SYNTHESIS AND CHARACTERIZATION OF NEW THIAZOLIDINONES AND 2-OXOPYRROLIDINES DERIVED FROM SCHIFF BASES

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New thiazolidinones and γ-lactams were prepared from mixtures of Schiff base (imine) and thioglycolic acid or phenylsuccinic anhydride, respectively, in moderate yields (52-71 %). The structures of these new thiazolidinones and γ-lactams were established on the basis of the IR, ¹H-NMR, ¹³C-NMR, ¹³C-NMR DEPT and mass spectral data.

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Introduction

Thiazolidinones (Figure 1a) are classified as doubly unsaturated five-membered heterocyclic compounds contain one nitrogen, one sulfur and three carbon atoms including a carbonyl group. Thiazolidinones and their derivatives show a large variety of biological activities such as antibiotic, diuretic, tuberculostatic, organoleptic, antileukemic and antiparasitic.¹ ² As far as literature is concerned, only a few information is available about thiazolidinones and their bioactivity. The chemistry of thiazolidin-4-one ring system is considerable interest because it is the core structure in various pharmaceuticals.

Five-membered ring lactams, which are known as γ-lactams or 2-oxopyrrolidines (Figure 1b), are essential structural motifs in biologically active natural products and used in medicines and approved drugs.³ γ-Lactams have attracted considerable attention in recent years because they are valuable building blocks in the structure of several biologically active molecules.⁴ Substituted γ-lactams, in particular, have potential application in drug synthesis, but the development of the stereoselective synthesis of chiral γ-lactams remains a challenge.⁵ ⁶ Various γ-lactams are components of natural products,⁷ and some biologically important lactams⁸ are obtained from the reaction of imines with phenylsuccinic anhydride.

Experimental part

All solvents were distilled/dried prior to use, whenever this seemed necessary, by standard methods. All solvent extracts were dried over anhydrous sodium sulfate unless otherwise specified.

FT-IR spectra were recorded using a Shimadzu FT-IR spectrophotometer as KBr. The absorption bands of interest are reported and expressed in cm⁻¹.

¹H-NMR spectra were recorded using a Bruker Varian NMR spectrometer (500 MHz). The chemical shift values are expressed in δ(ppm), using tetramethylsilane (TMS) as internal standard and DMSO-d₆ as a solvent. ¹³C-NMR spectra and ¹³C-NMR DEPT spectra were recorded using a Bruker Varian spectrometer (75 MHz). The chemical shift values are expressed in δ(ppm), δ(ppm), using tetramethylsilane (TMS) as internal standard and CDCl₃ as a solvent.

Mass spectra were recorded using a 70 eV HPLC-LCQ Fleet/Thermo Scientific instrument with 5973 type mass selective detector.

General procedure for preparation of imines

In general, the imines (2a-2d) were prepared by reaction the corresponding amines with an aldehyde or a ketone in 40 mL of methanol and 4-6 drops of glacial acetic acid with refluxing the reaction mixtures for 1-5 h under stirring. The progress of the reaction is followed by TLC. After completion the reaction, the solvent was evaporated then the residue was recrystallized from a suitable solvent. The physical data of the prepared imines (2a-2f) are gathered in Table 1.

3-Bromo-2-(pyridin-2-yliminomethyl)phenol (2a)

This compound was prepared by reacting of 2-aminopyridine (0.01 mol, 1 g) with 5-bromo-2-hydroxybenzaldehyde (0.01 mol, 2.4 g). Rf=1.2. Yield = 79.6 %, m.p. = 138-139 °C. IR (KBr disk): 1610 cm⁻¹ (C=N).
3-Bromo-2-(pyridin-3-yl)iminomethyl)phenol (2b)

This compound was prepared by reacting of 3-aminopyridine (0.01 mol, 1 g) with 5-bromo-2-hydroxybenzaldehyde (0.01 mol, 2.4 g). Rf=0.4, yield was 81.6 %, m.p. = 125-126 ºC. IR (KBr disk): 1615 cm⁻¹ (C=N).

