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Facile synthesis of non-steroidal anti-inflammatory active bisbenzamide-containing compounds

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Abstract—A variety of *N*,*N*′-bis{2-[1,2-ethanediylbis(oxy-2,1-phenylene)]-1-(substituted carbonyl)ethenyl}benzamides **7a–c**, **9a–d** were synthesized via nucleophilic attack of either primary **8** or secondary amines **6** on bisoxazol-5(4*H*)-one **5**. The latter was obtained through the reaction of 2,2′-[1,2-ethanediylbis(oxy)]bisbenzaldehyde (**4**) with hippuric acid in acetic anhydride in the presence of anhydrous sodium acetate. The anti-inflammatory properties of the prepared compounds were screened using carrageenan-induced paw oedema in rats. Many of the prepared bisbenzamide-containing compounds show considerable in vivo anti-inflammatory activity, especially **7b** which reveals remarkable pharmacological properties comparable with ketoprofen (which was used as a reference standard) at successive time intervals (1, 2, 3, 4 and 24 h).

1. Introduction

Non-steroidal anti-inflammatory drugs are a main-stay in the treatment of inflammation and they owe their therapeutic and side effects in large part to the inhibition of cyclooxygenase (COX). The separation of the therapeutic effects from the side effects has been a major challenge in the design and synthesis of these drugs. The discovery of a second isoform of cyclooxygenase, namely COX-2, has opened a new line of research based on the assumption that pathological prostaglandins are produced by the inducible isoform COX-2 while physiological prostaglandins are produced by the constitutive isoform COX-1. On this premise several new inhibitors have been developed and some are now commercially available.[1,2] Many benzamide derivatives have been reported to possess anti-inflammatory properties. One of the most famous analogues is parsalmide '5-amino-*N*-butyl-2-(2-propynyloxy)benzamide' (**1**), which is commercially available as a non-steroidal anti-inflammatory active drug for more than 20 years. It has been widely used to treat arthritic patients exhibiting spare gastric mucosa and also to prevent gastric lesions induced by many other non-steroidal anti-inflammatory active drugs.[2–7]

Roflumilast '3-cyclopropylmethoxy-4-difluoromethoxy-*N*-[(3,5-dichloropyridine)-4-yl]benzamide' (**2**) is also a well-known anti-inflammatory active agent identified as a potent and selective phosphodiesterase (PDE4) inhibitor.[8] Inhibition of PDE4 in inflammatory cells influences several of the cell-specific responses. PDE4 activity, when localized in smooth muscle cells of airways, is associated with several inflammatory states, for example, asthma, chronic obstructive and pulmonary disease. Thus, selective inhibition of PDE4 could potentially be a mechanism of treating these diseases.[9] In addition, recent publications reported about synthesis of several benzamide derivatives of selective PDE4 inhibitor, which evaluated as potential anticonvulsant.[10] Meanwhile, methotrexate '*N*-[4-[[(2,4-diamino-6-pteridinyl)methyl]methylamino]benzoyl]-L-glutamic acid' (**3**) is a well-known antirheumatic as well as antineoplastic therapeutically active drug.[11]

On the other hand, many benzamidic derivatives were reported to possess specific inhibition towards epidermal growth factor receptor (EGFR) protein tyrosine kinase (PTK), which is one of the important kinases that play a fundamental role in signal transduction pathways.[12] EGFR and its ligands (EGF, TGF-α) have been implicated in numerous tumours of epithelial origin[13,14] and

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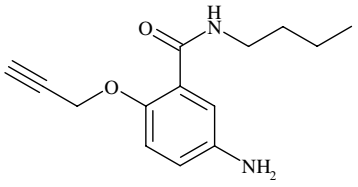
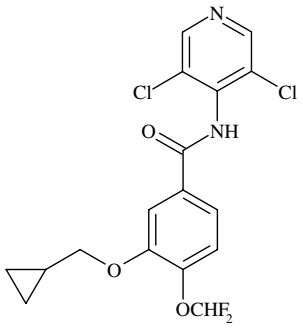
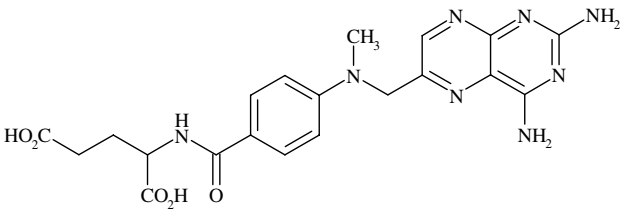


