Green synthesis and antimicrobial activity of 1,3-diaryl pyrazole based chalcone derivatives

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Abstract
We report a facile green synthetic protocol for the synthesis of 1,3-diaryl pyrazole based chalcone derivatives by the condensation of 3-Aryl-1-phenyl-1H-pyrazole-4-carbaldehydes with arylmethylketones in the presence of base in both microwave and ultrasound irradiation method. The synthesized compounds were evaluated for in vitro antimicrobial activity against four bacterial organisms and two fungal organisms showing moderate to good activity.

Keywords: Pyrazole, MWI, Ultrasound synthesis, Vilsmeier-Haack reaction, Antimicrobial activity.

Introduction
Heterocyclic compounds containing nitrogen atom have been considered as a source of potential biological active compounds and they are frequently used in generating new therapeutic compounds. A vast number of nitrogen atom containing heterocyclic building blocks have applications in pharmaceutical, agrochemical research and drug discovery. In addition, pyrazole nucleus is a frequently occurring motif in many pharmaceuticals and biologically active compounds, agrochemicals, dyes, fluorescent materials and ligands of complexing agents.

In the class of pyrazole derivatives, 1,3-diaryl pyrazoles attract great interest owing to their wide range of pharmacological activities such as antimicrobial, anti-inflammatory, antitubercular, antitumour, antiangiogenesis, antiparasitic, antiviral and also possess analgesic and anxiolytic activity. Nowadays green chemical syntheses and ultrasound assisted condensation strategy attained greater value, as the target molecules are obtained in short reaction time with high yield which minimize the use of hazardous organic solvents, operation energy, tedious work-up procedures and environmental hazardous wastes.

We made an attempt to synthesize 1,3-diaryl pyrazole based chalcone derivatives under both microwave and ultrasound synthetic protocol by using 3-Aryl-1-phenyl-1H-pyrazole-4-carbaldehydes with arylmethylketones in the presence of base.

Material and Methods
Experimental: Melting points were determined in open capillary tubes and are uncorrected. The purity of the compounds was checked by TLC using precoated silica gel plates 60s4 (Merck). 1H NMR and 13C NMR spectra were recorded on Bruker Advance II 400 MHz spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a GCMS-QP 1000 EX mass spectrometer.

General synthetic procedure for 1,3-diaryl pyrazole based chalcone derivatives (7a-h):
Microwave irradiation method: A mixture of 3-Aryl-1-phenyl-1H-pyrazole-4-carbaldehydes (4) (1 mmol), aryl methyl keones (5a-h) (1 mmol) and NaOAc (2 mmol) in ethanol (10 ml) was irradiated under MW for 5-6 min. Progress of the reaction was monitored by TLC after completion of the reaction. The reaction mixture was poured into ice cold water, slowly the solid separates out, filtered, washed with water, dried and purified by using column chromatography using n-hexane:ethyl acetate (9:1) to afford pure 1,3-diaryl pyrazole based chalcone derivatives (7a-h).

Scheme 1: Synthesis of 1,3-diaryl pyrazole based chalcone derivatives
Ultrasound irradiation method: A mixture of 3-Aryl-1-phenyl-1H-pyrazole-4-carbaldehydes (4) (1 mmol), aryl methyl ketones (5a-h) (1 mmol) and NaOAc (2 mmol) in ethanol (10 ml) was irradiated under ultrasound for 10-12 min. Progress of the reaction was monitored by TLC after completion of the reaction. The reaction mixture was poured into ice cold water, slowly the solid separates out, filtered, washed with water, dried and purified by using column chromatography using n-hexane:ethyl acetate (9:1) to afford pure 1,3-diaryl pyrazole based chalcone derivatives (7a-h).

<table>
<thead>
<tr>
<th>Comp.</th>
<th>S.aureus</th>
<th>B.subtilis</th>
<th>P.aeruginosa</th>
<th>E. coli</th>
<th>A.Niger</th>
<th>S.fsi</th>
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<tr>
<td>7a. Phenyl</td>
<td>8.6</td>
<td>12.4</td>
<td>15.2</td>
<td>10.3</td>
<td>7.8</td>
<td>11.0</td>
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<tr>
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<td>10.2</td>
<td>12.8</td>
<td>18.0</td>
<td>9.6</td>
<td>6.5</td>
<td>10.5</td>
</tr>
<tr>
<td>7c. 4-methoxyphenyl</td>
<td>7.5</td>
<td>9.0</td>
<td>12.2</td>
<td>11.0</td>
<td>9.0</td>
<td>9.8</td>
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<td>7d. 3-methoxyphenyl</td>
<td>14.5</td>
<td>10.1</td>
<td>11.5</td>
<td>9.9</td>
<td>7.0</td>
<td>12.0</td>
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<td>8.7</td>
<td>10.6</td>
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<td>10.0</td>
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<td>10.1</td>
<td>9.7</td>
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<td>7g. 2,4-dimethoxyphenyl</td>
<td>18.2</td>
<td>12.1</td>
<td>13.4</td>
<td>12.3</td>
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<td>9.7</td>
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<tr>
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<td>19.2</td>
<td>24.2</td>
<td>24.0</td>
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<tr>
<td>Ketoconazole</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>18.3</td>
<td>22.1</td>
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</table>

