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PII: S0960-894X(17)30037-9
DOI: http://dx.doi.org/10.1016/j.bmcl.2017.01.024
Reference: BMCL 24600

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 4 November 2016
Revised Date: 8 January 2017
Accepted Date: 9 January 2017

Please cite this article as: Avalos-Alanís, F.G., Hernández-Fernández, E., Carranza-Rosales, P., López-Cortina, S., Hernández-Fernández, J., Ordó ñez, M., Guzmán-Delgado, N.E., Morales-Vargas, A., Velázquez-Moreno, V.M., Santiago-Mauricio, M.G., Synthesis, antimycobacterial and cytotoxic activity of α,β-unsaturated amides and 2,4-disubstituted oxazoline derivatives, *Bioorganic & Medicinal Chemistry Letters* (2017), doi: http://dx.doi.org/10.1016/j.bmcl.2017.01.024

Synthesis, antimycobacterial and cytotoxic activity of α,β-unsaturated amides and 2,4-disubstituted oxazoline derivatives

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Abstract: The synthesis of six α,β-unsaturated amides and six 2,4-disubstituted oxazolines derivatives and their evaluation against two *Mycobacterium tuberculosis* strains (sensitive H37Rv and a resistant clinical isolate) is reported. 2,4-Disubstituted oxazolines (*S*)-**3b,d,e** were the most active in the sensitive strain with a MIC of 14.2, 13.6 and 10.8 μM, respectively, and the compounds (*S*)-**3d**,**f** were the most active against resistant strain with a MIC of 6.8 and 7.4 μM. The *ex-vivo* evaluation of hepatotoxicity on precision-cut rat liver slices was also tested for the α,β-unsaturated amides (*S*)-**2b** and (*S*)-**2d**,**f** and for the oxazolines (*S*)-**3b** and (*S*)-**3d,f** at different concentrations (5, 15 and 30 μg/mL). The results indicate that these compounds possess promising antimycobacterial activity and at the same time are not hepatotoxic. These findings open the possibility for development of new drugs against tuberculosis.

Keywords:
Organic synthesis
Unsaturated amides
α,β-2,4-Disubstituted oxazolines
Antimycobacterial activity
Hepatotoxic activity

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (Mtb) that has become a serious global health problem. According to World Health Organization (WHO) it is estimated that one-third of the world's population is infected with Mtb.[1,2] Patients infected with TB do not necessarily show any symptoms of the disease, but the association of TB with human immunodeficiency virus (HIV) or its presence in patients with diseases related to certain deficiencies in the immune system, would represent a high risk of TB reactivation.[3] Besides that, the effectiveness of anti-tuberculosis treatments is affected by the emergence of multi- and extensively drug-resistant Mtb strains, along with

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totally drug resistant strains.[2,4] Therefore, exists a critical need and a growing interest for novel intervention strategies related to anti-TB agents with enhanced activity, reduced toxicity and good effect in the intracellular environment.[5,6]

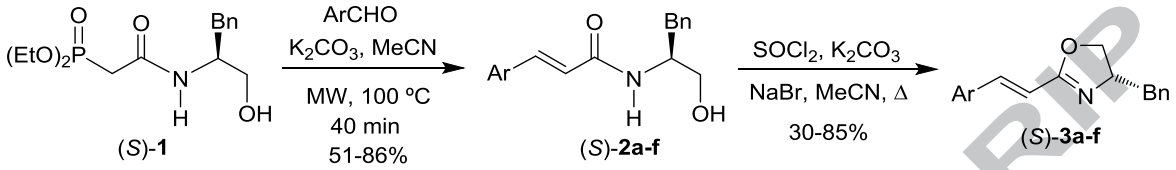
In recent years, synthesis and biological evaluation of several compounds bearing amides or oxazolines in their structures have shown a wide variety of interesting biological activities, including antimycobacterial effect. Cinnamic acid-based drug derivatives (amides, thioesters and hydrazides) display antioxidative, antitumor, anti-hepatitis C virus, antimicrobial activity and several other biological properties.[7] On the other hand, the oxazoline based compounds have shown remarkable activity against Mtb with extremely low toxicity, and therefore high therapeutic indexes, as well as activity against even the more recalcitrant non-replicant forms of Mtb.[8]

Based on the above, the design of new compounds bearing these features, amide and oxazoline groups, represents an important challenge given their potential application as alternative anti-TB drugs. A goal of our research group during the last few years has been the development of fast and effective synthesis of anti-TB agents.[9] We herein report the synthesis of α,β-unsaturated amides under microwave irradiation as an alternative preparation method, which were converted into 2,4-disubstituted oxazolines. Additionally, we also report the antimycobacterial and hepatotoxic activity of these α,β-unsaturated amides and 2,4-disubstituted oxazolines.

