SYNTHESIS OF BENZOXAEPINE DERIVATIVES FROM PYRAZOLE-CHALCONE VIA A SIMPLE AND CONVENIENT PROTOCOL USING BASIC ALUMINA AS SOLID SUPPORT

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ABSTRACT

In the present study a series of novel benzoazepine (5a-h) derivatives were synthesized by the thermal cyclization reaction of various pyrazole-chalcones (3a-h) with 2-aminophenol, by conventional heating and microwave irradiation (180 W) in solvent-free conditions in short reaction times (9–12 min), giving high yields of products (80–88%). The homogeneity of all the newly synthesized compounds has been checked by TLC. Their IR, NMR, ESI-mass spectral data and elemental analysis are in accord with the assigned structure. The title compounds were evaluated for their antibacterial activity against Gram-positive bacteria Staphylococcus aureus, Bacillus subtilis, and Gram-negative bacteria Pseudomonas aeruginosa, Escherichia coli. Compounds 3c, 3h, 5b, 5e, 5g and 5h were found to show good antibacterial activity when compared with that of standard drug Ampicillin. Furthermore, the same library of compounds were evaluated for antifungal activity against Aspergillus nigerzeae, Penicillium italicum and Fusarium oxysporum using Griseofulvin as standard drug. The results of the above studies show that the compounds 5b, 5c, 5e, 5h, 5a, 5c, 5g and 5h showed good antifungal activity against all the tested organisms.

Keywords: Pyrazole, Chalcone, benzoazepine, microwave irradiation, basic alumina.

INTRODUCTION

The prominence in attaining chalcones has numerous applications in the field of pharmaceuticals and also in the production of pesticides, cosmetics2-3. Chalcone and its functionalized derivatives display diverse pharmaceutical properties have been discovered as, antimicrobial4-8, antitumor5-10, anticancer11-12, anti-inflammatory13-14, and antioxidant15-16 activities. Chalcones bear very good synthetic framework so that variety of novel heterocycles with good pharmaceutical profile can be designed. On the other hand, pyrazoles represent a key motif in heterocyclic chemistry and occupy a prime place in medicine and pesticide chemistry due to their capability to exhibit a wide range of bioactivities such as antimicrobial, anti-inflammatory, anticancer and antiviral17-21. Benzoxazepine derivatives are well-known pharmacophores showing capable properties against various diseases such as antipsychotic22, central nervous system damage23 and anticancer activities24. Usually, benzoazepine derivatives preparation involves multistep synthesis25-27. Therefore, an efficient, eco-friendly, straightforward synthetic method toward benzoxazepine still represents an interesting assignment for chemists.

The science of green chemistry was developed to change the increasing demand for environmentally gentle chemical practices. Solvent free synthesis has received considerable attention in recent years. Microwave heating has a prominence in the search for green synthesis28. Microwave irradiation conditions extensively reduce reaction time without promoting any side reactions29-32. Alumina like solid support, holds excellent capability to absorb the organic compounds on their surface, and transmits microwave irradiation. Previous reports have also shown that the basic oxides, like alumina, assist as a good alternative for catalyzed heterocoupling reactions due to its character as a base ion in the solid framework33. This provoked us to discover an efficient yet simple and one-pot green protocol using basic alumina as solid support in microwave irradiation.

In the current study, we aimed to obtain new compounds containing both pyrazole and benzoazepine rings in the same structure, via the cyclo-condensation reaction, solvent free microwave irradiation conditions. This non-conventional protocol offers several applications such as simple procedure, fast reaction conditions and good yields as compared to conventional methods. It involves the exposure of neat reagents to give high yields of pure products, easy work-up, low cost and economical. The use of basic alumina as a solid support assists and it eliminates the use of K2CO3 and ethanol solvent. Herein, we have shown (Scheme 1) the synthesis of benzoazepines derivatives from pyrazole-chalcone reaction with 2-aminophenol, basic alumina as a solid support using as a catalyst under microwave irradiation (180 W).

