WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 11, 982-993. Research Article ISSN 2277– 7105

SYNTHESIS, CHARACTERIZATION AND ANTI-INFLAMMATORY ACTIVITY OF HYDRAZONES BEARING 5-NITRO-FURAN MOIETY AND 5-IODO-VANILLIN HYBRID

A. L. V. Kumar Reddy*[1] and Niren E. Kathale[2]

[1]Research Scholar, Department of Chemistry, Gondwana University, Gadchiroli-442 605, Maharashtra, India.

[2]Assistant Professor, Department of Chemistry, Sardar Patel Mahavidyalaya, Chandrapur, Maharashtra, India.

Article Received on
02 August 2017,

Revised on 23 August 2017,
Accepted on 13 Sept. 2017

DOI: 10.20959/wjpr201711-9635

***Corresponding Author**
A. L. V. Kumar Reddy
Research Scholar,
Department of Chemistry,
Gondwana University,
Gadchiroli-442 605,
Maharashtra, India.

ABSTRACT

The present paper describes the synthesis and anti-inflammatory activity of some new hydrazide-hydrazone derivatives (4a-n) from commercially available vanillin as starting material in three synthetic steps. Step 1 involves the iodination of vanillin in presence of benzyltrimethylammonium dichloroiodate as iodinating reagent; Step 2 involves the coupling of 2-(bromomethyl)-5-nitrofuran with 5-iodovanillin in presence of room temperature ionic liquid such as [bmim] [PF_6]; Step 3 involves condensation of 4-((5-nitrofuran-2-yl) methoxy)-3-iodo-5-methoxybenzaldehyde with various benzohydrazides under solvent free conditions resulting in the formation of final compounds, hydrazide-hydrazone derivatives. The structures of these derivatives were determined by ^{1}H NMR, IR, mass spectroscopic techniques and evaluated for anti-inflammatory activity (carrageenan induced inflammatory rat model). Compounds with substitution R = 4-F, 4-OH, 4-SO_2Me, 2,4-difluoro and R = 3,4,5-trimethoxy in the main scaffold displayed significant anti-inflammatory activity.

KEYWORDS: Anti-inflammatory Activity, Vanillin, Synthesis, Hydrazone, Furan.

INTRODUCTION

Furan ring is a very important structural unit in various biologically active and natural products.[1,2] Furan derivatives exhibits wide range of insecticidal and phytocidal activities.[3,4] Furthermore, they were found to show interesting pharmacological properties

viz., anti-depressant, anti-anxiolytic, anti-inflammatory, anti-hypertensive, anti-glaucoma, anti-arrhythmatic, anti-ulcer, anti-diuretic, anti-neoplastic, anti-ageing, anti-parkinsonism, anti-histaminic.[5,6]

Hydrazide–hydrazones represent a class of organic compounds embedded with azomethine group (–NH–N=CH–) linked with carbonyl group that have occupied a prominent place in the branch of medicinal chemistry and exhibits various pharmaceutical applications[7] Some of the examples of chemotherapeutic agents that are known to contain hydrazide-hydrazone moiety are nitrofurazone,[8] furazolidone[9,10] and nitrofurantoin.[11,12] In addition to the above example, a lot of biologically important hydrazide–hydrazone derivatives were found to possess antiprotozoal,[13] anticonvulsant,[14] anticancer,[15-18] antiviral[19] and anti-inflammatory[20] activities.

Combination of different pharmacophores in the same molecule would probably lead for the development of new compounds in the drug development program in order to reach a better biological activity. Therefore the combination of furan, 5-iodo-Vanilin and hydrazone type compounds might offer new effective chemotherapeutic agents candidate against anti-inflammatory activity. Encouraged by the various biological activities associated with furan derivatives and in continuation to our research on hydrazide-hydrazone derivatives [21], the present paper describes the synthesis of some new hydrazide-hydrazone derivatives (4a-n) from commercially available vanillin in three synthetic steps. The newly synthesized hydrazide-hydrazone derivatives 4a-n was characterized by[1] H NMR, mass and IR spectral data and was further evaluated for anti-inflammatory activity.

MATERIALS AND METHODS

Chemical and solvents used were purchased either from Fluka or Merck. All the reagents were of analytical grade. Thin-layer chromatography (TLC) was performed on E. Merck AL silica gel 60 F254 plates and visualized under UV light. IR spectra were recorded as KBr pellet with a PerkinElmer spectrum gx-FTIR instrument and only diagnostic and/or intense peaks are reported. 1H NMR spectra were recorded in DMSO- d_6 with a Varian Mercury plus 400 MHz instrument. 13C NMR spectra were recorded in DMSO- d_6 with a Varian Gemini 100 MHz instrument. All the chemical shifts were reported in δ (ppm) using TMS as an internal standard. The 1H NMR chemical shifts and coupling constants were determined assuming first-order behavior. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad); the list of coupling

constants (*J*) corresponds to the order of multiplicity assignment. Mass spectra were recorded with a PE Sciex model API 3000 instrument.

