A novel one-pot synthesis and preliminary biological activity evaluation of *cis*-restricted polyhydroxy stilbenes incorporating protocatechuic acid and cinnamic acid fragments

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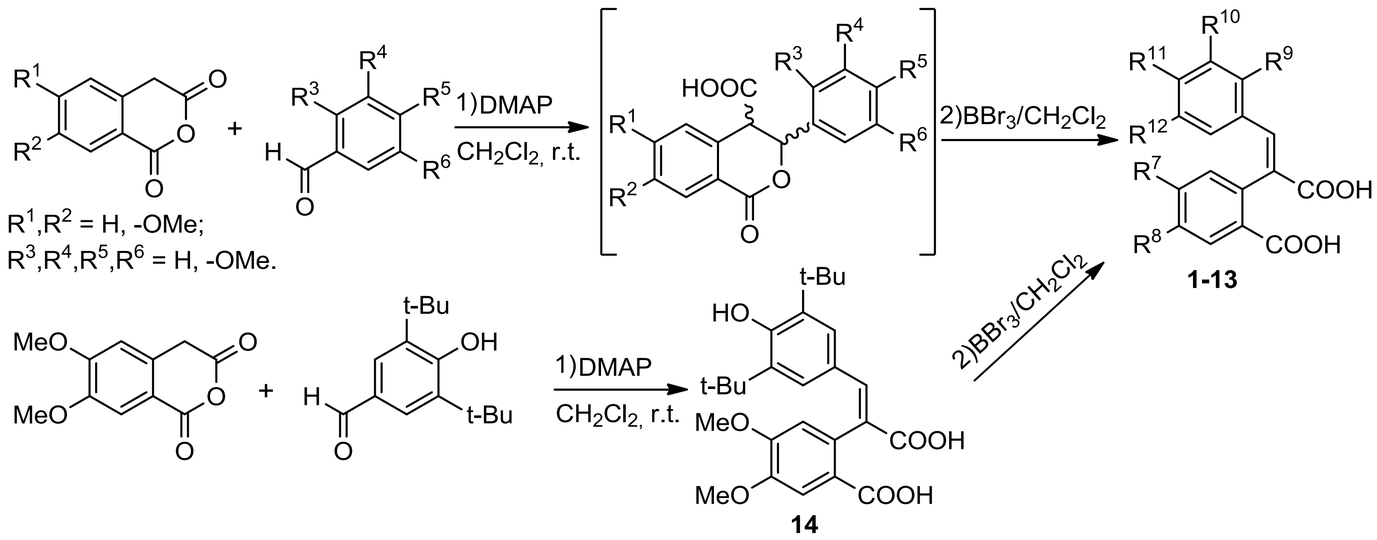
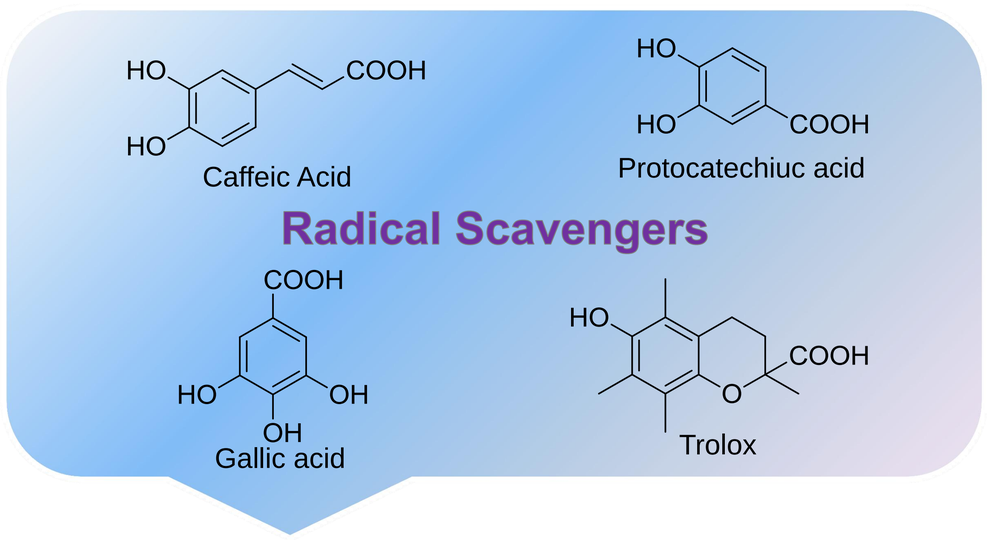
A series of 14 novel stilbenes was synthesized through a one-pot Perkin-like reaction between homophthalic anhydrides and various aromatic aldehydes, followed by treatment with BBr_3 [1]. This straightforward synthesis allows polyhydroxylated *cis*-stilbenes combining the two well-known pharmacophoric fragments of protocatechuic and caffeic acids, to be obtained in good yields and for short reaction times. The structure of the newly synthesized compounds was established by spectroscopic methods (^{1}H NMR, ^{13}C NMR, IR and HRMS) and the double bond configuration was unequivocally elucidated by means of gated decoupling ^{13}C NMR spectra and 2D NOESY experiments. Differentiating screening of their radical scavenging and antioxidant activity against 1,1-diphenyl-2-picrylhydrazyl (DPPH$^\bullet$), hydroxyl ($^\bullet$OH) and superoxide ($O_2^{-\bullet}$) radicals and Folin-Ciocalteu reagent. Trolox, protocatechuic acid, caffeic acid and gallic acid were used as reference antioxidants. The results obtained showed that several of the tested compounds are highly effective in micromolar concentrations, possessing higher activities than the standards used. Moreover, some of them demonstrated a triple biological action, simultaneously acting as efficient antioxidants, tyrosinase inhibitors and antifungal agents.



