Med Chem Res (2011) 20:1147–1153
DOI 10.1007/s00044-010-9451-x

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of some new 3,4-dihydro-2*H*-1,3-benzoxazines under microwave irradiation in solvent-free conditions and their biological activity

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Received: 31 May 2010 / Accepted: 21 September 2010 / Published online: 7 October 2010

Abstract A series of some new benzoxazines derivatives have been synthesized using conventional method and solvent-free microwave thermolysis. It was observed that the solvent-free microwave thermolysis is a convenient, rapid, high-yielding, and environmental friendly protocol for the synthesis of benzoxazines when compared with conventional reaction in a solution phase. All the compounds synthesized were tested for anti-inflammatory activity. Compound **3f**, **3h**, and **3l** showed 74.87, 70.39, and 71.89% of inhibition in rat paw edema, 57.38, 54.27, and 55.47% of protection against acetic acid induced writhings, and 0.08, 0.17, and 0.17 of severity index (SI), respectively compared to 82.33, 63.06, and 1.0 values of ibuprofen. The study showed that these compounds are good and safe anti-inflammatory agents and can be used to develop potent and safe anti-inflammatory agents.

Keywords 1,3-Benzoxazine · Microwave · Chalcones · Anti-inflammatory · Analgesic

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Introduction

The NSAIDs are among the most widely used of all therapeutic agents. They are useful in the treatment of rheumatoid arthritis and other inflammatory diseases. However, long-term use of the NSAIDs has been associated with gastrointestinal ulceration, bleeding, and nephrotoxicity. Therefore, an investigation of new anti-inflammatory agents is still a challenge.

Benzoxazine based heterocyclic compounds forms an important class of benzfuzed heterocyles with wide spectrum of biological activities and are in the development phase as potential new drugs. Benzoxazines are, therefore, reported to exhibit anti-inflammatory (Khalaj *et al*., 2002; Mashevakaya *et al*., 2001), analgesic (Gokhan *et al*., 1999), antibacterial (Beach and Frechette, 1997), neuroprotective (Kamei *et al*., 2006), D_2 receptor antagonistic activity (Ilas *et al*., 2005), antimycobacterial (Waisser *et al*., 2003), antiviral (Wittmann *et al*., 2000; Pandey *et al*., 1999), antifungal (Waisser *et al*., 2002) etc.

A cursory look at the literature cited in relation to chalcones in recent years indicates that there is a growing interest in evaluating the pharmaceutically important biological activities of chalcones and its derivatives, presuming their role in the prevention of various degenerative diseases and other human ailments. The compounds with the backbone of chalcone have been reported to exhibit a wide variety of pharmacological effects, including anti-inflammatory (Herencia *et al*., 1998), antileishmanial (Nielsen *et al*., 1998), antibacterial (Liu *et al*., 2008), antifungal (Tsuchiya *et al*., 1994), antitumour (Go *et al*., 2005), antimalarial (Mishra *et al*., 2008; Domínguez *et al*., 2005; Larsen *et al*., 2005), and anti-TB activity (Chiaradia *et al*., 2008).

An alternative to conventional heating is microwave radiation which has been very widely explored by organic

chemists. Microwave-assisted heating has been shown to be an invaluable technology in synthesis since it often dramatically reduces reaction times, typically from days or hours to minutes or even seconds. Pure products in quantitative yields have been reported with the use of microwave. Solvent-free reaction techniques have been successfully coupled with microwave synthesis. Low boiling point, toxic, and poisonous solvents are often avoided in microwave synthesis to avoid accidents. The use of microwave for the synthesis of organic compounds proved to be efficient safe and environmentally benign techniques with shorter reaction time. In view of the above findings and in continuation of our work synthesis of biologically important heterocycles (Akhter *et al*., 2009; Hasan *et al*., 2009) herein we wish to report a simple, convenient microwave-assisted synthesis of the title compounds and comparison to the conventional method of synthesis of 1,3-benzoxazine derivatives.

