Synthesis and Antimicrobial Evaluation of Some Heterocyclic Chalcone Derivatives

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Abstract: Some new heterocyclic compounds containing isoxazole, pyrazole and oxadiazole ring systems were prepared from various chalcones. The synthesized compounds have been characterized by elemental analysis and spectral methods. These compounds were screened for their antimicrobial activities.

Keywords: chalcones; isoxazoles; pyrazoles; oxadiazoles; antimicrobial

1. Introduction

Chalcones are synthesized by condensing ketones with aromatic aldehydes in the presence of suitable bases. They are very useful intermediates for the synthesis of five-[1,2], six-[1,3] and seven-membered [4] heterocyclic compounds. Chalcone derivatives exhibit diverse pharmacological activities [5-14]. It is therefore, not surprising that many synthetic methods have been developed for the preparation of heterocycles starting from chalcone precursors that have been tested for their antimicrobial activities.

2. Results and Discussion

All of our results are shown in Scheme 1. The starting chalcones 1a–c were obtained in good yields by a base catalyzed condensation [15-16] of appropriately substituted benzaldehydes and cyclopropylmethyl ketone [17]. The method is attractive since it specifically generates the (E) isomer [18].
Scheme 1. Synthesis of 2a–f, 3a–f, 4a–f and 5a–f.

The hydrazones 2a–f were prepared by the reaction of chalcones 1a–c with benzoyl hydrazine derivatives and were subsequently used for the syntheses of various pyrazoles 3a–f and oxadiazoles 4a–f. The IR spectra of these hydrazones revealed the characteristic bands for vinyl CH=CH at 1582–1617, C=N at 1616–1647, C=O at 1664–1698 and NH at 3330–3420 cm\(^{-1}\). The \(^1\)H-NMR spectra showed the presence of a singlet at \(\delta = 9.97–10.82\) ppm for the NH proton, a multiplet at \(\delta = 7.17–8.45\) ppm characteristic for the aromatic protons and the olefinic =C–CH=CH, a doublet at \(\delta = 6.60–6.95\) ppm
characteristic for the olefinic =C–CH=CH proton. The cyclopropyl ring protons appeared as two multiplets in the range δ = 1.56–2.64 ppm (CH) and δ = 0.70–1.46 ppm (2CH₂), respectively.

The pyrazole derivatives 3a–f were obtained by treatment of hydrazones 2a–f with 30% hydrochloric acid. The IR of 3a–f showed the characteristic bands for C=C–Ar at 1519–1596, C=N at 1623–1644 and amide carbonyl band at 1660–1686 cm⁻¹, while the ¹H-NMR spectra showed a singlet at δ = 6.64–7.12 ppm for the pyrazole–C₄–H. On the other hand, refluxing of hydrazones 2a–f with acetic anhydride gave the corresponding dihydro-1,3,4-oxadiazole derivatives 4a–f. The mechanism of cyclization reaction has been well studied [19-20]. The IR spectra of the dihydro-oxadiazoles 4a–f lacked the NH, but showed a carbonyl absorption at 1667–1677 cm⁻¹ for the acetyl group. Their structures were further confirmed from the ¹H-NMR spectra which does not reveal the presence of NH signal present in the starting hydrazone 2, moreover, the ¹H-NMR of 4 exhibited a singlet of three protons intensity at δ = 2.10–2.16 ppm for the COCH₃. Finally, treatment of chalcones 1a–c with hydroxylamine hydrochloride in presence of sodium acetate produced isoxazoles 5a–c in moderate yield. The structure of 5 was fully confirmed by spectral method. For example, the IR of 5 does not show the presence of carbonyl band characteristic for the starting chalcone 1. The ¹H-NMR of 5 exhibited a singlet of one proton intensity at δ = 5.42–5.69 ppm characteristic for the isoxazole–C₄–H. Melting points, elemental analysis and spectral methods are outlined in Tables 1 and 2.

