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Modified POM Analysis of Substituted 8-Hydroxyquinolines as Perspective Antibacterial Agents In Silico and Their In Vitro Antibacterial Activity Screening

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Abstract: The collection of forty-nine 8-hydroxyquinoline derivatives, substituted at C5, C6 or C7, **was designed and studied** by computational methods of **modified POM analysis, using** SwissADME, Osiris and Molinspiration tool. POM analysis (Petra/Osiris/Molinspiration) and its modified version using SwissADME instead of Petra software are indisputably tools of modern chemoinformatics, often published in the professional literature as well as in the field of research of new antibacterial active compounds, developed to replace existing antibiotics that fail due to increased resistance of bacteria. Nitroxoline™ and the group of 8-hydroxyquinoline derivatives with their broad antibacterial effect and the possibility of extensive derivatization of the skeleton, represent a promising direction in the research of new antibacterial active substances. Twenty 8-hydroxyquinoline derivatives were also evaluated on their antibacterial activity against **eight selected** G^+ and G^- **bacterial strains with a defined resistance mechanism.** All structures were in accordance with Lipinski's criteria, twenty-one structures were interesting from the point of view of individual or average value of the bioactivity prediction score and fourteen structures showed one or more mechanisms of toxicity prediction. Furthermore, eleven structures showed a low rate of GI absorption or the inability to cross the BBB barrier, fourteen substances showed a BRENK or PAIN warning, eleven substances are an undesirable substrate of P-glycoprotein and all structures predicted the same level of bioavailability and a relatively low rate of metabolism in the liver. Five structures were selected by the intersection of the POM criteria. The virtual structures **17**, **25**, **35** and **43** can be favored for the continuity of next study. The resulting scores of bioactivity can indicate the potential of studied structures to be used for the design and development of new active antibacterial agents.

Keywords: quinoline; antibacterial activity; swissadme; osiris; molinspiration; in silico

1. Introduction

Overuse or inappropriate prescribing of antibiotics as well as the extensive agricultural use caused the development of antibiotic resistance [1,2], which becomes a globally important problem. A growing number of infections are becoming harder to treat and may even be untreatable with conventional antibiotics, as the antibiotics used to treat them become less effective. The search for new structures with antibacterial efficacy as perspective antibiotic candidates is becoming a research challenge. The next strategy lies in the revisiting known classes of antibacterial agents. Quinoline derivatives are known for their antibacterial activity [3,4] and some quinolone derivatives show promising activity against multidrug-resistant strains [5].

8-Hydroxyquinoline 1 (Figure 1) and its derivatives represent an important subgroup of the quinoline family. 8-Hydroxyquinoline derivatives become important because of their significant

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biological activity, such as antiviral [6], antibacterial [7–9], antifungal [10], antioxidant [11–13] or anticancer [14,15]. The 8-hydroxyquinoline scaffold is regarded as a privileged structure due to its chemical accessibility and broad scope of potential medicinal applications. The antibacterial activity of 8-hydroxyquinoline derivatives is well-known since long time. Nitroxoline™ (5-nitro-8-hydroxyquinoline) and clioquinol (5-chloro-7-iodo-8-hydroxyquinoline) are well-known therapeuticals to treat microbial infections [16]. The rediscovery of quinoline derivatives could be therefore an interesting strategy to synthesize new antibacterial agents. Increasing their effectiveness by structural modifications can play the profound role in treating the infections, caused by multidrug-resistant strains.

The main problems of the synthetic drugs are associated with their possible side effects. The potential drug should have good biological activity with good pharmacokinetic properties and should be non-toxic. To estimate rapidly potential biological activity and pharmacokinetic properties of new compounds to be synthetized, various *in silico* techniques and tools are known [17]. Petra, Osiris and Molinspiration (POM) analysis represents a frequently published and well-established *in silico* tool to access the pharmacokinetic profile of the synthesized molecules [18,19]. Molinspiration Cheminformatics [20] free web application has been designed for the prediction of Lipinski parameters [21,22] to evaluate the druglikeness of screened compounds (drawn as structures) as well as for the prediction of bioactivity score for important drug targets. Osiris Property Explorer [23] is a free accessible tool for predicting toxicological properties (mutagenic effect, tumorigenicity, irritancy, and reproductive toxicity) as well as various physicochemical properties, finally expressed as a complex drug score. Petra program package comprises various empirical methods for the calculation of physicochemical properties in organic molecules. [24]. Petra software has been replaced by some authors with one of Swiss Drug Design tools [25]. Thus, SwissADME [26–29] or SwissTargetPrediction softwares [30] were used. The term "modified" or "adapted" POM analysis [28,29] is used for the simultaneous use of SwissADME, Osiris and Molinspiration. The SwissADME web tool enables the computation of key physicochemical, pharmacokinetic, drug-like and related parameters and prediction of ADME parameters for one or multiple molecules [31].

The main goal of this study was to discover the role of an additional substituent on benzene ring of 8-hydroxyquinoline core, mainly at C5 position, to druglikeness, drug score and pharmacological properties of the 8-hydroxyquinoline core by computational methods using SwissADME, Osiris and Molinspiration tools and to realize a prediction to reveal the most promising derivatives, possessing plausible ADME parameters and non-toxic as potential drug candidates. Finally, the goal of our research was to determine the biological activity of a collection of 8-hydroxyquinolines to selected bacterial strains and make such guideline and proposal for following collection of the compounds.

2. Results

2.1. Antibacterial Activity

The results of the antibacterial activity of twenty selected 8-hydroxyquinoline derivatives are given in Table 1. The activity is expressed by the MIC parameter in mg/L. A limited number of known 8-hydroxyquinoline derivatives were subjected to the screening with an intention of finding out whether the derivatization leads to the increase of antibacterial activity. The spectrum of selected quinoline derivatives cover substitution mainly at C5, with hydroxy group at C8 of quinoline skeleton (Figure 1).

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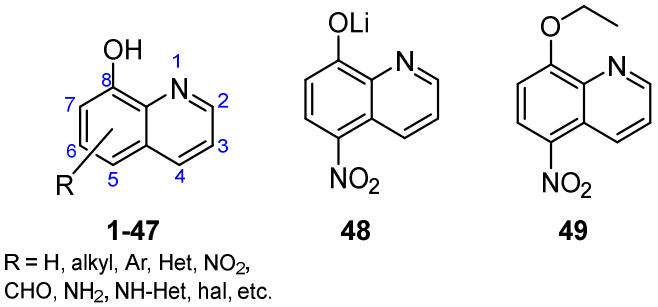

Figure 1. C5-C7 Substituted 8-hydroxyquinolines **1-47**, lithium 5-nitroquinolinate **48**, 8-ethoxy-5-nitroquinoline **49**.

According to the achieved results only 8-hydroxyquinoline-5-carbaldehyde **14** expressed antibacterial activity (MIC = 1-32 mg/L) comparable to clinical standard Nitroxoline™ **47** (MIC = 2.1-11.4 mg/L). Four compounds **30, 32, 36** and **37** express a complete lack of antibacterial activity. Other compounds either expressed only marginal antibacterial activity in the range over 128 mg/L or targeted only one to five selected bacterial strains.

Table 1. Antibacterial activity of tested 8-hydroxyquinolines on eight selected bacterial strains expressed via MIC parameter in mg/L. "Over" means MIC parameter over 256 mg/L. Compounds are ranked in order of decreasing number of targeted strains and efficiency, expressed as average MIC value (MIC_{av}).

