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Heterocyclic Resveratrol Analogs. Synthesis and Physiological Activity: Part 1—Analogs Obtained by the Replacement of Aryl Residues with Heterocyclic Fragments

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Abstract—Resveratrol is a polyphenolic phytoalexin, a stilbene derivative, whose physiological activities have been studied in a large number of studies. It demonstrated antioxidant, antitumor, neuroprotective, anti-inflammatory, antibacterial, and antiviral properties. In the last decade, much attention was paid to the development of resveratrol derivatives with the goal of improving its pharmacological profile and pharmacokinetics. Part 1 of the review is devoted to resveratrol synthetic analogs obtained by the replacement one or two phenyl moieties of the stilbene backbone with bioisosteric heterocyclic fragments. Attention was focused on the methods of synthesis of resveratrol analogs and their biological activity.

Keywords: anti-inflammatory activity, antioxidants, antitumor activity, heterocyclic analogs, neuroprotective agents, resveratrol

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INTRODUCTION

Resveratrol (3,5,4'-trihydroxystilbene) belongs to polyphenolic phytoalexins, a group of widely spread phytogenic compounds. Due to the presence of a double C=C bond it can exist in both *cis* and *trans* configurations (Fig. 1), which smoothly run into each other under certain conditions.

A stable *trans*-resveratrol first found and isolated by the Japanese researcher Takaoka as early as in 1941 from one of the *Veratrum grandiflorum* species dominant in the wild [1]. Later this phytoalexin was identified in many natural objects, particularly, in pine bark, nuts (peanuts and pistachio nuts), cocoa beans, berries (raspberry, plum, and grapes), and others. Currently, extracts of grape skins and seed, as well as an extract of Japanese knotweed, are major natural sources of resveratrol.

The interest in resveratrol dramatically increased in 1992, when cardioprotective effects of red wine and the so called "French paradox" were linked to a relatively low rate of cardiovascular disorders in those regions of France where a high calorie diet with a high level of saturated fat is accompanied with a big volume of red wine [2]. Numerous further studies demonstrated not only cardioprotective properties of resveratrol [3] but also antitumor [4], neuroprotective [5], and anti-inflammatory effects [6], as well as its capacity to slow down the processes of aging and increase the expectancy of life for some organisms (yeasts, worms, flies, and fish) [7, 8]. Many of these effects are mediated by noticeable antioxidant properties of resveratrol [9].

However, in practice multiple biological activities of resveratrol are associated with a relatively low clinical efficacy. The authors explained poor therapeutic efficacy of the drug in humans by its low bioavailability due to a very fast presystemic elimination in guts and liver [10, 11]. This is the reason for the intensive search for resveratrol synthetic analogs targeted at an increase in its pharmacological activity or selectivity as well as optimization of pharmacokinetics. The known structural modifications of the native compound including bioisosteric substitutions can be referred to three major groups: variations of the type and number of substitu-

Abbreviations: AChE, acetyl choline esterase; AMPK, 5'AMP-activated protein kinase; Ab, beta amyloid; CD, cluster differentiation; Cdk, cyclin-dependent protein kinase; COX, cyclooxygenase; DIBAL-H, diisobutylaluminium hydride; IL, interleukin; iNOS, inducible NO synthase; LPS, lipopolysaccharides; LSD, lysine-specific histone demethylase; MAPK, mitogen-activated protein kinase; MOM, methoxymethyl; MW, microwave irradiation; Myc, proto-oncogene Myc protein; NF, nuclear transcription factor; PGC, coactivator of peroxisome proliferator-activated receptor; PGE, prostaglandin; PMB, p-methoxybenzyl; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species; SIRT, sirtuin; TBAB, tetrabutylammonium bromide; TERT, telomerase reverse transcriptase; TLR, toll-like receptor; TNF, tumour necrosis factor; UCP, mitochondrial uncoupling protein; VEGF, vascular endothelial growth factor; MAO, monoaminooxidase.

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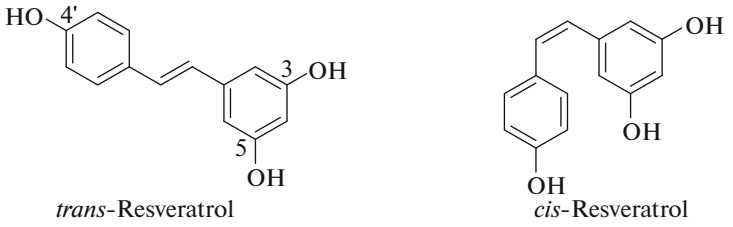


Fig. 1. Structures of resveratrol isomers.

ents in the resveratrol stilbene backbone, the replacement of aryl fragments by heterocyclic residues; and modifications of the linker joining benzene rings.

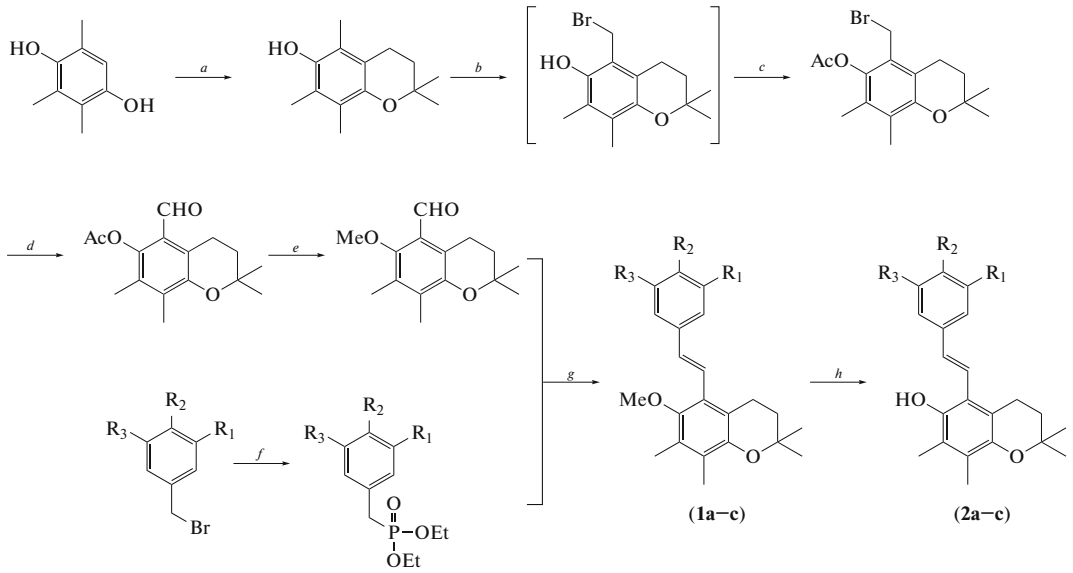
The first part of the review describes transformations of the native molecule by the second variant. Methods of synthesis and biological activity of each series of analogs will be reviewed.

THE REPLACEMENT OF RESVERATROL ARYL FRAGMENTS BY BIOISOSTERIC HETEROCYCLIC RESIDUES

A general strategy for the synthesis of analogs of this type is commonly based on the formation of an unsaturated linker joining cyclic fragments of any nature. To that end, various Wittig modifications as well as cross-coupling reactions in the presence of metal complex catalysts are used.

Analogs Displaying Antioxidant Activity

In many cases antioxidant properties of resveratrol are considered as a background for its physiological effects. Based on this hypothesis many publications are devoted to the creation of analogs with an improved capacity of inhibiting ROS-induced negative effects. On the other hand, resveratrol prooxidant activity demonstrated in some experiments is also of apparent interest. For heterocyclic analogs, modulation of activities of these types is mainly based on the creation of hybrid molecules comprising a combination of several pharmacophores. Currently, this approach in medicinal chemistry attracts much attention. The synthesis of resveratrol derivatives containing a residue of vitamin E can serve an example [12]. A key stage for the preparation of structures (**1**) and (**2**) was the Wittig–Horner reaction of the preliminarily synthesized aldehyde bearing a chromane backbone and appropriate diethyl phosphonates (Scheme 1).



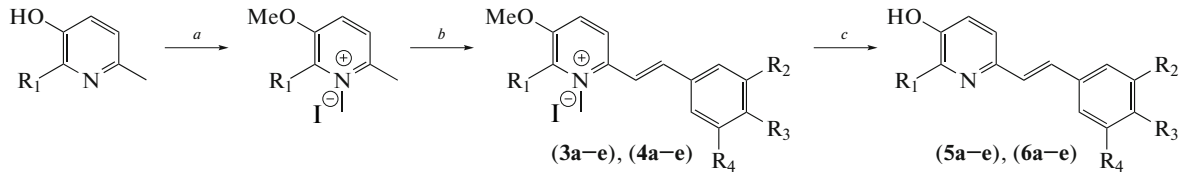
(**1a**): $R_1 = R_3 = OMe$; $R_2 = H$ (**2a**): $R_1 = R_3 = OH$; $R_2 = H$
(**1b**): $R_1 = R_3 = H$; $R_2 = OMe$ (**2b**): $R_1 = R_3 = H$; $R_2 = OH$
(**1c**): $R_1 = R_2 = OMe$; $R_3 = H$ (**2c**): $R_1 = R_2 = OH$; $R_3 = H$

Scheme 1. The synthesis of (**1**) and (**2**). Reagents and reaction conditions:
(*a*) 2-methylbut-3-en-2-ol, TFA; (*b*) Br_2; (*c*) Ac_2O, AcOH, H_2SO_4; (*d*) *N*-methylmorpholine *N*-oxide; (*e*) 1. NH_4OAc, 2. MeI, K_2CO_3; (*f*) $(EtO)_3P$; (*g*) NaH; (*h*) NaH, EtSH.

