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Research Letter

Synthesis of Some Novel 2-[2-(aroyl-aroxy)-methyl]-4-phenyl-1,3-thiazoles as Potent Anti-Inflammatory Agents

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A series of 2-[2-(aroyl-aroxy)-methyl]-4-phenyl-1,3-thiazoles 4a–j were obtained via multiple step synthesis sequence beginning with the hydroxybenzophenones (1a–g). Hydroxybenzophenones on reaction with chloroacetonitrile affords [(2-benzoyl) phenoxy] acetonitrile (2a–g), which reacts with H_2S/NH_4OH and yields [(2-benzoyl) phenoxy] acetothiamide (3a–g), which on treatment with phenacylbromides affords 2-[2-(aroyl-aroxy)-methyl]-4-phenyl-1,3-thiazoles (4a–j). All the newly synthesized compounds were evaluated for their anti-inflammatory activity and were compared with standard drugs. Of the compounds studied, (4g), compounds with chloro substituents showed more potent activity than the standard drug phenyl butazone at all doses tested.

Key words: anti-inflammatory activity, benzophenones, 1,3-thiazoles

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Inflammatory responses are considered to be intervened by the prostaglandins (PGs) derived from arachidonic acid by the action of PG H synthase, which is also referred to as cyclooxygenase (COX) (1,2). Recent studies have shown that COX exists in two isoforms COX-1 and COX-2. Both COXs are constitutively expressed in most tissues, but COX-2, in contrast to COX-1, is the mitogen-inducible isoform. The inducing stimuli for COX-2 include pro-inflammatory cytokines and growth factors, implying a role for COX-2 in both inflammation and control of cell growth (3–5). Cyclooxygenase isoforms are almost identical in structure but have important differences in substrate and inhibitor selectivity and in their intracellular locations (6). Protective PGs, which preserve the integrity of the stomach lining and maintain normal renal function in a compromised kidney, are synthesized by COX-1. In addition to the induction of COX-2 in inflammatory lesions, it is present constitutively in the brain and spinal cord, where it may be involved in nerve transmission, particularly those for pain and fever. Cyclooxygenase is the principal target of non-steroidal anti-inflammatory drugs, and metabolites of the COX pathway are widely accepted as mediators of the inflammatory response. Non-steroidal anti-inflammatory drugs block the formation of PGs and have anti-inflammatory, analgesic and antipyretic activity (7,8). The discovery of COX-2 has made possible the design of drugs that reduce inflammation without removing the protective PGs in the stomach and kidney made by COX-1.

The thiazole ring is very important, in nature they appear in variety of biologic compounds, for example, thiamine (vitamin B_1) (9,10). Some synthetic thiazoles have also exhibited a range of biologic activities, such as antitumor (11–13), antibiotic (14) antifungal (15) and anti-inflammatory activities (16–18) as well as agrochemical products. Among them, ritonavir is a well-known anti-HIV drug, and imidacloprid is an important insecticide.

The proficiency of benzophenone analogues as chemotherapeutic agent especially as anti-inflammatory is well documented (19). Recently, synthesis and structural activity relationship of benzophenones as novel class of p38 MAP kinase inhibitors with high anti-inflammatory activity have been reported (20). In light of these observations and our exploration for new molecules with anti-inflammatory activity (21,22) encouraged us to integrate 1,3 thiazole moiety in benzophenone framework, because these systems posses well-documented anti-inflammatory activity. We have focused our interest on the synthesis and biologic evaluation of substituted 2-[2-(aroyl-aroxy)-methyl]-4-phenyl-1,3-thiazoles **4a–j**, using electron withdrawing and electron donating substituents on the aromatic rings, for a rational study of the structural activity relationships.

Experimental Section

Materials and methods

Chemicals were purchased from Aldrich Chemical Co (Milwaukee, WI, USA). TLC was performed on Merck (India) 60 F-254 silica gel plates with visualization by UV-light. Melting points were determined on a Büchi (Switzerland) Melting Point B-545. The IR spectra (in KBr pellets) were recorded on a Nicolet 6700 FT-IR (Thermo Fisher Scientific Inc., Waltham, MA, USA). ^{1}H NMR spectra were recorded on Bruker (USA) spectrometer 300 and 400 MHz instruments, in $CDCl_3$. Chemical shifts were recorded in parts per million downfield from tetramethylsilane. Mass spectra were recorded

using LC-MS- Agilent (USA) 1100 series with MSD (Ion trap) using 0.1% aqueous trifluoroacetic acid in acetonitrile system on C18-BDS column for 10 min duration, and elemental analysis was performed on Thermo Finnigan (USA) FLASH EA 1112 CHN analyzer, analysis results are within 0.4% of the calculated value. Column chromatography was performed on silica gel (230–400 mesh) supplied by PD Navkar Bio Chem Pvt. Ltd. (Bangalore, India).

