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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Library design, synthesis and biological exploration of novel 3,4′-bicarbostyril derivatives as potent antimicrobial, antitubercular and antimalarial agents

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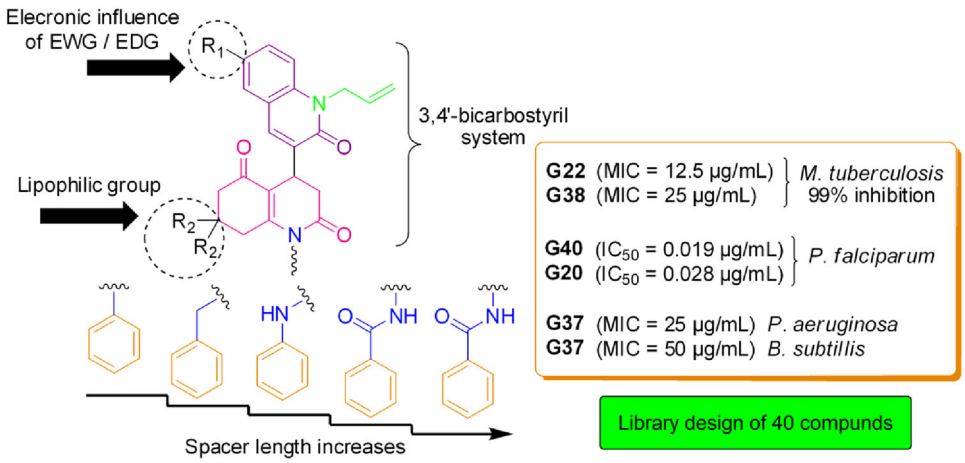
Abstract A library comprises diversely substituted novel 3,4′-bicarbostyril derivatives have been designed by molecular hybridization technique and synthesized via multi-component reaction . Compounds **G22** (MIC = 12.5 µg/mL) and **G38** (MIC = 25 µg/mL) exhibited 99% inhibition against *Mycobacterium tuberculosis*, while compounds **G40** (IC_{50} = 0.019 µg/mL) and **G20** (IC_{50} = 0.028 µg/mL) found to have excellent activity against *Plasmodium falciparum*. Compounds **G37** (MIC = 25 µg/mL) and **G8**, **G18**, and **G38** (MIC = 50 µg/mL) elicited excellent antimicrobial activity compared to standard drugs. Biological results revealed that the potency of the title compounds strongly depends on the length and flexibility of various spacers at *N*−1, the electronic influence of substituent at R_1 and lipophilicity of CH_3 group at R_2 position on bicarbostyril system.

Graphical Abstract



Keywords Carbostyril · Quinoline · Multi-component reaction · Antimicrobial activity · Antitubercular activity · Antimalarial activity

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Introduction

Malaria is a vicious and endemic infectious disease across Asia, Africa, Europe, and America (Cures et al. 2013). Also, the treatment and control of malaria became more difficult because of the spread of drug resistance to most antimalarial drugs including chloroquine, mefloquine, atovaquone, primaquine and sulphadoxine (Jagoe 2014). Consequently, the World Health Organization suggested developing efficient vaccines for the elimination of malaria (WHO 2014a). On the other hand, tuberculosis is one of the world's deadliest diseases, caused by *Mycobacterium tuberculosis* bacteria (MTB) (WHO 2014b). The prevalence of multidrug-resistant TB and extensively drug-resistant TB substantiates the urgent need for the development of new antitubercular drugs (Mdluli et al. 2015). Moreover, the treatment of infectious diseases caused by bacteria and fungi remains an important and challenging problem due to multi-drug resistant microbial pathogens. Hence, Infectious Diseases Society of America gives a proposal for a "10 × 20 initiative" in which they noted 'Time has came for a global commitment to develop new antibacterial drugs" and suggested that minimum ten new drugs should be developed by 2020 (Infectious Diseases Society of America 2010). In order to defeat these issues, there is an urgent need to discover competent antimicrobial, antitubercular and antimalarial drugs for the effective chemotherapy.

The carbostyril (2-quinolone) is a biologically vital scaffold and found in number of alkaloids such as, Buchapine (McCormick et al. 1996), Semecarpifoline (Chen et al. 2001), Peniprequinolone (Hayashi et al. 1997) and Penigequinolone B (Kimura et al. 1996) (Fig. 1). In recent years, medicinal chemists have gained special attention towards the development of a new class of antimicrobial, antitubercular and antimalarial agents based on quinolone moiety (Plech et al. 2013; Cui et al. 2013; Asif et al. 2013; Kathrotiya and Patel 2013). As a result, Delafloxacin (Butler et al. 2013), Bedaquiline (TMC 207) (Butler et al. 2013) and SJ733 (Jiménez-Díaz et al. 2014) were derived as potential drug candidates for the antibacterial, anti-TB and antimalarial activities, respectively (Fig. 1). On the other hand, spacers like amine –NH– and amide –CONH– (specifically isoniazid) were incorporated in the molecules by adopting molecular hybridization approach to boost the activities of resultant compounds, e.g., SJ733 (Jiménez-Díaz et al. 2014), DSM265 (Coteron et al. 2011), Sudoterb (LL3858) (Arora et al. 2010) (Fig. 1). Also, the allyl group at the heterocyclic *N*-atom has been found to enhance antimicrobial activity and plays an imperative role in the development of new antimicrobial agents (Jardosh and Patel 2012, 2013a, b, c, d, 2014). Over the last few years, molecular hybridization technique proved to be a very successful technique (Jardosh and Patel 2012, 2013a, b, c, d, 2014; Sangani et al. 2014; Jardosh et al. 2013e; Kanani and Patel 2014; Srivastava et al. 2015; Narhe et al. 2014), which allows a combination of two or more bio-potent moieties and pharmacophoric groups in a single scaffold could lead to the creation of successful drugs. Moreover, the diversity oriented synthesis (DOS) has exhibited considerable importance and proved to explore the library of complex and diverse biologically important heterocyclic compounds in less time (Srivastava et al. 2015; Narhe et al. 2014; Kumar et al. 2011). In the context of our goal to discover biologically potent bicarbostyril system and our incessant efforts towards the development of quinoline based heterocyclic compounds (Kathrotiya and Patel 2013; Jardosh and Patel 2012, 2013a, b, c, d, e, 2014; Sangani et al. 2014; Kanani and Patel 2014), we have designed and synthesized small library of hitherto novel 3,4′-bicarbostyril derivatives by incorporating:

i) Spacers having different length at the *N*-1 position of carbostyril: phenyl (Ph), benzyl, phenyl hydrazine (PHZ), benzohydrazide (BHZ) and isoniazid (INH)
ii) Electron donating and withdrawing groups at the C-4 position of *N*-allyl carbostyril: H, CH_3, OCH_3, and Cl
iii) Lipophilic methyl group at C-7 position of carbostyril ring

In the light of aforesaid findings and mentioned hypothesis, we report herein the library design and synthesis of novel 3,4′-bicarbostyril derivatives via three component cyclo-condensation reaction between 1-allyl-2-oxo-1,2-dihydroquinoline-3-carbaldehydes, Meldrum's acid and various β-enaminones. The structures of title derivatives were elucidated on the basis of FT-IR, ^{1}H NMR, ^{13}C NMR (APT), mass spectra and elemental analysis. All these derivatives were evaluated for their in vitro antimicrobial activity against a representative panel of bacteria and fungi, antitubercular activity against *M. tuberculosis bacteria* and antimalarial activity against *P. falciparum* (Fig. 2).

