DESIGN AND SYNTHESIS OF NOVEL TERREMIDE DERIVATIVES FOR PHARMACOLOGICAL EVALUATION

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ABSTRACT

clinicians and chemists are directed in those days toward the biologically active compounds to reduce the mortality and morbidity. Quinazolines were reported previously as a scaffold that possesses antitumor and antimicrobial activities. 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. Using quinazoline heterocyclic compound to try to synthesi**ze** compound**s** similar to terremide to enhance the activity. In the present work, advantageous moieties have been combined together to generate new hybrid scaffolds of quinazoline with the objective of synthesizing new moieties enhancing the antimicrobial biological activity and drug-like properties.

Keywords: *quinazoline; terramide; MRSA; antimicrobial resistance; antitumor.*

I. INTRODUCTION

is a compound made up of two fused six-membered simple aromatic rings-benzene and pyrimidine rings. The last ten to fifteen years of research in the field of medicinal chemistry has been characterized by significant advances. In 1968 only two derivatives were used, soporific & anticonvulsant- methaqualone and diuretic quinathazone. By 1980, about 50 kinds of derivatives of this class includes medicinal with different biological actions like 'soporific, sedative, tranquilizing, analgesic, anticonvulsant, antitussive, myorelexant, antirheumatic, hypotensive, antiallergic, bronchodilator, antidiabetic, cholagogue, diuretic, antimalarial and antimicrobial etc. (Selvam, James, *et al.*, 2015).

Due to the increasing number of antibiotic resistances globally, it is important that everyone plays their part in preventing the development of new antimicrobial agents. In our lab, we started 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).

Recently, the development of a new generation of scaffolds has been focused on improving their metabolic profile and anti-biofilm activity. However, their solubility was not encouraging. One of the main factors that could affect the solubility of the resulting compounds was the linker between the head and the scaffold. (ElAwamy *et al.*, 2018; M. M. Elsebaei, N. S. Abutaleb, *et al.*, 2019; Elsebaei *et al.*, 2018; Hammad *et al.*, 2019).

Therefore, this study is a trial to change the scaffold to explain its activity against the variance of the microbial organisms and to broaden our knowledge of the structure-activity relationship of this new class of antibacterial agents.

The idea of the present scaffold is based on replacing the phenythiazole with a quinazoline scaffold, which is suggested to have antibacterial activity against a wide range of microorganisms.

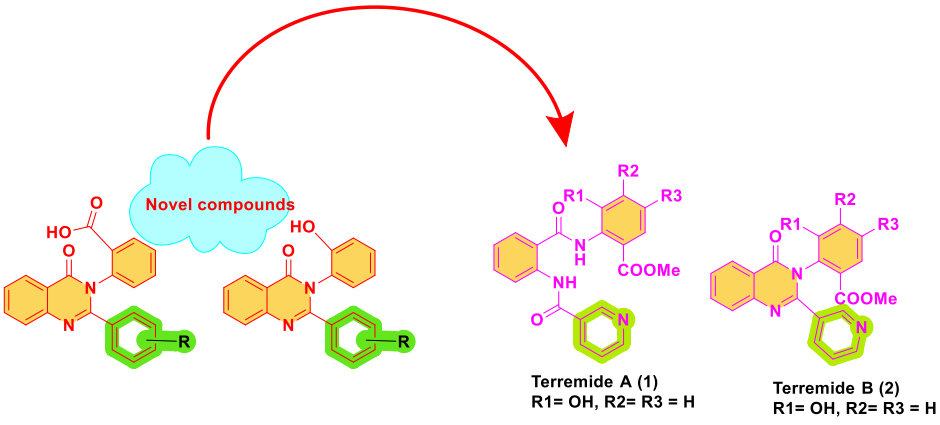


Figure 1; Rational design for terremide derivatives

In this work we designed the synthesized compounds that related to the terremide **B**. Terremide compounds were the natural products isolated from microorganisms provide a vast source of drug leads with potent biological activities against cancer and other diseases. One example of biologically active molecules from natural sources are terremides (Figure 1), a series of novel alkaloids isolated from the fungus Aspergillus terreus. Terremide A (1) inhibits the growth of the bacteria *Enterobacter Aerogenes* with a minimum inhibitory concentration (MIC) of 63 mM, while terremide B (2) is active against *Staphylococcus aureus* with a MIC of 35 mM. Thus, our goal in this work is to synthesize the terremides using new synthetic methods, study their antimicrobial potential.

II- 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. All final products were established by HPLC. 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). Anthranilic acid was allowed to react with commercially available benzoyl chloride derivatives in dry pyridine to afford compounds **3a-l**, which reacted with anthranilic acid and 2-aminophenol to give compounds **4-27** with good yield. The crude compounds were purified using column chromatography using hexane: ethyl acetate 6:4 as eluent.

