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Synthesis of chalcones and *in vitro* and *in silico* evaluation for *Helicobacter pylori* and gastric adenocarcinoma cells

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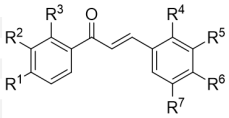
ABSTRACT

Helicobacter pylori is a gram-negative bacterium that colonizes the human stomach and is a major risk factor for the development of inflammatory gastrointestinal diseases, including cancer[1,2], which is why it is classified as group 1 carcinogen by World Health Organization[3]. NF-kB and MAPK pathways are triggered by *H. pylori* infection[4–6], specially cagA$^+$ strains, and are usually overexpressed in cancer. The objective of this study was to synthesize 10 hydroxylated and methoxylated chalcones and evaluate their anti-*H. pylori* and gastric antitumor effects. The chalcones were synthesized through *Claisen-Schmidt*[7,8] condensation within yields of 15-52%, then characterized by ^{1}H and ^{13}C Nuclear Magnetic Resonance and Mass Spectrometry. Predictive *in silico* data revealed possibility of anti-*H. pylori*, anti-inflammatory and MMP-9 inhibition for the chalcones. Three of the ten chalcones (**1**, **6**, **7**) showed strong *H. pylori* growth inhibition results (MIC and MBC ranging from 1-2 µg/mL). Compound **7** also presented significant MMP-9 inhibition docking score and CI_{50} for AGS cells (32.25 ± 5.43 µM). Then, these results reveal that compound **7** is promising as a possible drug for *H. pylori* treatment, that may act synergically reducing the inflammatory response and the possibilities for developing gastric tumor.

Compound	R^1	R^2	R^3	R^4	R^5	R^6	R^7	MIC (µg/mL)	MBC (µg/mL)	L929 IC_{50} (µM)	AGS IC_{50} (µM)	SI	S (kcal mol^{-1})
1	-OH	-H	-OH	-H	-H	-OMe	-H	1	2	177.30 ± 6.81 ****	48.21 ± 1.04	3.60 **	-7,26
2	-OMe	-H	-OH	-OMe	-H	-H	-H	4	8	352.05 ± 7.46 ****	55.92 ± 12.84	6.30 ****	-7,37
3	-OMe	-H	-OH	-H	-H	-OMe	-H	2	4	92.19 ± 16.21 ****	108.58 ± 16.36 ****	0.85	-7,63
4	-OMe	-H	-OH	-OMe	-H	-OMe	-H	2	4	135.81 ± 9.35 ****	186.39 ± 14.70 ****	0.73	-7,75
5	-OMe	-H	-OH	-OMe	-H	-H	-Br	4	8	233.58 ± 28.69 ****	32.49 ± 0.36	7.19 ****	-7,82
6	-OMe	-H	-OH	-Cl	-H	-H	-H	2	2	100.34 ± 10.15 ***	53.89 ± 3.88	1.86	-7,03
7	-OMe	-OMe	-OMe	-H	-H	-H	-H	2	2	84.03 ± 1.01 ***	32.25 ± 5.43	2.61	-7,91
8	-H	-	-	-	-	-	-	4	8	95.55 ± 0.36 ***	25.34 ± 0.47	3.77 **	-7,31
9	-OMe	-	-	-	-	-	-	8	16	43.18 ± 9.46	135.74 ± 12.35 ****	0.32	-7,31
10	-Cl	-	-	-	-	-	-	8	8	303.67 ± 9.36 ****	28.70 ± 14.22	10.58 ****	-7,40
amoxicilin	-	-	-	-	-	-	-	0.0625	0.125	-	-	-	-
cisplatin	-	-	-	-	-	-	-	-	-	24.05 ± 6.04	39.59 ± 0.66	0.61	-
marimastat	-	-	-	-	-	-	-	-	-	-	-	-	-6,00

MIC: minimum inhibitory concetration; MBC: minimum bactericidal concentration; IC_{50}: Half-maximal inhibitory concentration; SI: selectivity index; ****: p < 0.0001; ***: p < 0.001; **: p < 0.01 compared to cisplatin; S: Ligand/receptor interaction energy of compounds against MMP-9 (lower is better);



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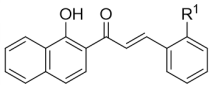

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