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Cs_2CO_3-mediated facile synthesis, characterizations, and biological activities of 4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidin-4-ylidene)acetonitrile derivatives

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RESEARCH ARTICLE

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ABSTRACT

In this study, we report the newer method for the synthesis of 4*H*-benzo[4,5]thiazolo[3,2-a]pyrimidin-4-ylidene) acetonitrile and the biological activities of the derivatives were systematically evaluated. The antimicrobial potential of the compounds was assessed against three bacterial and three fungal strains using the agar diffusion method. Among the derivatives tested, compounds 3b, 3e, and 3h demonstrated notable antibacterial and antifungal activities. Furthermore, the antioxidant capacity of the selected compounds was investigated through the DPPH radical scavenging assay. Compounds 3e and 3f exhibited significant radical scavenging activity, achieving effective inhibition at a concentration of 0.1 mg/mL. These findings highlight the promising antimicrobial and antioxidant properties of the investigated thiazolopyrimidine derivatives and support their potential for further biological and pharmacological studies.

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1. Introduction

In recent decades, there has been an unpredicted development in the research of the synthesis of nitrogen-containing heterocyclic compounds due to their efficacy in several applications, such as pharmaceuticals, explosives, propellants, pyrotechnics, and chemotherapy [1]. Through the ring transformation strategy, numerous heterocyclic compounds are synthesized using 2*H*-pyran-2-ones [2-5]. Many pyrimidine ring systems have been incorporated into a wide variety of therapeutically interesting drug candidates, including glycosidase inhibitory activities [6], diuretic [7], anticancer [8], antiproliferative [9], anti-inflammatory [10], antimicrobial [11], antibacterial [12], antimalarial [13], antifungal [14], antioxidant [15], *etc*. The number of compounds containing pyrimidine synthesized via ring transformation reaction using 2*H*-pyran-2-one [6,16-18]. The compounds with pyranone skeleton are widely found in plants, animals, bacteria, insects, and marine organisms and participate in several biological activities [19,20]. Compounds containing the pyranone motif have been known for more than 10 decades, but their usefulness in organic synthesis was noticed after 1960 [19]. 2*H*-pyran-2-ones have been used as precursors for the synthesis of various biologically active compounds such as glucose-6-phosphatase inhibitors [21], antihyperglycemic [22,23], anti-leishmanial [24], antidyslipidemic [25], anticancer [26], anti-depressant [27]. In the present article, we report a newer, simpler, and efficient method for the synthesis of (*Z*)-2-(2-phenyl-4H-benzo[4, 5]thiazolo[3, 2-a]pyrimidin-4-ylidene) acetonitrile derivatives was achieved through the reaction of ring transformation of 2*H*-pyran-3-carbonitriles using substituted 2-aminobenzothiazole. The catalytic condition used for ring transformation reaction was mild base Cs_2CO_3 in DMF (Scheme 1). Precursor 2*H*-pyran-3-carbonitriles were synthesized using ethyl 2-cyano-3,3-bis(methylthio) acrylate and acetophenone in the presence of KOH in DMF [28].

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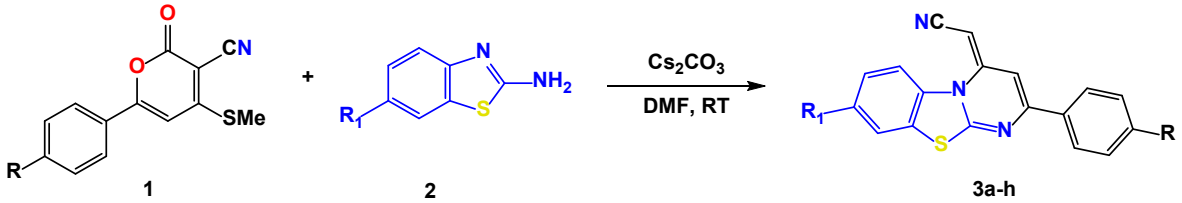

Compound	R	R_1
3a	H	OCH_3
3b	Cl	H
3c	OCH_3	H
3d	CH_3	H
3e	OCH_3	OCH_3
3f	CH_3	OCH_3
3g	H	H
3h	Thiophenyl	H

Scheme 1. General scheme for the synthesis of compounds 3a–3h.

