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# Convenient One-Pot Synthesis of Spirooxindole-4*H*-pyrans in the Presence of SBA-Pr-$NH_2$ and Evaluation of their Urease Inhibitory Activities

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## Abstract

A simple and efficient one-pot three-component synthesis of the biologically important spirooxindole-4*H*-pyrans was carried out by the reaction of isatin, activated methylene reagents, and 4-hydroxycoumarin in aqueous medium. SBA-Pr-$NH_2$ was found to be an efficient heterogeneous nanoporous solid basic catalyst (pore size of 6 nm) which can be easily handled and removed from the reaction mixture by simple filtration. This method is of great value because of its environmentally benign character, high yield processing, and easy handling. The biological activity of target compounds was screened by evaluation of their urease enzyme inhibition.



## 1. Introduction

The 4*H*-pyran derivatives are found to possess useful biological and pharmacological properties such as antitumor [1], antibacterial [2], antiviral [3], and diuretic activities [4]. Furthermore, isatin and its derivatives have interesting biological properties and are extensively used in organic synthesis [5, 6]. Spirooxindole ring system is one of the most important spirocycles found in a variety of natural products [7]. It is also, the central structural framework of bioactive molecules [8]. There are several reports on multicomponent entries to the synthesis of spirooxindole-4*H*-pyrans. Although different catalysts such as sodium stearate [9], *L*-proline [10], triethylbenzylammonium chloride (TEBA) [11], and $InCl_3$ [12] have been used for the synthesis of

these compounds, there is still a demand for simple and facile methods.

In recent years, there is a rapid growth in research and development of mesoporous materials. In this regard, mesoporous silicas have attracted considerable attention as fascinating functional materials. Mesoporous silica SBA-15 having high surface area, large pore size with narrow pore size distribution and high thermal stability is a unique inorganic solid support. Integration of acidic or basic functional groups into SBA-15 has been investigated to make promising solid catalysts. Application of these organic-inorganic hybrid materials as catalyst in a variety of organic transformations has been reported [13-15]. As part of our ongoing interest in the application of heterogeneous solid catalysts in organic synthesis [16-19], herein we report a simple, efficient, and green method for the synthesis of spirooxindole-4*H*-pyran derivatives through the three-component condensation of isatin, activated methylene reagents, and 4-hydroxycoumarin using SBA-Pr-$NH_2$ as a nano catalyst in aqueous medium. Recently we have reported the application of SBA-Pr-$SO_3H$ as an efficient catalyst in this reaction [20].

## 2. Experimental procedure

### 2. 1. SBA-15 nanoporous silica synthesis and functionalization

The synthesis of SBA-15 was similar to that described previously in the literature [21, 22] and involved the use of Pluronic P123 nonionic surfactant as a structure directing agent and TEOS under acidic conditions. Surface modifications over the nanoporous silica with aminopropyl moieties were performed using the post-synthesis grafting method [23]. In a typical process, calcined SBA-15 (5 g) was activated at 200 °C under vacuum for 5 h to remove any surface humidity and subsequently refluxed in dry toluene (150 ml). APTES (30.2 mmol) was then slowly added to the mixture and the reaction was refluxed at 110 °C for a further 24 h. The mixture was then filtered and washed with toluene and any residual organosilane was removed by Soxhlet extraction in ethanol over a 24 h period. The resulting material was denoted as $NH_2$-SBA-15.

### 2. 2. General procedure for the preparation of spirooxindole-4*H*-pyrans

A mixture of isatin (0.29 g, 2 mmol), malononitrile (0.13 g, 2 mmol), 4-hydroxycoumarin (0.32 g, 2 mmol), and SBA-Pr-$NH_2$ (0.02 g) in refluxing water (5 mL) was stirred for about 20 min. Upon completion, monitored by TLC, the generated solid product was filtered from the water and dissolved in ethyl acetate, which was then filtered for removing the unsolvable catalyst, and the filtrate was cooled to afford the pure product **4a**.