EXPERIMENTAL

All the melting points were determined in open capillary tubes and are uncorrected. The purity of the compounds was checked by TLC on silica gel 60 F254 (Merck).1H NMR and 13C NMR spectra were recorded on Avance 400 spectrometer using CDCl3, solvent TMS as an internal standard. IR spectra were recorded in KBr Shimadzu FTIR 8400 S spectrophotometer. Mass spectra were recorded on LCMS-2010A Shimadzu spectrophotometer. Elemental analysis was determined by using the EA1112 ThermoFinnigan CHNS analyzer. Microwave reactions were carried out in a Multisynth series microwave system (Milestone).

Conventional heating method (A)

A mixture of chalcone (3a-h) [30] (0.01 mol), 2-aminophenol (7) (0.01 mol) were dissolved in 10 ml of ethanol and to this K2CO3 (2 g) was added. The contents were refluxed for appropriate time mentioned in Table-1. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and poured into water. The product was extracted with acetone and was recrystallized with acetone to afford pure compounds (5a-h).

Microwave irradiation method (B)

A mixture of chalcone (3a-h) (0.01mol), 2-aminophenol (7) (0.01 mol) was adsorbed on basic alumina (3 g). The adsorbed material was taken in a quartz tube and inserted into the Teflon vial with screw capped and then subjected to microwave irradiation for an appropriate given time in Table-1. After completion of the reaction, cooled to room temperature and the product was extracted with acetone and was recrystallized with acetone to afford pure compounds (5a-h).

2-(E)-2,3-dihydro-2-(1,3-diphenyl-1H-pyrazol-4-yl)benzo[b]1,4] oxazepin-4-ylphenol (5a)

White solid; IR spectrum, ν cm \(^{-1}\): 3135 (OH), 1607 (C=N), 1238 (C-O-C).

H NMR spectrum, δ ppm: 8.12 (s, 1H, pyrazole-H), 7.98-6.99 (m, 18H, Ar-H), 5.67 (dd, 1H, J=11.4Hz, J=3.2Hz), 3.24 (dd, 1H, J=16.8Hz, J=12.4Hz), 3.04 (dd, 1H, J=16.8Hz, J=3.2Hz). 13CNMR spectrum, δ ppm: 154.5, 152.1, 147.3, 139.8, 133, 129.5, 128.7, 128.3, 128.2, 126.7, 126.1, 125.7, 124.9, 124.7, 124.6, 123.2, 120.3, 119.5, 119.2, 112.5, 70, 42.5. Found, %: C 78.71; H 5.04; N 9.23. Calculated, %: C 78.75; H 5.07; N 9.18. MS: 458 [M+H].

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Table 1: Conventional heating and Microwave irradiation optimization for the synthesis of 5a-h.

| Compound Number | Molecular Formula (Mol. Wt) | M.P. (°C) | Conventional heating (A) | Microwave irradiation (B) |
|-----------------|-----------------------------|----------|--------------------------|--------------------------|
|                 |                             |          | Time (h) | Yield (%) | Time (min) | Yield (%) |
| 5a              | C₈H₈N₂O₂ (457)              | 180-182  | 6        | 60        | 9          | 85        |
| 5b              | C₈H₈N₂O₂ (471)              | 193-195  | 8        | 62        | 10         | 83        |
| 5c              | C₈H₈N₂O₃ (487)              | 188-190  | 8        | 70        | 10         | 85        |
| 5d              | C₉H₈CIN₂O₂ (491)            | 176-178  | 8        | 68        | 12         | 80        |
| 5e              | C₉H₈BrN₂O₂ (535)            | 222-224  | 9        | 65        | 9          | 88        |
| 5f              | C₉H₈BrN₂O₂ (535)            | 254-256  | 9        | 62        | 9          | 85        |
| 5g              | C₉H₈BrN₂O₂ (549)            | 226-268  | 7        | 60        | 10         | 80        |
| 5h              | C₉H₈BrN₂O₂ (565)            | 252-254  | 8        | 62        | 9          | 82        |

1H NMR spectrum, δ, ppm: 8.13 (s, 1H, pyrazole-H), 7.98-7.07 (m, 17H, Ar-H), 5.67 (dd, 1H, Jₓᵧ=12.4H, Jᵧₓ=2.8H), 3.22 (dd, 1H, Jᵧₓ=16.8H, Jₓᵧ=12.4H).

