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REACTION OF SCHIFF BASES WITH THIOGLYCOLIC ACID: SYNTHESIS OF THIAZEPINE-1(2H)-ONE AND THIAZOLIDINE-4-ONE COMPOUNDS

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Abstract. Reaction of Schiff bases with thioglycolic acid was set up with the Dean stark apparatus in toluene. The Schiff bases of aniline (**1a)** and *p*-bromoaniline (**2a)** gave 2-(4-hydroxy-3-methoxy-5-nitrophenyl)-3-phenylthiazolidine-4-one (**1b**) and 3-(4-bromophenyl)-2-(4-hydroxy-3-methoxy-5-nitrophenyl)thiazolidine-4-one (**2b)** only; 1-naphthyl amine **(3a)** gave a mixture of 2-(4-hydroxy-3-methoxy-5-nitrophenyl)-1,2-dihydronaphtho[1,2-d][1,3]thiazepine-5(4H)-one (**3b**) and 2-(4-hydroxy-3-methoxy-5-nitrophenyl)-3-(naphthalen-1-yl)thiazolidine-4-one (**3b'**) compounds; 2-naphthyl amine (**4a**) gave 4-(4-hydroxy-3-methoxy-5-nitrophenyl)-4,5-dihydronaphtho[2,1-d][1,3]thiazepine-1(2H)-one (**4b**). The yields of the reaction were moderate to high. The structures of these compounds were elucidated using ^{1}H-NMR and ^{13}C-NMR and mass spectral analysis. The biological test showed that Schiff base **4a** was not active on any bacteria. Thiazolidine-4-one compound **1b** was not active on bacteria and fungi but was active against cancer cell line KB with IC_{50} 21.33 μg/mL. Thiazepine compound **4b** exhibited an activity on *Staphyloccccus aureus* bacterium with IC_{50} 64.00 μg/mL and KB with IC_{50} 11.52 μg/mL.

Keywords: thiazolidine-4-one, thiazepine-1(2H)-one, 2-naphthyl amine, 1-naphthyl amine, Schiff base, thioglycolic acid

1 Introduction

Thiazolidine-4-one is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activity such as anti-mycobacterial, anti-fungal [1,2,3], anticancer [4], anti-tuberculosis, anti-convulsant, anti-inflammatory, antioxidant [5], and analgesic [6] activities. The reaction of a Schiff base with thioglycolic acid is an effective method to synthesize thethiazolidine-4-one ring [4,7].

According to the literature, the synthesis of the thiazepine-1(2H)-one ring was not reported. In this paper, we reported the initial study on using the reaction of a Schiff base with thioglycolic acid to obtain both thiazolidine-4-one ring and thiazepine-1(2H)-one ring (Scheme 1).

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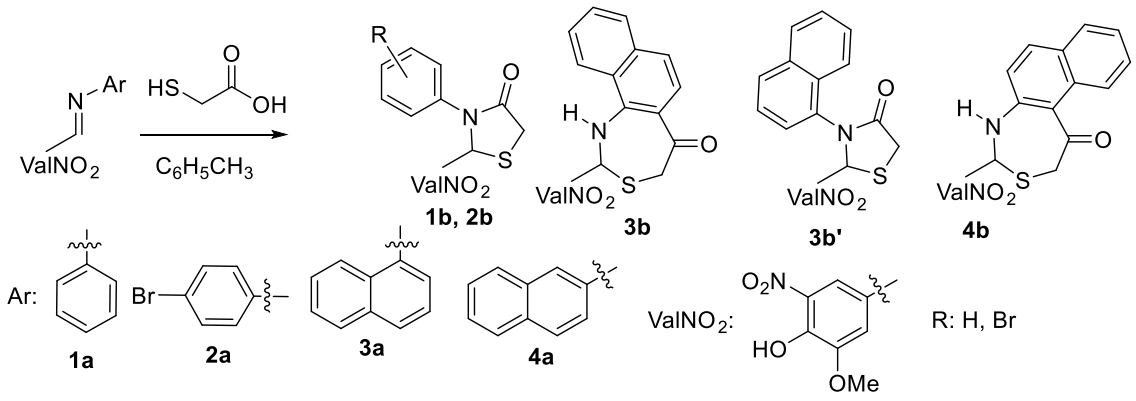


