# Chemistry and Biological Activities of 1,3-Benzoxathiol-2-ones

Walcimar T. Vellasco Júnior[1], Claudia R. B. Gomes[2] and Thatyana R. A. Vasconcelos[1,*]

[1]*Universidade Federal Fluminense, Instituto de Química, Departamento de Química Orgânica, Outeiro de São João Batista, s/no, Centro, Niterói, 24020-141, Rio de Janeiro, Brazil*

[2]*Fundação Oswaldo Cruz, Instituto de Tecnologia em Fármacos – Farmanguinhos, Rua Sizenando Nabuco 100, Manguinhos, 21041-250, Rio de Janeiro, RJ, Brazil*

**Abstract:** Benzoxathiolones and its derivatives are important pharmacophores with diversified pharmacological activities like antibacterial, antimycotic, antioxidant and anti-inflammatory. These different biological applications for benzoxathiolone compounds have motivated new studies in searching novel derivatives with better activity results and also other applications in pharmaceutical industry. Owing to the importance of this system, the aim of this review is to present the main aspects of the chemistry and biological properties of 1,3-benzoxathiol-2-ones.

**Keywords:** 1,3-benzoxathiol-2-ones, synthetic methods, biological activity.

## INTRODUCTION

Several heterocyclic systems with five-membered rings fused to a benzene nucleus have been reported to possess a wide range of biological activities. Benzoxathiolones and its derivatives are important pharmacophores with diversified pharmacological activities like antibacterial, antimycotic, antioxidant and anti-inflammatory [1-3].

1,3-Benzoxathiol-2-ones represent an important class of heterocycles that possess an atom of oxygen at position 1, an atom of sulfur at position 3 and a carbonyl group at position 2 (Fig. **1**). Owing to the importance of this system, the aim of this review is to present the main aspects of the chemistry and biological properties of this class of compounds.

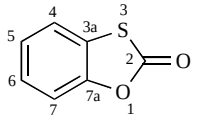



**Fig. (1).** General structure for 1,3-benzoxathiol-2-ones.

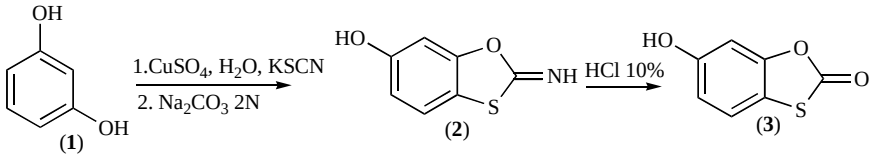
### Synthetical Procedures for 1,3-Benzoxathiol-2-ones

Werner have reported the first synthetical procedure to prepare 1,3-benzoxathiol-2-ones from resorcinol. The methodology involved the formation of an imino-carbonate intermediate (**2**) through reaction between resorcinol (**1**) and potassium thiocyanate. A subsequent heating with diluted hydrochloric acid resulted in 6-hydroxy-1,3-benzoxathiol-2-one (**3**) in 95% yield, also called thioxolone, that melted at 158ºC (Scheme **1**) [4].

Seven years later, a new study brought a point of confusion over this result. Pantlitschko and Benger have reported that the formed compound toward this process was the 4-hydroxy derivative, that melted at 160ºC, and it was characterized after conversion to 2,6-dihydroxythiophenol with melting point 83-84ºC [5]. In order to clarify this question, Urushibara and Koga carried out an analogous synthetic process, excluding sodium carbonate, and the 6-hydroxy derivative was obtained and converted to 2,4-dihydroxythiophenol melting at 110-111ºC. These results corroborated with those obtained by Werner. However, analysis by melting point brought another inconsistence to these previous results: the melting point obtained by Urushibara and Koga, which ranged from 154,5-155ºC, contrasted with the one formerly described by Werner, that was 158ºC [6].

