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New thioureas based on thiazolidines with antioxidant potential

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ABSTRACT

Thiazolidine and pyrrolidine compounds containing a thiourea moiety were prepared using boric acid as a coupling agent in a multicomponent methodology. In addition, the antioxidant activity, as reflected by free radical scavenging, was evaluated. Some compounds were selected and tested in different antioxidant experiments and all of them were shown to be useful for the prevention of oxidative stress in biological systems and thus capable of reducing cellular injury.

Introduction

Recently, compounds containing a thiourea moiety have received attention due their broad applications as organocatalysts[1] in different asymmetric chemical reactions, such as Michael,[2] Mannich,[3] Diels–Alder,[4] Friedel Craft[5] and other reactions. Furthermore, thiourea has been applied as selective chemical sensor for heavy metals[6] as well as other environmentally toxic compounds. Additionally this important class of compounds has shown important biological properties such as anti-cancer,[7] human anti-parasitic[8] and other activities. Thiourea derivatives are also very promising as building blocks for the synthesis of polymers[9] or as antioxidant[9a] components in polymer synthesis.

The classical methodologies for the synthesis of thioureas[1e,10] are very efficient, leading to good or excellent product yields. However, the classical methods involve the use of isothiocyanate, thiophosgene and thiocyanate salts, which are very toxic and harmful to the environment.[10] Therefore new methodologies have been developed to avoid using toxic starting materials while retaining good yields. The use of carbonylimidazole (CDI)[10d] as a substitute for thiophosgene, and the use of sunlight[10a] as the reaction promoter are examples of safe, cheap and environmental friendly methodologies.

In connection with this, thiazolidine derivatives have broad applicability in medicinal chemistry having anti-cancer,[11] anti-HIV[12e] and other important biological activities. Thiazolidine and its derivatives are important drug candidates, and they have already been screened against several disorders. Anti-convulsant, sedative, antidepressant, anti-inflammatory, anti-hypertensive, antihistaminic and anti-arthritic activities are a few among many other biologically important properties shown by these promising compounds.[12a] Recently, our group reported that besides their antioxidant properties Se-phenyl thiazolidine derivatives produced anti-nociceptive activity in experimental models and did not modify any biochemical or locomotor parameters or exploratory activities in mice.[12b–d] In addition, they also have been used as important chiral pools for the synthesis of several chiral ligands and organocatalysts.[13]

To the best of our knowledge, this is the first Letter in which a thiourea containing a thiazolidine moiety has been described. Therefore, it seems interesting to join together these two molecular fragments that have already proved separately to have important biological activities. Herein we describe our efforts on the development of a new methodology to synthesise new thioureas based on thiazolidine and pyrrolidine heterocycles through a multicomponent reaction using boric and boronic acids as coupling agents. An important feature of this new methodology is that it avoids the use of high-cost coupling reagents, protection groups or multiple steps to afford the final product.

Results and discussion

In 1996, Yamamoto described the synthesis of amides using boronic acids as coupling reagents and organic acids and amines as starting materials.[14a] An extension of this work was later

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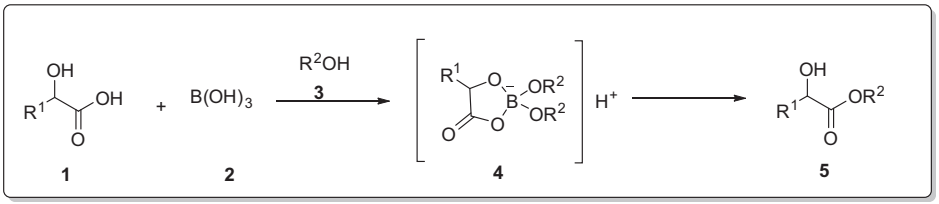
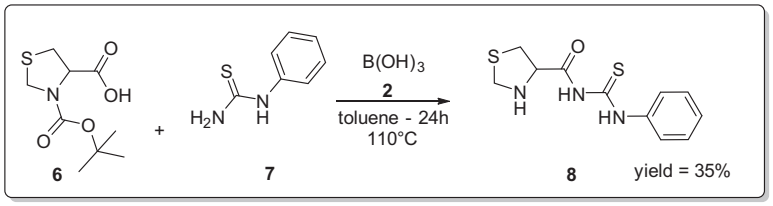
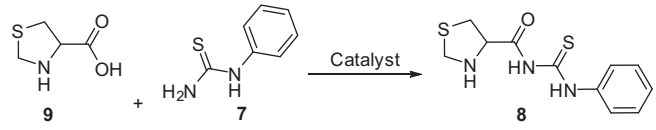


