Indian Journal of Chemistry
Vol. 61, March 2022, pp. 293-297

Synthesis, characterization and evaluation of thiopyrimidine derivatives as possible antimicrobial agents

J Bharath Kumar[a,b], I Rajyalaxmi[a,c], K Venkateshwarlu[a] & K Sirisha*[a]

[a] Department of Pharmaceutical Chemistry, Vaagdevi College of Pharmacy Ramnagar, Hanamkonda 506 001, India

[b] Pathfinder Institute of Pharmacy Education and Research, Mamnoor, Warangal 506 166, India

[c] MLR Institute of Pharmacy, Dundigal, Quthbullapur, Hyderabad 500 043, India

E-mail: venkataindica@yahoo.com; ragisirisha@yahoo.com

Received 7 June 2020; accepted (revised) 8 November 2021

A series of new thiopyrimidine derivatives have been synthesized *via* the reaction of Chalcones **3a-c** with thiourea to give the corresponding pyrimidine thiones **4a-c**. S-alkylation of pyrimidine thiones have resulted in novel 4,6-diaryl-2-alkyl thiopyrimidine **5a-i** derivatives. Molecular properties like number of hydrogen bond acceptors, number of hydrogen bond donors, volume, polar surface area, molar refractivity, number of rotatable bonds and drug likeness for synthesized compounds have been predicted by using different softwares such as Molinspiration, Molsoft and Chemsketch. The newly synthesized 4,6-diaryl-2-alkyl thiopyrimidine derivatives **5a-i** have been evaluated for their possible anti-microbial activity. Compounds **5b**, **5d** and **5e** have revealed significant activity against *E. coli*, *P. aerugenosa* (Gram +ve) and *B. subtilis*, *S. aureus* (Gram −ve) species while compounds **5a**, **5c**, **5f-i** are moderately active as compared to the standard drug Ciprofloxacin. Compounds **5c** and **5g** show potent anti-fungal activity against *Penicillium* species amongst the series in comparison to the standard Fluconazole.

Keywords: Chalcone, thiopyrimidine, S-alkylation, molecular properties, anti-microbial

Pyrimidine is one of the most important heterocycles exhibiting remarkable pharmacological activities. It contains two nitrogen atoms at positions 1 and 3 of the six-membered ring exhibiting a wide range of biological activities. Numerous methods for the synthesis of pyrimidine offer enormous scope in the field of medicinal chemistry[1,2]. Condensed pyrimidine derivatives have been reported as anti-microbial, analgesic, anti-viral, anti -inflammatory, anti- HIV, anti-tubercular, anti-tumor, anti-neoplastic, anti-malarial, diuretic, cardiovascular agents and hypnotic drugs for the nervous system, calcium-sensing receptor antagonists, adenosine receptor antagonists, *etc*.[3] Thiopyrimidines (Figure 1) are broadly found in bioorganic and medicinal chemistry with applications in drug discovery and developments[4]. They are reported to possess broad spectrum of biological activities such as antibacterial, fungicidal, insecticidal, antihypertensive, tranquilizing, analgesic, antidiabetic, anticancer, *etc*.[5,6] Recent reports revealed thiopyrimidine derivatives as platelet aggregation inhibitors and as selective inhibitors of CDK2 transferase[7].

Thus, in view of their biological potential and to produce new molecules to combat the problem of drug resistance in microbial infections, some new thiopyrimidine derivatives have been designed in the present work based on our earlier studies on thiopyrimidines[8]. Herein, we report the synthesis and antimicrobial activity of some 4,6-diaryl-2-alkyl thiopyrimidines **5a-i**.

