SYNTHESIS AND BIOLOGICAL ACTIVITY OF SOME NEW 1,2,3-TRIAZOLE HYDRAZONE DERIVATIVES

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A family of novel 1,2,3-triazoles **3-7** were prepared by one pot reaction of 1,2,3-triazol-4-carbohydazides **1** with different reagents such as hydrazonoyl chlorides and methyl ketones. The novel compounds were evaluated for their antimicrobial activity. The results of antimicrobial screening showed that, compound **5** has the highest inhibitory effects on the growth of a wide range of the tested microbes due to the presence of sulphonyl moiety in its structure.

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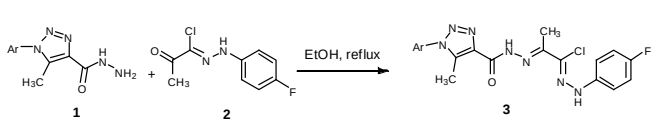
INTRODUCTION

Recently 1,2,3-triazoles, have found a wide range of important applications in the agrochemical, pharmaceutical, polymer, and materials field.[1,2] In addition, several compounds of the 1,2,3-triazole family have shown a broad spectrum of biological properties such as antibacterial,[3] and anti-HIV activity.[4] In addition, hydrazones have been reported as useful as antibacterial,[5] whereas arylhydrazones inhibited the replication of HIV-1.[6] Because of our interest in the synthesis of new 1,2,4-triazole derivatives of biological interest,[7-10] we decided here to synthesize the title compounds for evaluation of their antimicrobial activity.

RESULTS and DISCUSSION

The synthesis of 2-(2-(1,2,3-triazole-4-carbonyl)hydrazono)-*N*'-propanehydrazonoyl chlorides **3a-c**, the necessary intermediate for the production of *N*'-(4-(4-fluorophenyl)-1-(hydrazono)-1-(piperidin-1-yl)but-3-en-2-ylidene)- 1,2,3-triazole-4-carbohydrazide **4** and N'-(1-(2-arylhydrazono)-1-(phenylsulfonyl)propan-2-ylidene)- 1,2,3-triazole-4-carbohydrazide **5**, is easy and is shown in Scheme 1. Condensation of 1,2,3-triazol-4-carbohydrazides **1a-c** with hydrazonoyl halide **2** in ethanol afforded the bishydrazones **3**.

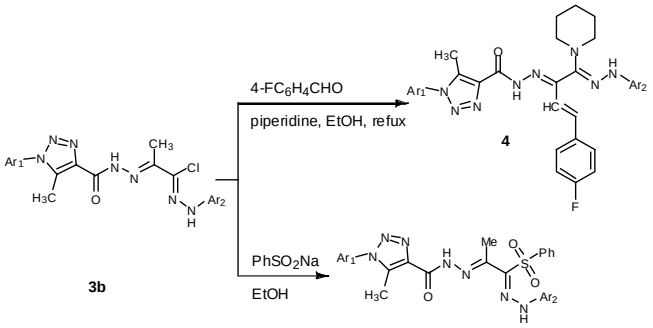


1 **2** **3**

a Ph; **b** 4-MeC_6H_4; **c** 4-FC_6H_4

Scheme 1

When chloro bis-hydrazones **3b** were allowed to react with a molar ratio of both 4-fluorobenzaldehyde and piperidine in refluxing ethanol, they furnished compound **4**. On the other hand, when compound **3b** was treated with sodium benzenesulfinate under the same experimental conditions, it afforded **5** in good yield (Scheme 2).



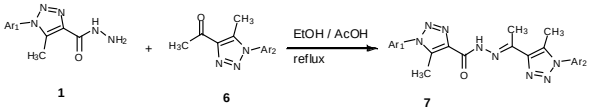
3b **4** **5**

Scheme 2

Ar_1 = 4-MeC_6H_4; Ar_2 = 4-FC_6H_4

The structure of **4** and **5** was confirmed on the basis of their spectroscopic data. For example, the IR spectrum of **4** showed absorption bands in the region 3380–3130 cm^{-1} of two NH groups, and the band of the carbonyl group at 1680 cm^{-1}. Its ^{1}H-NMR spectrum revealed two D_2O exchangeable singlet signals (three NH) at δ 10.78, 11.12 ppm, whereas its mass spectrum showed a peak corresponding to its molecular ion at m/z: 582 [M^+].

