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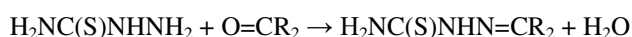
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Beneficial Therapeutic Effects of Heterocyclic Thiosemicarbazones

Chandrashekhar Meena

Assistant Professor, Chemistry, Government College, Gangapur City, Rajasthan, India

ABSTRACT: A thiosemicarbazone is an organosulfur compound with the formula $H_2NC(S)NHN=CR_2$. Many variations exist, including those where some or all of the NH centers are substituted by organic groups. Thiosemicarbazones are usually produced by condensation of a thiosemicarbazide with an aldehyde or ketone:

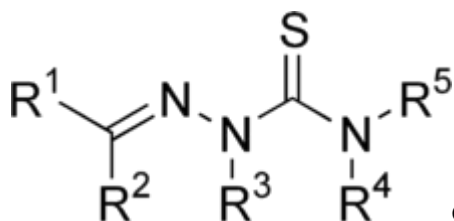


In terms of their chemical structures, the CSN₃ core atoms are coplanar.^[1]

Some thiosemicarbazones have medicinal properties, e.g. the antiviral metisazone and the antibiotic thioacetazone. Thiosemicarbazones are also widely used as ligands in coordination chemistry.^[2] The affinity of thiosemicarbazones for metal ions is exploited in controlling iron overload.^[3]

KEYWORDS-Thiosemicarbazones, Therapeutic, Heterocyclic, Organosulphur, Antibiotic

I. INTRODUCTION

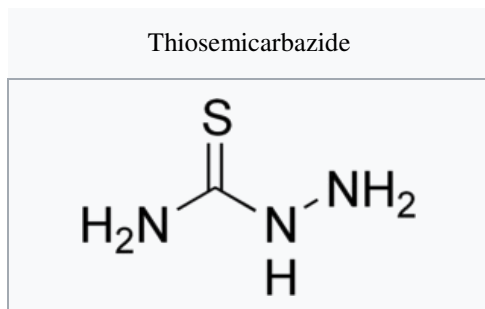


General chemical structure of a thiosemicarbazone

Thiosemicarbazide is the chemical compound with the formula $H_2NC(S)NHNH_2$. A white, odorless solid, it is related to thiourea ($H_2NC(S)NH_2$) by the insertion of an NH center. They are commonly used as ligands for transition metals.^[2] Many thiosemicarbazides are known. These feature an organic substituent in place of one or more H's of the parent molecule. 4-Methyl-3-thiosemicarbazide is a simple example.

According to X-ray crystallography, the CSN₃ core of the molecule is planar as are the three H's nearest the thiocarbonyl group.^[3]

Thiosemicarbazides are precursors to thiosemicarbazones. They are precursors to heterocycles.^[4] Formylation of thiosemicarbazide provides access to triazole.^[5]



Following induction of inflammation, the nuclear factor kappa B (NF- κ B) in activated macrophages induces the transcription of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α), interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and cyclooxygenase (COX), an inflammatory enzyme implicated in the synthesis of prostaglandins (PGs). The latter are involved in the transition and the maintenance of chronic inflammation underlying various chronic disorders[1-5] that require treatment. Concerning this, many anti-inflammatory drugs are available to treat the inflammatory disorders, but their therapeutic use is associated with a variety of side

effects. Therefore, the discovery of new safer and potential anti-inflammatory drugs is necessary. In this regard, thiosemicarbazones (TSC) compounds and their metals complexes attracted high interest due to their wide range of biological activities, interestingly, the anti-inflammatory activity. They are formed by the action of thiosemicarbazide on an aldehyde or ketone, and contain a sulfur atom in place of the oxygen atom. Their ability to form a stable complex with transition metal is known to enhance the biological activity and reduces the side effects of the parent compound. [7-12]

Inflammation is the immune response against harmful factors, including infection, injury, tissues damage, and tumors. Upon foreign invasion, the innate immune system, the first line of host defense, is immediately activated and evokes an acute inflammatory response against the invading pathogens [1]. The acute phase of inflammation comprises cardinal signs, including redness, heat, swelling and pain. It lasts hours to days, and is characterized by the rapid influx of granulocytes, firstly neutrophils, followed by monocytes that mature into macrophages. The latter are versatile immune cells. They exert a wide range of function involved in both the innate and adaptive immune system, such as phagocytosis, antigen presentation, cytokine secretion, and are considered the sentinel of the immune system due to the detection of pathogen associated molecular patterns (PAMPs) through the pattern recognition receptors (PRRs) which include Toll-like-receptor (TLRs) family.

