ISSN: 0974 - 7516 Volume 8 Issue 7

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 8(7), 2012 [269-273]

Synthesis and biological screening of 6"-[2-(4'-chlorophenyl)-6-methylimidazo [1,2-a] pyridin-3-yl]- 4"-arylpyrimidin-2"(1"H)-ones

D.M.Purohit*, V.V.Bhuva

Shree M.& N.Virani Science College, Chemistry Department, Kalawad Road, Rajkot-5, Gujarat, (INDIA)

E-mail : purohitdm@yahoo.com

Received: 19th December, 2011 ; Accepted: 9th January, 2012

ABSTRACT

Looking to the interesting therapeutic activity of pyrimidinone ring system, It was considered worthwile to synthesis compounds bearing pyrimidine liked to the pyrimidinone nucleus. In the past years considerable evidence has been accumulated to demonstrate the efficiency of pyrimidinones. some new 6" - [2 - (4'-chlorophenyl)-6-methylimidazo [1, 2-a] pyridin-3-yl]- 4"-arylpyrimidin-2"(1"H)-ones (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

Oxo pyrimidines;
(Heterocyclic chemistry).

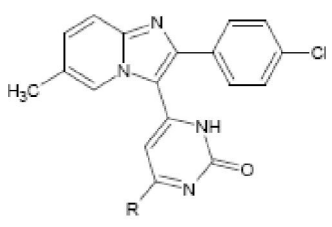
INTRODUCTION

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, Antifungal[1-3], Antiallergic[4], Analgesic[5], Antagonist[6, 7], Antitumor[8], CNS active agent[9], Cytotoxic[10], Inhibitors of cell proliferation[11], Gastric acid secretion inhibitor[12], Antimicrobial[13], etc. In view of getting to synthesized imidazo [1,2-a] pyridines derivatives and evaluated for their antimicrobial activity.

Pyrimidine derivatives like uracil (I), thymine (II) and cytosine (III) occur widely in nature showing remarkable pharmaceutical importance because of their diverse pharmacological activities. Pyrimidine derivatives which occurs in natural products like nucleic acid, vitamin-B and having remarkable pharmaceutical importance because of their broad spectrum of biological activities. Anticonvulsant[14], Fungicidal[15], Insecticidal[16], Tranquilizer[17].

Several analogues of nucleic acid have been used as a compound that interfere with the synthesis and function of nucleic acids, an example is fluorouracil which has been used in cancer treatment. Pyrimidines are among those molecules that make like possible as being some of the building blockers of DNA and RNA.

