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# Solvent-Free and Conventional Approach to the Synthesis of Indazole Derivatives through Cyclohexenone and Their Antibacterial Activity

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## ABSTRACT

Microwave assisted solvent free synthesis of cyclohexenone and indazole derivatives were carried out by chalcones derived from different acetophenones and 1-naphthaldehyde. Structures of the compounds have been characterized by IR, $^1$H NMR, Mass spectrometry and elemental analysis. All the synthesized indazole derivatives were screened for antibacterial activity and are found to posses moderate to good activity against some species of bacteria.

**Keywords:** 1-napthaldehyde, chalcones, cyclohexenone, indazole, antibacterial, microwave irradiation.

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## INTRODUCTION

Indazole or benzpyrazole or isoindazone[1], is a heterocyclic aromatic compound with a rare occurrence in nature. The indazole nucleus is a pharmaceutically important and emerging heterocycle with a broad spectrum of activities. These are found to posses anticancer[2] anti-inflammatory[3,4] antiproliferative[5,6] hypotensive[7] antitubercular[8] protein kinase inhibition[9], anti-angiogenic[10] antimicrobial activities [11-13] etc. A number of interesting organic syntheses have been performed using the technique of solvent free synthesis. The solvent-free synthesis is found to be environmentally friendly and economical since it avoids the use of solvents and offers easy work-up procedure[14,15] Also, the yield of product is found to be more than that of conventional technique.

## MATERIALS AND METHOD

The materials were obtained from commercial suppliers and were used without further purification. Melting points were determined in an open capillary tube and are uncorrected. The reactions were monitored by thin-layer chromatography (TLC) analysis using silica gel (Merck 60 $F_{254}$) plates. Compounds were visualized by UV irradiation. IR spectra were recorded in KBr on a Perkin-Elmer spectrometer (RX-IFTIR). $^1$H NMR spectra were recorded on a Bruker Avance II 400 NMR spectrometer in DMSO as solvent and TMS as an internal standard. Mass spectra were recorded on Advion mass spectrometer by ESI source. Elemental analysis was carried out at Thermo Scientific (FLASH 2000) CHN elemental analyzer. Microwave irradiation was carried out in a CEM Discover scientific microwave oven.

### Synthesis of Chalcones(3a-g)

Various aromatic acetophenones (0.01 mol) in ethanol 30 ml and 1-napthaldehyde (0.01 mol) were taken and the solution was heated to near boiling. Aqueous 40% NaOH solution (0.03 mol, 3 ml) was added to it dropwise with constant stirring. The mixture was further stirred at room temperature to yield solid mass. The reaction mixture was kept overnight. Then it was poured over crushed ice and acidified with conc. HCl. The solid thus obtained was filtered, washed with water and purified by crystallization using proper solvent.

### Process I (Conventional Method)

### Synthesis of Cyclohexenone derivatives (4a-g)

A mixture of chalcone (0.01 mol), ethyl acetoacetate (0.01 mol) and 0.5 ml 10% NaOH in 20 ml ethanol was refluxed for 1-5 hrs. After completion of reaction as indicated by TLC, the product was isolated by extracting with diethyl ether. The ether phase was separated and dried over anhydrous $Na_2SO_4$ prior to be subjected to solvent removal. The solid residue obtained was recrystallized from aqueous ethanol.

**Synthesis of Indazole derivatives (5a-g)**

To a solution of compound **(4a-g)** (0.01 mol) in absolute ethanol (10 ml) containing glacial acetic acid (0.5 ml), hydrazine hydrate (0.02 mol) was added. The reaction mixture was refluxed for 2-5 hrs. After the completion of reaction as indicated by TLC, the reaction mixture was cooled and poured over crushed ice with constant stirring. The solid formed was filtered off, dried and recrystallized from ethanol.

