ANGIOTENSIN-I-CONVERTING ENZYME INHIBITION AND ANTIOXIDANT ACTIVITY OF BENZAMIDE APPENDED OXADIAZOLE DERIVATIVES

Shilpa C. Patil¹, Ravikumar N. Naik¹, Satish Sreedharamurthy², Pramod H², Sudha B. Satyanarayana*.

¹Department of Chemistry, Yuvaraja’s College, University of Mysore, Mysore- 570 005, Karnataka, India
²Department of Studies in Microbiology, Manasagangotri, University of Mysore, Mysore - 570 006, Karnataka, India

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In continuation of our research on the synthesis of benzamide appended heterocyclic compounds, here in some new benzamide appended oxadiazole derivatives (2a-i) were prepared and structures were confirmed by their spectral studies. ACE-I inhibition activity was investigated, Compounds 2a and 2i proved to be potent ACE-I inhibitors with IC₅₀ value of 27.50 μg/μl and the compounds 2b-e showed moderate ACE-I inhibition with IC₅₀ value in the range of 34-36 μg/μl when compared to standard lisinopril (IC₅₀=30.83 μg/μl).. Compounds 2g-h exhibit least ACE inhibition activity with IC₅₀ values of 41.66 μg/μl and 43.33 μg/μl . Antioxidant activities was probed by DPPH assay, lipid peroxidation assay and super radical scavenging activity. DPPH assay revealed that compounds 2a-e were moderate radical scavengers with IC₅₀ value in the range of 16-20 μg/μl when compared to standard Ascorbic acid (IC₅₀ value = 9.73μg/μl). The compounds 2a-f showed moderate anti-lipid peroxidation activity when compared to standard α-tocopherol (IC₅₀ value = 30.47 mg/ml). By Superoxide radical scavenging assay, compounds 2a-g were found to be moderate superoxide radical scavengers with activity in the range of 35-29% when compared to standard Butylated hydroxyanisole (39.93%). By antioxidant assay it was proved that the compound 2h was potent radical scavenger.


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INTRODUCTION

The renin-angiotensin system (RAS) has an established role in the regulation of blood pressure. Treatment of hypertension has been achieved through administration of angiotensin converting enzyme (ACE) inhibitors. Angiotensin-II-converting enzyme (ACE) inhibitors are well established in the treatment of hypertension and heart failure. They decrease angiotensin II (ANG) generation by blocking the circulating and local renin-angiotensin systems (RAS) and by preventing the degradation of bradykinin. Both mechanisms seem to be involved in the antihypertensive and cardioprotective effects [1]. Several ACE inhibitors are in clinical use for treatment of hypertension. All these drugs also produce side effects (like dry cough, hyperkalemia, rashes, loss of taste, first dose hypotension and acute renal failure), thus justifying the search for newer analogues of ACE inhibitors for safe use.

Oxadiazoles represent a class of heterocyclic compounds of great biological importance. The widespread use of oxadiazoles as a scaffold in medicinal chemistry establishes this moiety as an important bio-active class of heterocycles. Naik et al have synthesized 1,3,4-oxadizole based Schiff bases and reported their anti bacterial and antifungal activities[2]. The well established antihypertensive drugs like Tiodazosin [3] and Nesapidil [4] possess oxadiazole nucleus. Yong-yan Nie et al have proven that series of new compounds with 5-oxo-1, 2, 4-oxadiazole group possess antihypertension activity [5]. The compounds bearing the oxadiazole ring on benzimidazole ring have been reported to exhibit good antioxidant activities [6]. Additionally disubstituted (1, 3, 4)-oxadiazoles carrying 4-(methylsulfonyl/sulfanyl)benzoyl moieties [7] and 2-{(2-(4-chlorophenyl)-1H-benzo[d]imidazole-1-yl)methyl}-5-(4-fluorophenyl)-1,3,4 oxadiazole [8] have been reported to possess antioxidant activity.

