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Synthesis and antimicrobial evaluation of some novel 6-(4-benzylpiperidin-1-yl)l)-4-amino/benzylamino/phenylamino/phenoxy-pyrimidine derivatives

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Abstract: A series of novel 6-(4-benzylpiperidin-1-yl)-4-amino/benzylamino/phenylamino /phenoxy-pyrimidine derivatives were prepared by using different aliphatic amine, cyclic amines, benzyl amines, anilines and phenols. All the synthesized compounds (**6a-6j**, **7a-7c** and **8a-8d**) were evaluated for their antibacterial and antifungal activity.

Keywords: Amines, Anti-bacterial, Anti-fungal, Antimicrobial, Piperidine, Pyrimidine.

Introduction

As a part of our research program, we became interested in the synthesis and biological evaluation of 4,6-disubstituted pyrimidine core and their antibacterial and antifungal activities. The multiple diverse functionalizations of heterocycles are showing significant importance in the preparation of drugs, in among all heterocyclic derivatives pyrimidine derivatives have a broad pharmacological profile. Pyrimidines have an important role in our regular life, which includes its presence in vitamins, DNA, RNA and co-enzymes. Pyrimidines are also the building blocks of so many natural compounds. The condensed pyrimidine derivatives are highly effective in antibacterial [1,2], antifungal [3], anti-inflammatory [4], anti-infective [5], analgesic [6], anticancer [7] etc. and HIV induced effect [8]. Apart from these, pyrimidines are key compounds in antiallergic, cardiovascular [9], antiviral [10] and hypnotic drug for the central nervous system [11].

Since the pyrimidines had like these good properties, from past century research is going on pyrimidines and its derivatives among all heterocyclic derivatives.

Piperidines are also becoming very important in medicinal chemistry now days. Piperidne derivatives are selectively acting as antagonist in the M3 Muscarinic series [12]. The M3-R (M3 muscarinic receptor) playing the key activity in contraction of smooth muscle in different organs and apart from that M3-R explains the therapeutic efficacy of drugs which are using in urinary diseases. Piperidine derivatives showing significant activity in human heat shock protein 70 inhibitors for the treatment of drug resistant tumours [13]. In the same way piperidines and its derivatives are widely using as key compound in several drugs. So many piperidine derivatives are acting as inhibitors which are very useful in medicinal chemistry. The substituted bipiperidines are using in treatment for asthma, as CCR3 antagonist [14]. These are all saying that piperidines are also playing a key role in medicinal chemistry.

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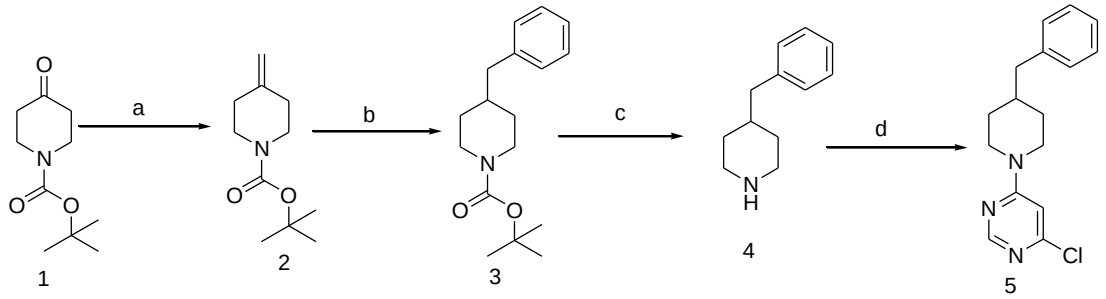
Drug resistance against many diseases paved the way to develop new synthetic molecules which can have better antimicrobial property. The superbugs resistant to most antimicrobials and lead to resistant infection which can spread to others, may kill, and inflict huge costs to individuals and society. Drug resistance is the reduction in effectiveness of a drug against to disease and the drug is not intended to kill or inhibit a pathogen and it will lead to drug tolerance. Now days an antimicrobial resistance and antineoplastic resistance becoming challenge in clinical care and need to synthesize small hetero cyclic molecules. The development of antibiotic resistance in particular stems from the drugs targeting only specific bacterial molecules (proteins). Because, the drug mutation in these molecules will interfere with or negate its destructive effect resulting in antibiotic resistance. Drug resistance by pathogenic microorganisms looms as possibly one of the most significant public health. Henceforth synthesis of molecules which can have better antimicrobial properties is highly desirable.

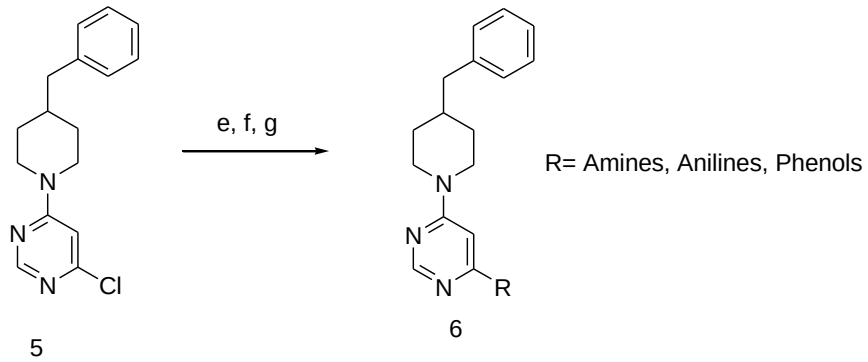
The major aim of the research presented in this paper is to explore a series of new pyrimidine derivatives as antimicrobial agents. This may allow the discovery of some novel analogues of 4,6-disubstituted pyrimidine core with improved antimicrobial activities. In view of the significant biological properties of pyrimidines and piperidines, we have herein synthesized combination of pyrimidines and piperidines derivatives. Accordingly we have synthesized **6-(4-benzylpiperidin-1-yl)-4-amino/benzylamino/ phenyl amino/phenoxy-pyrimidine** derivatives towards antimicrobial activity.

