http://dx.doi.org/10.4314/jpb.v10i2.3
Vol. 10 no. 2, pp. 52-56 (September 2013)
http://ajol.info/index.php/jpb

Journal of
PHARMACY AND BIORESOURCES

Comparison of antimicrobial activity of six 5-amino tetrazole Schiff bases with their corresponding oxazepine derivatives

Ezekiel O. Afolabi* and Shalom Galaya

Department of Pharmaceutical Chemistry, University of Jos, Jos. 930001, Plateau State, Nigeria

Received 5th August 2013; Accepted 2nd September 2013

Abstract
Six novel five-amino tetrazole Schiff bases were synthesized by the condensation reaction of 5H–tetrazol-5-amine with three substituted aldehydes and three corresponding ketones, alongside their corresponding oxazepine derivatives by the reaction of the different five-amino tetrazole Schiff bases with furan-2,5-dione (maleic anhydride). The five-amino tetrazole Schiff bases have a wider range of percentage yield (17% - 87%) than their oxazepine derivatives which range from 17.98% to 53.68%. The detailed chemical and spectroscopic analyses are discussed. The prepared tetrazole Schiff bases and their corresponding oxazepine derivatives showed significantly different biological activities against two types of bacteria and fungi. The two bacteria used were *Staphylococcus aureus* (Gram positive) and *Pseudomonas aeruginosa* (Gram negative) while the fungus used is *Candida albicans*.

Keywords: Schiff base, Oxazepine, Antimicrobial screening

INTRODUCTION

One of the major challenges facing the health sector is the increased resistance of microorganisms to the currently available antimicrobial drugs; which is the major cause of morbidity and mortality throughout the world. Thus there is high demand for the development of novel antimicrobial drugs. The compounds with the azomethine functional group (-C=N-) are known as Schiff bases. They are very versatile in organic chemistry because they are simply prepared. They also show a broad range of biological activities.

A Schiff base is a nitrogen analog of an aldehyde or ketone carbonyl group in which the C = O group is replaced by C = N – R group. It is usually formed by condensation of the aldehyde or ketone with a primary amine. Schiff bases with substituents on the aryl ring are substantially more stable and are more readily prepared, while those with substituted alkyl groups are relatively unstable. Schiff bases of aliphatic aldehydes are relatively unstable and readily hydrolyzed while those of aromatic aldehydes with effective conjugation are more stable. The formation of a Schiff base from an aldehyde or ketone is a reversible reaction and generally takes place under acidic or basic catalysis, or upon heating.

Oxazepine is a seven-member unsaturated heterocycle containing five carbon atoms, one nitrogen, one oxygen atom,

* Corresponding author. *E-mail*: afolabie@yahoo.co.uk *Tel*: +234 (0) 8035889579
ISSN 0189-8442

and three double bonds. The classical methods for preparing oxazepine ring are limited. Recently, cycloaddition reaction, which is a type of pericyclic reaction is used to synthesize 1,3-oxazepine ring. This type of reaction is not limited and gives various 1,3-oxazepine derivatives. Synthesis of these compounds in this work is a class of pericyclic reaction which is classified as a 5 + 2 = 7, implying five-atom plus two-atom components leading to a seven-member ring. Oxazepine derivatives showed biological activities against different types of bacteria, in addition to their uses as inhibitors of some enzyme action.

EXPERIMENTAL

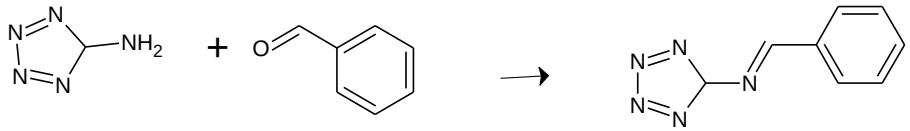
Preparation of 5-amino tetrazole Schiff base using aldehyde as example. The Schiff base was prepared from the reaction of 5-amino tetrazole (1 mole), with benzaldehyde (1 mole), in 20 mL ethanol absolute and few drops of glacial acetic acid. This mixture was refluxed for 3 hours. The mixture was cooled; and the precipitate obtained was recrystallized from ethanol. The same procedure was employed for the remaining aldehydes and ketones. The purity of the compounds synthesized was confirmed by their TLC-profile. The compounds were dissolved in methanol. Using capillary tubes, spots were made on the pre-coated silica gel TLC plate. The plate was developed in a chromatographic tank with a solvent system containing methanol, ethyl acetate, concentrated ammonium hydroxide and toluene (35ml, 55ml, 2.5ml and 5ml respectively). The solvent was allowed to run to about 90% of the plate. The solvent front and the R_F were determined.