Materials and methods

Chemistry

All the reagents and solvents used were procured from E Merck (India) Ltd. All the solvents used were dried and distilled before use. Melting points were determined in open end capillary tubes using Kjeldhal flask containing liquid paraffin and are uncorrected. The purity of the compounds was monitored by ascending thin layer chromatography (TLC) on silica gel G (Merck), in the solvent system toluene–ethyl formate–formic acid (5:4:1) and ethylacetate:hexane (2:8), the spots were located under iodine vapors or UV light. IR spectra were recorded in KBr on Perkin-Elmer 1720 FTIR spectrometer, and proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on Brucker Avance (300 MHz) spectrometer using TMS as internal standard in $CDCl_3$/DMSO-d_6. Chemical shifts are reported in parts per million (ppm). Mass spectra were recorded on Bruker Esquire 300 quadrupole ion trap mass spectrometer. Elemental analysis of all the synthesized compounds was within ±0.4%. Microwave-assisted synthesis was carried out in Microwave oven (900 W).

*General procedure for synthesis of 3-phenyl-6-acetyl-3,4-dihydro-2H-1,3-benzoxazine compounds (**2**)*

To a solution of aromatic primary amine (0.025 mol) in methanol (0.05 mol), formaldehyde was added and the solution was refluxed for 10 min. To this solution, 4-hydroxy acetophenone (0.025 mol, 3.4 g) was added, and refluxing was continued for a specified period. The reaction was followed by TLC (toluene:ethylacetate:formic acid, 5:4:1), after the completion of reaction, excess of solvent was distilled off, and the reaction mixture was cooled to room temperature and poured onto crushed ice. The solid thus separated was filtered, dried, and crystallized from methanol.

3-(4-Methoxy phenyl)-6-acetyl-3,4-dihydro-2H-1,3-benzoxazine (**2a**) Yield: 64%; mp: 144–46°C; R*f*: 0.81; ^{1}H-NMR (ppm): 2.52 (3H, s, $COCH_3$), 3.73 (3H, s, OCH_3), 4.4 (2H, s, NCH_2), 5.3 (2H, s, OCH_2N), 6.76 (2H, d, J = 8.6 Hz, ArH), 7.2 (2H, d, J = 8.6 Hz, ArH), 7.40 (1H, d, J = 8.1 Hz, H_8), 7.56 (1H, d, J = 8.1 Hz, H_7), 7.9 (1H, s, H_5); MS *m/z*: 282 (M^+); Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.21; H, 6.03; N, 4.93.

3-(4-Methyl phenyl)-6-acetyl-3,4-dihydro-2H-1,3-benzoxazine (**2b**) Yield: 59%; mp: 134–36°C; R*f*: 0.73; ^{1}H-NMR (ppm): 2.15 (3H, s, CH_3), 2.51 (3H, s, $COCH_3$), 4.34 (2H, s, NCH_2), 5.34 (2H, s, OCH_2), 6.71 (2H, d, J = 8.6 Hz, ArH), 7.12 (2H, d, J = 8.6 Hz, ArH), 7.24 (1H, d, J = 8.1 Hz, H_8), 7.76 (1H, d, J = 8.1 Hz, H_7), 7.89 (1H, s, H_5); MS *m/z*: 266 (M^+); Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.18; H, 6.40; N, 5.23.

*General procedure for microwave-assisted synthesis of 1,3-diphenyl-3,4-dihydro-2H-benzo[e][1,3]oxazine-6-yl] propenone (**3**)*

Compound **2a–b** (0.01 mol) was titrated with two flakes of KOH in a pestle motor and (0.0l mol) of aromatic aldehyde was added. The contents were mixed throughly and transferred to a 25 ml beaker. The beaker was placed in a microwave oven for 4–6 min (900 W) (four pulses each of 1–1.5 min). The reaction conditions for a single reaction were optimized in terms of power, pulse (time), and cooling time of reaction mixture. The optimum time for microwave synthesis was found to be a cycle of 1–2 min of irradiation followed by 2 min off. The microwave irradiations were repeated 3–4 times giving a total time of 4–6 min to achieve the completion of the reaction.

The reactions were followed by TLC (ethylacetate:hexane, 2:8). After completion of the reaction, crushed ice was added to the reaction mixture in beaker and then acidified with dilute HCl to obtain the product. The product obtained was filtered on suction, dried, and crystallized from methanol.

