



## Original article

# Synthesis and biological evaluation of some new pyrazoline substituted benzenesulfonylurea/thiourea derivatives as anti-hyperglycaemic agents and aldose reductase inhibitors



Syed Ovais<sup>a</sup>, H. Pushpalatha<sup>b</sup>, G. Bhanuprakash Reddy<sup>b</sup>, Pooja Rathore<sup>a</sup>, Rafia Bashir<sup>a</sup>, Shafiya Yaseen<sup>a</sup>, Alhamza Dheyaa<sup>a</sup>, Raed Yaseen<sup>a</sup>, Omprakash Tanwar<sup>c</sup>, Mymoon Akthar<sup>c</sup>, Mohammed Samim<sup>a</sup>, Kalim Javed<sup>a,\*</sup>

<sup>a</sup> Department of Chemistry, Faculty of Science, Jamia Hamdard (Hamdard University), New Delhi 110 062, India

<sup>b</sup> Biochemistry Division, National Institute of Nutrition, Hyderabad, India

<sup>c</sup> Drug Design and Medicinal Chemistry Lab, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard (Hamdard University), New Delhi, India

## ARTICLE INFO

## Article history:

Received 24 December 2013

Received in revised form

6 March 2014

Accepted 14 April 2014

Available online 15 April 2014

## Keywords:

Benzenesulfonylurea/thiourea

Docking

Aldose reductase inhibition

NADPH

Anti-hyperglycaemic

Anti-diabetic

## ABSTRACT

Seventeen new pyrazoline substituted benzenesulfonylurea/thiourea derivatives (**2a–q**) were synthesized and characterized by elemental analysis and various spectroscopic techniques viz; IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, and MS data. Thirteen compounds showed moderate to good anti-hyperglycaemic activity in glucose fed hyperglycaemic normal rats at the dose of 0.05 mM/kg b.w. On the basis of docking results nine compounds (**2a**, **2c**, **2e**, **2h**, **2k**, **2l**, **2n**, **2o** and **2q**) were evaluated for their ability to inhibit rat lens aldose reductase. Out of these six compounds (**2h**, **2k**, **2l**, **2n**, **2o** and **2q**) were found more effective than the known ARI sorbinil. Five compounds (**2h**, **2k**, **2l**, **2n** and **2o**) showed significant dual action (anti-hyperglycaemic and aldose reductase inhibition).

© 2014 Elsevier Masson SAS. All rights reserved.

## 1. Introduction

Diabetes mellitus (DM) is one of the most daunting challenges posed by chronic diseases across the world and number of patients is on rise. In 2011 there were 366 million people with diabetes globally, and this is expected to rise to 552 million by 2030 [1]. Most people with diabetes live in low- and middle-income countries like India, and the numbers will increase drastically in next few years [1]. The recently published ICMR-INDIAB national study reported that there are 62.4 million people with type 2 diabetes (T2DM) and 77 million people with pre-diabetes in India [2]. These numbers are projected to increase to 101 million by the year 2030 [1]. T2DM is the most common form of diabetes and has been found 90% of all diabetes [3]. It is a debilitating disease characterized by

hyperglycaemia due to insulin resistance in liver and peripheral tissues. It also occurs due to the high caloric intake, sedentary life styles and lack of exercise. Patients with diabetes mellitus are at high risk for developing long term complications including neuropathy, nephropathy, retinopathy and cataract [4,5]. Although strict glycemic control is expected to prevent diabetic complications but perfect glycemic control is not always possible.

Aldose reductase (AR), the key enzyme of the polyol pathway, has been demonstrated to play important roles in the pathogenesis of the diabetic complications such as neuropathy, nephropathy, retinopathy and cataract [4,5]. In hyperglycaemic conditions, aldose reductase catalyzes an NADPH-dependent reduction of glucose to sorbitol, which in turn is oxidised to fructose by an NAD<sup>+</sup>-dependent sorbitol dehydrogenase (Fig. 1). Once sorbitol is accumulated inside the cells, it cannot diffuse easily across the cell membrane as a result osmotic pressure increases causing cellular damage. Moreover depletion of NADPH and NAD<sup>+</sup> cofactors compromises body's anti-oxidant defence system. In addition, high blood levels of fructose may account for increased glycation and accelerating

\* Corresponding author.

E-mail addresses: [kjaved@jamiahamdard.ac.in](mailto:kjaved@jamiahamdard.ac.in), [kjavedchem@yahoo.co.in](mailto:kjavedchem@yahoo.co.in) (K. Javed).

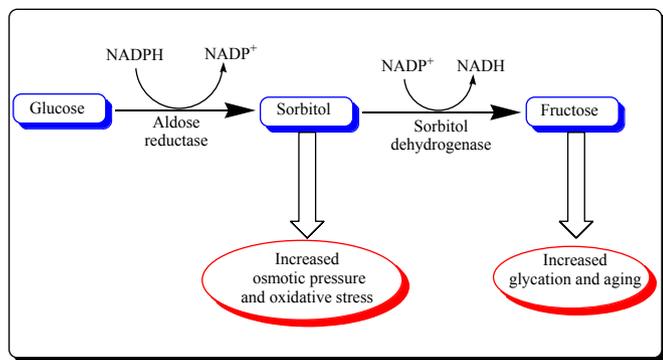


Fig. 1. Schematic diagram for polyol pathway and its side effects.

ageing [6,7] (Fig. 1). Thus inhibition of AR is one of the important targets and its inhibition could be the key for the treatment of many diabetic complications [8]. Aldose reductase inhibitors (ARIs) have been shown to reduce tissue sorbitol accumulation in diabetic

animals [9] and there are evidences that blockage of AR can have beneficial effect in diabetic complications [10,11].

Variety of structurally different compounds have been identified as potent *in vitro* ARIs and a number of them are in clinical trials to test their efficacy in the prevention and treatment of peripheral neuropathy in diabetes [5,12]. They can be classified into various groups based on their structures: acetic acid derivatives (e.g. epalrestat, Imirestat), cyclic imides (especially spirohydantoin, e.g. sorbinil, fidarestat) (Fig. 2) etc. Despite being structurally different, all ARIs possess two peculiar pharmacophoric elements: i) an acidic moiety which is able to interact with the “anion-binding site” of the catalytic site, and ii) a lipophilic scaffold which can bind to the highly flexible specificity pocket of the catalytic site [13]. Our interest in studying the molecular determinants for binding to the aldose reductase inhibitor site led us to study the aldose reductase inhibitory activity of target compounds possessing benzenesulfonylurea/thiourea as carboxylic acid surrogates. Besides this benzenesulfoamide derivatives have been already reported as ARI [14,15]. The SO<sub>2</sub> group of the benzenesulfonamide forms the hydrogen bond with the amino acid residues of the anionic binding site of the AR enzyme [16].

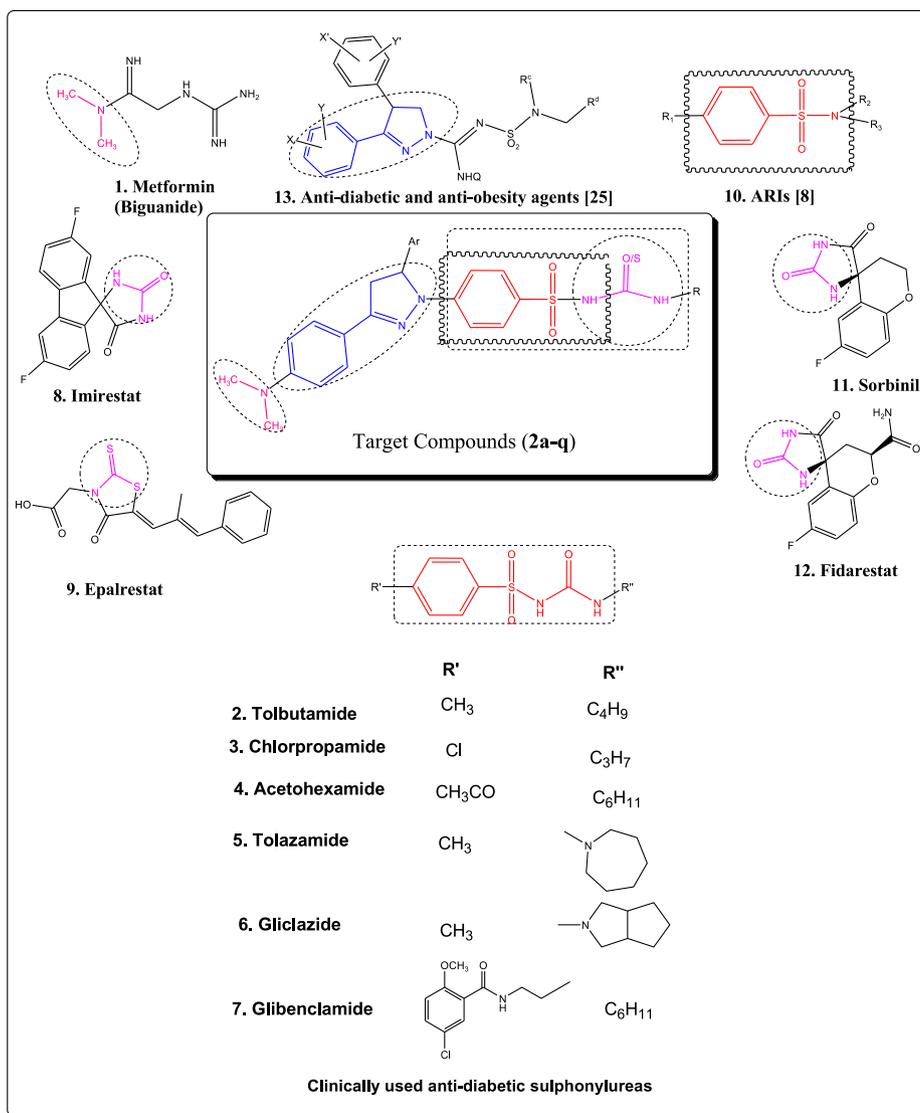


Fig. 2. Structure of anti-diabetic drugs (1–7), ARIs (8–12) and pyrazoline derivatives patented as anti-diabetic and anti-obesity agents (13). Rationally designed template for targeted compound (2a–q).