7f. (E)-3-(3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-phenylprop-2-en-1-one: ^1^H NMR (CDCl₃): δ 7.17-7.93 (m, 16H, Ar-H), 8.27 (s, 1H, Ar-H); ^1^C NMR (CDCl₃): δ 119.0, 119.4, 121.3, 121.3, 124.6, 126.3, 126.9, 127.4, 129.6, 131.5, 131.7, 132.9, 135.5, 139.6, 142.3, 147.7, 149.1, 150.8, 191.5; ESI-MS: m/z=429 & 431 [M+H]^+. 

7g. (E)-3-(3-(2,4-dimethoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-1-phenylprop-2-en-1-one: ^1^H NMR (CDCl₃): δ 3.91 (s, 3H, OCH₃), 6.84-6.86 (d, 1H, Ar-H), 7.04-7.06 (d, 1H, Ar-H), 7.21-7.75 (m, 13H, Ar-H), 8.25 (s, 1H, Ar-H); ^1^C NMR (CDCl₃): δ 55.3, 55.8, 114.3, 118.5, 119.4, 122.8, 123.9, 124.8, 126.4, 127.9, 128.9, 129.6, 130.7, 131.4, 132.8, 139.9, 141.5, 145.4, 146.9, 152.6, 152.8, 191.0; ESI-MS: m/z=411 [M+H]^+. 

7h. (E)-3-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-phenylprop-2-en-1-one: ^1^H NMR (CDCl₃): δ 7.29-7.79 (m, 14H, Ar-H), 8.11-8.13 (d, 2H, Ar-H), 8.29 (s, 1H, Ar-H); ^1^C NMR (CDCl₃): δ 118.7, 122.8, 123.6, 123.9, 124.8, 126.7, 127.9, 128.9, 129.3, 130.2, 130.7, 131.4, 132.8, 139.9, 141.5, 145.4, 146.9, 194.2, 156.2, 192.1; MS: m/z=396 [M+H]^+. 

Results and Discussion

Generally, the chalcone derivatives were synthesized by the condensation of aldehyde with methyl ketone in the presence of acid and base under conventional heating method. The traditional conventional condensation methods had various drawbacks, hence we made a successful attempt to synthesize the chalcone derivatives (7a-h) by using both microwave and ultrasound irradiation method synthetic protocol from 3-Aryl-1-phenyl-1H-pyrazole-4-carbaldehydes (4) and arylmethyleneketones (5a-h) in the presence of mild base sodium acetate in ethanol medium.

This synthetic protocol proved to be easy, giving high yield with short reaction times, consuming lesser energy and more eco-friendly.
Biological activity

Antibacterial activity: The synthesized compounds (7a-h) were evaluated for in vitro antibacterial activity against four bacterial strains: gram-positive (Staphylococcus aureus and Bacillus subtilis) and gram-negative (Pseudomonas aeruginosa and Escherichia coli) by paper disc method and norfloxacin used as the standard drug by measuring the zone of inhibition in mm. The compounds were screened at the concentrations of 100μg/ml in DMSO. The compounds 7d, 7g and 7k showed good antibacterial activity against all the bacterial strains and the rest compounds showed moderate to low activity (Table 1).

Antifungal activity: The synthesized compounds (7a-h) were evaluated for in vitro antifungal activity against two fungal strains (Sclerotium rolfsii and Aspergillus niger) at a concentration of 500 mg/mL by disc diffusion method, zone of inhibition measured in mm and ketoconazole used as the standard. Careful observation of the results shows that compounds 7e, 7f and 7h showed better antifungal activity and the remaining compounds showed moderate activity against both the organisms (Table 1).

Conclusion

In conclusion we have successfully synthesised various pyrazole chalcone derivatives by under microwave and ultrasound irradiation synthetic protocol. The protocol proved an easy, simple, one synthetic chemical step and gave higher yields. The synthesised compounds structures were established by using different spectral techniques and screening results of the synthesised compounds showed moderate to good activity against both bacterial organism and fungal organisms.

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References


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