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Exploring synthetic and therapeutic prospects of new thiazoline derivatives as aldose reductase (ALR2) inhibitors†

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Inhibition of aldose reductase (ALR2) by using small heterocyclic compounds provides a viable approach for the development of new antidiabetic agents. With our ongoing interest towards aldose reductase (ALR2) inhibition, we have synthesized and screened a series of thiazoline derivatives (5a–k, 6a–f, 7a–1 & 8a–j) to find a lead as a potential new antidiabetic agent. The bioactivity results showed the thiazoline-based compound 7b having a benzyl substituent and nitrophenyl substituent-bearing compound 8e were identified as the most potent molecules with IC$_{50}$ values of 1.39 ± 2.21 μM and 1.52 ± 0.78 μM respectively compared with the reference sorbinil with an IC$_{50}$ value of 3.14 ± 0.02 μM. Compound 7b with only 23.4% inhibition for ALR1 showed excellent selectivity for the targeted ALR2 to act as a potential lead for the development of new therapeutic agents for diabetic complications.

1 Introduction

The incidence of Diabetes mellitus (DM) disease is increasing alarmingly and more than 400 million people are affected all over the world.[1] Diabetes complications affect about 25% of the elderly population over the age of 65, and this proportion is steadily growing.[2] The majority of the population affected with DM belongs to under-developed or developing regions of the world.[3–6] According to a recent study between COVID-19 and diabetes, the COVID-19 patients with diabetes have a two-fold higher risk of mortality and disease incidence than COVID-19

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patients without diabetes [00]. In case of progression of this disease severe diabetic complications result such as neuropathy, nephropathy, mood disorders, diabetic retinopathy. These complications are generally a result of hyperglycemia[7] which initiates the polyol pathway due to non-insulin dependent glucose uptake. This pathway primarily involves NADPH dependent reduction of glucose to sorbitol, the enzyme responsible for this reduction is aldose reductase (AR; ALR2; EC 1.1.1.21) belonging to aldo-keto reductase enzyme superfamily. The sorbitol in turn converts metabolically via another enzyme sorbitol dehydrogenase into fructose, resulting in increase in the glucose flux.[8] High glucose level in diabetes promotes the combination of glucose to ALR2 and metabolized about one third of the total glucose to sorbitol via the polyol pathway in tissues such as retina, lens, peripheral nerves and kidneys. As a result, the regulated polyol pathway accumulates the sorbitol in cells causing swelling of cell, osmotic imbalance and changes in permeability of membrane. Sorbitol does not penetrate the cellular membranes especially that of eye lens. Moreover, the drastic lessening of NAD$^+$ and NADPH alters the cellular redox potentials and weakens the enzymatic activities like that of glutathione reductase and nitric oxide synthase (NOS); worsening the intracellular oxidative stress level. Stress level is also increased via free radicals produced from a number of radical precursors like protein kinase C (PKC) isomer, advanced glycation end products (AGEs), poly-ADP-ribose polymerase (PARP) and mitogen-activated protein kinase (MAPK). High level of free radicals damages a number of tissues. Hence, all the oxidative stress reactions mediated by ALR2 along with the polyol pathway represent important pathogenesis of diabetic complications.[9]

From aldo-keto reductase (AKR), those reducing the aldehydes are called aldehyde reductases (ALR1, EC 1.1.1.2) while those involved in the reduction of ketones are termed as ketoreductases (also belonging to AKR family). Both enzymes have almost similar structure differing just in their active sites.[10] The one accurately capable to reduce the aldehyde functionality of glucose in polyol pathway is ALR1. This enzyme is also involved in metabolism of 3-deoxyglucosone and methyl glyoxal causing toxic glycation end products. In contrast, it also assists the reductive detoxification of reactive aldehydes. An example is the reduction of aldehyde phospholipids to regulate the pro-inflammatory response.[11]

There are a number of studies reported the aldose reductase inhibitors (ARIs).[12–17] Up to yet now, only one ARI drug; Epalrestat, ONO Pharmaceutical, Osaka, Japan has been marketed.[18,19] Though the polyol pathway inhibition is more challenging to reduce the complications of diabetes; some isolated natural products have been used as potent ARIs. Some synthesized compounds have same active functionalities as that of potent natural product and have been entered in to clinical trials (Fig. 1). It is of utmost importance to develop potent and selective ARIs (ALR1 and ALR2 share about 65% sequence homology), which can regulate the polyol pathway and combat secondary diabetic complications.[20,21] The present work focuses on the synthesis of a series of novel thiazoline based inhibitors and their evaluation as ARIs.

The compounds containing benzoxazinone, adamantyl, benzodioxane and indole nuclei have been synthesized and investigated for their diverse biological activities as many of these moieties are also the part of bioactive natural products.[22–33] Incorporation or conjugation of thiazoline moieties with another biologically important nucleus is expected to enhance their biological potential. In view of this and in search of novel bioactive molecules, the study was designed and aimed to prepare a number of various thiazolines possessing benzoxazinone, adamantyl, benzodioxane and indole moieties to evaluate their enzyme inhibition potential with an expectation that they may display more potent activity and thus result into the development of different compounds of medicinal interest.

2. Results and discussion

2.1 Chemistry of thiazolines derivatives 5a–k, 6a–f, 7a–i and 8a–j

In the current study, the thiazoline derivatives **5–8** were designed and prepared in variable yields (76–92%) by using four different types of carbonyl group bearing compounds **1** *i.e.* 6-acetyl-2H-benzo[b][1,4]oxazin-3(4H)-one, 1-acetyl adamantane, 1,4-benzodioxan-6-yl methyl ketone and indole-3-carboxaldehyde. The starting materials bearing carbonyl group were treated in equimolar quantities with N-substituted thiosemicarbazides **2** in methanol as solvent. The reaction was catalyzed by using glacial acetic acid as catalyst to get thiosemicarbazones **3** as intermediate.[34,35] Further, the thiosemicarbazone derivatives **3** were reacted with a range of 4-substituted 2-bromoacetophenones **4** in solvent ethanol along with sodium acetate. The resulting mixture was heated at reflux till the complete consumption of starting material, monitored by TLC analysis. The pure product was obtained *via* recrystallization from absolute ethanol (Scheme 1).

The structures of thiazoline derivatives (**5a–k, 6a–f, 7a–i** and **8a–j**) were confirmed by using different spectroscopic
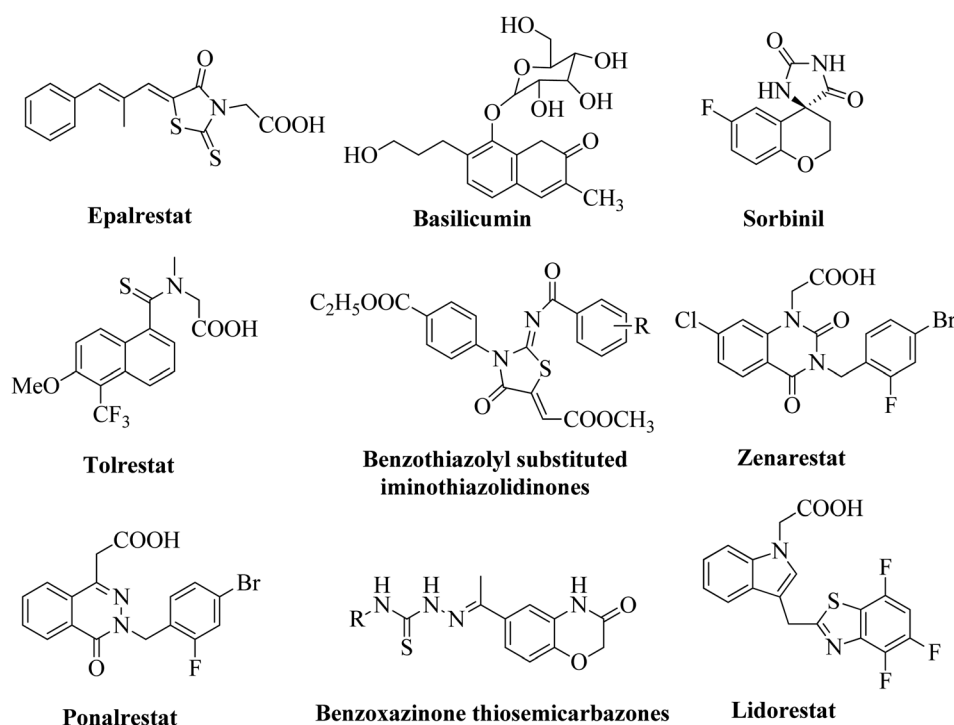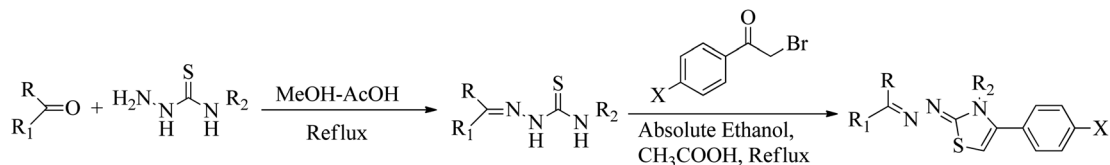

Epalrestat

Basilicumin

Sorbinil

Tolrestat

Benzothiazolyl substituted iminothiazolidinones

Zenarestat

Ponalrestat

Benzoxazinone thiosemicarbazones

Lidorestat

Fig. 1 Examples of some known ALR2 inhibitors.

Scheme 1 Preparation of thiazoline derivatives **5a–k**, **6a–f**, **7a–i** and **8a–j**.
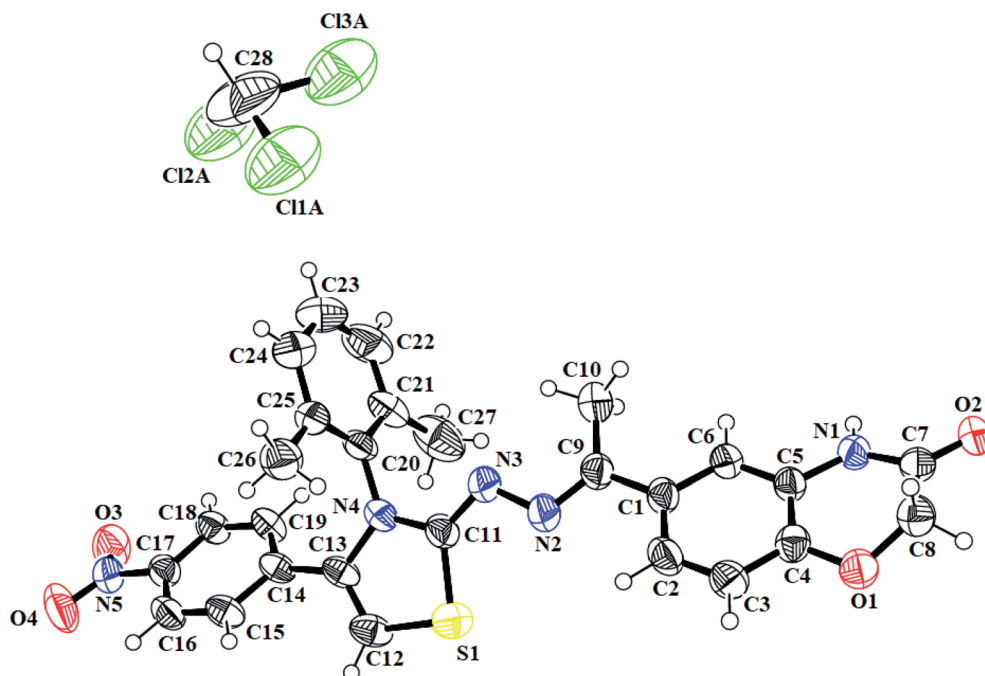

Fig. 2 The X-ray crystal structure of thiazoline derivative **5h**. *Note*: the ORTEP diagram of **5h** drawn at 50% probability level with H-atoms as small circles of arbitrary radii. The minor disordered parts of chloroform are not shown for clarity.

techniques that include IR spectra, NMR spectroscopy and microanalysis (CHN). The infrared spectra of a typical thiazolines from **5a–k** series showed a stretching band of NH group at 3184–3338 cm^{-1}, carbonyl group (C=O) of lactam moiety at 1663–1748 cm^{-1} and imine group C=N bands were appeared at 1578–1593 cm^{-1} regions consequently, the compounds in

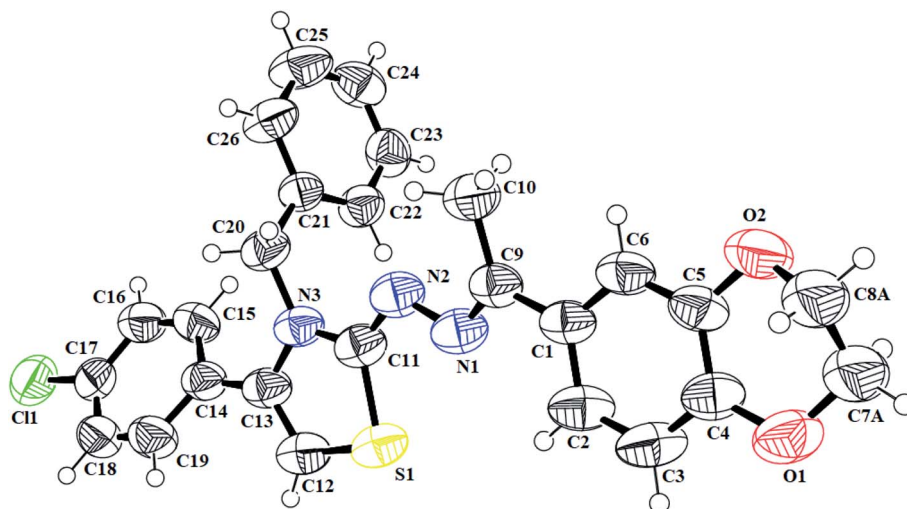**Fig. 3** The X-ray crystal structure of thiazoline derivative **7i**. *Note*: the ORTEP diagram of **7i** drawn at 50% probability level with H-atoms as small circles of arbitrary radii. The minor disordered part is not shown for clarity.
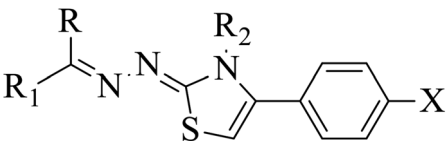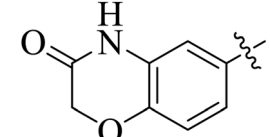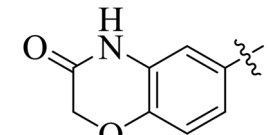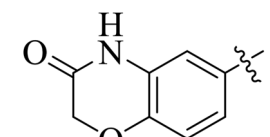
Table 1 Thiazoline derivatives **5a–k**, **6a–f**, **7a–i** and **8a–j**