Werner's results were also corroborated by Fiedler [7]. In his study he had prepared 5,7-dissubstituted-6-hydroxy-benzoxathiolones by a similar methodology to Werner. The starting material was 2,4-dibromo-resorcinol that over the same conditions - except by replacement of potassium thiocyanate to ammonium thiocyanate - produced a solid that melted at 185-186ºC, in 25% yield. After bromation of Werner's product, the same results were obtained, and it was characterized as 5,7-dibromo-6-hydroxy-benzoxathiolone. In this study, Fiedler also demonstrated that 5- and 7- positions at benzoxathiolone ring facile gave aromatic electrophilic substitution, with good yields.

Later, Traxler developed a new synthetic procedure for 1,3-benzoxathiol-2-ones. According to this process, *O*-(2-methoxyphenyl) *N*,*N*-dimethyl-thiocarbamates (**5**) generated their respective *S*-isomers (**6**) via a thionecarbamate-thiolcarbamate rearragement




**Scheme 1.** First synthetical procedure for benzoxathiolones.

followed by cyclization into various 1,3-benzoxathiol-2-ones (**7**) (Scheme **2**) [8]. This procedure allowed to solve the conflicting results about the 6-hydroxy-1,3-benzoxathiol-2-ones preparation described by Werner, Pantlitschko and Urushibara. He reproduced the methodology that was used by Pantlitschko and Benger, and the

*Address correspondence to this author at the Universidade Federal Fluminense, Instituto de Química, Departamento de Química Orgânica, Outeiro de São João Batista, s/no, Centro, Niterói, 24020-141, Rio de Janeiro, Brazil; Tel: +552126292230; Fax: +552126292144; E-mail: gqothatyana@vm.uff.br

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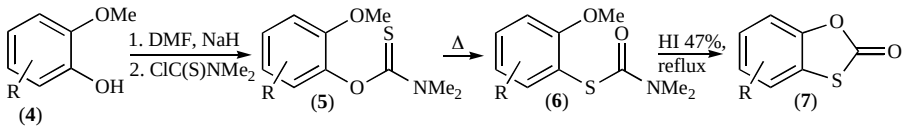



| R | Yield (%) | R | Yield (%) |
|---|---|---|---|
| H | 88 | 7-OH | 87 |
| 6-Me | 100 | 4-OH | 67 |
| 6-Cl | 81 | 4-OMe | 44 |

**Scheme 2.** Synthetic route via thionecarbamate-thiolcarbamate rearrangement.

results were in disagreement with those obtained by them and in agreement with the ones obtained by Urushibara and Koga.

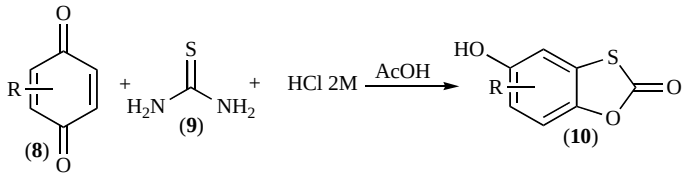
In order to improve the yields and also the laborious reactions conditions, other new synthetic methodologies to obtain 1,3-benzoxathiol-2-ones were developed. Burton and David have described the synthesis of 1,3-benzoxathiol-2-ones from reactions between quinones (**8**) and thiourea (**9**) at diluted acids under reflux for two hours. Then, the products were readily filtered off after precipitation (Scheme **3**) [9].

It was proposed by Burton that this is an 1,4-addition reaction with the thiourea being added to the protonated quinone and that the process occurs via a thiouronium salt intermediate (**A**). In a posterior study to verify the viability of this procedure, Lau and Kestner could not only confirm the formation of Burton's intermediate but also detect a second intermediate, the correspondent iminobenzoxathiol (**B**), whose hydrolysis allows to complete the synthesis of the various 1,3-benzoxathiol-2-ones (Scheme **4**) [10].

