Chem Biol Drug Des 2013; **82:** 147–155

Research Article

Synthesis, Hypoglycaemic, Hypolipidemic and PPARγ Agonist Activities of 5-(2-Alkyl/aryl-6-Arylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene-1,3-Thiazolidinediones

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A novel series of 5-(2-alkyl/aryl-6-arylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene-1,3-thiazolidinediones were synthesized as possible PPARγ agonists. The structures of these target molecules were established by spectral and analytical data. All the newly synthesized compounds were screened for their *in vivo* hypoglycaemic and hypolipidemic activity in male Wistar rats. Further, compounds with good activity were screened for PPARγ agonist activity. Among the screened compounds, 5-{[2-Cyclohexyl-6-(4-methoxy phenyl)imidazo[2,1-b] [1,3,4]thiadiazol-5-yl]methylene}-1,3-thiazolidine-2,4-dione (3i) exhibits promising hypoglycaemic and hypolipidemic activity via potential PPARγ agonist activity.

Key words: 5-(2-alkyl/aryl-6-arylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene-1,3-thiazolidinediones, hypoglycaemic, hypolipidemic, PPARγ agonist activity

Received 19 December 2012, revised 13 February 2013 and accepted for publication 25 March 2013

The treatment of type 2 diabetes has been revolutionized with the advent of thiazolidinedione (TZD) class of molecules that ameliorate insulin resistance and thereby normalize elevated blood glucose levels (1,2). Thiazolidinediones are synthetic, high-affinity ligands of peroxisome proliferator-activated receptor-gamma (PPARγ), a member of the nuclear receptor family that controls the expression of genes in the target tissues of insulin action (3,4). The peroxisome proliferator-activated receptors (PPARs) are legitimate molecular targets for the development of the antidiabetic agents. The reported synthetic ligands such as Pioglitazone (3,5) had high affinity for PPARγ receptor and have significantly improved the clinical situation of type 2 diabetics with serious side-effects of hepatotoxicity, weight gain and oedema. This situation leads to identify strategies to develop new highly effective, safe and orally active antidiabetic agents that could retain the insulin-sensitizing properties of TZDs through PPARγ agonist activity with minimum or no side-effects.

Imidazo[2,1-b][1,3,4]thiadiazole derivatives have attracted the interest of medicinal chemists for many years because of their diverse pharmacological properties such as anticancer (6), antitubercular (7), antibacterial (8), antifungal (9), anticonvulsant, analgesic (10) and antisecretory (11) activities. They have been reported to selectively inhibit several therapeutic receptors and enzymes, extending their applications in modern drug design. Further, there are reports in the literature about the antidiabetic activity of the derivatives containing thiadiazole ring system (12).

In view of the above facts, we herein report the synthesis of novel prototype structures (Figure 1) having fused imidazo[2,1-*b*][1,3,4]thiadiazoles ring linked with various alkyl/aryl/heterocycle moieties at 2nd and 6th position with the objective of exploring the pharmacologically important imidazo[2,1-*b*][1,3,4]thiadiazoles ring system for developing new TZDs to obtain drug candidates with better hypoglycaemic, hypolipidemic and PPARγ agonist activity.

Methods and Materials

Chemistry – general aspects

All reagents were of analytical grade and were used directly. Thin-layer chromatography (TLC) was performed on silica gel plates (60 F254; Merck). Column chromatography was performed using silica gel (100–200 and 60–120 mesh size; Merck). Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on Nicolet Impact 410 FT IR spectrophotometer using KBr pellets. ^{1}H and ^{13}C NMR were recorded on Bruker 300-MHz and 75-MHz FT NMR spectrometer in $CDCl_3$ and TFA with TMS as internal standard. Mass spectra were recorded on Finnigan MAT (Model MAT8200) spectrometer, Shimadzu GCMS-QP2010S, and elemental

 doi: 10.1111/cbdd.12140

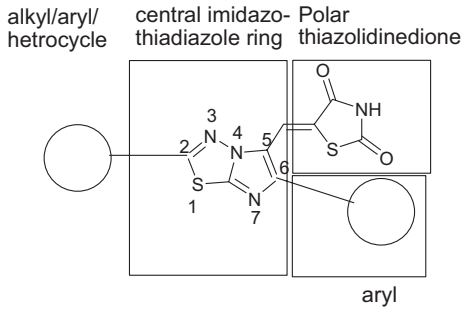


Figure 1: Representation of designed novel prototype structure.

analyses were carried out using Heraus CHN rapid analyzer.

General procedure for preparation of 5-(2-alkyl/aryl-6-arylimidazo [2, 1-b][1,3,4]thiadiazol-5-yl) methylene-1,3-thiazolidinediones (3a–r)

A mixture of 2-alkyl/aryl-6-arylimidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehyde **2** (0.001 mol) and 1,3-thiazolidine-2,4-dione (0.11 g, 0.001 mol) was refluxed in toluene (25 mL) with catalytic amount of piperidine acetate for 2 h. The yellow solid separated was collected by filtration, washed with hot benzene and methanol. The products were recrystallized from dimethylformamide.