Results and Discussion

Chemistry

α,β-Unsaturated ketones (chalcones) **3a-c** have been prepared according to crossed aldol condensation by condensing aromatic/heteroaromatic methyl ketone **1** with different aromatic/heteroaromatic aldehydes **2** in dilute ethanolic sodium hydroxide solution at RT. Reaction of appropriate chalcones **3a-c** with thiourea and sodium hydroxide in ethanol produced thiopyrimidines **4a-c**. S-alkylation of thiopyrimidines **4a-c** using appropriate alkyl halides in presence of ethanolic sodium hydroxide solution *via* nucleophilic substitution reaction afforded 4,6-diaryl-2-alkyl thiopyrimidines **5a-i** (Scheme I).

Molecular Properties Prediction

Various molecular properties for synthesized compounds were predicted by using different softwares such as Molinspiration, Molsoft and Chemsketch[9].

Table I shows the calculated drug-related properties of newly synthesized compounds **5a-i.** Lipinski's rule of five is widely used as filter to estimate molecular drug-likeness. According to this rule, a drug like molecule has log P< 5(accepted range 0.4-5.6), molecular weight < 500 g/mol, hydrogen bond acceptors ≤ 10, hydrogen bond donors ≤ 5 and molecular refractivity between 40-130. Molecules violating more than one of these rules are not expected to be viable drug candidates. Molecular polar surface area (PSA) is a very useful parameter for the prediction of drug transport propertiesn (PSA must be ≤140 A^2). Number of rotatable bonds decides binding of receptors or channels (they should be ≤ 10).

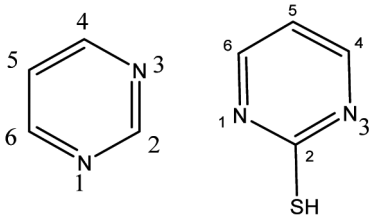
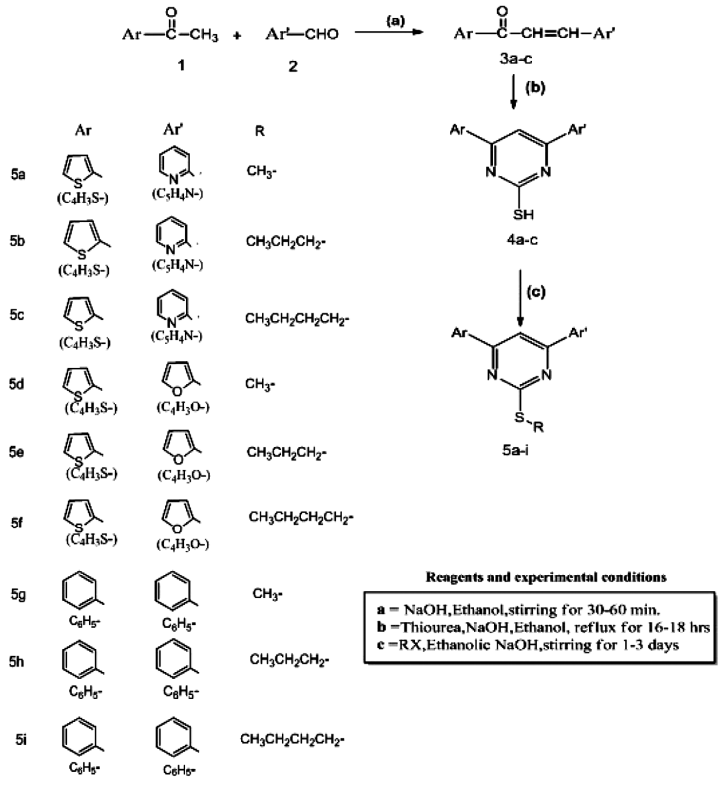


Figure 1 — Structures of pyrimidine and thiopyrimidine scaffold

The values of log P ranged from 3.69 to 6.49 for the synthesized molecules. Except compounds **5h** & **5i** all are within the accepted range. Molecular weights were in accepted range *i.e*., in between 274 to 327. All the synthesized molecules have rotatable bonds between 3 and 6, 3 H-bond acceptors for compounds **5g-i** and 5 for **5a-f**. There are no H-bond donating groups for the designed compounds. The polar surface area (PSA) of all compounds was less than 30 A^2. Molar refractivity values for synthesized compounds were between 75 and 98, which are in the accepted range. All the compounds showed small negative values for drug likeness, ranging from -1.32 to -0.53 which is even evidenced with some of the marketed drugs like fluconazole (-1.13), chloramphenicol (-4.61) and linezolid (-4.08)[10].

