EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 3
Issue: 9
588-595
Year: 2016

N-(3-(BENZOFURAN-3-YL)-3-OXO-1-PHENYLPROPYL) ACETAMIDE SCAFFOLDS: SYNTHESIS AND MOLECULAR DOCKING STUDIES TOWARDS EXPLORING OF ANTI-INFLAMMATORY ACTIVITY

Javarappa Rangaswamy[1], Honnaiah Vijay Kumar[2] and Nagaraja Naik[*1]

[1]Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore –570006, Karnataka, India.
[2]Department of Chemistry, University of Minnesota, Minneapolis, MN 55455, USA.

Corresponding Author: Dr. Nagaraja Naik
Department of Studies in Chemistry, University of Mysore, Manasagangotri, Mysore –570006, Karnataka, India.

Article Received on 19/07/2016 **Article Revised on 10/08/2016** **Article Accepted on 01/09/2016**

ABSTRACT
In the present study, a series of *N*-(3-(benzofuran-3-yl)-3-oxo-1-phenylpropyl)acetamide scaffolds **(4a-j)** were synthesized by multicomponent one pot reaction. The structures of the synthesized compounds were confirmed by analytical and spectral techniques and further screened for their *in vitro* anti-inflamatory activities. All the synthesized scaffolds in this series showed comparably equal or less activity to the standard. Among them interestingly, compounds **4d** and **4f** exhibited maximum anti-inflamatory effect. Molecular docking interactions of synthesized derivatives against cyclooxygenase-2 enzymes (COX-2) were studied. Resulting in the finding that, these classes of derivatives have displayed the significant anti-inflamatory activity.

KEYWORDS: *N*-(3-(benzofuran-3-yl)-3-oxo-1-phenylpropyl)acetamide scaffolds, substituted benzaldehyde, anti-inflammatory activity.

INTRODUCTION
In multi-cellular organisms, inflammation is a cardinal host defense response to tissue damage, injury, infectious agents or autoimmune responses and is an integral part of the immune response.[1] Symptoms of inflammation include swelling, redness of the area, pain, and sometimes loss of function.[2] Non-steroidal anti-inflammatory drugs (NSAIDs) showed promising effect in the treatment of acute and chronic inflammation,[3] pain,[4] and fever,[5] through inhibition of cyclooxygenase (COX). However, their clinical usage is associated with undesirable and numerous side effects such as nephrotoxicity, gastrointestinal lesions, and bleeding;[6,7] meanwhile, the resistance of body to anti-inflammatory drugs is widespread.[8] Therefore, it is particularly important to find and research new targets of prevention and treatment to inflammation with less adverse effects.

Multi-component reactions (MCRs) have emerged as an efficient and powerful tool in modern synthetic organic chemistry allowing the facile creation of several new bonds in a one-pot reaction.[9] The strategy of MCRs especially for the preparation of heterocyclic compounds is a particularly attractive field in light of the paramount role of these targets in pharmaceutical chemistry.[10]

Heterocyclic synthesis has emerged as powerful technique for generating new molecules useful for drug discovery.[11] Heterocyclic compounds provide scaffolds on which pharmacophores can arrange to yield potent and selective drugs.[12] Benzofurans are highly valuable molecular motifs often found in various natural products. An intense effort has been made directed towards the synthesis of benzofuran derivatives[13] due to their biological activity as potential pharmacological agents[14-16] and to their occurrence in nature. Many compounds that synthesized from 2-acetylbenzofurans have shown antitumor, anti-inflammatory and fungicidal activities.[17-19] Examples include bacterial enzymes involved in the methionine cycle (e.g. methionine aminopeptidase and deformylase), enzymes involved in peptidoglycan synthesis (e.g. UDP-*N*-acetylmuramyl-*L*-alanine ligase) and chorismate synthesis.[20]

Hence, we are interested to build a library of small molecules incorporating the 2-acetyl benzofuran moiety for assessing anti-inflammatory propery by employing *in vitro* method. To the best of our knowledge, there was no report on the synthesis and anti-inflammatory activity of *N*-(3-(benzofuran-3-yl)-3-oxo-1-phenylpropyl)acetamide scaffolds. In continuation of our research work on the synthesis and biological activity of novel classes heterocyclic derivatives[21-24] herein, we wish to synthesis *N*-(3-(benzofuran-3-yl)-3-oxo-1-phenylpropyl)acetamide scaffolds and evaluated their free biological potentials.

MATERIALS AND METHODS

All reagents and solvents were purchased from Merck (Darmstadt, Germany) chemical AR grade and were used as provided. TLC analysis was performed on alumina sheets precoated with silica gel 60F-254 and SiO_2, 200-400 mesh (Merck) was used for column chromatography. ^{1}H NMR (300 MHz) ^{13}C NMR (100 MHz) were obtained AC Bruker spectrometer in the appropriate (DMSO) solvent. Melting points were obtained on a reichert thermopan melting point apparatus, equipped with a microscope and are uncorrected. Mass spectra were obtained on an Electron Impact mass spectrometer at 70 ev ionizing beam and using a direct insertion probe. Micro analytical data were obtained by elemental-Vario EL-III.

