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PII: S0223-5234(17)30275-1

DOI: 10.1016/j.ejmech.2017.04.021

Reference: EJMECH 9368

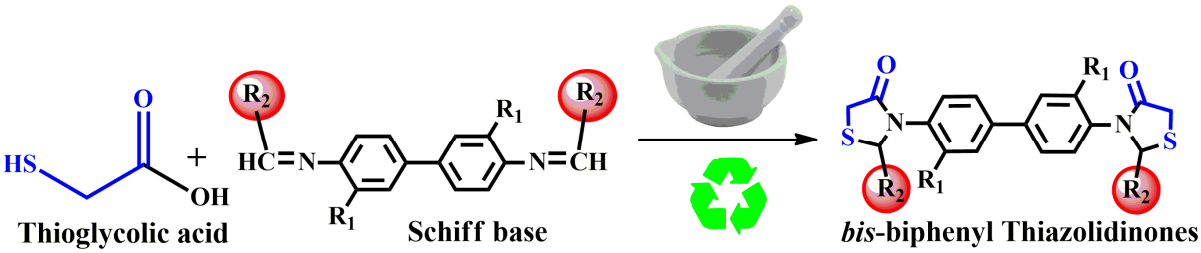
To appear in: *European Journal of Medicinal Chemistry*

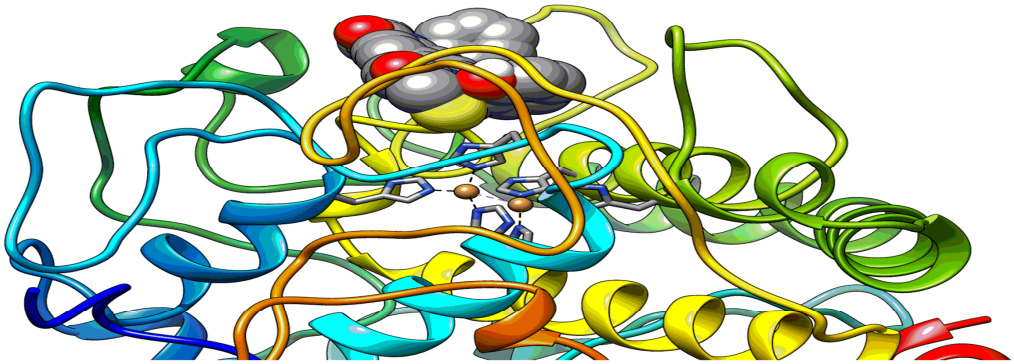
Received Date: 29 January 2017

Revised Date: 18 March 2017

Accepted Date: 11 April 2017

Please cite this article as: S. Mutahir, M.A. Khan, I.U. Khan, M. Yar, M. Ashraf, S. Tariq, R.-l. Ye, B.-j. Zhou, Organocatalyzed and mechanochemical solvent-free synthesis of novel and functionalized *bis*-biphenyl substituted thiazolidinones as potent tyrosinase inhibitors: SAR and molecular modeling studies, *European Journal of Medicinal Chemistry* (2017), doi: 10.1016/j.ejmech.2017.04.021.





Most Potent Inhibitor 3c inside the binding pocket

IC_{50} µM 0.61±0.05

Organocatalyzed and Mechanochemical Solvent-free Synthesis of Novel and Functionalized *bis*-Biphenyl Substituted Thiazolidinones as Potent Tyrosinase Inhibitors: SAR and Molecular Modeling Studies

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Abstract

Eluding the involvement of solvents in organic synthesis and introducing environment friendly procedures can control environmental problems. A facile and an efficient solvent free mechanochemical method (grinding) is achieved to synthesize novel *bis*-biphenyl substituted thiazolidinones using non-toxic and cheap *N*-acetyl glycine (NAG). Organocatalytic condensation of a series of Schiff's bases bearing different substituents with thioglycolic acid produces a variety of thiazolidinones derivatives in good to excellent yield. *In vitro* inhibition studies against mushroom tyrosinase of these thiazolidinone analogues revealed that many of them possessed good to excellent tyrosinase inhibition at low micro-molar concentrations. In particular, six compounds exhibited potent inhibitory potential with IC_{50} values ranging from 0.61±0.31 to 21.61±0.11 µM as compared with that of standard kojic acid (IC_{50} 6.04±0.11 µM). Further molecular docking studies revealed that the thiazolidinones moiety plays a key role in the inhibition mechanism by well fitting into the enzyme bounding pocket

Keywords: *N*-acetyl glycine, Thiazolidinones, Tyrosinase Inhibition

Introduction

Environmentally benign synthesis of chemicals and pharmaceutical agents remain a challenge from the very beginning. It has received great attention of scientists and technologists because of global ecosystem [1-3]. To solve this issue safe solvents, especially water and supercritical CO_2 or solvents with minimum vapour pressure (ionic liquids) are usually recommended. It has also been a good saying that "the best solvent is no solvent" [3]. The harmful effects of chemicals on the environment can be addressed by omitting solvents from synthetic cycle. Organic synthesis can be carried out in solvent free conditions [4] for example Mannich reactions [5], Mukaiyama-Aldol condensation [6], Prins cyclization [7], Suzuki-Miyara coupling reaction [8] and Passerini reaction [9]. One of the most important approaches for solvent free synthesis is known as mechanochemistry and its significance has been recognized for long time [10, 11]. Mechanochemical methods have gained interest [12-16] and provide a way to perform reactions in a neat environment. It follows the twelve rules of green chemistry [17], reduces the E factor and increases the sustainability of the chemistry [18, 19].

Many reactions have been performed very efficiently and conveniently even with solid reactants in eco-friendly conditions, which also reduce the cost of solvent. In the present work we explored the solvent free synthesis of thiazolidinones, an essential pharmacophore by the constitution. We employed the mechanochemical method by simply using mortar and pestle.

Tyrosinase (EC 1.14.18.1) is a multifunctional, glycosylated, copper-containing enzyme, and it is found exclusively in melanocytes. Tyrosinase is synthesized by melanosomal ribosomes found on the rough endoplasmic reticulum and catalyzes two distinct reactions both of which are essential for biosynthesis of melanin. This process proceeds *via* conversion of tyrosine to 3,4-dihydroxy phenylalanine (DOPA), a process termed tyrosinase monophenolase activity. The next step is the oxidation of DOPA into DOPA quinone, a process called diphenolase activity. The reactive ortho quinone, DOPA quinone, spontaneously polymerizes to high molecular weight melanin nonenzymatically [20, 21]. This process is a determinant of mammalian skin color and is closely related to local hyperpigmentations such as melasma, ephelide and lentigo. Recently, it has also been suggested that tyrosinase contributes to the neurodegeneration associated with Parkinson's disease [22]. Indeed, the unregulated action of tyrosinase can be a factor in a number of human disease etiologies. Thus, tyrosinase inhibition has been ardently explored as an avenue for therapies to these diseases. Over the last few decades, a large number of naturally occurring and synthetic compounds that can act as tyrosinase inhibitors have been reported, but only a few

of them are put into a practical use due to their weak activity or safety concerns. Tyrosinase inhibitors typically either render the copper within the active site inactive by chelation, obviating the substrate– enzyme interaction, or they inhibit oxidation *via* an electrochemical process [23]. We sought to evaluate thiazolidinone skeleton for their tyrosinase inhibition properties and to elucidate their inhibition mechanisms by molecular docking studies.

