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Research Article

SYNTHESIS, CHARACTERIZATION & BIOLOGICAL EVALUATION OF SOME NOVEL PYRIDO[1,2-A] PYRIMIDIN-4-ONE DERIVATIVES

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ABSTRACT

Pyrido[1,2-a]pyrimidin-4-one and their derivatives are found to be key intermediates in the synthesis of medicinally active compounds. Therefore an efficient and convenient procedure has been developed for the synthesis of some novel pyrido[1,2-a]pyrimidin-4-one derivatives like aryl-N-(2-(2-methyl-4-oxo-8-(trifluoromethyl)-4H-pyrido[1,2-a]pyrimidin-3-yl)ethyl) carboxamide and alkyl-N-(2-(2-methyl-4-oxo-8-(trifluoromethyl)-4H-pyrido[1,2-a]pyrimidin-3-yl)ethyl)carboxamide. The structures of the new compounds have been evaluated on the basis of FT-IR, ^{1}H NMR and Mass spectroscopy data. They have also been screened for their antimicrobial activities against various strains of bacteria and fungi.

Keywords: Pyrido[1,2-a]pyrimidin-4-one, Pyridine, Pyrimidine, Antimicrobial activity

1. INTRODUCTION

The organic chemistry and the development of heterocycles initiated accompany since isolated from plants and microorganisms. Nowadays, the majority of articles published in different areas dealing with natural compounds or medicines are related to heterocycles [1]. Pyrido[1,2-a]pyrimidin-4-one structure containing two fused six member rings with one nitrogen atom at the ring junction. Presence of different functional groups on pyridine or pyrimidine ring affected the biological activities of these pyrimidine bases. Various compounds in this product class show biologically activities (mainly because pyridopyrimidines can act as isosteres of biologically active quinazolines or pteridines) [2]. Therefore pyrido[1,2-a]pyrimidin-4-one is important fused nucleus of pyridine and pyrimidine. The chemical structure of pyrido[1,2-a]pyrimidin-4-one is described in Fig. 1.

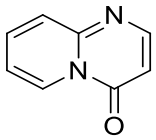


Fig. 1: Chemical structure of pyrido[1,2-a] pyrimidin-4-one

The pyrimidine being a fundamental nucleus in DNA & RNA, pyrido[1,2-a] pyrimidine also collect diverse biological activities. Pyrimidine based compounds have a long and significant history extending from the days of their invention as key ingredient of nucleic acid to their current use in the chemotherapy [3]. 7,8-dihydropyrrolo[1,2-a]pyrimidin-4(6H)-one exhibit anti microbial activity [4]. Last few decades of research on pyrido[1,2-a]pyrimidin-4-one derivatives discovered that, they had wide range of therapeutic applications such as antitumor [5], antimicrobial [6], antifungal [7], anti-inflammatory [8], antiHIV [9], antimalarial [10], Parkinson's disease [11], antianxiety disorders [12] and depression [13].

The pyrido[1,2-*a*]pyrimidine moiety is present in antipsychotic drug, Risperidone **(1)** [14], and its active metabolite Paliperidone **(2)** [15]. This pyrido[1,2-a]pyrimidin-4-one is present in the tranquilizer-Pirenperone **(3)** [16], antihistamine-Ramastine **(4)** [17], the antihypertensive-Seganserin **(5)** [18], analgesic-Rimazolium **(6)** [19], antiallergic-Pemirolast **(7)** [20] and antidepressant-Lusaperidone **(8)** [21]. The chemical structures of these bioactive molecules containing pyrido[1,2-a]pyrimidin-4-one skeleton are represented in Fig. 2.

Based on literature, versatile method for synthesis of novel 3-(2-aminoethyl)-2-methyl-8-(trifluoromethyl)-4H-pyrido[1,2-a]pyrimidin-4-one derivative is describe in **(Scheme 1).**

