# SUPPORTING INFORMATION

# 4,5-Diaryl 3(2H)Furanones: Anti-Inflammatory Activity and Influence on Cancer Growth

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1.Structures of known COX-1/2 inhibitors (E1-E14 ) used for prediction of inhibitory action



Figure S1. Structures of known COX-1/2 inhibitors (E1-E14)

2. Synthesis of auxiliary compounds



Scheme S1. Synthesis of starting diaryl ketones by oxidation of substituted toluenes or benzaldehydes. For *m*-F substituted compounds Schiemann reaction is the most rational (Table S1)

Х	Oxidation of	Oxidation	Schiemann	Acylation by Friedel-	Overall
	aldehyde	of toluene	reaction	Crafts*	yield
<i>m</i> -Cl	-	40 %	-	66 %	26 %
<i>m</i> -F	-	-	35 %	38 %	13 %
p-Cl	66 %	-	-	70 %	46 %
<i>p</i> -F	42 %	-	-	75 %	32 %

Table S1. Yields of the synthesis of starting diaryl ketones and their precursors according to Scheme S1.

\* Synthesis of benzoic acid chlorides was carried out without its isolation.

**Example:** synthesis of 4'-(methylthio)phenyl(4'-fluorophenyl)methanone

To p-fluorobenzene aldehyde (10.7 g) dissolved in acetic acid (60 ml )at 70 °C a solution of  $CrO_3$  (5.5 g ) in 70 % acetic acid (60 ml ) was added dropwise during 1.5 hours. After completion of the reaction cold HCl (35 %,100 mL ) was added to the mixture. Precipitated *p*-fluorobenzoic acid was filtered, washed twice by 10% HCl, and recrystallized from MeOH/CH<sub>2</sub>Cl<sub>2</sub>, and the mother liquor was passed through a column of silica gel. Yield after vacuum drying: 4.96 g (42 %). *p*-fluorobenzoic acid, <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>),  $\delta$ , ppm: 7.154 t (2H, <sup>3</sup>J<sub>HH</sub> = 8.6 Hz), 8.135 dd (2H, <sup>3</sup>J<sub>HH</sub> = 8.7 Hz, <sup>4</sup>J<sub>HF</sub> = 5.4 Hz).

In the next stage to *p*-fluorobenzoic acid (4.96 g) in CCL4 (25ml) fresh SOCl<sub>2</sub> (4ml) and DMFA (0.05 ml) in CCl<sub>4</sub> (25 ml)were added. The mixture was refluxed during 5 hours until the end of release of gaseous products. The solvent and excess of SOCl<sub>2</sub> were removed in vacuum. Obtained oil (5.6 g ,97 % of theoretical yield) , without additional purification, was dissolved in cold DCM (20 mL). This solution was added dropwise to cold suspension of AlCl<sub>3</sub> (5 g) and thioanisole (4.38 g ,35 mmol) in of DCM (30 mL). The mixture was refluxed during 4 hours until the end of emission of HCl. Obtained product was carefully hydrolyzed by 5 % HCl, then extracted by CH<sub>2</sub>Cl<sub>2</sub>, (3x30 mL) and dried over Na<sub>2</sub>SO<sub>4</sub>. After removing of the solvent the residue was recrystallized from *n*-hexane to purify the product from traces of thioanisole. Yield: 6.48 g (75 %), colorless crystals, mp. 107-108 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>), δ, ppm: 2.535 s (3H, SCH<sub>3</sub>), 7.15 t (2H, <sup>3</sup>J<sub>HH</sub> = 8.6 Hz), 7.29 d (2H, <sup>3</sup>J<sub>HH</sub> = 8.4 Hz), 7.71 d (2H, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz), 7.81 dd (2H, <sup>3</sup>J<sub>HH</sub> = 8.7 Hz, <sup>4</sup>J<sub>HF</sub> = 5.5 Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>), δ, ppm: 14.8 (SCH<sub>3</sub>), 115.4 d (2C), 124.9 (2C), 130.4 (2C), 132.4 *μ* (2C), 133.4, 133.8, 145.4, 137.7, 145.2, 165.2 *μ* (<sup>1</sup>J<sub>CF</sub> = 254 Hz), 194.3 (C=O). <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>), δ, ppm: -106.3. HRMS, m/z, calculated: 247.0588, found: 247.0598 [MH]<sup>+</sup>.

