Synthesis and Biological Evaluation of Chalcones Possessing Ring Activating Groups as Potent of Anticancer Agents

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Abstract. Some novel anticancer agents based on chalcone scaffold were synthesized with potential therapeutic application for many types of cancer. Hydroxy and methoxy substitution on aryl ring of chalcone, depending upon positions in aryl ring influence anticancer and other activities. These chalcone molecules were evaluated for their in vitro cytotoxic activity against five cancer cell lines including human chronic myelogenous leukemia K-562, human breast adenocarcinoma MCF-7, human prostate carcinoma DU-145, human lung adenocarcinoma A-549 and normal VERO cell line. Most of the compounds being active cytotoxic agents and were shown to be non-toxic to normal cells. The synthesized compounds were characterized by means of their FT-IR, MASS and ¹HNMR spectral study.

1. Introduction

Cancer is very tremendous disease with superfluous and stout biological network. Due to the structural uniqueness and potent bioactivity, the synthesis of novel chalcones has attracted much attention in recent years. Chemically chalcones can be considered open chain flavonoids bearing 1,3-diphenyl prop-2-en 1-one as a basic template, play a vital role in identification of bioactive molecules. Most of the anticancer agents of natural or synthetic origin, exhibit enone function in their structure [1, 2].

Many naturally occurring chalcones with potent anticancer efficacy against a variety of cancer lines have been reported. Some prominent examples of this series of chalcones are Xanthohumol, Butein, Flavokawain A, B and C, Dimethyl amino chalcone etc. [3]

![Chemical Structure of bioactive naturally occurring chalcones possessing ring activating groups.](https://example.com/structure.png)

Figure 1. Chemical Structure of bioactive naturally occurring chalcones possessing ring activating groups.

Xanthohumol(1), a prenylated chalcone isolated from the hop cones, is suggested to exhibited broad spectrum anticancer properties against different types of human cancer cells like 40-16 human colon cancer cell through inhibition of the proliferation and induction of human cancer cell apoptosis [4,5]. Butein(2), isolated from the stems of Rhus verniciflua, has been shown to inhibit human colon adenocarcinoma cell proliferation and also it induces apoptosis in HL-60 cells [6].
Flavokawain A, B and C(3) isolated from kava extracts have been shown to possess strong antiproliferative and apoptotic effect in human bladder cancer cells [7]. Other natural chalcones such as Dimethyl amino chalcone(4) and cardamonin(5) have been reported to possess anticancer and anti-inflammatory activities [8]. The anticancer activity of chalcone is believed to be a result of binding to the tubulin assembly and thereby preventing it from polymerisation to microtubule [9].

The majority of these are naturally occurring chalcones substituted with ring activating hydroxyl and/or methoxy groups at various positions. The interesting implication of naturally occurring chalcones as a potent of anticancer agents have invigorated numerous synthetic efforts to develop a novel synthetic chalcone containing electron donating groups with anticancer properties. The present chemist and pharmacist focus on medicinal chemistry strategies for design and development of anticancer chalcones.

2. Experiments

2.1 Material and Measurement

The all starting materials and solvents were purchased from Sigma-Aldrich and SD Fine and used without further purification. Melting points were determined by conventional method and then by electro capillary apparatus and are uncorrected. All the synthesized compounds were inspected by thin layer chromatography on silica gel (E-Merck) and the spots were identified by UV lamp. IR spectra and proton 1H NMR spectra in DMSO at 500 MHz were recorded at CSMCRI Bhavnagar.

2.2 General procedure of synthesis of chalcone

The synthesis of chalcone analogs was conducted according to the procedure reported in the reference [10-12]. Aminoaacetophenone derivative (2.5 milimole) and substituted aldehydes (2.5milimole) were dissolved in 30 ml methanol. To the solution, 10 ml NaOH (20%) solution was added drop wise and reaction mixture was stirred for 1-2 hour at room temperature by magnetic stirrer and kept for overnight. Subsequently, it was poured in ice water and neutralized by HCl. The solid precipitates were filtered off and recrystallized from methanol or ethyl acetate.

\[
\text{Ar-CHO} + \text{NaOH} \rightarrow \text{Ar} \text{C=O} \text{Ar}
\]

Figure 2. Synthesis of Chalcone analogs possessing ring activating groups 1a-1e.

