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Synthesis, Characterization and Biological Evaluation of Some New Methylxanthine-Bearing Chalcone Derivatives as Antiproliferative agents

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ABSTRACT

Chalcones are an important class of naturally occurring and synthetic compounds that have attracted considerable attention owing to their wide range of biological and pharmacological activities, including anticancer, antimicrobial, anti-inflammatory, and antioxidant properties. In the present study, a series of methylxanthine-based chalcone derivatives, N-(substituted aryl)acryloyl theophyllines 3(a–e), were synthesized through a Claisen–Schmidt condensation reaction involving aromatic aldehyde derivatives and acetylated theophylline precursors in ethanol under basic or acidic catalytic conditions. The synthesized compounds were purified by recrystallization and subsequently characterized using Fourier Transform Infrared (FTIR) spectroscopy and Proton Nuclear Magnetic Resonance (^1H NMR) spectroscopy to confirm their chemical structures. The antiproliferative potential of the synthesized derivatives was evaluated against the human Hep-2 cancer cell line using the MTT assay. The results demonstrated that several of the synthesized N-(substituted aryl)acryloyl theophylline derivatives exhibited notable cytotoxic and antiproliferative effects, indicating their ability to inhibit cancer cell growth. The observed biological activity suggests that the incorporation of both chalcone and methylxanthine pharmacophores may contribute to enhanced anticancer properties. These findings highlight the potential of the synthesized compounds as promising lead molecules for the development of novel anticancer agents and warrant further pharmacological and mechanistic investigations.

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1. Introduction

Chalcones are an important class of open-chain flavonoids chemically known as 1,3-diphenyl-2-propen-1-ones, in which two aromatic rings are connected through a three-carbon α,β-unsaturated carbonyl framework. Their characteristic structure contains a ketoethylenic moiety (–CO–CH=CH–) that serves as a highly reactive pharmacophoric unit responsible for many of their biological activities. The presence of conjugated double bonds and delocalized π-electron systems across the aromatic rings and carbonyl group contributes to their unique chemical reactivity and diverse pharmacological properties. Chalcones are commonly synthesized through the Claisen–Schmidt condensation reaction, a convenient and efficient method involving the condensation of aromatic aldehydes with appropriate ketones under either basic or acidic conditions, followed by dehydration to yield the corresponding α,β-unsaturated ketones. Owing to its simplicity, high efficiency, and versatility, this synthetic approach remains the most widely employed route for the preparation of chalcone derivatives with diverse structural modifications. Naturally occurring chalcones are widely distributed throughout the plant kingdom, ranging from lower plants such as ferns to higher flowering plants. They are commonly found in fruits, vegetables, spices, tea, soy-based products, and numerous medicinal plants.

As important intermediates in the biosynthesis of flavonoids and isoflavonoids, chalcones play a crucial role in plant metabolism and defense mechanisms. Their abundance in dietary sources has attracted considerable scientific interest due to their potential health-promoting effects.

Over the past several decades, both natural and synthetic chalcones have been extensively investigated because of their broad spectrum of biological and pharmacological activities. Numerous studies have demonstrated their potential as anticancer, antimicrobial, anti-inflammatory, antioxidant, antimalarial, antiviral, antidiabetic, and neuroprotective agents. The structural flexibility of the chalcone scaffold allows the introduction of various functional groups, enabling the development of novel derivatives with enhanced biological efficacy and improved pharmacokinetic properties. Consequently, chalcones have emerged as valuable lead compounds in medicinal chemistry and continue to serve as important templates for the design and development of new therapeutic agents. Their aromatic compounds with an unsaturated side chain are often cytotoxic in vitro anticancer [1], anti-proliferative [2], antioxidant [3], anti-inflammatory [4], antiulcer [5], anti-anxiety [6], anti-depression [6], analgesic [6], anticholinergic [7], antiplatelet [8], antileishmanial [9], Antidiabetic [10], antihyperglycemic [11], acetyl cholinesterase inhibitors [12], Xanthine oxidase inhibitors [13], radical scavengers [13], non-purine xanthine oxidase inhibitors [14],

monoamine oxidase inhibitors [15], enoyl ACP reductase inhibitors [16], Alzheimer's disease [17], antimalarial [18], antimicrobial [19-22] and against coronavirus [23].