Initially benzamide appended thiazole was synthesized and their ACE-I inhibition activity and antioxidant property was determined [9]. In view of the above facts and in continuation of our search for ACE-I inhibition activity and antioxidant activity active molecules has encouraged us to synthesize some novel molecules of fused oxadizone-benzamide and carry out their preliminary ACE –I inhibition and antioxidant activity. In this paper we report the synthesis and spectral studies of a novel series N-(4-{(5-Thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy}phenyl)benzamide derivatives and evaluation of in vitro ACE –I inhibition and antioxidant activity. Screening of all the newly synthesized benzamide derivatives (2a-i) by ACE-I inhibition assay and antioxidant activity like DPPH assay, lipid peroxidation assay and super radical scavenging activity was carried out.

MATERIALS AND METHODS

Chemistry

The FTIR spectra were measured on Shimadzu instrument from R L Fine Chem. Unit II, Bangalore. 1H (300 MHz) NMR spectra were recorded on a Bruker NRC-IISC, Bangalore at ambient temperature. Chemical shifts are given as δ values (ppm). Analytical LC–MS was performed on Agilent LCMS system equipped with a BEH C8, 30 x 4.6mm, 1.7um, column, at a flow rate of 1.0 ml/min. The mobile phase consisted of H2O/ CH3CN/ 0.05% Ammonium acetate. Other chemicals and solvents used were purchased from sigma aldrich, and used without further purification unless stated. Thin-layer chromatography was performed on aluminium plates precoated with silica gel 60 F254 (Merck) and visualized in UV light.

General procedure for the synthesis of N-[4-{(2-Hydrazinyl-2-oxoethoxy)phenyl}benzamide (1a-1i):

The appropriate Ethyl {4-{[phenylcarbonyl]amino}phenoxy}acetate (0.006347mol) was added to hydrazine hydrate (0.0095mol) in 30ml methanol. The mixture was refluxed for 7-8 h in an oil bath. After evaporating under reduced pressure, the residue was washed with water (10mlx2) and Et2O. The solid residue was then recrystallized in MeOH: H2O (5:1). The solid was filtered, washed with Et2O and dried in air.

General procedure for the synthesis of N-[4-{(5-Thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy}phenyl]benzamide (2a-2i):

The mixture of suitable N-{4-{(2-Hydrazinyl-2-oxoethoxy)phenyl}benzamide (0.0050mol), KOH(0.0196mol) and carbon disulfide (0.0091mol) was dissolved in 20ml ethylene glycol. The mixture was stirred at 80-85°C for 9-10 h. To this mixture 100ml water was added and then suspended with 10% HCl. The solid was filtered and washed with water (10mlx2). The crude product was purified by column chromatography (Acetone: Dichloromethane/ 10:90 v/v).

Scheme 1 (I) KOH + CS2 in ethylene glycol at 80-85°C for 7-8 h.

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N-[4-[[5-Thioxo-4,5-dihydro-1,3,4-oxadiazo-2-yl]methoxy]phenyl]benzamide (2a)

Pale yellow crystals, 65% yield, mp: 213°C, m/z (%): 327.10 (M+), IR (cm⁻¹): 3391, 1649, 1600, 1243 and 1248. ¹H NMR (300 MHz, DMSO-d6): δ 4.30 (s, 2H, H-8), 6.75 (d, 2H, H-9,H-13), 7.53 (d, 2H,H,10-H,12), 7.44 (d, 2H, H-18,H-20), 7.51 (d, 1H, H-19), 7.95 (d,2H,H,17-H,21), 9.56 (s,1H, amide - NH).

4-Chloro-N-[4-[[5-thioxo-4,5-dihydro-1,3,4-oxadiazo-2-yl]methoxy]phenyl]benzamide (2b)

Pale yellow crystals, 63% yield, mp: 220°C, m/z (%): 361.06 (M+), 363.06 (M+2), IR (cm⁻¹): 3395, 1653, 1609, 1243 and 1250. ¹H NMR (300 MHz, DMSO-d6): δ 4.30 (s, 2H, H-6),6.75 (d, 2H, H-9,H-13), 7.53 (d,2H,H,10-H,12), 7.45 (d, 2H, H-18,H-20),7.89 (d,2H,H,17-H,21), 9.81 (s,1H, amide - NH), 8.65 (s, 1H, oxadizol-NH).