Table 1 (*Contd.*)
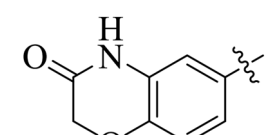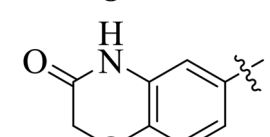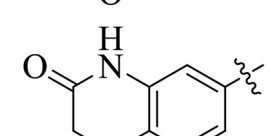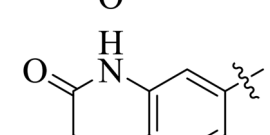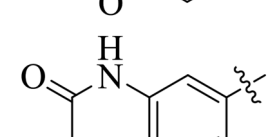
Compound	R	R_1	R_2	X
5a		CH_3	C_6H_5	Br
5b		CH_3	$3\text{-}OCH_3C_6H_4$	Br
5c		CH_3	$2,6\text{-}(CH_3)_2C_6H_3$	Br
5d		CH_3	$2\text{-}CH_3C_6H_4$	Br
5e		CH_3	C_6H_5	NO_2
5f		CH_3	$3\text{-}OCH_3C_6H_4$	NO_2
5g		CH_3	$4\text{-}FC_6H_4$	NO_2
5h		CH_3	$2,6\text{-}(CH_3)_2C_6H_3$	NO_2
5i		CH_3	C_6H_5	Cl
5j		CH_3	$3\text{-}OCH_3C_6H_4$	Cl
5k		CH_3	$4\text{-}FC_6H_4$	Cl
6a		CH_3	C_6H_5	Br
6b		CH_3	$C_{10}H_7$	Br
6c		CH_3	$2\text{-}CH_3C_6H_4$	Br
6d		CH_3	$2,6\text{-}(CH_3)_2C_6H_3$	Br
6e		CH_3	$C_6H_5CH_2$	Cl
6f		CH_3	$2,6\text{-}(CH_3)_2C_6H_3$	Cl
7a		CH_3	C_6H_5	Br
7b		CH_3	$C_6H_5CH_2$	Br
7c		CH_3	$2,6\text{-}(CH_3)_2C_6H_3$	Br
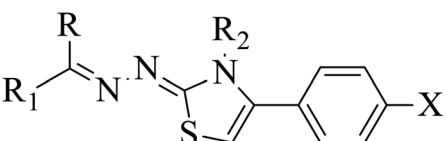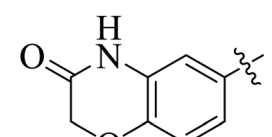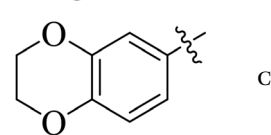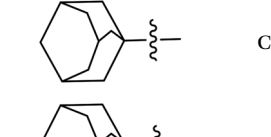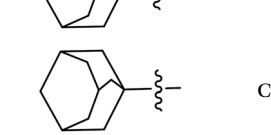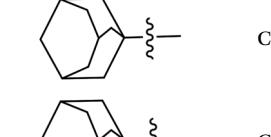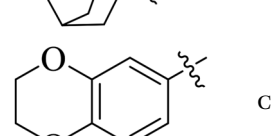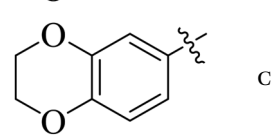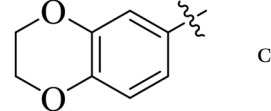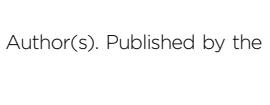
Table 1 (*Contd.*)

Compound	R	R_1	R_2	X
7d	2,3-dihydrobenzo[b][1,4]dioxine	CH_3	$4\text{-}FC_6H_4$	NO_2
7e	2,3-dihydrobenzo[b][1,4]dioxine	CH_3	$C_6H_5CH_2$	NO_2
7f	2,3-dihydrobenzo[b][1,4]dioxine	CH_3	$2,6\text{-}(CH_3)_2C_6H_3$	NO_2
7g	2,3-dihydrobenzo[b][1,4]dioxine	CH_3	C_6H_5	Cl
7h	2,3-dihydrobenzo[b][1,4]dioxine	CH_3	$4\text{-}FC_6H_4$	Cl
7i	2,3-dihydrobenzo[b][1,4]dioxine	CH_3	$C_6H_5CH_2$	Cl
8a	indole	H	C_6H_5	Br
8b	indole	H	C_6H_{11}	Br
8c	indole	H	$4\text{-}FC_6H_4$	NO_2

Table 1 (*Contd.*)

Compound	R	R_1	R_2	X
8d	indole	H	C_6H_5	NO_2
8e	indole	H	$C_6H_5CH_2$	NO_2
8f	indole	H	$3\text{-}OCH_3C_6H_4$	NO_2
8g	indole	H	C_6H_5	Cl
8h	indole	H	$C_6H_5CH_2$	Cl
8i	indole	H	$4\text{-}FC_6H_4$	Cl
8j	indole	H	$2,6\text{-}(CH_3)_2C_6H_3$	Cl

thiazoline series **6a–f** and **7a–i**, showed imine group (C=N) in the range of 1558–1617 cm^{-1}. Furthermore, the indole-based thiazolines **8a–j**, showed NH stretching band at 3125–3444 cm^{-1} while C=N bond in the range of 1603–1615 cm^{-1}. The proton ^{1}H-NMR spectra of different thiazoline series **5a–k** and **8a–j**, displayed broad singlets for lactam NH and indole NH
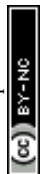
Table 2 *In vitro* Inhibitory activity of thiazoline derivatives against Aldehyde (ALR1) and Aldose (ALR2) reductase enzymes

Code	Structure	ALR2 IC$_{50}$(μM) ± SEM[a]/Percent inhibition	ALR1
5a		13.4%	22.6%
5b		27.4%	31.9%
5c		22.7%	12.4%
5d		19.5%	6.7%
5e		20.83%	31.4%
5f		3.13 ± 1.45	3.24 ± 2.72

Table 2 (*Contd.*)

		ALR2	ALR1
Code	Structure	IC$_{50}$(μM) $\pm$ SEM[a]/Percent inhibition	
5g		31.73%	24.7%
5h		18%	19.6%
5i		16.77%	31.3%
5j		5.16%	32.8%
5k		35.19%	22.6%
6a		4.40 $\pm$ 1.45	3.29 $\pm$ 1.47

Table 2 (Contd.)

Code	Structure	ALR2	ALR1
		$IC_{50}(\mu M) \pm SEM^{a}$/Percent inhibition	
6b		12.9 ± 0.39	4.93 ± 1.86
6c		10.19 ± 1.35	4.07 ± 2.35
6d		4.21 ± 2.35	11.6%
6e		2.18 ± 0.83	33.5%
6f		3.51 ± 2.31	19.7%
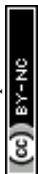
Table 2 (*Contd.*)

Code	Structure	ALR2	ALR1
		IC$_{50}$(µM) $\pm$ SEM^a/Percent inhibition	
7a		5.96 $\pm$ 1.05	23.7%
7b		1.39 $\pm$ 2.21	23.4%
7c		3.14 $\pm$ 1.87	33.4%
7d		11%	4.5%
7e		14%	23.6%
7f		23%	21.7%
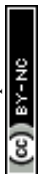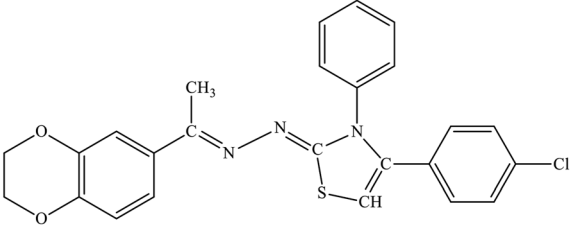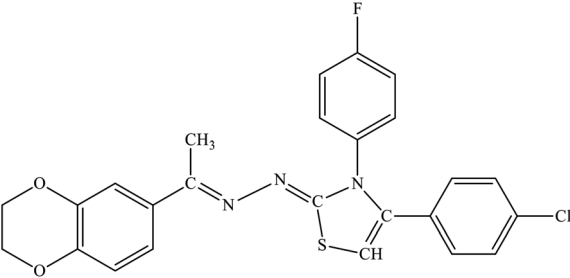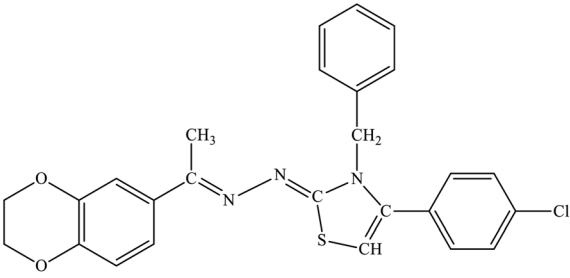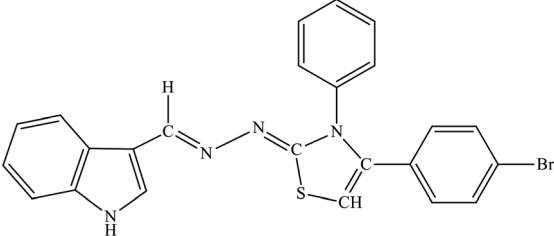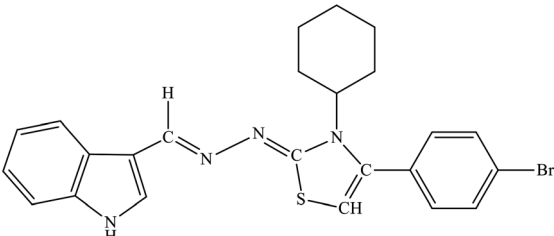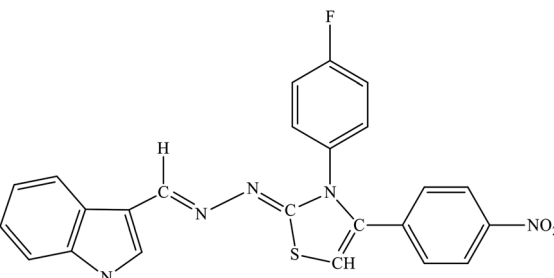
Table 2 (Contd.)

Code	Structure	ALR2	ALR1
		IC$_{50}$(μM) ± SEM^a/Percent inhibition	
7g		14.49 ± 1.49	3.14 ± 0.41
7h		9.63 ± 1.21	2.94 ± 1.73
7i		29.62 ±	2.20 ± 0.92
8a		13.4%	15.6%
8b		37.4%	29.4%
8c		6.74%	35.4%
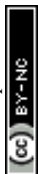
Table 2 (*Contd.*)

		ALR2	ALR1
Code	Structure	IC$_{50}$(μM) ± SEM^a/Percent inhibition	
8d		31%	18.6%
8e		1.52 ± 0.78	2.94 ± 1.34
8f		4.21 ± 1.63	12.4%
8g		5.16%	23.5%
8h		10.32%	33.4%
8i		23.22%	12.5%

Table 2 (*Contd.*)

Code	Structure	ALR2	ALR1
		$IC_{50}(\mu M) \pm SEM^a$/Percent inhibition	
8j		34.83%	27.8%
	Valproic acid[b]	—	57.4 ± 0.89
	Sorbinil[b]	3.14 ± 0.02	—

[a] Half maximal inhibitory concentration. [b] Standard inhibitor.

group in the range from δ_H 10.78–10.83 and δ_H 11.51–10.55 ppm, respectively. The singlet of thiazoline –CH– appeared in the range of δ_H 5.79–7.01 ppm. The other of different protons in all the series of thiazolines were in well agreement to confirm the structures of desired compounds. Moreover, the crystal structure of the compounds **5h** and **7i** further confirm the structure of thiazoline derivatives (Fig. 2, 3) (Table 1).

2.2 Biological activity

The synthetic thiazoline derivatives (**5a–k, 6a–f, 7a–1 & 8a–j**) were tested against aldehyde reductase enzyme (ALR1), and their anti-diabetic potential by evaluating inhibitory activity against aldose reductase (ALR2). Results indicated that out of thirty six compounds tested, eight of them, **5f, 6a, 6b, 6c, 7g, 7h, 7i**, and **8e** were found active inhibitors of ALR2 and ALR1

(6d)
% Inhibition = 11.6% for ALR1
IC_{50} = 4.21 ± 2.35 μM for ALR2

(6e)
% Inhibition = 33.5% for ALR1
IC_{50} = 2.18 ± 0.83 μM for ALR2

(6f)
% Inhibition = 19.7% for ALR1
IC_{50} = 3.51 ± 2.31 μM for ALR2

(7a)
% Inhibition = 23.7% for ALR1
IC_{50} = 5.96 ± 1.05 μM for ALR2

(7b)
% Inhibition = 23.4% for ALR1
IC_{50} = 1.39 ± 2.21 μM for ALR2

(8f)
% Inhibition = 12.4% for ALR1
IC_{50} = 4.21 ± 1.63 μM for ALR2
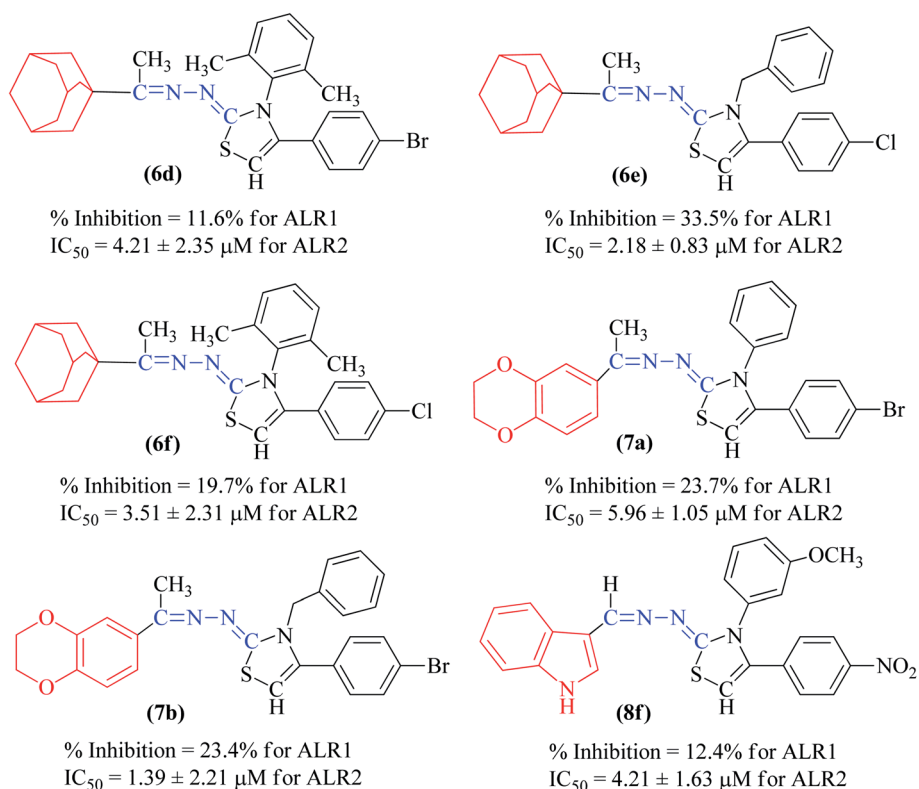
Fig. 4 Selective ALR2 inhibitory activity of thiazoline derivatives (**6d, 6e, 6f, 7a, 7b** and **8f**).

