DESIGN AND SYNTHESIS OF NOVEL TERREMIDE AND SULFONAIDES DERIVATIVES FOR PHARMACOLOGICAL EVALUATION

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Abstract

Bacterial infections were first recorded back at 3000 B.C.E. Since then, there have been an enormous number of pandemics that hit the world. Countless doctors and researchers have been working on a definitive solution to exterminate all bacterial infections of all kinds. Marine microorganisms have been widely used as a valid source for pharmacologically active components, and recently the amount of metabolites produced by marine-derived fungi have been increased magnificently, which provided not only wide spectrum of highly active compounds but also gave an enormous number of opportunities for chemists to modify theses incredible entities into more effective and less harmful compounds that can be used as cytotoxic, antiviral, antibacterial and antifungal agents.(He et al., 2013) Quinazolines have been spotted as a new group of agents of decent promising and potential chemotherapeutic and antimicrobial activities.(Raghavendra, Gurubasavarajaswamy, Nagaranavile, & Parameshwaran, 2009) The structure activity relationship of quinazolines has shown it has a very weak antimicrobial activity,(Alafeefy, 2009) Close inspection of the structure-activity-relationships (SAR) of quinazolines revealed important structural features necessary for their antimicrobial activity: a nitrogenous ring and a side chain. Quinazoline heterocyclic compounds have been used to synthesize compounds like terremide B to enhance the activity. Currently, advantageous moieties have been combined to generate new hybrid scaffolds of quinazoline with the objective of synthesizing new moieties enhancing the biological activity and drug-like properties.

Keywords: *quinazoline; terremide B; MRSA; antimicrobial resistance; antitumor.*

Introduction

Quinazoline have shown a magnificent interest in food, agrochemical, and pharmacological industries. All of which display a considerate structural diversity which include polyketides, sterols, terpenoids, and alkaloids, etc. and exhibit a wide range of biological activities: such as antifouling, antibacterial, cytotoxic, anti-inflammatory, antiviral, and anti-HIV activities.

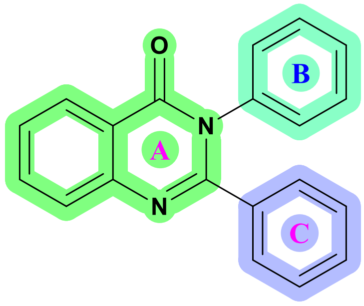
Although the great efforts of the researchers in the field of bacterial infections, still remains the most reluctant reason that they never cease to exist is Resistance. Resistance can develop in either hospitalized or community settings, therefore, they can be unpredictable. Community-acquired infections have been a major cause of deaths over a long period of time. Nonetheless, nosocomial or healthcare related infections can be as life-threatening as community-acquired if not more. These types of infections can influence many people all over the world. For instance in the USA, MRSA kills around 19000 yearly.(Khameneh, Diab, Ghazvini, & Fazly Bazzaz, 2016)

In our lab, we began by investigating the use of phenylthiazole as a potential new antimicrobial agent. (M. M. Elsebaei, N. S. Abutaleb, et al., 2019; Mohamed M Elsebaei et al., 2019; Elsebaei et al., 2018; M. M. Elsebaei, H. Mohammad, et al., 2019; Hagras et al., 2018; Hagras et al., 2020; Hosny et al., 2020; Mancy et al., 2019; Mohammad et al., 2014).(El-Gamal, Sherbiny, & El-Morsi, 2015).

Then, new generation of scaffolds improvement has been studied through developing their metabolic profile and anti-biofilm activity. However, their solubility was a little disappointing. One of the main factors that could increase the solubility of the resulting compounds was the linker between the head and the scaffold. (Alswah, 2021; ElAwamy et al., 2018; M. M. Elsebaei, N. S. Abutaleb, et al., 2019; Elsebaei et al., 2018; Elsebaie et al., 2022; Hammad et al., 2019; Helal, Sayed, Omara, Elsebaei, & Mayhoub, 2019).

