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Synthesis of 5-(1,2,3-Triazol-4-yl)-1,3,4-Oxa(thia) diazol-2-Amines as Antimicrobial Agents

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AN EFFICIENT method for the synthesis of new 1,2,3-triazol-4-yl-1,3,4-oxadiazol-2-amines (4a-c) from phenyliso-thiocyanate and 1,2,3-triazolyl-4-hydrazides (3a-c) through cyclo-desulfurization in the presence of sodium acetate is reported. Also, cyclization of 3a-c with concentrated H_2SO_4 afforded the corresponding triazol-4-ylthiadiazoles (6a-c). The new products were screened for their antimicrobial activities, and compounds; 4a-c showed excellent antimicrobial activities compared with the reference drugs. Also, the minimum inhibitory concentration (MIC) against the tested organisms was determined in which, compounds 2c and 4a showed the lowest MIC.

Keywords: Triazolyloxadiazoles, Triazolylthiadiazoles, Antimicrobial activity and MIC .

1,3,4-Oxadiazoles containing different functional groups have attracted a great deal of attention from synthetic and medicinal chemists that has led to production of novel compounds with improved pharmacological properties. For instance, compounds containing 2-amino-1,3,4-oxadiazole possess various biological activities such as muscle relaxants[(1)], anti-mitotics[(2)], antibacterial and fungicidal[(3-5)]. Also, 1,3,4-thiadiazoles exhibit antimicrobial[(6)] and antitubercular[(7–9)] activities, while other derivatives act on the CNS as anticonvulsants[(10–12)] or as antidepressant and anxiolitic[(13)] agents. Moreover, 1,2,3-triazoles displayed anti-HIV activity [(14, 15)], antimicrobial activity against Gram positive bacteria[(16)], antiviral[(17)] and antiproliferative[(18)] . The current paper presents an efficient approach for the synthesis of new 1,3,4-oxadiazoles and 1,3,4-thiadiazoles having 1,2,3-triazole nucleus for antimicrobial screening.

Results and Discussion

Chemistry

1,2,3-Triazole-4-carbohydrazide (2a-b) were prepared by treatment of 1,2,3-triazol-4-ester (1a,b) with excess hydrazine hydrate[(19)]. 1-(4-Fluorophenyl)-5-methyl-1*H*-1,2,3-triazole-4-carbohydrazide (2c) was synthesized based on literature procedure[(19)] . Thiosemicarbazides (3a-c) were prepared in good yields by mixing equimolar amounts of the corresponding hydrazides (2a-c) and phenylisothiocyanate in boiling absolute EtOH for 4 hr. 2-(1,2,3-Triazol-4-yl)-

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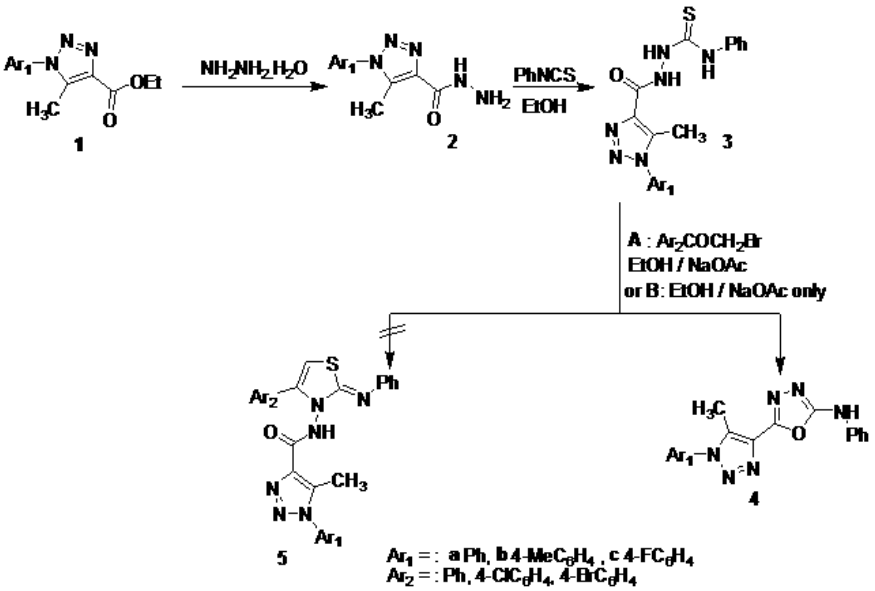
1,3,4-oxadiazoles (4a-c) were synthesized, instead of product 5, via a desulfurization reaction of thiosemicarbazides (3a-c) with phenacylbromides in ethanol in the presence of anhydrous sodium acetate. Alternatively, 1,3,4-oxadiazoles 4a-c were prepared by heating 3a-c in ethanol in the presence of anhydrous sodium acetate (Scheme 1).



