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Synthesis and biological screening of 6"-[2 -(4'-chlorophenyl)-6-methyl imidazo [1,2-a] pyridin - 3 - yl] -4" - aryl pyrimidine-2" -(1"H)-thiones

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ABSTRACT

Pyrimidine nucleus plays an important role in medicine, agriculture and industrial chemistry. With a view of biological activities and variety of industrial applications, some new 6" -[2-(4'-chlorophenyl)-6-methyl imidazo [1, 2-a] pyridin-3-yl]- 4"-aryl pyrimidine-2"-(1"H)-thiones (4a-4l) have been synthesized. The products have been assayed for their biological activity against Gram +ve,Gram –ve bacteria and fungi. Some of the products showed moderate activity in concentration 50µg/ml. The structures of the products have been elucidated by IR,^{1}HNMR, Mass spectral data, elemental analysis and thin layer chromatography.

KEYWORDS

Thiopyrimidines
(Heterocyclic chemistry)

INTRODUCTION

Imidazo[1, 2-a] pyridines are potential bioactive agents due to their wide spectrum of therapeutic importance. A large number of substituted imidazo[1,2–a]pyridine derivatives are prepared and tested for varieties of biological activities such as, Antiallergic[1], Antagonist[2, 3] Antifungal[4], Antiepileptic[5], Antibacteria[6]. Anticonvulsant[7], Antitubercular[8], Analgesic[9], Insecticidal[10], Antisoriasis[11], Antihypertensive[12] etc. In view of getting to synthesized imidazo [1,2-a] pyridines derivatives and evaluated for their antimicrobial activitiy.

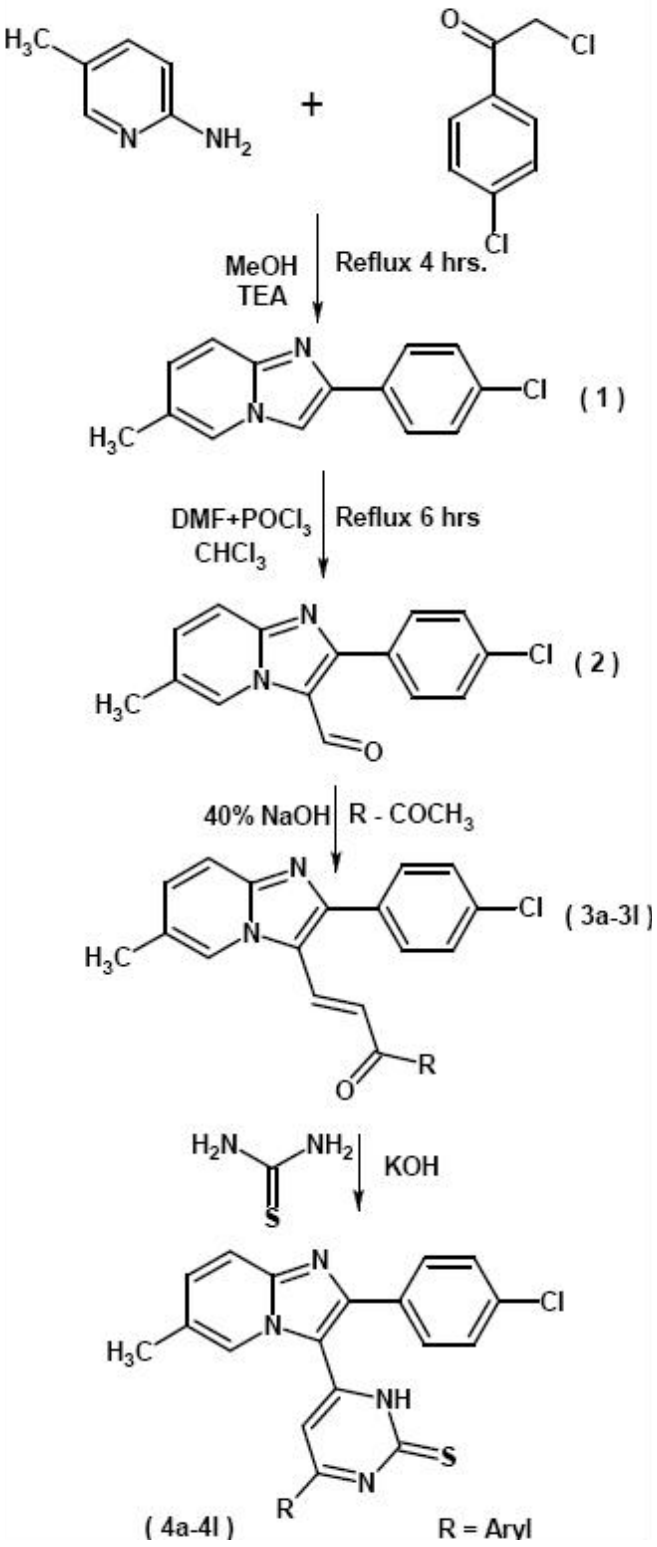
Compounds containing pyrimidine ring are widely available in nature. Many thio pyrimidine derivatives are reported to possess different therapeutic activities Antitubercular[13], Antidiabetic[14], Anticonvulsant[15], Fungicidal[16], Insecticidal[17].