General procedure for the synthesis of [(2-benzoyl)phenoxy]acetonitrile 2a–g

A mixture of **1a**, (10 g, 0.036 mol) chloroacetonitrile (2.71 g, 0.036 mol) in dry acetone and anhydrous potassium carbonate (5 g, 0.036 mol) was refluxed with catalytic amount of sodium iodide for 8 h, the reaction mixture was cooled and filtered through celite, and filtrate was concentrated. The residue was purified by column chromatography (60–120 silica gel mesh), using 1–5% ethyl acetate-pet ether and solvent was concentrated to get 2a (yield 75%) as a brown oil.

(2-benzoyl-4-bromophenoxy)acetonitrile 2a

Yield 75%; oily product; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.9 (s, 2*H*, OCH_2), 7.09–7.11 (d, 1*H*), 7.3 (m, 1*H*), 7.42–7.55 (m, 3*H*), 7.60–7.62 (m, 1*H*), 7.81 (m, 2*H*). MS: *m/z* = 316.0 (M^+).

(2-benzoyl-4-chlorophenoxy)acetonitrile 2b

Yield 70%; oily product; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.91 (s, 2*H*, OCH_2), 7.10–7.12 (d, 1*H*), 7.32 (m, 1*H*), 7.40–7.53 (m, 3*H*), 7.60–7.62 (m, 1*H*), 7.80 (m, 2*H*). MS: *m/z* = 272.0 (M^+).

(2-benzoyl-4-methylphenoxy)acetonitrile 2c

Yield 78%; oily product; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 3*H*), 4.7 (s, 2*H*, OCH_2), 7.03–7.061 (d, 1*H*), 7.23 (m, 1*H*), 7.32–7.35 (m, 2*H*), 7.44–7.49 (m, 2*H*), 7.57–7.62 (m, 1*H*), 7.79–7.81 (d, 1*H*). MS: *m/z* = 252.0 (M^+).

[2-(4-chlorobenzoyl)-4-methylphenoxy]acetonitrile 2d

Yield 67%; oily product ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 3*H*, CH_3), 4.7 (s, 2*H*, OCH_2), 7.09–7.11 (d, 1*H*), 7.3 (m, 1*H*), 7.42–7.55 (m, 2*H*), 7.60–7.62 (m, 2*H*), 7.81 (m, 1*H*). MS: *m/z* = 286.0 (M^+).

[4-chloro-2-(4-chlorobenzoyl)phenoxy]acetonitrile 2e

Yield 56%; oily product ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.7 (s, 2*H*, OCH_2), 7.10–7.13 (d, 1*H*), 7.3 (m, 1*H*), 7.42–7.55 (m, 3*H*), 7.60–7.62 (m, 1*H*), 7.81 (m, 1*H*). MS: *m/z* = 306.0 (M^+).

[2-(4-bromobenzoyl)-4-methylphenoxy]acetonitrile 2f

Yield 77%; oily product ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.34 (s, 3*H*, CH_3), 4.7 (s, 2*H*, OCH_2), 7.09–7.11 (d, 1*H*), 7.3 (m, 1*H*), 7.42–7.55 (m, 2*H*), 7.60–7.62 (m, 2*H*), 7.81 (m, 1*H*). MS: *m/z* = 330.0 (M^+).

[2-(4-bromobenzoyl)-4-chlorophenoxy]acetonitrile 2g

Yield 78%; oily product ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.7 (s, 2*H*, OCH_2), 7.09–7.11 (d, 1*H*), 7.3 (m, 2*H*), 7.42–7.45 (m, 1*H*), 7.60–7.62 (m, 1*H*), 7.81 (m, 2*H*). MS: *m/z* = 351.0 (M^+).

General procedure for the synthesis of [(2-benzoyl) phenoxy] acetothiamide (3a–g)

To a solution of **2a** (5 g, 0.014 mol) in ethanol (100 mL) and ammonium hydroxide (50 mL), hydrogen sulfide gas was passed. After about 2 h, the flask was closed and allowed to stand over night. The solvent was evaporated, and the desired product was purified by flash column chromatography (230–400 silica gel mesh) with ethylacetate-hexane (2:1) to get 3.76g of 3a (yield 68%).

2-(2-benzoyl-4-bromophenoxy)ethanethioamide 3a

Yield 68%; m.p. 184.5–185.1 °C; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.9 (s, 2*H*, OCH_2), 6.92–6.94 (d, 1*H*), 7.62–7.65 (m, 4*H*), 7.66 (br, s 1*H*), 7.77 (m, 1*H*) 7.80–7.82 (m, 2*H*), 8.5 (br, s 1*H*). MS: *m/z* = 351.0 (M^+).

