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Synthesis and antiproliferative evaluation of 2-hydroxylated (*E*)-stilbenes

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ABSTRACT

A simple synthesis of 2-hydroxylated (*E*)-stilbenes was accomplished in good yields via oxidative coupling of 2-hydroxystyrenes and arylboronic acids, with Rh(III)-catalyst and $Cu(OAc)_2$ as oxidant. The antiproliferative evaluation of all the synthesized compounds were assessed on four different human cancer cell lines (Colo-205, MDA-468, HT29, and MGC80-3), and the results showed that several compounds exhibit strong antiproliferative activities (up to IC_{50} = 35 nM for MGC80-3).

Stilbenes are privileged molecules in medicinal chemistry because of their wide range of different biological activities.[1] Particularly, hydroxylated stilbenes are largely presented in nature and play a significant role in antioxidant, antitumor and cardioprotection (Fig. 1). Examples are (*E*)-resveratrol and (*Z*)-combretastatin A-4. (*E*)-Resveratrol, which is isolated from edible materials such as grape skins, peanuts, and red wine, has been suggested as an anticancer agent acting by the inhibition of cell proliferation.[2] (*Z*)-Combretastatin A-4, from the bark of South African bush willow *Combretum caffrum*, also showed significant antitumor activity.[3] Therefore, the synthesis and bioactivity evaluation of hydroxylated stilbene derivatives received much attention and interests in medicinal chemistry.[4]

Literature methods for the synthesis of hydroxylated stilbenes include conventional Wittig reaction, Horner–Wadsworth–Emmons reaction, and Mizoroki–Heck coupling reaction. Wittig reaction and Horner–Wadsworth–Emmons reaction suffer from limitations of slightly low yields, low *E*/*Z* selectivity and stoichiometric generation of triphenylphosphine oxide as byproduct. Respecting to Mizoroki–Heck reaction, this coupling reaction offers a simple and direct approach toward hydroxylated stilbenes, with hydroxystyrenes and iodobenzenes as starting materials. Despite that, the diversity of iodobenzenes is limited.[5] The currently reported Pd-catalyzed oxidative Mizoroki–Heck reaction also offers an alternative approach to stilbenes, but these reaction are limited to narrow substrate scope of simple acrylates, and their synthesis toward hydroxylated (*E*)-stilbenes has rarely been reported.[6] Therefore, the development of simple and distinct methods for construction of hydroxylated stilbenes still remains attention.

While resveratrol and combretastatin A-4 represent 3-hydroxylated stilbenes, the investigation concerning 2-hydroxylated stilbenes is attractive and interesting. As a consequence of our continued interest in the synthesis of biologically interesting small molecules via Rh(III)-catalysis,[7] herein we report a new strategy for rapid assembly of 2-hydroxylated (*E*)-stilbenes, via oxidative coupling of readily available 2-hydroxystyrenes and arylboronic acids (Scheme 1), and the antiproliferative evaluation on four different human cancer cell lines (Colo-205, MDA-468, HT29, and MGC80-3) showed that several compounds exhibit strong proliferative inhibition.

Recently, Macareñas and Gulías reported that 2-hydroxystyrenes could take C–H activation on the olefin position under

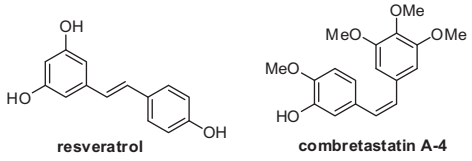

Figure 1. Representative structure of pharmaceutical interesting hydroxylated stilbenes.

