Synthesis, characterization and pharmacological evaluation of substituted phenoxy acetamide derivatives

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Abstract

A novel series of 2-(substituted phenoxy)-*N*-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)acetamide and *N*-(2-bromocyclohexyl)-2-(substituted phenoxy)acetamide derivatives having cyclohexyl nucleus as common in both types were synthesized and assessed for their anti-inflammatory activity by a carrageenan induced rat paw oedema method, analgesic activity by Eddy's hot plate method and antipyretic activity by brewer's yeast induced pyrexia method. All the novel derivatives have been synthesized by the reaction of camphor and similar ketone having cyclohexane nucleus (*e.g.*, 2-bromocyclohexanone) with ammonium carbonate and formic acid resulting in the formation of aromatic amines **1a** and **1b**. These amines on further chloroacetylation with chloroacetylchloride give compounds **2a** and **2b**. Compounds **2a** and **2b** are converted to 2-(substituted phenoxy)-*N*-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl) acetamide and *N*-(2-bromocyclohexyl)-2-(substituted phenoxy)-acetamide derivatives on treatment with substituted phenol. Among the series **3a**–**f**, **3i**, **3k** and **3l** compounds showed significant anti-inflammatory activity as compared to the standard drug diclofenac sodium and also compounds **3a**–**f**, **3h**, **3j** and **3k** exhibit significant analgesic activity as compared to the standard drug. Compounds **3a**–**f** and **3k** showed antipyretic activity nearly to the standard drug indomethacin. Compounds **3a**–**f** and **3k** possess anti-inflammatory, analgesic and antipyretic activities near to the standard.

Keywords: 2-(substituted phenoxy)-*N*-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)acetamide, *N*-(2-bromocyclohexyl)-2-(substituted phenoxy)acetamide, anti-inflammatory activity, analgesic activity, antipyretic activity.

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Inflammation is a complicated process, but it may be explained as a complex reaction in the form of body's response of local tissues to inactivate injurious agents, such as microbes and to remove dead cells and tissues and to initiate the process of healing [1]. This complex reaction consists of series of events such as vascular responses, migration and activation of leucocytes, and systemic reactions. Body's first inflammatory response is the change in blood circulation. During this event, smooth muscle cells regulate the flow of blood into the capillaries and relaxation of smooth muscle cells allows blood to rush into the capillaries. This results in the redness and heat. Increased pressure is transmitted from capillaries to venules. This results in the plasma filtration through the vessel wall and finally oedema formation [2]. Body's second response is adhesion of leucocytes to the surface of venules by the surface adhesion molecules. During inflammation these are activated by mediators of inflammation. Body's third response is the change in vessel wall permeability. There are various mediators of inflammation such as chemical mediators, biogenic amines, peptides and arachidonic acid derivatives [3,4]. Out of these arachidonic acid derivatives play an important role as mediators of inflammation. There are four main symptoms of inflammation namely redness, swelling, heat and pain. These symptoms can be essentially targeted to examine analgesic and antipyretic activities of the synthesized compounds. Arachidonic acid is synthesized from cell membrane phospholipids by the action of phospholipases [5]. Further prostaglandin and 5-HPETE (hydroperoxy-eicosatetraenoic acids) are synthesized by the action of cyclooxygenase and 5-lipoxygenase respectively on the arachidonic acid. There are five types of PGs synthesized from arachidonic acid. These PGs are PGD_2, PGE_2, PGI_2 (prostacyclin), TXA_2 (thromboxane A_2) and $PGF_{2\alpha}$. These PGs are involved in skin inflammation where PGs activate the inflammatory action of platelet activating factor (PAF). PGS are effected plysiologically by G-protein-coupled prostanoid receptors (GPCRs). These

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GPCRs comprise of nine members (DP, EP1-4, FP, IP, TP and CRTH-2). TP is thromboxane A_2 (TXA_2) receptor. TXA_2 act as mediator to change in the shape of platelet and aggregation of platelet. DP and CRTH-2 are PGD_2 receptors. PGD_2 act as a mediator for smooth muscle contraction and relaxation. EP1-4 are PGE_2 receptors. PGE_2 plays a protective role for gastrointestinal mucosa. IP is PGI_2 receptor. PGI_2 increases the microvascular permeability. FP is $PGF_{2\alpha}$ receptor. $PGF_{2\alpha}$ facilitates the inflammatory pain and transmission of pain. Hence for non-steroidal anti-inflammatory drugs (NSAIDs), the most important mechanism of action is forbiddance of the synthesis of prostaglandin and 5-HPETE [6,7]. NSAIDs are the most widely prescribed worldwide. These are used in various inflammatory diseases including rheumatoid and osteoarthritis. However, their therapeutic use is often limited by common side effects, such as gastrointestinal bleeding and ulceration [8]. In addition, there is evidence to suggest that leukotriene promotes gastric ulceration, which limits the therapeutic utilization of these drugs [9]. In spite of many NSAIDs, there is still need to develop new drugs that have potent anti-inflammatory effect with minimum side effects [10,11].

Compounds with a 2-phenoxy-*N*-phenylacetamide core structure have attracted considerable research interest as these entities established a long range of pharmacological activities such as anti-inflammatory [12], antibacterial [13], antiparasitic [14], anticancer [15], antiviral [1] and antihypoglycemic [16] effects. This enhances the chemotherapeutic utilization [17]. Recently, in a program of high throughput screening for biological evaluation, the hit compound methyl 2-(4-(2-(2,4-dimethylphenoxy)acetamido)phenoxy) acetate (**I**, Figure 1) [18] was reported to possess potent anti-tuberculosis activity, which indicates that 2-phenoxy-*N*-phenylacetamide (**II**, Figure 1) may be a promising scaffold for develop novel anti-inflammatory agents. The synthetic ease of the 2-phenoxy-*N*-phenylacetamide scaffold provides a strong motivation for the development of effective and affordable anti-inflammatory agents. To date there have been no reports describing the synthesis and anti-inflammatory assessment of its derivatives. In the vision of above facts, a novel class of titled compounds has been synthesized. In extension of our research plan on synthesis and pharmacological importance of various phenoxy acetamide derivatives, now we are reporting the synthesis, anti-inflammatory, analgesic and antipyretic activity of titled derivatives. Compounds which showed significant activities in acute anti-inflammatory, analgesic and antipyretic model were mentioned in the result and discussion part. The structural assignments of the new compounds were based on their spectral (IR, ^{1}H-NMR, ^{13}C-NMR and mass) data. The characterization data of all the new compounds have been given in the experimental part.

EXPERIMENTAL

General considerations. All research chemicals were purchased from CDH (Central Drug House P. Ltd., New Delhi, India) and used as such for the reactions. Solvents without laboratory reagent mark were dehydrated and purified according to the literature whenever necessary. Purification of the compounds was carried out by the recrystallization with appropriate solvent in case of solids but by distillation in case of liquids. Purity of the compounds and completion of reactions were monitored by thin layer chromatography (TLC) on silica gel plates and spots were visualized by exposure to iodine vapor.

