



Received on 24 August 2020; received in revised form, 23 September 2020; accepted, 22 November 2020; published 31 December 2020

BENZOQUINONE MONO OXIMES DERIVATIVES WITH ANTICANCER ACTIVITY

Chistiane Mendes Feitosa ^{* 1}, Sosthenes de Sousa Silva ¹, Gardenia Gadelha Carmem Militão ², Damião Pergentino de Sousa ³, Khaled Rashed ⁴ and Layana Karine Farias Lima ⁵

Post-graduate Programs in Chemistry and Pharmaceutical Sciences ¹, Federal University of Piauí, Ininga, 64.049-550, Teresina, Piauí, Brazil.

Department of Physiology and Pharmacology ², Federal University of Pernambuco, 50670-901, Recife, PE, Brazil.

Departamento de Ciências Farmacêuticas ³, Universidade Federal da Paraíba, Campus I, Cidade Universitária, 58051900, João Pessoa-Paraíba, Brasil.

Department of Pharmacognosy ⁴, National Research Centre, 33 El-Bohouth st.-Dokki, Giza, Egypt-P.O.12622.

Laboratory of Natural Products and Experimental Neurochemistry ⁵, Federal University of Piauí, Ininga, 64.049-550, Teresina, Piauí, Brazil.

Keywords:

Oximes, Cytotoxic, Anticancer

Correspondence to Author:

Chistiane Mendes Feitosa

Post-graduate Programs in Chemistry and Pharmaceutical Sciences, Federal University of Piauí, Ininga, 64.049-550, Teresina, Piauí, Brazil.

E-mail: chistiane@ufpi.edu.br

ABSTRACT: Objective: The aim of this study was to evaluate the anticancer activity of a series of six structurally related [1, 4]-Benzoquinone monooximes and to investigate structure-activity relationships (SAR) of these compounds. **Materials and Method:** The mono-oximes obtained by oximation of para-benzoquinones 1-4 had their structures confirmed by ¹H NMR, ¹³C NMR. The cytotoxic study was assessed by the MTT assay on three tumor cell lines: HL60 (promyelocytic leukemia), NCI-H292 (lung cancer), and MCF-7 (breast adenocarcinoma). **Results:** Six oximes were synthesized 2 - methyl-[1,4]-benzoquinone oxime tosylate (I), 5-isopropyl-2-methyl-[1,4]-benzoquinone oxime tosylate (II), 5-isopropyl-5-methyl-[1,4]-benzoquinone oxime tosylate (III), 5-isopropyl-2-methyl-[1,4]-benzoquinone oxime (IV), 2,5-dimethyl-[1,4]-benzoquinone oxime tosylate (V), 2-methyl-[1,4]-benzoquinone oxime tosylate (VI). Compounds II to V showed significant activity against all cell lines; while compound I and VI presented low or no activity. **Conclusion:** These experimental data lead to the conclusion that oximes (II –V) may be used as potential starting structures for the design of novel anticancer agents.

INTRODUCTION: Cancer figures among the leading cause of death worldwide, and it is expected that the annual cancer cases will rise to 22 million within the next two decades, according to the World Health Organization (WHO) ¹. The cancers that are well diagnosed are skin cancer, prostate, female breast, colorectal, lung, stomach, and cervical.

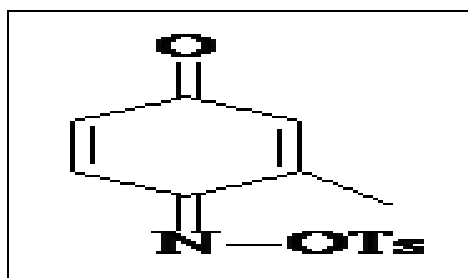
Cancer has been considered a major public health problem ². According to the National Institute of Cancer, it was estimated for the biennium 2016-2017, 600 thousand new cases in Brazil ³.

Oximes contained secondary metabolites that constitute an important group of bioactive compounds and have been described and frequently updated in the literature due to their pharmacological properties, such as antioxidants ⁴ acetylcholinesterase inhibitors ⁵ and antitumor ⁶. Oximes are substances that have been investigated for many years as compounds with high potential in the treatment against poisoning, including, for example, organophosphates (OPs), including

