

# Synthesis and docking analysis of new heterocyclic system of tetrazolo[5',1':2,3][1,3,4]thiadiazepino [7,6-*b*]quinolines as aldose reductase inhibitors

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ARTICLE INFO	ABSTRACT
<p><b>Article type:</b> Original article</p>	<p><b>Objective(s):</b> In recent years, the chemistry of Tetrazolo[5',1':2,3][1,3,4]thiadiazepino [7,6-<i>b</i>]quinolines have received considerable attention owing to their synthetic and effective biological importance which exhibits a wide variety of biological activity. As the inhibitor of aldose reductase, the aforementioned compounds may have implication in preventing complications of diabetes.</p> <p><b>Materials and Methods:</b> A group of tetrazolo[5',1':2,3][1,3,4]thiadiazepino [7,6-<i>b</i>]quinoline derivatives were synthesized, and theoretically evaluated for their inhibitory potency against aldose reductase (ALR) via docking process. The docking calculation was done in Genetic Optimization for Ligand Docking (GOLD) 5.2 software using Genetic algorithm.</p> <p><b>Results:</b> Compounds <b>3a</b> and <b>3f</b> showed the best inhibitory potency by GOLD score value of 78.83 and 76.88 respectively.</p> <p><b>Conclusion:</b> All of the best models formed strong hydrogen bonds with Trp 111 and Tyr 209 via tetrazole moiety. It was found that pi-pi interaction between Tyr 209, Trp 20 and His 110 side chain and quinolin moiety was one of the common factors in enzyme-inhibitor junction. It was found that both hydrogen bonding and hydrophobic interactions are important in the structure and function of biological molecules, especially for inhibition in a complex.</p>
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## Introduction

Human aldose reductase (hAR) is a member of the aldo-keto-reductase superfamily (AKR1 member B1, EC 1.1.1.21) (1). This cytosolic enzyme exists with different concentrations in many tissues, including kidney with the highest concentration, and sciatic nerve, lens, and testis. This enzyme is involved in glucose metabolism in the polyol pathway (2). During the catalysis, the cofactor nicotinamide adenine dinucleotide phosphate (NADPH) is bound first, followed by binding the sugar or other aldehyde to the hAR. C1 of the substrate is reduced by a hydride transfer from the cofactor to the substrate's carbonyl carbon and a concerted proton transfer from Tyr 48 via His 110 to the substrate (3, 4). Subsequently, the product is released. The dissociation of the now oxidized cofactor NADP<sup>+</sup> is conditional upon a conformational change of the protein, and thus, is a slow process (5).

Docking is important in the study of protein ligand interaction properties such as binding energy,

geometry complementarity, hydrogen bond donor acceptor, hydrophobicity, electron distribution and polarizability thus it plays a major role in the drug discovery for the identification of suitable molecular scaffold and distinguishing selectivity for the target protein (6).

GOLD, the first algorithm to be evaluated on a large data set of complex poses, an empirical free energy scoring function that estimates the free energy of binding permitting inhibition constant for protein ligand complex. It is a package of program for structure visualization and manipulation for docking, the post processing and visualization of the results (7). The objective of the present work is to study the *In silico* aldose reductase inhibitory activity of some new synthetic tetrazolo[5',1':2,3][1,3,4]thiadiazepino[7,6-*b*]quinolines.

Quinoline and its derivatives have always attracted both synthetic and biological chemist because of its diverse chemical and pharmacological properties (8). For example quinine has been used

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**Table 1.** Synthesis of tetrazolo[5',1':2,3][1,3,4]thiadiazepino[7,6-*b*]quinoline derivatives

