# Stereochemical Investigations of Diastereomeric $N$-[2-(Aryl)-5-methyl-4-oxo-1,3-thiazolidine-3-yl]-pyridine-3-carboxamides by Nuclear Magnetic Resonance Spectroscopy (1D and 2D) 

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#### Abstract

Some new $N$-[2-(aryl)-5-methyl-4-oxo-1,3-thiazolidine-3-yl]-pyridine-3-carboxamides were synthesized and their structures were investigated by IR, NMR ( ${ }^{1} \mathrm{H},{ }^{13} \mathrm{C}$, and 2D) , and mass spectra. The presence of $\mathrm{C}-2$ and $\mathrm{C}-5$ stereogenic centers on the thiazolidinone ring resulted in diastereoisomeric pairs. The configurations of two stereogenic centers were assigned based upon ${ }^{1} \mathrm{H}$ NMR analysis of coupling constants and 2D nuclear overhauser enhancement spectroscopy (NOESY) experiment. Resolution of the diastereoisomers was performed by high performance liquid chromatography (HPLC) using a chiral stationary phase.


## 1. Introduction

Pyridine-3-carboxamide (nicotinamide), known as vitamin PP (pellagra protective), is part of the vitamin B group and plays an important role in biological oxidative chemistry. Pyridine-3-carboxamide derivatives have gained attention because of their diverse pharmacological activities, such as cytoprotective [1], antiviral [2], antitumor [3], and anxiolytic [4] activities.

Thiazolidin-4-one derivatives possess versatile biological activities [5], including antifungal [6], antibacterial [7, 8], anticancer [9, 10], anti-inflammatory [11-13], analgesic [14], anticonvulsant $[15,16]$, antiviral $[17,18]$, and antidiabetic activities [19, 20].

Currently, nearly $50 \%$ of the drugs are in use as racemates. But stereochemical factors generally have important influence on biological activity of the drug molecules. The two enantiomers present in a racemic mixture can possess different biological activities; that is, one enantiomer has therapeutic value; the other enantiomer may be less effective, inactive, or highly toxic [21-27]. Therefore, the identification and separation of stereoisomers are considered to be important. Chiral compounds bearing thiazolidin-4-one ring have
also been studied for their stereochemistry. Several studies have been done on these compounds regarding enantiodifferentiation of stereoisomers in the presence of chiral auxiliary [28], separation of enantiomers by chiral HPLC [29, 30], and determination of absolute conformations [31, 32].

It is well known that combinations of two or more heterocyclic scaffolds in one molecule can provide a series of compounds with a broad spectrum of biological activity. Here, we combine thiazolidin-4-one and pyridine-3-carboxamide scaffolds together as part of an ongoing project directed towards the design and synthesis of biologically active nitrogen and sulfur containing heterocyclic compounds [33]. Our research focused on stereochemical investigations on diastereomeric $N$-[2-(aryl)-5-methyl-4-oxo-1,3-thiazolidine-3-yl]-pyridine3 -carboxamides (2a-f) (Figure 1) by one- and two-dimensional NMR techniques. In addition, the analytical chromatographic separation of some derivatives by chiral HPLC has been examined using a chiral column.

## 2. Experimental

2.1. General. $1 \mathrm{D}{ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR spectra of all compounds were recorded on a Varian-Unity Inova 500 spectrometer

Table 1: ${ }^{1} \mathrm{H}$ NMR ( 500 MHz ) data of compounds $2 \mathbf{a}-\mathbf{2 f}$ in DMSO- $d_{6} .{ }^{a}$

