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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Design, synthesis, and evaluation of novel 1-methyl-3-substituted quinazoline-2,4-dione derivatives as antimicrobial agents

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Abstract A series of novel 1-methyl-3-substituted quinazoline-2,4-dione derivatives was designed, synthesized, and evaluated for their antimicrobial activities against six strains of bacteria and five fungi in vitro. The synthesized compounds were characterized by spectral methods. The bioactive assays showed that most of the compounds exhibited moderate antimicrobial activities against the tested strains.

Keywords Quinazoline-2,4-dione · Amide · Antibacterial · Antifungal agents

Introduction

In recent years, the widespread use of various antibiotics have led to the development of drug resistance (Zervosen *et al*., 2012) and antimicrobial resistance has become a global public health problem. The consequences of antimicrobial resistance are serious when pathogens are resistant to antimicrobials that are currently used in the treatment of human disease, for the use of the standard antibacterial therapies has resulted in failures; however, the use of increasingly costly and toxic antimicrobials would extend hospital stays and increase morbidity, mortality, and costs (Gonzales and Maisch, 2012; Canno *et al*., 2009). Although a large number of antibiotics and chemotherapeutics are available for medical use, the emergence of resistant bacterial strains constitutes an urgent need for new classes of antibacterial agents (Theuretzbacher, 2012; Sutcliffe, 2003).

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Quinazoline-2,4-dione nucleus which resembles with the quinolone nucleus but lacks the quinolone keto acid is an interesting pharmacophore. Quinazoline-2,4-dione nucleus and its derivatives have emerged abundantly due to the advance of modern organic chemistry and these compounds have a variety of promising medical applications as antibacterial (Beylin *et al*., 2007), antifungal (Ryu *et al*., 2004), anticancer (Oger *et al*., 2010), antihypertensive (Ismail *et al*., 2006), antidiabetic (Feng *et al*., 2007), anti-inflammatory (Ukrainets *et al*., 2006), and antitumor (Caldwell *et al*., 2011) agents. 8-Methyl-quinazoline-2,4-dione has been shown to overcome quinolone-resistant bacteria.(Aldred *et al*., 2012). Amides derivatives possessed a variety of medical applications such as antiviral (Bylov *et al*., 1999), antiproliferative (Nemmani *et al*., 2009), anti-inflammatory (Spasova *et al*., 2008), antibacterial (Priya *et al*., 2005), and antifungal (Bansode *et al*., 2009) agents.

Due to the diverse range of the pharmacological activities of quinazolinone-2,4-dione derivatives and amide derivatives, there has been an interest in developing of hybrid molecules through the combination of the two pharmacophores in one frame that may lead to compounds with interesting biological and pharmacological profiles. Thus, a series of novel quinazoline-2,4-dione derivatives was designed through combining the quinazoline-2,4-dione with amide by a linker (Fig. 1), synthesized, and evaluated for their antimicrobial activity in vitro.

Results and discussion

Chemistry

The synthetic route used to prepare the title compounds is outlined in Scheme 1. The starting material methyl

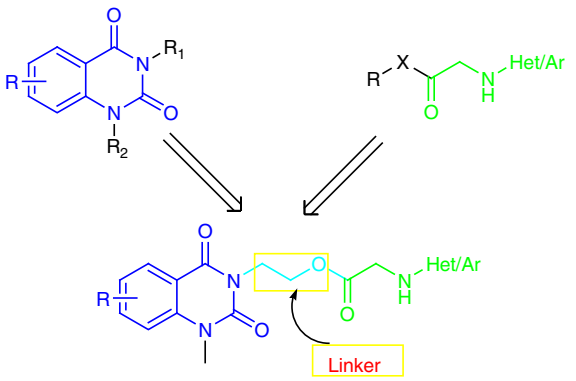
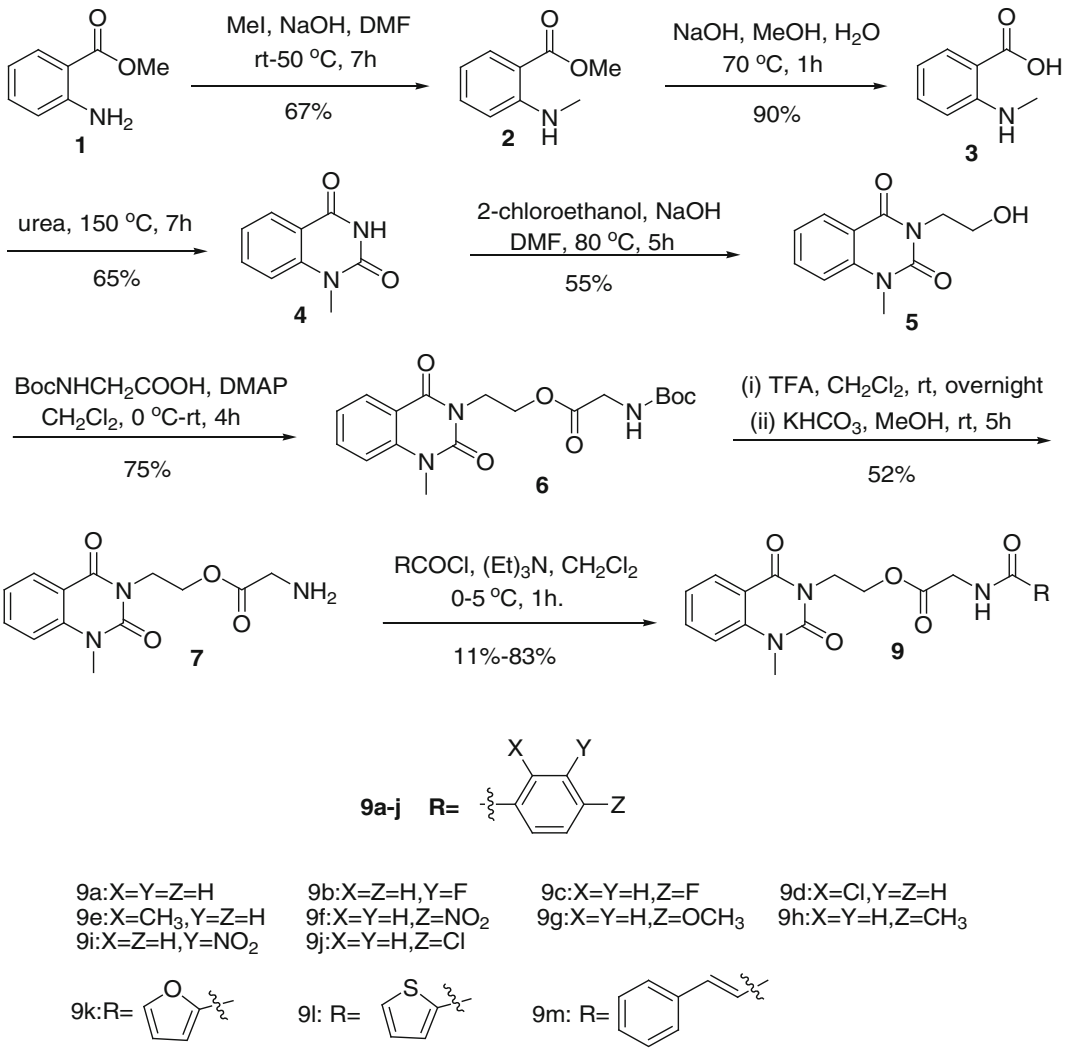


