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Design, synthesis and *in vitro* antimicrobial activity of furan-based pyrimidine-thiazolidinones as potential bioactive molecules

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Antimicrobial resistance (AMR) to currently available drugs is a major source of worry for researchers. Antibiotic treatment is insufficient and ineffective against many bacteria and fungi as a result of antimicrobial resistance. Novel antimicrobial drugs that can successfully combat microbial resistance are urgently needed. In order to assess their antimicrobial activity, furan-based thiazolidinone and pyrimidine scaffolds (**8a–o**) have been developed and synthesized. IR, ^{1}H and ^{13}C NMR, and mass spectrometry have been used to characterize the structures of the newly synthesized analogues (**8a–o**). The synthesized compounds have been tested for their antimicrobial properties against diverse bacterial and fungal strains. At MIC 12.5 µg/mL, compound **8k** shows efficacy against *E. coli*. Compounds **8d** and **8e** demonstrate antifungal activity against *A. niger* at 100 µg/mL. Chloramphenicol, ciprofloxacin and griseofulvin have been employed as reference drugs.

Keywords: Antimicrobial activity, Furan, Thiazolidinone, Pyrimidine

Throughout human history, harmful bacteria and fungi have fought humans for survival[1]. The growth of drug resistance to overprescribed antimicrobials, which causes the return of various infectious diseases, is the main issue with treating bacterial and fungal infections[2]. Intense research is presently being done to bring novel antimicrobial drugs to the market as a result of the world's continuously rising resistance to conventional antibiotics[3]. Numerous bioactive compounds commonly include heterocyclic motifs[4]. These motifs exhibit a wide range of biological activities, including antibacterial, antifungal, antiviral, anticancer, anticonvulsant, and anti-inflammatory properties[5,6]. Some of them, such as the derivatives of furan, thiazolidinone, and pyrimidines, have significance to the science of pharmaceuticals and medicinal chemistry. Five-membered heterocyclic rings are strongly reactive with furan rings. A wider spectrum of potential treatments for different clinical diseases is offered by pharmaceuticals based on the furans moiety.

Many derivatives of furans[7-9] have been employed as antibacterial, antitubercular, antimalarial, anticancer, and anti-inflammatory medications due to their bioactivity[10,11]. In naturally occurring compounds, the pyrimidine structure is pervasive. Pyrimidines are a well-known class of six-membered heterocyclic compounds that contain nitrogen and are significant in medicinal chemistry[12,13]. The antibacterial[14], anticancer[15], antitubercular[16], and anti-inflammatory[17] properties of its compounds are well known. Numerous drugs, such as raltegravir, zibotentan, tiodazosin, and complera/rilpivirine, are based on the pyrimidine moiety[18]. In addition, a large number of pharmaceutical substances with a wide range of therapeutic actions have the thiazolidinone ring skeleton[19]. Thiazolidinone has demonstrated a wide range of biological activity, including antioxidant, antibacterial, fungicidal, anti-HIV, and anticancer properties[19-23]. The extensive use of drugs has led to an increase in the antibiotic resistance of bacteria. The development of antibiotics with greater efficacy and fewer adverse effects is challenging. A successful strategy for addressing antibiotic resistance is the development of new antimicrobial drugs having mechanisms of action different from those of currently available drugs[24].

In keeping with the aforementioned hypothesis, our research group is developing furan-based pyrimidine and thiazolidinone as the building block of our targeted compounds and evaluating the effectiveness of those compounds' antimicrobial properties, which

could be useful in establishing potential antimicrobial compounds for future development.

By combining various bioactive pharmacophores with varied activities into a single molecular framework, the drug design achieves its distinctiveness. Our research group synthesized targeted compounds by modifying the drugs alogliptin and nitazoxanide, which are currently available in the market. The framework for the design and synthesis of diverse bioactive scaffolds was based on the furan-based pyrimidine and thiazolidinone targets. Thiazolidine, the -NH linker, and the electron-releasing group (-NO_2) that showed potency are all present in nitazoxanide. The pyrimidine moiety is present in alogliptin. To increase the efficacy, we modified the target molecule's piperidine amine to a furan motif (Fig. 1).