Experimental Section

Chemistry

Preparation of 4-hydroxy-3-iodo-5-methoxybenzaldehyde(2)

A mixture of Vanillin (10 g, 65.80 mmol), benzyltrimethylammonium dichloroiodate (CAS No: 114971-52-7, 27.5 g, 79.02 mm0l) in methanol: dichloromethane (1:1, 60 mL: 60 ml) was stirred at room temperature for 24 h. The reaction mixture was evaporated under reduced pressure and the residue was extracted with isopropylacetate (150 mL) and washed with 5% hypo solution followed by water and brine solution. The organic was separated, dried over anhydrous Na_2SO_4, filtered and evaporated under vacuum to obtain 5-iodovanillin. Yellow solid; Yield; 17 g, 88%; M.p 183-184^oC; IR (KBr): υ_{max} 3006, 2971, 1740, 1663, 1572, 1490, 1458, 1415, 1354, 1294, 1231, 1216, 1143, 1038, 968, 853, 783 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40 (s, 1H), 7.90 (s, 1H), 9.75 (s, 1H), 10.70 (br. s, 1H); ESI-MS: m/z, 278.2 (M+1).

Preparation of 4-((5-nitrofuran-2-yl)methoxy)-3-iodo-5-methoxybenzaldehyde(3)

NaOH (21.60 mmol) in water (20.0 mL) was added to a vigorously stirred solution of 2-(bromomethyl)-5-nitro-furan (1.2 eq.) and 5-iodovanillin (2 g, 7.2 mmol) in [bmim] [PF_6] (4.15 mL) at room temperature for 24 h in sealed tube. The course of the reaction was followed by TLC (eluent: n-hexane/ethyl acetate, 80:20). The reaction mixture was extracted with isopropyl acetate (10 x 3 mL) and the combined organic phases were dried over $MgSO_4$, filtered and evaporated in *vacuo* and the residue was passed through a small flash chromatography. After partial evaporation of the solvent, the compound **3** precipitated from the isopropylacetate solution. Yield: 82%. Yellow solid; Yield:90%; M. p 113-114^oC; ^1H NMR (DMSO-d_6,400 MHz): δ 3.90 (s, 3H), 5.18 (s, 2H), 6.68 (d, *J* = 2.8 Hz, 1H), 7.18 (s, 1H), 7.54 (s, 1H), 7.92 (s, 1H), 9.86 (s, 1H); ESI-MS: m/z, 426.1 (M+1).

Preparation of (5-nitrofuran-2-yl) methanol (IV)

To a stirred solution of 5-Nitrofurfural III (5g, 35.44 mmol) in methanol (100 mL), cooled to 0°C, was added sodium borohydride (1.47g, 38.98 mmol) portion-wise and continued to stir for additional 30 min. After completion of the reaction, checked by T.L.C, the solvent was concentrated under reduced pressure and the residue was quenched with water (2 mL) and extracted with cyclopentyl methylether (4 × 25 mL). The organic layer was washed with

water (2 X 30 mL), dried over Na_2SO_4 and evaporated to obtain (5-nitrofuran-2-yl) methanol IV. Pale yellow oil; Yield: 2.33g, 46%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (br s, 1H, OH), 4.73 (s, 2H, -CH_2), 6.57 (d, 1H, *J* = 4 Hz, H_3-furan), 7.30 (d, 1H, *J* = 4.0 Hz, H_4-furan).

Preparation of 2-(bromomethyl)-5-nitrofuran (2A)

To a stirred solution of triphenyl phosphine (39.40g, 150. 24 mmol, 4.3 eq) in dichloromethane (200 mL) was added tribromoisocyanuric acid (14.05g, 38.34 mmol, 1.5 eq). After 30 min, the alcohol IV (5g, 34.94 mmol, 1eq) was added and the suspension was stirred at room temperature for 4h. After completion of the reaction, the precipitated cyanuric acid was filtered off and the organic layer was washed with water (4 X 100 mL) followed by brine solution. The organic layer was dried over Na_2SO_4, filtered and evaporated under reduced pressure. The obtained residue was treated with n-Hexane and filtered through a short column packed with silica gel (100-200 mesh). Evaporation of n-Hexane gave the desired 2-(bromomethyl)-5-nitrofuran 2A. Yellow oily liquid; Yield: 6.33g, 84%; IR (KBr): υ_{max} 1526 and 1345 (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.49 (s, 2H), 6.64 (d, *J* = 4.0 Hz, 1H, H_3-furan), 7.28 (d, *J* = 4.0 Hz, 1H, H_4-furan).