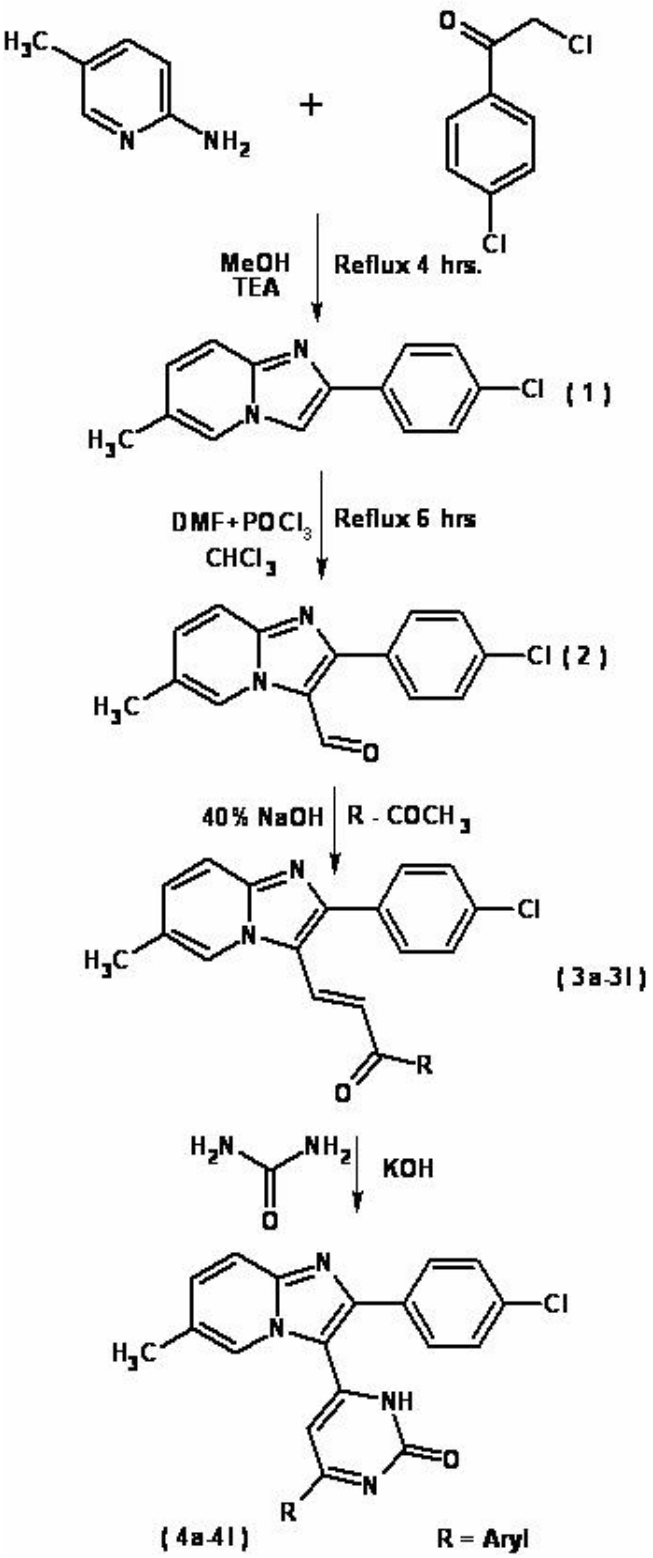
6" - [2 - (4'-Chlorophenyl)-6-methylimidazo [1, 2-



(4a-4l) R=Aryl

Full Paper

Reaction scheme



a] pyridin-3-yl]- 4''-arylpyrimidin-2''(1''H)-ones(4a-4l) have been prepared by the condensation of 2-(4'-chlorophenyl)-6-methyl-3-[1''-aryl-2''-propene-1''-one-3-yl]-imidazo[1,2-a]pyridine with urea in the presence of basic catslyst

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.

ANTIMICROBIAL ACTIVITY

6'' - [2 - (4'-chlorophenyl)-6-methylimidazo [1, 2-a] pyridin-3-yl]- 4''-arylpyrimidin-2''(1''H)-ones. 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 standerad 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 wim 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 (γmax 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

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.Subtilies	S.aureus	B. Cereus	E.Coli	A. arogens	S. typhi	P. Valgaris	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-	$C_{24}H_{17}ClN_4O$	189	15	15	12	13	23	17	17	19	22	17	13.57	13.56
4b	3-Cl-C_6H_4-	$C_{24}H_{16}Cl_2N_4O$	168	22	18	19	15	17	19	19	21	17	19	12.53	12.51
4c	4-Cl-C_6H_4-	$C_{24}H_{16}Cl_2N_4O$	155	15	20	16	19	15	20	16	20	18	21	12.53	12.51
4d	2-4-$(Cl)_2$-C_6H_3-	$C_{24}H_{15}Cl_3N_4O$	190	16	17	15	18	20	21	14	18	22	16	11.63	11.60
4e	4 -F-C_6H_4-	$C_{24}H_{16}ClFN_4O$	183	21	19	14	16	16	19	13	16	18	18	13.00	13.00
4f	4-Br-C_6H_4-	$C_{24}H_{16}BrClN_4O$	192	14	21	20	19	14	17	21	15	14	20	11.39	11.35
4g	4 -OH-C_6H_4-	$C_{24}H_{17}ClN_4O_2$	170	17	22	18	20	23	15	15	19	15	19	13.06	13.03
4h	4-NH_2-C_6H_4-	$C_{24}H_{18}ClN_5O$	205	17	18	12	17	22	19	17	20	16	18	16.37	16.35
4i	4-CH_3-C_6H_4-	$C_{25}H_{19}ClN_4O$	165	15	17	14	18	16	16	21	19	15	17	13.12	13.11
4j	4-OCH_3-C_6H_4-	$C_{25}H_{19}ClN_4O_2$	198	22	20	22	16	16	17	24	21	22	22	12.65	12.63
4k	3-NO_2-C_6H_4-	$C_{24}H_{16}ClN_5O_3$	166	13	21	15	20	17	16	16	19	18	19	15.30	15.28
4l	4-NO_2-C_6H_4-	$C_{24}H_{16}ClN_5O_3$	174	16	18	23	19	15	20	17	21	19	20	15.30	15.27

