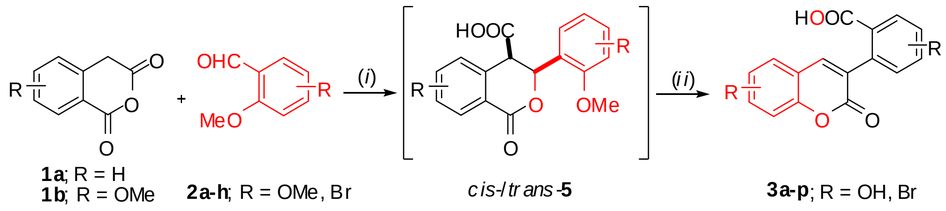
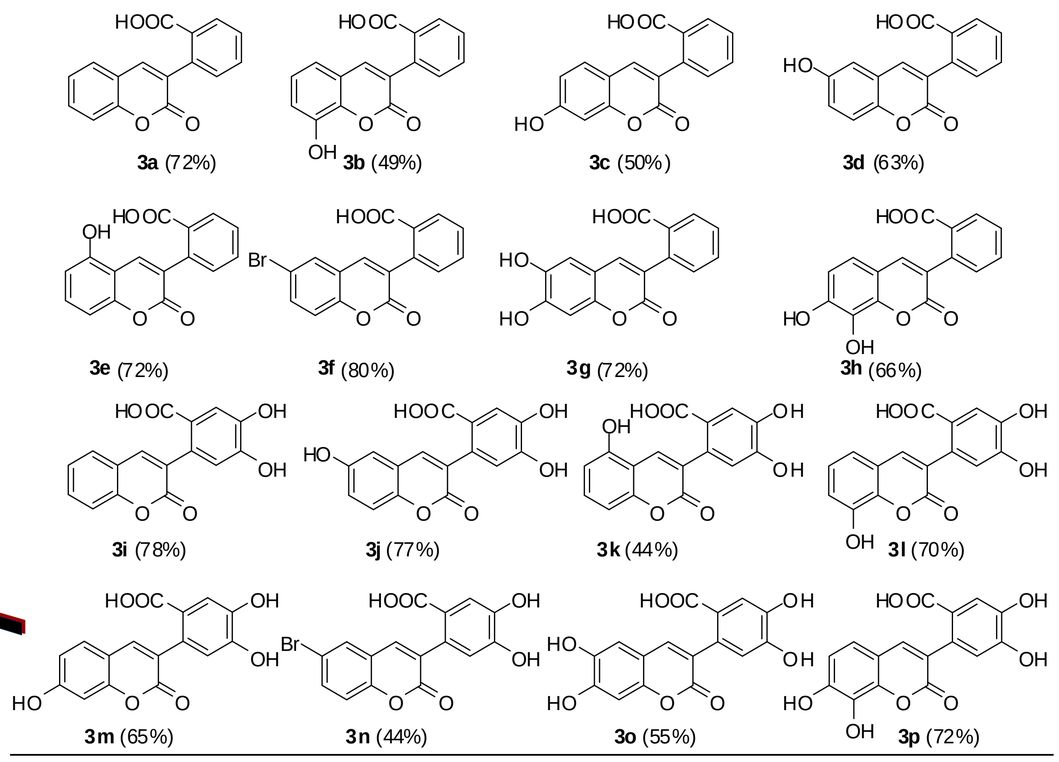
One-pot synthesis, radical scavenging and antioxidant activity of novel polyhydroxylated 3-arylcoumarins

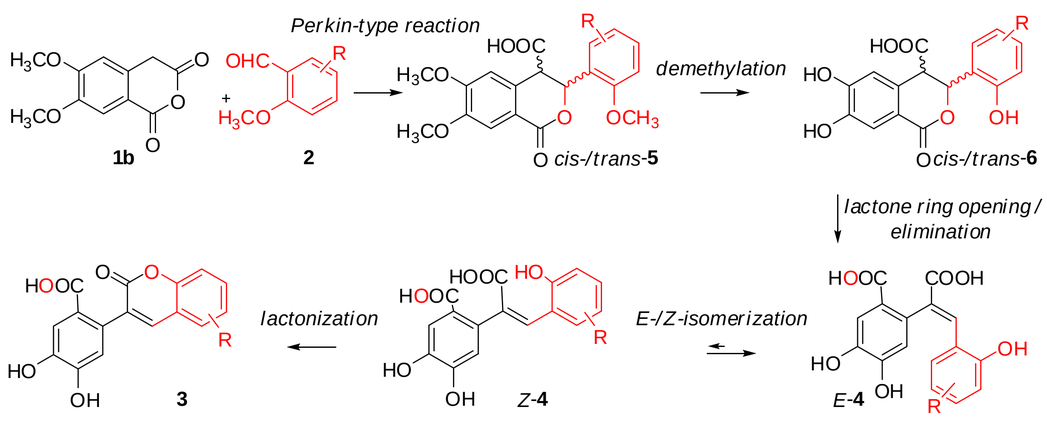
Ivan Svinyarov, Milen G. Bogdanov*
Faculty of Chemistry and Pharmacy, University of Sofia "St. Kl. Ohridski", 1, J. Bourchier Blvd., 1164 Sofia, Bulgaria
*E-mail: mbogdanov@chem.uni-sofia.bg

