Original Article

Design, syntheses, characterization, and evaluation of 2-substituted-1,3-bis(1-naphthylmethyl)-imidazolidine derivatives in search of safer nonsteroidal anti-inflammatory drugs

Abstract

Background: 1,2,3-trisubstituted imidazolidines are reported to have better anti-inflammatory activity than the reference drug indomethacin. Similarly, naphthalene nucleus plays a significant role in the drug design. Nabumetone and naproxen are naphthalene nucleus containing anti-inflammatory drugs available in the market. There are also reports that compounds having two naphthalene rings incorporated with a heterocyclic nucleus have good medicinal value. Based on these reports it was planned to synthesize hybrid compounds containing two naphthalene rings with imidazolidine nucleus. **Aim:** To obtain potent compounds having anti-inflammatory and analgesic activities with reduced gastrointestinal side effects. **Materials and Methods:** The reaction scheme includes the reaction between 1-naphthaldehyde with ethylenediamine to obtain diSchiff's base (1) Reduction of this diSchiff's base with $NaBH_4$ gave tetrahydrodiSchiff's base (2) Further cyclization of 2 with appropriate aldehyde in the presence of ethanol formed 2-substituted-1,3-bis(1-naphthylmethyl)-imidazolidine derivatives (3a-n). The structures of these compounds were established on the basis of spectral data. All these compounds were tested for their anti-inflammatory, analgesic, ulcerogenic, and lipid peroxidation activities. **Results and Discussion:** The tested compounds (3a-n) showed anti-inflammatory activity ranging between 27.61% and 53.43%. The compound 3h showed the highest activity of 53.43% and 3n showed 53.02% inhibition at 20 mg/kg dose in rats compared with the standard drug indomethacin which showed 61.45% inhibition at the same dose. It was encouraging to note that both the compounds showed reduced ulcerogenic activity (less than half) compared to the standard drug indomethacin.

Key words:
Anti-inflammatory, imidazolidine, lipid peroxidation, naphthalene, ulcerogenic

Introduction

The five-membered nitrogen heterocycles are the most researchable, advanced topic at this time. They constitute a greater part of many synthetic and biological drugs. Among these, the imidazole nucleus is a part of several natural products (pilocarpine, pilosine, etc.) and serves as a lead compound. As a lead compound, it acts as a primary molecular scaffold upon which characteristic pharmacophores[1,2] can be assembled to create several drugs. Examples are antithrombolytic (anagrelide), antibacterial (azlocillin), muscle relaxant (dantrolene), anticonvulsant (ethotoin) etc. According to the literature survey, imidazolidine derivatives are key components in the development of bioactive compounds for the treatment of many diseases, such as hypertension, neoplasia, inflammation, and nasal decongestion.[3] Our previous work has shown that 1,2,3-trisubstituted imidazolidines (a) have

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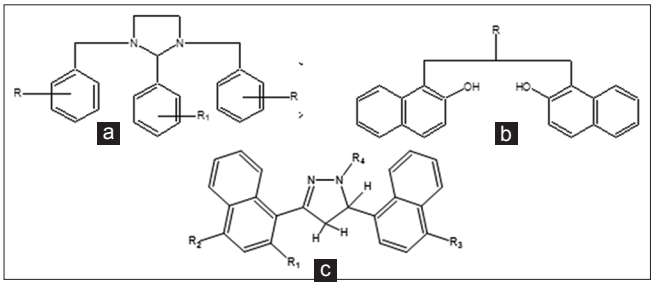
better anti-inflammatory activity than the reference drug indomethacin.[4] Similarly, the naphthalene nucleus plays a significant role in drug design. This nucleus is reported to have numerous biological activities, such as anti-inflammatory, antibacterial, and antimicrobial. Nabumetone and naproxen are naphthalene nucleus containing anti-inflammatory drugs available in the market. There are reports that the incorporation of the naphthalene nucleus in a compound increases its biological activity.[5,6] During the literature survey, it was also found that compounds containing two naphthalene rings (b) have significant anti-inflammatory activity. There are reports that compounds having two naphthalene rings incorporated with a heterocyclic nucleus (c) also have medicinal value.[7-10] Based on above reports, it was planned to synthesize hybrid compounds containing two naphthalene rings and an imidazolidine nucleus with the aim of obtaining compounds having good anti-inflammatory and analgesic activities with reduced gastrointestinal side effects. It is reported that nonsteroidal anti-inflammatory drugs (NSAIDs) are used as anti-inflammatory, antipyretic, and analgesic agents, but they cause gastrointestinal bleeding along with other adverse effects.

We hereby report the syntheses of 14 new 2-substituted-1, 3-bis(1-naphthylmethyl)-imidazolidines (3a-n). The scheme followed in synthesizing these compounds consisted of preparing diSchiff's base by reacting ethylenediamine with 1-naphthaldehyde. The obtained diSchiff's base was reduced with $NaBH_4$ to get the tetrahydro diSchiff's base. Finally, this derivative was condensed with the appropriate aldehyde to obtain the corresponding naphthalene-incorporated imidazolidine. The structures of all these compounds were established on the basis of infrared (IR) spectroscopy, nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectroscopy and mass spectral data. These compounds were evaluated for their anti-inflammatory, analgesic, ulcerogenic, and lipid peroxidation activities. Indomethacin and aspirin were used as reference compounds for evaluating anti-inflammatory and analgesic activities, respectively.



Materials and Methods

The chemicals and solvents used for the experimental work were commercially procured from different chemical suppliers, such as E. Merck India Ltd. Mumbai (India), S.D. Fine-Chem Ltd. Mumbai (India), CDH Mumbai (India), and Qualigens, Mumbai (India). The solvents and reagents were of laboratory reagent grade. All the synthesized compounds were dried in vacuum desiccators over silica gel. The melting point (m.p.) of each compound was determined using open capillary tubes in the HICON digital instrument (India). Elemental analysis was performed on the vario EL III CHNOS analyzer, Hanau (Germany) using sulfanilic acid as a standard. Completion of the reaction was monitored using thin-layer chromatography (TLC). The spots were visualized either by exposing the developed and dried plates to iodine vapors or in the ultraviolet (UV) chamber. The IR spectra of the synthesized compounds were recorded in the region 4000-400/cm range using potassium bromide (KBr) discs on the Fourier transform IR Shimadzu 8400S spectrometer, (Japan), with a resolution of 8 cm^{-1} and a total number of 20 scans. The ^{1}H NMR spectra of the compounds were recorded on the Bruker DPX-300 NMR spectrometer (Germany) at 300 MHz and some at 400 MHz, using deutero-dimethyl sulfoxide (DMSO-d_6) as solvent. The ^{13}C NMR spectra of compounds were recorded on the Bruker DPX-300 NMR spectrometer, using DMSO-d_6 as solvent. Tetramethylsilane was used as an internal standard, and the values of the chemical shift were given in the δ scale. Mass spectra of the compounds were recorded using a Perkin-Elmer 500 spectrometer, Edinburgh (UK).

Synthesis of *N*, *N*'-bis(1-naphthylmethylene) ethane-1, 2-diamine (1)

A mixture of 1-naphthaldehyde (5.4 mL, 0.04 mol) and ethylenediamine (1.5 mL, 0.02 mol) in dry benzene (30 mL) was refluxed in a round-bottomed flask after fitting the Dean-Stark apparatus in order to remove the water azeotropically. After removal of water, the reaction mixture was refluxed for another 8 h and then left at room temperature overnight. A brownish white compound crystallized out, which was filtered and recrystallized from methanol to give pure, yellow crystals (1), m.p. 116–118°C, yield (4.78 g, 71%).

