Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2016, 8(7):192-199
(http://derpharmachemica.com/archive.html)

Synthesis of 5, 5'-methylenebis (benzofuran-5,2-diyl))bis(phenylmethanone) and its phenylhydrazonoe, benzenesulfonate derivatives and their anti-inflammatory activity

Bhookya Shankar[a], Pochampally Jalapathi*[a], Sunitha Vianala[a] and Karunakar Rao Kudle[b]

[a]*Department of Chemistry, University College of Science, Osmania University, Saifabad, Hyderabad-500004, Telangana State, India*
[b]*Department of Bio Chemistry, University College of Science, Osmania University, Hyderabad-500 007, Telangana State, India*

ABSTRACT

Some novel anti-inflammatory entities derived from 5, 5'-methylenebis (benzofuran-5,2-diyl))bis(phenylmethanone, the structures of these compounds were elucidated by FTIR, ^{1}H-NMR, ^{13}C-NMR and Mass spectral analysis. Furthermore, all the compounds were evaluated for their activity using the carrageenan-induced rat paw edema method. Among the synthesized compounds, 4b, 4d, 4f, 6a and 6c showed significant ($p < 0.01$) reduction of rat paw edema volume, 4b & 6c showed the maximum anti-inflammatory activity after 24 h from the admin of the carrageenan compared to the standard drug, Ibuprofen.

Keywords: Phenylhydrazonoe, *bis*-Benzenesulfonate, Benzofuran, $NaBH_4$, Anti-inflammatory activity.

INTRODUCTION

Due to the increase of population and changes in climatic situation several new diseases are probable which have an effect on the human beings. So, there is a nonstop require for the synthesis of new biologically active organic compounds by using a fast and efficient approach. Inflammation is also one of the major burning problems which effect on human beings. It is multifaceted biological response of vascular tissues to damaging stimuli like pathogens cells and irritants [1]. The therapeutic anti-inflammatory effect of non-steroidal anti-inflammatory drugs (NSAID) occurs during inhibition of prostaglandin biosynthesis and the choosy inhibition of cyclooxygenase (COX). The NSAIDs are able to overcome side effects of steroid therapy through this mechanism [2]. Further, NSAIDs have several drawbacks such as gastrointestinal toxicity [3], gastric ulcer [4], kidney damage [5] and some of the NSAIDs also cause hepatotoxicity [6]. Even with selective celecoxib that inhibit only COX-2 unexpected cardiovascular undesirable effects were observed [7]. Hence there remains a convincing require for successful NSAIDs with a better safety profile. Therefore there is an urgent need for new targets that are required for the development of novel anti-inflammatory agents as an alternative to NSAIDs. In view of this, new generations of phenylhydrazonoe analogous bearing *bis*-benzofuran moiety as therapeutic agents which nullify these drawbacks are developed.

Hydrazone derivatives represent an important class of compounds in medicinal chemistry. Literature survey reviled that these compounds exhibit attractive biological activities [8] such as anti-inflammatory [10], analgesic [11] and antipyretic [12] as well as chelating properties towards various metal ions [9]. Savini et al. evaluated heterocyclic

hydrazones designed for anticancer, anti-HIV and antimicrobial activity [13]. Hydrazones also acting as anti-malarial drugs [14] and as inhibitors of macrophage migration inhibitory factor tautomerase activity [15]. Therefore, phenyl hydrazones may represent a good scaffold in the finding and evaluated *in vitro* nematicidal activity and a metabolomics approach perhaps helpful in understanding their mechanisms of toxicity and mode of action [16]. Moreover, diflunisal hydrazones were also reported as possible dual acting antimicrobial and ant tuberculosis agents with anti-inflammatory activities [17]. A large number of biologically important hydrazone derivatives with a number of functional groups have been reported from aliphatic and aromatic compounds [18]. In an attempt to achieve new compounds with promising anti-inflammatory activity, it is emerged to synthesize some new phenylhydrazonoe and *bis*-benzenesulfonate derivatives from 5,5'-methylenebis (benzofuran-5,2-diyl))bis (phenylmethanone).

MATERIALS AND METHODS

Melting points are uncorrected and were found out in open capillary tubes in sulfuric acid bath. Thin Layer Chromatography (TLC) was carried out on E.Merk AL Silica gel plates and spotting was done by using the UV light. IR spectra were recorded by using Perkin-Elmer 1000 instrument in KBr phase. ^{1}H-NMR spectra were recorded on variant as 400 MHz instrument in $CDCl_3$ and calibrated using solvent signals [7.25(CDC_{l3})]. All chemical shifts recorded in δ (ppm) using TMS as an internal standard and coupling constants (*J*) are expressed in Hertz (Hz). ^{13}C NMR spectra were recorded with a Bruker Avance 400 (100 MHz) spectrometer. Mass spectra on Agilent LC- MS instrument is being given only the values of (M^++H) and spectrometer at energy of ionizing electron equal to 70ev. The majority of the reagents were purchased from Aldrich chemical company, Fluka and Merck Company. Other reagents were all analytically or chemically pure compounds get from the market and not further processed.

Experimental animals

Male Swiss albino rats (180-200 g) were used for anti-inflammatory activity. All of the animals were left for 2 days in the laboratory used for acclimatization before the day of experiment. A minimum of 6 animals were used in each group. All pharmacological activities were approved out as per CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals) norms (Registered No:1757/PO/RcBiBt/S/14 CPCSEA), after obtaining the approval from the Animal Ethics Committee from Jeeva life science, Uppal Industrial are, Hyderabad, Telangana state, India.