Our research group synthesized fifteen bioactive compounds with antimicrobial properties that are effective against various bacterial and fungal strains. In order to investigate their *in vitro* antibacterial activity against *Bacillus subtilis* and *Micrococcus luteus* as well as their antifungal efficacy against *Aspergillus niger*, *Candida albicans*, *Candida 6*, and *Candida 51*[25], Gopalakrishnan *et al*. synthesized 2-phenyl-3-(4,6-diarylpyrimidin-2-yl)thiazolidin-4-ones motifs. On identified antibacterial compounds, the structural alteration was carried out by substituting a furan ring with a phenyl ring in order to increase the potency of the desired molecule. We have an installation of -NH linker and electron-releasing group (-NO_2) on present work for expanding antimicrobial activities. Addition of electron-releasing groups and electron-withdrawing groups on phenyl ring for increasing antimicrobial activities. Fig. 2 showed the rationale based on the above discussion.

Results and Discussion

Chemistry

The synthesis of 3-((4-(furan-2-yl)-6-(4-nitrophenyl) pyrimidin-2-yl)amino)-4-arylthiazolidin-2-ones **8a-o** is shown in Scheme 1. Chalcone **3** formation by using furan-2-carbaldehyde, *p*-nitroacetophenone, and methanolic KOH solution. Compound **5** was synthesized by cyclizing chalcone **3** with thiourea in the presence of an ethanolic sodium hydroxide solution. Compound **6** was produced by refluxing 4-(furan-2-yl)-6-(4-nitrophenyl)pyrimidine-2-thiol **5** and hydrazine hydrate in ethanol (99.9%) for 6 to 8 h while catalytic amounts of acetic acid were added. Intermediates **7a–o** were formed by dissolving compound **6** and substituted benzaldehydes in ethanol with a few drops of acetic acid as a catalyst. In order to synthesize the desired products **8a-o**, compounds **7a-o** were dissolved in 1,4-dioxane along with thioglycolic acid and a little amount of anhydrous $ZnCl_2$ was added as a catalyst. IR spectra were used to characterize the structures of **8a–o**, which revealed distinct absorption bands at 1752 cm^{-1} and 1609 cm^{-1} for the stretching of >C=O and >C=N, respectively. The C-O-C stretching vibration of the furan ring was the cause of the distinctive absorption seen at 1213 cm^{-1}. The recognizable peak of (-NH) is a strong absorption band that is detected at 3125 cm^{-1}.