II-1. Experimental

Synthesis of 2-(Substitutedphenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one 3a-l. General procedure: In a round bottom flask a mixture of anthranilic acid *(***1**, 1 equiv.) and substituted benzoyl chloride (**2**, 1.2 equiv.) were dissolved in dry pyridine (10 mL) in ice-bath for 1h, then the reaction mixture was heated at 50 °C for 4h. After cooling to room temperature, the reaction mixture was poured in ice-cold water with vigorously stirring. The insoluble solid was filtered, washed with water, and air-dried to give the compounds **3a-l**. Yields, physical properties, and spectral data of isolated purified products are listed below:

2-(6-Chloropyridin-3-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one 3a. Off-white solid (550 mg, 58%): ^{1}H NMR (DMSO-d_6); δ 9.13 (s, 1H), 8.55 (d, *J* = 8.1 Hz, 1H), 8.20 (d, *J* = 6.8 Hz, 2H), 8.00 (t, *J* = 6.0 Hz, 1H), 7.78 (d, *J* = 6.9 Hz, 1H), 7.69 (t, *J* = 6.4 Hz, 1H), MS (*m/z*) for $C_{13}H_7N_2O_2Cl$; 258.01 (M^+, 98.41%), 260.01 (M^{+2}).

2-Phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one 3b. White solid (600 mg, 73%): ^{1}H NMR (DMSO-d_6); δ 8.73 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 7.6 Hz, 1H), 7.97 (d, *J* = 6.8 Hz, 2H), 7.67-7.57 (m, 4H), 7.22 (t, *J* = 7.6 Hz, 1H), MS (*m/z*) for $C_{14}H_9NO_2$; 223 (M^+, 89.11%).

2-(4-Iodophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one 3c. White solid (850 mg, 66%): ^{1}H NMR (DMSO-d_6); δ 8.67 (d, *J* = 8.0 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 2H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.68 (t, *J* = 8.8 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), MS (*m/z*) for $C_{14}H_8NIO_2$; 349 (M^+, 87.71%).

2-(2-Fluorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one 3d. Light-brown solid (480 mg, 54%): ^{1}H NMR (DMSO-d_6); δ 8.71 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 7.93 (t, *J* = 7.2 Hz, 1H), 7.66 (t, *J* = 7.2 Hz, 1H), 7.42-7.37 (m, 3H), 7.23 (t, *J* = 7.8 Hz, 1H), MS (*m/z*) for $C_{14}H_8NFO_2$; 241 (M^+, 93.64%).

2-(4-Oxo-4*H*-benzo[*d*][1,3]oxazin-2-yl)benzonitrile 3e. White solid (710 mg, 78%): ^{1}H NMR (DMSO-d_6); δ 8.66 (d, *J* = 8.0 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 2H), 8.09 (d, *J* = 7.8 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.17 (t, *J* = 7.2 Hz, 1H), MS (*m/z*) for $C_{15}H_8N_2O_2$; 248 (M^+, 100%).

2-(2,6-Dichlorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one 3f. White solid (610 mg, 57%): ^{1}H NMR (DMSO-d_6); δ 8.81 (d, *J* = 6.8 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 7.93 (t, *J* = 6.8 Hz, 1H), 7.76 (t, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 6.8 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.08 (t, *J* = 6.4 Hz, 1H), MS (*m/z*) for $C_{14}H_7NCl_2O_2$; 292 (M^+, 100%), 294 (M^{+2}), 296 (M^{+4}).

2-(3,5-Dichlorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one 3g. White solid (600 mg, 56%): ^{1}H NMR (DMSO-d_6); δ 8.56 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.90 (s, 2H), 7.85 (s, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 7.2 Hz, 1H), MS (*m/z*) for $C_{14}H_7NCl_2O_2$; 292 (M^+, 100%), 294 (M^{+2}), 296 (M^{+4}).

2-(Naphthalen-2-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one 3h. White solid (650 mg, 65%): ^{1}H NMR (DMSO-d_6); δ 8.79 (d, *J* = 7.2 Hz, 1H), 8.60 (s, 1H), 8.14-7.99 (m, 5H), 7.64-7.58 (m, 3H), 7.19 (t, *J* = 7.6 Hz, 1H), MS (*m/z*) for $C_{18}H_{11}NO_2$; 273 (M^+, 77.31%).

