HL
http://heteroletters.org
ISSN: 2231 – 3087(print) / 2230 – 9632 (Online)
Vol. 2: (1), 2012, 99-105

SYNTHESIS OF NEW HETEROCYCLIC SCHIFF BASE, THIAZOLIDINONE AND AZETIDINONE COMPOUNDS AND THEIR ANTIBACTERIAL ACTIVITY AND ANTI –HIV ACTIVITIES

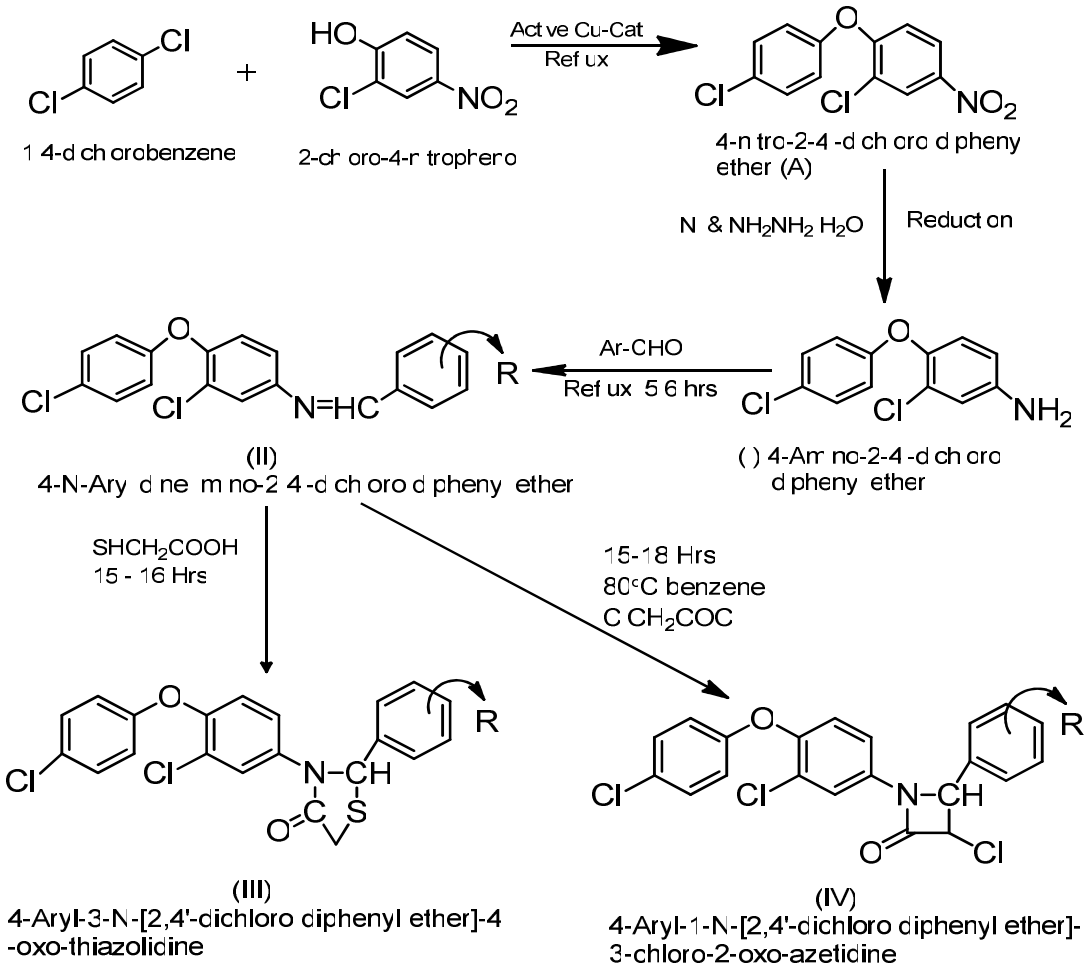
RAJARSHI N. PATEL[1]*, P.V.PATEL[2],K.R. DESAI[2],P.Y. PUROHIT[2],K.S.NIMAVAT[3] AND K.B. VYAS[4]

