October 2007 Volume 1 Issue 3

Trade Science Inc.

BIOCHEMISTRY
An Indian Journal

Regular Paper

BCAIJ, 1(3), 2007 [122-125]

Pharmacological Activities Of Two New 8-Hydroxyquinoline Derivatives

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Received: 3rd August, 2007 ; Accepted: 8nd August, 2007

ABSTRACT

In this work, the acute experimental toxicity of two new 8-hydroxyquinoline derivatives products was evaluated following oral administration in mice(Iops Ofa). The LD_{50} obtained were 283.70mg/kg for**(2a)** and >3000mg/kg for**(2b)**. Their *in vitro* antibacterial and antifungal activities were evaluated against reference strains.

KEYWORDS

5-Azidomethyl-8-hydroxyquinoline;
5-Cyanométhyl-8-hydroxyquinoline;
Acute toxicity;
Antimicrobial agents.

INTRODUCTION

8-hydroxyquinoline, a heterocyclic phenol, is a metal chelator. It is a bivalent cations chelater due to the hyroxyl group relative to the nitrogen ring[1]. A large number of 8-hydroxyquinoline derivatives have already been synthesized and shown to be active agents. Indeed, they have been reported to possess antipoison (chelation of the toxic metals as Hg or Pb)[2], anti-tumor[3], antimicrobial[4,5] and anti-HIV activities[6]. The 8-hydroxyquinoline derivatives showed a strong biological activity when they were administrated as a metal complex form[7,8]. In our laboratory many 8-hydroxyquinoline derivatives have been recently synthesized and evaluated for their biological activities[9,10]. Here, we report the antibacterial, antifungal activity and the toxicity of two 5-substituted-8-hydroxyquinoline derivatives[11].

Chemistry

The preparation and synthesis of products **(2a)** and **(2b)** (Figure 1) were previously done in a reported work[11].

EXPERIMENTAL

Microbiological evaluation

1. Bacteriological assays

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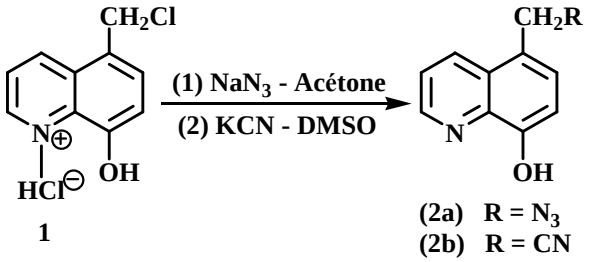

Figure : 1

The synthetic compounds were tested for their antibacterial activity against the following micro organisms: *Staphylococcus aureus*(ATCC 6538), *Bacillus subtilis*(ATCC 6633), *Eschericie coli* (ATCC 8739), *Pseudomonas aeruginosa*(CIP 82118) and *Clostridium sporogenes*(ATCC 31793).

MIC of compounds (**2a)** and (**2b)** were determined by agar diffusion method using tryptone soy agar medium(Biokar diagnostics) for bacteria. Micro organisms were defrosted and grown on nutrient agar. An inoculum(10^8-10^9 UFC/ml) was prepared in nutrient broth and speared out evenly onto the surface of the culture medium. The concentrations of mother solutions were 4mg/ml in(Dimethyl sulfoxide). Sixty µl of every dilution was deposited in stainless steel sterile cylinders beforehand arranged on the surface of the medium. Each concentration was tested in triplicate. Amoxicillin/ clavulamic acid and ampicillin were used as reference antibacterial agents. % DMSO alone was included in the assay as control. After 18-h incubation at 35^0C, the inhibition zone diameters(including the 6-mm hole) were measured. A diameter of more than 6mm indicated growth inhibition.

2. Antifungal assays

The antifungal activity was tested against *Aspergillus Niger*(ATCC 16404) and *Candida albicans*(ATCC 10231).

Antifungal activity against *Aspergillus Niger* and *Candida albicans* was carried out as described previously, the conidial suspension(10^4 UFC/ml) was spread out evenly onto the surface of the sabouraud dextrose agar containing chloramphenicol(CONDA). Voriconazol was used as positive control. Plates were incubated at 28^0C for 48h.

3. Acute toxicity

The tests of acute toxicity were carried out on mice(Iops ofa) of the two sexes, in the same number. 2 to 2 and half months(weigh 20 to 25g), the females are no gravid.

Drugs were administered orally to 18 hours starved mice. Animals were not fed during the following 3 hours.

The following doses were administrated at correspond to 100, 200, 300, 400, and 500mg/kg for com pound**(2a)**; and 300, 400, 1000, 2000 and 3000mg /kg for compound**(2b)** in 25ml/kg of body weight. Drugs were dissolved in dimethyl sulfoxyd-olive oil(5/95, v/v).

Mice are kept in observation during 14days, until occurred obvious clinical signs (the variations of corporal weight and the death rate.

The LD_{50} was calculated by the method of the computerized Probit[12].

