

# Original Article

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## Synthesis of new 1,3-thiazoline-2-thiones as potential antimycobacterial agents

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### Abstract

As a continuation of our efforts in developing new antimycobacterial agents, a series of new 1,3-thiazolidine-2-thione derivatives were synthesized. The chemical structures of the compounds were elucidated by FT-IR, <sup>1</sup>H-NMR and Mass spectra. The analysis of theoretical toxicity risks, drug-likeness and drug-score for these series using Osiris program showed acceptable results.

**Key words:** Tuberculosis, Mycobacterium, 1,3-thiazolidine-2-thione

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## 1. Introduction

Tuberculosis caused by *Mycobacterium tuberculosis*, is a growing global health problem due to the lack of proper therapeutic agents for its remedy. Because of the emergence of multiple drug resistant strains, it is critical to discover new drugs acting with different mechanisms (Babaoglu, Page et al. 2003; Maddry, Anathan et al. 2009). Thiazoles and thiazolidinones have attracted interest because of their various biological activities and recently used for developing drugs for treatment of allergies, hypertension, HIV infection. More recently the agents have been utilized for developing medications against pain, as fibrinogen receptor antagonists with antithrombotic activity.

The agents also considered as new inhibitors of bacterial DNA gyrase B and particularly tuberculosis, compounds 1 (Fig.1) (Fugikawa et al., 1969; Danila et al., 1978; Turan-Zitouni et al., 2008). However, there are some reports on the antimycobacterial activity of diphenyl ether compounds, linked to different heterocyclic rings, compound 2 (Fig.1). It has been shown that hydrazone type containing compounds can act as antimycobacterial agents, compound 3 (Fig.1) (Kini, Bhat et al. 2009; Almasirad, Samiee et al. 2011).

As a part of our efforts to develop new compounds applied for the therapy of mycobacterium infection, we have synthesized new 1,3-thiazolidine-2-thiones (Almasirad, Samiee et al. 2011). The rational design of these new derivatives was planned by molecular hybridation of previously described antimycobacterial compounds 1-3 (Fig.2).

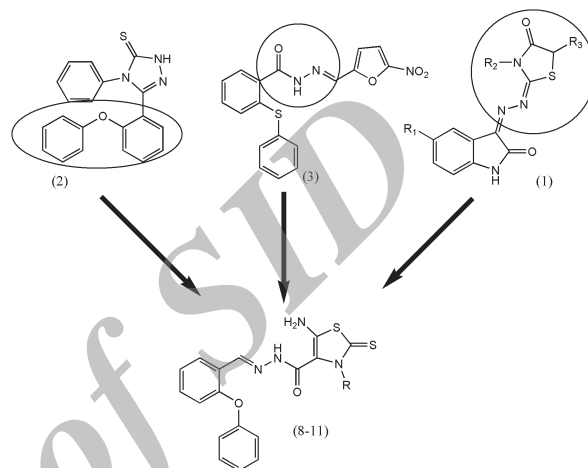


Figure 2: Design of target compounds

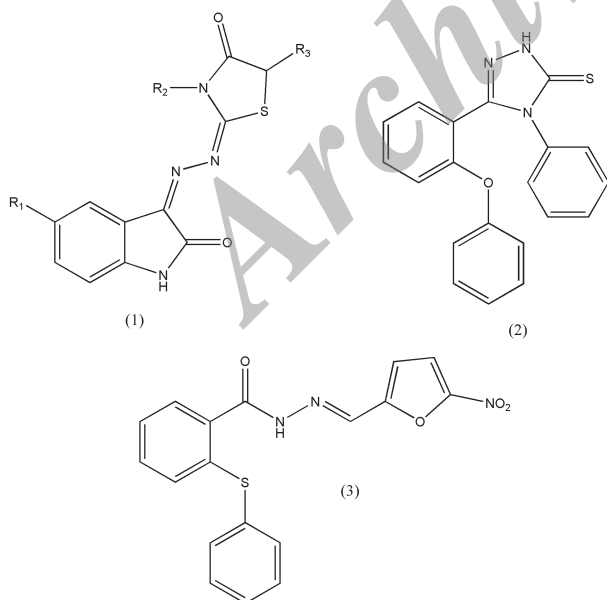


Figure 1: Different classes of antimycobacterial compounds

## 2. Materials and Methods

### 2.1. Chemistry

The designed compounds were synthesized according to Fig. 3. 2-phenoxybenzaldehyde 6 was prepared by ullman reaction of salicylaldehyde 4 and bromobenzene 5. The key intermediate 7 was prepared by condensing 6 with cyano acetic acid hydrazide (Groberts, Youseti et al. 2004). Taking the advantages of the Gewald reaction and using the Schiff's base of cyano acetic acid hydrazide 7, as the nitrile containing active methylene moiety, final compounds 8-11 were prepared by the reaction of 7 with sulfur and different isothiocyanates in the presence of triethylamine as a basic catalyst (Gewald et al., 1966). The thiazolopyrimidine 12 was prepared by heating 10 with a mixture of triethylorthoformate and acetic anhydride.