Results and discussion

A major diversity of 4,6-disubstituted pyrimidine analogues employing (Scheme **2**) the synthesis of the key scaffold (**5**) was accomplished as shown in Scheme **1**. The chloro intermediate (**5**) is highly activated; we envisioned that displacing the functionality with aliphatic amines, cyclicamines, benzyl amines, anilines and phenols would result in terms of pyrimidine analogues which can have good biological properties. Therefore we synthesized novel analogues based on 4,6-disubstituted pyrimidine core and explored antimicrobial studies.



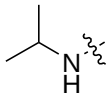
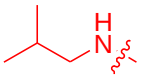
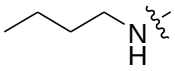
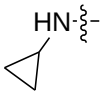
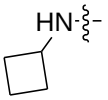
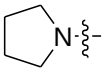
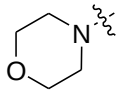
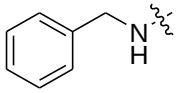
Scheme 1: (a) methyl triphenylphosphomnium bromide, n-butyl lthium, THF, -78 ^{o}C to RT, 14 h; (b) 9-BBN, THF, Iodo benzene, K_2CO_3, [1,1′-Bis(diphenylphosphino)ferrocene] dichloro palladium(II), 60 ^{o}C, 14 h; (c) 4M HCl in dioxane, 1,4-dioxane, RT, 4 h; (d) 4,6-dichloro pyrimidine, DIPEA, 110 ^{o}C, 14 h.

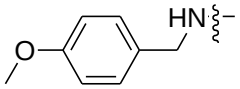
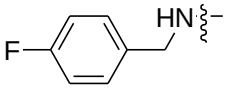
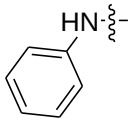
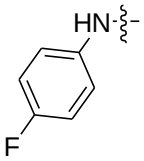
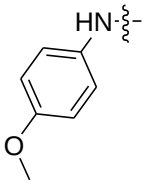
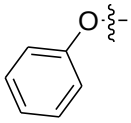
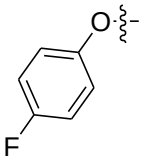
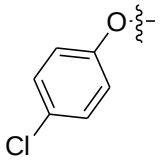
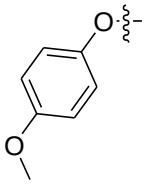


Scheme 2: (e) If R= Amine; DIPEA, n-BuOH, 140 ^{o}C, 14 h.; (f) If R= Aniline; p-TSA, DMF, 140 ^{o}C, MW, 1.5 h.; (g) If R= Phenol, K_2CO_3, DMF, 140 ^{o}C, MW, 1.5 h.

In this work intermediate **5** is the key scaffold, which used for synthesize different substituted analogues and was made in the follow path. *N*-Boc-piperidinone (**1)** treated with methyl triphenylphosphomnium bromide and n-butyl lithium in THF to yield tert-butyl 4-methylenepiperidine-1-carboxylate (**2**). Compound (**2**) was treated with 9-BBN to make boronate complex which reacted with iodobenzene in presence of potassium carbonate to get tert-butyl 4-benzylpiperidine-1-carboxylate (**3**). The next step involved the formation of 4-benzylpiperidine hydrochloride (**4**) which was obtained by treating compound (**3**) with 4M HCl in 1,4-dioxane. Compound (**4**) was then reacted with 4,6-dichloropyrimidine and DIPEA (diisopropylethyl amine) to get 4-(4-benzylpiperidin-1-yl)-6-chloropyrimidine (**5**) and this compound was used as scaffold to get different analogues. Herein, the intermediate (**5**) with amine in presence of DIPEA in 1,4-dioxane heated to 110 ^{o} C for 14 h. In this condition we have observed very less product (~5%) formation. Reaction condition was changed to n-BuOH and 140 ^{o} C for 14 h. In this condition major desired product formation observed. By using this condition aliphatic amine, cyclic amine and benzyl amine derivatives were successfully made. When moved to aniline analogues, in previous condition product formation was very low. Then reaction was performed in the presence of acidic media (p-TSA) and DMF as solvent at 140 ^{o}C in micro wave for 1.5 h to make aniline analogues. For phenol analogues phenols were treated with potassium carbonate to make potassium salts of phenolates which were good nucleophiles reacted with 4-(4-benzylpiperidin-1-yl)-6-chloropyrimidine (**5**) in DMF at 140 ^{o}C by using micro wave for 1.5 h resulted phenol substituted analogues.

Table 1: Structural details of the final compounds (**6a-6j, 7a-7c and 8a-8d)**

Entry	Compound code	R
1	6a	
2	6b	
3	6c	
4	6d	
5	6e	
6	6f	
7	6g	
8	6h	

9	6i	
10	6j	
11	7a	
12	7b	
13	7c	
14	8a	
15	8b	
16	8c	
17	8d	

Structural-activity relationship:

The antimicrobial activity of synthesized compounds was summarized in Table **2** and **3**. Over all series compounds showed moderate potency in both antibacterial and antifungal activity. We have synthesized aliphatic amines, cyclic amines, benzyl amines, anilines & phenols coupled derivatives and each compound was screened for antibacterial and antifungal activity in four different stains respectively. In the terms of antimicrobial activity aliphatic amine derivatives have better profile than cyclic amine

derivatives. In benzyl amine derivatives, simple benzyl amine analogue (**6h**) shows good activity. When we kept electron donating group on benzyl amine (**6i**), it tendency to loose potency and electron withdrawing group (**6j**) helps to gain the potency. The same advantage with 'electron withdrawing groups' presence we have observed in aniline derivatives and phenols too. The electron withdrawing groups improves the activity of the compounds towards antimicrobial.

