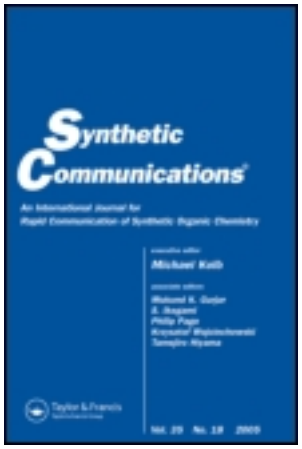

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Design and Synthesis of Benzimidazole-Linked meta-Substituted Benzylidenes/Benzyls as Biologically Significant New Chemical Entities

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DESIGN AND SYNTHESIS OF BENZIMIDAZOLE-LINKED *META*-SUBSTITUTED BENZYLIDENES/BENZYLS AS BIOLOGICALLY SIGNIFICANT NEW CHEMICAL ENTITIES

Raman K. Verma, Rajiv Mall, Prithwish Ghosh, and Vijay Kumar

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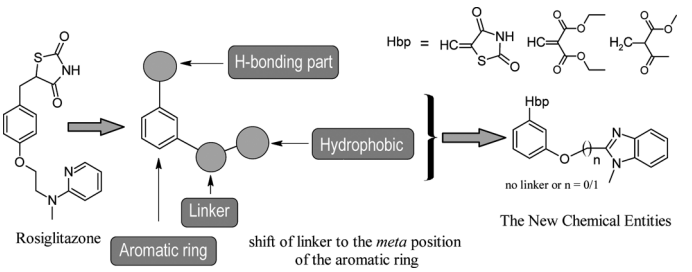
GRAPHICAL ABSTRACT



Abstract meta-*Linked thiazolidinedione (TZD)– and diethyl malonate (DEM)–based benzylidenes and methyl acetoacetate (MAA)–based benzyl moieties linked to the 2-position of* N*-methyl benzimidazole were synthesized. TZD- and DEM-based compounds were synthesized by condensation of 2,4-thiazolidinedone and DEM respectively with the corresponding 3-substituted benzaldehyde, whereas MAA-based compounds were obtained by halogen displacement with the corresponding 3-substituted phenol. These new chemical entities were designed to provide a balanced agonism at the peroxisome proliferator activated receptor alpha/gamma (PPARα/γ) in the management of type 2 diabetes: a move from glitazones to selective PPARγ modulators (SPPARγMs).*

Supplemental materials are available for this article. Go to the publisher's online edition of Synthetic Communications® *to view the free supplemental file.*

Keywords Benzimidazole; benzylidene; diethylmalonate; methyl acetoacetate; 2,4-thiazolidinedione

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INTRODUCTION

The derivatives of chemically significant benzimidazole, an important heterocyclic nucleus in drug discovery research, have been reported with diverse therapeutic activities such as: antiparasitic,[1] antiprotozoal,[2] antitubercular,[3] antiviral,[4,5] antifungal,[6] antitumor,[7] antihypertensive,[8] antihistaminic,[9] anxitolytic,[10] and topoisomerase-I inhibitor[11] activities. Peroxisome proliferator activated receptors (PPARs), especially the α and γ subtypes, are very important therapeutic targets for the treatment of type 2 diabetes mellitus.

One class of effective chemotherapeutic agents for T2DM is the thiazolidinediones (TZDs). These compounds function as sensitizers of endogenous insulin via activation of peroxisome proliferator activated receptor gamma (PPARγ). The full potential of these drugs has not been realized because of undesirable weight gain, peripheral edema, and anemia following prolonged usage. Mechanism-based side effects including weight gain, edema, and congestive heart failure, as well as recently reported possible bone fracture following rosiglitazone treatment, are among the major safety hurdles associated with PPARγ full agonists.[12,13]

It has recently been suggested that to improve blood glucose lowering and reduce weight gain and other adverse effects, compounds with marginal PPARα affinity but with selective PPARγ modulating activity provide a possible solution for effective treatment with lesser side effects.[13] PPARα/γ agonists usually possess essential pharmacophoric elements,[14–16] that is, an acidic group or a hydrogen bonding part attached to a central flat aromatic ring, a linker, and a large hydrophobic group. Dual PPARα/γ agonists possess a flexible alkyl ether linkage, which allows the molecule to adopt a bioactive U-shaped conformation that well fits into the arms of Y-shaped PPAR active sites.[17] Extensive research has been reported for the dual agonism of the glitazars with the said scaffold, though they have not yet made their way to clinical use. In recently reported studies, highly selective and active PPARα/γ dual agonists with nanomolar and picomolar EC_{50} values were obtained by replacing the alkyl ether central linker with a rigid linker.[18]

More recently, it has been reported that the *meta*-substituted aryl unit for the central flat aromatic ring part has been found to be the best candidate scaffolds in molecules with a rigid linker on the basis of comparisons of binding energy scores and binding modes.[19] 2,4-Thizolidinedione[20] (2,4-TZD) compounds with 2,4-TZD unit and 1,3-diester compounds[21] with 1,3-diester unit as the hydrogen bonding part have been well established as potent PPAR activators in the literature. Lohray et al. also reported a series of potent benzylidene thiazolidinediones with euglycemic as well as hypolipidemic acitivities.[22]

Although there are reports related to derivatization with a linker at the 1(N)-position of indoles[22] and benzimidazoles,[22] reports related to derivatization with a linker at the 2-position of the benzimidazole ring could be found in the literature.

In the present work, new chemical entities were designed by the theoretical modification of the PPARγ full agonist rosiglitazone (Fig. 1), and the designed molecules (being novel) were synthesized. The predicted binding affinities at the PPARα and PPARγ for all the designed at the active site of the receptors protein concerned for the prediction and synthesized compounds are also reported to support the design.

