Published in final edited form as:
Tetrahedron Lett. 2011 August 24; 52(34): 4375–4377. doi:10.1016/j.tetlet.2011.05.114.

An efficient microwave assisted synthesis of novel class of Rhodanine derivatives as potential HIV-1 and JSP-1 inhibitors

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Abstract

(*Z*)-5-(2-(1*H*-Indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one (**7a-q**) derivatives have been synthesized by the condensation reaction of 3-phenyl-2-thioxothiazolidin-4-ones (**3a-h**) with suitably substituted 2-(1*H*-indol-3-yl)-2-oxoacetaldehyde (**6a-d**) under microwave condition. The thioxothiazolidine-4-ones were prepared from corresponding aromatic amines (**1a-e**) and di-(carboxymethyl)-trithiocarbonyl (**2**). The aldehydes (**6a-h)** were synthesized from the corresponding acidchlorides (**5a-d**) using $HSnBu_3$.

Keywords

3-phenyl-2-thioxothiazolidin-4-one; 2-(1*H*-indol-3-yl)-2-oxoacetaldehyde; acid chloride; $HSnBu_3$; MW irradiation

Introduction

United Nations Program On HIVAIDS (UNAIDS) estimates approximately 35.2 million people worldwide are living with HIV and more than 25 million people have died of AIDS. Thus so far, 28 anti-HIV drugs have been licensed by the United States Food and Drug Administration (FDA). Most of these drugs belong to two categories: reverse transcriptase inhibitors (RTI) and protease inhibitors (PI). Combined application of these antiretroviral drugs has shown significant synergistic effects.[1] However, an increasing number of patients with HIV infection/AIDS can no longer use such drugs as a result of drug resistance and serious adverse effects.[2] Therefore it is essential to develop novel anti-HIV drugs targeting HIV entry. A recent report[3] identified 2-aryl-5-(4-oxo-3- phenethyl-2-thioxothiazolidinylidenemethyl)-furans (**A**, Fig. 1) with Rhodanine as a core molecule exhibited anti-HIV-1 activity. On the other hand, Rhodanine[4] and its derivatives possessing hydrogen attached to the nitrogen atom have been patented as fungicides while the compounds containing nitrogen atom[5] were patented as pesticides, with mention being made of their usefulness as fungicides. 5-Benzylidine-3-pheny-2-thioxo-thiazolidin-4-one core (**B**, Fig. 1) was shown to inhibit the Jun NH_2-terminal kinase (Jnk) stimulatory phosphatase-1 (JSP-1).[6] In addition Rhodanine-based molecules are popular as small molecule inhibitors of numerous targets such as HCV NS3 protease,[7a] aldose reductase,[7b,c] β-lactamase,[7d] UDP-N-acetylmuramate/L-alanine ligase,[7e] antidiabetic agents,[7f] cathepsin D,[7g] and histidine decarboxylase.[7h] For the past few years our group has been preparing and evaluating

biologically important compounds.[8] Herein we report the synthesis of a novel class of rhodanine-based small molecule with the aim of investigating their inhibitory properties against JSP-1 and HIV-1 in the low micro molar range.

5-(2-(1*H*-Indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thiox-othiaz- olidin-4-ones (**7a-q**) were synthesized by a Knoevenagel condensation of 3-phenyl-2-thioxothiazolidin-4-ones (**3a-h**) derivatives with suitably substituted 2-(1*H*-indol-3-yl)-2-oxoacetaldehydes (**6a-d**) using MW irradiation and catalytic amount of 2,2,6,6-tetramethyl piperidine (TMP) in ethanol (Scheme 1). Although other bases (Table 1) can be used as catalyst {e.g,; piperidine, pyridine, *N*-methyl piperidine (NMP), DBU}, TMP works best. The same reaction under conventional reflux condition using ethanol as solvent gave lower yields (11 to 69%),[3] longer time (5 h) and/or compounds required rigorous purification. However the MW reaction provides cleaner reaction, 15 min time and the products only required to be washed with cold ethanol. The yields are good to excellent (Table 3). The optimum temperature and condition for this MW assisted reaction was determined by a series of reaction of 3-phenyl-2-thioxothiazolidin-4-one (**3b**) and 2-(1*H*-indol-3-yl)-2-oxoacetaldehyde (**6a**). The results are summarized in Table 1. From this table it is clear that MW irradiation at 90 °C for 15 min in ethanol is the optimum condition for the synthesis of these molecules. All the compounds **7a-q** were isolated as single (*Z*) isomer and was confirmed by comparing the vinylic proton shift in ^{1}H NMR with previously reported[3,6] data which appears around δ 8.00 ppm.