Pyrimidine and pyrimido[4,5-d]pyrimidine have an extensive history in medicinal chemistry research due to their synthetic and therapeutic importance. Because pyrimidine derivatives play an essential role in biological activities, they are valuable leads for drug discovery. Since dangerous bacteria constantly develop defensive mechanisms against current antibiotics, it is crucial to find new and potent antibacterial drugs in order to fight bacterial resistance and create successful therapies [29,30].

The biological potential of the compounds investigated was evaluated through comprehensive antioxidant and antimicrobial studies. Antimicrobial activity was assessed against three fungal species (*Aspergillus niger*, *A. flavus* and *A. fumigatus*) and three bacterial strains (*Escherichia coli*, *Staphylococcus aureus*, and *Bacillus subtilis*). The results revealed that compounds 3b, 3e, and 3h exhibited pronounced antifungal and antibacterial activities. Furthermore, antioxidant properties were examined using the DPPH radical scavenging assay, in which compounds 3e and 3f demonstrated effective radical scavenging activity at a concentration of 0.1 mg/mL. These findings underscore the significance of benzofused thiazolopyrimidine derivatives as promising candidates for the development of multifunctional agents with both antimicrobial and antioxidant potential.

2. Experimental

2.1. Materials and methods

All chemicals and reagents were purchased from Sigma-Aldrich, while solvents were obtained from Merck and used as received without further purification. The progress was monitored by thin layer chromatography (TLC) on silica gel 60 F_{254} aluminum plates, and spots were visualized under ultraviolet light (254 nm) and by iodine vapor. Melting points were determined using a Guna digital melting point apparatus with open capillary tubes and are reported without correction. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II spectrometer operating at 400 MHz and 100 MHz, respectively, using tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (J) in Hertz (Hz). Infrared spectra were recorded using a Shimadzu FTIR-8400 spectrophotometer. LC–MS analyses were performed in positive-ion mode on a Waters Q-TOF Micromass YB 361 mass spectrometer. Antioxidant activity measurements were carried out using a Shimadzu UV-2450 spectrophotometer.

2.2. General procedure for the synthesis of compounds 3a-3h

The synthesis of compounds 3a-3h was carried out according to previously reported procedures [30,31]. A mixture of 2-aminobenzothiazole (1 mmol) and Cs_2CO_3 (2 mmol) was suspended in dry DMF (10 mL) and stirred for 15-20 min. Subsequently, 2*H*-pyran-3-carbonitriles (1 mmol) were added to the reaction mixture under constant stirring. The progress of the reaction was monitored by TLC using ethyl acetate/hexane (2:8) as the eluent. On completion of the analysis, the reaction mixture was filtered, washed with cold water, and dried. The crude products were purified by recrystallization from a chloroform/hexane mixture to produce the desired compounds 3a-3h (Scheme 1). The structures of the synthesized compounds were confirmed by ^{1}H NMR, ^{13}C NMR, FT-IR, and LC-MS analyses. All spectral and physicochemical data were in good agreement with the values reported in the literature [30], confirming the successful formation and purity of compounds 3a-3h.

2.3. Antimicrobial activity

The *in vitro* antimicrobial activity of the compounds was evaluated using the microbroth dilution method against a panel of selected microorganisms, following reported procedures [32]. The tested microbial strains included *Pseudomonas aeruginosa* (NCIM 5031), *Escherichia coli* (NCIM 2065), *Bacillus subtilis* (NCIM 2699), *Aspergillus niger* (NCIM 620), *Aspergillus fumigatus* (NCIM 902) and *Aspergillus flavus* (NCIM 549), which were obtained from the National Chemical Laboratory (NCL), Pune, India. The fungal strains were cultured in Sabouraud dextrose broth, while the bacterial strains were maintained in nutrient broth (NB) and incubated at 37 °C before antimicrobial evaluation.