Experimental

Materials and methods

All the reagents were procured from Sigma-Aldrich and were used without further purification. Organic solvents were purchased from Merck and purified by standard methods and stored over molecular sieves. All reactions were monitored by thin-layer chromatography (TLC, on aluminum plates coated with silica gel $60F_{254}$, 0.25 mm thickness, Merck) carried on fluorescent coated plates and detection of the components was made by exposure to iodine vapors or ultra-violet light. The course of the reaction was followed by TLC using solvent system chloroform: methanol::9:1. Melting points of all the title compounds

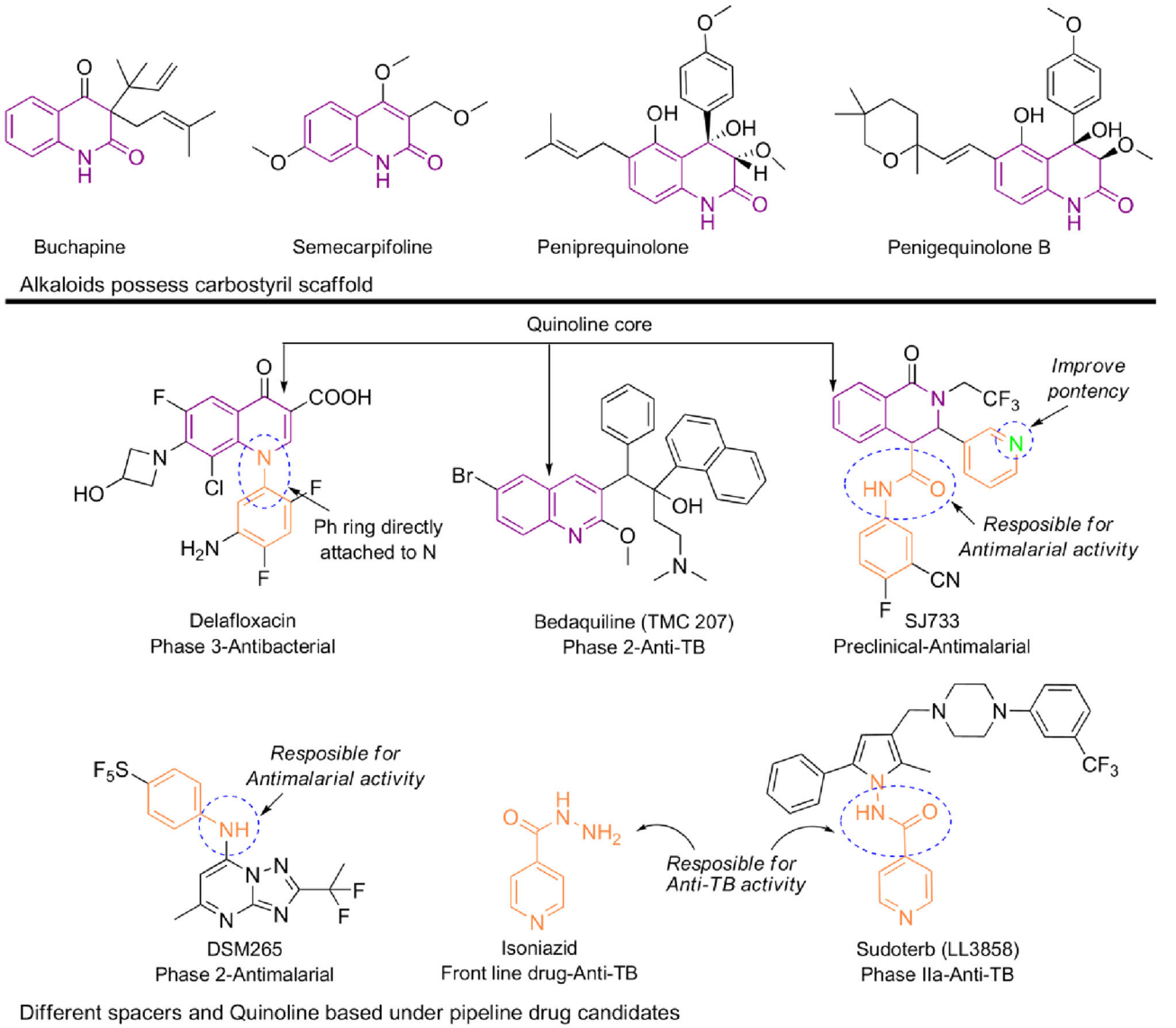


Fig. 1 Quinoline based alkaloids and repurposed drugs

were determined by the open tube capillary method (using silicon oil 350 cst) and are uncorrected. The IR spectra were recorded on a Perkin-Elmer Spectrum GX FT-IR Spectrophotometer (Perkin-Elmer, USA) using potassium bromide pellets in the range 4000–400 cm^{-1} and frequencies of only characteristic peaks are expressed in cm^{-1}. ^{1}H NMR and ^{13}C NMR (APT) spectra were recorded in DMSO-d_6 on a Bruker Avance 400F (MHz) spectrometer (Bruker Scientific Corporation Ltd., Switzerland) using TMS as an internal standard at 400 and 100 MHz, respectively. Chemical shifts are reported in parts per million (ppm). Splitting patterns are designated as s, for singlet; d, for doublet; m, for multiplet. The mass spectra were scanned on a Shimadzu LCMS 8030 mass spectrometer (Shimadzu, Tokyo, Japan). ESI source and triple quardrupole mass analyzer were used for analysis. Elemental analysis (% C, H, N) was carried out using a Perkin-Elmer 2400 series-II elemental analyzer (Perkin-Elmer, USA) and all compounds are within ±0.4% of the theoretical compositions. Standard drugs ampicillin, ciprofloxacin, chloramphenicol, griseofulvin, nystatin, isoniazid, rifampicin, quinine and chloroquine were commercial.

General procedure for the synthesis of β-enaminones ***E(1–10)***

In a round-bottom flask, equimolar (3 mmol) mixture of 1,3-cyclohexanedione/dimedone **C(1–2)** and aniline **D1**/benzyl amine **D2**/BHZ **D3**/INH **D4** heated at 120 °C till the completion of the reaction as confirmed by the TLC (30 min.). The crude products obtained were purified by recrystalization with ethanol: water (1:4) mixture and dried. The products were obtained quantitatively with an excellent purity.