Anti-microbial activity

All the synthesized compounds were evaluated for their antimicrobial activity. The antimicrobial activity of the test compounds were assayed systematically against four different strains of bacteria *i.e*., *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Bacillus subtilis* and fungal



Scheme I — Synthesis of thiopyrimidine derivatives **5a-i**

strain *i.e.*, *Pencillium chrysogenum* by agar diffusion method[11].

Table II shows the antimicrobial activity of the newly synthesized 4,6-diaryl-2-alkylthiopyrimidine derivatives **5a-i**. All the compounds exhibited mild to moderate antibacterial activity against the test organisms employed in the present investigation. However, the zone of inhibition varied with the test compound and the test microorganisms.

Amongst the series, compounds **5b**, **5d** and **5e** displayed significant antibacterial activity. Compounds **5b** and **5d** exhibited good activity against *S.aureus*. Compounds **5b** and **5e** showed higher activity against *B. subtilis*. Compound **5b** was found to be a relatively more potent antibacterial. At higher concentration (500µg/mL) it was almost equipotent to the standard. Compound **5c** and **5g** displayed moderate antifungal activity against *Pencillium* species.

It could be observed from the results of the present investigation that, compared to the standard drug ciprofloxacin, the synthesized compounds were less potent against the tested micro-organisms.

Compounds containing propyl substituent exhibited good antibacterial activity compared to methyl and butyl substituents. Compounds containing butyl substituents displayed good antifungal activity.

In the present investigation heteroaryl derivatives have shown potent antimicrobial activity than phenyl derivatives.

Experimental Section

Melting points were determined by Micro control based meltingpoint instrument and are uncorrected. All reactions weremonitored by thin-layer chromatography. Infra red (IR) spectra were recorded byusing KBr pellet on a Thermo Nicolet Nexus 670 FT-IR spectrophotometer,^{1}H NMR spectra were recorded in $CDCl_3$ on BrukerAvance-400F spectrometer (400 MHz) using tetramethylsilane as internal standard (Chemical shift(δ) ppm). The ^{13}C NMR spectra were recorded in $CDCl_3$ on AVANCE (300 MHz) NMR spectrometer. Mass spectra were recorded on a 70eV GC-MS

Table I — Drug related property profile for newly synthesized compounds **5a-i**

Compd	MF	MW	LOGP	LOGS	NHBA	NHBD	VOL (A^3)	PSA (A^2)	MR	nrotb	Drug Likeness
5a	$C_{14}H_{11}N_3S_2$	285.38	3.69	−4.56	5	0	243.84	27.05	80.34	3	−1.00
5b	$C_{16}H_{15}N_3S_2$	313.44	4.57	−4.73	5	0	284.57	27.05	89.60	5	−0.54
5c	$C_{17}H_{17}N_3S_2$	327.46	5.13	−5.26	5	0	302.48	27.05	94.23	6	−0.71
5d	$C_{13}H_{10}N_2OS_2$	274.36	3.98	−4.38	5	0	233.25	26.59	75.02	3	−1.00
5e	$C_{15}H_{14}N_2OS_2$	302.41	4.86	−4.55	5	0	273.99	26.59	84.28	5	−0.53
5f	$C_{16}H_{16}N_2OS_2$	316.44	5.42	−5.08	5	0	291.89	26.59	88.91	6	−0.67
5g	$C_{17}H_{14}N_2S$	278.37	5.05	−5.75	3	0	254.68	16.99	84.40	3	−1.32
5h	$C_{19}H_{18}N_2S$	306.42	5.93	−5.92	3	0	295.42	16.99	93.66	5	−0.72
5i	$C_{20}H_{20}N_2S$	320.45	6.49	−6.45	3	0	313.32	16.99	98.29	6	−0.74

