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Combination of click chemistry and sulfonamides to develop three-armed triazole compounds

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ABSTRACT

Fragment-based drug discovery is a valuable tool in hit identification, as well as the combination of different small fragments showing a minimal binding activity against biological receptors or enzymes to give merged hits. A high number of fragments on the same scaffold improve the probability to find a candidate showing single- or multi-target affinities. A rapid and versatile approach for synthesizing libraries of densely fragment-functionalized scaffolds is reported. Many fragments were assembled in few steps around a triazole ring starting from amino alcohols and other readily available building blocks. A binding assay against integrin $\alpha_v\beta_3$ was used as a test-bed in order to demonstrate the potential of such an approach in hit discovery strategies.

1. Introduction

The interactions between biological targets (either receptors or enzymes) and pharmacophoric subunits are the fundamental concept of fragment-based approach to drug discovery issues. Many repeating subunits responsible of such useful interactions can be identified in bioactive molecules.[1–14] Thus, the combination of different 'binder' fragments within a single molecule dramatically increase the probability of finding new promising 'hit' candidates, both for single- and multi-target purposes.[15,16]

Copper (I) catalyzed Azide-Alkyne Cycloaddition (CuAAC), the main tool of the so-called 'click-chemistry', is a versatile reaction allowing for the synthesis of functionalized triazole ring in high yield and mild reaction conditions, and nowadays is one of the most widespread used reaction in chemical synthesis.[17–24] Furthermore, the triazole ring has been proposed as a stable isostere of the peptide bond,[25–27] thus, click chemistry is considered a very promising tool in the synthesis of bioactive ligands.[28,29]

In the present work we propose a versatile 'click-based' approach in developing libraries of densely functionalized scaffolds containing three fragments.[30]

2. Results and discussion

As CuAAC is usually intended to couple an azide and an alkyne, it can be easily exploited in a basic approach in order to achieve a difunctional scaffold. In view of further expanding the combination of multiple fragments in a single molecule, our aim was to develop highly functionalized structures still applying the click chemistry (Fig. 1), as versatility and mild reaction conditions are fundamental requirements in a useful library development technique. Thus, we envisaged the synthesis of building blocks containing three more pharmacophoric moieties in a modular approach, and specifically we focused our attention on single-fragment-bearing alkyne and multi-fragment-bearing azides.

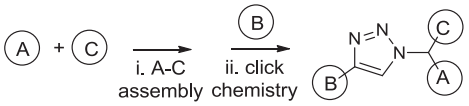

Fig. 1. Schematic of a high-density fragments bearing triazole.

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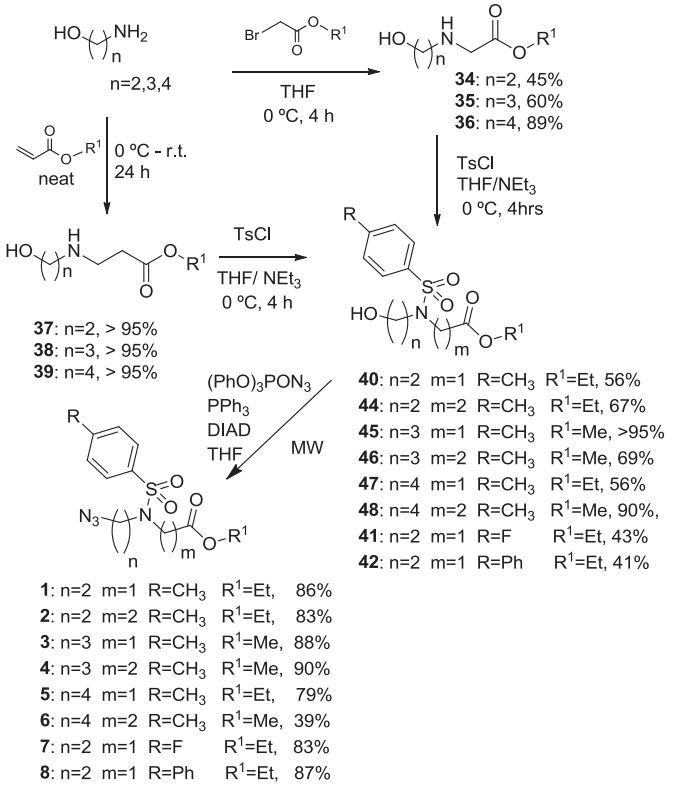
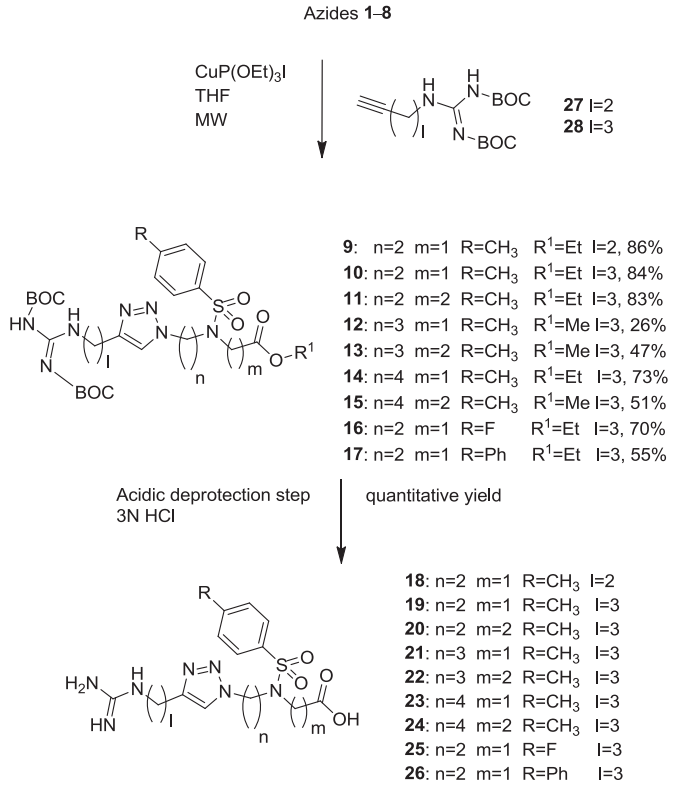
In choosing our model bioactive fragments, we opted for one basic group and one acidic group, which can be found in many peptidic and non-peptidic drug-candidates.[31] Such moieties were used in their protected forms, in order to perform reaction and purification steps with the benefits of organic solvent-soluble substances. Additional common fragments found in enzymes and receptors ligands are π-stacking capable aromatic rings and heteroatom-based bonds, one the most widespread being the sulfonamidic bond. Sulfonamides are widely used in medicinal chemistry for targeting many different receptors, thus, using this versatile scaffold increase the probability to find a multi-target hit, which is a noteworthy additional advantage in designing drug candidates.[32–34]