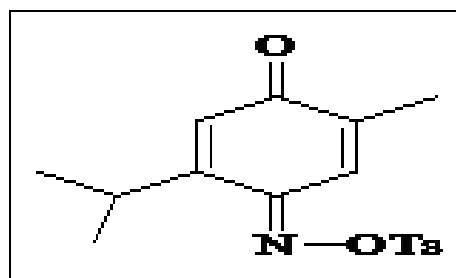
	<p>QUICK RESPONSE CODE</p> <p>DOI: 10.13040/IJPSR.0975-8232.IJP.7(12).369-75</p>
	<p>The article can be accessed online on www.ijournal.com</p>
<p>DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.IJP.7(12).369-75</p>	

pesticides and nerve agents; however, currently, few oximes have clinical application. One of the purposes of its use involves the reactivation of acetylcholinesterase (AChE) enzyme; however, still has disadvantages and limited action in the reactivation of this enzyme^{7, 8}. However, the limitation of conventional oximes has encouraged the synthesis of new oximes with various structural modifications⁹. Oxidative stress is the imbalance between antioxidant defenses and free radicals and reactive metabolites, so-called oxidants or reactive oxygen species (ROS) that under prolonged stress condition can induce neoplastic transformations¹⁰. Major research suggests that the oximes acted decreasing lipid peroxidation after poisoning with malathion, hyperstimulation experiment in the cholinergic system, and oxidative stress in the prefrontal cortex of rats⁴. In promising research oximes synthesized as follows: paraoxon, pralidoxime, thiophene - 2 - aldoxime, 4-methoxy-benzaldoxime, benzaldoxime, 4 - Fluor - benzaldoxime, 4-chloro-benzaldoxime and 4-nitro-benzaldoxime showed potent inhibition action

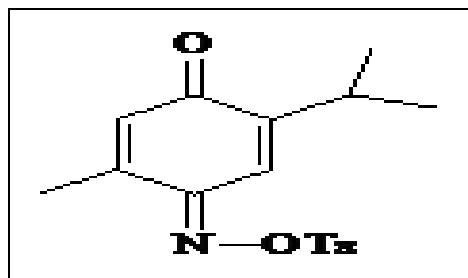
AChE and promise for the future development of drugs for alzheimer's disease⁵. Oxime tosylate (I), 5-isopropyl-2-methyl-[1,4]-benzoquinone oxime tosylate (II), 5-isopropyl-5-methyl-[1,4]-benzoquinone oxime tosylate (III), 5-isopropyl-2-methyl-[1,4]-benzoquinone oxime (IV), 2,5-dimethyl-[1,4]-benzoquinone oxime tosylate (V), 2-methyl-[1,4]-benzoquinone oxime tosylate (VI) and others oxime derivatives are reported with larvicidal activity against *Aedes aegypti* L.¹¹. The (4E) oxime of 2-isopropyl-5-methyl-para-benzoquinone and the corresponding 2-diethyl-amino-ethyl derivative were reported with antidepressant activities potent¹². Thus, the aim of this study was to evaluate the cytotoxic activity of a series of six structurally related [1,4]-Benzo-quinone mono oximes and to investigate structure-activity relationships (SAR) of these compounds. The cytotoxic study was conducted by the method salt 3-(4,5-dimethyl-2-thiazole)-2,5-diphenyl-2-H-tetrazolium bromide (MTT), on tumor cell lines: HL60 (leukemia pro-myelocytic), NCI-H292 (lung cancer) and MCF-7 (breast cancer).



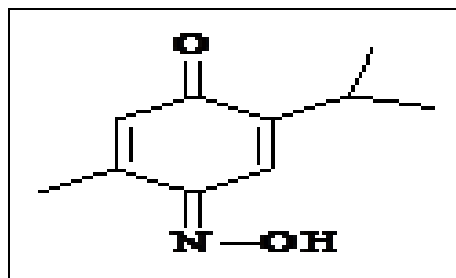
2-methyl-[1,4]-benzoquinone oxime tosylate (I)



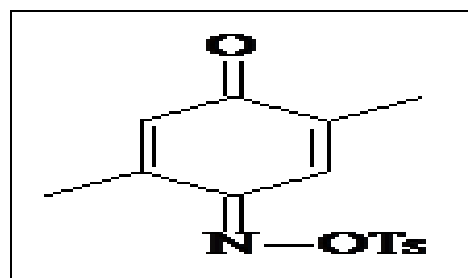
5-isopropyl-2-methyl-[1,4]-benzoquinone oxime tosylate (II)



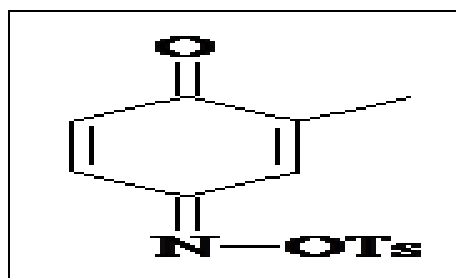
5-isopropyl-5-methyl-[1,4]-benzoquinone oxime tosylate (III)