Materials and Methods

All starting materials, reagents, and solvents used in the present study were of analytical grade and were procured from commercial suppliers, including Merck (Germany). The chemicals were used as received without further purification unless otherwise stated. The progress of the reactions and the purity of the synthesized compounds were monitored by analytical thin-layer chromatography (TLC) using Merck silica gel 60 F254 precoated aluminum plates. The chromatograms were visualized under ultraviolet (UV) light and, where necessary, by exposure to appropriate staining reagents. Infrared (IR) spectra were recorded on a Fourier Transform Infrared (FT-IR) spectrophotometer using standard sample preparation techniques, and the characteristic absorption frequencies are reported in cm^{-1}. Proton nuclear magnetic resonance (^1H NMR) spectra were obtained using a Bruker 400 MHz NMR spectrometer. Chemical shifts (δ) are expressed in ppm. parts per million (ppm) relative to tetramethylsilane (TMS) as the internal standard, and coupling constants (J) are reported in hertz (Hz). The melting points of the synthesized compounds were determined using a digital melting point apparatus and are reported uncorrected. The purity and identity of the synthesized compounds were established through chromatographic analysis and spectroscopic characterization.

Of several bioactive heterocyclic compounds. Many common medicines available for different diseases are found to containing 1,2,4-triazole as heterocyclic moiety. The examples include Ribavirin which is antiviraldrug, Rizatriptan is used to cure migrain, Estazolam and Alprazolam are anxiolytic, Letrozole and Anastrozole are anticancer drugs. Triazole derivatives found in drugs like Itraconazole, Fluconazole, Posaconazole are useful for the treatment of fungal infections where as Ruficonamide is well known anticonvulsant [8-19]. Triazole derivatives also found to possess moderate to good antibacterial and antifungal activities [20]. Many methods are reported for the preparation of bioactive triazole derivatives. One of them is Biginelli reaction which involves condensation of 1,2,4-triazole-5-amine and β-keto ester with different aldehydes. Looking to the pharmacological importance we have synthesized a new series of compounds containing triazole and dihydropyrimidine moieties in one frame work using reported method [21, 22].

Materials and methods: General: All the chemicals required are obtained from Spectrochem, Finar and Sigma Aldrich. Merck Kieselgel 60 F254 plates were recorded in DMSO d6 solution in 5 mm tubes at room temperature, on a BRUKER 400 MHz FT-NMR, with TMS as internal standard. IR Spectra were recorded on SHIMADZU FT-IR 8400 using potassium bromide pallets. Mass spectra were recorded on SHIMADZU QP-2010. The antimicrobial activity was carried out using broth dilution method to determine minimum inhibitory concentration (MIC).

Synthesis and Characterization

Synthesis of Sodium salt of theophylline (1)

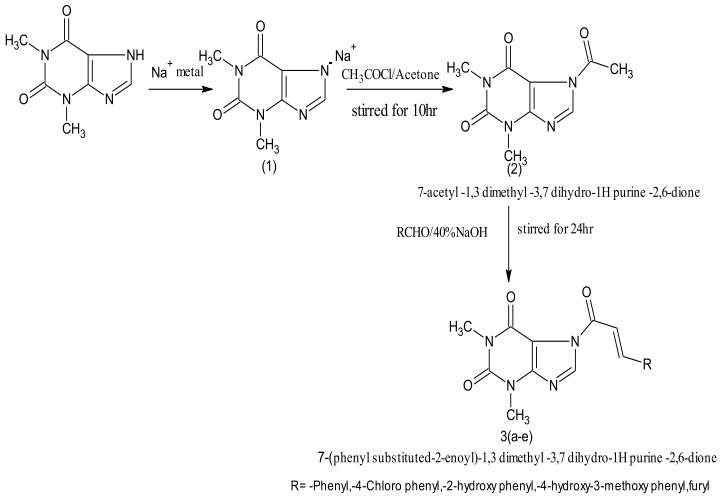
To theophylline (0.04mol or 7.3gm) in a stoppered conical flask was added sodium metal (0.04mol 0.88gm) little by little, till effervescence ceased. Solid separated on cooling was used as such for the next step.