[1] *Suleshvari pharma, Ankleshwar -393 002, Gujarat, India.*
[2.] *Department of Chemistry, South Gujarat University, Surat – 395007 (India)*
[3.] *Department of Chemistry, Government Science College ,Gandhinagar-382 015,Gujarat,India.*
[4.] *Department of Chemistry, Sheth .L.H. Science Collage– Mansa-382 845, Gujarat, India.*
**Corresponding author: Phone: +91-9033231942, E-mail: Dadaji.raja@gmail.com*

ABSTRACT
Thiazolidines and azetidinopnes have been prepared by the reaction of various Schiff bases with thioglycine acid chloroacetyl chloride respectively. The intermediate Schiff bases were synthesized by the condensation of 4-amino-2,4'-dichloro diphenyl ether with various aldehydes. The structures of the compounds have been confirmed by elemental analysis and spectral analysis. The antibacterial and anti HIV activities of the compounds have been also screened.

INTRODUCTION
The biological activities of Schiff base derivatives to azomethine linkage. A large number of Schiff base derivatives were prepares and known to exhibit some important biological activities such as tuberculostatic, funficidal[1], bacteriacidal[2], anesthetic, anticobvulsant and antitubercukar[3] etc. Thiozolidinones are known to exhibit antitubercular, antibacterial[4,5], anticonvulsant[6,7] antifungal[8], antithyroid, CNC depressant and amoebicidal[9] activities. Azetidinones (β-lactums) were tested as antibiotics, antidepressants, and sedatives. In recent past these derivatives are also found to be moderately active against several cell lines of cancer and HIV[11,12] Keeping in view the importance of the title heterocyclic compounds in medical chemistry, we report herein the synthesize some thiozolidinones and azetidinones using 4-amino-2,4'-dichloro diphenyl either as the starting material and test the starting material and test them as anti HIV drugs. 4-amino-2,4'-dichloro diphenyl either (I) was condensed with different aromativ aldehydes to yield schieff base (II). The Schiff base (II) were further reacted with thioglycolic acid and chloroacetyl chloride to yield thiozolidinones (III) Azetidinones (IV) respectively.[13]

REACTION SCHEME:



EXPERIMENTAL

All the melting points are taken in an open capillary and uncorrected. The IR spectra was recorded with KBr pellets on Perkin-Elmer 783 Spectrophotometer and ^{1}H-NMR spectra on a Instrum DPX 300 MHz using solvent DMSO-d_6. Purity of the compounds in addition to elemental analysis was checked by TLC.

***Preparation of 4-nitro-2,4'-dichloro diphenyl ether (A):**

4-Nitro-2-chloro phenol (0.17 mol., 29.49g) and KOH (0.14 mol., 80g) were placed in a 250 ml. flask and the mixture was cool to 130-140^{0}C, until all the alkali was dissolved. The mixture was then cooled to 100-110^0 C and p-dichloro benzene (0.05 mol., 7.85 g.) was added. The contents of the was stirred, and warmed with a Bunsen burner to 150-160 ^{0}C till the KCI separated. The flame was removed during this reaction. Boiling was ceased within five to seven minutes, and another –dichloro benzene (0.05 mol., 7.85 g) was added. The mixture was then cooled to 100-110^{0}C and p-dichloro benzene (0.05 mol., 7.85 g.) was added. The contents of the was stirred, and warned with a Bunsen burner to 150-160 ^{0}C till the KCl separated. The flame was removed during the reaction. Boiling was ceased within five to seven minutes, and another p-dichloro benzene (0.05 mol. 7.85 g) was added. The contents of the was stirred, and warmed with a

Bunsen burner to 150-160^{0}C till the KCI separated. Te flame was removed during this reaction. Boiling was ceased within five to seven minutes, and another p-dichloro benezene (0.05 mol., 7.85 g) was added. The mixture was again heated as before until a second spontaneous reaction begins. This also proceeds for about five minutes without the application of heat, When boiling due to the exothermic reaction had cause, heat was applied and the temperature 150-160 ^{0}C was maintained for additional thirty minutes. The dark colored melt was then poured in to 500 ml of crushed ice water and 5-10g. Excess NaOH to remove unreacted phenol. The crude 4-nitro-2,4'-dichloro diphenyl ether was separated as a dark brown crystalline mass, which was allowed to settle. The product was filtered, washed with 200 ml of water, dried and melted at 104^{0}C. The yield was 78.8%.