Product	R	Time (h)	Yield (%)
3a	H	7	96
3b	8-Me	6.5	92
3c	8-OMe	7	88
3d	8-Et	6	88
3e	8-OEt	8	95
3f	8-Cl	8	93
3g	7-Me	7.7	90
3h	7-MeO	7.5	88
3i	8-Isopropyl	8	85

for the treatment of malaria (9), dynemicin A and streptonigrin, are naturally occurring members of the class of antitumor antibiotic (10, 11). According to the best of our review of the literature, we found that compounds containing quinoline (12-15), or tetrazole (15-19) functionality have been reported to exhibit anti-inflammatory activity. For instance various tetrazolo[1,5-*a*]quinoline derivatives containing pyrimidine ring were reported to possess dual anti-inflammatory and antibacterial activity (20). To study the combined effect of these two heterocyclic moieties (quinoline and tetrazole) in a single network, there is an interest in the synthesis of tetrazolo[5',1':2,3][1,3,4]thiadiazepino [7,6-*b*]quinolines (3a-3i). The resulting compound had high structural similarity to the 3-(2,4-dichlorophenyl)[1,2,4]triazolo[3',4':2,3][1,3,4]thiadiazepino[7,6-*b*]quinolines (ChemSpider ID: [2336312](#)) which was identified as a potential hAR in Chemspider search with lasso score of 1. Therefore, we proposed our compound as a potential inhibitor of hAR enzyme.

## Materials and Methods

### Experimental

The products were characterized by spectroscopic data (IR, <sup>1</sup>H NMR, and <sup>13</sup>C NMR). The purity determinations of the products were accomplished by TLC on silica gel polygram STL G/UV 254 plates. Melting points were determined with an Electrothermal Type 9100 melting point apparatus. Elemental analyses were made by a Thermo Finning Flash EA1112 CHNO-S analyzer and agreed with the calculated values. The FTIR spectra were recorded on an Avatar 370 FTIR Thermo Nicolet spectrometer. The NMR spectra were recorded on a Bruker Avance 100 and 400 MHz instrument in CDCl<sub>3</sub>. The <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts (δ) in ppm were downfield from tetramethylsilane (CDCl<sub>3</sub>: δ<sub>C</sub>=77.0 ppm; residual CHCl<sub>3</sub> in CDCl<sub>3</sub>: δ<sub>H</sub>=7.26 ppm).

### General experimental procedure for the preparation of tetrazolo[5',1':2,3][1,3,4]thiadiazepino[7,6-*b*]quinoline (3a-i)

A mixture of 2-chloroquinoline-3-carbaldehydes (1 mmol, 0.1916 g) (1), 1-amino-1H-tetrazole-5-thiol (1 mmol, 0.1171 g) (2), triethylamine (2.5 mol, 0.35 ml) and 50 mL EtOH in a 100 ml flask was stirred at

reflux for periods indicated in Table 1. After completion of the reaction (monitored by TLC, ethyl acetate/*n*-hexane, 1/1), 75 ml of distilled water was added to the reaction mixture, the resulting solid was separated by filtration, and recrystallized from ethanol to afford pure product.

### Tetrazolo[5',1':2,3][1,3,4]thiadiazepino[7,6-*b*]quinoline (3a)

Yield: 96%; mp 216-217 °C; IR (KBr) ν cm<sup>-1</sup>: 3047, 3023, (CH aromatic), 1609 (C=C), 1556 (C=N), 1055 (N-N), 837 (C-S). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25 °C, ppm) δ: 8.55 (s, 1H, ArH), 8.40 (s, 1H, ArH), 8.16 (d, 1H, *J*= 8.4, ArH), 7.97 (d, 1H, *J*= 8.4, ArH), 7.78 (s, 1H, ArH). Anal. Calcd. for C<sub>11</sub>H<sub>6</sub>N<sub>6</sub>S: C, 51.96; H, 2.38; N, 33.05; S, 12.61. Found: C, 52.02; H, 2.65; N, 33.50; S, 12.06.

