European Journal of Pharmaceutical Sciences 51 (2014) 196–203

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

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

Synthesis of pharmacologically active 1-amino-isoquinolines prepared via silver triflate-catalyzed cyclization of *o*-alkynylbenzaldoximes with isocyanates ☆

Anderson C. Mantovani, Ana Paula Pesarico, Tuane B. Sampaio, Cristina W. Nogueira, Gilson Zeni *

Laboratório de Síntese, Reatividade e Avaliação Farmacológica e Toxicológica de Organocalcogênios, Universidade Federal de Santa Maria, CEP 97105-900 Santa Maria, RS, Brazil

ARTICLE INFO

Article history:
Received 26 July 2013
Received in revised form 24 September 2013
Accepted 25 September 2013
Available online 4 October 2013

Keywords:
Antioxidant
Antidepressant-like
Isoquinolines
Cyclization reaction
Silver cycloaddition

ABSTRACT

The synthesis of a series of 1-amino-isoquinolines prepared via electrophilic cyclization [3+2] cycloaddition/rearrangement reactions of o-alkynylbenzaldoxime **1** with isocyanates **2** in the presence of catalytic amount of AgOTf was demonstrated. The cyclized products were obtained in good yields under an air atmosphere. 1-Amino-isoquinoline derivatives **3a**, **3b**, **3j** and **3t** were screened *in vitro* for the antioxidant potential and efficacy to inhibit cerebral monoamine oxidase (MAO) activity. The antidepressant-like action of some 1-amino-isoquinolines was performed in the mouse forced swimming test (FST). The pharmacological screening of 1-amino-isoquinoline derivatives indicated that **3a**, **3b**, **3j** and **3t** were antioxidants and inhibited cerebral MAO-A and B activities at low concentrations. Although at different doses **3a**, **3b**, **3j** and **3t** were effective antidepressant-like drugs in the mouse FST. None of 1-amino-isoquinolines tested caused acute cerebral, hepatic or renal toxicity in mice.

1. Introduction

The synthesis and application of isoquinolines have been of great interest for chemists due to their remarkable pharmacological properties that render these heterocycles extensive applications in medicinal chemistry (Saito et al., 1986, 1998; Wei et al., 2011). In particular, isoquinolines have been reported as antifungal (Cieslik et al., 2012; Jampilek et al., 2009; Musiol et al., 2010a, 2010b), antitumoral (Podeszwa et al., 2007), antibacterial(Cieslik et al., 2012), antiprotozoic (Nava-Zuazo et al., 2010) and antineoplastic drugs (Gonzalez-Sanchez et al., 2011).

1-Methyl-1,2,3,4-tetrahydroisoquinoline, an endogenous isoquinoline, has been reported as a neuroprotector, anti-addictive and antidepressant agent (Wasik et al., 2013). The mechanisms of action of this isoquinoline involve the inhibition of monoamine oxidase A (MAO-A) and MAO-B activities, and the increase in the levels of cerebral monoamines (Antkiewicz-Michaluk et al., 2007). Berberine, an isoquinoline plant alkaloid, also demonstrates multiple pharmacological activities such as anti-inflammatory, antitumor, antimalarial, antioxidant (Imanshahidi and Hosseinzadeh, 2008) and antidepressant (Kong et al., 2001). In addition to these properties studies have demonstrated that berberine is an inhibitor of MAO-A (Kong et al., 2001), acetylcholinesterase, butyrylcholinesterase activities and reduced β-amyloid (Aβ) aggregation (Su et al., 2013). Zajdel et al. (2013) reported that isoquinolines elicited antidepressant-like activity in a mouse model of depression.