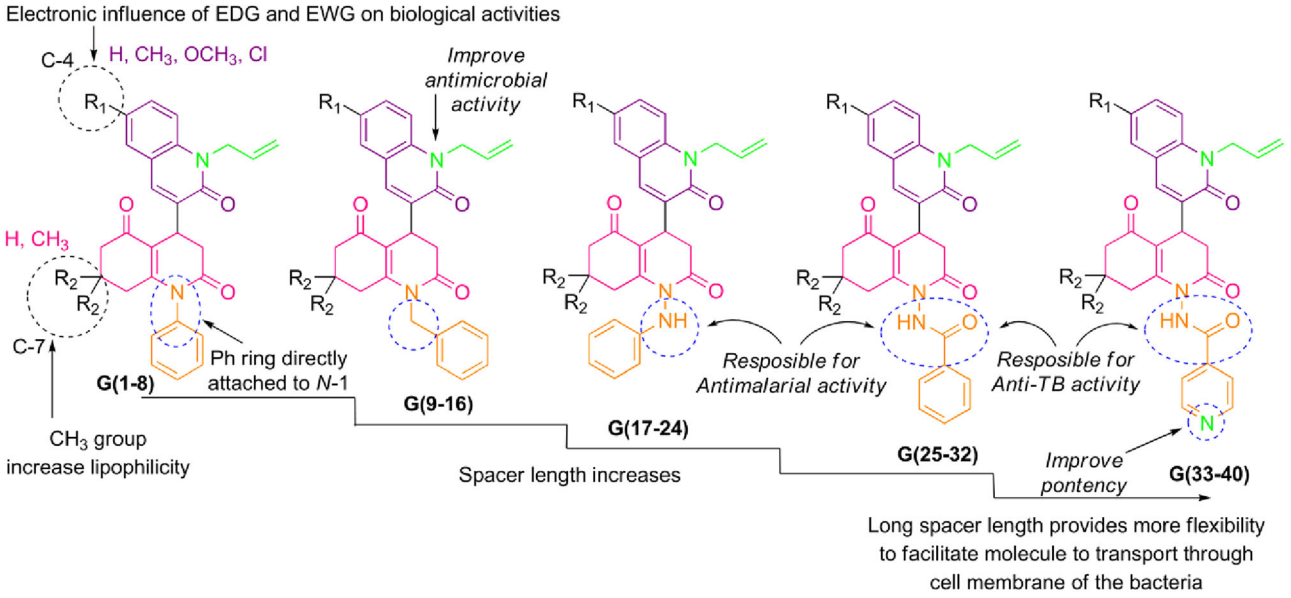


Fig. 2 Design of 3,4′-bicarbostyril derivatives

General procedure for the synthesis of 3,4′-bicarbostyrilderivatives ***G(1–40)***

A 100 mL round bottomed flask, fitted with a reflux condenser, was charged with a mixture of 1-allyl-2-oxo-1,2-dihydroquinoline-3-carbaldehydes **B(1–4)** (1 mmol), Meldrum's acid **F** (1 mmol), various β-enaminones **E(1–10)** (1 mmol) and a catalytic amount of piperidine (0.2 mmol) in ethanol (10 mL). The reaction mixture was heated under reflux for 3–4 h and the progress of the reaction was monitored by TLC. After completion of the reaction (as evidenced by TLC), the reaction mixture was cooled to room temperature and stirred magnetically for further 20 min, the solid mass separated was collected by filtration, washed well with ethanol (15 mL) and purified by recrystalization from equal volume ratio of chloroform and methanol (20 mL) to obtain a pure solid sample.

1-Allyl-1′-phenyl-3′,4′,7′,8′-tetrahydro-3,4′-biquinoline-2,2′,5′(1H,1′H,6′H)-trione **(G1)** Yield: 72%; mp: 224–226 °C; IR (KBr, ν_{max}, cm^{-1}): 3020 (Ar C–H str.), 1702, 1642, and 1620 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.94–2.41 (m, 6H, 3 × CH_2 of cyclohexenone ring), 2.74 (dd, 1H, $J_1 = 15.6$ Hz, $J_2 = 16.0$ Hz, H-3), 3.10 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 8.0$ Hz, H-3), 4.42 (t, 1H, $J_1 = 7.2$, $J_2 = 7.6$ Hz, C<u>H</u>, H-4), 4.85 (d, 2H, $J = 6.4$ Hz, N-C<u>H_2</u>), 4.90 (d, 1H, $J = 16.8$ Hz, N-CH_2CH=C<u>H</u>-*trans*), 5.10 (d, 1H, $J = 10.4$ Hz, N-CH_2CH=C<u>H</u>-*cis*), 5.90 (m, 1H, C<u>H</u>=CH_2), 7.23–8.05 (m, 10H, Ar–H); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 21.27 (CH_2), 26.95 (CH_2), 29.67 (quinolone C-4), 35.54 (quinolone C-3), 36.44 (<u>CH_2</u>–CO), 44.74 (allylic N–<u>CH_2</u>–CH), 116.12, 117.10, 117.36, 121.70, 126.66, 127.55, 128.21, 128.87, 129.87, 132.10, 132.62, 133.24, 133.62, 137.00, 137.45, and 157.65 (16C, Ar–C+allylic C=C), 160.52 (C=O), 169.49 (C=O), 195.48 (C=O); MS (ESI) *m/z* 424.6 $[M]^+$; anal. calcd. for $C_{27}H_{24}N_2O_3$ (424.49 g/mol): C, 76.39; H, 5.70; N, 6.60; Found: C, 76.63; H, 5.54; N, 6.58.

1-Allyl-6-methyl-1′-phenyl-3′,4′,7′,8′-tetrahydro-3,4′-biquinoline-2,2′,5′(1H,1′H,6′H)-trione **(G2)** Yield: 75%; mp: 226–228 °C; IR (KBr, ν_{max}, cm^{-1}): 3020 (Ar C–H str.), 1705, 1642, and 1628 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.92–2.69 (m, 9H, 3 × CH_2 of cyclohexenone ring+CH_3), 2.80 (dd, 1H, $J_1 = 15.6$ Hz, $J_2 = 16.0$ Hz, H-3), 3.03 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 8.0$ Hz, H-3), 4.43 (t, 1H, $J_1 = 7.2$, $J_2 = 7.6$ Hz, C<u>H</u>, H-4), 4.89 (d, 2H, $J = 6.4$ Hz, N–C<u>H_2</u>), 4.92 (d, 1H, $J = 16.8$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.11 (d, 1H, $J = 10.4$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.90 (m, 1H, C<u>H</u>=CH_2), 7.26–8.07 (m, 9H, Ar–H); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 20.42 (CH_3), 21.32 (CH_2), 27.02 (CH_2), 29.72 (quinolone C-4), 35.44 (quinolone C-3), 36.47 (<u>CH_2</u>–CO), 44.72 (allylic N–<u>CH_2</u>–CH), 116.10, 117.04, 117.30, 121.68, 126.61, 127.50, 128.19, 128.79, 129.81, 132.12, 132.66, 133.21, 133.63, 137.05, 137.44, and 157.67 (16C, Ar–C +allylic C=C), 160.53 (C=O), 169.50 (C=O), 195.46 (C=O); MS (ESI) *m/z* 438.7 $[M]^+$; anal. calcd. for $C_{28}H_{26}N_2O_3$ (438.52 g/mol): C, 76.69; H, 5.98; N, 6.39; found: C, 76.62; H, 5.99; N, 6.50.

