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Research Article

Synthesis and Structural Elucidation of Aminoacetylenic Derivatives of 7-Methoxy- 2-Naphthole as Antimicrobial Agents

Abu-Safieh Rana[1], Muhi-Eldeen Zuhair[1*], Alsarahni Aseel[2], Al-Kaissi Elham[2]

[1]*Department of Medicinal Chemistry and Pharmacognosy, Faculty of Pharmacy, University of Petra, Amman, Jordan.*
[2]*Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, University of Petra, Amman, Jordan.*

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ABSTRACT

A new series of 7-methoxy-2-[4-(t-amino-1-yl)oxy]-naphthalene derivatives; 7-methoxy-2-{[4-(2-methylpiperidine)but-2-yn-1-yl]oxy}-naphthalene (**RZ2**), 7-methoxy-2-{[4-(2,6-dimethylpiperidine)but-2-yn-1-yl]oxy}-naphthalene (**RZ3**), 7-methoxy-2{[4-(piperidine)but-2-yn-1-yl]oxy}-naphthalene (**RZ4**), 7-methoxy-2-{[4-(pyrrolidine)but-2-yn-1-yl]oxy}-naphthalene (**RZ5**), 7-methoxy-2-{[4-(N-methylpiperazine)but-2-yn-1-yl]oxy}-naphthalene (**RZ6**), 7-methoxy -2-{[4-(hexamethyleneimine)but-2-yn-1-yl]oxy}-naphthalene (**RZ7**) were synthesized and screened in *vitro* as potential antimicrobial agents. Antimicrobial activity were evaluated by measuring the minimum inhibitory and bactericidal/fungicidal concentration (MIC, MBC and MFC). **RZ2**, **RZ5**, **RZ6** and **RZ7** showed the highest antimicrobial activity against *S. aureus* with MIC value 62.5 µg/ml, compounds **RZ2, RZ4, RZ5**, and **RZ7** have the highest antimicrobial activity against *B. subtilis* with MIC vale 62.5 µg/ml**, RZ3, RZ6** have the same antimicrobial activity with MIC value 125µg/ml, compounds. **RZ4, RZ5, RZ6** and **RZ7** have the highest antimicrobial activity against *E. coli* with MIC value 125 µg/ml, all compounds have the same MIC value against *P. aeruginosa* (125 µg/ml). **RZ2**, **RZ4**, **RZ5**, **RZ6**, **RZ7** showed the highest antifungal activity with MIC of 62.5 µg/ml. In conclusion, the synthesized compounds showed good antimicrobial activity and promising potency against gram positive bacteria, gram negative bacteria and fungi.

Keywords: Aryloxy; Aminoacetylenic; Antimicrobial; Alkylation; Mannich Reaction.

INTRODUCTION

The need for modern, safe and more effective antimicrobial agents are becoming an urgent need as many bacteria and fungi were becoming multi-antimicrobial resistant, due to unavoidable consequence of the widespread and misuse of the commonly available antimicrobial agents[1-6].

Goksu et al. 2005 synthesized naphthalene derivatives 5-bromo-6methoxynapthalene-2-carboxylic acid and 5,6-dimethoxynapthalene-2-carboxylic acid (Figure 1), these derivatives showed in vitro antimicrobial activity against some types of bacteria[7].

Chakkaravarthi et al. 2014, synthesized novel naphthalene derivative 1-[(3-hydroxy naphthalene-2-yl) methyl]Thioreau (figure 2), this derivative was screened as an antimicrobial agent on *Staphylococcus aureus*, *Mycobacterium smegmatis*, *Pseudomonas aeruginosa*, *Candida albicans*, *Candida tropicalis* and *Candida glabrata*. The synthesized compound showed better activity against tested microbial strains and significant anti-oxidant activities[8].

