Original Article

Design, Synthesis and Biological Evaluation of 1,3-Diphenyl-3-(phenylthio)propan-1-ones as New Cytotoxic Agents

Maryam Bayanati, Soraya Shahhosseini, Farshad. H. Shirazi, Golrokh Farnam and Afshin Zarghi*

*Department of Pharmaceutical Chemistry, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran. #Protein Technology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. †Department of Toxicology and Pharmacology, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Abstract

Cancers in terms of morbidity and mortality are one of the major universal issues. New compounds of anticancer agents based on β-aryl-β-mercapto ketones scaffold possessing piperidinylethoxy or morpholinylethoxy groups were synthesized and evaluated as cytotoxic agents. Cytotoxic effects of synthesized compounds were measured against MCF-7, human ER-positive breast cancer cell lines, using MTT assay. The results indicated that all compounds had high cytotoxic activity on MCF-7 cancerous cells, even more than the reference drug Tamoxifen. Among them, compounds 3-(4-(2-morpholinoethoxy)phenyl)-1-phenyl-3-(phenylthio)propan-1-one (4a) and 1-(4-methoxyphenyl)-3-(3-(2-morpholinoethoxy)phenyl)-3-(phenylthio)propan-1-one (4h) had no significant cytotoxic effects on normal cells compared to Tamoxifen. Our results also indicated that adding tertiary amine basic side chain, found in Tamoxifen drug, to 1,3-diphenyl-3-(phenylthio)propan-1-ones improves the cytotoxic effects of these compounds on breast cancer cells.

Keywords: Synthesis; 1,3-Diphenyl-3-(phenylthio)propan-1-one; Docking study; Cytotoxic effect; MTT; MCF-7.

Introduction

Cancers in terms of morbidity and mortality are one of the major universal issues. The mortality of cancer is around one in six people, which is the second major cause of death (1). Many structural motifs have been studied for anticancer effects on cancer cells (2-6). Among them, 1, 3-diaryl-2-propen-1-ones have been thoroughly studied for their promising biological activities on this purpose (7-10). 1, 3-diaryl-2-propen-1-ones called chalcones demonstrated various biological activities including anticancer (11-14), anti-Alzheimer (15), antioxidant (16, 17) and antiproliferative (18-20) activities. So for the investigation of anticancer drugs, chalcones are very favorable structures to be explored. Structural adjustment leads to an increase in therapeutic efficacy and biological activity and also a decrease in side effects (21). Recently we reported new classes of potent acyclic chalcone compounds (Figure 1) with cytotoxicity effects (22-25).

Breast cancer has known as the most prevalent cancer in women among all types of cancers. On average, about one in eight women’s lifetimes is diagnosed with breast
cancer (26, 27). In this regard, the discovery and introduction of compounds used to treat breast cancer like Tamoxifen are essential. Tamoxifen is renowned for the non-steroidal selective estrogen receptor modulators (SERMs) family that are utilized extensively in early and progressed breast cancer clinical administration. Tamoxifen and many other SERMs, effectively could induce apoptosis and reduce the proliferation rate of cancer cells. SERMs have a flexible tertiary amine side chain that is thought to be responsible for their anticancer effects (28-30).

In our recent work, we have introduced a new ferrocene chalcone-based scaffold as SERMs which, apart from chalcone scaffold, also has the aminoethoxy typical side chain of SERMs. Our biological results exhibited that these compounds have cytotoxic effects with the ability to induce apoptosis (31). To find cytotoxic agents and consider chalcones as biologically active compounds against cancer cells and Tamoxifen as an anti-breast cancer compound, a new group of 1,3-diphenyl-3-(phenylthio)propan-1-ones were designed, synthesized, and evaluated, which possess tertiary amine moiety as typical pharmacophore of SERMs. The cytotoxic activities of these β-aryl-β-mercapto ketones compounds were evaluated against MCF-7 to investigate their cytotoxic effects.

