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RESEARCH ARTICLE

MEDICINAL CHEMISTRY

SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF SUBSTITUTED TRICYCLIC COMPOUNDS: 5,6,7,8-TETRAHYDRO PYRIDO[4',3':4,5]THIENO[2,3-*D*]PYRIMIDINES

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ABSTRACT

As a part of systematic investigation for synthesis, characterization and biological activity of several new substituted tricyclic compounds: 7-(phenylsulfonyl)-N-(phenyl)-5,6,7,8-tetrahydropyrido[4',3':4,5]-thieno[2,3-d]pyrimidin-4-amine (7a-7t) have been synthesized from 7-(phenylsulfonyl)-4-(chloro)-5,6,7,8-tetrahydropyrido[4',3':4,5]-thieno[2,3-d]pyrimidine (6a-6e) using piperidin-4-one Hydrochloride and benzenesulfonyl chloride as the starting material. All the synthesized products were evaluated for their antibacterial activity against *Bacillus substilis, Escherichia coli. Klebsiella pneumoniae* and *Streptococcus aureus* bacteria and antifungal activity against *Aspergillus niger, Aspergillus flavus, Fusarium oxisporium* and *Trichoderma viride* fungi respectively. Most of the synthesized compounds exhibited significant anti-bacterial and anti-fungal activities. The structures of all the synthesized compounds have been determined by their spectral and microanalytical data.

KEYWORDS

Pyridothiophene, Pyridothienopyrimidines, Sulphonamides, Antibacterial activity

INTRODUCTION

Pyridothiophene and Pyridothienopyrimidines are highly versatile ring systems and well established medicinally useful class of compounds, have received great attention in recent days, because of their wide range of therapeutic and pharmacological properties like anti-microbial, anti-fungal, analgesic, anti-tubercular, anthelmintic activity. Synthesis of 2-aminothiophene is well reported by Gewald's reaction. We have applied same reaction on N-Substituted 4-piperidone to give phenylsulfonylpiperidin-4-one as starting material that was converted into pyrimidine ring to give tricyclic ring system. Their chemical structure was confirmed by IR, ^{1}HNMR, Mass spectral and Elemental analysis. Substituted aniline derivative of tricyclic ring system were screened for their antibacterial activity against gram + Ve bacteria, gram - Ve bacteria, and anti-fungal activities by paper disc diffusion technique.

MATERIALS AND METHODS

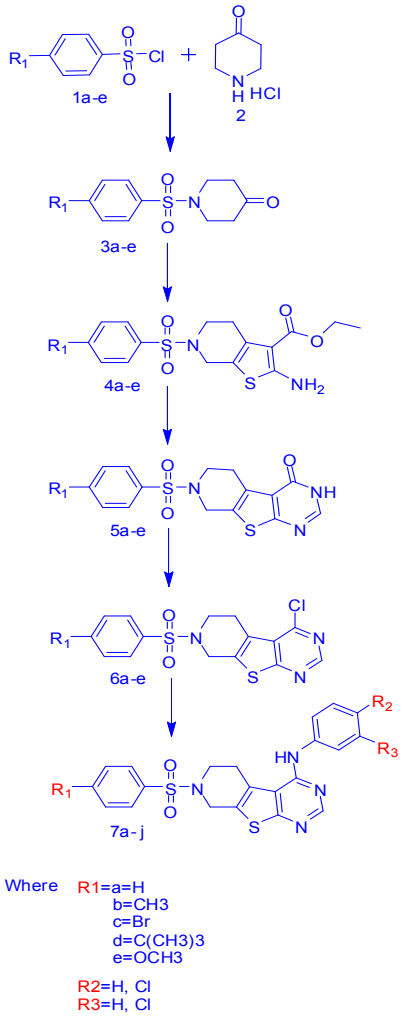
The melting points were taken in open capillary tube and are uncorrected. The IR Spectra of the compounds were recorded on ABB Bomem FTIR spectrometer MB 104 with KBr pellets. The $_{1}$H-NMR (400 MHz) spectra were recorded on a Bruker 400 NMR spectrometer (with TMS as internal references). Mass spectra were recorded on Shimadzu GC MS QP 5000. The purity of the compounds was checked by TLC on pre-coated SiO2 gel (HF254, 200 mesh) aluminium plates (E Merk) using Ethylacetate and Hexane visualized in UV light. The reagent grade chemicals were purchased from the commercial sources and purified by either distillation or recrystallisation before use.

