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Synthesis and structure–activity relationship of thiobarbituric acid derivatives as potent inhibitors of urease

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ABSTRACT

A series of thiobarbituric acid derivatives **1**–**27** were synthesized and evaluated for their urease inhibitory potential. Exciting results were obtained from the screening of these compounds **1**–**27**. Compounds **5**, **7**, **8**, **11**, **16**, **17**, **22**, **23** and **24** showed excellent urease inhibition with IC_{50} values 18.1 ± 0.52, 16.0 ± 0.45, 16.0 ± 0.22, 14.3 ± 0.27, 6.7 ± 0.27, 10.6 ± 0.17, 19.2 ± 0.29, 18.2 ± 0.76 and 1.61 ± 0.18 μM, respectively, much better than the standard urease inhibitor thiourea (IC_{50} = 21 ± 0.11 μM). Compound **3**, **4**, **10**, and **26** exhibited comparable activities to the standard with IC_{50} values 21.4 ± 1.04 and 21.5 ± 0.61 μM, 22.8 ± 0.32, 25.2 ± 0.63, respectively. However the remaining compounds also showed prominent inhibitory potential The structure–activity relationship was established for these compounds. This study identified a novel class of urease inhibitors. The structures of all compounds were confirmed through spectroscopic techniques such as EI-MS and ^{1}H NMR.

1. Introduction

Urease enzyme is a virulence factor in certain human and animal ailments. It contributes to the development of kidney stones, pyelonephritis, peptic ulcers leading to gastric cancers and other diseases.[1] It also causes the pathogenesis of pyelonephritis, hepatic encephalopathy, hepatic coma urolithiasis, ammonia and urinary catheter encrustation.[2] The obvious cure for treating bacterial infection with antimicrobials, however, often proved to be unsuccessful.[3] Currently it was reported that the gastric cancer[4,5] is the fourth most common cancer and the second most common cause of cancer-related deaths worldwide.[6] It is also a cause of pathologies due to *Helicobacter pylori*, which lets bacteria to persist at the low pH of the stomach during colonization lead pathogenesis of gastric and peptic ulcer which in the long run may cause cancer.[7]

The barbiturates and thiobarbiturates showed a wide range of pharmacological applications, such as general anesthesia, sedation and anticonvulsant and anxiolytic effects. Barbiturate compounds also showed urease inhibition.[8] Barbituric and thiobarbituric acid derivatives also exhibited antimicrobial,[9,10] antifungal,[11] antiviral,[12] and antitumor activities.[13] From literature study it is clear that barbiturates and thiobarbiturate derivatives show diverse biological activities such as potential mushroom tyrosinase inhibition,[14] antituberculosos,[15] radio-sensitization,[16] anticancer with anti-inflammatory activities,[17] inhibition for diaminopimelate aminotransferase,[18] and anesthesia.[19] Barbiturate analogues also showed anti-proliferative activity.[20]

Our research group is involved in the search for simple but biologically interesting molecules that are easy to synthesize with no tedious chemistry and that could be accomplished in just fewer steps with high yields. This type of chemistry is easily and ideally adopted by the pharmaceutical industry for commercialization. Previously, our research group reported arylidene barbiturates as urease inhibitors their other activities.[21] In view of these studies; we planned to synthesize thiobarbiturate derivatives with the aim to discover their urease inhibition.

2. Results and discussion

2.1. Chemistry

The synthesis of thiobarbituric acid derivatives (**1**–**27**) was carried out by the reaction of thiobarbituric acid (1 mmol) with

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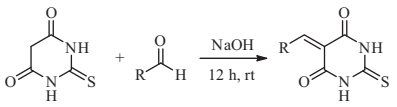


Scheme 1. General Scheme for the synthesis of thiobarbituric acid derivatives **1**–**27**.

