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Synthesis, characterization and acute toxicity of new Schiff base derived from phenylethyl amine and 2-hydroxy naphthaldehyde

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ABSTRACT

There is an urgent need for the design and development of new and safer drugs, this has attracted organic chemists to synthesize new compounds with potential of biological and chemotherapeutic activities. Here we report, the condensation of phenylethylamine with 2-hydroxy naphthaldehyde yielded Schiff base derivative in good yield. Characterization of synthesized compound was carried by elemental analysis, IR, ^{1}H-, ^{13}C- and HSQC-NMR spectroscopy. The toxicity of the synthesized compound was determined using Balb/c mice model. Dixon's up and down method was found to have an LD_{50} of 827.2 mg/kg of body weight, moderate toxicity.

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1. Introduction

Phenylethylamine or *β*-phenethylamine, is an organic compound and a natural mono amine alkaloid, a trace amine, and also the name of a class of chemicals with many members well known for psychoactive drug and stimulant effects [1]. Phenylethylamine functions as a neuromodulator or neurotransmitter in the mammalian central nervous system [2]. The chemistry of the carbon-nitrogen double bond plays a vital role in progresses of chemistry science. Schiff base exhibit a plethora of bioactivities viz, antitubercular, anticancer, antibacterial, antifungal, analgesic, CNS depressant, anti-inflammatory, anticonvulsant, insecticidal, plant growth inhibitors, antimouse hepititis virus (MHV), inhibition of herpes simplex virus type 1 (HSV-1) and adenovirus type 5 (Ad5), antimosqito larvae and herbicidal activities [3,4].

Schiff bases include industrial synthesis of high value lifesaving beta lactam antibiotics from class of penicillin's and cephalosporin's. Schiff bases are used as starting material for the synthesis of various bioactive heterocyclic compounds like 4-thiazolidinones, 2-azetidinones, benzoxazines and formazans. Schiff-base compounds have been used as fine chemicals and medical substrates [5]. El-Ajaily *et al.* were prepared Schiff base derived from phenylethylamine and salicyldehyde as precursor techniques in coordination chemistry [6].

The aim of present work is to synthesis and investigate the structure of the Schiff base derived from phynylethylamine and 2-hydroxy naphthaldehyde and characterized by using physical and spectral techniques, including elemental analysis, IR and NMR. Acute toxicity of synthesized compound was performed.

2. Experimental

2.1. Instrumentation

The IR spectra were recorded in the range 4000-200 cm^{-1} on a Pye-Unicam SP3-300 spectrometer using KBr discs at Department of Chemistry, College of Education for Pure Sciences, University of Basrah, Basrah, Iraq. ^{1}H, ^{13}C-NMR and 2D HSQC-NMR spectra were measured on a Bruker at 600 MHz, with TMS as internal reference at Konstanz University, Germany. Melting point was measured by a Philip Harris melting point apparatus at College of Veterinary Medicine, University of Basrah, Basrah, Iraq.

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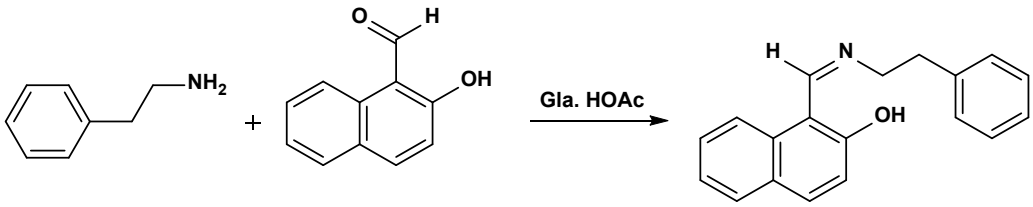
Table 1. Dixon values.

Second part of serial	+ K represented serial tests as follows				
	0	**00**	**000**	**0000**	
XOOO	-0.157	-0.154	-0.154	-0.154	OXXX
XOOX	-0.878	-0.861	-0.860	-0.860	OXXO
XOXO	0.701	0.747	0.741	0.741	OXOX
XOXX	0.084	0.169	0.181	0.182	OXOO
XXOO	0.305	0.372	0.380	0.381	OOXX
XXOX	-0.305	0.169	-0.144	-0.142	OOXO
XXXO	1.288	1.500	1.544	-1.549	OOOX
XXXX	0.555	0.897	0.985	1.000	OOOO
	X	**XX**	**XXX**	**XXXX**	**Second part of serial**
	- K represented serial results as follows				

* LD_{50} = XF + K × d = Median lethal dose; XF = Last dose used in the experiment; K = Factor of change from the table; d = Difference between doses.



