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# Synthesis, Characterization, and Evaluation Of Antibacterial 4H-1,2,4-triazole-5-(4-Bromophenoxymethyl)-3-(4-substitued Benzyl) sulfide

## 4H-1,2,4-triazol-5-(4-Bromofenoksümetil)-3-(4-Substitue Benzil) Sülfidin Sentezi, Karakterizasyonu ve Antibakteriyel Aktivitesinin Değerlendirilmesi

Research Article

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### ABSTRACT

A series of 4H-1,2,4-triazole-5-(4-Bromophenoxymethyl)- 3-(4-substituedBenzyl) sulfide derivative (6a-6g) were designed and prepared. The structures have been confirmed using FT-IR spectroscopy, elemental analysis and <sup>1</sup>H NMR. Antibacterial study was done using gram+ve (*Staphylococcus aureus*, and *Bacillus cereus*) and gram-ve microorganisms (*E. coli*, and *Pseudomonas aeruginosa*) and disc diffusion method for evaluation of antibacterial activity. Compound 6d showed the highest effect, while compound 6a showed the lowest. All of the prepared compound has antibacterial activity, but none of them has higher effect than the standard Cefuroxime.

### Key Words

1,2,4-triazole, antibacterial, sulfide.

### öz

4H-1, 2,4-triazol-5-(4-Bromofenoksümetil)-3-(4-substitue benzil) sülfid türevli serisi (6a-6g) tasarlanmış ve hazırlanmıştır. Yapılar, FT-IR spektroskopisi, elemental analiz ve <sup>1</sup>H NMR kullanılarak doğrulanmıştır. Antibakteriyel çalışmalar, gram+ve (*Staphylococcus aureus* ve *Bacillus cereus*) ve gram mikro organizmalar (*Escherichia coli* ve *Pseudomonas aeruginosa*) kullanılmış ve disk difüzyon yöntemi ile antibakteriyel aktivitenin değerlendirilmesiyle gerçekleştirilmiştir. Bileşik 6a en düşük etkiyi gösterirken, bileşik 6d en yüksek etkiyi göstermiştir. Hazırlanan bileşiklerin hepsi antibakteriyel etkiye sahiptir. Fakat bunların hiçbiri standart Sefuroksime göre daha yüksek etkiye sahip değildir.

### Anahtar Kelimeler

1,2,4-triazol, antibakteriyel, sülfid.

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## INTRODUCTION

In the last years, 1,2,4-triazole has get a growing attention due to its synthetic and biological effects. It represent one of the most important biologically active heterocyclic products [1,2]. There are a lot of research have been made for synthesis and design of 1,2,4- triazole containing compounds with potential biological effects [3-6]. 1,2,4-triazole derivatives has many pharmacological effects. It has antibacterial, [7], Antineoplastic [8], anti fungal [9], anti tubercular [10], anti inflammatory, analgesic [11] antiviral [12], anticonvulsant [13], and antidepressant properties [14].

Triazole nucleus has been founded in many therapeutically active agents. For example, it's present in antiviral (ribavirin), anti migraine (rizatriptane), anxiolytics (estazolam and alprazolam), anti cancer (letrozole and anastrozole), anti fungal (itraconazole and flu console), and anticonvulsant (rufinamide).

Microbial resistance for antibiotics leads to increased demand to get, design and synthesize a new chemicals with antibacterial effects [15]. The highly increased number of immunodeficient people due to chemotherapy, tissue transplantation or HIV, in addition to misuse of the present antibiotics represent the major factors leading to this increment [16,17].

All of the above leads to urgent need to get a new and more active antibacterial agent with less tendency for bacterial resistance, and with fewer side effects [18]. In our research, we tried to get a step forward in synthesis and design a new compound with potential antibacterial effects.

