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Design, synthesis, biological evaluation and molecular modelling studies of novel diaryl substituted pyrazolyl thiazolidinediones as potent pancreatic lipase inhibitors

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ABSTRACT

A series of novel diaryl substituted pyrazolyl 2,4-thiazolidinediones were synthesized via reaction of appropriate pyrazolecarboxaldehydes with 2,4-thiazolidinedione (TZD) and nitrobenzyl substituted 2,4-thiazolidinedione. The resulting compounds were screened *in vitro* for pancreatic lipase (PL) inhibitory activity. Two assay protocols were performed *viz.,* methods A and B using *p*-nitrophenyl butyrate and tributyrin as substrates, respectively. Compound **11e** exhibited potent PL inhibitory activity (IC_{50} = 4.81 μM and X_{i50} = 10.01, respectively in method A and B), comparable to that of the standard drug, orlistat (IC_{50} = 0.99 μM and X_{i50} = 3.72). Presence of nitrobenzyl group at N-3 position of TZD and nature of substituent at *para* position of phenyl ring at C-3 position of pyrazole ring notably affected the PL inhibitory activity of the tested compounds. Enzyme inhibition kinetics of **11e** revealed its reversible competitive inhibition, similar to that of orlistat. Molecular docking studies validated the rationale of pharmacophoric design and are in accordance to the *in vitro* results. Compound **11e** exhibited a potential MolDock score of −153.349 kcal/mol. Further, the diaryl pyrazolyl wing exhibited hydrophobic interactions with the amino acids of the hydrophobic lid domain. Moreover, the carbonyl group at 2nd position of the TZD ring existed adjacent to Ser 152 (≈3 Å) similar to that of orlistat. A 10 ns molecular dynamics simulation of **11e**–**PL** complex revealed a stable binding conformation of **11e** in the active site of PL (Maximum RMSD ≈ 3 Å). The present study identified novel thiazolidinedione based leads with promising PL inhibitory activity. Further development of the leads might result in potent PL inhibitors.

Obesity is a multifactorial metabolic disorder, characterised by excessive deposition of lipids in the body.[1] Recent statistics has projected a rapid growth in obesity with 600 million obese people worldwide.[2] Moreover, obesity is associated with various comorbid conditions including diabetes mellitus and cardiovascular diseases, posing major health risk to the obese patients.[3] With over 2.8 million deaths per year, obesity ranks fifth among global deaths.[4] Pancreatic lipase (PL) or triacylglycerol lipase (EC 3.1.1.3), a digestive enzyme secreted from the pancreatic exocrine, is primarily involved in the hydrolysis of dietary lipids.[5] Structurally, the active site of Human PL (PDB ID: 1LPB) consists of the catalytic triad, Ser 152 - Asp 176 - His 263, which is enclosed within a hydrophobic lid domain comprised of Gly 76 - Lys 80 and Leu 213 - Met 217.[6,7]

Orlistat, a potent PL inhibitor, remains to be the only drug approved for long term treatment of obesity.[8,9] However, recent reports from the United States Food and Drug Administration (USFDA) indicated severe adverse effects with long term administration of orlistat, including hepatotoxicity and acute pancreatitis etc.[10] These events highlighted the necessity for the development of safer and effective anti-obesity drugs.

Thiazolidinediones (TZDs) represent a renowned class of anti-diabetic medications, used in the treatment of type II diabetes mellitus.[11] Further, they have also been widely explored for their activity against obesity through PTP1b inhibition.[12–14] However, there are no reports available on thiazolidinediones in relation to their PL inhibition. Previously, amide containing compounds have been reported as potential PL inhibitors.[15,16] Further, we have identified carbazolyl oxoacetamides as potential PL inhibitors in our previous study, wherein the amide interacted with Ser 152, while the carbazole (containing a five-membered nitrogen heterocycle) aided in hydrophobic interactions with the lid domain.[17] Since

