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Synthesis, Characterization, and Antimicrobial Properties of 6-Methoxy-2,3-Dihydro-4H-Chromen-4-One Based Chalcones

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ABSTRACT

A new series of α, β-unsaturated ketones were synthesized by the reaction of different aromatic aldehydes with 6-methoxy-2, 3-dihydro-4H-chromen-2-one. The newly synthesized chalcone derivatives 3a–h were characterized by their ^{1}H-NMR, ^{13}C-NMR, IR, and mass spectral data and were further screened for their antibacterial activity. All the synthesized compounds showed good activities in comparison with standard drug nitrofurazone. Among the tested compounds, 3a, 3c, 3e, and 3h showed excellent activity against all four bacterial strains.

Key words: Antimicrobial activity, Chalcones, Claisen-Schmidt reaction, Flavonoids.

1. INTRODUCTION

The chemistry of chalcones generated intensive scientific studies throughout the world, especially interesting for their biological and industrial applications. Chalcones act as precursors in the synthesis of numerous constructive compounds such as flavonoids and isoflavonoids [1]. Flavonoids are the customary constituents of human diet. Chalcone derivatives are also useful intermediates in the synthesis of several heterocyclic ring systems such as pyrazoles, cyanopyridines, isoxazoles, and pyrimidines [2]. Besides, its use as synthons, chalcones, and its derivatives are known to exhibit broad spectrum of biological properties such as antibacterial, antifungal [3], anti-inflammatory [4-7], antimalarial [8], antitubercular [9], antioxidant [10], anti-leishmanial [11], and anticancer [12]. The presence of highly reactive keto ethylenic group (-CO-CH=CH-) is responsible for the wide range of biological properties. Encouraged by these diverse pharmacological properties, we have designed and synthesized 6-methoxy chromanone-based chalcones and also evaluated their antimicrobial properties. Chromanones are natural bioactive molecules and its structural modification by incorporating an α,β-unsaturated ketone system would result in a new class of chalcones which is expected to exhibit diverse biological properties.

There are numerous methods available for the synthesis of chalcones, Claisen-Schmidt base-catalyzed condensation is the most convenient method among all the available methods. Herein, we wish to report the synthesis and biological evaluation of 6-methoxy chromanone based α, β-unsaturated ketone compounds.

2. MATERIALS AND METHODS

All chemicals used for the synthesis were of reagent grade and procured from Sigma-Aldrich, Bengaluru, India. ^{1}H- and ^{13}C-NMR spectra were recorded on AS 400 MHz Varian NMR spectrometer using TMS as an internal standard. IR spectra were recorded using Perkin-Elmer Spectrum 100 Series FT-IR spectrometer. Mass spectra were recorded on Agilent 1200 Series LC/MSD VL system. Melting points were determined using Buchi melting point B-545 instrument and are uncorrected. All the reactions were monitored by thin-layer chromatography (TLC) using pre-coated silica 60 F254, 0.25 mm aluminum plates (Merck) [Scheme 1].

2.1. General Procedure for the Synthesis of Chalcone Derivatives (3a–h)

The mixture of 6-Methoxy chromanone **1** (200 mg, 1.12 mmol), aldehydes **2a–h** (1.0 eq), and piperidine (477 mg, 5.61 mmol, 5.0 eq) in ethanol (10 vol) were heated to reflux for 2–3 h. After completion of the reaction as monitored by TLC, cooled the reaction to room temperature, ice-cold water was added to the reaction mass and stirred for 15 min. The precipitated solid was filtered and dried at vacuum. The crude product was stirred with diethyl ether (~10 mL) for 15 min and filtered, washed the solid with hexane (~5 mL), and dried at suction to afford the title compound in 65–70% yield.

All the new compounds were well characterized by their ^{1}H-NMR, ^{13}C-NMR, IR, MS, and melting point; and the data are given below.

2.1.1. (3E)-3-benzylidene-6-methoxy-2,3-dihydro-4H-chromen-4-one (3a)

Yield 70%; pale yellow solid; mp: 117–119 °C; IR (KBr) ν cm^{-1}: 3048, 1613, 1485, 1283, 1008, 697; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.7 (s,1H), 7.46–7.50 (m, 5H), 7.31 (d, *J* = 3.2 Hz, 1H), 7.2 (dd, *J* = 3.2, 9.2 Hz, 1H), 7.0 (d, *J* = 9.2 Hz, 1H), 5.37 (d, *J* = 1.2 Hz, 2H), 3.79 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 182.3, 155.9, 154.6, 137.5, 134.5, 131.1, 130.2, 129.5, 128.8, 125.1, 122.6, 119.3, 108.3, 67.7, 55.9; MS (ESI): 267 $[M+H]^+$.

