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[1-(4-Nitrobenzyl)-2-butyl-4-chloro-1*H*-imidazol-5-yl]-4, 5-dihydro-1-phenyl-1*H*-pyrazole: Synthesis, Anti-Inflammatory and Analgesic Activities

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ABSTRACT

In the present investigation, series of *Bis* (heterocycle)s bearing pyrazoline in combination of the imidazole derivatives have been synthesized via 1,3-dipolar cycloaddition reactions of *N*-(nitrobenzyl)-imidazole nitrile imines with different dipolarophiles. All the newly synthesized compounds were characterized and screened for analgesic-anti-inflammatory activities and were compared with the standard drugs. The compounds exhibited excellent anti-inflammatory and analgesic activities. Out of the compounds studied 4b, 4d and 4g compounds shown statistically significant activity comparable to the standard drugs Ibuprofen and Aspirin at the same dose.

Keywords: Anti-Inflammatory; Analgesic; *N*-(nitrobenzyl)-imidazole aldehyde; Chloramine-T

1. Introduction

By targeting the synthesis of nitrogen containing heterocylcles of biological interest, we synthesized new series of compounds. Heterocyclic compounds hold a special place in organic chemistry. Their role as lead candidates in drug design cannot be overstated and the appearance of heterocyclic motifs in natural products is astronomically frequent. Many heterocycles (e.g. thiazole, oxazole, isoxazoline, pyrazoline and imidazole etc.) have received enormous amount of attention from synthetic chemists from the standpoint of both their synthesis and their biological activity. Amongst five membered heterocycles, isoxazolines and pyrazoline are representing a class of compounds of great importance in biological chemistry. For instance, compounds including a pyrazole nucleus are known to possess analgesic, anti-inflammatory, antipyretic, antiarrhythmic, tranquillizing, muscle relaxant, psychoanaleptic, anticonvulsant, hypotensive, monoamine oxidase inhibitor, antidiabetic and antibacterial activities [1]. In fact, Celecoxib, a pyrazole derivative and Valdecoxib, an isoxazole derivative are now widely used in the market as anti-inflammatory drugs [2]. Isoxazoline possess broad spectrum of biological activities like antituberculosis, antifungal, anticancer, antiviral, insecticidal, antibiotic activities and act as precursors for different natural products [3]. Imidazole derivatives are gaining synthetic interest in recent years due to their broad spectrum of biological activities like anti-inflammatory [4], analgesic [5], antibacterial [6], antifungal [7], antituberculosis[8], anticonvolusant [9] and potential anticytokine agents [10]. Compounds possessing imidazole moiety acts as new potent and selective 20-HETE synthase inhibitors [11], 2-n-butyl-4-chloro-5-farmyl-imidazole is a key intermediate for the synthesis of Losartan a non-peptide angiotensin antagonist, which is an orally active antihypertensive drug [12].

1,3-Dipolar cycloaddition reactions are useful tools for constructing biologically potent five membered heterocycles [13]. Apart from the various dipolar reagents known, nitrile imines are used in numerous 1,3-dipolar-cycloaddition reactions leading to pyrazoles, pyrazolines, pyrazolidines and other heterocyclic compounds [14]. Huisgen [15] and co-workers first reported the authentic in situ generation of nitrile imines by the thermolysis of 2,5-diphenyl tetrazole in the presence of ethyl phenyl propionate and obtained 2,3,5-triphenyl carbethoxypyrazole. Nitrile imines can be generated by photolysis of sydnones [16] and oxidation of aryl aldehyde hydrazones with lead tetraacetate [17], chloramine-T [18] etc.

In our laboratory, we extensively used chloramine-T for the generation of nitrile oxide and nitrile imine from aldoxime and aldehyde hydrazone in the syntheses of

isoxazoline and pyrazoline respectively [18]. Literature studies reveals that *Bis* (heterocycle)s bearing pyrazoline [19] were synthesized via 1,3-dipolar cycloaddition reaction of divinyl ketone/sulfone as dipolarophiles with nitrile imines, generated from aldehyde hydrazone using chloramine-T as 1,3-dipole. Recently, we have reported the synthesis of ether-linked *Bis* (isoxazoline) and *Bis* (hererocycle)s bearing isoxazoline and 1,3,4-oxadiazole via 1,3-dipolar cycloaddition reactions of nitrile oxides with allyl alcohol and allyl ethers [20].