General procedure for synthesis of N-(3-(benzofuran-3-yl)-3-oxo-1-phenylpropyl)acetamide scaffolds (4a-j)

A solution of the substituted benzaldehyde **(2a-j)** (2 mmol), 2-acetyl benzofuran **(1)** (2 mmol), acetyl chloride (4 mmol), acetonitrile (4 ml) and Zinc oxide (ZnO) (1 mmol) taken in a 100ml round bottomed flask, the reaction mixture was stirred for 6 hrs at room temperature, the progress of reaction was monitored by TLC. After completion of the reaction, the mixture was poured into 50 ml of ice water. The solid residue was purified by column chromatography n-hexane:ethylacetate (80:20) used as eluent to furnish *N*-(3-(benzofuran-3-yl)-3-oxo-1-phenylpropyl)acetamide scaffolds **(4a-j)**.

N-(3-(benzofuran-3-yl)-3-oxo-1-phenylpropyl)acetamide (4a): Yellow solid; IR (KBr)λmax(cm^{-1}): 2857 (Ar-H), 3240 (NH), 1751 (amide C=O); ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 8.93 (s, 1H, furan CH), 8.05 (d, 1H, NH), 7.27-7.85 (m, 9H, Ar-H), 5.18 (q, 1H, β-acetamide proton), 3.10 (d, 2H, CH_2), 1.83 (s, 3H, CH_3-CO); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 194.3, 170.7, 160.0, 156.3, 143.4, 128.0, 126.8, 125.4, 124.5, 123.0, 120.7, 11.5, 71.6, 51.4, 23.5; Mass (m/z%): M$^+$ 307.12; Anal.calcd. for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56; Found: C, 74.20; H, 5.62; N, 4.50%

N-(3-(benzofuran-3-yl)-3-oxo-1-p-tolylpropyl)acetamide (4b): Off white solid; IR (KBr)λmax(cm^{-1}): 2857 (Ar-H), 3240 (NH), 1751 (amide C=O); ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 8.90 (s, 1H, furan CH), 8.08 (d, 1H, NH), 7.17-7.86 (m, 8H, Ar-H), 5.18 (q, 1H, β-acetamide proton), 3.10 (d, 2H, CH_2), 2.34 (s, 3H, Ar-CH_3), 1.83 (s, 3H, CH_3-CO); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 194.6, 170.7, 160.1, 156.3, 140.4, 136.2, 128.8, 125.8, 125.3, 124.7, 123.2, 120.9, 111.4, 71.7, 51.4, 23.6, 21.3; Mass (m/z%): M$^+$ 321.14; Anal.calcd. for $C_{20}H_{19}NO_3$: C, 74.75; H, 5.96; N, 4.36; Found: C, 74.73; H, 5.89; N, 4.39%

N-(3-(benzofuran-3-yl)-1-(4-methoxyphenyl)-3-oxopropyl)acetamide (4c): Light brown solid; IR (KBr)λmax(cm^{-1}): 2855 (Ar-H), 3243 (NH), 1774 (amide C=O); ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 8.92 (s, 1H, furan CH), 8.03 (d, 1H, NH), 6.94-7.92 (m, 8H, Ar-H), 5.20 (q, 1H, β-acetamide proton), 3.83 (s, 3H, OCH_3), 3.13 (d, 2H, CH_2), 1.84 (s, 3H, CH_3-CO); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 190.0, 170.5, 160.0, 158.6, 156.5, 135.8, 126.6, 125.8, 124.8, 123.3, 120.9, 114.1, 111.4, 71.5, 55.8, 51.5, 23.6; Mass (m/z%): M$^+$ 337.13; Anal.calcd. for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15; Found: C, 71.18; H, 5.35; N, 4.22%

N-(3-(benzofuran-3-yl)-1-(4-nitrophenyl)-3-oxopropyl)acetamide (4d): Blackish red solid; IR (KBr)λmax(cm^{-1}): 2856 (Ar-H), 3238 (NH), 1768 (amide C=O); ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 8.93 (s, 1H, furan CH), 7.32-8.21 (m, 8H, Ar-H), 8.05 (d, 1H, NH), 5.15 (q, 1H, β-acetamide proton), 3.08 (d, 2H, CH_2), 1.85 (s, 3H, CH_3-CO); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 190.5, 170.7, 160.0, 156.3, 149.6, 145.9, 125.8, 124.7, 123.7, 123.4, 123.1, 120.8, 111.2, 71.7, 51.5, 23.5; Mass (m/z%): M$^+$ 352.11; Anal.calcd. for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95; Found: C, 64.79; H, 4.62; N, 8.05%

N-(3-(benzofuran-3-yl)-1-(2-hydroxyphenyl)-3-oxopropyl)acetamide (4e): Yellow solid; IR (KBr)λmax(cm^{-1}): 2862 (Ar-H), 3263 (NH), 1751 (amide C=O); ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 8.95 (s, 1H, furan CH), 8.05 (d, 1H, NH), 6.90-7.85 (m, 8H, Ar-H), 5.33 (s, 1H, OH), 5.15 (q, 1H, β-acetamide proton), 3.10 (d, 2H, CH_2), 1.83 (s, 3H, CH_3-CO); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 194.2, 170.5, 160.1, 156.2, 154.0, 130.9, 128.1, 126.5, 125.8, 124.7, 123.2, 121.1, 120.5, 115.3, 111.4, 72.0, 45.2, 23.3; Mass (m/z%): M$^+$ 323.12; Anal.calcd. for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33; Found: C, 70.58; H, 5.30; N, 4.33%

