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Design, synthesis and biological evaluation of novel 1,2,3-triazole linked coumarinopyrazole conjugates as potent anticholinesterase, anti-5-lipoxygenase, anti-tyrosinase and anti-cancer agents

Samia Chekir[a,b], Meriem Debbabi[b], Anne Regazzetti[c], Delphine Dargère[c], Olivier Laprévote[c], Hichem Ben Jannet[b,*], Rafik Gharbi[a,*]

[a] Laboratory of Applied Chemistry and Environment, Faculty of Science of Monastir, University of Monastir, 5019 Monastir, Tunisia
[b] Laboratory of Heterocyclic Chemistry, Natural Products and Reactivity (LR11ES39), Team: Medicinal Chemistry and Natural Products and Reactivity, Faculty of Science of Monastir, University of Monastir, 5019 Monastir, Tunisia
[c] Laboratory C-TAC Faculty of Pharmaceutical and Biological Sciences, 4 avenue de l'Observatoire 75270 Paris cedex 06, France

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ABSTRACT

A series of new 1,2,3-triazole linked coumarinopyrazole conjugates **4a-e** and **5a-e** have been synthesized *via* the Copper(I)-catalysed Alkyne-Azide Cycloaddition (CuAAC). Going through the reaction of compound **2** with the 3-propargyl bromide gave a mixture of propargylated regioisomers **3** + **3′** used as a dipolarophile to access to triazoles **4a-e** and **5a-e**. The structures of the prepared cycloadducts were determined by ^{1}H, ^{13}C and 2D-NMR techniques and by HRMS analysis. All the synthesized derivatives have been evaluated for their anticholinesterase, anti-5-lipoxygenase, anti-tyrosinase, and cytotoxic activities.

1. Introduction

The design and construction of novel poly-heterocycles containing different privileged substructures within a same molecule, represent an important strategy in medicinal chemistry [1]. Indeed it is generally proven that the presence of two or more heterocyclic pharmacophores linked and/or fused within a same framework could contribute to provide a significant positive effect on the overall biological efficiency in the resulting poly-heterocycle [2].

This encouraged us to prepare new classes of heterocyclic compounds associating within a same scaffold the coumarin, the pyrazole and the triazole moieties.

Indeed and as commonly reported, coumarins represent an important class of oxygenated heterocycles extensively distributed in nature and very valued for their anti-inflammatory [3], anticancer [4], and antimicrobial activities [5]. Recently, coumarinic derivatives have also been reported to exhibit anti-tyrosinase [6], antioxidant [7], antimicrobial [8], anticoagulant [9] and anti-cholinesterase potentials [10].

On another hand, pyrazoles, are widely found as the core structure in a large variety of compounds of great biological and pharmaceutical value exhibiting anti-HCV [11], antitumor [12], cytotoxic[13], and antioxidant activities [14].

Finally, 1,2,3-triazoles have attracted the interest of medicinal chemists due to their broad spectrum of applications in medicinal chemistry and biochemical [15]. Thus there are known as anti-tumoral [16] anticholinesterase [17], anti-5-lipoxygenase [18], anti-tyrosinase [19], and cytotoxic [20] agents.

Encouraged by these data, we were prompted to explore versatile possibilities of access to novel hybrid conjugates associating these three aforementioned substructures within a same molecular target namely the 1,2,3-triazolo-coumarino[4,3-*c*]pyrazole and study their possible anticholinesterase, anti-5-lipoxygenase, anti-tyrosinase, and cytotoxic potentials.

2. Results and discussion

2.1. Chemical structure

A straight forward one-step route to the targeted pyrazolocoumarinotriazoles **4** and **5**, was performed *via* the “click” methodology based on a Cu(I)-catalyzed dipolar cycloaddition

* Corresponding authors.
E-mail address: hich.benjannet@yahoo.fr (H. Ben Jannet).

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between *N*-propargylpyrazolocoumarins (dipolarophile) and arylazides (*1,3*-dipoles).