### 8-Methyltetrazolo[5',1':2,3][1,3,4]thiadiazepino[7,6-*b*]quinoline (3b)

Yield: 92%; mp 215-217°C; IR (KBr) ν cm<sup>-1</sup>: 3054, 3019 (CH aromatic), 2953, 2929, 2888 (CH aliphatic), 1607 (C=C), 1568 (C=N), 1058 (N-N), 828 (C-S). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25°C, ppm) δ: 8.53 (s, 1H, ArH), 8.29 (s, 1H, ArH), 8.03 (d, 1H, *J*= 8.4, ArH), 7.77 (d, 1H, *J*= 8.4, ArH), 7.72 (s, 1H, ArH), 2.62 (s, 3H), <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, 25°C, ppm) δ: 155.4, 149.2, 148.1, 145.9, 142.1, 140.1, 136.4, 128.9, 127.5, 126.2, 126.1, 21.8. Anal. Calcd. for C<sub>12</sub>H<sub>8</sub>N<sub>6</sub>S: C, 53.72; H, 3.01; N, 31.32; S, 11.95. Found: C, 52.82; H, 3.05; N, 32.50; S, 11.86.

### 8-Methoxytetrazolo[5',1':2,3][1,3,4]thiadiazepino[7,6-*b*]quinoline (3c)

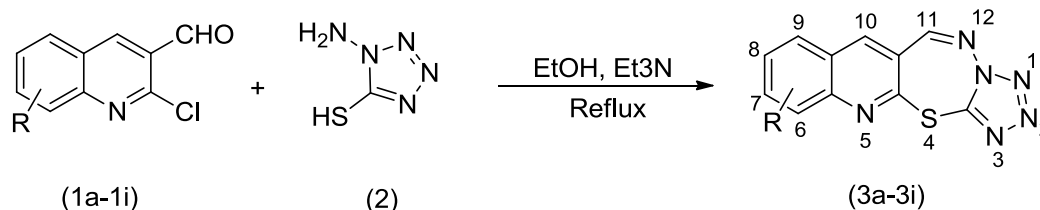
Yield: 88%; mp 222-224°C; IR (KBr) ν cm<sup>-1</sup>: 3080, 3056 (CH aromatic), 2970, 2937, 2831 (CH aliphatic), 1623 (C=C), 1573 (C=N), 1061 (N-N), 844 (C-S). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25°C, ppm) δ: 8.55-7.65 (m, 5H, ArH), 3.85 (s, 3H, OCH<sub>3</sub>). Anal. Calcd. for C<sub>12</sub>H<sub>8</sub>N<sub>6</sub>OS: C, 50.70; H, 2.84; N, 29.56; S, 11.28. Found: C, 50.90; H, 2.61; N, 30.05; S, 11.46.

### 8-Ethyltetrazolo[5',1':2,3][1,3,4]thiadiazepino[7,6-*b*]quinoline (3d)

Yield: 88%; mp 150-152°C; IR (KBr) ν cm<sup>-1</sup>: 3051 (CH aromatic), 2967, 2933, 2876, (CH aliphatic), 1612 (C=C), 1570 (C=N), 1052 (N-N), 835 (C-S). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25°C, ppm) δ: 8.55-7.70 (m, 5H, ArH), 2.80 (q, 2H, *J*= 5.4, CH<sub>2</sub>CH<sub>3</sub>). 1.25 (t, 3H, *J*= 5.4, CH<sub>2</sub>CH<sub>3</sub>). Anal. Calcd. for C<sub>13</sub>H<sub>10</sub>N<sub>6</sub>S: C, 55.30; H, 3.57; N, 29.77; S, 11.36. Found: C, 55.86; H, 3.91; N, 30.12; S, 11.72.

### 8-Ethoxytetrazolo[5',1':2,3][1,3,4]thiadiazepino[7,6-*b*]quinoline (3e)

Yield: 95%; mp 137-140°C; IR (KBr) ν cm<sup>-1</sup>: 3064 (CH aromatic), 2990, 2926, 2831 (CH aliphatic), 1621 (C=N), 1593 (C=N), 1056 (N-N), 839 (C-S). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 25°C, ppm) δ: 8.55-7.72 (m, 5H,



Scheme 1

ArH), 4.42 (q, 2H,  $J = 5.4$ ,  $\text{CH}_2\text{CH}_3$ ). 1.45 (t, 3H,  $J = 5.4$ ,  $\text{CH}_2\text{CH}_3$ ). Anal. Calcd. for  $\text{C}_{13}\text{H}_{10}\text{N}_6\text{OS}$ : C, 52.34; H, 3.38; N, 28.17; S, 10.75. Found: C, 52.63; H, 3.97; N, 28.59; S, 11.12.