Scheme 1. Synthesis of the target compounds

2 Experimental

2.1 Experimental section

Solvents and other chemicals were purchased from Sigma-Aldrich, Merck and were used as received, unless indicated. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on the Bruker Avance 500 NMR spectrometer in DMSO-d_6. The chemical-shift data for each signal were reported in ppm units. Mass spectra were obtained from Mass Spectrometry Facility of Vietnam Academy of Science and Technology on an LC-MSD-Trap-SL spectrometer.

2.2 Synthetic procedure

General procedure:

A solution of the Schiff base (1 mmol) in toluene (80 mL) was added to thioglycolic acid (0.7 mL; 1.2 eq., 92 g/mol, d=1.32 g/mL). The resulting solution was refluxed with the Dean stark trap. The progress of the reaction was monitored by TLC (eluent: *n*-hexane/ ethyl acetate = 1/1 (v/v)). The mixture was washed with a 3% $NaHCO_3$ solution (3 × 10 mL) and brine. The organic layer was dried over Na_2SO_4 then concentrated *in vacuo*. The products were re-crystallized in ethanol.

Synthesis of 2-(4-hydroxy-3-methoxy-5-nitrophenyl)-3-phenylthiazolidine-4-one (***1b***):

Following the general procedure, the reaction of Schiff base **1a** (272 mg, 1 mmol,272 g/mol) andthioglycolic acid (0.7 mL; 1.2 eq., 92 g/mol, d = 1.32 g/mL) gave **1b** as a yellow powder (250 mg, 346 g/mol, 72 %), mp. 260 °C. IR (cm^{-1}): 3207 (br), 3077, 2977, 2860, 1675, 1622 (shoulder), 1545, 1240, 1110; ^{1}H-NMR (DMSO-d_6, 500 MHz) δ (ppm): 10.53 (br, 1H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.32 (d, *J* = 9.0 Hz, 4H), 7.30 (d, *J* = 2.0 Hz, 1H), 7.16 (m, 1H), 6.51 (s, 1H), 4.07 (dd, *J* = 15.5, 1.5 Hz, 1H), 3.87 (d, *J* = 15.5 Hz, 1H), 3.83 (s, 3H);^{13}C-NMR (DMSO-d_6, 125 MHz) ◎ (ppm): 170.2,

149.8, 142.6, 137.4, 136.3, 130.3, 128.7, 126.6, 125.8, 114.7, 114.4, 62.6, 56.7, 32.6; ESI-MS *m*/*z*: 347 $[C_{16}H_{15}N_2O_5S]^+$ and 345 $[C_{16}H_{13}N_2O_5S]^-$.

Synthesis of 3-(4-bromophenyl)-2-(4-hydroxy-3-methoxy-5-nitrophenyl)thiazolidine-4-one (***2b***)*:*

Following the general procedure, the reaction ofSchiff base **2a** (351 mg, 1 mmol, 351 g/mol) and thioglycolic acid (0.7 mL; 1.2 eq., 92 g/mol, d = 1.32 g/mL) gave **2b** as a pale yellow powder (360 mg, 425 g/mol, 85 %), mp. 201°C; IR (cm^{-1}): 3217 (br), 3078, 2971, 2860, 1676, 1622 (shoulder), 1540, 1242, 1112; ^{1}H-NMR (DMSO-d_6, 500 MHz) δ (ppm): 11.00–10.20 (br, 1H), 7.52 (dd, *J* = 9.0, 2.0 Hz, 2H), 7.46 (d, *J*= 2.0 Hz, 1H), 7.31 (dd, *J* = 8.5, 2.0 Hz, 2H), 7.30 (d, *J* = 2.0 Hz, 1H), 6.50 (s, 1H), 4.04 (dd, *J* = 15.5, 1.5 Hz, 1H), 3.87 (d, *J* = 15.5 Hz, 1H), 3.81 (s, 3H); ^{13}C-NMR (DMSO-d_6, 125 MHz) δ (ppm): 170.3, 149.9, 142.6, 136.7, 136.3, 131.6, 127.7, 126.5, 119.1, 114.8, 114.3, 62.3, 56.8, 32.7; ESI-MS *m*/*z*: 425; 427 $[C_{16}H_{14}BrN_2O_5S]^+$ and 423; 425 $[C_{16}H_{12}BrN_2O_5S]^-$.