Melting points were determined in open capillaries on Thomas Hoover apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-435 spectrophotometer using KBr pellets, ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance II 400 NMR spectrometer (Bruker Corporation, Billerica, MA, USA) instrument using tetramethylsilane (TMS) as an internal standard and DMSO-d_6 as a solvent. Mass spectra were

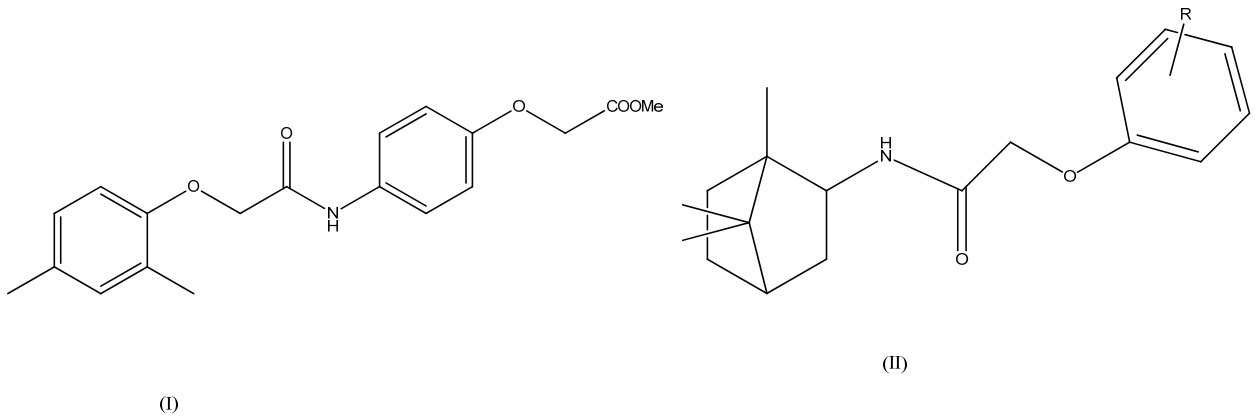


*Figure 1. The chemical structures of methyl 2-(4-(2-(2,4-dimethylphenoxy)acetamido) phenoxy)acetate (**I**) 2-(substituted phenoxy)-N-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)acetamide (**II**) derivatives.*

recorded on Micromass Q-Tof Micro (Waters Corporation Milford, MA, USA). Chemical shifts are given in ppm. The anti-inflammatory and analgesic screening is carried out at Pharmacology laboratory of School of Pharmaceutical Sciences, IFTM University, Moradabad. The anti-inflammatory activity was carried out using digital plethysmometer. All the animal experiments were approved by Institutional Animal Ethical Committee (IAEC). Elemental analysis was carried out using Elementar Vario EL III, elementar Analysensysteme GmbH, Hanau, Germany.

Synthesis of 2-bromocyclohexanone from cyclohexanone [19]. Cyclohexanone (5.3 ml, 0.05 mol) and water (30 ml) are placed in a three necked flask equipped with a stirrer and a dropping funnel. Bromine (2.58 ml, 0.05 mol) is added dropwise during 1 h at 5 °C to the mixture while stirring. After the addition is complete, the stirring is complete at room temperature until the reaction mixture becomes colorless (about 1 h). The reaction mixture is allowed to warm during this period. The upper layer of bromo-cyclohexanone is separated by ether extraction (3×20 ml). The ether extract is washed with water, saturated sodium chloride solution and dried (anhydrous sodium sulphate). Then, the ether is distilled. 2-Bromocyclohexanone is collected by distillation in vacuum.

*General method for the synthesis of 1,7,7-trimethylbicyclo[2.2.1]heptan-2-amine (**1a**) and 2-bromocyclohexylamine (**1b**) starting from camphor and 2-bromocyclohexanone*. This procedure of Leuckart reaction [19] was followed for the preparation of amines from ketones. Ammonium carbonate (215 g, 4 mol) was placed in a 1-l three necked round bottom flask, fitted with a thermometer, a dropping funnel and a bent tube attached for distillation to a short condenser. Formic acid (98%, 109 ml) was taken in the dropping funnel and added drop wise. When the reaction subsided, the mixture was heated slowly until the temperature increased to about 165 °C. The ketone (1 mol) was added in one lot and the temperature was slowly raised to 180–185 °C. Water, ammonia, carbon dioxide and some of the ketone distilled over. The distilled ketone was separated and returned to the reaction mixture. The mixture which gradually became homogenous was maintained at 180–18 °C (for 2-bromocyclohexanone) and at 160–165 °C (for camphor) for 4–5 h. Deposited camphor in the condenser was scratched with glass rod at 15 min interval and returned to the reaction mixture. When the reaction was complete, the mixture was cooled and stirred thoroughly with twice its volume of water. The aqueous layer was separated and the formyl derivative of the amine so obtained was refluxed with 100–150 ml of concentrated hydrochloric acid for 2–3 h. After the hydrolysis, the reaction mixture was cooled and extracted with ether to remove any unreacted ketone. The aqueous solution was made strongly alkaline with 30% sodium hydroxide solution and the separated amine was extracted with ether. The ethereal extract was dried over anhydrous sodium sulphate and after removal of the solvent, the product distilled under reduced pressure.

Amines 1,7,7-trimethylbicycloheptan-2-amine (**1a**) and 2-bromocyclohexylamine (**1b**) are synthesized by the above reaction from camphor and 2-bromocyclohexanone respectively.

*General method for the synthesis of 2-chloro-N--1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)acetamide (**2a**) and N-(2-bromocyclohexyl)-2-chloroacetamide (**2b**) from **1a** and **1b**, respectively*. To an ice-cooled aqueous solution of sodium hydroxide (50 ml, 10%) taken in two different well-corked conical flask, 0.1 mol of synthesized compounds **1a** and **1b** was added in both the flasks followed by addition of chloroacetyl chloride (11.93 ml, 0.15 mol) with constant stirring and shaking. The reaction was vigorously shaken until odour of chloroacetylchloride disappeared. The pH of reaction mixture was kept around 9–10 by the addition of sodium hydroxide solution. The solid amides **2a** and **2b** that formed was collected by filtration and washed thoroughly with water, dried and recrystallized from ethanol.

*2-Chloro-N-1,7,7-trimethylbicyclo[2.2.1]heptan-2--yl)acetamide (**2a**).* Yield 78%; M.p.: 102–104 °C. IR (KBr) cm^{-1}: 3275, 3050, 2875, 1680.

*N-(2-bromocyclohexyl)-2-chloroacetamide (**2b**)*. Yield 69%; M.p.: 91–93 °C. IR (KBr) cm^{-1}: 3215, 2910, 1735.

*General method for the synthesis of 2-(substituted phenoxy)-N-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)-acetamides (**3a**–**3f**) and N-(2-bromocyclohexyl)-2-(substituted phenoxy)acetamides (**3g**–**3l**) from **2a** and **2b**, resrespectively*. Phenoxy acetamide derivatives were prepared by reacting **2a** and **2b** (0.01 mol) with different substituted phenols (0.01 mol) in presence of anhydrous potassium carbonate (0.01 mol) and catalytic amount of potassium iodide in refluxing dry acetone. In some cases unreacted phenol was removed from the final product by treating the substance with 10%, *w*/*V*, sodium carbonate solution in water. The compound was then filtered and washed thoroughly with water and recrystallised from appropriate solvent. The completion of the reaction was monitored by TLC.

*2-Phenoxy-N-(1,7,7-trimethylbicyclo[2.2.1]heptan-2--yl)acetamide (**3a**)*. Colourless crystals, $C_{18}H_{25}NO_2$, yield 58.6%. M.p.: 178–180 °C. IR (KBr) cm^{-1} : 3210, 3150, 3010, 2930, 1775, 1640, 1315, 1270. ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 8.90 (*s*, 1H, NH), 7.41 (*t*, *J* = = 7.4 Hz, 2H, H-3'', H-5''), 7.30–6.90 (*m*, 3H, H-2'', H-4'', H-6''), 4.28 (*s*, 2H, CH_2-2), 3.50 (*t*, *J* = 7.2 Hz, 1H, CH-2'), 2.82–2.55(*m*, 2H, CH_2-3'), 2.48–2.30 (*m*, 5H,

CH-4′, CH_2-5′, CH_2-6′), 1.56 (*s*, 3H, CH_3-1′), 1.11 (*s*, 6H, $(CH_3)_2$-7′). ^{13}C-NMR (DMSO-d_6, δ / ppm): 167.1 (C=O, NHCO), 157.9 (C, C-1′′), 128.1 (C, C-3′′,C-5′′), 122.1 (C, C-4′′), 115.8 (C, C-2′′,C-6′′), 68.1 (CH_2), 58.1 (CH, C-2′), 49.4 (C, C-1′), 48.1 (C, C-7′), 44.5 (CH, C-4′), 37.1 (CH_2, C-3′), 33.4 (CH_2, C-6′), 26.1 (CH_2, C-5′), 19.1 (2XCH_3, $(CH_3)_2$-C7′), 13.8 (CH_3, CH_3-C1′). mass: m/z 287 (M^+), 288 (M +1, 20.1%), 289 (M +2 , 1.5%). Anal. Calc. for $C_{18}H_{25}NO_2$: C 75.22, H 8.77, N 4.87, O 11.13. Found: C 75.15, H 8.62, N 4.80, O 10.95.

