3-Hydroxy-2-phenyl-4(1*H*)-quinolinones as Promising Biologically Active Compounds

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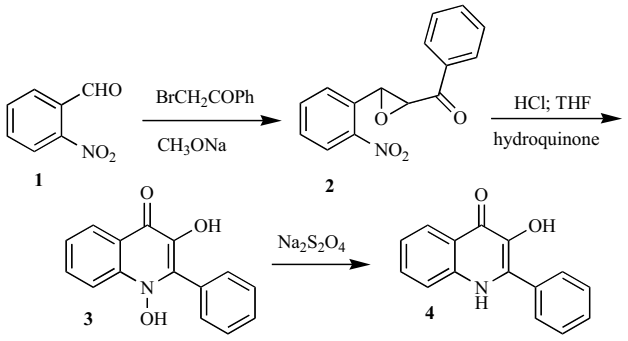
Abstract: 2-Phenyl-3-hydroxy-4(1*H*)-quinolinones can be considered as aza-analogues of flavones, compounds which are known for the wide-range of their biological activity. These quinolinones were studied as inhibitors of topoisomerase, gyrase and IMPDH. They were tested for anticancer activity *in-vitro* and were also shown to possess immunosuppressive properties.

This review is the first summarizing the synthesis and activity of the mentioned quinolinones.

Key Words: Quinolinones, anticancer activity, antibacterial activity, inhibition.

INTRODUCTION

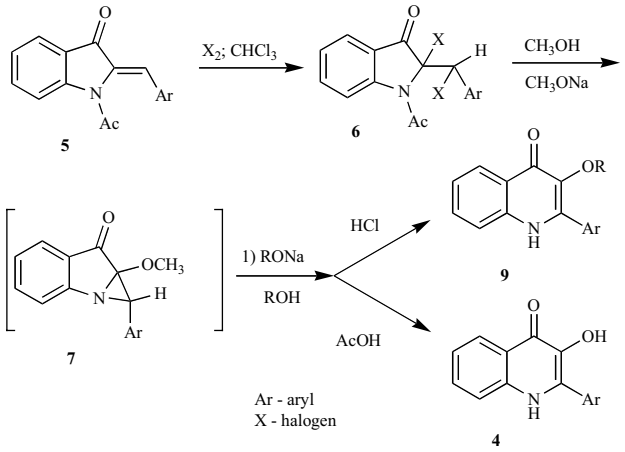
The first paper describing the structure of 3-hydroxy-2-phenyl-4(1*H*)-quinolinone was published in 1971 [1], when reaction of 2-nitrobenzaldehyde **1** through 2-nitrochalcone epoxide **2** yielded 1,3-dihydroxy-2-phenylquinolin-4(1*H*)-one **3**, which was subsequently converted to the final 3-hydroxy-2-phenylquinolinone **4** (Scheme **1**).



Scheme 1. Synthesis of 3-hydroxy-2-phenyl-4(1*H*)-quinolinone according to reference [1].

This method of preparation, employing the Darzens reaction, was studied by other research groups in the same year [2] and, in 1976, was used for synthesis of japonine [3]. However, the low availability of the parent substituted 2-nitrobenzaldehydes made the method somewhat disadvantageous.

A quite different method was developed in 1992. It was based on expansion of the 5-membered ring in indol derivative **5** through aza-cyclopropa[a]indene **7** to the desired quinolinone **4** (Scheme **2**) [4].



Scheme 2. Synthesis of 3-hydroxy-2-phenyl-4(1*H*)-quinolinone according to reference [4].

Introduction of a hydroxyl group to position 3 was performed by oxidation of 2-aryl-4-quinolone **10** (Scheme **3**). Unfortunately this reaction is applicable only to specific cases, because its yield is low [5].

A more broadly applicable synthetic route was developed in 1995 by one of us, when the cyclization of phenacylesters of the anthranilic acid **14**, prepared by alkylation of anthranilic acid **12** with bromoacetophenones **13** was studied (Scheme **4**) [6].