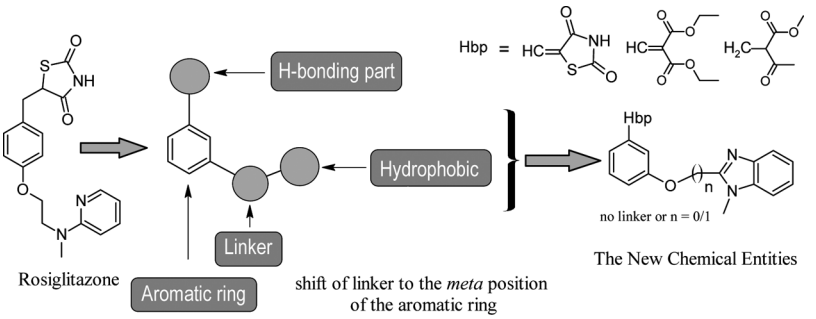


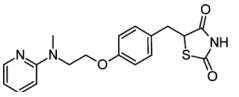
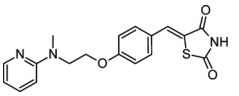
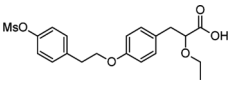
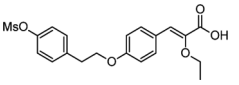
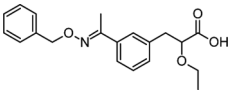
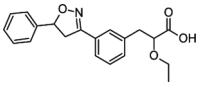
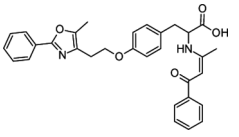
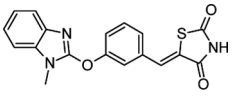
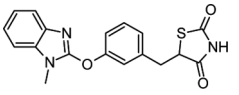
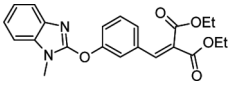
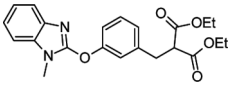
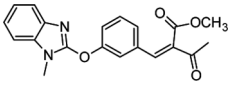
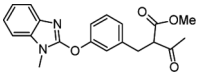
Figure 1. Design of selective PPARγ modulators (SPPARγMs).

RESULTS AND DISCUSSION

New chemical entities were designed by the theoretical modification of the PPARγ full agonist rosiglitazone: The 2-N-methylpyridyl moiety of rosiglitazone was modified to N-methyl benzimidazole (a fused heterocycle) while simultaneously reducing the length of the linker from ethoxy (3 atom) of rosiglitazone to methoxy (2 atom), oxy (1 atom), and direct linked (no atom) and further constraining the subsequent expansion by incorporating *meta*-substituted benzylidene-linked thiazolidinedione and diethyl malonate and also *meta*-substituted benzyl-linked methyl acetoacetae rather than the *para*-substitued benzyl thiazolidinedione as the hydrogen bonding parts (Fig. 1, Table 1). All the designed molecules (Table 1) possess almost all the structural features to be expected for achieving marginal PPARα affinity but selective PPARγ modulating activity[19] and were docked (with Surflex dock module of Sybyl 7.3, a Tripos Inc. software available at our *in silico* drug design laboratony) at the active site of the receptors' protein for the prediction of binding affinities (gold score energies, Table 1) in reference to some selected standard molecules (template rosiglitazone). This parameter was used as criteria for the selection of compounds for synthesis with the aim of achieving marginal PPARα affinity but selective PPARγ modulating activity.

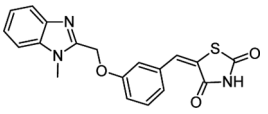
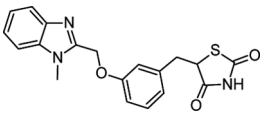
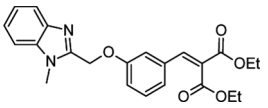
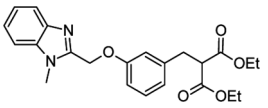
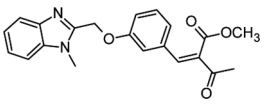
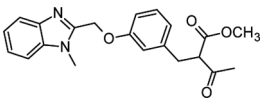
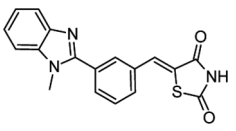
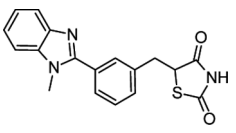
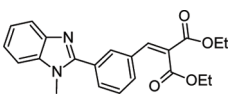
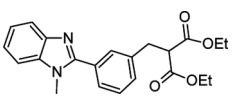
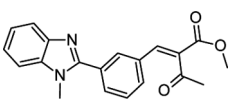
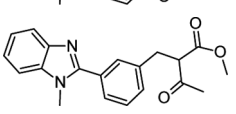
It was found from the analysis of the results of docking studies that benzylidenes exhibit lesser PPARα affinities (Table 1: compounds 3 and 4) and also PPARγ affinities (Table 1: compounds 1 and 2) in comparison to the corresponding benzyls. It was also observed that introduction of conformational constraint into the linker (with a double bond, heteroatom or heterocycle) reduces the PPARα affinity to a considerable extent (Table 1: compounds 3, 5, and 6). The G-score data thus generated for the designed new molecules (Table 1) being a reflection of the observation (goodness of fit) of selected standard molecules, not only provided experimental support to the hypothesis but has also helped us to set out criteria (much less PPARα affinities and lesser or comparative PPARγ affinities with respect to the template) to select molecules (Table 1: compounds 8, 11, 13, 14, 16, 19, 20, and 22) for further synthesis. Because two (Table 1: compounds 12 and 18) of the three (Table 1: compounds 12, 18, and 24) of the set of similar benzylidene-based compounds showed greater PPARα affinities than rosiglitazone were not synthesized, compound 24 therefore was also not synthesized despite having lower PPARα affinity. GW409544 was

Table 1. Comparison of predicted binding energy scores of the synthesized compounds with the standard compounds for PPARα and PPARγ

Serial no.	Code	Structure	Binding energy score (gold score[a])	
			PPARα	PPARγ
1	Rosiglitazone		−189.05	−223.25
2	3[20]*b*		−218.99	−209.91
3	Tesaglitazar		−260.26	−247.50
4	Tesaglitazar(db)		−146.68	−204.54
5	E[19]*b*		−204.21	−240.04
6	F[19]*b*		−194.87	−261.57
7	GW409544		−387.26	−353.17
8	5a		−158.78	−207.83
9	5a(sb)		−181.78	−214.37
10	5b		−125.98	−213.18
11	5b(sb)		−235.48	−288.31
12	12a(db)		−222.97	−202.50
13	12a		−184.61	−250.48