*2-(4-Bromophenoxy)-N-(1,7,7-trimethylbicyclo[2.2.1]-heptan-2-yl)acetamide (**3b**)*. Colourless amorphous powder, $C_{18}H_{24}BrNO_2$, yield: 61.0%. M.p.: 110–112 °C. IR (KBr) cm^{-1}: 3305, 3120, 3000, 2875, 1690, 1600, 1345, 1050. ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 9.10 (*s*, 1H, NH), 7.32 (*d*, *J* = 1.5 Hz, 2H, H-3′′, H-5′′), 6.86 (*d*, *J* = 1.5 Hz, 2H, H-2′′, H-6′′), 4.31 (*s*, 2H, CH_2-2), 3.15 (*t*, *J* = 7.2 Hz, 1H, CH-2′), 2.75–2.47 (*m*, 2H, CH_2-3′), 2.30–2.15 (*m*, 5H, CH-4′, CH_2-5′, CH_2-6′), 1.61 (*s*, 3H, CH_3-1′), 1.12 (*s*, 6H, $(CH_3)_2$-7′). ^{13}C-NMR (DMSO-d_6, δ / ppm): 168.4 (C=O, NHCO), 156.2 (C, C-1′′), 131.2 (C, C-3′′,C-5′′), 116.9 (C, C-2′′,C-6′′), 114.4 (C, C-4′′), 67.8 (CH_2), 59.2 (CH, C-2′), 48.6 (C, C-1′), 47.3 (C, C-7′), 44.8 (CH, C-4′), 36.4 (CH_2, C-3′), 33.9(CH_2, C-6′), 25.8 (CH_2, C-5′), 19.7 (2×CH_3, $(CH_3)_2$-C7′), 12.2 (CH_3, CH_3-C1′). MS: *m/z* 365 (M^+), 367 (M+2, 97.6%), 366 (M+1, 19.8%). Anal. Calcd. for $C_{18}H_{24}BrNO_2$: C 59.02, H 6.60, Br 21.81, N 3.82, O 8.74. Found: C 58.94, H 6.51, Br 21.89, N 3.91, O 8.68.

*2-(4-Nitrophenoxy)-N-(1,7,7-trimethylbicyclo[2.2.1]-heptan-2-yl)acetamide (**3c**)*. Very light yellow amorphous powder, $C_{18}H_{24}N_2O_4$, yield: 57.8%. M.p.: 165–167 °C. IR (KBr) cm^{-1}: 3265, 3200, 3075, 2805, 1715, 1575, 1535, 1220, 1095. ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 8.55 (*d*, *J* = 1.5 Hz, 2H, H-3′′, H-5′′), 8.42 (*s*, 1H, NH), 7.34 (*d*, *J* = 1.5 Hz, 2H, H-2′′, H-6′′), 4.20 (*s*, 2H, CH_2-2), 3.26 (*t*, *J* = 7.2 Hz, 1H, CH-2′), 2.80–2.49 (*m*, 2H, CH_2-3′), 2.41–2.23 (*m*, 5H, CH-4′, CH_2-5′, CH_2-6′), 1.54 (*s*, 3H, CH_3-1′), 1.22 (*s*, 6H, $(CH_3)_2$-7′). ^{13}C-NMR (DMSO-d_6, δ / ppm): 168.9 (C=O, NHCO), 163.3 (C, C-1′′), 138.1 (C, C-4′′), 125.1 (C, C-3′′,C-5′′), 113.6 (C, C-2′′,C-6′′), 67.1 (CH_2, C-2), 56.8 (CH, C-2′), 48.4 (C, C-1′), 47.8 (C, C-7′), 43.1 (CH, C-4′), 37.9 (CH_2, C-3′), 31.1 (CH_2, C-6′), 26.1 (CH_2, C-5′), 18.9 (2XCH_3, $(CH_3)_2$-C7′), 12.8 (CH_3, CH_3-C1′). MS: *m/z* 332 (M^+), 333 (M+1, 19.6%), 334 (M+2, 2.4%). Anal. Calcd. for $C_{18}H_{24}N_2O_4$: C 65.04, H 7.28, N 8.43, O 19.25. Found: C 65.11, H 7.15, N 8.56, O 19.31.

*2-(4-(tert-Butyl)phenoxy)-N-(1,7,7-trimethylbicyclo-[2.2.1]heptan-2-yl)acetamide (**3d**)*. White crystals, $C_{22}H_{33}NO_2$, yield: 70.0%. M.p.: 105–107 °C. IR (KBr) cm^{-1}: 3280, 3195, 2990, 2800, 1735, 1505, 1293, 1155. ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 8.27 (*s*, 1H, NH), 7.30 (*d*, *J* = 1.5 Hz, 2H, H-3′′, H-5′′), 6.81 (*d*, *J* = 1.5 Hz, 2H, H-2′′, H-6′′), 4.13 (*s*, 2H, CH_2-2), 3.41 (*t*, *J* = 7.2 Hz, 1H, CH-2′), 2.78–2.34 (*m*, 2H, CH_2-3′), 2-14–1.42 (*m*, 2H, CH_2-5′), 1.31 (*s*, 9H, $(CH_3)_3$), 1.29–1.25 (*m*, 3H, CH-4′, CH_2-6′), 1.21 (*s*, 3H, CH_3-1′), 1.18 (*s*, 6H, $(CH_3)_2$-7′). ^{13}C-NMR (DMSO-d_6, δ / ppm): 167.1 (C=O, NHCO), 162.8 (C, C-1′′), 137.9 (C, C-4′′), 124.7 (C, C-3′′,C-5′′), 112.4 (C, C-2′′,C-6′′), 67.9 (CH_2), 55.6 (CH, C-2′), 48.1 (C, C-1′), 46.9 (C, C-7′), 44.2 (CH, C-4′), 38.4 (CH_2, C-3′), 34.9 (C, C–$(CH_3)_3$), 31.9 (CH_2, C-6′), 29.1 (3×CH_3, $(CH_3)_3$–C–C4′′)), 26.7 (CH_2, C-5′), 19.1 (2×CH_3, $(CH_3)_2$-C7′), 12.1 (CH_3, CH_3-C1′). MS: *m/z* 343 (M^+), 344 (M+1, 24.2%), 345 (M+2, 3.1%). Anal. Calcd. for $C_{22}H_{33}NO_2$: C 76.92, H 9.68, N 4.08, O 9.32. Found: C 76.81, H 9.75, N 4.19, O 9.22.