General procedure for the preparation of Hydrazone derivatives (4a-n)

A mixture of compound 3 (100 mg, 0.34 mmol) and corresponding benzohydrazides (0.34 mmol) was grounded by pestle and mortar at room temperature for 15 min. The reaction mixture was diluted with cold ethanol and filtered, washed with pet-ether, to obtain the pure compounds 4a-n. Yields of the products varied between 90-96%.

(*E*)-N'-(4-((5-nitrofuran-2-yl)methoxy)-3-iodo-5-methoxybenzylidene)benzohydrazide

(4a) White solid; Yield:94%; M.p 86-87^{o}C; ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.89 (s, 3H), 5.10 (s, 2H), 6.67 (s, 1H), 7.18 (s, 1H), 7.41 (s, 1H), 7.60-7.51 (m, 5H), 7.68 (s, 1H), 7.90 (d, *J* = 5.2 Hz, 2H), 8.35 (s, 1H), 11.92 (s, 1H); ESI-MS: m/z, 521.2 (M+1).

(*E*)-N'-(4-((5-nitrofuran-2-yl)methoxy)-3-iodo-5-methoxybenzylidene)-4-bromobenzohydrazide (4b)

Off white solid; Yield:95%; M.p 113-114^{o}C; ^{1}H NMR (DMSO-d_6,400 MHz): δ 3.89 (s, 3H), 5.10 (s, 2H), 6.68 (s, 1H), 7.18 (s, 1H), 7.58 (s, 1H), 7.87-7.58 (m, 6H), 8.34 (s, 1H), 11.99 (s, 1H); ESI-MS: m/z, 600.1 (M+1).

(*E*)-N'-(4-((5-nitrofuran-2-yl)methoxy)-3-iodo-5-methoxybenzylidene)-4-chlorobenzohydrazide (4c)

White solid; Yield:94%; M.p 95-96^{o}C; ^{1}H NMR (DMSO-d_6,400 MHz): δ 3.89 (s, 3H), 5.10 (s, 2H), 6.68 (s, 1H), 7.18 (s, 1H), 7.41 (s, 1H), 7.60 (d, *J* = 6.0 Hz, 2H), 7.68 (s, 1H), 7.92 (d, *J* = 6.0 Hz, 2H), 8.34 (s, 1H), 11.99 (s, 1H); ESI-MS: m/z, 555.3 (M+1).

(*E*)-N'-(4-((5-nitrofuran-2-yl)methoxy)-3-iodo-5-methoxybenzylidene)-4-fluorobenzohydrazide (4d)

White solid; Yield: 90%; M.p 107-108^{o}C; ^{1}H NMR (DMSO-d_6,400 MHz): δ 3.89 (s, 3H), 5.10 (s, 2H), 6.67 (s, 1H), 7.18 (s, 1H), 7.41-7.35 (m, 3H), 7.68 (s, 1H), 7.98 (s, 2H), 8.35 (s, 1H), 11.94 (s, 1H); ESI-MS: m/z, 539.2 (M+1).

(*E*)-N'-(4-((5-nitrofuran-2-yl)methoxy)-3-iodo-5-methoxybenzylidene)-4-hydroxybenzohydrazide (4e)

Light brown solid; Yield:92%; M. p 121-122^{o}C; ^{1}H NMR (DMSO-d_6,400 MHz): δ 3.88 (s, 3H), 5.09 (s, 2H), 6.68 (s, 1H), 6.85 (d, *J* = 7.2 Hz, 2H), 7.18 (s, 1H), 7.38 (s, 1H), 7.65 (s, 1H), 7.88 (d, *J* = 7.2 Hz, 2H), 8.31 (s, 1H), 10.11 (s, 1H), 11.70 (s, 1H); ESI-MS: m/z, 537.3 (M+1).

(*E*)-N'-(4-((5-nitrofuran-2-yl)methoxy)-3-iodo-5-methoxybenzylidene)-4-methoxybenzohydrazide (4f)

Brown solid; Yield: 96%; M.p 126-127^{o}C; ^{1}H NMR (DMSO-d_6,400 MHz): δ 3.84 (s, 3H), 3.88 (s, 3H), 5.09 (s, 2H), 6.68 (s, 1H), 7.05 (d, *J* = 6.8 Hz, 2H), 7.18 (s, 1H), 7.40 (s, 1H), 7.66 (s, 1H), 7.90 (d, *J* = 6.8 Hz, 2H), 8.34 (s, 1H), 11.80 (s, 1H); ESI-MS: m/z, 551.3 (M+1).

(*E*)-N'-(4-((5-nitrofuran-2-yl)methoxy)-3-iodo-5-methoxybenzylidene)-4-(methylsulfonyl)benzohydrazide (4g)

Off white solid; Yield; 90%; M.p 105-106 ^{o}C; ^{1}H NMR (DMSO-d_6,400 MHz): δ 3.89 (s, 3H), 5.11 (s, 2H), 6.67 (s, 1H), 7.19 (s, 1H), 7.43 (s, 1H), 7.70 (s, 1H), 8.14-8.10 (m, 4H), 8.35 (s, 1H), 12.14 (s, 1H); ESI-MS: m/z, 599.1 (M+1).