Scheme 1

^{1}H NMR spectrum of 4a-c showed a peak at 10.75 ppm which excluded the formation of 1,3,4-oxadiazol-2-amines not thiazoles 5 [20]. The mass spectrum of 4c showed the molecular ion peak at *m/z* 336. The structure of 4b was confirmed by X-ray crystallography (Fig. 1).

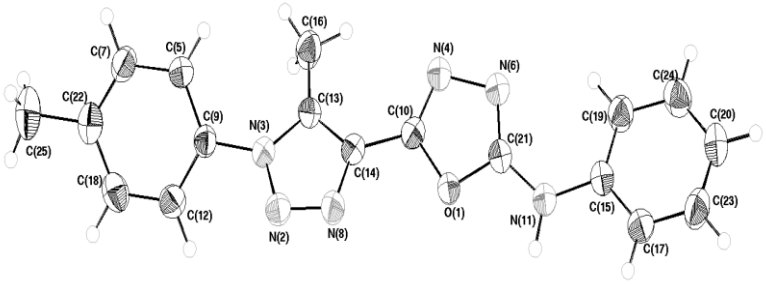
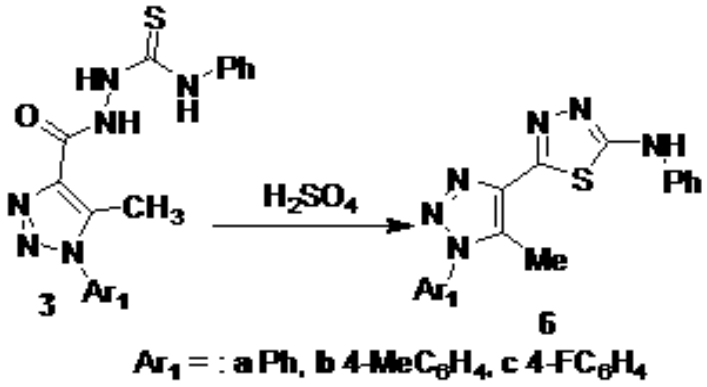


Fig. 1. X-ray structure of compound 4b.

Treatment of the thiosemicarbazide derivatives 3a-c with cold concentrated sulfuric acid afforded the corresponding 5-(1,2,3-triazol-4-yl)-1,3,4-thiadiazol-2-amines (6) (Scheme 2).



Scheme 2

The ^{1}H NMR spectra of compounds 6a-c indicated the absence of NH signal as a result of cyclodehydration of 3a-c. The structures of 6a-c were further confirmed by mass spectroscopy. For example, mass spectrum of 6c showed a molecular ion peak at m/z 352.

Antimicrobial activity

The new compounds were screened for their antibacterial activities against three Gram positive bacteria (*Staphelococcus aureus* ATCC 29213; *B. subtilis ATCC6633*; and *B. megaterium ATCC* 9885), three Gram negative bacteria (*Klebseilla peneumoniae* ATCC13883; *Pseudomonas. aeroginosa* ATCC27953; and *E. coli ATCC 25922*) at a concentration 100 g/ml. Also, the products were tested for their antifungal activities against *A. niger* and two yeasts (*Saccharomyces cervesia* and *Candida albicans* NRRL Y-477). Ciprofloxacin and Ketoconazole were used as standard antibacterial and antifungal reference, respectively. Antimicrobial tests were carried out by disc diffusion method[16]. Table 1 summarizes the results of antimicrobial studies, in which compounds 4a-c exhibited a considerably broader antimicrobial activity compared to Ciprofloxacin and Clotrimazole drugs. Products 2c, 3a-c and 6a-c showed good to moderate activity against the tested microorganisms.

TABLE 1. Antimicrobial activity of products expressed as inhibition diameter zones in millimeters (mm) against the pathological strains based on well diffusion assay.

