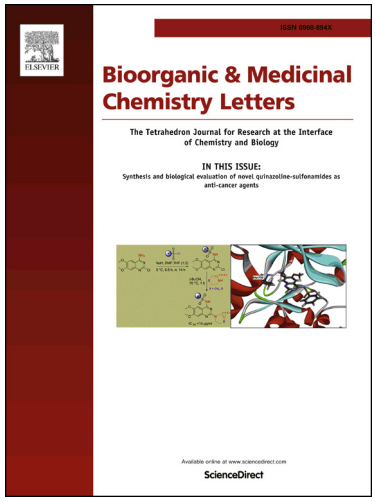


Identification of Low Micromolar Dual Inhibitors for Aldose Reductase (ALR2) and Poly (ADP-ribose) Polymerase (PARP-1) using Structure Based Design Approach

Navriti Chadha, Om Silakari

PII: S0960-894X(17)30412-2
DOI: http://dx.doi.org/10.1016/j.bmcl.2017.04.038
Reference: BMCL 24891

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 9 December 2016
Revised Date: 10 March 2017
Accepted Date: 12 April 2017

Please cite this article as: Chadha, N., Silakari, O., Identification of Low Micromolar Dual Inhibitors for Aldose Reductase (ALR2) and Poly (ADP-ribose) Polymerase (PARP-1) using Structure Based Design Approach, *Bioorganic & Medicinal Chemistry Letters* (2017), doi: http://dx.doi.org/10.1016/j.bmcl.2017.04.038

Graphical Abstract

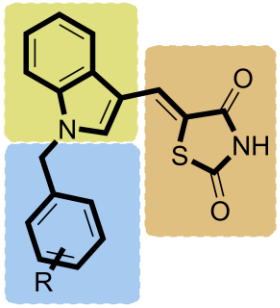
Identification of Low Micromolar Dual Inhibitors for Aldose Reductase (ALR2) and Poly (ADP-ribose) Polymerase (PARP-1) using Structure Based Design Approach

Navriti Chadha, Om Silakari*

Leave this area blank for abstract info.

Indole nucleus:
Interact with hydrophobic residues of ALR2 and PARP-1

Benzyl group:
Interact with large hydrophobic pocket of ALR2
Interact with hydrophobic groove of PARP-1



Thiazolidine-2,,4-dione:
Interact with Tyr48, His110 and Trp111 of ALR2
Interact with Gly202 and Ser243 of PARP-1

Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

Identification of Low Micromolar Dual Inhibitors for Aldose Reductase (ALR2) and Poly (ADP-ribose) Polymerase (PARP-1) using Structure Based Design Approach

Navriti Chadha[a] and Om Silakari[a*]

[a]*Molecular Modeling Lab (MML), Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala, Punjab, 147002, India.*

ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

Keywords:
Molecular docking
Molecular dynamics simulation
Aldose reductase
Poly (ADP-ribose) polymerase
Structure activity relationship

ABSTRACT

Clinical studies have revealed that diabetic retinopathy is a multifactorial disorder. Moreover, studies also suggest that ALR2 and PARP-1 co-occur in retinal cells, making them appropriate targets for the treatment of diabetic retinopathy. To find the dual inhibitors of ALR2 and PARP-1, the structure based design was carried out in parallel for both the target proteins. A series of novel thiazolidine-2,4-dione (TZD) derivatives were therefore rationally designed, synthesized and their *in-vitro* inhibitory activities against ALR2 and PARP-1 were evaluated. The experimental results showed that compounds 5b and 5f, with 2-chloro and 4-fluoro substitutions, showed biochemical activities in micromolar and submicromolar range (IC_{50} 1.34 – 5.03 μM) against both the targeted enzymes. The structure-activity relationship elucidated for these novel inhibitors against both the enzymes provide new insight into the binding mode of the inhibitors to the active sites of enzymes. The positive results of the biochemical assay suggest that these compounds may be further optimized and utilized for the treatment of diabetic retinopathy.

* Corresponding author; Tel.: +91-9501542696; Fax: +91-1752283075; e-mail: omsilakari@gmail.com

From 1983 to 1993, Diabetes Control and Complications Trials (DCCT) were conducted that established the role of hyperglycemia in the pathogenesis of chronic diabetic complications [1]. Hyperglycemia is reported to show its complications *via* various mechanisms, including increased aldose reductase activity, non-enzymatic glycation and glycoxidation, activation of protein kinase C (PKC) and oxidative nitrosative stress. Moreover, reactive oxidative and nitrogen species induce activation of mitogen-activated protein kinases (MAPKs), poly (ADP-ribose) polymerase (PARP) and other downstream targets [2]. The complex etiopathology of diabetic complications and unifying mechanism discussed by Brownlee *et al* exhibit that the use of multi-targeted agents with multiple complementary biochemical activities would be a promising therapeutic option for the intervention of the disease over single targeted drugs [2,3]. Moreover, the encouraging results provided by a clinical candidate 'benfotiamine' (Figure 1) shows that it blocks three pathways, *i.e.* hexosamine pathway, AGEs pathway and protein kinase C pathway [4].

Diabetic retinopathy is a common reason of vision loss characterized by retinal capillary cell loss, capillary basement membrane thickening, increased vascular permeability and increased leukocyte adhesion to endothelial cells. The selective destruction of retinal pericytes has been linked to accumulation of sorbitol which results in osmotic stress due to excessive hydration, gain of Na^+ and loss of K^+ ions [5, 6]. In addition, literature reports highlight that increased aldose reductase activity is responsible for enhancing oxidative stress, up-regulates retinal vascular endothelial growth factor (VEGF) and activation of PARP in diabetic retinal cells which may lead to cataract formation and diabetic retinopathy [7-10]. Moreover, the two enzymes: ALR2 and PARP-1 were found to co-express in the retina cells [5,11,12]. The complexity of the disease as well as the above reports suggest that dual inhibition of both the enzymes would provide an efficient strategy to ameliorate the pathology of diabetic retinopathy.