2.3.1. Preparation of inoculums

The bacteria strains used as inocula were cultured at 37 °C until an optical density of 0.6 at 600 nm was reached. Colony formation units (CFU) were determined using the serial dilution plate technique, and the bacterial suspensions were adjusted to a final concentration of 1×10^5-1×10^6 CFU/mL for antimicrobial susceptibility tests [33]. The fungal inocula were prepared from 10-day cultures grown on potato dextrose agar (PDA). Conidia were harvested by flooding the plates with 8-10 mL of sterile distilled water and gently scraping the surface with a sterile spatula.

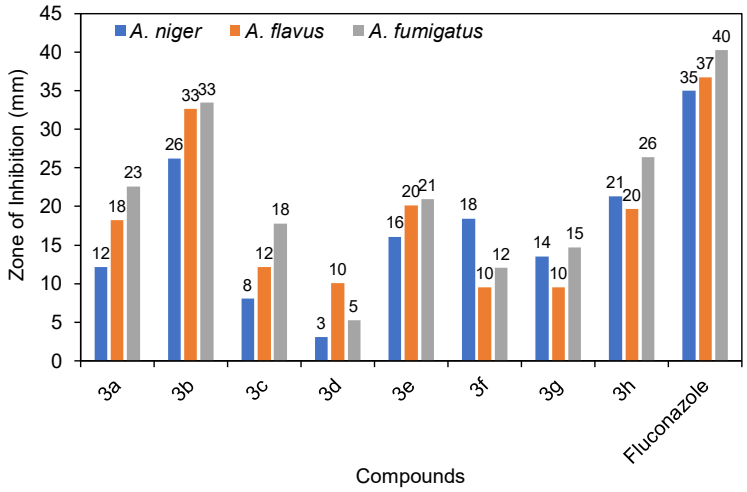

Figure 1. Antifungal susceptibility testing of synthesized compounds 3a-3h against different fungal species.

The spore density of each fungal suspension was adjusted spectrophotometrically at 595 nm (A_{595}) to obtain a final concentration of approximately 1×10^5 spores/mL [34].

2.3.2. Micro broth dilution assay

The microbroth dilution method was used in the compounds tested according to the NCCLS guidelines [35]. A two-fold serial dilution was prepared in 96-well microtiter plates to obtain a concentration of 50 mg/mL of each compound using DMSO as the solvent [36]. Fluconazole and ofloxacin were used as reference standards for fungal and bacterial strains, respectively. Inoculated 96-well plates were incubated at 37 °C for 24 h for bacterial strains and 48 h for fungal strains, after which MIC values were determined [37].

2.4. Antioxidant activity

The antioxidant activity of the compounds tested was evaluated using the DPPH free radical scavenging assay. 1,1-Diphenyl-2-picrylhydrazyl (DPPH) is a stable free radical that exhibits a strong absorption band at λ_{max} = 517 nm in an alcoholic solution due to the presence of an unpaired electron. Upon reaction with antioxidant molecules capable of donating an electron or hydrogen atom, DPPH is reduced to a nonradical form, resulting in a decrease in absorbance at 517 nm. The degree of discoloration is directly proportional to the radical scavenging capacity of the tested compound. In the assay, 1.0 mL of a 0.1 mg/mL DPPH solution prepared in alcohol was added to the test compound solution at a concentration of 0.1 mg/mL prepared in water. The reaction mixtures were incubated at room temperature and the absorbance was measured at 517 nm after 30 min. Ascorbic acid was used as a reference standard [38].

3. Results and discussion

3.1. Chemistry

2*H*-Pyran-3-carbonitriles are well-recognized heterocyclic precursors and have attracted considerable attention due to their structural versatility and reactivity. These six-membered non-aromatic oxygen-containing heterocycles possess two double bonds, a cyano substituent at the 3-position, and a hybridized carbon at the 2-position (or at the 4-position in the case of 4*H*-pyran derivatives). Due to their occurrence in numerous biologically active natural products, pyran-based scaffolds are widely regarded privileged structures in medicinal and heterocyclic chemistry [14].

