

Synthesis and characterization of fully substituted pyrimidines by using ketene dithioacetal as potent antimicrobial agent

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ABSTRACT

Various ketene dithioacetals of acetoacetanilides were reacted with guanidine nitrate in the presence of base to produce the 2-amino-4-isopropyl-6-alkoxy-*N*-arylpyrimidine-5-carboxamide derivatives with good yields. All the synthesized compounds were characterized by mass, NMR and IR and also evaluated for antimicrobial activity against five different bacterial and fungal strains. The compounds 4i, 4k and 4l has found comparatively good active against all the bacterial strains.

Keywords: Ketene dithioacetal; Pyrimidines; Guanidine; Biginelli reaction

1. INTRODUCTION

From the beginning of pharmaceutical research nitrogen containing heterocyclic compounds have been considered as the privileged structure because of the different biological property and its tremendous applications e.g., anticancer, diuretic, anticonvulsant, anti-inflammatory and antihypertensive activities [1]. Particularly pyridine nucleus which is the important constructive part of many natural products and used as antimalarial [2], antitoxoplasma [3], fungicidal [4], antibacterial [5], anti-inflammatory and antitumor agent [6]. The Biginelli reaction [7] has been reported for the synthesis of many pyrimidine derivatives by the one-pot condensation of active methylene, urea and aldehydes. There are some other methods are also reported with some little modification in Biginelli reaction by the condensation of aldehydes, urea and arylketones in acetic acid using a catalytic amount of KHSO₄ [8], in basic condition [9] and by microwave irradiation [10]. Now a days of literature have been reported for the synthesis of thiophene, furan, isooxazole, pyrazole, pyridine and pyrimidine etc. heterocycles by using dithioacetal in place of aldehyde [11,12]. Thus, above literature promote us to synthesize novel pyrimidine analogues using ketene dithioacetal and their biological screening.

2. RESULT AND DISCUSSION

In our current research variety of acetoacetanilides 2a-t were prepared from methyl 4-methyl-3-oxopentanoate (Scheme 1). These acetoacetanilides on reaction with CS₂ and methyl iodide in presence of potassium carbonate produce ketene dithioacetal 3a-t (Scheme 2) on active methylene. These dithioacetals behave as a precursor of aldehyde, which on reaction with guanidine nitrate in presence of sodium methoxide or sodium ethoxide lead to the formation of fully substituted pyrimidine 4a-t (Scheme 2). Here base replaces one thiomethoxy group and after cyclization methoxy or ethoxy group is introduced at the position of thiomethoxy group. Various ketenedithioacetal was used for the synthesis of pyrimidine, is listed in Table 1.

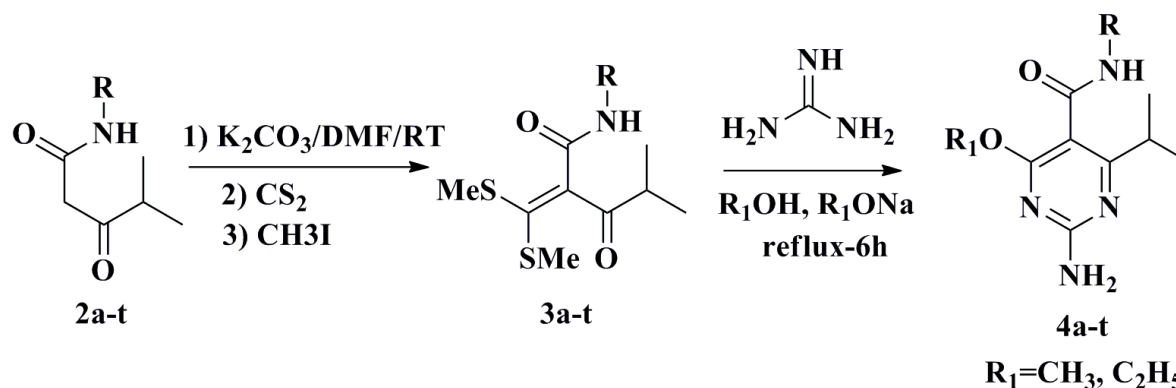
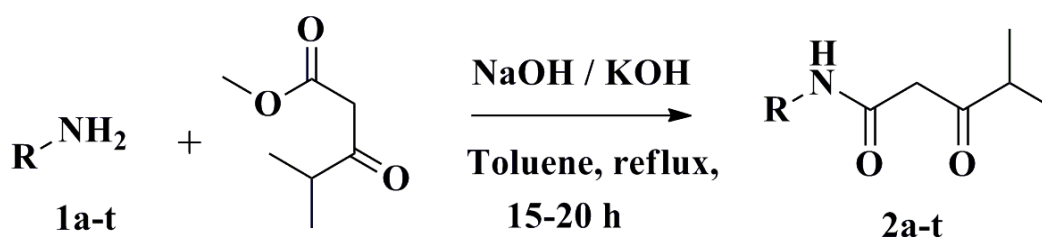


Table 1. Various ketene dithioacetal used for the synthesis of pyrimidines.

