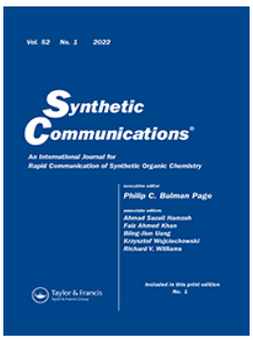

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A novel synthetic protocol for the synthesis of *pulvinones,* and naturally occurring *Aspulvinone E*, molecules of medicinal interest

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A novel synthetic protocol for the synthesis of *pulvinones,* and naturally occurring *Aspulvinone E*, molecules of medicinal interest

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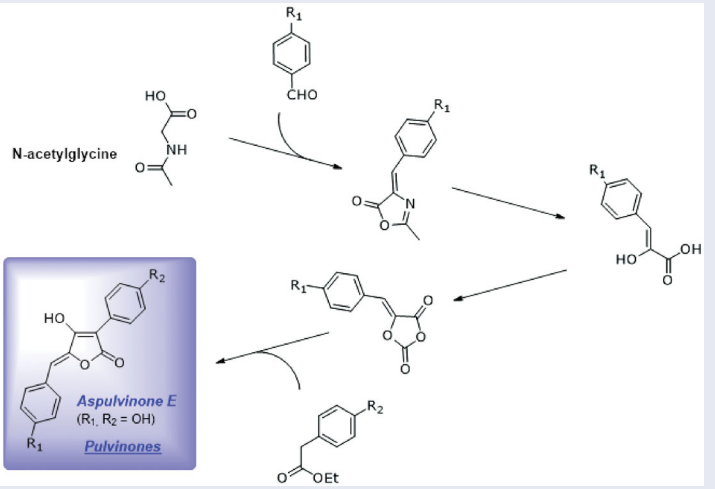
ABSTRACT

A novel two step methodology for readily accessible natural "pulvinone" derivatives in excellent yields has been developed starting from activated precursors, bearing a functionalized 1,3-dioxolane-2,4-diones (OCA's), as dually protected-activated synthons of α-hydroxy acids. The present procedure is based on a tandem C-acylation-cyclization process under mild conditions with good yields. Additionally, pulvinones show an important medicinal profile with the tetronate heterocycle exhibiting favorable pharmacokinetic (PK) and ADME-Tox properties that can be considered unexploited so far due to synthetic limitations.

GRAPHICAL ABSTRACT



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Introduction

Despite the profound progress of medicinal chemistry nature and identification of natural products still remains an important source of inspiration for drug design throughout the years.[1] Such examples are pulvinones, which have been first reported during the 19th century.[2] Core structure of this class of compounds is the tetronic acid ring, a 5-membered oxygen containing heterocycle. Documented derivatives so far have found either chemical applications as pigments[3] or medicinal applications. The later exhibited biological activities can be summarized on radioprotection,[4] antibacterial,[5,6] antioxidant,[7–9] anticoagulant,[10] antiinflammatory,[9,11,12] antipyretic,[11] analgesic[11] and antiviral.[13] Recently, pulvinone derivatives have been attracting again interest in the context of reevaluating undeveloped compounds on the efforts to combat bacterial resistance.[14]

Tetronates mechanism of action is still unknown but the moiety has been classified as a bioisoster for carboxylate, phosphate or sulfate groups.[15] Tautomeric forms of tetronates is shown in Figure 1.[15]

Therefore tetronates constitute an excellent bioactive ring in preparation of pharmaceuticals, showing important biological activities. Among the large group of structurally related tetronates, those of 5-arylidene-3-aryl substituted natural tetronic acids concentrate great research interest (Figure 2).