Fig. 1 Design of novel 1-methyl-3-substituted quinazoline-2,4-dione derivatives

aminobenzoate **1** was reacted with methyl iodide in the presence of sodium hydroxide in DMF to form methyl 2-(methylamino)benzoate **2** which was hydrolyzed to produce 2-(methylamino)benzoic acid **3**. The acid **3** reacted with urea to afford 1-methylquinazoline-2,4-dione **4,** which reacted with 2-chloroethanol in DMF to form 1-methyl-3-substituted quinazoline-2,4-dione **5**. Under the catalysis of DMAP, **5** reacted with 2-((tert-butoxycarbonyl)amino)acetic acid in the presence of DCC to obtain 2-(1-methyl-2,4-dioxo-1,2-dihydroquinazolin-3-yl)-ethyl-2-((tert-butoxycarbonyl)amino)acetate **6**. The protective group of **6** was removed by trifluoroacetate to obtain 2-(1-methyl-2,4-dioxo-1,2-dihydroquinazolin-3-yl)-ethyl-2-aminoacetate **7**. Finally, the compound **7** reacted with the aromatic acyl chloride to form the corresponding target compounds **9a**–**9m**. The structures of the new compounds were confirmed by ^{1}H NMR, ^{13}C NMR, and MS spectra.

Antimicrobial activity

All the newly synthesized compounds were evaluated for their antibacterial activity against six strains of bacteria including three Gram-positive organisms viz. *Staphylococcus aureus*



Scheme 1 Preparation of 1-methyl-3-substituted quinazoline-2,4(1*H*,3*H*)-dione derivatives

ATCC 25923, *Bacillus subtilis* ATCC 6633, and methicillin-resistant *S. aureus* N 315 (MRSA) and three Gram-negative organisms viz. *Bacillus proteus*, *Escherichia coli* JM 109, and *Pseudomonas aeruginosa* CR 56; and antifungal activity against five fungi viz. *Cryptococcus Neoformans* (extracted from patient), *Candida mycoderma*, *Candida albicans* ATCC 76615, *Saccharomyces cerevisiae* CGMCC2.145, and *Aspergillus flavus* 3905 by disk diffusion method in vitro. Streptomycin and fluconazole were used as positive control for antibacterial and antifungal activity, respectively. Screening results of antibacterial activity are summarized in Table 1 and the results of antifungal activity are deposited in Table 2.

Most synthesized compounds showed moderate to good antibacterial activities against the tested bacteria, some compounds showed higher antibacterial activities than streptomycin. All compounds exhibited high activities against MRSA and *B. subtilis* while showed weak activities against *S. aureus*. Compounds **9g**, **9k**, and **9m** showed good activity against *B. subtilis* with the MIC values of 4 μg/mL while the MIC value of streptomycin was 32 μg/mL. Compounds **9b**, **9c**, **9e**, **9f**, **9i**, **9l**, and **9m** showed good

Table 1 The antibacterial activities of compounds **9a–9m** expressed as MIC (μg/mL)

Compounds	Yield (%)	m.p. (°C)	Gram-positive bacteria			Gram-negative bacteria		
			S. aureus	*MRSA*	*B. subtilis*	*E. coli*	*B. proteus*	*P. aeruginosa*
9a	33.3	169.0–170.0	256	>512	512	128	>512	>512
9b	83.3	167.0–168.0	128	32	256	128	512	128
9c	57.6	171.0–172.0	256	4	128	64	512	256
9d	50.3	144.0–145.0	512	>512	64	512	128	128
9e	31.6	176.0–177.0	512	32	64	32	32	256
9f	31.6	233.0–234.0	256	8	512	128	128	64
9g	45.9	123.0–124.0	512	256	4	512	512	128
9h	76.6	131.0–131.0	512	512	64	512	32	128
9i	34	157.0–158.0	128	4	256	16	128	512
9j	11.5	127.0–128.0	128	512	128	256	256	256
9k	60.1	183.0–185.0	256	>512	4	4	128	128
9l	29	166.0–167.0	512	32	32	64	64	64
9m	16	150.0–151.0	128	4	4	16	256	>512
Streptomycin			32	512	32	64	16	64

Table 2 The antifungal activities of compounds **9a–9m** expressed as MIC (μg/mL)

