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Synthesis of 2-Substituted-4,6-Diphenylpyridazinones as Potent Anti-Inflammatory Agents

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ABSTRACT

A new series of 2-substituted-4,6-diphenylpyridazin-3(2*H*)-one derivatives was synthesized and the structures were established using various spectroscopic techniques. The target compounds were screened for anti-inflammatory using carrageen rat paw edema model at 20 and 40 mg/kg. To assess the side effects of the synthesized compounds the gastric ulcerogenic potential of the synthesized compounds was also studied. 2-(3-(N-methylpiperazino)propyl)-4,6-diphenyl pyridazin-3(2*H*)-one (**8)** displayed most potent anti-inflammatory activity with ulcerogenic sparing effects.

Keywords: Pyridazin-3(2*H*)-one, Anti-inflammatory, Gastric ulcerogenic activity, Cyclooxygenase.

INTRODUCTION

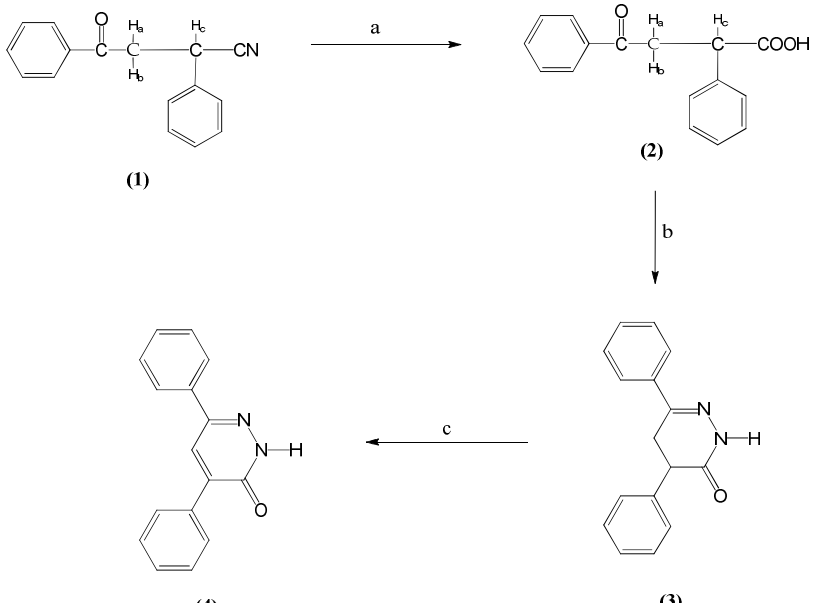
Inflammation is a local response or reaction of the living tissues being subjected to trauma of some kind, which causes tissue injury.[1] It is a normal and essential response to any noxious stimulus that threatens the host and may vary from a localized response to a generalized response. Non-steroidal anti-inflammatory drugs (NSAIDs) continue to be one of the most widely used group of the therapeutic agents for controlling pain and inflammation.[2] It is widely held that the inhibition of cyclooxygenase and subsequent inhibition of prostaglandin synthesis by NSAIDs is responsible for their analgesic, anti-inflammatory and antipyretic activities.[3,4] The traditional NSAIDs inhibit both COX-1 and COX-2 enzymes with a varying degree of selectivity and generally cause greater gastrointestinal bleeding and renal toxicity in comparison to those with greater selectivity for COX-2 enzyme.[5,6] Therefore, the development of safer and potent anti-inflammatory agents with increased selectivity towards COX-2 is still a necessity to overcome the side effects of the existing agents.

Pyridazin-3(2*H*)-one derivatives have attracted the attention of medicinal chemists during the last decade due to their diverse pharmacological activities. Easy functionalization of pyridazinone nucleus results in the designing and synthesis of new drugs of potential therapeutic utility.[7] Pyridazinones show a diverse range of agrochemical and pharmacological activities, including cardiotonic, antibacterial, antifungal, anti-inflammatory, antiulcer, and antiplatelet activity.[8-10] In this regard a considerable number of 3(2*H*)-pyridazinone derivatives endowed with potent anti-inflammatory properties along with good COX-2 selectivity have been well cited in various literature reports.[11-13] Keeping in mind the easy functionalization of various ring positions of pyridazinone skeleton, we envisaged the new structural modifications of the this core nucleus to produce derivatives with good anti-inflammatory potential without any ulcerogenic effects.