| Entry | C-6 methyl | C-5 methine | C-2 methine | CO-NH |
| :---: | :---: | :---: | :---: | :---: |
| 2a | 1.55 (d, $J=7.0 \mathrm{~Hz})$ | $\begin{gathered} 4.13(\mathrm{qd}, J=7.0 \mathrm{~Hz}, 0.97 \mathrm{~Hz}) \\ 4.23(\mathrm{qd}, J=7.0,1.47 \mathrm{~Hz})^{\mathrm{b}} \end{gathered}$ | 5.92 (s) | 10.94 (s) |
| 2b | $\begin{gathered} 1.54(\mathrm{~d}, J=7.0) \\ 1.55(\mathrm{~d}, J=6.8 \mathrm{~Hz}) \end{gathered}$ | $\begin{aligned} & 4.12(\mathrm{q}, J=6.8 \mathrm{~Hz})^{\mathrm{b}} \\ & 4.22(\mathrm{q}, J=6.8 \mathrm{~Hz})^{\mathrm{c}} \\ & \hline \end{aligned}$ | 5.90 (s) | $\begin{aligned} & \hline 10.94(\mathrm{~s}) \\ & 10.95(\mathrm{~s}) \\ & \hline \end{aligned}$ |
| 2c | $\begin{aligned} & 1.55(\mathrm{~d}, J=7.3 \mathrm{~Hz}) \\ & 1.57(\mathrm{~d}, J=7.3 \mathrm{~Hz}) \\ & \hline \end{aligned}$ | $\begin{gathered} 4.15(\mathrm{q}, J=6.8 \mathrm{~Hz})^{\mathrm{b}} \\ 4.25(\mathrm{qd}, J=6.8,1.47 \mathrm{~Hz}) \end{gathered}$ | $\begin{gathered} \hline 6.01(\mathrm{~d}, J=1.47 \mathrm{~Hz}) \\ 6.02(\mathrm{~s}) \\ \hline \end{gathered}$ | $\begin{gathered} 10.99(\mathrm{~s}) \\ 11.01(\mathrm{~s}) \\ \hline \end{gathered}$ |
| 2d | $\begin{aligned} & 1.53(\mathrm{~d}, J=7.3 \mathrm{~Hz}) \\ & 1.55(\mathrm{~d}, J=7.3 \mathrm{~Hz}) \\ & \hline \end{aligned}$ | $\begin{gathered} 4.10(\mathrm{q}, J=7.3 \mathrm{~Hz}) \\ 4.16(\mathrm{qd}, J=7.3,1.47 \mathrm{~Hz})^{\mathrm{b}} \end{gathered}$ | $\begin{gathered} 5.87(\mathrm{~s}) \\ 5.88(\mathrm{~d}, J=1.47 \mathrm{~Hz}) \end{gathered}$ | 10.90 (s) |
| 2 e | $\begin{gathered} 1.54(\mathrm{~d}, J=7.3) \\ 1.55(\mathrm{~d}, J=6.8 \mathrm{~Hz}) \end{gathered}$ | $\begin{gathered} 4.11(\mathrm{q}, J=6.8 \mathrm{~Hz})^{\mathrm{b}} \\ 4.18(\mathrm{qd}, J=6.8,1.46 \mathrm{~Hz}) \end{gathered}$ | $\begin{aligned} & 5.89(\mathrm{~s}) \\ & 5.90(\mathrm{~s}) \end{aligned}$ | 10.97 (s) |
| 2 f | $\begin{gathered} 1.48(\mathrm{~d}, J=7.3) \\ 1.52(\mathrm{~d}, J=6.8 \mathrm{~Hz}) \end{gathered}$ | $\begin{gathered} 4.10(\mathrm{q}, J=7.0 \mathrm{~Hz})^{\mathrm{b}} \\ 4.21(\mathrm{qd}, J=7.0,1.96 \mathrm{~Hz}) \end{gathered}$ | $\begin{gathered} 6.22(\mathrm{~d}, J=1.96 \mathrm{~Hz}) \\ 6.26(\mathrm{~s}) \end{gathered}$ | $\begin{aligned} & 11.04(\mathrm{~s}) \\ & 11.05(\mathrm{~s}) \end{aligned}$ |

${ }^{\mathrm{a}}$ For ${ }^{1} \mathrm{H}$ NMR data of the other protons, see Section 2.
${ }^{\mathrm{b}}$ The signals corresponding to major diastereomer.
${ }^{\text {c }}$ Coupling with C-2 methine was observed as a shoulder.


Figure 1: The synthesized compounds, 2a-f.
operating at 499.7 MHz for ${ }^{1} \mathrm{H}$ and 124.9 MHz for ${ }^{13} \mathrm{C}$, using tetramethylsilane (TMS) as an internal standard. Chemical shifts ( $\delta$ ) were reported in parts per million (ppm). Spectral widths of 14 and 230 ppm were used in ${ }^{1} \mathrm{H}$ and ${ }^{13} \mathrm{C}$ NMR, respectively. The splitting patterns of ${ }^{1} \mathrm{H}$ NMR were designed as follows: s: singlet, d: doublet, q: quartet, qd: quartet of doublets, dd: doublet of doublets, and $m$ : multiplet. NOESY experiment was performed on a Varian-Mercury VX-400BB (spectrometer frequency: 399.98 MHz , temperature: $24^{\circ} \mathrm{C}$, relaxation delay: 2.0 sec , acquisition time: 0.15 sec , number of increments: the number of points in tl: 200, number of points in each FID (t2): 1920, and spectral width: ${ }^{1} \mathrm{H}$ channel; 14 ppm$)$. HMBC experiment was performed on a Varian-Unity Inova 500 spectrometer (spectrometer frequency: 499.7 MHz , temperature: $30^{\circ} \mathrm{C}$, relaxation delay: 1.0 sec , acquisition time: $0.128 \mathrm{sec}, 400$ increments, and spectral width: ${ }^{1} \mathrm{H}$ channel; $14 \mathrm{ppm},{ }^{13} \mathrm{C}$ channel: 230 ppm ). IR analyses were performed on a Shimadzu IR AffinityI FTIR using KBr discs; peaks are reported in $\mathrm{cm}^{-1}$. UV analyses were performed on Shimadzu UV-1601; wavelengths are reported in nm. Liquid chromatography analyses were performed on Shimadzu SCL-10AVP with a diode array detector and using Chiralpak AD column (particle size: $5 \mu \mathrm{~m}$, column size: $250 \times 4.6 \mathrm{~mm}$ ). Eluent was n-hexane: 2 -propanol $(85: 15)(\mathrm{v}: \mathrm{v})$ with a flow rate of $0.9 \mathrm{~mL} \mathrm{~min}^{-1}$. Reactions
were followed by TLC using silica gel $60-\mathrm{F}_{254}$. Elemental analyses were performed on Thermo Finnigan Flash EA 1112 CHNS-932 analyzer. Melting points were recorded using Buchi B-540 melting point apparatus. The mass spectra were obtained using Finnigan LCQ Advantage Max Waters 2695 Alliance Micromass ZQ.
2.1.1. General Procedure for the Preparation of N-[2-(Aryl)-5-methyl-4-oxo-1,3-thiazolidine-3-yl]-pyridine-3-carboxamides. To a suspension of 0.01 mol of aryl $N^{\prime}$-(substituted benzyl-idene)pyridine-3-carbohydrazide (1a-f) in 30 mL dry ben zene was added 2.5 mL ( 0.028 mol ) of 2-sulfanylpropanoic acid. The mixture was refluxed for 6-18 hours using a DeanStark trap. Excess benzene was evaporated in vacuo. The resulting residue was triturated with $\mathrm{NaHCO}_{3}$ solution until $\mathrm{CO}_{2}$ evolution ceased and was allowed to stand refrigerated until solidification. The solid thus obtained was washed with water, dried, and recrystallized from ethanol.