(**1**) Parsalmide



(**2**) Roflumilast



(**3**) Methotrexate

proliferative disorders of the epidermis such as psoriasis.[15]

From all the above reports and in continuation of our previous work directed towards construction of pharmacologically active agents,[16,17] it is intended in the present work to investigate the synthesis of novel bisbenzamide-containing compounds adopting facile synthetic approaches and utilizing easily accessible starting materials. Construction of organic compounds possessing two biologically active moieties (benzamide functions) may enhance the total observed pharmacological properties and could be a hint for determining highly promising active analogues. So, the anti-inflammatory properties of the newly prepared benzamide derivatives will be screened aiming to isolate a new pharmacologically active agent.

2. Results and discussion

2.1. Chemistry

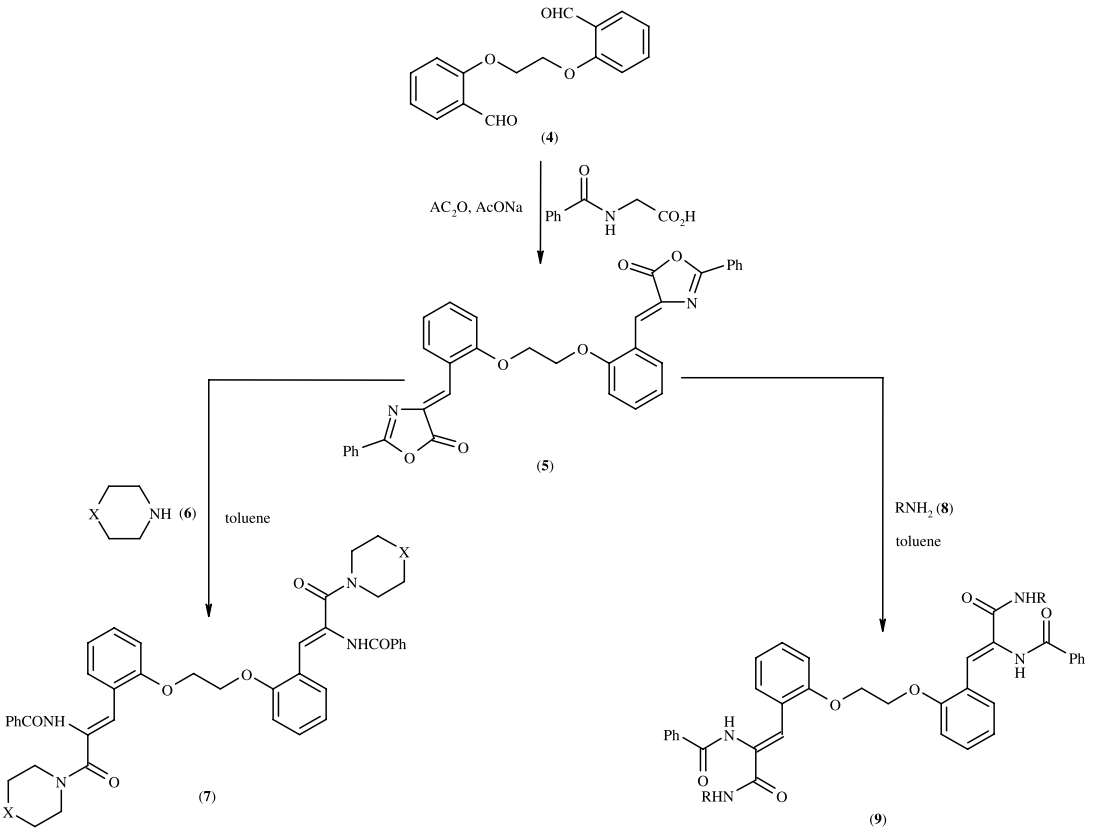
Reaction of 2,2′-[1,2-ethanediylbis(oxy)]bisbenzaldehyde (**4**) with hippuric acid in acetic anhydride in the presence of anhydrous sodium acetate afforded the corresponding 4,4′-[1,2-ethanediylbis(oxy-2,1-phenylenemethylidene)]bis(2- phenyl-5(4*H*)-oxazolone) (**5**) in good yield. The structure of **5** was inferred from spectroscopic (IR, ^{1}H NMR) and elemental analyses data. The IR spectrum of **5** exhibits a strong carbonyl stretching vibration band at $\nu = 1789$ cm^{-1} confirming the formation of cyclized form structure. In addition, the absence of any band assignable for carboxylic OH or amidic NH function supports the formation of bis-oxazolone heterocyclic system. ^{1}H NMR spectrum of **5** reveals the two methylene group protons as a sharp singlet signal at $\delta = 4.58$. However, the olefinic methine protons are hidden under the aromatic multiplet signals (Scheme 1).