2-(4-Ethylphenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one 3i. White solid (820 mg, 89%): ^{1}H NMR (DMSO-d_6); δ 8.74 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.19 (t, *J* = 7.8 Hz, 1H), 2.72 (q, *J* = 7.8 Hz, 2H), 1.23 (t, *J* = 7.8 Hz, 3H), MS (*m/z*) for $C_{16}H_{13}NO_2$; 251 (M^+, 96.71%).

2-(2-Chloropyridin-3-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one 3j. White solid (730 mg, 77%): ^{1}H NMR (DMSO-d_6); δ 8.54 (d, *J* = 8.0 Hz, 1H), 8.46 (d, *J* = 7.2 Hz, 2H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 4.4 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 6.54 (t, *J* = 7.8 Hz, 1H), MS (*m/z*) for $C_{13}H_7N_2O_2Cl$; 258.01 (M^+, 98.41%), 260.01 (M^{+2}).

2-(Benzo[*d*][1,3]dioxol-5-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one 3k. White solid (760 mg, 78%): ^{1}H NMR (DMSO-d_6); δ 8.15 (d, *J* = 9.2 Hz, 1H), 7.96 (t, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 7.2 Hz, 1H), 7.63 (s, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.19 (s, 2H), MS (*m/z*) for $C_{15}H_9N_2O_2$; 267 (M^+, 100%).

2-(3-Nitrophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one 3l. Beige solid (680 mg, 69%): ^{1}H NMR (DMSO-d_6); δ 8.73 (s, 1H), 8.65 (d, *J* = 7.8 Hz, 1H), 8.45 (d, *J* = 7.8 Hz, 1H), 8.39

(d, *J* = 7.2 Hz, 1H), 8.09 (d, *J* = 7.2 Hz, 1H), 7.88 (t, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.22 (t, *J* = 7.2 Hz, 1H), MS (*m/z*) for $C_{14}H_8N_2O_4$; 268 (M^+, 98.41%).

Synthesis of 2-(2-(Substitutedphenyl)-4-oxoquinazolin-3(4*H*)-yl)benzoic acid and 2-(4-Substituted phenyl)-3-(2-hydroxyphenyl)quinazolin-4(3*H*)-one 4-27. General procedure: In a round bottom flask a mixture of compounds **3a-l** (**1**, 1 equiv.) and substituted anthranilic acid (**2**, 1.5 equiv.) were dissolved in dry glacial acetic acid (10 mL), the reaction mixture was heated at 200 °C for 24h. After cooling to room temperature, the reaction mixture was poured in ice-cold water with vigorously stirring. The insoluble solid was filtered, washed with water, and air-dried to afford the compounds **4-27**. Yields, physical properties, and spectral data of isolated purified products are listed below:

2-(2-(6-Chloropyridin-3-yl)-4-oxoquinazolin-3(4*H*)-yl)benzoic acid 4. Off-white solid (550 mg, 58%): ^{1}H NMR (DMSO-d_6); δ 12.8(s, 1H), 9.13 (s, 1H), 8.55 (d, *J* = 8.1 Hz, 1H), 8.51 (d, *J* = 7.5 Hz, 1H), 8.20 (d, *J* = 6.8 Hz, 2H) , 8.09 (d, *J* = 7.4 Hz, 1H) , 8.05 (t, *J* = 7.2 Hz, 1H), 8.00 (t, *J* = 6.0 Hz, 1H), 7.78 (d, *J* = 6.9 Hz, 1H), 7.69 (t, *J* = 6.4 Hz, 1H), 7.34 (t, *J* = 7.34 Hz, 1H), MS (*m/z*) for $C_{20}H_{12}ClN_3O_3$; 377.06 (100.0%), 379.05 (32.0%); Purity/% = 99.09 $R_{t/min}$ = 19.54.

2-(4-Oxo-2-phenylquinazolin-3(4*H*)-yl)benzoic acid 5. White solid (600 mg, 73%): ^{1}H NMR (DMSO-d_6); δ 12.2 (s, 1H), 8.73 (d, *J* = 8.4 Hz, 1H), 8.51 (d, *J* = 7.5 Hz, 1H), 8.09 (d, *J* = 7.4 Hz, 1H), 8.07 (d, *J* = 7.6 Hz, 1H), 8.05 (t, *J* = 7.2 Hz, 1H), 7.97 (d, *J* = 6.8 Hz, 2H), 7.67-7.57 (m, 4H), 7.34 (t, *J* = 7.34 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), MS (*m/z*) for $C_{21}H_{14}N_2O_3$; 342.10 (100.0%), 343.10 (22.7%); Purity/% = 98.23 $R_{t/min}$ = 4.84.