2,4-Dichloro-N-[4-[[5-thioxo-4,5-dihydro-1,3,4-oxadiazo-2-yl]methoxy]phenyl]benzamide (2c)

Pale yellow crystals, 68% yield, mp: 201°C, m/z (%): 394.01 (M+), 396.08 (M+2), 398.10 (M+4), IR (cm⁻¹): 3389, 1645, 1605, 1239 and 1240. ¹H NMR (300 MHz, DMSO-d6): δ 4.30 (s, 2H, H-6),6.75 (d, 2H, H-9,H-13), 7.33 (d,1H,H-18), 7.45 (s, 1H,H-20), 7.53 (d, 2H,H,10-H,12),7.83 (s, 1H,H,17) , 9.81 (s,1H, amide - NH), 8.65 (s, 1H, oxadizol-NH).

2-Chloro-N-[4-[[5-thioxo-4,5-dihydro-1,3,4-oxadiazo-2-yl]methoxy]phenyl]benzamide (2d)

Pale yellow crystals, 61% yield, mp: 213°C, m/z (%): 361.08 (M+), 363.05 (M+2), IR (cm⁻¹): 3391, 1649, 1600, 1243 and 1248. ¹H NMR (300 MHz, DMSO-d6): δ 4.30 (s, 2H, H-6),6.75 (d, 2H, H-9,H-13), 7.32 (d,1H,H-18), 7.43 (s, 1H,H-19) 7.45 (s, 1H,H-20), 7.53 (d, 2H,H,10-H,12), 7.89 (s, 1H,H,17), 9.81 (s,1H, amide - NH), 8.65 (s, 1H, oxadizol-NH).

4-Bromo-N-[4-[[5-thioxo-4,5-dihydro-1,3,4-oxadiazo-2-yl]methoxy]phenyl]benzamide (2e)

Pale yellow crystals, 64% yield, mp: 218°C, m/z (%): 404.98 (M+), 405.10 (M+2), IR (cm⁻¹): 3386, 1640, 1605, 1238 and 1240. ¹H NMR (300 MHz, DMSO-d6): δ 4.30 (s, 2H, H-6),6.75 (d, 2H, H-9,H-13), 7.53 (d,2H,H,10-H,12), 7.61 (d, 2H, H-18,H-20) 7.85 (s, 1H,H,17,H21) , 9.81 (s,1H, amide - NH), 8.65 (s, 1H, oxadizol-NH).

3-Bromo-N-[4-[[5-thioxo-4,5-dihydro-1,3,4-oxadiazo-2-yl]methoxy]phenyl]benzamide (2f)

Pale yellow crystals, 61% yield, mp: 226°C, m/z (%): 404.98 (M+), 405.13 (M+2), IR (cm⁻¹): 3391, 1645, 1610, 1240 and 1243. ¹H NMR (300 MHz, DMSO-d6): δ 4.30 (s, 2H, H-6),6.75 (d, 2H, H-9,H-13), 7.53 (d,2H,H,10-H,12), 7.33 (d,1H,H-18), 7.68 (d, 1H,H-19) 7.45 (s, 1H,H-20), 7.89 (d, 1H,H-17), 8.21(s,1H,H21) , 9.81 (s,1H, amide - NH), 8.65 (s, 1H, oxadizol-NH).

4-Fluoro-N-[4-[[5-thioxo-4,5-dihydro-1,3,4-oxadiazo-2-yl]methoxy]phenyl]benzamide (2g)

Pale yellow crystals, 65% yield, mp: 249°C, m/z (%): 345.07 (M+), IR (cm⁻¹) : 3390, 1643, 1608, 1235, 1230 and 1031. ¹H NMR (300 MHz, DMSO-d6): δ 4.30 (s, 2H, H-6),6.75 (d, 2H, H-9,H-13), 7.53 (d,2H,H,10-H,12), 7.15 (d, 2H, H-18,H-20),7.93 (d,2H,H,17-H,21), 9.81 (s,1H, amide - NH), 8.65 (s, 1H, oxadizol-NH).