N-(3-(benzofuran-3-yl)-1-(4-chlorophenyl)-3-oxopropyl)acetamide (4f): Light yellow solid; IR (KBr)λmax(cm^{-1}): 2854(Ar-H), 3235 (NH), 1762 (amide C=O); ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 8.93 (s, 1H, furan CH), 8.10 (d, 1H, NH), 7.44-7.90 (m, 8H, Ar-H), 5.18 (q, 1H, β-acetamide proton), 3.10 (d, 2H, CH_2), 1.84 (s, 3H, CH_3-CO); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 194.4, 170.7, 160.3, 156.2, 141.6, 132.3, 128.6, 127.2, 125.8, 124.7, 123.1, 111.2, 71.5, 51.4, 23.6; Mass (m/z%): M$^+$ 341.08; Anal.calcd. for $C_{19}H_{16}ClNO_3$: C, 66.77; H, 4.72; Cl, 10.37; N, 4.10; Found: C, 66.75; H, 4.81; Cl, 10.32; N, 4.08%

N-(3-(benzofuran-3-yl)-1-(4-hydroxy-3-methoxyphenyl)-3-oxopropyl)acetamide (4g): Dark brown solid; IR (KBr)λmax(cm^{-1}): 2860 (Ar-H), 3248 (NH), 1751 (amide C=O); ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 8.88 (s, 1H, furan CH), 8.05 (d, 1H, NH), 6.68-7.87 (m, 7H, Ar-H), 5.35 (s, 1H, OH), 5.15 (q, 1H, β-acetamide proton), 3.82 (s, 3H, OCH_3), 3.12 (d, 2H, CH_2), 1.85 (s, 3H, CH_3-CO); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 194.5, 170.3, 160.3, 156.3, 147.3, 146.7, 137.1, 125.7, 124.6, 123.3, 123.1, 120.9, 119.3, 115.4, 111.4, 110.2, 71.5, 56.1, 51.5, 23.5; Mass (m/z%): M$^+$

353.13; Anal.calcd. for $C_{20}H_{19}NO_5$: C, 67.98; H, 5.42; N, 3.96; Found: C, 68.01; H, 5.38; N, 4.03%

N-(3-(benzofuran-3-yl)-1-(3,4-dimethoxyphenyl)-3-oxopropyl)acetamide (4h): Light yellow solid; IR (KBr)λmax(cm^{-1}): 2858 (Ar-H), 3252 (NH), 1748 (amide C=O); ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 8.93 (s, 1H, furan CH), 8.03 (d, 1H, NH), 6.74-7.89 (m, 7H, Ar-H), 5.16 (q, 1H, β-acetamide proton), 3.83 (s, 6H, OCH_3), 3.08 (d, 2H, CH_2), 1.84 (s, 3H, CH_3-CO); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 194.3, 170.7, 160.1, 156.0, 149.6, 147.8, 136.8, 125.7, 124.6, 123.2, 121.9, 120.7, 118.9, 111.8, 109.8, 71.3, 56.1, 51.5, 23.2; Mass (m/z%): M^+ 367.14; Anal.calcd. for $C_{21}H_{21}NO_5$: C, 68.65; H, 5.76; N, 3.81; Found: C, 68.65; H, 5.76; N, 3.81%

N-(3-(benzofuran-3-yl)-1-(4-hydroxyphenyl)-3-oxopropyl)acetamide (4i): Yellow solid; IR (KBr)λmax(cm^{-1}): 2853 (Ar-H), 3245 (NH), 1755 (amide C=O); ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 8.93 (s, 1H, furan CH), 8.03 (d, 1H, NH), 6.70-7.92 (m, 8H, Ar-H), 5.35 (s, 1H, OH), 5.15 (q, 1H, β-acetamide proton), 3.07 (d, 2H, CH_2), 1.84 (s, 3H, CH_3-CO); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 194.5, 170.7, 160.1, 156.5, 156.3, 136.1, 127.0, 125.6, 124.5, 123.3, 120.9, 115.5, 111.5, 71.7, 51.4, 23.6; Mass (m/z%): M^+ 323.12; Anal.calcd. for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33; Found: C, 70.61; H, 5.35; N, 4.30%

N-(3-(benzofuran-3-yl)-3-oxo-1-(3,4,5-trimethoxyphenyl)propyl)acetamide (4j): Light yellow solid; IR (KBr)λmax(cm^{-1}): 2855 (Ar-H), 3238 (NH), 1750 (amide C=O); ^{1}H NMR (300 MHz) (DMSO-d_6) δ (ppm): 8.90 (s, 1H, furan CH), 8.07 (d, 1H, NH), 6.52-7.87 (m, 6H, Ar-H), 5.15 (q, 1H, β-acetamide proton), 3.80 (s, 9H, OCH_3), 3.05 (d, 2H, CH_2), 1.88 (s, 3H, CH_3-CO); ^{13}C NMR (DMSO-d_6 100 MHz) δ ppm: 193.8, 170.7, 160.1, 156.3, 152.7, 137.5, 137.0, 125.4, 124.8, 123.2, 120.5, 111.5, 102.0, 70.5, 60.7, 56.0, 51.8, 23.4; Mass (m/z%): M^+ 397.15; Anal.calcd. for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52; Found: C, 66.45; H, 5.79; N, 3.58%

Anti-inflammatory activity

The synthesized compounds were screened for anti-inflammatory activity by using inhibition of albumin denaturation technique with minor modification.[25] The standard drug and synthesized compounds were dissolved in minimum quantity of Dimethyl formamide (DMF) and diluted with phosphate buffer (0.2 M, PH 7.4). Final concentration of DMF in all solution was less than 2.5%. Test Solution (4 mL) containing different concentrations of drug was mixed with 1 mL of 1 mM albumin solution in phosphate buffer and incubated at 37 °C in incubator for 15 min. Denaturation was induced by keeping the reaction mixture at 70°C in water bath for 15 min. After cooling, the turbidity was measured at 660 nm. Percentage of Inhibition of denaturation was calculated from control where no drug was added. The diclofenac sodium was used as standard drug. The percentage inhibition of denaturation was calculated by using following formula.