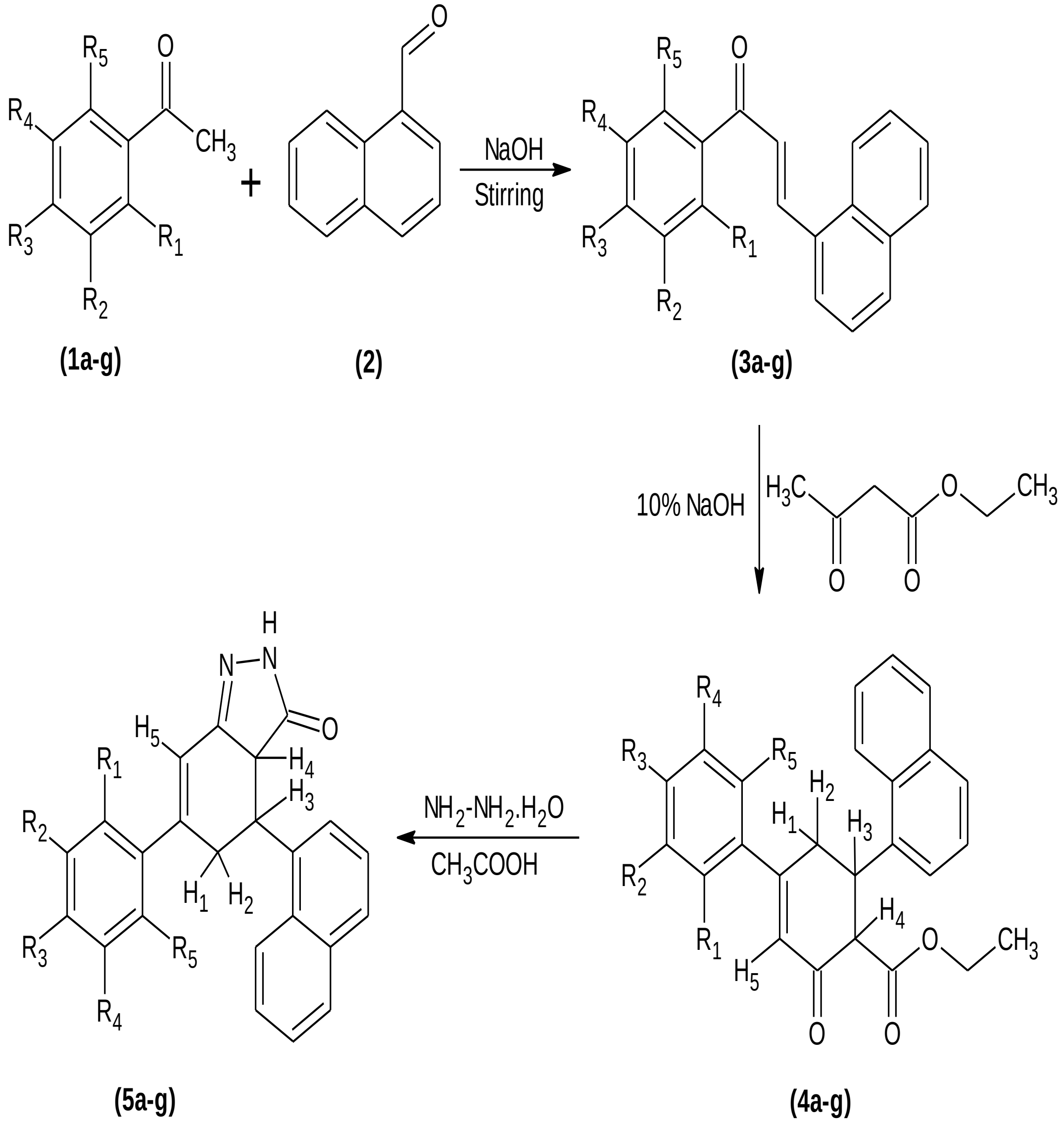

**Figure-1: Synthesis of Cyclohexenone and Indazole Derivatives**

Where

**4a, 5a:** $R_1$, $R_2$, $R_3$, $R_4$, $R_5$=H

**4b, 5b:** $R_1$=OH; $R_2$, $R_3$, $R_4$, $R_5$=H

**4c, 5c:** $R_1$, $R_2$, $R_4$, $R_5$=H; $R_3$=OH

**4d, 5d:** $R_1$=OH; $R_2$, $R_3$, $R_5$=H; $R_4$=$CH_3$

**4e, 5e:** $R_1$=OH; $R_2$, $R_3$, $R_5$=H; $R_4$=Cl

**4f, 5f:** $R_1$=OH; $R_2$, $R_3$, $R_5$=H; $R_4$=Br

**4g, 5g:** $R_1$=OH; $R_2$, $R_4$=Cl; $R_3$, $R_5$=H

### Process II (Microwave method)

### Synthesis of Cyclohexenone derivatives (4a-g)

A mixture of chalcone (0.01 mol), ethyl acetoacetate (0.01 mol) and 0.5 ml 10% NaOH were taken in a 100 ml RB flask and irradiated in a microwave oven at 300 Watts for 2.5 - 6 min with intermittent cooling after 30 sec. After the completion of reaction as indicated by TLC, cold water was added to the flask and stirred for few minutes. The product formed was filtered and dried. It was recrystallized from aqueous ethanol to afford the desired product.

### Synthesis of Indazole derivatives (5a-g)

A mixture of compound **(4a-g)** (0.01 mol), hydrazine hydrate (0.02 mol) and glacial acetic acid (0.5 ml) was taken in a 100 ml RB flask and irradiated in a microwave oven at 300 Watts for 2 - 5.5 min with intermittent cooling after 30 sec. After the completion of reaction as indicated by TLC, cold water was added to the flask and stirred for few minutes. The product formed was filtered and dried. It was recrystallized from ethanol to afford the desired product.