## EXPERIMENTAL

### Synthesis of Ethyl-2-(4-Bromophenoxy) Acetate (2)

4-Bromo-phenol (6.3 g, 28 mmol) was added to a suspension of Sodium hydride (1.1 g, 45 mmol,) in 100 ml DMF with stirring for 30 min. ethylbromoacetate (10 g, 110 mmol,) then added drop with stirring for 3 h. The mixture was poured in crushed ice, extracted with Ethyl acetate. The organic layer washed twice with water, and

dried over magnesium sulfate. The solvent then evaporated under reduced pressure. The crude product then re-crystallized from ethyl acetate/Petroleum ether to get pure Ethyl-2-(4-bromophenoxy) acetate. (Yield: 69%).

IR spectral data of compound (2): Aromatic Ar-H (3055  $\text{cm}^{-1}$ ), aliphatic- $\text{CH}_2$ - (2921  $\text{cm}^{-1}$ ) and  $>\text{C}=\text{O}$  of  $-\text{COOEt}$  (1659  $\text{cm}^{-1}$ ).

### Synthesis of 2-(4-Bromophenoxy) Acetohydrazide (3)

A mixture of hydrazine hydrate (2 g , 40 mmol) and compound (2) (6.5 g, 25 mmol) in ethanol (75 ml) was refluxed for 16 h. The mixture then cooled to room temperature and filtered to obtained a solid precipitate, which was washed with cold ethanol and dried under vacuum to get compound (3). (Yield: 76%).

IR spectral data of compound (3):  $\text{NH}_2$  (3422  $\text{cm}^{-1}$ );  $\text{NH}$  (3123  $\text{cm}^{-1}$ ); Aromatic Ar-H (3062  $\text{cm}^{-1}$ ); aliphatic  $-\text{CH}_2-$ , (2928  $\text{cm}^{-1}$ ) and  $>\text{C}=\text{O}$  of  $-\text{CO}-\text{NH}-$  (1647  $\text{cm}^{-1}$ ).

### Synthesis of 1-(2-(4-Bromophenoxy)acetyl) Thiosemicarbazide (4)

Potassium thiocyanate (9.72 g, 100 mmol) was added to a stirred solution of compound (3) (4.9 g, 20 mmol) in  $\text{H}_2\text{O}$  (30 ml) and HCl (7 ml). The reaction mixture then heated to 90°C in water bath for 5 h. The mixture was cooled to room temperature, diluted with 30 ml of water and filtered. The solid precipitate obtained was dried under vacuum pressure to get compound (4) (Yield: 69%).

IR spectral data of compound (4):  $\text{NH}_2$  (3422  $\text{cm}^{-1}$ );  $\text{NH}$  (3133  $\text{cm}^{-1}$ ); Aromatic Ar-H (3061  $\text{cm}^{-1}$ ); aliphatic  $\text{CH}_2-$  (2928  $\text{cm}^{-1}$ );  $>\text{C}=\text{O}$  of  $-\text{CONH}-$  (1645  $\text{cm}^{-1}$ ); N-N (1552  $\text{cm}^{-1}$ ) and C-S (1130  $\text{cm}^{-1}$ ).

### Synthesis of 5-(4-Bromophenoxy)methyl)-2,4-Dihydro-1,2,4-Triazole-3-Thione (5)

1-(2-(4-bromophenoxy)acetyl) thiosemicarbazide (4) (0.92 g, 3 mmol) was dissolved in a saturated solution of  $\text{K}_2\text{CO}_3$  (70.0 ml) and stirred at room temperature for 48 h. The reaction mixture filtered and acidified with 2 N HCl. The mixture then filtered and the solid obtained was dried

under vacuum to get compound (5). (Yield: 76%).

IR spectral data of compound (5): NH (3133  $\text{cm}^{-1}$ ); Aromatic Ar-H (3061  $\text{cm}^{-1}$ ); aliphatic  $-\text{CH}_2-$  (2930  $\text{cm}^{-1}$ );  $> \text{C-N}$ , (1599  $\text{cm}^{-1}$ ); N-N (1615  $\text{cm}^{-1}$ ) and C-S (1140  $\text{cm}^{-1}$ ).

