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The Perspectives of Synthetic Aducts (Salts) of Nitroxoline™ and 2-Aminoquinolin-8-ol as Promising Antibacterial Agents †

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Abstract: The threatening phenomenon of antibiotic failure in the future determines the intensive research of antibacterial active compounds to be promising candidates as antibiotics. Quinolines with only representative in clinical practice—Nitroxoline™ are, in addition to successful beta-lactams, macrolides, tetracyclines and other antibiotic categories forgotten antibiotics. The perspective the antibacterial efficiency of Nitroxoline™ and 2-aminoquinolin-8-ol on eight selected, the most problematic, highly resistant bacterial species (*Klebsiella ssp.*, *Enterococcus ssp.*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Staphylococcus aureus*) could lead to higher solubility and thus bioavailability and increasing of antibacterial effect. In the first phase, basic salts of Nitroxoline™ with sodium hydroxide, benzylamine, 4-(aminomethyl)pyridine and other primary amines were synthesized. Within the second phase, opposite acidic salts of 2-aminoquinolin-8-ol were synthesized with following acids: oxalic acid, pyrazine-2,3-dicarboxylic acid, chelidonic acid, quinaldic acid, 3,5-dinitrosalycilic acid, quinoline-2-carboxylic acid, quinoline-3-carboxylic acid, kynurenic acid, xanthurenic acid. Nitroxoline™ and 2-aminoquinolin-8-ol both expressed flat antibacterial effect with average value on eight mentioned bacterial strains: 16 mg/L (84 μM), respectively 50 mg/L (301 μM). The synthetized salts of both quinolinols expressed significantly higher solubility and slightly increased antibacterial activity. The identity and purity of prepared products were determined by NMR and IR spectroscopy. The MW values of both quinolinols are relatively low and offer better use of the largest molecule limit, defined by Lipinski's rule of five at 500 g/M. The options of the choice of amines or acids offers the achievement of quaternary salts with improved antibacterial activity.

Keywords: Nitroxoline™; 2-amino-8-quinolinol; salts; antibacterial activity; antibiotic resistance

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1. Introduction

The 8-hydroxyquinolines (8OHQ's) are the one of the subjects of intensive research. Its antibacterial activity it is really known for several centuries, because it was a part of the formulation of the disinfectants in army medicine. The 8OHQ was known to be produced by roots of several plants, such as *Broussonetia zeylanica*, or *Allium stipitatum*, grown in Mediterranean area of the Europe [1]. The 8OHQ's were the subject of intensive research during last four decades up to now, what could be documented by several patent inventions [2,3] as well as by original, scientific papers [4–7]. Only clinically approved and launched antibiotic of this structural group is Nitroxoline™ (NQ), prescribed for therapy of urinary system infections [8–10]. The numerous collection of 8OHQ derivatives (n ≥ 100) were screened on eight, the most problematic clinical isolates with clearly defined mechanism of resistance, within our previous research (yet not published data). Surprisingly, flat antibacterial effect was observed on our "alert collection" of selected bacterial

strains. The flat antibacterial effect, but on the other hand with no known mechanism (ions chelating effect in bacterial cells is published) means the main impulse to application of our current research and this paper. The published [2,11] category of the NQ or 8OHQ salts seems to be perspective from at least two points of view—antibacterial activity and increasing solubility in polar solvents and water.

2. Methods

All chemicals /Nitroxoline™, sodium hydroxide, benzylamine, 4-(aminomethyl)pyridine, 2-amino-8-quinoplinol, oxalic acid, pyrazine-2,3-dicarboxylic acid, chelidonic acid, quinaldic acid, 3,5-dinitrosalycilic acid, quinoline-2-carboxylic acid, quinoline-3-carboxylic acid, xanthurenic acid and kynurenic acid as well as solvents for synthesis 2-propanol and tetrahydrofuran were purchased from Meck/Sigma-Aldrich/highest purity grade.

All synthesis were carried out by mixing (10 mL) of 100 mM solutions of both reactants, solved in THF (2-propanol eventually) at room temperature for 24 h in darkness, followed by filtration, washing and drying of synthetized crystals. The identity and purity of prepared products were determined by ^{1}H NMR spectroscopy in deuterd methanol (with Me_4Si as internal standard) and IR spectroscopy using KBr.

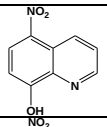
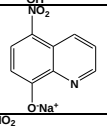
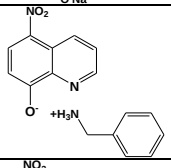
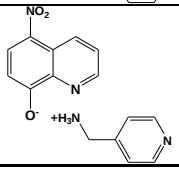
The solubility of the prepared salts and mother compounds (Nitroxoline™, and 2A8OHQ) was determined gravimetrically from saturated solutions at 25 °C, after filtration and evaporation.

