www.sphinxsai.com

ChemTech

International Journal of ChemTech Research
CODEN(USA): IJCRGG ISSN : 0974-4290
Vol.1, No.4, pp 1000-1004, Oct-Dec 2009

Synthesis, characterisation and pharmacological evaluation of novel 4-aryl 3-chloro n-pyridine 2-yl 2-azetidinone

Natarajan Ramalakshmishmi[1*], Selvaraj Deepa [1] Antro jenny[1], Gopi[1], Subramani Arunkumar[2] ,Ayarivan Puratchikody[3] ,Raj Vijaya Bharathi[4].

[1]Department of Pharmaceutical Chemistry, C.L. Baid Metha college of pharmacy, Thoraipakkam,Chennai-600097,India.
[2]Department of Pharmaceutical Chemistry. S.R.M college of Pharmacy, Kattankulathur, Chennai-603203, India.
[3]Department of Pharmaceutical Engineering and Technology, Anna University, Trichirapalli-620024, India.
[4]Department of pharmacognosy, Madras Medical college,Chennai-6000001, India.

Corres.author: ramalakshminatarajan@yahoo.co.in.
Ph no: 9840207950

ABSTRACT: In the present study 3-chloro 4-Aryl N-Pyridine -2-yl 2-Azetidinone derivatives were prepared based on the literature review. All the synthesized compounds showed characteristic I.R, ^{1}H-NMR, Peaks and expected molecular ion peak (M^+) in the spectral studies. All the compounds were subjected to leptospirocidal study. Among the synthesized compounds C_1 ,C_2 ,C_3 ,C_4 ,C_5 and C_{12} showed significant activity. And the compounds C_8 ,C_9 ,C_{10} ,C_{11} showed moderate activity. From the above summary it reveals that forming Azetidinone nucleus at the side chain of 2-amino pyridine showed significant leptospirocidal activity.
KEY WORDS: Nicotinic acid, Azetidinones, leptospirosis.

INTRODUCTION

Pyridine is reported to posses various pharmacological activities like vasodilator[1], neuromuscular transmission[2]. The β-lactam drug are still the most prescribed antibiotics used in medicine. The azetidinones were tested as Anaesthetic[3], Anticonvulsant[4], Anti-inflammatory[5], Antimicrobial[6], Antiviral[7], Antitubercular[8], Hypolipidemic activity[9]. Recently 2-Azetidinones have been assessed for Antiparkinsonism[10]. The present work involved synthesis of 12-Azetidinones of 2-aminopyridines. The present work involved the synthesis of 12 azetidinones. 2-aminopyridine was reacted with 12 aromatic aldehydes to yield corresponding Schiff bases which on cyclization with chloroacetylchloride yielded respective azetidinones. The reaction is shown in the syntheticscheme. The synthesized compounds were confirmed by IR,NMR and mass studies. The compounds were then subjected to *in-vitro* leptospirocidal activity.

EXPERIMENTAL

The melting points were taken in open capillary tubes and are uncorrected. The IR spectra [12] of the compounds were recorded on ABB BOMEN FTIR spectrometer MB 104 with potassium bromide pellets. ^{1}H NMR spectra [12] in $CDCl_3$ or DMSO-d6 recorded on Burker AV 400 MHz spectrometer. Mass spectra were recorded on GCMS QP 5000 Shimadzu. The purity of the compounds was checked by TLC on pre-coated aluminium plates of silica gel. The spots were visualized by UV light. The physical data are tabulated in Table 1.