This cyclization was performed originally thermally without any solvent or by heating with polyphosphoric acid [6-8], but later different methods of cyclization in acetic or trifluoroacetic acid were also developed. The advantage of this method is its simplicity, the availability of a large num-

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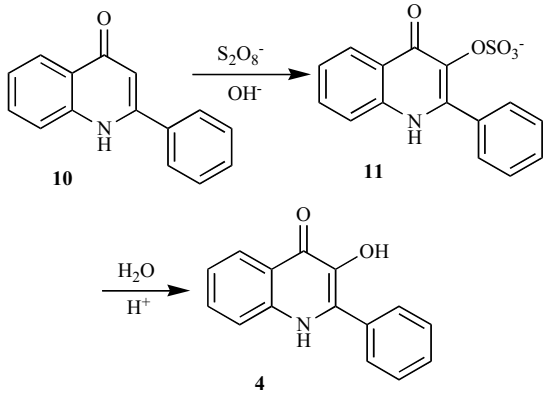
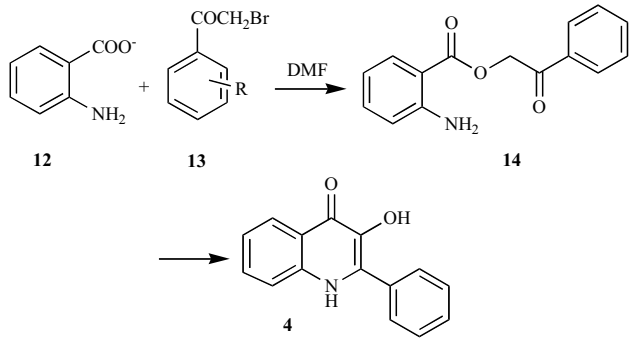


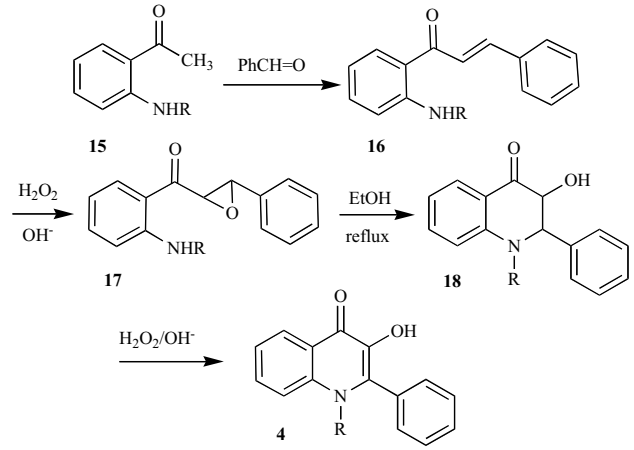
Scheme 3. Synthesis of 3-hydroxy-2-phenyl-4(1*H*)-quinolionone according to reference [5].



Scheme 4. Synthesis of 3-hydroxy-2-phenyl-4(1*H*)-quinolinone according to reference [6].

ber of starting materials and its high yield. Therefore, this procedure was also used for the preparation of variously substituted 3-hydroxy-4-4(1*H*)-quinolone derivatives in several patents and articles [8-14].

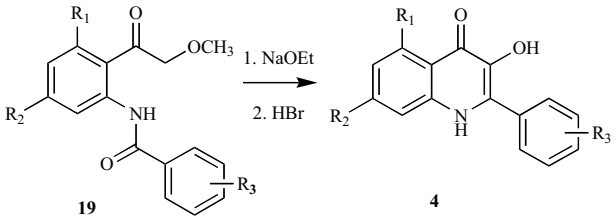
More recently, the N-substituted acetophenones **15**, which can afford the desired quinolinones **4** (Scheme **5**) through (2-amino-phenyl)-(3-phenyl-oxiranyl)-methanone **17** as an intermediate by refluxing in ethanol and subsequent oxida



Scheme 5. Synthesis of 3-hydroxy-2-phenyl-4(1*H*)-quinolinone according to reference [15].

tion, were used for synthesis. This synthesis, however, has little practical importance owing to the difficult availability of starting materials and the very low overall reaction yield of about 1% [15].