RESULTS AND DISCUSSION

Antibacterial activities

Antibacterial activity of 8-hydroxyquinoline derivatives**(2a)** and **(2b)** was tested on *Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa* and *Clostridium sporogenes*. As show in TABLE 1 the MIC of the two compounds and reference. The 8-hydroxyquinoline derivatives **(2a)** and **(2b)** exhibited antibacterial activity aginst all bacteria tested (0.625≤MIC≤3.13mg/mL) for compound **(2a)** and (0.0312≤MIC≤0.250 mg/mL)

TABLE 1 : Antibacterial activity of 8-hydroxyquinoline derivatives (2a) and (2b) . The experiments was performed in triplicate and data are expressed as mean of three experiment

Microorganisms	MIC (µg /ml)x10^{-3}		
	Compound (2a)	Compound (2b)	Reference*
Escherichia coli (ATCC 8739)	0.625	0.25	≥0.25 Amoxicillin
Pseudomonas aeruginosa (CIP 82118)	3.13	0.18	≥0.125 Ampicilline
Staphylococcus aureus (ATCC 6538)	1.25	0.125	≥ 4.88 10^{-4} Amoxicillin
Bacillus subtilis (ATCC 6633)	0.625	0.125	≥7.81 10^{-3} Amoxicillin
Clostridium sporogenes (ATCC 31793)	0.625	0.031	≥1.22 10^{-4} Amoxicillin

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for compound**(2b)**. Reference antibiotics showed a strong activity against bacteria.

The *in* vitro antibacterial activity of the 8-hydroxyquinoline derivatives**(2a)** and **(2b)** was investigated aginst gram-positive and gram-negative bacteria. Our results clearly show that the compound**(2b)** was more active against gram-positive than gram-negative bacteria. The strongest antibacterial activity was observed against clostridium sporogenes(MIC≥31µg/mL), while the compound seemed less active against *Saphylococcus aureus* and *Bacillus subtilis* (MIC≥125µg/mL). In comparison to gram-positive bacteria, a moderate antibacterial activity of the compound was observed against all the gram-negative bacteria tested(MIC≥180µg/mL).These poor results obtained against gram-negative bacteria were not surprising and this may be explained by the presence of an outer membrane in gram-negative bacteria which decreases the transfer of the compound**(2b)** across the cytoplasmic membrane.

Our data also indicate that the compound**(2a)** was less active than the compound**(2b)**. In fact, gram-positive and gram-negative bacteria were resistant to compound**(2a)**; the MIC were 1.25mg/mL for *Escherichia coli* and *Clostridium sporogenes*, 2.5mg/mL for *Staphylococcus aureus* and *Bacillus subtilis*. *Pseudomonas aeruginosa* was very resistant to the action of the compound; the MIC was 3.13mg/mL. The weak activity of the compound a can be explain by its chemical structure.

Antifungal activities

Results of the antifungal activity are reported in TABLE 2, the two compound exhibited antifungal activity against fungi strains tested with the strong activity against *Candida albicans* MIC>0.16mg/ml for compound **(2a)** and MIC>0.0625mg/ml for compound **(2b)**.

The 8-hydroxyquinoline derivatives **(2a)** and **(2b)** were also tested for their antifungal activity against *Aspergillus Niger* and *Candida albicans*. *Candida albicans* was more sensitive than *Aspergillus Niger* to the two compound, MIC of >60µg/ml for compound **(2a)** and MIC of 62.5µg/ml for compound **(2b)**. Even though, the MIC were >625µg/ml and <1000µg/ml for compound **(2a)** and **(2b)** respectively.

Acute toxicity

TABLE 2: Antifungal activity of 8-hydroxyquinoline derivatives (2a) and (2b). The experiments have been done in triplicate and the results were averaged

Microorganism	MIC(µg/ml)×10^{-3}		
	Compound(2a)	Compound(2b)	Voriconazol
Aspergillus niger (ATCC16404)	>0,625	>1	>0,03
Candida albicans (ATCC10231)	>0,16	>0,0625	1,22.10^{-3}

TABLE 3: Lethal dose 50% of the compound (2a) administrated orally

Dose(mg/Kg)	Mortality%	LD_{50}(mg/Kg)
100	0	LD_{50}=283.70 (269,60-298,50)
200	20	
300	50	
400	80	
500	100	

LD_{50} is the dose lethal causing 50% of mortality in mice. Numbers in parentheses are 95% confidence range

TABLE 4: Lethal dose 50% of the compound (2b) administrated orally

Dose mg/Kg	Mortalité %	LD_{50}(mg/Kg)
300	0	LD_{50} › 3000 mg/Kg
400	0	
500	0	
1000	0	
3000	0	

TABLES 3 and 4 showed the results of toxicity test of the 8-hydroxyquinoline derivatives **(2a)** and **(2b)**. The mortality rate increased according to the concentration of the compound **(2a)** (LD_{50} of 283.70mg/kg). No mortality was observed when **(2b)** was administered.

Toxicity of the compounds**(2a)** and**(2b)** was evaluated on suiss mice. The results showed the increase of the mortality rate according to the administrated concentration of the compound**(2a)**(LD_{50} of 283.70mg/kg). Compound**(2a)** caused death generally between the 1st and 14th day of the administration and loss of body weight from 5 to 10% starting from the 7th day. Mice recover weight after 7th day of the treatment. TheTrevan curve indicate mortaliry percentage according the the compound doses.

In case of derivative**(2b),** LD_{50} was superior to 3000 mg/kg. In fact, no mortality was shown up to the dose of 3000mg/kg.

ACKNOWLEDGMENTS

The authors are very grateful to Pr M.Errasfa (Faculty of Medicine and Pharmacy, Fes) and Dr Z.Dardari (Faculty of Science Ben M'sik, Casablanca) for critical

reading of the manuscript.

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