Compounds **7a-q** were obtained in 89-96% yields with high melting point (>300 °C). They were insoluble in usual organic solvent, water or hexane. The IR (KBr) spectra of compounds **7a-q** exhibit absorption bands due to the stretching vibrations of NH group of indole cycles (3200 cm^{-1} range). The spectra of compounds **7a-q** display characteristic bands and C=S group (intense bands at 1628-1610 cm^{-1}). The 3-phenyl due to stretching vibrations of two C=O groups (1720 cm^{-1} range -2-thioxothiazolidin-4-ones (**3a-h**) derivatives were prepared by the literature[9] procedure by refluxing equimolar amounts of suitably substituted aromatic amines (**1a-e**) and di-(carboxymethyl)-trithiocarbonyl (**2**). The aldehydes **6a-d** were synthesized by treating corresponding acid chlorides with $HSnBu_3$.[10] The acid chlorides were prepared by acylation of indole (or substituted indole) with oxalylchloride.[11] All compounds were characterized by ^{1}H NMR, ^{13}C NMR, DEPT-135, IR and HRMS studies.

In conclusion we have successfully developed an easy access to a novel series of (Z)-5-(2-(1*H*-indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one (**7a-q**) derivatives. The mild reaction conditions, easy workup, good to excellent yields, and easily available substrate make this reaction an attractive method for the preparation of 3-phenyl-2-thioxothiazolidin-4-ones. Efforts towards the synthesis of other important drug molecules with a Rhodanine moiety by MW irradiation are ongoing in our laboratory. Also work is in progress to obtain biological activity (antibacterial, antifungal, anticancer and neuroprotective kinase inhibitor activity) of these important compounds. Results in these areas will be presented in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors are grateful to NIH (1RC2NS064950) for generous financial support.

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14. All compounds gave satisfactory spectroscopic and analytical data. Compounds **3a**,[13] **3b**,[13] **3c**,[13] **3d** [12] were prepared according to the method described in the literature. The other related compounds, **3e**, **3f**, **3g** and **3h** were prepared by the same method. Foe details, see supplementary data.

15. MW assisted general synthesis of compound **7a-q:** Equimolar amount of **3a** and **6a** were mixed properly in a mortar pestle and was taken in specially designed MW test tube. Ethanol (2 mL) was added to the mixture followed by 1-2 drops of TMP. The test tube after being sealed was irradiated for 15 min at 90 °C and 150 psi pressure. After cooling, the solid mass was crushed into 20 ml of 95% ethanol and filtered. The solid mass collected was washed with ethanol (20 ml) and dried under vacuum to get the desired (Z)-5-(2-(1*H*-Indol-3-yl)-2-oxoethylidene)-3-phenyl-2-thioxothiazolidin-4-one (**7a**) as orange solid. Mp 324-326 °C. IR (KBr-disk) 3375, 1726, 1626,

1555, 1516, 1496, 1439, 1219, 1168 cm^{-1}. ^{1}H NMR (500 Mhz, dmso- d_6): δ 12.44 (brs, 1H, NH), 8.96 (s, 1H, Ar-CH), 8.28 (dd, J = 1.7 Hz, 8 Hz, 1H, Ar-CH), 8.02 (s, 1H, vinylic proton), 7.55-7.39 (m, 6H, Ar-CH), 7.27-7.25 (m, 2H, Ar-CH). ^{13}C NMR (500 Mhz, dmso- d_6) 201.1 (C=S), 182.3 (C=O), 167.3 (C=O), 138.2 (C), 137.8 (CH), 137.6 (C), 129.9 (CH), 129.8 (CH), 129.3 (CH), 125.9 (C), 124.5 (CH), 123.3 (CH), 122.1 (CH), 113.1 (CH). HRMS (ESI^{+}) m/z 365.0430, calcd for $C_{19}H_{12}N_2O_2S_2$: 365.0420. The related compounds (**7b-q**) were prepared in the same way.

