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DESIGN, SYNTHESIS, STRUCTURE, AND ANTICANCER OF SOME HYDRAZIDE - HYDRAZONES CONTAINING BENZOTHIAZOLE

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Abstract. Four new hydrazide derivatives containing benzothiazole **T4a**, **T4b**, **T4c,** and **T4d** were designed and synthesized successfully in a 4-step route in high yield. Structures of all samples were determined by ^{1}H NMR, ^{13}C NMR, HMBC, HSQC, and HRMS. All synthesized derivatives were tested for cytotoxic activity on the KB cell line. The results indicated moderate activity with an IC_{50} range of 18 - 52 µg/mL. Among them, compound **T4a** exhibited the highest activity.

Keywords: hydrazide, benzothiazole, *o*-hydroxy benzaldehyde, cytotoxic activity**,** KB cell line.

1. Introduction

A benzothiazole ring plays an important role in pharmacological target diseases, including metabolic diseases [1], cancer [2], anti-inflammatory [3], neurodegeneration, viral diseases, bacterial infections, fibrosis, and thrombosis [4]. Hydrazone-hydrazide derivatives are present in numerous biological molecules and play a significant role in medicine and pharmacology. They exhibit various interesting biological activities, such as antibacterial, antitubercular, antifungal, anticancer, anti-inflammatory, anticonvulsant, and antiviral properties [5]. Therefore, these compounds have attracted significant interest and study from many researchers. Specifically, the compound **4e**, synthesized by Osmaniye *et al.* in 2018, has demonstrated potent anticancer activity, approaching that of cisplatin [6]. The chelating compound **4**, synthesized by Brogyányi *et al*. in 2022, has recently shown high toxicity towards pancreatic cancer cell lines with very high selectivity [7]. Alternatively, compound **7(PAC-1)**, also a hydrazone-hydrazide derivative, has been synthesized and studied by numerous research groups, demonstrating the ability to activate procaspase-3 into caspase-3 [8]. Due to the intriguing properties of the benzothiazole scaffold and the hydrazone-hydrazide moiety, replacing the heterocyclic part of **7(PAC-1)** [8] with the benzothiazole scaffold, as in compound **4e** [6], would result

in a new scaffold containing both hydrazone-hydrazide and benzothiazole. This new scaffold has also attracted significant interest and study from various research groups.

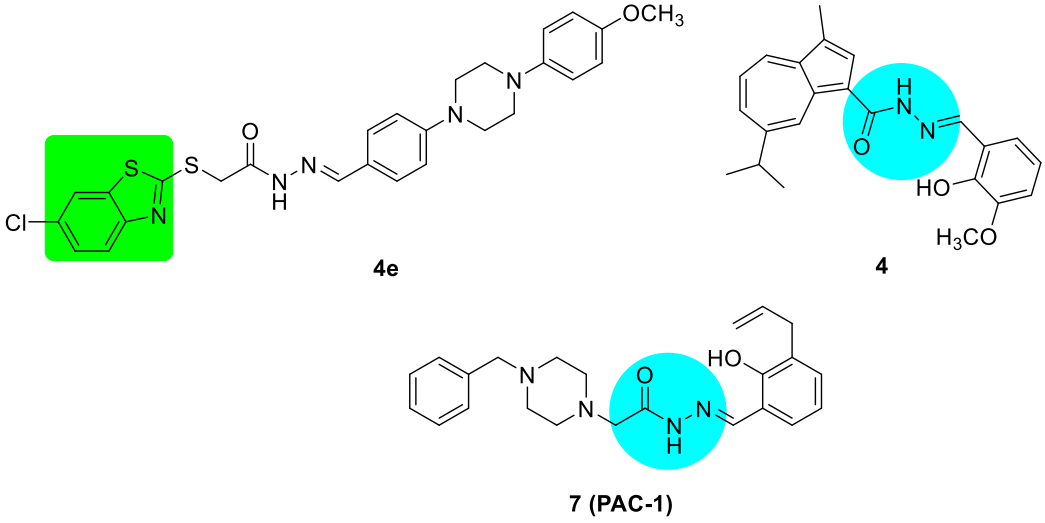


Figure 1. Some examples of hydrazone-hydrazide derivatives [6]-[8]

Recently, hydrazide **1** has been considered as a valuable starting material to make compound **2**. The molecular docking results of compound **2** have shown that the *para*-positioned hydroxyl group on the condensed aldehyde moiety interacts with breast cancer cells, Figure 2 [9]. Therefore, if this hydroxyl group were positioned at the *ortho* position instead of the *para* position, the scaffold would also have the potential for breast cancer activity.