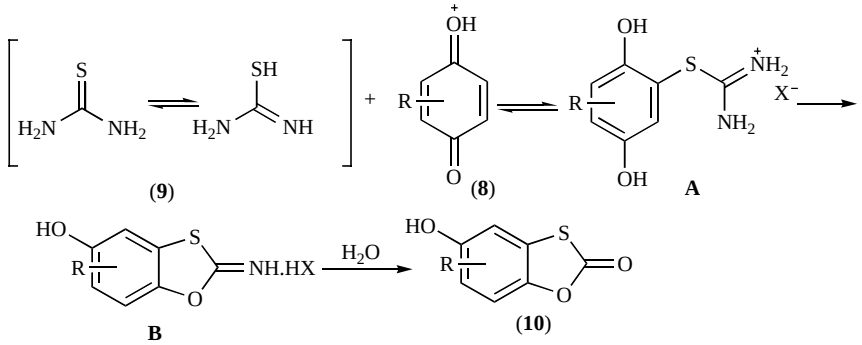
In this study, listed in Table **1**, they determined the effect of different components (like acidity constant, the number and nature of substitutes in quinones) in the way of reaction and it was noted that the best results were obtained with strong acids, like hydrochloric or sulphuric. Otherwise, the weak ones like acetic acid or the absence of anyone gave unpurified products.

They also reported that unsubstituted, disubstituted or trisubstituted quinones gave only a single product but when the monosubstituted ones were used, one or more products were generated, depending on the nature of the substituent. Those data are presented in Table **2**.

Posteriorly, Obushak *et al.* have demonstrated that the occurrence of cyclization depends on the reaction conditions and when keeping some of these parameters under control, as heating the mixture in HCl 2N for 1h, a regioselectivity goes successfully [11]. Since that, this process became very explored on synthesis of benzoxathiol and benzoxathiazol derivatives and has also been applied in the achievement of heterocycles with diterpenoids fragments, which some of them present antifungal and insecticidal properties [12]. In that study, the diterpenoids-benzoxathiolones derivatives **13**




**Scheme 3.** A facile method to obtain benzoxathiolones.

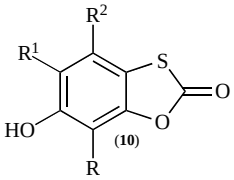



**Scheme 4.** Intermediates on thioureation of protonated quinones.

**Table 1. Effect of Different Components on Thioureation of Quinones**

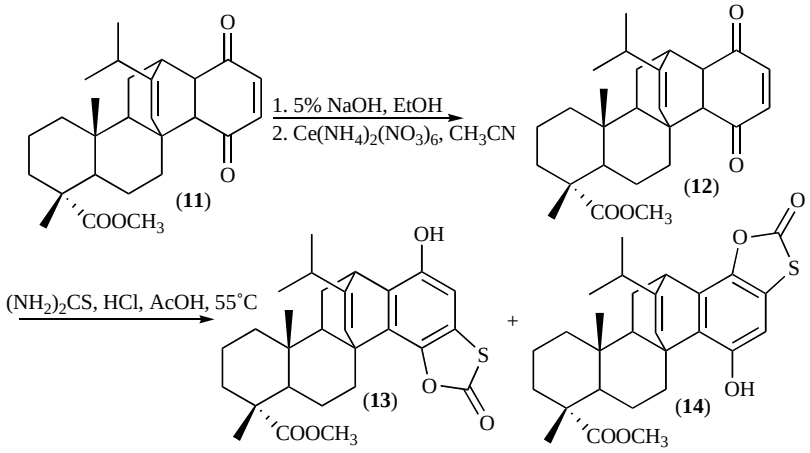
| Acid | Molar Ratio | Benzoquinone Molar Ratio | Thiourea Molar Ratio | Yield (%) |
|---|---|---|---|---|
| — | — | 1.0 | 1.5 | 0 |
| HCl | 3.0 | 1.0 | 1.5 | 92 |
| HCl | 1.0 | 1.0 | 1.5 | 60 |
| HCl | 0.5 | 1.0 | 1.5 | 21 |
| HCl | 3.0 | 2.0 | 1.0 | 10 |
| $H_2SO_4$ | 3.0 | 1.0 | 1.5 | 94 |
| $CF_3CO_2H$ | 10.0 | 1.0 | 1.5 | 85 |
| HOAc | 10.0 | 1.0 | 1.5 | 45 |