Compounds	*Candida mycoderma*	*Candida albicans*	*Saccharomyces cerevisiae*	*Aspergillus flavus*	*Cryptococcus neoformans*
9a	>512	512	–	64	32
9b	512	16	–	64	256
9c	64	32	–	64	16
9d	64	32	–	128	128
9e	512	512	–	128	16
9f	64	512	–	–	–
9g	512	32	–	128	32
9h	512	32	–	64	16
9i	16	64	–	64	128
9j	512	64	–	32	32
9k	64	32	–	64	128
9l	512	512	–	64	256
9m	512	512	–	32	8
Polyoxine D	8	32	16	32	0.03125
Fluconazole	8	16	>512	64	0.03125

activity against *MRSA*, especially, compounds **9c**, **9i**, and **9m** showed promising activities with the MIC values of 4 μg/mL while MIC of streptomycin was higher than 512 μg/mL. The tested compounds showed much higher activities against *E. coli* and *P. Aeruginosa than* against *B. proteus,* compounds **9e**, **9i**, **9k**, and **9m** showed antibacterial activity against *E. coli* with MIC values of 32, 16, 4, and 32 μg/mL, respectively. Compounds **9f** and **9l** exhibited antibacterial activity against *P. Aeruginosa* as well as the control drug whose value is 64 μg/mL.

Similarly, the antifungal evaluation in vitro revealed that all the synthesized compounds exhibited moderate to good antifungal activities against all tested fungi except for *S. cerevisiae* on which the experiment in vitro showed that all compounds have no effect in test concentration.

As seen in Table 2, Compounds **9b**, **9c**, **9d**, **9g**, **9h**, and **9k** showed excellent activity against *C. albicans*. The MIC values of compounds **9c**, **9d**, **9i, 9k**, and **9l** were equivalency with the positive control drug polyoxin D whose MIC was 32 μg/mL; compound **9b** showed excellent activity against *C. albicans* with the MIC value of 16 μg/mL. For the *A. flavus,* all the compounds except compounds **9d**, **9e**, **9f**, and **9g** have shown good antifungal activity that are comparable to fluconazole. But these compounds showed weak activities against the *C. Neoformans*, the best active compound **9m** showed activity against *C. Neoformans* with the MIC value of 8 μg/mL.

From the in vitro antimicrobial activity data, preliminary structure–activity relationship of the synthesized compounds **9a**–**9m** was studied. The compounds **9a**–**9m** exhibited moderate to good antibacterial activity against *B. subtilis*, methicillin-resistant *S. aureus*, *E. coli*, and *P. Aeruginosa* and antifungal activity against fungi *C. albicans* and *A. flavus*. Different amides have different effects on the bioactivities of compounds; the non-aromatic amide, for example, compound **9m** exhibited more activity than aromatic amides against bacteria. Meanwhile, in aromatic amides, the aromatic ring with strong polarity substituent group was beneficial for antibacterial activity, such as compound **9c** (Z = F, MIC = 4 μg/mL), which showed higher activity against MRSA, and also exhibited higher inhibitory effect against *E. coli* than compound **9h** (Z = CH_3, MIC = 512 μg/mL) bearing weak polarity substituent group. Moreover, the position of substituent group has some effects on antibacterial activity, and the substituent group on para-position was beneficial.

In summary, a series of 1-methyl-3-substituted quinazoline-2,4-dione derivatives was designed, synthesized, and evaluated for their antibacterial and antifungal actions. The evaluation in vitro for the antibacterial and antifungal actions showed that most of the newly compounds exhibited moderate to good antimicrobial activities. Almost all designed compounds showed activities against MRSA which has emerged resistance against streptomycin, especially compounds **9c**, **9i**, and **9m** showed good activity against MRSA with the MIC values of 4 μg/mL. The antifungal activities against *A. flavus* of all the compounds except for compounds **9d**, **9e**, **9f**, and **9g** were comparable to fluconazole. It was concluded that polar substituent group on para-position improved the biological activity of these compounds against MRSA.

Experimental

Chemicals and analysis

All chemicals and solvents used were of reagent grade without purification but $CHCl_3$ and CH_2Cl_2 used for preparing the target compounds **9a–9m** were dried before use. Melting points were measured on X-6 precise micro melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on BrukerAv 300 MHz spectrometer using DMSO-d_6 or $CDCl_3$ as solvent. Chemical shifts are given in ppm with TMS as an internal reference. Mass spectral data were obtained on a HTC liquid gromatograph and mass spectro ESI–MS (*m*/*z*). Reactions were monitored by thin-layer chromatography (TLC) on glass plates coated with Silica Gel GF-254.

*Synthetic procedure for methyl 2-(methylamino)benzoate (**2**)*

To a solution of methyl 2-aminobenzoate **1** (16.00 g, 0.11 mol) suspended in DMF (80 mL), sodium hydroxide (5.04 g, 0.13 mol) was added, and the mixture was stirred at room temperature for 10 min. Iodomethane (15.68 g, 0.11 mol) in DMF (20 mL) was added dropwise over 30 min. The reaction mixture was stirred at room temperature for further 1 h and then heated at 50 °C for 7 h. The reaction mixture was cooled to room temperature and water (200 mL) was added to quench the reaction. The mixture solution was extracted with EtOAc (60 mL ×3) and the organic layer was dried over anhydrous $MgSO_4$, concentrated to give the crude product which was purified by column chromatography on silica gel (petroleum ether/EtOAc = 50:1) to afford compound **2** as flavescens liquid (11.65 g, 67 %); ^{1}H NMR ($CDCl_3$, 300 Mz) δ: 2.92 (s, 3H, N–CH_3), 3.86 (s, 3H, O–CH_3), 6.59–6.71 (m, 2H, Ar-3, 5-H), 7.40 (t, J = 6 Hz, 1H, Ar-4-H), 7.92 (t, J = 6 Hz, 1H, Ar-6-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 29.5(N–CH_3), 51.2(O–CH_3), 110.4(1-C), 113.4(3-C), 117.1(5-C), 130.1(6-C), 133.2(4-C), 149.2(2-C), 166.5(C=O). MS(ESI) *m*/*z*: 166(M+H)$^+$.

