Indian Journal of Chemistry
Vol. 61, January 2022, pp. 81-87

Synthesis, characterization and biological screening of various pharmacophoric derivatives of 4-alkylpyrimidine-5-carbonitrile

Pragna H Thanki*[a], Dhaval V Hingrajia[b] & Jayesh J Modha[c]

[a] Shree V. J. Modha College, Porbandar (Affiliated to Bhakt Kavi Narsinh Mehta University, Junagadh)

[b] Intas Pharmaceuticals Ltd.

[c] M. D. Science College, Porbandar (Affiliated to Bhakt Kavi Narsinh Mehta University Junagadh)

E-mail: pragnathanki@gmail.com; drpateldv@gmail.com; drjjmodha@gmail.com

Received 23 April 2020; accepted (revised) 26 October 2021

4-Isobutyl-1,6-dihydro-1-methyl-2-(methylthio)-6-oxopyrimidine-5-carbonitrile has been used as a starting material. Reaction of 4-isobutyl-1,6-dihydro-1-methyl-2-(methylthio)-6-oxopyrimidine-5-carbonitrile with hydrazine hydrate and amine gives 2-hydrazino and 2-(alkyl/ substituted aryl amino)-4-isobutyl-1,6-dihydro-1-methyl-6-oxopyrimidine-5-carbonitrile compounds respectively. The hydrazino compounds react with different aromatic aldehydes, substituted benzene sulphonyl chloride and s-triazine derivative to form Schiff base, sulphonamide and s-triazine derivatives respectively. Reaction of Schiff base with mercapto lactic acid and chloroacetyl chloride yield 4-thiazolidinones and 2-azetidinones respectively.

Keywords: Derivatives of 4-isobutyl-1,6-dihydro-1-Methyl-6-oxo pyrimidine-5-carbonitrile, antimicrobial, anticancer, CO-ADD, DTP

The chemistry of heterocyclic compounds is important in the discovery of novel drugs. Various naturalcompounds such as amino acids, alkaloids, vitamins, hormones, hemoglobin, and many synthetic drugs and dyes contain heterocyclic ring systems. Large numbers of synthetic heterocyclic compounds like pyrimidines, pyrrole, pyrrolidine, furan, thiophene, piperidine, pyridine and thiazole show significant biological activity. Among these pyrimidines are of great interest[1].

Pyrimidine which is an integral part of DNA and RNA imparts diverse pharmacological properties. The pyrimidine has been isolated from the nucleic acid hydrolyses and is much weaker base than pyridine and soluble in water[2]. Pyrimidine and its derivatives have been reported to possess wide range of biological potential i.e. anticancer[3], antiviral[4], antimicrobial[5], anti-inflammatory[6], analgesic[7] and antioxidant[8]. Pyrimidines derivatives have been used in coordination chemistry, metal-cage complexes[9] and also act as CDK 4 inhibitors[10].

Pyrimidine nucleus is also a significant pharmacophore which exhibit excellent pharmacological activities[11].

The growing health problems demands for a search and synthesis of a new class of antimicrobial molecules which are effective against pathogenic microorganisms. Despite advances in antibacterial and antifungal therapies, many problems remain to be solved for most antimicrobial drugs available. The extensive use of antibiotics has led to the appearance of multidrug resistant microbial pathogens which necessitated the search for new chemical entities for treatment of microbial infections[12]. Combination of two biologically active constituent to explore for a better therapeutic agent is one of the important aspect in drug chemistry.

Multi-component reactions (MCRs) are one-pot processes in which three or more reactants come together in a single reaction vessel to give a final product. MCRs is currently an important part of numerous research work involved in the drug discoveries to achieve synthetic targets in effective way, because they are easy to carry out and provide rapid access to libraries of organic compounds with diverse substitution patterns[13].

We have synthesized some new 2-(substituted)-4-isobuty-1,6-dihydro-1-methyl-6-oxopyrimidine-5-carbonitrile by associating 4-Isobuty-1,6-dihydro-1-methyl-2-(methylthio)-6-oxopyrimidine-5-carbonitrile with different pharmacologically active species using different methods[14]. Various structurally important

derivatives have been synthesized by reported method[15] and are screened for antibiotic activity.