Entry	Code	R	R ₁	Yield (%)	Time (h)
1	4a	4-BrC ₆ H ₄	C ₂ H ₅	92	6.0
2	4b	4-OCH ₃ C ₆ H ₄	CH ₃	91	6.0
3	4c	C ₆ H ₅	CH ₃	84	5.7
4	4d	C ₆ H ₁₁	C ₂ H ₅	90	5.0
5	4e	2,5-di-CH ₃ C ₆ H ₃	CH ₃	86	5.5
6	4f	C ₆ H ₁₁	CH ₃	92	5.6
7	4g	4-FC ₆ H ₄	CH ₃	90	6.0
8	4h	4-ClC ₆ H ₄	C ₂ H ₅	86	5.8

9	4i	3-Cl,4-FC ₆ H ₃	CH ₃	93	5.5
10	4j	3,4-di-FC ₆ H ₃	CH ₃	91	6.0
11	4k	3-ClC ₆ H ₄	CH ₃	88	5.4
12	4l	3,4-di-ClC ₆ H ₃	CH ₃	92	5.7
13	4m	4-CH ₃ C ₆ H ₄	CH ₃	90	5.6
14	4n	2-CH ₃ C ₆ H ₄	CH ₃	87	5.8
15	4o	2-OCH ₃ C ₆ H ₄	CH ₃	85	5.5
16	4p	2-FC ₆ H ₄	CH ₃	93	6.0
17	4q	2-BrC ₆ H ₄	CH ₃	90	5.6
18	4r	C ₆ H ₅	C ₂ H ₅	89	6.0
19	4s	4-ClC ₆ H ₄	CH ₃	85	5.7
20	4t	3-ClC ₆ H ₄	C ₂ H ₅	92	5.4

2. 1. Experimental

Thin-layer chromatography was accomplished on 0.2-mm precoated plates of silica gel G60 F₂₅₄ (Merck). Visualization was made with UV light (254 and 365 nm). IR spectra were recorded on a FT-IR-8400 spectrophotometer using DRS prob. ¹H (400 MHz) and ¹³C (100 MHz) NMR spectra were recorded on a Bruker AVANCE II spectrometer in CDCl₃. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Melting points were measured in open capillaries and are uncorrected.

2. 1. 1. General procedure for the synthesis of substituted isopropylacetanilide(2a-t)

A mixture containing the primary amine (10 mmol), methyl isobutyrylacetate (10 mmol) and catalytic amount of sodium or potassium hydroxide (10 %) was reflux at 110 °C for the approximately 15-20 h. The reaction was monitored by TLC. After completion of reaction, the solvent was removed under vacuum. The solid or oil was crystallized from methanol to give pure product 2a-t.

2. 1. 2. General procedure for the synthesis of ketene dithioacetals (3a-t)

A mixture of 4-methyl-3-oxo-*N*-arylpentanamide 2a-t, (10 mmol) and dried K₂CO₃ (10 mmol) in DMF was stirred for 2 h at room temperature. Then CS₂ (30 mmol) was added and the mixture was stirred for an additional 2 h at room temperature. Methyl iodide (20 mmol) was added at 0-5 °C and reaction mixture was stirred again for 4 h at RT. After completion of reaction, reaction mixture was poured in to cold water (40 mL). The precipitated crude product was filtered and crystallized in EtOH.

2. 1. 3. General procedure for the synthesis of 2-amino-4,6-disubstituted pyrimidine-5-carboxamide derivatives (4a-t)

Ketene dithioacetals 3a-t (10 mmol) was added in the mixture of guanidine nitrate (10 mmol) and sodium methoxide or sodium ethoxide (20 mmol) in methanol or ethanol within 10-15 min. The resulting reaction mixtures was further stirred at room temperature for 15 min then refluxed for 6h. After completion of the reaction, the mixture was poured in to cold water. Precipitated solid was filtered, wash with water, dried and crystallization from EtOH to afford analytically pure products 4a-t.

