



Design, Microwave-Assisted Synthesis and Anti-Diabetic Activity of 2,4,6-Trisubstituted 2-Aminopyrimidine Derivatives

A. Jayakumar ^[1], Sivaprakash. K^[1], Srikanth. S^[1], Subhashini. D^[1], Sumithra. D^[1], Dr. J. Karthi ^[2], Dr. S. Swarnalatha ^[3]

^[1] Department of Pharmaceutical Chemistry-Pallavan Pharmacy College

^[2] Department of Pharmacognosy-Pallavan Pharmacy College

^[3] Department of Pharmacology-Pallavan Pharmacy College

Email id: annamalaijayakumar@gmail.com

ABSTRACT:

Pyrimidine-based heterocyclic scaffolds continue to attract strong interest in medicinal chemistry, since even small changes in substitution pattern can dramatically shift biological activity. In this study, four 2,4,6-trisubstituted 2-aminopyrimidine derivatives (coded TSA-1 to TSA-4) were designed with a pyridine-2-yl group at the 4-position and differently substituted aryl rings at the 6-position. They were synthesized via a two-step route: base-catalysed Claisen–Schmidt condensation of 2-acetylpyridine with substituted benzaldehydes to form chalcones, followed by microwave-promoted cyclocondensation with guanidine hydrochloride to give the target pyrimidines. The microwave step, run at 240 W for no more than five minutes, replaced several hours of conventional reflux, delivering products in 70–92% yield with minimal side-product formation. Structures were confirmed through melting point, solubility studies, and spectral analysis (FT-IR and ¹H-NMR), consistent with the proposed pyrimidin-2-amine framework. The four compounds were evaluated for antidiabetic potential using an in vitro α -amylase inhibition assay, benchmarked against a standard inhibitor. Percentage inhibition varied strongly with the 4-aryl substituent. The nitro-substituted analogue TSA-2 showed the highest activity, approaching the standard's potency at higher concentrations, while the fluoro derivative TSA-3 was the weakest inhibitor. Chloro- and meta-nitro analogues showed intermediate activity. These results suggest a clear structure–activity relationship, where strongly electron-withdrawing, para-oriented substituents favour α -amylase inhibition within this pyridinyl-aminopyrimidine series, reinforcing microwave irradiation as a fast, efficient, low-waste synthetic strategy.

Keywords: 2-Aminopyrimidine; Chalcone; Microwave-assisted synthesis; Guanidine cyclocondensation; α -Amylase inhibition; Antidiabetic activity; Green chemistry

1. INTRODUCTION

Diabetes mellitus has evolved from a manageable chronic condition into one of the major public health challenges of this century. Global burden estimates indicate that the number of adults living with the disease has surpassed half a billion, with an upward trajectory across most regions and income groups, and type 2 diabetes accounting for most cases. Since type 2 diabetes is primarily driven by insulin resistance rather than absolute insulin deficiency, a widely used therapeutic strategy involves slowing the breakdown of dietary starch in the gut to blunt postprandial glucose spikes. This is achieved by inhibiting enzymes such as pancreatic α -amylase and intestinal α -glucosidase — the mechanism underlying acarbose and similar drugs. However, the gastrointestinal side effects associated with existing inhibitors at higher doses continue to drive the search for structurally novel, better-tolerated alternatives. Among heterocyclic scaffolds explored for this purpose, the pyrimidine ring holds a privileged position, being an intrinsic component of nucleic acid bases (cytosine, thymine, uracil) and possessing a nitrogen-rich, electron-poor character favourable for enzyme and receptor interactions. Substituted 2-aminopyrimidines have demonstrated a broad spectrum of biological activities, including antibacterial, antifungal, anticancer, anti-inflammatory, and antidiabetic effects, with the 2-amino group serving as a convenient site for further derivatization. Notably, several studies on 4,6-diaryl- and 4-aryl-6-heteroaryl-2-aminopyrimidines have reported dual α -glucosidase/ α -amylase inhibitory potencies comparable to or exceeding acarbose, reinforcing the pharmacological relevance of this scaffold.