1-Allyl-6-methoxy-1′-phenyl-3′,4′,7′,8′-tetrahydro-3,4′-biquinoline-2,2′,5′(1H,1′H,6′H)-trione **(G3)** Yield: 68%; mp: 237–239 °C; IR (KBr, ν_{max}, cm^{-1}): 3070 (Ar C–H str.),

1702, 1641, and 1620 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.94–2.42 (m, 6H, 3 × CH_2 of cyclohexenone ring), 2.78 (dd, 1H, $J_1 = 15.6$ Hz, $J_2 = 16.0$ Hz, H-3), 3.08 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 8.0$ Hz, H-3), 3.80 (s, 3H, OCH_3), 4.49 (t, 1H, $J_1 = 7.2$, $J_2 = 7.6$ Hz, C<u>H</u>, H-4), 4.84 (d, 2H, $J = 6.4$ Hz, N–C<u>H</u>$_2$), 4.91 (d, 1H, $J = 16.8$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.09 (d, 1H, $J = 10.4$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.89 (m, 1H, C<u>H</u>=CH_2), 7.21–8.06 (m, 9H, Ar–H); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 21.18 (CH_2), 26.52 (CH_2), 29.60 (quinolone C-4), 35.55 (quinolone C-3), 36.47 (<u>C</u>H$_2$–CO), 44.75 (allylic N–<u>C</u>H$_2$–CH), 55.90 (OCH_3), 115.36, 117.07, 117.32, 121.62, 126.64, 127.52, 128.23, 129.90, 132.02, 132.41, 133.26, 133.68, 137.12, 137.84, 154.24, and 157.62 (16C, Ar–C +allylic C=C), 160.48 (C=O), 169.52 (C=O), 195.46 (C=O); MS (ESI) *m/z* 454.6 $[M]^+$; anal. calcd. for $C_{28}H_{26}N_2O_4$ (454.52 g/mol): C, 73.99; H, 5.77; N, 6.16; found: C, 74.13; H, 5.56; N, 6.31.

1-Allyl-6-chloro-1′-phenyl-3′,4′,7′,8′-tetrahydro-3,4′-biquinoline-2,2′,5′(1H,1′H,6′H)-trione **(G4)** Yield: 80%; mp: 243–245 °C; IR (KBr, ν_{max}, cm^{-1}): 3070 (Ar C–H str.), 1705, 1643, and 1620 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.96–2.42 (m, 6H, 3 × CH_2 of cyclohexenone ring), 2.76 (dd, 1H, $J_1 = 15.6$ Hz, $J_2 = 16.0$ Hz, H-3), 3.11 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 8.0$ Hz, H-3), 4.40 (t, 1H, $J_1 = 7.2$, $J_2 = 7.6$ Hz, C<u>H</u>, H-4), 4.88 (d, 2H, $J = 6.4$ Hz, N–C<u>H</u>$_2$), 4.93 (d, 1H, $J = 16.8$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.14 (d, 1H, $J = 10.4$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.91 (m, 1H, C<u>H</u>=CH_2), 7.31–8.10 (m, 9H, Ar–H); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 21.84 (CH_2), 28.49 (CH_2), 30.02 (quinolone C-4), 36.16 (quinolone C-3), 36.42 (<u>C</u>H$_2$–CO), 44.81 (allylic N–<u>C</u>H$_2$–CH), 115.05, 117.07, 117.34, 121.68, 126.70, 128.15, 128.34, 128.95, 130.03, 132.23, 132.74, 133.57, 133.77, 137.24, 137.55, and 158.02 (16C, Ar–C+allylic C=C), 160.57 (C=O), 169.56 (C=O), 195.52 (C=O); MS (ESI) *m/z* 458.7 $[M]^+$, 460.5 $[M+2]^+$; anal. calcd. for $C_{27}H_{23}ClN_2O_3$ (458.94 g/mol): C, 70.66; H, 5.05; N, 6.10; Found: C, 70.63; H, 5.30; N, 6.34.

1-Allyl-7′,7′-dimethyl-1′-phenyl-3′,4′,7′,8′-tetrahydro-3,4′-biquinoline-2,2′,5′(1H,1′H,6′H)-trione **(G5)** Yield: 72%; mp: 228–230 °C; IR (KBr, ν_{max}, cm^{-1}): 3070 (Ar C–H str.), 1702, 1643, and 1628 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.96 (s, 3H, CH_3 of dimedone ring), 1.01 (s, 3H, CH_3 of dimedone ring), 1.73–2.69 (m, 4H, 2 × CH_2 of dimedone ring), 2.76 (dd, 1H, $J_1 = 15.2$ Hz, $J_2 = 15.6$ Hz, H-3), 3.08 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 8.4$ Hz, H-3), 4.45 (t, 1H, $J_1 = 7.2$, $J_2 = 7.6$ Hz, C<u>H</u>, H-4), 4.90 (d, 2H, $J = 5.2$ Hz, N–C<u>H</u>$_2$), 4.95 (d, 1H, $J = 17.2$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.15 (d, 1H, $J = 10.4$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.90 (m, 1H, C<u>H</u>=CH_2), 7.25–8.07 (m, 10H, Ar–H); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 24.62, 25.69 (2 × CH_3 of dimedone ring), 29.60 (quinolone C-4), 32.97 (CH_2), 35.67 (quinolone C-3), 38.82 (<u>C</u>(CH_3)$_2$), 44.57 (<u>C</u>H$_2$–CO), 49.61 (allylic N–<u>C</u>H$_2$–CH), 114.65, 115.85, 117.18, 119.82, 122.52, 126.71, 127.62, 128.82, 129.00, 130.66, 130.87, 132.55, 134.45, 138.19, 138.46, and 155.82 (16C, Ar–C+allylic C=C), 160.67 (C=O), 170.25 (C=O), 195.21 (C=O); MS (ESI) *m/z* 452.7 $[M]^+$; anal. calcd. for $C_{29}H_{28}N_2O_3$ (452.54 g/mol): C, 76.97; H, 6.24; N, 6.19; found: C, 76.89; H, 6.55; N, 5.83.

1-Allyl-6,7′,7′-trimethyl-1′-phenyl-3′,4′,7′,8′-tetrahydro-3,4′-biquinoline-2,2′,5′(1H,1′H,6′H)-trione **(G6)** Yield: 74%; mp: 235–237 °C; IR (KBr, ν_{max}, cm^{-1}): 3070 (Ar C–H str.), 1704, 1641, and 1620 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.98 (s, 3H, CH_3 of dimedone ring), 1.02 (s, 3H, CH_3 of dimedone ring), 1.71–2.69 (m, 7H, 2 × CH_2 of dimedone ring+CH_3), 2.80 (dd, 1H, $J_1 = 15.2$ Hz, $J_2 = 15.6$ Hz, H-3), 3.10 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 8.4$ Hz, H-3), 4.48 (t, 1H, $J_1 = 7.6$, $J_2 = 8.0$ Hz, C<u>H</u>, H-4), 4.92 (d, 2H, $J = 5.2$ Hz, N–C<u>H</u>$_2$), 4.99 (d, 1H, $J = 17.2$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.14 (d, 1H, $J = 10.4$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.92 (m, 1H, C<u>H</u>=CH_2), 7.23–8.07 (m, 9H, Ar–H); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 24.58, 25.67 (2 × CH_3 of dimedone ring), 29.51 (CH_3), 29.62 (quinolone C-4), 32.98 (CH_2), 35.65 (quinolone C-3), 38.78 (<u>C</u>(CH_3)$_2$), 44.56 (<u>C</u>H$_2$–CO), 49.64 (allylic N–<u>C</u>H$_2$–CH), 114.66, 115.82, 117.15, 119.81, 116.41, 126.80, 127.57, 128.83, 129.12, 130.57, 130.93, 132.54, 134.47, 138.20, 138.51, and 155.77 (16C, Ar–C+allylic C=C), 160.68 (C=O), 170.22 (C=O), 195.19 (C=O); MS (ESI) *m/z* 466.6 $[M]^+$; anal. calcd. for $C_{30}H_{30}N_2O_3$ (466.57 g/mol): C, 77.23; H, 6.48; N, 6.00; found: C, 77.40; H, 6.47; N, 6.04.