**Table 2. Effect of the Number of Substituents on Complexity of Reaction**




| R | $R^1$ | $R^2$ | Yield (%) | Product ratio[a] (%) | R | $R^1$ | $R^2$ | Yield (%) | Product ratio[a] (%) |
|---|---|---|---|---|---|---|---|---|---|
| H | H | H | 92 | — | H | Ph | H | 3 | 7 |
| H | $CH_3$ | $CH_3$ | 73 | — | H | H | Ph | 90 | 93 |
| $CH_3$ | H | $CH_3$ | 95 | — | H | $CH_3$ | H | 7 | 10 |
| $CH_3$ | $CH_3$ | H | 38 | — | H | H | $CH_3$ | 82 | 90 |
| $CH_3$ | $CH_3$ | $CH_3$ | 72 | — | Cl | H | H | 25 | 18 |
| $CH_3$ | H | $CH(CH_3)_2$ | 96 | — | H | Cl | H | 25 | 20 |
| Ph | H | Ph | 98 | — | H | H | Cl | 53 | 62 |
| Cl | H | Cl | 87 | — | H | PhS | H | 2 | 3 |
| Cl | Cl | H | 87 | — | H | H | PhS | 96 | 97 |

[a] Product ratio of isomeric mixture.

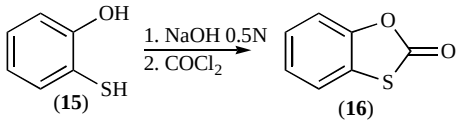



**Scheme 5.** Benzoxathiolones with diterpenoids fragments.

and **14** were obtained in an overall yield of 87%, at a 1:4 ratio (Scheme **5**).

All those procedures lead to substituted 1,3-benzoxathiol-2-ones which shows the necessity of a group in the aromatic ring that directs the regioselectivity of thiocyanation to the *o*-position [13]. Obushak and co-workers have reported a later study with quinone rings showing that acidic conditions and the presence of electron-withdrawing groups increase the selectivity on nucleophilic addition reactions. On the other hand, mild conditions and electron-releasing groups present on quinone ring decrease this selectivity [14]. These results are in agreement and corroborate with the previous Lau's observations for this reaction.

An alternative to synthesize unsubstituted 1,3-benzoxathiol-2-one is the reaction between carbonyl chloride and *o*-hydroxybenzenethiol in alcaline solutions, which results in the title compound in very good yield (Scheme **6**) [13].



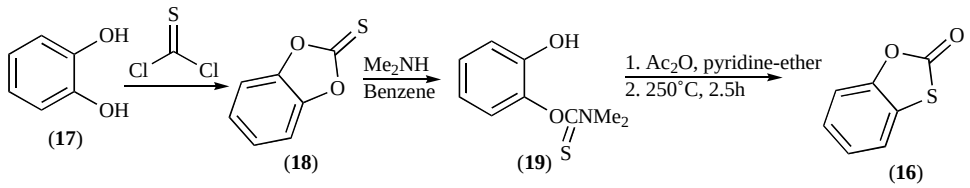

**Scheme 6.** First procedure for synthesis of unsubstituted 1,3-benzoxathiol-2-one.

Dodson and Hanson have described the synthesis of 1,3-benzoxathiol-2-ones from catechol and thiophosgene involving a thionocarbamate-thiolcarbamate rearrangement. The synthetic methodology was based on 1,3-benzodioxole-2-thione (**18**) which was converted to the corresponding thiocarbamate (**19**) in the presence of dimethylamine in benzene. This intermediate after acetylation and thermolysis furnished the title compounds (Scheme **7**). The interesting point of this process is the possibility to obtain unsubstituted benzoxathiolones, like the previous one [15].

