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Concise semisynthesis of novel phenazine-vitamin E hybrids *via* regioselective tocopheryl *ortho*-quinone formation

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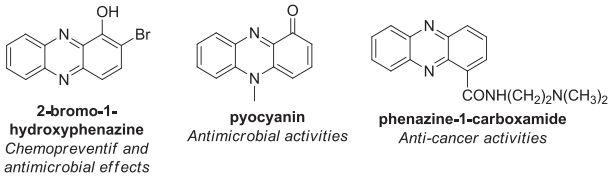
ABSTRACT

A regioselective method for the semisynthesis of phenazine derivatives has been disclosed through an efficient IBX mediated *ortho*-quinone formation from vitamin E derivatives. High chemo- and regio-selectivity was observed during the oxidation step and the corresponding 5,6-*ortho*-quinones could react with various phenylenediamines. Thus, this methodology proves its interest as a concise semisynthetic pathway to phenazine-vitamin E hybrids with moderate to good yields.

In recent years, organic chemists have been prompted to invest research efforts into designing new molecules by combining two distinct entities of bioactive natural or unnatural molecules in order to improve the biological activity of the parent compounds.[1] These hybrids can also interact with different biological targets and offer a better strategy to counteract multifactorial diseases.[2]

Phenazine natural products are secondary metabolites produced by bacteria such as *Pseudomonas* or *Streptomyces*. The biological properties of this class of natural or synthetic products include antibiotic, antitumor, antiparasitic, and neuroprotective activities.[3] For example, 2-bromo-1-hydroxyphenazine, pyocyanin and phenazine-1-carboxamide (Fig. 1) exhibit anticancer and antibacterial properties.[4]

Vitamin E is the generic name of two groups of methyl substituted 2-methyl-2-(4,8,12-trimethyltridecyl)chroman-6-ol, the (2*R*,4′*R*,8′*R*)-tocopherols and the (2*R*)-tocotrienols (Fig. 2). These natural products are found in a wide range of plants and microorganisms as well as, due to their lipophilicity, in high amount in vegetable oils. Vitamin E derivatives possess a large range of biological activities including antioxidant, anti-angiogenic, antiproliferative, cholesterol-lowering, and neuroprotective activities.[5,6] Recently, isoforms of garcinoic acid, a group of four ω-oxidized, tocotrienols showed promising anti-inflammatory properties (Fig. 2).[7]

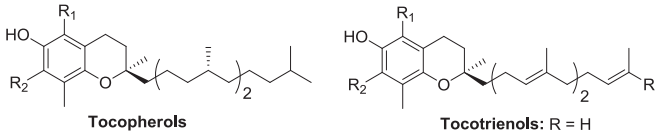


2-bromo-1-hydroxyphenazine
Chemopreventif and antimicrobial effects

pyocyanin
Antimicrobial activities

phenazine-1-carboxamide
Anti-cancer activities

Fig. 1. Example of bioactive natural and synthetic phenazines.



Tocopherols
Anti-oxydant effect

R_1 = H or CH_3
R_2 = H or CH_3

Tocotrienols: R = H
Anti-cancer, neuroprotection and hypocholesterolemic effects

Garcinoic acids: R = CO_2H
Anti-inflammatory effect

Fig. 2. Example of bioactive natural vitamin E derivatives.

In our continuous effort to develop new pharmacologically relevant entities, we turned our attention to the synthesis of hybrid compounds combining vitamin E backbone with a bioactive scaffold. Such approach has already been successfully developed for the synthesis of vitamin E hybrids with antiarrhythmic or antineurodegenerative activities.[8] Beside novel phenazine-vitamin E

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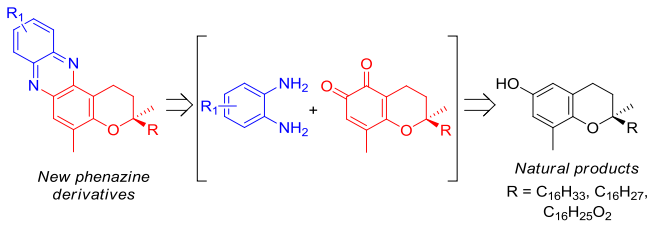


Scheme 1. Design of new phenazine-vitamin E hybrids.

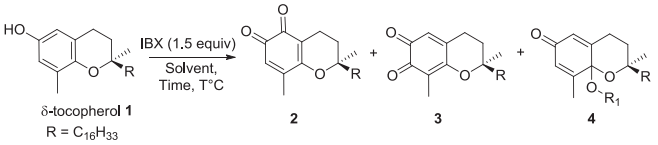
hybrids could be obtained by condensation of an *ortho*-phenylenediamine with a tocopheryl *ortho*-quinone, synthesized through the oxidation of a vitamin E derivative as indicated in Scheme 1.

However, depending on the oxidizing agent, the reported methods for direct tocopherol oxidation using $FeCl_3$, $AgNO_3$, oxygen-metal complex, H_2O_2/rhenium catalyst, HOCl, peroxynitrite, alkylperoxyde or microorganisms usually led to a complex mixture of bicyclic 5,6 and 6,7-*ortho*-quinone, monocyclic *para*-quinone as well as hemiketal and other byproducts (*e.g.* chloro or nitro derivatives).[9] A cleaner but limited synthesis (yield < 10%) of 5,6-tocoquinone was also achieved after formylation of γ-tocopherol[10] followed by Baeyer-Villiger oxidation.[11] Moreover, the oxidant (H_2O_2) used here would probably exhibit a lack of selectivity and react with tocotrienols side chain.

