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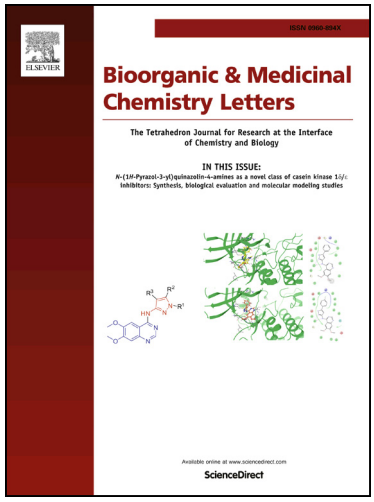


Design, Synthesis, Biological Evaluation and Molecular Modelling Studies of Novel Diaryl Substituted Pyrazolyl Thiazolidinediones as Potent Pancreatic Lipase Inhibitors

S.N.C. Sridhar, Deendyal Bhurta, Dharmvir Kantiwal, Ginson George, Vikramdeep Monga, Atish T. Paul

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**Title Page**

**Title:**

Design, Synthesis, Biological Evaluation and Molecular Modelling Studies of Novel Diaryl Substituted Pyrazolyl Thiazolidinediones as Potent Pancreatic Lipase Inhibitors

**Authors:**

Sridhar S N C[a], Deendyal Bhurta[b], Dharmvir Kantiwal[b], Ginson George[a], Vikramdeep Monga[b,*] Atish T. Paul[a,*].

**Affiliations:**

[a]Laboratory of Natural Drugs, Department of Pharmacy, Birla Institute of Technology and Science, Pilani (Pilani campus), Pilani - 333 031, Rajasthan, India.

[b]Department of Pharmaceutical Chemistry, Rajendra Institute of Technology & Sciences, Sirsa-125 055, Haryana, India

**Corresponding authors:**

Dr. Vikramdeep Monga

vikramdeepmonga@gmail.com

vikramdeepmonga@yahoo.com

Dr. Atish T. Paul

atish.paul@pilani.bits-pilani.ac.in

paulatish@gmail.com

**Present Address:**

Dr. Vikramdeep Monga,

Professor & Head,

Department of Pharmaceutical Chemistry,

Rajendra Institute of Technology & Sciences,

Sirsa-125055, Haryana, India

Dr. Atish T. Paul,

Assistant Professor,

3170-U, Department of Pharmacy,

Birla Institute of Technology and Science, Pilani (Pilani Campus),

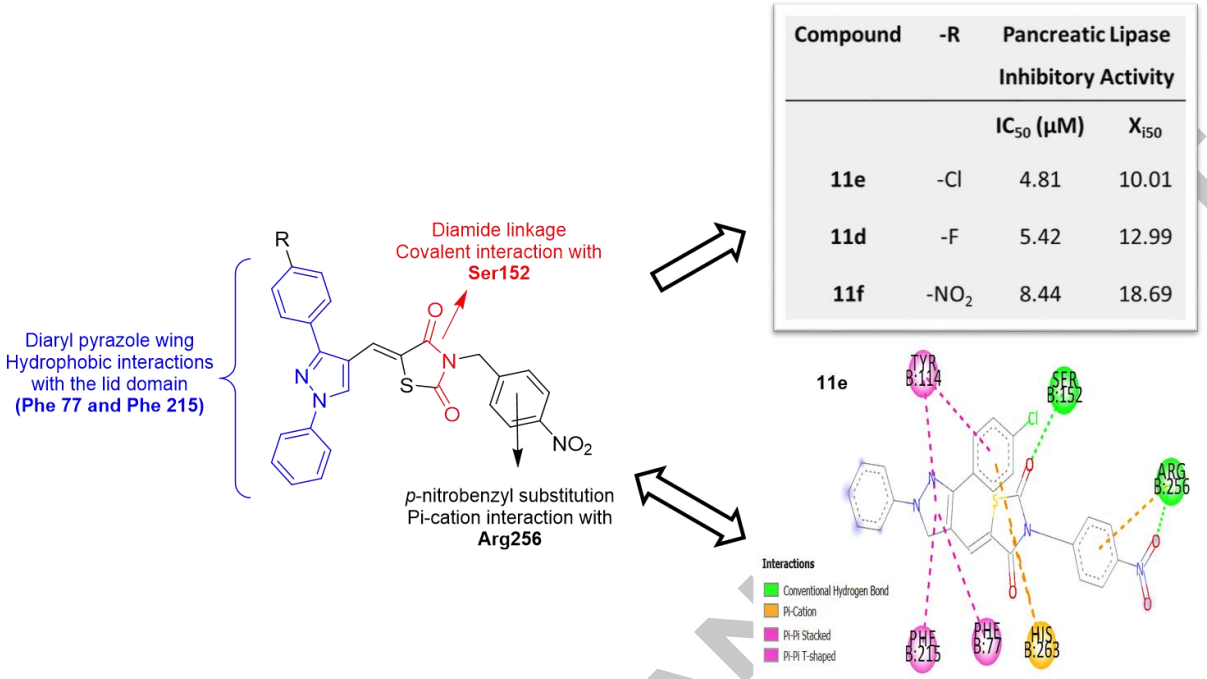
Pilani - 333 031, Rajasthan, India.