### 2. 3. Spectral data of products

*Methyl 2-amino-5-oxo-spiro[(3'H)-5'-chloro-indol-3',4-4(H)-pyrano(3,2-c)chromen]-(1'H)-2'-one-3-carbonitrile* (***4e***). [20] Mp 279-281 °C. IR (KBr): 3369, 3307, 3189, 2940, 1719, 1661, 1612, 1481, 1353, 1288, 1111, 1027, 989, 762 $cm^{-1}$. $^1H$ NMR (500 MHz, DMSO-$d_6$) δ = 10.56 (s, 1H, NH), 8.44 (s, 2H,$NH_2$), 8.02 (t, 1H, ArH), 7.72 (t, 1H, ArH), 7.51 (t, 1H, ArH), 7.43 (d, 1H, ArH), 7.13-7.17 (m, 2H, ArH), 6.75 (d, 1H, ArH), 3.46 (s, 3H, $CH_3$). MS *m/z* = 424 ($M^+$), 372, 279, 267, 167, 149 (100), 81, 69, 57, 43.

*Methyl 2-amino-5-oxo-spiro[(3'H)-5'-bromo-indol-3',4-4(H)-pyrano(3,2-c)chromen]-(1'H)-2'-one-3-carbonitrile* (***4f***). Mp 288-290 °C. IR (KBr): 3426,

3367, 3306, 3134, 2951, 1700, 1651, 1609, 1478, 1350, 1283, 1114, 1077, 991,758. $^1$H NMR (500 MHz, DMSO-$d_6$) δ = 10.57 (s, 1H, NH), 8.11 (s, 2H, $NH_2$), 8.03-8.04 (m, 1H, ArH), 7.73-7.75 (m, 1H, ArH), 7.51 (t, 1H, ArH), 7.43 (d, 1H, ArH), 7.27 (t, 2H, ArH), 6.71 (d, 1H, ArH), 3.78 (s, 3H, $CH_3$). MS *m/z* = 468 ($M^+$), 310, 267, 177, 149, 119, 91 (100), 69, 57, 43 [20].

### 2. 4. Biological assay

Urease inhibitory activities has been determined according to the literature reported by Tanaka [24]. Briefly, the assay mixture, containing 15 µL of jack bean urease (12 kU/L) and 30 µL of the tested compounds of various concentrations (dissolved in the solution of DMSO : $H_2O$ = 1:1 (v/v)), was preincubated for 30 min at 37 °C. Then 500 mM urea and 0.002% phenol red in phosphate buffer pH 6.8 were added and incubated at 37 °C. The reaction time to produce enough ammonium to raise the pH of a mixture from 6.8 to 7.7 has been optimized to 1 h by the color changes of phenol red as indicator. Then measurements to determine $IC_{50}$ values were done by UV-Vis spectrophotometer at 570 nm.

### 2. 5. Docking protocol

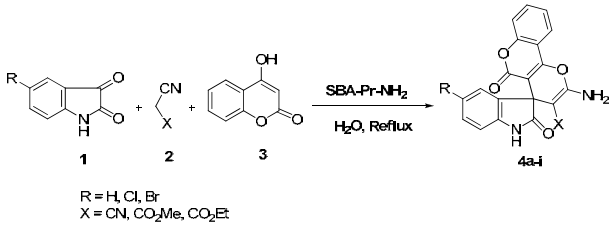
To insight to the site of interaction of compounds, AutoDock 4.0 is used as the docking engine to achieve binding affinity and position of ligands on receptor. In this study the nine newly synthesized compounds were docked on urease (PDB ID: 4gy7) with the grid-box of 126 Å (x, y and z) and the spacing of 0.5 Å. Docking calculation parameters were set to these values: number of Lamarckian job = 100; initial population = 100; maximum number of energy evaluations = $25\times10^5$; maximum generations = 27000; mutation rate of 0.02; and a crossover rate of 0.80. For better understanding of interactions and access to respective pharmacophore, LIGSCOT3.0 program was used [25, 26].

