Synthesis and Antioxidant Properties of New Oxazole-5(4H)-one Derivatives

Yeni Oksazol-5(4H)-one Türevlerinin Sentez ve Antioksidan Özellikleri

Canan KUŞ1*, Ezgi UĞURLU1, Elçin D. ÖZDAMAR2, Benay CAN-EKE2

1Ankara University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, Ankara, Turkey
2Ankara University, Faculty of Pharmacy, Department of Pharmaceutical Toxicology, Ankara, Turkey

ABSTRACT

Objectives: To synthesize and characterize 4-(substituted benzylidene)-2-(substituted phenyl)oxazol-5(4H)-one derivatives (E1-E10), and evaluate them for antioxidant activity.

Materials and Methods: Required oxazole-5(4H)-one derivatives were synthesized in two steps to obtain novel hippuric acid derivatives (7-13); glycine and acylated appropriate benzoic acid derivatives were used and then, final compounds were obtained with condensation of 7-13 with appropriate benzaldehydes (E1-E10). These products were purified by column chromatography using ethyl acetate/n-hexane as eluent. All the compounds were unequivocally characterized using the combination of 1H and 13C-nuclear magnetic resonance, mass spectrometry (ESI-MS), and elemental analysis. The inhibition of lipid peroxidation and its effects on hepatic cytochrome P450-dependent ethoxyresorufin-O-deethylase (EROD) enzyme were determined in rats in vitro.

Results: The most active analogue on the microsomal EROD activity was E3 which inhibited the microsomal EROD activity (89%) and was similarly better than that of the specific inhibitor caffeine (85%) at 10-3 M concentration.

Conclusion: The findings of this study indicate that the synthesized compounds, such as E3, display significant antioxidant activity.

Key words: Oxazolidinones, synthesis, antioxidant activity, lipid peroxidation, EROD activity

ÖZ

Amaç: Bu çalışma, 4-(substitüe benziliden)-2-(substitüetfenil)oksazol-5(4H)-on (E1-E10) türevlerini sentezlemek, yapılarını aydınlatmak ve antioksidan etkilerini araştırmaktır.

Gereç ve Yöntemler: Oksazol-5(4H)-on türevleri iki yolak ile sentezlenmiştir. Yeni hıpürik asit türevlerini (7-13) elde etmek için, glisin ve açıllenmiş benzoik asitler kullanıldı ve bu bileşikler (7-13) uygun benzaldehitler ile kondensasyon reaksiyonu ile de sonuç ürünler (E1-E10) ulaşılmıştır. Bu ürünler etil asetat/n-hekzan solvan sistemi kullanılarak kolon kromatografisi ile temizlenmiştir. Tüm bileşikler için 1H and 13C-nükleer manyetik rezonans, mass spektrometresi (ESI-MS), elemental analiz yöntemleri kullanılarak yapıları tanımlanmıştır. Lipid peroksidasyon inhibisyonu ve karaciğer sitokrom P450 bağlı Etoksiyrozorfin-O-deethylaz (EROD) enzimi üzerindeki etkileri sıçranarda in vitro olarak tespit edildi.

Bulgular: Mikroozomal EROD aktivitesi üzerinde en aktif analog, EROD aktivitesini %89 ile inhibe eden E3 tü, benzer şekilde 10-3 M konsantrasyonda spesifik inhibitör kafeinden (%85) daha iyi idi.

Sonuç: Bu çalışmanın bulguları, E3 gibi sentezlenen bileşiklerin, önemli antioksidan aktivite sergilediğini göstermektedir.

Anahtar kelimeler: Oksazolidinonlar, sentez, antioksidan aktivite, lipid peroksidasyon, EROD aktivite
INTRODUCTION

Oxazolone ring is an important scaffold in the area of drug discovery. Oxazolone and its derivatives make a prominent structure of number of well established marketed drugs such as rilmenidine, furazolidone, nifurantoin, oxaprozin, and especially linezolid, which is an active against methicillin-resistant Staphylococcus aureus. Indeed, oxazolone based derivatives have shown diverse biological and pharmacological applications such as anticancer, antibacterial, antimycobacterial against tuberculosis, and antioxidant activity.