We have initiated the work by the treatment of compound **2** with propargyl bromide using NaH as catalyst under refluxing anhydrous DMF for two hours. The reaction provided a mixture of dipolarophiles (**3** + **3′**). These latter were identified on the basis of their spectral data (^{1}H and ^{13}C NMR). The ^{1}H NMR spectrum recorded in $CDCl_3$ at 300 MHz revealed a resolution of δ_H signals (8.49 and 8.20) attributable to protons H_3 and $H_{3'}$, respectively, and (5.40 and 5.16) attributable to methylene protons $H_{10'}$ and H_{10}, respectively, and also the signals at δ_H (2.69 and 2.55) corresponding to the methine protons (H_{12} and $H_{12'}$, respectively). These attributions were based on the study of the NOESY spectrum of the mixture **3** + **3′**. Indeed, in the case of the regioisomer 3′ a *nOe* was observed between $H_{3'}$ and $H_{10'}$.

The ^{13}C NMR spectrum reinforced this structure by the appearance of the signal splitting at δ_C 109 ($C_{3'}$), 108.2 (C_3), two methine carbon signals at δ_C 75.9 ($C_{12'}$ and C_{12}) and two methylene carbon signals at δ_C 42.8 and 42.3 corresponding to C_{10} and $C_{10'}$, respectively. The gas chromatography (GC) analysis confirmed these findings by the presence of two peaks at the retention times: 38.29 min and 39.25 min.

We have studied the behavior of a mixture of alkynes (**3** + **3′**) and arylazides. The synthesis of various 1,2,3-triazole linked coumarinopyrazole conjugates **4a-e** and **5a-e** was carried out under a microwave irradiation (250 W, 30 min) with excess of arylazides in the presence of a catalytic amount of CuI (5%) and a triethylamine (1.5 eqv) as a base, in anhydrous DMF. The reaction was found to be regiospecific, and a chromatographic separation on silica gel (6:4 petroleum ether/ethyl acetate) allowed the isolation of the derivatives **4a-e** and **5a-e** (Scheme 1).

The structures of the 1,4-substituted triazoles regioisomers **4a-e** and **5a-e** were evidenced by mean of 1D and 2D NMR experiments. The ^{1}H NMR spectra of both **4a-e** and **5a-e** showed two characteristic singlets which were assigned to H_{14} in the triazolic moiety (δ_H 8.09 (**4a**) and 7.92 (**5a**)) and to H_3 in the pyrazolic moiety (δ_H 8.37 and 8.23 in compounds **4a** and **5a**, respectively). The ^{13}C NMR spectrum reinforced the above spectral data by the non-appearance of a signal at around δ_C 74 relative to the terminal alkynic C_{12} in favor of the appearance of new signals attributable to C_{14} and the aromatic carbons in the triazole moiety. Additional 2D studies enabled us determine a whole set of NMR data. In addition, the ESI-HRMS of **4a**, recorded showed a pseudo-molecular ion peak $[M+H]^+$ at *m/z* 344.1147 which is consistent with the molecular formula of $C_{19}H_{14}N_5O_2$.