### 2. 6. Instruments

IR spectra were recorded from KBr disks using an FT-IR Bruker Tensor 27 instrument. Melting points were measured using the capillary tube method with an Electrothermal 9200 apparatus. $^1$H NMR was run on a Bruker DPX at 500 MHz using TMS as an internal standard. Gas chromatography-mass spectrometry (GC-MS) analysis was performed on an Agilent 6890-5973 GC/MS detector. The specific surface area ($A_{BET}$) was evaluated using the Brunauer-Emmett-Teller (BET) equation, and the pore size distribution ($D_{BJH}$) was obtained from the desorption branches by means of the Barret-Joyner-Halenda (BJH) model, with the pore volume being taken at $p/p_0$ = 0.995. The low-angle powder X-ray diffraction (XRD) patterns were recorded over a range of 0.5° < 2θ < 8° on a Philips X'pert MPD diffractometer equipped with a liquid nitrogen-cooled germanium solid-state detector using Cu $K_\alpha$ radiation (40 kV, 30 mA) at a step width of 0.02°. Transmission electron microscopy (TEM) analysis was performed on a Tecnai $G^2$ F30 at 300 kV.

## 3. Results and discussion

In this paper, the condensation of isatin **1**, activated methylene reagents **2**, and 4-hydroxycoumarin **3** in the presence of nanoporous solid basic catalyst (SBA-Pr-$NH_2$) for the preparation of spirooxindole-4*H*-pyran derivatives has been studied (Scheme 1).




**Scheme 1.** Synthesis of spirooxindole-4*H*-pyrans **4a-i** in the presence of SBA-Pr-$NH_2$.

In our initial study, evaluation of various solvents was carried out for the synthesis of 2-amino-5-oxo-spiro[(3'H)-indol-3',4-4(H)-pyrano(3,2-*c*)chromen]-(1'H)-2'-one-3-carbonitrile **4a** by reacting isatin, malononitrile, and 4-hydroxycoumarin in the presence of SBA-Pr-$NH_2$. Among the tested solvents such as $H_2O$, MeCN, EtOH and solvent-free system, the most encouraging result was obtained when water was employed as the solvent in the presence of a catalytic amount of SBA-Pr-$NH_2$ under refluxing conditions (Table 1).

Under the optimized reaction conditions, a series of spirooxindole-4*H*-pyran derivatives **4a-i** were synthesized (Table 2). As shown in Table 2, it was found that this method works with a wide variety of substrates. A series of substituted isatins and molononitrile or ethyl cyanoacetate or methyl cyanoacetate were used in this reaction. The time of reactions was within 20–40 min and high yields of products were obtained.

**Table 1.** The optimization of reaction condition in the synthesis of spirooxindole-4*H*-pyran **4a**.[a]

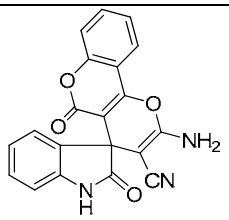
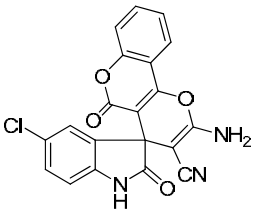
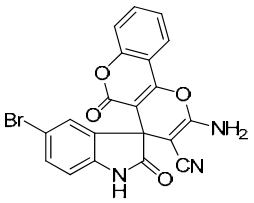
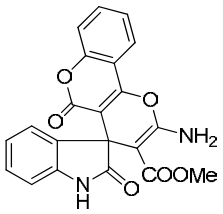
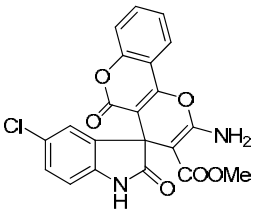
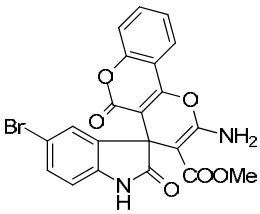
| Entry | Solvent | Time (min) | Yield (%)[b] |
|---|---|---|---|
| **1** | EtOH | 40 | 70 |
| **2** | MeCN | 30 | 75 |
| **3** | $H_2O$ | 20 | 88 |
| **4** | neat (100 °C) | 50 | 70 |