2.1. Antimicrobial Activity

All the synthesized heterocyclic derivatives, pyrazoles 3a–f oxadiazoles 4a–f and isoxazoles 5a–c were assayed for their antimicrobial activity against four test organisms: Staphylococcus aureus ATCC6538P, Escherichia coli ATCC8739, Pseudomonas aeruginosa ATCC9027 and Candida albicans ATCC2091 using rifampicin (5 µg/disc) and ampicillin (10 µg/disc) as standard drugs following agar well-diffusion method [21].

The tested heterocyclic compounds showed no significant effect against Pseudomonas aeruginosa and Candida albicans, whereas they showed a potent activity against Staphylococcus aureus and Escherichia coli. The maximum activity (+ + +) (MIC = 25 µg/mL) was indicated for compounds 3a, 3b, 4a, 4b and 5a. These results suggest that the electron-withdrawing nitro group plays a crucial role in enhancing the observed activity.

Compounds 3e, 4c, 4e and 4f showed a moderate activity (+ +) (MIC = 50 µg/mL) against Staphylococcus, while these compounds exhibited slight activity (+) (MIC = 75 µg/mL) against Escherichia coli. All other compounds were inactive towards the different strains of bacteria. The results are summarized in Table 3.
Table 1. Physical and analytical data of compounds, 2a–f, 3a–f, 4a–f and 5a–c.

| Compound | X     | Y     | Yield (%) | Mp (ºC) | Molecular Formula | Calculated % | Found % |
|----------|-------|-------|-----------|---------|-------------------|--------------|---------|
|          |       |       |           |         |                   | C  | H  | N  | C  | H  | N  |
| 2a       | NO₂   | Me    | 72        | 181     | C₂₀ H₁₉ N₃ O₃    | 68.77        | 5.44  | 12.03 | 68.71 | 5.39 | 12.09 |
| 2b       | NO₂   | NO₂   | 79        | 201     | C₁₉ H₁₆ N₄ O₅    | 60.00        | 4.21  | 14.74 | 60.06 | 4.19 | 14.77 |
| 2c       | H     | H     | 66        | 166     | C₁₉ H₁₈ N₂ O     | 78.62        | 6.21  | 9.66  | 78.59 | 6.19 | 9.62  |
| 2d       | H     | Me    | 65        | 180     | C₂₀ H₂₀ O N₂     | 78.95        | 6.58  | 9.21  | 79.01 | 6.49 | 9.28  |
| 2e       | OMe   | Me    | 69        | 190     | C₂₁ H₂₂ O₂ N₂    | 75.45        | 6.59  | 8.38  | 75.49 | 6.62 | 8.44  |
| 2f       | OMe   | H     | 74        | 160     | C₂₀ H₂₀ O₂ N₂    | 75.00        | 6.25  | 8.75  | 74.97 | 6.26 | 8.77  |
| 3a       | NO₂   | Me    | 81        | 183     | C₂₀ H₁₇ O₃ N₃    | 69.16        | 4.90  | 12.10 | 69.22 | 4.87 | 12.08 |
| 3b       | NO₂   | NO₂   | 92        | 197     | C₁₉ H₁₄ O₅ N₄    | 60.32        | 3.70  | 14.81 | 60.06 | 3.69 | 14.77 |
| 3c       | H     | H     | 62        | 159     | C₁₉ H₁₆ O N₂     | 79.17        | 5.56  | 9.72  | 79.21 | 5.53 | 9.71  |
| 3d       | H     | Me    | 66        | 164     | C₂₀ H₁₈ O N₂     | 79.47        | 5.96  | 9.27  | 79.51 | 5.91 | 9.27  |
| 3e       | OMe   | Me    | 64        | 171     | C₂₁ H₂₀ O₂ N₂    | 75.90        | 6.02  | 8.43  | 75.93 | 6.06 | 8.51  |
| 3f       | OMe   | H     | 59        | 180     | C₂₀ H₁₈ O₂ N₂    | 75.47        | 5.66  | 8.81  | 75.52 | 5.60 | 8.86  |
| 4a       | NO₂   | Me    | 83        | 201     | C₂₂ H₂₁ O₄ N₃    | 67.52        | 5.37  | 10.74 | 67.52 | 5.43 | 10.80 |
| 4b       | NO₂   | NO₂   | 97        | 210     | C₂₁ H₁₈ O₆ N₄    | 59.72        | 4.27  | 13.27 | 59.69 | 4.26 | 13.22 |
| 4c       | H     | H     | 59        | 177     | C₂₁ H₂₀ O₂ N₂    | 57.90        | 6.02  | 8.43  | 57.84 | 5.99 | 8.44  |
| 4d       | H     | Me    | 58        | 179     | C₂₂ H₂₂ O₂ N₂    | 76.30        | 6.36  | 8.09  | 76.28 | 6.31 | 8.12  |
| 4e       | OMe   | Me    | 67        | 189     | C₂₃ H₂₄ O₃ N₂    | 73.40        | 6.38  | 7.45  | 73.44 | 6.39 | 7.49  |
| 4f       | OMe   | H     | 80        | 162     | C₂₂ H₂₂ O₃ N₂    | 72.93        | 6.08  | 7.73  | 72.91 | 6.01 | 7.76  |
| 5a       | NO₂   | —     | 54        | 165     | C₁₂ H₁₀ O₃ N₂    | 62.61        | 4.35  | 12.17 | 62.66 | 4.29 | 12.21 |
| 5b       | H     | —     | 49        | 159     | C₁₂ H₁₁ O N      | 77.84        | 5.95  | 7.57  | 77.90 | 5.99 | 7.62  |
| 5c       | OMe   | —     | 74        | 161     | C₁₃ H₁₃ O₂ N     | 72.56        | 6.05  | 6.51  | 72.60 | 6.01 | 6.48  |
Table 2. IR and $^1$H-NMR spectral data of compounds 2a–f, 3a–f, 4a–f and 5a–c.

