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Supplementary Materials

Chalcones as Promising Antitumor Agents by Targeting the p53 Pathway: An Overview and New Insights in Drug-Likeness

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Table S1. Natural chalcones with interference in p53 pathway.

Chalcones	Cellular/molecular mechanisms	Cell line [Ref]/ Cytotoxic effect (IC_{50})/ p53 activation (Method)
8	Increase of p53, Fas-ligand, Fas-receptor, Bax and NOXA expression, p21/WAF1 and Bak levels, and caspase-9 activity Decrease of Bcl-2 and Bcl-X_L, PCNA, MDM2, p-GSK-3β, p-Akt, p-c-Raf and p-PTEN expression levels	A549 [1] IC_{50} = n.d. p53 activity = 20 μM (ELISA) Hep G2 [2] IC_{50} = n.d. p53 activity = 10 μg/mL (ELISA) HeLa [3] IC_{50} = 9.8 μM p53 activity = 10 μM (ELISA) Caki [4] IC_{50} = n.d. p53 activity = 50 μM (Western Blot)
Flavokawin A (9)	Increase in p21/WAF1, p27/KIP1, Cdc25C and CDK1 levels Decrease of CDK2, CDK1, Myt1 and Wee1 levels	HT1197 [5] IC_{50} = 7.9 μM p53 activity = 40 μM (Flow Cytometry)
10	Increase of p53, Fas, FasL, and Bcl-2 family proteins expression Increase of caspases -3, -8 and -9 expression PARP cleavage Release of cytochrome C	SW 872 [6] IC_{50} = 3.8 μM p53 activity = 5 μM (Western Blot)
HTMC (11)	Inhibition of phosphorylation of cdc2 (Tyr15 and Tyr161) and Rb (Ser795 and Ser807/811) Increase of p53 and p21 expression	A549 [7] IC_{50} = 47 μM p53 activity = 6.25 μM (Western Blot)
Flavokawain B (12)	Increase in p53, p21/WAF1, Wee1 and Bax levels Activation of caspase-3,-8 and -9 PARP and Bid cleavage Decrease of Bcl-2, cyclins A and B1, Cdc2 and Cdc25C levels Release of cytochrome *c*	KB [8] IC_{50} = 30.0 μg/mL p53 activity = 5 μg/mL (Western Blot)
13	Suppression of ERK1/2 and p90RSK kinases Inhibition of phosphorylation and activation of the CREB protein Increase in p53 and p21 expression Down-regulation of cyclin D1	A549 [9] IC_{50} = 20.9 μM p53 activity = 10 μM (Western Blot)
14	Decrease of Sp1, Sp3 and Sp4 expression Down-regulation of Top2A and MMP-2 transcripts (Sp1 target genes), and MN1 Up-regulation of Gadd45A, p21 DNAJB1, ATF3 (p53 target genes), TP53AIP1 and PLK2 Increase of p53 expression Decrease of β-catenin expression Cell cycle arrest in G0/G1 phase	U2OS [10] IC_{50} = n.d. p53 activity = 50 μM (Western Blot; RNA-Seq, RT-PCR and Western Blot) HCT-116 [11] IC_{50} = n.d. p53 activity = 50 μM (Western Blot) FaDu [11] IC_{50} = n.d. p53 activity = 50 μM (Western Blot) SJSA1 [11] IC_{50} = n.d. p53 activity = 50 μM (Western Blot) HuH7.5 [12] IC_{50} = 23.66 μM

		p53 activity = 23.66 μM (Immunocyto-chemical assay)

Table S2. Synthetic chalcones and their analogues with interference in p53 pathway.