*2-(4-Methoxyphenoxy)-N-(1,7,7-trimethylbicyclo-[2.2.1]heptan-2-yl)acetamide (**3e**)*. White amorphous powder, $C_{19}H_{27}NO_3$, yield: 67.4%. M.p.: 170–172 °C. IR (KBr) cm^{-1}: 3275, 3125, 2975, 2915, 2795, 1655, 1560, 1200, 1125. ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 9.13 (*s*, 1H, NH), 7.41 (*s*, 4H, H-2′′, H-3′′, H-5′′, H-6′′), 4.46 (*s*, 2H, CH_2-2), 3.81(*s*, 3H, OCH_3), 3.35 (*t*, *J* = 7.2 Hz, 1H, CH-2′), 2.71–2.45 (*m*, 2H, CH_2-3′), 2.35–2.12 (*m*, 5H, CH-4′, CH_2-5′, CH_2-6′), 1.34 (*s*, 3H, CH_3-1′), 1.24 (*s*, 6H, $(CH_3)_2$-7′). ^{13}C-NMR (DMSO-d_6, δ / ppm): 166.8 (C=O, NHCO), 150.2 (C, C-4′′), 149.3 (C, C-1′′), 127.2 (C, C-3′′,C-5′′), 112.8 (C, C-2′′, C-6′′), 68.4 (CH_2), 56.1 (CH, C-2′), 54.1 (CH_3, O–CH_3), 48.9 (C, C-1′), 48.4 (C, C-7′), 43.9 (CH, C-4′), 36.2 (CH_2, C-3′), 31.8 (CH_2, C-6′), 27.8 (CH_2, C-5′), 18.6 (2×CH_3, $(CH_3)_2$-C7′), 13.9 (CH_3, CH_3-C1′). MS: *m/z* 317 (M^+), 318 (M+1, 21.1%), 319 (M+2, 2.3%). Anal. Calcd. for $C_{19}H_{27}NO_3$: C 71.89, H 8.57, N 4.41, O 15.12. Found: C 71.96, H 8.64, N 4.58, O 15.27.

*2-(2-nitrophenoxy)-N-(1,7,7-trimethylbicyclo[2.2.1]-heptan-2-yl)acetamide (**3f**)*. Pale yellow crystals, $C_{18}H_{24}N_2O_4$, yield: 62.0%. M.p.: 210–212 °C. IR (KBr) cm^{-1}: 3205, 2990, 3010, 2895, 1785, 1570, 1490, 1275, 1215. ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 8.75 (*d*, 1H, H-3′′), 8.30 (*s*, 1H, NH), 7.37 (*t*, *J* = 7.2 Hz, 1H, H-5′′), 7.21 (*t*, *J* = 7.4 Hz, 1H, H-2′′), 6.87 (*d*, *J* = 1.5 Hz, 1H, H-6′′), 4.45 (*s*, 2H, CH_2-2), 3.42 (*t*, *J* = 7.4 Hz, 1H, CH-2′), 2.55–2.31 (*m*, 2H, CH_2-3′), 2.22–2.16 (*m*, 5H, CH-4′, CH_2-5′, CH_2-6′), 1.24 (*s*, 3H, CH_3-1′), 1.10 (*s*, 6H, $(CH_3)_2$-7′). ^{13}C-NMR (DMSO-d_6, δ / ppm): 167.1 (C=O, NHCO), 162.8 (C, C-1′′), 139.8 (C, C-2′′), 130.1 (C, C-5′′), 126.5 (C, C-3′′), 122.2 (C, C-4′′), 115.9 (C, C-6′′), 67.8 (CH_2), 57.9 (CH, C-2′), 48.8 (C, C-1′), 46.4 (C, C-7′), 43.7 (CH, C-4′), 36.8 (CH_2, C-3′), 32.6 (CH_2, C-6′), 26.9 (CH_2, C-5′), 16.8 (2×CH_3, $(CH_3)_2$-C7′), 13.1 (CH_3, CH_3-C1′). MS: *m/z* 332 (M^+), 333 (M+1, 19.9%), 334 (M+2, 2.5%). Anal. Calcd. for $C_{18}H_{24}N_2O_4$: C 65.04, H 7.28, N 8.43, O 19.25. Found: C 65.19, H 7.17, N 8.36, O 19.37.

*N-(2-Bromocyclohexyl)-2-phenoxyacetamide (**3g**)*. White crystals, $C_{14}H_{18}BrNO_2$, yield: 57.0%. M.p.: 189–191 °C. IR (KBr) cm^{-1}: 3285, 3050, 2930, 2075, 1660, 1600, 1250, 1050. ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 8.13 (*s*, 1H, NH), 7.41 (*t*, *J* = 7.2 Hz, 2H, H-3′′,

H-5''), 7.30–7.05 (*m*, 3H, H-2'', H-4'', H-6''), 5.14 (*s*, 2H, CH_2-2), 4.12–3.23 (*m*, 2H, CH-1', CH-2'), 2.83–2.67 (*m*, 2H, CH_2-3'), 2.55–2.45 (*m*, 2H, CH_2-6'), 2.39–2.12 (*m*, 2H, CH_2-4'), 1.93–1.52 (*m*, 2H, CH_2-5'). ^{13}C-NMR (DMSO-d_6, δ ppm): 167.4 (C=O, NHCO), 157.6 (C, C-1''), 127.4 (C, C-3'',C-5''), 120.1 (C, C-4''), 110.5 (C, C-2'',C-6''), 69.4 (CH_2), 60.7 (CH, C-2'), 58.4 (CH, C-1'), 34.8 (CH_2, C-3'), 31.3 (CH_2, C-6'), 23.1 (CH_2, C-4'), 21.5 (CH_2, C-5'). MS: *m/z* 311 (M^+), 313 (M+2, 97.3%), 312 (M+1, 15.3%). Anal. Calcd. for $C_{14}H_{18}BrNO_2$: C 53.86, H 5.81, Br 25.59, N 4.49, O 10.25. Found: C 53.98, H 5.72, Br 25.68, N 4.61, O 10.39.

*N-(2-bromocyclohexyl)-2-(4-bromophenoxy)acetamide (**3h**)*. Pale yellow amorphous powder, $C_{14}H_{17}Br_2NO_2$, yield: 66.2%. M.p.: 205–207 °C. IR (KBr) cm^{-1}: 3290, 3055, 2925, 2875, 1655, 1550, 1250, 1055. ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 8.20 (*s*, 1H, NH), 7.46 (*d*, *J* = 2.0 Hz, 2H, H-3'', H-5''), 7.07 (*d*, *J* = 2.0 Hz, 2H, H-2'', H-6''), 5.35 (*s*, 2H, CH_2-2), 4.05–3.14 (*m*, 2H, CH-1', CH-2'), 2.15–2.11 (*m*, 2H, CH_2-3'), 2.07–1.98 (*m*, 2H, CH_2-6'), 1.87–1.76 (*m*, 2H, CH_2-4'), 1.71–1.68 (*m*, 2H, CH_2-5'). ^{13}C-NMR (DMSO-d_6, δ / ppm): 169.1 (C=O, NHCO), 156.9 (C, C-1''), 126.3 (C, C-3'',C-5''), 119.4 (C, C-4''), 110.8 (C, C-2'',C-6''), 71.4 (CH_2), 61.4 (CH, C-2'), 59.6 (CH, C-1'), 37.3 (CH_2, C-3'), 32.4 (CH_2, C-6'), 24.8 (CH_2, C-4'), 21.9 (CH_2, C-5'). MS: *m/z* 390 (M^+), 388 (M–2, 51.2%), 392 (M+2 , 49.0%). Anal. Calcd. for $C_{14}H_{17}Br_2NO_2$: C 42.99, H 4.38, Br 40.86, N 3.58, O 8.18. Found: C 42.81, H 4.24, Br 40.71, N 3.70, O 8.35.

