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Synthesis and biological screening of 2-[(4'-chlorophenyl)-6-methyl imidazo [1, 2-a] pyridin-3-yl]-(1"-propene-3"-aryl-3"-yl)-pyrimidine- 2"', 4"', 6"'-(3"'H, 5"'H)-triones

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ABSTRACT

Barbiturates derivatives possess good therapeutic activity in the field of medicinal chemistry, Prompted by these facts, the preparation of 2-[(4'-chlorophenyl)-6-methyl imidazo [1,2-a] pyridin-3-yl]-(1"-propene-3"-aryl-3"-yl)- pyrimidine- 2"',4"',6"'-(3"'H, 5"'H)-triones. (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

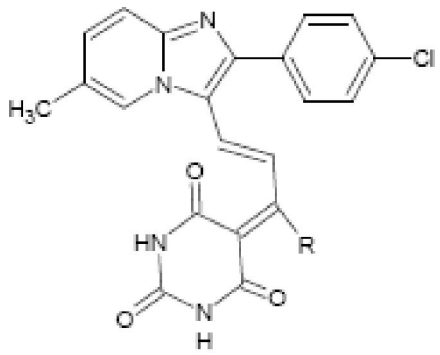
Barbitones;
(Heterocyclic chemistry).

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 hypnotic[1], anthelmintic[2], antiulcer[3, 4], hypnoselective and anxioselective activities[5]. bamyloidformation inhibitors[6], antiinflammatory, analgesic, antipyretic[7, 8] etc. In view of getting to synthesized imidazo [1,2-a] pyridines derivatives and evaluated for their antimicrobial activitiy.

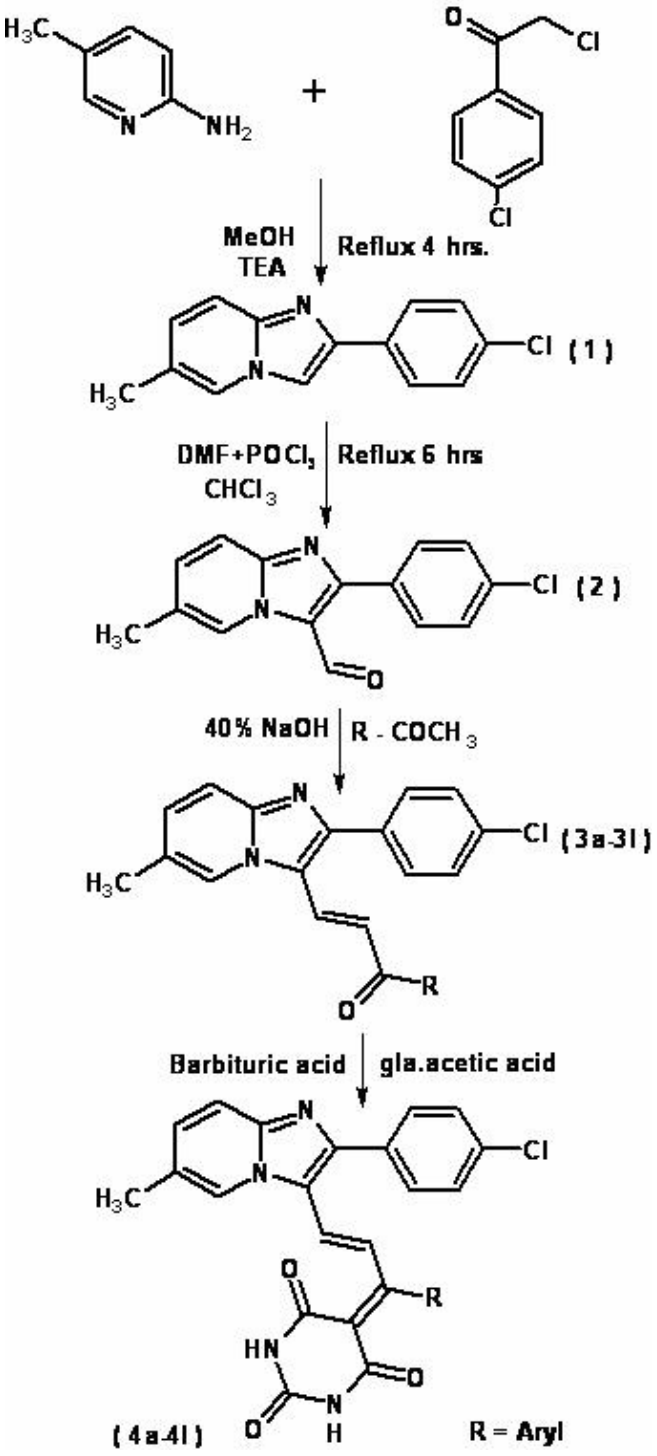
*B*arbitones, which belongs to an important group of nitrogen containing heterocyclic compounds have been extensively explored for their application in the field of medicine. Most important is the effect of barbiturates on CNS. Barbituric acid derivatives possessing diverse biodynamic properties including hypnotic, sedative, anticonvulsant,cardiovascular etc.

