Supplementary materials

Biomedical Promise of Sustainable Microwave-Engineered Symmetric Curcumin Derivatives

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Table S1. The acceptable values of compounds' physicochemical properties according to the drug-likeness rules of Lipinski, Ghose, Veber, Egan and Muegge , and the compliance of analyzed compounds with these rules. The abbreviation of properties is in agreement with those in Table 1.

Rule	Acceptable ranges for compounds' properties	D1 enol	D1 keto	D2 enol	D2 keto
Lipinski	MW ≤ 500; MLPGP ≤ 4.15; HBA ≤ 10; HBD ≤ 5	yes	yes	yes	yes
Ghose	160 ≤ MW ≤ 480; -4 ≤ WLOGP ≤ 5.6;	yes	yes	yes	yes
Veber	40 ≤ MR ≤ 130; 20 ≤ atoms ≤ 70	yes	yes	yes	yes
Egan	NRB ≤ 10; TPSA ≤ 140	yes	yes	yes	yes
Muegge	WLOGP ≤ 5.88; TPSA ≤ 131.6	yes	yes	yes	yes

Table S2. Predicted pharmacokinetic properties of analyzed compounds grouped under absorption, distribution, metabolism, excretion, and toxicity.

	Property	D1 enol	D1 keto	D2 enol	D2 keto
Absorption	CaCo2 permeability (log Papp in 10^{-6} cm/s)	0.598	0.382	1.106	1.02
	Intestinal absorption human (% absorbed)	78.154	83.25	89.571	90.805

Distribution	Steady state volume of distribution -VDss (log L/kg)	-0.139	-0.285	-0.09	-0.247
	BBB permeability (log BB)	-0.772	-0.19	-0.679	-0.207
	CNS permeability (log PS)	-2.459	-2.414	-2.425	-2.332
Metabolism	CYP2D6 substrate (Yes/No)	No	No	No	No
	CYP3A4 substrate (Yes/No)	Yes	Yes	No	Yes
	CYP1A2 inhibitor (Yes/No)	No	No	Yes	Yes
	CYP2C19 inhibitor (Yes/No)	Yes	Yes	Yes	Yes
	CYP2C9 inhibitor (Yes/No)	Yes	Yes	Yes	Yes
	CYP2D6 inhibitor (Yes/No)	No	No	No	No
	CYP3A4 inhibitor (Yes/No)	Yes	Yes	Yes	Yes
Excretion	Total clearance (log ml/min/kg)	0.36	0.199	0.205	0.041
	Renal OCT2 substrate (Yes/No)	No	No	No	No

Table S3. The toxicity profile of compounds as predicted by ProTox-II web server. For each target we used "I" for inactive and "A" for active. The probability is written in brackets.

Classification	**Target**	**Prediction (Probability)**			
		D1 enol	**D1 keto**	**D2 enol**	**D2 keto**
Organ toxicity	Hepatotoxicity	I (0.75)	I (0.60)	I (0.63)	I (0.65)
Toxicity endpoints	Carcinogenicity	I (0.94)	I (0.65)	I (0.69)	I (0.64)
	Immunotoxicity	I (0.98)	I (0.97)	I (0.96)	I (0.90)
	Mutagenicity	I (0.88)	I (0.74)	I (0.81)	I (0.82)
	Cytotoxicity	I (0.80)	I (0.71)	I (0.88)	I (0.93)
Tox21-Nuclear receptor signaling pathways	Aryl hydrocarbon Receptor (AhR)	I (0.98)	I (0.65)	I (0.74)	I (0.62)
	Androgen Receptor (AR)	I (0.88)	I (0.94)	I (0.82)	I (0.86)
	Androgen Receptor Ligand Binding Domain (AR-LBD)	I (0.86)	I (0.97)	I (0.99)	I (0.99)
	Aromatase	I (0.86)	I (0.88)	I (0.84)	I (0.86)
	Estrogen Receptor Alpha (ER)	I (0.67)	I (0.67)	A (0.67)	A (0.70)
	Estrogen Receptor Ligand Binding Domain (ER-LBD)	I (0.84)	I (0.97)	I (0.51)	I (0.52)
	Peroxisome Proliferator Activated Receptor Gamma (PPAR-Gamma)	I (0.92)	I (0.92)	I (0.78)	I (0.78)