Aryloxy derivatives as antifungal agents as in tolnaftate or arylallylamine as naftifine[8] and many heterocyclic compounds[9-13], promoted our interest to envision a new and novel series of aryloxyaminoacetylenic derivatives (**RZ2-7**) as potential antimicrobial agents with minimal resistant development. These new molecules provide the following interaction that inhibit various sites within microbial cells. Hydrogen bonding with ether oxygen. π–overlap with naphthyloxy group. Electrostatic interaction with acetylenic moiety and ionic interaction that provided by cyclic amine in addition to the appropriate distance between aryloxy and cyclic amine. The observed antifungal and antibacterial activity presented in table 1 support our vision.

MATERIALS AND METHODS

Experimental

Chemicals

7-methoxy-2-naphtol, propargyl bromide, cyclic amine, 1-methylpiperazine 99%, 2-methylpiperidine 98%, Cis-2,6-dimethylpiperidine 98%, hexamethyleneimine (Azepane) 99%, pyrrolidine 99%, piperidine 99% (Sigma Aldrich, USA), potassium carbonate anhydrous (Gainland Chemical Company, UK), potassium hydroxide (Lonover, UK), para formaldehyde polymer (BDH chemicals Ltd Poole, England), potassium bromide (Scharlau, Spain), cuprous chloride LRG (East Anglia Chemicals, Hadleighlpswich), acetonitrile 99.7% (PanReAcQuimca SA, EU), 1,4-dioxane (FULL Time, China), chloroform (TEDIA, USA), dimethyl sulfoxide (DMSO) (BBC Chemicals for lab, EU).

**Author for Correspondence: zeldeen@uop.edu.jo*

Instrumentation

Analytical balance with a precision 0.01 mg (Phoenix instrument , USA), hot plate with magnetic stirrer (Dragon, China), rotary evaporator 0-100Kpa/0-700mmHg (Rocker 600, Germany), melting point apparatus (Gallenkamp, USA), FT-IR spectrophotometer 7800 to 400 cm-1 (evisa, Poland), DSC (Mettler Toledo, Int Co), UV-VIS (Evolution 160, USA), HPLC-UV (FinniGan Surveyor, USA), NMR 300 MHZ (Varian 300 MHZ, USA), NMR 500 MHZ (Varian 500 MHZ, USA), elemental analyzer with variation range ±4 (Euro Vector, Italy), balance (BoEco, Germany), autoclave machine (Rypa, Spain), incubator (EuroStar, EU), vortex mixer (Labinco, India), hot plate magnetic stirrer (Dragon, china).

Culture media and microorganisms

Mueller Hinton agar (MHA) (Mastgrp Ltd, UK), Muller Hinton broth (MHB) (Mastgrp Ltd, UK), Sabourauds dextrose agar (SDA) (Mastgrp Ltd, UK), Sabourauds dextrose broth (SDB) (Himedia, India). *Staphylococcus aureus* (*S. aureus* ATCC 6538), *Bacillus subtilis* (*B. Subtilis* ATCC 6633), *Pseudomonas aeruginosa* (*P. aeruginosa* ATCC 9027), *Escherichia coli* (*E. coli* ATCC 8739), *Candida albicans* (*C. albicans* ATCC 10231). All these pure culture of bacterial strains were obtained from Dar Al Dawa (Na'ur, Jordan).

Synthesis

*7-methoxy-2-(prop-2-yn-1-yloxy)-naphthalene **(RZ1)***

7-methoxy 2-naphthol (3.485 g, 0.020 mol), potassium carbonate anhydrous (2.75 g, 0.020 mol) and 30-40 ml acetonitrile (ACN) were heated and stirred under reflux until the temperature becomes 75 C, then the propargyl bromide (4.76 g, 0.040 mol) was added dropwise. The mixture was heated and stirred under reflux for an hour, then it was filtered and reduced under reduced pressure. The product was extracted with 1:1 chloroform and distilled water. The chloroform layers were collected and concentrated by reducing pressure. The brown powder $C_{12}H_{12}O_2$, 2.64g, 61.8% yield, m.p (47° C-51° C), retention time UV HPLC (3.348 min), IR spectra (KBr cm^{-1}): 3274 (acetylenic C-H stretching), 2129 (acetylenic C≡C stretching), 1500,1600 (Ar C=C stretching), 828 (Ar C-H stretching), 1031 (ethers C-O stretching), 2954 (CH_3C-H stretching); H^1 NMR (DMSO-d_6): δ(ppm) 3.6 (1H,of ≡CH, singlet), 3.8 (3H, of O-CH_3), 4.9 (2H, of O-CH_2, singlet), 7.0-7.8 (6H, Ar H, multiplet). Elemental analysis: for **$C_{14}H_{12}O_2$**: Calcd: C, 79.22%; H, 5.70%. Found: C, 79.54%; H, 6.02%.

