Tetrahedron 73 (2017) 5144–5152

Contents lists available at ScienceDirect

Tetrahedron

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

One-pot, four-component synthesis of spiroindoloquinazoline derivatives as phospholipase inhibitors

Maryam Beyrati [a], Maryam Forutan [a], Alireza Hasaninejad [a, *], Erik Rakovský [b], Somayyeh Babaei [a], Ammar Maryamabadi [a], Gholamhossein Mohebbi [c]

[a] Department of Chemistry, Faculty of Sciences, Persian Gulf University, Bushehr, 75169, Iran
[b] Comenius University, Faculty of Natural Sciences, Department of Inorganic Chemistry, Mlynskádolina, Ilkovičova 6, 842 15, Bratislava, Slovak Republic
[c] The Persian Gulf Marine Biotechnology Research Center, The Persian Gulf Biomedical Research Center, Bushehr University of Medical Sciences, Bushehr, Iran

ARTICLE INFO

Article history:
Received 2 May 2017
Received in revised form
23 June 2017
Accepted 3 July 2017
Available online 5 July 2017

Keywords:
One-pot synthesis
Spiroindoloquinazoline
DABCO
Phospholipase inhibitors
Molecular docking

ABSTRACT

An efficient, one-pot, two-step, four-component reaction for the synthesis of spiroindoloquinazoline derivatives in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) is described. The syntheses are achieved by the condensation reaction of isatin derivatives, isatoic anhydride, malononitrile and carbonyl compounds under reflux in acetonitrile. Several of the resulting compounds showed moderate activity as phospholipase A2 inhibitors.

1. Introduction

Multi-component reactions (MCRs) have attracted great attention having an undeniable status in biological and medicinal chemistry as well as modern organic synthesis. This is due to their ability in bringing together three or more components in one-pot, affording high selectivity and high atom economy. MCRs demonstrate several benefits over classic methods in many ways such as synthetic efficiency, reduction of isolation and purification steps, ease of operation, minimization of costs, energy, time and waste production.[1–4]

Derivatives of quinazolinone are important class of six-membered nitrogen-containing heterocyclic systems that have been intensively studied because of their presence in different categories of natural alkaloids and synthetic drugs (Fig. 1).[5–11] These compounds also exhibit significant antitumor,[12,13] anticonvulsant,[14] antifungal,[15] antitubercular[16] and antimicrobial activities.[17]

Tryptanthrin (indolo[2,1-*b*]quinazoline-6,12-dione) consists of indole and quinazoline core structure is an active ingredient isolated from isatis root. It was first isolated from *Strobilanthes cusia* as an anti-fungal agent against dermatophytes and was later shown to strongly inhibit cycloxygenase-2 (COX-2) in cellular assays (IC_{50} = 64 nM in Mono Mac 6 cells).[18,19] In addition, antimicrobial, antimalarial, tuberculostatic and 5-LOX inhibitory activities of tryptanthrin have been reported.[20,21] Hence tryptanthrin derivatives area pharmacologically important class of heterocyclic compounds.[22–25]

Because of the pharmacological interest in these compounds, which belong to the indoloquinazoline family and also as a part of our ongoing research program on the synthesis of biologically important heterocyclic compounds,[26,27] herein we report a synthetic route for the preparation of a novel class of spiroindoloquinazolines.

2. Results and discussion

2.1. Chemistry

Previously, we reported three component synthesis of

* Corresponding author.
E-mail addresses: a_hasaninejad@yahoo.com, hasaninejad@pgu.ac.ir (A. Hasaninejad).

http://dx.doi.org/10.1016/j.tet.2017.07.005
0040-4020/

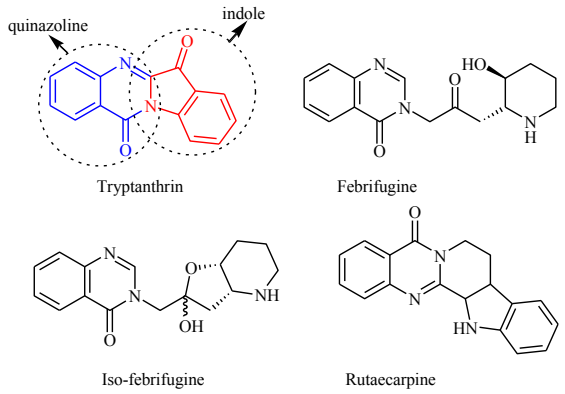


Fig. 1. Representative molecules containing quinazoline structural motif with biological activity.

spiroindoloquinazoline using tryptanthrin, C–H activated carbonyl compounds and malononitrile in the presence of ammonium acetate.[28] Herein we would like to report a one-pot four component synthesis of spiroindoloquinazoline derivatives by in situ preparation of tryptanthrin through the reaction between isatoic anhydride (**1**) and isatin (**2**) and subsequent reaction to synthesize the target spiroindoloquinazoline derivatives (Scheme 1). The synthesis of tryptanthrin derivatives has been previously reported with different reaction conditions[29,30] However, those procedures are not suitable for further formation of our desired spiro compounds in a one-pot process.