5-{[6-(4-Chlorophenyl)-2-ethylimidazo[2,1-b][1,3,4] thiadiazol-5-yl]methylene}-1,3-thiazolidine-2, 4-dione (3a)

Yellow granules (DMF), yield 92%, m.p. 276–728 °C; IR (KBr)/υcm: 3154, 2931, 1730, 1702, 1605, 1549; ^{1}H NMR (300 MHz, $CDCl_3$ + TFA) δ: 1.57(t, J = 3.3 Hz, 3H, $CH_2\underline{CH_3}$), 3.29(q, J = 3.5 Hz, 2H, $\underline{CH_2}CH_3$), 7.47(d, J = 8.9 Hz, 2H, C_3, C_5-H, phenyl), 7.81(d, J = 8.8 Hz, 2H, C_2, C_6-H, phenyl), 7.98 (s, 1H, vinylic proton), ^{13}C NMR (75 MHz, $CDCl_3$ + TFA): 13.7, 21.8, 113.2, 117.1, 119.3, 124.8, 127.0, 130.5, 133.4, 141.5, 146.5, 167.5, 169.4 and 172.0. MS *m/z:* 392 (M + 2), 390 (M^+). Anal. calcd. for $C_{16}H_{11}ClN_4O_2S_2$: C, 49.17; H, 2.84; N, 14.33. Found: C, 49.35; H, 2.89; N, 14.16.

5-{[2-Ethyl-6-(4-methylphenyl)imidazo[2,1-b][1,3,4] thiadiazol-5-yl]methylene}-1,3-thiazolidine-2, 4-dione (3b)

Yellow granules (DMF), yield 90%, m.p. 265–268 °C; IR (KBr)/υcm: 3120, 2924, 1727, 1693, 1604, 1553; ^{1}H NMR (300 MHz, $CDCl_3$ + TFA) δ: 1.61 (t, J = 3.3 Hz, 3H, $CH_2\underline{CH_3}$), 2.46(s, 3H, CH_3), 3.27(q, J = 3.1 Hz, 2H, $\underline{CH_2}CH_3$), 7.42(m, 4H, phenyl), 7.97(s, 1H, vinylic proton); ^{13}C NMR (75 MHz, $CDCl_3$ + TFA) δ: 13.5, 21, 21.8, 113.2, 117.1, 119.0, 124.5, 126.8, 130.5, 132.4, 141.5, 146.5, 167.5, 169.4 and 172.2. MS *m/z:* 370 (M^+). Anal. calcd. for $C_{17}H_{14}N_4O_2S_2$: C, 55.12; H, 3.81; N, 15.12. Found: C, 55.34; H, 3.88; N, 15.01.

5-{[2-Ethyl-6-(4-methoxyphenyl)imidazo[2,1-b] [1,3,4]thiadiazol-5-yl]methylene}-1,3-thiazolidine-2,4-dione (3c)

Yellow granules (DMF), yield 90%, m.p. 258–262 °C;IR (KBr)/υcm: 3158, 2923, 1729, 1698, 1606, 1550, 1177; ^{1}H NMR (300 MHz, $CDCl_3$ + TFA) δ: 1.59(t, J = 7.4 Hz, 3H, $CH_2\underline{CH_3}$), 3.28(q, J = 7.5 Hz, 2H, $\underline{CH_2}CH_3$), 3.86(s, 3H, OCH_3), 7.13(d, J = 8.5 Hz, 2H, C_3, C_5-H, phenyl), 7.53 (d, J = 8.8 Hz, 2H, C_2, C_6-H phenyl), 7.96(s, 1H, vinylic proton); ^{13}C NMR (75 MHz, $CDCl_3$ + TFA): 13.2, 25.9, 55.9, 115.8, 117.9, 118.2, 122.8, 125.7, 131.0, 131.4, 143.2, 162.7, 167.7, 168.3 and 171.0. MS *m/z:* 386 (M^+). Anal. calcd. for $C_{17}H_{14}N_4O_3S_2$: C, 52.84; H, 3.65; N, 14.50. Found: C, 52.97; H, 3.76; N, 14.35.

5-{[6-(4-Chlorophenyl)-2-propylimidazo[2,1-b] [1,3,4]thiadiazol-5-yl]methylene}-1,3-thiazolidine-2,4-dione (3d)

Bright yellow granules (DMF), yield 93%, m.p. 272–276 °C; IR (KBr)/υcm: 3162, 2893, 1729, 1696, 1614, 1556; ^{1}H NMR (300 MHz, C_6D_6 + TFA) δ: 1.08(t, J = 6.3 Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.88 (sextet, J_{CH2CH3} = 6.1 Hz, J_{CH2CH2} = 6.3 Hz, 2H, $CH_2\underline{CH_2}CH_3$), 3.10(t, J = 6.6 Hz, 2H, $\underline{CH_2}CH_2CH_3$), 7.60(d, J = 8.4 Hz, 2H, C_3, C_5-H, phenyl), 7.78(d, J = 8.9 Hz, 2H, C_2, C_6-H, phenyl), 7.98 (s, 1H, vinylic proton); ^{13}C NMR (75 MHz, C_6D_6 + TFA) δ: 13.3, 22.3, 33.0, 55.2, 115.7, 117.6, 118.0, 124.2, 124.9, 126.5, 130.9, 133.0, 142.8, 162.9, 167.3 and 171.2.MS *m/z:* 406 (M + 2), 404 (M^+). Anal. calcd. for $C_{17}H_{13}ClN_4O_2S_2$: C, 50.43; H, 3.24; N, 13.84. Found: C, 50.76; H, 3.32; N, 13.64.