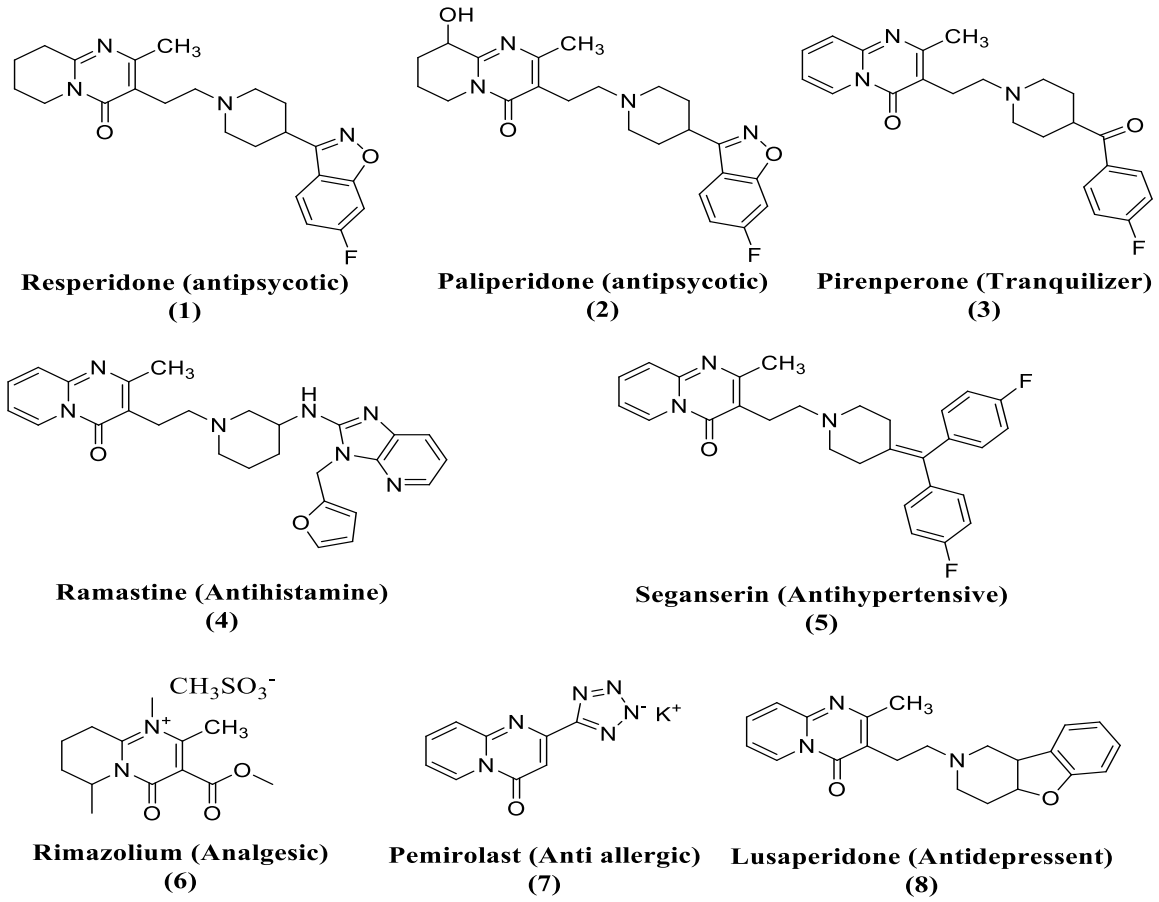
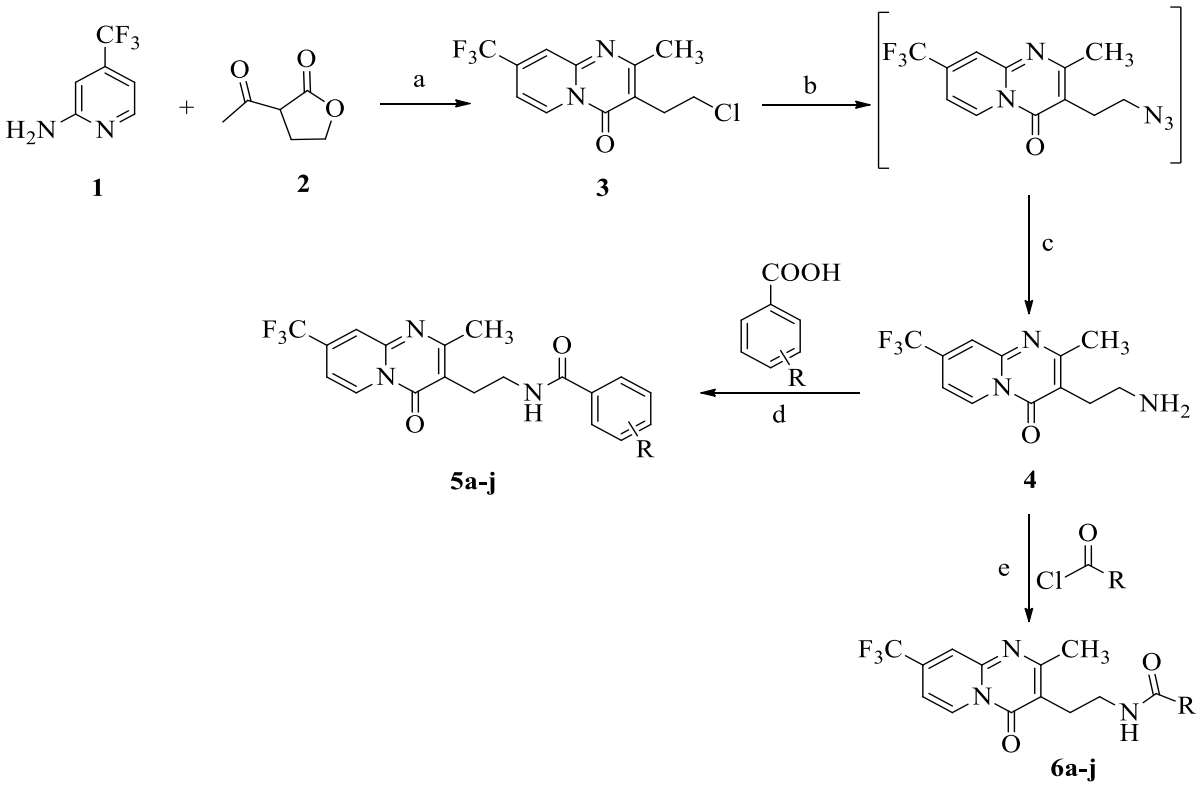


