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Original Article

SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF FUSED ISOXAZOLE DERIVATIVES USING GRINDING METHOD

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ABSTRACT

Objective: A facile and efficient synthesis of new pyrazoloisoxazole, isoxazolopyridine and isoxazolopyrimidine derivatives is discribed through interaction of isoxazolone derivative with different nitrogen nucleophiles. Nine of the newly synthesized compounds were tested for antibacterial activities.

Methods: Interaction of isoxazolone derivative with different nitrogen nucleophiles under grinding conditions.

Results: New pyrazoloisoxazole, isoxazolopyridine and isoxazolopyrimidine derivatives were synthesized and the structures of the prepared compounds were elucidated from spectral data.

Conclusion: 4-(4-Chlorobenzylidene)-3-phenylisoxazol-5(4*H*)-one was utilized as key intermediate for the synthesis of some new heterocycles, namely pyrazoloisoxazole, isoxazolopyridine and isoxazolopyrimidine derivatives under grinding conditions. Most of the newly synthesized products revealed moderate activity against Gram-negative and Gram-positive bacteria.

Keywords: Isoxazolone derivative, Pyrazoloisoxazole derivatives, Hydrazino and hydrazides compounds, Grinding and antimicrobial activity.

INTRODUCTION

In a previous work we reported that some of our newly substituted heterocyclic compounds exhibited antitumor [1-4], antimicrobial [5-9] and 5-α-reductase inhibitors [10] activities. Pyrazoloisoxazole ring system presents interesting pharmacological and biological activities as chemotherapeutic agents, previous work showed the use of such compounds in treatment of Alzheimer's disease [11]. In addition, pyrazoloisoxazoles possess various biological activities including antimicrobial [12,13], herbicide [14], hence, pyrazoloisoxazoles have wide applications in pharmaceutical field as well as in agrochemical industry. Numerous compounds containing pyrazoloisoxazoles moieties have been shown to exhibit anti-hyperglycemic, analgesic, anti-inflammatory, antiviral, antitumor, antifungal and anti-depressant activities [15-27], they are also useful intermediate for many industrial products [28, 29]. In view of these reports and in continuation of our previous works in synthesis of bioactive heterocyclic compounds, we have herein interested in synthesis of novel pyrazoloisoxazoles and investigation their antibacterial activity.

MATERIALS AND METHODS

Melting points were measured on Electrothermal IA 9000 series digital melting point apparatus. The IR spectra were recorded in potassium bromide discs on a Pye Unicam SP 3300 and Shimadzu FT IR 8101 PC infrared spectrophotometer. ^{1}H NMR spectra was recorded in deuterated dimethyl sulfoxide (DMSO-*d*6) using a Varian Gemini 300 NMR spectrometer. Mass spectra were recorded on a Shimadzu GCMS-QP1000 EX mass spectrometer at 70 eV. Elemental analysis and antibacterial measurements were carried out at the Microanalytical Centre of Cairo University, Giza, Egypt. All reactions were followed by TLC (Silica gel, Merck). 4-(4-Chlorobenzylidene)-3-phenylisoxazol-5(4*H*)-one [30] was prepared as reported in the literature.

Synthesis of pyrazolo[4,3-d]isoxazoles 3a,b, 7, 9, 11 and isoxazolo[5,4-c]isoxazole 5

General procedure

A mixture of 4-(4-chlorobenzylidene)-3-phenylisoxazol-5(4*H*)-one **1** (0.283 g, 1 mmol) and each of the appropriate hydrazine derivatives, namely hydrazinehydrate **2a**, phenylhydrazine **2b**, (2,6-dichloro-4-(trifluoromethyl)phenyl)hydrazine **6**, 2-hydrazinyl-4,4-diphenyl-1*H*-imidazol-5(4*H*)-one **8**, 3-hydrazinyl-5,6-diphenyl-1,2,4-triazine **10** or hydroxylamine hydrochloride **4** (1 mmol) and few drops of acetic acid was thoroughly ground with a pestle in an open mortar at room temperature for 3-6 min until the mixture turned into a melt. The initial syrupy continued for 5-15 min and the reaction was monitored by TLC. The solid was washed with water and crystallized from the appropriate solvent to give pyrazolo[4,3-d]isoxazoles **3a,b**, **7**, **9**, **11** and isoxazolo[5,4-c]isoxazole **5,** respectively**.** The synthesized compounds **3a,b**, **5**, **7**, **9** and **11** together with their physical and spectral data are listed below.

