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# 1-[2-(4-Methyl-7-coumarinyloxy)ethyl]-4-(5-{1-[2-(4-methyl-7-coumarinyloxy)ethyl]-1*H*-1,2,3-triazol-4-yl}pentyl)-1*H*-1,2,3-triazole

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Academic Editor: Norbert Haider
Received: 8 February 2016; Accepted: 31 March 2016; Published: 11 April 2016

**Abstract:** Nature often produces compounds with a high degree of symmetry to reduce structural information and complexity. Synthesis of identical twin drugs, through the linkage of two identical pharmacophoric entities, is a classical strategy to produce more potent and/or selective drugs. Herein, two units of the privileged core of the coumarin hymecromone were linked together using "click chemistry". Synthesis of 1-[2-(4-Methyl-7-coumarinyloxy)ethyl]-4-(5-{1-[2-(4-methyl-7-coumarinyloxy)ethyl]-1*H*-1,2,3-triazol-4-yl}pentyl)-1*H*-1,2,3-triazole was achieved by coupling of two identical units of an azido coumarin with a symmetrical alkine using copper(I)-catalyzed alkyne-azide cycloaddition reaction, in good yields and with complete regioselectivity.

**Keywords:** coumarins; twin drugs; click chemistry; pechmann condensation

## 1. Introduction

Aiming to reduce structural information and complexity, nature often produces compounds with a high degree of symmetry, as observed for the macromolecules HIV protease, hemoglobin and insulin. The linkage of two identical pharmacophoric entities, generating an "identical twin drug" or homodimer derivative, is a classical strategy used in medicinal chemistry to produce more potent and/or selective drugs compared to the single entities. These new compounds will have specific pharmacokinetic and pharmacodynamic properties, which normally differ from what it would be expected by simple doubling the dose of the drug [1].

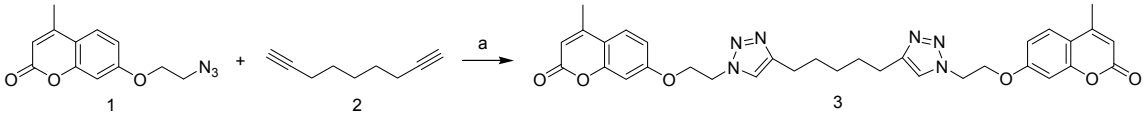
Coumarins are a large class of compounds that display a wide variety of interesting biological properties [2–7], being their 2*H*-chromen-2-one nuclei the structural feature responsible for this "privileged" pharmacological profile. This planar ring system is composed by one aromatic ring, capable of establishing hydrophobic, π-π, CH-π and cation-π interactions, and one lactone ring, which contains two oxygen atoms that may interact via hydrogen bonding with a series of amino acid residues, such as serine, threonine, cysteine, asparagine, glutamine, and tyrosine [8].

In order to explore the possibility of potency and selectivity enhancements provided by the synthesis of twin drugs, two units of the privileged 2*H*-chromen-2-one nuclei of hymecromone (7-hydroxy-4-methylcoumarin) were linked together using "click chemistry", a set of highly efficient conjugation reactions commonly used to join two or more entities [9].

## 2. Experimental Section

### *2.1. General Information*

All chemicals were purchased as reagent grade and used without further purification. Solvents were distilled and/or dried according to standard methods [11]. Column chromatography was performed on silica gel 60 (0.040–0.063 mm) using $CH_2Cl_2$ and $CH_2Cl_2$/EtOAc (5:1 v/v or 2:1 v/v). Microwave-assisted reactions were performed on a CEM Discover® Microwave System. Melting points were determined on a Fisatom 431 apparatus, which were uncorrected. MS spectra were recorded on Q-Tof micro Waters high resolution mass spectrometer, operating in electrospray ionization mode. Nuclear magnetic resonance spectra were recorded on Bruker Advance DPX 400 (400 MHz) spectrometer. Chemical shifts (δ) are given in parts per million downfield from tetramethylsilane. 7-(2-Azidoethoxy)-4-methyl-2*H*-chromen-2-one (**1**) was synthesized according to reported methods [10] and coupled with commercial 1,8-nonadiyne (**2**) by using the copper(I)-catalyzed alkyne-azide cycloaddition reaction, in good yields and with complete regioselectivity (Scheme 1).