This wide range of biological properties and the emerging interest of novel medicinal applications are among the reasons of the continuous synthetic efforts found in literature (Scheme 1) regarding the development of effective methodologies for the construction of functionalized 3-aryl-5-arylidene-tetronic acids. So far described methodologies include mainly cross-coupling reactions from suitable intermediates (i.e. Suzuki–Miyaura, Stille, and Sonogashira).[16,17] Alternatively derivatives have been obtained from stereoselective aldol condensation reactions followed by catalytic intermolecular C–H insertion reactions,[18] from arylacetylenes triple bond activation by Ag(I) salts and respective ring closures,[19,20] from a common diester precursor with ether function reactions via tandem Dieckmann condensation–alkoxide β-eliminations[21–23] and through Wittig reactions.[11]

In continuation to our previous work on the synthesis of functionalized tetronic acids, by the use of 1,3-dioxolane2,4-diones as novel protected-activated synthons of α-hydroxy acids,[24] we present herein a general synthetic methodology for the construction of functionalized pulvinone molecules, with potential pharmaceutical interest. Nonetheless, pulvinones can serve also as valuable precursors for the preparation of five-membered oxygen heterocycles containing the β-diketo moiety, with additional pharmacological interest on development of new supramolecular archirectures.[24]

Results and discussion

In connection to our previous studies,[24] the main focus on our group remains the development of new methodologies for the synthesis of five-membered nitrogen, oxygen and sulfur containing heterocycles, i.e. tetramic, tetronic and thiotetronic acids respectively. Recently, we reported a new synthetic protocol to fully functionalized 4-hydroxy-5[*H*]-furan-2-ones (tetronic acids), using for the first time in literature the 1,3-

Figure 1. Existing tautomeric keto-enol forms of the tetronate moiety.

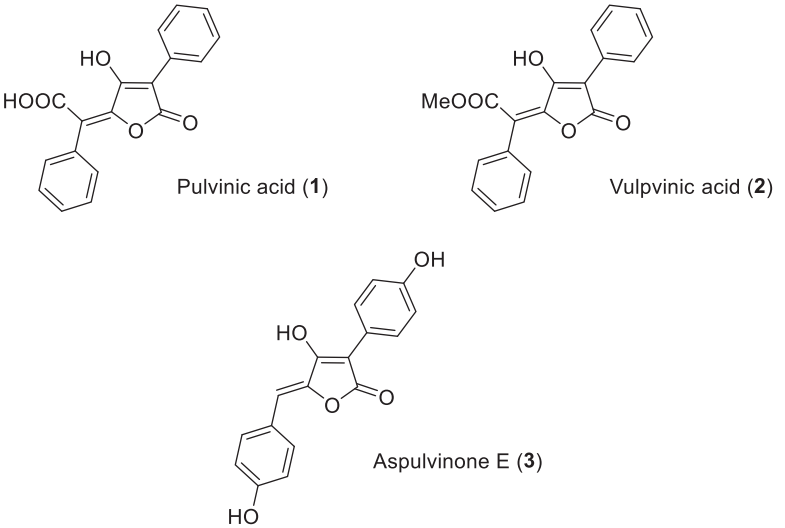
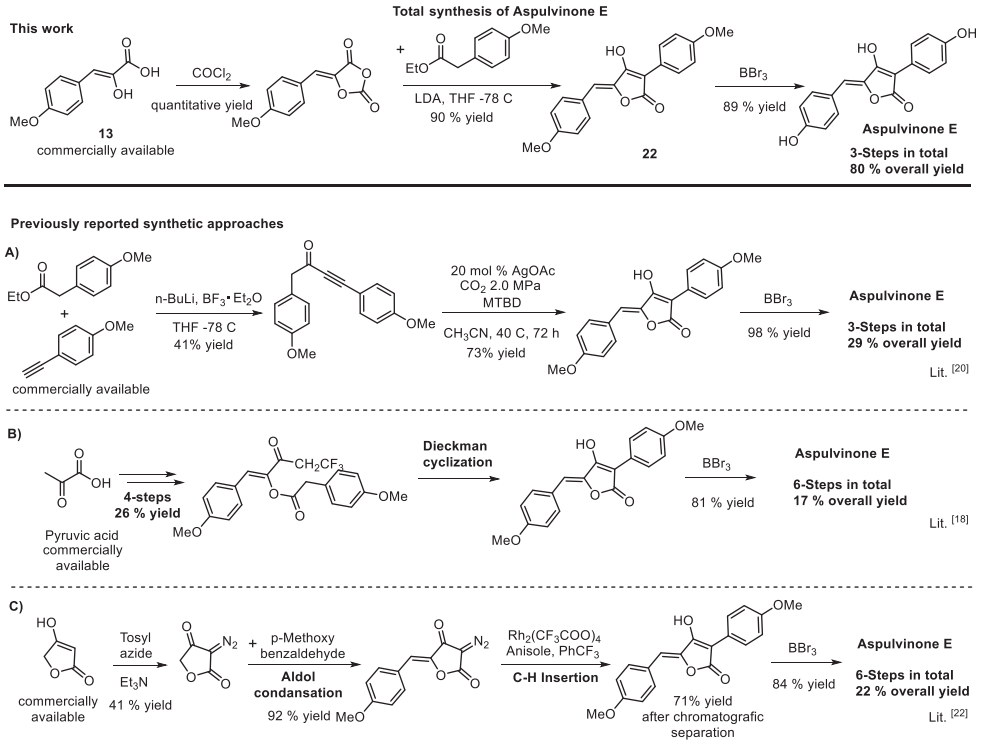