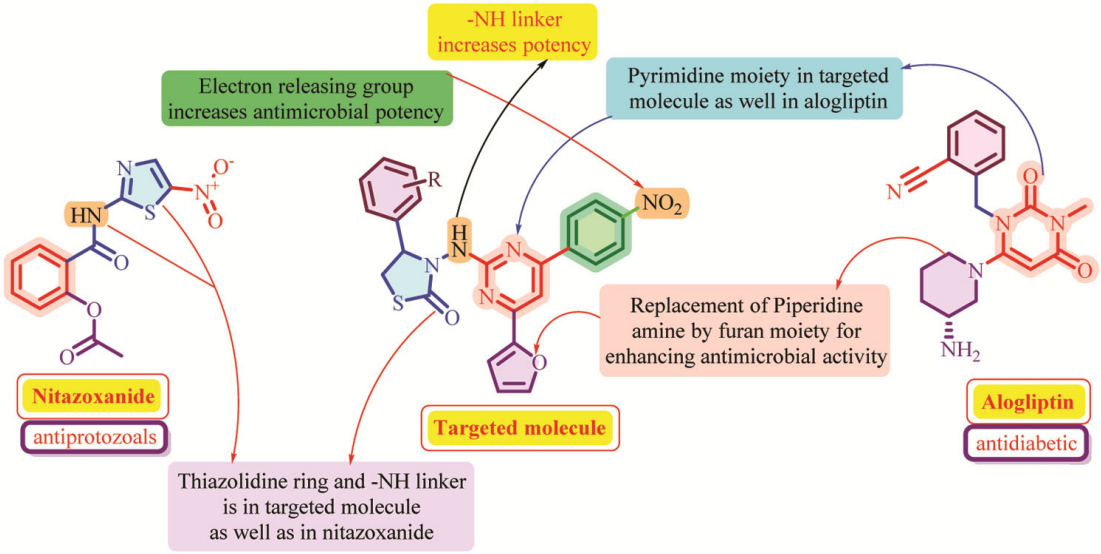


Fig. 1 — Concept of a drug designed from commercially available drugs *versus* targeted molecules **8a-o**

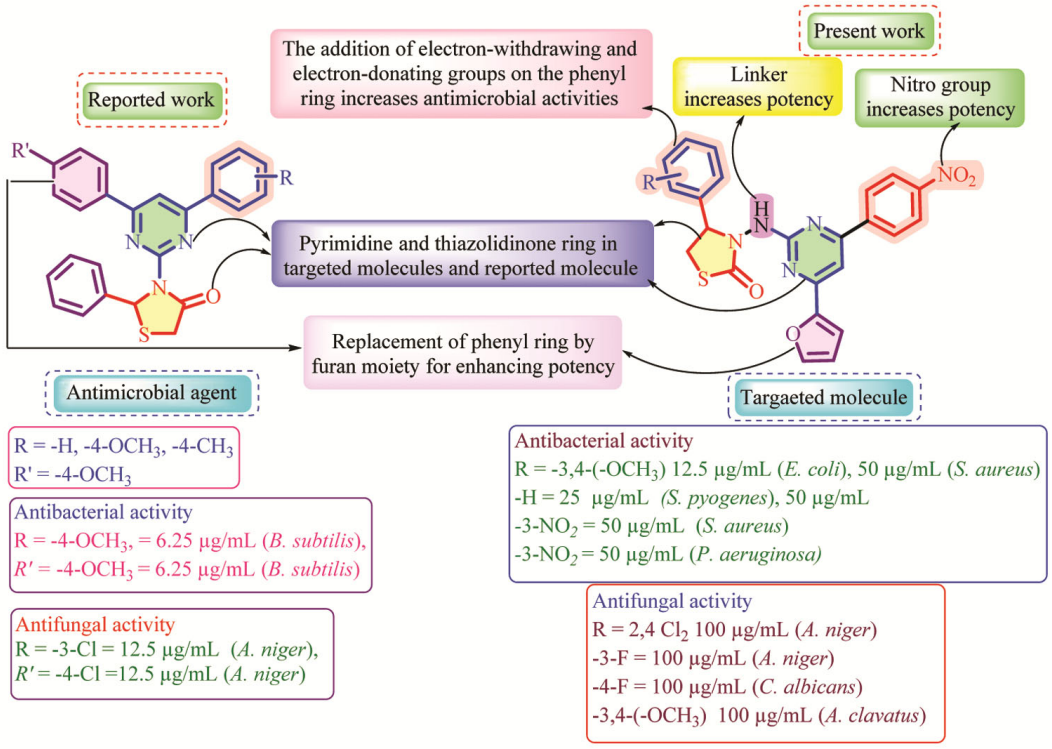


Fig. 2 — Rationale for the present study is based on previously published work

A singlet signal at 7.47 ppm in the ^{1}H NMR spectra proved to be the proton of the -NH- group. The presence of carbon atoms in synthesized molecules was confirmed by multiplet signals produced by aromatic protons in the 7.00–8.24 ppm range of data, and synthetic product **8a** showed a signal at 169.33 ppm originating from the >C=O group on the thiazolidine ring. The existence of -C-NO_2 in the arylidene ring was confirmed by the signal detected in the vicinity of 146.57 ppm. The molecular ion peak of chemical **8a** is seen at *m/z* = 457.08.