A very interesting and broadly applicable cyclization of alkyl(2-aminophenyl)ketone derivatives **19** to final quinolinone **4** (Scheme **6**) was described in 1999 [16]. The starting material is easily available by transformation of 2-halogenketones in quite good yields. The method was used mostly for the preparation of 3-alkyl derivatives, but preparation of hydroxyderivatives by demethylation of appropriate 3-methoxy derivatives by HBr or pyridinium chloride can also succeed.

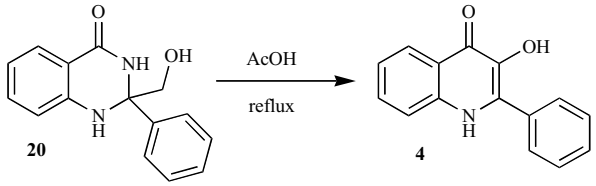


R_1, R_2 = H, OH, CH_3, F

R_3 = OH, halogen, CF_3, NH_2, alkyl, COOH, COOEt in various position

Scheme 6. Synthesis of 3-hydroxy-2-phenyl-4(1*H*)-quinolinone according to reference [16].

It is also possible to obtain 3-hydroxy-4(1*H*)-quinolinone in 56 % yield by the rearrangement of dihydroquinazoline derivative **20** (Scheme **7**) in acetic acid [17].



Scheme 7. Synthesis of 3-hydroxy-2-phenyl-4(1*H*)-quinolinone according to reference [17].

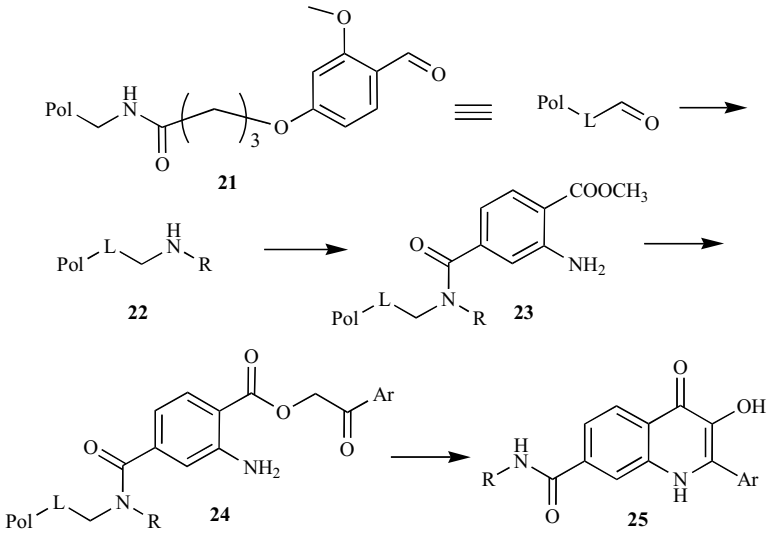
The general applicability of this reaction is limited, because the yields strongly depend on substitution and appropriate starting materials are again not easily available.

Recently we described the synthesis of some new hydroxyquinolinones using synthesis on a polymer support. The starting anthranilic acid was immobilized *via* amide group on polystyrene resin and an efficient non-traceless solid phase synthesis of quinolinone-carboxamides **25** [12] (Scheme **8**) was developed.

The described solid phase synthesis of carboxamides can be considered as the beginning of a new age in exploration of biological activity of hydroxyquinolinones based on the systematic exploration of the most potent combination of the quinolinone scaffold substitution.

BIOLOGICAL ACTIVITY OF 3-HYDROXY-2-PHENYL-4(1*H*)-QUINOLINONES

The first mention of biological activity of derivatives of the titled quinolinones dates back to 1986, when 3-hydroxy-



Scheme 8. Method of solid-phase synthesis of quinolinone-carboxamides chemical library according to reference [12].

graveoline was isolated from the aerial parts of *Ruta chalepensis (fringed rue)*.