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

Compounds	B.mega	B.Subtilis	S.aureus	B.Cereus	E.Coli	A.arogans	S.typhi	P.Valgaries	A.niger	A. awamori
(4a – 4l)	4b, 4e, 4j	4f, 4g, 4k	4h,4f,4j,4l	4g, 4k	4a,4d,4g,4h	4c, 4d, 4l	4f,4i,4j	4b, 4j, 4l	4a,4d,4j	4c, 4f, 4j, 4l
Activity of standard drugs.										
drugs	**B.mega**	**B.Subtilis**	**S.aureus**	**B.Cereus**	**E.Coli**	**A.arogans**	**S.typhi**	**P.Valgaries**	**A.niger**	**A. awamori**
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

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 ^{o}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 ^{o}C.,

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

Full Paper

84 ml DMF and 1.0 lit $CHCl_3$ in RBF and cool at 0 - 5 °C. Start drop wise addition of 165ml $POCl_3$ within 1.0 h (exothermicity observe) stir 30 min at 0-5 °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 °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 catalytical amount 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 °C,

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, 65,77, 91, 102, 119, 129, 153, 167, 175, 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-methylimidazo [1, 2-a] pyridin-3- yl]- 4"-(4"'methylphenyl) pyrimidin-2"(1"H)-ones(4i)

A mixture of 2-(4'-chlorophenyl)-6-methyl-3-[1"-(4"'methylphenyl)- 2"-propene-1"-one-3-yl]-imidazo [1,2-a]pyridine (4.27gm, 0.01 mol) and urea (0.60gm, 0.01 mol) in ethanol (15 ml) was refluxed in presence of alcoholic KOH for 12 hrs. The excess solvent was distilled out and the product was poured in to crused ice, the separated solid was filtered out and crystallized from ethanol. Yield 65 %, m.p. 165°C

Anal. Calcd. For $C_{25}H_{19}ClN_4O$; Required : C, 70.34; H, 4.49; N, 13.12%; found : C, 70.33; H, 4.45; N, 13.11%;)IR (KBr) : 2871 (C-H str., Sym,) ; 1377 (C-H def., sym.) ; 1446 (C-H def., asym.); 3053 (C-H Str., Aromatic); 1475 (C=C str.); 1128 (C-N str.); 1677 (C=O); 1627 (C=N); 779(C-Cl) ^{1}HNMR ($CDCl_3$); 2.30-2.35 (s, 6H $-CH_3$); 7.11-8.14 (m, 12H Ar-H); 4.88 (S, 1H Ar-H); m/z: 44, 65, 77, 92, 103, 111, 130, 158, 171, 158, 171, 185, 207, 226, 232, 242, 265, 267, 294, 315, 335, 335, 369, 384, 427.

Similarly, other 6" - [2 - (4'-chlorophenyl)-6-methylimidazo [1, 2-a] pyridine 3- yl]- 4"-arylpyrimidin-2"(1"H)-ones.(4a-4l) were prepared. The physical data are recorded in TABLE 1.