#### 8-Chlorotetrazolo[5',1':2,3][1,3,4] thiadiazepino[7,6-b]quinoline (3f)

Yield: 93%; mp 224-225 °C; IR (KBr)  $\nu$   $\text{cm}^{-1}$ : 3068, 3047 ( $\text{CH}$  aromatic), 1623 (C=C), 1555 (C=N), 1055 (N-N), 837 (C-S).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , 25 °C, ppm)  $\delta$ : 8.92 (s, 1H, ArH), 8.52 (s, 1H, ArH), 8.05 (s, 1H, ArH), 7.82 (d, 1H,  $J = 8.4$ , ArH), 7.78 (d, 1H,  $J = 8.4$ , ArH). Anal. Calcd. for  $\text{C}_{11}\text{H}_5\text{ClN}_6\text{S}$ : C, 45.76; H, 1.75; N, 29.11; S, 11.11. Found: C, 45.82; H, 1.98; N, 30.08; S, 11.72.

#### 7-Methyltetrazolo[5',1':2,3][1,3,4] thiadiazepino[7,6-b]quinoline (3g)

Yield: 90%; mp 172-174 °C; IR (KBr)  $\nu$   $\text{cm}^{-1}$ : 3039 ( $\text{CH}$  aromatic), 2977, 2924 ( $\text{CH}$  aliphatic), 1606 (C=C), 1549 (C=N), 1059 (N-N), 851 (C-S).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , 25 °C, ppm)  $\delta$ : 8.53 (s, 1H, ArH), 8.29 (s, 1H, ArH), 8.03 (d, 1H,  $J = 8.4$ , ArH), 7.78 (d, 1H,  $J = 8.4$ , ArH), 7.71 (s, 1H, ArH), 2.62 (s, 3H,  $\text{OCH}_3$ ). Anal. Calcd. for  $\text{C}_{12}\text{H}_8\text{N}_6\text{S}$ : C, 53.72; H, 3.01; N, 31.32; S, 11.95. Found: C, 52.82; H, 3.05; N, 32.50; S, 11.86.

#### 7-Methoxytetrazolo[5',1':2,3][1,3,4] thiadiazepino[7,6-b]quinoline (3h)

Yield: 88%; mp more than 300 °C; IR (KBr)  $\nu$   $\text{cm}^{-1}$ : 3007 ( $\text{CH}$  aromatic), 2932, 2835 ( $\text{CH}$  aliphatic), 1621 (C=C), 1489 (C=N), 1023 (N-N), 849 (C-S).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , 25 °C, ppm)  $\delta$ : 8.52 (s, 1H, ArH), 8.29 (s, 1H, ArH), 8.04 (d, 1H,  $J = 8.4$ , ArH), 7.78 (d, 1H,  $J = 8.4$ , ArH), 7.71 (s, 1H, ArH), 3.82 (s, 3H,  $\text{OCH}_3$ ). Anal. Calcd. for  $\text{C}_{12}\text{H}_8\text{N}_6\text{OS}$ : C, 50.70; H, 2.84; N, 29.56; S, 11.28. Found: C, 50.90; H, 2.61; N, 30.05; S, 11.46.