Thiazolidinones have been under great intention due to their privileged status in pharmaceutical sciences. The wonder nucleus gives out different derivatives with all different types of biological activities [24]. They exhibit a range of pharmacological activities including anti-hyperglycemic [25], anti-cancer [26], antiarthritic [27, 28], anti-inflammatory [29], anti-microbial [30], anti-convulsant [31], antidiarrheal [32], antihistaminic [33], anti-diabetic [34], cyclooxygenase (COX) inhibitory [35], antagonist [36], cardioprotective [37], necrosis factor-α antagonist [38], antitubercular [39] and as anti-HIV agents [40].

The first ever pharmacological evaluation of thiazolidinone as anti-tuberculosis (TB) agent was reported by Italian scientist, Vistentini' in 1954 [41] and then Marshall and Vallance reported the anti-convulsing activity in the same year [42]. In 1982, Sohda and co-workers evaluated thiazolidinones in hyperglycemia. Later in 1997, FDA (Food and Drug Administration) approved "troglitazone" (TZD) in hyperglycemic conditions [43, 44]. Thereafter, in 1999, two more TZD derivatives, 'rosiglitazone' and 'pioglitazone' gained FDA (Food and Drug Administration) approval [45]. Moreover, a vast of studies have been done on the role of thiazolidinones and the risk of incident congestive heart failure among patients with type-2 diabetes mellitus [46-48]. In 2011, Wei and Wan studied the role of thiazolidinones in bone remodeling [49, 50].

In the recent decades, the synthesis of substituted thiazolidinones and related compounds has attracted considerable attention because these compounds constitute the structural frameworks of several naturally occurring alkaloids that show a wide range of pharmaceutical and industrial importance [51]. Subsequently, there have been uninterrupted curiosities in the improvement of new synthetic protocols for the construction of the 4-thiazolidinone scaffold [52-62].

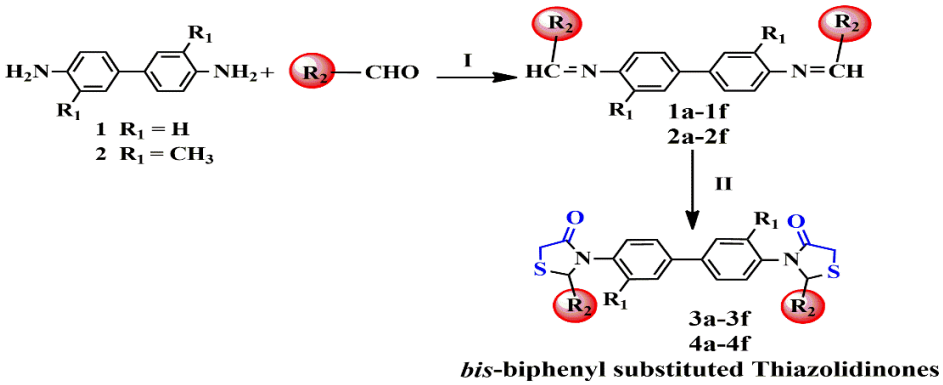
Moisture and oxygen free, inexpensive and non-toxic organocatalysts are very effective for chemical conversions [4]. They are usually preferred over transition metal catalysts in pharmaceutical synthesis. Our group planned to seek potent and environment friendly organocatalyst for the synthesis of novel biologically potent pharmacophores [63-66] with better yield and easy purification workup [67]. Here, we propose a novel synthetic protocol for the synthesis of new benzidine based thiazolidinone analogues using NAG as an organocatalyst.

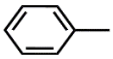
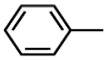
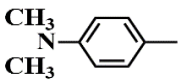
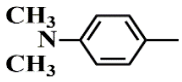
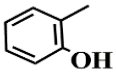
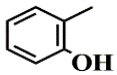
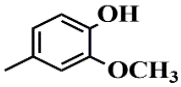
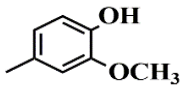
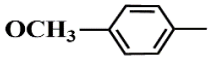
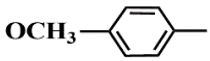
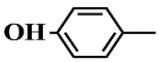
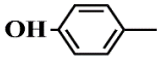
Keeping in view the synthetic chemistry of thiazolidinones in literature, it was thought that a catalyst is required, which can facilitate the removal of water during the cyclocondensation step of the synthesis as it seems the most critical step in obtaining the higher yields of 4-thiazolidinones and it can be enhanced by the use of appropriate catalyst. Therefore, we decided to explore the catalytic potential of NAG as it activates the removal of water by protonation of in *situ* moieties (scheme 2).

Results and Discussion

Chemistry

In general, our protocol comprises of synthesis of *bis*-biphenyl thiazolidinones in two steps. Firstly the selected diamines, benzidine (**1**) and *o*-toluidine (**2**) were refluxed with different aromatic aldehydes for 4-5 hrs by using ethyl alcohol as ~~a~~ solvent and glacial acetic (few drops) acid as ~~a~~ catalyst. Solid which appeared after cooling was filtered, washed with *n*-hexane and dried. In the second step the intermediates (**1a-1f & 2a-2f**) formed in the first step condensed with thioglycolic acid in different conditions and got 5- membered *bis*-biphenyl substituted thiazolidinones (**3a-3f & 4a-4f**) (scheme 1). We selected the reaction of Schiff base (**1e**) with thioglycolic acid to optimize the reaction conditions. We performed the reaction under different catalysts, solvents, and also optimized the temperature and finally summarized the result (table 1). We started the optimization process in the absence of catalyst and using toluene as solvent where the product was obtained 52 % after 12 hr of reflux (table 1 entry 1). We further tested reaction under different conditions (table 1, entry 2-6). The changes in the conditions led to different yields of the product (**3e**) ranging from 25 - 94 %. The minimum yield of the product was observed in the reaction having Et_3N as catalyst (table 1, entry 3). The poor performance is presumably due to Et_3N not promoting a clean cyclisation process in the conversion of Schiff base to thiazolidinone (**3e**). The yield of the product was improved by performing the reaction in the presence of NAG as catalyst and toluene as solvent resulting in the production of 88 % of **3e** (table 1, entry 5). The catalytic action of NAG was also observed in the absence of solvent only providing mechanochemical conditions. After screening all the conditions, it was found that this mechanical energy has promotion effects on the reaction and this was emerged as the best choice among all provided conditions which yield the maximum % age (94 %) of the product (table 1, entry 6).