With this background, it is considered worthwhile to synthesize hitherto unknown series of *Bis* (heterocycle) bearing imidazole and pyrazoline ring systems by 1,3-ipolar cycloaddition reaction of *N*-(nitrobenzyl)-midazole nitrile imines with different dipolarophiles and their anti-nflammatory and analgesic activities have been evaluated.

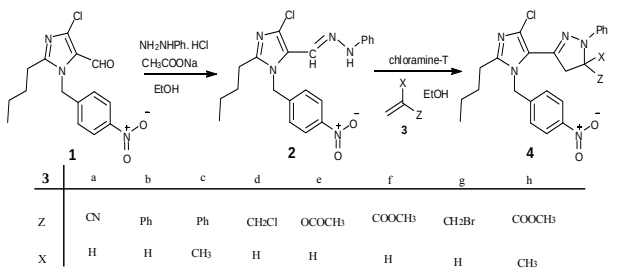
2. Results and Discussion

2.1. Chemistry

The starting material *N*-(nitrobenzyl)-imidazole aldehyde 1 and its hydrazones 2 were prepared according to the literature procedure [21]. Oxidative dehydrogenation of *N*-(nitrobenzyl)-imidazole aldehyde hydrazone 2 by chloramine-T trihydrate afforded nitrile imines, which was intercepted in situ by different alkenes 3a-h in refluxing ethanol. The pale yellow solids obtained were identified by NMR spectroscopy as 3-[2-butyl-4-chloro-(4-nitrobenzyl)-1H-imidazol-5-yl]-4,5-dihydropyrazoline derivatives 4a-h (**Scheme 1**). Compound 4a (X=H) exhibits as doublet of doublet in the region δ 5.10 - 5.80 assigned to 5-H of the pyrazoline ring, while in cycloadducts 4c (when X=CH_3) there was no signal in this region. 4-CH_AH_B protons resonate as doublet of doublet in the region δ 3.20 - 3.60. Remaining protons are resonates at expected region.

2.2. Pharmacological Results and Discussion

All the compounds were tested for anti-inflammatory activity in carrageenan-induced edema assay in rats at a dosage of 100 mg/kg po (**Table 1**). Three compounds



Scheme 1. Synthesis of *Bis* (heterocycle)s bearing pyrazoline derivatives.

Table 1. Anti-inflammatory activities of 4(a-h).

Compound	±SD[1] Edema volume in ml	(%)[2] Edema inhibition
4a	0.17 ± 0.07[3]	*59.5
4b	0.21 ± 0.06[4]	55.3
4c	0.24 ± 0.08[4]	48.9
4d	0.15 + 0.03[3]	*64.3
4e	0.24 ± 0.05[3]	42.8
4f	0.23 ± 0.08[3]	45.2
4g	0.16 ± 0.05[3]	*61.9
4h	0.30 ± 0.04[5]	45.4
Ibuprofen	0.16 ± 0.07[5]	*71.0

[1]At 100 mg/kg, po edema volume measured 3 h after carrageenan injection, and expressed as mean ± standard deviations (n = 4); [2]percent edema inhibition calculated by comparing with the vehicle-treated control animals; [3]control edema volume = 0.42 ± 0.03; [4]control edema volume = 0.47 ± 0.04; [5]control edema volume = 0.55 ± 0.03; *statistically significant.

(4b, 4d and 4g) have statistically significant activity. Amongst these compounds, the two halogenated derivatives, 4d and 4g have more than 60% activity. At all of the doses they were less active than Ibuprofen. All of these compounds were tested for analgesic activity at 100 mg/kg in acetic-acid induced assay in mice (**Table 2**). Six compounds had significant activity and the compound 4d exhibited the highest activity in the series.

3. Experimental Section

Melting points were determined on Thomas Hoover melting point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM 300 MHz spectrometer using $CDCl_3$ as solvent and tetramethylsilane as internal standard. ^{13}C NMR spectra were measured on Jeol 400 (100 MHz) instrument. The chemical shifts are expressed in δ and following abbreviations were used. S = singlet, d = doublet, t = triplet and m = multiplet. Infrared (IR) spectra were recorded on Shimadzu 8300 IR spectrometer. Elemental analyses were obtained on a Vario-EL instrument. Thin layer chromatography was carried out with BDH silica gel G on glass slides.