(6a)

$IC_{50} = 3.29 \pm 1.47 \ \mu M$ for ALR1
$IC_{50} = 4.40 \pm 1.45 \ \mu M$ for ALR2

(6b)

$IC_{50} = 4.93 \pm 1.86 \ \mu M$ for ALR1
$IC_{50} = 12.9 \pm 0.39 \ \mu M$ for ALR2

(6c)

$IC_{50} = 4.07 \pm 2.35 \ \mu M$ for ALR1
$IC_{50} = 10.19 \pm 1.35 \ \mu M$ for ALR2
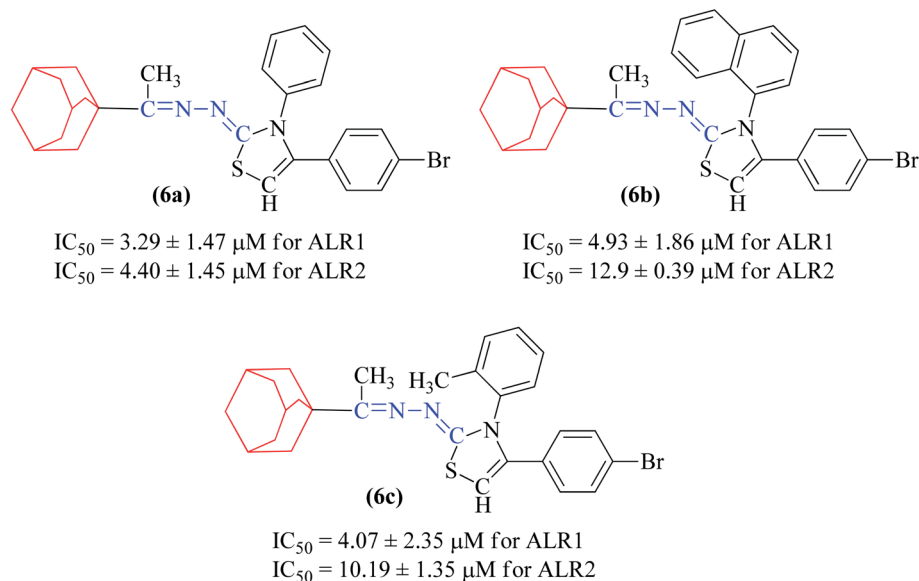
Fig. 5 ALR1/ALR2 inhibitory activities of adamantyl substituted compounds **6a**, **6b** & **6c**.

enzymes (Table 2). However, compound **6d**, **6e**, **6f**, **7a**, **7b**, **7c** and **8f** were identified as selective ALR2 inhibitors (Fig. 4).

Compound **5f**, one of the 2H-1,4-benzoxazin-3(4H)-one bearing derivatives were active against ALR1 and ALR2 having IC_{50} value of $3.13 \pm 1.45 \ \mu M$ and $3.24 \pm 2.72 \ \mu M$, respectively. The substitution of nitrophenyl with bromophenyl or chlorophenyl, as in compound **5b** and **5j**, showed weak activity against both ARL1 and ARL2 enzymes in comparison to sorbinil and valproic acid with respective IC_{50} values of $3.14 \pm 0.02 \ \mu M$ and $57.4 \pm 0.89 \ \mu M$ (Table 2).

In general, compounds (**6a–6f**) containing adamantane substituent demonstrated the most promising activity among all the derivatives. Out of six, three compounds **6d**, **6e** and **6f** showed a good inhibitory activity and selectively against ALR2

with IC_{50} values $4.21 \pm 2.35 \ \mu M$, $2.18 \pm 0.83 \ \mu M$ and 3.51 ± 2.31 μM respectively. Compounds **6a**, **6b** and **6c** were also found to be active against ALR1 and ALR2 enzymes (Fig. 5).

Among the series, compound **7b** showed high inhibition potential against ALR2 ($IC_{50} = 1.39 \pm 2.21 \ \mu M$). However, compound **7b** was found to have considerably selective activity against ARL2 exhibiting only 23.4% inhibition against ALR1. The inhibition potential of chlorophenyl substituted thiazoline derivative **7i** against ALR2 was much lower than the aforementioned compound with IC_{50} of $38.2 \pm 1.43 \ \mu M$. Furthermore, an improved inhibitor potency of compound **7i** was also observed against ALR1 (IC_{50} $4.01 \pm 0.39 \ \mu M$).

Among the indolyl substituted thiazoline derivatives, compound **8e** having a nitrophenyl moiety showed high

(8e)

$IC_{50} = 2.94 \pm 1.34 \ \mu M$ for ALR1
$IC_{50} = 1.52 \pm 0.78 \ \mu M$ for ALR2

(8f)

% Inhibition = 12.4% for ALR1
$IC_{50} = 4.21 \pm 1.63 \ \mu M$ for ALR2

(8h)

% Inhibition = 33.4% for ALR1
% Inhibition = 10.32% for ALR2

Fig. 6 Bioactivity of indolyl substituted thiazoline derivatives.

Fig. 7 Overlap of ALR1 inhibitors **7h** (dark pink), **7i** (purple) and **8e** (light pink) with the co-crystallized inhibitor FX4 ([5-(3-carboxymethoxy-4-methoxybenzylidene)-2,4-dioxothiazolidin-3-yl]acetic acid) (black), NADP is shown in grey.

inhibitory potency against ARL2 and ARL1, with IC_{50} values of 1.52 ± 0.78 μM and 2.94 ± 1.34 μM respectively. However, the inhibitory activity of chlorophenyl substituted thiazoline derivative **8h**, was weakened for both enzymes ALR2 and ALR1 demonstrating 10.32% and 33.4% inhibition respectively. Furthermore, the compound **8f** was a selective ALR2 inhibitor than ALR1 exhibiting only 12.4% inhibition (Fig. 6). The other indolyl substituted compounds (**8a, 8b, 8c,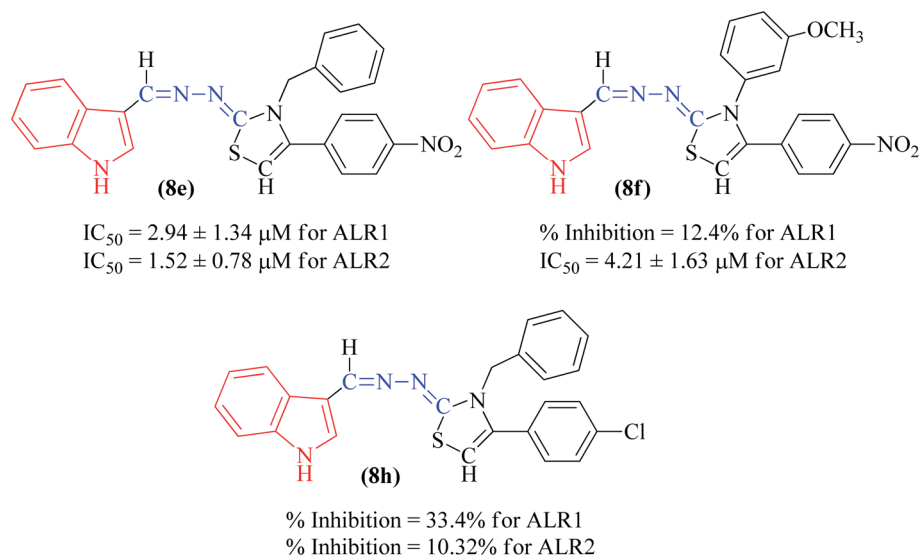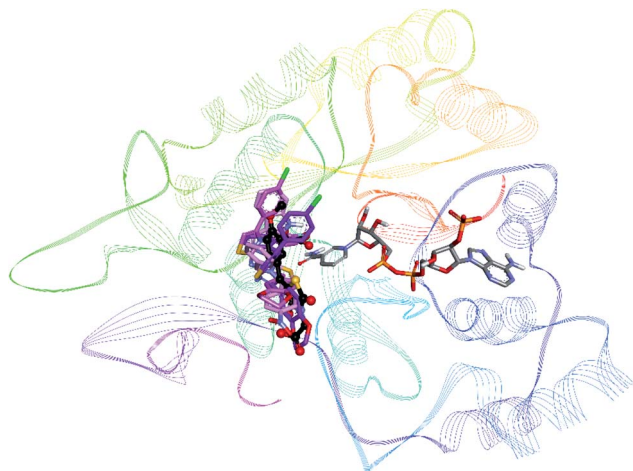 8d, 8g, 8h, 8i,** & **8j**) were found inactive with less than 50% inhibitory activity against ALR2 as well against ARL1 enzymes.

3. Docking studies

3.1 Molecular docking studies of ALR1 and ALR2 inhibitors

To rationalize the mode of binding and nature of binding site interactions, molecular docking studies were carried out using BioSolveIT's LeadIT software.[36] For each inhibitor, the top 10 docked conformations were further evaluated for their binding

free energy using HYDE utility (part of LeadIT software), the conformation with most favorable binding free energy was retained for further analysis The crystal structures of porcine ALR1 (ref. 37) and human ALR2 (ref. 38) were downloaded from the Protein Data Bank [PDB ids: 3FX4 at 1.99 Å and 1US0 at 0.66 Å respectively].[39] Docking protocol was validated by re-docking of the co-crystallized ligand. The docking protocol was able to reproduce the experimentally bound conformation of co-crystallized ligand (FX4) with an rmsd of 1.03. For docking against ALR1, three of the most active inhibitors **7h**, **7i** and **8e** were selected. All compounds were found to bind in the same area of the binding pocket as the co-crystallized inhibitor FX4 (Fig. 7).

By analyzing the binding site interactions of the co-crystallized ligand (ALR1 inhibitor), FX4 ([5-(3-carboxymethoxy-4-methoxybenzylidene)-2,4-dioxothiazolidin-3-yl]acetic acid) it can be seen that the amino acid residues that are important for binding are Arg312, Phe298, Trp220, Trp22, Arg309, and Ala219. When docking studies of ALR1 inhibitors (**7h, 7i, 8e**) were carried out, same amino acids were found to be involved in binding these inhibitors (Table S1†). Fig. S1† shows the docked conformation of compound **7h**. The oxygen atom of the benzodioxane ring was making hydrogen bond with Met302. The nitrogen atom of the C═N moiety next to the thiazole ring was making a hydrogen bond with Arg312. The OH group of Tyr50 was acting as a hydrogen bond donor towards the fluorine atom. The carbonyl oxygen atom of Tyr 50 was acting as a halogen bond acceptor towards the chlorine atom. A number of hydrophobic interactions were also observed. Phe125 was making pi–pi stacked interactions with the thiazole and the phenyl ring attached to thiazole ring. Ile299 was making alkyl and pi-alkyl interactions with the methyl group and the phenyl ring of benzodioxane ring respectively. Ile49 was making pi-alkyl interactions with both chlorophenyl and fluorophenyl rings, whereas Trp114 was making pi-alkyl interaction with the methyl group.

Docking of compound **7i** revealed hydrogen bonded interactions between the oxygen atom of the benzodioxane ring and
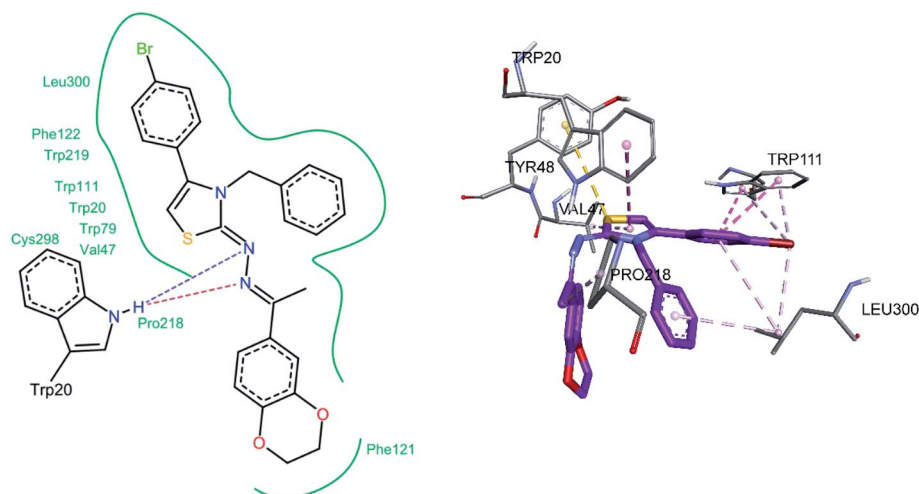

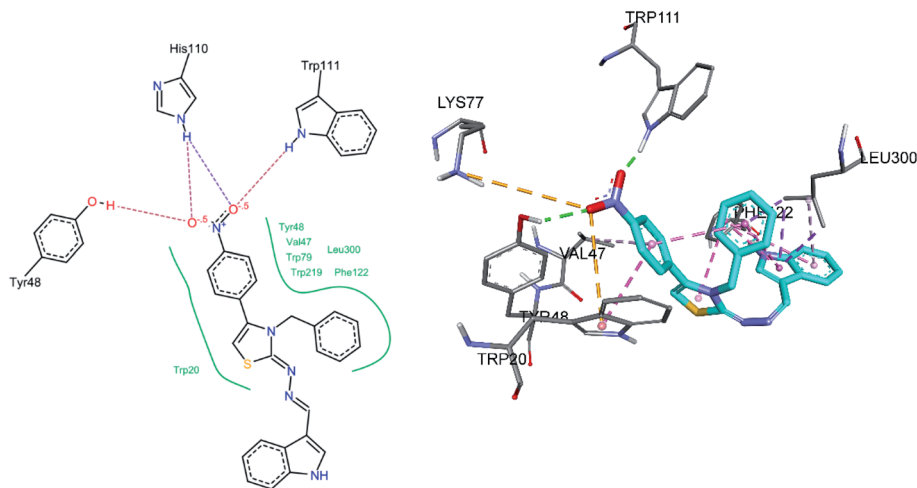**Fig. 8** Docked conformation of ALR2 inhibitor **7b**.

Fig. 9 Docked conformation of ALR2 inhibitor **8e**.

Val300, and between the nitrogen atom of the C=N group and Met302 (Fig. S2†). A number of hydrophobic interactions were also observed. Ile299 was making alkyl and pi-alkyl interactions with the methyl group and phenyl ring of benzodioxane ring respectively. Pro301 was making also alkyl interaction with the methyl group. Lys23 was alkyl interaction with the chlorine atom and pi-alkyl interaction with chlorophenyl ring. Arg218 was making pi-alkyl interaction with the phenyl ring of benzodioxane ring, whereas Ala219 was making pi-alkyl interaction with the thiazole ring.

Docking of compound **8e** revealed two hydrogen bonds of Arg309 and Arg312 with nitrogen atom of C=N bond and oxygen atom of the nitro group (Fig. S3†). Notable hydrophobic interactions include pi-sigma and pi-alkyl interaction of Ile49 with indole phenyl ring and pyrrole ring of indole respectively. Tyr50 was making pi–pi stacked interaction with pyrrole ring of indole. Ile299 and Met302 were making pi-alkyl interactions with thiazole ring and nitro phenyl ring respectively.

Docking studies of ALR2 inhibitors were also carried out for most active inhibitors **6e**, **7b** and **8e**. Prior to docking, the docking protocol was verified by re-docking the co-crystallized ligand LDT ({2-[(4-bromo-2-fluorobenzyl)carbamothioyl]-5-fluorophenoxy}acetic acid) from the ALR2 (PDB id: 1su0). The docking protocol was able to reproduce the experimentally observed conformation of LDT with rmsd of <2. Moreover all compounds were found to bind at the same region of the active site as that of the co-crystallized inhibitor LDT (Fig. S4†).

