Novel diazepine derivatives of naphthofuran: synthesis, structural characterization, and biological assessment

Suraj K. Shewale

Manguli Institute of Pharmaceutical Sciences, Shahpur, Yadgir District, Karnataka, India

Corresponding author: Suraj K. Shewale

Received 14 Aug 2025; Accepted 12 Sep 2025; Published 9 Oct 2025

Abstract

2-Hydroxy-1-naphthaldehyde (1) was reacted with chloroacetone and anhydrous K_2CO_3 in dry acetone to yield 2-acetylnaphtho[2,1-b]furan (2). Subsequent treatment of compound (2) with isatin, piperidine, and ethanol afforded the corresponding 2-(3′-hydroxy-2′-oxoindolyl)acetylnaphtho[2,1-b]furan (3), which upon dehydration produced the α,β-unsaturated ketones (4). Cyclocondensation of compound (4) with substituted o-phenylenediamines furnished a series of novel 4′-[naphtho[2,1-b]furan-2-yl]spiro[3H-indole-3,2′-1,5-benzodiazepine]-2(1H)-one derivatives (C1–C7).

Molecular docking studies were performed, and the best-scoring compounds were synthesized and structurally confirmed using IR, NMR, and mass spectral analyses. These derivatives were further evaluated for their antimicrobial activity using the MIC method.

Keywords: Acetylnaphtho[2,1-*b*]furan, 1,5-benzodiazepines, Molecular docking, Antimicrobial activity, Minimum Inhibitory Concentration [MIC]

Introduction

1,5-Benzodiazepines are seven-membered heterocyclic compounds containing two nitrogen atoms in the ring system and have been reported to exhibit a wide range of biological activities, including antibacterial, antifungal, anthelmintic, analgesic, anti-inflammatory, antidepressive, antianxiety, anticancer, antiviral, and cardiovascular effects [1]. Isatin derivatives are well-known for their diverse pharmacological potential, including antimicrobial, anti-inflammatory, antiviral, anticancer, and analgesic activities [2]. Naphthofuran derivatives, isolated from various natural sources such as *Fusarium oxysporum* and *Gossypium barbadense*, have demonstrated multiple biological activities, including antibacterial, antifungal, anthelmintic, anti-inflammatory, antitumor, antifertility, and estrogenic effects [3].

Considering the potential of naphthofuran and diazepine scaffolds, the present study focuses on enhancing antimicrobial activity through the design and synthesis of novel diazepine derivatives of naphthofuran. The strategy involved molecular docking to identify promising lead compounds, followed by synthesis, structural characterization, and antimicrobial evaluation. The workflow included:

- Molecular docking of diazepine derivatives of naphthofuran.
- Synthesis of the best-docked molecule.
- Characterization of the synthesized compound.
- Evaluation of antimicrobial activity.

Materials and Methods

Websites and software for molecular docking

KEGG, NCBI, BLAST, PDB, SAVES, SPDV, CASTp, ChemSketch, HyperChem, AutoDock Vina.

Selection and preparation of proteins

Pathways relevant to antimicrobial activity were identified, and template sequences were retrieved using Protein BLAST. Proteins 1D2P, 5DIZ, and 4IIB were downloaded in PDB format and validated using ERRAT and VERIFY3D. Homology modelling with Ramachandran plots was performed to optimize the proteins for docking, and active sites were predicted.

Selection and preparation of ligands

Ligand structures were drawn using ChemSketch and optimized for single-point energy, molecular dynamics, and geometry using HyperChem.

Molecular docking

The docking study indicated that compound C7 (5-Nitro-4′-[naphtho[2,1-b]furan-2-yl]spiro[3H-indole-3,2′-1,5-benzodiazepine]-2[1H]-one) exhibited the best binding energy with bacterial proteins and beta-glucosidase, suggesting its potential as an antimicrobial lead molecule.

Experimental characterization techniques

Melting points were determined using open capillaries. Purity

was verified by TLC. IR spectra were recorded on Bruker Alpha II, NMR spectra on Bruker 300 MHz FT-NMR (DMSO as internal standard), and mass spectra on a JEOL JMS D-300 instrument at 70 eV.