(*Continued*)

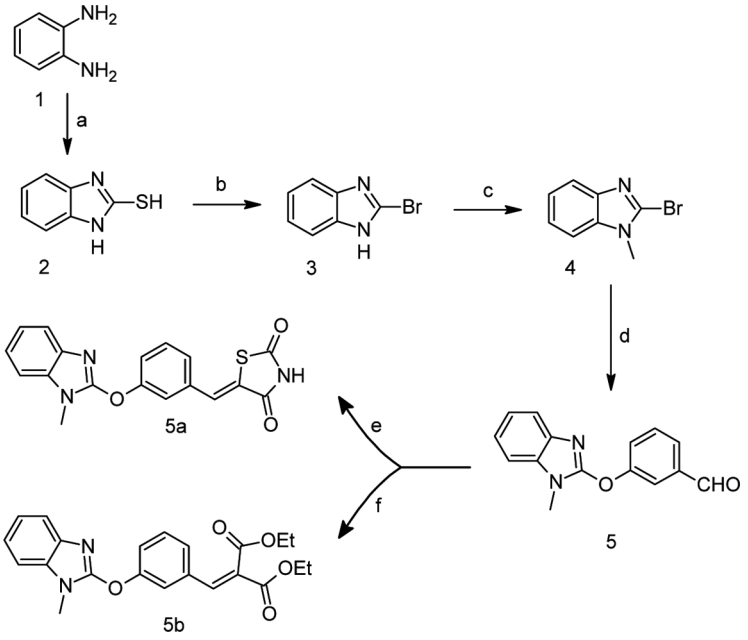
Table 1. Continued

Serial no.	Code	Structure	Binding energy score (gold score[a]) PPARα	PPARγ
14	8a		−179.93	−194.26
15	8a[(sb)]		−229.35	−256.89
16	8b		−151.40	−264.95
17	8b[(sb)]		−194.63	−265.15
18	12b[(db)]		−206.89	−201.08
19	12b		−185.64	−235.31
20	13a		−180.07	−200.93
21	13a[(sb)]		−209.66	−198.86
22	13b		−110.77	−224.75
23	13b[(sb)]		−166.75	−217.10
24	—		−147.32	−215.66
25	—		−199.87	−237.78

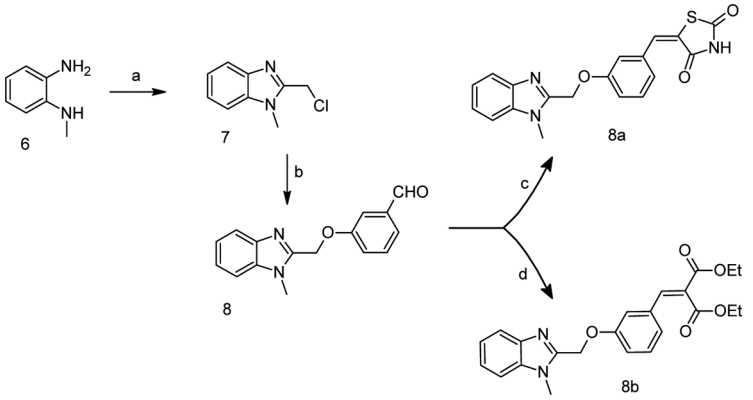
[a]Gold score[25] of the best docked conformation.
[b]The code written is as given in the reference.
Notes. db, double bond; sb, single bond.

included in the list of selected standard molecules as it is the bound ligand in the crystal structure of PPARα (PDB code: 1k7l).

The synthesis of ether-linked benzylidene TZD and DEM target molecules is shown in Scheme 1. 2-Mercaptobenzimidazole[24] **(2)** and 2-bromo-1-methyl-*1H*-benzimidazole[25] **(4)** were prepared in good yields as per reported procedures using commercially available 1,2-phenylenediamine **(1)**. Compound **4** was converted to the corresponding benzimidazole-linked 3-substituted benzldehyde **(5)** by bromo displacement of **4** with the phenoxide resulting from 3-hydroxybenzaldehyde in the presence of a base. The synthesized benzaldehyde was subsequently condensed with 2,4-TZD and DEM to yield the corresponding benzylidene targets **5a** and **5b** respectively, in fair yields. The synthesis of methylene ether-linked benzylidene TZD and diethylmalonate (DEM) target molecules is shown in Scheme 2. 2-Chloromethyl benzimidazole **(7)** was prepared by condensation of commercially available N-methyl-1,2-phenylenediamine **(6)** with chloroacetic acid in the presence of hydrochloric acid. The corresponding benzimidazole linked 3-substituted benzldehyde **(8)** was obtained from **7** in a similar way for synthesizing **5**. The corresponding benzylidene targets **8a** and **8b** were synthesized similarly in fair yields as described in Scheme 1. Repeated attempts to condense methyl acetoacetate with the benzimidazole linked benzaldehydes **(5** and **8)** in the presence of a base (piperidinium acetate) failed to give the desired benzylidene based ketoesters, which could be further reduced to obtaine the desired compounds **12a** and **b**, which promptd us to optfor

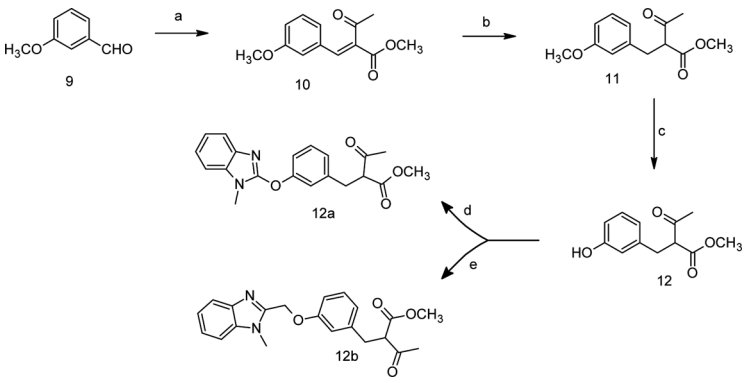


Scheme 1. Synthesis of -O- linked molecules: (a) carbon disulfide, ethanol, water, glacial AcOH, Norit; (b) HBr/glacial AcOH, Br_2, water, NaOH; (c) 1 N NaOH solution, dimethyl sulfate; (d) K_2CO_3. 3-hydroxybenzaldehyde, Cu powder, pyridine; (e) piperidine acetate, toluene, 2,4-thiazolidinedione; and (f) piperidine acetate, toluene, diethylmalonate.