ANTI-MICROBIAL SCREENING

The anti-bacterial activity of the synthesized compounds was tested against *Staphylococcus aureus (*ATCC 9144), *Escherichia coli (*ATCC 25922), *Pseudomonas aeruginosa* using nutrient agar medium (Hi-Media Laboratories, India). The antifungal activities of the compounds were tested against *Aspergillus niger (* ATCC 9029) and *Aspergillus fumigatus* using sabouraud dextrose agar medium (Hi-Media Laboratories, India).

***Paper disc diffusion technique*:** The Sterilized 78 (autoclaved at 120°C for 30min) medium (40-50°C) was inoculated (1mL/100mL of medium) with the suspension (105 cfu mL-1) of the micro-organism (matched to McFarland barium sulphate standard) and poured into a petridish to give a depth of 3-4 mm. The paper impregnated with the test compounds (100 µg/disc) was placed on the solidified medium. The plates were pre-incubated for 1 hr at room temperature and incubated at 37°C for 24 and 48 hrs for anti-bacterial and anti-fungal activities, respectively. Ciprofloxacin (100 µg/disc) and Fluconazole (100 µg/disc) were used as standard for anti-bacterial and anti-fungal activities, respectively.

Synthetic Shceme

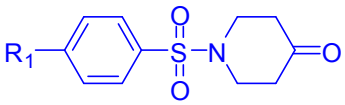


RESULTS & DISCUSSIONS

(A) Chemistry

Table -1

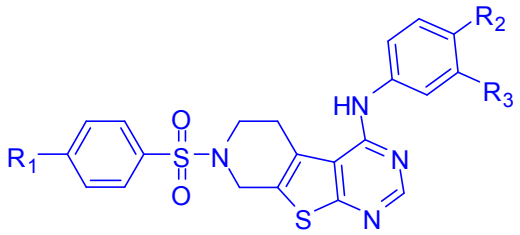
Synthesis of 1-(phenylsulfonyl)piperidin-4-one (3a-3e)



S. No.	Compound Name	R1	M.Wt.	M.Formula	Yield
1.	3a	-H	239.29	$C_{11}H_{13}NO_3S$	95%
2.	3b	$-CH_3$	253.32	$C_{12}H_{15}NO_3S$	92%
3.	3c	-Br	318.19	$C_{11}H_{12}BrNO_3S$	91%
4.	3d	$-C(CH_3)_3$	295.40	$C_{15}H_{21}NO_3S$	85%
5.	3e	$-OCH_3$	269.32	$C_{12}H_{15}NO_4S$	79%

Table -2

Synthesis of 7-(phenylsulfonyl)-N-(phenyl)-5,6,7,8-tetrahydropyrido[4',3':4,5]-thieno[2,3-d]pyrimidin-4-amine (7a-7t)



S. No.	Compound Name	R_1	R_2	R_3	M.Wt.	Mo.Formla	Yield %
1.	7a	-H	-Cl	-H	456.97	$C_{21}H_{17}ClN_4O_2S_2$	67.6 %
2.	7b	$-CH_3$	-Cl	-H	470.99	$C_{22}H_{19}ClN_4O_2S_2$	69.7 %
3.	7c	-Br	-Cl	-H	535.86	$C_{21}H_{16}BrClN_4O_2S_2$	72.3 %
4.	7d	$-C(CH_3)_3$	-Cl	-H	513.07	$C_{25}H_{25}ClN_4O_2S_2$	65.6 %
5.	7e	$-OCH_3$	-Cl	-H	486.99	$C_{22}H_{19}ClN_4O_3S_2$	67.6 %
6.	7f	-H	-Cl	-Cl	491.41	$C_{21}H_{16}Cl_2N_4O_2S_2$	72.3 %
7.	7g	$-CH_3$	-Cl	-Cl	505.44	$C_{22}H_{18}Cl_2N_4O_2S_2$	61.6 %
8.	7h	-Br	-Cl	-Cl	570.31	$C_{21}H_{15}BrCl_2N_4O_2S_2$	67.6 %
9.	7i	$-C(CH_3)_3$	-Cl	-Cl	547.52	$C_{25}H_{24}Cl_2N_4O_2S_2$	71.2 %
10.	7j	$-OCH_3$	-Cl	-Cl	521.44	$C_{22}H_{18}Cl_2N_4O_3S_2$	67.6 %