ANTIMICROBIAL STUDIES:

Antibacterial activity:

All the synthesized compounds (**6a-6j**, **7a-7c** and **8a-8d**) were screened for antimicrobial activity (antibacterial and antifungal activity). In case of antibacterial activity all the compounds were screened against four strains of bacteria *viz. Escherichia coli* (ATTC-25922), *Staphylococcus aureus* (ATTC-25923), *Pseudomonas aeruginosa* (ATTC-27853) and *Klebsiella pneumonia* by serial plate dilution method [15]. Phosphate buffer was used to adjust pH upto 5.0 and all test bacterium were incubated for 20-22 h at 37 ^{o}C.

All the antibacterial discs were placed on the agar, 20 mL of agar media was poured into each Petri dish. By using incubator all the plates were dried for one hour at 37 ^{o}C. The test compounds were dissolved in dimethyl sulfoxide (DMSO) and added Petri dishes. All the Petri dishes were prepared in triplicate method and kept for 3-4 days by maintaining at 37 ^{o}C. Inhibition zone of antibacterial activity was determined by measuring the diameter. Activity of each compound was measured by comparing with ciprofloxacin as standard. The used concentrations ranges were 1.56 µg/mL, 6.25 µg/mL, 12.5 µg/mL and 25 µg/mL and the average reading of each was taken. Zone of inhibition values and the MIC values in µg/mL was determined for **6a-6j**, **7a-7c** and **8a-8d** and results are summarized in Table **2**.

Table 3: Antibacterial activity data of compounds (**6a-6j, 7a-7c** and **8a-8d**)

Compound No.	MIC [μg/mL] and zone of inhibition (mm) in parentheses			
	S. aureus	*E. coli*	*P. aeruginosa*	*K. pneumonia*
6a	6.25 (20)	6.25 (19)	6.25 (18)	6.25 (20)
6b	6.25 (17)	6.25 (18)	6.25 (16)	6.25 (20)
6c	6.25 (21)	6.25 (20)	6.25 (21)	6.25 (19)
6d	12.5 (12)	12.5 (12)	12.5 (11)	12.5 (13)
6e	12.5 (11)	12.5 (14)	12.5 (13)	12.5 (12)
6f	12.5 (14)	12.5 (15)	12.5 (15)	12.5 (14)
6g	25 (8)	25 (7)	25 (8)	25 (7)
6h	6.25 (20)	6.25 (19)	6.25 (18)	6.25 (20)
6i	12.5 (11)	12.5 (12)	12.5 (13)	12.5 (13)
6j	6.25 (23)	6.25 (21)	6.25 (22)	6.25 (20)
7a	12.5 (12)	12.5 (11)	12.5 (11)	12.5 (13)
7b	6.25 (20)	6.25 (20)	6.25 (19)	6.25 (19)
7c	12.5 (11)	12.5 (12)	12.5 (11)	12.5 (13)
8a	25 (7)	25 (8)	25 (9)	25 (8)
8b	12.5 (15)	12.5 (13)	12.5 (14)	12.5 (12)
8c	12.5 (12)	12.5 (15)	12.5 (14)	12.5 (15)
8d	25 (8)	25 (7)	25 (8)	25 (6)
Standard (Ciprofloxacin)	1.56 (22-30)	6.25 (30-40)	6.25 (25-33)	6.25 (23-27)

Antifungal activity:

All the newly synthesized compounds were also screened for antifungal activity against four strains of fungi, *viz. Aspergilus flavus* (NCIM No. 524), *Aspergilus fumigatus* (NCIM No. 902), *Penicillium maneffei* (recultured) and *Trichophyton mentagrophytes* (recultured) by serial plate dilution method [16]. By using peptone (1 g), D-glucose (4 g) and agar (2 g) in distilled water (100 mL); Sabourauds agar media was prepared and pH was adjusted to 5.7. 3mL of saline and a loopful of particular fungal strain were mixed to get a suspension of corresponding species. Each Petri dish was filled with 20 mL of agar media and plates were dried by placing in an incubator at 37 ^{o}C for 1h. In all seeded agar plates wells were made by using a punch and these wells were filled with the test compounds which dissolved in DMSO. For 3-4 days the Petri dishes were maintained at 37 ^{o}C and prepared in triplicate method and antifungal activity was determined by measuring the diameter of inhibition zone with respect to Ciclopiroxololamine as standard. Zones of inhibition were determined for **6a-6j, 7a-7c** and **8a-8d,** the results of which are summarized in **Table 3**. The MIC values were evaluated at concentrations of 6.25 µg/mL, 12.5 µg/mL and 25 µg/mL and the average reading of each was taken.

Table 3: Antifungal activity data of compounds (**6a-6j**, **7a-7c** and **8a-8d**)

Compound No.	MIC [μg/mL] and zone of inhibition (mm) in parentheses			
	P. marneffei	*T. mentagrophytes*	*A. flavus*	*A. fumigates*
6a	6.25 (18)	6.25 (21)	6.25 (22)	6.25 (19)
6b	6.25 (22)	6.25 (23)	6.25 (21)	6.25 (24)
6c	6.25 (24)	6.25 (22)	6.25 (24)	6.25 (25)
6d	12.5 (14)	12.5 (13)	12.5 (12)	12.5 (12)
6e	12.5 (13)	12.5 (11)	12.5 (11)	12.5 (14)
6f	12.5 (15)	12.5 (14)	12.5 (12)	12.5 (13)
6g	25 (8)	25 (9)	25 (7)	25 (8)
6h	6.25 (19)	6.25 (20)	6.25 (20)	6.25 (19)
6i	12.5 (12)	12.5 (11)	12.5 (13)	12.5 (11)
6j	6.25 (21)	6.25 (24)	6.25 (25)	6.25 (26)
7a	12.5 (15)	12.5 (11)	12.5 (13)	12.5 (15)
7b	6.25 (20)	6.25 (20)	6.25 (19)	6.25 (20)
7c	12.5 (11)	12.5 (13)	12.5 (12)	12.5 (14)
8a	25 (5)	25 (4)	25 (6)	25 (8)
8b	12.5 (15)	12.5 (13)	12.5 (12)	12.5 (14)
8c	12.5 (18)	12.5 (15)	12.5 (17)	12.5 (13)
8d	25 (8)	25 (9)	25 (5)	25 (7)
Standard (Ciclopiroxololamine)	1.56 (22-30)	6.25 (30-40)	6.25 (25-35)	6.25 (23-27)