Results and Discussion

All synthesized compounds have been screened for antimicrobial activity and anticancer activity. Five compounds 2-(ethylamino)-1,6-dihydro-4-isobutyl-1-methyl-6-oxopyrimidine-5-carbonitrile,2-(2-(4,6-bis(phenylamino)-1,3,5-triazin-2-yl) hydrazinyl)-4-isobutyl-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carbonitrile, N'-(5-cyano-4-isobutyl-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)benzenesulfonohydrazide, 4-isobuty-1-methyl-2-(2-(3-nitrobenzylidene) hydrazinyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile and 2-(5-methyl-4-oxo-2-phenylthiazolidin-3-ylamino)-1,6-dihydro-4-isobutyl-1-methyl-6-oxopyrimidine-5-carbonitrile (Scheme I, Table I),have been found tobeactive andshowed50% bacterialinhibitionat

Scheme I

32µg/mLand 2-(3-chloro-2-(4-fluorophenyl)-4-oxoazetidin-1-ylamino)-1,6-dihydro-4-isobutyl-1-methyl-6-oxopyrimidine-5-carbonitrilecompound showed 100%bacterialinhibition at 32µg/mL in single pointbacterialinhibitionagainst five bacterialstrains. Four were gram –ve and one gram +ve(Table II, Table III). While2-(ethylamino)-1,6-dihydro-4-isobutyl-1-methyl-6-oxopyrimidine-5-carbonitrile and N'-(5-cyano-4-isobutyl-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)benzene sulfonohydrazide have been found active in MIC(Table IV), also compound2-(ethylamino)-1,6-dihydro-4-isobutyl-1-methyl-6-oxopyrimidine-5-carbonitrile exhibited anticancer activity(Table V).

Materials and Methods

Melting points were recorded in open capillary and are not corrected. Progress of reaction was checked by TLC. Mass spectra weredeterminedon Shimadzu-QP2010 spectrometer. IR spectrawererecorded onShimadzu-FTIR-8400 using KBrpellet. ^{1}H-NMR spectra were recorded in Bruker-Avance-II (400MHz) using DMSO-d_6 as a solvent and TMS as an internal standard and the chemical shifts are reported as parts per million (ppm).

Synthesis of novel derivatives

Synthesis of 1,6-dihydro-4-isobutyl-1-methyl-2-(methylthio)-6-oxopyrimidine-5-carbonitrile, 1 [14]

A solution of 1,2,3,4-tetrahydro-6-isobutyl-4-oxo-2-thioxo pyrimidine-5-carbonitrile (0.05 mol) in DMF (70 ml) was stirred for 3 h with potassium carbonate (0.1 mol) and methyl iodide (0.1 mol). After completion of reaction, the reaction mixture was poured into crushed ice and washed with water. Solid product was filtered, dried and crystallized from DMF.

Synthesis of 2-(ethylamino)-1,6-dihydro-4-isobutyl-1-methyl-6-oxopyrimidine-5-carbonitrile, 2

A mixture of (1) (0.01mol) an ethyl amine (5 ml) in absolute alcohol (30 ml) was refluxed for 10 h. The progress of reaction was monitored by thin layer chromatography. After completion of reaction, the

Table I — Charaterization data of the compounds **2-8**

S. No.	Compd	R'	Mol. Formula	Mol. Wt.	m.p.(°C)	Yield(%)	N%Calcd(Found)
1	2	$-C_2H_5$	$C_{12}H_{18}N_4O$	234	201	51	23.91(23.89)
2	4	$-C_6H_5$	$C_{25}H_{26}N_{10}O$	482	240	68	29.03(29.04)
3	5	$-C_6H_5$	$C_{16}H_{19}N_5O_3S$	361	190	53	19.38(19.40)
4	6	$4\text{-}NO_2\text{-}C_6H_4-$	$C_{17}H_{18}N_6O_3$	354	222	61	23.72(23.69)
5	7	$-C_6H_5$	$C_{20}H_{23}N_5O_2S$	397	170	66	17.62(17.69)
6	8	$4\text{-}F\text{-}C_6H_4-$	$C_{19}H_{19}FClN_5O_2$	404	202	58	17.34(17.33)

Table II — Tested bacteria strains

ID	Organism	Strain	Description	Type
GN_001:02	*Escherichia coli*	ATCC 25922	control strain	G −ve
GN_003:02	*Klebsiellapneumoniae*	ATCC 700603	MDR	G −ve
GN_034:02	*Acinetobacterbaumannii*	ATCC 19606	type strain	G −ve
GN_042:02	*Pseudomonas aeruginosa*	ATCC 27853	type strain	G −ve
GP_020:02	*Staphylococcus aureus*	ATCC 43300	MRSA	G +ve