5-isopropyl-2-methyl-[1,4]-benzoquinone oxime (IV)



2,5-dimethyl-[1,4]-benzoquinone oxime tosylate (V)



2-methyl-[1,4]-benzoquinone oxime tosylate (VI)

FIG. 1: BENZOQUINONE MONO OXIMES DERIVATIVES COMPOUNDS

MATERIALS AND METHODS:

General Procedure for the Synthesis of the 1, 4-Benzoquinone Mono-oximes (I-VI): The phenol (73.5 mmol) was dissolved in 10 M hydrochloric acid (50 ml) and 95 % ethanol (50 ml). Sodium nitrite (7.5 g, 108.7 mmol) was added at 0 °C for over 5 min with stirring, and the reaction mixture was then stirred for an hour at 0 °C. Ethanol (10 ml) was then added, and stirring continued for a further hour at room temperature. The reaction mixture was diluted with water (500 ml) and extracted with diethyl ether. The ethereal extract was then washed with 10% aqueous sodium carbonate solution. The aqueous solution, on acidification with 3 M hydrochloric acid, yielded a dirty yellow precipitate which was filtered. The solid residue was washed with hexane to eliminate soluble impurities to give the product (I–VI).

Preparation of the Oxime Derivatives: ¹H and ¹³C NMR spectra were obtained on a Bruker DRX400 spectrometer at 400 and 100 MHz, respectively, with CDCl₃ as a solvent.

Chemical shifts are reported in ppm downfield from tetramethylsilane internal standard. Infrared spectra were recorded on a Bomem Michelson model 102 FTIR or a Hartman & Braun MB, and the most intense or representative bands are reported (in cm⁻¹).

Melting points were determined on a Micro Quimic model APF 301 apparatus and are uncorrected. Solvents and reagents were used directly from the supplier or purified when required by standard procedures.

Compound I: 80% Yield: ¹H RMN (CDCl₃, 400 MHz) δ: 2.13 (CH₃, d, J=1.3 Hz); 2.47 (CH₃, s); 6.33 (CH, m); 6.45 (CH, dd, J=10.3 Hz, 2.0 Hz); 7.38 (CH, d, J=8.3 Hz); 7.57 (CH, d, J=10.3 Hz); 7.91 (CH, d, J=8.3 Hz). ¹³C RMN (CDCl₃, 100 MHz) δ: 17.2; 21.7; 124.8; 129.2; 129.8; 131.0; 131.4; 133.6; 145.0; 146.1; 153.6; 186.1. IR (ν_{max.}, KBr, cm⁻¹): 2974, 1649, 1593, 1386, 1196, 1175, 1092.

Compound II: 80% Yield: ¹H RMN (CDCl₃, 400 MHz) δ: 1.07 (CH₃, d, J=7.1 Hz); 2.01 (CH₃, d, J=1.5 Hz); 2.45 (CH₃, s); 3.08 (CH, d hept, J=0.7 Hz, 7.1 Hz); 6.31 (CH, d, J=0.7 Hz); 7.36 (CH, J=8.3 Hz); 7.40 (CH, q, J=1.5 Hz); 7.89 (CH, J=8.3 Hz).

¹³C RMN (CDCl₃, 100 MHz) δ: 15.8; 21.7; 21.9; 27.4; 121.6; 127.3; 129.1; 129.7; 131.7; 142.3; 145.8; 152.4; 154.5; 186.8. IR (ν_{max.}, KBr, cm⁻¹): 2958, 1654, 1386, 1195, 1176, 1091.

Compound III: 79% Yield: ¹H RMN (CDCl₃, 400 MHz) δ: 1.10 (CH₃, d, J=6.8 Hz); 2.08 (CH₃, d, J=1.5 Hz); 2.46 (CH₃, s); 3.04 (CH, d hept, J=1.3 Hz, 6.8 Hz); 6.30 (CH, q, J=1.5 Hz); 7.27 (CH, d, J=1.3 Hz); 7.37 (CH, d J=8.3 Hz); 7.92 (CH, d, J=8.5 Hz). ¹³C RMN (CDCl₃, 100MHz) δ: 16.7; 21.5; 21.7; 26.9; 118.2; 129.2; 129.7; 131.4; 131.7; 144.2; 145.8; 152.2; 154.0; 185.6. IR (ν_{max.}, KBr, cm⁻¹): 2964, 1647, 1599, 1382, 1195, 1181, 1095.