*N-(2-bromocyclohexyl)-2-(4-nitrophenoxy)acetamide (**3i**)*. Pale yellow crystals, $C_{14}H_{17}BrN_2O_4$, yield: 64.1%. M.p.: 155–157 °C. IR (KBr) cm^{-1}: 3325, 3060, 3025, 2900, 1670, 1580, 1525, 1250, 1075. ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 8.34 (*d*, *J* = 2.0 Hz, 2H, H-3'', H-5''), 8.12 (*s*, 1H, NH), 7.18 (*d*, *J* = 2.0 Hz, 2H, H-2'', H-6''), 5.30 (*s*, 2H, CH_2-2), 4.28–3.14 (*m*, 2H, CH-1', CH-2'), 2.13-2.02 (*m*, 2H, CH_2-3'), 1.91–1.77 (*m*, 2H, CH_2-6'), 1.62–1.43 (*m*, 2H, CH_2-4'), 1.41–1.36 (*m*, 2H, CH_2-5'). ^{13}C-NMR (DMSO-d_6, δ / ppm): 164.3 (C=O, NHCO), 154.6 (C, C-1''), 135.4 (C, C-4''), 130.2 (C, C-3'',C-5''), 111.5 (C, C-2'',C-6''), 68.6 (CH_2), 61.6 (CH, C-2'), 57.8 (CH, C-1'), 33.9 (CH_2, C-3'), 31.8 (CH_2, C-6'), 22.8 (CH_2, C-4'), 20.7 (CH_2, C-5'). MS: *m/z* 356 (M^+), 358 (M+2, 99.2%), 357 (M+1, 15.5%). Anal. Calcd. for $C_{14}H_{17}BrN_2O_4$: C 47.07, H 4.80, Br 22.37, N 7.84, O 17.92. Found: C 47.18, H 4.67, Br 22.51, N 7.65, O 17.79.

*N-(2-bromocyclohexyl)-2-(4-(tert-butyl)phenoxy)-acetamide (**3j**).* Colourless crystals, $C_{18}H_{26}BrNO_2$, yield: 68.0%. M.p.: 195–197 °C. IR (KBr) cm^{-1}: 3360, 3025, 3000, 2955, 2925, 1600, 1575, 1260, 1080. ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 8.45 (*s*, 1H, NH), 7.68 (*d*, *J* = 2.0 Hz, 2H, H-3'', H-5''), 7.44 (*d*, *J* = 2.0 Hz, 2H, H-2'', H-6''), 5.21 (*s*, 2H, CH_2-2), 4.05–3.15 (*m*, 2H, CH-1', CH-2'), 2.92–2.76 (*m*, 2H, CH_2-3'), 2.68–2.37 (*m*, 2H, CH_2-6'), 2.22–1.87 (*m*, 2H, CH_2-4'), 1.81 (*s*, 9H, $(CH_3)_3$), 1.54–1.31 (*m*, 2H, CH_2-5'). ^{13}C-NMR (DMSO-d_6, δ / ppm): 166.9 (C=O, NHCO), 151.4 (C, C-1''), 145.1 (C, C-4''), 126.4 (C, C-3'',C-5''), 115.4 (C, C-2'', C-6''), 68.1 (CH_2), 61.6 (CH, C-2'), 57.1 (CH, C-1'), 35.6 (CH_2, C-3'), 33.3 (C, C-$(CH_3)_3$), 30.6 (3×CH_3, $(CH_3)_3$-C-C4''), 29.8 (CH_2, C-6'), 24.8 (CH_2, C-4'), 20.1 (CH_2, C-5'). MS: *m/z* 367 (M^+), 369 (M+2, 97.2%), 368 (M+1, 19.6%). Anal. Calcd. for $C_{18}H_{26}BrNO_2$: C 58.70, H 7.12, Br 21.69, N 3.80, O 8.69. Found: C 58.57, H 7.29, Br 21.81, N 3.69, O 8.78.

*N-(2-bromocyclohexyl)-2-(4-methoxyphenoxy)acetamide (**3k**).* Pale yellow needles, $C_{15}H_{20}BrNO_3$, yield: 61.0%. M.p.: 220–222 °C. IR (KBr) cm^{-1}: 3200, 2920, 2900, 2810, 2055, 1655, 1550, 1300, 1050. ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 8.56 (*s*, 1H, NH), 7.82 (*s*, 4H, H-2'', H-3'', H-5'', H-6''), 5.32 (*s*, 2H, CH_2-2), 4.12–3.23 (*m*, 2H, CH-1', CH-2'), 3.18 (*s*, 3H, OCH_3) 2.21–2.06 (*m*, 2H, CH_2-3'), 1.91–1.82 (*m*, 2H, CH_2-6'), 1.78–1.63 (*m*, 2H, CH_2-4'), 1.54-1.48 (*m*, 2H, CH_2-5'). ^{13}C NMR (DMSO-d_6, δ / ppm): 169.4 (C=O, NHCO), 154.3 (C, C-4''), 152.7 (C, C-1''), 110.8 (C, C-2'',C-3'',C-5'',C-6''), 66.1 (CH_2), 61.8 (CH, C-2'), 53.9 (CH_3, O–CH_3), 53.1 (CH, C-1'), 35.6 (CH_2, C-3'), 31.8 (CH_2, C-6'), 27.4 (CH_2, C-4'), 25.2 (CH_2, C-5'). MS: *m/z* 341 (M^+), 343 (M+2, 97.3%), 342 (M+1, 16.3%). Anal. Calcd. for $C_{15}H_{20}BrNO_3$: C 52.64, H 5.89, Br 23.35, N 4.09, O 14.03. Found: C 52.81, H 5.97, Br 23.51, N 3.94, O 14.15.

*N-(2-bromocyclohexyl)-2-(2-nitroyphenoxy)acetamide (**3l**)*. Pale yellow amorphous powder, $C_{14}H_{17}BrN_2O_4$, yield: 67.0%. Mp: 115–117 °C. IR (KBr) cm^{-1}: 3205, 3115, 3000, 2995, 1705, 1550, 1515, 1305, 1090. ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 8.55 (*d*, *J* = 2.0 Hz, 1H, H-3''), 8.30 (*s*, 1H, NH), 7.41(*t*, *J* = 7.2 Hz, 1H, H-5''), 7.33 (*t*, *J* = 7.2 Hz, 1H, H-4''), 6.92 (*d*, *J* = 2.0 Hz, 1H, H-6''), 5.22 (*s*, 2H, CH_2-2), 4.06–3.10 (*m*, 2H, CH-1', CH-2'), 2.65–2.47 (*m*, 2H, CH_2-3'), 2.39–2.07 (*m*, 2H, CH_2-6'), 1.78–1.64 (*m*, 2H, CH_2-4'), 1.33–1.16 (*m*, 2H, CH_2-5'). ^{13}C-NMR (DMSO-d_6, δ / ppm): 165.3 (C=O, NHCO), 158.1 (C, C-1''), 145.1 (C, C-2''), 130.4 (C, C5''), 127.8 (C, C-3''), 122.7 (C, C-4''), 116.1 (C, C-6''), 68.7 (CH_2), 61.7 (CH, C-2'), 59.8 (CH, C-1'), 33.9 (CH_2, C-3'), 32.3 (CH_2, C-6'), 23.9 (CH_2, C-4'), 20.4 (CH_2, C-5'). MS: *m/z* 356 (M^+), 358 (M+2, 99.1%), 357 (M+1, 15.2%). Anal. Calcd. for $C_{14}H_{17}BrN_2O_4$: C 47.07, H 4.80, Br 22.37, N 7.84, O 17.92. Found: C 46.92, H 4.91, Br 22.46, N 7.59, O 17.79.

Pharmacological screening

Animals. Wistar albino rats of either sex weighing 140–180 g were obtained. The animals were divided into several groups of five each. All the animals were housed under standard ambient conditions of temperature (25±2 °C) and relative humidity of 50±5%. A 12:12 h light:dark cycle was maintained. All the animals were allowed to have free access to water and standard palletized laboratory animal diet 12 h prior to pharmaco-

logical studies. All the experimental procedures and protocols used in this study were reviewed and approved by the institutional Animal Ethical Committee (IAEC).

Preparation of test compounds. Test samples and the reference drugs were prepared as a suspension in 1% Tween 80. Group one (control) received 0.1 ml of tween 80 suspension orally. Group second (standard) was treated by suspension of diclofenac sodium with a dose of 50 mg/kg. Test groups were administered with a dose of 150 mg/kg of final synthesized compounds.