Preparation of (5, 5'-methylenebis (benzofuran-5,2-diyl))bis(phenylmethanone) (3):

A mixture of methalene bis salicylaldehyde (**3**) (1.2mol), phenacylebromide (1.0 mol) and K_2CO_3 (1.0 mol) was stirred in acetone (15 ml) at room temperature for 12 h. After completion of the reaction as indicated by TLC, the reaction mixture was filtered and washed with acetone (3-15 ml). Then organic layer was washed with water, brine and dried over Na_2SO_4. The filtrate was concentrated, and the residue was chromatographer on silica gel (petroleum ether: ethyl acetate 10:1) to afford the compounds (**3**). The desired compound **(3)** was obtained as light white colored solid.

Yield = 85 %; m.p.: 130-132 ^{o}C; IR (KBr, cm^{-1}): 2900 (C-H, aromatic), 1650 (C=C, aromatic), 1690 (C=O); ^{1}H NMR 400 MHz ($CDCl_3$): 8.03 (d, *J* = 7.83 Hz, 2H, Ar-H), 7.78-7.51 (m, 10H, Ar-H), 7.23 (s, 2H, Ar-H), 6.89 (d, *J* = 8.3 Hz, 2H, Ar-H), 4.02 (s, 2H, -CH_2-); ^{13}C NMR- 500 MHz (DMSO-d_6): δ 183.3 (2C), 154.0 (2C), 151.0 (2C), 137.3 (2C), 136.6 (2C), 132.9 (2C), 129.7 (2C), 129.0 (4C), 128.6 (4C), 126.9 (2C), 123.0 (2C), 116.9 (2C), 112.1 (2C), 40.2 (-CH_2-); ESI-MS, m/z 457.06 (M^++H).

General Procedure for Synthesis of phenylhydrazonoe derivatives (4a-h):

Different substituted phenylhydrazines (1.5 mmol.) were added to compound **3** (1.0 mmol.) it was dissolved in dry ethanol/acetic acid (5:1 mL) under nitrogen atmosphere and the reaction mixtures was stirred at refluxed temperature 90 ^{o}C in sealed tube for 8 hrs. The completion of the reaction was monitored by TLC. The reaction mass was diluted with water and extracted with DCM. Washed the organic layer with water, brine, dried over Na_2SO_4, filtered and concentrated to yield crude residue, it was purified by column chromatography eluting with 20% ethyl acetate in hexane. The Phenylhydrazine derivatives 4**a-h** was obtained as yellow solids. Yields: 67-82%.

(Z)-phenyl(5-((2-(phenyl(2-phenylhydrazono)methyl)benzofuran-5-yl)methyl)benzofuran-2-yl)methanone (4a)

Yield = 68 %; m.p.: 120-125 ^{o}C; IR (KBr, cm^{-1}): 3339 (N-H), 1687 (C=O), 1685 (C=N), 1656 (C=C); ^{1}H NMR 400 MHz ($CDCl_3$): δ 8.03 (d, 2H, *J* = 7.5 Hz, Ar-H), 7.74 (d, 2H, *J* = 8.5 Hz, 2H, Ar-H), 7.65-7.50 (m, 10H, Ar-H),

7.48-7.41 (m, 4H, Ar-H), 7.40-7.32 (m, 3H, Ar-H), 7.12 (m, 2H, NH, Ar-H), 6.87 (t, 1H, *J* = 7.5 Hz, Ar-H), 4.08 (s, 2H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 184.3, 158.5, 154.8, 154.7, 152.5, 152.4, 144.3, 143.7, 137.5, 137.1, 132.9, 132.8, 130.8, 130.7, 129.8, 129.7, 129.6, 129.5, 129.3, 129.2, 129.1, 128.4, 128.3, 128.2, 128.0, 122.9, 122.8 (3C), 120.6 (2C), 116.5, 116.3, 113.2, 113.1, 112.5, 112.3, 106.4, 41.4; ESI-MS, m/z 547.18 (M^++H).

(Z)-(5-((2-((2-(4-fluorophenyl)hydrazono)(phenyl)methyl)benzofuran-5-yl)methyl)benzofuran-2-yl)(phenyl) methanone (4b)

Yield = 72 %; m.p.: 225-227 ^{o}C; IR (KBr, cm^{-1}): 3345 (N-H), 1690 (C=O), 1674 (C=N), 1646 (C=C), ^{1}H NMR 400 MHz ($CDCl_3$): δ 8.05 (d, 2H, *J* = 7.8 Hz, Ar-H), 7.70 (d, 2H, *J* = 8.5 Hz, 2H, Ar-H), 7.62-7.35 (m, 10H, Ar-H), 7.19-7.12 (m, 3H, Ar-H), 7.10-7.03 (m, 4H, NH, Ar-H), 7.0-6.95 (m, 2H, Ar-H), 4.16 (s, 2H, CH_2); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 184.4, 160.1, 15.9, 154.9, 152.6, 137.1, 137.0, 132.9, 132.8, 132.9, 132.8, 131.3(2C), 130.1, 129.8, 129.7, 129.2, 128.5, 128.4, 128.1, 128.0, 127.3, 122.9, 120.6, 116.6, 116.4, 116.0, 114.7, 114.4, 112.6, 106.3, 41.4; ESI-MS, m/z 565.19 (M^++H).