2.2.1. (2E)-1-(4-aminophenyl)-3-(4-hydroxy-3-methoxyphenyl)prop-2-en-1-one(1a)

Yellow solid, Yield 58.9 %. M.P 105-107 °C, Rf 0.71

FT-IR (\(\nu, \text{ cm}^{-1}\)): 3395(-OH), 3330, 3225 (-NH\(_2\)), 3063(aromatic C-H), 1649 (>C=O), 1590(-HC=CH-), 1277, 1305 (C-N str)

1H NMR (500 MHz DMSO, Me\(_4\)Si): 3.50 (br, s, -NH\(_2\)), 3.85(s, -OCH\(_3\)), 6.027(s,1H, H\(_2\)), 6.62(d, 1H\(_\alpha\)), 7.66 (d, 1H\(_\beta\)).

GC-MS (EI, m/z): 269(M\(^+\)), 266, 239, 214, 191, 171, 99, 62.
2.2. (2E)-1-(4-aminophenyl)-3-(4-hydroxy-3,5-dimethoxyphenyl)prop-2-en-1-one (1b)

Yellow solid, Yield 57.5%, M.P 98-100°C, Rf 0.66
FT-IR (v, cm⁻¹): 3396(−OH), 3331, 3225(−NH₂), 3064(amine C-H), 1648(−C=O), 1590(−H⁻C−CH⁻), 1276, 1304(C-N str)
¹H NMR (500 MHz DMSO, Me₄Si): 3.49(br, s, −NH₂), 3.71(s, −OCH₃), 3.82(s, −OCH₃), 6.028(s, 1H, H₁ₓ), 6.58(d, 1H₀), 7.68(d, 1H₀).
GC-MS (EI, m/z): 299(M⁺), 266, 229, 214, 181, 166, 62.

2.2.3. (2E)-1-(4-aminophenyl)-3-(2-hydroxyphenyl)prop-2-en-1-one (1c)

Pale Yellow solid, Yield 62.5%, M.P 110-112°C, Rf 0.68
FT-IR (v, cm⁻¹): 3570(−OH), 3338, 3328(−NH₂), 3050(amine C-H), 1676(−C=O), 1595(−H⁻C−CH⁻), 1270,1364(C-N str)
¹H NMR (500 MHz DMSO, Me₄Si): 3.47(br, s, −NH₂), 6.57(d, 1H₀), 7.51(d, 1H₀), 7.013(m, H₂), 7.72(m, H₃, H₄).
GC-MS (EI, m/z): 239(M⁺), 214, 166, 122, 62.

2.2.4. (2E)-1-(4-aminophenyl)-3-(2,4-dihydroxyphenyl)prop-2-en-1-one (1d)

Yellow solid, Yield 87.0%, M.P 98-100°C, Rf 0.72
FT-IR (v, cm⁻¹): 3680(−OH), 3652(−OH), 3370, 3325(−NH₂), 3062(amine C-H), 1673(−C=O), 1596(−H⁻C−CH⁻), 1270,1364(C-N str)
¹H NMR (500 MHz DMSO, Me₄Si): 3.48(br, s, −NH₂), 6.32(s,1H, H₂), 6.55(d, 1H₀), 7.48(d, 1H₀), 7.55(d, 1H₀, H₅), 7.76(d,1H₁, H₂).
GC-MS (EI, m/z): 257(M⁺), 243, 196, 176, 155, 139, 116, 102.

2.2.5. (2E)-1-(4-aminophenyl)-3-(2,4-dihydroxynapthalen-1-yl)prop-2-en-1-one (1e)

Brick Red solid, Yield 73.6%, M.P 182-185°C, Rf 0.53
FT-IR (v, cm⁻¹): 3652(−OH), 3322, 3335(−NH₂), 3044(amine C-H), 1668(−C=O), 1587(−H⁻C−CH⁻), 1267,1349(C-N str)
¹H NMR (500 MHz DMSO, Me₄Si): 3.49(br, s, −NH₂), 6.58(d, 1H₀), 7.68(d, 1H₁), 7.42(m, C-H₂), 7.85(d,1H₁, H₃), 8.05(d,1H₁, H₂).
GC-MS (EI, m/z): 290(M⁺), 248, 211, 156, 122, 102, 74, 58.