*General procedure for the synthesis of 1,3-diphenyl-3,4-dihydro-2H-benzo[e][1,3]oxazine-6-yl] propenone (**3**)*

To a solution of (0.01 mol) **2a–b** in ethanol was added KOH (15%, 3 ml) and refluxed for 10 min, followed by addition of aromatic aldehyde (0.01 mol). The refluxing

was continued for a specified time with stirring. After completion of reaction, excess of solvent was distilled off. The mixture was cooled to room temperature and poured onto the crushed ice and acidified with dil. HCl. The solid thus separated was filtered, dried, and crystallized from methanol.

3-(2′-Chlorophenyl)-1-[3-(4-methoxyphenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazine-6-yl] propenone (**3a**) mp: 125–27°C; R*f*: 0.46; IR (KBr) cm^{-1}: 1322, 1693, 1757; ^{1}H-NMR (ppm): 3.68 (3H, s, OCH_3), 4.59 (2H, s, NCH_2), 5.5 (2H, s, OCH_2), 6.64 (1H, d, J = 8.1 Hz, COCH=), 6.86 (2H, d, J = 8.6 Hz, ArH), 7.21–7.29 (4H, m, ArH), 7.39 (1H, d, J = 8.1 Hz, H_8), 7.63 (2H, d, J = 8.6 Hz, ArH), 7.81 (1H, d, J = 8.1 Hz, H_7), 7.89 (1H, s, H_5), 8.32 (1H, d, J = 8.1 Hz, =CH–Ar); MS *m/z*: 404(M^+), 406(M + 2); Anal. Calcd. for $C_{24}H_{20}ClNO_3$: C, 71.02; H, 4.97; N, 3.45. Found: C, 71.21; H, 4.96; N, 3.46.

3-(4′-Methoxyphenyl)-1-[3-(4-methoxyphenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazine-6-yl] propenone (**3b**) mp: 123–125°C; R*f*: 0.53; IR (KBr) cm^{-1}: 1321, 1696, 1758; ^{1}H-NMR (ppm): 3.83 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.3 (2H, s, NCH_2), 4.95 (2H, s, OCH_2), 6.55 (1H, d, J = 8.6 Hz, COCH=), 6.64 (2H, d, J = 8.6 Hz, ArH), 7.2–7.43 (6H, m, H_7, H_8, ArH), 7.69 (2H, d, J = 8.6 Hz, ArH), 7.8 (1H, s, H_5), 8.62 (1H, d, J = 8.6 Hz, =CH–Ar); MS *m/z*: 400(M^+); Anal. Calcd. for $C_{25}H_{23}NO_4$: C, 74.80; H, 5.77; N, 3.49. Found: C, 74.92; H, 5.76; N, 3.48.

3-(2′-Hydroxyphenyl)-1-[3-(4-methoxyphenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazine-6-yl]-propenone (**3c**) mp: 112–14°C; R*f*: 0.47; IR (KBr) cm^{-1}: 1320, 1696, 1769; ^{1}H-NMR (ppm): 3.79 (3H, s, OCH_3), 3.99 (2H, s, NCH_2), 5.68 (2H, s, OCH_2), 6.78 (1H, d, J = 8.1 Hz, COCH=), 6.92–7.2 (4H, m, ArH), 7.32–7.48 (6H, m, H_7, H_8, ArH), 7.65 (1H, s, H_5), 8.56 (1H, d, J = 8.1 Hz, =CH–Ar), 11.07 (1H, s, OH); MS *m/z*: 386 (M^+); Anal. Calcd. for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.46; N, 3.62. Found: C, 74.56; H, 5.47; N, 3.61.

3-(3′,4′,5′-Trimethoxyphenyl)-1-[3-(4-methoxyphenyl)-3,4-dihydro-2H-benzo[e][1,3] oxazine-6-yl]-propenone (**3d**) mp: 108–10°C; R*f*: 0.41; IR (KBr) cm^{-1}: 1320, 1698, 1753; ^{1}H-NMR (ppm) 3.86 (12H, s, 4×OCH_3), 4.4 (2H, s, NCH_2), 5.20 (2H, s, OCH_2), 6.62 (1H, d, J = 8.6 Hz, COCH=), 6.74–6.77 (2H, m, ArH), 6.82 and 7.2 (4H, 2×d, J = 8.1 Hz each, ArH), 7.44 (1H, d, J = 8.1 Hz, H_8), 7.64 (1H, d, J = 8.1 Hz, H_7), 7.80 (1H, s, H_5), 8.42 (1H, d, J = 8.6 Hz, =CH–Ar); MS *m/z*: 460 (M^+); Anal. Calcd. for $C_{27}H_{27}NO_6$: C, 70.27; H, 5.90; N, 3.03. Found: C, 70.35; H, 5.91; N, 3.02.