Chem. Cpds.	Gram positive bacteria			Gram negative bacteria			Yeast		Fungi
	Staphelococcus aureus ATCC 29213	*B. subtilis* ATCC6633	*B. megaterium* ATCC 9885	*Klebseilla peneumoniae* ATCC 13883	*Pseudomonas. aeroginosa* ATCC 27953	*E. coli* ATCC 2592	*Saccharomyces cervesia*	*Candida albicans* NRRL Y-477	*A.niger*
2c	15	18	19	15	15	N.A.	N.A.	N.A.	15
3a	12	16	18	16	N.A.	18	17	15	N.A.
3b	15	15	16	17	N.A.	15	19	18	20
3c	N.A.	20	22	14	16	16	15	N.A.	N.A.
4a	35	34	32	28	32	28	30	29	28
4b	35	N.A.	12	33	N.A.	16	17	30	26
4c	36	27	28	38	35	33	34	31	32
6a	15	15	18	17	16	15	18	15	15
6b	20	15	18	18	15	18	17	15	18
6c	20	18	20	18	17	18	20	18	38
Ciprofloxacin	20	22	24	28	24	23	N.A.	N.A.	N.A.
Clotrimazole	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	30	29	30

The experiment was carried out in triplicate and the average zone of inhibition was calculated.

Minimum inhibitory concentration (MIC)

The minimum inhibitory concentration (MIC) of the new products is reported in Table 2. Compounds 2c and 4a exhibited the lowest MIC (25 g/ml) against *Staphelococcus aureus* ATCC 29213. While Compound 4a showed the lowest MIC (25 g/ml) against *B. subtilis ATCC6633* and *Klebseilla peneumoniae* ATCC13883, respectively. Compounds 4c and 6b revealed the highest MIC (200 g/ml) against most of the tested bacteria.

TABLE 2. Minimum inhibitory concentration (mg/ml) against the pathological strains based on two fold serial dilution technique.

Chem. Cpds.	Gram positive bacteria			Gram negative bacteria			Yeast		Fungi
	Staphelococcus aureus ATCC 29213	*B. subtilis* ATCC6633	*B. megaterium* ATCC 9885	*Klebseilla peneumoniae* ATCC13883	*Pseudomonas. aeroginosa* ATCC 279532	*E. coli* ATCC 25922	*Saccharomyces cervesia*	*Candida albicans* NRRL Y-477	*A.niger*
2c	25	-	-	50	-	-	-	50	100
3a	N.A.	200	100	N.A.	200	200	200	N.A.	N.A.
3b	N.A.	N.A.	200	200	N.A.	200	200	N.A.	N.A.
3c	N.A.	200	100	N.A.	200	200	N.A.	N.A.	N.A.
4a	25	25	50	25	32	50	50	50	100
4b	N.A.	N.A.	200	200	200	N.A.	200	N.A.	N.A.
4c	200	N.A.	200	200	N.A.	200	200	N.A.	200
6a	N.A.	200	200	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.
6b	200	200	200	200	200	200	200	200	25
6c	N.A.	N.A.	200	200	N.A.	N.A.	200	200	200
Ciprofloxacin	25	25	25	25	25	25	N.A.	N.A.	N.A.
Clotrimazole	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	25	25	25

The experiment was carried out in triplicate and the average zone of inhibition was calculated.

Conclusion

A facile and efficient approach for the synthesis of 1,2,3-triazol-4-yl-1,3,4-oxadiazol-2-amines and 1,2,3-triazol-4-yl-1,3,4-thiadiazoles through direct cyclization reaction of thiosemicarbazides was reported. Compounds 4a-c exhibited excellent antimicrobial activity compared to the reference drugs.

Experimental

Chemistry

General

All melting points were determined on Electrothermal IA 9000 series digital melting point apparatus. Elemental analytical data were carried out at the Microanalytical Unit, Cairo University, Giza, Egypt. The IR spectra were recorded in potassium bromide disks on a JASCO FT/IR-6100. ^{1}H-NMR and ^{13}C-NMR spectra were run on JOEL-ECA 500 MHz in (DMSO-d_6). Chemical shifts values (δ) are given in parts per million (ppm). The mass spectra were performed using mass Varian MAT CH-5 spectrometer at 70eV.

1-(4-Fluorophenyl)-5-methyl-1H-1,2,3-triazole-4-carbohydrazide (2c)

A mixture of 4-acetyl-1,2,3-triazole (1c) (10 mmol, 2.5 g) and hydrazine hydrate (80%, 30 mmol, 1.5g) in absolute ethanol (20 ml) was heated under reflux for 2 hr. The product obtained was collected by filtration, washed with ethanol and dried.