Barbituric acid usually represented as the trione was first made about 1864 and it has no hypnotic properties. The origin of the name is lost, although there are several possible explanations associated with St. Barbara's feast day, a favourite Munchen *Kellnerin* rejoicing in that given name, and even the *barba* which



(4a-4l) R=Aryl

Reaction Scheme



is a beard of the business end of a key.

2-[(4'-chlorophenyl)-6-methyl imidazo [1,2-a] pyridin-3-yl]-(1"-propene-3"-aryl-3"-yl)- pyrimidine-2"',4"',6"'-(3"'H, 5"'H)-triones have been prepared, by the cyclocondensation of 2-(4'-chlorophenyl)-6-methyl-3-(1"-aryl- 2"-propene-1"-one-3-yl) -imidazo [1,2-a] pyridines in with barbituric acid and glacial aceticacid.

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

2-[(4'-chlorophenyl)-6-methyl imidazo [1,2-a] pyridin-3-yl]-(1"-propene-3"-aryl-3"-yl)- pyrimidine-2"',4"',6"'-(3"'H, 5"'H)-triones 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[9]. After 24 hrs of incubation at 37 °C, The zones of inhibition were measured in mm. The activity of synthesised compounds 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 metha-

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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-tilies	S. aureus	B. Ce reus	E. Coli	A. rogens	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-	$C_{27}H_{19}ClN_4O_3$	165	14	19	19	17	18	21	17	19	18	16	11.60	11.58
4b	3-Cl-C_6H_4 -	$C_{27}H_{18}Cl_2N_4O_3$	195	16	15	14	16	16	14	20	18	16	17	10.83	10.81
4c	4-Cl-C_6H_4 -	$C_{27}H_{18}Cl_2N_4O_3$	155	15	16	14	14	18	18	17	17	13	19	10.83	10.80
4d	2-4-$(Cl)_2$-C_6H_3-	$C_{27}H_{17}Cl_3N_4O_3$	205	28	19	16	18	21	15	20	20	20	21	10.15	10.12
4e	4 -F-C_6H_4-	$C_{27}H_{18}ClFN_4O_3$	190	20	21	20	20	17	19	20	18	16	22	11.19	11.17
4f	4-Br-C_6H_4-	$C_{27}H_{18}BrClN_4O_3$	167	12	19	16	18	13	21	21	20	22	18	9.97	9.96
4g	4 -OH-C_6H_4-	$C_{27}H_{19}ClN_4O_4$	158	21	20	14	17	12	16	14	19	19	17	11.23	11.21
4h	4-NH_2-C_6H_4-	$C_{27}H_{20}ClN_5O_3$	165	20	22	18	19	19	17	16	20	18	20	14.06	14.04
4i	4-CH_3-C_6H_4-	$C_{28}H_{21}ClN_4O_3$	170	14	17	16	14	16	18	18	20	11	20	11.27	11.25
4j	4-OCH_3-C_6H_4-	$C_{28}H_{21}ClN_4O_4$	200	17	19	20	16	21	20	16	19	12	17	10.92	10.90
4k	3-NO_2-C_6H_4-	$C_{27}H_{18}ClN_5O_5$	165	14	18	19	17	18	21	13	20	21	18	13.27	13.24
4l	4-NO_2-C_6H_4-	$C_{27}H_{18}ClN_5O_5$	177	13	15	20	18	17	16	15	18	13	22	13.27	13.25