RESULTS AND DISCUSSION

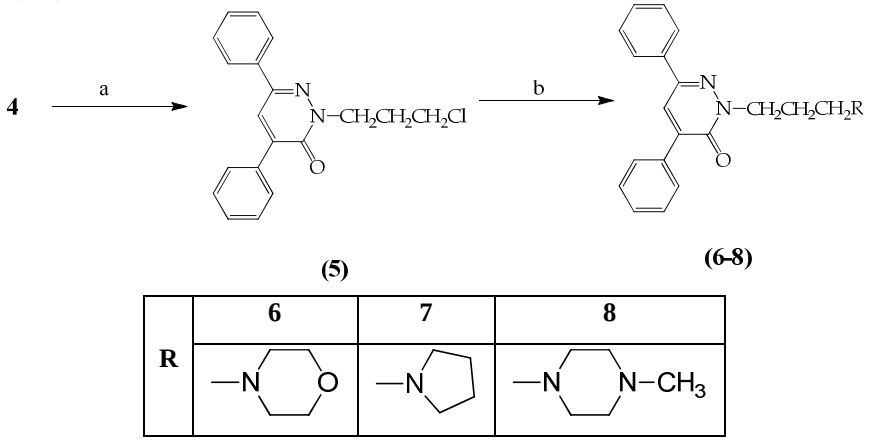
Chemistry

2,4-Diphenyl-4-oxobutyronitrile (**1**) was synthesized by refluxing in acetone cyanohydrin and aqueous tetramethylammonium hydroxide (25%) according to the reported procedure.[14] Acidic hydrolysis followed by subsequent cyclization of γ-keto acid (**2**) by hydrazine hydrate in 1-butanol afforded 4,6-diphenyl-4,5-dihydro-3(2*H*)-pyridazinone (**3**). The dehydrogenation of pyridazinone nucleus at the 4 and 5 positions was achieved by simultaneous stirring and heating for 3 h at 70°C in bromine-acetic acid to afford of 4,6-diphenylpyridazin-3(2*H*)-one (**4**)[15] as shown in scheme 1.



Scheme 1 Synthetic route to the formation of 4,6-diphenylpyridazin-3(2*H*)-one (4). Reagents and reaction conditions: a) 10N HCl, reflux; b) *n*-butanol, hydrazine hydrate, reflux; c) acetic acid, bromine, heat.

It has been reported in the literature that substitution at position 2 of the pyridazinone ring exhibit significant increase in the anti-inflammatory activity.[16] It is further indicated that substitution of aminoalkyl moieties at N-2 of pyridazinone ring results in improved anti-inflammatory potency. Therefore it was planned to synthesize various 2-substituted pyridazinones. For synthesis of such derivatives, a chloropropyl side chain was introduced by treating **4** with 1-bromo-3-chloropropane in ethylmethyl ketone to afford 2-(3-chloropropyl)-4,6-diphenylpyridazin-3(2*H*)-one (**5**) as depicted in scheme 2. In NMR spectrum, alkyl side chain protons resonated as triplets at δ 2.42 (-C*H*$_2$-), 3.68 (-NC*H*$_2$-) and 4.50 ppm (-C*H*$_2$Cl) and aromatic protons as multiplets at 7.47 and 7.85 ppm. *N*-chloropropyl substituted pyridazinone **5** on treatment with various heterocyclic amines such as morpholine, pyrrolidine and *N*-methylpiperazine afforded the target 2-aminoalkyl substituted 4,6-diaryl pyridazin-3(2*H*)-ones **6-8**.