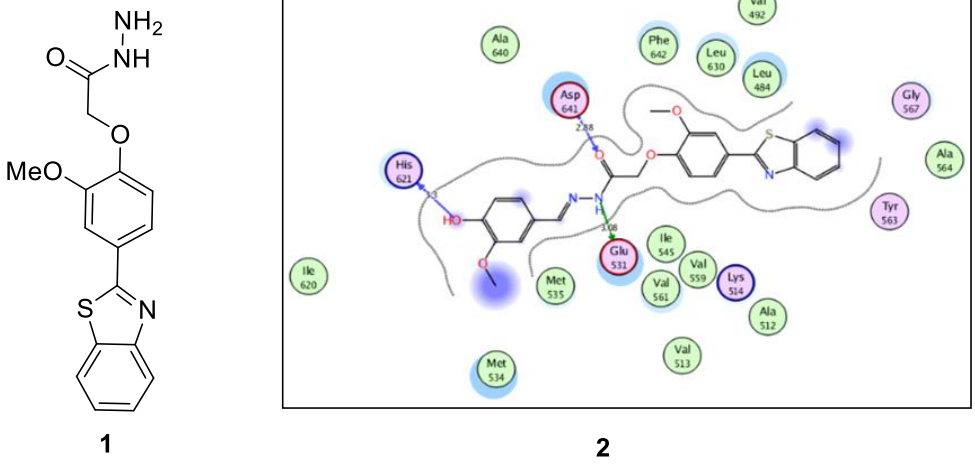


Figure 2. Structure of hydrazide 1 and molecular docking of compound 2 for breast cancer activity [9]

Several previous reports have indicated that the benzothiazole derivatives have exhibited strong cytotoxic activity, particularly with high specificity against the MCF-7 cell line [10]-[13]. In addition, El-Megild's group and colleagues combined their scaffolds to design the target molecules with a C=O as an H-bond acceptor. The synthesized derivatives exhibited excellent anticancer activity against liver and breast cancer cells [14].

Based on this scaffold, the group replaced the amide moiety with a hydrazone-hydrazide moiety, incorporating an ortho-positioned hydroxyl group on the condensed aldehyde ring. This was done to discover new derivatives with even greater activity and potential applications in future medical treatments from compound **1**.

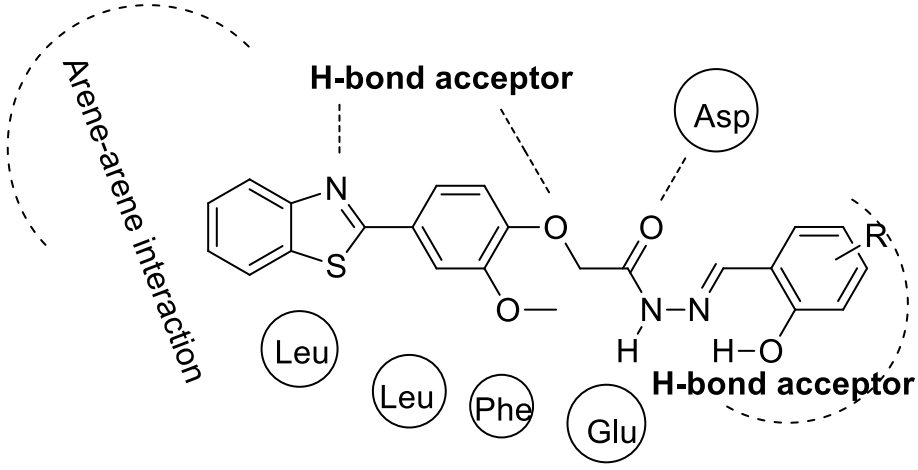


Figure 3. The structure of target molecules T4a, b, c, d[14]

2. Content

2.1. Experiments

2.1.1. Chemicals and equipment

All reagents, solvents, and other chemicals were purchased from commercial sources such as Sigma-Aldrich, Merck Corp, Aladdin, Vietnamese, and Chinese companies and used as received unless indicated. The 1D and 2D NMRs spectra were recorded on the Bruker Avance 600 NMR spectrometer in dimethyl sulfoxide-d6 ($DMSO_{d6}$). Electrolux EMG20K38GWP, made in Vietnam, in 2023, was used to irradiate the condensation reaction.