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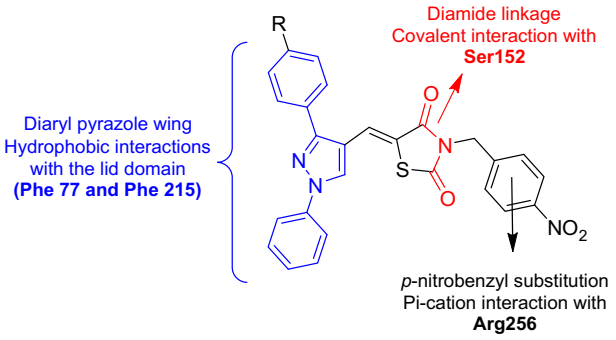


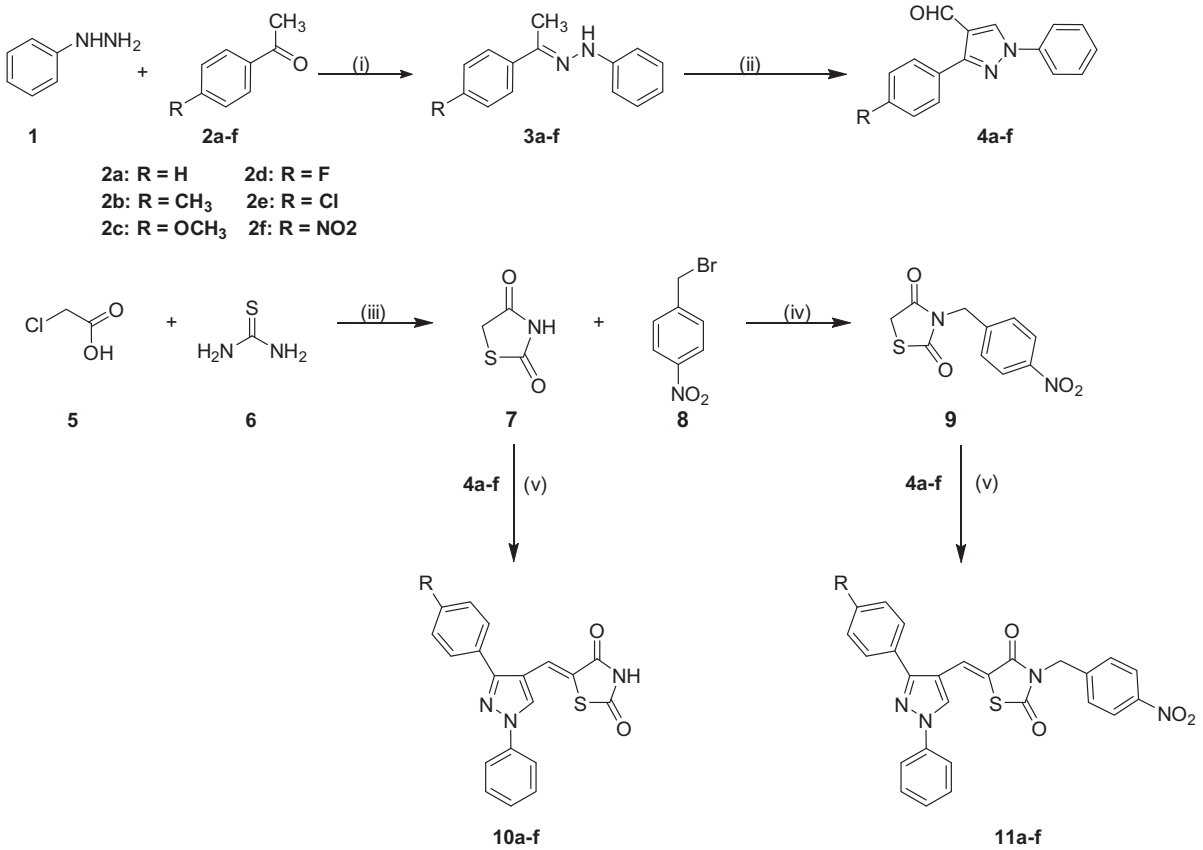
Fig. 1. Representation of the pharmacophoric design for PL inhibition.