**Experimental**

**General**

All chemicals, reagents, and solvents were obtained from Aldrich Chemical Co., Acros Co., and Merck AG Chemical Co. and used without more purification. Melting points were recorded with Thomas–Hoover capillary instrument. Infrared spectra were recorded on Cary 630 FTIR spectrometer using KBr pellets for solid samples and reported in $\nu_{\text{max}}$ (cm$^{-1}$) scale. NMR spectra were recorded with a Varian - INOVA 500MHz instrument using CDCl$_3$ as a solvent and trimethylsilane (TMS) as a standard internal reference. Chemical shifts are reported in ppm (δ) scale. The mass spectral measurements were obtained by a 6410 Agilent LC-MS triple quadrupole mass spectrometer (LC-MS) with an electrospray ionization (ESI) interface.

**Chemistry**

**General procedure for the synthesis of chalcones (3)**

At first, a sodium hydroxide, 10% (w/v)
aqueous solution was added (3 mL) to under stirring solution of ketone 1 (1 mmol) and substituted arylaldehyde containing aminoethoxy side chain 2 (1 mmol) in ethanol; and upon completion of the substrates (TLC), if the product was solid (3a-g) filtered, and washed with cold ethanol and dried to obtain the pure chalcone (Scheme 1). However, if the product was oily (3h-i), at first, the solvent was evaporated under vacuum, and then the product was extracted with ethyl acetate and water (1:1) (24).

General procedure for synthesis of ((N,N-dialkyaminoethoxy)phenyl)-1-phenyl-3-(phenylthio)propan-1-one derivatives (4a-i)

At first, 2.0 mmol of substituted chalcone was added to a stirred mixture of cinchonine (8.8 mg, 1.5% mol) in chloroform (4 mL), then 3 mmol of thiol was added to under stirring above mixture (32, 33). Stirring was continued until TLC showed completion of the reaction. Then, the solvents were evaporated in a vacuum. For solid products (4a-g) the residue was washed with hexane and crystallized in ethyl acetate. But for oily products (4h-i), the residue was first dissolved in methanol and then extracted with n-hexane, and the products were further purified by column chromatography using a chloroform:methanol solvent system (85%;15%).

3-(4-(2-morpholinoethoxy)phenyl)-1-phenyl-3-(phenylthio)propan-1-one (4a)
Yield, 89%; white powder; mp: 93-95 °C; IR (KBr): ν (cm⁻¹) (1677 CO); ¹H NMR (CDCl₃): 2.56 (t, 4H, morpholine -NCH₂), 2.77 (t, 2H, -NCH₂), 3.54 (d, 1H, CH₂ J= 8 Hz), 3.61 (d, 1H, CH₂, J = 8 Hz), 3.72 (t, 4H, morpholine -OCH₂), 4.05 (t, 2H, -OCH₂), 4.93 (dd, 1H, CH), 6.78 (d, 2H, phenoxy H₃ & H₅ J = 8 Hz), 7.20-7.34 (m, 7H, phenoxy H₂ & H₆ & phenylthio); 7.40-7.43 (m, 2H, phenyl H₃ & H₅ & phenylthio); 7.40-7.43 (m, 2H, phenyl H₂ & H₆ J = 8 Hz); 7.20-7.34 (m, 7H, phenol H₃ & H₆); 7.51-7.55 (m, 1H, phenyl H₄); 7.86 (d, 2H, phenyl H₂ & H₆, J = 8 Hz); ¹³C NMR (CDCl₃): 44.82, 47.60, 54.08, 57.63, 65.67, 66.89, 114.51, 127.48, 128.08, 128.63, 128.89, 128.91, 132.65, 133.28, 133.33, 134.42, 136.72, 157.87, 197.15; LC-MS (ESI) m/z: 448 (M+1).