Synthesis of N-Acetyl theophylline (2)

Sodium salt of theophylline (1) (0.03mol or 5.2 gm) was suspended in acetone and acetyl chloride (0.03mol, 2.5ml) while stirring and cooling. It was stirred for 1 hr and K_2CO_3 (0.2mol or 28gms) was added as a base. It was further stirred for another 10hr. The progress and completion of the reaction were confirmed by TLC (Mobile Phase 7.5:2:0.5 Toluene: Methanol: Ammonia). A solid was obtained after the distillation of acetone and recrystallised from ethanol.

Synthesis of N-(substituted aryl) acryloyl theophylline 3(a-e)

N-acetyl theophylline (2) (0.01mol, 2.23.grm) was added to different aromatic aldehydes in 20ml of ethanol and added 40% sodium hydroxide solution. The reaction mixture was stirred at room temperature for 24 h to ensure complete conversion of the starting materials. The progress of the reaction was monitored periodically by thin-layer chromatography (TLC) using a chloroform (9:1, v/v) solvent system as the mobile phase. Upon completion of the reaction, as indicated by the disappearance of the starting materials on TLC, the reaction mixture was carefully poured onto crushed ice containing 10% hydrochloric acid with continuous stirring. The resulting precipitated solid was collected by filtration, thoroughly washed with cold water to remove residual impurities, and dried under ambient conditions. The crude product was subsequently purified by recrystallization from aqueous ethanol to afford the corresponding target compounds in pure form. The synthesized derivatives, designated as compounds 3a–3e, were obtained following the synthetic pathway outlined in Scheme 1 and were further characterized using appropriate spectroscopic and analytical techniques.



Physical and Spectral data of some of the synthesized compounds

7-acetyl-1, 3dimethyl-3, 7 dihydro-1H purine-2, 6-dione (2)

Yield: 72%, mp. 154-157 °C, IRVmax: 3105.20 (C-H stretching in aromatic), 2818.15(N- CH_3 stretching), 1700.70(C=C stretching), 1690.41(C=N Stretching), 1650.62(C=O), 1560.46(C=C stretching in aromatic), 1215.50(C-N stretching).

1,3-dimethyl-7-(-3-phenylprop-2-enoyl)-3,7-dihydro-1H-purine-2,6-dione (3a)

Yield: 72.68%, mp. 265-268 °C, Molecular formula: $C_{16}H_{14}N_4O_3$, Mol.wt:310.30, Composition: C (61.93%) H (4.55%) N (18.06%) O (15.47%).

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IRVmax: 3005.2 (C-H stretching in aromatic), 2808.15 (N-CH_3 stretching), 1683.98(C=C stretching), 1660.55(C=N Stretching), 1637.97(C=O), 1531.53(C=C stretching in aromatic), 1315.86(C-N stretching). 1H NMR (400 MHz-CDCl3) (δ ppm): δ 2.77 (3H, s), 2.97 (3H, s), 6.84-7.24(5H, m) 7.53 (1H, d) 7.80 (1H, d). Mass (m/z): 309.

1,3-dimethyl-7-(-3-(4-chlorophenyl) prop-2-enoyl)-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (3b)

Yield: 69.48%, mp. 252-256°C, Molecular formula: $C_{16}H_{13}ClN_4O_3$, Mol.wt:344.75, Composition: C (55.74%) H (3.80%) Cl (10.28%) N (16.25%) O (13.92%). IRVmax: 3088.41 (C-H stretching in aromatic), 2811.55 (N-CH_3 stretching), 1716.98(C=C stretching), 1681.55c), 1637.97(C=O), 1531.53(C=C stretching in aromatic), 1315.86(C-N stretching),744(C-Cl stretching). 1H NMR (400 MHz-CDCl3) (δ ppm): δ 2.77 (3H, s), 2.97 (3H, s), 6.84-7.24(4H, m) 7.50 (1H, d) 7.74 (1H, d). Mass (m/z): 343.