**Ethyl 6-(naphthalen-1-yl)-2-oxo-4-phenylcyclohex-3-enecarboxylate (4a):**

MS: $[M+H]^+$ 371; IR (KBr) $cm^{-1}$: 1728 (C=O ester), 1630 (C=O cyclic); $^1H$ NMR (δ, DMSO): δ 0.84-0.88 (3H, t, J= 7.2 Hz, $-CH_2-CH_3$), 2.50-2.53 (2H, m, $H_1$ & $H_2$), 3.06-3.08 (1H, d, J= 8 Hz, $H_4$), 3.20-3.22 (1H, m, $H_3$), 4.55-4.60 (2H, q, $-CH_2-CH_3$), 6.58 (1H, s, $H_5$), 7.08- 8.22 (12H, m, Ar-H); Anal.Calcd for $C_{25}H_{22}O_3$: C, 81.06; H, 5.99. Found: C, 81.15; H, 5.80%.

**Ethyl 4-(2-hydroxyphenyl)-6-(naphthalen-1-yl)-2-oxocyclohex-3-enecarboxylate (4b):**

MS: $[M+H]^+$ 387; IR (KBr) $cm^{-1}$: 1732 (C=O ester), 1636 (C=O cyclic); $^1H$ NMR (δ, DMSO): δ 0.85-0.90 (3H, t, J = 8 Hz, $-CH_2-CH_3$), 2.50-2.51 (2H, m, $H_1$ & $H_2$), 3.03-3.05 (1H, d, J = 8 Hz, $H_4$), 3.15-3.21 (1H, m, $H_3$), 4.58-4.61 (2H, q, $-CH_2-CH_3$), 6.43 (1H, s, $H_5$), 6.43-8.22 (11H, m, Ar-H), 9.98 (1H, s, OH); Anal.Calcd for $C_{25}H_{22}O_4$: C, 77.70; H, 5.74. Found: C, 77.84; H, 5.69%.

**Ethyl 4-(4-hydroxyphenyl)-6-(naphthalen-1-yl)-2-oxocyclohex-3-enecarboxylate (4c):**

MS: $[M+H]^+$ 387; IR (KBr) $cm^{-1}$: 1725 (C=O ester), 1628 (C=O cyclic); $^1H$ NMR (δ, DMSO): δ 0.84-0.87 (3H, t, J= 7.4 Hz, $-CH_2-CH_3$), 2.47-2.52 (2H, m, H1 & H2), 3.01-3.03 (1H, d, J= 7.8 Hz, $H_4$), 3.17-3.19 (1H, m, $H_3$), 4.50-4.53 (2H, q, $-CH_2-CH_3$), 6.54 (1H, s, $H_5$), 6.50-8.34 (11H, m, Ar-H), 9.87 (1H, s, OH); Anal.Calcd for $C_{25}H_{22}O_4$: C, 77.70; H, 5.74. Found: C, 77.62; H, 5.69%.