Compound IV: 65% Yield: ¹H RMN (CDCl₃, 400 MHz) δ: 1.13 (CH₃, d, J=6.8 Hz); 2.20 (CH₃, d, J=1.3 Hz); 3.06 (CH, d hept, J=1.2 Hz, 6.8 Hz); 6.26 (CH, q, J=1.3 Hz); 7.56 (CH, d, J=1.2 Hz). ¹³C RMN (CDCl₃, 100MHz) δ: 16.9; 21.5; 26.4; 118.4; 128.5; 146.2; 147.9; 150.2; 186.9. IR (ν_{max.}, KBr, cm⁻¹): 3480, 2961, 1638, 1604, 1439, 1241, 1055 Mp 142.6-143.2 °C.

Compound V: 88% Yield: ¹H RMN (CDCl₃, 400 MHz) δ: 2.00 (CH₃, d, J=1.5 Hz); 2.09 (CH₃, d, J=1.2 Hz); 2.45 (CH, s); 6.30 (CH, q, J=1.2 Hz); 7.36 (CH, d, J=8.3 Hz); 7.37 (CH, q, J=1.5 Hz); 7.90 (CH, d, J=8.3 Hz). ¹³C RMN (CDCl₃, 100 MHz) δ: 15.9; 19.8; 21.7; 121.3; 129.1; 129.8; 130.9; 131.7; 142.8; 144.8; 145.9; 153.9; 186.4. IR (ν_{max.}, KBr, cm⁻¹): 2926, 1654, 1602, 1377, 1191, 1176, 1091.

Compound VI: 85% Yield: ¹H RMN (CDCl₃, 400 MHz) δ: 2.02 (CH₃, d J=1.5 Hz); 2.07 (CH₃, d J=1.5 Hz); 2.48 (CH₃, s); 6.53 (CH, d, J=10.1 Hz); 6.54 (CH, d, J=10.1 Hz); 6.96 (CH, m); 7.09 (CH, dd, J=10.1 Hz, 2.5 Hz); 7.38 (CH, d, J=8.5 Hz); 7.40 (CH, d, J=8.5 Hz); 7.46 (CH, m); 7.57 (CH, dd, J=10.1 Hz, 2.5 Hz); 7.91 (CH, d, J=8.5 Hz); 7.93 (CH, d, J=8.5 Hz). ¹³C RMN (CDCl₃, 100 MHz) δ: 15.7; 16.4; 21.7; 120.9; 124.1; 129.0; 129.1; 129.8; 131.1; 131.5; 132.4; 132.5; 134.3; 135.1; 145.9; 153.4; 153.6; 186.3; 186.4. IR (ν_{max.}, KBr, cm⁻¹): 2926, 1641, 1634, 1387, 1193, 1176, 1091.

Antiproliferative Activity: The human tumor cell lines used in this work were HL-60 (promyelocytic leukemia), MCF-7 (breast carcinoma), NCI-H292 (lung carcinoma), and these cells were obtained

from Rio de Janeiro Cell Bank (RJ, Brazil). Cancer cells were maintained in RPMI 1640 medium or DMEN supplemented with 10% fetal bovine serum, 2 mM glutamine, 100 U/mL penicillin, 100 µg/mL streptomycin at 37 °C with 5% CO₂. We assessed the cytotoxicity of the compounds against four tumor cell lines using the 3-(4, 5-dimethyl-2-thiazolyl)-2, 5-diphenyl-2H tetrazolium bromide (MTT) (Sigma Aldrich Co., St. Louis, MO, USA) reduction assay.

For all experiments, tumor cells were plated in 96-well plates (105 cells/mL for adherent cells or 3 x 10⁵ cells /mL for leukemia)¹³. After 24 h, compounds dissolved in DMSO 0.5% were added to the wells at 25 µg/ml for initial screening. Compounds that presented over 75% cell growth inhibition were considered to be active. Further, active compounds were tested in serial dilutions (0.3-25 µg/mL). Control groups received the same amount of DMSO. After 69 h of treatment, 25 µL of MTT (5 mg/mL) was added, three hours later, the MTT formazan product was dissolved in 100 µL of DMSO, and absorbance was measured at 595 nm in plate spectrophotometer.

Doxorubicin (0.01–5 µg/mL) was used as positive control. IC₅₀ values and their 95% confidence intervals for two different experiments were obtained by non linear regression using Graphpad Prism version 5.0 for Windows (GraphPad Software, San Diego, California, USA)^{14,15}.

