Turk J Chem
35 (2011) , 915 – 924.

doi:10.3906/kim-1012-888

Synthesis and antimicrobial activity of novel 2-(pyridin-2-yl)thieno[2,3-*d*]pyrimidin-4 (3*H*)-ones

Nitin G. HASWANI, Sanjaykumar B. BARI*
Department of Pharmaceutical Chemistry, R.C. Patel Institute of Pharmaceutical Education and Research, Shirpur Near Karwand Naka, Shirpur 425 405 Dist-Dhule-INDIA
e-mails: nitin_haswani@yahoo.com, nhsb2010@gmail.com

Received: 21.12.2010

In the present study, some new 2-(pyridin-2-yl)thieno[2,3-*d*]pyrimidin-4(3*H*)-ones derivatives (**IIa-o**) were synthesized. The target compounds (**IIa-o**) were synthesized through the acid catalyzed condensation of 2-cyano, 3-cyano, and 4-cyano-pyridines with various 2-amino-3-carbethoxythiophenes (Ia-e). All thiophene derivatives were synthesized by Gewald reaction. The structures of the newly synthesized compounds were confirmed by UV-Visible, FT-IR, ^{1}H-NMR, and mass spectral studies. All synthesized compounds were evaluated for their antimicrobial activity against various gram-positive and gram-negative bacterial and fungal strains. Amongst the synthesized compounds **IIa**, **IIb**, **IId**, **IIe**, and **IIm** were found to be active.

Key Words: Thienopyrimidine, Gewald reaction, antimicrobial activity

Introduction

A large number of thienopyrimidines are reported in the literature as virucides, bactericides, fungicides, acaricides, and insecticides.[1,2] Condensed thienopyrimidines exhibited interesting biological activities like antibacterial,[3] antihistaminic,[4] analgesic, anti-inflammatory[5] and anti-malarial.[6] Various condensed quinazoline and thienopyrimidine systems were studied for their biological activities.[7] A large number of tetrahydrobenzothieno derivatives have been reported as anticancer, antibacterial, and antifungal agents.[8] Several thienopyrimidones were also synthesized and evaluated for their anticonvulsant activity.[9] To further explore these bioactive thienopyrimidines,[10] we aimed to synthesize and characterize some new substituted pyridin-2-yl thienopyrimidine-4(3*H*)-one derivatives and to evaluate these compounds for antimicrobial activity. It

*Corresponding author

was observed that both moieties are pharmacophores showing potential antimicrobial activity. Moreover, there are reports on antibacterial activity observed in condensed and mononuclear pyrimidines possessing pyridinyl substituents at 2-, 4-, and 5-positions.

Experimental

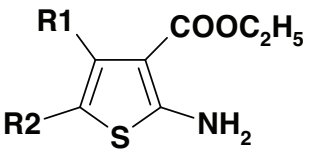
All chemicals used were of laboratory grade (Qualigen, Merck). The melting points were determined by open capillary method on a Campbel electronic apparatus and are uncorrected. The ultraviolet absorption spectra were determined in methanol by using a Shimadzu 1601 UV-Visible double beam spectrophotometer. The IR spectra of synthesized compounds were recorded on a Shimadzu 8400S FT-IR in potassium bromide disks. The ^{1}H-NMR was recorded in $CDCl_3$ using a NMR Varian-Mercury 300 MHz spectrometer and chemical shifts are given in units as δ ppm, downfield from tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained on an Electron Impact mass spectrometer at 70 eV ionizing beam and using a direct insertion probe.

The progress of reactions was monitored by thin layer chromatography using chloroform-methanol or chloroform-methanol-ammonia as the solvent systems and spots were visualized after exposure to iodine vapors or under ultraviolet (UV) light.

Synthesis of 2-amino-3-carbethoxythiophenes (Ia-e) (Table 1)

he 2-amino-3-carbethoxythiophenes were synthesized by the variant of the well-known Gewald synthesis.[11–15] The following method was used to prepare thiophene-o-aminoesters (I a-e).

Table 1. 2-Amino-3-carbethoxythiophenes (Ia-e).

