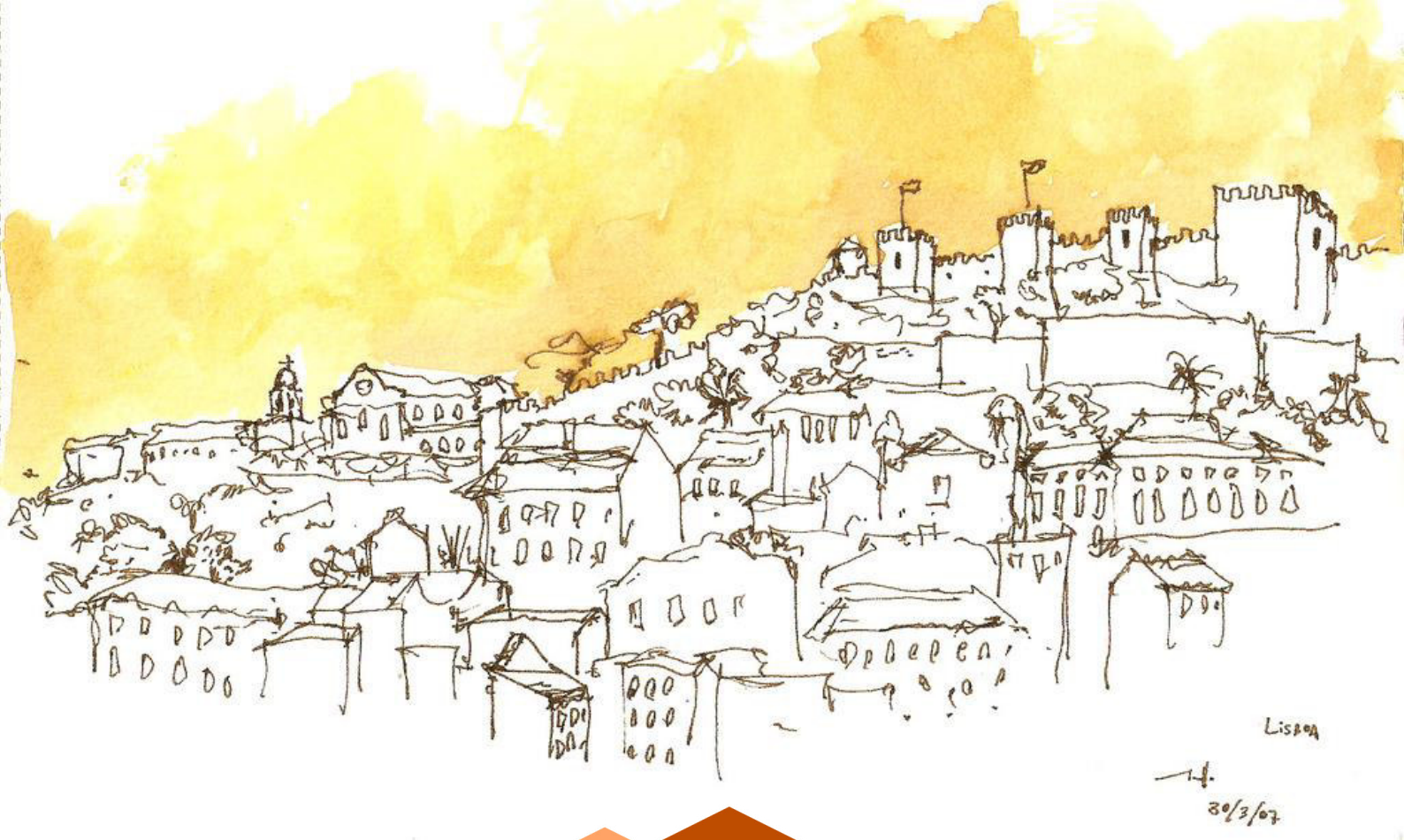

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SYNTHESIS OF XANTHONE-1,2,3-TRIAZOLE DYADS