Docked conformation of compound **6e** is shown in Fig. S5.† The nitrogen atom of the C=N group was making a hydrogen bond with Trp20. A number of hydrophobic interactions were observed that are deemed necessary for efficient binding. Leu300 was making a pi-sigma interaction with the chloro phenyl ring. Trp20 was making pi–pi stacked and pi-alkyl interactions with the benzyl ring and the methyl group respectively. Trp111 was making a pi-stacked interaction with the chloro phenyl ring and a pi-alkyl interaction with the chloro group. Two pi-sulfur interactions were also observed. Trp219 was making a pi-sulfur contact with the sulfur atom of the

thiazole ring, whereas the sulfur atom of Cys298 was making pi-sulfur contact with the benzyl ring.

For compound **7b** (Fig. 8), similar interactions were observed. Trp20 was within hydrogen bond distance (1.99 Å and 2.12 Å) of both nitrogen atoms of C=N groups. Hydrophobic interactions include Trp111 making a pi–pi stacked interaction with the bromo phenyl ring and a pi-alkyl interaction with the bromine atom. Trp20 was making a pi–pi T-shaped interaction with the thiazole ring. Pro218 was making a pi-alkyl interaction with the methyl group. Leu300 was making pi-alkyl interaction with both benzyl and bromo phenyl ring, whereas Val47 was making pi-alkyl interaction with the thiazole ring. A pi-sulfur interaction was also observed between Tyr48 and the sulfur atom of thiazole ring.

Docking of compound **8e** was also carried out, its docked conformation along with binding site interactions are shown in Fig. 9. Both oxygen atoms of the nitro group were making hydrogen bonds with Trp111 and Tyr48, His110 is also within hydrogen bond distance to the nitro group. It is important to note that Trp111, Tyr48 and His110 are the same amino acids that are involved in binding the carboxylate group of standard inhibitor LDT. Leu300 was making hydrophobic interactions, pi-sigma and pi-alkyl with pyrrole ring of indole, and the phenyl indole ring respectively. Phe122 was making pi–pi T-shaped interaction with both thiazole and indole rings. Another pi–pi T-shaped interaction was observed between Trp20 and nitro phenyl ring. Moreover, an intramolecular pi–pi T shaped contact was also observed between the nitro phenyl and benzyl ring, this orientation may additionally stabilize the binding of inhibitor. The nitro phenyl ring was also found to be involved in a pi-alkyl interaction with Val47. An electrostatic attractive interaction was observed between Lys77 and the oxygen atom of the nitro group. Another electrostatic (pi-anion) interaction was observed between Trp20 and same oxygen atom of the nitro group.

Radius of Gyration

Fig. 10 Radius of gyration (R_g) of 1US0, protein plus cognate ligand (LDT) and protein plus selective compound (**7b**) during 50 ns MD-simulation run.

RMSD

Fig. 11 Root mean square deviation (RMSD) of 1US0, protein plus cognate ligand (LDT) and protein plus selective compound (**7b**) during 50 ns MD-simulation run.

RMS Fluctuation

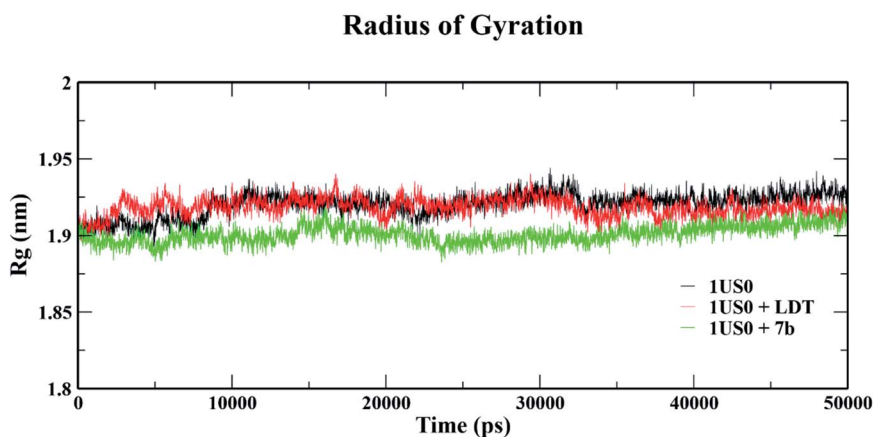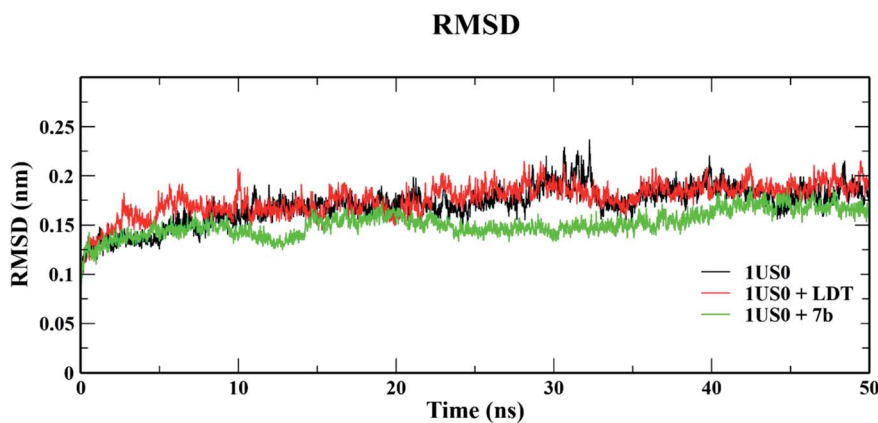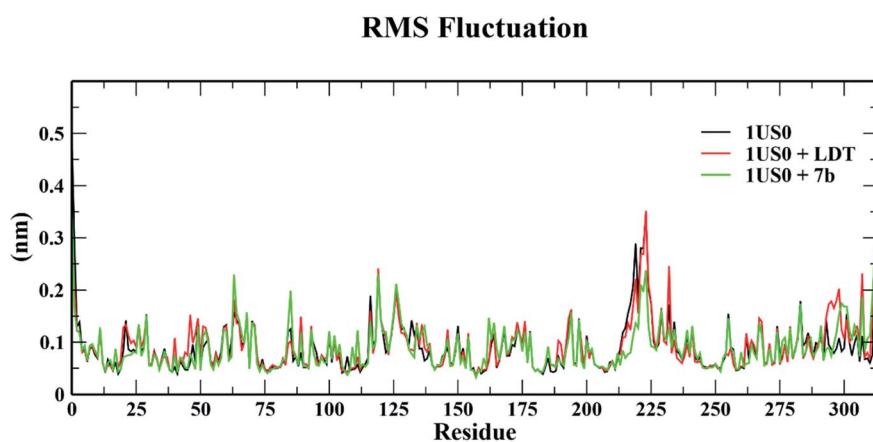**Fig. 12** Root mean square fluctuation (RMSF) of 1US0, protein plus cognate ligand (LDT) and protein plus selective compound (**7b**) during 50 ns MD-simulation run.

4. Molecular dynamics simulation

The conformational stabilities of the apoenzymes (ALR1 and ALR2) and their protein + ligand complexes, both cognate and test compounds, were performed to simulate protein flexibility. The structure of proteins (apoproteins) were first subjected to MD run of 50 ns and then docked poses of cognate ligands and selected ligands (holoenzymes) were submitted to MD run for 50 ns. The time evolution of the radius of gyration of 3FX4 and 1US0, apoenzymes and holoenzymes, exposed in the applied electric fields are shown in Fig. S6† and 10, respectively. The graph indicating that the average value of R_g slightly fluctuating between 1.92–1.97 nm for ALR1 (3FX4), while for ALR2 (1US0), the radius of gyration lies between 1.89 and 1.93 nm, signifying a fine degree of compactness. The average values of RMSD over a period 50 ns for 3FX4 and 1US0, apoenzymes and holoenzymes, exhibited minute fluctuations, reaffirming stable complex formation between enzymes and test compounds, as shown in Fig. S7† and 11, respectively. RMSF analyzes the portions of structure that are fluctuating from their mean structure the most (or least). The (RMSF) of ALR1 and ALR2 were examined, it was observed that residues were found stable in both the cases (Fig. S8,† and 12).

5. Conclusions

In this research, we have synthesized thiazoline derivatives (**5a–k, 6a–f, 7a–1 & 8a–j**), which were tested against aldehyde reductase (ALR1), and aldose reductase (ALR2) enzymes to study their anti-diabetic potential. The results demonstrated that compounds containing adamantyl substituent (**6a–6f**) have most promising activity among all the derivatives. The compound **7b** (with benzyl substituent) among the series was found significantly selective against ARL2 with IC$_{50}$ value of 1.39 ± 2.21 μM compare to sorbinil, a reference inhibitor, with IC$_{50}$ values of 3.14 ± 0.02 μM. Furthermore, the compounds **6e** also showed potency against ALR2 with IC$_{50}$ values of 2.18 ± 0.83 μM, whilst **6f** presented slightly higher with IC$_{50}$ value of 3.51 ± 2.31 μM when compared with standard sorbinil. The compound **8e** (with nitrophenyl substituent) demonstrated high potency and selectivity against ALR2 enzyme with IC$_{50}$ values of 1.52 ± 0.78 μM. *In silico* molecular docking study was also performed to further study the putative binding of active compounds with the target enzyme to find lead compound for further steps of drug development.

6 Experimental section

6.1 General procedure for the synthesis of thiosemicarbazones (3)

A solution of corresponding aldehyde or ketone **1** (6-acetyl-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one, 1-acetyl adamantane, 1,4-benzodioxan-6-yl methyl ketone and indole-3-carboxaldehyde; 0.01 mol) in methanol (10 mL) was added to a hot stirred solution of appropriate N^4-substituted thiosemicarbazide **2** (0.01 mol) in methanol (10 mL). After adding few drops of glacial acetic acid as catalyst, the reaction mixture was heated under reflux for 2–6 h. Upon completion of reaction, monitored through TLC, the hot reaction mixture was cooled to room temperature. The solid product obtained in each case was filtered, washed several times with hot methanol and dried under vacuum to afford the desired thiosemicarbazones **3** in pure form. The resultant thiosemicarbazone derivatives were used as such in the next step without any further purification.

6.2 General procedure for the synthesis of thiazoline derivatives (5–8)

A mixture of equimolar amounts of appropriate thiosemicarbazone derivative **3** (0.005 mol), 4-substituted (bromo, nitro, chloro) phenacyl bromide **4** (0.005 mol) and anhydrous sodium acetate (0.005 mol) in absolute ethanol (25 mL) was heated under reflux with continuous stirring for 12–24 h. The reaction mixture was then partially concentrated on a rotary evaporator and left overnight. The precipitate formed in each case was filtered off, washed with warm diethyl ether, dried and recrystallized from absolute ethanol to furnish the target thiazoline derivatives **5–8** in pure form.

The different compounds are characterized as under:

6-((*E*)-1-((*Z*)-(4-(4-bromophenyl)-3-phenylthiazol-2(3*H*)-ylidene)hydrazono)ethyl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (5a). Yield 81%; m.p. 228–230 °C; IR v_{max} (cm^{-1}): 3188 (N–H), 3022 (Ar-H), 2942 (CH$_3$), 1748 (C=O), 1581 (C=N), 1539, 1506 (Ar-C=C); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ ppm: 2.13 (s, 3H, CH$_3$–C=N), 4.60 (s, 2H, O–CH$_2$–CO), 6.73 (s, 1H, CH-S), 6.96 (d, 1H, J = 8.4 Hz, Ar-H), 7.12 (d, 2H, J = 8.4 Hz, Ar-H), 7.28–7.36 (m, 4H, Ar-H), 7.38–7.39 (m, 2H, Ar-H), 7.43–7.47 (m, 3H, Ar-H), 10.80 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 14.82 (CH$_3$), 67.25 (OCH$_2$), 103.11 (S-CH=), 113.79 (Ar-C), 116.30 (Ar-C), 121.58 (Ar-C), 122.14 (Ar-C), 127.55 (Ar-C), 128.21 (Ar-C), 128.88 (Ar-C), 129.29 (Ar-C), 130.53 (Ar-C), 131.73 (Ar-C), 133.19 (Ar-C), 138.11 (Ar-C), 138.79 (Ar-C), 144.59 (N–C=), 155.60 (C=N–N), 165.13 (N–C=N), 168.69 (HN–C=O); anal. calcd for C$_{25}$H$_{19}$BrN$_4$O$_2$S (519.41): C, 57.81; H, 3.69; N, 10.79; found: C, 57.88; H, 3.65; N, 10.85.

6-((*E*)-1-((*Z*)-(4-(4-bromophenyl)-3-(3-methoxyphenyl)thiazol-2(3*H*)-ylidene) hydrazono) ethyl)-2*H*-benzo[*b*][1,4]oxazin-3(4*H*)-one (5b). Yield 84%; m.p. 276–278 °C; IR v_{max} (cm^{-1}): 3184 (N–H), 3012 (Ar-H), 2950 (CH$_3$), 1690 (C=O), 1585 (C=N), 1536, 1509 (Ar-C=C); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ ppm: 2.15 (s, 3H, CH$_3$–C=N), 3.69 (s, 3H, OCH$_3$), 4.59 (s, 2H, O–CH$_2$–CO), 6.70 (s, 1H, CH–S), 6.75–6.77 (m, 1H, Ar-H), 6.86–6.88 (dd, 1H, J = 0.8 Hz, 8.4 Hz, Ar-H), 6.94–6.97 (m, 2H, Ar-H), 7.14 (d, 2H, J = 2.0 Hz, Ar-H), 7.25 (t, 1H, J = 8.0 Hz, Ar-H), 7.34 (dd, 1H, J = 2.4 Hz, 8.8 Hz, Ar-H), 7.42 (d, 1H, J = 2.0 Hz, Ar-H), 7.47 (d, 2H, J = 2.0 Hz, Ar-H), 10.78 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 14.87 (CH$_3$), 55.77 (OCH$_3$), 67.25 (O–CH$_2$), 103.14 (S-CH=), 113.81 (Ar-C), 113.98 (Ar-C), 114.74 (Ar-C), 116.31 (Ar-C), 120.87 (Ar-C), 122.13 (Ar-C), 127.56 (Ar-C), 129.87 (Ar-C), 130.43 (Ar-C), 130.71 (Ar-C), 131.73 (Ar-C), 133.19 (Ar-C), 138.79 (Ar-C), 139.09 (Ar-C), 144.61 (Ar-C), 155.70 (N–C=), 159.75 (C=N–N), 165.13 (N–C=N), 168.55 (HN–C=O); anal. calcd for C$_{26}$H$_{21}$BrN$_4$O$_3$S (549.44): C, 56.84; H, 3.85; N, 10.20; found: C, 56.80; H, 3.89; N, 10.24.