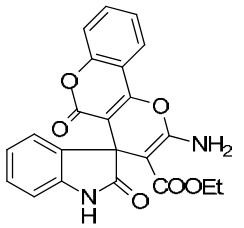
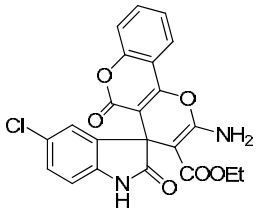
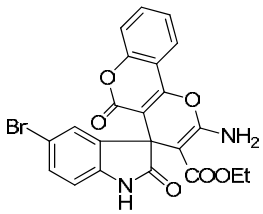
[a]Reaction conditions: isatin (2 mmol), 4-hydroxycoumarine (2 mmol), malononitrile (2 mmol), SBA-Pr-$NH_2$ (0.02 g).
[b]Isolated yield.

After completion of the reaction (monitored by TLC), the crude product was dissolved in hot ethyl acetate, the heterogeneous solid catalyst was removed easily by simple filtration, and after cooling of the filtrate, the pure crystals of products were obtained. The recovered catalyst was then washed sequentially with a diluted aqueous $Et_3N$ solution, water, and acetone, and dried under vacuum.

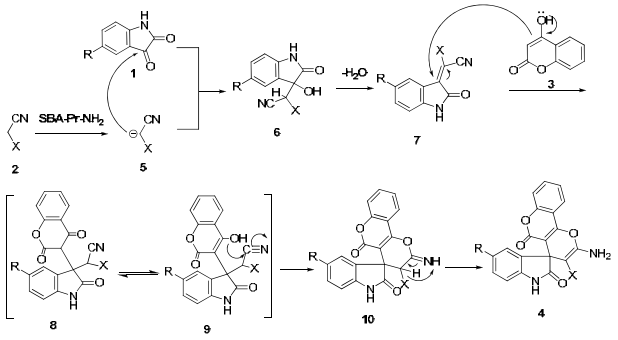
We proposed the possible mechanism for the formation of spirooxindole-4*H*-pyran derivatives **4** as showed in Scheme 2. The initiation step begins with the deprotonation of malononitrile or the cyanoacetic esters **2** by SBA-Pr-$NH_2$. Then a fast Knoevenagel condensation occurs between **1** and CH-acidic of compound **2** to afford isatilidene malononitrile derivatives **7**. Michael addition of **7** with 4-hydroxycoumarin **3** followed by cycloaddition of hydroxyl group to the cyano moiety provides the desired product **4** (Scheme 2).

**Table 2:** Synthesis of spirooxindole-4*H*-pyran derivatives in the presence of SBA-Pr-$NH_2$ under reflux conditions.

| Entry | R | X | Product | Time (min) | Yield[a](%) | mp (°C) | mp (Lit.) |
|---|---|---|---|---|---|---|---|
| 1 | H | CN |  **4a** | 20 | 88 | >300 | 303 [27] |
| 2 | Cl | CN |  **4b** | 20 | 80 | >300 | >300 [9] |
| 3 | Br | CN |  **4c** | 25 | 80 | >300 | >300 [10] |
| 4 | H | COOMe |  **4d** | 25 | 70 | 272-273 | 275-277 [11] |
| 5 | Cl | COOMe |  **4e** | 30 | 85 | 279-281 | 287-288 [20] |
| 6 | Br | COOMe |  **4f** | 40 | 70 | 288-290 | 296-298 [20] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 7 | H | COOEt |  **4g** | 30 | 80 | 252-254 | 251-253 [10] |
| 8 | Cl | COOEt |  **4h** | 25 | 85 | 275-277 | 280-282 [20] |
| 9 | Br | COOEt |  **4i** | 40 | 75 | 280-282 | 285-286 [20] |

[a]Isolated yield.