Synthesis of 2-(4-hydroxy-3-methoxy-5-nitrophenyl)-1,2-dihydronaphtho[1,2-d][1,3]thiazepine-5(4H)-one (***3b***) *and 2-(4-hydroxy-3-methoxy-5-nitrophenyl)-3-(naphthalen-1-yl)thiazolidine-4-one* (***3b'***)*:*

Following the general procedure, the reaction ofSchiff base **3a** (322 mg, 1 mmol, 322 g/mol) and thioglycolic acid (0.7 mL; 1.2 eq., 92 g/mol, d = 1.32 g/mL) gave a mixture **3b** and **3b'**. The mixture was checked by ^{1}H-NMR spectrum in DMSO-d_6 only (see results and discussion).

Synthesis 4-(4-hydroxy-3-methoxy-5-nitrophenyl)-4,5-dihydronaphtho[2,1-d][1,3]thiazepine-1(2H)-one (***4b***)*:*

Following the general procedure, the reaction ofSchiff base **4a** (322 mg, 1 mmol, 322 g/mol) and thioglycolic acid (0.7 mL; 1.2 eq., 92 g/mol, d = 1.32 g/mL) gave **4b** as a white powder (328 mg, 396 g/mol, 83 %), mp. 170–171 °C. IR (cm^{-1}): 3550–3150 (br), 3231, 3100, 2930, 2869, 1669, 1600 (shoulder), 1542, 1243, 1126; ESI-MS *m*/*z*: 397 $[C_{20}H_{17}N_2O_5S]^+$ and 395 $[C_{20}H_{15}N_2O_5S]^-$.

2.3 Bioactivity test

The bioactivity tests were performed using the Broth dilution method [8]. Compounds **1b**, **4a**, and **4b** were selected for the bacterial test including Gram (+) (*Staphylococcus aureus, Bacillus subtilis, Lactobacillus fermentum*), Gram (–) (*Salmonella enteric, Escherichia coli, Pseudomonas aeruginosa*), fungal test (*Candida albicans*), and cancer cell line KB. All tests were screened in the Laboratory of Applied Biochemistry of Vietnam Academy of Science and Technology.

3 Results and discussion

3.1 Synthesis

The synthesis of the Schiff bases was conducted following the procedure reported by our group [9]. The Schiff bases reacted with thioglycolic acid in the same conditions. The formation of thiazolidine-4-one was explained by Isloor*et al.* [4] in which the attack of the N-nucleophile to the carbonyl group of the carboxylic acid is the key step to form the thiazolidine-4-one ring. In

the cases of Schiff bases **1a** and **2a**, only the formation of the thiazolidine-4-one ring was observed. Meanwhile, the formation of both thiazolidine-4-one and thiazepine-1-one was observed in the case of Schiff base **3a**. In contrast, in the case of Schiff base **4a,** only thiazepine-1-one was formed.

This was the results of different nucleophiles attacking the carbonyl groups as an electrophilic center (E^+) (Fig. 1). If nitrogen attacks the carbonyl group, the reaction will form the thiazolidine-4-one ring (cases **a** and **b**). On the other hand, if C_β (case **b**) or C_α (case **c**) attack the carbonyl group, the reaction will form the thiazepine ring.