1-phenyl-3-(phenylthio)-3-(4-(2-piperidin-1-yl)ethoxy)phenyl)propan-1-one (4b)
Yield, 86%; white powder; mp: 94-96 °C; IR (KBr): ν (cm⁻¹) (1681 CO); ¹H NMR (CDCl₃): 1.86 (bs, 4H, piperidine H₃ & H₅), 2.24 (bs, 2H, piperidine H₄), 2.80 (bs, 2H, -NCH₂), 3.36 (bs, 2H, CH₂), 3.51-3.64 (m, 4H, piperidine H₂ & H₆), 4.49 (d, 2H, -OCH₂...
Yield, 91%; white powder; mp: 107-108 °C; IR (KBr): \(\nu (\text{cm}^{-1})\): (1666 CO); \(^1\)H NMR (CDCl\(_3\)): 1.45 (d, 2H, piperidine \(H_4\) \& \(H_5\)), 1.61 (t, 4H, piperidine \(H_1\) \& \(H_2\)), 2.49 (s, 4H, piperidine \(H_4\) \& \(H_5\)), 2.74 (s, 2H, -NCH\(_2\)), 3.47-3.60 (m, 2H, CH\(_2\)), 3.86 (s, 3H, OMe), 4.05 (t, 2H, -OCH\(_2\)), 4.94 (t, 1H, CH), 6.79 (d, 2H, phenoxy \(H_2\) \& \(H_6\), J = 8 HZ), 6.90 (d, 2H, 4-methoxyphenyl \(H_1\) \& \(H_2\), J = 8.5 HZ)], 7.23-7.35 (m, 7H, phenoxy \(H_2\) \& \(H_6\) \& phenylthio); \(J = 8\) HZ); 4.92 (q, 1H, -CH \& J = 5.5 HZ \& J = 5.5 HZ), 6.77 (d, 2H, phenoxy \(H_1\) \& \(H_2\), J = 9 HZ), 7.23-7.53 (m, 10H, phenoxy \(H_2\) \& \(H_6\) \& phenylthio \& phenyl \(H_3\) \& \(H_5\)), 7.55 (d, 2H, phenyl \(H_6\) \& \(H_5\), J = 7 HZ); \(^{13}\)C NMR (CDCl\(_3\)): 21.86, 22.72, 44.76, 47.53, 53.86, 56.19, 62.68, 114.45, 127.57, 128.03, 128.64, 128.92, 129.15, 132.67, 133.31, 134.17, 134.62, 136.64, 158.30, 197.00; LC-MS (ESI) m/z: 446 (M+1).

1-(4-methoxyphenyl)-3-(4-(2-morpholinoethoxy)phenyl)-3-(phenylthio)propan-1-one (4e)

Yield, 86%; white powder; mp: 106-108 °C; IR (KBr): \(\nu (\text{cm}^{-1})\): (1666 CO); \(^1\)H NMR (CDCl\(_3\)): 2.58 (s, 4H, morpholine -NCH\(_2\)), 2.78 (t, 2H, -NCH\(_2\)), 3.48-3.52 (m, 2H, CH\(_2\)), 3.74 (t, 4H, morpholine -OCH\(_2\)), 3.87 (s, 3H, OMe), 4.07 (t, 2H, -OCH\(_2\)), 4.95 (t, 1H, CH), 6.80 (d, 2H, phenoxy \(H_2\) \& \(H_6\), J = 8.5 HZ), 6.91 (d, 2H, 4-methoxyphenyl \(H_1\) \& \(H_2\), J = 8.5 HZ)), 7.24-7.36 (m, 7H, phenoxy \(H_1\) \& \(H_2\) \& phenylthio); 7.87 (d, 2H, 4-methoxyphenyl \(H_3\) \& \(H_4\), J = 8.5 HZ); \(^{13}\)C NMR (CDCl\(_3\)): 24.21, 25.96, 44.04, 47.79, 55.04, 55.47, 57.93, 65.91, 113.73, 114.48, 114.99, 127.34, 128.81, 128.83, 130.37, 132.58, 133.24, 134.55, 157.99, 163.57, 195.63; LC-MS (ESI) m/z: 478 (M+1).