Fig. 2: Chemical structures of bioactive molecules containing pyrido[1,2-a]pyrimidin-4-one compound



Scheme 1: Reaction scheme for synthesis of 5a-j and 6a-j

Reagents: (a) $POCl_3$, Toluene, reflux; (b) Sodium azide, DMF, 80-90°C; (c) Triphenyl phosphine, Toluene, 70-80°C; (d) $SOCl_2$, TEA, DCM, DMF, RT; (e) TEA, DCM, RT

2. MATERIAL AND METHODS

All chemicals purchased were of laboratory grade and used without further purification. The progress of the reaction was monitored by TLC on precoated plates (silica gel 60, F_{254}) and visualized with UV light. Melting points were recorded on Spectral Lab melting point (Model no. Check Melt-2). NMR spectra were recorded using DMSO-d_6 as a solvent on a Bruker 400 MH and chemical shifts are expressed in parts per million (ppm) related to internal standard TMS. IR spectra were determined on a "IR Affinity-1S" (Shimadzu) spectrophotometer. Mass spectrometry data were recorded on LC/MS (Waters): electro spray (+) ionization, mass ranges 100-800 Da, 20-V cone voltage, and Xterra MS C18 column (2.1 mm x 50 mm x 3.5 µm).

2.1. Preparation of 3-(2-chloroethyl)-2-methyl-8-(trifluoromethyl)-4H-pyrido[1,2-a] pyrimidin-4-one (3)

A mixture of 2-amino-4-(trifluoromethyl)pyridine **1** (100.0 g, 0.6168 mole) and alpha-acetylbutyrolactone **2** (197.6 g, 1.542 mole) were dissolved in toluene (2000 ml). Phosphorus oxychloride (500 ml, 5.347 mole) was added drop wise into the reaction mixture at 25-35°C. Resulting reaction mixture was heated at reflux temperature for 5 hr. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was concentrated under vacuum and residue was poured into crush ice and pH was adjust to 10-11 with aqueous ammonia solution and product was extracted in dichloromethane. Organic layer was concentrated under vacuum and this crude compound was purified in mixture of methanol: water (1:1) and the resulting solid was filtered, washed with water and dried under vacuum at 50-60°C to obtain pure 3-(2-chloroethyl)-2-methyl-8-(trifluoromethyl)-4H-pyrido[1,2-a]pyrimidin-4-one **3** (105.0 g); yield 58.65%.