5-{[6-(4-Methylphenyl)-2-propylimidazo[2,1-b] [1,3,4]thiadiazol-5-yl]methylene}-1,3-thiazolidine-2,4-dione (3e)

Bright yellow granules (DMF), yield 88%, m.p. 262–264 °C; IR (KBr)/υcm: 3153, 3042, 2927, 2854, 1733, 1702, 1616,1545; ^{1}H NMR (300 MHz, C_6D_6 + TFA) δ: 1.08(t, J = 6.3 Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.88(sextet, J_{CH2CH3} = 6.1 Hz and J_{CH2CH2} = 6.1 Hz, 2H, $CH_2\underline{CH_2}CH_3$), 2.44(s, 3H, CH_3), 3.10(t, J = 6.0 Hz, 2H, $\underline{CH_2}CH_2CH_3$), 7.32(d, J = 8.9 Hz, 2H, C_3, C_5-H, phenyl), 7.66(d, J = 8.9 Hz, 2H, C_2, C_6-H, phenyl), 7.98(s, 1H, vinylic proton); ^{13}C NMR (75 MHz, C_6D_6 + TFA) δ: 13.3, 22.0, 22.6, 33.5, 55.2, 115.7, 117.6, 124.9, 125.2, 127.5, 128.0, 130.9, 131.0, 142.8, 162.9, 167.3 and 171.0. MS *m/z:* 384 (M^+). Anal. calcd. for $C_{18}H_{16}N_4O_2S_2$: C, 56.23; H, 4.19; N, 14.57. Found: C, 56.48; H, 4.27; N, 14.40.

5-{[6-(4-Methoxyphenyl)-2-propylimidazo[2,1-b] [1,3,4]thiadiazol-5-yl]methylene}-1,3-thiazolidine-2,4-dione (3f)

Yellow granules (DMF), yield 91%, m.p. 266–270 °C; IR (KBr)/υcm: 3104, 3022, 2927, 1730, 1685, 1585, 1209;

^{1}H NMR (300 MHz, C_6D_6 + TFA) δ: 1.10(t, J = 6.3 Hz, 3H, $CH_2CH_2\underline{CH_3}$), 1.89(sextet, J_{CH2CH3} = 6.0 Hz, J_{CH2CH2} = 6.1 Hz, 2H, $CH_2\underline{CH_2}CH_3$), 3.10(t, J = 6.0 Hz, 2H, $\underline{CH_2}CH_2CH_3$), 3.82(s, 3H, OCH_3), 6.98(d, J = 7.8 Hz, 2H, C_3, C_5-H, phenyl), 7.55(d, J = 7.8 Hz, 2H, C_2, C_6-H, phenyl), 8.00(s, 1H, vinylic proton); ^{13}C NMR (75 MHz, C_6D_6 + TFA) δ: 13.3, 22.3, 33.0, 55.2, 113.8, 115.7, 117.6, 117.8, 118.3, 124.9, 130.9, 142.8, 145.8, 162.9, 167.3 and 171.2. MS *m/z:* 400 (M^+). Anal. cald. for $C_{18}H_{16}N_4O_3S_2$: C, 53.98; H, 4.03%; N, 13.99. Found: C, 54.16; H, 4.08; N, 13.75.

5-{[6-(4-Chlorophenyl)-2-cyclohexylimidazo[2,1-b][1,3,4]thiadiazol-5-yl]methylene}-1,3-thiazolidine-2,4-dione (3g)

Bright yellow granules (DMF), yield 94%, m.p. >300 °C; IR (KBr)/υcm: 3158, 2943, 2887, 1735, 1702, 1616, 1547; ^{1}H NMR (300 MHz, $CDCl_3$ + TFA) δ: 1.35–2.31(m, 10H, cyclohexyl), 3.24(m, 1H, C_1-H, cyclohexyl), 7.37(d, J = 8.3 Hz, 2H, C_3, C_5-H, phenyl),7.63(d, J = 8.3 Hz, 2H, C_2, C_6-H, phenyl), 7.93(s, 1H, vinylic proton); ^{13}C NMR (75 MHz, $CDCl_3$ + TFA) δ: 25.4, 25.7, 33.1, 41.7, 162.9, 130.9,142.8, 117.6, 124.9, 115.7, 171.0,167.2,128.0, 121.2,125.0,133.0. MS *m/z:* 446 (M + 2), 444 (M^+). Anal. calcd. for $C_{20}H_{17}ClN_4O_2S_2$: C, 53.99; H, 3.85; N, 12.59. Found: C, 53.78; H, 3.92; N, 12.44.

5-{[2-Cyclohexyl-6-(4-methylphenyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methylene}-1,3-thiazolidine-2,4-dione (3h)

Bright yellow granules (DMF), yield 91%, m.p. >300 °C; IR (KBr)/υcm: 3154, 2933, 2889, 1736, 1704, 1608, 1563; ^{1}H NMR (300 MHz, C_6D_6 + TFA) δ: 1.14–1.98(m, 10H, cyclohexyl), 2.25(s, 3H, CH_3), 2.70(m, 1H, C_1-H, cyclohexyl), 7.24(d, J = 7.1 Hz, 2H, C_3, C_5-H, phenyl), 7.45(d, J = 7.4 Hz, 2H, C_2, C_6-H, phenyl), 7.76(s, 1H, vinylic proton). MS *m/z:* 424 (M^+). Anal. calcd. for $C_{21}H_{20}N_4O_2S_2$: C, 59.41; H, 4.75; N, 13.20. Found: C, 59.70; H, 4.72; N, 13.08.

5-{[2-Cyclohexyl-6-(4-methoxyphenyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methylene}-1,3-thiazolidine-2,4-dione (3i)

Bright yellow granules (DMF), yield 94%, m.p. >300 °C; IR (KBr)/υcm: 3172, 2952, 2865, 1734, 1698, 1611, 1575, 1184; ^{1}H NMR (300 MHz, $CDCl_3$ + TFA) δ: 1.35–2.30(m, 10H, cyclohexyl), 3.24 (m, 1H, C_1-H, cyclohexyl), 3.93(s, 3H, OCH_3), 7.14(d, J = 8.6 Hz, 2H, C_3, C_5-H, phenyl), 7.52(d, J = 8.5 Hz, 2H, C_2, C_6-H, phenyl), 7.76(s, 1H, vinylic proton); ^{13}C NMR (75 MHz, $CDCl_3$ + TFA) δ: 25.4, 25.7, 33.1, 41.7, 55.4, 162.9, 130.9, 142.8, 117.6, 124.9, 115.7, 171.0, 167.2, 118.1, 118.4, 113.6, 145.0. MS *m/z:* 440 (M^+). Anal. calcd. for $C_{21}H_{20}$ $N_4O_3S_2$: C, 57.25; H, 4.58; N, 12.72. Found: C, 57.38; H, 4.64; N, 12.65.