**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 2$^{nd}$ 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.

**Keywords:** Thiazolidinedione; pH indicator; Pyrazole; Knoevenagel; Molecular Modelling; Pancreatic Lipase; Obesity; Orlistat

## Graphical Abstract




| Compound | -R | Pancreatic Lipase Inhibitory Activity | |
|---|---|---|---|
| | | $IC_{50}$ (μM) | $X_{i50}$ |
| **11e** | -Cl | 4.81 | 10.01 |
| **11d** | -F | 5.42 | 12.99 |
| **11f** | $-NO_2$ | 8.44 | 18.69 |

## Highlights

- A series of novel diaryl substituted pyrazolyl thiazolidinediones were synthesized
- Pancreatic lipase inhibition assay was performed using two methods
- Compound **11e** exhibited potent and reversible competitive inhibition ($IC_{50}$ = 4.81 μM)
- Molecular dynamics of **11e** indicated its stable binding conformation (RMSD ≈ 3 Å)

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, Ser152 - Asp176 - His263, 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 the Ser 152, while the carbazole (containing a five-membered nitrogen heterocycle) aided in hydrophobic interactions with the lid domain[17]. Since TZD possesses 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.

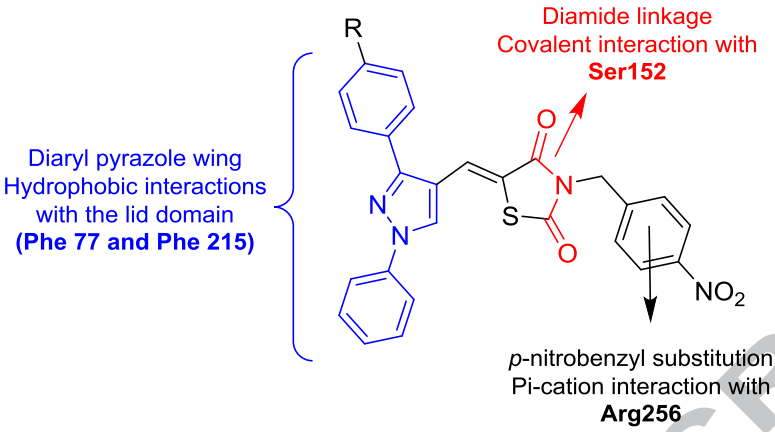
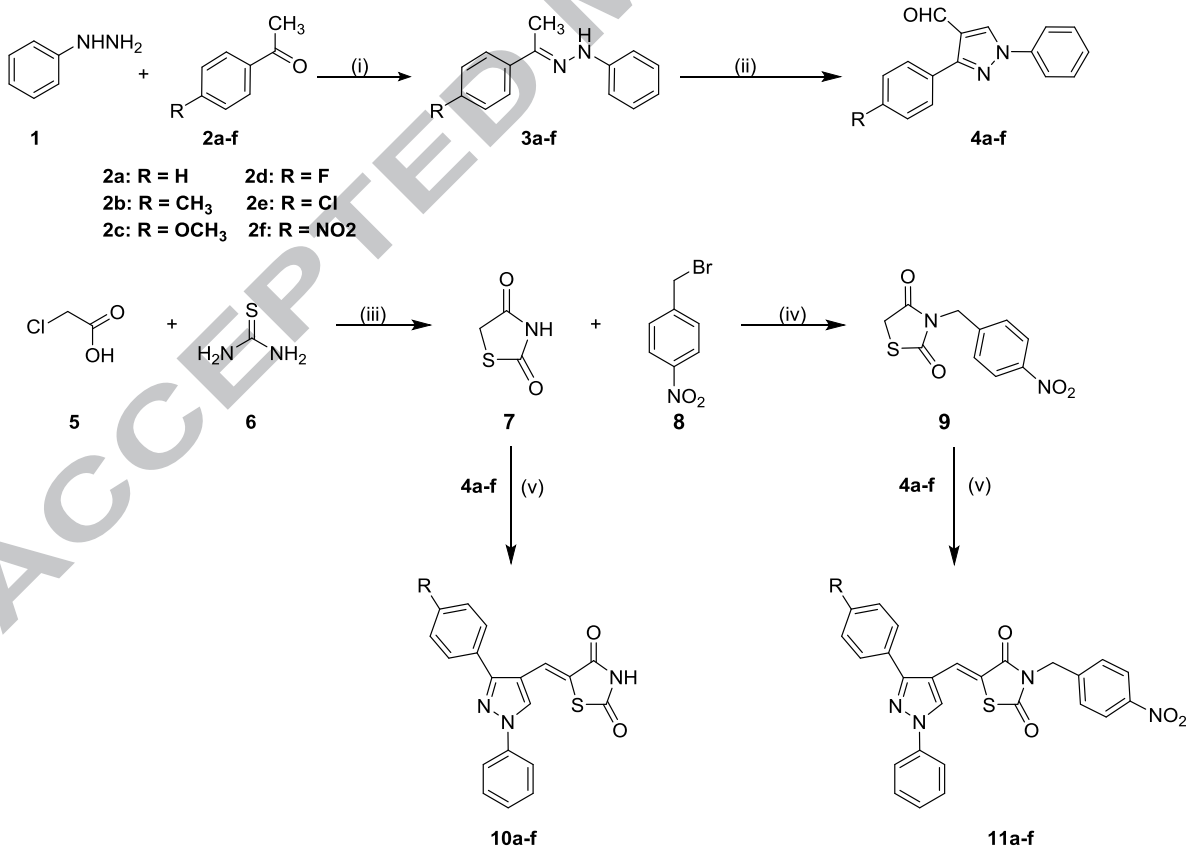