*Synthetic procedure for 2-(methylamino)benzoic acid (**3**)*

Compound **2** (9.242 g, 0.061 mol) was dissolved in the mixture solution of water (40 mL) and methanol (30 mL),

NaOH (4.200 g, 0.105 mol) was added, and the mixture reaction was heated at 60 °C for 1 h. Methanol was removed by evaporation and the residue was adjusted pH 7–8 with diluted HCl aqueous solution. The desired product (**3**) was obtained by filtration and then washed with water (30 mL ×3) as white powder solid (7.54 g, 90 %); m.p. 182–184 °C; ^{1}H NMR ($CDCl_3$, 300 Mz) δ: 2.96 (s, 3H, N–CH_3), 6.66 (t, $J = 15$ Hz, 1H, Ar-5-H), 6.73 (d, $J = 6$ Hz, Ar-3-H), 7.45 (t, $J = 15$ Hz, 1H, Ar-4-H), 7.99 (d, $J = 6$ Hz, Ar-6-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.9(N–CH_3), 109.1(1-C), 112.8(3-C), 118.1(5-C), 130.5(6-C), 133.6(4-C), 150.2(2-C), 170.1(C=O). MS(ESI) *m/z*: 152(M+H)$^+$.

*Synthetic procedure for 1-methylquinazoline-2,4(3H)-dione (**4**)*

Compound **3** (7.01 g, 0.046 mol) and urea (28.00 g, 0.47 mol) were mixed and stirred at 150 °C for 5 h. The mixture was cooled below 100 °C and then water (70 mL) was added to quench the reaction. The crude product was obtained by filtration and then washed in sequence with water (50 mL ×3) and EtOAc (30 mL ×3) to give flavescens powder solid 8.23 g, which was recrystallized from the mixture solution of acetone (10 mL) and water (100 mL) to afford compound **4** as white powder solid (5.25 g, 64.3 %); m.p. 278–279 °C; ^{1}H NMR ($CDCl_3$, 300 Mz) δ: 3.43 (s, 3H, N–CH_3), 7.26 (t, $J = 12$ Hz, 1H, quinazolone-6-H), 7.41 (d, $J = 12$ Hz, 1H, quinazolone-5-H), 7.75 (t, $J = 15$ Hz, 1H, quinazolone-7-H), 7.98 (d, $J = 6$ Hz, 1H, quinazolone-8-H), 11.54 (s, 1H, CO–NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 32.9(N–CH_3), 115.1(8-C), 116.2(10-C), 124.1(6-C), 127.5(5-C), 132.6(7-C), 136.6 (9-C), 152.2(2-C=O), 158.1(4-C=O). MS(ESI) *m/z*: 177(M+H)$^+$.

*Synthetic procedure for 3-(2-hydroxyethyl)-1-methylquinazoline-2,4(1H,3H)-dione (**5**)*

To a solution of compound **4** (5.00 g, 0.028 mol) and sodium hydroxide (1.3 g, 0.032 mol) in DMF (10 mL), 2-chloroethanol (2.64 g, 0.033 mol) in DMF (10 mL) was added, and the reaction mixture was heated up to 80 °C for 5 h. After completion of the reaction, the solution was cooled down to room temperature; water (100 mL) was added to quench the reaction. The mixture solution was extracted with EtOAc (50 mL ×3), the combined organic layer was washed with water (30 mL ×3), dried over anhydrous $MgSO_4$, and the organic solvent was removed to get crude product 4.12 g. The crude product was recrystallized from EtOAc to obtain the desired product **5** as white granular fluffy solid (3.37 g, 54.8 %); m.p. 154–155 °C; ^{1}H NMR ($CDCl_3$–d_1) δ (ppm): 3.62 (s, 3H, quinazolone-1-CH_3), 3.94 (t, $J = 15$ Hz, 2H, CH_2), 4.38 (t, $J = 12$ Hz, 2H, CH_2), 7.22–7.32 (m, 2H, quinazolone-5,6-H), 7.71 (t, $J = 15$ Hz, 1H, quinazolone-7-H), 8.23 (d, $J = 6$ Hz, quinazolone-8-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 32.6(N–CH_3), 43.4(3-N–CH_2–), 57.6(–CH_2–OH), 115.2(8-C), 117.1(10-C), 124.2(6-C), 127.5(5-C), 132.6 (7-C), 136.6(9-C), 152.2(2-C=O), 159.1(4-C=O). MS(ESI) *m/z*: 177(M+H)$^+$.

*Synthetic procedure for N-[(1,1-dimethylethoxy)carbonyl]-glycine-2-(1,4-dihydro-1-methyl-2,4-dioxo-3(2H)-quinazolinyl)ethyl ester (**6**)*

Compound **5** (3.20 g, 0.015 mol) was dissolved in CH_2Cl_2 (50 mL) and cooled with ice bath, and DCC (3.40 g, 0.016 mol), DMAP (0.11 g, 0.90 mmol) were then added. Then 2-((tert-butoxycarbonyl)amino)acetic acid (3.025 g, 0.017 mol) in CH_2Cl_2 (20 mL) was added dropwise over 30 min. The reaction mixture was stirred for 4 h at 0 °C. After filtration, filtrate was washed with saturated sodium bicarbonate aqueous solution (50 mL ×3) and water (50 mL ×3), and dried with anhydrous $MgSO_4$. The solvent was removed to obtain the desired compound **6** as white solid (4.301 g, 75 %); m.p. 113–114 °C; ^{1}H NMR($CDCl_3$-d_1) δ (ppm): 1.37 (s, 9H), 3.62 (s, 3H, quinazolone-1-CH_3), 3.92(s, 2H, CH_2), 3.94 (t, $J = 15$ Hz, 2H, CH_2), 4.38 (t, $J = 12$ Hz, 2H, CH_2), 7.22–7.32 (m, 2H, quinazolone-5,6-H), 7.71 (t, $J = 15$ Hz, 1H, quinazolone-7-H), 8.23 (d, $J = 6$ Hz, quinazolone-8-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.1(CH_3, 3C), 32.6(N–CH_3), 40.4(2′-C), 42.3(2-C), 60.4(1′-C), 79.6(*tert*-C), 114.2(8″–C), 1115.3(10″-C), 124.5(6″-C), 127.7(5″-C), 132.4 (7″-C), 136.4(9″-C), 151.2(2″-C=O), 156.3(4-C=O), 159.5(4″-C=O), 169.5(1-C=O), MS(ESI) *m/z*: 378(M+H)$^+$.