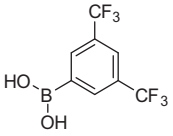
Scheme 1. Proposed mechanism for the boric acid-catalysed esterification.[13c]



Scheme 2. Coupling reaction between *N*-protected compound **6** and thiourea **7**.

Table 1
Catalytic activities of boronic and boric acid[a]

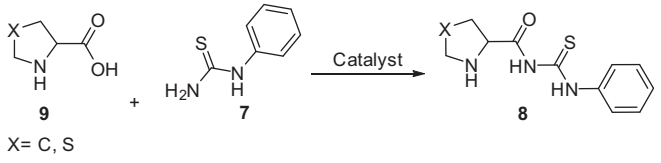


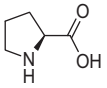
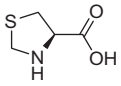
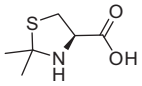
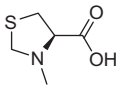
Entry	Catalyst	Catalyst load (mol %)	Solvent	Time (h)	Yield[b] (%)
1		10	Toluene	24	36
2		10	Toluene	24	33
3		10	*o*-Xylene	24	4
4		20	Toluene	24	41
5		30	Toluene	24	47
6		40	Toluene	24	45
7		30	Toluene	12	51
8		30	Toluene	6	30

[a] Experimental details: carboxylic acid (2.0 mmol), thiourea (2.2 mmol), solvent (10 mL).
[b] Isolated yields.

reported in which they used boronic acids for the coupling of α-hydroxy-acids and alcohols to afford esters in good to excellent yields, keeping the stereoisomeric information from the carboxylic acid.[14a,b] In both Letters the ordinary intermediate **4**, a bis-chelated compound from α-hydroxy-acid -to boron catalyst, was reported (Scheme 1).[14a–f]

Table 2
Thioureas synthesised by reaction coupling using boric acid[a]

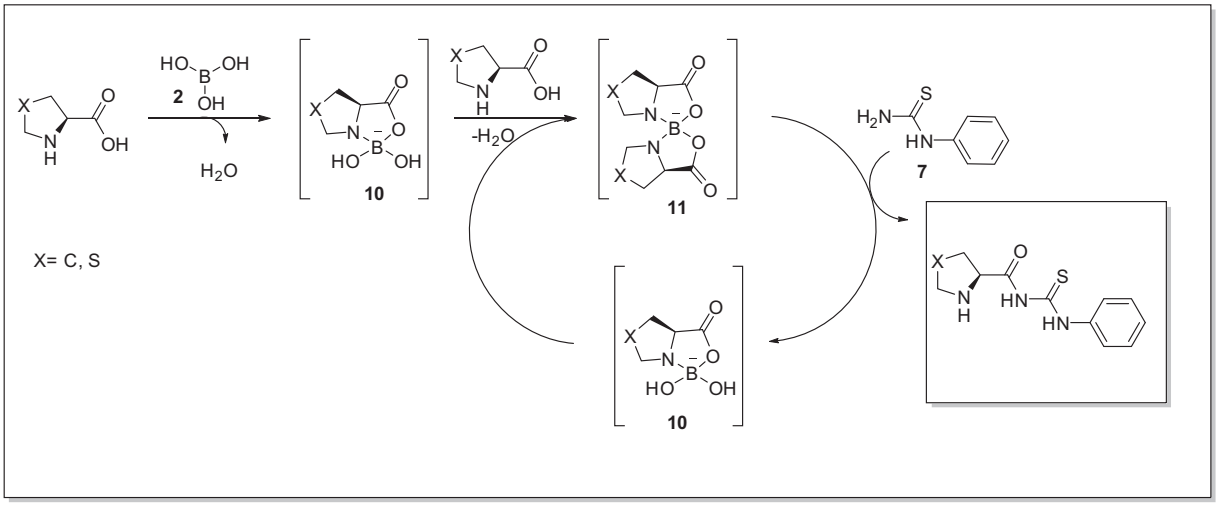


Entry	Carboxylic acid	Load of catalyst (mol %)	Solvent	Time (h)	Yield[b] (%)
1		30	Toluene	12	47
2		30	Toluene	12	51
3		30	Toluene	12	—
4		30	Toluene	12	—