The 3-acetyl-1,2,3-triazoles **6** condensed with 1,2,3-triazol-4-carbohydrazide **1a,c** in absolute ethanol and acetic acid as catalyst to give the bis-1,2,3-triazoles **7a-c** (Scheme 3).



1 **6** **7**

a: Ar_1 = Ph, Ar_2 = 4-FC_6H_4
b: Ar_1 = 4-FC_6H_4, Ar_2 = 4-MeC_6H_4
c: Ar_1 = Ar_2 = 4-FC_6H_4

Scheme 3

Table 1. Antimicrobial activity (mm) of chemical compounds

Compd.	Gram positive bacteria				Gram negative bacteria			Yeast	
	Staphelococcus aureus ATCC 29213	*B. subtilis ATCC6633*	*B. megaterium ATCC* 9885	*Sarcina lutea*	*Klebseilla peneumoniae* ATCC13883	*Pseudomonas. Aeroginosa* ATCC27953	*E. coli ATCC 25922*	*Saccharomy-ces cervesia*	*Candida Albicans* NRRL Y-477
3a	32	24	20	29	N.A.	N.A.	N.A.	30	30
3b	32	13	14	30	15	16	17	24	22
3c	34	18	14	28	19	19	18	20	18
4	35	N.A.	12	33	N.A.	16	17	30	26
5	36	27	28	38	35	33	34	31	32
7a	32	15	16	27	29	28	26	30	28
7b	35	34	32	28	32	28	30	29	28
7c	30	30	24	32	27	24	27	28	25
Ciprofloxacin	20	22	24	20	25	24	23	N.A.	N.A.
Ketoconazole	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	23	22

Table 2. Minimum inhibitory concentration (μg mL^{-1})

Compd.	Gram positive bacteria				Gram negative bacteria			Yeast	
	Staphelococcus aureus ATCC 29213	*B. subtilis ATCC6633*	*B. megate-rium ATCC* 9885	*Sarcina lutea*	*Klebseilla peneumoniae* ATCC13883	*Pseudomonas. Aeroginosa* ATCC27953	*E. coli ATCC 25922*	*Saccharomyces cervesia*	*Candida Albicans* NRRL Y-477
3a	50	100	200	50	-	-	-.	50	50
3b	50		-	50	-	-	-	50	100
3c	25	200	-	50	200	200	-	100	-
4	25	-	-	50	-	-	-	50	100
5	25	50	50	25		50	50	50	50
7a	50	-	-	50	50	50	50	50	50
7b	25	25	50	25	32	50	50	50	100
7c	50	50	50	50	50	50	50	100	50
Ciprofloxacin	25	25	25	25	25	25	25	-	-
Ketoconazole	-.	-	-	-.	-	-	-	25	25

The ^{1}H NMR spectra of the latter products showed one signal in the regions δ 10.77 ppm assigned to the NH group. whereas the mass spectra of compounds **7a-c** showed a peaks at m/z 418, 432 and 436 corresponding to their molecular ions respectively.

Antimicrobial activity

The antimicrobial activity of the new compounds has been evaluated by filter paper disc method.[7] The novel compounds have been tested for their antibacterial activity against Gram positive bacteria (*Staphylococcus aureus ATCC 29213, Bacillus subtilis ATCC6633*, and *Bacillus megaterium ATCC* 9885); Gram negative bacteria (*Klebseillapeneumoniae*ATCC13883, *Pseudomonas. Aeroginosa* ATCC27953 and *Echerichia coli ATCC 25922*) and fungal (*Saccharomyces cervesia*, *Candida Albicans* NRRL Y-477 and Aspergillus niger) and two yeast (*Saccharomyces cervesia* and *Candida Albicans* NRRL Y-477). at a concentration of 100 μg/mL in DMSO. Ciprofloxacin and Ketoconazole were respectively used as standard antibacterial and antifungal reference, respectively.

Minimal inhibitory concentration (MIC)

The minimum inhibitory concentration (MIC) of the synthesized compounds against highly inhibited organisms is reported in Table 2.

Compounds **5** revealed the lowest MIC (25 μg/ml) against *Staphelococcus Aureus* ATCC 29213 and *SarcinaLutea.* While **7b** exhibited low MIC (25 μg mL^{-1}) against *Staphelococcus aureus* ATCC 29213 and *B. subtili ATCC6633 and SarcinaLutea* (Table 2).