For the synthesis of the target compounds **2** and **3**, in the first step we carried out the Horner-Wadsworth-Emmons reaction of the β-phosphonoamide[10] **1** bearing L-phenylalaninol group with commercially available aryl aldehydes such as benzaldehyde, 4-fluorobenzaldehyde, 4-chlorobenzaldehyde, 4-methoxybenzaldehyde, 4-(benzyloxy)-benzaldehyde and 2-thiophenecarboxaldehyde, in the presence of K_2CO_3 and acetonitrile as solvent under microwave irradiation at 100 ºC for 40 min, obtaining the α,β-unsaturated amides (*S*)-**2a-f** in 51 to 86% yield. The second step was carried out following the procedure recently described by our research group.[9] Thus, the α,β-unsaturated amides (*S*)-**2a-f** were reacted with $SOCl_2$ in acetonitrile at reflux for 4 h in the presence of NaBr and

K_2CO_3, obtaining the 2,4-disubstituted oxazolines (*S*)-**3a-f** in 30 to 85% yield**.** The results are shown in Table 1.

Table 1. Preparation of α,β-unsaturated amides (*S*)-**2a-f** and 2,4-disubstituted oxazolines (*S*)-**3a-f**.



Entry	Product	Yield (%)[a]	Product	Yield (%)[a]
1	**2a;** Ar = C_6H_5	60	**3a;** Ar = C_6H_5	60
2	**2b;** Ar = 4-FC_6H_4	86	**3b;** Ar = 4-FC_6H_4	30
3	**2c;** Ar = 4-ClC_6H_4	58	**3c;** Ar = 4-ClC_6H_4	32
4	**2d;** Ar = 4-$MeOC_6H_4$	53	**3d;** Ar = 4-$MeOC_6H_4$	85
5	**2e;** Ar = 4-$BnOC_6H_4$	51	**3e;** Ar = 4-$BnOC_6H_4$	64
6	**2f;** Ar = 2-thienyl	57	**3f;** Ar = 2-thienyl	63

[a] Isolated after purification by column chromatography.

The most important contribution of the proposed method was the reduced reaction time of the Horner-Wadsworth-Emmons step for the synthesis of the amide derivatives (*S*)-**2a-f**. The synthesis was carried out in only 40 min by the microwave assisted method compared to 4 h by the conventional reported method.[9]

It is also important to mention that the compounds (*S*)-**2f** and (*S*)-**3f** have not been previously reported elsewhere, therefore they represent structural novelty derivatives.

The ^{1}H NMR and ^{13}C NMR data for the synthesized compounds correspond to those previously reported by our research group confirming their structures. The data of the newly synthesized compounds (*S*)-**2f** and (*S*)-**3f** also correspond to the expected.

In this work, we decided to evaluate the compounds (*S*)-**2a-f** and (*S*)-**3a-f** making a comparison between amides and oxazolines α,β-unsaturated with different groups only on C-4 position in phenyl ring based on the results reported by others research groups,[11] where they explored the Structure-Activity-Relationship (SAR) and described that the substituents

on the position C-4 in the phenyl ring are more actives than compounds substituted on C-3 and C-2 position.

The antimycobacterial activity of the twelve synthetic compounds (*S*)-**2a-f** and (*S*)-**3a-f**, and four pharmacological controls, Isoniazid (I), Rifampicin (R), Ethambutol (E) and Ofloxacin (Ofx) were evaluated under the same experimental conditions using the microplate Alamar blue assay.[12] Chemical structures are shown in Figure 1.