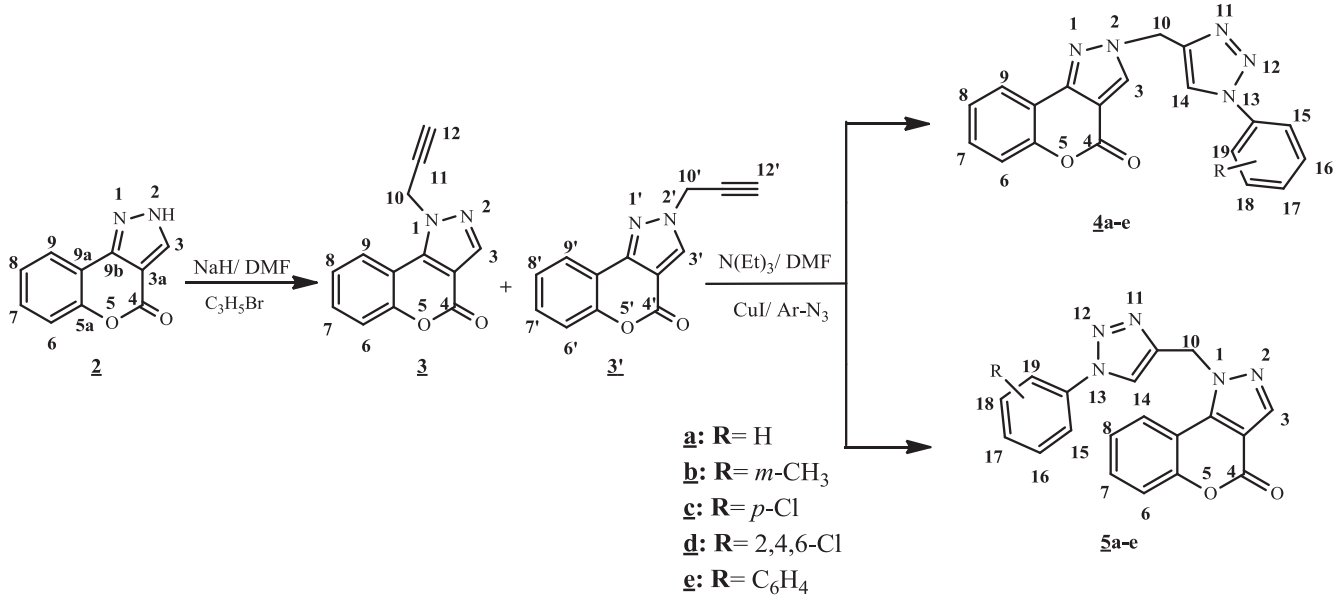
The orientation of the regiochemistry in derivatives **4** and **5** was determined by mean of the NOESY experiment. Thus, the NOESY-map showed a NOE-peak between H_{14}triazole/H_{10} methylene while no correlation between $H_{10}/H_{15,19}$ was detected. The 1,4-regiochemistry in the sole isomer formed is thus consistent with that reported in the literature [21]. Furthermore, the NOESY spectrum showed a NOE between H_{10} and H_3 in **4a-e** and also a NOE peak between H_{10} and the aromatic protons of the 1,4-regioisomer **5a-e**. As an illustration example, compounds **4a** and **5a** showed the NOE-peaks H_{10} (δ_H 5.72, s)/H_3 (δ_H 8.37, s) and H_{10} (δ_H 6.03, s)/H_9 (δ_H 8.31, dd, J_1 = 8.1 Hz, J_2 = 1.2 Hz).

In order to study the possible biological activities of this class of compounds, most prepared 1,2,3-triazolocoumariopyrazoles were tested for their anti-cholinesterase, anti-5-lipoxygenase, anti-tyrosinase, and cytotoxic potentialities.

2.2. Biological activity

2.2.1. Anti-butyrylcholinesterase (BChE) activity

The anti-butyrylcholinesterase potential of compounds **2**, **3** + **3′**, **4a-d** and **5a-d** has been assayed and expressed in IC_{50} (μM). As shown in Table 1, the relatively weak activity of the mixture **3** + **3′** (IC_{50} = 152 ± 3.0 μM) compared to that of compound **2** (IC_{50} = 90 ± 1.0 μM) is certainly due to the propargylation of the nitrogen atoms of the pyrazole ring. The results showed that triazoles **4a-d** (IC_{50} = 29 ± 1.8–120 ± 2.0 μM) and **5a-d** (IC_{50} = 18 ± 1.0–96.0 ± 3.0 μM) proved to inhibit more the BChE than the starting dipolarophiles **3** + **3′**, hence the contribution of the introduced triazole system to improve the anti-BChE potential. This finding was found in agreement with a previous work showing the importance of the triazole ring to enhance the activity compared to the starting propargylated compound [22]. Independently of the nature of the substituent attached to the aromatic ring borne by the triazole, compounds **4b-d** were found to be more active than the cycloadduct **4a** where the triazole carries a phenyl group. Compound **4b** (3-CH_3-Ph) was found to be relatively less active than the chlorinated cycloadduct **4c** (4-Cl-Ph) followed by **4d** (2,4,6-Cl-Ph) (IC_{50} = 75.0 ± 2.0, 70.0 ± 3.0 and 29.0 ± 1.8 μM, respectively). This result showed the importance of the chlorine atom, characterized by an electro-attractor effect, compared to the methyl group which, on the contrary, has an electro-donor effect. This finding is reinforced by the relatively high activity of compound **4d** in which the triazole bears



Scheme 1. Synthesis of coumarinopyrazolotriazoles **4a-e** and **5a-e.**