Free radicals, such as hydroxyl, superoxide anion (O$_2^-$), nitric oxide (NO) and peroxide ion (RO$_2^-$), reactive oxygen species, are involved in different physiological processes. Antioxidants can act as direct scavengers of free radicals and reactive oxygen species, or they can indirectly metabolize free radicals or their intermediates into harmless products. Oxidative damage to DNA and other macromolecules appears to have a major role in aging, degenerative diseases and cancer. Due to oxidative cellular damage, development of cancers, cardiovascular diseases and ageing increase in the world. Antioxidant agents are able to either prevent or mitigate oxidative stress to cells that is an important area of investigation.

In light of the foregoing, novel oxazole-5(4H)-one derivatives were synthesized and evaluated their antioxidant activity. Molecular structure of designed compounds (E1-E10) is shown in Figure 1.

In this study, firstly some of hippuric acid derivatives (7-13) were synthesized according to the literature. The synthetic route for hippuric acid derivatives (7-13) is displayed in Scheme 1.

In the second step, cyclization reactions of hippuric acid derivatives with corresponding benzaldehydes afforded the target compounds (E1-E10), which are analogs of 4-(substituted benzylidene)-2-(substituted phenyl) oxazol-5(4H)-on, were synthesized (see Scheme 2). Among the synthesized compounds, 9 out of 10 were original except, E1. Compound E1 was synthesized with one step reaction using hyppuric acid as starting material.

![Figure 1. Molecular structure of designed compounds (E1-E10)](image)

R = -H, 4-F, 4-CH$_3$, 4-NO$_2$, 4-Cl, 4-OCH$_3$, 4-Ph
X = -H, 2,4-di-F, 2,4-di-CH$_3$, 4-Cl

![Scheme 1. Synthesis of hippuric acid derivatives (7-13)](image)

| R     | mp ºC | Literature |
|-------|-------|------------|
| -H    | 138   | Commercial |
| 4-F   | 165   | [11]       |
| 4-CH$_3$ | 184  | [12]       |
| 4-NO$_2$ | 153-155 | [11]   |
| 4-Cl  | 176   | [13]       |
| 4-OCH$_3$ | 149-149 | [14] |
| 4-Ph  | 218-219 | [15]    |

![Scheme 2. Synthesis of the desired compounds (E1-E10)](image)

**EXPERIMENTAL**

**Chemical methods**

Uncorrected melting points were measured on an Electrothermal 9100 capillary melting point apparatus. H-NMR and C-NMR spectra were recorded on a Varian Mercury 400 MHz and 100 MHz FT spectrometer, chemical shifts (δ) are in ppm relative to tetramethylsilane, and coupling constants (J) are reported in Hertz. Mass spectra were taken on a Waters Micromass ZQ using the Electrospray Ionization (ESI) (+) method. Microanalyses were performed by Leco CHNS-932. All chemicals and solvents were purchased from commercial sources and used without further purification. p-Fluorophippuric acid, p-methylhippuric acid, p-nitrohippuric acid, p-chlorohippuric acid, p-methoxyhippuric acid and p-phenylhippuric acid were prepared according to the literature.

**Synthesis of hippuric acid derivatives (7-13):** One of appropriate benzoic acid derivatives 1-6 (1.5 mmol) was refluxed in benzene (5 mL) with SOCl$_2$ (5 mL) for 2 h at 80ºC. Then solvent and excess of SOCl$_2$ were evaporated completely. Glycine (0.10 mol)
was dissolved in a 100 mL of 10% sodium hydroxide solution and appropriate benzoyl chloride (0.12 mol) was added portion-wise into it and the reaction mixture was shaken vigorously after each addition until all the chloride has been reacted for 1 h at 5°C and then at room temperature for 1 h, again. 2N HCl added to the reaction mixture, until it was acidic to litmus paper. The resulting precipitate of sufficient benzoyl glycine so obtained was filtered, washed several times with cold distilled water, dried and crystallized form carbon tetrachloride (see Scheme 1).