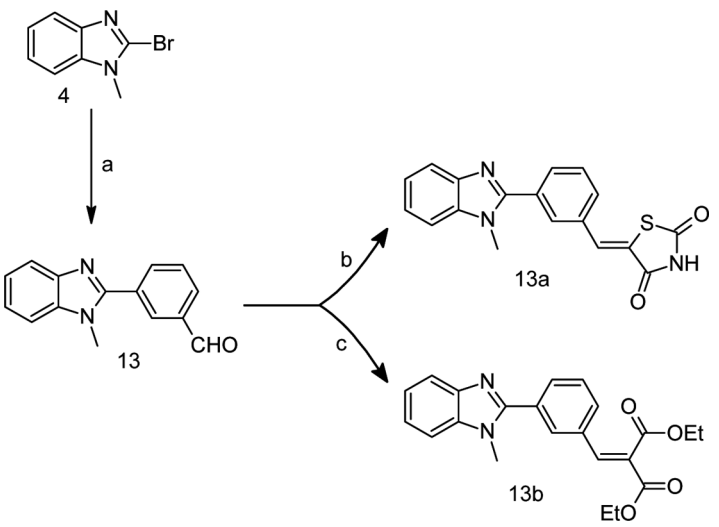


Scheme 2. Synthesis of -CH_2O- linked molecules: (a) chloroacetic acid, HCl; (b) NaH, dry DMF, 3-hydroxybenzaldehyde; (c) piperidine acetate, toluene, 2,4-thiazolidinedione; and (d) piperidine acetate, toluene, diethylmalonate.

an alternative route (Scheme 3) for their synthesis. Condensation of commercially available *m*-anisaldehyde **(9)** and methylacetoacetate (MAA) gave the corresponding benzylidene **(10)** as a mixture of the two geometrical isomers (1:2), which upon catalytic hydrogenation gave the corresponding benzyl MAA product **(11)**. The product **11** was subsequently demethylated using BBr_3 to obtain the required phenol **(12)**, which in turn was coupled with **4** (Scheme 1) and **7** (Scheme 2) in a similar way as for the preparation of **5** (Scheme 1) to generate the desired targets **12a** and **12b** respectively. 3-(1-Methyl-1*H*-benzimidazol-2-yl)benzaldehyde **(13)** was synthesized by Suzuki coupling of **4** and 3-boronobenzaldehyde, which subsequently upon condensation with 2,4-TZD and DEM gave the required benzylidene targets **13a** and **13b** respectively in fairly good yields (Scheme 4).



Scheme 3. Synthesis of β-ketoester-based molecule: (a) piperidine acetate, methylacetoacetate, toluene, Dean–Stark; (b) Pd/C, H_2, MeOH/dioxane, parr hydrogenater; (c) BBr_3, dichloromethane; (d) 2-bromo-1-methyl-1*H*-benzimidazole, pyridine, Cu powder, K_2CO_3; (e) 2-(chloromethyl)-1-methyl-1*H*-benzimidazole, pyridine, Cu powder, K_2CO_3.



Scheme 4. Synthesis of benzylidene molecules with no linker. (a) K_2CO_3, 3-boronobenzaldehyde, toluene-ethanol, $Pd(PPh_3)_4$; (b) piperidine acetate, toluene, 2,4-thiazolidinedione; and (c) piperidine acetate, toluene, diethylmalonate.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker 400-MHz instrument in $CDCl_3$ and dimethylsulfoxide (DMSO-d_6) using tetramethylsilane (TMS) as an internal standard. The mass spectra were recorded on a Shimadzu QP-2010 gas chromatography–mass spectrometer (GCMS) and APCI corona Liquid chromatography–mass spectrometer (LCMS). The infrared (IR) spectra (KBr) were recorded on a Perkin-Elmer Fourier transform (FT)–IR spectrometer. The elemental analyses were performed on a Vario Micro V1 elemental analyzer. Melting points were measured in a Buchi melting-point apparatus and are uncorrected. Thin-layer chromatographic (TLC) analysis was carried out on glass plates coated with silica gel-GF254 (Loba Chemie), and spots were visualized using an ultraviolet (UV) cabinet (Perfit, India). Column chromatography was performed using silica gel (100–200 mesh, Loba Chemie). All chemicals were purchased from Sigma Aldrich. Compound **2** and **4** were prepared as per reported procedures.[23,24]

3-[(1-Methyl-1*h*-benzimidazol-2-yl)oxy]benzaldehyde (5)

A mixture of **4** (0.211 g; 1 mmol), 3-hydroxybenzaldehyde (0.122 g; 1 mmol), K_2CO_3 (0.414 g; 3 mmol), and Cu powder (0.00063 g; 0.01 mmol) in pyridine was heated to 140 °C for 24 h. The reaction mixture was allowed to cool, taken up in EtOAc (30 ml), and then washed three times with 0.5 N NaOH. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give an oil that was subjected to column chromatography using a mixture of acetone/hexane (1:9) to afford the title compound as a white solid (0.075 g, 30%). Mp: 115–117 °C. IR (KBr): 3049, 3011, 2947 and 2838, 2806 and 2738, 1701, 1622, 1587, 1520, 1490, 1454,

1383, 1254, 737, 783 and 679 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.76 (s, 3H, N-CH_3), 7.20–7.27 (m, 3H, Ar), 7.56–7.58 (m, 1H, Ar), 7.60–7.64 (m,1H, Ar), 7.69–7.72 (m, 1H, Ar), 7.77–7.80 (m, 1H, Ar), 7.91–7.92 (s, 1H, Ar), 10.03 (s, 1H, -CHO); GCMS m/z (%): 252 $[M]^+$ (100). Anal. calcd. for $C_{15}H_{12}N_2O_2$: C, 71.42; H, 4.79; N, 11.10. Found: C, 71.66; H, 4.52; N, 10.92.

