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Synthesis, characterization and the antibacterial activity of a new [1,2,3]triazole derivative

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Abstract

The synthesis via the Cu(I)-catalyzed Huisgen dipolar cycloaddition *of N*(triazolyl) *N-(2-nitrophényl)diamine* from *N-(2-nitrophényl)diamine with a good yield (80%).* The newly synthesized compounds were characterized by elemental analysis, FT-IR, MS and NMR spectroscopies. The antibacterial activity of these compounds was evaluated and screened "*in vitro"* using the disc diffusion technique against bacterial strains Gram-positive and Gram-negative. The antibacterial screening results reveal that the three compounds screened showed a good antibacterial activity against bacterial strains Gram-positive (17-38 mm).

1. Introduction

Triazoles and their derivatives are well known to be effective pesticides, fungicides and insecticides [1-3] as well as their anti-inflammatory, antimicrobial, antitumor, antibacterial, antifungal and antiviral agents [4-10]. They have been reported to be inhibitors of enzymes [11], antagonists and agonists of receptors [12-14] and they shown neuroleptic, anti-HIV-1, cytotoxic, antihistaminic, and antiproliferative activities [15-19].Thus, the design and synthesis of novel triazole derivatives are the prospective direction of medicinal chemistry for the scientists working in this field.

The synthesis of triazoles by click chemistry was established by Sharpless et al. for a large type of reactions [20]. These concept offer simple purification methods and benign reaction conditions, and which are therefore particularly suited to link building blocks as the name suggests. Then Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) established by Huisguen has become the prime example of click reactions, being even used synonymously with click chemistry and many applications thereof not only aimed to link two units together but also to synthesize the triazole moiety [21]. This type of reaction was later classified by Huisgen as (3+2) 1,3-dipolar cycloaddition, i.e. the concerted addition of a 1,3-dipole to a multiple bond [22].

We reported herein the synthesis of new [1,2,3]triazole derivative via the Cu(I)-catalyzed version of the Huisgen reaction between a *N-(2-nitrophenyl)ethylenediamine* and a benzyl azide. The prepared compounds were characterized by elemental analysis, FT-IR, MS and NMR spectroscopies.

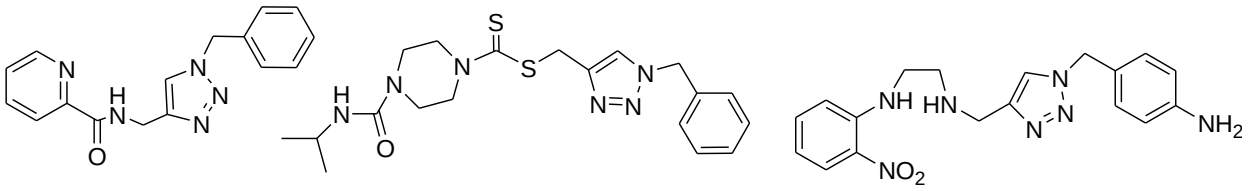
The present study investigates the antibacterial activity of *N-(2-nitrophenyl)ethylenediamine* (**1**); *N-(2 nitrophényl)propylenediamine* (**2**) and *N-[1-(4-Amino-benzyl)-1H-[1,2,3]triazol-4-ylmethyl]-N'-(2-nitro-phenyl)-ethane-1,2-diamine* (**3**) (Scheme.1) against *Listeria, staphylococcus aureus, pseudomonas sp, and escherichia coli.*

2. Experimental details

2.1. Materials

Chemicals and solvents (reagent grade or better) were purchased from Sigma-Aldrich. Anhydrous solvents were dried by usual procedures and stored over 4Å molecular sieves under Argon before use. Chromatography was carried out using basic Al_2O_3. ^1H & ^{13}C-NMR spectra were recorded at room temperature in $CDCl_3$ on a BRUKER AC 200 operating at 200.13 MHz for ^1H and 50.32 MHz for ^{13}C. Data are listed in parts per million

(ppm) and are reported relative to tetramethylsilane; residual solvent peaks of the deuterated solvents were used as internal standard. FT-IR spectra were obtained from KBr-pellets (if not other stated) on a Perkin Elmer Spectrum 1000 spectrophotometer. Low resolution mass spectrometry was carried out on an Agilent 1100 Series LC/MSD apparatus.