3-(4′-Chlorophenyl)-1-[3-(4-methoxyphenyl)-3,4-dihydro-2H-benzo [e] [1,3] oxazine-6-yl] propenone (**3e**) mp: 134–37°C; R*f:* 0.62; IR (KBr) cm^{-1}: 1318, 1707, 1772; ^{1}H-NMR (ppm): 3.74 (3H, s, OCH_3), 4.21 (2H, s, NCH_2), 5.61 (2H, s, OCH_2), 6.60 (1H, d, J = 8.1 Hz, COCH=), 6.94 (2H, d, J = 8.6 Hz, ArH), 7.11–7.23 (4H, m, ArH), 7.42 (1H, d, J = 8.1 Hz, H_8), 7.56 (2H, d, J = 8.6 Hz, ArH), 7.64 (1H, d, J = 8.1 Hz, H_7), 7.75 (1H, s, H_5), 8.36 (1H, d, J = 8.1 Hz, =CH–Ar); MS *m/z*: 404(M^+), 406(M + 2); Anal. Calcd. for $C_{24}H_{20}ClNO_3$: C, 71.02; H, 4.97; N, 3.45. Found: C, 70.89; H, 4.98; N, 3.44.

3-(2′,4′-Dichlorophenyl)-1-[3-(4-methoxyphenyl)-3,4-dihydro-2H-benzo[e][1,3] oxazine-6-yl] propenone (**3f**) mp: 158–60°C; R*f:* 0.69; IR (KBr) cm^{-1}: 1316, 1700, 1769; ^{1}H-NMR (ppm): 3.65 (3H, s, OCH_3), 4.32 (2H, s, NCH_2), 5.66 (2H, s, OCH_2), 6.59 (2H, d, J = 8.6 Hz, ArH), 6.69 (1H, d, J = 8.1 Hz, COCH=), 6.96 (2H, d, J = 8.6 Hz, ArH), 7.09–7.18 (3H, m, ArH), 7.42 (1H, d, J = 8.1 Hz, H_8), 7.64 (1H, d, J = 8.1 Hz, H_7), 7.75 (1H, s, H_5), 8.16 (1H, d, J = 8.1 Hz, =CH–Ar); MS *m/z*: 439(M^+), 441(M + 2) Anal. Calcd. for $C_{24}H_{19}Cl_2NO_3$: C, 65.47; H, 4.35; N, 3.18. Found: C, 65.62; H, 4.36; N, 3.17.

3-(2′-Chlorophenyl)-1-[3-(4-methylphenyl)-3,4-dihydro-2H-benzo[e][1,3] oxazine-6-yl] propenone (**3g**) mp: 146–48°C; R*f:* 0.73; IR (KBr) cm^{-1}: 1324, 1679, 1757; ^{1}H-NMR (ppm): 2.21 (3H, s, CH_3), 4.5 (2H, s, NCH_2), 5.51 (2H, s, OCH_2), 6.46 (2H, d, J = 8.6 Hz, ArH), 6.90 (2H, d, J = 8.6 Hz, ArH), 7.18 (1H, d, J = 8.1, COCH=), 7.35–7.51 (6H, m, H_7, H_8, ArH), 7.60 (1H, s, H_5), 8.11 (1H, d, J = 8.1 Hz, =CH–Ar); MS *m/z*: 389(M^+), 391(M + 2); Anal. Calcd. for $C_{24}H_{20}ClNO_2$: C, 73.94; H, 5.17; N, 3.59. Found: C, 74.08; H, 5.18; N, 3.60.