#### 8-Isopropyltetrazolo[5',1':2,3][1,3,4] thiadiazepino[7,6-b]quinoline (3i)

Yield: 85%; mp 176-178 °C; IR (KBr)  $\nu$   $\text{cm}^{-1}$ : 3043 ( $\text{CH}$  aromatic), 2900, 2868 ( $\text{CH}$  aliphatic), 1613 (C=C), 1557 (C=N), 1053 (N-N), 851 (C-S).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ , 25 °C, ppm)  $\delta$ : 8.95 (s, 1H, ArH), 8.05 (s, 1H, ArH), 7.99 (d, 1H,  $J = 8.4$ , ArH), 7.78 (d, 1H,  $J = 8.4$ , ArH), 7.71 (s, 1H, ArH), 2.95 (m, 1H,  $\text{CH}(\text{CH}_3)_2$ ), 1.48 (d, 6H,  $J = 5.2$ , 2 $\text{CH}_3$ ). Anal. Calcd. for  $\text{C}_{14}\text{H}_{12}\text{N}_6\text{S}$ :

C, 56.74; H, 4.08; N, 28.36; S, 10.82. Found: C, 56.82; H, 4.35; N, 28.87; S, 11.04.

#### Structure optimization

Three dimensional structures of the 3a-i were simulated in Hyper Chem7.5 using MM+ method (RMS gradient = 0.1 kcal mol<sup>-1</sup>) (HyperChem® Release 7, Hypercube Inc., <http://www.hyper.com/>). In the second optimization, output files were minimized under Semi empirical AM1 methods (Convergence limit = 0.01; Iteration limit = 50; RMS gradient = 0.1 kcal mol<sup>-1</sup>; Polak-Ribiere optimizer algorithm) (21, 22).

Crystal structures of class aldose reductase (EC: 1.1.1.21) were retrieved from RCSB Protein Data Bank (PDB entry: 1AH3).

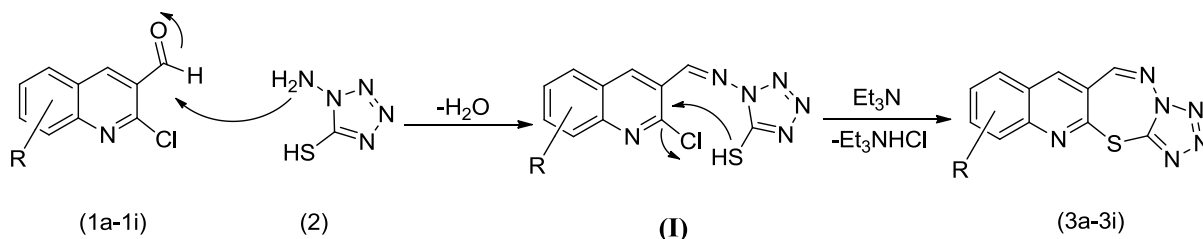
#### Molecular docking

Docking was carried out using Genetic optimization for Ligand Docking (GOLD) 5.2. Software based on the GoldScore fitness function that uses the Genetic algorithm (GA). All water molecules and hetero atoms were omitted from the protein to evaluate the two scoring functions in GOLD. For each of the 25 independent GA runs, a maximum number of 100000 GA functions were established on a set of five groups with a population size of 100 individuals. Mutation, migration and operator weights for crossover were set to 95, 10, and 95, respectively. Default cut-off values of 4.0 Å for van der Waals distance and 2.5 Å (dH-X) for hydrogen bonds were employed. When the top three solutions achieved RMSD values enough 1.5 Å, GA docking was terminated. The RMSD values for the docking computations are based on the RMSD matrix of the ranked solutions and observed that the best ranked solutions were always among the first 50 GA runs, and further analyzing of the conformation of molecules performed on the best fitness score. The docking procedure was validated by redocking of tolrestat to the ALR crystal structure 1AH3.

## Results

### Chemistry

To formation the products (3a-3i), the reaction took place between 2-chloroquinoline-3-carbaldehydes (1a-1i) and 1-amino-1H-tetrazole-5-thiol (2) as the starting materials, scheme 1.