*7-methoxy-2-{[4-(t-amino-1-yl)but-2-yn-1-yl]oxy}-naphthalene by Mannich reaction **(RZ2-7)***

7-methoxy-2-(prop-2-yn-1-yloxy) naphthalene (**RZ1**) (2.12 g, 0.01 mole), Para formaldehyde (0.5 g, 0.015 mole), 0.01 molecyclic amine (1-methylpiperazine, 2-methyl piperidine, 2,6-dimethyl piperidine, azepane, pyrolidine, piperidine) and a catalytic amount of cuprous chloride (0.03g) in 30 ml dioxane were stirred and heated under reflux at 70-75 °C for three hours. The mixture was filtered and evaporated under reduced pressure. The final products were **RZ2-7** as presented in figure 3.

*7-methoxy-2-{[4-(2-methylPiperidine)but-2-yn-1-yl]oxy}-naphthalene **(RZ2)***

RZ2 was synthesized using the procedure described for the synthesis of 7-methoxy 2{[4-(t-amino-1-yl)but-2-yn-1-yl]oxy} naphthalene by Mannich reaction in 1.00g, Yield 31.00%, m.p (78 °C-80 °C), retention time UV-HPLC (2.247 min); FT-IR spectrum (KBr cm^{-1}):δ2921, 2835, 2788 (Alkanes C-H stretching), 1604, 1500 (Ar C=C stretching), 821(Ar C-H bending), 1200 (N-C stretching), 1004 (Ar ether C-O stretching). ^{1}H-NMR (DMSO-d_6) δ (ppm): 0.85 (3H, CH_3, doublet), 0.96-2.56 (9H, protons of cyclic amines, multiplet), 3.51-3.54 (2H, ≡C-CH_2-N, singlet), 4.89 (2H, O-CH_2, singlet), 3.81-3.87 (3H, O-CH_3, singlet), 6.95-7.76 (6H, Ar H, multiplet).

^{13}C-NMR (DMSO-d_6) δ (ppm): 20.06 (CH_3 of cyclic amine), 43.26, 34.59, 26.17 24.44 (cyclic amine carbons), 52.93 (CH_2N carbon), 54.35 (OCH_3 carbon in benzene ring), 56.17 (OCH_2 carbon), 82.41, 80.53 (C≡C carbons), 158.23, 156.04, 135.91, 129.50, 124.52, 116.53, 106.93 (naphthalene ring carbons).

Elemental analysis: for **$C_{21}H_{25}NO_2$**: Calcd: C, 77.98%; H, 7.79; N, 4.33%. Found: C, 77.83%; H, 7.99%; N, 4.73%.

*7-methoxy-2-{[4-(2,6-dimethyl Piperidine)but-2-yn-1-yl]oxy}-naphthalene **(RZ3)***