Figure 2. Chemical structures of naturally occurring 3-aryl-5-arylidene-tetronic acids.

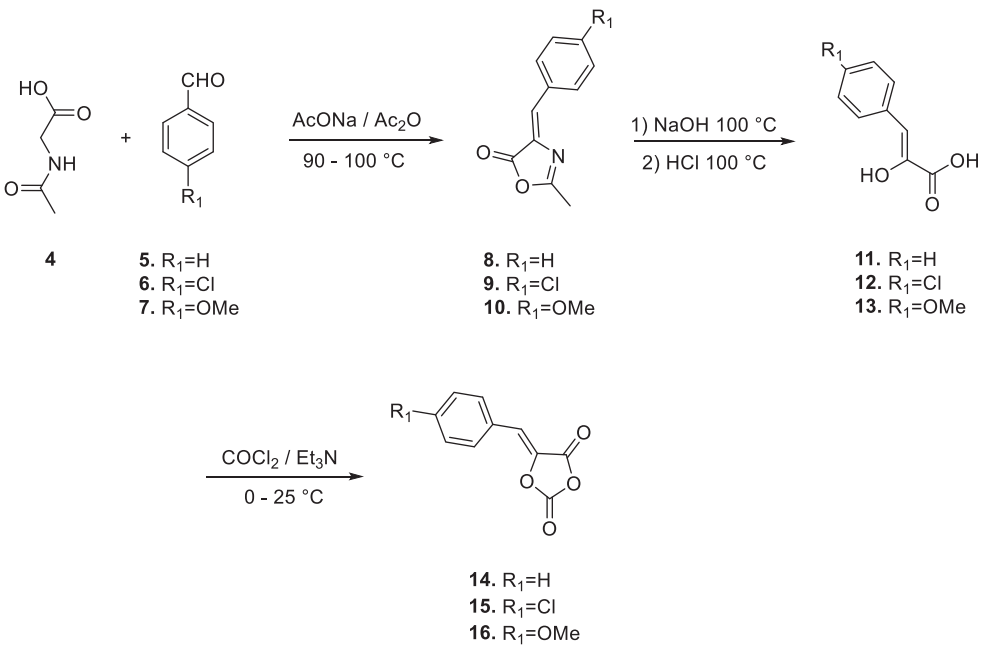
dioxolane-2,4-diones scaffold as "model synthons" for the synthesis of optically active tetronic acids.[24]