Chalcones	Cellular/molecular mechanisms	Cell line [Ref]/ Cytotoxic effect (IC_{50})/ p53 activation (Method)
Chalcone derivatives with phenyl rings: α, β-nonsubstituted chalcones		
15	Increase of caspase-3 and -9 expressions Increase of PARP, cytochrome c, calpain-1 and -2 expressions Phosphorylation of histone H2AX, checkpoint kinases 2 and of p53	SCC4 [13] IC_{50} = 3 μM p53 activity = 1 μM (Western Blot)
16	Increase of Bax expression Decrease of Bcl-2 and Bcl-xL Inhibition of phosphorylation of STAT3 and tyrosine kinases c-Src Down-regulation of cyclin D1 and c-myc Up-regulation of p53 and PTEN	A2780 [14] IC_{50} = 3.5 μM p53 activity = 10 μM (Western Blot)
SKLB-M8 (17)	Increase of cleaved Caspase-3 Decrease of cleaved procaspase-9 levels and of p-mTOR expression Activation of PARP Down-regulation of AKT and cdc2 Up-regulation of cyclin B1 and p53	A2058 [15] IC_{50} = 0.07 μM p53 activity = 0.5 μM (Western Blot) CHL-1 [15] IC_{50} = 0.25 μM P53 activity = 0.5 μM (Western Blot)
18	Increase of p53 and caspase-3 levels Pro-caspase 3 cleavage	SK-N-SW [16] IC_{50} = 2.03 μM P53 activity = 5 μM (Western Blot)
SSE14106 (19)	Accumulation of p53	HCT116 [17] IC_{50} = n.d. p53 activity = 6.25 μM (Western Blot)
SSE14105 (20)	Accumulation of p53	HCT116 [17] IC_{50} = n.d. p53 activity = 12.5 μM (Western Blot)
21	Increase of p53, p21 and of caspases -7, -8 and -9 expression and of TNF-R1, Fas-L and Bax levels Externalization of phosphatidylserine Release of cytochrome *c* ROS formation Decrease of Bcl-2 expression	MCF-7 [18] IC_{50} = 21 μM p53 activity = 21 μM (Flow Cytometry)
22	Increase of p53, p21, Bax and Bcl-2 expression	BGC-823 [19] IC_{50} = n.d. p53 activity = 10 μM (*in vitro*); 15 μM (*in vivo*) (Western Blot)
23	upregulation of p53 expression	MCF-7 [20] IC_{50} = 13.2 ± 3.5 μM p53 activity = 10 μM (Western Blot)
24	Formation of free radicals (phenoxide radicals) Increase expression of p53 and caspases-3 and -9	HepG2 [21] IC_{50} = 10.3 ± 1.8 μM p53 activity = 100 nM (qRT-PCR)
25	Cell cycle arrest at the G2/M phase ROS formation Induced PARP cleavage	SK-Mel-28 [22] IC_{50} = 1.368 μM p53 activity = 5 μM (RNA-seq)

	Increased of BAX expression Decreased of Bcl-2 expression	
Chalcone derivatives with phenyl rings: α-substituted chalcones		
CH027 (26)	Increase in p53 activity Up-regulation of $p21^{Cip1}$ PARP cleavage	LNCaP [23] IC_{50} = 13 nM p53 activity = 10 nM (Western Blot) 22Rv1 [23] IC_{50} = 15 nM p53 activity = 10 nM (Western Blot)
27	Cell cycle arrest in S and G2/M phase Activation of PARP Up-regulation of p53	HCC1954 [24] IC_{50} = 0.63 ± 0.06 μM HCT116 [24] IC_{50} = 0.69 ± 0.04 μM p53 activity = 1.56 μM (Western Blot)
28	Cell cycle arrest in S and G2/M phase PARP cleavage Up-regulation of p53	HCC1954 [24] IC_{50} = 0.63 ± 0.06 μM HCT116 [24] IC_{50} = 0.69 ± 0.04 μM p53 activity = 1.56 μM (Western Blot)
Chalcone derivatives with simple aryl ring		
29	Decrease of Bcl-2 expression Increase of Bax expression Up-regulation of caspase-9, p53 and p21 Down-regulation of survivin	HT-29 [25] IC_{50} = 13.4 μM p53 activity = 20 μM (RT-PCR)
30	Decrease of Bcl-2 expression Increase of Bax expression Up-regulation of caspase-9 and p53 Down-regulation of survivin	HT-29 [25] IC_{50} = 19.5 μM p53 activity = 40 μM (RT-PCR)
31	Increase of p53 and caspase-3 levels Pro-caspase 3 cleavage	SK-N-SW [26] IC_{50} = 1.53 μM p53 activity = 5 μM (Western Blot)
32	upregulation of p53 expression	MCF-7 [20] IC_{50} = 15.7 ± 5.9 μM p53 activity = 10 μM (Western Blot) MDA-MB-231 [20] IC_{50} = 33.9 ± 7.1 μM
Chalcone derivatives with fused aryl ring		
33	Increase in cyclins D1, A and E1, CDK4 and IKKα levels Decrease in NF-κB Up-regulation of caspase-9, p53, p21, p27 and chk2	MCF-7 [27] IC_{50} = n.d. p53 activity = 4 μM (Western Blot)
34	Increase in cyclins D1, A and E1, CDK4 and IKKα levels Decrease in NF-κB Up-regulation of caspase-9, p53, p21, p27 and chk2	MCF-7 [27] IC_{50} = n.d. p53 activity = 4 μM (Western Blot)
35	Increase in p53 and Bax expression and in caspase-9 activity	L-1210 [28] IC_{50} = 54 μM p53 activity = 100 μM (Flow Cytometry)
36	PARP and caspase-7 cleavage Increase of p53, γ-H2AX, p-Chk2 and Bax levels	HCT116 [29] IC_{50} = n.d.

