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Synthesis of new rofecoxib analogs of expected anti- inflammatory activity

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ABSTRACT

*A condensation-cyclization reaction of a 4-[N-alkyl-N-(tert-butyloxycarbonyl)amino]phenylacetic acid (**12a-b**) with 2-bromo-4-(methylsulphonyl)acetophenone (**6**) in the presence of triethylamine and 1,8-diazabicyclo[5.4.0]undec-7-ene afforded 4-[4-(methanesulphonyl)phenyl]-3-[4-(N-alkyl-N-tert-butyloxy carbonyl)amino)phenyl]-5H-furan-2-ones (**13a-b**) which upon reaction with HCl–saturated methanol gave non-protected furanones **14a-b**. Subsequent reaction of the furanone **14a** with nitric oxide (40 psi) proceeded via a N-methylamino-N-diazen-1-ium-1,2-diolate intermediate that undergoes protonation of the more basic diazen-1-ium-1,2-diolate N^2-nitrogen and then loss of a nitroxyl (HNO) species to furnish the N-nitroso product **15**.*

Key words: furanone celecoxib rofecoxib, cyclooxygenase , anti-inflammatory

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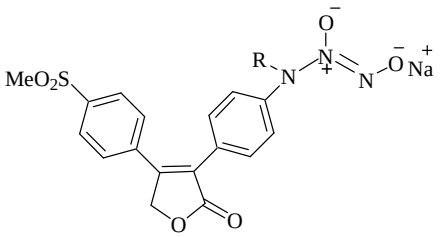
INTRODUCTION

The development of celecoxib (Celebrex®) [1], rofecoxib (Vioxx®) [2] and valdecoxib (Bextra®) [3] validated the original concept that selective cyclooxygenase-2 (COX-2) inhibitors would be effective anti-inflammatory agents with a diminished gastrointestinal (GI) and renal toxicity [4-7]. Unfortunately, some selective COX-2 inhibitory drugs that include rofecoxib and valdecoxib alter the natural balance in the COX pathway. In this regard, the amount of the desirable vasodilatory and anti-aggregtory prostacyclin (PGI_2) produced is decreased together with a simultaneous increase in the level of the undesirable vasoconstrictory and prothrombotic thromboxane A_2 (TxA_2) [8-10]. These two adverse biochemical changes in the COX pathway are believed to be responsible for the increased incidences of high blood pressure and myocardial infarction that ultimately prompted the withdrawal of rofecoxib (Vioxx®) and valdecoxib (Bextra®) [11, 12]. Nitric oxide (NO) exhibits a number of useful pharmacological actions that include vascular relaxation (vasodilation), and inhibition of platelet aggregation and adhesion [13]. Accordingly, attachment of a NO-donor moiety to highly selective COX-2 inhibitors (NONO-coxibs) offers a potential drug design concept to circumvent the adverse cardiovascular events. Recently, we reported NONO-coxib ester prodrugs having a NO-donor diazen-1-ium-1,2-diolate moiety that are effectively cleaved by esterases to release NO [14-16]. We now report an investigation directed toward NO donor selective COX-2 inhibitory anti-inflammatory agents that would be devoid of adverse cardiovascular effects. (see structure **1** in Figure 1).



1, R= alkyl

Figure 1. Structure of putative hybrid nitric oxide donor *N*-diazen-1-ium-1,2-diolate derivatives of selective COX-2 inhibitory 4-[4-(methanesulphonyl)phenyl]-3-[4-(*N*-alkylamino)phenyl]-5H-furan-2-ones.

MATERIALS AND METHODS

Melting points were determined on a Thomas–Hoover capillary apparatus and are uncorrected. Infrared (IR) spectra were recorded as films on NaCl plates using a Nicolet 550 Series II Magna FT-IR spectrometer. ^{1}H NMR spectra were measured on a Bruker AM-300 spectrometer in D_2O, $CDCl_3$, CD_3OD or DMSO-d_6 with TMS as the internal standard, where *J* (coupling constant) values are estimated in hertz (Hz). Microanalyses were performed for C, H, N (Micro Analytical Service Laboratory, Department of Chemistry, University of Alberta). The prepared compounds showed a single spot on Macherey-Nagel Polygram Sil G/UV254 silica gel plates (0.2 mm) using a low, medium, and highly polar solvent system, and no residue remained after combustion, indicating a purity of >95%. Silica gel column chromatography was performed using Merck silica gel 60 ASTM (70–230 mesh). All other reagents, purchased from the Aldrich Chemical Company (Milwaukee, WI) and were used without further purification.