| Compound | IR cm$^{-1}$ (KBr) | $^1$H NMR (δ / ppm)$^a$ | Pyrazole–C$_4$–H (s) or isoxazole–C$_4$–H (s) | Cyclopropyl ring H’s | Ar–CH$_3$ (s) | Ar–OCH$_3$ and CH$_3$CO– |
|----------|---------------------|--------------------------|-----------------------------------------------|----------------------|---------------|-----------------------------|
|          | C=C | C=N | C=O | NH | Ar–H’s and =C–CH=CH (m) | =C–CH=CH (d), J =12 Hz | NH (s) | CH (m) | 2 (CH$_2$) (m) |                         |
| 2a       | 1592 | 1629 | 1678 | 3420 | 7.36–7.91 | 6.72 | 10.66 | 1.91–2.55 | 0.75–1.37 | 2.21 |
| 2b       | 1617 | 1647 | 1698 | 3390 | 7.23–8.45 | 6.93 | 10.45 | 1.80–2.64 | 0.71–1.40 |    |
| 2c       | 1582 | 1616 | 1664 | 3330 | 7.19–7.63 | 6.60 | 9.97  | 1.82–2.49 | 0.78–1.29 |    |
| 2d       | 1587 | 1636 | 1669 | 3336 | 7.29–7.82 | 6.71 | 10.82 | 1.71–2.36 | 0.70–1.40 | 2.10 |
| 2e       | 1601 | 1628 | 1687 | 3411 | 7.20–7.71 | 6.75 | 10.73 | 1.63–2.40 | 0.77–1.46 | 2.19, 3.49 |
| 2f       | 1617 | 1644 | 1681 | 3332 | 7.17–7.49 | 6.95 | 9.99  | 1.56–2.59 | 0.78–1.16 | 3.42 |
| 3a       | 1519 | 1629 | 1670 | 3420 | 7.26–7.92 $^b$ | 6.85 | 9.99  | 1.90–2.48 | 0.69–1.21 | 2.13 |
| 3b       | 1586 | 1633 | 1684 | 3411 | 7.24–8.33 $^b$ | 7.12  | 1.76–2.66 | 0.80–1.36 | 2.13 |
| 3c       | 1556 | 1641 | 1660 | 3420 | 7.22–7.71 $^b$ | 6.78  | 1.73–2.40 | 0.71–1.28 | 2.13 |
| 3d       | 1590 | 1644 | 1678 | 3420 | 7.24–7.77 $^b$ | 6.64  | 1.75–2.41 | 0.77–1.33 | 2.11 |
| 3e       | 1571 | 1623 | 1686 | 3411 | 7.21–7.68 $^b$ | 6.69  | 1.66–2.39 | 0.71–1.33 | 2.10, 3.44 |
| 3f       | 1596 | 1633 | 1664 | 3411 | 7.11–7.62 $^b$ | 6.74  | 1.49–2.55 | 0.77–1.19 | 3.39 |
| 4a       | 1587 | 1645 | 1669 | 3420 | 7.18–7.79 $^b$ | 6.74  | 1.92–2.41 | 0.67–1.32 | 2.01, 2.16 |
| 4b       | 1610 | 1646 | 1667 | 3411 | 7.22–8.22 $^b$ | 6.74  | 1.70–2.66 | 0.71–1.40 | 2.13 |
| 4c       | 1602 | 1626 | 1669 | 3420 | 7.16–7.75 $^b$ | 6.74  | 1.68–2.39 | 0.75–1.26 | 2.11 |
| 4d       | 1594 | 1630 | 1670 | 3420 | 7.33–7.76 $^b$ | 6.74  | 1.73–2.44 | 0.71–1.38 | 1.99, 2.13 |
| 4e       | 1600 | 1633 | 1677 | 3411 | 7.26–7.72 $^b$ | 6.74  | 1.60–2.47 | 0.71–1.26 | 2.13, 3.32, 2.15 |
| 4f       | 1615 | 1646 | 1671 | 3411 | 7.25–7.51 $^b$ | 6.74  | 1.47–2.61 | 0.76–1.33 | 3.34, 2.10 |
| 5a       | 1580 | 1627 | 3420 | 7.19–7.99 $^b$ | 5.69  | 1.82–2.51 | 0.71–1.36 | 2.13 |
| 5b       | 1571 | 1629 | 3420 | 7.22–7.62 $^b$ | 5.42  | 1.43–2.45 | 0.69–1.27 | 2.13 |
| 5c       | 1569 | 1633 | 3420 | 7.26–7.70 $^b$ | 5.46  | 1.57–2.41 | 0.67–1.29 | 3.30 |