In sum, this study is a trial to alter the scaffold in order to evaluate this new scaffold activity against the various types of the microbial organisms and to expand our horizons about the structure-activity relationship of this new class of antibacterial agents.

The current idea is based on changing from the phenythiazole to quinazoline scaffold, which is proposed to have an antibacterial activity against a wide range of microorganisms. This new family of compounds consists of three main rings: Ring (A) made up of two fused six-membered simple aromatic rings- benzene and pyrimidine ring, both rings (B) & (C) are aromatic rings that are derived from different origins. Ring (B) is derived from an aromatic amine and ring (C) is derived from an aromatic acid. While the project is divided among altering these three rings, this review is mainly concerned with the fixation of both rings (A) & (C) and substituting several different derivatives of ring (B) “the amine ring”.



Chemistry

All melting points were carried on Gallen Kamp point apparatus and are uncorrected. ^{1}HNMR spectra were recorded or Bruker-400-MHz spectrophotometer using DMSO-d_6 as a solvent and TMS as internal reference. Chemical shift values were recorded in δ ppm downfield the TMS signal. Mass spectra were recorded on AZH-ph-AR-XO_2 Mass spectrometer. Elemental analyses were performed on C H N analyzer. All spectral measurements have been performed at the Micro analytical Center, Ain Shams University, Egypt.

The designed compounds were synthesized as outlined in scheme (1). 1 gm of nicotinic acid was dissolved in sufficient amount of tetrahydrofuran and the solution is flushed with nitrogen for 10 minutes to make degassing of the solvent. 1.6 gm of carbonyldiimidazole (CDI) (1 equiv.) is added to the solution and the tightly closed air free sealed flask is left for 2 hrs. over stirring on 70 ^{o}C. After then 1.11 gm of anthranilic acid is added to the solution and left overnight, to afford compound (**3**), which was reacted with acetic anhydride and left for 1 hour on reflux to give compound (**4)**. Both the freshly prepared compound (**4**) and the different commercially available aromatic amine derivatives are melted together by fusion using porcelain mortar and pestle to yield the finely powdered particles, then both are mixed gradually and moved into the bottom of a rounded small glass flask. The flask is then placed over a hot plate on different temperatures based on both compound (**4**) and the amines' melting points (the temperature has to be slightly higher than the two separate entities' melting points but not higher than this of their corresponding product) to give compounds (**5-21**). The crude compounds were purified using column chromatography using n.hexane:ethylacetate 1:1 as eluent.

Experimental

Synthesis of 2-(nicotinamido)benzoic acid (3). General procedure:

In a tightly closed air free sealed flask, nicotinic acid (2, 1 equiv.) was dissolved in sufficient amount of tetrahydrofuran and the solution was flushed with nitrogen for 10 minutes in order to make the dissolved oxygen escape from the solution. 320 mg of carbonyldiimidazole (1 equiv.) was added to the solution and the tightly closed air free sealed flask was left for 2 hours over stirring on 70^o c. After 2 hrs, 222 mg of anthranilic acid (1, 1 equiv.) was added to the solution and left overnight. The reaction mixture was poured over ice-cold water with vigorously stirring. The insoluble solid was filtered, washed with water, and air-dried to give the **2-(nicotinamido)benzoic acid 3**. Buff white solid (1.2 g, 60%) m.p = 210-211 ^{o}C as reported (Zentmyer & Wagner, 1949):

Synthesis of 2-(pyridin-3-yl)-4H-benzo[d][1,3]oxazin-4-one 4. General procedure:

Compound 3 was dissolved in acetic anhydride and left for 1 hour on reflux heating. The reaction mixture was poured over ice-cold water with vigorously stirring. The insoluble solid was filtered, washed with water, and air-dried to give **2-(pyridin-3-yl)-4H-benzo[d][1,3]oxazin-4-one 4**. Pale yellow solid (1 g, 90%) as reported (Burbiel et al., 2016):