Aldose reductase (ALR2) is a cytosolic NADPH-dependent oxidoreductase acting as first and rate controlling enzyme of polyol pathway [13]. Physiologically, it catalyzes the reduction of various aldehydes and carbonyls, primarily glucose to sorbitol. In diabetes, the excess intracellular sorbitol produced by the over-activation of ALR2 leads to osmotic damage to cells that eventually leads to diabetic complications [14]. Numerous ALR2 inhibitors have been developed to prevent retinal and neuronal damage, including tolrestat, epalrestat, fidarestat and ranirestat, etc (Figure 1). Out of these, epalrestat has been approved in Japan while tolrestat was withdrawn from market owing to hepatotoxicity. Fidarestat and ranirestat are under clinical evaluation [15]. Dual inhibitors of ALR2 and antioxidants/ protein tyrosine phosphatase (PTP1B) have also been reported in literature [16,17].

Poly (ADP-ribose) polymerase (PARP-1) is a nuclear enzyme that regulates DNA repair, cellular division, differentiation, DNA replication, transformation, gene expression and amplification, mitochondrial function, and cell death [18]. The overexpression of PARP in the retina of diabetic rats has been reported to occur due to DNA damage induced by cell death [19]. Though none of the inhibitor has been reported with activity in diabetic complications, olaparib is one PARP inhibitor, which is in reach the market implicated in advanced ovarian cancer. Others are under clinical trials, including veliparib and rucaparib (Figure 1) [20]. Dual inhibitors of PARP-1 and dihydroorotate dehydrogenase (DHODH) have been reported in literature with benzimidazole nucleus [21].

Based on the above hypothesis, the present study was undertaken to design and evaluate novel dual inhibitors for ALR2 and PARP-1 using structure based design approach. The use of molecular docking has often been unfruitful due to the flaws in the protein-ligand binding free energy function to score putative inhibitors leading to poor correlation between computational and experimental measurements of biological potencies. To cope with this problem, molecular dynamics simulation was incorporated into the structure based design protocol. The designed inhibitors were further synthesized and biologically evaluated using *in-vitro* enzyme assay against ALR2 and PARP-1.

Prior to docking and molecular dynamics simulations, the crystal structures of ALR2 and PARP-1 proteins complexed with respective inhibitors were thoroughly studied for their interaction pattern within the active sites. The inspection of interaction pattern of inhibitors within ALR2 active site revealed that the hydrogen bond interaction with His110 and Tyr48 amino acid residues remain conserved (Table S1, Supplementary Material). The formation of π-π interactions with Trp111 is highly conserved and seems to play important role in binding. Hydrogen bond interaction with Leu300 and π-π interaction with Trp20 were also present in some of the crystal structures. Moreover, studies suggest that interaction with amino acid Leu300 is important as it is part of the selectivity pocket of the ALR2 binding site. In PARP-1 crystal complexes, it was observed that hydrogen bond interactions with Gly202 and Ser243 amino acid residues are conserved in the available crystal structures (Table S2, Supplementary Material). Additionally, π-π interactions with aromatic residues Tyr246 and His201, and π-cation interaction with Lys242 amino acid residue were retained in most of the crystal complexes.

From the information extracted from ALR2 active site, it was observed that the presence of an acidic moiety in inhibitor was required for interaction with Tyr48, His110 and Trp111 amino acid residues. For PARP-1 it was observed that an acceptor and donor feature is required for interaction with Gly202 and Ser243 amino acids. Moreover, the pharmacophores in the clinical trial molecules as well as marketed drugs against ALR2 suggest that acidic group (for interaction with basic amino acid His110) and large hydrophobic/aromatic group are required for interaction. In PARP inhibitors, paired acceptor donor is present in the form of amide linkage within the molecule. Therefore, it was thought that the presence of thiazolidine-2,4-dione (TZD) ring in the inhibitor would serve as acidic moiety for ALR2 and would also provide acceptor and donor paired feature for PARP-1. In addition, it has been reported that a hydrophobic group in inhibitor is required to occupy the specificity pocket of the ALR2 active site lined by Trp111, Phe122 and Leu300 amino acid residues [22]. For PARP-1 inhibitor, hydrophobic group is required for interaction with aromatic residues Tyr246 and His201. To sustain hydrophobic interaction between the designed molecules and active sites of both enzymes, substitution of benzyl along with hydrophobic substituents was considered to be beneficial. Keeping the above facts and synthetic feasibility in mind, a series of novel compounds (5a-5l) containing TZD ring and substituted benzyl groups linked via indole ring were designed. These designed molecules were duly synthesized and optimized to obtain potent dual ALR2 and PARP-1 inhibitors (Figure 2).

The designed inhibitors were subsequently subjected to docking analysis in ALR2 (PDB ID: 1US0) and PARP-1 (PDB ID: 2RD6) proteins. As depicted in Figure 3A, the docked pose of designed inhibitor in ALR2 active site revealed that the carbonyl group of the TZD moiety formed hydrogen bonding interaction with Tyr48 and His110, while the indole ring forms π-

π interaction with Phe122 and Trp111 amino acid residues. The substituted benzyl ring is accommodated within the hydrophobic pocket of the active site of ALR2. It was thus observed that the designed inhibitor showed interactions with the essential amino acids His110 and Trp111 of ALR2 active site that were discussed above. The docking analysis of compound 5b within PARP-1 protein showed hydrogen bonding interaction of carbonyl group of TZD with essential amino acids Gly202 and Ser243, π-π stacking interaction between the substituted benzyl and Tyr246 amino acid residue (Figure 3B). Similar interaction pattern was observed for the other compounds in the series. The docking interaction observed within both proteins showed that the compound were able to form favorable interactions with active sites of both ALR2 and PARP-1 proteins. The docking interaction energies obtained for the designed candidates docked within the active site of both the proteins showed good scores and the poses were further optimized using Prime MM-GBSA method. The scores obtained from both the methodologies, *i.e.* CDOCKER interaction energies as well as MM-GBSA binding energies are mentioned in the Table 1.

