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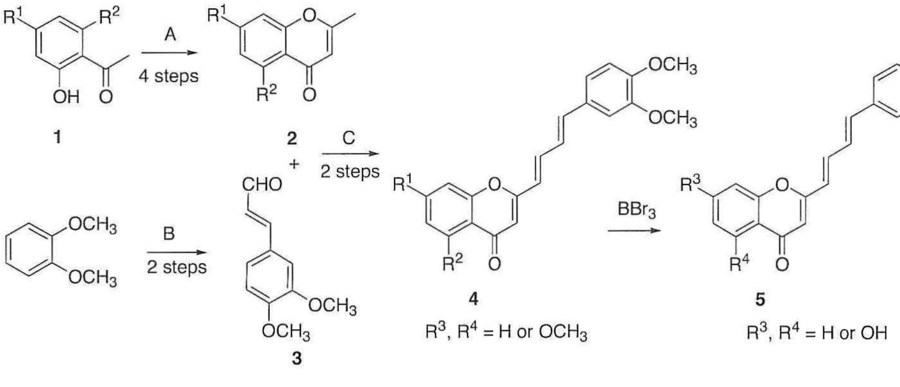
Synthesis of novel hydroxylated 2-butadienylchromone derivatives

Hélio Albuquerque,[a] Clementina M. M. Santos,[a,b] Cátia I. C. Esteves,[a] Artur M. S. Silva,[a] José A. S. Cavaleiro[a]

[a]Department of Chemistry & QOPNA, University of Aveiro, 3810-193 Aveiro, Portugal; [b]Department of Vegetal and Production Technology, School of Agriculture, Polytechnic Institute of Bragança, 5301-855 Bragança, Portugal

Chromones are a group of naturally occurring compounds with a benzoannelated γ-pyrone ring. A large number of chromone derivatives have been isolated from natural sources and a wide range of biological properties have been attribute to them, such as anti-fungal, anti-allergenic, antiviral, antitubulin, anti-hypertensive, anticancer and antioxidant activities.[1] Studies with 2-styrylchromones demonstrated that the number and position of the hydroxyl groups in the A-ring and the 3', 4'-dihydroxy substitution on B-ring play an important role in their radical scavenger activity. In addition the molecular stabilization promoted by the carbonyl carbon C-4 and $C_\alpha{=}C_\beta$ double bond, also seem to contribute to the scavenging effect of these compounds.[2]

Taking into account these considerations we establish a new synthetic route for the preparation of novel hydroxylated 2-butadienylchromone derivatives **5**. Our methodology involves the condensation of methoxy-2-methylchromones **2**[3] with 3,4-dimethoxy-cinnamaldehyde **3**[4] leading to (*E,E*)-2-(4-arylbuta-1,3-dien-1-yl)-4*H*-chromen-4-ones **4**. The final step involves the cleavage of methyl group of **4** in order to obtain the desired hydroxylated derivatives **5** (Scheme). In this communication we will present the synthetic details of all described transformations as well as the structural characterisation (by 1D and 2D NMR studies) of the new synthesised compounds.



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References

[1] Sharma S. K., Kumar S., Chand K., Kathuria A., Gupta A. and Jain R. *Curr. Med. Chem.* **2011**, *18*, 3825.
[2] Gomes A., Fernandes E., Silva A. M. S., Santos C. M. M., Pinto D. C. G. A., Cavaleiro J. A. S., Lima J. L. *Biorg. Med. Chem.* **2007**, *15*, 6027.
[3] (a) Mahal, H. S.; Venkataraman, K. *J. Chem. Soc.* **1934**, 1767. (b) Baker, W. *J. Chem. Soc.* **1933**, 1381.
[4] Battistuzzi, G.; Cachi, S.; Fabrizi, G. *Org. Lett.* **2003**, *5*, 777.