*Synthetic procedure for glycine-2-(1,4-dihydro-1-methyl-2,4-dioxo-3(2H)-quinazolinyl)ethyl ester (**7**)*

Compound **6** was dissolved in CH_2Cl_2 and cooled down to 0 °C with ice-water bath, and TFA (3.4 mL) was added slowly. Then reaction mixture was stirred at room temperature for overnight. The solvent was removed by evaporation, methanol (15 mL) and $KHCO_3$ (1.90 g, 0.019 mol) were added to the residue, and the resulting mixture was stirred for 5 h at room temperature. After filtration, the filtrate was dried over anhydrous $MgSO_4$, concentrated, and the crude product was recrystallized from EtOAc to obtain the desired product **7** as white powder solid (1.501 g, 51.7 %); m.p. 175–176 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.43(s, 2H, CO–CH_2–H), 3.60(s, 3H, quinazolone-1-CH_3), 4.39(t, $J = 9$ Hz, 2H, CH_2), 4.52(t, $J = 9$ Hz, 2H, CH_2), 7.22(t, $J = 15$ Hz, 1H, quinazolone-6-H), 7.28(d, $J = 9$ Hz, 1H, quinazolone-5-H), 7.69(t, $J = 15$ Hz, 1H,

quinazolone-7-H), 8.20(d, $J = 9$ Hz, quinazolone-8-H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.1(CH_3, 3C), 32.6(N–CH_3), 40.4(2-C), 40.3(2′-C), 60.4(1′-C), 115.7(8″-C), 116.3(10″-C), 124.5(5″-C), 127.7 (4″-C), 132.4 (6″-C), 136.4(9″-C), 151.2(2″-C=O), 159.5(4″-C=O), 169.5(1-C=O), MS(ESI) *m/z*: 278(M+H)$^+$.

General procedure for synthesis of the target compounds (**9a**–**9m**)

Compound **7** (0.60 mmol) was dissolved in DCM (10 ml) and cooled with ice bath, the solution of the aromatic acyl chloride compound (0.7 mmol) in DCM was added dropwise, and then triethylamine was added. The mixture was stirred for 1 h at 0 °C and quenched with water. The water phase was extracted with DCM; the combined organic layer was washed with saturated $NaHCO_3$ (10 mL ×2) and water (10 mL ×3), and dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated and crude product was recrystallized from EtOAc to obtain the target compounds (**9a**–**9m**).

*N-benzoyl-glycine-2-(1,4-dihydro-1-methyl-2,4-dioxo-3(2H)-quinazolinyl)ethyl ester (**9a**)*

Yield 83 %; m.p. 167.0–168.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.58 (s, 3H, quinazolone-1-CH_3), 4.21–4.23 (d, $J = 6$ Hz, 2H, CH_2), 4.43 (t, $J = 9$ Hz, 2H, CH_2), 4.52 (t, $J = 6$ Hz, 2H, CH_2), 6.83 (s, 1H, NH), 7.22 (t, $J = 12$ Hz, 1H, quinazolone-6-H), 7.27 (d, $J = 6$ Hz, 1H, quinazolone-5-H), 7.40–7.45 (t, $J = 15$ Hz, 2H, benzene-3,5-H), 7.51 (t, $J = 9$ Hz, 1H, benzene-4-H), 7.71 (t, $J = 18$ Hz, 1H, quinazolone-7-H), 7.81–7.83 (m, 2H, benzene-2,6-H), 8.17 (d, $J = 6$ Hz, quinazolone-8-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.8(N–CH_3), 40.2(2′-C), 42.9(2-C), 62.4(1′-C), 114.8(8″-C), 115.8(10″-C), 124.4(6″-C), 127.5(5″-C), 127.7(8-C), 129.0(6′,10′-2C), 129.1(7″-C), 132.3(7′,9′-2C), 134.3(5-C), 140.4(9″-C), 150.7(2″-C=O), 162.1(4″-C=O), 167.8(4-C=O), 169.6(1-C=O); ESI–MS(*m/z*): 392[M+H]$^+$.

*N-(3-fluorobenzoyl)-glycine-2-(1,4-dihydro-1-methyl-2,4-dioxo-3(2H)-quinazolinyl)ethyl ester (**9b**)*

Yield 33 %; m.p. 169.0–170.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.59 (s, 3H, quinazolone-1-CH_3), 4.21–4.23 (d, $J = 6$ Hz, 2H, CH_2), 4.43 (t, $J = 9$ Hz, 2H, CH_2), 4.53 (t, $J = 12$ Hz, 2H, CH_2), 6.85 (s, 1H, NH), 7.20–7.24 (m, 3H, benzene-4-H, quinazolone-5,6-H), 7.37–7.44 (m, 1H, benzene-5-H), 7.58 (t, $J = 21$ Hz, 2H, benzene-2,6-H), 7.70 (t, $J = 15$ Hz, 1H, quinazolone-7-H), 8.17 (d, $J = 6$ Hz, 1H, quinazolone-8-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.8 (N–CH_3), 40.5(2′-C), 42.1(2-C), 62.8(1′-C), 113.9(8″-C), 114.4(10″-C), 114.7(6″-C), 115.17(10-C), 118.5(5″-C), 118.8(6-C), 122.6(9-C), 123.2(7″-C), 128.8(8′-C), 130.2(5-C), 135.4(9″-C), 150.9(2″-C=O), 160.9(4″-C=O), 163.2(7-C), 164.2(4-C=O), 169.7(1-C=O). ESI–MS (*m/z*): 400[M+H]$^+$.

