Synthesis And Anticancer Screening Of Novel Spiro[Chroman-2,4'-Piperidin]-4-One Derivatives With Apoptosis-Inducing Activity

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ARTICLE INFO

Article History:
Received on: 27/08/2017
Accepted on: 20/11/2017
Available online: 28/01/2018

Key words: Spiro[chroman-2,4’-piperidin]-4-one, cytotoxic, MTT, apoptosis, cell cycle analysis

ABSTRACT

A novel series of spiro[chroman-2,4’-piperidin]-4-one derivatives was synthesized and evaluated as cytotoxic agents against three human cancer cell lines; MCF-7 (human breast carcinoma), A2780 (human ovarian cancer) and HT-29 (human colorectal adenocarcinoma) using MTT assay. Compound 16 with a sulfonyl spacer exhibited the most potent activity with IC\textsubscript{50} values between 0.31 and 5.62 μM. However, the trimethoxyphenyl derivative 15 was the least potent with IC\textsubscript{50} values between 18.77 and 47.05 μM. The most active compound 16 was selected for further mechanistic studies, which revealed that it induced more than three folds early apoptosis in MCF-7 cells treated for 24 h. Additionally, it increased MCF-7 cells in the sub-G1 and G2-M cell cycle phases, following the same treatment duration. Together, these compounds could be promising cytotoxic candidates, thus further structural optimization, \textit{in vitro} and \textit{in vivo} studies are recommended to be developed into potential cytotoxic agents.

INTRODUCTION

Cancer is a life-threatening disease that is manifested by out-of-control abnormal cell growth with the possibility of invading other tissues. Currently, there are several approaches for cancer treatment including chemotherapy, hormonal therapy, immunotherapy, surgery and radiation. However, chemotherapy remains one of the prevailing options used for treating cancer (Gerber, 2008). Despite all the treatment approaches mentioned above and the remarkable breakthrough in cancer chemotherapy, the existence of a perfect and outright cure is still a challenging goal (Raguz and Yague, 2008). Accordingly, there is an urgent need to develop more potential anticancer agents. The discovery of apoptosis-inducing agents has become one of the most promising strategies of cancer treatment (Sun \textit{et al.}, 2004). Apoptosis is considered a highly regulated and critically biological programmed cell death mechanism used to get rid of the depressive and imperfect cells (McDonald and El-Deiry, 2005). It has an essential role in maintenance of tissue growth and homeostasis of multicellular organisms (Fulda and Debatin, 2006). Consequently, it was believed that the deregulation or impairment of this pivotal process is one of the main causes of incidence of cancer, autoimmune and neurodegeneration diseases (Lowe and Lin, 2000; Ponder, 2001). On the contrary, the induction of apoptosis machinery is feasibly one of the most potent defense strategies against cancer (Zhang \textit{et al.}, 2007). Therefore, the discovery and design of novel apoptotic-inducing agents have received widespread attention as a potential, less toxic and promising approach in cancer chemotherapy (Sharma \textit{et al.}, 2016; Jung \textit{et al.}, 2017).
On the other hand, spiro heterocycles have currently attracted a great attention due to their existence as a main skeleton in a wide variety of biologically active natural as well as synthetic compounds in addition to their interesting conformational features. Indeed, these molecules have become an elegant target for medicinal chemists to develop a large number of derivatives and evaluate their pharmacological potentials with emphasis on their medicinal applications. Among this class of compounds, spirochromanone is a well-recognized privileged structure that has been commonly found in a plenty of chemical compounds with diverse biological activities. These compounds exhibit significant biological activities such as anticancer (Atta et al., 2010; El-Desoky et al., 2013), antitubercular (Mujahid et al., 2013; Mujahid et al., 2015), antimicrobials (Feng et al., 2014), histamine-3 antagonists (Becknell et al., 2012), antiarrhythmic (Elliott et al., 1992), acetyl-CoA carboxylase (ACC) inhibitors (Shinde et al., 2009; Huang et al., 2015), stearoyl-CoA desaturase-1 (SCD)-1 inhibitors (Uto et al., 2010), histone deacetylase (HDAC) inhibitors (Varasi et al., 2011; Thaler et al., 2016), antimalarial (Roberts et al., 2016), growth hormone secretagogues (Yang et al., 1998) and δ opioid receptor agonists (Le Bourdonnec et al., 2008). Thaler et al. have reported a series of spirochromanones and evaluated their activity against HDAC as a well-established anticancer target (Thaler et al., 2016). These studies demonstrated that the prepared spirochroman derivatives possessed potent HDAC inhibitory activity that could be successfully developed into potential anticancer agents. Compounds 1 and 2 were the most potent HDAC inhibitors with good oral bioavailability and tumor growth inhibition. Moreover, a series of spirofurochromones was synthesized and screened for their antitumor activity where the selenium-containing compound 3 recorded the most promising activity against breast carcinoma (MCF-7) (Atta et al., 2010), Figure 1. Another set of benzopyranones was reported and tested in vitro and in vivo for their anticancer potential. Compound 4 was highly potent against a panel of cancerous cell lines with IC₅₀ values between 0.09 and 0.21 μM compared to 5-fluorouracil as a reference drug (El-Desoky et al., 2013).

