VI Seminario Nazionale per Dottorandi in Farmacologia e Scienze Affini
Siena, Certosa di Pontignano, 23 - 26 Settembre 2002

SYNTHESYS, REACTIVITY AND POTENTIAL ANTIOXIDANT PROPERTIES OF HETEROARYL-SUBSTITUTED 1,4-DIPHENOLS

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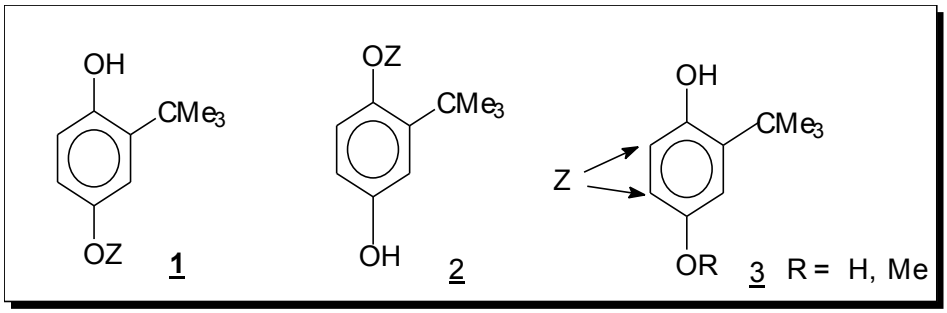
Chemical modifications of antioxidant molecules like the well known phenols tert-butylhydroxyanisole (BHA) and tert-butylhydroquinon (BHQ) can afford new compounds having different hydrophilic/lipophilic character, and consequently different cell permeability. In this way it is possible to obtain a control of the biological activity of the antioxidant.
On the other hand, the electron-donor or acceptor properties of the substituents change the oxidation potential of the phenolic system and therefore the antioxidant properties of the molecule.
Following previous researches on *O*- and *C*-glycosides of hindered phenols [1,2], the attack of BHQ and BHA on heterocycles (1,2- and 1,3-oxazole, 1,2,4-oxadiazole, 1,2- and 1,3-oxazolopyridine or thiophene derivatives) is considered.
The heterocyclic moiety can modify the properties of the antioxidant in the following aspects:
a) Due to the facile omolytic cleavage of the N-O bond by thermal/photochemical activation or in presence of radicals, the 1,2-oxazole system could play an important role in the antioxidant activity.
b) The redox potential of the hydroquinone-quinone system is modified according to the electron-donating or attracting character of the heterocyclic ring, controlling the antioxidant power;
c) The ring nitrogen can be quaternarized, either before or after the coupling with the diphenol, to give a highly hydrophilic molecule.
d) Rearrangements of the heterocyclic moiety are well known. As a consequence, the preparation of a single compound open the access to a series of omo- and heterocyclic derivatives and/or open chain compounds. For example, after etherification with BHQ, 1,2-oxazole derivatives can be easily rearranged by thermal or photochemical activation to new interesting compounds.
The synthesis of new ethers **1,2** reported in the following scheme involves nucleophilic substitution of an activated halo-heterocycle by the sodium salt of a suitable phenol. The best way to *C*-substituted derivatives **3** is the photo-Fries rearrangement of *O*-derivatives **1,2**. Spectroscopic methods (nmr, ms) and, in some case, single crystal X-ray diffractometry were used for the structural assignment of new compounds.

Preliminary investigation of antioxidant properties of new derivatives was carried out by measuring the oxidation of linoleic acid initiated by 2,2'-azobis-2-amidinopropane hydrochloride (AAPH), a thermolable azo compound which, on decomposition, forms radical that abstract hydrogen atoms from linoleic acid. Among the compound tested, the derivatives **3** (R = H), which present two p-OH groups, seem to be more efficient in the inhibition of linoleic acid peroxidation.

References

1. F. Ponticelli, A. Trendafilova, M. Valoti, S. Saponara, G. P. Sgaragli, *Carbohydr. Res.* , 330, 459 – 468 (2001);
2. F. Ponticelli, G.L. Giorgi, L. Salvini, F. Pessina, M. Valoti, *Europ. J. Org. Chem.*, 2002, submitted.



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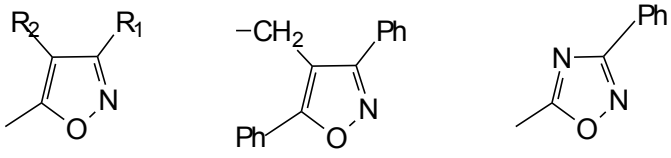

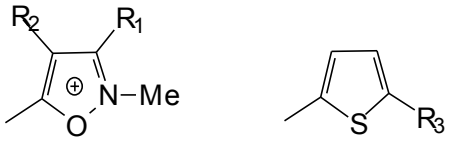

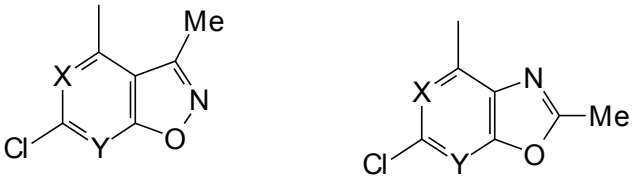

X = CH, Y = N
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