4-Methoxy-N-[4-[[5-thioxo-4,5-dihydro-1,3,4-oxadiazo-2-yl]methoxy]phenyl]benzamide (2h)

Pale yellow crystals, 63% yield, mp: 251°C, m/z (%): 357.10 (M+), IR (cm⁻¹): 3388, 1646, 1605, 1244 and 1238. ¹H NMR (300 MHz, DMSO-d6): δ 4.30 (s, 2H, H-6),6.75 (d, 2H, H-9,H-13), 7.53 (d,2H,H,10-H,12), 6.95 (d, 2H, H-18,H-20),7.84 (d,2H,H,17-H,21), 9.81 (s,1H, amide - NH), 8.65 (s, 1H, oxadizol-NH).

4-Nitro-N-[4-[[5-thioxo-4,5-dihydro-1,3,4-oxadiazo-2-yl]methoxy]phenyl]benzamide (2i)

Pale yellow crystals, 66% yield, mp: 225°C, m/z (%): 372.08 (M+), IR (cm⁻¹): 3383, 1645, 1618, 1236, 1216, and 1308. ¹H NMR (300 MHz, DMSO-d6): δ 4.30 (s, 2H, H-6),6.75 (d, 2H, H-9,H-13), 7.53 (d,2H,H,10-H,12), 8.23 (d, 2H, H-18,H-20),8.37 (d,2H,H,17-H,21), 9.81 (s,1H, amide - NH), 8.65 (s, 1H, oxadizol-NH).

Pharmacology

In vitro ACE-I inhibition assay

ACE-I activity was assayed by monitoring the release of HA from the substrate HHL as described by Jimsheena et al [10, 11]. The assay mixture contained 0.125 ml of 50mM sodium borate buffer with approximate pH 8.2, 0.3M NaCl solution, 0.05 ml of 5mM HHL and 25 µl of ACE-I enzyme extracted from rat kidney. The reaction mixture was incubated at 37°C for 30 min and stopped by adding 0.2 ml 1M HCl followed by 0.4 ml of pyridine and 0.2 ml of BSC. The colour developed was measured at 410 nm in a UV- VIS spectrophotometer (Shimadzu). One unit of ACE-I activity was defined as the amount of enzyme, which released 1 µM of HA per min at 37°C. ACE-I was pre-incubated with different concentrations of the test fractions and the percentage inhibition was determined by plotting concentration of test samples on X-axis and percentage inhibition on Y-axis. The percentage inhibition curves were plotted using minimum of five determinations.

Antioxidant assays

DPPH radical scavenging assay

The ethanolic solutions of DPPH (100µM) and the test samples of different concentrations were incubated. The absorbance was examined spectrophotometrically at 517 nm. The percentage reduction of the DPPH absorbance gave the DPPH scavenging activity of the test samples and was used as a marker of their antioxidant activities. The concentrations (IC₅₀) of the test samples that induced a 50% decrease of the DPPH absorbance during 30 min observation were calculated by carrying out
concentration-dependent studies [12]. An ethanolic solution of the DPPH was used as the blank, while α-tocopherol was the positive control. The potency of DPPH scavenging activity was calculated using the formula.

\[
\text{DPPH scavenging (\%)} = \frac{A_{\text{control}} - A_{\text{test}}}{A_{\text{control}}} \times 100
\]

**Lipid peroxidation assay**

A modified thiobarbituric acid reactive species assay was used to measure lipid peroxides formed using egg yolk homogenates as lipid rich media [13]. Malonaldehyde, a secondary product of oxidation of polyunsaturated fatty acid reacts with two molecules of thiobarbituric acid yielding pinkish red chromogen with absorbance maxima at 540 nm. In this technique, 0.5 ml of egg yolk homogenate and various concentrations of test compounds were mixed in the test tube and volume was made up to 1 ml by using triple distilled water. Finally, 0.05 ml of 0.07M FeSO\(_4\) was added to above mixture and incubated for 30 min to induce lipid peroxidation. Thereafter, 1.5 ml of 20% acetic acid (~ pH 3.5) and 1.5 ml of 0.8% thiobarbituric acid and 0.05 ml of 20% Trichloro acetic acid were added, vertexed and incubated at 100°C for 1 h. After cooling, 5 ml of butanol was added to each tube and centrifuged at 3000 rpm for 10 min. The absorbance of organic layer was measured at 540 nm.