3-(4′-Methoxyphenyl)-1-[3-(4-methylphenyl)-3,4-dihydro-2H-benzo[e][1,3] oxazine-6-yl] propenone (**3h**) mp: 100–02°C; R*f:* 0.49; IR (KBr) cm^{-1}: 1319, 1681, 1753; ^{1}H-NMR (ppm): 2.10 (3H, s, CH_3), 3.53 (3H, s, OCH_3), 4.48 (2H, s, NCH_2), 5.49 (2H, s, OCH_2), 6.66 (2H, d, J = 8.6 Hz, ArH), 6.89 (1H, d, J = 8.1, COCH=), 7.16 (2H, d, J = 8.6 Hz, ArH), 7.26 (1H, s, H_8), 6.37 (2H, d, J = 8.1 Hz, ArH), 7.59(1H, s, H_7), 7.69 (2H, d, J = 8.1 Hz, ArH), 7.80 (1H, s, H_5), 8.06 (1H, d, J = 8.1 Hz, =CH–Ar); MS *m/z*: 384(M^+); Anal. Calcd. for $C_{25}H_{23}NO_3$: C, 77.90; H, 6.01; N, 3.63. Found: C, 77.68; H, 6.00; N, 3.62.

3-(2′-Hydroxyphenyl)-1-[3-(4-methylphenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazine-6-yl] propenone (**3i**) mp: 137–40°C; R*f:* 0.61; IR (KBr) cm^{-1}: 1322, 1701, 1770; ^{1}H-NMR (ppm): 2.29 (3H, s, CH_3), 4.5 (2H, s, NCH_2), 5.58 (2H, s, OCH_2), 6.73 (1H, d, J = 8.1, COCH=), 6.81–6.94 (4H, m, ArH), 7.29 (1H, d, J = 8.1 Hz, H_8), 7.28 (2H, d, J = 8.5 Hz, ArH), 7.36 (1H, s, H_5), 7.40 (2H, d, J = 8.5 Hz, ArH), 7.72 (1H, d, J = 8.1 Hz, H_7), 8.21 (1H, d, J = 8.1 Hz, =CH–Ar), 11.16 (1H, s, OH); MS *m/z*: 370(M^+); Anal. Calcd. for $C_{24}H_{21}NO_3$: C, 77.61; H, 5.70; N, 3.77. Found: C, 77.52; H, 5.68; N, 3.76.

3-(3′,4′,5′-Trimethoxyphenyl)-1-[3-(4-methylphenyl)-3,4-dihydro-2H-benzo[e][1,3] oxazine-6-yl] propenone (**3j**) mp: 156–58°C; R*f:* 0.56; IR (KBr) cm^{-1}: 1321, 1700,

1773; ^{1}H-NMR (ppm): 2.37 (3H, s, CH_3), 3.64 (9H, s, 3×OCH_3), 4.2 (2H, s, NCH_2), 5.6 (2H, s, OCH_2), 6.69 (1H, d, J = 8.1, COCH=), 7.24 (2H, d, J = 8.5 Hz, ArH), 7.29–7.41 (2H, m, ArH), 7.56 (1H, d, J = 8.1 Hz, H_8), 7.61 (2H, d, J = 8.5 Hz, ArH), 7.70 (1H, d, J = 8.1 Hz, H_7), 7.79 (1H, s, H_5), 8.01 (1H, d, J = 8.1 Hz, =CH–Ar); MS *m/z*: 444(M^+); Anal. Calcd. for $C_{27}H_{27}NO_5$: C, 72.79; H, 6.11; N, 3.14. Found: C, 72.59; H, 6.12; N, 3.13.

3-(4′-Chlorophenyl)-1-[3-(4-methylphenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazine-6-yl] propenone (**3k**) mp: 98–100°C; R*f:* 0.44; IR (KBr) cm^{-1}: 1321, 1697, 1765; ^{1}H-NMR (ppm): 2.14 (3H, s, CH_3), 4.29 (2H, s, NCH_2), 5.60 (2H, s, OCH_2), 6.65 (1H, d, J = 8.1, COCH=), 6.82(2H, d, J = 8.5 Hz, ArH), 7.18 (2H, d, J = 8.6 Hz, ArH), 7.45 (2H, d, J = 8.6 Hz, ArH) 7.61(2H, m, H_5, H_7), 7.68 (2H, d, J = 8.6 Hz, ArH), 7.78 (1H, s, H_5), 8.12 (1H, d, J = 8.1 Hz, =CH–Ar); MS *m/z*: 389(M^+), 391(M + 2); Anal. Calcd. for $C_{24}H_{20}ClNO_2$: C, 73.94; H, 5.17; N, 3.59. Found: C, 73.78; H, 5.16; N, 3.58.