5-{[2-Benzyl-6-(4-chlorophenyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methylene}-1,3-thiazolidine-2,4-dione (3j)

Yellow solid (DMF), yield: 86%, m.p. 290–292 °C; IR (KBr)/υcm: 3154, 3043, 1732, 1699, 1604; ^{1}H NMR (300 MHz, $CDCl_3$ + TFA) δ: 4.02(s, 2H, CH_2), 7.28–7.87 (m, 9H, Ar-H), 8.01(s, 1H, vinylic proton). MS *m/z:* 454 (M + 2), 452 (M^+). Anal. calcd. for $C_{21}H_{13}ClN_4O_2S_2$: C, 55.69; H, 2.89; N, 12.37, Found C, 55.88; H, 2.95; N, 12.21.

5-{[2-Benzyl-6-(4-methylphenyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methylene}-1,3-thiazolidine-2,4-dione (3k)

Bright yellow granules (DMF), yield 86%, m.p. 286–290 °C; IR (KBr)/υcm: 3162, 3048, 1733, 1701, 1598, 1561, 1184; ^{1}H NMR (300 MHz, $CDCl_3$ + TFA) δ: 2.29(s, 3H, CH_3), 3.96(s, 2H, CH_2), 7.16–7.75(m, 9H, Ar-H), 7.92 (s, 1H, vinylic proton). MS *m/z:* 452 (M^+). Anal. calcd. for $C_{22}H_{16}N_4O_2S_2$: C, 61.09; H, 3.73; N, 12.95. Found: C, 61.32; H, 3.78; N, 12.86.

5-{[2-Benzyl-6-(4-methoxyphenyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methylene}-1,3-thiazolidine-2,4-dione (3l)

Pale yellow solid (DMF), yield 90%, m.p.276–278 °C IR (KBr)/υcm: 3167, 3054, 1729, 1705, 1602, 1561; ^{1}H NMR (300 MHz, $CDCl_3$ + TFA) δ: 3.94(s, 3H, OCH_3), 4.06 (s, 2H, CH_2), 7.07–7.76(m, 9H, Ar-H), 7.97(s, 1H, vinylic proton). MS *m/z:* 448 (M^+). Anal. calcd. for $C_{22}H_{16}N_4O_3S_2$: C, 58.91; H, 3.60; N,12.49. Found: C, 59.15; H, 3.74; N, 12.28.

5-{[6-(4-Chlorophenyl)-2-thien-2-ylimidazo[2,1-b][1,3,4]thiadiazol-5-yl]methylene}-1,3-thiazolidine-2,4-dione (3m)

Orange yellow granules (DMF), yield 85%, m.p.290–294 °C; IR (KBr)/υcm: 3146, 3036, 2985, 1732, 1699, 1611, 1561; ^{1}H NMR (300 MHz, $CDCl_3$ + TFA) δ: 7.18 (dd, J_{H3H4} = 3.1 Hz, J_{H4H5} = 3.3 Hz, 1H, C_4-H, thiophene), 7.20–7.91(m, 6H, C_3, C_5-H, thiophene and phenyl protons), 8.02(s, 1H, vinylic proton); ^{13}C NMR (75 MHz, $CDCl_3$ + TFA) δ: 110.2, 113.3, 117.0, 117.9, 120.8, 121.0, 125.0, 128.0, 129.0, 129.3, 131.0, 133.0, 133.9, 161.5, 167.1 and 169.2. MS *m/z*: 445.9 (M + 2), 443.9 (M^+), Anal. calcd. for $C_{18}H_9ClN_4O_2S_3$: C, 48.59; H, 2.04; N, 12.59. Found: C, 48.59; H, 2.04; N, 12.59.

5-{[6-(4-Methylphenyl)-2-thien-2-ylimidazo[2,1-b][1,3,4]thiadiazol-5-yl]methylene}-1,3-thiazolidine-2,4-dione (3n)

Bright yellow solid (DMF), yield 92%, m.p. 288–292 °C; IR (KBr)/υcm: 3158, 1733, 1697, 1605; ^{1}H NMR (300 MHz,

C_6D_6 + TFA) δ: 2.27(s, 3H, CH_3), 6.74(t, J = 4.5 Hz, 1H, C_4-H, thiophene), 7.08(d, J = 4.7 Hz, 1H, C_3-H, thiophene), 7.28(d, J = 6.0 Hz, 2H, C_3, C_5-H phenyl), 7.42–7.46(m, 3H, C_5-H, thiophene; C_2, C_6-H phenyl), 7.77(s, 1H, vinylic proton); ^{13}C NMR (75 MHz, C_6D_6 + TFA) δ: 21.0, 110.2, 113.3, 117.0, 117.9, 120.8, 125.3, 127.7, 128.3, 129.0, 129.3, 131.0, 132.9, 133.9, 161.5, 167.1 and 169.2. MS *m/z:* 424 (M^+). Anal. calcd. for $C_{19}H_{12}N_4O_2S_3$: C, 53.76; H, 2.85; N, 13.20. Found: C, 53.95; H, 2.94; N, 13.07.