	Nuclear factor (erythroid-derived 2)-like 2/antioxidant responsive element (nrf2/ARE)	I (0.75)	I (0.84)	I (0.73)	I (0.71)
	Heat shock factor response element (HSE)	I (0.94)	I (0.84)	I (0.73)	I (0.71)
Tox21-Stress response pathways	Mitochondrial Membrane Potential (MMP)	I (0.98)	I (0.58)	A (0.62)	A (0.78)
	Phosphoprotein (Tumor Suppressor) p53	I (0.88)	I (0.81)	I (0.65)	I (0.66)
	ATPase family AAA domain-containing protein 5 (ATAD5)	I (0.80)	I (0.88)	I (0.75)	I (0.66)

Figure S1. The binding probability of compounds to 18 crystal structures belonging to the following nuclear receptors: AR – androgen receptor, ERα – estrogen receptor alpha, ERβ – estrogen receptor beta, GR – glucocorticoid receptor, LXRα – liver X receptor alpha, LXRβ – liver X receptor beta, MR – mineralocorticoid receptor, PPARα – peroxisome proliferator-activated receptor alpha, PPARβ – peroxisome proliferator-activated receptor beta, PPARγ – peroxisome proliferator-activated receptor gamma, PR – progesterone receptor, RXRα – retinoid X receptor alpha, TRα – thyroid hormone receptor

alpha, TRβ – thyroid hormone receptor beta. The high binding probability is marked with red (sensitivity < 0.25), orange (0.25 < sensitivity < 0.5) and yellow (0.5 < sensitivity < 0.75) were used to highlight decreasing probabilities, and green (sensitivity > 0.75) is used to mark the low binding probability. The docking scores are labeled next to each receptor, more negative values being associated with a higher affinity binding. Results were generated by the Endocrine Disruptome web server [20].

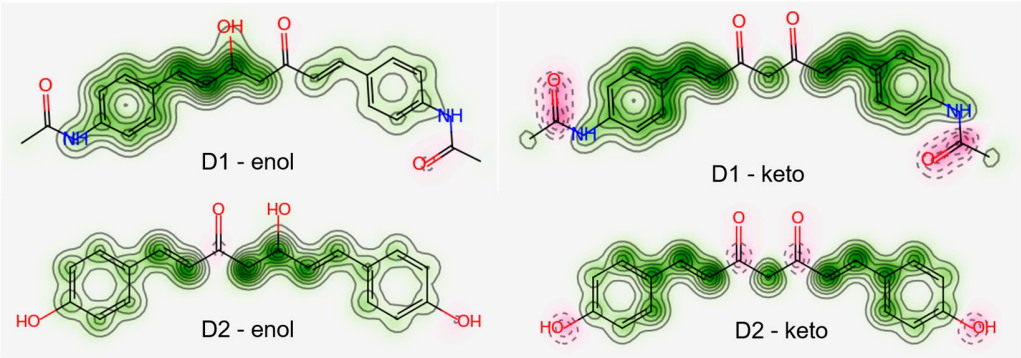

Figure S2. The structures of D2 and D3 compounds are colored according to the contributions of their atoms or fragments to hERG blockade. The fragments with a positive contribution are colored with green. Higher positive contributions are shown with a more intense green color and with more contour lines. The negative contributions to the blockade are highlighted in pink. Images were generated by Pred-hERG4.2 web server.

Table S4. Molinspiration bioactivity scores v2021.03.

Bioactivity	**Predicted scores**			
	D1 enol	D1 keto	D2 enol	D2 keto
G-protein coupled receptor (GPCR) ligand	0.04	-0.10	0.17	0.00
Ion channel modulator	-0.17	-0.25	-0.05	-0.14
Kinase inhibitor	-0.27	-0.28	-0.26	-0.26
Nuclear receptor ligand	-0.06	-0.07	0.24	0.25
Protease inhibitor	0.04	-0.11	0.08	-0.08
Enzyme inhibitor	0.23	-0.02	0.45	0.15