The docking results were further validated for the presence and strength of these interactions by subjecting the docked complexes to molecular dynamics simulations using Desmond software for a period of 10ns for each complex. The RMSD values of the protein-inhibitor complexes with and PARP-1 proteins showed a value ranging from 1.0 to 2.5 Å indicating the complexes to be stabilized during the simulation process (Figure S1 and S2, Supplementary material). The RMSD *vs* time step plots of simulation of 5b-ALR2 and 5b-PARP-1 complexes are depicted in Figure 4 and Figure 5, respectively. The simulation interaction diagram (SID) obtained for 5b-ALR2 complex displayed in Figure 6A showed that TZD moiety forms hydrogen bonding interaction with the basic amino acid His110 in 43% of the conformations obtained during the 10ns simulation process while the benzyl group forms π-π interaction with amino acid Trp20 in 43% of the total conformations. The SID obtained for 5b-PARP-1 complex showed that NH of TZD forms hydrogen bonding interaction with Ser243 amino acid which remains conserved in 94% of the total conformations while one of the carbonyl group forms hydrogen bonding interaction with Gly202 in 98% of the total conformations (Figure 6B). As the complexes obtained from simulation studies showed good interaction with both the proteins, the compounds were selected for synthesis. These molecules were duly synthesized by substituting various hydrophobic groups onto the benzyl ring of the skeleton structure (5). To estimate the 'drug-like' properties of the designed molecules, Lipinski filter was applied. All the calculated properties were within the limit of Lipinski Rule of Five, i.e. molecular weight ≤ 500, partition coefficient AlogP ≤ 5, hydrogen bond donor ≤ 5 and hydrogen bond acceptor ≤ 10. The values obtained for the designed molecules are mentioned in Table 1.

The synthetic route followed to obtain final compounds has been mentioned in Scheme 1, and their substituents are listed in Table 2. The structures of the synthesized compounds were characterized by infrared (IR), ^{1}H and ^{13}C NMR and mass spectroscopy. All the final compounds were obtained in high yields and were purified by column chromatography. The spectral data of the compounds has been listed in Supplementary material.

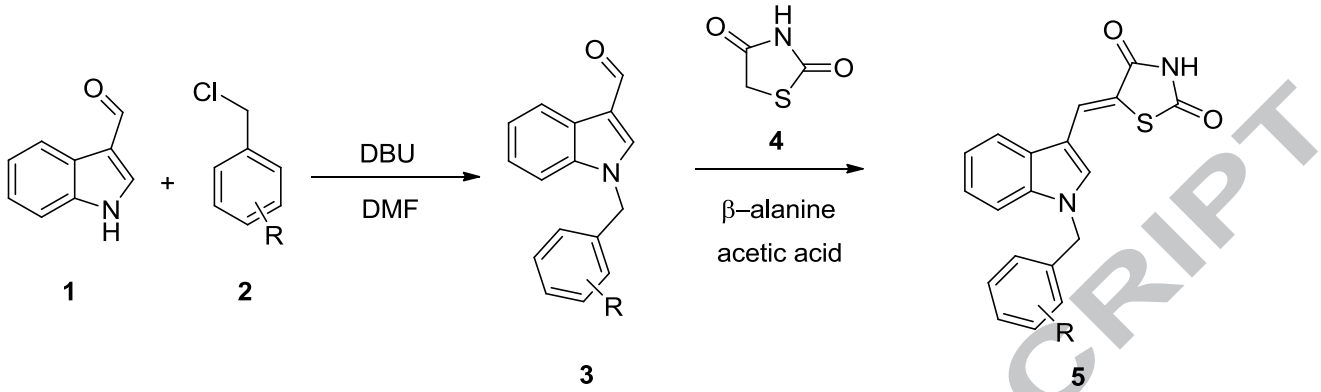
To evaluate the inhibitory activities of the synthesized compounds, IC_{50} values against ALR2 and PARP-1 were calculated using colorimetric and ELISA based enzymatic assay. As listed in Table 2, the compounds showed micro-molar inhibitory activities against both the enzymes. The structure activity relationship developed at R position of the skeleton structure 5 showed that substitution of small hydrophobic group such as fluoro at 4th position (5f) yields compound with low micromolar activity against ALR2 enzyme (IC_{50} = 1.70 ± 0.39 μM). The effect of chloro substituent on the activity of compound is position-dependent, *i.e.* substitution at 2nd position (5b, IC_{50} = 4.72 ± 1.72 μM) has better activity while substitution at 3rd and 4th position (5c and 5d, respectively) lower the activities by 3-5 folds. The dichloro substitution on the benzyl ring (5e) diminished ALR2 inhibitory activity (IC_{50} = 24.41 ± 1.15 μM). Further, it was observed that reduction in ALR2 inhibitory activity depends on the size of alkyl group substituent. The 4-methyl (5g), 4-ethyl (5l), 3-trifluromethyl (5h), 4-isopropyl (5i) and 4-*tert*-butyl (5k) substituents decreased the inhibitory activities against ALR2 enzyme as IC_{50} values were found to be 11.49 ± 1.58, 13.86 ± 1.8, 22.85 ± 2.08, 39.97 ± 5.19 and 48.50 ± 3.94 μM, respectively. This decrease of activity may be owed to steric clashes within the hydrophobic pocket as large groups cannot be accommodated in this pocket. The fluoro group substituent was found to be optimal for the ALR2 inhibitory activity.

On the contrary, the study of inhibitory activities against PARP-1 enzyme showed that substitution of large hydrophobic group yielded compounds with better inhibitory activities. The compound with 4-isopropyl (5i) and 4-*tert*-butyl (5k) substituents showed low micromolar activity (IC_{50} = 0.74 ± 0.25 and 0.82 ± 0.11 μM), while 2,4-dichloro (5e), 4-methyl (5g), 4-ethyl (5l) 4-fluoro (5f), 3-trifluromethyl (5h), 3-chloro (5c) substituents showed PARP-1 inhibitory activity ranging from 1.34 to 13.95 μM. However, removal of hydrophobic group (5a and 5j) was found to be detrimental to the activity (IC_{50} > 100 μM).

These results signify that the selection of optimum hydrophobic substituent is required for the dual inhibitory activity against ALR2 and PARP-1 enzymes. Thus, the compounds with 2-chloro and 4-fluoro substitution can be considered to be good dual inhibitors with low micromolar biochemical potency.