$^a$ Solution in DMSO-d$_6$; $^b$ The chemical shift only indicates Ar–H’s.
Table 3. Antibacterial activities of newly synthesized compounds 3–5.

| Compound | X  | Y  | Staphylococcus aureus | Escherichia coli |
|----------|----|----|----------------------|-----------------|
| 3a       | NO₂| Me | +++                  | +++             |
| 3b       | NO₂| NO₂| +++                  | +++             |
| 4a       | NO₂| Me | +++                  | +++             |
| 4b       | NO₂| NO₂| +++                  | +++             |
| 5a       | NO₂| —  | +++                  | +++             |
| 3c       | OMe| Me | +++                  | +               |
| 4c       | H  | H  | ++                   | +               |
| 4d       | OMe| H  | ++                   | +               |
| 3d       | H  | Me | —                    | —               |
| 3f       | OMe| H  | —                    | —               |
| 4d       | H  | Me | —                    | —               |
| 5b       | H  | —  | —                    | —               |
| 5c       | OMe| —  | —                    | —               |

+++ for maximum activity, MIC = 25 μg/mL; ++ for moderate activity, MIC = 50 μg/mL; + for slight activity, MIC = 75 μg/mL and – for inactive.

3. Experimental

3.1. General

Melting points were taken in open capillary tubes using Electrothermal apparatus 9100 (UK) and are uncorrected. Microanalyses were performed at Faculty of Science, Cairo University, Cairo, Egypt, using a Elementary Vario el III C, H, N, S Analyzer (Germany). IR spectra were recorded using potassium bromide disks on a Perkin-Elmer 1650 spectrophotometer (Faculty of Science, Alexandria University, Alex, Egypt). ¹H-NMR spectra were determined on a Varian EM-390 MHz spectrophotometer, using TMS as internal standard.