(*E*)-N'-(4-((5-nitrofuran-2-yl)methoxy)–3–iodo–5-methoxybenzylidene)–2,4-dichlorobenzohydrazide (4h)

White solid; Yield: 92%; M.p 100-101^{o}C; ^{1}H NMR (DMSO-d_6,400 MHz): δ 3.88 (* 3.70, s, 3H), 5.10 (* 5.02, s, 2H), 6.67 (* 6.62, s, 1H), 7.74-7.03 (m, 6H), 8.16 (* 7.93, s, 1H), 12.15 (* 12.02, s, 1H); ESI-MS: m/z, 590.6 (M+1).

(*E*)-N'-(4-((5-nitrofuran-2-yl)methoxy)–3–iodo–5-methoxybenzylidene)-3,5-dichlorobenzohydrazide (4i)

Off White solid; Yield: 90%; M.p 118-119^{o}C; ^{1}H NMR (DMSO-d_6,400 MHz): δ 3.89 (s, 3H), 5.10 (s, 2H), 6.68 (s, 1H), 7.20 (s, 1H), 7.42 (s, 1H), 7.69 (s, 1H), 7.92-7.84 (m, 3H), 8.32 (s, 1H), 12.07 (s, 1H); ESI-MS: m/z, 590.1 (M+1).

(*E*)-N'-(4-((5-nitrofuran-2-yl)methoxy)-3-iodo-5-methoxybenzylidene)-2,5-difluorobenzohydrazide (4j)

Pale yellow solid; Yield: 90%; M.p 88-89^{o}C; ^{1}H NMR (DMSO-d_6,400 MHz): δ 3.88 (* 3.71, s, 3H), 5.10 (* 5.03, s, 2H), 6.67 (* 6.62, s, 1H), 7.18 (* 7.10, s, 1H), 7.42-7.38 (m, 4H), 7.69 (* 7.52, s, 1H), 8.21 (* 7.95, s, 1H), 12.16 (* 11.99, s, 1H); ESI-MS: m/z, 557.3 (M+1).

(*E*)-N'-(4-((5-nitrofuran-2-yl)methoxy)-3-iodo-5-methoxybenzylidene)-2-bromobenzohydrazide (4k)

Yellow solid; Yield: 90%; M.p 127-128^{o}C; ^{1}H NMR (DMSO-d_6,400 MHz): δ 3.89 (* 3.68, s, 3H), 5.10 (*5.03, s, 2H), 6.67 (* 6.61, s, 1H), 7.18 (* 7.15, s, 1H), 7.53-7.36 (m, 4H), 8.16 (* 7.93, s, 1H), 12.06 (* 11.98, s, 1H); ESI-MS: m/z, 600.1 (M+1).

(*E*)-N'-(4-((5-nitrofuran-2-yl)methoxy)-3-iodo-5-methoxybenzylidene)-2-iodobenzohydrazide (4l)

Pale yellow solid; Yield: 94%; M.p 130-131^{o}C; ^{1}H NMR (DMSO-d_6,400 MHz): δ 3.89 (* 3.68, s, 3H), 5.10 (* 5.01, s, 2H), 6.67 (* 6.62, s, 1H), 7.50-7.42 (* 7.37-7.06, m, 6H), 7.93 (* 7.89, s, 1H), 8.16 (* 7.67, s, 1H), 12.03 (* 11.92, s, 1H); ESI-MS: m/z, 647.1.6 (M+1).

(*E*)-N'-(4-((5-nitrofuran-2-yl)methoxy)-3-iodo-5-methoxybenzylidene)-3-nitrobenzohydrazide (4m)

Yellow solid; Yield: 90%; M.p 90-91^{o}C; ^{1}H NMR (DMSO-d_6,400 MHz): δ 3.90 (s, 3H), 5.11 (s, 2H), 6.68 (s, 1H), 7.19 (s, 1H), 7.44 (s, 1H), 7.70 (s, 1H), 7.83 (s, 1H), 7.85 (t, *J* = 6.0 Hz, 1H), 8.35 (d, *J* = 8.0 Hz, 2H), 8.46 (d, *J* = 6.4 Hz, 1H), 8.74 (s, 1H), 12.24 (s, 1H); ESI-MS: m/z, 566.2 (M+1).