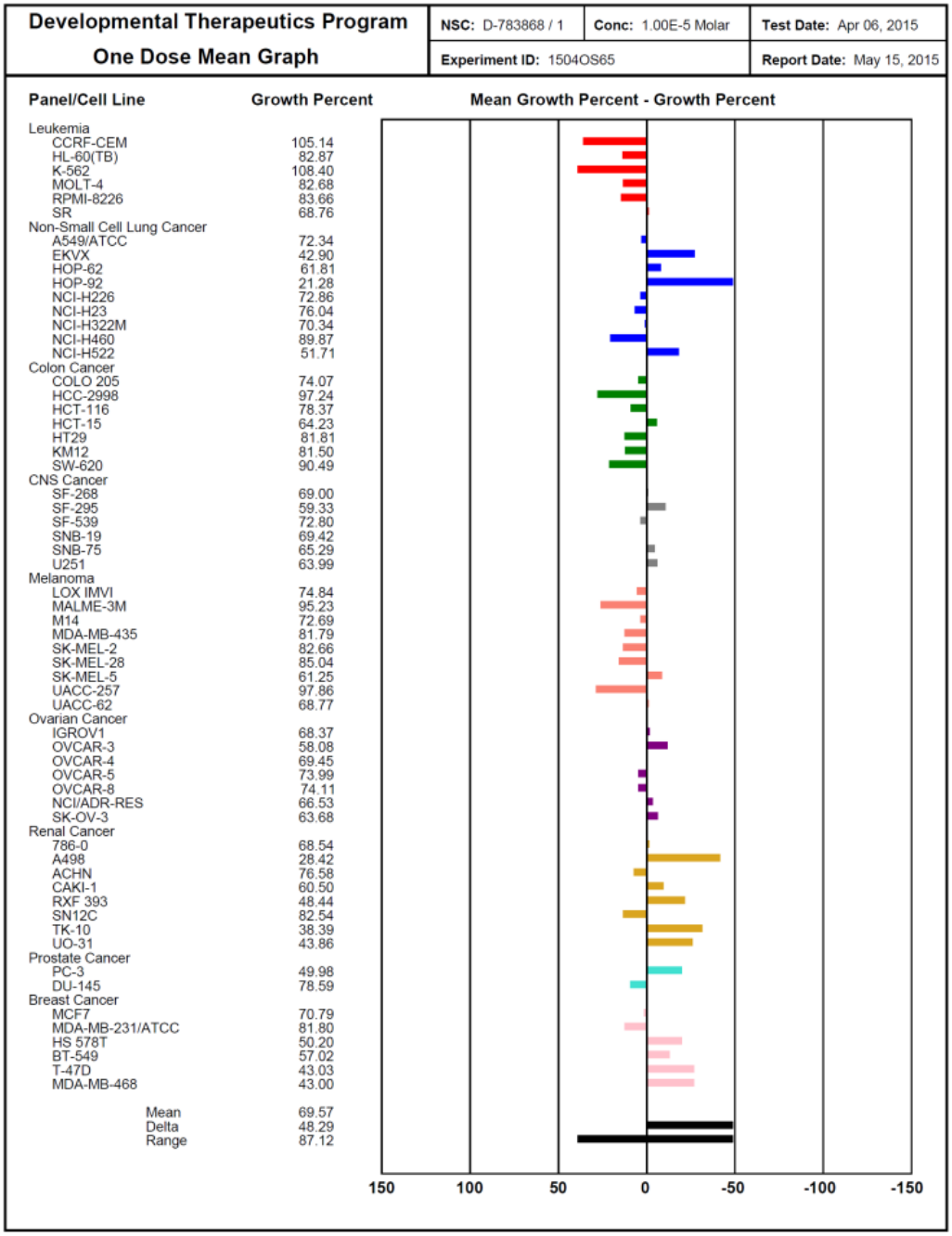
Table III — Single point bacterial inhibition

S. No.	Compd	*E. coli* (ATCC25922)	*K. pneumoniae* (ATCC700603)	*A. buamanii* (ATCC19606)	*P. aeruginosa* (ATCC27853)	*S. aureus* (ATCC 43300)
1	2	>32	32	>32	>32	>32
2	4	>32	>32	>32	>32	32
3	5	>32	>32	32	>32	>32
4	6	>32	>32	>32	>32	>32
5	7	>32	>32	>32	32	>32
6	8	>32	>32	>32	>32	32
100% inhibition at 32µg/Ml		50% inhibition at 32µg/mL			> 32 µg/Ml	

