Chapter 2

Recent Advances in the Biological Importance of Rhodanine Derivatives

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Additional information is available at the end of the chapter

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Abstract

Heterocyclic compounds are an important part of the synthetic medicinal chemistry. They offer a high degree of structural variety and have proven to be widely useful as therapeutic agents. Heterocyclic compounds play an important role in the biological processes. They are widespread as natural products. Heterocyclic compounds are widely found in nature categorically in plant alkaloids, nucleic acids, anthocyanins, and flavones. They are also present as in chlorophyll and hemoglobin. Additionally, some proteins, hormones, and vitamins also contain aromatic heterocyclic system. Heterocycles have huge potential as the most promising molecules as lead structures for the design of new drugs. About one half of over 6 million compounds recorded so far in chemical abstracts are heterocyclic. The proposed book chapter entitled, *Recent Advances in the Biological Importance of Rhodanine Derivatives* gives an outline of importance and applications of the various rhodanine derivatives in medicinal chemistry from 2004 to 2014.

Keywords: Rhodanine, biological activities, structure activity relationship and selectivity of rhodanine derivatives

1. Introduction

Rhodanine is a five-membered heterocyclic molecule containing a thiazole nucleus with thioxo group on second carbon and carbonyl group on fourth carbon. It was first discovered in 1877 by Marceli Nencki, who named it "Rhodaninsaure." Structural modifications of rhodanine derivatives (Figure 1) constantly result in compounds with a broad spectrum of pharmacological activities [1, 2]. Rhodanine derivatives recently have grabbed the attention of researchers because of their broad range of pharmacological activities. Since past 10 years, the number of scientific publications and patents describing a plenty of the different biological activities of rhodanine-based compounds is increasing continuously (Figure 2). It has been reached at

the peak in 2014 with 461 publications. A majority of the biologically active rhodanines are 5-arylmethylidenerhodanines (Figure 1), which contain the exocyclic double bond. Because the latter is conjugated to the carbonyl group at position 4 of the rhodanine ring, such compounds are electrophilic and potentially reactive due to possible Michael addition of the nucleophilic protein residues to the exocyclic double bond [3–5].

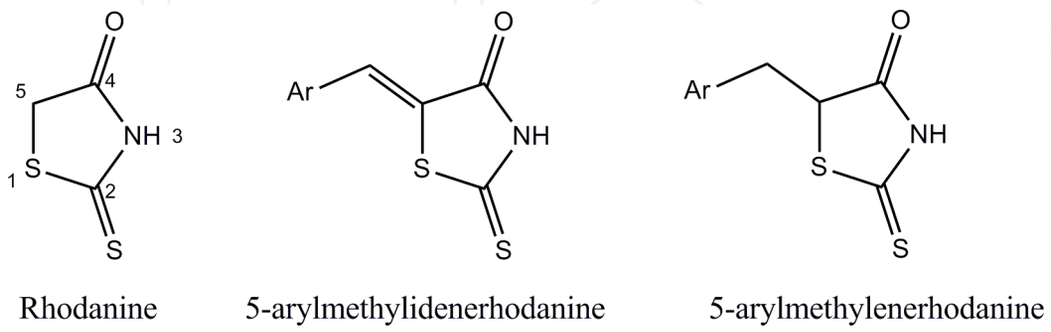

Figure 1. Chemical structures of the important rhodanine-based derivatives.