Acute toxicity. The acute toxicity study was carried out as per OECD guidelines [20] to found the successful dose of the test compounds after getting ethical clearance. Wistar albino rats of either sex weighing between 140–170 g were divided into several groups of 5 animals each. Animals were starved for 12 h with water ad libitum prior to test. On the day of the experiment, animals were treated with different compounds to different groups in an increasing order of 10, 20, 100, 200, 1000 and 1500 mg/kg body weight orally. The animals were then observed continuously for 3 h for common behavioral, neurological, autonomic profiles and then every 30 min for next 3 h and finally for next 24 h or till death.

From above toxicity test, it was observed that animals were found to be secure up to a highest dose of 1500 mg/kg body weight. But few changes were found in the behavioral reaction like touch response, alertness, and restlessness. As a result, 1/10th of the highest tolerated dose, *i.e.*, 150 mg/kg body weight (b.w.) was chosen for the studies.

Anti-inflammatory activity. Carrageenan induced rat paw edema method [21] was employed for screening of the anti-inflammatory activity of the synthesized compounds listed in Table 1. The animals were divided into fourteen groups of five each.

One hour after oral administration of the drug, acute inflammation was produced by preparing aqueous suspension of carrageenan (1%, *w*/*V*, 0.1 ml) which was injected in the right hind paw in the subplantar region of each rat.

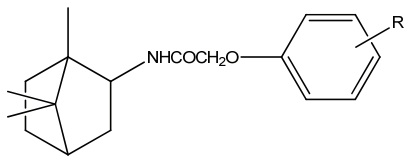
A mark was applied on the leg at the malleolus to facilitate subsequent readings. The paw volume was measured plethysmometrically at 30 min, 2 and 4 h after the injection of carrageenan. The %Inhibition was calculated by applying Newbould formula [22]:

$$\%\text{Inhibition} = 100(1 - Vt/Vc)$$

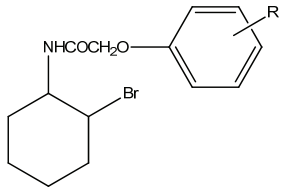
where *Vt* and *Vc* are the mean change in paw volume of treated and control rats respectively.

Analgesic activity. The compounds exhibited an important analgesic profile measured by the Eddy's hot plate method [23,24]. Animals were individually placed on a hot plate maintained at a constant temperature (55 °C) and the reaction of animals, such as paw licking or jump response (whichever appears first) was taken as the end point. A cut-off time of 15 s was taken as

*Table 1. Characterization data of 2-(substituted phenoxy)-N-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)acetamide and N-(2-bromocyclohexyl)-2-(substituted phenoxy)acetamide derivatives. *Recrystallization with ethanol. # Stationary phase: Silica gel, Mobile phase: n-Hexane: ethyl acetate (1:1), Iodine vapors as visualizing agent*



3a–f



3g–l

Compound	R	Yield, %	Melting point range[a], °C	*Rf* Value[b]	Molecular formula
3a	H	58.6	178–180	0.47	$C_{18}H_{25}NO_2$
3b	4-Br	61.0	110–112	0.41	$C_{18}H_{24}BrNO_2$
3c	4-NO_2	57.8	165–167	0.39	$C_{18}H_{24}N_2O_4$
3d	4-C-$(CH_3)_3$	70.0	105–107	0.44	$C_{22}H_{33}NO_2$
3e	4-OCH_3	67.4	170–172	0.41	$C_{19}H_{27}NO_3$
3f	2-NO_2	62.0	210–112	0.47	$C_{18}H_{24}N_2O_4$
3g	H	57.0	189–191	0.38	$C_{14}H_{18}BrNO_2$
3h	4-Br	66.2	205–207	0.45	$C_{14}H_{17}Br_2NO_2$
3i	4-NO_2	64.1	155–157	0.44	$C_{14}H_{17}BrN_2O_4$
3j	4- C-$(CH_3)_3$	68.0	195–197	0.39	$C_{18}H_{26}BrNO_2$
3k	4-OCH_3	61.0	220–222	0.35	$C_{15}H_{20}BrNO_3$
3l	2-NO_2	67.0	115–117	0.44	$C_{14}H_{17}BrN_2O_4$

[a]Recrystallization with ethanol; [b]stationary phase: silica gel, mobile phase: *n*-hexane:ethyl acetate (1:1), iodine vapors as visualizing agent

maximum analgesic response to avoid injury to the paws. The reference group was administered with a dose of 50 mg/kg of the suspension of diclofenac sodium (standard). The reaction time for each animal was noted on the hot plate at 30, 60 and 90 min after the drug administration.

Antipyretic activity. The antipyretic activity of the test compounds on the feverish body temperature was determined following a reported process [25,26]. Groups of five fasted rats (12 h) were injected subcutaneously with brewer's yeast in physiological saline at a dose of 150 mg/kg body weight. After 17 h, the initial body temperature was measured and the test compounds were administered orally. The body temperature was recorded after 1, 2 and 4 h from the administration of the test compounds.

Statistical analysis

The results of anti-inflammatory activity and analgesic activity are shown in the Tables 2 and 3, respectively. The results were expressed as mean ± *SEM* and were analyzed using one-way analysis of variance (ANOVA) followed by Dunnett's *t*-test. The probability of 0.05 or less was considered statistically significant. Statistical analysis of the results was performed using one way ANOVA or Dunnett's test followed by least significant difference test. Statistical analysis was computed with the GraphPad Prism software version 5.01, GraphPad Software Inc., USA.

RESULTS AND DISCUSSION

A series of titled derivatives 2-(substituted phenoxy)-*N*-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)acetamide and *N*-(2-bromocyclohexyl)-2-(substituted phenoxy) acetamide derivatives **3a**–**l** were synthesized as per scheme in Figure 2. Camphor and 2-bromocyclohexanone were separately treated with ammonium carbonate and formic acid resulting in the formation of amines **1a** and **1b**, respectively. These amines on chloroacetylation with chloroacetyl chloride at 0°C at 10% sodium hydroxide medium gives chloro compounds **2a** and **2b** which converted to **3a**–**l** by the reaction with different substituted phenols in presence of potassium iodide and potassium carbonate in dry acetone as a solvent. The structure of newly synthesized compounds was confirmed by spectral data (IR, ^{1}H-NMR,^{13}C-NMR and MS). Table 1 shows the physical data of compounds **3a**–**l**.

IR spectrum of compounds **2a** and **2b** showed strong absorption bands at 3275/3215 cm^{-1} (due to NH) and 1680/1735 cm^{-1} (characteristic of C=O). This indicates the presence of linkage. Further IR spectrum of compounds **3a**–**l** showed characteristic absorption bands at range of 3205–3310cm^{-1} was attributed to NH, 1600–1785 cm^{-1} accounting for C=O of amide group and 1490–1640 cm^{-1} for C=C in the aromatic ring. Two peaks at range of 1200–1345 cm^{-1} and 1050––1270 cm^{-1} indicates the presence of C–O–C linkage. The structure of compounds was further supported by mass spectral data.

All compounds **3a**–**l** were subjected for preliminary toxicity test as per Organization for Economic Co-operation and Development [20] guidelines in rats. Compounds were found to be safe up to 1500 mg/kg b.w. Hence 1/10th of highest tolerated dose, *i.e*., 150 mg/kg was used as therapeutic dose.

