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Synthesis and antimicrobial activities of hydrazones derived from 4-hydroxy-3-nitrobenzaldehyde

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Abstract. Eight hydrazones **7a-h** containing benzo[*d*]thiazole were synthesized in high yield *via* 6 step-route, in which, two out of six steps, benzothiazole cyclization and condensation reaction were carried out with a household microwave oven. Especially, the condensation reaction of *N*-(5-(benzo[*d*]thiazol-2-yl)-2-(2-hydrazinyl-2-oxoethoxy)phenyl) acetamide (**6**) derived from 4-hydroxy-3-nitrobenzaldehyde with aromatic aldehydes was facilitated in up to 94% yield for from 10 to 30 minutes. Structures of these derivatives **7a-h** were elucidated by IR, NMR, and MS analysis. The NMR spectra showed that in solution, hydrazones might exist in two conformations $E_{N\text{-}C(O)}Z_{N\text{-}C(O)}E_{C=N}$ and $Z_{N\text{-}C(O)}Z_{N\text{-}C(O)}E_{C=N}$, the relative ratio of these two conformations was about 3:2. Four compounds **7a**, **7c**, **7e**, **7g** were screened for antimicrobial activities. Compounds **7c**, **7e,** and **7g** exhibited weak antibacterial and antifungal activity against *B. subtillis* and *S.cerevisiae*, *E.coli*, or *P.aeruginosa* at 200 µg/L. The electron donating groups of the aldehyde moiety increased slightly antibacterial activity in the order of hydroxyl (in **7g**), *N*-dimethylamino (in **7e**), and bromo (in **7c**) groups. Nevertheless, the nitro group (in **7a**) decreased the antibacterial activity.

Keywords: 4-hydroxy-3-nitrobenzaldehyde, benzo[*d*]thiazole, hydrazone, microwave.

Classification numbers: 1.1.2, 1.1.3, 1.1.6, 1.2.1.

1. INTRODUCTION

Hydrazones are common compounds in organic synthesis and received great attention from scientists. They show remarkable bioactivities such as: antibacterial, anti-cancer [1, 2], anti-tuberculosis [3, 4], and anti-inflammatory [5]. Hydrazones have been used as drugs for the treatment of some diseases. For example, fivazide is used to treat tuberculosis [6]; glyconiazide is used to treat tuberculosis and cancer [7]; furazolidone and fifuroxazide are oral antibiotic drugs which are used to treat inflammatory bowel disease and enterit caused by bacteria or

protozoan infections [8]. Nitrofurazone is used for the treatment of skin infections caused by skin grafts and nitrofurantoin is used for the treatment of urinary tract infections [9, 10]. The common point of these compounds is that they all contain heterocycles apart from the hydrazone functional group. Therefore, the combination of hydrazone moiety and benzo[*d*]thiazole ring is a useful direction to find new compounds with potentially important biological activities. In this article, we present the synthesis of eight hydrazones containing benzo[*d*]thiazole from 4-hydroxy-3-nitrobenzaldehyde via 6 steps of which 2 steps were facilitated with a household microwave oven.

2. MATERIALS AND METHODS

2.1. Materials

Solvents and chemicals used were purchased from Sigma-Aldrich, Merck Corp, Aladdin, China. NMR spectra were measured on a Bruker Avance 500 instrument in DMSO-d_6; IR spectra were measured on an FT-IR 4700 machine at the Center of Structural Analysis, Vietnam Academy of Science and Technology. The chemical shifts of the signals in the NMR spectrum were performed in relative units of ppm. Some stages in the synthesis process were carried out using a Sharp R21A1 microwave oven (made in Thailand, 2015).

2.2. Methods

The synthesis of 4-(benzo[*d*]thiazol-2-yl)-2-nitrophenol **(2)**, 2-amino-4-(benzo[*d*]thiazol-2-yl)phenol **(3)**, N-(5-(benzo[*d*]thiazol-2-yl)-2-hydroxyphenyl)acetamide **(4)**, ethyl- 2-acetamido-(4-(benzo[*d*]thiazol-2-yl)-phenoxy) acetate **(5)** and *N*-(5-(benzo[*d*]thiazol-2-yl)-2-(2-hydrazinyl-) 2-oxoethoxy)phenyl)acetamide **(6)** was performed according to the literature [11, 12].