Kinetic studies demonstrated that the antioxidant effect of the synthesized molecules is aligned with the mechanism of proton separation followed by sequential proton-loss electron transfer (SPLET) and

accompanied by a significant growth of antiradical activity if compared with the parent structures.

We also synthesized hybrid antioxidants with a 3-hydroxypyridine fragment at the resveratrol backbone [13, 14], which is the structural basis of such drugs as emoxipine and mexidol. The synthesis of the analogs was performed according to Scheme 2 and included the preparation of quaternary pyridinium salts followed by their coupling with commercially available aldehydes under conditions of the Knoevenagel reaction.



(**3a–e**), (**4a–e**) (**5a–e**), (**6a–e**)

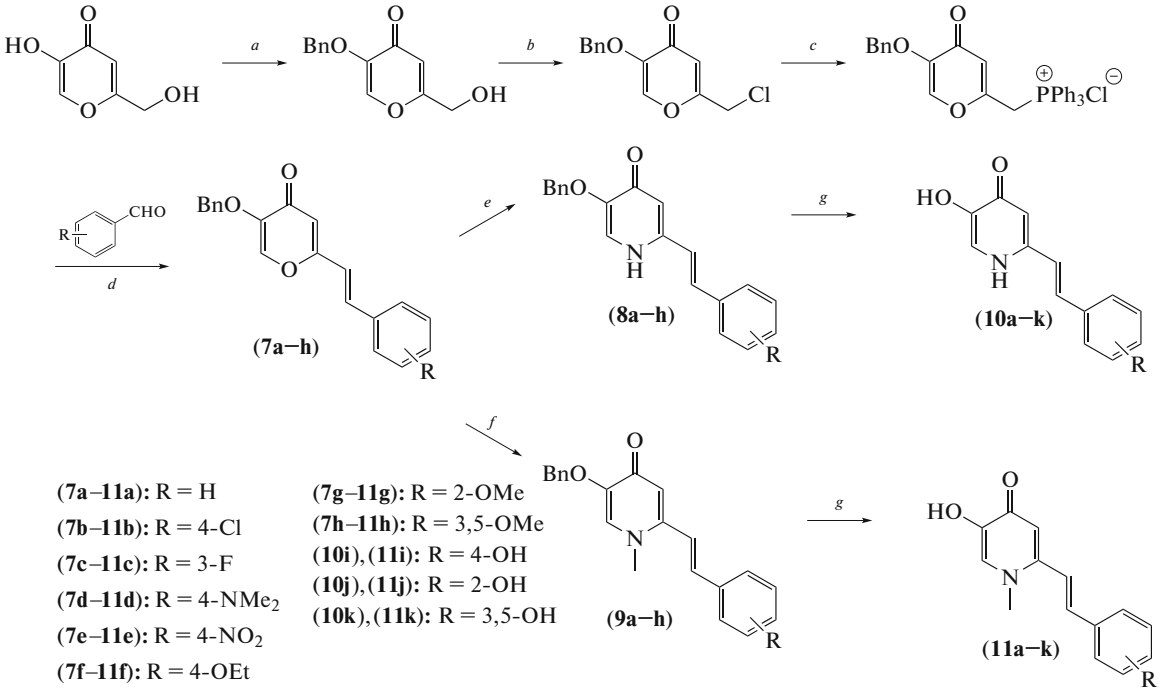
(**3a**): $R_1 = R_2 = R_3 = R_4 = H$
(**3b**): $R_1 = R_2 = R_4 = H$, $R_3 = OMe$
(**3c**): $R_1 = R_4 = H$, $R_2 = R_3 = OMe$
(**3d**): $R_1 = R_3 = H$, $R_2 = R_4 = OMe$
(**3e**): $R_1 = H$, $R_2 = R_3 = R_4 = OMe$
(**4a**): $R_1 = Et$, $R_2 = R_3 = R_4 = H$
(**4b**): $R_1 = Et$, $R_2 = R_4 = H$, $R_3 = OMe$
(**4c**): $R_1 = Et$, $R_2 = R_3 = OMe$, $R_4 = H$
(**4d**): $R_1 = Et$, $R_2 = R_4 = OMe$, $R_3 = H$
(**4e**): $R_1 = Et$, $R_2 = R_3 = R_4 = OMe$

(**5a**): $R_1 = R_2 = R_3 = R_4 = H$
(**5b**): $R_1 = R_2 = R_4 = H$, $R_3 = OH$
(**5c**): $R_1 = R_4 = H$, $R_2 = R_3 = OH$
(**5d**): $R_1 = R_3 = H$, $R_2 = R_4 = OH$
(**5e**): $R_1 = H$, $R_2 = R_3 = R_4 = OH$
(**6a**): $R_1 = Et$, $R_2 = R_3 = R_4 = H$
(**6b**): $R_1 = Et$, $R_2 = R_4 = H$, $R_3 = OH$
(**6c**): $R_1 = Et$, $R_2 = R_3 = OH$, $R_4 = H$
(**6d**): $R_1 = Et$, $R_2 = R_4 = OH$, $R_3 = H$
(**6e**): $R_1 = Et$, $R_2 = R_3 = R_4 = OH$

Scheme 2. The synthesis of compounds (**3**–**6**). Reagents and reaction conditions: (*a*) 1. CH_3ONa, CH_3OH, MW. 2. CH_3I, MW or 1. CH_2N_2, Et_2O. 2. CH_3I, $CHCl_3$, MW; (*b*) ArCHO, BuOH, piperidine; (*c*) Py · HCl.

Most of the synthesized derivatives manifested high antiradical (DPPH test) and antioxidant (on a model of iron-ascorbate-mediated peroxidation of mitochondrial lipid membranes) activities, which exceeded those of the prototype, and were of low toxicity. Derivatives (**5b**, **c**) and (**6b**, **c**) displayed the best characteristics.

Another example is the synthesis of resveratrol hybrid with deferiprone, a known chelating agent (Scheme 3) [15]. A principal stage is the Wittig reaction of kojic acid-derived ylides with available substituted benzaldehydes.

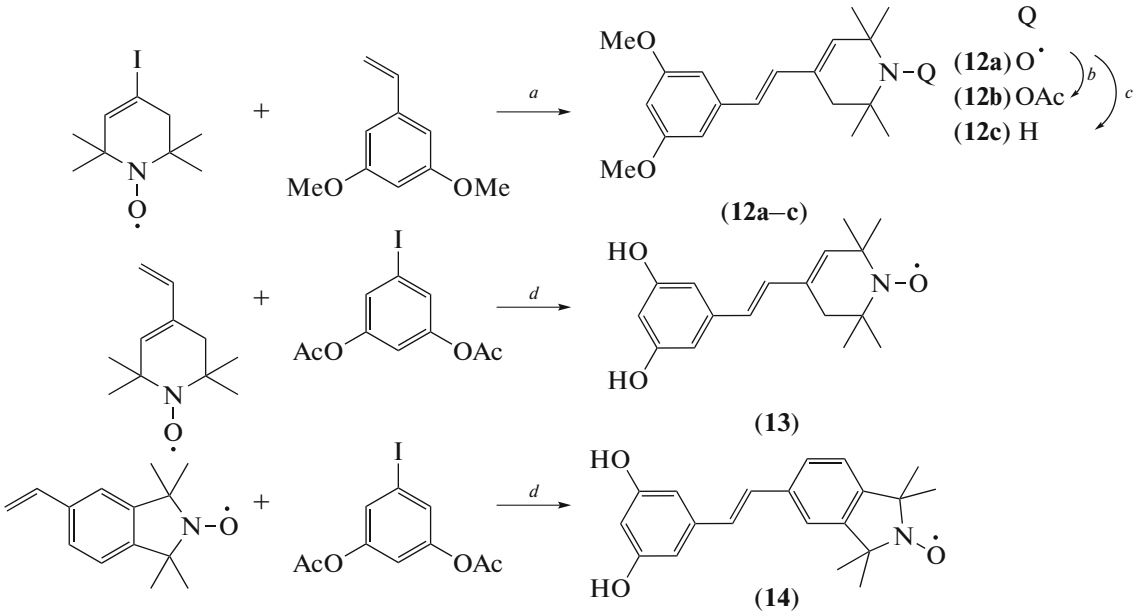


(**7a–h**) (**8a–h**) (**10a–k**)

(**9a–h**) (**11a–k**)

(**7a**–**11a**): R = H
(**7b**–**11b**): R = 4-Cl
(**7c**–**11c**): R = 3-F
(**7d**–**11d**): R = 4-NMe_2
(**7e**–**11e**): R = 4-NO_2
(**7f**–**11f**): R = 4-OEt
(**7g**–**11g**): R = 2-OMe
(**7h**–**11h**): R = 3,5-OMe
(**10i**),(**11i**): R = 4-OH
(**10j**),(**11j**): R = 2-OH
(**10k**),(**11k**): R = 3,5-OH

Scheme 3. The synthesis of compounds (**7**–**11**). Reagents and reaction conditions: (*a*) BnCl, MeOH, reflux, 16 h; (*b*) $SOCl_2$, 2 h; (*c*) PPh_3, $CHCl_3$, 24 h; (*d*) NaOH; (*e*) $NH_3 \cdot H_2O$; (*f*) $MeNH_2$; (*g*) 6N HCl or BBr_3.