(*E*)-N'-(4-((5-nitrofuran-2-yl)methoxy)-3-iodo-5-methoxybenzylidene)-3,4,5-trimethoxybenzohydrazide (4n)

Off white solid; Yield: 86%; M.p 121-122 ^{o}C; ^{1}H NMR (DMSO-d_6,400 MHz): δ 3.69 (s, 3H), 3.86 (s, 6H), 3.89 (s, 3H), 5.10 (s, 2H), 6.68 (s, 1H), 7.19-7.16 (m, 3H), 7.41 (s, 1H), 7.68 (s, 1H), 8.36 (s, 1H), 11.78 (s, 1H); ESI-MS: m/z, 611.3 (M+1).

Biology Experimental

Ant-inflammatory activity

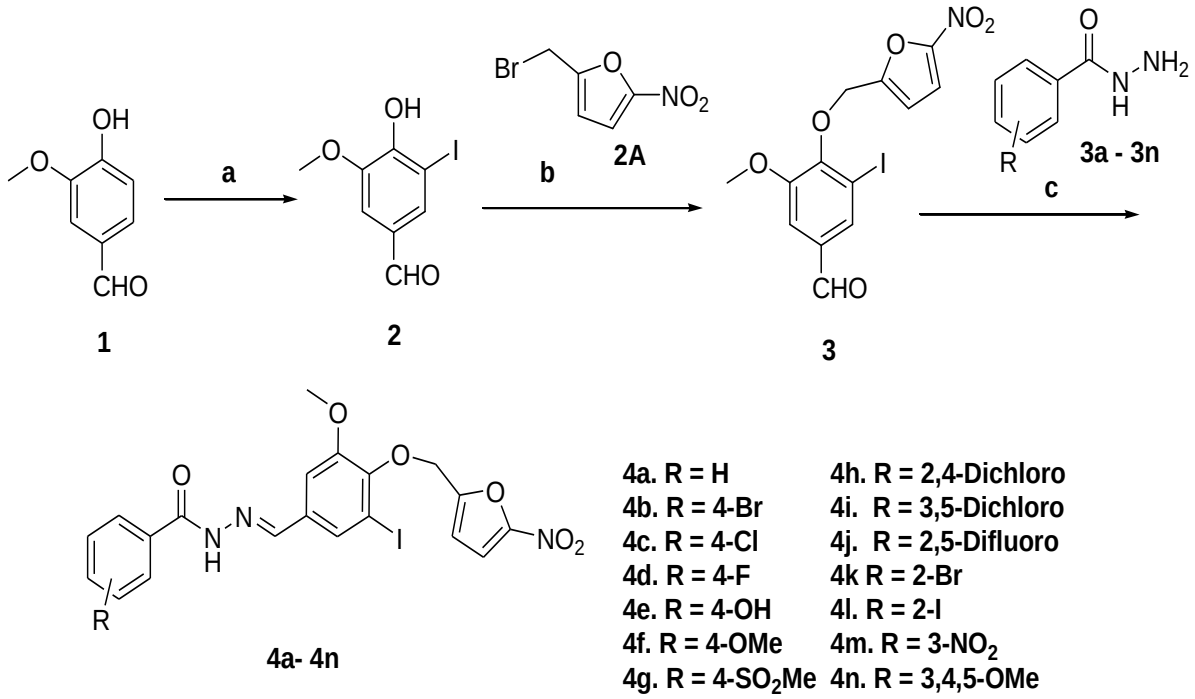
A standard model system, carrageenan induced inflammatory rat model [21] was followed for the experimentation on acute inflammatory conditions. Adult wistar rats weighing between 150-200g were used for the study. Under standard laboratory conditions, rats were maintained (temperature 25 ± 2°C) with normal daily cycle (12/12h). Before the start of experiments, the rats were made to accustom to laboratory condition for 10 days. The study was accordingly permitted by the Institutional Animal Ethical Committee (IAEC) of CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on Animals). The animals were starved overnight. Diclofenac sodium (standard drug) at dose of 10 mg/kg and test compounds (4a-n, 10 mg/kg i.p), were controlled orally using gastric canula, 30 min before the carrageenan injection in sub plantar region of left hind paw. Paw edema was induced by injecting 0.1 ml of 1% w/v carrageenan suspended in 1% CMC into sub-plantar tissues of the left hind paw of each rat. The degree of paw thickness of all the groups was measured (in millimeters) using a vernier caliper after 1h, 2h and 3h of carrageenan injection. *Computational analysis:* The paw thickness was measured in millimeters and presented as mean ± SEM and were determined using analysis of variance and group means were differentiated with Tukey–Kramer Post ANOVA test. The readings were considered when $P < 0.01$.