(Z)-(5-((2-((2-(4-chlorophenyl)hydrazono)(phenyl)methyl)benzofuran-5-l)methyl)benzofuran-2-yl)(phenyl) methanone (4c)

Yield = 78 %; m.p.: 234-236 ^{o}C; IR (KBr, cm^{-1}): 3425 (N-H), 1680 (C=O), 1675 (C=N), 1656 (C=C); ^{1}H NMR 400 MHz ($CDCl_3$): δ 8.08-7.90 (m, 4H,Ar-H), 7.85-7.42 (m, 12H, Ar-H), 7.15-7.02 (m, 3H, Ar-H), 7.10-6.95 (m, 4H, NH, Ar-H), 4.08 (s, 2H, CH_2), 3.83 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 184.2, 158.6, 157.4, 154.3, 152.2, 143.0, 142.4, 137.5, 136.3, 132.8, 130.6, 130.0, 129.7, 129.4, 129.1, 128.5, 128.2, 128.1, 126.2, 125.2, 125.1, 121.5, 120.7, 114.4, 114.3, 112.4, 111.4, 111.2, 107.0, 106.9, 41.5; ESI-MS, m/z 581.06 (M^++H).

(Z)-(5-((2-((2-(4-bromophenyl)hydrazono)(phenyl)methyl)benzofuran-5-l)methyl)benzofuran-2-yl)(phenyl) methanone (4d)

Yield = 82 %; m.p.: 120-125 ^{o}C; IR (KBr, cm^{-1}): 3325 (N-H), 1690 (C=O), 1671 (C=N), 1645 (C=C); ^{1}H NMR 400 MHz ($CDCl_3$): δ 8.02-7.86(m, 4H, Ar-H), 7.78-7.58 (m, 10H, Ar-H), 7.40-7.28 (m, 4H, Ar-H), 7.15 (s, 1H, Ar-H), 7.02-6.98 (d, 2H, J = 7.85 Hz, NH, Ar-H), 6.68-6.63 (d, 2H, *J* = 8.0 Hz, Ar-H), 4.02 (s, 3H, CH_2); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 184.2, 158.6, 157.4, 154.3, 152.2, 143.0, 142.4, 137.5, 136.3, 132.8, 130.6, 130.0, 129.7, 129.4, 129.1, 128.5, 128.2, 128.1, 126.2, 125.2, 125.1, 121.5, 120.7, 114.4, 114.3, 112.4, 111.4, 111.2, 107.0, 106.9, 41.5; ESI-MS, m/z 625.15 (M^++H).

(Z)-(5-((2-((2-(4-methoxyphenyl)hydrazono)(phenyl)methyl)benzofuran-5-yl)methyl)benzofuran-2-yl)(phenyl) methanone (4e)

Yield = 69 %; m.p.: 120-125 ^{o}C; IR (KBr, cm^{-1}): 3384 (N-H), 1684 (C=O), 1654 (C=N), 1636 (C=C); ^{1}H NMR 400 MHz ($CDCl_3$): δ 8.06-7.99 (m, 4H, Ar-H), 7.60-7.44 (m, 12H, Ar-H), 7.40-7.34 (d, 2H, *J* = 7.68 Hz, Ar-H), 7.06 (s, 1H), 6.91-6.85 (m, 4H, NH, Ar-H), 4.18 (s, 2H, CH_2), 3.81 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 184.3, 154.8, 154.1, 153.9, 152.5, 152.4, 138.3, 137.1(2C), 136.9, 135.3, 132.9, 132.8, 131.1 (2C), 129.7, 129.4, 129.2 (3C), 128.5 (3C), 127.2, 124.2 (2C), 122.9 (2C), 120.6, 116.4, 116.0, 114.7 (2C), 114.4, 112.5 (2C), 105.9, 55.6, 41.3; ESI-MS, m/z 577.08 (M^++H).

(Z)-phenyl(5-((2-(phenyl(2-(p-tolyl)hydrazono)methyl)benzofuran-5-yl)methyl)benzofuran-2-yl)methanone (4f)

Yield = 67 %; m.p.: 215-217 ^{o}C; IR (KBr, cm^{-1}): 3325 (N-H), 1670 (C=O), 1684 (C=N), 1626 (C=C); ^{1}H NMR 400 MHz ($CDCl_3$): δ 8.05-7.82(m, 4H, Ar-H), 7.72-7.68 (m, 10H, Ar-H), 7.40-7.28 (m, 2H, Ar-H), 7.15 (s, 1H, Ar-H), 7.02-6.98 (d, 4H, *J* = 7.85 Hz, NH, Ar-H), 6.65-6.62 (d, 2H, *J* = 7.89 Hz, Ar-H), 4.03 (s, 3H, CH_2), 2.50 (s, 3H, Ar-H); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 184.5, 158.5, 155.8 (2C), 152.8, 145.0, 138.6, 137.6, 137.2, 134.5, 132.9, 132.8, 131.2, 130.8 (2C), 129.8 (2C), 129.5 (2C), 129.2 (3C), 128.7 (4C), 124.9, 119.9 (2C), 116.6 (3C), 112.3 (2C), 102.4, 42.5, 25.5; ESI-MS, m/z 561.51 (M^++H).

