RJC

RASĀYAN *J. Chem.*
Vol. 9 | No. 1 |84 - 88 | January - March | 2016
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

SYNTHESIS AND BIOLOGICAL EVALUATION OF AZITIDINONE AND THEIR DERIVATIVE AS ANTIMICROBIAL AND ANTIFUNGAL AGENTS

Chandrakant Patel* and C.P.Bhasin
Department of Chemistry, Hemchandracharya North Gujarat University, Patan.
*E-mail : cbpatel_81@yahoo.in

ABSTRACT

In our present study 2-Chloro 7-trifluoromethyl 3- Carbaldehydeis condensed with different substituted aromatic amine to form respective Schiff bases. The Schiff bases are cyclized with chloroacetylchloride in triethylamine to yield the corresponding 2-azetidinones.Structures of synthesized compounds are confirmed by physical & spectral analysis. The compounds are evaluated for their antimicrobial and antifungal properties. All the compounds have shown comparable antimicrobial and anti fungal activities. The activities are due to C=O, C-N linkages in 2-azetidinones.

Keywords: Quinoline, Schiff base, Azitidinone, Antibacterial and Antifungal activity.

INTRODUCTION

β-Lactam drugs are still the most widely prescribed antibiotics in medicine.[1] Azetidinones which are part of antibiotics structure are known to exhibit interesting biological activities. A large number of 3-chloro monocyclic β-lactam possesses powerful antibacterial, antimicrobial, anti-inflammatory, anticonvulsant & anti-tubercular activities. They also function as enzyme inhibitors & are effective on the central nervous system.[2-4] they are the carbonyl derivatives of azetidines containing carbonyl group at the position-2. These are also known as 2-azetidinone or more commonly β-lactam.[5] Azetidinones or β-lactam chemistry is of great importance because of the use of β-lactam derivatives as antibacterial agents.[6-7] Cycloaddition of monochloro acetylchloride with imine (Schiff base) result in formation of 2-azetidinone(β-lactam). The reaction involves direct acylation of imine with monochloro acetylchloride. The reaction is carried out with base as triethylamine gives β-lactams.[8] Although variety of drugs have been developed fortreating bacterial and fungal diseases, the basic difficulty experienced with these infections are the rapid development of drug résistance to the infectious strains. Review of literature reveals that 2-azetidinones are reported to possess significant anti-tubercular, antibacterial & antifungal activities. *p*-anisidine, which is aniline derivative have been found to be biologically interesting compound for many years. Since 2-azetidinones of *p*-anisidine are not available, these derivatives can be done and resulting analogues aretested for their antimicrobial activity.

The constitution of all compounds synthesized was established by elemental analysis, IR and 1H NMR spectral study. Compounds were also evaluated for anti bacterial and anti-fungal activities.

EXPERIMENTAL

All the chemicals used were of pure grade (Finar and Sigma Aldrich). The melting points of all compounds were determined by open capillary method and were uncorrected.

General procedure

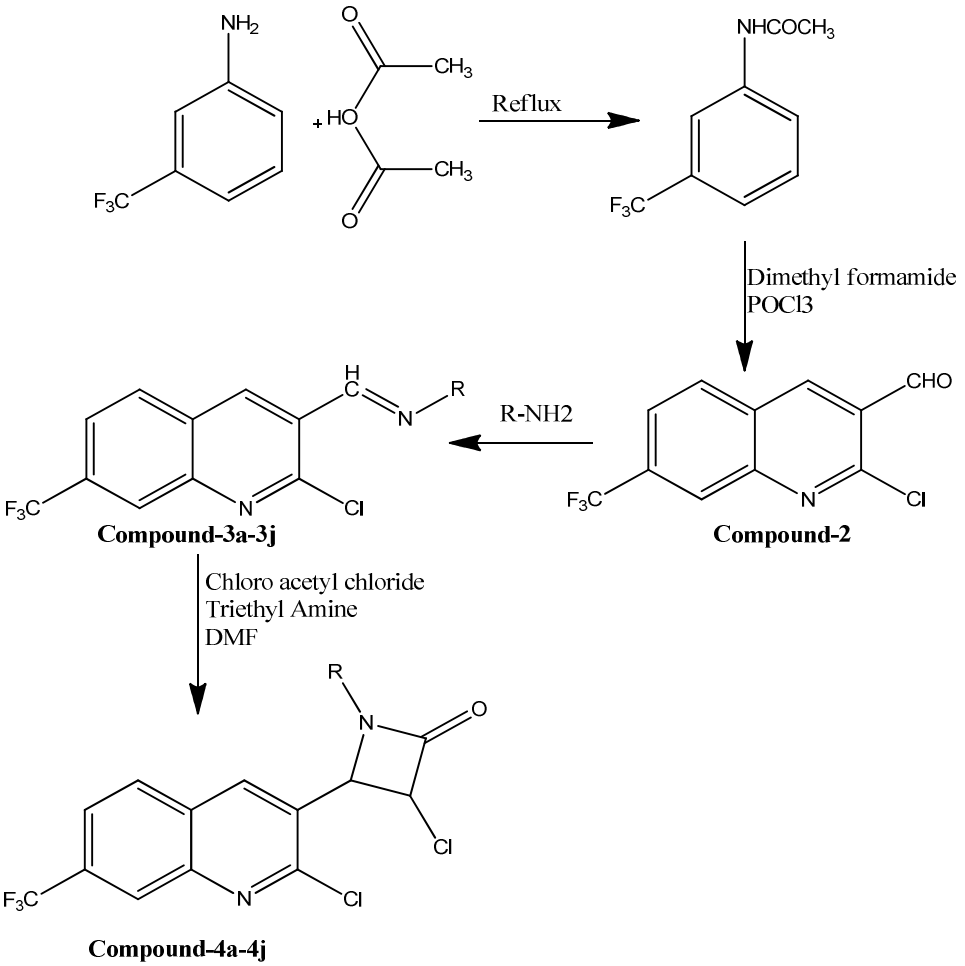
Synthesis of 2-Chloro 7-trifluoromethyl 3- Carbaldehyde (2)