Furthermore, trimethoxyphenyl and adamantly moieties are frequently used in design of several anticancer agents. Trimethoxyphenyl has an important role in mitosis, microtubules which represent a crucial target in development of new anticancer agents (Jordan and Wilson, 2004). In this regard, colchicine 5 (Lin et al., 2016), the diarylthiazole derivative 6 (Wang et al., 2015) and combretastatin A4 7 (Pettit et al., 1989), are examples of this class where their anticancer activity is mediated by binding to tubulin. Meanwhile, adamantyl moiety was found to enhance the various activities of several compounds positively such as anticancer agents. One of such compounds, the dianimophenyladamantane derivative 8 exhibited strong anticancer activity in vitro with G₀/G₁ cell cycle arrest mechanism (Wang et al., 2004). Moreover, the adamantyl-1,2,4-triazole-3(4H)-thione derivative 9 was found to exert moderate in vitro anticancer activity against breast cancer with IC₅₀ value of 8.15 μM with a suggested inhibition to BRCA2 protein (Genc et al., 2015). The anti-prostate cancer activity was reported for compound 10 with potent inhibitory activity against 17α-hydroxylase and C₁₇,20-lyase activities of human testicular cytochrome P450₁₇α (Chan et al., 1996). The adamantane-gold complex 11 displayed potent cytotoxic activity in comparison to cisplatin and auranofin and could inhibit the thioredoxin reductase enzyme (Garcia et al., 2016), Figure 2.

As part of our ongoing research work to develop novel anticancer agents, we describe herein the design and synthesis of some new chemical entities based on a spirochromanone framework tethered to known small moieties such as trimethoxyphenyl and adamantly via various linkers using fragment-based drug design approach. The evaluation of their anticancer activity against a panel of cancer cell lines in addition to their ability to induce apoptosis and cell cycle analysis were also performed. It was conceptualized that these novel spiro hybrids could serve as promising leads for developing potent and safer anticancer agents. Figure 3 shows the suggested pharmacophore of the newly synthesized compounds.
MATERIALS AND METHODS

Chemistry

Chemical reagents and solvents were obtained from commercial sources. Solvents were dried by standard methods when necessary. Elemental analyses were carried out at the micro-analytical center in the Faculty of Science, Cairo University. ¹H NMR spectra were recorded with Bruker APX400 spectrometer at 400 MHz in DMSO-d₆. Chemical shifts were reported on the δ scale. The high-resolution mass spectra (HRMS) were recorded on Agilent 6230 Series Accurate-Mass Time-Of-Flight (TOF) LC/MS. Thin layer chromatography (TLC) was done by silica gel plates 60 GF254, cellulose plates (20 × 20 cm) from Sigma-Aldrich company for chemicals and ethyl acetate/hexane were used as the eluting system.

**Tert-butyl 4-oxospiro[chroman-2,4'-piperidine]-1'-carboxylate** (12) (Kabbe, 1978). Pyrrolidine (4.2 mL, 0.05 mol) was added under stirring to a mixture of N-Boc piperidine (5 g, 0.0249 mol) and 2-hydroxyacetophenone (3.4 g, 0.0249 mol) in anhydrous methanol (40 mL) at rt. The reaction mixture was refluxed overnight, then concentrated under reduced pressure and ethyl acetate (40 mL) was added. The combined organic layers were washed with 1 N HCl, 1 N NaOH, brine, and dried over Na₂SO₄. The organic solvent was removed in vacuo and hexane (30 mL) was added. The resulting off-white solid was filtered off, washed with hexane, Yield: 79%. ¹H NMR (CDCl₃) δ 7.90 (d, J = 7.5, 1H), 7.63 (t, J = 7.3, 1H), 7.11 (m, 2H), 3.89 (m, 2H), 3.25 (m, 2H), 2.75 (s, 2H), 2.12 (d, J = 7.1, 2H), 1.63 (m, 2H), 1.48 (s, 9H).