^{1}H NMR (DMSO-d_6) δ (ppm): 4.04 (s, 4H, 2×CH_2), 7.36-7.64 (m, 8H, naphthalene), 7.79-8.14 (m, 6 h, naphthalene), 8.98 (s, 2H, aldimine protons).

Synthesis of *N*, *N*'-bis(1-naphthylmethyl) ethane-1, 2-diamine (2)

The above diSchiff's base (1) (3.36 g, 0.01 mol) was dissolved in a mixture of methanol and dichloromethane (30 mL + 10 mL). A solution of sodium borohydride (1.0 g) in 2N NaOH solution (2.0 mL) was diluted with water (12.0 mL). This solution was added to the solution of (1) while stirring magnetically under ice-cold conditions at such a rate that the reaction temperature did not rise above 18°C. The contents were then stirred for 7 h. After completion of the reaction, methanol was distilled off, and the residue was diluted with water (25.0 mL). It was then extracted with diethyl ether (3 × 20 mL). The ethereal layer was dried

over sodium sulfate. After filtering off the inorganic salt, the ether was distilled off. A yellowish white solid mass was obtained. The purity of the tetrahydrodiSchiff's base was checked by TLC using benzene: acetone (8:2) as mobile phase, m.p. 68–70°C, yield (2.21 g, 65%).

^{1}H NMR (DMSO-d_6) δ (ppm): 2.13 (s, 2H, NH) 2.50 (s, 4H, 2×CH_2), 4.11 (s, 4H, 2×CH_2, naphthylmethylene), 7.38–7.65 (m, 8H, naphthalene), 7.76–8.12 (m, 6H, naphthalene).

General method for the synthesis of 2-substituted-1, 3-bis(1-naphthylmethyl)-imidazolidine (3a-n)

Compound 2 (0.680 g, 0.002 mol) was dissolved in absolute alcohol (12 mL) in a flat-bottomed flask. To this solution, an equimolar amount of appropriate aldehyde was added, and the mixture was stirred on a magnetic stirrer for 6 h. It was then left in a refrigerator overnight. A solid mass thus formed was filtered, washed with ethanol, and dried, giving 3a-n.

2-(Phenyl)-1, 3-bis(1-naphthylmethyl)-imidazolidine (3a):

Fourier transform infrared (KBr pellet) cm^{-1}: 3186 (aromatic C-H stretch), 2869 (aliphatic C-H stretch), 1596, 1560, 1524 (C = C ring stretch), 1307 (C-N ring stretch), 748 (C-N bending). ^{1}H NMR (DMSO-d_6) δ (ppm): 2.50, 2.63 (m, 4H, 2×CH_2, imidazolidine), 3.58, 3.62 (d, 4H, *J* =3.9 Hz, 2×CH_2, naphthylmethylene) 4.12 (s, CH, imidazolidine), 7.32 (m, 2H, naphthalene), 7.40–7.55 (m, 5H, ArH), 7.60–7.66 (m, 6H, naphthalene), 7.73–7.86 (m, 6H, naphthalene). ^{13}C NMR (DMSO-d_6) δ (ppm): 138.4 (1C), 137.5 (2C), 137.2 (2C), 129.8 (2C), 128.3 (2C), 128.1 (2C), 127.7 (1C), 126.9 (2C), 126.1 (2C), 122.4 (2C), 122.1 (2C), 120.3 (2C), 118.6 (2C), 116.9 (2C), 88.1 (1C), 52.2 (2C), 43.7 (2C). MS: m/z 428 (M+), 351, 300, 287, 141, 91, 65. Anal. Calcd for $C_{31}H_{28}N_2$: C, 86.88; H, 6.59; N, 6.54; Found C, 86.40; H, 6.61; N, 6.48%.

2-(1-Naphthyl)-1,3-bis(1-naphthylmethyl)-imidazolidine (3b)

Fourier transform infrared (KBr pellet) cm^{-1}: 3016 (aromatic C-H stretch), 2885 (aliphatic C-H stretch), 1623, 1492, 1469 (C = C ring stretch), 1272 (C-N ring stretch), 806 (C-N bending). ^{1}H NMR (DMSO-d_6) δ (ppm): 2.48, 2.90 (m, 4H, 2×CH_2, imidazolidine), 3.75, 4.09 (d, 4H, 2×CH_2, naphthylmethylene) 5.03 (s, CH, imidazolidine), 7.27–8.47 (m, 21H, naphthalene). ^{13}C NMR (DMSO-d_6) δ (ppm): 139.7 (1C), 137.3 (2C), 129.6 (3C), 128.5 (3C), 127.6 (3C), 126.5 (1C), 126.1 (2C), 121.4 (3C), 121.0 (3C), 120.4 (3C), 118.6 (3C), 117.3 (3C), 89.3 (1C), 52.1 (2C), 43.8 (2C).

2-(2-Hydroxyphenyl)-1,3-bis(1-naphthylmethyl)-imidazolidine (3c)

Fourier transform infrared (KBr pellet) cm^{-1}: 3382 (OH), 3089 (aromatic C-H stretch), 2923 (aliphatic C-H stretch), 1623, 1496, 1454 (C = C ring stretch), 1272 (C-N ring stretch), 1188 (C-O), 748 (C-N bending). ^{1}H NMR (DMSO-d_6) δ (ppm): 2.49, 2.71 (m, 4H, 2×CH_2, imidazolidine), 4.47, 5.25 (d, 4H, 2×CH_2, naphthylmethylene) 5.65 (s, CH, imidazolidine), 5.98 (s, 1H, OH), 7.30 (m, 2H, naphthalene), 7.38-7.48 (m, 4H, ArH), 7.50-8.60 (m, 12H, naphthalene). ^{13}C NMR (DMSO-d_6) δ (ppm): 142.7 (1C), 138.5 (2C), 137.2 (2C), 129.8 (1C), 128.3 (2C), 128.1 (2C), 127.9 (2C), 126.8 (2C), 126.1 (2C), 123.4 (2C), 122.3 (1C), 121.0 (2C) 120.5 (2C), 117.6 (2C), 114.3 (1C), 88.1 (1C), 52.2 (2C), 43.7 (2C).

2-(4-Methoxyphenyl)-1,3-bis(1-naphthylmethyl)-imidazolidine (3d)

Fourier transform infrared (KBr pellet) cm^{-1}: 3039 (aromatic C-H stretch), 2862 (aliphatic C-H stretch), 1623, 1550, 1527 (C = C ring stretch), 1307 (C-N ring stretch), 1207 (C-O), 744 (C-N bending). ^{1}H NMR (DMSO-d_6) δ (ppm): 2.48, 2.74 (m, 4H, 2×CH_2, imidazolidine), 3.56, 3.80 (d, 4H, 2×CH_2, naphthylmethylene), 4.09 (s, 3H, OCH_3), 4.38 (s, CH, imidazolidine), 7.07 (dd, 2H, *J* =6.9 Hz, *J* =2.1 Hz, ArH), 7.12 (dd, 2H, *J* =5.7 Hz, *J* =1.8 Hz, ArH), 7.33-7.98 (m, 14H, naphthalene).

^{13}C NMR (DMSO-d_6) δ (ppm): 143.8 (1C), 137.4 (2C), 136.7 (2C), 131.5 (1C), 130.6 (2C), 128.6 (2C), 128.3 (2C), 127.2 (2C), 126.3 (2C), 122.5 (2C), 122.0 (2C), 121.3 (2C), 119.7 (2C), 118.4 (2C), 86.4 (1C), 54.7 (1C), 53.2 (2C), 44.3 (2C). MS: m/z 458 (M+), 351, 330, 317, 141, 121.