4-(Methylsulphonyl)acetophenone (5). 4-Fluoro-acetophenone **(2)** (2.76 g, 20 mmoles) and sodium methanesulfinate (2.25 g, 22 mmoles) were dissolved in dimethyl sulphoxide (15 mL). The mixture was stirred at 120 °C for 15 hours and then poured over 50 g of ice. The solid thus formed was collected and dried to give **5** (2.77 g, 70%) as white powder: mp 117 – 119 °C as reported, IR (film) 1684 (CO), 1318, 1154 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.68 (s, 3H, COC*H*$_3$), 3.09 (s, 3H, SO_2C*H*$_3$), 8.06 (dd, *J* = 1.8, 6.7 Hz, 2H, phenyl H-2, H-6), 8.14 (dd, *J* = 1.8, 6.7 Hz, 2H, phenyl H-3, H-5).

2-Bromo-4-(methylsulphonyl)acetophenone (6). To a solution of 4-(methylsulphonyl)acetophenone **(5)** (4.1 g, 20.65 mmoles) in 50 mL of chloroform, cooled to -5 °C and under argon, 1.0 mg of aluminium chloride and (0.89 mL, 17.75 mmoles) of bromine in 6 mL of chloroform were added. The mixture was maintained at -5 °C for 1 hour with stirring, 50 mL water was added and the layers were separated. The aqueous phase was extracted with ethyl acetate, and the combined organic phases were dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using ethyl acetate /hexane (1:1, v/v) as the eluent to give **6** (4.2 g, 74%) as a white powder: mp 124 - 126 °C, IR (film) 1655 (CO), 1317, 1151 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.11 (s, 3H, SO_2C*H*$_3$), 4.47 (s, 2H, C*H*$_2$Br), 8.08 (dd, *J* = 1.5, 7.6 Hz, 2H, phenyl H-2, H-6), 8.18 (dd, *J* = 1.5, 7.6 Hz, 2H, phenyl H-3, H-5). Anal. Calcd for $C_9H_9BrO_3S$: C, 39.00; H, 3.27; S, 11.57. Found: C, 39.10; H, 3.20; S, 11.60

Ethyl 4-aminophenylacetate (8). A mixture of 4-aminophenylacetic acid **(7)** (2.12 g, 13.9 mmoles) and concentrated sulphuric acid (2 mL, 27.8 mmoles) in absolute ethanol (30 mL) was heated under reflux for 20 minutes. The reaction mixture was cooled and mixed with aqueous sodium carbonate solution (till pH 8) and extracted with ethyl acetate. The organic extract was dried using anhydrous sodium sulphate and the solvent was removed under reduced pressure to give the ester **8** (2.4 g, 94%) as a pure brown oil: ^{1}H NMR ($CDCl_3$) δ 1.25 (t, *J* = 7.1 Hz, 3H, CH_2C*H*$_3$), 3.50 (s, 2H, C*H*$_2$COO), 3.59 (br. s, 2H, N*H*$_2$, D_2O exchangeable), 4.14 (q, *J* = 7.1 Hz, 2H, C*H*$_2$$CH_3$), 6.66 (d, *J* = 8.3 Hz, 2H, phenyl H-2, H-6), 7.08 (d, *J* = 8.3 Hz, 2H, phenyl H-3, H-5). Anal. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 67.20; H, 7.50; N, 7.60

Ethyl 4-(*N*-formylamino)phenylacetate (9a). Formic acid (1.4 mL, 35.9 mmoles) was added to acetic anhydride (2.8 mL, 29.2 mmoles) at 0 °C and then the mixture was heated at 50 °C for 30 minutes. The mixture was cooled to 0 °C and tetrahydrofuran (20 mL) added. A solution of **8** (2.0 g, 11.2 mmoles) in tetrahydrofuran (20 mL) was added drop wise and the solution was stirred at -10 °C for 30 minutes. The solvent was removed under reduced

pressure to give **9a** (2.1g, 92%) as a yellow syrup: IR (film) 3275 (NH), 2985 (C-H aromatic), 2937 (C-H aliphatic), 1732 (CO_2), 1692 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 3.59 (s, 2H, CH_2COO), 4.15 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 7.24 (d, *J* = 8.5 Hz, 2H, phenyl H-3, H-5), 7.49 (d, *J* = 8.5 Hz, 2H, phenyl H-2, H-6), 8.33 (br. s, 1H, NH, D_2O exchangeable), 8.34 (s, 1H, HCO). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.60; H, 6.30; N, 6.70

Ethyl 4-(*N*-acetylamino)phenylacetate (9b). A mixture of acetic anhydride (3.1 g, 30.6 mmoles) and ethyl 4-aminophenylacetate **(8)** (1.8 g, 10.20 mmoles) was stirred at -10 °C for 30 min. The solvent was removed under reduced pressure to give **9b** (1.8 g, 81%) as yellowish white solid: mp 75 - 77 °C, IR (film) 3305 (NH), 2984 (C-H aromatic), 2936 (C-H aliphatic), 1733 (CO_2), 1667 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 2.16 (s, 3H, $COCH_3$), 3.58 (s, 2H, CH_2COO), 4.15 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 7.23 (d, *J* = 8.6 Hz, 2H, phenyl H-3, H-5), 7.45 (d, *J* = 8.6 Hz, 2H, phenyl H-2, H-6). Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.20; H, 6.80; N, 6.30