In curing diabetes sulfonylureas and biguanides have represented the backbone of oral therapy in non-insulin dependent diabetes mellitus (NIDDM) for more than 30 years [17]. An NIDDM patient is characterized by a low response in insulin secretion toward increased blood glucose levels. Sulfonylureas directly interact with the  $\beta$ -cells of Langerhans islets which results in increased insulin secretion [18]. However, the main side effect of the sulfonylurea therapy is weight gain [19,20].

Pyrazolines are well known and important nitrogen containing five membered heterocyclic compounds. Pyrazolines have been reported to show a wide range of biological activities like anti-inflammatory, anti-cancer, anti-microbial etc [21]. Apart from these biological activities pyrazoline derivatives have been reported to possess anti-diabetic [22–24] and anti-obesity activities [25,26].

In the view of the above fact, we report the synthesis of new pyrazoline substituted benzenesulfonylurea/thiourea derivatives (**2a–q**) incorporating with known bioactive moieties highlighted in Fig. 2. In the context to increase the efficacy we have introduced variety of diaryl substituted pyrazoline moiety at *para* position of benzenesulphonamide and variety of substitutions (benzyl, butyl and cyclohexyl groups) were made at  $N^2$  position of the uriedoi/

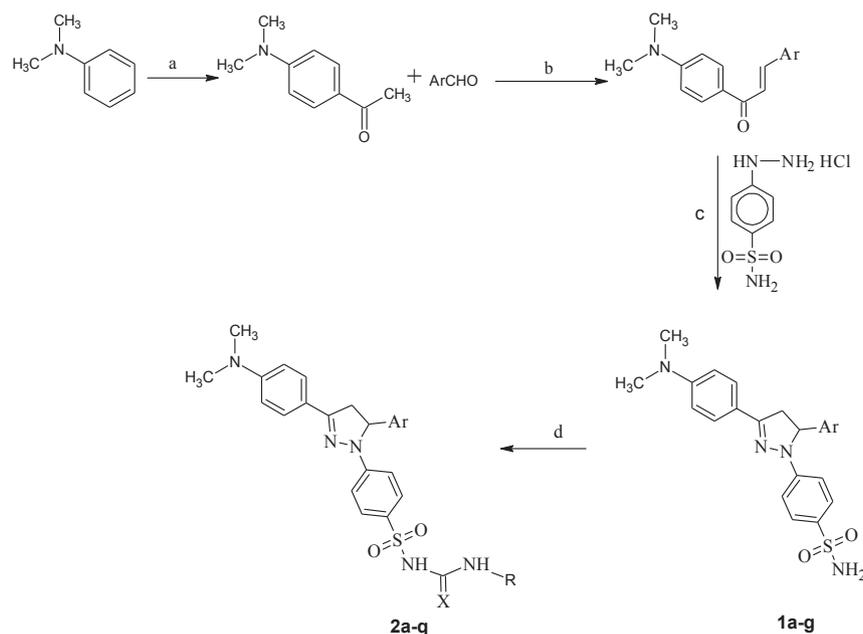
thioureido group, keeping the core structure intact (Fig. 2). These compounds (**2a–q**) were evaluated for anti-hyperglycaemic effects in glucose fed hyperglycaemic normal rats. In silico molecular docking studies of these compounds (**2a–q**) were performed with respect to aldose reductase. Compounds showing good docking results were evaluated for their ability to inhibit rat lens aldose reductase.

## 2. Chemistry

The targeted compounds (**2a–q**) were synthesised by condensing appropriate pyrazoline bearing benzenesulphonamide with appropriate isocyanate or isothiocyanate by refluxing in acetone containing dry  $K_2CO_3$  (Scheme 1). The pyrazoline substituted benzenesulphonamides (**1a–g**) were synthesized through reported method [27].

## 3. Pharmacology

Newly synthesised compounds (**2a–q**) were evaluated for anti-hyperglycaemic effects at the dose of 0.05 mM/kg b.w. in glucose-fed hyperglycaemic normal rats [28]. The marketed sulfonylurea drug gliclazide was used as positive control. Docking studies were



2a: Ar = Phenyl, X = O, R =  $C_6H_5-CH_2-$

2c: Ar = 4-Methoxyphenyl, X = O, R =  $C_6H_5-CH_2-$

2e: Ar = 2-Chlorophenyl, X = O, R =  $C_6H_5-CH_2-$

2g: Ar = 3,4,5-Trimethoxyphenyl, X = O, R =  $C_6H_5-CH_2-$

2i: Ar = 4-Chlorophenyl, X=S, R =  $C_6H_5-CH_2-$

2k: Ar = 4-Methylphenyl, X=S, R =  $C_6H_5-CH_2-$

2m: Ar = 3,4,5-Trimethoxyphenyl, X=S, R =  $C_6H_5-CH_2-$

2o: Ar = 4-Chlorophenyl, X=S, R =  $C_4H_9-$

2q: Ar = Phenyl, X=S, R =  $C_6H_{11}-$

2b: Ar = 4-Chlorophenyl, X = O, R =  $C_6H_5-CH_2-$

2d: Ar = 4-Methylphenyl, X = O, R =  $C_6H_5-CH_2-$

2f: Ar = 3,4-Dimethoxyphenyl, X = O, R =  $C_6H_5-CH_2-$

2h: Ar = Phenyl, X=S, R =  $C_6H_5-CH_2-$

2j: 4-Methoxyphenyl, X=S, R =  $C_6H_5-CH_2-$

2l: Ar = 2-Chlorophenyl, X=S, R =  $C_6H_5-CH_2-$

2n: Ar = Phenyl, X=S, R =  $C_4H_9-$

2p: Ar = 4-Methoxyphenyl, X=S, R =  $C_4H_9-$

**Scheme 1.** Synthesis of pyrazoline based benzenesulfonylurea/thiourea derivatives (**2a–q**). Reagents and conditions: (a)  $CH_3COCl$ ,  $CH_2Cl_2$ ,  $AlCl_3$ ; (b) Claisen–Schmidt Reaction,  $NaOH$ ; (c) Absolute alcohol, Reflux 12–18 h; (d) Appropriate isocyanate and isothiocyanate,  $K_2CO_3$ , dry acetone, reflux 24–72 h.

performed by using Glide module of the Schrodinger-9 software in order to get better comprehension of the aldose reductase inhibitory potency of the newly synthesised compounds (**2a–q**) at molecular level. On the basis of the docking studies nine synthesized compounds (three benzenesulfonylurea **2a**, **2c**, **2e** and six benzenesulfonylthiourea **2h**, **2k**, **2l**, **2n**, **2o**, **2q**) were evaluated *in vitro* for their ability to inhibit activity of partially purified rat lens aldose reductase (AR) [29]. Their effectiveness was evaluated with respect to known ARI sorbinil.

## 4. Result and discussion

### 4.1. Chemistry

The structure of newly synthesised benzenesulfonylurea/thiourea derivatives (**2a–q**) were determined on the basis of elemental analysis and various spectroscopic methods such as IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR and MS. Elemental analysis (C, H, N and S) data were within  $\pm 0.5\%$  of the theoretical values. All the peaks corresponding to IR, <sup>1</sup>H NMR and <sup>13</sup>C NMR were observed at expected positions in respective spectra (for details see experimental section).

### 4.2. Pharmacology

#### 4.2.1. Blood glucose lowering effect

In the present study, oral anti-hyperglycaemic effects of seventeen compounds (**2a–q**) were assessed in glucose-fed hyperglycaemic normal rats at the dose of 0.05 mM/kg b.w. The marketed sulfonylurea drug gliclazide at the dose 0.05 mM/kg b.w. was used as positive control. The results are summarized in Table 1. Quantitative glucose tolerance of each animal was calculated by area under curve (AUC) method by using prism software. Comparing AUC of experimental and control groups determined the percentage anti-hyperglycaemic activity. Statistical comparison was made by Dunnett's test. Samples showing significant inhibition ( $p < 0.05$ ) on postprandial hyperglycaemia (AUC) were considered as active samples. Thirteen compounds showed moderate to good activity in the range of 10–29.3%. Compounds **2g** and **2m** showed anti-hyperglycaemic activity comparable to the standard drug gliclazide.

With relation to SAR we observed that introduction of chlorine atom at C-4/C-2 position of 5-phenyl ring of pyrazoline decreases

the activity (**2b** vs **2a**, **2e** vs **2a**, **2i** vs **2h** and **2l** vs **2h**). Similarly introduction of methyl group at C-4 position of 5-phenyl ring of pyrazoline decreases the activity (**2d** vs **2a** and **2k** vs **2h**). It is interesting to note that in case of benzenesulfonylurea derivatives increase in the number of methoxyl groups on 5-phenyl ring of pyrazoline increases the activity (**2c** vs **2a**, **2f** vs **2c**, **2g** vs **2f**). **2i** and **2j** derivatives consisting benzyl unit at thiourea group were found less effective than corresponding **2o** and **2p** derivatives having butyl chain (Table 1). No SAR could be developed when benzenesulfonylurea derivatives were compared to their corresponding benzenesulfonylthiourea derivatives.

As the compounds evaluated for the anti-hyperglycaemic activity have structural resemblances with the clinically used sulfonylureas based anti-diabetic drugs. Therefore, it may be assumed that compounds (**2a–q**) interact with the receptors which exist on the ATP-sensitive K<sup>+</sup> channel on the pancreatic  $\beta$ -cell membrane surface. This interaction inhibits K<sup>+</sup> efflux, causing membrane depolarization followed by an increase in Ca<sup>2+</sup> influx through voltage-dependent Ca<sup>2+</sup> channels. The increase in cytoplasmic Ca<sup>2+</sup> concentration eventually triggers insulin secretion from pancreatic islets. However this needs further exploration.

#### 4.2.2. Docking

Docking studies of the newly synthesised compounds (**2a–q**) were performed in order to get better comprehension of the aldose reductase inhibitory potency at molecular level and to shed light on the interactions in the active site of aldose reductase. Docking studies were performed using Glide module of the Schrodinger-9 software on the falcipain-2 receptor (PDB id: 1EL3, 1USO, 2FZD, 2PDK). The most relevant poses were obtained with PDB id: 1EL3 and 1USO. However, the docking studies were performed with PDB id: 1E13 because this structure is bound with IDD384, which is a sulphonamide derivative and is relevant with our study. The re-docking of reference ligand (IDD384) into active site of ALR2 reveals that it occupies the same binding pocket with root mean square deviation (RMSD) of 0.56 Å which further validates the present docking protocol (Fig. 3A and B). Docking results reveal that the compounds **2o** and **2q** bound tightly in the active site of aldose reductase (ALR2). These compounds (**2o** and **2q**) well occupied in the receptor cavity and forms hydrogen bonds and hydrophobic interactions (Fig. 3C and D). The sulphonamide group of **2o** and **2q** is anchored into the anion binding site formed by Tyr48, His110 and Trp111 and forms hydrogen-bonding with Trp111, which is key residue in binding and catalysis [30,31]. The pyrazoline ring core gets tightly trapped in the hydrophobic pocket formed by Phe122, Leu300, Leu301, Trp219, and Trp295. The 3-phenyl ring of pyrazoline ring forms  $\pi$  interaction with Trp219. In addition to these interactions, the aliphatic side chain (**2o**) and cyclohexyl ring (**2q**) also show some important interaction as they area ligand into the small hydrophobic pocket formed by Val47, Tyr48, Trp20, Trp219, Pro218 and Phe122.