Some spectral and X-ray crystallographic data of compounds $\mathbf{2 a}, \mathbf{2 b}$, and $\mathbf{2 f}$ were reported regardless of stereochemistry in our previously published articles [34-36].
2.1.2. N-[2-(4-Chlorophenyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]-pyridine-3-carboxamide (2a). Diastereomer ratio \% (major/ minor): $54: 46 .{ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{DMSO}-d_{6}\right) \delta: 7.43-7.47$ $(2 \mathrm{H}, \mathrm{m}$, phenyl-H); 7.48-7.50 ( 1 H , m, pyridine-H); 7.52-7.53 $(2 \mathrm{H}, \mathrm{m}$, phenyl-H); 8.04-8.09 ( $1 \mathrm{H}, \mathrm{m}$, pyridine-H); 8.73 $(1 \mathrm{H}, \mathrm{dd}, J=6.3 \mathrm{~Hz}, 1.4 \mathrm{~Hz}$, pyridine-H); $8.84,8.85(1 \mathrm{H}, 2 \mathrm{~d}$, $J=2.9 \mathrm{~Hz}, 1.4 \mathrm{~Hz}$, pyridine-H) [35] (for ${ }^{1} \mathrm{H}$ NMR data of other protons see Table 1). ${ }^{13} \mathrm{C}$-NMR $(125 \mathrm{MHz})\left(\right.$ DMSO- $d_{6}$ ) $\delta(\mathrm{ppm}): 20.6\left(\mathrm{C}-6, \mathrm{CH}_{3}\right) ; 39.8,39.9(\mathrm{C}-5, \mathrm{CH}) ; 60.4,60.6(\mathrm{C}-$ 2, CH); 124.3, 124.4 (C13, CH); 127.9, 128.0 (C9, C); 129.3, 129.4 (C16, 20, CH); 130.4, 130.7 (C17, 19, CH); 134.2, 134.4 (C18, C); 135.9, 136.0 (C14, CH); 137.2, 138.1 (C15, C); 149.1, 149.2 (C10, CH); 153.5, 153.6 (C12, CH); 164.5, 164.6 (C-8, C=O); 172.5, 172.6 ( $\mathrm{C}-4, \mathrm{C}=\mathrm{O}$ ) (for designations of carbons see Figure 3).
2.1.3. $N$-[2-(4-Bromophenyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yll-pyridine-3-carboxamide (2b). Diastereomer ratio \% (major/ minor): $60: 40 .{ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{DMSO}-d_{6}\right) \delta: 7.44-7.46$
( $2 \mathrm{H}, \mathrm{m}$, phenyl-H); 7.49-7.56 (1H, m, pyridine-H); 7.57-7.60 $(2 \mathrm{H}, \mathrm{m}$, phenyl-H); 8.05-8.09 ( 1 H, m, pyridine-H); 8.72-8.73 $(1 \mathrm{H}, \mathrm{m}$, pyridine-H); $8.86,8.87(1 \mathrm{H}, 2 \mathrm{~d}, J=1 \mathrm{~Hz}$, pyridineH) [36] (for ${ }^{1} \mathrm{H}$ NMR data of other protons see Table 1). ${ }^{13} \mathrm{C}-\mathrm{NMR}(125 \mathrm{MHz})\left(\mathrm{DMSO}-d_{6}\right) \delta(\mathrm{ppm}): 20.2\left(\mathrm{CH}_{3}, \mathrm{C}-6\right.$; $60 \%), 20.6\left(\mathrm{CH}_{3}, \mathrm{C}-6 ; 40 \%\right) ; 39.7$ (CH, C-5; 40\%), 39.8 (CH, C-5; 60\%); 60.4 (CH, C-2; 40\%), 60.7 (CH, C-2; 60\%); 122.8 (C, C18; 40\%), 123.1 (C, C18; 60\%); 124.3 (CH, C13; 40\%), 124.4 (CH, C13; 60\%); 127.8 (С, C9; 60\%), 127.9 (C, C9; 40\%); 130.7 (CH, C16, 20; 40\%), 130.9 (CH, C16, 20; 60\%); 132.2 (CH, C17, 19; 40\%), 132.3 (CH, C17, 19; 60\%); 135.9 (CH, C14; 60\%), 136.0 (CH, C14; 40\%); 137.7 (C, C15; 60\%), 138.6 (C, C15; 40\%); 149.1 (CH, C10; 60\%), 149.2 (CH, C10; 40\%); 153.6 (CH, C12; 40\%), 153.7 (CH, C12; 60\%); 164.5 (C=O, C-8; $40 \%$ ), 164.6 (C=O, C-8; 60\%); 172.6 (C=O, C-4; 40\%), 172.7 ( $\mathrm{C}=\mathrm{O}, \mathrm{C}-4 ; 60 \%$ ) (for designations of carbons see Figure 3).
2.1.4. N-[2-(4-Trifluoromethylphenyl)-5-methyl-4-oxo-1,3-thi-azolidin-3-yll-pyridine-3-carboxamide (2c). Diastereomer ratio \% (major/minor): 53:47. White powder ( $2.78 \mathrm{~g}, 73 \%$ ); mp $170.0-173.1^{\circ} \mathrm{C} ;{ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}, \mathrm{DMSO}-d_{6}\right) \delta: 7.49-7.51$ ( $1 \mathrm{H}, \mathrm{m}$, pyridine-H); 7.72-7.78 (4H, m, 2-phenyl-H); 8.05$8.10(1 \mathrm{H}, \mathrm{m}$, pyridine-H); 8.72-8.73 ( $1 \mathrm{H}, \mathrm{m}$, pyridine-H); 8.85, $8.88\left(1 \mathrm{H}, 2 \mathrm{~d}, J=2.0 \mathrm{~Hz}\right.