2-(4-Dimethylaminophenyl)-1,3-bis (1-naphthylmethyl) -imidazolidine (3e)

Fourier transform infrared (KBr pellet) cm^{-1}: 3043 (aromatic C-H stretch), 2854 (aliphatic C-H stretch), 1623, 1550, 1527 (C = C ring stretch), 1305 (C-N ring stretch), 748 (C-N bending). ^{1}H NMR (DMSO-d_6) δ (ppm): 2.48, 2.98 (m, 4H, 2×CH_2, imidazolidine), 2.73 (s, 6H, 2×CH_3), 3.71, 3.82 (d, 4H, 2×CH_2, naphthylmethylene), 4.95 (s, CH, imidazolidine), 7.27 (dd, 2H, *J* = 7.2 Hz, *J* = 2.4 Hz, ArH), 7.40 (dd, 2H, *J* = 5.4 Hz, *J* = 1.8 Hz, ArH), 7.77–8.47 (m, 14H, naphthalene). ^{13}C NMR (DMSO-d_6) δ (ppm): 140.1 (1C), 134.2 (2C), 132.3 (2C), 129.3 (2C), 128.4 (2C), 127.7 (2C), 127.2 (1C), 126.8 (2C), 126.1 (2C), 122.9 (2C), 122.4 (2C), 120.6 (2C), 118.3 (2C), 117.4 (2C), 87.8 (1C), 51.6 (2C), 42.9 (2C), 38.1 (2C).

2-(4-Chlorophenyl)-1,3-bis(1-naphthylmethyl)-imidazolidine (3f)

Fourier transform infrared (KBr pellet) cm^{-1}: 3047 (aromatic C-H stretch), 2854 (aliphatic C-H stretch), 1623, 1527, 1477 (C = C ring stretch), 1292 (C-N ring stretch), 802 (C-N bending), 705 (C-Cl). ^{1}H NMR (DMSO-d_6) δ (ppm): 2.50, 2.63 (m, 4H, 2×CH_2, imidazolidine), 3.88, 4.20, (d, 4H, 2×CH_2, naphthylmethylene) 4.47 (s, CH, imidazolidine), 7.16 (dd, 2H, *J* = 5.1 Hz, *J* = 1.8 Hz, ArH), 7.33 (dd, 2H, *J* = 6.1 Hz, *J* = 2.4 Hz, ArH), 7.42-8.19 (m, 14H, naphthalene). ^{13}C NMR (DMSO-d_6) δ (ppm): 136.1 (1C), 133.7 (2C), 132.1 (2C), 127.9 (2C), 127.6 (2C), 126.5 (2C), 126.0 (1C), 125.2 (2C), 123.7 (2C), 122.6 (2C), 121.1 (2C), 120.6 (2C), 118.8 (2C), 117.2 (2C), 88.2 (1C), 52.4 (2C), 43.7 (2C). MS: m/z 465 (M + 2), 463 (M+), 351, 334, 321, 141, 125.

2-(3, 4-Dimethoxyphenyl)-1, 3-bis(1-naphthylmethyl) -imidazolidine (3g)

Fourier transform infrared (KBr pellet) cm^{-1}: 3085 (aromatic C-H stretch), 2850 (aliphatic C-H stretch), 1623, 1492, 1469 (C = C ring stretch), 1272 (C-N ring stretch), 752 (C-N bending). ^{1}H NMR (DMSO-d_6) δ (ppm): 2.53, 2.74 (m, 4H, 2×CH_2, imidazolidine), 3.29, 3.38 (d, 4H, 2×CH_2, naphthylmethylene), 3.94 (s, 6H, 2×OCH_3), 4.38 (s, CH, imidazolidine), 7.09–7.33 (m, 3H, ArH), 7.38-7.98 (m, 14H, naphthalene). ^{13}C NMR (DMSO-d_6) δ (ppm): 137.6 (1C), 137.4 (1C), 134.8 (2C), 131.6 (2C), 131.2 (2C), 129.2 (2C), 128.0 (1C), 127.5 (1C), 126.2 (2C), 126.0 (2C), 123.6 (2C), 122.4 (2C), 121.1 (2C), 118.7 (2C), 116.5 (2C), 87.3 (1C), 53.1 (2C), 51.6 (2C),41.4 (2C). MS: m/z 488 (M+), 360, 351, 347, 151, 141.

2-(3-Nitrophenyl)-1,3-bis(1-naphthylmethyl)-imidazolidine (3h)

Fourier transform infrared (KBr pellet) cm^{-1}: 3213 (aromatic C-H stretch), 2854 (aliphatic C-H stretch), 1604, 1577, 1539 (C = C ring stretch), 1261 (C-N ring stretch), 756 (C-N bending). ^{1}H NMR (DMSO-d_6) δ (ppm): 2.56, 2.71 (m, 4H, 2×CH_2, imidazolidine), 3.58, 3.62 (d, 4H, 2×CH_2, naphthylmethylene) 4.32 (s, CH, imidazolidine), 7.34–7.66 (m, 14H, naphthalene), 7.73-7.79 (m, 4H, ArH). ^{13}C NMR (DMSO-d_6) δ (ppm): 146.1 (1C), 141.9 (1C), 140.7 (1C), 140.2 (1C), 132.7 (2C), 129.6 (2C), 128.5 (2C), 127.7 (2C), 126.8 (2C), 126.4 (2C), 124.6 (1C), 123.2 (1C), 122.8 (2C), 120.2 (2C), 117.6 (2C), 117.1 (2C), 88.1 (1C), 52.2 (2C), 43.9 (2C).

2-(4-Nitrophenyl)-1,3-bis(1-naphthylmethyl) -imidazolidine (3i)

Fourier transform infrared (KBr pellet) cm^{-1}: 3066 (aromatic C-H stretch), 2927 (aliphatic C-H stretch), 1654, 1639 (C = C ring stretch), 1319 (C-N ring stretch), 748 (C-N bending). ^{1}H NMR (DMSO-d_6) δ (ppm): 2.57, 2.78 (m, 4H, 2×CH_2, imidazolidine), 3.52, 3.62 (d, 4H, 2×CH_2, naphthylmethylene) 4.34 (s, CH, imidazolidine), 7.32-7.63 (m, 14H, naphthalene), 7.73 (dd, 2H, *J* = 5.7 Hz, *J* = 2.1 Hz, ArH), 7.84 (dd, 2H, *J* = 6.1 Hz, *J* = 1.8 Hz, ArH). ^{13}C NMR (DMSO-d_6) δ (ppm): 136.4 (1C), 135.2 (1C), 134.1 (2C), 129.8 (2C), 128.9 (2C), 128.5 (2C), 127.8 (2C), 124.6 (2C), 123.5 (2C), 121.6 (2C), 119.8 (2C), 119.3 (2C), 118.2 (2C), 115.9 (2C), 86.2 (1C), 53.6 (2C), 42.7 (2C).