Synthesis of Substituted-2-(pyridin-3-yl)quinazolin-4(3H)-one 5-21. General procedure:

Both the freshly prepared compound **4** and the different commercially available aromatic amine derivatives were milled using porcelain mortar and pestle to yield the finely powdered particles, then, both were mixed gradually and moved into the bottom of a rounded small glass flask. The flask was then placed over a hot plate on different temperatures based on both compound **4** and the amines' melting points the temperature has to be slightly higher than the two separate melting points but not higher than their corresponding product. The product was completely dissolved in the least amount of ethanol then poured over ice-cold water with vigorously stirring. The insoluble solid was filtered, washed with water, and air-dried to give compounds (**5-21**). Physical properties, and spectral data of isolated purified products are listed below:

3-(4-bromophenyl)-2-(pyridin-3-yl)quinazolin-4(3H)-one 5. Pale grey solid (120 mg, 65%); %): ^{1}H NMR (DMSO-d_6); δ 9.20 (s, 1H), 8.77 (d, *J* = 8.1 Hz, 1H), 8.74 (d, *J* = 7.5 Hz, 1H), 8.66 (d, *J* = 6.8 Hz, 1H), 8.05 (d, *J* = 7.4 Hz, 1H), 7.81 (t, *J* = 7.2 Hz, 1H), 7.68-7.58 (m, 6H); ^{13}C NMR (DMSO-d6); δ 160.03, 156.61, 151.03, 148.02, 144.49, 137.72, 134.45, 133.08, 131.86, 128.69, 127.29, 126.61, 123.18, 122.40, 120.31, 86.23; MS (m/z) for $C_{19}H_{12}BrN_3O$; 377.06 (100.0%), 379.05 (32.0%); Purity/% = 97.09 $R_{t/min}$ = 19.146.

3-(4-iodophenyl)-2-(pyridin-3-yl)quinazolin-4(3H)-one 6. White solid (110 mg, 65%); ^{1}H NMR (DMSO-d_6); δ 9.03 (s, 1H), 8.75 (d, *J* = 8.1 Hz, 1H), 8.69 (d, *J* = 7.5 Hz, 1H), 8.61 (d, *J* = 6.8 Hz, 1H), 7.99 (d, *J* = 7.4 Hz, 1H), 7.71 (t, *J* = 7.2 Hz, 1H), 7.61-7.52 (m, 6H); MS (*m/z*) for $C_{19}H_{12}IN_3O$; 425.22 (89.0%); Purity/% = 95.09 $R_{t/min}$ = 19.11.

3-(4-chlorophenyl)-2-(pyridin-3-yl)quinazolin-4(3H)-one 7. Yellowish white solid (90mg, 58%); ^{1}H NMR (DMSO-d_6); δ 9.10 (s, 1H), 8.76 (d, *J* = 8.1 Hz, 1H), 8.71 (d, *J* = 7.5 Hz, 1H), 8.59 (d, *J* = 6.8 Hz, 1H), 8.03 (d, *J* = 7.4 Hz, 1H), 7.76 (t, *J* = 7.2 Hz, 1H), 7.63-7.53 (m, 6H); ^{13}C NMR (DMSO-d6); δ 161.05, 157.63, 152.07, 149.02, 144.41, 137.69, 134.35, 133.18, 131.76, 128.61, 127.39, 126.63, 123.28, 122.47, 121.02, 85.23; MS (m/z) for $C_{19}H_{12}ClN_3O$; 333.06 (100.0%), 335.05 (36.0%); Purity/% = 98.09 $R_{t/min}$ = 19.18.