Ethyl 4-(*N*-methylamino)phenylacetate (10a). To a solution of **9a** (2.73 g, 13.3 mmoles) in tetrahydrofuran (40 mL), 2M solution of borane dimethylsulfide (16.6 mL, 33.25 mmoles) was added slowly. The solution was stirred at room temperature for 1 hour, methanol (4 mL) carefully added, the mixture stirred for 15 minutes. 1 M hydrochloric acid (4 mL) was added and the mixture stirred at 40 °C for 30 minutes. The solvent was removed under reduced pressure and the residue partitioned between ethyl acetate (80 mL) and saturated aqueous sodium bicarbonate (80 mL). the aqueous fraction was extracted with ethyl acetate (40 mL), the combined organic fractions were dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was chromatographed, eluting with ethyl acetate/ light petroleum ether (1 : 4) to give **10a** (1.84 g, 72 %) as colorless oil: IR (film) 3380 (NH), 2977 (C-H aromatic), 2930 (C-H aliphatic), 1732 (CO_2); ^1H NMR ($CDCl_3$) δ 1.25 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 2.86 (s, 3H, NCH_3), 3.52 (s, 2H, CH_2COO), 4.14 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 6.72 (d, *J* = 8.5 Hz, 2H, phenyl H-2, H-6), 7.15 (d, *J* = 8.5 Hz, 2H, phenyl H-3, H-5).Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.30; H, 7.70; N, 7.30

Ethyl 4-(*N*-ethylamino)phenylacetate (10b). The title compound was prepared from ethyl 4-(N-acetylamino)phenylacetate **(9b)** using the same procedure described above as a yellowish brown oil in 51% yield: IR (film) 3347 (NH), 2972 (C-H aromatic), 2927 (C-H aliphatic), 1734 (CO_2); ^1H NMR ($CDCl_3$) δ 1.23 (t, *J* = 7.1 Hz, 3H, $COOCH_2CH_3$), 1.27 (t, *J* = 7.3 Hz, 3H, NCH_2CH_3), 3.19 (q, *J* = 7.3 Hz, 2H, NCH_2CH_3), 3.52 (s, 2H, CH_2COO), 4.13 (q, *J* = 7.1 Hz, 2H, $COOCH_2CH_3$), 6.77 (d, *J* = 8.6 Hz, 2H, phenyl H-2, H-6), 7.16 (d, *J* = 8.5 Hz, 2H, phenyl H-3, H-5).Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.39; H, 8.40; N, 6.70

Ethyl 4-[*N*-methy-*N*-(tert-butyloxycarbonyl)amino] phenylacetate (11a). A solution of **10a** (1.84 g, 9.63 mmoles), 1 M solution of di-tert-butyl dicarbonate (14.4 mL, 14.4 mmoles) and 4-dimethylaminopyridine (117 mg, 0.96 mmoles) in tetrahydrofuran (40 mL) was heated at reflux temperature for 16 hours. The solution was cooled to room temperature and the solvent removed under reduced pressure. the residue partitioned between ethyl acetate (40 mL) and saturated aqueous sodium bicarbonate (40 mL) and the aqueous fraction was extracted with ethyl acetate (2 x 40 mL), the combined organic fractions were washed with water (2 x 40 mL), brine (40 mL), dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography using gradient ethyl acetate / light petroleum ether (10 – 30%) as eluent to give **11a** (1.32 g, 47%) as a yellow oil: IR (film) 2977(C-H aromatic), 2935 (C-H aliphatic), 1735, 1701 (CO_2); ^1H NMR ($CDCl_3$) δ 1.26 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.46 (s, 9H, $C(CH_3)_3$), 3.25 (s, 3H, NCH_3), 3.59 (s, 2H, CH_2COO), 4.16 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 7.23 (m, 4H, phenyl H). Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.39; H, 8.40; N, 5.15.

Ethyl 4-[*N*-ethyl-*N*-(tert-butyloxycarbonyl)amino] phenylacetate (11b). The title compound was prepared from ethyl 4-(*N*-ethylamino)phenylacetate **(10b)** using the same procedure described above as a yellow oil in 56% yield: IR (film) 2961 (C-H aromatic), 2928 (C-H aliphatic), 1737, 1703 (CO_2); ^1H NMR ($CDCl_3$) δ 1.15 (t, *J* = 7.3 Hz, 3H, NCH_2CH_3), 1.21 (t, *J* = 7.1 Hz, 3H, $COOCH_2CH_3$), 1.46 (s, 9H, $C(CH_3)_3$), 3.53 (s, 2H, CH_2COO), 3.64 (q, *J* = 7.3 Hz, 2H, NCH_2CH_3), 4.13 (q, *J* = 7.1 Hz, 2H, $COOCH_2CH_3$), 7.14 (d, *J* = 8.1 Hz, 2H, phenyl H-2, H-6), 7.21 (d, *J* = 8.1 Hz, 2H, phenyl H-3, H-5).Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4,81. Found: C, 70.10; H, 8.70; N, 4.90.