By means of structure based design using molecular docking and molecular dynamics simulations, a total of twelve common inhibitors for ALR2 and PARP-1 were designed with biochemical potencies ranging from low micromolar to submicromolar levels. The designed compounds were duly synthesized, characterized and their inhibitory activities against ALR2 and PARP-1 were examined. The enzymatic results suggest that substituents on benzyl ring significantly influence the inhibitory activity against both the enzymes. With 4-fluoro and 2-chloro substitutions at R position, the corresponding compounds exhibited better ALR2 and PARP-1 inhibitory activities, with IC_{50} values of 1.34 – 5.03 μM. The substitution of bigger groups (4-ethyl, 3-trifluromethyl, 4-isopropyl, 2,4-dichloro and 4-*tert*-butyl) at R position of benzyl ring significantly lowered ALR2 inhibitory activities. On the other hand, PARP-1 inhibitory activities were significantly improved with these substitutions. The possible reason for the same has been analyzed via the use of molecular docking and MD simulation strategies. The results suggest that this may be due to the difference in the hydrophobic pockets of the two enzymes and optimization of the R group may yield potent dual inhibitors. Among the obtained hits, compound 5b exhibited highest activity against PARP-1 enzyme (IC_{50} = 1.34 μM) and low micromolar ALR2 inhibitory activity (IC_{50} = 4.72 μM). Another compound 5f showed highest inhibitory activity against ALR2 (IC_{50} = 1.70 μM) and good activity against PARP-1 (IC_{50} = 5.03 μM). The

positive results provide new insight into the binding modes of the inhibitors within ALR2 and PARP-1 active site. On the basis of the present study it can be concluded that close monitoring of N-benzyl group on indolylated TZD may lead to optimum substitution that would be accommodated in the hydrophobic pocket of both enzymes and would provide dual inhibitors of therapeutic significance.



Scheme 1. General synthetic route for compounds 5a-5l. DBU, 1,8-Diazabicyclo[5.4.0]undec-7-ene; DMF, N,N-dimethylformamide.

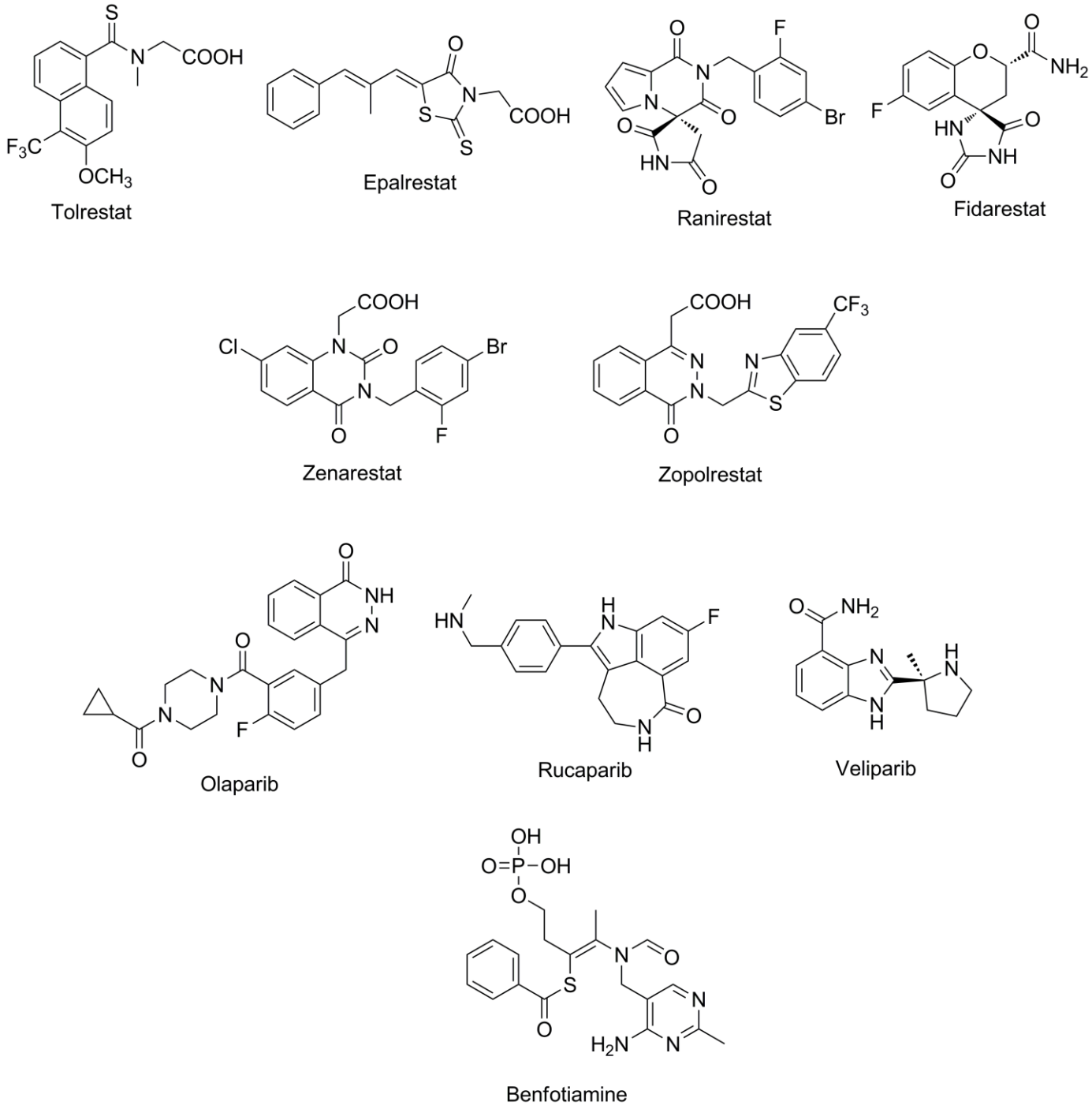


Figure 1. Some important ALR2 and PARP-1 inhibitors under clinical trials.

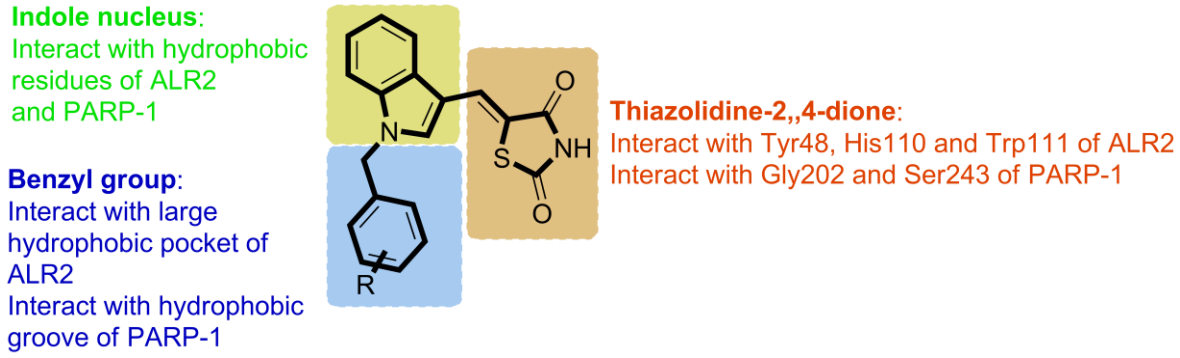


Figure 2. Rationale for designing synthesized molecules.