General procedure for synthesis of (3a-3e)

1-(phenylsulfonyl)piperidin-4-one(3a): Piperidin-4-one hydrochloride (0.1 mol) and Triethylamine (0.2 mol) were dissolved in Tetrahydrofuran (15 ml), under stirring Benzenesulfonyl chloride (0.1 mol) was added drop wise. The reaction mixture was stirred at room temperature and kept for 14-16 hr. After completion of reaction by TLC examination, the reaction mixture was diluted with water and product was extracted with ethyl acetate. Organic layer was dried over Na_2SO_4 and distilled out at reduced pressure to obtain product (**3a**) Yield 95%, Mp 284-288 °C. ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 1.66-1.71 (m, 2H), 1.93-1.98 (m, 2H), 2.84-2.90 (m, 2H), 3.30-3.36 (m, 2H), 7.66-7.75 (m, 5H), MS *m*/*z* 240.06 (M + H+).

1-Tosylpiperidin-4-one (3b): Compound 3b was synthesized according to the procedure same as (3a) from 4-methylbenzene-1-sulfonyl chloride and Piperidin-4-one hydrochloride. Yield 92%, Mp 262-265 °C. ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 1.66-1.71 (m, 2H), 1.93-1.98 (m, 2H), 2.29 (s, 3H), 2.84-2.90 (m, 2H), 3.30-3.36 (m, 2H), 7.69-7.77 (m, 4H). MS *m*/*z* 254.3 (M + H+).

1-(4-bromophenylsulfonyl)piperidin-4-one (3c) Compound 3c was synthesized according to the procedure same as (3a) from 4-bromobenzene-1-sulfonyl chloride and Piperidin-4-one hydrochloride. Yield 91%, Mp 255-261 °C. ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 1.66-1.71 (m, 2H). 1.93-1.98 (m, 2H), 2.84-2.90 (m, 2H), 3.30-3.36 (m, 2H), 7.55-7.57 (d, 2H), 7.73-7.75 (d, 2H), MS *m*/*z* 318.9 (M + H+).

1-(4-tert-butylphenylsulfonyl)piperidin-4-one (3d) Compound 3d was synthesized

according to the procedure same as (3a) from 4-tert-butylbenzene-1-sulfonyl chloride and Piperidin-4-one hydrochloride. Yield 85%, Mp 275-277 °C.^{1}H NMR (400 MHz, DMSO-*d*6): 1.41 (s, 9H). 1.66-1.71 (m, 2H),1.93-1.98 (m, 2H), 2.84-2.90 (m, 2H), 3.30-3.36 (m, 2H), 7.55-7.57 (d, 2H),7.73-7.75 (d, 2H), MS *m*/*z* 296.1 (M + H+).

1-(4-methoxyphenylsulfonyl)piperidin-4-one (3e) Compound 3e was synthesized according to the procedure same as (3a) from 4-methoxybenzene-1-sulfonyl chloride and Piperidin-4-one hydrochloride. Yield 88%, Mp 280-285°C. ^{1}H NMR (400 MHz, DMSO-*d*6):, 1.66-1.71 (m, 2H), 1.93-1.98 (m, 2H), 2.84-2.90 (m, 2H), 3.30-3.36 (m, 2H), 3.61 (s, 3H), 7.54-7.56 (d, 2H), 7.71-7.73 (d, 2H), MS *m*/*z* 270.1 (M + H+).

