Bulgarian Chemical Communications, Volume 49, Special Edition B (pp. 71 – 75) 2017

Synthesis and cytotoxic activity of new heterocyclic analogues of resveratrol, containing benzoxazolone ring

M. S. Gerova[1], E. A. Aleksandrova[1,2], Y. B. Ivanova[3], D. V. Stanisheva[1], G. Ts. Momekov[4], O. I. Petrov[1]*

[1] *Department of Pharmaceutical and Applied Organic Chemistry, Faculty of Chemistry and Pharmacy, Sofia University "St. Kliment Ohridski", 1 James Bourchier Blvd, 1164 Sofia, Bulgaria*
[2] *Department of General and Clinical Pathology, Medical Faculty, Trakia University, 11 Armeiska Str., 6000 Stara Zagora, Bulgaria*
[3] *Department of Plant Pathology and Chemistry, Faculty of Ecology and Landscape Architecture, University of Forestry, 10 Kliment Ohridsky Blvd, 1756 Sofia, Bulgaria*
[4] *Department of Pharmacology, Pharmacotherapy and Toxicology, Faculty of Pharmacy, Medical University-Sofia, 2 Dunav Str., Sofia 1000, Bulgaria*

Received March 01, 2017; Revised March 15, 2017

Dedicated to Acad. Bogdan Kurtev on the occasion of his 100th birth anniversary

New heterocycle analogues of resveratrol were designed and synthesized as potential anticancer agents. The compounds contain 3,5-dimethoxy- or 3,5-dihydroxystyryl fragment attached to the C5 or C6 position of a benzoxazolone ring. The compounds were tested for their cytotoxic activity against three human cancer cell lines (HL-60, MGF-7 and MDA-MB-321) and some of them were found to exhibit significant antiproliferative effect. Generally, the obtained 5-styrylbenzoxazolones were more active in compare to the corresponding 6-styrylbenzoxazolone positional isomers.

Key words: resveratrol; benzoxazolone; stilbene; cytotoxicity

INTRODUCTION

Resveratrol (Fig. 1) belongs to a group of naturally occurring polyphenols possessing the *trans*-stilbene scaffold. Found in more than 70 plants, the compound has been shown to exhibit a variety of health-beneficial properties such as antioxidant, anti-inflammatory, anti-diabetic, cardio- and neuroprotective activities [1–5]. Additionally, resveratrol has been recognized as a promising chemopreventive and anticancer agent due to its capability to inhibit tumorigenesis by modulation of several cellular process including apoptosis, cell cycle progression as well as angiogenesis [2, 6–9]. A number of methoxy derivatives of resveratrol have been also reported to exert high cytotoxicity against various human cancer cell lines [10–14]. Some of the synthetic analogues showed better activity compared to the natural compound [10, 11, 14].

In search of new anticancer agents, we have planned the synthesis of a small series of heterocyclic derivatives of resveratrol, in which the 4'-hydroxyphenyl moiety in the parent molecule was replaced with a benzoxazolone (Fig. 1). Considered to be a "privileged scaffold" in medicinal chemistry, the benzoxazolone heterocyclic system has been extensively used in drug discovery as a phenol and pyrocatechol bioisostere [15]. The 3,5-dihydroxyphenyl fragment of the parent resveratrol molecule was left intact or replaced with a 3,5-dimethoxyphenyl moiety, with the aim to systematically evaluate the role of the isolated fragments on the biological activity of the compounds.

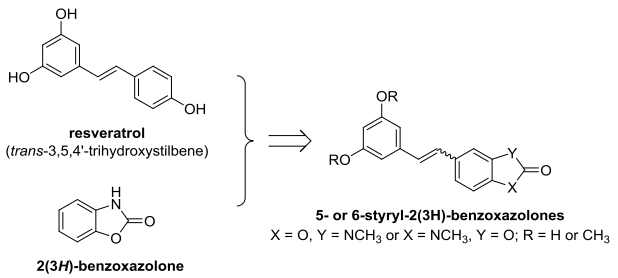


Fig. 1. Chemical structure of resveratrol, 2(3*H*)-benzoxazolone and target 5- and 6-styryl-2(3*H*)-benzoxazolones.