TLRs are integral glycoproteins expressed in many cell types in addition to macrophages, such as dendritic cells (DC) and neutrophils, and are characterized by external or luminal ligand-binding domain, and a cytoplasmic signaling Toll/interleukin 1 (IL-1) receptor homology (TIR) domain [2]. Till now, ten TLRs have been identified in humans [3], each recognize distinct PAMPs derived from bacteria, virus, fungi or protozoa [4]: TLR-1, -2, -4, -5, -6 and -10 are localized in the cell surface and recognize the bacterial product; whereas, the rest are localized in the intracellular compartments, including endosomes and lysosomes, and recognize the nucleic acid. On the other hand, PAMPs are conserved structures on pathogens, essential for their survival [5]. Among them, the endotoxin lipopolysaccharide (LPS) is one of the most powerful activators of macrophages. It is an essential component of the outer membrane of Gram-negative bacteria. The LPS-TLR interaction induces the receptor oligomerization which subsequently triggers the activation of multitude of intracellular signaling pathways, such as nuclear factor kappa B (NF- κ B) and mitogen activated protein kinase (MAPKs) pathways [6], that activates in turn the transcription of a broad range of inflammatory genes, including pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF- α), interleukin-1 β (IL-1 β) and IL-6, chemokines such as monocyte chemoattractant protein-1 (MCP-1) or chemokine (C-C motif) ligand (CCL) 2 [7], and cyclooxygenase (COX) which is an inflammatory enzyme implicated in the synthesis of prostaglandins (PGs), a class of eicosanoids that plays a critical role in inflammation.

In the normal conditions, an acute inflammation is resolved by various mechanisms, including elimination of the inciting stimulus, negative regulation of chemokines and cytokines to stop further inflammatory cells influx, temporal switch in lipid mediator of eicosanoids from prostaglandins to lipoxins which have anti-inflammatory and pro-resolving functions by reducing the vascular permeability [8], retarding the entry of new neutrophils into the inflammatory sites [9] and stimulating macrophages to phagocyte apoptotic neutrophils [10] in a process known as efferocytosis [11]. The latter process also triggers the conversion of pro-inflammatory phagocytosing macrophages to anti-inflammatory and pro-resolution phenotype [12] characterized by the upregulation of co-inhibitory molecules such as programmed death ligand 1 (PDL1) and inducible co-stimulator (ICOS) ligand, and the secretion of anti-inflammatory cytokines such as transforming growth factor- β 1 (TGF- β 1) and IL-10. On the other hand, the omega-3 polyunsaturated fatty acids are used to generate other lipid mediators called resolvins and protectins [13], [14], [15], [16] which contribute to the inflammatory response termination [17]. Thus, once the offending factors are cleared, the acute inflammation is resolved and the tissue homeostasis is restored. However, when the resolution fails, the acute inflammation persists and becomes chronic, lasts weeks to months to years and predisposes the body to various chronic disorders such as cardiovascular, neurodegenerative, cancer, vascular metabolic and autoimmune diseases [18].

In this regard, many anti-inflammatory drugs are available to treat the inflammatory disorders, but their therapeutic use is associated with a variety of side effects. Therefore, the synthesis of new potential and safer anti-inflammatory agents is necessary. Indeed, over the last 50 years, thiosemicarbazones (TSCs) biological activities, including the anti-inflammatory activity attracted the attention. Thiosemicarbazones represent a class of compounds analogous to semicarbazones and formed by the action of thiosemicarbazide on an aldehyde or ketone. They contain a sulfur atom in place of the oxygen atom and they have the ability to gain different biological activities by changing the N4 substitution and/or the binding metals ions, such as iron (Fe), nickel (Ni), copper (Cu) and zinc (Zn). Moreover, the metal binding reduced the side effects of the parent compound. Thus, in this review article we describe the inflammatory axis of NF- κ B-COX-PGs stimulated by LPS-binding TLR, and summarize the anti-inflammatory activity of different thiosemicarbazones derivatives synthesized in research area.

