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Synthesis and Characterization of Some Novel Fused Pyrimidine Derivatives

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KEYWORDS

Fused Pyrimidine, Synthesis, IR, NMR, LC-MS Elemental analysis

ABSTRACT:

Introduction: Fused pyrimidines are wonder moiety in the field of drug discovery and development that has caught attention of medicinal chemists owing to their facile chemical transformations and are known to exhibit various pharmacological properties as it is an inextricable part of physiological molecules including DNA & RNA. Pyrimidine-condensed compounds as the pharmacophore exhibits broader spectrum of therapeutic activities as it elicits synergistic action on the biological efficacy of the derivatives.

Objectives: The research work aims to synthesize some novel fused pyrimidine derivatives (SSR1-SS9) bearing various nitrogen containing substituents along with their spectral characterization using different techniques such as IR,^{1}H NMR, ^{13}C NMR, LC-MS and Elemental analysis.

Methods: In this study, an attempt has been made to synthesize a series of nine fused pyrimidine derivatives using various substituted amines such as Allyl Amine, Ammonia, Hexylamine, Cyclopropylamine, 2-ethyl-1-hexyl Amine, Diethoxy ethylamine, Isobutyl amine, Benzyl amine and Cyclohexyl amine utilizing Ethyl(2Z)-2-(ethoxymethylidine)-3-oxobutanoate and S-methyl isothiouronium hemisulfate as starting materials.

Results: Structural analysis of the synthesized fused pyrimidine derivatives was carried out by various characterization techniques such as IR,^{1}H NMR, ^{13}C NMR, LC-MS and Elemental analysis.

Conclusions: The outcome of this research brings to light the facile and efficient synthesis of novel compounds which provides a broader relevance for further development of the compounds as potent therapeutic agents.

1. Introduction

Fused pyrimidines constitute a fascinating class of heterocyclic compounds that has garnered significant attention from medicinal chemists due to their diverse and promising pharmacological activities. These compounds have been extensively studied and utilized in drug discovery and development, primarily because they are found in various physiological molecules and exhibit a wide range of pharmacological effects. Pyrimidine is a 6-membered heterocyclic ring comprising of five carbon atoms and one nitrogen atom whereas pyrimidine also a 6-membered heterocyclic ring comprising of four carbon atoms and two nitrogen atoms at 1st and 3rd position of the ring [1,2]. The fused pyrimidines play a vital role in biochemical processes because the essential components of living system such as DNA & RNA are based on aromatic heterocycles Some well-known examples of fused pyrimidine-containing molecules include Adenine and guanine, which are essential components of DNA and RNA [3]. Several fused pyrimidine molecules such as purines, xanthines, pteridines, alloxazines, quinazolines, pyrrolopyrimidines, pyridopyrimidines, triazolo pyrimidines, pyrimidoazepines, furopyrimidines and thiazolopyrimidines are well-established as antibacterial, antioxidant, anticancer, antifungal, and anti- inflammatory agents [4-8]. Several marketed fused pyrimidine-based drugs include- Tisopurine (Disorders associated with hyperuricaemia), Dipyridamole (vasodilators), Trapidil (vasodilators), Piritrexim (antineoplastic), Methotrexate (antineoplastic), Piromidic Acid (antibacterial), Pipemidic Acid (Urinary tract infection). Fused pyrimidines can be synthesized by different mechanisms including Dimroth rearrangement, aza wittig reaction, domino reaction, biginelli like reaction etc [9-12]. Dimroth rearrangement which involves isomerization proceeding by fission of ring and subsequent recyclization in which nitrogen containing ring and the substituents attached exchanges position with

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an imino group which is in the position alpha to it. Aza wittig reaction involves reaction of phosphazenes to form a carbon-nitrogen double bond of an imine for formation of six membered nitrogen heterocycles. Domino reaction is a process which involves two or more bond forming cyclization reaction initiated by electricity, enzymes, photosensitizers, organocatalysts and transition metals. Biginelli like reaction involves acid-catalysed reaction between an aldehyde, urea and β-ketoester for synthesis of pyrimidinones/pyrimidines.

This study deals with synthesis of some novel pyrimidine derivatives (SSR1-SSR9) fused with pyridine ring containing various nitrogen bearing substituents as well as spectral characterization of the synthesized compounds.