No.	R (or name) \ Strain No.:	1	2	3	4	5	6	7	8	MIC_{av}
		2151	3541	500	3396	3333	636	1942	3401	
		MIC (mg/L)								
47	5-NO_2 (Nitroxoline™)	11.4	7.1	3.7	8.9	3.5	4.2	2.1	6.7	5.95
14	5-CHO	16	16	16	32	4	1	4	16	13.13
48	(Lithium 8-Quinolinolate)	64	32	64	96	8	256	128	64	89.00
28*	5-$NH_3^+Cl^-$	128	128	128	64	48	64	64	128	94.00
15*	5-CH_2Cl	256	256	256	384	48	64	256	256	222.00
33	5-CH=N-NHCO-(furan-2-yl)	64	64	64	64	32	64	32	over	54.86
46	7-Br	48	32	over	over	16	12	2	48	26.33
34	5-CH_2(morpholin-4-yl)	128	over	over	32	64	over	64	over	72.00
31	5-N=N-(C_6H_4-4-SO_3H)	over	over	over	64	128	128	512	over	208.00
1	H	48	over	over	384	48	over	over	over	160.00
29	5-NH(2-oxo-2,5-dihydro-1*H*-pyrrol-4-yl)	over	over	over	32	over	over	32	over	32.00
49	(8-Ethoxy-5-nitroquinoline)	over	over	over	over	over	64	256	over	160.00
17*	5-$CH_2NH_3^+Cl^-$	over	over	over	over	over	8	over	over	8.00
16	5-CH_2NH_2	over	over	over	32	over	over	over	over	32.00
13	5-$SO_3H.H_2O$	over	128	over	over	over	over	over	over	128.00
35	5-CH_2NHCOPh	over	over	over	32	over	over	over	over	32.00
30	5-(3-oxo-7-CO_2Me-pyrazolo[4,3-*c*]pyridin-5-yl)	over	over	over	over	over	over	over	over	-
32	5-N=N-(C_6H_4-3-COOH)	over	over	over	over	over	over	over	over	-
36	5-CH_2NHCO(7-oxoazepan-2-yl)	over	over	over	over	over	over	over	over	-
37	5-CH_2S(benzothiazol-2-yl)	over	over	over	over	over	over	over	over	-

over - MIC value over 256 mg/L, *quinoline hydrochloride.

The comparison of 8-hydroxyquinoline **1** and its lithium salt **48** is very interesting whereas lithium 8-quinolate exhibits antibacterial activity against all bacterial strains with MIC = 8 - 256 mg/L. It is evident, the presence of an oxygen atom as a significant H-bond acceptor at C8 position is necessary. On the other hand, when 8-hydroxy group is transformed to ethoxy, almost complete loss of antibacterial activity was observed. Thus 8-ethoxy-5-nitroquinoline **49**, compared to Nitroxoline™

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47 exhibits almost complete loss of antibacterial activity, except against *Enterococcus faecium* (MIC = 64 mg/L).

It is important to keep in mind the possibilities of chemical synthesis of quinoline derivatives with substituent in individual position of the benzene ring. Position C7 is relatively perspective beside the positions C5 and C8, whereas position C6 is more difficult to make a derivatization.

2.2. In Silico Calculations

Software Osiris [32] and two free web applications: Molinspiration [20], and SwissADME [33] were used to find the 8-hydroxyquinoline-based structure with physicochemical parameters and biological properties promising candidate to the antibacterial agent. The collection of forty-seven derivatives of 8-hydroxyquinoline, bearing one substituent at C5, C6 or C7 carbon, respectively was used for calculations *in silico*, as well as lithium 5-nitroquinolinate **48** and 8-ethoxy-5-nitroquinoline **49** (Figure 1). All structures represent two subgroups: the first of them includes structures used only for *in silico* study. They have been chosen from SciFinder database [34] with a view to their possible synthetic accessibility, but their antibacterial activity evaluation is not a part of this work. The second one represents 8-hydroxyquinoline structures that underwent also antibacterial activity screening (Table 1) and these structures are highlighted in bold in Tables 2–5.

2.2.1. Molinspiration Calculations

The results of the MOLINSPIRATION calculations showed none of the modeled structures have any violation according to RO5. The calculated logP values for investigated structures **1-49** are in -1.38 to 4.68 range, which is in accordance with RO5 for the drugs to be able to penetrate through biomembranes to various compartments. 5-(Chloromethyl)quinolin-8-ol hydrochloride **15** or dihydrochlorides **17** and **28**, 8-hydroxyquinoline-5-sulfonic acid monohydrate **13** as well as lithium 8-quinolate **48** are highly hydrophilic molecules with LogP of range from -0.30 to -1.38 values. The molecular weights of proposed structures **1-49** vary from 145.16 to 324.43, indicating that they are rather low molecular weight compounds. The values of TPSA of **1-49** are of 33.12 - 112.22 Å^2 range, which is also in the proposed standards (TPSA < 140 Å^2) for good oral bioavailability [35]. The number of hydrogen bond acceptors (O and N atoms) of all structures **1-49** was found under 8 and the number of hydrogen bond donors (NH and OH) varies from 0 to 5, which is in accordance with RO5. The results of Lipinski parameters calculations for 8-hydroxyquinoline structures **1-49** are given in Table 2.

Table 2. MOLINSPIRATION calculations of molecular properties of 8-hydroxyquinolines **1-49**.

No.	R	LogP	TPSA	nAT	MW	nA	nD	nviol	nRB	Vol
1	**H**	1.68	33.12	11	145.16	2	1	0	0	131.90
2	5-CH_3	2.38	33.12	12	159.19	2	1	0	0	148.46
3	5-$CH(CH_3)_2$	2.97	33.12	14	187.24	2	1	0	1	181.85
4	5-$C(CH_3)_3$	3.64	33.12	15	201.27	2	1	0	1	198.08
5	7-CH_2CH=$CHCH_3$	2.70	33.12	15	199.25	2	1	0	2	192.68
6	5-(cyclopenthen-1-yl)	2.83	33.12	16	211.26	2	1	0	1	198.88
7	5-cyclohexen-1-yl	3.81	33.12	17	225.29	2	1	0	1	215.68
8	5-Ph	3.73	33.12	17	221.26	2	1	0	1	203.31
9	7-Ph	3.42	33.12	17	221.26	2	1	0	1	203.31
10	6-COOH	1.54	70.42	14	189.17	4	2	0	1	158.90
11	7-COOH	1.62	70.42	14	189.17	4	2	0	1	158.90
12	5-SO_2NH_2	0.62	93.28	15	224.24	5	3	0	1	174.62
13	**5-$SO_3H.H_2O$**	-1.08	87.49	15	225.22	5	2	0	1	171.35
14	**5-CHO**	1.72	50.19	13	137.17	3	1	0	1	150.88
15*	**5-CH_2Cl**	-0.30	34.37	13	194.64	2	2	0	1	165.09
16	**5-CH_2NH_2**	1.11	59.14	13	174.20	3	3	0	1	159.99

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17*	**5-$CH_2NH_3^+Cl^-$**	-1.37	62.01	13	176.22	3	5	0	1	163.64
18	5-OH	1.71	53.35	12	161.16	3	2	0	0	139.91
19	5-CH_2OH	1.27	53.35	13	175.19	3	2	0	1	156.72
20	5-$(CH_2)_2OH$	1.47	53.35	14	189.52	3	2	0	2	173.52
21	5-CH_2COOH	1.35	70.42	15	203.20	4	2	0	2	175.70
22	5-$(CH_2)_2COOH$	1.87	70.42	16	217.22	4	2	0	3	192.50
23	6-(C_6H_4-3-COOH)	3.31	70.42	20	265.27	4	2	0	2	230.31
24	5-C≡C-(4-pyridyl)	2.07	46.01	19	246.27	3	1	0	0	221.29
25	5-C≡C-[4,6-$(OMe)_2$-1,3,5-triazin-2-yl]	1.58	90.26	23	308.30	7	1	0	2	264.07
26	**5-NH_2**	1.41	59.14	12	160.18	3	3	0	0	143.19
27	6-NH_2	0.70	59.14	12	160.18	3	3	0	0	143.19
28*	**5-$NH_3^+Cl^-$**	-1.27	62.01	12	162.19	3	5	0	0	146.84
29	**5-NH(2-oxo-2,5-dihydro-1*H*-pyrrol-4-yl)**	1.38	74.25	18	241.25	5	3	0	2	209.06
30	**5-(3-oxo-7-CO_2Me-pyrazolo[4,3-*c*]pyridin-5-yl)**	0.52	110.11	25	336.31	8	2	0	3	277.01
31	**5-N=N-(C_6H_4-4-SO_3H)**	1.11	112.22	23	329.34	7	2	0	1	261.86
32	**5-N=N-(C_6H_4-3-COOH)**	4.01	95.15	22	293.28	6	2	0	3	249.41
33	**5-CH=N-NHCO-(furan-2-yl)**	2.35	87.72	21	281.27	6	2	0	3	239.52
34	**5-CH_2(morpholin-4-yl)**	1.58	45.51	18	244.29	4	1	0	2	226.83
35	**5-$CH_2NHCOPh$**	2.52	62.22	21	278.31	4	2	0	3	251.49
36	**5-CH_2NHCO(7-oxoazepan-2-yl)**	1.32	91.32	32	313.36	6	3	0	3	284.66
37	**5-CH_2S(benzothiazol-2-yl)**	4.68	46.01	22	324.43	3	1	0	3	268.78
38	5-(benzimidazol-2-yl)	3.54	61.80	20	261.28	4	2	0	1	228.13
39	5-(4-pyridyl)	2.44	46.01	17	222.25	3	1	0	1	199.15
40	6-(3-pyridyl)	2.35	46.01	17	222.25	3	1	0	1	199.15
41	5-(indol-2-yl)	3.83	48.91	20	260.30	3	2	0	1	232.28
42	5-(imidazol-1-yl)	1.47	50.95	16	211.22	4	1	0	1	184.52
43	6-(5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)	3.63	61.80	21	340.18	4	2	0	1	246.01
44	7-(2-NH_2-1*H*-benzimidazol-1-yl)	2.48	76.97	21	276.30	5	3	0	1	239.80
45	5-Cl	2.61	33.12	12	179.61	2	1	0	0	145.43
46	**7-Br**	2.44	33.12	12	224.06	2	1	0	0	149.78
47	**5-NO_2**	1.89	78.94	14	190.16	5	1	0	1	155.23
48	**(Lithium 8-quinolate)**	-1.38	35.95	11	144.15	2	0	0	0	129.15
49	**(8-ethoxy-5-nitroquinoline)**	2.54	67.95	16	218.21	5	0	0	3	189.56