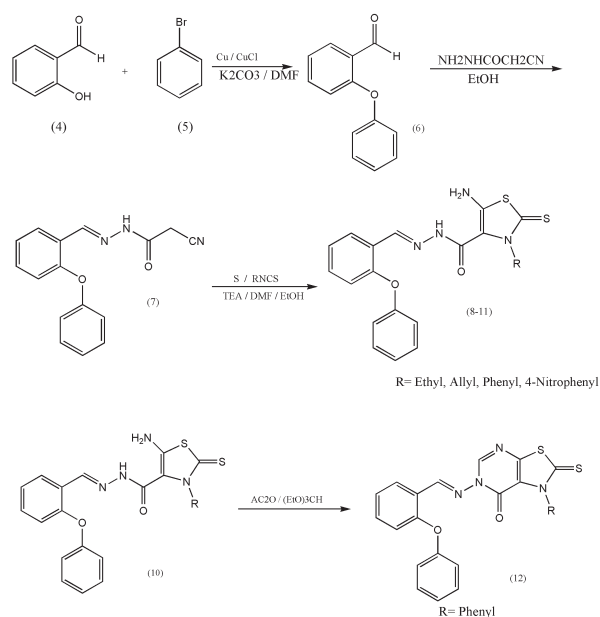


Figure 3: Synthetic route used for the preparation of compounds 8-12

Chemicals were purchased from Merck chemical company (Tehran, Iran). Melting points were taken of a Kofler hot-stage apparatus (Richert, Vienna, Austria) and are uncorrected. <sup>1</sup>H-NMR spectra were obtained using a Bruker FT-400 spectrometer (Bruker, Rheinstetten, Germany). Mass spectra were obtained using a Finnigan-MAT TSQ-70 spectrometer at 70 eV (Finnigan, Bremen, Germany). The IR spectra were obtained using Nicolet FT-IR Magna 550 spectrographs (KBr disks) (Nicolet, Madison, WI, USA).

## 2.2. Synthesis of target compounds

### Synthesis of 2-(Phenoxy) benzaldehyde (6)

To a mixture salicylaldehyde 4 (10 ml, 95.5 mmol), bromobenzene 5 (10.5 ml, 100.3 mmol)

and anhydrous potassium carbonate (26.2 g, 189 mmol) in sieve dried DMF (100 ml), Cu (1.4 g) and CuCl (1.4 g) was added and the mixture was refluxed under nitrogen gas. After 15 hr, the content was poured into water (200 ml) and extracted with diethylether to give compound 3 as a liquid and then purified by steam distillation. The yield was 15g (57%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz): 10.51(s, 1H, CHO), 7.94(dd, 1H, J=7.60, 1.9Hz, aromatic), 7.62-6.63(m, 8H, aromatic). Mass: m/z (rel.int): 198(M<sup>+</sup>, 97), 197(100), 181(22), 169(11), 141(32), 120(63), 115(23), 105(20), 77(39), 51(47).

### Synthesis of N-(2-Phenoxybenzylidene)-2-cyanoacetohydrazide (7)

An equimolar mixture of 6 (1ml, 5mmol) and cyanoacetic acid hydrazide (0.5g, 5 mmol) in absolute ethanol (10 ml) was heated under reflux for 2h. The precipitate formed after cooling was filtered off and dried. The yield was 1g (67%); IR (KBr): ν<sub>cm<sup>-1</sup></sub> 3190(NH), 2270(CN), 1684(C=O), 1659(C=N). <sup>1</sup>H NMR (DMSO, 400MHz): 11.78(s, 1H, NH), 8.30(s, 1H, CH=N), 8.01(d, 1H, J=7.2Hz, aromatic), 4.20(s, 2H, CH<sub>2</sub>).

### General procedure for the preparation of compounds 8-11

To a stirred solution of 7 (1g, 3.5 mmol), finely divided sulfur (0.11g, 3.5 mmol) in absolute ethanol (5 ml) and DMF (5 ml), corresponding isothiocyanate (3.5mmol) was added. The reaction mixture was heated under reflux for 12h, and after cooling, the precipitate was filtered off, dried and recrystallized from ethanol. Melting points, recrystallization solvents and yields for compounds 8-11 are reported in Table1.