An unexpected domino rearrangement brought about the development of a novel one-pot procedure for synthesis of coumarins [1]. This protocol allowed the gram-scale synthesis of a variety of polyhydroxylated derivatives **3a-p**, from readily available starting materials at a low cost. Based on two proven intermediates, a probable mechanism consisting of boron tribromide induced demethylation/lactone ring opening/elimination/isomerization/lactone ring closure reaction sequence of *in situ* formed 3-aryl-3,4-dihydroisocoumarin-4-carboxylic acids was deduced. Compared to the common methods, used for the synthesis of coumarins, the proposed herein possesses great advantages, such as mild conditions, good yields for short reaction time, simple work-up procedure and easy isolation of the final products. The structure of the newly synthesized compounds **3a-p** was established by spectroscopic methods (^{1}H NMR, ^{13}C NMR, IR, MS and HRMS) and their antioxidant and radical scavenging activities were evaluated *in vitro* against HO$^{\bullet}$, $O_2^{-\bullet}$, 2,2-diphenyl-1-picrylhydrazyl (DPPH$^{\bullet}$) free radicals and Folin-Ciocalteu reagent (FCR). The results obtained showed that compounds **3h**, **3o** and **3p**, possessing two or four phenolic hydroxyl groups in their structure, exhibit higher radical scavenging activities than well-known antioxidants such as trolox, protocatechuic acid, caffeic acid and gallic acid, which in turn allows promising *in vivo* antioxidant properties of these compounds to be expected.

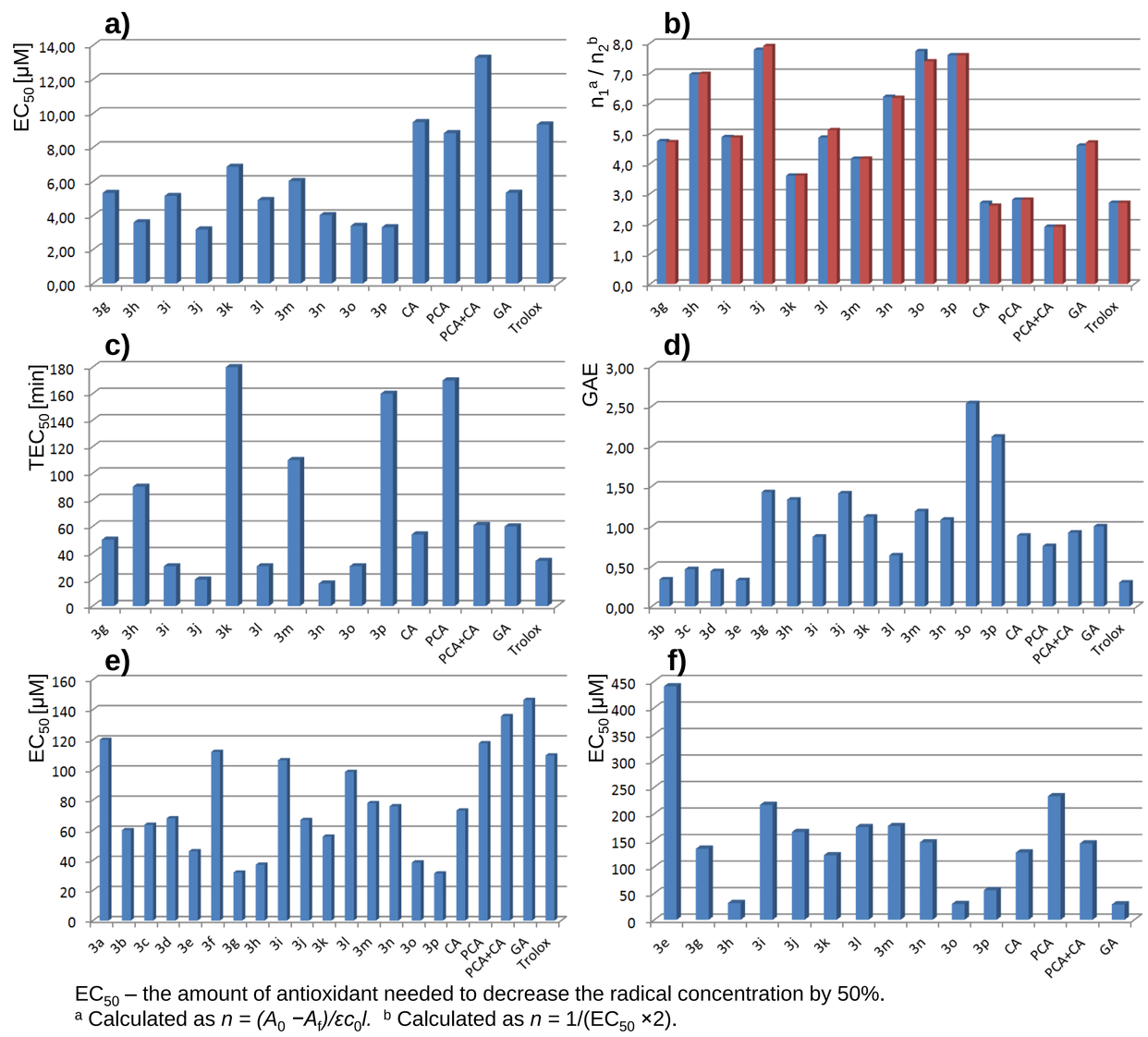
Table 1. One-pot synthesis of polyhydroxylated coumarins. *Reagents and conditions:* (*i*) DMAP/CH_2Cl_2, 10-15 min, rt, then (*ii*) BBr_3/CH_2Cl_2, rt, 4h. Yields refer to isolated crystalline products.







