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# Imidazole analogues of resveratrol: synthesis and cancer cell growth evaluation

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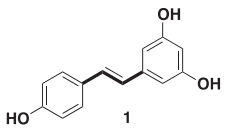
ABSTRACT

Novel trans-restricted analogues of resveratrol in which the C–C double bond of the natural derivative has been replaced by diaryl substituted imidazole analogues have been designed. The syntheses of 1,4-, 2,4-, and 2,5-diarylimidazoles, in which the two aryl moieties are linked to the heteroaromatic core in a 1,3 fashion in order to preserve the trans stereochemistry, have been successfully carried out by regioselective sequential transition metal-catalyzed arylations of simple, commercially available imidazole precursors. The anticancer activity of selected analogues has been evaluated in vitro against the NCI-60 human tumor cell lines panel. From this screening, we were able to select a synthetic candidate that resulted more active than its natural lead.



## 1. Introduction

Stilbenes belong to the nonflavonoid class of polyphenols.[1] They are 1,2-diarylethenes presenting a trans-configured double bond substituted with a phenyl group on both carbon atoms of the double bond. The most well known natural stilbene is resveratrol (**1**), firstly isolated in 1939 from roots of *Veratrum grandiflorum* (white hellebore)[2] and since then found in various edible plants, notably in *Vitis vinifera* L. (Vitaceae).[3]

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Resveratrol is a natural phytoalexin; it is produced by at least 72 species of plants distributed among 31 genera and 12 families in response to stress, injury, fungal infection, and UV irradiation.[4]

Resveratrol attracted little interest until 1992, when it was postulated to explain some of the cardioprotective effects of red wine, the so-called 'French Paradox'.[5] Since then, a significant high number of papers have attributed to **1** antioxidant,[6] antiobesity,[7] antiviral,[8] antidiabetic,[9] and anticancer[4a,10] activities based on in vitro and animal models.[4b,11] In particular, several studies have shown that **1** is an inhibitor of carcinogenesis at multiple stages via its ability to inhibit cyclooxygenase,[10a,12] and is an anticancer agent with a role in anti-angiogenesis.[10a] Moreover, both in vitro and in vivo studies showed that **1** induces cell cycle arrest and apoptosis in tumor cells.[10c,13]

However, the potential beneficial effects of **1** on health are compromised by its low bioavailability in vivo, thus hindering its arrival at target tissues. Clinical studies in humans evidenced that about 70% of administered **1** (25 mg) is rapidly (<30 min) absorbed after oral intake, and that the low level observed in the blood stream is caused by a fast conversion by conjugation with sulfate and glucuronic acid, or reduction by the intestine microflora, into metabolites that are readily excreted from the body.[4b] The trans-configured double bond of **1** constitutes a critical requirement for its activity, because it may be prone to *E*/*Z* isomerization or reduction. In fact, conjugates of reduced resveratrol may account for as much as 50% of an oral dose of **1**,[14] and reduced resveratrol has a strong proliferative effect on hormone-sensitive cancer cell lines such as breast cancer cell line MCF-7.[15] As a consequence, considerable efforts have been aimed at modifying **1**, and bioavailable trans-restricted analogues based on the bioisosteric replacement of the olefinic double bond of the natural derivative with heteroaromatic nuclei, in analogy to the strategy used to improve the antitumor activity of the *cis*-stilbene Combretastatin A-4,[16] have been developed. Tron, Genazzani and co-workers employed click chemistry to generate a series of 1,4-diaryl-substituted triazole analogues of

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**1**, and evaluated their cytotoxicity against MDA-MB-431 breast cancer cell line.[17] Some of the screened compounds resulted more active than **1** as antiproliferative/cytotoxic agents, displayng $IC_{50}$ values between 10 μM and 10 nM. In 2010 Macchia and co-workers developed new resveratrol analogues in which the trans double bond of **1** was embedded into benzofuran, quinoline or benzothiazole scaffolds.[18] These compounds displayed strong antiproliferative activity against MDA-MB-431 cell line; in particular, 3-(3,5-dihydroxyphenyl)-7-hydroxyquinoline exhibited the most potent antiproliferative effect ($IC_{50}$=17.4 μM). Two years later, Cushman and co-workers replaced the *trans* stilbene double bond of **1** with a 1,2,4-thiadiazole scaffold, and to keep the trans geometry close to that of **1** the two phenyl rings were attached on the 1 and 3 positions of this five-membered heterocyclic core.[19] The 3,5-diaryl-1,2,4-thiadiazoles so obtained were evaluated against the MCF-7 breast cancer cell line but, except 3,5-bis(4-hydroxyphenyl)-1,2,4-thiadiazole ($IC_{50}$ 4.7 μM), all of the compounds had weak antiproliferative activities.