The conventional synthetic route to these compounds involves a two-step sequence: Claisen–Schmidt condensation of an aryl methyl ketone with an aromatic aldehyde to yield a chalcone, followed by cyclocondensation with guanidine (typically as its hydrochloride salt) to construct the pyrimidine ring and install the 2-amino substituent. Chalcones themselves are pharmacologically significant, exhibiting documented antioxidant, anti-inflammatory, antimicrobial, and anticancer properties. While the cyclization step under conventional reflux often requires several hours to a day—with associated solvent consumption and risk of side-product formation—microwave-assisted synthesis offers a practical alternative. By directly coupling energy into

polar molecules and ionic intermediates, microwave irradiation can compress reaction times to a few minutes while improving yield and purity, aligning with green chemistry principles through reduced solvent use, waste generation, and energy consumption.

Building on this precedent, the present study designed a focused series of 2,4,6-trisubstituted 2-aminopyrimidines with a fixed pyridin-2-yl group at the 6-position—selected for its additional ring nitrogen, which may enhance enzyme binding—while varying the 4-aryl substituent (chloro, para-nitro, fluoro, and meta-nitro). The target compounds were synthesized via microwave-assisted cyclocondensation of the corresponding chalcones with guanidine hydrochloride, characterized by physicochemical and spectral analysis, and evaluated for *in vitro* α -amylase inhibitory activity to establish structure–activity relationships within this series.

2. MATERIALS AND METHODS

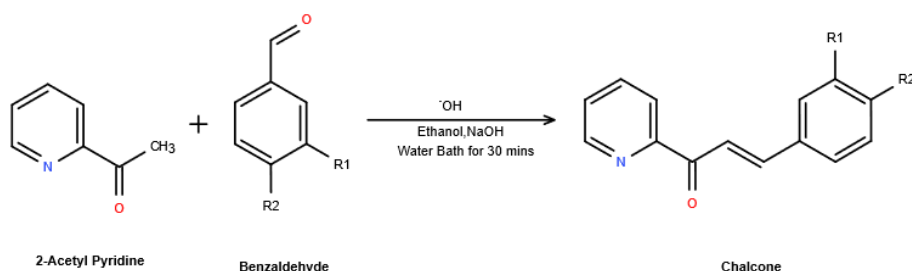
2.1 Chemicals and Instrumentation

2-Acetylpyridine, 4-chlorobenzaldehyde, 4-nitrobenzaldehyde, 4-fluorobenzaldehyde, m-nitro benzaldehyde and guanidine hydrochloride were procured from Sisco Research Laboratories Pvt. Ltd. and Loba Chemie Pvt. Ltd. (laboratory-reagent grade) and used as received. Ethanol and sodium hydroxide pellets were of laboratory-reagent grade. Reactions were monitored by thin-layer chromatography on silica gel using n-hexane: chloroform (9:1) as the mobile phase. Microwave irradiation was carried out in a domestic 20 L solo microwave oven (Panasonic). Melting points were recorded on a Lab therm melting point apparatus and are uncorrected. FT-IR spectra were acquired on a Thermo Scientific Nicolet iS5 spectrometer, and ^1H -NMR spectra were recorded on a Bruker Avance NEO instrument operating at 500 MHz. Absorbance readings for the enzyme-inhibition assay were taken on a UV-visible spectrophotometer at 540 nm.

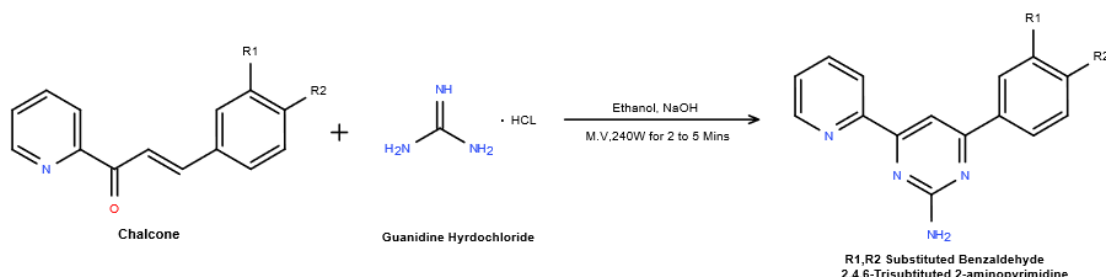
2.2 Scheme:

Microwave Assisted Synthesis of 2,4,6 Trisubstituted 2-Amino Pyrimidine Derivatives

STEP 1:



STEP 2:



2.3 Synthesis of Pyridinyl Chalcone Intermediates

Equimolar quantities (0.01 mol) of 2-acetylpyridine and the appropriate substituted benzaldehyde were dissolved together in 20 mL of absolute ethanol. 0.5g NaOH Pellets dissolved in 5ml Distilled water in RBF. a continuous stirring, and the mixture was stirred at room temperature for about ten minutes before being warmed on a water bath at 70–80 °C for roughly half an hour, in line with the standard Claisen–Schmidt protocol used widely for pyridyl and aryl chalcones. Reaction progress was followed by TLC, and once the starting ketone had been consumed the mixture was poured into ice-cold water and acidified with dilute hydrochloric acid to precipitate the chalcone. The solid was filtered, washed thoroughly with distilled water, dried and recrystallised from ethanol.

2.4 Microwave-Assisted Synthesis of the 2-Aminopyrimidine Derivatives

The chalcone obtained above (0.01 mol), and guanidine hydrochloride (0.015 mol) were dissolved together in 20 mL of absolute ethanol in an open 100 mL beaker, and a few drops of 10% sodium hydroxide Pellet solution were added to generate the free guanidine base in situ. Once a homogeneous solution had formed, the beaker was placed in the microwave oven and irradiated at 240 W for five minutes, following the general strategy used elsewhere for microwave-promoted guanidine cyclocondensation of chalcones to 2-aminopyrimidines. TLC in n-hexane: chloroform (9:1) confirmed the disappearance of the chalcone spot. The mixture was allowed to cool to room temperature and was then poured into ice-cold water to precipitate the crude product, which was filtered, washed with distilled water, dried in a hot-air oven and recrystallised from ethanol to give the pure 2,4,6-trisubstituted 2-aminopyrimidine. Four derivatives were prepared in this way, differing only in the substituent carried by the 4-aryl ring, and were coded TSA-1 (4-chlorophenyl), TSA-2 (4-nitrophenyl),

DESCRIPTION

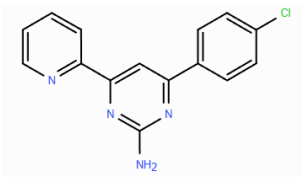
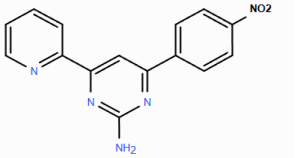
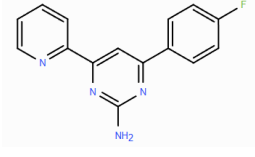
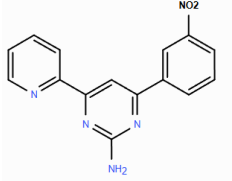
S.NO	BENZALDEHYDE DERIVATIVES	R1	R2
1	TSA-1  4-(4-chlorophenyl)-6-pyridin-2-yl pyrimidine-2-amine	H	Cl
2	TSA-2  4-(4-nitrophenyl)-6-pyridin-2-yl pyrimidine-2-amine	H	NO ₂
3	TSA-3  4-(4-fluorophenyl)-6-pyridin-2-yl pyrimidine-2-amine	H	F
4	TSA-4  3-(3-nitrophenyl)-6-pyridin-2-yl pyrimidine-2-amine	NO ₂	H

Table: 1

2.5 Structural Characterisation

Each compound was characterised by colour, odour, melting point, solubility behaviour and percentage yield, and structures were confirmed by FT-IR and ¹H-NMR spectroscopy. Full spectral assignments are given in the Results and Discussion section.