*N-(4-fluorobenzoyl)-glycine-2-(1,4-dihydro-1-methyl-2,4-dioxo-3(2H)-quinazolinyl)ethyl ester (**9c**)*

Yield 58 %; m.p. 171.0–172.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.59 (s, 3H, quinazolone-1-CH_3), 4.22 (d, $J = 3$ Hz, 2H, CH_2), 4.44 (t, $J = 12$ Hz, 2H, CH_2), 4.54 (t, $J = 12$ Hz, 2H, CH_2), 6.76 (s, 1H, NH), 7.11 (t, $J = 18$ Hz, 2H, benzene-3,5-H), 7.21–7.23 (m, 2H, quinazolone-5,6-H), 7.71 (t, $J = 15$ Hz, 1H, quinazolone-7-H), 7.83–7.88 (m, 2H, benzene-2,6-H), 8.17(d, $J = 6$ Hz, quinazolone-8-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.8(N–CH_3), 40.3 (2′-C), 42.9(2-C), 62.3(1′-C), 114.8 (7,9-2C), 115.8(8″-C), 124.2(10″-C), 127.7(6″-C), 128.9(5″-C), 128.9(6,10-2C), 129.7(5-C), 132.4(7″-C), 140.5(9″-C), 150.7(2″-C=O), 162.0(4″-C=O), 166.2(8-C), 167.9(4-C=O), 169.8(1-C=O), ESI–MS (*m/z*): 400[M+H]$^+$.

*N-(2-chlorobenzoyl)-glycine-2-(1,4-dihydro-1-methyl-2,4-dioxo-3(2H)-quinazolinyl)ethyl ester (**9d**)*

Yield 51 %; m.p. 144.0–145.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.57 (s, 3H, quinazolone-1-CH_3), 4.25 (d, $J = 9$ Hz, 2H, CH_2), 4.43 (t, $J = 12$ Hz, 2H, CH_2), 4.54 (d, $J = 9$ Hz, 2H, CH_2), 6.85 (s, 1H, NH), 7.11 (t, $J = 12$ Hz, 2H, benzene-5,6-H), 7.21–7.30 (m, 2H, quinazolone-5,6-H), 7.71 (t, 1H, quinazolone-7-H), 7.83–7.88 (m, 2H, benzene-3,4-H), 8.17(d, $J = 9$ Hz, 1H, quinazolone-8-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.9(N–CH_3), 40.6(2′-C), 42.2(2-C), 62.8(1′-C), 113.8(8″-C), 123.3(10″-C), 127.1(6″-C), 128.9(5″-C), 129.0(9-C), 130.3(10-C), 131.0(7-C), 131.5(6-C), 131.7(5-C), 131.7(7″-C), 133.5(8-C), 140.6(9″-C), 150.8 (2″-C=O), 162.1(4″-C=O), 166.5(4-C=O), 169.6(1-C=O), ESI–MS (*m/z*): 416[M+H]$^+$.

*N-(2-methylbenzoyl)-glycine-2-(1,4-dihydro-1-methyl-2,4-dioxo-3(2H)-quinazolinyl)ethyl ester (**9e**)*

Yield 32 %; m.p. 176.0–177.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.42 (s, 3H, benzene-CH_3), 3.64 (s, 3H, quinazolone-1-CH_3), 4.21 (d, $J = 6$ Hz, 2H, CH_2), 4.42 (t, $J = 9$ Hz, 2H, CH_2), 4.53 (s, $J = 9$ Hz, 2H, CH_2), 6.42 (s, 1H, NH), 7.15–7.23 (m, 3H, quinazolone-6-H, benzene-3,5-H), 7.27–7.32 (m, 2H, quinazolone-5-H, benzene-4-H), 7.41 (d, $J = 6$ Hz, 1H, benzene-6-H), 7.70 (t, $J = 15$ Hz, 1H, quinazolone-7-H), 8.14 (d, $J = 9$ Hz, 1H, quinazolone-8-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 18.23(Ph-CH_3), 30.76(N–CH_3), 40.58(2′-C), 42.96(2-C), 62.34(1′-C), 115.80 (8″-C), 115.86(10″-C), 124.27(6″-C), 127.66(9-C),127.76(10-C), 128.78(5″-C), 131.53(7-C), 132.46(8-C),

132.57(7″-C), 137.28(5-C),139.25(9″-C), 140.46(6-C),,150.81(2″-C=O), 162.03(4″-C=O), 167.51(4-C=O), 169.58(1-C=O). ESI–MS (*m*/*z*): 396[M+H]$^+$.

*N-(4-nitrobenzoyl)-glycine-2-(1,4-dihydro-1-methyl-2,4-dioxo-3(2H)-quinazolinyl)ethyl ester (**9f**)*

Yield 45 %; m.p. 233.0–234.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.60 (s, 3H, quinazolone-1-CH_3), 4.25 (d, $J = 6$ Hz, 2H, CH_2), 4.45 (t, $J = 9$ Hz, 2H, CH_2), 4.56 (s, $J = 9$ Hz, 2H, CH_2), 6.95 (s, 1H, NH), 7.23–7.30(m, 2H, quinazolone-5,6-H), 7.72 (t, $J = 15$ Hz, 1H, quinazolone-7-H), 8.02 (d, $J = 9$ Hz, 2H, benzene-2,6-H), 8.15 (d, $J = 9$ Hz, 1H, quinazolone-8-H), 8.32 (d, $J = 9$ Hz, 2H, benzene-3,5-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.76(N–CH_3), 40.68(2′-C), 42.78(2-C), 62.58(1′-C), 115.72(7,9-2C), 115.87(8″-C), 123.89(10″-C), 123.97(6″-C), 127.46(5″-C), 127.76(6,10-2C), 132.37(7″-C), 133.15 (9″-C), 141.46(5-C), 150.75(8-C), 151.31(2″-C=O), 162.09(4″-C=O), 167.85(4-C=O),169.55(1-C=O). ESI–MS (*m*/*z*): 427[M+H]$^+$.