2.2. Preparation of 3-(2-aminoethyl)-2-methyl-8-(trifluoromethyl)-4H-pyrido[1,2-a] pyrimi - din-4-one (4)

A mixture of 3-(2-chloroethyl)-2-methyl-8-(trifluoromethyl)-4H-pyrido[1,2-a]pyrimidin-4-one **3** (40.0 g, 0.1376 mole) and sodium azide (9.8 g, 0.1513 mole) were dissolved in N,N-dimethyl formamide (200 ml). Resulting reaction mixture was heated at 80-90°C for 5 hr. The progress of the reaction was monitored by TLC. After completion of the reaction, reaction mixture was poured into water (600 ml) and product was extracted in toluene (400 ml). Organic layer and aqueous layer were separated and organic layer was washed with water (200 ml). A mixture of organic layer and water (40 ml) was taken into another RBF. A solution of triphenylphosphine (39.7 g, 0.1513 mole) in toluene (120 ml) was added drop wise into reaction mixture at 25-35°C. Resulting reaction mixture was heated at 70-80°C for 3 hr. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mass was cooled at 25-35°C and water (400 ml) was added into the reaction mixture and pH was adjusted to 1-2 with concentrated hydrochloric acid. Organic layer and aqueous layer were separated and aqueous layer was washed with toluene. pH of aqueous layer was adjusted to 10-11 with ammonia solution and product was extract with dichloromethane and organic layer was concentrated under vacuum give pure 3-(2-aminoethyl)-2-methyl-8-(trifluoromethyl)-4H-pyrido[1,2-a]pyrimidin -4-one **4** (32.0 g), yield 86.0%. Mass: m/z 272.1 $[M+H]^+$.

2.3. General procedure for synthesis of substituted aryl-N-(2-(2-methyl-4-oxo-8-(trifluoromethyl)-4H-pyrido[1,2-a]pyrimidin -3-yl)ethyl)carboxamide (5a-j)

A mixture of substituted aromatic acid (0.53 g, 0.0043 mole) was dissolved in dichloromethane (5 ml) and N,N-dimethyl formamide (0.5 ml). Thionyl chloride (0.80 g, 0.0065 mole) was added slowly into reaction mixture. The resulting reaction mixture was heated at reflux temperature for 1 hour. The progress of reaction was monitored by TLC. After completion of reaction, reaction mixture was concentrated under vacuum and residue was dissolved in dichloromethane (5 ml). A mixture of 3-(2-aminoethyl)-2-methyl-8-(trifluoromeths -yl)-4H-pyrido[1,2-a]pyrimidin-4-one **4** (1.0 gm, 0.0036) and triethylamine (0.6 g, 0.0054 mole) was dissolved in dichloromethane (5 ml) into another RBF. Above acid chloride solution was added into reaction mixture at 0-10°C. The resulting reaction mixture was stirred at 25-35°C for 1 hour. The progress of reaction was monitored by TLC. After completion of reaction, water (10 ml) was added into reaction mixture and layer was separated. Organic layer was washed with saturated sodium bicarbonate solution (10 ml X 2) and organic layer was concentrated under vacuum to give crude product. This crude compound was purified in ethyl acetate and the resulting solid was filtered, washed with ethyl acetate and

dried in under vacuum at 40-50°C to give pure substituted aryl-N-(2-(2-methyl-4-oxo-8-(trifluorometh -yl)-4H-pyrido[1,2-a]pyrimidin-3-yl)ethyl)carboxamide **5a-j** (0.90 g), 57-71 %.

2.4. General procedure for synthesis of substituted alkyl-N-(2-(2-methyl-4-oxo-8-(trifluoromethyl)-4H-pyrido[1,2-a]pyrimidin-3-yl)ethyl)carboxa-mide (6a-j)

A mixture of 3-(2-aminoethyl)-2-methyl-8-(trifluoromethyl)-4H-pyrido[1,2-a]pyrimidin-4-one **4** (1.0 g, 0.0036) and triethylamine (0.6 g, 0.0054 mole) was dissolved in dichloromethane (5 ml). Substituted acetyl chloride (0.6 g, 0.0054 mole) was added into reaction mixture at 0-10°C. Reaction mixture was stirred at 25-35°C for 1 hour. The progress of reaction was monitored by thin layer chromatography. After completion of reaction, water (10 ml) was added into reaction mixture and layer was separated. Organic layer was washed saturated sodium bicarbonate solution (10 ml X 2) and organic layer was concentrated under vacuum to give crude product and this crude compound was purified in ethyl acetate and the resulting solid was filtered, wash with ethyl acetate and dried in under vacuum at 40-50°C to give substituted alkyl-N-(2-(2-methyl-4-oxo-8-(trifluoromethyl)-4H-pyrido[1,2-a]pyri -midin-3-yl)ethyl)carbo -xamide **6a-j** (0.80 g), 56-74%.

