SYNTHESIS OF NOVEL 1, 4-BENZOTHIAZEPINES AND IN VITRO SCREENING OF THEIR ANTIMICROBIAL ACTIVITY

K.R. RAGHAVENDRA1, K. AJAY KUMAR2* AND S. SHASHIKANTH1*

1Department of Chemistry, University of Mysore, Mysore, India., 2Department of Chemistry, Yuvaraja College, University of Mysore, Mysore, India. Email: shashis1956@gmail.com, ajaykkchem@gmail.com

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ABSTRACT

Objective: In search of new potential antimicrobial agents, the aim of the present study was to synthesize the series of 1, 4-Benzothiazepine analogs by a simple and accessible approach and evaluate for their antimicrobial activity.

Methods: Synthetic methodology involves the reaction of α, β-unsaturated ketones (3 and 6) with 2-aminothiophenol and 3-4 drops of conc. HCl in methanol at 160°C, which afforded a series of novel 1,4-thiazepine derivatives (4a-f and 7a-c) in good yields.

Results: The structures of the synthesized compounds were provided by spectral and elemental analysis, and by single crystal X-ray diffraction studies. The synthesized compounds were tested for their antimicrobial activity against different fungi and bacteria species in vitro.

Conclusion: The results of the study reveal that the new compounds possess promising antimicrobial activities.

Keywords: Antibacterial, Antifungal, Chalcones, Ketone, MIC.

INTRODUCTION

1, 4-Benzothiazepine skeleton is considered as an important moiety in synthetic and pharmaceutical chemistry. Chalcone is an aromatic α, β-unsaturated ketone that forms the central core for a variety of important biological compounds. Chalcones are used as key precursors in the synthesis of biologically important heterocycles such as benzothiazepine [1-4] and pyrazolines [5,6]. The broad spectrum of pharmaceutical importance and commercial success associated with benzothiazepines has led researchers all over to work in this area. 1,4-Benzothiazepine derivatives are known to exhibit biological activities such as antioxidant and cytotoxic [7], antimicrobial [8], and anticancer [9] activities. The diverse biological applications associated with benzothiazepines prompted us to undertake this project of synthesis and biological screening of new benzothiazepine derivatives.

MATERIALS AND METHODS

The precursor chalcones (3) were prepared by the condensation of 2-acetyl thiophene (1) with aromatic aldehyde (2) in ethyl alcohol under alkali conditions. The compounds (7) were obtained by the condensation of aromatic ketone (5) and aromatic aldehyde (2) under similar conditions.

A mixture of chalcones (6a-c) (3mmol), 2-aminothiophenol (3mmol) and 3-4 drops of conc. HCl in methanol (10mL) was refluxed at 160°C for 4h. Then the mixture was extracted into dichloromethane (30mL), washed successively with dilute hydrochloric acid and then with water. The solvent was evaporated to dryness to obtain products (7a-c) in good yields. The reaction pathway is depicted in scheme-2.

Scheme-1: Synthetic route for the synthesis of thiazepines 4a-f

A mixture of chalcones (6a-c) (3mmol), 2-aminothiophenol (3mmol) and 3-4 drops of conc. HCl in methanol (10 mL) was refluxed at 160°C for 4h. Then the mixture was extracted into dichloromethane (30 mL), washed successively with dilute hydrochloric acid and water. The solvent was evaporated to dryness to obtain products (7a-c) in good yields. The reaction pathway is depicted in scheme-2.
**RESULTS AND DISCUSSION**

Chemistry:

2-(3,4-Dimethoxyphenyl)-4-(thiophen-2-yl)-2,3-dihydropyridobenz[b][1,4]thiazepine, 4a:

Obtained from 3-[3,4-dimethoxyphenyl]-1-(thiophen-2-yl)prop-2-en-1-one, 3a (0.004 mmol) and 2-aminothiophenol (0.004 mmol) as yellow crystals in 88% yield. M.P. 96-98°C. ^1H NMR (CDCl_3): δ 1.820 (dd, 1H, C-H), 2.112 (dd, 1H, C=O), 3.665 (dd, 1H, C=O), 3.845 (s, 6H, OCH_3), 6.950-7.568 (m, 10H, Ar- & 5m ring-H). ^13C NMR (CDCl_3): δ 40.40 (1C), 50.12 (1C), 55.22 (1C), 110.13 (1C), 112.12 (1C), 117.04 (1C), 122.61 (1C), 124.22 (1C), 125.08 (1C), 125.33 (1C), 127.04 (1C), 127.50 (1C), 127.86 (1C), 133.28 (1C), 137.52 (1C), 137.92 (1C), 147.90 (1C), 149.82 (1C), 151.15 (1C), 164.33 (1C). MS (m/z): 362 (M+1, base peak). Anal. Calcd. for C_29H_23NO_5S: C, 66.11; H, 5.02; N, 3.67%; Found C, 66.10, H, 5.08; N, 3.61%.