13C NMR spectrum, δₒ, ppm: 161.4, 152.2, 140.3, 138.4, 136.1, 129.5, 129.4, 128.5, 127.3, 126.8, 121.8, 121.6, 119.7, 119.6, 119.3, 118.2, 72.4, 43.8, 21.8.

Found, %: C 78.93, H 5.32, N 8.94. C₈H₈N₂O₂. Calculated, %: C 78.96; H 5.34; N 8.91. MS: 472 [M+H]+.

IR spectrum, ν, cm⁻¹: 3141 (OH), 1611 (C=N), 1231 (C-O-C).

2-((E)-2,3-dihydro-2-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)benzo[b][1,4]oxazepin-4-yl)phenol (5b)

White solid; IR spectrum, ν cm⁻¹: 3141 (OH), 1611 (C=N), 1231 (C-O-C).

1H NMR spectrum, δ, ppm: 8.13 (s, 1H, pyrazole-H), 7.98-7.07 (m, 17H, Ar-H), 5.67 (dd, 1H, Jₓᵧ=12.4H, Jᵧₓ=2.8H), 3.22 (dd, 1H, Jᵧₓ=16.8H, Jₓᵧ=12.4H).

13C NMR spectrum, δₒ, ppm: 161.4, 152.2, 140.3, 138.4, 136.1, 129.5, 129.4, 128.5, 127.3, 126.8, 121.8, 121.6, 119.7, 119.6, 119.3, 118.2, 72.4, 43.8, 21.8.

Found, %: C 78.93, H 5.32, N 8.94. C₈H₈N₂O₂. Calculated, %: C 78.96; H 5.34; N 8.91. MS: 472 [M+H]+.

2-((E)-2,3-dihydro-2-(3-(1-phenyl-4-methoxyphenyl)-1H-pyrazol-4-yl)benzo[b][1,4]oxazepin-4-yl)phenol (5c)

White solid; IR spectrum, ν cm⁻¹: 3141 (OH), 1600 (C≡N), 1239 (C-O-C).

1H NMR spectrum, δ, ppm: 8.11 (s, 1H, pyrazole-H), 7.98-7.06 (m, 17H, Ar-H), 5.65 (dd, 1H, Jₓᵧ=12.4H, Jᵧₓ=2.8H), 3.22 (dd, 1H, Jᵧₓ=16.8H, Jₓᵧ=12.4H).

13C NMR spectrum, δₒ, ppm: 163.7, 161.2, 160.1, 153.7, 151.8, 140.1, 135.9, 129.5, 129.3, 127.1, 126.6, 125.4, 121.6, 119.4, 119.2, 118, 114.3, 72.3, 55.3, 43.5, 29.5.

Found, %: C 76.40, H 5.18, N 8.67. C₉H₈BrN₂O₃. Calculated, %: C 76.37; H 5.17; N 8.62. MS: 488 [M+H]+.

2-(E)-2,3-dihydro-2-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)benzo[b][1,4]oxazepin-4-yl)phenol (5d)

White solid; IR spectrum, ν cm⁻¹: 3142 (OH), 1600 (C≡N), 1239 (C-O-C).

1H NMR spectrum, δ, ppm: 8.13 (s, 1H, pyrazole-H), 7.98-7.06 (m, 17H, Ar-H), 5.65 (dd, 1H, Jₓᵧ=12.4H, Jᵧₓ=2.8H), 3.22 (dd, 1H, Jᵧₓ=16.8H, Jₓᵧ=12.4H).