		p53 activity = 10 μM (Western Blot) SW620 [30] IC_{50} = 14.5 μM P53 activity = 10 μM (Western Blot)
S009-131 (37)	Increase of cytochrome c release Increase of Bax, Bak and p53 expression Decrease of Bcl-2 and Bcl-xL expression Increase of p53 expression Cleavage of caspase-7 and -9	C33A [31] IC_{50} = 4.7 ± 1.0 μM p53 activity = 4.7 μM (Western Blot)
N9 (38)	Inhibition in the expression of cyclins A and E Decrease of CDK2 and CDK6 expression and of MDM2 levels Rb inactivation ROS formation Increase of Bax, p53 and p21 levels Caspase-9 cleavage	U87-MG [32] IC_{50} = 0.72 μg/mL p53 activity = 0.1 μg/mL (Western Blot)
HMP (39)	Caspase-7 cleavage PARP cleavage γ-H2AX formation ROS formation Up-regulation of p53 and Egr-1	HCT116 [33] IC_{50} = n.d. p53 activity = 50 μM (Western Blot)
40	Inhibition of EGFR and STAT3 axis Increase of p53, p21 and Bax levels Decrease of Bcl-2 and procaspase-9 levels	A549 [34] IC_{50} = 2.9 ± 0.3 μM p53 activity = 2 μM (RT-PCR, Western Blot)
41	Inhibition of EGFR and STAT3 axis Increase of p53, p21 and Bax levels Decrease of Bcl-2 and procaspase-9 levels	A549 [34] IC_{50} = 3.9 ± 0.4 μM p53 activity = 2 μM (RT-PCR, Western Blot)
42	Inhibition of EGFR and STAT3 axis Increase of p53, p21 and Bax levels Decrease of Bcl-2 and procaspase-9 levels	A549 [34] IC_{50} = 7.2 ± 0.4 μM p53 activity = 2 μM (RT-PCR, Western Blot)
43	Up-regulation of E-cadherin Downregulation of MMP-2 and MMP-9 proteolytic activities, and of vimetin, N-cadherin and β-catenin mRNA levels Decrease of *Slug* gene expression	U2OS [35] IC_{50} = n.d. p53 activity = 27 μM (Western Blot)
44	Up-regulation of E-cadherin Downregulation of MMP-2 and MMP-9 proteolytic activities, and of vimetin, N-cadherin and β-catenin mRNA levels Decrease of *Slug* gene expression	U2OS [35] IC_{50} = n.d. p53 activity = 27 μM (Western Blot)
45	Up-regulation of Bax, p53 and caspase-3 Down-regulation of BCL2, MMP1 and CDK4	MCF-7 [36] IC_{50} = 50.05 μg/mL p53 activity = 50.05 μg/mL (RT-PCR)
46	Up-regulation of Bax, p53 and caspase-3 Down-regulation of BCL2, MMP1 and CDK4	MCF-7 [36] IC_{50} = 27.15 μg/mL p53 activity = 27.15 μg/mL (RT-PCR)
47	Cell cycle arrest in G2/M phase Up-regulation of p53 and p21 expression Decreased of cdc2 levels	HCT116 [37] IC_{50} = 1.34 ± 0.12 μM p53 activity = 5 μM
48	Cell cycle arrest in G2/M phase Up-regulation of p53 and p21 expression Decreased of cdc2 levels	HCT116 [37] IC_{50} = 1.63 ± 0.15 μM p53 activity = 5 μM