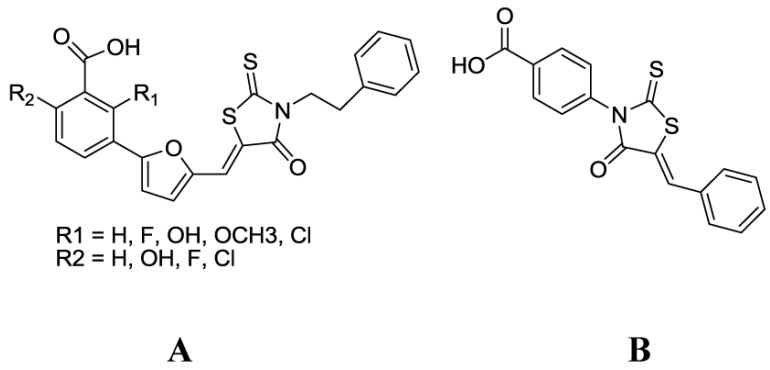
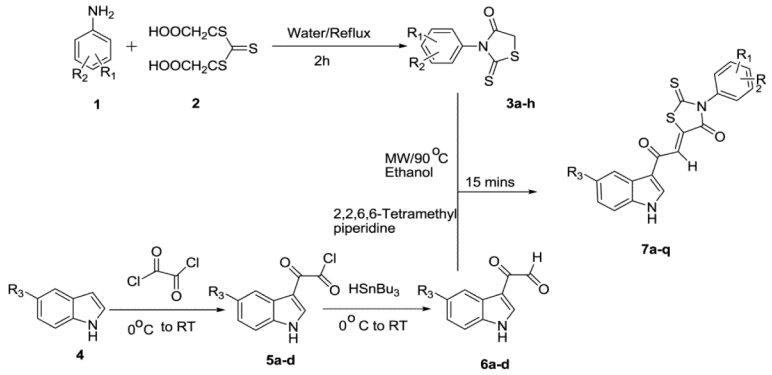


Fig. 1.
Competitive inhibitor of HIV-1 and JSP-1



Scheme 1.
Schematic representation for the synthesis of **7a-q**

Table 1

Screening of solvents, reaction time and temperature for the synthesis of **7b**

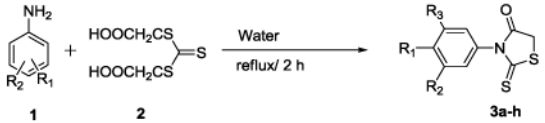
Base	Condition[a]	Temp (°C)	Time (mins)	Yield[b] (%)
-	No solvent	90	15	Trace
-	Ethanol	90	15	Trace
Piperidene	Ethanol	90	15	80
TMP	Ethanol	90	15	96
TMP	No solvent	90	15	Trace
DBU / pyridine	Ethanol	90	20	20
TMP	Acetonitrile	90	15	76
TMP	Acetonitrile	130	15	15
DBU	Acetonitrile	90	30	Trace
TMP	DMF	90	15	45
	DMF	90	30	10
NMP				
DBU	DMF	120-140	15	Trace
TMP	Water	90	15	Trace
TMP	Water	130	15	Trace
-	Water	130	30	Trace
TMP	Toluene	90	15	Trace
TMP	Isopropanol	90	15	45
TMP	THF	90	15	38
TMP	n-Butanol	90	15	33

[a] All the reaction was carried out in equimolar amount of each compound in 2 ml of solvent at 150 psi pressure.