3-[(1-Methyl-1*H*-benzimidazol-2-yl)methoxy]benzaldehyde (8)

3-Hydroxybenzaldehyde (0.122 g, 1 mmol) was added to a suspension of sodium hydride (0.048 g, 2 mmol, 60% dispersion) in dry dimethylformamide (30 ml) at 0 °C. When hydrogen evolution ceased, a solution of **7** (0.180 g; 1 mmol) in DMF (5 ml) was added, and the mixture was stirred at room temperature for 24 h. Then the solution was poured into ice water (50 ml) and extracted with ethyl acetate (3 × 20 ml). The combined organic extracts were washed with water (50 ml) and brine (50 mL), dried over sodium sulfate, and concentrated. The crude product was purified by column chromatography using a mixture of methanol/chloroform (1:99) as eluent to give the title compound (0.235 g, 88%) as light greenish solid. Mp: 118–120 °C. IR (KBr): 3065, 3023, 2942 and 2870, 2817 and 2736, 1698, 1594, 1582, 1523, 1442 and 1369, 1255, 747, 788 and 721 cm^{-1}; ^1H NMR($CDCl_3$) δ: 3.89 (s, 3H, N-CH_3), 5.44 (s, 2H, -CH_2-), 7.29–7.39 (m, 4H, Ar), 7.44–7.52 (m, 2H, Ar), 7.57–7.58 (m, 1H, Ar), 7.79 (d, 1H, Ar), 9.97 (s, 1H, -CHO); GCMS m/z (%): 266 $[M]^+$ (10), 145 (100). Anal. calcd. for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.30; N, 10.52. Found: C, 71.93; H, 5.57; N, 10.68.

3-(1-Methyl-1*H*-benzimidazol-2-yl)benzaldehyde (13)

To a solution of **4** (0.211 gm, 1 mmol) and 3-boronobenzaldehyde (0.224 g, 1.5 mmol) in 25 mL of toluene–ethanol (4:1) was added K_2CO_3 (0.414 g, 3 mmol). The resulting mixture was degassed and stirred at ambient temperature for 20 min, and catalytic amount (0.005 mmol) of $Pd(PPh_3)_4$ was added. The mixture was degassed again and then refluxed under nitrogen gas for 8 h. It was allowed to cool, filtered through celite, and extracted using EtOAc (3 × 20 ml). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give an oil that was subjected to column chromatography using a mixture of acetone/hexane (2:8) to afford the title compound as a viscous mass (0.200 g, 85%). IR (KBr): 3049, 3011, 2947 and 2838, 2806 and 2738, 1701, 1622, 1587, 1520, 1490, 1454, 1383, 1254, 737, 783 and 679 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 3.91 (s, 3H, N-CH_3), 7.33–7.38 (m, 2H, Ar), 7.41–7.44 (m, 1H, Ar), 7.72 (t, 1H, Ar), 7.83–7.85 (m, 1H, Ar), 8.01–8.03 (m, 1H, Ar), 8.06–8.09 (m, 1H, Ar), 8.28–8.29 (m, 1H, Ar), 10.14 (s, 1H, -CHO); GCMS m/z (%): 236 $[M]^+$ (100). Anal. calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.71; H, 5.27; N, 11.97.

Synthesis of 5a, 8a, 13a, 5b, 8b, and 13b

General procedure. A mixture of **(5/8/13)** (1 mmol), thiazolidine-2,4-dione/diethylmalonate (1 mmol), and piperidinium acetate (catalytic amount) in toluene (25 ml) was refluxed for 7/14 h with continuous removal of water using a Dean–Stark

trap. The reaction mixture was cooled to room temperature, refrigerated overnight, and concentrated. The precipitate was collected by filtration under vacuum, washed with cold hexane, and dried/purified by column chromatography using methanol/chloroform (1:99) as eluent to give the target compound **(5a/8a/13a/5b/8b/13b).**

5-{3-[(1-Methyl-1*H*-benzimidazol-2-yl)oxy]benzylidene}-1,3-thiazolidine-2,4-dione (5a). Yield: 77%. Mp: 262–265 °C. IR (KBr): 3500–3300, 3060, 2944 and 2840, 1741, 1699, 1610, 1517, 1485, 1458 and 1325, 1237, 744, 762 and 683; ^{1}H NMR (DMSO-d_6) δ: 3.70 (s, 3H, N-CH_3), 7.11–7.20 (m, 4H, Ar), 7.31–7.34 (m, 2H, Ar), 7.44–7.48 (m, 2H, Ar), 7.59 (s, 1H, benzylidene); LCMS m/z (%): 352 $[M+1]^+$ (100). Anal. calcd. for $C_{19}H_{15}N_3O_3S$: C, 62.45; H, 4.14; N, 11.50. Found: C, 62.71; H, 4.27; N, 11.37.

5-[3-(1-Methyl-1*H*-benzoimidazol-2-ylmethoxy)-benzylidene]-thiazolidine-2,4-dione (8a). Yield 82%. Mp: 265–268 °C. IR (KBr): 3341, 3061, 2943 and 2840, 1741and 1709, 1611, 1599, 1582, 1484, 1446 and 1374, 1254, 733, 770 and 679 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 3.90 (s, 3H, N-CH_3), 5.46 (s, 2H, -CH_2O-), 7.15–7.24 (m, 3H, Ar), 7.26–7.31 (m, 2H, Ar), 7.40–7.44 (m, 1H, Ar), 7.50–7.52 (m, 1H, Ar), 7.64–7.67 (m, 2H, 1Ar and 1 benzylidene); LCMS m/z (%): 366 $[M+1]^+$ (100). Anal. calcd. for $C_{19}H_{15}N_3O_3S$: C, 62.45; H, 4.14; N, 11.50; S, 8.78. Found: C, 62.80; H, 4.49; N, 11.42; S, 8.25.