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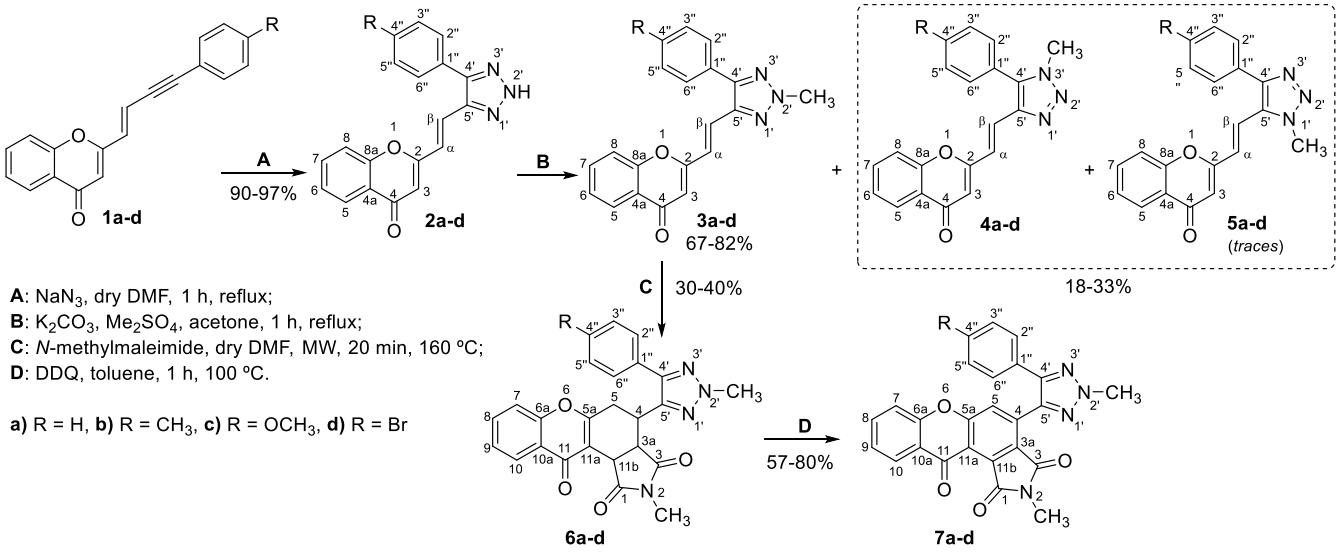
Xanthones and 1,2,3-triazoles are known to exhibit several biological, pharmacological and biocidal properties[1]. The potential applications of these two classes of heterocycles led us to develop new strategies to synthesize xanthone-1,2,3-triazole dyads, aiming to get potentially improved therapeutic agents[2]. With this rational in mind we designed and synthesized novel chromone derivatives **1a-d** to be used as building motifs and to explore the reactivity of the two unsaturated systems (the diene and the alkyne). In the present communication we will present a new synthetic route towards the synthesis of xanthone-1,2,3-triazole dyads **7a-d** using consecutively the azide-alkyne Huisgen 1,3-dipolar cycloaddition and Diels-Alder reaction. Our approach involves the synthesis chromone-triazole derivatives **2a-d** using the reaction of **1a-d** with sodium azide, followed by the methylation of the NH of the triazole moiety. The methylation afforded three isomers **3a-d**, **4a-d** and **5a-d**, as expected. The major isomers **3a-d** were used in the Diels-Alder reaction with *N*-methylmaleimide, and the adducts obtained **6a-d** were oxidized to afford the xanthone-1,2,3-triazole dyads **7a-d**. All the synthetic details as well as the structural characterization (by 1D and 2D NMR studies) of the new synthesised compounds will be presented and discussed.



Acknowledgements: Thanks are due to University of Aveiro, Polytechnic Institute of Bragança, Fundação para a Ciência e Tecnologia (FCT), EU, QREN, FEDER e COMPETE for funding the QOPNA Research Unit (Ref UID/QUI/00062/2013) and The Portuguese National NMR Network. Hélio Albuquerque also thanks his PhD grant (SFRH/BD/86277/2012).

References:

[1] (a) H. R. El-Seedi, M. A. El-Barbary, D. M. El-Ghorab, L. Bohlin, A. K. Borg-Karlson, U. Goransson, R. Verpoorte, *Curr. Med. Chem.* **2010**, *17*, 854-901; (b) A. Massarotti, S. Aprile, V. Mercalli, E. Del Grosso, G. Grosa, G. Sorba, G. C. Tron, *ChemMedChem* **2014**, *9*, 2497-2508.
[2] Y. Zou, Q. Zhao, H. Hu, L. Hu, S. Yu, M. Xu, Q. Wu, *Arch. Pharm. Res.* **2012**, *35*, 2093-2104.