4-[*N*-Methyl-*N*-(tert-butyloxycarbonyl)amino]phenyl acetic acid (12a). A solution of **11a** (1.32g, 4.53 mmoles) in methanol (16 mL) and 1M lithium hydroxide (22.6 mL, 22.6 mmoles) was stirred at 50 °C for 30 minutes. The solution was cooled at 2 °C, washed with ether (20 mL) and the pH was adjusted to 4 with 5 M hydrochloric acid. The suspension was stirred at 2 °C for 30 minutes and filtered to give **16a** (0.68 g, 65%) as a white powder: mp 113 - 115 °C; IR (film) 3405 (O-H), 2978 (C-H aromatic), 2931 (C-H aliphatic), 1733, 1699 (CO_2); ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9H, C(C*H*$_3$)$_3$), 3.25 (s, 3H, NC*H*$_3$), 3.63 (s, 2H, C*H*$_2$COO), 7.24 (m, 4H, phenyl H). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5,62. Found: C, 67.49; H, 7.70; N, 5.50.

4-[*N*-Ethyl-*N*-(tert-butyloxycarbonyl)amino]phenyl acetic acid (12b). The title compound was prepared from ethyl 4-[*N*-ethyl-N-(tert-butyloxycarbonyl)amino] phenyl acetate **(11b**) using the same procedure described above as a white powder in 54% yield: mp 96 - 98 °C; IR (film) 3425 (OH), 2961 (C-H aromatic), 2928 (C-H aliphatic), 1735, 1697 (CO_2); ^{1}H NMR ($CDCl_3$) δ 1.15 (t, *J* = 7.3 Hz, 3H, NCH$_2$C*H*$_3$), 1.44 (s, 9H, C(C*H*$_3$)$_3$), 3.63 (s, 2H, C*H*$_2$COO), 3.69 (q, *J* = 7.3 Hz, 2H, NC*H*$_2$CH$_3$), 7.13 (d, *J* = 8.1 Hz, 2H, phenyl H-2, H-6), 7.22 (d, *J* = 8.1 Hz, 2H, phenyl H-3, H-5). Anal. Calcd for $C_{15}H_{21}NO_3$ C, 68.42; H, 8.04; N, 5.32. Found: C, 68.39; H, 8.10; N, 5.39

4-[4-(Methanesulphonyl)phenyl]-3-[4-(*N*-methyl-*N*-tert-butyloxycarbonyl)amino)phenyl]-5*H*-furan-2-one (13a). To a mixture of 4-[*N*-methyl-*N*-(tert-butyloxycarb-onyl)amino]phenylacetic acid **(12a)** (0.54 g, 2 mmoles), 8 mL of acetonitrile and (0.61g, 2.25 mmoles) of 2-bromo-4-(methylsulphonyl)acetophenone **(6)**, triethyl amine (0.7 mL, 5 mmoles) was added drop wise and under argon. The resulting mixture was stirred for 1 hour at room temperature and then cooled to 0 °C followed by adding (0.58 mL, 3.88 mmoles) of diazabicyclo[5.4.0]-undec-7-ene and the mixture was stirred for another 2 hours at this temperature. Then 7 mL of 1 N hydrochloric acid was added and the mixture was extracted with ethyl acetate. The organic extract was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was chromatographed, eluting with ethyl acetate / hexane (2 : 1) to give **13a** (0.48 g, 54%) as a yellow gum: IR (film) 2974 (C-H aromatic), 2930 (C-H aliphatic), 1751, 1697 (CO_2), 1318, 1151 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9H, C(C*H*$_3$)$_3$), 3.09 (s, 3H, SO$_2$C*H*$_3$), 3.29 (s, 3H, NC*H*$_3$), 5.19 (s, 2H, furanone C*H*$_2$), 7.29 (d, *J* = 8.5 Hz, 2H, N-methylaminophenyl H-3, H-5), 7.39 (d, *J* = 8.5 Hz, 2H, N-methylaminophenyl H-2, H-6), 7.56 (d, *J* = 7.1 Hz, 2H, methanesulfonylphenyl H-3, H-5), 7.95 (d, *J* = 7.1 Hz, 2H, methanesulfonylphenyl H-2, H-6).Anal. Calcd for $C_{23}H_{25}NO_5S$: C, 64,62; H, 5.89; N, 3.28. Found: C, 64.60; H, 5.70; N, 3.30