HRMS Calcd. for C₁₄H₁₆O₂ [M + H]⁺ 317.1627, Found 318.1631.

**Spiro[chroman-2,4'-piperidin]-4-one** (13). Trifluoroacetic acid (5.16 mL, 67.05 mmol) was added slowly to a solution of tert-butyl 4-oxospiro[chroman-2,4'-piperidine]-1'-carboxylate 12 (3.86 g, 12.19 mmol) in methylene chloride (30 mL). The mixture was stirred at rt for 5 h. The mixture was then concentrated in vacuo and a solution of NaHCO₃ (30 mL) was added to the residue and extracted with methylene chloride (3 x 30 mL). The organic layer was separated, washed with brine, dried over Na₂SO₄ and evaporated to afford compound 13 (85%) which was used directly.
for the next step without any further purification. MS (EI) m/z 218 (M+1).

**General procedure A for the synthesis of compounds 14 and 15.** The appropriate acid chloride (1.2 mmol) was added slowly to a solution of spiro[chroman-2,4'-piperidin]-4-one 13 (0.22 g, 1 mmol) in dry THF (15 mL) in presence of catalytic amount of triethyl amine. The reaction mixture was allowed to stir for 6 h at room temperature. The reaction mixture was then treated with water (30 mL). The obtained precipitate was filtered off, washed with water and then recrystallized from ethanol to afford the final targeted compounds as off-white solid in good yields.

1'-Adamantane-1-carbonylspiro[chroman-2,4'-piperidin]-4-one (14). General Procedure A, off-white solid (67%). 1H NMR (400 MHz, DMSO-d6) δ 7.86 (d, J = 7.5, 1H), 7.49 (t, J = 7.3, 1H), 7.30 – 7.21 (m, 2H), 3.76 (t, J = 7.1, 2H), 3.13 (t, J = 7.1, 2H), 2.65 (s, 2H), 2.09 (t, J = 7, 2H), 1.63 (t, J = 7, 2H), 1.55 – 1.46 (m, 6H), 1.39 – 1.29 (m, 9H). 13C NMR (101 MHz, DMSO-d6) δ 190.54 (C=O), 176.91 (N-C=O), 160.49, 133.72, 127.30, 121.29, 120.94, 114.68, 68.73, 44.61, 40.39, 39.12, 36.10, 35.41, 34.25, 26.80. HRMS Calcd. for C32H35NO9: [M + H]+ 579.2147. Found 579.2321. Anal. Calcd. for: C, 69.63; H, 6.91; N, 3.44. Found: C, 69.75; H, 7.95; N, 3.87.

1'-(3,4,5-Trimethoxybenzoylspiro[chroman-2,4'-piperidin]-4-one (15). General Procedure A, off-white solid (69%). 1H NMR (400 MHz, DMSO-d6) δ 7.93 (d, J = 7.5, 1H), 7.71 (t, J = 7.3, 1H), 7.65 (s, J = 7.1, 2H), 7.30 – 7.21 (m, 2H), 3.89 (s, 9H), 3.53 (t, J = 7.1, 2H), 3.21 (t, J = 7.1, 2H), 2.67 (s, 2H), 2.11 (t, J = 7, 2H). 13C NMR (101 MHz, DMSO-d6) δ 189.85 (C=O), 173.67 (N-C=O), 160.54, 152.42, 140.84, 133.24, 129.65, 127.74, 121.33, 120.71, 114.99, 105.91, 68.26, 60.64, 56.53, 44.33, 38.92, 34.21. HRMS Calcd. for C29H29NO6 [M + H]+ 411.1682, Found 412.1237. Anal. Calcd. for: C, 67.14; H, 6.12; N, 3.40. Found: C, 67.37; H, 6.42; N, 3.81.

**General procedure B for the synthesis of compounds 16-18.** An appropriate sulfonyl chloride derivative (1.3 mmol) was added to a stirred solution spiro[benzo[h]chromene-2,1'-cyanoclohexan]-4(3H)-ylidenehydrazine 13 (0.22 g, 1 mmol) in DCM (15 mL) in presence of catalytic amount of triethyl amine. The reaction mixture was allowed to stir for 6 h at room temperature. The resulting mixture was concentrated under reduced pressure and then treated with water (30 mL). The obtained precipitate was collected, washed with water and recrystallized from ethanol to afford the targeted final compounds 16-18 in good yields.