Conclusion

In conclusion, successfully synthesized some novel 6-(4-benzylpiperidin-1-yl)-4-amino/benzylamino /phenylamino/phenoxy-pyrimidine derivatives the combination of pyrimidine and piperidine nucleus. Over all 17 compounds were synthesized by varying different aliphatic, alicyclic, cyclic, benzyl amines,

anilnes and phenoxy substitutions and all the compounds were screened for antibacterial and antifungal activity. The overall 6-(4-benzylpiperidin-1-yl)-4-amino/benzyl amino/phenyl amino/phenoxy-pyrimidine derivatives showed good activity.

Experimental Section

Material and instruments:

All chemicals and solvents were procured from Sigma Aldrich, Alfa and Spectrochem Chemicals Pvt.Ltd. All the solvents were distilled and dried before usage. The progress of the reactions was monitored by TLC. All the synthesized compounds were purified by recrystallization and flash column chromatography by using silica gel (60-120 mesh). Mass spectra were recorded on an Agilent 1100 MSD/TRAP/XCT system. Melting point of the synthesized compounds was recorded by a Stuart SMP3 melting point apparatus and is uncorrected. The ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ and DMSO-d_6. Chemical shifts values are reported as values in ppm relative to TMS as internal standard and abbreviations for multiplicity of chemical shift values are s= singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

Synthesis:

Tert-butyl 4-methylenepiperidine-1-carboxylate (2):

To a stirred solution of methyl triphenylphosphomnium bromide (5.4 g, 15.05 mmol) in THF (100 mL) was added n-butyl lithium (7.5 mL of 2M in THF, 15.05 mmol) drop wise at -78 °C. The reaction mixture was allowed to stir for one hour. Then N-boc-piperidinone (2 g, 10.03 mmol) in THF (15 mL) was added at -78 °C. The reaction mixture was slowly warmed to room temperature and stirred for overnight [17]. THF was removed under reduced pressure and to that residue water (50 mL) was added and extracted with ethyl acetate (2 x 50 mL). The combined organic layers were washed with brine solution (2 x 50 mL), dried over sodium sulfate and concentrated under reduced pressure. The crude compound was purified by flash column chromatography (30% ethyl acetate/n-hexane) to afford *tert*-butyl 4-methylenepiperidine-1-carboxylate **(2)** (1.8g, 9.1mmol, 91% yield) as colorless thick gummy mass. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 4.76 (s, 2H), 3.32-3-35 (m, 4H), 2.12 (t, *J* = 6.00 Hz, 4H), 1.42 (s, 9H). ms: m/z 198 (M+H). ^{13}C NMR (100 MHz, DMSO-d6): δ 162.32, 153.47, 115.46, 88.95, 57.83, 43.47, 31.93. Anal. Calcd. For $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.85; H, 9.66; N, 7.12.

Tert-butyl 4-benzylpiperidine-1-carboxylate (3):

To a stirred solution of tert-butyl 4-methylenepiperidine-1-carboxylate (**2**) (0.5 g, 2.5 mmol) in THF (25 mL) was purged with nitrogen for 10 minutes. Then 9-BBN (2.5 mL, 1M in THF, 2.5 mmol) was added and heated to reflux for one hour under inert atmosphere. The reaction mass was cooled to room temperature and this reaction mixture was added to a solution of iodobenzene (0.62 g, 3.04 mmol) in DMF (10 mL) and water (1 mL) along with K_2CO_3 (0.69 g, 5.0 mmol) and purged with nitrogen for 10 minutes. Then [1,1′-Bis(diphenylphosphino)ferrocene] dichloro palladium(II) (0.204 g, 0.25 mmol) was added and heated to 60 °C [18-19]. The reaction mixture was stirred for overnight. The reaction mass was cooled to room temperature, concentrated under reduced pressure. The compound was purified by flash column chromatography (silica gel, 30% ethyl acetate/n-hexane) to afford tert-butyl 4-benzylpiperidine-1-carboxylate **(3)** (0.5 g, 1.82 mmol, 71% yield) as brown thick mass. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.37-7.38 (m, 2H), 7.32-7.33 (m, 3H), 3.75-3.84 (m, 2H), 3.43-3.52 (m, 2H), 2.73 (d, *J* = 8 Hz, 2H), 1.92-1.93 (m, 1H), 1.72-1.81 (m, 2H), 1.54-1-65 (m, 2H), 1.42 (s, 9H). ms: m/z 276 (M+H). ^{13}C NMR (100 MHz, DMSO-d6): 165.15, 142.76, 131.52, 130.98, 129.53, 85.38, 47.68, 42.74, 32.36, 31.64, 27.76. Anal. Calcd. For $C_{17}H_{25}NO_2$: C, 74.14; H, 9.15; N, 5.09. Found: C, 74.29; H, 9.21; N, 5.04.

4-Benzylpiperidine hydrochloride (4):

To a stirred solution of tert-butyl 4-benzylpiperidne-1-carboxylate (**3**) (1 g, 3.63 mmol) in 1,4-dioxane (10 mL), 4M HCl in 1,4-dioxane (10 mL) was added and stirred at room temperature for 4 h [20]. The reaction mixture was concentrated under reduced pressure. The residue was washed with ethyl acetate (2 x 25 mL) and dried under reduced pressure to afford 4-benzylpiperidine hydrochloride (**4**) as an off white semi solid (0.7g, 0.33 mmol, 91% yield). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.35-7.36 (m, 2H), 7.29-7.30 (m, 3H), 3.42-3.51 (m, 2H), 2.98-2.99 (m, 2H), 2.65 (d, *J* = 8 Hz, 2H), 1.87-1.88 (m, 1H), 1.65-1.74 (m, 2H), 1.48-1-49 (m, 2H). ms: m/z 176 (M+H). ^{13}C NMR (100 MHz, DMSO-d6): 141.54, 130.76, 129.87, 129.24, 47.43, 42.61, 36.31, 28.43. Anal. Calcd. For $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.31; H, 9.82; N, 7.86.