**Fig. 1.** Representation of the pharmacophoric design for PL inhibition.

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].




**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.

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 product (*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 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 whereas bands due to $NO_2$ group stretching vibrations appeared at 1521 - 1529 & 1332 - 1346 $cm^{-1}$ for compounds **11a-f**. Further, absorption band appeared in the range of 1592 - 1619 $cm^{-1}$ due to C=N stretching. In the $^{1}$H NMR spectrum, all the products showed characteristic singlet at δ 8.21 - 8.86 due to $C_5$-H of pyrazole ring. Disappearance of peak due to methylene group and appearance of arylidene (=CH-) peak further confirms the Knoevenagel condensation between various pyrazole aldehydes and TZD (**7**) or 3-(4-nitrobenzyl)thiazolidine-2,4-dione (**9**). Proton of arylidene group appeared either as singlet or multiplet in the range of 7.43 - 7.99. In the $^{1}$H NMR spectrum, =CH- proton was deshielded more (δ = 7.4 - 7.9 ppm) as expected in *Z*-form, relative to the slightly shielded protons of the *E*-form (δ = 6.2 - 6.3 ppm), thus indicating that all the derivatives were obtained exclusively in *Z*-form. This deshielding of the arylidene proton is caused by the anisotropic effect exerted by the nearby carbonyl group of various 2,4-thiazolidinedione derivatives in *Z*-isomer. Moreover, *Z*-isomer is thermodynamically more stable because of intramolecular hydrogen bond that can be formed between the hydrogen bond of =CH and oxygen atom of carbonyl group in TZD[26]. Further, a broad singlet due NH proton appeared in the range of δ 11.38 -

12.59 for compounds **10a-f** whereas, protons of methylene group (-N-$CH_2$) in case of compounds **11a-f** were resonated as a singlet at δ 4.95 - 4.99 ppm. All other protons were observed at expected regions. In $^{13}$C NMR, signals due to two carbonyl carbons of TZD ring ($C_2$=O and $C_4$=O) were appeared at δ 166.57 - 168.04 and 165.37 – 167.79 respectively. All the compounds showed prominent signals at δ 139.03 - 139.82 and 150.28 - 155.37 due to arylidene carbon (-CH=) and C-3 of pyrazolyl ring. Further, compounds **11a-f** also showed characteristic signal in the range of δ 44.46 - 44.63 due to carbon of $CH_2$ group attached to N-3 of TZD ring. Finally, the assigned structures of various compounds were confirmed by their mass spectra where characteristic $[M+1]^+$ peak was observed. All compounds gave satisfactory elemental analysis.