**Scheme 2.** Plausible mechanism for synthesis of spirooxindole-4*H*-pyrans **4a-i** in the presence of SBA-Pr-$NH_2$.

Several different conditions have been reported in the literature for the synthesis of spirooxindole-4*H*-pyran derivatives, as shown in Table 3. The current methodology offers several advantages, such as a simple procedure, short reaction times, facile synthesis, simple work-up, high yields, and green conditions.

The preparation of SBA-15 as a nanoporous silica can be achieved using the commercially available triblock copolymer Pluronic P123 as a structure directing agent [34, 35]. The amino functionalized SBA-15 was typically synthesized through post-grafting. The calcined SBA-15 silica was functionalized with APTES to provide SBA-Pr-$NH_2$ as solid basic nanocatalyst.

The textural properties of SBA-15 and SBA-Pr-$NH_2$ are summarized in Table 4. It is observed that the surface area, the pore volume, and pore size decrease with modification which confirms the surface modification takes place inner surface of silica wall.

**Table 3**: Comparison of efficiency of various catalysts in synthesis of 2-amino-5-oxo-spiro[(3'H)-indol-3',4-4(H)-pyrano(3,2-*c*)chromen]-(1'H)-2'-one-3-carbonitrile **4a**.

| Entry | Catalyst | Solvent | Condition | Time | Yield (%) | Year |
|---|---|---|---|---|---|---|
| 1 | $Et_3N$ | EtOH | Heating | 10 min | 92 | 2005 [28] |
| 2 | $InCl_3$ | $CH_3CN$ | Reflux | 1.5 h | 72 | 2007 [12] |
| 3 | TEBA[a] | $H_2O$ | Heating | 3 h | 88 | 2007 [11] |
| 4 | $NEt_3$ | EtOH | Reflux | 5 min | 95 | 2008 [29] |
| 5 | β-CD[b] | $H_2O$ | Heating | 8 h | 88 | 2009 [30] |
| 6 | *L*-proline | $H_2O$ | Heating | 15 min | 94 | 2010 [10] |
| 7 | EDDA[c] | $H_2O$ | Heating | 1 h | 92 | 2010 [31] |
| 8 | Sodium stearate | $H_2O$ | Heating | 3 h | 92 | 2010 [9] |
| 9 | - | PEG | Heating | 90 min | 91 | 2010 [32] |
| 10 | Alum | $H_2O$ | Heating | 2 h | 93 | 2010 [27] |
| 11 | TBAB[d] | $H_2O$ | Reflux | 40 min | 90 | 2011 [33] |
| 12 | SBA-Pr-$NH_2$ | $H_2O$ | Reflux | 20 min | 88 | This work |

[a] TEBA = Triethylbenzylammonium chloride.

[b] β-CD = β-Cyclodextrin.

[c] EDDA = Ethylenediamine diacetate.

[d] TBAB = Tetrabutylammonium bromide.

**Table 4**: Characteristics of the synthesized materials derived from nitrogen adsorption-desorption.

| Sample | Textural properties | | |
|---|---|---|---|
| | $S_{BET}$ ($m^2/g$) | $V_{total}$ ($cm^3/g$) | $D_{BJH}$ (nm) |
| SBA-15 | 481 | 1.3 | 5.9 |
| SBA-Pr-$NH_2$ | 356 | 1.0 | 3.6 |

The XRD pattern of SBA-15 showed the (100), (110), and (200) reflections typical of an ordered mesoscopic structured silica [34] which exhibit a two-dimensional hexagonal symmetrical array of nano-channels (Fig. 1). $NH_2$-SBA-15 was also characterized by the same pattern, indicating that the grafting of APTES did not affect the structural integrity of SBA-15.