2-(2-(4-Iodophenyl)-4-oxoquinazolin-3(4*H*)-yl)benzoic acid 6. White solid (850 mg, 66%): ^{1}H NMR (DMSO-d_6); δ 12.2(s, 1H), 8.67 (d, *J* = 8.0 Hz, 1H),), 8.51 (d, *J* = 7.5 Hz, 1H), 8.09 (d, *J* = 7.4 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 8.05 (t, *J* = 7.2 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 2H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.68 (t, *J* = 8.8 Hz, 1H), 7.34 (t, *J* = 7.34 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), MS (*m/z*) for $C_{21}H_{13}IN_2O_3$; 468.00 (100.0%), 469.00 (22.7%); Purity/% = 93.32 $R_{t/min}$ = 16.87.

2-(2-(2-Fluorophenyl)-4-oxoquinazolin-3(4*H*)-yl)benzoic acid 7. Light-brown solid (480 mg, 54%): ^{1}H NMR (DMSO-d_6); δ 12.2 (s, 1H), 8.71 (d, *J* = 8.4 Hz, 1H), 8.51 (d, *J* = 7.5 Hz, 1H), 8.09 (d, *J* = 7.4 Hz, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 8.05 (t, *J* = 7.2 Hz, 1H), 7.93 (t, *J* = 7.2 Hz, 1H), 7.66 (t, *J* = 7.2 Hz, 1H), 7.34 (t, *J* = 7.34 Hz, 1H), 7.42-7.37 (m, 3H), 7.23 (t, *J* = 7.8 Hz, 1H), MS (*m/z*) for $C_{21}H_{13}FN_2O_3$; 360.09 (100.0%), 361.09 (22.7%); Purity/% = 95.69 $R_{t/min}$ = 19.50.

2-(2-(4-Cyanophenyl)-4-oxoquinazolin-3(4*H*)-yl)benzoic acid 8. White solid (710 mg, 78%): ^{1}H NMR (DMSO-d_6); δ 14.1 (s, 1H), 8.66 (d, *J* = 8.0 Hz, 1H), 8.51 (d, *J* = 7.5 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 2H), 8.09 (d, *J* = 7.4 Hz, 1H), 8.09 (d, *J* = 7.8 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 2H), 8.05 (t, *J* = 7.2 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.34 (t, *J* = 7.34 Hz, 1H), 7.17 (t, *J* = 7.2 Hz, 1H), MS (*m/z*) for $C_{22}H_{13}N_3O_3$; 367.10 (100.0%), 368.10 (23.8%); Purity/% = 98.20 $R_{t/min}$ = 19.17.

2-(2-(2,6-Dichlorophenyl)-4-oxoquinazolin-3(4*H*)-yl)benzoic acid 9. White solid (610 mg, 57%): ^{1}H NMR (DMSO-d_6); δ 12.2 (s, 1H), 8.81 (d, *J* = 6.8 Hz, 1H), 8.51 (d, *J* = 7.5 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 8.09 (d, *J* = 7.4 Hz, 1H), 8.05 (t, *J* = 7.2 Hz, 1H), 7.93 (t, *J* = 6.8 Hz, 1H), 7.76 (t, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 6.8 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.34 (t, *J* = 7.34 Hz, 1H), 7.08 (t, *J* = 6.4 Hz, 1H), MS (*m/z*) for $C_{21}H_{12}Cl_2N_2O_3$; 410.02 (100.0%), 412.02 (63.9%); Purity/% = 98.99 $R_{t/min}$ = 11.10.

2-(2-(3,5-Dichlorophenyl)-4-oxoquinazolin-3(4*H*)-yl)benzoic acid 10. White solid (610 mg, 57%): ^{1}H NMR (DMSO-d_6); δ 12.2 (s, 1H), 8.81 (d, *J* = 6.8 Hz, 1H), 8.51 (d, *J* = 7.5 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 8.09 (d, *J* = 7.4 Hz, 1H), 8.05 (t, *J* = 7.2 Hz, 1H), 7.93 (t, *J* = 6.8 Hz, 1H), 7.76 (t, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 6.8 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.34 (t, *J* = 7.34 Hz, 1H), 7.08 (t, *J* = 6.4 Hz, 1H), MS (*m/z*) for $C_{21}H_{12}Cl_2N_2O_3$; 410.02 (100.0%), 412.02 (63.9%); Purity/% = 90.29 $R_{t/min}$ = 10.74.