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 gans	S.typhi	P.Valgaries	A.niger	A. awa mori
(4a – 4l)	4e, 4g, 4h	4e, eg, 4h	4a, 4e, 4k, 4l	4e	4a, 4c, 4d, 4h, 4j	4f, 4j, 4k	4b, 4d, 4e, 4f	4d, 4f, 4h, 4i, 4k	4d, 4f, 4k.	4d, 4e, 4h, 4i, 4l
Activity of standard drugs.										
drugs	**B.mega**	**B.Sub tilis**	**S.aureus**	**B.Cereus**	**E.Coli**	**A.aro gans**	**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

nol 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 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 °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, 102, 119, 129, 153, 167, 176, 193, 204, 215, 232, 242, 267, 294, 321, 349, 367, 386.

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

[D] Synthesis of 2-[(4'-chlorophenyl)-6-methyl imidazo [1,2-a] pyridin-3-yl]-(1"-propene-3"-(4""-methylphenyl)-3"-yl)-pyrimidine-2"', 4"', 6"' (3"'H, 5"'-H)-triones(4i).

A mixture of 2-(4'-chlorophenyl)-6-methyl-3-[1"-(4"'-methylphenyl)- 2"-propene-1"-one-3-yl]-imidazo [1,2-a]pyridine (3.8 g, 0.01 mol), barbituric acid (1.28 g, 0.01 mol) in glacial acetic acid was refluxed for 10 hrs. in oil bath. The contents were poured in to ice and product was isolated, crystallized from DMF. Yield, 69%, m.p.170°C.

Anal. Calcd. For $C_{28}H_{21}ClN_4O_3$; Required : C, 67.67; H, 4.26; N, 11.27%; found : C, 67.65; H, 4.25; N, 11.25%;) IR (KBr): 2877 (C-H str., Sym,) ; 1394 (C-H def., sym.) ; 1440 (C-H def., asym.); 3056 (C-H Str., Aromatic); 1537 (C=C str.) ; 1070 (C-N str.); 2950 (C-H Str.); 1600 (C=N); 750(C-Cl)^1 HNMR ($CDCl_3$); 2.30-2.40 (s, 6H -CH_3); 6.95-8.09(m,13HAr-H); m/z: 52, 65, 77, 91, 111, 126, 156, 164, 207, 219, 229, 255, 267, 294, 339, 359, 441, 465, 496.

Similarly other 2-[(4'-chlorophenyl)-6-methyl imidazo [1,2-a] pyridin-3-yl]-(1"-propene-3"-aryl-3"-yl)- pyrimidine- 2"',4"',6"'-(3"'H, 5"'H)-triones were synthesized. The physical data are recorded in TABLE No. 1.

SUMMARY

2-[(4'-chlorophenyl)-6-methyl imidazo [1,2-a] pyridin-3-yl]-(1"-propene-3"-aryl-3"-yl)- pyrimidine-2"', 4"', 6"'- (3"'H, 5"'H)- triones (4a-4l) have been synthesized. The compounds 4e, 4g, 4h, 4j, 4k, showed good remarkable antibacterial and antifungal activity with compare to known standard drugs e.g. ampicillin, chloramphenicol, norfloxacin and griseofulvin at same concentration 50µg/ml.

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