Table 1: Physical data of synthesized compounds

Compound No	R	Recrystallization solvent	yield %	MP°C	Molecular Weight	Formula
8	Ethyl	Ethanol	29	247-149	398	C <sub>19</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub> S <sub>2</sub>
9	Allyl	Ethanol	31	222-224	410	C <sub>20</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub> S <sub>2</sub>
10	Phenyl	Ethanol	39	233-226	446	C <sub>23</sub> H <sub>18</sub> N <sub>4</sub> O <sub>2</sub> S <sub>2</sub>
11	4-Nitrophenyl	Ethanol	26	190-191	491	C <sub>23</sub> H <sub>17</sub> N <sub>5</sub> O <sub>4</sub> S <sub>2</sub>
12	-	Methanol	38	238-240	456	C <sub>24</sub> H <sub>16</sub> N <sub>4</sub> O <sub>2</sub> S <sub>2</sub>

**N/-(2-Phenoxybenzyliden)-5-amino-3-ethyl-2,3-dihydro-2-thioxothiazole-4-carbohydrazide (8)**

IR (KBr) :  $\text{vcm}^{-1}$  3433, 3306, 3231(NH<sub>2</sub>,NH), 1628(C=O), 1235(C=S). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz) : 10.45(s, 1H, NH), 8.29(s, 1H, CH=N), 8.16(dd, 1H, J=7.6, 1.6Hz, aromatic), 7.46-7.11(m, 5H, aromatic), 6.97(dd, J=8Hz, 2H, aromatic), 6.87(d, 1H, J=8.4Hz, aromatic), 6.68(bs, 2H, NH<sub>2</sub>), 4.35(q, 2H, CH<sub>2</sub>), 1.34(t, 3H, CH<sub>3</sub>).

**N/-(2-Phenoxybenzylidene)-3-allyl-5-amino-2,3-dihydro-2-thioxothiazole-4-carbohydrazide (9)**

IR (KBr) :  $\text{vcm}^{-1}$  3425, 3350, 3256(NH), 1639(C=O), 1234(C=S). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz) : 10.55(s, 1H, NH), 8.31(s, 1H, CH=N), 8.16(dd, 1H, J=8.0, 1.6Hz, aromatic), 7.45-7.09(m, 6H, aromatic), 6.97(d, 2H, J=8.0Hz, aromatic), 6.88(d, 1H, J=8.0Hz, aromatic), 6.71(bs, 2H, NH<sub>2</sub>), 5.90(m, 1H, CH=), 5.28(q, 2H, =CH<sub>2</sub>), 4.99(d, 2H, J=5.2Hz, CH<sub>2</sub>).

**N-(2-phenoxybenzylidene)-5-amino-2,3-dihydro-3-phenyl-2-thioxothiazole-4-carbohydrazide (10)**

IR (KBr) :  $\text{vcm}^{-1}$ , 3430, 3325, 3244(NH<sub>2</sub>,NH), 1630(C=O), 1236(C=S). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz) : 11.15(s, 1H, NH), 8.37(s, 1H, CH=), 8.17(dd, 1H, J=8.0, 1.6Hz, aromatic), 7.67-7.11(m, 10H, aromatic), 6.97(d, 2H, J=8.2Hz, aromatic), 6.89(d, 1H, J=8.0Hz, aromatic), 6.70(bs, 2H, NH<sub>2</sub>).

**N-(2-phenoxybenzylidene)-5-amino-2,3-dihydro-3-(4-nitrophenyl)-2-thioxothiazole-4-carbohydrazide (11)**

IR (KBr) :  $\text{vcm}^{-1}$  3425, 3331, 3280(NH<sub>2</sub>,NH), 1635(C=O), 1530, 1348(NO<sub>2</sub>), 1238(C=S). <sup>1</sup>H NMR (DMSO, 400MHz) : 11.5(s, 1H, NH), 8.46(d, 2H, J=8.2Hz, aromatic), 8.35(s, 1H, CH=N), 8.06(dd, 1H, J=8.0, 1.0Hz, aromatic), 7.75(d, 2H, J=6.8Hz, aromatic), 7.47-7.14(m, 5H, aromatic), 7.02(dd, 2H, J=8.91Hz, aromatic), 6.95(d, 1H, J=8.0Hz, aromatic), 6.79(bs, 2H, NH<sub>2</sub>). Mass : m/z (rel.int) : 491(M<sup>+</sup>, 10), 399(40), 306(96), 196(22), 181(100), 134(68), 77(30), 51(15).