RESULTS AND DISCUSSION: In the present investigation, six analogs of the [1, 4] benzoquinone oxime were synthesized and subjected to cytotoxic bioassay on tumor cell lines: HL-60 (promyelocytic leukemia), MCF-7 (breast adenocarcinoma) and NCI-H292 (lung carcinoma). In addition, the structure-activity relationship (SAR) was investigated. The synthesis of the [1, 4] benzoquinone oxime compounds **Fig. 1** and structural determination of these compounds are consistent with those described by¹¹. The parameter is most commonly used to evaluate the cytotoxicity and cell viability, which can be detected by the technique of vital dyes such as neutral red, which allows the distinction between living cells and dead¹⁶. In this study, cells were performed using the formazan dye (formed by the reduction of salt 3-(4, 5-dimethyl-2-thiazole)-2, 5-

diphenyl-2H-tetrazolium bromide (MTT). In this colorimetric method, the activity of viable cells with active metabolism converts the salt MTT to the purple-colored dye MTT-formazan, which can be quantified spectrophotometrically¹⁷.

Inhibition of cell growth, an indicator of cytotoxicity caused by the compounds being valued for antineoplastic activity in this study were visualized in cells HL60 (promyelocytic leukemia), NCI-H292 (lung cancer) and MCF-7 (breast adenocarcinoma), however, other cells may be used to find out further, studies: Hep2 (ATCC - CCL-23, de carcinoma de laringe), B16-F10 (ATCC CRL-6322, células de melanoma), 786 (ATCC – CRL1932, carcinoma de rim), NCI-ADR (carcinoma de ovário resistente a adriamicina), OVCAR 5 3 (ATCC HTB 161, ovarian carcinoma), UACC-62 (melanoma), HT-29 (ATCC HTB-38, colon carcinoma), PC03 (ATCC CRL 1435, próstata carcinoma). According to the International Standard Organization, ISO10993, the *in-vitro* cytotoxicity as say is the first test to evaluate the toxic effects in animal models; having proven its non-toxicity study may continue carrying out necessary tests in the animal laboratory.

In-vitro methods have advantages over *in-vivo* such as might limit the number of experimental variables, to obtain meaningful data more easily beyond the test period is in most cases, shorter¹⁸. The problem of extrapolation of the data obtained *in-vitro* for the clinical application of biomaterial scan is overcome by the use of appropriate reference material currently used in clinics.

Studies using these methods showed that the tests with cell cultures could be used successfully as they are reproducible, fast, sensitive, and affordable for the implementation of *in-vitro* biocompatibility study¹⁹.

The synthesized compounds were screened at 25 µg. mL⁻¹ against HL-60 (promyelocytic leukemia), MCF-7 (breast adenocarcinoma), NCI-H292 (lung carcinoma), tumor cells lineages. The samples with growth inhibition over 90% were used to determine the IC₅₀ values (concentration that causes 50% growth inhibition). Analogs II, III, IV, V and VI exhibited good cytotoxicities, and their IC₅₀ values are described in **Table 1**.

TABLE 1: CONCENTRATIONS THAT INHIBIT 50% CELL GROWTH (IC₅₀) µg/ml AND CONFIDENCE INTERVALS (CI 95%) OF COMPOUNDS IN THREE TUMOR CELL LINES AFTER 72 H OF INCUBATION

Compounds	HL-60	MCF-7	NCI-H292
	CI ₅₀ (Confidence Intervals) µg/mL		
II	<0.3	3.6 (3.0 – 4.4)	1.6 (1.4 – 1.9)
III	<0.3	3.1 (2.7 – 3.7)	1.7 (1.5 – 1.8)
IV	1.9 (1.6 – 2.2)	14.8 (12.3 – 17.9)	9.0 (7.7 – 10.5)
V	0.3 (0.2– 0.3)	5.9 (4.9 – 7.0)	NT*
VI	4.1 (3.1 – 5.5)	16.3 (8.5 – 31.1)	>25
Doxorubicin	0.02 (0.01-0.02)	0.30 (0.20-0.50)	0.01 (0.01-0.03)

NT* Not Tested

When tested at single concentration of 25 µg/mL, compounds II to V were active at all cell lines, while compound VI was high active only at HL60 and compound I showed no activity (see **Table 1** and **2**).

TABLE 2: CELL GROWTH INHIBITION (IC %) OF COMPOUNDS ON THREE TUMOR CELL LINES

Samples	Cell Lines (IC %)		
	HL60	MCF-7	NCI-H292
I	0.0	0.0	0.0
II	97.2 ± 0.6	93.7 ± 0.8	96.1 ± 0.5
III	96.5 ± 2.6	88.1 ± 2.8	93.04 ± 5.5
IV	96.3 ± 3.0	81.4 ± 9.6	91.7 ± 7.2
V	99.1 ± 0.3	92.9 ± 2.2	96.1 ± 1.1
VI	91.0 ± 3.6	54.7 ± 13.0	42.4 ± 2.8

Derivatives were tested at 25 µg/ml on cells for 72 h of incubation.

