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METHOD DEVELOPMENT OF PERSUASIVE PYRIMIDINE DERIVATIVE HAVING ANTMICROBIAL ACTIVITY

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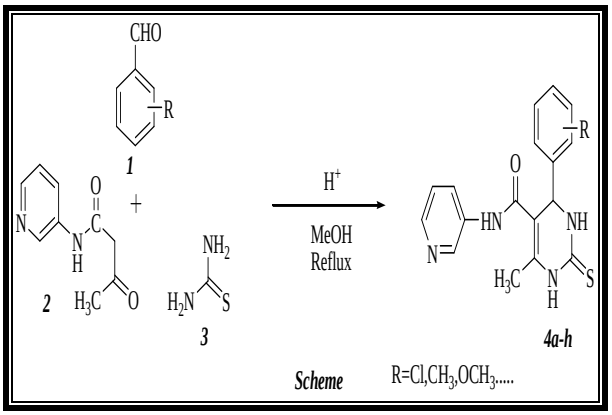
ABSTRACT
Synthesis of a series of ***1,2,3,4-tetrahydro-4-(substitutedphenyl)-6-methyl-N-(pyridin-3-yl)-2-thioxo pyrimidine-5-carboxamide (4a-h)*** was achieved from different Aldehydes, N-(pyridin-3-yl)-3-thioxo-butanamide and thiourea using catalytical amount of concentrated hydrochloric acid in ethanol the product obtained was isolated and recrystallized from ethanol. So to the fine yield. The structures of the products were supported by FTIR, ^{1}H NMR and mass spectral data.

KEYWORDS: N-(pyridin-3-yl)-3-thioxo-butanamide, Aldehyde, Hydrochloric acid and Thiourea only refluxed.

INTRODUCTION
Nitrogen containing heterocyclic ring such as pyrimidine is promising structural moiety for drug design. Pyrimidine derivative form a component in various useful drugs and are associated with many biological and therapeutically activities. Condensed pyrimidine have been reported as antimicrobial[1-3], anti-inflammatory[4,5], analgesic[6,7], anticancer[8-10] anti-Hiv[11], antitubrcular, antimalarial, diuretic and cardiovascular disease.[12]

The present work is synthesis, biological evaluation and validation of novel pyrimidine derivatives. Research worker have synthesized pyrimidine derivatives. Among them exhibited maximum antimicrobial. And some novel pyrazolo[3,4-d] pyrimidine derivatives[13], inventive synthesis of narrative cyano pyridines[14], 1,4-dihydropyrimido[1,2-a] benzimidazoles and evaluation of their biological activity[15], A One-pot microwave irradiation synthesis of Pyrimido[1,2-a] benzimidazoles[16], Fluoro Containing Pyrimidine Derivatives[17] synthesis 4-(2-chloro-6-fluorophenyl)-1,2,3,4-tetrahydro-6-isopropyl-N-phenyl)-2-thioxopyrimidine-5- carboxamide and this pyrimidine derivatives.[18]

We have urbanized a new etiquette for the synthesis 1,2,3,4-tetrahydro-4-(substitutedphenyl)-6-methyl-2-thioxo-N-(pyridin-3-yl)pyrimidine-5-carboxamide ***(4a-h)*** with the advantage of fine yield and environmentally easiness (**Scheme**).



EXPERIMENTAL
Typical experimental procedure
A mixture of N-(pyridin-3-yl)-3-thioxo-butanamide, appropriate aromatic aldehydes, thiourea and few drops of concentrated hydrochloric acid in ethanol was heated under reflux condition for 8 to10 hrs. The reaction mixture was kept at room temperature for 24 hrs. The product obtained was isolated and recrystallized from ethanol.