2-(4-Hydroxyphenyl)-1,3-bis(1-naphthylmethyl)-imidazolidine (3j)

Fourier transform infrared (KBr pellet) cm^{-1}: 3344 (O-H), 3047 (aromatic C-H stretch), 2941 (aliphatic C-H stretch), 1596, 1508, 1434 (C = C ring stretch), 1249 (C-N ring stretch), 1215 (C-O), 779 (C-N bending). ^{1}H NMR (DMSO-d_6) δ (ppm): 2.43, 2.76 (m, 4H, 2×CH_2, imidazolidine), 4.41, 5.21 (d, 4H, 2×CH_2, naphthylmethylene) 5.65 (s, CH, imidazolidine), 5.97 (s, 1H, OH), 7.26 (m, 2H, naphthalene), 7.32 (dd, 2H, *J* = 6.1 Hz, *J* = 2.1 Hz, ArH), 7.45 (dd, 2H, *J* = 5.4 Hz, *J* = 1.8 Hz, ArH), 7.54–8.42 (m, 12H, naphthalene). ^{13}C NMR (DMSO-d_6) δ (ppm): 143.7 (1C), 132.0 (2C), 131.5 (2C), 128.6 (2C), 128.3 (2C), 128.1 (1C), 127.0 (2C), 126.6 (2C), 124.4 (2C), 122.3 (2C), 121.4 (2C), 120.5 (2C), 119.7 (2C), 118.3 (2C), 86.2 (1C), 54.6 (2C), 45.3 (2C). MS: m/z 444 (M+), 351, 316, 303, 141, 107.

2-(2-Furanyl)-1,3-bis(1-naphthylmethyl) -imidazolidine (3k)

Fourier transform infrared (KBr pellet) cm^{-1}: 3109 (aromatic C-H stretch), 2885 (aliphatic C-H stretch), 1608, 1577, 1524 (C = C ring stretch), 1384 (C-N imide ring stretch), 1265 (asymmetric C-O-C), 752 (C-N bending). ^{1}H NMR (DMSO-d_6) δ (ppm): 2.49, 2.62 (m, 4H, 2×CH_2, imidazolidine), 3.54, 3.71 (d, 4H, 2×CH_2, naphthylmethylene) 4.76 (s, CH, imidazolidine), 6.97-7.10 (m, 3H, furan), 7.28-7.76 (m, 14H, naphthalene). ^{13}C NMR (DMSO-d_6) δ (ppm): 146.5 (1C), 141.8 (1C), 129.4 (2C), 128.1 (2C), 126.3 (2C), 125.2 (2C), 124.6 (2C), 123.5 (2C), 121.6 (2C), 121.4 (2C), 120.7 (2C), 116.2 (2C), 112.6 (1C), 110.3 (1C), 88.4 (1C), 51.2 (2C), 46.2 (2C). MS: m/z 418 (M+), 351, 290, 277, 141, 81.

2-(4-Hydroxy-3-methoxyphenyl)-1,3-bis(1-naphthylmethyl)-imidazolidine (3l)

Fourier transform infrared (KBr pellet) cm^{-1}: 3398 (O-H), 3043 (aromatic C-H stretch), 2854 (aliphatic C-H stretch), 1704 (C = O), 1523, 1527, 1481 (C = C ring stretch), 1292 (C-N ring stretch), 1207 (C-O stretch), 748 (C-N bending). ^{1}H NMR (DMSO-d_6) δ (ppm): 2.53, 2.74 (m, 4H, 2×CH_2, imidazolidine), 3.38, 3.52 (d, 4H, 2×CH_2, naphthylmethylene), 3.94 (s, 3H, OCH_3), 4.38 (s, CH, imidazolidine), 7.07-7.12 (m, 3H, ArH), 7.36-7.87 (m, 14H, naphthalene), 9.85 (s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ (ppm): 145.2 (1C), 141.4 (1C), 141.1 (1C), 133.2 (2C), 129.2 (2C), 128.6 (2C), 127.8 (2C), 127.4 (2C), 126.6 (2C), 126.2 (2C), 123.1 (1C), 122.7 (2C), 121.6 (2C), 119.1 (1C), 118.7 (1C), 117.2 (2C), 84.3 (1C), 50.6 (2C), 46.3 (1C), 43.7 (2C).

2-(4-Fluorophenyl)-1,3-bis(1-naphthylmethyl)-imidazolidine (3m)

Fourier transform infrared (KBr pellet) cm^{-1}: 3228 (aromatic C-H stretch), 2842 (aliphatic C-H stretch), 1539, 1515, 1428 (C = C ring stretch), 1384 (C-F), 1269 (C-N ring stretch), 748 (C-N bending). ^{1}H NMR (DMSO-d_6) δ (ppm): 2.51, 2.63 (m, 4H, 2×CH_2, imidazolidine), 3.67, 3.82 (d, 4H, 2×CH_2, naphthylmethylene) 4.78 (s, CH, imidazolidine), 7.04 (dd, 2H, *J* = 6.9 Hz, *J* = 2.1 Hz, ArH), 7.45 (dd, 2H, *J* = 5.7 Hz, *J* = 1.8 Hz, ArH), 7.60-7.94 (m, 14H, naphthalene). ^{13}C NMR (DMSO-d_6) δ (ppm): 148.6 (1C), 136.8 (2C), 136.0 (1C), 131.2 (2C), 127.5 (2C), 127.1 (2C), 126.2 (2C), 124.8 (2C), 124.6 (2C), 123.4 (2C), 122.8 (2C), 119.6 (2C), 118.9 (2C), 116.6 (2C), 88.1 (1C), 51.8 (2C), 46.3 (2C).

2-(2-Chlorophenyl)-1,3-bis(1-naphthylmethyl) -imidazolidine (3n)

Fourier transform infrared (KBr pellet) cm^{-1}: 3082 (aromatic C-H stretch), 2858 (aliphatic C-H stretch), 1596, 1527,

1473 (C = C ring stretch), 1307 (C-N ring stretch), 848 (C-Cl stretch), 750 (C-N bending). ^{1}H NMR (DMSO-d_6) δ (ppm): 2.48, 2.62 (m, 4H, 2×CH_2, imidazolidine), 3.54, 3.71 (d, 4H, 2×CH_2, naphthylmethylene) 4.72 (s, CH, imidazolidine), 7.06-7.15 (m, 4H, ArH), 7.32-7.83 (m, 14H, naphthalene). ^{13}C NMR (DMSO-d_6) δ (ppm): 134.1 (1C), 133.9 (2C), 133.6 (2C), 129.6 (2C), 128.6 (2C), 127.3 (1C), 126.1 (2C), 124.7 (2C), 124.5 (2C), 122.1 (2C), 120.6 (2C), 119.3 (2C), 118.6 (2C), 117.2 (2C), 86.4 (1C), 54.2 (2C), 46.7 (2C).

Animals

Adult Wistar albino rats of either sex, weighing between 160 and 200 g were used to investigate anti-inflammatory, ulcerogenic, and lipid peroxidation activities, whereas Swiss albino mice of either sex, weighing between 18 and 25 g were used to evaluate analgesic activity. The animals were randomly distributed into groups at the beginning of all the experiments. In each group, six animals were placed. All animals were allowed food and water *ad libitum* except during the experiments. All the test compounds and the reference drug were administered orally, suspended in 1% carboxymethyl cellulose (CMC), with one drop of tween 80 solution wherever required. The experimental protocol was approved by the Animal Ethics Committee of Jamia Hamdard.

Anti-inflammatory activity

Anti-inflammatory activity was evaluated by the carrageenan-induced hind paw edema method.[11] After 1 hr of the administration of the test compounds and standard drug, 0.1 mL of 1% carrageenan solution in saline was injected subcutaneously into the subplantar region of the right hind paw of each rat. The control group received only a solution of 10 mL/kg, 1% CMC, with one drop of Tween 80. The standard drug indomethacin was administered orally at a dose of 20 mg/kg. The test compounds were also administered orally at the same dose of 20 mg/kg. The right hind paw volume was measured with a digital plethysmometer (Panlab LE 7500), (Barcelona, Spain) before and after 1 h, 3 h, and 4 h of carrageenan treatment. The percentage of anti-inflammatory activity was calculated according to the following formula:

$$\text{Percent edema inhibition} = \{Vc - Vt / Vc\} \times 100$$

Where, *Vc* represents the mean increase in paw volume in the control group of rats and *Vt* represents the mean increase in paw volume in rats treated with the test compounds and standard drug.