The binding pose of compound **2a** (Fig. 3E) reveals why it is inactive. It does not fit well in the receptor binding site and does not show hydrogen bonding like **2o** and **2q**. This may be explained on the basis that the sulphonamide attached to the thiourea moiety attains more planar structure than sulphonamide attached to the urea moiety. Moreover, all other groups attached to the pyrazoline ring show different poses when compared to the **2o** and **2q** (Fig. 3F). Therefore it misses all the important interactions required for ALR2 inhibition. The fact is also validated by Fig. 3F, where **2a** was superimposed on **2o** and it is clear that compound **2o** has more relaxed conformation that compound **2a**.

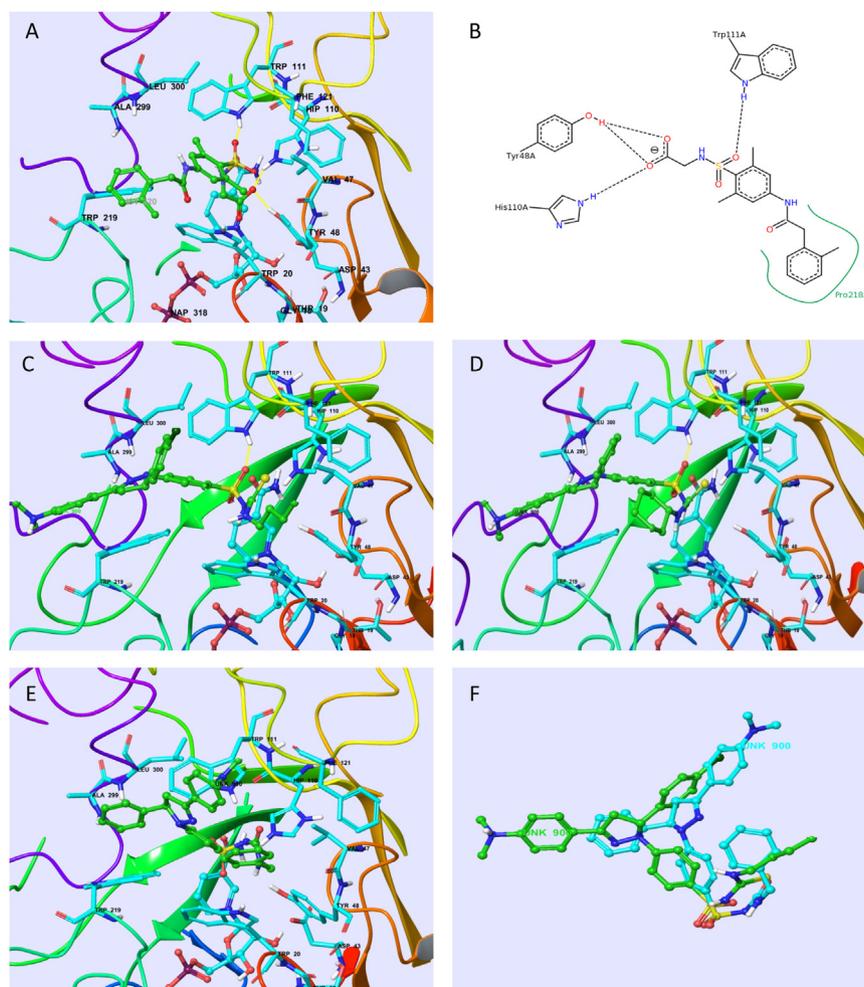
#### 4.2.3. Aldose reductase inhibition

Nine synthesized compounds (three benzenesulfonylurea **2a**, **2c**, **2e** and six benzenesulfonylthiourea **2h**, **2k**, **2l**, **2n**, **2o**, **2q**) were

**Table 1**

Effect of pyrazolines based benzenesulfonylurea/thiourea (0.05 mM/kg) on blood glucose levels in glucose (3 g/kg) fed normal hyperglycaemic rats.

Group no.	Treatment (0.05 mmol/kg)	% Activity	Significance
I	Control	0.0	–
II	Gliclazide	25.4	$P < 0.05$
III	<b>2a</b>	15.5	$P < 0.05$
IV	<b>2b</b>	6.7	$P > 0.05$
V	<b>2c</b>	17.5	$P < 0.02$
VI	<b>2d</b>	12.0	$P < 0.05$
VII	<b>2e</b>	4.7	$P > 0.05$
VIII	<b>2f</b>	18.0	$P < 0.05$
IX	<b>2g</b>	29.3	$P < 0.02$
X	<b>2h</b>	24.2	$P < 0.05$
XI	<b>2i</b>	4.2	$P > 0.05$
XII	<b>2j</b>	11.7	$P < 0.05$
XIII	<b>2k</b>	21.7	$P < 0.05$
XIV	<b>2l</b>	15.3	$P < 0.05$
XV	<b>2m</b>	28.6	$P < 0.05$
XVI	<b>2n</b>	10.5	$P < 0.02$
XVII	<b>2o</b>	18.9	$P < 0.05$
XVIII	<b>2p</b>	17.2	$P < 0.05$
XIX	<b>2q</b>	2.7	$P > 0.05$



**Fig. 3.** Ligands are shown as ball and stick (carbon as green, oxygen as red, sulphur as yellow and nitrogen as blue), Hydrogen bonding shown as yellow lines, (A, B): Crystal pose of IDD384 and Ligplot picture of IDD384 obtained from Protein databank, (C–E): Docking pose of compounds **2o**, **2q** and **2a**, (F): Superimposed pose of **2a** (carbon as ice blue) and **2o** (carbon as green). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

evaluated *in vitro* for their ability to inhibit activity of partially purified rat lens aldose reductase (AR). It has been shown that there is an approximately 85% sequence similarity between rat lens and human aldose reductase (ALR2), while the proposed active sites of both enzymes are identical [32]. The performed assay was based on a spectrometric measurement, which is proven to be a reliable method [33], with DL-glyceraldehyde as the substrate and NADPH as the cofactor. Sorbinil, a known ARI was used as a positive control. Results are presented in Table 2.

Benzenesulfonylthiourea derivatives (**2h**, **2k**, **2l**, **2n**, **2o** and **2q**) displayed good activity with  $IC_{50}$  ranging from 0.0178 to 0.090  $\mu$ M (Table 2). These compounds were found more effective than the known ARI sorbinil. Among these benzenesulfonylthiourea derivatives compounds **2o** showed maximum inhibition with the  $IC_{50}$  values equal to 0.0175  $\mu$ M followed by **2q**, **2n**, **2k**, **2l**, and **2h** with 0.0175, 0.0430, 0.0699, 0.0850 and 0.0901  $\mu$ M, respectively. With regard to SAR of benzenesulfonylthiourea derivatives we observed that replacement of benzyl group by butyl chain or cyclohexyl ring at thiouredio group increased the activity (**2h** vs **2n** and **2q**).

Interestingly benzenesulfonylurea derivatives (**2a**, **2c** and **2e**) did not show ARI activity at all. This may be attributed to the wrong pose due to which they do not fit well in the receptor binding site.

**Table 2**  
Aldose reductase (AR) inhibitory activity data.

Treatment	$IC_{50}$ ( $\mu$ M) <sup>a</sup>
<b>2a</b>	n.a. <sup>b</sup>
<b>2c</b>	n.a.
<b>2e</b>	n.a.
<b>2h</b>	0.0901
<b>2k</b>	0.0699
<b>2l</b>	0.0850
<b>2n</b>	0.0430
<b>2o</b>	0.0175
<b>2q</b>	0.0178
Sorbinil	8

<sup>a</sup>  $IC_{50}$  values, represent the concentration required to produce 50% enzyme inhibition.

<sup>b</sup> n.a.: not active.

## 5. Conclusion

In the present study seventeen novel pyrazoline substituted benzenesulfonylurea/thiourea derivatives (**2a–q**) were synthesized. The synthesized compounds are well supported by the spectroscopic data and elemental analysis. Thirteen compounds

showed moderate to good anti-hyperglycaemic activity in glucose fed hyperglycaemic normal rats at the dose of 0.05 mM/kg b.w. ranging from 10 to 29.3%. Two compounds **2g** and **2m** showed anti-hyperglycaemic activity comparable to the standard drug gliclazide. On the basis of docking results nine compounds (**2a**, **2c**, **2e**, **2h**, **2k**, **2l**, **2n**, **2o** and **2q**) were selected for evaluating their ability to inhibit rat lens AR. Out of these six compounds (**2h**, **2k**, **2l**, **2n**, **2o** and **2q**) were found more effective than the known ARI sorbinil. Five compounds (**2h**, **2k**, **2l**, **2n** and **2o**) showed significant dual action (anti-hyperglycaemic and aldose reductase inhibition).

## 6. Experimental

### 6.1. Chemistry

Melting points were determined by open capillary tubes and are uncorrected. Purity of the compounds was checked on TLC plates (silica gel G) which were visualized by exposing to iodine vapours. Infrared (IR) spectra were recorded (in KBr) on a BIO-RAD FTS-135 spectrophotometer and <sup>1</sup>H NMR spectra were recorded on a Bruker Spectrospin DPX 200–400 MHz spectrometer using deuterated DMSO as solvent and tetramethyl silane (TMS) as an internal standard. Chemical shifts are given in  $\delta$  (ppm) scale and coupling constants (J values) are expressed in Hz. Mass spectra (MS) were recorded on MALDI-TOF. Elemental analysis was carried out on CHNS Elementar (Vario EL III).