4-(5-Aminonaphthaleneylimino)pentan-2-one (2c)

This compound was prepared by reacting of 1,5-diamino naphthalene (0.006 mol, 1 g) with acetylacetone (0.006 mol, 0.63 g, 0.65ml). Rf=0.5,. Yield = 52.6 %, m.p = 90.9 ºC. IR (KBr disk): 1612 cm⁻¹ (C=N).

4-(4-Aminophenylimino)pentan-2-one (2d)

This compound is prepared by reacting of p-phenylenediamine (0.0099 mol, 1 g) with acetylacetone (0.0099 mol, 0.93 g, 0.95 ml). Rf=0.5, yield = 90.9 %, m.p. = 94-95 ºC. IR (KBr disk): 1601 cm⁻¹ (C=N).

4-(Pyridin-3-yl)iminopentan-2-one (2e)

This compound was prepared by reacting of 3-aminopyridine (0.01 mol, 1 g) with acetylacetone (0.01 mol, 1.06 g, 1.09 ml). Rf=2, yield = 93.5 %, m.p = 129-132 ºC. IR (KBr disk): 1676 cm⁻¹ (–N–C=O). 1H NMR (500 MHz, DMSO-d₆, δ, ppm) 3.88 (d, 1H), 4.07 (d, 1H), 1.90 (s, 3H), 2.79 (s, 3H), 4.65 (s, 2H) and 7.55-7.73 (m, 4H). 13C-NMR (75 MHz, CDCl₃, δ, ppm) 38.65, 48.02, 122.03-158.52, 125.95-135.95, 127.89-138.11, 172.13 and 185.88.

3-Bromo-2-(pyridin-3-yl)iminomethyl)phenol (2b)

This compound was prepared by reacting 3b (0.003 mol, 1 g) and (0.003 mol, 0.33 g, 0.25 mL) of thioglycolic acid. Rf=1.2, yield = 71 %, m. p. = 98-99 ºC. IR (KBr disk): 1672 cm⁻¹ (–N=C=O). 1H-NMR (500 MHz, DMSO-d₆, δ, ppm) 3.91(d, 1H), 4.31(d, 1H), 5.61(s, 1H), 6.22-7.51 (m, 3H), 4.29 (s, 2H), 4.60 (s, 2H) and 7.30-7.57 (m, 4H). 13C-NMR (75 MHz, CDCl₃, δ, ppm) 42.96, 52.12, 72.40-74.68, 74.92, 83.90, 119.06, 122.31-130.96, 130.97-141.65, 141.35, 148.55, 152.68, 178.93 and 201.15.

3-(5-Aminonaphthalen-1-yl)-2-methyl-2-(2-oxopropyl)-thiazolidin-4-one (3c)

This compound was prepared by reacting 3e (0.001 mol, 0.41 g) and (0.001 mol, 0.157 g, 0.12 mL) of thioglycolic acid. Rf=0.6, Yield = 69 %, m. p. = 139-140 ºC. IR (KBr disk): 1676 cm⁻¹ (–N–C=O). 1H NMR (500 MHz, DMSO-d₆, δ, ppm) 3.88 (d, 1H), 4.07 (d, 1H), 1.90 (s, 3H), 2.79 (s, 3H), 4.65 (s, 2H), 4.75 (s, 2H) and 7.55-7.73 (m, 4H). 13C-NMR (75 MHz, CDCl₃, δ, ppm) 40.80, 61.85, 18.28,26.78, 36.95, 124.44-156.76, 178.19 and 177.86.