1'-Naphthalen-1-ylsulfonylspiro[chroman-2,4'-piperidin]-4-one (16). General Procedure B, off-white solid (71%). 1H NMR (400 MHz, DMSO-d6) δ 7.93 – 7.83 (m, 2H), 7.77 – 7.71 (m, 4H), 7.61 – 7.39 (m, 3H), 3.38 (t, J = 7.1, 2H), 3.31 (t, J = 7.1, 2H), 2.66 (s, 2H), 2.24 (t, J = 7, 2H), 1.61 (t, J = 7, 2H). 13C NMR (101 MHz, DMSO-d6) δ 190.87 (C=O), 160.54, 137.61, 133.42, 131.63, 129.72, 127.69, 121.26, 120.27, 114.99, 68.26, 44.30, 40.83, 33.51. HRMS Calcd. for C27H21NO7 [M + H]+ 550.1213. Found 550.1219. Anal. Calcd. for: C, 64.89; H, 5.63; N, 4.02. Found: C, 64.89; H, 5.63; N, 4.02.

**Biological screening**

**Cell culture**

MCF-7 (human breast adenocarcinoma), A2780 (human ovary adenocarcinoma) and HT29 (human colon adenocarcinoma) were all purchased from the ATCC, USA. Cells were sub-cultured using RPMI-1640 media (10% FBS).

**Cytotoxicity assay**

The cytotoxicity of the five compounds were evaluated by MTT assay, as previously described (Abdelazeem et al., 2014; Gouda et al., 2014). The three cell lines were separately cultured in 96-well (3 x 10^4/well), and incubated at 37°C overnight. Final compound concentrations: 0, 0.05, 0.5, 5, 25, 50 µM (DMSO 0.1%; n = 3). Plates were incubated for 72 h, then MTT was added to each well. Plates were incubated for 3 h, supernatant was aspirated, and DMSO was added to each well. Absorbance was read on multi-plate reader. Optical density of the purple formazan A was used to treat cells (0, 5, 10 and 20 µM). After 24 h, supernatant of the wells was removed, and then cells were trypsinized and incubated at 37°C before being added to the tubes. MCF-7 cells were centrifuged (2000 rpm), washed with PBS (x1), centrifuged again, pellets re-suspended in binding buffer (100 µL, x1) and annexin V FITC (10 µL). Tubes were incubated at room temperature in dark for 20 minutes before adding the binding buffer (400 µL, x1) and 10 µL propidium iodide (PI). Analysis was performed by flow cytometry (NovoCyte Flow Cytometer, Acea Biosciences Inc., California, USA). Different cell populations were identified by annexin V and PI staining (Vermes et al., 1995).
**Cell cycle analysis**

Perturbation of cell cycle was done for MCF-7 cells cultured in 6 well plates (1 × 10^5 cells) overnight at 37°C. Treated cells with compound 3Z (0, 5, 10 and 20 μM) were washed with cold PBS x1 and trypsinized. Collected cells were spun at 2000 rpm. The resulting pellets were washed in cold PBS x1 again, spinned and fixed overnight in 70% ice cold ethanol. Cells were re-suspended in cold PBS x1 with addition of ribonuclease A (15 min), followed by PI (2 μL/mL). Samples were held on ice and analysed by flow cytometry. Data analysis of DNA contents (PI bound to DNA) of 20000 events was carried out (Bkhaitan et al., 2017).

![Scheme 1: Reagents and Reaction Conditions](image)

**RESULTS AND DISCUSSION**

**Chemistry**

The general synthetic pathway used for the preparation of the novel targeted spiro derivatives is shown in Scheme 1. The starting spiro material, tert-butyl 4-oxospiro[chroman-2,4′-piperidine]-1′-carboxylate 12, was prepared using the reported multi-component reaction developed by Kabbe where a thermal condensation reaction of 2-hydroxyacetophenone and N-Boc piperidone in methanol was carried out in presence of pyrrolidine (Kabbe, 1978). The furnished spiro protected compound 12 was subjected to a deprotecting process using TFA in DCM to give the free-boc intermediate 13 in a quantitative yield which in turn was coupled with the appropriate acid chloride or sulfonyl chloride reagents in presence of TEA affording the final targeted compounds (14-18) in good yields. All the final compounds were fully characterized using NMR, mass, CHN spectral analysis.