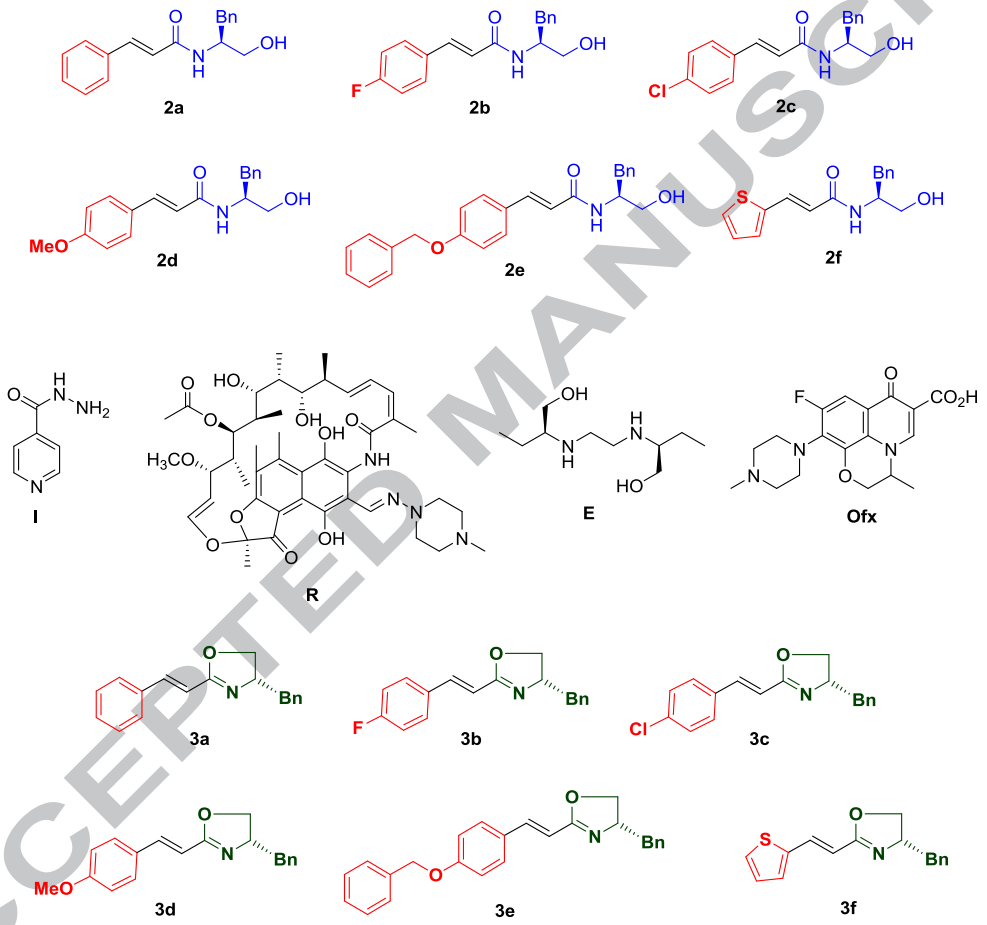


Figure 1. Compounds evaluated against *Mycobacterium tuberculosis* strains.

The synthesized compounds (*S*)-**2a-f** and (*S*)-**3a-f** were evaluated against two *Mycobacterium tuberculosis* strains, the H37Rv strain which is sensitive to the first-line drugs Isoniazid, Rifampicin and Ethambutol; and a clinical isolate which is resistant to treatment with Isoniazid, Rifampicin and Ethambutol drugs. The tested concentrations were 256, 128, 64, 32, 16, 8, 4, 2 and 1 μg/mL. In particular, the α,β-unsaturated amides (*S*)-**2a**,

(*S*)-**2e** and (*S*)-**2f** showed the lowest antitubercular activity with MIC = 56.8, 41.2 and 55.6 μM, for the two tested strains (Table 2, entries 1, 5 and 6); whereas α,β-unsaturated amides (*S*)-**2b**, (*S*)-**2c** and (*S*)-**2d** showed a better activity with MIC values of 26.7, 25.3 and 25.6 μM for the H37Rv strain (Table 2, entries 2, 3 and 4), these values are similar to Ethambutol drug (39.1 μM) under the same study conditions.

On the other hand, oxazolines (*S*)-**3a**, (*S*)-**3c** and (*S*)-**3f** showed the highest MIC values against the H37Rv strain (60.8, 26.9 and 29.7 μM, respectively). However, a better activity was observed with the oxazolines (*S*)-**3b**, (*S*)-**3d** and (*S*)-**3e** (14.2, 13.6 and 10.8 μM, respectively) for the same strain; these MIC values are similar to the reference drugs Ethambutol and Rifampicin (39.1 and 4.8 μM). It is important to mention that the compounds (*S*)-**3d** and (*S*)-**3f** tested for the resistant strain (isolated clinical) were the most active with MIC values of 6.8 and 7.4 μM, these values are better than Isoniazid (58.3 μM), Rifampicin (19.4 μM) and Ethambutol (>1,252.9 μM).

These results seem to suggest that these molecules possess promising therapeutic potential, especially against drug-resistant strains. MIC values for the anti-mycobacterial effect of all tested compounds are summarized in Table 2.