4-(4-Chlorophenyl)-3-phenyl-5,6-dihydro-4*H*-pyrazolo[4,3-d]isoxazole (3a). Yield 72%; white solid; mp 238-240 °C; ^{1}HNMR (DMSO-d_6): δ 4.73 (s, 1H, Pyrazole-H), 7.21-7.87 (m, 9H, ArH), 8.60, 11.23 (2s, 2H, D_2O exchangeable, 2NH); IR (KBr): ν_{max} 1636 (C=N), 3195, 3336 (2NH) cm^{-1}; MS m/z (%): 299(M^++2, 5), 297(M^+, 14), 282(31), 160(59), 103(89), 51(100). Anal.Calcd for $C_{16}H_{12}ClN_3O$ (297.74): C, 64.54; H, 4.06; N, 14.11. Found C, 64.59; H, 4.02; N, 14.04%.

4-(4-Chlorophenyl)-3,5-diphenyl-5,6-dihydro-4*H*-pyrazolo[4,3-d]isoxazole (3b). Yield 78%; white solid; mp 230-232 °C; ^{1}HNMR (DMSO-d_6): δ 4.77 (s, 1H, Pyrazole-H), 7.17-7.82 (m, 14H, ArH), 8.61 (s, 1H, D_2O exchangeable, NH); IR (KBr): ν_{max} 1638 (C=N), 3332 (NH) cm^{-1}; MS m/z (%): 375(M^++2, 8), 373(M^+, 26), 186(54), 147(42), 130(87), 60(100). Anal. Calcd for $C_{22}H_{16}ClN_3O$ (373.83): C, 70.68; H, 4.31; N, 11.24. Found C, 70.55; H, 4.25; N, 11.16%.

4-(4-Chlorophenyl)-5-(2,6-dichloro-4-(trifluoromethyl)phenyl)-3-phenyl-5,6-dihydro-4*H*-pyrazolo[4,3-d]isoxazole (5). Yield 71%; white solid; mp 123-125 °C; ^{1}HNMR (DMSO-d_6): δ 4.82 (s, 1H, Pyrazole-H), 7.11-7.84 (m, 11H, ArH), 8.63 (s, 1H, D_2O exchangeable, NH); IR (KBr): ν_{max} 1602 (C=N), 3331 (NH) cm^{-1}; MS m/z (%): 510(M^+, 13), 343(43), 208(42), 111(87), 75(100). Anal. Calcd for $C_{23}H_{13}Cl_3F_3N_3O$ (510.72): C, 54.09; H, 2.57; N, 8.23. Found C, 54.17; H, 2.50; N, 8.17%.

2-(4-(4-Chlorophenyl)-3-phenyl-4*H*-pyrazolo[4,3-d]isoxazol-5(6*H*)-yl)-4,4-diphenyl-1*H*-imidazol-5(4*H*)-one (7). Yield 78%; white solid; mp 322-324 °C; ^{1}HNMR (DMSO-d_6): δ 4.68 (s, 1H,

Pyrazole-H), 7.07-7.73 (m, 19H, ArH), 8.63 (s, 1H, D_2O exchangeable, NH), 10.18 (s, 1H, D_2O exchangeable, NH); IR (KBr): ν_{max} 1606 (C=N), 1645 (C=O), 3166, 3339 (2NH) cm^{-1}; MS m/z (%): 533(M^++2, 13), 531(M^+, 35), 357(64), 220(64), 152(63), 59(100). Anal. Calcd for $C_{31}H_{22}ClN_5O_2$ (531.99): C, 69.99; H, 4.17; N, 13.16. Found C, 69.91; H, 4.12; N, 13.05%.

4-(4-Chlorophenyl)-5-(5,6-diphenyl-1,2,4-triazin-3-yl)-3-phenyl-5,6-dihydro-4*H*-pyrazolo [4,3-d]isoxazole (9). Yield 75%; yellow solid; mp 292-294 °C; ^{1}HNMR (DMSO-d_6): δ 4.66 (s, 1H, Pyrazole-H), 7.12-7.79 (m, 19H, ArH), 8.66 (s, 1H, D_2O exchangeable, NH); IR (KBr): ν_{max} 1600 (C=N), 3332 (NH) cm^{-1}; MS m/z (%): 530(M^++2, 6), 528(M^+, 17), 499(76), 306(84), 105(89), 77(100). Anal. Calcd for $C_{31}H_{21}ClN_6O$ (528.99): C, 70.39; H, 4.00; N, 15.89. Found C, 70.26; H, 4.04; N, 15.77%.