% of Inhibition = 100 x (At - Ac) / At. At = O.D. of test solution. Ac = O.D. of control.

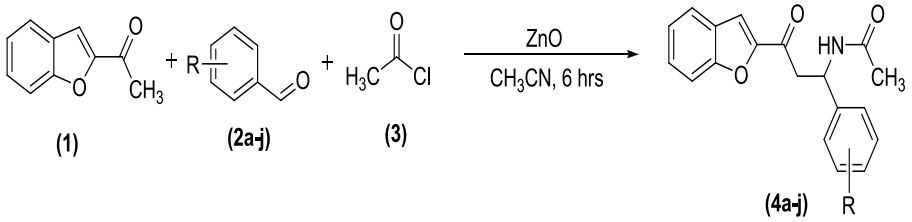
Molecular docking

Molecular docking was performed with the aid of Maestro 9.3.5 version of the Schrodinger software suite, 2011. The 3D crystallographic structure of protein cyclooxygenase-2 (PDB ID: 4COX) was retrieved from Protein Data Bank (www.rcsb.org/pdb). The protein structures were pre-processed and refined by Protein Preparation Wizard. Further, it was minimized by OPLS-2005 (Optimized Potential for Liquid Simulations) forcefield until the root mean square deviation (RMSD) reached the value of 0.3 A. The ligands were optimized by LigPrep program using the OPLS-2005 force field to generate lowest energy state of ligands. The molecular docking studies of the ligand and protein were carried out by GLIDE. The best fit ligands with the target protein were ranked based on docking score.