2-(2-benzoyl-4-chlorophenoxy)ethanethioamide 3b

Yield 75%; m.p. 192.2–193.1 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.01 (s, 2*H*, OCH_2), 6.90–6.92 (d, 1*H*), 7.63–7.67 (m. 4*H*), 7.68 (br, s, 1*H*), 7.75 (m, 1*H*) 7.82–7.84 (m, 2*H*), 8.48 (br, s, 1*H*). MS: *m/z* = 306.0 (M^+).

2-(2-benzoyl-4-methylphenoxy)ethanethioamide 3c

Yield 67%; m.p. 187.3–188.5 °C, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.37 (s, 3*H*), 4.94 (s, 2*H*, OCH_2), 6.93–6.96 (d, 1*H*), 7.60–7.63 (m, 4*H*), 7.66 (br, s, 1*H*), 7.78 (m, 1*H*) 7.80–7.82 (m, 2*H*), 8.60 (br, s, 1*H*). MS: *m/z* = 286.0 (M^+).

2-[2-(4-chlorobenzoyl)-4-methylphenoxy]ethanethioamide 3d

Yield 77%; m.p. 191.2–192.5 °C, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3*H*, CH_3), 4.9 (s, 2*H*, OCH_2), 6.92–6.94 (d, 1*H*), 7.63–7.64 (m, 3*H*), 7.67 (br, s, 1*H*), 7.77 (m, 1*H*) 7.80–7.82 (m, 2*H*), 8.5 (br, s, 1*H*). MS: *m/z* = 320.0 (M^+).

2-[4-chloro-2-(4-chlorobenzoyl)phenoxy]ethanethioamide 3e

Yield 74%; m.p. 179.5–180.7 °C, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.9 (s, 2*H*, OCH_2), 6.92–6.94 (d, 1*H*), 7.60–7.63 (m, 3*H*), 7.68 (br, s, 1*H*), 7.76 (m, 1*H*) 7.79–7.81 (m, 2*H*), 8.5 (br, s, 1*H*). MS: *m/z* = 340.0 (M^+).

2-[2-(4-bromobenzoyl)-4-methylphenoxy]ethanethioamide 3f

Yield 75%; m.p. 123.2–124.5 °C, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.35 (s, 3*H*, CH_3), 4.9 (s, 2*H*, OCH_2), 6.92–6.94 (d, 1*H*), 7.63–7.64 (m, 3*H*),

7.67 (br, s, 1*H*), 7.77 (m, 1*H*) 7. 80–7.82 (m, 2*H*), 8.5 (br, s, 1*H*). MS: *m/z* = 365.0 (M^+).

2-[2-(4-bromobenzoyl)-4-chlorophenoxy]ethanethioamide 3g

Yield 73%; m.p. 182.5–183.7 °C, ^{1}H-NMR (300 MHz, $CDCl_3$): δ 5.1 (s, 2*H*, OCH_2), 6.93–6.95 (d, 1*H*), 7.60–7.65 (m, 3*H*), 7.67 (br, s, 1*H*), 7.75 (m, 1*H*) 7. 78–7.81 (m, 2*H*), 8.6 (br, s, 1*H*). MS: *m/z* = 384.0 (M^+).

General procedure for the synthesis of 2-[2-(aroyl-aroxy)-methyl]-4-phenyl-1,3-thiazoles 4a–j

A mixture of **3a** (5 g, 0.014 mol) and phenacyl bromide (3.3 g, 0.014 mol) in ethanol (50 mL) was refluxed for 8 h. Reaction mixture was concentrated and purified by silica gel flash column chromatography with ethylacetate–hexane (1:9), to give 5.2 g of **4a** in 76% yield.

(5-bromo-2-{[4-(4-chlorophenyl)-1,3-thiazol-2-yl]methoxy}phenyl)(phenyl)methanone 4a

Yield 76%; m.p.132.2–133.1 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.3 (s, 2*H*, OCH_2), 6.99–7.01 (d, 1*H*), 7.36–7.40 (m, 2*H*), 7.44–7.49 (m, 2*H*), 7.54–7.60 (m, 3*H*), 7.60–7.61 (m, 3*H*), 7.71–7.76 (d, 2*H*); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 68.11, 114.01, 114.38, 114.60, 127.50, 128.54, 129.85, 131.19, 132.50, 132.58, 133.49, 134.05, 134.63, 137.24, 154.10, 154.36, 165.96, 194.37. MS: *m/z* = 486.0 (M^+); IR (KBr) (ν_{max}/cm): 754, 1592 (C=N), 1447, 1659 (C=O), 3123 (CH Aromatic); Anal. Calcd. for $C_{23}H_{15}BrClNO_2S$: C, 56.98; H, 3.12; N, 2.89. Found: C, 56.88; H, 3.23; N, 2.90.