**Biological screening**

**Cytotoxic activity**

The cytotoxic activity of the newly synthesized compounds was assessed in vitro against three cancer cell lines; MCF-7 (human breast carcinoma), A2780 (human ovarian cancer) and HT-29 (human colorectal adenocarcinoma) using MTT assay (Abdelazeem et al., 2014; Gouda et al., 2014). The results were summarized in Table 1 and expressed in terms of IC_{50} values where doxorubicin was used as a positive control. Generally, it was noticed that the compounds containing a sulfonyl moiety (16-18) exhibited higher activity than compounds (14, 15) containing a carbonyl spacer. Among the tested derivatives, compound 16 was the most potent anticancer agent against the three cancer cell lines with IC_{50} values between 0.31 and 5.62 μM. Nevertheless, the trimethoxyphenyl derivative 15 showed the least potency with IC_{50} values between 18.77 and 47.05 μM. It was found that the replacement of the phenyl group in compound 16 with a p-tolyl group in compound 17 resulted in a sharp decrease in the potency,
especially against HT-29 cell line suggesting a possible significant effect of electron-donating substituents on the activity. However, the replacement with a naphthyl moiety as in compound 18 slightly affected the activity against MCF-7 and HT-29 cell lines compared with compound 16. Of the other substituents, the carbonyl adamantyl bearing analog 14 displayed moderate activity against HT-29 with IC$_{50}$ value of 8.46 μM but with a weak activity against the other used cell lines. These results indicate that the influence of the substitutions on the activity was mainly electronically more than sterically.

**Annexin V FITC/PI apoptosis assay**

Compound 16, with the highest activity against the three cell lines, was selected for further investigations to explain its mechanism of action. Annexin V FITC/PI assay was used to evaluate whether it can induce apoptosis or not in MCF-7 cells following 24 h treatment. Doses of compound 16 were selected based...
on its IC_{50} (x1, x2 and x4, respectively). Compound 16 increased the early apoptotic MCF-7 cell populations in a dose dependent manner, more than three folds compared to control; combined by increase in late apoptosis at 5 and 10 μM; all at expense of live cells which decreased consequently, Figure 4.

### Table 1: IC_{50} values of the newly synthesized compounds against three cancer cell lines; MCF-7, HT-29 and A2780 cell lines.

| Comp. | Anticancer activity IC_{50} (μM) ± SD |
|-------|-------------------------------------|
|       | MCF-7 | A2780 | HT-29 |
| 14    | 23.86 ± 1.55 | 22.68 ± 1.37 | 8.46 ± 1.31 |
| 15    | 47.05 ± 2.66 | 18.77 ± 1.82 | 23.20 ± 2.21 |
| 16    | 5.62 ± 1.33 | 0.31 ± 0.11 | 0.47 ± 0.17 |
| 17    | 6.78 ± 1.21 | 1.79 ± 1.65 | 16.03 ± 1.68 |
| 18    | 6.02 ± 1.07 | 0.316 ± 0.16 | 0.69 ± 0.14 |
| Doxorubicin | 1.5 ± 0.8 | 2.11 ± 0.55 | 1.53 ± 0.62 |

Three human cancer cell lines were used; MCF-7 (human breast carcinoma), A2780 (human ovarian cancer) and HT-29 (human colorectal adenocarcinoma). Cells were treated with the test compounds or vehicle for 72 h and cell viability was assessed by MTT assay. Data were reported as mean ± S.D. (n = 6). Doxorubicin was used as a positive control.

### Cell cycle analysis

The cell cycle distribution assay of MCF-7 cells treated with compound 16 (24 h), revealed an increase in the sub-G1 pro-apoptotic cells (from 0.30% at 0 μM, to 1.02% and 1.54% at 5 μM and 10 μM, respectively). Compound 16 blocked MCF-7 cells at the G2-M phase in a dose dependent manner (Figure 5 and Table 2) and that was supported by the annexin V assay results.