Table 1: Details of the physical data of the Synthesized Compounds

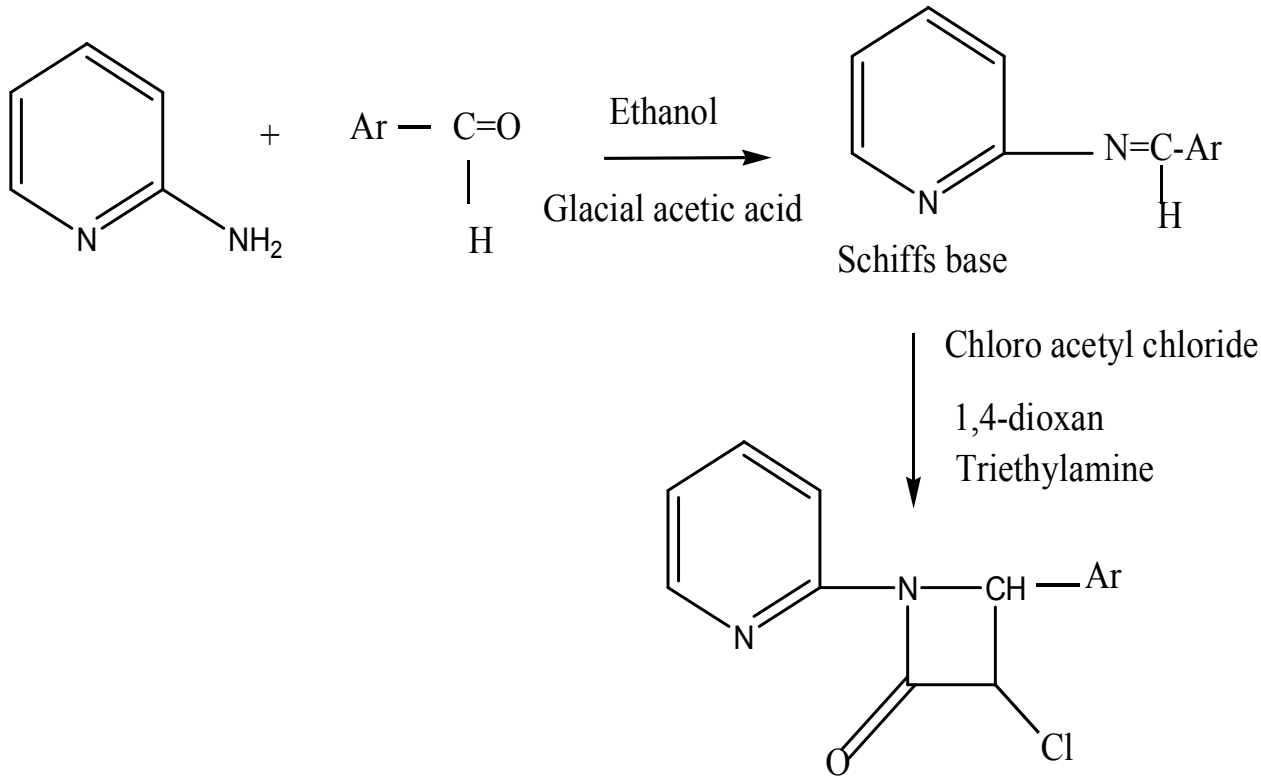
Compounds	Molecular Formula	Melting point	Solvent system	R.F. Value	Yield (%)	IR	NMR	Mass
C_1	$C_{14}H_{11}N_2O_2Cl$	205	Benzene Ethyl Acetate (8:4:1)	0.5135	61.75	1627,1778,3046,1301	6.7 - 7.7, 4.4, 3.8, 2.8	301
C_2	$C_{14}H_{11}N_2O_2Cl$	195		0.7329	52.66	1628,1741,3084,1355	6.4 - 7.6, 4.6, 4.2	303
C_3	$C_{15}H_{13}N_2O_2Cl$	183		0.6053	55.18	1621,681,3089,3392	7.2 - 8.3, 4.7, 3.7	303
C_4	$C_{14}H_{10}N_2OCl_2$	188		0.5000	47.68	1627,1778,3046,1301	6.9 - 7.4, 4.7, 3.7, 11.3	274
C_5	$C_{14}H_{10}N_2OCl_2$	188		0.7941	62.80	1673,1717,3019,3389	6.9 - 7.4, 4.6, 3.7, 11.2	273
C_6	$C_{15}H_{13}N_2OCl$	208		0.7436	80.01	1654,1770,2998,3395	6.9 - 7.9, 4.5, 3.2, 11.3	274
C_7	$C_{16}H_{16}N_3OCl$	240		0.6111	70.20	1667,1772,3062,3392	6.9 - 7.7, 4.6, 4.2, 10.8	290
C_8	$C_{14}H_{10}N_3O_3Cl$	216		0.5294	27.97	1621,1763,3048,2851	7.2 - 7.7, 4.6, 3.5, 2.4	272
C_9	$C_{12}H_9N_2O_2Cl$	179		0.5000	58.33	1619,1734,3058,1251	6.9 - 7.7, 4.6, 3.6, 3.8	288
C_{10}	$C_{15}H_{13}N_2O_3Cl$	211		0.4706	11.48	1622,1749,3061,1232	7.0 - 7.2, 4.6, 3.7, 3.9	348
C_{11}	$C_{14}H_{10}N_3O_3Cl$	205		0.5278	45.78	1624,1785,3048,815	7.0 - 8.2, 4.0, 3.7	292
C_{12}	$C_{14}H_{11}N_2OCl$	189		0.3899	62.94	1628,1741,3054,824	7.2 - 7.7, 4.9, 4.2	292