[a] Experimental details: carboxylic acid (2.0 mmol), thiourea (2.2 mmol), toluene in refluxing (10 mL) using Dean–Stark apparatus, 12 h.
[b] Isolated yields.

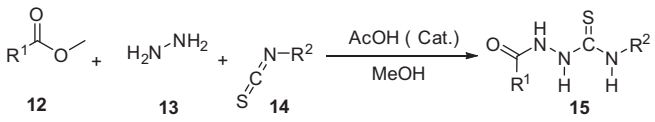
Based on these previous results we envisioned the use of this methodology for the coupling of thioureas and thiazolidine carboxylic acids. As the starting point, we chose the thiazolidine-N-Boc-protected **6** as an analogous α-hydroxy-acid, to react with *N*-phenyl thiourea **7** using 10 mol % of boric acid **2** as the coupling reagent, in azeotropic reflux of toluene for 24 h. To our delight, we obtained the unprotected compound **8** at 35% yield in one single step (Scheme 2). This result suggests a dual role for the boric acid, where it can act as a coupling reagent as well as a deprotecting agent. With this result in hand, we performed another experiment, now using the thiazolidine–4-carboxilic acid **9** without the amino group protection under the same conditions and as expected, after 24 h, we obtained the compound **8** at 36% yield (entry 1—Table 1).

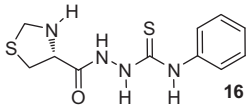
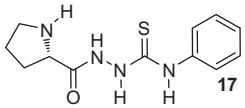
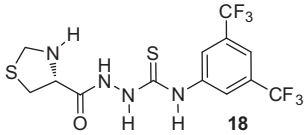
To establish the best reaction conditions we investigated the effect of catalyst loading, reaction time, solvent and temperature



Scheme 3. Proposed reaction mechanism.

Table 3
Multicomponent reaction to synthesise thiosemicarbazides based on pyrrolidine and thiazolidine[a]



Entry	Products	Yield[b] (%)
1	 16	35
2	 17	35
3	 18	43

[a] Experimental details: **12** (2.0 mmol), **13** (2.0 mmol), **14** (2.0 mmol), acetic acid (droplet), refluxing methanol (10 mL), 12 h.
[b] Isolated yields.

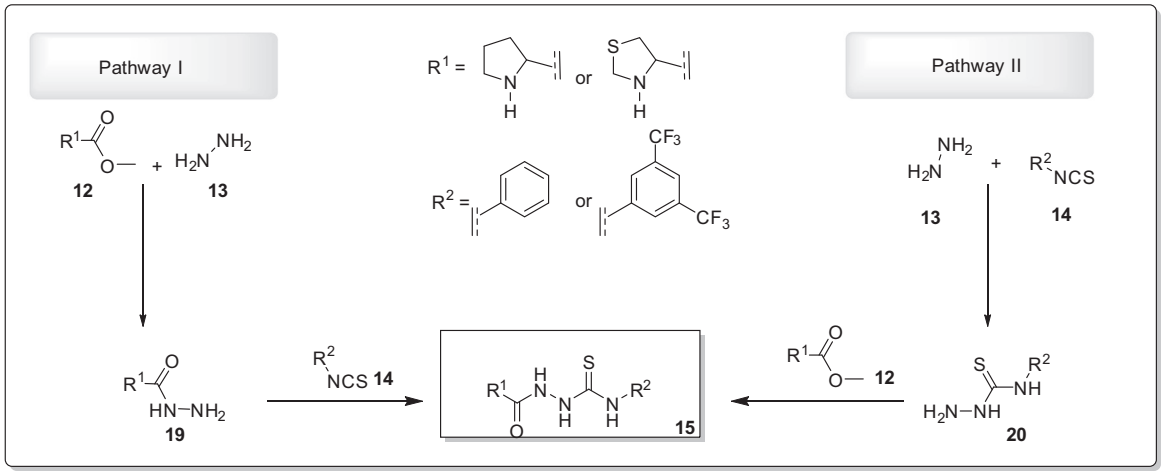
on the reaction yield (Table 1). As can be seen from Table 1, boric acid (entry 1—Table 1) and boronic acid (entry 2—Table 1) furnished the desired product in similar yields. However due to the nature of boric acid, which is cheap and easily available, we decided to continue our studies by employing it as the catalyst.