In fact, compounds II and III, the most active ones, presented similar IC₅₀ values ranging from concentrations below 0.3 µg/mL to 3.6 µg/mL. After performing the test for the determination of 50% inhibitory concentration for these compounds on tumor cells was observed IC₅₀ values lower than 0.3 µg /mL for HL60 and IC₅₀ ranging from 1.6 to 16.3 in the adhered cells (MCF-7 and NCIH292), demonstrating that the II, III, IV and VI compounds contain moderate to high cytotoxicity. Pure substances that had IC₅₀ < 1 µg /mL are considered very active^{20, 21}. According to the functional and structural characteristics and the observed cytotoxic activity, the tested compounds can be divided into two classes, para-benzoquinone oxime derivatives with presence or absence of alkyl groups, while the second group involve tosylatedoxime derivatives with additional alkyl groups. To investigate if the introduction of a methyl group in the chemical structure influences the larvicidal activity, benzoquinoneoxime (I) was compared to benzoquinone oxime (V). Compound (V) was more bioactive than (I) indicating that the addition of a lipophilic group improves the activity^{11, 22, 23}

demonstrated that the presence of methyl groups in unsubstituted quinones promoted a significant increase of larvicidal activity against different mosquito species.

Compound IV and V showed to be moderated cytotoxic. Compound (VI) was low active. Replacement of a methyl at carbon 2 by an isopropyl group contributed to increase the cytotoxic activity; 5- isopropyl- 2- methyl-[1,4]-benzoquinone oxime tosylate (II) was more bioactive than the 2, 5-dimethyl-[1, 4]-benzoquinone oxime (V). Searches a novel series of 4-aminopyrimidine-5-carboxaldehyde oxime that have activity against as antiproliferative VEGFR-2 inhibitor has been identified and structure-activity relationships (SAR). The best potency was achieved with 4-fluoro-2-methylindol-5-yloxy at the-6-position. On the oximeside chain, lipophilic alkyl groups were preferred over hydrophilic amino sidechain²⁴. It can be seen that [3, 1]-benzothiazepine and [3, 1] benzoaxazepine derivatives displayed moderate cytotoxic activity against all tested cancer cell lines, being more active for HL60 cells²⁵.

One of these derivatives exhibited better anti-proliferative activity against HL-60 and HT-29 cell lines, being also more active for HL-60 with an IC₅₀ = 2.1 µg mL⁻¹, demonstrating the potential of the newly synthesized compounds as antitumoral agents. Our results were more promising, II, III and IV oximes exhibited better anti-proliferative activity against HL-60 (< 2 µg/mL). A promising study was released with other benzoquinones as cytotoxic evaluation: cytotoxicity activity of analogues 3 and 6 alkyl-Substituted. 3- and 6-alkyl-2-methoxy-1, 4-benzoquinone derivatives analogues, Tests were performed to evaluate the cytotoxicity activity with continuous chain KB cells (epidermoid carcinoma of the floor of the

mouth). In this series 6-methyl-2-methoxy-1, 4-benzoquinone was the most active that showed the highest inhibition on KB cells ($IC_{50} = 0.27 \mu\text{g/ml}$)²⁶. The compounds synthesize 5 - (pentyl) - 3 - (m-tolyl)- 1, 2, 4-oxadiazole, (p-bromophenyl)-5-(pentyl)-1,2,4-oxadiazol and p - chlorophenyl) - 5 - (pentyl) -1, 2, 4 - oxadiazol: was tested against three human cell lines (NCI H292; HL-60 and HT29) exhibited moderate anti-proliferative activity against HL-60 cancer cell lines with IC_{50} values of 42.1, 19.0 and 28 μM , respectively²⁷ II, III and IV oximes exhibited better anti-proliferative activity against HL-60 ($< 2 \mu\text{g/mL}$). In **Table 1**, the results of cytotoxicity of the compounds (I-VI) in comparison with oxorubic in anticancer drug, widely used as a chemotherapeutic drug, are listed. The oximes II to V demonstrated significant activity against all tested tumor cell lines, with a result above the control doxorubicin drug.