{5-bromo-2-[(4-phenyl-1,3-thiazol-2-yl)methoxy]phenyl}(phenyl)methanone 4b

Yield 80%; m.p.134.4–139.5 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.3 (s, 2*H*, OCH_2), 6.99–7.01 (d, 1*H*), 7.27 (s, 1*H*), 7.37–7.48 (m, 2*H*), 7.52–7.61 (m, 5*H*), 7.69–7.71 (m, 2*H*), 7.83–7.85 (m, 2*H*); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 68.0, 114.05, 122.18, 127.72, 128.49, 129.78, 131.12, 132.43, 132.95, 133.42, 134.57, 137.18, 154.29, 165.89, 194.28. MS: *m/z* = 530.1 (M^+); IR (KBr) (ν_{max}/cm): 747, 1448, 1591 (C=N), 1665 (C=O), 3104/cm (CH Aromatic); Anal. Calcd. for $C_{23}H_{15}Br_2NO_2S$: C, 52.20; H, 2.86; N, 2.65. Found: C, 52.17; H, 2.95, N, 2.55.

{5-chloro-2-[(4-phenyl-1,3-thiazol-2-yl)methoxy]phenyl}(phenyl)methanone 4c

Yield 67%; m.p.138.3–139.6 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.32 (s, 2*H*, OCH_2), 7.04–7.06 (d, 1*H*), 7.26–7.40 (m, 3*H*), 7.42–7.48 (m, 4*H*), 7.56–7.60 (m, 1*H*), 7.75–7.78 (m, 2*H*), 7.84–7.88 (m, 2*H*); ^{13}C-NMR (100 MHz, $CDCl_3$): δ, 68.18, 114.03, 114.20, 114.60, 127.20, 127.50, 128.56, 128.95, 129.68, 129.85, 130.77, 131.69, 132.59, 133.49, 134.01, 137.25, 153.86, 154.05, 165.97, 194.48. MS: *m/z* = 440.5 (M^+); IR (KBr) (ν_{max}/cm): 778 (C–S–C), 1499, 1595 (C=N), 1656 (C=O), 3099/cm (CH Aromatic); Anal. Calcd. for $C_{23}H_{15}Cl_2NO_2S$: C, 62.73; H, 3.43; N, 3.18. Found: C, 62.60; H, 3.62; N, 2.97.

(2-{[4-(4-bromophenyl)-1,3-thiazol-2-yl]methoxy}-5-chlorophenyl)(phenyl)methanone 4d

Yield 82%; m.p. 128.5–130.8 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.33 (s, 2*H*, OCH_2), 7.04–7.01 (d, 1*H*), 7.27 (s, 1*H*), 7.37–7.48 (m, 4*H*), 7.49–7.61 (m, 3*H*), 7.69–7.72 (d, 2*H*), 7.84–7.87 (d, 2*H*); ^{13}C-NMR (100 MHz, $CDCl_3$): δ, 68.12, 114.04, 114.14, 114.60, 122.17, 127.15, 127.72, 128.48, 129.62, 129.78, 130.72, 131.62, 131.83, 132.96, 133.42, 137.19, 153.78, 154.02, 165.95, 194.41. MS: *m/z* = 486.0 (M^+); IR (KBr) (ν_{max}/cm): 755 (C–S–C), 1454, 1594 (C=N), 1658 (C=O), 3098/cm (CH Aromatic); Anal. Calcd. for $C_{23}H_{15}BrClNO_2S$: C, 56.98; H, 3.12; N, 2.89. Found: C, 56.87; H, 3.25; N, 2.72.

(2-{[4-(4-chlorophenyl)-1,3-thiazol-2-yl]methoxy}-5-methylphenyl)(phenyl)methanone 4e

Yield 70%; m.p. 137.1–138.2 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.3 (s, 3*H*, CH3), 5.5 (s, 2*H*, OCH_2), 7.02–7.05 (d, 1*H*), 7.26–7.32 (m, 2*H*), 7.43–7.49 (m, 5*H*), 7.53–7.58 (m, 1*H*), 7.78–7.89 (m, 4*H*); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.39, 68.05, 113.78, 128.31, 129.16, 130.37, 130.41, 130.45, 130.47, 130.48, 130.50, 130.53, 130.67, 131.45, 132.97, 137.93, 153.25, 153.85, 166.87, 196.28. MS: *m/z* = 420.2 (M^+); IR (KBr) (ν_{max}/cm): 776 (C–S–C), 1457, 1609 (C=N), 1651 (C=O), 3100/cm (CH Aromatic); Anal. Calcd. for $C_{24}H_{18}ClNO_2S$: C, 68.64; H, 4.32; N, 3.34. Found: C, 68.49; H, 4.54; N, 3.19.