Yield 65 %; m.p. 121-123°C; IR (KBr) max/cm^{-1}, 1670(C=O), 3161-3350 (NH, NH_2); ^{1}H NMR (DMSO-d_6) 2.34 (s, 3H, CH_3), 4.49 (s, 2H, NH_2), 7.31-7.60 (m, 4H, Ar-H), 9.97 (s, 1H, NH, D_2O exchangeable); MS m/z (%): 236 [(M + 1)$^{+}$, 18], 235 (M^{+}, 14), 91 (100); Anal. Calcd for $C_{10}H_{10}FN_5O$ (235.22): C, 51.06; H, 4.29; N, 29.77%. Found: C, 51.13; H, 4.36; N, 29.91%.

2-(5-Methyl-1-aryl-1H-1,2,3- triazole-4- carbonyl) -N-phenylhydrazinecarbothioamides (3a-c)

A mixture of 2a-c (2 mmol) and phenylisothiocyante (2 mmol, 0.27 g) in absolute ethanol (20 ml) was heated under reflux for 3 hr. The solid obtained was filtered and recrystallized from a mixture of EtOH - DMF (5:1 by volume) to give 3a-c.

2-(5-Methyl-1- phenyl-1H- 1,2,3- triazole-4-carbonyl)-N-phenylhydrazinecarbothioamide (3a) : Yield 72 %; m.p. 165-166°C; IR (KBr) max/cm^{-1}, 1258(C=S), 1660 (C=O), 3159-3310 (NH); ^{1}H NMR (DMSO-d_6) 2.34 (s, 3H, CH_3), 7.27-7.62(m, 10H, Ar-H), 9.46, 9.97, 10.42 (3s, 3H, 3 NH, D_2O exchangeable); MS m/z (%): 352 (M^{+}, 16), 91 (100); Anal. Calcd for $C_{17}H_{16}N_6OS$ (352.41): C, 57.94; H, 4.58; N, 23.85%. Found: C, 58.01; H, 4.66; N, 23.92%.

2-(5-Methyl-1-p-tolyl-1H-1,2,3- triazole-4- carbonyl) -N-phenylhydrazinecarbothioamide (3b) : Yield 78 %; m.p. 172-174°C; IR (KBr) max/cm^{-1}, 1259(C=S), 1658 (C=O), 3160-3310 (NH); ^{1}H NMR (DMSO-d_6) 2.34, 2.40 (2s, 6H, 2 CH_3), 7.28-7.63 (m, 9 H, Ar-H), 9.45, 9.97, 10.43 (3s, 3H, 3 NH, D_2O exchangeable); MS m/z (%): 366 (M^+, 16), 91 (100); Anal. Calcd for $C_{18}H_{18}N_6OS$ (366.44): C, 59.00; H, 4.95; N, 22.93%. Found: C, 59.11; H, 4.99; N, 23.06%.

2-(1-(4-Fluorophenyl)-5- methyl-1H-1,2,3-triazole-4-carbonyl)-N-phenylhydrazinecarbothioamide (3c) : Yield 66 %; m.p. 205-206°C; IR (KBr) max/cm^{-1}, 1260(C=S), 1659 (C=O), 3160-3315 (NH); ^{1}H NMR (DMSO-d_6) 2.35 (s, 3H, CH_3), 7.30-7.67 (m, 9 H, Ar-H), 9.44, 9.96, 10.44 (3s, 3H, 3 NH, D_2O exchangeable); MS m/z (%): 370 (M^+, 21), 91 (100); Anal. Calcd for $C_{17}H_{15}FN_6OS$ (370.40): C, 55.12; H, 4.08; N, 22.69 %. Found: C, 55.30; H, 4.17; N, 22.79%.

5-(5-Methyl-1-aryl-1H-1,2,3-triazol-4-yl)-N-phenyl-1,3,4-oxadiazol-2-amines (4a-c)

Method A: A mixture of appropriate 3a-c (1 mmol) and phenacylbromide (1 mmol, 0.2 g) in absolute ethanol (20 ml) containing anhydrous sodium acetate (2 mmol, 0.16 g) was heated under reflux for 6 hr. The reaction mixture was cooled and the formed solid was filtered, washed with water, and recrystallized from a mixture of EtOH - DMF (4:1 by volume).

Method B: A solution of appropriate 3a-c (1 mmol) in absolute ethanol (20 ml) containing anhydrous sodium acetate (2 mmol, 0.16 g) was heated under reflux for 6 hr. The formed solid was filtered, washed with water, and recrystallized from a mixture of EtOH - DMF (4:1 by volume).