Scheme 1. One-pot synthesis of polyhydroxylated stilbenes.

Table 1. Substituents pattern and crystalline yields after column chromatography and recrystallization

	R^7	R^8	R^9	R^{10}	R^{11}	R^{12}	Yield [%]
1	OH	OH	H	H	H	H	51
2	OH	OH	H	H	H	H	47
3	OH	OH	H	OH	H	H	43
4	OH	OH	H	OH	OH	OH	42
5	OH	OH	H	t-Bu	OH	t-Bu	50
6	H	H	H	H	H	H	54
7	H	H	H	H	OH	H	25
8	H	H	H	OH	OH	H	35
9	H	H	H	OH	OH	OH	25
10	OH	OH	OH	H	H	H	17
11	OH	OH	OH	OH	H	H	20
12	OH	OH	OH	H	OH	H	13
13	OH	OH	OH	H	H	OH	15



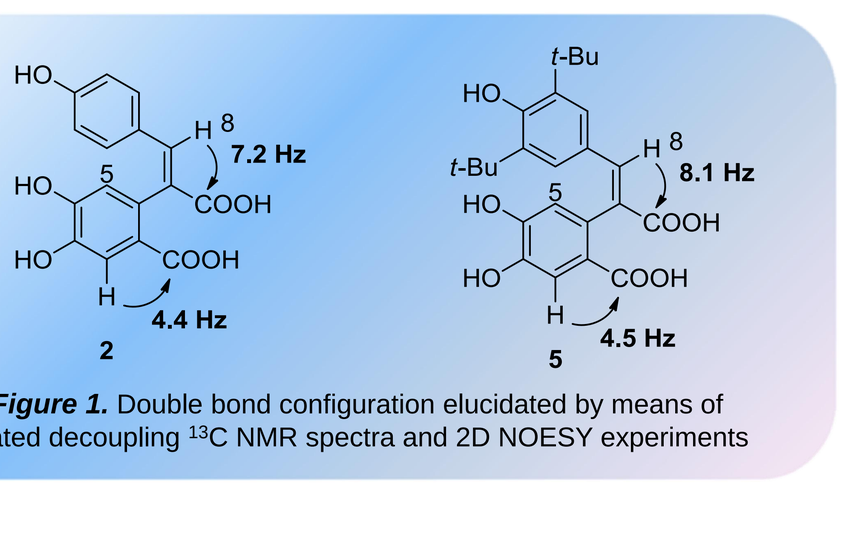


Figure 1. Double bond configuration elucidated by means of gated decoupling ^{13}C NMR spectra and 2D NOESY experiments