3. Result and Discussion

3.1 Chemistry

A novel target chalcone scaffolds 1a-1e were synthesized using the base-catalysed Claisen-Schmidt condensation of various electron donating group possessing substituted aromatic aldehydes with 4-Aminoacetophenone. Ring activating group like hydroxy and methoxy possessing chalcones, depending upon positions in aryl ring, were synthesized to influence anticancer and other activities. Structures of all the synthesized chalcones were characterized by ¹H NMR spectra which showed double doublet in the range of δ 6-7.50 ppm indicating that prop-2-ene linkage was formed. In the 1H NMR spectral analysis, two singlets at δ 3.71 and δ 3.82 ppm were assigned to two methoxy protons on aromatic ring. Also 1H NMR spectrum showed the disappearance of the singlet at δ 2.47 corresponding to keto group of 4-aminoacetophenone indicate formation of chalcone linkage. The IR spectra of synthesized compounds exhibited absorption bands of C=O and CH=CH of chalcone linkage at 1650 cm⁻¹ and 1590 cm⁻¹ respectively. Further, structures of the entire compound were supported by molecular ion peaks corresponding to the molecular formula.

3.2 In-Vitro Cytotoxicity

In the present investigation, cytotoxicity of all the synthesized chalcone derivatives were investigated against selected human cancer cell lines; MCF-7(breast carcinoma), DU-145 (prostate carcinoma), K-562 (chronic myelogenous leukemia) and A-549 (lung carcinoma) at different
concentration, as summarized in Tables 1-4. These compounds were also evaluated for non-cancerous cell line (Vero) derived from African green monkey kidney, as well as standard anticancer drug Doxorubicin. Dose Response Curve (DRC) against all cell lines was plotted with 10 analysis point i.e. with 10 different drug concentrations. The concentration causing 50% cell growth inhibition (IC_{50}) was determined from DRC using Graph Pad Prism software (Ver. 5.04) (Graph Pad Software, Inc., USA) and Microsoft Excel 2007 (Microsoft Corporation, USA) application.

Result showed that most of the tested chalcone molecules exerted significant in-vitro cytotoxicity. It was found that compound 1b showed a potent activity against human breast cancer line MCF-7 while compound 1e showed almost two time higher activity than Doxorubicin against human prostate cancer cell DU-145. Compounds 1b, 1c and 1e exhibited more potent activity against human myogenous leukaemia cancer cell K-562. Furthermore, 1b and 1c chalcones showed good potency against human lung adenocarcinoma epithelial cell line A-549.

Table 1. Cytotoxicity of synthesized compounds against human breast cancer cell line MCF-7 at different concentration.

| Conc. µg/ml | Log conc. | % Cell Inhibition | 1a | 1b | 1c | 1d | 1e | STD |
|-------------|-----------|-------------------|----|----|----|----|----|-----|
| 0.01        | -2.29     | 7.880             | -0.789 | 1.410 | 2.130 | 2.050 | 9.230 |
| 0.02        | -1.82     | 9.400             | -1.760 | 6.280 | 8.180 | 10.070 | 13.530 |
| 0.05        | -1.34     | 8.470             | 3.320 | 3.230 | 12.040 | 9.330 | 14.300 |
| 0.14        | -0.86     | 18.210            | 8.110 | -1.930 | 13.110 | 11.210 | 18.320 |
| 0.41        | -0.39     | 22.460            | 12.370 | 2.790 | 13.940 | 15.170 | 28.080 |
| 1.23        | 0.09      | 24.350            | 26.140 | 0.000 | 19.240 | 21.420 | 33.910 |
| 3.70        | 0.57      | 26.270            | 38.220 | 10.630 | 18.090 | 26.010 | 41.250 |
| 11.11       | 1.05      | 30.340            | 40.110 | 23.850 | 21.310 | 28.940 | 47.020 |
| 33.33       | 1.52      | 58.990            | 41.130 | 39.450 | 51.210 | 53.170 | 69.320 |
| 100.00      | 2.00      | 67.960            | 87.900 | 72.790 | 66.340 | 76.190 | 82.010 |

| Log IC_{50} (µM/ml) | 20.58 | 8.377 | 56.57 | 39.53 | 32.65 | 7.940 |
|--------------------|-------|-------|-------|-------|-------|-------|
| R^2                | 0.9288 | 0.9362 | 0.9837 | 0.9460 | 0.9569 | 0.9430 |

Table 2. Cytotoxicity of synthesized compounds against human prostate cancer cell line DU-145 at different concentration.

