Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2015, 7(5):787-789

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Synthesis and biological activities of indolinospirobenzoxazine

Victor N. Mkpenie*, Emmanuel E. Essien and Basil N. Ita

Department of Chemistry, University of Uyo, Uyo, Nigeria

ABSTRACT

Indolinospirobenzoxazine was synthesized by direct condensation of 4-amino-2-nitrosophenol with 1,3,3-trimethyl-2-methylene indoline. Its biological effects on bacteria species, Salmonella typhi, Escherichia coli, Staphylococcus aureus and fungi species, Candida albican have been determined. Indolinospirobenzoxazine was found to be highly active on all the bacteria species tested, with inhibition zone >12 mm. Moderate activity was observed against Candida albican (inhibition zone 11 mm) which represented the lowest sensitivity among the microorganisms tested.

Keywords: Spirooxazine; biological activities; antibacterial; antifungal; indoline.

INTRODUCTION

Spirooxazines represent an important class of photochromic molecules that are widely used in various fields of science and engineering for the design of light filters and optically controlled molecular switches [1]. They undergo reversible rearrangements between two main states characterized by strongly differing spectral parameters. Spirooxazines are families that are widely studied because of their good photoactivity, high sensitivity, fatigue resistance and high resolving power. Although vast majority of spirooxazines are known, spiroxazines belonging to the indoline series are the most investigated [2-5]. Various modification of the indoline and spiroxazine fragments with sulphur-containing groups and heterocyclics have also been studied [6]. Being heterocyclic compounds, spirooxazines have been investigated for possible application in medical field as drugs for treatment of movement disorder such as cerebral palsy [7] and potential neuroleptic agent [8]. Indolinospirooxazines is a combination of indoline fragment and oxazine fragment.

Benzoxazines have been noted to exhibit various biological activities including anti-bacterial [9-10] and anti-inflammatory [11] whereas indole derivatives possess wide spectrum of biological activities including antibacterial [12], anti-fungal [13-14], anti-tumor [15], antiviral [16-17], antioxidant activity [18], cytotoxic activity [19-21] and analgesic anti-inflammatory [22].

It therefore appears that indolinospirobenxozaxine will exhibit a synergy of antimicrobial activities contributed by both the indole and oxazine fragments. In this paper, the use of spirooxazine of the indoline series as anti-microbial agent is reported.

EXPERIMENTAL SECTION

General

All chemicals used were of analytical grade. The IR spectra were recorded on a Shimadzu FTIR-IR Prestige (200VCE) as KBr pellets. The C, H, N data were determined using a Perkin-Elmer Instrument (200B). The purity of the test compounds was determined by TLC. A single green-brown spot obtained confirmed the purity of indolinospirozenzoxazine.

Synthesis of indolinospirobenzoxazine.

Indolinospirobenzoxazine was synthesized according to the method reported earlier [5]. 4-Aminophenol (0.1 mol, 10.913 g) was weighed and dissolved in warm solution of 0.1 mol (4.0 g) sodium hydroxide in 50 ml of water. The solution was cooled to 0ºC. Sodium nitrite (0.1 mol, 6.9 g) was weighed and added and the solution was stirred for one hour while maintaining the temperature at 0ºC. 0.3 mol HCl was added and the product formed was filtered, washed with water and dried. The 4-amino 2-nitrosophenol obtained was purified by recrystallation from hot ethanol. The 4-amino-2-nitrosophenol (0.01 mol, 1.381 g) was weighed and refluxed in 50 ml of methanol and to the hot solution, was added in drops over 15 minutes, a solution of 1,3,3-trimethyl-2-methylene indoline (0.01 mol). The solution was refluxed for eight hour. The precipitate was filtered and recrystallized from hot ethanol to obtain indolinospirobenzoxazine. Yield: 1.88 g (64%); IR (KBr)$\tilde{\nu}_{max}$/cm^{-1}: 3798 (NH_2), 3397-3389 (C-H, benzene), 3370 (C-H, CH=N), 3320-3278 (C-H, methyl), 1855 (C-N), 1796-1777 (C-C, benzene); *Anal*. Calcd. mass fractions of elements, w / % , for $C_{18}H_{19}N_3O$ (M_r = 293.36) are: C 73.69, H 6.53, N 14.32; found C 73.61, H 6.42, N 14.26.

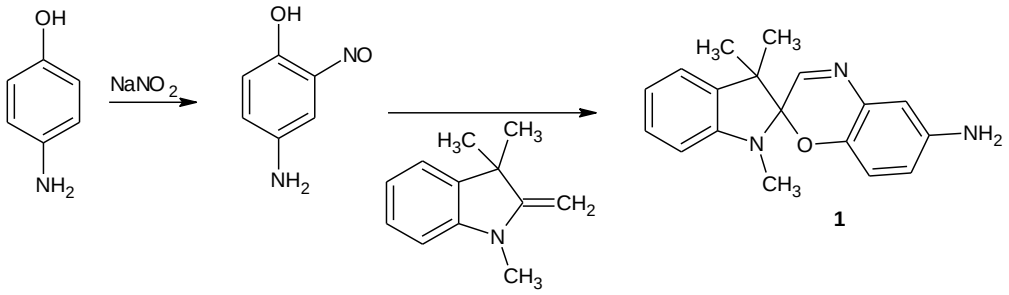
Antimicrobial activity

The indolinospirobenzoxazine was screened for the presence of antimicrobial constituents against four microorganisms: *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhi*, *Candida albican* using disk diffusion method [23]. The tested compounds were dissolved in ethanol to give 10 mg/2 mL solutions. 20 µL solutions of these were applied to sterile disks and placed on Nutrient Agar (NA) plates with *Escherichia coli* and *Staphylococcus aureus*, Salmonella Shigella Agar (SSA) plates with *Salmonella typhi* and Sobouraud Dextrose Agar (SDA) plates with *Candida albican*. The plates were incubated for 24 hours except SSA plates with incubation period of 48 hours. The zones of inhibition were measured. Clarithromycin and cerftriflaxon were used as reference antibiotics. Ethanol showed no inhibition zones on all the bacteria and fungi tested.