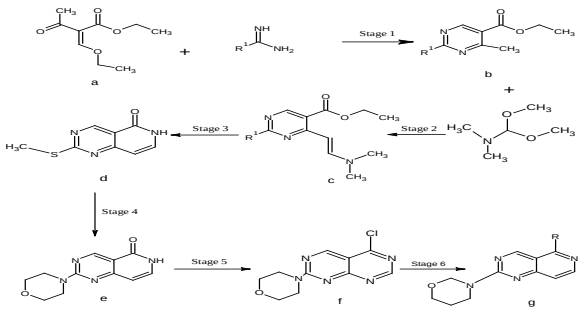
2. Objectives

The research work aims to synthesize some novel fused pyrimidine derivatives bearing various nitrogen containing substituents utilizing Ethyl(2Z)-2-(ethoxymethylidine)-3-oxobutanoate and S-methyl isothiouronium hemisulfate as starting materials.

The synthesized crude compounds were purified by column chromatography and the title compounds (SSR1-SSR9) were obtained as pale yellow solid and the formation of the final product was characterized by UV, IR, ^{1}H NMR,^{13}C NMR, LCMS, and Elemental analysis.

3. Methods

To obtain the target compounds, the synthetic pathway started by dissolving Ethyl(2Z)-2-(ethoxymethylidine)-3-oxobutanoate (1.0740 mol, 1.0 eq) in ethanol (5.0 vol) and then Triethylamine (1.0740 mol, 1.0 eq) and S-methyl isothiouronium hemisulfate (1.0740mol ,1.0 eq) were added under vigorous stirring and reaction was heated to reflux at 85°C overnight under nitrogen atmosphere to obtain ethyl-4-methyl-2-(methylsulfanyl) pyrimidine-5-carboxylate. Ethyl-4-methyl-2-(methylsulfanyl) pyrimidine-5-carboxylate (0.9657 mol, 1.0 eq) was suspended in Dimethylformamide (5.0 vol) and N, N dimethyl formamide dimethyl acetal (1.9315mol, 2.0 eq) was added dropwise. The reaction was stirred overnight at 100 °C under nitrogen atmosphere. The progress of reaction was monitored by TLC and after completion of the reaction the mixture was cooled down to ambient temperature and suspended in 2.5L o ice-cold water. The yellow precipitate so formed was stirred for half an hour and suctioned by vacuum followed by washing with water and drying for 2 hours at 40°C. The carboxylic acid ethyl ester so obtained 4– (2-Methyl amino vinyl)- 2- methyl sulfanyl pyrimidine- 5- carboxylic acid ethyl ester (0.5818mol, 1.0 eq) was suspended in ethanol (5.0 vol) and ammonium acetate (5.0818 mol, 10.0eq) was added. The orange red suspension so formed was heated up to 85 °C under nitrogen atmosphere. After 20 mins of reflux, an almost clear red solution was obtained which started to became a red orange suspension on overnight reflux and completion of the reaction was monitored by TLC. After completion of reaction, it was cool down to room temperature. The orange suspension so formed was filtered and washed with ice water. The obtained red precipitate was dried in vacuum. 2-(methyl sulfanyl) pyrido [4,3-*d*] pyrimidin-5(6*H*)-one (0.5175 mol, 1.0 eq) was kept in 2000 ml round bottom flask and to this, Morpholine (10.0 vol) was added under nitrogen atmosphere at ambient temperature. The reaction mixture was heated at 85°C and stirred for 24 hrs at 85°C under nitrogen atmosphere. The progress of reaction was monitored by using TLC with Methanol: DCM (0.3:9.7) as mobile phase. After completion of reaction, the reaction mixture was cooled to room temperature and diluted with Methyl tert-Butyl Ether (10.0 vol) and the resulted suspension was stirred for 30 min at room temperature. Solids were filtered anddried at 40 °C to afford off white solid 2-(morpholin-4-yl) pyrido [4,3-*d*]pyrimidin-5(6*H*)-one. To the 2-(morpholin-4-yl) pyrido [4,3-*d*] pyrimidin-5(6*H*)-one (0.2586 mol, 1.0eq), phosphoryl chloride (5 vol) was added slowly within 15 mins. The reaction mixture was refluxed for 4-5 hrs at110°C under nitrogen atmosphere. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with chilled 10% $NaHCO_3$ solution at 0°C and the product was extracted with ethyl acetate (3times). The combined organic extracts were dried with anhydrous sodium sulphate, filtered and concentrated under reduced pressure at temperature below 50˚C. The crude compounds was purified by column chromatography and the title compounds (SSR1-SSR9) were obtained as pale yellow solid and the formation of the final product was characterized by UV, IR, ^{1}H NMR,^{13}C NMR, LCMS, and Elemental analysis.