The compound was tested for its effects on the prevention of early pregnancy in rats, but it was inactive [18].

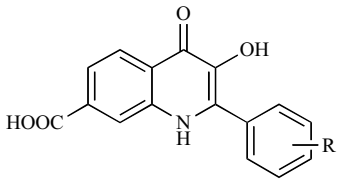
The nineties of the last century saw the beginning of studies on biological activity, during the course of which isosteric flavones were found to be biologically active and because other types of 4(1*H*)-quinolinones were found to be antibacterial agents with gyrase inhibition activity. Apart from topoisomerase, additional target enzymes, the activity of which was studied in connection with 3-hydroxy-4(1*H*)-quinolinones, were dioxygenases and inosinmonophosphate dehydrogenase.

The quinolinones were lately reported for their cytotoxic activity against cancer cell lines and as potential antibacterial agents.

1. Anticancer Activity

In the literature, only two papers and one patent describing the results of testing of anticancer activity *in-vitro*, have been published. Up to the present published results include two approaches for screening this activity. The first of them is based on MTT cytotoxic test on cell lines derived from normal tissues and malignant tumors. They include K562 (human myeloid leukaemia), K562-tax (human myeloid leukaemia resistant to paclitaxel and expressing the multidrug resistant phenotype, which depends on expression of the mdr1 gene), CEM (T-lymphoblastic leukaemia), CEM-DNR-bulk (T-lymphoblastic leukemia resistant to doxorubicine, expressing the multidrug resistant phenotype which depends on expression of the mrp1 gene and lacking topoisomerase IIα gene) and A549 lung adenocarcinoma cell line. The methodology of the cytotoxic MTT test and cell line descriptions has been published previously [19].

Using the MTT based screening system, *in-vitro* the anticancer activity of the 3-hydroxy-2-phenyl-4(*1H*)-quinolinones-7-carboxylic acids **26** shown in Fig. (**1**) was reported [20].



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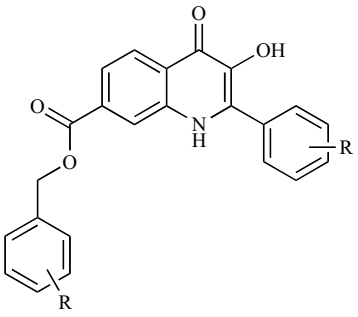
R = H; 2-I; 2-Cl; 2-Br; 3-Cl; 4-CH_3; 3,5-diCl-4-NH_2; 2-NO_2; 3-NO_2; 4-NO_2

Fig. (1). Structure of derivatives **26** studied in cytotoxic activity against cancer lines *in-vitro*.

Furthermore, the carboxylic group in position 7 of the quinolinone skeleton was introduced to aid the insertion of various substituents into this position. When the carboxylic group remained unmodified, no substitution in the 2-phenyl ring assured significant cytotoxic activity towards chemosensitive CEM cells (IC_{50} >130μM). One possible reason could be the low permeability of the compounds through the cell membrane. The only exception to this rule was 4-amino-3,5-dichlorophenyl moiety, which was consistently more active for about one log.

When the carboxylic group was esterified by a phenacyl moiety with the same substitution as the 2-phenyl ring to give derivatives **27** shown in Fig. (**2**), the activity of some derivatives increased sharply.

The unsubstituted derivative and three possible mononitro derivatives were completely inactive against all four lines (IC_{50} > 25 μM). Moderate activity was exhibited by the 2-chloro derivative in CEM (IC_{50} = 16 μM) and K562 cell lines (IC_{50} = 17 μM). 2-Iodo, 2-bromo, 3-chloro, 4-methyl and



27

R = H; 2-I; 2-Cl; 2-Br; 3-Cl; 4-CH_3; 3,5-diCl-4-NH_2; 2-NO_2; 3-NO_2; 4-NO_2

Fig. (2). Structure of derivatives **27** studied in cytotoxic activity against cancer lines *in-vitro*.