2.5. Antibacterial and antifungal activities

The newly synthesized compounds were analyzed for their *in vitro* antibacterial activity against gram negative *Escherichia coli* and *Pseudomonas aeruginosa*, gram positive *Staphylococcus aureus* and *Bacillus subtilis* and antifungal activity against *Aspergillus paraciticus* and *Rhizopus* by micro broth dilution method. The standard strains used for screening antibacterial and antifungal activities were procured from Atmiya Institute of Pharmacy *in vitro* testing Laboratory, Rajkot, Gujarat, India. The standard drugs Streptomycin and Ampicillin were used for antibacterial activity and Nystatin was used for antifungal activity. 1000 µg/ml, 500 µg/ml, 250 µg/ml, 125 µg/ml and 62.5 µg/ml, concentrations of the synthesized compounds were taken.

3. RESULTS AND DISCUSSION

3.1. Characteristics Physical data

As described in synthetic Scheme 1, 2-amino-4-(trifluoromethyl)pyridine **1** is reacted with alpha-acetylbutyrolactone **2** in the presence of phosphorus oxychloride in toluene at reflux temperature to give 3-(2-chloroethyl)-2-methyl-8-(trifluoromethyl)-4H-pyrido [1,2-a]pyrimidin-4-one **3**, which is reacted with sodium azide in N,N-dimethyl formamide at 80-90°C to give azide intermediate which is insitu reacted with triphenyl phosphine in toluene at 70-80°C to give -(2-aminoethyl)-2-methyl-8-(trifluoromethyl)-4H-pyrido[1,2-a]pyrimidin -4-one **4.**

This amine scaffold **4** then converted into amide by the reaction of different substituted aromatic acid in the presence of thionyl chloride, N,N-dimethyl formamide and triethylamine in DCM at RT to give novel substituted N-aryl(2-(2-methyl-4-oxo-8-(trifluorometh -yl)-4H-pyrido[1,2-a]pyrimidin-3-yl)ethyl) carboxamide **5a-j**. The characterization physical data are reported in **Table 1**.

Table 1: Characteristics Physical data of Compound 5a-j

Compound	Substitution R	Color	M.P.	Yield
5a	-H	Off white	186-188°C	57.0
5b	2-Br	Cream	186-188°C	71.0
5c	4-Cl	Cream	162-164°C	68.0
5d	3-I	Cream	182-184°C	70.0
5e	5-Br,2-Cl	Cream	188-190°C	65.0
5f	3-OCH_3	Cream	150-152°C	63.0
5g	3,4-dimethoxy	Cream	159-161°C	64.0
5h	4-NO_2	Light yellow	215-217°C	67.0
5i	4-OH	Light yellow	203-205°C	60.0
5j	2-$OCOCH_3$	Off white	169-171°C	62.0

This amine scaffold **4** was then converted into amide by the reaction of different substituted acetyl chloride in the presence of triethylamine in DCM at RT to give novel substituted N-alkyl(2-(2-methyl-4-oxo-8-(trifluoromethyl)-4H-pyrido[1,2-a]pyrimidin-3-yl)ethyl)carboxamide **6a-j**. The characterization physical data are reported in Table 2.

Table 2: Characteristics Physical data of Compound 6a-j

Compound	Substitution R	Color	M.P.	Yield
6a	$-CH_3$	Cream	131-133°C	74.0
6b	$-CH_2Cl$	Gray	139-141°C	67.0
6c	$-CHCl_2$	Cream	145-147°C	59.0
6d	$-CH_2CN$	Off white	161-163°C	61.0
6e	$-C(CH_3)_3$	Off white	126-128°C	67.0
6f	$-CH_2CH_3$	Off white	156-158°C	70.0
6g	$-CH_2CH_2CH_3$	Cream	175-177°C	68.0
6h	$-CH(CH3)_2$	Off white	181-183°C	58.0
6i	$-CH_2(CH2)_2CH_3$	Off white	142-144°C	62.0
6j	$-CH_2(CH_2)_5CH_3$	Off white	133-135°C	56.0

3.2.Spectral data of synthesized compounds

The structure of synthesized compounds was established on the basis of ^{1}H NMR, Mass and FTIR spectral data.

3.2.1. 3-(2-chloroethyl)-2-methyl-8-(trifluorometh -yl)-4H-pyrido[1,2-a]pyrimidin-4-one (3)

Off white Solid; **^{1}H NMR (400 MHz, DMSO-d_6):** 2.56 (3H, s), 3.10-3.13 (2H, t), 3.81-3.84 (2H, t), 7.58-7.60 (1H, dd), 8.17 (1H, s), 9.04-9.06 (1H, d) ppm; **MS:** m/z 290.8 & 293.0 $[M+H]^+$.