13C NMR spectrum, δₒ, ppm: 160.9, 150.8, 139.8, 134.6, 131.3, 129.5, 129.4, 128.8, 127.1, 126.9, 121.8, 121.2, 119.4, 119.3, 117.9, 71.9, 43.3.

Found, %: C 73.21; H 4.48; N 8.57. C₉H₈BrN₂O₂. Calculated, %: C 73.24; H 4.51; N 8.54. MS: 492 [M+H]+.
Table 2: Antibacterial activity of compounds 3a-h and 5a-h.

| Compound | Zone of Inhibition, mm |
|----------|------------------------|
|          | Gram-positive bacteria  | Gram-negative bacteria |
|          | Staphylococcus aureus   | Bacillus subtilis   | Pseudomonas aeruginosa | Escherichia coli |
| 3a       | 23                     | 05                     | 04                     | 10              |
| 3b       | 24                     | 10                     | 08                     | 25              |
| 3c       | 30                     | 12                     | 09                     | 32              |
| 3d       | 21                     | 07                     | 08                     | 25              |
| 3e       | 12                     | 04                     | 03                     | 12              |
| 3f       | 10                     | 08                     | 02                     | 23              |
| 3g       | 22                     | 10                     | 07                     | 22              |
| 3h       | 28                     | 12                     | 11                     | 29              |
| 5a       | 22                     | 08                     | 05                     | 17              |
| 5b       | 27                     | 10                     | 08                     | 28              |
| 5c       | 28                     | 11                     | 08                     | 32              |
| 5d       | 20                     | 07                     | 05                     | 22              |
| 5e       | 18                     | 10                     | 08                     | 21              |
| 5f       | 15                     | 09                     | 06                     | 18              |
| 5g       | 28                     | 11                     | 09                     | 28              |
| 5h       | 32                     | 11                     | 10                     | 28              |
| Aminicillin | 30                     | 12                     | 10                     | 30              |

**Antifungal activity**

The antifungal activity of synthesized compounds 3a-h, 4a-h was tested against three pathogenic fungi, namely Aspergillus niger, Penicillium italicum, and Fusarium oxysporum, by the poison plate technique at a concentration of 50 µg/mL. Three kinds of fungi were incubated in PDA at 25±1 °C for 5 days to get new mycelium for antifungal assay, then a mycelia as disks of approximately 0.45 cm diameter cut from the culture medium were picked up with a sterilized inoculation needle and inoculated in the center of PDA plate. Test compounds were dissolved in acetone (10 mL) then added to the Potato Dextrose Agar medium (PDA, 90 mL). The final concentration of compounds in the medium was adjusted to 50 µg/mL. The inoculated plates were incubated at 25±1 °C for 5 days. Acetone was diluted with sterilized distilled water and used as control, while Grieseofulvin (50 µg/mL) was used as standard control for each treatment three replicates of experiments were carried out. The radial growth of the fungal colonies was measured on the sixth day. The Antifungal activity was evaluated and the results are presented in Table 3.

**RESULTS AND DISCUSSION**

Chemistry

Several synthetic methodologies are available for the synthesis of chalcones. Generally, the condensation of acetoephone with aldehyde in the presence of basic media is widely used. By the keeping of view in green methods we have selected to synthesize an efficient solvent free synthesis of chalcones by grinding equimolar quantities of 2-hydroxy acetophenone in the presence of Ba(OH)$_2$, at room temperature for 10 min. Further, these pyrazole-chalcones (3a-h) on thermal cyclization with 2-aminophenol in the presence of basic alumina under microwave irradiation resulted benzoxazepines (5a-h) in good yields (Scheme 1). All the reactions were carried out using microwave irradiations in 9–12 min., while same reactions under conventional condition, the time period required for the completion of the reaction was quite long and gave moderate yields. Hence, the microwave assisted synthesis bids clean and cheaper alternative path to that of conventional heating, indicating that the microwave irradiation simplifies the polarization of molecules producing reaction to occur at shorter reaction times in good yields. The use of microwave irradiation in present investigation gave 80-88% yields of products under, whereas moderate yields were obtained by conventional methods. All the synthesized compounds were characterized by $^1$H NMR, $^{13}$C NMR, Mass and IR spectral data.