**Scheme 1.** Synthesis of 1-[2-(4-Methyl-7-coumarinyloxy)ethyl]-4-(5-{1-[2-(4-methyl-7-coumarinyloxy) ethyl]-1*H*-1,2,3-triazol-4-yl}pentyl)-1*H*-1,2,3-triazole. Reagents, conditions and yields: (a) $CuSO_4$, sodium ascorbate, DMF, MW 70 °C (18 W), 40 min (67%).

### *2.2. Synthesis of 1-[2-(4-Methyl-7-coumarinyloxy)ethyl]-4-(5-{1-[2-(4-methyl-7-coumarinyloxy)ethyl]-1H-1,2,3-triazol-4-yl}pentyl)-1H-1,2,3-triazole* (**3**)

1,8-nonadiyne (**2**) (0.15 mL, 1.1 equiv) was added to a solution of **1** in DMF (0.5–1 M, 0.1 mL) in a microwave flask (0.2 mL) equipped with a stirring bar. Sodium ascorbate (0.1 equiv) and $CuSO_4$ (0.03 equiv) were added, the tube was sealed, and the mixture was stirred for 25 seconds at room temperature, followed by heating under microwave irradiation at 70 °C (18 W) in 2 cycles of 20 min. Consumption of the reactant was followed by TLC ($CH_2Cl_2$/EtOAc 2:1 v/v). The reaction mixture was partitioned between $H_2O$ and EtOAc, the aqueous phase was extracted with EtOAc three times. The organic phase was dried over $MgSO_4$, filtered, concentrated, and the residue purified by column chromatography with a $CH_2Cl_2$/EtOAc gradient [10]. Yield 67%; mp 168 °C; $^1$H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.90 (s, 2H), 7.64 (d, 2H, *J* 8.8 Hz), 6.96 (d, 2H, *J* 2.6 Hz), 6.91 (dd, 2H, *J* 8.8, 2.6 Hz), 6.19 (d, 2H, *J* 1.2 Hz), 4.73 (t, 4H, *J* 5.0 Hz), 4.50 (t, 4H, *J* 5.0 Hz), 2.57 (t, 4H, *J* 7.6 Hz), 2.36 (d, 6H, *J* 1.2 Hz), 1.57 (quint, 4H, *J* 7.6 Hz), 1.31 (quint, 2H, *J* 7.6 Hz); $^{13}$C NMR (100 MHz, DMSO-$d_6$) $\delta$ 160.9, 160.1, 154.6, 153.4, 146.9, 126.5, 122.4, 113.5, 112.5, 111.4, 101.4, 66.9, 48.7, 28.7, 28.1, 24.9, 18.1; HRMS (ESI) *m/z*, calcd. for $C_{33}H_{35}N_6O_6$ $[M + H]^+$: 611.2573, found: 611.3377.

**Supplementary Materials:** $^1$H, $^{13}$C-NMR and HRMS spectra for compound **3** and the molfiles can be found at http://www.mdpi.com/1422-8599/2016/2/M894.

**Acknowledgments:** The authors thank the Brazilian funding agencies CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior), CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico), FAPERGS (Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul), FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo), and Instituto Nacional de Ciência e Tecnologia para Inovação Farmacêutica (INCT-IF) for the financial support. The authors are thankful to Prof. Saulo Fernandes de Andrade (PPGCF/UFRGS) and Prof. Francisco Paulo dos Santos (IQ/UFRGS) for the support on the NMR analyses and to Maristela Cabral da Silva Piedade (LaSOM/UFRGS) and Maribete Homrich Holzschuh (PPGCF/UFRGS) for the technical support.

**Author Contributions:** Fernando Torres, Gabriel Azambuja, Itamar Gonçalves and Guilherme Gonçalves: experimental work; Gilsane von Poser, Daniel Kawano and Vera Eifler: literature search, design of the synthesis and writing of the paper.

**Conflicts of Interest:** The authors declare no conflict of interest.

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