2.1.2. Synthetic procedure

**** General experimental procedure for the synthesis of benzo[d]thiazole derivative, T4a - T4d***

Step 1: The compound ethyl 2-(4-(benzo[*d*]thiazol-2-yl)-2-methoxyphenoxy)acetate was dissolved in absolute ethanol and stirred in a round-bottomed flask. Subsequently, 5 mL of 80% hydrazone hydrate was slowly added to the flask. The resulting mixture was refluxed at 80 °C for 8 hours. Upon cooling to room temperature, a precipitate formed. The solid was then filtered and washed multiple times with cold ethanol to yield compound **T3** in 80% yield.

Step 2: The mixture consisting of a 2-hydroxybenzaldehyde derivatives (5 mmol) and 2-(4-(benzo[*d*]thiazol-2-yl)-2-methoxyphenoxy)acetohydrazide (**T3**, 1645 mg, 5 mmol) was added to DMF (1 mL) containing a few drops of acetic acid as a catalyst. The reaction was conducted under microwave irradiation using a domestic microwave oven for 7 minutes. Upon completion of the reaction, the crude product was recrystallized in ethanol to obtain compounds **T4a - T4d**.

**** Synthesis of (E)-2-(4-(benzo[d]thiazol-2-yl)-2-methoxyphenoxy)-N'-(2-hydroxy benzylidene)acetohydrazide (T4a)***

Following the general procedure from 2-hydroxybenzaldehyde (610 mg, 5 mmol), 2-(4-(benzo[*d*]thiazole-2-yl)-2-methoxyphenoxy)acetohydrazide (**T3**, 1645 mg, 5 mmol), some drops of HOAc and anhydrous DMF (1 mL) gave 2-(4-(benzo[*d*]thiazol-2-yl)-2-methoxyphenoxy)-*N*'-(2-hydroxybenzylidene)acetohydrazide (**T4a**) (1991 mg, 92%); ^{1}H NMR (600 MHz, DMSO) δ (ppm): 11.91/11.62 (s, 1H), 11.07/10.06 (s, 1H), 8.55/8.36 (s, 1H), 4.83/5.27 (s, 2H), 3.96/3.94 (s, 3H), 8.11/8.10 (d, *J* = 7.8, 1H), 8,05/8.04 (d, *J* = 7.8, 1H), 7.75 (dd, *J* = 6.6, 1.2 Hz, 1H), 7.96/7.72 (dq, *J* = 1.8 Hz, 1H), 7.62/7.58 (dd, *J* = 6.6, 1.8 Hz, 1H), 7.54/7.30 (m, 1H), 7.04/7.13 (d, *J* = 8.4 Hz, 1H), 7.31/7.27 (dq, *J* = 6.6, 1.8 Hz, 1H), 6.94 (m, 1H), 6.89 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (150 MHz, DMSO) δ (ppm): 191.1, 168.3, 167.2, 167.0, 163.9, 157.4, 156.4, 153.6, 153.5, 150.5, 150.1, 149.5, 149.2, 148.3, 141.6, 136.4, 134.4, 134.3, 131.6, 131.3, 129.3, 126.7, 126.6, 126.5, 125.9, 125.2, 125.1, 122.6, 122.5, 122.2, 122.1, 120.8, 120.7, 120.0, 119.5, 119.4, 119.3, 118.6, 117.2, 116.4, 116.2, 114.0, 113.2, 109.9, 109.8, 67.2, 65.2, 55.8, 55.7. HRMS (ESI-TOF) m/z $[M+H]^+$ calcd. for $C_{23}H_{19}N_3O_4S$, 434.1158, found 434.1169.