Scheme 1: Synthesis of various fused pyrimidine derivatives

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Table 1: Compound code along with the R substituents

Compound code	R
SSR-1	C_3H_7N (Allyl Amine)
SSR-2	NH_2 (Ammonia)
SSR-3	$C_6H_{15}N$ (Hexylamine)
SSR-4	C_3H_7N(Cyclopropylamine)
SSR-5	$C_8H_{19}N$ (2-ethyl-1-hexyl Amine)
SSR-6	$C_4H_{11}NO$ (Diethoxy ethylamine)
SSR-7	$C_4H_{11}NO$ (Isobutyl amine)
SSR-8	C_7H_9N (Benzyl amine)
SSR-9	$C_6H_{13}N$ (Cyclohexyl amine)

4. Results

Physical and Spectral data

All the compounds in the series (SSR1-SSR9) were synthesized according to the standard procedures as outlined in Scheme 1. Spectroscopic as well as other physical data of the synthesized compounds in series (SSR1-SSR9) is explained below:

1. 2-(morpholin-4-yl)-*N*-(prop-2-en-1-yl)pyrido[4,3-*d*]pyrimidin-5-amine (SSR$_1$): Yellow solid; Yield:89%; mp:189^{0}C; IR(KBr)cm^{-1}: 3289.0(N-H str), 1325.1(C-N str) 1244.0(C-O str), 3076.9(Ar C-H), 2855.0(-CH). 2855.1 (Ar C-H str), 1539.4 (Ar C-C str) 2957.6 (CH_2 Str; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.826 (2H, t, J=4.8Hz, CH2), 3.67 (2H, t, J=9.6Hz, CH2), 4.117 (1H, m, J=6.4Hz, NH), 3.82(2H, t, J=7.2Hz, CH_2), 5.18(2H, t, CH_2), 5.95(1H, d, J=4.8Hz, CH), 6.4 (1H, d, J=6.4Hz, CH), 7.93 (1H, d, J=7.6Hz, CH), 7.974 (1H, d, J=6.0Hz, CH) ; ^{13}C NMR (101 MHz, $CDCl_3$ δ 42.8 (C-15), 43.9(C-1&5), 66.0(C-2&4), 104.3(C-10), 107.8(C-14), 115.2(C-17), 135.8(C-16), 150.89(C-11, C-5) 156.8 (C-19) 157.0 (C-9) 160.0 (C-13); LC-MS m/z 272[M+1]; Anal. Calc for $C_{14}H_{17}N_5O$:C(61.98%), H(6.32%), N(25.81%), O(5.90%); Found-C(61.58%), H (6.23%), N (25.75%), O (5.80%)

2. 2-(morpholin-4-yl)pyrido[4,3-*d*]pyrimidin-5-amine(SSR$_2$) : Off white solid; Yield:89%; mp:185^{0}C; IR(KBr)cm^{-1}: 3421.7(-NH_2 str), 1660.5(C=O), 1021.0(C-O-C), 3181.3(Ar C-H str), 14481324.0(C-N str).; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.806 (2H, t, CH_2), 3.66 (2H, t, CH_2), 6.457 (1H, d, J=5.6Hz, CH_2), 7.905 (1H, d, J=5.6Hz, CH), 9.349(1H, s, CH), ^{13}C NMR (101 MHz, $CDCl_3$ δ 43.92(C-1&5), 66.01(C-2&4), 103.8(C-10) 107.8(C-15), 150.62(C-11), 150.0(C-16), 158.62(C-13), 160.16(C-7); LC-MS: m/z 231[M+]; Anal. Calc for $C_{11}H_{13}N_5O$: C (57.13%), H (5.67%), N (30.28%), O (6.92%); Found- C (57.08%), H (5.72%), N (30.22%), O (6.82%)