Synthesis of Novel Hydroxylated 2-Butadienylchromone Derivatives

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[a]Department of Chemistry & QOPNA, University of Aveiro, 3810-193 Aveiro, Portugal
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Introduction

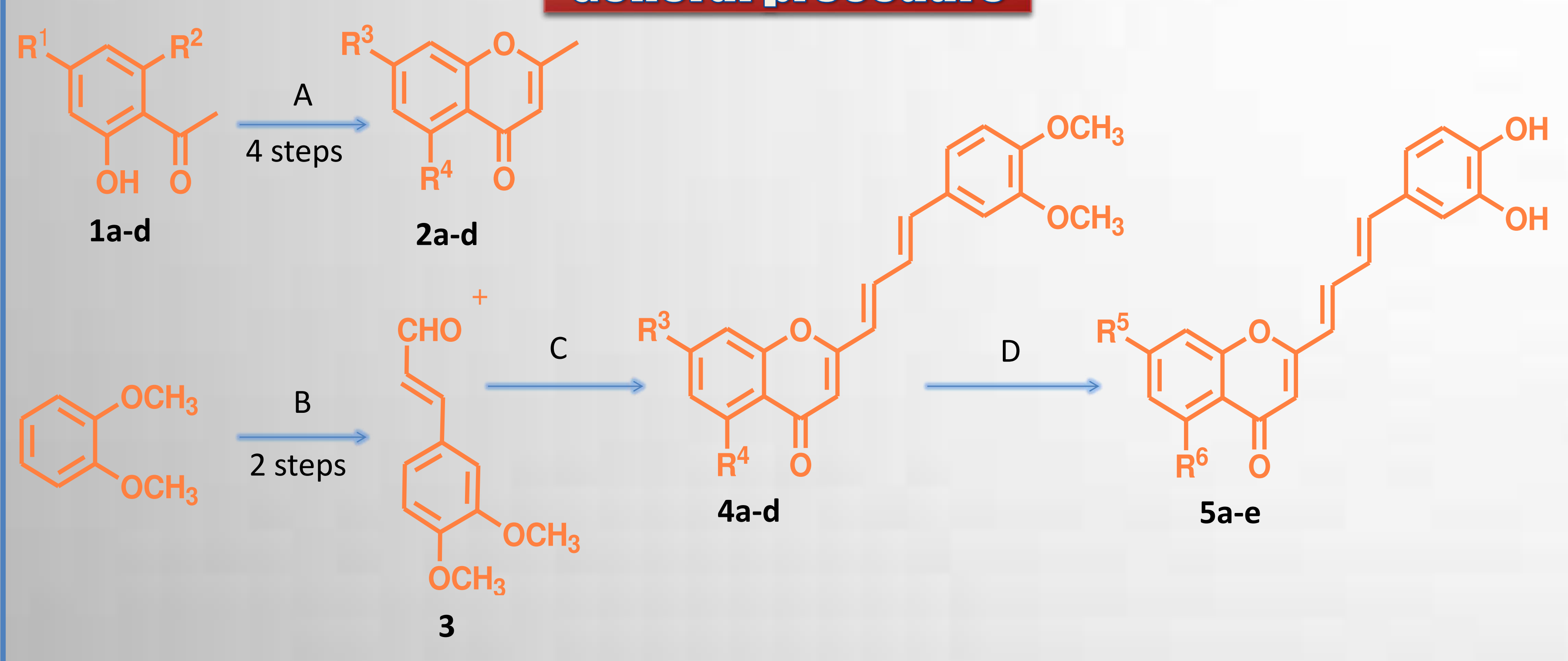
Chromones are a group of naturally occurring compounds with a benzoannelated γ-pyrone ring . A large number of chromone derivatives have been isolated from natural sources and a wide range of biological properties have been attribute to them, such as antifungal, anti-allergenic, antiviral, antitubulin, anti-hypertensive, anticancer and antioxidant activities [1]. Studies with 2-styrylchromone derivatives demonstrated that the number and position of hydroxyl groups in the A-ring and the 3', 4'-dihydroxy (catechol) substitution on B-ring play an important role in their scavenger activity. In addition, the molecular stabilization promoted by the carbonyl carbon C-4 and $C_\alpha = C_\beta$ double bond, also seem to contribute to the scavenging effect of these compounds [2].

Experimental and results

In this work, hydroxylated 2-butadienylchromones were prepared through the following synthetic route:

- Condensation of methoxy-2-methylchromones **2a-d** [3] with 3,4-dimethoxycinnamaldehyde **3** [4] leading to (*E*,*E*)-2-(4-arylbuta-1,3-dien-1-yl)-4*H*-chromen-4-ones **4a-d**;
- The final step involves the cleavage of methyl group of compounds **4a-d** in order to obtain the desired hydroxylated derivatives **5a-e**.