### Table 2: Effect of compound 16 on MCF-7 cell cycle phases (24h).

| Cell stage | Control | 5 μM | 10 μM | 20 μM |
|------------|---------|------|-------|-------|
| Sub-G1     | 0.30%   | 1.02% | 1.54% | 0.51% |
| G1         | 34.74%  | 35.07% | 31.79% | 36.29% |
| S          | 28.30%  | 27.48% | 25.85% | 22.56% |
| G2-M       | 32.74%  | 33.38% | 36.01% | 37.55% |

### CONCLUSION

A new series of spiro[chroman-2,4’-piperidin]-4-one derivatives was synthesized and evaluated as anticancer agents against a panel of human cancer cell lines using MTT assay. Compound 16 with a sulfonl spacer exhibited the most potent activity with IC_{50} values between 0.31 and 5.62 μM. However, the trimethoxyphenyl derivative 15 was the least potent with IC_{50} values between 18.77 and 47.05 μM. The most active compound 16 could induce more than three folds early apoptosis in MCF-7 cells treated for 24 h. Moreover, it increased MCF-7 cells in the sub-G1 and G2-M cell cycle phases, following the same treatment duration. These compounds could be considered as good leads that need further structural optimization to be developed into potential anticancer agents.

### CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

### REFERENCES

Abdelazeeem, A. H., Gouda, A. M., Omar, H. A., Tolba, M. F. Design, synthesis and biological evaluation of novel diphenylhiazole-based cyclooxygenase inhibitors as potential anticancer agents. Bioorg. Chem. 2014; 57: 132-41.

Atta, S. M., Farrag D. S., Sweed A. M., Abdel-Rahman A. H. Preparation of new polycyclic compounds derived from benzofurans and furochromones. An approach to novel 1,2,3-thia-, and selendiazolofurochromones of anticipated antitumor activities. Eur. J. Med. Chem. 2010; 45: 4920-27.

Becknell, N. C., Dandu, R. R., Lyons, J. A., Aimone, L. D., Raddatz, R., Hudkins, R. L. Synthesis and evaluation of 4-alkoxy[10-cyclobutyl-spiro[3,4-dihydrobenzopyran-2,4-piperidine]] analogues as histamine-3 receptor antagonists. Bioorg. Med. Chem. Lett. 2012; 22: 186-89.

Bkhaitan, M., Mizra, Z., Abdalla, A., Shamshad, H., Ul-Haq, Z., Alarjah, M., Piperno, A. Reprofiling of Full-length Phosphonated Carbocyclic 2’-Oxa-3’-Aza Nucleosides towards Antiproliferative Agents: Synthesis, Antiproliferative Activity and Molecular Docking Study. Chem. Biol. Drug Des. 2017; DOI: 10.1111/cbsd.12987.

Chen, F. C. Y., Potter, G. A., Barrie, S. E., B. P. Haynes, M. G. Rowland, J., Houghton, M. Jarman. 3- and 4-Pyridylalkyl adamantaneacarbonylates: Inhibition of human Cytochrome P45017a (17a-hydroxylase/ C17,20-lyase) Potential non-steroid agent for the treatment of prostatic cancer. J. Med. Chem. 1996; 39: 3319-23.

El-Desoky, S. I., Badria, F. A., Abozeid, M. A., Kandeel, E. A., Abdel-Rahman, A. H. Synthesis and antitumor studies of novel benzopyran-1,2,3-selenadiazolo and spiro[benzopyran]-1,3-thiadiazoline derivatives. Med. Chem. Res. 2013; 22: 2105-14.

Elliott, J. M., Selnick, H. G., Claremont, D. A., Baldwin, J. J., Buhrow, S. A., Butcher, J.W., Habecker, C.N., King, S.W., Lynch, J. J., Jr., Phillips, B. T. 4-Oxospir[benzopyran-2,4-piperidines] as class III anti-arhythmic agents. Pharmacological studies on 3,4-dihydro-10-[(2-[benzofuran-5-yl]-ethyl]-6-methanesulfonylodiospiro[(2H)-1-benzopyran-2,4-piperidin]-4-one (L-691,121). J. Med. Chem. 1992; 35: 3973-76.

Feng, L., Maddox, M. M., Alam, Md. Z., Tsutsui, L. S., Narula, G., Bruhn, D. F., Wu, X., Sandhaus, S., Lee, R. B., Simmons, C. J., Tse-Dinh, Y-C., Hurde, G. J., Lee, R. E., Sun, D. Synthesis, Structure–Activity Relationship Studies, and Antibacterial Evaluation of 4-Chromones and Chalcones, as Well as Olympicin A and Derivatives. J. Med. Chem. 2014; 57: 8398-20.

Fulda, S., Debatin, K.-M. Extrinsic versus intrinsic apoptosis pathways in anticancer chemotherapy. Oncogene 2006; 25: 4798-11.