Synthesis of hydrazones 7a-h

General procedure

A solution containing compound **6** (290 mg, 0.75 mmol), aromatic aldehydes (0.825 mmol), DMF (3 mL), and acetic acid (3 drops) was irradiated with a household microwave oven at a power level of 400 W. The reaction progress was monitored by TLC in *n*-hexane/ethyl acetate (1/4). The reaction time was about 10 ÷ 30 minutes. The precipitate was filtered and washed with hot alcohol. Products denoted **7a**, **7b**, **7c**, **7d**, **7e**, **7f**, **7g**, and **7h** were obtained with high yield (80 - 94 %).

*Synthesis of (E)-N-(5-(benzo[d]thiazol-2-yl)-2-(2-(2-(4-nitrobenzylidene)hydrazinyl)-2-oxoethoxy)phenyl) acetamide (**7a**)*

Compound **7a** was synthesized from **6** (290 mg, 0.75 mmol) and 4-nitrobenzaldehyde (125 mg, 0.825 mmol) by following the general procedure with a yield of 94 % as a pale-yellow solid, mp. 278 - 279 ^oC. IR (ν, cm^{-1}): 3316, 3080, 2950, 2897, 2843, 1701, 1664, 1600, 1547, 1516, 1484, 1422, 1398, 1344, 1274, 1254, 1221, ^1H NMR (500 MHz, DMSO-d_6), δ_C: *J* (Hz): 12.0/11.9 (s, 1H, NH-a), 9.62/9.47 (s, 1H, NH-b), 8.89/8.75 (s, 1H, H-13), 8.28 (t, *J* = 1.5, 8.5, 2H, H-19/H-21), 8.45/8.16 (s, 1H, H-16), 8.10 (dd, *J* = 8.0, 3.0, 1H, H-2), 8.03 (m, 1H, H-5), 8.01/7.99 (m, 2H, H-18/H-22), 7.82/7.76 (dd, *J* = 8.5, 2.0, 1H, H-9), 7.52 (t, *J* = 8.0, 1H, H-4), 7.42 (td, *J* = 7.5, 2.5, 1H, H-3), 7.23/7.17 (d, *J* = 8.5, 1H, H-10), 5.41/4.93 (s, 2H, H-14), and

2.21/2.18 (s, 3H, H12-b);^{13}C NMR (125 MHz, DMSO-d_6), δ_C: 134.2 (C-1), 122.1 (C-2), 125.2/125.1 (C-3), 126.5 (C-4), 122.5 (C-5), 153.6 (C-6), 167.1 (C-7), 126.1/125.8 (C-8), 123.0 (C-9), 113.7/113.2 (C-10), 150.6 (C-11), 128.8 (C-12), 168.8 (C-12a), 24.0 (C-12b), 119.7 (C-13), 67.1/66.3 (C-14), 169.3/164.3 (C-15), 141.9/145.7 (C-16), 140.2/140.1 (C-17), 128.1/128.2 (C-18), 124.0/123.9 (C-19), 147.9/147.8 (C-20), 124.0/123.9 (C-21), and 128.1/128.2 (C-22). ESI-MS *m/z*: 489.9 $[M+H]^+$.

*Synthesis of (E)-N-(5-(benzo[d]thiazol-2-yl)-2-(2-(2-benzylidenehydrazinyl)-2-oxoethoxy) phenyl) acetamide (**7b**)*