2. 1. 4. Spectroscopic data for the compounds 4a-t**2-Amino-N-(4-bromophenyl)-4-ethoxy-6-isopropylpyrimidine-5-carboxamide(4a):**

white solid, mp 185-187°C; IR (KBr): 3459, 3327, 3193, 2999, 1648, 1586, 1261, 1061 cm⁻¹; ¹H NMR: δ 1.18-1.20 (d, 6H, 2 x ¹prCH₃), 1.29-1.33 (t, 3H, CH₃), 3.07-3.13 (m, 1H, ¹prCH), 4.32-4.37 (q, 2H, CH₂), 5.86 (s, 2H, NH₂), 7.38-7.40 (d, 2H, Ar-H, *j*=8.8Hz), 7.63-7.65 (d, 2H, Ar-H, *j*=8.8Hz), 9.97 (br, s, 1H, -CONH); MS (*m/z*): 379 (M⁺); Anal. Calcd for C₁₆H₁₉BrN₄O₂: C, 50.67; H, 5.05; N, 14.77; Found: C, 50.48; H, 5.15; N, 14.52.

2-Amino-4-isopropyl-6-methoxy-N-(4-methoxyphenyl)pyrimidine-5-carboxamide(4b):

Yellow solid; mp 180-184°C; IR (KBr): 3452, 3307, 3223, 2980, 1653, 1509, 1461, 1051 cm⁻¹; ¹H NMR: δ 1.19-1.25 (d, 6H, 2 x ¹prCH₃), 3.07-3.13 (m, 1H, ¹prCH), 3.78 (s, 3H, OCH₃), 3.82 (s, 3H, OCH₃), 5.69 (s, 2H, NH₂), 6.82-6.85 (d, 2H, Ar-H, *j*=8.8Hz), 7.60-7.62 (d, 2H, Ar-H, *j*=8.8Hz), 9.58 (s, 1H, CONH); MS (*m/z*): 316 (M⁺); Anal. Calcd for C₁₆H₂₀N₄O₃: C, 60.75; H, 6.37; N, 17.71; Found: C, 60.48; H, 6.15; N, 17.52.

2-Amino-4-isopropyl-6-methoxy-N-phenylpyrimidine-5-carboxamide (4c):

Yellow solid; mp 210-212°C; IR (KBr): 3412, 3317, 3253, 2950, 1613, 15039, 1431, 1041 cm⁻¹; ¹H NMR: δ 1.19-1.25 (d, 6H, 2 x ¹prCH₃), 3.07-3.13 (m, 1H, ¹prCH), 3.82 (s, 3H, OCH₃), 5.69 (s, 2H, NH₂), 9.58 (s, 1H, CONH), 6.60-6.62 (d, 2H, Ar-H, *j*=8.8Hz), 7.10-7.13 (m, 2H, Ar-H), 6.40-6.43 (m, 1H, Ar-H); MS (*m/z*): 286 (M⁺); Anal. Calcd for C₁₅H₁₈N₄O₂: C, 60.92; H, 6.34; N, 19.57; Found: C, 60.48; H, 6.15; N, 19.32.

2-Amino-N-cyclohexyl-4-ethoxy-6-isopropylpyrimidine-5-carboxamide (4d):

white solid; mp 196-198°C; IR (KBr): 3429, 3307, 3123, 2959, 1658, 1546, 1265, 1041 cm⁻¹; ¹H NMR: δ 1.19-1.20 (d, 6H, 2 x ¹prCH₃), 1.22-1.25 (t, 3H, CH₃), 1.28-1.93 (m, 10H, 5 x CH₂), 3.07-3.14 (m, 1H, ¹prCH), 3.79-3.86 (m, 1H, CH), 4.26-4.31 (q, 2H, CH₂), 5.73 (s, 2H, NH₂), 7.21 (s, 1H, CONH); MS (*m/z*): 306 (M⁺); Anal. Calcd for C₁₆H₂₆N₄O₂: C, 62.72; H, 8.55; N, 18.29; Found: C, 62.38; H, 8.10; N, 18.