General procedure for synthesis of (4a-4e)

Ethyl 2-amino-6- (phenylsulfonyl) -4,5,6,7-tetrahydrothieno [2,3-c]pyridine-3-carboxylate(4a): 1-(phenylsulfonyl)piperidin-4-one(3a) (0.505 mmol) was dissolved in ethanol and ethyl cyanoacetate (0.505 mmol) and sulphur (0.531 mmol) were added. The mixture was stirred for a couple of minutes, and the morpholine (0.505 mmol) was added. The mixture as stirred at room temperature overnight. The precipitate was collected by suction filtration and washed with ethanol to obtain the title compound. Yield 86%.^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 1.25 (t, 3H), 2.63-2.68 (m, 2H), 3.51 (t, 2H), 4.15 (q, 2H).4.24 (br.s, 2H), 7.32-7.35 (d, 2H), 7.62-7.71 (m, 3H), 7.86-7.89 (m, 2H). MS ESI+ *m*/*z* 367.52 (M + H)+.

Ethyl 2-amino-6-tosyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate(4b):Compound 4b was synthesized according to the procedure same as (4a) from 1-tosyl piperidin-4-one(3b Yield 82%,. ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 1.25 (t, 3H), 2.63-2.68 (m, 2H), 3.51 (t, 2H), 2.29 (s, 3H), 4.15 (q, 2H), 4.24 (br.s, 2H), 7.32-7.35 (d, 2H), 7.62-7.71 (d, 2H), 7.86-7.89 (m, 2H). MS ESI+ *m*/*z* 381.2 (M + H)+.

Ethyl 2-amino-6-(4-bromophenylsulfonyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate(4c) Compound 4c was synthesized according to the procedure same as (4a) from 1-(4-bromophenylsulfonyl)piperidin-4-one (3c) Yield 79%, ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 1.25 (t, 3H), 2.63-2.68 (m, 2H), 3.51 (t, 2H), 4.15 (q, 2H), 4.24 (br.s, 2H), 7.32-7.35 (d, 2H), 7.62-7.71 (d, 2H), 7.86-7.89 (m, 2H).MS ESI+ *m*/*z* 447.2 (M + 2H)+.

Ethyl 2-amino-6-(4-tert-butylphenylsulfonyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate(4d) Compound 4d was synthesized according to the procedure same as (4a) from 1-(4-tert-butylphenylsulfonyl)piperidin-4-one (3d) Yield 86%, ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 1.25 (t, 3H), 1.41 (s, 9H), 2.63-2.68 (m, 2H), 3.51 (t, 2H), 4.15 (q, 2H), 4.24 (br.s, 2H), 7.32-7.35 (d, 2H), 7.62-7.71 (d, 2H), 7.86-7.89 (m, 2H). MS ESI+ *m*/*z* 423.5 (M + H)+.

Ethyl 2-amino-6-(4-methoxyphenylsulfonyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate(4e) Compound 4e was synthesized according to the procedure same as (4a) from 1-(4-methoxyphenylsulfonyl)piperidin-4-one (3e) Yield 89%,. ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 1.25 (t, 3H), 2.63-2.68 (m, 2H), 3.51 (t, 2H), 3.61 (s, 3H), 4.15 (q, 2H), 4.24 (br.s, 2H), 7.32-7.35 (d, 2H), 7.62-7.71 (d, 2H), 7.86-7.89 (m, 2H).. MS ESI+ *m*/*z* 397.2 (M + H)+.

General procedure for synthesis of "(5a-5t)"

7-(phenylsulfonyl)-4-oxo-5,6,7,8-tetrahydropyrido [4',3':4,5]-thieno[2,3-d]pyrimidine(5a):

To a solution of Ethyl 2-amino-6-(phenylsulfonyl) -4,5,6,7-tetrahydrothieno [2,3-c] pyridine-3-carboxylate(4a)(3.37mmol) in DMF was added formamidine acetate (5.65mmol). The mixture was heated to 100°C overnight. The solvent was removed in vacuo. The residue was stirred with ethyl acetate for 2 h. the precipitate was collected by suction filtration and rinsed with ethyl acetate. The solid was dried to obtain the title compound.