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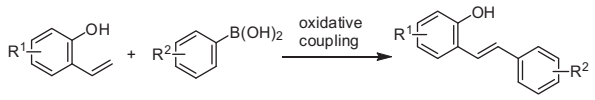
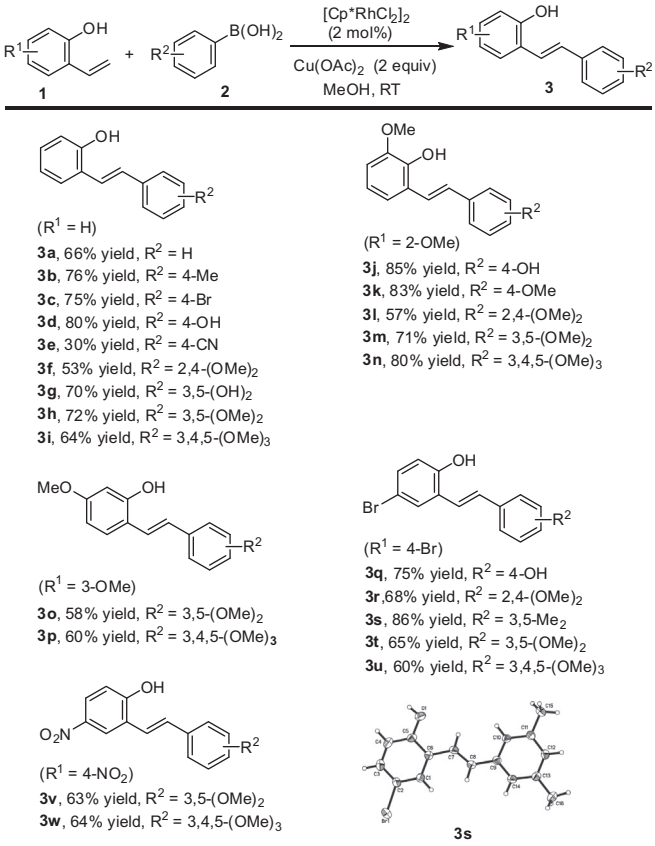


Scheme 1. Synthesis of 2-hydroxylated (*E*)-stilbenes via oxidative coupling of 2-hydroxystyrenes and arylboronic acids.



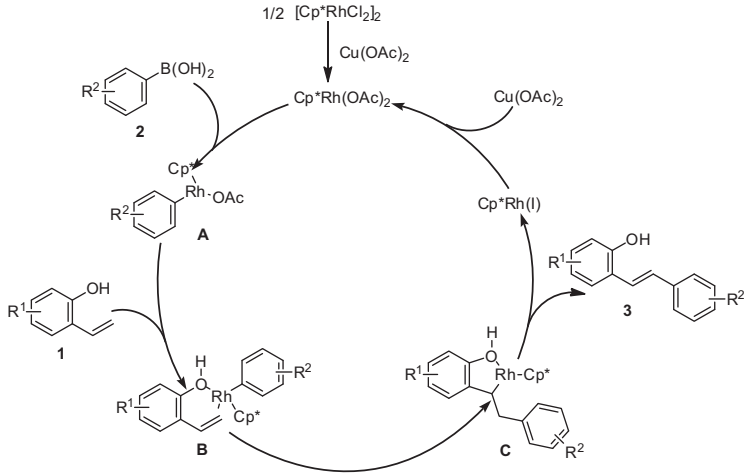
Scheme 2. Synthesis of 2-hydroxylated (*E*)-stilbenes.[10]

Rh(III)-catalysis,[8] which indicated that Rh(III)-catalyzed divergent functionalization of 2-hydroxystyrenes for access to their biological interesting derivatives would be possible. Meanwhile, Miura reported that the commercial available arylboronic acids could change to organometallic reagent and serve as arylation source under Rh(III)-catalysis.[9] Therefore, we assumed that the combination of 2-hydroxystyrenes and arylboronic acids under Rh(III)-catalysis would probably lead to arylation of 2-hydroxystyrenes, and this would deliver structural differential 2-hydroxylated stilbenes.