The synthesized compounds (**10a-f** and **11a-f)** were subjected to *in vitro* PL inhibitory assay using two methods (A and B using *p*-nitrophenyl butyrate (PNPB) and tributyrin as substrates, respectively). The assay procedure for method A was performed using the protocol standardized in our laboratory[27], while method B (a pH indicator based assay) was implemented from the literature[28] with relevant modifications[17,18] (see Supplementary data for detailed assay procedures).

**Table 1**

PL inhibitory activity of the synthesized compounds using method A ($IC_{50}$) and B ($X_{i50}$).

| Compound | Activity | | Compound | Activity | |
|---|---|---|---|---|---|
| | **$IC_{50}$ (μM)*** | **$X_{i50}$*** | | **$IC_{50}$ (μM)*** | **$X_{i50}$*** |
| **10a** | 18.81 ± 0.21 | 65.1 ± 2.98 | **11a** | 12.46 ± 2.92 | 21.76 ± 2.11 |
| **10b** | 15.12 ± 0.83 | 27.18 ± 1.15 | **11b** | 9.87 ± 1.03 | 19.34 ± 2.70 |
| **10c** | 13.05 ± 2.81 | 24.36 ± 2.61 | **11c** | 9.40 ± 0.88 | 18.12 ± 2.33 |
| **10d** | 12.90 ± 0.89 | 25.39 ± 2.24 | **11d** | 5.42 ± 0.43 | 12.99 ± 0.96 |
| **10e** | 10.30 ± 1.27 | 19.30 ± 2.75 | **11e** | 4.81 ± 0.82 | 10.01 ± 1.16 |
| **10f** | 17.32 ± 0.48 | 39.47 ± 2.96 | **11f** | 8.44 ± 0.32 | 18.69 ± 1.57 |
| Orlistat | 0.99 ± 0.11[17] | 3.72 ± 0.21 | | | |

*All experiments were performed in triplicate and the results were expressed as Mean ± S.E.M.

Table 1 represents the PL inhibitory activity of the synthesized compounds, **10a-f** and **11a-f**. Compound **11e** exhibited the most potent PL inhibitory activity ($IC_{50}$ = 4.81 μM, $X_{i50}$ = 10.01), comparable to that of orlistat ($IC_{50}$ = 0.99 μM, $X_{i50}$ = 3.72), followed by **11d** ($IC_{50}$ = 5.42 μM, $X_{i50}$ = 12.99). Analogues **11f, 11c** and **11b** exhibited potential activity (8–10 μM). However, analogues **10a-f** and **11a** exhibited moderate PL inhibitory activity (> 10 μM)**.** Enzyme kinetic study was performed for **11e** using the optimized protocol[27], to understand its nature of inhibition. The protocol was performed at three concentration levels

of the inhibitor, and a double reciprocal Lineweaver-Burk plot was acquired. As represented in Fig. 2 and Table 2, the $k_m$ values increased with inhibitor concentration, indicating a reversible competitive inhibition similar to that of orlistat[17]. Further, compound **11e** exhibited an inhibition constant ($K_i$) value of 14.4 μM (calculated from Dixon plot).

**Table 2**

$V_{max}$ and $K_m$ values calculated from Lineweaver-Burk plot at different concentrations of **11e** [I].

| [I] (μM) | $V_{max}$ (μM.min$^{-1}$) | $K_m$ (μM) |
|---|---|---|
| **0** | 0.0545 | 69.32 |
| **2.5** | 0.0565 | 125.15 |
| **5** | 0.0557 | 145.37 |
| **10** | 0.0566 | 165.11 |