Scheme 2: Synthetic route to the formation of pyridazinones 5-8. Reagents and reaction conditions: a) chloro bromo propane, ethyl methyl ketone, anhyd. K_2CO_3, heating; b) Requisite amine, heating

The structures of compounds **6-8** were characterized using ^{1}HNMR and mass spectral analyses. Morpholine substituted derivative **6** could not be crystallized out, so its hydrochloride salt was prepared by passing dry hydrogen chloride gas through the etheral solution. In NMR spectrum, 4 methylene protons attached to nitrogen of morpholine resonated at δ 2.4 while (OC*H*$_2$)$_2$ protons appeared downfield at 3.6 ppm. 2-(3-Pyrrolidinopropyl)-4,6-diphenylpyridazin-3(2*H*)-one (**7**) showed broad peaks of 4 methylene protons attached to nitrogen of pyrrolidine separately at δ 2.90 and 3.26 ppm. *N*-methylpiperazine substituted pyridazinone **8** showed a 10 protons multiplet ranging from δ 2.56-2.67 ppm for protons of piperazine ring. Molecular ion peak at 376.5 (M^+), 360.5 (M^+) and 389.5 (M^+) with 100% intensity in mass spectra confirmed the formation of compounds **6-8**.

Biological evaluation

Anti-inflammatory activity

The pyridazinones **6-8** were evaluated for their anti-inflammatory potency using carrageenan induced hind paw edema model in male wistar rats.[17] The compounds were given orally as suspension at doses of 20 mg/kg and 40 mg/kg. Celecoxib and indomethacin were used as a standards at 20 mg/Kg. Paw edema was measured at 0, 30, 60, 120, 180 and 240 min after the administration of carrageenan. The results obtained have been summarized in table-1. All the 2-aminoalkyl-4,6-diphenylpyridazinone derivatives exhibited potent anti-inflammatory effects showing 67.39 to 93.48% inhibition of edema at 40 mg/kg after 240 min. In general, all the tested compounds produced dose dependent inhibition of edema, being more effective at 40 mg/kg than 20 mg/kg. *N*-methylpiperazine substituted derivative (**8)** seems to be the most potent of all the newly synthesized derivatives with 93.48 % inhibition of edema in comparison to indomethacin (80.8%) as well as celecoxib (82.61%) at 20 mg/kg.

Table 1 Anti-inflammatory activity and Gastric Ulcer Index (G.I.) of various newly synthesized pyridazinones and standard drugs

Compd. No.	Dose (mg/kg)	Edema Volume (ml) ± SEM (% inhibition)						
		30 min	60 min	90 min	120 min	180 min	240 min	G.I.
6	20	0.2±0.03 (4.76)	0.30±0.03 (23.08)	0.29±0.02 (32.56)*	0.25±0.02 (43.18)**	0.23±0.02 (50.00)***	0.22±0.04 (52.17)**	0/5
	40	0.19±0.02 (9.52)	0.23±0.04 (41.03)*	0.19±0.05 (55.81)**	0.18±0.04 (59.09)***	0.09±0.02 (80.43)***	0.07±0.04 (84.78)***	0/5
7	20	0.19±0.03 (9.52)	0.28±0.04 (28.21)	0.25±0.06 (41.86)*	0.26±0.04 (40.19)*	0.24±0.03 (47.83)**	0.24±0.02 (47.83)**	0/5
	40	0.21±0.05 (0.00)	0.28±0.05 (28.21)	0.21±0.04 (51.16)*	0.20±0.05 (54.55)**	0.18±0.02 (60.87)***	0.15±0.02 (67.39)***	0/5
8	20	0.18±0.04 (14.29)	0.23±0.03 (41.03)*	0.20±0.04 (53.49)**	0.13±0.03 (70.45)***	0.10±0.04 (78.26)***	0.09±0.02 (80.43)***	0/5
	40	0.19±0.02 (9.52)	0.20±0.05 (48.22)*	0.15±0.04 (65.12)***	0.06±0.03 (86.36)***	0.05±0.02 (89.13)***	0.03±0.02 (93.48)***	0/5
Control		0.21±0.01	0.39±0.04	0.43±0.04	0.44±0.03	0.46±0.05	0.46±0.06	0/6
Celecoxib	20	0.20±0.03 (4.76)	0.20±0.05 (48.72)**	0.17±0.04 (60.47)***	0.13±0.02 (70.45)***	0.08±0.03 (82.61)***	0.08±0.02 (82.61)***	0/6
Indomethacin	20	0.13±0.03 (38.1)*	0.22±0.02 (43.6)**	0.21±0.01 (51.2)***	0.15±0.001 (65.1)***	0.08±0.005 (82.6)***	0.05±0.00 (80.8)*	1/6

Data is represented as mean±S.E.M. (n=5). Results were analyzed using one way ANOVA followed by post hoc Dunnett's test. *p<0.05, **p<0.01 and ***p<0.001 as compared to control value at respective time point.