Compd	R_1	R_2	Compd	R_1	R_2
3a	H		4a	CH_3	
3b	H		4b	CH_3	
3c	H		4c	CH_3	
3d	H		4d	CH_3	
3e	H		4e	CH_3	
3f	H		4f	CH_3	

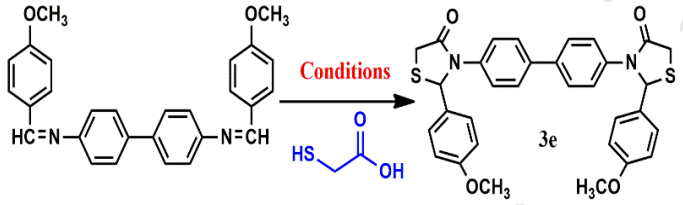
Scheme 1: Synthesis of Schiff bases from 1 & 2 (1a-1f) and (2a-2f). Synthesis of *bis*-biphenyl substituted thiazolidinones (3a-3f & 4a-4f) from 1a-1f and 2a-2f.

Subsequently, the amount of NAG required for this reaction in solvent-free and mechanochemical environment was also investigated (table 1, entry 1-4). The maximum amount of the product was calculated by using 2.0 equivalents of NAG as catalyst (table 1, entry 4) and it was observed that the amount of NAG is reciprocal to the product yield up to the maximum concentration of 2 equivalents. Decreasing amount of NAG decreased the amount of product (table 1, entry1-3) and vice versa. Thus, 2 equivalent of NAG as catalyst in solvent-free environment is the optimized condition for this reaction (graph 1). With the optimized conditions in hands, a series of Schiff bases were applied to establish the scope and generality of this protocol affording the respective thiazolidinone in good to excellent (79-92 %) yields in 5-8 hrs

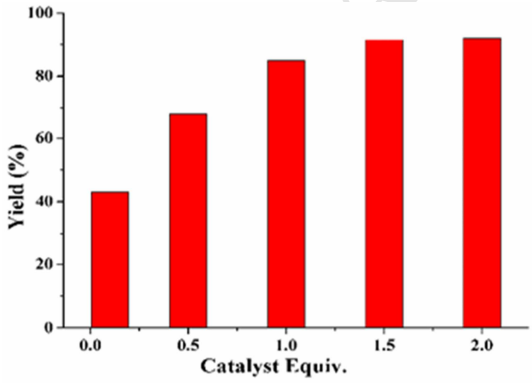
of reflux (figure 1). The final products were identified by FTIR, ^{1}HNMR, ^{13}CNMR and CHNS analysis (**see SI**).

Table 1: Optimization of conditions for the synthesis of **3e**

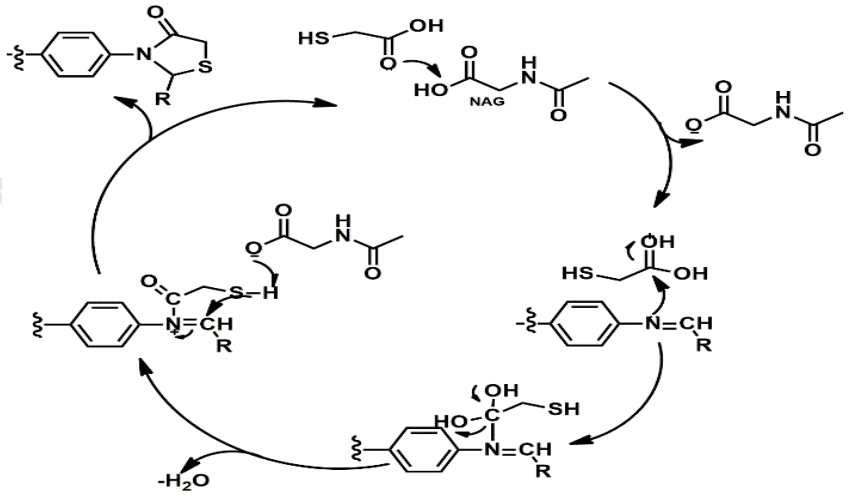
Entry	Catalyst	Solvent	Temp (^{0}C)	Time (hr)	Yield (%)
1	None	toluene	reflux	12	52
2	Et_3N	Et_3N	r.t	24	25
3	Pyridine	toluene	reflux	11	46
4	Hunig Base	toluene	reflux	10	85
5	NAG	toluene	reflux	7	88
6	NAG	None	80 ^{0}C	5	94
7	NAG	None	100 ^{0}C	7	89



Scheme 2: Synthetic protocol for model substrate (**3e**) under different conditions described in table 1.



Graph 1: Optimization of concentration of NAG in solvent-free environment.



Scheme 3: Proposed mechanism of thiazolidinone synthesis *via* NAG.

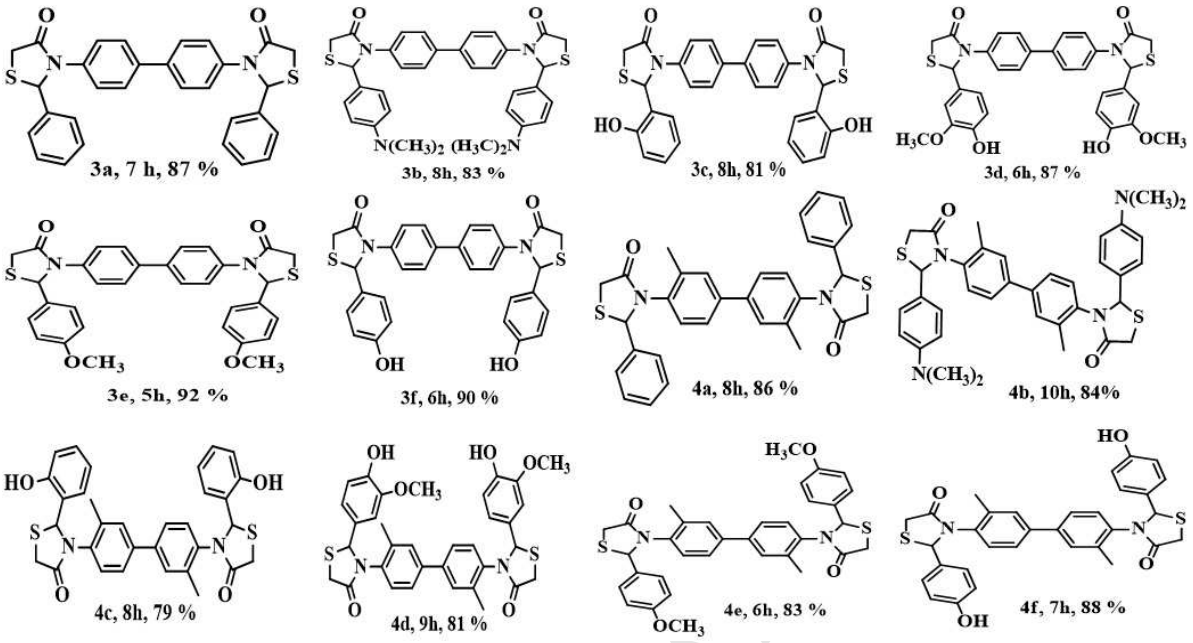


Figure 1: Structures of *bis*-biphenyl thiazolidinones (**3a-3f & 4a-4f**) synthesized *via* the solvent free protocol using NAG as the catalyst.