II. DISCUSSION

Function and members

During the inflammatory response, different signaling pathways are activated and coordinate together in order to regulate the expression of both pro and anti-inflammatory mediators in innate and adaptive immune cells, tissues residents or recruited from the blood. Among them, the most important one is the NF- κ B pathway. NF- κ B is a key transcription factor discovered in 1986 as a nuclear factor that binds to the enhancer element of the immunoglobulin kappa light-chain of activated B cells.[13-19]

Cyclooxygenase (COX)

Cyclooxygenase (COX), also known as prostaglandin (PG) rate-limiting synthase, catalyzes the first step in the production of prostanoids, a large family of paracrine mediators comprising prostacyclin, thromboxanes, and prostaglandins through the metabolism of arachidonic acid (AA), a polyunsaturated fatty acid released from the sn-2 position of phospholipids in the plasma membrane under the action of phospholipase A₂ (PLA₂). COX is an integral membrane glycoprotein

Biosynthesis and function

Firstly, COX-2 converts the arachidonic acid to the intermediate prostaglandin-H₂ (PGH₂), a common substrate for a series of specific isomerases and synthase enzymes, which is converted latter into thromboxane-A₂ (TxA₂) and prostaglandins. In vivo, there are four bioactive prostaglandins generated: prostaglandin E₂ (PGE₂), prostaglandin D₂ (PGD₂), prostacyclin (PGI₂), and prostaglandin F_{2 α} (PGF_{2 α})

PGs are ubiquitous substances synthesized in most tissues by one or two dominant products

Transition of acute inflammation to chronic: Role of PGE₂

Recent studies showed that the expression of COX-2 is often observed in tissues of chronic inflammatory disorders [44], [45] and supported the involvement of PGs in the transition and the maintenance of chronic inflammation. Among the potential mechanisms contributing to the chronic inflammation: conversion of acute inflammation to long lasting immune inflammation, and activation of a positive feedback loop by repetitive stimuli. Among the PGs, the most significant role is attributed to PGE₂

Discovery, structure and biological activities

Thiosemicarbazones compounds were discovered by Domagk upon investigating the anti-tuberculous activity of a series of sulfathiadiazoles prepared by cyclization of corresponding thiosemicarbazones [52]. Two products were generated: the end product was uninteresting; however, the intermediate product "thiosemicarbazone" was found to be a strong in vivo tuberculostatic agent [53]. Afterwards, the compound of interest was also tested by Harmer's group at the Squibb Institute for Medical Research