Compound **7b** was synthesized from **6** (290 mg, 0.75 mmol) and benzaldehyde (87.5 mg, 0.825 mmol) by following the general procedure with a yield of 85 % as a milky white solid, mp. 257 - 258 ^oC. ^{1}H NMR (500 MHz, DMSO-d_6), δ_C: *J* (Hz): 11.7/11.6 (s, 1H, NH-a), 9.63/9.50 (s, 1H, NH-b), 8.90/8.75 (s, 1H, H-13), 7.43/7.41 (m, 2H, H-19/H-21), 8.35/8.16 (s, 1H, H-16), 8.11 (dd, *J* = 7.5, 3.5, 1H, H-2), 8.04 (d, *J* = 8.0, 1H, H-5), 7.75 (m, 2H, H-18/H-22), 7.82/7.76 (m, 1H, H-9), 7.52 (t, *J* = 7.5, 1H, H-4), 7.42 (m, 1H, H-3), 7.22/7.18 (d, *J* = 8.5, 1H, H-10), 5.36/4.88 (s, 2H, H-14), and 2.21/2.18(s, 3H, H-12b); ^{13}C NMR (125 MHz, DMSO-d_6) δ_C: 134.2 (C-1), 122.1/122.2 (C-2), 125.2/125.1 (C-3), 126.5/126.4 (C-4), 122.5 (C-5), 153.6 (C-6), 167.1/166.8 (C-7), 126.1/125.8 (C-8), 123.0/123.7 (C-9), 113.8/113.2 (C-10), 150.6/150.4 (C-11), 128.2 (C-12), 168.9/168.8 (C-12a), 24.0 (C-12b), 119.6/120.8 (C-13), 67.1/66.4 (C-14), 169.0/163.8 (C-15), 148.2/144.3 (C-16), 133.9/133.8 (C-17), 128.8/128.7 (C-18), 127.1 (C-19), 130.2/130.0 (C-20), 126.9 (C-21), and 128.8/128.7 (C-22). ESI-MS *m/z*: 445.0 $[M+H]^+$.

*Synthesis of (E)-N-(5-(benzo[d]thiazol-2-yl)-2-(2-(2-(4-bromobenzylidene)hydrazinyl)-2-oxoethoxy)phenyl) acetamide (**7c**)*

Compound **7c** was synthesized from **6** (290 mg, 0.75 mmol) and 4-bromobenzaldehyde (152.6 mg, 0.825 mmol) by following the general method with a yield of 80 % as a white solid, mp. 267 - 268 ^oC. ^{1}H NMR (500 MHz, DMSO-d_6), δ_C: *J* (Hz): 11.43/11.30 (s, 1H, NH-a), 9.64/9.53 (s, 1H, NH-b), 8.90/8.73 (s, 1H, H-13), 7.74 (dd, *J* = 7.0, 2.5, 2H, H-19/H-21), 8.19/7.95 (s, 1H, H-16), 8.11 (dd, *J* = 8.0, 4.0, 1H, H-2), 8.04 (d, *J* = 8.5, 1H, H-5), 7.51 (t, *J* = 8.5, 2H, H-18/H-22), 7.81/7.75 (dd, *J* = 8.5, 2.0, 1H, H-9), 7.51 (m, 1H, H-4), 7.42 (m, 1H, H-3), 7.23/7.16 (d, *J* = 8.5, 1H, H-10), 5.30/4.83 (s, 2H, H-14), and 2.21/2.18 (s, 3H, H-12b);^{13}C NMR (125 MHz, DMSO-d_6), δ_C: 134.2 (C-1), 122.1/122.2 (C-2), 125.2/125.1 (C-3), 126.5/126.4 (C-4), 122.5 (C-5), 153.6 (C-6), 167.1/166.8 (C-7), 125.7 (C-8), 123.0/123.7 (C-9), 113.9/113.2 (C-10), 151.6 (C-11), 128.9 (C-12), 168.8/168.2 (C-12a), 24.0/23.9 (C-12b), 119.5/120.8 (C-13), 67.2/66.5 (C-14), 169.0/163.1 (C-15), 145.1/149.1 (C-16), 121.1 (C-17), 128.5 (C-18), 111.7 (C-19), 151.4 (C-20), 111.7 (C-21), 128.2 (C-22), 30.7 (C-23), and 35.77 (C-24); ESI-MS *m/z*: 522.9, 524.9 $[M+H]^+$.

*Synthesis of (E)-N-(5-(benzo[d]thiazol-2-yl)-2-(2-(2-(4-chlorobenzylidene)hydrazinyl)-2-oxoethoxy)phenyl) acetamide (**7d**)*

Compound **7d** was synthesized from **6** (290 mg, 0.75 mmol) and 4-chlorobenzaldehyde (115 mg, 0.825 mmol) by following the general method with a yield of 80 % as a brown solid, mp. 262 - 263 ^oC. ^{1}H NMR (500 MHz, DMSO-d_6), δ_C: *J* (Hz): 11.73 (s, 1H, NH-a), 9.63/9.48 (s, 1H, NH-b), 8.90/8.75 (s, 1H, H-13), 7.75 (t, *J* = 8.0, 2H, H-19/H-21), 8.34/8.01 (s, 1H, H-16), 8.10 (dd. *J* = 7.5, 3.0, 1H, H-2), 8.03 (d, *J* = 7.5, 1H, H-5), 7.49/7.53 (m, 2H, H-18/H-22),