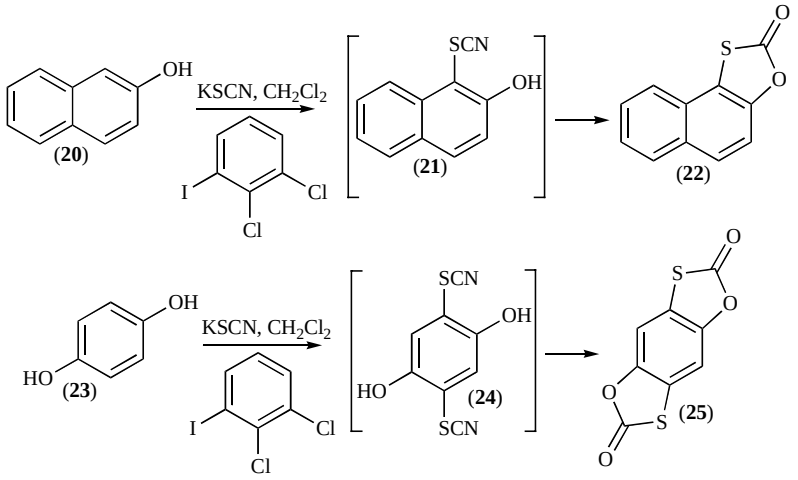
Prakash and co-workers have developed a new synthetic procedure to obtain benzoxathiolones from thiocyanation of phenols (Scheme **8**). The procedure involves a suspension of potassium thiocyanate and dichloroiodobenzene in dichloromethane at 0ºC which was stirred for 15-20 min and then was added the corresponding phenol, leading to the title compounds (**22** and **25**) in good yields [16]. This reagent system was earlier reported by the same authors for α-thiocyanation of carbonyl and β-dicarbonyl compounds as an excellent alternative method to improve the experimental procedure and to avoid the use of toxic and expensive lead thiocyanate.

## Biological Properties

The 1,3-benzoxathiol-2-ones compounds possess antioxidant activity and this can be associated to their skeleton characters. They




**Scheme 7.** Alternative process *via* thionecarbamate-thiolcarbamate rearrangement.




**Scheme 8.** Benzoxathiolones obtained *via* thiocyanation of phenols.

present a five-membered oxathiolane cycle and also a phenol hydroxyl making them analogs of *α*-tocopherol (**26**), a natural antioxidant with a six-membered chroman cycle (Fig. **2**). *α*-Tocopherol is one of the liposoluble vitamins presents in the human body and represents the form of vitamin E, that is preferentially absorbed and accumulated in humans. This structural change associated with the hydroxyl position on the ring leads to a significant increase in the antioxidant activity [2].

This α-tocopherol analogy also has the ability to regulate free-radical reactions of various types, considering the presence of hydroxyl and carbonyl groups in their structures attributing to them the capacity of oxidizing alcohols radicals. These features permit the block fragmentation reactions of α-hydroxyl-containing radicals that occur in biologically important molecules, and make these substances interesting as potential radioprotectors, medicinal drug products and industrial antioxidants [17]. Moreover, they present cytostatic, antipsoriatic, antibacterial and antimycotic properties [3], antiviral activity [2] and also cosmetic applications [1]. They are also used as intermediates on synthesis of glycopeptides because their hydrolysis products, *o*-hydroxythiophenols, easily obtained in alkali hydroxide solutions, have the capacity of building peptidic bonds independent of an N-terminal cysteine [18].

## Derivatives with Benzoxathiolone Core

These different biological applications for benzoxathiolone compounds motivated new studies in searching novel derivatives with better activity results and also others applications in pharmaceutical industry.

Dunbar described that several benzoxathiolones with carbamates in the 5-position (**27**, Fig. **3**) were suitable for use as fungicides and some of them were capable to inhibit urease enzyme [19]. Dieckman reported that the alkylation of hydroxyl group (**28**), Fig. **3**, make them excellent substances for control of insects, especially when applied to earlier stages of development like embryo, larvae or pupae stages affecting metamorphosis and reproduction of several classes, including roaches [20].