RESULTS AND DISCUSSION

Indolinospirobenzoxazine (**1**) was synthesized as shown in scheme 1.The indolinospirobenzoxazine was examined *in-vitro* against bacteria and fungi. The test results are presented in Table 1. Indolinospirobanzoxazine was highly active against the bacteria tested, showing inhibition zones between 15mm and 18mm, and moderately active against fungi with inhibition zone of 11mm. *Staphylococcus aureus* showed the highest sensitivity of all the bacteria tested.

Scheme 1



1

Cerftriaxon and Clarithromycin which are well known antibacterial substances showed inhibition zones 11-12 mm and 6-8 mm respectively for the same pathogenic bacteria. Thus, the higher antimicrobial activities of indolinospirobenzoxazine can be attributed to the combined activities contributed by benzoxazine and indoline fragments, each of which has been independently reported with biological activities.

Table 1. Biological activities exhibited by bacteria and fungi against indolinospirobenzoxazine

Compound / Microorganisms	Clarithromycin	Cerftriaxon	Indolinospirobenzoxazine
Staphylococcus aureus	+	++	+++
Escherichia coli	+	+++	+++
Salmonella typhi	+	++	+++
Candida albican	+	++	++

Highly active= +++ (inhibition zone > 12 mm)
Moderately active= ++ (inhibition zone 9-12 mm)
Slightly active= + (inhibition zone 6-8 mm)
Inactive= - (inhibition zone < 5 mm)

CONCLUSION

Indolinospirobenzoxazine was tested against certain species bacteria and fungi. *Staphylococcus aureus* recorded the highest biological activities and the least resistant against indolinospirobenzoxazine. *Candida albican* was slightly resistant with moderate activity. The higher antimicrobial activities exhibited by indolinospirobenzoxazine makes the compound a good and potential antibacterial and antifungal agent.

REFERENCES

[1] G Berkovic;V Krongauz;V Weiss. *Chem. Rev*., **2000**,100, 174-176.
[2] V Lokshin;ASamat; AMetelitsa.*Russ. Chem. Rev*., **2002**,**71**893-916.
[3] NA Voloshin; AVMetelitsa; CMicheau;EN Voloshina;SOBesugliy.*Russ. Chem. Bull*., **2003**,52**,**2038-2047.
[4] C Ko;L Wu;KM Wong;N Zhu;VW Yam. *Eur. J. Chem.*,**2003**, 10766-776.
[5] AV Metelitsa;JC Micheau;SO Besugliy;EB Gaeva;NA Voloshin;EN Voloshina;A Samat;VI Minkin.*Int. J. Photoenergy*, **2004**,6,199-204.
[6] T Deglieorgiev;SMinkovska;BJejiazkova;SRakovsky.*Dyes and Pigments*, **2002**,53,101-108.
[7] M Egert;BWagner;TLemke;ABrune;MWFriedrich.*Applied and Environ. Microbiology*, **2003**,69, 6659-6668.
[8] AR Milliani;GJ Favaro.*J. Phys. Organic Chem.*,**2000**, 13,141-150.
[9] C Cimarelli;G Palmieri;E Volpini.*Can. J. Chem.*, **2004**,82, 1314-1326.
[10] Y Su;L Li;Y Su;F Zang.*Chem. Res. Chin. Univ.*, **2008**,24**,**65-68.
[11] K Kondo;M Seki;T Kuroda;T Yamanaka;T Iwasaki.*J. Org. Chem.*, **1995**,60, 1096-1097.
[12] RS Varma; KPGarg. *ActaPharm. Jugosl*., **1980**,30, 199-204.
[13] SP Singh;AV Singh;KC Gupta. *ActaPharm. Jugosl*., **1986**, 36, 19-26.
[14] MG Bhovi; GSGadaginamath.*Indian Journal of Heterocyclic Chemistry*, **2004**,4, 15-18.
[15] I Labouta;H Salama;NH Eshba;E El-Chrbini. *ActaPharm. Jugosl*., **1988**,38,189-194.
[16] SP Singh;RK Jha.*ZentralblattfürMikrobiolgie*, **1989**,144, 105-109.
[17] SK Sridhar;SN Pandeya;SKBajpal; HManjula. *Indian Drugs*, **1999**,36, 412-414.
[18] NV Cinchana;PS Sujan-Ganapathy;SD Shruthi.*Res. J. Pharm. Biol. Chem. Sci*., **2011**,2, 358-368.
[19] R Herb;AR Carroll;WY Yoshida;PJScheuer; VJPaul.*Tetrahedron*, **1990**,46**,**3089-3092.
[20] H Muratake;T Seino;MNatsume.*Tetrahedron Letters*, **1993**, 34, 4815-4818.
[21] H Muratake;AMikawa;T Seino; MNatsume. *Chem. Pharm. Bull*., **1994**,42, 854-864.
[22] SC Bobzin;DJ Faulkner.*J. Org. Chem.*, **1991**,56**,**4403-4407.
[23] S Goksu;MT Uguz;H Ozdemir;H Secen.*Turk. J. Chem.*, **2005**,29, 199-205.