3.2.2. 2-bromo-N-(2-(2-methyl-4-oxo-8-(trifluoro methyl)-4H-pyrido[1,2-a]pyrimidin-3-yl) ethyl)benzamide (5b)

Cream Solid; M.p.: 186-188°C, Yield: 71%. **^{1}H NMR (400 MHz, DMSO-d_6):** 2.53 (3H, s), 2.89-2.92 (2H, t), 3.44-3.49 (2H, q), 7.33-7.35 (2H, m), 7.40-7.46 (2H, dd), 7.62-7.63 (1H, d), 7.99 (1H, s), 8.47-8.50 (1H, t), 8.98-9.00 (1H, d) ppm; **MS:** m/z 454.0 & 456.1 $[M+H]^+$, **IR Cm^{-1}:** 3279, 3063, 1651, 1543, 1303, 1234, 895,779.

3.2.3. 4-chloro-N-(2-(2-methyl-4-oxo-8-(trifluoro -methyl)-4H-pyrido[1,2-a]pyrimidin-3-yl) ethyl)benzamide (5c)

Cream Solid; M.p.: 162-164°C, Yield: 68.0%. **^{1}H NMR (400 MHz, DMSO-d_6):** 2.44 (3H, s), 2.88-2.92 (2H, t). 3.45-3.50 (2H, q), 7.51-7.55 (2H, m), 7.70-7.72 (1H, dd), 7.79-7.81 (2H, d), 7.98 (1H, s), 8.66-8.69 (1H, t), 8.98-9.00 (1H, d) ppm; **MS:** m/z 410.1 & 412.1 $[M+H]^+$, **IR Cm^{-1}:** 3279, 3086, 1674, 1635, 1535, 1303, 1234, 895, 840,786.

3.2.4. 3-methoxy-N-(2-(2-methyl-4-oxo-8-(triflu-oromethyl)-4H-pyrido[1,2-a]pyrimidin-3-yl)ethyl)benzamide (5f)

Cream Solid; M.p.: 150-152°C, Yield: 63%. **^{1}H NMR (400 MHz, DMSO-d_6):** 2.45 (3H, s), 2.88-2.92 (2H, t), 3.45-3.50 (2H, q), 3.78 (3H, s), 7.05-7.08 (1H, m), 7.33-7.36 (3H, m), 7.44-7.46 (1H, dd), 7.99 (1H, s), 8.56-8.59 (1H, t), 8.99-9.01 (1H, d) ppm; **MS:** m/z 406.2 $[M+H]^+$, **IR Cm^{-1}:** 3348, 3078, 1674, 1635, 1535, 1311, 1234, 887,779.

3.2.5. N-(2-(2-methyl-4-oxo-8-(trifluoromethyl)-4H-pyrido[1,2-a]pyrimidin-3-yl)ethyl) pivalamide (6e)

Off white Solid; M.p.: 126-128°C, Yield: 67%. **^{1}H NMR (400 MHz, DMSO-d_6):** 1.03 (9H, s), 2.47 (3H, s), 2.76-2.79 (2H, t), 3.24-3.29 (2H, q), 7.42-7.45 (1H, dd), 7.59-7.62 (1H, t), 7.98 (1H, s), 8.97-8.98 (1H, d) ppm; **MS:** m/z 356.2 $[M+H]^+$, **IR Cm^{-1}:** 3325, 3070, 2970, 1674, 1635, 1535, 1303, 1226, 910,779, 686.

3.2.6. N-(2-(2-methyl-4-oxo-8-(trifluoromethyl)-4H-pyrido[1,2-a]pyrimidin-3-yl)ethyl) propionamide (6f)

Off white Solid; M.p.: 156-158°C, Yield: 70%. **^{1}H NMR (400 MHz, DMSO-d_6):** 0.93-0.97 (3H, s), 1.98-2.04 (2H, q), 2.46 (3H, s), 2.74-2.78 (2H, t),

3.22-3.27 (2H, q), 7.43-7.45 (1H, dd), 7.85-7.87 (1H, t), 7.99 (1H, s), 8.96-8.98 (1H, d) ppm; **MS:** m/z 328.1 $[M+H]^+$, **IR Cm^{-1}:** 3302, 3086, 2985, 1674, 1643, 1543, 1303, 1234, 895,779, 702.