LogP - Octanol-water partition coefficient, **TPSA**- Total polar surface area, **nAT** - Number of heavy atoms, **MW** - Molecular weight, **nA** - Number of hydrogen-bond acceptors (O and N atoms), **nD** -Number of hydrogen-bond donors (OH and NH groups), **nviol -** Number of RO5 violations **nRB** - Number of rotatable bonds, **Vol** - Molecular volume, *quinoline hydrochloride.

The results of MOLINSPIRATION bioactivity score prediction show that proposed 8-hydroxyquinolines **1-49** are good candidates to interact mainly with various enzymatic targets, receptor ligands, or ion channels as indicated in Table 3. 8-Hydroxyquinoline **1** score in

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Molinspiration as a protease inhibitor (PI) is -1.07 and as an enzyme inhibitor (EI) is - 0.12, which indicate low activity. Comparable negative score results were obtained for salt **48**.

Table 3. MOLINSPIRATION bioactivity scores of 8-hydroxyquinolines **1**-**49**.

No.	R	GPCR	ICM	KI	NRL	PI	EI
1	**H**	-0.56	-0.11	-0.49	-0.86	-1.07	-0.12
2	5-CH_3	-0.58	-0.26	-0.50	-0.67	-1.02	-0.18
3	5-$CH(CH_3)_2$	-0.26	0.04	-0.29	-0.31	-0.64	0.07
4	5-$C(CH_3)_3$	-0.15	0.23	-0.10	-0.19	-0.58	0.15
5	7-CH_2CH=$CHCH_3$	-0.23	0.08	-0.30	-0.31	-0.56	0.33
6	5-cyclopenthen-1-yl	0.36	0.36	0.34	0.17	-0.42	**0.66**
7	5-cyclohexen-1-yl	0.43	0.42	0.29	0.19	-0.22	**0.56**
8	5-Ph	0.03	0.19	0.26	0.05	-0.42	0.29
9	7-Ph	0.02	0.36	0.14	-0.06	-0.18	0.22
10	6-COOH	-0.26	-0.03	-0.30	-0.23	-0.66	0.15
11	7-COOH	-0.44	-0.01	-0.26	-0.52	-0.56	0.15
12	5-SO_2NH_2	-0.34	-0.16	-0.13	-0.84	-0.39	0.36
13	**5-$SO_3H.H_2O$**	0.03	0.12	-0.35	-0.93	-0.33	0.45
14	**5-CHO**	-0.48	-0.02	-0.29	-0.30	-0.98	-0.08
15*	**5-CH_2Cl**	-0.90	-0.02	-1.31	-1.72	-0.88	-0.32
16	**5-CH_2NH_2**	-0.19	0.16	-0.10	-0.88	-0.36	0.20
17*	**5-$CH_2NH_3^+Cl^-$**	-0.57	0.20	-1.00	-1.39	-0.81	0.08
18	5-OH	-0.43	0.08	-0.24	-0.61	-0.88	0.10
19	5-CH_2OH	-0.33	0.09	-0.28	-0.40	-0.50	0.15
20	5-$(CH_2)_2OH$	-0.17	0.18	-0.06	-0.22	-0.50	0.25
21	5-CH_2COOH	0.02	0.20	-0.20	0.13	-0.29	0.32
22	5-$(CH_2)_2COOH$	0.14	0.18	-0.13	0.17	-0.20	0.33
23	6-(C_6H_4-3-COOH)	0.21	0.16	0.34	0.33	-0.09	0.39

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24	5-C≡C-(4-pyridyl)	0.34	0.27	0.44	0.28	-0.03	0.49
25	5-C≡C-[4,6-(OMe)$_2$-1,3,5-triazin-2-yl]	**0.66**	0.13	**0.52**	0.26	-0.01	**0.56**
26	**5-NH$_2$**	-0.32	0.18	-0.06	-1.04	-0.96	0.19
27	6-NH$_2$	-0.35	0.10	-0.06	-0.88	-0.76	0.16
28*	**5-NH$_3^+$Cl$^-$**	-0.78	-0.28	-0.27	-0.72	-1.03	-0.20
29	**5-NH(2-oxo-2,5-dihydro-1*H*-pyrrol-4-yl)**	-0.10	0.11	-0.03	-0.55	-0.54	0.04
30	**5-(3-oxo-7-CO$_2$Me-pyrazolo[4,3-c]pyridin-5-yl)**	0.02	0.03	0.32	-0.18	-0.49	0.31
31	**5-N=N-(C$_6$H$_4$-4-SO$_3$H)**	0.19	0.14	0.15	-0.65	0.07	0.36
32	**5-N=N-(C$_6$H$_4$-3-COOH)**	0.06	0.02	0.22	-0.25	-0.15	0.24
33	**5-CH=N-NHCO-(furan-2-yl)**	-0.30	-0.91	-0.49	-0.65	-0.84	-0.41
34	**5-CH$_2$(morpholin-4-yl)**	0.06	0.02	0.14	-0.18	-0.23	0.17
35	**5-CH$_2$NHCOPh**	0.12	0.01	0.17	-0.05	-0.03	0.17
36	**5-CH$_2$NHCO(7-oxoazepan-2-yl)**	0.34	0.10	0.09	0.01	0.36	0.27
37	**5-CH$_2$S(benzothiazol-2-yl)**	-0.26	-0.84	-0.14	-0.25	-0.33	0.02
38	5-(benzimidazol-2-yl)	0.33	0.18	**0.56**	0.07	-0.26	0.42
39	5-(4-pyridyl)	0.05	0.24	0.36	0.04	-0.41	0.34
40	6-(3-pyridyl)	0.19	0.39	**0.53**	0.05	-0.22	0.46
41	5-(indol-2-yl)	0.43	0.21	**0.74**	0.41	-0.14	0.43
42	5-(imidazol-1-yl)	0.05	0.27	0.10	-0.63	-0.61	0.37
43	6-(5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)	0.34	0.38	**1.09**	0.00	-0.22	**0.68**
44	7-(2-NH$_2$-1*H*-benzimidazol-1-yl)	0.30	0.16	**0.56**	-0.26	-0.15	0.30
45	5-Cl	-0.59	-0.04	-0.64	-0.70	-0.97	-0.10
46	**7-Br**	-0.74	-0.27	-0.56	-0.97	-1.15	-0.27
47	**5-NO$_2$**	-0.61	-0.04	-0.37	-0.66	-0.99	-0.09
48	**Lithium 8-quinolate**	-0.72	-0.12	-0.58	-1.08	-1.02	-0.30
49	**8-ethoxy-5-nitroquinoline**	-0.56	-0.16	-0.39	-0.61	-0.90	-0.19

GPCR - GPCR ligand, **ICM-** ion channel modulator, **KI -** kinase inhibitor, **NRL -** nuclear receptor ligand, **PI -** protease inhibitor, **EI -** enzyme inhibitor. *quinoline hydrochloride.