49	Up-regulation of BAX, p53, and caspases -3, and -9 expression Decreased of Bcl-2, CDK4, andMMP1 expression Cell cycle arrest at the G2/M phase Increase of cytochrome c release	A549 [38] IC_{50} = 19 μg/mL p53 activity = 19 μg/mL (RT-PCR)
50	Up-regulation of BAX, p53, and caspases -3, and -9 expression Decreased of Bcl-2, CDK4, andMMP1 expression Cell cycle arrest at the G2/M phase Increase of cytochrome c release	A549 [38] IC_{50} = 12 μg/mL p53 activity = 12 μg/mL (RT-PCR)
Chalcone analogues		
AM-146 (51)	Accumulation of p21 Inhibition of 20S proteasome activity Up-regulation of p53, $p27^{Kip1}$ and $p16^{Ink4A}$ Suppression of UCH-L1, UCH-L3, USP2, USP5 and USP8 activity	HCT116 [39] IC_{50} = 1.49 μM P53 activity = 1 μM (Western Blot) HCT116 [40] IC_{50} = 2.8 μM P53 activity = 2.8 μM (MTT) MDA MB 231 [41] IC_{50} = 10.71 μM p53 activity = 5 μM (Western Blot)
EF24 (52)	Upregulation of PTEN Decrease of Akt Increase of p53 expression	CR [42] IC50 = 0.65 μM p53 activity = 2 μM (Western Blot)
HO-3867 (53)	Upregulation of p53 and p21 Decrease of cdk2, Cyclin-A, STAT3 (Tyr705) and JAK1 phosphorylation Increase of Fas/CD95 Activation of caspase-3 and -8	A2780 [43] IC50 = n.d. p53 activity = 10 μM (Western Blot)
RAMB1 (54)	Increase in p53 levels and caspase-3 activity Decrease of cyclin D1 expression PARP cleavage	CaSki [44] IC_{50} = n.d. p53 activity = 2 μM (Western Blot)
HMNES (55)	Decrease of tyrosine-kinase activity, Top-IIα and Top IIβ and Bcl-2 expression Caspase-3 and -9 cleavage Up-regulation of p53 and Bax Up-regulation of Bax	Capan-1 [45] IC_{50} = 2.9 μM p53 activity = 1.6 μM (Western Blot)

Table S3. Chalcones as disruptors of the p53-MDM2 interaction

Chalcone	Method [Ref]/ Cytotoxic effect (IC_{50}, Cell line)
56	ELISA [46]: IC_{50} = 206 μM
57	ELISA [46]: IC_{50} = 49 μM
58	ELISA [46]: IC_{50} = 250 μM
59	ELISA [46]: IC_{50} = 117 μM
60	ELISA [46]: IC_{50} = n.d.
61	ELISA [46]: IC_{50} = n.d.
62	Yeast screening assay [47] 20 % reversion of MDM2 effect at 5 μM (% of solvent) GI_{50} = 65 μM (HCT116)
63	Yeast screening assay [47] 40 % reversion of MDM2 effect at 5 μM (% of solvent) GI_{50} = 4 μM (HCT116)
CPI-7c (64)	RT-PCR [48] IC_{50} = n.d.
65	Co-IP [49] At 0.1 μM IC_{50} = 0.06 ± 1.45 μM (HCT116)
66	Co-IP [49] At 0.1 μM IC_{50} = 0.04 ± 0.02 μM (HCT116)
67	Co-IP [49] At 0.5 μM IC_{50} = 0.58 ± 0.11 μM (HCT116)
68	Yeast screening assay [50] ~95% reversion of MDM2 effect at 10 μM (% of control) GI_{50} = 10.6 μM (HCT116)
69	Yeast screening assay [50] ~70% reversion of MDM2 effect at 10 μM (% of control) GI_{50} = 50.0 μM (HCT116)
70	Yeast screening assay [50] ~75% reversion of MDM2 effect at 10 μM (% of control) GI_{50} = 2.1 μM (HCT116)
71	Yeast screening assay [50] ~80% reversion of MDM2 effect at 10 μM (% of control) GI_{50} = 11.7 μM (HCT116)
72	Yeast screening assay [50] : ~80% reversion of MDM2 effect at 10 μM (% of control) GI_{50} = 29.5 μM (HCT116)
73	Yeast screening assay [51]: 79.4 % growth inhibition (% of p53 effect) GI_{50} = 2.6 μM (HCT116 $p53^{+/+}$) GI_{50} = 2.1 μM (NCI-H460)

