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Microwave Assisted Synthesis of Indolyl Chalcones

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Abstract
Chalcones exhibit diverse pharmacological activities such as antimalarial, anti-inflammatory, antitubercular, antioxidant, anti-AIDS, antibacterial, antileishmanial, anticancer, antipyretic and analgesic. Some chalcones possess bactericidal, antifungal and insecticidal activity and some of their derivatives are reported to be chemo preventive activity, antimutagenic, cardiovascular disease, cytotoxic activity, antiprolifirative activity and antiviral activity and have been used as intermediate for the preparations of compounds having therapeutic value. Indole heterocycles are also an important bioactive compounds and it serves as a fundamental skeleton in naturally occurring alkaloids. Indole derivatives are known for their role as insecticidal, antimicrobial, painkillers, antiviral, antiinflammatory, anti-tubercular, depression medications, antineoplastic, antioxidants, antihypertensives, and anti-diabetic agents. In this work, we in search of new bioactive compounds Indole and different ketones are used to prepare a series of Indolyl-chalcones (3a-g) by microwave irradiation method and characterized by different spectroscopic techniques.

Keywords: Microwave, Chalcones, Indole, Anti-tubercular, Indole chalcones.

Introduction

The chalcones are α, β-unsaturated ketones containing the reactive ketoethylenic group. They are abundantly present in nature from ferns to higher plants [1]. Chalcones are most important precursors used for the preparations of compounds having therapeutic value. Literature review reveals that chalcone derivatives exhibit diverse pharmacological activities such as antimalarial, [2] anti-inflammatory, [3] antitubercular, [4] antioxidant, [5] anti-AIDS, [6] antibacterial, [7] antileishmanial, [8] anticancer, [9] antipyretic and analgesic. [10] Some chalcones possess bactericidal, antifungal and insecticidal activity and some of their derivatives are reported to be chemo preventive activity, [11] antimutagenic, [12] cardiovascular disease, [13] cytotoxic activity, antiprolifirative activity [14] and antiviral activity [15].

N-heterocyclic compounds are also one of the most important pharmacophore for designing new and efficient drugs. Indole heterocycles is an important bioactive compound and it serves as a crucial skeleton in naturally occurring alkaloids like tryptophan, serotonin, reserpine and indole 3-acetic acid. [16] In addition, marine and bacterial Indole alkaloids show anti-cancer, [17] anti-bacterial, [18] antiviral, [19] and anti-HIV [20] properties. Moreover, Indole derivatives are known for their role as insecticidal, [21] antimicrobial, [22,23] painkillers, [24] antiviral, [25] antiinflammatory, [26] anti-tubercular, [27,28] depression medications, [29] antineoplastic, [30] antioxidants, [17] antihypertensives, [31] and anti-diabetic [29] agents. The Food and Drug Administration has even published a database highlighting the importance of N-containing heterocyclic compounds in 2015 and Indole derivatives ranks 9th among the top 25 Food and Drug Administration approved drugs with 17 Indole containing drugs in the market [32].

Considering the above aspects it is noted that chalcones and Indol compounds combining can produce good results. That's why in a search new and novel biological active compounds molecular hybridization of Indole and Chalcone in drug designing is considered in the present study. Hybrid molecules can have modified selectivity, contrasting approaches of action, lesser unwanted aftereffects, improved solubility and oral bioavailability. Some biologically active Indol-Chalcones are as shown in figure 1.