Typical preparation of oxazepine derivative using the Schiff base of acetophenone and 5-amino tetrazole. A mixture of the Schiff base of acetophenone and 5-amino tetrazole (0.0012 mole) and maleic anhydride (0.0012 mole) was dissolved in (20ml) dry toluene. The mixture was refluxed for 5 hours on water bath at (70^oC), excess solvent was distilled, and the precipitate was filtered and recrystallized from ethanol. The same procedure was used for the remaining Schiff bases.

The purity of the synthesized compounds was confirmed using the thin layer chromatography (TLC). The synthesized compounds were dissolved in methanol, using capillary tubes, spots were made on the pre-coated silica gel TLC plate. The plate was developed in a chromatographic tank with a solvent system containing methanol, ethyl acetate, concentrated ammonium hydroxide and toluene (35ml, 55ml, 2.5ml and 5ml respectively). The solvent was allowed to run to about 90% of the plate. The solvent front and the R_F were determined.

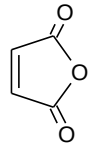
Antimicrobial screening. The antimicrobial activity of the synthesized compounds was tested by cup plate method against gram (+) bacteria (*Staphylococcus aureus*) and gram (-) bacteria (*Pseudomonas aeruginosa*) using nutrient agar medium. Anti fungal activity was tested against a fungus (*Candida albicans*) using sabouraud dextrose medium.

By pouring the sterile agar into Petri-dishes in aseptic conditions, 0.1ml of each standardized test organisms culture was spread onto agar plates. The test compounds (30µg/ml), the standardized drug solutions and the solvent control chloroform were placed in the cup separately. The plates were maintained at room temperature for 2 hours to allow the diffusion of solution into the medium. All the bacterial plates were incubated at 37^oC for 24 hours and fungal plates were incubated at 28^oC for 48 hours. The zone of inhibition was measured in mm.

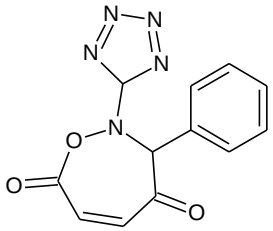


5*H*-tetrazol-5-amine benzaldehyde *N*-[(1*E*)-phenylmethylidene]-5*H*-tetrazol-5-amine

Aldehydes	Ketones
Benzaldehyde	Acetophenone
3-nitro benzaldehyde	4-nitro acetophenone
4-methyl benzaldehyd	4-methyl acetophenone



furan-2,5-dione



3-phenyl-2-(5*H*-tetrazol-5-yl)-2,3-dihydro-1,2-oxazepine-4,7-dione

Scheme I

Reagent	Compound ID	Tetrazole Schiff base	Compound ID	Oxazepine derivatives
Benzaldehyde	C_1	$C_8H_7N_5$	Z_1	$C_{13}H_{11}N_5O_3$
Acetophenone	C_2	$C_9H_9N_5$	Z_2	$C_{14}H_{13}N_5O_3$
3-Nitrobenzaldehyde	C_3	$C_9H_9N_5$	Z_3	$C_{14}H_{13}N_5O_3$
4-Nitro acetophenone	C_4	$C_{10}H_{11}N_5$	Z_4	$C_{15}H_{15}N_5O_3$
4-Methyl benzaldehyde	C_5	$C_8H_6N_6O_2$	Z_5	$C_{13}H_{10}N_6O_5$
4-Methyl acetophenone	C_6	$C_9H_8N_6O_2$	Z_6	$C_{14}H_{12}N_6O_5$

Table 1: Physical properties of tetrazole Schiff bases

Compound ID	Formula	F. Weight	mp ^oC	R_F	Yield %
C_1	$C_8H_7N_5$	173.17	199	0.628	28%
C_2	$C_9H_9N_5$	187.20	202	0.666	87%
C_3	$C_9H_9N_5$	187.20	229	0.679	17%
C_4	$C_{10}H_{11}N_5$	201.22	221	0.628	25%
C_5	$C_8H_6N_6O_2$	218.17	201	0.628	50%
C_6	$C_9H_8N_6O_2$	232.19	204	0.615	43%