5-{[6-(4-Methoxyphenyl)-2-thien-2-ylimidazo[2,1-b][1,3,4]thiadiazol-5-yl]methylene}-1,3-thiazolidine-2,4-dione (3o)

Bright yellow solid (DMF), yield 84%, m.p. 276–278 °C; IR (KBr)/υcm: 3216, 1736, 1704, 1610, 1560, 1174; ^{1}H NMR (300 MHz, $CDCl_3$ + TFA) δ: 3.95(s, 3H, OCH_3), 7.16(dd, J_{H3H4} = 3.8 Hz, J_{H4H5} = 3.9 Hz, 1H, C_4-H, thiophene), 7.32–7.38(m, 3H, C_3-H, thiophene; C_3, C_5-H, phenyl), 7.55(d, J = 7.4 Hz, C_5-H, thiophene), 7.84 (d, J = 7.4, 2H, C_2, C_6-H), 8.02(s, 1H, vinylic proton) ^{13}C NMR (75 MHz, $CDCl_3$ + TFA) δ: 21.0, 55.9, 110.2, 113.3, 117.0, 117.9, 120.8, 118.5, 114.2, 117.8, 129.0, 129.3, 131.0, 145.4, 133.9, 161.3, 167.1 and 169.4. MS *m/z:* 440 (M^+). Anal. calcd. for $C_{19}H_{12}N_4O_3S_3$: C, 51.80; H, 2.75; N, 12.72. Found: C, 52.06; H, 2.78; N, 12.54.

5-{[6-(4-Chlorophenyl)-2-(2-furyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methylene}-1,3-thiazolidine-2,4-dione (3p)

Bright orange yellow solid (DMF), yield 89%, m.p. >300 °C; IR (KBr)/υcm: 3226, 3042, 1733, 1701, 1614, 1562; ^{1}H NMR (300 MHz, $CDCl_3$ + TFA) δ: 6.78(dd, J_{H3H4}=3.0 Hz, J_{H4H5}=3.5 Hz, 1H, C_4-H, furan), 7.45(d, J = 8.9 Hz, 2H, C_3, C_5-H, phenyl), 7.53(d, J = 3.0 Hz, 1H,C_3-H, furan), 7.75 (d, J = 8.9 Hz, 2H, C_2, C_6-H, phenyl), 7.79(d, J = 3.2 Hz, 1H, C_5-H, furan), 7.97(s, 1H, vinylic proton). MS *m/z:* 430 (M + 2), 428 (M^+). Anal. calcd. for $C_{18}H_9ClN_4O_3S_2$: C, 50.41; H, 2.12; N, 13.06. Found: C, 50.65; H, 2.18; N, 12.93.

5-{[2-(2-Furyl)-6-(4-methylphenyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methylene}-1,3-thiazolidine-2,4-dione (3q)

Bright yellow solid (DMF), yield 89%, m.p. >300 °C; IR (KBr)/υcm: 3164, 1735, 1702, 1607, 1558; ^{1}H NMR (300 MHz, $CDCl_3$ + TFA) δ: 2.26(s, 3H, CH_3), 6.73 (dd, J_{H3H4}=3.4 Hz, J_{H4H5} = 3.5 Hz, 1H, C_4-H, furan), 7.28(d, J = 7.6 Hz, 2H, C_3, C_5-H, phenyl), 7.52(d, J = 3.9 Hz, 1H, C_3-H, furan), 7.67(d, J = 7.8 Hz, 2H, C_2, C_6-H, phenyl), 7.75(d, J = 3.1 Hz, 1H, C_5-H, furan), 7.96(s, 1H, vinylic). MS *m/z:* 408 (M^+). Anal. calcd. for $C_{19}H_{12}N_4O_3S_2$: C, 55.87; H, 2.96; N, 13.72. Found: C, 55.98; H, 3.08; N, 13.56.

5-{[2-(2-Furyl)-6-(4-methoxyphenyl)imidazo[2,1-b][1,3,4]thiadiazol-5-yl]methylene}-1,3-thiazolidine-2,4-dione (3r)

Orange yellow granules (DMF), yield 82%, m.p. >300 °C; IR (KBr)/υcm: 3213, 1730, 1698, 1604, 1564, 1176; ^{1}H NMR (300 MHz, $CDCl_3$ + TFA) δ: 3.82(s, 3H, OCH_3), 6.76 (dd, J_{H3H4} = 3.4 Hz, J_{H4H5} = 3.3 Hz, 1H, C_4-H, furan), 7.10(d, J = 7 Hz, 2H, C_3, C_5-H, phenyl), 7.51(d, J = 4.1 Hz, 1H, C_3-H, furan), 7.68(d, J = 6.8 Hz, 2H, C_2, C_6-H, phenyl), 7.76(d, J = 3.3 Hz, 1H, C_5-H, furan), 7.96 (s, 1H, vinylic). MS *m/z:* 424 (M^+). Anal. calcd. for $C_{19}H_{12}NO_4S_2$: C, 53.76, H, 2.85; N, 13.20. Found: C, 53.93; H, 2.78; N, 13.16.

Biological evaluation

Hypoglycaemic and hypolipidemic activity

Male Wistar rats weighing 150–200 g were used for this study (13). All animals were maintained under 12 h light and 12 h dark cycle at 25 ± 1 °C. All animals were given standard chow (National Institute of Nutrition, India) and water *ad libitum*. The experiments were designed and conducted in accordance with the guidelines of institutional animal's ethics committee. The acclimatized animals were kept fasting for 24 h with water *ad libitum* and alloxan monohydrate (120 mg/kg i.p.) in normal saline was then administered. Serum glucose level was checked after 72 h. Animals with serum glucose levels >250 mg/dL were considered diabetic and were used for the study. The animals were divided into two groups of six animals each. Group I animals were termed as control or untreated and group II animals were termed as treated. Group II animals were administered with compounds to be screened for euglycemic effect. The suspension of the compound was prepared in water with 1% carboxy methyl cellulose as suspending agent. All the test compounds were orally administered at different doses (3, 10, 30, 100 mg/kg) for 15 days. Pioglitazone was used as standard drug. On the final day, the blood samples were collected from the tail vein. Plasma was separated from whole blood of each group by centrifugation. Plasma glucose (PG) and triglyceride (TG) levels were estimated using commercial kits (14–16).