The plausible catalytic mechanism of our reaction is illustrated in scheme 3. The first step of the mechanism involves ~~in~~ the protonation of thioglycolic acid from NAG followed by the nucleophilic attack of lone pairs of –*N* of Schiff base at the nucleophilic carbon center producing an intermediate having germinal diol. Geminal diol is an unstable moiety which is readily converted to ketonic group by removing the water molecule. In the next step, deprotonation of this intermediate is facilitated by the attack of *N*-acetyl ethanoate on the –H of the thio group followed by the cyclization of the intermediate.

Inhibition against tyrosinase

The six compounds of this novel series of thiazolidinones showed potent inhibitory potentials against mushroom tyrosinase which is a key enzyme for melanin biosynthesis (both in plants and animals) **[68]**. The inhibitory potential depends upon the size, shape and the interactive forces between the inhibitor and the enzyme. In order to explore the structure activity relationship, the two parent molecules, benzidine (**1**) and 3,3'-dimethylbihenyl-4,4'-diamine (**2**) and twelve

thiazolidinones derivatives (**3a-3f & 4a-4f**) were subjected to *in vitro* tyrosinase inhibition assay using kojic acid (IC_{50} 6.04±0.11 µM) as the standard. Kojic acid is the famous whitening agent and widely used in cosmetics, but due to its cytotoxicity level, there is a need to search for better tyrosinase inhibitors with no or less toxic. The parent molecules have shown negligible activity (only 20-23 % inhibition for both for both **1** and **2**). But the *bis*-biphenyl substituted thiazolidinones showed significant potential than the parent molecules and even some of them show inhibition efficiency better than the standard and their lowest IC_{50} values reaches 0.61±0.31µM. The *bis*-biphenyl substituted thiazolidinones contain the electron donating groups such as hydroxyl, methoxy, dimethyl amino and electron withdrawing groups such as phenyl ring. The inhibition potential against tyrosinase by six best thiazolidinones derivatives synthesized decreased as: **3c > 3d > 4d > 3e > 4a > 3a**. Among them, **3c** was the most potent with an IC_{50} value of 0.61±0.31µM. The compound **3c** possessed the hydroxyl group along with thiazolidinone group which might be responsible for its inhibitory potential.

Both compounds **3d** (IC_{50} = 2.41±0.32) and **4d** (IC_{50} = 2.81±0.06) also exhibited potent inhibition than the standard. Methyl substitutions on the biphenyl ring of **4d** seem to have a trifle effect on its inhibition ability towards the tyrosinase. The analogue **3e** (IC_{50} = 4.41±0.10) also showed the potent inhibition having methoxy group along with thiazolidinone ring. The compound **4a** having IC_{50} = 7.71±0.21 also showed good inhibition against the enzyme wherein thiazolidinone ring is effectively taking part in the inhibition of tyrosinase, though hydroxyl and methoxy groups enhanced their inhibitory potential. **3a** also showed inhibitory potential (IC_{50} = 21.61±0.11) but three-fold less than **4a** having the same skeleton instead of methyl groups at biphenyl ring.

On the other hand, analogues **3b** and **4b** did not show any remarkable inhibition against tyrosinase, which might be due to bulky substituents of these analogues. Compounds **3f, 4c** and **4f** also did not show any notable inhibition either, suggesting that the positions of substituents are very crucial. Thus, *para*- hydoxyl substituted analogues were inactive while *ortho* substituted showed inhibition potential. However, in the case of **4c**, which is a combination of **3c** and **4a**, methyl groups at biphenyl ring render it inactive. These comparisons suggest that thiazolidinone moiety is necessary but not sufficient to achieve higher inhibition potency.

Table 2: *In vitro* tyrosinase inhibitory activity of compounds (**1 & 2**) and **(3a-3f & 4a-4f)** (inhibition percentage and IC_{50} values are means given with SEM).

Sample Codes	Inhibition (%) at 0.5 mM	IC_{50} µM
1	23.35±0.17	-
2	20.25±0.15	-
3a	94.85±0.18	21.61±0.11
3b	20.96±0.19	-
3c	99.08±0.16	0.61±0.05
3d	96.32±0.48	2.41±0.32
3e	98.91±0.19	4.41±0.11
3f	78.03±0.21	342.52±0.17
4a	99.63±0.16	7.71±0.12
4b	51.63±0.14	<500
4c	22.79±0.15	-
4d	98.43±0.12	2.81±0.06
4e	49.36±0.47	-
4f	39.41±0.61	-
Kojic Acid	93.51±0.91	6.04±0.11

Order of inhibition of Tyrosinase

3c > 3d > 4d > 3e > 4a > 3a > 3f

Molecular Docking Studies

Molecular dockings were carried out for the inhibitors **3a, 3c, 4a** and **4d** in order to further investigate the binding mechanism. Apparently, their large sizes prevent them from entering the narrow binuclear copper-binding site, however, they are well accommodated and bound at the surface of the enzyme binding pocket. Thus, the binuclear copper-binding site at the bottom of the enzyme binding pocket is efficiently blocked so that small ligand such as tropolone is competitively excluded (see Sec. 3 of the Supporting Information). In general, the two central benzene rings of the inhibitors are in parallel with the enzyme surface, while one of the two end benzene substituted TZD moieties fits into the residue pocket formed by Asn81, Cys83, His85, Glu322, and Thr324. As shown in Fig. 2 (a), both hydroxyl groups at the ortho-position of **3c** form H bonds with the oxygen atoms of two residues, i.e., Gly281 and Glu322, with bond lengths of 1.77 Å and 2.05 Å respectively. However, no H bond is observed between **4d**, whose hydroxyl groups are at the para- positions, and enzyme. Thus, the interaction between the inhibitor **3c** and enzyme is enhanced by the H bonding interactions, which can lead to high binding affinity. The similar binding poses of **3c** and **4d** are compared in fig. 2 (e). For **3a** and

4a, their end benzene rings contain no substitutions. We expect their binding by the enzyme less strong, but more flexible. The methyl groups in the biphenyl ring alter the orientation of the end benzene groups, which leads to more favorable interactions between the inhibitor and the enzyme. As compared in fig. 2 (f), the end moieties of **4a** orient toward the enzyme binding pockets better than that of **3a** despite the high resemblance of their binding poses. This results in better shape fitness of the former with the host and thus its higher activity toward the tyrosinase.

