Bioorganic Chemistry 79 (2018) 34–45

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

Synthetic nicotinic/isonicotinic thiosemicarbazides: *In vitro* urease inhibitory activities and molecular docking studies

Basharat Ali[a], Khalid Mohammed Khan[a,e,*], Arshia[a], Kanwal[a], Shafqat Hussain[a], Safdar Hussain[b], Muhammad Ashraf[b], Muhammad Riaz[c], Abdul Wadood[d], Shahnaz Perveen[e]

[a] *H. E. J. Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi 75270, Pakistan*
[b] *Department of Chemistry, The Islamia University of Bahawalpur, Bahawalpur 63100, Pakistan*
[c] *Department of Biochemistry, Computational Medicinal Chemistry Laboratory, UCSS, Abdul Wali Khan University, Mardan, Pakistan*
[d] *PCSIR Laboratoires Complex, Karachi, Shahrah-e-Dr. Salimuzzaman Siddiqui, Karachi 75280, Pakistan*
[e] *Department of Clinical Pharmacy, Institute for Research and Medical Consultations (IRMC), Imam Abdulrahman Bin Faisal University, P.O. Box 31441, Dammam, Saudi Arabia*

ARTICLE INFO

Keywords:
Synthesis
Nicotinic/isonicotinic
Thiosemicarbazide
Urease inhibition
In vitro
In silico
Structure-activity relationship

ABSTRACT

Nicotinic and isonicotinic thiosemicarbazide or hydrazine carbothioamides **3–27** were synthesized and the structures of synthetic compounds were elucidated by various spectroscopic techniques such as EI-MS, ^{1}H-, and ^{13}C NMR. Synthetic derivatives were evaluated for their urease inhibitory activity which revealed that except few all derivatives demonstrated excellent inhibition in the range of IC_{50} values of 1.21–51.42 μM as compared to the standard thiourea (IC_{50} = 21.25 ± 0.13 μM). Among the twenty-five synthetic derivatives nineteen **1–5**, **7**, **8**, **10**, **12**, **14–18**, **20–22**, **24–27** were found to be more active showing IC_{50} values between 1.13 and 19.74 μM showing superior activity than the standard. Limited structure-activity relationship demonstrated that the positions of substituent as well as position of nitrogen in pyridine ring are very important for inhibitory activity of this class of compound. To verify these interpretations, *in silico* study was also performed. A good correlation was obtained between the biological evaluation of active compounds and docking study.

1. Introduction

Urease (urea amidohydrolase, EC 3.5.1.5) is a well-known nickel containing metalloenzyme that catalyzes the hydrolysis of urea into ammonia and carbamate [1]. At normal physiological pH carbamate moiety spontaneously hydrolyses to form bicarbonate and a second molecule of ammonia [2]. Consequently, these reactions cause significant alkalinity due to release of large quantities of ammonia. The increase in pH is directly associated with the development of numerous health complications in humans which depend on colonization site by urease-producing microorganisms and primarily include urinary and gastrointestinal tract infections. Increase stomach acid secretion in response of *H. pylori* destroys colonization of mucosal membrane and causes gastric ulcers [3]. Development of kidney stone, pyelonephritis, hepatic coma *etc* are also associated with urease complication. Therefore, it is necessary to control urease activity by urease inhibitors. A close structural likeness of thiosemicarbazide with thiourea which is used as one of the standards in urease inhibitory assay draws considerable attention of medicinal chemist for screening thiosemicarbazide for evaluating their potential as urease inhibitors [4].

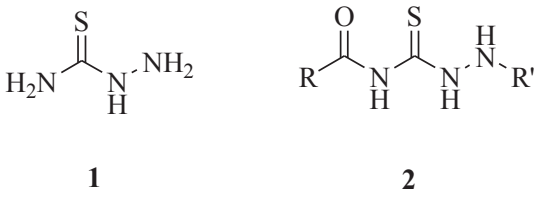
Thiosemicarbazide or hydrazine carbothioamide **1** (Fig. 1) is derived from thiocarbamic acid with hydrazine moiety. Its chemical behavior is same as semicarbazide which is its oxygen counterpart, however, due to presence of thio group it has great chemical versatility and varying behavior then semicarbazide [5].

Thiosemicarbazide has a major role in the drug industry due to its wide range of pharmacological activities such as antitubercular [6], herbicidal [7], antibacterial [8], antiviral [9], antinociceptive [10], and antioxidant properties. Since our research group is continuously engaged in search of urease inhibitors [11–16] and we have also previously reported benzophenone semicarbazide (semicarbazone), istain and benzophenone thiosemicarbazide (thiosemicarbazone) derivatives as a potent urease inhibitors (Fig. 2) [17–20].

The current study is an expansion of our previous studies based on optimization of new urease inhibitors with enhanced efficacy. In this regard, we have synthesized a series of nicotinic/isonicotinic thiosemicarbazide derivatives **3–27** since nicotinic/isonicotinic thiosemicarbazide have itself medicinal importance [21–22] by reacting nicotinic/isonicotinic hydrazides with various substituted phenyl isothiocyanates. To the best of our knowledge compound **4**, **10**, **20**, and

* Corresponding author at: H. E. J. Research Institute of Chemistry, International Center for Chemical and Biological Sciences, University of Karachi, Karachi 75270, Pakistan.
E-mail address: khalid.khan@iccs.edu (K. Mohammed Khan).

https://doi.org/10.1016/j.bioorg.2018.04.004
Received 15 March 2018; Received in revised form 12 April 2018; Accepted 12 April 2018
Available online 16 April 2018
0045-2068/



1 **2**

Fig. 1. Structure of thiosemicarbazide 1 and acyl thiosemicarbazide **2** (**3–27**).