RZ3 was synthesized using the procedure described for the synthesis of 7-methoxy 2{[4-(t-amino-1-yl)but-2-yn-1-yl]oxy}-naphthalene by Mannich reaction in 1.72 g, yield 50.45%, m.p(97C-102C), retention time UV-HPLC (2.335 min). FT-IR spectra (KBr cm^{-1}) δ: 3064 (Ar C-H stretching), 2912, 2822 (alkanes C-H stretching), 1621, 1511, 1442 (Ar C=C stretching), 839, 790 (Ar C-H bending), 1022 (aryl, alkyl C-O stretching), 1201, 1115 (3° amines N-C stretching). ^{1}H-NMR (DMSO-d_6) δ(ppm): 0.84(6H, 3H of each branched methyl group on cyclic amine, singlet), 2.20 – 1.02 (8H, cyclic amine, multiplet), 3.49 (2H, ≡V-CH_2N, singlet), 3.84-3.91(3H, OCH_3,singlet), 4.89-4.94 (2H, O-CH_2 , singlet), 6.95-7.75 (6H,Ar H, multiplet). ^{13}C-NMR (DMSO-d_6) δ (ppm): 21.19 (CH_3 carbons on cyclic amine), 37.41, 35.19, 24.48 (cyclic amine carbons), 54.92 (CH_2N carbon), 55.53 (OCH_3 carbon on naphthalene ring), 56.23(O-CH_2 carbon), 82.41, 80.53 (C≡C carbons), 158.20, 155.99, 135.89, 129.47, 124.55, 116.58, 107.04 (naphthalene carbons). Elemental analysis: for **$C_{22}H_{27}NO_2$**: Calcd: C, 78.03%; H, 8.06; N, 4.15%. Found: C, 78.41%; H, 8.02%; N, 4.34%.

*7-methoxy-2-{[4-(Piperidine)but-2-yn-1-yl]oxy}-naphthalene **(RZ4)***

RZ4 was synthesized using the procedure described for the synthesis of 7-methoxy-2-{[4-(t-amino-1-yl)but-2-yn-1-yl]oxy}-naphthalene by Mannich reaction in 1.2 g, yield 38.83%, m.p (38C-44C), retention time UV-HPLC (2.235 min). FT-IR (KBr cm^{-1}) δ: 3056 (Ar C-H stretching), 2927, 2852 (alkanes C-H stretching), 1625, 1521, 1461 (Ar C=C stretching), 829 (Ar C-H bending), 1022 (aryl, alkyl C-O stretching), 1216, 1125 (3° amines N-C stretching). ^{1}H-NMR (DMSO-d_6): δ (ppm) 1.37-3.20 (10H, cyclic amine, multiplet), 3.53 (2H, ≡C-CH_2-N, singlet), 3.86 (3H, O-CH_3, singlet), 4.91 (2H, O-CH_2, singlet), 6.95-7.75 (6H, Ar H, multiplet). Elemental analysis: for **$C_{20}H_{23}NO_2$**: Calcd: C, 77.64%; H, 7.49%; N, 453%. Found: C, 77.94%; H, 7.83%; N, 4.88%.

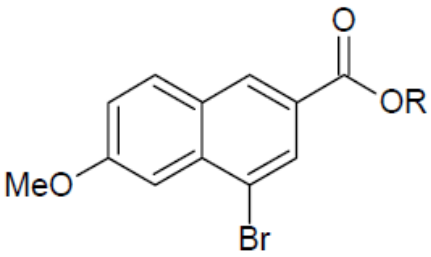


Figure 1: 5-bromo-6methoxynapthalene-2-carboxylic acid[7].

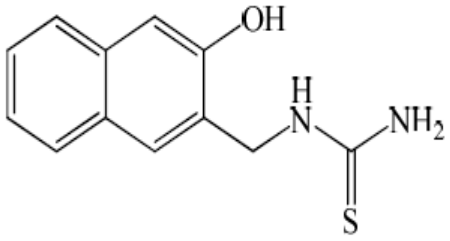


Figure 2: 1-[(3-hydroxy naphthalene-2-yl)methyl]thiourea[8].