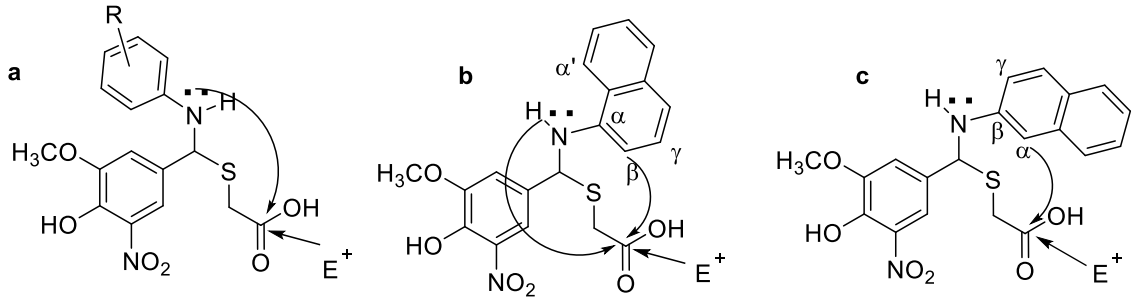
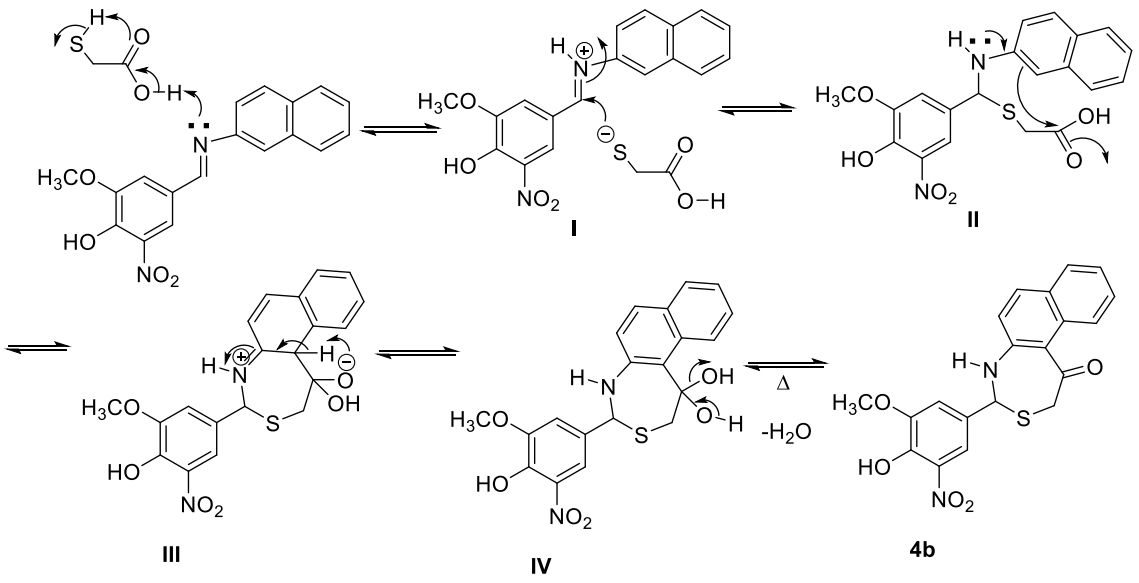


Fig. 1. Nucleophilic addition to the carbonyl group



Scheme 2. Suggested mechanism for **4b**

The mechanism of the formation of thiazepine-1-one **4b** is shown in Scheme 2. The >C=N- group was first activated by a proton of thioglycolic acid to form intermediate **I** that was then attacked by the nucleophilic sulfide to form intermediate **II**. Next, the electrophilic substitution at C_α of the naphthyl group took place to form intermediate **III,** followed by the substitution of a proton at C_α, and finally, a molecule of water was eliminated to form thiazepine-1-one **4b**.