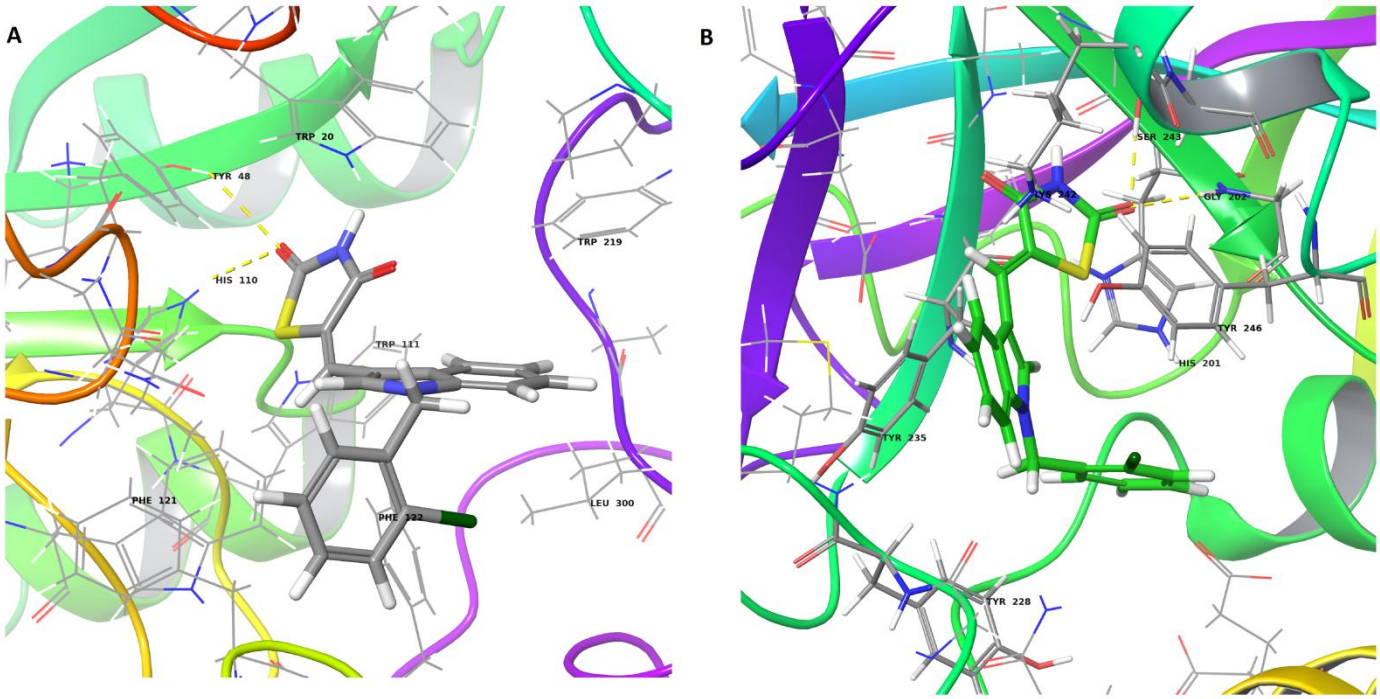


Figure 3. Docking interactions of 5b within (A) ALR2 active site (B) PARP-1 active site. Dotted lines (yellow color) represent the hydrogen bonding interaction. *Colored figure available online.*