The structure of *agaricus bisporus* mushroom tyrosinase was obtained from the protein data bank (PDB code: 2Y9X) [69]. The structures of inhibitors were optimized at B3LYP/6-31G (d) level using Gaussian03 [70]. Docking studies were performed for four inhibitors using Autodock package [71]. Residues within 5 Å of the inhibitors were identified using VMD program [72]. The distance cut off and angle threshold were set to 3 Å and 150 Å, respectively, in order to identify the H bonds between the inhibitor and the enzyme.

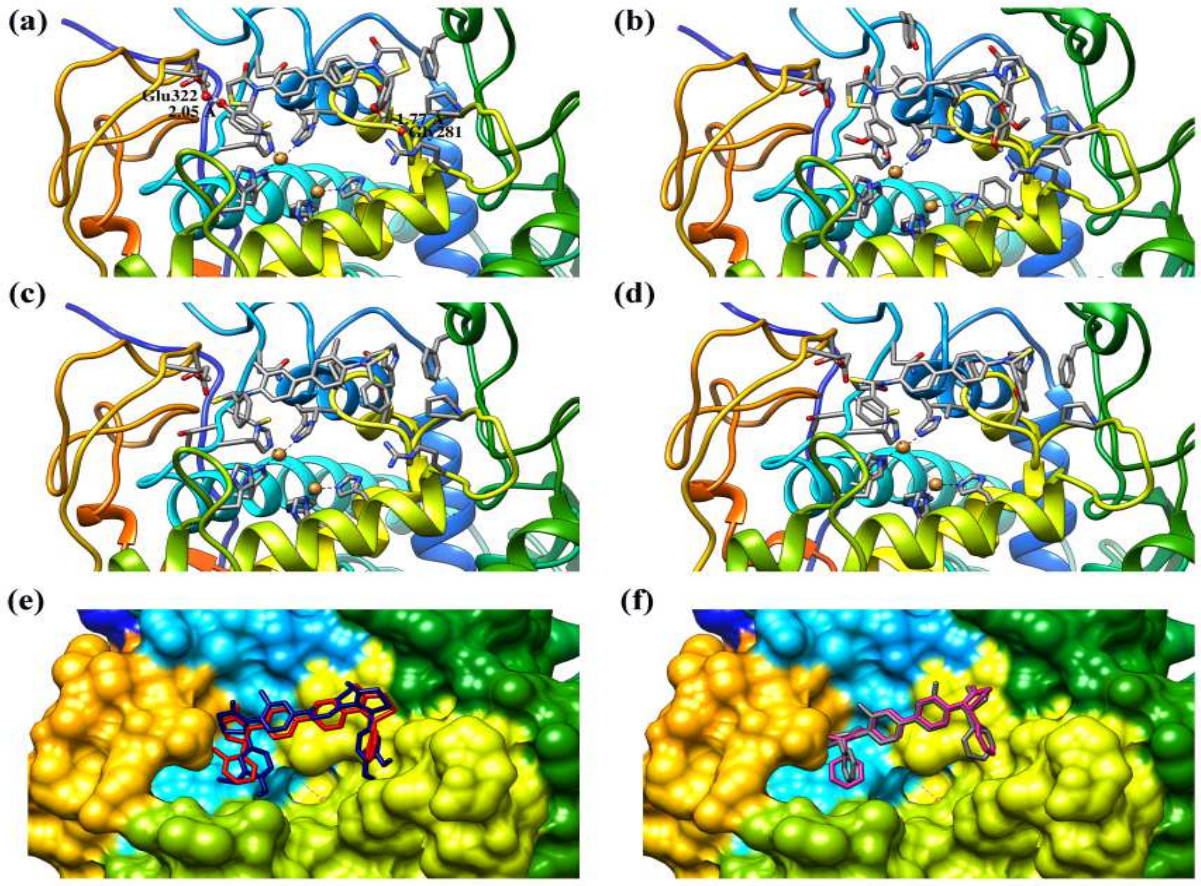


Figure 2: Illustrations of close contacts between the residues and inhibitors: (a) **3c**, (b) **4d**, (c) **4a**, (d) **3a**. Cu^{2+} ions are displayed in green spheres. Two H bonds are represented with black dash lines in (a). Binding modes of **3c** (red sticks)and **4d** (blue sticks) are compared in (e) and those of **4a** (grey stick) and **3a** (pink stick) are compared in (f). Surface representations are employed for the enzyme.

Conclusions

In summary, we have developed an efficient process for the synthesis of thiazolidinones, in which the use of NAG as a catalyst along with mechanical energy leads to better yields than other solvents and catalysts. A mechanistic insight reveals that the catalytic protonation and subsequent removal of water molecule during the cyclo-condensation of thiazolidinone is the key step of the reaction. This new catalytic method provides distinct advantages, including: (i) mild conditions, (ii) high yields, (iii) free of organic solvents with economic and environmental-friendly perspective (iv), easy to prepare the catalyst and (v) simple work-up procedures, making it more environmentally friendly and suitable for large scale operations. The new bioactive compounds were also shown good to excellent inhibition against tyrosinase.

Experimental Section

General Method

Reagents were purchased from common commercial suppliers and were used without further purification. Solvents were purified and dried by standard procedures, when necessary. TLC was performed on silica coated aluminum plates ($6F_{254}$, 0.2 mm). ^{1}H and ^{13}CNMR were recorded at 400 and 175 MHz, respectively, and DMSO was used as internal standard. IR spectra were recorded on a Jasco A-302 IR spectrophotometer.

General procedure for the synthesis of Schiff bases (Intermediate)

Schiff bases of selected diamines were synthesized by reported method with slight modification [73].To a solution of benzidine (1) or 3, 3'-dimethylbiphenyl-4,4'-diamine (2) (0.01 mol or 1 eq) in absolute ethanol (8-10 ml) added few drops of acetic acid . Then respective aldehyde (0.022 mol or 2 eq) was added into the solution and mixture was refluxed at 80 ^{0}C for 5-8 hrs. The reaction was monitored by TLC. After the completion of reaction, kept the reaction mixture in refrigerator for overnight. The solid was obtained, filtered and washed with water followed by *n*-hexane and recrystallized with suitable solvent.

General procedure for the synthesis of thiazolidinones derivatives (3a-3f & 4a-4f) without any catalyst or reagent

In the reaction flask (50ml) added Schiff base (1 mmol) and marcaptoacetic acid (2.05 mmol) in the presence of toluene (10 ml) and refluxed for 8-12 hours at 80 ^{0}C. After completion of the reaction, as confirmed by TLC the reaction mixture was cooled to RT. The solvent was evaporated under reduced pressure and solid product was washed with aqueous $NaHCO_3$ solution to remove excess of marcaptoacetic acid. The solid product was then dried and percentage yield was calculated.