#### 6.1.1. General procedure for synthesis of sulfonylureas (**2a–q**)

A solution of appropriate pyrazoline (1 mmol) in dry acetone was refluxed over anhydrous K<sub>2</sub>CO<sub>3</sub> (2 mmol) for 1–1.5 h. At this temperature, a solution of the appropriate isocyanate or isothiocyanate (1.2 mmol) in dry acetone 5 ml was added in a drop wise manner. It was refluxed for 24–72 h. Acetone was removed under reduced pressure. The solid residue thus obtained was suspended in water and acidified with acetic acid. It was stirred for 30 min and filtered. The residue was washed with plenty of distilled water in order to make the residue free from potassium acetate. It was dried and crystallized from methanol.

**6.1.1.1. N-(benzylcarbamoyl)-4-(3-(4-(dimethylamino)phenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (2a).** Orange crystals; yield = 41%; m.p. 209–210 °C; *R*<sub>f</sub> = 0.85 (toluene:ethyl acetate:formic acid, 5:4:1); IR<sub>max</sub> (KBr, in cm<sup>-1</sup>): 3337, 3034 and 2909 (NH–CO–NH), 1712 and 1530 (C=O of urea), 1593 (C=N), 1329 and 1160 (SO<sub>2</sub>N); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>,  $\delta$ ): 2.96 [6H, s, N(CH<sub>3</sub>)<sub>2</sub>], 3.09 [1H, dd, *J* = 4.2 Hz, *J* = 11.7 Hz H-*trans* (pyrazoline)], 3.91 [1H, dd, *J* = 8.7 Hz, *J* = 12.6 Hz, H-4 *cis* (pyrazoline)], 4.10 (2H, m, –CH<sub>2</sub>–Phenyl), 4.38 [1H, dd, *J* = 3.9 Hz, *J* = 8.7 Hz, H-5 (pyrazoline)], 6.58 (1H, brs, CONH), 6.75 (2H, d, *J* = 6.6 Hz, H-3', H-5'), 6.93 (2H, d, *J* = 5.7 Hz, H-3'', H-5''), 7.13–7.36 (11H, m, phenyl, benzyl protons and SO<sub>2</sub>NH), 7.54 (2H, d, *J* = 5.7 Hz, H-2'', H-6''), 7.61 (2H, d, *J* = 6.3 Hz, H-2', H-6'); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>,  $\delta$ ): 43.42 (CH<sub>2</sub>NH), 66.94 (C-5 pyrazoline), 151.4 (C-3 pyrazoline), 156.40 (C=O); MALDI (*m/z*): 553 [M<sup>+</sup>], 552 [M–1]; CHNS Analysis for C<sub>31</sub>H<sub>31</sub>N<sub>5</sub>O<sub>3</sub>S Found (Calculated): C: 67.21 (67.25), H: 5.66 (5.64), N: 12.66 (12.65), S: 5.81 (5.79).

**6.1.1.2. N-(benzylcarbamoyl)-4-(5-(4-(chlorophenyl)-3-(4-(dimethylamino)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (2b).** Light yellow crystals; yield = 38%; m.p. 196–197 °C; *R*<sub>f</sub> = 0.78 (toluene:ethyl acetate:formic acid, 5:4:1); IR<sub>max</sub> (KBr, in cm<sup>-1</sup>): 3365, 3026 and 2913 (NH–CO–NH), 1692 and 1505 (C=O of urea), 1593 (C=N), 1337 and 1151 (SO<sub>2</sub>N); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>,  $\delta$ ): 2.96 [6H, s, N(CH<sub>3</sub>)<sub>2</sub>], 3.09 [1H, dd, *J* = 5.2 Hz, *J* = 17.2 Hz, H-*trans* (pyrazoline)], 3.42 (1H, brs, CONH), 3.89 [1H, dd, *J* = 12.4 Hz,

17.6 Hz, H-4 *cis* (pyrazoline)], 4.09–4.11 (2H, m, –CH<sub>2</sub>–Phenyl), 5.52 [1H, dd, *J* = 4.8 Hz, *J* = 11.6 Hz, H-5 (pyrazoline)], 6.68 (1H, brs, SO<sub>2</sub>NH), 6.71 (2H, d, *J* = 8.8 Hz, H-3', H-5'), 6.92 (2H, d, *J* = 8.0 Hz, H-2'', H-6''), 7.13–7.20 (5H, m, H-3'', H-4'', H-5'', H-2'', H-6''), 7.41 (2H, d, *J* = 8.0 Hz, H-2, H-6), 7.55 (2H, d, *J* = 8.0 Hz, H-3'', H-5''), 7.60 (2H, d, *J* = 8.4 Hz, H-2', H-6'); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>,  $\delta$ ): 43.65 (CH<sub>2</sub>NH), 66.90 (C-5 pyrazoline), 151.62 (C-3 pyrazoline), 153.35 (C=O); MALDI (*m/z*): 588 [M<sup>+</sup>], 589 [M+1], 590 [M+2], 586 [M–2]; CHNS Analysis for C<sub>31</sub>H<sub>30</sub>ClN<sub>5</sub>O<sub>3</sub>S Found (Calculated) C: 63.33 (63.31), H: 5.71 (5.14), N: 11.89 (11.91), S: 5.46 (5.45).

**6.1.1.3. N-(benzylcarbamoyl)-4-(3-(4-(dimethylamino)phenyl)-5-(methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (2c).** Light yellow crystals; yield = 51%; m.p. 197–198 °C; *R*<sub>f</sub> = 0.70 (toluene:ethyl acetate:formic acid, 5:4:1); IR<sub>max</sub> (KBr, in cm<sup>-1</sup>): 3348, 3030 and 2934 (NH–CO–NH), 1692 and 1507 (C=O of urea), 1592 (C=N), 1336 and 1151 (SO<sub>2</sub>N); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>,  $\delta$ ): 2.97 [6H, s, N(CH<sub>3</sub>)<sub>2</sub>], 3.09 [1H, dd, *J* = 4.4 Hz, *J* = 17.6 Hz H-*trans* (pyrazoline)], 3.71 (3H, s, OCH<sub>3</sub>), 3.89 [1H, dd, *J* = 9.0 Hz, *J* = 17.6 Hz, H-4 *cis* (pyrazoline)], 4.14 (2H, d, *J* = 5.6 Hz –CH<sub>2</sub>–Phenyl), 5.47 [1H, dd, *J* = 4.4 Hz, *J* = 11.6 Hz, H-5 (pyrazoline)], 6.76 (2H, d, *J* = 8.4 Hz, H-3', H-5'), 6.85 (1H, brs, CONH), 6.90 (2H, d, *J* = 8.0 Hz, H-3, H-5), 7.00 (2H, d, *J* = 8.0 Hz, H-2, H-6), 7.11 (2H, d, *J* = 6.8 Hz, H-3'', H-5''), 7.18–7.22 (5H, m, for benzyl protons), 7.59–7.63 (4H, m, H-2', H-6', H-2'', H-6''), 10.44 (1H, brs, SO<sub>2</sub>NH); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>,  $\delta$ ): 42.69 (CH<sub>2</sub>NH), 55.57 (OCH<sub>3</sub> at C-4), 66.39 (C-5 pyrazoline), 151.78 (C-3 pyrazoline), 155.80 (C=O); MALDI (*m/z*): 583 [M<sup>+</sup>], 584 [M+1], 585 [M+2], 582 [M–1]; CHNS Analysis for C<sub>32</sub>H<sub>33</sub>N<sub>5</sub>O<sub>4</sub>S Found (Calculated) C: 65.88 (65.85), H: 5.71 (5.70), N: 11.98 (12.00), S: 5.51 (5.49).

**6.1.1.4. N-(benzylcarbamoyl)-4-(3-(4-(dimethylamino)phenyl)-5-*p*-tolyl-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (2d).** Yellow crystals; yield = 42%; m.p. 217–218 °C; *R*<sub>f</sub> = 0.88 (chloroform:acetone, 8:2); IR<sub>max</sub> (KBr, in cm<sup>-1</sup>): 3321, 3040 and 2968 (NH–CO–NH), 1711 and 1507 (C=O of urea), 1595 (C=N), 1332 and 1159 (SO<sub>2</sub>N); <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>,  $\delta$ ): 2.24 (3H, s, CH<sub>3</sub>), 2.95 [6H, s, N(CH<sub>3</sub>)<sub>2</sub>], 3.07 [1H, dd, *J* = 5.8 Hz, *J* = 14.1 Hz, H-*trans* (pyrazoline)], 3.88 [1H, dd, *J* = 6.9 Hz, *J* = 17.1 Hz, H-4 *cis* (pyrazoline)], 4.05–4.07 (2H, m, –CH<sub>2</sub>–Phenyl), 5.40 [1H, dd, *J* = 4.2 Hz, *J* = 11.6 Hz, H-5 (pyrazoline)], 6.29 (1H, brs, CONH), 6.75 (2H, d, *J* = 8.4 Hz, H-3', H-5'), 6.87 (2H, d, *J* = 8.7 Hz, H-3'', H-5''), 7.00–7.60 (13H, m, H-2', H-6', H-2, H-3, H-4, H-5, H-6, H-2'', H-6'' H-3'', H-4'', H-5'', H-6'' and SO<sub>2</sub>NH); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>,  $\delta$ ): 21.18 (CH<sub>3</sub> at C-4), 43.86 (CH<sub>2</sub>NH), 66.79 (C-5 pyrazoline), 152.09 (C-3 pyrazoline), 154.58 (C=O); MALDI (*m/z*): 567 [M<sup>+</sup>], 568 [M+1], 566 [M–1], 565 [M–2]; CHNS Analysis for C<sub>32</sub>H<sub>33</sub>N<sub>5</sub>O<sub>3</sub>S Found (Calculated) C: 67.72 (67.70), H: 5.88 (5.86), N: 12.33 (12.34), S: 5.64 (5.65).