According to the observations above, therefore, the nucleophility of carbons at the ortho position of aniline and vanillin parts might be weaker than that of nitrogen in the cases of **1a** and **2a** (Picture **a** in Fig. 1). So, the nucleophile nitrogen attacking the carbonyl group was preferred to form thiazolidine-4-one only. In the case of **3a**, the mixture of products was recorded by ^{1}H-NMR spectrum since all the purification methods failed. It was found that the ratio of thiazepine/thiazolidine was 2.5/1.0 from the signals of H8 in **3b** and **3b'** (Fig. 2). This result revealed that the formation of thiazepine was more favourable than that of thiazolidine, but both could be formed. In the case of Schiff base **4a**, the C_α was the best nucleophile [10], hence, the attack to the carbonyl group was the easiest way to form thiazepine product **4b** (Fig. 1(c) and Scheme 2).

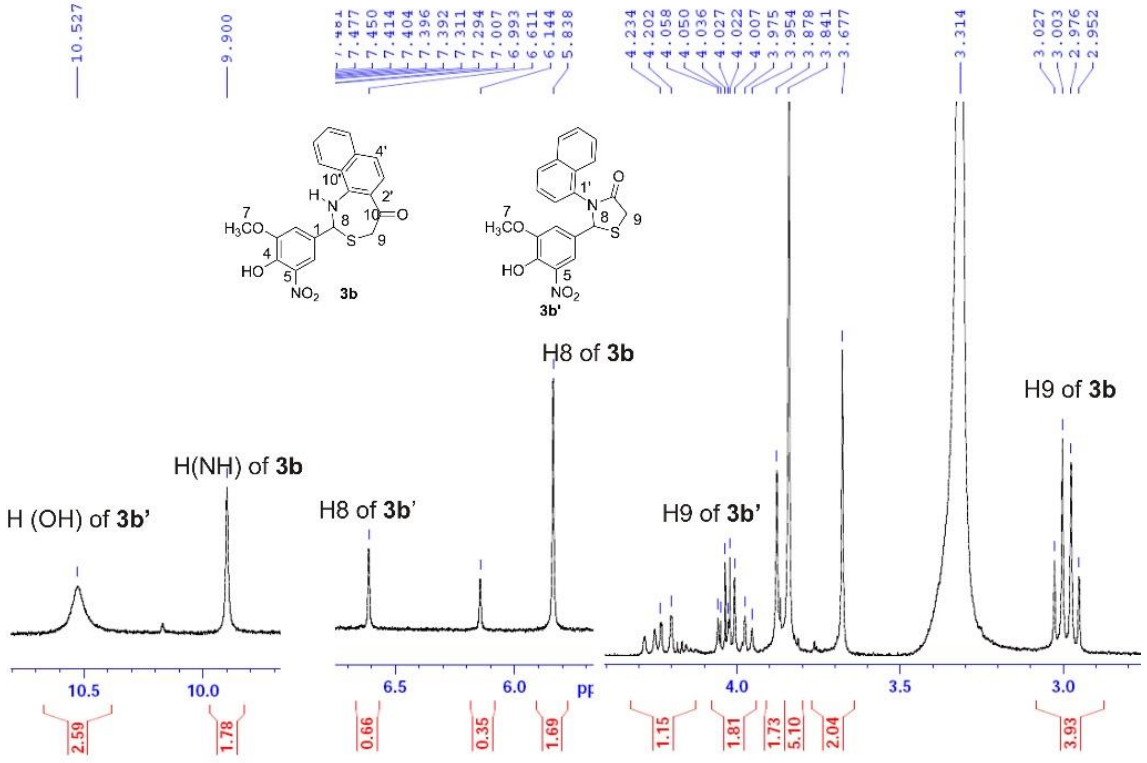


Fig. 2. 1H-NMR spectrum of 3b and 3b'

3.2 Structure determination

The mass spectrometry data of compounds **1b, 2b** and **4b** agreed with the expected structures. For example, +MS of compound **1b** had a peak at *m*/*z* 347 indicating that the molecular formula of **1b** must be $C_{16}H_{14}N_2O_5S$ with a molecular weight of 346 g/mol. +MS of compound **2b** also gave pseudo molecular peaks at *m*/*z* 425 au and m/z 427 audue to isotopes ^{79}Br and ^{81}Br that agreed with molecular formula $C_{16}H_{13}BrN_2O_5S$. +MS of compound **4b** showed a base peak at *m*/*z* 397 au and –MS showed a base peak at *m*/*z* 395 au indicating that the molecular weight of compound **4b** was 396 g/mol matching molecular formula $C_{20}H_{16}N_2O_5S$ (see experimental section).