Garcia, A., Machado, R. C., Grazul, R. M., Lopes, M. T. P., Corrêa, C. C., Dos Santos, H. F., de Almeida, M. V., Silva, H. Novel antitumor adamantane-azole gold(I) complexes as potential inhibitors of thioredoxin reductase. J. Biol. Inorg. Chem. 2016; 21: 275-92.

Gerber, D.E. Targeted Therapies: A New Generation of Cancer Treatments. Am. Fam. Physician. 2008; 77: 311-19.

Gouda, A. M., Abdelazeem, A. H., Arafà, E-S. A., Abdelatiff, K. R. A. Design, synthesis and pharmacological evaluation of novel pyrrolizine derivatives as potential anticancer agents. Bioorg. Chem. 2014; 53: 1-7.

Huang, T., Sun, J. Wang, Q., Gao, J., Liu, Y. Synthesis, Biological Evaluation and Molecular Docking Study. Chem. Biol. Intermed. 2015; 41: 6229-44.

Jung, K.-Y., Park, J., Han, Y.-S., Lee, Y. H., Shin, S. Y., Lim, Y. Synthesis and biological evaluation of hesperetin derivatives as agents inducing apoptosis. Bioorg. Med. Chem. 2017; 25: 397-07.
Kabbe, H. J. Eine einfache synthese von 4-chromanonen. Synthesis, 1978; 866-67.
Le Bourdonnec, B., Windh, R. T., Ajello, C. W., Leister, L. K., Gu, M., Chu, G. H., Tuthill, P. A., Barker, W. M., Koblish, M., Wiant, D. D., Graczyk, T. M., Belanger, S., Cassel, J. A., Feschenko, M. S., Borgdon, B. L., Smith, S. A., Christ, D. D., Derelanko, M. J., Kutz, S., Little, P. J., DeHaven, R. N., De Haven-Hudkins, D. L. Dolle, R. E. Potent, orally bioavailable delta opioid receptor agonists for the treatment of pain: discovery of N,N-diethyl-4-(5-hydroxyxyspiro[chromene-2,4'-piperidine]-4-yl) benzamide (ADL5859). J. Med. Chem. 2008; 51: 5893-96.
Lin, Z-Y., Kuo, C-H., Wu, D-C., & Chuang, W-L. Anticancer effects of clinically acceptable colchicine concentrations on human gastric cancer cell lines. Kaohsiung J. Med. Sci. 2016; 32: 68-73.
Lowe, S.W., Lin, A.W. Apoptosis in cancer. Carcinogenesis, 2000; 21: 485-95.
McDonald, E.R., El-Deiry, W. S. Cell cycle control as a basis for cancer drug development (Review). Cancer Ther. 2005; 1:41.
Mujahid, M., Gonnade, R.G., Yogeewari, P., Srimar, D., Muthukrishnan, M. Synthesis and antitubercular activity of amino alcohol fused spirochromone conjugates. Bioorg. Med. Chem. Lett. 2013; 23: 1416-19.
Mujahid, M., Yogeewari, P., Srimar, D., Basavanag, U. M. V., Diaz-Cervantes, E., Cordoba-Bahena, L., Robles, J., Gonnade, R. G., Karthikeyan, M., Vyas, R., Muthukrishnan, M. Spirochromone-chalcone conjugates as antitubercular agents: synthesis, bio evaluation and molecular modeling studies. RSC Adv. 2015; 5: 106448-60.
Petit, G. R., Singh, S. B., Hamel, E., Lin, C. M., Alberts, D. S., Garcia-Kendall, D. Isolation and structure of the strong cell growth and apoptosis inducing studies. RSC Adv. 2015; 5: 106448-60.
Ponder, B.A.J. Cancer genetics. Nature, 2001; 411: 336-41.
Pettit, G. R., Singh, S. B., Hamel, E., Lin, C. M., Alberts, D. S., Garcia-Kendall, D. Isolation and structure of the strong cell growth and apoptosis inducing studies. RSC Adv. 2015; 5: 106448-60.
Ragu, S., Yague, E. Resistance to chemotherapy: new treatments and novel insights into an old problem. Br. J. Cancer, 2008; 99: 387-91.