| Conc. µg/ml | Log conc. | % Cell Inhibition | 1a | 1b | 1c | 1d | 1e | STD |
|-------------|-----------|-------------------|----|----|----|----|----|-----|
| 0.01        | -2.29     | 0.23              | -22.44 | -27.93 | -30.25 | -34.46 | -39.665 |
| 0.02        | -1.82     | 1.10              | -19.54 | -27.93 | -22.88 | -33.44 | -35.5214 |
| 0.05        | -1.34     | 4.29              | -19.54 | -25.78 | -30.25 | -31.94 | -22.9854 |
| 0.14        | -0.86     | 11.71             | -12.34 | -23.88 | -12.41 | -27.84 | -19.3512 |
| 0.41        | -0.39     | 23.18             | -11.54 | -17.95 | -22.88 | -23.15 | -13.8918 |
| 1.23        | 0.09      | 27.05             | -0.69  | -3.71  | -6.54  | -7.18  | -12.7835 |
| 3.70        | 0.57      | 32.09             | 0.11   | -0.82  | -1.98  | -3.42  | -10.3969 |
| 11.11       | 1.05      | 48.12             | 2.21   | 0.22   | 7.52   | -0.56  | 48.80412 |
| 33.33       | 1.52      | 52.10             | 33.00  | 60.53  | 51.90  | 26.38  | 65.69072 |
| 100.00      | 2.00      | 68.02             | 36.26  | 60.53  | 52.65  | 31.41  | 78.20103 |

| Log IC_{50} (µM/ml) | 10.33 | 13.24 | 17.34 | 13.23 | 5.137 | 9.034 |
|--------------------|-------|-------|-------|-------|-------|-------|
| R^2                | 0.9621 | 0.9182 | 0.9229 | 0.9380 | 0.9347 | 0.9551 |
Table 3. Cytotoxicity of synthesized compounds against human myelogenous leukaemia cell line K-562 at different concentration.

| Conc. µg/ml | Log conc. | % Cell Inhibition |
|-------------|-----------|-------------------|
|             |           | 1a | 1b | 1c | 1d | 1e | STD |
| 0.01        | -2.29     | -12.57 | -35.18 | -23.47 | -21.37 | -24.68 | -40.87 |
| 0.02        | -1.82     | -11.07 | -24.16 | -23.47 | -18.89 | -11.14 | -32.81 |
| 0.05        | -1.34     | -9.02 | -17.68 | -13.63 | -11.63 | -12.74 | -29.69 |
| 0.14        | -0.86     | -6.69 | -13.14 | -7.64 | -10.93 | -3.21 | -17.63 |
| 0.41        | -0.39     | -6.69 | -6.70 | 5.84 | 1.26 | 6.43 | -14.34 |
| 1.23        | 0.09      | -4.17 | -2.60 | 3.57 | 4.52 | 6.97 | -12.55 |
| 3.70        | 0.57      | -1.97 | 6.81 | 16.37 | 11.22 | 14.71 | -11.17 |
| 11.11       | 1.05      | -0.07 | 7.91 | 13.16 | 11.22 | 15.19 | 48.35 |
| 33.33       | 1.52      | 36.83 | 46.01 | 49.39 | 48.41 | 51.22 | 71.32 |
| 100.00      | 2.00      | 45.34 | 49.05 | 53.60 | 53.22 | 53.82 | 86.69 |
| Log IC<sub>50</sub> (µM/ml) | 34.52 | 9.722 | 7.455 | 12.00 | 9.705 | 10.33 |
| R<sup>2</sup> | 0.9476 | 0.9975 | 0.973 | 0.9054 | 0.9755 | 0.9621 |

Table 4. Cytotoxicity of synthesized compounds against human lung adenocarcinoma epithelial cell line A-549 at different concentration.

| Conc. µg/ml | Log conc. | % Cell Inhibition |
|-------------|-----------|-------------------|
|             |           | 1a | 1b | 1c | 1d | 1e | STD |
| 0.01        | -2.29     | 1.06 | 7.29 | 0.07 | 0.12 | -0.32 | 6.96 |
| 0.02        | -1.82     | 1.56 | 16.98 | 1.25 | 0.35 | 0.06 | 10.36 |
| 0.05        | -1.34     | 2.36 | 14.34 | 1.63 | 0.98 | 0.78 | 16.22 |
| 0.14        | -0.86     | 4.63 | 2.87 | 4.56 | 0.55 | 2.05 | 24.05 |
| 0.41        | -0.39     | 3.25 | 13.75 | 17.23 | 1.05 | 4.30 | 29.31 |
| 1.23        | 0.09      | 10.22 | 11.77 | 22.70 | 1.56 | 9.31 | 38.87 |
| 3.70        | 0.57      | 13.56 | 30.63 | 32.45 | 2.06 | 17.28 | 44.86 |
| 11.11       | 1.05      | 28.31 | 56.95 | 42.31 | 5.35 | 28.69 | 50.32 |
| 33.33       | 1.52      | 31.25 | 61.20 | 48.64 | 6.35 | 42.65 | 71.35 |
| 100.00      | 2.00      | 42.36 | 49.56 | 65.23 | 32.12 | 66.34 | 85.33 |
| Log IC<sub>50</sub> (µM/ml) | 8.061 | 4.283 | 2.809 | >100 | 21.11 | 5.052 |
| R<sup>2</sup> | 0.9797 | 0.8908 | 0.9562 | 0.9736 | 0.9842 | 0.9178 |
Table 5. Cytotoxicity of synthesized compounds against normal Vero cell line at different concentration.