Thus, in continuation of our previous studies on the synthesis of heterocyclic stilbenes [16], here we report the preparation of 5- and 6-(3,5-dimethoxy-

* To whom all correspondence should be sent:
E-mail: *opetrov@chem.uni-sofia.bg*

or 3,5-dihydroxystyryl)-2(3*H*)-benzoxazolones as closely related resveratrol analogues. Their *in vitro* cytotoxicity was examined against three human cancer cell lines.

EXPERIMENTAL

Chemistry

Melting points (mp) were determined on a Boetius hot-stage microscope and are uncorrected. Infrared spectra (IR) were recorded on a Specord 71 spectrometer. ^{1}H NMR spectra were obtained on a Bruker DRX250 or Bruker DRX400 spectrometers. Chemical shifts were reported in parts per million (ppm, δ) relative to the solvent peak ($CDCl_3$, 7.26 ppm; DMSO-d_6, 2.50 ppm; acetone-d_6, 2.05 ppm). Elemental analyses (C, H, N) were performed on a Vario III microanalyzer and the obtained results were within 0.4% of theoretical values. All reactions were monitored by thin-layer chromatography (TLC) on silica gel plates (Kieselgel 60 F_{254}), using hexane/acetone (2:1 v/v) as eluent. Column chromatography on Merck silica gel 60 (230–400 mesh) was applied for the separation of diastereomers. Phosphonium bromides **1a-b** were synthesized as described previously [16].

General procedure for the synthesis of stilbene derivatives via Wittig reaction

A mixture of appropriate phosphonium bromide **1a-b** (1.51 g, 3 mmol), 3,5-dimethoxybenzaldehyde (0.50 g, 3 mmol), powdered potassium carbonate (1.38 g, 10 mmol) and 18-crown-6 (0.01 g) in THF/DCM (20 mL, 2:1 v/v) was refluxed for 3 h (monitored by TLC). The inorganic salts were filtered off and the filtrate was concentrated under reduced pressure to obtain a mixture of the corresponding *E*- and *Z*-stilbenes and triphenylphosphine oxide. Both diastereomers were isolated by column chromatography using petroleum ether/acetone (10:1 v/v) as eluent.

*(Z)-5-(3,5-Dimethoxystyryl)-3-methyl-2(3H)-benzoxazolone (**2a**)*

Yield: 48% (0.48 g), colourless oil. IR (capillary film, cm^{-1}): 1780 (C=O). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.27 (s, 3H, NCH_3), 3.67 (s, 6H, OCH_3), 6.34 (t, 1H, ArH, *J* = 2.3 Hz), 6.39 (d, 2H, ArH, *J* = 2.3 Hz), 6.57 (s, 2H, =CH), 6.84 (br s, 1H, ArH), 7.04–7.05 (m, 2H, ArH). ^{1}H NMR (acetone-d_6, 500 MHz): δ 3.29 (s, 3H, NCH_3), 3.65 (s, 6H, OCH_3), 6.36 (t, 1H, ArH, *J* = 2.2 Hz), 6.42 (d, 2H, ArH, *J* = 2.1 Hz), 6.58 (d, 1H, =CH, *J* = 12.2 Hz), 6.65 (d, 1H, =CH, *J* = 12.2 Hz), 7.04–7.06 (m, 2H, ArH), 7.12 (d, 1H, ArH, *J* = 8.0 Hz). Anal. Calcd. for $C_{18}H_{17}NO_4$ (311.34): C 69.44, H 5.50, N 4.50. Found: C 69.62, H 5.62, N 4.30.

*(E)-5-(3,5-Dimethoxystyryl)-3-methyl-2(3H)-benzoxazolone (**3a**)*

Yield: 43% (0.40 g), mp 164–165 °C. IR (nujol, cm^{-1}): 1760 (C=O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.44 (s, 3H, NCH_3), 3.84 (s, 6H, OCH_3), 6.41 (t, 1H, ArH, *J* = 2.1 Hz), 6.67 (d, 2H, ArH, *J* = 2.3 Hz), 6.99 (s, 1H, =CH, *J* = 16.2 Hz), 7.08 (s, 1H, =CH, *J* = 16.3 Hz), 7.12 (br s, 1H, ArH), 7.17 (d, 1H, ArH, *J* = 8.3 Hz), 7.23 (dd, 1H, ArH, *J* = 1.0 Hz, *J* = 8.3 Hz). Anal. Calcd. for $C_{18}H_{17}NO_4$ (311.34): C 69.44, H 5.50, N 4.50. Found: C 69.21, H 5.37, N 4.53.

