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PUBLICATIONS:


List of papers presented in Conferences (International / National)

1. INTERNATIONAL CONFERENCE ON INNOVATIONS IN CHEMISTRY FOR SUSTAINABLE DEVELOPMENT (ICSD-2011) Organized by dept. of Chemistry, Panjab University Chandigarh on 01-03 December 2011

2. CHEMICAL CONSTELLATION CHEMINAR-2012

Theme: Chemistry for sustainable Development and Innovations (An International Conference) Organized by dept. of Chemistry, Dr. B R Ambedkar National Institute of Technology Jalandhar


5. RACENT ADVANCES IN CHEMICAL AND ENVIRONMENT SCIENCES at Department of Chemistry, MULTANI MAL MODI COLLEGE , PATIALA-147002 (February 28-March 1, 2011)

6. Impact of Science and Technology on societal Development at SHAHEED UDHAM SINGH Group of institution, TANGARI, Maholi : Punjab (November 3-5, 2011)


8. RACENT ADVANCES IN CHEMICAL AND ENVIRONMENT SCIENCES at Department of Chemistry, MULTANI MAL MODI COLLEGE , PATIALA-147002 (March 03, 2012)

9. NEW FRONTIERS IN CHEMISTRY Department of Chemistry, Punjabi University, Patiala-147002 (February 15-16, 2013)
10. National seminar on New Paradigm in Chemical Sciences-2014 at Department of Chemistry, Punjabi University, Patiala-147002 (February 13, 2014)

**Workshop attended**

1. Practical Aspects on the Importance of Patents in Research (PAIPR-2013) held on February 12, 2013 at Punjabi University Patiala
Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

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

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

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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
Synthetic Organic and Medicinal Chemistry Laboratory, Department of Chemistry, Punjabi University, Patiala, India

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-thiazolidinedione 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 (PPAR\(\alpha/\gamma\)) in the management of type 2 diabetes: a move from glitazones to selective PPAR\(\gamma\) modulators (SPPAR\(\gamma\)Ms).

Supplemental materials are available for this article. Go to the publisher’s online edition of Synthetic Communications\(^{1}\) to view the free supplemental file.

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

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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 EC₅₀ 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 activities.[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.
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-substituted 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 laboratory) 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 PPAR\(\alpha\) and PPAR\(\gamma\)

<table>
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<tr>
<th>Serial no.</th>
<th>Code</th>
<th>Structure</th>
<th>Binding energy score (gold score(^a))</th>
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<td>2</td>
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<td><img src="image" alt="Structure" /></td>
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<td>Tesaglitazar(^{[db]})</td>
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<td>E(^{[19]})</td>
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<td>F(^{[19]})</td>
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<td>GW409544</td>
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<td>5(^a)</td>
<td><img src="image" alt="Structure" /></td>
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<td>5(^a)(^{[db]})</td>
<td><img src="image" alt="Structure" /></td>
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<tr>
<td>10</td>
<td>5(^b)</td>
<td><img src="image" alt="Structure" /></td>
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</table>

<sup>a</sup>Gold score<sup>[25]</sup> of the best docked conformation.

<sup>b</sup>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 PPAR\(\alpha\) (PDB code: 1k71).

The synthesis of ether-linked benzylidene TZD and DEM target molecules is shown in Scheme 1. 2-Mercaptobenzimidazole{\textsuperscript{24}} (2) and 2-bromo-1-methyl-1\(H\)-benzimidazole{\textsuperscript{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 benzaldehyde (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 benzaldehyde (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 obtain the desired compounds 12a and 12b, which prompted us to opt for

Scheme 1. Synthesis of -O- linked molecules: (a) carbon disulfide, ethanol, water, glacial AcOH, Norit; (b) HBr/glacial AcOH, Br₂, water, NaOH; (c) 1 N NaOH solution, dimethyl sulfate; (d) K₂CO₃, 3-hydroxybenzaldehyde, Cu powder, pyridine; (e) piperidine acetate, toluene, 2,4-thiazolidinedione; and (f) 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 BBr₃ 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-1H-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).
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-1h-benzimidazol-2-yl)oxy]benzaldehyde (5)