***Preparation of 4-amino-2,4'dichloro diphenyl ether I:**
In a hood a solution of 4-nitro-2,4'-dichloro diphenyl either (0.05 mol., 14.2g) in 150 ml of ethylene glycol was stirred in a water bath which maintained the reaction temperature below 35^{0}C to this solution 8 ml of 95% hydrazine hydrate and 18 g of rane nickel was added. The reaction mixture was then stirred for 24 hrs. Maintaining room temperature below 35^{0}C. The reacton mixture was then poured in to water. The precipitated product and rane nickel were removed by filteration and dried. The product was extracted and recrystallined from 95% ethanol. The yield 97%, m.p-64^{0}C.

***Preparation of 4-N-arylidine imino-2,4'-dichloro diphenyl ether (Schiff bases) II.**
4-amino-2,4'-dichloro diphenyl ether (0.05 mol, 12.7 g.) was taken in benzene in a Dean Stark apparatus and to it benzaldehyde (0.05 mol., 5.3 g.) was added over a period of 15 minutes. Then the mixture was refluxed for 5 hours. During the course of the reaction the water was removed continuously. The benzene was then distilled off to get the product. The Schiff base was recrystallised in benzene. Other substituted Schiff bases were prepared in a similar manner. The analytical data for various substituted Schiff base are given in Table – I.
P-2 : IR (KBr) : 1617 (N=CH), 1258 (C-O-C) and 670 (C – CI).
P-8: IR (KBr) : 1616 (N=CH), 1255 (C-O-C) and 663 (C-CI).
P-9 :IR (KBr) : 1620 (N=CH), 1254 (C-O-C) and 668 (C-CI).
P-10: IR (KBr): 1618 (N=CH), 1254 (C-O-C) and 667 (C-CI).
P-4: 'H-NMR : 6.8-7.8 (m,12H, Ar-H); (s,3H, - OCH_3); 9.0 (s, 1H,-OH).

***Preparation of 2-aryl-3-N-[2,4'-dichloro diphenyl ether] – 4 – oxo thiazolidines.III.**
The Schiff base (0.05 mo., 17.1g.) in benzene was taken in Dean-Stark apparatus. To it thioglycolic acid (0.05 mol., 4.6g.) in benzene was added slowly. Then it was refluxed for 15-16 hours. During the course of the reaction the water was removed continuously. The benzene was distilled off to get the product. Other substituted thiazolidinones were prepared in similar manner. The analytical data for different substituted thiazolidinones are given Table-2.
P-15: ^{1}H-NMR : 6.8-7.4 (m, 12H, Ar-H): 3.2-3.8 (S, 3H, - OCH_3); 9.0 (S, 1H, - OH).

***Preparation of 4-aryl-1-N-[2,4'-dichloro dephenyl ether]-3-chloro-2-oxo-azetidines.IV.**
The Schiff base (0.05 mol., 17.1 g.) in benzene was taken in a 50 ml flat bottomed flask. To it chloroacetyl chloride (0.05 mol, 5.65 g) and triethy amine (0.05 mol., 6.7 ml in benzene were added slowly. It was then refluxed for 15-16 hours. The triethylamine hydrochloride was removed and the benzene was distilled off to get the product. Other substituted azetidinones were

prepared in a similar manner. The analytical data for different substituted azetidinones are given in Table – 3.
P-23 : IR (KBr) : 1728 (C=O), 1255 (C-O-C) and 663 (C-CI).

RESULTS AND DISCUSSION

Structures of compounds synthesized have been elucidated by elemental analyses, IR and ^{1}H-NMR spectral data the antimicrobial profile of the compounds synthesized has been studied against several microbes. The Schiff base of above starting compound shows IR absorption peak at 1587 – 1548 cm^{-1} (C=N Stretching). 1660-1580 cm^{-1} (N=CH strentching). The thiazolidinone compounds were characterized by their IR absorption bands at 720 – 600 cm^{-1} (C-S stretching), 1750-1680 cm^{-1} (C=O stretching) and 1590-1560 cm^{-1} (C-N stretching). The azetidinone compounds were characterized by their IR absorption bands at 1730-1680 cm^{-1} (C=O stretching), 1715 cm^{-1} 730 cm^{-1} (C-CI stretching and bending).

