

Review on Biological activity of β -Lactams, Pyrazoles, Thiazoles and Quinones

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Abstract: The present review article is concerned about the biological activity of β -Lactams, Pyrazoles, Thiazoles and quinones, in this review article emphasis is given on the biological activities of β -Lactams, Pyrazoles, Thiazoles and quinones derivatives. Some derivatives of β -Lactams possess various other useful pharmacological effects, for example, inhibitors of human leucocyte elastase, cholesterol acyl transferase, an thrombin.

Key Words: Biological activity, β -Lactams, Pyrazoles, Thiazoles, quinines.

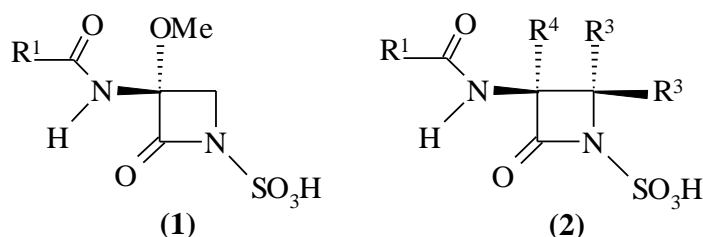
I. Introduction:

I. Biological activity of β -Lactams:

Since the discovery of penicillin, β -lactams (including penicillin, cephalosporins, monobactams, and carbapenems) have become a major class of antibacterial agents. Because of their widespread use. Bacterial resistance has developed into a major health problem worldwide over the past few decades. Some derivatives of β -Lactams possess various other useful pharmacological effects, for example, inhibitors of human leucocyte elastase, cholesterol acyl transferase, an thrombin. Azetidin-2-one derivatives are versatile intermediates in the construction of complex heterocycles, non-proteogenic amino acid derivatives, peptides and turn mimetics. They can be used in synthesis of different natural compounds, such as apioporamide or taxol derivatives.

Peter Cosomo et al., 2008.¹

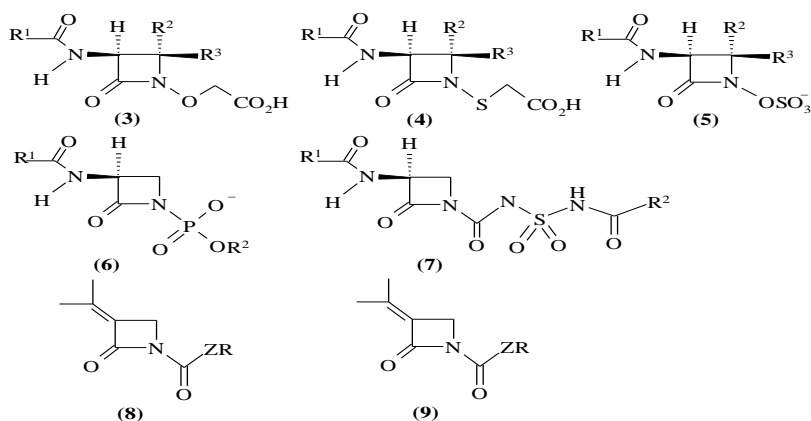
The explosive interest in β -Lactams and related derivatives stems from the fact that some monocyclic β -Lactams exhibit antibacterial activities. Some examples comprise the naturally occurring mono-bactams (1) and nocardicins (2) Durckheimer et al., 1985². Contrary to penicillins, cephalosporins, or nocardicins, monobactams were not produced by fungi or actinomycetes, but from bacteria, for example, Bacillus, pseudomonas, Cimarusti et al., 1983³. Nocardicins proved the relationship with cephalosporins and penicillins via the corresponding β -configuration at C₍₃₎, but they have no therapeutic significance.