PPARγ agonist activity

The ligand-binding domains (LBDs) of hPPARγ (amino acids 163–477) were generated by PCR amplification using Pfu polymerase (Stratagene, La Jolla, CA, USA), and gene-specific primers flanked with restriction enzymes BamHI and XbaI. The LBDs were subcloned in-frame into the pFA-CMV vector (Stratagene) to prepare pFA-Gal4-PPARa-LBD, PPARd-LBD and -PPARg-LBD. At 75–90% confluence, NIH3T3 cells were transiently cotransfected with the expression vectors for pFA-Gal4-PPAR-LBDs together with pFR-Luc and pRL-CMV (Promega) using Lipofectamine PLUS reagent according to the instructions of manufacturer (Invitrogen, Carlsbad, CA, USA). After 24-

h incubation, the cells were treated with various concentrations of compounds and pioglitazone as a positive control and incubated for 16 h. Luciferase assay was performed using dual-luciferase reporter assay system according to the instructions of the manufacturer (Promega, Madison, WI, USA), and the activity was determined in Luminoskan (Thermo Fisher Scientific Co., Waltham, MA, USA) by measuring light emission for 10 s. The results were normalized to the activity of renilla expressed by cotransfected Rluc gene under the control of a constitutive promoter. The EC50 values of compounds were determined using Prism 4 software (GraphPad Software, Inc., La Jolla, CA, USA).

Results and Discussion

Chemistry

The reaction sequence employed for the synthesis of title compounds is shown in Scheme 1. The fused imidazo [2,1-b][1,3,4]thiadiazole nucleus **1a**–**r** were prepared by the condensation of 2-aminothiadiazole with α-haloaryl ketones under reflux in dry ethanol. Further, Vilsmeier–Haack formylation reaction of Imidazo[2,1-b][1,3,4]thiadiazoles **1a**–**r** affords imidazo[2,1-b] [1,3,4]thiadiazole-5-carbaldehydes **2a**–**r** (17,18).

The imidazo[2,1-*b*][1,3,4]thiadiazole-5-carbaldehydes **2a**–**r** were exploited successfully for the preparation of target molecules by Knoevenagel condensation with thiazolidine-2,4-dione in the presence of piperidinium acetate in refluxing toluene. This series of compounds are characterized by the presence of one carbon atom spacer between thiazolidine-2, 4-dione moiety and fused heterocyclic ring.

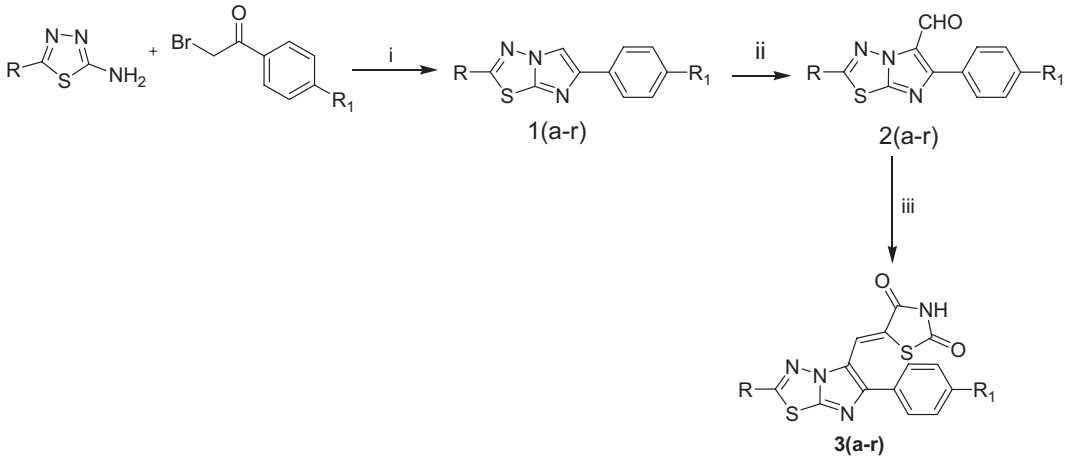
All the TZD derivatives **3a**–**r** are having high melting points compared with their starting materials due to formation of rigid and very stable structural framework. The formation of 5-[(2-alkyl/aryl-6-arylimidazo[2,1-*b*][1,3,4]thiadiazol-5-yl) methylene]-1,3-thiazolidine-2,4-diones **3a**–**r** were confirmed by their IR spectra, which displayed the $\nu_{C=O}$ bands around 1735 and 1700/cm. The ν_{N-H} is observed in the region of 3226–3104/cm. Further, they are confirmed by ^{1}H NMR spectra, where aldehydic proton disappeared and the vinylic proton resonated in the region of δ 7.70–7.90 as a singlet. These compounds were further confirmed by their ^{13}C NMR and mass spectral data.

The configuration of the title compounds were established based on ^{1}H NMR analysis (olefinic C-H around δ 7.70–8.0), (19,20) theoretical calculations (21–24) and thermodynamic stability (25,26). All these observation support the Z configuration. Hence, the Z configuration was confirmed for the TZD derivatives.

Biological evaluation

All the newly synthesized 5-(2-alkyl/aryl-6-arylimidazo [2,1-b][1,3,4]thiadiazol-5-yl)methylene-1,3-thiazolidnedione derivatives were screened for their *in vivo* hypoglycaemic and hypolipidemic activities in alloxan-induced male Wistar rats through oral treatment for 15 days. Acute toxicity studies were performed and doses were fixed. Hypoglycaemic and hypolipidemic activities summarized in terms of percentage reduction in PG and TG levels. Pioglitazone was used as a standard (Tables 1 and 2).