With this mind, the investigation was then carried out. After optimization, we found that the reaction of 2-hydroxystyrenes and arylboronic acids could indeed afford the 2-hydroxylated (*E*)-stilbenes in good yields upon 2 mol % $[Cp^*RhCl_2]_2$ catalyst and equivalent amount of $Cu(OAc)_2$ as oxidant, and the reaction condition was pretty mild. Interestingly, when $Pd(OAc)_2$ was used as catalyst under this condition, it was inferior to afford only trace product, thus demonstrating the importance of Rh(III)-catalysis. As shown in Scheme 2, various arylboronic acids with valuable functional groups, such as methyl, methoxy, bromo, cyano, hydroxy were well tolerated in this protocol to generate diverse products (**3a**–**3i**), and differential substituted 2-hydroxystyrenes regardless of the electron-donating or electron-withdrawing properties on the aromatic ring, were also well applicable in this oxidative coupling to afford the 2-hydroxylated (*E*)-stilbenes (**3j**–**3w**). Moreover, the structure was confirmed by single X-ray analysis of compound **3s**,[11] identical to characterization. It should be noted that the starting material 2-hydroxystyrenes was easily prepared from salicylaldehydes in one-step, and the arylboronic acids were commercial available. Considering that the reaction condition was mild and the yields were good, and a gram-scale reaction demonstrated its practicality,[12] therefore this synthetic route to 2-hydroxylated (*E*)-stilbenes is general and practical.

Control reaction showed that simple styrene was not amenable in this protocol, which suggested that the hydroxy group is crucial in this oxidative coupling. A plausible mechanism for this reaction is outlined in Scheme 3. The initial rhodium acetate is generated from $[Cp^*RhCl_2]_2$ and $Cu(OAc)_2$, and then take a transmetalation with arylboronic acids **2** to form arylrhodium intermediate **A**. The subsequent bidentate type coordination of 2-hydroxystyrenes **1** with **A** affords **B** and the following insertion generates **C**. A next β-hydrogen elimination delivers 2-hydroxylaed (*E*)-stilbenes **3** and Rh(I) species. Finally, the oxidation of Rh(I) by $Cu(OAc)_2$ regenerates Rh(III) catalysis and enables the catalytic cycle.

All the synthesized compounds (and resveratrol as a standard) were subjected to in vitro antiproliferative evaluation using the MTT assay in four human cancer cell lines, including Colo-205 (colon), MDA-468 (breast), HT29 (colon), and MGC80-3 (stomach),



Scheme 3. Plausible mechanism.

Table 1
Antiproliferative activities of 2-hydroxylated (*E*)-stilbenes

Compd	IC_{50}[a] (μM)			
	Colo-205	MDA-468	HT29	MGC80-3
3a	—	19.3 ± 5.4	—	—
3b	—	21.9 ± 7.3	22.9 ± 5.4	—
3c	21.1 ± 1.8	7.4 ± 1.6	14.4 ± 0.8	—
3d	—	—	33.5 ± 1.7	—
3e	—	—	—	3.1 ± 0.3
3f	—	—	—	—
3g	—	—	26.2 ± 7.3	—
3h	—	12.6 ± 1.1	26.2 ± 1.9	6.3 ± 1.2
3i	—	—	—	—
3j		6.9 ± 2.8	—	—
3k	20.2 ± 3.4	—	—	—
3l	—	5.1 ± 0.6	—	—
3m	—	—	—	—
3n	—	2.6 ± 1.8	—	1.1 ± 0.1
3o	—	8.4 ± 2.3	—	0.8 ± 0.2
3p	5.3 ± 3.6	5.3 ± 3.6	9.7 ± 0.9	0.035 ± 0.007
3q	—	3.5 ± 3.4	26.7 ± 2.1	—
3r	—	3.7 ± 0.6	10 ± 4.7	3.5 ± 0.7
3s		7.2 ± 2.6	13.3 ± 8.2	5 ± 0.3
3t	16.4 ± 4.5	6.1 ± 3.2	9.5 ± 2.7	3.3 ± 0.8
3u	—	14.2 ± 4.2	18.5 ± 0.1	4.5 ± 3.1
3v	—	—	12.6 ± 0.7	10.6 ± 2.2
3w	—	—	—	14.7 ± 3.3
Resveratrol	23.5 ± 0.8	45.2 ± 6.9	87.2 ± 7.7	42 ± 9.7