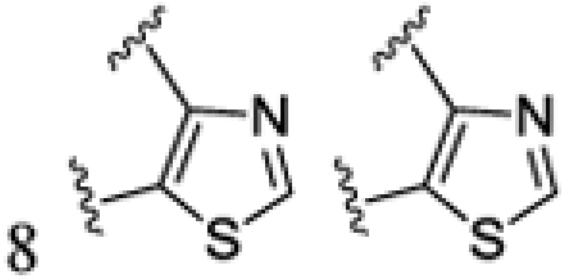
[b] Isolated yield

Table 2

Reaction of various aromatic amines with di-(carboxymethyl)-trithiocarbonyl



1 **2** **3a-h**

Entry	R_1	R_2	R_3	Time (h)	Product	Yield[a] (%)
1	H	H	H	3.0	**3a**	75
2	CH_3	H	H	2.5	**3b**	73
3	CH_3	CH_3	H	2.5	**3c**	76
4	OCH_3	H	H	2.0	**3d**	75
5	CN	H	H	4.0	**3e**	71
6	OH	Br	Br	3.0	**3f**	78
7	OH	Cl	Cl	3.0	**3g**	76
8			H	4.0	**3h**	75

[a] Isolated yield.

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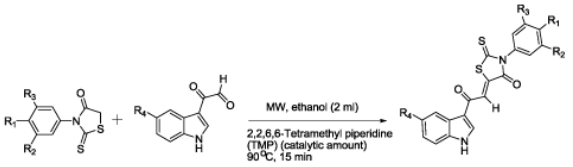
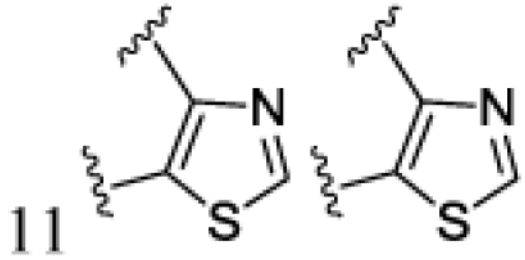
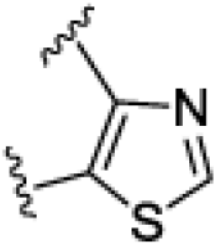
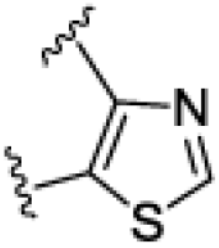
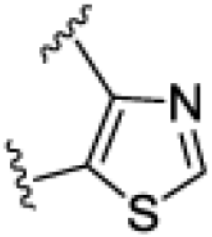
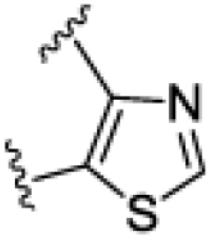
Table 3

Reaction of various indole based aldehydes with Rhodanine derivatives



3a-h **6a-d** **7a-q**

Entry (%)	R_1	R_2	R_3	R_4	product	Yield[a,b]
1	H	H	H	H	**7a**	95
2	CH_3	H	H	H	**7b**	96
3	CH_3	CH_3	H	H	**7c**	90
4	CH_3	H	H	OCH_3	**7d**	93
5	OCH_3	H	H	H	**7e**	95
6	OCH_3	H	H	OCH_3	**7f**	92
7	H	H	H	OCH_3	**7g**	94
8	CN	H	H	OCH_3	**7h**	90
9	CN	H	H	H	**7i**	91
10	H	H	H	Cl	**7j**	89
11			H	H	**7k**	95

Entry (%)	R_1	R_2	R_3	R_4	product	Yield[a,b]
12			H	OCH_3	**7l**	93
13			H	CN	**7m**	91
14	OH	Br	Br	H	**7n**	90
15	OH	Cl	Cl	H	**7o**	89
16	OH	Br	Br	OCH_3	**7p**	96
17	OH	Cl	Cl	OCH_3	**7q**	90

[a] Isolated yield;

[b] All the compounds were characterized by ^1H NMR, ^{13}C NMR, DEPT-135, IR and HRMS analysis.

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