**Synthesis of 4H-1,2,4-Triazole-5-(4-Bromophenoxyethyl)-3-(4-Substituted Benzyl) Sulfide (6a-g)**

To a solution of potassium hydroxide (KOH) in ethanol (0.300 g in 20 ml), compound (5) (0.286 g, 1 mmol) and p-substituted benzyl chloride (1.1 mmol) were added gradually. The reaction mixture was refluxed for 6-8 h. The reaction mixture then cooled to room temperature, diluted with 35 ml of water and extracted with ethyl acetate. The organic layer was washed with water and dried over magnesium sulfate and the solvent was evaporated under low pressure. The product were re-crystallized from a mixture of ethyl acetate-petroleum ether (1:1).

**IR Spectral Data** of 4H-1,2,4-triazole-5-(4-bromophenoxyethyl)-3-benzyl sulfide (6a): NH (3142  $\text{cm}^{-1}$ ); Aromatic Ar-H (3065  $\text{cm}^{-1}$ ); aliphatic  $-\text{CH}_2-$  (2936  $\text{cm}^{-1}$ ); 1029 (C-S);  $> \text{C-N}$  (1599  $\text{cm}^{-1}$ ) and N-N (1641  $\text{cm}^{-1}$ ).

**$^1\text{H}$  NMR Spectral Data** of (6a): 4.87 (s, 2H,  $-\text{S-CH}_2-$ ); 5.35 (s, 2H,  $-\text{O-CH}_2-$ ); 6.7 (d, 2H, Ar-H); 6.91 (d, 2H, Ar-H); 7.3-7.38 (m, 5H,  $\text{C}_5\text{H}_5$  attached to S- $\text{CH}_2-$ ); 13.7 (broad signal due to thiol-thione tautomerism).

**IR Spectral Data** of 4H-1,2,4-triazole-5-(4-bromophenoxyethyl)-3-(4-methyl Benzyl) (6b): NH (3139  $\text{cm}^{-1}$ ); Aromatic Ar-H (3060  $\text{cm}^{-1}$ ); aliphatic  $-\text{CH}_2-$  (2931  $\text{cm}^{-1}$ ); 1030 (C-S); 1520 (C-N); 1616 (N-N).

**$^1\text{H}$  NMR Spectral Data** of 6b: 2.80 (s, 3H,  $-\text{CH}_3$ ); 4.83 (s, 2H,  $-\text{S-CH}_2-$ ); 5.13 (s, 2H,  $-\text{O-CH}_2-$ ); 6.42 (d, 2H, Ar-H); 6.84 (d, 2H, Ar-H); 7.03 (d, 2H, Ar-H); 7.13 (d, 2H, Ar-H).

**IR Spectral Data** of 4H-1,2,4-triazole-5-(4-bromophenoxyethyl)-3-(4-methoxy Benzyl) sulfide 6c: NH (3141  $\text{cm}^{-1}$ ); Aromatic Ar-H (3059  $\text{cm}^{-1}$ ); aliphatic  $-\text{CH}_2-$  (2931  $\text{cm}^{-1}$ ); 1032 (C-S); 1523 (C-N); 1628 (N-N).

**$^1\text{H}$  NMR Spectral Data** of 6c: 3.40 (s, 3H,  $-\text{CH}_3$ ); 4.90 (s, 2H,  $-\text{S-CH}_2-$ ); 5.25 (s, 2H,  $-\text{O-CH}_2-$ ); 6.53 (d, 2H, Ar-H); 6.88 (d, 2H, Ar-H); 6.90 (d, 2H, Ar-H); 7.19 (d, 2H, Ar-H).