4-(4-Benzylpiperidin-1-yl)-6-chloropyrimidine (5):

To a stirred solution of 4-benzylpiperidine hydrochloride (**4**) (1.0 g, 4.72mmol) in 1,4-dioxane (10 mL), diisopropylethylamine (2.96 mL, 17 mmol) was added followed by 4,6-dichloropyrimidine (0.703g, 4.72 mmol) and heated to 110 ^{o}C for 14 h [21]. Reaction mass was cooled to room temperature and concentrated under reduced pressure. To this residue, water (25 mL) was added and extracted with ethyl acetate (2 x 30 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel) to afford 4-(4-benzylpiperidin-1-yl)-6-chloropyrimidine **(5)** (1.0 g, 3.484 mmol, 73% yield) as brown solid, mp = 226-228 ^{o}C. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.55 (s, 1H), 7.20-7.26 (m, 2H), 7.02-7.05 (m, 3H), 6.56 (s, 1H), 4.23 (d, *J* = 12.20 Hz, 2H), 2.78 (t, *J* = 8.20 Hz, 2H), 2.41 (d, *J* = 6.80 Hz, 2H), 1.63-1.67 (m, 1H), 1.51 (d, *J* = 12.20 Hz, 2H), 1.10-1.13 (m, 2H); ms: m/z 288 (M+H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.37, 165.82, 162.36, 143.76, 132.65, 131.98, 129.73,, 57.32, 44.24, 33.47, 28.79. Anal. Calcd. For $C_{16}H_{18}ClN_3$: 66.78; H, 6.30; N, 14.60. Found: 66.71; H, 6.37; N, 14.55.

General procedure for the synthesis of compounds (6a-6j):

To a stirred solution of 4-(4-benzylpiperidin-1-yl)-6-chloropyrimidine (**5**) (0.5 g, 1.7 mmol) in n-BuOH (5 mL) was added diisopropylethylamine (0.9 mL, 5.1 mmol) followed by isopropylamine (0.3 g, 5.1 mmol) and heated to 140 °C for 14 h [22]. Reaction mass was cooled to room temperature, concentrated under reduced pressure. To this residue water (25 mL) was added and extracted with ethyl acetate (2 x 30 mL), the combined organic layers were dried over sodium sulphate and concentrated under reduced pressure. The crude was purified by column chromatography to yield the target compound.

6-(4-Benzylpiperidin-1-yl)-N-isopropylpyrimidin-4-amine (6a):

45% yield, brown solid, mp = 260-262 ^{o}C. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.95 (s, 1H), 7.26-7.30 (m, 2H), 7.16-7.19 (m, 3H), 6.41 (d, *J* = 8.00 Hz, 1H), 5.54 (s, 1H), 4.17 (d, *J* = 12.80 Hz, 2H), 3.92-3.95 (m, 1H), 2.67 (t, *J* = 8.80 Hz, 2H), 2.53 (d, *J* = 6.00 Hz, 2H), 1.74-1.77 (m, 1H), 1.58 (d, *J* = 12.00 Hz, 2H), 1.13-1.17 (m, 2H), 1.11 (d, *J* = 10.80 Hz, 6H); ms: m/z 311 (M+H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.45, 162.18, 158.12, 141.35, 129.26, 128.48, 126.34, 81.57, 44.13, 43.79, 43.14, 37.15, 31.31, 24.14. Anal. Calcd. For $C_{19}H_{26}N_4$: C, 73.51; H, 8.44; N, 18.05. Found: C, 73.58; H, 8.41; N, 18.12.

6-(4-Benzylpiperidin-1-yl)-N-isobutylpyrimidin-4-amine (6b):

44% yield, off white semi solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.94 (s, 1H), 7.26-7.30 (m, 2H), 7.16-7.20 (m, 3H), 6.62 (t, *J* = 10.80 Hz, 1H), 5.57 (s, 1H), 4.18 (d, *J* = 12.40 Hz, 2H), 3.00 (t, *J* = 12.40 Hz, 2H), 2.68 (m, 2H), 2.53 (d, *J* = 6.00 Hz, 2H), 1.73-1.81 (m, 2H), 1.58 (d, *J* = 11.20 Hz, 2H), 1.05-1.14 (m, 2H), 0.87 (d, *J* = 6.80 Hz, 6H); ms: m/z 325 (M+H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.43, 162.14, 158.08, 141.23, 129.17, 128.39, 126.23, 81.51, 50.76, 44.08, 43.70, 43.11, 37.13, 31.31, 30.97, 21.12, 9.87. Anal. Calcd. For $C_{20}H_{28}N_4$: C, 74.03; H, 8.70; N, 17.27. Found: C, 74.12; H, 8.68; N, 17.31.

6-(4-Benzylpiperidin-1-yl)-N-butylpyrimidin-4-amine (6c):

45% yield, Yellow solid, mp = 280-282 ^{o}C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.94 (s, 1H), 7.26-7.31 (m, 2H), 7.16- 7.20 (m, 3H), 6.57 (t, *J* = 11.10 Hz, 1H), 5.54 (s, 1H), 4.19 (d, *J* = 12.00 Hz, 2H), 3.12-3.19 (m, 2H), 2.68 (t, *J* = 13.40 Hz, 2H), 2.53 (d, *J* = 4.50 Hz, 2H), 1.73-1.77 (m, 1H), 1.58 (d, *J* = 12.00 Hz, 2H), 1.41-1.48 (m, 2H), 1.27-1.37 (m, 2H), 1.07-1.15 (m, 2H), 0.88 (t, *J* = 11.40 Hz, 3H); ms: m/z 325 (M+H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.42, 162.15, 158.11, 141.23, 129.11, 128.42, 126.21, 81.55, 45.71, 44.11, 43.73, 43.15, 37.17, 32.76, 31.38, 21.35, 15.24. Anal. Calcd. For $C_{19}H_{24}N_4$: C, 74.03; H, 8.70; N, 17.27. Found: C, 74.09; H, 8.72; N, 17.37.