ANTIMICROBIAL ACTIVITY:

ANTIBACTERIAL ACTIVITY[14]:

All the compounds were screened in –vitro for antibacterial activity against Stamph. Aureus and E.coli. by disc diffusion method at 0.5 μg/5μg activity 50 μg per disc concentration levels. None of the compounds showed antibacterial activity even at 50 μg per disc concentration level. Against Staphylocous aureus: Maximum activity were found in compounds P-7 (Zone of Inhibition – 14.0 mm) and minimum activity were found in compounds P-1, P-2,P-4,P-5,P-8,P-9 and P-10 (zone of inhibition – 6.0 mm) and P-21, P-23 and P-29 (zone of inhibition – 6.0 mm). Against Escherichai Coli: Maximum activity were found in compounds P-10 (zone of inhibition – 8.0 mm). & P-16 (zone of inhibition – 7.0 mm). & P-21 (zone of inhibition – 11.0 mm) and minimum activity were found in compounds P-1, P-2,P-4,P-5,P-8 and P-9 (zone of inhibition 6.0 mm) and P-11, P-12, P-13, P-14, P-15, P-17, P-18, P-19 and P-20 (zone of inhibition – 6.0 mm) and P-22, P-23, P-25, P-28 and P-29 (zone of inhibition 6.0 mm).The compounds possess moderate to good activity against all stains in compression with amplicillin, penicillin and teracline. (Table 1,2 and 3).

Table – 1 THE ANALYTICAL DATA OF THE SCHIFF'S BASE (II) AND ANTIMICROBIAL ACTIVITY.

Compound Number	Substituent R	Molecular Formula	Molecular Weight (gms)	Melting Point ^{0}C	% Yield	Elemental Analysis, % Theoretical (Practical)		
						C	H	N
P-I	H	$C_{19}H_{12}NOCl_2$	34.211	69	93	66.68(66.70)	3.80(3.79)	4.07(4.09)
P-2	2-OH	$C_{19}H_{13}NO_2Cl_2$	358.11	81	93	63.71(63.72)	3.62(3.63)	3.92(3.95)
P-3	4-OH	$C_{19}H_{13}NO_2Cl_2$	358.11	109	93	59.42(59.43)	3.62(3.63)	3.92(3.90)
P-4	4-OH, 3-OCH_3	$C_{19}H_{15}NO_4Cl_2$	404.12	115	90	68.53(68.51)	3.70(3.71)	3.45(3.46)
P-5	-CH=CH-C_6H_5	$C_{21}H_{15}NOCl_2$	368.13	60	93	60.58(60.59)	4.08(4.07)	3.81(3.83)
P-6	4-CI	$C_{19}H_{12}NOCl_3$	376.57	102	90	55.53(55.51)	3.18(3.19)	3.70(3.71)
P-7	2,4-CI	$C_{19}H_{11}NOCl_4$	411.03	135	96	58.95(58.96)	2.68(2.67)	3.42(3.40)
P-8	4-NO_2	$C_{19}H_{12}N_2O_3Cl_2$	387.11	112	79	64.55(64.57)	3.08(3.09)	7.23(7.30)
P-9	4-OCH_3	$C_{20}H_{15}NO_2Cl_2$	372.12	69	81	60.87(69.36)	4.04(4.06)	3.76(3.76)
P-10	3,4,5-$(OCH_3)_3$	$C_{22}H_{12}N_4O_4Cl_2$	434.14	129	85	69.34(60.87)	4.84(4.83)	3.21(3.22)

Zone of inhibition (mm)		
Compound Number	**Staph. Aureus (Antibacterial)**	**E.Coli (Antibacterial)**
P-I	6.0	6.0
P-2	6.0	6.0
P-3	7.0	6.0
P-4	6.0	6.0
P-5	6.0	6.0
P-6	8.0	6.0
P-7	9.0	7.0
P-8	6.0	6.0
P-9	6.0	6.0
P-10	6.0	8.0