MF-Molecular formula; MW-Molecular weight; HBA-No.of hydrogen bond acceptors; HBD-No.of hydrogen bond donars; VOL-Volume;PSA-Polar surface area;MR-Molar refractivity;nrotb-No.of rotatable bonds

Table II — Zone of inhibition for compounds **5a-i**

Compd	*E.coli*			*P.aerugenosa*			*B.subtilis*			*S.aureus*			*Pencillium chrysogenum*		
	100 µg/mL	250 µg/mL	500 µg/mL	100 µg/mL	250 µg/mL	500 µg/mL	100 µg/mL	250 µg/mL	500 µg/mL	100 µg/mL	250 µg/mL	500 µg/mL	100 µg/mL	250 µg/mL	500 µg/mL
5a	-	-	7	-	-	8	-	7	8	-	8	13	-	-	-
5b	-	8	14	-	7	16	7	11	16	8	12	18	-		-
5c	-	-	7	-	-	7	-	7	9	-	8	9	-	8	10
5d	-	7	8	-	-	11	-	8	10	7	8	12	-	-	-
5e	-	8	10	-	-	5	-	8	12	-	8	10	-	-	7
5f	-	7	8	-	-	6	-	7	10	7	7	9	-	-	-
5g	-	-	8	-	-	7	-	-	7	7	8	10	-	8	10
5h	-	-	8	-	-	-	-	8	10	-	7	8	-	-	-
5i	-	-	8	-	-	-	-	-	8	-	-	8	-	-	-
Std.	8	10	18	8	10	16	8	14	20	10	14	20	8	10	14

(-)= No zone of inhibition, Standard= Ciprofloxacin (for bacteria), Fluconazole (for fungi)

Shimadzu instrument. Elemental analysis (C,H,N) of the compounds were obtained from Perkin Elmer 240B analyzer and were within ±0.4% of theoretical values.

General procedure for the synthesis of 1,3-diaryl chalcones, 3a-c

A mixture of 22gm of sodium hydroxide and 100gm (122.5mol) of rectified spirit were taken in a 500 mL round bottomed flask provided with a mechanical stirrer. The flak was immersed in a bath of crushed ice, 0.43mol of freshly distilled aryl ketone or heteroaryl ketone **1** was added while stirring and then 0.43 mole of pure aryl aldehyde or hetero aryl aldehyde**2** was added. The temperature of the mixture was kept at 25°C (limits are 15-30°C) and stirred vigorously until the mixture was so thick that stirring is no longer effective (2-3 hr). Stirrer was removed and the reaction mixture was kept in an ice chest or refrigerator overnight. Thus obtained product was filtered and washed with cold water until the washings were neutral to litmus and then with 20 mL of ice cold rectified spirit and dried. It was purified by recrystallization from ethanol to give a pure compound[12].

General procedure for the synthesis of 4,6-diaryl-2-thiopyrimidines, 4a-c

Equimolar quantity of sodium hydroxide and ethanol (0.02mol) were taken in a round bottom flask. To this 0.02 mol of Chalcone **3** and 0.02 mol of thiourea were added and heated under reflux for 16-18 hours. The progress of the reaction was monitored by TLC. The reaction mixture was poured in a beaker and neutralized the mixture with the addition of acid. Filtered the precipitate and recrystallized from ethanol to obtain the pure compound[13].

General procedure for the synthesis of 4,6-diaryl-2-alkyl thiopyrimidine derivatives, 5a-i Haloalkane (12.4 mmol) was added drop wise into a solution of 4,6-diaryl-2-alkylthiopyrimidine **4** (12.4 mmol) in 1 M NaOH (12.4 mL). The reaction mixture was stirred at RT for 1-3 days, until TLC (EtOAc/MeOH-15:1, v/v) indicated the completion of reaction. The mixture was neutralized with acetic acid. The resulting solid was collected by filtration, washed with petroleum ether (10 mL) and water (10 mL) and dried[14].