General procedure for the preparation of 4-(substituted benzylidene)-2-(substituted phenyl) oxazol-5(4H)-on derivatives (E1-E10): Into a sample of polyphosphoric acid (0.01 mol), appropriate benzaldehyde (1-6) and reasonable hippocuric acid (7-13) (0.01 mol) were added. The mixture was heated in an oil bath (90°C) for 4 h followed by pouring water into the reaction mixture. The precipitate formed from the mixture was then washed several times with water, air-dried and then purified by column chromatography with convenient solvent.

4-Benzylidene-2-phenyloxazole-5(4H)-on (E1): Light yellow crystal; (yield 75%); ethyl acetate/n-hexane= 1/4; mp: 169.4-169.9°C (168-169°C).$^{17}$ 1H-NMR (Acetone-d$_6$): δ ppm: 7.30 (s, H, =CH), 7.52-7.57 (m, H), 7.62-7.67 (t, H), 7.71-7.75 (t, H), 8.20 (d, H), 8.22 (s, H), 8.35-8.37 (d, H). 13C NMR (Acetone-d$_6$): δ ppm: 171.7, 168.5, 138.6, 138.4, 138.3, 137.2, 135.6, 135.6, 134.0, 133.7, 132.9, 130.5; ESI-mass spectrometer (MS) m/z: 250.27 (M+1); Anal. Calculated for C$_{13}$H$_{11}$NO (C, H, N): C 77.11, H 4.42, N 5.62; Found: C 76.77, H 4.26, N 5.97.

4-(2,4-Difluorobenzylidene)-2-(4-fluorophenyl)oxazol-5(4H)-on (E2): Light yellow solid; (yield 13%), ethyl acetate/n-hexane= 1/1.9; mp: 229.4-231.3°C (168-169°C).$^{17}$ 1H-NMR (DMSO-d$_6$): δ ppm: 7.23 (s, H, =CH), 7.31-7.36 (t, H), 7.45-7.53 (m, H), 8.21-8.24 (dd, H), 8.87-8.89 (q, H, H), 8.94-8.98 (m, H); ESI-MS m/z: 300.6 (M+1); Anal. Calculated for C$_{14}$H$_{14}$F$_2$NO (C, H, N): C 63.37, H 2.64, N 4.62; Found: C 63.02, H 2.62, N 4.70 %.

4-(2,4-Difluorobenzylidene)-2-p-tolylxazol-5(4H)-on (E3): Light yellow solid; (yield 29.3%); ethyl acetate/n-hexane= 1/4; mp: 196.9°C. 1H-NMR (DMSO-d$_6$): δ ppm: 2.44 (s, H, =CH$_3$), 7.19 (s, H, =CH), 7.32-7.36 (t, H), 7.44-7.49 (m, H), 8.04-8.06 (dd, H, H), J=8 Hz), 8.87-8.93 (q, H); ESI-MS m/z: 346.81 (M+47); Anal. Calculated for C$_{16}$H$_{16}$F$_2$NO (C, H, N): C 68.23, H 3.68, N 4.44; Found: C 68.03, H 3.54, N 4.78, %. 

4-(2,4-Difluorobenzylidene)-2-(4-nitrophenyl)oxazol-5(4H)-on (E4): Light yellow solid; (yield 13.7%); ethyl acetate/n-hexane= 1/4; mp: 227.5°C. 1H-NMR (DMSO-d$_6$): δ ppm: 7.34 (s, H, =CH), 7.37 (dd, H, H, J=2 Hz), 7.51 (t, H, H, J=2 Hz), J=8 Hz), 8.36-8.48 (m, H, Ar-H$_2$), 8.86-8.94 (q, H, H, H$_2$); ESI-MS m/z: 377.96 (M+47); Anal. Calculated for C$_{16}$H$_{16}$F$_2$NO$_2$O$_2$H$_2$: C 57.48, H 2.49, N 8.48; Found: C 57.48, H 2.59, N 8.29, %.