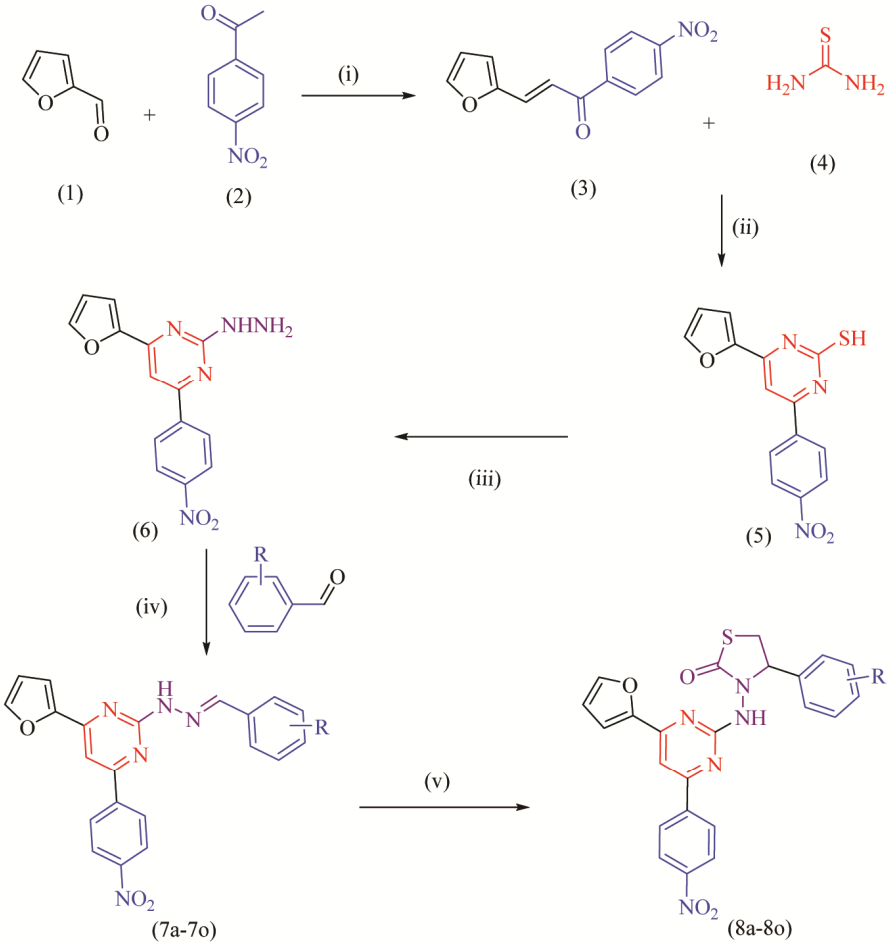
Antimicrobial assay

Antibacterial bioassay

The newly synthesized compounds were screened for their antibacterial activity against Gram-positive bacteria (*Staphylococcus aureus* (MTCC-96), *Streptococcus pyogenes* (MTCC-442)) and Gram-negative bacteria (*Escherichia coli* (MTCC-443), *Pseudomonas aeruginosa* (MTCC-1688)). The strains used for the antimicrobial activity of newly synthesized compounds were procured from IMTECH, Chandigarh. Mueller Hinton Broth dilution method (Becton Dickinson, USA) was used for the antibacterial assay of synthesized compounds. The compounds **8a-o** were screened for their antibacterial activity in triplicate sets against these bacteria at different concentrations of 1000, 500, 250, and 200 µg/mL. The drugs which were found to be active in primary analysis were further diluted and evaluated. 10 µg/mL suspensions were further inoculated on appropriate media and the growth was noted after one or two days. The minimum inhibitory concentration is the lowest concentration, which shows no growth of microbes after spot subculture for each drug. The test mixture should contain 10^8 cells/mL. In this study, Dimethyl sulfoxide (DMSO) and sterilized distilled water were used as negative controls while chloramphenicol and ciprofloxacin was used as positive control for evaluating the antibacterial activity[26].