1,2,3,4-tetrahydro-6-methyl-2-thioxo-4-phenyl-N-(pyridin-3-yl)pyrimidine-5-carboxamide (4a)
Yield: 64%; mp 167-169ºC; IR (cm-1): 3290 (N-H stretching of primary amide), 3192 (N-H stretching of pyrimidine ring), 3099 (C-H symmetrical stretching of CH_3 group), 2874 (C-H asymmetrical stretching of CH_3 group), 1662 (C=O stretching of amide), 1589 (N-H

deformation of pyrimidine ring), 1523 and 1471 (C=C stretching of aromatic ring), 1433 (C-H asymmetrical deformation of CH_3 group), 1338 (C-N-C stretching of pyrimidine ring), 1290 (C-H symmetrical deformation of CH_3 group), 1242 (C-N stretching of pyrimidine ring), 1201 (C=S stretching), 1031 (C-H in plane deformation of aromatic ring), 758 and 721 (C-H out of plane deformation of mono substituted benzene ring); ^{1}H NMR (DMSO-d6) δ ppm: 2.50 (s, 3H, Ha), 5.43 (s, 1H, Hb), 7.24-7.38 (m, 6H, Hcc'-f), 7.96-7.98 (d, 1H, Hg, J = 8.0 Hz), 8.22-8.24 (d, 1H, Hh, J = 8.0 Hz), 8.70 (s, 1H, Hi,), 9.53 (s, 1H, Hj), 9.94 (s, 1H, Hk), 10.08 (s, 1H, Hl); MS: m/z 324; Anal. Calcd. for $C_{17}H_{16}N_4OS$: C, 62.94; H, 4.97; N, 17.27; O, 4.93; S, 9.88. Found: C, 62.85; H, 4.91; N, 17.20; O, 4.83; S, 9.80%.

1,2,3,4-tetrahydro-6-methyl-2-thioxo-N-(pyridin-3-yl)-4-p-tolylpyrimidine-5-carboxamide (4b)

Yield: 74%; mp 231-233ºC; IR (cm-1): 3271 (N-H stretching of secondary amide), 3036 (C-H symmetrical stretching of CH_3 group), 2924 (C-H asymmetrical stretching of CH_3 group), 1708 (C=O stretching of amide), 1629 (N-H deformation of pyrimidine ring), 1591 and 1512 (C=C stretching of aromatic ring), 1408 (C-H asymmetrical deformation of CH_3 group), 1338 (C-H symmetrical deformation of CH_3 group), 1263 (C-N-C stretching of pyrimidine ring), 1236 (C-N stretching of pyrimidine ring), 1149 (C=S stretching); ^{1}H NMR (DMSO-d6) δ ppm: 2.11 (s, 3H, Ha), 2.53-2.55 (s, 3H, Hb), 5.46-5.47 (s, 1H, Hc), 7.19-7.23 (m, 1H, Hd), 7.31 (s, 4H, He-f'), 7.62 (s, 1H, Hg), 7.97-8.00 (m, 1H, Hh), 8.18-8.20 (m, 1H, Hi), 8.70-8.71 (d, 1H, Hj, J = 4.0 Hz), 8.80 (s, 1H, Hk), 9.68 (s, 1H, Hl); MS: m/z 338; Anal. Calcd. for $C_{18}H_{18}N_4OS$: C, 63.88; H, 5.36; N, 16.56; O, 4.73; S, 9.47. Found: C, 63.80; H, 5.28; N, 16.50; O, 4.68; S, 9.40%.

1,2,3,4-tetrahydro-4-(4-methoxyphenyl)-6-methyl-2-thioxo-N-(pyridin-3-yl) pyrimidine-5-carboxamide (4c)

Yield: 70%; mp 181-183ºC; IR (cm-1): 3363 (N-H stretching of primary amide), 3319 (N-H stretching of pyrimidine ring), 3099 (C-H symmetrical stretching of CH_3 group), 2966 (C-H asymmetrical stretching of CH_3 group), 1672 (C=O stretching of amide), 1566 (N-H deformation of pyrimidine ring), 1516 and 1481 (C=C stretching of aromatic ring), 1415 (C-H asymmetrical deformation of CH_3 group), 1388 (C-H symmetrical deformation of CH_3 group), 1340 (C-N-C stretching of pyrimidine ring), 1280 (C-N stretching of pyrimidine ring), 1197 (Ph-O-C asymmetrical stretching of ether linkage), 1187 (C=S stretching), 1033 (Ph-O-C symmetrical stretching of ether linkage), 954 (C-H in plane deformation of aromatic ring), 804 (C-H out of plane deformation of 1,4-disubstitution); ^{1}H NMR (DMSO-d6) δ ppm: 2.15 (s, 3H, Ha), 3.74 (s, 1H, Hb), 5.45 (s, 1H, Hc), 6.83-6.85 (d, 2H, Hdd', J = 8.0 Hz), 7.19-7.25 (m, 3H, He-f), 7.99-8.01 (d, 1H, Hg, J = 8.0 Hz), 8.20-8.22 (d, 1H, Hh, J = 8.0 Hz), 8.70-8.71 (d, 1H, Hi, J = 4.0 Hz), 9.35 (s, 1H, Hj), 9.74 (s, 1H, Hk), 9.88 (s, 1H, Hl); MS: m/z 354; Anal. Calcd. for $C_{18}H_{18}N_4O_2S$: C, 61.00; H, 5.12; N, 15.81; O, 9.03; S, 9.05. Found: C, 60.00; H, 5.05; N, 15.73; O, 8.95; S, 9.00%.