SYNTHETIC METHODS

PREPARATION OF 2-AZETIDINONES: GENERAL METHOD OF PREPARATION (COMPOUND C1-C12)

Schiff bases were prepared according to literature procedure[11]. A mixture of Schiff base (0.002 mol) and Triethyl amine (0.004 mol) was dissolved in 1,4-Dioxan (50 ml). To this well stirred cooled solution of chloroacetyl chloride (0.004 mol) was added dropwise during 20 mins. The reaction mixture was then stirred for further 3 hour and left at room temperature for 48 hour. The resultant mixture was concentrated, cooled, then poured into ice-cold water and dried. Recrystallised from n-hexane / spirit gave compounds C1 to C12. All the compounds were characterized by spectral analytical data, given in Table 1.

SYNTHETIC SCHEME



BIOLOGICAL EVALUATION

MICROPLATE – BASED MICROBIAL ASSAY:

In vitro leptospirocidal activity was determined using a sensitive and quick micro plate method (Jenny Gabrielson et al. 2003) with 50 µg/ml concentration of the synthesized compounds which is dissolved in an solvent DMF. The micro plate used in the assay were 96 – well round bottomed micro titer plates of polystyrene. The plates were sterilized and examined for absence of any external contaminating microbial growth in the wells. Leptospirocidal activity of the synthesized compounds was examined using cultures of *leptospira icterohaemorrhagiae* in EMJH medium at 37°C.The cultures were diluted in the EMJH medium to give approximately 5.0×10^5 cfu/ml.90 µl of the culture suspension was transformed to a 96- well plate.

Ten micro liter of the synthesized compounds dissolved in DMF were transformed into the first well, and serial dilutions were performed so that concentrations in the range of 50- 0.005 mg/ml were obtained. Benzyl Penicillin was used as standard reference in the same concentration and culture in EMJH medium was used as control. The plates were covered and incubated for 7 days at 37°C.The absorbance was measured at 420 nm by a micro plate reader model 550 (Bio-Rad) before and after incubation.

For comparison, three computation methods for determination of the level of inhibition were evaluated. The minimal inhibitory concentration (MIC) is the lowest tested concentration of the test drug at which full inhibition of microbial growth is observed. The IC_{50} value is the concentration of test drug at which 50% of inhibition of microbial growth is observed and shown in Table 2

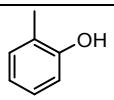
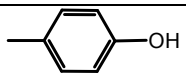
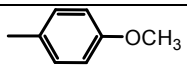
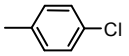
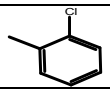
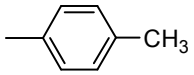
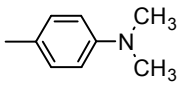
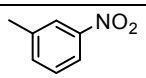
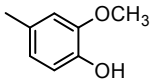
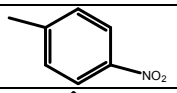
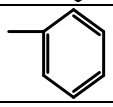
RESULTS AND DISCUSSION