2-(2-(Naphthalen-2-yl)-4-oxoquinazolin-3(4*H*)-yl)benzoic acid 11. White solid (650 mg, 65%): ^{1}H NMR (DMSO-d_6); δ 13.58 (s, 1H), 8.79 (d, *J* = 7.2 Hz, 1H), 8.60 (s, 1H), 8.51 (d, *J* = 7.5 Hz, 1H), 8.14-7.99 (m, 5H), 8.09 (d, *J* = 7.4 Hz, 1H), 8.05 (t, *J* = 7.2 Hz, 1H), 7.64-7.58 (m, 3H), 7.34 (t, *J* = 7.34 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), MS (*m/z*) for $C_{25}H_{16}N_2O_3$; 392.12 (100.0%), 393.12 (27.0%); Purity/% = 92.90 $R_{t/min}$ = 10.84.

2-(4-Ethylphenyl))-4-oxoquinazolin-3(4*H*)-yl)benzoic acid 12. White solid (820 mg, 89%): ^{1}H NMR (DMSO-d_6); δ 12.59 (s, 1H), 8.74 (d, *J* = 8.0 Hz, 1H), 8.51 (d, *J* = 7.5 Hz, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 8.06 (d, *J* = 7.4 Hz, 1H), 8.05 (t, *J* = 7.2 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.34 (t, *J* = 7.34 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 2.72 (q, *J* = 7.8 Hz, 2H), 1.23 (t, *J* = 7.8 Hz, 3H), MS (*m/z*) for $C_{23}H_{18}N_2O_3$; 370.13 (100.0%), 371.14 (24.9%); Purity/% = 98.17 $R_{t/min}$ = 22.10.

2-(2-(2-Chloropyridin-3-yl)-4-oxoquinazolin-3(4H)-yl)benzoic acid 13. White solid (730 mg, 77%): ^{1}H NMR (DMSO-d_6); δ 12.8 (s, 1H), 8.54 (d, *J* = 8.0 Hz, 1H), 8.51 (d, *J* = 7.5 Hz, 1H), 8.46 (d, *J* = 7.2 Hz, 2H), 8.06 (d, *J* = 7.4 Hz, 1H), 8.05 (t, *J* = 7.2 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 4.4 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.34 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 6.54 (t, *J* = 7.8 Hz, 1H), MS (*m/z*) for $C_{20}H_{12}ClN_3O_3$; 377.06 (100.0%), 379.05 (32.0%); Purity/% = 93.80 $R_{t/min}$ = 22.10.

2-(2-(Benzo[d][1,3]dioxol-5-yl)-4-oxoquinazolin-3(4H)-yl)benzoic acid 14. White solid (760 mg, 78%): ^{1}H NMR (DMSO-d_6); δ 12.8 (s, 1H), 8.51 (d, *J* = 7.5 Hz, 1H), 8.15 (d, *J* = 9.2 Hz, 1H), 8.06 (d, *J* = 7.4 Hz, 1H), 8.05 (t, *J* = 7.2 Hz, 1H), 7.96 (t, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 7.2 Hz, 1H), 7.63 (s, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.34 (t, *J* = 7.34 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.19 (s, 2H), MS (*m/z*) for $C_{22}H_{14}N_2O_5$; 386.09 (100.0%), 387.09 (23.8%); Purity/% = 99.05 $R_{t/min}$ = 10.72.

2-(2-(3-Nitrophenyl)-4-oxoquinazolin-3(4H)-yl)benzoic acid 15. Beige solid (680 mg, 69%): ^{1}H NMR (DMSO-d_6); δ 13.2 (s, 1H), 8.73 (s, 1H), 8.65 (d, *J* = 7.8 Hz, 1H), 8.51 (d, *J* = 7.5 Hz, 1H), 8.45 (d, *J* = 7.8 Hz, 1H), 8.39 (d, *J* = 7.2 Hz, 1H), 8.09 (d, *J* = 7.2 Hz, 1H), 8.06 (d, *J* = 7.4 Hz, 1H), 8.05 (t, *J* = 7.2 Hz, 1H), 7.88 (t, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.34 (t, *J* = 7.34 Hz, 1H), 7.22 (t, *J* = 7.2 Hz, 1H), MS (*m/z*) for $C_{21}H_{13}N_3O_5$; 387.09 (100.0%), 388.09 (22.7%); Purity/% = 91.29 $R_{t/min}$ = 19.90.

2-(6-Chloropyridin-3-yl)-3-(2-hydroxyphenyl)quinazolin-4(3H)-one 16. Off-white solid (550 mg, 58%): ^{1}H NMR (DMSO-d_6); δ 9.89 (s, 1H), 9.13 (s, 1H), 8.55 (d, *J* = 8.1 Hz, 1H), 8.20 (d, *J* = 6.8 Hz, 2H) , 8.00 (t, *J* = 6.0 Hz, 1H), 7.78 (d, *J* = 6.9 Hz, 1H), 7.69 (t, *J* = 6.4 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 7.2 Hz, 1H), 6.92 (t, *J* = 7.26 Hz, 1H), MS (*m/z*) for $C_{19}H_{12}ClN_3O_2$; 349.06 (100.0%), 351.06 (32.0%); Purity/% = 90.89 $R_{t/min}$ = 17.70.