6-(4-Benzylpiperidin-1-yl)-N-cyclopropylpyrimidin-4-amine (6d):

41% yield, white solid, mp = 265-267 ^{o}C. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.94 (s, 1H), 7.26-7.30 (m, 2H), 7.17-7.20 (m, 3H), 6.88 (s, 1H), 5.71 (s, 1H), 4.24 (d, *J* = 12.80 Hz, 2H), 2.74 (t, *J* = 11.80 Hz, 2H), 2.53 (d, *J* = 6.00 Hz, 2H), 2.42-2.45 (m, 1H), 1.75-1.79 (m, 1H), 1.60 (d, *J* = 10.80 Hz, 2H), 1.08-1.14 (m, 2H), 0.66-0.70 (m, 2H), 0.39-0.42 (m, 2H); ms: m/z 309 (M+H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.12, 163.05, 158.12, 141.56, 129.87, 128.97, 126.34, 81.51, 44.829, 42.74, 38.41, 25.43, 8.62. Anal. Calcd. For $C_{19}H_{24}N_4$: C, 73.99; H, 7.84; N, 18.17. Found: C, 73.91; H, 7.81; N, 18.21.

6-(4-Benzylpiperidin-1-yl)-N-cyclobutylpyrimidin-4-amine (6e):

39% yield, brown thick mass. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 7.94 (s, 1H), 7.26-7.31 (m, 2H), 7.16-7.20 (m, 3H), 6.87 (d, *J* = 7.50 Hz, 1H), 5.48 (s, 1H), 4.19 (d, *J* = 12.60 Hz, 3H), 2.69 (t, *J* = 13.10 Hz, 2H), 2.53 (d, *J* = 4.50 Hz, 2H), 2.22-2.27 (m, 2H), 1.82-1.88 (m, 3H), 1.56-1.67 (m, 4H), 1.05-1.11 (m, 2H); ms: m/z 323 (M+H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.65, 162.37, 157.80, 140.60, 129.48, 128.61, 126.25, 81.26, 46.00, 44.29, 42.74, 38.15, 31.51, 30.94, 15.12. Anal. Calcd. For $C_{20}H_{26}N_4$: C, 74.50; H, 8.13; N, 17.38. Found: C, 74.58; H, 8.17; N, 17.41.

4-(4-Benzylpiperidin-1-yl)-6-(pyrrolidin-1-yl)pyrimidine (6f):

47% yield, brown semi solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.99 (s, 1H), 7.26-7.30 (m, 2H), 7.16-7.20 (m, 3H), 5.48 (s, 1H), 4.28 (d, *J* = 13.20 Hz, 2H), 3.31-3.36 (m, 4H), 2.72 (t, *J* = 11.00 Hz, 2H), 2.53 (d, *J* = 6.00 Hz, 2H), 1.89 (t, *J* = 9.60 Hz, 4H) 1.75-1.80 (m, 1H), 1.58 (d, *J* = 12.00 Hz, 2H), 1.04-1.15 (m, 2H); ms: m/z 323 (M+H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.65, 162.37, 157.80, 140.60, 129.48, 128.61, 126.25, 81.26, 54.12, 47.13, 41.24, 39.19, 30.57, 30.94, 27.19. Anal. Calcd. For $C_{20}H_{26}N_4$: C, 74.50; H, 8.13; N, 17.38. Found: C, 74.46; H, 8.08; N, 17.31.

4-(4-Benzylpiperidin-1-yl)-6-morpholinopyrimidine (6g):

52% yield, brown solid; mp = 295-297 ^{o}C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.05 (s, 1H), 7.26-7.31 (m, 2H), 7.16-7.20 (m, 3H), 5.87 (s, 1H), 4.34 (d, *J* = 13.50 Hz, 2H), 3.63 (t, *J* = 9.60 Hz, 4H), 3.47 (t, *J* = 9.90 Hz, 4H), 2.72 (t, *J* = 12.70 Hz, 2H), 2.53 (d, *J* = 4.50 Hz, 2H), 1.77-1.79 (m, 1H), 1.58 (d, *J* = 10.80 Hz, 2H), 1.06-1.44 (m, 2H); ms: m/z 339 (M+H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.43, 162.56, 157.37, 140.53, 129.72, 128.32, 126.53, 81.11, 65.28, 53.65, 44.29, 42.74, 38.15, 38.76, 30.14. Anal. Calcd. For $C_{20}H_{26}N_4O$: C, 70.98; H, 7.74; N, 16.55. Found: C, 70.91; H, 7.68; N, 16.59.

N-benzyl-6-(4-benzylpiperidin-1-yl)pyrimidin-4-amine (6h):

48% yield, yellow semi solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.97 (s, 1H), 7.26- 7.30 (m, 6H), 7.13-7.23 (m, 5H), 5.61 (s, 1H), 4.43 (d, *J* = 6.40 Hz, 2H), 4.16 (d, *J* = 12.80 Hz, 2H), 2.68 (t, *J* = 13.60 Hz, 2H), 2.53 (d, *J* = 6.00 Hz, 2H), 1.72-1.78 (m, 1H), 1.57 (d, *J* = 12.80 Hz, 2H), 1.05-1.11 (m, 2H); ms: m/z 359 (M+H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.66, 162.25, 157.81, 140.60, 129.48, 128.68, 128.61, 127.61, 127.05, 126.26, 81.89, 44.27, 44.12, 42.71, 38.11, 34.19. Anal. Calcd. For $C_{23}H_{26}N_4$: C, 77.06; H, 7.31; N, 15.63. Found: C, 77.12; H, 7.38; N, 15.72.