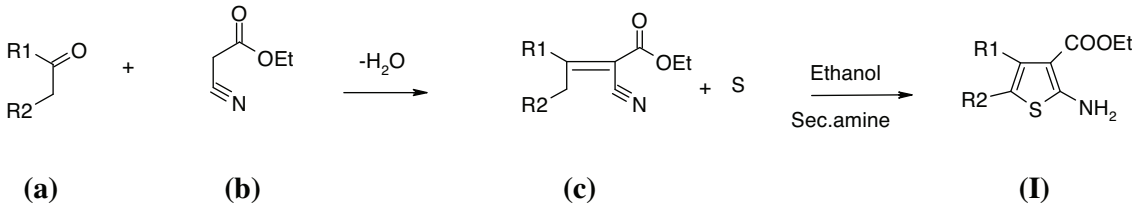


Compound ID	R^1	R^2
Ia	$-CH_3$	$-CH_3$
Ib	-H	$-C_2H_5$
Ic	$-(CH_2)_4-$	
Id	$4-ClC_6H_4$	-H
Ie	$-_6H_5$	

General method[16,17]

The first step was carried out for prior condensation of an aldehyde or ketone (a) with an appropriate cyanomethylene compound (b), usually under the influence of sodium or ammonium acetate to obtain α, β-unsaturated nitrile (c) (Knoevenagel condensation product, which is otherwise known as alkylidine intermediate) in a suitable solvent like benzene. Water molecules formed during the reaction were removed using a Dean-Stark condenser.

In the second step the alkylidine intermediate was reacted with sulfur in ethanol containing a secondary base such as diethylamine at around 50 °C to complete the preparation (Scheme 1).



(a) **(b)** **(c)** **(I)**

Scheme 1

Synthesis of ethyl 2-amino-4, 5-dimethylthiophene-3-carboxylate (Ia)

2-Butanone (0.1 mol), sulfur (0.1 mol), ethyl cyanoacetate (0.1 mol), and ethanol (20 mL) were mixed and stirred together. To this well stirred mixture diethylamine (0.125 mol) was added dropwise for up to half an hour and it was stirred for 3 h. The reaction mixture was kept in a refrigerator overnight. The solid separated was filtered, and washed with chilled 50% methanol. Yield 64.7%, mp 91-92 °C.

IR (KBr) cm^{-1}: 3155 (N-H), 2984 (CH), 1657 (COOEt); UV (MeOH) λmax: 310.4 nm

Synthesis of ethyl 2-amino-3-carbethoxy-5-ethylthiophene-3-carboxylate (Ib)

The mixture of butyraldehyde (0.1 mol), sulfur (0.1 mol), and ethyl cyanoacetate (0.1 mol) in dimethylformamide (15.2 mL) was stirred at 50 °C for 6 h. Triethylamine (0.1 mol) was added dropwise for up to half an hour and stirring continued for another 12 h at ambient temperature. The reaction mixture was kept in a refrigerator overnight. The solid separated was filtered the next day, and washed with 20 mL of chilled 50% methanol. Yield 68.7%, mp 62-63 °C.

IR (KBr) cm^{-1}: 3167 (NH), 2966 (CH), 1660 (COOEt); UV (MeOH) λmax: 305.2 nm.

Synthesis of ethyl 2-amino-4, 5, 6, 7-tetrahydrobenzo[b]thiophene-3-carboxylate (Ic)

Cyclohexanone (0.1 mol), sulfur (0.1 mol), ethyl cyanoacetate (0.1 mol), and ethanol (20 mL) were mixed and stirred together. To this mixture diethylamine (0.125 mol) was added dropwise for up to half an hour and stirring continued for another 3 h at ambient temperature. The reaction mixture was kept in a refrigerator overnight. The solid separated was filtered the next day, and washed with 20 mL of chilled 50% methanol. Yield 88.9%, mp 110-112 °C.

IR (KBr) cm^{-1}: 3165 (NH), 2988 (CH) 1649, (COOEt); UV (MeOH); λmax: 311.0 nm.