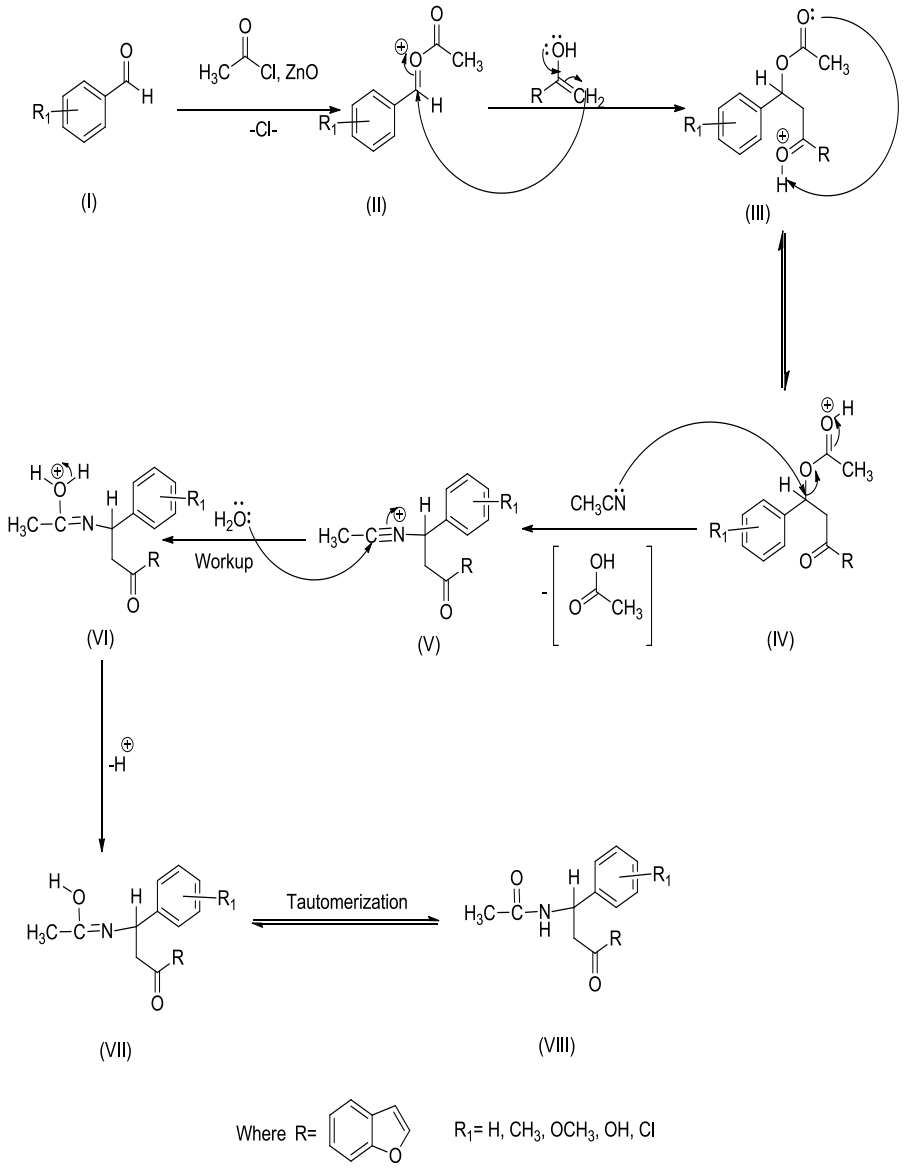
RESULTS AND DISCUSSION

Chemistry

The 2-acetyl benzofuran was synthesized by literature method.[26] An efficient one pot, multicomponent synthesis of *N*-(3-(benzofuran-3-yl)-3-oxo-1-phenylpropyl)acetamide scaffolds **(4a-j)** was done by condensing of 2-acetyl benzofuran **(1)**, substituted benzaldehyde **(2a-j)**, acetyl chloride **(3)** and acetonitrile in the presense of Zinc oxide (ZnO) as catalyst **Scheme 1**. The reaction was carried on the basis of previously reported mechanism,[27] it is suggested that the aldehyde was first acylated to an intermediate **I** which then reacts with the enol form of acetophenone derivative to produce **III** after exchange of H^+ from **II.** Next, acetonitrile attacks **III,** with elimination of acetate to give **IV**. Generated HCl could be trapped by ZnO which is converted to $ZnCl_2$. Hydrolysis of **IV** accompanied by tautomerization gave the desired *N*-(3-(benzofuran-3-yl)-3-oxo-1-phenylpropyl)acetamide scaffolds (**Scheme 2**) in good yields. The synthesized compounds was characterized by various physico-chemical and spectroscopic techniques.

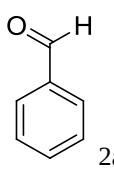
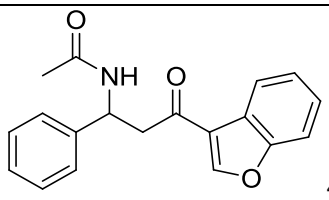


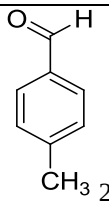
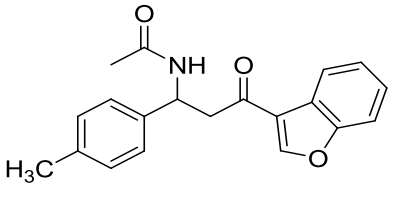
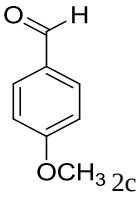
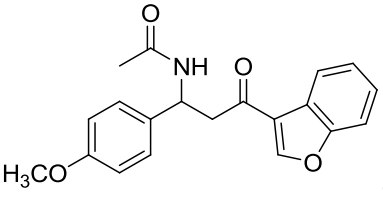
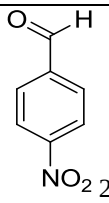
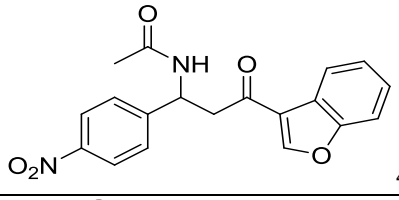
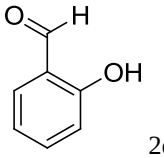
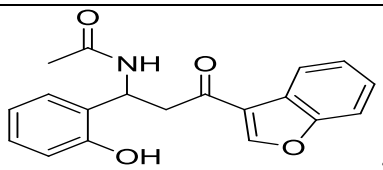
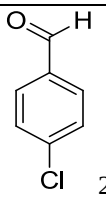
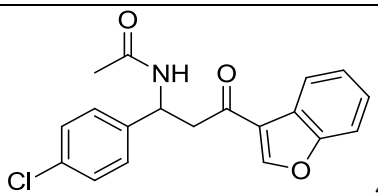
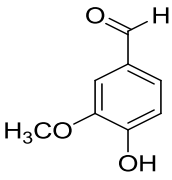
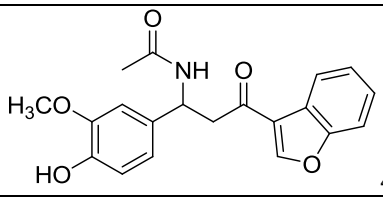
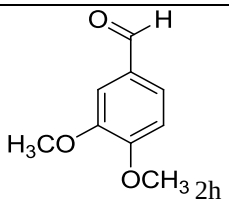
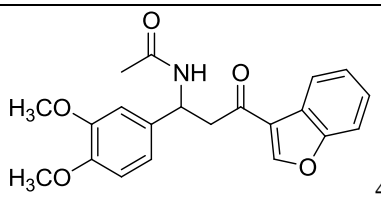
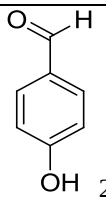
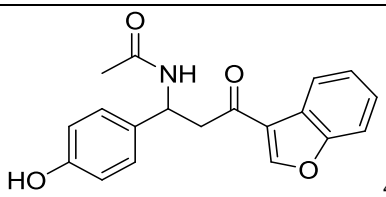
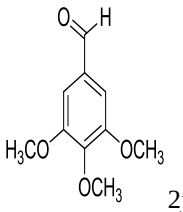
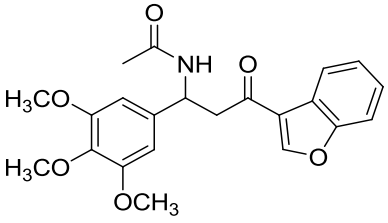
Scheme: 1. Protocol for the synthesis of *N*-(3-(benzofuran-2-yl)-3-oxo-1-phenylpropyl)acetamidescaffolds (4a-j)



Scheme 2. General synthetic mechanism for title compounds

Table: 1 Synthesis of *N*-(3-(benzofuran-3-yl)-3-oxo-1-phenylpropyl)acetamide scaffolds (4a-j)