Reaction of **5** with secondary amines (namely, piperidine, morpholine and 4-methylpiperazine) **6a**–**c**, as strong nucleophilic agents, in refluxing dry toluene leads to oxazolone ring opening giving *N*,*N*′-bis{2-[1,2-ethanediylbis(oxy-2,1-phenylene)]-1-(substituted carbonyl)ethenyl}benzamides **7a**–**c**. The structure of **7** was established through IR, ^{1}H NMR spectroscopic as well as elemental analyses data. The IR spectra of **7a**–**c** reveal the presence of carbonyl stretching vibration band at $\nu = 1661$–1651 cm^{-1} in addition to the amidic NH function at $\nu = 3260$–3217 cm^{-1} region. ^{1}H NMR spectra of **7a**–**c** show the two olefinic methine protons as a singlet signal at $\delta = 6.43$–6.46.

Similarly, reaction of **5** with primary aromatic amines (aniline, *p*-toluidine, *p*-anisidine, *p*-chloroaniline) **8a**–**d** in refluxing dry toluene yielded the corresponding *N*,*N*′-bis{1-[(arylamino)carbonyl]-2-[1,2-ethanediylbis(oxy-2,1-phenylene)]ethenyl}benzamides **9a**–**d** whose structures were deduced through spectroscopic and elemental analyses data.

2.2. Anti-inflammatory activity

The anti-inflammatory activity of the prepared bisbenzamide-containing compounds **7** and **9** was determined in vivo by the carrageenan-induced paw oedema standard method in rats.[17–20] The anti-inflammatory properties were recorded at successive time intervals (1, 2, 3, 4 and 24 h) and compared with that of ketoprofen which was used as a reference standard. From the obtained results (Table 1, Figs. 1 and 2), it has been noticed that most of the prepared benzamidic derivatives show



6a, **7a**, X = CH_2
6b, **7b**, X = O
6c, **7c**, X = NCH_3

8a, **9a**, R = Ph
8b, **9b**, R = 4-$H_3CC_6H_4$
8c, **9c**, R = 4-$H_3COC_6H_4$
8d, **9d**, R = 4-ClC_6H_4

Scheme 1.

Table 1. Anti-inflammatory activity of bisbenzamide-containing compounds using carrageenan-induced paw oedema in rats

Compound	Mean swelling volume 'ml' (% inhibition of oedema)				
	1 h	2 h	3 h	4 h	24 h
Control	0.127 ± 0.017 (00.0)	0.087 ± 0.022 (00.0)	0.132 ± 0.027 (00.0)	0.173 ± 0.017 (00.0)	0.140 ± 0.023 (00.0)
Ketoprofen	0.120 ± 0.012 (5.5)	0.073 ± 0.018 (16.1)	0.115 ± 0.018 (12.9)	0.087 ± 0.013* (49.7)	0.130 ± 0.013 (7.1)
7a	0.070 ± 0.012* (44.9)	0.052 ± 0.015 (40.2)	0.087 ± 0.023 (34.1)	0.067 ± 0.020* (61.3)	0.078 ± 0.023* (44.3)
7b	0.043 ± 0.016* (66.1)	0.037 ± 0.008* (57.5)	0.067 ± 0.014* (49.2)	0.047 ± 0.010* (72.8)	0.095 ± 0.009* (32.1)
7c	0.078 ± 0.016* (38.6)	0.083 ± 0.008 (4.6)	0.088 ± 0.020 (33.3)	0.050 ± 0.007* (71.1)	0.097 ± 0.020* (30.7)
9a	0.103 ± 0.016 (18.9)	0.070 ± 0.021 (19.5)	0.117 ± 0.027 (11.4)	0.097 ± 0.029* (43.9)	0.126 ± 0.012 (10.0)
9b	0.077 ± 0.013* (39.4)	0.083 ± 0.007 (4.6)	0.098 ± 0.015 (25.8)	0.097 ± 0.017* (43.9)	0.135 ± 0.005 (3.6)
9c	0.090 ± 0.009 (29.1)	0.077 ± 0.019 (11.5)	0.113 ± 0.008 (14.4)	0.078 ± 0.010* (54.9)	0.120 ± 0.015 (14.3)
9d	0.118 ± 0.013 (7.1)	0.068 ± 0.011 (21.8)	0.095 ± 0.013 (28.0)	0.058 ± 0.013* (66.5)	0.127 ± 0.009 (9.3)