6-((E)-1-((Z)-(4-(4-bromophenyl)-3-(2,6-dimethylphenyl)thiazol-2(3H)-ylidene) hydrazono) ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (5c). Yield 80%; m.p. 260–262 °C; IR v_{max} (cm^{-1}): 3246 (N–H), 3049 (Ar-H), 2935 (CH$_3$), 1695 (C=O), 1583 (C=N), 1541, 1487 (Ar-C=C); ^{1}H-NMR (CDCl$_3$, 400 MHz) δ ppm: 1.70 (s, 6H, 2×CH$_3$-Ar), 2.29 (s, 3H, CH$_3$–C=N), 4.76 (s, 2H, O–CH$_2$–CO), 6.35 (s, 1H, CH–S), 7.06–7.10 (m, 3H, Ar-H), 7.17–7.19 (m, 2H, Ar-H), 7.27–7.31 (m, 1H, Ar-H), 7.42–7.44 (m, 2H, Ar-H), 7.49–7.51 (m, 1H, Ar-H), 7.54 (d, 1H, J = 2.0 Hz, Ar-H), 7.86 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 14.45 (CH$_3$), 18.25 (2×CH$_3$-Ar), 67.43 (OCH$_2$), 100.90 (S-CH=), 113.29 (Ar-C), 116.37 (Ar-C), 122.43 (Ar-C), 125.81 (Ar-C), 128.51 (Ar-C), 128.74 (Ar-C), 128.85 (Ar-C), 129.85 (Ar-C), 131.48 (Ar-C), 134.07 (Ar-C), 136.54 (Ar-C), 139.23 (Ar-C), 144.28 (N–C=), 155.54 (C=N–N), 164.94 (N–C=N), 166.68 (HN–C=O); anal. calcd for C$_{27}$H$_{23}$BrN$_4$O$_2$S (547.47): C, 59.23; H, 4.23; N, 10.23; found: C, 59.30; H, 4.25; N, 10.20.

6-((E)-1-((Z)-(4-(4-bromophenyl)-3-(o-tolyl)thiazol-2(3H)-ylidene)hydrazono) ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (5d). Yield 86%: m.p. 294–296 °C; IR v_{max} (cm^{-1}): 3285 (N–H), 3045 (Ar-H), 2942 (CH$_3$), 1701 (C=O), 1590 (C=N), 1570, 1510 (Ar-C=C); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ ppm: 2.06 (s, 3H, CH$_3$-Ar), 2.17 (s, 3H, CH$_3$–C=N), 4.59 (s, 2H, O–CH$_2$–CO), 6.73 (s, 1H, CH–S), 6.96 (d, 1H, J = 8.4 Hz, Ar-H), 7.08–7.10 (m, 2H, Ar-H), 7.17–7.19 (m, 2H, Ar-H), 7.30–7.34 (m, 3H, Ar-H), 7.41–7.44 (m, 3H, Ar-H), 10.78 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 14.66 (CH$_3$), 18.05 (CH$_3$), 67.25 (OCH$_2$), 102.49 (S-CH=), 113.76 (Ar-C), 116.29 (Ar-C), 127.16 (Ar-C), 127.53 (Ar-C), 129.19 (Ar-C),, 129.72 (Ar-C), 130.31 (Ar-C), 130.35 (Ar-C), 131.33 (Ar-C), 131.74 (Ar-C), 133.22 (Ar-C), 136.49 (Ar-C), 137.32 (Ar-C), 139.00 (Ar-C), 144.53 (N–C=), 155.32 (C=N–N), 165.12 (N–C=N), 167.92 (HN–C=O); anal. calcd for C$_{26}$H$_{21}$BrN$_4$O$_2$S (533.44): C, 58.54; H, 3.97; N, 10.50; found: C, 58.50; H, 3.96; N, 10.54.

6-((E)-1-((Z)-(4-(4-nitrophenyl)-3-phenylthiazol-2(3H)-ylidene)hydrazono)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (5e). Yield 87%; m.p. 296–298 °C; IR v_{max} (cm^{-1}): 3240 (N–H), 3028 (Ar-H), 2959 (CH$_3$), 1685 (C=O), 1578 (C=N), 1544, 1494 (Ar-C=C); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ ppm: 2.15 (s, 3H, CH$_3$–C=N), 4.60 (s, 2H, O–CH$_2$–CO), 6.96 (d, 1H, J = 8.4 Hz, Ar-H),7.00 (s, 1H, CH–S), 7.32–7.36 (m, 4H, Ar-H), 7.36–7.49 (m, 5H, Ar-H), 8.09–8.11 (m, 2H, Ar-H), 10.80 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 14.90 (CH$_3$), 67.25 (OCH$_2$), 106.36 (S-CH=), 113.83 (Ar-C), 116.32 (Ar-C), 119.49 (Ar-C), 121.66 (Ar-C), 123.96 (Ar-C), 127.57 (Ar-C), 128.35 (Ar-C), 128.71 (Ar-C), 129.39 (Ar-C), 129.42 (Ar-C), 133.06 (Ar-C), 137.51 (Ar-C), 138.02 (Ar-C), 144.68 (Ar-C), 147.16 (N–C=), 156.13 (C=N–N), 165.13 (N–C=N), 168.46 (HN–C=O); anal. calcd for C$_{25}$H$_{19}$N$_5$O$_4$S (485.51): C, 61.85; H, 3.94; N, 11.42; found: C, 61.80; H, 3.98; N, 11.36.

6-((E)-1-((Z)-(3-(3-methoxyphenyl)-4-(4-nitrophenyl)thiazol-2(3H)-ylidene) hydrazono)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (5f). Yield 88%; m.p. 210–212 °C; IR v_{max} (cm^{-1}): 3200 (N–H), 3050 (Ar-H), 2948 (CH$_3$), 1664 (C=O), 1593 (C=N), 1561, 1485 (Ar-C=C); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ ppm: 2.13 (s, 3H, CH$_3$–C=N), 3.62 (s, 3H, OCH$_3$), 4.59 (s, 2H, O–CH$_2$–CO), 6.62–6.65 (m, 1H, Ar-H), 6.90–6.98 (m, 3H, CH–S, Ar-H), 7.08 (t,

1H, J = 8.0 Hz, Ar-H), 7.35–7.43 (m, 2H, Ar-H), 7.79 (s, 1H, Ar-H), 7.82–7.84 (m, 2H, Ar-H), 8.12–8.14 (m, 2H, Ar-H), 10.82 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 14.49 (CH$_3$), 55.95 (OCH$_3$), 67.25 (O–CH$_2$), 94.87 (S-CH=), 103.19 (Ar-C), 113.46 (Ar-C), 114.01 (Ar-C), 116.07 (Ar-C), 117.16 (Ar-C), 121.70 (Ar-C), 123.63 (Ar-C), 126.06 (Ar-C), 127.56 (Ar-C), 128.71 (Ar-C), 133.14 (Ar-C), 140.39 (Ar-C), 147.51 (Ar-C), 149.61 (Ar-C), 157.01 (Ar-C), 157.40 (Ar-C), 159.20 (N–C=), 164.92 (C=N–N), 165.15 (N–C=N), 167.07 (HN–C=O); anal. calcd for C$_{26}$H$_{21}$N$_5$O$_5$S (515.54): C, 60.57; H, 4.11; N, 13.58; found: C, 60.51; H, 4.15; N, 13.52.

6-((E)-1-((Z)-(3-(4-fluorophenyl)-4-(4-nitrophenyl)thiazol-2(3H)-ylidene) hydrazono)ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (5g). Yield 78%; m.p. 236–238 °C; IR v_{max} (cm^{-1}): 3338 (N–H), 3029 (Ar-H), 2964 (CH$_3$), 1659 (C=O), 1589 (C=N), 1557, 1508 (Ar-C=C); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ ppm: 2.10 (s, 3H, CH$_3$–C=N), 4.60 (s, 2H, O–CH$_2$–CO), 6.97 (s, 1H, CH–S), 7.05 (t, 2H, J = 8.8 Hz, Ar-H), 7.31–7.38 (m, 3H, Ar-H), 7.43 (d, 1H, J = 2.4 Hz, Ar-H), 7.82 (s, 1H, Ar-H), 7.86 (dd, 2H, J = 1.6 Hz, 6.8 Hz, Ar-H), 8.15 (dd, 2H, J = 2.0 Hz, 7.2 Hz, Ar-H), 10.83 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 14.81 (CH$_3$), 67.24 (OCH$_2$), 94.60 (S-CH=), 113.91 (Ar-C), 115.28 (Ar-C), 115.51 (Ar-C), 116.33 (Ar-C), 121.69 (Ar-C), 123.65 (Ar-C), 127.55 (Ar-C), 128.78 (Ar-C), 130.48 (Ar-C), 130.57 (Ar-C), 133.13 (Ar-C), 135.53 (Ar-C), 144.75 (Ar-C), 147.56 (Ar-C), 149.36 (Ar-C), 157.06 (Ar-C), 159.27 (N–C=), 161.69 (C=N–N), 165.15 (N–C=N), 167.40 (HN–C=O); anal. calcd for C$_{25}$H$_{18}$FN$_5$O$_4$S (503.50): C, 59.64; H, 3.60; N, 13.91; found: C, 59.68; H, 3.64; N, 13.85.

6-((E)-1-((Z)-(3-(2,6-dimethylphenyl)-4-(4-nitrophenyl)thiazol-2(3H)-ylidene) hydrazono) ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (5h). Yield 81%; m.p. 218–220 °C; IR v_{max} (cm^{-1}): 3200 (N–H), 3022 (Ar-H), 2957 (CH$_3$), 1687 (C=O), 1587 (C=N), 1570, 1498 (Ar-C=C); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ ppm: 2.07 (s, 3H, CH$_3$–C=N), 2.12 (s, 6H, 2×CH$_3$-Ar), 4.60 (s, 2H, O–CH$_2$–CO), 6.97 (d, 1H, J = 8.4 Hz, Ar-H), 7.06 (s, 1H, CH–S), 7.13–7.22 (m, 3H, Ar-H), 7.32–7.43 (m, 4H, Ar-H), 8.08 (dd, 2H, J = 2.0 Hz, 6.8 Hz, Ar-H), 10.78 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 14.69 (CH$_3$), 18.22 (2×CH$_3$-Ar), 67.24 (OCH$_2$), 105.63 (S-CH=), 112.75 (Ar-C), 113.78 (Ar-C), 116.30 (Ar-C), 121.60 (Ar-C), 124.08 (Ar-C), 127.53 (Ar-C), 128.58 (Ar-C), 129.46 (Ar-C), 133.07 (Ar-C), 136.47 (Ar-C), 136.90 (Ar-C), 138.03 (Ar-C), 143.19 (Ar-C), 144.59 (Ar-C), 147.39 (N–C=), 155.78 (C=N–N), 165.11 (N–C=N), 166.58 (HN–C=O); fnal calcd for C$_{27}$H$_{23}$N$_5$O$_4$S (513.57): C, 63.14; H, 4.51; N, 13.64; found: C, 63.18; H, 4.54; N, 13.57.

6-((E)-1-((Z)-(4-(4-chlorophenyl)-3-phenylthiazol-2(3H)-ylidene)hydrazono) ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (5i). Yield 87%; m.p. 248–250 °C; IR v_{max} (cm^{-1}): 3326 (N–H), 3054 (Ar-H), 2974 (CH$_3$), 1664 (C=O), 1587 (C=N), 1572, 1489 (Ar-C=C); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ ppm: 2.09 (s, 3H, CH$_3$–C=N), 4.60 (s, 2H, O–CH$_2$–CO), 6.59–7.08 (m, 2H, CH–S, Ar-H), 7.20 (t, 2H, J = 7.2 Hz, Ar-H), 7.28–7.43 (m, 6H, Ar-H), 7.53–7.56 (m, 3H, Ar-H), 10.82 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 14.81 (CH$_3$), 67.24 (OCH$_2$), 94.94 (S-CH=), 113.87 (Ar-C), 116.31 (Ar-C), 121.63 (Ar-C), 126.28 (Ar-C), 127.53 (Ar-C), 128.20 (Ar-C), 128.39 (Ar-C), 129.16 (Ar-C), 132.96 (Ar-C), 133.23 (Ar-C), 139.57 (Ar-C), 141.29 (Ar-C), 144.67 (N–C=), 156.57 (C=N–N), 165.16 (N–C=N), 167.36 (HN–C=O); anal. calcd for

$C_{25}H_{19}ClN_4O_2S$ (474.96): C, 63.22; H, 4.03; N, 11.80; found: C, 63.25; H, 4.08; N, 10.76.

6-((E)-1-((Z)-(4-(4-chlorophenyl)-3-(3-methoxyphenyl)thiazol-2(3H)-ylidene) hydrazono) ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (5j). Yield 79%; m.p. 228–230 °C; IR v_{max} (cm^{-1}): 3320 (N–H), 3045 (Ar–H), 2935 (CH$_3$), 1668 (C=O), 1593 (C=N), 1541, 1488 (Ar–C=C); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ ppm: 2.13 (s, 3H, CH$_3$–C=N), 3.63 (s, 3H, OCH$_3$), 4.60 (s, 2H, O–CH$_2$–CO), 6.62–6.65 (m, 1H, Ar–H), 6.87–6.97 (m, 3H, CH–S, Ar–H), 7.08 (t, 1H, J = 8.0 Hz, Ar–H), 7.32–7.37 (m, 3H, Ar–H), 7.42 (d, 1H, J = 1.6 Hz, Ar–H), 7.53–7.56 (m, 2H, Ar–H), 7.57 (s, 1H, Ar-H), 10.82 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 14.89 (CH$_3$), 55.43 (OCH$_3$), 67.25 (O–CH$_2$), 95.04 (S-CH=), 111.65 (Ar-C), 113.89 (Ar-C), 114.01 (Ar-C), 116.31 (Ar-C), 120.33 (Ar-C), 121.66 (Ar-C), 127.54 (Ar-C), 128.41 (Ar-C), 128.89 (Ar-C), 129.11 (Ar-C), 132.97 (Ar-C), 133.22 (Ar-C), 140.62 (Ar-C), 141.33 (Ar-C), 144.69 (Ar-C), 156.69 (N–C=), 159.11 (C=N–N), 165.15 (N–C=N), 167.17 (HN–C=O); anal. calcd for $C_{26}H_{21}ClN_4O_3S$ (504.99): C, 61.84; H, 4.19; N, 11.09; found: C, 61.80; H, 4.24; N, 11.13.

6-((E)-1-((Z)-(4-(4-chlorophenyl)-3-(4-fluorophenyl)thiazol-2(3H)-ylidene) hydrazono) ethyl)-2H-benzo[b][1,4]oxazin-3(4H)-one (5k). Yield 78%; m.p. 230–232 °C; IR v_{max} (cm^{-1}): 3310 (N–H), 3064 (Ar–H), 2932 (CH$_3$), 1663 (C=O), 1587 (C=N), 1529, 1496 (Ar–C=C); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ ppm: 2.08 (s, 3H, CH$_3$–C=N), 4.59 (s, 2H, O–CH$_2$–CO), 6.54–7.06 (m, 3H, CH–S, Ar–H), 7.28–7.34 (m, 5H, Ar–H), 7.41–7.42 (m, 1H, Ar–H), 7.54–7.57 (m, 3H, Ar–H), 10.81 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 14.78 (CH$_3$), 67.25 (O–CH$_2$), 94.76 (S-CH=), 100.04 (Ar-C), 113.89 (Ar-C), 115.34 (Ar-C), 116.31 (Ar-C), 127.54 (Ar-C), 128.45 (Ar-C), 129.18 (Ar-C), 130.41 (Ar-C), 130.49 (Ar-C), 133.20 (Ar-C), 141.08 (Ar-C), 144.70 (Ar-C), 156.74 (Ar-C), 159.48 (N–C=), 161.62 (C=N–N), 165.15 (N–C=N), 167.50 (HN–C=O); anal. calcd for $C_{25}H_{18}ClFN_4O_2S$ (492.95): C, 60.91; H, 3.68; N, 11.37; found: C, 60.95; H, 3.65; N, 11.32.