**6.1.1.5. N-(benzylcarbamoyl)-4-(5-(2-chlorophenyl)-3-(4-(dimethylamino)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (2e).** Light yellow crystals; yield = 51%; m.p. 209–210 °C; *R*<sub>f</sub> = 0.79 (toluene:ethyl acetate:formic acid, 5:4:1); IR<sub>max</sub> (KBr, in cm<sup>-1</sup>): 3346, 3067 and 2984 (NH–CO–NH), 1710 and 1507 (C=O of urea), 1604 (C=N), 1337 and 1161 (SO<sub>2</sub>N); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>,  $\delta$ ): 2.96 [6H, s, N(CH<sub>3</sub>)<sub>2</sub>], 3.07 [1H, dd, *J* = 4.8 Hz, *J* = 17.2 Hz, H-*trans* (pyrazoline)], 3.70–3.72 (1H, m, CONH), 4.01 [1H, dd, *J* = 12.4 Hz, 17.6 Hz, H-4 *cis* (pyrazoline)], 4.11 (2H, d, *J* = 4.4 Hz, –CH<sub>2</sub>–Phenyl), 5.68 [1H, dd, *J* = 4.8 Hz, *J* = 11.6 Hz, H-5 (pyrazoline)], 6.68 (1H, brs, SO<sub>2</sub>NH), 6.74 (2H, d, *J* = 8.4 Hz, H-3', H-5'), 6.84 (2H, d, *J* = 8.0 Hz, H-2'', H-6''), 7.04–7.62 (13H, m, H-2', H-6', H-3'', H-5'', H-3, H-4, H-5, H-6, H-2'', H-3'', H-4'', H-5'', H-6''); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>,  $\delta$ ): 43.78 (CH<sub>2</sub>NH), 68.14 (C-5 pyrazoline), 152.66 (C-3 pyrazoline), 155.86 (C=O). MALDI (*m/z*): 588 [M<sup>+</sup>], 589 [M+1], 590 [M+2], 587

[M–1]; CHNS Analysis for C<sub>31</sub>H<sub>30</sub>ClN<sub>5</sub>O<sub>3</sub>S Found (Calculated) C: 63.33 (63.31), H: 5.17 (5.14), N: 11.93 (11.91), S: 5.48 (5.45).

6.1.1.6. *N*-(benzylcarbamoyl)-4-(3-(4-(dimethylamino)phenyl)-5-(3,4-dimethoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (**2f**). Reddish brown crystals; yield = 31%; m.p. 189–190 °C; *R*<sub>f</sub> = 0.56 (toluene:ethyl acetate:formic acid, 5:4:1); IR<sub>ν</sub><sub>max</sub> (KBr, in cm<sup>-1</sup>): 3334, 3034 and 2999 (NH–CO–NH), 1692 and 1519 (C=O of urea), 1592 (C=N), 1330 and 1152 (SO<sub>2</sub>N); 1H NMR (400 MHz, DMSO-*d*<sub>6</sub>, δ): 2.95 [6H, s, N(CH<sub>3</sub>)<sub>2</sub>], 3.12 [1H, dd, *J* = 12.4 Hz, *J* = 17.6 Hz, H-*trans* (pyrazoline)], 3.15–3.20 (1H, m, CONH), 3.69 (3H, s, OCH<sub>3</sub>), 3.71 (3H, s, OCH<sub>3</sub>), 3.88 [1H, dd, *J* = 8.7 Hz, 13.2 Hz, H-4 *cis* (pyrazoline)], 4.13–4.15 (1H, m, –CH<sub>2</sub>–phenyl), 5.43 [1H, dd, *J* = 3.9 Hz, 8.7 Hz, H-5 (pyrazoline)], 5.75 (1H, brs, SO<sub>2</sub>NH), 6.69–7.23 (12H, m, H-3', H-5', H-2, H-5, H-6, H-3'', H-5'', H-2'', H-3''', H-4'', H-5'', H-6'''), 7.60–7.63 (4H, m, H-2', H-6', H-2'', H-6''); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>, δ): 43.36 (CH<sub>2</sub>NH), 55.72 (OCH<sub>3</sub> at C-3' and C-4'), 68.85 (C-5 pyrazoline), 152.69 (C-3 pyrazoline), 155.72 (C=O); MALDI (*m/z*): 613 [M<sup>+</sup>], 614 [M+1], 612 [M–1]; CHNS Analysis for C<sub>33</sub>H<sub>35</sub>N<sub>5</sub>O<sub>5</sub>S Found (Calculated) C: 64.54 (64.58), H: 5.73 (5.75), N: 11.44 (11.41), S: 5.25 (5.22).

6.1.1.7. *N*-(benzylcarbamoyl)-4-(3-(4-(dimethylamino)phenyl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (**2g**). Brown crystals; yield = 42%; m.p. 130–131 °C; *R*<sub>f</sub> = 0.83 (chloroform:acetone, 9:1); IR<sub>ν</sub><sub>max</sub> (KBr, in cm<sup>-1</sup>): 3339, 3061 and 2930 (NH–CO–NH), 1693 and 1504 (C=O of urea), 1592 (C=N), 1331 and 1151 (SO<sub>2</sub>N); 1H NMR (200 MHz, DMSO-*d*<sub>6</sub>, δ): 2.96 [6H, s, N(CH<sub>3</sub>)<sub>2</sub>], 3.43–3.48 [1H, m, H-*trans* (pyrazoline)], 3.63 (3H, s, OCH<sub>3</sub> at C-4), 3.71 (6H, s, OCH<sub>3</sub> X 2 at C-3 and C-5), 4.41 [1H, dd, *J* = 12.4 Hz, 17.6 Hz, H-4 *cis* (pyrazoline)], 4.60–4.64 (1H, m, –CH<sub>2</sub>–phenyl), 5.01–5.04 [1H, m, H-5 (pyrazoline)], 6.24 (1H, brs, –CONH–), 6.62 (2H, s, H-2, H-6), 6.76 (2H, d, *J* = 8.0 Hz, H-3', H-5'), 6.92–7.50 (7H, m, H-3'', H-5'', H-2'', H-3''', H-4'', H-5'', H-6'''), 7.91 (1H, broad singlet, SO<sub>2</sub>NH); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>, δ): 43.44 (CH<sub>2</sub>NH), 56.17 (OCH<sub>3</sub> at C-3' and C-5'), 60.69 (OCH<sub>3</sub> at C-4'), 64.52 (C-5 pyrazoline), 154.62 (C-3 pyrazoline), 157.55 (C=O); MALDI (*m/z*): 643 [M<sup>+</sup>], 644 [M+1], 645 [M+2], 642 [M–1]. CHNS Analysis for C<sub>34</sub>H<sub>37</sub>N<sub>5</sub>O<sub>6</sub>S Found (Calculated) C: 63.40 (63.43), H: 5.77 (5.79), N: 10.90 (10.88), S: 4.99 (4.98).

6.1.1.8. *N*-(benzylcarbamothioyl)-4-(3-(4-(dimethylamino)phenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (**2h**). Yellow crystals; yield = 56%; m.p. 204–205 °C; *R*<sub>f</sub> = 0.88 (toluene:ethyl acetate:formic acid, 5:4:1); IR<sub>ν</sub><sub>max</sub> (KBr, in cm<sup>-1</sup>): 3323, 3076 and 2948 (NH–CS–NH), 1528 and 1455 (C=S of thiourea), 1592 (C=N), 1328 and 1125 (SO<sub>2</sub>N); 1H NMR (400 MHz, DMSO-*d*<sub>6</sub>, δ): 2.96 [6H, s, N(CH<sub>3</sub>)<sub>2</sub>], 3.06 [1H, dd, *J* = 9.9 Hz, *J* = 13.2 Hz H-*trans* (pyrazoline)], 3.89 [1H, dd, *J* = 9.6 Hz, *J* = 12.6 Hz, H-4 *cis* (pyrazoline)], 4.26–4.28 (1H, m, CSNH), 4.62–4.67 (m, –CH<sub>2</sub>–Phenyl), 5.45 [1H, dd, *J* = 3.9 Hz, *J* = 7.8 Hz, H-5 (pyrazoline)], 6.75 (2H, d, *J* = 6.6 Hz, H-3', H-5'), 6.83–6.90 (2H, m, H-3'', H-5''), 7.16–7.48 (10H, m, for phenyl and benzyl protons), 7.60 (2H, d, *J* = 6.3 Hz, H-2', H-6'), 7.90–7.91 (1H, m, SO<sub>2</sub>NH); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>, δ): 52.41 (CH<sub>2</sub>NH), 66.94 (C-5 pyrazoline), 151.40 (C-3 pyrazoline), 176.25 (C=S); MALDI (*m/z*): 569 [M<sup>+</sup>], 570 [M+1], 568 [M–1]. CHNS Analysis for C<sub>31</sub>H<sub>31</sub>N<sub>5</sub>O<sub>2</sub>S<sub>2</sub> Found (Calculated) C: 65.39 (65.35), H: 5.45 (5.48), N: 12.31 (12.29), S: 11.22 (11.26).

6.1.1.9. *N*-(Benzylcarbamothioyl)-4-(5-(4-chlorophenyl)-3-(4-(dimethylamino)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (**2i**). Yellow crystals; yield = 44%; m.p. 229–230 °C; *R*<sub>f</sub> = 0.87 (toluene:ethyl acetate:formic acid, 5:4:1); IR<sub>ν</sub><sub>max</sub> (KBr, in cm<sup>-1</sup>): 3339, 3064 and 2974 (NH–CS–NH), 1551 and 1495 (C=S of thiourea), 1591 (C=N), 1344 and 1165 (SO<sub>2</sub>N); 1H NMR (400 MHz,

DMSO-*d*<sub>6</sub>, δ): 2.96 [6H, s, N(CH<sub>3</sub>)<sub>2</sub>], 3.44–3.47 [1H, m, H-*trans* (pyrazoline)], 4.04 [1H, dd, *J* = 5.1 Hz, *J* = 15.2 Hz, H-*cis* (pyrazoline)], 4.07–4.09 (2H, m, –CH<sub>2</sub>–Phenyl), 5.51 [1H, dd, *J* = 4.6 Hz, *J* = 12.0 Hz, H-5 (pyrazoline)], 6.74 (2H, d, *J* = 8.1 Hz, H-3'', H-5''), 6.99–7.62 (13H, H-2', H-6', H-2, H-3, H-5, H-6, H-2'', H-6'', H-2''', H-3''', H-4'', H-5'', H-6'''), 8.10 (1H, brs, SO<sub>2</sub>NH); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>, δ): 52.33 (CH<sub>2</sub>NH), 66.83 (C-5 pyrazoline), 151.47 (C-3 pyrazoline), 176.69 (C=S); MALDI (*m/z*): 604 [M<sup>+</sup>], 605 [M+1]. CHNS Analysis for C<sub>31</sub>H<sub>30</sub>ClN<sub>5</sub>O<sub>2</sub>S<sub>2</sub> Found (Calculated) C: 61.65 (61.63), H: 5.03 (5.00), N: 11.60 (11.59), S: 10.62 (10.61).