7.81/7.79 (d, *J* = 1.5, 1H, H-9), 7.51 (m, 1H, H-4), 7.42 (m, 1H, H-3), 7.23/7.17 (d, *J* = 8.5, 1H, H-10), 5.36/4.89 (s, 2H, H1-4), and 2.21/2.18 (s, 3H, H-12b); ^{13}C NMR (125 MHz, DMSO-d_6), δ_C: 134.2 (C-1), 122.1 (C-2), 125.2/125.1 (C-3), 126.5/126.4 (C-4), 122.5 (C-5), 153.6 (C-6), 167.1/166.8 (C-7), 125.8 (C-8), 123.0 (C-9), 113.8/113.2 (C-10), 150.6/150.4 (C-11), 128.2 (C-12), 168.8 (C-12a), 24.0/23.9 (C-12b), 119.6/120.8 (C-13), 67.1/66.4 (C-14), 169.0/163.9 (C-15), 146.9/143.0 (C-16), 132.3/132.8 (C-17), 134.4 (C-18), 128.8/128.9 (C-19), 134.4 (C-20), 128.8/128.9 (C-21), and134.4 (C-22); ESI-MS *m/z*: 478.9, 480.9 $[M+H]^+$.

*Synthesis of (E)-N-(5-(benzo[d]thiazol-2-yl)-2-(2-(2-(4-N,N-dimethylbenzylidene)hydrazinyl)-2-oxoethoxy)phenyl) acetamide (**7e**)*

Compound **7e** was synthesized from **6** (290 mg, 0.75 mmol) and 4-(*N*,*N*-dimethyl)benzaldehyde (123 mg, 0.825 mmol) by following the general method with a yield of 87 % as a light yellow, mp. 265 - 266 ^{o}C. ^{1}H NMR (500 MHz, DMSO-d_6), δ_C: *J* (Hz): 11.43/11.30 (s, 1H, NH-a), 9.64/9.53 (s, 1H, NH-b), 8.90/8.73 (s, 1H, H-13), 7.74 (dd, *J* = 7.0, 2.5, 2H, H-19/H-21), 8.19/7.95 (s, 1H, H-16), 8.11 (dd, *J* = 8.0, 4.0, 1H, H-2), 8.04 (d, *J* = 8.5, 1H, H-5), 7.51 (t, *J* = 8.5, 2H, H-18/H-22), 7.81/7.75 (dd, *J* = 8.5, 2,0, 1H, H-9), 7.51 (m, 1H, H-4), 7.42 (m, 1H, H-3), 7.23/7.16 (d, *J* = 8.5, 1H, H-10), 5.30/4.83 (s, 2H, H-14), and 2.21/2.18 (s, 3H, H-12b); ^{13}C NMR (125 MHz, DMSO-d_6), δ_C: 134.2 (C-1), 122.1/122.2 (C-2), 125.2/125.1 (C-3), 126.5/126.4 (C-4), 122.5 (C-5), 153.6 (C-6), 167.1/166.8 (C-7), 125.7 (C-8), 123.0/123.7 (C-9), 113.9/113.2 (C-10), 151.6 (C-11), 128.9 (C-12), 168.8/168.2 (C-12a), 24.0/23.9 (C-12b), 119.5/120.8 (C-13), 67.2/66.5 (C-14), 169.0/163.1 (C-15), 145.1/149.1 (C-16), 121.1 (C-17), 128.5 (C-18), 111.7 (C-19), 151.4 (C-20), 111.7 (C-21), 128.2 (C-22), 30.7 (C-23), and 35.7 (C-24); ESI-MS *m/z*: 488.0 $[M+H]^+$.