(2Z)-2-((1-(adamantan-1-yl)ethylidene)hydrazono)-4-(4-bromophenyl)-3-phenyl-2,3-dihydrothiazole (6a). Yield 81%; m.p. 258–260 °C; IR v_{max} (cm^{-1}): 3049 (Ar–H), 2965 (CH$_3$), 1616 (C=N), 1541, 1487 (Ar–C=C); ^{1}H-NMR (CDCl$_3$, 400 MHz) δ ppm: 1.67–1.75 (m, 6H, adamantane –CH$_2$), 1.81 (m, 6H, adamantane –CH$_2$), 1.85 (s, 3H, CH$_3$–C=N), 2.01–2.02 (bs, 3H, adamantane –CH$_2$), 6.11 (s, 1H, CH–S), 6.95 (d, 2H, J = 8.8 Hz, Ar–H), 7.19–7.21 (m, 3H, Ar–H), 7.27–7.31 (m, 4H, Ar–H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 12.48 (CH$_3$), 28.46 (adamantane-C), 36.98 (adamantane-C), 39.94 (adamantane-C), 40.38 (adamantane-C), 102.08 (S-CH=), 122.24 (Ar-C), 127.39 (Ar-C), 128.21 (Ar-C), 128.69 (Ar-C), 129.45 (Ar-C), 130.55 (Ar-C), 131.43 (Ar-C), 136.08 (Ar-C), 137.97 (N–C=), 167.51 (C=N–N), 169.44 (N–C=N); anal. calcd for $C_{27}H_{28}BrN_3S$ (506.50): C, 64.03; H, 5.57; N, 8.30; found: C, 64.10; H, 5.52; N, 8.34.

(2Z)-2-((1-(adamantan-1-yl)ethylidene)hydrazono)-4-(4-bromophenyl)-3-(naphthalen-1-yl)-2,3-dihydrothiazole (6b). Yield 90%; m.p. >300 °C; IR v_{max} (cm^{-1}): 3035 (Ar–H), 2941 (CH$_3$), 1616 (C=N), 1545, 1507 (Ar–C=C); ^{1}H-NMR (CDCl$_3$, 400 MHz) δ ppm: 1.54 (s, 3H, CH$_3$–C=N), 1.65–1.70 (m, 6H, adamantane –CH$_2$), 1.73–1.77 (bs, 6H, adamantane –CH$_2$), 2.00 (bs, 3H, adamantane –CH$_2$), 6.18 (s, 1H, CH–S), 6.89 (dd, 2H, J =

2.0 Hz, 6.8 Hz, Ar–H), 7.13 (dd, 2H, J = 2.0 Hz, 6.8 Hz, Ar–H), 7.22 (dd, 1H, J = 1.2 Hz, 7.2 Hz, Ar–H), 7.36 (t, 1H, J = 7.6 Hz, Ar–H), 7.47–7.50 (m, 2H, Ar–H), 7.77–7.89 (m, 3H, Ar–H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 12.24 (CH$_3$), 28.43 (adamantane-C), 36.96 (adamantane-C), 39.86 (adamantane-C), 40.26 (adamantane-C), 97.91 (S-CH=), 123.84 (Ar-C), 125.34 (Ar-C), 126.31 (Ar-C), 126.72 (Ar-C), 127.18 (Ar-C), 128.26 (Ar-C), 128.82 (Ar-C), 129.04 (Ar-C), 131.26 (Ar-C), 134.27 (Ar-C), 135.09 (Ar-C), 136.87 (Ar-C), 155.38 (N–C=), 166.17 (C=N–N), 169.88 (N–C=N); anal. calcd for $C_{31}H_{30}BrN_3S$ (556.56): C, 66.90; H, 5.43; N, 7.55; found: C, 66.95; H, 5.45; N, 7.52.

(2Z)-2-((1-(adamantan-1-yl)ethylidene)hydrazono)-4-(4-bromophenyl)-3-(o-tolyl)-2,3-dihydrothiazole (6c). Yield 82%; m.p. 270–272 °C; IR v_{max} (cm^{-1}): 3064 (Ar–H), 2954 (CH$_3$), 1617 (C=N), 1581, 1514 (Ar–C=C); ^{1}H-NMR (CDCl$_3$, 400 MHz) δ ppm: 1.56 (bs, 6H, CH$_3$–C=N, CH$_3$-Ar), 1.66–1.72 (m, 6H, adamantane –CH$_2$), 1.75–1.80 (bs, 6H, adamantane –CH$_2$), 2.00–2.02 (bs, 3H, adamantane –CH$_2$), 6.12 (s, 1H, CH–S), 6.91–6.94 (m, 2H, Ar–H), 7.02 (d, 1H, J = 7.6 Hz, Ar–H), 7.09–7.13 (m, 1H, Ar–H), 7.19–7.21 (m, 2H, Ar–H), 7.27–7.29 (m, 2H, Ar–H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 13.00 (CH$_3$), 18.21 (CH$_3$-Ar), 28.44 (adamantane-C), 36.96 (adamantane-C), 39.86 (adamantane-C), 40.36 (adamantane-C), 93.39 (S-CH=), 126.51 (Ar-C), 127.32 (Ar-C), 128.11 (Ar-C), 128.84 (Ar-C), 129.23 (Ar-C), 130.86 (Ar-C), 131.00 (Ar-C), 131.33 (Ar-C), 131.39 (Ar-C), 143.59 (N–C=), 166.18 (C=N–N), 167.53 (N–C=N); anal. calcd for $C_{28}H_{30}BrN_3S$ (520.53): C, 64.61; H, 5.81; N, 8.07; found: C, 64.58; H, 5.85; N, 8.12.

(2Z)-2-((1-(adamantan-1-yl)ethylidene)hydrazono)-4-(4-bromophenyl)-3-(2,6-dimethylphenyl)-2,3-dihydrothiazole (6d). Yield 90%; m.p. 254–256 °C; IR v_{max} (cm^{-1}): 3059 (Ar–H), 2943 (CH$_3$), 1617 (C=N), 1547, 1509 (Ar–C=C); ^{1}H-NMR (CDCl$_3$, 400 MHz) δ ppm: 1.56 (s, 6H, CH$_3$–C=N, CH$_3$-Ar), 1.69–1.71 (m, 6H, adamantane –CH$_2$), 1.77–1.80 (bs, 6H, adamantane –CH$_2$), 2.00–2.02 (bs, 3H, adamantane –CH$_2$), 2.15 (s, 3H, CH$_3$-Ar), 6.13 (s, 1H, CH–S), 6.93 (d, 2H, J = 8.4 Hz, Ar–H), 7.02 (d, 2H, J = 7.2 Hz, Ar–H), 7.12 (t, 1H, J = 7.2 Hz, Ar–H), 7.28 (d, 2H, J = 8.8 Hz, Ar–H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 12.17 (CH$_3$), 18.17 (2×CH$_3$–Ar), 28.27 (adamantane-C), 36.79 (adamantane-C), 39.67 (adamantane-C), 40.08 (adamantane-C), 100.18 (S-CH=), 128.22 (Ar-C), 128.32 (Ar-C), 129.60 (Ar-C), 134.01 (Ar-C), 136.01 (Ar-C), 136.53 (Ar-C), 138.77 (Ar-C), 143.56 (N–C=), 164.19 (C=N–N), 168.63 (N–C=N); anal. calcd for $C_{29}H_{32}BrN_3S$ (534.55): C, 65.16; H, 6.03; N, 7.86; found: C, 65.20; H, 6.09; N, 7.80.

(2Z)-2-((1-(adamantan-1-yl)ethylidene)hydrazono)-3-benzyl-4-(4-chlorophenyl)-2,3-dihydrothiazole (6e). Yield 88%; m.p. 146–148 °C; IR v_{max} (cm^{-1}): 3066 (Ar–H), 2935 (CH$_3$), 1616 (C=N), 1556, 1488 (Ar–C=C); ^{1}H-NMR (CDCl$_3$, 400 MHz) δ ppm: 1.63–1.68 (m, 6H, adamantane –CH$_2$), 1.73–1.74 (m, 6H, adamantane –CH$_2$), 1.81 (s, 3H, CH$_3$–C=N), 1.98 (bs, 3H, adamantane –CH$_2$), 4.96 (s, 2H, CH$_2$), 6.31 (s, 1H, CH–S), 6.98–7.00 (m, 2H, Ar–H), 7.18–7.26 (m, 3H, Ar–H), 7.35 (dd, 2H, J = 2.0 Hz, 6.4 Hz, Ar–H), 7.46 (dd, 2H, J = 2.0 Hz, 6.8 Hz, Ar–H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 12.48 (CH$_3$), 28.26 (adamantane-C), 36.90 (adamantane-C), 39.19 (adamantane-C), 40.67 (adamantane-C), 101.07 (S-CH=), 127.08 (Ar-C), 127.55 (Ar-C),

128.84 (Ar-C), 129.18 (Ar-C), 130.23 (Ar-C), 130.90 (Ar-C), 134.25 (Ar-C), 137.63 (Ar-C), 139.11 (N–C=), 166.81 (C=N–N), 167.41 (N–C=N); anal. calcd for $C_{28}H_{30}ClN_3S$ (476.08): C, 70.64; H, 6.35; N, 8.83; found: C, 70.68; H, 6.30; N, 8.87.

(2Z)-2-((1-(adamantan-1-yl)ethylidene)hydrazono)-4-(4-chlorophenyl)-3-(2,6-dimethyl phenyl)-2,3-dihydrothiazole (6f). Yield 82%; m.p. 160–162 °C; IR v_{max} (cm^{-1}): 3056 (Ar-H), 2959 (CH$_3$), 1617 (C=N), 1541, 1493 (Ar-C=C); ^{1}H-NMR (CDCl$_3$, 400 MHz) δ ppm: 1.65–1.69 (m, 6H, adamantane –CH$_2$), 1.74 (s, 3H, CH$_3$–C=N), 1.78–1.79 (bs, 6H, adamantane –CH$_2$), 2.00 (bs, 3H, adamantane –CH$_2$), 2.13 (s, 6H, 2×CH$_3$–Ar), 6.08 (s, 1H, CH–S), 6.96–7.00 (m, 4H, Ar-H), 7.08–7.10 (m, 3H, Ar-H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 12.37 (CH$_3$), 18.36 (2×CH$_3$–Ar), 28.46 (adamantane-C), 36.98 (adamantane-C), 39.86 (adamantane-C), 40.28 (adamantane-C), 100.37 (S-CH=), 128.41 (Ar-C), 128.47 (Ar-C), 128.51 (Ar-C), 129.79 (Ar-C), 134.21 (Ar-C), 136.21 (Ar-C), 136.72 (Ar-C), 138.96 (N–C=), 164.39 (C=N–N), 168.82 (N–C=N); anal. calcd for $C_{29}H_{32}ClN_3S$ (490.10): C, 71.07; H, 6.58; N, 8.57; found: C, 71.01; H, 6.62; N, 8.53.

(Z)-4-(4-bromophenyl)-2-((E)-(1-(2,3-dihydrobenzo[b][1,4] dioxin-6-yl) ethylidene) hydrazono)-3-phenyl-2,3-dihydrothiazole (7a). Yield 85%; m.p. 272–274 °C; IR v_{max} (cm^{-1}): 3055 (Ar-H), 2975 (CH$_3$), 1604 (C=N), 1539, 1498 (Ar-C=C); ^{1}H-NMR (CDCl$_3$, 400 MHz) δ ppm: 2.23 (s, 3H, CH$_3$–C=N), 4.27 (s, 4H, –OCH$_2$CH$_2$O–), 6.16 (s, 1H, CH–S), 6.85 (d, 1H, J = 8.4 Hz, Ar-H), 6.96–7.00 (m, 2H, Ar-H), 7.22–7.27 (m, 3H, Ar-H), 7.30–7.33 (m, 4H, Ar-H), 7.34–7.38 (m, 1H, Ar-H), 7.40 (d, 1H, J = 2.4 Hz, Ar-H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 14.70 (CH$_3$), 64.33 (O–CH$_2$), 64.56 (O–CH$_2$), 102.25 (S-CH=), 115.33 (Ar-C), 116.85 (Ar-C), 119.86 (Ar-C), 122.37 (Ar-C), 127.40 (Ar-C), 128.30 (Ar-C), 128.72 (Ar-C), 129.53 (Ar-C), 131.48 (Ar-C), 132.75 (Ar-C), 137.90 (Ar-C), 138.90 (Ar-C), 143.14 (Ar-C), 144.47 (N–C=), 156.72 (C=N–N), 168.36 (N–C=N); anal. calcd for $C_{25}H_{20}BrN_3O_2S$ (506.41): C, 59.29; H, 3.98; N, 8.30; found: C, 59.35; H, 3.95; N, 8.34.

(Z)-3-benzyl-4-(4-bromophenyl)-2-((E)-(1-(2,3-dihydrobenzo [b][1,4]dioxin-6-yl)ethylidene)hydrazono)-2,3-dihydrothiazole (7b). Yield 92%; m.p. 284–286 °C; IR v_{max} (cm^{-1}): 3055 (Ar-H), 2969 (CH$_3$), 1610 (C=N), 1533, 1496 (Ar-C=C); ^{1}H-NMR (CDCl$_3$, 400 MHz) δ ppm: 2.30 (s, 3H, CH$_3$–C=N), 4.28 (s, 4H, –OCH$_2$CH$_2$O–), 5.03 (s, 2H, –CH$_2$–), 5.95 (s, 1H, CH–S), 6.85 (d, 1H, J = 8.4 Hz, Ar-H), 7.07–7.10 (m, 4H, Ar-H), 7.22–7.26 (m, 3H, Ar-H), 7.37–7.47 (m, 4H, Ar-H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 14.45 (CH$_3$), 49.30 (CH$_2$), 64.34 (O–CH$_2$), 64.56 (O–CH$_2$), 100.75 (S-CH=), 115.23 (Ar-C), 116.86 (Ar-C), 119.76 (Ar-C), 123.36 (Ar-C), 127.15 (Ar-C), 128.43 (Ar-C), 130.27 (Ar-C), 130.56 (Ar-C), 131.77 (Ar-C), 132.92 (Ar-C), 137.17 (Ar-C), 139.49 (Ar-C), 143.16 (Ar-C), 144.34 (Ar-C), 155.69 (N–C=), 163.82 (C=N–N), 168.55 (N–C=N); anal. calcd for $C_{26}H_{22}$-BrN$_3$O$_2$S (520.44): C, 60.00; H, 4.26; N, 8.07; found: C, 60.07; H, 4.22; N, 8.12.

