# Microwave assisted synthesis of substituted (*E*)-{3-[2-(1,3-Diphenyl-1*H*-Pyrazol-4-YL)Vinyl]Benzofuran-2-YL}(Phenyl)Methanone and their antimicrobial activity

**Ashok D.[1]*, Nalaparju Nagaraju[1], Ram Reddy M.[1], Ravinder D.[1], Katta Ramakrishna[1] and Sarasija M.[2]**
1. Green and Medicinal Chemistry Laboratory, Department of Chemistry, Osmania University, Hyderabad- 500 007, INDIA
2. Department of Chemistry, Satavahana University, Karimnagar, 505001, Telangana, INDIA
*ashokdou@gmail.com

***Abstract***

*A series of new pyrazole based benzofuran derivatives has been synthesized from their chalcone moiety reacting with different 2-bromo-1-phenylethanone in the presence of anhydrous $K_2CO_3$ under conventional, ultrasound and microwave irradiation methods. The reaction gave higher yield within shorter reaction times under the microwave irradiation approach as an advanced method to synthesize the title compounds.*

*The structures of the newly synthesized compounds were characterized by $^1$HNMR, $^{13}$CNMR, IR, mass spectral data and elemental analysis. All the synthesized compounds were screened for their antibacterial and antifungal activities. Most of the title compounds exhibited good antimicrobial activity and few compounds were emerged as better antimicrobial agents by displaying promising microbial inhibitory potency.*

**Keywords:** Antimicrobial activity, benzofuran, microwave irradiation, pyrazole.

## Introduction

In recent year scientific interest has focused on nitrogen-heterocyclic compounds due to their wide range of applications in the field of drug discovery and agricultural research[1-3]. Pyrazole derivatives are an important class of nitrogen-containing five-membered heterocyclic compounds known to possess a wide range of activities, such as anticancer[4], antimicrobial[5], antitubercular[6], antiviral[7], antihypertensive[8], antidepressant[9], insecticidal[10], antioxidant[11], 5α-reductase inhibitory[12], antiproliferative[13], antiparasitic[14], herbicidal[15], antiprotozoal[16], analgesic[17] and androgen receptor modulatory[18] activities. The pyrazole ring is present as the core in a variety of leading drugs such as lonazolac[19], rimonabant[20] present already in the market (Figure 1).

On the other hand, benzofurans are important pharmacophores present in a variety of natural products especially in the *Moraceae* family, known to exhibit antibacterial and antifungal activities[21]. Moracin K and its analogs are natural occurring products used as antioxidant agents[22] (Figure 1). Benzofuran scaffolds possess a wide range of biological activities including antiviral[23], antitumor[24,25], antifungal[26], 5α-reductase-inhibitory[27], anti-inflammatory[28,29], analgesic[29], antihyperglycemic[30], antiparasitic[31], antitumor and kinase inhibitory[32] activities.

In today's world, synthetic chemists in industry are constantly challenged to consider more environmentally benign methods for generation of the desired target molecules. Microwave-assisted organic synthesis has attracted considerable attention as a powerful tool for rapid and efficient synthesis of a variety of compounds because of selective absorption of microwave energy by polar molecules[33].

The microwave technique offers a simple, clean, fast, efficient and economical method for the synthesis of a large number of organic molecules. Synthesis of a variety of organic molecules using microwave irradiation has merits over conventional heating shown to dramatically reduce reaction times, increase product yields and enhance product purities by reducing unwanted side reactions compared to conventional synthetic methods[34].

Pharmacological importance of pyrazole and benzofuran moieties inspired us to synthesise new compounds 5a-k under conventional heating, ultrasound and microwave irradiation methods.

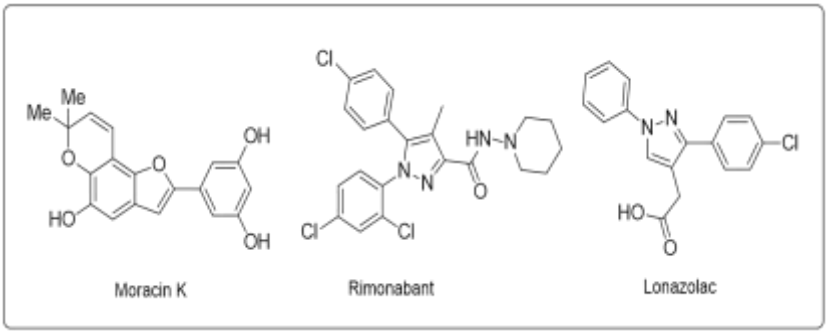



**Figure 1: Structures of some biologically active benzofuran and pyrazole drugs.**

We have taken up the synthesis of pyrazole based benzofuran derivatives under microwave giving better yields as compared to ultrasound and conventional heating methods. All the synthesized compounds have been tested for their *in vitro* antimicrobial activity as a part of the search for new antimicrobial drugs.

## Material and Methods

IR spectra were recorded on a Shimadzu FTIR 8400 S spectrometer in KBr pellets. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker Avance 400 spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ using TMS as internal reference. Mass spectra (EI, 70 eV) were recorded on a Finnigan MAT 1020 mass spectrometer. Elemental analyses were recorded on a Karlo Erba 1106 elemental analyzer.

All melting points were recorded on a Stuart SMP3 melting point apparatus and are uncorrected. Microwave irradiation experiments were performed in a CEM Discover microwave system and reaction temperatures were monitored by an equipped IR sensor. All the reactions were monitored by TLC method on percolated silica gel Merck 60 F254 plates and visualized with UV light.

**Experimental procedure**

**Synthesis of compounds 5a–l- Conventional heating method:** To a well stirred solution of chalcone 3a–d (1 mmol) and anhydrous $K_2CO_3$ (2 mmol) in dry acetone (10 ml), different 2-bromo-1-phenylethanone 4a-c (1 mmol) was added and the reaction mixture was refluxed for 6–8 h. After completion of the reaction (TLC control), the solvent was evaporated under reduced pressure and the solid residue was purified by column chromatography on silica gel using hexane:ethylacetate (7:3), as eluent to afford compounds 5a–l.