N-(4-methoxybenzyl)-6-(4-benzylpiperidin-1-yl)pyrimidin-4-amine (6i):

42% yield, brown thick mass. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.96 (s, 1H), 7.16-7.30 (m, 7H), 7.06 (t, *J* = 8.00 Hz, 1H), 6.86 (d, *J* = 8.80 Hz, 2H), 5.59 (s, 1H), 4.34 (d, *J* = 6.00 Hz, 2H), 4.16 (d, *J* = 13.60 Hz, 2H), 3.72 (s, 3H), 2.67 (t, *J* = 13.60 Hz, 2H), 2.53 (d, *J* = 6.00 Hz, 2H), 1.72-1.78 (m, 1H), 1.57 (d, *J* = 12.80 Hz, 2H), 1.01-1.11 (m, 2H); ms: m/z 389 (M+H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 164.21, 163.15, 159.52, 157.81, 132.68, 129.83, 129.12, 127.99, 127.89, 126.65, 118.72, 82.13, 59.43, 44.49, 44.26, 43.06, 38.52, 34.36. Anal. Calcd. For $C_{24}H_{28}N_4O$: C, 74.20; H, 7.26; N, 14.42. Found: C, 74.29; H, 7.32; N, 14.48.

N-(4-fluorobenzyl)-6-(4-benzylpiperidin-1-yl)pyrimidin-4-amine (6j):

41% yield, brown thick mass. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 7.97 (s, 1H), 7.26-7.34 (m, 4H), 7.10-7.20 (m, 6H), 5.60 (s, 1H), 4.41 (d, *J* = 6.00 Hz, 2H), 4.16 (d, *J* = 12.80 Hz, 2H), 2.68 (t, *J* = 11.60 Hz, 2H), 2.53 (d, *J* = 6.00 Hz, 2H), 1.73-1.78 (m, 1H), 1.57 (d, *J* = 11.20 Hz, 2H), 1.04-1.10 (m, 2H); ms: m/z 377 (M+H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.82, 162.73, 162.13, 158.21, 133.28, 129.81, 128.12, 128.47, 127.53, 126.48, 119.24, 83.12, 45.13, 44.87, 42.63, 38.87, 34.96. Anal. Calcd. For $C_{23}H_{25}FN_4$: C, 73.38; H, 6.69; N, 14.88. Found: C, 73.51; H, 6.76; N, 14.95.

General procedure for the synthesis of compounds (7a-7c):

To a stirred solution of 4-(4-benzylpiperidin-1-yl)-6-chloropyrimidine (0.25 g, 0.85 mmol) in DMF (2 mL) was added p-TSA (0.292 g, 1.7 mmol) followed by aniline (0.237 g, 2.55 mmol) and heated to 140 ^{o}C in micro wave for 1.5 h [23]. Reaction mass was cooled to room temperature and diluted with ethyl acetate (20 mL), washed with sodium bicarbonate (10%) solution (2 x 15 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure. The crude was purified by flash column chromatography (silica gel, 70% ethyl acetate: n-hexane) to afford 6-(4-

benzylpiperidin-1-yl)-N-phenylpyrimidin-4-amine (120 mg, 0.348 mmol).

6-(4-Benzylpiperidin-1-yl)-N-phenylpyrimidin-4-amine (7a):

40% yield, brown solid , mp = 287-289 ^{o}C. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.97 (s, 1H), 8.16 (s, 1H), 7.57 (d, *J* = 12.80 Hz, 2H), 7.24-7.33 (m, 4H), 7.17-7.20 (m, 3H), 6.92 (t, *J* = 11.40 Hz, 1H), 5.94 (s, 1H), 4.20 (d, *J* = 12.80 Hz, 2H), 2.77 (t, *J* = 12.80 Hz, 2H), 2.54 (d, *J* = 8.00 Hz, 2H), 1.76-1.82 (m, 1H), 1.62 (d, *J* = 12.40 Hz, 2H), 1.08-1.17 (m, 2H); ms: m/z 345 (M+H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.34, 161.50, 157.85, 141.29, 140.56, 129.48, 129.10, 128.62, 126.27, 121.76, 119.79, 84.45, 44.30, 42.69, 38.06, 31.48. Anal. Calcd. For $C_{22}H_{24}N_4$: C, 76.71; H, 7.02; N, 16.27. Found: C, 76.61; H, 7.08; N, 16.36.

6-(4-Benzylpiperidin-1-yl)-N-(4-fluorophenyl)pyrimidin-4-amine (7b):

38% yield, brown thick mass. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 9.01 (s, 1H), 8.15 (s, 1H), 7.55-7.59 (m, 2H), 7.29 (t, *J* = 14.70 Hz, 2H), 7.07-7.20 (m, 5H), 5.88 (s, 1H), 4.20 (d, *J* = 12.60 Hz, 2H), 2.77 (t, *J* = 11.10 Hz, 2H), 2.53 (d, *J* = 6.00 Hz, 2H), 1.78-1.82 (m, 1H), 1.62 (d, *J* = 13.20 Hz, 2H), 1.09-1.14 (m, 2H); ms: m/z 363 (M+H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.31, 161.44, 157.83, 140.58, 137.62, 129.49, 128.63, 126.28, 121.53, 121.45, 115.70, 115.48, 84.18, 44.29, 42.67, 38.06, 31.48. Anal. Calcd. For $C_{22}H_{23}FN_4$: C, 72.90; H, 6.40; N, 15.46. Found: C, 72.79; H, 6.45; N, 15.34.