(Z)-4-(4-bromophenyl)-2-((E)-(1-(2,3-dihydrobenzo[b][1,4] dioxin-6-yl) ethylidene) hydrazono)-3-(2,6-dimethylphenyl)-2,3-dihydrothiazole (7c). Yield 81%; m.p. 236–238 °C; IR v_{max} (cm^{-1}): 3025 (Ar-H), 2983 (CH$_3$), 1606 (C=N), 1589, 1483 (Ar-C=C); ^{1}H-NMR (CDCl$_3$, 400 MHz) δ ppm: 2.15 (s, 3H, CH$_3$–C=N), 2.16 (s, 3H, CH$_3$-Ar), 2.17 (s, 3H, CH$_3$-Ar), 4.27 (s, 4H,

–OCH$_2$CH$_2$O–), 6.19 (s, 1H, CH–S), 6.83 (d, 1H, J = 8.4 Hz, Ar-H), 6.94–6.97 (m, 2H, Ar-H), 7.03–7.05 (m, 2H, Ar-H), 7.13–7.15 (m, 1H, Ar-H), 7.28–7.30 (m, 2H, Ar-H), 7.35–7.39 (m, 2H, Ar-H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 14.52 (CH$_3$), 18.29 (2×CH$_3$-Ar), 64.32 (O–CH$_2$), 64.55 (O–CH$_2$), 100.99 (S-CH=), 115.23 (Ar-C), 116.84 (Ar-C), 119.74 (Ar-C), 122.61 (Ar-C), 128.46 (Ar-C), 128.63 (Ar-C), 128.82 (Ar-C), 130.02 (Ar-C), 131.43 (Ar-C), 132.78 (Ar-C), 136.62 (Ar-C), 139.03 (Ar-C), 143.13 (Ar-C), 144.37 (N–C=), 156.32 (C=N–N), 166.19 (N–C=N); anal. calcd for $C_{27}H_{24}BrN_3O_2S$ (534.47): C, 60.68; H, 4.53; N, 7.86; found: C, 60.74; H, 4.57; N, 7.81.

(Z)-2-((E)-(1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethylidene) hydrazono)-3-(4-fluorophenyl)-4-(4-nitrophenyl)-2,3-dihydrothiazole (7d). Yield 79%; m.p. 224–226 °C; IR v_{max} (cm^{-1}): 3041 (Ar-H), 2942 (CH$_3$), 1594 (C=N), 1577, 1545 (Ar-C=C); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ ppm: 2.14 (s, 3H, CH$_3$–C=N), 4.25 (s, 4H, –OCH$_2$CH$_2$O–), 6.88 (d, 1H, J = 8.4 Hz, Ar-H), 6.93 (s, 1H, CH–S), 7.21–7.30 (m, 4H, Ar-H), 7.36–7.45 (m, 4H, Ar-H), 8.12 (dd, 2H, J = 2.0 Hz, 7.2 Hz, Ar-H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 14.84 (CH$_3$), 64.51 (O–CH$_2$), 64.75 (O–CH$_2$), 106.12 (S-CH=), 115.03 (Ar-C), 116.19 (Ar-C), 116.42 (Ar-C), 117.27 (Ar-C), 119.84 (Ar-C), 124.01 (Ar-C), 129.52 (Ar-C), 130.98 (Ar-C), 132.03 (Ar-C), 134.28 (Ar-C), 137.33 (Ar-C), 137.91 (Ar-C), 143.54 (Ar-C), 145.02 (Ar-C), 147.24 (N–C=), 156.45 (C=N–N), 168.29 (N–C=N); anal. calcd for $C_{25}H_{19}FN_4O_4S$ (490.51): C, 61.22; H, 3.90; N, 11.42; found: C, 61.27; H, 3.85; N, 11.45.

(Z)-3-benzyl-2-((E)-(1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl) ethylidene) hydrazono)-4-(4-nitrophenyl)-2,3-dihydrothiazole (7e). Yield 90%; m.p. 202–204 °C; IR v_{max} (cm^{-1}): 3051 (Ar-H), 2931 (CH$_3$), 1558 (C=N), 1538, 1497 (Ar-C=C); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ ppm: 2.24 (s, 3H, CH$_3$–C=N), 4.26 (s, 4H, –OCH$_2$CH$_2$O–), 5.12 (s, 2H, –CH$_2$–), 6.66 (s, 1H, CH–S), 6.88 (d, 1H, J = 8.8 Hz, Ar-H), 7.02 (d, 2H, J = 7.2 Hz, Ar-H), 7.19–7.24 (m, 4H, Ar-H), 7.31 (s, 1H, Ar-H), 7.67 (dd, 2H, J = 2.0 Hz, 6.8 Hz, Ar-H), 8.25 (dd, 2H, Ar-H, J = 1.6 Hz, 6.8 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 14.67 (CH$_3$), 49.07 (CH$_2$), 64.50 (O–CH$_2$), 64.74 (O–CH$_2$), 104.16 (S-CH=), 114.95 (Ar-C), 117.26 (Ar-C), 119.72 (Ar-C), 124.31 (Ar-C), 127.17 (Ar-C), 127.75 (Ar-C), 128.97 (Ar-C), 130.20 (Ar-C), 132.26 (Ar-C), 137.23 (Ar-C), 137.47 (Ar-C), 138.73 (Ar-C), 143.53 (Ar-C), 144.83 (Ar-C), 147.92 (N–C=), 155.26 (C=N–N), 168.42 (N–C=N); anal. calcd for $C_{26}H_{22}N_4O_4S$ (486.54): C, 64.18; H, 4.56; N, 11.52; found: C, 64.22; H, 4.50; N, 11.55.

(Z)-2-((E)-(1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethylidene) hydrazono)-3-(2,6-dimethylphenyl)-4-(4-nitrophenyl)-2,3-dihydrothiazole (7f). Yield 86%; m.p. 208–210 °C; IR v_{max} (cm^{-1}): 3008 (Ar-H), 2970 (CH$_3$), 1590 (C=N). 1557, 1482 (Ar-C=C); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ ppm: 2.05 (s, 3H, CH$_3$–C=N), 2.12 (s, 6H, 2×CH$_3$-Ar), 4.25 (s, 4H, –OCH$_2$CH$_2$O–), 6.88 (d, 1H, J = 9.2 Hz, Ar-H), 7.01 (s, 1H, CH–S), 7.13–7.21 (m, 3H, Ar-H), 7.26–7.29 (m, 2H, Ar-H), 7.37 (dd, 2H, J = 2.0 Hz, 7.2 Hz, Ar-H), 8.08 (dd, 2H, J = 2.0 Hz, 7.2 Hz, Ar-H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 14.63 (CH$_3$), 18.22 (2×CH$_3$-Ar), 64.50 (O–CH$_2$), 64.73 (O–CH$_2$), 105.56 (S-CH=), 110.17 (Ar-C), 114.96 (Ar-C), 117.26 (Ar-C), 119.73 (Ar-C), 124.06 (Ar-C), 128.57 (Ar-C), 129.06 (Ar-C), 129.43 (Ar-C), 132.04 (Ar-C), 136.47 (Ar-C),

136.93 (Ar-C), 138.03 (Ar-C), 143.52 (Ar-C), 144.90 (Ar-C), 147.37 (N–C=), 155.95 (C=N–N), 166.42 (N–C=N); anal. calcd for $C_{27}H_{24}N_4O_4S$ (500.57): C, 64.78; H, 4.83; N, 11.19; found: C, 64.72; H, 4.85; N, 11.15.

(Z)-4-(4-chlorophenyl)-2-((E)-(1-(2,3-dihydrobenzo[b][1,4] dioxin-6-yl)ethylidene) hydrazono)-3-phenyl-2,3-dihydrothiazole (7g). Yield 78%; m.p. 172–174 °C; IR ν_{max} (cm^{-1}): 3067 (Ar-H), 2931 (CH$_3$), 1601 (C=N), 1545, 1501 (Ar-C=C); ^{1}H-NMR (CDCl$_3$, 400 MHz) δ ppm: 2.21 (s, 3H, CH$_3$–C=N), 4.25 (s, 4H, –OCH$_2$CH$_2$O–), 6.13 (s, 1H, CH–S), 6.83 (d, 1H, J = 8.4 Hz, Ar-H), 7.01–7.03 (m, 2H, Ar-H), 7.13–7.15 (m, 2H, Ar-H), 7.20–7.23 (m, 3H, Ar-H), 7.28–7.36 (m, 3H, Ar-H), 7.39 (d, 1H, J = 2.0 Hz, Ar-H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 14.72 (CH$_3$), 64.33 (O–CH$_2$), 64.56 (O–CH$_2$), 102.19 (S-CH=), 115.33 (Ar-C), 116.86 (Ar-C), 119.86 (Ar-C), 127.40 (Ar-C), 128.31 (Ar-C), 128.53 (Ar-C), 128.72 (Ar-C), 129.29 (Ar-C), 129.93 (Ar-C), 132.75 (Ar-C), 137.89 (Ar-C), 143.13 (Ar-C), 144.47 (N–C=), 156.69 (C=N–N), 168.40 (N–C=N); anal. calcd for $C_{25}H_{20}$-ClN$_3$O$_2$S (461.96): C, 65.00; H, 4.36; N, 9.10; found: C, 65.04; H, 4.31; N, 9.16.

(Z)-4-(4-chlorophenyl)-2-((E)-(1-(2,3-dihydrobenzo[b][1,4] dioxin-6-yl)ethylidene) hydrazono)-3-(4-fluorophenyl)-2,3-dihydrothiazole (7h). Yield 81%; m.p. 170–172 °C; IR ν_{max} (cm^{-1}): 3050 (Ar-H), 2948 (CH$_3$), 1596 (C=N), 1560, 1517 (Ar-C=C); ^{1}H-NMR (CDCl$_3$, 400 MHz) δ ppm: 2.12 (s, 3H, CH$_3$–C=N), 4.25 (s, 4H, –OCH$_2$CH$_2$O–), 6.13 (s, 1H, CH–S), 6.82 (d, 1H, J = 8.4 Hz, Ar-H), 6.96–7.02 (m, 4H, Ar-H), 7.15–7.19 (m, 4H, Ar-H), 7.34 (dd, 1H, J = 2.4 Hz, 8.8 Hz, Ar-H) 7.39 (d, 1H, J = 2.0 Hz, Ar-H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 14.69 (CH$_3$), 64.33 (O–CH$_2$), 64.56 (O–CH$_2$), 102.21 (S-CH=), 115.34 (Ar-C), 115.62 (Ar-C), 115.84 (Ar-C), 116.88 (Ar-C), 119.87 (Ar-C), 128.67 (Ar-C), 129.35 (Ar-C), 129.65 (Ar-C), 129.94 (Ar-C), 130.03 (Ar-C), 132.63 (Ar-C), 143.15 (Ar-C), 144.54 (Ar-C), 156.92 (Ar-C), 160.08 (N–C=), 162.54 (C=N–N), 168.33 (N–C=N); anal. calcd for $C_{25}H_{19}$ClFN$_3$O$_2$S (479.95): C, 62.56; H, 3.99; N, 8.76; found: C, 62.63; H, 3.92; N, 8.84.

(Z)-3-benzyl-4-(4-chlorophenyl)-2-((E)-(1-(2,3-dihydrobenzo [b][1,4]dioxin-6-yl)ethylidene)hydrazono)-2,3-dihydrothiazole (7i). Yield 84%; m.p. 150–152 °C; IR ν_{max} (cm^{-1}): 3012 (Ar-H), 2960 (CH$_3$), 1602 (C=N), 1578, 1507 (Ar-C=C); ^{1}H-NMR (CDCl$_3$, 400 MHz) δ ppm: 2.27 (s, 3H, CH$_3$–C=N), 4.25 (s, 4H, –OCH$_2$CH$_2$O–), 5.00 (s, 2H, –CH$_2$–), 5.92 (s, 1H, CH–S), 6.82 (d, 1H, J = 8.4 Hz, Ar-H), 7.05–7.07 (m, 2H, Ar-H), 7.10–7.12 (m, 2H, Ar-H),7.19–7.23 (m, 3H, Ar-H), 7.26–7.28 (m, 2H, Ar-H) 7.37 (dd, 1H, J = 2.0 Hz, 8.4 Hz, Ar-H) 7.40 (d, 1H, J = 2.4 Hz, Ar-H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 14.46 (CH$_3$), 49.28 (CH$_2$), 64.34 (O–CH$_2$), 64.56 (O–CH$_2$), 100.74 (S-CH=), 115.23 (Ar-C), 116.87 (Ar-C), 119.76 (Ar-C), 127.16 (Ar-C), 127.26 (Ar-C), 128.43 (Ar-C), 128.81 (Ar-C), 130.33 (Ar-C), 132.92 (Ar-C), 137.18 (Ar-C), 139.45 (Ar-C), 143.16 (Ar-C), 144.33 (N–C=), 155.67 (C=N–N), 168.58 (N–C=N); anal. calcd for $C_{26}H_{22}$-ClN$_3$O$_2$S (475.99): C, 65.61; H, 4.66; N, 8.83; found; C, 65.69; H, 4.61; N, 8.87.

(Z)-2-((E)-((1H-indol-3-yl)methylene)hydrazono)-4-(4-bromophenyl)-3-phenyl-2,3-dihydrothiazole (8a). Yield 89%; m.p. >300 °C; IR ν_{max} (cm^{-1}): 3224 (N–H), 3050 (Ar-H), 1610 (C=N), 1572, 1497 (Ar-C=C); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ ppm:

6.66 (s, 1H, CH–S), 7.12–7.21 (m, 4H, Ar-H), 7.29–7.33 (m, 3H, Ar-H), 7.38–7.46 (m, 5H, Ar-H), 7.68 (s, 1H, CH=N), 8.27–8.29 (m, 1H, Ar-H), 8.36 (s, 1H, indole CH), 11.51 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 102.50 (S-CH=), 112.30 (Ar-C), 113.01 (Ar-C), 120.91 (Ar-C), 122.05 (Ar-C), 122.52 (Ar-C), 122.95 (Ar-C), 124.96 (Ar-C), 128.18 (Ar-C), 129.15 (Ar-C), 129.40 (Ar-C), 130.52 (Ar-C), 128.75 (Ar-C), 130.72 (Ar-C), 131.69 (Ar-C), 137.57 (Ar-C), 138.24 (Ar-C), 138.79 (N–C=), 149.27 (C=N–N), 167.09 (N–C=N); anal. calcd for $C_{24}H_{17}$BrN$_4$S (473.39): C, 60.89; H, 3.62; N, 11.84; found: C, 60.82; H, 3.68; N, 11.89.