3-(4-aminophenyl)-2-(pyridin-3-yl)quinazolin-4(3H)-one 8. Buff solid (105 mg, 67%); ^{1}H NMR (DMSO-d_6); δ 9.11 (s, 1H), 8.79 (d, *J* = 8.1 Hz, 1H), 8.64 (d, *J* = 7.5

Hz, 1H), 8.59 (d, *J* = 6.8 Hz, 1H), 8.00 (d, *J* = 7.4 Hz, 1H), 7.74 (t, *J* = 7.2 Hz, 1H), 7.71-7.50 (m, 6H), 5.32 (brs, 2H); MS (*m/z*) for $C_{19}H_{14}N_4O$; 314.34 (85.0%); Purity/% = 94.79 $R_{t/min}$ = 20.21.

3-(4-hydroxyphenyl)-2-(pyridin-3-yl)quinazolin-4(3H)-one 9. White solid (115mg, 70%); ^{1}H NMR (DMSO-*d*$_6$); δ 9.12 (s, 1H), 8.77 (d, *J* = 8.1 Hz, 1H), 8.67 (d, *J* = 7.5 Hz, 1H), 8.57 (d, *J* = 6.8 Hz, 1H), 8.01 (d, *J* = 7.4 Hz, 1H), 7.76 (t, *J* = 7.2 Hz, 1H), 7.61-7.52 (m, 6H), 5.82 (brs, 1H); MS (*m/z*) for $C_{19}H_{13}N_3O_2$; 315.33 (95.0%); Purity/% = 96.79 $R_{t/min}$ = 21.21.

3-(4-methoxyphenyl)-2-(pyridin-3-yl)quinazolin-4(3H)-one 10. Buff solid (75 mg, 48%): ^{1}H NMR (DMSO-*d*$_6$); δ 9.08 (s, 1H), 8.77 (d, *J* = 8.1 Hz, 1H), 8.62 (d, *J* = 7.5 Hz, 1H), 8.58 (d, *J* = 6.8 Hz, 1H), 8.04 (d, *J* = 7.4 Hz, 1H), 7.76 (t, *J* = 7.2 Hz, 1H), 7.57-7.46 (m, 6H), 3.92 (s, 3H); MS (*m/z*) for $C_{20}H_{15}N_3O_2$; 329.35 (79.0%); Purity/% = 94.16 $R_{t/min}$ = 22.01.

2-(pyridin-3-yl)-3-(p-tolyl)quinazolin-4(3H)-one 11. Buff solid (110mg, 68%); ^{1}H NMR (DMSO-*d*$_6$); δ 9.09 (s, 1H), 8.78 (d, *J* = 8.1 Hz, 1H), 8.62 (d, *J* = 7.5 Hz, 1H), 8.59 (d, *J* = 6.8 Hz, 1H), 8.05 (d, *J* = 7.4 Hz, 1H), 7.73 (t, *J* = 7.2 Hz, 1H), 7.66-7.56 (m, 6H), 2.67 (s, 3H); MS (*m/z*) for $C_{20}H_{15}N_3O$; 313.36 (82.0%); Purity/% = 95.06 $R_{t/min}$ = 19.01.

4-(4-oxo-2-(pyridin-3-yl)quinazolin-3(4H)-yl)benzoic acid 12. Yellow solid (130 mg, 66%); ^{1}H NMR (DMSO-*d*$_6$); δ 11.54 (s, 1H), 9.01 (s, 1H), 8.71 (d, *J* = 8.1 Hz, 1H), 8.59 (d, *J* = 7.5 Hz, 1H), 8.51 (d, *J* = 6.8 Hz, 1H), 8.03 (d, *J* = 7.4 Hz, 1H), 7.71 (t, *J* = 7.2 Hz, 1H), 7.67-7.57 (m, 6H); MS (*m/z*) for $C_{20}H_{13}N_3O_3$; 343.34 (89.0%); Purity/% = 94.86 $R_{t/min}$ = 19.31.