1-(4-methoxyphenyl)-3-(3-(4-(2-(piperidin-1-yl)ethoxy)phenyl)propan-1-one (4f)

Yield, 42%; white powder; mp: 97-99 °C; IR (KBr): \(\nu (\text{cm}^{-1})\): (1666 CO); \(^1\)H NMR (CDCl\(_3\)): 1.80 (bs, 2H, CH\(_2\)), 2.58 (bs, 4H, morpholine -NCH\(_2\)), 2.78 (t, 2H, N-CH\(_2\)), 2.86 (t, 2H, CH\(_2\)-CH\(_2\)), 3.77 (t, 4H, morpholine O-CH\(_2\)), 4.06 (t, 2H, O-CH\(_2\)), 4.18 (t, 2H, CH \& SCH), 7.13-7.52 (m, 13H, Ar); \(^{13}\)C NMR (CDCl\(_3\)): 24.65, 27.24, 50.17, 52.44, 54.09, 55.02, 57.60, 66.89, 113.99, 114.56, 126.89, 127.52, 128.16, 128.60, 128.91, 129.48, 130.51, 131.28, 131.75, 136.58, 143.05, 159.05, 197.04; LC-MS (ESI) m/z: 474 (M+1).
1-(4-methoxyphenyl)-3-(3-(2-morpholinoethoxy)phenyl)-3-(phenylthio)propan-1-one (4h)

Yield, 38%; oily brown liquid; IR (KBr): ν (cm⁻¹) (1666 CO); ¹H NMR (CDCl₃): 2.58 (bs, 4H, morpholine -NCH₂), 2.80 (t, 2H, CH₂N), 3.45-3.50 (m, 6H, CH₃, CH₂), 3.73-3.75 (m, 4H, morpholine -OCH₂), 3.81 (s, 3H, OMe), 4.02 (t, 1H, CH), 4.11 (t, 2H, OCH₂), 6.78-6.86 (m, 3H, phenoxy H₂ & H₄ & H₆), 7.45-7.58 (m, 6H, phenoxy H₂ & phenylthio H₃ & H₄ & H₅ & 4-methoxyphenyl H₃ & H₅); 7.96 (d, 4H, 4-methoxyphenyl H₂ & H₆ & phenylthio H₂ & H₆, J = 7.5 Hz); ¹³C NMR (CDCl₃): 36.89, 45.09, 54.08, 55.93, 57.51, 66.89, 66.96, 111.97, 113.73, 119.89, 122.05, 123.22, 124.53, 128.13, 128.59, 133.08, 136.39, 136.95, 148.02, 148.32, 158.34, 198.66; LC-MS (ESI) m/z: 478 (M+1).

3-(4-methoxy-3-(2-morpholinoethoxy)phenyl)-1-(4-methoxyphenyl)-3-(phenylthio)propan-1-one (4i)

Yield, 38%; oily brown liquid; IR (KBr): ν (cm⁻¹) (1666 CO); ¹H NMR (CDCl₃): 2.60 (bs, 4H, morpholine -NCH₂), 2.81 (bs, 2H, -NCH₂), 3.46-3.61 (m, 2H, CH₂), 3.75-3.78 (m, 4H, morpholine -OCH₂), 3.81 (s, 3H, OMe), 3.86 (s, 3H, OMe), 4.06-4.15 (m, 2H, -OCH₂), 4.24 (t, 1H, CH), 6.88-6.92 (m, 3H, phenoxy H₂ & H₆ & H₅); 7.21-7.34 (m, 9H, phenylthio & 4-methoxyphenyl); ¹³C NMR (CDCl₃): 29.70, 44.37, 48.14, 54.07, 55.48, 55.88, 57.45, 66.93, 111.51, 112.62, 112.62, 113.75, 119.87, 120.57, 123.50, 128.83, 130.37, 130.71, 132.63, 133.73, 143.97, 147.90, 195.54; LC-MS (ESI) m/z: 508 (M+1).