Synthesis of ethyl 2-amino-5-(4-chlorophenyl)thiophene-3-carboxylate (Id)

Step I

In a round-bottomed flask fitted with a Dean-Stark condenser, 4-chloroacetophenone (0.1 mol), ethyl cyanoacetate (0.1 mol), glacial acetic acid (0.08 mol), ammonium acetate (0.02 mol), and benzene (50 mL) were refluxed, until the water was totally removed (slight excess of the calculated value). Benzene was distilled out thereafter

and the reaction mixture was dissolved in dichloromethane (50 mL) and washed with $NaHCO_3$ (10% solution), NaCl (10% solution), and water (20 mL). The organic layer was separated and dried, and dichloromethane was distilled out. The solid product alkylidene ethyl cyanoacetate obtained was used as such for the second step, without purification.

Step II

The intermediate isolated in Step I (0.082 mol) was dissolved in methanol (30 mL) and reacted with sulfur (0.082 mol) and diethylamine (0.103 mol) to yield 19.5 g crystalline product (69.23% yield), mp 102-104 °C.

IR (KBr) cm^{-1}: 3109 (NH), 2890 (CH), 1660 (COOEt); UV (MeOH); λmax: 286.2 nm.

Synthesis of ethyl 2-amino-5-methyl-4-phenylthiophene-3-carboxylate (Ie)

Step I

Propiophenone (0.1 mol), ethyl cyanoacetate (0.1 mol), glacial acetic acid (0.08 mol), ammonium acetate (0.02 mol), and benzene (50 mL) were reacted as per the procedure described for compound Id (Method B).

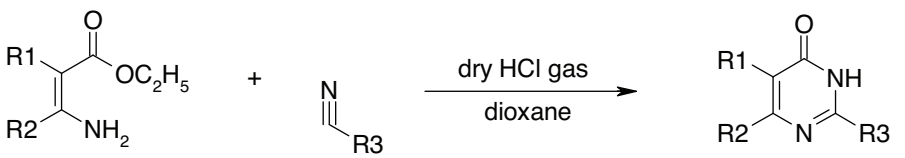
Step II

The intermediate (0.08 mol) isolated was reacted with sulfur (0.08 mol) and diethylamine (0.1 mol) to yield crystalline product yield 64.3%, mp 91-93 °C.

IR (KBr) cm^{-1}: 3154 (NH), 2986 (CH), 1649 (COOEt); UV (MeOH); λmax: 307.8 nm.

Synthesis of 2-(pyridine-2-yl)thieno[2,3-d]pyrimidin-4(3*H*)-ones (**II a-o**) (Table 2)

The target compounds, namely 2-(pyridine-2-yl)thieno[2,3-d]pyrimidin-4(3*H*)-ones (II a-o), were synthesized by dry HCl gas catalyzed one pot condensation of the appropriate 2-amino-3-carbethoxythiophenes (**Ia-e**) and cyanopyridines (III) in excellent yields (Scheme 2).[18–20]



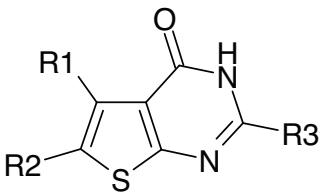
(Ia-e) **(III)** **(II a-o)**

Scheme 2

General method for the synthesis of compounds IIa-o

The mixture of the corresponding compound I, the appropriate cyanopyridine (III), and saturated solution of HCl in dioxane (7 M) was stirred at 0-5 °C for 6 h, followed by further stirring for 2 h at room temperature and heating on a boiling water-bath for 2 h. The reaction mixture was then worked up as usual, involving pouring on an ice-water mixture and making it alkaline with concentrated ammonium hydroxide to give the target compounds (**IIa-o**).

Table 2. Substituted 2-(pyridine-2-yl)thieno[2,3-d]pyrimidin-4(3H)-ones(IIa-o).