(E)-(5-((2-((2-(2,4-dinitrophenyl)hydrazono)(phenyl)methyl)benzofuran-5-yl)methyl)benzofuran-2-yl)(phenyl) methanone(4g)

Yield = 80 %; m.p.: 250-252 ^{o}C; IR (KBr, cm^{-1}): 3347 (N-H), 1690 (C=O), 1654 (C=N), 1626 (C=C); ^{1}H NMR 400 MHz ($CDCl_3$): δ 8.65 (s, 1H, Ar-H), 8.42 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.90-7.52 (m, 14H, Ar-H), 7.30-7.29 (s, 2H, Ar-H), 7.15 (s, 1H, Ar-H), 7.00-6.98 (m, 2H, Ar-H), 4.06 (s, 2H, CH_2); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 184.1, 158.9, 155.6 (2C), 153.0, 146.0, 138.3, 137.6 (2C), 134.8, 132.6, 132.6, 131.9, 130.8 (2C), 129.9 (2C), 129.2 (3C), 129.0, 128.7 (4C), 124.5, 123.4, 119.8 (2C), 116.6 (2C), 112.4 (2C), 103.4, 42.8; ESI-MS, m/z 636.27(M^++H).

(Z)-(5-((2-((2-(2,4-dimethylphenyl)hydrazono)(phenyl)methyl)benzofuran-5-yl)methyl)benzofuran-2-yl)(phenyl) methanone (4h)

Yield = 75 %; m.p.: 234-236 ^{o}C; IR (KBr, cm^{-1}): 3337 (N-H), 1680 (C=O), 1644 (C=N), 1646 (C=C); ^{1}H NMR 400 MHz ($CDCl_3$): δ 8.42-7.89 (m, 4H, Ar-H), 7.80-7.54 (m, 10H, Ar-H), 7.30 (s, 2H, Ar-H), 7.18 (s, 1H, Ar-H), 7.07-6.99 (m, 2H, NH, Ar-H), 6.85- 6.82 (m, 3H, Ar-H), 4.08 (s, 2H, CH_2), 3.02 (s, 1H, CH_3), 2.85 (s, 1H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 183.8, 160.5, 158.8 (2C), 154.8, 145.0, 138.6, 137.5, 137.2,137.0, 134.5, 132.8, 132.4, 131.7, 131.2, 131.0, 128.8 (5C), 127.6, 125.7 (2C), 120.4 (2C), 116.6, 116.1, 112.8 (2C), 100.4, 42.8, 30.2, 28.5; ESI-MS, m/z 575.5 (M^++H).

(5, 5'-methylenebis (benzofuran-5, 2-diyl))bis(phenylmethanol) (5):

To a stirred solution of compound 3 (15 mmol) in DCM/MeOH (30 mL, 1:1) at ^{0}C was added $NaBH_4$ (7.5 mmol) in small portions over a period of 20 min, and then at ambient temperature for 2 h. Than reaction progress was monitored by TLC. A small amount of water was added and the mixture was stirred for 15 min before rotary evaporation. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (petroleum ether: ethyl acetate 1:1) to afford the pure products 4 (3.19 g, 92 %) as white colored solid;

Yield = 92 %; m.p.: 120-125 ^{o}C; IR (KBr, cm^{-1}): 2800 (C-H, aromatic), 1650 (C=C, aromatic), 1720 (C=O), 3550 (-OH); ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.47 (d, 4H, J = 8.3 Hz, Ar-H), 7.41-7.28 (m, 12H, Ar-H), 7.08 (d, 2H, Ar-H), 6.44 (s, 2H, 2OH), 5.92 (s, 2H, CH-OH), 4.09 (s, 2H, CH_2); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 158.2 (2C), 156.3 (2C), 142.4 (2C), 138.7 (2C), 130.2 (2C), 128.6 (4C), 127.6 (2C), 128.7 (4C), 125.2 (2C), 120.4 (2C), 112.4 (2C), 102.5 (2C), 72.5 (2C), 42.7 (2C); ESI-MS, m/z 461.2 (M^++H).

General procedure for the preparation of (5, 5'-methylene bis (benzofuran-5, 2-diyl)) bis (phenylmethylene) dibenzene sulfonate derivatives (6a-c):

The compound 6 (a-c) were synthesized by the reaction of the compound 5 (1.1 mmol) and phenyl benzenesulfonate (1.0 mmol) with DCM (5 mL) in round bottom flask (50 mL), at room temperature. The reaction mixture was stirred until the reaction completion and the progress was observed by TLC. Addition of water (20 mL) resulted in the precipitation of crude solid residues. The crude mixtures were chromatographed on silica gel columns to afford compounds 6 (a-c) good yields.

(5,5'-methylenebis(benzofuran-5,2-diyl))bis(phenylmethylene) dibenzenesulfonate (6a)

Yield = 51 %; m.p.: 265-267 ^{o}C; IR (KBr, cm^{-1}): 2895 (C-H, aromatic), 1650 (C=C, aromatic), 1750 (C=O), 975, 769; ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.78-7.14 (m, 22H, Ar-H), 7.13-6.98 (m, 3H, Ar-H), 6.80 (s, 2H, CH-O), 6.45 (m, 2H, Ar-H), 4.08 (s, 2H, CH_2); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 158. 9 (2C), 153.6 (2C), 145.4 (2C), 138.1 (2C), 137.5 (2C), 134.5 (2C), 130.0 (2C), 130.5 (4C), 129.5 (4C), 128.4 (4C), 127.3 (2C), 127.0 (4C), 126.2 (2C), 118.9 (2C), 112.0 (2C), 100.8 (2C), 79.5 (2C), 41.8; ESI-MS, m/z 741.15(M^++H).