5-(5-Methyl-1-phenyl-1H-1,2,3- triazol-4-yl)-N- phenyl-1,3,4- oxadiazol-2-amine (4a) : Yield 52 %; m.p. 215-216°C; IR (KBr) max/cm^{-1}, 3175 (NH); ^{1}H NMR (DMSO-d_6) 2.39 (s, 3H, CH_3), 6.84-7.51 (m, 10 H, Ar-H), 10.62 (s, 1H, 1 NH, D_2O exchangeable); MS m/z (%): 318 (M^+, 28), 91 (100); Anal. Calcd for $C_{17}H_{14}N_6O$ (318.33): C, 64.14; H, 4.43; N, 26.40 %. Found: C, 64.28; H, 4.57; N, 26.78%.

5-(5-Methyl-1-p- tolyl-1H-1,2,3-triazol-4-yl)- N-phenyl-1,3,4- oxadiazol-2-amine (4b) : Yield 58 %; m.p. 230-231°C; IR (KBr) max/cm^{-1}, 3180 (NH); ^{1}H NMR (DMSO-d_6) 2.39, 2.46 (2s, 6H, 2 CH_3), 6.82-7.50 (m, 9 H, Ar-H), 10.79 (s, 1H, 1 NH, D_2O exchangeable); MS m/z (%): 332 (M^+, 32), 91 (100); Anal. Calcd for $C_{18}H_{16}N_6O$ (332.36): C, 65.05; H, 4.85; N, 25.29%. Found: C, 65.20; H, 4.98; N, 25.63%.

5-(1-(4-Fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-N-phenyl-1,3,4-oxadiazol-2-amine (4c) : Yield 56 %; m.p. 258-259°C; IR (KBr) max/cm^{-1} 3183 (NH); ^{1}H NMR (DMSO-d_6) 2.36 (s, 3H, CH_3), 6.81-7.54 (m, 9 H, Ar-H), 10.67 (s, 1H, 1

NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) 10.9, 111, 112, 116.3, 118, 122, 125, 128, 129.8, 136.9, 139, 148, 154, 162; MS m/z (%): 336 (M^+, 28), 91 (100); Anal. Calcd for $C_{17}H_{13}FN_6O$ (336.32): C, 60.71; H, 3.90; N, 24.99 %. Found: C, 60.82; H, 3.99; N, 25.11%.

5-(5-Methyl-1-aryl-1H-1,2,3-triazol-4-yl)- N-phenyl-1,3,4-thiadiazol-2-amine (6a-c)

A suspension of appropriate 3a-c (1mmol) in concentrated sulfuric acid (5 ml) was stirred in an ice bath for 1 hr. The reaction mixture was left to stand overnight, then poured into ice-water and neutralized with 2N NaOH. The formed solid was filtered, dried, and crystallized from ethanol.

5-(5-Methyl-1- phenyl-1H- 1,2,3-triazol-4-yl)- N-phenyl-1,3,4-thiadiazol-2-amine (6a) : Yield 68 %; m.p. 207-209°C; IR (KBr) max/cm^{-1} 3220 (NH); ^1H NMR (DMSO-d_6) 2.40 (s, 3H, CH_3), 7.34-7.65 (m, 10 H, Ar-H), 10.62 (s, 1H, 1 NH, D_2O exchangeable); MS m/z (%): 335 [$(M+1)^+$, 34)], 334 (M^+, 22), 91 (100); Anal. Calcd for $C_{17}H_{14}N_6S$ (334.40): C, 61.06; H, 4.22; N, 25.13 %. Found: C, 61.32; H, 4.66; N, 25.33%.

5-(5-Methyl-1-p- tolyl-1H-1,2,3-triazol-4-yl)- N- phenyl-1,3,4- thiadiazol-2-amine (6b) : Yield 64 %; m.p. 268-269°C; IR (KBr) max/cm^{-1} 3220 (NH); ^1H NMR (DMSO-d_6) 2.40, 2.47 (2s, 6H, 2 CH_3), 7.30-7.64 (m, 9 H, Ar-H), 10.63 (s, 1H, 1 NH, D_2O exchangeable); MS m/z (%): 349 [$(M+1)^+$, 32)], 348 (M^+, 22), 91 (100); Anal. Calcd for $C_{18}H_{16}N_6S$ (348.42): C, 62.05; H, 4.63; N, 24.12%. Found: C, 62.61; H, 4.73; N, 24.32%.