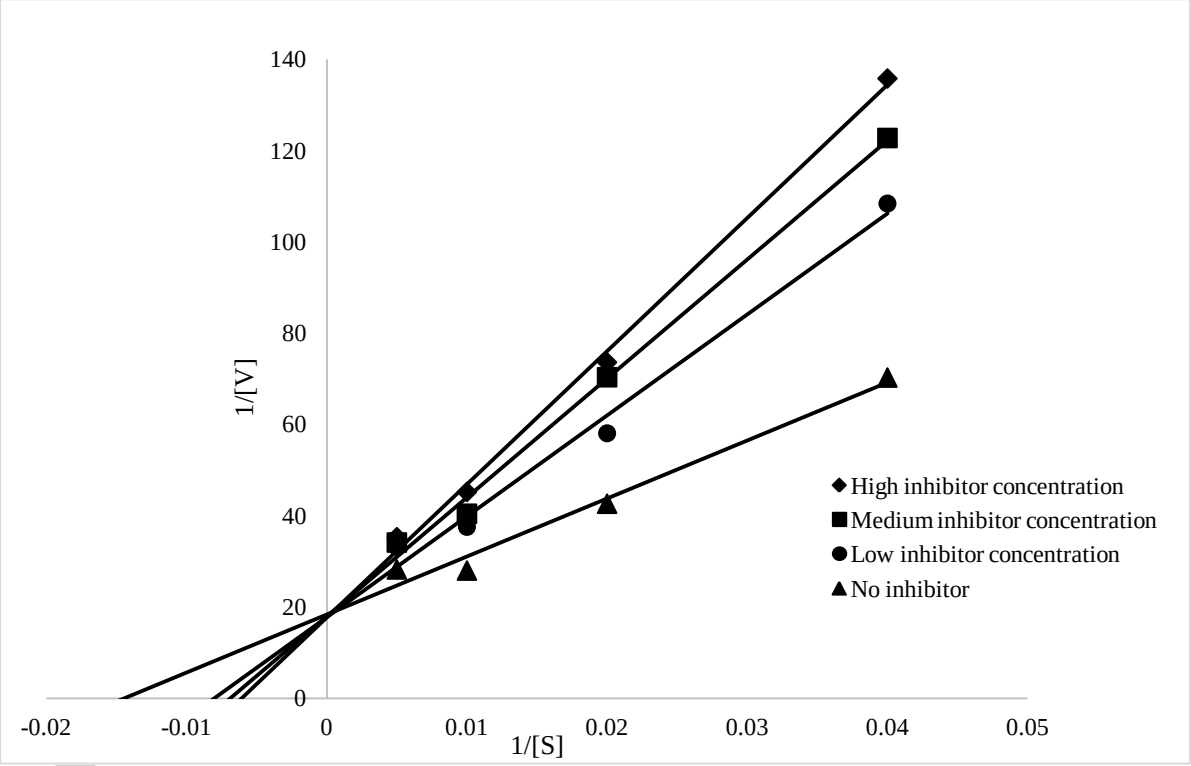



**Fig. 2.** Lineweaver-Burk plot of **11e** representing reversible competitive inhibition.

A preliminary structure-activity relationship of the compounds **10a-f** and **11a-f** with reference to their PL inhibitory activity has been analysed (Fig. 3). Significant variation in the PL inhibitory activity was observed with reference to the introduction of *p*-nitrobenzyl substitution on the ring nitrogen of TZD, wherein the activity was significantly potent with the tested analogues (**11a-f**) over their unsubstituted counterparts (**10a-f**). Moreover, nature of the substitution at *para* position of the 3-phenyl ring (-$R^1$) played an important role in the PL inhibition. The PL inhibitory activity did not vary significantly with the substitution of electron donating groups, as observed with **11c** (-$OCH_3$), **11b** (-$CH_3$) and **11a** (-H). However,

the presence of an electron withdrawing group resulted in potent PL inhibitory activity (as seen with **11e** (-Cl),**11d** (-F) and **11f** (-$NO_2$)). Compound **11f** exhibited lower inhibitory activity in comparison to **11d** and **11e**. This might be due to the comparatively higher electron withdrawing potential of the nitro group which resulted in an electron pull, thus reducing the hydrophobicity of the diaryl pyrazole moiety. The fact can be further confirmed with the partition coefficient values of the analogues, **11d-f**, wherein the PL inhibitory potential was in correlation to their respective ClogP values (6.31 for **11f**, 6.68 for **11d** and 7.04 for **11e**).

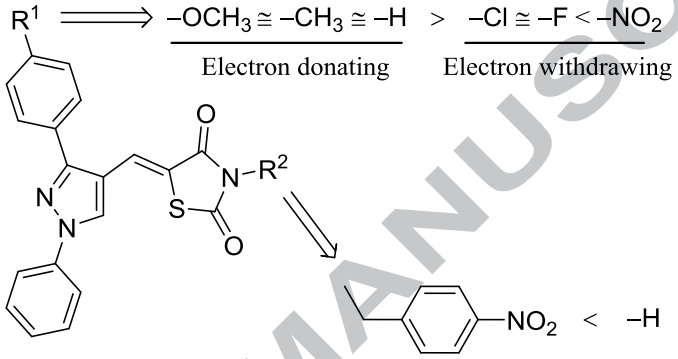



**Fig. 3.** Preliminary SAR for pyrazolyl thiazolidinediones**10a-f** and **11a-f** depicting the PL inhibitory potency ($IC_{50}$ or $X_{i50}$) vs. substitution.