*Synthesis of (E)-N-(5-(benzo[d]thiazol-2-yl)-2-(2-(2-(furan-2-ylmethylene)hydrazinyl)-2-oxoethoxy)phenyl) acetamide (**7f**)*

Compound **7f** was synthesized from **6** (290 mg, 0.75 mmol) and fufural (79.2 mg, 0.825 mmol) by following the general method with a yield of 85 % as a brown solid, mp. 263 - 264 ^{o}C. ^{1}H NMR (500 MHz, DMSO-d_6), δ_C: *J* (Hz): 11.67/11.60 (s, 1H, NH-a), 9.63/9.48 (s, 1H, NH-b), 8.90/8.73 (s, 1H, H-13), 6.94 (m, 1H, H-19), 8.25/7.93 (s, 1H, H-16), 8.11 (dd, *J* = 8.0, 4.0, 1H, H-2), 8.03 (d, *J* = 8.0, 1H, H-5), 7.81/7.74 (dd, *J* = 8.5, 2.0, 1H, H-9), 7.52 (m, 1H, H-4), 7.42 (m, 1H, H-3), 7.21/7.14 (d, *J* = 8.5, 1H, H-10), 7.84 (s, 1H, H-18), 6.63 (m, 1H, H-20), 5.27/4.87 (s, 2H, H-14), and 2.20/2.18 (s, 3H, H-12b);^{13}C NMR (125 MHz, DMSO-d_6), δ_C: 134.2/134.4 (C-1), 122.1/122.2 (C-2), 125.2/125.1 (C-3), 126.5 (C-4), 122.5 (C-5), 153.6 (C-6), 167.1/166.8 (C-7), 125.8/126.1 (C-8), 123.0/123.7 (C-9), 113.8/113.2 (C-10), 150.6/150.4 (C-11), 128.9/128.2 (C-12), 168.8/168.6 (C-12a), 24.0/23.9 (C-12b), 119.6/120.9 (C-13), 67.1/66.2 (C-14), 169.0/163.4 (C-15), 145.1/138.0 (C-16), 114.0/113.9 (C-17), 149.0/148.8 (C-18), 145.3 (C-19), and 112.1 (C-20); ESI-MS *m/z*: 434.9 $[M+H]^+$.

*Synthesis of (E)-N-(5-(benzo[d]thiazol-2-yl)-2-(2-(2-(4-hydroxybenzylidene)hydrazinyl)-2-oxoethoxy)phenyl) acetamide (**7g**)*

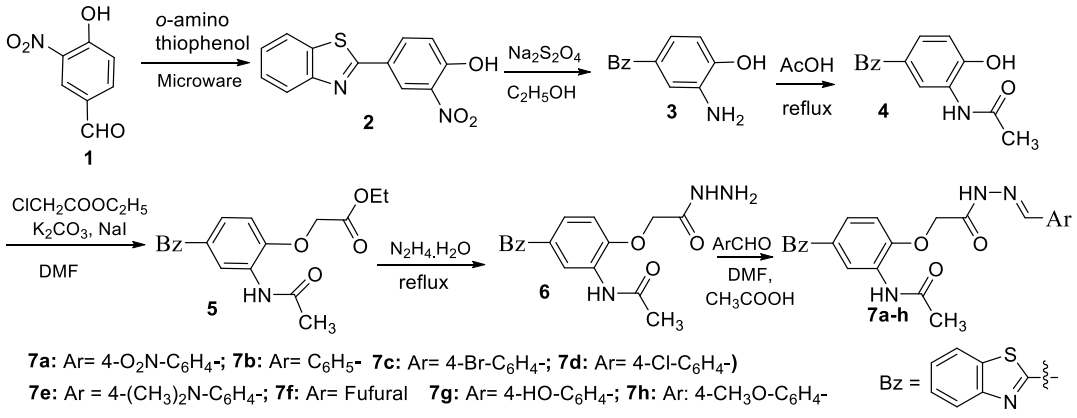
Compound **7g** was synthesized from **6** (290 mg, 0.75 mmol) and 4-hydroxybenzaldehyde (100 mg, 0.825 mmol) by following the general method with a yield of 85 % as a white solid, mp. 257 - 258 ^{o}C. ^{1}H NMR (500 MHz, DMSO-d_6), δ_C: *J* (Hz): 11.51/11.40 (s, 1H, NH-a), 9.63/9.51 (s, 1H, NH-b), 8.90/8.73 (s, 1H, H-13), 6.83 (dd, *J* = 9.0, 2.5, 2H, H-19/H-21),