74	Yeast screening assay [51]: 97.2 % growth inhibition (% of p53 effect) GI_{50} = 5.9 μM (HCT116 $p53^{+/+}$) GI_{50} = 3.3 μM (NCI-H460)
75	Yeast screening assay [51]: 63.7 % growth inhibition (% of p53 effect)
76	Yeast screening assay [51]: 68.8% growth inhibition (% of p53 effect)
77	Yeast screening assay [51]: 77.9% growth inhibition (% of p53 effect)
78	Yeast screening assay [51]: 95.2% growth inhibition (% of p53 effect)
79	Yeast screening assay [51]: 78.3% growth inhibition (% of p53 effect)
80	Yeast screening assay [51]: 97.0% growth inhibition (% of p53 effect)

Table S4. Molecular descriptors of compounds reported as disruptors of the p53-MDM2 interaction.

Molecule	Formula	MW	Nº HA	Nº AHA	Far	Fsp^3	RB	Nº HBA	Nº HBD
Selected representative small-molecules targeting MDM2 in clinical trials									
1	$C_{38}H_{48}Cl_2N_4O_4S$	727.78	49	18	0.37	0.47	12	6	0
2	$C_{34}H_{38}Cl_2FN_3O_4$	642.59	44	12	0.27	0.56	6	6	3
3	$C_{28}H_{35}Cl_2NO_5S$	555.41	38	23	0.61	0.27	6	7	0
4	$C_{26}H_{24}Cl_2N_6O_4$	562.5	38	12	0.32	0.52	6	5	4
5	$C_{29}H_{34}Cl_2FN_3O_3$	618.53	42	12	0.29	0.53	5	7	4
6	$C_{30}H_{34}Cl_2FN_5O_4$	616.48	42	18	0.43	0.32	9	8	3
7	$C_{31}H_{29}Cl_2F_2N_3O_4$	568.55	37	12	0.32	0.5	9	5	1
Mean	-	613.12	41.43	15.29	0.37	0.45	7.57	6.29	2.14
Chalcones reported as disruptors of the p53-MDM2 interaction									
56	$C_{17}H_{13}ClO_4$	316.74	22	12	0.55	0.06	6	4	1
57	$C_{17}H_{12}Cl_2O_4$	351.18	23	12	0.52	0.06	6	4	1
58	$C_{19}H_{17}ClO_5$	360.79	25	12	0.48	0.16	6	5	1
59	$C_{17}H_{12}Cl_2O_5$	367.18	24	12	0.5	0.06	6	5	1
60	$C_{17}H_{12}Cl_2N_4O_2$	375.21	25	17	0.68	0.06	6	5	1
61	$C_{21}H_{14}Br_2O_4$	490.14	27	16	0.59	0.05	6	4	1
62	$C_{20}H_{22}O_7$	374.38	27	12	0.44	0.25	8	7	1
63	$C_{25}H_{30}O_7$	442.5	32	12	0.38	0.32	11	7	0
64	$C_{22}H_{18}N_2O_3$	358.39	27	19	0.70	0.09	5	4	1
65	$C_{15}H_{11}N_3O$	249.27	19	15	0.79	0	3	3	1
66	$C_{16}H_{11}ClN_2O$	282.72	20	15	0.75	0	3	2	1
67	$C_{17}H_{14}N_2O_2$	278.31	21	15	0.71	0.06	4	3	1
68	$C_{18}H_{18}O_5$	314.33	23	12	0.52	0.17	6	5	1
69	$C_{19}H_{20}O_6$	344.36	25	12	0.48	0.21	7	6	1
70	$C_{22}H_{23}BrO_4$	431.32	27	12	0.44	0.23	8	4	0
71	$C_{24}H_{28}O_6$	412.48	30	12	0.4	0.29	10	6	0
72	$C_{24}H_{28}O_6$	412.48	30	12	0.4	0.29	9	6	1
73	$C_{22}H_{26}O_6$	386.44	28	12	0.43	0.32	9	6	1
74	$C_{21}H_{24}O_5$	356.41	26	12	0.46	0.29	8	5	1
75	$C_{21}H_{24}O_5$	356.41	26	12	0.46	0.29	8	5	1
76	$C_{22}H_{26}O_6$	386.44	28	12	0.43	0.32	9	6	1
77	$C_{22}H_{18}O_4$	346.38	26	18	0.69	0.05	6	4	2
78	$C_{21}H_{24}O_6$	372.41	27	12	0.44	0.29	8	6	2
79	$C_{21}H_{24}O_6$	372.41	27	12	0.44	0.29	8	6	2
80	$C_{19}H_{20}O_4$	312.36	23	12	0.52	0.21	6	4	2
Mean	-	362.04	25.52	13.24	0.53	0.18	6.88	4.88	1.04