To an ice-cooled solution of N,N-dimethylformamide (10.95g, 0.15 mol) and Phosphoryloxy chloride (53.7 g, 0.35 mol) was added drop wise under cooling, stirring for 1/2 hr add m-tri Fluoro Acetinilide

(10.15g, 0.05 mole) and CTBAB (cetyltetrabutylammonium bromide) Start heating slowly to 75°c for 20 hrs. A mixture of poured in ice and temp maintain 0 to 10° for 1hr. Product was isolated and filter and wash by water. Crystallized from ethyl acetate. Yield (9.77g, 68%) m.p. 170-175^{O}C

Synthesis of N-[{2-chloro-7-(trifluoromethyl) quinoline-3-yl} methylene] benzenamine, (3a-3j)
A mixture of 2-Chloro 7-trifluoromethyl 3- Carbaldehyde (0.01M, 2.22gm) and different aromatic aldehydes was taken in ethanol and 2-3 drops of glacial acetic acid was added and the reaction mixture was refluxed for 10 hours. The product was isolated and crystallized by absolute alcohol.

Synthesis of 3- chloro-4-(2-chloro-7-(trifluoro methyl) quinolin-3-yl) -1-phenyl azetidin-2-one, (4a-4j)
A mixture of N-[{2-chloro-7-(trifluoromethyl) quinoline-3-yl} ethylene] benzenamine (0.01 mole, 3.72 g) in N, N-dimethylformamide was taken in a RBF. To it chloroacetylchloride (0.01 mole, 1.12 mL) and triethylamine (1 mL) in benzene were added slowly. It was reflux for 5-6 hr. The triethylamine hydrochloride was removed and the benzene was distilled off to get product 3- chloro-4-(2-chloro-7-(trifluoro methyl) quinolin-3-yl)-1-phenyl azetidin-2-one. The solid product was filtered, dried and recrystallized from ethanol, yield 70%, mp 172-175^{o}C.

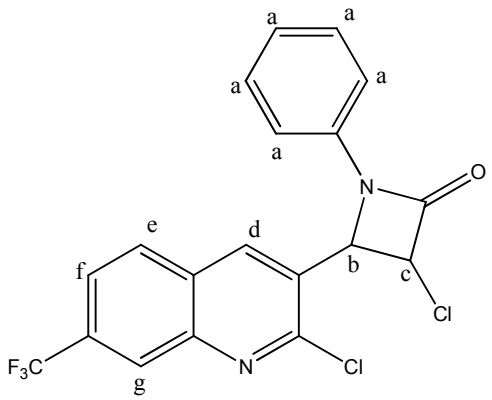


Scheme-1

Table-1: Characterization Table of-Physical constants of 3-chloro-4-(2-chloro-7-(trifluoromethyl) quinoline-3-yl)-1-(2-phenyl) azetidin-2-one

S. No.	Molecular Formula	R	Molecular Weight	M.P °C	Yield %
1a	$C_{19}H_{11}Cl_2F_3N_2O$	C_6H_5-	411.20	172	52
1b	$C_{19}H_{11}Cl_2F_3N_2O_2$	4-OH-C_6H_4-	427.20	186	57
1c	$C_{20}H_{13}Cl_2F_3N_2O_2$	4-OCH_3- C_6H_4-	441.23	196	60
1d	$C_{19}H_{10}Cl_2F_4N_2O$	4-F- C_6H_4-	429.20	213	55
1e	$C_{19}H_{10}Cl_3F_3N_2O$	4-Cl- C_6H_4-	445.65	210	60
1f	$C_{21}H_{16}Cl_2F_3N_3O$	4(N,NdiCH_3)- C_6H_4-	454.27	178	51
1g	$C_{19}H_{10}Cl_2F_3N_3O_3$	3-NO_2- C_6H_4-	456.20	232	50
1h	$C_{19}H_{10}Cl_3F_3N_2O$	2-Cl-C_6H_4-	445.65	210	53
1i	$C_{19}H_{10}BrCl_2F_3N_2O$	2-Br-C_6H_4-	490.10	225	57
1j	$C_{20}H_{13}Cl_2F_3N_2O$	4-CH_3- C_6H_4-	425.23	180	60