**Ultrasound irradiation method:** To a well stirred solution of chalcone 3a–d (1 mmol) and anhydrous $K_2CO_3$ (2 mmol) in dry acetone (10 ml), different 2-bromo-1-phenylethanones 4a-c (1 mmol) were added and the reaction mixture was subjected to ultrasound irradiation for 1.5–2 h at 60°C.

After completion of the reaction (TLC control), the solvent was evaporated under reduced pressure and the solid residue was purified by column chromatography on silica gel using hexane:ethylacetate (7:3), as eluent to afford compounds 5a–l.

**Microwave irradiation method:** To a mixture of chalcone **3a**–**d** (1 mmol) and anhydrous $K_2CO_3$ (2 mmol) in dry acetone (10 ml), different 2-bromo-1-phenylethanones 4a-c (1 mmol) were added and subjected to microwave irradiation at for 5–7 min. Progress of the reaction was monitored by TLC.

After completion of the reaction, the solvent was evaporated under reduced pressure and the solid residue was purified by column chromatography on silica gel using hexane:ethylacetate (7:3), as eluent to afford compounds 5a–l.

**Antibacterial activity:** All the synthesized compounds were screened *in vitro* for antibacterial activity against gram-positive organisms [i.e. *Staphylococcus aureus* (ATCC 6538) and *Bacillus subtilis* (ATCC 6633)] and gram negative bacterial strains [*Klebsiella pneumonia* (ATCC 13883) and *Escherichia coli* (ATCC 25922)] at 20 and 40 μg $mL^{-1}$ concentrations (Table 2). The bacterial cultures were grown in nutrient agar media and subcultured for the better growth in a liquid nutrient broth medium and further subcultured onto Petri plates for the experiments. The broth cultures were diluted with sterilized saline to bring the final size of inoculum to approximately to $10^5$–$10^6$ CFU $ml^{-1}$.

The compounds were dissolved in DMSO for the biological assays and pure solvent DMSO showed no inhibition zone. For disc diffusion method, the test compound was introduced onto the disc and then allowed to dry. Once a disc was completely saturated with the test compound, it was introduced onto the upper layer of the medium containing the bacterial inoculums. The Petri dishes were incubated overnight at 37 °C for 24 h. The diameters of the zones of inhibition were measured to determine the antibacterial activity. Triplicates for all the compounds were run and the results are expressed as zone of inhibition in mm. The results for the newly synthesized compounds were compared with ampicillin as the standard antibiotic drug.

**Antifungal activity:** All the compounds were screened *in vitro* for their antifungal activity against *Aspergillus niger* (ATCC 20057), *Aspergillus flavus* (ATCC 11497) and *Fusarium oxysporum* (ATCC-7601) using amphotericin-B as the standard drug. The test compounds were dissolved in DMSO before mixing with potato dextrose agar medium (PDA, 20 mL). The final concentration of compounds in the medium was maintained to be 50μg $mL^{-1}$. Above mentioned types of fungi were incubated in PDA at 25±1 °C for 3–4 days to obtain good mycelium growth for antifungal assay; then, amycelia disk of approximately 0.45 cm diameter cut from the culture medium was picked up with a sterilized inoculation needle and inoculated in the center of PDA plate. The inoculated plates were incubated at 25±1 °C for 5 days.

DMSO in sterilized distilled water was used as control, while amphotericin-B was used as standard for all the treatment; three replicates were performed. The radial growth of the fungal colonies was measured on the fourth day and the data were statistically analyzed. The *in vitro* inhibition effects of the test compounds on the fungi were calculated by the given formula

$$CV = A–B/A$$

where *A* represents the diameter of fungi growth on untreated PDA (control of DMSO), *B* represents the

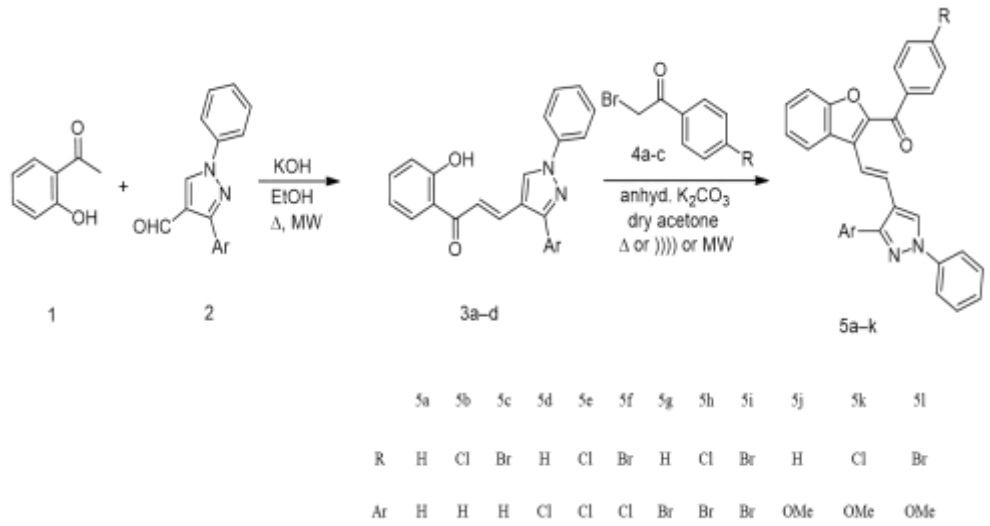
diameter of fungi on treated PDA (diameter of synthetic compounds 5a–l) and *CV* represents the zone of inhibition.