4-(4-chlorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-thioxo-N-(pyridin-3-yl) pyrimidine-5-carboxamide (4d)

Yield: 72%; mp 216-218ºC; MS: m/z 358; IR (cm-1): 3375 (N-H stretching of primary amide), 3314 (N-H stretching of pyrimidine ring), 3099 (C-H symmetrical stretching of CH_3 group), 2963 (C-H asymmetrical stretching of CH_3 group), 1674 (C=O stretching of amide), 1563 (N-H deformation of pyrimidine ring), 1516 and 1485 (C=C stretching of aromatic ring), 1413 (C-H asymmetrical deformation of CH_3 group), 1380 (C-H symmetrical deformation of CH_3 group), 1343 (C-N-C stretching of pyrimidine ring), 1285 (C-N stretching of pyrimidine ring), 1197 (Ph-O-C asymmetrical stretching of ether linkage), 1181 (C=S stretching), 1031 (Ph-O-C symmetrical stretching of ether linkage), 954 (C-H in plane deformation of aromatic ring), 804 (C-H out of plane deformation of 1,4-disubstitution), 786 (C-Cl stretching); Anal. Calcd. for $C_{17}H_{15}ClN_4OS$: C, 56.90; H, 4.21; N, 15.61; O, 4.46; S, 8.94. Found: C, 56.79; H, 4.15; N, 15.55; O, 4.40; S, 8.88%.

4-(4-fluorophenyl)-1,2,3,4-tetrahydro-6-methyl-2-thioxo-N-(pyridin-3-yl)pyrimidine-5-carboxamide (4e)

Yield: 77%; mp 209-211ºC; IR (cm-1): 3263 (N-H stretching of secondary amide), 3044 (C-H symmetrical stretching of CH_3 group), 2920 (C-H asymmetrical stretching of CH_3 group), 1701(C=O stretching of amide), 1620 (N-H deformation of pyrimidine ring), 1576 and 1505 (C=C stretching of aromatic ring), 1413 (C-H asymmetrical deformation of CH_3 group), 1346 (C-H symmetrical deformation of CH_3 group), 1260 (C-N-C stretching of pyrimidine ring), 1213 (C-N stretching of pyrimidine ring), 1159 (C=S stretching), 1025 (C-F stretching); MS: m/z 342; Anal. Calcd. for $C_{17}H_{15}FN_4OS$: C, 59.63; H, 4.42; N, 16.36; O, 4.67; S, 9.37. Found: C, 59.57; H, 4.36; N, 16.28; O, 4.62; S, 9.30%.

1,2,3,4-tetrahydro-6-methyl-4-(4-nitrophenyl)-2-thioxo-N-(pyridin-3-yl) pyrimidine-5-carboxamide (4f)

Yield: 65%; mp 236-238ºC; IR (cm-1): 3277 (N-H stretching of secondary amide), 3038 (C-H symmetrical stretching of CH_3 group), 2922 (C-H asymmetrical stretching of CH_3 group), 1715 (C=O stretching of amide), 1620 (N-H deformation of pyrimidine ring), 1583 (C-NO_2 symmetrical stretching), 1516 (C=C stretching of aromatic ring), 1463 (C-H asymmetrical deformation of CH_3 group), 1335 (C-H symmetrical deformation of CH_3 group), 1260 (C-N-C stretching of pyrimidine ring), 1214 (C-N stretching of pyrimidine ring), 1163 (C=S stretching); MS: m/z 369; Anal. Calcd. for $C_{17}H_{15}N_5O_3S$: C, 55.27; H, 4.09; N, 18.96; O, 12.99; S, 8.68. Found: C, 55.20; H, 4.00; N, 18.90; O, 12.90; S, 8.60%.