(2-{[4-(4-bromophenyl)-1,3-thiazol-2-yl]methoxy}-5-methylphenyl)(phenyl)methanone 4f

Yield 76%; m.p. 139.8–140.9 °C ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.3 (s, 3*H*, CH_3), 5.5 (s, 2*H*, OCH_2), 7.02–7.05 (d, 1*H*), 7.26–7.32 (m, 2*H*), 7.43–7.49 (m, 5*H*), 7.53–7.58 (m, 1*H*), 7.78–7.89 (m, 4*H*); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.39, 68.05, 113.78, 128.31, 129.16, 130.37, 130.38, 130.39, 130.40, 130.41, 130.43, 130.44, 130.48, 131.45, 132.97, 137.93, 153.25, 153.85, 166.87, 196.28. MS: *m/z* = 465.2 (M^+); IR (KBr) (ν_{max}/cm): 768 (C–S–C), 1450, 1620 (C=N), 1658 (C=O), 3098/cm (CH Aromatic); Anal. Calcd. for $C_{24}H_{18}BrNO_2S$: C, 62.07; H, 3.91; N, 3.02. Found: C, 61.95; H, 4.10; N, 2.90.

(5-chloro-2-{[4-(4-chlorophenyl)-1,3-thiazol-2-yl]methoxy}phenyl)(4-chlorophenyl)methanone 4g

Yield 73%; m.p. 134.2–135.3 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ δ 5.5 (s, 2*H*, OCH_2), 7.04–7.07 (d, 1*H*), 7.25–7.31 (m, 2*H*), 7.42–7.48 (m, 4*H*), 7.52–7.57 (m, 1*H*), 7.77–7.87 (m, 4*H*); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 68.10, 113.77, 128.34, 129.05, 130.37, 130.38, 130.39, 130.40, 130.41, 130.43, 130.44, 130.48, 131.45, 132.97, 137.99, 153.23, 153.85, 166.86, 196.30. MS: *m/z* = 475.2 (M^+); IR (KBr) (ν_{max}/cm): 760 (C–S–C), 1446, 1620 (C=N), 1648 (C=O), 3012/cm (CH Aromatic); Anal. Calcd. for $C_{23}H_{14}Cl_3NO_2S$: C, 58.18; H, 2.97; N, 2.95. Found: C, 57.96; H, 3.18; N, 2.80.

(4-chlorophenyl)(5-methyl-2-{[4-(4-methylphenyl)-1,3-thiazol-2-yl]methoxy}phenyl)methanone 4h

Yield 87%; m.p. 135.7–136.7 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.32–2.35 (2s, 6*H*, $2CH_3$), 5.5 (s, 2*H*, OCH_2), 7.02–7.05 (d, 1*H*), 7.26–7.32 (m, 2*H*), 7.43–7.49 (m, 4*H*), 7.53–7.58 (m, 2*H*), 7.78–7.89 (m, 3*H*); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.39, 20.41, 68.11, 113.75, 128.36, 129.10,

130.37, 130.38, 130.40.130.42, 130.45, 130.46, 130.48, 130.49, 131.45, 132.97, 137.99, 153.30, 153.85, 166.86, 197.1. MS: m/z = 435.2 (M^+); IR (KBr) (ν_{max}/cm): 778 (C–S–C), 1450, 1602 (C=N), 1649, 3078/cm (CH Aromatic); Anal. Calcd. for $C_{25}H_{20}ClNO_2S$: C, 69.19; H, 4.65; N, 3.23. Found: C, 68.98; H, 4.75; N, 2.95.

(4-bromophenyl)(5-chloro-2-{[4-(4-chlorophenyl)-1,3-thiazol-2-yl]methoxy}phenyl)methanone 4i

Yield 77%; m.p. 131.2–132.1 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.46 (s, 2*H* OCH_2), 7.02–7.05 (d, 1*H*), 7.26–7.32 (m, 2*H*), 7.46–7.52 (m, 4*H*), 7.54–7.56 (m, 1*H*), 7.78–7.89 (m, 4*H*); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 68.10, 113.77, 128.34, 129.05, 130.37, 130.38, 130.39, 130.40, 130.41, 130.43, 130.44, 130.48, 131.45, 132.97, 137.99, 153.23, 153.85, 166.86, 196.30. MS: m/z = 520.1 (M^+); IR (KBr) (ν_{max}/cm): 776 (C–S–C), 1448, 1623 (C=N), 1649, 3088/cm (CH Aromatic); Anal. Calcd. for $C_{23}H_{14}BrCl_2NO_2S$: C, 53.20; H, 2.72; N, 2.70. Found: C, 52.94; H, 2.95; N, 2.56.