## Results and Discussion

The synthetic route for the synthesis of (E)-(3-(2-(1,3-diphenyl-1H-pyrazol-4-yl)vinyl)benzofuran-2-yl)(phenyl) methanone 5a is illustrated in scheme 1. The title compounds 5a have been prepared by reacting 2-bromo-1-phenylethanone 4a with 2-hydroxychalcones 3a, which were obtained from 1-(2-hydroxyphenyl)ethanone 1 and 1,3-diphenyl-1H-pyrazole-4-carbaldehyde 2 under Claisen–Schmidt conditions in the presence of powdered NaOH under microwave irradiation for 5–8 min.

Initially, an optimization study was performed for the synthesised compound 5a in the presence of various bases like $Na_2CO_3$ and $K_2CO_3$ and the solvents like ethanol, acetonitrile and acetone. Optimization study results revealed that in the presence of $K_2CO_3$ in acetone at reflux temperature for 6–7 h, the reaction gave good yield compared to other base and solvent. However, this method still suffered from moderate yield of the product 5a. In order to improve the better yields and shorter reaction time, the synthesis of compound 5a was carried out under ultrasound and microwave irradiation. Similarly, the synthesis of compounds 5b–l was studied**.** Comparison of the results under conventional, ultrasound and microwave irradiation methods is shown in table 1.

The synthesized derivatives 5a–l were evaluated for their *in vitro* antimicrobial activity against gram-positive organisms [i.e.; *Staphylococcus aureus* (ATCC 6538) and *Bacillus subtilis* (ATCC 6633)] and gram negative bacterial strains (*Klebsiella pneumonia* [ATCC 13883) and *Escherichia coli* (ATCC 25922)] at 20 and 40 µg $mL^{-1}$ concentrations (Table 2) Ampicillin as standard antibacterial drug. The results obtained as minimum inhibitory concentration (MIC) in µg/mL and measurements are presented in table 2.




| | 5a | 5b | 5c | 5d | 5e | 5f | 5g | 5h | 5i | 5j | 5k | 5l |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| R | H | Cl | Br | H | Cl | Br | H | Cl | Br | H | Cl | Br |
| Ar | H | H | H | Cl | Cl | Cl | Br | Br | Br | OMe | OMe | OMe |

**Scheme 1: The synthetic route for compounds 5a-l**

**Table 1**
**Reaction time and yields for the synthesis of compounds 5a–l**

| Compound no. | Conventional | | Ultrasound | | MWI | |
|---|---|---|---|---|---|---|
| | Time, h | Yield, % | Time, h | Yield, % | Time, min | Yield, % |
| 5a | 6.5 | 55 | 2 | 63 | 4 | 84 |
| 5b | 6.5 | 60 | 1.5 | 65 | 4 | 79 |
| 5c | 8 | 58 | 2 | 64 | 5 | 80 |
| 5d | 7.5 | 56 | 2 | 68 | 6 | 85 |
| 5e | 8 | 58 | 1.5 | 70 | 5 | 81 |
| 5f | 7 | 54 | 1.5 | 65 | 5 | 81 |
| 5g | 6.5 | 57 | 2 | 69 | 6 | 84 |
| 5h | 8 | 58 | 2 | 64 | 5 | 80 |
| 5i | 7.5 | 57 | 2 | 68 | 6 | 85 |
| 5j | 6.5 | 60 | 1.5 | 70 | 5 | 81 |
| 5k | 8 | 55 | 1.5 | 65 | 5 | 81 |
| 5l | 7 | 61 | 2 | 68 | 6 | 79 |

**Table 2**
**Antibacterial activities (zone of inhibition, mm) of synthesized compounds 5a-l**

| Compound no. | S. aureus | | B. subtilis | | K. pneumoniae | | E. coli | |
|---|---|---|---|---|---|---|---|---|
| | 20µg $mL^{-1}$ | 40µg $mL^{-1}$ | 20µg $mL^{-1}$ | 40µg $mL^{-1}$ | 20µg $mL^{-1}$ | 40µg $mL^{-1}$ | 20µg $mL^{-1}$ | 40µg $mL^{-1}$ |
| 5a | 13.9 | 23.8 | 12.5 | 18.1 | 20.3 | 22.2 | 16.8 | 24.8 |
| 5b | 11.5 | 22.4 | 14.9 | 16.5 | 10.5 | 16.8 | 9.8 | 17.5 |
| 5c | 11.2 | 22.1 | 10.4 | 14.5 | 11.5 | 18.1 | 10.5 | 25.6 |
| 5d | 12.8 | 12.9 | 9.4 | 13.6 | 15.4 | 19.4 | 10.0 | 20.5 |
| 5e | 12.1 | 25.9 | 12.9 | 20.0 | 17.2 | 30.0 | 14.8 | 30.8 |
| 5f | 12.4 | 25.4 | 13.4 | 24.4 | 18.4 | 30.9 | 13.0 | 28.0 |
| 5g | 10.9 | 17.4 | 12.0 | 16.9 | 11.5 | 24.9 | 14.6 | 21.1 |
| 5h | 12.9 | 25.7 | 13.5 | 20.9 | 18.4 | 30.7 | 14.2 | 30.6 |
| 5i | 13.4 | 26.4 | 13.4 | 25.4 | 19.4 | 30.1 | 13.2 | 28.9 |
| 5j | 14.0 | 27.4 | 15.4 | 29.4 | 21.4 | 33.1 | 16.9 | 33.8 |
| 5k | 14.7 | 27.1 | 14.6 | 28.5 | 22.3 | 33.9 | 17.1 | 34.2 |
| 5l | 14.3 | 26.9 | 14.9 | 29.1 | 21.4 | 31.4 | 17.5 | 33.9 |
| Ampicillin | 15 | 28 | 16 | 30 | 23 | 35 | 18 | 35 |