3-(4-acetylphenyl)-2-(pyridin-3-yl)quinazolin-4(3H)-one 13. Pale white solid (110mg, 65%); ^{1}H NMR (DMSO-*d*$_6$); δ 9.11 (s, 1H), 8.72 (d, *J* = 8.1 Hz, 1H), 8.58 (d, *J* = 7.5 Hz, 1H), 8.51 (d, *J* = 6.8 Hz, 1H), 8.02 (d, *J* = 7.4 Hz, 1H), 7.71 (t, *J* = 7.2 Hz, 1H), 7.69-7.55 (m, 6H), 2.38 (s, 3H); MS (*m/z*) for $C_{21}H_{15}N_3O_2$; 341.37 (93.0%); Purity/% = 96.56 $R_{t/min}$ = 19.71.

3-(4-nitrophenyl)-2-(pyridin-3-yl)quinazolin-4(3H)-one 14. Orange solid (95 mg, 62%); ^{1}H NMR (DMSO-*d*$_6$); δ 9.07 (s, 1H), 8.75 (d, *J* = 8.1 Hz, 1H), 8.62 (d, *J* = 7.5 Hz, 1H), 8.53 (d, *J* = 6.8 Hz, 1H), 8.13 (d, *J* = 7.4 Hz, 1H), 7.70 (t, *J* = 7.2 Hz, 1H), 7.65-7.53 (m, 6H); MS (*m/z*) for $C_{19}H_{12}N_4O_3$; 344.33 (89.2%); Purity/% = 96.86 $R_{t/min}$ = 18.91.

3-(3-aminophenyl)-2-(pyridin-3-yl)quinazolin-4(3H)-one 15. Buff solid (100 mg, 65%); ^{1}H NMR (DMSO-*d*$_6$); δ 9.10 (s, 1H), 8.79 (d, *J* = 8.1 Hz, 1H), 8.65 (d, *J* = 7.5 Hz, 1H), 8.59 (d, *J* = 6.8 Hz, 1H), 8.03 (d, *J* = 7.4 Hz, 1H), 7.74 (t, *J* = 7.2 Hz, 1H), 7.71-7.50 (m, 6H), 5.32 (brs, 2H); MS (*m/z*) for $C_{19}H_{14}N_4O$; 314.34 (81.0%); Purity/% = 93.99 $R_{t/min}$ = 20.12.

3-(6-aminopyridin-2-yl)-2-(pyridin-3-yl)quinazolin-4(3H)-one 16. Yellowish white solid (80mg, 50%); ^{1}H NMR (DMSO-*d*$_6$); δ 9.10 (s, 1H), 8.79 (d, *J* = 8.1 Hz, 1H), 8.65 (d, *J* = 7.5 Hz, 1H), 8.59 (d, *J* = 6.8 Hz, 1H), 8.03 (d, *J* = 7.4 Hz, 1H), 7.74 (t, *J* =

7.2 Hz, 1H), 7.71-7.50 (m, 5H), 5.32 (brs, 2H); MS (*m/z*) for $C_{18}H_{13}N_5O$; 315.33 (71.0%); Purity/% = 92.99 $R_{t/min}$ = 19.82.

2-(4-oxo-2-(pyridin-3-yl)quinazolin-3(4H)-yl)benzoic acid 17. Yellow solid (115mg, 70%); ^{1}H NMR (DMSO-d_6); δ 11.64 (s, 1H), 9.01 (s, 1H), 8.71 (d, *J* = 8.1 Hz, 1H), 8.60 (d, *J* = 7.5 Hz, 1H), 8.52 (d, *J* = 6.8 Hz, 1H), 8.02 (d, *J* = 7.4 Hz, 1H), 7.71 (t, *J* = 7.2 Hz, 1H), 7.68-7.57 (m, 6H); MS (*m/z*) for $C_{20}H_{13}N_3O_3$; 343.34 (89.0%); Purity/% = 94.56 $R_{t/min}$ = 19.08.