3-(2′,4′-Dichlorophenyl)-1-[3-(4-methylphenyl)-3,4-dihydro-2H-benzo[e][1,3]oxazine-6-yl] propenone (**3l**) mp: 134–36°C; R*f:* 0.71; IR (KBr) cm^{-1}: 1319, 1692, 1761; ^{1}H-NMR (ppm): 2.14 (3H, s, CH_3), 4.49 (2H, s, NCH_2), 5.62 (2H, s, OCH_2), 6.65 (1H, d, J = 8.1, COCH=), 7.18 (2H, d, J = 8.6 Hz, ArH), 7.31–7.45 (5H, m, H_7, H_8, ArH), 7.58 (2H, d, J = 8.6 Hz, ArH), 7.78 (1H, s, H_5), 8.12 (1H, d, J = 8.1 Hz, =CH–Ar); MS *m/z*: 423(M^+), 425(M + 2); Anal. Calcd. for $C_{24}H_{19}Cl_2NO_2$: C, 67.93; H, 4.51; N, 3.30. Found: C, 67.98; H, 4.52; N, 3.29.

Pharmacology

Protocol of animal experiments has been approved by the Institutional Animal Ethics Committee (IAEC). All the compounds synthesized were evaluated for their anti-inflammatory activity; most potent compounds were further evaluated for analgesic activity and ulcerogenic studies.

Anti-inflammatory activity

The anti-inflammatory activity was evaluated using carrageenan induced rat paw edema method (Winter *et al*., 1962). Wistar rats (150–200 g) were divided into groups of six animals each. Group I served control and was administered vehicle only, group II received ibuprofen 20 mg kg^{-1}, and other groups received test drugs in dose molecularly equivalent to the ibuprofen. Drug solutions were prepared as a homogeneous suspension in aqueous solution of sodium CMC (0.5% w/v) and were administered orally to the animals. The measurement of the hind paw volume was carried out using a Ugo Basile Plethysmometer before any treatment (V_o) and after 3 h of the administration of the drugs. All the results are expressed as mean ±S.E.M.

Analgesic activity

Compounds **3e**, **3f**, **3h**, and **3l** were tested for analgesic activity. Analgesic activity was carried out using acetic acid induced writhing method (Seigmund *et al*., 1957) in Swiss albino mice (25–30 g) of either sex at 20 mg kg^{-1} body weight. A 1% v/v solution of acetic acid was used as writhing inducing agent intraperitoneally. The analgesic effect was studied after 3 h of drug administration. Mice were divided into groups of six animals each. Number of writhings were counted for 10 min in control, standard and test compounds after acetic acid administration and compared. Analgesic activity was measured as percent decrease in writhings in comparison to control. All the results are expressed as mean ±S.E.M.

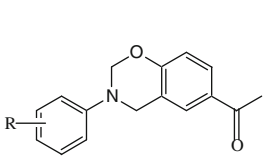
Acute ulcerogenesis

The studies were carried out on healthy Wistar rats (150–200 g) at a dose three times the anti-inflammatory dose viz 60 mg kg^{-1}. The animals were divided into different groups of six each, group I served as control and received vehicle only and groups II received pure ibuprofen 60 mg kg^{-1}. Other groups were administered test compounds in dose molecularly equivalent to 60 mg kg^{-1} of ibuprofen. The ulcerogenic activity was carried out according to the reported method (Cioli *et al*., 1979). The mean score of each treated group minus the mean score of the control group was considered as the "severity index" (SI) of gastric damage.

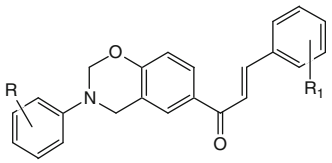
Results and discussion

3-Phenyl-1-(3-phenyl-3,4-dihydro-2*H*-benzo[e][1,3]oxazin-6-yl)propenone derivatives described in the study are shown in Table 1, and the reaction sequence for the preparation is outlined in Scheme 1. The study compared the conventional method of synthesis with the microwave-assisted synthesis of benzoxazine derivatives. It was observed the use of microwave not only reduces the time of reaction but also improves the yield in solvent-free conditions. The required intermediate 3-aryl-6-acetyl 1,3-benzoxazine (**2a–b**) were synthesized by Mannich type aminomethylation reaction by condensing 4-hydroxy acetophenone with primary aromatic amines in the presence of formaldehyde. The corresponding chalcone derivatives (**3a–l**) were synthesized by base-catalyzed Claisen Schmidt condensation of the acetyl 1,3-benzoxazines with aromatic aldehydes. Spectral data of all the newly synthesized