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The addition of another substituent at C5, C6 or C7 carbons of the 8-hydroxyquinoline core increased the score for most of the studied compounds. Applying the score calculation to the commercially used antibiotic Nitroxoline™ (5-amino-8-hydroxyquinoline) **47** the PI = -0.99 and EI = -0.09 values were obtained. The attachment of alkyl, aromatic and carbocyclic groups generally increased the score (structures **2**-**9**). The presence of cyclopenthen-1-yl or cyclohexen-1-yl group at C-5 of quinoline core of **6** and **7**, respectively is particularly attractive, the calculated EI scores reached high values (0.66 and 0.56) as well as the GPCR, ICM or KI scores were found in 0.29-0.43 range. When alkyl or aryl is additionally substituted by OH, NH_2 or COOH groups (structures **17**, **19**-**23**) the score EI significantly increased (0.08 - 0.39). The introduction of carboxylic acid substituent (structures **10, 11**) is reflected in an increase in the score, and we found that the position of COOH at quinoline core has not much effect. 8-Hydroxyquinoline-derived sulfonamide **12** or sulfonic acid **13** achieved high scores in the EI section (0.36, 0.45). The sulfonamide group (–SO_2NH–) is present in many pharmacologically interesting compounds and well-established drugs with antibacterial, anticancer or COX-2 inhibition activities [36,37]. Triple bond was found as one of the structural units with the potential to increase the score of other modeled structures. Generally, acetylenic group of great interest in medicinal chemistry and the pharmaceutical industry [38]. It moreover functions as a key pharmacophoric unit in acetylenic antibiotics [39]. Propargylic chalcones were screened for antimycobacterial activity [40]. A high EI score (0.49 ad 0.56) was observed in the case of structures **24** and **25** with aryl-substituted ethynyl groups. Moreover, compound **25** had remarkable score as GPCR ligand (0.66) or kinase inhibitor (0.52). Various heteroaryl groups at C5, C6 or C7 of quinoline core led to positive EI as well as KI scores. Particularly in case of benzimidazol-2-yl group at C5 (structure **38**), 3-pyridyl group at C6 (structure **40**) or 7-(2-NH_2-1*H*-benzimidazol-1-yl) group at C6 (structure **44**), the EI scores are in 0.53-0.56 and KI scores are in 0.30-0.46 ranges, respectively. 8-hydroxyquinolines **41** with indol-2-yl group at C5 or **43** with 5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl group at C6 should be potential kinase inhibitors with 0.74 and 1.09 scores, respectively. Both **41** and **43** exhibit also high score as the enzyme inhibitors (0.43 and 0.68). The presence of halogen atom (structures **45** and **46**) does not affect positively the results and calculated scores are comparable to unsubstituted 8-hydroxyquinoline **1**.

2.2.2. Osiris Calculations

Osiris software was used primarily for the prediction of toxicity risks. The toxicity of a compound is determined by the mutagenicity, tumorigenicity, irritant and reproductive effects. Molecular properties, such as clog P, solubility, molecular weight, TPSA as well as drug score and drug likeness were also calculated. The results of OSIRIS software calculations for structures **1**-**49** are shown in Table 4.

Table 4. OSIRIS calculations of 8-hydroxyquinolines.

No.	R	MUT	TUM	IRR	RE	clogP	solub	MW	TPSA	DL	DS
1	**H**	●	●	●	●	1.63	-2.03	145.0	33.12	-1.55	0.12
2	5-CH_3	●	●	●	●	1.97	-2.37	159.0	33.12	-1.78	0.54
3	5-$CH(CH_3)_2$	●	●	●	●	2.82	-2.90	187.0	33.12	-1.55	0.52
4	5-$C(CH_3)_3$	●	●	●	●	3.21	-3.19	201.0	33.12	-4.48	0.43
5	7-CH_2CH=$CHCH_3$	●	●	●	●	3.05	-2.84	199.0	33.12	-3.69	0.46
6	5-cyclopenthen-1-yl	●	●	●	●	2.66	-3.02	211.0	33.12	-3.96	0.27
7	5-cyclohexen-1-yl	●	●	●	●	3.0	-3.29	225.0	33.12	-6.29	0.26
8	5-Ph	●	●	●	●	3.29	-4.11	221.0	33.12	-1.21	0.48
9	7-Ph	●	●	●	●	3.29	-4.11	221.0	33.12	-1.21	0.29
10	6-COOH	●	●	●	●	1.12	-2.04	189.0	70.42	-0.33	0.68
11	7-COOH	●	●	●	●	1.12	-2.04	189.0	70.42	-1.16	0.35
12	5-SO_2NH_2	●	●	●	●	0.39	-1.92	224.0	101.6	-0.14	0.7
13	5-$SO_3H.H_2O$	●	●	●	●	-0.6	-0.63	225.0	95.87	-2.64	0.31
14	**5-CHO**	●	●	●	●	1.56	-2.35	173.0	50.19	-3.4	0.29
15*	**5-CH_2Cl**	●	●	●	●	2.16	-3.14	193.0	33.12	-1.44	0.12

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16	**5-CH_2NH_2**	●	●	●	●	0.63	-1.99	174.0	59.14	-1.49	0.57
17*	**5-$CH_2NH_3^+Cl^-$**	●	●	●	●	0.63	-1.99	174.0	59.14	-1.49	0.57
18	5-OH	●	●	●	●	1.28	-1.73	161.0	53.35	-1.74	0.55
19	5-CH_2OH	●	●	●	●	1.03	-1.91	175.0	53.35	-1.44	0.57
20	5-$(CH_2)_2OH$	●	●	●	●	1.46	-2.02	189.0	53.35	-3.33	0.49
21	5-CH_2COOH	●	●	●	●	1.11	-2.0	203.0	70.42	-1.07	0.6
22	5-$(CH_2)_2COOH$	●	●	●	●	1.57	-2.27	217.0	70.42	-2.12	0.52
23	6-(C_6H_4-3-COOH)	●	●	●	●	2.77	-4.12	265.0	70.42	-3.97	0.4
24	5-C≡C-(4-pyridyl)	●	●	●	●	2.81	-2.27	246.0	46.01	-5.2	0.45
25	5-C≡C-[4,6-$(OMe)_2$-1,3,5-triazin-2-yl]	●	●	●	●	2.62	-2.03	308.0	90.25	-5.05	0.27
26	**5-NH_2**	●	●	●	●	0.95	-2.1	160.0	59.14	-1.73	0.55
27	6-NH_2	●	●	●	●	0.95	-2.1	160.0	59.14	-1.26	0.47
28	**5-$NH_3^+Cl^-$**	●	●	●	●	0.95	-2.1	160.0	59.14	-1.73	0.55
29	**5-NH(2-oxo-2,5-dihydro-1*H*-pyrrol-4-yl)**	●	●	●	●	0.69	-2.45	241.0	74.25	0.52	0.76
30	**5-(3-oxo-7-CO_2Me-pyrazolo[4,3-c]pyridin-5-yl)**	●	●	●	●	0.15	-3.13	336.0	104.1	2.64	0.84
31	**5-N=N-(C_6H_4-4-SO_3H)**	●	●	●	●	1.5	-3.12	329.0	120.5	-10.18	0.06
32	**5-N=N-(C_6H_4-3-COOH)**	●	●	●	●	3.32	-4.53	293.0	95.14	-8.29	0.08
33	**5-CH=N-NHCO-(furan-2-yl)**	●	●	●	●	2.36	-3.81	291.0	87.72	4.55	0.82
34	**5-CH_2(morpholin-4-yl)**	●	●	●	●	1.22	-1.61	244.0	45.59	1.52	0.87
35	**5-$CH_2NHCOPh$**	●	●	●	●	2.49	-3.35	278.0	62.22	1.63	0.79
36	**5-CH_2NHCO(7-oxoazepan-2-yl)**	●	●	●	●	0.91	-2.95	313.0	91.32	-3.62	0.46
37	**5-CH_2S(benzothiazol-2-yl)**	●	●	●	●	4.09	-5.29	324.0	99.55	0.91	0.5
38	5-(benzimidazol-2-yl)	●	●	●	●	2.87	-4.38	261.0	61.8	0.65	0.63
39	5-(4-pyridyl)	●	●	●	●	2.29	-3.32	222.0	46.01	-1.47	0.52
40	6-(3-pyridyl)	●	●	●	●	2.29	-3.32	222.0	46.01	0.15	0.67
41	5-(indol-2-yl)	●	●	●	●	3.42	-4.33	260.0	48.91	1.7	0.41
42	5-(imidazol-1-yl)	●	●	●	●	1.25	-4.13	211.0	50.94	1.36	0.75
43	6-(5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)	●	●	●	●	3.34	-5.52	339.0	61.80	-1.58	0.35
44	7-(2-NH_2-1*H*-benzimidazol-1-yl)	●	●	●	●	2.38	-5.87	276.0	7696	0.96	0.52
45	**5-Cl**	●	●	●	●	2.24	-2.76	179.0	33.12	-1.58	0.32
46	**7-Br**	●	●	●	●	2.36	-2.86	223.0	33.12	-3.53	0.46
47	**5-NO_2**	●	●	●	●	0.71	-2.49	190.0	78.94	-6.95	0.47
48	**Lithium 8-quinolate**	●	●	●	●	0.05	-2.03	151.0	35.95	-5.03	0.49
49	**8-ethoxy-5-nitroquinoline**	●	●	●	●	1.39	-3.1	218.0	69.74	-8.05	0.45

MUT- mutagenicity, **TUM**- tumorigenicity, **IRR-** irritant, **RE** – reproductive effect, **cLogP** - octanol-water partition coefficient, **solub** – solubility, **MW** – molecular weight, **TPSA**- Total polar surface area, **DL**-druglikeness, **DS** – drug score. * - quinoline hydrochloride.

