Several computational approaches were applied to a small diterpenic library (n = 25) obtained by chemical derivatization of compounds isolated from *Euphorbia boetica* (Matos, A.M., *et al. J. Nat. Prod.* 2015, *78*, 2215). A virtual screening procedure involving pharmacophoric identification followed by molecular docking was used to select and predict experimentally active MDR-reversal molecules (Ferreira, R.J., *et al. J. Chem. Theory Comput.* 2012, *8*, 1853; Ferreira, R.J., *et al. J. Chem. Inf. Model.* 2013, *53*, 1747), while ligand-based drug discovery techniques as quantitative structure-activity relationship (QSAR, Weka software) and pharmacophore modeling (calculated from molecular interaction fields with Open3DQSAR) were used to characterize the relationship between chemical modifications and the respective modulation capabilities (Baptista R., *et al., Future Med. Chem.* 2015, *submitted*). From these procedures, a thorough characterization of the groups involved in the MDR-reversal activity was obtained, which can be further used to guide chemical derivatization, hopefully avoiding the synthesis of low-activity compounds.

3.13. The Anti-HIV Drug Rilpivirine: Covalent Adducts with Amino Acids and Proteins (MC23)

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Rilpivirine (RPV) is a 2nd-generation non-nucleoside reverse transcriptase inhibitor (NNRTI) that was added to the available therapeutic options with the aim to overcome the most common adverse effects of the 1st-generation NNRTIs as well as their viral cross-resistance. However, post-marketing reports of RPV-associated depressive disorders are a cause for concern when contemplating chronic administration regimens. Therefore the development of reliable prognostic tools for pharmacovigilance procedures is urgent.

Covalent adduct formation with cysteine residues of synaptic proteins is considered a major mechanism of neurotoxicity induced by chemical toxicants such as acrylamide (LoPachin, R.M., *et al. Environ. Health Perspect*. 2012, *120*, 1650–1657). The identification of urinary Phase II conjugates stemming from initial 1,4 Michael addition of glutathione (GSH) to the α,β-unsaturated system of RPV supports the likelihood of reaction with proteins *in vivo* (Pereira, S.A., *et al. Adv. Mol. Toxicol.* 2012, *6*, 1–40).

With the ultimate goals of disclosing the mechanisms underlying RPV-induced neurotoxicity and developing suitable biomarkers of toxicity, the reactivity of RPV towards amino acids (*N*-acetyl-lysine and *N*-acetyl-cysteine) and model proteins such as Human Serum Albumin (HSA) was investigated by liquid chromatography—mass spectrometry (LC-MS) methodologies. The results obtained suggest the key role of RPV-derived covalent adduct formation in the onset of the adverse effects induced by this 2nd generation NNRTI.

Acknowledgments: This work was supported in part by Fundação para a Ciência e a Tecnologia (FCT), Portugal (RECI/QEQ-MED/0330/2012, UID/QUI/00100/2013 and IF/01091/2013/CP1163/CT0001). AMM also acknowledges Programa Operacional Potencial Humano from FCT and the European Social Fund (IF/01091/2013), and the LRI Innovative Science Award. We thank the Portuguese MS network (IST node) for providing access to the MS facility.

3.14. Interaction of Xanthone with Double Stranded DNA—A Contribution for Xanthone Derivative Drugs (MC24)

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Xanthones are an important group of oxygenated heterocyclic compounds, which are known to exhibit interesting pharmacological properties, such as anti-tumoral activity. Numerous studies have revealed that DNA is a primary intracellular target of anticancer drugs, due to the interaction of small molecules with DNA. Hence, characterization of the interaction of xanthones with DNA can be an important contribution for the development of a new class of anti-cancer agents.

In this communication we report the study of the interaction of xanthone with double stranded DNA, using UV-vis spectroscopy, including UV melting experiments, and viscosity measurements. The denaturation temperature and the thermodynamic parameters of DNA thermal denaturation were obtained from the curves of melted base pairs as a function of temperature. The binding constant of the xanthone–DNA complex, at 293 K, was calculated from the UV spectra.

The results indicate a strong binding affinity of xanthone with DNA, affecting the stability of the double helix, and suggest the binding of xanthone to DNA mainly by intercalation.

3.15. Synthesis of Phenolic Compounds Sulfate Metabolites (MC25)

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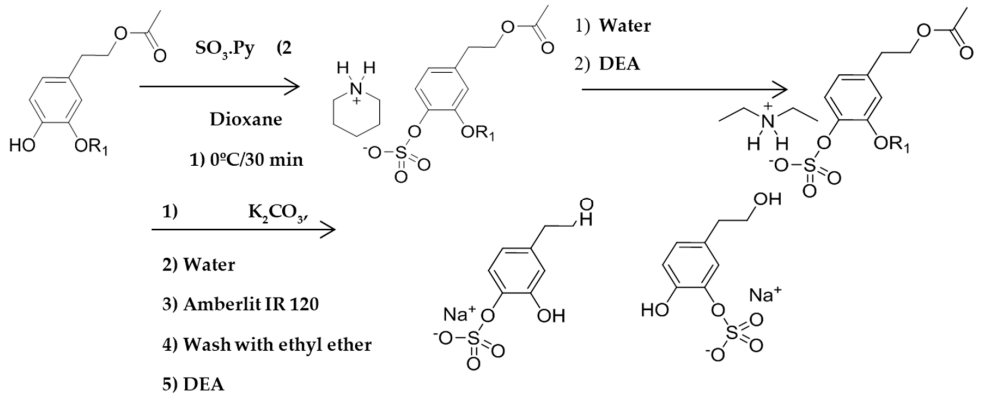
The biological properties of olive oil polyphenols *in vivo* depend on the extent to which they are absorbed and metabolized. In a recent work, the metabolites hydroxytyrosol (3,4-dihydroxyphenylethanol) sulfate and hydroxytyrosol acetate sulfate were found to be the most useful metabolites for monitoring the intake compliance of extra virgin olive oil (Rubió, L., *et al. Food Res. Int.* 2014, *65*, 59–68).



The growing interest in the bioactivity of natural polyphenols requires their metabolites to be used in bioassays and as standards in research protocols. Therefore, we report here the synthesis of several polyphenol sulfates namely hydroxytyrosol, hydroxytyrosol acetate, homovanillyl alcohol, homovanillyl alcohol acetate, homovanillilic acid, ferulic acid, and 3,4-dihydroxyphenylethanoic acid sulfates. A relatively fast and cheap synthetic solution based on avoidance of high temperature conditions during the synthesis and of low pressure conditions during purification has been established. Compounds were efficiently synthesized in 1–2 steps in a good yield (>75%).

3.16. Flavonoids Effects in Proinflammatory Signaling Systems: In Vitro Structure/Activity Studies (MC27)

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