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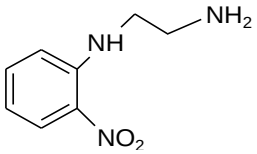
Scheme 1: reported 1,2,3-triazole derivatives in the recent literature as anticancer agent and synthesized 1,2,3-triazole derivative **3.**

2.2. Synthesis

N-(2-nitrophényl)diamine **1** and **2** were prepared by following literature procedures [23].

(10 g, 0.063 mol) of 2- nitrochlorobenzene and diamine (0.67 mol) were stirred 1 h under reflux. The excess of ethylenediamine was removed by distillation and the crude was acidified with 2 N HCl until pH = 6, then heated to 90°C for 5 min and filtered to remove the impurities. The filtrate was cooled and the solid collected by filtration to give 13.5 g of N-(2-nitrophenyl)diamine hydrochloride were collected as orange needles. The product was dissolved in water (10 mL). The solution was basified at pH 12 and extracted twice with chloroform (15 mL). The organic layer was dried over sodium sulfate, filtered and concentrated to dryness under reduce pressure.



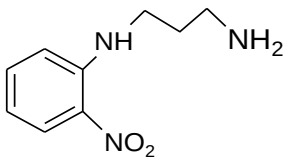
1 from ethylenediamine (10g), orange oil (10.8 g, 95%)

^{1}H NMR (300 MHz, $CDCl_3$) δ_H(ppm) : 1.32 (s large, 2H, NH_2), 3.04 (m, 2H, NCH_2), 3.35 (m, 2H, NCH_2), 6.62 (m, 1H, H-5), 6.85 (dd, 1H, *J* = 0.9 Hz et *J* = 8.7 Hz, 1H, H-3), 7.41 (m, 1H, H-4), 8.13 (dd, 1H, *J* = 1.6 Hz et *J* = 8.7 Hz, H-6), 8.24 (s large, 1H, NH)

^{13}C NMR {^{1}H} (80 MHz, $CDCl_3$) δ_C(ppm) : 40.8 (NCH_2), 45.7 (NCH_2), 113.6 (C-3), 115.3 (C-5), 126.9 (C-6), 133.0 (C-2), 136.2 (C-4), 145.6 (C-1)

IR (KBr) : ν_{N-H} = 3371 cm^{-1}

EA :($C_8H_{11}N_3O_2$, HCl) calculated (Found) : C = 44.2 (44.2); H = 5.6 (5.6); N = 19.7 (19.3), MP = 261°C. MS: calcd. for $C_8H_{11}N_3O_2$ $[M + H]^+$ 182.0, found 182.0.



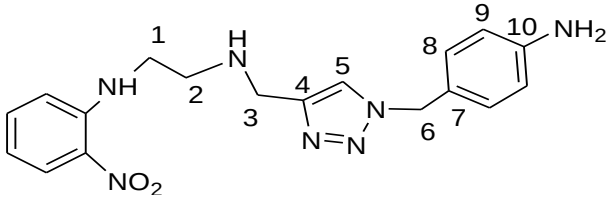
2 from 1,3-diaminopropane (13.85 g), red-orange oil (11.34 g, Rdt = 92%).

^{1}H NMR (300 MHz, $CDCl_3$) δ_H(ppm): 1.82 (q, 2H, *J* = 7.0 Hz, CH_2), 2.82 (t, *J* = 7.0 Hz, 2H, NCH_2), 3.33 (m, 2H, NCH_2), 6.56 (m, 1H, H-5), 6.80 (m, 1H, H-3), 7.35 (m, 1H, H-4), 8.04 (m, 1H, H-6), 8.11 (s large, 1H, NH)

^{13}C NMR {^{1}H} (80 MHz, $CDCl_3$) δ_C(ppm) : 32.3 (CH_2), 39.8 (NCH_2), 41.0 (NCH_2), 113.9 (C-3), 115.7 (C-5), 126.9 (C-6), 131.8 (C-2), 136.4 (C-4), 145.7 (C-1).