1-Allyl-6-methoxy-7′,7′-dimethyl-1′-phenyl-3′,4′,7′,8′-tetrahydro-3,4′-biquinoline-2,2′,5′(1H,1′H,6′H)-trione **(G7)** Yield: 67%; mp: 241–243 °C; IR (KBr, ν_{max}, cm^{-1}): 3020 (Ar C–H str.), 1702, 1642, and 1628 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.97 (s, 3H, CH_3 of dimedone ring), 1.02 (s, 3H, CH_3 of dimedone ring), 1.72–2.70 (m, 4H, 2 × CH_2 of dimedone ring), 2.80 (dd, 1H, $J_1 = 15.2$ Hz, $J_2 = 15.6$ Hz, H-3), 3.07 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 8.0$ Hz, H-3), 3.82 (s, 3H, OCH_3), 4.46 (t, 1H, $J_1 = 8.0$, $J_2 = 8.4$ Hz, C<u>H</u>, H-4), 4.93 (d, 2H, $J = 6.4$ Hz, N–C<u>H</u>$_2$), 4.97 (d, 1H, $J = 16.4$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.13 (d, 1H, $J = 10.0$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.91 (m, 1H, C<u>H</u>=CH_2), 7.22–8.08 (m, 9H, Ar–H); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 24.62, 26.30 (2 × CH_3 of dimedone ring), 29.64 (quinolone C-4), 33.01 (CH_2), 35.62 (quinolone C-3), 38.80 (<u>C</u>(CH_3)$_2$), 44.57 (<u>C</u>H$_2$–CO), 49.74 (allylic N–<u>C</u>H$_2$–CH), 55.86 (OCH_3), 115.71, 117.16, 119.78, 122.39, 126.85, 127.58, 128.87, 129.09, 130.51, 130.88, 132.58, 134.46, 138.20, 138.46, 154.89, and 156.18

(16C, Ar–C+allylic C=C), 160.68 (C=O), 169.98 (C=O), 195.20 (C=O); MS (ESI) *m/z* 482.7 $[M]^+$; anal. calcd. for $C_{30}H_{30}N_2O_4$ (482.57 g/mol): C, 74.67; H, 6.27; N, 5.81; found: C, 74.83; H, 6.02; N, 5.64.

1-Allyl-6-chloro-7′,7′-dimethyl-1′-phenyl-3′,4′,7′,8′-tetrahydro-3,4′-biquinoline-2,2′,5′(1H,1′H,6′H)-trione **(G8)** Yield: 81%; mp: 254–256 °C; IR (KBr, ν_{max}, cm^{-1}): 3070 (Ar C–H str.), 1705, 1643, and 1628 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.96 (s, 3H, CH_3 of dimedone ring), 1.01 (s, 3H, CH_3 of dimedone ring), 1.73–2.69 (m, 4H, $2 \times CH_2$ of dimedone ring), 2.78 (dd, 1H, $J_1 = 15.6$ Hz, $J_2 = 16.0$ Hz, H-3), 3.10 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 8.0$ Hz, H-3), 4.47 (t, 1H, $J_1 = 7.2$, $J_2 = 7.6$ Hz, C<u>H</u>, H-4), 4.89 (d, 2H, $J = 6.4$ Hz, N–C<u>H</u>$_2$), 4.96 (d, 1H, $J = 17.2$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.13 (d, 1H, $J = 10.8$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.87 (m, 1H, C<u>H</u>=CH_2), 7.31–8.11 (m, 9H, Ar–H); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 24.51, 25.53 ($2 \times CH_3$ of dimedone ring), 29.58 (quinolone C-4), 32.96 (CH_2), 35.61 (quinolone C-3), 38.77 (<u>C</u>(CH_3)$_2$), 44.58 (<u>C</u>H$_2$–CO), 49.63 (allylic N–<u>C</u>H$_2$–CH), 114.68, 115.87, 117.20, 119.77, 122.51, 126.74, 127.58, 128.81, 129.18, 130.52, 130.69, 132.54, 134.36, 138.22, 138.52, and 157.27 (16C, Ar–C+allylic C=C), 160.58 (C=O), 169.59 (C=O), 195.25 (C=O); MS (ESI) *m/z* 487.0 $[M]^+$, 488.9 $[M+2]^+$; anal. calcd. for $C_{29}H_{27}ClN_2O_3$ (486.99 g/mol): C, 71.52; H, 5.59; N, 5.75; found: C, 71.21; H, 5.38; N, 5.66.

1-Allyl-1′-benzyl-3′,4′,7′,8′-tetrahydro-3,4′-biquinoline-2,2′,5′(1H,1′H,6′H)-trione **(G9)** Yield: 62%; mp: 220–222 °C; IR (KBr, ν_{max}, cm^{-1}): 2955 (Ar C–H str.), 1690, 1643, and 1605 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.04–2.71 (m, 6H, $3 \times CH_2$ of cyclohexenone ring), 2.80 (dd, 1H, $J_1 = 15.2$ Hz, $J_2 = 15.6$ Hz, H_3), 3.01 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 8.4$ Hz, H-3), 4.34 (t, 1H, $J_1 = 7.6$, $J_2 = 8.0$ Hz, C<u>H</u>, H-4), 4.87 (d, 2H, $J = 16.4$ Hz, BnC<u>H</u>$_2$), 4.98 (d, 2H, $J = 6.4$ Hz, N–C<u>H</u>$_2$), 5.05 (d, 1H, $J = 16.4$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.15 (d, 1H, $J = 10.4$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.91 (m, 1H, C<u>H</u>=CH_2), 7.18–7.58 (m, 10H, Ar–H); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 21.80 (CH_2), 26.69 (CH_2), 29.59 (quinolone C-4), 35.70 (quinolone C-3), 36.16 (<u>C</u>H$_2$-CO), 44.64 (Bn<u>C</u>H$_2$), 44.95 (allylic N–<u>C</u>H$_2$–CH), 115.31, 115.57, 117.12, 119.93, 126.52, 126.84, 127.15, 127.61, 129.17, 130.55, 130.67, 133.01, 134.73, 138.12, 138.48, and 157.93 (16C, Ar–C+allylic C=C), 160.78 (C=O), 170.14 (C=O), 195.37 (C=O); MS (ESI) *m/z* 438.6 $[M]^+$; anal. calcd. for $C_{28}H_{26}N_2O_3$ (438.52 g/mol): C, 76.69; H, 5.98; N, 6.39; found: C, 76.90; H, 5.80; N, 6.29.