3.2. General Procedure for Preparation of E-1-Cyclopropyl-3-(p-substituted-phenyl)-2-propenenones 1a–c

To a cold solution of sodium hydroxide (3 g) in aqueous ethanol (50 mL, 60%), cyclopropylmethyl ketone (10 mmol), was added dropwise (30 min), while rapidly stirring and the temperature kept below 20 °C, then the desired p-substituted benzanldehyde (10 mmol) was added dropwise (30 min). After five hours, the mixture was left overnight in refrigerator. The separated solid was filtered, washed with water and dried, then recrystallized from ethanol as colorless needles. The physical properties and all the spectral data were as reported in the literature [17].
3.3. General Procedure for Preparation of 1-Cyclopropyl-3-(p-substituted-phenyl)-2-propene-1-aroyl hydrazones 2a–e

A solution of chalcones 1a–c (10 mmol) in ethanol (10 mL) was refluxed with the appropriate aroyl hydrazines (10 mmol) in glacial acetic acid (2 mL) for about six hours, then the reaction mixture was poured onto crushed ice and was kept overnight at room temperature, the separated solid was filtered off, washed successively with water and dried, then recrystallized from methanol. IR and NMR data: see Tables 1 and 2.

3.4. General Procedure for Preparation of 1-Aroyl-3-cyclopropyl-5-(p-substituted-phenyl)-pyrazoles 3a–e

A solution of the appropriate hydrazone 3a–e (10 mmol) in 30% hydrochloric acid (15 mL) was refluxed for about two hours, the reaction mixture was concentrated, separated solid was filtered off, washed with water, dried and recrystallized from methanol. IR and NMR data: see Tables 1 and 2.

3.5. General Procedure for Preparation of 3-Acetyl-2-cyclopropyl-2-(p-substituted styryl)-5-(p-substituted phenyl)-1,3,4-oxadiazoles 4a–e

A mixture of the appropriate hydrazone 2a–e (10 mmol) and acetic anhydride (15 mL) was heated under reflux for three hours. After the reaction mixture attained room temperature, it was poured into crushed ice and the oily product deposited was decanted from water and extracted with ether. The ether layer was washed with sodium bicarbonate, followed by water, dried over anhydrous sodium sulphate and evaporated to give the corresponding oxadiazoles 4a–e as needles. IR and NMR data: see Tables 1 and 2.

3.6. General Procedure for Preparation of 3-Cyclopropyl-5-(p-substituted Phenyl)isoxazole 5a–c

A mixture of chalcone 1a–c (20 mmol), hydroxylamine hydrochloride (20 mmol) and sodium acetate (20 mmol) in ethanol (25 mL) was refluxed for six hours. The mixture was concentrated by distilling out the solvent under reduced pressure and poured into ice-water. The precipitate obtained was filtered, washed and recrystallized from ethanol to give isoxazole 5 as needles. IR and NMR data: see Tables 1 and 2.

3.7. Determination of Antimicrobial Activity

All the synthesized heterocyclic compounds 3a–f, 4a–f and 5a–f were tested against four different microorganisms: Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa and Candida albicans. The agar well-diffusion method was applied for the determination of inhibition zone and minimum inhibitory concentration (MIC). Briefly, 0.75 mL of broth culture containing ca. 106 colon-forming units (CFU) per mL of the test strain was added to 75 mL of nutrient agar medium at 45 ºC, mixed well, and then poured into a 15 cm sterile metallic Petri plate. The medium was allowed to solidify, and 8 mm wells were dug with a sterile metallic borer. Then, a DMSO solution of the test sample (1 mL) at 1 mg/mL was added to the respective wells. DMSO served as negative control, and the standard antimicrobial drugs rifampicin (5 μg/disc) and ampicillin (10 μg/disc) were used as
positive controls. Triplicate plates of each microorganism strain were prepared and were incubated aerobically at 37 °C for 24 h. The activity was determined by measuring the diameter of zone showing complete inhibition (mm), thereby, the zones were precisely measured with the aid of a Vernier Caliper (precision 0.1 mm). The growth inhibition was calculated with reference to the positive control.

4. Conclusions

In summary, this work demonstrates a rapid, efficient method for synthesis of new heterocyclic compounds of pharmacological interest.

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*Sample Availability*: Samples of all the compounds are available from the authors.

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