Scheme 4. The synthesis of compounds (**12**–**14**). Reagents and reaction conditions: (*a*) K_2CO_3, $Pd(OAc)_2$, Bu_4NBr, DMF; (*b*) 1. Ascorbic acid, N_2, dioxane, H_2O; 2. Et_3N, AcCl; (*c*) Fe, AcOH; (*d*) 1. KOAc, $Pd(OAc)_2$, Bu_4NBr, DMF, 2. MeONa, MeOH.

The in vitro experiments showed that most of the synthesized compounds displayed both antioxidant and metal chelating properties. Derivatives (**10i**) and (**11f**) proved to be the most promising agents.

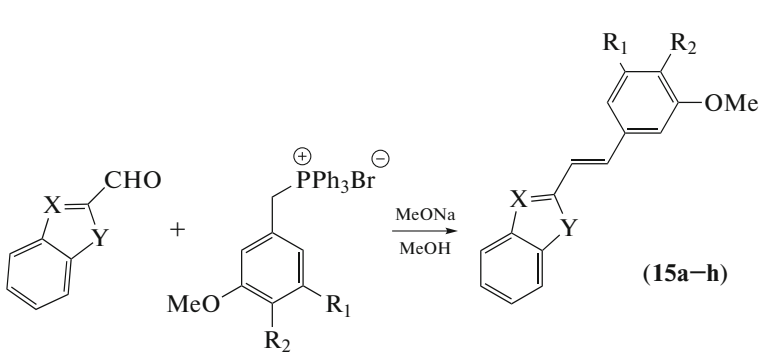
New resveratrol analogs bearing five- and six-membered nitroxides and isoindoline nitroxides were obtained using a cross-coupling reaction (Scheme 4) [16].

Unfortunately, their capacity to capture free radicals was not higher than that of the prototype.

Analogs Displaying Antitumor Activity

According to the published data resveratrol antitumor properties can be realized in different ways, one of which is its antimitotic effect on various phases of the cell cycle. In particular, it was found that resveratrol could inhibit microtube functions. The highest effect on tubulin was shown for methoxy derivatives, for example, (*E*)-3,4,5,4'-tetramethoxystilbene (DMU-212) [17] structurally similar to combretastatin A-4 (Fig. 2).

Considering a potential key role of a trimethoxystyryl fragment for the activity, a series of DMU-212 analogs was synthesized with indolyl, benzofuranyl, or benzothiazolyl groups in place of a 4-methoxyphenyl residue [18]. The key step was the Wittig reaction of the proper heterocyclic aldehydes and triphenylphosphonium salts (Scheme 5).



(15a): X = CH, Y = NH, $R_1 = R_2$ = OMe
(15b): X = CH, Y = NH, R_1 = H, R_2 = OMe
(15c): X = CH, Y = NH, R_1 = OMe, R_2 = H
(15d): X = CH, Y = O, $R_1 = R_2$ = OMe
(15e): X = CH, Y = O, R_1 = OMe, R_2 = H
(15f): X = N, Y = S, $R_1 = R_2$ = OMe
(15g): X = CH, Y = S, $R_1 = R_2$ = OMe
(15h): X = CH, Y = S, R_1 = OMe, R_2 = H

Scheme 5. The synthesis of compound (**15**).

Analogs bearing a *trans*-3,4,5-trimethoxystyryl fragment (**15a**), (**15d**), (**15f**), and (**15g**) manifested a powerful inhibitory effect with $GI_{50} < 1$ μM in 85% of 60 studies on human tumor cell lines. At the same time 3,4- and 3,5-dimethoxysubstituted derivatives showed a much lower inhibition degree.

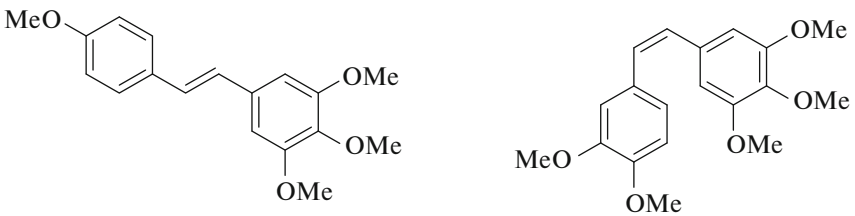
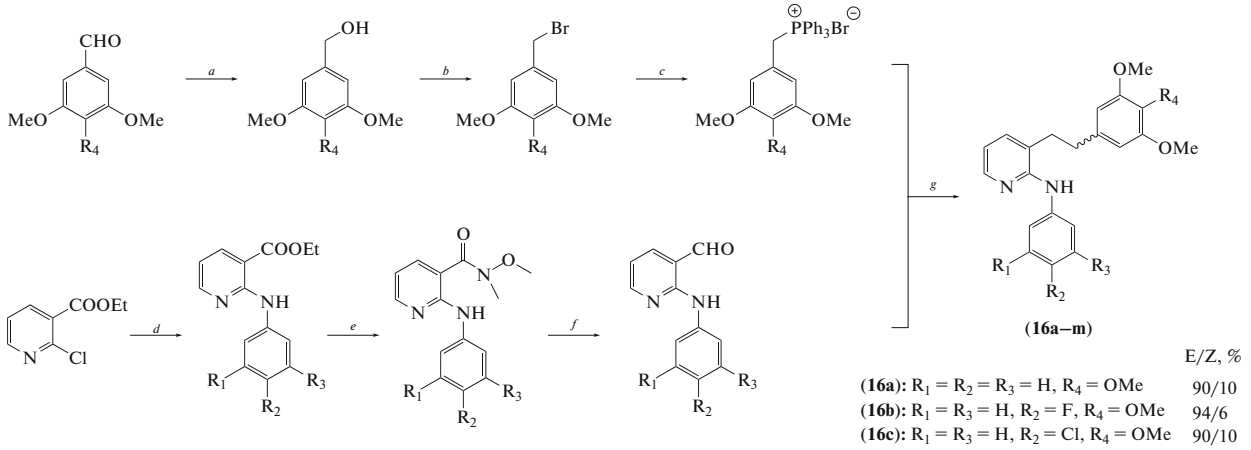


Fig. 2. DMU-212 and combretastatin A-4 structures.

Molecular modelling demonstrated that the four most active compounds (**15a**), (**15d**), (**15f**), and (**15g**) effectively interacted with a colchicine binding site of tubulin.

Also, another hybrid molecule derived from resveratrol and 2-anilinopyridine sulfonamide (E7010), a known inhibitor of tubulin polymerization, was prepared (Scheme 6) [19].

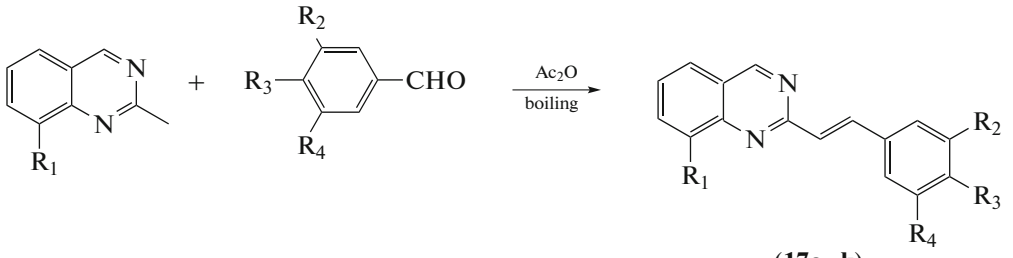


	E/Z, %
(16a): $R_1 = R_2 = R_3 = H$, $R_4 = OMe$	90/10
(16b): $R_1 = R_3 = H$, $R_2 = F$, $R_4 = OMe$	94/6
(16c): $R_1 = R_3 = H$, $R_2 = Cl$, $R_4 = OMe$	90/10
(16d): $R_1 = R_3 = H$, $R_2 = OH$, $R_4 = OMe$	94/6
(16e): $R_1 = R_3 = H$, $R_2 = R_4 = OMe$	93/7
(16f): $R_1 = H$, $R_2 = R_3 = R_4 = OMe$	94/6
(16g): $R_1 = R_2 = R_3 = R_4 = OMe$	95/5
(16h): $R_1 = R_2 = R_3 = F$, $R_4 = OMe$	95/5
(16i): $R_1 = R_2 = R_3 = R_4 = H$	90/10
(16j): $R_1 = R_3 = R_4 = H$, $R_2 = F$	92/8
(16k): $R_1 = R_3 = R_4 = H$, $R_2 = Cl$	92/8
(16l): $R_1 = R_3 = R_4 = H$, $R_2 = OMe$	90/10
(16m): $R_1 = R_4 = H$, $R_2 = R_3 = OMe$	94/6

Scheme 6. The synthesis of compounds (**16**). Reagents and reaction conditions: (*a*) $NaBH_4$, MeOH; (*b*) PBr_3, CH_2Cl_2; (*c*) PPh_3, toluene; (*d*) $ArNH_2$, ethyleneglycol; (*e*) *N*,*O*-dimethylhydroxylamine, $AlMe_3$, CH_2Cl_2; (*f*) DIBAL-H, CH_2Cl_2; (*g*) NaH, THF.