General procedure for the synthesis of thiazolidinones in different solvents by using catalyst

Schiff base **3e** (1 mmol) and thioglycolic acid (2.05 mmol) were refluxed together in a round bottom flask (50ml) in the presence of 10 ml of selected solvents and appropriate catalyst and refluxed for 8-12 hours at 80 ^{0}C. At the end of the reaction, after confirmation through TLC, the solvent was evaporated and solid product was washed with aq. $NaHCO_3$ solution to remove excess of thioglycolic acid. The solid product was then dried and percentage yield was calculated.

General procedure for the synthesis of thiazolidinones in the absence of solvent by using NAG as catalyst

A mixture of Schiff base (1 mmol), thioglycolic acid (2.05 mmol) and NAG (2.0 mmol) were finely ground in a mortar and pestle. Then finely grounded mixture was transferred to the Pyrex glass round bottom flask which was stirred for 3-5 hours at 100 ^{0}C. After the completion of reaction (TLC analysis), the solid was washed with 5 % solution of $NaHCO_3$ to remove excess of thioglycolic acid. Product was isolated with solvent extraction in ethyl acetate, crystallized, dried and % age yield was also calculated.

Spectral Data

3,3'-(biphenyl-4,4'-diyl)bis(2-phenylthiazolidin-4-one) (3a)

Brown solid; mp = 235-237 $^\circ$C; IR (KBr) ν_{max}: 1340 (C-N), 1712 (C=O), 3014 (Ar-C); ^{1}H-NMR: (500 MHz, DMSO): 7.63-7.58 (4H, m, ArH), 7.42 (4H, d, *J* = 7.05 Hz, ArH), 7.36-7.29 (10H, m, ArH), 5.37 (2H, s, CH), 3.52 (2H, d, CH_2), 3.43 (2H, d, CH_2), ^{13}C-NMR: (175 MHz, DMSO); 170.8 (C=O, 2C), 139.7 (2C), 139.1 (2C), 128.7 (2C), 128.2 (2C), 127.5 (2C), 127.5 (2C). 126.9

(2C), 126.6 (2C), 125.7 (4C), 119.9 (2C), 119.5 (2C), 52.9, 52.7, 34.2, 34.3; CHNS; Calculated: C, 70.84; H, 4.76; N, 5.51; O, 6.29; S, 12.61. Found: C, 70.75; H, 4.66; N, 5.56; S, 12.62.

3,3'-(biphenyl-4,4'-diyl)bis(2-(4-(dimethylamino)phenyl)thiazolidin-4-one) (3b)

Light Brown solid; mp = 238-240 °C; IR (KBr) ν_{max}: 1348(C-N). 1693 (C=O), 3310 (Ar-C); ^{1}H-NMR: (500 MHz, DMSO): 7.64-7.59 (4H, m, ArH), 7.19 (4H, d, *J* = 8.8 Hz, ArH), 7.11 (4H, d, *J* = 8.4 Hz, ArH), 6.68-6.61 (4H, m, ArH), 5.16 (2H, s, CH), 3.92 (2H, d, CH_2), 3.75 (2H, d, CH_2), 3.06 (12H, s, N-CH_3); ^{13}C-NMR: (150 MHz, DMSO): 170.3 (C=O, 2C), 150.0 (2C), 137.9 (2C), 134.7 (2C), 129.6 (2C), 128.3 (2C), 126.5 (2C), 122.6 (4C), 119.6 (4C), 112.7 (2C), 111.9 (2C), 52.5 (2C), 42.9 (4C, CH_3), 33.9 (2C); CHNS: Calculated: C, 68.66; H, 5.76; N, 9.42; O, 5.38; S, 10.78. Found: C, 68.61; H, 5.75; N, 9.47; S, 68.60.

3,3'-(biphenyl-4,4'-diyl)bis(2-(2-hydroxyphenyl)thiazolidin-4-one): (3c)

Yellow solid; m.p.: 232-234 °C; IR (KBr) ν_{max}: 1330(C-N), 1713 (C=O), 3340 (Ar-OH); ^{1}H-NMR: (500 MHz, DMSO): 7.58 (4H, d, *J* = 9.5 Hz, ArH), 7.35 (4H, d, *J* = 7.06 Hz, ArH), 7.09-7.06 (4H, m, ArH), 6.81-6.72 (4H, m, ArH), 5.56 (2H, s, CH,), 5.02 (2H, s, OH), 3.61 (2H, d, CH_2), 3.55 (2H, d, CH_2); ^{13}C-NMR: (175 MHz, DMSO): 167.0 (C=O, 2C), 154.6 (2C), 139.1 (2C), 138.5 (2C), 128.2 (2C), 127.5 (2C), 127.1 (4C), 126.5 (2C), 119.7 (2C), 119.4 (2C), 118.9 (2C), 114.4 (2C), 52.9 (2C), 35.6 (2C); CHNS: Calculated C, 66.65; H, 4.47; N, 5.18; O, 11.84; S, 11.86. Found: C, 66.60; H, 4.45; N, 5.20; S, 11.85.

3,3'-(biphenyl-4,4'-diyl)bis(2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one): (3d)

Yellowish-Brown solid; m.p.: 237-239 °C; IR (KBr) ν_{max}: 1712 (C=O), 1546 (C=C), 1340 (C-N); ^{1}H-NMR: (500 MHz, DMSO): 7.63 (4H, d, *J* = 8.25 Hz, ArH), 7.42 (2H, s, ArH), 7.09-6.91 (6H, m, ArH), 6.77 (2H, d, *J* = 9.75 Hz, ArH), 5.57 (2H, s, CH), 5.17 (2H, s, OH-ArH), 3.85 (2H, d, CH_2), 3.73 (2H, d, CH_2), 3.65 (6H, s, OCH_3); ^{13}C-NMR: (175 MHz, DMSO): 170.6 (C=O, 2C), 147.5 (2C), 146.5 (2C), 132.8, 132.8, 139.1 (2C), 134.6 (2C), 126.8 (2C), 126.6 (2C), 120.3 (2C), 120.0 (2C), 119.7, 119.5, 115.5, 115.3, 111.5 (2C), 55.7 (2C), 55.6 (2C), 34.2, 34.9; CHNS: Calculated C, 63.98; H, 4.70; N, 4.66; O, 15.98; S, 10.68. Found: 63.94; H, 4.70; N, 4.68; S, 10.66.