2.6 In Vitro α -Amylase Inhibitory Assay

Antidiabetic potential was assessed using the starch–DNS (3,5-dinitrosalicylic acid) method described by Dong and co-workers, with minor modification [30]. Test solutions of each pyrimidine derivative were prepared at 100, 250 and 500 μ g/mL and mixed with 200 μ L of α -amylase solution (1.0 U/mL in phosphate buffer, pH 6.9), then pre-incubated at 25 °C for 30 minutes. The reaction was initiated by adding 400 μ L of 0.25% starch solution

in the same buffer and allowed to proceed at 37 °C for five minutes before being quenched with 1.0 mL of DNS reagent (1% 3,5-dinitrosalicylic acid and 12% sodium potassium tartrate in 0.4 M NaOH). Tubes were held in a boiling water bath for ten minutes, cooled to room temperature, diluted to 10 mL with distilled water, and read at 540 nm. Control tubes (100% enzyme activity) replaced the test extract with buffer, and background tubes replaced the enzyme with buffer to correct for any inherent absorbance of the test compound. Percentage inhibition was calculated as:

$$\% \text{ Inhibition} = \frac{A_{\text{control}} - (A_{\text{test}} - A_{\text{background}})}{A_{\text{control}}} \times 100$$

where A control, A test and A background denote the absorbance of the enzyme-only control, the test sample with enzyme, and the test sample without enzyme, respectively. All readings were compared against a standard inhibitor tested under identical conditions.

3. RESULTS AND DISCUSSION

3.1 Physical Characteristics and Yield

The four target compounds were obtained as crystalline solids whose colour ranged from pale yellow through orange to dark brown, a spread that tracks fairly closely with the electronic character of the 4-aryl substituent — the electron-withdrawing nitro-substituted analogues (TSA-2 and TSA-4) were noticeably darker than the halogen-substituted TSA-1 and TSA-3. All four were sparingly soluble in water and chloroform but dissolved readily in hot ethanol or methanol, which is consistent with the moderately polar, hydrogen-bonding character expected of a 2-aminopyrimidine. Melting points were sharp, generally within a two- or three-degree range on repeat determination, suggesting reasonably pure material after a single recrystallisation. Table 1 summarises the physical data.

Compound	Colour	M.P. (°C)	Mol. formula	Mol. Wt. (g/mol)	Yield (%)
TSA-1	Orange	233	C ₁₅ H ₁₁ ClN ₄	282.73	77
TSA-2	Dark brown	254	C ₁₅ H ₁₁ N ₅ O ₂	293.28	92
TSA-3	Pale yellow	226	C ₁₅ H ₁₁ FN ₄	266.27	70
TSA-4	Dark brown	248	C ₁₅ H ₁₁ N ₅ O ₂	293.28	86

Table 2. Physical characteristics of the synthesised 2,4,6-trisubstituted 2-aminopyrimidine derivatives.

Yields ranged from 70% for the fluoro derivative TSA-3 to 92% for the nitro-substituted TSA-2. The comparatively lower yield obtained for TSA-3 is not unusual for fluorinated aromatic substrates in base-catalysed condensations, where the strong inductive electron withdrawal of fluorine can slow the initial Claisen–Schmidt step relative to the more resonance-active nitro group; a similar yield pattern favouring nitro-substituted chalcone derivatives over halogenated ones has been noted in comparable microwave cyclocondensation studies. The short five-minute irradiation time needed to complete the cyclocondensation step compares favourably with the several hours typically required under conventional reflux for structurally related aminopyrimidines, underscoring the efficiency gain that microwave dielectric heating brings to this class of reaction.

SPECTRAL DATA

The synthesised compounds were characterised by various methods such as FT

TSA-1

4-(4-chlorophenyl)-6-pyridin-2-ylpyrimidine-2-amine (TSA-1)

¹H NMR (CDCl₃), δ, ppm: 5.5–6.5 (s, 2H: NH₂); 6.5–7.0 (s, 1H: H-5); 7.1–8.6 (m, aromatic protons); FT-IR (ATR), cm⁻¹: 3356.14 ν(N-H); 1683.86 ν(C=N); 1087.85 ν(C-Cl); 819.75, 783.10 ν(C-H); Mass: 282.73 (M+H); Colour: Orange; m.p. 233°C; Yield: 77%.