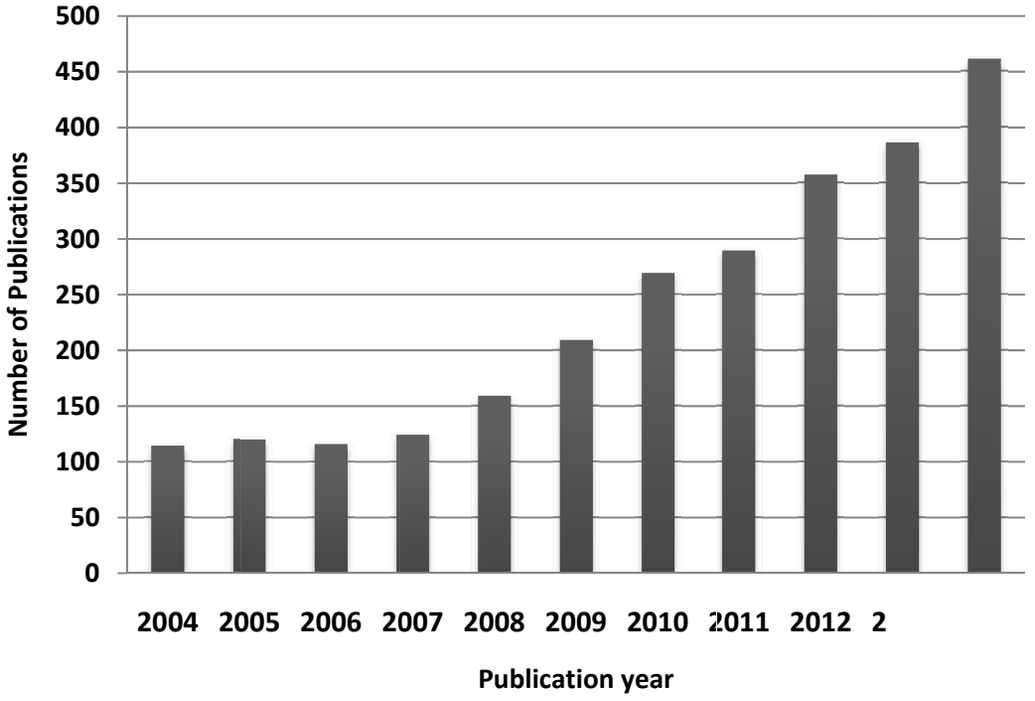

Figure 2. SciFinder search for recent publications, including biological activity of rhodanines sorted by year, as determined on 10 August 2015.

Rhodanine have been found to possess various biological activities, such as antidiabetic, antibacterial, antifungal, anti-infective, pesticidal, antimycobacterial, antineoplastic, and so on [6–19]. They also exhibit antitubercular, anti–human immunodeficiency virus (HIV), and antimalarial activities. Due to the various possibilities of structural derivatization of the

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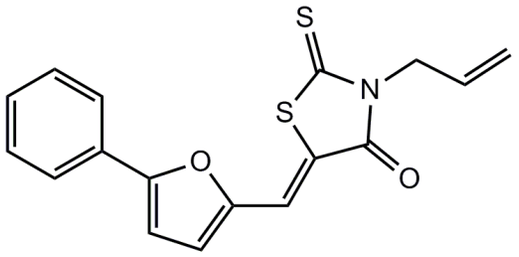
rhodanine ring, their derivatives will probably remain a privileged scaffold in drug discovery [20]. We therefore want to review the biological activities, mechanism of action, structure–activity relationship (SAR), and selectivity of rhodanine derivatives against various targets in this chapter.

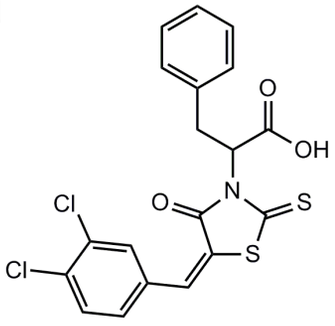
1.1. Antibacterial activity

Villain-Guillot et al. [21] have reported design, synthesis, and SAR of furanyl-substituted rhodanine derivatives as RNA polymerase (RNAP) inhibitors. These derivatives were found to inhibit transcription and affect growth of bacteria living in suspension or in a biofilm. The derivative (I) is found as most active among all the reported rhodanine derivatives. It inhibits the *Escherichia coli* RNAP transcription at minimum inhibition concentration of ≤10 μM. It also have high efficacy against various gram-positive bacteria, including *Staphylococcus epidermidis*.



(I)

Hardej et al. [22] have synthesized a series of rhodanine derivatives containing various substituents at the N_3- and C_5-positions and tested for in vitro antibacterial activity against a panel of clinically relevant methicillin-resistant *Staphylococcus aureus* (MRSA) strains. The anti-MRSA activity of compounds II (minimum inhibitory concentration (MIC)=3.9 μg/mL) and III (MIC=1.95 μg/mL) were significantly greater than that of the reference antibiotics penicillin G (MIC=31.25 μg/mL) and ciprofloxacin (MIC=7.8 μg/mL).