In order to evaluate the effect of the reaction temperature, we changed the solvent to xylene for the azeotropic reflux and observed a dramatic decrease in the reaction yield. The poor yield obtained for compound **8** in this case can be ascribed to the high boiling point of the xylene, which can induce decomposition of the starting material, as could be observed by TLC (Table 1, entry 3). The catalyst loading was shown to be crucial in order to obtain of the desired product in satisfactory yields. Next, we observed that the amount of the boric acid catalyst is an important feature, since an improvement in yield from 36% to 47% was achieved when 30 mol % of boric acid was used (Table 1, entries 1 and 5). A further increase in the amount of catalyst from 30 mol % to 40 mol % did not improve the reaction yield (Table 1, entries 5 and 6). Having established the optimum amount of catalyst we carried out two more experiments with reduced reaction times, and found that after 12 h the desired product was obtained with satisfactory yields (Table 1, entry 7).

With the optimal condition in hand, we extended the protocol to other thiazolidine derivatives as well as to L-proline. When L-proline was reacted with the respective thiourea **7**, the desired product was obtained at 46% yield (Table 2, entry 1). However the reaction failed when substituted thiazolidine derivatives were used (Table 2, entries 3 and 4). Probably the methyl group at the nitrogen (entry 3), as well as, the bis-methyl group at position-2 of the heterocycle (entry 4) can negatively affect intermediate formation through steric hindrance, as can be seen in Scheme 3.

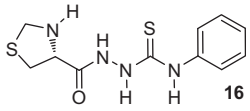
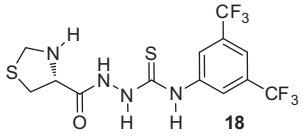
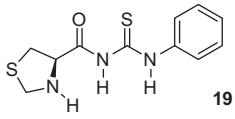
Taking into account the results obtained from the carboxylic acid variation we propose a reasonable mechanism for this coupling reaction, also based on Yamamoto's previous work.[14f] First the complex **10** can be formed between the boric acid and carboxylic acid, as has been proposed for α-hydroxyl-acid derivatives. It was also reported in previous work that this complex **10** can exist in equilibrium with the dimeric form **11**, which can explain the lack of reactivity of substituted thiazolidines (Table 2, entries 3 and 4). The subsequent nucleophilic attack of the amino moiety from the thiourea derivative to the carbonyl moiety in complex **11** releases the respective product and retrieves the boron catalyst back to the reaction medium.

Keeping in mind the importance of this class of compounds and combined with our long-term interest in the synthesis of thiazolidine derivatives, we next turned our attention to the synthesis of new thiazolidines containing a thiosemicarbazide moiety, in order to evaluate the influence of their chemical structure on their biological activities. According to the literature, thiosemicarbazide derivatives have been described as potential anti-parasitic,[15a,b,h] antibiotic,[15i,e] and antioxidant1[4c,d,f,g,j] agents, among other properties. This class of molecules also has a thiourea moiety embedded in the molecular structure, which makes them interesting for comparison with our previously synthesised thiazolidines. Usually the synthesis of thiosemicarbazide derivatives takes more than two steps and requires purification by chromatographic techniques.[15] This fact prompted us to explore a new approach for the development of a more efficient and general method to obtain thiosemicarbazides. For that purpose we designed a one-pot multicomponent reaction between the methyl



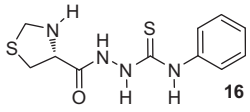
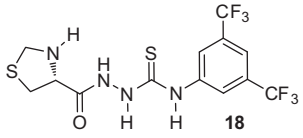
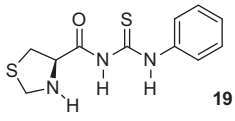
Scheme 4. Mechanism proposed for the multicomponent reaction to synthesise thiosemicarbazides based on pyrrolidine and thiazolidine.