4-(4-Chlorophenyl)-3-phenyl-4,6-dihydroisoxazolo[5,4-c]isoxazole (11)

Yield 78%; yellow solid; mp 195-196 °C; ^{1}HNMR (DMSO-d_6): δ 4.83 (s, 1H, isoxazole-H), 7.22-7.69 (m, 9H, ArH), 9.19 (s, 1H, D_2O exchangeable, NH); IR (KBr): ν_{max} 1614 (C=N), 3348 (NH) cm^{-1}; MS m/z (%): 300(M^++2, 45), 298(M^+, 37), 238(76), 189(59), 80(100). Anal. Calcd for $C_{16}H_{11}ClN_2O_2$ (298.72): C, 64.33; H, 3.71; N, 9.38. Found C, 64.27; H, 3.56; N, 9.23%.

Reaction of arylidene 1 with acid hydrazides 12, 14 and 16

A mixture of **1** (0.283 g, 1 mmol) and each of benzohydrazide **12**, benzenesulfonohydrazide **14** or terephthalohydrazide **16** (1 mmol) and few drops of acetic acid was thoroughly ground with a pestle in an open mortar at room temperature for 3-6 min until the mixture turned into a melt and grinding was continued for further 5-15 min (monitored by TLC).

The solid formed was washed with water and crystallized from the appropriate solvent to give pyrazolo[4,3-d]isoxazole **13, 15** and bispyrazolo[4,3-d]isoxazole **17** derivatives**,** respectively**.**

(4-(4-Chlorophenyl)-3-phenyl-4*H*-pyrazolo[4,3-d]isoxazol-5(6*H*)-yl)(phenyl)methanone (13). Yield 69%; white solid; mp 183-185 °C; ^{1}HNMR (DMSO-d_6): δ 4.68 (s, 1H, Pyrazole-H), 7.16-7.94 (m, 14H, ArH), 8.72 (s, 1H, D_2O exchangeable, NH); IR (KBr): ν_{max} 1598 (C=N), 1651 (C=O), 3329 (NH) cm^{-1}; MS m/z (%): 403(M^++2, 17), 401(M^+, 46), 317(64), 234(78), 109(75), 53(100). Anal. Calcd for $C_{23}H_{16}ClN_3O_2$ (401.85): C, 68.74; H, 4.01; N, 10.46. Found C, 68.64; H, 4.00; N, 10.32%.

4-(4-Chlorophenyl)-3-phenyl-5-(phenylsulfonyl)-5,6-dihydro-4*H*-pyrazolo[4,3-d]isoxazole

(15). Yield 74%; white solid; mp 146-148 °C; ^{1}HNMR (DMSO-d_6): δ 4.86 (s, 1H, Pyrazole-H), 7.23-7.90 (m, 14H, ArH), 9.32 (s, 1H, D_2O exchangeable, NH); IR (KBr): ν_{max} 1594 (C=N), 3303 (NH) cm^{-1}; MS m/z (%): 439(M^++2, 33), 437(M^+, 86), 321(54), 222(69), 124(82), 89(100). Anal. Calcd for $C_{22}H_{16}ClN_3O_3S$ (437.90): C, 60.34; H, 3.68; N, 9.60. Found C, 60.17; H, 3.61; N, 9.39%.

1,4-Phenylenebis((4-(4-chlorophenyl)-3-phenyl-4*H*-pyrazolo[4,3-d]isoxazol-5(6*H*)-yl) methanone) (17). Yield 63%; white solid; mp 342-344 °C; ^{1}HNMR (DMSO-d_6): δ 4.63 (s, 2H, 2Pyrazole-H), 7.19-7.64 (m, 14H, ArH), 7.86 (s, 8H, ArH), 8.78 (s, 2H, D_2O exchangeable, 2NH); IR (KBr): ν_{max} 1599 (C=N), 1647 (C=O), 3324 (NH) cm^{-1}; MS m/z (%): 726(M^++2, 46), 724(M^+, 88), 594(100), 487(90), 357(72), 148(81), 73(83). Anal. Calcd for $C_{40}H_{26}Cl_2N_6O_4$ (725.58): C, 66.21; H, 3.61; N, 11.58. Found C, 66.05; H, 3.54; N, 11.44%.