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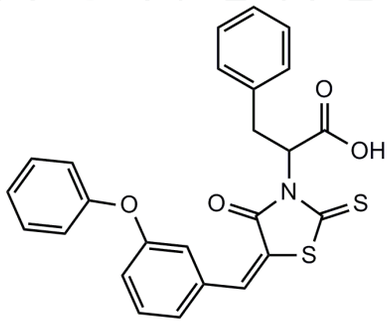
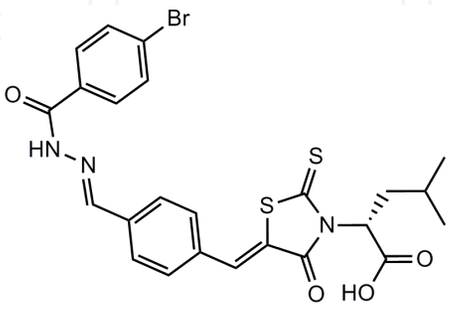


(III)

Li et al. [23] have synthesized a series of arylhydrazone derivatives bearing a rhodanine moiety and evaluated as antibacterial activity against several different strains of gram-positive bacteria, including multidrug-resistant clinical isolates. Of all the compounds tested, IV and V were identified as the most effective, with minimum inhibitory concentration values of 2–4 μg/mL against methicillin-resistant and quinolone-resistant *S. aureus*.



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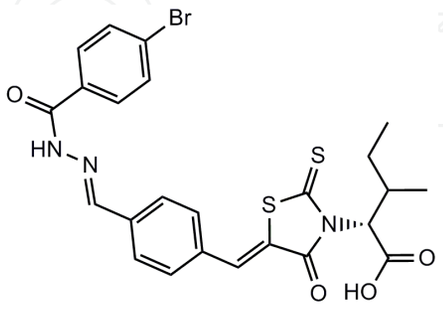
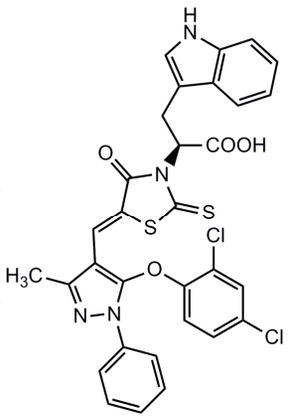


(V)

Zheng et al. [24] have synthesized three novel series of 5-aryloxypyrazole derivatives and tested for their antibacterial activity. The majority of the synthesized compounds showed potent inhibitory activity against gram-positive bacteria *S. aureus* 4220, especially against the strains of multidrug-resistant clinical isolates (MRSA3167/3506 and QRSA3505/3519). Among which, compounds VI, VII, and VIII showed the most potent levels of activity (MIC=1 μg/mL), and cytotoxic activity assay showed that the compounds tested did not affect cell viability on the human cervical (HeLa) cells at their MICs.



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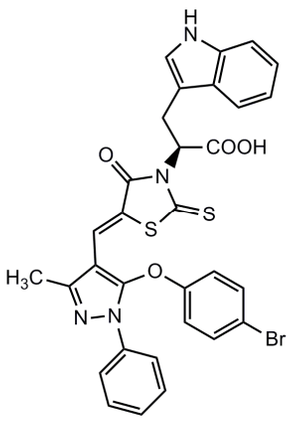

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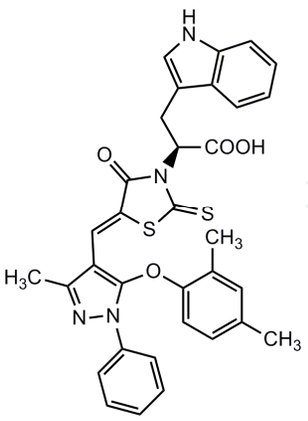

(VIII)

Xu et al. [25] synthesized pyrazole-substituted derivatives bearing rhodanine-3-fatty acid moieties and analyzed their antimicrobial activities against various gram-positive as well as gram-negative bacteria. Compound (IX) bearing a rhodanine-3-pentanoic acid displayed the most potent activity with a MIC of 2 μg/mL against MRSA.