In the present study, the investigated benzo[4,5]thiazolo [3,2-a]pyrimidin-4-ylidene)acetonitrile derivatives were synthesized following previously reported procedures described in the literature [30]. As detailed synthetic methodologies have already been established, the current work focuses on the structural and biological evaluation of these compounds rather than on their preparation. The synthesized derivatives belong to a class of fused heterocyclic systems incorporating sulfur and nitrogen atoms, consisting of a pyrimidine ring fused with a benzothiazole moiety. These compounds exist predominantly in the ylidene tautomeric form, which is generally more stable in both solution and solid states. The enhanced stability of this tautomer is often attributed to its planar or near-planar molecular conformation, facilitated by intramolecular electronic interactions. Such structural features are considered important for observed biological activities and support further investigation of this heterocyclic framework for pharmacological applications.

3.2. Biological evaluation

3.2.1. Antimicrobial activity

Pyrimidine derivatives have a great deal of antimicrobial potential; some synthetic compounds have robust antifungal and antibacterial properties. *In vitro* diffusion assays, which assess the efficacy of a compound by measuring its capacity to impede microbial growth on agar medium, are commonly used to assess its activity [39,40]. The agar diffusion method was used to assess the antibacterial efficacy of the synthesized compounds against six microbial species.

According to bioassay studies, compounds 3b and 3h showed good antifungal activity (Figure 1), while compounds 3b, 3f and 3h reflected satisfactory antibacterial activity. At 50 µg/mL, the remaining compounds showed mild inhibitory activity. As observed in Figure 1, *Aspergillus fumigatus* was found to be the most sensitive of the fungal strains, while *A. niger* was the most resistant. *Escherichia coli, Staphylococcus aureus,* and *Bacillus subtilis* were found to be the most susceptible bacterial strains (Figure 2). Therefore, the presence of electron-withdrawing groups in the synthesized compounds may be the cause for the observed antibacterial actions.

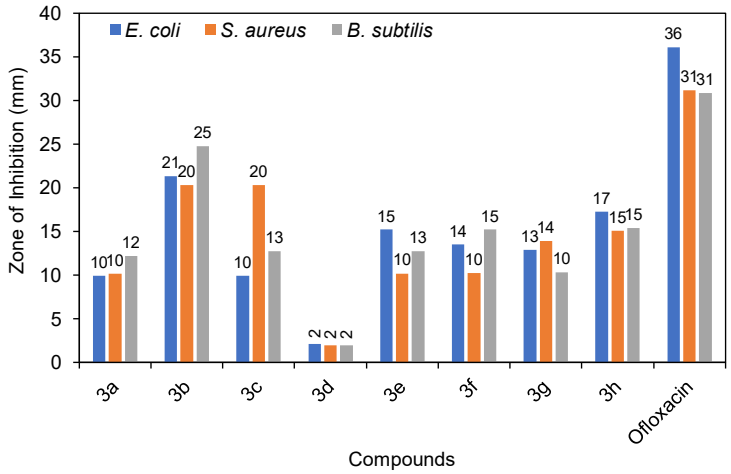

Figure 2. Antibacterial susceptibility testing of synthesized compounds 3a-3h against different fungal species.

