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Synthesis of 4-thiazolidinone analogs as potent *in vitro* anti-urease agents

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ABSTRACT

4-Thiazolidinone analogs **1–20** were synthesized, characterized by ^{1}H NMR and EI–MS and investigated for urease inhibitory activity. All twenty (20) analogs exhibited varied degree of urease inhibitory potential with IC_{50} values 1.73–69.65 μM, if compared with standard thiourea having IC_{50} value of 21.25 ± 0.15 μM. Among the series, eight derivatives **3**, **6**, **8**, **10**, **15**, **17**, **19**, and **20** showed outstanding urease inhibitory potential with IC_{50} values of 9.34 ± 0.02, 14.62 ± 0.03, 8.43 ± 0.01, 7.3 ± 0.04, 2.31 ± 0.002, 5.75 ± 0.003, 8.81 ± 0.005, and 1.73 ± 0.001 μM, respectively, which is better than the standard thiourea. The remaining analogs showed good to excellent urease inhibition. The binding interactions of these compounds were confirmed through molecular docking studies.

1. Introduction

Urease enzymes catalyze the hydrolysis of urea into carbamate and ammonia [1–3]. The carbamate decomposes readily into another molecule of ammonia. These reactions cause substantial rise in pH which may cause adverse effects of urease activity on agriculture, animal and human health [4]. Clinically this enzyme is used as indicative to fix manifestation of pathogen in urinary and gastrointestinal tracts. The bacterial urease results in stomach ulcer, infectious stones, peptic ulcer and damaging infections both in animals and human [5]. It also causes the pathogenesis of pyelonephritis, hepatic coma urolithiasis, hepatic encephalopathy, ammonia and urinary catheter encrustation [2]. Lot of microorganisms uses this enzyme to give cradle of nitrogen for growth. In germination process this enzyme has key role in metabolism of plants [2,6].

Heterocyclic compounds are important for medicinal chemists [7]. Thiazole analogs have medical claims such as bacteriostatic, antibiotics [8], diuretics [9], local anesthetics [10,7g], anti-inflammatory [11], analgesics [12,13], and anti-HIV [14,15].

4-Thiazolidinones are the derivatives of thiazole that have been extensively studied and found it to be a part of vitamin-B, Penicillins and antibacterial thiazoles. Reduced thiazole occurs as structural units in compounds of biological importance that serves in the study of polypeptide and proteins [16]. 4-Thiazolidinones have been reported to possess a varied range of biological activities including antitubercular [17], antibacterial [18], antitumor [19], antihistaminic [20], anti-inflammatory [21] and anticonvulsant activity [22].

Our research group is continuously doing effort in search of biologically potent scaffolds [23], which are easy to synthesize and have no tedious chemistry. Previously our group has reported thiobarbituric acid analogs as potent urease inhibitors [24]. In a continued effort in search for biologically active molecules, here we are going to report synthesis of 4-thiazolidinone derivatives and their urease inhibition activity that has not been published earlier.

2. Results and discussion

2.1. Chemistry

Synthesis of 4-thiazolidinone analogs was done in two steps [25]. First, substituted benzaldehyde/acetophenone (1 mmol) was

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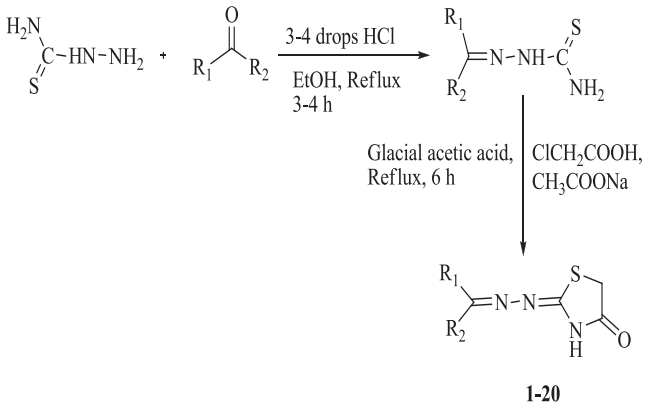

Scheme 1. Synthesis of 4-thiazolidinone analogs **1–20**.

reacted with thiosemicarbazide and 2–3 ml of HCl in ethanol and reflux for 3–4 h. The color change showed reaction completion which was monitored by TLC. On completion, reaction mixture was filtered, washed with *n*-hexane to get Schiff base intermediate.

In step-2, Schiff base intermediate product was reacted with chloro acetic acid (1 mmol) and sodium acetate (1 mmol) in acetic acid and reflux for 6 h. Reaction completion was monitored by TLC. On completion, mixture was filtered, washed with *n*-hexane/ethanol to obtain 4-thiazolidinone analogs (see Scheme 1).