2-Amino-4-isopropyl-6-methoxy-N-(2,5-dimethylphenyl)pyrimidine-5-carboxamide(4e):

yellow solid; mp 186-188°C; IR (KBr): 3420, 3341, 32631, 2930, 1610, 1553, 1411, 1060 cm⁻¹; ¹H NMR: δ 1.19-1.25 (d, 6H, 2 x ¹prCH₃), 3.07-3.13 (m, 1H, ¹prCH), 3.82 (s, 3H, OCH₃), 5.69 (s, 2H, NH₂), 9.58 (s, 1H, CONH), 6.62 (s, 1H, Ar-H), 6.90-6.92 (d, 1H, Ar-H, *j*=8.8Hz), 6.72-6.74 (d, 1H, Ar-H, *j*=8.8Hz), 2.34 (s, 3H, CH₃), 2.32 (s, 3H, CH₃); MS (*m/z*): 314 (M⁺); Anal. Calcd for C₁₇H₂₂N₄O₂: C, 64.58; H, 7.05; N, 17.82; Found: C, 64.48; H, 7.15; N, 17.62.

2-Amino-N-cyclohexyl-4-isopropyl-6-methoxypyrimidine-5-carboxamide(4f):

yellow solid; mp 190-192°C; IR (KBr): 3462, 3307, 3223, 2990, 1653, 1509, 1461, 1061 cm⁻¹; ¹³C NMR: δ 21.20, 24.42, 25.02, 31.60, 32.16, 38.90-40.16, 47.97, 53.01, 106.73, 161.89, 164.94, 166.47, 173.41. ¹H NMR: δ 1.19-1.25 (d, 6H, 2 x ¹prCH₃), 3.07-3.13 (m, 1H, ¹prCH), 3.82 (s, 3H, OCH₃), 5.69 (s, 2H, NH₂), 9.58 (s, 1H, CONH), 1.28-1.93 (m, 10H, 5 x CH₂), 3.79-3.86 (m, 1H, CH); MS (*m/z*): 292 (M⁺); Anal. Calcd for C₁₅H₂₄N₄O₂: C, 61.62; H, 8.27; N, 19.16; Found: C, 61.58; H, 8.15; N, 19.12.

2-Amino-N-(4-fluorophenyl)-4-isopropyl-6-methoxypyrimidine-5-carboxamide(4g):

Yellow solid; mp 180-182°C; IR (KBr): 3459, 3327, 3173, 2989, 1648, 1586, 1261, 1061 cm⁻¹; ¹H NMR: δ 1.19-1.25 (d, 6H, 2 x ¹prCH₃), 3.07-3.13 (m, 1H, ¹prCH), 3.82 (s, 3H, OCH₃), 5.69 (s, 2H, NH₂), 9.58 (s, 1H, CONH), 7.38-7.40 (d, 2H, Ar-H, *j*=8.8Hz) 7.63-7.65 (d, 2H,

Ar-H, $j=8.8\text{Hz}$); MS (m/z): 304 (M^+); Anal. Calcd for $C_{15}H_{17}FN_4O_2$: C, 59.20; H, 5.63; N, 18.41; Found: C, 59.13; H, 5.45; N, 18.52.

2-Amino-*N*-(4-chlorophenyl)-4-ethoxy-6-isopropylpyrimidine-5-carboxamide (4h):

white solid; mp 194-196°C; IR (KBr): 3449, 3331, 3182, 3055, 2952, 1651, 1568, 1491, 1247, 1049 cm^{-1} ; ^1H NMR: δ 1.17-1.94 (d, 6H, 2 x $^1\text{prCH}_3$), 1.28-1.31 (t, 3H, CH_3), 3.05-3.09 (m, 1H, $^1\text{prCH}$), 4.31-4.36 (q, 2H, CH_2), 6.09 (s, 2H, NH_2), 7.24-7.26 (d, 2H, Ar-H, $j=8.8\text{Hz}$), 7.68-7.70 (d, 2H, Ar-H, $j=8.8\text{Hz}$), 10.07 (s, 1H, CONH); MS (m/z): 334 (M^+); Anal. Calcd for $C_{16}H_{19}ClN_4O_2$: C, 57.40; H, 5.72; N, 16.73; Found: C, 57.41; H, 5.55; N, 16.63.