Antifungal bioassay

The same newly synthesized compounds **8a-o** were screened for their antifungal activity in six sets against three fungi at various primary concentrations of 1000, 500, and 250 µg/mL. The primary screened active compounds were similarly diluted to obtain 200, 125, 100, 62.5, 50, 25, and 12.5 µg/mL concentrations for secondary screening to test in the second set of dilutions against all microorganisms. 'Griseofulvin' was used as a standard drug for antifungal activity,



Scheme 1 — Synthetic scheme for the preparation of compounds **8a-o**

which showed 500 µg/mL MIC against *C. albicans*. For the growth of fungi, in the present procedure, Sabourauds dextrose broth had been used and incubated at 28°C in aerobic conditions for 48 h. DMSO and sterilized distilled water were used as negative controls while 'Griseofulvin' (1 U strength) was used as a positive control[26].

Discussion on antimicrobial activity

Antibacterial activity

Table 1 shows the outcomes of the *in vitro* antibacterial and antifungal screening of compounds **8a–o**. According to the screening results, compound **8a** is noticeably effective against the bacterial strains *P. aeruginosa*, *S. aureus*, and *S. pyogenes*, with MIC values of 50, 62.5, and 25 µg/mL, respectively. In compound **8e**, the fluoro group is present in the third position which displayed antibacterial potency against *S. pyogenes* at an MIC value of 62.5 µg/mL. The fluoro group is present in the fourth position on compound **8f,** which showed potency against *P. aeruginosa* at the MIC value of 62.5 µg/mL. Compound **8h** exhibited potency against *S. pyogenes* at an MIC value of 62.5 µg/mL and compound **8k** exhibited potency against *E. coli* and *S. aureus* having MIC at 12.5 and 50 µg/mL, respectively. Compound **8n** possessed activity against *S. aureus* and *S. pyogenes* with MIC of 50, and 62.5 µg/mL, and

Table 1 — Antimicrobial activity of 3-((4-(furan-2-yl)-6-(4-nitrophenyl)pyrimidin-2-yl)amino)-4-arylthiazol-2(3*H*)-ones **8a-o**

S. No.	–R	Minimum inhibitory concentration (MIC) for bacteria (μg/mL)				Minimum inhibitory concentration (MIC) for fungi (μg/mL)		
		E.c.	*P.a.*	*S.a.*	*S.p.*	*C.a.*	*A.n.*	*A.c.*
8a	–H	100	50	62.5	25	500	500	1000
8b	–4-Cl	125	100	125	250	250	500	1000
8c	–2,3-Cl_2	250	125	100	100	500	1000	1000
8d	–2,4-Cl_2	100	125	100	100	250	100	500
8e	–3-F	250	125	100	62.5	500	100	1000
8f	–4-F	100	62.5	100	125	100	1000	500
8g	–2-OH	250	125	250	100	1000	1000	1000
8h	–4-OH	125	100	100	62.5	500	500	500
8i	–3-CH_3	125	250	250	100	1000	>1000	>1000
8j	–4-CH_3	250	250	500	250	>1000	500	500
8k	–3,4-$(OCH_3)_2$	12.5	250	50	125	500	1000	100
8l	–3,4,5-$(OCH_3)_3$	250	100	100	125	500	1000	1000
8m	–4-OCH_2CH_3	250	125	250	500	250	>1000	>1000
8n	–3-NO_2	100	125	50	62.5	500	500	500
8o	–4-NO_2	100	50	250	500	1000	250	250
	Chloramphenicol	50	50	50	50	–	–	–
	Ciprofloxacin	25	25	50	50	–	–	–
	Griseofulvin	–	–	–	–	500	100	100

Escherichia coli (E.c.) MTCC-442; *Pseudomonas aeruginosa (P.a.)* MTCC-441; *Staphylococcus aureus (S.a.)* MTCC-96; *Streptococcus pyogenes* (S.p.) MTCC-443; *Candida albicans (C.a.)* MTCC-227; *Aspergillus niger (A.n.)* MTCC-282; *Aspergillus clavatus (A.c.)* MTCC-1323.

compound **8o** furnished potency against *P. aeruginosa* at an MIC value of 50 μg/mL.