(5,5'-methylenebis(benzofuran-5,2-diyl))bis(phenylmethylene)bis(4-methylbenzenesulfonate) ***(6b)***

Yield = 59 %; m.p.: 260-262 ^{o}C; IR (KBr, cm^{-1}): 2950 (C-H, aromatic), 1680 (C=C, aromatic), 1738 (C=O), 979, 697; ^{1}H NMR 400 MHz ($CDCl_3$): δ 7.79 (d, 4H, J = 7.5 Hz, Ar-H), 7.68 (s, 2H, Ar-H), 7.56-7.45 (m, 14H, Ar-H), 7.30-6.99 (m, 4H, Ar-H), 6.58 (s, 2H, 2CH-O), 4.05 (s, 2H, CH_2), 2.89 (s, 6H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 158. 7 (2C), 153.9 (2C), 143.6 (2C), 140.2 (2C), 139.2 (2C), 137.5 (2C), 131.9 (2C), 130.7 (4C), 129.0 (2C), 128.6 (4C), 127.9 (2C), 127.0 (4C), 125.4 (2C), 120.1 (2C), 111.9 (2C), 100.9 (2), 76.8 (2C), 42. 5, 23.8; ESI-MS, m/z 769.51 (M^++H).

(5,5'-methylenebis(benzofuran-5,2-diyl))bis(phenylmethylene) bis(4-nitrobenzenesulfonate) (6c)

Yield = 68 %; m.p.: 270-272 ^{o}C; IR (KBr, cm^{-1}): 2987 (C-H, aromatic), 1690 (C=C, aromatic), 1745 (C=O), 989, 689; ^{1}H NMR 400 MHz ($CDCl_3$): 8.39-8.35 (d, 4H, J = 8.0 Hz, Ar-H), 8.15-8..13 (d, 4H, J = 8.02 Hz, Ar-H), 7.57 (s, 2H, CH), 7.54 (s, 2H, Ar-H), 7.42-7.38 (m, 2H, Ar-H), 7.08-6.98 (m, 4H, Ar-H), 42.02 (s, 2H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz, δ ppm): 157. 9 (2C), 154.7 (4C), 154.1 (2C), 140.8 (2C), 138.9 (2C), 132 (4C), 130.5 (2C), 129.8 (2C), 127.6 (2C), 127.2 (4C), 126.4 (4C), 124.7 (2C), 118.9 (2C), 112.8 (2C), 102.9 (2C), 75.7 (2C), 42.5; ESI-MS, m/z 831.5 (M^++H).

Anti-inflammatory activity

In this paper investigation of *in vivo* anti-inflammatory activity was evaluated for the entire novel synthesized compounds 4(a-h) using the carrageenan-induced rat paws edema protocol. For the determination of anti-

inflammatory effect, the carrageenan-induced paw edema model [22] was employed. Each rat was injected with a freshly prepared 0.1 mL of 1% carrageenan suspension in normal saline (0.9% NaCl) into sub plantar tissue of the right hind paw. The intraperitoneally (i.p) administration of control, test samples (synthesis compounds) and reference drug, for the control, 10 mg/kg saline solution was administered. Paw edema was measured every 60 min for 3hr after induction of inflammation. Results were expressed as the mean ± SE difference between disease control (control) leaven compound and one standard drug treated animals using one way analysis of variance *ANOVA*, followed by Dennett's test for multiple comparisons. The anti-inflammatory activity of the tested compounds and reference drug (Ibuprofen 10mg/kg) were determined as the increase in paw edema volume (control) and the results are summarized in Table 1 and as percentage inhibition summarized in Table 2.

Acute toxicity
All animals used in the inflammatory experiments were observed for 24 hr and mortality of animals recorded where present for each group at the end of observation period.

$$\text{Percentage of Inhibition} = \frac{\text{Mean paw inflammation of control} - \text{Mean paw inflammation of test}}{\text{Mean paw inflammation of control}} \text{ x } 100$$

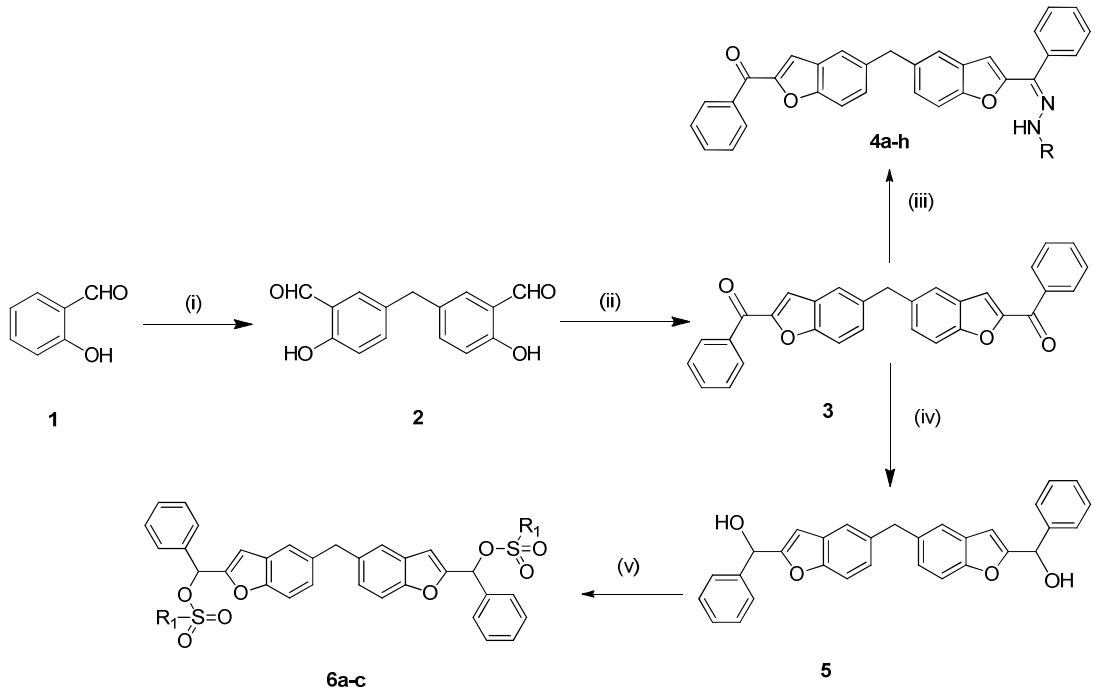
Statistical analysis: The anti-inflammatory activity was determined as increase in the paw edema volume percentage in the treated animals (Tables 1). Results were expressed as the mean ±SE, and different groups were compared using one way analysis of variance (*ANOVA*) followed by Dennett's test for multiple comparisons, test where $p < 0.01$ was accepted to be a significant difference.