3.2.7. N-(2-(2-methyl-4-oxo-8-(trifluoromethyl)-4H-pyrido[1,2-a]pyrimidin-3-yl)ethyl) isobutyramide (6h)

Off white Solid; M.p.: 181-183°C, Yield: 58%. **^{1}H NMR (400 MHz, DMSO-d$_6$):** 0.94-0.95 (6H, d), 2.24-2.27 (1H, m), 2.75-2.78 (2H, t), 3.23-3.28 (2H, q), 7.43-7.45 (1H, dd), 7.81-7.84 (1H, t), 7.98 (1H, s), 8.96-8.98 (1H, d) ppm; **MS:** m/z 342.0 $[M+H]^+$, **IR Cm^{-1}:** 3286, 3055, 2970, 1674, 1643, 1543, 1303, 1234, 895,779, 702.

3.3. Antimicrobial Evaluation

Broth dilution methods have been used to determine the minimal concentration of antimicrobial agent that inhibits the growth of microorganisms. The MIC values are given in Table 3 and 4.

Table 3: Antibacterial and Antifungal activity of 5a-j

Compound Codes	Antibacterial MIC (µg/ml)				Antifungal MIC (µg/ml)	
	Staphylococ cusaureus	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Escherichia coli*	*Aspergillus paraciticus*	*Rhizopus*
Streptomycin			50	50		
Ampicillin	100	100				
Nystatin					100	100
5a	1000	1000	1000	500	500	500
5b	1000	1000	1000	1000	500	500
5c	500	250	250	250	250	125
5d	1000	1000	1000	1000	1000	500
5e	1000	1000	1000	1000	1000	1000
5f	500	1000	1000	500	1000	1000
5g	500	500	500	1000	1000	1000
5h	500	500	1000	500	1000	1000
5i	1000	1000	500	500	1000	1000
5j	500	500	500	500	500	250

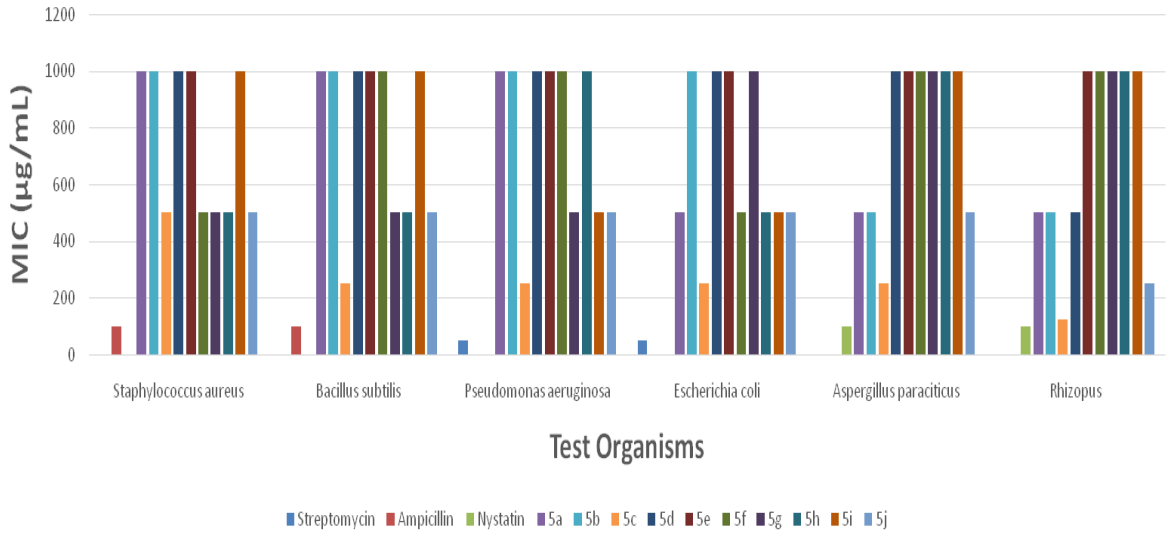


Fig. 3: Antibacterial and antifungal activity, Minimum Inhibition Concentration (Graphical form) of 5a-j

Table 4: Antibacterial and Antifungal activity of 6a-j

Compound Codes	Antibacterial MIC (µg/ml)				Antifungal MIC (µg/ml)	
	Staphylococ cusaureus	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Escherichia coli*	*Aspergillus paraciticus*	*Rhizopus*
Streptomycin			50	50		
Ampicillin	100	100				
Nystatin					100	100
6a	1000	1000	1000	1000	1000	1000
6b	1000	1000	1000	1000	1000	1000
6c	500	1000	1000	1000	500	500
6d	1000	1000	1000	1000	1000	1000
6e	500	500	500	500	500	500
6f	500	500	500	500	250	250
6g	500	500	500	500	1000	1000
6h	250	250	1000	250	1000	1000
6i	1000	500	500	500	125	125
6j	125	125	125	125	500	500