Compound ID	R^1	R^2	R^3
IIa	CH_3-	CH_3-	2-C_5H_4N
IIb	CH_3-	CH_3-	3-C_5H_4N
IIc	CH_3-	CH_3-	4-C_5H_4N
IId	H	-C_2H_5	2-C_5H_4N
IIe	H	-C_2H_5	3-C_5H_4N
IIf	H	-C_2H_5	4-C_5H_4N
IIg	-$(CH_2)_4$-		2-C_5H_4N
IIh	-$(CH_2)_4$-		3-C_5H_4N
IIi	-$(CH_2)_4$-		4-C_5H_4N
IIj	4-ClC_6H_4	H	2-C_5H_4N
IIk	4-ClC_6H_4	H	3-C_5H_4N
IIl	4-ClC_6H_4	H	4-C_5H_4N
IIm	C_6H_5	CH_3	2-C_5H_4N
IIn	C_6H_5	CH_3	3-C_5H_4N
IIo	C_6H_5	CH_3	4-C_5H_4N

5, 6-dimethyl-2-(pyridin-2-yl)thieno[2,3-*d*]pyrimidin-4(3*H*)-one (IIa)

Yield 88%; mp 188-191 °C; IR (KBr) cm^{-1}: 3116.75 (N-H), 2856.67 (CH), 1661.61 (CONH); UV (MeOH) λmax: 348.0 nm; ^{1}H-NMR ($CDCl_3$)δ (ppm): 7.97-8.70 (4H, m, arom.), 9.05 (1H, s, N-H), 2.22 (3H, s, CH_3), 2.26 (3H, s, CH_3); MS m/z (%): 258 $[M+1]^+$

5, 6-dimethyl-2-(pyridin-3-yl)thieno[2,3-*d*]pyrimidin-4(3*H*)-one (IIb)

Yield 98%; mp 299-302 °C, IR (KBr) cm^{-1}: 3060.11 (N-H), 2920.03 (CH), 1654.91 (CONH); UV (MeOH) λmax : 337.0 nm; ^{1}H-NMR ($CDCl_3$)δ (ppm): 9.05-8.02 (4H, m, arom.), 8.02 (1H, s, CONH), 2.25 (3H, s, CH_3), 2.26 (3H, s, CH_3); MS m/z (%): 257, 258$[M+1]^+$, 225, 184.

5, 6-dimethyl-2-(pyridin-4-yl)thieno[2,3-*d*]pyrimidin-4(3*H*)-one (IIc)

Colorless crystals, Yield 79%; 342-345 °C; IR (KBr) cm^{-1}: 3095.54 (N-H), 2958.60 (CH), 1662.52 (CONH); UV (MeOH) λmax: 346.0 nm; ^{1}H-NMR ($CDCl_3$)δ (ppm): 8.72-7.82 (4H, m, arom.), 8.74 (1H, s, CONH), 2.22 (3H, s, CH_3), 2.24 (3H, s, CH_3); MS m/z (%) 257, 258$[M+1]^+$, 225, 184.

6-ethyl-2-(pyridin-2-yl)thieno[2,3-d]pyrimidin-4(3H)-one (IId) Colorless crystals, Yield 76%; mp 148-151 °C, IR (KBr) cm^{-1}: 3299.98 (N-H), 2935.46 (CH), 1693.38 (CONH); UV (MeOH) λmax: 339.0 nm; ^{1}H-NMR ($CDCl_3$)δ (ppm): 8.02-7.94 (5H, m, arom.), 8.72 (1H, s, CONH), 2.22-1.20 (5H, m, aliphatic), MS m/z (%) 257, 258$[M+1]^+$, 225.

6-ethyl-2-(pyridin-3-yl)thieno[2,3-*d*] pyrimidin-4(3*H*)-one (IIe)

Crystalline solid, Yield 85%; mp 223-226 °C, IR (KBr) cm^{-1}: 3064.68 (N-H), 2877.60 (CH), 1697.24 (CONH); UV (MeOH) λmax: 328.0 nm; ^{1}H-NMR ($CDCl_3$)δ (ppm): 9.02-8.01 (5H, m, arom.), 8.58 (1H, s, CONH), 2.12-1.22 (5H, m, aliphatic); MS m/z (%) 257, 258$[M+1]^+$, 225.