Preparation of test samples for bioassay
All test samples (50 mg/kg) were suspended in a mixture of 0.5% carboxyl methylcellulose (CMC) and distilled water were given intraperitoneally (i.p.) to the experiment animals. The animals of the control group received the same experimental handling except that the test drug treatment was replaced with appropriate volumes of the vehicle. Ibroprofen (10 mg/kg) for anti-inflammatory was used as standard drugs.

RESULTS AND DISCUSSION

All the described reactions proceeded expeditiously and delivered good yields, the friendly isolation procedure simply involved the filtration of the precipitated hydrazones. The key intermediate, **4** required for the synthesis of title compounds was prepared according to the procedure outlined in the Scheme 1. The condensation of salicylaldehyde **1** with trioxane in the presence of a mixture of conc. H_2SO_4 and AcOH obtained methylene-bis-salicylaldehyde **2** in good yield [19]. Thus, the key step in the formation of the phenylbenzofuran backbone was readily achieved by reacting methylene-bis-salicylaldehyde **2** with phenacyl bromide to produce (5, 5'-methylenebis (benzofuran-5, 2-diyl)) bis (phenylmethanone) (**3**, 92% yield) in base-mediated reaction for 12 h [20]. Then the compound **3** was reduced with $NaBH_4$ to obtained corresponding (5, 5'-methylenebis (benzofuran-5, 2-diyl))bis(phenylmethanol) (**5,** 95% yields). Furtherly the compound **5** was allowed to react with substituted benzenesulfonyl chloride individually in the presence of base to offered the corresponding desired molecules (5, 5'-methylene bis (benzofuran-5, 2-diyl)) bis (phenyl methylene)dibenzenesulfonate **(6a-c)**[20]. And the (Z)-phenyl (5-((2-(phenyl (2-phenylhydrazono) methyl) benzofuran-5-yl) methyl) benzofuran-2-yl) methanones **(4a-h)** were also derived from compound **3** with different phenyl hydrazines in the presence of mixture of EtOH and glacial AcOH at reflux temperature [21]. The structures of all the synthesized compounds were confirmed by their IR, ^{1}H-NMR, ^{13}C-NMR, and Mass spectral data.

Scheme 1



Reagents and condition: *(i) trioxane, H_2SO_4/AcOH, reflux, 81%; (ii) phenacyl bromide, K_2CO_3/Acetone, rt, 92%; (iii) Phenyle hydrazine, AcOH/EtOH, reflux, 24hrs; (iv) $NaBH_4$, MeOH/DCM, 0 ^oC; (v) benzenesulfonyl chloride, DCM/Et_3N, rt, 12 hrs.*

Table -1: The compounds (4a-h) and 6a-c) along their yields

Entry	Products	R	R_1	Time (h)	M.pt	Yield (%)
1	4a	C_6H_5	-	8	210-212	68
2	4b	4F-C_6H_4	-	8	225-227	72
3	4c	4Cl-C_6H_4	-	8	221-223	78
4	4d	4Br-C_6H_4	-	8	234-236	82
5	4e	4OMe-C_6H_4	-	8	228-230	69
6	4f	4CH_3-C_6H_4	-	8	215-217	67
7	4g	2,4 Di NO_2-C_6H_3	-	8	250-252	80
8	4h	2,4 Di Me-C_6H_3	-	8	234-236	75
9	6a	-	C_6H_5	12	265-267	51
10	6b	-	4CH_3-C_6H_5	12	260-262	59
11	6c	-	4NO_2-C_6H_5	12	270-272	68

BIOLOGICAL SCREENING

In the current investigation the *in vivo* anti-inflammatory activity was evaluated for all the novel synthesized compounds 4(a-h) & 6(a-c) using the carrageenan-induced rat paw edema protocol. The anti-inflammatory activity of title compounds were evaluated on male swiss albino rats at (10 mg/kg) by carrageenan-induced paw edema model [19] and data is given in the Table 2. All the exhibited derivatives of anti-inflammatory activities that listed for every three hours with potency that increased with time. The results were expressed as the increase in paw volume at various intervals of time in comparison to the initial values Table 2. The increase of volumes in percentage was calculated by subtracting the initial paw volumes from the paw volumes obtained after the carrageenan agent was injected. The paw edema volume was screened 3, 6, 9, 12 and 24hr after the induction of inflammation. The anti-inflammatory activity of the tested compounds and reference drug (Ibuprofen) were determined as the increase in paw edema volume and the results are summarized in Table 2 and as percentage inhibition (% inhibition) and summarized in Table 3. Results were expressed as the mean ± SE difference between control and treated animals using one way analysis of variance (ANOVA), followed by followed by Dennett's test for multiple comparisons.