3-(2-Hydroxyphenyl)-2-phenylquinazolin-4(3H)-one 17. White solid (600 mg, 73%): ^{1}H NMR (DMSO-d_6); δ 9.89 (s, 1H), 8.73 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 7.6 Hz, 1H), 7.97 (d, *J* = 6.8 Hz, 2H), 7.67-7.57 (m, 4H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 7.2 Hz, 1H), 6.92 (t, *J* = 7.26 Hz, 1H), MS (*m/z*) for $C_{20}H_{14}N_2O_2$; 314.11 (100.0%), 315.11 (21.6%); Purity/% = 92.48 $R_{t/min}$ = 10.88.

3-(2-Hydroxyphenyl)-2-(4-iodophenyl)quinazolin-4(3H)-one 18. White solid (850 mg, 66%): ^{1}H NMR (DMSO-d_6); δ 9.89 (s, 1H), 8.67 (d, *J* = 8.0 Hz, 1H), 8.07 (d, *J* = 8.0 Hz, 1H), 7.99 (d, *J* = 7.8 Hz, 2H), 7.73 (d, *J* = 8.8 Hz, 2H), 7.68 (t, *J* = 8.8 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 7.2 Hz, 1H), 6.92 (t, *J* = 7.26 Hz, 1H), MS (*m/z*) for $C_{20}H_{13}IN_2O_2$; 440.00 (100.0%), 441.01 (21.6%); Purity/% = 99.25 $R_{t/min}$ = 19.04.

2-(2-Fluorophenyl)-3-(2-hydroxyphenyl)quinazolin-4(3H)-one 19. Light-brown solid (480 mg, 54%): ^{1}H NMR (DMSO-d_6); δ 9.89 (s, 1H), 8.71 (d, *J* = 8.4 Hz, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 7.93 (t, *J* = 7.2 Hz, 1H), 7.66 (t, *J* = 7.2 Hz, 1H), 7.42-7.37 (m, 3H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 7.2 Hz, 1H), 6.92 (t, *J* = 7.26 Hz, 1H), MS (*m/z*) for $C_{20}H_{13}FN_2O_2$; 332.10 (100.0%), 333.10 (21.6%); Purity/% = 98.84 $R_{t/min}$ = 19.02.

4-(3-(2-Hydroxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)benzonitrile 20. White solid (710 mg, 78%): ^{1}H NMR (DMSO-d_6); δ 9.89 (s, 1H), 8.66 (d, *J* = 8.0 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 2H), 8.09 (d, *J* = 7.8 Hz, 1H), 8.06 (d, *J* = 8.0 Hz, 2H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 7.2 Hz, 1H), 6.92 (t, *J* = 7.26 Hz, 1H), MS (*m/z*) for $C_{21}H_{13}N_3O_2$; 339.10 (100.0%), 340.10 (22.7%).

2-(2,6-Dichlorophenyl)-3-(2-hydroxyphenyl)quinazolin-4(3H)-one 21. White solid (610 mg, 57%): ^{1}H NMR (DMSO-d_6); δ 9.89 (s, 1H), 8.81 (d, *J* = 6.8 Hz, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 7.93 (t, *J* = 6.8 Hz, 1H), 7.76 (t, *J* = 8.4 Hz, 1H), 7.72 (d, *J* = 6.8 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 7.08 (t, *J* = 6.4 Hz, 1H), 6.99 (d, *J* = 7.2 Hz, 1H), 6.92 (t, *J* = 7.26 Hz, 1H), MS (*m/z*) for $C_{20}H_{12}Cl_2N_2O_2$; 382.03 (100.0%), 384.02 (63.9%); Purity/% = 93.84 $R_{t/min}$ = 17.74.

2-(3,5-Dichlorophenyl)-3-(2-hydroxyphenyl)quinazolin-4(3H)-one 22. White solid (600 mg, 56%): ^{1}H NMR (DMSO-d_6); δ 9.89 (s, 1H), 8.56 (d, *J* = 8.0 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.90 (s, 2H), 7.85 (s, 1H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.24 (t, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 7.2 Hz, 1H), 6.92 (t, *J* = 7.26 Hz, 1H), MS (*m/z*) for $C_{20}H_{12}Cl_2N_2O_2$; 382.03 (100.0%), 384.02 (63.9%); Purity/% = 85.79 $R_{t/min}$ = 10.94.