Scheme 2

**Table 2.** Estimated inhibitory constant ( $K_i$ ), free energy of binding, GOLD score and amino acids involved in hydrogen binding with synthetic compounds

Compound	GOLD score	$\Delta G$ (kJ/mol)	$K_i$	Residues involved in hydrogen binding
3a	78.83	-31.89	2.58E-06	Trp 111-Tyr 209-His 110
3b	75.71	-28.91	8.60E-06	Trp 111-Tyr 209-Asp 160
3c	74.91	-27.80	1.34E-05	Trp 111-Tyr 209-
3d	75.91	-28.72	9.29E-06	Ser 210-Tyr 48
3e	71.14	-31.19	3.43E-06	Trp 111-Tyr 209
3f	76.88	-29.44	6.95E-06	Trp 111-Tyr 209-His 110
3g	69.69	-28.91	8.60E-06	Trp 111-Tyr 209
3h	73.05	-28.44	1.04E-05	Trp 111-Tyr 209-Asp 160
3i	72.05	-33.97	1.11E-06	Tyr 48-Ser 210
Tolrestat	76.45	-30.68	4.21E-06	Tyr 48- His 110- Asp 160

The completion of the reaction was monitored by TLC, and the disappearance of the starting material was observed within 6-8 hrs. The results are summarized in Table 1. All the products were characterized and confirmed by their spectroscopic data.

For more study, 8-methyltetrazolo[5',1':2,3][1,3,4]thiadiazepino[7,6-b]quinoline (3b) was also further characterized by  $^1\text{H}$ ,  $^{13}\text{C}$  NMR spectroscopy and elemental analysis data. Our observation showed that the tetrazole ring in the product is relatively stable.

Although the mechanism of this reaction was not studied, the plausible mechanism for the synthesis of tetrazolo[5',1':2,3][1,3,4]thiadiazepino[7,6-b]quinoline derivatives is proposed in Scheme 2.

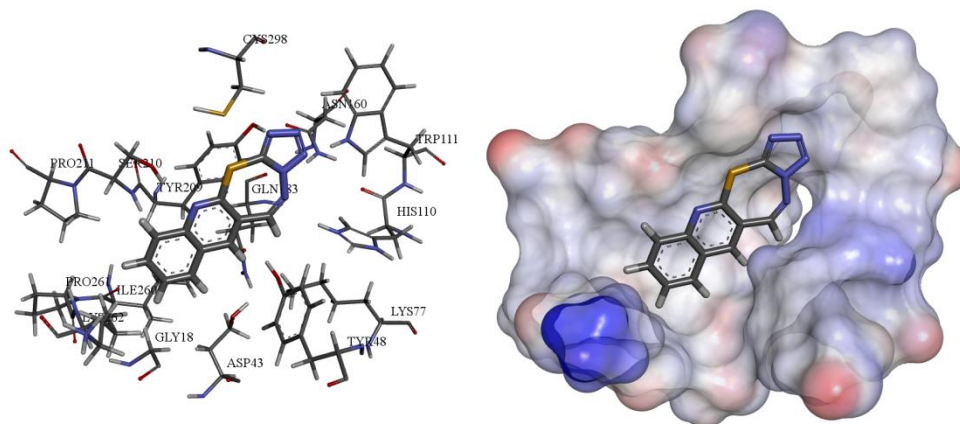
As shown in the Scheme 2, dehydration in the first step makes the intermediate (I) which, without isolating, converts to the products (3a-3i), in the presence of triethylamine as a mild base.

In order to study the generality of this method, we extended our studies to synthesis of some tetrazolo[5',1':2,3][1,3,4]thiadiazepino[7,6-b]quinoline

derivatives (3a-3i). The reactions proceeded very efficiently in relatively high yields as showed in Table 1.

### Docking

The receptor 1AH3 is a complex structure of enzyme with Tolrestat (ALR inhibitor) and NADP. The possible active site was identified using Accelrys DS Visualizer. Nine active site residues as Trp 20, Tyr 48, His 110, Trp 111, Thr 113, Phe 115, Phe 122, Leu 300 and Ser 302 were found by the removal of both tolrestat and NADP. Therefore it is chosen as a most biologically favourable site for docking. All of the best models formed strong hydrogen bonds with Tyr 209 and Trp 111 via tetrazole moiety (Figure 1). Pi-pi interaction between Tyr 209, Trp 20 and His 110 side chain and quinoline moiety was one of the common factors in enzyme-inhibitor junction. Amongst the synthetic compounds, 3g showed the lowest score while 3a possessed the highest score. The estimated inhibitory constant of the docked compounds are outlined in Table 2.