(4-bromophenyl)(5-methyl-2-{[4-(4-methylphenyl)-1,3-thiazol-2-yl]methoxy}phenyl)methanone 4j

Yield 66%; m.p. 128.3–129.4 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.32–2.34 (2s, 6*H*, $2CH_3$), 5.5 (s, 2*H*, OCH_2), 7.02–7.05 (d, 1*H*), 7.26–7.32 (m, 2*H*), 7.43–7.49 (m, 4*H*), 7.53–7.58 (m, 2*H*), 7.78–7.89 (m, 3*H*); ^{13}C-NMR (100 MHz, $CDCl_3$): δ 20.38, 20.40, 68.11, 113.75, 128.36, 129.10, 130.37, 130.38, 130.42, 130.45, 130.46, 130.48, 130.49, 131.45, 132.97, 137.99, 153.30, 153.85, 166.86, 197.10. MS: m/z = 478.3 (M^+); IR (KBr) (ν_{max}/cm): 780 (C–S–C), 1460, 1621 (C=N), 1647, 3099/cm (CH Aromatic); Anal. Calcd. for $C_{25}H_{20}BrNO_2S$: C, 62.76; H, 4.21; N, 2.93. Found: C, 62.56; H, 4.42; N, 2.75.

Results and Discussions

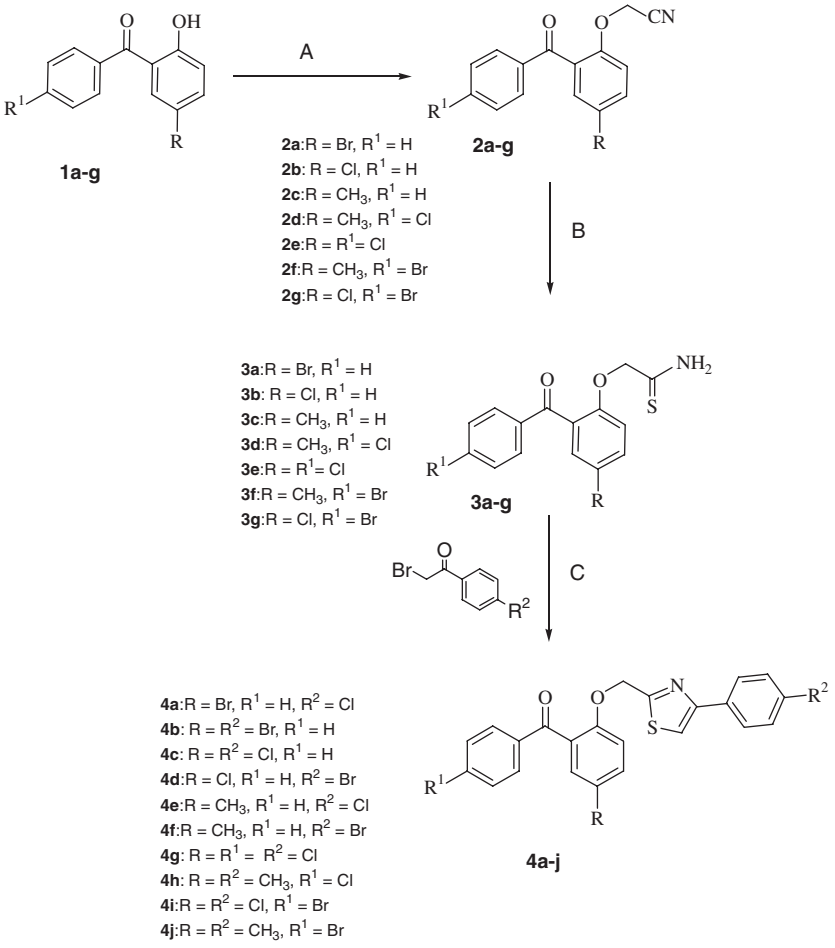
Chemistry

The synthesis of [(2-benzoyl) phenoxy] acetonitriles **2a–g**, was carried out by reaction of hydroxybenzophenone with chloroacetonitrile in excellent yield. This upon treatment with H_2S/NH_4OH yields [(2-benzoyl)phenoxy]acetothiamide **3a–g** (23). The preparation of novel 2-[2-(aroyl-aroxy)-methyl]-4-phenyl-1,3-thiazoles **4a–j** were achieved from **3a–g** with substituted phenacylbromides. The compounds **4a–j** were characterized by IR, ^{1}H, ^{13}C NMR and mass spectrometer (see Scheme 1).

Biologic results and discussions

Anti-inflammatory activity

Adopting winter *et al.* (24) method and using Albino rats paw edema, inhibition test was performed on compounds **4a–j**. To the groups of five rats (body weight 125–160 g), doses of a test



Scheme 1: Reagents and conditions: (A) $ClCH_2CN$, K_2CO_3, acetone, reflux, 8 h; (B) Ethanol, H_2S/NH_4OH, room temperature; (C) Ethanol, reflux.

compounds **4a–j** were dissolved in dimethyl sulphoxide and administrated orally. After 30 min, 0.2 mL of 1% carrageenan suspension in 0.9% sodium chloride solution was injected subcutaneously into planter aponeurosis of the hind paw, and the paw volume was measured by a water plethysmometer socrel and then measured again after a time span of 3 h. The mean increase in paw volume at each time interval was compared with that of control group (five rats treated with carrageenan, but not with test compounds) at the same time intervals. The percentage inhibition values were calculated using the formula:

$$\% \text{ anti-inflammatory activity} = 1 - G_t/G_c \times 100$$

where G_t and G_c represent tested and controls groups, respectively.