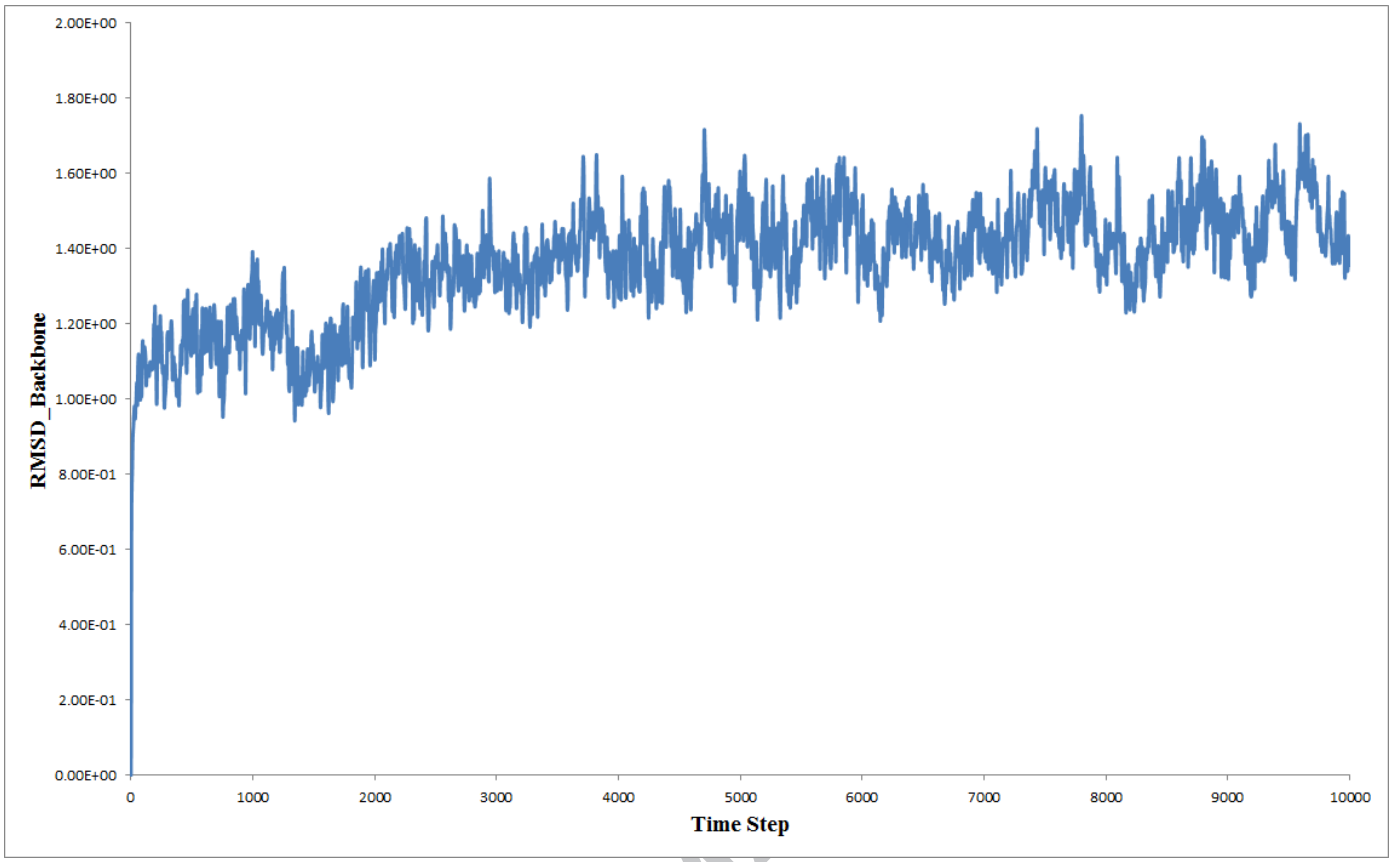


Figure 4. The RMSD (Å) profile of the backbone atoms of molecule 5b in complex with ALR2 protein for checking the overall stability of the system during 10ns simulations.

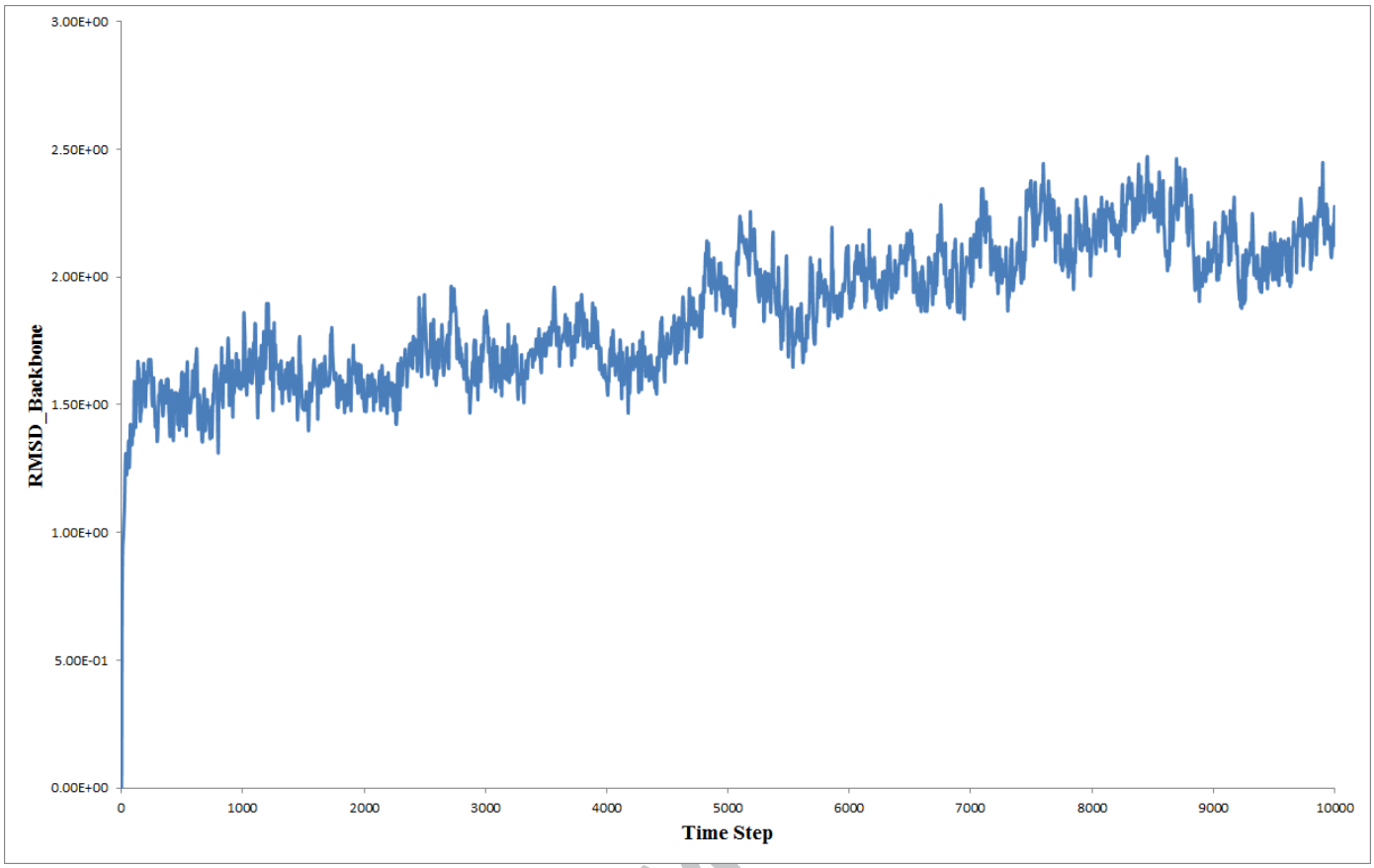


Figure 5. The RMSD (Å) profile of the backbone atoms of molecule 5b in complex with PARP-1 protein for checking the overall stability of the system during 10ns simulations.