5-[3-(1-Methyl-1*H*-benzimidazol-2-yl)benzylidene]-1,3-thiazolidine-2,4-dione) (13a). Yield: 88%. Mp: 265–267 °C. IR (KBr): 3500–3300, 3060, 2929 and 2855, 2739, 1741, 1701, 1614, 1576, 1485, 1458 and 1384, 1325, 1237, 918, 801, 762 and 689; ^{1}H NMR ($CDCl_3$) δ: 3.93 (s, 3H, N-CH_3), 7.35 (m, 3H, Ar), 7.64 (m, 2H, Ar), 7.85 (m, 3H, Ar), 7.90 (s, 1H, Ar); LCMS m/z (%): 336 $[M+1]^+$ (100). Anal. calcd. for $C_{18}H_{13}N_3O_2S$: C, 64.46; H, 3.91; N, 12.53; S, 9.56. Found: C, 64.51; H, 4.07; N, 12.67; S, 9.64.

2-[3-(1-Methyl-1H-benzoimidazol-2-yloxy)-benzylidene]-malonic acid diethyl ester (5b). Yield: 50%. Mp: 185–187 °C. IR (KBr): 3475, 2918 and 2850, 1727, 1622, 1520, 1453, 1226, 746, 798 and 702; ^{1}H NMR ($CDCl_3$) δ: 1.18 (t, 3H, -OCH_2**CH_3**), 1.26 (t, 3H, -OCH_2**CH_3**), 3.66 (s, 3H, N-CH_3), 4.22 (two overlapping quartets, 4H, -**OCH_2**CH_3), 7.12–7.19 (m, 3H, Ar), 7.28–7.29 (m, 1H, Ar), 7.38–7.39 (m, 2H, Ar), 7.42 (d, 1H, Ar), 7.48–7.50 (m, 1H, Ar), 7.65 (s, 1H, benzylidene); LCMS m/z (%): 395 $[M+1]^+$ (45), 320 (100). Anal. calcd. for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 66.74; H, 5.43; N, 6.86.

2-[(1-Methyl-1*H*-benzoimidazol-2-ylmethoxy)-benzylidene]-malonic acid diethyl ester (8b). Yield: 60%. Mp: 120–123 °C. IR (KBr): 3017, 2982, 2962, 2933, 2858, 1740, 1733, 1586, 1483, 1447, 1406, 1370, 1256, 755, 668 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 1.27 (t, $J=7.16$ Hz, 3H, -OCH_2**CH_3**), 1.33 (t, $J=7.16$ Hz, 3H, -OCH_2**CH_3**), 3.87 (s, 3H, N-CH_3), 4.30 (two overlapping quartets, $J=7.08$, 2H each, -**OCH_2**CH_3), 5.37 (s, 2H, -CH_2O-), 7.08–7.09 (d, 1H, Ar), 7.13–7.16 (m, 2H, Ar), 7.26–7.36 (m, 4H, Ar), 7.69 (s, 1H, benzylidene), 7.78 (d, 1H, Ar); LCMS m/z (%): 409 $[M+1]^+$ (100). Anal. calcd. for $C_{23}H_{24}N_2O_5$: C, 67.63; H, 5.92; N, 6.86. Found: C, 67.41; H, 5.57; N, 6.92.

Diethyl [3-(1-Methyl-1*H*-benzimidazol-2-yl)benzylidene] propanedioate (13b)

A mixture of **13** (0.236 g, 1 mmol), diethylmalonate (0.160 g, 1 mmol), and piperidinium acetate (catalytic amount) in toluene (25 ml) was refluxed for 14 h with continuous removal of water using a Dean–Stark trap. After cooling to the room temperature, the solution was concentrated to crude reaction mixture, which was purified by column chromatography using methanol/chloroform (1:99) as eluent to afford the title compound **(13b)** (0.250 g, 66%) as a viscous mass. IR (KBr): 3369, 2917 and 2849, 1726, 1631, 1607, 1514, 1460, 1266, 798, 745 and 702; ^{1}H NMR ($CDCl_3$) δ: 1.27 (t, 3H, -$OCH_2\mathbf{CH_3}$), 1.35 (t, 3H, -$\mathbf{OCH_2}CH_3$), 3.89 (s, 3H, N-CH_3), 4.33 (two overlapping quartets, 4H, -$\mathbf{OCH_2}CH_3$), 7.34 (m, 2H, Ar), 7.42 (m, 1H, Ar), 7.58 (m, 2H, Ar), 7.84 (s, 4H, Ar); LCMS m/z (%): 379 $[M+1]^+$ (100). Anal. calcd. for $C_{22}H_{22}N_2O_4$: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.91; H, 5.97; N, 7.47.

Methyl 2-(3-Hydroxybenzyl)-3-oxobutanoate (12)

Boron tribromide (1.0 N solution of dichloromethane, 4 ml) was added to a solution of **11** (0.944 g, 4 mmol) in dichloromethane (7 ml) at 0 °C. The reaction mixture was stirred at room temperature overnight. The reaction was then quenched with ice water and partitioned. The organic layer was washed with water and dried over sodium sulfate. After filtering the drying agent, the filtrate was evaporated and the residue was purified by silica-gel chromatography eluting with a mixture of EtOAc/hexane (3:7) to give the title compound (0.75 g, 84%) as a brown viscous mass. IR (KBr): 3300–3400, 1737, 1719, 756 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.18 (s, 3H, -$COCH_3$), 3.10 (d, 2H, -CH_2-), 3.70 (s, 3H, -OCH_3), 3.80 (t, 1H, -CH-), 6.66–6.72 (m, 3H, Ar), 7.11–7. 15 (m, 1H, Ar); GCMS m/z (%): 222 $[M]^+$ (10), 204 (30), 179 (30), 147 (100). Anal. calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.61; H, 6.22.