Synthesis of 4-(4-chlorophenyl)-3-phenyl-4,10-dihydrobenzo [b] isoxazolo[5,4-e][1,4] thiazepine (19). A mixture **1** (0.283 g, 1 mmol), 2-aminobenzenethiol **18** (0.125 g, 1 mmol) and few drops of acetic acid was thoroughly ground with a pestle in an open mortar at room temperature for 3 min until the mixture turned into a melt. The initial syrupy continued for 15 min. The solid was washed with water and crystallized from DMF to give **19** in 66 % yield as yellow solid; mp 112-114 °C; ^{1}HNMR (DMSO-d_6): δ 4.81 (s, 1H, Pyrazole-H), 7.20-7.78 (m, 13H, ArH), 12.26 (s, 1H, D_2O exchangeable, NH); IR (KBr): ν_{max} 1590 (C=N), 3422 (NH) cm^{-1}; MS m/z (%): 392(M^++1, 7), 390(M^+, 69), 301(74), 208(67), 130(100), 66(74). Anal. Calcd for $C_{22}H_{15}ClN_2OS$ (390.89): C, 67.60; H, 3.87; N, 7.17. Found C, 67.46; H, 3.77; N, 7.03%.

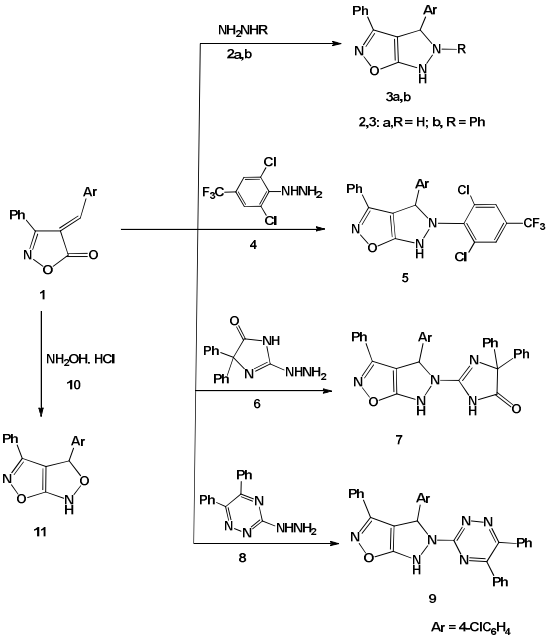
Synthesis of 5-acetyl-4-(4-chlorophenyl)-3,7-diphenylisoxazolo [5,4-b]pyridin-6(7H)-one (21).A mixture **1** (0.283 g, 1 mmol), acetoacetanilide **20** (0.177 g, 1 mmol), and potassium carbonate (0.3 g) was thoroughly ground with a pestle in an open mortar at room temperature for 4 min until the mixture turned into a melt. The initial syrupy continued for 15 min. The solid was washed with water and crystallized from DMF to give **21** in 72 % yield as yellow solid; mp 250-252°C; ^{1}HNMR (DMSO-d_6): δ 2.48 (s, 3H, CH_3CO), 7.12-7.87 (m, 14H, ArH); IR (KBr): ν_{max} 1599 (C=N), 1705, 1647 (2C=O), 3323 (NH) cm^{-1}; MS m/z (%): 442(M^++2, 16), 440(M^+, 50), 325(56), 183(83), 80(57), 64(100). Anal. Calcd for $C_{26}H_{17}ClN_2O_3$ (440.88): C, 70.83; H, 3.89; N, 6.35. Found C, 70.69; H, 3.91; N, 6.28%.

Agar diffusion well method to determine the antimicrobial activity: The microorganism inoculums were uniformly spread using sterile cotton swabs on a sterile Petri dish containing nutrient agar. One hundred cubic millimeters of each sample was added to each well (10-mm-diameter holes were cut in the agar gel). The systems were incubated for 24–48 h at 37 °C. After incubation, the microorganism growth was observed. Inhibition zones of the bacterial growth were measured in millimeters. Tests were performed in triplicate [31].