Table IV — MIC (Minimum Inhibitory Concentration) Confirmation Assay

WADI Compd ID	Compd ID	*E. coli* (ATCC25922)	*K.pneumoniae* (ATCC700603)	*A. buamanii* (ATCC19606)	*P.aeruginosa* (ATCC27853)	*S. aureus* (ATCC 43300)
MCC_000094	Colistin	0.06	0.015-0.03	0.03	0.025	–
MCC_000636	Polymyxin B	0.03	0.015	0.015	0.025	–
MCC_000095	Vancomycin	–	–	–	–	1
MCC_000561	Daptomycin	–	–	–	–	1
WADI_0133261	2	–	–	8	–	–
WADI_0133335	5	–	–	4	–	–
≤ 0.015 - 0.06 µg/Ml		0.125 - 0.5 µg/mL		1 - 4 µg/mL	8-32 µg/mL	>32 µg/mL

Table V — Graphical study of anticancer active compound



reaction mixture was poured into crushed ice. The product obtained was isolated and recrystallized from absolute alcohol.

Synthesis of2-hydrazinyl-1,6-dihydro-4-isobutyl-1-methyl-6-oxo pyrimidine-5-carbonitrile, 3

A mixture of (1) (0.01mol) and hydrazine hydrate (4 ml) in absolute alcohol (30 ml) was refluxed for 8 hour. The progress of reaction was monitored by thin layer chromatography. The content was then dilute with ice water, neutralized with gl. Acetic acid and kept overnight. The product obtained was isolated and recrystallized from absolute alcohol.

Synthesis of2-(2-(4,6-bis(phenylamino)-1,3,5-triazin-2-yl) hydrazinyl)-4-isobutyl-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carbonitrile, 4

A mixture of (3) (0.01mol) and 2,4-bis (phenyl amino)-6-chloro-s-triazine(2.0g, 0.01mol) in dioxane (25 ml) was refluxed for 3 h during which solution of sodium bicarbonate (0.84g, 0.01mol) was added in fractions. The content was then poured in ice, product isolated and crystallized from ethanol.

Synthesis of N'-(5-cyano-4-isobutyl-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)benzene sulfonohydrazide, 5

A mixture of (3) (0.01mol) and benzenesulphonyl chloride (1.90g, 0.01 M) in dry pyridine (8 ml) was refluxed for 4 h. The excess of pyridine was distilled of and the content was poured into crushed ice. After neutralization the solid separated was filtered, washed and crystallized from ethanol.

Synthesis of 4-Isobuty-1-methyl-2-(2-(3-nitro-benzylidene)hydrazinyl)-6-oxo-1,6-dihydro-pyrimidine-5-carbonitrile, 6

Compound (3) (0.01mol), and 3-nitro benzaldehyde (1.18ml, 0.01mol) in absolute alcohol (20ml)were taken and 2-3 drop of gl.acetic acid was added. The reaction mixture was refluxed for 3 h. The progress of reaction was monitored by thin layer chromatography. The content was then diluted with ice water and neutralized. The product obtained was isolated and crystallized from absolute alcohol.

Synthesis of 2-(5-methyl-4-oxo-2-phenylthiazolidin-3-ylamino)-1,6-dihydro-4-isobutyl-1-methyl-6-oxopyrimidine-5-carbonitrile, 7

A mixture of (6) (0.01mol) and mercaptolactic acid (1.59g, 0.015M) was fused at 120˚C for 10-12 h. The reaction mixture was cooled and titureted with 10% sodium bicarbonate solution. The solid product was isolated and crystallized from absolute alcohol.

Synthesis of 2-(3-chloro-2-(4-fluorophenyl)-4-oxoazetidin-1-ylamino)-1,6-dihydro-4-isobutyl-1-methyl-6-oxopyrimidine-5-carbonitrile, 8

To a well stirred mixture of chloroacetyl chloride (0.95 ml, 0.012 mol)and triethylamine (1.65 ml, 0.012 mol) in dry dioxane (15ml), was added a solution of (6) (0.01mol) in dry dioxane at 0˚C. The reaction mixture was then stirred a room temperature for 20-22 hrs and kept at RT for 2 days. The product was isolated and crystallized from ethanol.