* Significantly different from the control value at $p < 0.05$.

considerable pharmacological properties. However, the tested benzamidic derivatives **7a–c** reveal better anti-inflammatory activities than most of the corresponding analogues **9a–d**, explaining the role of alycyclic-amino functions (piperidinyl, morpholinyl or piperazinyl) in enhancing the total pharmacological effects compared with the (un)substituted arylamino residues. Among all the tested compounds, it has been observed that, compound **7b** reveals the best anti-inflammatory activity (% inhibition of oedema 66.1, 57.5, 49.2, 72.8, and 32.1 after 1, 2, 3, 4, and 24 h time intervals, respectively) even than ketoprofen (reference standard) itself (% inhibition of oedema 5.5, 16.1, 12.9, 49.7, and 7.1 after 1, 2, 3, 4 and 24 h time intervals, respectively). This observation could be attributed to the role of morpholinyl function that governs the total observed pharmacological effects.

Generally, it could be concluded that, construction of bisbenzamide-containing compounds may be considered an effective tool for determining a promising pharmacologically active agent, which could be a hint for developing a novel non-steroidal anti-inflammatory bioactive substance.

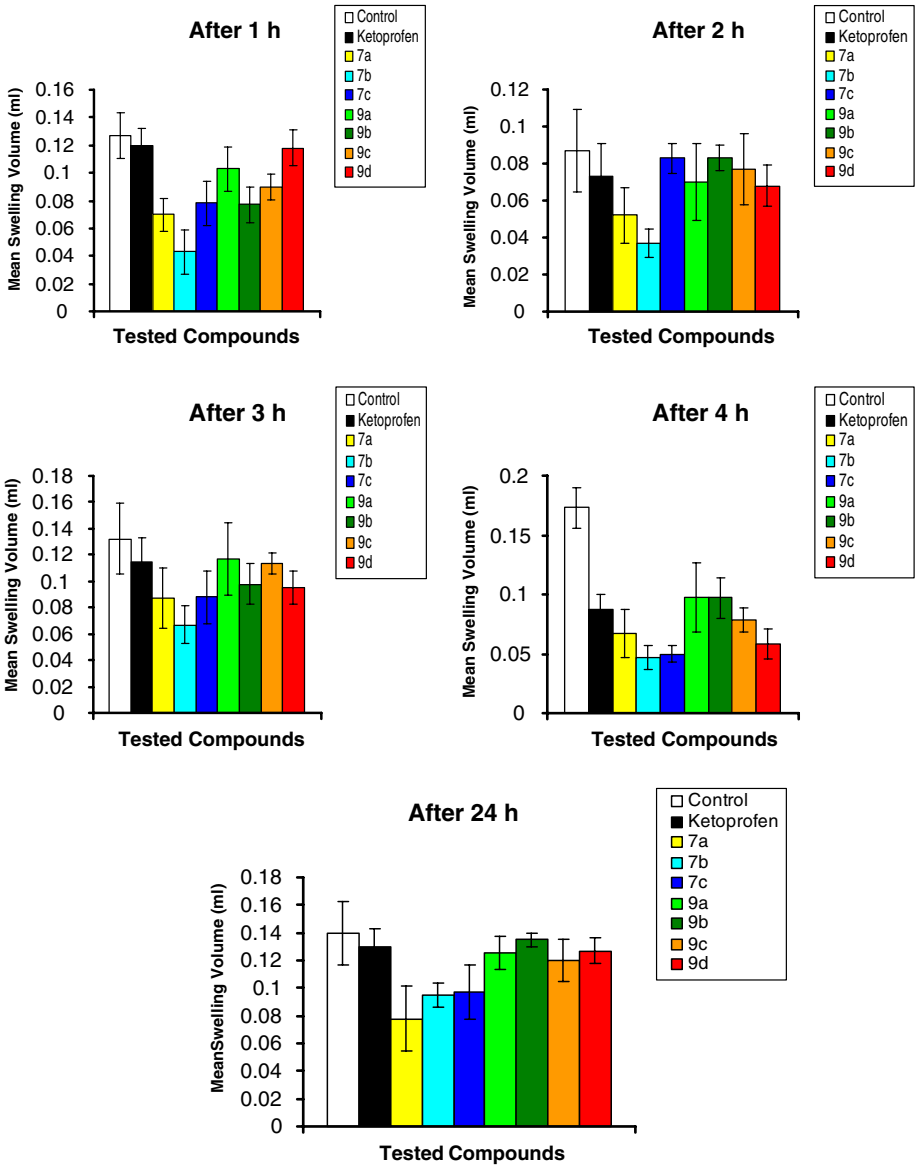


Figure 1. Mean oedema volume (ml) of the tested compounds at successive time intervals.