*N-(4-methoxybenzoyl)-glycine-2-(1,4-dihydro-1-methyl-2,4-dioxo-3(2H)-quinazolinyl)ethyl ester (**9g**)*

Yield 29 %; m.p. 157.0–158.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.58 (s, 3H, quinazolone-1-CH_3), 3.85 (s, 3H, O–CH_3), 4.21 (d, $J = 3$ Hz, 2H, CH_2), 4.43 (t, $J = 9$ Hz, 2H, CH_2), 4.52 (t, $J = 12$ Hz, 2H, CH_2), 6.72 (s, 1H, NH), 6.91 (d, 2H, benzene-3,5-H), 7.20–7.29 (m, 2H, quinazolone-5,6-H), 7.70 (t, $J = 15$ Hz, 1H, quinazolone-7-H), 7.79 (d, $J = 6$ Hz, 2H, benzene-2,6-H), 8.20 (d, 1H, quinazolone-8-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.76(N–CH_3), 40.48(2′-C), 42.86(2-C), 55.92(O–CH_3), 62.46(1′-C), 114.26(7,9-2C), 115.48(8″-C), 115.75(10″-C), 115.81(6″-C), 124.46(5-C), 126.46(6″-C), 127.76(6,10-2C), 131.96(7″-C), 132.86(9″-C), 150.75(2″-C=O), 162.23(4″-C=O), 164.05(8-C), 167.85(4-C=O), 169.56(1-C=O). ESI–MS (*m*/*z*): 412[M+H]$^+$.

*N-(4-methylbenzoyl)-glycine-2-(1,4-dihydro-1-methyl-2,4-dioxo-3(2H)-quinazolinyl)ethyl ester (**9h**)*

Yield 63 %; m.p. 157.0–158.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.58 (s, 3H, quinazolone-1-CH_3), 3.85 (s, 3H, O–CH_3), 4.21 (d, $J = 3$ Hz, 2H, CH_2), 4.43 (t, $J = 9$ Hz, 2H, CH_2), 4.52 (t, $J = 12$ Hz, 2H, CH_2), 6.72 (s, 1H, NH), 6.91 (d, 2H, benzene-3,5-H), 7.20–7.29 (m, 2H, quinazolone-5,6-H), 7.70 (t, $J = 15$ Hz, 1H, quinazolone-7-H), 7.79 (d, $J = 6$ Hz, 2H, benzene-2,6-H), 8.20 (d, 1H, quinazolone-8-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 21.37(Ph-CH_3), 30.72(N–CH_3), 40.48(2′-C), 42.89(2-C), 62.38 (1′-C), 115.72(8″-C), 115.76(10″-C), 124.43(6″-C), 127.46(6,10-2C), 127.76(5″-C), 129.18(7,9-2C), 131.26(5-C), 132.37(7″-C), 140.45(9″-C), 141.86(8-C), 150.71(2″-C=O), 162.06(4″-C=O), 167.85(4-C=O), 169.75(1-C=O), ESI–MS (*m*/*z*): 396[M+H]$^+$.

*N-(3-nitrobenzoyl)-glycine-2-(1,4-dihydro-1-methyl-2,4-dioxo-3(2H)-quinazolinyl)ethyl ester (**9i**)*

Yield 51 %; m.p. 183.0–185.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.61 (s, 3H, quinazolone-1-CH_3), 4.25 (d, $J = 3$ Hz, 2H, CH_2), 4.45 (t, $J = 12$ Hz, 2H, CH_2), 4.56 (t, $J = 9$ Hz, 2H, CH_2), 6.99 (s, 1H, NH), 7.21–7.29 (m, 2H, quinazolone-5,6-H), 7.64–7.73 (m, 3H, benzene-5-H, quinazolone-7-H), 8.16 (d, $J = 9$ Hz, 1H, quinazolone-8-H), 8.21 (d, $J = 6$ Hz, 1H, benzene-4-H), 8.39 (d, $J = 9$ Hz, 1H, benzene-6-H), 8.70 (s, 1H, benzene-2-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.73(N–CH_3), 40.56 (2′-C), 42.74(2-C), 62.54(1′-C), 114.97(8″-C), 115.72(6-C), 122.65(10″-C), 124.51(8-C), 127.37(6″-C), 128.07(5″-C), 129.79(9-C), 132.36(7″-C), 133.69(10-C), 135.19(5-C), 140.46(9″-C), 148.14(7-C), 150.74(2″-C=O), 162.09(4″-C=O), 166.22(4-C=O), 169.73(1-C=O). ESI–MS (*m*/*z*): 427[M+H]$^+$.

*N-(4-chlorobenzoyl)-glycine-2-(1,4-dihydro-1-methyl-2,4-dioxo-3(2H)-quinazolinyl)ethyl ester (**9j**)*

Yield 50 %; m.p. 166.0–167.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.59 (s, 3H, quinazolone-1-CH_3), 4.22 (d, $J = 6$ Hz, 2H, CH_2), 4.44 (t, $J = 12$ Hz, 2H, CH_2), 4.53 (t, $J = 6$ Hz, 2H, CH_2), 6.80 (s, 1H, NH), 7.21–7.30 (m, 2H, quinazolone-5,6-H), 7.41 (d, $J = 6$ Hz, benzene-3,5H), 7.69–7.79 (m, 3H, quinazolone-7-H, benzene-2,6-H), 8.15 (d, $J = 9$ Hz, quinazolone-8-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.73(N–CH_3), 40.25(2′-C), 42.87(2-C), 62.36(1′-C), 115.78(8″-C), 115.83(10″-C), 124.45(6″-C), 127.75(5″-C), 128.89(6,10-2C), 130.36(7,9-2C), 132.40(5,7″-2C), 136.8(9″-C),140.46(8-C), 150.72(2″-C=O), 162.04(4″-C=O), 167.65(4-C=O), 169.57(1-C=O). ESI–MS (*m*/*z*): 416[M+H]$^+$.