5-(1-(4-Fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-N-phenyl-1,3,4-thiadiazol-2-amine (6c) : Yield 58 %; m.p. 315-317°C; IR (KBr) max/cm^{-1} 3220 (NH); ^1H NMR (DMSO-d_6) 2.40 (s, 3H, CH_3), 7.32-7.65(m, 9 H, Ar-H), 10.67 (s, 1H, 1 NH, D_2O exchangeable); ^{13}C NMR (DMSO-d_6) 10.9, 111, 115, 117, 122, 123, 125, 128.6, 131, 133, 136.7, 144, 153.2, 162; MS m/z (%): 353 [$(M+1)^+$, 38)], 352 (M^+, 24), 91 (100); Anal. Calcd for $C_{17}H_{13}FN_6S$ (352.39): C, 57.94; H, 3.72; N, 23.85%. Found: C, 58.11; H, 3.84; N, 25.08 %.

Antimicrobial activity

Antimicrobial tests were carried out by the agar well diffusion method[16] .

Minimal inhibitory concentration (MIC) measurement

The bacteriostatic activity of the active compounds was evaluated using the two fold serial dilution technique[16] .

X-ray crystallography

A single crystal of compound 4b was obtained by slow evaporation at room temperature, from dimethylformamide (DMF). The crystal structure was solved and refined using MaXus (Bruker Nonius, Deflt and MacScience, Japan)[21] . Mo K_α radiation (λ = 0.71073Å) and a graphite monochromator were used for data

collection. The chemical formula and ring labeling system is shown in Fig. 1. Crystal data for compound 4b: $C_{18}H_{16}N_6O$, Mr, 332.367; system, orthorhombic; Space group, $P2_12_12_1$; unit cell dimensions, a, 6.4629 (2) Å; b, 10.7257 (4)Å; c, 12.5359 (4)Å; α, 108.565 (2)°; β, 99.650 (2)°; γ, 95.2020 (13)°; V, 802.40 (5)Å^3; Z, 2; D_x, 1.376 Mg m^{-3}; θ_{max} = 30.07 °; μ (Mo- K_α), 0.09 mm^{-1}; T = 298 K; independent reflections, 5257; measured reflections, 11255; observed reflections, 2389; R_{int}, 0.050; R(all), 0.124; R(gt), 0.050; wR(ref), 0.095; wR(all), 0.109; wR(gt), 0.095; S(ref), 0.719; S(all), 0.683; S(gt), 0.721; Δ/σ_{max}, 0.013, $\Delta\rho_{max}$, 0.39 eÅ^3; $\Delta\rho_{min}$ .0.36 eÅ^3.

Crystallographic data for the structures 4b have been deposited at the Cambridge Crystallographic Data Center (CCDC) under the number 993032. Copies of the data can be obtained, free of charge, on application to CCDC 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or at www.ccdc.cam.ac.uk].

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تشييد مركبات 5-(1,2,3-تيريازول)-1,3,4-اوكسا(ثيا)ديازول-2-امين الجديدة كمضادات للفطريات و البكتيريا

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مركبات 5-(1,2,3-تيريازول)-1,3,4-اوكسا(ثيا)ديازول-2-امين تتمتع بخواص بيولوجية عالية كمضادات للبكتيريا و الفطريات. لذلك تم فى هذا البحث تشييد مركبات جديدة من 5-(1,2,3-تيريازول)-1,3,4-اوكساديازول-2-امين عن طريق تفاعل الهيدرازيد تيرازول مع الفنييل ايزوسيوسينات ثم التفاعل مع الفيناسيل بروميد. تم ايضا تحضير مشتقات جديدة من 5-(1,2,3-تيريازول)-1,3,4-ثياديازول-2-امين عن طريق تفاعل الثيو سيمى كبرزيد مع حمض الكبرتيك المركز. تم اثبات التركيب البنائى باستخدام التحاليل الطيفية و التحاليل الدقيقة و ايضا باستخدام تقنية البلورة الاحادية فى اشعة اكس. تم اجراء مسح بيولوجى للمركبات الجديدة ضد بعض البكتيريا و الفطريات و اثبتت مركبات 5-(1,2,3-تيريازول)-1,3,4-اوكساديازول-2-امين فاعليتها ضد معظم الميكروبات قيد المسح. ايضا تم اجراء اختبار اقل تركيز لمنع نمو الميكروبات.