Experimental Section

Spectral analysis of novel derivatives

Synthesis of 2-(ethylamino)-1,6-dihydro-4-isobutyl-1-methyl-6-oxopyrimidine-5-carbonitrile

$MassM^+$= 234;IR(KBr): 3325 (-NH, secondary)str.,2964 (-CH_3,Asym.)str., 2872 (-CH_3, sym.)str., 2216 (-CN)str.,1651 (-CO)str.,1346 (N-C)str.,777 (N-H)wag ;^{1}HNMR(δ ppm)(400MHz, DMSO): δ3.25 (s,3H,N-C*H*$_3$),δ0.92 (d,6H,CH_2-CH-(C*H*$_3$)$_2$), δ2.12 (m,1H,CH_2-C*H*-(CH_3)$_2$), δ 3.41 (q, 2H, CH_3-C*H*$_2$-NH),δ 1.51 (t, 3H, C*H*$_3$-CH_2-NH),δ2.41 (d,1H,-CH-C*H*$_2$-(CH_3)$_2$),δ7.99 (s,1H,N-*H*).

Synthesis of 2-(2-(4,6-bis(phenylamino)-1,3,5-triazin-2-yl) hydrazinyl)-4-isobutyl-1-methyl-6-oxo-1,6-dihydropyrimidine-5-carbonitrile

$MassM^+$= 482;IR(KBr): 3196 (-NH,secondary) str.,2954 (-CH_3,Asym.)str., 2822 (-CH_3,Asym.)str., 2225 (-CN)str.,1658 (-CO)str.,1602, 1529 (C=C + C=N) ;^{1}HNMR(δ ppm)(400MHz,DMSO)δ3.43 (s,3H,N-C*H*$_3$),δ0.74 (d,6H,CH_2-CH-(C*H*$_3$)$_2$), δ1.92 (m,1H,CH_2-C*H*-(CH_3)$_2$), δ2.38 (d,1H,-CH-C*H*$_2$-(CH_3)$_2$),δ7.01-7.77 (m,10H,Ar-*H*).

Synthesis of N'-(5-cyano-4-isobutyl-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)benzene sulfonohydrazide

M^+= 361;IR(KBr): 3196 (-NH, secondary)str.,2954 (-CH_3,Asym.)str., 2822 (-CH_3,sym.)str., 2225 (-CN)str.,1658 (-CO)str.,1602, 1529 (C=C + C=N) ;^{1}HNMR(δ ppm)(400MHz,DMSO)δ3.37 (s,3H,N-C*H*$_3$),δ0.77-0.96 (d,6H,CH_2-CH-(C*H*$_3$)$_2$), δ1.80 (m,1H,CH_2-C*H*-(CH_3)$_2$), δ2.06 (d,1H,-CH-C*H*$_2$-(CH_3)$_2$),δ7.42-7.85 (m,5H,Ar-*H*).

Synthesis of 4-Isobuty-1-methyl-2-(2-(3-nitrobenzylidene)hydrazinyl)-6-oxo-1,6-dihydro pyrimidine-5-carbonitrile

$MassM^+$= 454;IR(KBr): 3238 (-NH,secondary) str., 2966 (-CH_3,Asym.)str., 2872 (-CH_3, sym.) str.,

2222 (-CN)str.,1662 (-CO)str.,1313 (N-C)str.,734 (N-H)wag, 1458 & 1496 (C-H) def, 1622 (C=N-C) str.; ^{1}HNMR(δ ppm) (400MHz, DMSO)δ3.24 (s,3H,N-C*H*$_3$),δ0.98 (d,6H,CH_2-CH-(C*H*$_3$)$_2$), δ2.08 (m,1H,CH_2-C*H*-(CH_3)$_2$), δ2.71 (d,1H,-CH-C*H*$_2$-(CH_3)$_2$),δ8.45 (s,1H,N-*H*), δ7.45-7.94 (m,5H,Ar-*H*), δ10.97 (s,1H,=C*H*).