Compounds **10a-f** and **11a-f** were docked into the active site of the human PL to understand their interactions with the active site amino acids. Molegro Virtual Docker (v 6.0) was used to perform the docking, and the validated grid parameters were opted from our previous studies[17,27]. The MolDock scores and the interactions exhibited by the analogues **10a-f** and **11a-f** are summarized in Table 3. The major H-bond interactions included with that of Gly 76, Phe 77, His 151, Ser 152 and Arg 256. Further, the diaryl substituted pyrazole moiety played an important role in maintaining π-π stacking interactions with the amino acids of the lid domain (Phe 77 and Phe 215), along with Tyr 114. Additionally, the *p*-nitrobenzyl substituted analogues (**11a-f**) exhibited a π-cation interaction with Arg 256, which was not observed with their unsubstituted counterparts (**10a-f**). Previously, Lowe *et al*. reported that the open lid conformation of human PL is attained through formation of salt bridge between Arg 256-Asp 257 and Tyr 267-Lys 268[29]. Further, Birari *et. al*. suggested the role of Arg 256 interaction for potential PL inhibitory activity[30]. This fact can be correlated to the potent activity exhibited by the nitrobenzyl substituted thiazolidinediones (**11a-f**) over their counterparts (**10a-f**). Further, in an attempt to understand the probable role of the diamide linkage in covalent interaction with Ser 152 of the active site, the binding pose of **11e** was superimposed with that of orlistat (Fig. 4c). The reactive carbonyl groups of both the

molecules existed equidistance from Ser 152 with minor deviation. Molecular docking results are in accordance to the PL inhibitory activity exhibited by the analogues, **10a-f** and **11a-f**. Further, the binding pose analysis has validated the rationale for designing the pyrazolyl thiazolidinediones as PL inhibitors.

**Table 3**
Summary of MolDock Scores and interactions exhibited by **10a-f** and **11a-f**.

| Compound | MolDock Score (kcal/mol) | H Bond | Pi-Pi | Pi-Cation |
|---|---|---|---|---|
| **10a** | -131.687 | Arg 256, His 263 | Phe 215 | His 151, His 263 |
| **10b** | -135.151 | Gly 76, Asp 79, His 151, His 263 | Tyr 114, Phe 215 | NA |
| **10c** | -136.617 | Gly 76, Asp 79, His 151, His 263 | Phe 77, Tyr 114, Phe 215 | NA |
| **10d** | -134.406 | Gly 76, Asp 79, His 151, His 263 | Phe 77, Tyr 114, Phe 215 | NA |
| **10e** | -134.509 | Gly 76, His 151, His 263 | Phe 77, Tyr 114, Phe 215 | NA |
| **10f** | -136.016 | Gly 76, Trp 85, Arg 256 | Phe 77, Tyr 114, Phe 215 | His 151, His 263 |
| **11a** | -143.745 | Gly 76, Phe 77, His 151 | Phe 77, Tyr 114, Phe 215, His 263 | His 151, Arg 256, His 263 |
| **11b** | -144.022 | Arg 256 | Phe 77, Tyr 114, Phe 215 | His 151, Arg 256, His 263 |
| **11c** | -149.634 | Ser 152, Arg 256 | Phe 77, Tyr 114, Phe 215 | His 151, Arg 256, His 263 |
| **11d** | -155.43 | Ser 152, Arg 256 | Phe 77, Tyr 114, Phe 215 | His 151, Arg 256, His 263 |
| **11e** | -153.349 | Ser 152, Arg 256 | Phe 77, Tyr 114, Phe 215 | Arg 256, His 263 |
| **11f** | -145.567 | Arg 256 | Phe 77, Tyr 114, Phe 215 | Arg 256, His 263 |
| Orlistat | -152.58 | His 151, Ser 152 | NA | NA |