3,5-dichloro-4-aminophenyl substituents exhibited good activity against the drug sensitive cell lines CEM and K562 (IC_{50} = 0.76-8.0 μM). Last two of the above-mentioned compounds were, however, active also against drug resistant cell lines K562-tax and CEM-DNR-bulk (IC_{50} = 1.2-4.9 μM).

What can be gleaned from these results is that substitution at positions 3 and 4 in the 2-phenyl moiety seems crucial for the activity, if the 2-phenyl ring is not substituted by strong electron-withdrawing substituents as in case of nitro-compounds.

Although nitrophenyl substituents in position 2 are inactive in this case, a combination of 3-nitro and 4-aminophenyl substituents (Fig. **3**) brought about very interesting results in activity testing [21].

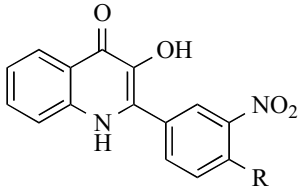


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Fig. (3). Structure of derivatives **28** studied in cytotoxic activity against cancer lines *in-vitro*. For R see Table **1** and Table **2**.

All studied derivatives were active against the leukemia cell line CEM at low micromolar or submicromolar concentrations. Nonetheless, only derivatives bearing a hydrophobic substituent were active against the leukemia cell line resistant to daunorubicine CEM-DNR-BULK in micromolar concentrations.

Interestingly, even a slight change of substitution significantly affects the activity against drug resistant cell lines. When a di-n-propylamino group is inserted at position 4, the compound becomes active against all lines. In the case of the N-ethyl-N-methylamino group the compound is active only against drug susceptible lines (Table **1**).

In view of the fact that the lines CEM-DNR-BULK, K562-TAX and A549 were shown to overexpress the multidrug resistance proteins Pgp and/or MRP1 from the family of the ABC membrane transporters, we anticipate that some compounds possessing a capacity to overcome tumor multidrug resistance might thus bring new hope and perspective in the therapy of drug resistant cancers.

The second approach reported for testing anticancer activity *in-vitro* was developed at NCI and involves primary testing against three cancer lines: MCF7 (breast cancer), NCI-H460 (non-small cell lung cancer) and SF-268 (brain tumor). Compounds sufficiently reducing the growth of any one of the cell lines are then passed for further evaluation on extended panels of 60 cell lines.

Using the NCI *in-vitro* drug evaluation system, the various chloroquinolinones **29** bearing an unsubstituted phenyl at position 2 shown in Fig. (**4**) were studied. None of the monochloro derivatives showed significant activity against three screening cancer lines and therefore, none of them was included in further testing.

Some dichloro derivatives showed better activity. Three of them (5,7-dichloro; 5,8-dichloro and 6,8-dichloro-3-hydroxy-4(1*H*)-quinolinones) reduced the growth activity to ≤30% in at least one cell line. The best *in-vitro* activity was exhibited by 5,8-dichloro derivatives with range of IC_{50} values between 11-20 μM.

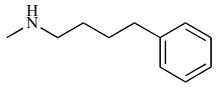
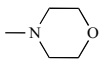
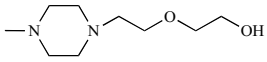
These derivatives were then tested against the full panel of 60 cancer lines, however none of them exhibited significant activity. 6,8-Dichloroquinolinone did not show the Log_{10} GI_{50} concentration under –4.80. The 5,7-dichloroquinolinone was slightly more potent against non-small cell lung cancer, colon cancer, melanoma and breast cancer, but the $Log_{10}GI_{50}$ never exceeded the value –5.80. Comparable activity was found in the case of 5,8-dichloroquinolinone against non-small cell lung cancer, colon cancer, ovarian cancer and breast cancer cell lines.

