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In Silico Evaluation of Ibuprofen and Two Benzoylpropionic Acid Derivatives with Potential Anti-Inflammatory Activity

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SUPPLEMENTARY MATERIAL

Figure S1. Theoretical synthetic route for the preparation of compound 4-(4-methoxyphenyl)-4-oxobutanoic acid (B).

Figure S2. Theoretical synthetic route for the preparation of compound 2,4-dihydroxyphenyl)-4-oxobutanoic acid (C). DMF (*N*, *N*-dimethylformamide), TIPS-Cl (triisopropylsilyl chloride), Imidazole (i) succinic anhydride and aluminum chloride and DCM (dichloromethane), (ii) TBAF (tetra-*n*-butylammonium fluoride) and THF (tetrahydrofuran).

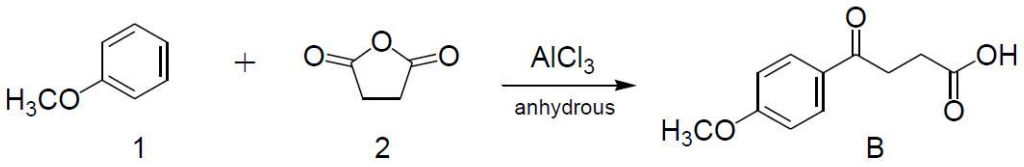

Figure S1. Theoretical synthetic route for the preparation of compound 4-(4-methoxyphenyl)-4-oxobutanoic acid (B).

The 4-(4-methoxyphenyl)-4-oxobutanoic acid (B) was synthesized by anisole with succinic anhydride in the presence of anhydrous aluminum chloride under Friedel-Crafts acylation reaction conditions. The synthesis of 4-(4-methoxyphenyl)-4-oxobutanoic acid has been recently reported by Soliman et al. (2018) [1] is a one-step process and the synthetic strategy known to synthesize efficiently phenyloxobutanoic acids from aromatic hydrocarbon, anisole, in a 1 step process: acylation of anisole with succininc anhydride catalyzed by anhydrous aluminum chloride under conditions of under Friedel-Crafts acylation reaction.

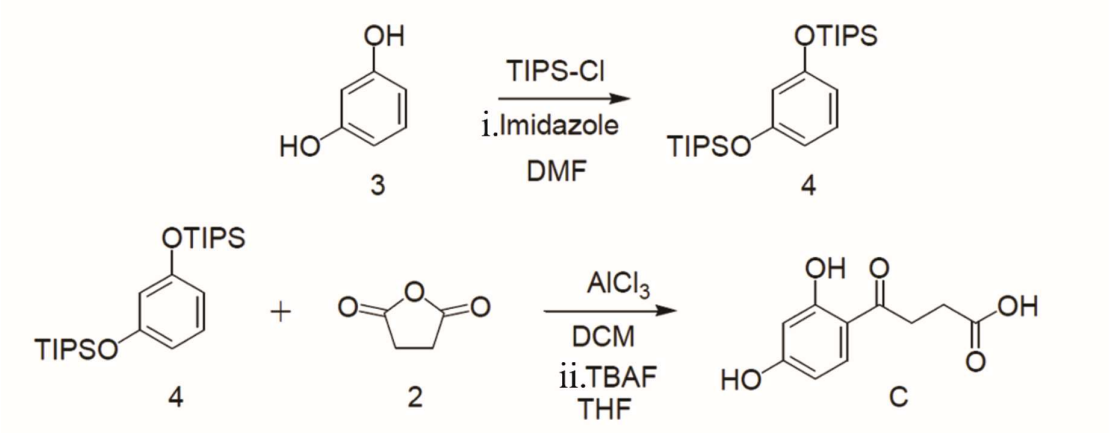

Figure 2. Theoretical synthetic route for the preparation of compound 2,4-dihydroxyphenyl)-4-oxobutanoic acid (C). DMF (*N*, *N*-dimethylformamide), TIPS-Cl (triisopropylsilyl chloride), Imidazole (i) succinic anhydride and aluminum chloride and DCM (dichloromethane), (ii) TBAF (tetra-n-butylammonium fluoride) and THF (tetrahydrofuran).

The synthesis of 2,4-dihydroxyphenyl)-4-oxobutanoic acid (C) has been reported by Liu et al. (2014) [2]. The theoretical synthetic route (See Figure S2) here proposed consists of two steps, in analogy to two variants with carboxylic acid functionalities and anhydrous aluminum chloride in the presence of TBAF (tetra-*n*-butylammonium fluoride), DCM (dichloromethane) and THF (tetrahydrofuran).

In the first step it consists resorcinol e *N*, *N*-dimethylformamide under temperature of conditions that depend on the reaction medium, subsequently, added triisopropylsilyl chloride and imidazole at room temperature for 24 hours. Then, in the second step, in 1,3-*bis*((triisopropylsilyl)oxy)benzene and anhydrous dichloromethane under a temperature of conditions that depend on the reaction medium. Subsequently, succinic anhydride and aluminum chloride are added. The oil formed is dissolved in tetrahydrofuran and will react with tetra-*n*-butylammonium fluoride.

References

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2. Liu, D.S.; Nivón, L.G.; Richter, F.; Goldman, P.J.; Deerinck, T.J.; Yao, J.Z.; Drennan, C.L. Computational design of a red fluorophore ligase for site-specific protein labeling in living cells. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, E4551–E4559, doi:10.1073/pnas.1404736111