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# Triazole-curcuminoids: A new class of derivatives for 'tuning' curcumin bioactivities?

Diego Caprioglio [†], Simone Torretta [†], Maila Ferrari, Cristina Travelli, Ambra A. Grolla, Fabrizio Condorelli, Armando A. Genazzani [*], Alberto Minassi [*]

*Dipartimento di Scienze del Farmaco, Università del Piemonte Orientale, Via Bovio 6, Novara 28100, Italy*

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ABSTRACT

Curcumin is a unique blend of pharmacophores responsible for the pleiotropy of this natural pigment. In the present study we have replaced the 1,3-dicarbonyl moiety with a 1,2,3-triazole ring to furnish a new class of triazole-curcuminoids as a possible strategy to generate new compounds with different potency and selectivity compared to curcumin. We obtained a proof-of-principle library of 28 compounds tested for their cytotoxicity (SY-SY5Y and HeLa cells) and for their ability to inhibit NF-κB. Furthermore, we also generated 1,3-dicarbonyl curcuminoids of selected click compounds. Triazole-curcuminoids lost their ability to be Michael's acceptors, yet maintained some of the features of the parent compounds and disclosed new ones. In particular, we found that some compounds were able to inhibit NF-κB without showing cytotoxicity, while others, unlike curcumin, activated NF-κB signalling. This validates the hypothesis that click libraries can be used to investigate the biological activities of curcumin as well as generate analogs with selected features.



## 1. Introduction

Natural pigments are widely used in the food and textile industry, and besides their chromatic features some of them, like flavonoids and carotenoids, have also important biological properties. *Curcuma longa* (turmeric) is a perennial plant of the ginger family and its deep yellow powder is commonly used for flavouring food in the Southeast Asian and Middle Eastern countries. In India it has been used for thousand years as a spice for flavouring curry, as a dye for the holy robes in Hindu religion and it still represents a common remedy in Ayurvedic medicine for its anti-inflammatory and antibacterial activities.[1] Turmeric owes its colour to a group of pigments all belonging to the diarylheptanoid family extracted from the roots. The major constituent of this group of compounds, called curcuminoids, is curcumin (**1**) that is also the active phytochemical of turmeric. In the last decades curcumin has emerged as an important scientific topic for its pleiotropy due to its ability to act directly on more than 100 molecular targets[2] (e.g., NF-κB,[3] Nrf2,[4] STAT-3,[5] PPAR-γ[6]). Furthermore, from a medicinal chemistry standpoint, the pharmacophore of curcumin is a unique blend: Michael acceptor, metal chelating, and antioxidant.[7] These pleiotropic actions make curcumin an interesting scaffold from a medicinal chemistry point of view.[8] On the other hand, the lack of specificity and the low potency of most of its actions call for analogs to be synthetized with increased potency and higher specificity. For this to be achieved, enough analogs should be synthesized to gather a good insight on the structure–activity relationships for each action.

The structure of curcumin has indeed been widely explored by different SAR studies.[9] In a number of these, the 1,3-dicarbonyl system has been replaced with success with different cycles or heterocycles;[10–14] in particular the pyrazole derivative of curcumin has received attention due to its improved potency in different biological assays compared to the natural dye.[15,16]

In the present contribution, we decided to proceed with a proof of principle library to investigate whether the copper-catalyzed Huigsen cycloaddition reaction could be applied to this end. The copper-catalyzed 1,3-dipolar cycloaddition of an azide and an alkyne is an increasingly popular strategy to connect different structural units through the introduction of a stable permanent link,[17–21] represents a new, powerful tool in the drug discovery process,[22–27] and is the archeotype of click chemistry reactions. It should be noticed that we have previously reported C5-curcumin analogs synthetized via the Pabon reaction, which also may be considered a click reaction.[28] Curcumin is a symmetric feruloyl dimer, and most of the SAR studies carried out on this natural pigment

* Corresponding authors.
*E-mail addresses:* armando.genazzani@uniupo.it (A.A. Genazzani), alberto.minassi@uniupo.it (A. Minassi).
† These authors contribute equally to this work.

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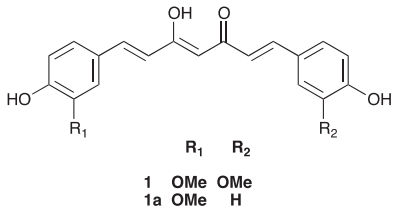
have focused on symmetric analogs,[9] despite the increased potency, in several anti-inflammatory and biochemical assays, of monodemethoxycurcumin[29] (**1a**). Furthermore, it should be noted that many tubulin inhibiting compounds have a heterodimeric structure (Vinca alkaloids, combretastatins and podophyllotoxin). We therefore postulated that the insertion of a 1,2,3-triazole ring in place of the 1,3-dicarbonyl moiety, provided us with easy access to asymmetric derivatives with different aryl substitution patterns, extending the structure–activity relationship of curcuminoids on different biological targets. We now report that this strategy would be amenable to be exploited to generate a large number of analogs with just selected properties of curcumin.