6-ethyl-2-(pyridin-4-yl)thieno[2,3-*d*]pyrimidin-4(3*H*)-one (IIf)

Colorless crystals, Yield 78%; mp 226-229 °C; IR (KBr) cm^{-1}: 3159.18 (N-H), 2939.31 (CH), 1650.95 (CONH); UV (MeOH) λmax: 336.0 nm; ^{1}H-NMR ($CDCl_3$)δ (ppm): 8.02-7.83 (5H, m, arom.), 8.58 (1H, s, CONH), 2.02-1.20 (5H, m, aliphatic); MS m/z (%) 257, 258$[M+1]^+$, 225.

2-(pyridin-2-yl)-5,6,7,8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (IIg)

Fine needles, Yield 91%; mp 196-200 °C; IR (KBr) cm^{-1}: 3309.62 (N-H), 2925.81 (CH), 1676.03 (CONH); UV (MeOH) λmax: 355.0 nm; ^{1}H-NMR ($CDCl_3$)δ (ppm): 7.97-8.70 (4H, m, arom.), 7.82 (1H, s, CONH), 2.95-2.89 (8H, m, aliphatic); MS m/z (%) 284 $[M+1]^+$, 252, 206.

2-(pyridin-3-yl)-5, 6, 7, 8-tetrahydro[1]benzothieno[2,3-*d*]pyrimidin-4(3*H*)-one (IIh)

Fine needles, Yield 97%; mp 302-305 °C, IR (KBr) cm^{-1}: 3172.68 (N-H), 2935.45 (CH), 1647.10 (CONH); UV (MeOH) λmax: 338.0 nm; ^{1}H-NMR ($CDCl_3$)δ (ppm): 8.55-7.54 (4H, m, arom.), 7.77 (1H, s, CONH), 2.95-2.90 (8H, m, aliphatic); MS m/z (%) 284 $[M+1]^+$, 252, 206.

2-(pyridin-4-yl)-5, 6, 7, 8-tetrahydro[1]benzothieno[2, 3-*d*]pyrimidin-4(3*H*)-one (IIi)

Fine needles, Yield 92.35%; mp 311-314 °C; IR (KBr) cm^{-1}: 3107.11 (N-H), 2937.38 (CH), 1654.91 (CONH); UV (MeOH) λmax: 348.0 nm; ^{1}H-NMR ($CDCl_3$)δ (ppm): 8.71-7.82 (4H, m, arom.), 7.77 (1H, s, CONH), 2.95-2.91 (8H, m, aliphatic); MS m/z (%) 284 $[M+1]^+$, 252, 206.

5-(4-chlorophenyl)-2-(pyridin-2-yl)thieno[2,3-*d*]pyrimidin-4(3*H*)-one (IIj)

Colorless crystalline solid, Yield 91.79%; mp 303-306 °C, IR (KBr) cm^{-1}: 3213.19 (N-H), 3076.10 (CH), 1686.67 (CONH), 779.19 (Cl); UV (MeOH) λmax: 337.5 nm; ^{1}H-NMR ($CDCl_3$)δ (ppm): 7.61-8.02 (9H, m, arom.), 8.73 (1H, s, CONH); MS m/z (%) 341$[M+1]^+$, 343$[M+2]^+$, 308, 262.

5-(4-Chloro-phenyl)-2-(pyridin-3-yl)thieno[2, 3-*d*]pyrimidin-4(3*H*)-one (IIk)

Colorless crystalline solid, Yield 95%; mp 302-305 °C; IR (KBr) cm^{-1}: 3069.75(N-H), 2958.60 (CH), 1649.02 (CONH), 783.05 (Cl); UV (MeOH) λmax: 330.0 nm; ^{1}H-NMR ($CDCl_3$)δ (ppm): 7.60-8.61 (9H, m, arom.), 8.35 (1H, s, -CONH); MS m/z (%) 341$[M+1]^+$, 343$[M+2]^+$, 308, 262.

5-(4-Chloro-phenyl)-2-(pyridin-4-yl)thieno[2, 3-*d*]pyrimidin-4(3*H*)-one (IIl)

Colorless crystalline solid, Yield 92%; mp 302-305 °C, IR (KBr) cm^{-1}: 3089.75 (N-H), 2871.81 (CH), 1697.24 (CONH), 767.62 (Cl); UV (MeOH) λmax: 338.0 nm; ^{1}H-NMR ($CDCl_3$)δ (ppm): 7.59-8.79 (9H, m, arom.), 8.76 (1H, s, CONH); MS m/z (%) 341$[M+1]^+$, 343$[M+2]^+$, 308, 262.