3.1. General Procedure for the Synthesis of Compounds 4(a-h)

3.1.1. 3-(1-(4-Nitrobenzyl)-2-butyl-4-chloro-1*H*-imizol-5-yl)-4,5-dihydro-1-phenyl-1*H*-pyrazole-5-carbonitrile [4a]

Typical Procedure: A mixture of 2a (0.50 g, 1.21 mmol) and chloramine-T trihydrate (0.35 g, 1.21 mmol) in ethanol (15 mL) was stirred at room temperature for 5 min. To this mixture, 3a (0.065 g, 1.22 mmol) in ethanol (5 mL) was added and the reaction mixture was heated on a water bath for 3 h. After completion of the reaction (monitored by TLC) the reaction mixture was cooled to room temperature. Sodium chloride formed was filtered off and

Table 2. Analgesic activities of 4(a-h).

Compound	No. of writhes in 15 min ± SD[1]	% Reduction from control[2]
4a	30 ± 10[3]	50.8
4b	29 ± 08[5]	*57.9
4c	40 ± 13[5]	49.3
4d	26 ± 08[4]	*62.3
4e	41 ± 10[5]	48.1
4f	44 ±12[5]	44.3
4g	27 ± 07[4]	*60.8
4h	47 ± 13[5]	40.5
Aspirin	29 ± 07[4]	*63.3

[1]At 100 mg/kg po, number of writhes in 15 min beginning 5 min after acetic acid injection, expressed mean ± standard deviation (n = 6); [2]percentage writhing inhibition calculated by comparing with vehicle-treated control animals; [3]control number of writhes = 61 ± 11; [4]control number of writhes = 69 ± 6; [5]control number of writhes = 79 ± 7; *statistically significant.

washed with ethanol (15 mL). Filtrate and washing were combined and evaporated in vacuum. The residue was extracted with ether (25 mL), the ether extract was washed successively with water (2 × 15 mL), 5% NaOH (2 × 15 mL) and saturated brine solution (10 mL). The organic layer was dried over anhydrous sodium sulphate. After evaporation of the solvent the product was purified by the column chromatography using the chloroform/ acetone (8:2) as eluent, and yellow oil 4a was obtained (0.36 g, 64 %). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (t, 3H, CH_3), 1.34 (m, 2H, CH_2), 1.63 (m, 2H, CH_2), 2.57 (t, 2H, CH_2), 3.20 (dd, J = 7.8, 2.2 Hz, 1H, 4-CH_A), 3.47 (dd, *J* = 7.8, 2.2 Hz, 1H, 4-CH_B), 4.99 (s, 2H, CH_2), 5.08 (dd, *J* = 6.0, 2.4 Hz, 1H, 5-CH), 6.45 - 6.98 (m, 5H, H_{Ar}), 7.4 - 8.1 (m, 4H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4 (CH_3), 22.8 (CH_2), 25.9 (CH_2), 32.5 (CH_2), 39.9 (CH_2), 33.8 (CH_2), 40.7 (CH), 113.7 (2CH), 116.8 (C), 117.3 (CH), 121.1 (2C), 123.1 (C), 126.2 (C), 129.8 (2CH), 130.4 (2CH), 142.5 (C), 143.7 (C), 145.7 (C), 148.1 (C), 155.7 (C). IR (KBr pellets cm^{-1}) *ν* 2941, 2225, 1689, 1663, 1326, 1271. Anal. Calcd.for $C_{24}H_{23}ClN_6O_2$: C, 62.27; H, 5.01; N, 18.15; Found: C, 62.29, H, 5.06, N, 18.17%.