Recently, in continuation of our investigations into the synthesis and evaluation of the cytotoxic activity of diaryl-substituted five-membered heterocycles,[16a,20] in order to obtain derivatives with enhanced metabolic stability we devoted our synthetic efforts to the preparation of trans-restricted analogues of **1** in which the stilbene double bond of this derivative is embedded in an imidazole nucleus. To keep the trans geometry, the two aryl rings were linked to the heteroaromatic core in a 1,3 fashion (Fig. 1). It was hypothesized that this design should give derivatives with improved metabolic stability but retaining the chemopreventive properties of the trans stilbene scaffold.[19]

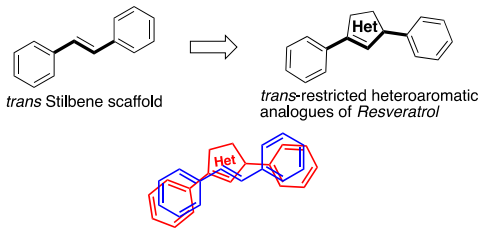
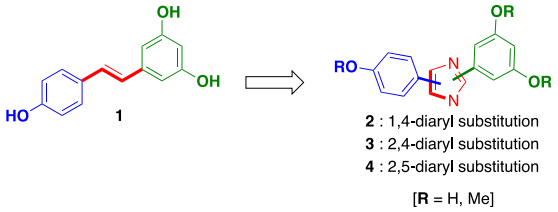



**Fig. 1.** From the *trans* stilbene scaffold of resveratrol (**1**) to 1,3-diaryl-substituted heteroaromatic analogues.

There are a number of established de novo methods for the synthesis of substituted imidazoles where the imidazole ring is constructed via cyclo-condensation reactions.[21] Although these traditional approaches have been greatly improved over the past decade, each method has its scope and efficiency limitations. Often, condensation methods are inefficient for the assembly of series of compounds: for example, regioisomers (2,4- vs 4,5-substitution pattern) or focused analogues (different arene rings in the 4-position). In most cases, the synthesis of each analogue of the library will require the entire de novo synthetic sequence, which translates to parallel repetition of linear synthetic sequences.

A more general strategy for the synthesis of functionalized imidazole derivatives, also developed in recent years, involves the regioselective introduction of substituents into the preformed imidazole ring via transition metal-catalyzed reactions.[22] According to this last synthetic approach, in this paper we describe the selective preparation of *O*-methylated and OH-free 1,4-, 2,4-, and 2,5-diaryl-1*H*-imidazoles of general structures **2**, **3**, and **4**, respectively, which may be regarded as potential trans-restricted analogues of **1** (Scheme 1).

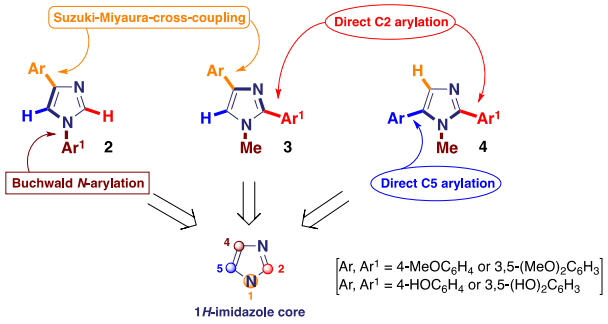
In fact, these structural patterns (1,4-, 2,4-, and 2,5-disubstitution) are the only that allow the 1,3 relative spatial relationship between the 4-hydroxyphenyl and the 3,5-dihydroxyphenyl rings typical of **1**. The synthetic strategies to




**Scheme 1.** General structures of diaryl-substituted imidazoles **2**–**4**, trans analogues of resveratrol (**1**).

compounds **2**–**4** were conceived in order to allow ones the preparation not only of the trihydroxyphenyl derivatives, but also of their methyl ethers, because it has been reported that the replacement of hydroxyl groups with methoxy groups may improve the cytotoxic activity and the chemopreventive properties of resveratrol's analogues.[23]

As depicted in Scheme 2, imidazoles **2**–**4** were efficiently obtained through sequential transition metal-catalyzed regioselective arylation reactions, which included palladium-catalyzed Suzuki–Miyaura cross-couplings, copper-catalyzed Buchwald N-arylation, and palladium–copper mediated direct C–H arylation protocols.




**Scheme 2.** Retrosynthetic pathways to compounds **2**–**4**.

In order to address their anticancer activity, some selected imidazole-based resveratrol analogues were then evaluated in vitro against the NCI-60 DTP human tumor cell lines panel. From this screening, we were able to select a candidate that resulted more active than its natural lead.

## 2. Results and discussion

### 2.1. Synthesis of *O*-methylated and OH-free 1,4-diaryl-1*H*-imidazoles analogues of 1: sequential Suzuki–Miyaura coupling and Buchwald N-arylation

Despite their potential biological activity,[24] to the best of our knowledge only two general methods have been reported in the literature for the synthesis of 1,4-diaryl-1*H*-imidazoles **2**. The first one involves the construction of the imidazole ring by multi-step sequences that generally starts from the condensation between phenacyl bromides and anilines,[25] while copper-promoted direct N-arylation of 4(5)-arylimidazoles **5** with arylboronic acids[26] or aryl halides[27] represents the key synthetic step of the second protocol. The latter methodology undoubtedly offers a number of advantages over the first procedure, including convenience, simplicity, and the use of readily available starting materials, and despite sometimes the tautomeric nature of **5** gave only moderate regioselectivities,[26] their Cu-catalyzed arylation seemed to us the best choice for the preparation of the target compounds **2**.