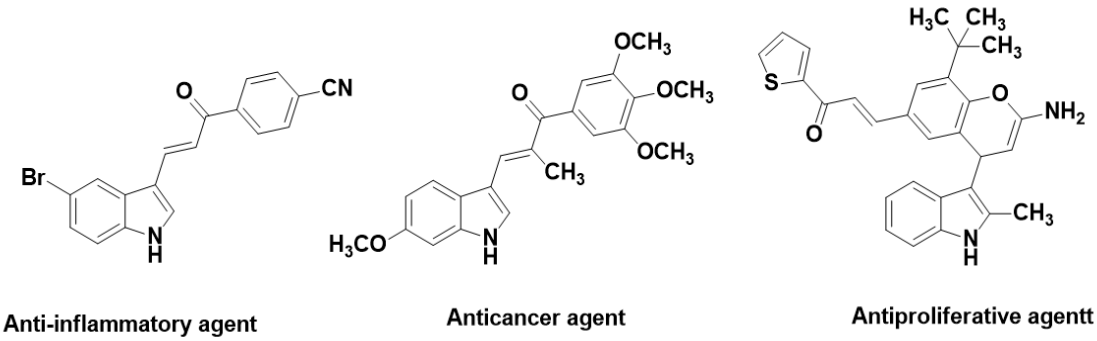


Fig 1: Some Biologically active Indol-Chalcones

For synthesis of these hybrid Indole-chalcones different methods and catalyst have been used, but still there is scope for the development of the synthetic method for preparation of these compounds. Microwave-assisted synthesis, in general, has a large impact on synthetic organic chemistry compared to traditional processing of organic synthesis. Therefore, in the present investigation it has been considered worthwhile to synthesize some new Indolyl-chalcones by microwave irradiation method. Important features of this technique are easy access to very high temperature, good control over energy input in a reaction, higher yields and rapid synthesis of organic compounds. The synthesized compounds were purified by recrystallization and chromatography.

Materials and Methods

All reactions were run in dried glassware. Reagents were purchased (Spectrochem, Avra, SRL or Sigma-Aldrich) and used without further purification. Reactions were carried out in a domestic microwave oven. ^{1}H NMR spectrum was obtained in DMSO d6 on Bruker AV-400 (400 MHz) spectrometers using TMS as an internal standard.

General Procedure for Synthesis of Indolyl Chalcones Under Microwave Irradiation

Indole 3-carboxaldehyde (0.01 mole) and acetophenones (0.01 mole) was dissolved in aqueous ethanol (5 mL) taken in a borosil conical flask (100 mL) and potassium hydroxide (0.02 mole) was added in the reaction mixture. This conical flask was then placed inside a domestic microwave oven for 30 sec to 3 minutes at 50% power input. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled at room temperature and was poured into crushed ice (40 mL). Extraction was carried out with diethyl ether (15 x 3 mL) and dried over anhydrous sodium sulphate. Solvent was removed by simple heating on hot water bath (40 ^{0}C) and further purification was done by column chromatography.

Spectral Data

1. (E)-1-(4-fluorophenyl)-3-(1H-indol-3-yl)prop-2-en-1-one (3a)

Yellow solid, Yield: 85%, ^{1}H NMR (DMSO-d6, 400 MHz): δ 6.93 (1H d, J=36.1 Hz), 7.26 (s, 4H), 7.57 (2H d, J=43.5 Hz,), 7.80 (s, 1H), 8.06 (d, J=14.2 Hz, 2H), 8.15 (2H d, J=27.8 Hz), 11.83 (s, 1H). ^{13}C NMR (DMSO-d6, 101 MHz): δ 187.94 (s), 139.81 (s), 137.98 (s), 135.52 (s), 133.90 (s), 131.48, 130.70 (s), 125.55 (s), 123.27 (s), 121.72 (s), 120.88 (s), 116.20 (s), 115.98 (s), 115.43 (s), 113.28, 112.95 (s). IR (KBr, cm^{-1}): 3412.5, 3060.4, 1715.5, 1606.4, 1417.6, 1607.6 and 1234.1 cm^{-1}.

2. (E)-1-(2,4-dichlorophenyl)-3-(1H-indol-3-yl)prop-2-en-1-one (3b)

Yellow Solid, Yield: 90%, **^{1}H NMR** (DMSO-d6, 400 MHz): δ 7.07 (d, J=15.9 Hz, 1H), 7.27 – 7.19 (m, 2H), 7.38 (dd, J=8.2, 1.8 Hz, 1H), 7.47 (dd, J=16.1, 5.1 Hz, 3H), 7.65 (dd, J=28.9, 9.3 Hz, 2H), 7.89 (d, J=7.9 Hz, 1H), 11.45 (s, 1H). ^{13}C NMR (DMSO-d6, 101 MHz): δ 197.45 (s), 146.90 (s), 143.11 (s), 142.72 (s), 140.62 (s), 137.44 (s), 136.69 (s), 134.98 (s), 134.64 (s), 131.94 (s), 129.91 (s), 127.89 (s), 126.34 (s), 125.25 (s), 125.01 (s), 117.73 (s). IR (KBr, cm^{-1}): 3435.2, 3051.0, 1726.6, 1692.2 and 792.4 cm^{-1}.

3. (E)-1-(4-bromophenyl)-3-(1H-indol-3-yl)prop-2-en-1-one (3c)

Yellow Solid, Yield: 90%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 – 6.97 (m, 2H), 7.20 (d, *J*=3.5 Hz, 1H), 7.28 (d, *J*=4.3 Hz,1 H), 7.51 – 7.36 (d, 3H), 7.79 – 7.62 (m, 3H), 7.90 (d, *J*=15.4, 3.1 Hz, 1H), 10.90 (s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.45 (s), 140.12 (s), 137.79 (s), 132.03 (s), 131.63 (s), 129.75 (s), 125.28 (s), 122.98 (s), 121.36 (s), 120.30 (s), 115.83 (s), 113.47 (s), 112.48 (s). IR (KBr, cm^{-1}): 3401.7, 3261.9, 1709.1, 1613.0, 1073 cm^{-1}.