1-Allyl-1′-benzyl-6-methyl-3′,4′,7′,8′-tetrahydro-3,4′-biquinoline-2,2′,5′(1H,1′H,6′H)-trione **(G10)** Yield: 61%; mp: 229–231 °C; IR (KBr, ν_{max}, cm^{-1}): 2955 (Ar C–H str.), 1690, 1643, and 1612 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.01–2.73 (m, 9H, $3 \times CH_2$ of cyclohexenone ring+CH_3), 2.81 (dd, 1H, $J_1 = 15.2$ Hz, $J_2 = 15.6$ Hz, H-3), 3.05 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 8.4$ Hz, H-3), 4.37 (t, 1H, $J_1 = 7.6$, $J_2 = 8.0$ Hz, C<u>H</u>, H-4), 4.87 (d, 2H, $J = 16.4$ Hz, BnC<u>H</u>$_2$), 4.98 (d, 2H, $J = 6.4$ Hz, N–C<u>H</u>$_2$–CH), 5.04 (d, 1H, $J = 16.4$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.14 (d, 1H, $J = 10.4$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.90 (m, 1H, C<u>H</u>=CH_2), 7.17–7.58 (m, 9H, Ar–H); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 20.53 (CH_3), 21.82 (CH_2), 26.67 (CH_2), 29.61 (quinolone C-4), 35.71 (quinolone C-3), 36.15 (<u>C</u>H$_2$–CO), 44.62 (Bn<u>C</u>H$_2$), 44.94 (allylic N–<u>C</u>H$_2$–CH), 115.29, 115.54, 117.07, 119.94, 126.50, 126.82, 127.17, 127.62, 129.20, 130.54, 130.65, 132.98, 134.70, 138.15, 138.52, and 157.94 (16C, Ar–C+allylic C=C), 160.79 (C=O), 170.15 (C=O), 195.35 (C=O); MS (ESI) *m/z* 452.7 $[M]^+$; anal. calcd. for $C_{29}H_{28}N_2O_3$ (452.54 g/mol): C, 76.97; H, 6.24; N, 6.19; found: C, 76.79; H, 6.29; N, 6.11.

1-Allyl-1′-benzyl-6-methoxy-3′,4′,7′,8′-tetrahydro-3,4′-biquinoline-2,2′,5′(1H,1′H,6′H)-trione **(G11)** Yield: 63%; mp: 235–237 °C; IR (KBr, ν_{max}, cm^{-1}): 2955 (Ar C–H str.), 1697, 1643, and 1605 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.06–2.72 (m, 6H, $3 \times CH_2$ of cyclohexenone ring), 2.80 (dd, 1H, $J_1 = 15.6$ Hz, $J_2 = 16.0$ Hz, H-3), 3.00 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 8.0$ Hz, H-3), 3.82 (s, 3H, OCH_3), 4.33 (t, 1H, $J_1 = 7.2$, $J_2 = 7.6$ Hz, C<u>H</u>, H-4), 4.88 (d, 2H, $J = 16.4$ Hz, BnC<u>H</u>$_2$), 4.95 (d, 2H, $J = 7.2$ Hz, N–C<u>H</u>$_2$–CH), 5.04 (d, 1H, $J = 16.8$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.14 (d, 1H, $J = 10.8$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.89 (m, 1H, C<u>H</u>=CH_2), 7.07–7.39 (m, 9H, Ar–H); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 21.81 (CH_2), 26.75 (CH_2), 29.81 (quinolone C-4), 35.76 (quinolone C-3), 36.22 (<u>C</u>H$_2$–CO), 44.74 (Bn<u>C</u>H$_2$), 44.97 (allylic N–<u>C</u>H$_2$–CH), 56.16 (OCH_3), 110.11, 110.93, 115.67, 116.69, 117.08, 120.74, 126.87, 127.23, 127.72, 129.25, 131.05, 132.96, 133.18, 138.14, 154.58, and 157.89 (16C, Ar–C+allylic C=C), 160.31 (C=O), 170.17 (C=O), 195.36 (C=O); MS (ESI) *m/z* 468.3 $(M^{+\cdot})$; anal. calcd. for $C_{29}H_{28}N_2O_4$ (468.54 g/mol): C, 74.34; H, 6.02; N, 5.98; found: C, 74.35; H, 6.06; N, 6.14.

1-Allyl-1′-benzyl-6-chloro-3′,4′,7′,8′-tetrahydro-3,4′-biquinoline-2,2′,5′(1H,1′H,6′H)-trione **(G12)** Yield: 70%; mp: 241–243 °C; IR (KBr, ν_{max}, cm^{-1}): 2955 (Ar C–H str.), 1690, 1643, and 1605 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.05–2.70 (m, 6H, $3 \times CH_2$ of cyclohexenone ring), 2.81 (dd, 1H, $J_1 = 15.6$ Hz, $J_2 = 16.0$ Hz, H-3), 3.09 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 8.0$ Hz, H-3), 4.36 (t, 1H, $J_1 = 7.2$, $J_2 = 7.6$ Hz, C<u>H</u>, H-4), 4.90 (d, 2H, $J = 16.0$ Hz, BnC<u>H</u>$_2$), 4.99 (d, 2H, $J = 6.4$ Hz, N–C<u>H</u>$_2$–CH),

5.07 (d, 1H, $J = 16.4$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.18 (d, 1H, $J = 10.4$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.93 (m, 1H, C<u>H</u>=CH_2), 7.20–7.61 (m, 9H, Ar–H); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 21.85 (CH_2), 26.72 (CH_2), 29.64 (quinolone C-4), 35.72 (quinolone C-3), 36.15 (<u>C</u>H_2–CO), 44.61 (Bn<u>C</u>H_2), 44.96 (allylic N–<u>C</u>H_2–CH), 115.30, 115.60, 117.16, 119.90, 126.50, 126.86, 127.19, 127.68, 129.22, 130.58, 130.70, 133.12, 134.70, 138.21, 138.56, and 157.96 (16C, Ar–C+allylic C=C), 160.75 (C=O), 170.18 (C=O), 195.35 (C=O); MS (ESI) *m/z* 473.0 $[M]^+$, 474.9 $[M+2]^+$; anal. calcd. for $C_{28}H_{25}ClN_2O_3$ (472.96 g/mol): C, 71.10; H, 5.33; N, 5.92; found: C, 71.02; H, 5.17; N, 5.73.

1-Allyl-1′-benzyl-7′,7′-dimethyl-3′,4′,7′,8′-tetrahydro-3,4′-biquinoline-2,2′,5′(1H,1′H,6′H)-trione **(G13)** Yield: 65%; mp: 228–230 °C; IR (KBr, ν_{max}, cm^{-1}): 2955 (Ar C–H str.), 1697, 1643, and 1612 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.99 (s, 3H, CH_3 of dimedone ring), 1.05 (s, 3H, CH_3 of dimedone ring), 2.16–2.80 (m, 4H, 2 × CH_2 of dimedone ring), 2.83 (dd, 1H, $J_1 = 15.2$ Hz, $J_2 = 15.6$ Hz, H-3), 3.06 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 8.4$ Hz, H-3), 4.37 (t, 1H, $J_1 = 8.0$, $J_2 = 8.4$ Hz, C<u>H</u>, H-4), 4.84 (d, 2H, $J = 16.0$ Hz, Bn<u>C</u>H_2), 4.91 (d, 2H, $J = 4.4$ Hz, N–<u>C</u>H_2–CH), 4.98 (d, 1H, $J = 19.2$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.14 (d, 1H, $J = 11.9$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.90 (m, 1H, C<u>H</u>=CH_2), 7.19–7.57 (m, 10H, Ar–H); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 27.60, 29.25 (2 × CH_3 of dimedone ring), 29.58 (quinolone C-4), 33.06 (CH_2), 35.76 (quinolone C-3), 39.88 (<u>C</u>$(CH_3)_2$), 44.65 (<u>C</u>H_2–CO), 44.81 (Bn<u>C</u>H_2), 49.64 (allylic N–<u>C</u>H_2–CH), 114.54, 115.35, 117.14, 119.84, 122.48, 127.07, 127.65, 128.99, 129.08, 130.70, 130.87, 132.99, 134.68, 138.21, 138.49, and 155.78 (16C, Ar–C+allylic C=C), 160.76 (C=O), 170.29 (C=O), 195.19 (C=O); MS (ESI) *m/z* 467.0 $[M]^+$; anal. calcd. for $C_{30}H_{30}N_2O_3$ (466.57 g/mol): C, 77.23; H, 6.48; N, 6.00; found: C, 77.42; H, 6.77; N, 5.91.