Table 2: Physical Properties of oxazepine derivatives

Compound ID	Formula	F. Weight	mp ^oC	R_F	Yield %
Z_1	$C_{13}H_{11}N_5O_3$	285.25	189	0.662	53.68
Z_2	$C_{14}H_{13}N_5O_3$	299.28	187	0.675	17.98
Z_3	$C_{14}H_{13}N_5O_3$	299.28	247	0.662	24.86
Z_4	$C_{15}H_{15}N_5O_3$	313.31	143	0.649	27.29
Z_5	$C_{13}H_{10}N_6O_5$	330.25	182	0.623	29.27
Z_6	$C_{14}H_{12}N_6O_5$	344.28	199	0.636	25.21

Table 3: Antimicrobial activity of 5-amino tetrazole Schiff bases

Compound ID (30µg/ml)	Zone of Inhibition (mm)		
	Gram Positive *S. aureus*	Gram Negative *P. aeruginosa*	Fungi *C. albicans*
C_1	28	15	19
C_2	16	10	–
C_3	14	14	20
C_4	13	15	15
C_5	15	13	15
C_6	–	13	10

Table 4: Antimicrobial activity of oxazepine derivatives

Compound ID (30µg/ml)	Zone of inhibition (mm)		
	Gram Positive *S. aureus*	Gram Negative *P. aeruginosa*	Fungi *C. albicans*
Z_1	20	15	12
Z_2	15	9	15
Z_3	14	16	20
Z_4	17	11	16
Z_5	–	–	–
Z_6	–	13	–

Table 5: Antimicrobial activity of standard drugs

Compound ID (30µg/ml)	Zone of inhibition (mm)		
	Gram Positive *S. aureus*	Gram Negative *P. aeruginosa*	Fungi *C. albicans*
Std drugs I	29	18	-
Std drug II	-	-	25
Solvent control	15	11	10

Std drug I (30µg/ml) = Gentamicin; Std drug II (30µG/mL) = Ketocomazole; Solvent Control = Methanol

RESULTS & DISCUSSION

The test result showed that the 5-amino tetrazole Schiff bases showed a very good antimicrobial activity against the three microorganisms: *Staphylococcus aureus* (a Gram positive bacteria); *Pseudomonas aeruginosa* (a Gram negative bacteria) and *Candida albicans* (a fungus). The antimicrobial activity seen in 5-amino tetrazole Schiff bases are higher compared to what were observed with oxazepine derivatives. These high activities were seen in compounds C_1 and C_2. This implies that the conjugation effect of neither the electron withdrawing substituent effect like the nitro (NO_2) group nor the electron releasing effect like the methyl (CH_3) group on aromatic ring have no significant effect on anti-microbial activities of both 5-amino tetrazole Schiff base and there corresponding oxazepine derivatives.

REFERENCES

Azzouz A. and Ali R. (2010). Synthesis of Schiff bases from benzaldehyde and salicylaldehyde with some amino acids by a new develop method. *National Journal of Chemistry*, 37, 158-168

Bhaskar V. and Mohite P. (2010). Synthesis, Characterization and QSAR study of some substituted N-(Arylidene)-2-(5-Phenyl-1H-tetrazole-1-yl) Acetohydrazide. Digest *Journal of Nanomaterials and Biostructures* 5(1), 177-183

Chaluvaraju. K. and Zaranappa, (2011). Synthesis and biological evaluation of some isatin derivatives for antimicrobial properties. *Research Journal of Pharmaceutical, Biological and Chemical Sciences.* 2(1):541-546

Dilipkumar P., Tanmoy D. and Arvind K. (2013). Review on antimicrobial activity of some Mannich Base and Schiff Base of Isatin Derivatives. *An*

International Journal of Advances in Pharmaceutical Sciences. 4(2), 223-236

Pignatello R., Panico A., Mazzone R., Pinizzito M., Carozzo A. and Furneki P. (1984,). Schiff Bases of N-hydroxy-N-aminoguanadimines as Anticancer and Antiviral Agencies. *Journal of Medicinal Chemistry*. 24, 236-238

Rhaman T., (2011). Synthesis and Characterisation of some New Tetrazole and 1,3-oxazepine Derivatives. *Journal of Kerbala University*, 9(3).

Ramachandran S, (2011). Synthesis and Antimicrobial evaluation of some novel Schiff and Mannich Bases of Isatin derivatives. *International Journal of Research in Pharmacy and Chemistry* 1(3): 289-294.

Zarei M. and Jarrahpour A, (2011). Green and Efficient Synthesis of Azo Schiff Bases. *Iranian Journal of Science and Technology*, IJST A3: 235-242.