3.1.2. Spectral Data of the Compounds

1) 1-(4-Nitrobenzyl)-2-Butyl-4-Chloro-5-(4,5-Dihydro-1, 5-Diphenyl-1*H*-Pyrazol-3-yl)-1*H*-Imidazole [4b]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (t, 3H, CH_3), 1.32 (m, 2H, CH_2), 1.61 (m, 2H, CH_2), 2.54 (t, 2H, CH_2), 3.29 (dd, *J* = 7.6, 2.0 Hz, 1H, 4-CH_A), 3.56 (dd, *J* = 7.6, 2.0 Hz, 1H, 4-CH_B), 4.97 (s, 2H, CH_2), 5.29 (dd, *J* = 5.8, 2.0 Hz, 1H, 5-CH), 6.45 - 6.65 (m, 3H, H_{Ar}), 7.05 - 7.24 (m, 7H, H_{Ar}), 7.34 - 8.10 (m, 4H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2 (CH_3), 22.6 (CH_2), 25.7 (CH_2), 33.7 (CH_2), 39.8 (CH_2), 40.5 (CH_2), 53.7 (CH), 113.7 (2CH), 117.3 (CH), 121.1 (2CH), 123.1 (C), 126.2 (C), 126.9 (CH), 127.3 (2CH), 128.7 (2CH), 129.8 (2CH), 130.3 (2CH), 142.5 (C), 143.6 (C), 143.7 (C), 145.5 (C), 148.1 (C), 155.7 (C). IR (KBr pellets cm^{-1}) *ν* 2947, 1691, 1686, 1331, 1292. Anal. Calcd.for $C_{29}H_{28}ClN_5O_2$: C, 67.76; H, 5.49; N, 13.62; Found: C, 67.79, H, 5.44, N, 13.65. Yield 58%. Thick oil.

2) 1-(4-Nitrobenzyl)-2-Butyl-4-Chloro-5-(4,5-Dihdro-5-Methyl-1,5-Diphenyl-1*H*-Pyrazol-3-Yl)-1*H*-Imidazo le [4c]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (t, 3H, CH_3), 1.35 (m, 2H, CH_2), 1.61 (s, 3H, CH_3), 1.64 (m, 2H, CH_2), 2.55 (t, 2H, CH_2), 3.22 (s, 2H,CH_2), 4.97 (s, 2H, CH_2), 6.45 - 6.60 (m, 3H, H_{Ar}), 7.04-7.20 (m, 7H, H_{Ar}), 7.32 - 8.10 (m, 4H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4 (CH_3), 22.5 (CH_2), 25.6 (CH_2), 29.8 (CH_3), 33.7 (CH_2), 40.5 (CH_2), 47.6 (CH_2), 56.2 (CH), 113.7 (2CH), 117.2 (CH), 121.1 (2CH), 123.3 (C), 126.3 (C), 126.2 (CH), 126.4 (2CH), 128.7 (2CH), 129.7 (2CH), 130.3 (2CH), 142.7 (C), 143.9 (C), 144.9 (C), 145.6 (C), 148.3 (C), 155.7 (C). IR (KBr pellets cm^{-1}) *ν* 2931, 1689, 1682, 1666, 1332, 1292. Anal. Calcd. for $C_{30}H_{30}ClN_5O_2$: C, 68.24; H, 5.73; N, 13.26; Found: C, 68.29, H, 5.70, N, 13.25. Yield 61%. mp 131˚C - 133˚C.

3) 1-(4-nitrobenzyl)-2-butyl-4-chloro-5-(5-(chloro-methyl)-4,5-dihydro-1-phenyl-1H-pyrazol-3-yl)-1H-imidazole [4d]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (t, 3H, CH_3), 1.35 (m, 2H, CH_2), 1.62 (m, 2H, CH_2), 2.58 (t, 2H, CH_2), 3.26 - 3.72 (m, 4H, $2CH_2$), 4.98 (s, 2H, CH_2), 4.98 (m, 1H, 5-CH), 6.45 - 7.08 (m, 5H, HAr), 7.33 - 8.10 (m, 4H, HAr). 13C NMR (100 MHz, $CDCl_3$): δ 14.3 (CH_3), 22.6 (CH_2), 25.6 (CH_2), 35.8 (CH_2), 34.7 (CH_2), 40.7 (CH_2), 52.3 (CH_2), 53.5 (CH), 113.7 (2CH), 117.4 (CH), 121.2 (2CH), 123.0 (C), 126.3 (C), 129.7 (2CH), 130.1 (2CH), 142.5 (C), 143.9 (C), 145.6 (C), 148.2 (C), 155.7 (C). IR (KBr pellets cm^{-1}) ν 2931, 1679, 1662, 1332, 1291, 1193. Anal. Calcd. for $C_{24}H_{25}Cl_2N_5O_2$: C, 59.26; H, 5.18; N, 14.40; Found: C, 59.22, H, 5.15, N, 14.44. Yield 56%. mp 147˚C - 149˚C.