3-[4-(*N*-Ethyl-*N*-tert-butyloxycarbonyl)amino)phenyl]-4-[4-(methanesulphonyl)-phenyl]-5*H*-furan-2-one (13b). The title compound was prepared from ethyl 4-[*N*-ethyl-*N*-(tert-butyloxycarbonyl)amino]phenylacetate **(12b**) and 2-bromo-4-(methylsulphonyl)acetophenone **(10)** using the same procedure described above in 51% as a yellow gum: IR (film) 2975 (C-H aromatic), 2933 (C-H aliphatic), 1753, 1699 (CO_2), 1318, 1154 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16 (t, *J* = 7.1 Hz, 3H, CH$_2$C*H*$_3$), 1.47 (s, 9H, C(C*H*$_3$)$_3$), 3.09 (s, 3H, SO$_2$C*H*$_3$), 3.69 (q, *J* = 7.1 Hz, 2H, C*H*$_2$CH$_3$), 5.19 (s, 2H, furanone C*H*$_2$), 7.26 (d, *J* = 8.5 Hz, 2H, N-ethylaminophenyl H-3, H-5), 7.39 (d, *J* = 8.5 Hz, 2H, N-ethylaminophenyl H-2, H-6), 7.55 (d, *J* = 8.5 Hz, 2H, methanesulfonylphenyl H-3, H-5), 7.94 (d, *J* = 7.1 Hz, 2H, methanesulfonylphenyl H-2, H-6). Anal. Calcd for $C_{24}H_{27}NO_5S$: C, 65.28; H, 6.16; N, 3.17. Found: C, 65.30; H, 6.10; N, 3.30

4-[4-(Methanesulphonyl)phenyl]-3-[4-(*N*-methyl-amino)phenyl]-5*H*-furan-2-one (14a). A solution of **13a** (0.446 g, 1 mmoles) in HCl – saturated methanol (25 mL) was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure, aqueous sodium carbonate was added to the residue till pH 8 and the aqueous solution was extracted with ethyl acetate. The organic extract was dried using anhydrous sodium sulphate and the solvent was removed under reduced pressure to give **14a** (0.326 g, 95%) as an orange gum: IR (film) 3223 (NH), 2985 (C-H aromatic), 2925 (C-H aliphatic), 1744 (CO), 1305, 1147 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.90 (s, 3H, NC*H*$_3$), 3.09 (s, 3H, SO$_2$C*H*$_3$), 5.14 (s, 2H, furanone C*H*$_2$), 6.76 (d, *J* = 8.5 Hz, 2H, N-methylaminophenyl H-3, H-5), 7.31 (d, *J* = 8.5 Hz, 2H, N-methylaminophenyl H-2, H-6), 7.57 (d, *J* = 8.5 Hz, 2H, methanesulfonylphenyl H-3, H-5), 7.97 (d, *J* = 8.5 Hz, 2H, methanesulfonyl-phenyl H-2, H-6). MS 344.04 (M + 1).Anal. Calcd for $C_{18}H_{17}NO_4S$: C, 62.96; H, 4.99; N, 4.08. Found: C, 62.90; H, 5.00; N, 4.00.

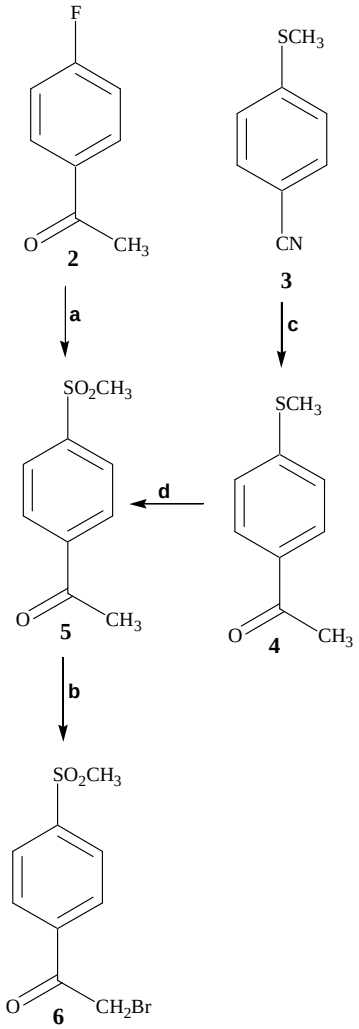
3-[4-(*N*-Ethylamino)phenyl]-4-[4-(methanesulphon-yl)phenyl]-5*H*-furan-2-one (14b). The title compound was prepared from 3-[4-(*N*-ethyl-*N*-tert-butyloxycarbo-nyl)amino)phenyl]-4-[4-(methanesulphonyl)phenyl]-5H-furan-2-one **(13b)** using the same procedure described above in 91% as an orange gum: IR (film) 3225 (NH), 2983 (C-H aromatic), 2925 (C-H aliphatic), 1742 (CO), 1307, 1147 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16 (t, *J*= 7.1 Hz, 3H, CH$_2$C*H*$_3$),3.10 (s, 3H, SO$_2$C*H*$_3$), 3.69 (q, *J*= 7.1 Hz, 2H, C*H*$_2$CH$_3$), 5.15 (s, 2H, furanone C*H*$_2$), 6.77 (d, *J* = 8.5 Hz,

2H, N-ethylaminophenyl H-3, H-5), 7.31 (d, *J* = 8.5 Hz, 2H, N-ethylaminophenyl H-2, H-6), 7.57 (d, *J* = 8.5 Hz, 2H, methanesulfonylphenyl H-3, H-5), 7.94 (d, *J* = 8.5 Hz, 2H, methanesulfonylphenyl H-2, H-6). MS 358.11 (M + 1). Anal. Calcd for $C_{19}H_{19}NO_4S$: C, 63.85; H, 5.36; N, 3.92. Found: C, 63.85; H, 5.35; N, 3.90.