From the above results, we can say that, the hydrazone moiety is responsible for the antimicrobial activity and the compound bearing sulfonyl group (compound **5**) is more effective than the other tested compounds.

EXPERIMENTAL

All melting points were taken on Electrothermal IA 9000 series digital melting point apparatus. Elemental analytical data were carried from 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 spectra were run on JOEL-ECA 500MHz in deuterated dimethylsulphoxide (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. 1,2,3-Triazol-4-carbohydrazides **1a-c**,[11] hydrazonoyl halide **2**,[12] and 3-acetyl-1,2,3-triazoles **6**[13] were prepared according to literature.

Synthesis of compounds 3a-c

A mixture of 5-methyl-1-aryl-1*H*-1,2,3-triazole-4-carbohydrazide **1a-c** (10 mmol) and N'-(4-fluorophenyl)-2-oxopropanehydrazonoyl chloride **2** (2.4g, 10 mmol) in absolute ethanol (30 mL) was refluxed for 4 h. The formed solid was filtered off, washed with ethanol to afford the corresponding propanehydrazonoyl chlorides **3a–c**, respectively.

(1*Z*,2*E*)-N'-(4-Fluorophenyl)-2-(2-(5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carbonyl)hydrazono)propanehydrazonoyl chloride (3a)

Yield 68 %; m.p. 222-223°C; IR (KBr) ν_{max}/cm^{-1} 1686 (C=O), 3322, 3185 (2 NH); ^{1}H NMR (DMSO-d_6) δ 2.35, 2.49 (2s, 6H, 2CH_3), 7.01-7.54 (m, 9 H, Ar-H), 10.22, 10.70 (2s, 2H, NH, D_2O exchangeable); MS m/z (%): 413 (M^+, 12), 91(100); Anal. Calcd for $C_{19}H_{17}ClFN_7O$ (413.84): C, 55.14; H, 4.14; N, 23.69 %. Found: C, 55.23; H, 4.28; N, 23.82% .

(1*Z*,2*E*)-N'-(4-Fluorophenyl)-2-(2-(5-methyl-1-*p*-tolyl-1*H*-1,2,3-triazole-4-carbonyl)hydrazono)propanehydrazonoyl chloride (3b)

Yield 69 %; m.p. 200-201 °C; IR (KBr) ν_{max}/cm^{-1} 1682 (C=O), 3320, 3181 (2 NH); ^{1}H NMR (DMSO-d_6) δ 2.35, 2.49, 2.51 (3s, 9H, 3CH_3), 7.13-7.55 (m, 8 H, Ar-H), 10.21, 10.70 (2s, 2H, 2 NH, D_2O exchangeable); MS m/z (%): 427 (M^+, 16), 91(100); Anal. Calcd for $C_{20}H_{19}ClFN_7O$ (427.86): C, 56.14; H, 4.48; N, 22.92; %. Found: C, 56.21; H, 4.51; N, 22.80% .

(1Z,2E)-N'-(4-Fluorophenyl)-2-(2-(1-(4-fluorophenyl)-5-methyl-1H-1,2,3-triazole-4-carbonyl)hydrazono)propanehydrazonoyl chloride (3c)

Yield 71 %; m.p. 218-220 °C; IR (KBr) ν_{max}/cm^{-1} 1680 (C=O), 3317, 3183 (2 NH); ^{1}H NMR (DMSO-d_6) δ 2.35, 2.49 (2s, 6H, 2CH_3), 7.12-7.54 (m, 8 H, Ar-H), 10.20, 10.69 (2s, 2H, 2 NH, D_2O exchangeable); MS m/z (%): 431 (M^+, 13), 91(100); Anal. Calcd for $C_{19}H_{16}ClF_2N_7O$ (431.83): C, 52.85; H, 3.73; N, 22.71 %. Found: C, 52.91; H, 3.83; N, 22.89% .

(*E*)-N'-((1*Z*,3*E*)-4-(4-Fluorophenyl)-1-(2-(4-fluorophenyl)-hydrazono)-1-(piperidin-1-yl)but-3-en-2-ylidene)-5-methyl-1-*p*-tolyl-1*H*-1,2,3-triazole-4-carbohydrazide (4)

To a solution of propanehydrazonoyl chloride **3a–c** (1 mmol) in ethanol (20 mL), piperidine (0.34 g, 4 mmol) and the 4-fluorobenzaldehyde (0.13g, 1 mmol) were added. The reaction mixture was refluxed for 6 h. The precipitated product was filtered off to afford **4**.