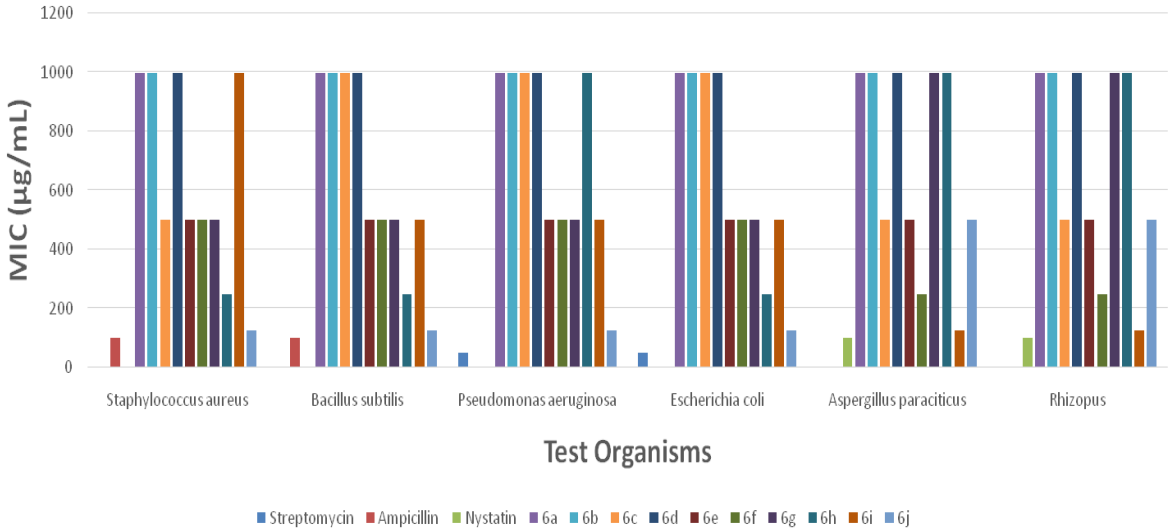


Fig. 4: Antibacterial and antifungal activity, Minimum Inhibition Concentration (Graphical form) of 6a-j

The newly synthesized compounds were analyzed for their *in vitro* antibacterial and anti fungal activity. The analysis of antimicrobial and antifungal screening data shows that compounds **5c** (4-chlorobenzyl)**, 5j** (2-acetoxybenzyl)**, 6e** (tert-butyl)**, 6f** (ethyl), **6i** (butyl) and **6j** (heptyl) are broad spectrum compound which can reduce the growth of gram positive, gram negative bacteria and fungi. Compounds **6g** (propyl) and **6h** (isopropyl) are potentially efficient against both gram-positive and gram-negative bacteria but not able to inhibit fungi. Compound **5a** (benzyl), **5b** (2-bromobenzyl) and **6c** (1,1-dichloromethyl) exhibited mainly antifungal activity.

It is observed that compound **5e** (5-bromo-2-chlorobenzyl), **6a** (methyl), **6b** (chloromethyl), **6d** (cyanomethyl) are poorly active against gram positive, gram negative bacteria and fungi. Compound **5d** (3-iodobenzyl) is poorly active against gram positive and gram negative bacteria but moderately active against fungi. Whereas rests of the compounds are also potent

compound, gives narrow spectrum action against pathogenic microbes.

4. CONCLUSION

In summary, we have developed an efficient and convenient procedure for the preparation of pyrido[1,2-a]pyrimidin-4-one derivative. The structure of all newly synthesized compound **5a-j** and **6a-j** was established on the basis of spectral analysis like IR, ^{1}H NMR, and LC-Mass spectroscopic analysis.

All the synthesized compounds were analyzed for their antimicrobial activity. The investigation of antimicrobial and antifungal screening data revealed that compounds **5c, 5j, 6e, 6f, 6i** and **6j** are broad spectrum compound which can inhibit the growth of gram-positive, gram-negative bacteria as well as fungi. Compounds **6g** and **6h** are potentially efficient against both gram-positive and gram-negative bacteria but not able to inhibit fungi. Compounds **5a, 5b** and **6c** exhibited mainly antifungal activity. Whereas rest of the compounds is also potent compound, gives narrow spectrum action against pathogenic microbes.

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