As the first step, synthesis of phenazine–vitamin E hybrids in high yield required to optimize *ortho*-tocoquinone preparation. The use of IBX (2-iodoxybenzoic acid) appeared to be a better choice for efficient regioselective *ortho*-quinone formation. Indeed, this reagent was previously used to selectively oxidize phenol or naphtol to the corresponding *ortho*-quinones,[12] which were later engaged in phenazine formation.[13] Taking into account the preferential reactivity of the C5-position of chromanol ring explained by the strain-induced bond localization (SIBL) theory,[14] the IBX-mediated δ-tocopherol oxidation was evaluated to obtain the 5,6-tocoquinone **2** as the major reaction product (Table 1).

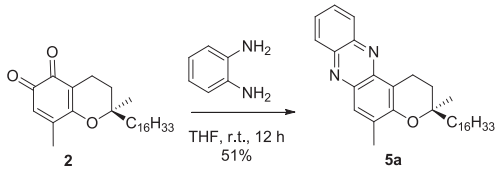
In accordance with the phenazine formation in protic solvent,[3] the reaction was first carried out in methanol at 0 °C for half an hour and three products were isolated (Table 1, entry 1). Two of them were *ortho*-quinones **2** and **3** obtained in 52% and 13% yield respectively. The third product was the monoketal **4** isolated in a substantial 23% yield. This latter compound probably resulted from the nucleophilic attack of a *para*-quinonium intermediate by the hydroxyl group of the solvent.[9 g,i,j] In order to limit the formation of this monoketal, bulkier alcohols were used as solvent (Table 1, entries 2 and 3). As a result the yield of ketal **4** was lowered to 7% in iso-PrOH at room temperature after 3 h, but this side product still contaminated *ortho*-quinones, and **2** was isolated in 65% yield. Thereafter, to prevent formation of the ketalic side product, non hydroxylic solvents were evaluated (Table 1, entries 4–9). Under these conditions, neither ketal **4,** nor the corresponding *para*-quinone were observed. Concerning the *ortho*-quinones, best yields were noticed in THF (85%, Table 1,

Table 1
Optimization of the oxidation conditions.



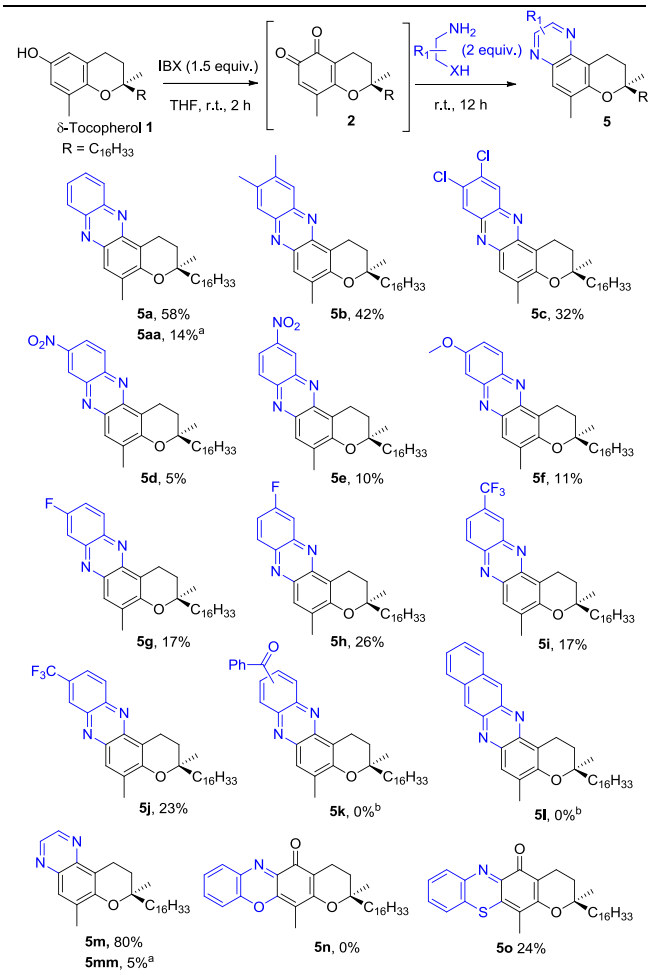
Entry	Solvent	T (°C)	Time (h)	Yield **2**[a]/**3**[b]/**4**[b] (%)
1	MeOH	0	0.5	52/13/23 (R_1 = Me)
2	EtOH	0	1	49/19/11 (R_1 = Et)
3	iso-PrOH	r.t.	3	65/6/7 (R_1 = iso-Pr)
4	DCM	r.t.	2.5	41/13/0
5	EtOAc	r.t.	12	59/13/0
6	CH_3CN	r.t.	12	36/8/0
7	DMF	0	1	43/17/0
8	DMSO	r.t.	0.5	49/22/0
9	THF	r.t.	2	68/17/0
10[c]	EtOAc	40	16	22/1/0

[a] Isolated yield.
[b] Determined by ^{1}H NMR.
[c] Catalytic conditions: 1 (0.1 mmol), Oxone® (0.2 mmol), K_2CO_3 (0.2 mmol), 2-iodobenzenesulfonic acid (0.005 mmol), nBu_4NHSO_4 (0.01 mmol), Na_2SO_4 (0.1 g), EtOAc, 40 °C.



Scheme 2. Reaction between quinone **2** and phenylenediamine.

Table 2
Reaction scope.



[a] 6,7-regioisomer yield.
[b] Degradation occurred during purification step.