## 4'-(methylthio)phenyl(4'-chlorophenyl)methanone: yield 4.3 g (70 %), colorless crystals, mp. 132-133 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>), δ, ppm: 2.524 s (3H, SCH<sub>3</sub>), 7.28 d (2H, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz), 7.44 d (2H, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz), 7.70 d (2H, <sup>3</sup>J<sub>HH</sub> = 8.7 Hz), 7.71 d (2H, <sup>3</sup>J<sub>HH</sub> = 8.8 Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>), δ, ppm: 14.7 (SCH<sub>3</sub>), 124.8 (2C), 128.5 (2C), 130.4 (2C), 131.2 (2C), 133.1, 136.1, 138.5, 145.6, 194.4 (C=O).

# **4'-(methylthio)phenyl(3'-fluorophenyl)methanone:** yield 0.71 g (39 %), colorless crystals, mp. 67-68 °C.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>), δ, ppm: 2.54 s (3H, SCH<sub>3</sub>), 7.30 d (2H, <sup>3</sup>J<sub>HH</sub> = 8.4 Hz), 7.46-7.48 m (2H), 7.53 d (1H, <sup>3</sup>J<sub>HH</sub> = 7.6 Hz), 7.74 d (2H, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>), δ, ppm: 14.8 (SCH<sub>3</sub>), 116.5 d (2C), 119.1 d, 124.9 (2C), 125.5 d (1C), 129.9 d (1C), 130.5 (2C), 133.0, 140.0 d, 145.9, 162.4 d (<sup>1</sup>J<sub>CF</sub> = 247 Hz), 194.3 (C=O). <sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>), δ, ppm: -112.0.

4'-(methylthio)phenyl(3'-chlorophenyl)methanone: yield 5.15 g (66 %), colorless crystals, mp. 73-74 °C. <sup>1</sup><sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>), δ, ppm: 2.54 s (3H, SCH<sub>3</sub>), 7.30 d (2H, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz), 7.41 t (1H, <sup>3</sup>J<sub>HH</sub> = 7.8 Hz), 7.54 d (1H, J<sub>HH</sub> = 8.0 Hz), 7.63 d (1H, <sup>3</sup>J<sub>HH</sub> = 7.7 Hz), 7.73 d (3H, <sup>3</sup>J<sub>HH</sub> = 8.5 Hz). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>), δ, ppm: 14.8 (SCH<sub>3</sub>), 124.9 (2C), 127.8, 129.6, 129.7, 130.5 (2C), 132.1, 132.9, 134.5, 139.5, 146.0, 194.2 (C=O).

### 3. General procedure for the preparation of compounds 3 and analytical data.

#### 3. General procedure for the synthesis of 2.2-dimethyl-4,5-diphenylfuran-3(2H)-one

To a solution of diazoketone **4** (1 mmol )in CHCl<sub>3</sub> (10mL) a trifluoroacetic acid (TFA, 0.1 mL) in CHCl<sub>3</sub> (5 mL) was added. The mixture was refluxed during 2 hours until complete decomposition of the initial diazoketone (controlled by TLC). After the reaction completion the mixture was washed by water/NaHCO<sub>3</sub>, pure water (2x10 mL) and dried over  $K_2CO_3$  (24 h). After removal of the solvent, about 0.9 mmol (~ 98%) of a mixture of two regioisomeric 2,2-dialkyl-4,5-diaryl-dihydrofuran-3(2*H*)-ones **3** (approximate ratio - 3:1) was obtained as a light yellow oil. The regioisomers were separated by repeated twice chromatography on plates (or on column, eluent: n-hexane/CH<sub>2</sub>Cl<sub>2</sub>) and around 0.66 mmol (~ 72 %) of desired 3(2*H*)furanone was obtained, slightly yellow crystals. The compounds **3** were described previously [38,

3Medvedev, J.; A New Powerful Approach to Multi-Substituted 3(2H)-Furanones via Brønsted Acid-Catalyzed Reactions of 4-Diazodihydrofuran-3-ones. *Synthesis*. **2016**, 48(24), 4525-4532].