6.1.1.10. *N*-(benzylcarbamothioyl)-4-(3-(4-(dimethylamino)phenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (**2j**). Light yellow; yield = 51%; m.p. 226–227 °C; *R*<sub>f</sub> = 0.65 (toluene:ethyl acetate:formic acid, 5:4:1); IR<sub>ν</sub><sub>max</sub> (KBr, in cm<sup>-1</sup>): 3323, 3061 and 2975 (NH–CS–NH), 1539 and 1505 (C=S of thiourea), 1594 (C=N), 1329 and 1125 (SO<sub>2</sub>N); 1H NMR (400 MHz, DMSO-*d*<sub>6</sub>, δ): 2.96 [6H, s, N(CH<sub>3</sub>)<sub>2</sub>], 3.06–3.08 [1H, m, H-*trans* (pyrazoline)], 3.71 (3H, s, OCH<sub>3</sub>), 3.88 [1H, dd, *J* = 11.2 Hz, *J* = 17.8 Hz, H-4 *cis* (pyrazoline)], 4.41–4.44 (2H, m, –CH<sub>2</sub>–Phenyl), 5.41–5.44 [1H, m, H-5 (pyrazoline)], 6.75 (2H, d, *J* = 8.4 Hz, H-3', H-5'), 6.83–7.61 (15H, m, for aromatic protons), 8.01–8.04 (1H, m, SO<sub>2</sub>NH); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>, δ): 53.30 (CH<sub>2</sub>NH), 55.38 (OCH<sub>3</sub> at C-4), 66.89 (C-5 pyrazoline), 151.64 (C-3 pyrazoline), 176.71 (C=S). MALDI (*m/z*): 599 [M<sup>+</sup>], 600 [M+1], 598 [M–1]. CHNS Analysis for C<sub>32</sub>H<sub>33</sub>N<sub>5</sub>O<sub>2</sub>S<sub>2</sub> Found (Calculated) C: 64.10 (64.08), H: 5.56 (5.55), N: 11.66 (11.68), S: 10.71 (10.69).

6.1.1.11. *N*-(benzylcarbamothioyl)-4-(3-(4-(dimethylamino)phenyl)-5-*p*-tolyl-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (**2k**). Light orange crystals; yield = 31%; m.p. 191–193 °C; *R*<sub>f</sub> = 0.90 (chloroform:acetone, 9:1); IR<sub>ν</sub><sub>max</sub> (KBr, in cm<sup>-1</sup>): 3344, 3048 and 2985 (NH–CS–NH), 1528 and 1502 (C=S), 1592 (C=N), 1331 and 1125 (SO<sub>2</sub>N); 1H NMR (500 MHz, DMSO-*d*<sub>6</sub>, δ): 2.25 (3H, s, CH<sub>3</sub>), 2.95 [6H, s, N(CH<sub>3</sub>)<sub>2</sub>], 3.02–3.04 [1H, m, H-*trans* (pyrazoline)], 3.30–3.32 (1H, m, CSNH), 3.84–3.86 [1H, m, H-4 *cis* (pyrazoline)], 4.27–4.28 (2H, m, –CH<sub>2</sub>–Phenyl), 5.34–5.39 [1H, m, H-5 (pyrazoline)], 6.74 (2H, d, *J* = 9.0 Hz, H-3', H-5'), 6.38 (2H, d, *J* = 8.0 Hz, H-3'', H-5''), 7.13–7.20 (9H, m, for tolyl and benzyl aromatic protons), 7.43 (2H, d, *J* = 8.0 Hz, H-2'', H-6''), 7.58 (2H, d, *J* = 9.0 Hz, H-2', H-6'), 7.59 (1H, brs, SO<sub>2</sub>NH); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>, δ): 20.93 (CH<sub>3</sub> at C-4), 51.92 (CH<sub>2</sub>NH), 55.20 (OCH<sub>3</sub> at C-4), 66.04 (C-5 pyrazoline), 151.31 (C-3 pyrazoline), 175.95 (C=S); MALDI (*m/z*): 583 [M<sup>+</sup>], 584 [M+1], 582 [M–1]; CHNS Analysis for C<sub>32</sub>H<sub>33</sub>N<sub>5</sub>O<sub>2</sub>S<sub>2</sub> Found (Calculated) C: 65.80 (65.84), H: 5.71 (5.70), N: 12.01 (12.00), S: 10.97 (10.99).

6.1.1.12. *N*-(benzylcarbamothioyl)-4-(5-(2-chlorophenyl)-3-(4-(dimethylamino)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (**2l**). Yellow crystals; yield = 41%; m.p. 194–195 °C; *R*<sub>f</sub> = 0.75 (toluene:ethyl acetate:formic acid, 5:4:1); IR<sub>ν</sub><sub>max</sub> (KBr, in cm<sup>-1</sup>): 3342, 3034 and 2982 (NH–CS–NH), 1551 and 1507 (C=S of thiourea), 1591 (C=N), 1334 and 1136 (SO<sub>2</sub>N); 1H NMR (400 MHz, DMSO-*d*<sub>6</sub>, δ): 2.97 [6H, s, N(CH<sub>3</sub>)<sub>2</sub>], 3.15 [1H, dd, *J* = 4.4 Hz, *J* = 17.6 Hz, H-*trans* (pyrazoline)], 3.94 [1H, dd, *J* = 12.4 Hz, 18.0 Hz, H-4 *cis* (pyrazoline)], 4.66–4.71 (2H, m, –CH<sub>2</sub>–Phenyl), 5.59 [1H, dd, *J* = 4.8 Hz, *J* = 11.6 Hz, H-5 (pyrazoline)], 6.67 (2H, d, *J* = 8.8 Hz, H-3', H-5'), 7.01 (2H, d, *J* = 8.4 Hz, H-2'', H-6''), 7.09–7.65 (13H, m, H-4', H-6', H-3'', H-5'', H-3, H-4, H-5, H-6, H-2'', H-3''', H-4''', H-5''', H-6'''), 8.76–8.78 (1H, m, CSNH), 11.43–11.44 (1H, m, SO<sub>2</sub>NH); <sup>13</sup>C NMR (75 MHz, DMSO-*d*<sub>6</sub>, δ): 52.85 (CH<sub>2</sub>NH), 66.58 (C-5 pyrazoline), 151.71 (C-3 pyrazoline), 175.98 (C=S); MALDI (*m/z*): 603 [M<sup>+</sup>], 604 [M+1], 605 [M+2]; CHNS Analysis for C<sub>31</sub>H<sub>30</sub>ClN<sub>5</sub>O<sub>2</sub>S<sub>2</sub> Found (Calculated) C: 61.65 (61.63), H: 5.04 (5.00), N: 11.63 (11.59), S: 10.58 (10.61).

6.1.1.13. *N*-(benzylcarbamothioyl)-4-(3-(4-(dimethylamino)phenyl)-5-(3,4,5-trimethoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (**2m**). Yellow crystals; yield = 44%; m.p. 204–205 °C;  $R_f$  = 0.92 (toluene:ethyl acetate:formic acid, 5:4:1); IR $\nu_{\max}$  (KBr, in  $\text{cm}^{-1}$ ): 3362, 3052 and 2940 (NH–CS–NH), 1548 and 1502 (C=S of thiourea), 1581 (C=N), 1338 and 1120 (SO $_2$ N);  $^1\text{H}$  NMR (300 MHz, DMSO- $d_6$ ,  $\delta$ ): 2.96 [6H, s, N(CH $_3$ ) $_2$ ], 3.43–3.48 [1H, m, H-*trans* (pyrazoline)], 3.62 (3H, s, OCH $_3$  at C-4), 3.69 (6H, s, OCH $_3$  X 2 at C-3 and C-5), 3.85 [1H, dd,  $J$  = 7.8 Hz, 17.1 Hz, H-4 *cis* (pyrazoline)], 4.24–4.27 (1H, m, –CH $_2$ –phenyl), 5.29 [1H, dd,  $J$  = 4.6 Hz, 11.6 Hz, H-5 (pyrazoline)], 6.59 (2H, s, H-2, H-6), 6.75 (2H, d,  $J$  = 8.1 Hz, H-3, H-5), 6.84–7.60 (11H, m, H-2', H-6', H-2'', H-3'', H-5'', H-6'', H-2''', H-3''', H-4''', H-5''', H-6'''), 7.85–7.87 (1H, m, CSNH), 8.31 (1H, s, SO $_2$ NH);  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ,  $\delta$ ): 53.53 (CH $_2$ NH), 56.65 (OCH $_3$  at C-3' and C-5'), 60.64 (OCH $_3$  at C-4'), 66.90 (C-5 pyrazoline), 151.29 (C-3 pyrazoline), 174.64 (C=S); MALDI ( $m/z$ ): 659 [M $^+$ ], 660 [M+1], 659 [M–1]; CHNS Analysis for C $_{34}$ H $_{37}$ N $_5$ O $_5$ S Found (Calculated) C: 61.91 (61.89), H: 5.63 (5.65), N: 10.62 (10.61), S: 9.74 (9.72).

6.1.1.14. *N*-(butylcarbamothioyl)-4-(3-(4-(dimethylamino)phenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (**2n**). Yellow crystals; yield = 46%; m.p. 205–207 °C;  $R_f$  = 0.88 (toluene:ethyl acetate:formic acid, 5:4:1); IR $\nu_{\max}$  (KBr, in  $\text{cm}^{-1}$ ): 3348, 3030 and 2934 (NH–CS–NH), 1553 and 1502 (C=S), 1591 (C=N), 1341 and 1146 (SO $_2$ N);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ ): 0.74–0.82 (3H, m, –CH $_2$ –CH $_2$ –CH $_2$ –CH $_3$ ), 1.23–1.40 (2H, m, –CH $_2$ –CH $_2$ –CH $_2$ –CH $_3$ ), 1.41–1.44 (2H, m, –CH $_2$ –CH $_2$ –CH $_2$ –CH $_3$ ), 2.34–2.36 (2H, m, –CH $_2$ –CH $_2$ –CH $_2$ –CH $_3$ ), 2.97 [6H, s, N(CH $_3$ ) $_2$ ], 3.14 [1H, dd,  $J$  = 3.6 Hz,  $J$  = 13.5 Hz H-*trans* (pyrazoline)], 3.93 [1H, dd,  $J$  = 9.3 Hz,  $J$  = 13.5 Hz, H-4 *cis* (pyrazoline)], 5.58 [1H, dd,  $J$  = 4.8 Hz,  $J$  = 12.0 Hz, H-5 (pyrazoline)], 6.76 (2H, d,  $J$  = 8.0 Hz, H-3', H-5'), 7.03 (2H, d,  $J$  = 8.0 Hz, H-3'', H-5''), 7.23–7.36 (5H, m, H-2', H-4', H-6', H-2'', H-6''), 7.93–8.00 (1H, m, CSNH), 8.36–8.39 (1H, m, SO $_2$ NH);  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ,  $\delta$ ): 14.58 (–CH $_2$ –CH $_2$ –CH $_2$ –CH $_3$ ), 20.90 (–CH $_2$ –CH $_2$ –CH $_2$ –CH $_3$ ), 31.68 (–CH $_2$ –CH $_2$ –CH $_2$ –CH $_3$ ), 47.56 (–CH $_2$ –CH $_2$ –CH $_2$ –CH $_3$ ), 52.53 (CH $_2$ NH), 66.95 (C-5 pyrazoline), 152.43 (C-3 pyrazoline), 175.74 (C=S). MALDI ( $m/z$ ): 535 [M $^+$ ], 536 [M+1]. CHNS Analysis for C $_{28}$ H $_{33}$ N $_5$ O $_2$ S $_2$  Found (Calculated) C: 62.79 (62.77), H: 6.24 (6.21), N: 13.09 (13.07), S: 11.96 (11.97).