*(Z)-6-(3,5-Dimethoxystyryl)-3-methyl-2(3H)-benzoxazolone (**2b**)*

Yield: 48% (0.48 g), mp 89–91 °C. IR (nujol, cm^{-1}): 1770 (C=O). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 3.37 (s, 3H, NCH_3), 3.68 (s, 6H, OCH_3), 6.34 (t, 1H, ArH, *J* = 2.3 Hz), 6.39 (d, 2H, ArH, *J* = 2.3 Hz), 6.54 (s, 2H, =CH), 6.81 (d, 1H, ArH, *J* = 8.4 Hz), 7.09–7.13 (m, 2H, ArH). ^{1}H NMR (acetone-d_6, 250 MHz): δ 3.38 (s, 3H, NCH_3), 3.67 (s, 6H, OCH_3), 6.37 (t, 1H, ArH, *J* = 2.1 Hz), 6.42 (d, 2H, ArH, *J* = 2.1 Hz), 6.56 (d, 1H, =CH, *J* = 12.2 Hz), 6.64 (d, 1H, =CH, *J* = 12.2 Hz), 7.08 (d, 1H, ArH, *J* = 8.1 Hz), 7.11 (br s, 1H, ArH), 7.16 (dd, 1H, ArH, *J* = 1.1 Hz, *J* = 8.4 Hz). Anal. Calcd. for $C_{18}H_{17}NO_4$ (311.34): C 69.44, H 5.50, N 4.50. Found: C 69.52, H 5.83, N 4.23.

*(E)-6-(3,5-Dimethoxystyryl)-3-methyl-2(3H)-benzoxazolone (**3b**)*

Yield: 35% (0.33 g), mp 164–165 °C. IR (nujol, cm^{-1}): 1770 (C=O). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.42 (s, 3H, NCH_3), 3.84 (s, 6H, OCH_3), 6.41 (t, 1H, ArH, *J* = 2.2 Hz), 6.66 (d, 2H, ArH, *J* = 2.2 Hz), 6.92–6.99 (m, 2H, =CH, ArH), 7.07 (s, 1H, =CH, *J* = 16.2 Hz), 7.31 (dd, 1H, ArH, *J* = 1.2 Hz, *J* = 8.1 Hz), 7.40 (br s, 1H, ArH). Anal. Calcd. for $C_{18}H_{17}NO_4$ (311.34): C 69.44, H 5.50, N 4.50. Found: C 69.38, H 5.37, N 4.53.

General procedure for the demethylation of the methoxy groups with BBr_3

Boron tribromide (1.7 M in DCM, 0.53 mL, 0.9 mmol) was added to a stirred solution of corresponding 3,5-dimethoxysubstituted (*E*)-stilbene **3a-b** (0.16 g, 0.5 mmol) in anhydrous DCM (10 mL) at –10 °C. The resulting mixture was stirred for 1 h at –10 °C, allowed to warm to room temperature, and stirred for another 48 h. Then,

water (15 mL) was added and the obtained precipitate was filtered off and air-dried. The product was purified by recrystallization.