Table S5. Physicochemical properties of compounds reported as disruptors of the p53-MDM2 interaction.

Compound ID	TPSA	Log P (iLOGP)	Log P (XLOGP3)	Log P (WLOGP)	Log P (MLOGP)	Log P (SILICOS-IT)	Log P (Consensus)	Mean of Log P values	Log S (ESOL)	Log S (Ali)	Log S (SILICOS-IT)	Mean of Log S values
Selected representative small-molecules targeting MDM2 in clinical trials												
1	90.90	5.40	7.27	7.10	5.36	7.97	6.62	6.62	-8.41	-9.00	-12.13	-9.85
2	98.74	3.80	3.57	6.27	5.02	6.40	5.01	5.01	-5.88	-5.33	-9.99	-7.07
3	100.13	3.34	5.78	6.76	4.42	5.77	5.21	5.21	-6.65	-7.65	-8.22	-7.51
4	104.37	4.45	3.57	3.99	2.53	3.84	3.68	3.68	-5.58	-5.45	-7.92	-6.32
5	90.46	4.21	5.26	4.77	4.17	5.48	4.78	4.78	-6.48	-6.91	-9.09	-7.49
6	135.44	3.23	3.38	3.43	2.32	4.36	3.34	3.34	-5.69	-5.90	-9.02	-6.87
7	111.45	3.96	4.29	7.21	4.75	6.96	5.43	5.43	-6.09	-6.34	-10.56	-7.66
Mean	104.50	4.06	4.73	5.65	4.08	5.83	4.87	-	-6.40	-6.65	-9.56	-
Chalcones reported as disruptors of the p53-MDM2 interaction												
56	63.60	2.51	3.88	3.59	2.78	3.92	3.34	3.34	-4.26	-4.91	-5.07	-4.75
57	63.60	2.66	4.58	4.24	3.28	4.58	3.87	3.87	-4.89	-5.64	-5.66	-5.40
58	63.60	0.00	3.86	4.25	2.41	4.39	2.98	2.98	-4.47	-4.89	-5.47	-4.94
59	63.60	0.00	4.04	4.13	2.45	4.58	3.04	3.04	-4.64	-5.08	-5.66	-5.13
60	80.76	2.30	4.00	3.72	3.17	4.58	3.55	3.55	-4.79	-5.40	-6.88	-5.69
61	63.60	3.19	5.89	5.62	4.20	5.73	4.92	4.93	-6.63	-7.00	-7.68	-7.10
62	83.45	3.36	3.74	3.22	1.14	3.77	3.05	3.05	-4.32	-5.18	-4.96	-4.82
63	72.45	4.39	5.02	4.86	2.14	5.65	4.41	4.41	-5.30	-6.28	-6.48	-6.02
64	64.21	2.95	4.06	4.52	1.93	5.09	3.71	3.71	-4.81	-5.11	-7.35	-5.76
65	58.64	2.18	2.55	2.75	1.18	3.41	2.41	2.41	-3.38	-3.43	-5.1	-3.97
66	45.75	2.57	4.22	4	2.79	4.59	3.64	3.64	-4.61	-4.89	-6.08	-5.19
67	54.98	2.72	3.56	3.36	1.94	3.99	3.11	3.11	-4.07	-4.4	-5.59	-4.69
68	64.99	2.98	3.80	3.21	1.75	3.60	3.07	3.07	-4.17	-4.86	-4.74	-4.59
69	74.22	3.54	3.77	3.21	1.44	3.69	3.13	3.13	-4.24	-5.02	-4.85	-4.70
70	44.76	4.39	5.79	5.60	3.73	6.04	5.11	5.11	-5.96	-6.50	-6.96	-6.47
71	63.22	4.34	5.05	4.85	2.46	5.54	4.45	4.45	-5.21	-6.12	-6.38	-5.90