Roberts, B. F., Iyamu, I. D., Lee, S., Lee, E., Aiyong, L., Kyle, D. E., Yuan, Y., Manetsch, R., Chakrabarti, D. Spirocyclic chromones exhibit antiplasmodial activities and inhibit all intraerythrocytic life cycle stages. Int. J. Parasitol. Drugs Drug Resist. 2016; 6: 85-92.
Sharma, P., Thummiuri, D., Reddy, T.S., Senwar, K.R., Naidu, V.G.M., Srinivasulu, G., Bharghava, S.K., Shankariah, N. New (E)-1-alkyl-1H-benzo[d]imidazol-2-yl)methylene)indolin-2-ones: synthesis, in vitro cytotoxicity evaluation and apoptosis inducing studies. Eur. J. Med. Chem. 2016; 122: 584-00.
Shinde, P., Srivastava, S. K., Odedara, R., Tuli, D., Munshi, S., Patel, J., Zambad, S. P., Sonawane, R., Gupta, R. C., Chauthaiwale, V., Dutt, C. Synthesis of spiro[chroman-2,4'-piperidin]-4-one derivatives as acetyl-CoA carboxylase inhibitors. Bioorg. Med. Chem. Lett. 2009; 19: 949-53.
Sun, S., Hail, N., Lotan, R J., J. Natl. Cancer Inst. 2004; 96: 662-72.
Thaler, F., Moretti, L., Amici, R., Abate, A., Colombo, A., Carenzio, G., Fulco, M. C., Boggio, R., Dondio, G., Gagliardi, S., Minucci, S., Sartori, L., Varasi, M., Mercurio, C. Synthesis, biological characterization and molecular modeling insights of spirochromanes as potent HDAC inhibitors. Eur. J. Med. Chem. 2016; 108: 53-67.
Uto, Y., Ueno, Y., Kiyotsuka, Y., Miyazawa, Y., Kurata, H., Ogata, T., Yamada, M., Deguchi, T., Konishi, M., Takagi, T., Wakimoto, S., Ohsumi, J. Synthesis and evaluation of novel stearyl-CoA desaturase 1 inhibitors: 10-[6-[5-(pyridin-3-ylmethyl)-1,3,4-oxadiazol-2-yl]pyridazin-3-yl]-3,4-dihydropiro[chromene-2,4'-piperidine] analogs. Eur. J. Med. Chem. 2010; 45: 4788-96.
Varasi, M., Thaler, F., Abate, A., Bigogno, C., Boggio, R., Carenzio, G., Cataudella, T., Zuffo, R. D., Fulco, R. M., Rozio, M. G., Mai, A., Dondio, G., Minucci, S., Mercurio, C. Discovery, Synthesis, and Pharmacological Evaluation of Spiropiperidine Hydroxamic Acid Based Derivatives as Structurally Novel Histone Deacetylase (HDAC) Inhibitors. J. Med. Chem. 2011; 54: 3051-64.
Vermes, I., Haanen, C., Steffens-Nakken, H., Reutelingsperger, C. A novel assay for apoptosis. Flow cytometric detection of phosphatidylserine expression on early apoptotic cells using fluorescein labelled Annexin V. J. Immunol. Methods, 1995; 184: 39-51.
Wang, F., Yang, Z., Liu, Y., Ma, L., Wu, Y., He, L., Chen, L. Synthesis and biological evaluation of diarylthiazole derivatives as antimiticotic and antivascular agents with potent antitumor activity. Bioorg. Med. Chem. 2015; 23: 3337-50.
Wang, J. J., Chen, Y-H., Chih, C-W., Huang K-T., Chen, Y-T. In vitro and in vivo growth inhibition and GI arrest in human cancer cell lines by diaminophenyladamantane derivatives. Anticancer Drugs, 2004; 15: 697-05.
Yang, L., Morriello, G.; Prendergast, K.; Cheng, K.; Jacks, T.; Chan, W. W.; Schleim, K. D.; Smith, R. G.; Patchett, A. A. Potent 3-spiropiperidine growth hormone secretagogues. Bioorg. Med. Chem. Lett. 1998; 8: 107-12.
Zhang, Z., Jin, L., Qian, X., Wei, M., Wang, Y., Wang, J., Yang, Y., Xu, Q., Xu, Y., Liu, F., ChemBioChem, 2007; 8: 113-21.
How to cite this article:
Abdelatef SA, El-Saadi MT, Amin NH, Abdelazeem, AH Abdellatif KRA. Synthesis and anticancer screening of novel spiro[chroman-2,4'-piperidin]-4-one derivatives with apoptosis-inducing activity. J App Pharm Sci, 2018; 8 (01): 009-016.