$, pyridine-H) (for ${ }^{1} \mathrm{H}$ NMR data of other protons see Table 1); ${ }^{13} \mathrm{C}-\mathrm{NMR}\left(100 \mathrm{MHz}\right.$, DMSO- $d_{6}$ ) $\delta: 20.2,20.3\left(\mathrm{C}-6, \mathrm{CH}_{3}\right) ; 38.6,39.2(\mathrm{C}-5, \mathrm{CH}) ; 60.1,60.4(\mathrm{C}-$ 2, CH); 124.2, $124.3(\mathrm{C} 13, \mathrm{CH}) ; 124.6\left(\mathrm{CF}_{3}, \mathrm{q}, J=271 \mathrm{~Hz}\right)$; 126.1, 126.2 (C17, 19, CH); 127.6, 127.7 (C9, C); 129.0, 129.4 (C16, 20, CH); 129.8 and $130.0(\mathrm{Cl} 8, \mathrm{C}, \mathrm{q}, J=32 \mathrm{~Hz}) ; 135.8,135.9$ (C14, CH); 143.1, 144.0 (C15, C); 148.9, 149.0 (C10, CH); 153.5, 153.6 (C12, CH); 164.4, 164.5 (C-8, C=O); 172.5, 172.7 (C-4, $\mathrm{C}=\mathrm{O}$ ) (for designations of carbons see Figure 3); IR ( KBr ): $v_{\text {max }}=3143,3037,1732,1676,1620,1595,1544 ; \mathrm{UV}(\mathrm{EtOH})$ : $\lambda_{\max }(\log \varepsilon)=203.2$ (28135), 219.6 (23655), 262.8 (63.68); ESI MS: $m / z=380.08\left([\mathrm{M}-\mathrm{H}]^{-}, 100\right)$; Anal. Calcd. for $\mathrm{C}_{17} \mathrm{H}_{14} \mathrm{~F}_{3} \mathrm{~N}_{3} \mathrm{O}_{2} \mathrm{~S}: \mathrm{C}, 53.54 ; \mathrm{H}, 3.70 ; \mathrm{N}, 11.02 \%$. Found: C, 53.75 ; H, 3.92; N, 10.96\%.
2.1.5. N-[2-(4-Benzyloxyphenyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yll-pyridine-3-carboxamide (2d). Diastereomer ratio \% (major/minor): 80:20. White powder; yield: 3.68 g (88\%); mp $140.4-143.5^{\circ} \mathrm{C} ;{ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}\right.$, DMSO- $d_{6}$ ) $\delta: 5.08$ $\left(2 \mathrm{H}, \mathrm{s}, \mathrm{O}-\mathrm{CH}_{2}-\mathrm{C}_{6} \mathrm{H}_{5}\right) ; 6.99-7.02$ ( $2 \mathrm{H}, \mathrm{m}, ~ 2$-phenyl-H); 7.31-7.35 ( $1 \mathrm{H}, \mathrm{m}$, pyridine-H); 7.37-7.51 ( $7 \mathrm{H}, \mathrm{m}, 2$-phenyl and $\left.-\mathrm{O}-\mathrm{CH}_{2}-\mathrm{C}_{6} \underline{\mathrm{H}}_{5}\right) ; 8.06-8.09(1 \mathrm{H}, \mathrm{m}$, pyridine-H); 8.73 $(1 \mathrm{H}, \mathrm{dd}, J=7.5 \mathrm{~Hz}, 2.0 \mathrm{~Hz}$, pyridine-H); $8.84,8.86(1 \mathrm{H}, 2 \mathrm{~d}$, $J=2.0 \mathrm{~Hz}$, pyridine-H) (for ${ }^{1} \mathrm{H}$ NMR data of other protons see Table 1); ${ }^{13} \mathrm{C}-\mathrm{NMR}\left(125 \mathrm{MHz}, \mathrm{DMSO}-d_{6}\right) \delta: 20.0\left(\mathrm{CH}_{3}\right.$, C-6; 20\%), $20.8\left(\mathrm{CH}_{3}, \mathrm{C}-6 ; 80 \%\right) ; 39.8$ (CH, C-5; 20\%), 39.9 (CH, C-5; 80\%); 60.8 (CH, C-2); $70.0\left(\mathrm{CH}_{2}, \mathrm{C} 21\right) ; 115.5$ (C17, 19, CH); 124.3 (CH, C13; 80\%), 124.4 (CH, C13; 20\%); 128.0 (C9, C); 128.3 (CH, C24, 26; 80\%), 128.4 (CH, C24, 26; 20\%); 128.6 (CH, C25); 129.1 (CH, C23, 27); 130.0 (CH, C16, 20; 80\%), 130.3 (CH, C16, 20; 20\%); 130.6 (C15, C); 135.9 (CH, C14; 20\%), 136.0 (CH, C14; 80\%); 137.5 (C, C22; 20\%), 137.6 (C, C22; 80\%); 149.1 (CH, C10; 20\%), 149.2 (CH, C10; 80\%); 153.6 (C12, CH); 159.6 (C18, C); 164.5 (C-8, C=O); 172.6 (C-4, $\mathrm{C}=\mathrm{O}$ ) (for designations of carbons see Figure 5); IR ( KBr ):
$\nu_{\max }=3473,3163,3066,1710,1672,1606,1591 ; 1244 . \mathrm{UV}$ $(\mathrm{EtOH}): \lambda_{\text {max }}(\log \varepsilon)=204.8$ (59593), 233.2 (280.89), 266.8 (13560). ESI MS: $m / z=418.10\left([\mathrm{M}-\mathrm{H}]^{-}, 100\right)$; Anal. Calcd. for $\mathrm{C}_{23} \mathrm{H}_{21} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~S}: \mathrm{C}, 64.47 ; \mathrm{H}, 5.17 ; \mathrm{N}, 9.81 \%$. Found: C, 64.63; H, 5.06; N, 9.76\%.