In view of these findings, it was considered worthwhile to synthesize some new 6" -[2-(4'-chlorophenyl)-6-methyl imidazo [1, 2-a] pyridin-3-yl]- 4"-aryl pyrimidine-2"-(1"H)-thiones have been prepared by the reaction of 2-(4'-chlorophenyl)-6-methyl-3-[1"-aryl- 2"-propene-1"-one-3-yl]-imidazo[1,2-a]pyridine with thiourea in presence of basic catalyst KOH.

The products (4a-4l) were assigned the IR ^{1}HNMR, Mass spectral data, elemental analysis and TLC. The physical data and antimicrobial activities are represented in TABLE-1.

(4a-4l) R=Aryl

Reaction scheme



ANTIMICROBIAL ACTIVITY

6" - [2 - (4'-chlorophenyl)-6-methyl imidazo [1, 2-a] pyridin-3-yl]- 4"-aryl pyrimidine-2"-(1"H)-thiones products were evaluated in vitro for their antimicrobial activities against *Gram +ve bacteria like Bascillus megaterium, Bacillus Subtillus, Staphylo Coccus aureus, Bacillus Cereus. Gram –ve bacteria like Escherichia coli, Antrobactor Arogens, Salmonella Taphimurium, Pscudonomus valgaries. Fungi Aspergillus niger, Aspergillus awamori* using DMF as solvent at 50 µg / ml. concentration by cup-plate method[18]. After 24 hrs of incubation at 37 °C, The zones of inhibition were measured in mm. The activity was compared with the known standard drugs, viz, ampicillin, chloramphenicol, norfloxacin, gresiofulvin at same concentration.

All the synthesized compounds (1), (2), (3i), (4a-4l) showed moderate to good and remarkable activities with compare to known standard drugs at the same concentration, which is represented in TABLE-1. The comparable antimicrobial activity are represented in TABLE-2.

EXPERIMENTAL SECTION

All the melting point were measured by open glass capillary method and are uncorrected. IR absorption spectra (vmax in cm^{-1}) were recorded on a shimadzu IR -435 spectrophotometer using KBr pellet method, ^{1}HNMR spectra on Hitachi, R-1200 (300-MHz) spectrometer using DMSO-d6 method, as internal stadrard (chemical shift in, δ ppm) and mass spectra on a joel 300 ev. The compounds were routinely checked by the TLC using silica gel-G

[A] Synthesis of 6-methyl-2-(4'-chlorophenyl) imidazo [1,2-a]pyridine(1)

Arranged 1.0 lit 4/N RBF equipped with stirrer tharmopocket and condensor. Charge 100ml methanol and 21.3g (0.1 mole) (4-chlorophenyl)acetyl chloride and then charge 11.9g (0.11mole) 2-amino-5- methyl pyridine at room temperature stir till clear solution. Add drops wise tri ethyl amine at room temperature till P^H adjust 8 to 9. After addition complete heat 60-65 °C for 3 to 4 hrs. then check TLC. After complies TLC cool reaction mass at room temperature and poured in 1.0 lit water & filter it. Yield 86%, m.p200 °C.,

Anal. Calcd. For $C_{14}H_{11}ClN_2$ Require : C, 69.28,

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TABLE 1 : The physical data and antimicrobial activities of compounds (1), (2), (3i), (4a-4l), [Zone of nhibition in mm]