*(E)-5-(3,5-Dihydroxystyryl)-3-methyl-2(3H)-benzoxazolone (**4a**)*

Yield: 70% (0.10 g), mp 252–254 °C (ethanol). IR (nujol, cm^{-1}): 3200-3400 (OH), 1720 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.38 (s, 3H, NCH_3), 6.16 (t, 1H, ArH, *J* = 2.1 Hz), 6.43 (d, 2H, ArH, *J* = 2.1 Hz), 7.08 (s, 2H, =CH), 7.29 (s, 2H, ArH), 7.58 (s, 1H, ArH), 9.26 (s, 2H, OH). ^{1}H NMR (acetone-d_6, 500 MHz): δ 3.43 (s, 3H, NCH_3), 6.30 (br s, 1H, ArH), 6.57 (d, 2H, ArH, *J* = 1.9 Hz), 7.09 (d, 1H, =CH, *J* = 16.3 Hz), 7.13 (d, 1H, =CH, *J* = 16.3 Hz), 7.21 (d, 1H, ArH, *J* = 8.2 Hz), 7.29 (dd, 1H, ArH, *J* = 1.3 Hz, *J* = 8.2 Hz), 7.47 (br s, 1H, ArH), 8.46 (br s, 2H, OH). Anal. Calcd. for $C_{16}H_{13}NO_4$ (283.28): C 67.84, H 4.63, N 4.94. Found: C 67.54, H 4.81, N 4.71.

*(E)-6-(3,5-Dihydroxystyryl)-3-methyl-2(3H)-benzoxazolone (**4b**)*

Yield: 77% (0.11 g), mp 281–283 °C (acetone/water, 1:1 v/v). IR (nujol, cm^{-1}): 3150-3400 (OH), 1740 (C=O). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.35 (s, 3H, NCH_3), 6.14 (t, 1H, ArH, *J* = 2.1 Hz), 6.42 (d, 2H, ArH, *J* = 2.1 Hz), 7.05 (d, 2H, =CH), 7.23 (d, 1H, ArH, *J* = 8.1 Hz), 7.42 (dd, 1H, ArH, *J* = 1.1 Hz, *J* = 8.1 Hz), 7.65 (d, 1H, ArH, *J* = 1.1 Hz), 9.23 (s, 2H, OH). ^{1}H NMR (acetone-d_6, 500 MHz): δ 3.41 (s, 3H, NCH_3), 6.29 (t, 1H, ArH, *J* = 2.0 Hz), 6.57 (d, 2H, ArH, *J* = 2.0 Hz), 7.05 (d, 1H, =CH, *J* = 16.3 Hz), 7.12 (d, 1H, =CH, *J* = 16.3 Hz), 7.16 (d, 1H, ArH, *J* = 8.1 Hz), 7.40 (dd, 1H, ArH, *J* = 1.2 Hz, *J* = 8.1 Hz), 7.52 (d, 1H, ArH, *J* = 1.1 Hz), 8.43 (br s, 2H, OH). Anal. Calcd. for $C_{16}H_{13}NO_4$ (283.28): C 67.84, H 4.63, N 4.94. Found: C 67.68, H 4.57, N 4.73.

Biology

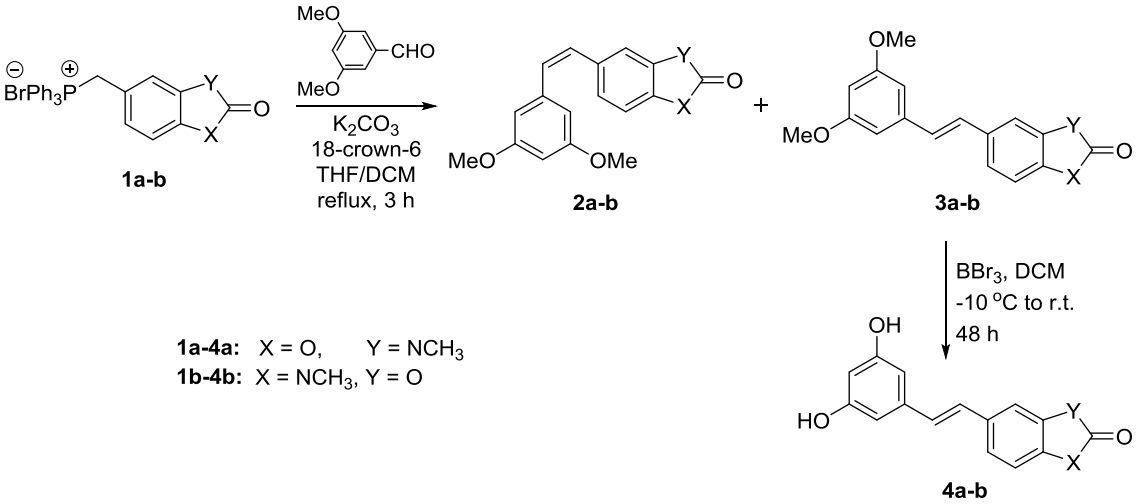
Cytotoxicity tests were carried out on three tumor cell lines with different origin, namely HL-60 (human promyelocytic leukemia), MCF-7 (human breast cancer) and MDA-MB-231 (human breast adenocarcinoma). The cells were maintained as suspension type cultures (leukemia and adenocarcinoma) or as adherent culture (breast cancer) in controlled environment: RPMI-1640 medium, supplemented by 10% FBS and 2 mM L-glutamine at 37 °C in a "Heraeus" incubator with humidified atmosphere and 5% CO_2. In order to keep cells in log phase, the cultures were refed with fresh RPMI-1640 medium two or three times a week.