Toxicity risk analysis using Osiris software showed most of studied structures exhibit low risk of mutagenicity, tumorigenicity, irritation and reproductive effects. A high risk of being mutagenic was calculated for seven compounds: 8-hydroxyquinoline **1** and its derivatives with the presence of either chlorine atom or sulfonic and formyl groups or N=N structural unit (**13-15**, **27, 31, 32** and **45**). Only three compounds were identified as the irritants. Except 8-hydroxyquinoline **1,** the irritant effect was calculated for compound **25** with C≡C – linked triazinyl substituent and for azo-derivative **31.**

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The Osiris analysis indicates a high risk in the category of tumorigenicity for compounds **1**, **9** (7-Ph), **11** (7-COOH), **15** (5-CH_2Cl), **31** and **32** (azo-compounds).

Finally, the high risk of being reproductive toxic was observed at compounds **6** and **7** (5-cycloalkyl), **15** (5-CH_2Cl), **31** and **32** (azo-compounds) or **41** (5-indol-2-yl). In general, studied 8-hydroxyquinolines are low-toxic and safe compounds, excluding 8-hydroxyquinoline **1**, 5-chloromethyl-8-hydroxyquinoline **15** and both azo-derivatives: 4-[2-(8-hydroxyquinolin-5-yl)diazen-1-yl]benzene-1-sulfonic acid **31** and 3-[2-(8-hydroxyquinolin-5-yl)diazen-1-yl]benzoic acid **32**, which exhibit the high risk at least in three categories. On the other hand, when 8-hydroxyquinoline **1** was transformed to the lithium salt **48**, toxicity risk was significantly reduced.

The Osiris data (Table 4) shows that the values of clogP, TPSA and MW are in the optimal range. All studied 8-hydroxyquinolines **1-49** were found to be within the range of lipophilicity (< 5). The acceptable TPSA value (< 140) and molecular weight (<500) were also observed for all studied compounds **1-49**. Solubility values of compounds **37, 43, 44** are found out of the optimal range (< 5). Overall drug score values are calculated from drug-likeness, cLogP, logS, molecular weight and toxicity risks. The overall drug score indicates the potential of the compound to qualify as a drug. Among studied 8-hydroxyquinolines, structures **10** (6-COOH), **12** (5-SO_2NH_2), **21** (5-CH_2COOH), **29** and **30** (5-pyrrole or pyrazole derived substituents), **33-35** (5-C-linked heteroaryl substituents), **38**, **40** and **42** (5- or 6-heterocyclic substituents) exhibit good drug score.

2.2.3. SwissADME Calculations

The SwissADME calculations served to the study of modeled 8-hydroxyquinolines **1-48** from a pharmacokinetic point of view, including medicinal chemistry and drug-likeness score calculation parameters. The results are presented in Table 5.

Table 5. The SwissADME calculations of 8-hydroxyquinolines **1-49**.

No.	R	GI	BBB	Pgp	CYP	Lipinski	Ghose	Veber	Egan	Muegge	PAINS	Brenk	LL	SA	LogKp	BA
1	**H**	H	Y	N	Y,N,N,N,N	Y	N	Y	Y	N	0	0	N	1.07	-5.75	0.55
2	5-CH_3	H	Y	N	Y,N,N,N,N	Y	Y	Y	Y	N	0	0	N	1.13	-5.59	0.55
3	5-$CH(CH_3)_2$	H	Y	N	Y,N,N,N,N	Y	Y	Y	Y	N	0	0	N	1.38	-5.22	0.55
4	5-$C(CH_3)_3$	H	Y	N	Y,N,N,N,N	Y	Y	Y	Y	Y	0	0	N	1.48	-4.91	0.55
5	7-$CH_2CH{=}CHCH_3$	H	Y	N	Y,N,N,N,N	Y	Y	Y	Y	N	0	1	N	1.82	-5.17	0.55
6	5-cyclopenthen-1-yl	H	Y	Y	Y,Y,N,Y,N	Y	Y	Y	Y	Y	0	0	N	2.28	-5.33	0.55
7	5-cyclohexen-1-yl	H	Y	Y	Y,Y,N,Y,N	Y	Y	Y	Y	Y	0	0	N	2.35	-5.03	0.55
8	5-Ph	H	Y	N	Y,Y,N,Y,Y	Y	Y	Y	Y	Y	0	0	N	1.57	-5.07	0.55
9	7-Ph	H	Y	N	Y,Y,N,Y,Y	Y	Y	Y	Y	Y	0	0	N	1.67	-5.19	0.55

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10	6-COOH	H	Y	N	N,N,N,N,N	Y	Y	Y	Y	N	0	0	N	1.30	-6.49	0.85
11	7-COOH	H	Y	N	N,N,N,N,N	Y	N	Y	Y	N	0	0	N	1.33	-6.10	0.85
12	5-SO_2NH_2	H	N	N	N,N,N,N,N	Y	Y	Y	Y	Y	0	0	N	1.89	-7.62	0.55
13	**5-$SO_3H.H_2O$**	H	N	N	N,N,N,N,N	Y	Y	Y	Y	Y	0	1	N	1.94	-7.30	0.56
14	**5-CHO**	H	Y	N	Y,N,N,N,N	Y	Y	Y	Y	N	0	1	N	1.19	-6.20	0.55
15*	**5-CH_2Cl**	L	N	N	N,N,N,N,N	Y	N	Y	Y	N	0	1	N	1.57	-5.04	0.55
16	**5-CH_2NH_2**	H	Y	N	Y,N,N,N,N	Y	Y	Y	Y	N	0	0	N	1.27	-6.84	0.55
17*	**5-$CH_2NH_3^+Cl^-$**	L	N	N	N,N,N,N,N	Y	N	Y	Y	Y	0	0	N	1.42	-6.14	0.55
18	5-OH	H	Y	N	Y,N,N,N,N	Y	N	Y	Y	N	0	0	N	1.32	-6.84	0.55
19	5-CH_2OH	H	Y	N	Y,N,N,N,N	Y	Y	Y	Y	N	0	0	N	1.27	-6.66	0.55
20	5-$(CH_2)_2OH$	H	Y	N	Y,N,N,N,N	Y	Y	Y	Y	N	0	0	N	1.42	-6.33	0.55
21	5-CH_2COOH	H	Y	N	N,N,N,N,N	Y	Y	Y	Y	Y	0	0	N	1.48	-6.64	0.85
22	5-$(CH_2)_2COOH$	H	Y	N	N,N,N,N,N	Y	Y	Y	Y	Y	0	0	N	1.46	-6.38	0.85
23	6-(C_6H_4-3-COOH)	H	Y	N	Y,N,N,N,N	Y	Y	Y	Y	Y	0	0	Y	1.98	-5.80	0.85
24	5-C≡C-(4-pyridyl)	H	Y	N	Y,N,N,Y,Y	Y	Y	Y	Y	Y	0	1	N	2.20	-5.70	0.55
25	5-C≡C-[4,6-$(OMe)_2$-1,3,5-triazin-2-yl]	H	N	N	Y,N,Y,Y,Y	Y	Y	Y	Y	Y	0	1	Y	2.95	-6.25	0.55
26	5-NH_2	H	Y	N	Y,N,N,N,N	Y	Y	Y	Y	N	0	2	N	1.39	-7.36	0.55
27	6-NH_2	H	Y	N	Y,N,N,N,Y	Y	Y	Y	Y	N	0	1	N	1.32	-6.33	0.55