Table 4
DPPH scavenging activity of thiourea

Compound	Concentration (μM)				IC_{50}
	10	50	100	500	
 16	21.83 ± 4.04***	86.43 ± 5.26***	92.25 ± 3.60***	95.44 ± 1.39***	27.66 ± 2.51
 18	36.01 ± 5.69***	94.13 ± 0.56***	94.90 ± 0.92***	92.16 ± 0.99***	20.33 ± 2.31
 19	37.69 ± 3.99***	91.68 ± 1.81***	93.11 ± 1.63***	93.25 ± 2.57***	23.00 ± 2.64

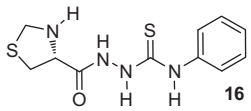
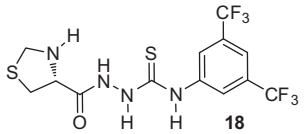
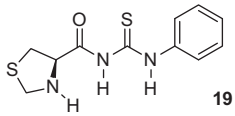
Each value is expressed as mean ± SD ($n = 3$). Asterisks represent a significant effect compared with controls without thiourea assessed using Newman–Keuls multiple range tests. IC_{50} is the concentration (μM) of thiourea required to reduce the initial concentration of DPPH radicals by 50%.
*** $p < 0.001$.

Table 5
ABTS radical scavenging activity of thiourea

Compound	Concentration (μM)					IC_{50}
	1	5	10	50	100	
 16	10.41 ± 4.37	58.03 ± 13.94***	90.60 ± 10.16***	–	–	2.83 ± 0.7
 18	5.38 ± 2.35	55.02 ± 10.94***	73.97 ± 4.38***	93.79 ± 7.33***	97.14 ± 0.77***	4.54 ± 0.5
 19	8.78 ± 3.89	48.54 ± 8.56***	80.57 ± 24.32***	98.81 ± 1.61***	98.45 ± 1.10***	5.15 ± 1.5

Each value is expressed as mean ± SD ($n = 3$). Asterisks represent significant effects compared with controls without thiourea assessed using Newman–Keuls multiple range tests. IC_{50} is the concentration (μM) of thiourea required to reduce the initial concentration of ABTS radicals by 50%.
*** $p < 0.001$.

Table 6
Ferric reducing-antioxidant power (FRAP) assay

Compound	Concentration (μM)			
	1	5	10	50
 **16**	0.223 ± 0.02	0.428 ± 0.04***	0.645 ± 0.06***	–
 **18**	0.190 ± 0.07	0.201 ± 0.09	0.641 ± 0.13**	1.515 ± 0.29***
 **19**	0.150 ± 0.01	0.387 ± 0.07*	0.448 ± 0.13**	1.638 ± 0.18***

Each value is expressed as mean ± SD (n = 3). Asterisks represent significant effects compared with controls without thiourea assessed using Newman–Keuls multiple range tests.
* p <0.05.
** p <0.01.
*** p <0.001.

ester from L-proline or thiazolidine derivatives, hydrazine hydrate and aryl isothiocyanate. In our first attempt, the reaction was carried out using acetic acid as the catalyst in methanol, and after 12 h the desired thiosemicarbazide was obtained in 35% yield, after only one purification step. It is important to mention that this new procedure fulfils some important criteria consistent with green chemistry principles such as reducing synthesis steps, reducing purification steps and atom economy, therefore adding an environmental and financial value to this multicomponent strategy.

This new methodology was next applied and three new thiosemicarbazides were synthesised, with the variation at the heterocyclic ring or at the aromatic portion of the molecule (Table 3).

For this reaction we proposed a reaction mechanism where the pathways to reach the product are degenerate as described previously for the synthesis of thiosemicarbazones.[16] The reaction can follow the pathway 1 (Scheme 4) where the first step is the reaction between the methyl ester **12** and hydrazine **13** to afford, as intermediate, compound **19** which, at the end, reacts with aryl isothiocyanate resulting in thiosemicarbazide **15**. On the other hand, following pathway 2, the thiosemicarbazide **20** is produced first and thereafter reacts with methyl ester **12** derivatives furnishing the thiosemicarbazide **15**. Thus, both pathways lead to the same product, and therefore they are degenerate pathways (Scheme 4).