Yield 52 %; m.p. 147-148 °C; IR (KBr) ν_{max}/cm-1 1680 (C=O), 3381, 3236 (2 NH); ^{1}H NMR (DMSO-d_6) δ 1.61 (m, 6H, 3CH_2 of piperidine), 2.34, 2.50 (2s, 6H, 2CH_3), 3.31 (m, 4H, 2CH_2 of piperidine), 6.91, 6.96 (2d, 2H, olefinic-CH, *J* = 12 Hz) ,7.13-7.98 (m, 12 H, Ar-H), 10.78, 11.12 (2s, 2H, 2 NH, D_2O exchangeable); MS m/z (%): 582 (M^+, 40), 91(100); Anal. Calcd for $C_{32}H_{32}F_2N_8O$ (582.65): C, 65.96; H, 5.54; N, 19.23%. Found: C, 66.21; H, 5.67; N, 19.50% .

(E)-N'-((Z)-1-(2-(4-Fluorophenyl)hydrazono)-1-(phenylsulfonyl)propan-2-ylidene)-5-methyl-1-*p*-tolyl-1*H*-1,2,3-triazole-4-carbohydrazide (5).

To a solution of the appropriate propanehydrazonoyl chloride **3c** (0.43g, 1 mmol) in absolute ethanol (20 mL), sodium benzenesulphinate dihydrate (0.4 g, 2 mmol) was added. The mixture was refluxed for 12 h, then left to cool. The reaction mixture was poured into cold water and the solid product filtered off, washed with water, dried to afford the corresponding sulphone **5**.

Yield 52 %; m.p. 180-181 °C; IR (KBr) ν_{max}/cm-1 1683 (C=O), 3386, 3230 (2 NH); ^{1}H NMR (DMSO-d_6) δ 2.20, 2.41, 2.49 (3s, 9H, 3CH_3), 6.92-7.98 (m, 8 H, Ar-H), 11.75, 14.45 (2s, 2H, 2 NH, D_2O exchangeable); MS m/z (%): 534 (M^++1, 56), 533 (M^+, 53), 91(100); Anal. Calcd for $C_{26}H_{24}FN_7O_3S$ (533.58): C, 58.53; H, 4.53; N, 18.38%. Found: C, 58.64; H, 4.62; N, 18.42% .

Synthesis of compounds 7

A mixture of appropriate carbohydrazide **1** (1 mmol) and 1-(5-methyl-1-aryl-1*H*-1,2,3-triazol-4-yl)ethanones **6** (1 mmol) in absolute ethanol (50 mL) and acetic acid (0.5 mL) was refluxed for 5 h. The formed solid was filtered off, washed with ethanol, to afford the corresponding hydrazones **7a-c**.

(E)-N'-(1-(1-(4-Fluorophenyl)-5-methyl-1H-1,2,3-triazol-4-yl)-ethylidene)-5-methyl-1-phenyl-1H-1,2,3-triazole-4-carbohydrazide (7a)

Yield 76 %; m.p. 224-225 °C; IR (KBr) ν_{max}/cm-1 1670 (C=O), 3198 (NH); ^{1}H NMR (DMSO-d_6) δ 2.43, 2.47, 2.48 (3s, 9H, 3CH_3), 7.43-7.76 (m, 9 H, Ar-H), 10.75 (s, H, NH, D_2O exchangeable); MS m/z (%): 418 (M^+, 90), 95(100); Anal. Calcd for $C_{21}H_{19}FN_8O$ (418.43): C, 60.28; H, 4.58; N, 26.78 %. Found: C, 60.34; H, 4.63; N, 26.87% .

(E)-1-(4-Fluorophenyl)-5-methyl-N'-(1-(5-methyl-1-p-tolyl-1H-1,2,3-triazol-4-yl)ethylidene)-1H-1,2,3-triazole-4-carbohydrazide (7b)

Yield 78 %; m.p. 220-221 °C; IR (KBr) ν_{max}/cm-1 1668 (C=O), 3199 (NH); ^{1}H NMR (DMSO-d_6) δ 2.43, 2.47, 2.48, 2.50 (4s, 12H, 4CH_3), 7.46-7.75 (m, 8 H, Ar-H), 10.76 (s, H, NH, D_2O exchangeable); MS m/z (%): 432 (M^+, 92), 95(100); Anal. Calcd for $C_{22}H_{21}FN_8O$ (432.45): C, 61.10; H, 4.89; N, 25.91 %. Found: C, 61.24; H, 4.94; N, 26.06% .