TSA-2

4-(4-nitrophenyl)-6-pyridin-2-ylpyrimidine-2-amine (TSA-2)

¹H NMR (CDCl₃), δ, ppm: 7.94 (s, 2H: NH₂); 7.98 (s, 1H: H-5); 8.32–8.77 (m, aromatic protons); FT-IR (ATR), cm⁻¹: 3346.50 ν(N-H); 1654.92 ν(C=N); 1510.26 ν(-NO₂); 835.18, 788.89 ν(C-H); Mass: 293.28 (M+H); Colour: Dark Brown; m.p. 254°C; Yield: 92%.

TSA-3

4-(4-fluorophenyl)-6-pyridin-2-ylpyrimidine-2-amine (TSA-3)

^1H NMR (CDCl_3), δ , ppm: 7.13–7.17 (s, 1H: H-5); 7.15–8.16 (m, aromatic protons); FT-IR (ATR), cm^{-1} : 3076.46 $\nu(\text{N-H})$; 1670.35 $\nu(\text{C=N})$; 1220.94 $\nu(\text{C-F})$; 842.89, 765.74 $\nu(\text{C-H})$; Mass: 266.27 (M+H); Colour: Pale yellow; m.p. 226°C; Yield: 70%.

TSA-4

3-(3-nitrophenyl)-6-pyridin-2-ylpyrimidine-2-amine (TSA-4)

^1H NMR (CDCl_3), δ , ppm: 7.77 (s, 2H: NH_2); 7.81–8.78 (m, aromatic protons); FT-IR (ATR), cm^{-1} : 3358.07 $\nu(\text{N-H})$; 1660.71 $\nu(\text{C=N})$; 1521.84 $\nu(\text{-NO}_2)$; 788.89, 738.74 $\nu(\text{C-H})$; Mass: 293.28 (M+H); Colour: Dark brown; m.p. 248°C; Yield: 86%.

3.4 α -Amylase Inhibitory Activity

Sample	% Inhibition (100 $\mu\text{g/mL}$)	% Inhibition (250 $\mu\text{g/mL}$)	% Inhibition (500 $\mu\text{g/mL}$)
Standard	84.49	86.52	87.00
TSA-1	70.16	73.79	81.81
TSA-2	74.33	83.85	86.52
TSA-3	65.00	69.58	72.15
TSA-4	73.04	80.00	82.99

Table 2. Percentage α -amylase inhibition of the synthesised derivatives relative to a reference standard inhibitor.