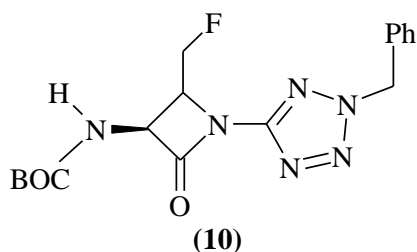
The synthetic oxamazins (3) Woulfe et al., 1984, 1985⁴ and Breuer et al., 1985⁵, thiamazins (4), Woulfe et al., 1986⁶, and monosulfactams (5) Miller et al., 1983⁷, showed some antibacterial activity which raised again a major interest in the area of 2-azetidinone chemistry. Other examples include monophosphams (6) and monocarbams (7) Durckheimer et al., 1985².

The activated β -Lactam unit was a salient feature of these antibacterials, but also the nature and sterical arrangement of the substituents play a major role in the antibacterial activity and pharmacokinetics Durckheimer et al., 1985².

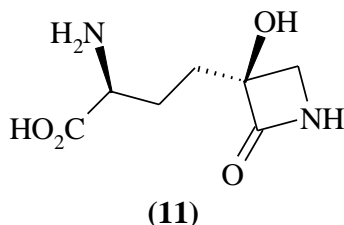
The 3-isopropylidene- and 2-isopropyl N-acylazetidin-2-ones (8), (9) and further functionalized derivatives are novel synthetic monocyclic β -Lactams exhibiting in vitro antibacterial activity versus anaerodes and Gram-positive aerobes Brickner et al., 1987⁸, 1992⁹, 1993¹⁰. A unique structural aspect differentiating them from other classes of β -Lactam antibiotics is the lack of any negatively charged group appended to the Lactam nitrogen.



Analogs of monobactams in which the sulfonic group has been replaced by the isosteric tetrazole, for example, (10), represent a new class of antibacterials *Andrus et al., 1984*¹¹, *Klich et al., 1984*¹², *1993*¹³, and *Yoshida et al., 1986*¹⁴.



The so-called tabtoxinine- β -Lactam (11) is considered to be the active form of tabtoxin, a dipeptide exotoxin, produced by *Pseudomonas tabaci*, the organism responsible for the wildfire disease of tobacco plants *Baldwin et al., 1986*¹⁵.

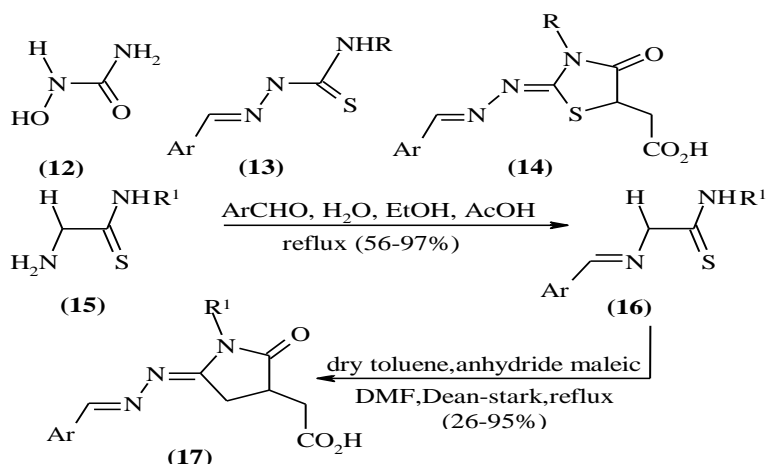


Antielastase activity of 1,3,4-trisubstituted 2-azeti-dinones has been determined against enzymes, for example, human leucocyte elastase *Shah et al., 1993*¹⁶ and *Adonias et al., 1993*¹⁷.