4-(2-Thiophenyl)-6-(2-pyridyl)-2-methyl thiopyrimidine, 5a: Brown Solid, m.p. 185-188ºC, Yield 65%. R_f 0.85 (EtOAc/MeOH-15:1, v/v); IR(KBr, γ cm^{-1}): 3116 (Ar-CH), 2953 (C-H),1663 (C=N), 1596(C=C), 693 (C-S); ^{1}H NMR ($CDCl_3$,δ ppm):1.22(s,3H,-CH_3), 6.91-8.63 (m,8H,Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm):14.8, 101.1, 121.5, 123.7, 128.2, 129.9, 137.2, 142.5, 150.1, 156.3, 160.8, 164.7.172.3; MS *m/z*: 286 $[M+H]^+$. Anal. Calcd(%) for $C_{14}H_{11}N_3S_2$: C, 58.92; H, 3.89; N, 14.72. Found: C,58.95; H, 3.85; N, 14.74%.

4-(2-Thiophenyl)-6-(2-pyridyl)-2-propyl thiopyrimidine, 5b: Pale Yellow Solid, m.p. 205-208ºC, Yield 74%. R_f 0.64 (EtOAc/MeOH-15:1, v/v); IR (KBr, γ cm^{-1}): 3057 (Ar-CH), 2923 (C-H),1670 (C=N), 1598 (Ar-C=C), 694 (C-S); ^{1}H NMR ($CDCl_3$, δ ppm):3.12(t,3H,-CH_3),4.01-4.37(m,2H,-CH_2), 4.52-4.65(t,2H,-CH_2),6.68-8.12(m,8H,Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 13.8, 22.7, 40.1, 101.5, 121.4, 124.1, 127.7, 128.2, 137.2, 142.8, 149.1, 160.5, 165.1, 173.4; MS *m/z*: 314 $[M+H]^+$. Anal. Calcd for $C_{16}H_{15}N_3S_2$: C, 61.31; H, 4.82; N, 13.41. Found: C, 61.33; H, 4.84; N, 13.38%.

4-(2-Thiophenyl)-6-(2-pyridyl)-2-butyl thiopyrimidine, 5c: Yellow Solid, m.p. 210-215ºC, Yield 39%. R_f 0.72 (EtOAc/MeOH-15:1, v/v); IR (KBr, γ cm^{-1}): 3107 (Ar-CH), 2991 (C-H),1619 (C=N), 1571 (C=C), 697 (C-S); ^{1}H NMR ($CDCl_3$, δ ppm): 0.94 (t,3H,-CH_3), 2.90-3.12 (m,6H,-CH_2), 7.37-8.59 (m,8H,Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 13.4, 21.6, 32.5, 36.7, 100.8, 122.6, 123.4, 127.6, 128.0, 137.2, 142.5, 149.2, 155.6, 160.7, 165.1, 174.8; MS *m/z*: 328 $[M+H]^+$. Anal. Calcd for $C_{17}H_{17}N_3S_2$: C, 62.35; H, 5.23; N, 12.83. Found: C, 62.38; H, 5.19; N, 12.85%.

4-(2-Thiophenyl)-6-(2-furyl)-2-methyl thiopyrimidine, 5d: Brown Solid, m.p. 195-198ºC, Yield 52%. R_f 0.68 (EtOAc/MeOH-15:1, v/v); IR(KBr, γ cm^{-1}): 3096 (Ar-CH), 2923 (C-H), 1616 (C= N), 1589 (C=C), 1220 (C-N), 738 (C-O), 698 (C-S); ^{1}H NMR ($CDCl_3$, δ ppm): 0.91(s,3H,-CH_3), 7.13-7.95 (m,7H,Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 14.8, 23.8, 109.9,116.1, 125.6, 127.3, 143.6, 165.9, 168.2, MS *m/z*: 275 $[M+H]^+$. Anal. Calcd for $C_{13}H_{10}N_2OS_2$: C, 56.91; H, 3.67; N, 10.21. Found: C, 56.94; H, 3.65; N, 10.25%.