Entry	Aldehydes	Products	Yield (%)	Melting points (°C)
1	 2a	 4a	78.10	120-123

2	 2b	 4b	66.20	183-186
3	 2c	 4c	58.00	170-173
4	 2d	 4d	88.25	105-108
5	 2e	 4e	69.00	188-191
6	 2f	 4f	78.30	160-163
7	 2g	 4g	77.00	127-130
8	 2h	 4h	89.75	165-168
9	 2i	 4i	87.30	175-178
10	 2j	 4j	85.40	168-171

Anti-inflammatory activity

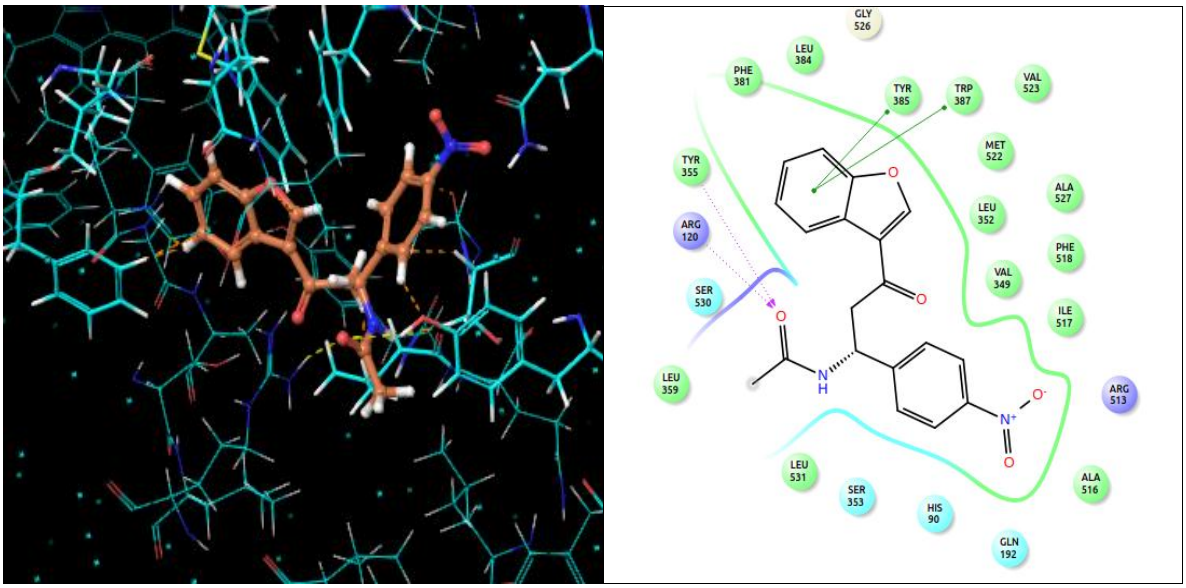
The synthesized compounds were tested for their *in vitro* anti-inflammatory activity by protein denaturation technique using bovine serum albumin assay followed by the literature.[25] The half maximal inhibitory concentration (IC_{50}) values are represented in Table 2 using diclofenac sodium drug to compare these activities. Among *N*-(3-(benzofuran-3-yl)-3-oxo-1-phenylpropyl)acetamide (**4a-j**), the compound **4d** and **4f** with 4-nitro and 4-chloro aldehyde skeleton has shown more anti-inflammatory property. However compounds derivatives **4b** and **4c** have shown good activity may due to presence of methoxy and methyl group. But other compounds **4a**, **4e** and **4g-j** have low potency in this series. Hence, these compounds can further serve as leads for development of more potent anti-inflammatory agents which is currently under investigation.

Table 2. Anti-inflammatory activity of synthesized compounds (4a–j)

Compounds	IC_{50} (µg/ml)
1	983.83
4a	756.96
4b	150.35
4c	180.87
4d	**55.49**
4e	585.13
4f	**69.35**
4g	865.15
4h	623.43
4i	613.51
4j	834.72
Diclofenac sodium	**52.95**

Molecular docking

These series of *N*-(3-(benzofuran-3-yl)-3-oxo-1-phenylpropyl)acetamide scaffolds **(4a-j)** derivatives were evaluated for cyclooxygenase inhibitors studies by using molecular docking method. The active site of 4COX is considered to be constituted of the amino acid residues ARG120, SER530, TYR385 and GLU524 following the reported literature.[28] As shown in Table 3, out of the 10 compounds, in the *N*-(3-(benzofuran-3-yl)-3-oxo-1-phenylpropyl)acetamide scaffolds **(4a-j),** The compound **4d** and **4f** was found to better dock into the active site of COX in least binding energy of -10.881 and -10.903 kcal/mol than other derivatives. The compound **4d** and **4f** formed two hydrogen bond interaction with positive charged residue of ARG120 and hydrophobic residue of TYR355 through the active site of COX and bonding distance between carbonyl group amide and OH of ARG120 and TYR355 was found to be 2.28 and 2.15 Å (C=O…HO) respectively. Compounds **4d** and **4f** also formed π-π stacking with hydrophobic residue of TYR385 and TRP387 (Figure 1). Based on these results, it was concluded that the carbonyl group (CO) amide, were responsible for the interactions with the amino acid residues.