Gastric ulcerogenic activity

Rats were killed under deep ether anesthesia 24h after the anti-inflammatory activity experiment, and their stomachs were removed.[18] The results revealed that at 40 mg/kg none of the synthesized derivative showed any sign of gastric complications in comparison to standard drugs celecoxib and indomethacin.

EXPERIMENTAL

Instrumentation and chemicals

elting points of synthesized compounds were determined on a Veego melting point apparatus and are uncorrected. IR spectra were recorded on Perkin-Elmer RX1 FTIR spectrophotometer model as potassium bromide pellets (υ_{max} in cm^{-1}). The ^{1}H NMR and ^{13}C

NMR were recorded on Bruker AC-400F, 400 MHz spectrophotometer using either DMSO-d_6 or $CDCl_3$ as solvent. Chemical shifts are reported in δ ppm units with respect to TMS as internal standard. Mass spectra were determined on an Applied Biosystems API 2000^{TM} mass spectrometer. The purity of the compounds was established by thin layer chromatography (TLC) and elemental analysis. The monitoring of the rate of reaction was done on TLC plates prepared according to Stahl's method using ethyl acetate as solvent and plates were activated at temperature of 110^o C for 30 min. The elemental analysis (C, H, N) of the compounds was performed on Perkin-Elmer-2400 CHN elemental analyzer. Results of elemental analysis were within ± 0.4% of the theoretical values. The spin multiplicities are denoted as singlet (s), broad singlet (br s), doublet (d), double doublet (dd), triplet (t), doublet of triplets (dt), etc. All the chemicals and reagents used in the synthesis were purchased from Aldrich, Himedia, Qualigens and Merck. The *in vivo* acute anti-inflammatory activity was carried out using digital plethysmometer (Ugo-Basile, Italy).

2,4-Diphenyl-4-oxobutanoic acid (2)

A solution of 2,4-diphenyl-4-oxobutyronitrile (**1**, 1 g, 3.9 mmol) in hydrochloric acid (10 N, 23 ml) was stirred at room temperature for 2 h, and then heated on a steam bath for 3 h. The reaction mixture was cooled and the product obtained was filtered, washed with water and dried. Yield: 37.03%; mp: 112-115 °C (lit[15] 127 °C; ^{1}H NMR ($CDCl_3$): δ 3.30 (dd, 1H, -COCH(*H*)-, J_{ac} = 4.2 Hz, J_{ab} = 18.08 Hz), 3.90 (dd, 1H, -COC(*H*)H, J_{bc} = 10.10 Hz, J_{ab} = 18.08 Hz), 4.31 (dd, 1H, -$COCH_2CHCOOH$-, J_{ac} = 4.20 Hz, J_{bc} = 10.12 Hz), 7.25-7.38 (m, 5H, Ar*H*), 7.45 (t, 2H, Ar*H*, J_o = 7.66 Hz), 7.56 (t, 1H, Ar*H*, J_o = 7.38 Hz) and 7.96 ppm (dd, 2H, Ar*H*, J_o = 8.23 Hz, J_m = 1.16 Hz).