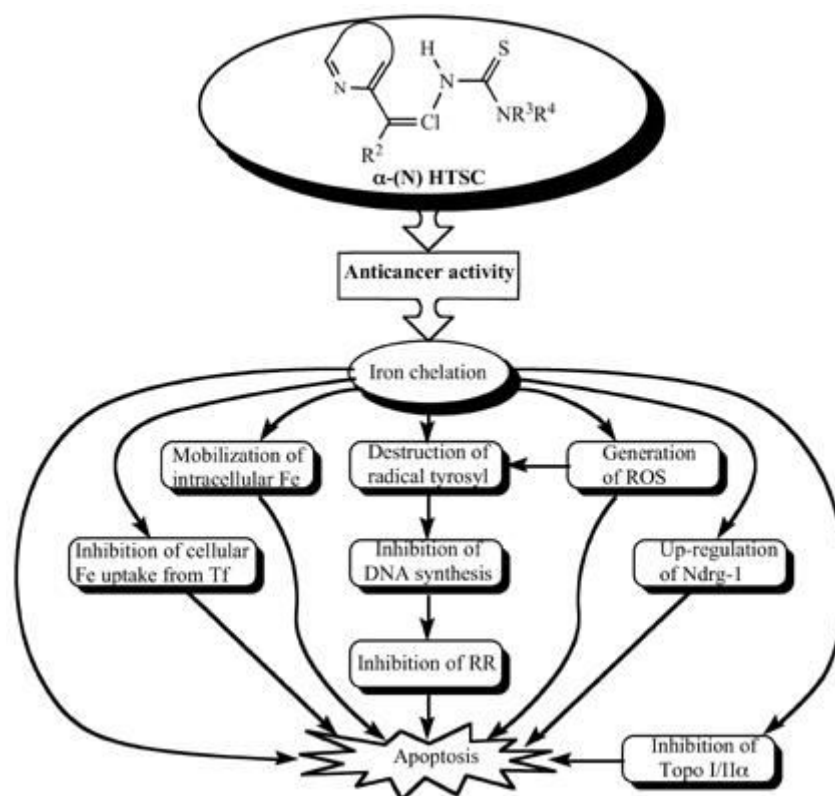
Inflammation and treatment

Heterogeneous class of anti-inflammatory drugs are available to control inflammation, such as non-steroidal anti-inflammatory drugs (NSAIDs) [107] and COX-2 selective inhibitors (COXIBs) that treat a variety of inflammatory pathologies by targeting the PG-pathway through the inhibition of COX enzymatic activity. NSAIDs are among the most frequently used worldwide anti-inflammatory, anti-nociception and anti-analgesic therapeutic agents.

III. RESULTS

Conclusively, NF- κ B activates the transcription of multiple pro-inflammatory genes, including COX enzyme that is implicated in the PGs synthesis. The latter are involved in the transition and the maintenance of chronic inflammation, the basis of various chronic disorders. In this review article, various thiosemicarbazones derivatives were reported for being safer and their potential and promising anti-inflammatory activity may be further explored for the treatment of

several diseases. Thiosemicarbazones (TSCs) are a class of Schiff bases usually obtained by the condensation of thiosemicarbazide with a suitable aldehyde or ketone. TSCs have been the focus of chemists and biologists due to their wide range of pharmacological effects. One of the promising areas in which these excellent metal chelators are being developed is their use against cancer. TSCs have a wide clinical antitumor spectrum with efficacy in various tumor types such as leukemia, pancreatic cancer, breast cancer, non-small cell lung cancer, cervical cancer, prostate cancer and bladder cancer. To obtain better activity, different series of TSCs have been developed by modifying the heteroaromatic system in their molecules. These compounds possessed significant antineoplastic activity when the carbonyl attachment of the side chain was located at a position α to the ring nitrogen atom, whereas attachment of the side chain β or γ to the heterocyclic N atom resulted in inactive antitumor agents. In addition, replacement of the heterocyclic ring N with C also resulted in a biologically inactive compound suggesting that a conjugated N,N,S-tridentate donor set is essential for the biological activities of thiosemicarbazones. Several possible mechanisms have been implemented for the anticancer activity of thiosemicarbazones.[20-25]



IV. CONCLUSIONS

Thiosemicarbazones (TSCs) are a varied class of compounds with common N-N-S coordinates. They were discovered in the 1950s with anti-bacterial, anti-fungal, and anti-tumor activities [8,9]. TSCs are multi-target drugs and the molecular mechanisms involved metal chelation, DNA interference, topoisomerase inhibition and ribonucleotide reductase inhibition [10]. Many metal-TSC complexes have been synthesized and were found to be more effective in cell toxicity experiments than the ligand form of the TSC [10,11]. The cell toxicity of metal-TSCs included a decrease in de novo purine synthesis and inhibition of IMP dehydrogenase, DNA polymerase activity, and topoisomerase II activity [10,11,12]. Recent studies in yeast have uncovered other cellular mechanisms for metal-bis(TSC), which includes chromatin remodeling, cytoskeleton organization, mitochondrial function, and iron metabolism [13]. Due to the varied structures of TSCs, they impact multiple cellular targets. In this paper, we summarize the TSCs that are targeting Tops with a particular emphasis on metal-TSCs.