**IR Spectral Data** of 4H-1,2,4-triazole-5-(4-bromophenoxyethyl)-3-(4-nitro Benzyl) sulfide 6d: NH (3141  $\text{cm}^{-1}$ ); Aromatic Ar-H (3069  $\text{cm}^{-1}$ ); aliphatic  $-\text{CH}_2-$  (2927  $\text{cm}^{-1}$ ); 1038 (C-S); 1532 (C-N); 1623 (N-N).

**$^1\text{H}$  NMR Spectral Data** of 6d: 4.91 (s, 2H,  $-\text{S-CH}_2-$ ); 5.28 (s, 2H,  $-\text{OCH}_2-$ ); 6.58 (d, 2H, Ar-H); 6.86 (d, 2H, Ar-H); 7.15 (d, 2H, Ar-H); 7.90 (d, 2H, Ar-H);

**IR Spectral Data** of 4H-1,2,4-triazole-5-(4-bromophenoxyethyl)-3-(4-chloro Benzyl) sulfide 6e: NH (3145  $\text{cm}^{-1}$ ); Aromatic Ar-H (3061  $\text{cm}^{-1}$ ); aliphatic  $-\text{CH}_2-$  (2929  $\text{cm}^{-1}$ ); 1029 (C-S); 1522 (C-N); 1616 (N-N).

**$^1\text{H}$  NMR Spectral Data** of 6e: 4.92 (s, 2H,  $-\text{S-CH}_2-$ ); 5.29 (s, 2H,  $-\text{OCH}_2-$ ); 6.60 (d, 2H, Ar-H); 6.87 (d, 2H, Ar-H); 7.10 (d, 2H, Ar-H); 7.43 (d, 2H, Ar-H);

**IR Spectral Data** of 4H-1,2,4-triazole-5-(4-bromophenoxyethyl)-3-(4-bromo benzyl) sulfide 6f: NH (3136  $\text{cm}^{-1}$ ); Aromatic Ar-H (3060  $\text{cm}^{-1}$ ); aliphatic  $-\text{CH}_2-$  (2931  $\text{cm}^{-1}$ ); 1027 (C-S); 1524 (C-N); 1617 (N-N).

**$^1\text{H}$  NMR Spectral Data** of 6f: 4.85 (s, 2H,  $-\text{S-CH}_2-$ ); 5.26 (s, 2H,  $-\text{O-CH}_2-$ ); 6.54 (d, 2H, Ar-H); 6.85 (d, 2H, Ar-H); 7.12 (d, 2H, Ar-H); 7.40 (d, 2H, Ar-H);

**IR Spectral Data** of 4H-1,2,4-triazole-5-(4-bromophenoxyethyl)-3-(4-fluoro benzyl) sulfide 6g: NH (3144  $\text{cm}^{-1}$ ); Aromatic Ar-H (3065  $\text{cm}^{-1}$ ); aliphatic  $-\text{CH}_2-$  (2933  $\text{cm}^{-1}$ ); 1028 (C-S); 1526 (C-N); 1619 (N-N).

**$^1\text{H}$  NMR Spectral Data** of 6g: 4.93 (s, 2H,  $-\text{S-CH}_2-$ ); 5.30 (s, 2H,  $-\text{O-CH}_2-$ ); 6.62 (d, 2H, Ar-H); 6.89 (d, 2H, Ar-H); 7.12 (d, 2H, Ar-H); 6.90 (d, 2H, Ar-H);

**Antibacterial Activity**

A nutrient agar plates were inoculated with a standardized inoculums of the bacterial strains used. Sterile discs made from filter paper with

a diameter of 6 mm were soaked in solutions of the prepared compounds (2 mg/ml). Cefuroxime was used as a standard substance (10 mg/ml) and untreated disc served as a control. Three plates were made to minimize the technical errors. The plates incubated in the incubator at 37°C for 18 hours and evaluated for antibacterial activity. The inhibition zone diameter was measured, and the average inhibition zone then calculated and compared with the standard [19].