**Ethyl4-(2-hydroxy-5-methylphenyl)-6-(naphthalen-1-yl)-2-oxocyclohex-3-enecarboxylate (4d):**

MS: $[M+H]^+$ 401; IR (KBr) $cm^{-1}$: 1734 (C=O ester), 1642 (C=O cyclic); $^1H$ NMR (δ, DMSO): δ 0.80-0.86 (3H, t, J= 6.9 Hz, $-CH_2-CH_3$), 2.36 (3H, s, $-CH_3$), 2.38-2.47 (2H, m, $H_1$ & $H_2$), 3.04-3.06 (1H, d, J= 7.9 Hz, $H_4$), 3.22-3.24 (1H, m, $H_3$), 4.48-4.52 (2H, q, $-CH_2-CH_3$), 6.40 (1H, s, $H_5$), 6.87-7.98 (10H, m, Ar-H), 9.60 (1H, s, OH); Anal.Calcd for $C_{26}H_{24}O_4$: C, 77.98; H, 6.04. Found: C, 78.06; H, 5.94%.

**Ethyl4-(5-chloro-2-hydroxyphenyl)-6-(naphthalen-1-yl)-2-oxocyclohex-3-enecarboxylate (4e):**

MS: $[M+H]^+$ 422; IR (KBr) $cm^{-1}$: 1748 (C=O ester), 1654 (C=O cyclic); $^1H$ NMR (δ, DMSO): δ 0.86-0.92 (3H, t, J= 7.6 Hz, $-CH_2-CH_3$), 2.46-2.50 (2H, m, $H_1$ & $H_2$), 3.08-3.10 (1H, d, J= 7.8 Hz, $H_4$), 3.15-3.19 (1H, m, $H_3$), 4.46-4.50 (2H, q, - $CH_2-CH_3$), 6.42 (1H, s, $H_5$), 6.64-7.89 (10H, m, Ar-H), 10.01 (1H, s, OH); Anal.Calcd for $C_{25}H_{21}ClO_4$: C, 71.34; H, 5.03. Found: C, 71.44; H, 5.16%.

**Ethyl4-(5-bromo-2-hydroxyphenyl)-6-(naphthalen-1-yl)-2-oxocyclohex-3-enecarboxylate (4f):**

MS: $[M+H]^+$ 466; IR (KBr) $cm^{-1}$: 1752 (C=O ester), 1657 (C=O cyclic); $^1H$ NMR (δ, DMSO): δ 0.89-0.93 (3H, t, J= 7.8 Hz, $-CH_2-CH_3$), 2.49-2.54 (2H, m, $H_1$ & $H_2$), 3.10-3.12 (1H, d, J= 8 Hz, $H_4$), 3.18-3.24 (1H, m, $H_3$), 4.61-4.65 (2H, q, - $CH_2-CH_3$), 6.39 (1H, s, $H_5$), 6.54-7.71 (10H, m, Ar-H) , 10.05 (1H, s, OH); Anal.Calcd for $C_{25}H_{21}BrO_4$: C, 64.53; H, 4.55. Found: C, 64.38; H, 4.67%.

**Ethyl 4-(3,5-dichloro-2-hydroxyphenyl)-6-(naphthalen-1-yl)-2-oxocyclohex-3-enecarboxylate (4g):**

MS: $[M+H]^+$ 456; IR (KBr) $cm^{-1}$: 1742 (C=O ester), 1672 (C=O cyclic); $^1H$ NMR (δ, DMSO): δ 0.91-0.94 (3H, t, J= 6.8 Hz, $-CH_2-CH_3$), 2.44-2.48 (2H, m, $H_1$ & $H_2$), 3.09-3.11 (1H, d, J= 7.9 Hz, $H_4$), 3.19-3.22 (1H, m, $H_3$), 4.48-4.51 (2H, q, - $CH_2-CH_3$), 6.48 (1H, s, $H_5$), 6.92-8.24 (9H, m, Ar-H), 10.12 (1H, s, OH); Anal.Calcd for $C_{25}H_{20}Cl_2O_4$: C, 65.95; H, 4.43. Found: C, 65.78; H 4.56%.