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28*	**5-$NH_3^+Cl^-$**	L	N	N	N,N,N,N,N	Y	N	Y	Y	Y	0	0	N	1.54	-6.66	0.55
29	**5-NH(2-oxo-2,5-dihydro-1*H*-pyrrol-4-yl)**	H	N	N	Y,N,N,N,N	Y	Y	Y	Y	Y	0	1	N	2.45	-7.23	0.55
30	**5-(3-oxo-7-CO_2Me-pyrazolo[4,3-c]pyridin-5-yl)**	H	N	N	N,N,N,N,N	Y	Y	Y	Y	Y	0	0	Y	2.56	-7.40	0.55
31	**5-N=N-(C_6H_4-4-SO_3H)**	L	N	N	N,N,N,N,N	Y	Y	Y	Y	Y	1	2	Y	2.79	-6.68	0.56
32	**5-N=N-(C_6H_4-3-COOH)**	H	N	N	Y,N,N,N,N	Y	Y	Y	Y	Y	1	1	Y	2.35	-5.90	0.56
33	**5-CH=N-NHCO-(furan-2-yl)**	H	N	N	Y,N,N,Y,N	Y	Y	Y	Y	Y	1	1	Y	2.68	-6.25	0.55
34	**5-CH_2(morpholin-4-yl)**	H	Y	Y	Y,N,N,N,N	Y	Y	Y	Y	Y	0	0	N	1.81	-6.83	0.55
35	**5-CH_2NHCOPh**	H	Y	N	Y,N,N,Y,Y	Y	Y	Y	Y	Y	0	0	Y	1.68	-6.11	0.55
36	**5-CH_2NHCO(7-oxoazepan-2-yl)**	H	N	Y	N,N,N,N,N	Y	Y	Y	Y	Y	0	0	Y	2.55	-7.42	0.55
37	**5-CH_2S(benzothiazol-2-yl)**	H	N	N	Y,Y,Y,Y,Y	Y	Y	Y	Y	Y	0	0	N	3.01	-5.33	0.55
38	5-(benzimidazol-2-yl)	H	Y	Y	Y,N,N,Y,Y	Y	Y	Y	Y	Y	0	0	Y	1.87	-5.72	0.55
39	5-(4-pyridyl)	H	Y	Y	Y,N,N,Y,Y	Y	Y	Y	Y	Y	0	0	N	1.54	-5.84	0.55
40	6-(3-pyridyl)	H	Y	Y	Y,N,N,Y,Y	Y	Y	Y	Y	Y	0	0	N	1.99	-5.96	0.55
41	5-(indol-2-yl)	H	Y	Y	Y,N,N,Y,Y	Y	Y	Y	Y	Y	0	0	N	2.01	-5.32	0.55
42	5-(imidazol-1-yl)	H	Y	N	Y,N,N,Y,Y	Y	Y	Y	Y	Y	0	0	N	1.74	-6.51	0.55
43	6-(5-bromo-1*H*-pyrrolo[2,3	H	Y	Y	Y,Y,N,Y,Y	Y	Y	Y	Y	Y	0	0	N	2.18	-5.86	0.55

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	-*b*]pyridin-3-yl)															
44	7-(2-NH_2-1*H*-benzimidazol-1-yl)	H	Y	Y	Y,Y,N,Y,Y	Y	Y	Y	Y	Y	0	0	Y	2.22	-6.10	0.55
45	5-Cl	H	Y	N	Y,N,N,N,N	Y	N	Y	Y	N	0	0	N	1.34	-5.35	0.55
46	**7-Br**	H	Y	N	Y,N,N,N,N	Y	N	Y	Y	Y	0	0	N	1.49	-5.87	0.55
47	**5-NO_2**	H	N	N	Y,N,N,N,N	Y	Y	Y	Y	N	0	1	N	1.67	-6.05	0.55
48	**lithium 8-quinolate**	H	Y	Y	N,N,N,N,N	Y	Y	Y	Y	N	0	0	N	1.26	-5.53	0.55
49	**8-ethoxy-5-nitroquinoline**	H	Y	N	Y,Y,N,N,N	Y	Y	Y	Y	Y	0	1	N	1.99	-5.73	0.55

GI- gastrointestinal absorption, **BBB**- blood brain barrier permeation, **Pgp** - P-glycoprotein substrate, **CYP**- cytochrome P450 (in exact order 1A2, 2C19, 2C9, 2D6, 3A4) inhibitors, **PAINS** - pan assay interference structures, **Brenk** - structural alert by Brenk, **LL**-leadlikeness, **SA**- synthetic accessibility, **LogK_P**- skin permeation (cm/s), **BA**- bioavailability score, **H**- high, **L**- low, **Y** – yes, **N** - no. *quinoline hydrochloride.

Most of studied 8-hydroxyquinolines showed good levels of gastrointestinal absorption, except **15**, **17, 28** and **31**. The ability to cross the blood–brain barrier (BBB) is assumed for most of the structures, mainly with alkyl, aryl or heteroaryl substituents, while 8-hydroxyquinoline derived amines (**17**, **28**, **29**)**,** sulfonic acids and sulfonamides **12**, **13** or azo-derivatives and hydrazide (**31-33**) were predicted to be unable to permeat the BBB. Most of studied structures were predicted not to be substrates of P-glycoprotein (P-gp), except some carbocycle or- heteroaryl substituted compounds, e.g. **6, 7, 34, 36, 38-41** or quinolate **48** and only **37** and **48,** respectively can be inhibitors of all five important CYP isoenzymes.

Calculation of druglikeness according to Lipinski, Ghose, Weber, Egan and Muegge filters showed, most of the studied compounds **1-49** should be convenient drug candidates, except compounds **1,11 18** and **45** which violate two filters or compounds **2,3, 10, 14, 17, 26-28** and **46** with one filter violation due to their low molecular weight or number of atoms. In the section of medicinal chemistry structural alert, consisting of the calculation of pan assays interference structure (PAINS) and Brenk structural alert, was calculated. Only three 8-hydroxyquinolines (**31-33**) were identified by PAINS alert due to the presence of N=N or C=N structural units. One or two Brenk alerts were found at thirteen quinoline derivatives (**5**, **13**-**15**, **24-27**, **29**, **31-33**, and **47**) related to the presence of C≡C, N=N, C=N structural units, C(H)=O, SO_3H, NO_2 substituents, and NH_2, NH or OH group at C5 which represents either aniline or hydroquinone structure together with 8-OH. Calculated results show criteria for leadlikeness accomplished for ten compounds and all studied molecules exhibit good skin permeation (LogK_P -4.03 to – 8.79), bioavailability score and synthetic accessibility.

Based on the SwissADME calculations, two compounds: (8-hydroxyquinolin-5-yl)acetic acid **21** and 3-(8-hydroxyquinolin-5-yl)propanoic acid **22** are suitable candidates as drug-like, because of high GI, positive BBB. Both compounds are neither P-gp substrates nor CYP 450 inhibitors, they exhibit positive drug-like parameters according to all five filters, good skin permeation and bioavailability score with no structural alerts. (8-Hydroxyquinolin-5-yl)acetic acid **21** was evaluated on the antibacterial activity against *Streptomyces mutans* [41] and was inactive. 3-(8-Hydroxyquinolin-5-yl)propanoic acid **22** was prepared and used in further synthesis of biologically active compounds [42] or metal complexes [43]. The biological activity of **22** has not been evaluated.

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3. Discussion

Twenty 8-hydroxyquinolines were randomly selected for the antibacterial activity screening on eight bacterial strains with clinically used antibiotic Nitroxoline™ (5-nitro-8-hydroxyquinoline) 47 as a standard. From the structural point of view, substituents on C5 (C7) of screened compounds represent a variety of structural units, from a single atom (Br) or simple functional group (NH_2, CHO, SO_3H) to more complex substituent with potentially beneficial effect to bioactivity. Thus, the presence of amino group [44] or halogen [45] is known to increase the biological activity of quinoline derivatives. 8-Hydroxyquinoline derived azo-compounds were screened for their antibacterial activity on *Staphylococcus aureus, Bacillus cereus,* and *Escherichia coli* [46] and biological activity of 8-hydroxyquinolines with heterocyclic substituents has been also studied [47,48].