4. (E)-3-(1H-indol-3-yl)-1-(p-tolyl)prop-2-en-1-one (3d)

Yellow Brown Solid, Yield: 89%, ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H), 8.10 (d, J=15.6 Hz, 1H), 8.04 – 7.96 (m, 2H), 7.88 – 7.81 (m, 2H), 7.59 (dd, J=8.6, 6.9 Hz, 2H), 7.46 (dd, J=6.2, 2.8 Hz, 1H), 7.34 – 7.27 (m, 4H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 192.35 – 189.35 (m), 143.15 (s), 138.97 (s), 137.41 (s), 136.35 (s), 129.30 (s), 128.51 (s), 125.39 (s), 123.45 (s), 121.69 (s), 120.65 (s), 117.63 (s), 114.36 (s), 112.16 (s), 21.68 (s). IR (KBr, cm^{-1}): 3232.5, 1632.1, 1610.1, 1361.5 cm^{-1}.

5. (E)-3-(1H-indol-3-yl)-1-(3-methoxyphenyl)prop-2-en-1-one (3e)

Brown solid, Yield: 85%, **^{1}H NMR** (400 MHz, CDCl3): δ 10.02 (s, 1H), 8.12 (d, J=15.6 Hz, 1H), 8.03 – 7.97 (m, 1H), 7.65 (d, J =7.6 Hz, 1H), 7.61 – 7.54 (m, 3H), 7.50 – 7.38 (m, 2H), 7.29 (dd, J=5.8, 2.7 Hz, 2H), 7.13 (dd, J =8.1, 2.6 Hz, 1H), 3.88 (s, 3H). ^{13}C NMR (101 MHz, CDCl3): δ 191.12 (s), 159.86 (s), 140.46 (s), 139.51(s), 137.44 (s), 129.58 (s), 125.37 (s), 123.51 (s), 122.99 (s), 121.78 (s), 121.18 (s), 120.91 (s), 120.65(s), 119.70 (s), 118.69 (s), 117.61 (s), 114.31 (s), 112.95 (s), 112.21 (s), 55.50 (s). **IR** (KBr, cm^{-1}): 3412.8, 3042.0, 1709.0, 1609.0 1289.2 cm^{-1}.

6. (E)-1-(3-aminophenyl)-3-(1H-indol-3-yl)prop-2-en-1-one (3f)

Yellow Solid, Yield: 86%, ^{1}H NMR (400 MHz, DMSO-d6): δ 12.00 (s, 1H), 8.39 (d, J=79.9 Hz, 1H), 8.12 (dd, J=30.2,

18.3 Hz, 3H), 7.77 – 7.66 (m, 1H), 7.56 (dd, J=19.5, 12.7 Hz, 3H), 7.42 – 7.33 (m, 1H), 7.24 (dd, J=10.0, 6.1 Hz, 3H), 7.08 (d, J=7.7 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d6): δ 189.24 (s), 148 (s), 139.92 (s), 139.44 (s), 138.04 (s), 133.87 (s), 129.93 (s), 125.51 (s), 123.19 (s), 121.65 (s), 121.13 (s), 115.89 (s), 113.21 (s), 113.00 (s). IR (KBr, cm^{-1}): 3439.2, 3182.0, 1647.1, 1560.1, 3347.1, 1605.8 cm^{-1}.

7. (E)-3-(1H-indol-3-yl)-1-(3-nitrophenyl)prop-2-en-1-one (3g)

Orange Solid, Yield: 81%, ^{1}H NMR (DMSO-d6, 400 MHz): δ 7.12 (dd, J=23.2, 19.1 Hz, 2H), 7.34 – 7.28 (m, 2H), 7.55 – 7.50 (m, 2H), 7.82 – 7.77 (m, 1H), 8.00 (d, J=15.4 Hz, 1H), 8.23 – 8.15 (m, 2H), 8.64 (s, 1H), 10.94 (s, 1H).^{13}C NMR (DMSO-d6, 101 MHz): δ 188.03 (s), 148.27 (s), 141.36 (s), 140.56 (s), 137.84 (s), 133.87 (s), 132.61 (s), 129.69 (s), 126.22 (s), 125.30 (s), 123.17 (s), 122.91 (s), 121.61 (s), 120.32 (s), 115.05 (s), 113.52 (s), 112.55 (s). IR (KBr, cm^{-1}): 3317.1 3211.2 1532.0, 1352.2 1710.9 1601.0 cm^{-1}.