3. *N*-hexyl-2-(morpholin-4-yl)pyrido[4,3-*d*]pyrimidin-5-amine(SSR$_3$): Brown yellow solid; Yield:72%; mp:184-186^{0}C; IR(KBr)cm^{-1}: 3352(secondary amine -NH str), 1658.7(C=Ostr), 1112.6(C-O-CH str), 2860.0(C-H str), 1440.6 (-CH bending), 1244.9(C-N str), 2927.6(Ar C-H str).; ^{1}H NMR (400 MHz, $CDCl_3$) δ δ 1.2(3H, s, CH_3), 1.31(3H, t, H_2), 1.29(2H, t, CH_2),1.611(2H, t, H_2), 3.330(2H, t, J= 11.6 Hz, H_2), 3.79(2H, s, H_2), 3.649(2H, q, CH_2), 3.817(1H, d, J=4.4Hz, NH), 6.422(1H, d, J=6.0Hz, H),7.95(1H,d, J=5.6Hz, H), 9.360(1H,s,H); ^{13}C NMR(101 MHz, $CDCl_3$) δ13.89(C-18), 22.09(C-17), 26.32(C-15), 28.11(C-14), 31.12(C-16), 40.7(C-13), 43.90(C-1&5), 66.01(C-2&4), 104.40(C-21), 107.3(C-10), 150.9(C-20), 156.5(C-9),156.9(C-22),160.0(C-11); LC-MS: m/z 339.78[M+1]; Anal. Calc for $C_{17}H_{25}N_5O$: C (64.73%), H (7.99%), N (22.20%), O (5.07%); Found- C (64.75%), H (7.89%), N (22.22%), O (5.17%)

4. *N*-cyclopropyl-2-(morpholin-4-yl)pyrido[4,3-*d*]pyrimidin-5-amine(SSR4) Off white solid; Yield:79%; mp:185^{0}C; IR(KBr)cm^{-1}: 3281.9(-NH str), 1012.0(C-O str), 1326.9(C-N str), 1440.6(C-H bending), 2957.6(C-H str), 1671.7(Ar C-C Str).; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.755 (2H, q, CH_2), 0.15 (2H, d, J=20.0 Hz, CH_2), 3.79 (2H, s, CH_2), 3.69(2H, q, CH_2), 3.9 (1H, q, NH) 6.5 (1H, d, J=6.0 Hz CH), 7.809 (1H, s, CH)9.33 (2H s, CH_2); ^{13}C NMR(101 MHz, $CDCl_3$) 6.375(C-17&16), 24.21(C-15), 43.89(C-1&5), 66.00(C-2&4), 104.3(C-16), 108.5(C-18), 150.88(C-11), 156.8 (C-19), 157.4 (C-9), 160.07 (C-13) LC-MS: m/z 340.77[M+]; Anal. Calc for $C_{14}H_{17}N_5O$: C (61.98%), H (6.32%), N (25.81%), O (5.90%); Found- C (61.89%), H (6.12%), N (25.80%), O (5.89%).

5. 5-chloro-2-(morpholin-4-yl)pyrido[4,3-*d*]pyrimidine(SSR$_5$) Dark yellow solid; Yield:72%; mp:147^{0}C; IR(KBr)cm^{-1}: 3380.2(-NH str), 1325.0(C-N str), 1567.3(Ar C-C str), 3347.0(Ar-CH bending), 2959.5(C-H str), 1263.6 (C-O str). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (3H, s, CH_3), 1.399 (2H, m, CH_2), 1.68 (2H, s, CH_2), 3.17(2H, s,CH_2), 3.78(2H, s,CH_2), 3.66(2H, t,2H), 3.81 (1H d, J=5.2Hz, NH) 6.4 (1H ,d, J=5.2Hz, 1H) 7.956 (1H ,d, J=8.0 Hz, 1H), 9.39(1H, s, 1H); ^{13}C NMR(101 MHz, $CDCl_3$) 10.6(C-21), 13.9(C-25), 28.5(C-24), 28.2(C-20), 30.2(C-23), 30.4(C-22), 39.7(C-19), 44.0 (C-7&11), 13.9 (C-18). 66.0 (C-8&10) 101.4 (C-3) 107.2 (C-15) 150.9(C-2) 156.7(C-14) 157.0 (C-4) 157.58 (C-16) 160.06 (C-6); LC-MS: m/z 354.80[M+]; Anal. Calc for $C_{19}H_{24}N_5O$: C (66.44%), H (8.51%), N (20.39%), O (4.66%); Found- C (66.40%), H (8.53%), N (20.35%), O (4.62%).