4-(2,4-Difluorobenzylidene)-2-(4-chlorophenyl)oxazol-5(4H)-on (E5): Light yellow solid; (yield 17.7%); ethyl acetate/n-hexane= 1/4; mp: 238-240°C. 1H-NMR (DMSO-d$_6$): δ ppm: 7.22 (s, H, =CH), 7.29-7.34 (t, H), 7.43-7.48 (t, H), 7.69-7.72 (d, H, J=8 Hz), 8.11-8.14 (d, H, J=8 Hz), 8.84-8.90 (q, H, H), ESI-MS m/z: 366.79 (M+47); Anal. Calculated for C$_{16}$H$_{14}$ClF$_2$NO$_2$: C 60.11, H 2.52, N 4.39; Found: C 60.08, H 2.54, N 4.51, %.

Biological methods

Assay of lipid peroxidation

Male albino Wistar rats (200-225 g) were used in the experiments. The animals were fed with standard laboratory rat chow and tap water add libitum. The animals were fasted for 24 h prior to sacrifice by decapitation under anesthesia. The livers were removed immediately and washed in ice-cold water and the microsomes were prepared, as described previously.18 NADPH-dependent lipid peroxidation (LP) was determined using the optimum conditions determined and described previously.18 NADPH-dependent LP was measured spectrophotometrically by estimated the thiobarbituric acid reactant substances (TBARS). The amounts of TBARS were expressed in terms of nmol malondialdehyde/mg protein. The assay was essentially derived from the methods reported by Wills19,20 and modified by Bishaye and Balasubramanian.21 A typical optimized assay
mixture contained 0.2 nM Fe++, 90 mM KCl, 62.5 mM potassium-phosphate buffer (pH 7.4), a NADPH generating system consisting of 0.25 mM NADP+, 2.5 mM MgCl₂, 2.5 mM glucose-6-phosphate, 1.0 U glucose-6-phosphate dehydrogenase and 14.2 mM potassium phosphate buffer (pH 7.8) and 0.2 mg of the microsomal protein in a final volume of 1.0 mL.

**Assay of ethoxyresorufin O-deethylation**

Ethoxyresorufin O-deethylation (EROD) activity was measured by the spectrofluorometric method of Burke et al. A typical optimized assay mixture contained 1.0 mM ethoxyresorufin, 100 mM Tris-HCl buffer (pH 7.8), NADPH generating system consisting of 0.25 mM NADP+, 2.5 mM MgCl₂, 2.5 mM glucose-6-phosphate, 1.0 U glucose-6-phosphate dehydrogenase, and 14.2 mM potassium phosphate buffer (pH 7.8) and 0.2 mg liver microsomal protein in a final volume of 1.0 mL.

**RESULTS**

Carpy et al. released that benzylic proton (Ar-CH=C) of 4-(2-chloro-4,5-dimethoxybenzylidene)-2-methyl-5-oxazolone was at 6.91 ppm and that if there were only one signal for the benzylic proton, this showed that Z-isomer existed. E-isomer is clarified by benzylic proton shift and absorbed magnetic resonance at up-field (~7.5 ppm). Similar results have also been published by other researchers. Our final compounds showed parallel results at ¹H-NMR spectra as singlet Ar-CH=C proton at 7.14-7.40 ppm. 4-Benzylidene-2-phenyloxazole-5(4H)-on (E1) has 16 carbon atoms. 4-(4-chlorobenzylidene)-2-[4-(phenyl)phenyl]oxazole-5(4H)-on (E10) has 18 carbon atoms and there are only 12 and 16 signals at ¹³C-NMR spectra, respectively. These findings are very normal and similar results were published by Younesi et al.