In the present work, the key control element of the proposed protocol has been the utilization of O-carboxy anhydrides (OCA'S) of arylidene α-hydroxy acids, the (*Z*)-5-arylidene-1,3-dioxolan-2,4-diones, as privileged acylating scaffolds toward the synthesis of pulvinone derivatives. Importantly, the proposed methodology found to be applicable to the total synthesis of the aspulvinone E natural product, isolated from *Aspergillus terreus,* having an important bioactivity profile.[25–29]

The synthetic strategy followed for the preparation of the final (*Z*)-5-arylylidene-3-aryl-4-hydroxyfuran-2(5H)-ones **19–24** is depicted in Schemes 2 and 3. Thus, the synthesis of (*Z*)-5-arylylidene-1,3-dioxolane-2,4-dione **14–16** is presented in Scheme 2 and accomplished using the corresponding aromatic aldehydes **5–7** and acetylglycin **4** as the starting materials. The previous condensation was achieved in the presence of anhydrous sodium acetate and acetic anhydride under heating at 90–100 °C to afford (*Z*)-4-arylidene-2-methyloxazol-5(4*H*)-ones **8–10.** These intermediates were hydrolyzed first with aq.NaOH and then with c.HCl to afford (*Z*)-2-hydroxy-3-arylacrylic acids **11–13** which in turn react with phosgene solution in toluene in the presence of dry triethylamine to yield (*Z*)-5-arylidene-1,3-dioxolan-2,4-diones **14–16** in moderate to quantitative yields.



Scheme 1. Overview of the various approaches on the total synthesis of aspulvinone E.



4

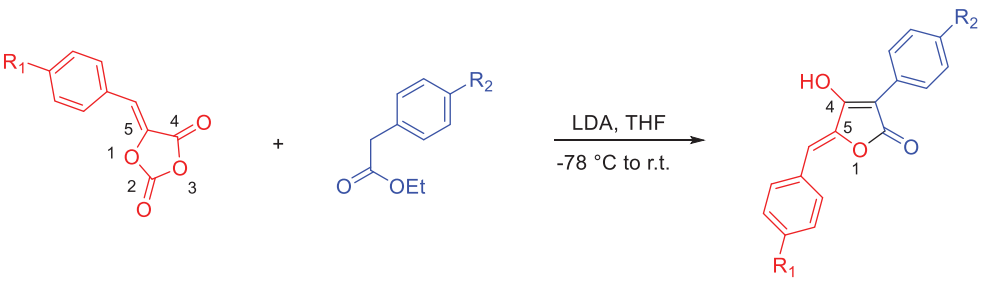
5. R_1=H
6. R_1=Cl
7. R_1=OMe

8. R_1=H
9. R_1=Cl
10. R_1=OMe

11. R_1=H
12. R_1=Cl
13. R_1=OMe

14. R_1=H
15. R_1=Cl
16. R_1=OMe

Scheme 2. Synthetic route and conditions for the preparation of activated arylidene OCA's.



14. R_1=H
15. R_1=Cl
16. R_1=OMe

17. R_2=H
18. R_2= OMe

19. R_1=R_2=H
20. R_1=H, R_2=OMe
21. R_1=OMe, R_2=H
22. R_1=R_2=OMe
23. R_1=Cl, R_2=H
24. R_1=Cl, R_2=OMe

Scheme 3. Colored atom/bond representation and experimental conditions for obtaining the respective pulvinone derivatives.