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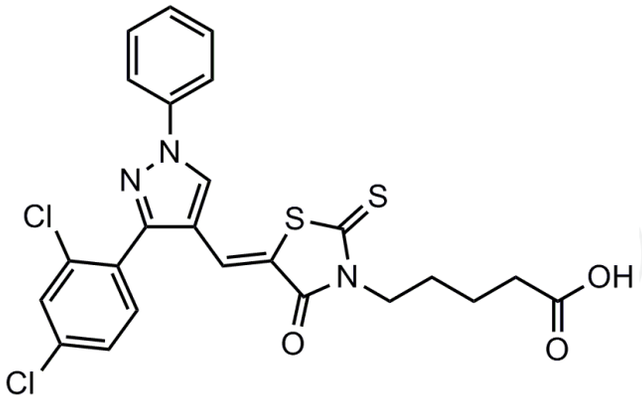
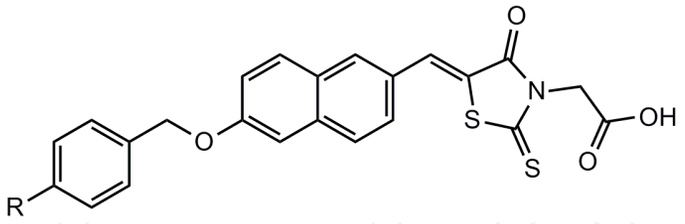


(IX)

Miao et al. [26] have synthesized a series of rhodanine-3-acetic acid derivatives and investigated for their antibacterial activity against gram-positive bacteria, including multidrug-resistant clinical isolates. The compounds X, XI, XII, XIII, XIV, and XV presented better activities against multidrug-resistant *S. aureus* than the standard drug, especially XIII with a MIC of 1 μg/mL. However, none of the compounds were active against gram-negative bacteria at 64 μg/mL.



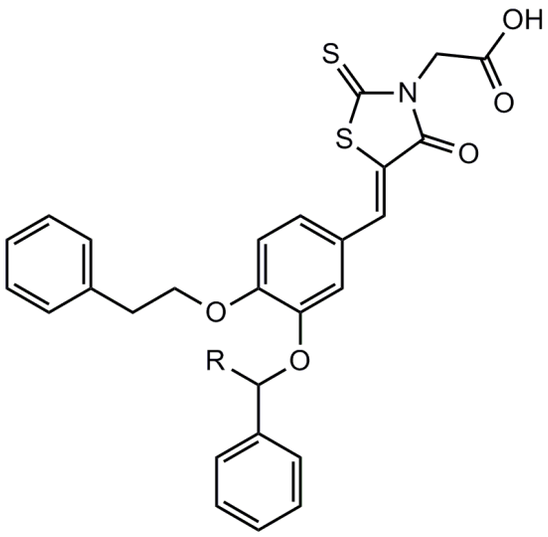
(X)-(XV)

(X)= CH_3, (XI)= OCH_3, (XII)= F,

(XIII)= Br, (XIV)= Cl, (XV)= CF_3

1.2. Antifungal activity

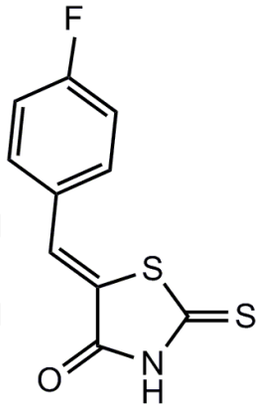
Orchard et al. [27] have synthesized rhodanine-3-acetic acid derivatives XVI, XVII, and XVIII inhibit *Candida albicans* PMT1 with inhibition concentration 50% (IC_{50}) values 0.17, 0.2, and 0.35 μM, respectively. These compounds could serve as useful tools for studying the effects of protein O-mannosylation and its relevance in the search for novel antifungal agents.

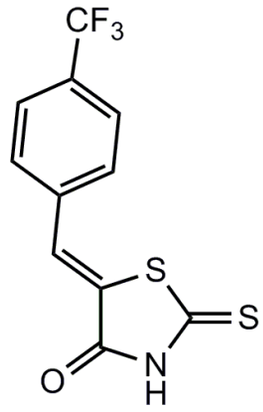


(XVI)-(XVIII)

(XVI)= CH_2OH, (XVII)= CH_3, (XVIII)= $CONH_2$

Sortino et al. [28] reported a series of benzylidene–rhodanines acting as antifungal agents. Among them, compounds XIX and XX showed to be fungicides and were the most active against *Candida genus* and *Candida neoformans*, including clinical isolates.