3-(2-Hydroxyphenyl)-2-(naphthalen-2-yl)quinazolin-4(3H)-one 23. White solid (650 mg, 65%): ^{1}H NMR (DMSO-d_6); δ 9.89 (s, 1H), 8.79 (d, *J* = 7.2 Hz, 1H), 8.60 (s, 1H), 8.14-7.99 (m, 5H), 7.64-7.58 (m, 3H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 7.2 Hz, 1H), 6.92 (t, *J* = 7.26 Hz, 1H), MS (*m/z*) for $C_{24}H_{16}N_2O_2$; 364.12 (100.0%), 365.12 (26.0%); Purity/% = 97.66 $R_{t/min}$ = 11.19.

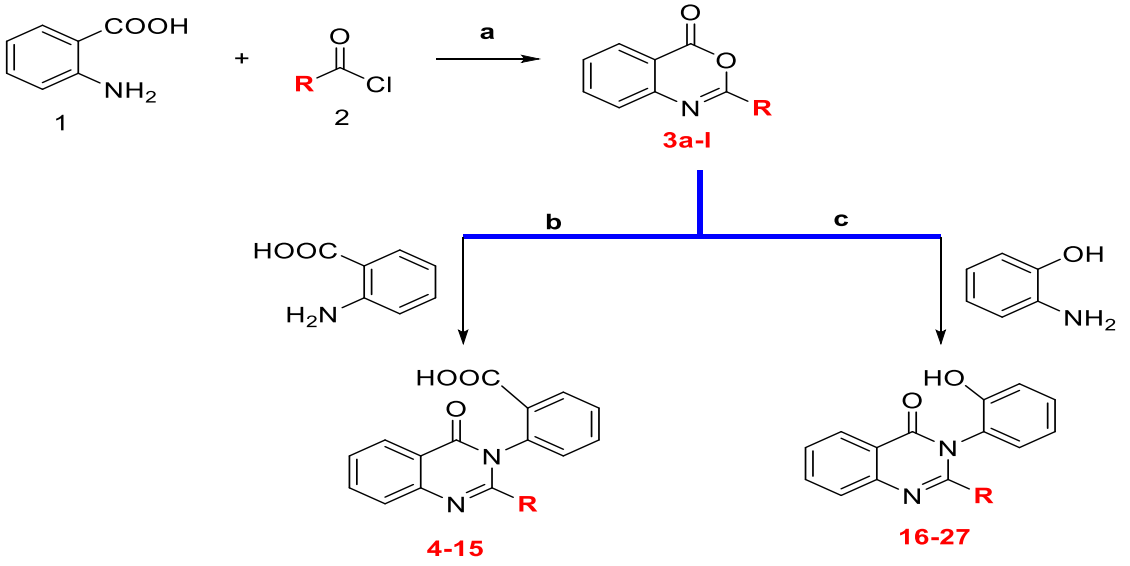
2-(4-Ethylphenyl)-3-(2-hydroxyphenyl)quinazolin-4(3H)-one 24. White solid (820 mg, 89%): ^{1}H NMR (DMSO-d_6); δ 9.89 (s, 1H), 8.74 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 7.8 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 2H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 7.2 Hz, 1H), 6.92 (t, *J* = 7.26 Hz, 1H), 2.72 (q, *J* = 7.8 Hz, 2H), 1.23 (t, *J* = 7.8 Hz, 3H), MS (*m/z*) for $C_{22}H_{18}N_2O_2$; 342.14 (100.0%), 343.14 (23.8%); Purity/% = 89.50 $R_{t/min}$ = 4.54.

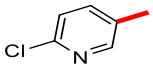
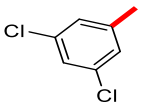
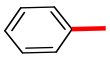
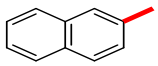
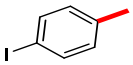
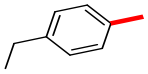
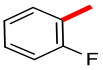
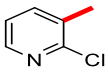
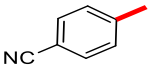
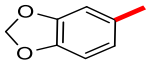
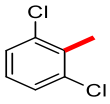
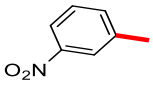
2-(2-Chloropyridin-3-yl)-3-(2-hydroxyphenyl)quinazolin-4(3H)-one 25. White solid (730 mg, 77%): ^{1}H NMR (DMSO-d_6); δ 9.89 (s, 1H), 8.54 (d, *J* = 8.0 Hz, 1H), 8.46 (d, *J* = 7.2 Hz, 2H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 4.4 Hz, 1H), 7.56 (t, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 7.2 Hz, 1H), 6.92 (t, *J* = 7.26 Hz, 1H), 6.54 (t, *J* = 7.8 Hz, 1H), MS (*m/z*) for $C_{19}H_{12}ClN_3O_2$; 349.06 (100.0%), 351.06 (32.0%); Purity/% = 79.90 $R_{t/min}$ = 16.94.