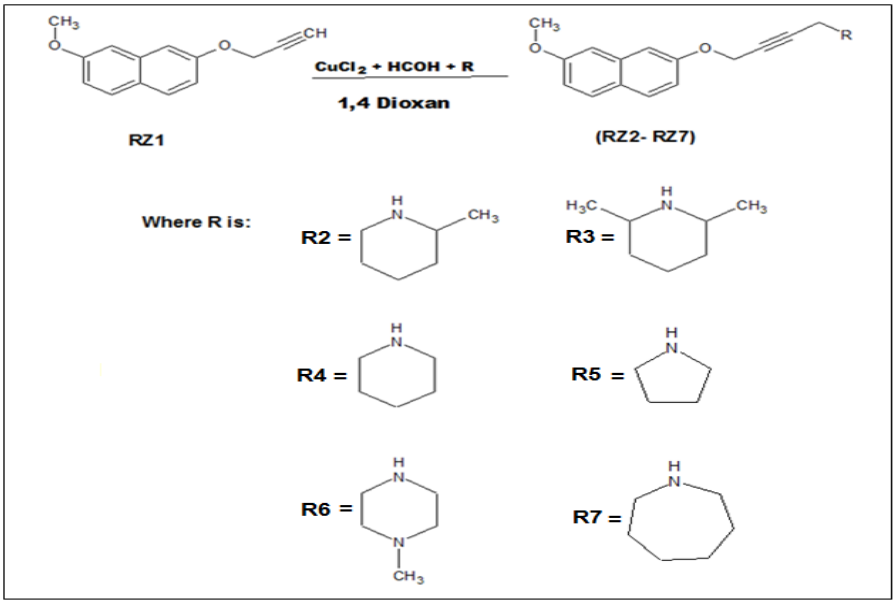


Figure 3: Synthesis of 7-methoxy-2-{[4-(t-amino-1-yl)but-2-yn-1-yl]oxy}- naphthalene derivatives by Mannich reaction (RZ2-RZ7).

*7-methoxy-2-{[4-(Pyrrolidine)but-2-yn-1-yl]oxy}-naphthalene **(RZ5)***

RZ5 was synthesized using the procedure described for the synthesis of 7-methoxy-2-{[4-(t-amino-1-yl)but-2-yn-1-yl]oxy}-naphthalene by Mannich reaction in 1.7 g, yield 57.63%, retention time (2.16 min), FT-IR (KBr cm^{-1}): 3045 (Ar C-H stretching), 2948 (alkanes C-H stretching), 1621, 1521, 1465 (Ar C=C stretching), 833 (Ar C-H bending), 1027 (aryl, alkyl C-O stretching), 1224, 1137 (3º amines N-C stretching).^{1}H-NMR (DMSO-d_6) δ(ppm): 1.55-2.40 (8H, cyclic amine, multiplet), 3.53 (2H,≡C-CH_2-N, singlet), 3.96-3.87 (3H, O-CH_3,singlet), 4.93, 4.88 (2H, O-CH_2, singlet), 6.95-7.75 (6H, Ar H, multiplet). 13C-NMR (DMSO-d_6) δ (ppm): 42.89, 23.72 (cyclic amine carbons), 52.13 (CH_2N carbon), 55.47 (OCH_3 on naphthalene), 56.14 (OCH_2 carbon), 82.79, 80.17 (C≡C carbons), 158.21, 156.05, 135.97, 129.60, 124.59, 116.30, 106.74 (naphthalene carbons). Elemental analysis: **($C_{19}H_{21}NO_2$),** Calcd: C, 77.26%; H, 7.17%; N 4.74%. Found: C, 77.67%; H, 7.34%; N, 5.03%.

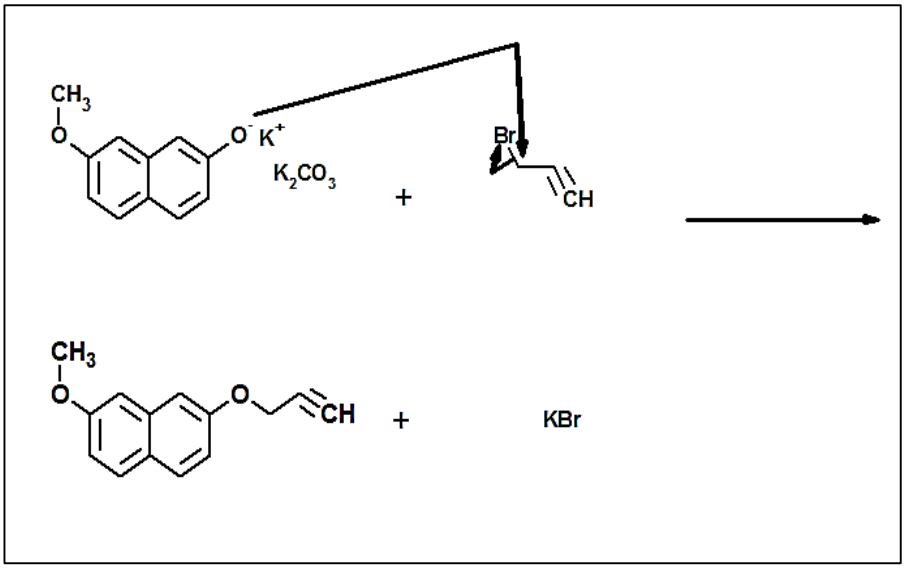
*7-methoxy-2-{[4-(N-methylPiperazine)but-2-yn-1-yl]oxy}-naphthalene **(RZ6)***