(XIX) (XX)

In an effort to develop highly potent antifungal agents, Chauhan et al. [29] have reported potent antifungal rhodanine analogs. Some derivatives XXI, XXII, and XXIII were found to be very effective (MIC=0.78 μg/mL) against *C. albicans* MTCC183. The potent compounds were further tested for in vitro anticandidal activity and amphotericin B–resistant strain of *C. albicans*.

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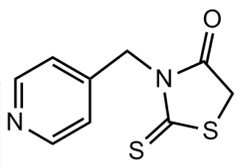
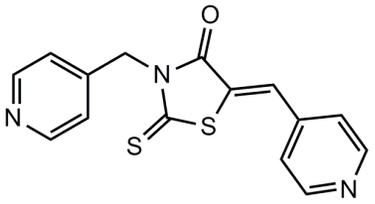
Moreover, these analogs did not exhibit any toxicity up to MIC 3.12 μg/mL against mammalian cell line L929.



(XXI)



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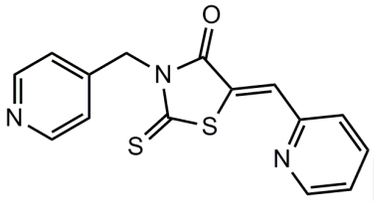
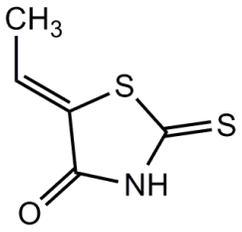


(XXIII)

Insuasty et al. [30] have synthesized several simple rhodanine derivatives and tested for their antifungal activity against 10 different fungal strains. Compound XXIV showed high activity against *Saccharomyces cerevisiae* (MIC 3.9 μg/mL) of all the tested derivatives.



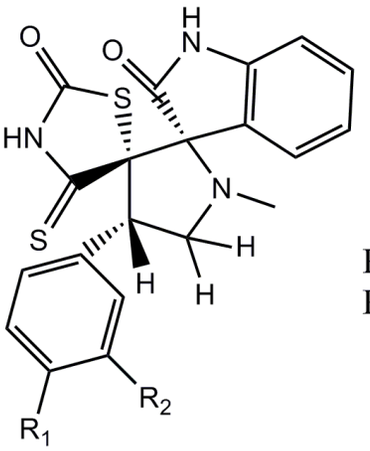
(XXIV)

1.3. Antidiabetic activity

Murugan et al. [31] illustrated simple and efficient synthesis of regio- and stereo-controlled dispiropyrrolidine derivatives of rhodanine XXV, which are found to exhibit attractive antidiabetic properties to male Wistar rats. Among the eight rhodanine compounds, particularly two compounds showed the excellent antidiabetic activity

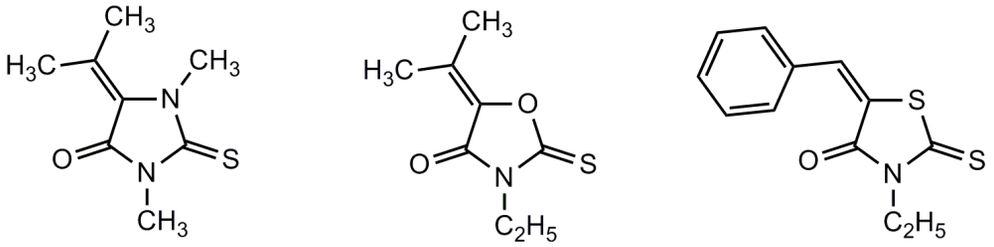
1.4. Anticancer activity

Moorthy et al. [32] have synthesized 5-isopropylidiene derivatives of 3-dimethyl-2-thiohydantoin XXVI, 3-ethyl-2-thio-2,4-oxazolidinedione XXVII, and 5-benzilidene-3-ethyl rhodanine XXVIII, which are cytotoxic against leukemic cell line in concentration-dependent manner. The results of the trypan blue and MTT assays indicated that the compound XXVIII found to be fivefold to sevenfold more potent than XXVI and XXVII with IC_{50}<10 μM. XXVIII found to affect DNA replication by inducing a block at S phase on the basis of cell cycle analysis and tritiated thymidine assays. Moreover, the treatment of XXVIII led to increased level of reactive oxygen species (ROS) production and DNA strand breaks. This suggests the activation of apoptosis for induction of cell death.