Several examples of ligand TSCs that have been studied either clinically or in animal models. Triapine (3-aminopyridine-2-carboxaldehyde thiosemicarbazone; 3-AP) is the first thiosemicarbazone to be approved for clinical trials. It inhibits ribonucleotide reductase and chelates iron to kill cancer cells. There are more than 30 Phase I and Phase II clinical trials with Triapine, but it has disadvantages of adverse events, such as methemoglobinemia, and a short plasma half-life [14]. In recent years, TSCs gained more attention as potential anticancer drugs since they impact

multiple potential targets. Polypharmacology is particularly useful in the metastasis stage of cancer treatment. Dp44mT, (di-2-pyridylketone-4,4-dimethyl-3-thiosemicarbazone) has potent and broad antitumor activities in a panel of human xenografts in nude mice [15]. It not only chelates iron but also has redox properties, similar to Triapine [15]. Dp44mT showed conflicting results in Top inhibition, which is discussed later in this article. DpC, (di-2-pyridylketone 4-cyclohexyl-4-methyl-3-thiosemi-carbazone), optimized based on the structure of Dp44mT, has superior activity against human pancreatic cancer xenografts in nude mice [16].

COTI-2 [4-(2-pyridinyl)-2-(6,7-dihydro-8(5H)-quinolinylidene)-hydrazide], a TSC ligand, was identified through in silico screening and was found to inhibit many human cell lines in vivo [17]. COTI-2 has been shown to have anticancer activities through p53-dependent and p53-independent mechanisms [18]. Bis(thiosemicarbazone) metal complexes have been recently applied to neurodegenerative disease since they are able to restore metal balance in neurons. They showed promising results in animal models for Alzheimer's disease, Parkinson disease, and amyotrophic lateral sclerosis [19].

2. Thiosemicarbazones as Inhibitors of Topoisomerases

TSCs have been studied for decades for antiviral, antifungal and antiproliferation activity (Table 1). In recent years, Triapine a member of TSC family, has been studied in phase I and II clinical trials [20,21,22,23]. The major molecular target of Triapine was identified as ribonucleotide reductase [23,24]. Triapine showed some inhibition of Top2A but only in the presence of Cu(II) [25]. Previous work on Triapine did not show any inhibition of relaxation or poisoning of plasmid DNA cleavage with Top2 α [26].

In a series of TSC compounds, Top2 was discovered as one of the molecular targets for the ligand TSC24 (Figure 1) [27]. TSC24 showed high potent activity with an IC₅₀ of 0.02 μ M against the HT-29 cell line [27]. TSC24 inhibited tumor growth of S-180 sarcoma-bearing mice in a dose-dependent manner, with inhibitory rates of 17.6%, 35.8%, and 76.7% at doses of 12.5, 25, and 50 (mg/kg)/day, respectively, after it was administered intraperitoneal (IP) for 7 days [21].

The pattern of TSC antiproliferative effects against the human cancer cell line (NCI-60) is similar to those found with recognized anticancer treatments [27]. These investigations revealed TSC24's profile is comparable to known Top2 agents. TSC24 was further investigated and it was found that it hindered DNA relaxing and decatenation by inhibiting the Top2 α ATPase domain [27].