8.23/7.95 (s, 1H, H-16), 8.11 (dd, *J* = 8.0, 3.5, 1H, H-2), 8.03 (d, *J* = 8.0, 1H, H-5), 7.54 (m, 2H, H-18/H-22), 7.80/7.74 (dd, *J* = 8.5, 2.5, 1H, H-9), 7.52 (m, 1H, H-4), 7.42 (m, 1H, H-3), 7.21/7.16 (d, *J* = 8.5, 1H, H-10), 5.31/4.84 (s, 2H, H-14), 2.20/2.18 (s, 3H, H-12b), and 9.93/9.90 (s, 1H, OH);^{13}C NMR (125 MHz, DMSO-d_6), δ_C: 134.2 (C-1), 122.1/122.2 (C-2), 125.2/125.1 (C-3), 126.5 (C-4), 122.5 (C-5), 153.6 (C-6), 167.1/166.8 (C-7), 125.8/126.1 (C-8), 123.0/123.7 (C-9), 113.9/113.2 (C-10), 150.7/150.5 (C-11), 128.2 (C-12), 168.8/168.5 (C-12a), 24.0/23.9 (C-12b), 119.6/120.8 (C-13), 67.2/66.5 (C-14), 169.0/163.4 (C-15), 148.6/144.6 (C-16), 124.8 (C-17), 128.9 (C-18), 115.6 (C-19), 159.5/159.3 (C-20), 115.6 (C-21), and 128.9 (C-22); ESI-MS *m/z*: 461.0 $[M+H]^+$.

*Synthesis of (E)-N-(5-(benzo[d]thiazol-2-yl)-2-(2-(2-(4-methoxybenzylidene)hydrazinyl)-2-oxoethoxy)phenyl) acetamide (**7h**)*

Compound **7h** was synthesized from **6** (290 mg, 0.75 mmol) and 4-methoxybenzaldehyde (112 mg, 0.825 mmol) by following the general method with a yield of 83 % as a gray solid, mp. 267 - 268 ^{o}C. ^{1}H NMR (500 MHz, DMSO-d_6), δ_C: *J* (Hz): 11.60/11.52 (s, 1H, NH-a), 9.64/9.51 (s, 1H, NH-b), 8.91/8.75 (s, 1H, H-13), 6.99 (m, 2H, H-19/H-21), 8.29/7.99 (s, 1H, H-16), 8.10 (dd, *J* = 8.0, 4.0, 1H, H-2), 8.03 (d, *J* = 8.0, 1H, H-5), 7.66 (m, 2H, H-18/H-22), 7.81/7.75 (dd, *J* = 8.5, 2.0, 1H, H-9), 7.51 (m, 1H, H-4), 7.42 (m, 1H, H-3), 7.23/7.16 (d, *J* = 8.5, 1H, H-10), 5.34/4.86 (s, 2H, H-14), 2.21/2.18 (s, 3H, H-12b), and 3.79 (s, 3H, H-23); ^{13}C NMR (125 MHz, DMSO-d_6), δ_C: 134.3/134.2 (C-1), 122.1 (C-2), 125.1 (C-3), 126.5 (C-4), 122.5 (C-5), 153.6 (C-6), 167.1/166.8 (C-7), 125.8/126.1 (C-8), 123.0/123.7 (C-9), 113.9/113.2 (C-10), 150.6/150.5 (C-11), 128.2/128.9 (C-12), 168.8/168.6 (C-12a), 24.0/23.9 (C-12b), 119.6/120.8 (C-13), 67.2/66.5 (C-14), 169.0/163.5 (C-15), 148.2/144.5 (C-16), 126.4 (C-17), 128.5 (C-18), 114.3 (C-19), 160.9/160.7 (C-20), 114.2 (C-21), 128.9 (C-22), and 55.2 (C-23); ESI-MS *m/z*: 475.0 $[M+H]^+$.

3. RESULTS AND DISCUSSION



Scheme 1. Synthesis of hydrazones from 4-hydroxy-3-nitrobenzaldehyde.

Hydrazones were synthesized following scheme 1. Compound **2** was synthesized following the protocol reported by Mai *et al.* [12]. The conversion of the nitro group to the amino group was accomplished with $Na_2S_2O_4$ under neutral conditions to form compound **3** with an yield of 80 % [10]. Compound **4** was easily obtained from compound **3** in quantitative yield [16]. The

desired ester **5** was obtained by the Williamson ether synthesis method in high yield. The conversion of compound **5** to hydrazide **6** was achieved by refluxing ester **5** with 80 % hydrazine hydrate [12]. The condensation of hydrazide **6** and aldehydes, catalyzed with acetic acid in DMF, was irradiated with a householed microwave oven for 10 ÷ 30 minutes to form hydrazones **7a-h** with a yield of 80 - 94 %.