2.1.6. N-[2-(3-Methoxyphenyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]-piridine-3-carboxamide (2e). Diastereomer ratio \% (major/minor): 73:27. White powder; yield: 2.24 g (65\%); mp 101.0-105.0 ${ }^{\circ} \mathrm{C}$; ${ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}\right.$, DMSO- $d_{6}$ ) $\delta: 3.74$ ( $3 \mathrm{~h}, \mathrm{~s}, \mathrm{OCH}_{3}$ ); 6.90-6.93 (1H, m, 2-phenyl-H); 7.02-7.04 (2H, m, 2-phenyl-H); 7.27-7.30 ( $1 \mathrm{H}, \mathrm{m}, 2$-phenyl-H); 7.50 $(1 \mathrm{H}, \mathrm{dd}, J=5.3,4.8 \mathrm{~Hz}$, pyridine-H); 8.05-8.08 $(1 \mathrm{H}, \mathrm{m}$, pyridine-H); $8.72(1 \mathrm{H}, \mathrm{dd}, J=7.8,2.0 \mathrm{~Hz}$, pyridine-H); 8.85 (major diastereomer), 8.87 (minor diastereomer) $(1 \mathrm{H}, 2 \mathrm{~d}$, $J=1.9 \mathrm{~Hz}, J=1.9 \mathrm{~Hz}$, pyridine-H) (for ${ }^{1} \mathrm{H}$ NMR data of other protons see Table 1). ${ }^{13} \mathrm{C}$-NMR ( 125 MHz , DMSO- $d_{6}$ ) $\delta: 20.2\left(\mathrm{CH}_{3}, \mathrm{C}-6 ; 73 \%\right), 20.6\left(\mathrm{CH}_{3}, \mathrm{C}-6 ; 27 \%\right) ; 39.8(\mathrm{CH}$, C-5; 27\%), $39.9(\mathrm{CH}, \mathrm{C}-5 ; 73 \%) ; 55.8\left(\mathrm{OCH}_{3}\right) ; 60.9(\mathrm{CH}$, C-2; 27\%), 61.2 (CH, C-2; 73\%); 113.5 (CH, C18; 27\%), 113.8 (CH, C18; 73\%); 115.3 (CH, C16; 27\%), 115.4 (CH, C16; 73\%); 120.4 (CH, C20; 27\%), 120.8 (CH, C20; 73\%); 124.3 (CH, C13; 27\%), 124.4 (CH, C13; 73\%); 127.9 (C, C9; 73\%), 128.0 (C, C9; 27\%); 130.4 (CH, C19; 27\%), 130.5 (CH, C19; 73\%); 136.0 (CH, C14; 73\%), 136.1 (CH, C14; 27\%); 139.8 (C, C15; 73\%), 140.5 (C, C15; 27\%); 149.1 (CH, C10; 73\%), 149.2 (CH, C10; 27\%); 153.6 (CH, C12); 160.1 (C, C17; 73\%), 160.2 (C, C17; 27\%); 164.6 (C-8, C=O); 172.8 (C=O, C-4; 27\%), 172.9 (C=O, C-4; $73 \%$ ) (for designations of carbons see Figure 3); IR ( KBr ): $\nu_{\text {max }}=3487,3176,3076,1707,1670,1610,1591,1546 ; 1260 ; \mathrm{UV}$ $(\mathrm{EtOH}): \lambda_{\max }(\log \varepsilon)=204.0$ (42863), 225.0 (17859), 263.8 (6101); ESI MS: $m / z=342.23$ ([M - H ],$~ 100)$; Anal. Calcd. for $\mathrm{C}_{17} \mathrm{H}_{17} \mathrm{~N}_{3} \mathrm{O}_{3} \mathrm{~S}$ : C, $56.50, \mathrm{H}, 5.30, \mathrm{~N}, 11.63 \%$. Found: C, 56.47; H, 4.77; N, 11.50\%.
2.1.7. N-[2-(2-Nitrophenyl)-5-methyl-4-oxo-1,3-thiazolidin-3-yl]-piridine-3-carboxamide (2f). Diastereomer ratio \% (major/ minor): $52: 48 .{ }^{1} \mathrm{H}-\mathrm{NMR}\left(500 \mathrm{MHz}, ~ D M S O-d_{6}\right) \delta: 7.51$ $(1 \mathrm{H}, \mathrm{dd}, J=4.8 \mathrm{~Hz}, 4.4 \mathrm{~Hz}$, pyridine-H); 7.61-7.65 $(1 \mathrm{H}, \mathrm{m}$, 2-phenyl-H); 7.85-7.90 (2H, m, 2-phenyl-H); 8.04-8.11 (2H, m, 2-phenyl-H and pyridine-H); $8.73(1 \mathrm{H}, \mathrm{dd}, J=8.3 \mathrm{~Hz}$, 2.0 Hz , pyridine-H); $8.71,8.79(1 \mathrm{H}, 2 \mathrm{~d}, J=2.4 \mathrm{~Hz}, J=2.4 \mathrm{~Hz}$, pyridine-H) [34] (for ${ }^{1} \mathrm{H}$ NMR data of other protons see Table 1). ${ }^{13} \mathrm{C}-\mathrm{NMR}(125 \mathrm{MHz})\left(\mathrm{DMSO}-d_{6}\right) \delta(\mathrm{ppm}): 19.0$, 21.9 (C-6, $\mathrm{CH}_{3}$ ); 37.2, 39.2 (C-5, CH); 56.6, 56.7 (C-2, CH); 124.2, 124.3 (C13, CH); 125.6, 125.7 (C9, C); 127.9, 128.0 (C17, CH); 128.3, 128.5 (C20, CH); 130,3, 130.5 (C19, CH); 135.3, 135,4 (C18, CH); 135.5, 135.8 (C15, C); 136.1, 136.2 (C14, CH); 148.1, 148.6 (C16, C); 149.2, 149.3 (C10, CH); 153.5, 153.6 (C12, CH ); 164.7, 164.8 (C-8, C=O); 172.8, 173.2 (C-4, C=O) (for designations of carbons see Figure 3).