6.1.1.15. *N*-(butylcarbamothioyl)-4-(5-(4-chlorophenyl)-3-(4-(dimethylamino)phenyl)-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (**2o**). Yellow crystals; yield = 46%; m.p. 221–223 °C;  $R_f$  = 0.66 (toluene:ethyl acetate:formic acid, 5:4:1); IR $\nu_{\max}$  (KBr, in  $\text{cm}^{-1}$ ): 3349, 3048 and 2929 (NH–CS–NH), 1558 and 1503 (C=S of thiourea), 1593 (C=N), 1331 and 1128 (SO $_2$ N);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ ): 0.75 (3H, t, –CH $_2$ –CH $_2$ –CH $_2$ –CH $_3$ ), 1.21–1.23 (2H, m, –CH $_2$ –CH $_2$ –CH $_2$ –CH $_3$ ), 1.35–1.38 (2H, m, –CH $_2$ –CH $_2$ –CH $_2$ –CH $_3$ ), 2.95–2.97 [8H, m, –CH $_2$ –CH $_2$ –CH $_2$ –CH $_3$ , N(CH $_3$ ) $_2$ ], 3.21–3.23 [1H, m, H-*trans* (pyrazoline)], 3.86 [1H, dd,  $J$  = 9.6 Hz,  $J$  = 17.3 Hz, H-4 *cis* (pyrazoline)], 5.48 [1H, dd,  $J$  = 4.8 Hz,  $J$  = 12.1 Hz, H-5 (pyrazoline)], 6.51–6.53 (1H, m, CSNH), 6.74 (2H, d,  $J$  = 6.0 Hz, H-3', H-5'), 6.87 (2H, d,  $J$  = 6.6 Hz, H-3'', H-5''), 7.27 (2H, d,  $J$  = 5.1 Hz, H-3, H-5), 7.39 (2H, d,  $J$  = 5.1 Hz, H-2, H-6), 7.45–7.51 (3H, m, H-2', H-6', SO $_2$ NH), 7.58 (2H, d,  $J$  = 6.3 Hz, H-2'', H-6'');  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ,  $\delta$ ): 14.98 (–CH $_2$ –CH $_2$ –CH $_2$ –CH $_3$ ), 21.76 (–CH $_2$ –CH $_2$ –CH $_2$ –CH $_3$ ), 31.72 (–CH $_2$ –CH $_2$ –CH $_2$ –CH $_3$ ), 47.93 (–CH $_2$ –CH $_2$ –CH $_2$ –CH $_3$ ), 52.55 (CH $_2$ NH), 67.04 (C-5 pyrazoline), 151.75 (C-3 pyrazoline), 174.75 (C=S); MALDI ( $m/z$ ): 570 [M $^+$ ], 571 [M+1], 572 [M+2], 569 [M–1], 568 [M–2]; CHNS Analysis for C $_{28}$ H $_{32}$ ClN $_5$ O $_2$ S $_2$  Found (Calculated) C: 58.99 (58.98), H: 5.67 (5.66), N: 12.29 (12.28), S: 11.27 (11.25).

6.1.1.16. *N*-(butylcarbamothioyl)-4-(3-(4-(dimethylamino)phenyl)-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)

benzenesulfonamide (**2p**). Light yellow crystals; yield = 42%; m.p. 224–225 °C;  $R_f$  = 0.90 (toluene:ethyl acetate:formic acid, 5:4:1); IR $\nu_{\max}$  (KBr, in  $\text{cm}^{-1}$ ): 3349, 3038 and 2945 (NH–CS–NH), 1554 and 1502 (C=S of thiourea), 1591 (C=N), 1338 and 1144 (SO $_2$ N);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ ): 0.81–0.83 (3H, m, –CH $_2$ –CH $_2$ –CH $_2$ –CH $_3$ ), 1.17–1.20 (2H, m, –CH $_2$ –CH $_2$ –CH $_2$ –CH $_3$ ), 1.35–1.38 (2H, m, –CH $_2$ –CH $_2$ –CH $_2$ –CH $_3$ ), 2.95–2.97 [8H, m, –CH $_2$ –CH $_2$ –CH $_2$ –CH $_3$ , N(CH $_3$ ) $_2$ ], 3.01–3.04 [1H, m, H-*trans* (pyrazoline)], 3.71 (3H, s, OCH $_3$ ), 3.86 [1H, dd,  $J$  = 9.6 Hz,  $J$  = 17.6 Hz, H-4 *cis* (pyrazoline)], 5.42–5.44 [1H, m, H-5 (pyrazoline)], 6.51–6.54 (1H, m, CSNH), 6.75 (2H, d,  $J$  = 7.2 Hz, H-3', H-5'), 6.89 (2H, d,  $J$  = 7.2 Hz, H-3, H-5), 6.93 (2H, d,  $J$  = 9.2 Hz, H-2, H-6), 7.17 (2H, d,  $J$  = 7.6 Hz, H-3'', H-5''), 7.51 (2H, d,  $J$  = 8.4 Hz, H-2'', H-6''), 7.60 (2H, d,  $J$  = 6.7 Hz, H-2', H-6'), 7.83–7.85 (1H, m, SO $_2$ NH).  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ,  $\delta$ ): 14.62 (–CH $_2$ –CH $_2$ –CH $_2$ –CH $_3$ ), 20.83 (–CH $_2$ –CH $_2$ –CH $_2$ –CH $_3$ ), 31.75 (–CH $_2$ –CH $_2$ –CH $_2$ –CH $_3$ ), 46.21 (–CH $_2$ –CH $_2$ –CH $_2$ –CH $_3$ ), 52.83 (CH $_2$ NH), 55.38 (OCH $_3$  at C-4), 67.61 (C-5 pyrazoline), 151.69 (C-3 pyrazoline), 174.74 (C=S); MALDI ( $m/z$ ): 565 [M $^+$ ], 564 [M–1]; CHNS Analysis for C $_{29}$ H $_{35}$ N $_5$ O $_3$ S $_2$  Found (Calculated) C: 61.55 (61.57), H: 6.24 (6.24), N: 12.60 (12.38), S: 11.36 (11.34).

6.1.1.17. *N*-(cyclohexylcarbamothioyl)-4-(3-(4-(dimethylamino)phenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl)benzenesulfonamide (**2q**). Yellow crystals; yield = 56%; m.p. 142–143 °C;  $R_f$  = 0.97 (toluene:ethyl acetate:formic acid, 5:4:1); IR $\nu_{\max}$  (KBr, in  $\text{cm}^{-1}$ ): 3327, 3071 and 2931 (NH–CS–NH), 1533 and 1504 (C=S of thiourea), 1590 (C=N), 1364 and 1149 (SO $_2$ N);  $^1\text{H}$  NMR (400 MHz, DMSO- $d_6$ ,  $\delta$ ): 1.23–1.76 (10H, m, cyclohexyl ring), 2.94 (1H, s, axial-H at C-1 of cyclohexyl ring), 2.97 [6H, s, N(CH $_3$ ) $_2$ ], 3.14 [1H, dd,  $J$  = 3.6 Hz,  $J$  = 13.8 Hz H-*trans* (pyrazoline)], 3.96 [1H, dd,  $J$  = 9.3 Hz,  $J$  = 13.2 Hz, H-4 *cis* (pyrazoline)], 5.58 [1H, dd,  $J$  = 3.3 Hz,  $J$  = 9.0 Hz, H-5 (pyrazoline)], 6.76 (2H, d,  $J$  = 6.9 Hz, H-3', H-5'), 7.03 (2H, d,  $J$  = 6.6 Hz, H-3'', H-5''), 7.23–7.36 (5H, m, H-2, H-3, H-4, H-5, H-6), 7.60–7.64 (4H, m, H-2', H-6', H-2'', H-6''), 8.05–8.13 (1H, m, SO $_2$ NH);  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ,  $\delta$ ): 52.33 (CH $_2$ NH), 66.90 (C-5 pyrazoline), 151.40 (C-3 pyrazoline), 176.05 (C=S); MALDI ( $m/z$ ): 561 [M $^+$ ], 562 [M+1], 560 [M–1], 559 [M–2]; CHNS Analysis for C $_{30}$ H $_{35}$ N $_5$ O $_2$ S $_2$  Found (Calculated) C: 64.16 (64.14), H: 6.30 (6.28), N: 12.49 (12.47), S: 11.44 (11.42).

## 6.2. Pharmacology

### 6.2.1. Anti-hyperglycaemic activity

All the experiments were carried out in albino rats of Wistar strain (either sex) were procured from Central Animal House of Jamia Hamdard, New Delhi (Registration no. 173/CPCSEA). The experiments were performed in accordance with the guidelines for the care and use of laboratory animals, laid down by the Committee for the Purpose of Control and Supervision of Experiments in Animals (CPCSEA), Ministry of Social Justice and Empowerment, Govt. of India, Jan. 2000. Animals described as fasted were deprived of food for at least 16 h but allowed free access to water. Carboxymethyl cellulose CMC (1%w/v) in distilled water was used as vehicle for dosing in all the experiments. All treatments were given orally using gauge.