RZ6 was synthesized using the procedure described for the synthesis of 7-methoxy-2-{[4-(t-amino-1-yl)but-2-yn-1-yl]oxy}-naphthalene by Mannich reaction in 1.9g, yield (58.82%) and UV-HPLC retention time: (2.205 min). FT-IR (KBr cm^{-1}): δ 3064 (Ar C-H stretching), 2929 (alkanes C-H stretching), 1506, 1440 (Ar C=C stretching), 829 (Ar C-H bending), 1272 (aryl, alkyl C-O stretching), 1220 (3º amines N-C stretching). 1H-NMR: δ (ppm) 2.09 (3H, of N-CH3, singlet), 2.39-3.255 (8H of cyclic amine, multiplet), 3.53 (2H, ≡C-CH_2-N, singlet), 3.88-3.98 (3H, O-CH3, singlet), 4.94, 4.88, (2H, O-CH_2, singlet), 6.95-7.76 (6H, Ar H). Elemental analysis: **$C_{20}H_{24}N_2O_2$**, Calcd: C, 74.04%; H, 7.46%; N, 8.64%. Found: C, 47.42%; H, 7.85%; N, 8.97%.

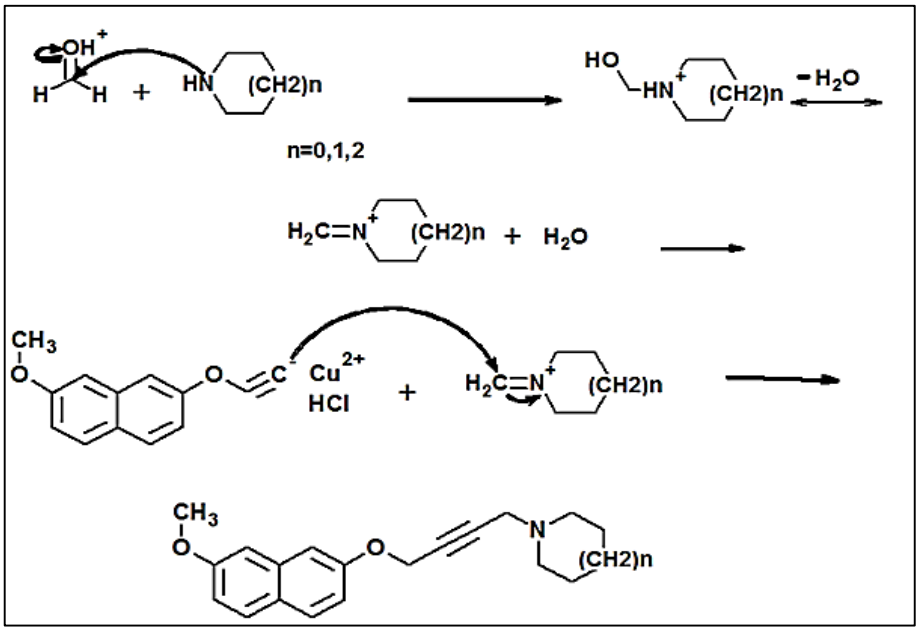
*7-methoxy-2-{[4-(Hexamethyleneimine)but-2-yn-1-yl]oxy}-naphthalene **(RZ7)***