1-Allyl-1′-benzyl-6,7′,7′-trimethyl-3′,4′,7′,8′-tetrahydro-3,4′-biquinoline-2,2′,5′(1H,1′H,6′H)-trione **(G14)** Yield: 64%; mp: 236–238 °C; IR (KBr, ν_{max}, cm^{-1}): 2955 (Ar C–H str.), 1697, 1643, and 1605 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.98 (s, 3H, CH_3 of dimedone ring), 1.01 (s, 3H, CH_3 of dimedone ring), 2.14–2.81 (m, 7H, 2 × CH_2 of dimedone ring+CH_3), 2.85 (dd, 1H, $J_1 = 15.2$ Hz, $J_2 = 15.6$ Hz, H-3), 3.10 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 8.0$ Hz, H-3), 4.38 (t, 1H, $J_1 = 7.2$, $J_2 = 7.6$ Hz, C<u>H</u>, H-4), 4.86 (d, 2H, $J = 16.4$ Hz, Bn<u>C</u>H_2), 4.92 (d, 2H, $J = 5.2$ Hz, N–<u>C</u>H_2–CH), 4.97 (d, 1H, $J = 17.2$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.13 (d, 1H, $J = 10.8$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.90 (m, 1H, C<u>H</u>=CH_2), 7.18–7.55 (m, 9H, Ar–H); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 27.58, 28.22 (2 × CH_3 of dimedone ring), 28.97 (CH_3), 29.60 (quinolone C-4), 33.05 (CH_2), 35.74 (quinolone C-3), 39.83 (<u>C</u>$(CH_3)_2$), 44.64 (<u>C</u>H_2–CO), 44.83 (Bn<u>C</u>H_2), 49.65 (allylic N–<u>C</u>H_2–CH), 114.56, 115.32, 117.16, 119.87, 122.50, 127.11, 127.66, 128.92, 129.05, 130.71, 130.84, 132.94, 134.66, 138.22, 138.45, and 155.76 (16C, Ar–C +allylic C=C), 160.74 (C=O), 170.27 (C=O), 195.18 (C=O); MS (ESI) *m/z* 480.8 $[M]^+$; anal. calcd. for $C_{31}H_{32}N_2O_3$ (480.60 g/mol): C, 77.47; H, 6.71; N, 5.83; found: C, 77.22; H, 6.41; N, 5.61.

1-Allyl-1′-benzyl-6-methoxy-7′,7′-dimethyl-3′,4′,7′,8′-tetrahydro-3,4′-biquinoline-2,2′,5′(1H,1′H,6′H)-trione **(G15)** Yield: 69%; mp: 244–246 °C; IR (KBr, ν_{max}, cm^{-1}): 2955 (Ar C–H str.), 1690, 1643, and 1612 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.99 (s, 3H, CH_3 of dimedone ring), 1.03 (s, 3H, CH_3 of dimedone ring), 2.15–2.78 (m, 4H, 2 × CH_2 of dimedone ring), 2.82 (dd, 1H, $J_1 = 15.2$ Hz, $J_2 = 15.6$ Hz, H-3), 3.07 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 8.4$ Hz, H-3), 3.81 (s, 3H, OCH_3), 4.35 (t, 1H, $J_1 = 7.2$, $J_2 = 7.6$ Hz, C<u>H</u>, H-4), 4.82 (d, 2H, $J = 16.4$ Hz, Bn<u>C</u>H_2), 4.89 (d, 2H, $J = 6.4$ Hz, N–<u>C</u>H_2–CH), 4.95 (d, 1H, $J = 17.2$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.10 (d, 1H, $J = 10.4$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.89 (m, 1H, C<u>H</u>=CH_2), 7.16–7.54 (m, 9H, Ar–H); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 27.42, 29.18 (2 × CH_3 of dimedone ring), 29.54 (quinolone C-4), 33.04 (CH_2), 35.75 (quinolone C-3), 39.82 (<u>C</u>$(CH_3)_2$), 44.65 (<u>C</u>H_2–CO), 44.84 (Bn<u>C</u>H_2), 49.62 (allylic N–<u>C</u>H_2–CH), 55.92 (OCH_3), 114.55, 115.36, 117.11, 119.85, 122.47, 127.10, 127.61, 128.87, 129.07, 130.75, 132.91, 134.65, 138.25, 138.48, 154.36, and 156.23 (16C, Ar–C+allylic C=C), 160.76 (C=O), 170.24 (C=O), 195.19 (C=O); MS (ESI) *m/z* 496.8 $[M]^+$; anal. calcd. for $C_{31}H_{32}N_2O_4$ (496.60 g/mol): C, 74.98; H, 6.50; N, 5.64; found: C, 75.10; H, 6.78; N, 5.79.

1-Allyl-1′-benzyl-6-chloro-7′,7′-dimethyl-3′,4′,7′,8′-tetrahydro-3,4′-biquinoline-2,2′,5′(1H,1′H,6′H)-trione **(G16)** Yield: 73%; mp: 254–256 °C; IR (KBr, ν_{max}, cm^{-1}): 2955 (Ar C–H str.), 1697, 1643, and 1612 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.01 (s, 3H, CH_3 of dimedone ring), 1.04 (s, 3H, CH_3 of dimedone ring), 2.13–2.79 (m, 4H, 2 × CH_2 of dimedone ring), 2.84 (dd, 1H, $J_1 = 17.2$ Hz, $J_2 = 17.6$ Hz, H-3), 3.06 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 8.4$ Hz, H-3), 4.33 (t, 1H, $J_1 = 7.2$, $J_2 = 7.6$ Hz, C<u>H</u>, H-4), 4.85 (d, 2H, $J = 10.8$ Hz, Bn<u>C</u>H_2), 4.92 (d, 2H, $J = 7.6$ Hz, N–<u>C</u>H_2–CH), 5.00 (d, 1H, $J = 16.4$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.14 (d, 1H, $J = 10.4$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.90 (m, 1H, C<u>H</u>=CH_2), 7.20–7.59 (m, 9H, Ar–H); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 21.16, 22.06 (2 × CH_3 of dimedone ring), 29.64 (quinolone C-4), 33.14 (CH_2), 35.55 (quinolone C-3), 38.78 (<u>C</u>$(CH_3)_2$), 44.32 (<u>C</u>H_2–CO), 44.81 (Bn<u>C</u>H_2), 49.58 (allylic N–<u>C</u>H_2–CH), 111.39, 114.57, 116.95, 117.45, 121.16, 126.47,

127.04, 127.34, 128.01, 128.89, 130.23, 132.13, 132.75, 137.23, 138.20, and 155.88 (16C, Ar–C+allylic C=C), 160.76 (C=O), 170.29 (C=O), 195.19 (C=O); MS (ESI) *m/z* 501.1 $[M]^+$, 503.0 $[M+2]^+$; anal. calcd. for $C_{30}H_{29}ClN_2O_3$ (501.02 g/mol): C, 71.92; H, 5.83; N, 5.59; found: C, 72.08; H, 5.86; N, 5.85.