IR (KBr) : ν_{N-H} = 3334, 3372 cm^{-1}

MS (DCI/NH_3) : $[M+H]^+$ = 196, calculated (Found) for ($C_9H_{13}N_3O_2$, HCl) : C = 46.7 (46.8); H = 6.2 (6.1); N = 18.2 (18.2). MP = 174°C.



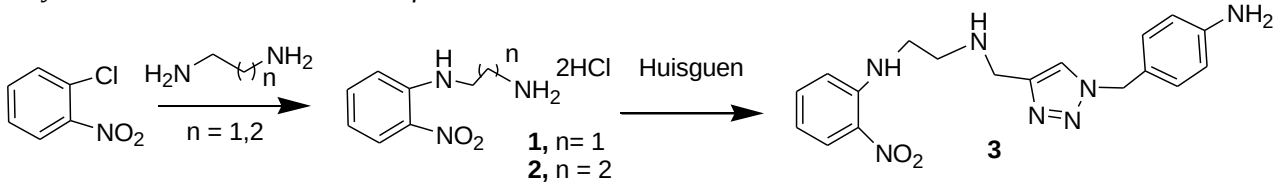
To (nitrophenyl)diamine (8.52 mmol) in 10 mL acteonitrile/water (1:1, v/v) was added triethylamine (20 mmol) and propargyl bromide (2.05 g, 34.04 mmol). After stirring at rt for 2 h, 4-(azidomethyl)aniline (8.52 mmol), sodium ascorbate (2 mmol) and $CuSO_4$ (0.5 mmol) were added to the reaction mixture, and was stirred at room temperature over night. The reaction mixture was concentrated in vacuum to give a crude oil residue. The pure products were purified by liquid chromatography (LC) on silica with mixtures of CH_2Cl_2–MeOH as eluents.

3 ^{1}HNMR(250 MHz, $CDCl_3$): δ 8.42 (sl, 1H, NH), 8.16 (d, 1H, Harom), 7.67 (s, 2H, $H_{Triazol}$), 7.27-7.47 (m, *5H*, H_{arom}), 6.80 (d, 1H, H_{arom}), 6.64 (t, 1H, H_{arom}), 5.51 (s, 4H, CH_2aniline), 3.79 (s, 4H, CH_2triazol), 3.40 (m, 2H, C^1H_2NH), 2.87 (m, 2H, C_2H_2N).
MS: calcd. for $C_{28}H_{29}N_9O_2$ $[M + H]^+$ 367.2, found 367.2.
IR (KBr) : ν_{N-H} = 3370 cm^{-1}

2.3. Antimicrobial activity
2.3.1. Tested microorganisms
The essential oil was tested on different microorganisms, including Gram positive bacteria – *Listeria monocytogenes*, *Staphylococcus aureus*, Gram negative bacteria – *Escherichia coli*, *Pseudomonas Sp*. These species were inoculated on the culture medium Mueller-Hinton agar. All the Microorganisms were procured from the Microbial Type Culture Collection (MTCC), of *Laboratoire Régional de Diagnostic Epidémiologique et d'Hygiène du Milieu, Direction Régionale de la Santé, Hôpital EL GHASSANI, Fès, Maroc.*

2.3.2. Disk-diffusion assay
The disk diffusion method was used for the determination of antibacterial activity. Bacterial species were cultured on Muller Hinton agar media. Sterile filter paper disc was saturated with 10 µl of 0.5 µl/ml v/v solution of the synthesized compounds under investigation in dimethyl sulfoxyde (DMSO). DMSO alone showed no inhibition. The plates and discs were then incubated at 37 °C for 24 h. Each experiment was replicated three times. The antimicrobial activities were evaluated by measuring the inhibition zone diameters (millimeters) surrounding each disk [24].

