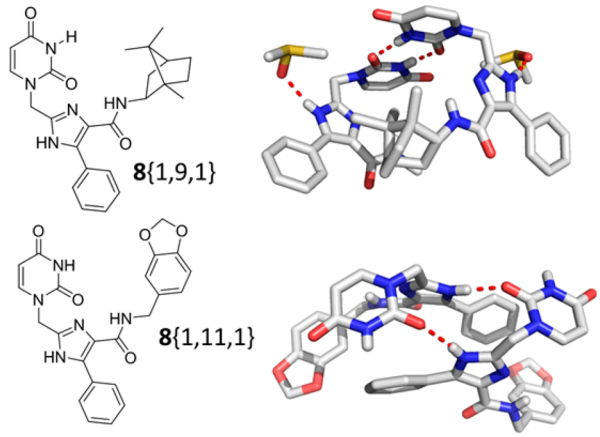


Figure 6. Crystal structures of two trisubstituted imidazoles (**8**{*1,9,1*} and **8**{*1,11,1*}).

spectra (ESI-MS) were recorded on a Waters Investigator Semiprep 15 SFC-MS instrument.

Typical Procedures for the Synthesis of Compounds 6 and 8. *Procedure A.* General procedure for the synthesis of imidazole derivatives **6**: In an ordinary glass vial equipped with a magnetic stirring bar, to a mixture of DCM:DMF (1:1) (0.5 M) were added amine (1.0 mmol) and 2-oxo-2-phenylacetaldehyde (1.0 mmol). After stirring for a minute, were added isocyanide (1.0 mmol) and acid (1.0 mmol). The reaction mixture was stirred at 25 °C for 24 to 48 h. The crude mixture was filtered through a pad of silica eluting with DCM:MeOH (9:1). Resulting mixture was treated with NH_4OAc (15 equiv) in AcOH (0.5 M) at 120 °C for 1 h. The crude reaction mixture was worked up with saturated $NaHCO_3$ solution and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure products were obtained through column chromatography (silica gel, mixture of DCM/MeOH).

Procedure B. General procedure for the synthesis of free NH-imidazole derivatives **8**: In an ordinary glass vial equipped with a magnetic stirring bar, to a mixture of DCM:DMF (1:1) (0.5 M) were added 2-oxo-2-phenylacetaldehyde (1.0 mmol) isocyanide (1.0 mmol) and acid (1.0 mmol). The reaction mixture was stirred at 25 °C for 24 to 48 h. The crude mixture was filtered through a pad of silica eluting with DCM:MeOH (9:1), evaporated to dry and resulting mixture was treated with NH_4OAc (15 equiv) in AcOH (0.5 M) at 120 °C for 1 h. The crude reaction mixture was worked up with saturated $NaHCO_3$ solution and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Pure products were obtained through column chromatography (silica gel, mixture of DCM/MeOH).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.7b00145.

Crystallographic information file for compound **5j** (CIF)
Crystallographic information file for compound **5k** (CIF)
General experimental procedures, compound characterization data, and ^1H and ^{13}C spectra of all compounds (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Author Contributions

[§]K. K. and K-T. J contributed for crystal structure analysis.

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Notes

The authors declare no competing financial interest.

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