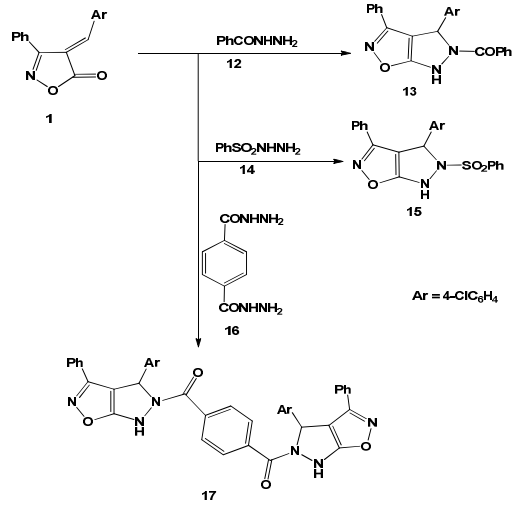
RESULTS AND DISCUSSION

Our synthetic strategy is based on the reaction of the key intermediate isoxazolone derivative 1(easily prepared from ethyl benzoylacetate, hydroxyl amine hydrochloride and aromatic aldehyde as depicted in literature [30]) with different nucleophilic reagents. The carbonyl group in combination with the arylidene double bond, provide a rich opportunity for heterocyclic construction. Herein, the carbonyl oxygen could be removed as a molecule of water with hydrogens bearing compounds and the arylidene double bond could disappear through Michael-like type addition; synthetic strategy successfully provides a concise one-pot reaction to afford the target compounds in fairly good yields. In a first experiment, The reaction of compound 1 with different nitrogen nucleophiles such as hydrazine and phenylhydrazine simply furnished the pyrazoloisoxazole derivative 3a,b (scheme 1). The reaction was performed through grinding at room temperature without addition of any solvent. The structures of the synthesized compounds were established on the basis of IR, ^{1}HNMR, elemental analysis and molecular weights of them were confirmed by mass spectrometry. The IR spectrum of compound 3a revealed absorption bands in the range of 3195-3336 due to the NH stretching vibrations while the absorption bands of the carbonyl and the arylidene double bond functipns have been disappeared, Furthermore, the mass spectra for compound 3a,b showed the correct molecular ion peaks consistent with the proposed structures. In the ^{1}HNMR spectrum of compound 3a, very characteristic signal at 4.73 ppm attributed to the benzylic proton in the pyrazole ring, in addition, two exchangeable protons signals at 8.60 and 11.23 ppm due to the two NH functions. The simplicity and effeciency of such reactions, forced us to investigate the combination of title compound 1 with more versatile hydrazino compounds, 2,6-dichloro-4-trifluoromethyl-phenyl hydrazine 4 reacted in the same manner with compound 1 under same conditions to afford compound 5. In addition, the isoxazolone derivative 1 reacted with hydrazinohydantoin 6 and hydrazinotriazine 8 under same conditions to give the corresponding pyrazoloisoxazole derivatives 7 and 9 respectively (scheme 1). The structures of compounds 5, 7 and 9 were elucidated based on their elemental analysis and spectral data, IR spectra of all compounds displayed absorption bands in the range 3331-3339 cm-1due to NH functions, in addition an absorption band in the spectrum of compound 7 at 1645 cm-1 assigned to the hydantoin carbonyl group. The mass spectra of compounds 5 and 7 showed the correct molecular ion peaks at m/e = 510 and m/e = 531 respectively. However, the 1HNMR spectrum of compound 9 gave a signal at 4.66 ppm characteristic to benzylic proton (pyrazole ring), also, the aromatic region displayed signals in the range 7.12-7.79 ppm integrating for 19 protons (in comparison with 9 protons in the

starting material), a downfield one exchangeable proton signal at 8.66 ppm related to the NH group. On the other hand, the combination between compound 1 and hydroxylamine hydrochloride under grinding proceeded in the same manner but furnished the isoxazoloisoxazole derivative 11 in a very good yield (scheme 1). Structure confirmations of compound 11 were assisted from its IR mass spectrum and elemental analysis.