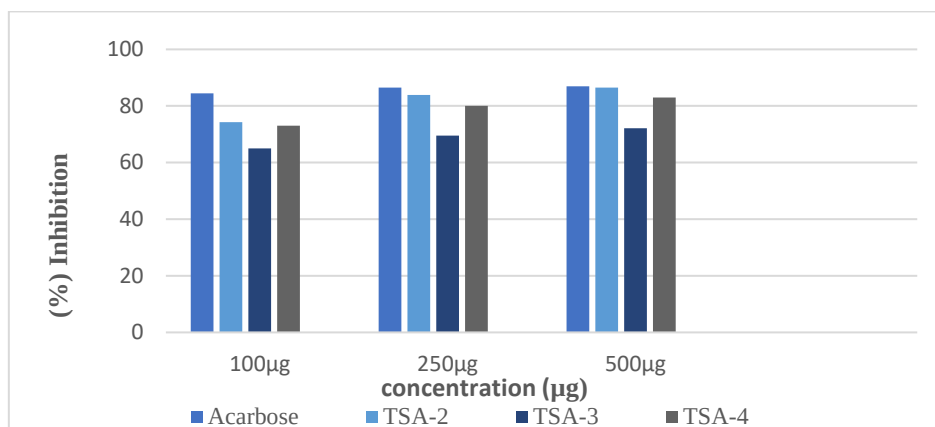


FIGURE: 1 α AAI-Assay

3.DISCUSION

- The present study focused on the design, microwave-assisted synthesis, characterization, and antidiabetic evaluation of four novel 2,4,6-Trisubstituted 2-Aminopyrimidine derivatives (TSA-1 to TSA-4).
- All synthesized 2-Aminopyrimidine derivatives were obtained as crystalline solids with distinct colors ranging from Pale yellow to Dark brown, indicating the influence of different substituents on the aromatic ring. The melting points were sharp and reproducible, suggesting good purity of the synthesized compounds. Solubility in Hot ethanol/methanol soluble; Water-poorly soluble; Chloroform-sparingly soluble further supports their suitability for recrystallization and analytical studies.
- Among the compounds, TSA-2 showed the highest percentage yield (92%), while TSA-3 exhibited a comparatively lower yield (70%), possibly due to the electronic effect of the fluorine substituent affecting reaction efficiency.
- FT-IR spectroscopy confirmed the successful formation of 2-Aminopyrimidine derivatives. All compounds exhibited a characteristic -NH_2 -stretching band around 3358.07-3076.46 cm^{-1} , indicating the presence of the amino moiety. The appearance of a strong pyrimidine (-C=N-) stretching vibration in the range of 1683–1591 cm^{-1} confirmed the Cyclocondensation of 2-Aminopyrimidine with substituted benzaldehydes.

- ¹H-NMR spectral data further validated the proposed structures of the synthesized compounds. The presence of a singlet corresponding to the pyrimidine proton (–C=N–) in the range of δ 6.5–7.17 ppm is a characteristic feature of 2-Aminopyrimidine derivatives. The NH2 proton resonance observed around δ 5.5–7.94 ppm confirms the amino linkage. Overall, the NMR data strongly supports the successful synthesis of the intended 2-aminopyrimidine derivatives.
- The antidiabetic potential of all synthesized compounds was evaluated using the alpha amylase inhibitory assay. All derivatives exhibited measurable antidiabetic activity, indicating their ability to electrons withdraw and reduce NO2 group.
- Among the synthesized compounds, TSA-2 (4-Nitrobenzaldehyde 2-Aminopyrimidine) exhibited the highest antidiabetic activity (µg/g), followed by TSA-1 and TSA-4 showed intermediate activity. The enhanced activity of TSA-2 may be attributed to the presence of a nitro substituent, which can influence electron density and stabilize radical intermediates.
- TSA-2, containing a strong electron-withdrawing Nitro group, also demonstrated significant antidiabetic activity, supporting the role of electron-withdrawing substituents in enhancing reducing power. In contrast, TSA-3 showed the lowest antidiabetic activity, possibly due to the electron-withdrawing nature of the fluoro substituent, which reduces electron-donating ability.
- The observed variation in α-amylase inhibitory values highlights a clear structure–activity relationship, where both the nature and position of substituents on the aromatic ring significantly influence antidiabetic potential.

4. CONCLUSION

Four 2,4,6-trisubstituted 2-aminopyrimidine derivatives carrying a fixed pyridin-2-yl group at the 4-position and a variable substituted aryl group at the 6-position were synthesised through a two-step route combining conventional Claisen–Schmidt chalcone formation with microwave-assisted guanidine cyclocondensation. The microwave step reduced the cyclisation time to five minutes while giving yields of 70–92%, reinforcing the value of microwave dielectric heating as a fast and comparatively eco-friendly alternative to prolonged reflux for this class of heterocycle. FT-IR and ¹H-NMR data were consistent with the proposed pyrimidin-2-amine structures in all four cases. In vitro α-amylase inhibition assays showed a clear, substituent-dependent trend in antidiabetic potential, with the para-nitro-substituted derivative TSA-2 emerging as the most active member of the series and approaching the potency of the reference standard at the highest concentration tested, while the fluoro-substituted TSA-3 was the least active. These results support the 2,4,6-trisubstituted 2-aminopyrimidine scaffold, and particularly its nitro-substituted variants, as a reasonable lead for further antidiabetic drug development, and they point toward electron-withdrawing, para-oriented aryl substitution as a useful design principle for future analogues. Further work extending the series, together with kinetic characterisation of the enzyme inhibition and in vivo evaluation, would help establish how far this early structure–activity trend can be pushed.

ACKNOWLEDGEMENT

We would like to acknowledge the Tamil Nadu chemists and druggist educational trust (TNCDE) and Pallavan pharmacy college for their extended support. Disclosure of conflict of interest: There is no conflict of interest.