1,3-dimethyl-7-(-3-(2-hydroxyphenyl) prop-2-enoyl)-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (3c)

Yield: 65.43%, mp. 246-248 °C, Molecular formula: $C_{16}H_{14}N_4O_4$, Mol.wt:326.30, Composition: C (58.89%) H (4.32%) N (17.17%) O (19.61%). IRVmax: 3460.41 (OH stretching), 3060.41 (C-H stretching in aromatic), 2815.55 (N-CH_3 stretching), 1771.98(C=C stretching), 1666.55(C=N Stretching), 1627.97(C=O), 1531.53(C=C stretching in aromatic), 1332.86(C-N stretching). 1H NMR (400 MHz-CDCl3) (δ ppm): δ 2.77 (3H, s), 2.97 (3H, s), 6.84-7.24(4H, m) 7.32 (1H, d) 7.78 (1H, d), 9.95(1H, s). Mass (m/z): 326.

1,3-dimethyl-7-[-3-(4-hydroxy-3-methoxyphenyl) prop-2-enoyl]-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (3d)

Yield: 72.78%, mp. 269-271 °C, Molecular formula: $C_{17}H_{16}N_4O_5$, Mol.wt:356.33, Composition: C (57.30%) H (4.53%) N (15.72%) O (22.45%). IRVmax: 3511(OH stretching), 3086.21 (C-H stretching in aromatic), 2815.55 (N-CH3 stretching), 1681.98(C=C stretching), 1666.55(C=N Stretching), 1627.97(C=O), 1531.53(C=C stretching in aromatic), 1332.86(C-N stretching), 1172.76 (C-O-C stretching). 1H NMR: (400 MHz-CDCl3): δ 2.77 (3H, s), 2.97 (3H, s), 3.87, (3H, s), 6.5-7.7.2(3H, m) 7.41(1H, d) 7.78 (1H, d), 9.95(1H, s). Mass (m/z): 356.

1,3-dimethyl-7-(-2-(furan-2-yl) prop-2-enoyl]-1,3-dimethyl-3,7-dihydro-1H-purine-2,6-dione (3e)

Yield: 79.8%, mp. 210-213 °C, Molecular formula: $C_{14}H_{12}N_4O_4$, Mol.wt:300.26, Composition: C (56.00%) H (4.03%) N (18.66%) O (21.31%),IRVmax: 3086.21 (C-H stretching in aromatic), 2815.15(N-CH_3 stretching), 1683.91(C=C stretching), 1660.77(C=N Stretching), 1627.97(C=O), 1531.53(C=C stretching in aromatic),1330.93(C-N stretching),1170.83(C-O-C Stretching). 1H NMR (400 MHz-CDCl3) (δ ppm): δ δ 2.77 (3H, s), 2.97 (3H, s), 3.15-3.25(3H, m) 7.54 (1H, d) 7.79 (1H, d). Mass (m/z): 300.

Cell proliferation MTT assay

The reaction mixture was stirred at room temperature for 24 h to facilitate the completion of the condensation reaction. The progress and completion of the reaction were monitored by thin-layer chromatography (TLC) using a chloroform (9:1, v/v) solvent system as the mobile phase. After confirming the completion of the reaction, the reaction mixture was carefully poured onto crushed ice containing 10% hydrochloric acid, resulting in the formation of a solid precipitate.

