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Short communication

A new series of chalcones endowed with potent anticancer activity towards A549 cells

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Introduction

Lung cancer remains a deadly disease threatening public health and causing significant mortality and morbidity worldwide, as a result of the aging and growth of the population, as well as the increase in cancer-causing habits, particularly smoking (Jemal et al., 2011).

Lung cancer is divided into two groups, namely small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC is responsible for 85% of all lung cancer cases and consists of three subgroups: squamous cell carcinoma, adenocarcinoma, and large cell carcinoma (Zappa and Mousa, 2016).

The best treatment option for NSCLC is still the complete surgical resection (Nascimento *et al*., 2015). However, NSCLC is mostly diagnosed at locally advanced or metastatic stages when surgery is no longer an option. In these cases, radiotherapy and chemotherapy become important therapeutic approaches (Li et al., 2016).

Chemotherapeutic agents destroy not only cancer cells but also normal cells and correspondingly have many side effects (e.g. fatigue, alopecia, anemia, bleeding). Besides, the resistance to existing chemotherapeutic agents limits the efficacy of chemotherapy. As a result, the discovery of potent anticancer agents devoid of severe side effects is still an uphill task for researchers (Iksen et al., 2021).

Chalcones have come into prominence as promising lead compounds for the treatment of cancer owing to their structural features allowing these ligands to interact with biological targets, high therapeutic index, negligible side effects, and ease of synthesis (Sharma et al., 2015).

Prompted by the scientific reports related to chalcone-based anticancer agents, herein new chalcones were synthesized efficiently and evaluated for their cytotoxic effects on A549 human lung adenocarcinoma cells.

Materials and methods

Chemistry

All chemicals were purchased from commercial suppliers and used without further purification. Melting points (m.p.) were detected on a digital melting point apparatus (Electrothermal, Staffordshire, UK) and are uncorrected. Infrared (IR) spectra were recorded on a Fourier Transform IR spectrophotometer (Shimadzu, Tokyo, Japan). Nuclear magnetic resonance (NMR, ^{1}H and ^{13}C) spectra were acquired using a NMR spectrometer (Bruker, Billerica, MA, USA). High Resolution Mass Spectrometry (HRMS) spectra were recorded on a LCMS-IT-TOF system (Shimadzu, Kyoto, Japan).

*General procedure for the preparation of chalcones (**1a-g**)*

A mixture of substituted 2-acetylthiophene (0.01 mol) and aromatic aldehyde (0.01 mol) in the presence of 40% (w/v) aqueous sodium hydroxide (5 mL) in ethanol (35 mL) was stirred at room temperature for 48 h. Upon completion of the reaction, the reaction mixture was poured into crushed ice. The precipitated solid was filtered, washed with water, and dried. The product was crystallized from ethanol (Özdemir et al., 2015).

All spectral data of compounds **1a** and **1b** were presented below:

*1-(4-Methylthiophen-2-yl)-3-(1-methoxynaphthalen-2-yl)prop-2-en-1-one (**1a**)* Yield: 91%, M.p.: 123-124 °C. IR ν_{max} (cm^{-1}): 3068.75, 3055.24, 2935.66, 2837.29, 1631.78, 1579.70, 1556.55, 1510.26, 1463.97, 1454.33, 1417.68, 1352.10, 1298.09, 1269.16, 1247.94, 1232.51, 1188.15, 1149.57, 1101.35, 1043.49, 1028.06, 968.27, 839.03, 796.60, 744.52, 713.66, 686.66, 624.94. ^{1}H NMR (300 MHz, DMSO-d_6): 2.29 (s, 3H), 4.07 (s, 3H), 7.26 (d, *J*=