Our initial investigations focused on the optimization of reaction conditions, and on the efficiency of the arylidene OCA's of α-hydroxy acids as acylating agents to the proposed reaction. These substituted anhydrides serve as privileged acylating agents used as the starting material for the final reactions (Scheme 3). More specifically, the intermediates **14**–**16** reacted with lithium enolates of ethyl aryl-acetate **17** and **18** to generate the 3-aryl-5-arylidenetetronic acids **19**−**24** (pulvinones) in 52−90% yield, via an in situ intramolecular cyclization of the intermediate structure. The C-acylation/cyclization reactions were conducted at −78 °C using lithium diisopropylamide (LDA) base in THF, to achieve the desired pulvinones, possessing a 5-arylidene moiety and an aromatic ring at position 3. Interestingly, when substituted lithium phenyl acetate of **17** and **18** was used as the enolate source, the corresponding 3,5-diphenyltetronates **(19–24)** were obtained through the attack of the enolate selectively on the carbonyl of the OCAs at position 4.

Moreover, capitalizing on this novel methodology the natural aspulvinone E can be obtained in just three steps in excellent overall yield reaching up to 80% from (*Z*)-3-(4-methoxyphenyl)-2-hydroxyacrylic acid **(13)** which is also a commercially available starting material (Scheme 1). Unlike previously reported methodologies that exhibit demanding multistep synthesis and low overall yields[18,22] with the best one being just 29% (over three steps).[20]

Targeted drug design has strict rules and properties that need to be met simultaneously (i.e. absorption, distribution, metabolism, toxicity). Therefore, prediction tools serve medicinal chemists greatly in their efforts to identify suitable candidate molecules. In an attempt to outline the potential pharmacological importance of aspulvinone E (**3**) and their derivatives in medicinal chemistry we predict the PK and ADME-Tox properties of mother compound **3**. Interestingly, although the core structure incorporates an arylidene-heterocycle motif that it could be conceived as pan assay interference compounds (PAINS)[30,31] alert at first, this is not the case. In contrast to other know

Table 1. Compound **3** (aspulvinone E) drug-likeness properties predicted.

	Compound **3**
MW (<500Da)	296.28
logP(<5)	2.63
logD	1.97
logSw	−3.46
tPSA(<140Å^2)	86.66
Fsp^3(0-1)	0.0
HBD(<5)	3
HBA(<10)	5
Rotatable bonds (<10)	2
Rigid bonds	19

Table 2. Predicted compound **3** ADME-Tox profile.

	Compound **3**
Oral bioavailability (VEBER)[33]	Good
Oral bioavailability (EGAN)[34]	Good
Solubility	Good
Phospholipidosis[35]	No inducer
GSK 4/400 rule[36]	Good
Pfizer 3/75 rule[37]	Good
Lilly Medchem rules[30]	Acylated enol

five-membered arylidene heterocycles like rhodanines, thiazolidinones, thiohydantoins and hydantoins that have documented promiscuity.[32] Tables 1 and 2 summarizes all generated descriptors in ADME-Tox screening that was carried over the FAF-Drugs4 server.[38]

In Table 1 compound **3** is found within all acceptable limits and no Lipinski's rule of 5[39] are violated. Additionally, as summarized in Table 2 both the Veber[33] and Egan[34] bioavailability are considered good. Veber calculation takes into consideration number of rotatable bonds and tPSA,[33] whilst Egan correlates tPSA with lipophilicity instead.[34] As regarding to phospholipidosis,[35] GSK 4/400 rule,[36] the Pfizer 3/75 rule[37] and Lilly Medchem rules[30] it was found acceptable.

Conclusion

In conclusion we have developed a convenient and efficient methodology for the construction of functionalized substituted pulvinones, possessing an arylidene substituent at position 5 and an aryl group at position 3 of the tetronate nucleus. The proposed methodology was conducted to the total synthesis of the natural product aspulvinone E with 80% overall yield starting from the commercially available arylidene hydroxy acid. Our efforts, are directed toward the synthesis of more complex pulvinones concerning the aromatic substituents, providing new compounds with antiviral activities. Since, as we witnessed from ADME-Tox predicted descriptors the tetronic acid moiety incorporated in pulvinone like derivatives provides a remarkably suitable starting profile for use in drug designing efforts with no alerts being raised.