**Table 3**
**Antifungal activities (zone of inhibition, mm) of synthesized compounds 5a-l**

| Compound no. | *Aspergillus nigerzeae* | Aspergillus *flavus* | *Fusarium oxysporum* |
|---|---|---|---|
| | 50µg $mL^{-1}$ | 50µg $mL^{-1}$ | 50 µg $mL^{-1}$ |
| 5a | 6.9 | 7.9 | 8.0 |
| 5b | 8.9 | 7.0 | 8.1 |
| 5c | 9.4 | 8.1 | 10.9 |
| 5d | 9.6 | 8.6 | 11.0 |
| 5e | 10.6 | 8.9 | 12.0 |
| 5f | 11.5 | 10.6 | 11.5 |
| 5g | 9.5 | 8.5 | 10.7 |
| 5h | 10.4 | 8.8 | 12.0 |
| 5i | 11.2 | 10.4 | 12.9 |
| 5j | 13.4 | 11 | 13.8 |
| 5k | 13.6 | 12.1 | 14.6 |
| 5l | 13.1 | 11.4 | 14.8 |
| Amphotericin-B | 14 | 12.5 | 15.2 |

As evident from table 2, compounds 5j–l with electron-donating methoxy substituents on phenyl ring have the highest antibacterial activity against all tested organisms, compounds 5e, 5f, 5h and 5i exhibit good activity due to presence of di halogen atoms. The reaming compounds showed poor activity as compared to stranded drug. However, the activities depend much on the presence of electronegative Cl and Br atoms.

The synthesised new compounds 5a-l were evaluated for their *in vitro* antifungal activity against *Aspergillus niger*, *Penicillium italicum* and *Fusarium oxysporum* at 50 µg $mL^{-1}$ concentrations (Table 3). Amphotericin-B was used as standard antifungal drug. Compound 5j-l emerged as the most promising antifungal agent against all fungies. Compounds 5e, 5f, 5h, 5i was showed minimum growth inhibitory activity. It was envisaged from the analysis of antimicrobial activity results that compounds 5j-l with methoxy substitution on the phenyl ring exhibited the most promising antimicrobial activity. The electron-donating substituents showed significant role in evaluating the antimicrobial activity.

***(E)-(3-(2-(1,3-diphenyl-1H-pyrazol-4-yl)vinyl)benzofuran-2-yl)(phenyl)methanone (5a):*** Yellow colored solid; m.p.: 141-143°C; IR (KBr, $cm^{-1}$): 1630 (C=O); $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.36 (s, 1H, Ar-H), 7.99-8.97 (m, 3H, Ar-H), 7.93 (d, 1H, *J*=16.8 Hz, $H_\alpha$), 7.84-7.78 (m, 4H, Ar-H), 7.68 (d, 2H, *J* =8.5Hz, Ar-H), 7.60-7.45 (m, 9H, Ar-H), 7.37-7.31 (m, 2H, Ar-H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 186.0, 154.7, 152.2, 157.7, 139.7, 137.9, 136.8, 133.0, 132.7, 129.8, 129.5, 138.7,128.5, 128.3, 127.3, 126.7, 125.5, 124.9, 123.1, 124.1,

120.3, 119.8, 119.1, 112.6, 145.1. Mass spectrum, *m/z* (*I*rel, %): 467 [M+H]; Found, %: C 82.38; H 4.75; N 6.00: $C_{33}H_{22}N_2O_2$. Calculated, %: C 82.35; H 4.79; N 6.10.

***(E)-(4-chlorophenyl)(3-(2-(1,3-diphenyl-1H-pyrazol-4-yl) vinyl)benzofuran-2-yl)methanone*** (**5b**): Yellow colored solid; m.p.: 162-164°C; IR (KBr, $cm^{-1}$): 1625 (C=O); $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.38 (s, 1H, Ar-H), 8.07 (d, 2H, *J*=8.5 Hz, Ar-H), 7.99(d, 1H, *J*=8.0 Hz, Ar-H), 7.95(d, 1H, *J*=16.8 Hz, $H_\alpha$), 7.84-7.79 (m, 4H, Ar-H), 7.61-7.45 (m, 10H, Ar-H), 7.38-7.37 (m, 2H, Ar-H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 183.9, 154.1, 151.6, 146.6, 139.1, 136.0, 132.3, 131.0, 130.7, 128.8, 128.1, 127.9, 127.7, 127.2, 127.1, 126.2, 125.3, 125.2, 124.3, 120.6, 122.5, 119.6, 119.0, 118.5, 112.0. Mass spectrum, *m/z* (*I*rel, %): 501 [M+H]; Found, %: C 76.72; H 4.23; Cl 7.08; N 5.59: $C_{33}H_{21}ClN_2O_2$. Calculated, %: C 76.79; H 4.28; Cl 7.18; N 5.62.

***(E)-(4-bromophenyl)(3-(2-(1,3-diphenyl-1H-pyrazol-4-yl) vinyl)benzofuran-2-yl)methanone*** (**5c**): Yellow colored solid; m.p.: 140-142°C; IR (KBr, $cm^{-1}$): 1634 (C=O); $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.32 (s, 1H, Ar-H), 8.00 (d, 2H, *J*=8.0 Hz, Ar-H), 7.90(d, 1H, *J*=16.8 Hz, $H_\alpha$), 7.84-7.80 (m, 4H, Ar-H), 7.66-7.45 (m, 11H, Ar-H), 7.43-7.34 (m, 2H, Ar-H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 184.6, 154.7, 152.2, 147.3, 139.7, 136.6, 132.9, 131.6, 131.3, 129.5, 128.7, 128.6, 127.9, 127.8, 126.8, 126.0, 125.8, 124.9, 124.2, 123.1, 120.2, 119.6, 119.1, 112.6. Mass spectrum, *m/z* (*I*rel, %): 545 [M+H]; Found, %: C 70.47; H 3.88; Br 14.65; N 5.14: $C_{33}H_{21}ClBrN_2O_2$. Calculated, %: C 70.46; H 3.84; Br 14.69; N 5.10.