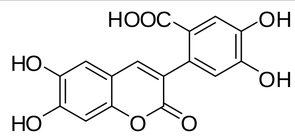
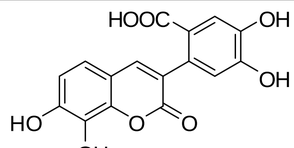
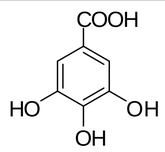
Scheme 1. Probable reaction pathway for the proposed one-pot synthesis of coumarins.



EC_{50} – the amount of antioxidant needed to decrease the radical concentration by 50%.
[a] Calculated as $n = (A_0 - A_f)/\varepsilon c_0 l$. [b] Calculated as $n = 1/(EC_{50} \times 2)$.

Figure 1. Radical scavenging and antioxidant parameters of compounds **3a-p** and referents – caffeic acid (CA), protocatechuic acid (PCA), gallic acid (GA) and Trolox: **a)** EC_{50} against 2,2-diphenyl-1-picrylhydrazyl (DPPH$^{\bullet}$) radical; **b)** Stoichiometry of reaction determined by DPPH$^{\bullet}$ radical; **c)** Time at equilibrium reached with a concentration of antioxidant equal to EC_{50} determined by DPPH$^{\bullet}$ radical; **d)** Reduction power determined with Folin-Ciocalteu reagent (FCR) expressed as gallic acid equivalents (GAE); **e)** EC_{50} against hydroxyl radical (HO$^{\bullet}$); **f)** EC_{50} against superoxide anion radical ($O_2^{-\bullet}$).

Table 2. Radical scavenging and antioxidant parameters of the most active compounds compared with the most active referent – gallic acid.

Method	Parameter	 **3o**	 **3p**	 GA
DPPH$^{\bullet}$	SC_{50} [μM]	3.39 ± 0.05	3.30 ± 0.03	5.33 ± 0.34
	n_1 / n_2	6.2 / 6.2	7.7 / 7.4	4.6 / 4.7
	TEC_{50} [min]	30	160	60
FCR	GAE	2.54 ± 0.82	2.12 ± 0.17	1.00 ± 0.02
HO$^{\bullet}$	SC_{50} [μM]	39 ± 3	31 ± 2	146 ± 5
$O_2^{-\bullet}$	SC_{50} [μM]	30 ± 4	56 ± 11	29 ± 1

References
[1] I. Svinyarov, M.G. Bogdanov, Eur. J. Med. Chem. 78 (**2014**) 198-206.

Project BG051PO001-3.3.06-0040 ***"Establishment of interdisciplinary teams of young scientists in the field of fundamental and applied research relevant to medical practice"*** *The project is implemented with financial support of the operative program "Human Resources Development" financed by the European Social Fund of the European Union; This document has been prepared with the financial assistance of the European Social Fund. Sofia University "St. Kliment Ohridski"– Faculty of Medicine bears full responsibility for the content of this document and in no circumstances can be regarded as official position of the European Union or the Bulgarian Ministry of Education and Science.*
The financial support of the National Science Fund of Bulgaria at the Ministry of Education, Youth and Science (project DMU-03-10/2011) and Sofia University Fund (project 029/2013) is greatly acknowledged by the authors.