3. Results and Discussions:
*3.1. Synthesis and characterization of **3**:*



Scheme 2: One-pot synthesis of **3** via the Cu(I)-catalyzed Huisgen reaction.

Compound **3** was isolated in fair to good yield using the one-pot Cu(I)-catalyzed Huisgen reaction [25] from *2-Nitrochlorobenzene* (i.e Scheme 2).The product was purified by silica chromatography to give satisfactory yield (65%) (**Figure 1**).
3 structure was unambiguously ascertained by ^{1}H & ^{13}C NMR, FT-IR, and ES^+-MS. ^{1}H NMR spectrum of this compound exhibit the expected time-averaged 2-fold symmetry and the characteristic aromatic singlet between 6.5 and 8.5 ppm for aromatic protons and the triazol proton at 7.68 ppm at the NMR time scale ($CDCl_3$, 298 K). Further information about the isolation and full characterization of this compound is provided in the experimental section.

4. Antimicrobial activity:
The antimicrobial activity of the synthesized compounds was tested against four different microorganisms: Gram positive bacteria – *Listeria monocytogenes*, *Staphylococcus aureus*, Gram negative bacteria – *Escherichia coli*, *Pseudomonas Sp*. These species were inoculated on the culture medium Mueller-Hinton agar. Antibacterial activity was determined using the disc diffusion assay and the developing inhibition zones were quantified (Table 1). The results of antibacterial activity of the synthesized products are reported in Table 1. The antibacterial activity was measured in terms of zone inhibition diameter (ZI, in mm). the results showed in general, according to the classification of Duraffourd et al.[26], that **1** exhibited a good activity against Gram-positive bacteria (17-38 mm) and moderate activity on Gram-negative bacteria (12-20 mm) and that **2** and **3** are inactive on Gram negative bacteria whereas they exhibit good activity on Gram positive bacteria. The *Staphylococcus aureus* strain (SRSA) showed the greatest sensitivity with a an inhibition zone of 38 mm in the presence of the three products, followed by *Listeria monocytogen* with an inhibition zone range of 6-38 mm.

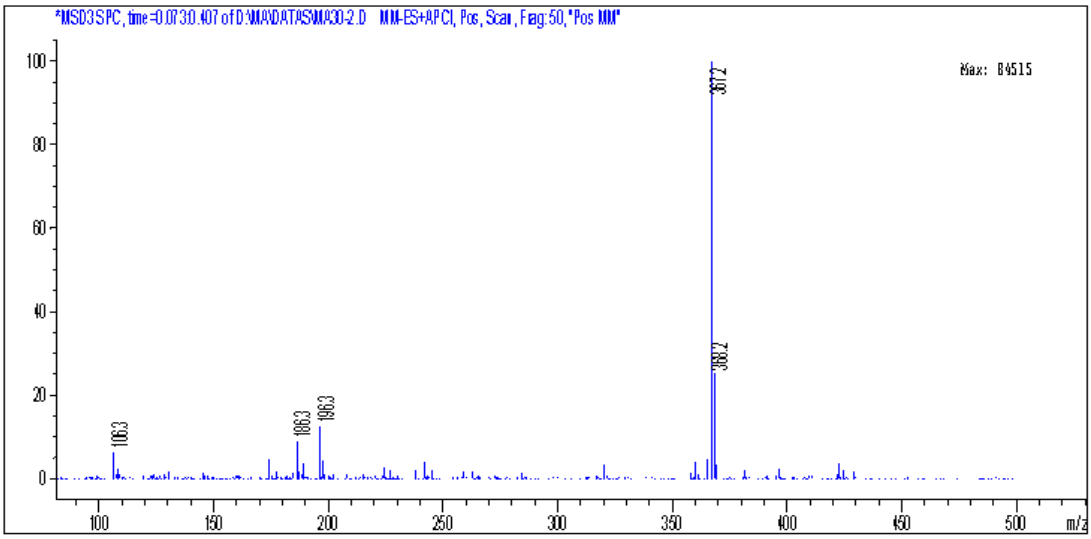


Figure 1: Mass spectrum of **3**

Table 1: Antibacterial activity data.