2-Amino-*N*-(3-chloro-4-fluorophenyl)-4-isopropyl-6-methoxypyrimidine-5-carboxamide

(4i): Yellow solid; mp 185-187°C; IR (KBr): 3443, 3325, 3153, 2989, 1648, 1506, 1251, 1064 cm^{-1} ; ^1H NMR: δ 1.19-1.25 (d, 6H, 2 x $^1\text{prCH}_3$), 3.07-3.13 (m, 1H, $^1\text{prCH}$), 3.82 (s, 3H, OCH_3), 5.69 (s, 2H, NH_2), 9.58 (s, 1H, CONH), 7.80 (s, 1H, Ar-H), 7.10-7.12 (d, 1H, Ar-H, $j=8.8\text{Hz}$), 7.24-7.26 (d, 1H, Ar-H, $j=8.8\text{Hz}$); MS (m/z): 338 (M^+); Anal. Calcd for $C_{15}H_{16}ClFN_4O_2$: C, 53.18; H, 4.76; N, 16.54; Found: C, 53.13; H, 4.65; N, 16.52.

2-Amino-*N*-(3,4-di-fluorophenyl)-4-isopropyl-6-methoxypyrimidine-5-carboxamide (4j):

Yellow solid; mp 245-247°C; IR (KBr): 3442, 3226, 3143, 2986, 1642, 1566, 1241, 1061 cm^{-1} ; ^1H NMR: δ 1.19-1.25 (d, 6H, 2 x $^1\text{prCH}_3$), 3.07-3.13 (m, 1H, $^1\text{prCH}$), 3.82 (s, 3H, OCH_3), 5.69 (s, 2H, NH_2), 9.58 (s, 1H, CONH), 7.90 (s, 1H, Ar-H), 7.16-7.18 (d, 1H, Ar-H, $j=8.8\text{Hz}$), 7.26-7.28 (d, 1H, Ar-H, $j=8.8\text{Hz}$); MS (m/z): 322 (M^+); Anal. Calcd for $C_{15}H_{16}F_2N_4O_2$: C, 55.90; H, 5.00; N, 17.38; Found: C, 55.73; H, 4.94; N, 17.32.

2-Amino-*N*-(3-chlorophenyl)-4-isopropyl-6-methoxypyrimidine-5-carboxamide (4k):

Yellow solid; mp 256-258°C; IR (KBr): 3459, 3252, 3143, 2919, 1648, 1586, 1241, 1051 cm^{-1} ; ^1H NMR: δ 1.19-1.25 (d, 6H, 2 x $^1\text{prCH}_3$), 3.07-3.13 (m, 1H, $^1\text{prCH}$), 3.82 (s, 3H, OCH_3), 5.69 (s, 2H, NH_2), 9.58 (s, 1H, CONH), 7.92 (s, 1H, Ar-H), 7.60-7.62 (d, 1H, Ar-H, $j=8.8\text{Hz}$), 7.51-7.53 (d, 1H, Ar-H, $j=8.8\text{Hz}$), 7.42-7.45 (m, 1H, Ar-H); MS (m/z): 320 (M^+); Anal. Calcd for $C_{15}H_{17}ClN_4O_2$: C, 56.16; H, 5.34; N, 17.47; Found: C, 56.23; H, 5.25; N, 17.52.

2-Amino-*N*-(3,4-di-chlorophenyl)-4-isopropyl-6-methoxypyrimidine-5-carboxamide (4l):

Yellow solid; mp 240-242°C; IR (KBr): 3420, 3226, 3143, 2988, 1632, 1546, 1231, 1061 cm^{-1} ; ^1H NMR: δ 1.19-1.25 (d, 6H, 2 x $^1\text{prCH}_3$), 3.07-3.10 (m, 1H, $^1\text{prCH}$), 3.82 (s, 3H, OCH_3), 5.69 (s, 2H, NH_2), 9.58 (s, 1H, CONH), 7.93 (s, 1H, Ar-H), 7.16-7.18 (d, 1H, Ar-H, $j=8.8\text{Hz}$), 7.28-7.30 (d, 1H, Ar-H, $j=8.8\text{Hz}$); MS (m/z): 354 (M^+); Anal. Calcd for $C_{15}H_{16}Cl_2N_4O_2$: C, 50.72; H, 4.54; N, 15.77; Found: C, 55.73; H, 4.64; N, 15.62.

2-Amino-4-isopropyl-6-methoxy-*N-p*-tolylpyrimidine-5-carboxamide (4m):

Yellow solid; mp 194-196°C; IR (KBr): 3412, 3317, 3253, 2950, 1613, 1539, 1431, 1061 cm^{-1} ; ^1H NMR: δ 1.19-1.25 (d, 6H, 2 x $^1\text{prCH}_3$), 3.07-3.13 (m, 4H, $^1\text{prCH}$), 3.78 (s, 3H, OCH_3), 2.62 (s, 3H, CH_3), 5.69 (s, 2H, NH_2), 6.83-6.85 (d, 1H, Ar-H, $j=8.8\text{Hz}$), 7.60-7.62 (d, 1H, Ar-H, $j=8.8\text{Hz}$), 9.58 (s, 1H, CONH); MS (m/z): 300 (M^+); Anal. Calcd for $C_{16}H_{20}N_4O_2$: C, 63.98; H, 6.71; N, 18.65; Found: C, 63.88; H, 6.65; N, 18.52.