2-(Benzo[d][1,3]dioxol-5-yl)-3-(2-hydroxyphenyl)quinazolin-4(3H)-one 26. White solid (760 mg, 78%): ^{1}H NMR (DMSO-d_6); δ 9.89 (s, 1H), 8.15 (d, *J* = 9.2 Hz, 1H), 7.96 (t, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 8.8 Hz, 1H), 7.69 (d, *J* = 7.2 Hz, 1H), 7.63 (s, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 7.2 Hz, 1H), 6.92 (t, *J* = 7.26 Hz, 1H), 6.19 (s, 2H), MS (*m/z*) for $C_{15}H_9N_2O_2$; 267 (M^+, 100%); Purity/% = 89.64 $R_{t/min}$ = 16.63.

3-(2-Hydroxyphenyl)-2-(3-nitrophenyl)quinazolin-4(3H)-one 27. Beige solid (680 mg, 69%): ^{1}H NMR (DMSO-d_6); δ 9.89 (s, 1H), 8.73 (s, 1H), 8.65 (d, *J* = 7.8 Hz, 1H), 8.45 (d, *J* = 7.8 Hz, 1H), 8.39 (d, *J* = 7.2 Hz, 1H), 8.09 (d, *J* = 7.2 Hz, 1H), 7.88 (t, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 6.99 (d, *J* = 7.2 Hz, 1H), 6.92 (t, *J* = 7.26 Hz, 1H), MS (*m/z*) for $C_{20}H_{13}N_3O_4$; 359.09 (100.0%), 360.09 (21.6%); Purity/% = 97.19 $R_{t/min}$ = 19.34.

Scheme 1;



	R		R
3a,4.16		3g,10,22	
3b,5,17		3h,11,23	
3c,6,18		3i,12,24	
3d,7,19		3j,13,25	
3e,8,20		3k,14,26	
3f,9,21		3l,15,27	

Reaction condition; a) pyridine, heat with stirring at 50 °C for 24h; b&c) glacial acetic, reflux at 200 °C for 24h.

IV-Conclusion

From the previously mentioned scheme, the addition of anthranilic acid to different benzoyl chloride derivatives produced different heterocyclic derivatives. This step applied to imitate the terremide compounds for antimicrobial activity, but all tested compounds lack of anti-MRSA activity. So, the new scaffold of quinazoline derivatives to be enrolled in other studies to be examined biologically.

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تصميم وتشييد مشتقات التيراميد الجديدة للتقييم الفارماكولوجيكال

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- تعتبر مركبات الكينازولين من المركبات الحلقية غير المتجانسة الناتجة عن دمج حلقتي البنزين والبيريميدين. في السنوات الأخيرة أظهرت تلك المركبات العديد من الأنشطة الحيوية المختلفة كمضادات الصرع ومضادات الكحة والمركبات المستخدمة كباسط للعضلات والمركبات المستخدمة في علاج ضغط الدم المنخفض ومضادات الحساسة وموسعات الشعب الهوائية المستخدمة في علاج الأمراض التنفسية بالإضافة لمعالجات مرض السكري ومدرات البول ومضادات السرطان ومضادات الملاريا وذلك على سبيل المثال لا الحصر لمختلف المركبات المشتقة.
- في الآونة الأخيرة تم تشييد العديد من المركبات الحلقية غير المتجانسة وذلك في إطار القضاء على العدوات البكتيرية حيث إن تشييد مركبات الكينازولين جاء في محاولة لشبيهتها من حيث الحلقية كمركبات التيراميد ومن حيث النشاط الحيوي كمركبات الفينيل ثايازول.
- شملت الدراسة أيضا في محاولة لتكوين وتشييد مركبات جديدة لها القدرة على اختراق وتحطيم الغشاء البكتيري بالإضافة لتحسين مستوى الذوبان وذلك عن طريق وجود بعض المجموعات الكيميائية المضافة لتلك المركبات الحلقية غير المتجانسة.
- في هذه الدراسة تم دراسة الأنشطة الكيميائية من حيث التكوين وذلك عن طريق استبدال حلقة الفينايلثايازول لتصبح الكينازولين وذلك في محاولة لدراسة الانشطة الحيوية كمضادات للبكتيريا. وجاءت عملية التشييد والتكوين كمحاكاة للطرق الجديدة والتقليدية المتبعة.

الكلمات المفتاحية : الكينازولين , التيراميد , MRSA , مضادات الميكروبات , مضاد الورم