Inhibition zone diameter (mm)																					
Compound	Gram positive bacteria										Gram negative bacteria										
	Listeria					*S. aureus*						*E. coli*						*Pseudomonas Sp*				
	L1	*L2*	*L5*	*L6*	*L10*	*SRSA*	*SA1*	*SA2*	*SA3*	*SA4*	*SA5*	*ECR*	*EC1*	*EC2*	*EC3*	*EC4*	*EC5*	*PS36*	*PS40*	*PS29*	*PS48*	*PS12*
1	6	20	36	36	17	> 38	20	28	> 38	> 38	25	12	15	12	18	15	20	14	-	-	-	13
2	10	24	38	36	30	> 38	20	-	> 38	> 38	25	31	-	10	10	-	-	-	-	-	-	-
3	10	-	36	38	22	> 38	23	15	> 38	21	13	-	-	-	-	-	-	-	-	-	-	28

All the products tested did not show activity against the tested Pseudomonas Sp strains except against SP36 and SP12. The Escherichia coli strains, developed resistance to **2** and **3**. The excellent response of **1** than **2** suggests the dependence of antibacterial activity of the length of carbon chain of the organic N,N-diamine. Introduction of triazole moiety and especially aniline attached to the triazole nucleus resulted in loss of antibacterial activity due to the decrease of the lipophilicity of the molecule which did not allow it to enter the bacterial cell membrane.

All products have an almost similar structure; they differ only by the position of nitro group or the presence or not of triazole moiety. The findings of the present study revealed that the considerable variations of these effects were seen with each structural change, the possible electronic effects induced by the nitro group are responsible for the inhibitory actions of the studied bacteria.

Conclusion

In summary, we reported in this paper the synthesis of new compound containing [1,2,3]triazole using the one-pot Cu(I)-catalyzed Huisgen reaction. The structure of the synthesized compounds was confirmed by IR, NMR, and Mass spectra. All the synthesized compounds were screened for their in-vitro antibacterial activity against gram-positive and gram-negative bacteria. In summary, preliminary results indicate that Compound **1**, displays a good antibacterial activity against Gram positive bacteria, and Gram negative bacteria. Introduction of triazole moiety on **1** resulted in loss of antibacterial activity against Gram negative bacteria.

References

1. Khanmohammadia H., Mohammad H.A, Hosseinzadeh A., Erfantalab M., *Spectrchim. Acta A* 71 (2008) 1474.
2. Singh K., Barwam M.S., Tyagi P. Eur *P., J. Med. Chem.* 41 (2006)147.
3. Liu K., Shi W., Cheng P., *Dalton Trans* .40 (2011) 8475.