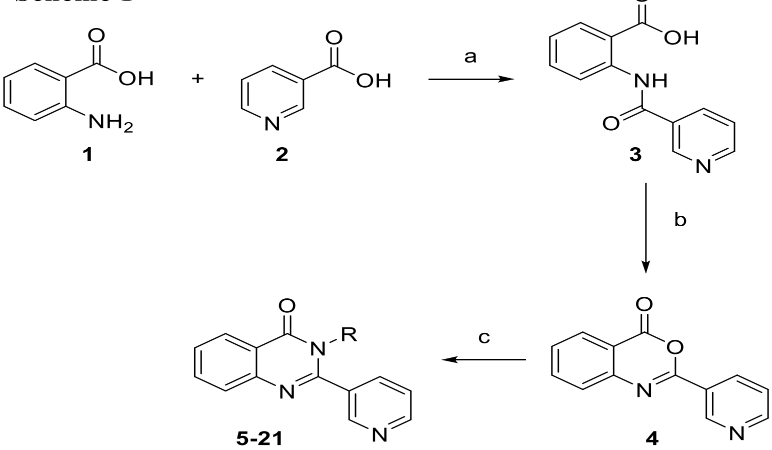
3-(pyridin-2-yl)-2-(pyridin-3-yl)quinazolin-4(3H)-one 18. Pale white solid (80 mg, 50%); ^{1}H NMR (DMSO-d_6); δ 9.11 (s, 1H), 8.80 (d, *J* = 8.1 Hz, 1H), 8.63 (d, *J* = 7.5 Hz, 1H), 8.59 (d, *J* = 6.8 Hz, 1H), 8.03 (d, *J* = 7.4 Hz, 1H), 7.74 (t, *J* = 7.2 Hz, 1H), 7.71-7.50 (m, 6H); MS (*m/z*) for $C_{18}H_{12}N_4O$; 300.33 (85.0%); Purity/% = 94.99 $R_{t/min}$ = 20.32.

2,3-di(pyridin-3-yl)quinazolin-4(3H)-one 19. Buff solid (85 mg, 52%): ^{1}H NMR (DMSO-d_6); δ 9.11 (s, 1H), 8.80 (d, *J* = 8.1 Hz, 1H), 8.77 (s, 1H), 8.63 (d, *J* = 7.5 Hz, 1H), 8.59 (d, *J* = 6.8 Hz, 1H), 8.03 (d, *J* = 7.4 Hz, 1H), 7.74 (t, *J* = 7.2 Hz, 1H), 7.71-7.50 (m, 5H); MS (*m/z*) for $C_{18}H_{12}N_4O$; 300.33 (85.0%); Purity/% = 94.99 $R_{t/min}$ = 20.32.

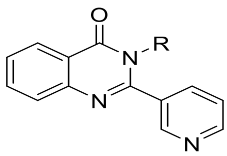
3-(naphthalen-1-yl)-2-(pyridin-3-yl)quinazolin-4(3H)-one 20. Brownish yellow solid (120mg, 65%); ^{1}H NMR (DMSO-d_6); δ 9.07 (s, 1H), 8.75 (d, *J* = 8.1 Hz, 1H), 8.62 (d, *J* = 7.5 Hz, 1H), 8.53 (d, *J* = 6.8 Hz, 1H), 8.13 (d, *J* = 7.4 Hz, 1H), 7.70 (t, *J* = 7.2 Hz, 1H), 7.65-7.53 (m, 9H); MS (*m/z*) for $C_{23}H_{15}N_3O$; 349.39 (96.2%); Purity/% = 96.86 $R_{t/min}$ = 19.91.