3,3'-(biphenyl-4,4'-diyl)bis(2-(4-methoxyphenyl)thiazolidin-4-one) (3e)

Dark Brown solid; m.p.: 246-248 °C; IR (KBr) ν_{max}: 1715 (C=O), 1546 (C=C), 1340 (C-N); ^{1}H-NMR: (500 MHz, DMSO): 7.66-7.58 (8H, m, ArH), 7.34 (4H, d, *J* = 8.5 Hz, ArH), 6.76-6.74 (4H, d, *J* = 9.5 Hz, ArH), 5.56 (2H, s, CH), 3.73 (2H, d, CH_2), 3.66 (2H, d, CH_2), 3.33 (6H, s, OCH_3); ^{13}C-NMR: (175 MHz, DMSO): 170.8 (C=O, 2C), 159.2 (2C), 139.3 (2C), 137.9 (2C), 134.8 (2C), 130.6 (4C), 128.7 (4C), 126.4 (4C), 114.0 (2C), 55.1 (2C), 52.2 (2C), 36.5 (2C);

CHNS: Calculated C, 67.58; H, 4.96; N, 4.93; O, 11.25; S, 11.28. Found: C, 67.66; H, 4.97; N, 4.89; S, 11.29.

3,3'-(biphenyl-4,4'-diyl)bis(2-(4-hydroxyphenyl)thiazolidin-4-one) (3f)

Yellow Solid; M.P.: 239-241 ^{0}C; IR (KBr) ν_{max}: 1712 (C=O), 1546 (C=C), 3340 (OH); ^{1}H-NMR: (500 MHz, DMSO): 7.63-7.59 (8H, m, ArH), 7.42 (2H, d, *J* =7.6 Hz, ArH), 7.33 (4H, d, *J* = 9.5 Hz, ArH), 5.62 (2H, s, CH), 5.57 (2H, s, OH-ArH), 3.52 (2H, d, CH_2), 3.39(2H, d, CH_2); ^{13}C-NMR: (175 MHz, DMSO): 170.8 (2C), 156.9 (2C), 139.1 (2C), 138.5 (2C), 133.5 (2C), 131.5 (2C), 128.5 (2C), 127.1 (2C), 126.5 (2C), 119.7 (2C), 119.4 (2C), 115.1 (2C), 111.4 (2C), 55.1 (2C), 36.5, 34.0 CHNS: Calculated: C, 66.65; H, 4.47; N, 5.18; O, 11.84; S, 11.86.
Found: C, 66.59; H, 4.57; N, 5.20; S, 11.79.

3,3'-(3,3'-dimethylbiphenyl-4,4'-diyl)bis(2-phenylthiazolidin-4-one) (4a)

Coffee-Brown solid; M.P.: 245-247 ^{0}C; IR (KBr) ν_{max}: 1735 (C=O), 1546 (C=C), 2340 (C-C); ^{1}H-NMR: (500 MHz, DMSO): 7.52 (2H, s, ArH), 7.46 (2H, d, *J* = 8.5 Hz, ArH), 6.88-6.84 (2H, m, ArH), 6.76-6.74 (2H, m, ArH), 5.62 (2H, s, CH), 3.35 (2H, d, CH_2), 3.27 (2H, d, CH_2), 2.48 (6H, s, CH_3); ^{13}C-NMR: (175 MHz, DMSO): 170.8(2C), 139.3 (2C), 137.9 (2C), 136.4 (2C), 135.6, 135.7, 135.1, 133.6, 131.7, 129.1, 128.6, 128.6, 128.2, 128.1, 127.6, 127.5, 125.0, 124.2, 124.0 (2C), 52.9 (2C), 34.2, 34.0, 18.2, 17.9. CHNS: Calculated: C, 71.61; H, 5.26; N, 5.22; O, 5.96; S, 11.95. Found: C, 71.64; H, 5.36; N, 5.28; S, 11.97.

3,3'-(3,3'-dimethylbiphenyl-4,4'-diyl)bis (2-(4-(dimethylamino) phenyl) thiazolidin-4-one) (4b)

Dark Brown Solid; M.P.: 250-252 ^{0}C; IR (KBr) ν_{max}: 1732 (C=O), 1546 (C=C), 1340 (C-N); ^{1}H-NMR (500 MHz, DMSO): 7.50-7.44 (4H, m, ArH), 7.32 (2H, d, *J* = 8.05 Hz, ArH), 7.21 (4H, d, *J* = 8.55 Hz, ArH), 6.67-6.63 (4H, m, ArH), 5.50 (2H, s, CH), 3.81 (2H, d, CH_2), 3.69 (2H, d, CH_2), 3.06 (12H, s, N-CH_3), 2.48 (6H, s, CH_3); ^{13}C-NMR (175 MHz, DMSO): 167.0 (2C), 149.5 (2C), 135.27 (2C), 131.64 (2C), 129.86 (2C), 129.66 (2C), 128.89 (2C), 128.29 (2C), 124.79 (2C), 124.0 (4C), 112.7 (2C), 112.3 (2C), 52.7 (2C), 40.1 (2C), 40.0 (2C), 38.9 (2C), 17.9 (2C); CHNS: Calculated C, 69.42; H, 6.15; N, 9.00; O, 5.14; S, 10.30. Found: C, 69.48; H, 6.17 N, 9.09; S, 10.31.

3,3'-(3,3'-dimethylbiphenyl-4,4'-diyl)bis(2-(2-hydroxyphenyl)thiazolidin-4-one) (4c)

Light Brown Solid; M.P.: 247-249 ^{0}C; IR (KBr) ν_{max}: 17132 (C=O), 1546 (C=C), 1340 (C-N); ^{1}H-NMR: (500 MHz, DMSO): 7.53 (2H, m, ArH), 7.44 (2H, d, *J* = 9.5 Hz, ArH), 7.32 (2H, d, *J* = 7.5 Hz, ArH), 6.73 (4H, m, ArH), 6.67-6.61 (4H, m, ArH), 5.56 (2H, s, CH), 5.20 (2H, s, OH-

ArH), 4.15 (2H, d ,CH_2), 4.00 (2H, d ,CH_2), 2.28 (6H, s, CH_3); ^{13}C-NMR: (175 MHz, DMSO): 167.4 (2C), 159.1 (2C), 137.9 (2C), 134.8 (2C), 129.5 (2C), 128.0 (2C), 126.5 (2C), 125.1 (2C), 122.1 (2C), 125.1 (2C), 119.7 (2C), 118.9 (2C), 113.6 (2C), 52.9 (2C), 36.6 (2C), 17.8 (2C); CHNS: Calculated C, 67.58; H, 4.96; N, 4.93; O, 11.25; S, 11.28. Found: C, 67.58; H, 4.97; N, 4.95; S, 11.31.