4-(2-Thiophenyl)-6-(2-furyl)-2-propyl thiopyrimidine, 5e: Pale Yellow Solid, m.p. 205-208ºC, Yield 60%. R_f 0.59 (EtOAc/MeOH-15:1, v/v); IR (KBr, γ cm^{-1}): 3102 (Ar-C-H),2922 (C-H), 1616 (C=N),1589 (C=C), 1220 (C-N),743 (C-O), 698 (C-S); ^{1}H NMR ($CDCl_3$, δ ppm): 1.25(t,3H,-CH_3),

3.03 (m,4H,-CH_2), 6.9-7.86 (m,7H,Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 13.0, 21.6, 23.8, 38.9, 109.9, 116.1, 125.6, 127.3, 143.6, 168.2, 171.1; MS *m/z*: 303 $[M+H]^+$. Anal. Calcd for $C_{15}H_{14}N_2OS_2$: C, 59.58; H, 4.67; N, 9.26. Found: C, 59.62; H, 4.69; N, 9.29%.

4-(2-Thiophenyl)-6-(2-furyl)-2-butyl thiopyrimidine, 5f: Pale Yellow Solid, m.p.218-220ºC, Yield 35%. R_f 0.54 (EtOAc/MeOH-15:1, v/v); IR (KBr, γ cm^{-1}): 3056(Ar-C-H),2923 (C-H), 1625 (C=N),1557 (C=C), 1232 **(**C-N), 742 (C-O str), 692 (C-S); ^{1}H NMR ($CDCl_3$, δ ppm): 1.16(t,3H,-CH_3), 2.93 (m,6H,-CH_2), 7.41-7.86 (m,7H,Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 13.4, 21.6, 23.8, 32.4, 36.4, 109.9, 116.1, 125.6, 127.3, 143.6, 168.2, 171.1; MS *m/z*: 317$[M+H]^+$. Anal. Calcd for $C_{16}H_{16}N_2OS_2$: C, 60.73; H, 5.10; N, 8.85. Found: C, 60.76; H, 5.06; N, 8.87%.

4,6-Diphenyl-2-methyl thiopyrimidine, 5g: Brown Solid, m.p.190-195ºC, Yield 32%. R_f 0.65 (EtOAc/MeOH-15:1, v/v); IR (KBr, γ cm^{-1}): 3126 (Ar-C-H),2905 (C-H),1675 (C=N),1559(C=C), 1220 **(**C-N),695 (C-S); ^{1}H NMR ($CDCl_3$, δ ppm): 1.52 (s,3H,-CH_3), 7.29-8.44 (m,11H,Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 14.8, 23.8, 116.1, 129.2, 165.9, 168.2; MS *m/z*: 279 $[M+H]^+$. Anal. Calcd for $C_{17}H_{14}N_2S$: C, 73.35; H, 5.07; N, 10.06. Found: C, 73.38; H, 5.09; N, 10.09%.

4,6-Diphenyl-2-propyl thiopyrimidine, 5h: Pale Yellow Solid,m.p.200-205ºC, Yield 45%. R_f 0.78 (EtOAc/MeOH-15:1, v/v); IR (KBr, γ cm^{-1}): 3099 (Ar-C-H), 2928 (C-H),1662 (C=N),1536(C=C), 1216 **(**C-N),698 (C-S); ^{1}H NMR ($CDCl_3$, δ ppm): 1.06(t,3H,-CH_3), 2.87 (q,4H,-CH_2), 6.98-8.24 (m,11H,Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 13.0, 21.6, 23.8, 38.9, 116.1, 129.2, 168.2, 171.1; MS *m/z*: 307 $[M+H]^+$. Anal. Calcd for $C_{19}H_{18}N_2S$: C, 74.47; H, 5.92; N, 9.14. Found: C, 74.51; H, 5.89; N, 9.16%.