Ulcerogenic activity

Groups of 10 rats (body weight 200–230 g) were fasted for 24 h. and were treated with an oral dose of test compound **4a–j**, except control group. All animals were killed 5 h after the completion of dosing. With the aid of a microscope, the stomach and small intestine of the rats were examined to find the incidence of hyperaemia, shedding of epithelium, petechial, frank hemorrhages, and erosion or discrete ulceration with or without perforation. The presence of any of these criteria was considered to be the evidence of ulcerogenic activity (25).

Cyclooxygenase activity

The *in vitro* test on the microsomal fraction of the mucosal preparation of rabbit distal colon was carried out to search out the plausible mechanism of the compounds. By adopting Calderano *et al.* (26) procedure, the preparation was carried out. About 2–3 g of stripped, colonic mucosa was minced and homogenized in three volumes of Tris-buffer 0.1 M, pH 8.0, and the homogenized sample was centrifuged. The precipitate was suspended in Tris-buffer 0.1 M, pH 8.0 and recentrifuged. For enzyme assay COX activity, the microsomal pellet was used immediately. By measuring the rate of conversion of arachidonic acid to PGE_2, COX activity was assayed. About 50 mL of microsomal fractions were incubated with test agents for 10 min at 37 °C in 30 μL Tris–HCl, pH 8.0 containing 2 mM reduced glutathione, 5 mM L-tryptophan, and 1 μM hematin. The substrate 20 μM arachidonic acid with trace amount of [1-^{14}C] arachidonic acid was then added, and the reaction was proceeded for 5 min at 37 °C. The reaction was stopped by the addition of 0.2 mL of ether/methanol/citric acid 0.2 M (30:4:1), which was precooled at −25 °C PGE_2, was extracted twice into the same mixture. The solvent was evaporated under nitrogen stream, and radiolabeled arachidonic acid was separated, and from this radiolabeled arachidonic acid PGE_3 were separated by Reverse Phase HPLC with 2 nmol unlabeled PGE_2 as an internal standard. Prostaglandin G chromatographic profile was obtained by isocratic elution with 150 mM H_3PO_4 in water, pH 3.5, containing 30% acetonitrile, a flow rate of 1 mL/min monitoring the UV absorption at 214 nm. Radioactivity that co-eluted with authentic PGE_2 was quantified by liquid scintillation spectrometry. Test samples were compared to paired control incubations. The percentage of inhibition was calculated as follows:

$$[(\text{c.p.m. control} - \text{c.p.m. test}/(\text{c.p.m. control})) \times 100]$$

Acute toxicity study

Nearly 50% lethal dose (ALD_{50}) of the compounds was determined in albino mice (body weight 25–30 g). The test compounds were injected intraperitoneally at different dose levels in groups of 10 animals. After 24 h of drug administration, percent mortality in each group was observed from the data obtained, ALD_{50} was calculated by adopting Smith (27) method.

Anti-inflammatory activity

The anti-inflammatory activities of all the synthesized compounds have been shown in Table 1. All the compounds **4a–j** have shown

Table 1: Anti-inflammatory data of compounds **4a–j**

Compound	Dose (mg/kg p.o.)	Anti-inflammatory activity % oedema inhibition relative to control	±SEM[a]
4a	20	29.2	±0.0016
	40	30.4	±0.0034
	80	50.5	±0.0009
4b	20	14.7	±0.0044
	40	24.2	±0.0014
	80	47.5	±0.0021
4c	20	16.6	±0.0352
	40	44.6	±0.0101
	80	64.1	±0.0177
4d	20	15.1	±0.0004
	40	29.9	±0.0011
	80	56.4	±0.0004
4e	20	20.6	±0.0232
	40	30.5	±0.0311
	80	60.1	±0.0055
4f	20	15.5	±0.0050
	40	29.4	±0.1002
	80	46.5	±0.0673
4g	20	35.5	±0.1002
	40	48.5	±0.0707
	80	77.1	±0.0013
4h	20	31.4	±0.0180
	40	46.5	±0.0088
	80	63.8	±0.0705
4i	20	23.4	±0.0053
	40	46.5	±0.0067
	80	60.1	±0.0055
4j	20	20.5	±0.0015
	40	35.5	±0.0001
	80	50.5	±0.0009
Phenyl butazone	20	30.1	±0.0002
	40	33.0	±0.0012
	80	55.1	±0.0003
Control	20		
	40	–	–
	60		