The structures of the hydrazones were characterized by modern spectroscopic methods, giving satisfactory analytical data consistent with their assigned structures. For example, the IR spectrum of hydrazone **7a** indicates stretching vibration of N-H bonds at 3316 cm^{-1}; C=O at 1701 and 1664 cm^{-1}; C-H at 3080, 2950, 2897, 2843 cm^{-1}; C=C and C=N at 1600, 1547, 1448 cm^{-1}. It also shows a broad peak of N-H in the range of 2500 - 3600 cm^{-1} caused by hydrogen bonding. In addition, the mass spectrum of compound **7a** shows a pseudo molecular peak at *m/z* 489.9 which belongs to ion $[M+H]^+$.

The proton and carbon signals were assigned through the analysis of ^1H, ^{13}C NMR, HSQC, and HMBC spectra [14]. The proton and carbon signals were first determined specifically in compound **7a** and then the signals in the remaining compounds were inferred. In addition, the assignment was also inherited from our previous work [11, 15].

The structure of the hydrazones **7a-h** consists of two parts: the acetohydrazide part (derived from 4-hydroxy-3-nitrobenzaldehyde) and the other from the aromatic aldehydes, thus the resonance signal of the protons and carbons in the acetohydrazide part of all compounds would be nearly the same when spectra were recorded in the same solvent. However, NMR spectra were very complicated due to forming different conformers around the -CO-NH- bonds. For example, it was found that the ^1H NMR spectra of compounds **7a-h** had almost twice the number of resonance signals as the number of non-equivalent protons.

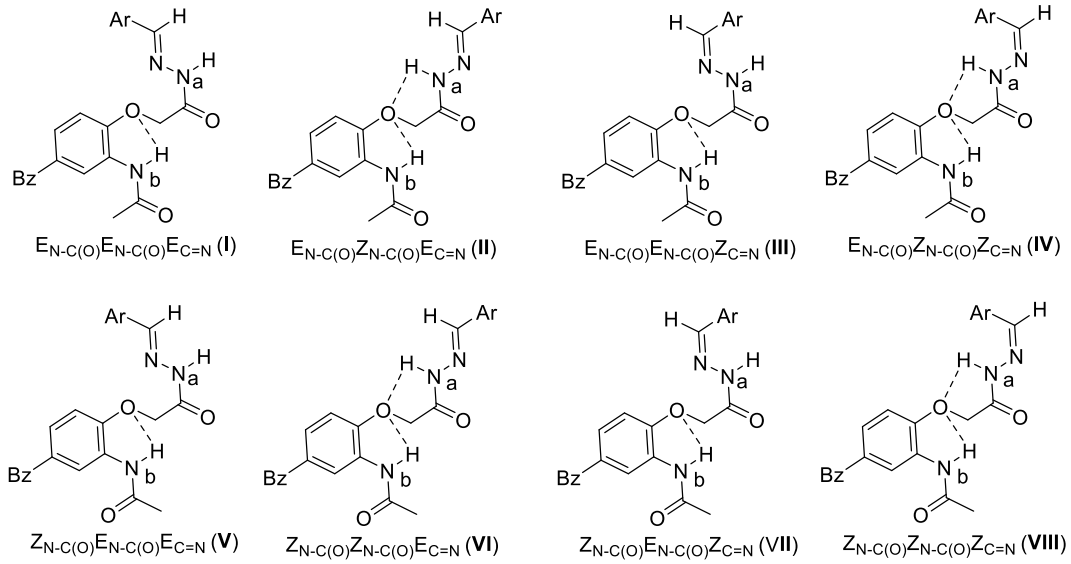


Figure 1. Eight possible isomers of the considered hydrazide-hydrazones.