The antiproliferative activity of the compounds was studied in four human cell lines (A549, HepG2, HeLa, and Du145). The range of GI_{50} values varied within 2.1 to 20 μM. The GI_{50} values of compounds (**16a**) and (**16k**) were 13 times lower than those of resveratrol and 1.1–2 times lower than those of E7010 towards the human cervical cancer HepG2 cell line. It was found in these experiments that compounds (**16a**) and (**16k**) actively interacted with a colchicine binding site, inhibited tubulin assembling, depolymerized microtubes, and terminated the cell cycle at phase G_2/M. They also demonstrated a high efficacy and selectivity on a panel of human tumor NCI 60 cells.

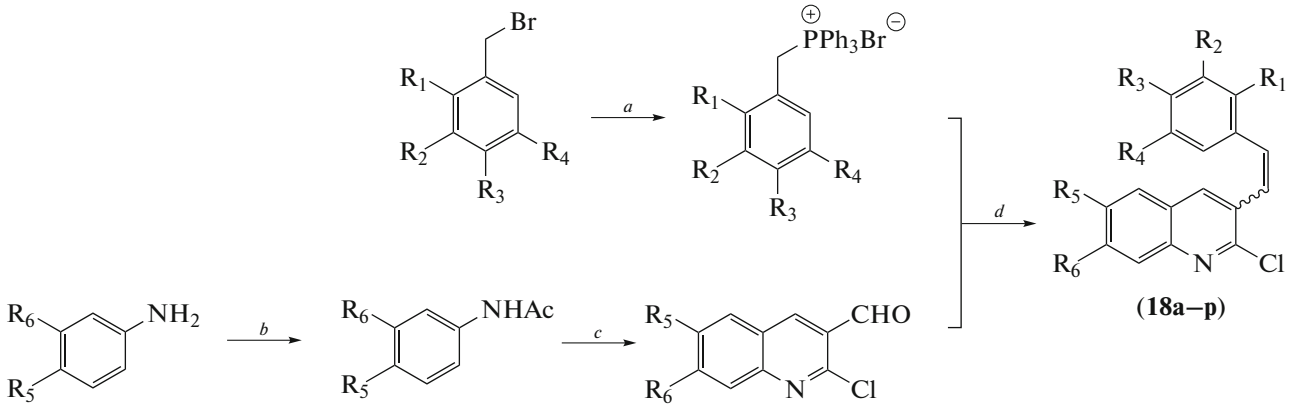
Also, the antimitotic activity of styryl quinazoline analogs [20] synthesized by the Knoevenagel reaction (Scheme 7) was assessed [21].



(17a–k)

(17a): $R_1 = R_2 = R_3 = OH$, $R_4 = H$
(17b): $R_1 = R_4 = H$, $R_2 = R_3 = OH$
(17c): $R_1 = OMe$, $R_2 = R_3 = OH$, $R_4 = H$
(17d): $R_1 = R_3 = OMe$, $R_2 = OH$, $R_4 = H$
(17e): $R_1 = R_4 = H$, $R_2 = R_3 = OAc$
(17f): $R_1 = OMe$, $R_2 = R_3 = OAc$, $R_4 = H$
(17g): $R_1 = R_2 = R_3 = OAc$, $R_4 = H$
(17h): $R_1 = OMe$, $R_2 = R_4 = H$, $R_3 = OH$
(17i): $R_1 = R_3 = OH$, $R_2 = R_4 = H$
(17j): $R_1 = OMe$, $R_2 = R_4 = H$, $R_3 = OAc$
(17k): $R_1 = OMe$, $R_2 = R_4 = Br$, $R_3 = OAc$

Scheme 7. The synthesis of compounds (**17**).



(18a–p)

(18a): $R_1 = R_2 = R_4 = R_5 = R_6 = H$, $R_3 = CF_3$
(18b): $R_1 = R_2 = R_4 = R_5 = R_6 = H$, $R_3 = F$
(18c): $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = CF_3$, $R_6 = Cl$
(18d): $R_1 = R_2 = R_4 = R_5 = H$, $R_3 = F$, $R_6 = Cl$
(18e): $R_1 = R_2 = R_4 = R_6 = H$, $R_3 = CF_3$, $R_5 = OMe$
(18f): $R_1 = R_2 = R_4 = R_6 = H$, $R_3 = F$, $R_5 = OMe$
(18g): $R_1 = R_3 = R_4 = R_5 = R_6 = H$, $R_2 = CF_3$
(18h): $R_1 = R_3 = R_4 = R_6 = H$, $R_2 = CF_3$, $R_5 = OMe$
(18i): $R_1 = R_3 = R_6 = H$, $R_2 = R_4 = CF_3$, $R_5 = OMe$
(18j): $R_1 = R_3 = R_5 = R_6 = H$, $R_2 = R_4 = CF_3$
(18k): $R_1 = R_3 = R_5 = H$, $R_2 = R_4 = CF_3$, $R_6 = Cl$
(18l): $R_1 = R_3 = CF_3$, $R_2 = R_4 = R_5 = R_6 = H$
(18m): $R_1 = R_3 = CF_3$, $R_2 = R_4 = R_6 = H$, $R_5 = OMe$
(18n): $R_1 = R_3 = H$, $R_2 = R_4 = CF_3$, $R_5 + R_6 = –OCH_2O–$
(18o): $R_1 = R_3 = R_4 = H$, $R_2 = CF_3$, $R_5 + R_6 = –OCH_2O–$
(18p): $R_1 = CF_3$, $R_2 = R_3 = R_4 = R_6 = H$, $R_5 = OMe$

Scheme 8. The synthesis of compounds (**18**). Reagents and reaction conditions: (*a*) PPh_3, PhMe, reflux; (*b*) HCl, Ac_2O; (*c*) $POCl_3$: DMF 3 : 1; (*d*) NaOH, DMSO.

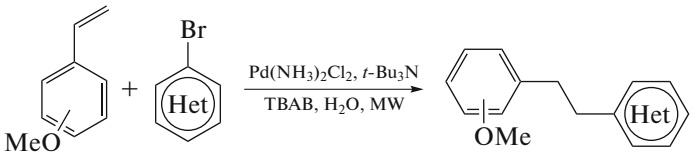
The vast majority of the synthesized derivatives displayed more noticeable inhibitory properties than resveratrol towards three tumor HeLa, HL-60, and A549 cell lines. The highest cytotoxic effect was shown for the triacetyl derivative (**17g**), which demonstrated cytostatic and cytocidic properties towards human

cervical cancer HeLa cells at 2–10 μM and 10 μM, respectively. It was found that compound (**17g**) inhibited HeLa proliferation by termination of the cell cycle at the G_2/M phase. This stage is associated with the activation of cyclin B1 expression due to the intensified phosphorylation of cyclin-dependent protein kinase 1(Cdk1) and protein Cdc25C as well as due to an increase in the concentration of protein $p21^{CIP1/WAF1}$ following the p53-dependent mechanism. The next studies on leukemia HL-60 cell line showed that compound (**17g**) stimulated apoptosis by the Fas-mediated caspase-8-dependent pathway via ROS generation and, to a lesser extent, by activation of cytochrome C and caspase-9 release [22].

A set of hybrid molecules containing a quinoline fragment was obtained by Scheme 8 with the Wittig reaction as a key stage [23].

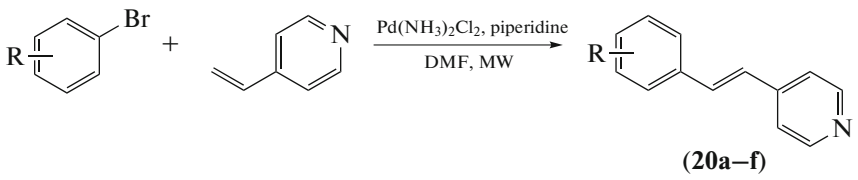
The activity studies performed on four cell lines (HeLa, MDA-MB231, MCF7, and MDA-MB468) showed that *Z*-isomers of the three derivatives (**18g**), (**18h**), and (**18p**) displayed not only rather powerful antiproliferative properties (IC_{50} < 4 mM) but also approximately a twofold selectivity towards tumor cells versus normal cells. The three other compounds (**18a**), (**18i**), and (**18j**) in the form of *Z*-isomers showed a relatively good activity with IC_{50} values in the range of 4 to 10 mM. Compound (**18b**) in the form of *E* isomer was highly active only towards MDA-MB468 (IC_{50} 0.12 mM) and caused a considerable DNA damage and termination of the cell cycle in phase S. Derivative (**18g**) in the form of *Z* isomer was effective against all the tested tumor cell lines. It terminated the cell cycle by inhibition of microtube polymerization followed by apoptosis. The effect was mediated by the interaction with tubulin at the binding site inherent for podofyllotoxin.

Along with the direct cytostatic effect the resveratrol antitumor activity associated with the inhibition of tumor angiogenesis was evaluated [24]. In particular, this inhibitory effect is a result of affecting the vascular endothelial growth factor (VEGF), super expression of which is often observed in tumor cells of different types. It supports their proliferation and migration as well as vascular permeability. Also, it was reported that resveratrol had an impact on the expression of genes involved in the activation of telomerase, an enzyme, whose expression is limited or does not occur in normal somatic human cells but is activated in 90% of tumor cells [25]. With the goal of increasing the efficacy of anticancer therapy many attempts are being made to combine a high cytotoxic activity and capacity to inhibit tumor angiogenesis and expression of genes involved in telomerase activation. Particularly, a set of resveratrol pyridine and pyrimidine analogs was synthesized using the Heck reaction (Scheme 9) [26].