4. Guda D., Wang T., Cho H.M., Lee E., *Tetrahedron Letters*, 53 (2012) 5238.
5. Yang Y., Zhang X. ,Hong J. , *Trans.Met. Chem*. 34 (2009) 791.
6. Nasser S., Khalil A., *Eur. J. Med. Chem*. 45 (2010) 5265.
7. Subashchandrabose S., A. Krishnan A.R., Saleem H., Parameswari R. Sundaraganesan N., Thanikachalam V., Manikandan G., *Spectrochim. Acta, Part A* 77 (2010) 877.
8. Bermejo E., Carballo R., Castineiras A., Dominguez R., Maichle-Mossmer C., Strahle J., West D., Polyhedron, 18 (1999) 3695.
9. Almajan G.L., Barbuceanu S.F., Almajan E.R., Draghici C., Saramet G., *Eur. J. Med. Chem.* 43 (2008) 1.
10. a) Joshi S.D. , Vagdevi H.M. , Vadya, V.P., Gadaginamath G.S., *Eur. J. Med. Chem.* 43 (2008) 1989. b) Ma L-Y., Pang L-P., Wang B., Zhang M., BHu B., Xue D-Q., Shao K-P., Zhang B-L., Liu Y., Zhang E., Liu H-M., , *Eur. J. Med. Chem.* 86 (2014) 368.
11. Olesen P.H., Sorensen A.R., Urso B., Kurtzhals P., Bowler A.N., Ehrbar U., Hansen B.F., *J. Med. Chem*. 46 (2003) 3333.
12. Bascal Z., Holden-Dye L, Willis RJ, Smith SWG, Walker RJ. *Parasitology*. 112 (1996) 253.
13. Biagi G, Giorgi I., Livi O., Lucacchini A., Martini C., Scartoni V.J., *Pharm Sci*. 82 (1993) 893.
14. Moltzen EK, Pedersen H, Bogeso KP, Meier E, Frederiksen K, Sanchez C, Lembol KL. *J Med Chem* 37(1994)4085.
15. Chakrabarti J.K., Hotten T.M., Pullar I.A., Steggles D.J., *J. Med Chem*. 32 (1989) 2375.
16. Alvarez R., Velazquez S., San-Felix A., Aquaro S., De Clercq E., Perno C.F., Karlsson A., Balzarini J., Camarasa M.J., *J Med Chem*. 37 (1994) 4185.
17. Sanghvi Y.S., Bhattacharya B.K., Kini G.D., Matsumoto S.S., Larson S.B., Jolley W.B., Robins R.K., Revankar G.R., *J Med Chem*. 33(1990)336.
18. Buckle DR, Rockell CJM, Smith H, Spicer B.A., *J Med Chem*. 29(1986)2262.
19. Hupe DJ, Boltz R, Cohen CJ, Felix J, Ham E, Miller D, Soderman D, Van Skiver D., *J Biol Chem*. 266(1991)10136.
20. Kolb H. C, Finn M. G and Sharpless K. B., *Angew. Chem., Int. Ed*., 40(2001), 2004.
21. Rostovtsev V. V, Green L. G, Fokin V.V and Sharpless K. B, *Angew. Chem., Int. Ed*., 41(2002), 2596.
22. a) Huisgen R., Szeimies G. and Mo¨bius L., *Chem. Ber*., 100(1967), 2494. b) Bra¨se S, Gil C, Knepper K and Zimmermann V., *Angew. Chem., Int. Ed*., 44 (2005), 5188.
23. a) Allali M., Benoist E., Habbadi N., Gressier M., Souizi A., Dartiguenave M., *Tetrahedron*. 60 (2004) 1167. b) Allali M., Jaud J., Dartiguenave M., Beauchamp A.L., Benoist E., *Eur. J. Inorg. Chem.* 11 (2009) 1488.c) Allali M., Cousinie S., Gressier M., Tessier C., Beauchamp A.L., Coulais Y., Dartiguenave M., Benoist E., *Inorg. Chim. Acta* 359(7) (2006*)* 2128. d). Allali M., Benoist E., Habbadi N., Gressier M., Souizi A., Dartiguenave M., *Dalton trans*. 20 (2004*)* 3178.
24. Ozcan B., Esen M., Sangun M.K., Coleri A., Caliskan M., *J Environ Biol*. 31 (2010) 637.
25. a) Allali M., Mouacha Y., Allali N., Zarrouk A., Habbadi N., *J. Mater. Environ. Sci.*, 7 (7) *(*2016) 3035.
b) Allali M., Mouacha Y., Allali N., Zarrouk A., Habbadi N., *J. Mater. Environ. Sci.*, 7(6) (2016) 2042.
c) Benkhellat Z., Allali M., Beley M., Wenger E., Henry B., Parizel N., Selmeczi K., Joly J.-P., *New J. Chem.* 38 (2014) 419.
d) Selmeczi K., Joly J.-P., Allali M., Yeguas V., Henry B., Ruiz-Lopez M., *Eur. J. Inorg. Chem.* (2014) 4934
26. Duraffourd C., D'Hervicourt L. & Lapraz J.C., 1990.- Cahiers de phytothérapie clinique. 1. Examens de laboratoires galénique. Eléments thérapeutiques synergiques. 2ème éd. Masson, Paris

(2017) ; http://www.jmaterenvironsci.com