**** Synthesis of (E)-2-(4-(benzo[d]thiazol-2-yl)-2-methoxyphenoxy)-N'-(3,5-dichloro-2-hydroxybenzylidene)acetohydrazide (T4b)***

Following the general procedure from 3,5-dichloro-2-hydroxybenzaldehyde (950 mg, 5 mmol), 2-(4-(benzo[*d*]thiazol-2-yl)-2-methoxyphenoxy)acetohydrazide (**T3**, 1645 mg, 5 mmol), some drops of HOAc and anhydrous DMF (1 mL) gave 2-(4-(benzo[*d*]thiazol-2-yl)-2-methoxyphenoxy)-*N*'-(3,5-dichloro-2-hydroxybenzylidene)acetohydrazide (**T4b**) (2254 mg, 90%); ^{1}H NMR (600 MHz, DMSO) δ (ppm): 12.3/12.2 (s, 1H), 11.8/10.4 (s, 1H), 8.5/8.3 (s, 1H), 8.1 (dd, *J* = 7.8, 7.8 Hz, 1H), 8.05 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.73/7.70 (s, 1H), 7,61 (d, *J* = 7.4 Hz, 2H), 7.57 (d, *J* = 7.8 Hz, 2H), 7.5 (m, 1H), 7.4 (m, 1H), 7.15/7.08 (d, *J* = 8.4, 8.4, 1H), 5.3/4.9 (s, 1H), 3.97/3.94 (s, 1H). ^{13}C NMR (150 MHz, DMSO) δ (ppm): 168.6, 167.2, 166.9, 164.4, 162.3, 153.6, 153.5, 152.1, 150.8, 150.4, 149.9, 149.4, 149.2, 147.2, 140.3, 134.4, 134.3, 130.4, 130.0, 128.3, 126.8, 126.6, 126.5, 125.9, 125.4, 125.2, 125.1, 123.9, 123.8, 122.9, 122.6, 122.5, 122.4, 122.2, 122.1, 121.5, 120.7, 120.6, 114.1, 113.3, 109.9, 109.8, 67.1, 65.3, 55.8, 55.7, 35.8, 30.8. ESI-MS, $[M+H]^+$, m/z (au)/relative intensity (%): 502.4/100.

**** Synthesis of (E)-2-(4-(benzo[d]thiazol-2-yl)-2-methoxyphenoxy)-N'-(2-hydroxy-4-methoxybenzylidene)acetohydrazide (T4c)***

Following the general procedure from 2-hydroxy-4-methoxybenzaldehyde (760 mg, 5 mmol), 2-(4-(benzo[*d*]thiazol-2-yl)-2-methoxyphenoxy)acetohydrazide (**T3**, 1645 mg, 5 mmol), some drops of HOAc and anhydrous DMF (1 mL) gave 2-(4-(benzo[*d*]thiazol-2-yl)-2-methoxyphenoxy)-*N*'-(2-hydroxy-4-methoxybenzylidene)acetohydrazide (**T4c**) (1967 mg, 85%) ; ^{1}H NMR (600 MHz, DMSO) δ (ppm): 11.48/11.78 (s, 1H), 11.38/10.15 (s, 1H), 8.45/8.26 (s, 1H), 8.12 (t, *J* = 2.4, 8.2 Hz, 1H), 8.04 (t, *J* = 3.6, 7.2 Hz, 1H), 4.81/3.87 (s, 1H), 4.17/3.87 (s, 3H). ^{13}C NMR (150 MHz, MHz, DMSO) δ (ppm): 167.9, 167.2, 167.0, 163.6, 162.2, 161.9, 159.3, 157.9, 153.6, 153.5, 150.5, 150.1, 149.4, 149.1, 148.8, 142.0, 134.8, 134.3, 132.7, 131.0, 128.0, 126.7, 126.5, 126.4, 125.9, 125.2, 125.1, 122.6, 122.5, 122.2, 122.1, 120.8, 120.7, 113.9, 113.1, 112.9, 111.6, 109.9, 106.5, 106.4,

101.1, 100.9, 67.2, 65.2, 55.7, 55.6, 55.3, 55.1. HRMS (ESI-TOF) m/z $[M+H]^+$ calcd. for $C_{24}H_{21}N_3O_5S$, 436.12, found 463.34.