Compounds **3h, 3i** and **3o** (Figure 2) displayed promising *in vivo* hypoglycaemic and hypolipidemic activities. Further, the mode of action for hypoglycaemic activity of these compounds was determined by performing PPARγ agonist activity (PPARγ transactivation (Figure 3 and Table 3). Compound **3i** showed significant PPARγ agonist activity with receptor activation potential of 64% (compared with



Scheme 1: Synthesis of 5-(2-alkyl/aryl-6-arylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene-1,3-thiazolidinedione. Reagents and conditions: (i) dry ethanol, reflux, Na_2CO_3 (ii) DMF, $POCl_3$ (iii) 1, 3-thiazolidinedione, piperidine acetate, toluene, reflux. R = Ethyl, Propyl, cyclohexyl, benzyl, 2-furyl, 2-thienyl. R_1 = p-Cl-Phenyl, p-CH_3–phenyl, p-OCH_3–phenyl.

Table 1: Plasma glucose (PG) level of **3a–r** at various drug doses

Compound	% Decrease in plasma glucose (PG) level at various drug doses (mg/kg body weight)			
	3 mg	10 mg	30 mg	100 mg
Pioglitazone	41.60 ± 2.25	47.25 ± 5.50	64.59 ± 5.42	75.43 ± 3.40
3a	27.56 ± 0.96	31.47 ± 1.72	35.77 ± 1.68	49.34 ± 1.25
3b	22.55 ± 1.08	25.86 ± 1.08	26.40 ± 1.26	34.12 ± 1.86
3c	24.58 ± 0.66	27.58 ± 1.84	29.68 ± 2.08	36.19 ± 2.08
3d	25.70 ± 0.89	29.20 ± 1.70	29.61 ± 1.10	44.24 ± 1.14
3e	18.28 ± 1.42	22.80 ± 1.98	25.81 ± 2.08	35.82 ± 2.48
3f	26.36 ± 1.85	31.89 ± 2.38	33.84 ± 1.08	40.58 ± 2.08
3g	30.58 ± 0.088	34.86 ± 1.38	36.08 ± 1.87	40.89 ± 2.08
3h	39.68 ± 2.92	41.86 ± 3.21	55.63 ± 3.25	70.49 ± 1.53
3i	40.08 ± 1.92	44.16 ± 1.72	59.20 ± 1.25	73.08 ± 1.23
3j	28.56 ± 1.27	31.08 ± 1.92	30.73 ± 2.85	34.85 ± 3.08
3k	20.62 ± 0.62	21.20 ± 1.81	28.40 ± 2.18	40.52 ± 1.38
3l	16.82 ± 0.67	20.87 ± 1.01	23.68 ± 3.05	29.54 ± 2.56
3m	31.20 ± 1.58	34.64 ± 2.11	37.85 ± 2.72	41.85 ± 3.12
3n	19.68 ± 0.13	22.08 ± 1.21	24.48 ± 1.86	31.82 ± 1.54
3o	40.01 ± 1.69	43.74 ± 1.62	57.54 ± 2.42	71.78 ± 3.68
3p	31.08 ± 1.54	35.08 ± 2.22	36.84 ± 3.05	41.08 ± 2.82
3q	27.33 ± 0.92	24.69 ± 1.55	37.44 ± 1.46	42.83 ± 1.22
3r	21.82 ± 1.84	23.85 ± 2.45	26.82 ± 2.97	31.92 ± 3.08

Each value represents the mean ± SEM (n = 6). Percentage reduction was calculated according to the formula: [(PG in control – PG in treated)/PG in control]×100; [(TG in control – TG in treated)/TG in control]×100.

Table 2: Triglyceride (TG) level of **3a–r** at various drug doses.

Compound	% Decrease in triglyceride (TG) level at various drug doses (mg/kg body weight)			
	3 mg	10 mg	30 mg	100 mg
Pioglitazone	47.02 ± 14.39	35.25 ± 20.42	40.96 ± 17.59	45.89 ± 2.24
3a	16.84 ± 1.85	27.02 ± 2.28	30.352 ± 1.74	40.1 ± 1.58
3b	20.16 ± 0.05	28.62 ± 1.18	33.44 ± 2.86	36.12 ± 1.05
3c	18.64 ± 1.65	26.12 ± 2.08	32.28 ± 1.56	36.42 ± 1.38
3d	11.75 ± 2.14	19.67 ± 1.92	18.82 ± 1.90	27.44 ± 1.11
3e	22.46 ± 2.02	28.12 ± 1.52	31.01 ± 1.72	36.42 ± 2.10
3f	17.26 ± 0.65	24.62 ± 2.16	40.00 ± 1.86	34.12 ± 1.86
3g	14.12 ± 2.38	20.62 ± 2.16	26.00 ± 2.24	31.04 ± 2.26
3h	30.68 ± 1.08	33.09 ± 3.28	37.83 ± 3.18	42.25 ± 1.55
3i	36.24 ± 1.25	35.84 ± 1.65	38.16 ± 2.36	44.52 ± 1.64
3j	23.46 ± 1.14	28.62 ± 1.25	31.55 ± 1.56	34.48 ± 1.07
3k	12.42 ± 2.85	14.09 ± 1.49	17.16 ± 3.07	25.20 ± 2.03
3l	19.86 ± 2.02	23.42 ± 2.36	25.08 ± 1.27	29.28 ± 2.04
3m	20.82 ± 1.35	29.63 ± 1.80	31.68 ± 2.06	35.61 ± 2.86
3n	12.28 ± 0.32	19.81 ± 1.52	23.65 ± 1.71	29.05 ± 2.03
3o	27.62 ± 1.14	31.42 ± 1.53	37.16 ± 1.11	42.46 ± 0.98
3p	15.52 ± 0.48	20.28 ± 1.80	19.48 ± 1.01	24.69 ± 1.22
3q	16.87 ± 1.01	20.36 ± 1.20	22.64 ± 4.05	29.73 ± 1.39
3r	18.25 ± 1.48	23.92 ± 2.05	25.29 ± 2.86	31.95 ± 3.08