**Figure 1.** The best docked structure of 3a in the active site pocket of ALR (PDB entry: 1AH3) in stick (left) and solvent surface (right) views



## Discussion

The complete spectral and elemental analytical data of the products, confirmed the formation of new tetrazolo[5',1':2,3][1,3,4] thiadiazepino[7,6-*b*] quinoline derivatives (3a-3i). The <sup>1</sup>H NMR spectrum of 3b consist of three singlet signals at  $\delta$  8.53, 8.29, 7.72 due to two aromatic and one vinylic hydrogen, respectively. The singlet signal at  $\delta$  2.62 due to the methyl protons and two doublets for the two *ortho* hydrogens (on the aromatic ring of quinolines at  $\delta$  8.03 and 7.77 ppm) were confirmed to the structure. The <sup>1</sup>H decoupled <sup>13</sup>C NMR spectrum of 3b showed 12 distinct resonances at 155.4, 149.2, 148.1, 145.9, 142.1, 140.1, 136.4, 128.9, 127.5, 126.2, 126.1, and 21.8 in which they were in agreement with the suggested structure. Also the absence of the stretching vibration band at 1665 cm<sup>-1</sup> due to the carbonyl group (C=O) in IR spectrum confirmed the structure of **3b**. Comparison of the elemental analyses data of this compound which was in high agreement with calculated data was the final proof for this structure. Docking of tetrazolo[5',1':2,3][1,3,4]thiadiazepino[7,6-*b*]quinolines with ALR was performed by using of GoldScore fitness function. The algorithm exhaustively searched the entire rotational and translational spaces of the ligand with respect to the receptors. The various solutions valuated by a score, which is equivalent to the absolute value of the total energy of the ligand in the protein environment. For each compound the best docking solutions of GOLD score was considered. GoldScore carries out a force field based scoring function and is made up of four components: 1) Ligand internal van der Waals energy (internal vdw); 2) Ligand intermolecular hydrogen bond energy (internal-H-bond); 3) Protein-ligand hydrogen bond energy (external H-bond); 4) Protein-ligand van der Waals energy (external vdw). When the total fitness score is computed the external vdw score is multiplied by a factor of 1.375. This is an empirical correction to persuade protein-ligand hydrophobic interaction. The fitness function has been optimized for the divination of ligand binding positions. Goldscore was calculated by this formula: GoldScore =  $S_{(hb\_ext)} + S_{(vdw\_ext)} + S_{(hb\_int)} + S_{(vdw\_int)}$ ; where  $S_{(hb\_ext)}$  is the protein-ligand hydrogen bond score,  $S_{(vdw\_ext)}$  is the protein-ligand van der Waals score,  $S_{(hb\_int)}$  is the score from intermolecular hydrogen bond in the ligand and  $S_{(vdw\_int)}$  is the score from intramolecular strain in the ligand. Redocking of tolrestat resulted  $\Delta G = -30.68$  and  $K_i = 4.21E-06$ , bonding model of the mentioned molecule was similar to which was reported in the crystal structure of 1AH3. It was noted that GOLD scores of 3a and 3f are 78.83 and 76.88, respectively, which are greater than the other scores as shown in table.

## Conclusion

In summary we described an efficient and convenient synthesis of tetrazolo[5',1':2,3][1,3,4]

thiadiazepino[7,6-*b*]quinolines in valuing cyclocondensation reaction of 2-chloroquinoline-3-carbaldehydes and 1-amino-1H-tetrazole-5-thiol in catalyst-free condition. Docking was carried out using GOLD 5.2. It was found that both hydrogen bonding and hydrophobic interaction play important roles in the structure and function of biological molecules, peculiarly for inhibition in a complex. It was noted that GOLD scores of 3a and 3f are greater than the other scores.

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