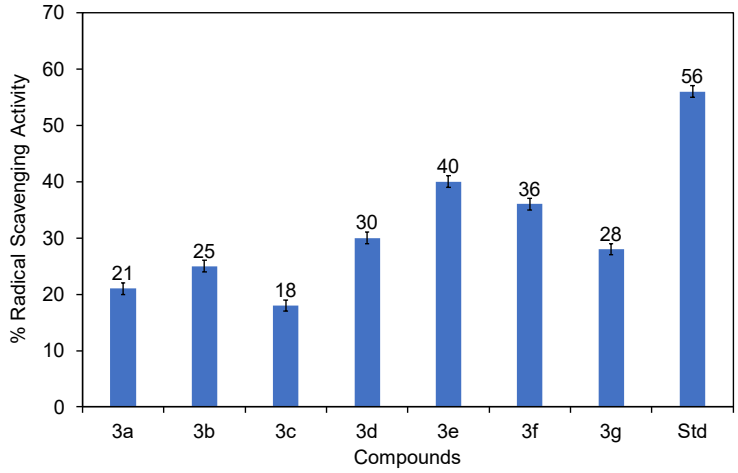

Figure 3. *In vitro* antioxidant activity of the synthesized compounds 3a-3h using DPPH radical scavenging assay. (Std. ascorbic acid).

3.2.2. In vitro antioxidant activity

The rapid, simple and inexpensive 2,2-diphenyl-1-picrylhydrazyl (DPPH) method is widely used for the measuring of antioxidant characteristics. It involves the use of free radicals to evaluate a substance's ability to act as a hydrogen supplier or a free radical scavenger (FRS). The removal of DPPH, a stabilized free radical, is linked to the DPPH testing method. Compounds' ability to contribute electrons or hydrogen atoms to the DPPH radical and form stable diamagnetic scaffolds is linked to their antioxidant activity. The DPPH is a stable free radical that transforms into a stable diamagnetic molecule by taking an electron or hydrogen atom. The decrease in DPPH radicals caused by antioxidants indicated the reduction in their capacity [41]. Figure 3 shows the percentage inhibition of some of the synthesized compounds 3a-3h on DPPH radicals. In comparison to normal ascorbic acid, the ability of the synthesized compounds to scavenge DPPH radicals was found to be good to moderate. Some previous reports showed that pyrimidine derivatives reflect potential antioxidant properties by removing DPPH radicals, commonly due to the electron-donating groups of the pyrimidine ring [42]. The DPPH radical scavenging activity of compounds 3a–3g was evaluated at a concentration of 0.1 mg/mL. Among the compounds tested, compound 3e exhibited the highest radical scavenging activity (40.12%), followed by 3f (36.05%) and 3d (30.48%). Moderate activity was observed for compounds 3g (28.10%), 3b (24.66%) and 3a (20.85%), while compound 3c showed the lowest activity (18.24%). The standard, ascorbic acid, showed significantly higher radical scavenging activity, with a value of 56.10%.

4. Conclusions

Two reactive moieties (-2-(2-phenyl-4*H*-benzo[4,5] thiazolo[3,2-a]pyrimidin-4-ylidene)acetonitrile and 2-amino benzothiazole) are successfully used in a newer simple method for the synthesis of pyrimidine derivatives. The novel catalytic system in use provides high reaction yields, fast reaction times, and moderate conditions. Furthermore, the compounds produced showed good to moderate antibacterial and antioxidant activity in bioassay investigations. Additionally, more environmentally friendly procedures may increase the synthetic application of the current method.

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Disclosure statement

Conflict of interest: The authors declare that they have no conflict of interest.
Ethical approval: All ethical guidelines have been adhered to.
Sample availability: Samples of the compounds are available from the author.

CRediT authorship contribution statement

Conceptualization: Jamatsing Darbarsing Rajput; Methodology: Raosaheb Shivaji Patil; Software: Atul Shivaji Patil; Validation: Atul Shivaji Patil; Formal Analysis: Raosaheb Shivaji Patil; Investigation: Raosaheb Shivaji Patil; Resources: Atul Shivaji Patil; Data Curation: Raosaheb Shivaji Patil; Writing - Original Draft: Gautam Prabhakar Sadawarte; Writing - Review and Editing: Gautam Prabhakar Sadawarte; Visualization: Pramod Pandurang Mahulikar; Funding acquisition: Pramod Pandurang Mahulikar; Supervision: Jamatsing Darbarsing Rajput; Project Administration: Pramod Pandurang Mahulikar.

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