Scheme 1: Reaction of 1 with hydrazines and hydroxylamine



Scheme 2: Reaction of 1 with acid hydrazides 12, 14 and bis-hydrazides 16

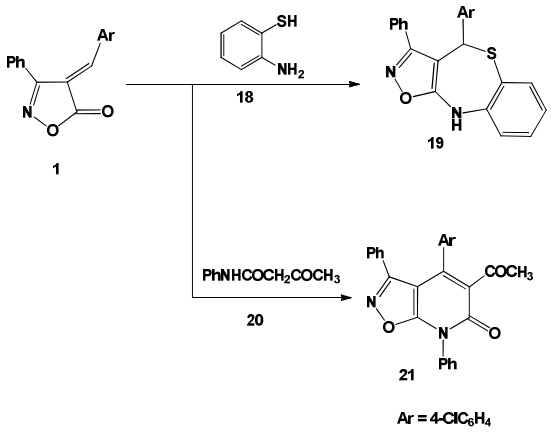
Furthermore, the high reactivity of the isoxazolone **1** towards nitrogen nucleophiles was also appeared from its reaction with hydrazides represented in compounds **12**, **14** and **16 (**two equivalents of **1** were used as **16** contained two hydrazide functions) which all reacted under same conditions to afford compounds **13**, **15** and **17** respectively (scheme 2). The presence of the carbonyl group in the hydrazide structure doesn't affect the reactivity of the NH group so much except the yields were not so good. The structures of these products were assisted from their elemental analysis and spectral data, The IR of all displayed strong absorption bands from 3303 to 3329 cm^{-1} attributable to NH groups, compounds **13** and **17** showed absorption bands at 1651 and 1647 cm^{-1} respectively related to the amide carbonyl groups. The mass spectrum for example for compound **13** revealed a molecular ion peak at m/e = 401 consistent with proposed structure, in the ^{1}HNMR spectrum of compound **15** a singlet signal at 4.86 ppm assigned to benzylic proton (pyrazole ring), the aromatic region at 7.23-7.90 ppm integrating for 14 protons and a downfield signal at 9.32 ppm (NH proton).

2-Aminothiophenol as a bifunctional group compound possesing a nucleophilic sulfur atom which can add to the arylidene double bond of the isoxazolone **1** in a Michael-like type protocol; the amino function can add to the isoxazolone cabonyl group followed by loss of a molecule of water furnishing at the end the tricyclic isoxazolobenzothiazepine **19**.

The IR spectrum of compound **19** is devoid from absorption bands in the carbonyl region, in addition an absorption band at 2945 cm-1 due to CH aliphatic and NH stretching vibration appeared at 3354 cm-1. The EI mass spectrum showed the correct molecular ion peak at m/e = 391.

Finally, Pyridines such as compound **21** were obtainable from the isoxazolone **1** when combined with acetoacetanilide **20** in alcohol and NaOH at room temperature (scheme 3); the reaction proceeded through addition of the methylene group in compound **20** to the arylidene double bond in compound **1** followed by tautomerization to the enol form which underwent water removal to give the product **21**.

The IR spectrum of compound **21** showed two characteristic bands at 1705 and 1647 cm^{-1} attributable to the acetyl and cyclic carbonyl groups, in its ^{1}HNMR spectrum, a singlet signal at 2.48 ppm assigned to methyl protons, also aromatic region enriched with additional five protons.



Scheme 3: Reaction of 1 with compounds 18 and 20

Antimicrobial evaluation

The antibacterial activity of the newly synthesized compounds (**3a**, **3b**, **5**, **7**, **9**, **11**, **13**, **15** and **17**) was evaluated *in vitro* against Staphylococcus aureus (SA, RCMB 000106) and Bacillis subtilis (BS, RCMB 000107) as examples of Gram-positive bacteria and Pseudomonas aeruginosa (PA, RCMB 000102) and Escherichia coli (EC, RCMB 000103) as examples of Gram-negative bacteria. The inhibition zone diameter (IZD) in millimeters was used as a criterion for the antimicrobial activity using the agar diffusion method.

Streptomycin was used as reference to evaluate the potency of the tested compounds under the same conditions. The results are depicted in Tables 1.

The results revealed that most of the tested compounds displayed variable inhibitory effects on the growth of the tested Gram-positive bacteria and Gram-negative bacteria strains.

In general, most of the tested compounds revealed better activity against the Gram-positive bacteria than against the Gram-negative bacteria. Compounds **5** and **15** have high inhibition effects against the four bacteria strains due to presence of fluorine or sulphone moieties.

Compounds **3a**, **3b**, **13** and **17** exhibited no activity against PA while compounds **3b**, **9** and **13** exhibited no activity against SA.

Table 1: Antibacterial activity of the tested compounds

Sample number	Inhibition zone diameter (mm / mg sample)			
	Gram-positive Bacteria		Gram-negative Bacteria	
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*
3a	11	14	13	-
3b	-	11	-	-
5	20	26	23	21
7	19	22	21	22
9	-	16	18	15
11	17	15	18	14
13	-	11	13	-
15	23	26	20	24
17	12	14	-	-
Streptomycin	25	29	24	25

(-) No inhibition zone

CONFLICT OF INTERESTS

Declared None

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