Tested compounds were dissolved in DMSO and the solutions were diluted with RPMI-1640 medium to yield the desired final concentrations. Cytotoxicity of the compounds was assessed using the MTT-dye reduction assay [17], with minor modifications [18]. Exponentially growing cells were seeded in 96-well plates (100 μL/well at a density of 1×10^5 cells/mL). After 24 h incubation (37 °C, 5% CO_2 and maximum humidity), they were exposed to various concentrations of the tested compounds (200, 50, 25, 12.5, 6.25 μM) for 72 h. Then, MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) solution (10 mg/mL in PBS) was added (10 μL/well). Plates were further incubated for 3 hours at 37 °C. To dissolve the formazan crystals formed, 5% solution of formic acid in isopropanol (100 μL/well) was used. Absorption was measured on an ELISA reader at 580 nm. A mixture of 100 μL RPMI-1640 medium, 10 μL MTT stock and 100 μL 5% formic acid in isopropanol was used as control. For each concentration tested a set of six separate wells was used. The IC_{50} value (the concentration that inhibit 50% of cell growth) for each compound was calculated using OriginLab program.

RESULTS AND DISCUSSION

As depicted in Scheme 1, the synthesis of target stilbene derivatives **2a-b** and **3a-b** was achieved by applying the Wittig methodology on 3,5-dimethoxybenzaldehyde and the appropriate heterocyclic ylide, in turn obtained from the phosphonium bromides **1a-b** in the presence of potassium carbonate and 18-crown-6. The reactions were carried out in THF/DCM at reflux for 3 h and produced the corresponding 3,5-dimethoxystyrylbenzoxazolones as mixtures of π-diastereomers. The pure *Z*- and *E*-stilbenes (**2a-b**, respectively **3a-b**) were separated by column chromatography. As the natural resveratrol is in the *E*-configuration, the obtained methoxy substituted *E*-stilbenes **3a-b** were subjected to a reaction of demethylation with boron tribromide to afford **4a-b** in high yields. The demethylation of the *Z*-isomers **2a-b** in these conditions led to a mixture of products caused by additionally isomerization of the double bond.

The structures of all newly synthesized benzoxazolone-containing stilbene derivatives **2a-b – 4a-b** were confirmed by ^{1}H NMR spectroscopy. The geometry of the double bond was assigned on the basis of the coupling constants of the olefinic protons signals (*J* = 12.2 Hz for *Z*-stilbene **2a-b**,



Scheme 1. Synthesis of 5- and 6-styryl-2(3*H*)-benzoxazolones.

and *J* = 16.2 or 16.3 Hz for *E*-stilbene **3a-b** and **4a-b**). Consistent with the coupling constant data, both doublets for the olefinic protons of the *Z*-isomers appeared at 6.54–6.65 ppm whereas those for *E*-stilbenes shifted downfield to 6.99–7.13 ppm.