REFERENCES

1. Phan TAT, et al. 2-Amino-4,6-diarylpyrimidines as potential chronic myeloid leukaemia cell inhibitors targeting anti-ABL1 kinase: microwave-assisted synthesis, biological evaluation, molecular docking, and dynamics studies. RSC Adv. 2025;15(6):4458–4471.
2. Al-Shehri O, et al. One-pot synthesis of novel pyrimidine derivatives with potential antidiabetic activity through dual α-glucosidase and α-amylase inhibitors. Molecules. 2025;30(13):2857.
3. Onipko OV, et al. Synthesis of novel derivatives of 4,6-diarylpyrimidines and dihydro-pyrimidin-4-one and in silico screening of their anticancer activity. Curr Org Synth. 2025;22(4):556–567.
4. Banerjee S, Periyasamy S, Muthukumar doss K, Deivasigamani P, Saravanan V. Revolutionizing organic synthesis through green chemistry: metal-free, bio-based, and microwave-assisted methods. Front Chem. 2025; 13:1656935.
5. Hashem H, Elshamsy AM, Rabea SM, Marzouk AA, Bräse S, Hetta HF, et al. Design, synthesis, and mechanistic study of novel ciprofloxacin/thiazole chalcone hybrids as potential anticancer agents. Pharmaceuticals. 2025;18(11):1700.
6. Nammalwar B, Bunce RA. Recent advances in pyrimidine-based drugs. Pharmaceuticals. 2024;17(1):104.
7. Nair AR, et al. Unveiling the dual-state emissive behaviour of 4,6-diarylpyrimidin-2-amines through a plug-and-play approach. Sci Rep. 2024;14(1):29795.
8. Shulgau Z, Palamarchuk I, Sergazy S, Urazbayeva A, Gulyayev A, Ramankulov Y, Kulakov I. Synthesis, computational study, and in vitro α-glucosidase inhibitory action of thiourea derivatives based on 3-aminopyridin-2(1H)-ones. Molecules. 2024;29(15):3627.
9. Nkoana JK, Mphahlele MJ, More GK, Choong YS. Exploring the 3,5-dibromo-4,6-dimethoxychalcones and their flavone derivatives as dual α-glucosidase and α-amylase inhibitors with antioxidant and anticancer potential. Antioxidants. 2024;13(10):1255.