The IR spectra of all compounds showed the vibration of O–H bond at about 3200 cm^{-1} (br), C–H bond in the region of3100–2800 cm^{-1}; >C=O bonds at about 1669–1675 cm^{-1} and >C=C<,>C=N– bonds in the region of 1500–1610 cm^{-1}. Especially, the IR spectrum of compound **4b** had a vibration at 3231 cm^{-1} indicating the stretching vibration of the N–H bond which was different from that of thiazolidine compounds **1b** and **2b**.

Thiazolidine compounds **1b** and **2b** had quite similar structures. Their ^{1}H-NMR and ^{13}C-NMR showed peaks at 6.51 (s, 1H) for H8, 4.07 (dd, J = 15.5, 1.5 Hz, 1H), and 3.88 (d, J = 15.5 Hz, 1H) for H9 (see numbering on Fig. 3) indicating the formation of the thiazolidine ring. Their ^{13}C-NMR spectra also indicated C8 at 62.2 ppm and C9 at 32.6 ppm. Other signals were assigned in the experiment section.

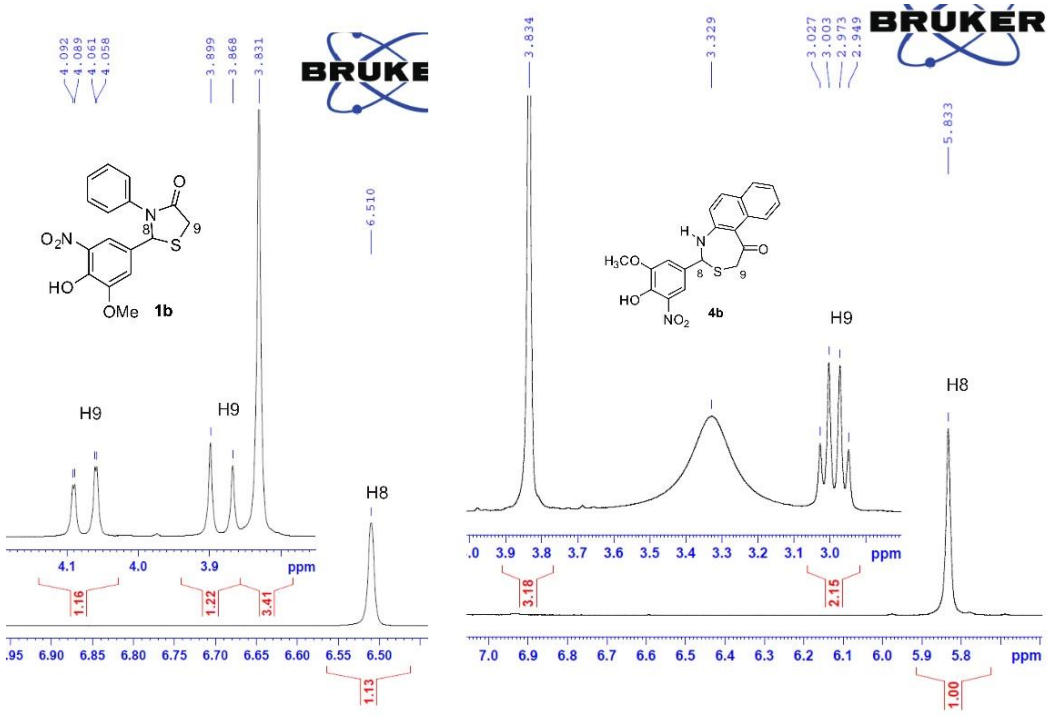


Fig. 3. Comparisonof H8 and H9 of **1b** and **4b**

The ^{1}H-NMR and ^{13}C-NMR spectra of compound **4b** did not have H8 and H9 peaks as in **1b** (Fig. 3). They moved into a stronger field: H8 was a singlet peak at 5.83 ppm that had a cross peak with C6 at 115.9 ppm, C2 at 116.6 ppm, C10′ at 125.5 ppm, C1 at 128.1 ppm, C1′ at 130.7 ppm, C2′ at 132.9 ppm on the HMBC correlation spectrum. Two protons H9 were at 3.00 ppm (d, J = 12.0 Hz) and at 2.96 ppm (d, J = 12.0 Hz) that had the cross peaks with C8 at 46.6 ppm and C10 (>C=O) at 169.0 ppm. In addition, there were 8 aromatic protons belonging to the benzene and naphthalene rings in **4b** compared