(—) denotes value of testing compound larger than value of standard compound.
[a] Values were obtained from MTT assays after 72 h of treatment; the values were averaged from three independent experiments.

and IC_{50} (μM) are listed in Table 1. Many compounds showed prominent antiproliferative activities. Among them, the compounds **3p** and **3t** exhibited much higher activities than resveratrol with broad spectrum of activities. When R^1-group was –H, the 2-hydroxylated (*E*)-stilbene derivatives (**3a**–**3i**) had slightly narrow spectrum of activities, except for bromo and 3,5-dimethoxy substituted compounds (**3c** and **3h**), which showed broad spectrum and high antiproliferative activities. When R^1-group was 2-OMe, the compounds (**3j**–**3n**) also had narrow spectrum of antiproliferative activities, albeit with selective high activities. When R^1-group was 3-OMe, the compounds (**3o** and **3p**) showed high activities, especially when R^2-group was 3,4,5-$(OMe)_3$, the compound **3p** exhibited extraordinary high and wide spectrum of antiproliferative activities. The highest antiproliferative activity for the compound **3p** was found in stomach cancer cell line (IC_{50} = 35 nM). When R^1-group was 4-Br, the compounds (**3q**–**3u**) were also found to be broad spectrum and active. When R^1-group was 4-NO_2, the compounds (**3v**–**3w**) had narrow spectrum of activities against only one or two tumor cells. The wide range observed for the compounds **3a**–**3w** indicated that the nature of substituents greatly affected the activity profile of these compounds, while methoxy and bromo are privileged groups in these 2-hydroxylated (*E*)-stilbenes.

In summary, we have developed a simple and efficient approach to synthesize 2-hydroxylated (*E*)-stilbenes via Rh(III)-catalyzed oxidative coupling of 2-hydroxystyrenes and arylboronic acids. Moreover, the antiproliferative activities of these compounds were evaluated in vitro on four different cancer cell lines (Colo-205, MDA-468, HT29, and MGC80-3), and the results showed that several compounds exhibited wide spectrum and good antiproliferative activities.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2014.10.009.

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10. Representative procedure for the Rh(III)-catalyzed synthesis of 2-hydroxylated (*E*)-stilbenes: $[Cp^*RhCl_2]_2$ (2.5 mg, 2 mol %), 2-hydroxy styrenes **1a** (24 mg, 0.2 mmol), $Cu(OAc)_2$ (80 mg, 0.4 mmol), and phenylboronic acid **2** (48.8 mg, 0.4 mmol) were added to a vial, then MeOH (2 mL) was added via syringe. The reaction mixture was kept at room temperature. After completion within 2 hours, it was diluted with CH_2Cl_2 and transferred to a round bottom flask, silica gel (500 mg) was added to the flask and all the volatiles were evaporated under vacuum. The purification was performed by flash column chromatography on silica gel using mixture of ethyl acetate/petroleum ether (v/v, 1:10) as eluent to give product **3a**: white solid; yield 66%; mp 141–143 °C; IR (KBr, ν cm^{-1}): 3533, 3047, 3018, 1584, 1499, 1456, 1333, 1251, 1196, 1088, 978, 846, 761, 727, 694; ^1H NMR ($CDCl_3$, 400 MHz, δ ppm): 7.52 (m, 3H), 7.39–7.33 (m, 3H), 7.25 (m, 1H), 7.15–7.09 (m, 2H), 6.94 (t, J = 7.2 Hz, 1H), 6.78 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H), 5.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz, δ ppm): 153.1, 137.7, 130.3, 128.8, 127.8, 127.4, 126.7, 124.8, 123.1, 121.3, 116.1; HRMS (EI) (m/z): calcd for $C_{14}H_{12}O$ (M^+), 196.0888; found, 196.0891.
11. CCDC 995487 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data_request/cif.
12. See Supplementary data.