The main role of an antioxidant molecule is decreasing oxidative stress during any cell injury.[17] A large number of cellular processes including those related to injuries generate reactive oxygen species—ROS—which are quite harmful to cell integrity.[17a,c,d] Therefore, suitable antioxidant molecules must have a high capacity to trap ROS before they can cause injury to cells.[17b,c] Furthermore, these compounds must present their antioxidant activity at low concentration as well as with low toxicity.[17e] From our set of synthesised molecules we chose those molecules containing a thiazolidine heterocycle for the evaluation of their antioxidant activity, because their biological activity as antioxidants,[18b–e,i] antibiotics[18a,f–h] and anticancer agents[11] has previously been reported in the literature.

Thioureas exhibited antioxidant activity in the DPPH and ABTS radical scavenging assays at different concentrations. In the DPPH assay thioureas **16**, **18** and **19** exhibited scavenging activity for this radical present at 10 μM with IC_{50} values of 27.66 ± 2.51, 20.33 ± 2.31 and 23.00 ± 2.64 μM, respectively (Table 4). These results demonstrate that thiourea **18** is more potent than thiourea **16** but is not different from thiourea **19** at scavenging the DPPH radical.

In the ABTS assay thioureas **16**, **18** and **19** exhibited scavenging activity of ABTS present at 5 μM, with IC_{50} values of 2.83 ± 0.76, 4.54 ± 0.5 and 5.15 ± 1.5 μM, respectively (Table 5). These results demonstrate that thiourea **16** is more potent than thiourea **18** and **19** at scavenging the ABTS radical.

Based on these results, thioureas **16**, **18** and **19** neutralised the DPPH radical and quenched the ABTS free radicals. The DPPH and ABTS radicals are stable free radicals commonly used as substrates to evaluate in vitro antioxidant activity and to evaluate the ability of antioxidants to scavenge free radicals, which are known to be a major factor in the biological damage caused by oxidative stress. Antioxidants can scavenge DPPH radicals by hydrogen donation, which causes a decrease in DPPH absorbance[19a,c,d] and the ABTS radical reacts quickly to electron donors. Thus, thioureas **16**, **18** and **19** could prevent or decrease the damage to the human body caused by free radicals, which attack biological macromolecules such as lipids, proteins and DNA by hydrogen donation or by acting as electron donors.

In addition to the antioxidant capacity of the thioureas in the DPPH and ABTS assays, thioureas **16**, **18** and **19** also showed reducing properties. The FRAP method is based on a redox reaction, in which an easily reduced oxidant (Fe^{3+}) is used in stoichiometric excess and antioxidants act as reductants.[19b] Several previous studies have shown that the electron donation capacity of bioactive compounds, reflecting their reducing power, is associated with their antioxidant activity.[20] Thus, the reducing capacity of a compound may serve as a significant indicator of its potential antioxidant activity. In this study, thiourea **16** had a reducing capacity at concentrations ranging from 5 to 10 μM reaching the maximum absorbance at 50 μM. Thiourea **18** had a reducing capacity at concentrations ranging from 10 to 50 μM reaching the maximum absorbance at 100 μM and thiourea **19** had a reducing capacity at concentrations ranging from 5 to 50 μM reaching the maximum absorbance at 100 μM (see Table 6).

Conclusion

We have developed two new methodologies to synthesise novel compounds based on thiourea, thiazolidine and pyrrolidine. The

use of boric acid as a catalyst that also acts as a coupling agent has proved to be an efficient, low cost, environmental friendly and versatile process. It has made a new contribution to boron chemistry in coupling reactions. Furthermore, we have synthesised thiosemicarbazide derivatives using an efficient multicomponent methodology, which allows us to quickly access an important class of new molecules. The selected thiazolidines show antioxidant activities, and are able to act against oxidative stress in biological systems. It is important to mention that the same compounds also show reducing properties. Thus, we have presented a new class of compounds based on thiourea that are easy to prepare, with antioxidant properties and biological activity.

Acknowledgments

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Supplementary data

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References and notes

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