4,6-Diphenyl-4,5-dihydropyridazin-3(2*H*)-one (3)

Hydrazine hydrate (2 ml) was added to a solution of 2,4-diphenyl-4-oxobutanoic acid (**2**, 0.5 g, 1.96 mmol) in 1-butanol (9.5 ml). The reaction mixture was refluxed for 6 h and the reaction was monitored by TLC for completion. Then the mixture was concentrated and cooled. The solid product separated was filtered off, washed with water, dried and recrystallized from ethanol (0.35 g, 70%), mp: 163-165 °C (lit[15] 163 °C) ^{1}H NMR ($CDCl_3$): δ 3.22 (dd, 1H, -COCH(*H*)-, J_{gem} = 16.92 Hz, J_{vic} = 9.4 Hz), 3.32 (dd, 1H, -COC(*H*)H, J_{gem} = 16.94 Hz, J_{vic} = 7.14 Hz), 3.86 (dd, 1H, 4-C*H*, pyridazinone, J_{vic} = 9.34 Hz, J_{vic} = 7.18 Hz), 7.25-7.31 (m, 3H, Ar*H*), 7.33-7.37 (m, 2H, Ar*H*), 7.39-7.42 (m, 3H, Ar*H*), 7.69-7.74 (m, 2H, Ar*H*) and 8.8 ppm (s, 1H, -N*H*, pyridazinone).

4,6-Diphenylpyridazin-3(2*H*)-one (4)

A vigorously stirred solution of 4,5-diphenyl-4,5-dihydro-3(2*H*)-pyridazinone (**3**, 0.5 g, 2.0 mmol) in acetic acid (9 ml) was heated to about 60-70°C. Bromine (0.5 ml) was added dropwise for 15 min. The mixture was further stirred for 3 h and then poured into ice water. The solid thus separated was filtered off, washed with water, dried and recrystallized from ethanol (0.48 g, 96.8%), mp: 179-181 °C (lit[15] 181 °C).

IR (KBr)υ_{max}: 3284.8 (NH), 3017.6 (C-H, aromatic), 2941.5 (C-H, aliphatic), 1645.6 (C=O), 1592.7 (C=C, aromatic) and 1574.2 cm^{-1} (C=N); ^{1}H NMR ($CDCl_3$): δ 7.42-7.52 (m, 6H, Ar*H* and 5-C*H*, pyridazinone), 7.82-7.85 (m, 3H, Ar*H*), 7.91 (dd, 2H, Ar*H*, J_o = 7.08 Hz, J_m = 1.68 Hz) and 12.4 ppm (s, 1H, -N*H*, pyridazinone).

2-(3-Chloropropyl)-4,6-diphenylpyridazin-3(2*H*)-one (5)

1-Bromo-3-chloropropane (0.5 ml, 5.06 mmol) was added to a stirred and refluxing suspension of 4,6-diphenylpyridazin-3(2*H*)-one (**4**, 0.5 g, 2.0 mmol) and potassium carbonate (1.5 g) in ethyl methyl ketone (50 ml). The reaction mixture was further refluxed for 4 h with continuous stirring. The completion of the reaction was monitored by TLC. On completion, the reaction mixture was cooled, filtered and the excess solvent was removed under reduced pressure to obtain an oily residue, which solidified on keeping.

Yield: 75.0%; mp: 62-65 °C; IR (KBr)υ_{max}: 3064.7 (C-H, aromatic), 2952.5 (C-H, aliphatic), 1642.3 (C=O) and 1595.07 cm^{-1} (C=C, aromatic); ^{1}H NMR ($CDCl_3$): δ 2.4 (p, 2H, -CH_2-, *J* = 6.66 Hz), 3.68 (t, 2H, NCH_2-, *J* = 6.56 Hz), 4.5 (t, 2H, -CH_2Cl, *J* = 6.8 Hz), 7.44-7.50 (m, 6H, Ar*H*), 7.79 (s, 1H, 5-C*H*, pyridazinone) and 7.82-7.85 ppm (m, 4H, Ar*H*); Anal. Calcd. for $C_{19}H_{17}N_2OCl$: C, 70.26; H, 5.28; N, 8.62%. Found: C, 70.59; H, 5.49; N, 8.97%.