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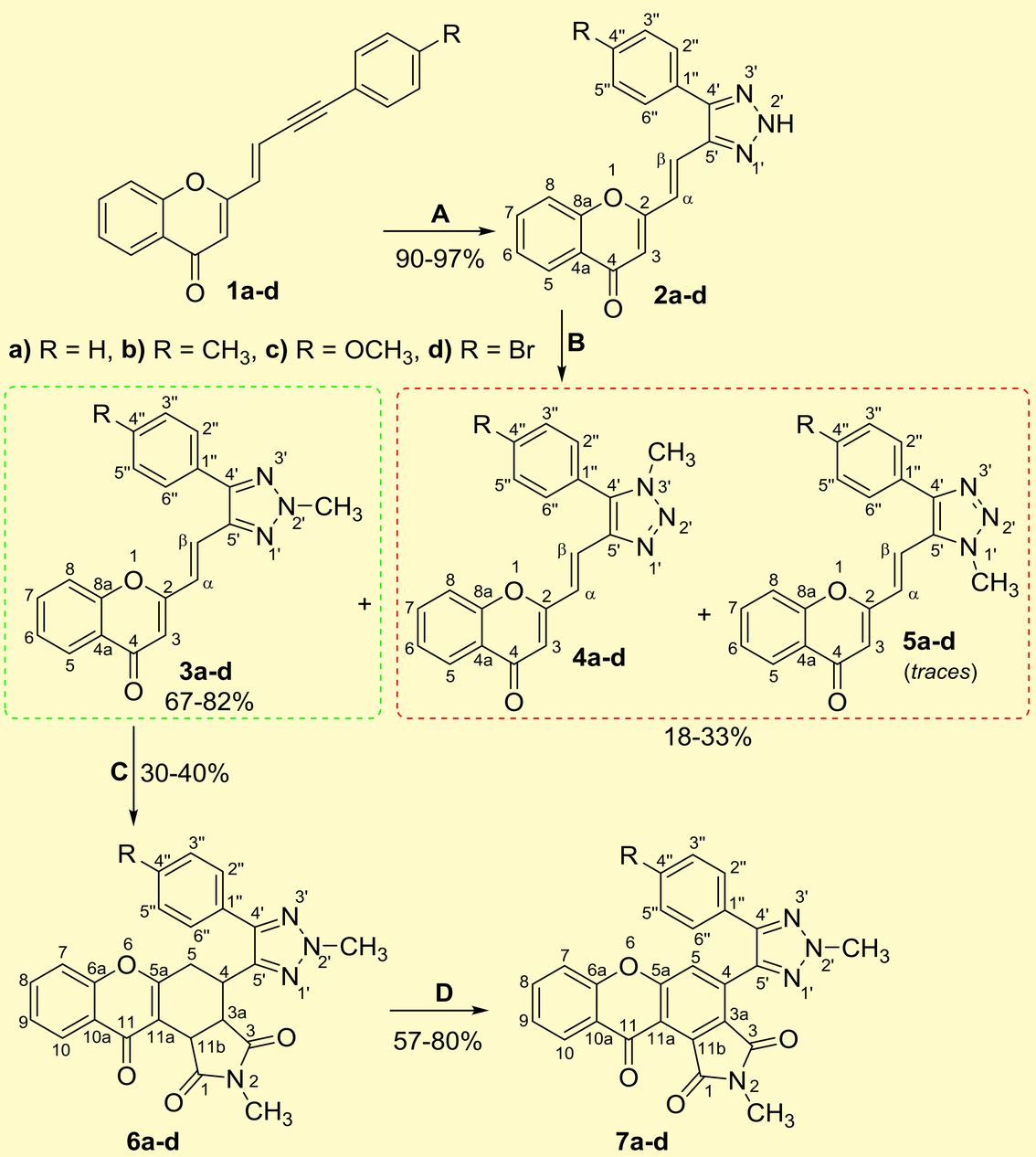
INTRODUCTION

Xanthone and 1,2,3-triazole derivatives received much attention over the last years because of their biological, pharmacological and biocidal potential.[1] The applications of these two well-know heterocycles prompted us to develop new methods to build xanthone-1,2,3-triazole dyads. Intenting to synthesize new molecules with potential improved therapeutic interest over the single heterocycles.[2] With this concept in mind, we designed and synthesized novel chromone derivatives **1a-d** which were used as building motifs to explore the reactivity of their two unsaturated systems (the diene and the alkyne moieties). In the present communication we will present a new synthetic route towards the synthesis of xanthone-1,2,3-triazole dyads **7a-d** using consecutively the azide-alkyne Huisgen 1,3-dipolar cycloaddition and a Diels-Alder reaction.[3] All the synthetic details as well as the structural characterization (by 1D and 2D NMR studies) of the new synthesized compounds are presented and discussed.