72	74.22	4.30	5.70	4.72	2.46	5.52	4.54	4.54	-5.69	-7.02	-6.07	-6.26
73	74.22	4.10	5.11	4.17	2.11	5.03	4.10	4.10	-5.18	-6.41	-6.02	-5.87
74	64.99	3.95	5.14	4.16	2.44	4.94	4.13	4.13	-5.10	-6.25	-5.91	-5.75
75	64.99	3.71	5.14	4.16	2.44	4.94	4.08	4.08	-5.10	-6.25	-5.91	-5.75
76	74.22	4.11	5.11	4.17	2.11	5.03	4.11	4.11	-5.18	-6.41	-6.02	-5.87
77	66.76	3.00	5.00	4.31	2.99	4.52	3.96	3.96	-5.25	-6.14	-6.43	-5.94
78	85.22	3.61	4.78	3.86	1.89	4.48	3.72	3.72	-4.96	-6.30	-5.33	-5.53
79	85.22	3.75	4.78	3.86	1.89	4.48	3.75	3.75	-4.96	-6.30	-5.33	-5.53
80	66.76	3.03	4.84	3.85	2.55	4.31	3.71	3.72	-4.82	-5.98	-5.11	-5.30
Mean	67.28	3.11	4.54	4.10	2.39	4.66	3.76	-	-4.88	-5.67	-5.88	-