General procedure of γ-lactams (4)

In general the γ-lactam were prepared by reaction the mixture of imines 2a, 2b, 2e and 2f) with phenylsuccinic anhydride in 20 mL of chloroform, then the mixture was refluxed for 1-12 h with stirring. The progress of the reaction was followed by TLC. After completion the solvent was evaporated and the residue was recrystallized from ethanol. The following γ-lactams were prepared:

2-(2-Bromo-6-hydroxyphenyl)-3-(pyridin-3-yl)thiazolidin-4-one (3a)

This compound was prepared by reacting 2a (0.003 mol, 1 g) and (0.003 mol, 0.64 g) of phenylsuccinic anhydride. Rf=0.7, yield = 55 %, m. p. = 121-122 ºC. IR (KBr disk): 1638 cm⁻¹ (–N=C=O), 1727 cm⁻¹ (HO–C=O), 1H NMR (500 MHz, DMSO-d₆, δ, ppm) 3.28 (d, 1H), 3.52 (d, 1H), 4.12 (s, 1H), 6.15-6.70 (m, 5H), 7.63-8.35 (m, 7H), 10.31 (s, 1H) and 11.42 (s, 1H). ¹³C NMR (75 MHz, CDCl₃, δ, ppm) 42.88, 53.02, 59.79, 121.23-151.02, 125.95-135.95, 127.89-138.11, 172.13 and 185.88.
2-(2-Bromo-6-hydroxyphenyl)-5-oxo-3-phenyl-1-(pyridin-3-yl)pyrrolidine-3-carboxylic acid (4b)

This compound was prepared by reacting 2b (0.003 mol, 1 g) and (0.003 mol, 0.64 g) of phenylsuccinic anhydride. Rf=0.6, yield = 61 %, m. p. = 113-114 °C. IR (KBr disk): 1655 cm⁻¹ (–N–C=O), 1719 cm⁻¹ (HO–C=O). ¹H-NMR (500 MHz, DMSO-d₆, δ, ppm) 3.51 (d, 1H), 3.81 (d, 1H), 4.55 (s, 1H), 6.08-6.54 (m, 5H), 7.18-8.02 (m, 7H), 9.98 (s, 1H) and 11.40 (s, 1H). ¹³C NMR (75 MHz, CDCl₃, δ, ppm) 41.56, 51.07, 57.96, 120.53-152.74, 124.45-133.90, 171.25 and 178.25.

2-(2-Bromo-6-hydroxyphenyl)-5-oxo-3-phenyl-1-(pyridin-3-yl)pyrrolidine-3-carboxylic acid (4e)

This compound was prepared by reacting 2e (0.005 mol, 1 g) and (0.005 mol, 1 g) of phenylsuccinic anhydride. Rf=0.5, yield = 68.4 %, m. p. = 168-169 °C. IR (KBr disk): 1602 cm⁻¹ (–N–C=O), 1697 cm⁻¹ (HO–C=O). ¹H NMR (500 MHz, DMSO-d₆, δ, ppm) 3.25 (d, 1H), 3.56 (d, 1H), 1.91 (s, 3H), 2.28 (s, 3H), 3.98 (s, 2H), 6.21-8.08 (m, 9H), and 11.07 (s, 1H). ¹³C NMR (75 MHz, CDCl₃, δ, ppm) 16.02, 27.23, 37.84, 41.12, 52.11, 59.23, 121.66-157.17, 125.33-139.17, 168.94, 180.73 and 206.85.

2-(4-Chlorophenyl)-5-oxo-3-phenyl-1-(pyridin-3-yl)pyrrolidine-3-carboxylic acid (4f)

This compound was prepared by reacting 2f (0.0046 mol, 1 g) and (0.0046 mol, 0.8 g) of phenylsuccinic anhydride. Rf=0.1, yield =55 %, m. p. = 159 -160 °C. IR (KBr disk): 1602 cm⁻¹ (–N–C=O), 1695 cm⁻¹ (HO–C=O). ¹H NMR (500 MHz, DMSO-d₆, δ, ppm) 3.32 (d, 1H), 3.56 (d, 1H), 4.53 (s, 1H), 6.21-6.64 (m, 5H), 7.30-8.20 (m, 7H), and 11.40 (s, 1H). ¹³C NMR (75 MHz, CDCl₃, δ, ppm) 40.13, 51.28, 58.54, 121.67-151.66 124.56-138.54, 169.18 and 183.05.