***(E)-(3-(2-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl) vinyl)benzofuran-2 yl)(phenyl)methanone*** (**5d**): Yellow colored solid; m.p.: 147-149°C; IR (KBr, $cm^{-1}$): 1629 (C=O); $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.10 (s, 1H, Ar-H), 7.86 (d, 2H, *J*=8.2 Hz, Ar-H), 7.72(d, 2H, *J*=8.0 Hz, Ar-H), 7.70(d, 1H, *J*=16.0 Hz, $H_\alpha$), 7.56(d, 2H, *J*=7.78 Hz, Ar-H), 7.45-7.23 (m, 12H, Ar-H), 7.16-7.07 (m, 2H, Ar-H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 186.0, 154.7, 150.9, 147.8, 139.6, 137.9, 134.3, 132.7, 131.5, 12.8, 129.7, 129.5, 128.9, 128.3, 127.1, 126.9, 125.8, 125.1, 125.0, 124.2, 122.0, 120.3, 120.3, 119.2, 112.7. Mass spectrum, *m/z* (*I*rel, %): 501 [M+H]; Found, %: C 76.72; H 4.23; Cl 7.08; N 5.59; $C_{32}H_{21}ClN_2O_2$. Calculated, %: C 76.78; H 4.20; Cl 7.18; N 5.55.

***(E)-(4-chlorophenyl)(3-(2-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)vinyl)benzofuran-2-yl)methanone*** (**5e**): Yellow colored solid; m.p.: 171-173°C; IR (KBr, $cm^{-1}$): 1631 (C=O); $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.35 (s, 1H, Ar-H), 7.99 (d, 3H, *J*=8.5 Hz, Ar-H), 7.94(d, 1H, *J*=16.8 Hz, $H_\alpha$), 7.82(d, 2H, *J*=7.52 Hz, Ar-H), 7.70-7.63 (m, 6H, Ar-H), 7.6-7.48 (m, 5H, Ar-H), 7.42-7.33(m, 2H, Ar-H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 183.1, 153.3, 149.5, 146.0, 138.2, 135.2, 132.9, 130.2, 130.0, 129.9, 128.3, 128.1, 127.5, 127.2, 126.4, 126.2, 125.5, 124.3, 124.0, 123.7, 122.9, 121.5, 118.8, 118.7, 117.8, 111.3. Mass spectrum, *m/z* (*I*rel, %): 535 [M+H]; Found, %: C 71.78; H 3.77; Cl 13.24; N 5.23; $C_{32}H_{20}Cl_2N_2O_2$. Calculated, %: C 71.70; H 3.75; Cl 13.29; N 5.28.

***(E)-(4-bromophenyl)(3-(2-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)vinyl)benzofuran-2-yl)methanone*** (**5f**): Yellow colored solid; m.p.: 166-168°C; IR (KBr, $cm^{-1}$):1625 (C=O); $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.35 (s, 1H, Ar-H), 7.99 (d, 3H, *J*=8.5 Hz, Ar-H), 7.94(d, 1H, *J*=16.8 Hz, $H_\alpha$), 7.81(d, 2H, *J*=7.53 Hz, Ar-H), 7.70-7.63 (m, 6H, Ar-H), 7.57-7.48 (m, 5H, Ar-H), 7.41-7.32(m, 2H, Ar-H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 184.6, 154.7, 150.9, 147.4,139.6, 136.6, 134.3, 131.6, 131.53, 131.3, 129.7, 129.5, 128.9, 128.6, 127.8, 127.6, 126.9, 125.7, 125.4, 123.0, 120.2, 120.1, 119.2, 112.7. Mass spectrum, *m/z* (*I*rel, %): 579 [M+H]; Found, %: C 66.28; H 3.48; Br 13.78; Cl 6.11; N 4.83; $C_{32}H_{20}BrClN_2O_2$. Calculated, %: C 66.22; H 3.44; Br 13.70; Cl 6.15; N 4.85.

***(E)-(3-(2-(3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl) vinyl)benzofuran-2-yl)(phenyl)methanone*** (**5g**): Yellow colored solid; m.p.: 158-160°C; IR (KBr, $cm^{-1}$): 1630 (C=O); $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.34 (s, 1H, Ar-H), 8.13 (d, 2H, *J*=7.7 Hz, Ar-H), 7.97(d, 3H, *J*=8.0 Hz, Ar-H), 7.94(d, 1H, *J*=16.8 Hz, $H_\alpha$), 7.80(d, 2H, *J*=7.7 Hz, Ar-H), 7.69-7.57 (m, 10H, Ar-H), 7.48-7.31 (m, 2H, Ar-H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 185.9, 154.7, 150.8, 147.8,139.6, 137.9, 132.7, 132.0, 131.8, 130.0, 129.8, 129.5, 128.3, 127.1, 126.9, 125.8, 125.1, 124.9, 124.2, 122.9, 122.5, 120.3, 119.2, 112.7. Mass spectrum, *m/z* (*I*rel, %): 545 [M+H]; Found, %: C 70.47; H 3.88; Br 14.65; N 5.14; $C_{32}H_{21}BrN_2O_2$. Calculated, %: C 70.40; H 3.85; Br 14.70; N 5.20.