Synthesis of compounds

- 2-Acetylnaphtho[2,1-b]furan (2): 2-Hydroxy-1-naphthaldehyde (5.16 g), chloroacetone (4.1 mL), and anhydrous K_2CO_3 (41.5 g) were refluxed in dry acetone (50 mL) for 24 h. The mixture was filtered, solvent evaporated, and the product recrystallized from ethanol.
- 2-[3′-Hydroxy-2′-oxo-indolyl]acetylnaphtho[2,1-b]furan (3): Compound (2) (1.88 g) and isatin (1.47 g) in absolute alcohol with 2 drops of piperidine were stirred at room temperature for 30 min and left overnight. The precipitate was filtered and recrystallized from alcohol-dioxane.
- 2-[2′-Oxo-3′-indolyl]-α,β-unsaturated ketones (4): Compound (3) (3.35 g) in acetic acid (25 mL) was treated with concentrated HCl (0.5 mL) and heated for 1 h. The precipitate was filtered and recrystallized from alcohol-dioxane.
- 4′-[Naphtho[2,1-b]furan-2-yl]spiro[3H-indole-3,2′-1,5-benzodiazepine]-2[1H]-one (C7): Compound (4) (1.58 g) in ethanol (20 mL) was reacted with o-phenylenediamine (0.6 g) and acetic acid (0.5 mL) under reflux for 10 h. The precipitate was filtered and recrystallized to afford the spirobenzodiazepine.

Antimicrobial activity

The synthesized compound C7 was evaluated using the broth dilution method against *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans*, and *Aspergillus niger*. Brain Heart Infusion (BHI) broth was used as the culture medium. Compound C7 showed significant antibacterial activity against *S. aureus* at 6 µg/mL and antifungal activity against *A. niger* at 8 µg/mL, comparable to standard drugs ciprofloxacin and fluconazole.

Results and Discussion

Molecular docking data revealed that compound C7 exhibited the lowest binding energy, indicating strong interaction with bacterial proteins and beta-glucosidase. This was consistent with its significant antimicrobial activity. Structural analysis indicated that derivatives containing electron-withdrawing groups displayed higher activity than those with electron-donating groups. The compound was successfully synthesized, characterized by IR, NMR, and mass spectroscopy, and demonstrated potent antimicrobial properties, confirming its potential as a lead molecule [4, 20].