with 9 in **4a**. This indicated that the electrophilic aromatic substitution happened at C2 (C_α) of the naphthyl group where the richest electron area was and made a seven-member thiazepine ring. Another peak at 9.9 ppm (s, 1H) did not attach to any carbons (no cross peak in HSQC), but it had a cross peak with C9 and C1′, therefore, it had to be the proton on a nitrogen. The other protons and carbons were assigned and shown in Table 1 and Fig. 4. For example, H2 was at 7.36 ppm as a singlet peak correlating with C6 at 115.9 ppm, and so on.

Table 1.NMR data of compound **4b** [δ (ppm), J (Hz)]

^{1}H-NMR		**^{13}C-NMR**		**HSQC**	**HMBC**
–	–	C1	128.1	–	C1x∅
H2	7.36, s	C2	116.6	C2	H2xC3; C2xH6, H8
–	–	C3	149.5	–	C3xH7
–	–	C4	142.5	–	C4xH2
–	–	C5	143.0	–	C5xH6
H6	7.60, s	C6	115.9	C6	C6xH2, H8
H7	3.83, s	C7	56.5	C7	H7xC3 C7x ∅
H8	5.83, s	C8	46.6	C8	H8xC2, C6,C1′, C2′, C10′, C1 C8xH2′, H2, H6, H10′, H9′
H9e H9a	3.00, d, 12.0 2.97, d, 12.0	C9	31.1	C9	H9xC8, C10 C9xH8, H(NH)

^{1}H-NMR		**^{13}C-NMR**		**HSQC**	**HMBC**
–	–	C10	169.0	–	C10xH9
–	–	C1′	130.7	–	C1′xH9′
–	–	C2′	132.9	C2′	C2′xH5′
–	–	C3′	136.5	C3′	C3′xH9′
H4′	7.30, d, 8.0	C4′	123.0	C4′	H4′xC6′, C9′ C4′xH6′
H5′	7.56, d, 7.0	C5′	126.7	C5′	H5′xC7′, C2′ C5′xH7′
H6′	7.58, d, 7.5	C6′	128.7	C6′	H6′xC4′, C8′ C6′xH4′
H7′	7.94, d, 7.0	C7′	127.9	C7′	H7′xC5′,C9′, C8′ C7′xH5′, H6′
–		C8′	132.7	C8′	C8′xH4′
H9′	7.84, d, 9.0	C9′	127.1	C9′	H9′xC1′, C7′ C9′xH7′
H10′	8.03, d, 8.0	C10′	125.5	C10′	H10′xC9′C8′ C10′x∅
H (OH)	3.3 (s, br)	–	–	–	–
H (NH)	9.9, s	–	–	–	H(NH)xC9, C1′
Note: ∅ =none					