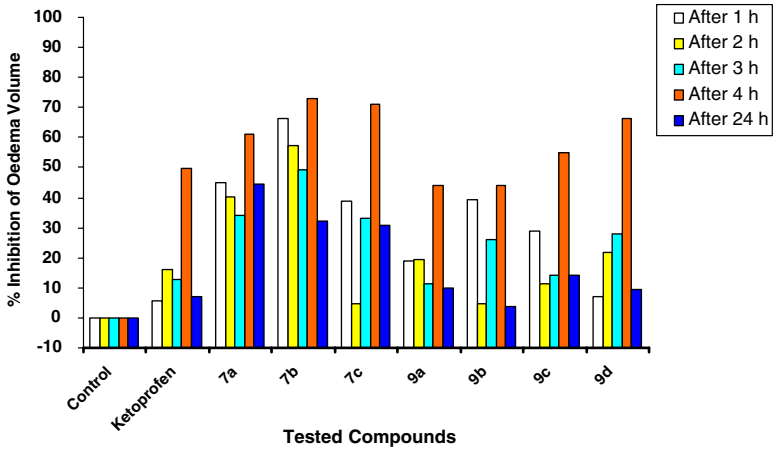


Figure 2. % inhibition of oedema for the tested compounds at successive time intervals.

3. Experimental

Melting points are uncorrected and recorded on an Electrothermal 9100 digital melting point apparatus. IR spectra (KBr) were recorded on a Nexus 670 FT-IR spectrophotometer. ^{1}H NMR spectra (in DMSO-d_6) were recorded on a Varian MERCURY (300 MHz) spectrometer. The starting compound **4** was prepared according to the previously reported procedure.[21]

3.1. 4,4′-[1,2-Ethanediylbis(oxy-2,1-phenylenemethylidene)]bis(2-phenyl-5(4*H*)oxazolone) (5)

A mixture of 2,2′-[1,2-ethanediylbis(oxy)]bisbenzaldehyde (**4**) (10 mmol) and hippuric acid (20 mmol) in acetic anhydride (15 ml) containing anhydrous sodium acetate (40 mmol) was heated at boiling point until solubility of all the reactants. Then, heating on a boiling water bath was continued for 7 h. The separated solid upon addition of methanol (25 ml) to the reaction mixture was collected, washed with water and crystallized from toluene affording **5** as yellow crystals, mp 243–244 °C, yield 72%. IR: ν_{max}/cm^{-1} 1789 (C=O), 1646, 1595 (C=N, C=C). ^{1}H NMR: δ 4.58 (s, 4H, 2 OCH_2), 7.15–8.81 (m, 20H, 18 arom H+2 olefinic CH). Anal. Calcd for $C_{34}H_{24}N_2O_6$ (556.55): C, 73.37; H, 4.35; N, 5.03. Found: C, 73.56; H, 4.42; N, 5.26.