*Table 2. Results of anti-inflammatory activity of compounds (**3a**–**l**) against carrageenan induced rat paw edema model in rats; data analyzed by one-way ANOVA followed by Dennett's test (n = 5); *p < 0.05 significant from control.; **p < 0.01 significant from control*

Compound	Mean values ± *SEM* of oedema volume			Anti-inflammatory activity (% inhibition)		
	30 min	2 h	4 h	30 min	2 h	4 h
Control	0.600±0.004	0.500±0.006	0.400±0.005	–	–	–
Diclofenac sodium	0.090±0.010	0.100±0.015	0.140±0.009	85.00±0.53	80.00±0.50	65.00±0.53
3a**	0.192±0.004	0.292±0.004	0.292±0.004	68.00±0.62	51.33±0.62	51.33±0.62
3b**	0.094±0.002	0.291±0.004	0.192±0.004	84.33±0.41	51.33±0.62	68.00±0.62
3c**	0.304±0.005	0.204±0.005	0.204±0.005	49.33±0.85	66.00±0.85	66.00±0.85
3d**	0.302±0.007	0.204±0.005	0.204±0.005	49.67±1.11	66.00±0.85	66.00±0.85
3e**	0.204±0.005	0.304±0.005	0.204±0.005	66.00±0.85	49.33±0.85	66.00±0.85
3f**	0.304±0.005	0.302±0.006	0.204±0.005	49.33±0.85	49.66±0.97	66.00±0.85
3g*	0.308±0.004	0.404±0.000	0.304±0.005	48.66±0.62	32.67±0.85	49.33±0.85
3h*	0.204±0.005	0.204±0.005	0.204±0.005	66.00±0.85	66.00±0.85	66.00±0.85
3i**	0.304±0.005	0.204±0.005	0.204±0.005	49.33±0.85	66.00±0.85	66.00±0.85
3j*	0.404±0.005	0.304±0.005	0.304±0.005	32.66±0.85	49.33±0.85	49.33±0.85
3k**	0.304±0.005	0.404±0.005	0.406±0.007	49.33±0.85	32.66±0.85	32.33±1.13
3l**	0.308±0.004	0.204±0.005	0.204±0.005	48.66±0.62	66.00±0.85	66.00±0.85

*Table 3. Results of analgesic activity of compounds **3a–l***

Compound	Reaction time, s, after drug administration (mean ± *SEM*)			%Inhibition		
	30 min	60 min	90 min	30 min	60 min	90 min
Control	2.690±0.020	2.700±0.023	2.720±0.027	–	–	–
Diclofenac sodium	5.100±0.030	5.400±0.019	5.800±0.014	79.03±0.214	69.62±0.217	55.70±1.620
3a**	5.627±0.015	6.110±0.032	6.643±0.023	60.07±0.214	43.33±0.214	27.51±0.214
3b**	6.743±0.023	6.943±0.023	6.943±0.023	18.44±0.214	12.59±0.214	14.27±0.211
3c**	5.640±0.021	5.913±0.009	6.523±0.018	59.33±0.214	50.74±0.214	31.92±0.214
3d**	6.027±0.015	6.200±0.012	6.320±0.012	45.32±0.329	39.87±0.329	39.29±0.199
3e**	6.802±0.015	6.900±0.021	7.113±0.015	15.84±0.217	14.07±0.214	10.48±0.326
3f**	6.540± 0.021	6.743±0.023	7.047± 0.026	25.50±0.214	19.98±0.217	12.80±0.211
3g*	4.903±0.015	5.900±0.017	6.217±0.009	86.47±0.214	51.11±0.214	44.32±1.190
3h**	6.743±0.023	6.820± 0.015	7.050±0.029	18.07±0.217	17.03±0.214	12.44±0.211
3i*	5.023±0.015	6.357±0.329	7.197±0.026	81.63±0.217	34.07±0.214	7.270±0.199
3j**	6.513±0.019	6.940±0.021	7.090± 0.021	26.62±0.217	12.59±0.214	10.97±0.211
3k**	5.207±0.012	5.630±0.021	6.023±0.015	74.94±0.214	61.11±0.214	50.30±0.211
3l*	6.003±0.023	6.993±0.015	7.200±0.012	45.20±0.214	10.93±0.185	6.800±0.323

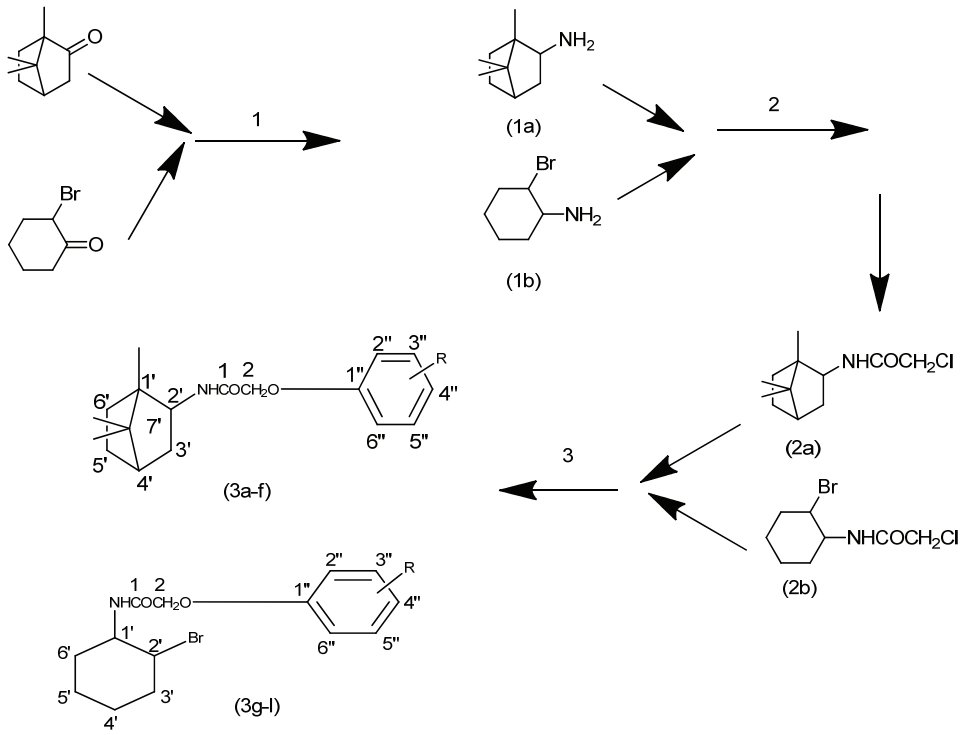


*Figure 2. Synthesis of 2-(substituted phenoxy)-N-(1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)acetamide **3a–f** and N-(2-bromocyclo-hexyl)-2-(substituted phenoxy)acetamide **3g–l** derivatives. Reagents and conditions: 1) ammonium carbonate and formic acid, heat very slowly heating to 165 °C → ketone, heat,4–5 h, 180–185 °C → reflux, concentrated hydrochloric acid, 2–3 h, water bath → extraction, diethylether → strongly alkaline, 30% sodium hydroxide → extraction, diethylether; 2) chloroacetyl chloride, 10% sodium hydroxide, ice bath, pH 9–10; 3) substituted phenols, dry acetone, potassium carbonate, potassium iodide, reflux, 30–40 h.*

Acute anti-inflammatory activity was performed by carrageenan induced rat paw edema method by Winter and his co-workers [21]. Diclofenac sodium was used as a reference standard. Compounds **3a–f**, **3i**, **3k** and **3l** exhibited significant anti-inflammatory activity similar to the standard, table 2 and Figure 3. The analgesic effects of compounds **3a–f**, **3h**, **3j** and **3k** were found to be nearly of diclofenac sodium, table 3 and Figure 4. Compounds **3a–f** and **3k** were found to exhibit potent antipyretic activity.