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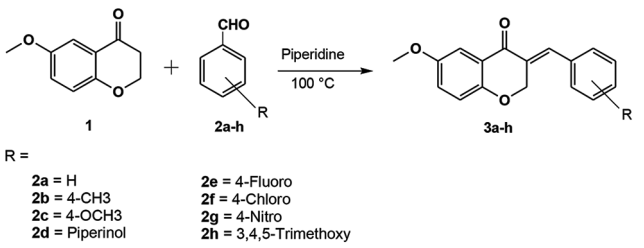
Table 1: Antibacterial data (MIC) of synthesized compounds

Compounds	Antibacterial activity minimum inhibitory concentration in µg/mL			
	Staphylococcus aureus	*Escherichia coli*	*Pseudomonas aeruginosa*	*Klebsiella pneumoniae*
3a	6.25	12.5	6.25	6.25
3b	12.5	50	12.5	12.5
3c	6.25	6.25	6.25	12.5
3d	12.5	12.5	12.5	12.5
3e	6.25	6.25	6.25	12.5
3f	6.25	12.5	12.5	50
3g	6.25	12.5	6.25	12.5
3h	6.25	12.5	6.25	6.25
Nitrofurazone	<6.25	<6.25	<6.25	<6.25
DMSO (1%) solvent control	00	00	00	00



Scheme 1: Synthetic route to compounds 3(a-h)

2.1.2. (3E)-6-methoxy-3-(4-methylbenzylidene)-2,3-dihydro-4H-chromen-4-one (3b)

Yield 62%; pale yellow solid; mp: 116–119°C; IR (KBr) ν cm^{-1}: 3005, 1661, 1493, 1296, 731; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.7 (s,1H), 7.31–7.35 (m, 5H), 7.2 (d, J = 7.2 Hz, 1H), 7.0 (d, J = 8.8 Hz, 1H), 5.3 (s, 2H), 3.7 (s, 3H), 2.3 (s, 3H); MS (ESI): 281 $[M+H]^+$.

2.1.3. (3E)-6-methoxy-3-(4-methoxybenzylidene)-2,3-dihydro-4H-chromen-4-one (3c)

Yield 65%; pale yellow solid; mp: 109–111°C; IR (KBr) ν cm^{-1}: 2960, 1670, 1489, 1255, 828; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.7 (s,1H), 7.4 (d, J = 8.0 Hz, 2H), 7.3 (s,1H), 7.2 (d, J = 7.2 Hz, 1H), 7.0 (dd, J = 7.6, 18.0 Hz, 3H), 5.3 (s, 2H), 3.8 (s, 6H); MS (ESI): 297 $[M+H]^+$.

2.1.4. (3E)-3-(1,3-benzodioxol-5-ylmethylidene)-6-methoxy-2,3-dihydro-4H-chromen-4-one (3d)

Yield 60%; pale yellow solid; mp: 118–119°C; IR (KBr) ν cm^{-1}: 2903, 1670, 1491, 1248, 814; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.6 (s,1H), 7.31–7.35 (m, 4H), 7.2 (d, J = 7.2 Hz, 1H), 5.5 (s, 2H), 5.3 (s, 2H), 3.7 (s, 3H); MS (ESI): 281 $[M+H]^+$.

2.1.5. (3E)-3-(4-fluorobenzylidene)-6-methoxy-2,3-dihydro-4H-chromen-4-one (3e)

Yield 68%; pale yellow solid; mp: 157–159°C; IR (KBr) ν cm^{-1}: 2975, 1671, 1492, 1235, 1036, 827; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.75 (s, 1H), 7.57 (s, 2H), 7.2–7.3 (m, 4H), 7.04 (d, J = 8.8 Hz, 1H), 5.3 (s, 2H), 3.7 (s, 3H); MS (ESI): 285 $[M+H]^+$.

2.1.6. (3E)-3-(4-chlorobenzylidene)-6-methoxy-2,3-dihydro-4H-chromen-4-one (3f)

Yield 70%; pale yellow solid; mp: 154–157°C; IR (KBr) ν cm^{-1}: 3009, 2835, 1715, 1663, 1598, 1291, 1094; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.6 (s, 1H),7.42 (s, 2H), 7.31–7.35 (m, 4H), 7.2 (d, J = 7.2 Hz, 1H), 5.3 (s, 2H), 3.7 (s, 3H); MS (ESI): 301 $[M+H]^+$.