Table 1 Physical constants of the newly synthesized 1,3 benzoxazines derivatives



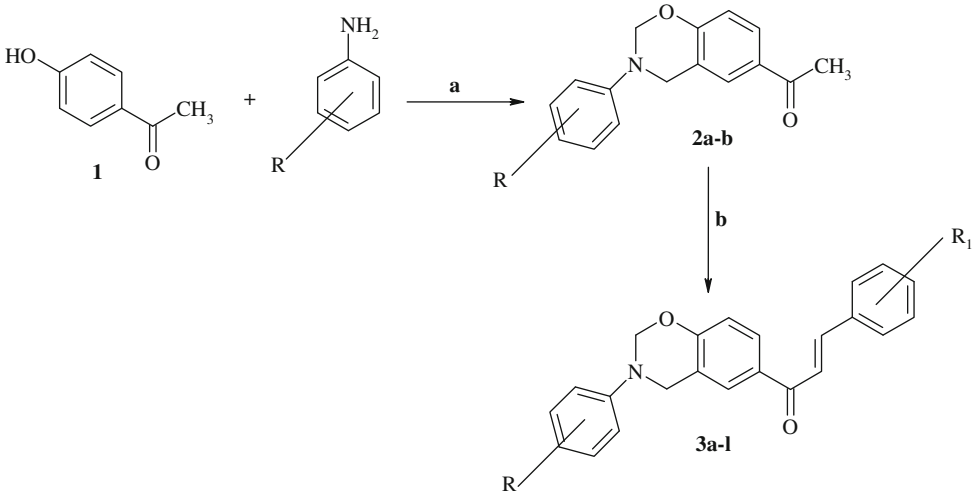
2a-b



3a-l

Compd	*R*	R_1	m.p. (°C)	R*f*	Conventional method		Microwave method	
					Time (h)	Yield (%)	Time (min)	Yield (%)
2a	4-OCH_3	–	144–46	0.85	2	64	–	–
2b	4-CH_3	–	134–36	0.71	2	59	–	–
3a	4-OCH_3	2-Cl	125–27	0.46	8	54	6	68
3b	4-OCH_3	4-OCH_3	123–25	0.53	10	45	4	59
3c	4-OCH_3	2-OH	112–14	0.47	10	44	6	60
3d	4-OCH_3	3,4,5 $(OCH_3)_3$	108–10	0.41	12	46	4	58
3e	4-OCH_3	4-Cl	134–37	0.62	10	57	6	69
3f	4-OCH_3	2,4-$(Cl)_2$	158–60	0.69	14	52	6	69
3g	4-CH_3	2-Cl	146–48	0.73	11	58	6	71
3h	4-CH_3	4-OCH_3	100–02	0.49	12	41	4	70
3i	4-CH_3	2-OH	137–40	0.61	10	45	6	67
3j	4-CH_3	3,4,5 $(OCH_3)_3$	156–58	0.56	8	58	4	74
3k	4-CH_3	4-Cl	98–100	0.44	14	39	6	56
3l	4-CH_3	2,4-$(Cl)_2$	134–36	0.71	10	34	4	57

Scheme 1 Reagents and conditions: **a** formaldehyde, methanol, reflux and **b** EtOH, substituted aromatic aldehydes, 25% KOH, reflux



compounds were in full agreement with the proposed structures. In general, Infra Red spectra (IR) revealed C=O and C–N peaks in the range of 1650–1750 and 1280–1340 cm^{-1}, respectively. In the Nuclear Magnetic Resonance spectra (^{1}H-NMR), the signals of the respective protons of the prepared titled compounds were verified on the basis of their chemical shifts, multiplicities, and coupling constants. The spectra showed two singlets in the range of δ 3.99–4.6 and 4.9–5.68 ppm corresponding to NCH_2 and OCH_2 groups of oxazine ring, respectively; two doublets in the range of at δ 6.55–7.18 and 8.01–8.62 ppm corresponding to protons of CO–CH and =CH–Ar of the chalcone moiety, respectively.