Depression is a serious disorder in today's society characterized by expression and regulation of mood and emotions (Palucha and Pilc, 2002). It is an illness that has a lifetime prevalence approaching 15–25% associated with significant morbidity and mortality (Nemeroff, 2007). Isoquinoline derivatives represent a class of natural and synthetic compounds that have been evaluated as inhibitors of both MAO-A and MAO-B enzyme activities, a family of enzymes target for the treatment of depression. The inhibition of these enzymes could lead to the increase of monoaminergic neurotransmitter levels in the brain (Patsenka and Antkiewicz-Michaluk, 2004), among them of serotonin (5-HT), the most important neurotransmitter in depression (Nutt, 2008).

As a consequence of their wide application, extensive efforts have been made to develop convenient and efficient methods for the synthesis of isoquinolines. Of the classical routes, their formation by the Pomeranz-Fritsch (Kametani and Fukumoto, 1981), Bischeler-Napieralski (Whaley and Govindachari, 1951a) and Pictet-Spengler reactions (Whaley and Govindachari, 1951b) were widely exploited. Besides the already classical procedures mentioned

☆ *Source of funding*: UFSM, CAPES, CNPq, FAPERGS/CNPq (PRONEX) research Grant #10/0005-1 and FAPERGS research Grant #10/0711-6.

* Corresponding author. Address: Laboratório de Síntese, Reatividade e Avaliação Farmacológica e Toxicológica de Organocalcogênios, Centro de Ciências Naturais e Exatas, Universidade Federal de Santa Maria, 97105-900 Santa Maria, RS, Brazil. Tel.: +55 55 32208140.

E-mail address: gzeni@ufsm.br (G. Zeni).

0928-0987/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ejps.2013.09.021

above, advances include the use of annulations of internal acetylenes catalyzed by palladium salts, palladium/copper-catalyzed coupling and cyclization of terminal alkynes and imines (Roesch and Larock, 2002). In addition, the use of *o*-alkynylbenzaldoximes in association with gold- (Yeom et al., 2008), silver- (Li et al., 2012) and bismuth-catalyzed (Chen et al., 2009) reactions also proved to be a powerful tool for the synthesis of these heterocycles. Although much attention has been paid to the synthesis of isoquinolines, mainly by the use of isothiocyanates, their preparation by using isocyanates was not described in the literature.

Keeping in mind that isocyanates are easily available in lower cost and based on the fact that the isoquinoline family has pharmacological properties, we searched an alternative route to 1-amino-isoquinolines **3** via electrophilic cyclization [3+2] cycloaddition/rearrangement reactions of *o*-alkynylbenzaldoximes **1** with isocyanates **2** in the presence of AgOTf (Scheme 1). 1-Amino-isoquinoline derivatives **3a**, **3b**, **3j** and **3t** were screened *in vitro* for the antioxidant potential and efficacy to inhibit the activities of both cerebral isoforms of MAO. The antidepressant-like action of some 1-amino-isoquinolines was performed in the mouse forced swimming test (FST).

2. Materials and methods

2.1. Chemistry

Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 200 MHz on a DPX-200 NMR spectrometer or at 400 MHz on a DPX-400 NMR spectrometer. Spectra were recorded in $CDCl_3$ solutions. Chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$ or tetramethylsilane (TMS) as the external reference. Data are reported as follows: chemical shift (δ), multiplicity, coupling constant (J) in Hertz and integrated intensity. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained either at 50 MHz on a DPX-200 NMR spectrometer or at 100 MHz on a DPX-400 NMR spectrometer. Spectra were recorded in $CDCl_3$ solutions. All synthesized and tested compounds were obtained in purity superior to 98% determined by combustion analysis, HPLC and gas chromatography. All reagents and solvents were obtained from commercial suppliers and used without further purification unless otherwise stated. Solvents were dried using standard procedures and reactions requiring anhydrous conditions were performed under an argon atmosphere. Column chromatography was performed on 70–230 mesh silica gel. Reactions were monitored by Thin Layer Chromatography (TLC) on pre-coated silica gel F254 plates with a UV indicator.

