Antimicrobial evaluation of some monoazaphenoxazines Carboxamides:

Structure activity relationship (SAR)

Anoh, V. A, [1]*, Agbo, S. A[1], and Swande, P. I.[2]

Division of Organic Chemistry, Department of Chemistry, Benue State University, Makurdi, Nigeria.

Email: anohvitalis@gmail.com

Abstract - *A series of monoazaphenoxazines Carboxamides were evaluated against Salmonella typhi, Staphylococcus aureus, Escherichia coli, Klebsiella pneumonia, Streptococcus pyogene, and Pseudomonas aeruginosa, in a micro-dilution broth assay. The results obtained showed that these compounds exhibited considerable antibacterial activity depending on the substituent on the monoazaphenoxazine ring. The best activities were obtained with substituents containing nitro-group as in 3-(4-nitrobenzamido)-1-azaphenoxazine and chloride group as in 3-trichloromethanamido-1-azaphenoxazine respectively.*

1. Introduction

Phenoxazines is a tricyclic heterocycle consisting of two benzene rings fused to oxazine.[1] Phenoxazines possess diverse pharmacological activities such as antiviral [2], antibacterial [3-4], antifungal [5], anti-inflammatory [6-7], antitumor [8-9] and multidrug resistance reversal activity [10]. They have been found to prevent human amyloid disorders [11] and to protect neuronal cells from death by oxidative stress.[12] Bacteria are remarkably adaptive organisms and for each new antibiotic that has been developed, resistant bacteria strains arise through the widespread use and abuse of the antibiotic. Thus, there is being constant need to develop new antibiotics to combat cases of antibiotic-resistant bacteria strains. Bearing this in mind, and in view of the continuous interest in developing new antibacterial agents, a series of monoazaphenoxazine carboxamides were studied taking into account the effects of their structural modifications on activity against various gram-positive and gram-negative bacteria strains.

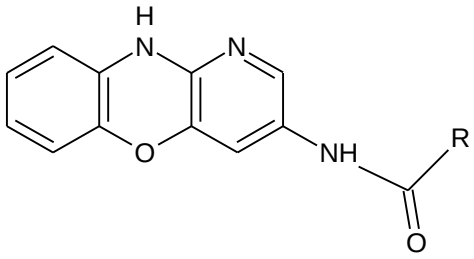
2. **Results and Discussion**

Monoazaphenoxazine carboxamides **1a-e** were prepared by coupling 3-chloro-1-azaphenoxazine with various amides (**R**) using triphenylphospine as ligand and nickel (II) chloride as catalysts carried out under nitrogen atmosphere.[13] The antimicrobial analysis result revealed that all the synthesized phenoxazine derivatives showed considerable and varied activity against the selected microorganisms. The structure activity relationship (SAR) study of the substitution pattern of the phenoxazine derivatives reveals that electron releasing group decreases the activity while electron withdrawing group on the ring increases the activity remarkably. The compound **1e** with a nitro group exhibits the highest activity which is slightly less potent than the standard ampicillin. Chlorine substituted phenoxazine compound **1d** has a weaker antimicrobial activity than the nitro substituted one due to the less electron withdrawing ability of the chlorine. Although, these two compounds **1d** and **1e** possess stronger antibacterial activity than others. The compounds **1a, 1b, 1c** and **1d** with less electron withdrawing group showed less activity respectively.

3. Experimental

Antibacterial activity test. Broth micro-dilution assay were performed in accordance with the guideline in CLSI document (M100 S16 Vol. 26 – 3, M7 – A7, Vol. 26 – 2, M2 – A9, Vol. 26 – 1) using nutrient agar as the culture media, an inoculums of 5.0 x 10^{3} cells per mL, and incubated at 37^{o}C. MICs were determined after 24 hours of incubation, as the lowest concentration of drug that caused no detectable growth. Stock solutions of the synthesized compounds and drug were prepared at concentrations of 100 μg/mL of ethanol and 0.1 mL of the solution was placed on Whatmann paper disc of 6mm diameter and the solvent was left to evaporate. These saturated discs were placed carefully on the surface of measuring the diameter of inhibition zone at the end 24 hours at 37^{o}C as shown in Table I. The culture bacteria used were *Salmonella typhi, Staphylococcus aureus, Escherichia coli, Klebsiella pneumonia, Streptococcus pyogene, and Pseudomonas aeruginosa*.

TABLE I: Antibacterial activity of the synthesized phenoxazine derivatives (MIC, µg/mL)



3-amido derivatives	R	*S. typhi*	*S. aureus*	*E. coli*	*K. pneumonia*	*S. pyogenes*	*P. aeruginosa*
1a	C_6H_5	15	2.50	15.0	2.50	15	15
1b	H	15.0	2.50	15.0	2.50	5.00	15.0
1c	NH_2	2.50	15.0	5.00	15.0	5.00	1.25
1d	CCl_3	1.25	15.0	1.25	1.25	15.0	15.0
1e	$C_6H_5NO_2$	15.0	2.50	2.50	2.25	2.50	15.0

TABLE I: MIC result of Ampicillin used as positive control and ethanol used in preparing the test solutions / dissolving the azaphenoxazine derivatives (MIC, µg/mL)

Controls	R	*S. typhi*	*S. aureus*	*E. coli*	*K. pneumonia*	*S. pyogenes*	*P. aeruginosa*
Ampicillin	-	**15.0**	**2.50**	**15.0**	**1.25**	**1.25**	**5.00**
Ethanol	-	-	-	-	-	-	-

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