3-[4-(*N*-Methyl-*N*-nitrosoamino)phenyl]-4-[4-(methanesulphonyl)phenyl]-5*H*-furan -2-one (15). 4-[4-(Methanesulphonyl)phenyl]-3-[4-(*N*-methyl)phenyl]-5*H*-furan-2-one (**14a**) (0.343 g, 1 mmole) was added to a solution of sodium methoxide (1 mmole, 0.22 mL of a 25% w/v solution in mehanol) and diethyl ether (5 mL) with stirring at 25 °C. This mixture was purged with dry nitrogen for 5 minutes, and then the reaction was allowed to proceed under an atmosphere of nitric oxide (40 psi internal pressure) with stirring at 25 °C for 24 hours. The solvents were removed under reduced pressure and the residue was purified by silica gel column chromatography using ethyl acetate / hexane (1:1, v/v) as the eluent to give **15** (4.2 g, 45%) as a yellow solid: IR (film) 2988 (C-H aromatic), 2923 (C-H aliphatic), 1744 (CO), 1309, 1147 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.09 (s, 3H, SO_2CH_3), 3.47 (s, 3H, NCH_3), 5.23 (s, 2H, furanone CH_2), 7.55 (m, 4H, N-methylaminophenyl H-2, H-3, H-5, H-6), 7.57 (d, *J* = 8.5 Hz, 2H, methanesulfonylphenyl H-3, H-5), 7.98 (d, *J* = 8.5 Hz, 2H, methanesulfonylphenyl H-2, H-6). MS 394.99 (M + Na). Anal. Calcd for $C_{18}H_{16}N_2O_5S.1/4H_2O$: C, 57.32; H, 4.41; N, 7.43. Found: C, 57.39; H, 4.70; N, 7.39.

RESULTS AND DISCUSSION

Scheme 1

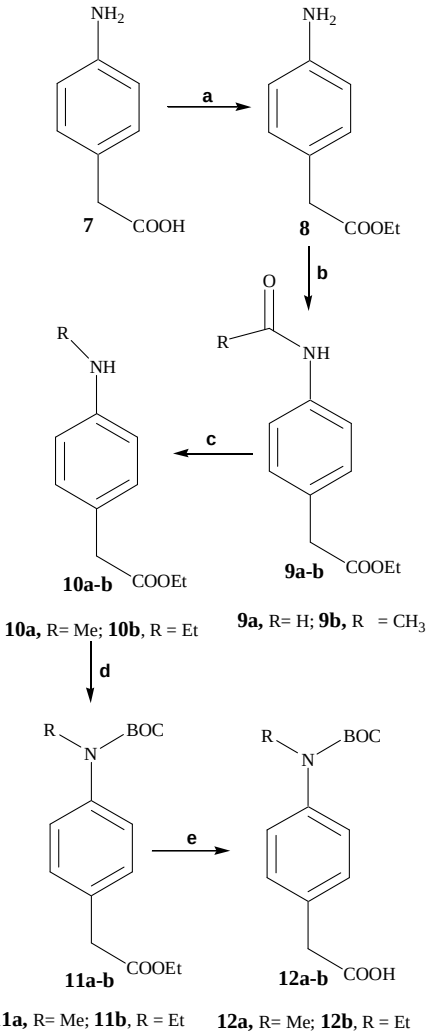


Reagents and conditions: a) DMSO, CH_3SO_2Na, 120 °C, 15 hours; b) $CHCl_3$, $AlCl_3$, Br_2, -5 °C, 1 hour; c) 1. THF, MeLi, -78 °C, 2. 25 °C, 3 hours, 3. 3N HCl, 25 °C, 18 hours; d) CH_2Cl_2, mCBPA, 18 hours.

The synthetic strategy employed to prepare putative model compounds of general structure **1** (see Figure 1) is illustrated in Schemes 1, 2, 3. Thus, 4-(methylsulphonyl)acetophenone **(5)** was prepared from 4-(methylthio)benzonitrile **(3)** in 2 steps according to reported procedures [17, 18] or by sulfinate anion replacement of an activated fluoride involving an aromatic nucleophilic substitution reaction. Bromination of **5** using bromine in chloroform gave the precursor compound **6** (scheme 1).