**4-(naphthalen-1-yl)-6-phenyl-4,5-dihydro-2H-indazol-3(3aH)-one (5a):**

MS: $[M+H]^+$ 339; IR (KBr) $cm^{-1}$: 3300 (N-H), 1685 (C=O), 1640 (C=N); $^1H$ NMR (δ, DMSO): δ 2.64-2.86 (2H, m, $H_1$ & $H_2$), 4.71-4.73 (1H, d, J= 8 Hz, $H_4$), 5.0-5.05 (1H, m, $H_3$), 6.92-7.80 (12H, m, Ar-H), 8.10 (1H, s, $H_5$), 8.30 (1H, bs, -NH); Anal.Calcd for $C_{23}H_{18}N_2O$: C, 81.63; H, 5.36; N, 8.28. Found: C, 81.74; H, 5.45; N, 8.15%.

**6-(2-hydroxyphenyl)-4-(naphthalen-1-yl)-4,5-dihydro-2H-indazol-3(3aH)-one (5b):**

MS: $[M+H]^+$ 355; IR (KBr) $cm^{-1}$: 3219 (N-H), 1690 (C=O), 1630 (C=N); $^1H$ NMR (δ, DMSO): δ 2.79-3.32 (2H, m, $H_1$ & $H_2$), 3.92-3.94 (1H, d, J= 8 Hz, $H_4$), 4.97-5.00 (1H, m, $H_3$), 6.58-7.85 (11H, m, Ar-H), 8.15 (1H, s, $H_5$), 8.28 (1H, bs, -NH), 9.25 (1H, s, -OH); Anal.Calcd for $C_{23}H_{18}N_2O_2$: C, 77.95; H, 5.12; N, 7.90. Found: C, 78.03; H, 5.00; N, 8.11%.

**6-(4-hydroxyphenyl)-4-(naphthalen-1-yl)-4,5-dihydro-2H-indazol-3(3aH)-one (5c):**

MS: $[M+H]^+$ 355; IR (KBr) $cm^{-1}$: 3280 (N-H), 1680 (C=O), 1600 (C=N); $^1H$ NMR (δ, DMSO): δ 2.76-3.10 (2H, m, $H_1$ & $H_2$), 4.42-4.44 (1H, d, J= 8 Hz, $H_4$), 4.86-4.92 (1H, m, $H_3$), 6.66-7.82 (11H, m, Ar-H), 8.09 (1H, s, $H_5$), 8.24 (1H, bs, -NH), 8.64 (1H, s, -OH); Anal.Calcd for $C_{23}H_{18}N_2O_2$: C, 77.95; H, 5.12; N, 7.90. Found: C, 78.07; H, 5.23; N, 7.81%.

**6-(2-hydroxy-5-methylphenyl)-4-(naphthalen-1-yl)-4,5-dihydro-2H-indazol-3(3aH)-one (5d):**

MS: $[M+H]^+$ 369; IR (KBr) $cm^{-1}$: 3320 (N-H), 1650 (C=O), 1580 (C=N); $^1H$ NMR (δ, DMSO): δ 2.28 (3H, s, $-CH_3$), 2.72-3.20 (2H, m, $H_1$ & $H_2$), 3.99-4.01 (1H, d, J= 7.8 Hz, $H_4$), 4.99-5.05 (1H, m, $H_3$), 6.48-7.79 (10H, m, Ar-H), 8.18 (1H, s, $H_5$), 8.30 (1H, bs, -NH), 8.55 (1H, s, -OH); Anal.Calcd for $C_{24}H_{20}N_2O_2$: C, 78.24; H, 5.47; N, 7.60. Found: C, 78.11; H, 5.35; N, 7.66%.