(19a–o)

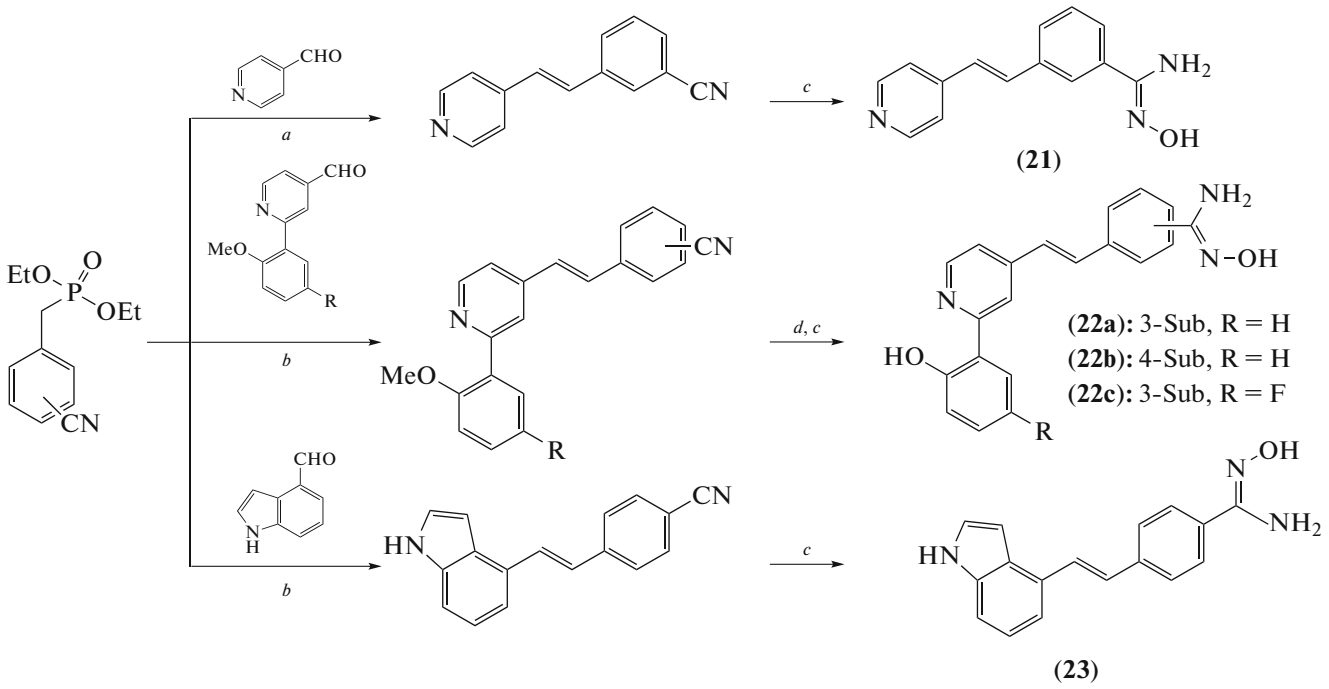
(19a): 2-OMe, Het = 2-Py
(19b): 3-OMe, Het = 2-Py
(19c): 4-OMe, Het = 2-Py
(19d): 2-OMe, Het = 3-Py
(19e): 3-OMe, Het = 3-Py
(19f): 4-OMe, Het = 3-Py
(19g): 2-OMe, Het = 4-Py
(19h): 3-OMe, Het = 4-Py
(19i): 4-OMe, Het = 4-Py
(19j): 2-OMe, Het = 2-pyrimidinyl
(19k): 3-OMe, Het = 2-pyrimidinyl
(19l): 4-OMe, Het = 2-pyrimidinyl
(19m): 2-OMe, Het = 5-pyrimidinyl
(19n): 3-OMe, Het = 5-pyrimidinyl
(19o): 4-OMe, Het = 5-pyrimidinyl



(20a–f)

(20a): R = 2-OH
(20b): R = 3-OH
(20c): R = 4-OH
(20d): R = 2-NH_2
(20e): R = 3-NH_2
(20f): R = 4-NH_2

Scheme 9. The synthesis of compounds (**19**) and (**20**).



Scheme 10. The synthesis of compounds (**21**–**23**). Reagents and reaction conditions: (*a*) *t*-BuOH, *t*-BuOK; (*b*) *t*-BuOK, DMF; (*c*) $NH_2OH \cdot HCl$, Et_3N, CH_3OH, reflux, 3–8 h; (*d*) BBr_3, CH_2Cl_2.

Compounds (**19c**), (**19e**), (**19g**), (**19h**), and (**19i**) displayed lower IC_{50} values than resveratrol towards tumor HT-29 cell line and higher IC_{50} values towards a nontumor HEK-293 cell line. The most active compounds were methoxy substituted derivatives (**19g**–**i**) containing a 4-pyridine ring.

Compound (**19g**) could also decrease the production of the VEGF protein and expression of the hTERT gene at the concentrations lower than IC_{50} values in the experiments on noncancerous HEK-293 cells. Along with a high toxicity towards HT-29 and downregulation of the VEGF production, derivative (**19h**) decreased the c-Myc gene expression. At the same time hydroxy substituted analogs (**20a**–**c**) were poorly active, which was also confirmed in [27], where compound (**20c**) was prepared by an alternative scheme and was shown to exert moderate cytotoxicity on pancreatic cancer AsPC-1, Capan-2, and BxPC-3 cell lines similar to that of resveratrol.

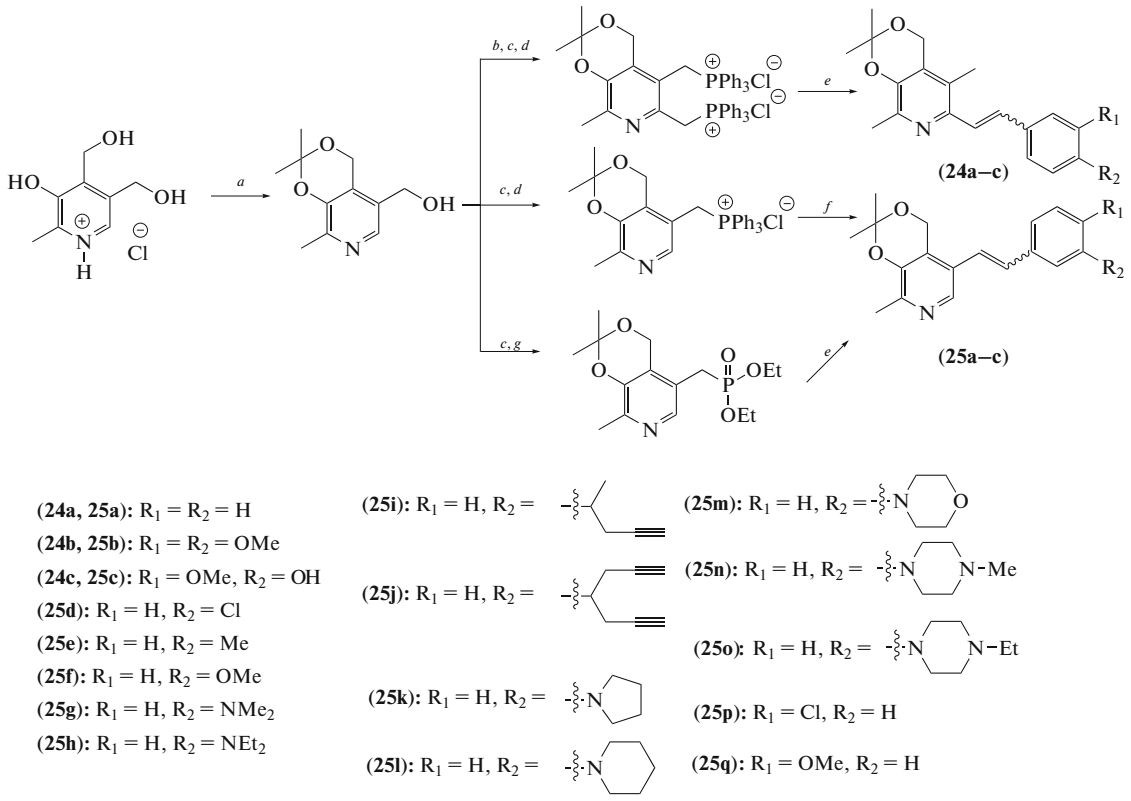
Another promising target for the development of antitumor agents is lysine-specific histone demethylase (LSD1), an enzyme playing an important role in the cell growth and differentiation, whose excessive expression is observed in malignant tumors of different types and is associated with the onset and progression of tumor growth. It was shown that resveratrol significantly inhibited LSD1 activity. The inhibitory effect was stronger than that of the known inhibitor *trans*-2-phenylcyclopropylamine [28]. The attempts to design new reversible LSD1 inhibitors were taken with resveratrol as a structural basis [29, 30]. The synthesis of these analogs is shown in Scheme 10.

