OBAFEMI AWOLOWO UNIVERSITY

STRUCTURE-ACTIVITY RELATIONSHIP STUDIES OF PHENYLNITROETHANE ANALOGUES

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STRUCTURE-ACTIVITY RELATIONSHIP STUDIES OF PHENYLNITROETHANE ANALOGUES

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B.Sc. Chemistry (Bowen)

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This is to certify that Adebisi Oluwaseun AJIBOYE of the Department of Pharmaceutical Chemistry, Faculty of Pharmacy carried out this research under my supervision. This was in accordance with the requirement for the award of Master of Science (M.Sc.) degree in Pharmaceutical Chemistry, Obafemi Awolowo University, Ile-Ife, Nigeria.

Prof. T.A. Olugbade .....
(Supervisor) Signature and Date

Dr. J.O. Soyinka .....
(Head of Department) Signature and Date

DEDICATION

To the One who made the earth and ALL that is in it. I give you all the glory.

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Finally, I thank God for sparing my life to see the end of the programme and the beginning of another one.

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ABBREVIATIONS

AGC	Accelerated Gradient Chromatography
APT	Attached Proton Test
Bn	benzyl
BPNE	β-phenylnitroethane
Cbz	benzyloxycarbonyl
DBN	1,5-diazabicyclo[4.3.0]nonene-5
DBU	1,8-diazabicylo[5.4.0]undecene-7
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
TLC	Thin Layer Chromatography
TMG	*N,N,N'N'* Tetramethylguanidine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	tetramethylsilane
NMR	Nuclear Magnetic Resonance
PTZ	Pentylene tetrazole
VLC	Vacuum Liquid Chromatography
VS spray	Vanillin-sulphuric acid spray

ABSTRACT

This study synthesized analogues of phenylnitroethane, determined their physico-chemical properties, evaluated the pharmacological potencies and investigated the correlation between their potencies and the physico-chemical parameters. This was with a view of optimizing the lead molecule - β-phenylnitroethane (BPNE) through the evaluation of synthetic analogues for the central nervous system activities.

Derivatives of BPNE were prepared from the corresponding nitroalcohols by direct deoxygenation with triethylsilane and trifluoroacetic acid. The precursor nitroalcohols were obtained employing Henry reaction using tetramethylguanidine as a base. The starting reagents were the benzaldehyde derivatives which were initially protected by benzylation where phenolic. Intermediate and final products were purified by chromatography and identified by Nuclear Magnetic Resonance spectroscopy. The final nitroethanes and the intermediate nitroalcohols were evaluated for hypnotic effect assessed by ketamine-induced hypnosis, hypothermic effect evaluated by measuring variation in rectal temperature using rectal thermometer and anticonvulsant effect assessed by pentylene tetrazole (PTZ) - induced convulsions. Log P values were obtained using ALOGPS 2.1 applet from Virtual computational chemistry laboratory (VCCLAB). Correlation between log P and individual neuropharmacological activity was evaluated.

Seven nitroalcohols and two analogues of BPNE were obtained in addition to the lead molecule (BPNE). Four nitroalcohols [1-phenyl-2-nitroethanol (BZA), 1-(4-methoxyphenyl)-2-nitroethanol (MBP), 1-(3,4,5-trimethoxyphenyl)-2-nitroethanol ($MeOB_3X$) and 1-(3,4-

methylenedioxyphenyl)-2-nitroethanol (POH)] and two nitroethanes [1-(3,4-dimethoxyphenyl)-2-nitroethane (DMNE) and 1-(4-benzyloxy-3-methoxyphenyl)-2-nitroethane (BVNE)] showed significant ($P<0.05$) decrease in sleep latency (SL) with BVNE [56.20 ± 2.47] showing superior activity to the lead molecule (BPNE) [74.60 ± 6.10]. Two nitroalcohols (MBP and POH) showed significant ($P<0.05$) prolongation of total sleeping time (TST) with MBP [3296.80 ± 280.79] showing the best activity among the test compounds while BPNE showed a superior TST of 4584.60 ± 249.06. None of the two test analogues of nitroethane exhibited significant ($P< 0.05$) effect on TST. Five nitroalcohols [BZA, POH, 1-(3,4-dimethoxyphenyl)-2-nitroethanol (DMP), 1-(4-benzyloxy-3-methoxyphenyl)-2-nitroethanol (BZV-ALC) and 1-(3, 4-dibenzyloxyphenyl)-2-nitroethanol (DBP)] and one nitroethane (BVNE) caused significant reduction in rectal temperature at 30 mins. Depression in the rectal temperatures for the active compounds at 60 mins post treatment were MBP (2.68 ± 0.23), DMP (2.50 ± 0.15) and DBP (2.08 ± 0.37); and that of BPNE was (1.96 ± 0.42) while that of the negative control (5% Tween 80) was 0.44 ± 0.23. BPNE showed 100% protection on the PTZ-induced convulsions at 100 mg/kg, i.p. while none of the test compounds showed any significant anticonvulsant activity.

The study concluded that nitroalcohols with log P value less than 2.0 are likely to be hypnotically active and there is no correlation between log P, hypothermic and anticonvulsant effects. While the nitroethanes available are too few for quantitative correlation studies, the lead molecule was unique in its hypnotic and anticonvulsant activities.