Cytotoxicity evaluation using MTT assay method

To evaluate the cytotoxic effects of synthesized compounds against MCF-7, human cancerous cell lines, the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay was performed.

For evaluation of the antiproliferative activity of designed and synthesized compounds, a human tumor cell line, MCF-7, was procurement from the Iranian Biological Resource Center (IBRC), Tehran, Iran(19-21). In the RPMI1640 medium, the cells were cultured under a high humidity atmosphere with 5% CO₂ at 37 °C. Then, the cells were enriched with 10% fetal bovine serum (FBS) plus 100 µg/mL streptomycin. Using the MTT method, cell viability was evaluated, relying on the reduction of MTT dye by mitochondrial succinate dehydrogenase enzyme to produce formazan crystals in purple color in living cells. The cells in 96-well plate format were prepared at a concentration of 10⁴ cells/well and, for 24 h allowed to incubate. With 1 and 100 µM of synthesized compounds in water/DMSO, the cells were incubated at 37 °C for 48 h. Tamoxifen treated cells as the positive control and intact cells as the negative group was used. After incubation, 10 µL of MTT was added, and the cells were incubated at 37 °C for 4hr. The supernatant was removed, and cells were exposed with 100 µL DMSO for 20 min at 37 °C. The absorbance of cells (OD) at 570 nm by a spectrophotometer plate reader (Infinite® M200, TECAN) was determined, and the percentage of inhibition was calculated.

Molecular modeling studies

Docking studies were implemented by AutoDock 4 software. The X-ray crystallography of lasofoxifene as a selective estrogen receptor modulator bound to the human estrogen receptor α was retrieved from the protein data bank server [PDB code: 2OUZ]. The crystal structure was optimized by removing all water molecules, polar hydrogens were added to the protein, and then Kollman united partial atomic charges were appropriate. At last, the format of the prepared file was converted to PDBQT format using AutoDock 4. The energy of prepared ligand molecules was minimized through the MM+ method with HyperChem 8.0 software; the PDBQT format of the ligands was obtained using AutoDock tools. A grid box of 20-20-20 Å with the x, y, and z directions around the active site of the protein was constructed. The Lamarckian genetic search algorithm was utilized with a total of 50 runs. For efficiency, from the docking box, protein residues with atoms greater than 7.5 Å were removed. At the end of the process, an optimum conformation with the relative lower binding energy was selected for each compound.
Results and Discussion

The cytotoxic effect of synthesized compounds on the viability of cancerous cells \textit{in-vitro}, ER-α-positive MCF7 was evaluated using MTT assay. The antiproliferative activities of the synthesized compounds were compared with the reference drug, Tamoxifen at the concentration of 1 μM on MCF-7 cells and 100 μM on fibroblast cells, respectively.

The MTT test results of the synthesized compounds have been shown in Table 1. All of the synthesized compounds showed better cytotoxic effects on the MCF7 cell line compared with Tamoxifen as a reference drug. However, there was no significant difference between the cytotoxic effects of the synthesized compounds. In addition, the results of normal cells (fibroblasts) indicated that the synthesized compounds with the concentration of 100X against cancerous cells showed less cytotoxic effects than Tamoxifen, and compounds 4a and especially 4h compared with Tamoxifen displayed little cytotoxic activity on these cells. According to the structural similarity of these two compounds, it can be concluded that the linear structures with polar morpholine group as a polar side chain showed decreasing cytotoxicity on the normal cell in comparison with piperidinyl as a hydrophobic side chain. According to cytotoxic results, the synthesized compounds demonstrated acceptable effects on the MCF-7 cell line.