The best potency was achieved with 5 - isopropyl - 2 - methyl - [1, 4]-benzoquinone oxime tosylate at the 5-isopropyl position (oxime II). Oxime (I) showed no cytotoxic action. Oximes (II, III, IV, and V) showed significant activity against breast, leukemia, and lung cell lines. These experimental data lead to the conclusion that oximes (II - V) may be regarded as potential starting structures for the design of novel anticancer agents. The results suggest that the II and III derivatives are suitable for *in-vivo* testing, according to the NCI (National Cancer Institute), since they have IC_{50} equal to or less than 4 $\mu\text{g} /\text{mL}$ for all cell lines, whereas the compounds IV and V in HL-60 cell line²⁶.

CONCLUSION: Oximes (II, III, IV, and V) showed significant activity against all cell lines. These experimental data lead to the conclusion that oximes (II - V) may be used as potential starting structures for the design of novel anticancer agents. These results are being published for the first time in this work.

ACKNOWLEDGEMENT: The authors wish to thank the Brazilian financial agencies CNPq.

CONFLICTS OF INTEREST: The authors declare that there are no conflicts of interest.

REFERENCES:

1. World Health Organization: World's health ministers renew commitment to cancer prevention and control.

1. <http://www.who.int/cancer/media/news/cancer-prevention-resolution/en/> (11 July 2017, date last accessed).
2. Rosas MSL, Silva BNM, Pinto RGMP, Silva BV, Silva AR, Guerra LR, Soares GCMT, Castro HC and Lione VOF: Incidência do Câncer no Brasil e o Potencial Uso dos Derivados de Isatinas na Cancerologia Experimental. *Rev Virtual Quim* 2013; 5(2): 243-65.
3. Estimativa INCA: Incidência de câncer no Brasil." Rio de Janeiro: INCA (2016). <http://www.inca.gov.br/estimativa/2016/> (11 July 2017, date last accessed).
4. Da-Silva AP; Farina M, Franco JL, Dafre AL and Kassa KJ: Kuca Temporal effects of newly developed oximes (K027, K048) on malathion-induced acetylcholinesterase inhibition and lipid peroxidation in mouse prefrontal cortex. *Neuro Toxicology* 2008; 29(1): 184-89.
5. Soares SFCX, Vieira AA, Delfino RT and Figueroa-Villar JD: NMR determination of Electrophorus electricus acetyl cholinesterase inhibition and reactivation by neutral oxime. *Bioorg Med Chem* 2013; 1: 5923-30.
6. Soga S, Sharma SV, Shiotsu Y, Shimizu M, Tahara H, Yamaguchi K, Ikuina Y, Murakata C, Tamaoki Kurebayashi TJ, Schulte TW, Neckers LM and Akinaga S: Stereospecific antitumor activity of radicicoloxime derivatives. *Cancer Chemother Pharmacol* 2001; 48(6): 435-45.
7. Eyer P, Szinicz L, Thiermann H, Worek F and Zilker T: Testing of antidotes for organophosphorus compounds: experimental procedures and clinical reality. *Toxicology* 2007; 233(1): 108-19.
8. Moshiri M, Darchini-Maragheh E and Balali-Mood M: Advances in toxicology and medical treatment of chemical warfare nerve agents. *DARU Journal of Pharmaceutical Sciences* 2012; 20(1): 81.
9. Sharma R, Gupta B, Acharya J, Kaushik MP and Ghosh KK: Interactions between xylene-linked carbamoyl bis-pyridinium mono-oximes and organophosphates inhibited-AChE: a kinetic study. *Toxicology* 2014; 316: 1-8.
10. Reuter S, Gupta SC, Chaturvedi MM and Aggarwal BB: Oxidative stress, inflammation and cancer: how are they linked. *Free Radic Biol Med* 2010; 49(11): 1603-16.
11. Lima TC, Santos SRL, Uliana MP, Santos RLC, Santos, Brocksom TLSC, de Holanda Cavalcanti and de Sousa DP: Oxime derivatives with larvicidal activity against *Aedes aegypti* L. *Parasitol Res* 2015; 114(8): 2883-91.
12. De Sousa DP, Schefer RR, Brocksom U and Brocksom TJ: Synthesis and Antidepressant Evaluation of Three para-Benzoquinone Mono-oximes and Their Oxy Derivatives *Molecules* 2006; 11(2): 148-55.
13. Skehan P, Storeng R, Scudiero D, Monks A, McMahon J, Vistica D, Warren JT, Bokesch H, Kenney S and Boyd MR: New Colorimetric Cytotoxicity Assay for Anticancer-Drug Screening. *J Natl Cancer Inst* 1990; 82(13) 1107-12.
14. Junior VGM, Goncalves TDO, Regasini, Regasini LO, Ferreira PMP, Pessoa CDO, Costa Lotufo LV and Cavalheiro AJ: Cytotoxic clerodanedi terpenoids from *Casearia obliqua*. *J Nat Prod* 2009; 72(10): 1847-850.
15. Mosmann T: Rapid colorimetric assay for cellular growth and survival: application to proliferation and cytotoxicity assays. *J Immunol Methods* 1983; 65: 55-63.
16. Sülsen VP, Cazorla SI, Frank FM, Redko FC, Anesini CA, Coussio DJ, Malchiodi EL, Martino VS and Muschietti LV: Trypanocidal and Leishmanicidal Activities of Flavonoids from Argentine Medicinal Plants. *Am J Trop Med Hyg* 2007; 77(4): 654-59.
17. Riss TL, Moravec RA, Niles AL, Duellman S, Benink HA, Worzella TJL: *Minor Cell viability assays- Assay Guidance Manual* 2016; 1-36.