**** Synthesis of (E)-2-(4-(benzo[d]thiazol-2-yl)-2-methoxyphenoxy)-N'-(2-hydroxy-5-methylbenzylidene)acetohydrazide (T4d)***

Following the general procedure from 5-ethyl-2-hydroxybenzaldehyde (680 mg, 5 mmol), 2-(4-(benzo[*d*]thiazol-2-yl)-2-methoxyphenoxy)acetohydrazide (**T3**, 1645 mg, 5 mmol), some drops of HOAc and anhydrous DMF (1 mL) gave 2-(4-(benzo[*d*]thiazol-2 yl)-2-methoxyphenoxy)-*N*'-(2-hydroxy-4-methoxybenzylidene)acetohydrazide (**T4d**) (1832 mg, 82%); ^{1}H NMR (600 MHz, DMSO) δ (ppm): 11.62/11.87 (s, 1H), 10.78/9.89 (s, 1H), 8,08 (dd, J = 2.5, 6.8 Hz, 1H), 8.02 (t, J = 7.2, 2.3 Hz, 1H), 7.74 (s, 1H), 7.53 (s, 1H), 7.34 (s, 1H), 4.78/ 5.38 (s, 1H), 3.95 (s, 3H), 2.2 (s, 3H) . ^{13}C NMR (150 MHz, DMSO) δ (ppm): 168.3, 167.3, 167.1, 163.9, 155.3,154.4, 153.7, 153.6, 150.6, 150.1, 149.5, 149.2, 148.2, 141.8, 134.4, 134.3, 132.3, 132.0, 129.2, 128.0, 126.8, 126.6, 126.5, 125.9, 125.3, 125.2, 122.6, 122.5, 122.2, 122.1, 120.8, 119.6, 118.3, 116.3, 116.1, 114.1, 113.2, 109.9, 109.8, 67.2, 65.3, 55.8, 55.7, 20.1, 19.9. ESI-MS, $[M-H]^-$, m/z (au)/relative intensity (%): 446.1/100.

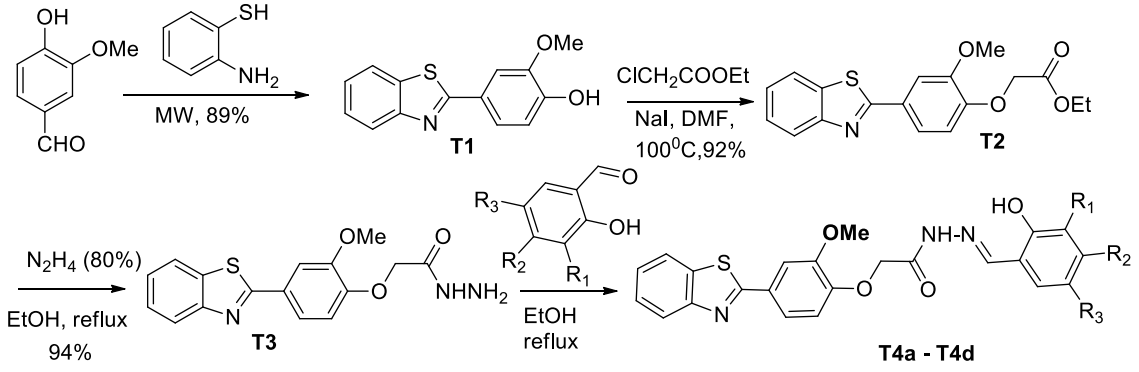
2.1.3. Anticancer evaluation

The cytotoxic activity of all synthesized benzothiazole hydrazide-hydrazones **T4a, b, c, d** was evaluated by the MTT assay method [15]-[17] using Ellipticine as the standard reference. The cytotoxic screening was done in vitro for all derivatives against KB cancer cell lines.

2.2. Results and discussion

2.2.1. Synthesis

Synthesis of **T3** has followed the protocol of Abd El-Meguild *et al* [14]. The condensation of **T3** and *o*-hydroxy belzaldehydes was irradiated with a domestic Electrolux microwave oven in about 90% yield [18], Scheme 1.



R_1, R_2, R_3 = H: **T4a**; R_1, R_3 = Cl, R_2 = H: **T4b**; R_1, R_3 = H, R_2 = OCH_3: **T4c**; R_1, R_2 = H, R_3 = CH_3: **T4d**

Scheme 1. Synthesis of hydrazide- hydrazones T4a - T4d

2.2.2. Structural determination

High-resolution mass spectroscopy of **T4a** matched with the calculation of $C_{23}H_{19}N_3O_4S$ which confirmed the quality of sample; however, the ^{1}H NMR and ^{13}C

NMR spectra of **T4a** were quite complicated because of syn and anti-conformational existence of C=N bond and -NH-CO- group in ratio of 1:1. In addition, intramolecular and intermolecular hydrogen bonding plays an important role in stability of these structures. It might exist in two conformers **I** and **II**. First of all, both structures **I** and **II** were first stabilized by the intramolecular hydrogen bond so the Z isomer was favoured. Secondly, the *o*-hydroxy group classified as phenolic could form strong hydrogen bonding. In which, structure **I** was stabilized by intermolecular, on the other hand, structure **II** was supported by intramolecular hydrogen bonds.