RESULTS AND DISCUSSION

Chemistry

The synthesis of hydrazide-hydrazone derivatives 4a-n (prepared from commercially available vanillin) is presented in Scheme-1. Ch. Krishna Prasad *et al.*,[22] have reported the synthesis of 5-iodovanillin under thermal conditions utilizing I_2 / $NaHCO_3$ / in aqueous media at reflux for 10 h. In the present case, conversion of vanillin 1 to 5-Iodovanaillin was accomplished at room temperature utilizing benzyltrimethylammonium dichloroiodate (CAS No: 114971-52-7) as iodinating reagent in presence of methanol: dichloromethane. Coupling of 2-(bromomethyl)-5-nitrofuran (Scheme 2) with 5-iodovanillin was carried out in [bmim][PF_6] as RTILs (room temperature ionic liquid) in presence of NaOH and water, the presence of room temperature ionic liquid and water makes the reaction system a greener method.[23-24] Condensation of aldehyde 3 with benzohydrazides 3a-n was carried out under solvent free conditions at room temperature for 15 min to afford hydrazo-hydrazide derivatives 4a-n in 80-95% yield. Furthermore, encouraged by the recent literature

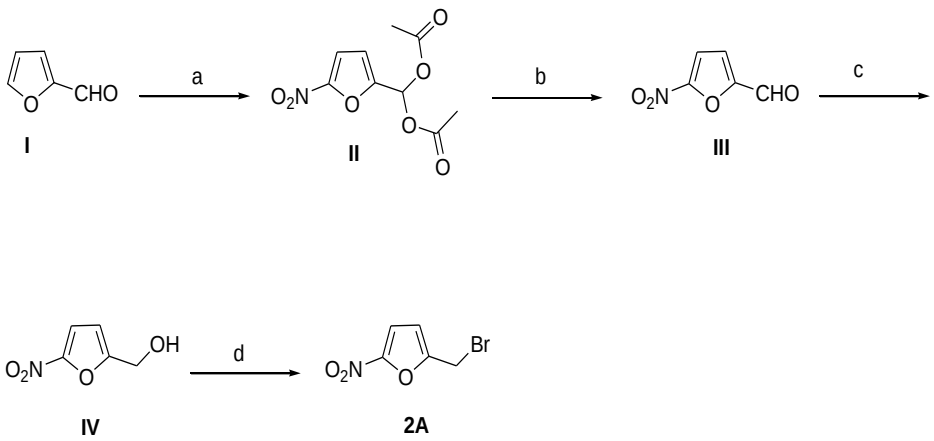
information on the usage of isopropyl acetate, we have also utilized isopropyl acetate as the choice of solvents in our experiments for the isolation of compounds 2 and 3.[24,25] The benzohydrazide derivatives 3a-n was prepared according to the literature procedures.[26,27] The structures of the synthesized hydrazide-hydrazone derivatives 4a-n were in agreement with the 1H NMR and MS spectral data.



Scheme 1: Synthesis of novel hydrazo-hydrazides 4a–4n

Experimental Conditions: a) Benzyltrimethylammonium dichloroiodate, methanol: dichloromethane, r.t., 24 h; b) 2A, NaOH, water, [bmim] [PF_6], sealed tube, r.t, 24 h e) Benzohydrazides 3a-n, grinding, r.t., 15 min.

The synthesis of intermediate coupling partner 2-(bromomethyl)-5-nitrofuran 2A is illustrated in scheme 2. The 5-nitrofurfural diacetate II and 5-nitrofurfural III was prepared according to the reported literature method.[28] Reduction of 5-nitrofurfural III in presence of $NaBH_4$ in methanol at 0^oC for 30 min gave the desired (5-nitrofuran-2-yl)methanol IV. Treatment of alcohol IV with triphenylphosphine and tribromoisocyanuric acid[29] in dichloromethane at room temperature for 4h produced the desired intermediate 2-(bromomethyl)-5-nitrofuran 2A.



Scheme 2: Synthesis of the key intermediate 2-(bromomethyl)-5-nitrofuran 2A.

Reaction conditions: a) conc; HNO_3, cat.conc;H_2SO_4, Ac_2O, O^oC, 1h, 82%; b) 50% Aq; H_2SO_4, 100^oC, 10 min, 88%; c) $NaBH_4$, MeOH, 0^oC, 30 min, 46%; d) Triphenylphosphine, Tribromoisocyanuric acid, room temperature, 4h, 84%;

Anti-inflammatory activity

The results of the anti-inflammatory activity (dosage: 10 mg/Kg po) of the synthesized hydrazide-hydrazone derivatives 4a-n is presented in Table 1. Compounds 4a (R = H), 4f (R = 4-OMe) and 4m (R = 3-NO_2) showed moderate anti-inflammatory activity while the compounds 4d (R = 4-F), 4e (R = 4-OH), 4g (R = 4-SO_2Me), 4j (R = 2,4-difluoro) and 4n (R = 3,4,5-trimethox) exhibited good anti-inflammatory activity. The remaining compounds in the series *viz.*, compounds 4b (R = 4-Br), 4c (R = 4-Cl), 4h (R = 2,4-dichloro), 4i (R = 3,5-dichloro), 4k (R = 2-Br) and 4l (R = 2-I) were found to be inactive towards anti-inflammatory activity.

