Benzothiazoles: a sodium bisulfite-catalyzed synthesis and inhibitory effect on the ureolytic activity of ureases

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Introdução

Urease catalyzes urea hydrolysis to ammonia (NH_3) and carbon dioxide (CO_2), being associated with the cause of some diseases and pathogen infections in humans and animals, as well as nitrogen (N) losses in agriculture[1]. Thus, the use of urease inhibitors has been demonstrated to be effective to both the treatment of urease-triggered diseases and enhancement of food productivity in urea-fertilized fields. Benzothiazoles (**BZTs**) comprise a class of heterocyclic compounds that bear a benzene ring fused to a thiazole ring at positions 4 and 5. The **BZT** core is a privileged scaffold as attested by its use for the development of products of agricultural, pharmaceutical and technological interests[2]. As for the biological activities, the potential of **BZTs** as ureases inhibitors is still poorly investigated. Taking all of these into account, we describe herein the use of sodium bisulfite ($NaHSO_3$) as an efficient catalyst for the preparation of 19 **BZTs**. The potential of **BZTs** synthesized as urease inhibitors of clinical and agricultural interested was also investigated in *in vitro* and in soil assays, respectively.

Resultados e Discussão

We first carried out several reactions of *o*-aminothiophenol with different (hetero)aromatic aldehydes or cyclohexanecarboxaldehyde in the presence of $NaHSO_3$ as catalyst to find the optimum reaction condition to synthesized **BZTs**. The *N*,*N*-dimethylacetamide (DMA) was used as solvent in reactions carried out for 15 or 30 min under microwave irradiation (MWI) at temperatures of 80, 100 or 120 ºC. The maximum reaction yield (80%-100%; Figure 1) was registered upon 30-min-reaction regardless of the use of temperatures higher than 120 ^{o}C. The effect of 19 **BZTs** synthesized on ureases activity was first addressed toward jack bean type III urease in reactions containing 10 mM urea and compounds-test at 1.6 mM. **BZT-15** was the most active jack bean urease inhibitor exhibiting a mechanism of action typical of mixed inhibitor. Its affinity to bind to the urease active site is 21-fold higher than that to bind to allosteric site(s). Assays using agricultural soil from Brazilian Cerrado were performed to investigate the ability of **BZTs** synthesized to inhibit ureases of agricultural interest. The **NBPT** was used as a reference of urease inhibitor active on soil. Interestingly, 14 out of 19 **BZTs** tested inhibited soil ureases at different extents. Results allowed us to categorize the **BZTs** in four groups: (*i*) group 1 constituted of inhibitors more active than **NBPT** (**BZT-10**); (*ii*) group 2 formed by **BZTs** as active as **NBPT** (**BZT-2**, **-8**, **-9**, **-15** and **-16**); (*iii*) group 3 formed by **BZTs** that inhibited soil ureases by lower than 13% and (*iv*) group 4 that includes non-active **BZTs** (**6**, **11**, **13**, **17** and **19**).

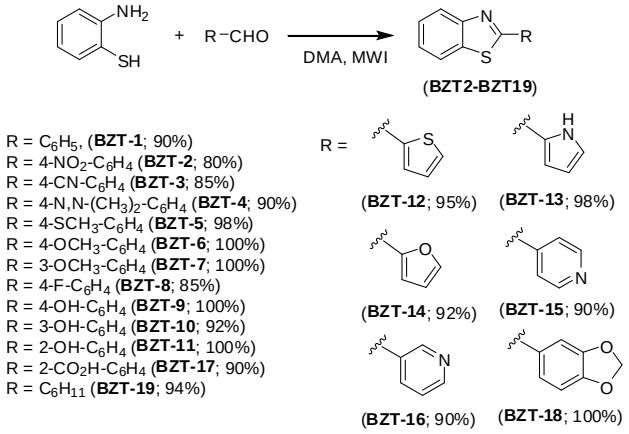

Figura 1. Structures of the **BZTs** synthesized.

Conclusões

This work shows that $NaHSO_3$ is an excellent catalyst for the synthesis of **BZTs**. It was demonstrated, for the first time, that **BZT-15** is a mixed-type urease inhibitor that might be used as a lead compound for the design of drugs to treat urease-associated diseases. We also disclosed the potential of six **BZTs** (**2**, **8**, **9**, **10**, **15** and **16**) for use as additive in urea-based fertilizers to improve N availability in soil for crop production.

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[1] Modolo, L.V.; Souza, A.X.; Horta, L.P.; de Araujo, D.P.; de Fátima, A. *J. Adv. Res.* **2015**, *6*, 35.
[2] Facchinetti, V.; Reis, R.R.; Gomes, C.R.B.; Vasconcelos, T.R.A. *Mini-Rev. Org. Chem.* **2012**, *9*, 44.