Experimental

General information

Mps were determined on a Gallenkamp MFB-595 melting point apparatus and are uncorrected. The NMR spectra were recorded at 300 (^{1}H) and 75 (^{13}C) MHz on a Varian 300 MHz spectrometer; chemical shifts are quoted in parts per million (s = singlet, d = doublet, dd = doublet of douplet, t = triplet, pt = pseudotriplet, q = quartet, m = multiplet, br = broad); *J* values are given in Hertz. Mass spectra were obtained on an ESI-MS (HPLC-LCQ Fleet/Thermo Scientific). All commercially available starting materials were used without further purification. Commercially available THF was dried prior to use by refluxing over Na. All other solvents (puriss. quality) were used without further purification. Column chromatography was performed with silica gel 60 with eluents given in parentheses.

Pharmacological profiling

Compound **3** was compiled on a smile formatted file (*.smi) and consequently generated its SDF 3 D structure file all with the use of the program Open Babel.[40] The later SDF file served as the required input file for the ADME-Tox calculations performed over FAF-Drugs4 server.[38]

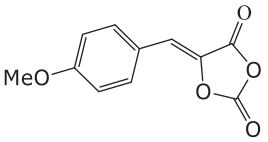
Selected descriptors were XLOGP3[41] for the predicted lipophilicity and the server's build-in filter for drug-likeness,[39,42–44] that takes into account common drug design properties like PKs and bioavailability. Moreover, compound **3** was positively checked for the detection of undesirable moieties[45] as well as PAINS.[31] Final descriptor applied was Lilly Medchem rules in order to identify possible interference with biological assays, included substrate chemical reactivity, instability and/or lack of druggability.[30] Setting of the Medchem rules was set to relaxed involving a 160-demerit cutoff.[30]

Experimental procedures and data

General procedure for the synthesis of (Z)-5-arylidene-1,3-dioxolan-2,4-diones (14-16)

Phosgene solution (3.38 mL, 6.86 mmol, 20% in toluene) was added to a solution of substituted 2-hydroxy-3-acrylic acid (5.49 mmol) in anhydrous diethylether (72 mL) at 0 °C. A solution of triethylamine (1.22 g, 12.07 mmol) in anhydrous diethylether (18 mL) was then added dropwise over a period of 1 h and the reaction mixture was stirred at the same temperature for additional 2 h. The white precipitate was filtred off, washed with a small amount of dry diethylether and the filtrates were evaporated under reduced pressure below 40 °C. The crude product solidified to a yellowish solid after tritutation with small volume anhydrous diethylether, was refrigerated for several hours and then filtered. The solid product was then washed with cold diethylether and dried under high vacuum over P_2O_5 for 1 h.[46]

Synthesis of (Z)-5-(4-Methoxybenzylidene)-1,3-dioxolane-2,4-dione (16).

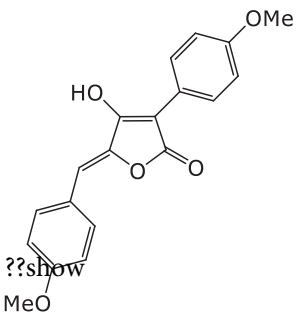


Starting from (Z)-2-hydroxy-3-(4-methoxyphenyl)acrylic acid **(13)** (5.50 mmol, 1.07 g), the title compound **(16)** was obtained as yellow solid (1.21 g, quantitative); Mp: 129−131 °C decomp.; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.86 (3H, s), 6.89 (1H, s), 6.98 (2H, d, $J = 9.0$ Hz) , 7.69 (2H, d, $J = 9.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.6, 115.0, 119.2, 122.5, 131.6, 133.8, 146.3, 157.9, 162.7.