Table 1: Results of Anti-inflammatory activity of hydrazide-hydrazone derivatives 4a-n.

Treatments	1 hr	2 hr	3 hr
Carrageenan Control	0.98 ± 0.09	1.25 ± 0.12	2.55 ± 0.12
4a	0.42 ± 0.55	0.58 ± 1.15	0.60 ± 0.40
4b	---	---	---
4c	---	---	---
4d	0.62 ± 0.18	0.76 ± 0.60	0.84 ± 0.45
4e	0.68 ± 0.42	0.86 ± 0.38	1.08 ± 0.22
4f	0.34 ± 0.80	0.52 ± 0.68	0.66 ± 0.24
4g	0.60 ± 0.40	0.78 ± 0.24	0.82 ± 0.25
4h	---	---	---
4i	---	---	---
4j	0.60 ± 0.64	0.82 ± 0.33	0.96 ± 0.22
4k	---	---	---

4l	---	---	---
4m	0.38 ± 0.78	0.48 ± 0.64	0.60 ± 0.38
4n	0.64 ± 0.75	0.72 ± 0.98	0.88 ± 062
Diclofenac sodium(10mg/kg)	0.75 ± 0.12	0.95 ± 0.12	1.16 ± 0.11

CONCLUSION

In summary, the present paper describes the synthesis and characterization of new hydrazide-hydrazone derivative 4a-n, linking furan moiety and 5-iodo-vanillin. These compounds were evaluated for anti-inflammatory activity and the results revealed that, compounds 4a (R = H), 4f (R = 4-OMe) and 4m (R = 3-NO_2) showed moderate anti-inflammatory activity while the compounds 4d (R = 4-F), 4e (R = 4-OH), 4g (R = 4-SO_2Me), 4j (R = 2,4-difluoro) and 4n (R = 3,4,5-trimethox) exhibited good anti-inflammatory activity.

ACKNOWLEDGEMENT

One of the authors (A.L.V) thanks Dr.B.Vasudha, Department of Pharmacy, Lalitha College of Pharmacy, Ghatkesar, and Hyderabad.

Conflict of Interest

"The author(s) declare(s) that there is no conflict of interest regarding publication of this article".

REFERENCES

1. Joule JA, Mills K. Heterocyclic chemistry. 5th ed. New Jersey: John Wiley and Sons, 2010.
2. Sniady A, Durham A, Morreale MS, Marcinek A, Szafert S, Lis T, Brzezinska KR, Iwasaki T, Ohshima T, Mashima K, Dembinski R. Zinc-catalyzed cycloisomerizations. Synthesis of substituted furans and furopyrimidine nucleosides. J Org Chem, 2008; 73(15): 5881-89.
3. Wakita T, Kinoshita K, Yamada E, Yasui N, Kawahara N, Naoi A, Nakaya M, Ebihara K, Matsuno H, Kodaka K. The discovery of dinotefuran: a novel neonicotinoid. Pest Manag Sci, 2003; 59(9): 1016-22.
4. Shimokawatoko Y, Yamada K. JP Patent, 2006; 131533.
5. Rumpa Benerjee, Kumar HKS, Mirtyunja Benerjee, Medical significance of furan: A Review. International journal of Review in Life Sciences, 2012; 2: 7-16.
6. Sireesha Malladi, Venkata Nadh R, Suresh Babu K, Suri Babu P. Synthesis and antibacterial activity studies of 2, 4- substituted furan derivatives. Beni-Suef University Journal of Basic and Applied Sciences, 2017. doi: http://dx.doi.org/10.1016/j.bjbas.2017.08.001.