3-(4-oxo-2-(pyridin-3-yl)quinazolin-3(4H)-yl)-2-naphthoic acid 21. Buff solid (115mg, 70%); ^{1}H NMR (DMSO-d_6); δ 11.67 (s, 1H), 9.07 (s, 1H), 8.75 (d, *J* = 8.1 Hz, 1H), 8.62 (d, *J* = 7.5 Hz, 1H), 8.53 (d, *J* = 6.8 Hz, 1H), 8.13 (d, *J* = 7.4 Hz, 1H), 7.70 (t, *J* = 7.2 Hz, 1H), 7.65-7.53 (m, 8H); MS (*m/z*) for $C_{24}H_{15}N_3O$; 393.40 (95.2%); Purity/% = 95.66 $R_{t/min}$ = 19.81.

Scheme 1



Reaction condition: a) THF, CDI, 70 °C, 24hr. b) acetic anhydride, Reflux. c) aromatic amine derivatives, fusion.



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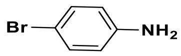
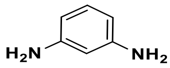
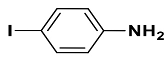
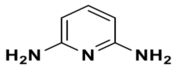
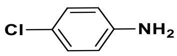
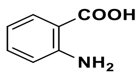
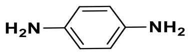
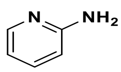
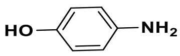
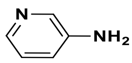
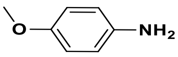
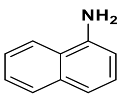
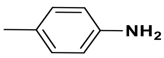
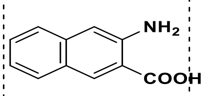
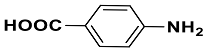
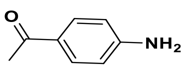
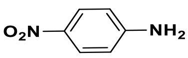
5		65	15		65
6		65	16		50
7		58	17		70
8		67	18		50
9		70	19		52
10		48	20		65
11		68	21		70
12		66			
13		65			
14		62			

Antimicrobial Activity

The minimum inhibitory concentrations (MICs) of the tested compounds and control drugs; linezolid, were determined using the broth microdilution method, according to guidelines outlined by the Clinical and Laboratory Standards Institute CLSI) or as described in previous reports with some modifications, against clinically-relevant bacterial (methicillin-resistant Staphylococcus aureus and Acinetobacter baumannii AB5075 (MRSA. S. aureus were grown aerobically overnight on tryptone soy agar plates at 37° C. Afterwards, a bacterial solution equivalent to 0.5 McFarland standard was prepared and diluted in cation-adjusted Mueller-Hinton broth (CAMHB) (for S. aureus and A. baumannii) to achieve a bacterial concentration of about 5 × 105 CFU/mL. Compounds and control drugs were added in the first row of the 96-well plates and serially diluted with the corresponding media containing bacteria. Plates were then, incubated as previously described. (Diep BA, 2006; Jacobs et al., 2014; Radaelli et al., 2016; Wayne, 2014)MICs reported in Table (1) are the minimum concentration of the compounds and control drugs that could completely inhibit the visual growth of bacteria.

Table (1); Antimicrobial activities of compounds 5-21

Compound	***S. aureus*** **USA300 MIC** ug/mL	***A. baumannii*** **AB5075 MIC** ug/mL
5	64 ug/mL	512
6	512 ug/mL	512 ug/mL
7	No inhibition	No inhibition
8	256 ug/mL	512 ug/mL
9	No inhibition	No inhibition
10	64 ug/mL	128 ug/mL
11	No inhibition	No inhibition
12	64 ug/mL	128 ug/mL
13	64 ug/mL	128 ug/mL
14	No inhibition	No inhibition
15	64 ug/mL	256 ug/mL
16	No inhibition	256 ug/mL
17	No inhibition	No inhibition
18	No inhibition	256 ug/mL