**6-(5-chloro-2-hydroxyphenyl)-4-(naphthalen-1-yl)-4,5-dihydro-2H-indazol-3(3aH)-one (5e):**

MS: $[M+H]^+$ 390; IR (KBr) $cm^{-1}$: 3380 (N-H), 1648 (C=O), 1590 (C=N); $^1H$ NMR (δ, DMSO): δ 2.81-3.41 (2H, m, $H_1$ & $H_2$), 4.16-4.18 (1H, d, J= 7.9 Hz, $H_4$), 4.76-4.87 (1H, m, $H_3$), 6.60-7.72 (10H, m, Ar-H), 8.23 (1H, s, $H_5$), 8.34 (1H, bs, -NH), 9.36 (1H, s, -OH); Anal.Calcd for $C_{23}H_{17}ClN_2O_2$: C, 71.04; H, 4.41; N, 7.20. Found: C, 71.17; H, 4.55; N, 7.27%.

**6-(5-bromo-2-hydroxyphenyl)-4-(naphthalen-1-yl)-4,5-dihydro-2H-indazol-3(3aH)-one (5f):**

MS: $[M+H]^+$ 434; IR (KBr) $cm^{-1}$: 3350 (N-H), 1675 (C=O), 1600 (C=N); $^1H$ NMR (δ, DMSO): δ 2.85-3.38 (2H, m, $H_1$ & $H_2$), 3.88-3.90 (1H, d, J= 8 Hz, $H_4$), 4.66-4.72 (1H, m, $H_3$), 6.50-7.86 (10H, m, Ar-H), 8.29 (1H, s, $H_5$), 8.35 (1H, bs, -NH), 9.39 (1H, s, -OH); Anal.Calcd for $C_{23}H_{17}BrN_2O_2$: C, 63.75; H, 3.95; N, 6.47. Found: C, 63.66; H, 3.84; N, 6.59%.

**6-(3,5-dichloro-2-hydroxyphenyl)-4-(naphthalen-1-yl)-4,5-dihydro-2H-indazol-3(3aH)-one (5g):**

MS: $[M+H]^+$ 424; IR (KBr) $cm^{-1}$: 3370 (N-H), 1662 (C=O), 1630 (C=N); $^1H$ NMR (δ, DMSO): δ 2.94-3.26 (2H, m, $H_1$ & $H_2$), 4.46-4.48 (1H, d, J= 8 Hz, $H_4$), 5.02-5.06 (1H, m, $H_3$), 6.87-7.77 (9H, m, Ar-H), 8.35 (1H, s, $H_5$), 8.40 (1H, bs, -NH), 10.26 (1H, s, -OH); Anal.Calcd for $C_{23}H_{16}Cl_2N_2O_2$: C, 65.26; H, 3.81; N, 6.62. Found: C, 65.05; H, 3.88; N, 6.49%.

## Antibacterial activity

All the synthesized indazole derivatives were tested for in vitro antibacterial activity against two gram positive (S. aureus, B. subtilis) and two gram negative (E. coli, K. aerogenes) bacteria by well diffusion method [16] and zone of inhibition was measured in mm. Amoxicillin was used as standard drug and DMSO as control solvent. The compounds were tested at 1mg/ml concentration. The results of the activity data is shown in table-2.

## RESULTS AND DISCUSSION

Mass spectra of the synthesized compounds showed peaks at $[M+H]^+$ which confirms the molecular mass of the compounds. IR spectra of cyclohexenone derivatives revealed a sharp strong band at 1725-1752 $cm^{-1}$ due to C=O of ester and another sharp strong band at 1628-1672 $cm^{-1}$ is due to the presence of cyclic C=O group. IR spectra of indazole derivatives showed a band at 3219-3380 $cm^{-1}$ due to the presence of N-H group in the structure. A sharp strong band at 1648-1690 $cm^{-1}$ is due to the presence of C=O group in the structure. C=N group in the structure gives a band between 1580-1640 $cm^{-1}$. The $^1$H NMR spectra of compounds **(4a-g)** gives a triplet at δ 0.80-0.94 and a quartet at δ 4.46-4.65 due to the presence of ethyl ester moiety in the structure of cyclohexenone. The two protons $H_1$ & $H_2$ appears as multiplet at δ 2.38-2.54.