***(E)-(3-(2-(3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl) vinyl)benzofuran-2-yl)(4-chlorophenyl)methanone*** (**5h**): Yellow colored solid; m.p.: 140-142°C; IR (KBr, $cm^{-1}$): 1623 (C=O); $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.38 (s, 1H, Ar-H), 8.01 (d, 3H, *J*=8.5 Hz, Ar-H), 7.96(d, 1H, *J*=16.5 Hz, $H_\alpha$), 7.85(d, 2H, *J*=7.7 Hz, Ar-H), 7.72-7.64 (m, 4H, Ar-H), 7.60-7.50 (m, 6H, Ar-H), 7.36 (d, 3H, *J*=7.7 Hz, Ar-H); $^{13}$C NMR ($CDCl_3$, 100 MHz) δ 184.9, 159.7, 149.9, 146.8, 138.6, 136.9, 131.7, 131.0, 130.9, 129.0, 128.8, 128.5, 127.4, 126.1, 125.9, 124.8, 124.1, 123.9, 123.3, 121.9, 121.6, 119.3, 118.2, 111.7. Mass spectrum, *m/z* (*I*rel, %): 579 [M+H]; Found, %: Mass spectrum, *m/z* (*I*rel, %): 545 [M+H]; Found, %: C 70.47; H 3.88; Br 14.65; N 5.14; $C_{32}H_{21}BrN_2O_2$. Calculated, %: Mass spectrum, *m/z* (*I*rel, %): 545 [M+H]; Found, %: C 70.47; H 3.88; Br 14.65; N 5.14; $C_{32}H_{21}BrN_2O_2$. Calculated, %: C 70.42; H 3.80; Br 14.75; N 5.15

***(E)-(4-bromophenyl)(3-(2-(3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)vinyl)benzofuran-2-yl)methanone*** **(5i):** Yellow colored solid; m.p.: 151-153°C; IR (KBr, $cm^{-1}$):1627 (C=O); $^1$H NMR ($CDCl_3$, 400 MHz): δ 8.38 (s, 1H, Ar-H), 8.01 (d, 3H, *J*=8.2 Hz, Ar-H), 7.95(d, 1H, *J*=16.5 Hz, $H_\alpha$), 7.84(d, 2H, *J*=7.7 Hz, Ar-H), 7.70-7.67 (m, 4H, Ar-H), 7.57-7.47 (m, 6H, Ar-H), 7.33 (d, 3H, *J*=8.2 Hz, Ar-H); $^{13}$C NMR

($CDCl_3$, 100 MHz) δ 183.1, 153.3, 149.5, 146.0, 138.2, 135.2, 132.9, 130.2, 129.9, 128.3, 128.1, 125.5, 127.2, 126.2, 125.5, 124.3, 124.0, 123.7, 122.9, 121.5, 118.8, 118.7, 117.8, 111.3. Mass spectrum, *m/z* (*I*rel, %): 623 [M+H]; Found, %: C 61.56; H 3.23; Br 25.60; N 4.49; $C_{32}H_{20}Br_2N_2O_2$. Calculated, %: C 61.50; H 3.28; Br 25.59; N 4.53.

***(E)-(3-(2-(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)vinyl)benzofuran-2-yl)(phenyl)methanone*** (**5j**): Yellow colored solid; m.p.: 164-166°C; IR (KBr, $cm^{-1}$): 1637 (C=O); $^1H$ NMR ($CDCl_3$, 400 MHz): δ 8.34 (s, 1H, Ar-H), 8.10 (d, 2H, *J*=7.0 Hz, Ar-H), 8.0(d, 1H, *J*=8.0 Hz, Ar-H), 7.93(d, 1H, *J*=16.8 Hz, $H_\alpha$), 7.82(d, 2H, *J*=8.7 Hz, Ar-H), 7.73(d, 4H, *J*=8.7 Hz, Ar-H), 7.65-7.04 (m, 8H, Ar-H), 7.05(d, 2H, *J*=8.7 Hz, Ar-H), 3.89 (s, 3H, $OCH_3$); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 184.6, 159.8, 154.7, 152.0, 147.2, 139.7, 136.6, 131.6, 131.3, 129.8, 129.4, 128.5, 126.9, 127.8, 126.7, 126.1, 125.8, 125.5, 124.8, 124.2, 123.2, 120.0, 119.4, 119.1, 114.2, 112.6, 55.4. Mass spectrum, *m/z* (*I*rel, %): 497 [M+H]; Found, %: C 79.82; H 4.87; N 5.64; $C_{33}H_{24}N_2O_3$. Calculated, %: C 79.86; H 4.82; N 5.60.

***(E)-(4-chlorophenyl)(3-(2-(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)vinyl)benzofuran-2-yl)methanone*** (**5k**): Yellow colored solid; m.p.: 155-157°C; IR (KBr, $cm^{-1}$): 1631 (C=O); $^1H$ NMR ($CDCl_3$, 400 MHz): δ 8.30 (s, 1H, Ar-H), 7.98 (d, 3H, *J*=8.2 Hz, Ar-H), 7.91(d, 1H, *J*=16.8 Hz, $H_\alpha$), 7.81(d, 2H, *J*=7.7 Hz, Ar-H), 7.73-7.66(m, 4H, Ar-H), 7.58-7.46 (m, 5H, Ar-H), 7.37-7.29 (m, 2H, Ar-H), 7.04(d, 2H, *J*=8.5 Hz, Ar-H), 3.84 (s, 3H, $OCH_3$); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 184.1, 154.2, 151.7, 146.7, 139.2, 137.7, 136.1, 131.1, 130.8, 129.5, 128.9, 127.9, 127.7, 127.4, 127.2, 126.6, 126.2, 125.6, 125.3, 124.8, 123.7, 122.7, 121.2, 119.6, 118.6, 117.6, 112.1, 53.7. Mass spectrum, *m/z* (*I*rel, %): 531 [M+H]; Found, %: C 74.64; H 4.37; Cl 6.68; N 5.28; $C_{33}H_{23}ClN_2O_3$. Calculated, %: C 74.60; H 4.35; Cl 6.66; N 5.22.