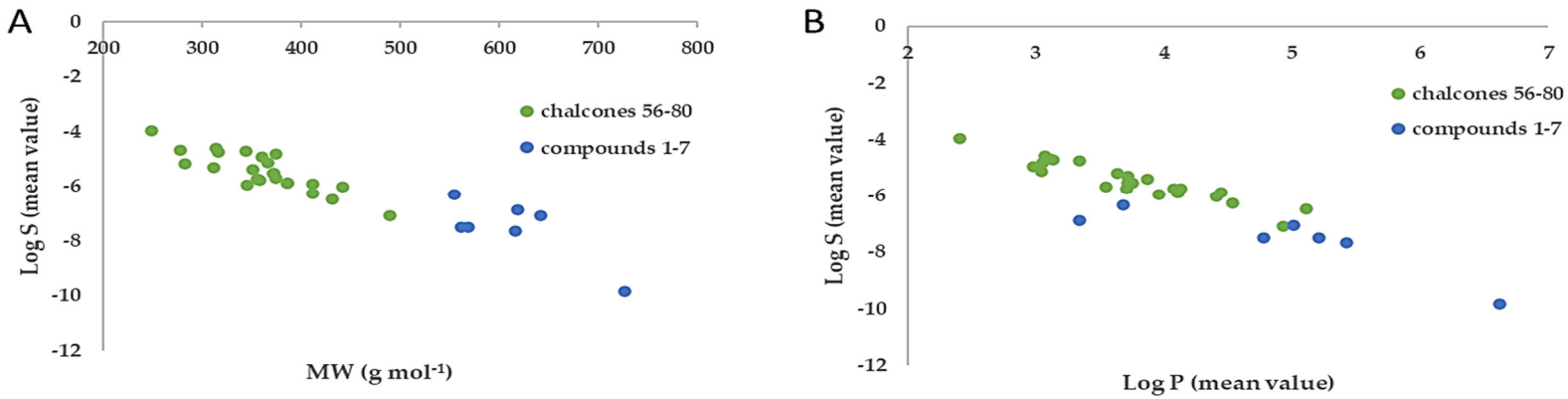

Figure S3. (**A**) Log S *vs* molecular weight (MW) of compounds **1**-**7** and chalcones **56**-**80**. For Log S mean values of all tested methods were taken into consideration. (**B**) Log S *vs* Log P of compounds **1**-**7** and chalcones **56**-**80**. For Log S and Log P mean values of all tested methods were taken into consideration.

Compound ID	1	2	3	4	5	6	7
Lipinski							
Ghose							
Veber							
Egan							
Muegge							

Full compliance
1 violation
>1 violation

Compound ID	56	57	58	59	60	61	62	63	64	65	66	67	69	69	70	71	72	73	74	75	76	77	78	70	80
Lipinski																									
Ghose																									
Veber																									
Egan																									
Muegge																									

Figure S4. Color map of the compliance with the rules of Medicinal Chemistry. (For interpretation of the references to color in this figure legend. the reader is referred to the Web version of this article.)

Table S6. Predictive pharmacokinetic properties of compounds reported as disruptors of the p53-MDM2 interaction.

	Pharmacokinetic properties							
Compound ID	**GI absorption**	**BBB permeant**	**Pgp substrate**	**CYP1A2 inhibitor**	**CYP2C19 inhibitor**	**CYP2C9 inhibitor**	**CYP2D6 inhibitor**	**CYP3A4 inhibitor**
Selected representative small-molecules targeting MDM2 in clinical trials								
1	Low	No	Yes	No	No	No	Yes	Yes
2	Low	No	Yes	No	No	No	No	Yes
3	Low	No	Yes	No	Yes	No	No	Yes
4	High	No	Yes	No	No	Yes	No	Yes
5	High	No	Yes	No	No	No	No	Yes
6	Low	No	Yes	No	No	No	No	Yes
7	Low	No	Yes	No	No	No	Yes	Yes
Chalcones reported as disruptors of the p53-MDM2 interaction								
56	High	Yes	No	Yes	Yes	Yes	No	No
57	High	Yes	No	Yes	Yes	Yes	No	Yes
58	High	Yes	No	No	No	No	No	Yes
59	High	Yes	No	No	No	No	No	No
60	High	No	No	Yes	Yes	Yes	No	No
61	High	No	No	Yes	Yes	Yes	No	No
62	High	No	No	No	No	Yes	No	Yes
63	High	No	No	No	No	Yes	Yes	Yes
64	High	Yes	No	Yes	Yes	Yes	No	Yes
65	High	Yes	No	Yes	Yes	No	No	No
66	High	Yes	No	Yes	Yes	Yes	No	No
67	High	Yes	No	Yes	Yes	Yes	Yes	No
68	High	Yes	No	Yes	Yes	Yes	No	Yes

69	High	Yes	No	No	Yes	Yes	No	Yes
70	High	Yes	No	Yes	No	Yes	Yes	Yes
71	High	Yes	No	No	No	Yes	Yes	Yes
72	High	No	No	No	No	Yes	No	Yes
73	High	Yes	No	No	No	Yes	Yes	Yes
74	High	Yes	No	Yes	Yes	Yes	Yes	Yes
75	High	Yes	No	Yes	Yes	Yes	Yes	Yes
76	High	Yes	No	No	No	Yes	Yes	Yes
77	High	Yes	No	Yes	Yes	Yes	Yes	Yes
78	High	No	No	No	No	Yes	No	Yes
79	High	No	No	No	No	Yes	No	Yes
80	High	Yes	No	Yes	Yes	Yes	Yes	Yes

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