*N-(2-furanylcarbonyl)-glycine-2-(1,4-dihydro-1-methyl-2,4-dioxo-3(2H)-quinazolinyl)ethyl ester (**9k**)*

Yield 47 %; m.p. 123.0–124.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.60 (s, 3H, quinazolone-1-CH_3), 4.18 (d, $J = 6$ Hz, 2H, CH_2), 4.43 (t, $J = 9$ Hz, 2H, CH_2), 4.50 (t, $J = 6$ Hz, 2H, CH_2), 6.47–6.49 (m, 1H, furan-4-H), 6.9 (s, 1H, NH), 7.12 (d, 1H, furan-2-H), 7.20–7.30 (m, 2H, quinazolone-5,6-H), 7.41 (s, 1H, furan-5-H), 7.70 (t, $J = 18$ Hz, 1H, quinazolone-7-H), 8.21 (d, $J = 6$ Hz, quinazolone-8-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.84(N–CH_3), 40.76(2′-C), 42.89(2-C), 62.54(1′-C), 111.76(7-C), 112.17(6-C), 115.67(8″-C), 115.85(10″-C), 124.46(6″-C), 127.78(5″-C), 132.39(7″-C), 140.46(9″-C), 143.83(8-C), 147.06(5-C), 150.72(2″-C=O), 158.65(4″-C=O), 162.02(4-C=O), 169.58(1-C=O). ESI–MS (*m*/*z*): 372[M+H]$^+$.

*N-(2-thienylcarboyl)-glycine-2-(1,4-dihydro-1-methyl-2,4-dioxo-3(2H)-quinazolinyl)ethyl ester (**9l**)*

Yield 77 %; m.p. 131.0–131.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.60 (s, 3H, quinazolone-1-CH_3), 4.20 (d, 2H, $J = 6$ Hz, CH_2), 4.44 (t, $J = 9$ Hz, 2H, CH_2), 4.53 (t, $J = 9$ Hz, 2H, CH_2), 6.65 (s, 1H, NH), 7.08 (t, 1H, thiophene-4-H), 7.021–7.29(m, 2H, quinazolone-5,6-H), 7.49(d, $J = 6$ Hz, 1H, thiophene-5-H), 7.61 (d, $J = 6$ Hz, 1H, thiophene-3-H), 7.7 (t, 15 Hz, 1H, quinazolone-7-H), 8.19 (d, $J = 9$ Hz, 1H, quinazolone-8-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 30.9(N–CH_3), 40.6(2′-C), 42.9(2-C), 62.6(1′-C), 115.6(8″-C), 115.9(10″-C), 124.5(6″-C), 127.8(5″-C), 129.1(7-C), 130.4(7″-C), 131.9(8-C), 132.3(9″-C), 137.6(6-C), 140.5(5-C), 150.8(2″-C=O), 161.7(4″-C=O), 162.1(4-C=O), 169.7 (1-C=O), ESI–MS (*m*/*z*): 388[M+H]$^+$.

*N-[(2Z)-1-oxo-3-phenyl-2-propen-1-yl]-glycine-2-(1,4-dihydro-1-methyl-2,4-dioxo-3(2H)-quinazolinyl)ethyl ester (**9m**)*

Yield 42 %; m.p. 150.0–151.0 °C; ^{1}1H NMR (300 MHz, $CDCl_3$) δ: 3.61 (s, 3H, quinazolone-1-CH_3), 4.16 (d, $J = 6$ Hz, 2H, CH_2), 4.43 (t, $J = 9$ Hz, 2H, CH_2), 4.52 (t, $J = 9$ Hz, 2H, CH_2), 6.36 (s, 1H, NH), 6.48 (d, $J = 18$ Hz, 1H, alkene-H), 7.23 (t, $J = 15$ Hz, 2H, quinazolone-6-H, benzene-4-H), 7.3–7.38 (m, 3H, benzene-3,5-H, quinazolone-5-H), 7.50 (t, $J = 9$ Hz, 2H, benzene-2, 6-H), 7.60 (s, 1H, CH = CH-H), 7.69(t, $J = 18$ Hz, 1H, quinazolone-7-H), 8.21(d, $J = 9$ Hz, quinazolone-8-H); 13C NMR (75 MHz, $CDCl_3$) δ: 30.8(N–CH_3), 40.3(2′-C), 41.9(2-C), 62.7(1′-C), 113.7(6-C), 115.2(8″-C), 120.0(10″-C), 123.2(6″-C), 127.8(8,12,-2C), 128.8(9,11-2C), 128.9(5″-C), 129.7(10-C), 134.7(7″-C), 135.4(9″-C), 140.5(7-C), 141.4(6-C), 150.9(2″-C=O), 162.1(4″-C=O), 165.8(4-C=O), 169.8(1-C=O). ESI–MS (*m*/*z*): 408[M+H]$^+$.

Antibacterial screening

The antibacterial activity of the synthesized compounds was evaluated against six different strains of Gram-positive and Gram-negative bacteria by the agar diffusion method. The media used in this assay was Beef Extract-peptone media containing 1 % peptone, 0.3 % beef extract, 0.5 % sodium chloride in distilled water, the solid media as well as 15 % agar. Stock solutions of all target compounds in DMSO were diluted to give serial 2-fold dilutions that were added to each medium resulting in concentrations ranging from 0.5 to 512 μg/mL. The final concentration of DMSO in the assay did not exceed 0.3 %. The antibacterial activity was evaluated by disk diffusion method. Tests were incubated overnight at 37 °C prior to recording the minimum inhibitory concentration (MIC) which was the lowest concentration of the test compound that resulted in no visible growth on the plate. Streptomycin was used as the positive control drug.

The antifungal activity was evaluated against five fungi. The media was modified Sabouraud chloramphenicol agar containing 1 % peptone, 2 % Glucose, and solid media as well as 15 % agar. Stock solutions were as previously described. The antifungal activity was evaluated by disk diffusion method. The tests were incubated overnight at 25 °C and the minimum inhibitory concentrations (MIC, μg/mL) were recorded. Fluconazole was used as the compared drug.

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