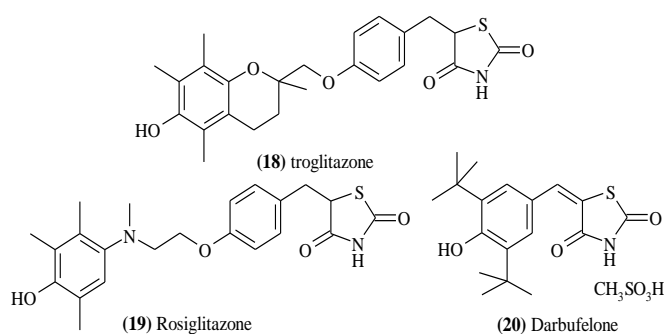
II. Biological activity of thiazoles:

*Paolo Vicini et al., 2006*¹⁸ were reported that, a totally synthetic molecule of the oxazolidinone class has been approved for human use and consistent with its activity against resistant Gram positive organism, appeared to have a unique mechanism of antibacterial activity. Also, They reported the synthesis of a new class of structurally novel 4-thiazolidinone derivatives incorporating two known bioactive heterocyclic nuclei such as thiazole and thiazolidinone *Paolo Vicini et al., 2006*¹⁸.

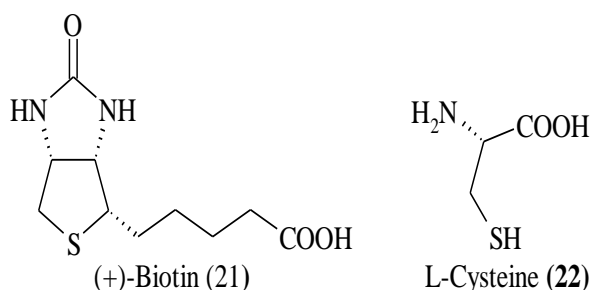
*Rosaria et al., 2005*¹⁹ were reported that, thiosemicarbazone and 4-thiazolidinone derivatives were synthesized in one and two steps from thiosemicarbazide. The synthesized compounds were submitted to evaluation against host cells infected with *Toxoplasma gondii*. Their studies showed that thiosemicarbazones (16) and 4-thiazolidinone derivatives (17) were effective against intracellular *T. gondii*. The biological activities of these thiosemicarbazones was related to their abilities to form complex with metal cations. The following scheme shows the synthetic route for the preparation of these compounds. Also, Thiosemicarbazone and 4-thiazolidinone derivatives were synthesized in one and two step from thiosemicarbazide, in satisfactory yield. Then, the synthesized compounds were submitted to evaluation against host cells infected with *Toxoplasma gondii*. Recent studies using hydroxyurea (HU) demonstrate its efficacy, in eliminating the intracellular parasites of *T. Gondii*, *Trypanosoma cruzi* and *Leishmania amazonensis* (12), (13) and (14). Biological activities of these thiosemicarbazones are related to their abilities to form complex with metal cations *Romulo P. Tenorio et al., 2005*²⁰.



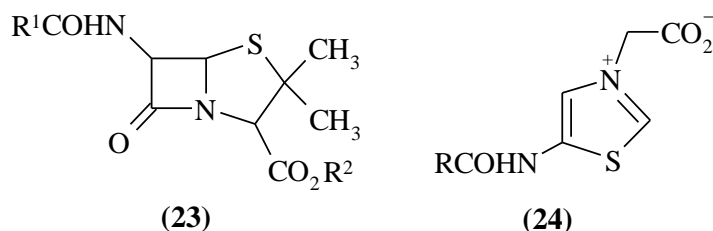
*Jérôme et al., 2004*²¹ were reported that, The heterocycles of thiazolidinone or its tautomeric form, display diverse biological activities such as tuberculostatic, anti-inflammatory, antidiabetic, antihydroidal, fungicidal, bactericidal and pesticidal, the 2,4-thiazolidinone (TZD) class is particularly important as therapeutic agents and has been thoroughly investigated as PPA- γ agonists that led to the development of several insulin-sensitizing drugs such as Troglitazone (**18**), and Rosiglitazone (**19**) and compound (**20**) exhibit anti-inflammatory *Jérôme et al., 2004*²¹.