22 are new while remaining compounds are previously reported [23–29].

2. Results and discussion

2.1. Chemistry

Nicotinic/isonicotinic hydrazides were reacted with various substituted phenyl isothiocyanates in ethanol to get desired nicotinic/isonicotinic thiosemicarbazide derivatives (**3–27**) Scheme 1. The reaction mixture containing nicotinic/isonicotinic hydrazides and phenyl isothiocyanates in absolute ethanol was refluxed at 80 °C for 30–50 min and monitored through TLC. After the completion of reaction, it was filtered and the solid part was washed with hot hexane then ethanol which later dried and collected Table 1. The synthetic compounds were characterized by using various spectroscopic techniques such as EI-MS, ^{1}H NMR, and ^{13}C NMR.

2.1.1. Spectral characterization of of most active compound 12

The ^{1}H NMR was recorded in DMSO on a 400 MHz instrument. Compound **12** with nicotinic moiety possess total eleven protons. The molecule contain three NH, the NH-4 was the most downfield signal appeared as sharp singlet at δ 10.83. The protons for NH-1 and -2 appeared as singlet and resonated at δ 10.11. The characteristic proton H-2′ of nicotine ring was appeared at δ 9.10 as a singlet. H-4′ was resonated as doublet at δ 8.76 (J = 5.6 Hz) and showed coupling with H-5′. H-5′ and H-6′ were appeared at δ 8.00 as doublet (J = 7.2 Hz). The H-2″ of aryl ring next to nitro group appeared as an overlap and resonated at δ 8.43. H-4″ was appeared at δ 8.29 as doublet (J = 7.2 Hz) showing coupling with H-5″. Two protons H-5″ and H-6″ were appeared at δ 7.63 as an overlap (Fig. 3).

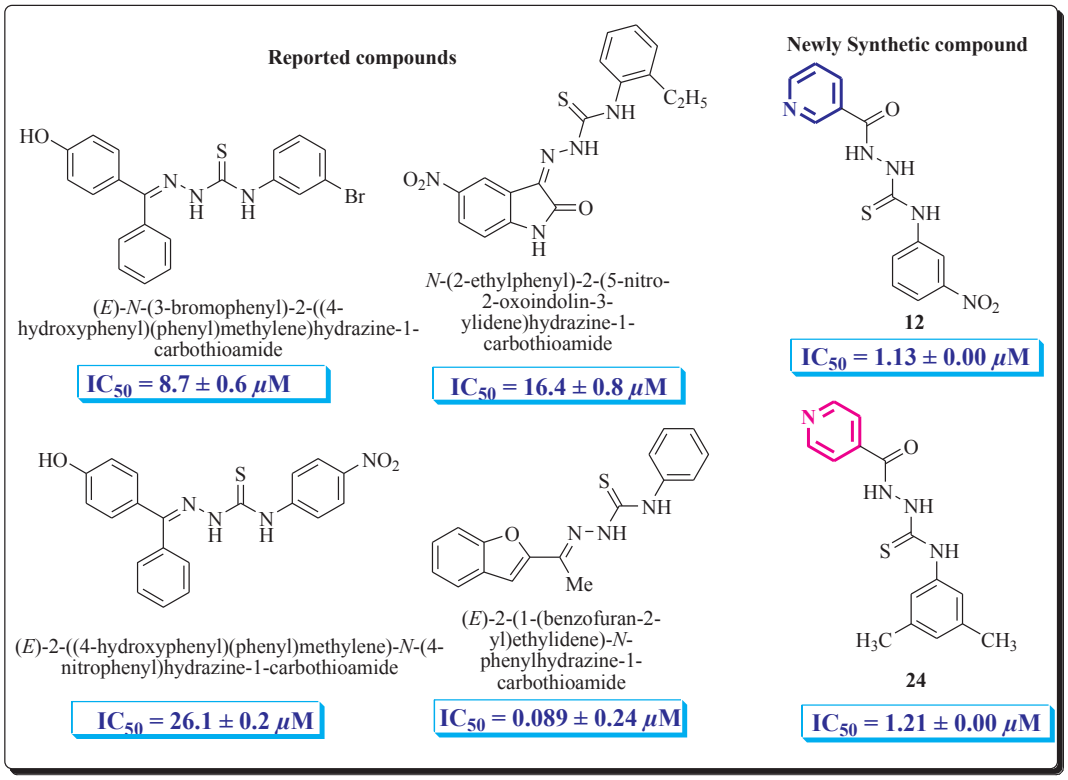
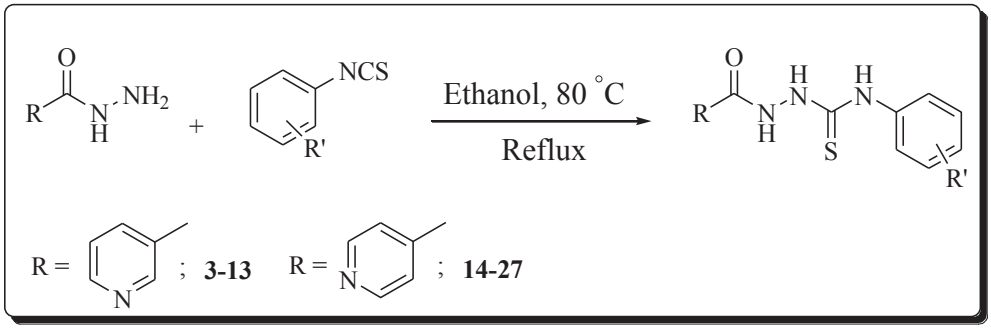


Fig. 2. Rationale of current studies.



Scheme 1. Synthesis of nicotinic and isonicotinic acylthiosemicrabazides.