Compounds **3a–f** and **3k** were found to possess anti-inflammatory, analgesic and antipyretic activities nearly to the standard because of the presence of nitro and bromo groups on ortho and para positions on the

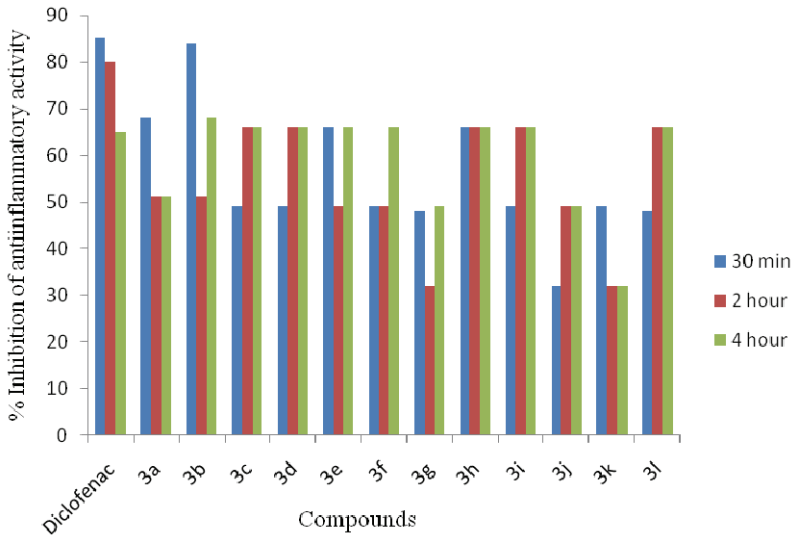


Figure 3. Graphical representation of (% inhibition) of anti-inflammatory activity.

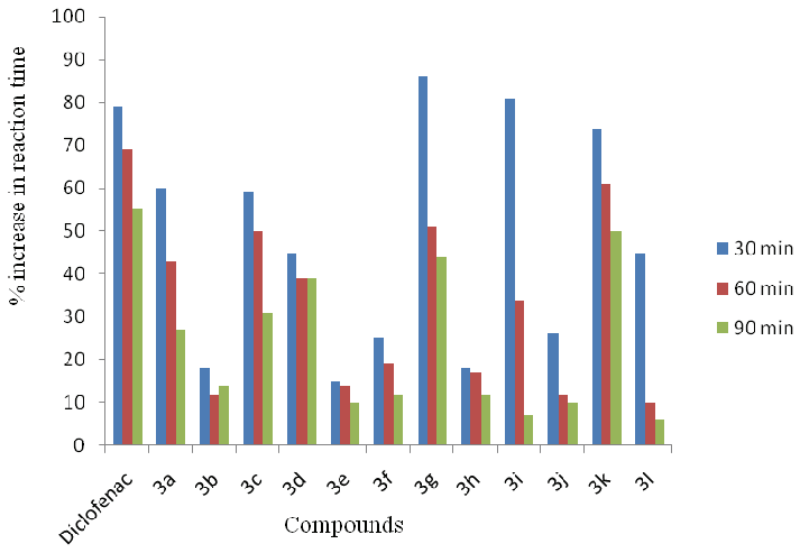


Figure 4. Graphical representation of % increase in reaction time for analgesic activity.

benzene ring. 2-Phenoxy-*N*-phenylacetamide is an intermediate in the synthesis of potent antiinflammatory drug diclofenac sodium, and its antiinflammatory activity is mainly due to the intermediate. Camphor and cyclohexanone derivative compounds are also known to show the antiinflammatory activity, and so we have attached camphor and bromocyclohexane to *N*-phenylacetamide to evaluate the antiinflammatory activity. When camphor was used as starting material, its all compounds showed anti-inflammatory, analgesic and antipyretic activities. But when 2-bromocyclohexanone was used as starting material, only compound **3k** was found to exhibit all the activities.

Compounds **3a–f** and **3k** exhibited significant antipyretic activity nearly to the standard (Table 4).

*Table 4. Results of antipyretic activity of compounds **3a–l***

Compound	Body temperature ± *SEM*, °C			
	0	1 h	2 h	4 h
Control	38.20±0.023	38.18±0.012	38.17±0.005	38.18±0.021
Indomethacin	38.21±0.010	37.42±0.011	36.35±0.016	36.23±0.069
3a	38.11±0.044	37.44±0.011	36.16±0.013	36.71±0.007
3b	38.27±0.014	37.51±0.064	36.55±0.023	36.43±0.020

Table 4. Continued

Compound	Body temperature ± *SEM*, °C			
	0	1 h	2 h	4 h
3c	38.24±0.069	37.28±0.024	37.14±0.009	36.71±0.013
3d	38.22±0.114	37.44±0.032	36.85±0.021	36.76±0.069
3e	38.23±0.320	37.45±0.041	37.38±0.008	36.22±0.021
3f	38.17±0.014	37.33±0.018	36.57±0.030	36.64±0.180
3g	38.24±0.019	37.71±0.078	37.18±0.013	37.16±0.019
3h	38.15±0.032	38.14±0.009	38.17±0.390	38.15±0.012
3i	38.18±0.031	37.78±0.018	37.28±0.011	37.68±0.023
3j	38.26±0.069	37.82±0.078	37.35±0.120	37.84±0.019
3k	38.24±0.014	37.44±0.016	37.13±0.039	36.25±0.011
3l	38.17±0.015	38.12±0.009	37.87±0.007	37.76±0.021

CONCLUSION

From the comprehensive analysis of the results in current studies, we conclude that synthesized compounds have anti-inflammatory and analgesic activities because of the presence of camphor and 2-bromocyclohexanone as basic rings. In analysis of these observations, we conclude that this series **3a–l** could be developed and explored as a novel class of NSAIDs. However, further detailed pharmacological program is required to recognize the potent molecule without various side effects.

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IZVOD

SINTEZA, KARAKTERIZACIJA I FARMAKOLOŠKA EVALUACIJA SUPSTITUISANIH DERIVATA FENOKSIACETAMIDA

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(Naučni rad)

Nove serije 2-(supstituisanih fenoksi)-*N*-(1,7,7-trimetilbiciklo[2.2.1]heptan-2--il)acetamida i derivata *N*-(2-bromocikloheksil)-2-(supstituisanih fenoksi)acetamida koji sadrže cikloheksanski prsten su sintetizovane i ispitivane u cilju određivanja njihove antiinflamatorne aktivnosti, analgetske aktivnosti i antipiretičkog dejstva. Sva nova jedinjenja su sintetizovana reakcijom kamfora ili sličnih ketona, koji sadrže cikloheksanski prsten (na primer 2-bromocikloheksanon), sa amonijum-karbonatom i mravljom kiselinom, pri čemu su se kao krajnji proizvod dobili aromatični amini **1a** i **1b**. Ovi amini su hloroacetilovanjem pomoću hloroacetilhlorida dali jedinjenja **2a** i **2b**. Jedinjenja **2a** i **2b** su prevedena u 2-(supstituisane fenoksi)-*N*-(1,7,7-trimetilbiciklo[2.2.1]heptan-2-il)acetamide i *N*-(2-bromocikloheksil)-2-(supstituisane fenoksi)acetamid derivate reakcijom sa supstituisanim fenolom. Jedinjenja **3a**–**f**, **3i**, **3k** i **3a** su pokazala značajnu antiinflamatornu aktivnost u poređenju sa standardnim lekom natrijum-diklofenakom, dok su jedinjenja **3a**–**f**, **3h**, **3j** i **3k** pokazala značajnu analgetsku aktivnost u poređenju sa standardnim lekovima. Jedinjenja **3a**–**f** i **3k** su pokazala antipiretičku aktivnost skoro kao i standardni lek indometacin. Jedinjenja **3a-f** i **3k** poseduju i antiinflamatornu, analgetsku i antipiretičku aktivnost kao odgovarajući standard.

Ključne reči: 2-(Supstituisani fenoksi)-*N*--(1,7,7-trimetilbiciklo[2.2.1]heptan-2-il)-acetamid • *N*-(2-Bromocikloheksil)-2--(supstituisani fenoksi)acetamid • Antiinflamatorna aktivnost • Analgetska aktivnost • Antipiretička aktivnost