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6. *N*-(2,2-diethoxyethyl)-2-(morpholin-4-yl)pyrido[4,3-*d*]pyrimidin-5-amine (SSR6):Brown yellow solid; Yield:72%; mp:125^{0}C; IR(KBr)cm^{-1}: 3423.6 (-NH str), 1392.2C-O), 2901.7(C-H str), 1537.5(Ar-C-C str), ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.113 (3H, m, CH_3), 3.30 (2H, m, CH_2), 3.515 (2H, d, J= 5.6 Hz, CH_2), 3.81 (2H, s, CH_2), 3.66 (2H, q, H_2), 4.735 (1H, t, CH), 6.46 (1H, d, J= 6.0 Hz CH), 7.87 (1H, t, CH), 9.40 (1H, s, CH), ; ^{13}C NMR(101 MHz, $CDCl_3$) 15.5(C-17&20), 43.95(C-13), 44.9(C-1&5), 111.5(C-14), 119.0(C-10), 140.1(C-22), 147.4(C-9), 153.8 (C-24),157.5(C-11) 162.9 (C-7)LC-MS: m/z 347[M+1]; Anal. Calc for $C_{17}H_{25}N_5O_3$: C (58.77%), H (7.25%), N (20.16%), O (13.82%).; Found-C (58.67%), H (7.30%), N (20.25%), O (13.72%).

7. *N*-(2-methylpropyl)-2-(morpholin-4-yl)pyrido[4,3-*d*]pyrimidin-5-amine(SSR$_7$): Yellow solid; Yield:52%; mp:134^{0}C; IR(KBr)cm^{-1}: 3438.5(-NH str), 1243.1(-C-O str) 2922.2, 2860.7(C-H str), 2957.6(Ar-CH str), 1470(Ar C-C str), 1265 (-CN bending).; ^{1}H NMR (400 MHz, $CDCl_3$) δ δ 0.91 (3H, d, J=6.8 Hz, CH_3), 1.992 (1H, t, CH), 3.267 (2H, t, CH_2), 3.817 (2H, t, CH_2), 3.670 (2H, t, CH_2), 6.42 (1H, d, J=6.0 Hz, CH), 7.94 (1H, d, J=6.0 Hz, CH), 9.40 (1H, s, CH); ^{13}C NMR(101 MHz, $CDCl_3$) δ: 20.39(C-17&18), 27.48(C-16), 42.23(C-1&5), 66.10(C-15), 104.39(C-10), 107.23(C-19), 150.87(C-11), 156.66 (C-20), 157.00 (C-9), 156.66 (C-20), 157.58 (C-13), 160.04 (C-7) LC-MS: m/z 287[M+]; Anal. Calc for $C_{15}H_{21}N_5O$**:** C (62.70%), H (7.37%), N (24.37%), O (5.57%); Found- C (62.73%), H (7.35%), N (24.38%), O (5.59%).

8. *N*-benzyl-2-(morpholin-4-yl)pyrido[4,3-*d*]pyrimidin-5-amine(SSR$_8$) Orange yellow; Yield:46%; mp: 160^{0}C; IR(KBr)cm^{-1}: 1263.1(-C-O str) 2952.6(Ar-CH str), 16400(C-N str), 1353 (-CN str).; ^{1}H NMR (400 MHz, $CDCl_3$) δ δ 3.809(2H, s, CH_2), 3.699 (2H, q, CH_2), 4.0 (1H, t, NH), 4.712 (1H, d, J= 6.0, CH), 6.474 (1H, d, J= 6.0, CH), 7.20 (1H, t, CH), 7.33 (1H, t, CH), 7.26 (1H, t, CH), 7.958 (1H, d, J= 6.0, CH), 9.44 (1H, s, CH),^{13}C NMR(101 MHz, $CDCl_3$) δ 43.9(C-1&5), 66.0(C-2&4), 43.92(C-15), 104.45(C-10), 126.08(C-21&27), 1258.0(C-20&18), 126.7(C-19), 150.17(C-11),150.8(C-23), 140.8(C-16), 156.3(C-9), 157.6(C-13).160.07 (C-7); LC-MS: m/z 321[M+]; Anal. Calc for $C_{18}H_{19}N_5O$: C (67.27%), H (5.96%), N (21.79%); Found- C (67.30%), H (5.98%), N (21.75%).

9. *N*-cyclohexyl-2-(morpholin-4-yl)pyrido[4,3-*d*]pyrimidin-5-amine(SSR$_9$) : BOff white; Yield:64%; mp: 189^{0}C; IR(KBr)cm^{-1}: 3367.6 (-NH str), 1023.3(C-O str), 1563.6(Ar C-C str), 3058.3(Ar C-H str), 1427 (C-H bending), 1248.7(C-N str). 2855 (C-H bending) ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.162 (2H, d, J=7.8Hz, CH_2), 1.311 (2H, s, CH_2), 1.74 (2H, s, CH_2), 3.702 (2H, q, CH_2), 2.503 (1H, d, J=1.6 CH) 3.676 (2H, t, CH2), 4.03 (1H, s, NH), 6.41(1H, d, J=27.6 Hz, CH), 7.96 (1H, d, J=4.8 Hz, CH), 9.41 (1H, s, NH); ^{13}C NMR(101 MHz, $CDCl_3$) δ: δ 25.5(C17&19), 32.9(C-16&20), 44.4(C-1&5), 49.6(C-15), 66.5(C-2&4), 104.8(C-10), 107.79(C-21) 151.50 (C-11) 156.32 (C-22) 157.57 (C-9) 158.2(C-13), 160.5(C-7); LC-MS: m/z 313[M+]; Anal. Calc for $C_{17}H_{23}N_5O$: C (65.15%), H (7.40%), N (22.35%), O (5.11%); Found- C (65.10%), H (7.41%), N (22.32%), O (5.12%).