The first phase of our approach was the synthesis of a sub-library differing only in the size of the backbone-chain (Scheme 1). Intermediates **34**–**39** were synthesized starting from amino alcohols and esters derivatives. Amino alcohols appeared to be the ideal starting materials, taking advantage of the orthogonality of oxygen and nitrogen atoms with respect to the reactivity with α-bromo acetates.[35] Similar profile was exploited for the Michael addition to acrylate ester, which was considered in order to achieve the isolation of the homologous products not achievable from bromo-propionic ester.[36]



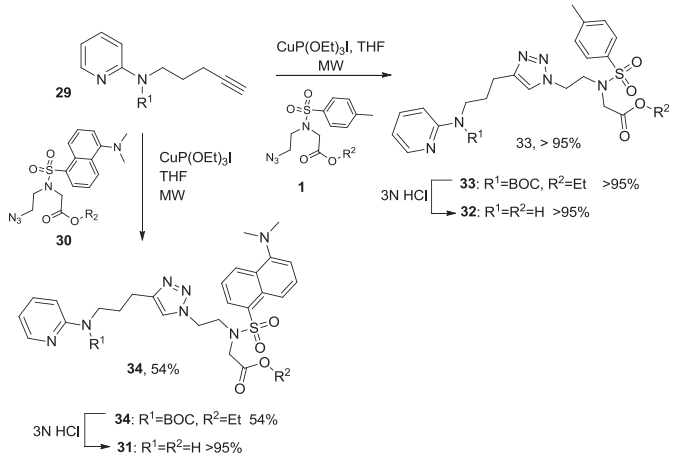
Scheme 1. Modular approach to azides containing two fragments.

The alkylated amino alcohols were subsequently reacted with the chosen aromatic sulfonyl chloride (yields ranging from 40% to quantitative) and converted into azides **1**–**8** via a Mitsunobu reaction. Then, the azides bearing two fragments were reacted via CuAAC with two different Boc-protected alkynes (**27**, **28**) bearing the basic moiety (Scheme 2). Full-organic reaction conditions (THF/CuP(OEt)$_3$I) were preferred for the CuAAC process to minimize the formation of copper-complexes, based upon our previous experience.[37] The cycloaddition step was performed under microwave irradiation in order to shorten the reaction times and improve yields, all being in the medium-to-excellent range after performing the reactions at 120 °C for 60 min. A final acidic deprotection step yielded the water-soluble form of compounds **18**–**26**, without need of further purification, except for solvent evaporation. The overall total yields for the five-step process were about 10–40% starting from the amino alcohols, appearing to be definitely fit for purpose.



Scheme 2. CuAAC and deprotection steps two achieve the three-fragment-bearing scaffolds.

In order to further explore the broad spectrum of functionalities, which can be included in such molecules, another subset of structures was synthesized, varying the basic and the aromatic moieties. Two different groups were chosen, representing many useful characteristics in bioactive candidates, including the fluorogenic dansyl ring and a 2-amino-pyridine as a less basic guanidine isostere (**31** and **32**, see Scheme 3).



Scheme 3. Scope of the modular approach employing a different alkyne and the dansyl group as additional fragments.