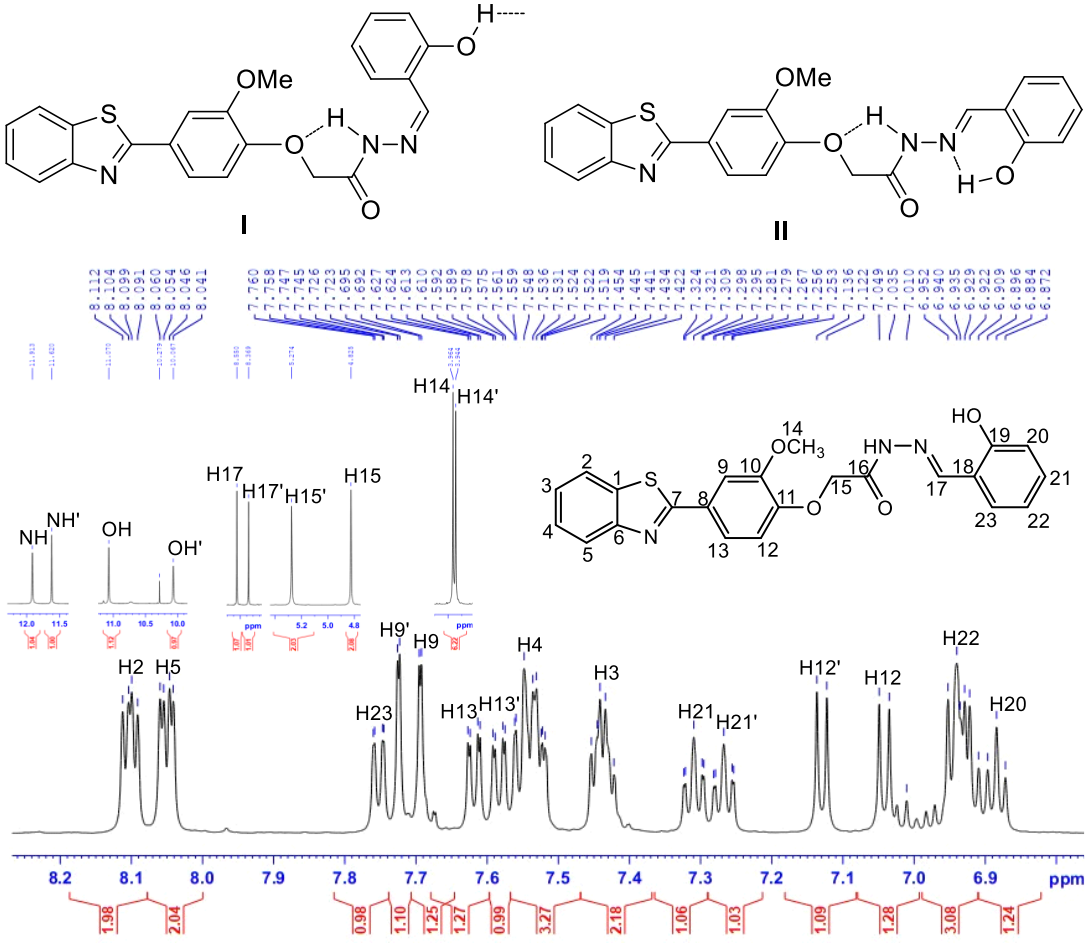


Figure 4. ^{1}H NMR spectrum of hydrazide-hydrazone T4a

In Figure 4, the ^{1}H NMR spectrum of compound **T4a** revealed a singlet at δ = 11.91 and δ = 11.62 ppm of -NH in structures **I** and **II**. The resonance of proton in the hydroxy group also appeared at δ = 11.07 ppm and δ = 10.06 ppm. The group –CH=N– also gives two singlet signals at δ = 8.55 ppm and δ = 8.36 ppm. The singlet signals at δ = 3.96 ppm and δ = 3.94 ppm are assigned to H14. Similarly, the singlet signals at δ = 4.83 ppm and δ = 5.27 ppm are also assigned to H15. The signals of H2 overlap with each other, including doublet signals at δ = 8.11 ppm with J = 7.8 Hz and δ = 8.10 ppm with J = 7.8 Hz. Similarly, the doublet at δ = 8.05 ppm with J = 8.4 Hz and δ = 8.04 ppm with J = 7.8 Hz are attributed to H5. The doublet–doublet signal at δ = 7.75 ppm with J = 6.6, 1.2 Hz