Analgesic activity

Analgesic activity was evaluated by the acetic acid-induced writhing method.[12] It was performed by an intraperitoneal (i.p.) injection of 1% aqueous acetic acid solution in a volume of 0.1 mL. The screening of analgesic activity was performed after i.p. administration of test compounds at a dose of 20 mg/kg. All the compounds were dissolved in 1% CMC. One group was kept as control and received per os (p.o.) administration of 1% CMC. Aspirin 20 mg/kg was used as the reference drug. After 1 h of drug administration, 0.1 mL of 1% acetic acid i.p. solution was given to mice. The total number of writhes was recorded for 10 min, beginning 5 min after the acetic acid injection. The analgesic activity was expressed in terms of percentage inhibition of the number of writhes.

$$\text{Analgesic activity (\%)} = \{Nc - Nt / Nc\} \times 100$$

Where, *Nc* represents the mean number of writhes in the control group of mice and *Nt* represents the mean number of writhes in the test group of mice.

Ulcerogenic activity

Acute ulcerogenicity screening was performed according to the method reported by Cioli *et al*.[13] Ulcerogenic activity was evaluated after p.o. administration of test compounds or indomethacin at a dose of 20 mg/kg. The control group received p.o. administration of the vehicle (suspension of 1% CMC). Food but not water was removed 24 h before administration of the test compounds and standard drug. After the drug treatment, each rat was fed with a normal diet for 17 h and then sacrificed under light ether anesthesia. The stomach was then removed and opened along the greater curvature, washed with distilled water, and cleaned gently by dipping in saline. The mucosal damage was examined by means of a magnifying glass. For each stomach, the mucosal damage was assessed according to the following scoring system:

- 0.5 Redness
- 1.0 Spot ulcers
- 1.5 Hemorrhagic streaks
- 2.0 Ulcers > 3, but ≤5
- 3.0 Ulcers > 5.

The mean score of each treated group minus the mean score of the control group was regarded as the severity index of gastric mucosal damage.

Lipid peroxidation

Lipid peroxidation in the gastric mucosa was evaluated according to the method reported by Ohkawa *et al*.[14] After screening for ulcerogenic effect of synthesized compounds, the gastric mucosae of the animals were scraped with two glass slides, weighed (100 mg), and homogenized in 1.8 mL of 1.15% ice-cold KCl solution. The homogenate was supplemented with 0.2 mL of 8.1% sodium dodecyl sulfate, 1.5 mL of acetate buffer (pH 3.5), and 1.5 mL of 0.8% thiobarbituric acid. The mixture was heated at 95°C for 60 min. After cooling, the contents were shaken vigorously for 1 min and centrifuged for 10 min at 4000 rpm after supplementing with 5 mL mixture of *n*-butanol and pyridine (15:1 v/v). The

supernatant organic layer was separated, and absorbance was measured at 532 nm on the UV spectrophotometer. The results are expressed as nmol of malondialdehyde (MDA)/100 mg tissue, using the extinction coefficient $1.56 \times 10^5 cm^{-1} M^{-1}$.

Re-evaluation at higher doses

Compounds showing significant anti-inflammatory activity were also studied at the dose of 40 mg/kg for above activities, that is, for anti-inflammatory, analgesic, ulcerogenic, and lipid peroxidation activities.

Acute toxicity study

Approximately 50% lethal dose (ALD_{50}) for each of the promising compounds was determined in albino mice by the reported method of Bekhit and Fahmy.[15] Swiss albino mice of either sex weighing 18–25 g were used. The test compounds at 500 mg/kg, 750 mg/kg, and 1000 mg/kg body weight doses in DMSO were injected i.p. The toxic symptoms and mortality rates in each group were recorded 24 h after drug administration.

Statistical analysis

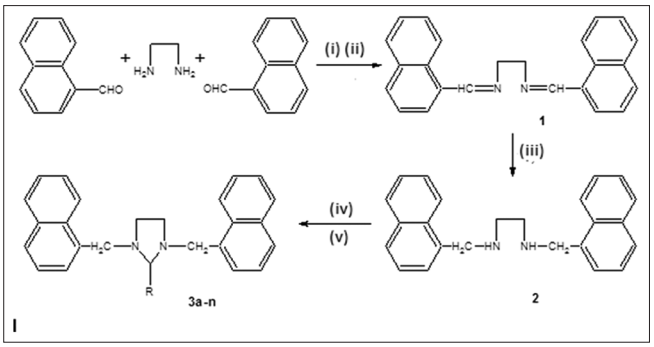
Statistical analysis was carried out using GraphPad Prism 3.0 (GraphPad software, San Diego, CA, USA). All the results were expressed as mean ± standard deviation graphs of data were compared with an analysis of variance (ANOVA), followed by Dunnett's multiple comparison test. Values were considered statistically significant at $P < 0.05$.

Results and Discussion

The reaction sequence involved in the synthesis of target compounds is shown in Scheme 1. The starting material *N*,*N*'-bis(1-naphthylmethylene) ethane-1,2-diamine 1, which is a diSchiff's base, was synthesized by reacting 1-naphthaldehyde with ethylenediamine. Compound 1 on reduction with sodium borohydride in methanol and dichloromethane yielded *N*,*N*'-bis(1-naphthylmethyl) ethane-1, 2-diamine 2, which is a tetrahydrodiSchiff's base. The 2-substituted-1, 3-bis (1-naphthylmethyl)-imidazolidines 3a-n were successfully obtained by reacting compound 2 with the appropriate aldehydes using absolute ethanol as solvent. The physical constants of the synthesized compounds are given in Table 1.

Anti-inflammatory activity

All the newly synthesized compounds 3a-n were evaluated for their *in vivo* anti-inflammatory activity by the carrageenan-induced rat paw edema method. The effect of various substituents at position 2 of the imidazolidine ring was studied. The compounds were tested at 20 mg/kg oral dose, and the response was compared with the standard drug indomethacin at the same oral dose. The percentage



Scheme 1: Reagents and conditions: Synthetic route to target compounds 3a-n. (i) dry benzene; (ii) azeotropic refluxing, 8 h; (iii) CH_3OH, dichloromethane, $NaBH_4$, stirred for 7 h, <18°C; (iv) absolute alcohol; (v) R-CHO, stirred at room temperature. Where a, R = C_6H_5; b, R = $C_{10}H_7$; c, R = 2-OH-C_6H_4; d, R = 4-OCH_3-C_6H_4; e, R = 4-N $(CH_3)_2$-C_6H_4; f, R = 4-Cl-C_6H_4; g, R = 3,4-OCH_3-C_6H_3; h, R = 3-NO_2-C_6H_4; i, R = 4-NO_2-C_6H_4; j, R = 4-OH-C_6H_4; k, R = C_4H_3O; l, R = 4-OH-3-OCH_3-C_6H_3; m, R = 4-F-C_6H_4; n, R = 2-Cl-C_6H_4

inhibition was calculated after 1 h, 3 h and 4 h of carrageenan treatment. As maximum inhibition was observed after 4 h, this was made the basis of discussion. The tested compounds showed anti-inflammatory activity ranging 27.61–53.43%, whereas the standard drug indomethacin showed 61.45% inhibition after 4 h.