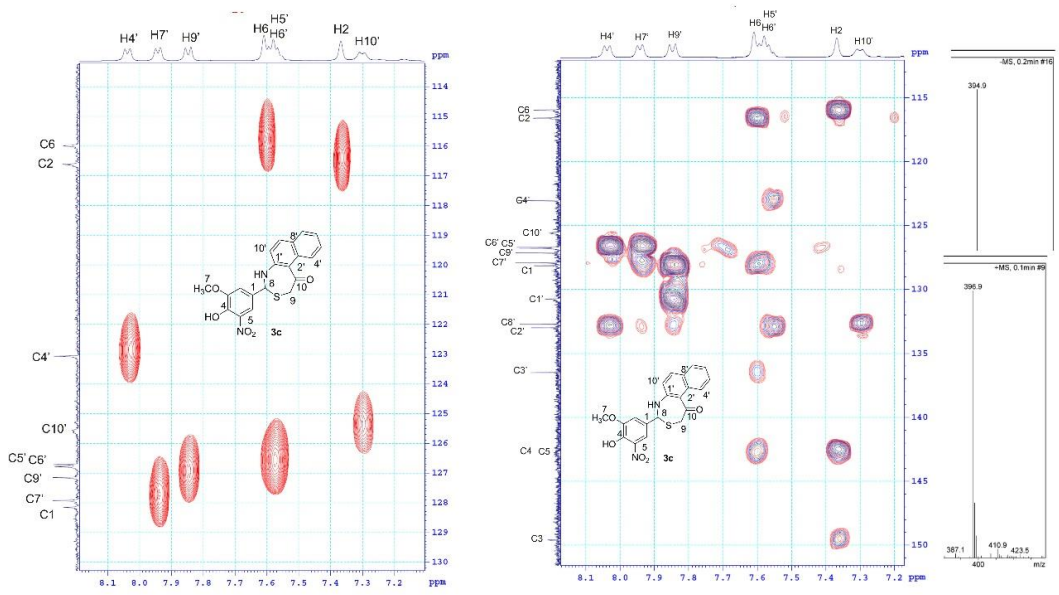


Fig. 4.NMR analysis of compound **4b**: a part of HSQC spectrum (left); a part ofHMBC spectrum (middle) and a part of MS spectrum (right)

3.3 Bioactivity evaluation

The bioactivity test results are shown in Table 2. Schiff base **4a** was not active on any bacteria. Thiazolidine compound **1b** was not active on bacteria and fungi but was active against cancer cell line KB with IC_{50} 21.33 µg/mL.Thiazepine compound **4b** exhibited an activity on *Staphyloccocus aureus* bacteriumwithIC_{50} 64.00 µg/mL and KB with IC_{50} 11.52 µg/mL.

Table 2. Bioactivity test results

Sample	IC_{50}(µg/mL)							
	Gram (+)			Gram (–)			Fungi	KB
	Staphylococccus aureus	*Bacillus subtilis*	*Lactobacillus fermentum*	*Salmonella enterica*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Candida albican*	
1b	>128	>128	>128	>128	>128	>128	>128	**21.33**
4a	>256	>256	>256	>256	>256	>256	>256	–
4b	**64**	>256	>256	>256	>256	>256	>256	**11.52**
Ellipticine	–	–	–	–	–	–	–	0.31

4 Conclusion

Both thiazolidine-4-one and thiazepine-1(2H)-one compounds could be synthesized from the reaction of Schiff bases and thioglycolic acid depending on the aromatic amines. Schiff bases **1a, 2a** containing aniline derivatives gave thiazolidine-4-one compounds **1b, 2b** only with 72–85 % yield; the Schiff base of 1-naphthylamine gave a mixture of thiazolidine-4-one and thiazepine-1(2H)-one compounds with a ratio of 2.5/1 (thiazepine/thiazolidine); 2-naphthyl amine gave thiazepine-1(2H)-one compound **4b** only with 83 % yield. The structures of these compounds were elucidated using IR, MS, 1D NMR and 2D NMR spectral methods. Thiazolidine-4-one compound **1b** was active against KB with IC_{50} 21.33 μg/mL. Thiazepine compound **4b** exhibited an activity on *Staphyloccocus aureus bacterium* withIC_{50} 64.00μg/mL and cancer cell line KB with IC_{50}11.52 μg/mL.

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