is assigned to H23 due to *meta* interaction with H21. Likewise, the doublet at δ = 7.96 ppm and δ = 7.72 ppm with J = 1.8 Hz are considered from H9 due to meta-interaction with H13. The doublet–doublet at δ = 7.62 ppm and δ = 7.58 ppm with J = 6.6, 1.8 Hz is assigned to H13 due to *meta* interaction with H9. The multiplet at δ = 7.54 ppm and δ = 7.30 ppm is attributed to H3 and H4. The doublet at δ = 7.04 ppm and δ = 7.13 ppm with J = 8.4 Hz is assigned to H12. Due to two *ortho* interactions and one *meta* interaction, the triplet–doublet at δ = 7.31 ppm and δ = 7.27 ppm with J = 6.6, 1.8 Hz is assigned to H21. Similarly, the multiplet signal at δ = 6.94 ppm is assigned to H22. Finally, the doublet signal at δ = 6.89 ppm with J = 7.8 Hz is attributed to H20.

In the ^{13}C NMR spectrum of **T4a**, 48 resonances corresponding to the two sets of C signals from structures **I** and **II** are observed. Based on chemical shift, the signals at δ = 55.73 ppm and δ = 55.76 ppm are assigned to C14. The aromatic carbon signals are determined through cross-peaks in the two-dimensional HSQC and HMBC spectra. In the HSQC spectrum of **T4a**, the direct correlations between C and H atoms reveal the accurate assignments for C2, C3, C4, C5, C9, C12, C13, C14, C15, C17, C20, C21, C22, C23.

Table 1. Cytotoxic activity results

No.	Comp.	Inhibition (%)				IC_{50}
		2(µg/mL)	*8(µg/mL)*	*32(µg/mL)*	*128(µg/mL)*	
1	**T4a**	12	32	63	88	18.32±0.62
2	**T4b**	7	24	57	87	26.93±0.81
3	**T4c**	10	23	42	85	49.82±2.57
4	**T4d**	9	17	40.5	86	52.06±1.80
5	Ellipticine	-	-	-	-	0.44 ± 0,02

All synthesized compounds were tested for their cytotoxic activity against KB cell lines. The results indicated that all synthesized compounds exhibited moderate activity with IC_{50} values ranging from 18.32 to 52.06 µg/mL. Among them, hydrazide-hydrazone derivatives containing only an –OH group in the *ortho* position (**T4a**) showed the highest inhibitory activity (IC_{50} = 18.32 µg/mL). However, when additional substituents such as –Cl was present (**T4b**), the inhibitory activity decreased (IC_{50} = 26.93 µg/mL). Notably, if the substituents were $–OCH_3$ or $–CH_3$ (**T4c** and **T4d)**, the inhibitory activity significantly decreased (IC_{50} = 49 – 52 µg/mL). These results suggest that introducing substituents into the hydrazine scaffold led to a certain degree of reduction in the cytotoxic activity against KB cell lines.

3. Conclusions

Hydrazide-hydrazone derivatives containing benzothiazole were successfully synthesized from vanillin through a simple 4-step process. The procedure utilized straightforward reactions and cost-effective and readily available chemicals, resulting in four new derivatives, **T4a**, **T4b**, **T4c**, and **T4d**, synthesized with very high yields ranging from 86% to 92%. The structures of the synthesized derivatives were accurately determined using modern spectroscopic methods such as ^{1}H NMR, ^{13}C NMR, HMBC,

HSQC, and HRMS. These four synthesized derivatives were also tested for cytotoxic activity on KB cell lines. The results indicated moderate activity with IC_{50} values ranging from 18 to 52 µg/mL. Among them, compound **T4a** exhibited the best anticancer activity in the test.

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