18. International standard: Biological Evaluation of Medical Devices Part5: Tests for Cytotoxicity: *in-vitro* methods. ISO 1992; 10993-5.
19. Rogero SO, Lugão AB and Ikeda TIAS: Cruz Teste *in-vitro* de Citotoxicidade: Estudo Comparativo entre duas Metodologias Mat Res 2003; 6(3): 317-320.
20. Pessoa C, Silveira ER, Lemos TLG, Wetmore LA, Moreaes MO and Leyva A: Antiproliferative effects of compounds derived from plants of Northeast Brazil Phytother Res 2000; 14(3): 187-91.
21. Bezerra DP, Pessoa C, Moraes MO, Alencar NM, Mesquita RO, Lima MW, Alves AP, Pessoa OD, Chaves JH, Silveira ER and Costa-Lotufo LV: *In-vivo* growth inhibition of sarcoma 180 by piperlonguminine, an alkaloid amide from the Piper species. J Appl Toxicol 2008; 28(5): 599-07.
22. Yang YC, Lim MY and Lee HS: Emodin isolated from *Cassia obtusifolia* (Leguminosae) seed shows larvicidal activity against three mosquito species. J Agric Food Chem 2003; 51(26): 7629-31.
23. Cheng SS, Huang CG, Chen WJ and Kuo YHST: Chang Larvicidal activity of tectoquinone isolated from red heartwood-type *Cryptomeria japonica* against two mosquito species. Biores Technol 2008; 99(9): 3617-22.
24. Huang S, Li R, Connolly PJ, Xu G, Gaul MD, Emanuel SL, Kenneth R, LaMontagne KR and Greenberger LM: Synthesis and biological study of 4-aminopyrimidine-5-carboxaldehyde oximes as antiproliferative VEGFR-2 inhibitors. Bioorg Med Chem Lett 2006; 16(23): 6063-66.
25. [Martinez MWR, Militão GCG, Silva TG, Silva RO and Menezes PH: Synthesis of novel [3, 1]-benzothiazepine and [3,1]-benzoxazepinederivates with antitumoral activity. RSC Adv 2014; 4(28): 14715-147184.
26. Brondani JD, Leite ACL, Nascimento SC, Lima RMOC and Bieber LW: Síntese, avaliação da atividade citotóxica e toxicidade aguda de análogos da Primina 3 e 6 Alquil-substituídas. Acta farm Bonaer 2006; 25(2): 248-51.
27. Barros CJB, Souza ZC, Freitas JJR, Silva PBN, Militão GCG, Silva TG, Freitas JCR and Filho JRF: A conveniente synthesis and cytotoxic activity of 3-Aryl-5-pentyl-1,2,4-oxadiazoles from carboxylic acid esters and arylamidoximes under solvent-free conditions. J Chil Chemi Soc 2014; 59(1): 2359-62.

How to cite this article:

Feitosa CM, Silva DSS, Militão GGC, Sousa DDP, Rashed K and Lima LKF: Benzoquinone mono oximes derivatives with anticancer activity. Int J Pharmacognosy 2020; 7(12): 369-75. doi link: [http://dx.doi.org/10.13040/IJPSR.0975-8232.IJP.7\(12\).369-75](http://dx.doi.org/10.13040/IJPSR.0975-8232.IJP.7(12).369-75).

This Journal licensed under a Creative Commons Attribution-Non-commercial-Share Alike 3.0 Unported License.

This article can be downloaded to **Android OS** based mobile. Scan QR Code using Code/Bar Scanner from your mobile. (Scanners are available on Google Playstore)