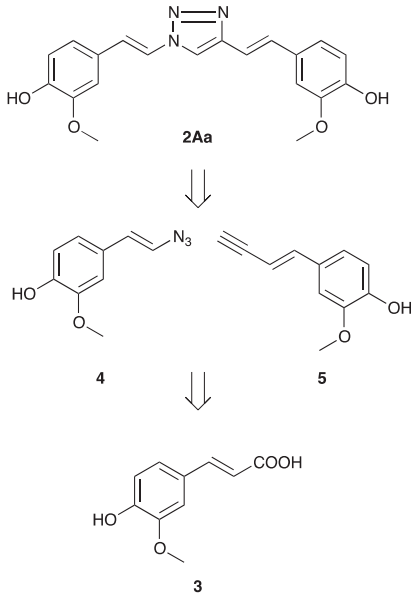



Last, given that a number of triazole-curcuminoids were close analogs of already reported curcuminoids, we compared the activity between selected triazole-curcuminoids and the corresponding 1,3-dicarbonyl analogs to evaluate whether the triazole ring on this scaffold confers novel properties or is only an experimental strategy to yield libraries in an efficient manner.

## 2. Results

### 2.1. Chemistry

In the present study the 1,3-dicarbonyl moiety of curcumin (**1**) has been replaced by a 1,2,3-triazole ring to give triazole-curcumin (**2Aa**) as the archetypal example of a new class of triazole-curcuminoids, by using the Huisgen [3+2] cycloaddition catalyzed by copper (I) salts. From a first retrosynthetic analysis we identified ferulic acid (**3**) as a possible starting material for the synthesis of both β-azidostyrene **4** and vanillic-enyne **5** (Scheme 1).

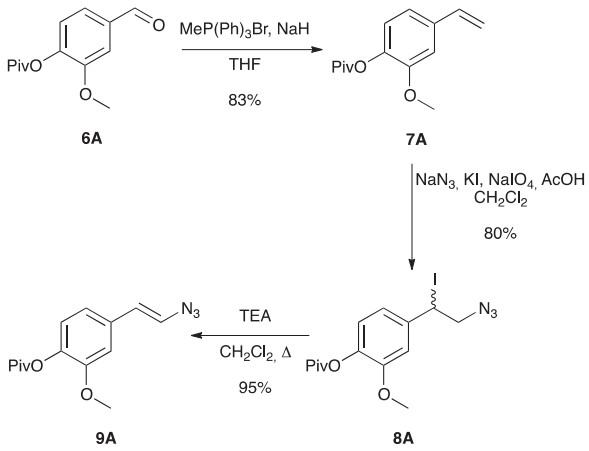



**Scheme 1.** Retrosynthetic analysis.

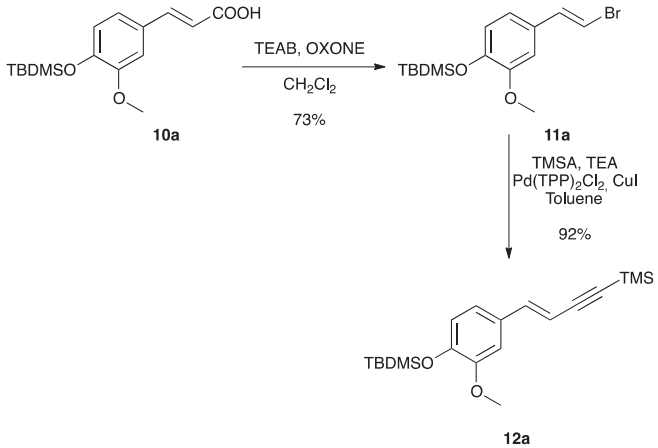
For the synthesis of the β-azidostyrene moiety we tried different methodologies found in the literature,[30–32] but we were not able to reproduce the same results and all efforts to obtain the vinylazide from ferulic acid failed. As a second approach to obtain the azide synthon we decided to start from styrene **7A**, derived from *O*-pivaloyl-vanilline **6A** after Wittig olefination, that undergoes an azoiodination reaction to give the corresponding 2-azido-1-iodoethyl derivative **8A**. The latter was obtained in high yield and with high regioselectivity by using a modified version of the azoiodination reaction of styrenes published by Sudalai, in which $CH_2Cl_2$ was used as solvent in place of AcOH.[33] By using AcOH as a solvent we obtained a 1:1 mixture of our product and 1-acetyl-2-iodoethyl derivative, probably due to the ability of AcOH to stabilize the benzylic carbocation and to trap it. By refluxing compound **8A** in $CH_2Cl_2$ in presence of TEA, we obtained the protected β-azidostyrene **9A** (Scheme 2).

The enyne moiety was obtained starting from *O*-silylated ferulic acid **10a** using the Hunsdiecker[34–38] reaction with triethylammonium bromide (TEAB) and oxone in $CH_2Cl_2$ to give the corresponding vinyl bromide **11a** that reacting with (trimethylsilyl)-acetylene under Sonogashira conditions, afforded the bis-protected vanillic-enyne **12a** in good yield (Scheme 3).

The azide **9A** and the alkyne **12a** were then reacted under the classical copper-catalyzed [3+2] azide-alkyne cycloaddition to give click-curcumin **2Aa** after complete deprotection with KOH/MeOH (Scheme 4).




**Scheme 2.** Synthesis of the protected β-azidostyrene **9A**.




**Scheme 3.** Synthesis of the bis-protected vanillic-enyne **12a**.