Several compounds inhibiting LSD1 with IC_{50} in the submicromolar range were found. Compound (**22c**) proved to be the most powerful reversible LSD1 inhibitor with IC_{50} 283 nM, which could amplify the expression of the CD86 surrogate cellular biomarker in human leukemia THP-1 cells. This compound effectively inhibited the THP-1 and MOLM-13 cell growth with IC_{50} 5.76 and 8.34 μM respectively. Also, compound (**22c**) inhibited the THP-1 cell fission in a dose-dependent mode.

The stilbene backbone of resveratrol allowed an assumption that with a high probability it may manifest estrogen-modulating effects, which were studied on various breast cancer cell lines (MCF-7, T47D, LY2, and S30). It was found that in the presence of estradiol resveratrol operated as an anti-estrogen and thus could serve a positive factor upon breast cancer chemotherapy [31].

New structures combining a protected pyridoxine fragment and a resveratrol backbone were designed (Scheme 11) [32–34].

Antitumor and cytotoxic properties of the synthesized compounds were studied in vitro. Analogs (*E*-**25b**) and (*E*-**25c**) were found to be nontoxic towards both tumor (MCF-7, SNB-19, and HCT-15) and normal (HEK-293) cells, whereas compound (*E*-**25a**) exerted a more noticeable effect towards HEK-293 than towards tumor cells. The most promising compounds (*E*-**24b**) and (*E*-**24c**) were highly selective towards the



Scheme 11. The synthesis of compounds (**24**) and (**25**). Reagents and reaction conditions: (*a*) $(CH_3)_2CO$, H^+; (*b*) H_2O, HCHO, NaOH, 70°C; (*c*) $SOCl_2$, CH_2Cl_2 or $PhCH_3$, reflux; (*d*) PPh_3, CH_3CN, reflux; (*e*) ArCHO, NaH, CH_2Cl_2 or THF; (*f*) ArCHO, Et_3N, CH_2Cl_2, reflux; (*g*) $P(OEt)_3$, reflux.

estrogen-dependent breast cancer MCF-7 cell line with IC_{50} from 1.9 to 7.9 μM. Compound (*E*-**24b**) was also selective towards the estrogen-dependent breast cancer MCF-7 cell line if compared with the estrogen-negative breast cancer MDA-MB-231 cell line (the selectivity index 10), which can imply an essential role of estrogen receptors as a potential target.

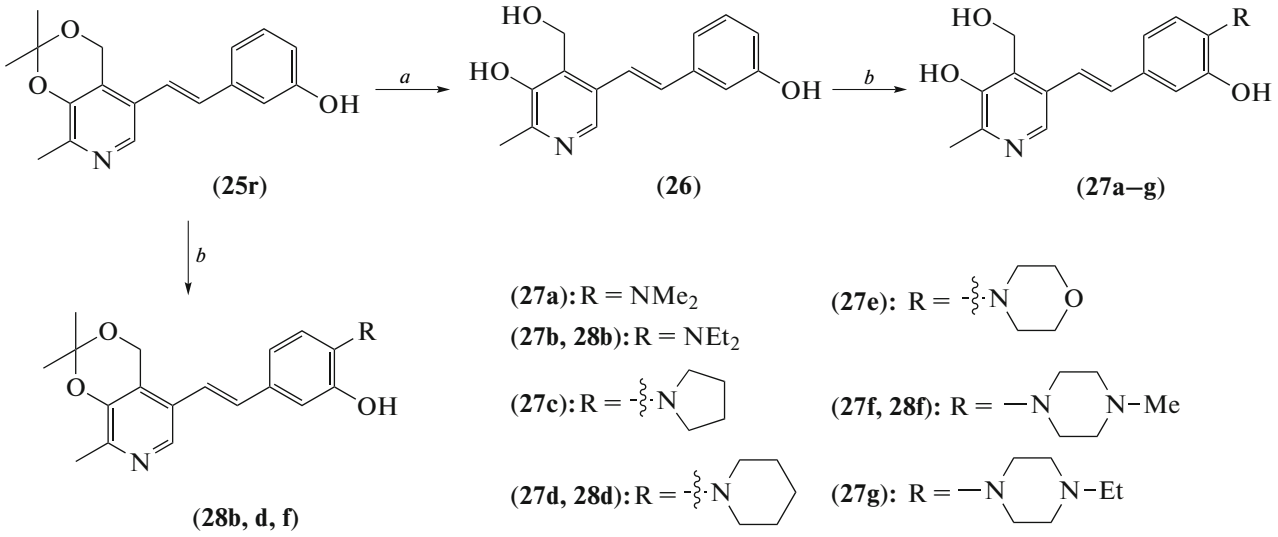
Analogs Displaying Neuroprotective Activity

As was shown in numerous studies, resveratrol exerted the neuroprotective activity by blocking the ROS-induced neuron death due to a direct antioxidant effect and sirtuin SIRT1 activation as well as due to other pathways, for example, via inhibition of the amyloid plaque growth (due to transformation of soluble oligomers and fibrillary β-amyloids to nontoxic forms), downregulation of microglia activation (by inhibition of anti-inflammatory mediators or inhibition of M1 polarization and activation of M2 polarization), mitochondrial biogenesis (due to stimulation of PGC-1α expression and AMPK activation), and prophylactics of apoptotic cell death in hippocampus (followed by an increase in mitochondrial UCP2 expression via PPAR-γ activation).

Design of resveratrol heterocyclic analogs with neuroprotective properties is usually based on the design of multitargeted ligands, which is driven by the complex pathogenesis of neurodegenerative diseases.

Derivatives (**25**) were studied as potential MAO-B inhibitors, agents for the treatment of Parkinson's disease [34]. Most of them demonstrated good inhibitory properties and high selectivity towards MAO-B. In particular, compounds (**25i**) and (**25n**) were the most effective hMAO-B inhibitors with IC_{50} 0.01–0.02 μM. Further experiments showed that (**25n**) and (**25i**) were reversible and irreversible MAO-B inhibitors respectively. The reasons for discrepancies and peculiarities of interactions with MAO-B were assessed by the molecular docking approach. In addition, (**25i**) and (**25n**) manifested a good antioxidant activity, neuroprotective properties in the H_2O_2-induced PC-12 cell damage test, and the capacity to penetrate through the blood–brain barrier, which may indicate a potential of these compounds for the treatment of Parkinson's disease.

Another set of multifunctional agents, pyridoxine–resveratrol hybrids and the corresponding Mannich bases, were synthesized as described in [35] (Scheme 12).



Scheme 12. The synthesis of compounds (**26**–**28**). Reagents and reaction conditions: (*a*) 10% HCl, THF, 70°C, 3 h; (*b*) amine, paraform, EtOH, reflux.

It was shown that most of these compounds could selectively inhibit AChE and MAO-B. The most potent AChE inhibitors were compounds (**27d**) and (**28b**) (IC_{50} 2.11 and 1.56 μM, respectively), whereas compound (**27e**) was the most effective towards MAO-B (IC_{50} 2.68 μM). The results of the kinetic analysis demonstrated that compound (**27d**) was an inhibitor of a mixed type and could simultaneously bind to AChE catalytic and peripheral anion sites. In addition, all the compounds under study exerted good antioxidant and metal chelating properties, which is important for the design of multifunctional agents for the treatment of Alzheimer's disease.

With the goal of designing effective agents for the treatment of Alzheimer disease the inhibitory effect on the Aβ aggregation was assessed for compounds (**10i**) and (**11f**), which displayed noticeable antioxidant and metal chelating activities. The tested compounds were shown to effectively interact with the Aβ1–42 C-end, inhibit both the inherent and metal-induced (iron or copper) β-sheet aggregation, and inhibit the fibril formation with a higher potential against Aβ1–42 aggregation than resveratrol.

In continuation of this pharmacophore-combined strategy a set of 2-substituted benzothiazoles was synthesized, in which deferiprone or maltol fragments were joined with thiogavine T, a fluorescent indicator wifely used in vitro for the evaluation of the Aβ aggregation (Scheme 13) [36].

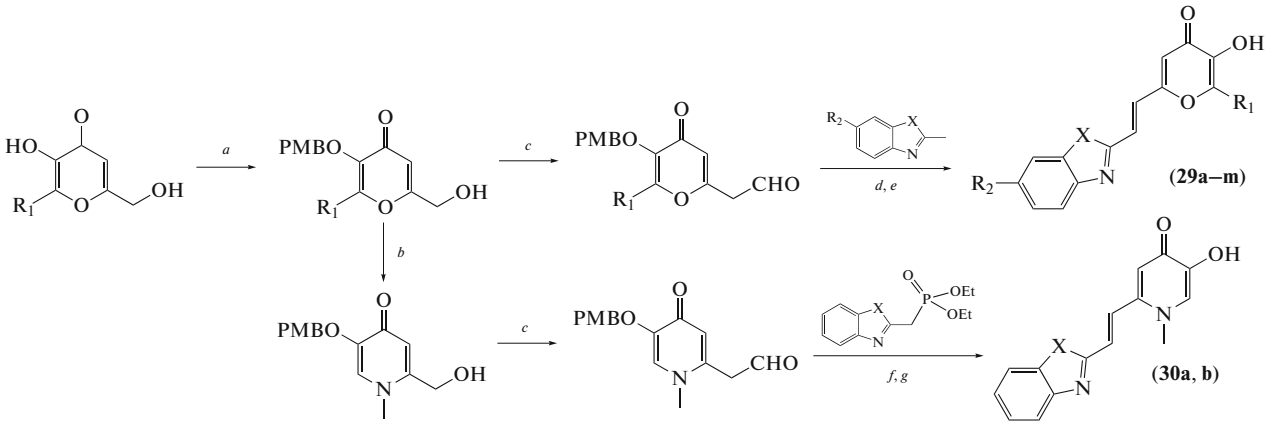
Derivatives (**29c**) and (**29i**) demonstrated the highest inhibitory activity towards Aβ1–42 aggregation, a high radical absorbing effect, and noticeable chelating properties towards biometals as well as disaggregation activity towards the previously formed Aβ1–42 fibrils.