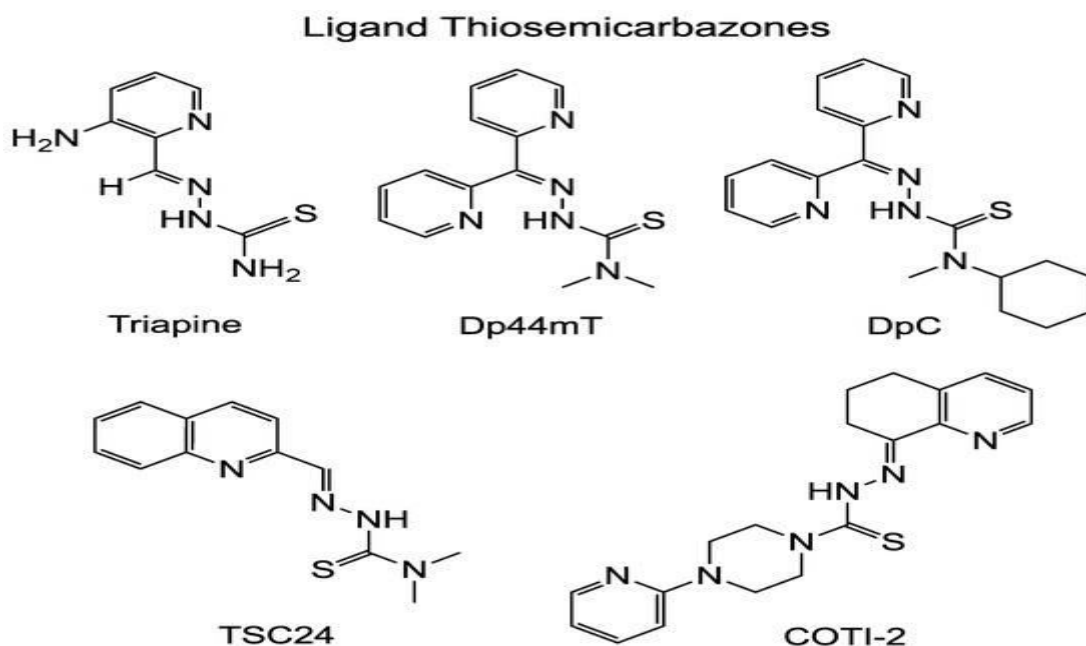


Figure 1. Ligand TSC compounds. Examples of several ligand TSCs are shown including some that have undergone clinical or pre-clinical trials. Some of these are known to chelate metals in cellular contexts. Structures prepared using ChemDraw 20.1.

Another TSC ligand that has been well studied is Dp44mT (Figure 1). It induces G1 cell cycle arrest and reduces cancer cell clonogenic growth in the breast cancer line MDA-MB-231 at nanomolar concentrations [22]. In relaxation and cleavage experiments, Dp44mT was shown to preferentially target Top2 α , with minimal effect on Top2 β and little inhibition of Top1 [28]. But this result is controversial as an additional study found that the ligand Dp44mT did not inhibit Top2 α or increase cellular cleavage complexes [26]. A more recent study on the ligand Dp44mT also found little effect of the compound alone, but they found inhibition when combined with Cu(II) [25]. The cell toxicity result is consistent with previous studies [22] and IC₅₀ against the cancer cell line is in a nanomolar concentration. The Cu(II) complex of Dp44mT showed similar or lower IC₅₀ compared with Dp44mT [25]. It is unclear whether it was the presence of Cu(II) alone or if the Cu(II) formed a complex with the ligand leading to the effect in this case. As is discussed below, it is possible that the ligand forms alone show little activity, while metal-chelated forms have varying levels of activity depending on the metal ion.

Computational docking and surface plasmon resonance studies support the ability of TSC24 to bind near the ATP binding pocket, but it is unclear if this is generalizable to other TSCs and whether this has been biochemically validated. Both TSC24 and Dp44mT appear to act as catalytic inhibitors, and there is an increase in DNA cleavage seen with Dp44mT [27,28]. TSC24 does not appear to increase strand breaks in cells, nor block the effects of VP16 [27].

A series of thiosemicarbazones and 4-thiazolindinones have been synthesized and some were identified with activity against Top2. The thiosemicarbazone (E)-2-(1H-indol-3-ylmethylene)-N-(naphthalen-1-yl)hydrazinecarbothioamide (compound 2b) has a IC₅₀ of 0.01 μ M against colorectal adenocarcinoma (HT-29) and leukemia (K562) cells and appear to weakly inhibit plasmid DNA relaxation by Top2 α [29]. Compound 3a [(Z)-2-(acridin-9-ylmethylene)-N-phenyl-hydrazinecarbothioamide] and (compound 3h) [(Z)-2-(acridin-9-ylmethylene)-N-(naphthalen-1-yl) hydrazinecarbothioamide] also had a limited ability to inhibit relaxation [30]. Detailed studies on the structure–activity relationship of TSCs against Top2 α showed that most TSC ligands inhibit Top2 α very weakly or not at all

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