RZ7 was synthesized using the procedure described for the synthesis of 7-methoxy -2-{[4-(t-amino-1-yl)but-2-yn-1-yl]oxy}-naphthalene by Mannich reaction in 1.6 g, yield (49.38%) and UV-HPLC retention time: (2.205 min). FTIR(KBr cm^{-1}): δ 3066 (Ar C-H stretching), 2931,2854 (alkanes C-H stretching), 1517, 1457 (Ar C=C stretching), 856, 839 (Ar C-H bending), 1224 (aryl, alkyl C-O stretching), 1027 (3º amines N-C stretching).1H-NMR: δ (ppm) 1.40-3.31 (12H of cyclic amine, multiplet), 3.53 (2H, ≡C-CH2-N, singlet), 3.82 (3H, O-CH3, singlet), 4.88 (2H, O-CH2, singlet), 6.95-7.76 (6H, Ar H). Elemental analysis: **$C_{21}H_{25}NO_2$**, Calcd: C, 77.98; H, 7.79%; N, 4.33%. Found: C, 78.29%; H, 7.63%; N, 4.63%.

Antimicrobial activity testing



Scheme 1: Alkylation reaction of 7-methoxy-2-naphthole.



Scheme 2: Mannich reaction proposed.

The novel synthesized compounds 7-methoxy 2{[4-(t-amino-1-yl)but-2-yn-1-yl]oxy} naphthalene (**RZ2-7**) were screened *in vitro* for antimicrobial activity against *Staphylococcus aureus* (*S . aureus*) ATCC 6538p , *Candida albicans (C . albicans)* ATCC 10231, *Pseudomonas aeruginosa (P. aeruginosa)* ATCC 9027, *Escherichia coli (E . coli)* ATCC 8739, and *Bacillus subtilis* (*B. subtilis*) ATCC 6633, by determining the minimum inhibitory concentration (MIC) by broth dilution methods [14], the minimum bactericidal concentration (MBC) and minimum fungicidal concentration (MFC) were also recorded against the selected microorganisms. Stock solutions of the compounds were first prepared by dissolving them in a solution of 30% DMSO in water. Then the stock solutions were serially diluted in twofold dilutions in Muller Hinton broth (MHB) for bacteria and Sabourauds dextrose broth (SDA) for fungi), so as to achieve the required concentrations of the compound ranging from 500-7.875µg/ml. 0.1 ml of the overnight bacterial or fungal broth were added to each tube. Negative control tube contained tested compound dilution in sterile MHB/SDB while, positive control tube contained 0.1 ml of overnight culture and sterile MHB/SDB. The tubes were incubated at 37 ^{O}C for 24 hours for bacteria and 48 hours for fungi. Each concentration tube turbidity was compared with the positive control tube turbidity; MIC tube is the lowest concentration of the compound in which no turbidity was observed. MIC tube and the tubes with dilutions preceded were cultured onto MHA/SDA plates, the plates were incubated at 37 ^{o}C for 24 hours /48 hours for bacteria and fungi respectively. The minimum bactericidal concentrations (MBC) and fungicidal concentrations (MFC) were the lowest concentration of the compound

Table 1: Minimum inhibitory concentration (MIC) of compounds (RZ2-7) in µg/ml against *S. aureus*, *B. subtilis*, *E. coli*, *P. aeruginosa* and *C. albicans.*

Compound Concentration	*P. aeruginosa* MIC/MBC (µg/ml)	*E. coli* MIC/MBC (µg/ml)	*S. aureus* MIC/MBC (µg/ml)	*B. subtilis* MIC/MBC (µg/ml)	*C. albicans* MIC/MBC (µg/ml)
RZ2	125/500	250/500	62.5/125	62.5/125	62.5/125
RZ3	125/500	250/500	125/250	125/250	125/250
RZ4	125/500	125/500	125/250	62.5/125	62.5/125
RZ5	125/500	125/500	62.5/125	62.5/125	62.5/125
RZ6	125/500	125/500	62.5/250	125/250	62.5/125
RZ7	125/500	125/500	62.5/125	62.5/125	62.5/125
Ciprofloxacin	50	25	50	25	
Fluconazole					8
Negative control	-	-	-	-	-