2-(3,4-Dimethoxyphenyl)-4-(4-chlorophenyl)-2-(3,4-dimethoxyphenyl)-2,3-dihydropyridobenz[b][1,4]thiazepine, 4d:

Obtained from 3-(4-chlorophenyl)-1-(thiophen-2-yl)prop-2-en-1-one, 3d (0.004 mmol) and 2-aminothiophenol (0.004 mmol) as yellow solid in 82% yield. M.P. 98-100°C. ^1H NMR (CDCl_3): δ 1.122 (t, 3H, CH_3), 1.814 (dd, 1H, C=O), 2.104 (dd, 1H, C=O), 2.580 (q, 2H, CH_2), 3.545 (dd, 1H, C=O), 7.121-7.618 (m, 11H, Ar- & 5m ring-H). ^13C NMR (CDCl_3): δ 13.9 (1C), 28.2 (1C), 40.1 (1C), 49.2 (1C), 59.4 (1C), 121.4 (1C), 126.2 (1C), 127.6 (2C), 133.0 (1C), 136.9 (1C), 140.8 (1C), 142.1 (1C), 151.6 (1C), 164.0 (1C). MS (m/z): 350 (M+1, base peak). Anal. Calcd. for C_29H_23NO_5S: C, 65.73; H, 4.48; N, 3.83%; Found C, 65.70; H, 4.09; N, 3.81%.

2-(3,4-Dimethoxyphenyl)-4-(thiophen-2-yl)-2,3-dihydropyridobenz[b][1,4]thiazepine, 4e:

Obtained from 3-[3,4-dimethoxyphenyl]-1-(thiophen-2-yl)prop-2-en-1-one, 3e (0.004 mmol) and 2-aminothiophenol (0.004 mmol) as yellow solid in 74% yield. M.P. 160-162°C. ^1H NMR (CDCl_3): δ 1.84 (dd, 1H, C=O), 2.04 (dd, 1H, C=O), 3.45 (dd, 1H, C=O), 6.98 (s, 2H, O-CH_3), 6.88-7.16 (m, 7H, Ar-H). ^13C NMR (CDCl_3): δ 40.40 (1C), 50.12 (1C), 55.50 (2C), 58.92 (1C), 102.34 (2C), 117.14 (1C), 124.33 (1C), 125.20 (1C), 125.62 (1C), 127.18 (2C), 127.46 (1C), 133.32 (1C), 136.06 (1C), 137.34 (1C), 137.48 (1C), 151.24 (1C), 152.92 (1C), 164.02 (1C). MS (m/z): 362 (M+1, base peak). Anal. Calcd. for C_29H_23NO_5S: C, 66.11; H, 5.02; N, 3.67%; Found C, 66.10, H, 5.08; N, 3.61%.

2-(3,4-Dimethoxyphenyl)-4-(4-(thiophen-2-yl)-2,3-dihydropyridobenz[b][1,4]thiazepine, 4f:

Obtained from 1-(4-aminophenyl)-3-(3,5-dichlorophenyl)prop-2-en-1-one, 3f (0.004 mmol) and 2-aminothiophenol (0.004 mmol) as yellow solid in 73% yield. M.P. 198-204°C. ^1H NMR (CDCl_3): δ 1.81 (dd, 1H, C=O), 2.112 (dd, 1H, C=O), 3.66 (dd, 1H, C=O), 3.85 (s, 6H, OCH_3), 6.94-7.20 (m, 9H, Ar- & 5m ring-H). ^13C NMR (CDCl_3): δ 40.40 (1C), 50.12 (1C), 55.50 (2C), 58.92 (1C), 102.34 (2C), 117.14 (1C), 124.33 (1C), 125.20 (1C), 125.62 (1C), 127.18 (2C), 127.46 (1C), 133.32 (1C), 136.06 (1C), 137.34 (1C), 137.48 (1C), 151.24 (1C), 152.92 (1C), 164.02 (1C). MS (m/z): 362 (M+1, base peak). Anal. Calcd. for C_29H_23NO_5S: C, 66.11; H, 5.02; N, 3.67%; Found C, 66.10, H, 5.08; N, 3.61%.