General procedure



Reaction Conditions:

A: (i) Me_2SO_4, K_2CO_3, acetone, reflux, 15 min; (ii) MeCOCl, dry pyridine, r.t., 12-15 h; (iii) NaH, dry THF, reflux, 2-5 h; (iv) *p*-TSA, DMSO, 100°C, 2-5 h.
B: (i) NIS, MeCN, reflux, 48 h; (ii) DMF, $Pd(OAc)_2$, NBu_4OAc, K_2CO_3, 90°C, 4 h
C: Sodium, dry EtOH, r.t., 12 h
D: BBr_3, dry CH_2Cl_2, -78°C to r.t., 2 h-11 days.

Results

Compound	R^3	R^4	R^5	R^6	Reaction Time	Yield (%)
4a	H	H	---	---	12 h	60
4b	OCH_3	H	---	---	12 h	77
4c	H	OCH_3	---	---	12 h	76
4d	OCH_3	OCH_3	---	---	12 h	80
5a	---	---	H	H	3 h	79
5b	---	---	OCH_3	H	2 h	71
5c	---	---	H	OH	4 h	75
5d	---	---	OH	OH	11 days	37
5e	---	---	OCH_3	OH	4 h	82

[1] Sharma S. K., Kumar S., Chand K., Kathuria A., Gupta A., Jain R. *Curr. Med. Chem.* **2011**, *18*, 3825.
[2] Gomes A., Fernandes E., Silva A. M. S., Santos C. M. M., Pinto D. C. G. A., Cavaleiro J. A. S., Lima J. L. F. C. *Biorg. Med. Chem.* **2007**, *15*, 6027.
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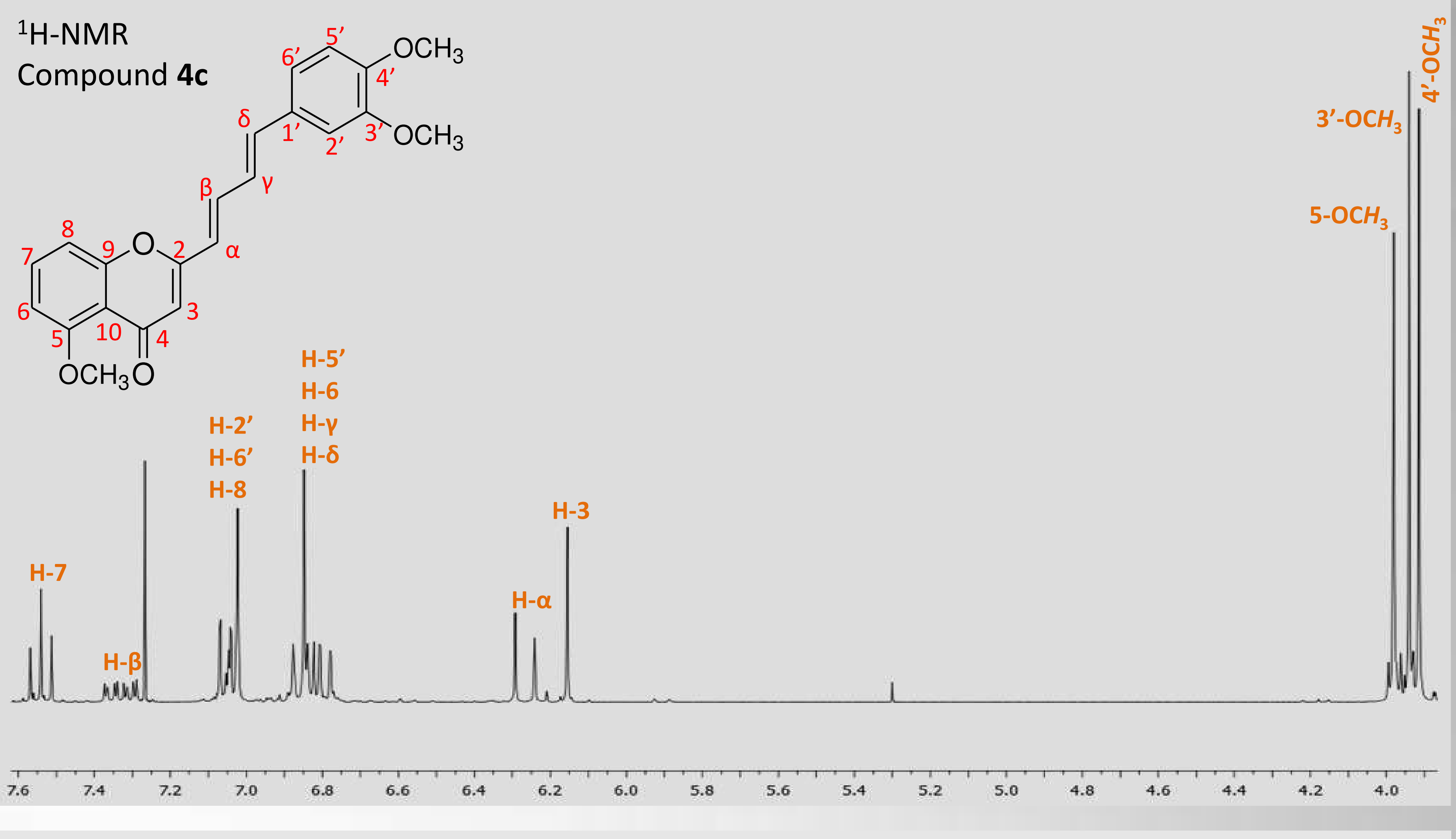
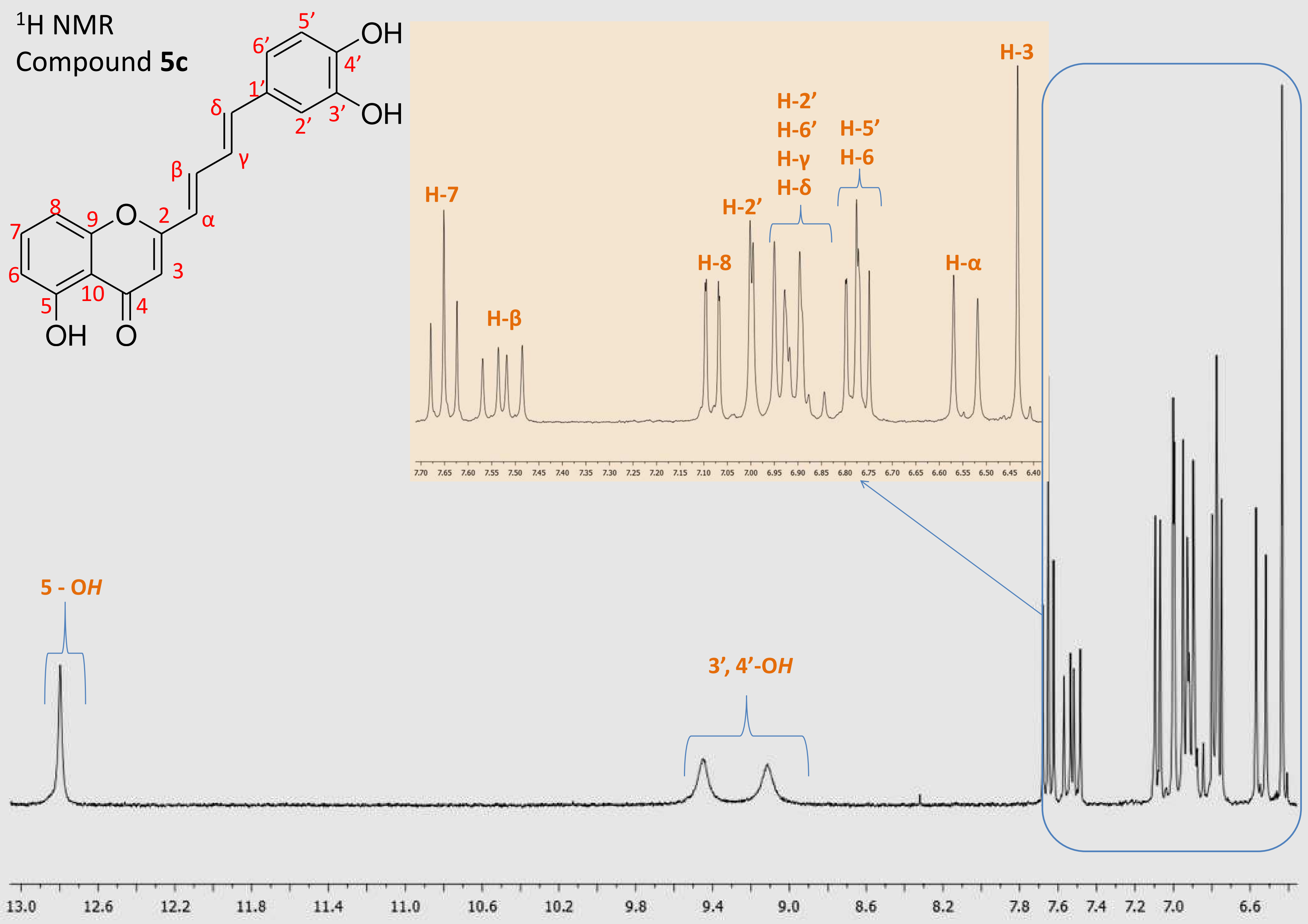
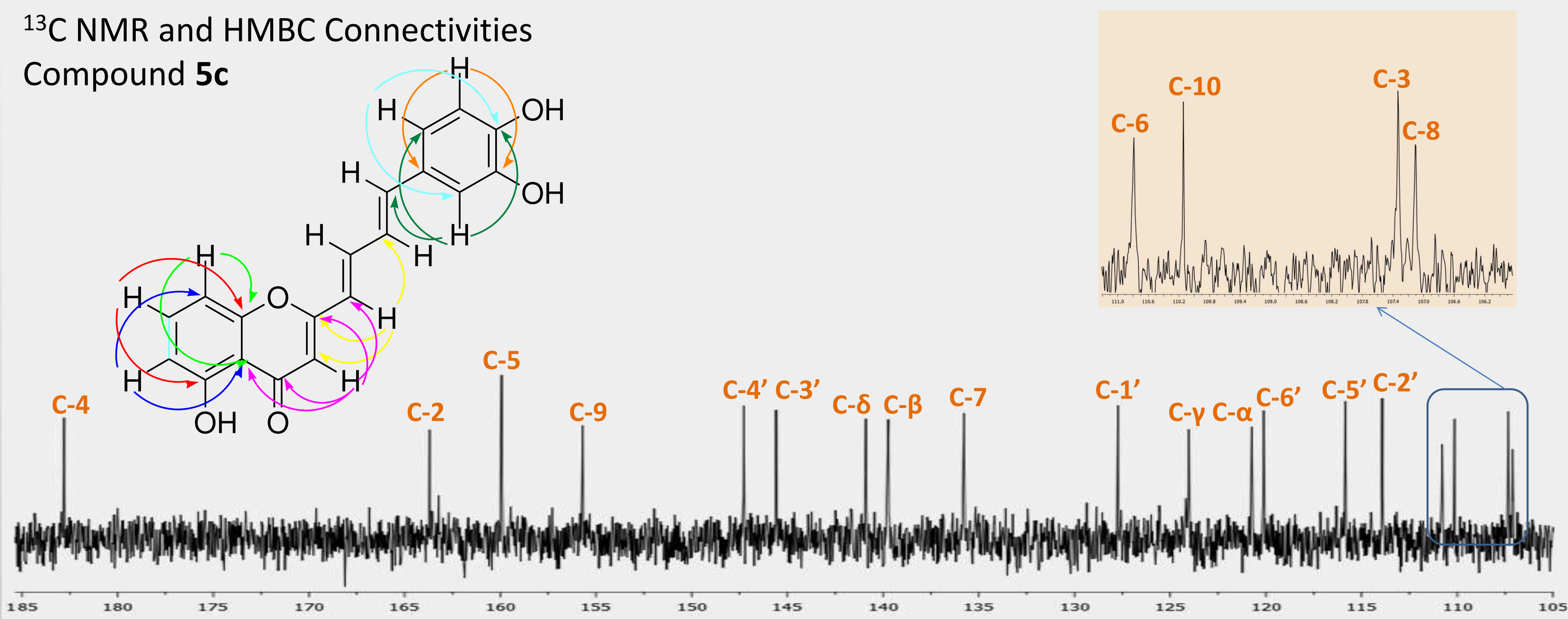
Structural elucidation

The structures of new methoxylated and hydroxylated 2-butadienyl-chromones **4** and **5** were established by NMR studies.







Conclusions

The (*E*,*E*)-2-(4-arylbuta-1,3-dien-1-yl)-4*H*-chromen-4-ones **4** were obtained *via* aldol condensation of methoxy-2-methylchromones **2** (obtained *via* Baker-Venkataraman methodology) with 3,4-dimethoxy-cinnamaldehyde **3**. The cleavage of the methyl groups with BBr_3 gave the desired hydroxylated 2-butadienylchromones in good yields.

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