Table 2. Antimycobacterial activity of α,β-unsaturated amides (*S*)-**2a-f** and oxazolines (*S*)-**3a-f**.

			MIC = µg/mL (µM)	
Compound	**MolWt**	**CLogP[b]**	**Sensitive Strain[c] (H37Rv)**	**Resistant Strain[d] (clinical isolated)**
2a	281.34	3.071	16 (56.8)	16 (56.8)
2b	299.33	3.214	8 (26.7)	16 (53.4)
2c	315.79	3.784	8 (25.3)	16 (50.6)
2d	311.37	2.99	8 (25.6)	16 (51.3)
2e	387.47	4.758	16 (41.2)	16 (41.2)
2f	287.37	2.717	16 (55.6)	16 (55.6)
3a	263.33	4.639	16 (60.8)	8 (30.4)
3b	281.32	4.782	4 (14.2)	16 (56.9)
3c	297.78	5.352	8 (26.9)	8 (26.9)
3d	293.36	4.558	4 (13.6)	2 (6.8)
3e	369.46	6.326	4 (10.8)	8 (21.6)
3f	269.36	4.285	8 (29.7)	2 (7.4)
I[a]	137.14	-0.668	<1 (<7.2)	8 (58.3)
R[a]	820.96	NC	4 (4.8)	16 (19.4)
E[a]	204.31	0.1188	8 (39.1)	>256 (>1,252.9)
Ofx[a]	361.14	-0.507	<1 (<2.7)	2 (5.5)

[a]Pharmacologic controls. I = Isoniazid, R = Rifampicin, E = Ethambutol, Ofx = Ofloxacin.
[b]CLogP was calculated using the Cambridge Soft ChemDraw Ultra 8.0 software.
[c]Sensitive to the first-line drugs I, R, E. [d]Resistant to the first-line drugs I, R, E.

To carry out the *ex-vivo* evaluation of hepatotoxicity on precision-cut rat liver slices, we selected the α,β-unsaturated amides (*S*)-**2b**, (*S*)-**2d** and (*S*)-**2f** and the oxazolines (*S*)-**3b**, (*S*)-**3d** and (*S*)-**3f** for two reasons, the first one was to make a comparison between amides and oxazolines containing the same type of substituent in its structure, and the secondly it was because the majority of these compounds are the most active compounds against MTb and therefore they were selected in order to evaluate their safety to hepatic tissue. In this sense, we evaluated the hepatotoxic potential of these compounds by using precision-cut rat liver slices, an *ex-vivo*-3D assay.[13] Different concentrations (5, 15, and 30 µg/mL) were chosen based on the results of Anti-MTb activity and Isoniazid was included as the reference control. Because none of the active compounds were hepatotoxic, we show representative images of liver slices incubated with oxazoline (*S*)-**3d**, one of the most effective Anti-MTb compounds (Figure 2).