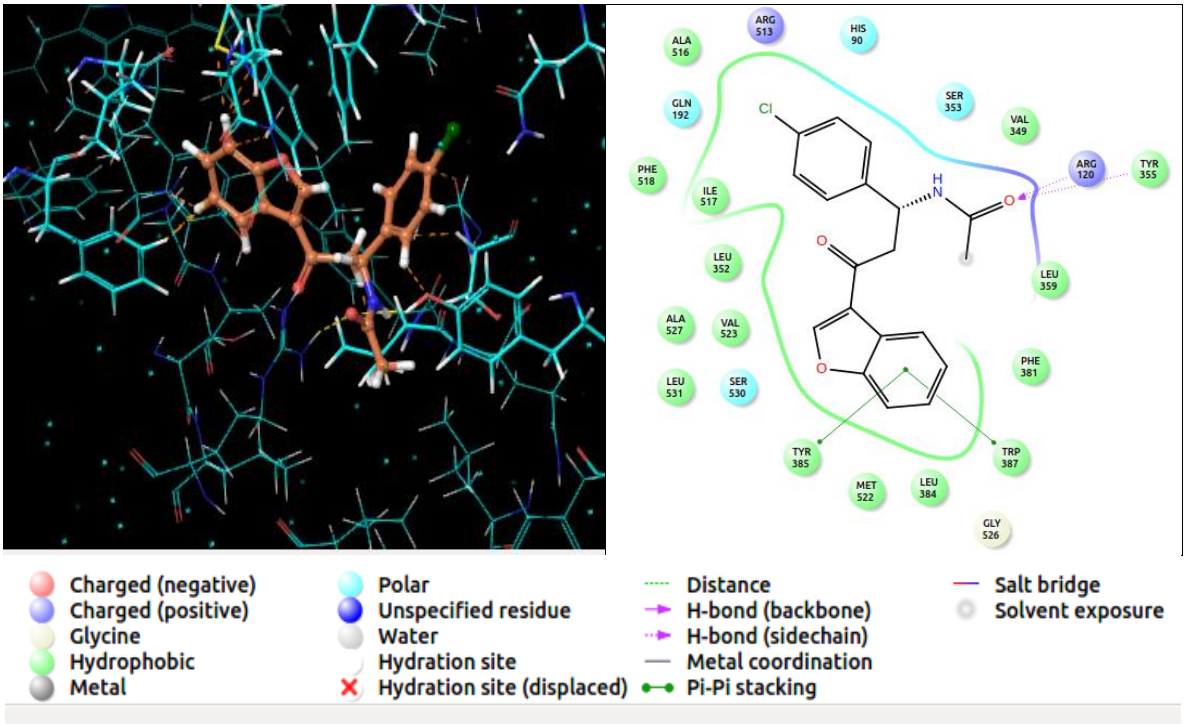


Figure: 1. 3-D and 2-D images of molecular docking studies of compounds 4d and4f with cyclooxygenase.

Table: 3. Molecular docking interaction of *N*-(3-(benzofuran-3-yl)-3-oxo-1- phenylpropyl)acetamide scaffolds (4a–j) against cyclooxygenase inhibitors (COX-2)

Compound	Docking score (kcal/mol)	Number of hydrogen bonds	Interacting residues
4a	-7.891	1	SER530
4b	-9.693	1	ARG120
4c	-9.865	1	SER530
4d	-10.874	2	ARG120, TYR355
4e	-6.670	1	TYR355
4f	-10.903	2	ARG120, TYR355
4g	-6.250	-	-
4h	-6.380	-	-
4i	-7.446	2	ARG120, HIS90
4j	-6.141	-	-

CONCLUSION

We have described a new series of ZnO assisted one pot, multicomponent synthesis of *N*-(3-(benzofuran-3-yl)-3-oxo-1-phenylpropyl)acetamide scaffolds **(4a-j)** in reasonably good yields. The newly synthesized analogues were evaluated for their *in vitro* anti-inflammatory potential. compounds **4d** and **4f** exhibits maximum anti-inflammatory effect. Molecular docking studies also proves the compounds has good cyclooxygenase inhibition. These results constitute a starting point enabling a better understanding of structure-activity relationships of this new series of compounds, and should facilitate future elaboration to more efficient and selective anti-inflammatory drug candidates, which may have applications in affecting the pathogenesis of inflammation disease.

ACKNOWLEDGEMENTS

The authors are grateful to the University Grants Commission, Government of India, for granting UGC-Post Doctoral Fellowship-PDFSS and UGC SAP Phase III.

REFERENCES

1. Quintans J. Immunol. Immunity and inflammation: the cosmic view. Cell Biol., 1994; 72: 262-266.
2. Ruedi, KB, Christina F, Paul N, Michael S, Sterner-Kock A, Kock M, Putney L, Ferrick DA, Hyde DM, Love RB. IL-17 producing gammadelta T cells are required for a controlled inflammatory response after bleomycin-induced lung injury. Inflammation, 2008; 31: 167-179.
3. Sng BL, Schug SA. The role of opioids in managing chronic non-cancer pain. Ann Acad Med Singap, 2009; 38: 960-966.