Yield 86%, ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 2.91-2.96 (m, 2H), 3.62 (t, 2H), 4.58 (d, 2H), 7.52-7.54 (m, 2H), 7.67-7.69 (m, 3H), 8.08 (s, 1H), 12.38 (br.s, 1H). MS ESI+ *m*/*z* 348.1 (M + H)+.

7-(tosylsulfonyl)-4-oxo-5,6,7,8-tetrahydropyrido[4',3':4,5]-thieno[2,3-d]pyrimidine(5b): Compound 5b was synthesized according to the procedure same as (5a) from Ethyl 2-amino-6-tosyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (4b) Yield 82%. ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 2.31 (s, 3H), 2.91-2.96 (m, 2H), 3.62 (t, 2H), 4.58 (d, 2H), 7.52-7.54 (m, 2H), 7.67-7.69 (d, 2H), 8.08 (s, 1H), 12.38 (br.s, 1H). MS ESI+ *m*/*z* 362.2 (M + H)+.

7-(4-bromophenylsulfonyl)-4-oxo-5,6,7,8-tetrahydropyrido [4',3':4,5]-thieno[2,3-d]pyrimidine(5c): Compound 5c was synthesized according to the procedure same as (5a) from Ethyl 2-amino-6-(4-bromophenylsulfonyl)-4,5,6,7-tetrahydrothieno[2,3-c]pyridine-3-carboxylate (4c) Yield 77%, ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 2.91-2.96 (m, 2H), 3.62 (t, 2H), 4.58 (d, 2H), 7.52-7.54 (m, 2H), 7.67-7.69 (d, 2H), 8.08 (s, 1H), 12.38 (br.s, 1H). MS ESI+ *m*/*z* 428.2 (M + 2H)+.

7-(4-tert-butylphenylsulfonyl)-4-oxo-5,6,7,8-tetrahydropyrido[4',3':4,5]-thieno[2,3-d] pyrimidine (5d): Compound 5d was synthesized according to the procedure same as (5a) from ethyl2-amino-6-(4-tert-butylphenylsulfonyl)-4,5,6,7tetrahydrothieno[2,3-c]pyridine-3 carboxylate (4d) Yield 84%. ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 1.41 (s, 9H), 2.91-2.96 (m, 2H), 3.62 (t, 2H), 4.58 (d, 2H), 7.52-7.54 (m, 2H), 7.67-7.69 (d, 2H), 8.08 (s, 1H), 12.38 (br.s, 1H). MS ESI+ *m*/*z* 404.5 (M + H)+.

7-(4-methoxyphenylsulfonyl)-4-oxo-5,6,7,8-tetrahydropyrido [4',3':4,5]-thieno[2,3-d]pyrimidine(5e): Compound 5e was synthesized according to the procedure same as (5a) from ethyl 2-amino-6- (4-methoxyphenylsulfonyl) -4,5,6,7-tetrahydrothieno [2,3-c] pyridine-3-carboxylate (4e) Yield 76%. ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 2.91-2.96 (m, 2H), 3.60 (s, 3H), 3.62 (t, 2H), 4.58 (d, 2H), 7.52-7.54 (m, 2H), 7.67-7.69 (d, 2H), 8.08 (s, 1H), 12.38 (br.s, 1H). MS ESI+ *m*/*z* 377.2 (M + H)+.

General procedure for synthesis of "(6a-6t)"

7-(phenylsulfonyl)-4-chloro-5,6,7,8- tetrahydropyrido [4',3':4,5]-thieno[2,3-d] pyrimidine (6a): To sulfolane was added Phosphoryl chloride ($POCl_3$) at room temperature. Triethylamine was added drop wise with water-bath cooling. 7-(phenylsulfonyl)-4-oxo-5,6,7,8-tetra hydropyrido [4',3':4,5]-thieno[2,3-d]pyrimidine(5a) and additional sulfolane were added to reaction mixture. The mixture was heated to 70°C for 2.5 hour. The mixture was cooled with an ice bath. After stirring at room temperature for 2 hours the precipitate was collected by suction filtration and washed three times with water. The residue was dried to obtain the title compound Yield 67%. ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 3.07-3.12 (m, 2H), 3.71 (t, 2H), 4.75 (d, 2H), 7.52-7.54 (m, 2H), 7.67-7.69 (m, 3H), 8.86 (s, 1H). MS ESI+ *m*/*z* 366.8 (M + H)+.

