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Synthesis of bioactive and fluorescent pyridine-triazole-coumarin peptidomimetics through sequential click-multicomponent reactions

T.V. Soumya, C. Muhammed Ajmal, D. Bahulayan *

Department of Chemistry, University of Calicut, Malappuram 673635, Kerala, India

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ABSTRACT

An easy synthetic protocol for the peptide randomization of 3,5-dicyano pyridine derivatives by linking the pyridine core with a coumarin chromophore spaced by a linker triazole via copper (I) catalyzed [3 + 2] azide-alkyne cycloaddition (CuAAC) is described. The new peptidomimetics thus obtained are extended rule of 5 (eRo5) molecules suitable for the development of therapeutic agents for undruggable targets. The structural and photophysical properties of the molecules are also promising for the development of potential bio imaging agents based on these molecules.

Peptide based drug molecules have gained considerable interest during the past two decades as potential therapeutic agents especially for metabolic diseases and oncology.[1] Currently, there are approximately 60 peptide based drugs that are available in the market, 140 are in clinical trials and another 500 are in preclinical trials.[1] The major drawbacks of peptide-based drugs are their susceptibility to oxidation and hydrolysis, tendency to aggregate in a biological environment, poor bioavailability & cell permeability, fast excretion and short circulating plasma half-life. One of the ways to increase the plasma half-life of peptide drugs is to limit the enzymatic cleavable sites in them by substitution with stable entities or functional groups. Such isostere-substituted peptide molecules are known as peptidomimetics.[2] However, the synthesis of such bioactive peptidomimetics is highly challenging due to the lack of general and convenient protocols. Outstanding research work of Sharpless and coworkers[3] resulted in the development of an expeditious synthetic strategy referred to as click reactions based on the use of structural scaffolds with built-in energy to undergo spontaneous and irreversible functional group pairing to produce complex molecules.

A brilliant example of such click reactions is the [3 + 2] cycloaddition between azides and acetylenes to afford a substituted 1,2,3 triazole extensively used for making functional molecules.[4] Triazoles are important peptide bond isosteres[5] having enormous biological applications and are found either as a fused heterocyclic or as a linker to connect fragments together to build a complex structure which is a quintessential property in drug discovery.[6]

A prerequisite for such an orthogonal chemistry is the availability of a robust synthetic methodology, which can yield the required privileged scaffolds decorated with spring-loaded functionalities in minimum number of steps with maximum atom economy and selectivity. Multicomponent reactions (MCRs)[7] are one of such green methodologies useful for the step economic synthesis of functional scaffolds including pharmacologically active heterocycles present in various drug classes.[8]

Among the numerous heterocycles, pyridine scaffolds attract considerable attention in medicinal chemistry due to their widespread occurrence in natural molecules with therapeutic properties.[9] Consequently, several synthetic drugs have been developed for example, isoniazid (anti-tuberculosis), sulphapyridine (antibacterial), A3 adenosine receptor antagonist (anti-inflammatory, anti asthmatic), amirone (cardiotonic) etc.[10] Drugs based on 3,5-dicyano pyridine derivatives are excellent inhibitors of adenosine receptors responsible for hypoxia, cancer, Parkinson disease, cardiovascular disease, asthma, and epilepsy.[11] Examples of drug molecules with broad spectrum of applications are presented in Fig. 1.[12] Due the presence of too many polar surface functional groups, the molecules presented in Fig. 1 are also have the drawbacks such as poor protease stability and less circulating plasma half-life. We envisaged that, the drug properties of these 3,5-dicyano pyridine derivatives can be increased manifold by peptidomimetic randomization of the pyridine core by linking a coumarin chromophore spaced by a linker triazole via copper (I)

* Corresponding author.
E-mail address: bahulayan@yahoo.com (D. Bahulayan).

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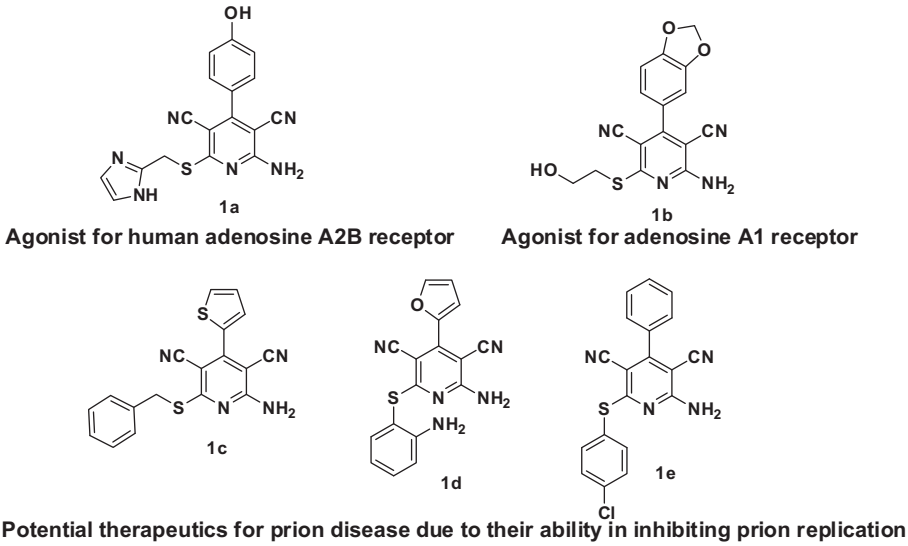