## 3. Results and Discussion

3.1. Chemistry. Novel compounds $2 \mathbf{a}-\mathbf{f}$ have been synthesized by the reaction of compounds la-f with racemic ( $\pm$ )-2-sulfanylpropanoic acid in dry benzene (Figure 2).

The structures of the compounds were determined by microanalysis, IR, ${ }^{1} \mathrm{H}$-NMR, ${ }^{13} \mathrm{C}-\mathrm{NMR}, \mathrm{HMBC}$, and ESI


Ar: 4-chlorophenyl, 4-bromophenyl, 4-trifluoromethylphenyl, 4-benzyloxyphenyl, 3-
methoxyphenyl, 2-nitrophenyl
Figure 2: The preparation of compounds 2a-f.


Figure 3: Selected HMBC correlations for 2b.
mass spectrometry. IR spectra of $\mathbf{2 a - f}$ showed common characteristic absorption bands at $3142-3176 \mathrm{~cm}^{-1}(\mathrm{NH}), 1707-$ $1732 \mathrm{~cm}^{-1}$ (thiazolidinone $\mathrm{C}=\mathrm{O}$ ), and $1670-1681 \mathrm{~cm}^{-1}$ ( $\mathrm{NH}-$ $\mathrm{C}=\mathrm{O}$ ) which provided evidence for the ring closure reaction between 1a-f and 2-sulfanylpropanoic acid. Disappearance of the peak at 8 ppm corresponding to $\mathrm{N}=\mathrm{CH}$ proton of $\mathbf{1 a}-$ $\mathbf{f}$ [37] and the observation of C-2 proton of 2a-f at 5.886.30 ppm in the ${ }^{1} \mathrm{H}$-NMR spectra were also taken as the proof of the formation of thiazolidin-4-one ring.