The proton $H_4$ appears as doublet at δ 3.01-3.12 while $H_3$ gives multiplet at δ 3.15-3.24. The vinylic proton $H_5$ appears as a singlet at higher chemical shift i.e. δ 6.39-6.58. The aromatic proton gives multiplet at δ 6.43-8.34. The –OH proton in compounds **(4b-g)** appears as singlet at δ 9.60-10.12. The $^1$H NMR spectra of compounds **(5a-g)** shows the absence of a triplet and a quartet at δ around 0.8 and 4.4 respectively. The –NH signal is obtained at δ 8.22-8.42. All the synthesized indazole derivatives **(5a-g)** are found to be active against S. aureus, B. subtilis, K. aerogenes while all are inactive against E.coli.

**Table-1: The physicochemical data for synthesized Cyclohexenone and Indazole derivatives by conventional (Process I) and microwave (Process II) methods.**

| Compound | Molecular Formula | Molecular Weight | Reaction Time Process I (hr) | Reaction Time Process II (min) | % yield Process I | % yield Process II | Melting Point (°C) |
|---|---|---|---|---|---|---|---|
| 4a | $C_{25}H_{22}O_3$ | 370 | 4 | 4 | 61 | 66 | 120 |
| 4b | $C_{25}H_{22}O_4$ | 386 | 1.5 | 2.5 | 71 | 74 | 155 |
| 4c | $C_{25}H_{22}O_4$ | 386 | 4 | 3 | 65 | 69 | 169 |
| 4d | $C_{26}H_{24}O_4$ | 400 | 2.5 | 2.5 | 68 | 76 | 172 |
| 4e | $C_{25}H_{21}ClO_4$ | 421 | 4 | 4 | 67 | 72 | 185 |
| 4f | $C_{25}H_{21}BrO_4$ | 465 | 4.5 | 4.5 | 70 | 77 | 204 |
| 4g | $C_{25}H_{20}Cl_2O_4$ | 455 | 5 | 6 | 65 | 72 | 217 |
| 5a | $C_{23}H_{18}N_2O$ | 338 | 3 | 3 | 67 | 74 | 196 |
| 5b | $C_{23}H_{18}N_2O_2$ | 354 | 2 | 2 | 70 | 76 | 230 |
| 5c | $C_{23}H_{18}N_2O_2$ | 354 | 2.5 | 3.5 | 62 | 68 | 244 |
| 5d | $C_{24}H_{20}N_2O_2$ | 368 | 2 | 2.5 | 72 | 81 | 264 |
| 5e | $C_{23}H_{17}ClN_2O_2$ | 389 | 3.5 | 4 | 74 | 83 | 257 |
| 5f | $C_{23}H_{17}BrN_2O_2$ | 433 | 4 | 4.5 | 68 | 75 | 270 |
| 5g | $C_{23}H_{16}Cl_2N_2O_2$ | 423 | 5 | 5.5 | 60 | 69 | 276 |

**Table-2: Antibacterial activity of indazole derivatives (5a-g)**

| Compound | S. aureus | B. subtilis | E. coli | K. aerogenes |
|---|---|---|---|---|
| 5a | + + | + + | - | + |
| 5b | + + + | + + + | - | + + + |
| 5c | + + | + + | - | + |
| 5d | + + + | + + + | - | + + |
| 5e | + + + | + + | - | + + |
| 5f | + + + | + + | - | + + |
| 5g | + + + + | + + + | - | + + |
| Amoxicillin | + + + + | + + + + | + + + + | + + + + |

Zone of inhibition: (-) 0-5 mm, inactive; (+) 6-10 mm, poor activity; (+ +) 11-15 mm, moderate activity; (+ + +) 16-20 mm, good activity; (+ + + +) >20 mm, very good activity.

## CONCLUSION

We herein report a microwave assisted method for the synthesis of cyclohexenone and indazole derivatives. This method is simple, efficient, high yielding as compared to conventional method and avoids the use of harmful solvents.

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