The precipitated product was collected by filtration, washed thoroughly with cold water to remove residual impurities, and dried under suitable conditions [24–26]. The resulting crude product was purified by recrystallization from aqueous ethanol to obtain the corresponding target compounds in pure form [24–26]. The synthesis of compounds 3a–3e was successfully achieved following the synthetic pathway depicted in Scheme 1 [24–26]. The purified compounds were subsequently characterized using appropriate spectroscopic and analytical techniques to confirm their structures and assess their purity [24–26].

$$\% \text{ viable cells} = \frac{Absorbance\ Sample - Absorbance\ blank}{Absorbance\ control - Absorbance\ blank} X\ 100$$

Table 1: % Cell viability of Hep-2 cells after exposure to the negative control, positive control, or different concentrations of a synthesized 1,3-dimethyl-7-(-3-phenylprop-2-enoyl)-3,7-dihydro-1H-purine-2,6-dione (3a)

Concentration(µg/ml)	Dilution	Absorbance	% Cell viability
Negative control		0.63	100
positive control		0.09	14.28
500	1:1	0.15	11.11
250	1:2	0.25	29.62
125	1:4	0.30	38.88
62.5	1:8	0.39	55.55
31.25	1:16	0.49	66.66
15.625	1:32	0.53	81.48
7.8125	1:64	0.62	98.14

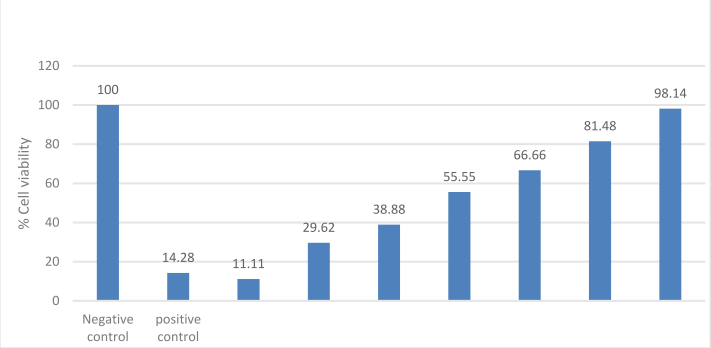

Fig 1: Graphical Representation of in-vitro Anti proliferation activity of synthesized 1,3-dimethyl-7-(-3-phenylprop-2-enoyl)-3,7-dihydro-1H-purine-2,6-dione (3a)

Results and Discussion

A series of 1,3-dimethyl-7-(3-aryl-substituted prop-2-enoyl)-3,7-dihydro-1H-purine-2,6-dione derivatives, designated as compounds 3a–3e, were successfully synthesized through a three-step synthetic protocol. The synthetic route is outlined in Scheme 1. Initially, theophylline was treated with sodium metal to generate the corresponding sodium salt of theophylline (1). Subsequently, the sodium salt underwent acetylation in the presence of acetone and acetyl chloride to afford N-acetyl theophylline (2). In the final step, compound 2 was subjected to Claisen–Schmidt condensation with various substituted aromatic aldehydes to yield the target chalcone derivatives, 1,3-dimethyl-7-(3-aryl-substituted prop-2-enoyl)-3,7-dihydro-1H-purine-2,6-diones (3a–3e), in moderate to good yields ranging from 65% to 79%. The formation of the α,β-unsaturated carbonyl system was achieved efficiently, demonstrating the suitability of the adopted synthetic methodology for the preparation of methylxanthine-based chalcone analogues.

The structures of the synthesized compounds were confirmed using FT-IR and ^{1}H NMR spectroscopic analyses.