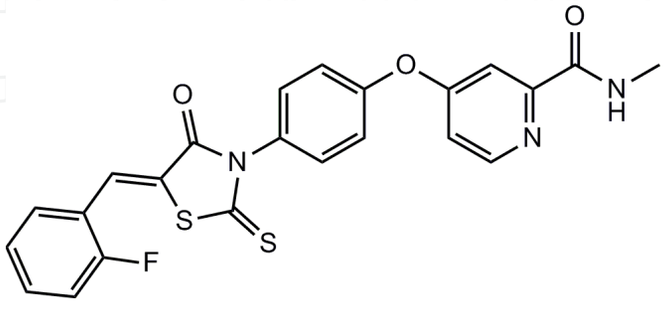


$R_1=R_2=F$
$R_1=R_2=OCH_3$

(XXV)



Li et al. [33] have synthesized a series of rhodanine-containing sorafenib derivatives. The in vitro pharmacological activity indicated that some of the target compounds possessed high antitumor activity against cancer cell lines, such as A549, H460, and HT29, compared to the standard drug sorafenib. The compound XXIX has displayed highest IC_{50} value of 0.8, 1.3, and 2.8 μM against A549, H460, and HT29 cell lines, respectively. The SAR data indicated that the activity strongly depends on the substitution pattern of the rhodanine motif at C-5 position.



(XXIX)

Liu et al. [34] synthesized a series of dihydropyrimidinone and rhodanine derivatives and tested their tyrosinase inhibitory activity. The results showed that some of the synthesized

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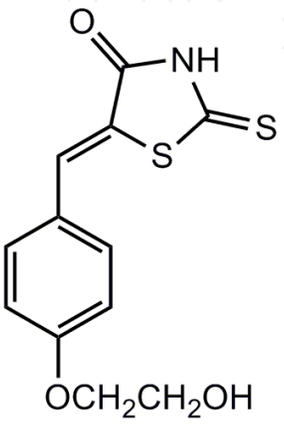
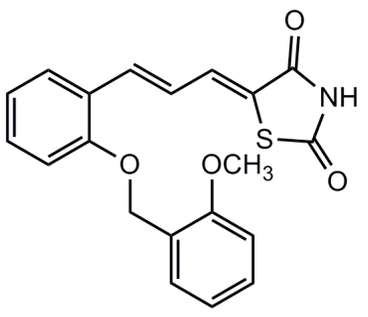
derivatives displayed significant inhibitory activities. The SAR data indicated that the compound XXX with the presence of hydroxyethoxyl group at position 4 of phenyl ring has displayed highest tyrosinase inhibitory activity with IC_{50} value of 0.56 μM. The inhibitory effect of compound XXX on the tyrosinase was found to be irreversible. These results suggested that such compounds might be served as lead for further designing of new potential tyrosinase inhibitors.



(XXX)

Min et al. [35] synthesized rhodanine derivatives, XXXI and XXXII, which inhibited protein tyrosine phosphatase type IVA, member 3 (PRL-3) enzymatic activity with IC_{50} values of 0.8 and 1.1 μM, respectively. These two derivatives highly inhibited the migration and invasion of PRL-3 overexpressing colon cancer cells. The phosphorylation recovery of known PRL-3 substrates, such as ezrin and cytokeratin, confirmed the specificity of the inhibitors on PRL-3 phosphatase activity. These compounds also selectively inhibited the PRL-3 when compared to the other phosphatases. Moreover, the derivative XXXI also found to regulate the epithelial-to-mesenchymal transition (EMT) marker proteins.