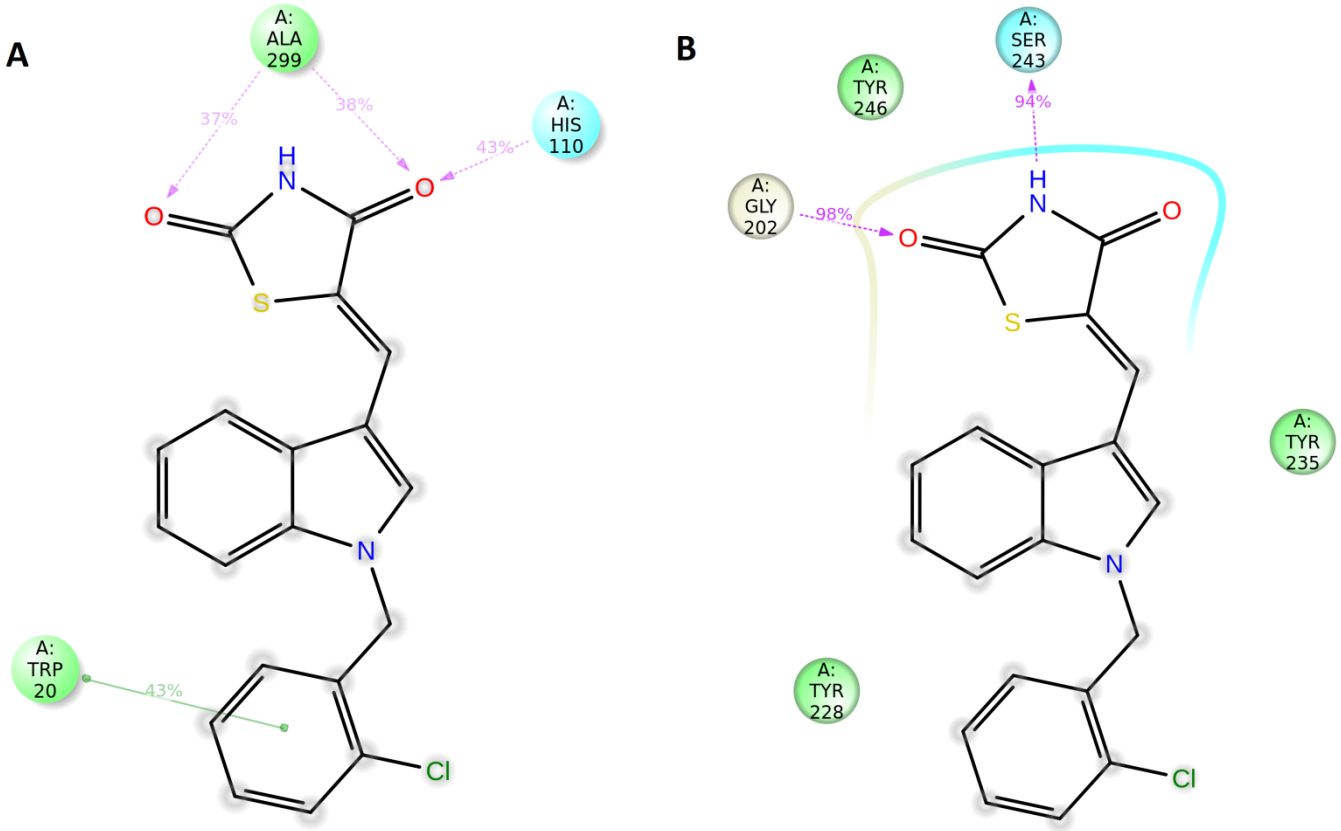


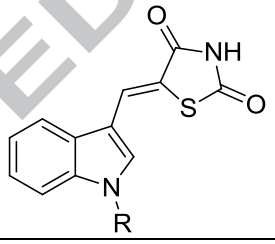
Figure 6. Simulation interaction diagram obtained for molecule 5b in complex with (A) ALR2 protein and (B) PARP-1 protein.

Table 1. Docking interaction scores, MM-GBSA scores and parameters obtained from Lipinski Rule of Five within the active site of ALR2 and PARP-1 enzymes.

Compound	CDOCKER Interaction Energy (ALR2)	CDOCKER Interaction Energy (PARP-1)	MM-GBSA score[a] (ALR2)	MM-GBSA score[a] (PARP-1)	Molecular weight	AlogP	Hydrogen bond donor	Hydrogen bond acceptor
5a	-28.69	-39.29	-46.95	-67.48	334.39	4.02	1	3
5b	-29.09	-40.12	-56.08	-77.95	368.83	4.69	1	3
5c	-30.78	-43.67	-52.44	-69.14	368.83	4.69	1	3
5d	-36.76	-43.54	-58.88	-80.62	368.83	4.69	1	3
5e	-34.41	-46.20	-64.14	-81.20	403.2	5.35	1	3
5f	-35.41	-41.90	-56.59	-66.48	352.38	4.23	1	3
5g	-36.58	-43.77	-58.79	-71.64	348.42	4.51	1	3
5h	-36.78	-44.72	-59.23	-72.07	402.39	4.97	1	3
5i	-30.59	-47.04	-63.18	-77.48	376.47	5.22	1	3
5j	-33.08	-28.59	-45.23	-43.85	244.27	2.23	2	3
5k	-37.89	-50.21	-61.72	-87.62	390.49	5.42	1	3
5l	-41.78	-45.62	-65.17	-79.86	362.44	4.96	1	3

[a]MM-GBSA score gives the binding energy of the inhibitor to the protein expressed as kcal/mol.

Table 2. Inhibitory activities of the compounds 5a-5l against ALR2 and PARP-1 enzymes.



Compound	R	IC_{50} ALR2 (µM)	IC_{50} PARP-1 (µM)
5a	benzyl	6.57 ± 0.89	>100
5b	2-chlorobenzyl	4.72 ± 1.72	1.34 ± 1.67
5c	3-chlorobenzyl	22.96 ± 6.74	4.81 ± 2.31
5d	4-chlorobenzyl	15.39 ± 3.38	>100
5e	2,4-dichlorobenzyl	24.41 ± 1.15	7.81 ± 1.26
5f	4-fluorobenzyl	1.70 ± 0.39	5.03 ± 2.19
5g	4-methylbenzyl	11.49 ± 1.58	13.95 ± 6.59
5h	3-(trifluoromethyl)benzyl	22.85 ± 2.08	3.07 ± 2.62
5i	4-isopropylbenzyl	39.97 ±5.19	0.74 ± 0.25
5j	H	16.45 ± 0.74	>100
5k	4-(*tert*-butyl)benzyl	48.50 ± 3.94	0.82 ± 0.11
5l	4-ethylbenzyl	13.86 ± 1.8	1.56 ± 0.54
Epalrestat		0.09 ± 0.03	-
3-Aminobenzamide		-	4.78

IC_{50} represents the dose of compound in mole required to produce 50% inhibition of aldose reductase and poly (ADP-ribose)polymerase enzyme. IC_{50} values expressed as mean±SD, n=2.