Synthesis of 12a and 12b

General procedure. A mixture of **4/7** (1 mmol), **12** (1 mmol), K_2CO_3 (0.414 g, 3 mmol), and Cu powder (0.00063 g; 0.01 mmol) in pyridine was heated to 140 °C for 24 h. The reaction mixture was allowed to cool and taken up in EtOAc (30 ml), and then the organic extracts were washed three times with 0.5 N NaOH. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give a brown viscous mass, which was subjected to column chromatography to afford title compound **(12a/12b)** as a yellow viscous mass.

Methyl 2-{3-[(1-methyl-1*H*-benzimidazol-2-yl)oxy]benzyl}-3-oxobutanoate (12a). Yield: 20%; IR (KBr): 3019, 2954, 2850, 1742, 1715, 1455, 1360, 1232, 756, 695, 667 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 2.07 (s, 3H, -$COCH_3$), 2.85 (dd, 1H, -CH-), 2.71 (overlapping double doublet, 1H, benzylic), 3.40 (s, 3H, N-CH_3), 3.63 (overlapping dd, 1H, benzylic), 3.66 (s, 3H, -OCH_3), 6.58 (m, 1H, Ar), 6.99–7.01(m, 1H, Ar), 7.11–7.16 (m, 4H, Ar), 7.24–7.26 (m, 1H, Ar), 7.36 (m, 1H, Ar); LCMS m/z (%): 353 $[M+1]^+$ (47), 295 (100). Anal. calcd. for $C_{20}H_{20}N_2O_4$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.46; H, 5.48; N, 8.12.

Methyl 2-{3-[(1-methyl-1*H*-benzimidazol-2-yl)methoxy]benzyl}-3-oxobutanoate (12b). Yield: 20%; IR (KBr): 3437, 1731, 1711, 1095 cm^{-1}; ^1H NMR ($CDCl_3$) δ: major 2.05 (s, 3H, -$COCH_3$), 3.57 (overlapping dd, 2H, benzylic), 3.64 (s, 3H, N-CH_3), 3.88 (s, 3H, -OCH_3), 5.38 (s, 2H, -CH_2O-), minor 2.50 (s, 3H, -$COCH_3$), 3.62 (s, 3H, N-CH_3), 3.85 (overlapping dd, 2H, -CH_2-, 3.87 (s, 3H, -OCH_3), δ 5.35 (s, 2H, -CH_2O-), 6.82 (t, 2H, aromatic: one each of the major and minor), 6.96 (d, 4H, aromatic: one each of the major and minor), 7.19–7.36 (m, 6H, aromatic: one each of the major and minor), 7.65–7.67 (d, 2H, aromatic: one each of the major and minor), 7.74–7.76 (d, 2H, Aromatic: one each of the major and minor). LCMS m/z (%): 367 $[M+1]^+$ (77), 335 (54). Anal. calcd. for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 68.55; H, 6.19; N, 7.49.

Molecular Docking Studies

All the theoretically designed molecules along with the standard molecules were built by ''sketch molecule'' module of Sybyl 7.3 on the crystal structure of rosiglitazone obtained from the crystal structure of the ligand with PPARγ (PDB code: 2prg). They were assigned Gasteiger–Huckel charges and subsequently minimized using the Powel method. The energy-optimized sketched molecules were subjected to docking run at the ligand binding site of PPARγ (PDB code: 2prg) and PPARα (PDB code: 1k7 l) by Surflex dock in Sybyl.[23] The predicted binding affinities in terms of gold score[19] energies of the synthesized molecules were recorded and compared to that of the selected standard molecules previously reported in the literature.

Complete spectral and experimental details are available online in the Supplemental Materials.

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REFERENCES

1. Villanueva, J. P.; Santos, R.; Campos, A. H.; Giulianotti, M. A.; Castillo, R.; Franco, J. L. Structure–activity relationships of benzimidazole derivatives as antiparasitic agents: Dual activity–difference (DAD) maps. *Med. Chem. Commun.* **2011**, *2*, 44.
2. Kazimierczuk, Z.; Upcroft, J. A.; Upcroft, P.; Górska1, A.; Starooeciak, B.; Laudy, A. Synthesis, antiprotozoal, and antibacterial activity of nitro- and halogeno-substituted benzimidazole derivatives. *Acta Biochim. Pol.* **2002**, *49*, 185.
3. Yar, M. S.; Abdullah, M. M.; Majeed, J. In vitro antitubercular screening of newly synthesized benzimidazole derivatives. *World Acad. Sci., Engineer. Tech.* **2009**, *55*, 593
4. Tebbe, M. J.; Spitzer, W. A.; Victor, F.; Miller, S. C.; Lee, C. C.; Sattelberg, T. R.; Mckinney, E.; Tang, C. J. Antirhino/enteroviral vinylacetylene benzimidazoles: A study of their activity and oral plasma levels in mice. *J. Med. Chem.* **1997**, *40*, 3937.