## Chalcones

Konieczny and co-workers developed chalcones (**32**) with interesting biological activities. The key intermediates (**29**) were obtained by acetylation of 5- or 6-hydroxy-benzoxathiolones (**10**, **3**), previously obtained using Burton and Werner methodologies, respectively, followed by a Fries rearrangement [21] and then separated by crystallization. The methylation and further condensation

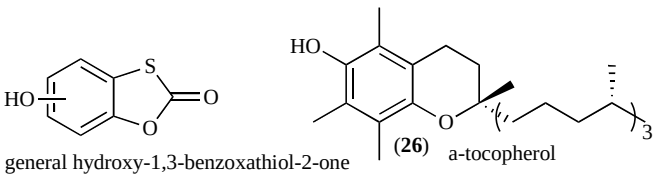



**Fig. (2).** Structural analogy of benzoxathiolones and *α*-tocopherol.

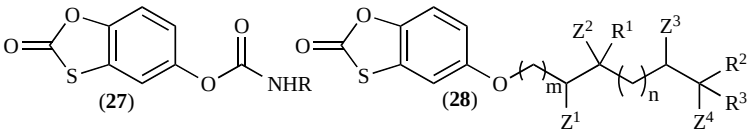



**Fig. (3).** 5-Hydroxy substituted benzoxathiolones with biological activities.

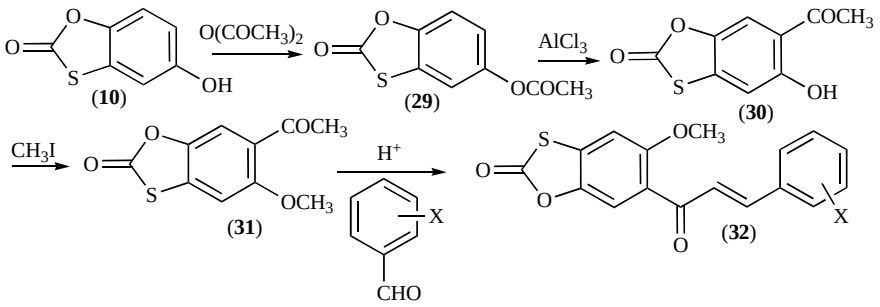
under acidic conditions with different benzaldehydes gave the corresponding chalcones (**32**), (Scheme **9**) [22]. The biological activity described for these compounds is due to their flexibility and also because they mask *p*-hydroquinone system. Most of these active compounds are hydroxyl substituted, and the oxathiolone ring can be considered as a protected bioisoster of catechole, a group that often contributes with a beneficial effect on the activity. Some compounds showed anticancer (**32a**, **32b**, **32c**), antimicrobial and antifungal potential activity (**32b, 32c**), and one compound (**32d**) exhibited tuberculostatic activity against *Mycobacterium tuberculosis* strain $H_{37}Rv$ (Fig. **4**) [23].

## Thioaurones

Benzoxathiolones are also used as starting material for the synthesis of another class of substances, thioaurones (**35**), that are little explored. They were first studied as thioindigo-like dyes and as photochromic compounds and recently had new applications studied after their chemistry was reviewed. They are also obtained by a simple manner from a 5-substituted benzoxathiolone (**33**) by reaction with several benzaldehydes (**34**) in anhydrous DMSO in presence of piperidine acetate, over heating in periods between one and two hours (Scheme **10**) [24].

## Iminobenzoxathiolones

Some derivatives with benzoxathiole core could mediate some of their pharmacological effects by modulating nuclear factor-κB (NF-κB) activation, which is closely linked to inflammation and cell proliferation. This nuclear factor is present in proliferative and inflammatory disorders like when an endotoxin released by Gram-negative bacteria, lipopolysaccharide (LPS), is present. When the LPS interacts with immune system, a several number of citokins, like NF-κB, are produced and the inflammatory process begins [25]. So, in order to stop this cascade prior to endotoxin shock, it's necessary to inhibit these citokins activation and compounds that exhibit this property are considered anti-inflammatory. One class of these compounds, iminobenzoxathiolones, was capable of inhibit