According to the achieved results, summarized in Table 1, surprisingly significant differences among screened derivatives are evident, which could indicate unknown or multifactorial mechanism of antibacterial effect. Some of screened compounds express complete lack of antibacterial activity, particularly methyl 5-(8-hydroxyquinolin-5-yl)-3-oxo-2*H*,3*H*,5*H*-pyrazolo[4,3-*c*]pyridine-7-carboxylate **30**, 3-[(1*E*)-2-(8-hydroxyquinolin-5-yl)diazen-1-yl]benzoic acid **32**, *N*-[(8-hydroxyquinolin-5-yl)methyl]-7-oxoazepane-2-carboxamide **36** and 5-[(1,3-benzothiazol-2-ylsulfanyl)methyl]quinolin-8-ol **37**, what supports the significance of the substituents in mentioned positions. Other compounds either expressed only marginal antibacterial activity in the range over 128 mg/L or targeted only one to five selected bacterial strains. Surprisingly, only four derivatives expressed flat effect (on all eight bacterial strains), besides clinically approved antibiotic (our standard) Nitroxoline™: Lithium 8-quinolinolate **48**, 8-hydroxyquinoline-5-carbaldehyde **14,** 5-(chloromethyl)quinolin-8-ol hydrochloride **15** and 5-amino-8-hydroxyquinoline dihydrochloride **17**. Evidently, the substitution at C5 (besides hydroxyl at C8) is crucial for the antibacterial activity but depends on the character of substituent. Paradoxically, both types of substituents (H-bond donors and H-bond acceptors as well) could be efficient in C5 position, what can be illustrated by 5-nitro group of nitroxoline **47** and on the other hand by 5-amino group of **26**.

The comparison of 8-hydroxyquinoline **1** and its lithium salt **48** is very interesting, resulting to the flat effect/or increase of antibacterial activity in case on two bacterial strains. It is evident, the presence of oxygen atom as significant H-bond acceptor at C8 position is necessary. On the other hand, when 8-hydroxy group is transformed to ethoxy, almost complete loss of antibacterial activity was observed. Thus 8-ethoxy-5-nitroquinoline **49**, comparing to Nitroxoline™ **47** exhibit almost complete loss of antibacterial activity, except low activity against *Enterococcus faecium* 636 *and Staphylococcus aureus* 1942 (MIC 64 and 256 mg/L, respectively).

Study *in silico*, described in this work, is focused on 8-hydroxyquinoline derivatives, bearing one additional substituent at benzene ring, predominantly at C5, but also at C6 or C7 positions. Quinoline derivatives, substituted at benzene ring are known to exhibit antibacterial activity [49,50]. Some structural-activity relationship (SAR) studies of 8-hydroxyquinolines were accomplished. Warner [51] found a high inverse correlation between antibacterial activity against S. *mutans* No. 6715 with the size of the substituents in the C5 position of a series of 5-substituted 8-hydroxyquinolines. Anticancer activity of 8-hydroxyquinoline-derived Mannich bases has been studied [52] and SARs results displayed that upon replacement of either sulfonyl moiety with methylene or piperazine ring with ethylenediamine group led to an increase in activity. 8-Hydroxyquinolines with single halogen or other functional groups at either C5 or C7 positions as well as 5,7-dihalogenated 8-hydroxyquinolines exhibit antifungal activity against *C. auris,* but the majority of tested compounds without an C8-hydroxy group lacked activity [53]**.**

These results led us to realize more detailed calculations *in silico* to predict the influence of C-5, C-6 or C-7 substituent to ADME parameters and toxicity of 8-hydroxyquinoline core with the intention to find a good drug candidate. Because our work is focused on the prediction of pharmacological parameters, we applied the modified POM analysis, where the PETRA software was replaced by the SwissADME accessible web application [33]. In the Results section, our study deals with the druglikeness parameters, calculated by the Molinspiration web application and the OSIRIS

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program, as well as by the estimation of pharmacological and medicinal-chemical parameters, calculated by the SwissADME web application.

From the point of view of Molinspiration druglikeness calculations, the structural group of 8-hydroxyquinoline derivatives usually fits easily into Lipinski's criteria, which also corresponds to our findings (Table 2). From the point of view of the Molinspiration bioactivity prediction, it must be emphasized this is only a prediction in any case. Most of the compounds 2-49 present positive values of bioactivity scores in enzyme inhibition category in comparison with unsubstituted 8-hydroxyquinoline 1. (Table 3), which is consistent with the assumption of a positive effect of substitution of 8-hydroxyquinoline at the benzene ring on biological activity.

The Osiris analysis of a series of tested compounds 1-49 shows that most of compounds represent no side effects, except compounds 1, 15, 31, 32 with high risk in three categories (Table 4). Results of Osiris analysis also revealed 8-hydroxyquinoline derivatives showed higher value of druglikeness (DL = 1.97-8.04), than Nitroxoline™ (DL = -6.95), except 8-ethoxy-5-nitroquinoline 49 (DL = -8.05) and both azo-compounds 31, 32 (DL = -10.18 and – 8.29, respectively). Particularly high druglikeness value was calculated for hydrazide 33 (DL = 4.55). Regarding good drug score, eleven structures showed good scores (green „semaphore“ light) and they can be considered therapeutic agents.

Thus, from the point of view of druglikeness, drug score, which also compresses four mechanisms of potential toxicity, from the point of view of a high score for predicting bioactivity in the next row from high values of bioavailability, permeability through the BBB, or the absence of warnings BRENK and PAIN, calculated by the SwissADME web application we can evaluate considered structures. The virtual structures 17, 25, 35 and 43 can be favored. The goal of our study could be fulfilled by the synthesis of the structurally similar derivatives of these compounds and by the proceeing a high-quality screening of antibacterial activity.

The topic of our research is current, and the achieved results can be discussed with analogous works. The perspective 7-aminomethyl derived 8-hydroxyquinolines with antibacterial activity comparable to the standard Nitroxoline™ and the POM analysis combined with docking to the FtsZ protein have been described in the work of El Faydy *et al.* [12]. However, it should be noted that those 7-aminomethyl- newly synthesized substances offer only one of the possibilities of the variability of the 8-hydroxyquinoline skeleton.

In contrast to El Faydy´s work, our study alternates the hydroxy group in the C8 position with the phenolate anion of 48, that leads to the positive result in the bioactivity increasing. On the other hand, the mechanism of action of Nitroxoline™ (and thus other structurally related substances) is not fully explained in this strict way, or it assumes a multifactorial mechanism of action, including possible excessive chelation of ions in the bacterial cell. The modified POM analysis, presented in our work, pointed to a certain variability of four types of toxicity, which seems to be individual with respect to the structure. However, the non-toxicity of the derivatives prevails, with exception of a few cases of tumorigenicity and irritation, which supports our findings.

8-Hydroxyquinolines, derived in the C7 positions, showed the entire spectrum of bioactivity primarily as enzyme or kinase inhibitors down to the lowest mechanisms of interaction with nuclear receptors. The substances analyzed in our study showed the most prediction of action by the general mechanism of enzyme inhibitors and kinase inhibitors, which is in the accordance with the work of El Faydy [12]. POM analysis has been used by Rbaa et al. [8,9,54], dealing with quinoline derivatives. The first work [8] is entitled "Synthesis of novel heterocyclic systems of oxazine derivatives of 8-hydroxyquinoline: Drug design and POM analysis of substituent effects on their potential antibacterial properties" and the possible shortcoming of that work lies in the fact, Nitroxoline™ was not chosen as the standard, but following antibiotics: Eyrthromycin, Penicillin G. and Norfloxacin. Only the third chosen standard, Norfloxacin, is relatively structurally closest to Nitroxoline™. In addition, the tested compounds did not match the standards in terms of effectiveness. Even though the studied compounds were structurally partially different, a similar finding was observed within the POM analysis. In the field of Osiris calculations, there was found a certain degree of tumorigenicity within a part of compounds, in the prediction of bioactivity an evident loss of potency

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by the mechanism of kinase inhibitors was found. On the other hand, a higher substance potential to occupy receptors associated with proteins was predicted. The prediction of pharmacophores in terms of antibacterial effect does not attribute significance to the hydrogen of the C8-bonded hydroxy group of quinolines, which is replaced in these substances by an oxygen atom involved in the cycle. In the next Rbaa´s work [9], dealing synthesis of 8-hydroxyquinoline derived benzoates, their antibacterial activity evaluation and POM analysis, Penicillin G was used as the standard. Beneficial effect of substituent at benzoate moiety of studied 8-hydroxyquinolines to antibacterial activity was observed, compared to the non-substituted compound as well as to the standard Penicillin G. Similarly to our work, POM analysis predicted low toxicity and good drug score of studied compounds.