4) 3-(1-(4-nitrobenzyl)-2-butyl-4-chloro-1H-imidazol-5-yl)-4,5-dihydro-1-phenyl-1H-pyrazol-5-yl acetate [4e]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (t, 3H, CH_3), 1.34 (m, 2H, CH_2), 1.64 (m, 2H, CH_2), 2.04 (s, 3H, CH_3), 2.58 (t, 2H, CH_2), 3.24 (dd, J = 8.0, 2.0 Hz, 1H, 4-CHA), 3.47 (dd, *J* = 8.0, 2.0 Hz, 1H, 4-CHB), 4.99 (s, 2H, CH_2), 5.54 (dd, *J* = 6.4, 2.2 Hz, 1H, 5-CH), 6.45 - 7.06 (m, 5H, HAr), 7.36 - 8.11 (m, 4H, HAr). 13C NMR (100 MHz, $CDCl_3$): δ 14.1 (CH_3), 20.8 (CH_3), 22.4 (CH_2), 25.5 (CH_2), 35.7 (CH_2), 37.9 (CH_2), 40.8 (CH_2), 78.7 (CH), 113.7 (2CH), 117.4 (CH), 121.3 (2C), 123.2 (C), 126.3 (C), 129.8 (2CH), 130.3 (2CH), 142.6 (C), 143.9 (C), 145.7 (C), 148.3 (C), 155.8 (C), 170.5 (C). IR (KBr pellets cm^{-1}) ν 2944, 1757, 1679, 1663, 1329, 1295. Anal. Calcd. for $C_{25}H_{26}ClN_5O_4$: C, 60.54; H, 5.28; N, 14.12; Found: C,

60.57, H, 5.24, N, 14.17. Yield 71%. mp 160˚C - 162˚C.

5) Methyl 3-(1-(4-nitrobenzyl)-2-butyl-4-chloro-1H-imidazol-5-yl)-4,5-dihydro-1-phenyl-1H-pyrazole-5-carboxylate [4f]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.96 (t, 3H, CH_3), 1.33 (m, 2H, CH_2), 1.63 (m, 2H, CH_2), 2.55 (t, 2H, CH_2), 3.23 (dd, J = 7.7, 2.0 Hz, 1H, 4-CHA), 3.48 (dd, J = 7.7, 2.0 Hz, 1H, 4-CHB), 3.69 (s, 3H, CH_3), 4.97 (s, 2H, CH_2), 5.22 (dd, J = 6.2, 2.0 Hz, 1H, 5-CH), 6.43 - 7.06 (m, 5H, HAr), 7.32 - 8.08 (m, 4H, HAr). 13C NMR (100 MHz, $CDCl_3$): δ 14.2 (CH_3), 22.6 (CH_2), 25.6 (CH_2), 33.7 (CH_2), 33.9 (CH_2), 40.6 (CH_2), 51.8 (CH_3), 55.7 (CH), 113.6 (2CH), 117.3 (CH), 121.2 (2C), 123.1 (C), 126.3 (C), 129.7 (2CH), 130.1 (2CH), 142.6 (C), 143.8 (C), 145.6 (C), 148.3 (C), 155.8 (C), 171.7 (C). IR (KBr pellets cm-1) ν 2929, 1755, 1670, 1658, 1323, 1279. Anal. Calcd. for $C_{25}H_{26}ClN_5O_4$: C, 60.54; H, 5.28; N, 14.12; Found: C, 60.51, H, 5.29, N, 14.15. Yield 75%. mp 160˚C - 162˚C.