5. Porcari, A. R.; Devivar, R. V.; Kucera, L. S.; Drach, J. C.; Townsend, L. B. Design, synthesis, and antiviral evaluations of 1-(substituted benzyl)-2-substituted-5,6-dichlorobenzimidazoles as nonnucleoside analogues of 2,5,6-trichloro-1-(a-D-ribofuranosyl) benzimidazole. *J. Med. Chem.* **1998**, *41*, 1252.
6. Gulgun, A.; Nurten, A. Synthesis and antifungal properties of some benzimidazole derivatives. *Turk. J. Chem.* **2006**, *30*, 223.
7. Denny, W. A.; Rewcastle, G. W.; Bagley, B. C. Potential antitumor agents, 59: Structure–activity relationships for 2-phenylbenzimidazole-4-carboxamides, a new class of "minimal" DNA-intercalating agents which may not act via topoisomerase II. *J. Med. Chem.* **1990**, *33*, 814.
8. Kubo, K.; Kohara, Y.; Yoshimura, Y.; Inada, Y.; Shibouta, Y.; Furukawa, Y.; Kato, T.; Nishikawa, K.; Naka, T. Nonpeptide angiotensin II receptor antagonists: Synthesis and biological activity of potential prodrugs of benzimidazole-7-carboxylic acids. *J. Med. Chem.* **1993**, *36*, 2343.
9. Terzioglu, N.; van Rijn, R.; Bakker, R. A.; De Esch, I. J. P.; Leurs, R. Synthesis and structure–activity relationships of indole and benzimidazole piperazines as histamine H_4 receptor antagonists. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5251.
10. Nannapaneni, D. T.; Gupta Atyam, V. G.; Reddy, M. I.; Raidu, S. C. Synthesis, characterization, and biological evaluation of benzimidazole derivatives as potential anxiolytics. *Pharm. Chem.* **2010**, *2*, 273.
11. Alper, S.; Arpaci, O. T.; Aki, E. S.; Yalçin, I. Some new bi- and ter-benzimidazole derivatives as topoisomerase I inhibitors. *Farmaco* **2003**, *58*, 497.
12. Kahn, S. E.; Zinman, B.; Lachin, J. M.; Haffner, S. M.; Herman, W. H.; Holman, R. R.; Kravitz, B. G.; Yu, D.; Heise, M. A.; Aftring, R. P.; Viberti, G. Rosiglitazone-associated fractures in type 2 diabetes: An analysis from a diabetes outcome progression trial (ADOPT). *Diabetes Care* **2008**, *31*, 845–851.
13. (a) Nesto, R. W.; Bell, D.; Bonow, R. O.; Fonseca, V.; Grundy, S. M.; Horton, E. S.; Winter, M. L.; Porte, D.; Semenkovich, C. F.; Smith, S.; Young, L. H.; Kahn, R. Thiazolidinedione use, fluid retention, and congestive heart failure: A consensus statement from the American Heart Association and American Diabetes Association. *Diabetes Care* **2004**, *27*, 256–263; (b) Fiévet, C.; Fruchart, J. C.; Staels, B. PPARα and PPARγ dual agonists for the treatment of type 2 diabetes and the metabolic syndrome. *Curr. Opin. Pharmacol.* **2006**, *6*, 606.
14. Cai, Z.; Feng, J.; Guo, Y.; Li, P.; Shen, Z.; Chu, F.; Guo, Z. Synthesis and evaluation of azaindole-α-alkyloxyphenylpropionic acid analogues as PPARα/γ agonists. *Bioorg. Med. Chem.* **2006**, *14*, 866.
15. Kim, N. J.; Lee, K. O.; Koo, B. W.; Li, F.; Yoo, J. K.; Park, H. J.; Min, K. H.; Lim, J. I.; Kim, M. K.; Kim, J. K.; Suh, Y. G. Design, synthesis, and structure–activity relationship of carbamate-tethered aryl propanoic acids as novel PPARα/γ dual agonists. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 3595.
16. Kuhn, B.; Hilpert, H.; Benz, J.; Binggeli, A.; Grether, U.; Humm, R.; Märki, H. P.; Meyer, M.; Mohr, P. Structure-based design of indole propionic acids as novel PPAR α/γ co-agonists. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4016.
17. Cronet, P.; Petersen, J. F.; Folmer, R.; Blomberg, N.; Sjöblom, K.; Karlsson, U.; Lindstedt, E. L.; Bamberg, K. Structure of the PPARα and -γ ligand binding domain in complex with AZ 242: Ligand selectivity and agonist activation in the PPAR family. *Structure* **2001**, *9*, 699.
18. Wang, W.; Devasthale, P.; Farrelly, D.; Gu, L.; Harrity, T.; Cap, M.; Chu, C.; Kunselman, L.; Morgan, N.; Ponticiello, R.; Zebo, R.; Zhang, L.; Locke, K.; Lippy, J.; O'Malley, K.; Hosagrahara, V.; Zhang, L.; Kadiyala, P.; Chang, C.; Muckelbauer, J.; Doweyko, A. M.; Zahler, R.; Ryono, D.; Hariharan, N.; Cheng, P. T. Discovery of

azetidinone acids as conformationally constrained dual PPARα/γ agonists. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1939.
19. Suh, Y. G.; Kim, N. J.; Koo, B. W.; Lee, K. O.; Moon, S. H.; Shin, D. H.; Jung, J. W.; Paek, S. M.; Chang, D. J.; Li, F.; Kang, H. J.; Le, T. V. T.; Chae, Y. N.; Shin, C. Y.; Kim, M. K.; Lim, J. I.; Ryu, J. S.; Park, H. J. Design, synthesis, and biological evaluation of novel constrained *meta*-substituted phenyl propanoic acids as peroxisome proliferator-activated receptor α and γ dual agonists. *J. Med. Chem.* **2008**, *51*, 6318.
20. Cantello, C. C.; Cawthorne, M. A.; Cottam, G. P.; Duff, P. T.; Haigh, D.; Hindley, R. M.; Lister, C. A.; Smith, S. A.; Thurlby, P. L. [ω-(Heterocyclylamino)alkoxy]benzyl]-2,4-thiazolidinediones as potent antihyperglycemic agents. *J. Med. Chem.* **1994**, *37*, 3977.
21. Shinkai, H.; Onogi, S.; Tanaka, M.; Shibata, T.; Iwao, M.; Wakitani, K.; Uchida, I. Isoxazolidine-3,5-dione and noncyclic 1,3-dicarbonyl compounds as hypoglycemic agents. *J. Med. Chem.* **1998**, *41*, 1927.
22. Lohray, B. B.; Bhushan, B.; Rao, B. P.; Madhavan, G. R.; Murali, N.; Rao, K. N.; Reddy, A. K.; Rajesh, B. M. Novel euglycemic and hypolipidemic agents. *J. Med. Chem.* **1998**, *41*, 1619.
23. Sybyl 7.3. St. Louis, MO, 2006.
24. Van Allan, J. A.; Deacon, B. D.2-Mercaptobenzimidazole. *Org. Synth. Coll.* Vol.4 1963, 569.
25. Ellingboe, J. W.; Spine, W.; Michael, W.; Nguyen, T. T.; Roderick, W.; Kitzen, J. M.; Baglit, J. F. Class I11 antiarrhythmic activity of novel substituted 44 (methylsulfonyl) amino] benzamides and sulfonamides. *J. Med. Chem.* **1992**, *35*, 705.