Comp	R	Moleculer Formula	M.P ^{0}C	Antibacterial Activity							Antifungl Activity		% of Nitrogen	
				B. mega	B.Sub tilics	S.au-reus	B. Ce reus	E. Coli	A. arogens	S. typhi	P. Val garis	A. niger	A. awamori	Caled	Found.
1	---	$C_{14}H_{11}ClN_2$	200	16	20	19	18	18	18	18	21	15	19	11.54	11.50
2	---	$C_{15}H_{11}ClN_2O$	180	13	23	15	20	20	19	20	23	18	20	10.35	10.33
3i	4-CH_3-C_6H_4-	$C_{24}H_{19}ClN_2O$	170	15	22	16	21	19	23	16	27	20	22	7.24	7.22
4a	C_6H_5-	$C_{24}H_{17}ClN_4S$	195	19	20	16	18	18	15	19	19	17	21	13.06	13.05
4b	3-Cl-C_6H_4 -	$C_{24}H_{16}Cl_2N_4S$	188	21	16	19	14	16	18	22	17	19	19	12.09	12.07
4c	4-Cl-C_6H_4 -	$C_{24}H_{16}Cl_2N_4S$	175	17	19	14	18	14	19	12	18	16	17	12.09	12.08
4d	2-4-$(Cl)_2$-C_6H_3-	$C_{24}H_{15}Cl_3N_4S$	165	19	21	15	20	17	18	20	20	18	20	11.25	11.23
4e	4 -F-C_6H_4-	$C_{24}H_{16}ClFN_4S$	178	15	20	22	21	19	20	14	19	18	16	12.54	12.51
4f	4-Br-C_6H_4-	$C_{24}H_{16}BrClN_4S$	190	20	15	17	16	16	17	18	21	19	19	11.03	11.01
4g	4 -OH-C_6H_4-	$C_{24}H_{17}ClN_4OS$	200	19	18	15	17	16	15	17	18	21	22	12.59	12.56
4h	4-NH_2-C_6H_4-	$C_{24}H_{18}ClN_5S$	168	21	17	23	15	22	16	18	17	21	17	15.78	15.77
4i	4-CH_3-C_6H_4-	$C_{25}H_{19}ClN_4S$	170	12	18	14	16	17	19	19	15	19	19	12.65	12.64
4j	4-OCH_3-C_6H_4-	$C_{25}H_{19}ClN_4OS$	177	17	22	13	18	14	20	22	16	18	18	12.21	12.20
4k	3-NO_2-C_6H_4-	$C_{24}H_{16}ClN_5O_2S$	160	22	15	20	14	24	18	23	18	17	20	14.78	14.76
4l	4-NO_2-C_6H_4-	$C_{24}H_{16}ClN_5O_2S$	180	12	16	13	17	17	15	16	20	16	18	14.78	14.75

TABLE 2 : Compounds showing comparable antimicrobial activity with known standerd drugs.

Compounds	B.mega	B.Sub tilis	S.aureus	B.Cereus	E.Coli	A.aro gens	S.typhi	P.Valgaries	A.niger	A. awa mori
(4a – 4l)	4b, 4f, 4h, 4k	4f, 4g, 4k	4b, 4e, 4h, 4k	4g, 4k	4a, 4e, 4h, 4k	4c, 4d, 4l	4b, 4i, 4j, 4k	4b, 4j, 4l	4g,4h	4c, 4f, 4j, 4l
Activity of standard drugs.										
drugs	**B.mega**	**B.Sub tilis**	**S.aureus**	**B.Cereus**	**E.Coli**	**A.aro gens**	**S.typhi**	**P.Valgaries**	**A.niger**	**A. awa mori**
1.Ampicillin	22	21	19	18	19	20	22	23	---	---
2.Chlorampenicol	22	23	23	20	22	21	25	22	---	---
3.Norfloxacin	22	22	22	21	24	23	23	24	---	---
4.Greseofulvin	---	--	---	--	---	--	---	--	22	23

H, 4.53, N, 11.54 %,Cl,14.63 ; Found: C, 69.26, H, 4.52, N, 11.50, Cl, 14.60 %.) IR (KBr) : 2958 (C-H str., Sym,); 1466, (C-H def., asym.) ; 1368 (C-H def., asym.); 3650 (C-H Str., Aromatic); 801 (C- H, Str., o.p.p def.); 1488 (C=C str.); 1350 (C-N str.); 760 (C-Cl Str.): 1648 (C=N Str.) ^{1}HNMR (DMSO-d6); 2.3 (s, 3H –CH_3); 7.02-7.94 (m, 8H Ar-H). m/z: 44, 65, 77, 92, 110, 219, 242.

[B] Synthesis of 6-methyl-2-(4'-chlorophenyl) imidazo[1,2-a]pyridine-3- carboxaldehyde (2)

Arranged 2.0 lit 4/N RBF equipped with stirrer, tharmopocket and condensor in water bath. Charge 84 ml DMF and 1.0 lit $CHCl_3$ in RBF and cool at 0 - 5 ^{o}C. Start drop wise addition of 165ml $POCl_3$ within 1.0 h (exothermicity observe) stir 30 min at 0-5 ^{o}C. Add 50g of 6-methyl-2-(4-chlorophenyl)imidazo[1,2-a]pyridine slowly temp raise till reflux for 6.0h. Remove $CHCl_3$ by vacuum distilation. Cool reaction mass at room temperature and poured in 2.0 lit ice cold water. Below room temperature P^H adjust neutral by coustic solution. Filter and crystallized from methanol. Yield 70%, mp180 ^{o}C.