To study the effect of reagent loading on the synthesis of spiroindoloquinazolines, the condensation reaction of isatoic anhydride (**1**), isatin (**2**), malononitrile (**4**), and dimedone (**5d**) was chosen as a model reaction. This reaction did not afford the desired product in the absence of catalyst, and so several added bases were tested as summarized in Table 1. DABCO (80 mol%) in acetonitrile under reflux conditions proved to be the best (Table 1, entry 14).

The synthetic pathway for the synthesis of titled compounds is consisting of two steps. At first, tryptanthrin (**3**) derivatives are obtain from the condensation reaction of isatoic anhydride (**1**) and isatin derivatives (**2**). Then, the resulting products are treated with malononitrile (**4**) and carbonyl compounds (**5**) to afford the related spiroindoloquinazoline derivatives (**6**) as the desired products.

As shown in Table 2, a variety of isatin (alkyl- and halo-substituted) and carbonyl (4-hydroxy coumarin, 1,3-cyclohexanedione, dimedone, triacetic acid lactone and 3-methyl-5-pyrazolone) components were tolerated in the synthesis of the corresponding spiroindoloquinazoline derivatives in good yields. However, only malononitrile was successfully incorporated; methyl cyanoacetate and ethyl cyanoacetate gave no reaction, presumably due to their slightly diminished C–H acidity. Among the isatins, the 5-nitro variant did not give the required nitro-tryptanthrin in the first step.

All compounds are stable solids whose structures were established by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy and elemental analysis. The structure of 6b was confirmed by a single-crystal X-ray analysis (Fig. 2). The crystal structure has been deposited at The Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 1448040.

The proposed mechanism for the synthesis of spiroindoloquinazoline derivatives compounds (**6**) in the presence of DABCO is shown in Scheme 2. Initially, isatoic anhydride (**1**) and isatin (**2**) react to form the corresponding tryptanthrin (**3**) in the presence of DABCO. Knoevenagel condensation of (**3**) with (**4**) affords an intermediate **A**, which undergoes Michael addition with the enolate form of carbonyl compound (**5**). The enolate O-atom of the formed intermediate **B** attacks the CN group, and subsequent H-atom shift leads to compound (**6**).

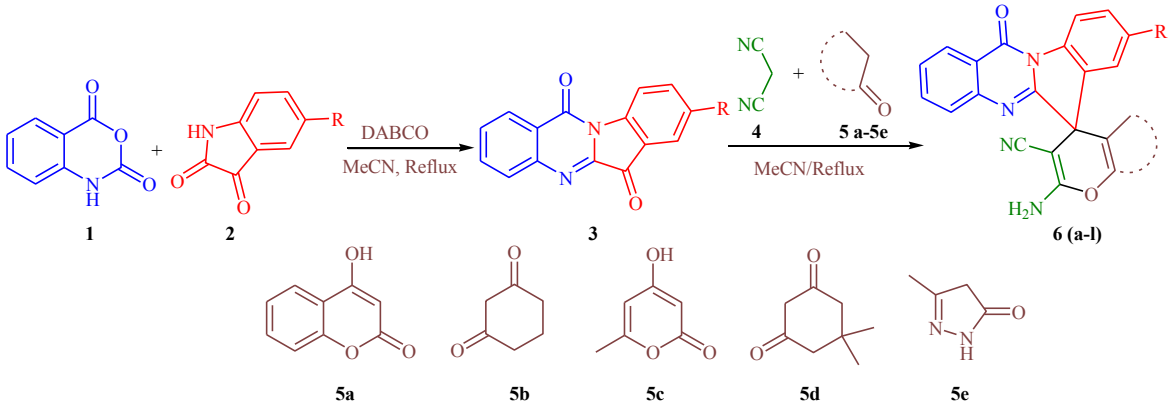
2.2. Biological activity

Phospholipases A2 (PLA2s) hydrolyze the sn-2 ester bond of glycerol phospholipids to release free fatty acid and lysophospholipid. They are a diverse class of enzymes with regard to function, localization, regulation, mechanism, sequence, structure, and role of divalent metal ions. The first non-pancreatic PLA2 recognized in mammals was the group IIA enzyme which plays significant roles in the initiation and intensification of the inflammatory response.[31]

PLA2 also provides precursors for eicosanoid generation when the cleaved fatty acid is arachidonic acid.[32] Arachidonic acid is metabolized by either the cyclo-oxygenase or the lipo-oxygenase enzymatic pathway to yield various families of eicosanoids including prostaglandins and leukotrienes which involved in inflammation related routes.[33,34]

It has been shown that tryptanthrin, which is the main backbone of our synthesized compounds, has tendency to reduce the development of topical inflammation.[35] Since there is a close relationship between inflammation and PLA2 activity, we decided to investigate the inhibition activity of obtained compounds against PLA2.

Phospholipase A2 inhibition activity was measured by the acidimetric method developed by Tan and Tan.[36] This procedure



Scheme 1. The synthesis of spiroindoloquinazoline derivatives *via* the reaction between isatin derivatives, isatoic anhydride, carbonyl compounds and malono derivative in the presence of DABCO in MeCN under reflux conditions.