Each value represents the mean ± SEM (n = 6). Percentage reduction was calculated according to the formula: [(PG in control – PG in treated)/PG in control]×100; [(TG in control – TG in treated)/TG in control]×100.

relative maximum efficacy to the percentage of the standard). The promising activity of compound **3i** is attributed to the presence of cyclohexyl group at 2nd position and *p*-methoxy phenyl group at 6th position of imidazo[2,1-b][1,3,4]thiadiazole ring system.

Conclusions

In conclusion, we have designed and synthesized a novel series of 5-(2-alkyl/aryl-6-arylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)methylene-1,3-thiazolidinedione derivatives. The

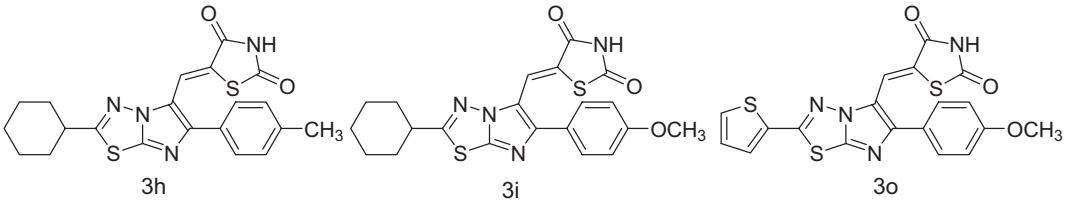


Figure 2: Structures of compounds exhibiting good results.

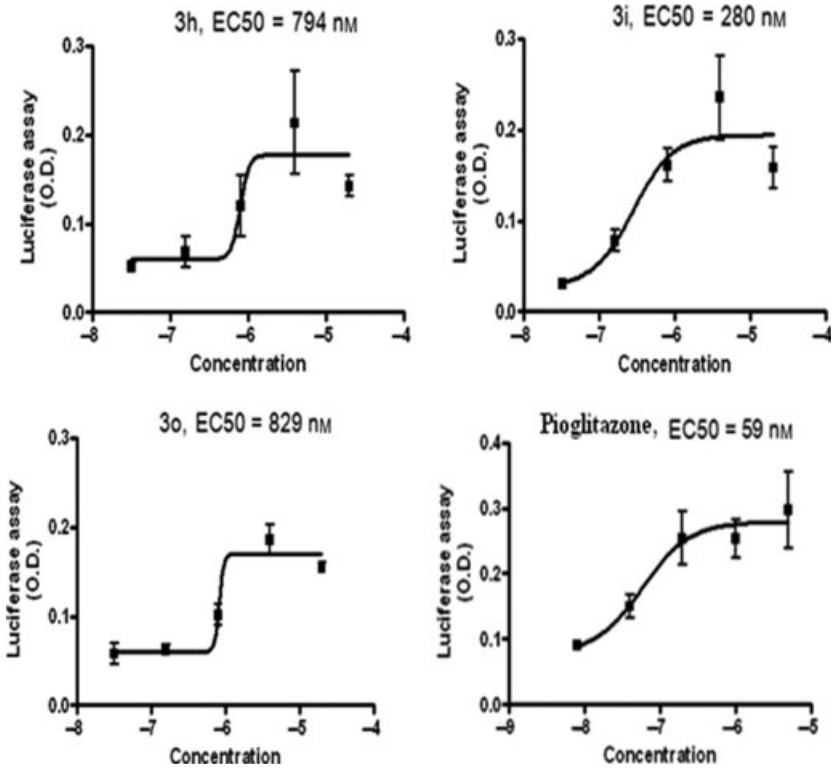
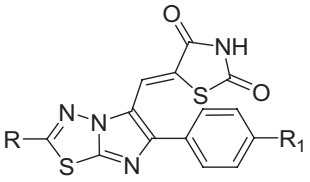


Figure 3: *In vitro* PPARγ agonist activity.

Table 3: *In vitro* PPARγ agonist activity data.



Compound	R	R_1	EC_{50} (nM)	% Max[a]
3h	Cyclohexyl	p-CH_3-ph	794	47
3i	Cyclohexyl	p-OCH_3-ph	280	64
3o	2-Thienyl	p-OCH_3-ph	829	40
Pioglitazone	–	–	59	100

[a]The relative maximum efficacy to the percentage of standard.

newly synthesized compounds were screened for their *in vivo* hypoglycaemic and hypolipidemic activity in male Wistar rats. Compounds **3h, 3i** and **3o** displayed interesting activity comparable with Pioglitazone. Further to know the mode of action for hypoglycaemic activity, these three compounds were screened for PPARγ agonist activity. From the results of these studies, we have demonstrated that a novel imidazo[2,1-*b*][1,3,4]thiadiazoles containing TZD **3i** with a cyclohexyl group substituted at 2nd position and *p*-methoxy phenyl group substituted at 6th position exhibit promising hypoglycaemic and hypolipidemic activity via potential PPARγ agonist activity.

Acknowledgments

The authors thank the Karnatak University, Dharwad and University Grants Commission (UGC), New Delhi, India, for financial support [F.No: 36-138/2009 (SR)] and thankful to the University Science Instruments Centre, Karnatak University, Dharwad, for providing the spectral data.

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