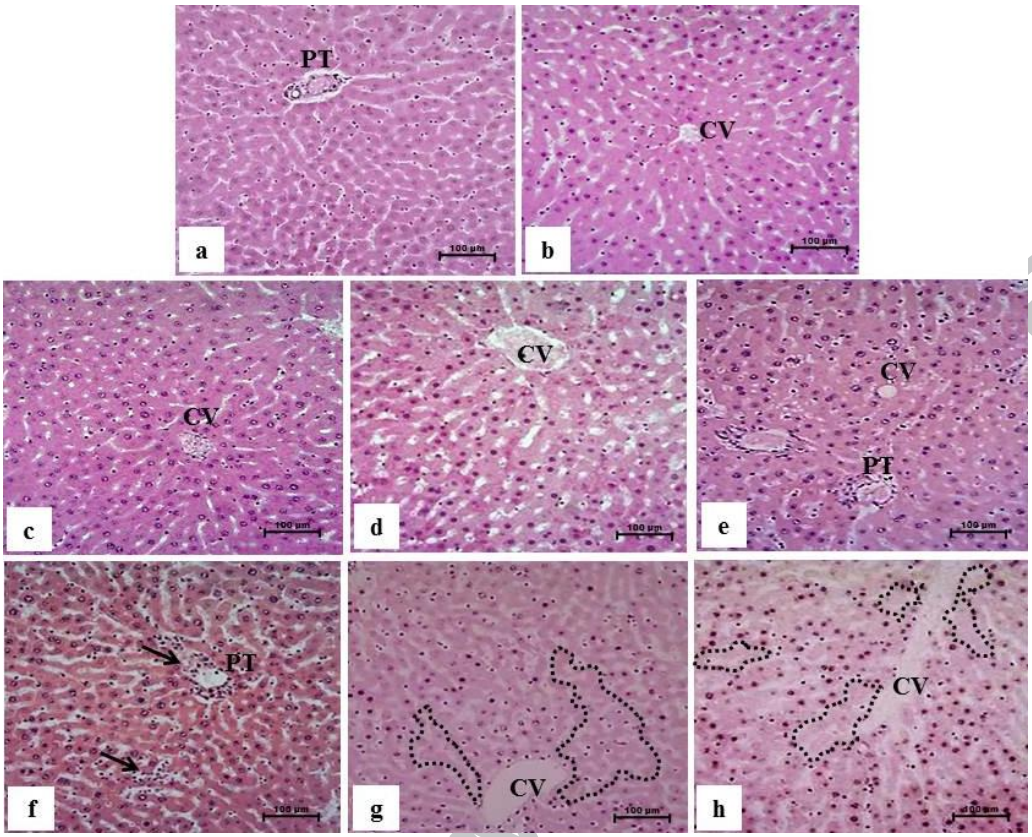


Figure 2. Representative photomicrographs of the cytotoxicity of compounds on precision-cut liver slices. Light bright field microscopy. H&E staining (40x).

As it can be seen, liver slices cultivated with (a) culture medium only (control) and (b) 0.5% DMSO (the solvent used to dissolve the compounds, negative control), show the characteristic histological architecture of normal hepatic tissue, with hepatocyte cords, portal triads (PT) and central veins (CV) well preserved. In liver slices cultured in the presence of 5, 15, and 30 µg/mL (c, d, and e, respectively) of compound **3d**, which showed the most relevant Anti-MTb activity, hepatotoxic effect was not observed; as in controls (a and b) where well preserved hepatic cords, portal triads and central veins were observed.

By contrast, in liver slices incubated with 5, 15, and 30 µg/mL of Isoniazid (f, g, and h, respectively) a marked histological damage was observed, being notable the presence of periportal inflammatory infiltrate (arrows) and centrilobular necrosis (dotted lines).

Histopathological analysis of the liver slices incubated during 24 h in the presence of the compounds possessing the most significant anti-MTb activity demonstrates that none of them are hepatotoxic because liver parenchyma, sinusoidal spaces and portal triads are well preserved in all the tested concentrations (Figure 2, c-e). Conversely, isoniazid (Figure 2, f-h) induces balonoid degeneration of the hepatocytes, foci of inflammatory cells, and cellular necrosis, especially at 15 and 30 µg/mL concentrations. Regarding to the last findings, it has been reported that this drug causes direct hepatotoxic damage which is characterized by centrilobulillar necrosis because throughout its metabolism in the liver it induces the elevation of enzymatic activity and release of toxic secondary metabolites.[14]

In summary, the results of this study have demonstrated in a general way that oxazolines (*S*)-**3a-e** are more active than the α,β-unsaturated amides (*S*)-**2a-e**. In the series of α,β-unsaturated amides screened, the compounds bearing the substituent fluoro, chloro and methoxy at C-4 position of the phenyl group [(*S*)-**2b-d**], were the most active compounds in the sensitive strain (H37Rv) shown the MIC value of 26.7, 25.3 and 25.6 µM, respectively. However, the antimycobacterial activity of these same compounds in the resistant strain was not better. On the other hand, in the series of oxazoline derivatives, compounds (*S*)-**3b**, (*S*)-**3d** and (*S*)-**3e** bearing the substituent fluoro, methoxy and benzyloxy at C-4 position of the phenyl group, were the most active in the sensitive strain. It is important to mention that oxazoline (*S*)-**3d** and (*S*)-**3f** derivatives were the most active in the resistant strain and even were more active than Isoniazid, Rifampicin and Ethambutol and very similar to Ofloxacin. The hepatotoxic activity using precision-cut rat liver slices for the most active compounds (*S*)-**2b**, (*S*)-**2d**, (*S*)-**2f**, (*S*)-**3b**, (*S*)-**3d** and (*S*)-**3f** were evaluated and none of these compounds were hepatotoxic. More detailed and complete studies of the biological activity of these compounds are currently in progress as they are needed to explore the mechanism of antimycobacterial activity.

Acknowledgments

The authors thank to CONACYT of México for the financial support via projects 101898 and 181816. We thank V. Labastida-Galván for the determination of the HRMS. F.G.A.A. also thanks CONACYT for a Graduate Scholarship.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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Graphical Abstract

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