**6-(2-phenoxybenzylideneamino)-1,2-dihydro-1-phenyl-2-thioxothiazolo[5,4-d] pyrimidin-7 (6H)-one (12)**

A solution of 10 (1g, 2.2 mmol) in a mixture of triethylorthoformate (2.5 ml) and acetic anhydride (2.5 ml) was heated under reflux for 3hr. The reaction mixture was cooled

and the precipitate was filtered off and dried. The yield was 0.5g (88%); IR (KBr) :  $\text{vcm}^{-1}$  1681(C=O), 1192(C=S). <sup>1</sup>H NMR (DMSO, 400MHz) : 9.46(s, 1H, CH=N, Pyrimidine), 8.66(s, 1H, CH=N), 8.15(d, 1H, J=7.6Hz, aromatic), 7.62-7.10(m, 10H, aromatic), 7.09(d, 2H, J=7.6Hz, aromatic), 6.96(d, 1H, J=8.8Hz, aromatic). Mass : m/z (rel.int) : 456(M<sup>+</sup>, 12), 260(32), 95(22), 81(55), 77(15), 69(100), 51(25).

### 3. Results

The structures of the synthesized compounds were assigned on the basis of FT-IR, <sup>1</sup>H-NMR and Mass spectra. The FT-IR spectrum of compounds 8-11 showed characteristic bands in the 3231-3433  $\text{cm}^{-1}$  due to the presence of NH, NH<sub>2</sub> groups and a strong band of C=O group in the 1628-1639  $\text{cm}^{-1}$ . There are some absorptions near to 1230  $\text{cm}^{-1}$  due to C=S group in compounds 8-11. In the FT-IR spectrum of compound 12 two bands were observed at 1681 and 1192 due to C=O and C=S respectively. In the <sup>1</sup>H NMR spectra of compounds 8-11, a NH proton appeared at 10.45-11.50 ppm and a singlet showed between 6.00-7.00 ppm due to NH<sub>2</sub> group. The <sup>1</sup>H NMR spectrum of compound 12 was characterized by the existence of thiazolopyrimidine C-5-H at 9.46 ppm. In the Mass spectra of compounds 11 and 12 Molecular Ions were observed.

### 4. Discussion

Currently, there are several approaches to assess the drug-likeness of the drug candidates. One such tool is the Osiris Property Explorer (OPE; organic chemistry portal., <http://www.organic-chemistry.org>) a web based system which is able to calculate properties such as toxicity risk assessment, log p prediction, solubility (log s) prediction, molecular weight, fragment-based drug-likeness prediction and overall drug-score. The overall drug-score combines drug-likeness, clogp, clogs, molecular weight and toxicity risk indices in one single value, where the occurrence frequency of each fragment is determined within the collection of traded drugs and within the supposedly non-drug like collection of Fluka compounds. A positive drug-likeness value (0.1-10) states that a molecule contains predominantly fragments which are frequently

present in commercial drugs. In this work, we used the OPE for calculation of the overall drug-score of the synthesized compounds using isoniazid and pyrazinamide as positive controls

(Table2). The Osiris study revealed that all compounds and isoniazide are supposed to be non-mutagenic, non-tumorigenic, non-irritant with no reproductive effects. However,

**Table 2: Drug-likeness of target compounds predicted by Osiris Property Explorer tool**

Compound	Toxicity risk <sup>a</sup>				cLogP	Drug-likeness	Drug-score
	M <sup>b</sup>	T <sup>c</sup>	I <sup>d</sup>	R <sup>e</sup>			
8	-	-	-	-	4.12	6.71	0.46
9	-	-	-	-	4.29	4.29	0.43
10	-	-	-	-	4.94	6.6	0.33
11	±	-	-	-	4.81	-4.93	0.12
12	-	-	-	-	5.26	6.17	0.3
Isoniazid	-	-	-	-	-1.09	-0.68	0.24
Pyrazinamide	+	+	-	-	-0.78	-5.06	0.49

. <sup>a</sup>Ranked according to: (-) no bad effect, (±) medium bad effect, (+) bad effect.

. <sup>b</sup>M, Mutagenic effect.

. <sup>c</sup>T, Tumorigenic effect.

. <sup>d</sup>I, Irritating effect.

. <sup>e</sup>R, Reproductive effect.

pyrazinamide showed high risk of mutagenic and tumorigenic effects and compound 11 showed medium risk of mutagenic effect. According to the Lipinski's rule of thumb and on the basis of the molecular weight and clogp of the compounds 8-11, one can assume these agents can be orally active (Lipinski et al., 1997). All compounds except 11 had positive drug-likeness values and their fragments of had a contribution to drug-likeness activities. In contrast, the two control drugs showed negative drug-likeness. The target compounds showed weak to good drug-scores (0.12-0.46) and the drug-score of compounds 8-11 was found better than pyrazinamide and comparable to isoniazid. It is important to note that the computational prediction of toxicity effects in this study does not compensate the need for wet-lab toxicological study of the compounds, nor does it guarantee the safety of their use. However, our predictive study encourages further experimental investigation of agents' profiles as potential drug candidates. Because of the presence of three antimycobacterial pharmacophore (hydrazone, diphenylether and thiazolidinethione) in the structure of the final compounds their antimycobacterial activity is plausible.

**Conflict of interests :** None declared.

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