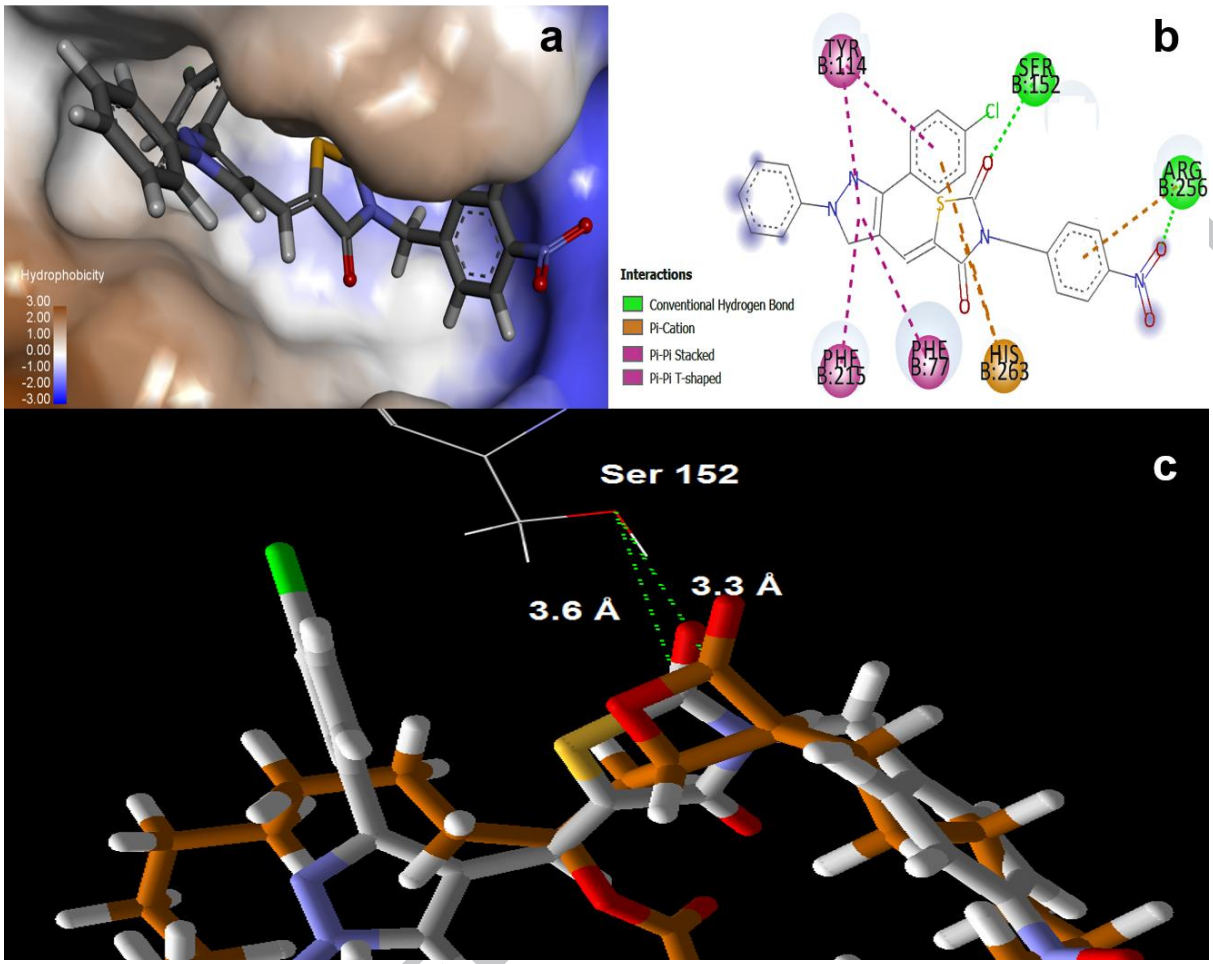



**Fig. 4.** (a) Binding pose of **11e** in the active site of PL; (b) 2D interaction diagram of **11e**; (c) Overlay diagram of **11e** (White) over orlistat (Brown) representing the distances of reactive carbonyl carbon from Ser 152.

In order to understand the binding mode and interactions in a dynamic environment, a 10 ns molecular dynamics (MD) simulation was performed for the **11e** – **PL** complex. The simulation parameters used for the study were earlier optimized[17,27]. Analogue **11e** exhibited a stable binding conformation throughout the MD run, as confirmed through the ligand RMSD (Fig. 5). **11e** exhibited a maximum RMSD of 3 Å in the active site of PL, as observed at 3$^{rd}$ ns. The interactions of **11e** with the active site of the PL through the 10 ns MD run are summarized in Table 4. The initial π-cation interaction of *p*-nitrobenzyl group with Arg 256 vanished with the initiation of MD. However, compound **11e** maintained stable π-π interactions with the amino acids of the lid domain. Further, H-bond interactions with Ser 152 and Arg 256 were prominent through the run, with an exception at 7$^{th}$ and 8$^{th}$ ns.