Synthesis of2-(5-methyl-4-oxo-2-phenylthiazolidin-3-ylamino)-1,6-dihydro-4-isobutyl-1-methyl-6-oxopyrimidine-5-carbonitrile

Mass M^+= 397;IR(KBr): 3278 (-NH,secondary) str.,2970 (-CH_3,Asym.)str., 2868 (-CH_3,sym.)str., 2225 (-CN)str.,1658 (-CO)str.,1251 (N-C)str.,709 (N-H)wag, 1562 (N-H) def, 669 (C-S-C)str.1722 (-CO)str. ;^{1}HNMR(δ ppm)(400MHz,DMSO)δ3.44 (s,3H,N-C*H*$_3$),δ0.93 (d,6H,CH_2-CH-(C*H*$_3$)$_2$), δ2.01 (m,1H,CH_2-C*H*-(CH_3)$_2$), δ2.44 (d,1H,-CH-C*H*$_2$-(CH_3)$_2$),δ13.01 (s,1H,N-*H*), δ5.75 (s,1H,Ar-C*H*-N),δ1.51 (m,1H,CH-C*H*$_3$) δ7.34-7.47 (m,5H,Ar-*H*).

Synthesis of 2-(3-chloro-2-(4-fluorophenyl)-4-oxoazetidin-1-ylamino)-1,6-dihydro-4-isobutyl-1-methyl-6-oxopyrimidine-5-carbonitrile

MassM^+= 404;IR(KBr): 3269 (-NH,secondary) str.,2968 (-CH_3,Asym.)str., 2870 (-CH_3,sym.)str., 2223 (-CN)str.,1636 (-CO)str.,1365 (N-C)str.,761 (N-H)wag, 1606 (N-H) def, 1230 (C-F)str., 783 (C-Cl)str., 1697 (-CO)str. ;^{1}HNMR(δ ppm) (400MHz,DMSO)δ3.23 (s,3H,N-C*H*$_3$),δ0.91 (d,6H,CH_2-CH-(C*H*$_3$)$_2$), δ1.73 (m,1H,CH_2-C*H*-(CH_3)$_2$), δ2.39 (d,1H,-CH-C*H*$_2$-(CH_3)$_2$),δ6.09 (s,1H,N-C*H*), δ7.01 (s,1H,-C*H*-Cl),δ 7.25-7.75 (m,5H,Ar-*H*).

Biological screening

The compounds were tested for bacterial growth inhibition activity against a primary panel including *Escherichia coli*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* (details given in Table II).

Antimicrobial activity of compounds

Compound preparation

Stock solutions were prepared at 10 mg/mL in DMSO, according to the weight for each compound. Gentle heating and sonication was required to solubilize the compounds.

Single point bacterial inhibition assay

The primary bacteria panel, including *Escherichia coli* ATCC 25922 (GN_001),*Klebsiella pneumonia* ATCC 700603 (GN_003), *Acinetobacterbaumannii* ATCC 19606 (GN_034), *Pseudomonas aeruginosa* ATCC 27853 (GN_042) and *Staphylococcus aureus* ATCC 43300 (MRSA) (GP_020) were cultured in Muller Hinton broth (MHB) at 37°C overnight. A sample of each culture was then diluted 40-fold in fresh MHB broth and incubated at 37°C for 1.5-3 h. The compounds were plated at a single test concentration of 64 μg/mL.Colistin,Polymyxin B,Vancomycin and Daptomycin were serially diluted two-fold across the wells, with compound concentrations ranging from 0.5 to 64 μg/mL, as controls of bacterial inhibitors. The resultant mid-log phase cultures were diluted to the final concentration of 5×105 CFU/mL, then 50 μL was added to each well of the compound containing 96-well plates (Corning; Cat. No 3641, NBS), giving a final compound concentration range of 0.25 μg/mL to 32 μg/mL for control inhibitors and 32 μg/mL for test compounds. All the plates were covered and incubated at 37 °C for 24 h.

Inhibition of bacterial growth was determined visually and were recorded at 32 μg/mL where 100% inhibition was identified(details in Table III).

MIC (Minimum Inhibitory Concentration) assay

The primary bacteria panel, including *Escherichia coli* ATCC 25922 (GN_001) and *Staphylococcus aureus* ATCC 43300 (MRSA) (GP_020) were cultured in Muller Hinton broth (MHB) at 37°C overnight. A sample of each culture was then diluted 40-fold in fresh MHB broth and incubated at 37°C for 1.5-3 h. The compounds were serially diluted two-fold across the wells of non-binding surface 96-well plates (Corning; Cat. No 3641, NBS), with compound concentrations ranging from 0.03 μg/mL to 64 μg/mL, plated in duplicate. The resultant mid-log phase cultures were diluted to the final concentration of 5×105 CFU/mL, then 50 μL was added to each well of the compound-containing 96-well plates, giving a final compound concentration range of 0.015 μg/mL to 32 μg/mL. All the plates were covered and incubated at 37°C for 24 h.