6-methyl-5-phenyl-2-(pyridin-2-yl)thieno[2,3-*d*]pyrimidin-4(3*H*)-one (IIm)

Crystalline product, Yield 84%; mp 164-167 °C; IR (KBr) cm^{-1}: 3215.11 (N-H), 2954.74 (CH), 1674.10 (CONH); UV (MeOH) λmax: 352.0 nm; ^{1}H-NMR ($CDCl_3$)δ (ppm): 9.02-8.34 (9H, m, arom.), 8.58 (1H, s, CONH), 2.29 (3H, s, aliphatic).

MS m/z (%) 319$[M+1]^+$, 320, 287, 242.

6-methyl-5-phenyl-2-(pyridin-3-yl)thieno[2,3-*d*]pyrimidin-4(3*H*)-one (IIn)

Crystalline product, Yield 98%; mp 282-285 °C; IR (KBr) cm^{-1}: 3182.33 (N-H), 2948.96 (CH), 1654.81 (CONH); UV (MeOH) λmax: 344.0 nm; ^{1}H-NMR ($CDCl_3$)δ (ppm): 8.34-7.84 (9H, m, arom.), 8.61 (1H, s, CONH), 2.28 (3H, s, aliphatic); MS m/z (%) 319, 320$[M+1]^+$, 287, 242.

6-methyl-5-phenyl-2-(pyridin-4-yl)thieno[2,3-*d*]pyrimidin-4(3*H*)-one (IIo)

Crystalline product, Yield 87%; mp 248-251 °C, IR (KBr) cm^{-1}: 3176.54(N-H), 2955.57 (CH), 1658.67 (CONH); UV (MeOH) λmax: 337.0 nm; ^{1}H-NMR ($CDCl_3$)δ (ppm): 8.77-7.82 (9H, m, arom.), 8.29 (1H, s, -CONH), 2.31 (3H, s, aliphatic).

MS m/z (%) 319,320$[M+1]^+$, 287, 242.

Antimicrobial activity

All test microorganisms were obtained from the National Chemical Laboratory, Pune, *Klebsiella pneumoniae* (NCIM-2789), *Staphylococcus aureus* (NCIM-2079), and *Pseudomonas aeruginosa* (NCIM-2036); the pathogenic microorganisms, *Shigella flexneri* (MTCC-1457), *Shigella sonnei* (MTCC-2957), *Salmonella paratyphi-A* (MTCC-735), *Candida albicans*, and *Aspergillus niger*, were procured from the Microbial Type Culture Collection, Institute of Microbial Technology, Chandigarh.

The compounds were dissolved in DMSO (20 μg/mL) and evaluated for antimicrobial activity by modified Kirby-Bayer method.[21] The original method of Kirby-Bayer was modified and, instead of disks, wells of 6 mm (according to standards prescribed by IP, BP, and USP) were used.

Results were interpreted in terms of the diameter of the inhibition zone.

Antimicrobial activity was evaluated by measuring the zone of inhibition against the test organism, using ampicillin (10 μg/mL disk) as standard drug for antibacterial and amphotericin B (10 μg/mL disk) as standard drug for antifungal activity. DMSO served as the control.

Results and discussion

A series of novel 2-(pyridine-2-yl)thieno[2,3-d]pyrimidin-4(3H)-one derivatives (**IIa-o**) (Table 2) were synthesized in good yield, characterized by different spectral studies, and their antimicrobial activities were determined against clinically important pathogens. Compounds **IIa**, **IIb**, **IId**, **IIe**, and **IIm** demonstrated good inhibition against the bacterial and fungal strains tested.

The SAR studies revealed that the presence of a long chain aliphatic substituent at position-2 of the thiophene ring in the compounds **II** increases the antifungal and antibacterial activity as observed in compound **IId**. Moreover, the presence of an aromatic substituent at position-1 also found to increase activity.