Table-2: Spectroscopic Data



Proton value

Signal	Signal Position (δ ppm)	Relative No of Protons	multiplicity	Inference
1	4.11-4.19	1H	Doublate	c
2	4.59-4.65	1H	Doublate	b
3	7.35-7.43	5H	Multiplet	a
4	7.80-7.82	1H	Doublate	e
5	8.21-8.22	1H	Doublate	d
6	8.41-8.42	1H	Doublate	f
7	8.71	1H	Singlet	g

Table-3

Type	Vibration mode	Frequency in cm-1
Aromatic	C-H stretching	3076
	C=C stretching	1481
Ketone	C=O stretching	1702
Halide	C-Cl stretching	782
Ether	C-O-C	1180

RESULTS AND DISCUSSION

All the synthesized final compounds were first purified by successive recrystallization using appropriate solvents. The purity of the synthesized compounds was checked by performing thin layer chromatography and determining melting points. Then the synthesized compounds were subjected to spectral analysis such as IR, NMR and Elemental analysis to confirm the structures. All the analytical details show satisfactory results. Our titled compounds are known to possess antimicrobial activity; the compounds were screened for their antibacterial and antifungal activity by cup-plate method. Two gram positive bacteria such as *S.aureus* and *B.megatwo* gram negative bacteria such as *E.coli* and *P.vulgaris* and a fungal species such as *A.Niger* is tested for the activities. The concentration of 40 of our titled compounds has been used. Ampicillin, Amoxicilin, Norfloxacin and β.penicillin been used as standards for anti-bacterial activity and greseofulvin have been used as standards for anti-fungal activity. All the compounds have shown mild to moderate activities.

^{1}H NMR Spectroscopy

Nuclear magnetic resonance (NMR) spectroscopy is one of the latest physical methods of investigating organic compounds. The scale of the spectrum is usually marked in parts per million (ppm) of the applied field or infrequency units (Hz). ^{1}H-NMR spectra were recorded on Bruker WM 400FT MHz NMR instrument using $CDCl_3$ orDMSO-d_6 as solvent and TMS as internal reference. The data of compound (2a) is summarized in Table -2.

Infrared spectra

The systematic interpretation of the infra-red spectrum is based upon the empirical data obtained by assigning infra-red absorption values to the structural units a characteristic of different structural units. Infra-red spectra were recorded in KBr on a Shimadzu FTIR spectrophotometer. The data of the structure is summarized in Table-3.

Table: 4-Biological Activity

Compounds	*B.mega*	*S.aureus*	*E.coli*	*P.valgaris*	*A.niger*
1a	20	18	20	19	19
1b	16	13	13	11	13
1c	12	16	19	18	10
1d	13	11	12	10	20
1e	14	10	18	15	17
1f	10	14	17	16	16
1g	16	18	21	10	14
1h	19	17	11	17	12
1i	14	12	14	19	21
1j	18	20	13	21	22
Ampicillin	23	22	21	25	-
Amoxicillin	22	23	21	24	-
Norfloxacin	24	17	23	19	-
Penicillin	25	24	19	20	-
Greseofulvin	-	-	-	-	25

CONCLUSATION

The work has approached towards the synthetic and biological approach of these wonder molecules. Anti-bacterialproperty of the synthesized compounds has exhibited very good inhibition; all compounds have exhibited mild activity towards gram positive bacteria. *B.mega*, *S. aureous*, when all compounds shows mild activity against gram negative bacteria E. coli and *P.aeruginosa* as compare to four standards. But thesystematic substitution at various position and other derived compounds have shown remarkable

antifungalproperties. *A.niger*. the remaining compounds have shown poorantifungal activity indicating less biological importance for a synthetic chemist.

REFERANCES

1. P. J. Naik, D. V. Parekh and P. S. Desai, *Advances in Applied Science Research*, **4,** 324 (2013)
2. Ameya A.Chavan and Nandini R. Pai, *Molecules*, **12,** 2467 (2007)
3. Freddy H. Havaldar and Sushil Kumar J. Mishra, *Indian J.Heterocycl Chem.* **13**, 197 (2004)
4. K.H Patel and A.G Mehta, *E.J.Chem*, **3**(13), 267 (2006)
5. A.Kumar, S. Gurtu, J.C Agrawal, J.N Sinha, K. P Bhargava and K. J Shanker. *Indian Chem. Soc*, **60**, 608 (1983)
6. Patel R.B, Desai P.S and, Chikhalia K.H, *Indian J.Chem*, , **45B**, 773 (2006)
7. P.Jitendra, Suryavanshi and Nandini Pai, *Indian J. Chem*, **45 B(5)**, 1227 (2006)
8. V.K Pandey, V.D Gupta, Mridula Upadhyway, V.K Singh and Meenal Tandon, *Indian J. Chem*, , **44(B)**, 15(2005)

[RJC-1381/2016]