**Scheme 9.** Chalcones obtained from 5-hydroxy-benzoxathiolones.

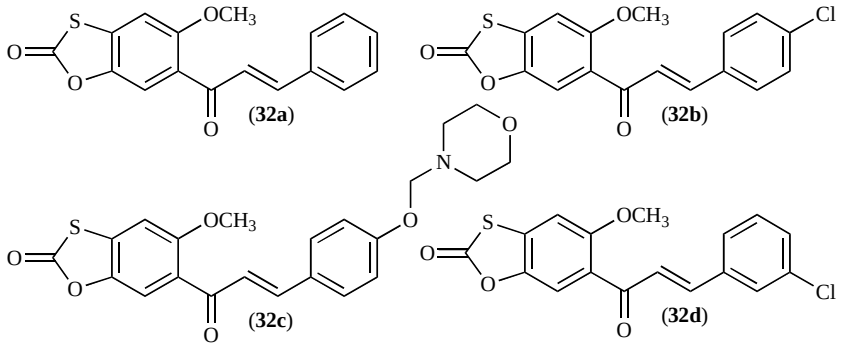
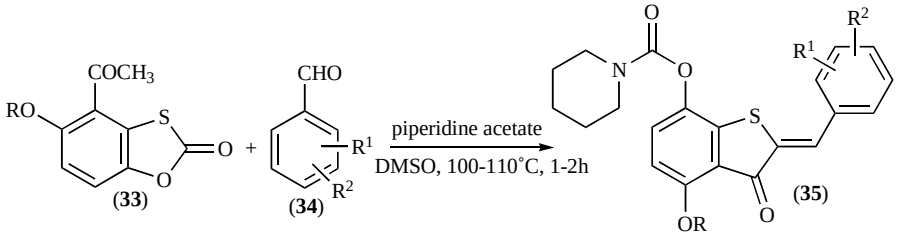
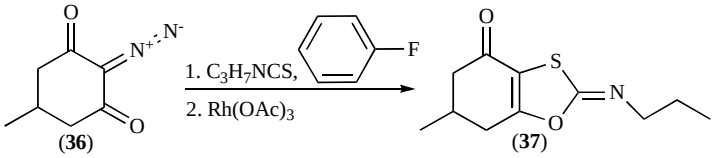



**Fig. (4).** Chalcones with pharmacological activities.




**Scheme 10.** A general procedure to obtain thioaurones.




**Scheme 11.** Synthetic procedure to obtain LYR-71.

the NF-κB activation in macrophages. A new promissory anti-inflammatory agent, called LYR-71 (**37**), (Scheme **11**), was obtained in 50% yield and >97% purity. These studies provided a molecular basis of pharmacological properties related to benzoxathiolones derivatives [26].

### Thioxolone - The First Synthesized Benzoxathiolone

Thioxolone, Fig. (**5**), has an almost planar structure which was determined by X-ray crystal structure analyses. The extensive O—H···O and C—H···O hydrogen bonding permits a linkage between molecules and these chains are stabilized by face-to-face π-π interactions, between oxathiolone and benzene rings in partially overlapping molecules. Examination of non-bonded contacts also revealed two intermolecular C—H···O bonds; each molecule of (**3**) is linked through six hydrogen bonds to five adjacent molecules [27].

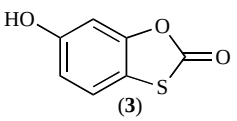
Thioxolone has been used in treatment of acne and possess cytostatic, antipsoriatic, antibacterial and antimycotic properties [1,3,26,28]. Due to its antibacterial and oil-regulating properties, it is added to some cosmetics like hair shampoos and skin cleaners [28] that present bactericidal and fungistatic activity and are also well tolerated by the human skin and scalp. These preparations have the ability to strengthen and harden the keratin of skin and hair, and the concentration of thioxolone or others benzoxathiolones for the care of hair and skin must be 0,01%, at least - lower contents are not sufficiently effective – and 15% at maximum, because of the irritant effect on the skin specially if it was infected or inflamed. The optimum effects were obtained with concentrations between 1% and 5% [1].