4-[*N*-Methy/ethyl-*N*-(tert-butyloxycarbonyl)amino] phenylacetic acids **(12a-b)** were prepared by estrification of the commercially available 4-aminophenylacetic acid **(7)** followed by acylation using either a mixture of formic acid and acetic anhydride, or acetic anhydride alone to give acyl derivatives **9a-b**. Reduction of **9a-b** using borane dimethylsulfide afforded the respective *N*-alkylphenylacetate esters **10a-b** which were protected as the BOC derivatives **11a-b** using di-tert-butyl dicarbonate and 4-dimethylaminopyridine**.** Selective hydrolysis of these esters provided the acids **12a-b** as illustrated in **scheme 2.**

Scheme 3

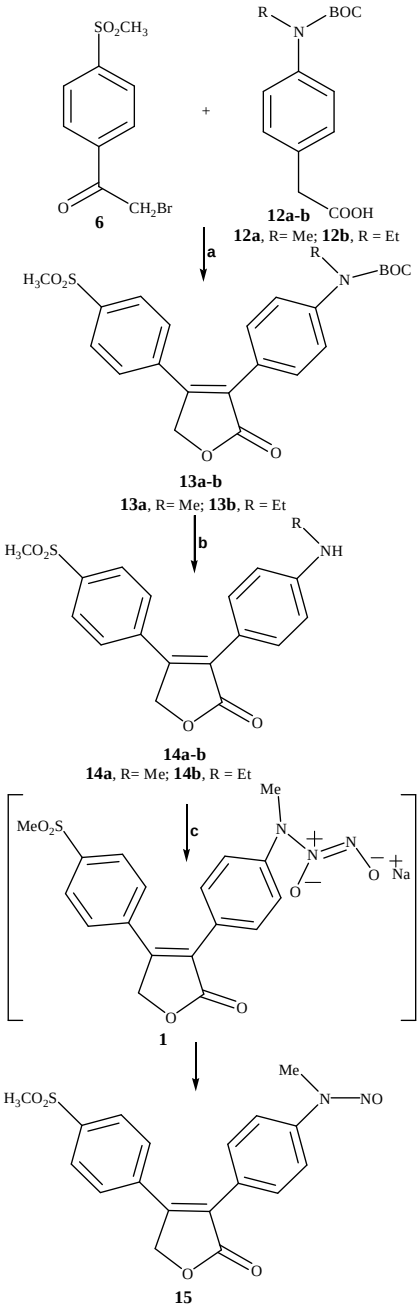


Reagents and conditions: a) EtOH, H_2SO_4, reflux, 20 minutes; b) THF, $(RCO)_2O$, -10 °C, 30 minutes; c) THF, BH_3.DMS, RT, 1 hour d) THF, di-tert-butyldicarbonate, DMAP, reflux, 16 hours; e) MeOH, 1M LiOH, 50 °C, 30 minutes.

Reaction of the bromoketone **6** with phenylacetic acid derivatives **12a-b** proceeded via a 2-step condensation-cyclization reaction that was performed as a one-pot procedure [19]. Thus reaction of the bromoacetophenone **6** with **12a-b** in the presence of triethylamine yielded the ester intermediate. Subsequent cooling to 0 °C and addition of

1,8-diazabicyclo[5.4.0]undec-7-ene induced the cyclization reaction to afford the 3,4-diaryl-5*H*-furan-2-one derivatives **13a-b**. The required alkylamino derivatives **14a-b** were obtained by deprotection of **13a-b** using HCl–saturated methanol.

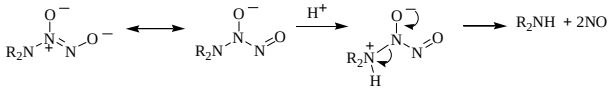
Scheme 3



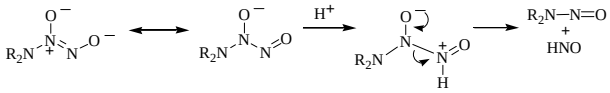
Reagents and conditions: a) 1. MeCN, Et_3N, 25 °C, 1 hour, 2. MeCN, DBU, 25 °C, 2 hours; b) MeOH, HCl, 25 °C, 1 hour; c) For **14a**, Nitric oxide (40 psi), MeOH, ether, MeONa, 25 °C, 24 hours.

Reaction of 4-[4-(methanesulphonyl)phenyl]-3-[4-(*N*-methylamino)phenyl]-5*H*-furan-2-one **(14a)** with nitric oxide gas (40 psi) at 25 °C in the presence of sodium methoxide yielded a product which exhibited a molecular ion in the mass spectrum (m/z 394.95 (M + Na)) and microanalytical data that was consistent with the *N*-nitroso product 3-[4-(*N*-methyl-*N*-nitrosoamino)phenyl]-4-[4-(methanesulphonyl)phenyl]-5*H*-furan-2-one**(15).** The spontaneous

decomposition pathway of the *N*-alkyl-*N*-diazen-1-ium-1,2-diolate moiety (see Figure 1) is dependent upon the site of protonation. In this regard, protonation at the amine nitrogen and then decomposition would produce the amine and 2 molecules of NO as illustrated below.