TZD possesses a nitrogen centred diamide linkage (Fig. 1), we presumed TZDs to possess potential PL inhibitory activity. In the recent years, five membered nitrogen heterocycles have gained prominent significance in PL inhibition. Examples include oxadiazoles[18,19] and 1,3-pyrazoles,[20,21] wherein the molecules exhibited potential PL inhibitory activity. Considering the above facts and the pharmacophoric requirements from our previous study,[17] we have designed a pharmacophore hybrid combining the TZD with diaryl substituted pyrazoles (Fig. 1). Accordingly, the present study involved synthesis, characterization, *in vitro* evaluation and molecular modelling studies of novel diaryl substituted pyrazolyl thiazolidinediones as potent PL inhibitors.

The synthetic route followed for the preparation of various intermediates and title compounds **10a–f** and **11a–f** has been illustrated in Scheme 1 (see Supplementary data for detailed description). The key starting materials, 3-(substituted phenyl)-1-phenyl-*1H*-pyrazole-4-carbaldehydes (**4a–f**) were synthesized by the reaction of various acetophenones (**2a–f**) with phenyl hydrazine (**1**) to produce corresponding hydrazones (**3a–f**), followed by their Vilsmeier-Haack cyclization in the presence of DMF/$POCl_3$ at 80–90 °C.[22]

TZD (**7**) was obtained by the condensation of monochloroacetic acid (**5**) with thiourea (**6**) under ice cold conditions to afford white precipitate of 2-iminothiazolidine-4-one which upon acidification and refluxing with HCl for 10 h afforded white crystals of 2,4-TZD.[23] The 4-nitrobenzyl derivative of the TZD was obtained by *N*(3)-alkylation of TZD (**7**) with 4-nitrobenzyl bromide (**8**) in the presence of sodium hydroxide in refluxing ethanol, leading to formation of the intermediate, 3-(4-nitrobenzyl)thiazolidine-2,4-dione (**9**).[24] Knoevenagel condensation was carried out by treating equimolar ratio of thiazolidine-2,4-dione (**7**) or 3-(4-nitro-benzyl)-thiazolidine-2,4-dione (**9**) with 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde (**4a**) in ethanol in the presence of catalytic amount of piperidine and few drops of glacial acetic acid by refluxing for 5–6 h. The usual work up of the reaction afforded the products, (*Z*)-5-((1,3-diphenyl-*1H*-pyrazol-4-yl)methylene)thiazolidine-2,4-dione (**10a**) and (*Z*)-5-((1,3-diphenyl-*1H*-pyrazol-4-yl)methylene)-3-(4-nitrobenzyl)thiazolidine-2,4-dione (**11a**) in good yield. All other compounds **10b–f** and **11b–f** were prepared by adopting the similar methodology.[25]

The synthesized compounds were characterized by FTIR, ^{1}H and ^{13}C NMR, mass spectroscopy and elemental analysis data which fully supported their structural identity. The IR spectrum of title compounds (**10a–f** and **11a–f**) showed strong absorption bands in the range of 1732–1747 cm^{-1} and 1681–1689 cm^{-1} due to two C=O groups stretching. Derivatives **10a–f** showed typical absorption at 3397–3442 cm^{-1} due to NH group stretching



Scheme 1. Reagents and conditions (i) EtOH, Glacial AcOH, reflux; (ii) DMF/$POCl_3$, reflux, 80–90 °C, 8–10 h; (iii) HCl, H_2O, reflux, 100–110 °C, 10 h; (iv) KOH, EtOH, 18 h and (v) EtOH, piperidine, Glacial CH_3COOH, Reflux 80–90 °C, 4–6 h.