*Masahiko Seki et al., 2003*²² have been reported that, the proper selection of a protective group is one of the most significant criteria for developing an efficient synthetic method. The protective group in order to produce the number of steps leading to the target compound. In our investigation toward a practical synthesis of (+)-biotin (**21**) development of a novel and efficient thiol protective group of cysteine (**22**) was needed *Masahiko Seki et al., 2003*²².

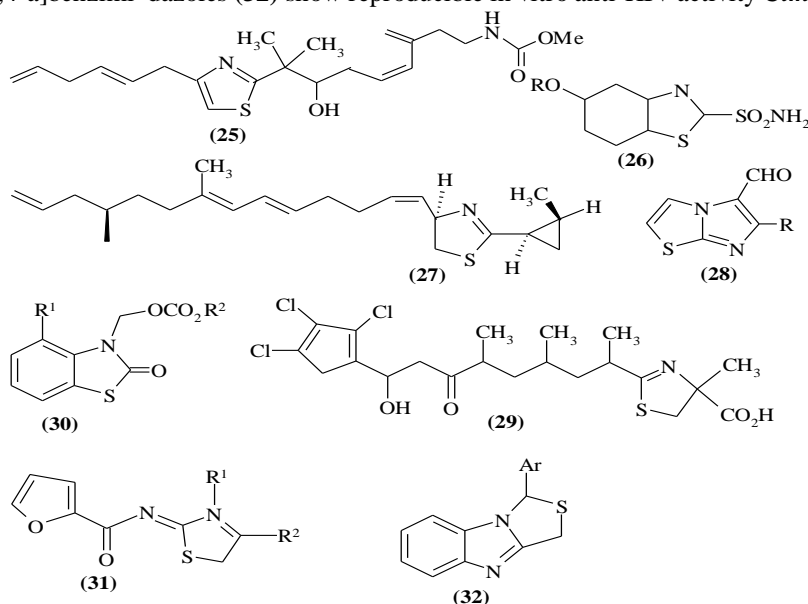


Thiazole derivatives such as penicillins (**23**) which have fused thiazolidine and β -Lactam rings were known and used as potent antibiotics *Foye et al., 1981*²³. Also 5-acyamino-thiazolium salts (**24**) and 5-acylamothiazolidine had been reported to exhibit antibiotic activity *Pirotte et al., 1991*²⁴. A wide range of thiazole-containing metabolites had isolated and characterized from marine organisms *North et al., 1990*²⁵ and *Pattenden et al., 1992*²⁶. Among those compounds were patellamides, a class of thiazole-containing cyclic peptides which exhibit antineoplastic and activities *Ireland et al., 1980*²⁷, *1982*²⁸, *Wasylyk et al., 1983*²⁹ and *McDonald et al., 1992*³⁰. Other thiazole-containing cyclic peptides of interest due to their antibiotic activity are keramamides *Itagaki et al., 1992*³¹, *Koerber et al., 1994*³² and thiotipin *Yun et al., 1994*³³. Cyclothiazomycin was a polythiazole containing peptide produced by streptomyces sp. which exhibited an important renin inhibitory activity *Aoki et al., 1991*³⁴.