[a]Values are means of three determinates and the values are <5%.

good anti-inflammatory activity in the range of 24.2–48.5% at a dose of 40 mg/kg p.o. Among **4a–j**, the compounds **4g** with three chloro groups at the para position, elicited maximum the inhibition of edema (48.5%). Compound **4h** (46.5%) with two methyl and one chloro groups at para position and **4i** (46.5%) with two chloro and one bromo groups at para position elicited same activity. On the other hand, compound **4c** (44.6%) with two chloro groups and among them one chloro attached para to the phenyl ring, which in turn attached to thiazole ring and another chloro attached to benzophenone ring, exhibited less activity compared to **4h** and **4i**. In a similar way, compound **4b** (24.2%) with two bromo groups also exhibited least activity. In addition, compound **4f** (29.4%) with one methyl and one bromo group and **4d** (29.9%) with a chloro and bromo group exhibited little higher activity compared to **4b**. Compound **4a** (30.4%) with a bromo and chloro group and **4e** (30.5%) with a methyl and chloro group have shown comparable activity. Compound **4j** (35.5%) with two methyl and a bromo group at para position in benzophenone moiety has also exhibited high activity. Based on the earlier mentioned results, title compounds have been tested at three graded doses (20, 40 and 80 mg/kg p.o.) and compared with standard drug phenyl butazone. The comparison results with standard drug are listed in Table 1.

Table 2: Ulcerogenic data of compounds **4a–j**

		Ulcerogenic activity	
Compound	Dose (mg/kg p.o.)	% of animal with hyperemia	% of animal with ulcer
4a	100	20	45
	200	35	55
	400	55	80
4b	100	40	10
	200	60	15
	400	80	20
4c	100	25	15
	200	50	25
	400	75	18
4d	100	50	10
	200	70	15
	400	100	20
4e	100	30	20
	200	55	25
	400	90	45
4f	100	25	50
	200	40	65
	400	50	75
4g	100	60	05
	200	80	10
	400	100	15
4h	100	50	15
	200	70	20
	400	90	25
4i	100	50	05
	200	70	10
	400	100	25
4j	100	30	20
	200	55	15
	400	90	45
Phenyl butazone	100	25	35
	200	50	65
	400	80	90
Control	30	–	–
	60		
	90		

p.o., peritoneal orally.

Ulcerogenic activity

The title compound **4a–j** exhibited low degree of ulcer production activity (10–65%) at 200 mg/kg p.o. (Table 2). Among **4a–j**, compound **4g** with three chloro groups at the para position in aromatic ring, exhibited lesser ulcerogenic activity (10%) compared to standard drug phenylbutazone.

Cyclooxygenase assay activity

Compounds **4a**, **4c**, **4g**, **4h**, **4i**, and **4j** showed good COX activity (Table 3), indicating that these compounds reduce inflammatory response by the inhibition of PGs. The other compounds **4b**, **4d**, **4e**, and **4f** did not inhibit the COX activity.

Acute toxicity study

The acute toxicity study of these compounds **4a–j** showed that none of the evaluated compounds produced lethal effects and did not induce any appreciable behavioral change at the administered doses during observation period.

Conclusions and Future Directions

We have described the preparation of 2-[2-(aroyl-aroxy)-methyl]-4-phenyl-1,3-thiazoles **4a–j**. Several compounds have been evaluated as potential anti-inflammatory agents devoid of ulcerogenic potential. In conclusion, this preliminary investigation showed that anti-inflammatory activity of 2-[2-(aroyl-aroxy)-methyl]-4-phenyl-1,3-thiazoles **4a–j** can be significantly modified by substitution on the benzophenone moiety. Among the synthesized compounds, **4g**

Table 3: Cyclooxygenase (COX) data of compounds **4a–j**

Compound	COX activity assay inhibitory action of some selected compound % inhibition 10 μM	ED_{50} (mg/kg p.o.)	ALD_{50} (mg/kg p.o.)
4a	40	60.5	>1000
4b	ni	77.9	>1000
4c	70	57.3	>1000
4d	ni	53.7	>1000
4e	ni	70.1	>1000
4f	ni	75.5	>1000
4g	85	65.5	>1000
4h	70	76.2	>1000
4i	65	63.6	>1000
4j	30	70.1	>1000
Phenyl butazone	85	–	–
Control	ni	–	–

ni, no inhibition; ALD_{50}, 50% lethal dose; p.o., peritoneal orally.

possessed the most prominent and consistent activity with no ulcerogenic effect. Therefore, such compounds would represent a fruitful matrix for the development of a new class of anti-inflammatory agents and would deserve further investigation and derivatization as a promising scaffold.

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