Scheme 1. Preparation of 1-((phenethylimido)methyl)naphthalen-2-ol.

2.2. Acute toxicity (LD_{50}) study

The lethal dose (50%) of the synthesized compound in Balb/c mice was determined using up-and-down method [7]. Male and female mice aged 4-6 weeks were injected intraperitoneally with different doses of the synthesized compound after conducting series of test levels. With equal spacing between doses, a series of trails were carried out using this method: increased dose following a negative response and decreased dose following a positive response. Testing continued until chosen "nominal" sample size was reached. LD_{50} were determined after reading final result (response-dead (X) or non-response alive (O), then the following equation was applied LD_{50} = XF + Kd.

The estimate of LD_{50} is XF + Kd, where XF is the final test level and K is the interval between dose levels. d is the tabulated value (Table 1).

2.3. Synthesis

2.3.1. Synthesis of 1-((phenethylimido)methyl)naphthalen-2-ol

Phenyl ethyl amine (3.36 mmol, 0.4 g) in 25 mL ethanol was added to hot ethanolic solution of 2-hydroxy naphthaldehyde (3.36 mmol, 0.58 g), two drops of glacial acetic acid was added and resulting solution was refluxed for 3 h and then lift overnight in refrigerator. The solid product obtained was filtered and washed with acetone and the final product was recrystallized by using chloroform: ethanol (8:2, *v*:*v*) to yield yellow-green crystals of 1-[(2-phenylethyl) carbonoimidoyl]naphthalene 2-ol. Color: Pale Yellow. Yield: 80%. M.p.: 192-194 °C. FT-IR (KBr, ν, cm^{-1}): 3300 (OH), 3068 and 3024 (CH-Ar-H); 2929 and 2858 (CH-Aliph.), 1639-1537 (C=C, C=N). ^{1}H NMR (600 MHz, $CDCl_3$, δ, ppm): 2.92-2.96 (t, 2H, CH_2-Ar), 3.72-3.74 (t, 2H, CH_2-N), 6.81-7.57 (m, 11H, Ar-H), 8.39 (s, 1H, CH=N), 14.36 (s, 1H, OH). ^{13}C NMR (150 MHz, $CDCl_3$, δ, ppm), 37.40 (1C, CH_2-Ar), 54.72 (1C, CH_2-N), 106.48-137.96 (15C, C-Ar), 158.01 (1C, CH=N), 176.47 (1C, C-OH). Anal. calcd. for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 83.14; H, 6.51; N, 5.26%.

3. Results and discussion

3.1. Chemistry

The present work describes the synthesis of some Schiff base by reaction of ethyl phenyl amine with 2-hydroxy naphthaldehyde in 1:1 ratio to produce the Schiff base derivatives, Scheme 1, in good yield. IR spectra for compound displayed common features in certain regions and characteristic bands in the fingerprint and other regions. The IR spectra confirm the presence of the azomethine group (-CH=N) stretching with a sharp region around 1537 cm^{-1}.

^{1}H NMR spectra of synthesized compound show signal due to azomethine proton (CH=N) at δ 8.39 ppm, ^{1}H NMR spectra of Schiff base show a triplet at the range δ 2.92-2.96 ppm due to CH_2-Ar and triplet at range δ 3.72-3.74 ppm due to CH_2-N group. The region at δ 6.81-7.57 ppm due to aromatic protons. ^{1}H NMR spectra of synthesize compound show singlet at δ 14.36 ppm due to phenolic OH.

The ^{13}C NMR spectrum of all compounds was measured in DMSO-d_6. ^{13}C NMR spectra gave further support to the formation of these compounds. The spectra revealed the presence of –CH=N group around δ 158.01 ppm. The signal at δ 176.47 ppm due to C-OH [8]. These spectra data sports the structure of synthesized compound.

The ^{1}H, ^{13}C HSQC NMR spectrum [9] of synthesized compound showed a cross peak at δ_H/δ_C = 14.35/178.4 ppm, belonged to Ar-OH. The cross peak at δ_H/δ_C = 8.39/158 ppm due to azomethine group (CH=N). Thus, the correlation of protons and carbon in aromatic rings such as, δ_H/δ_C = 7.57/137, 7.48/129 ppm and other positions can be assigned to the protons and carbon atoms of the aromatic rings [8], while the cross peak at δ_H/δ_C = 3.73/54.7 and δ_H/δ_C = 2.93/37.4 ppm can be attributed to methylene groups, Figures 1 and 2.