Antifungal activity

C. albicans, *A. niger*, and *A. clavatus* were used to perform antifungal activity of synthesized compounds **8a-o** and the results are displayed in Table 1. Compounds **8a**, **8c**, **8e**, **8h**, **8k**, **8l**, and **8n** possessed potent activities against *C. albicans* having MIC value of 500 μg/mL. Compounds **8b**, **8d**, and **8m** showed fungal activity against *C. albicans* at MIC value of 250 μg/mL, and compound **8f** indicated fungal activity at the same fungal strain at MIC value of 100 μg/mL. Compounds **8d** and **8e** showed activity against *A. niger* at the same MIC value of 100 μg/mL, and compound **8k** showed potency against *A. clavatus* at an MIC of 100 μg/mL.

Structure-activity relationship (SAR) study

As demonstrated in Fig. 3, the structural representation expresses the relationship between structural activity and the results of biological activity. Compound **8a** demonstrated potency against bacterial strains *P. aeruginosa*, *S. aureus*, and *S. pyogenes* as well as the fungal strain *C. albicans* based on the screening data results. Similar to this, compounds **8e, 8f, 8n,** and **8o** electron-withdrawing groups and compounds **8h** and **8k** containing electron-donating groups demonstrated effectiveness against bacterial strains. Compounds **8k,** and **8m**, which include electron-donating groups, and compounds **8b**, **8c, 8d, 8e,** and **8f,** which contain electron-withdrawing groups, both displayed antifungal activity in arylidene substituents against various fungi strains.

Experimental Section

Preparation of 3-(furan-2-yl)-1-(4-nitrophenyl)prop-2-en-1-one, 3

A basic solution of KOH in methanol, a furfural **1** (0.001 mol) and *p*-nitroacetophenone **2** (0.001 mol) were added together and the reaction mixture was agitated at room temperature for 24 h. The obtained chalcone derivative was filtered out, washed with distilled water, and then recrystallized with ethanol. Yield 72%; solid. m.p.116-118°C. Anal. Calcd for $C_{13}H_9NO_4$: C, 64.20; H, 3.73; N, 5.76. Found: C, 64.18; H, 3.72; N, 5.74%.

Preparation of 4-(furan-2-yl)-6-(4-nitrophenyl)pyrimidine-2-thiol, 5

In a sodium ethoxide solution, a chalcone **3** (0.001 mol) and thiourea **4** (0.001 mol) were dissolved. The resultant mixture was then refluxed for