**Superoxide Radical Scavenging Assay:**

The superoxide radical scavenging ability of 2a-i was assessed by a reported method [14]. The reaction mixture contained the following reagents in the final concentration stated: 2a-i (50 µg/ml), PMS (30 µM), NADH (338µM), and NBT (72 µM) in a phosphate buffer (0.1 M, pH 7.4) was incubated at room temperature for 5 min, and the absorbance of the solution at 560 nm was measured against an appropriate blank that did not contain any NADH. Butylated hydroxyanisole (BHA) was used as a reference inhibitor.

**Statistics:**

IC\(_{50}\) values were calculated by graphical method.

**RESULTS AND DISCUSSION**

**Spectral studies**

Final compound (2a) was obtained from 1a by using carbon disulfide and potassium hydroxide in ethylene glycol at 70-80°C for about 7-8 h [15]. The structures of all the compounds were supported by spectral data. The IR Spectrum for compounds 2a-2i shows presence of oxadiazolyl ring with ν = 1600-1610 cm\(^{-1}\) for C=O and 1236-1245 cm\(^{-1}\) for C=C, H\(^1\) NMR shows the presence of oxadiazoly NH at δ 8.65 ppm. In contrast, compounds 1a-1i shows amide stretching at 3220 cm\(^{-1}\) and carbonyl stretching at 1649 cm\(^{-1}\). In H\(^1\) NMR, compounds 2a-2i show two amide protons at δ 9.5-9.9 ppm and NH\(_2\) proton at δ 10-10.05 ppm.

**Pharmacological screening**

**ACE inhibitory activity:**

N-(4-((5-thioxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-benzamide and its derivatives (2a-2i) were synthesized and evaluated for ACE-I activity. Compounds 2a-i demonstrated ACE-I inhibition and their IC\(_{50}\) value are represented in Table 1. The compound 2a and 2i were found to be most active ACE-I inhibitors with lowest IC\(_{50}\) value of 27.50 µg/µl respectively in comparison to standard lisinopril (IC\(_{50}\)=30.83 µg/µl). Compounds 2b, 2c, 2d [16], 2e and 2f, showed moderate inhibitory activity with IC\(_{50}\) values 34.16, 34.58, 35.41, 37.08 and 36.25 µg/µl, respectively. The compounds 2g (IC\(_{50}\)=41.66 µg/µl) and 2h (IC\(_{50}\)=43.33 µg/µl) were least active. The dose dependant ACE-I inhibitor activities of compounds 2a-i and standard lisinopril are presented in Figure 1.

![Figure 1](image_url). Figure 1. Concentration-dependent angiotensin converting enzyme-I inhibitory activities of 2a-i and lisinopril. X-axis showing concentration of compounds 2a-i and Y-axis showing (%) inhibition of 2a-i (µg/µl).
Antioxidant activity:

Benzamide appended oxadiazoles were also tested for their antioxidant efficiency. DPPH radical scavenging assay, lipid-peroxidation assay and superoxide radical scavenging assay were studied.

DPPH Radical Scavenging Activity:

N-(4-((5-thioxo-4, 5-dihydro-1,3,4-oxadiazol-2-yl)methoxy)phenyl)-benzamide and its derivatives (2a-i) were screened for DPPH Radical Scavenging Assay. Compound 2h is a potent DPPH radical scavenger with IC<sub>50</sub> value of 8.47 μg/μl when compared to standard ascorbic acid (IC<sub>50</sub> = 9.73 μg/μl) and the compounds 2a, 2b, 2c, 2d, 2e, 2f and 2g are moderate DPPH radical scavenger with IC<sub>50</sub> value of 16.08, 17.39, 16.15, 19.34, 19.56, 20.02 and 20.43 μg/μl when compared to standard Ascorbic acid (IC<sub>50</sub> value = 9.73 μg/μl). Compound 2i demonstrated least DPPH radical scavenging activity with IC<sub>50</sub> value of 22.83 μg/μl. The dose dependant DPPH radical scavenging activity and IC<sub>50</sub> values of each compounds and standard were presented in Figure 2 and Table 1 respectively.