3.2. Reaction of 5 with amines 6 or 8 (general procedure)

A solution of **5** (2.5 mmol) in dry toluene (25 ml) containing the corresponding amines **6a–c** or **8a–d** (5.5 mmol) was boiled under reflux for the appropriate time. The separated solid while refluxing was collected and crystallized from a suitable solvent affording the corresponding **7a–c**, **9a–d**.

3.2.1. *N*,*N*′-Bis{2-[1,2-ethanediylbis(oxy-2,1-phenylene)]-1-[(1-piperidinyl)carbonyl]ethenyl}benzamide (7a). Reaction time 40 h, colourless crystals from *N*,*N*-dimethylformamide (50%), mp 249–251 °C, yield 83%. IR: ν_{max}/cm^{-1} 3250 (NH), 1661 (C=O), 1612, 1515 (C=C). ^{1}H NMR: δ 1.38 (br s, 12H, 6 pip. CH_2), 3.43 (br s, 8H, 4 pip. NCH_2), 4.39 (s, 4H, 2 OCH_2), 6.46 (s, 2H, 2 olefinic CH), 6.95–7.93 (m, 18H, arom. H), 10.15 (br s, 2H, 2 NH). Anal. Calcd for $C_{44}H_{46}N_4O_6$ (726.84): C, 72.70; H, 6.38; N, 7.71. Found: C, 72.96; H, 6.58; N, 7.85.

3.2.2. *N*,*N*′-Bis{2-[1,2-ethanediylbis(oxy-2,1-phenylene)]-1-[(4-morpholinyl)carbonyl]ethenyl}benzamide (7b). Reaction time 30 h, colourless crystals from methanol, mp 233–235 °C, yield 85%. IR: ν_{max}/cm^{-1} 3260 (NH), 1651 (C=O), 1613, 1509 (C=C). ^{1}H NMR: δ 3.51 (br s, 16H, 4 mor. NCH_2 + 4 mor. OCH_2), 4.39 (s, 4H, 2 OCH_2), 6.43 (s, 2H, 2 olefinic CH), 6.96–7.93 (m, 18H, arom. H), 10.13 (s, 2H, 2NH). Anal. Calcd for $C_{42}H_{42}N_4O_8$ (730.79): C, 69.02; H, 5.79; N, 7.67. Found: C, 69.08; H, 5.88; N, 7.51.

3.2.3. *N*,*N*′-Bis{2-[1,2-ethanediylbis(oxy-2,1-phenylene)]-1-[[1-(4-methylpiperazinyl)]carbonyl]ethenyl}benzamide (7c). Reaction time 45 h, colourless crystals from *N*,*N*-dimethylformamide (50%), mp 242–244 °C, yield 74%. IR: ν_{max}/cm^{-1} 3217 (NH), 1658 (C=O), 1612, 1510 (C=C). ^{1}H NMR: δ 1.96 (s, 6H, 2CH_3), 2.19 (br s, 8H, 4 pip. CH_3NCH_2), 3.40 (br s, 8H, 4 pip. $CONCH_2$), 4.38 (s, 4H, 2 OCH_2), 6.46 (s, 2H, 2 olefinic CH), 6.96–7.92 (m, 18H, arom. H), 10.11 (s, 2H, 2NH). Anal. Calcd for $C_{44}H_{48}N_6O_6$ (756.87): C, 69.82; H, 6.39; N, 11.10. Found: C, 69.56; H, 6.25; N, 11.02.

3.2.4. *N*,*N*′-Bis{2-[1,2-ethanediylbis(oxy-2,1-phenylene)]-1-[(phenylamino)carbonyl]ethenyl}benzamide (9a). Reaction time 50 h, colourless crystals from *N*,*N*-dimethylformamide (80%), mp 264–266 °C, yield 70%. IR: ν_{max}/cm^{-1} 3222 (NH), 1644 (C=O), 1598, 1544 (C=C). ^{1}H NMR: δ 4.45 (s, 4H, 2 OCH_2), 6.83–7.98 (m, 30H, 28 arom. H + 2 olefinic CH), 9.98 (s, 2H, 2NH), 10.06 (s, 2H, 2NH). Anal. Calcd for $C_{46}H_{38}N_4O_6$ (742.79): C, 74.38; H, 5.16; N, 7.54. Found: C, 74.21; H, 5.14; N, 7.30.