It was interesting to note that the compound 3a, having an unsubstituted aryl ring, showed the lowest anti-inflammatory activity (27.61%). When this phenyl ring was replaced by a naphthyl ring, the resulting compound 3b showed a significant increase in activity (49.05%). On the other hand, replacement by a furfuryl ring produced compound 3k, which had less activity (35.42%). The change in electronic parameter was studied by making different substitutions in the phenyl ring present at position 2 of the imidazolidine ring. Compound 3h with a nitro group at *m*-position of this phenyl ring showed the highest anti-inflammatory activity (53.43%), which was comparable with indomethacin. Compound 3n with a chloro group present at *o*-position also showed a good effect (53.02%). Similarly, the response was studied by synthesizing compounds having *o*-hydroxy (3c, 32.94%), *p*-methoxy (3d, 41.95%), *p*-dimethylamino (3e, 40.97%), *p*-chloro (3f, 35.25%), *m*, *p*-dimethoxy (3g, 46.86%), *p*-nitro (3i, 43.96%), *p*-hydroxy (3j, 37.45%), *p*-hydroxy-*m*-methoxy (3l, 38.50%), and *p*-fluoro (3m, 45.25%) groups, and the results are shown in Graph 1 and Table 2.

Statistical significance testing using ANOVA followed by Dunnett's multiple comparison test showed that the anti-inflammatory activity of all the tested compounds except 3h and 3n was in the range of $P < 0.01$ when compared

with indomethacin. The anti-inflammatory activity of compounds 3h and 3n was found to be comparable to indomethacin. Compounds having a potency >0.70 were further selected for determination of their analgesic and ulcerogenic activities.

Analgesic activity

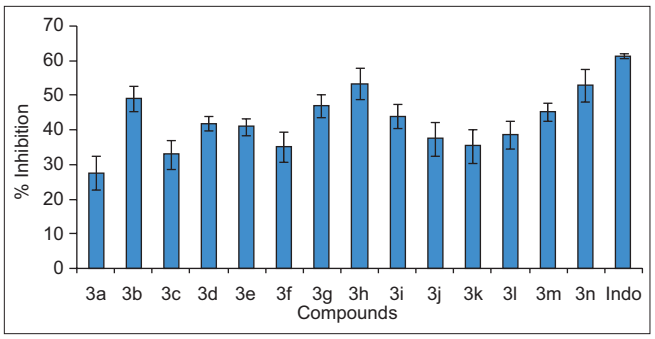
The analgesic activity of the synthesized compounds was evaluated by acetic acid-induced writhing method. The tested compounds showed analgesic activity ranging 44.50–53.24%, whereas aspirin showed 65.02% inhibition [Table 3]. It was observed that the compounds 3h and 3n with prominent anti-inflammatory activity also showed good analgesic activity (52.19% and 53.24%, respectively). Compounds 3b and 3 g also showed noticeable activity (49.95% and 48.02%, respectively) [Graph 2].

Acute ulcerogenic studies

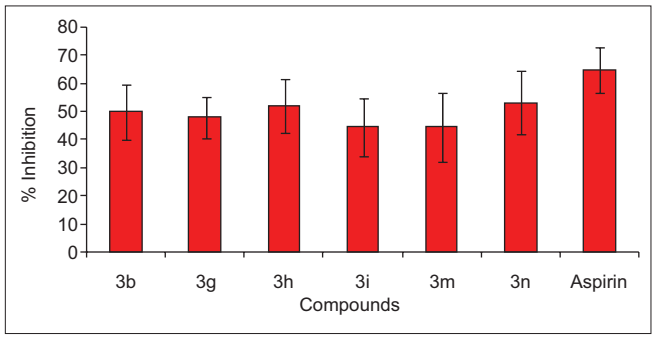
The ulcerogenic activity was done according to Cioli *et al*. The compounds showed ulcerogenic activity ranging 0.720–0.830. The standard drug indomethacin showed a high severity index of 1.750 [Table 4]. It was clear that the ulcerogenic effect of all the test compounds was appreciably less than that of indomethacin [Graph 3]. All the compounds (3b, 3h, 3g, 3i, 3m, and 3n) showed a severity index having half the value of indomethacin.

Lipid peroxidation

Compounds with low ulcerogenic activity are also reported to have reduced MDA content, a byproduct of lipid peroxidation. Therefore, by determining the MDA level, an attempt was made to correlate the reduction

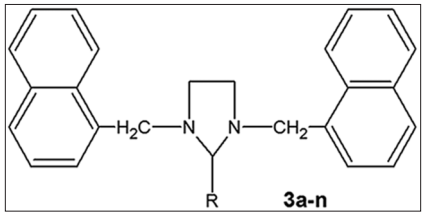


Graph 1: Anti-inflammatory activity of the synthesized compounds after oral administration (20 mg/kg) (3a-n)



Graph 2: Analgesic activity of the synthesized compounds after intraperitoneal dose (20 mg/kg) (3a-n)

Table 1: Physical constants of the synthesized compounds 3a-n



Compound	*R*	Yield (%)	M.P. (°C)	R_f	Molecular formula	Molecular weight
3a	C_6H_5	63	144-146	0.43	$C_{31}H_{28}N_2$	428.57
3b	$C_{10}H_7$	65	80-82	0.45	$C_{35}H_{30}N_2$	478.63
3c	2-OH-C_6H_4	55	124-126	0.37	$C_{31}H_{28}N_{20}$	444.57
3d	4-OCH_3-C_6H_4	57	102-106	0.36	$C_{32}H_{30}N_{20}$	458.59
3e	4-$N(CH_3)_2$-C_6H_4	58	126-130	0.33	$C_{33}H_{33}N_3$	471.64
3f	4-Cl-C_6H_4	72	110-114	0.44	$C_{31}H_{27}ClN_2$	463.01
3g	3,4-OCH_3-C_6H_3	41	106-108	0.30	$C_{33}H_{32}N_2O_2$	488.62
3h	3-NO_2-C_6H_4	62	112-114	0.41	$C_{31}H_{27}N_3O_2$	473.57
3i	4-NO_2-C_6H_4	66	94-98	0.35	$C_{31}H_{27}N_3O_2$	473.57
3j	4-OH-C_6H_4	38	102-104	0.33	$C_{31}H_{28}N_2O$	444.57
3k	C_4H_3O	68	108-112	0.44	$C_{29}H_{26}N_2O$	418.53
3l	4-OH-3-OCH_3-C_6H_3	35	115-117	0.37	$C_{32}H_{30}N_2O_2$	474.59
3m	4-F-C_6H_4	74	136-138	0.38	$C_{31}H_{27}FN_2$	446.56
3n	2-Cl-C_6H_4	69	124-126	0.46	$C_{31}H_{27}ClN_2$	463.01

M.P. – Melting point

Table 2: Anti-inflammatory activity of the synthesized compounds (3a-n) after oral administration (20 mg/kg)