2.2. General procedure for silver-promoted cyclization of *o*-alkynylbenzaldoximes and isocyanates

To a Schelenck tube, under air atmosphere, containing a mixture of 2-alkynylbenzaldoxime **1** (0.25 mmol) and isocyanate **2** (0.25 mmol) in DMF (2 mL), was added AgOTf (10 mol%). The solution was stirred overnight, under air atmosphere, at 140 °C. After that the solution was cooled at room temperature, diluted with ethyl acetate (10 mL), and washed with saturated aq NH_4Cl (3 × 10 mL). The organic phase was separated, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash chromatography on silica gel using hexane/ethyl acetate (20:1) as the eluent.

2.3. Pharmacological assays

2.3.1. Animals

The experiments were conducted using male adult Swiss mice (25–35 g) and male adult Wistar rats (200–300 g) from our own breeding colony. The animals were kept in a separate animal room, on a 12 h light/dark cycle with lights on at 7:00 a.m., at room temperature (22 ± 1 °C) with free access to water and food. All manipulations were carried out between 08:00 a.m. and 04:00 p.m. All *in vivo* experiments were performed on separate groups of animals (7–9 animals each). The animals were used according to the guidelines of the Committee on Care and Use of Experimental Animal Resources, the Federal University of Santa Maria, Brazil. All efforts were made to minimize animals suffering and to reduce the number of animals used in the experiments.

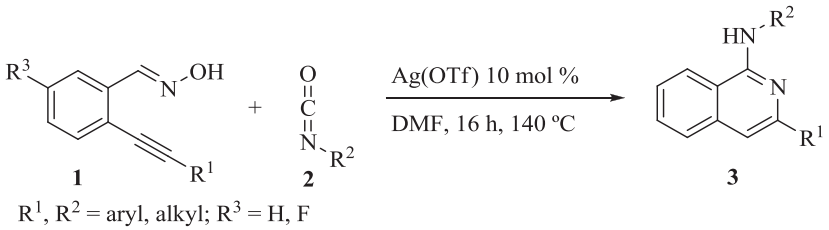
2.3.2. Drugs

1-Amino-isoquinolines **3a**, **3b**, **3j** and **3t** were dissolved in dimethyl sulfoxide (DMSO) for *in vitro* assays. The same compounds were dissolved in canola oil and administered intragastrically (i.g.) to mice at doses of 10and 25 mg/kg for tests *in vivo*. Paroxetine, a positive control, was dissolved in saline and administered intraperitoneally (i.p.) at a dose of 8 mg/kg (Gay et al., 2010). Mice received 1-amino-isoquinoline and paroxetine in a constant volume of 10 ml/kg of body weight. Appropriate vehicle-treated groups were also simultaneously assessed. All compounds were administered at different times of 30 min, 45 min and 1 h before the tests.

2.3.3. In vitro

Rats were killed by decapitation and samples of the whole brain were rapidly removed, placed on ice and weighed. Tissues were immediately homogenized in cold 50 mM Tris–HCl, pH 7.4 (1/5, weight/volume, w/v). The homogenate was centrifuged for 10 min at2400*g* for 10 min at 4 °C to yield a pellet that was discarded and a low-speed supernatant (S1) was obtained. S1 was used to carry out the effect of compounds **3a**, **3b**, **3j** and **3t** on lipid peroxidation and reactive species levels.

2.3.3.1. Lipid peroxidation assay. $FeCl_2$ and EDTA were used as classical inductors of lipid peroxidation. An aliquot of 200 μL of S1 was added to the reaction mixture containing: 10 μM $FeCl_2$/EDTA and compounds **3a**, **3b**, **3j** and **3t** at different concentrations (1–30 μM). The mixture was pre-incubated for 1 h at 37 °C. After the pre-incubation, 500 μL thiobarbituric acid (0.8%), 200 μL sodium dodecyl sulfate (SDS, 8.1%), and 500 μL acetic acid were added to the reaction medium and the mixture was incubated for 1 h at 95 °C. The formation of lipid peroxides in the reaction was mea-



Scheme 1. General scheme.