Results and discussion

The Schiff bases are formed by the condensation of primary amines and an aldehyde or ketone.

A simple synthetic way to prepare the biologically active thiazolidinones⁹,¹⁰ is based on the reaction of imines with thioglycolic acid:

The IR spectra of imines 2a-2f made is characterized by four principal band groups correspond to the stretching vibrations of the aromatic C-H bonds, aliphatic C-H bonds, azomethine bonds (C=N), and aromatic C=C bonds of the and substituted aromatic ring, which occur within the ranges of 3224-3047, 3007-2777, 1638-1610, and 1586-1475 cm⁻¹, respectively.
The $^{13}$C-NMR DEPT spectrum of 3a shows a signal at δ 48 (-) ppm for (CH$_3$), and a signal at δ 38(+) ppm for CH carbon of thiazolidin-4-one ring. There are signals belong to the aromatic region in the range (125-135) (+) ppm and there are signals at δ 122-148 (+) and (177) (+) ppm for the pyridine ring and the amide carbonyl.

γ-Lactams also represent important substructures for the synthesis of biologically relevant compounds in drug discovery$^1$ and natural products$^{12,13}$ The prevalence of small molecules for biological evaluation.$^{17,18}$ Based on these earlier studies, a practical way, the cyclization of imines with phenyl succinic anhydride in chloroform was followed:

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\begin{array}{c}
\text{R}^1\text{N}^+\text{R}^2 + \text{O} \rightarrow \text{R}^1\text{N}=\text{C}^\equiv \text{O} + \text{R}^2\\ \\
\text{CHCl}_3 \text{ reflux}
\end{array}
\]

The mass spectrum of 4a showed the molecular ion peak in 453,455 m/z and important fragmentation peaks at m/z=452, 454 m/z=424, 426, m/z= 382, 384, m/z=354, 356 m/z (these fragments contains two bromine isotopes), and fragments without bromine isotopes at m/z, 223, 181 103 78, 77 and 65. The 1H-NMR spectrum of 2-(2-bromo-6-hydroxyphenyl)-5-oxo-3-phenyl-1-(pyridin-2-yl)pyrrolidine-3-carboxylic acid (4a) (see Electronic Supplementary Information) showed signal at δ 2.57 ppm for the proton of the chiral carbon of thiazolidin-4-one ring. There are two singlet signals at δ 10.31 ppm and 11.42 ppm of phenol and carboxyl hydroxy groups, respectively.

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The 1H-NMR spectrum of 2-(2-bromo-6-hydroxyphenyl)-5-oxo-3-phenyl-1-(pyridin-2-yl)pyrrolidine-3-carboxylic acid (4a) (see Electronic Supplementary Information) showed signal at δ 2.57-2.58 ppm belongs to DMSO-d$_6$ solvent. Two doublet signals are appeared at δ 3.28 ppm and 3.52 ppm, (J=4 Hz) for methylene protons of pyrrolidine ring, a singlet at δ 4.12 ppm for the proton of the chiral carbon (No 2) atom (racemic), and two multiplet signals for the five protons of benzene ring at δ 6.15-6.70 and δ 7.63-8.35 for seven aromatic protons of phenol and pyridine rings, respectively.

Bands characterize the IR spectra of γ-lactams 4a, 4b, 4c, 4d and 4f belong to the stretching vibrations of the carboxylic OH, aromatic C-H, aliphatic C-H, carboxylic carbonyl group, carbonyl amide group, aromatic C=C and substituted aromatic ring in the ranges of 3134-3026, 3064-2742, 1727-1695, 1651-1586, 1602-1536 and 939-809 cm$^{-1}$, respectively.

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