2-Amino-4-isopropyl-6-methoxy-*N-o*-tolylpyrimidine-5-carboxamide (4n):

Yellow solid; mp 185-187°C; IR (KBr): 3442, 3327, 3253, 2980, 1623, 1569, 1431, 1051 cm^{-1} ; ^1H NMR: δ 1.19-1.25 (d, 6H, 2 x $^1\text{prCH}_3$), 3.07-3.13 (m, 1H, $^1\text{prCH}$), 3.78 (s, 3H, OCH_3), 2.52 (s, 3H, Ar- CH_3), 5.69 (s, 2H, NH_2), 7.22-7.24 (d, 1H, Ar-H, $j=8.8\text{Hz}$), 7.78-7.80 (d, 1H, Ar-

H, $j=8.8\text{Hz}$), 7.51-7.54(m, 1H, Ar-H), 7.57-7.60(m, 1H, Ar-H) MS (m/z): 300 (M^+); Anal. Calcd for $C_{16}H_{20}N_4O_2$: C, 63.98; H, 6.71; N, 18.65; Found: C, 63.88; H, 6.65; N, 18.52.

2-Amino-4-isopropyl-6-methoxy-*N*-(2-methoxyphenyl)pyrimidine-5-carboxamide (4o):
Yellow solid; mp 165-167°C; IR (KBr): 3462, 3327, 3220, 2980, 1623, 1509, 1461, 1051 cm^{-1} ; 9.58 (s, 1H, CONH); ^1H NMR: δ 1.19-1.25 (d, 6H, 2 x $^i\text{prCH}_3$), 3.07-3.13 (m, 1H, $^i\text{prCH}_2$), 3.78 (s, 3H, OCH₃), 3.82 (s, 3H, OCH₃), 5.69 (s, 2H, NH₂), 3.80 (s, 3H, OCH₃) 7.72-7.74 (d, 1H, Ar-H, $j=8.8\text{Hz}$), 7.10-7.12 (d, 1H, Ar-H, $j=8.8\text{Hz}$), 7.55-7.60 (m, 1H, Ar-H), 7.62-7.64 (m, 1H, Ar-H); MS (m/z): 316 (M^+); Anal. Calcd for $C_{16}H_{20}N_4O_3$: C, 60.75; H, 6.37; N, 17.71; Found: C, 60.68; H, 6.55; N, 17.62.

2-Amino-*N*-(2-fluorophenyl)-4-isopropyl-6-methoxypyrimidine-5-carboxamide (4p):

Yellow solid; mp 178-180°C; IR (KBr): 3442, 3327, 3173, 2989, 1653, 1586, 1261, 1061 cm^{-1} ; ^1H NMR: δ 1.19-1.25 (d, 6H, 2 x $^i\text{prCH}_3$), 3.07-3.13 (m, 1H, $^i\text{prCH}_2$), 3.82 (s, 3H, OCH₃), 5.69 (s, 2H, NH₂), 9.58 (s, 1H, CONH), 7.12-7.14 (d, 1H, Ar-H, $j=8.8\text{Hz}$), 7.71-7.73 (d, 1H, Ar-H, $j=8.8\text{Hz}$), 7.57-7.60 (m, 1H, Ar-H), 7.62-7.65 (m, 1H, Ar-H); MS (m/z): 304 (M^+); Anal. Calcd for $C_{15}H_{17}FN_4O_2$: C, 59.20; H, 5.63; N, 18.41; Found: C, 59.16; H, 5.55; N, 18.32.