19	No inhibition	256 ug/mL
20	No inhibition	256 ug/mL
21	No inhibition	No inhibition

Conclusion

From the previously mentioned scheme, we could conduct some conclusions; first, the presence of ether linkage in the amine will always reduce its melting point which results in huge difference between both amine and compound 4 melting points, this will cause reduction of the product yield intensively. Second, the presence of bulky group, multiple substituted amine, or electron-withdrawing groups such as nitro groups – pyridine, will also result in low yield as a result of the low reactivity nature of these compounds. This whole scheme was created in order to imitate the terramide compounds for further investigations biologically. The suspected biological activity was antitumor, antibacterial and antifungal. But, upon investigation on its antibacterial activity, it was easy to confirm that it can be quite neglected. On the other hand, the addition of amino derivatives in the final step, produced a new scaffold of quinazoline derivatives to be enrolled in other studies to be examined biologically.

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تصميم وتشييد مركبات تيريميد جديدة لدراسة فعاليتها الأقرباذينية

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- منذ عام 3000 قبل الميلاد، و تعتبر العدوي البكتيرية إحدي أهم الأسباب فى موت عدد كبير من البشرية. و منذ ذلك الحين و العديد من الأطباء و الباحثين عكفوا بل سخروا حياتهم من أجل حل تلك المشكلة. و لكن لم ينجح أحد حتى الان في الوصول الى حل جذري للقضاء على العدوى البكتيرية بشكل نهائي و ذلك يرجع للتطور السريع لمقاومة المضادات الحيوية من قبل البكتريا. فبالرغم من التطوير اليومي فى تصنيع و تشييد المضادات الحيوية المختلفة ألا إن البكتريا لازالت تواكب التطور للمقاومة من تأثير المضادات الحبوية الجديدة. إحدى أهم الأسباب التي تشارك فى مشكلة المقاومة البكتيرية بدور ليس بلقليل هي سوء إستخدام المضادات الحيوية من البشر نفسهم. فمعظم المرضى لا يلتزموا بشروط أخذ المضادات الحيوية سواء بعدم إتمام الجرعة المفروضة أو الإفراط فى أخذ المضاد الحيوي سواءاً هناك سبب لأخذه أم لا. ذلك يعزى إلى فقر الوعي العام الخاص بالمواطنين.
- هذا وقد أثبتت الدراسات الفاعلية الأقرباذينية الذي يضطلع به مركبات الفينل ثيازول ضد مسببات الأمراض البكتيرية المقاومة للأدوية المتعددة، ولا سيما المكورات العنقودية الذهبية المقاومة للميثيسيلين، بسبب تأثيرها المباشر على مستهدف جديد داخل جدار الخلايا. وتمت دراسة العلاقة بين تركيبها الكيميائى وفاعليتها ضد هذا المستهدف من خلال تحضير مايزيد عن 400 مركب من مشتقاتها وتقييم تأثيرها البيولوجى ودراسة الحركية الدوائية لبعضها.
- و من المخطط السابق ذكره، نستنج بعض الاستناجات الهامة :

- أولاً: وجود رابطة الإيثر توثر بالسلب على درجة ذوبانية المركبات مما ينتج عنه فارق كبير بين الأمين و المركب 4 السابق تحضيره مما يؤدى إلى تقليل فى كمية المركب الناتج .
- ثانياً: وجود المجموعات الكبيرة نسبياً، المركبات التي تحتوى على العديد من مجموعات الأمين أو المجموعات الساحبة للإلكترون ستؤدي إلى نفس النتيجة السابقة.
- ولأن هذا البحث غرضه الأساسي دراسة الفعالية الأقرباذنية لهذه المركبات، فبعد البحث و الدراسة استنتجنا أن المركبات تحتوى على فعالية ضعيفة جدا او قد تكون معدومة كمضادات بكتيرية و لكن يفضل البحث فى فعاليتها كمضادات للفطريات أو لعلاج السرطان.

الكلمات المفتاحية / الكينازولين – التيراميد- البكتيريا المقاومة للمسيثيلثين – المقاومة الميكروبية - علاج السرطان