The structure of $\mathbf{2 b}$ was confirmed by the HMBC spectrum in which the correlations of C-8 ( $\left.\delta_{\mathrm{C}} 164.5,164.6 \mathrm{ppm}\right)$ with $\mathrm{H}-10\left(\delta_{\mathrm{H}} 8.86 \mathrm{ppm}\right), \mathrm{H}-14\left(\delta_{\mathrm{H}} 8.07 \mathrm{ppm}\right)$, and $\mathrm{N}-\mathrm{H}$ (H-7) $\left(\delta_{\mathrm{H}} 10.94,10.95 \mathrm{ppm}\right)$; C-4 ( $\left.\delta_{\mathrm{C}} 172.6,172.7 \mathrm{ppm}\right)$ with $\mathrm{H}-5$ ( $\delta_{\mathrm{H}} 4.12,4.22 \mathrm{ppm}$ ) and H-6 ( $\delta_{\mathrm{H}} 1.54,1.55 \mathrm{ppm}$ ); and C-6 ( $\delta_{\mathrm{C}} 20.6,20.2 \mathrm{ppm}$ ) with H-2 ( $\delta_{\mathrm{H}} 5.90 \mathrm{ppm}$ ), H-5 ( $\delta_{\mathrm{H}}$ 4.12, 4.22 ppm ), and H-6 ( $\delta_{\mathrm{H}} 1.54,1.55 \mathrm{ppm}$ ) enabled definite assignment of $\mathrm{CONH}(\mathrm{C}-8)$ and thiazolidinone $\mathrm{C}=\mathrm{O}(\mathrm{C}-4)$ carbons (Figure 3).
3.2. Stereochemical Investigations. Due to the formation of a new stereocenter at C-2, in principle four stereoisomers were expected to form the following: two enantiomeric ( $2 S$ $5 R / 2 R-5 S, 2 S-5 S / 2 R-5 R$ ) and two diastereomeric pairs (2S$5 R / 2 S-5 S, 2 R-5 S / 2 R-5 R$ ) (Figure 4). In fact, compounds 2af were obtained as mixtures of unequal composition of two diastereomers which were differentiated by their ${ }^{1} \mathrm{H}$ NMR spectra (Figure 5). It has been observed that the ratios of the major and minor diastereomers calculated from the integration values of the C-5 methine proton signals were $54 \%: 46 \%, 40 \%: 60 \%, 47 \%: 53 \%, 80 \%: 20 \%, 27 \%: 73 \%$, and $48 \%: 52 \%$ for compounds $2 \mathbf{a}-\mathbf{f}$, respectively. ${ }^{13} \mathrm{C}$ signals at C-2, C-4, C-5, and C-6 positions for compounds $\mathbf{2 b}$ and $\mathbf{2 e}$
also appeared as double peaks in the HMBC spectra due to the formation diastereoisomers (see Section 2). Chiral HPLC of compounds $\mathbf{2 b}$ and $\mathbf{2 c}$ on the Chiralpak AD-H column resulted in four peaks (Figure 6) which further proved the presence of four stereoisomers.

For all diastereomeric compounds (Figure 4), it was observed that C-5 methine proton on the thiazolidinone moiety was coupled with C-6 methyl protons and appeared as two quartets (Table 1, Figure 5). Similarly the signal of C-6 methyl protons was coupled with C-5 methine and observed as two doublets for compounds $\mathbf{2 b - 2 f}$. In all of the ${ }^{1} \mathrm{H}$ NMR spectra of compounds $\mathbf{2 a} \mathbf{- 2 f}$ (except $\mathbf{2 b}$ ) the higher frequency signals of C-5 methine appeared as a quartet of doublets due to the long-range coupling with the C-2 proton. The two diastereotopic C-2 hydrogens could be observed separately only for compounds $\mathbf{2 c} \mathbf{- 2 f}$. Aromatic protons of pyridyl and $\mathrm{C}-2$ aryl rings gave signals between 6.9 and 9.0 ppm . In this region some of the aromatic peaks corresponding to two diastereomers could also be observed separately for all compounds (Figure 5). The N-H proton was observed at around 11 ppm as two singlets with unequal integral ratios for compounds $2 \mathbf{2 b}, 2 \mathbf{c}$, and $\mathbf{2 f}$ and only one singlet for $\mathbf{2 a}, 2 \mathbf{d}$, and $\mathbf{2 e}$.

We have previously elucidated the stereostructures of some oxazolidine derivatives by NOESY experiment [38-40]. The configurations of the major and minor stereoisomers of thiazolidin-4-one derivatives ( $\mathbf{2 a} \mathbf{- 2 f}$ ) were determined by means of ${ }^{1} \mathrm{H}$ NMR and NOESY spectra of compound 2f. The ${ }^{1} \mathrm{H}$ NMR spectrum of $\mathbf{2 f}$ showed that the major diastereomer had its $\mathrm{C}-5$ methine signal (quartet) at a lower frequency ( $4.10 \mathrm{ppm}, J_{\mathrm{H}-5, \mathrm{CH}_{3}-6}=7.0 \mathrm{~Hz}$ ) than the signal of the minor component ( $4.21 \mathrm{ppm}, \mathrm{qd}, J_{\mathrm{H}-5, \mathrm{CH}_{3}-6}=7.0 \mathrm{~Hz}$ $J_{\mathrm{H}-5, \mathrm{H}-2}: 1.96 \mathrm{~Hz}$ ). The signal of C-2 proton of compound 2f was observed as two separate signals ( $\Delta \delta: 0.04 \mathrm{ppm}$ ) corresponding to two diastereomers: a singlet at 6.26 ppm for the major diastereomer and a doublet at $6.22 \mathrm{ppm}\left({ }^{4} J_{\mathrm{H}-2, \mathrm{H}-5}=\right.$ 1.96 Hz ) for the minor diastereomer. The observed longrange coupling constant $\left({ }^{4} J\right)$ of the doublet, which is characteristic of trans protons [41], was consistent with that of the higher frequency quartet of minor diastereomer. Based on these results, the stereochemistry of the minor diastereomer was assigned as $2 S, 5 S$ or $2 R, 5 R$, in which C-2 and C-5 methine protons are trans to each other (Figure 4).

NOESY spectrum for compound 2 f was taken in order to further prove that the stereochemistry of the minor and the major diastereomers was $2 S, 5 S / 2 R, 5 R$ and $2 S, 5 R / 2 R$, $5 S$, respectively (Figure 7). Observation of the cross peaks at


Figure 4: The stereoisomers of compounds 2a-f.


