Bioorganic & Medicinal Chemistry Letters 25 (2015) 685–689

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Diversity oriented synthesis and IKK inhibition of aminobenzimidazole tethered quinazoline-2,4-diones, thioxoquinazolin-4-ones, benzodiazepine-2,3,5-triones, isoxazoles and isoxazolines

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ARTICLE INFO

Article history:
Received 1 November 2014
Revised 25 November 2014
Accepted 27 November 2014
Available online 8 December 2014

Keywords:
Solid-phase synthesis
Aminobenzimidazoles
Quinazolinediones
Thioxoquina-zolinones
Benzodiazepinetriones
Intramolecular cyclization
Isoxazoles
Isoxazolines
1,3-Dipolar cycloaddition
Heterocycles

ABSTRACT

The derivatization of resin-bound aminobenzimidazole toward the parallel solid-phase synthesis of aminobenzimidazole tethered pharmacologically important heterocycles such as quinazoline-2,4-diones, thioxoquinazolin-4-ones, benzodiazepine-2,3,5-triones, isoxazoles and isoxazolines is reported. All the compounds were tested for IKK inhibition. Only one compound elicited significant inhibition of IKKε, TBK-1 and IKK2.

One of the central objectives of organic and medicinal chemistry is the design, synthesis, and production of molecules having value as human therapeutic agents. Historically, the identification of such compounds has been carried out using compounds from plant and animal tissue extracts, microbial broth extracts, as well as individual compound collections resulting from fifty years of effort by synthetic chemists in academic and pharmaceutical organizations. Diversity-oriented synthesis (DOS), is a process by which multiple compounds are generated simultaneously, in a predictable fashion using techniques that involve parallel chemical transformations.[1–4] It allows chemists to achieve more structural complexity than in the early days of combinatorial chemistry.[4–7] Benzimidazoles are an important class of heterocycles displaying a wide array of biological properties,[8–10] and represent a key structural motif in angiotensin-II-antagonists, NMDA antagonists, anticoagulants, and gastric proton-pump inhibitors.[11–13] We previously reported the use of resin-bound aminobenzimidazoles for the synthesis of a variety of fused and/or tethered heterocyclic compounds.[14–18]

Continuing with our interest with the diversification of aminobenzimidazoles, we describe herein a multistep approach for the parallel synthesis of structurally diverse aminobenzimidazole tethered pharmacologically known heterocycles such as quinazoline-2,4-diones, thioxoquinazolin-4-ones, benzodiazepine-2,3,5-triones, isoxazoles and isoxazolines. Substituted quinazolinedione, thioxoquinazolinone and benzodiazepinetrione are found in natural products,[19] and in various drug based p38 kinase inhibitors,[20] aldose reductase inhibitors,[21] 5-HT2C agonist,[22] and CB2 agonists.[23] Recently, quinazolinediones have been developed as typical anti-psychotic agents for treating Schizophrenia and Alzheimer's diseases.[24] Likewise, benzodiazepines are found in several drugs including serotonin and dopamine receptors,[25] 5-HT2C receptors,[26] and glycogen synthase kinase-3 inhibitors.[27]

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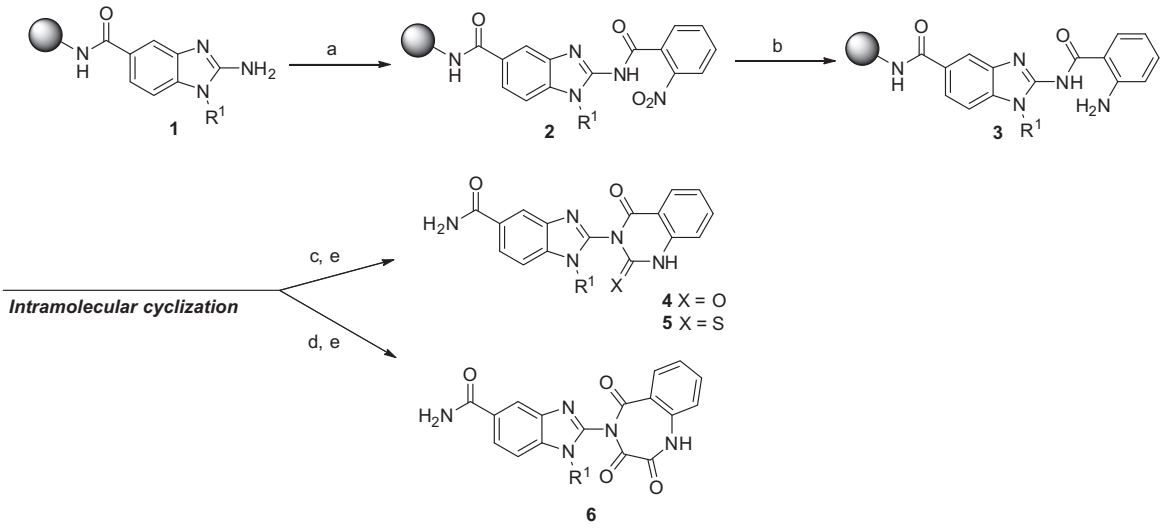
http://dx.doi.org/10.1016/j.bmcl.2014.11.078
0960-894X/