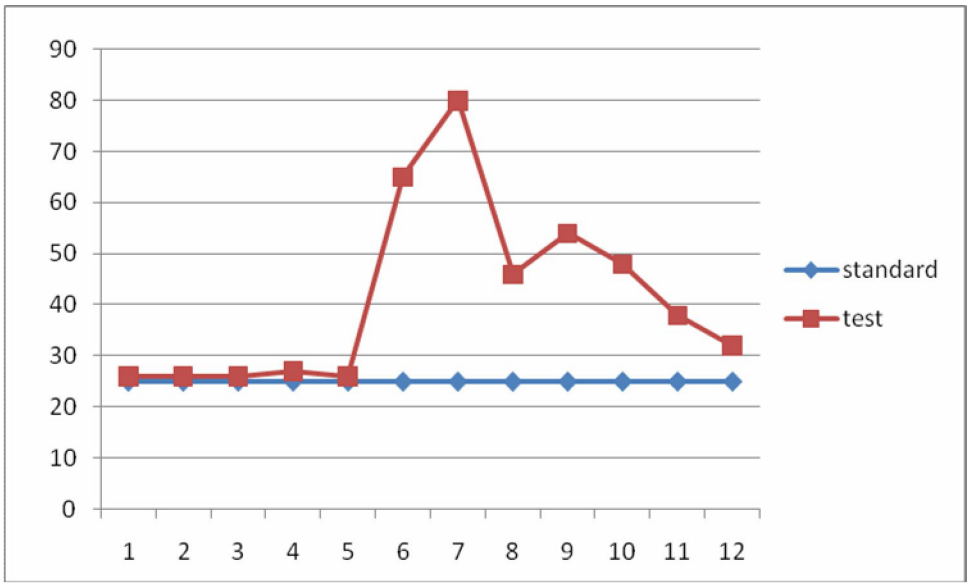
Compounds C_1 ,C_2 ,C_3 ,C_4 ,C_5 and C_{12} showed significant activity. And the compounds C_8 ,C_9 ,C_{10} ,C_{11} showed moderate activity. And compounds C_6 ,C_7 shows least activity.

CONCLUTION

From the above summary it reveals that forming Azetidinone nucleus at the side chain of 2-amino pyridine showed significant leptospirocidal activity. Especially Chloro, Hydroxyl and Methoxy substitutions showed significant activity. Methyl and N,N, Dimethyl amino substitution showed least activity.

Table 2: IC_{50} VALUES FOR SYNTHESIZED COMPOUNDS

Source code	%Inhibition at 50 ug/ml	IC_{50} Values	Ar
C_1	96.40	26	
C_2	95.50	26	
C_3	95.32	26	
C_4	91.18	27	
C_5	93.52	26	
C_6	38.48	65	
C_7	31.83	80	
C_8	54.85	46	
C_9	46.04	54	
C_{10}	52.15	48	
C_{11}	67.87	38	
C_{12}	76.44	32	
Benzyl penicillin	99.46	25	



ACKNOWLEDGMENTS

We gratefully acknowledge C.L.Baid Metha college of Pharmacy for providing necessary facilities for carrying out the research work

REFERENCES

1. Ryman T, Petersson J, Hogestatt E D *Pharmacol. Toxixol,* 1999, Aug; 85 (2) 80-4.
2. F. Valexzuela and F. Huidobro *Journal of Pharmacology And Experimental Therapeutics*, Vol. 92, Issue 1, 1-14, 1948
3. Srivastava, S.K, Soumya Srivastava, and Srivastava, SD, *Ind. J. of chem,*. 2002; Vol- 41B: pp:2357-2363
4. Kaneriya, C.R., *ori. J. of Chem*, 2003; Vol-19(3):pp: 677-680.
5. Ning, field & Sternback, *J. of Heterocyclic chem..,* 7, 475 (1970).
6. Srivastava, S.K, Srivastava, S.L., and Srivastava, SD, *Ind. J. of chem*,.2000; Vol- 39B: pp:464-467.
7. Pandey, V.K., *Ind. J. of chem,* 2005; Vol- 44B: pp: 158-162.
8. Patel, K.D., Mistry, B.D., and Desai, K.R., *Ori. J. of Chem*,. 2003; Vol 19(1); pp:245-246.
9. Tapar, G.S., Krishnamurthy, A., *Ind. J. of chem*, 1990; Vol 29B; pp 1134-1137.
10. Patel, P.V., desai, K.R.; *ori. J. of Chem.*, 2002 ;Vol-18(2); pp: 311-314.

*****