EXPERIMENTAL AND RESULTS

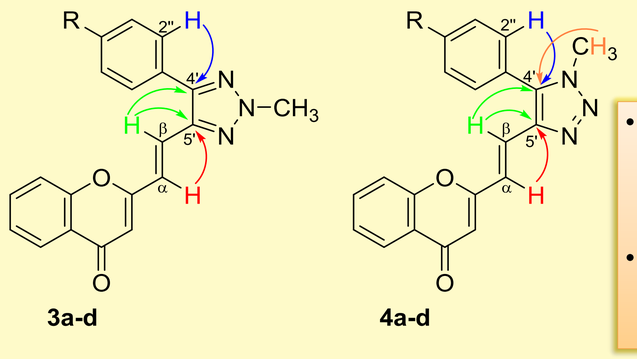


A: NaN_3, dry DMF, 1 h, reflux;
B: K_2CO_3, Me_2SO_4, acetone, 1 h, reflux;
C: *N*-methylmaleimide, dry DMF, MW, 20 min, 160 ºC;
D: DDQ, toluene, 1 h, 100 ºC.

In the present work, the synthesis of xanthone-1,2,3-triazole dyads 7a-d involved the following steps:

- **Step A**: 1,3-Cycloaddition reaction of chromones **1a-d** (obtained through base-catalyzed aldol reaction of 2-methylchromone with appropriate arylpropargyl aldehydes[3]) with sodium azide in refluxing DMF to afford the 1,2,3-triazole derivatives **2a-d**, in excellent yields;
- **Step B**: *N*-Methylation of triazoles **2a-d** with dimethyl sulfate, to avoid Michael addition of chromones **1a-d** on *N*-methylmaleimide. Three isomers were obtained: 2'-*N*CH_3 triazole **3a-d** (higher R_f value) was isolated as the major isomer (Figure 1); while 3'-*N*CH_3 (**4a-d**) (Figure 1) and 1'-*N*CH_3 (**5a-d**) triazoles were isolated together as an inseparable mixture. The ^{1}H NMR spectra analysis of the mixture alowed us to conclude that 1'-*N*CH_3 triazoles were obtained in trace amounts by the presence of less intense signals of the 1'-NC*H*$_3$ and H-3 protons.
- **Step C**: Diels-Alder (DA) reaction of methylated triazoles **3a-d** with *N*-methylmaleimide under microwave irradiation to give the cycloadducts **6a-d** (Figure 2). The reaction only occurs under microwave irradiation. 50-64 % of the starting methylated triazoles **3a-d** were recovered from the reaction mixtures and no side products were detected. The competition of the retro-DA reaction (often promoted at elevated temperatures) could be the reason for the low yields obtained.
- **Step D**: Oxidation/aromatization of cycloadducts **6a-d** with DDQ to afford the desired xanthone-1,2,3-triazole dyads **7a-d** (Figures 1 and 3).

STRUCTURAL ELUCIDATION (1D AND 2D NMR)



- In HMBC spectra of isomers **3a-d**, 2'-NCH_3 protons do not correlate with any carbon of the triazole ring;
- In HMBC spectra of isomers **4a-d**, correlations are observed between H-2'',6'' and 3'-NCH_3 with C-4' of the triazole ring.

Figure 1: Most important HMBC connectivities of isomers **3a-d** and **4a-d**.