***(E)-(4-bromophenyl)(3-(2-(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)vinyl)benzofuran-2-yl)methanone*** (**5l**): Yellow colored solid; m.p.: 162-164 °C; IR (KBr, $cm^{-1}$): 1634 (C=O); $^1H$ NMR ($CDCl_3$, 400 MHz): δ 8.33 (s, 1H, Ar-H), 7.98 (d, 3H, *J*=8.2 Hz, Ar-H), 7.91(d, 1H, *J*=16.8 Hz, $H_\alpha$), 7.81(d, 2H, *J*=7.7 Hz, Ar-H), 7.73-7.66(m, 4H, Ar-H), 7.58-7.47 (m, 5H, Ar-H), 7.37-7.30 (m, 2H, Ar-H), 7.10(d, 2H, *J*=8.5 Hz, Ar-H), 3.88 (s, 3H, $OCH_3$); $^{13}C$ NMR ($CDCl_3$, 100 MHz) δ 184.6, 154.7, 152.2, 147.2, 139.7, 138.2, 136.7, 131.6, 131.3, 130.0, 129.4, 128.4, 128.2, 127.9, 127.8, 127.1, 126.7, 126.2, 125.8, 124.8, 124.2, 123.2, 121.8, 120.1, 119.1, 118.1, 112.6, 54.2. Mass spectrum, *m/z* (*I*rel, %): 575 [M+H]; Found, %: C 68.88; H 4.03; Br 13.89; N 4.87; $C_{33}H_{23}BrN_2O_3$. Calculated, %: C 68.81; H 4.13; Br 13.93; N 4.84.

## Conclusion

In conclusion, we have synthesised pyrazole based benzofuran derivatives 5a-l under conventional, ultrasound and microwave irradiation conditions. The advantages of the microwave irradiation conditions demonstrated high yield and shorter reaction time compared to other reaction conditions.

All the screened compounds were evaluated for their *in vitro* antimicrobial activity. Some of the compounds 5j-l exhibited promising antimicrobial activity against selected microorganisms compared with the standard drugs.

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## References

1. Kumar V., Kaur K., Gupta G.K. and Kumar S., Developments in synthesis of the anti-inflammatory drug, celecoxib, *Recent Pat. Inflammation Allergy Drug Discovery*, **7(2)**, 124-134 **(2013)**

2. Vijesh A.M., Isloor A.M., Shetty P., Sundershan S. and Fun H.K., New pyrazole derivatives containing 1, 2, 4-triazoles and benzoxazoles as potent antimicrobial and analgesic agents, *Eur. J. Med. Chem.*, **62**, 410-415 **(2013)**

3. Aggarwal R., Kumar V., Kumar R. and Singh S.P., Approaches towards the synthesis of 5-aminopyrazoles, *Beilstein J. Org. Chem.*, **7(1)**, 179-197 **(2011)**

4. Koca I., Ozgur A., Coskun K.A. and Tutar Y., Synthesis and anticancer activity of acyl thioureas bearing pyrazole moiety, *Bioorg. Med. Chem*., **21(13)**, 3859-3865 **(2013)**

5. Tanitame A., Oyamada Y., Ofuji K., Terauchi H., Kawasaki M., Wachi M. and Yamagishi J.I., Synthesis and antibacterial activity of a novel series of DNA gyrase inhibitors: 5-[(E)-2-arylvinyl] pyrazoles, *Bioorg. Med. Chem. Lett.*, **15(19)**, 4299-4303 **(2005)**

6. Pattan S.R., Rabara P.A., Pattan J.S., Bukitagar A.A., Wakale V.S. and Musmade D.S., Synthesis and evaluation of some novel substituted 1, 3, 4-oxadiazole and pyrazole derivatives for antitubercular activity, *Indian J. Chem.*, **48B**, 1453 **(2009)**

7. Vinod K., Kamalneet K., Girish Kumar G. and Anil Kumar S., Pyrazole containing natural products: synthetic preview and biological significance, *Eur. J. Med. Chem.*, **69**, 735-753 **(2013)**

8. Ashok D., Padmavati K., Lakshmi B.V. and Sarasija M., Microwave-assisted one-pot synthesis of pyrazolyl-substituted benzochroman-4-one derivatives and evaluation of their anticancer activity, *Chem. Heterocycl. Com.*, **52(1),** 15-20 **(2016)**

9. Secci D., Bolasco A., Chimenti P. and Carradori S., The state of the art of pyrazole derivatives as monoamine oxidase inhibitors and antidepressant/anticonvulsant agents, *Curr. Med. Chem*., **18(33)**, 5114-5144 **(2011)**

10. Dongamanti A., Naji H.H., Bommidi V.L. and Madderla S., Microwave-assisted one-pot synthesis and antimicrobial evaluation of 2-(1-phenyl-3-(2-thienyl)-1H-pyrazol-4-yl) chroman-4-one derivatives, *Heterocycl. Commun*., **22(5)**, 259-264 **(2016)**

11. Padmaja A., Rajasekhar C., Muralikrishna A. and Padmavathi V., Synthesis and antioxidant activity of oxazolyl/thiazolylsulfonylmethyl pyrazoles and isoxazoles, *Eur. J. Med. Chem.*, **46(10)**, 5034-5038 **(2011)**

12. Amr A.G., Abdel-Latif N.A. and Abdalla M.M., Synthesis of some new testosterone derivatives fused with substituted pyrazoline ring as 5alpha-reductase inhibitors, *Acta Pharm*., **56(2)**, 203-218 **(2006)**

13. Ashok D., Ziauddin M., Lakshmi B.V. and Sarasija M., Microwave assisted synthesis of substituted (Z)-2-{[1-phenyl-3-(thiophen-2-yl)-1 H-pyrazol-4-yl] methylene} benzofuran-3 (2 H)-ones and their antimicrobial activity, *Russ. J. Gen. Chem.*, **86(7),** 1753-1757 **(2016)**

14. Dongamanti A., Naji H.H., Bommidi V.L. and Madderla S., Microwave-assisted one-pot synthesis and antimicrobial evaluation of 2-(1-phenyl-3-(2-thienyl)-1H-pyrazol-4-yl) chroman-4-one derivatives, *Heterocycl. Commun.*, **22(5)**, 259-264 **(2016)**