To examine the mass analysis of the final compounds (E1-E10), ESI-MS was used. Some of the desired compounds showed interesting results. E7 and E8 peaks were observed at (M+33) and E2, E3, E4, and E5 peaks were observed at (M+47) at their mass spectra. These peaks were shown in the spectra of the molecules, because of keeping the solvents as methanol and ethanol. In 2003, Kawai et al. explained these formations based on quantum chemical calculations. These findings are similar to other researchers’ results.

Compound E10 has only one chlorine atom, because of that, as usual, M+ and M+2 (3:1) signals were observed in its mass spectrum.

For the EROD activity of the final compounds, X substitutents on the benzylidene moiety is more important than R substituent, displayed in Scheme 2. As shown in Table 1, the most active compound on the microsomal EROD activity, E3 has 2,4-di-F as X substitutents on the benzylidene moiety. This compound interestingly enhanced the LP levels and not consistent with EROD results. Biphenyl substitution led to a reduction in the EROD activity nevertheless there is no observation like this in the LP levels. It can be said that there is no problem with biphenyl substitution for LP levels because these two compounds have somewhat moderate activity against LP.

| Code | EROD (pmol/mg/min) | % of control | LP (nmol/mg/min) | % of control |
|------|-------------------|-------------|-----------------|-------------|
| E1   | 8.71±0.51         | 21          | 18.79±0.62      | 115         |
| E2   | 13.23±2.57        | 32          | 15.89±2.06      | 98          |
| E3   | 4.47±0.04         | 11          | 27.97±2.81      | 172         |
| E4   | 11.13±1.27        | 28          | 26.59±3.21      | 163         |
| E5   | 10.38±0.64        | 25          | 11.94±0.31      | 73          |
| E6   | 12.72±0.76        | 30          | 9.01±0.86       | 55          |
| E7   | *                 | *           | *               | *           |
| E8   | 9.79±0.57         | 24          | 6.91±0.86       | 43          |
| E9   | 20.92±0.28        | 50          | 7.30±0.32       | 45          |
| E10  | 28.85±1.36        | 69          | 9.40±0.32       | 58          |
| BHT  | -                 | -           | 5.68±0.22       | 35          |
| Caffeine | 6.41±0.99     | 15          | -               | -           |
| DMSO | 41.53±0.99        | 100         | 16.25±1.45      | 100         |

EROD: Ethoxyresorufin O-deethylase, LP: Lipid peroxidation, *Not tested

It is highly difficult to compare the results from different assays. The biggest problem is the lack of a validated assay that can reliably measure the antioxidant capacity of foods and biological samples, due to distinct antioxidant effects of chemicals which have already been noted in different in vitro assay systems. Antioxidants scavenge and prevent the formation of free radicals so they are highly important for the treatment of these kind of diseases mentioned above. For this reason, there has been an increasing interest in finding novel antioxidant compounds in recent years.

The activity patterns of compounds on LP, and EROD activity were dissimilar because each method relates to the generation of a different radical, acting through a variety of mechanisms, and the measurement of a range of end points at a fixed time point or over a time period. It should also be realized that the analytical methods of measurement and the conditions can lead to variable results for the same compound.

Compounds E2 (2%), E5 (27%), E6 (45%), E8 (57%), E9 (55%) and E10 (42%) displayed highly limited inhibitory effects on LP and the rest of the compounds enhanced LP levels. Similar results, where thiadiazole derivatives enhanced LP levels were obtained in another study of ours on liver LP levels, too.

**CONCLUSION**

In conclusion, a series of 4-(substituted benzylidene)-2-(substituted phenyl) oxazole-5(4H)-ones (E1-E10) were synthesized and their antioxidant activity were evaluated. The inhibition of LP, and its effects on hepatic cytochrome P450 dependent EROD enzyme were determined in rats *in vitro*. The most active analogue on the microsomal EROD activity was E3, which inhibited the microsomal EROD activity (89%) and was
similarly better than that of the specific inhibitor caffeine (85%) at 10⁻³ M concentration.

Compound E3 displayed significant antioxidant activity so needs to study on its analogues.

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