Tetrahedron Letters 56 (2015) 2451–2455

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An efficient click-multicomponent strategy for the diversity oriented synthesis of 15–18 membered macrocyclic peptidomimetic fluorophores

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ARTICLE INFO

Article history:
Received 27 February 2015
Revised 16 March 2015
Accepted 18 March 2015
Available online 22 March 2015

Keywords:
Macrocycles
Multicomponent reaction
Click chemistry
Peptidomimetics
Fluorophores

ABSTRACT

A general methodology for the three step synthesis of macrocyclic peptidomimetic fluorophores with a range of ring size from 15 to 18 is described. The alternate Mannich type reaction between the halogen functionalized long chain alkyl nitriles with aldehydes and ketones in which one of them decorated with an alkyne functionality leads to the key precursor for the intramolecular copper catalyzed [3+2] azide-alkyne cycloaddition to make the macrocycles obeying Lipinski's rule of five.

Macrocyclic compounds have unique physicochemical and topological properties suitable for tackling biological targets with multiple binding sites.[1] Synthetic organic and medicinal chemists generally consider these class of compounds as cyclic molecules decorated with at least a 12 membered ring system with molecular weight up to 1 k Da and polar surface area up to 250 Å.[2,1b] The properties of macrocycles more often lies between small molecules and biologics and in many cases they do not obey the Lipinski's rule of five.[1b,2] Because of their high target binding affinity, selectivity, improved oral bioavailability, and cell permeability, macrocycles are now emerged as efficient inhibitors of targets with multiple binding sites such as G-protein-coupled receptors (GPCRs), protein–protein interactions (PPIs), and certain proteases.[1b,d,e] At present around 68 macrocyclic drugs are available in the market in which most of them are based on natural products.[1b] Examples include erythromycin, rapamycin, vancomycin, cyclosporine A, epothilone B, diazonamide A, etc.[1a]The major challenges in natural product based macrocyclic drug discovery include problems associated with the purification of natural molecules, identification of bioactive components, structure assignment, chemical modification, analog synthesis, scale-up, and most importantly, for a large number of therapeutic targets, no macrocyclic ligands are available from natural sources and that laid the motivation for chemists to develop synthetic macrocycles (Scheme 1).[1b,e] Synthetic macrocycles are generally derived from the multi-step construction of a linear core structure followed by ring closure using robust synthetic tools like macrolactonizations, macrolactamizations, transition metal catalyzed coupling reactions, ring-closing metathesis, Staudinger ligation, etc.[1e] Methodologies based on multistep protocols naturally escalates cost as well as the use of infrastructure and resources. Recent developments in the chemistry of multi-component coupling reactions[3,4] revealed that these class of reactions can effectively replace multi-step protocols for the cost effective and green synthesis of designer molecules. Moreover many multicomponent reactions are orthogonal in nature and are tolerant to the presence of a variety of reactive functionalities. These unprotected functionalities present in the initial MCR product can subsequently use for fragment ligation to form bioactive molecules including macrocycles.[1e]

Among the various synthetic tools useful for fragment ligation, copper catalyzed, and copper free (including organo catalytic) azide-alkyne [3+2] click cycloaddition reactions are particularly important because of their near perfect greenness and atom economy.[5,6] Moreover, the functional group pairing via copper catalyzed azide-alkyne cycloaddition places a 1,4-substituted 1,2,3 triazole moiety between the scaffolds and this 1,4 triazole can mimic the *trans* geometry of an amide bond. The net result is the conversion of a nonpeptidic molecule to a peptidic or peptidomimetic with high protease stability and rigidity useful for drug/lead discovery purpose. In our previous communication, we

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http://dx.doi.org/10.1016/j.tetlet.2015.03.081
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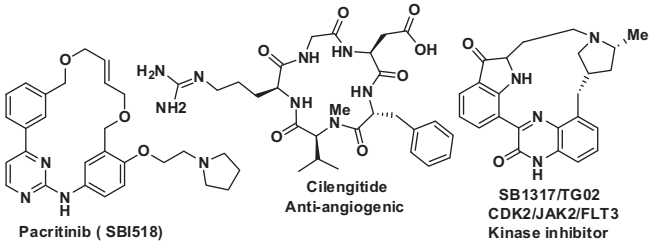


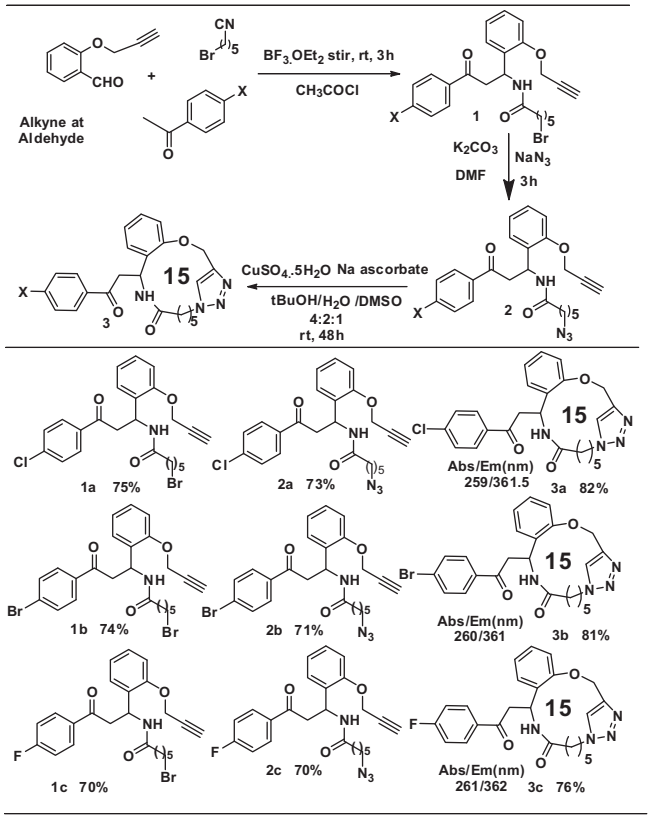
Scheme 1. Representative examples of synthetic macrocycles.