Table 2: The anti-inflammatory activity of the tested compounds and reference drug (Ibuprofen) in carrageenan-induced rat paw edema assay, values are expressed as mean ± SEM

Compound code	Increase in Paw Volume (Edema Volume) (mL)					
	Zero hr	3hr	6h	9hr	12hr	24hr
4a	0.464±0.08	0.356±0.03	0.352±0.04	0.352±0.06	0.313±0.09	0.251±0.05
4b	0.456±0.01	0.359±0.01	0.345±0.07	0.345±0.07	0.304±0.06	0.245±0.08
4c	0.456±0.01	0.449±0.07	0.406±0.05	0.406±0.04	0.308±0.03	0.253±0.07
4d	0.453±0.04	0.433±0.05	0.355±0.10	0.355±0.06	0.251±0.07	0.247±0.08
4e	0.459±0.07	0.433±0.06	0.425±0.07	0.125±0.08	0.321±0.08	0.254±0.06
4f	0.454±0.01	0.403±0.08	0.427±0.06	0.427±0.03	0.251±0.06	0.247±0.10
4g	0.454±0.03	0.428±0.01	0.413±0.08	0.413±0.07	0.248±0.03	0.255±0.07
4h	0.460±0.04	0.411±0.06	0.412±0.09	0.412±0.05	0.314±0.02	0.258±0.04
6a	0.467±0.07	0.423±0.09	0.358±0.02	0.358±0.04	0.254±0.06	0.252±0.09
6b	0.457±0.10	0.346±0.17	0.322±0.09	0.322±0.03	0.321±0.03	0.266±0.03
6c	0.455±0.06	0.364±0.05	0.344±0.01	0.344±0.06	0.309±0.09	0.249±0.02
Ibuprofen	0.456±0.09	0.435±0.07	0.310±0.02	0.310±0.07	0.253±0.02	0.250±0.07
Pawof Mice	0.252±0.03	0.251±0.06	0.256±0.02	0.252±0.04	0.254±0.06	0.249±0.06
Control(carrageenan)	0.455±0.09	0.458±0.02	0.465±0.08	0.469±0.04	0.472±0.05	0.470±0.05

Values are expressed as mean ±SEM; n=6 in each group

Table 3: Percentage of inhibition of inflammation (carrageenan-induced paw edema) of tested compounds

Sl.No	Compounds code	3h	6h	9h	12h	24h
1	4a	22.27	24.3	24.94	33.68	46.59
2	4b	21.61	25.8	26.43	35.59	47.87**
3	4c	1.96	12.68	13.43	34.74	46.17
4	4d	5.45	23.65	24.3	35.59	47.44**
5	4e	5.45	8.602	13.64	31.99	46.8
6	4f	12.0	14.62	18.97	46.82	47.44**
7	4g	6.55	11.18	11.94	47.45	45.74
8	4h	10.26	11.39	10.44	33.47	45.1
9	6a	7.64	23.01	23.66	45.89	46.38**
10	6b	24.45	30.75	31.34	31.99	43.4
11	6c	20.52	26.02	26.65	34.53	47.02**
12	Ibuprofen (10mg/kg)	5.02	33.33	33.9	46.39	46.8

*** The mean difference is significant at the P < 0.01 level.*
Data was analyses by one way ANOVA followed by Duneet's test.

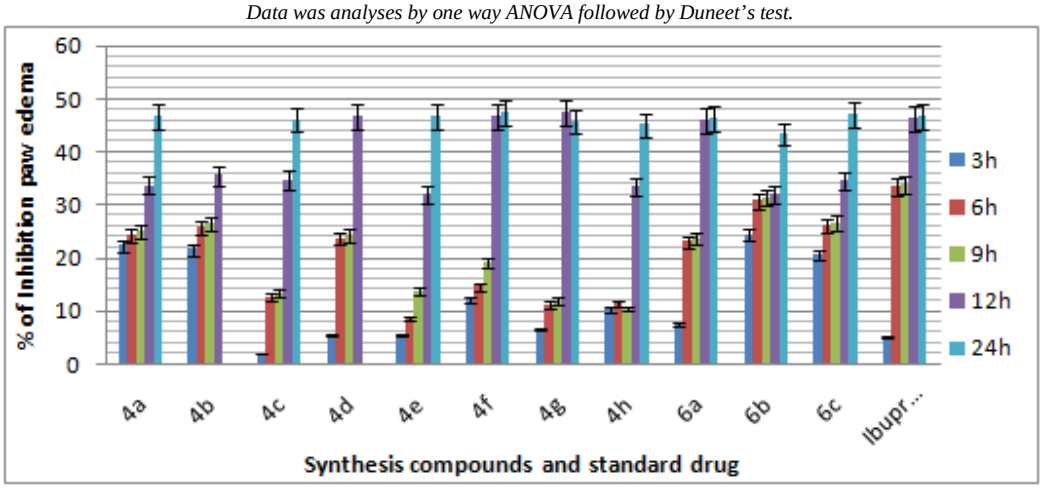


Figure 1: Percentage of Inhibition of acute inflammation (carrageenan-induced paw edema)