Another set of synthesized compounds targeted at the therapy of Alzheimer's disease was based on the combination of the resveratrol pharmacophore and clioquinol, a known metal chelator (Scheme 14) [37].

The hybrids were effective inhibitors of the autoinduced and copper(II)-induced Aβ aggregation. They manifested the antioxidant potential and chelating properties. Among these compounds derivative (**31c**) exerted the highest inhibitory activity towards autoinduced (IC_{50} 8.50 μM) and copper(II)-induced Aβ aggregation. It also supported disassembling of well-structured Aβ fibrils formed by the self-induced and copper(II)-induced Aβ aggregation. In addition, compound (**31c**) could regulate the production of hydroxyl radicals by halting copper redox cycling due to the complex formation, which was confirmed in the Cu(I)/Cu(II) system assay and ascorbate as a reducing agent. It is noteworthy that in the case of compound (**31c**) the lethal dose for mice was higher than 2 g/kg. Its capacity to penetrate through the brain barrier was also found.

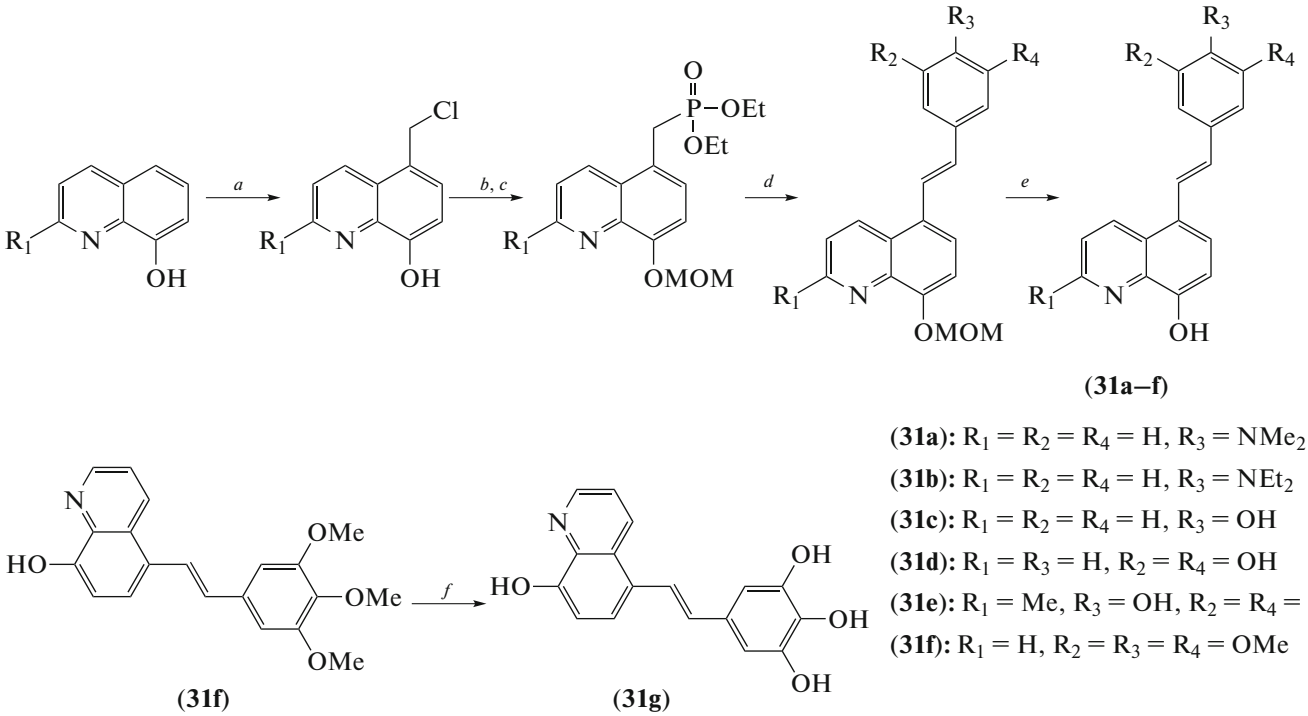
CNS resident macrophages, the so called microglia, are regarded as another potential target for the therapy of neurodegenerative disorders. Its superactivation (induced by various factors) initiates extra production of inflammatory mediators (nitric oxide, cytokines, or TNF-α), thus causing neuron damages and supporting pathogenesis of Alzheimer's disease, Parkinson's disease, and other neurodegenerative disorders.

On the basis of the resveratrol capacity to inhibit macrophage activation and control iNOS expression some heterocyclic analogs were synthesized (Scheme 15) and their inhibitory properties were studied on an experimental model of lipopolysaccharide-induced microglia activation [38, 39].



(**29a**): X = S, R_1 = R_2 = H
(**29b**): X = S, R_1 = Me, R_2 = H
(**29c**): X = O, R_1 = R_2 = H
(**29d**): X = O, R_1 = Me, R_2 = H
(**29e**): X = NMe, R_1 = R_2 = H
(**29f**): X = NMe, R_1 = Me, R_2 = H
(**29g**): X = S, R_1 = H, R_2 = OMe
(**29h**): X = S, R_1 = H, R_2 = Br
(**29i**): X = S, R_1 = H, R_2 = OH
(**29j**): X = O, R_1 = H, R_2 = OMe
(**29k**): X = O, R_1 = H, R_2 = OH
(**29l**): X = NMe, R_1 = H, R_2 = OMe
(**29m**): X = NMe, R_1 = H, R_2 = OH
(**30a**): X = S
(**30b**): X = O

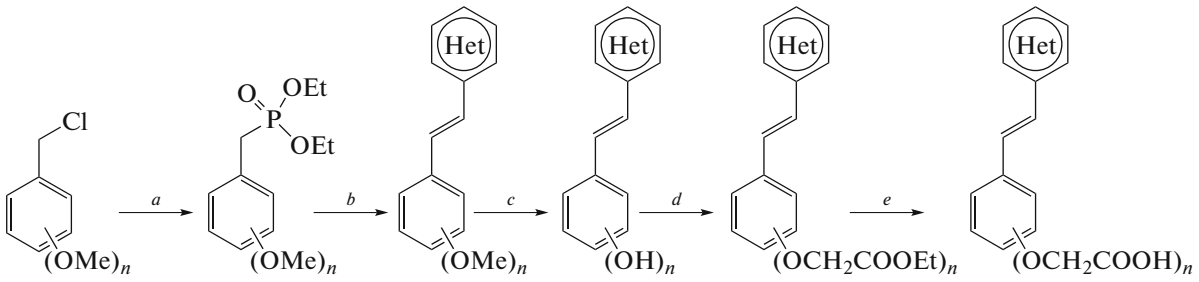
Scheme 13. The synthesis of compounds (**29**) and (**30**). Reagents and reaction conditions: (*a*) PMB-Cl, K_2CO_3, DMF, 80°C; (*b*) CH_3NH_2, H_2O, reflux; (*c*) MnO_2, $CHCl_3$, reflux; (*d*) AcOH, Ac_2O, MW; (*e*) K_2CO_3, MeOH; (*f*) NaH, THF; (*g*) CF_3COOH, CH_2Cl_2.



(**31a–f**)

(**31a**): R_1 = R_2 = R_4 = H, R_3 = NMe_2
(**31b**): R_1 = R_2 = R_4 = H, R_3 = NEt_2
(**31c**): R_1 = R_2 = R_4 = H, R_3 = OH
(**31d**): R_1 = R_3 = H, R_2 = R_4 = OH
(**31e**): R_1 = Me, R_3 = OH, R_2 = R_4 = H
(**31f**): R_1 = H, R_2 = R_3 = R_4 = OMe

Scheme 14. The synthesis of compounds (**31**). Reagents and reaction conditions: (*a*) 37% HCl, 37% HCHO; (*b*) $P(OEt)_3$, reflux; (*c*) MOMCl, (*i*-$Pr)_2NEt$, CH_2Cl_2; (*d*) ArCHO, CH_3ONa, DMF, 0–80°C; (*e*) 6 M HCl, CH_3OH, reflux; (*f*) BBr_3, CH_2Cl_2.