5. Discussion

The research work aims to synthesize some novel fused pyrimidine derivatives (SSR1-SS9) bearing various nitrogen containing substituents such as Allyl Amine, Ammonia, Hexylamine, Cyclopropylamine, 2-ethyl-1-hexyl Amine, Diethoxy ethylamine, Isobutyl amine, Benzyl amine and Cyclohexylamine using Ethyl(2Z)-2-(ethoxymethylidine)-3-oxobutanoate and S-methyl isothiouronium hemisulfate as starting materials. Structural analysis of the synthesized fused pyrimidine derivatives was carried out by various characterization techniques such as IR,^{1}H NMR, ^{13}C NMR, LC-MS and Elemental analysis. The outcome of this research brings to light the facile and efficient synthesis of novel compounds which provides a broader relevance for further development of the compounds as potent therapeutic agents.

References

1. Barupal DK, Fiehn O. Generating the blood exposome database using a comprehensive text mining and database fusion approach. Environmental health perspectives. 2019 Sep 26;127(9):097008.
2. Valverde MG, Torroba T. Sulfur-Nitrogen Heter Mol, 2005; 10(2): 318-320.
3. Balaba ATN, Oniciu DC, Katritzky AR. Chem Rev, 2004; 104(5): 2777- 2812.
4. Tolba MS, Ahmed M, Kamal El-Dean AM, Hassanien R, Farouk M. Synthesis of new fused thienopyrimidines derivatives as anti-inflammatory agents. *J Heterocycl Chem*. 2018 Feb;55(2):408–18.
5. Nassar E, El-Badry YAM, El Kazaz H. Synthesis, in vivo anti-inflammatory, and in vitro antimicrobial activity of new 5-benzofuranyl fused pyrimidines. *Chem Pharm Bull*. 2016;64(6):558–63.
6. Naidu Kalla RM, Karunakaran RS, Balaji M, Kim I. Catalyst-free synthesis of xanthene and pyrimidine-fused heterocyclic derivatives at water-ethanol medium and their antioxidant properties. *Chemistry Select*. 2019 Jan 17;4(2):644–9.
7. Radwan MAA, Alshubramy MA, Abdel-Motaal M, Hemdan BA, El-Kady DS. Synthesis, molecular docking and antimicrobial activity of new fused pyrimidine and pyridine derivatives. *Bioorganic Chem*.

2020 Mar;96:103516.

8. Nayak PS, Narayana B, Sarojini BK, Sheik S, Shashidhara KS, Chandrashekar KR.Design, synthesis, molecular docking and biological evaluation of imides, pyridazines, and imidazoles derived from itaconic anhydride for potential antioxidant and antimicrobial activities. Journal of Taibah University for Science. 2016 Oct;10(6):47.
9. Mohana Roopan S, Sompalle R. Synthetic chemistry of pyrimidines and fused pyrimidines: A review. Synthetic Communications. 2016 Apr 17;46(8):645-72.
10. Qingyun R, Xiaosong T, Hongwu H. Efficient synthesis of fused pyrimidine derivatives with biological activity via aza-wittig reaction. Current Organic Synthesis. 2011 Oct 1;8(5):752-63.
11. Panday AK, Mishra R, Jana A, Parvin T, Choudhury LH. Synthesis of pyrimidine fused quinolines by ligand-free copper-catalyzed domino reactions. The Journal of Organic Chemistry. 2018 Mar 23;83(7):3624-32.
12. Abdelmoniem AM, Abdelwahab RE, Elwahy AH, Abdelhamid IA. Regioselective synthesis of fused pyrimidines and quinazolines linked to Phenoxy-N-arylacetamide moieties as novel hybrid molecules via Biginelli-like reaction. Journal of Heterocyclic Chemistry. 2023 Oct;60(10):1699-706.