reported the synthesis of 12 and 14 membered macrocyclic peptidomimetics based on an intramolecular [3+2] azide-alkyne click cycloaddition of suitably functionalized Mannich type substrates.[7] We also predicted that it is possible to step-up the macrocyclic ring size by adjusting the chain length of the nitrile component used in the reaction.[7] As a justification of our prediction, here we report a general protocol for the synthesis of 15–18 membered macro cyclic peptidomimetic fluorophores via click-multi component strategy.

The overall process adopted for the synthesis of 15–18 membered macrocycles (Scheme 2) involves three synthetic steps in which the first step is a three component reaction between an aromatic aldehyde and an enolizable ketone (in which one of them is functionalized with an alkyne group) with a nitrile component in presence of an acid chloride leading to the formation of the amide alkynes **1**.[8] The replacement of the bromine in **1** with an azide moiety afforded the azido alkyne **2**. The subsequent copper catalyzed intramolecular [3+2] azide-alkyne click cycloaddition afforded the respective macrocycles **3** or **6** as shown in Scheme 2.

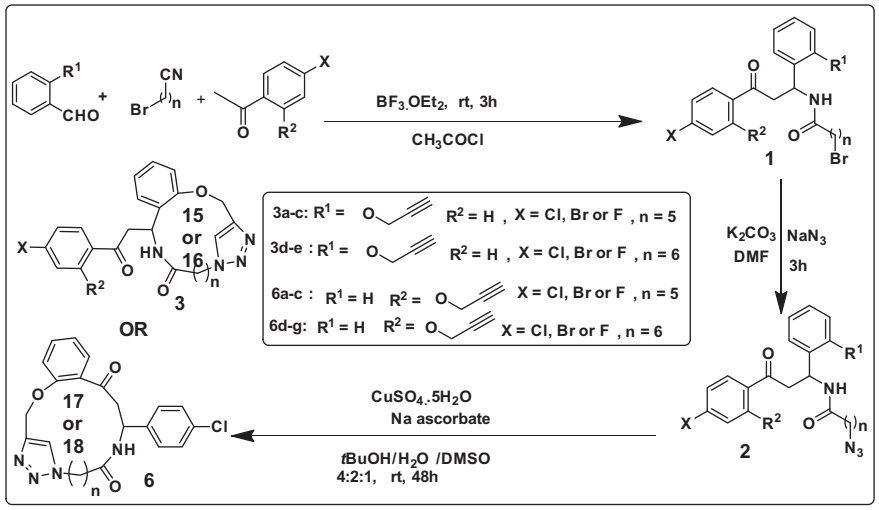
The studies were initiated with the synthesis of 15 membered macrocycles. The synthetic methodology and the details of the intermediate scaffolds and the final products are given in Table 1. The initial four component reaction was conducted as a solvent free reaction by stirring the alkyne functionalized aldehyde, ketone, and 6-bromohexanenitrile with slight excess of acetyl chloride in the presence of catalytic amount of boron trifluoride etherate at room temperature for 3 h. The subsequent aqueous workup followed by silica column chromatography afforded the alkynes **1** in 70–75% isolated yields. The bromine in **1** was then substituted with an azide moiety by a base catalyzed reaction of **1** with sodium azide in DMF at room temperature. The aqueous work of this reaction mixture afforded the azido alkynes **2** in 70–73% isolated yield. The azido

Table 1
General three step methodology for the synthesis of 15 membered macrocycles and their precursor diversity



alkynes **2** were then subjected to ring closure by an intramolecular copper catalyzed [3+2] azide-alkyne click cycloaddition in a solvent mixture comprising of *t*BuOH/H_2O/DMSO in the ratio 4:2:1 afforded the macrocycles **3** in 76–82% isolated yields.[9] Structurally, the macrocycles are decorated with an amide bond and two of its isosteres such as 1,2,3-triazole and an alkyl ether group within the cycle and an additional exocyclic keto functionality which is also isosteric with amide bonds.[10] These features are promising for obtaining excellent binding affinity toward both core as well as peripheral sites of a broad spectrum of therapeutic targets.[11]

We then proceeded to the synthesis of 16 membered macrocycles by choosing 7-bromoheptanenitrile as the nitrile



Scheme 2. General synthetic strategy adopted for the synthesis of 15–18 membered macrocyclic peptidomimetics.