2-(3,4-Dimethoxyphenyl)-4-(2-(2,4-dichlorophenyl)-2,3-dihydropyridobenz[b][1,4]thiazepin-4-yl)aniline, 4g:

Obtained from 1-(4-aminophenyl)-3-(3,5-dichlorophenyl)prop-2-en-1-one, 3f (0.004 mmol) and 2-aminothiophenol (0.004 mmol) as yellow solid in 74% yield. M.P. 180-184°C. MS (m/z): 338 (M+1, base peak). Anal. Calcd. for C_29H_23N_2O_5S: C, 67.62; H, 4.48; N, 4.15%; Found C, 67.57, H, 4.44; N, 4.12%.

antimicrobial activity of synthesized compounds (4a-f) and (7a-c) was carried out by paper disc diffusion method [10-13]. The test compounds at the concentration of 50 µg/mL in methanol on the nutrient agar media were screened for their antibacterial activity against the species Escherichia coli, Bacillus subtilis, Staphylococcus aureus and antifungal activity against the species Aspergillus niger, Aspergillus flavus, Fusarium oxysporum. The antibiotics ciprofloxacin and nystatin were used as standard drugs against bacteria and fungi species respectively. The screening tests were carried out in triplicate and the results were expressed as a mean of three determinations.

In vitro antimicrobial activity of synthesized compounds (4a-f) and (7a-c) was carried out by paper disc diffusion method [10-13]. The test compounds at the concentration of 50 µg/mL in methanol on the nutrient agar media were screened for their antibacterial activity against the species Escherichia coli, Bacillus subtilis, Staphylococcus aureus and antifungal activity against the species Aspergillus niger, Aspergillus flavus, Fusarium oxysporum. The antibiotics ciprofloxacin and nystatin were used as standard drugs against bacteria and fungi species respectively. The screening tests were carried out in triplicate and the results were expressed as a mean of three determinations.

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2-Methyl-4-phenyl-2,3-dihydrobenzo[b][1,4]thiazepine, 7c: Obtained from 1-phenylbut-2-en-1-one, 6c (0.004 mmol) and 2-aminothiophenol (0.004 mmol) as gummy mass in 76% yield. 'H NMR (CDCl₃): δ 1.322 (s, 3H, CH₃), 1.88 (dd, 1H, CH=), 2.08 (dd, 1H, C₆H₅), 3.48 (dd, 1H, CH=), 7.220-7.599 (m, 9H, Ar-H), 7.882 (dd, 2H, Ar-H). 'C NMR (CDCl₃): δ 21.2 (1C), 40.8 (1C), 48.6 (1C), 116.7 (1C), 126.1 (1C), 127.7 (1C), 128.6 (2C), 128.9 (2C), 130.9 (1C), 132.8 (1C), 137.5 (1C), 137.9 (1C), 154.6 (1C), 162.4 (1C). MS (m/z): 254 (M+1, base peak), 253 (M+, 12%). Anal. Calcd. for C₁₇H₁₃NS: C 75.85, H 5.97, N 5.53%; Found C 75.80, H 5.95, N 5.52%.

Designed series of molecules 4a-f and 7a-c were characterized by spectral and elemental analysis before being evaluated for their antimicrobial activity. The structural assignments were made by NMR analysis by considering compound (4a) as the representative compound. In its 'H NMR spectra, H₃, H₄, and H₅ protons of the benzothiazepine ring appeared as a doublet of doublet. The doublet of H₃ appeared at δ 1.822 ppm; doublet of H₅ appeared at δ 2.112 ppm; and that of H₄, appeared at δ 3.665 ppm. Doublets of H₃ and H₅ are due to diastereotopic nature of methylene protons. Among H₅, H₃, and H₄ protons, H₄ is the most deshielded due to its close proximity to benzene ring. H₃ protons not only with H₅ but also with H₄ appears as doublet of doublet instead of a triplet i.e., the methylene protons of benzothiazepine ring (H₅ and H₃) exhibited a typical ABX spin system with H₅ as a doublet of doublets as in diagram-1. Further it showed signals due to substituent and aromatic protons at the expected region. All compounds displayed the signals in the similar pattern.

The results of antibacterial activity of the synthesised new benzothiazepines against different bacterial species were shown in fig-1.

The results of antifungal activity of the synthesised new benzothiazepines against different fungal species were summarised in fig-2.

CONCLUSION

An accessible approach for the synthesis of 1,4-benzothiazepines was presented. The potential antimicrobial activity of the synthesised compounds validates the significance of this study. Among the synthesised compounds, 4-(4-chlorophenyl)-2,3-dihydrobenzo[b][1,4]thiazepine and 4-(2-(3,5-dichlorophenyl)-2,3-dihydrobenzo[b][1,4]thiazepin-4-yl)aniline acts as potential antifungal and antibacterial agents.

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