| Conc. µg/ml | Log conc. | % Cell Inhibition |
|-------------|-----------|-------------------|
| 0.01        | -2.29     | 1a 0.32 1b 0.21 1c -0.89 1d 0.25 1e -0.98 STD -0.98 |
| 0.02        | -1.82     | 1a -0.65 1b 0.65 1c -0.55 1d 0.35 1e 0.25 STD -0.65 |
| 0.05        | -1.34     | 1a 0.22 1b 1.12 1c 0.05 1d 0.87 1e 1.05 STD 0.05 |
| 0.14        | -0.86     | 1a 0.58 1b 1.85 1c 0.23 1d 1.15 1e 2.36 STD 0.56 |
| 0.41        | -0.39     | 1a 1.02 1b 2.15 1c 0.65 1d 2.01 1e 4.11 STD 0.98 |
| 1.23        | 0.09      | 1a 1.65 1b 3.65 1c 1.05 1d 2.36 1e 5.36 STD 1.15 |
| 3.70        | 0.57      | 1a 1.85 1b 4.35 1c 1.85 1d 3.11 1e 8.37 STD 1.68 |
| 11.11       | 1.05      | 1a 2.10 1b 6.22 1c 2.14 1d 4.30 1e 15.24 STD 2.46 |
| 33.33       | 1.52      | 1a 2.65 1b 15.35 1c 3.62 1d 11.20 1e 28.71 STD 5.51 |
| 100.00      | 2.00      | 1a 22.10 1b 45.35 1c 21.35 1d 44.21 1e 56.38 STD 29.38 |
| Log IC₅₀ (µM/ml) | | >100 >100 >100 >100 79.71 >100 |

R² 0.9402 0.9957 0.9645 0.9885 0.9902 0.9738

Figure 3. Effect of dose response of synthesized five chalcones against (1) MCF-7 (2) DU-145 (3) K-562 and (4) A-549 cell line using MTT assay. Dose Response Curve against all cell lines was plotted with 10 different drug concentrations and determined using Graph Pad Prism software.

A deep look to the structure activity relationship of the results in Tables 1-5, it was found that significant cytotoxic activity towards MCF-7 cell line was noted for 4-hydroxy-3-methoxy group on phenyl ring 1b (IC₅₀ = 8.377 µM). Aside from it, compound 1e showed inhibitory effect against human prostate cancer cells. Among these, 2-hydroxy or 4-hydroxy analogs 1b, 1c and 1e were shown to be more potent cytotoxic compounds against human myelogenous leukaemia cell line K-562 with IC₅₀ value 9.72, 7.45 and 9.70 µM respectively. Table 4 showed that 4-hydroxy-3,4-dimethoxy analog 1b and 4-hydroxy analog 1c chalcones were exhibited higher inhibitory activity.
against lung cancer cell lines A-549. Further the activity of all effective compounds series were tested against normal cell line (VERO cell line) and it was concluded that most of compounds were non-toxic to normal cell as they showed IC\textsubscript{50} values more than 100\,µM/ml except 1e (IC\textsubscript{50} value 79.71\,µM/ml) was found to be slight toxic for normal cell.

It should be noted that chalcones 1b and 1c showed cytotoxicity in broad spectrum of cancer cells i.e. K-562, DU-145 and MCF-7 with IC\textsubscript{50} value less than the range of standard drug doxorubicin without affecting normal cells.

4. Conclusion

In conclusion, cytotoxic activity testing revealed that most of the synthesized chalcones displayed cytotoxic activity against several cancer cell lines. In particular, compound 1b exhibited a significant cytotoxicity against MCF-7 cell line, compound 1e showed potent inhibitory effect on DU-145 cell line (IC\textsubscript{50} = 5.13 \,µM), but unfortunately it was toxic towards non-cancerous Vero cells. Compounds 1b and 1c displayed higher cytotoxicity against leukaemia cell lines K-562 and lung cancer cell line A-549, also non-toxic to Vero cells. Hence from this data it can be concluded that chalcone moieties possessing ring activating group on phenyl ring has not only enhanced the anticancer activity but has provided an insight in the design of such conjugates.

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