Alternatively, protonation of the diazen-1-ium-1,2-diolate N^2-nitrogen and then decomposition would furnish a nitrosamine (such as product **15** in Scheme 3) and a nitroxyl species (HNO) as indicated below.



The formation of the *N*-nitroso product **15** indicates that (i) the intermediate *N*-alkyl-*N*-diazen-1-ium-1,2-diolate product (see structure **1** in Figure 1) must undergo protonation of the more basic diazen-1-ium-1,2-diolate N^2-nitrogen that is unstable undergoing subsequent elimination of a HNO species species [20, 21], and (ii) that the attachment of an alkyl substituent to O^2 position prevents the spontaneous decomposition of diazen-1-ium-1,2-diolates [22].

Anti-inflammatory activity

Anti-inflammatory activity was evaluated using carrageenan - induced paw edema [23] . Adult male rats weighing between 150-180 g were maintained under normal laboratory conditions and kept in standard polypropylene cages at room temperature of 25-30°C, 60 to 65% relative humidity and provided with standard diet and water ad libitum. Four groups each of five rats were used and treated as follow; Group I served as control (administered saline), Group II administered rofecoxib (20 mg/kg bw) followed by carrageenan injection, Groups III and IV administered tested compounds (20 mg / kg bw) followed by carrageenan injection. rofecoxib and tested compounds were administered orally. After 30 min., all animals were injected with 0.1 ml of 1% carrageenan solution (prepared in normal saline) into the right hind paw of all groups. The edema was quantified by measuring the hind paw thickness immediately before subplantar injection, and at 1, 3, 5 hours post carrageenan treatment with a micrometer caliber. The increase in paw volume after carrageenan administration was recorded.

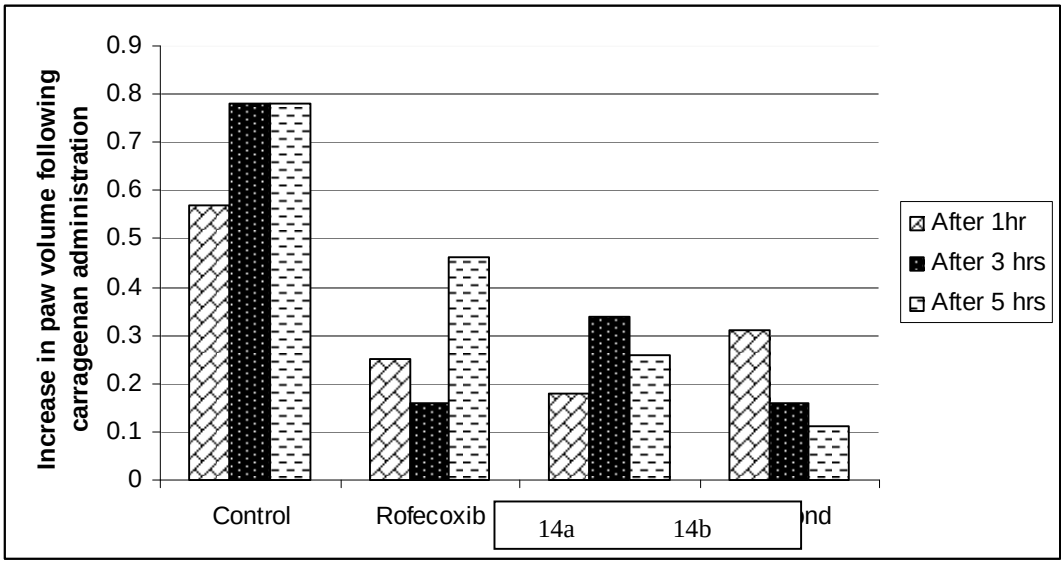


Figure 2

It was found that both tested compounds significantly decreased the effect of carrageenan in comparison with control group at 1, 3 and 5 hours post injection. Moreover, it was observed that the second compound is more potent than the first one at 5 hours post injection.(Table 1)

Treatment	After 1hr	After 3 hrs	After 5 hrs
Control	0.57±4.02 [a]	0.78±2.4 [a]	0.78±1.65 [a]
Rofecoxib	0.25±0.163 [bc]	0.16±0.22 [b]	0.46±2.07 [b]
14a	0.18±1.53 [c]	0.34±3.0 [c]	0.26±2.38 [c]
14b	0.31±0.06 [b]	0.16±3.8 [b]	0.11±4.41 [d]

Means, in the same columns, which are not significantly different, are followed by the same letters

CONCLUSION

Compounds 14a was showed the same activity with Rofecoxib after one hour but less potent after 3 hours . After 5 hours compound 14a showed potent activity than Rofecoxib.
Compound 14b had the same potency of Rofecoxib after 1 or 3hours but showed pronounced activity after 5 hours.

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