7-(tosylsulfonyl)-4-chloro-5,6,7,8- tetrahydropyrido [4',3':4,5]-thieno[2,3-d] pyrimidine (6b): Compound 6b was synthesized according to the procedure same as (6a) from 7-(tosyl sulfonyl l)-4-oxo-5,6,7,8-tetra hydropyrido[4',3':4,5]-thieno[2,3-d]pyrimidine(5b) Yield 76%. ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 2.31 (s, 3H), 3.07-3.12 (m, 2H), 3.71 (t, 2H), 4.75 (d, 2H), 7.49-7.51 (d, 2H), 7.65-7.67 (d, 2H), 8.85 (s, 1H). MS ESI+ *m*/*z* 380.8 (M + H)+.

7-(4-bromophenylsulfonyl)-4-chloro-5,6,7,8-tetrahydropyrido [4',3':4,5]-thieno[2,3-d] pyrimidine (6c): Compound 6c was synthesized according to the procedure same as (5a) from 7-(4-bromophenylsulfonyl)-4-oxo-5,6,7,8-tetra hydropyrido[4',3':4,5]-thieno[2,3-d]pyrimidine(5c) Yield 69%. ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 3.07-3.12 (m, 2H), 3.71 (t, 2H), 4.75 (d, 2H), 7.52-7.54 (m, 2H), 7.67-7.69 (d, 2H), 8.86 (s, 1H).MS ESI+ *m*/*z* 446.3 (M + 2H)+.

7-(4-tert-butylphenylsulfonyl)-4-chloro-5,6,7,8- tetrahydropyrido [4',3':4,5]-thieno[2,3-d] pyrimidine (6d): Compound 6d was synthesized according to the procedure same as (5a) from 7-(4-tert-butylphenylsulfonyl)-4-oxo-5,6,7,8-tetra hydropyrido[4',3':4,5]-thieno[2,3-d]pyrimidine (5d) Yield 72%. ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 1.41 (s, 9H), 3.07-3.12 (m, 2H), 3.71 (t, 2H), 4.75 (d, 2H), 7.52-7.54 (d, 2H), 7.67-7.69 (d, 2H), 8.86 (s, 1H). MS ESI+ *m*/*z* 423.2 (M + H)+.

7-(4-methoxyphenylsulfonyl)-4-chloro-5,6,7,8-tetrahydropyrido [4',3':4,5]-thieno[2,3-d] pyrimidine (6e): Compound 6e was synthesized according to the procedure same as (5a) from 7-(4-methoxyphenylsulfonyl)-4-oxo-5,6,7,8-tetra hydropyrido[4',3':4,5]-thieno[2,3-d]pyrimidine (5e) Yield 76%. ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 3.07-3.12 (m, 2H), 3.61 (s, 3H), 3.71 (t, 2H), 4.75 (d, 2H), 7.52-7.54 (d, 2H), 7.67-7.69 (d, 2H), 8.86 (s, 1H).MS ESI+ *m*/*z* 396.3 (M + H)+.

General procedure for synthesis of " (7a-7t)"

7-(phenylsulfonyl)-N-(4-chlorophenyl)-5,6,7,8-tetrahydropyrido [4',3':4,5] - thieno[2,3-d]pyrimidin-4-amine(7a): To a solution of 7-(phenylsulfonyl)-4-chloro-5,6,7,8- tetrahydro pyrido [4',3':4,5]-thieno[2,3-d] pyrimidine (6a) (1.54mmol) in 2-methoxyethanol, 4-chloroaniline (1.83mmol) and Triethylamine (6.14mmol) were at room temperature. The reaction mixture was heated to 100°C for 2 hours, then diluted with ethyl acetate and washed with water. The organic layer was dried over sodium sulphate and removed in vacuo. The crude product was purified by column chromatography on silica gel using ethyl acetate: Hexane(1:3) as mobile phase to obtain title compound. Yield 67.6%. ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 3.13-3.19 (m, 2H), 3.64-3.76 (m, 2H), 4.57-4.69 (m, 2H), 6.52 (s, 1H), 7.31(dd, 2H), 7.45 (dd, 2H), 7.52-7.54 (m, 2H), 7.67-7.69 (m, 3H), 8.24 (s, 1H). MS ESI+ *m*/*z* 458.9 (M + H)+.