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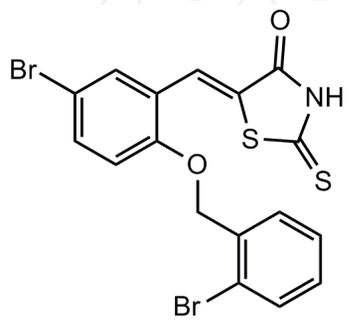
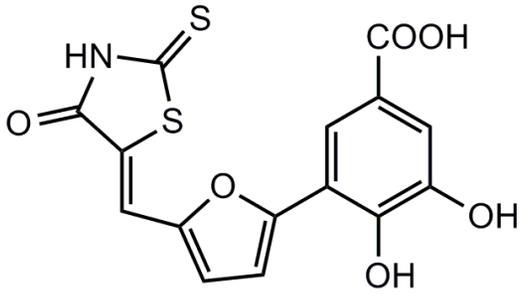


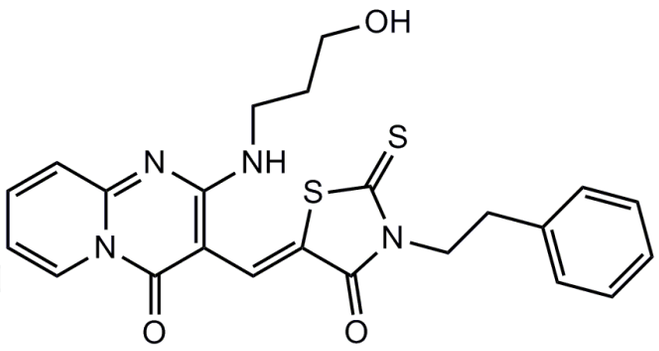
(XXXII)

1.5. Anti-HIV

Rajamaki et al. [36] have reported a novel series of rhodanine derivatives inhibiting HIV-1 integrase using virtual screening techniques. The compound XXXIII has displayed highest therapeutic index (7.0) of all the synthesized derivatives.



Maga et al. [37] synthesized a series of second-generation rhodanine derivatives with high inhibitory activity toward cellular DEAD (Asp-Glu-Ala-Asp) (DDX3) and HIV-1 replication using optimization protocol to the first non-nucleoside inhibitor of the adenylpyrophosphatase (ATPase) activity of human DEAD-box RNA helicase DDX3. Rationalized biological data in terms of SAR and docking simulations indicated that compound XXXIII displayed highest selectivity index (10.0) of all the synthesized rhodanine derivatives.



(XXXIII)

Jiang et al. [38] reported syntheses of furan-substituted rhodanine derivatives by Suzuki-Miyaura cross-coupling, followed by Knoevenagel condensation reaction. The derivatives XXXIV and XXXV have shown excellent potency against primary HIV-1 strains with effective concentration 50% (EC_{50}) at low nanomolar level of all the synthesized derivatives. The SAR data indicated that these derivatives also inhibit the HIV-1–mediated cell–cell fusion and the glycoprotein 41 (gp41) six-helix bundle formation.

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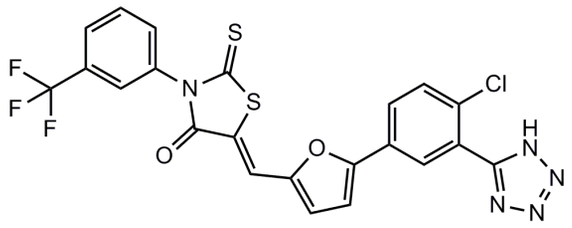

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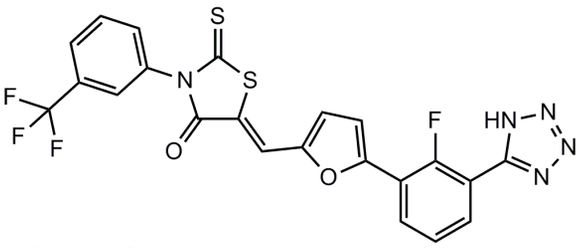
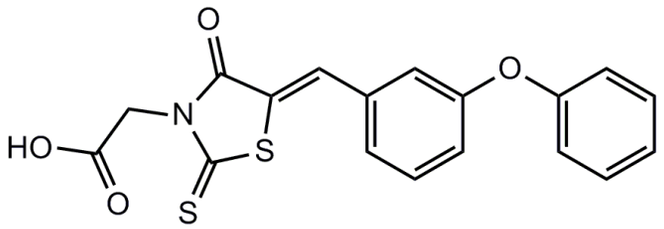


(XXXV)

1.6. Anti–hepatitis C virus activity

Talele et al. [39] reported novel allosteric inhibitors of hepatitis C virus (HCV) nonstructural protein 5B (NS5B) through a combination of structure-based virtual screening, synthesis, and SAR optimization approach. All the derivatives that exhibited IC_{50} values ranging from 7.7 to 68.0 μM were developed. Compound XXXVI, a novel rhodanine analog with NS5B inhibitory potency in the low micromolar level range may be a promising lead for future development of more potent NS5B inhibitors.