6-(4-Benzylpiperidin-1-yl)-N-(4-methoxyphenyl)pyrimidin-4-amine (7c):

40% yield, brown semi solid. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.75 (s, 1H), 8.10 (s, 1H), 7.39-7.42 (m, 2H), 7.26-7.30 (m, 2H), 7.17-7.20 (m, 3H), 6.86 (d, *J* = 8.80 Hz, 2H), 5.82 (s, 1H), 4.17 (d, *J* = 13.20 Hz, 2H), 3.71 (s, 3H), 2.74 (t, *J* = 11.60 Hz, 2H), 2.53 (d, *J* = 8.00 Hz, 2H), 1.75-1.81 (m, 1H), 1.60 (d, *J* = 10.80 Hz, 2H), 1.10-1.16 (m, 2H); ms: m/z 375 (M+H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.38, 161.58, 157.96, 141.41, 140.74, 129.72, 129.54, 128.91, 126.45, 120.36, 117.26, 84.53, 44.52, 42.71, 38.23, 31.52. Anal. Calcd. For $C_{23}H_{26}N_4O$: C, 73.77; H, 7.00; N, 14.96. Found: C, 73.86; H, 7.08; N, 14.91.

General procedure for the synthesis of compounds (8a-8d):

To a stirred solution of 4-(4-benzylpiperidin-1-yl)-6-chloropyrimidine (0.25 g, 0.85 mmol) in DMF (2 mL) was added K_2CO_3 (0.351 g, 2.55 mmol) followed by phenol (0.24 g, 2.55 mmol) and heated to 140 ^{o}C in micro wave for 1.5 h. Reaction mass was cooled to room temperature and was diluted with ethyl acetate (20 mL). The organic layer was washed with sodium bicarbonate (10%) solution (2 x 15 mL). The organic layer was dried over sodium sulphate and concentrated under reduced pressure, purified by column chromatography (silica gel, 80% ethyl acetate: n-hexane) to afford 4-(4-benzylpiperidin-1-yl)-6-phenoxypyrimidine (0.13 g, 0.376 mmol).

4-(4-Benzylpiperidin-1-yl)-6-phenoxypyrimidine (8a):

43% yield, brown solid, mp = 303-305 ^{o}C. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.15 (s, 1H), 7.40-7.42 (m, 2H), 7.26-7.29 (m, 2H), 7.17-7.22 (m, 5H), 7.10-7.12 (m, 2H), 4.31 (d, *J* = 12.00 Hz, 2H), 2.83 (t, *J* = 9.20 Hz, 2H), 2.53 (d, *J* = 8.00 Hz, 2H), 1.79-1.84 (m, 1H), 1.63 (d, *J* = 12.80 Hz, 2H), 1.10-1.16 (m, 2H); ms: m/z 346 (M+H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.21, 162.46, 157.96, 141.42, 140.71, 129.52, 129.41, 128.81, 128.31, 125.82, 122.12, 84.62, 44.51, 42.74, 38.13, 31.54. Anal. Calcd. For $C_{22}H_{23}N_3O$: C, 76.49; H, 6.71; N, 12.16. Found: C, 76.41; H, 6.62; N, 12.11.

4-(4-Fluorophenoxy)-6-(4-benzylpiperidin-1-yl)pyrimidine (8b):

44% yield, brown semi solid. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.15 (s, 1H), 7.17- 7.29 (m, 9H), 6.27 (s, 1H), 4.35 (d, *J* = 13.20 Hz, 2H), 2.84 (t, *J* = 22.80 Hz, 2H), 2.53 (d, *J* = 6.00 Hz, 2H), 1.82-1.87 (m, 1H), 1.63 (d, *J* = 15.00 Hz, 2H), 1.09-1.17 (m, 2H); ms: m/z 364 (M+H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.24, 162.62, 161.65, 158.13, 141.53, 140.82, 129.48, 129.52, 128.84, 124.73, 118.43, 84.68, 44.62, 42.83, 38.21, 31.59. Anal. Calcd. For $C_{22}H_{22}FN_3O$: C, 72.71; H, 6.10; N, 11.56. Found: C, 72.87; H, 6.19; N, 11.63.

4-(4-Chlorophenoxy)-6-(4-benzylpiperidin-1-yl)pyrimidine (8c):

44% yield, white solid, mp = 312-314 ^{o}C. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.15 (s, 1H), 7.17-7.29 (m, 9H), 6.27 (s, 1H), 4.35 (d, *J* = 13.20 Hz, 2H), 2.84 (t, *J* = 17.80 Hz, 2H), 2.53 (d, *J* = 6.00 Hz, 2H), 1.82-1.87 (m, 1H), 1.63 (d, *J* = 15.00 Hz, 2H), 1.09-1.17 (m, 2H); ms: m/z 380 (M+H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.29, 162.45, 158.32, 141.63, 140.91, 132.46, 131.65, 129.88, 129.32, 128.53, 124.42, 84.72, 44.51, 42.91, 38.45, 31.83. Anal. Calcd. For $C_{22}H_{22}ClN_3O$: C, 69.56; H, 5.84; N, 11.06. Found: C, 69.48; H, 5.74; N, 11.11.

4-(4-Methoxyphenoxy)-6-(4-benzylpiperidin-1-yl)pyrimidine (8d):

44% yield, white semi solid. ^{1}H-NMR (300 MHz, DMSO-d_6): δ 8.13 (s, 1H), 7.26-7.31 (m, 2H), 7.17-7.21 (m, 3H), 7.01-7.05 (m, 2H), 6.93-6.97 (m, 2H), 6.18 (s, 1H), 4.31 (d, *J* = 12.00 Hz, 2H), 3.76 (s, 3H), 2.81 (t, *J* = 15.20 Hz, 2H), 2.53 (d, *J* = 6.00 Hz, 2H), 1.80-1.83 (m, 1H), 1.62 (d, *J* = 12.90 Hz, 2H), 1.03-1.15 (m, 2H); ms: m/z 376 (M+H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.12, 162.32, 159.76, 158.54, 141.94, 140.54, 129.63, 129.522, 124.92, 118.47, 84.62, 59.72, 44.63, 42.54, 38.33, 31.91. Anal. Calcd. For $C_{23}H_{25}N_3O_2$: C, 73.57; H, 6.71; N, 11.19. Found: C, 73.74; H, 6.83; N, 11.31.

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