Table – 2 THE ANALYTICAL DATA OF THE THIAZOLIDINONES (III) AND ANTIMICROBIAL ACTIVITY

Compound Number	**Substituent R**	**Molecular Formula**	**Molecular Weight (gms)**	**Melting Point ^{0}C**	**% Yield**	**Elemental Analysis, % Theoretical (Practical)**		
						C	**H**	**N**
P-11	H	$C_{21}H_{15}NO_2Cl_2S$	416.19	140	60	60-58(60.59)	3.63(3.65)	3.37(3.38)
P-12	2-OH	$C_{21}H_{15}NO_3Cl_2S$	432.19	145	60	58.36(58.37)	3.47(3.49)	3.25(3.25)
P-13	4-OH	$C_{21}H_{15}NO_3Cl_2S$	432.19	156	60	58.36(58.39)	3.45(3.47)	3.23(3.26)
P-14	4-OH, 3-OCH_3	$C_{21}H_{15}NO_3Cl_2S$	478.20	148	58	55.26(55.25)	3.56(3.57)	2.92(2.93)
P-15	-CH=CH-C_6H_5	$C_{23}H_{17}NO_2Cl_2S$	442.21	180	59	62.42(62.48)	3.84(3.86)	3.16(3.19)
P-16	4-CI	$C_{21}H_{14}NO_2Cl_3S$	450.08	189	63	56.03(56.05)	3.11(3.14)	2.88(2.89)
P-17	2,4-CI	$C_{21}H_{13}NO_2Cl_4S$	485.11	202	65	51.96(51.99)	2.69(2.87)	3.11(3.13)
P-18	4-NO_2	$C_{21}H_{14}N_2O_2Cl_2S$	461.19	244	59	54.05(54.08)	3.03(3.05)	6.07(6.09)
P-19	4-OCH_3	$C_{22}H_{17}NO_3Cl_2S$	446.20	171	60	59.21(59.23)	3.80(3.82)	3.17(3.19)
P-20	3,4,5-$(OCH_3)_3$	$C_{24}H_{23}NO_5Cl_2S$	508.22	134	62	56.71(56.72)	4.52(4.54)	2.75(2.79)

Zone of inhibition (mm)		
Compound Number	**Staph. Aureus (Antibacterial)**	**E.Coli (Antibacterial)**
P-11	6.0	6.0
P-12	6.0	6.0
P-13	6.0	6.0
P-14	9.0	6.0
P-15	6.0	6.0
P-16	7.0	7.0
P-17	10.0	6.0
P-18	9.0	6.0
P-19	6.0	6.0
P-20	8.0	6.0

Table – 3 THE ANALYTICAL DATA OF THE AZETIDINONES (IV) AND ANTIMICROBIAL ACTIVITY

Compound Number	Substituent R	Molecular Formula	Molecular Weight (gms)	Melting Point ^{0}C	% Yield	Elemental Analysis, % Theoretical (Practical)		
						C	H	N
P-21	H	$C_{21}H_{14}NO_2Cl_3$	416.61	128	60	60.53(60.55)	3.36(3.39)	3.36(3.37)
P-22	2-OH	$C_{21}H_{14}NO_3Cl_3$	434.61	131	62	58.03(58.04)	3.22(3.25)	3.22(3.24)
P-23	4-OH	$C_{21}H_{14}NO_3Cl_3$	434.61	148	62	58.03(58.06)	3.22(3.26)	3.22(3.25)
P-24	4-OH, 3-OCH_3	$C_{22}H_{16}NO_5Cl_3$	480.62	142	61	54.97(54.99)	3.32(3.36)	2.91(2.96)
P-25	-CH=CH-C_6H_5	$C_{23}H_{16}NO_2Cl_3$	444.63	132	61	61.12(62.15)	2.86(2.96)	3.14(3.16)
P-26	4-CI	$C_{21}H_{13}NO_2Cl_4$	453.17	150	65	55.65(55.68)	2.86(2.87)	3.08(3.09)
P-27	2,4-CI	$C_{21}H_{12}NO_2Cl_5$	487.53	175	67	51.73(51.76)	2.86(2.47)	2.87(2.89)
P-28	4-NO_2	$C_{21}H_{13}N_2O_4Cl_3$	463.61	170	62	54.40(54.52)	2.83(2.80)	6.03(6.05)
P-29	4-OCH_3	$C_{22}H_{16}NO_3Cl_3$	448.62	153	62	58.89(58.90)	3.56(3.59)	3.12(3.15)
P-30	3,4,5-$(OCH_3)_3$	$C_{24}H_{23}NO_5Cl_3$	5610.64	173	64	56.44(56.46)	4.50(4.55)	2.74(2.76)