3,3'-(3,3'-dimethylbiphenyl-4,4'-diyl)bis(2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one) (4d)

Light Brown Solid; M.P.: 257-259 ^{0}C; IR (KBr) ν_{max}: 1735 (C=O), 1526 (C=C), 3340 (OH); ^{1}H-NMR: (500 MHz, DMSO); 7.63 (2H, s, ArH), 7.60 (2H, d, *J* = 8.25, ArH), 7.42 (2H, s, ArH), 7.32 (2H, d, *J* = 7.5, ArH), 7.09 (2H, m, ArH), 6.77 (2H, d, *J* = 9.5, ArH), 5.57 (2H, s, CH), 5.05 (2H, s, OH, ArH), 3.85 (2H, d, CH_2), 3.75 (2H, d, CH_2), 3.36 (6H, s, OCH_3), 2.48 (6H, s, CH_3); ^{13}C-NMR: (175 MHz, DMSO); 170.9, 170.6, 147.5 (2C), 146.5 (2C), 137.5 (2C), 137.2 (2C), 134.6 (2C), 130.0 (2C), 126.8 (2C), 126.6 (2C), 120.3 (2C), 119.7 (2C), 119.5 (2C), 115.5, 115.3, 55.7, 55.6, 40.7, 40.1, 34.2, 34.1, 17.9 (2C); CHNS: Calculated C, 64.95; H, 5.13; N, 4.46; O, 15.27; S, 10.20. Found: C, 64.94; 5.12; N, 4.41; S, 10.22.

3,3'-(3,3'-dimethylbiphenyl-4,4'-diyl)bis(2-(4-methoxyphenyl)thiazolidin-4-one) (4e)

Dark Brown Solid; M.P.: 256-258 ^{0}C; IR (KBr) ν_{max}: 1732 (C=O), 1549 (C=C), 1333(C-N); ^{1}H-NMR (500 MHz, DMSO): 7.66-7.58 (8H, m, ArH), 6.91 (4H, d, *J* = 7.0 Hz, ArH), 6.76-6.74 (2H, m, ArH), 5.23 (2H, s, CH), 3.84 (2H, d, CH_2), 3.74 (2H, d, CH_2), 3.49 (6H,s,OCH_3), 3.19 (6H, s, CH_3); ^{13}C-NMR (175 MHz, DMSO): 170.8 (2C), 159.1 (2C), 139.3 (2C), 137.9 (2C), 136.4 (2C), 135.6, 135.3, 135.0, 133.6, 131.7, 129.1, 128.7, 128.6, 128.3, 128.1, 127.6, 127.5, 125.0, 124.2, 124.0 (2C), 52.9, 52.7, 34.2, 34.0, 18.2, 17.9; CHNS: Calculated: C, 71.61; H, 5.26; N, 5.22; O, 5.96; S, 11.95. Found: C, 71.64; H, 5.26; N, 5.21; S, 11.91.

3,3'-(3,3'-dimethylbiphenyl-4,4'-diyl)bis(2-(4-hydroxyphenyl)thiazolidin-4-one): (4f)

Yellow Solid; M.P.: 240-242 ^{0}C; IR (KBr) ν_{max}: 1730 (C=O), 1596 (C=C) ,1342 (C-N); ^{1}H-NMR (500 MHz, DMSO): 7.82 (4H, d, *J* = 9.5 Hz, ArH), 7.78 (4H, d, *J* = 7.6 Hz, ArH), 7.47 (4H, d, *J* = 8.2 Hz, ArH), 7.39 (2H, d, *J* = 9.5 Hz, ArH), 7.35 (2H, d, *J* = 7.6 Hz, ArH), 7.12 (4H, d, *J* = 7.9 Hz, ArH), 5.56 (2H, s, CH), 5.20 (2H, s, OH-ArH), 3.89 (2H, d, CH_2), 3.83 (2H, d, CH_2), 2.49 (6H, s, CH_3); ^{13}C-NMR (175MHz, DMSO): 170.8 (2C), 159.1 (2C), 139.1 (2C), 138.5 (4C), 131.8 (2C), 132.0 (2C), 130.2 (2C), 125.5 (2C), 119.7 (2C), 119.42 (2C), 118.9 (2C), 114.4 (2C), 55.12 (2C), 34.00 (2C);17.91 (2C) CHNS: Calculated: C, 67.58; H, 4.96; N, 4.93; O, 11.25; S, 11.2. Found: C, 67.62; H, 5.06; N, 5.03; S, 11.1.

Tyrosinase Inhibition Assay

The method of Kim et al was employed for enzyme assay [74]. Total volume of 100 µL reaction mixture consisted of 60 µL 100 mM phosphate buffer having pH 6.8, 10 µL mushroom tyrosinase enzyme (5 units, Cat. No. T3824-50KU, Sigma Inc. USA) and 10 µL 0.5 mM test compound mixed in 96-well plate. Pre-incubation of contents was carried out for 5 minute at 37 ^{o}C. 20 µL of 10 mM L-dopamine was added as a substrate after incubation. Contents were mixed well and again incubated for about 30 min. At 490 nm absorbance was taken. All reactions were carried out thrice to attain accuracy. The positive and negative controls were included in the assay. The enzyme inhibition (%) was calculated by the formula.

$$\text{Inhibition (\%)} = \frac{\text{Control} - \text{Test} \times 100}{\text{Control}}$$

IC_{50} values (concentration at which there is 50% inhibition in enzyme activity) of active compounds were calculated using EZ-Fit Enzyme Kinetics Software (Perrella Scientific Inc. Amherst, USA) after suitable dilutions of the test compounds.

Molecular Docking

Docking studies are performed for the four inhibitors using Autodock package **[71]**. The structure of *agaricus bisporus* mushroom tyrosinase was obtained from the protein data bank (PDB code: 2Y9X) **[69]**. Before docking, the structures of the inhibitors were optimized at B3LYP/6-31G(d) level using Gaussian 09 [75]. The Gasteiger charges were adopted as the partial charge model. The number of grid points in three dimentions was set to 50 * 50 * 50 so that the grid box fully covered the potential binding zone of the binuclear copper site. The Lamarckian Genetic Algorithm was employed in conformation search. After docking calculations, cluster analysis was perfomed to identify the most stable docking conformation. The analysis of close contacts and hydrogen bonding between the enzyme and inhibitors was conducted with UCSF Chimera program [76], which was also employed to render Fig. 2 and Fig. S1.

Acknowledgements

We acknowledge Higher Education Commission and Ministry of Science and Technology Pakistan for financial support and National Natural Science Foundation of China (No: 51242001, 51572127 and 5122351). BZ gratefully acknowledges the financial support from “The Fundamental Research Funds for the Central Universities”, No. 30915011314.

Supplementary Data

Supplementary data (^{1}HNMR and ^{13}CNMR spectra of all Compounds, comparison of the binding modes of tropolone and a representative graph of the effect of incubation time on the tyrosinase enzyme activity) related to this article can be found in supporting file.

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Highlights:

- Using *bis*-biphenyl as a starting compound, a library of, new 4-thiazolidinone derivatives were designed and synthesized
- New green method has been reported for their synthesis by using NAG as organocatalyst
- All compounds were evaluated for their *in vitro* tyrosinase inhibitory activity.
- Six compounds potently inhibit tyrosinase; IC_{50} values ranging from 0.61±0.31 to 21.61±0.11 µM
- The most potent compound, **3c**, inhibited tyrosinase activity with an IC_{50} value of 0.61±0.31 µM
- SAR is established by molecular modeling studies