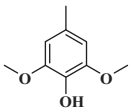
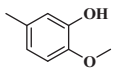
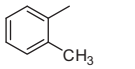
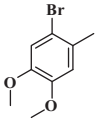
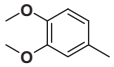
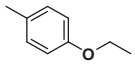
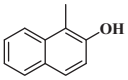
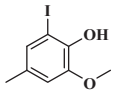
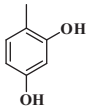
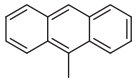
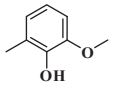
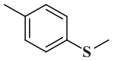
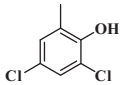
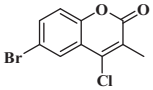
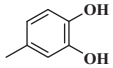
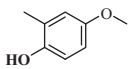
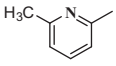
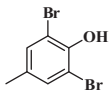
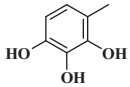
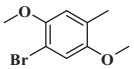
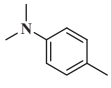
different aromatic aldehyde (1 mmol) in the presence of 10 ml of 20% NaOH. The reaction mixture was stirred for 12 h. The completion of reaction was monitored by TLC. After completion of the reaction, the mixture was poured onto crushed ice followed by acidification with dilute hydrochloric acid. The products (**1**–**27**) were precipitated out; the solid was filtered, dried and recrystallized from ethanol (Scheme 1, Table 1). Structures of synthetic compounds were identified by spectroscopic methods such as ^{1}H NMR and EIMS. All synthetic derivatives furnished satisfactory elemental analyses.

2.2. Urease Inhibitory Activity

Compounds **1**–**27** were evaluated for inhibition of urease enzyme. All compounds showed potent urease inhibitory activity (Table 2). Compounds **5**, **7**, **8**, **11**, **16**, **17**, **22**, **23** and **24** showed excellent urease inhibition with IC_{50} values 18.1 ± 0.52, 16.0 ± 0.45, 16.0 ± 0.22, 14.3 ± 0.27, 6.7 ± 0.27, 10.6 ± 0.17, 19.2 ± 0.29, 18.2 ± 0.76 and 1.61 ± 0.18 μM, respectively, much better than the standard inhibitor thiourea (IC_{50} = 21 ± 0.11 μM). Compound **3**, **4**, **10**, and **26** exhibited comparable activities to the standard with IC_{50} values 21.4 ± 1.04 and 21.5 ± 0.61μM, 22.8 ± 0.32, 25.2 ± 0.63, respectively . However, compounds **1**, **2**, **6**, **9**, **12**, **14**, **15**, **18**, **19**, **20**, **21**, and **25** also exhibited striking inhibitory potential with IC_{50} values 46.5 ± 0.56, 47.3 ± 0.62, 62.8 ± 1.71, 43.3 ± 1.06, 42.5 ± 1.3, 50.3 ± 0.81, 32.3 ± 0.62, 58.5 ± 1.28, 42.1 ± 1.91, 29.4 ± 0.59, 32.1 ± 0.34, and 32.7 ± 0.82 μM, respectively.

Structure–activity relationship suggested that the urease activity of a particular molecule is apparently governed by the substitution present at aromatic residues. The *p*-thiomethyl substituted analog **5** (IC_{50} = 18.1 ± 0.52 μM), pyridin-4-yl **7** (IC_{50} = 16.0 ± 0.45 μM), 2-methyl-*o*-pyridin-2-yl **8** (IC_{50} = 16.0 ± 0.22 μM), 3,4-dimetoxy **11** (IC_{50} = 14.3 ± 0.27 μM), *p*-phthalaldehydic **16** (IC_{50} = 6.7 ± 0.27 μM), 3,5-dibromo-4-hyroxy **17** (IC_{50} = 10.6 ± 0.17 μM), 2-hydroxy-3-methoxy **22** (IC_{50} = 19.2 ± 0.29 μM), 2-methylfuryl **23** (IC_{50} = 18.2 ± 0.76 μM), and 3,4-dihydroxy **24** (IC_{50} = 1.61 ± 0.18 μM), respectively, showed excellent inhibitory activities among the series. It was observed that variation in substitution pattern of benzaldehyde or aromatics resulted a difference in activities. Compound **24** (3,4-dihydroxy analog) is found to be the most active among the series with IC_{50} value 1.61 ± 0.18 μM. The two hydroxyl groups on phenyl ring might be involved in hydrogen bonding with nickel atoms present in urease enzyme. The compound **16** got second position among the series with IC_{50} value 6.7 ± 0.27 μM. This compound has one more sulfur group which might help in coordination with the nickels. The compounds **17** and **22** having *p*-hydroxy and *o*-hydroxy group with IC_{50} values 10.6 ± 0.17 and 19.2 ± 0.29 μM, respectively, also showed potent

Table 1
Synthesis of thiobarbituric acid derivatives **1**–**27**

S. no.	R	Yield (%)	S. no.	R	Yield (%)	S. no.	R	Yield (%)
1		93	10		93	19		93
2		92	11		92	20		91
3		93	12		90	21		93
4		93	13		88	22		95
5		93	14		92	23		93
6		93	15		93	24		94
7		95	16		91	25		93
8		93	17		89	26		93
9		92	18		91	27		89