## RESULTS and DISCUSSION

The structures of the prepared compounds were confirmed by FT-IR, elemental analysis, and nuclear magnetic resonance <sup>1</sup>H NMR.

The anti microbial activity of the prepared compounds was evaluated using disc diffusion method using two gram +ve microorganisms (*Staphylococcus aureus*, and *Bacillus cereus*)

and tow gram-ve microorganisms (*E. coli*, and *Pseudomonas aeruginosa*).

It's obvious that all synthesized compounds shows noticeable antimicrobial effect against the pathogens used, but none of these compounds has a higher activity than the standard substance (cefuroxim), as shown in Tables 1 and 2. Compound 6d shows the highest effect in comparison with the other substances prepared, followed by 6e, 6g, and 6f (i.e) compound having nitro, chloro, fluoro and bromo moiety, respectively, have higher effect. This finding may refer to that the electron withdrawal group substituent on para position may lead to more active compound. This result is similar to that obtained by Dinesh R.G. et. al. [20].

Many researches reveals that some molecules having the five member heterocyclic rings like thiadiazole or 1,2,4-triazole have a specific anti microbial effect, because it acts to prevent the

**Table 1.** Elemental analysis, melting points, and the percent of yield of the prepared compound 6a-6g.

Comp.	Molecular Formula	Yield (%)	Melting Point °C	Elemental Analysis Practical/calculated %			
				C	H	N	S
6a	C <sub>16</sub> H <sub>14</sub> BrN <sub>3</sub> OS 307.6	54	160-163	50.9/51.07	3.73/3.75	11.7/11.17	8.40/8.52
6b	C <sub>17</sub> H <sub>16</sub> BrN <sub>3</sub> OS 390.3	59	172-174	51.70/52.31	4.10/4.13	10.95/10.77	7.90/8.22
6c	C <sub>17</sub> H <sub>16</sub> BrN <sub>3</sub> O <sub>2</sub> S 406.3	51	165-168		3.90/3.97	10.54/10.34	7.85/7.89
6d	C <sub>16</sub> H <sub>13</sub> BrN <sub>4</sub> O <sub>3</sub> S 421.3	62	147-159	45.10/45.62	3.09/3.11	13.55/13.3	7.56/7.61
6e	C <sub>16</sub> H <sub>13</sub> BrClN <sub>3</sub> OS 410.7	57	161-164	46.13/46.79	3.15/3.19	10.51/10.23	7.78/7.81
6f	C <sub>16</sub> H <sub>13</sub> Br <sub>2</sub> N <sub>3</sub> OS 455.1	65	178-182	42.10/42.11	2.80/2.88	9.61/9.23	6.97/7.04
6g	C <sub>16</sub> H <sub>13</sub> BrFN <sub>3</sub> OS 394.3	47	167-170		3.18/3.32	10.90/10.66	8.10/8.13

**Table 2.** Antibacterial activity of 4H-1,2,4-triazole-3-(4-Bromophenoxyethyl)- 5-(4-substituted-Benzyl) sulfide.

Compound 2 mg/ml	Inhibition Zone (mm)			
	<i>Bacillus cereus</i>	<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>
6a	5.52	8.15	8.20	5.74
6b	6.14	7.72	7.30	7.40
6c	4.23	6.90	6.55	6.95
6d	14.73	16.13	13.1	12.90
6e	13.10	14.9	11.73	12.00
6f	11.70	12.85	9.46	8.50
6g	12.25	14.10	10.10	9.90
Cefuroxime 10 mg/ml	18.35	17.35	19.35	20.10

assembly and biosynthesis of peptidoglycan [21].

Peptidoglycan is an important constituent of bacterial cell wall, and its specific prokaryotic cells. Therefore, it represents an ideal site for selective targeting of the drug for inhibition of cell wall synthesis [22].

In conclusion, all of the previously prepared compounds have a variable antibacterial activity depending on the type of the substituent. It seems that electron withdrawal group may lead to increase the antibacterial activity.

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