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14.37 Hz, 1H), 7.34-7.39 (m, 1H), 7.43-7.47 (m, 1H), 7.55-7.62 (m, 1H), 7.67-7.74 (m, 1H), 7.83 (d, *J*= 15.69 Hz, 1H), 7.94-7.97 (m, 1H), 8.08 (d, *J*= 9.15 Hz, 1H), 8.20 (d, *J*= 8.61 Hz, 1H), 8.32 (d, *J*= 15.72 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): 15.72 (CH_3), 56.60 (CH_3), 113.81 (CH), 116.12 (C), 123.57 (d, *J*= 48.75 Hz, CH), 124.24 (d, *J*= 23.25 Hz, CH), 126.84 (d, *J*= 38.25 Hz, CH), 128.54 (d, *J*= 21.00 Hz, CH), 129.17 (d, *J*= 21.75 Hz, CH), 130.17 (CH), 131.55 (d, *J*= 27.75 Hz, CH), 132.78 (d, *J*= 12.75 Hz, CH), 135.42 (CH), 136.25 (2C), 139.60 (C), 145.34 (C), 157.75 (C), 182.35 (C). HRMS (ESI) (*m/z*) $[M+H]^+$ calcd. for $C_{19}H_{16}O_2S$: 309.0944, found: 309.0933.

1-(4-Methylthiophen-2-yl)-3-(4-(pyrrolidin-1-yl)phenyl)prop-2-en-1-one ***(1b)*** Yield: 80%, M.p.: 126-127 °C. IR ν_{max} (cm^{-1}): 3076.46, 3062.18, 2974.23, 2939.52, 2841.15, 1629.85, 1606.70, 1556.55, 1521.84, 1485.19, 1421.54, 1394.53, 1321.24, 1300.02, 1224.80, 1203.58, 1178.51, 1147.65, 989.48, 975.98, 860.25, 842.89, 808.17, 696.30. ^{1}H NMR (300 MHz, DMSO-d_6): 1.95-1.99 (m, 4H), 2.28 (s, 3H), 3.30-3.34 (m, 4H), 6.58 (d, *J*= 8.82 Hz, 2H), 7.51 (d, *J*= 15.33 Hz, 1H), 7.57 (s, 1H), 7.62 (d, *J*= 15.45 Hz, 1H), 7.68 (d, *J*= 8.82 Hz, 2H), 8.05 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): 15.85 (CH_3), 25.42 ($2CH_2$), 47.75 ($2CH_2$), 112.16 (2CH), 115.69 (CH), 121.77 (CH), 130.25 (CH), 131.44 (2CH), 134.65 (CH), 139.18 (C), 144.80 (C), 146.41 (C), 149.89 (C), 181.58 (C). HRMS (ESI) (*m/z*) $[M+H]^+$ calcd. for $C_{18}H_{19}NOS$: 298.1260, found: 298.1243.

Biochemistry

MTT assay was performed to assess the cytotoxic effects of compounds **1a-g** on A549 human lung adenocarcinoma cell line (ATCC® CCL-185™) as described earlier (Altıntop et al., 2018). Cisplatin was used as a positive control.

Results and discussion

Compounds **1a-g** were synthesized and investigated for their cytotoxic activities towards A549 human lung adenocarcinoma cells. Among compounds **1a-g**, compounds **1b** and **1a** showed stronger anticancer activity towards A549 cells than positive control cisplatin (IC_{50}= 18.33±0.94 µg/mL) with IC_{50} values of 11.61±2.47 µg/mL and 14.34±0.45 µg/mL, respectively. According to the *in vitro* data, the methyl substituent attached to the 4th position of the thiophene ring significantly enhanced the anticancer potency.

Conclusion

In conclusion, we described the synthesis and *in vitro* evaluation of a new series of chalcones (**1a-g**) as anti-NSCLC agents. Compounds **1a** and **1b** were the most potent anti-NSCLC agents in this series with IC_{50} values of 14.34±0.45 µg/mL and 11.61±2.47 µg/mL, respectively compared to cisplatin. In the continuation of this work, further studies are required to elucidate their mechanism of anti-NSCLC action.

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