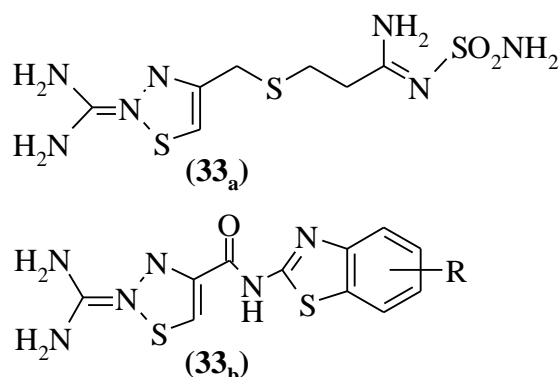


Mycothiazole (**25**) was isolated from *spongia mycofijiensis*, a marine sponge. This compound shows anti-helminthic activity in vitro while high toxicity was observed in mice *Crews et al., 1988*³⁵. 6-Hydroxybenzothiazole-2-sulfonamides (**26**, R=H) were topically active carbonic anhydrase inhibitors *Woltersdorf et al., 1989*³⁶. This activity confers to these compounds a potential utility as antiglaucoma drugs. Curacin A (**27**) is an anti-micotic which has been isolated from *Lygbya majuscula* a cyanobacteria *Gerwick et al., 1994*³⁷ and whose absolute configuration has been elucidated *Nagle et al., 1995*³⁸. Formyl imidazo-[2,1-b]thiazoles (**28**) have been proved to be effective as herbicides *Andreani et al., 1991*³⁹. Benzothiazolinones (**29**) show plant grow-stimulating effect *Tralic-kulenovic et al., 1993*⁴⁰ and *Sutoris et al., 1993*⁴¹. Some thiazolidin-2-thione derivatives showed hepatoprotective activities both in vitro and in vivo studies *Yoneda et al., 1993*⁴². Thiazolohalostatin (**30**) was produced by *Actinomadura* sp. It prevented cell death caused by calcium overload and exhibits an inhibitory activity against lipid peroxidation [*Yamagishi et al., 1993*⁴³].

Certain 4-thiazolin derivatives (**31**) show significant activity as anti-convulsant agents *Ergenc et al., 1994*⁴⁴. thiazolo[3,4-a]benzimidazoles (**32**) show reproducible in vitro anti-HIV activity *Cimirrie et al., 1991*⁴⁵.



*Schnur et al., 1991*⁴⁶ were reported that, Guanidino-thiazoles such as famotidine (**33_a**) were known to be inhibitors of gastric acids *Anglada et al., 1988*⁴⁷, and they had been used in the treatment of gastric ulcers *Montserrat et al., 1985*⁴⁸ *an Richter et al., 1986*⁴⁹. This class of compound, i.e., ω -aminoalkylthiazoles, was of interest because of their analogy with histamine *Liebscher et al., 1994*⁵⁰. Other guanidino-thiazoles like amides (**33_b**) were found to be systemically active against lung carcinomas *Schnur et al., 1991*⁴⁶.



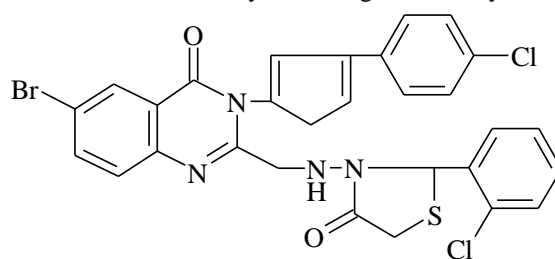
III. Biological activity of quinones and pyrazoles:

Tung T. Dang et al., 2008⁵¹ have found that, Pyrazole-3-carboxylic acid derivatives represent important building blocks in organic and medicinal chemistry because their pharmacological properties. For example, pyrazole-3-carboxylic acids and pyrazolo[1,5-c]quinazoline-2-carboxylates are nicotinic acid receptor agonists, bis(benzo[g]indazol-3-carboxamides) exhibit antiproliferative activity against various cancer cell lines. Ethyl-5-propyl-1H-pyrazol-3-carboxylate is a key intermediate for the synthesis of Viagra **Tung T. Dang et al., 2008**⁵¹.

Asuncion Burguete et al., 2007⁵² have been reported that, Quinoxalines, including their fused derivatives, display diverse pharmacological activities (antiviral, anticancer and antibacterial). The United Kingdom have found that, quinoxaline is a potential treatment for HIV infection and works well with lamivudine, abacavir and efavirenz. Oxidation of both nitrogens of the quinoline ring dramatically increased the diversity of certain biological properties such as antibacterial activity and hypoxia-selective anticancer activity. **Mogilaiah et al. 1999**⁵³, were involved in the synthesis and biological evaluation of new agents derived from quinoxaline-1,4-di-n-oxide **Asuncion Burguete et al., 2007**⁵².