2-(3-Morpholinopropyl)-4,6-diphenylpyridazin-3(2*H*)-one (6) hydrochloride

A mixture of 2-(3-chloropropyl)-4,6-diphenylpyridazin-3(2*H*)-one (**5**, 0.2 g, 0.53 mmol) in morpholine (1 ml, in excess) was heated at 70-80°C with continuous stirring. The mixture was further stirred with heating for 3 h and reaction was monitored by TLC. On completion, ice cold water was added to the reaction mixture. The precipitated sticky solid was washed several times with distilled water to remove any unreacted morpholine. As the sticky material could not be crystallized, its hydrochloride salt was prepared by passing dry HCl gas in etheral solution. The solid obtained was filtered, washed well with dry ether and crystallized from absolute ethanol to obtain hydrochloride salt of 2-(3-Morpholinopropyl)-4,6-diphenylpyridazin-3(2*H*)-one.

Yield: 43.14%; mp: 179-180 °C; IR (KBr)υ_{max}: 3055.6 (C-H, aromatic), 2925.6 (C-H, aliphatic), 1651.5 and 1635.2 (C=O), 1590.2 (C=C, aromatic), 1259.2 (C-N) and 1108.9 cm^{-1}(C-O-C); ^{1}H NMR (DMSO-d_6): δ 2.13 (p, 2H, -NCH_2CH_2CH_2N-, *J* = 6.0 Hz), 2.45 (4H, –N(CH_2)$_2$, morpholine), 2.51 (t, 2H, -CH_2N, *J* = 7.04 Hz), 3.68 (t, 4H, -O(CH_2)$_2$, morpholine, *J* = 4.6 Hz), 4.39 (t, 2H, -NCH_2CH_2CH_2N, *J* = 7.2 Hz), 7.42-7.49 (m, 6H, Ar*H*), 7.76 (s, 1H, 5-C*H*, pyridazinone) and 7.82-7.84 ppm (m, 4H, Ar*H*); ESI-MS = 376.5 [M^+]; Anal. Calcd. for $C_{23}H_{25}N_3O_2$.HCl: C, 67.06; H, 6.36; N, 10.20%. Found: C, 67.39; H, 6.49; N, 9.97%.

2-(3-Pyrrolidinopropyl)-4,6-diphenylpyridazin-3(2*H*)-one (7)

A mixture of 2-(3-chloropropyl)-4,6-diphenylpyridazin-3(2*H*)-one (**5**, 0.2 g, 0.55 mmol) in pyrrolidine (1 ml, in excess) was heated at 70-80°C with continuous stirring. The

mixture was further stirred with heating for 3 h and reaction was monitored by TLC. On completion, ice cold water was added to the reaction mixture. The precipitated sticky solid was washed several times with distilled water to remove any unreacted pyrrolidine. The sticky material was crystallized from aqueous ethanol.

Yield: 56.81%; mp: 114-116 °C; IR (KBr)υ_{max}: 3049.6 (C-H, aromatic), 2949.2 (C-H, aliphatic), 1639.2 (C=O), 1594.0 (C=C, aromatic), 1323.5 (C-N), 1144, 1026, 754 and 696 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.07 (s(br), 2H, -CH_2-, pyrrolidine, J = 7.6 Hz), 2.53-2.58 (m, 2H, –CH_2-, pyrrolidine), 2.90 (s(br), 2H, -NCH_2, pyrrolidine, J = 7.04 Hz), 3.26 (s(br), 2H, -NCH_2 , pyrrolidine, J = 4.60 Hz), 3.76 (s(br), 2H, -NCH_2, pyrrolidine), 4.45 (t, 2H, -NCH_2CH$_2$CH$_2$, J = 6.36 Hz) 7.47-7.58 (m, 6H, Ar*H*), 7.56 (s, 1H, 5-C*H*, pyridazinone) and 7.84-7.86 ppm (m, 4H, Ar*H*); ESI-MS = 360.5 [M^+]; Anal. Calcd. for $C_{23}H_{25}N_3O$: C, 76.85; H, 7.01; N, 11.69%. Found: C, 76.59; H, 7.79; N, 11.97%.