General procedure for the synthesis of (Z)-5-aryliden-4-hydroxy-3-arylfuran-2(5H)-one (19–24)

A solution of the appropriate aryl acetate **17** and **18** (3 mmol) in THF (2 mL) was added dropwise via a syringe over a period of 10 min to a solution of lithium diisopropylamide (LDA) 2.0 M solution in THF/hexane/ethylbenzene (3 mmol, 1.5 mL) in THF (7.5 mL) at −78 °C under nitrogen. The mixture was stirred for 45 min, then the appropriate 1,3-dioxolane-2,4-dione **14–16** (1.0 mmol) in THF (2 mL) was added dropwise over 10 min. The reaction mixture was stirred for 30 min at −78 °C and an additional hour to room temperature, quenched with water (5 mL), and the THF evaporated in vacuum. The resulting aqueous layer was then washed with Et_2O (15 mL) and acidified with HCl 10% to pH 1−2 in an ice-water bath, to give the corresponding compounds **19–24** as solid products, washed with diethylether and were dried in high vacuum over P_2O_5.

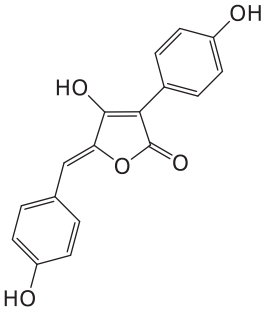
Synthesis of (Z)-5-(4-Methoxybenzylidene)-3-(4-methoxyphenyl)-4-hydroxyfuran-2(5H)-one (22).



Starting from ethyl 4-methoxyphenylacetate **(18)** (0.580 g) and (*Z*)-5-(4-methoxybenzylidene)-1,3-dioxolan-2,4-dione **(16)** (0.232 g), the title compound was obtained as yellow solid (0.270 g, 90%); Mp: 245−247 °C decomp, (Lit.[22] mp 244 − 247 °C decomp); ^{1}H NMR (300 MHz, DMSO-d_6): δ 3.77/3.80 (6H, 2 s), 6.67 (1H, s), 7.01 (4H, m, $J = 7.8$ Hz), 7.68 (2H, d, $J = 7.8$ Hz), 7.89 (2H, d, $J = 7.8$ Hz); ^{13}C NMR (75 MHz,

DMSO-d_6): δ 55.1, 55.2, 99.6, 107.2, 113.7, 114.5, 122.3, 125.4, 128.4, 131.7, 140.7, 158.1, 159.6, 162.4, 168.0; ESI-MS: *m/z* 323.15 $[M-H]^-$.

Synthesis of (Z)-4-Hydroxy-5-(4-hydroxybenzylidene)-3-(4-hydroxyphenyl)furan-2(5H)-one (3), (aspulvinone E)



To a suspension of pulvinone **(22)** (0.046 g, 0.153 mmol), in freshly distilled CH_2Cl_2 (9.2 mL) a solution of BBr_3 (0.918 mL, 0.918 mmol, 1.0 M in CH_2Cl_2) was added dropwise, and the reaction mixture was heated at reflux for overnight (12 h). The reaction was quenched with water under ice cooling and the mixture was extracted with EtOAc (3×30 mL). The organic layers were combined, dried over Na_2SO_4, and solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (silica gel, eluting solvent system: CH_2Cl_2/methanol/acetic acid, 94:4:2 to 92:6:2) to obtain aspulvinone E **(3)** as a yellow solid (0.037 mg, 89%); Mp: 262 – 263 °C decomp, (Lit.[18] mp 261–266 °C decomp); ^{1}H NMR (300 MHz, Acetone-d_6): δ 6.54 (s, 1H), 6.88 (m, $J = 8.4$ Hz, 4H), 7.66 (d, $J = 8.7$ Hz, 2H), d = 7.94 (d, $J = 8.5$ Hz, 2H); ^{13}C NMR (75 MHz, Acetone-d_6): δ 100.6, 107.0, 115.8, 116.6, 123.1, 126.1, 129.5, 132.8, 142.6, 157.2, 158.9, 164.4, 169.6; ESI-MS: *m/z* 295.13 $[M-H]^-$.

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