The TEM image of $NH_2$-SBA-15 showed the parallel channels, which resembled the configuration of the pores in SBA-15 (Fig. 2). This indicated that the pores in $NH_2$-SBA-15 had not collapsed during the functionalization reaction. This image was in good agreement with the XRD result for $NH_2$-SBA-15.

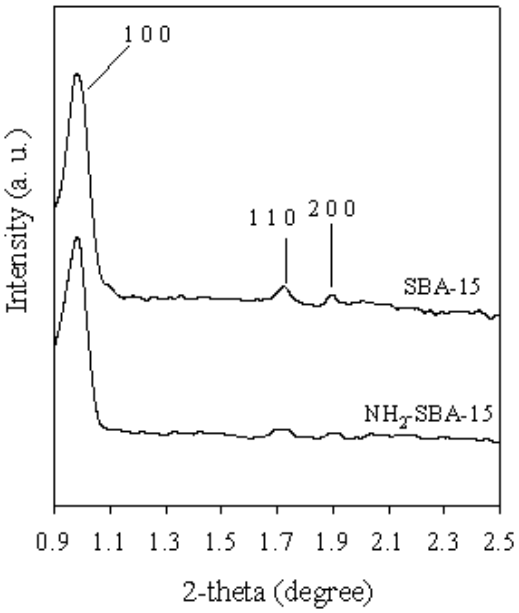



**Fig. 1.** Low-angle XRD patterns of SBA-15 and $NH_2$-SBA-15.

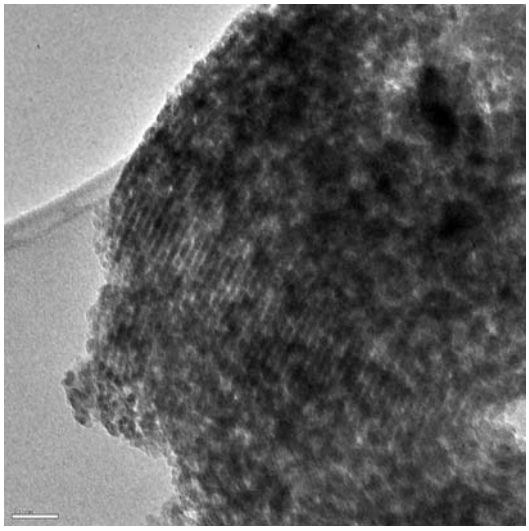


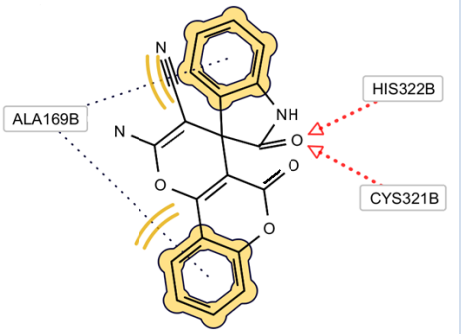
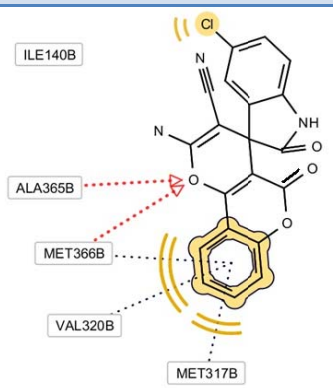
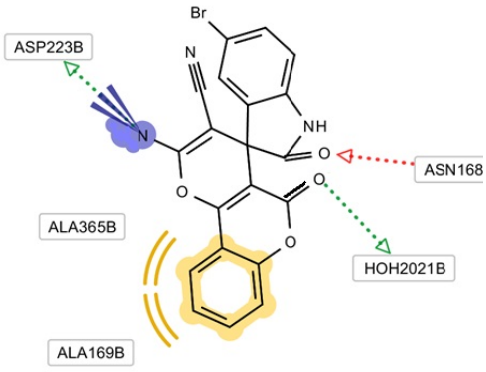
**Fig.2.** TEM image of $NH_2$-SBA-15.