The synthesized heterocyclic analogues of resveratrol were tested *in vitro* for their cytotoxicity against three human cancer cell lines (HL-60, MCF-7 and MDA-MB-231), using MTT-dye reduction assay. As presented in Table 1, the obtained results showed that most derivatives exert weak antiproliferative effects on the studied cancer cells lines. Compound **2a** bearing (*Z*)-3,5-dimethoxystyryl fragment on C5 position of benzoxazolone ring exhibited the highest activity with IC_{50} of 19 μM against HL-60, 42 μM against MCF-7 and 76 μM against MDA-MB-231 cells. The corresponding *E*-isomer **3a** was inactive, but the hydroxy substituted *E*-stilbene **4a** exerted a similar cytotoxic potential as **2a**.

Table 1. Cytotoxic effects (expressed as IC_{50}) of compounds **2a-b – 4a-b** on HL-60, MCF-7 and MDA-MB-231 cell lines.

Compd	IC_{50} (μM)±SD		
	HL-60	MCF-7	MDA-MB-231
2a	19±1.1	42±2.1	76±3.2
2b	13±1.3	> 200	> 200
3a	> 200	> 200	> 200
3b	> 200	40±2.2	> 200
4a	38±1.7	42±1.8	105±3.7
4b	> 200	84±2.9	> 200

These results showed that the biological activity of the compounds **2a-b – 4a-b** was influenced by the position of the styryl fragment in a benzoxazolone ring as the obtained 5-styrylbenzoxazolones were generally more active in compare to the corresponding 6-styryl-benzoxazolone positional isomers. Disregarding the configuration of the double bond in tested derivatives, the introduction of 3,5-dimethoxystyril or 3,5-dihydroxystyril moiety on C5 position of the heterocyclic system led to compounds closely resembling resveratrol.

CONCLUSION

In this study we reported the synthesis of six heterocycle analogues of resveratrol, containing a benzoxazolone ring. Evaluation of the cytotoxicity of the stilbene derivatives on HL-60, MCF-7 and MDA-MB-231 cancer cell lines showed that (*Z*)-3-methyl-5-(3,5-dimethoxystyryl)-2(3*H*)-benzoxazolone (**2a**) and (*E*)-3-methyl-5-(3,5-dihydroxystyryl)-2(3*H*)-benzoxazolone (**4a**) were the most active in the series.

Acknowledgements: *The authors are thankful to the Sofia University Scientific Research Fund (grants 85/2009, 99/2011) and the University of Forestry, Sofia, Bulgaria (grant 12/19.01.2016) for the financial support.*

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СИНТЕЗ И ЦИТОТОКСИЧНА АКТИВНОСТ НА НОВИ ХЕТЕРОЦИКЛЕНИ АНАЛОЗИ НА РЕСВЕРАТРОЛ, СЪДЪРЖАЩИ БЕНЗОКСАЗОЛОНОВ ПРЪСТЕН

М. С. Герова[1], Е. А. Александрова[1,2], Й. Б. Иванова[3], Д. В. Станишева[1], Г. Цв. Момеков[4], О. И. Петров[1]*

[1] Катедра Фармацевтична и приложна органична химия, Факултет по Химия и фармация, Софийски университет "Св. Климент Охридски", бул. Джеймс Баучър 1, София 1164, България
[2] Катедра Обща и клинична патология, Медицински факултет, Тракийски Университет, ул. Армейска 11, Стара Загора 6000, България
[3] Катедра Патология на растенията и химия, Факултет по Екология и ландшафтна архитектура, Лесотехнически университет, бул. Климент Охридски 10, София 1756, България
[4] Катедра Фармакология, фармакотерапия и токсикология, Фармацевтичен факултет, Медицински университет – София, ул. Дунав 2, София 1000, България

Постъпила на 01 март 2017 г.; Коригирана на 15 март 2017 г.

(Резюме)

Синтезирани са нови хетероциклени аналози на ресвератрол като потенциални противоракови средства. Съединенията съдържат 3,5-диметокси- или 3,5-дихидроксистирилов фрагмент, въведен в позиция С5 или С6 на бензоксазолонов пръстен. Цитотоксичната активност на съединенията е изследвана върху три туморни клетъчни линии (HL-60, MGF-7 and MDA-MB-321) и получените резултати показват, че някои от тях проявяват добър антипролиферативен ефект. В повечето случай, 5-стирилбензосазолоните са по-активни в сравнение с техните позиционни изомери, съответните 6-стирилбензосазолони.