7-(tosylsulfonyl)-N-(4-chlorophenyl)-5,6,7,8-tetrahydropyrido [4',3':4,5]-thieno[2,3-d]pyrimidin-4-amine(7b): Compound was synthesized according to the procedure same as (7a) Yield 69.7%. ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 2.29 (s, 3H), 3.13-3.19 (m, 2H), 3.64-3.76 (m, 2H), 4.57-4.69 (m, 2H), 6.52 (s, 1H), 7.31-7.33 (d, 2H), 7.45-7.47 (d, 2H), 7.52-7.54 (d, 2H), 7.67-7.69 (d, 2H), 8.24 (s, 1H). MS ESI+ *m*/*z* 472.1 (M + H)+.

7-(4-bromophenylsulfonyl)-N-(4-chlorophenyl)-5,6,7,8-tetrahydropyrido [4',3':4,5]-thieno[2,3-d]pyrimidin- 4 - amine(7c): Compound was synthesized according to the procedure same as (7a) Yield 72.3.6%. ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 3.13-3.19 (m, 2H), 3.64-3.76 (m, 2H), 4.57-4.69 (m, 2H), 6.52 (s, 1H), 7.31-7.33 (d, 2H), 7.45-7.47 (d, 2H), 7.62-7.64 (d, 2H), 7.87-7.89 (d, 2H), 8.24 (s, 1H). MS ESI+ *m*/*z* 537.3 (M + 2H)+.

7-(4-t-butylphenylsulfonyl)-N- (4 -chlorophenyl)-5,6,7,8-tetrahydropyrido [4',3':4,5]-thieno [2,3-d]pyrimidin-4-amine(7d): Compound was synthesized according to the procedure same as (7a) Yield 65.6%. ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 1.41 (s, 9H), 3.13-3.19 (m, 2H), 3.64-3.76 (m, 2H), 4.57-4.69 (m, 2H), 6.52 (s, 1H), 7.31-7.33 (d, 2H), 7.45-7.47 (d, 2H), 7.52-7.54 (d, 2H), 7.67-7.69 (d, 2H), 8.24 (s, 1H).. MS ESI+ *m*/*z* 514.2 (M + H)+.

7-(4-methoxyphenylsulfonyl)-N- (4 - chlorophenyl)-5,6,7,8-tetrahydropyrido [4',3':4,5]-thieno[2,3-d]pyrimidin- 4 - amine(7e): Compound was synthesized according to the procedure same as (7a) Yield 67.6%. ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 3.13-3.19 (m, 2H), 3.61 (s, 3H), 3.64-3.76 (m, 2H), 4.57-4.69 (m, 2H), 6.52 (s, 1H), 7.31-7.33 (d, 2H), 7.45-7.47 (d, 2H), 7.52-7.54 (d, 2H), 7.67-7.69 (d, 2H), 8.24 (s, 1H). MS ESI+ *m*/*z* 488.3 (M + H)+.

7-(phenylsulfonyl)-N-(3,4-chlorophenyl)-5,6,7,8-tetrahydropyrido [4',3':4,5]-thieno[2,3-d] pyrimidin-4-amine(7f): Compound was synthesized according to the procedure same as (7a) Yield 72.3.6%. ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 3.15-3.19 (m,

2H), 3.55-3.66 (m, 2H), 4.57-4.69 (m, 2H), 7.59 (d, 1H), 7.71 (dd, 1H), 8.04 (d, 1H), 7.52-7.54 (m, 2H), 7.67-7.69 (m, 3H), 8.34 (s, 1H), 8.47 (s, 1H). MS ESI+ *m*/*z* 492.1 (M + H)+.