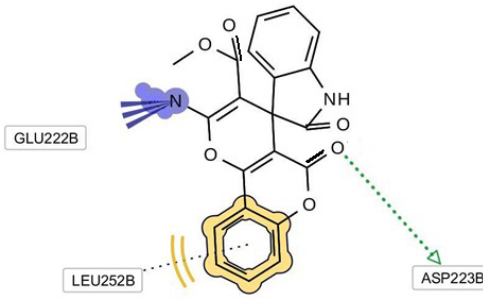
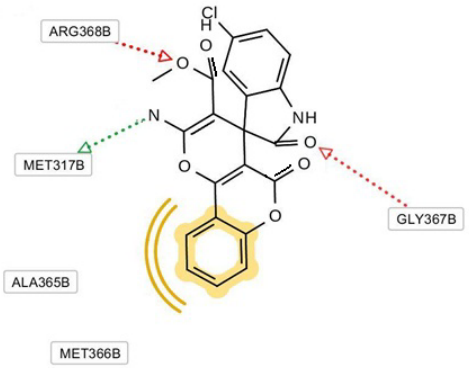
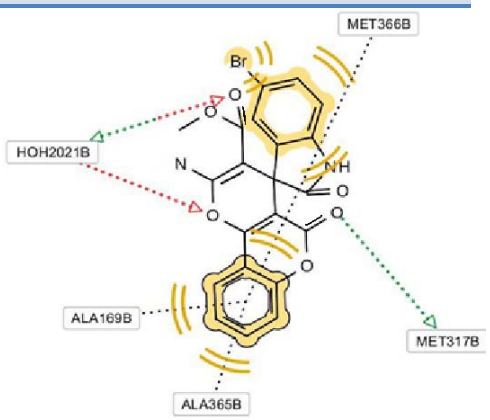
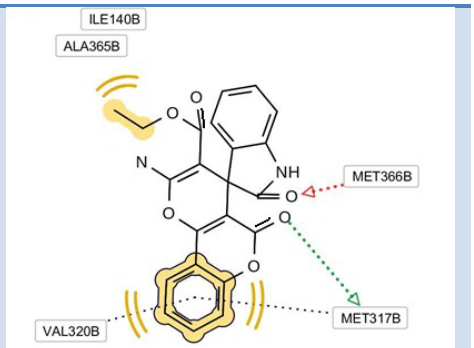
Nine newly synthesized compounds were evaluated against jack bean urease and five compounds (Table 5, entries 5-9) showed good urease enzyme inhibition at micromolar level in comparison with standard inhibitor, hydroxyurea ($IC_{50}$:95μM). However, docking studies revealed that due to the bulky and fused skeleton of compounds, none of them enter to the active site, but inhibit protein by interaction with active site entrance and thus block the active site (data not shown). Therefore, inserting substituents which make better stabilizing of compounds in this site resulted in higher conformational changes and better inhibition.