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FT-IR spectroscopy provided valuable information regarding the presence of characteristic functional groups within the synthesized molecules. The spectra of compounds 3a–3e exhibited broad absorption bands in the region of 3511–3460 cm^{-1}, which were attributed to O–H stretching vibrations in hydroxyl-substituted derivatives. Aromatic C–H stretching vibrations were observed between 3088 and 3005 cm^{-1}, while aliphatic N–CH_3 stretching bands appeared in the region of 2815–2808 cm^{-1}. The presence of the conjugated enone system was supported by characteristic absorption bands observed in the range of 1716–1681 cm^{-1}. Strong absorption bands corresponding to carbonyl (C=O) and imine-like (C=N) stretching vibrations appeared between 1681–1624 cm^{-1}, confirming the presence of the purinedione and chalcone functionalities. Additional bands observed at approximately 1172 cm^{-1} were assigned to C–O–C stretching vibrations, while peaks in the region of 1332–1315 cm^{-1} corresponded to C–N stretching vibrations. In the chloro-substituted derivative, an absorption band around 744 cm^{-1} was characteristic of aromatic C–Cl stretching, further supporting the proposed structures.

The ^1H NMR spectra of compounds 3a–3e were in excellent agreement with the expected molecular structures. The spectra displayed two distinct singlets at approximately δ 2.77 and δ 2.97 ppm, each integrating for three protons and corresponding to the two N-methyl groups attached to the xanthine nucleus. Signals attributable to aromatic and olefinic protons appeared as multiplets within the range of δ 6.46–7.95 ppm, with integration values consistent with the number and nature of substituents present on the aromatic rings. These resonances confirmed the successful incorporation of the aryl-substituted α,β-unsaturated carbonyl moiety into the theophylline scaffold. In the case of compound 3b, a highly deshielded singlet observed at δ 9.95 ppm was assigned to the phenolic hydroxyl proton, indicating the presence of a free hydroxyl group on the aromatic ring. Overall, the spectroscopic data obtained from FT-IR and ^1H NMR analyses provided strong evidence for the successful synthesis of the target compounds.

The antiproliferative activity of the synthesized derivatives was evaluated against the human Hep-2 cancer cell line using the MTT assay. Cell viability was determined based on the metabolic reduction of MTT, and the results were expressed as percentage cell viability relative to untreated control cells. Among the tested compounds, 1,3-dimethyl-7-(3-phenylprop-2-enoyl)-3,7-dihydro-1H-purine-2,6-dione (3a) was selected for preliminary biological evaluation. The results indicated that compound 3a exhibited negligible cytotoxicity toward Hep-2 cells under the experimental conditions employed, as evidenced by the high percentage of cell viability observed following treatment. In contrast, the positive control demonstrated significant cytotoxic activity, resulting in a substantial reduction in cell viability.

The absence of notable cytotoxic effects for compound 3a suggests that the unsubstituted phenyl derivative possesses limited antiproliferative activity against the Hep-2 cell line. This observation indicates that structural modification of the aromatic ring may be necessary to enhance biological activity. Electron-donating or electron-withdrawing substituents can significantly influence the electronic distribution, lipophilicity, and molecular interactions of chalcone derivatives with biological targets, thereby affecting their pharmacological properties.

Therefore, further investigation of the remaining derivatives (3b–3e) and additional structure–activity relationship studies may provide valuable insights into the molecular features required for improved anticancer activity.

Overall, the successful synthesis and spectroscopic characterization of compounds 3a–3e demonstrate the effectiveness of the adopted synthetic strategy for generating novel methylxanthine-based chalcone derivatives. Although compound 3a exhibited limited cytotoxic activity against the Hep-2 cell line, the structural framework developed in this study provides a promising platform for future optimization and biological evaluation aimed at the discovery of more potent anticancer agents.

Conclusion

A series of novel 1,3-dimethyl-7-(3-aryl-substituted prop-2-enoyl)-3,7-dihydro-1H-purine-2,6-dione derivatives (3a–3e) were successfully synthesized through a convenient three-step synthetic route involving theophylline as the starting material. The synthesized compounds were obtained in satisfactory yields and were characterized by FT-IR and ^1H NMR spectroscopy, which confirmed their proposed structures. Preliminary biological evaluation using the MTT assay against the Hep-2 cell line revealed that compound 3a exhibited low cytotoxicity under the tested conditions, suggesting that further structural modification is required to enhance anticancer activity. The successful incorporation of chalcone and methylxanthine pharmacophores provides a valuable framework for the development of new bioactive molecules.

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