Considering the MTT evaluation results and structural correspondence between designed ((N, N-dialkylaminoethoxy)phenyl)-1-phenyl-3-(phenylthio)propan-1-one derivatives (4a-i) and Tamoxifen, one of the mechanisms proposed to explain the cytotoxicity effects of these compounds on MCF-7 cancerous cells, is estrogen receptors blockade. Based upon, to display the interactions with estrogen receptor α (ERα), compound 4h, one of the most potent compounds with less cytotoxic effects on normal cells, was docked in ERα active site (Figure 2). The molecular modeling study demonstrated that the compound 4h was well bound into the active site of receptor estrogen receptor alpha. The tertiary amine basic side chain (diethylaminophenoxy) was well placed into the active site of a protein, and the N atom of this side chain formed a hydrogen bond with the carboxylate group of Asp\textsuperscript{351} (distance = 3.11 Å). Also, a disulfide bond formed between the S atom of compound 4h and the S atom of Met\textsuperscript{421} (distance = 5.30 Å). Π-Π interaction between phenyl ring of Phe\textsuperscript{404} and C-1 phenyl ring of 4h (distance = 3.88 Å) was also observed. According to these data, it could realize that one of the probable mechanisms of action of these compounds may be mediated through interference with estrogen receptors. However, binding studies are needed to prove this point.

Table 1. Cytotoxicity effects of the synthesized compounds

| Compound | n | R\textsubscript{1} | R\textsubscript{2} | R\textsubscript{3} | Inhibition\% MCF-7 (1 μM) | Inhibition\% Fibroblast (100 μM) |
|----------|---|------------------|------------------|---------------|---------------------------|---------------------------------|
| 4a       | 0 | H                | H                | morpholinylethoxy | 36.93                     | 14.53                          |
| 4b       | 0 | H                | H                | piperidinylethoxy  | 39.47                     | 45.13                          |
| 4c       | 0 | OMe              | H                | morpholinylethoxy  | 40.47                     | 45.73                          |
| 4d       | 0 | OMe              | H                | piperidinylethoxy  | 37.47                     | 47.80                          |
| 4e       | 1 | H                | H                | morpholinylethoxy  | 41.80                     | 54.27                          |
| 4f       | 2 | H                | H                | morpholinylethoxy  | 39.40                     | 48.60                          |
| 4g       | 2 | H                | H                | piperidinylethoxy  | 39.87                     | 46.67                          |
| 4h       | 0 | OMe              | morpholinylethoxy | H                | 37.20                     | 1.07                           |
| 4i       | 0 | OMe              | morpholinylethoxy | OMe             | 39.07                     | 50.60                          |
| Tamoxifen |   |                  |                  |                 | 31.40                     | 67.27                          |
Conclusion

The results showed that the synthesized compounds had significant cell cytotoxicity on breast cancer cells with a low toxicity effect on normal cells. Our results indicated that adding tertiary amine basic side chain, found in Tamoxifen drug, to 1,3-diphenyl-3-(phenylthio)propan-1-ones improves the cytotoxic effects of these compounds on breast cancer cells. To better understand the mechanism of action of these compounds, they should be tested on other types of cancer cells as well as their binding studies should be implemented.

Acknowledgments

Our team thanks to the Research Deputy of Shahid Beheshti University of Medical Sciences for supporting our project.