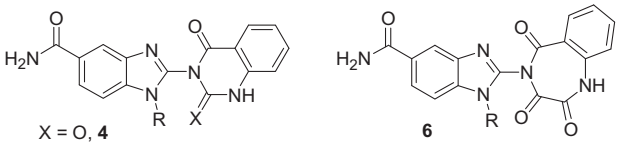


Scheme 1. Synthesis of quinazoline-2,4-dione, thioxoquinazolin-4-one, and benzodiazepine-2,3,5-trione derivatives. Reagents and conditions: (a) 2-nitrobenzoic acid (8 equiv, in anhyd DMF), PyBOP (8 equiv), DIEA (8 equiv), 8 h; (b) $SnCl_2 * 2H_2O$ (10 equiv, 1.0 M DMF), 24 h; (c) 1,1′-carbonyldiimidazole (or) 1,1′-thiocarbonyldiimidazole (10 equiv, 0.5 M in anhyd DMF), 80 °C, 8 h; (d) oxalyldiimidazole (10 equiv, 0.5 M in anhyd DMF), 80 °C, 8 h; (e) HF/anisole (99:1), 90 min, 0 °C.

The parallel solid-phase synthesis (tea-bag technology)[28] of aminobenzimidazole tethered quinazoline-2,4-diones, thioxoquinazolin-4-ones and benzodiazepine-2,3,5-triones is outlined in Scheme 1. Resin-bound aminobenzimidazole template **1**[29] was coupled to 2-nitrobenzoic acid in the presence of PyBOP to provide an essential N-benzimidazolylnitrobenzamide precursor **2** which, following tin (II) chloride reduction generated an amine **3**. Treatment of the amine **3** with 1,1′-carbonyldiimidazole generated an isocyanate intermediate which, upon intramolecular cyclization furnished the resin-bound quinazoline-2,4-diones **4**. Similarly, the separate treatment of compound **3** with 1,1′-thiocarbonyldiimidazole and oxalyldiimidazole afforded following thioxoquinazolin-4-ones **5** and benzodiazepine-2,3,5-triones **6**. The resin was cleaved with HF/anisole and the desired quinazoline-2,4-diones **4**, thioxoquinazolin-4-ones **5**, and benzodiazepine-2,3,5-triones **6** were isolated in moderate yields (30–55%) (Table 1).

The application of this solid-phase methodology was explored to a further extent and a series of aminobenzimidazole tethered isoxazoles and isoxazolines were synthesized. We envisioned that aminobenzimidazole coupled alkyne or alkene template would serve as a convenient partner for 1,3-dipolar cycloaddition studies. Recently, we documented the synthesis of an array of isoxazoles and isoxazolines via 1,3-dipolar cycloaddition using resin-bound alkenes and alkynes.[30] In order to build upon this premise, we decided to study the application of aminobenzimidazole based alkyne or alkene template to access a variety of tethered cycloaddition products. Aminobenzimidazole tethered isoxazoles and isoxazolines were obtained following on resin-bound 1,3-dipolar cycloaddition of aminobenzimidazole acylated with carboxylic acids bearing alkyne or alkene with nitrile oxides. Isoxazoles and isoxazolines are very important class of active compounds. They display antiviral,[31] antitubulin,[32] as well as anti-inflammatory activities.[33,34] Isoxazoline core is a prevalent feature for several spiroisoxazoline natural products[35–40] and isoxazole motif is found in pharmaceutical drugs such as bextra® and parecoxib.[41–45] Due to aforementioned applications, the syntheses of these isoxazole (isoxazoline) based structural units have received greater attention and a few examples representing isoxazoline (**7**–**12**) and isoxazole (**13**,**14**) structural motifs are presented in Figure 1.

Table 1
Benzimidazole tethered quinazoline-2,4-diones, thioxoquinazolin-4-ones and benzodiazepine-2,3,5-triones



Entry	R	Yield[a] (%)
4a	Cyclopentyl	37
4b	*n*-Butyl	40
4c	Cyclohexanemethyl	44
4d	*i*-Butyl	35
4e	3-(Trifluoromethyl)benzyl	38
5a	Cyclopentyl	46
5b	*n*-Butyl	42
5c	Cyclohexanemethyl	54
5d	*i*-Butyl	40
5e	3-(Trifluoromethyl)benzyl	34
6a	Cyclopentyl	51
6b	*n*-Butyl	48
6c	Cyclohexanemethyl	55
6d	*i*-Butyl	44
6e	3-(Trifluoromethyl)benzyl	30

Isolated yields of aminobenzimidazole tethered quinazoline-2,4-diones, thioxoquinazolin-4-ones and benzodiazepine-2,3,5-triones: the products were run on a Vydac column, gradients 5–95% formic acid in ACN in 7 min.

[a] The yields are based on the weight of purified products and are relative to the initial loading of the resin.

Our approach toward the synthesis of aminobenzimidazole tethered isoxazoles and isoxazolines is outlined in Scheme 2. Following the coupling of phenylpropiolic acid or 4-vinylbenzoic acid to resin-bound aminobenzimidazole 1, the generated alkyne **15** or alkene precursors **16** were treated with freshly prepared hydroximoyl chlorides in the presence of diisopropyldiethylamine (DIEA). The in situ formed nitrile oxides reacted with alkenes or alkynes in a 1,3-dipolar fashion[30,46–51] to furnish the corresponding