BIOLOGICAL ASSAY

**Antibacterial activity**

The synthesized novel compounds 3a-h, 5a-g were screened for their Antibacterial activity against different types of bacterial strains, they are Gram positive bacterial strains of Bacillus subtilis and Staphylococcus aureus; Gram negative bacterial strains of Pseudomonas aeruginosa and Escherichia coli, at a concentration of 50 µg/mL. The cultures were diluted with 5% autoclaved saline and the final volume was made with concentration approximately 10$^{-10}$ CFU/mL. The synthesized compounds were diluted in acetone for antibacterial biological assays. For agar disc diffusion method, the liquid form of test compound was soaked on to the disc and then allowed to air dry, such that the disc gets completely saturated with test compound. The saturated form of test compound was soaked on to the disc and then allowed to air dry, and then used as control, while Grieseofulvin (50 µg/mL) was used as standard control for each treatment three replicates of experiments were carried out. The results of the experiments were presented in Table 3.
Biological activities

Antibacterial activity

All the compounds were screened for their antibacterial activity against Staphylococcus aureus, Bacillus subtilis, Pseudomonas aeruginosa and Escherichia coli using Ampicillin as standard drug. The activity was determined using cup plate agar diffusion method by measuring the zone of inhibition in mm (Table 2). The compounds were screened at the concentration of 50 μg/ml in DMSO. From the screening studies it is evident that the synthesized compounds 3c, 3h, 3i, 5a, 5c, 5g and 5h showed good antibacterial activity against all the tested organisms, which shows that the electron releasing groups enhanced the antibacterial activity. Furthermore, methoxy (3c), bromo methoxy (3h), methyl (5b), methoxy (5c), bromo methyl (5g), and bromo methoxy (5h) group derivatives are potentially active.

Antifungal activity:

All the compounds were screened for their antifungal activity against Aspergillus niger, Penicillium italicum and Fusarium oxysporum using Grieseofulvin as standard drug. The activity was determined using cup plate agar diffusion method by measuring the zone of inhibition in mm. The compounds were screened at the concentration of 50 μg/ml in DMSO. From the screening studies it is evident that the synthesized compounds 3h, 3i, 5a, 5c, 5g and 5h showed good antifungal activity against all the tested organisms. However, in the case of the remaining compounds, the activity doesn’t depend much on the electronic nature of the compounds (Table 3).

CONCLUSIONS

In summary, we have demonstrated an efficient, economical, environmentally benign, and rapid process for the synthesis of benzoxazepines derivatives from pyrazole-chalcones reaction with 2-amino phenol. It was discovered that microwave-assisted method is highly efficient procedure for the preparation of benzoxazepines, especially in the solvent-free media. This method eliminates the use of K2CO3 and ethanol solvent. No additional base and solvent are required as basic alumina acts as solid support and base. Additionally, application of microwave decreases the time of the reaction extensively with a better-quality yield of the product. The uniqueness of the methodology lies in its eco-friendly operation, with excellent yield. In this study, a new hybrid molecule consisting of biologically important benzoxazepine derivatives (5a-h) from pyrazole-chalcones (3a-h) pharmacophores were synthesized and their antibacterial and antifungal activities were determined. Amongst the synthesized compounds, 3c, 3h, 5b, 5c, 5g and 5h showed good antibacterial activity. The antifungal activity of the synthesized compounds also showed that compounds 3h, 3i, 5a, 5c, 5g and 5h have good inhibition values. The experimental results of this study will likely provide a new basis for the design of interesting pyrazole-chalcones based benzoazepine, and further studies, including the design of new analogs of the heterocyclic moiety, are underway.

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