Compound	Paw volume±SD				Inhibition±SD (%)			Potency
	0 h (basal)	After 1 h	After 3 h	After 3 h	After 1 h	After 3 h	After 4 h	
3a	0.85±0.06	1.23±0.05	1.64±0.06	1.76±0.07	12.57±6.92	26.95±4.72	27.61±4.81**	0.45
3b	0.80±0.04	1.02±0.05	1.18±0.06	1.24±0.05	27.41±4.53	47.73±4.02	49.05±3.67**	0.80
3c	0.84±0.07	1.22±0.03	1.53±0.04	1.63±0.05	13.53±6.68	32.21±3.54	32.94±4.25**	0.54
3d	0.81±0.05	1.10±0.07	1.34±0.09	1.42±0.09	22.25±4.76	40.68±2.37	41.95±2.20**	0.68
3e	0.84±0.06	1.10±0.09	1.36±0.09	1.44±0.10	22.34±3.85	39.70±2.88	40.97±2.46**	0.67
3f	0.83±0.07	1.21±0.04	1.46±0.04	1.58±0.07	13.95±4.36	34.97±3.24	35.25±4.36**	0.57
3g	0.82±0.06	1.04±0.08	1.22±0.07	1.29±0.06	26.23±4.73	45.74±3.26	46.86±3.33**	0.76
3h	0.81±0.05	0.99±0.07	1.10±0.08	1.13±0.07	29.92±6.43	51.24±5.07	53.43±4.53	0.87
3i	0.82±0.07	1.08±0.05	1.31±0.09	1.37±0.09	23.23±3.35	41.80±3.45	43.96±3.43**	0.72
3j	0.83±0.06	1.15±0.06	1.42±0.11	1.52±0.12	18.45±2.55	36.78±5.07	37.45±5.00**	0.61
3k	0.85±0.06	1.20±0.05	1.47±0.06	1.57±0.09	14.73±3.15	34.89±3.87	35.42±4.88**	0.58
3l	0.83±0.07	1.12±0.08	1.40±0.11	1.50±0.12	20.89±3.65	37.91±4.02	38.50±4.03**	0.63
3m	0.85±0.06	1.05±0.05	1.26±0.07	1.33±0.06	25.32±3.89	43.99±3.01	45.25±2.60**	0.74
3n	0.79±0.05	0.99±0.07	1.10±0.08	1.14±0.07	30.20±3.78	50.97±5.36	53.02±4.72	0.86
Indomethacin	0.83±0.06	0.88±0.03	0.92±0.04	0.94±0.08	37.45±3.82	59.28±0.86	61.45±0.82	1.00
Control	0.82±0.08	1.41±0.09	2.25±0.08	2.44±0.09	---	---	---	---

Data were given as mean±SD and analyzed by ANOVA, followed by Dunnett's multiple comparison test $n=6$ (---depicts not tested), $^{**}P<0.01$ compared to the standard drug (indomethacin). SD – Standard deviation; ANOVA – Analysis of variance

Table 3: Analgesic activity of the synthesized compounds after intraperitoneal dose of 20 mg/kg

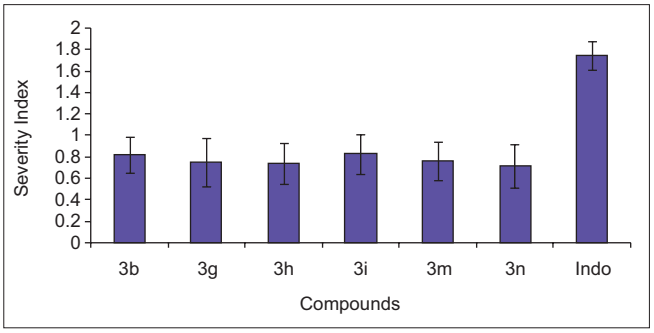
Compound	Analgesic activity±SD		
	Number of writhes in 15 min±SD	Inhibition %	Potency
3b	36.80±6.98	49.95±9.69**	0.77
3g	38.20±5.12	48.02±7.35**	0.74
3h	35.20±7.33	52.19±9.60*	0.80
3i	41.00±8.86	44.50±10.33**	0.68
3m	40.20±4.97	44.73±12.25**	0.69
3n	34.20±7.69	53.24±11.29	0.82
Aspirin	26.00±7.18	65.02±8.01	1.00
Control	74.00±9.30	---	---

Data were given as mean±SD and analyzed by ANOVA, followed by Dunnett's multiple comparison test $n=6$ (---depicts not tested), $^{**}P<0.01$, $^{*}P<0.05$, compared to the standard drug (aspirin) for analgesic activity. SD – Standard deviation; ANOVA – Analysis of variance

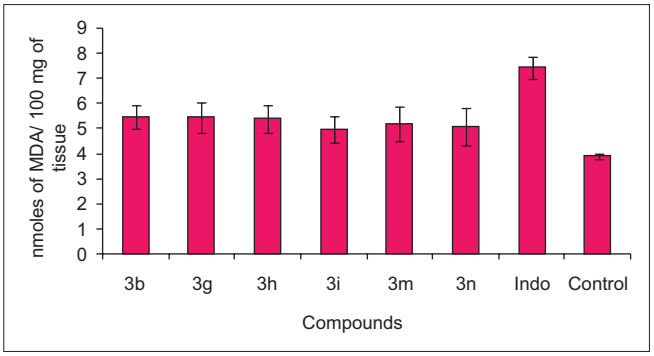
Table 4: Ulcerogenic and lipid peroxidation activities of the synthesized compounds after oral administration (20 mg/kg)

Compound	Ulcerogenic activity	Lipid peroxidation
3b	0.820±0.17**	5.474±0.45**
3g	0.750±0.22*	5.462±0.61**
3h	0.740±0.19*	5.392±0.54**
3i	0.830±0.19**	4.976±0.51*
3m	0.760±0.18*	5.196±0.71**
3n	0.720±0.20*	5.082±0.75*
Indomethacin	1.750±0.14**	7.430±0.43**
Control	0.000±0.00	3.902±0.13

Data were given as mean±SD and analyzed by ANOVA, followed by Dunnett's multiple comparison test $n=6$, $^{**}P<0.01$, $^{*}P<0.05$, compared to the standard drug (indomethacin) for ulcerogenic and lipid peroxidation studies, ANOVA – Analysis of variance



Graph 3: Ulcerogenic activity of the synthesized compounds after oral administration (20 mg/kg)



Graph 4: Lipid peroxidation activity of the synthesized compounds at dose (20 mg/kg)

in ulcerogenic activity of the compounds with that of lipid peroxidation. All the compounds that were evaluated for ulcerogenic activity were also subjected to lipid peroxidation studies. The animals treated with indomethacin showed a lipid peroxidation value of 7.430, whereas the control group showed 3.902 and the groups

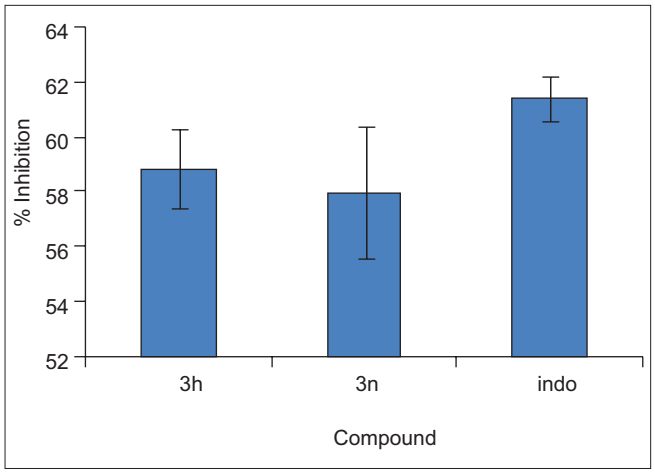
treated with the synthesized compounds showed it in the range 4.976–5.474 [Table 4]. These results further confirmed that the synthesized compounds have less ulcerogenic effects compared to the standard drug indomethacin [Graph 4].

Acute toxicity

Compounds 3h and 3n, exhibiting prominent anti-inflammatory and analgesic activities, were further selected for the evaluation of their ALD_{50} in mice. However, no toxic symptoms or mortality rates were observed 24 h post administration even at the dose of 1000 mg/kg body weight, suggesting a wide margin of safety for these compounds.