Acknowledgments

Authors thank Council of Scientific and Industrial Research (CSIR), New Delhi for providing funds for carrying out the research work (Grant No. 02(0111)/12/EMR-II); Department of Science and Technology (DST), New Delhi for providing INSPIRE fellowship (Grant No. IF150415). Authors also extend thanks to Dr. Amteshwar Singh Jaggi for providing support while performing ELISA based enzyme activity; Sophisticated Analytical Instrumentation Facility (SAIF) and Central

Instruments Laboratory (CIL), Panjab University, Chandigarh for performing spectroscopic analysis; and Apsara Innovations for extending technical support for performing in-silico studies.

References and notes

1. Association AD. Diabetes Control and Complications Trial (DCCT): Results of Feasibility Study. Diabetes Care. 1987;10:1-19.

2. Mabley JG, Soriano FG. Role of nitrosative stress and poly (ADP-ribose) polymerase activation in diabetic vascular dysfunction. Curr Vasc Pharmacol. 2005;3:247-52.

3. Brownlee M. The pathobiology of diabetic complications a unifying mechanism. Diabetes. 2005;54:1615-1625.

4. Hammes HP, Du X, Edelstein D, Taguchi T, Matsumura T, Ju Q, Lin J, Bierhaus A, Nawroth P, Hannak D. Benfotiamine blocks three major pathways of hyperglycemic damage and prevents experimental diabetic retinopathy. Nat Med. 2003;9:294-299.

5. Akagi Y, Kador PF, Kuwabara T, Kinoshita JH. Aldose reductase localization in human retinal mural cells. Invest Opthalmol Visual Sci., 1983; 24: 1516.

6. Lorenzi M. The polyol pathway as a mechanism for diabetic retinopathy: attractive, elusive and resilient. Exp Diabetes Res. 2007; 2007: 61038.

7.Obrosova IG, Pacher P, Szabó C, Zsengeller Z, Hirooka H, Stevens MJ, Yorek MA. Aldose reductase inhibition counteracts oxidative-nitrosative stress and poly (ADP-ribose) polymerase activation in tissue sites for diabetes complications. Diabetes. 2005;54:234-242.

8. Obrosova IG, Minchenko AG, Vasupuram R, White L, Abatan OI, Kumagai AK, Frank RN, Stevens MJ. Aldose reductase inhibitor fidarestat prevents retinal oxidative stress and vascular endothelial growth factor overexpression in streptozotocin-diabetic rats. Diabetes. 2003;52:864-871.

9. Harada C, Okumura A, Namekata K, Nakamura K, Mitamura Y, Ohguro H, Harada T. Role of monocyte chemotactic protein-1 and nuclear factor kappa B in the pathogenesis of proliferative diabetic retinopathy. Diabetes Res Clin Pract. 2006;74:249-256.

10. Sangshetti JN, Chouthe RS, Sakle NS, Gonjari I, Shinde BD. Aldose reductase: a multi-disease target. Curr Enz Inhib. 2014;10:2-12.

11. Mohammad G, Siddiquei MM, Abu El-Asrar AM. Poly (ADP-ribose) polymerase mediates diabetes-induced retinal neuropathy. Mediators Inflamm. 2013;2013:10.

12. Weise J, Isenmann S, Bähr M. Increased expression and activation of poly (ADP-ribose) polymerase (PARP) contribute to retinal ganglion cell death following rat optic nerve transection. Cell Death Differ. 2001;8:801.

13. Dvornik D, Porte D, Ward JD. *Aldose reductase inhibition: an approach to the prevention of diabetic complications*, McGraw-Hill; New York;1987.

14. Kinoshita JH, Nishimura C. The involvement of aldose reductase in diabetic complications. Diabetes/metabolism Rev. 1988;4:323-337.

15. Zhu C. *Aldose reductase inhibitors as potential therapeutic drugs of diabetic complications.* INTECH Open Access Publisher;2013.

16. Zhu S, Hao X, Zhang S, Qin X, Chen X, Zhu C. Synthesis of benzothiadiazine derivatives exhibiting dual activity as aldose reductase inhibitors and antioxidant agents. Bioorg Med Chem Lett. 2016;26:2880-2885.

17. Vyas B, Silakari O, Kaur M, Singh B. Integrated pharmacophore and docking-based designing of dual inhibitors of aldose reductase (ALR2) and protein tyrosine phosphatase 1B (PTP1B) as novel therapeutics for insulin-resistant diabetes and its complications. J. Chemometrics. 2015;29:109-125.

18. Kim MY, Zhang T, Kraus WL. Poly (ADP-ribosyl) ation by PARP-1:PAR-laying'NAD+ into a nuclear signal. Genes Dev. 2005;19:1951-1967.

19. Guzyk MM, Tykhomyrov AA, Nedzvetsky VS, Prischepa IV, Grinenko TV, Yanitska LV, Kuchmerovska TM. Poly (ADP-Ribose) Polymerase-1 (PARP-1) Inhibitors Reduce Reactive Gliosis and Improve Angiostatin Levels in Retina of Diabetic Rats. Neurochem Res. 2016;1-12.

20. Rouleau M, Patel A, Hendzel MJ, Kaufmann SH, Poirier GG. PARP inhibition: PARP1 and beyond. Nat Rev Cancer. 2010;10: 293-301.

21. Abdullah I, Chee CF, Lee YK, Thunuguntla SSR, Reddy KS, Nellore K, Antony T, Verma J, Mun KW, Othman S. Benzimidazole derivatives as potential dual inhibitors for PARP-1 and DHODH. Bioorg Med Chem. 2015;23:4669-4680.

22. Urzhumtsev A, Tete-Favier F, Mitschler A, Barbanton J, Barth P, Urzhumtseva L, Biellmann J, Podjarny A, Moras D. A 'specificity'pocket inferred from the crystal structures of the complexes of aldose reductase with the pharmaceutically important inhibitors tolrestat and sorbinil. Structure. 1997;5:601-612.

Supplementary Material

Supplementary data associated with this article can be found, in the online version

Highlights

1. Designing of thiazolidine-2,4-dione based dual ALR2/PARP-1 inhibitors.
2. Molecular docking and molecular dynamics simulation with both enzymes.
3. Synthesis and characterization of designed compounds.
4. *In-vitro* assay against the targeted enzymes.