Inhibition of bacterial growth was determined visually after 24 h, where the MIC is recorded as the lowest compound concentration with no visible growth(details given in Table IV).

Anticancer activity of compound

All synthesized compounds have been screened for anticancer activity studies by DTP (Development

Therapeutic Program NCI/NIH, USA) compounds were studied for one dose testing. Graphical study of compound2-(ethylamino)-1,6-dihydro-4-isobutyl-1-methyl-6-oxopyrimidine-5-carbonitrilegiven below.

Conclusions

Alkyl substituted pyrimidine-5-carbonitriletargeted were prepared by condensing4-Isobuty-1,6-dihydro-1-methyl-2-(methylthio)-6-oxopyrimidine-5-carbonitrile with different active pharmacophores(Scheme I) in good yield (Table I). Synthesized compounds were characterized by different spectroscopic methods. Result of constitutional characterization of the obtained products by IR, ^{1}H-NMR and Mass Spectroscopy showed good agreement with the constitution of the targeted molecules. Compound **2-8** showed single point bacterial inhibition and compound **2** and **5** showed confirmation assay MIC (Minimum Inhibitory Concentration) while compound **2** showed anticancer activity. These compounds appeared moderately promising as antimicrobial and anticancer agents (details in Table III, Table IV and Table V).

Supplementary Information

Supplementary information is available in the websitehttp://nopr.niscair.res.in/handle/123456789/58776.

Acknowledgements

Authors are thankful to Maharshi Dayanand Science College, Porbandar for providing Research facilities. The authors are grateful to the NFDD center, Saurashtra University, Rajkot for recording and providing^{1}H-NMR, Mass and IR Spectral data, and also thankful to CO-ADD for biological screening of synthesized compound. Anticancer activity studies by DTP (Development Therapeutic Program NCI/NIH, USA) compounds were studied for one dose testing.

References

1 Merugu R, Garimella S, Balla D & Sambaru K, Synthesis and Biological Activities of Pyrimidines: A Review, *Int J Pharm Tech Res*, 8 (2015) 88.

2 Rani J, Kumar S, Saini M, Mundlia J & Verma P K, *Res ChemIntermed*, 42 (2016) 6777, doi: 10.1007/s11164-016-2525-8.

3 Kumar S, Lim S M, Ramasamy K, Mani V, Shah S A A & Narasimhan B, *Chem Cent J*, 12 (2018) 73, 1.

4 Meneghesso S, Vanderlinden E, Stevaert A, Mc Guigan C, Balzarini J & Naesens L, *Antivir Res*, 94 (2012) 35. doi: 10.1016/j.antiviral.2012.01.007.

5 Yejella R P &Atla S R, *Chem Pharm Bull*, 59(9) (2011) 1079.

6 Ashour H M, Shaaban O G, Rizk O H & El-Ashmawy I M, *Eur J Med Chem*, 62 (2013) 341. doi: 10.1016/j.ejmech.2012.12.003.

7 Bhalgat C M, Ali M I, Ramesh B & Ramu G, *Arab J Chem*, 7 (2014) 986, doi: 10.1016/j.arabjc.2010.12.021.

8 Kumar S & Narasimhan B, *Chem Cent J*, 12 (2018) 38, doi: 10.1186/s13065-018-0406-5

9 Bhatewara A, Jetti S R, Kadre T, Paliwal P & Jain S, *Arch App Sci Res*, 4 (2012) 1274.

10 Shujian T, Shanshan W, Zhengguo H & Wenjuan H, *Chin J Chem*, 27 (2009).

11 Kumar S, Kaushik A & Narasimhan B, *BMC Chemistry*, 13 (2019) 85. https://doi.org/10.1186/s13065-019-0601-z

12 Kumar S, Lim S M, Ramasamy K, Vasudevan M, Shah S A A & Narasimhan B, *Chem Cent J*, 11(80) (2017) 1.

13 Shubakara K, Umesha B, Srikantamurthy N & Chethan J, *Int J Appl Biol Pharm Technol*, 4 (2014) 2.

14 Ram V J, *Arch Pharm*, 323(11) (1990) 895.

15 Thanki P, Hingrajia D & Modha J, *Indian J Heterocycl Chem*, 28 (2018) 201.