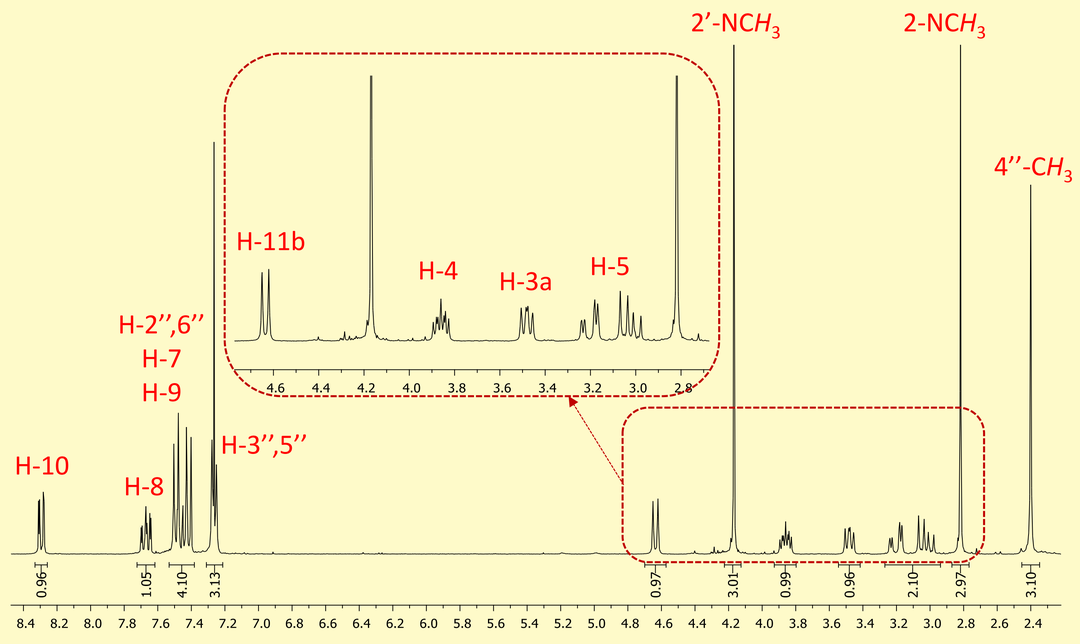


Figure 2: ^{1}H NMR spectrum of compound **6b**.

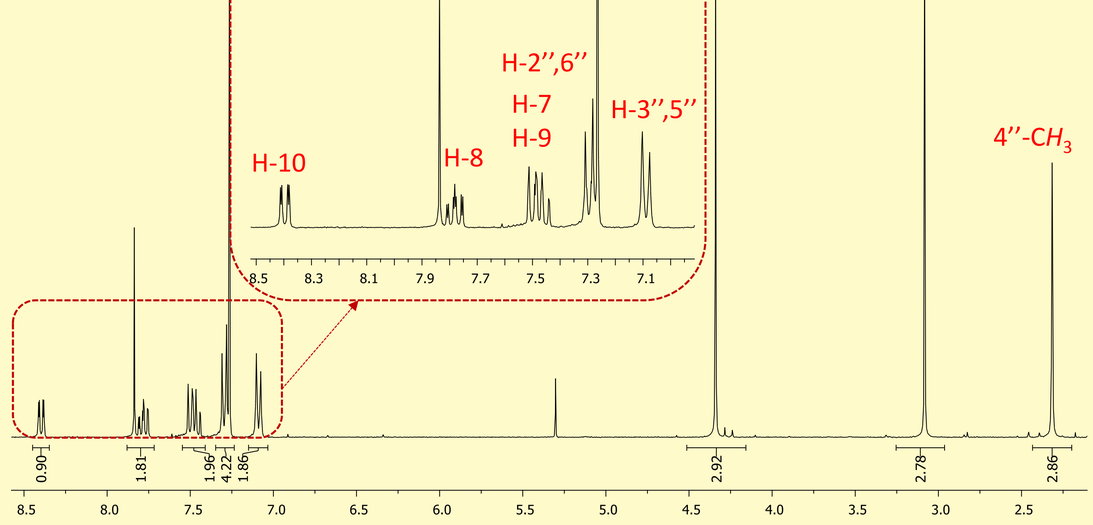


Figure 3: ^{1}H NMR spectrum of compound **7b**.

CONCLUSION

We successfully developed a new synthetic route towards the synthesis of xanthone-1,2,3-triazole dyads **7a-d**. The strategy involves a straightforward triazole synthesis and subsequent methylation which gave three isomers, as expected. The DA reaction was performed under microwave irradiation followed by oxidation/aromatization to afford the desired dyads.

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References:

[1] (a) H. R. El-Seedi, M. A. El-Barbary, D. M. El-Ghorab, L. Bohlin, A. K. Borg-Karlson, U. Goransson, R. Verpoorte, *Curr. Med. Chem.* **2010**, *17*, 854-901; (b) A. Massarotti, S. Aprile, V. Mercalli, E. Del Grosso, G. Grosa, G. Sorba, G. C. Tron, *Chem. Med. Chem.* **2014**, *9*, 2497-2508.
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