4. Zahradnik HP, Hanjalic-Beck A, Groth K. Nonsteroidal anti-inflammatory drugs and mhormonal contraceptives for pain relief from dysmenorrhea: a review. Contraception, 2010; 3: 185-196.
5. Eccles, R. Efficacy and safety of over-the-counter analgesics in the treatment of common cold and flu. J Clin Pharm Ther., 2006; 31: 309-319.
6. Rathee P, Chaudhary H, Rathee S, Rathee D, Kumar V, Kohli K. Mechanism of action of flavonoids as anti-inflammatory agents: a review. Inflamm. Allergy Drug Targets, 2009; 3: 229-235.
7. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA, 2001; 286: 954-959.
8. Van JR, Botting RM. New insights into the mode of action of anti-inflammatory drugs. Inflamm Res., 1995; 44: 1-10.
9. Nakamura I, Yamamoto Y. Transition-metal-catalyzed reactions in heterocyclic synthesis. Chem Rev., 2004; 104: 2127–2198.
10. Abbas R, Neda P. Synthesis of various heterocyclic compounds via multi‐component reactions in water J Iran Chem Soc., 2015; 12: 993–1036.
11. Safaei-Ghomi J, Ghasemzadeh MA. An efficient multicomponent synthesis of 14-aryl-14H-dibenzo[a,j]xanthene derivatives by AgI nanoparticles. J Saudi Chem Soc, 2012, http://dx.doi.org/ 10.1016/j.jscs.2012.05.007.
12. Hermakens PH, Ottenheijm HC. Solid-phase organic reactions II: A review of the literature Nov 95–Nov 96. Tetrahedron, 1997; 53: 5643-5678.
13. Gordon E, Barrett RW, Dower WJ, Foder SP. Applications of combinatorialtechnologies to drug discovery.Combinatorial organic synthesis, library screening strategies, and future directions. J Med Chem, 1994; 37:1485.
14. Cagniant P, Cagniant D. Recent Advances in the Chemistry of Benzo[b]furan and Its Derivatives. Part I: Occurrence and Synthesis. Adv Heterocycl Chem, 1975; 18: 337–482.
15. Malamas MS, Sredy J, Moxham C, Katz A, Xu W, McDevitt R, Adebayo FO, Sawicki DR, Seestaller L, Sullivan D, Taylor JR. Novel Benzofuran and Benzothiophene Biphenyls as inhibitors of Protein Tyrosine Phosphatase 1B with Antihyperglycemics properties. J Med Chem, 2000; 43: 1293–1310.
16. Wyatt PG, Allen MJ, Chilcott J, Gardner CJ, Livermore DG, Mordaunt JE, Nerozzi F, Patel M, Perren MJ, Weingarten GG, Shabbir S, Woollard PM, Zhou P. Identification of potent and selective oxytocin antagonists. Part 2: further investigation of benzofuran derivatives. Bioorg Med Chem Lett, 2002; 12: 1405–1411.
17. Fuganti C, Serra S. A new approach to 2-aryl-7-alkoxy-benzofurans: synthesis of ailanthoidol, a natural neolignan. Tetrahedron Lett, 1998; 39: 5609-5610.
18. Basawaraj R, Yadav B, Sangapure SS. Synthesis of some 1*H*-pyrazolines bearing benzofuran as biologically active agents. Ind J Heterocycl Chem, 2001; 11: 31-34.
19. Singh DV, Mishra AR, Mishra RM, Pandey AK, Singh, CR, Dwivedi AK. Synthesis and fungicidal activity of benzofuran incorporated substituted pyrimidines. Ind J Heterocycl Chem, 2005; 14: 319-322.
20. Basavaraja KM, Vaidya VP, Chandrashekhar C. Synthesis of benzofuro[3,2-*e*]-1,4-diazepines of pharmacological interest. E-J Chem, 2008; 5: 567-571.
21. Rangaswamy J, Kumar HV, Harini ST, Naik N. An easy eccess to benzofurans via DBU Induced condensation reaction of active 2-hydroxy acetophenones with phenacyl chlorides: A novel class of antioxidant agents. J Heterocycl Chem, 2015; 52: 938-943.
22. Rangaswamy J, Kumar HV, Harini ST, Naik N. Synthesis of novel benzofuran-gathered C-2,4,6-substituted pyrimidine derivatives conjugated by sulfonyl chlorides: orally bioavailable, selective, effective antioxidants and antimicrobials drug candidates. J Heterocycl Chem, 2015; 52: 1349-1360.
23. Rangaswamy J, Kumar HV, Harini ST, Naik N. Synthesis of benzofuran based 1,3,5-substituted pyrazole derivatives: As a new class of potent antioxidants and antimicrobials-A novel accost to amend biocompatibility. Bioorg Med Chem Lett, 2012; 22: 4773-4777.
24. Ashok B, Kumar Naik KH, Avinash P, Naik N. Efficient synthesis of novel diorganyl selenides via cleavage of Se–Se bond of diselenides by $RuCl_3$/zn and screened for their biological efficacy. World J Pharm Res, 2016, 5, 608-618.
25. Lavanya, A.; Sribalan, R.; Padmini, V. Synthesis and biological evaluation of new benzofuran carboxamide derivatives. J Saudi Chem Soc, doi:10.1016/j.jscs.2015.06.008.
26. Rangaswamy J, Kumar HV, Harini ST, Naik N. Functionalized 3-(benzofuran-2-yl)-5-(4 methoxyphenyl)-4,5-dihydro-1H-pyrazole scaffolds: A new class of antimicrobials and antioxidants Ara J Chem, 2013; doi:10.1016/j.arabjc.2013.10.012.
27. Malek TM, Asadollah H, Hamid RS, Sayyed MHK, Elaheh M. Zinc oxide as an economical and efficient catalyst for the one-pot preparation of b-acetamido ketones via a four-component condensation reaction. Tetrahedron Lett, 2007; 48: 1729–1734.
28. Handler, N.; Jaeger, W.; Puschacher, H.; Leisser, K.; Erker, T. Chem. Pharm. Bull, 2007; 55:64.