Fasted rats were divided into groups of six animals each. Animals of group-I were fed with the vehicle (CMC 1% w/v in distilled water) in a volume of 10 ml/kg, while animals of group II were given gliclazide 0.05 mM/kg suspended in the vehicle. Animals of the experimental group (III - XIX) were administered the suspension of the test compounds at a dosage of 0.05 mM/kg b.w. A glucose load (3 g/kg) was given to each animal exactly after 30 min post administration of the respective treatments. Blood samples were collected from retro-orbital plexus (under mild condition) just prior to and 60 min after the glucose loading and blood glucose

levels were measured with an autoanalyzer (Accu Check Active glucose kit) [26].

### 6.2.2. Docking

Docking studies were performed using Glide module of the Schrodinger-9 software on the aldose reductase (PDB id: 1EL3, 1USO, 2FZD and 2PDK). Receptor preparation was done using protein preparation wizard with defaults settings. The structures were sketched using maestro graphical user interface (GUI) and were energy minimized/cleaned up by Ligprep module of the same software using OPLS\_2005 force field and proper protonation states were assigned with the ionizer subprogram at pH  $7.2 \pm 0.2$  [34]. A grid space of 20 Å around co-crystallized ligand was set for the docking calculations. Glide XP module was used for final docking studies [35].

### 6.2.3. Aldose reductase

**6.2.3.1. Preparation of rat lens AR.** Crude AR was prepared from rat lens as described previously [29]. Institutional and national guidelines for the care and use of animals were followed and all experimental procedures involving animals were approved by the IAEC (institutional animal ethical committee) of the National Institute of Nutrition. Lenses were homogenized in 9 volumes of 100 mM potassium phosphate buffer, pH 6.2. The homogenate was centrifuged at  $15,000 \times g$  for 30 min at 4 °C and the resulting supernatant was used as the source of ALR2.

**6.2.3.2. AR activity assay.** AR activity was assayed as described previously [29]. All the experiments were performed in triplicate. The assay mixture in 1 mL contained 50 mM potassium phosphate buffer, pH 6.2, 0.4 M lithium sulphate, 5 mM  $\beta$ -mercaptoethanol, 10 mM DL-glyceraldehyde, 0.1 mM NADPH and enzyme preparation. Appropriate blanks were employed for corrections. The assay mixture was incubated at 37 °C and the reaction was initiated by the addition of NADPH at 37 °C. The change in the absorbance at 340 nm due to NADPH oxidation was followed in a spectrophotometer.

**6.2.3.3. Inhibition studies.** For inhibition studies, a concentrated stock of pyrazoline substituted benzenesulfonylurea/thiourea derivatives (**2a–q**) was prepared in DMSO. Aliquots drawn from a working solution were added to the enzyme assay mixture and incubated for 5 min before initiating the reaction by NADPH as described above. The percent inhibition with test compound was calculated considering the enzyme activity in the absence of inhibitor as 100%. The concentration of each test sample giving 50% inhibition ( $IC_{50}$ ) was determined by non-linear regression analysis of log concentration of compound versus percentage inhibition.

### Acknowledgement

The authors are grateful to the bioinformatics infrastructure facility (BIF) of Jamia Hamdard, for providing the facility for in silico studies. One of the authors, Syed Ovais is thankful to the Hamdard National Foundation (HNF) for awarding a fellowship.

### References

[1] D.R. Whiting, L. Guariguata, C. Weil, J. Shaw, *Diabetes Research and Clinical Practice* 94 (2011) 311–321.

- [2] R.M. Anjana, R. Pradeepa, M. Deepa, M. Datta, V. Sudha, R. Unnikrishnan, et al., *Diabetologia* 54 (2011) 3022–3027.
- [3] C.C. Cowie, M.S. Eberhardt, American Diabetes Association: *Diabetes*, Vital Statistics, VA, Alexandria, 1996.
- [4] D.M. Nathan, *The New England Journal of Medicine* 318 (1988) 1315–1321.
- [5] P. Alexiou, K. Pegklidou, M. Chatzopoulou, I. Nicolaou, V.J. Demopoulos, *Current Medicinal Chemistry* 16 (2009) 734–752.
- [6] J.M. Jez, M.J. Bennett, B.P. Schlegel, M. Lewis, T.M. Penning, *The Biochemical Journal* 326 (1997) 625–636.
- [7] D.L. Vander Jagt, N.S. Kolb, T.J. Vander Jagt, J. Chino, F.J. Marlinez, L.A. Hunsaker, R.E. Royer, *Biochimica et Biophysica Acta* 1249 (1995) 117–126.
- [8] P. Anil Kumar, G. Bhanuprakash Reddy, *Experimental Eye Research* 85 (2007) 739–740.
- [9] M.J. Peterson, R. Sarges, C.E. Aldinger, D.P. McDonald, *Metabolism* 28 (4.Supp 1) (1979) 456–461.
- [10] F.P. Kador, J.H. Kinoshita, N.E. Sharpless, *Journal of Medicinal Chemistry* 28 (1985) 841–849.
- [11] V.F. Carvalho, E.O. Barreto, M.F. Serra, R.S.B. Cordeiro, M.A. Martins, Z.B. Fortes, P.M.R. Silva, *European Journal of Pharmacology* 549 (2006) 173–178.
- [12] (a) F. Da Settimo, G. Primofiore, C. La Motta, S. Sartini, S. Taliani, F. Simorini, A.M. Marini, A. Lavecchia, E. Novellino, E. Boldrini, *Journal of Medicinal Chemistry* 48 (2005) 6897–6907; (b) O. El-Kabbani, V. Carbone, C. Darmanin, M. Oka, A. Mitschler, A. Podjarny, C. Schulze-Briese, R.P.-T. Chung, *Journal of Medicinal Chemistry* 48 (2005) 5536–5542; (c) K.E. Schemmel, R.S. Padiyara, J.J. D'Souza, *Journal of Diabetes and Complications* 24 (2010) 354–360.
- [13] A. Ramunno, S. Cosconati, S. Sartini, V. Maglio, S. Angiuoli, V. La Pietra, S. Di Maro, M. Giustiniano, C. La Motta, F. Da Settimo, L. Marinelli, E. Novellino, *European Journal of Medicinal Chemistry* 51 (2012) 216–226.
- [14] I.O. Donkora, Y.S. Abdel-Ghanyb, P.F. Kador, T. Mizoguchic, A. Bartoszko-Maliik, D.D. Millera, *European Journal of Medicinal Chemistry* 33 (1998) 15–22.
- [15] P. Alexiou, V.J. Demopoulos, *Journal of Medicinal Chemistry* 53 (2010) 7756–7766.
- [16] C. Zhu, *Diabetes Mellitus – Insights and Perspectives* (2013).
- [17] L.C. Groop, *Diabetes Care* 15 (1992) 737–754.
- [18] F.K. Gorus, F.C. Schuit, P.A. In't Veld, W. Gepts, D.G. Pipeleers, *Diabetes* 37 (1988) 1090–1095.
- [19] A.J. Krentz, C.J. Bailey, *Drugs* 65 (2005) 385–411.
- [20] D.M. Nathan, J.B. Buse, M.B. Davidson, E. Ferrannini, R.R. Holman, R. Sherwin, B. Zinman, *Diabetes Care* 32 (2009) 193–203.
- [21] A. Marella, M.R. Ali, M.T. Alam, R. Saha, O. Tanwar, M. Akhter, M. Shaquiquzzaman, M.M. Alam, *Mini Reviews in Medicinal Chemistry* 13 (2013) 921–931.
- [22] J.H. Ahn, H.M. Kim, S.H. Jung, S.K. Kang, K.R. Kim, S.D. Rhee, S.D. Yang, H.G. Cheon, S.S. Kim, *Bioorganic & Medicinal Chemistry Letters* 14 (2004) 4461–4465.
- [23] M.A. Jun, W.S. Park, S.K. Kang, K.Y. Kim, K.R. Kim, S.D. Rhee, M.A. Bae, N.S. Kang, S.K. Sohn, S.G. Kim, J.O. Lee, D.H. Lee, H.G. Cheon, S.S. Kim, J.H. Ahn, *European Journal of Medicinal Chemistry* 43 (2008) 1889–1902.
- [24] S. Ovais, R. Bashir, S. Yaseen, P. Rathore, M. Samim, K. Javed, *Medicinal Chemistry Research* 22 (2013) 1378–1385.
- [25] J.F. Mcelroy, R.J. Chorvat, *United States Patent Applications and Publications*, 2009. US 20090286758-20091119.
- [26] B.K. Srivastava, A. Joharapurkar, S. Raval, J.Z. Patel, R. Soni, P. Raval, A. Gite, A. Goswami, N. Sadhwani, N. Gandhi, H. Patel, B. Mishra, M. Solanki, B. Pandey, M.R. Jain, P.R. Patel, *Journal of Medicinal Chemistry* 50 (2007) 5951–5966.
- [27] S. Ovais, S. Yaseen, R. Bashir, P. Rathore, M. Samim, S. Singh, V. Nair, K. Javed, *Journal of Enzyme Inhibition and Medicinal Chemistry* 5 (2013) 1105–1112.
- [28] I.G. Rathish, K. Javed, S. Bano, S. Ahmad, M.S. Alam, K.K. Pillai, *European Journal of Medicinal Chemistry* 44 (2009) 2673–2678.
- [29] P. Suryanarayana, P.A. Kumar, M. Saraswat, J.M. Petrash, G.B. Reddy, *Molecular Vision* 10 (2004) 148–154.
- [30] K.M. Bohren, C.E. Grimshaw, C.J. Lai, D.H. Harrison, D. Ringe, G.A. Petsko, K.H. Gabbay, *Biochemistry* 33 (1994) 2021–2032.
- [31] C.E. Grimshaw, K.M. Bohren, C.J. Lai, K.H. Gabbay, *Biochemistry* 34 (1995) 14374–14384.
- [32] M. Chatzopoulou, E. Mamadou, M. Juskova, C. Koukoulitsa, I. Ioannis Nicolaou, M. Stefek, V.J. Demopoulos, *Bioorganic & Medicinal Chemistry* 19 (2011) 1426–1433.
- [33] A. Del Corso, L. Constantino, G. Rastelli, F. Buono, U. Mura, *Experimental Eye Research* 71 (2000) 515–521.
- [34] LigPrep, Version 2.3, Schrödinger, LLC, New York, 2009.
- [35] Glide, Version 5.5, Schrödinger, LLC, New York, 2009.