Re-evaluation of compounds 3h and 3n at a higher dose (40 mg/kg) for anti-inflammatory, analgesic, ulcerogenic, and lipid peroxidation activities

Based on the results obtained in above experiments, compounds 3h and 3n were selected for the evaluation of anti-inflammatory, analgesic, ulcerogenic, and lipid peroxidation actions at 40 mg/kg dose. Indomethacin was used as the standard drug at an oral dose of 20 mg/kg to study anti-inflammatory, ulcerogenic, and lipid peroxidation activities. Similarly, aspirin at an oral dose of 20 mg/kg was used as the standard drug to study the analgesic activity. The results are reported in Tables 5 and 6.



Graph 5: Anti-inflammatory activity of the compounds 3h and 3n at double dose (40 mg/kg)

Compounds 3h and 3n showed increased anti-inflammatory activity (3h, 53.43–58.85% and 3n, 53.02–57.98%) at double dose compared to indomethacin (61.45%), and analgesic activity (3h, 52.19–60.43% and 3n, 53.24–61.58%) at double dose compared to aspirin (65.02%). It was also observed that compounds 3h and 3n at this increased dose showed a little increased ulcerogenic activity (3h, 0.740–0.840 and 3n, 0.720–0.790) and lipid peroxidation (3h, 5.392–5.472 and 3n, 5.082–5.232), but these values were still appreciably less than with the standard drug indomethacin (1.750 and 7.430, respectively).

The results indicated that the anti-inflammatory and analgesic activities of select compounds (3h and 3n) increased with dose, maintaining gastrointestinal safety. Results are displayed in Graph 5 for anti-inflammatory activity, Graph 6 for analgesic activity, Graph 7 for ulcerogenic activity, and Graph 8 for lipid peroxidation, respectively.

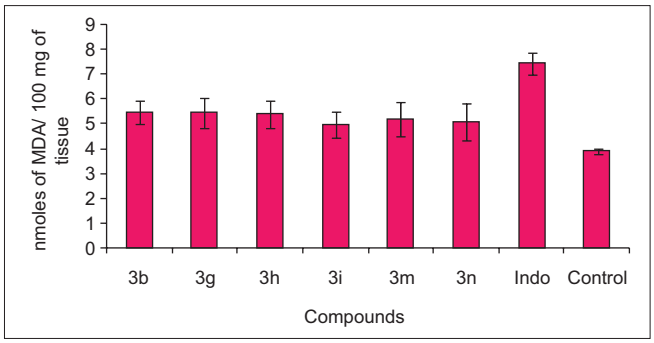
Conclusion

We report herein the syntheses of 14 new 2-substituted-1, 3-bis (1-naphthylmethyl)-imidazolidines (3a-n). The tested compounds (3a-n) showed anti-inflammatory activity ranging 27.61–53.43%, whereas the standard drug indomethacin showed 61.45% inhibition at the dose of 20 mg/kg in rats. Compound 3h showed the highest activity (53.43%). Compound 3n showed 53.02% inhibition. These two compounds were also tested at the dose of 40 mg/kg to detect any increase in activity. It was encouraging to note that both the compounds showed increased anti-inflammatory activity (58.85% and 57.98%, respectively). At this dose, both of these compounds showed reduced ulcerogenic activity (less than half) compared to the standard drug indomethacin. These two compounds also exhibited excellent analgesic activity. It was observed that both the compounds did not show toxic symptoms or mortality at the dose of 1000 mg/kg, indicating their wide margin of safety. Compounds 3h and 3n were identified as potential anti-inflammatory agents with

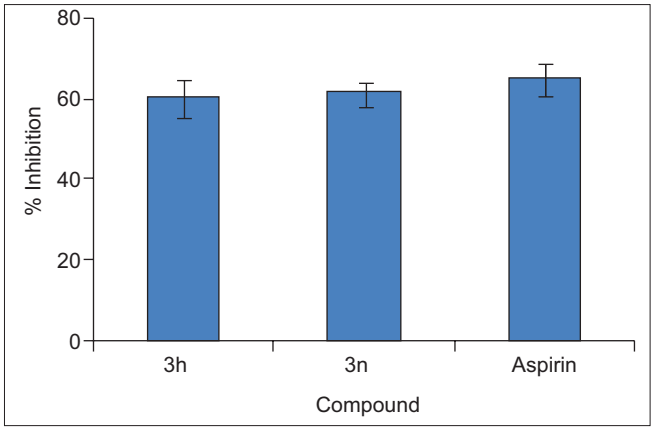
Table 5: Anti-inflammatory activity of the compounds 3h and 3n after oral administration

Compound	Paw volume±SD				Inhibition±SD %		
	0 h (basal)	After 1 h	After 3 h	After 4 h	After 1 h	After 3 h	After 4 h
3h	0.81±0.07	0.91±0.06	0.97±0.06	1.00±0.06	35.36±4.44	56.69±2.07	58.85±1.45
3n	0.80±0.06	0.90±0.07	0.99±0.05	1.03±0.05	36.32±4.58	56.28±3.66	57.98±2.43
Indomethacin	0.83±0.06	0.88±0.03	0.92±0.04	0.94±0.08	37.45±3.82	59.28±0.86	61.45±0.82
Control	0.82±0.08	1.41±0.09	2.25±0.08	2.44±0.09	---	---	---

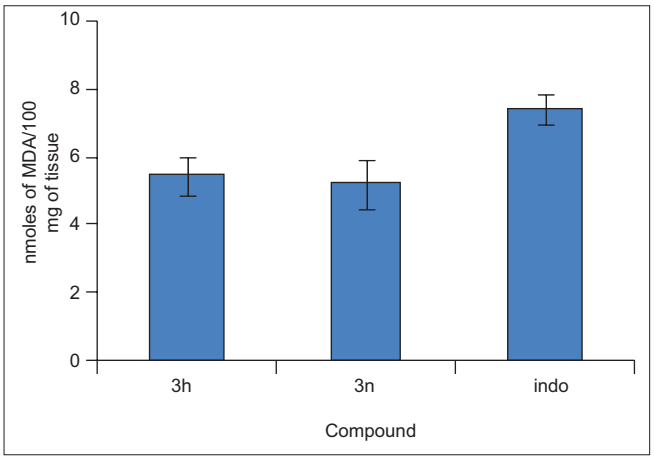
Data were given as mean±SD, *n*=6, standard drug (indomethacin), doses: Indomethacin 20 mg/kg and test compounds 40 mg/kg (---depicts not tested). SD – Standard deviation



Graph 6: Analgesic activity of the compounds 3h and 3n at double dose (40 mg/kg)



Graph 7: Ulcerogenic activity of the compounds 3h and 3n at double dose (40 mg/kg)



Graph 8: Lipid peroxidation activity of the compounds 3h and 3n at double dose (40 mg/kg)

less ulcerogenic activity and may be useful as lead molecules for the development of safer NSAIDs.

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Table 6: Analgesic, ulcerogenic, and lipid peroxidation activities of the compounds 3h and 3n

Compound	Analgesic activity±SD		Ulcerogenic activity	Lipid peroxidation
	Number of writhes in 15 min±SD	Inhibition %		
3h	29.40±6.98	60.43±4.86	0.840±0.19	5.472±0.54
3n	28.20±7.42	61.58±3.10	0.790±0.20	5.232±0.75
Aspirin	26.00±7.18	65.02±4.01	---	---
Indomethacin	---	---	1.750±0.14	7.430±0.43
Control	74.00±9.30	---	0.000±0.00	3.902±0.13

Data were given as mean±SD, $n=6$, standard drugs (indomethacin and aspirin) both 20 mg/kg and test compounds 40 mg/kg (---depicts not tested). SD – Standard deviation

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