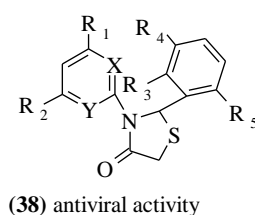
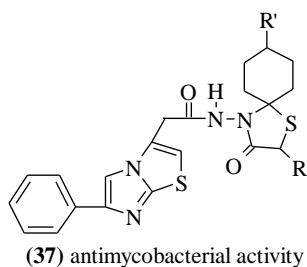
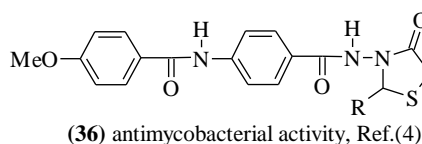
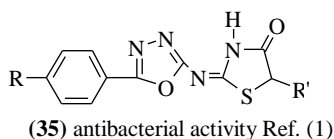
Claudia Valente et al., 2007⁵⁴ were reported that, Quinones play vital roles in the biochemistry of living cells, where, they are involved in cellular respiration, photosynthesis and cellular defence against bacteria, fungi and parasites. They became more important because their interesting pharmacological actions, like as, antitumor, trypanocidal, anti-inflammatory, antiviral and antifungal. Some have reached clinical use as antineoplastic drugs **Claudia Valente et al., 2007**⁵⁴.

Ashok Kumar et al., 2007⁵⁵ have been reported that, Quinazoline nucleus and its derivatives have been found to possess wide spectrum of activities like antibacterial, antifungal, anticonvulsant and anti-inflammatory. Compound (34) showed maximum anti-inflammatory and analgesic activity **Ashok Kumar et al., 2007**⁵⁵.

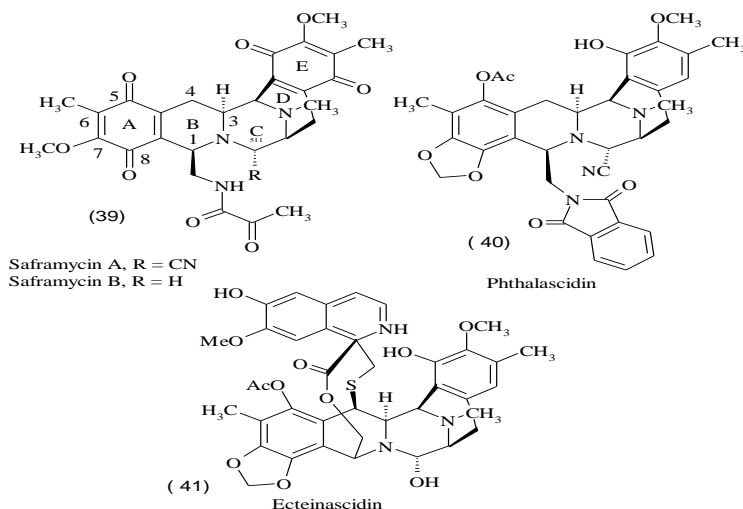


(34)

4-Thiazolidinone derivatives are known to possess antibacterial, antifungal, antiviral and antituberculosis properties (35), (36), (37), (38). Peptidoglycan is an essential component of the cell wall of both Gram-positive and Gram-negative bacteria. 4-Thiazolidinones have been reported as novel inhibitors of the bacterial enzyme Mur B which is a precursor acting during the biosynthesis of peptidoglycan **Guniz Kucukguzel et al., 2006**⁵⁶.



Juan Francisco et al., 2004⁵⁷ were reported that, Many tetrahydroisoquinoline antitumor antibiotics, such as saframycins and ecteinascidin 743 (ET-743, Yondelis) are potent cytotoxic agents and the side chain at the isoquinoline C1-position, it is known the antitumor activity of ET-743 (39),(40),(41) **Juan Francisco et al., 2004**⁵⁷.



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