6) 1-(4-Nitrobenzyl)-5-(5-(bromomethyl)-4,5-dihydro-1-phenyl-1*H*-pyrazol-3-yl)-2-butyl-4-chloro-1*H*-imidazole [4g]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (t, 3H, CH_3), 1.33 (m, 2H, CH_2), 1.61 (m, 2H, CH_2), 2.54 (t, 2H, CH_2), 3.22 - 3.69 (m, 4H, 2CH_2), 4.98 (s, 2H, CH_2), 5.04(m, 1H, 5-CH), 6.44 - 7.08 (m, 5H, H_{Ar}), 7.33 - 8.10 (m, 4H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5 (CH_3), 22.7 (CH_2), 25.8 (CH_2), 35.9 (CH_2), 35.9 (CH_2), 39.5 (CH_2), 40.7 (CH_2), 54.5 (CH), 113.7 (2CH), 117.5 (CH), 121.4 (2CH), 123.3 (C), 126.5 (C), 129.8 (2CH), 130.4 (2CH), 142.6 (C), 143.9 (C), 145.8 (C), 148.4 (C), 155.9 (C). IR (KBr pellets cm^{-1}) ν 2941, 1689, 1668, 1334, 1295, 1143. Anal. Calcd. for $C_{24}H_{25}BrClN_5O_2$: C, 54.30; H, 4.75; N, 13.19; Found: C, 54.33, H, 4.79, N, 13.18. Yield 58 %. mp 139˚C - 141˚C

7) Methyl 3-(1-(4-nitrobenzyl)-2-butyl-4-chloro-1*H*-midazol-5-yl)-4,5-dihydro-5-methyl-1-phenyl-1*H*-pyrazole-5-carboxylate [4h]: ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.98 (t, 3H, CH_3), 1.35 (m, 2H, CH_2), 1.53 (s, 3H,CH_3), 1.65 (m, 2H, CH_2), 2.57 (t, 2H, CH_2), 3.28-3.39 (s, 2H, CH_2), 3.68 (s, 3H, CH_3), 4.98 (s, 2H, CH_2), 6.45 - 7.08 (m, 5H, H_{Ar}), 7.32 - 8.07 (m, 4H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3 (CH_3), 22.6 (CH_2), 23.6 (CH_3), 25.5 (CH_2), 33.7 (CH_2), 47.1 (CH_2), 40.6 (CH_2), 52.4 (CH_3), 59.4 (C), 113.6 (2CH), 117.2 (CH), 121.1 (2CH), 123.1 (C), 126.2 (C), 129.7 (2CH), 130.0 (2CH), 142.4 (C), 143.9 (C), 145.5 (C), 148.1 (C), 155.6 (C), 171.9 (C). IR (KBr pellets cm^{-1}) ν 2949, 1751, 1689, 1668, 1659, 1330, 1267. Anal. Calcd. for $C_{26}H_{28}ClN_5O_4$: C, 61.23; H, 5.53; N, 13.73; Found: C, 61.20, H, 5.54, N, 14.77. Yield 69%. mp 165˚C - 167˚C.

3.2. Pharmacology

Albino rats of either sex (150 - 180 g) and albino mice of either sex (8 - 25 g) were used. The compounds were administered po using a feeding tube as homogenized suspensions in 0.5% sodium carboxymethyl cellulose; 0.5% sodium carboxymethyl cellulose was administered as the vehicle control.

3.2.1. Carrageenan-Induced Edema

Groups of four rats were dosed at 100 mg/kg po with the test compounds, 1 h before 0.05 ml of a 1% suspension of Type IV Lambda (Sigma) carrageenan was injected into the subplantar region at the right hind paw; additional groups of four rats were similarly pretreated with 100 mg/kg ibuprofen (positive control) or 10 ml/kg 0.5% sodium carboxymethyl cellulose (vehicle controls) [22]. Paw volumes were measured by water displacement in a plethysmograph immediately after carrageenan injection, and again 3 h later. Edema volumes for test-compound-treated and positive-control rats were compared statistically with those for the vehicle-treated control rats; data are reported as percentage edema inhibition.

3.2.2. Analgesic Activity

This method is based on acetic-acid-induced writhings in mice [23]. Groups of six mice each were dosed with the test compounds or with aspirin at a dose of 100 mg/kg po, 1 h before the ip injection of 0.6% acetic acid (10 ml/kg). Mice were observed for 1.5 min beginning 5 min after the acetic acid injection, and the total number of writhes recorded. The mean value of writhes for each group was calculated and compared statistically with that for the vehicle-treated control group (n = 6); data were reported as percent inhibition of the number of writhes. The test was repeated on additional groups of six mice, treated with compounds for which the reduction in writhes had been calculated to be >10%; these results are shown in **Table 2**.

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