RZ2: 7-methoxy-2-{[4-(2-methyl Piperidine)but-2-yn-1-yl]oxy}-naphthalene
RZ3: 7-methoxy-2-{[4-(2,6-dimethyl Piperidine)but-2-yn-1-yl]oxy}-naphthalene
RZ4: 7-methoxy-2-{[4-(Piperidine)but-2-yn-1-yl]oxy}-naphthalene
RZ5: 7-methoxy-2-{[4-(Pyrrolidine)but-2-yn-1-yl]oxy}-naphthalene
RZ6: 7-methoxy-2-{[4-(N-methyl Piperazine)but-2-yn-1-yl]oxy}-naphthalene
RZ7: 7-methoxy-2-{[4-(Hexamethyleneimine)but-2-yn-1-yl]oxy}-naphthalene
MIC: Minimum Inhibitory Concentration.
MBC: Minimum Bactericidal Concentration.
MFC: Minimum Fungicidal Concentration.

gave no growth[14]. The results of antimicrobial testing are reported and compared with those of the standard drugs (Ciprofloxacin 5 µg/ml and Fluconazole 500 µg/ml). Antimicrobial activity testing was performed in triplicates.

RESULTS AND DISCUSSION

Chemistry

Compounds (**RZ2-7**) were synthesized as illustrated in (scheme 1 and scheme 2). Scheme 1 involves the alkylation of 7-methoxy-2-naphthole by addition propargyl bromide under basic conditions. This reaction generates phenolate anion that displaces the bromine on β-carbon of propargyl bromide afforded 7-methoxy-2-(prop-2-oxy)-naphthalene. In Mannich reaction Schiff base formation was generated from condensation of the formaldehyde with the cyclic amine, followed by dehydration. The attack of the acetylenic anion of the methoxy-2-(prop-2-yn-1-yloxy) on the carbon double bond of the Schiff base yielded the desired compounds (**RZ2-7**) as an outline in scheme 2.

Antimicrobial activity

The novel synthesized compounds (**RZ2-7**) showed antimicrobial activity against all types of the microorganisms tested (Table 1). Compounds **RZ4-7**demonstrated the highest antimicrobial activity against *E. coli* with MIC value 125 µg/ml. Compounds**RZ2, RZ5, RZ6, RZ7** showed good antimicrobial activity against *S. aureus* with MIC value 62.5 µg/ml. Compound **RZ2**, **RZ4, RZ5, RZ7** exerted antimicrobial activity against *B. subtilis* with MIC value 62.5 µg/ml. Compounds **RZ2, RZ4, RZ5, RZ6, RZ7** showed antimicrobial activity against *C. albicans* with MIC value 62.5 µg/ml. All compounds exhibited antimicrobial activity against *P. aeruginosa* with MIC value 125 µg/ml. These results suggested that the newly synthesized compounds possess structural and electronic distribution that enable them to cross or penetrate the bacterial cells which are porins or lipid mediated pathway; this may be reflected in their activity against *P. aeruginosa* and *E. coli*. These compounds were also active against Gram positive bacteria (*S. aureus* and *B. subtilis*) were the peptidoglycan in Gram positive cells is more receptive to antimicrobial agent due to the absence of the outer membrane. Additionally the various electronic sites may interfere with various enzymes or sites in these microorganisms.

In considering the differences in potency with the cyclic amine we recognize that the steric factors lower the potency as in comparing **RZ3** with **RZ5** and **RZ2**. The size of cyclic amine or the lipophilicity of similar compounds were influenced on potency in various compounds.

CONCLUSION

In conclusion, a unique aminoacetylenic derivative of naphthol provides an additional force of interaction with various microorganisms that showed good and promising activity against bacteria and fungi, and open a new area of investigation.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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