10. He KJ, Wang H, Xu J, Gong G, Liu X, Guan H. Global burden of type 2 diabetes mellitus from 1990 to 2021, with projections of prevalence to 2044: a systematic analysis across SDI levels for the global burden of disease study 2021. *Front Endocrinol.* 2024; 15:1501690.
11. Mughal EU, Amjid S, Sadiq A, Naeem N, Nazir Y, Alrafai HA, Hassan AA, Al-Nami SY. Design and synthesis of 2-amino-4,6-diarylpyrimidine derivatives as potent α -glucosidase and α -amylase inhibitors: structure–activity relationship, in vitro, QSAR, molecular docking, MD simulations and drug-likeness studies. *J Biomol Struct Dyn.* 2024;42(1):244–260.
12. Baramaki I, Altıntop MD, Arslan R, Alyu Altınok F, Özdemir A, Dallali I, Hasan A, Bektaş Türkmen N. Design, synthesis, and in vivo evaluation of a new series of indole-chalcone hybrids as analgesic and anti-inflammatory agents. *ACS Omega.* 2024;9(10):11512–11524.
13. Becerra-Rivas CA, Cuervo-Prado PA, Orozco-Lopez F. A comparative study of microwave-assisted and conventional heating approaches for the multicomponent synthesis of 4,6-diarylpyrimidines. *Univ Sci.* 2023;28(3):300–315.
14. Lan H, Song J, Yuan J, Xing A, Zeng D, Hao Y, Zhang Z, Feng S. Synthesis, biological evaluation, DNA binding, and molecular docking of hybrid 4,6-dihydrazone pyrimidine derivatives as antitumor agents. *Molecules.* 2023;28(1):187.
15. Kudličková Z, Michalková R, Salayová A, Ksiažek M, Vilková M, Bekešová S, Mojžiš J. Design, synthesis, and evaluation of novel indole hybrid chalcones and their antiproliferative and antioxidant activity. *Molecules.* 2023;28(18):6583.
16. Lai W, Chen J, Gao X, Jin X, Chen G, Ye L. Design and synthesis of novel chalcone derivatives: anti-breast cancer activity evaluation and docking study. *Int J Mol Sci.* 2023;24(21):15549.
17. Iqbal S, Shaikh NN, Khan KM, Kiran S, Naz S, Ul-Haq Z, Perveen S, Choudhary MI. Synthesis of 2-aminopyrimidine derivatives and their evaluation as β -glucuronidase inhibitors: in vitro and in silico studies. *Molecules.* 2022;27(22):7786.
18. Val C, Rodríguez-García C, Prieto-Díaz R, Crespo A, Azuaje J, Carbajales C, et al. Optimization of 2-amino-4,6-diarylpyrimidine-5-carbonitriles as potent and selective A1 antagonists. *J Med Chem.* 2022;65(2):935–958.
19. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res Clin Pract.* 2022; 183:109119.
20. Bassyouni F, Tarek M, Salama A, Ibrahim B, Salah El Dine S, Yassin N, Hassanein A, Moharam M, Abdel-Rehim M. Promising antidiabetic and antimicrobial agents based on fused pyrimidine derivatives: molecular modelling. *Molecules.* 2021;26(8):2370.
21. Goyal K, Kaur R, Goyal A, Awasthi R. Chalcones: a review on synthesis and pharmacological activities. *J Appl Pharm Sci.* 2021;11(Suppl 1):001–014.
22. Marinescu M. Biginelli reaction mediated synthesis of antimicrobial pyrimidine derivatives and their therapeutic properties. *Molecules.* 2021;26(19):6022.
23. Kasetti AB, Singhvi I, Nagasuri R, Bhandare RR, Shaik AB. Thiazole–chalcone hybrids as prospective antitubercular and antiproliferative agents: design, synthesis, biological, molecular docking studies and in silico ADME evaluation. *Molecules.* 2021;26(10):2847.
24. Campestre C, Keglevich G, Kóti J, Scotti L, Gasbarri C, Angelini G. Microwave-assisted simple synthesis of 2-anilinopyrimidines by the reaction of 2-chloro-4,6-dimethylpyrimidine with aniline derivatives. *RSC Adv.* 2020;10(20):11884–11891.
25. Bayramoğlu D, Kurtay G, Güllü M. Ultrasound-assisted rapid synthesis of 2-aminopyrimidine and barbituric acid derivatives. *Synth Commun.* 2020;50(5):649–658.
26. Abdel Reheim MAM, Baker SM. Synthesis, characterization and in vitro antimicrobial activity of novel fused pyrazolo[3,4-c]pyridazine, pyrazolo[3,4-d]pyrimidine, thieno[3,2-c]pyrazole and pyrazolo[3',4':4,5]thieno[2,3-d]pyrimidine derivatives. *Chem Cent J.* 2017; 11:106.
27. Thirumurugan K, et al. Design, synthesis and anti-inflammatory activity of pyrimidine scaffold benzamide derivatives as epidermal growth factor receptor tyrosine kinase inhibitors. *J Mol Struct.* 2018; 1171:541–550.
28. Adib M, Peytam F, Rahmanian-Jazi M, Mahernia S, Bijanzadeh HR, Jahani M, Mohammadi-Khanaposhtani M, Imanparast S, Faramarzi MA, Mahdavi M, Larijani B. New 6-amino-pyrido[2,3-d] pyrimidine-2,4-diones as novel agents to treat type 2 diabetes: a simple and efficient synthesis, α -glucosidase inhibition, molecular modelling and kinetic study. *Eur J Med Chem.* 2018; 155:353–363.
29. Gong Z, Xie Z, Qiu J, Wang G. Synthesis, biological evaluation and molecular docking study of 2-substituted-4,6-diarylpyrimidines as α -glucosidase inhibitors. *Molecules.* 2017;22(11):1865.
30. Dong HQ, Li M, Zhu F, Liu FL, Huang JB. Inhibitory potential of trilobatin from *Lithocarpus polystachyus* Rehd against α -glucosidase and α -amylase linked to type 2 diabetes. *Food Chem.* 2012;130(2):261–266.