2-Amino-*N*-(2-bromophenyl)-4-isopropyl-6-methoxypyrimidine-5-carboxamide (4q):

Yellow solid; mp 190-192°C; IR (KBr): 3459, 3327, 3173, 2989, 1648, 1586, 1261, 1061 cm^{-1} ; ^1H NMR: δ 1.19-1.25 (d, 6H, 2 x $^i\text{prCH}_3$), 3.07-3.13 (m, 1H, $^i\text{prCH}_2$), 3.82 (s, 3H, OCH₃), 5.69 (s, 2H, NH₂), 9.58 (s, 1H, CONH), 7.15-7.17 (d, 1H, Ar-H, $j=8.8\text{Hz}$), 7.80-7.82 (d, 1H, Ar-H, $j=8.8\text{Hz}$), 7.55-7.57 (m, 1H, Ar-H), 7.60-7.63 (m, 1H, Ar-H); MS (m/z): 364 (M^+); Anal. Calcd for $C_{15}H_{17}BrN_4O_2$: C, 49.33; H, 4.69; N, 15.34; Found: C, 49.13; H, 4.45; N, 15.22.

2-Amino-4-ethoxy-6-isopropyl-*N*-phenyl pyrimidine-5-carboxamide (4r):

white solid; mp 198-200°C; IR (KBr): 3459, 3327, 3193, 2999, 1648, 1586, 1261, 1061 cm^{-1} ; ^1H NMR: δ 1.19-1.25 (d, 6H, 2 x $^i\text{prCH}_3$), 3.07-3.13 (m, 1H, $^i\text{prCH}_2$), 5.69 (s, 2H, NH₂), 9.58 (s, 1H, CONH), 1.29-1.33 (t, 3H, CH₃), 4.32-4.37 (q, 2H, CH₂), 6.60-6.62 (d, 2H, Ar-H, $j=8.8\text{Hz}$), 7.10-7.13 (m, 2H, Ar-H), 6.40-6.43 (m, 1H, Ar-H); MS (m/z): 300 (M^+); Anal. Calcd for $C_{16}H_{20}N_4O_2$: C, 63.98; H, 6.71; N, 18.65; Found: C, 63.92; H, 6.65; N, 18.56.

2-Amino-*N*-(4-chlorophenyl)-4-isopropyl-6-methoxypyrimidine-5-carboxamide(4s):

Yellow solid; mp 185-187°C; IR (KBr): 3459, 3252, 3143, 2919, 1648, 1586, 1241, 1051 cm^{-1} ; ^1H NMR: δ 1.19-1.25 (d, 6H, 2 x $^i\text{prCH}_3$), 3.07-3.13 (m, 1H, $^i\text{prCH}_2$), 3.82 (s, 3H, OCH₃), 5.69 (s, 2H, NH₂), 9.58 (s, 1H, CONH), 7.24-7.26 (d, 2H, Ar-H, $j=8.8\text{Hz}$), 7.68-7.70 (d, 2H, Ar-H, $j=8.8\text{Hz}$); MS (m/z): 320 (M^+); Anal. Calcd for $C_{15}H_{17}ClN_4O_2$: C, 56.16; H, 5.34; N, 17.47; Found: C, 56.20; H, 5.25; N, 17.42.

2-Amino-*N*-(3-chlorophenyl)-4-ethoxy-6-isopropylpyrimidine-5-carboxamide (4t):

white solid; mp 210-212°C; IR (KBr): 3449, 3227, 3193, 2966, 1628, 1522, 1217, 1041 cm^{-1} ; ^1H NMR: δ 1.19-1.25 (d, 6H, 2 x $^i\text{prCH}_3$), 3.07-3.13 (m, 1H, $^i\text{prCH}_2$), 5.69 (s, 2H, NH₂), 9.58 (s, 1H, CONH), 1.29-1.33 (t, 3H, CH₃), 4.32-4.37 (q, 2H, CH₂), 7.92 (s, 1H, Ar-H), 7.60-7.62 (d, 1H, Ar-H, $j=8.8\text{Hz}$), 7.51-7.53 (d, 1H, Ar-H, $j=8.8\text{Hz}$), 7.42-7.45 (m, 1H, Ar-H); MS (m/z): 334 (M^+); Anal. Calcd for $C_{16}H_{19}ClN_4O_2$: C, 57.40; H, 5.72; N, 16.73; Found: C, 57.44; H, 5.65; N, 16.67.

3. ANTIMICROBIAL SCREENING OF SYNTHESIZED PYRIMIDINES

All the synthesized compounds were tested against different bacterial and fungal strains i.e. *Pseudomonas aeruginosa*, *Proteus vulgaris*, *Escherichia Coli*, *Staphylococcus aureus*, *Candida albicans* for their in vitro antibacterial activity. Well Diffusion/Agar Cup Method was used and results are listed in Table 2. The investigation of antibacterial and antifungal screening data revealed that all the tested compounds 4a-t showed moderate to potent activity. The compounds 4i, 4k and 4l showed comparatively good activity against all the bacterial strains.