Anal. Calcd. For $C_{15}H_{11}ClN_2O$Require : C, 66.55, H, 4.10, N,10.35, Cl, 13.10 % ; Found: C, 66.54, H,

4.08, N, 10.33, Cl, 13.09 %.) IR (KBr) : 2900 (C-H str., Sym,); 1369 (C-H def., sym.) ; 1475 (C-H def., asym.); 3650 (C-H Str., Aromatic); 799 (C- H, Str., o.p.p def.) ; 1508 (C=C str.) ; 1110 (C-N str.); 1715 (C=O): 2820-2750(C-H Str.) 1680 (C=N)[1] HNMR (DMSO-d6); 2.4 (s, 3H –CH_3); 7.2-9.4(m,7H Ar-H); 10.0 (s, CHO). m/z: 44, 56, 65, 79, 111, 129, 230, 256, 270.

[C] Synthesis of 2-(4'-chlorophenyl)-6-methyl- 3-[1"-(4"'-methylphenyl)- 2"-prop-en-1"ones-3-yl]-imidazo [1,2-a]pyridine (3i)

Dissolve 6-methyl- 2 - (4'-chlorophenyl)imidazo [1,2 – a] pyridine3-carboxaldehyde (2.91gm,0.01mol) in a mixture of methanol (50 ml) + DMF (50 ml). To this add p-methylacetophenone (1.40gm, 0.01mol) and. Stirr the content at room temperature for 24 hrs. in presence of 40% NaOH. The resulting solution was poured on to crushed ice, thus the solid seprated was filterated and crystallized from ethanol, Yield 56 %, m. p. 170 ^oC,

Anal. Calcd. For $C_{24}H_{19}ClN_2O$ Require : C, 74.51, H, 4.95, N,7.24, Cl, 9.16 % ; Found: C, 74.50, H, 4.93, N, 7.22, Cl, 9.15 %.) IR(KBr) :2860 (C-H str., Sym,) ; 1470, (C-H def., asym.) ; 1350 (C-H def., asym.); 3640 (C-H Str., Aromatic); 750 (C- H, Str., o.p.p def.) ; 1530 (C=C str.) ; 1350 (C-N str.); 1693 (C=O) 650

(C-Cl Str.)[1] HNMR (DMSO-d6); 2.43-2.44 (s, 6H –CH_3); 7.22-8.14 (m, 13H Ar-H); m/z : 44, 65, 91,102, 119, 129, 153, 167, 176, 193, 204, 216, 232, 242, 267, 294, 321, 349, 369, 386.

Similarly other compounds (3a-3l) were prepared and their physical data are published.

[D] Synthesis of 6" - [2 - (4'-chlorophenyl) -6-methyl imidazo [1, 2-a] pyridin-3-yl]- 4"-(4"'-methylphenyl) pyrimidine-2"-(1"H)-thione(4i)

A mixture of 2-(4'-chlorophenyl)-6-methyl-3-[1"-(4"'methylphenyl)- 2"-prop-en-1"ones-3-yl]-imidazo [1,2-a]pyridine (4.27gm, 0.01 mol) and thiourea (0.60gm, 0.01 mol) in ethanol (20 ml) was refluxed in presence of alcoholic KOH for 12 hr. The excess solvent was distilled out and the residue was poured in to crused ice, the separated solid was filtered out and crystallized from ethanol. Yield 68 %, m.p. 170^oC

($C_{25}H_{19}ClN_4S$; Required : C, 67.79; H, 4.32; N, 12.65 %; found : C, 67.77; H, 4.30; N, 12.64 %;) IR (KBr): 2880 (C-H str., Sym,); 1460 (C-H def., sym.); 1460 (C-H def., asym.); 3060 (C-H Str., Aromatic); 1492 (C=C str.); 1080 (C-N str.); 3060(C-H Str.); 1598 (C=N); 779(C-Cl) ^{1}HNMR ($CDCl_3$); 2.33-2.36 (s, 6H –CH_3); 7.13-8.75 (m, 12H Ar-H); 4.97 (s, Ar-CH). m/z: 65,92, 103, 118, 132, 143, 159, 185, 202, 218, 232, 243, 282, 321, 332, 353, 385, 428, 442.

Similarly, other of 6" - [2 - (4'-chlorophenyl)-6-methyl imidazo [1, 2-a] pyridin-3-yl]- 4"-aryl pyrimidine-2"-(1"H)-thiones. were prepared. The physical data are recorded in TABLE 1.

SUMMARY

6" - [2 - (4'-chlorophenyl)-6-methyl imidazo [1, 2-a] pyridin-3-yl]- 4"-aryl pyrimidine-2"-(1"H)-thiones (4a-4l) have been synthesized. Some of the compounds 4b, 4d, 4e, 4j, 4k, 4l, showed good remarkable antibacterial and antifungal activity with compare to known standard drugs e.g. ampicillin, chloramphenicol, norfloxacin and gresiofulvin at same concentration 50µg/ml.

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