Physical and spectral characteristics of the compounds synthesized

2-amino-3-carbethoxythiphenes (Ia-e)

All the starting materials, o-aminocarbonylthiophenes were pale yellow to brown crystalline solids, freely soluble in chloroform, benzene, and methanol. They were all insoluble in water. They exhibited characteristic λmax (methanol) around 332.0 nm.

The solid state (KBr) IR spectra of these compounds revealed a characteristic peak at around 3100-3300 cm^{-1} (NH) and sharp carbonyl stretching vibration for the ester compound at around 1650-1700 cm^{-1}.

2-(pyridine-2-yl)thieno[2,3-d]pyrimidin-4(3H)-ones (IIa-o)

All the target compounds were colorless to pale yellow crystalline solids. They were irritants to the skin and eyes. They were insoluble in water, alcohol, and benzene, and sparingly soluble in dimethylformamide.

Most of them exhibited characteristic absorption (λmax) at around 310-317 nm (methanol).

The IR spectra of all these thienopyrimidin-4-ones were characterized by (C=O) at around 1660-1700 cm^{-1}. Additional (C=O, ester) vibrations were also observed in the IR spectrum of the 2-nicotinate compound (**IIm**) at around 1720 cm^{-1}.

The ^{1}H-NMR spectra of these compounds revealed a characteristic signal (singlet) for the 2-chloromethylene protons at around 4.5 δ ppm. This downfield position was attributable to the deshielded nature of these protons, due to the electronegative chloro group attached to them.

The fragmentation pattern seen in the mass spectrum of the compound **IIa** revealed a prominent M+ peak at m/e 284, which is observed as the base peak.

Antimicrobial activity

Some of the newly synthesized compounds were screened for their antimicrobial activity against 7 species of microorganisms, viz. *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Shigella flexneri*,

Shigella sonnei, and *Salmonella paratyphi-A*, and 2 species of fungi, *Candida albicans* and *Aspergillus niger*, by modified Kirby-Bayer method.[21] Activity of each compound was compared with that of ampicillin and amphotericin B as the standard.

Investigation of antifungal screening revealed that all tested compounds showed variable activities towards different species of microorganisms. All these compounds were biologically active due to the presence of different heterocycles and functional groups. Compounds **IIa**, **IIb**, **IId**, **IIe**, and **IIm**, showed very high activities against 7 species of bacteria and 2 species of fungi. The results are shown in Table 3.

Table 3. Biological screening data of synthesized compounds against different strains of microorganisms.

Compound ID	Microorganisms and zone of inhibition in mm								
	Sa	Sp	Pv	Kp	Pa	Sf	Ss	Ca	An
IIa	11	23	15	14	11	14	11	17	15
IIb	10	13	14	13	16	13	12	12	13
IIc	10	06	09	12	12	13	14	07	10
IId	14	20	12	18	16	16	16	25	22
IIe	06	13	05	13	10	07	16	07	16
IIf	07	14	14	11	12	08	08	11	10
IIg	11	13	13	07	11	06	06	13	09
IIh	07	07	13	05	15	12	15	06	10
IIi	08	09	10	09	14	10	11	11	15
IIj	07	13	13	10	10	11	13	07	11
IIk	06	08	08	08	11	14	12	16	14
IIl	12	13	12	09	13	11	14	12	14
IIm	12	17	15	15	11	15	07	23	20
IIn	12	10	12	08	12	13	15	13	10
IIo	05	10	13	13	15	16	06	12	10
Ampicillin	15	13	14	13	15	13	15		
Amphotericin B								14	16

Sa: *Staphylococcus aureus*, Sp: *Salmonella paratyphi*, Pv: *Protease vulgaris*, Kp: *Klebsiella pneumoniae*, Pa: *Pseudomonas aeruginosa*, Sf: *Shigella flexneri*, Ss*: Shigella sonnei*, Ca: *Candida albicans*, An: *Aspergillus niger*. Results were interpreted in terms of the diameter of the inhibition zone.

Very highly active = Inhibition zone $>$ 18 mm

Highly active = Inhibition zone 13-18 mm

Moderately active = Inhibition zone 8-13 mm

Low activity = Inhibition zone $<$ 8 mm

Acknowledgement

The authors are thankful to the Management and Principal of the Institute for providing the necessary facilities.

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