1,2,3,4-tetrahydro-6-methyl-4-(3-nitrophenyl)-2-thioxo-N-(pyridin-3-yl) pyrimidine-5-carboxamide (4g)
Yield: 63%; mp 229-231ºC; IR (cm-1): 3333 (N-H stretching of secondary amide), 3163 (C-H symmetrical stretching of CH_3 group), 2926 (C-H asymmetrical stretching of CH_3 group), 1705 (C=O stretching of amide), 1634 (N-H deformation of pyrimidine ring), 1575 (C-NO_2 symmetrical stretching), 1531 (C=C stretching of aromatic ring), 1443 (C-H asymmetrical deformation of CH_3 group), 1315 (C-H symmetrical deformation of CH_3 group), 1263 (C-N-C stretching of pyrimidine ring), 1224 (C-N stretching of pyrimidine ring), 1160 (C=S stretching); MS: m/z 369; Anal. Calcd. for $C_{17}H_{15}N_5O_3S$: C, 55.27; H, 4.09; N, 18.96; O, 12.99; S, 8.68. Found: C, 55.19; H, 3.98; N, 18.88; O, 12.91; S, 8.59%.

1,2,3,4-tetrahydro-6-methyl-4-(2-nitrophenyl)-2-thioxo-N-(pyridin-3-yl) pyrimidine-5-carboxamide (4h)
Yield: 68%; mp 234-236ºC; IR (cm-1): 3349 (N-H stretching of secondary amide), 3146 (C-H symmetrical stretching of CH_3 group), 2944 (C-H asymmetrical stretching of CH_3 group), 1746 (C=O stretching of amide), 1676 (N-H deformation of pyrimidine ring), 1574 (C-NO_2 symmetrical stretching), 1534 (C=C stretching of aromatic ring), 1475 (C-H asymmetrical deformation of CH_3 group), 1346 (C-H symmetrical deformation of CH_3 group), 1260 (C-N-C stretching of pyrimidine ring), 1234 (C-N stretching of pyrimidine ring), 1137 (C=S stretching); MS: m/z 369; Anal. Calcd. for $C_{17}H_{15}N_5O_3S$: C, 55.27; H, 4.09; N, 18.96; O, 12.99; S, 8.68. Found: C, 55.17; H, 3.96; N, 18.89; O, 12.91; S, 8.58%.

CONCLUSION

In pinnacle, we contain synthesized of imaginative pyrimidine derivatives using unproblematic and appropriate method. This method produces these products in first-class yields and trouble-free workup. Product is isolated by easy filtration. The isolated products are very pure and do not need any column purification. This study opens up a new area of beneficial synthesis of potentially biologically active narrative pyrimidine derivatives compounds.

Biological activity

All of the synthesized compounds () were tested for their antibacterial and antifungal activity (MIC) in vitro by broth dilution method[19-21] with two Gram-positive bacteria Staphylococcus aureus MTCC-96, Streptococcus pyogenes MTCC 443, two Gram-negative bacteria Escherichia coli MTCC 442, Pseudomonas aeruginosa MTCC 441 and three fungal strains Candida albicans MTCC 227, Aspergillus Niger MTCC 282, Aspergillus clavatus MTCC 1323 taking gentamycin, ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin and greseofulvin as standard drugs. The standard strains were procured from the Microbial Type Culture Collection (MTCC), Institute of Microbial Technology, Chandigarh, India. The results are summarized in Table.

Table: Antimicrobial activity of pyrimidine derivatives 4a–j.

Code No.	Minimal inhibition concentration (µg mL^{-1})						
	Gram-positive		Gram-negative		Fungal species		
	S.a.	***S. p.***	***E.c.***	***P.a.***	***C. a.***	***A. n.***	***A.c.***
4a	150	200	250	250	1000	500	500
4b	100	250	200	200	500	>1000	>1000
4c	150	150	62.5	100	>1000	>1000	>1000
4d	250	250	100	100	1000	500	1000
4e	200	200	100	100	>1000	>1000	>1000
4f	500	500	62.5	200	>1000	1000	1000
4g	250	500	250	250	500	1000	1000
4h	500	500	200	200	1000	500	1000

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