It was shown by a Tripp's group study that thioxolone is a promissor carbonic anhydrase inhibitor (CAI), a class of compounds that possess several medical applications, like in treatment of glaucoma, Alzheimer's disease, osteoporosis, in management of epilepsy and as diuretics. In a complementary study, Barrese *et al.* have determined that the inhibition of the CA-II isozyme was dose- and time- dependent for thioxolone, but after a crystallographic assay was observed that a hydrolysis product of thioxolone, 4-mercaptobenzene-1,3-diol, was present in crystal indicating that thioxolone has featured as prodrug in inhibiting CA-II, and the absence of hydroxyl group, like in a unsubstituted 1,3-benzoxathiol-2-one, leads to the extremely more active compound: 2-hydroxy-thiophenol [28]. In a latter study, Inocentti *et al* corroborated this observation and showed that this feature for thioxolone is only applied for hCA-I, one of the isozymes of the human carbonic anhidrase [29].

### Benzoxathiolones and the Synthesis of Proteins

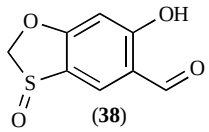
In chemical synthesis of small proteins, the crucial point is to keep the $C^{\alpha}$-integrity (epimerization) of the individual aminoacid residues during the formation of peptidic bonds in the molecules of protein. A previous study by Johnson *et al.* showed that 2-hydroxy-4-methoxybenzyl is an important backbone-amide protecting group [30]. However, in a later study it was demonstrated that this group drastically reduced the rate of coupling in the peptidic bond formation, specially due to the interaction between the hydroxyl group and the activated carboxyl group of the aminoacid, resulting in a 4,5-dihydro-8-methoxy-1,4-benzoxazepin-2(3H)-ones species. They verified that an electron-withdrawal group *para* at the hydroxyl group avoided this interconversion and kept the formation of peptidic bonds at excellent yields [31].

With these results on mind, they introduced a new class of benzoxathiolone derivatives, 6-hydroxy-5-formyl-1,3-benzoxathiole sulfoxide (**38**), Fig. (**6**), and used them as C-terminal backbone-amide protection group. The coupling yield in DIC/HOBt/DCM was 94% with <0.25% of epimerization, demonstrating their potential for the design of new proteins in laboratory [28]. If the benzoxathiol ring was opened, a new class of substances with the same synthetical abilities is formed (**39**), Fig. (**6**), [32], making benzoxathiolones an important source of reversible backbone-amides protection group for the proteic synthesis.

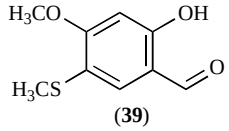



(**3**)

**Fig. (5).** Structure of thioxolone, 6-hydroxy-1,3-benzoxathiol-2-one.




(**38**)




(**39**)

**Fig. (6).** Benzoxathiolone derivatives used as reversible backbone-amides protection groups.

## CONCLUSION

Since first synthetical procedure to prepare 1,3-benzoxathiol-2-ones was reported, many studies have been described in order to improve the yields and also the laborious reactions conditions to obtain these compounds. The 1,3-benzoxathiol-2-ones and their derivatives have been reported with diversified biological activities such as: antioxidant, cytostatic, antipsoriatic, antibacterial, antimycotic, anti-inflammatory, anti-fungal and insecticide. Some benzoxathiolone derivatives have also been studied as dye and photochromic compounds. An important compound of this class is the thioxolone (6-hydroxy-1,3-benzoxathiol-2-one), which was the first benzoxathiolone synthesized. The thioxolane have been used in some cosmetics like hair shampoos and skin cleaners due to antibacterial, anti-fungicides and oil-regulating properties. Therefore, benzoxathiolone derivatives represent promissing compounds in the search of new drugs.

## ACKNOWLEDGEMENTS

The authors thank CAPES for fellowship granted to W.T.V.J. and Universidade Federal Fluminense and Farmanguinhos/Fiocruz for the financial support of the research.

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Received: January 19, 2010 Revised: July 06, 2010 Accepted: August 07, 2010