Table 2. Antibiotic Sensitivity Assay (Concentration 250/500/ 1000 μ G/mL).

Code No.	<i>Pseudomonas aeruginosa</i>			<i>Proteus vulgaris</i>			<i>Escherichia coli</i>			<i>Staphylococcus aureus</i>			<i>Candida albicans</i>		
	250	500	1000	250	500	1000	250	500	1000	250	500	1000	250	500	1000
4a	R	1.1	1.2	R	1.1	1.3	R	R	R	R	R	R	R	1	1.2
4b	1.2	1.4	2	1.1	1.3	1.6	R	R	R	R	1	1.2	R	1.2	1.5
4c	1.2	1.3	1.7	1.1	1.4	1.6	R	R	R	1.2	1.3	1.6	1	1.3	1.8
4d	1.1	1.3	1.5	R	1.1	1.4	1.1	1.2	1.3	R	1	1.2	1.1	1.5	2
4e	1.1	1.2	1.4	1	1.3	1.6	R	R	R	1.3	1.4	1.6	1.1	1.4	1.8
4f	1.2	1.3	1.6	R	1.2	1.4	R	R	R	1.2	1.4	1.6	1	1.3	1.7
4g	1.1	1.2	1.3	R	1	1.2	R	R	R	1.2	1.3	1.5	1	1.1	1.3
4h	1	1.3	1.5	1.1	1.4	1.7	1.2	1.4	1.8	1.1	1.3	1.4	R	1.1	1.4
4i	1.1	1.3	1.6	1.2	1.6	2	1.3	1.5	1.9	1.1	1.5	2.2	1.2	1.6	2.3
4j	1.3	1.5	1.9	1	1.2	1.3	1.3	1.4	1.7	1.1	1.4	1.5	1.1	1.4	1.8
4k	1.3	1.5	1.8	1.1	1.4	1.7	1.2	1.4	1.8	1.4	1.5	2	1.2	1.4	1.7
4l	1.4	1.7	2	1.1	1.3	1.5	1.1	1.1	1.3	1.4	1.6	2	1.1	1.3	1.5
4m	1.1	1.3	1.5	R	R	R	R	R	R	1.3	1.4	1.7	R	1.3	1.7
4n	1.3	1.5	1.5	1.9	R	R	1.5	1.5	1.7	R	1.3	R	1.3	R	1
4o	1.5	1.6	1.3	1.1	1.4	1.3	1.4	1.7	1	R	1.2	1.7	1.1	1.5	1.3
4p	1.7	1.8	1.5	1	1.6	1.2	1.3	1.9	1.1	1.7	1.5	1.5	R	1.1	1.4
4q	1.6	1	1.2	1.5	1.4	1.2	1.2	1.5	1.4	1.6	1.8	1.3	1.5	1.3	1.8
4r	2	1.8	1.3	1.1	1.3	1.5	1	1.2	1.5	1.1	1	1.4	1.8	1.1	1.6
4s	1.2	1.1	1.1	1.7	1.8	1.4	1.1	1	1.3	1.5	1.6	1.9	1.6	1	2
4t	R	1	2	1.3	1.3	1.2	1.5	1.7	1.2	1.3	1.2	1	1.2	1.8	1.7
A	1.8			1.8			1.9			1.9			-		
CPD	2.2			2.1			2.1			2.2			-		
GF	1.8			1.9			2.0			2.0			-		
GRF	-			-			-			-			2.6		
FLC	-			-			-			-			2.8		

Note: Zone of inhibition interpretation is as follows.

1. ZONE SIZE <1.0 C.M.- RESISTENT(R)
2. ZONE SIZE 1.0 To 1.5 – INTERMEDIATE
3. ZONE SIZE >1.5 – SENSITIVE

Std Antibiotic Sensitivity Assay Concentration 40 µG/ml

A: Ampicillin
CPD: CEFPODOXIME
GF: Gatifloxacin
GRF: GRESIOFULvin
FLC: FLUCONAZOLE

4. CONCLUSION

In summary, we have described the synthesis of substituted pyrimidine derivatives in excellent yields by little modification of classical Biginelli reaction. The spectral data are incorporate with the structure of compounds **4a-j**. The antimicrobial data reported here which may be the better reference for the future research in the class of pyrimidine derivatives.

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