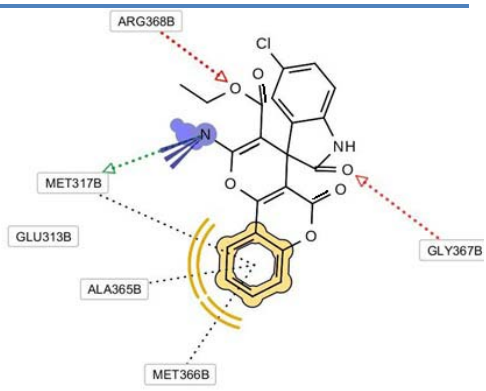
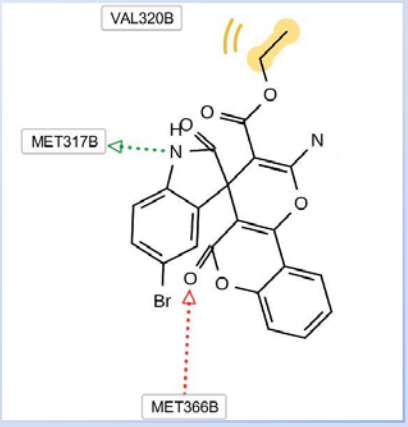
It is clear that replacing the CN group (Table 5, entry 1) by COOEt group (Table 5, entry 7) significantly increased the potency of inhibition. This observation may result by the appropriate placement of hydrophobic groups nearer to amino acids in hydrophobic binding pocket. The carboxyl group with higher hydrophobic groups as a factor in designing urease inhibitors has been approved by previously [36-38]. On the other hand, it has also been reported that thiol compounds that do not contain any carboxyl group, display a very weak inhibitory activity [39]. As it clear, this effect is reduced by replacing by $CO_2H$ possibly because of the long distance between adjacent hydrophobic amino acids and methyl group. This part of compound could be more optimized by insertion of bulkier hydrophobic groups.

From all, *p*-Cl substituted phenylene ring in comparison with Br substituted and non-substituted compounds makes better inhibition potency which is more obvious in entries 5 and 8 with $IC_{50}$: 42 and 25 μM respectively. In fact, topological hindrance caused by the bulkier halogen atom, Br, results in the lower effect. On the other hand, due to the long distance between the phenylene ring and aromatic amino acids, the formation of π-π stacking is impossible and inserting different groups that increase phenylene ring hydrophobicity may improve its effect through urease. As it is illustrated in Table 5, only in compounds 1 and 6 hydrophobic interaction of the ring with adjacent amino acids is constructed which resulted from appropriate configuration of ligands in binding site. Also it seems H-bond formation between the oxygen of ester and Arg 368 that makes better stabilization of compounds (Entries 5 and 8). Besides, dual interaction of Met 317 with amino group of compound 8 can be compared with compound 5 which the mentioned amino acids just participate in hydrogen interaction. On the other hand, Asp 223 in compound 3 shows this dual interaction, but destination of this interaction is higher than in compound 8. In compound 2 unlike compounds 5 and 8 the presence of the cyano group makes some hindrance in H-bond formation. By contrast, this compound can be better oriented that its Cl atom interacts with Ile 140 from B chain. It can be infer that, inhibition potency is affected by the type and size of the substituents on the phenylene ring.

**Table 5.** Urease inhibitory activities ($IC_{50}$ in µM) and interaction energies (kcal $mol^{-1}$) of spirooxindole-4*H*-pyran derivatives **4a-i**.

| Entry | Product | Docking energy (Kcal/ mol) | $IC_{50}$ (µM) | Structure |
|---|---|---|---|---|
| **1** | **4a** | -4.58 | 97.6 |  |
| **2** | **4b** | -5.46 | 78.6 |  |
| **3** | **4c** | -5 | 91.83 |  |

| | | | | |
|---|---|---|---|---|
| **4** | **4d** | -4.37 | 114.72 |   |
| **5** | **4e** | -6.06 | 42.81 |   |
| **6** | **4f** | -6.01 | 49.49 |   |
| **7** | **4g** | -5.72 | 52 |   |

| | | | | |
|---|---|---|---|---|
| **8** | **4h** | -6.13 | 25.8 |  |
| **9** | **4i** | -5.96 | 55 |  |





## 4. Conclusion

In conclusion, we have developed a nano-catalyzed multicomponent synthesis of spirooxindole-4*H*-pyrans in high yields. SBA-Pr-$NH_2$ as an efficient and active nano-reactor can be easily handled and removed from the reaction mixture by simple filtration. The simplicity of the reaction, recovery of catalyst without loss of reactivity, and high yield of products represent improvements over many existing methods. The compounds were tested for their activity as urease inhibitors and some of the compounds showed potent activity towards jack bean urease.

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