7-(tosylsulfonyl)-N-(3,4-chlorophenyl)-5,6,7,8-tetrahydropyrido [4',3':4,5]-thieno[2,3-d] pyrimidin-4-amine(7g): Compound was synthesized according to the procedure same as (7a) Yield 61.6%. ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 2.31 (s, 3H),3.15-3.19 (m, 2H), 3.55-3.66 (m, 2H), 4.57-4.69 (m, 2H), 7.59 (d, 1H), 7.71 (dd, 1H), 8.04 (d, 1H), 7.52-7.54 (d, 2H), 7.67-7.69 (d, 2H), 8.34 (s, 1H), 8.47 (s, 1H). MS ESI+ *m*/*z* 506.4 (M + H)+.

7-(4-bromophenylsulfonyl)-N-(3,4-chlorophenyl)-5,6,7,8-tetrahydropyrido [4',3':4,5]-thieno [2,3-d]pyrimidin-4-amine(7h): Compound was synthesized according to the procedure same as (7a) Yield 69.6%. ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 3.15-3.19 (m, 2H), 3.55-3.66 (m, 2H), 4.57-4.69 (m, 2H), 7.59 (d, 1H), 7.71 (dd, 1H), 8.04 (d, 1H), 7.55-7.57 (d, 2H), 7.67-7.69 (d, 2H), 8.34 (s, 1H), 8.47 (s, 1H). MS ESI+ *m*/*z* 572.4 (M + 2H)+.

7-(4-t-butylphenylsulfonyl)-N-(3,4-chlorophenyl)-5,6,7,8-tetrahydropyrido [4',3':4,5]-thieno [2,3-d]pyrimidin-4-amine(7i): Compound was synthesized according to the procedure same as (7a) Yield 71.2%. ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 1.42 (s, 9H), 3.15-3.19 (m, 2H), 3.55-3.66 (m, 2H), 4.57-4.69 (m, 2H), 7.59 (d, 1H), 7.71 (dd, 1H), 8.04 (d, 1H), 7.52-7.54 (d, 2H), 7.67-7.69 (d, 2H), 8.34 (s, 1H), 8.47 (s, 1H). MS ESI+ *m*/*z* 548.1 (M + H)+.

7-(4-methoxyphenylsulfonyl)-N-(4-chlorophenyl)-5,6,7,8-tetrahydropyrido [4',3':4,5]-thieno [2,3-d]pyrimidin-4-amine(7j): Compound was synthesized according to the procedure same as (7a) Yield 67.6%. ^{1}H NMR (400 MHz, DMSO-*d*6): *δ* 3.15-3.19 (m, 2H), 3.51-3.57 (m, 2H), 3.61 (s, 3H), 4.57-4.69 (m, 2H), 7.59 (d, 1H), 7.71 (dd, 1H), 8.04 (d, 1H), 7.52-7.54 (d, 2H), 7.67-7.69 (d, 2H), 8.34 (s, 1H), 8.47 (s, 1H) MS ESI+ *m*/*z* 522.5 (M + H)+.

(B) ANTI-MICROBIAL SCREENING:

Most of the synthesized compounds exhibited mild to moderate anti-microbial activity against the tested microorganisms. Compounds **5c, 6e,7c** and **7h** were found to possess significant anti-bacterial and anti-fungal activity when compared to standard drug (Ciprofloxacin and Fluconazole for anti-bacterial and anti-fungal respectively). Compounds **4e**, **7e, 7f and 7j** displayed moderate anti-microbial activity where as the remaining compounds shown lesser activity.

CONCLUSION

The entire synthesized compound exhibited better anti-bacterial activity than antifungal activity. In addition to that, many compounds are most active against gram '+'Ve bacteria than the gram '–'Ve one. The potent anti-microbial activity exhibited by **7c** and **7h** may be due to the 4-Bromo substitution.. In conclusion, the present study highlights the importance Pyridothiophene and Pyridothienopyrimidines ring features responsible for the antimicrobial activities and therefore may serve as a lead molecule for further modification to obtain clinically useful novel entities.

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