![DPPH radical scavenging activity](image1)

Figure 2. Concentration-dependent DPPH radical scavenging activities of 2a-i and Ascorbic acid. X-axis showing concentration of compounds 2a-i (µg/µl) and Y-axis showing the (%) of scavenging activity of 2a-i (µg/µl).

Lipid peroxidation activity:

Lipid-peroxidation activity demonstrated that compound 2h is potent with IC<sub>50</sub> value 31.90 mg/ml when compared to standard α-tocopherol (IC<sub>50</sub> value = 30.47 mg/ml). The compounds 2a, 2b, 2c, 2d, 2e, 2f and 2g showed moderate anti-lipid-peroxidation potential with IC<sub>50</sub> values, 40.95, 39.04, 40.00, 42.38, 41.42, 41.90 and 44.28 mg/ml respectively compared to standard α-tocopherol (IC<sub>50</sub> value = 30.47 mg/ml). Compound 2i showed least anti lipid peroxidation activity with IC<sub>50</sub> value 47.61 mg/ml. The dose dependant lipid peroxidation activity of compounds (2a-i) with standard α-tocopherol and IC<sub>50</sub> values are presented in Figure 3 and Table 1 respectively.

![Lipid peroxidation assay](image2)

Figure 3. Concentration-dependent lipid peroxidation assays of 2a-i and α-tocopherol. X-axis showing concentration of compounds 2a-i (mg/ml) and Y-axis showing the (%) of scavenging activity of 2a-i (mg/ml).
Table 1 IC\textsubscript{50} values of 2a-i, Lisinopril, Ascorbic Acid and α-tocopheral for ACE-I, DPPH and Lipid Peroxidation activities respectively.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>IC\textsubscript{50} values of 2a-i and Lisinopril for ACE-I inhibition. (µg/µl)</th>
<th>IC\textsubscript{50} values of 2a-i and Ascorbic acid for DPPH radical scavenging activity. (µg/µl)</th>
<th>IC\textsubscript{50} values of 2a-i and α-tocopheral for Lipid Peroxidation activity. (mg/ml)</th>
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<td>2a</td>
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<td>α-tocopheral</td>
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**Superoxide radical scavenging activity:**

The compounds 2a-2i were screened for superoxide radical scavenging assay in single concentration of 50 µg/mL. Compound 2h is most active superoxide radical scavengers with 41.85%, when compared to standard Butylated hydroxyanisole (42.33%). The superoxide radical scavenging activity of all derivatives (2a-i) is presented in Figure 4.

![Superoxide radical scavenging activity](image)

**CONCLUSION**

In summarizing our findings on the effects of modifications of heterocyclic ring on benzamide with oxadiazole we have found the following, introduction of oxadiazole ring on benzamide increased the activity when compared to thiadiazole ring. Herein it is demonstrated that benzenamides appended with oxadiazole, function as ACE-I inhibitor agents. The effect of substituents on benzamide showed that electron withdrawing Nitro (2i) group enhance the ACE-I inhibition activity. Chloro on para-(2b) and ortho-(2d) substitution on benzamide are moderate ACE-I inhibitors. Bromo substituted on meta-(2e), and para-(2f) on benzamide are moderate in their ACE-I inhibition activity. Para-Fluoro substituted (2g) and Para-methoxy (2h) group on benzamide exhibited decrease in ACE-I inhibition activity. Furthermore the synthesized compounds show better antioxidant activity. Para-methoxy group (2h) on benzamide showed enhanced antioxidant activity. The para-chloro (2b), para,meta-dichloro (6c) and ortho-chloro (2d) on benzamide displayed moderate activity. Para-bromo (2e) and meta-bromo (2f) substituents on benzamide are moderate in their antioxidant activity. The para-Fluoro substituted (2g) and electron withdrawing Para-Nitro (2i) on benzamide decreased the antioxidant activity. The information generated here could be of use to generate lead molecules for drug discovery.
Abbreviations:
HA (Hippuric acid),
HHL (Hippuryl-Histidyl-Leucine),
BSC (Benzene sulfonyl chloride),
PMS (Phenazine methosulfate),
NBT (Nitroblue tetrazolium chloride).

Authors’ Statements
Competing Interests
The authors declare no conflict of interest.

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