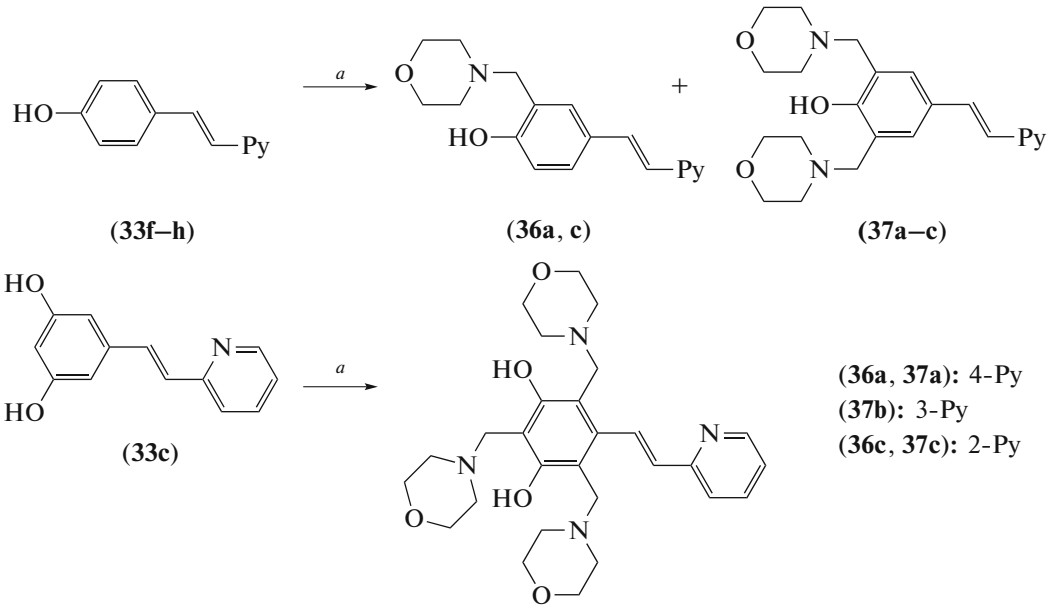
(32a–i) **(33a–c, e–i)** **(34a–c, e–h)** **(35a–c, f, g)**

(32a–35a): 3,5-Sub; Het = 4-Py
(32b–35b): 3,5-Sub; Het = 3-Py
(32c–35c): 3,5-Sub; Het = 2-Py
(32d): 3,5-Sub; Het = 2-furyl
(32e–34e): 3,5-Sub; Het = 4-quinolinyl
(32f–35f): 4-Sub; Het = 4-Py
(32g–35g): 4-Sub; Het = 3-Py
(32h–34h): 4-Sub; Het = 2-Py
(32i), (33i): 3,5-Sub; Het = 2-(4-bromofuryl)

Scheme 15. The synthesis of compounds (**32**–**35**). Reagents and reaction conditions: (*a*) $P(OEt)_3$, reflux, 3 h; (*b*) PyCHO, NaOEt, DMF; (*c*) BBr_3, CH_2Cl_2, −10°C, 2 h; (*d*) $ClCH_2COOEt$, KOH, DMF; (*e*) 1. NaOH; 2. HCl.

It was found that compounds (**32e**), (**33e**), and (**33i**) could effectively inhibit the microglia NO and TNF-α production by blocking IκBα phosphorylation and degradation but could not directly interact with NO in a nitroprusside sodium solution. Derivative (**33i**) could also block the ROS formation.

Similar properties were observed for a previously described derivative (**17g**). It could not only reduce iNOS and TNF-α expression and the mRNA level but also decrease IL-6 secretion and TLR4 expression and inhibit signaling pathways associated with MAPK and nuclear transcription factor NF-κB [40]. Thus, the



(**38**)

(36a, 37a): 4-Py
(37b): 3-Py
(36c, 37c): 2-Py

Scheme 16. The synthesis of compounds (**36**–**38**).
Reagents and reaction conditions: (*a*) HCHO, morpholine, EtOH, reflux, 2 h.

compounds manifesting powerful inhibitory effects on microglia activation are of interest for the treatment of neurodegenerative disorders associated with microglia activation.

Analogs Displaying Anti-Inflammatory Activity

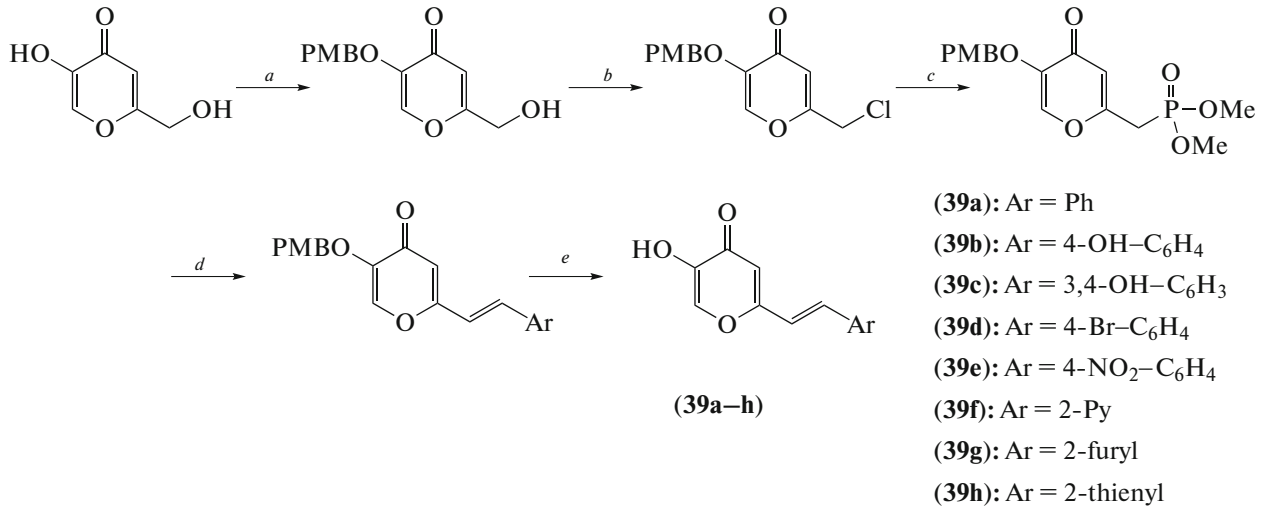
Resveratrol was found to display anti-inflammatory properties not only due to the inhibition of macrophage activation and control of iNOS expression but also due to the capacity to downregulate expression and activity of COX-1 and COX-2 [41]. Unfortunately, similarly to most of the nonsteroid agents the use of resveratrol resulted in adverse events in gastrointestinal tract, particularly, a noticeable negative effect on healing of indomethacin-induced gastric ulcer in mice due to insufficient selectivity of COX inhibition [42].

With the goal of designing more effective and safe anti-inflammatory agents the known derivatives (**33**)–(**35**) were synthesized and studied [43]. Some of them were transformed to Mannich bases (**36**–**38**) (Scheme 16).

In the experiments on a xylene-induced edema in mice resveratrol proved to be the most active compound, which inhibited the edema by 38.9%. Similar results (37.0%) were received for compound (**35c**). For the other derivatives (**35f**), (**37b**), and (**38**) the reduction was in the range of 30 to 35%.

The previously reported set of styryl quinazoline derivatives (**17a**–**k**) was also studied for the ability to inhibit COX-2 and decrease the PGE2 production. Except for 3,4-diacetyl styryl quinazolines (**17d**–**f**), these derivatives demonstrated similar or higher inhibitory activity than that of resveratrol and lower cytotoxicity on a RAW264.7 cell line. It was found that substituents in the styryl quinazoline benzene ring had a greater impact on the inhibitory activity than those in the quinolone cycle.

Pyronyl vinyl resveratrol analogs (**39**) were prepared by the Wittig–Horner reaction of pyronylphosphate and various aromatic carboxaldehydes (Scheme 17) [44].



Scheme 17. The synthesis of compounds (**39**). Reagents and reaction conditions: (*a*) PMB-Cl, K_2CO_3, DMF, 80°C; (*b*) $SOCl_2$, 2 h; (*c*) $P(OMe)_3$; (*d*) ArCHO, NaH, THF; (*e*) BBr_3, CH_2Cl_2.

The capacity to inhibit the NO and PGE2 production was evaluated on LPS-activated macrophages of the RAW264.7 cell line. The highest inhibitory activity and lower if compared with resveratrol cytotoxicity was found for derivative (**39b**).

Analogs With Other Physiological Properties

It was found recently that resveratrol could display an in vitro inhibitory activity towards the influenza virus [45]. Fifty resveratrol derivatives were tested for the anti-influenza activity using the neurominidaze activity assay [46]. Derivative (**33b**) was among the compounds manifesting inhibitory properties against influenza virus neurominidaze (A/PR/8/34 (H1N1 strain)) with IC_{50} 186.1 mM.

CONCLUSIONS

The studies on the design of resveratrol analogs in the context of the strategy under discussion are mainly focused on the preparation of hybrid structures. Their major advantage, a multitargeted action, is especially meaningful for the treatment of pathologies that are complicated from the point of view of pathogenesis pathways, such as oncological and neurodegenerative diseases. The basis of these studies is retention and potentiation of the antiradical activity inherent in the

prototype, as well as some other known target-oriented effects. In many cases such an approach proved to be effective and provided not only additive effects of single pharmacophore fragments but also a potentiating action. However, it is noteworthy that most of the studies were conducted on cell cultures, which is associated with some constraints. Therefore, the tests on the whole organism are necessary in order to confirm pharmacological effects and find the mode of action of the new compounds.

COMPLIANCE WITH ETHICAL STANDARDS

In this work, humans or animals were not involved as subjects of studies.

Conflict of Interests

The authors notified about the absence of conflict of interest.

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