2-(3-(N-methylpiperazino)propyl)-4,6-diphenylpyridazin-3(2*H*)-one (8) hydrochloride

A mixture of 2-(3-chloropropyl)-4,6-diphenylpyridazin-3(2*H*)-one (**5**, 0.3 g, 0.78 mmol) in morpholine (1.5 ml, in excess) was heated at 70-80°C with continuous stirring. The mixture was further stirred with heating for 3 h and reaction was monitored by TLC. On completion, ice cold water was added to the reaction mixture. The precipitated sticky solid was washed several times with distilled water to remove any unreacted *N*-methylpiperazine. As the sticky material could not be crystallized, its hydrochloride salt was prepared by passing dry HCl gas in etheral solution. The solid obtained was filtered, washed well with dry ether and was crystallized from absolute ethanol to obtain hydrochloride salt.

Yield: 39.05 %; mp 160-163 °C; IR (KBr)υ_{max}: 2950.8 (C-H, aliphatic), 1643.6 (C=O), 1592.4 (C=C, aromatic), 1490.7 (C=N) and 1322.6 cm^{-1} (C-N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.13 (p, 2H, -NCH$_2$CH_2CH$_2$N-), 2.44 (s, 3H, N-CH_3), 2.56-2.67 (m, 10H, -CH_2-N, 2×-N(CH_2)$_2$, *N*-methylpiperazine), 4.37 (t, 2H, -NCH_2CH$_2$CH$_2$N, J = 7.24), 7.42-7.48 (m, 5H, Ar*H*), 7.57 (s, 1H, 5-C*H*, pyridazinone), and 7.82-7.8 ppm6 (m, 5H, Ar*H*); ESI-MS = 389.5 [M^+]; Anal. Calcd. for $C_{24}H_{28}N_4O$.HCl: C, 67.83; H, 6.88; N, 13.18%. Found: C, 67.59; H, 6.59; N, 12.97%.

Biological activity

Anti-inflammatory activity

All the synthesized derivatives were evaluated for anti-inflammatory activity using carrageenan induced hind paw edema model[17] in male wistar rats (120-130 g). Animals were provided with regular rodent pellet diet (Ashirwad Industries, Chandigarh) and purified water ad libitum. The food was withdrawn one day before the experiment, but allowed free access to water. The experimental study protocol was duly approved by institutional animal ethics committee (IAEC), Panjab University and strictly carried out in accordance with the guidelines of committee for the purpose of control and supervision of experiments on animals (CPCSEA), Government of India. Acute edema in the hind paws of the rats was induced by injecting 0.1 ml of freshly prepared 1% solution of carrageenan

in distilled water under the plantar aponeurosis of right hind paw. The suspensions of 20 and 40 mg/kg of the respective compounds, uniformly dispersed in distilled water by adding 0.1 ml of Tween 80, were given to test animals orally an hour prior to the administration of carrageenan. The control group received the same experimental handling as test group except that equivalent doses of vehicle alone were administered by the same route in place of test compounds. The paw volumes were measured using plethysmometer (UGO BASILE) before and after 30, 60, 90, 120, 180 and 240 min of injecting carrageenan. Indomethacin and celecoxib were used as the standard anti-inflammatory drugs.

The percent inhibition of inflammation was calculated using following formula:

$$\%\ inhibition\ of\ inflammation = 100[1 - \frac{a - x}{b - y}]$$

where x and a are the mean foot volumes of the rats before and after the administration of carrageenan injection respectively, treated with test compounds or standard drug, whereas y and b are the mean foot volumes of the rats before and after the administration of carrageenan, respectively, in the control group. Animals were also observed for 24 h and the mortality rate was recorded for each group at the end of the observation period.

Gastric ulcerogenic effect

Rats were killed under deep ether anesthesia 24h after the anti-inflammatory experiment, and their stomachs were removed. The abdomen of each rat was opened through great curvature and examined for lesions or bleedings using a hand lens. 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 severity index of the gastric mucosal damage.[18]

CONCLUSION

The substitution of aminoalkyl moieties at N-2 of pyridazinone ring results in improved anti-inflammatory potency with excellent gastrointestinal safety profile. 2-(3-(*N*-methylpiperazino)propyl)-4,6-diphenylpyridazin-3(2*H*)-one (**8)** displayed most potent anti-inflammatory activity with no ulcerogenic effects.

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Conflict of interest

Authors declare no conflict of interest.

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