4,6-Diphenyl-2-butyl thiopyrimidine, 5i: Yellow Solid, m.p.220-224ºC, Yield 28%. R_f 0.40 (EtOAc/MeOH-15:1, v/v); IR (KBr, γ cm^{-1}): 3092 (Ar-C-H), 2922 (C-H), 1615 (C=N),1529(C=C), 1225 **(**C-N),693 (C-S); ^{1}H NMR ($CDCl_3$, δ ppm): 0.86(t,3H,-CH_3), 2.85(m,6H,-CH_2), 7.16-7.99 (m,11H,Ar-H); ^{13}C NMR ($CDCl_3$, δ ppm): 13.4, 21.6, 23.8, 32.4, 36.4, 116.1, 129.2, 168.2, 171.1; MS *m/z*: 321 $[M+H]^+$. Anal. Calcd for $C_{20}H_{20}N_2S$: C, 74.96; H, 6.29; N, 8.74. Found: C, 74.98; H, 6.27; N, 8.71%.

Conclusion

The novel 4,6-diaryl-2-alkyl thiopyrimidine derivatives like **5b, 5d** and **5e** have revealed significant antibacterial activity against Gram positive and Gram negative species while compounds **5a**, **5c**, **5f-i** were moderately active as compared to the standard drug Ciprofloxacin.Compounds **5c** and **5g** exhibited good anti fungal activity amongst the series. However they were less potent than the standard drug Fluconazole. Thus keeping in view the antimicrobial potency of the diaryl alkyl thiopyrimidines, further research can be carried out on this scaffold.

Acknowledgment

The authors thank the Management and Principal, Vaagdevi College of Pharmacy, Hanamkonda for providing the necessary facilities and support.

References

1 Singh R & Chouhan A, *World J Pharm Sci*, 3 (2014) 574.
2 *Burger's Medicinal Chemistry and Drug Discovery*, Vol V, 6th edn. p.281, 537, 884.
3 Al-Masoudi N A, Abbas A & Al-Asadi M J B, *Z Naturforsch*, 70 (2015) 343.
4 Eweas A F, Abdallah Q & Hassan E S I, *J Appl Pharm Sci*, 4 (2014) 102.
5 Cacciari B, Crepaldi P, Cheng C Y, Bossi E, Spalluto G, Federico S, Jacobson K A & Cattaneo M, *J Med Chem*, 15 (2019) 863.
6 Stolarczyk M, Bryndal I, Matera-Witkiewicz A, Lis T, Królewska-Golińska K, Cieślak M, Kaźmierczak-Barańska J & Cieplik J, *Acta Cryst*, 74 (2018) 1138.
7 Lal K, Paliwal L J & Bagade M B, *Mater Today Proc*, 5 (2018) 15354.
8 Venkateshwarlu K, Malla Reddy V & Narsimha Reddy Y, *J Korean Chem Soc*, 57 (2013) 234.
9 Sirisha K, Achaiah G & Raghu Ram Rao A, *Indian J Pharm Sci*, 76 (2014) 519.
10 Rodrigues C R, Leal B, de Oliveira K N, Ferreira A S S R, Bernardino A, Nunes R J, Ferreirad V, de Souza M C, Cunhad A C & Castro H C, *J Syst Cybern Inf*, 11 (2013) 62.
11 Vogel H G, *Drug Discovery and Evaluation*, *Pharmacological Assays*, 2nd edn. p.725.
12 Funiss B S, Hannford A J, Smith P W G & Tatchell A R, *Vogel's Textbook of Practical Organic Chemistry*, 5th edn. p.1032.
13 Abdel-Megid M, Elmahdy K M & Rashad A E, *Global J Sci Fron Res Chem*, 13 (2013) 7.
14 Liu G, Xu J, Park K C, Chen N, Zhang S, Ding Z, Wang F & Du H, *Tetrahedron*, 67 (2011) 5156.