**Table 4:** Summary of interactions exhibited by **11e** through the 10 ns MD run.

| Time frame (ns) | H-bond | Pi-Pi | Pi-cation |
|---|---|---|---|
| 0 | Phe 77, Ser 152 | Phe 77, Tyr 114, His 263 | Arg 256 |
| 1 | Ser 152, Arg 256 | Phe 77, Tyr 114 | - |
| 2 | Arg 256 | Phe 77, Tyr 114 | - |
| 3 | Arg 256 | Phe 77, Tyr 114, Phe 215 | - |
| 4 | Ser 152, Arg 256 | Phe 77, Tyr 114, Phe 215 | - |
| 5 | Arg 256 | Phe 77, Tyr 114, Phe 215 | - |
| 6 | Arg 256 | Phe 77, Tyr 114, Phe 215 | - |
| 7 | - | Phe 77, Tyr 114, Phe 215 | - |
| 8 | - | Phe 77, Tyr 114, Phe 215 | - |
| 9 | Ser 152 | Phe 77 | - |
| 10 | Ser 152 | Phe 77, Tyr 114 | - |

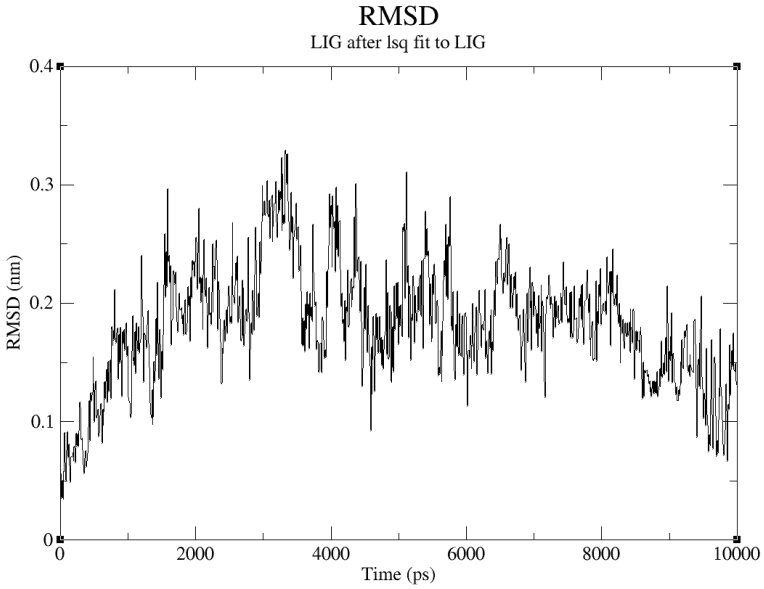



**Fig. 5.** Ligand RMSD of compound **11e** acquired through the 10 ns MD run.

To summarize, the present study involved design, synthesis, characterization, *in vitro* evaluation and molecular modelling studies of novel diaryl pyrazolyl thiazolidinedione analogues as potent PL inhibitors. Two assay protocols were performed to validate the potential of the analogues. **11e** exhibited potent PL inhibitory activity ($IC_{50}$ = 4.81 µM and $X_{i50}$ = 10.01) comparable to that of orlistat ($IC_{50}$ = 0.99 µM and $X_{i50}$ = 3.72). Further, enzyme kinetics established a reversible competitive nature of PL inhibition by **11e**. Molecular docking study of the synthesized analogues was in accordance to the *in vitro* results and validated the pharmacophoric design. MD simulation of **11e**, resulted in a stable binding conformation of **11e** (RMSD $\leq$ 3 Å). To conclude, the present study identified diaryl

substituted pyrazolyl thiazolidinediones as a novel class of potent PL inhibitors. Further studies would pave the way for the analogues as potential anti-obesity agents.

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**A. Supplementary Data**

All experimental procedures for synthesis, full characterization of compounds and pancreatic lipase inhibition assay protocols.

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**Highlights**

- A series of novel diaryl substituted pyrazolyl thiazolidinediones were synthesized
- Pancreatic lipase inhibition assay was performed using two methods
- Compound **11e** exhibited potent and reversible competitive inhibition ($IC_{50}$ = 4.81 µM)
- Molecular dynamics of **11e** indicated its stable binding conformation (RMSD ≈ 3 Å)