(E)-1-(4-Fluorophenyl)-*N*'-(1-(1-(4-fluorophenyl)-5-methyl-1*H*-1,2,3-triazol-4-yl)ethylidene)-5-methyl-1*H*-1,2,3-triazole-4-carbohydrazide (7c)

Yield 78 %; m.p. 240-241 °C; IR (KBr) ν_{max}/cm-1 1672 (C=O), 3280 (NH); ^{1}H NMR (DMSO-d_6) δ 2.41, 2.45, 2.47 (3s, 9H, 3CH_3), 7.46-7.76 (m, 8 H, Ar-H), 10.77 (s, H, NH, D_2O exchangeable); MS m/z (%): 436 (M^+, 88), 95(100); Anal. Calcd for $C_{21}H_{18}F_2N_8O$ (436.42): C, 57.79; H, 4.16; N, 25.68 %. Found: C, 57.83; H, 4.26; N, 25.75% .

Antimicrobial activity

Novel compounds were tested against a panel of gram positive and gram negative bacterial pathogens, yeast and fungi using the reported agar well diffusion method.[7]

Minimal inhibitory concentration (MIC) measurement

The bacterio-static activity of the active compounds (having inhibition zones (*IZ*) ≥ 16 mm) was then evaluated using the two fold serial dilution technique.[7]

REFERENCES

[1]Jin, T., Kamijo, S., Yamamoto, Y., *Eur. J. Org. Chem.* **2004**, *2004*, 3789–3791 .

[2]Liu D., Zheng Y., Steffen W., Wagner M., Buttand H.-J. Ikeda T., *Macromol. Chem. Phys.*, **2013**, *214*, 56–61.

[3]Wang, X.-L., Wan, K., Zhou, C.-H., *Eur. J. Med. Chem.* 2010, *45*, 4631–4639.

[4]San-Féalix, A., Alvarez, R., Veláazquez, S., De Clercq, E., Balzarini, J., Camarasa, M. J., *Nucl. Nucleot.* **1995**, *14*, 595-598.

[5]Moreira O. T., Delle M. F., Domeneghini C. L., Mascarello A., Regina S.T., Roberto Z. C., Bardini S. D., Regina M. B. C., de Fatima A. S. E., Viancelli A, Ariel T. G. L., Augusto Y. R., José N. R., Smânia A. J., *Bioorg Med Chem Lett.* **2012**, *22*, 225-30

[6]Abdel-Aziz, H. A., Abdel-Wahab, B. F., Badria, F. A., *Arch. Pharm.* **2010**, *343*, 152-159

[7]Abdel-Wahab B. F., Mohamed, H. A., Awad, G. E. A,. *Eur. Chem. Bull.*, **2014**, *3*, 1069-1074.

[8]Abdel-Wahab B. F., Mohamed, H. A., Awad, G. E. A., *J. Mod. Med. Chem.*, **2014**, *2*, 70-77.

[9]Mohamed, H. A., Abdel-Latif, E., Abdel-Wahab, B. F., Awad, G. E. A., *Int. J. Med. Chem.*, **2013**, 1-6. http://dx.doi.org/10.1155/2013/986536.

[10]El-Zahany, E. A. M., El-Seidy, A. M. A., Drweesh, S. A., Youssef, N. S., Abdel-Wahab, B. F., El-Beih, A. A., *J. Appl. Sci. Res.*, **2013**, *9*, 2268-2278.

[11]Zhang, Y., Qiao, R.-Z., Xu, P.-F., Zhang, Z.-Y., Wang, Q., Mao, L.-M., Yu, K.-B., *J. Chin. Chem. Soc*., **2002**, *49*, 369-.

[12]Dieckmann, W., Platz O., *Ber. Deutsch. Chem. Ges.*, **1906**, *38*, 2989–2995.

[13]Pokhodylo, N. T., Savka, R. D., Matiichuk, V. S., Obushak, N. D., *Russ. J. Gen. Chem.*, **2009**, *79*, 309–314.

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