Results and Discussion

Indolyl-Chalcone derivatives 3a-g was prepared by treating indole-3-carboxaldehyde 1 with different substituted acetophenones 2a-g through Claisene-Schmidt condensation under microwave irradiation using potassium hydroxide as base (Scheme 1) and ethanol is used as solvent. The reactions are carried in open borosil glass conical flasks. Structures of acetophenones and product chalcone were given in Table-1. The products obtained are in good yield (80-90%) in very shorter reaction time (1-3min.).

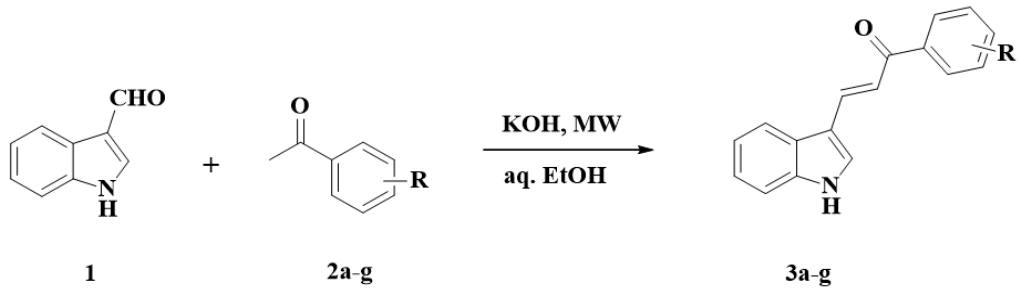
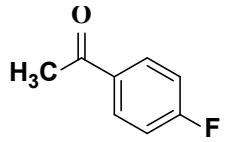
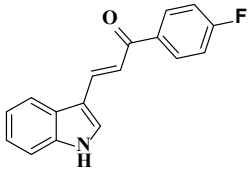
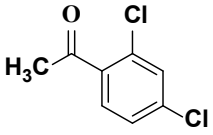
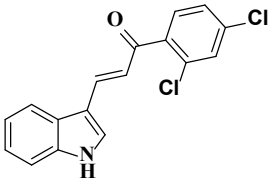
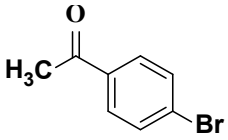
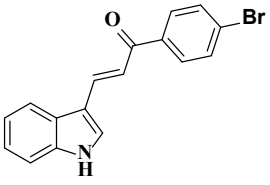
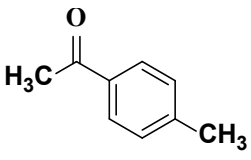
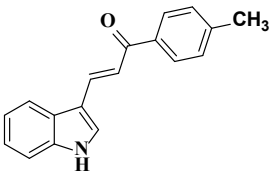
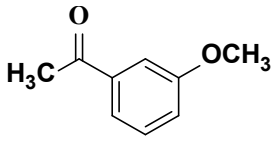
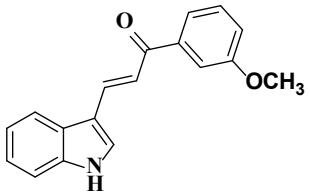
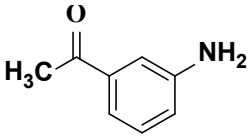
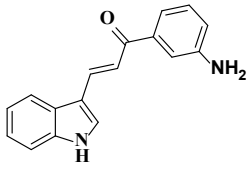
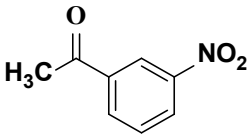
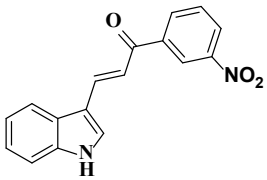


Fig 2: Scheme 1: Synthesis of Indolyl Chalcones

Table 1: Structures of Ketone (Substrate) and Indolyl-Chalcones (Product).

S. No.	Substrate (Ketone)	Product (Chalcone)	Yield (%)
01	 2a	 3a	85
02	 2b	 3b	90
03	 2c	 3c	90
04	 2d	 3d	89

05	 2e	 3e	85
06	 2f	 3f	86
07	 2g	 3g	81

Conclusion

In conclusion, we have developed a practically convenient methodology for the synthesis of Indole chalcones under microwave irradiation. The notable merits offered by this protocol are mild reaction condition, simple procedure, very short reaction time and excellent yield of the product. The identification of compounds was established by single spot TLC and spectral analysis involving IR, ^{1}H NMR, ^{13}C NMR spectroscopy.

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