References

1. Singh R, Kumar N, Yadav M, Patak D. Microwave-assisted, solvent free and parallel synthesis of some newer 2,4-disubstituted-1,5-benzodiazepines of biological interest. Int J Pharm Sci Drug Res. 2013;5(3):88-95.
2. Vijayabaskaran M, Lakshmi G, Senthilraja M, Sivakumar, Vaijayanthimala P, Perumal P. Synthesis, characterization and anti-microbial evaluation of substituted benzo[g]indol-2-one derivatives. Res J Sci Technol. 2011;3(6):313-7.
3. Sharda M, Acharya GD. Synthesis and biological evaluation of some new heterocyclic derivatives incorporating napthofuran moiety. Der Pharma Chemica. 2015;7(8):25-9.
4. Kusanur RA, Ghate M, Kulkarni MV. Synthesis of spiro[indolo-1,5-benzodiazepines] from 3-acetyl coumarins for use as possible antianxiety agents. J Chem Sci. 2004;116(5):265-70.
5. Kumar R, Joshi YC. Synthesis, spectral studies and biological activity of 3H-1,5-benzodiazepine derivatives. ARKIVOC. 2007;17(13):142-9.
6. Parveen A, Patil VA, Baseer MA, Ahmed SK. Mechanostic synthesis of 1,5-benzodiazepine using molecular iodine. Int J Ind Chem. 2011;2(3):144-53.
7. Misra A, Sharma S, Sharma D, Dubey S, Mishra A, Kishore D, Dwivedi J. Synthesis and molecular docking of pyrimidine incorporated novel analogue of 1,5-benzodiazepine as antibacterial agent. J Chem Sci. 2018;4(8):130-1.
8. Ilango SS, Remya PU, Ponnuswamy S. Synthesis and antimicrobial activity of novel 1,5-benzodiazepines. Indian J Chem B. 2013;52B(1):136-40.
9. Pareek A, Agarwal A, Sharma P, Kishore D. Antimicrobial and antifungal study of novel 2-chloro-4-methyl-3H-benzo[1,5]diazepine derivatives. Int J Pharm Sci Res. 2013;5(3):170-3.
10. Kumaraswamy MN, Chandrashekar C, Shivakumar H, Mathias DAP, Mahadevan KM, Vaidya VP. Synthesis and activity evaluation of 2-(1-naptho[2,1-b]furan-2-yl-carbonyl)-3,5-disubstituted-2,3-dihydro-1H-pyrazoles. Indian J Pharm Sci. 2008;70(6):715-20.
11. Veena K, Ramaiah M, Vanita GK, Avinash TS, Vaidya VP. Synthesis of symmetrical and asymmetrical azines encompassing naptho[2,1-b]furan by a novel approach. Eur J Chem. 2011;8(1):354-60.
12. Ravindra KC, Vagdevi HM, Vaidya VP, Padmashali B. Synthesis, antimicrobial and anti-inflammatory activities of 1,3,4-oxadiazoles linked to naptho(2,1-b)furan. Indian J Chem B. 2006;45B(3):2506-11.
13. Vagdevi HM, Vaidya VP, Latha KP, Padmashali B. Synthesis and pharmacological examination of some thiazolidine derivatives of naptho[2,1-b]furan. Indian J Pharm Sci. 2006;68(6):719-25.
14. Nagaraja GK, Prakash GK, Marilingaplara N, Kumarswamy, Vaidya VP, Mahadevan KM. Synthesis of novel nitrogen containing naptho[2,1-b]furan derivatives and investigation of their antimicrobial activities. ARKIVOC. 2006;15(8):160-8.
15. Patel A, Bari S, Taleli G, Patel J, Sarangapani M. Synthesis and antimicrobial activity of some new isatin derivatives. Int J Pharm Res. 2006;4(1):249-54.
16. Vagdevi HM, Vaidya VP. Studies in naphthofurans: Part III Synthesis of 2-substituted naphtho[2,1-b]furans, 2-(2'-

aryl-3'-acetyl-1,3,4-oxadiazolyl)aminonaphtho[2,1-b]furans and their biological activities. Indian J Heterocycl Chem. 2001;10(8):253-60.
17. Vagdevi HM, Latha KP, Vaidya VP, Vijayakumar ML, Pal KSR. Synthesis and pharmacological screening of some novel naphtho[2,1-b]furo-pyrazolines, isoxazoles and isoxazolines. Indian J Pharm Sci. 2001;63(4):286-91.
18. Mahadevan KM, Vaidya VP. Studies in naphthofurans: Part V Synthesis of some 2-isoxazolyl, pyrazolyl, pyrimidyl and quinolinyl naptho[2,1-b]furan derivatives and their biological activities. J Indian Council Chem. 2001;18(2):78-82.
19. Mahadevan KM, Padmashali B, Vaidya VP. Studies in naphthofurans: Part V Synthesis of 2-aryl-1,2,3,4-tetrahydropyrido(naphtho[2,1-b]furan)-4-ones and their biological activity. Indian J Heterocycl Chem. 2001;2(5):15-20.
20. Latha KP, Vaidya VP, Keshavayya J, Vagdevi HM. Synthesis, characterization and biological studies of complexes of 2-acetylnaphtho[2,1-b]furan hydrazone. J Indian Council Chem. 2001;18(1):31-6.
21. Latha KP, Vaidya VP, Keshavayya J, Vijaykumar ML, Shreedhara CS. Synthesis, characterization and biological studies of metal complexes of 2-acetylnaphtho[2,1-b]furan. Sci Lett. 2002;25(5):5-6.
22. Padmashali B, Vaidya VP, Vijayakumar ML. Synthesis and pharmacological evaluation of some naphtho[2,1-b]furo[3,2-d]pyrimidines. Indian J Heterocycl Chem. 2002;12(5):89-94.