In the ^1H NMR spectrum of **7a**, NHa exhibited two singlets at δ_H = 12.00 δ_H = 11.95; NHb also had two singlets at δ = 9.62 ppm and δ = 9.47 ppm; H16 appeared as two singlets at δ = 8.45 ppm and δ = 8.11 ppm; H14: two singlets at δ = 5.41 ppm and δ = 4.93 ppm and H12b also gave 2 sets of signals at δ = 2.21 ppm and δ = 2.18 ppm. The total intensity of these two signals

was 1.5 times the actual number of protons, and the relative intensity ratio of these two signals was 3:2. Palla *et al.* reported that the *E*-configuration at the N=CH bond of the similar compound predominated [16]. In DMSO-d6, the major compound was $E_{N—C(O)}E_{N=CH}$ and the minor compound was $Z_{N—C(O)}E_{N=CH}$ [17,18]. In our cases, they were eight possible isomers of the considered hydrazide-hydrazones (Figure 1). It seems that $E_{N—C(O)}Z_{N—C(O)}$ $E_{N=CH}$ and $Z_{N—C(O)}Z_{N—C(O)}$ $E_{N=CH}$ conformers are the most stable due to two intramolecular hydrogen bonds in which $E_{N—C(O)}Z_{N—C(O)}$ $E_{N=CH}$ is more favored than $Z_{N—C(O)}Z_{N—C(O)}$ $E_{N=CH}$ because $Z_{N—C(O)}$ conformer is less stable than $E_{N—C(O)}$ [18].

To assign the signals of carbons, first, based on the correlation peak of H12b (δ = 9.6 ppm), the signal of C12a (δ = 168.8 ppm) was determined; the correlation peak of H14 indicated the signal of C15 at δ = 169.3 ppm/164.3 ppm and the signal of C11 at δ = 150.6 ppm; the correlation peak of NHa inferred the signal of C14 at δ = 67.1 ppm/66.3 ppm and of C16 at δ = 145.7 ppm/141.9 ppm; the correlation peaks of H9 and H13, the signal of C7 could be determined at δ = 167.1 ppm; the correlation peaks of H2 and H4 could determine the signal of C6 at δ = 153.6 ppm; the correlation peaks of H3 and H5 confirmed the signal of C1 at δ = 134.2 ppm. In a similar way, the resonance signals of the remaining carbon atoms of compound **7a** could be determined as described in Section 2 (Materials and Methods).

Hydrazones **7a**, **7c**, **7e**, **7g** were selected for screening antibacterial effects. The results showed that **7a** did not exhibit antibacterial activity; **7c** showed antibacterial activity against *S.cerevisiae*; meanwhile, **7e** showed antibacterial activity against two strains *B.subtillis* and *S.cerevisiae*; **7g** showed antibacterial activity against *E.coli*, *P.aeruginosa* and *S.cerevisiae* with MIC = 200 µg/L (Table 1). It seems that the electron donating groups of the aldehyde moiety increased antibacterial activity in the order of hydroxyl (in **7g**), *N*-dimethylamino (in **7e**), and bromo (in **7c**) groups. In contrast, the nitro group (in **7a**) had no antibacterial effect in our cases

Table 1. Antibacterial activity of compounds **7a**, **7c**, **7e,** and **7g**.

Sample	MIC (µg/L)							
	E. coli	*P. aeruginosa*	*B. subtillis*	*S. aureus*	*A. niger*	*F. oxysporum*	*S. cerevisiae*	*C. albicans*
7g	200	200	-	-	200	-	-	-
7e	-	-	200	-	-	-	200	-
7c	-	-	-	-	-	-	200	-
7a	-	-	-	-	-	-	-	-

4. CONCLUSIONS

Eight hydrazones **7a**, **7b**, **7c**, **7d**, **7e**, **7f**, **7g,** and **7h** were synthesized through 6 steps from 4-hydroxy-3-nitrobenzaldehyde with high yield. The structure of eight hydrazones was accurately determined using IR, NMR, and MS spectroscopy methods. Both $E_{N—C(O)}$ $Z_{N—C(O)}$ $E_{N=CH}$ and $Z_{N—C(O)}$ $Z_{N—C(O)}$ $E_{N=CH}$ conformers were shown on the NMR spectra with a relative ratio of 3:2 in DMSO-d_6. Compound **7g** exhibited weak antibacterial activity against *E. coli*, *P. aeruginosa,* and *A.Niger* with MIC = 200 µg/L; compound **7c** was against *B. subtillis, and S. cerevisiae* with MIC = 200 µg/L; **7c** was against *S. cerevisiae* with MIC = 200 µg/L; whereas, **7a** did not exhibit antibacterial activity.

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