7. Rollas S, Küçükgüzel ŞG. Biological activities of hydrazone derivatives. Molecules, 2007; 12: 1910–1939.
8. McCalla DR, Reuvers A, Kaiser C. Mode of action of nitrofurazone. J Bacteriol, 1970; 104: 1126–1134.
9. Chatterjee SN, Ghosh S. Mechanism of action of furazolidone: inter-strand cross-linking in DNA & liquid holding recovery of Vibrio cholerae cells. Indian J Biochem Biophys, 1979; 16(3): 125–130.
10. Ali BH. Some pharmacological and toxicological properties of furazolidone. Vet Res Commun, 1983; 6: 1–11.
11. Mc Osker CC, Fitzpatrick PM. Nitrofurantoin: mechanism of action and implications for resistance development in common uropathogens. J Antimicrob Chemother, 1994; 33: 23–30.
12. Munoz-Davila MJ. Role of old antibiotics in the Era of antibiotic resistance. Highlighted nitrofurantoin for the treatment of lower urinary tract infections. Antibiotics, 2014; 3: 39–48.
13. Siddiqui AISM, Macedo TS, Moreira DRM, Leite ACL, Soares MBP, Azam A. Design, synthesis and biological evaluation of 3-[4-(7-chloro-quinolin-4-yl)-piperazin-1-yl]-propionic acid hydrazones as antiprotozoal agents. Eur J Med Chem, 2014; 75: 67–76.
14. Çakır B, Dağ Ö, Yıldırım E, Erol K, Şahin MF. Synthesis and anticonvulsant activity of some hydrazones of 2-[(3H)-oxobenzoxazolin-3-yl-aceto]hydrazide. J Fac Pharm Gazi, 2001; 18: 99–106.
15. Kumar D, Kumar NM, Ghosh S, Shah K. Novel bis(indolyl) hydrazide–hydrazones as potent cytotoxic agents. Bioorg Med Chem Lett, 2012; 22: 212–215.
16. Yadagiri B, Holagunda UD, Bantu R, Nagarapu L, Guguloth V, Polepally S, Jain N. Rational design, synthesis and antiproliferative evaluation of novel benzosuberone tethered with hydrazide–hydrazones. Bioorg Med Chem Lett, 2014; 24: 5041–5044.
17. Machakanur SS, Patil BR, Badiger DS, Bakale RP, Gudasi KB, Bligh SWA. Synthesis, characterization and anticancer evaluation of novel tri-arm star shaped 1, 3, 5-triazine hydrazones. J Mol Struct, 2012; 1011: 121–127.
18. Nasr T, Bondock S, Youns M. Anticancer activity of new coumarin substituted hydrazide–hydrazone derivatives. Eur J Med Chem, 2014; 76: 539–548.
19. Şenkardes S, Kaushik-Basu N, Durmaz İ, Manvar D, Basu A, Atalay R, Küçükgüzel ŞG. Synthesis of novel diflunisal hydrazide-hydrazones as anti-hepatitis C virus agents and hepatocellular carcinoma inhibitors. Eur J Med Chem, 2016, 10: 301–308.
20. Kumar V, Basavarajaswamy G, Rai MV, Poojary B, Pai VR, Shruthi N, Bhat M. Rapid ‘one-pot’ synthesis of a novel benzimidazole-5-carboxylate and its hydrazone derivatives as

potential anti-inflammatory and antimicrobial agents. Bioorg Med Chem Lett, 2015; 25: 1420–1426.

21. Kumar Reddy ALV, Niren Kathale E. Synthesis and Anti-Inflammatory Activity of Hydrazones Bearing Biphenyl Moiety and Vanillin Based Hybrids. Orient. J. Chem, 2017; 33(2): 971-978.
22. Ch. Krishna Prasad and Machi Raju PVS. Synthesis, Characterization and Antibacterial activity of Novel Benzo [b] furan Carbohydrazide Derivative of Intermediate Egonol. Journal of Applicable Chemistry, 2014; 3: 1460-1467.
23. Nuno Lourenco MT, Carlos A M. Ionic liquid as an efficient promoting medium for two-phase nucleophilic displacement reactions. Tetrahedron, 2003; 59: 789.
24. Subramanyam D, Balram B, Ram B and Taara B. Synthesis and antibacterial Activity of (±)-trans-2-[-methoxy-4-(4- chlorophenylthioethoxy) - 5 - (N-methyl-N-hydroxyureidyl) methylphenyl] -5- (3,4,5-trimethoxyphenyl) tetrahydrofuran and its intermediates. Der Pharma Chemica 2012; 4: 2239-2247.
25. Veerabhadra Swamy P, Bhaskara Venkata Prasad B, Balram B, Ram B and Taara B. Synthesis of 1, 4-Bis-(2, 4-Dimethoxyphenyl)-2, 3-Bis-(4-methoxybenzyl)-Butane-1, 4-Dione. Der Pharma Chemica 2012; 4: 2050-2054.
26. Chawla G, Kaushik D, Saroor A and Suresh K. *N*'-[(5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl) methylene] 2/4-substituted hydrazides: Synthesis and anticonvulsant activity. Eur. J. Med. Chem, 2010; 45: 3943-3949.
27. Jian-Zhong C, Shuang H, Xie X and Fei-Fei Z. Design, synthesis, biological evaluation, and comparative docking study of 1,2,4-triazolones as CB1 receptor selective antagonists. Eur.J. Med. Chem, 2014; 74: 73-84.
28. Hong Jin, Yucong Geng, Zhiyi Yu, Ke Tao and Taiping Hou. Lead optimization and anti-plant pathogenic fungi activities of daphneolone analogues from Stellera chamaejasme L. Pesticide Biochemistry and Physiology, 2009; 93: 133-137.
29. Vitor de Andrade SC, Marcio de Mattos CS. Tribromoisocyanuric cid/Triphenylphosphine: a New System for Conversion of Alcohols into Alkyl Bromides J. Braz. Chem. Soc, 2014; 25: 975.