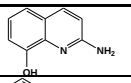
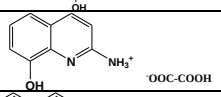
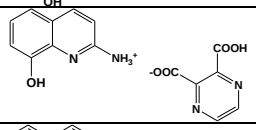
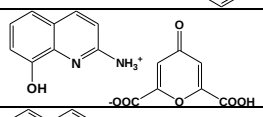
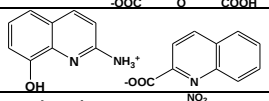
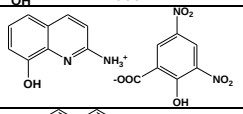
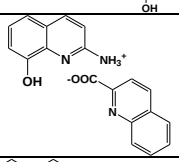
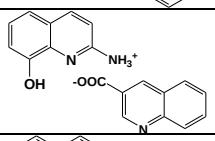
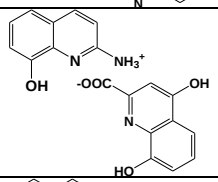
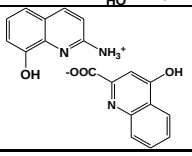
Antibacterial activity of prepared salts was screened on eight bacterial strains: *Klebsiella pneumonae*—two different strains No.: 4498 *and 4352*, *Klebsiella oxytoca* strain No.: 3541, *Klebsiella aerogenes* strain No.: 500, *Pseudomonas aeruginosa* strain No.: 3396, *Acinetobacter baumannii* strain No.: 3333, vancomycin-resistant *Enterococcus* strain No.: 636 and *Staphylococcus aureus* strain No.: 1942 in accordance with CLSI norm

3. Results

In the first phase, three basic salts of Nitroxoline™ with sodium hydroxide, benzylamine, 4-(aminomethyl)pyridine and other primary amines were synthesized. Within the second phase opposite, nine acidic salts of 2-aminoquinolin-8-ol were synthesized with following acids: oxalic acid, pyrazine-2,3-dicarboxylic acid, chelidonic acid, quinaldic acid, 3,5-dinitrosalycilic acid, quinoline-2-carboxylic acid, quinoline-3-carboxylic acid, xanthurenic acid and finally with kynurenic acid (Table 1).

Table 1. Structures of NQ, 2A8OHQ and synthesized salts.

Code	Compound	Structure
NQ	Nitroxoline™	
NQs1	Nitroxoline™, natrium salt	
NQs2	Nitroxoline™ salt with 4-benzylamine	
NQs3	Nitroxoline™ salt with, 4-(aminomethyl)pyridine	

2A8OHQ	2-Amino-8-hydroxyquinoline	
2A8OHQs1	2-Amino-8-hydroxyquinoline salt with oxalic acid	
2A8OHQs2	2-Amino-8-hydroxyquinoline salt with 2,3-pyrazinedicarboxylic acid	
2A8OHQs3	2-Amino-8-hydroxyquinoline salt with chelidonic acid	
2A8OHQs4	2-Amino-8-hydroxyquinoline salt with quinalid acid	
2A8OHQs5	2-Amino-8-hydroxyquinoline salt with 3,5-dinitrosalicylic acid	
2A8OHQs6	2-Amino-8-hydroxyquinoline salt with quinoline-2-carboxylic acid	
2A8OHQs7	2-Amino-8-hydroxyquinoline salt with quinoline-3-carboxylic acid	
2A8OHQs8	2-Amino-8-hydroxyquinoline salt with xanthurenic acid	
2A8OHQs9	2-Amino-8-hydroxyquinoline salt with kynurenic acid	

Mainly monocarboxylic aromatic acids with higher pKa values were selected for random synthesis of the salts of 2-aminoquinolin-8-ol. The products were brown or yellow crystals with moderate yield (50–75%) of sufficient purity over 95%. The solubility of prepared salts were in narrow spectrum of values and evident is increasing comparing to "mother" molecule, the solubility of Nitroxoline™ vs Nitroxoline™ salts, 0.03 g/L vs. 0.5–1 g/L. Similarly, 0.2 g/L for 2A8OHQ vs about 2 g/L for its salts.

All compounds of sufficient amount and purity were subjected to evaluation of antibacterial activity on eight selected bacterial strains—nosocomial, problematic infects. The results of antibacterial activity of standards—NQ, 2A8OHQ and 12 prepared salts and two mother compounds are in Table 2.

Table 2. Antibacterial activity of NQ, 2A8OHQ and prepared salts.

Strain No.:/	MIC (mg/L)							
Compound Code	4498	3541	500	3396	3333	636	1942	4352
NQ	32	16	16	16	8	16	8	32
NQs1	8	8	12	32	4	8	4	12
NQs2	16	16	8	32	8	8	4	8
NQs3	32	8	8	32	8	8	4	8
2A8OHQ	64	64	32	64	32	16	64	64
2A8OHQs1	64	32	32	64	32	16	32	64
2A8OHQs2	32	32	32	64	32	16	32	64
2A8OHQs3	64	32	32	64	32	8	32	64
2A8OHQs4	32	32	32	64	32	8	32	64
2A8OHQs5	32	32	32	32	32	16	32	64
2A8OHQs6	64	32	32	64	32	16	32	64
2A8OHQs7	64	32	32	64	32	4	16	64
2A8OHQs8	32	32	32	64	32	16	32	64
2A8OHQs9	64	32	32	64	32	4	16	64

Results presented in Table 2 shows all prepared salts are comparable or with lower MIC values, what means higher antibacterial activity. From the achieved results it is evident flat effect of both compounds and prepared salts from "mother"'s compounds.

4. Discussion

This short paper revealed the simple synthesis of perspective salts of "mother"'s molecules/compounds/, particularly Nitroxoline™ and 2-aminoquinolin-8-ol. Whereas Nitroxoline™ is well known, frequently published and sufficiently published flat, moderate antibacterial effective clinically applied antibiotic, 2-aminoquinolin-8-ol is less potent but flat antibacterial effective compound with the perspectives of more effective derivatives or salts. This study represents only brief, preliminary screening of three salts of Nitroxoline and nine slats of 2A8OHQ to demonstrate a presentiveness of this direction. The significant increase of water solubility (at least ten times) and conservation or improvement of antibacterial potency it is really evident.

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