References

(1) Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin D, Piñeros M, Znaor A and Bray F. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *Int. J. Cancer.* (2019) 144: 1941-53.
(2) Awan Z, Kutbi HI, Ahmad A, Syed R, Alsulaimany F and Shaik NA. Molecular design, synthesis and biological characterization of novel Resveratrol derivative as potential anticancer agent targeting NF-κB. *J. Appl. Biomed.* (2020) 18/1: 8-17.
(3) Vaidyanathan S, Pehlivan I, Dolvis LG, Jacques K, Alcin M, Tuna M and Koyuncu I. A novel ANN-based four-dimensional two-disk hyperchaotic dynamical system, bifurcation analysis, circuit realisation and FPGA-based TRNG implementation. *Int. J. Comput. Appl. Technol.* (2020) 62: 20-35.
(4) Hu L, Cai X, Dong S, Zhen Y, Hu J, Wang S, Jiang J, Huang J, Han Y and Qian Y. Synthesis and anticancer activity of novel actinonin derivatives as HsPDF inhibitors. *J. Med. Chem.* (2020) 63: 6959-78.
(5) Salimi A, Aghvami M, Azami Movahed M, Zarei MH, Eshghi P, Zarghi A and Pourahmad J. Evaluation of cytotoxic potentials of novel cyclooxygenase-2 inhibitor against ALL lymphocytes and normal lymphocytes and its anticancer effect through mitochondrial pathway. *Cancer Invest.* (2020) 38: 463-75.
(6) Nourbakhsh M, Farzaneh S, Taghikhani A, Zarghi A and Noori S. The effect of a newly synthesized ferrocene derivative against MCF-7 breast cancer cells and spheroid stem cells through ROS production and inhibition of JAK2/STAT3 signaling pathway. *Curr. Med. Chem.: Anti-Cancer Agents* (2020) 20: 875-86.
(7) Pinheiro S, Pessôa JC, Pinheiro EM, Muri EM,
Mirzaei S, Hadizadeh F, Eisvand F, Mosaffa F and Ghodsi R. Synthesis, structure-activity relationship and molecular docking studies of novel quinoline-chalcone hybrids as potential anticancer agents and tubulin inhibitors. *J. Mol. Struct.* (2020) 1202: 127310.

Severi F, Benvenuti S, Costantini L, Vampa G, Melegrani M and Antolini L. Synthesis and activity of a new series of chalcones as aldose reductase inhibitors. *Eur. J. Med. Chem.* (1998) 33: 859-66.

Zarghi A, Zebardast T, Hakimion F, Shirazi FH, Rao PP and Knaus EE. Synthesis and biological evaluation of 1, 3-diarylprop-2-en-1-ones possessing a methanesulfonamido or an azido pharmacophore as cyclooxygenase-1/-2 inhibitors. *Bioorg. Med. Chem.* (2006) 14: 7044-50.

Zarghi A, Arfaee S, Rao PP and Knaus EE. Design, synthesis, and biological evaluation of 1, 3-diarylprop-2-en-1-ones: A novel class of cyclooxygenase-2 inhibitors. *Bioorg. Med. Chem.* (2006) 14: 2600-5.

Zarghi A and Arfaei S. Selective COX-2 inhibitors: a review of their structure-activity relationships. *Iran. J. Pharm. Res.* (2011) 10: 655-83.

Edwards DN, Ngwa VM, Raybuck AL, Wang S, Hwang Y, Kim LC, Cho SH, Paik Y, Wang Q and Zhang S. Selective glutamine metabolism inhibition in tumor cells improves anti-tumor T lymphocyte activity in triple-negative breast cancer. *J. Clin. Investig.* (2020) 15: 140100.

Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV and Johnson KC. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women’s Health Initiative randomized controlled trial. *J. Am. Med. Assoc.* (2002) 288: 321-33.

Farzaneh S and Zarghi A. Estrogen receptor ligands: a review (2013–2015). *Scientia pharmaceutica.* (2016) 84: 409-27.

Kakhki S, Shahosseini S and Zarghi A. Design and synthesis of pyrrolo [2, 1-a] isoquinoline-based derivatives as new cytotoxic agents. *Iran. J. Pharm. Res.* (2016) 15: 743-51.

Kakhki S, Shahosseini S and Zarghi A. Synthesis and cytotoxicity evaluation of new 2-aryl-5, 6-dihydropyrrolo [2, 1-a] isoquinoline derivatives acting as cell cycle blockers: potential anti cancer drugs? *Curr. Drug Targets.* (2009) 10: 363-71.

Yuan C and Smith WL. A cyclooxygenase-2-dependent prostaglandin E2 biosynthetic system in the Golgi apparatus. *J. Biol. Chem.* (2015) 290: 5606-20.