Figure 5: $500 \mathrm{MHz}{ }^{1} \mathrm{H}$ NMR spectrum of compound 2d in DMSO- $d_{6}$. S: solvent.


Figure 6: (a) HPLC chromatogram of compound 2b; (b) HPLC chromatogram of compound 2c. Peaks marked with the same sign belong to enantiomers according to their \% areas. Column: Chiralpak AD-H; eluent: n-hexane: 2-propanol ( $85: 15$ ) (v:v); diode array detector.


2R, 5 S

$\begin{array}{lllllll}4.25 & 4.20 & 4.15 & 4.10 & 4.05 & 4.00 & 3.95\end{array}$

(a)

(c)


2S, $5 S$


(b)

(d)

Figure 7: Selected 2D NOESY correlations for compound 2 f (solvent: DMSO- $d_{6}, 400 \mathrm{MHz}$ ).

Table 2: The configurations of C-2 and C-5 centers of major and minor diastereomers.

| Compounds | Diastereomer <br> ratio, $\%$ | Configurations of C-2 and C-5 <br> Major <br> stereoisomer | Minor <br> stereoisomer |
| :--- | :---: | :---: | :---: |
| 2a | $54: 46$ | $2 S, 5 S$ or $2 R, 5 R$ | $2 S, 5 R$ or $2 R, 5 S$ |
| 2b | $60: 40$ | $2 S, 5 R$ or $2 R, 5 S$ | $2 S, 5 S$ or $2 R, 5 R$ |
| 2c | $53: 47$ | $2 S, 5 R$ or $2 R, 5 S$ | $2 S, 5 S$ or $2 R, 5 R$ |
| 2d | $80: 20$ | $2 S, 5 S$ or $2 R, 5 R$ | $2 S, 5 R$ or $2 R, 5 S$ |
| 2e | $73: 27$ | $2 S, 5 R$ or $2 R, 5 S$ | $2 S, 5 S$ or $2 R, 5 R$ |
| 2f | $52: 48$ | $2 S, 5 R$ or $2 R, 5 S$ | $2 S, 5 S$ or $2 R, 5 R$ |

6.26 ppm and 4.10 ppm in 2D NOESY spectrum indicated the spatial proximity of C-2 and C-5 methine hydrogens of the major diastereomer (Figure 7(a)). Cross peaks at 1.52 ppm and 7.86 ppm also revealed that C-6 methyl and the hydrogens of the aryl ring $[42,43]$ of the major diastereomer are in close proximity (Figure 7(b)). These observations were consistent with the $2 R, 5 S$ or $2 S, 5 R$ configurations. Similarly, for the minor diastereomer cross peaks between the signals of C-6 methyl and C-2 methine hydrogens were observed (Figure 7(c)). A NOESY correlation between C-5 methine and aromatic protons (Figure 7(d)) further confirmed that the configurations of C-2 and C-5 positions of the minor diastereomer were $2 S, 5 S$ or $2 R, 5 R$. Since the spectra of 2a-2f have the feature in common, by analogy, it could be concluded that all the deshielded signals of C-5 methine belong to $2 S, 5 S$ or $2 R, 5 R$ stereoisomer (Table 1). Based on these results, the configurations of C-2 and C-5 centers of the major and minor diastereomers are given in Table 2.

The diastereomeric isomer ratios of compounds $\mathbf{2 b}$ and 2c obtained by the integration of the ${ }^{1} \mathrm{H}$ NMR signals have been found identical with those obtained by HPLC analysis. Therefore, with the knowledge of the configurations of the C2 and C-5 centers of the major and minor diastereomers of $\mathbf{2 b}$ and 2c, the HPLC peaks (Figures 6(a) and 6(b)) marked by " $\phi$ " could be assigned to $2 S, 5 R$ or $2 R, 5 S$ (major) and the others to $2 S, 5 S$ or $2 R, 5 R$ (minor).

In order to determine the reason of the diastereoselectivity of the synthesis, samples of $\mathbf{2 d}$ and $2 \mathbf{e}$ were recrystallized once again from ethanol and the composition of crystals precipitated first was analyzed by NMR. We have found a different composition for $\mathbf{2 d}$ and $\mathbf{2 e}$. Therefore, the different isomer ratios showed that the obvious diastereoselectivity upon recrystallization from ethanol was due to different solubilities of the diastereomeric isomers in ethanol which was observed previously $[29,30,39,40]$ and not related to any remarkable favorable attack during ring closure. Nevertheless fractional crystallization of the product from ethanol allowed for an easy access to diastereomerically enriched $\mathbf{2 b}, \mathbf{2 d}$, and $\mathbf{2 e}$ (Table 2).

## 4. Conclusions

The reaction of aryl $N^{\prime}$-(substituted benzylidene)pyridine-3-carbohydrazide with 2-mercaptopropanoic acid produced
mixtures of unequal composition of two diastereomeric $N$-[2-(aryl)-5-methyl-4-oxo-1,3-thiazolidine-3-yl]-pyridine3 -carboxamide derivatives which were differentiated by ${ }^{1} \mathrm{H}$ NMR spectra. The configurations of C-2 and C-5 stereogenic centers of thiazolidin-4-one ring for the major and the minor diastereomers have been found via one- and twodimensional NMR spectroscopy. Four stereoisomers of compounds $\mathbf{2 b}$ and $\mathbf{2 c}$ were resolved by chiral HPLC.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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