3.2. Determination of the 50% of lethal dose (LD_{50}) of the synthesized Schiff base in-vivo

The LD_{50} of synthesized new compound was detected in the mice by using the "up-and-down" procedure described by Dixon [7] in the experiment we using 10 animals of white mice 7-8 weeks in age, Graded doses of injection to each one animal, a series of concentrations (600, 650, 700, 750 mg/kg.bw) in 0.1 mL dimethyl sulfoxide (DMSO) were administered and chosen with equal spacing (concentrations) between doses [10].

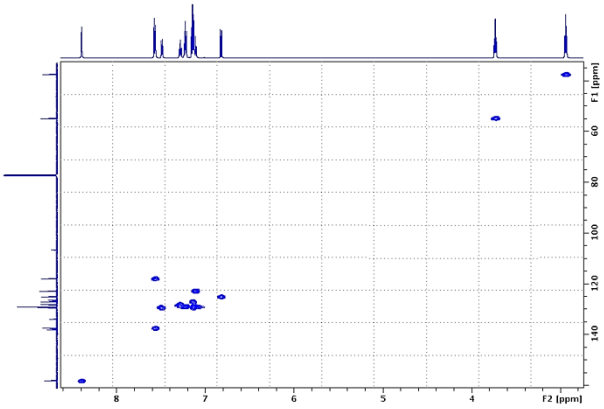


Figure 1. HSQC-NMR spectrum of 1-[(2-phenylethyl)carbonoimidoyl]naphthalen-2-ol.

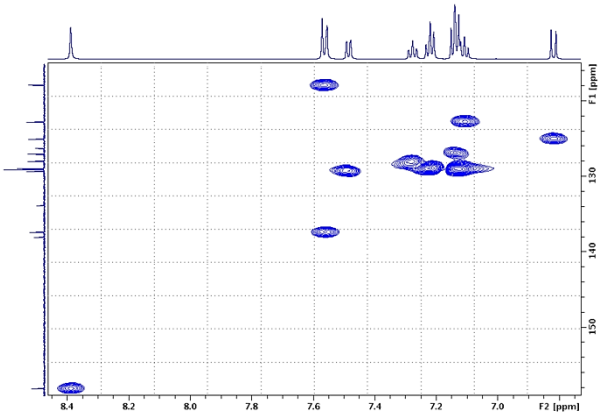


Figure 2. HSQC-2 NMR spectrum of 1-[(2-phenylethyl)carbonoimidoyl]naphthalen-2-ol.

Mortality was recorded after 24 h that each one animal treated with one dose and after 24 h was recorded as O if the animal lives and then increased the treated dose. While X recorded for the death of animal and then decreased the dose according for the result of the animal the code which formed as being (OOOX)and according for Dixon value was get and the LD_{50} was determined according to the formula employed by Dixon (D_{50} = X*f* + Kd; LD_{50} = 750 + 1.544 × 50 = 827.2 mg/kg.bw).

4. Conclusion

In conclusion a Schiff base of phenyl ethyl amine and 2-hydroxy naphthaldehyde compound was prepared by convenient method. Elemental analysis (CHN) and spectroscopic characterization of synthesized compound such as, infrared and nuclear magnetic resonance spectroscopy were supported the structure of synthesized compound. The synthesized compound appears to be safe with moderate toxicity. It's LD_{50}, calculated by Dixon, is 0.827 g/kg of body weight, and the safe dose was less than 0.08 g/kg. These results are promoted us to continue the study such as, physiological parameters and histopathological study to complete the pharmaceutical studies.

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Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.
Author contributions: All authors contributed equally to this work.
Ethical approval: All ethical guidelines have been adhered according to committee on the ethics of dealing with laboratory animals.
Sample availability: Samples of the compounds are available from the author.

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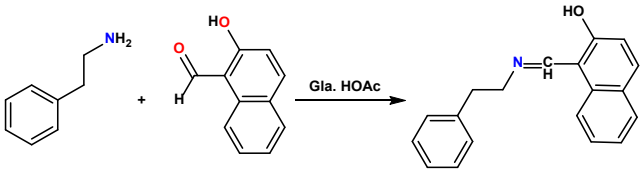
Graphical Abstract



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