SUMMARY

6" - [2 - (4'-chlorophenyl)-6-methylimidazo [1, 2-a] pyridine 3- yl]- 4"-arylpyrimidin-2"(1"H)-ones (4a-4l) have been synthesized. The compounds 4a, 4d, 4g, 4h, 4j, 14k, 4lshowed good remarkable antibacterial and antifungal activity with compare to known standard drugs e.g. ampicillin, chloramphenicol, norfloxacin and griseofulvin at same concentration 50µg/ml.

ACKNOWLEDGEMENT

The authors are thankful to management and principal of shree M.& N. virani science college, Rajkot for providing research facilities. We are also thankful university grant commission (Western Regional Office), Pune for Providing us financial supports (Minor research Project)

REFERENCES

[1] M.J.Anne, O'Mahony Mary Josephine, L.Stephen, D.Jacqueline; PCT Int.Appl. WO 98 27, 080; Chem.Abstr., **129**, 81666d **(1998)**.

[2] A.Z.Elassar, A.Abdel Zaher; Pharmazie, 1998; Chem.Abstr., **129**, 4562a **(1998)**.

[3] R.M.Shaker; Pharmazie, 1996, 51(3); Chem.Abstr., **125**, 10762p **(1996)**.

[4] D.B.Shinde, M.S.Shingare; Indian J.Chem., **30B**, 450 **(1991)**.

[5] P.Pere, G.Elisa; Span ES, 511, 501.

[6] G.A.Kileigil, R.Ertan; J.Heterocycl.Chem., **35**, 1485 **(1998)**.

[7] Saheyla Ozbey, Engin Kendi; J.Heterocycl.Chem., **35**, 1485 **(1998)**.

[8] W.Wuri, Li Tiechao, M.Robert, J.Yares, E.Hinnart, M.J.Luzzio, S.A.Noble, Attardo Giorgio; Bio.Org.Med.Chem.Lett., 1998; Chem.Abstr., **129**, 202833s **(1998)**.

[9] Y.D.Kulkarni, D.Srivastava, A.Bishnoi, P.R.Dua; J.Indian Chem.Soc., 73(45); Chem.Abstr., **125**, 86440c **(1996)**.

[10] R.Judith, B.Geneviere, T.Francois, R.Pierre, L.Stephane, P.Alan, A.Gharem; Chem.Pharm.Bull. 1998; Chem.Abstr., **128**, 180349p **(1998)**.

[11] Dell Colin Peter, Williams Andrew Carwyn; Eur.Pat.Appl.EP., 599, 514; Chem.Abstr., **121**, 108765j **(1994)**.

[12] L.H.Jochem, V.W.E.Gerlach, B.J.Chim, E.H.Christian, M.Hropot; Eur.Pat.Appl.EP., 807, 629; Chem.Abstr., **128**, 34684c **(1998)**.

[13] A.Dandia, V.Sehgal, P.Singh; Indian J.of Chem., **32B**, 1288-91 **(1993)**.

[14] Mochida Pharmaceutical Co. Ltd. JP, **81**, 127, 383 **(1981)**.

[15] N.Henrie Robert, J Peake Clinton, G.Cullen Thomas et al.; PCT Int Appl., WO 98,20,878, Appl.96/08, 17748 (1996); Chem.Abstr., **129**, 16136s **(1998)**.

[16] M.M.Ghorob, S.G.Abdel-Hamid; Indian J.Heterocycl.Chem., **4**, 103-06 **(1994)**.

[17] R.K.Russell, J.B.Press, R.A.Rampulla, J.J.Mc Nally et al.; J.Med.Chem., **31**, 1786 **(1988)**.

[18] A.L.Barry; The Antimicrobial Succeptibility Test, Principal and Practices, Edited by Illus Lee and Febiger 180; Bio.Abstr., **64**, 25183 **(1997)**.