**3.1** Mixture of 2,2-dimethyl-4-phenyl-5-(3'-chlorophenyl)furan-3(2*H*)-one and 2,2-dimethyl-5-phenyl-4-(3'-chlorophenyl)furan-3(2*H*)-one

<sup>1</sup>H NMR of mixture (300 MHz, 15 mg in 0.5 mL CDCl<sub>3</sub>, reference: CHCl<sub>3</sub> = 7.26 ppm), δ, ppm: 1.56 s (6H, 2CH<sub>3</sub>), 7.23-7.50 m (8-9H), 7.64-7.72 m (1.5H). <sup>13</sup>C NMR of mixture (75 MHz, 20 mg in 0.7 mL CDCl<sub>3</sub>, reference: CHCl<sub>3</sub> = 77.00 ppm), δ, ppm: 205.25, 204.77, 178.68, 176.21, 134.55, 134.32, 132.06, 131.86, 131.61, 129.76, 129.59, 129.37, 128.67, 128.50, 128.35, 128.01, 127.80, 127.59, 126.67, 124.06, 114.28, 112.27, 87.29, 87.15, 23.27.

# 2,2-dimethyl-5-phenyl-4-(4'-chlorophenyl)furan-3(2H)-one:

<sup>1</sup>H NMR (300 MHz, 15 mg in 0.6 mL CDCl<sub>3</sub>, reference: CHCl<sub>3</sub> = 7.26 ppm), δ, ppm: 1.57 s (6H, 2CH<sub>3</sub>), 7.25-7.51 m (7H), 7.65 d (2H, J = 10.1 Hz). <sup>13</sup>C NMR (75 MHz, 15 mg in 0.6 ml CDCl<sub>3</sub>, reference: CHCl<sub>3</sub> = 77.00 ppm), δ, ppm: 205.08, 178.50, 133.29, 131.99, 130.72, 129.63, 128.78, 128.49, 128.42, 128.33, 112.33, 87.24, 23.29.





**Figure S2.** Assessment of cell growth of MCF-7 cells in culture after their treatment with increasing concentrations of the tested compounds for 48 hours. Cell growth was assessed using a hemocytometer (Neubauer chamber) and is expressed as a percentage (%) relative to that for the untreated, control culture CTL). The data shown above indicate a representative experiment where 4 independent measurements for each concentration were used to calculate the average (± SD, Standard Deviation).

### 4. Compute modeling of pharmacological activity

List of the common terms and abbreviations used in the field of virtual screening.

Docking - computational approach to perform 3D analysis of supramolecular interactions between a ligand and biological target;

- **Pre-processing** energy minimization procedure and optimization of a biomolecular structure as well as ligand to obtain reliable 3D coordinates using the classical methods of molecular mechanics and dynamics;
- Annealing reconstruction of 3D structure of selected protein with a potential energy close to the predicted minimum;
- Stress conformational clashes of amino acid residues observed within the constructed protein structure;
- Dock Scoring energetic function (kcal/mol) routinely used for the assessment of ligand affinity towards a target;
- **RMSD** Root-mean-square deviation of atomic position.





(**c**)

**Figure S3 (a, b, c)**. Potential energy (NormEnergy, kcal/mol) shared by amino acids in *h*COX-2 (**a**) and *h*COX-1 (**b**) after annealing; **c**) amino acids in *h*COX-1 with high energy values (*grey spheres*); the binding site (*yellow sphere*).

5. Spectra













S15



S16







S19



YME YME, 356, BF = 400.13 MHz, Solvent - CDCl3, 22 Jul 2015 T=296 K



**⊢9000** 























YMEc, 357, BF = 100.612769 MHz, Solvent - CDCl3, 22 Jul 2015 T=296 K





YMEc

YMEc, 358, BF = 100.612769 MHz, Solvent - CDC3, 22 Jul 2015 T=296 K