15. Sherman T.D., Duke M.V., Clark R.D., Sanders E.F., Matsumoto H. and Duke O.S., Pyrazole phenyl ether herbicides inhibit protoporphyrinogen oxidase, *Pestic. Biochem. Phys*., **40(3)**, 236-245 **(1991)**

16. Hantoon M.A., Development of certain drugs, *Minn. Med.*, **84**, 102 **(2001)**

17. Mohy El-Din M.M., Senbel A.M., Bistawroos A.A., El-Mallah A., Nour El-Din N.A., Bekhit A.A. and Abd El Razik H.A., A Novel COX-2 Inhibitor Pyrazole Derivative Proven Effective as an Anti-Inflammatory and Analgesic Drug, *Basic Clin. Pharmacol. Toxicol.*, **108(4)**, 263-273 **(2011)**

18. Zhang X., Li X., Allan G.F., Sbriscia T., Linton O., Lundeen S.G. and Sui Z., Design, synthesis and in vivo SAR of a novel series of pyrazolines as potent selective androgen receptor modulators, *J. Med. Chem.*, **50(16)**, 3857-3869 **(2007)**

19. Yang X., Jin Y., Liu H., Jiang Y. and Fu H., Easy and efficient one-pot synthesis of pyrazolo [1, 5-c] quinazolines under mild copper-catalyzed conditions, *RSC Adv.*, **2(29)**, 11061-11066 **(2012)**

20. Fong T.M. and Heymsfield S.B., Cannabinoid-1 receptor inverse agonists: current understanding of mechanism of action and unanswered questions, *Int. J. Obes*., **33(9)**, 947 **(2009)**

21. Fukai T., Kaitou K. and Terada S., Antimicrobial activity of 2-arylbenzofurans from Morus species against methicillin-resistant Staphylococcus aureus, *Fitoterapia*, **76**, 708-711 **(2005)**

22. Ravi N., Dipesh S.H., Xuezhen X., Kyusic J. and Kyeong L., Bioactive benzofuran derivatives: Moracins A–Z in medicinal chemistry, *Eur. J. Med. Chem.*, **90**, 379-393 **(2015)**

23. Vinod K., Kamalneet K., Girish Kumar G. and Anil Kumar S., Pyrazole containing natural products: synthetic preview and biological significance, *Eur. J. Med. Chem*., **69**, 735-753 **(2013)**

24. Sangani C.B., Jigar Makawana A., Zhang X., Teraiya Shashikant B., Lin L. and Zhu H.L., Design, synthesis and molecular modeling of pyrazole–quinoline–pyridine hybrids as a new class of antimicrobial and anticancer agents, *Eur. J. Med. Chem*, **76**, 549-557 **(2014)**

25. Sankappa Rai U., Isloor A.M., Shetty P., Pai K.S.R. and Fun H.K., Synthesis and in vitro biological evaluation of new pyrazole chalcones and heterocyclic diamides as potential anticancer agents, *Arabian J. Chem.*, **8(3)**, 317-321 **(2015)**

26. Dong F., Chen X., Liu X., Xu J., Li Y., Shan W. and Zheng Y., Simultaneous determination of five pyrazole fungicides in cereals, vegetables and fruits using liquid chromatography/tandem mass spectrometry, *J. Chromatogr.*, **1262**, 98-106 **(2012)**

27. Amr A.G., Abdel L.N.A. and Abdalla M.M., Synthesis and antiandrogenic activity of some new 3-substituted androstano [17, 16-c]-5'-aryl-pyrazoline and their derivatives, *Bioorg. Med. Chem*., **14(2)**, 373-384 **(2006)**

28. Ragab A.F., Abdel Gawad N.M., Georgey H.H. and Said M.F., Synthesis of novel 1, 3, 4-trisubstituted pyrazoles as anti-inflammatory and analgesic agents, *Eur. J. Med. Chem.,* **63**, 645-654 **(2013)**

29. Mohy El-Din M.M, Senbel A.M., Bistawroos A.A., El-Mallah A., Nour El-Din N.A., Bekhit A.A. and Abd El Razik H.A., A Novel COX-2 Inhibitor Pyrazole Derivative Proven Effective as an Anti-Inflammatory and Analgesic Drug, *Basic Clin. Pharmacol. Toxicol.*, **108(4)**, 263-273 **(2011)**

30. Cottineau B., Toto P., Marot C., Pipaud A. and Chenault, Synthesis and hypoglycemic evaluation of substituted pyrazole-4-carboxylic acids, *J. Bioorg. Med. Chem. Lett.*, **12(16)**, 2105-2108 **(2002)**

31. Thevenin M., Thoret S., Grellier P. and Dubois J., Synthesis of polysubstituted benzofuran derivatives as novel inhibitors of parasitic growth, *Bioorg. Med. Chem.*, **21(17)**, 4885-4892 **(2013)**

32. Xie F., Zhu H., Zhang H., Lang Q., Tang L., Huang Q. and Yu L., In vitro and in vivo characterization of a benzofuran derivative, a potential anticancer agent, as a novel Aurora B kinase inhibitor, *Eur. J. Med. Chem.*, **89**, 310-319 **(2015)**

33. Ashok D., Lakshmi B.V., Ravi S. and Ganesh A., Microwave-assisted synthesis of some new coumarin–pyrazoline hybrids and their antimicrobial activity, *J. Serb. Chem. Soc.*, **80(3)**, 305-313 **(2015)**

34. Ashok D., Nagaraju N., Sarasija M. and Lakshmi B.V., Microwave assisted synthesis of 1H-tetrazole based flavonoid derivatives and their antimicrobial activity, *J. Serb. Chem. Soc*., **83(12)**, 1305-1313 **(2018)**.

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