In general, the data listed in Table 2 indicate that all of the novel synthesized compounds significantly ($P < 0.01$) reduce the rat paw edema volume 3 h after administration of the carrageenan. The compounds 4d, 4f, 4g and 4g showed a remarkable reduction of rat paw edema volume 12 h. All the tested compounds except 4b, 4d and 6c showed significant ($p < 0.01$) reduction of rat paw edema volume 24 h. In Table 3 compounds 4b, 4d and 6c revealed higher anti-inflammatory activity that exceed the activity of Ibuprofen itself with 35.59 % , 35.59 % and 34.53 % inhibition, respectively, at 12 h and 47.87 %, 47.44 % and 47.02 % inhibition, respectively, at 24h showed

a time-dependent increase in the inhibition of inflammation. In addition, compounds 4c, 4e and 6a exhibited similar anti-inflammatory activity to Ibuprofen at 24 h with 46.17 %, 46.8 % and 46.38 % inhibition, respectively. On the other hand, compounds 4g, 4h, and 6b showed a moderate to good anti-inflammatory activity than Ibuprofen at 24h with 45.74%, 45.1 % and 43.4 % inhibition, respectively. Moreover, the lowest activities were measured for compounds 4e, 6b and 4h at 12h with 31.99%, 31.99% and 33.47%, inhibition respectively (Figure 1).

CONCLUSION

Synthesis of some novel phenylhydrazonoe 4a-c and *bis*-benzenesulfonate 6a-c analogous is reported. All the synthesized compounds were characterized by IR, ^{1}H-NMR, 13C-NMR and *Mass* spectral properties. The anti-inflammatory activity revealed almost all title compounds exhibited moderate to good anti-inflammatory activity. Compounds 4b and 6c showed much more anti-inflammatory activity compared to the standard Ibuprofen and thus qualifying for further clinical evaluation so that, they can be used as effective anti-inflammatory agents.

Acknowledgements
Bhookya Shankar thanks to UGC- BSR (RFSMS), NEW Delhi, India for financial support in the form of senior research fellowship (SRF) and we thank CFRD, Osmania University, Hyderabad for providing the facilities of spectral analysis. We also thank to Jeeva life science, IDA Uppal, Hyderabad, telangana, india for providing facilities for biological activity studies.

REFERENCES

[1] L. Ferrero-Miliani, O.H. Nielsen, P.S. Andersen, S.E. Girardin, *Clin. Exp. Immunol*., **2007**, 147, 227–235.
[2] G. Kant, A. Parate, S.C. Chaturvedi, *Indian J. Pharm. Sci*., **2005**, 67, 116–119.
[3] L. Savini, P. Massarelli, V. Travagli, C. Pellerano, E. Novellino, S. Cosentino, M. B. Pisano, *Eur. J. Med. Chem.*, **2004,** 39, 113.
[4] I.A. Alsarra, M.O. Ahmed, F.K. Alanazi, K.E.H. ElTahir, M.A. Alsheikh, H.S. Neau, *Int. J. Med. Sci*. **2010**, 7, 232-239.
[5] J.G. Ruiz, D.T. Lowenthal, *Geriatr. Nephrol. Urol.*, **1997**, 7, 51-57.
[6] H.H. Tan, W.M.C. Ong, S.H. Lai, W.C. Chow, *Singapore Med. J.*, **2007**, 48, 582-585.
[7] J.A. Mitchell, T.D. Warner, *Nat. Rev. Drug Discov.*, **2006**, 5, 75-85.
[8] L. Savini, P. Massarelli, L. Chiasserini, A. Sega, C. Pellerano, A. Barzi, G. Nocentini, *Eur. J. Med. Chem.*, **1995**, 30, 547.
[9] M.R. Maurya, S. Agarwal, M. Abid, A. Azam, C. Bader, M. Ebel, D. Rehder, *Dalton Trans.*, **2006**, 937.
[10] S.M. Sondhi, M. Dinodia, A. Kumar, *Bioorg. Med. Chem.*, **2006**, 14, 4657.
[11] A.C. Cunha, J.L.M. Tributino, A.L.P. Miranda, C.A.M. Fraga, E.J. Barreiro, *Farmaco*, **2002**, 57, 999.
[12] S.K. Sridhar, A. Ramesh, *Biol. Pharm. Bull.*, **2001**, 24, 1149.
[13] N. Terzioglu, A. Gursoy, *Eur. J. Med. Chem.*, **2003**, 38, 781-786
[14] P. Melnyk, V. Leroux, C. Sergheraert, P. Grellier, *Bioorg. Med. Chem. Lett.*, **2006**, 16, 31.
[15] D.R. Dabideen, K.F. Cheng, B. Aljabari, E.J. Miller, V.A. Pavlov, Y. Al-Abed, *J. Med. Chem.*, **2007**, 50, 1993.
[16] K. Eloh, M. Demurtas, A. Deplano, A.N. Mfopa, A. Murgia, A. Maxia, V. Onnis, P. Caboni, *J. Agric. Food Chem.*, **2015**, 63, 9970−9976.
[18] S. Rollas, S.G. Kucukguzel, *Molecule*, **2007**, 12, 1910-1939.
[19] C.S. Marvel, N. Tarkoy, *J. Am. Chem. Soc.*, **1957**, 79 , 6000.
[20] W. Xue-Quan, L. Lan-Xiang, Y. Li, C.J. Sun, W. Chen, L. Li, Z. Hong-Bin, Y. Xiao-Dong, *European Journal of Medicinal Chemistry*, **2013**, 62, 111.
[21] T. Govindasami1, P. Anjana, P. Nithya, P. Ashutosh, *International Journal of Organic Chemistry*, **2011**, 1, 71-77
[22] C.A. Winter, E.A. Risley, G.W. Nuss, *Expe. Bio. Mad.*, **1962**, 111, 544-7.