The mechanism of the anticancer effect of 2-phenyl-3-hydroxy-4(1*H*)-quinolinone has not been elucidated. According to the results of *in-vitro* cytotoxic profiles of some selected quinolinones mentioned above against CEM-DNR-BULK and K562-tax it is possible to say that a number of these compounds quite certainly do not act as topoisomerase inhibitors, since they are active both in the multi-drug resistant cells K562-tax and CEM-DNR BULK. The latter cell line also expresses a multidrug resistance phenotype, but at the same time carries out deletion of the topoisomerase IIa gene.

Direct topoisomerase II enzyme inhibition was studied using some hydroxylic derivatives **30** [16].

The most potent derivative (R^1=R^2=R^3=R^4=R^5= -OH) exhibited value of IC_{50} 30nM. It appears that substitution in 2-phenyl ring is not crucial, since derivatives bearing R^1=R^2=-OH and R^3=R^4=R^5= -H, showed activity of IC_{50} at 1 μM. The role of 3-hydroxy substitution is not evident, because 3-ethyl and 3-unsubstituted 2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-4(1*H*)-quinolinones were also reported in this paper as active. Results of enzyme inhibition studies and cytotoxic activity testing on CEM-DNR-BULK and K562-tax lines demonstrate that the 2-phenyl-3-hydroxy-4(1*H*)-

Table 1. Cytotoxic Activity of the Most Potent Derivatives 28 Against Cancer Lines

Compound	R	IC_{50} (μM) in Following Cell Lines				
		CEM	CEM-DNR-BULK	K 562	K562-TAX	A 549
16a	-$NH(CH_2)_2OH$	2.7	98.8	7.3	44.9	46.8
16b	-$NH(CH_2)_3OH$	1.4	46.3	6.2	12.9	12.4
16c	-$NH(CH_2)_4OH$	0.7	15.1	1.8	8.6	5.7
16d	-$NH(CH_2)_5OH$	1.0	10.8	2.8	5.7	5.3
16e	-$NHCH(CH_3)_2$	1,6	6.8	2.1	3.0	2.8
16f		6.5	2.5	0.6	0.93	7.2
16g	-$N(CH_2CH_2OH)_2$	0.3	143	187	198	225
16h	-$N(CH_2CH_2CH_3)_2$	0.7	2.2	0.6	1.2	1.1
16i	-$N(CH_3)(CH_2CH_3)$	1.7	129.1	0.7	162.7	66.5
16j		1.4	3.4	0.7	2.1	1.7
16k		1.6	3.0	0.7	2.0	1.6
16l		3.1	10.5	3.1	3.3	2.8
16m		4.3	85.0	10.9	41.4	31.0

quinolinones can exhibit anticancer activity via inhibition of topoisomerase II, but other derivatives have other an/or additional targets.

3-Hydroxy-2-phenyl-4(1*H*)-quinolinones variously substituted by hydroxy groups have also been subjected to QSAR study [22], in which the calculated molar refractivity (CMR) was correlated against activity.

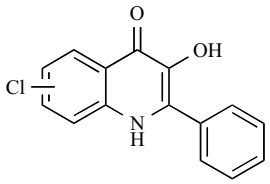


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Fig. (4). Structure of derivatives **29** investigated for cytotoxic activity against cancer lines *in-vitro*.

2. Antibacterial Activity

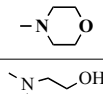
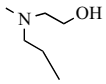
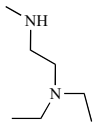
It is widely known that the 4(1*H*)-quinolinone structure is responsible in many cases for the observed antibacterial activity. For example, it is possible to cite some commercially used drugs like Gatifloxacin, Norfloxacin, etc. which exhibit such activity. The mechanism of action is based in most cases on the inhibition of gyrase. The active quinolinones usually bear a carboxyl group in position 3. When this carboxyl group is replaced by a 3-hydroxy group, only the inhibition of gyrase is observed [16].

In this paper the derivatives **30** already mentioned as well as 3,5,7-trihydroxy-2-phenyl-4(1*H*)quinolinones substituted in the para position of 2-phenyl with alkyl, amino, carboxy, ethoxycarbonyl moiety have also been studied.