(Z)-2-((E)-((1H-indol-3-yl)methylene)hydrazono)-4-(4-bromophenyl)-3-cyclohexyl-2,3-dihydrothiazole (8b). Yield 80%; m.p. 284–286 °C; IR ν_{max} (cm^{-1}): 3125 (N–H), 3052 (Ar-H), 1606 (C=N), 1533, 1489 (Ar-C=C); ^{1}H-NMR (CDCl$_3$, 400 MHz) δ ppm: 1.03–1.56 (m, 3H, cyclohexyl), 1.60–1.74 (m, 5H, cyclohexyl), 2.58–2.67 (m, 2H, cyclohexyl), 3.60–3.66 (m, 1H, cyclohexyl), 5.79 (s, 1H, CH–S), 7.14–7.22 (m, 4H, Ar-H), 7.30–7.36 (m, 2H, Ar-H), 7.48–7.51 (m, 2H, Ar-H), 8.25 (s, 1H, CH=N), 8.41–8.43 (m, 1H, Ar-H), 8.54 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 25.09 (cyclohexyl-C), 26.15 (cyclohexyl-C), 29.06 (cyclohexyl-C), 59.31 (cyclohexyl-C), 100.37 (S-CH=), 110.96 (Ar-C), 114.96 (Ar-C), 121.29 (Ar-C), 123.07 (Ar-C), 123.24 (Ar-C), 125.08 (Ar-C), 127.15 (Ar-C), 130.46 (Ar-C), 130.53 (Ar-C), 131.86 (Ar-C), 131.96 (Ar-C), 136.88 (Ar-C), 140.21 (N–C=), 146.94 (C=N–N), 167.77 (N–C=N); anal. calcd for $C_{24}H_{23}$BrN$_4$S (479.44): C, 60.12; H, 4.84; N, 11.69; found: C, 60.17; H, 4.80; N, 11.62.

(Z)-2-((E)-((1H-indol-3-yl)methylene)hydrazono)-3-(4-fluorophenyl)-4-(4-nitrophenyl)-2,3-dihydrothiazole (8c). Yield 83%; m.p. 238–240 °C; IR ν_{max} (cm^{-1}): 3342 (N–H), 3064 (Ar-H), 1610 (C=N), 1542, 1502 (Ar-C=C); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ ppm: 6.93 (s, 1H, CH–S), 7.18–7.28 (m, 4H, Ar-H), 7.39–7.48 (m, 5H, CH=N, Ar-H), 7.72 (d, 1H, J = 2.4 Hz, Ar-H), 8.13 (dd, 2H, J = 2.0 Hz, 6.8 Hz, Ar-H), 8.26–8.28 (m, 1H, Ar-H), 8.39 (s, 1H, indole CH), 11.55 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 105.80 (S-CH=), 112.86 (Ar-C), 116.55 (Ar-C), 120.85 (Ar-C), 120.94 (Ar-C), 122.49 (Ar-C), 123.07 (Ar-C), 124.01 (Ar-C), 124.87 (Ar-C), 129.49 (Ar-C), 131.04 (Ar-C), 131.22 (Ar-C), 134.49 (Ar-C), 137.25 (Ar-C), 137.64 (Ar-C), 138.00 (Ar-C), 147.25 (Ar-C), 149.89 (N–C=), 160.20 (C=N–N), 166.88 (N–C=N); anal. calcd for $C_{24}H_{16}$FN$_5$ O$_2$S (457.48): C, 63.01; H, 3.53; N, 15.31; found: C, 63.07; H, 3.48; N, 15.35.

(Z)-2-((E)-((1H-indol-3-yl)methylene)hydrazono)-4-(4-nitrophenyl)-3-phenyl-2,3-dihydrothiazole (8d). Yield 80%; m.p. 296–298 °C; IR ν_{max} (cm^{-1}): 3297 (N–H), 3041 (Ar-H), 1615 (C=N), 1553, 1499 (Ar-C=C); ^{1}H-NMR (Acetone + DMSO-d_6, 400 MHz) δ ppm: 6.93 (s, 1H, CH–S), 7.18–7.22 (m, 2H, Ar-H), 7.33–7.35 (m, 3H, Ar-H), 7.39–7.46 (m, 5H, Ar-H, CH=N), 7.71 (d, 1H, J = 2.8 Hz, Ar-H), 8.10 (dd, 2H, J = 2.0 Hz, 7.2 Hz, Ar-H), 8.26–8.29 (m, 1H, Ar-H), 8.39 (s, 1H, indole CH), 11.54 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 105.86 (S-CH=), 112.34 (Ar-C), 112.90 (Ar-C), 120.98 (Ar-C), 122.49 (Ar-C), 123.00 (Ar-C), 123.92 (Ar-C), 124.92 (Ar-C), 128.32 (Ar-C), 128.96 (Ar-C), 129.34 (Ar-C), 129.54 (Ar-C), 130.97 (Ar-C), 137.58 (Ar-C), 137.66 (Ar-C), 138.05 (Ar-C), 138.14 (Ar-C), 147.10 (N–C=), 149.73 (C=N–N),

166.81 (N–C=N); anal. calcd for $C_{24}H_{17}N_5O_2S$ (439.49): C, 65.59; H, 3.90; N, 15.94; found: C, 65.55; H, 3.95; N, 15.90.

(Z)-2-((E)-((1H-indol-3-yl)methylene)hydrazono)-3-benzyl-4-(4-nitrophenyl)-2,3-dihydrothiazole (8e). Yield 80%; m.p. 218–220 °C; IR ν_{max} (cm^{-1}): 3228 (N–H), 3032 (Ar-H), 1605 (C=N), 1536, 1491 (Ar-C=C); ^{1}H-NMR (Acetone + DMSO-d_6, 400 MHz) δ ppm: 5.12 (s, 2H, –CH$_2$–), 6.65 (s, 1H, CH–S), 7.02 (d, 2H, J = 6.8 Hz, Ar-H), 7.19–7.26 (m, 5H, Ar-H, CH=N), 7.44–7.46 (m, 1H, Ar-H), 7.66 (dd, 2H, J = 2.0 Hz, 6.8 Hz, Ar-H), 7.74 (d, 1H, J = 2.4 Hz, Ar-H), 8.23 (dd, 2H, J = 2.0 Hz, 7.2 Hz, Ar-H), 8.27–8.30 (m, 1H, Ar-H), 8.47 (s, 1H, indole CH), 11.53 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 48.82 (CH$_2$), 103.76 (S-CH=), 112.32 (Ar-C), 113.01 (Ar-C), 120.90 (Ar-C), 122.52 (Ar-C), 122.97 (Ar-C), 124.28 (Ar-C), 124.95 (Ar-C), 126.90 (Ar-C), 127.68 (Ar-C), 129.01 (Ar-C), 129.99 (Ar-C), 130.66 (Ar-C), 137.37 (Ar-C), 137.57 (Ar-C), 137.58 (Ar-C), 138.75 (Ar-C), 147.83 (N–C=), 148.94 (C=N–N), 166.94 (N–C=N); anal. calcd for $C_{25}H_{19}N_5O_2S$ (453.52): C, 66.21; H, 4.22; N, 15.44; found: C, 66.15; H, 4.19; N, 15.48.

(Z)-2-((E)-((1H-indol-3-yl)methylene)hydrazono)-3-(3-methoxyphenyl)-4-(4-nitrophenyl)-2,3-dihydrothiazole (8f). Yield 76%; m.p. 276–278 °C; IR ν_{max} (cm^{-1}): 3320 (N–H), 3012 (Ar-H), 1603 (C=N), 1545, 1496 (Ar-C=C); ^{1}H-NMR (Acetone + DMSO-d_6, 400 MHz) δ ppm: 3.71 (s, 3H, OCH$_3$), 6.82–6.84 (m, 1H, Ar-H), 6.89–6.92 (m, 2H, Ar-H, CH–S), 7.00 (t, 1H, J = 2.0 Hz, Ar-H), 7.18–7.20 (m, 2H, Ar-H), 7.26 (t, 1H, J = 8.4 Hz, Ar-H), 7.44–7.50 (m, 3H, Ar-H, CH=N), 7.72 (d, 1H, J = 2.8 Hz, Ar-H), 8.12 (d, 2H, J = 8.8 Hz, Ar-H), 8.26–8.28 (m, 1H, Ar-H), 8.41 (s, 1H, indole CH), 11.55 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 55.80 (OCH$_3$), 105.82 (S-CH=), 112.35 (Ar-C), 112.90 (Ar-C), 113.88 (Ar-C), 115.09 (Ar-C), 120.98 (Ar-C), 122.49 (Ar-C), 123.00 (Ar-C), 123.94 (Ar-C), 124.92 (Ar-C), 129.24 (Ar-C), 130.19 (Ar-C), 130.98 (Ar-C), 137.58 (Ar-C), 137.77 (Ar-C), 138.05 (Ar-C), 139.12 (Ar-C), 147.12 (Ar-C), 149.80 (N–C=), 159.95 (C=N–N), 166.73 (N–C=N); anal. calcd for $C_{25}H_{19}N_5O_3S$ (469.52): C, 63.95; H, 4.08; N, 14.92; found: C, 63.90; H, 4.12; N, 14.87.

(Z)-2-((E)-((1H-indol-3-yl)methylene)hydrazono)-4-(4-chlorophenyl)-3-phenyl-2,3-dihydrothiazole (8g). Yield 79%; m.p. >300 °C; IR ν_{max} (cm^{-1}): 3156 (N–H), 3029 (Ar-H), 1604 (C=N), 1577, 1506 (Ar-C=C); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ ppm: 6.65 (s, 1H, CH–S), 7.18–7.21 (m, 4H, Ar-H), 7.28–7.32 (m, 5H, Ar-H), 7.37–7.46 (m, 3H, CH=N, Ar-H), 7.68 (d, 1H, J = 2.8 Hz, Ar-H), 8.27–8.30 (m, 1H, Ar-H), 8.36 (s, 1H, indole CH), 11.52 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 102.47 (S-CH=), 112.31 (Ar-C), 113.00 (Ar-C), 120.93 (Ar-C), 122.53 (Ar-C), 122.96 (Ar-C), 124.95 (Ar-C), 128.18 (Ar-C), 128.78 (Ar-C), 129.15 (Ar-C), 129.40 (Ar-C), 130.28 (Ar-C), 130.34 (Ar-C), 130.72 (Ar-C), 133.39 (Ar-C), 137.57 (Ar-C), 138.22 (Ar-C), 138.73 (N–C=), 149.25 (C=N–N), 167.12 (N–C=N); anal. calcd for $C_{24}H_{17}ClN_4S$ (428.94): C, 67.20; H, 3.99; N, 13.06; found: C, 67.27; H, 3.92; N, 13.14.

(Z)-2-((E)-((1H-indol-3-yl)methylene)hydrazono)-3-benzyl-4-(4-chlorophenyl)-2,3-dihydrothiazole (8h). Yield 86%; m.p. 206–208 °C; IR ν_{max} (cm^{-1}): 3414 (N–H), 3008 (Ar-H), 1607 (C=N), 1564, 1520 (Ar-C=C); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ ppm: 5.03 (s, 2H, –CH$_2$–), 6.41 (s, 1H, CH–S), 7.01 (d, 2H, J = 7.2 Hz, Ar-H), 7.15–7.27 (m, 5H, Ar-H), 7.35–7.46 (m, 5H, CH=N, Ar-H), 7.70 (d, 1H, J = 2.8 Hz, Ar-H), 8.28 (d, 1H, J = 6.8 Hz, Ar-H), 8.43 (s,

1H, indole CH), 11.50 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 48.54 (CH$_2$), 101.10 (S-CH=), 112.29 (Ar-C), 113.10 (Ar-C), 120.86 (Ar-C), 122.55 (Ar-C), 122.93 (Ar-C), 124.97 (Ar-C), 126.56 (Ar-C), 126.81 (Ar-C), 127.57 (Ar-C), 128.95 (Ar-C), 129.19 (Ar-C), 129.29 (Ar-C), 130.11 (Ar-C), 130.87 (Ar-C), 134.31 (Ar-C), 137.60 (Ar-C), 139.39 (N–C=), 148.52 (C=N–N), 166.94 (N–C=N); anal. calcd for $C_{25}H_{19}ClN_4S$ (442.96): C, 67.79; H, 4.32; N, 12.65; found; C, 67.86; H, 4.36; N, 12.72.

(Z)-2-((E)-((1H-indol-3-yl)methylene)hydrazono)-4-(4-chlorophenyl)-3-(4-fluorophenyl)-2,3-dihydrothiazole (8i). Yield 78%; m.p. 256–258 °C; IR ν_{max} (cm^{-1}): 3444 (N–H), 3029 (Ar-H), 1607 (C=N), 1561, 1498 (Ar-C=C); ^{1}H-NMR (Acetone + DMSO-d_6, 400 MHz) δ ppm: 6.65 (s, 1H, CH–S), 7.17–7.25 (m, 6H, Ar-H), 7.33–7.37 (m, 4H, Ar-H, CH=N), 7.45 (dd, 1H, J = 1.6 Hz, 6.8 Hz, Ar-H), 7.69 (d, 1H, J = 2.8 Hz, Ar-H), 8.26–8.28 (m, 1H, Ar-H), 8.36 (s, 1H, indole CH), 11.53 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 102.36 (S-CH=), 112.32 (Ar-C), 112.96 (Ar-C), 116.18 (Ar-C), 116.40 (Ar-C), 120.94 (Ar-C), 122.51 (Ar-C), 122.97 (Ar-C), 124.93 (Ar-C), 128.86 (Ar-C), 130.15 (Ar-C), 130.42 (Ar-C), 130.80 (Ar-C), 131.28 (Ar-C), 131.37 (Ar-C), 133.52 (Ar-C), 137.56 (Ar-C), 138.62 (N–C=), 149.37 (C=N–N), 167.11 (N–C=N); anal. calcd for $C_{24}H_{16}ClFN_4S$ (446.93): C, 64.50; H, 3.61; N, 12.54; found: C, 64.58; H, 3.58; N, 12.57.

(Z)-2-((E)-((1H-indol-3-yl)methylene)hydrazono)-4-(4-chlorophenyl)-3-(2,6-dimethyl phenyl)-2,3-dihydrothiazole (8j). Yield 86%; m.p. 270–272 °C; IR ν_{max} (cm^{-1}): 3392 (N–H), 3048 (Ar-H), 1607 (C=N), 1565, 1503 (Ar-C=C); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ ppm: 2.11 (s, 6H, 2×CH$_3$-Ar), 6.72 (s, 1H, CH–S), 7.11–7.13 (m, 4H, Ar-H), 7.16–7.20 (m, 3H, Ar-H), 7.29–7.31 (m, 2H, Ar-H, CH=N), 7.44 (d, 1H, J = 6.8 Hz, Ar-H), 7.65 (d, 1H, J = 2.8 Hz, Ar-H), 8.25–8.28 (m, 1H, Ar-H), 8.30 (s, 1H, indole CH), 11.50 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm: 18.25 (2×CH$_3$-Ar), 101.92 (S-CH=), 112.24 (Ar-C), 112.95 (Ar-C), 120.87 (Ar-C), 122.47 (Ar-C), 123.04 (Ar-C), 124.89 (Ar-C), 128.87 (Ar-C), 129.24 (Ar-C), 129.46 (Ar-C), 129.88 (Ar-C), 130.59 (Ar-C), 130.64 (Ar-C), 133.72 (Ar-C), 136.69 (Ar-C), 137.55 (Ar-C), 137.63 (Ar-C), 138.65 (N–C=), 149.01 (C=N–N), 165.34 (N–C=N); anal. calcd for $C_{26}H_{21}ClN_4S$ (456.99): C, 68.33; H, 4.63; N, 12.26; found: C, 68.41; H, 4.66; N, 12.31.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgements

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