INTRODUCTION

1.1 GENERAL INTRODUCTION

The rapid development and innovation in modern chemistry in the 20th century enabled scientists to synthesize new compounds and to modify naturally occurring drugs. Many drugs formerly available only from animal and plant tissues can now be produced in the chemical laboratory in a pure form. In some cases, scientists have discovered new drug compounds either by accident or by actively screening various agents for their potential pharmacologic activity (Ganesan, 2008). Physicians have relied on chemical compounds produced by animals, plants and micro-organisms; so-called natural products to treat diseases and have been the most single productive source of leads for the development of drugs. The chemistry of naturally occurring compounds has long been pursued in the search for medicines, dyes, pesticides, flavours and fragrances. However, natural products are produced in nature and through biological assays are identified as leads which become candidates for drug development (Molinari, 2009).

Synthetic chemistry plays a key role in the multidisciplinary development process of new small molecules as pharmaceuticals. Drugs are mostly organic molecules produced through chemical synthesis (Martin, 2011). They are molecules that change the physiological state of the body when taken; some act by selective toxicity principle (e.g. antibiotics), some are receptors based (e. g neuroleptics, cardiovascular agents), while some are non-receptor based (antacids). The approach to drug discovery has been to understand how disease and infection are controlled at the molecular and physiological level and to target specific entities based on this knowledge. The resulting chemical entity called the lead compound elicits the desired biological activity but may have other undesirable qualities as toxicity, poor oral absorption, poor water solubility, and

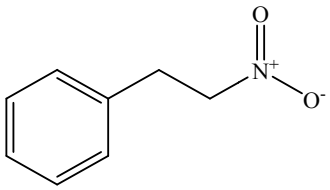
other poor pharmacokinetics properties. Thus, it is important to harness the desirable quality while the undesirable property is attenuated or eliminated. This approach is therefore called lead optimization (Olaniyi, 2005). Lead optimization is aimed at attenuating toxicity and improving the pharmacokinetic properties (absorption, distribution, metabolism and excretion) and physicochemical properties of the lead compound through modification (Olaniyi, 2005). Lead modification is achieved by first identifying the pharmacophore (the part of the lead responsible for the biological activity), homologation (increasing the carbon chain), chain branching, functional group modification, bioisosterism replacement, application of quantitative structure-activity relationship studies (Hansch, 1969).

With some classes of drugs, however, scientists have been able to discern a structure-activity relationship (i.e., a relationship between the chemical structure and the pharmacologic activity), and this information has guided the synthesis of new compounds. A structure-activity relationship (SAR) is used to determine the primary, secondary, and tertiary structure of chemicals as a means of ascertaining the relationship between the effects of different compounds on biological systems. The history of SARs is over 150 years old and goes back to the laboratory of Louis Lewin, who, in the nineteenth century, developed the early chlorinated methane derivatives chloroform, dichloromethane and carbon tetrachloride. The many derivatives of benzene (toluene, xylene, and others) also fall into this category. Once the organic chemists and medicinal chemists began to understand the impact of chemical structure on biological systems, the rudimentary basis of SARs commenced. By the 1920s, the chemistry of disinfectants, pesticides, and some drugs was based on SAR (Michael, 2002).

A classic example of an early SAR was the discovery of the benefits of acetylsalicylic acid (aspirin) and its near congeners, acetaminophen and salicylate. Another early classic

example of a SAR was the development of DDT and its analogs and congeners. Several organochlorine pesticides are members of this broad family. Modern SAR analysis is used to develop almost all drugs. Once the prototype drug is discovered and its three-dimensional characteristics determined, the scientists can then use the SAR to better understand the interaction between the drug and the affected protein or membrane (Michael, 2002).

1.2 DESCRIPTION OF β-PHENYLNITROETHANE



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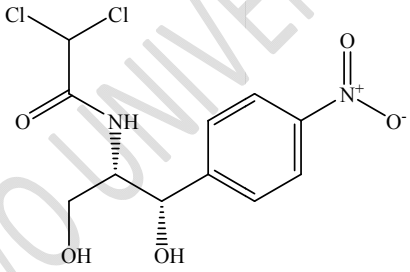

(2)

β-Phenylnitroethane **(1)** (1-nitro-2-phenylethane) is the second nitro compound which was isolated from nature while the first reported nitro compound from nature is the well-known antibiotic, chloramphenicol **(2)** which was isolated from a fungus, *Streptomyces venezuelae* (Horsfall, 1975).

1.2.1 Physico-chemical properties of β-phenylnitroethane

β-Phenylnitroethane is a colourless liquid of boiling point 260.5 ^{o}C at 760 mmHg. It has the molecular formula $C_8H_9NO_2$ and molecular weight of 151.1626 g/mol. The relative density of β-phenylnitroethane is 1.119 g/mL. It has a fragrant aroma with a pungent taste (Agbakwuru *et al.*, 1979).

1.2.2 Natural sources of β-phenylnitroethane

β-Phenylnitroethane was originally isolated from the essential oils of *Aniba canelilla* (Gottlieb and Magalhaes, 1959) and was identified to be responsible for the characteristic aroma of the essential oils of the plant. *A. canelilla* is a medicinal plant used in South