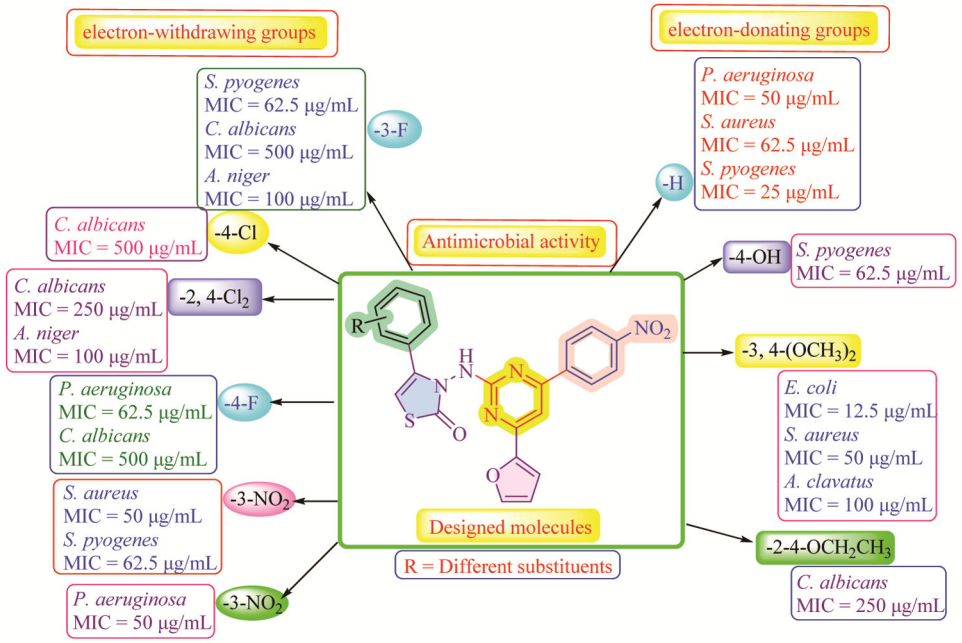


Fig. 3 — Structure-activity relationship (SAR) of the synthesized compounds **8a-o**

3–4 h. At RT, the reaction mass was allowed to cool. The reaction mixture was then placed onto crushed ice, and the required product was formed through a neutralization process using diluted HCl. Yield 68%; solid. m.p.198-200°C. Anal. Calcd for $C_{14}H_9N_3O_3S$: C, 56.18; H, 3.03; N, 14.04. Found: C, 56.16; H, 3.02; N, 14.02%.

Preparation of 4-(furan-2-yl)-2-hydrazineyl-6-(4-nitrophenyl) pyrimidine, 6

Compound **5** and hydrazine hydrate were mixed together and the mixture was refluxed for 6–8 h with the addition of catalytic amounts of acetic acid. After the evaporation process was over, the reaction was completed, and the crystal product **6** was collected. Yield 71%; solid. m.p.212-214°C. Anal. Calcd for $C_{14}H_{11}N_5O_3$: C, 56.57; H, 3.73; N, 23.56. Found: C, 56.55; H, 3.72; N, 23.55%.

Preparation of 2-(2-arylidenehydrazineyl)-4-(furan-2-yl)-6-(4-nitrophenyl)pyrimidines, 7a-o

In order to dissolve compound **6** and substituted aldehydes in ethanol, glacial acetic acid was used as a catalyst. After being refluxed for 3–4 h, the reaction mixture was cooled to RT and then poured over crushed ice. The compounds **7a-o** were obtained by filtering, drying, and recrystallizing the product derived from ethanol. Yield 65%; solid. m.p.208-210°C. Anal. Calcd for $C_{21}H_{15}N_5O_3$: C, 65.45; H, 3.92; N, 18.17. Found: C, 65.44; H, 3.91; N, 18.16%.

Preparation of 3-((4-(furan-2-yl)-6-(4-nitrophenyl)pyrimidin-2-yl)amino)-4-arylthiazolidin-2-ones, 8a-o

Thioglycolic acid (TGA) and compounds **7a-o** (0.01 mol) were mixed together to produce a solution, and $ZnCl_2$ was added as a catalyst. The reaction mass was agitated at 120°C for 8 h. The reaction mixture was added to crush ice and neutralised with $NaHCO_3$ solution after the required amount of stirring. To get the compounds **8a-o**, the resultant product was filtered, dried, and recrystallized from methanol. Yield 72%; solid. m.p.224-226°C. Anal. Calcd for $C_{23}H_{17}N_5O_4S$: C, 60.12; H, 3.73; N, 15.24. Found: C, 60.11; H, 3.72; N, 15.23%.

Conclusion

In this research, the potential for synthesized new bioactive compounds that may aid in the development of efficient antimicrobial drugs has been highlighted through the synthesis and screening of a novel series of thiazolidinone-pyrimidine derivatives **8a-o** based on furans. The *in vitro* antimicrobial activities of the novel synthesized compounds against various bacterial and fungal strains have been determined using the broth dilution method. It can be concluded that all the newly synthesized compounds exhibit notable *in vitro* antimicrobial activity. It is evident from the activity results that compounds with electron-donating and electron-withdrawing groups on the arylidene ring are active against both bacterial

and fungal strains. Compounds **8a**, **8e**, **8f**, **8h**, **8k**, **8n**, and **8o** demonstrate significant antibacterial action based on the results, whereas compounds **8b**, **8c**, **8d**, **8f**, **8k**, and **8m** suggested antifungal activity against various fungal strains.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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