3.2.5. *N*,*N*′-Bis{2-[1,2-ethanediylbis(oxy-2,1-phenylene)]-1-[[(4-methylphenyl)amino]carbonyl]ethenyl}benzamide (9b). Reaction time 50 h, colourless crystals from *N*,*N*-dimethylformamide (80%), mp 235–237 °C, yield 73%. IR: ν_{max}/cm^{-1} 3277 (NH), 1647 (C=O), 1600, 1515 (C=C). ^{1}H NMR: δ 2.25 (s, 6H, 2CH_3), 4.45 (s, 4H, 2 OCH_2), 6.83–7.97 (m, 28H, 26 arom. H + 2 olefinic CH), 9.95 (s, 2H, 2NH), 9.96 (s, 2H, 2NH). Anal. Calcd for $C_{48}H_{42}N_4O_6$ (770.85): C, 74.78; H, 5.49; N, 7.27. Found: C, 74.57; H, 5.33; N, 7.53.

3.2.6. *N*,*N*′-Bis{2-[1,2-ethanediylbis(oxy-2,1-phenylene)]-1-[[(4-methoxyphenyl)amino]carbonyl]ethenyl}benzamide (9c). Reaction time 45 h, colourless crystals from *N*,*N*-dimethylformamide (80%), mp 234–235 °C, yield 85%. IR: ν_{max}/cm^{-1} 3278 (NH), 1648 (C=O), 1602, 1513 (C=C). ^{1}H NMR: δ 3.72 (s, 6H, 2OCH_3), 4.45 (s, 4H, 2 OCH_2), 6.85-7.97 (m, 28H, 26 arom. H+2 olefinic CH), 9.91 (s, 2H, 2NH), 9.94 (s, 2H, 2NH). Anal. Calcd for $C_{48}H_{42}N_4O_8$ (802.85): C, 71.80; H, 5.27; N, 6.98. Found: C, 71.76; H, 5.21; N, 6.84.

3.2.7. *N*,*N*′-Bis{1-[[(4-chlorophenyl)amino]carbonyl]-2-[1,2-ethanediylbis(oxy-2,1-phenylene)]ethenyl}benzamide (9d). Reaction time 60 h, pale yellow crystals from *N*,*N*-dimethylformamide (80%), mp 263–265 °C, yield 64%. IR: ν_{max}/cm^{-1} 3254 (NH), 1639 (C=O), 1596, 1548 (C=C). ^{1}H NMR: δ 4.45 (s, 4H, 2OCH_2), 6.84–7.97 (m, 28H, 26 arom. H+2 olefinic CH), 10.00 (s, 2H, 2NH), 10.20 (s, 2H, 2NH). Anal. Calcd for $C_{46}H_{36}Cl_2N_4O_6$ (811.69): C, 68.06; H, 4.47; N, 6.90. Found: C, 68.31; H, 4.66; N, 6.69.

3.3. Anti-inflammatory activity

The anti-inflammatory activity screening was determined in vivo by the carrageenan-induced paw oedema standard method in rats.[17–20] Wister albino rats of either sex (pregnant female animals were excluded) weighing 160–190 g were divided into 9 groups of 6 animals each. Administration of ketoprofen (reference standard) dissolved in saline solution and the tested compounds **7a–c**, **9a–d** dissolved in DMSO, in a dose of 100 mg/kg (body weight) were given intraperitoneally 1 h before

induction of inflammation. The control group was given DMSO only. Carrageenan paw oedema was induced by subcutaneous injection of 1% solution of carrageenan in saline (0.1 ml/rat) into the right hind paw of rats. Paw volumes were measured volumetrically after successive time intervals (1, 2, 3, 4 and 24 h) with plethysmometer 7150 (UGO BASILE, Italy) and compared with the initial hind paw volume of each rat for determining the oedema volume. Data were collected, checked, revised and analyzed. Quantitative variables from normal distribution were expressed as means ± SE 'standard error.' The significant difference between groups was tested by using one-way ANOVA followed by LSD test at $p < 0.05$.

The anti-inflammatory activity was expressed as a percentage inhibition of oedema volume in treated animals in comparison with the control group (Table 1, Figs. 1 and 2).

$$\%\ \text{inhibition of oedema} = \frac{V_c - V_t}{V_c} \times 100$$

where V_c and V_t are the volumes of oedema for the control and drug-treated animal groups, respectively.

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