Fig. 1. Biologically important 3,5-dicyanopyridine derivatives.[12]

catalyzed [3 + 2] azide-alkyne cycloaddition (CuAAC). The selection of coumarin as the chromophore has been done mainly due to their excellent biological[13] and photophysical properties.[14] For example, a coumarin-piperidine diad spaced with an alkane-ether moiety has recently been reported as a novel therapeutic agent for schizophrenia.[15] The general structure of the new pyridine-triazole-coumarin peptidomimetics **5** reported in this paper is shown in Fig. 2.

We have started our studies with the synthesis of pyridine alkynes **2** by following a simple three-component reaction of an aldehyde having a propargyl group, malononitrile and thiophenol as shown in Scheme 1.[16] The alkyne functionalization of the aldehydes were done by treating different hydroxyl aldehydes with propargyl bromide in presence of a base catalyst. The propargylated aldehydes were then refluxed with malononitrile and thiophenol in ethanol in the presence of catalytic amount of triethyl amine to afford the pyridine alkynes **2** in 92–94% yield.

We then moved on to the synthesis of coumarin azides **4**. The synthesis of **4** was carried out by a two-step process comprising of an initial Mannich type four-component reaction followed by azide substitution. The four component reaction between 3-acetyl coumarin, bromopropionitrile, an aromatic aldehyde and acetyl chloride afforded the bromo derivative **3** (see supplementary information for mechanism of this reaction).[17] The bromine in **3** was then replaced with an azide moiety by treating them with sodium azide under basic condition to afford **4** in good to excellent yield (Scheme 2).

Among the six coumarin azides, those with electron donating substituents (**4a** and **4c**) formed in higher yields compared to that of electron withdrawing substituents. The azide and alkyne fragments were then assembled by following the CuAAC reaction as shown in Table 1. In a typical experiment, an equimolar mixture of pyridine alkyne **2a** and coumarin azide **4a** were dissolved in minimum amount of DMSO. To this, a solvent mixture of *t*-BuOH and H_2O (4:2) containing 0.2 equivalent of $CuSO_4$ and 0.4 equivalent of sodium ascorbate were added and stirred for 12 h at room temperature to complete the cycloaddition. The mixture was then diluted with ice-cold water to obtain the peptidomimetic **5a** in 92%

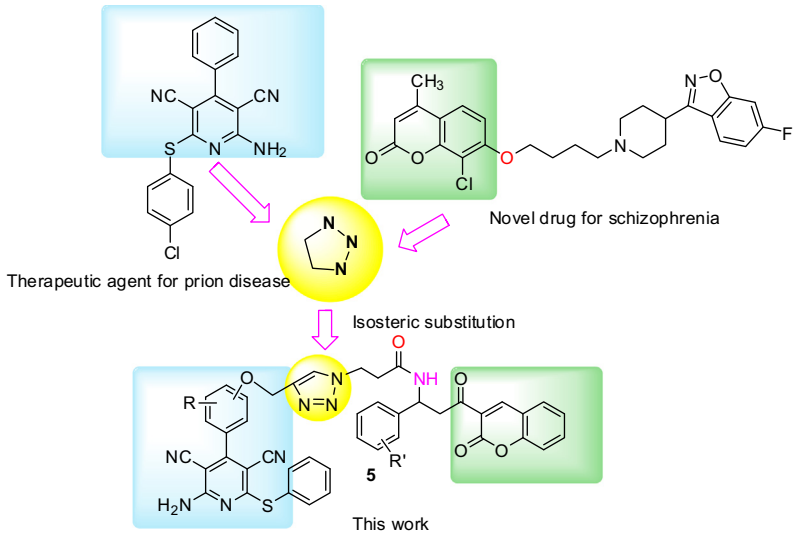

Fig. 2. The general structure of the pyridine-triazole-coumarin peptidomimetics **5** and its evolution from prion replication inhibitor[12d] and a potential drug candidate for schizophrenia.[15]