Of these, 2-(3,4-dihydroxyphenyl)-3-hydroxy-5,7-difluoro-4(1*H*)-quinolinone was found to have the most potent activity 190 μM.

Our research group has also carried out *in-vitro* activity testing on several derivatives of 3-hydroxy-4(1*H*)-quinolinones against standard reference gram-positive and gram-negative bacterial strains (*Enterococcus faecalis* CCM 4224, *Staphylococcus aureus* CCM 3953*, Escherichia coli* CCM 3954 and *Pseudomonas aeruginosa* CCM 3955*)* from the Czech Collection of Microorganisms (CCM, Faculty of Science, Masaryk University Brno), and against gram-positive and gram-negative bacteria obtained from Teaching Hospital Olomouc (methicillin resistant *Staphylococcus aureus* - MRSA, *Staphylococcus haemolyticus*, *Escherichia coli* and *Pseudomonas aeruginosa*) with resistance to fluoroquinolinones used in clinical practice. The great majority of them

Table 2. Antibacterial Activity of the Most Potent Derivatives 28 Against Various Strains

Compound	R	Minimal Inhibitory Concentration of Compounds (mg/l) in Following Strains							
		Enterococcus faecalis CCM 4224	*Staphylococcus aureus* CCM 3953	*Escherichia coli* CCM 3954	*Pseudomonas aerugi-nosa* CCM 3955	*Staphylococcus aureus (MRSA)*	*Staphylococcus haemolyticus*	*Escherichia coli*	*Pseudomonas aerugi-nosa*
16l		32	64	128	128	64	64	128	128
16n		128	64	-	128	64	64	128	128
16o		128	64	64	128	64	64	128	128
16p	-Cl	-	128	64	128	64	-	-	64

did not exhibit any activity. Up to now only low activity has been shown in the following derivatives (Table **2**).

3. Other Activities

2-Phenyl-3-hydroxy-4(1*H*)-quinolinones have been reported to inhibit inosin monophosphate dehydrogenase (IMPDH) [23] – one of the key enzymes in the regulation of cellular proliferation and differentiation, and so they are potential agents against IMPDH-associated disorders, especially cancer and allograft rejections.

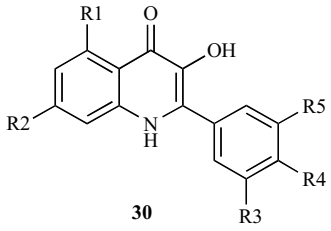


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Fig (5). Structure of derivatives **30** studied in topoisomerase inhibiton assay.

As yet, no anti-viral activity has been reported for the group of quinolones discussed above. Despite this, the 3-hydroxy-4(1*H*)-quinolinone skeleton still remains promising, as 3,5,8-trihydroxy-4(1*H*)-quinolinone, first isolated from the sponge Verongia aerophoba [24], has demonstrated significant activity against HIV [25].

The substances of structure **28** are reported as having immunosuppressive activity, due to their preferential growth inhibitory activity against stimulated and proliferating but not quiscent lymphocytes [21].

CONCLUSION

Derivatives of 3-hydroxy-2-phenyl-4(1*H*)-quinolinones are a relatively new group of biologically active compounds. In the ten years of their systematic exploration, they have demonstrated various biological activities. Because of the effects of some derivatives against selective catalytic enzymes, they possess potency as antibacterial and especially as anticancer agents or drugs against IMPDH associated disorders. Anticancer activity has been demonstrated under *in-vitro* conditions against various types of cancer cells, the results of which indicate, that topoisomerase inhibition cannot be the only molecular target in several cases.

The quinolinones mentioned were also reported as immunosuppresive agents with micromolar or submicromolar values of IC_{50} in inhibition of lymphocyte activation using polyclonal mitogen concanavalin A.

These reasons place the 3-hydroxy-2-phenyl-4(1*H*)-quinolinones among the promising biologically active compounds which, together with the development of their synthesis using combinatorial chemistry and SAR or QSAR studies, could bring about new drug candidates in a relatively short time.

ACKNOWLEDGEMENT

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