2.1.7. (3E)-6-methoxy-3-(4-nitrobenzylidene)-2,3-dihydro-4H-chromen-4-one (3g)

Yield 62%; yellow solid; mp: 168–169°C; IR (KBr) ν $cm^{-1:}$ 3058, 1628, 1513, 1488, 1346, 734; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.48 (s, 1H), 8.15 (d, J = 8 Hz, 2H), 7.6 (s, 3H), 7.39 (s, 2H), 3.87 (s, 2H), 3.83 (s, 3H); MS (ESI): 312 $[M+H]^+$.

2.1.8. (3E)-6-methoxy-3-(3,4,5-trimethoxybenzylidene)-2,3-dihydro-4H-chromen-4-one (3h)

Yield 70%; pale yellow solid; mp: 120–122°C; IR (KBr) ν cm^{-1}: 3012, 1668, 1492, 1242, 1128, 753; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.7 (s, 1H), 7.4 (d, J = 3.2 Hz, 1H), 7.1 (dd, J = 2.8, 8.8 Hz, 1H), 6.9 (d, J = 9.2 Hz, 1H), 6.5 (s, 2H), 5.3 (s, 2H), 3.9 (s, 9H), 3.8 (s, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 181.9, 155.7, 154.5, 153.3, 139.4, 137.5, 130.4, 129.9, 125, 122, 119.2, 108.3, 107.4, 67.7, 61, 56.3, 55.8; MS (ESI): 357 $[M+H]^+$.

2.2. Biological Evaluation

2.2.1. Antibacterial activity

The antibacterial activity of synthesized compounds 3a–h was carried out using agar well-diffusion method at *Vidya Herbs Pvt. Ltd., Bengaluru*. The newly synthesized compounds were screened for their antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa,* and *Klebsiella pneumoniae* strains by disk diffusion method [13]. The disks measuring 6.25 mm in diameter were punched from Whatman No.1 filter paper. Batches of 100 disks were dispensed to each screw capped bottles and sterilized by dry heat at 140°C for an hour. The test compounds were prepared with different concentrations using DMSO. One milliliter containing 100 times the amount of chemical required in each disk was added to each bottle which contained 100 disks. The disks of each concentration were placed in triplicate in nutrient agar medium seeded with fresh bacteria separately. The incubation was carried out at 37.8°C for 24 h. For comparison, nitrofurazone was used as a drug standard. Solvent and growth controls were kept. The zone of inhibition was determined for each compound in triplicate experiments; the values were averaged and are presented in Table 1.

3. RESULTS AND DISCUSSION

3.1. Chemistry

6-Methoxy chromanone was synthesized using the reported procedure [14]. The intermediate 1 was heated with various electron-withdrawing and electron-donating aromatic aldehydes 2a–h in the

presence of piperidine as base and ethanol as solvent at reflux condition for 2–3 h. The products 3a–h were isolated in 65–70% yield and well characterized by their ^{1}H-, ^{13}C-NMR, IR, mass, and melting point.

3.2. Antibacterial Activity

All the newly synthesized compounds were tested against four bacterial strains *S. aureus*, *E. coli*, *P. aeruginosa,* and *K. pneumoniae*. Nitrofurazone was used as standard drug. The results are given in Table 1. Compounds 3a, 3c, 3e, and 3h showed excellent activity against all the four bacterial strains with MIC value 6.25 µg/mL. Compounds 3b and 3d showed moderate inhibition with MIC value 12.5 µg/mL. Chalcone molecules having methoxy, fluoro, and nitro groups showed excellent activity whereas compounds possessing methyl, methylenedioxy, and chloro groups showed moderate activity. Hence, SAR study reveals that methoxy, fluoro, and nitro groups contribute for the broad spectrum of activity.

4. CONCLUSION

A series of eight novel chalcones (3a–3h) were synthesized and well characterized. All the analogs were investigated for antibacterial activities. In general, all compounds showed moderate-to-good activity against the bacterial strains. Four compounds 3a, 3c, 3e, and 3h were uniformly active against all bacterial strains used for the study. Methoxy, fluoro, and nitro substitution on the phenyl ring cause marked increase in antibacterial activity of the novel molecules.

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**Bibliographical Sketch*

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