A mixture of 4 (0.211 g; 1 mmol), 3-hydroxybenzaldehyde (0.122 g; 1 mmol), K$_2$CO$_3$ (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$_2$SO$_4$), 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\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\): 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\(_2\)O\(_2\): 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\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\): 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\(_2\)O\(_2\): 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\(_2\)CO\(_3\) (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\(_2\)SO\(_4\)), 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%) as light greenish solid. Mp: 118–120°C. IR (KBr): 3049, 3011, 2947 and 2838, 2806 and 2738, 1701, 1622, 1587, 1520, 1490, 1454, 1383, 1254, 737, 783 and 679 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \(\delta\): 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\(_2\)O: 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-[(1-Methyl-1H-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; H NMR (DMSO-d$_6$): 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 + H]$^+$ (100). Anal. calcd. for C$_{19}$H$_{15}$N$_3$O$_3$S: C, 62.45; H, 4.14; N, 11.50. Found: C, 62.71; H, 4.27; N, 11.37.

2-[3-(1-Methyl-1H-benzoimidazol-2-ylmethoxy)-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; H NMR (CDCl$_3$): 1.26 (t, 3H, -O.CH$_2$.CH$_3$), 1.26 (t, 3H, -O.CH$_2$.CH$_3$), 3.66 (s, 3H, N-CH$_3$), 4.22 (two overlapping quartets, 4H, -O.CH$_2$.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 + H]$^+$ (45), 320 (100). Anal. calcd. for C$_{22}$H$_{22}$N$_2$O$_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 66.74; H, 5.43; N, 6.86.
Diethyl [3-(1-Methyl-1H-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; 1H NMR (CDCl3) \( \delta \): 1.27 (t, 3H, -OCH2CH3), 1.35 (t, 3H, -OCH2CH3), 3.89 (s, 3H, N-CH3), 4.33 (two overlapping quartets, 4H, -OCH2CH3), 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 C22H22N2O4: 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\(^{-1}\); 1H NMR (CDCl3) \( \delta \): 2.18 (s, 3H, -COCH3), 3.10 (d, 2H, -CH2-), 3.70 (s, 3H, -OCH3), 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 C12H14O4: 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), K₂CO₃ (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 (Na₂SO₄), 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-1H-benzimidazol-2-yl]oxy}benzyl-3-oxobutanoate (12a). Yield: 20%; IR (KBr): 3019, 2954, 2850, 1742, 1715, 1455, 1360, 1232, 756, 695, 667 cm\(^{-1}\); 1H NMR (CDCl₃) \( \delta \): 2.07 (s, 3H, -COCH₃), 2.85 (dd, 1H, -CH₂), 2.71 (overlapping double doublet, 1H, benzylic), 3.40 (s, 3H, N-CH₃), 3.63 (overlapping dd, 1H, benzylic), 3.66 (s, 3H, -OCH₃), 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 C₁₂H₁₄N₂O₄: C, 68.46; H, 5.48; N, 8.12.
Methyl 2-\{3-[1-(methyl-1\text{H}-benzimidazol-2-yl)methoxy]benzyl\}-3-oxobutanoate (12b). Yield: 20%; IR (KBr): 3437, 1731, 1711, 1095 cm\(^{-1}\); \(^{1}\)H NMR (CDCl\(_3\)) \(\delta\): major 2.05 (s, 3H, \(-\text{COCH}_3\)), 3.57 (overlapping dd, 2H, benzylic), 3.64 (s, 3H, \(-\text{NCH}_3\)), 3.88 (s, 3H, \(-\text{OCH}_3\)), 5.38 (s, 2H, \(-\text{CH}_2\text{O}-\)), minor 2.50 (s, 3H, \(-\text{COCH}_3\)), 3.62 (s, 3H, \(-\text{NCH}_3\)), 3.85 (overlapping dd, 2H, \(-\text{CH}_2\text{-}\)), 3.87 (s, 3H, \(-\text{OCH}_3\)), \(\delta\) 5.35 (s, 2H, \(-\text{CH}_2\text{O}-\)), 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\(_2\)O\(_4\): 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 PPAR\(\gamma\) (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 PPAR\(\gamma\) (PDB code: 2prg) and PPAR\(\alpha\) (PDB code: 1k7l) 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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