In the third work of Rbaa´s team [54], the synthesis of 8-hydroxyquinoline derivatives with methylenethio-, methyleneamino- and methyleneoxo- structural units at C5 carbon was described. Regarding the POM analysis, it is possible to state comparability with our results, as regards the prediction of toxicity, or the generated drug score. Four compounds were synthesized, and a higher degree of antibacterial activity was exhibited by derivatives containing a sulfur atom.

4. Materials and Methods

4.1. Antibacterial Activity

Antibacterial activity of twenty 8-hydroxyquinoline derivatives (**1, 14-17, 26, 28-37** and **45-48**) was screened on eight bacterial strains: *Klebsiella pneumonae* - two different strains, *Klebsiella oxytoca, Klebsiella aerogenes, Pseudomonas aeruginosa, Acinetobacter baumannii),* Vancomycin-resistant *Enterococcus (636) and Staphylococcus aureus* in accordance with CLSI norm (Table 6).

Table 6. The characterisation of eight selected bacterial strains.

Strain No.	Bacterial strain	Mechanism of resistance	Type
2151	*Klebsiella pneumoniae*	producing carbapenemase /NDM/	G^-
3541	*Klebsiella. oxytoca*	producing carbapenemase /KPC/	G^-
500	*Klebsiella aerogenes*	producing extended-spectrum beta-lactamase /ESBL/	G^+
3396	*Pseudomonas aeruginosa*	multidrug-resistance /MDR/, carbapenem resistance	G^-
3333	*Acinetobaceter baumannii*	MDR, carbapenem resistance	G^-
636	*Enterococcus faecium*	vancomycin-resistant enterococcus /VRE/	G^+
1942	*Staphylococcus aureus*	methicillin-resistant *S. aureus* /MRSA/	G^+
3401	*Klebsiella pneumoniae*	producing ESBL	G^-

Briefly, the broth microdilution reference method was used to detect the antibacterial activity of quinolines *in vitro*. This is done by adding 100 µL of Mueller-Hinton broth (MHB) to all tested wells in a sterile microtiter U-plate. In the first well, MHB is always added in a 2-fold concentration than in the other wells. Subsequently, 100 µL of sterile quinolones solution with defined concentration of 64 µg/mL is added and result is the following concentration of 32 µg/mL After mixing and transferring to subsequent wells, the antimicrobial concentration is decreased to 16, 8, 4, 2, 1 µg/mL, and so on. Then 10 µL of the prepared bacterial suspension inoculum to 3 parallel wells is added, the 4th "parallel" is the sterility control of the tested sample without bacterial inoculum. Sterile aqua pro injectione is added in positive growth control instead of the antimicrobial agent. Then 10 µL of bacterial suspension (inoculum = 5 x 10^6 CFU/mL) is pipetted into the wells.

After 18 - 24 hours of incubation in a microtiter plate at the temperature of 35 ± 2 °C, the MIC value is determined. The MIC represents the first well with the lowest concentration of tested quinolones, in which there are no signs of growth (applied visible or chromogenic principle). The purity of the bacterial inoculum suspension was checked by subculturing on a non-selective agar plate during simultaneous incubation. As the result could be significantly influenced by the methodology, therefore the reproducibility of the results was carefully checked in our case, by repeated testing with 3 samples examined in parallel.

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4.2. Molinspiration Calculations

The physiochemical parameters and druglikeness, based on the Lipinski rule of five (RO5) were calculated. According to the RO5, for good oral bioavailability molecules must have hydrogen bond donor's ≤ 5 (OH and NH groups), hydrogen bond acceptors ≤ 10 (N and O atoms), molecular weight < 500, and log *P* coefficient < 5 [55,56]. Thus octanol/water partition coefficient (Log P), topological polar surface area (TPSA), molecular weight, molecular volume and number of rotatable bonds were calculated. Log P is calculated as a sum of fragment-based contributions and correction factors. TPSA, defined as the overall surface of polar atoms in a molecule, was calculated as a summation of polar fragment surface contributions (atoms regarding also their environment) [57]. Molecular volume calculation is based on group contributions obtained by the fitting sum of fragment contributions to "real" 3D volume for a training set of about twelve thousand, mostly drug-like molecules. 3D molecular geometries for a training set were fully optimized by the semiempirical AM1 method. The number of rotatable bonds makes the molecule more flexible with good binding affinity with the binding pocket [58].

4.3. SwissADME Calculations

The swissADME software [31] offers calculations in several sections. In the lipophilicity section, five different approaches (ilogP, XlogP3, WlogP, MlogP, SILICOS-IT) for prediction of *n*-octanol/water partition coefficient ($\log P_{o/w}$) are used and additionally, consensus log $P_{o/w}$ value, which is the arithmetic mean of the five predictive values is calculated. Water solubility is calculated by three different systems and each of them is exprimed as the decimal logarithm of the molar solubility in water (logS). Physicochemical properties (molecular weight, number of heavy atoms, number of aromatic heavy atoms, fraction CSP3, number of rotatable bonds, number of H-bond acceptors and donors, molar refractivity and TPSA) are calculated. Pharmacokinetic parameters, including gastrointestinal absorption (GI), blood-brain barrier permeation (BBB) [59] and inhibition of the most important CYP isoenzymes (1A2, 2C19, 2C9, 2D6, 3A4) [60] are also calculated as well as the capability of compounds being substrate or non-substrate of the P-glycoprotein (P-gp) [61]. Druglikeness score using five different approaches (Lipinski Ghose, Veber, Egan and Muegge) [22,62–65] was calculated as well as the skin permeability coefficient (K_P) [66]. In the section of medicinal chemistry, the structural alert with a list of potentially problematic fragments is implemented. Two complementary methods, Brenk filter [67] and PAINS (pan assay interference compounds) [68] are used. PAINS are molecules containing substructures showing potent response in assays irrespective of the protein target. Brenk filter consists in putatively toxic, chemically reactive, metabolically unstable fragments or fragments with properties responsible for poor pharmacokinetics. Leadlikeness, bioavailability score and the synthetic accessibility are calculated. Leadlikeness is characterized by the similarity with “lead” compound - structural unit suitable for optimization for further drug development [69], while bioavailability score (BS) predicts the probability of a compound to have at least 10% oral bioavailability in rat or measurable Caco-2 permeability [70]. Synthetic accessibility (SA) score is based primarily on the assumption that the frequency of molecular fragments in ‘really’ obtainable molecules correlates with the ease of synthesis.

4.4. Osiris Calculations

The OSRIS property explorer [23] software offers the calculation of the toxicity risk prediction due to the mutagenicity, tumorigenicity, irritating or reproductive effective properties of a molecule. The results are given as “semaphore” light colors. The calculation of the n-octanol/water partition coefficient (clogP) was implemented as increment system adding contributions of every atom based on its atom type. The solubility in water significantly affects its absorption and distribution characteristics. The estimated logS value is a unit-stripped logarithm (base 10) of a compound's solubility measured in mol/L. Druglikeness value prediction is based on the list of distinct substructure fragments with associated druglikeness scores and is calculated as the equation that

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sums up the score values of fragments present in the investigated molecule. A positive druglikeness value indicates that a molecule contains predominantly fragments, frequently present in commercial drugs. The overall drug score indicates the compound's overall potential to qualify as a drug and combines druglikeness, cLogP, logS, molecular weight and toxicity risks in one value.

5. Conclusions

This study identified a collection of modeled structures based on 8-hydroxyquinoline as potential lead molecules for future research to discover new, effective antibacterial agents. The application of Lipinski rules (RO5) shows, that designed compounds, theoretically, fulfil druglikeness criteria**.** Calculations of bioactivity score can be helpful in the prediction of the effect mechanism. Individual positive value as well as average relative maximal value of the particular compound is interesting. The filter of the whole forty-nine structures (compounds) collection works with SWISSADME and OSIRIS criteria to achieve only several the most perspective structures with high drug score, non-toxicity, good bioavailability, optimal ADME and medicinal chemistry parameters**.** The compounds with following derivatization in C5 position: 5-$CH_2NH_3^+Cl^-$ (**17**), 5-C≡C-[4,6-$(OMe)_2$-1,3,5-triazin-2-yl] (**25**), 5-CH_2NHCOPh (**35**) and finally 6-(5-bromo-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl) (**43**) in C6 position could be taken as leader for synthesis of next- generation collections.

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