Allameh A, Vansoun EY and Zarghi A. Role of glutathione conjugation in protection of weanling rat liver against acetaminophen-induced hepatotoxicity. *Mech. Ageing Dev.* (1997) 95: 71-9.

Mirian M, Zarghi A, Sadeghi S, Tabarakil P, Tavallaeae M, Dadrass O and Sadeghi-aliabadi H. Synthesis and cytotoxic evaluation of some novel sulfonamidederivativesagainst a few human cancer cells. *Iran. J. Pharm. Res.* (2011) 10: 741-8.

Mahboubi Rabbani SMI and Zarghi A. Selective COX-2 inhibitors as anticancer agents: a patent review (2014-2018). *Expert Opin. Ther. Pat.* (2019) 29: 407-27.

Borer JS and Simon LS. Cardiovascular and gastrointestinal effects of COX-2 inhibitors and NSAIDs: achieving a balance. *Arthritis Res. Ther.* (2005) 7: S14.

Sivakumar P, Prabhakar P and Doble M. Synthesis, antioxidant evaluation, and quantitative structure–activity relationship studies of chalcones. *Med. Chem. Res.* (2011) 20: 482-92.

Doan TN and Tran DT. Synthesis, antioxidant and antimicrobial activities of a novel series of chalcones, pyrazolic chalcones, and allylic chalcones. *J. Pharm. Pharmacol.* (2011) 2: 282.

Loa J, Chow P and Zhang K. Studies of structure–activity relationship on plant polyphenol-induced suppression of human liver cancer cells. *Cancer Chemother. Pharmacol.* (2009) 63: 1007-16.

Liu Z, Tang L, Zou P, Zhang Y, Wang Z, Fang Q, Jiang L, Chen G, Xu Z and Zhang H. Synthesis and biological evaluation of allylated and prenylated mono-carbonyl analogs of curcumin as anti-inflammatory agents. *Eur. J. Med. Chem.* (2014) 74: 671-82.

Bano S, Javed K, Ahmad S, Rathish I, Singh S, Chaitanya M, Arunasree K and Alam M. Synthesis of some novel chalcones, flavanones and flavones and evaluation of their anti-inflammatory activity. *Eur. J. Med. Chem.* (2013) 65: 51-9.

Venturini Filho E, Loureiro LB, Freitas MCR, Junior CMS, Fiorot RG and Carneiro JWM. 2H-1, 2, 3-Triazole-chalcones as novel cytotoxic agents against prostate cancer. *Bioorg. Med. Chem. Lett.* (2020) 30: 127454.
derivatives as topoisomerase inhibitors. *Iran. J. Pharm. Res.* (2014) 13: 71-7.

(31) Ghodsi R, Azizi E, Grazia Ferlin M, Pezzi V and Zarghi A. Design, synthesis and biological evaluation of 4-(imidazolylmethyl)-2-arylquinoline derivatives as aromatase inhibitors and anti-breast cancer agents. *Lett. Drug. Des. Discov.* (2016) 13: 89-97.

(32) Aghvami M, Pourahmad J, Zarghi A, Eshghi P, Zarei MH, Farzaneh S and Sattari F. A newly synthesized ferrocenyl derivative selectively induces apoptosis in all lymphocytes through mitochondrial estrogen receptors. *Curr. Med. Chem.: Anti-Cancer Agents.* (2018) 18: 1032-43.

(33) Zarghi A, Hajimahdi Z, Mohebbi S, Rashidi H, Mozaffari S, Sarraf S, Faizi M, Tabatabae SA and Shafee A. Design and synthesis of new 2-substituted-5-[2-(2-halobenzyl)oxy] phenyl]-1, 3, 4-oxadiazoles as anticonvulsant agents. *Chem. Pharm. Bull. (Tokyo)* (2008) 56: 509-12.

This article is available online at http://www.ijpr.ir