2.2. Biological activity

The urease inhibitory effects of newly synthesized 4-thiazolidinone analogs were measured, for *Bacillus pasteurii* the results are summarized in Table 2 and compared with urease well known inhibitor thiourea (IC_{50} value 21.25 ± 0.15 μM) as reference compound. Out of these twenty analogs, eight analogs **3**, **6**, **8**, **10**, **15**, **17**, **19**, and **20** showed outstanding urease inhibitory potential with IC_{50} values 9.34 ± 0.02, 14.62 ± 0.03, 8.43 ± 0.01, 7.3 ± 0.04, 2.31 ± 0.002, 5.75 ± 0.003, 8.81 ± 0.005, and 1.73 ± 0.001 μM respectively, which were many folds better than the standard. The remaining analogs also showed good to excellent urease inhibition. Structure–activity relationship suggested that the urease activity of a particular molecule is seemingly directed by the substitution pattern present at aromatic residues. In particular, the analog **20** having methoxy group at 2,5 position and bromine at 4-position on phenyl part was an excellent urease inhibitor with IC_{50} value 1.73 ± 0.001 which was better than the standard inhibitor thiourea. Compound **20** was when compared with analogs **7** and **9** having two methoxy groups with bromo and hydroxyl group respectively at phenyl part. The inhibitory potential of compound **20** was greater than **7** which were greater than **9**. The difference in potential was seem to be due difference in position of substituents. The compound **15** was found to be the second most active analog among the series having Br at position-2 while nitro at position-4 on the phenyl part. If we comparing compound **15** with analog **1** and **2** having only nitro group on phenyl ring, the compound **15** showed greater potential that is mainly because of extra bromo group. Similarly analog **17** the third most active compound among the series having methoxy group at position-3, while ethoxy at position-4 on the phenyl part. The greater potential of analog **17** then other disubstituted (EDG) analogs like **4** and **18** was mainly because of position difference of substituents. Similar affect was also observed in other analogs. In conclusion we observed here that both electrons donating as well as electron withdrawing groups on phenyl ring play role in the inhibition but the electron donating groups are superior up to some extent. The binding interactions were confirmed through molecular docking studies.

2.3. Molecular docking

In order to explore the binding mode of newly synthesized 4-thiazolidinone derivatives in the active site of *Bacillus pasteurii* urease (PDB Code: 4UBP) docking study was carried out using MOE (Molecular Operating Environment) software package. The docking results showed that all the compounds well accommodated in the binding pocket of *Bacillus pasteurii* urease. The docked conformation of the most active compound **20,** showed that the carbonyl oxygen of thiazolidin ring of the compound coordinates with both nickel ions like the hydroxyl oxygen in the acetohydroxamate (a potent urease inhibitor). In addition to nickel chelation, two hydrogen bonds and several hydrophobic interactions between the active site residues and the compound were also observed (Fig. 1a). The carbonyl oxygen of thiazolidin ring and nitrogen atom of imino moiety established hydrogen bonds with active site residues His222 and His323 respectively. If we compare the structures of compound **20**, **4**, **7** and **9** all the compounds have about similar structures the only difference in their structures is the presence or absence of bromine moiety and the position of methoxy moiety. The biological activities of these compounds showed that bromine moiety and the position of methoxy play a key role in the inhibitory activities of these compounds (Table 1). For example in case of compound **18**, although the compound have methoxy moieties but bromine is not present and the activity of this compound is less as compare to compound **20**. The binding mode of compound **18** showed poor interaction as compare to compound **20**. As shown in Fig. 1b, although compound **18** established coordinate bond with nickel ions but only one hydrogen bond was observed whereas in case of compound **20** two hydrogen bonds were observed. Furthermore, the distance between the nickel ions and carbonyl oxygen is more as compare to compound **20** (Fig. 1a and b).

Similarly, the positions of methoxy moiety play a key role in the biological activities as well as binding interactions. The docking results showed that the compounds having adjacent methoxy moiety showed poor interactions with active site residues of urease and less biological activities (compounds **4** and **7**). About similar experimental and docking results were observed for compounds **15** and **2**. In these compounds the bromine play the same role as in the above mentioned compounds. When bromine is present, for example compound **15**, good biological activity and strong bonding network was observed (Table 1 and Fig. 2a). But when bromine is absent from the structure (compound **2**), lower biological activity and poor interactions were observed (Table 1 and Fig. 2b).

In case of compounds having hydroxy phenyl ring in their structures (compounds **3**, **5** and **6**), it was observed that the presence and absence of chlorine moiety and the position of hydroxyl group play a pivotal role in the biological activities as well as the binding interactions of these compounds. For example when chlorine is present, compound **3**, the inhibitory activity and binding interactions are good (Table 1). But when chlorine is absent from the structure (compound **6**) both biological activity and binding interactions were poor (Fig. 3a). Like bromine and chlorine a key role was observed for benzoyloxy-4-methylbenzine and indole moieties. For example when these moieties present (compounds **11**, **12** and **18**) lower biological activities as well as poor interactions were observed for these compounds (Table 1 and Fig. 3b). These lower activities and poor interactions might be due to the steric clash produce by these bulky hydrophobic groups. The docking conformation of compound **12** showed that although the carbonyl oxygen of the thiazolidin ring coordinate with the nickel ions of the