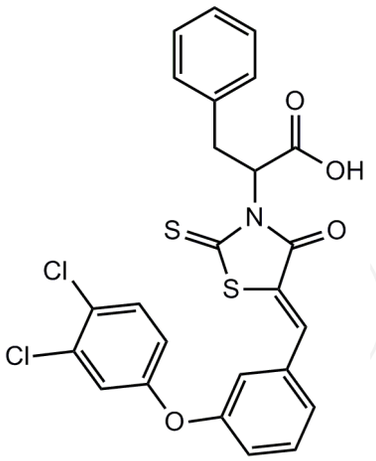


(XXXVI)

Patel et al. [40] have reported the synthesis and in vitro evaluation of anti-NS5B polymerase activity of some novel rhodanine derivatives. Depending on the nature of substituents, the tested compounds exhibited IC_{50} values ranging between 2 and 50 μM against NS5B polymerase. Analogue (XXXVII) have displayed highest IC_{50} (2.6 μM) of all the tested rhodanine derivatives.

1.7. Anti-Inflammatory agent

Cutshall et al. [41] have synthesized a series of rhodanine-based inhibitors and tested against the dual-specificity phosphatases (DSP) family member c-Jun N-terminal kinases (JNK)-stimulating phosphatase-1 (JSP-1). The SAR studies demonstrated that presence of stronger electron-withdrawing functional groups at aryl-benzylidene position provided analogs with the greatest potencies as illustrated by compound (XXXVIII). These derivatives may be useful for the treatment of inflammatory and proliferative disorders.



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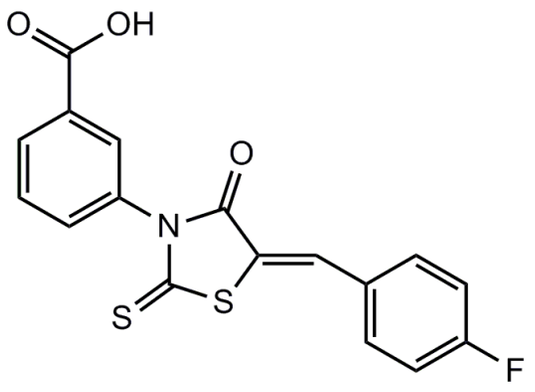
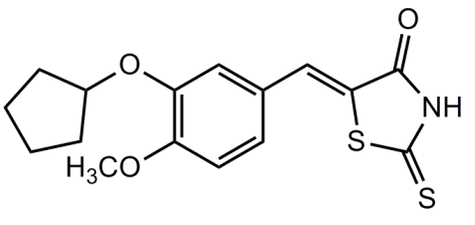
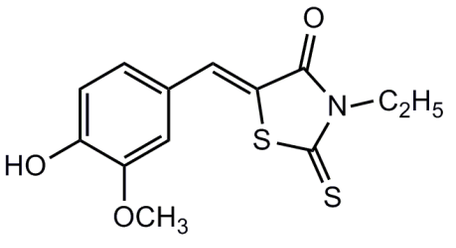


(XXXVIII)

Irvine et al. [42] have reported the in vitro anti-inflammatory activity of a novel series of rhodanine-based phosphodiesterase-4 (PDE4) inhibitors. From the SAR study, it was observed that analog XXXIX (IC_{50}=0.89 μM) and XXXX (IC_{50} 0.74 μM) displayed highest anti-inflammatory activity.



(XXXIX)



(XXXX)

2. Conclusion

This chapter describes rhodanine-based compounds that have been highly associated with biological activity, especially with antibacterial, antiviral, and anticancer activities. Rhodanine derivatives have attracted huge attention of millions of chemists and biologist in recent time because of their wide range of pharmacological activities and therefore, further improved protocol with better observation is still under progress. To conclude, rhodanines will probably remain a privileged scaffold in drug discovery due to their wide spectrum of pharmacological activity and the different possibilities of structural modification, which enable potent and selective drugs to be developed.

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