Zone of inhibition (mm)		
Compound Number	**Staph. Aureus (Antibacterial)**	**E.Coli (Antibacterial)**
P-21	6.0	11.0
P-22	8.0	6.0
P-23	6.0	6.0
P-24	9.0	8.0
P-25	8.0	6.0
P-26	11.0	7.0
P-27	14.0	10.0
P-28	8.0	6.0
P-29	6.0	6.0
P-30	14.0	9.0

REPORT ON THE ANTI – HIV ACTIVITY:

The procedure used in the National Cancer Institute's test for agents active against human immunodeficiency virus (HIV) is designed to detect agents acting at any stage of the varies reproductive cycle. The assay basically involves the killing of T_4 Lymphocytes by HIV. Candidates agent is dissolved in dimethyl sulfoxide the dilute 1:100 in cell culture medium before preparing serial half $\log_{10}$ dilutions. T_4 lymphocycles (CEN cell line) are added and after a brief interval HIV-I is added, resulting in a 1:200 final dilution of the infected and unaffected cells with the compound serve as a toxicity control and infected and unaffected cells without the compound serve as basic controls.

EXPERIMENTAL

The compound were also screened for their anti HIV by measuring their effect on percentage growth (PG) of more than two different cell lines for variety of cancer and HIV. They have been tested at 5 diferent concentration of the compound ($-4\log_{10}$ to $-8\log_{10}$). The optical density of SRB derived colour by the cell lines was measured at 0 time ($Mean_{zero}$) after 48 hours in presence of drugs ($Mean_{test}$) and in absence of drug after 48 hours ($Mean_{control}$). The PG was calculated from it using following formula,

If $Mean_{time} - Mean_{zero} > 0$, then,

$$PG = \frac{100 \times (Mean_{test} - Mean_{zero})}{(Mean_{control} - Mean_{zero})}$$

But if $(Mean_{test} - Mean_{zero}) < 0$ then,

$$PG = \frac{100 \times (Mean_{test} - Mean_{zero})}{(Mean_{control} - Mean_{zero})}$$

The effects were interpreted from dose response curves created by plotting PG's (-100 to +100) against log_{10} molar concentration (-4 to -8). Against HIV – I compound had produced good inhibitory activity. Compound P-6, P-7, P-12, P-16, P-22 and P-27 were found little activity.

ACKNOWLEDGEMENTS

The authors are grateful to the Department of Chemistry, South Gujarat University, Surat for providing with the necessary research facilities. They are also grateful to the Bioscience Department, South Gujarat University, Surat for screening the drugs for their antibacterial activities and National Cancer Institute, Maryland (USA) for screening drugs for their anti – HIV activities.

REFERENCES:

1. W.m. Farrow, C. Hanna and F.W.Schuler, J. Am. Pharm. Assoc, 43, 370 (1954).
2. S.Bahadur, A.K.Goel and R.S. Verma, J. Ind. Chem. Soc., 53, 590 (1976).
3. R.F. Doergee, "Wolson and Gisroldi" Text book of Organic medicine and Pharmaceutical Chemistry, 8th Ed. J.B. Liooincott company, 225 (1982).
4. K.J. Mehta, A.C. Chavda and A.P. Parikh, J. Ind. Chem. Soc., 56(2), 173-4 (1979).
5. K. Desai and A.J. Baxi, J. Ind. Chem. Soc., 69, 212 (1992).
6. C.Dwivedi, T.K. Gupta and S.C. Parmar, J. Med. Chem. 15, 553 (1992)
7. S.P. Singh, B. Ali, T.K. Auyong, S.S. Parmar and B.DE Boer, J. Pharm. SCI., 65, 391 (1976).
8. N.C. Misra and K.K. Patnaik, Ind. J. Appl. Chem., 34, 148 (1971).
9. K.A. Thaker, B.R. Parekh and N.C. Desai J. Ind. Chem. Soc., LXIV, 491 (1987).
10. P.G. Summer, Chem. Rev., 76, 113 (1976).
11. J.J. Bhatt, B.R.Shah, P.B. Trivedi and N.C. Desai, Indian, J. Chem. 32 B, 497 (1993).
12. Sunil Desai, P.B. Desai and K.R. Desai, J. Heterocyclic. Comm., 5, 4(1999).

Received on October 16, 2011.