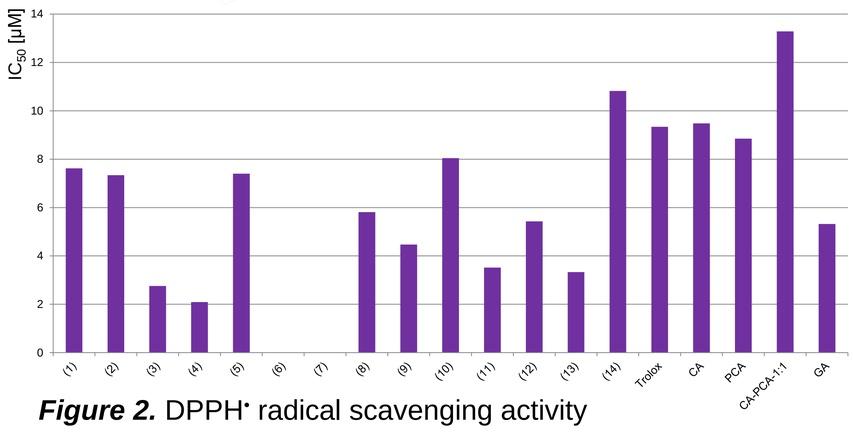


Figure 2. DPPH$^\bullet$ radical scavenging activity

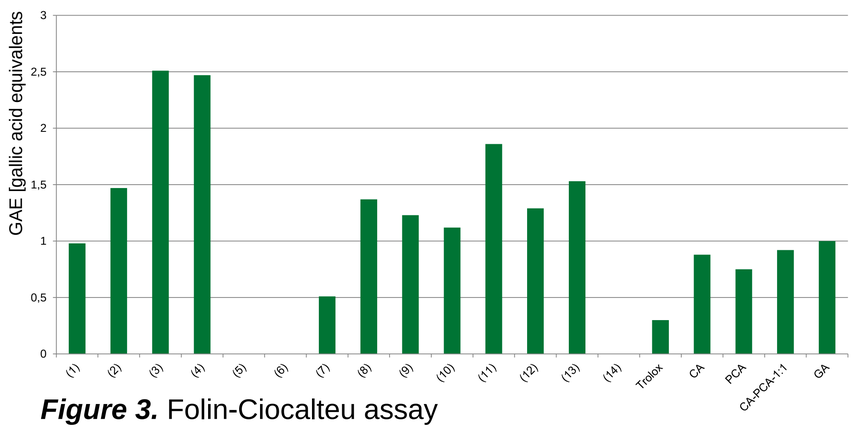


Figure 3. Folin-Ciocalteu assay

Antioxidant activity

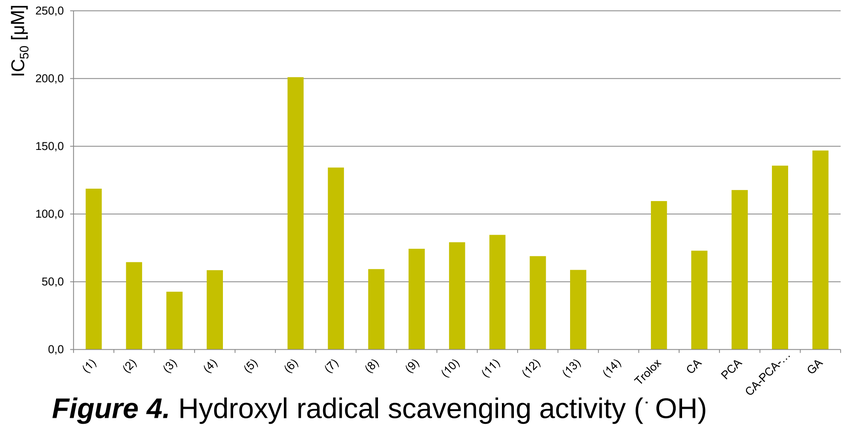


Figure 4. Hydroxyl radical scavenging activity ($^\cdot$OH)

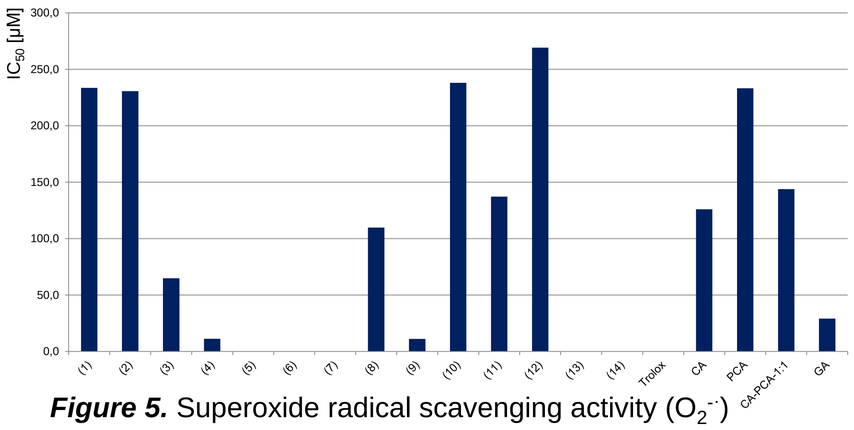


Figure 5. Superoxide radical scavenging activity ($O_2^{-\cdot}$)

References
M. Miliovsky, I. Svinyarov, Y. Mitrev, et al. *Eur. J. Med. Chem.* 66 (**2013**) 185.

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