All the newly synthesized compounds were screened for their anti-inflammatory, analgesic activity, and ulcerogenic effects. The inhibition of swelling in carrageenan induced edema in rat paw brought about by oral administration of the drugs is shown in Table 2. The percentages of swelling of the drugs were calculated using Eq. (1).

Table 2 Anti-inflammatory and analgesic evaluation of compound **3a–l**

Compd	Anti-inflammatory		Analgesic[b]	Ulcerogenic effect[b]
	Paw volume ± SEM[a]	%Inhibition ± SEM[b]		
3a	0.24 ± 0.07**	63.43 ± 10.54	–	–
3b	0.26 ± 0.06**	61.19 ± 10.14	–	–
3c	0.29 ± 0.01**	55.72 ± 2.24*	–	–
3d	0.25 ± 0.02**	62.18 ± 2.39	–	–
3e	0.22 ± 0.02**	67.41 ± 2.76	52.22 ± 1.69**	0.25 ± 0.12*
3f	0.17 ± 0.02**	74.87 ± 3.16	57.38 ± 1.17	0.08 ± 0.08**
3g	0.26 ± 0.01**	60.44 ± 1.88	–	–
3h	0.19 ± 0.07**	70.39 ± 10.09	54.27 ± 1.2**	0.17 ± 0.11**
3i	0.33 ± 0.02**	50.99 ± 2.73**	–	–
3j	0.29 ± 0.04**	56.46 ± 5.54*	–	–
3k	0.24 ± 0.02**	63.43 ± 2.90	–	–
3l	0.19 ± 0.06**	71.89 ± 8.72	55.47 ± 1.06**	0.17 ± 0.11**
Control	0.67 ± 0.04	–	–	0.0 ± 0.0
Ibuprofen	0.12 ± 0.03**	82.33 ± 4.45	63.06 ± 2.46	1 ± 0.32

* $P < 0.05$; ** $P < 0.01$

[a] Relative to their respective control and data were analyzed by one-way ANOVA followed by Dunnett's test for $n = 6$

[b] Relative to the standard (Ibuprofen) and data were analyzed by one-way ANOVA followed by Dunnett's test for $n = 6$

$$\text{Inhibition } (\%) = \left\{ \left[(V_t - V_o)_{\text{contol}} - (V_t - V_o)_{\text{treated}} \right] / (V_t - V_o)_{\text{contol}} \right\} \times 100 \quad (1)$$

(V_t and V_o relates to the average volume in the hind paw of the rats ($n = 6$) before any treatment and after anti-inflammatory agent treatment, respectively). All the synthesized compounds tested for anti-inflammatory activity showed inhibition of edema ranging from 50.99 to 74.87%. Compound **3f**, **3h**, and **3l** were found to be most potent compounds with percent inhibition of 74.87, 70.39, and 71.89, respectively. The one-way ANOVA test was applied, and test compounds were found to be significantly active compared to the control.

Analgesic activity was carried out on albino mice by Seigmund *et al*., 1957 method. Compounds (**3e**, **3f**, **3h**, and **3l**) showing more than 80% of inhibition of ibuprofen in swelling induced by carrageenan were further tested for analgesic activity at the same dose as used for anti-inflammatory activity. The percent protection was calculated using Eq. (2)

$$\text{Protection}(\%) = 100 - (\text{no. of writhings in test}/\text{no. of writhing in control}) \times 100 \quad (2)$$

The compounds tested showed analgesic activity in the range of 52.22–57.38% with compound **3f** the most active (57.38%) (Table 2).

The most active compounds were also tested for their gastric irritation, and it was found that these agents were less irritant to gastric mucosa than the standard as indicated by the SI. The tested compounds (**3e**, **3f**, **3h**, and **3l**) showed SI ranging from 0.08 to 0.25 in comparison to 1.0 of standard.

Conclusion

All the compounds have been synthesized by conventional method and microwave method successfully. It was observed that the solvent-free microwave thermolysis is a convenient, rapid, high-yielding, and environmental friendly protocol for the synthesis of benzoxazines when compared with conventional reaction in a solution phase. Further compound, **3f** was found to be most active and safe anti-inflammatory and analgesic agents and could be used to develop more potent and safe anti-inflammatory and analgesic agents.

Acknowledgments One of the authors Mymooona Akhter is thankful to UGC for financial support. The authors are grateful to Janab Abdul Mueed for providing infrastructure and facility to carry out this work.

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