1-Allyl-1′-(phenylamino)-3′,4′,7′,8′-tetrahydro-3,4′-biquinoline-2,2′,5′(1H,1′H,6′H)-trione **(G17)** Yield: 76%; mp: 235–237 °C; IR (KBr, ν_{max}, cm^{-1}): 3248 (NH str.), 2924 (Ar C–H str.), 1697, 1642, and 1605 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.18–2.71 (m, 6H, 3 × CH_2 of cyclohexenone ring), 2.80 (dd, 1H, $J_1 = 15.2$ Hz, $J_2 = 15.6$ Hz, H-3), 3.12 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 8.0$ Hz, H-3), 4.36 (t, 1H, $J_1 = 7.2$, $J_2 = 7.6$ Hz, C<u>H</u>, H-4), 4.87 (d, 2H, $J = 5.6$ Hz, N–C<u>H</u>$_2$–CH), 4.94 (d, 1H, $J = 17.6$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.10 (d, 1H, $J = 10.4$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.90 (m, 1H, C<u>H</u>=CH_2), 6.71–7.72 (m, 10H, Ar–H), 8.37 (s, 1H, NH); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 21.62 (CH_2), 25.37 (CH_2), 29.75 (quinolone C-4), 35.30 (quinolone C-3), 36.26 (<u>C</u>H$_2$–CO), 44.55 (allylic N–<u>C</u>H$_2$–CH), 112.40, 113.32, 113.71, 114.38, 115.25, 117.05, 120.15, 120.38, 130.12, 130.51, 131.46, 131.72, 133.06, 134.66, 136.51, and 148.12 (16C, Ar–C+allylic C=C), 160.36 (C=O), 168.55 (C=O), 195.45 (C=O); MS (ESI) *m/z* 439.6 $[M]^+$; anal. calcd. for $C_{27}H_{25}N_3O_3$ (439.51 g/mol): C, 73.78; H, 5.73; N, 9.56; found: C, 73.80; H, 5.71; N, 9.59.

1-Allyl-6-methyl-1′-(phenylamino)-3′,4′,7′,8′-tetrahydro-3,4′-biquinoline-2,2′,5′(1H,1′H,6′H)-trione **(G18)** Yield: 75%; mp: 240–242 °C; IR (KBr, ν_{max}, cm^{-1}): 3256 (NH str.), 3040 (Ar C–H str.), 1697, 1643, and 1605 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.17–2.75 (m, 9H, 3 × CH_2 of cyclohexenone ring+CH_3), 2.81 (dd, 1H, $J_1 = 13.2$ Hz, $J_2 = 13.6$ Hz, H-3), 3.16 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 8.0$ Hz, H-3), 4.38 (t, 1H, $J_1 = 7.2$, $J_2 = 7.6$ Hz, C<u>H</u>, H-4), 4.89 (d, 2H, $J = 5.6$ Hz, N–C<u>H</u>$_2$–CH), 4.95 (d, 1H, $J = 17.6$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.12 (d, 1H, $J = 10.4$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.91 (m, 1H, C<u>H</u>=CH_2), 6.70–7.70 (m, 9H, Ar–H), 8.35 (s, 1H, NH); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 20.49 (CH_3), 21.67 (CH_2), 25.40 (CH_2), 29.74 (quinolone C-4), 35.31 (quinolone C-3), 36.29 (<u>C</u>H$_2$–CO), 44.54 (allylic N–<u>C</u>H$_2$–CH), 112.38, 113.35, 113.73, 114.37, 115.24, 117.04, 120.14, 120.40, 130.14, 130.52, 131.44, 131.70, 133.07, 134.68, 136.52, and 148.11 (16C, Ar–C+allylic C=C), 160.38 (C=O), 168.56 (C=O), 195.45 (C=O); MS (ESI) *m/z* 453.6 $[M]^+$; anal. calcd. for $C_{28}H_{27}N_3O_3$ (453.53 g/mol): C, 74.15; H, 6.00; N, 9.27; found: C, 74.09; H, 5.89; N, 9.35.

1-Allyl-6-methoxy-1′-(phenylamino)-3′,4′,7′,8′-tetrahydro-3,4′-biquinoline-2,2′,5′(1H,1′H,6′H)-trione **(G19)** Yield: 79%; mp: 246–248 °C; IR (KBr, ν_{max}, cm^{-1}): 3248 (NH str.), 2924 (Ar C–H str.), 1697, 1643 and 1612 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.18–2.70 (m, 6H, 3 × CH_2 of cyclohexenone ring), 2.79 (dd, 1H, $J_1 = 14.8$ Hz, $J_2 = 15.2$ Hz, H-3), 3.09 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 8.4$ Hz, H-3), 3.79 (s, 3H, OCH_3), 4.37 (t, 1H, $J_1 = 8.0$, $J_2 = 8.4$ Hz, C<u>H</u>, H-4), 4.88 (d, 2H, $J = 6.4$ Hz, N–C<u>H</u>$_2$–CH), 4.93 (d, 1H, $J = 17.2$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.10 (d, 1H, $J = 10.4$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.88 (m, 1H, C<u>H</u>=CH_2), 6.69–7.70 (m, 9H, Ar–H), 8.34 (s, 1H, NH); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 21.64 (CH_2), 25.37 (CH_2), 29.68 (quinolone C-4), 35.29 (quinolone C-3), 36.28 (<u>C</u>H$_2$–CO), 44.52 (allylic N–<u>C</u>H$_2$–CH), 55.81 (OCH_3), 112.36, 113.34, 113.71, 114.38, 115.25, 117.06, 120.18, 120.46, 130.18, 130.53, 131.72, 133.05, 134.65, 136.51, 148.13, and 151.62 (16C, Ar–C+allylic C=C), 160.35 (C=O), 168.54 (C=O), 195.42 (C=O); MS (ESI) *m/z* 469.5 $[M]^+$; anal. calcd. for $C_{28}H_{27}N_3O_4$ (469.53 g/mol): C, 71.62; H, 5.80; N, 8.95; found: C, 71.94; H, 5.95; N, 9.12.

1-Allyl-6-chloro-1′-(phenylamino)-3′,4′,7′,8′-tetrahydro-3,4′-biquinoline-2,2′,5′(1H,1′H,6′H)-trione **(G20)** Yield: 84%; mp: 259–261; IR (KBr, ν_{max}, cm^{-1}): 3256 (NH str.), 3040 (Ar C–H str.), 1697, 1642 and 1605 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.19–2.70 (m, 6H, 3 × CH_2 of cyclohexenone ring), 2.80 (dd, 1H, $J_1 = 15.2$ Hz, $J_2 = 15.6$ Hz, H-3), 3.11 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 8.0$ Hz, H-3), 4.36 (t, 1H, $J_1 = 7.2$, $J_2 = 7.6$ Hz, C<u>H</u>, H-4), 4.86 (d, 2H, $J = 5.6$ Hz, N–C<u>H</u>$_2$–CH), 4.96 (d, 1H, $J = 17.6$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.12 (d, 1H, $J = 10.4$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.91 (m, 1H, C<u>H</u>=CH_2), 6.72–7.72 (m, 9H, Ar–H), 8.37 (s, 1H, NH); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 21.64 (CH_2), 25.38 (CH_2), 29.77 (quinolone C-4), 35.32 (quinolone C-3), 36.26 (<u>C</u>H$_2$–CO), 44.57 (allylic N–<u>C</u>H$_2$–CH), 112.43, 113.33, 113.75, 114.40, 115.24, 117.07, 120.14, 120.37, 130.16, 130.55, 131.50, 131.78, 133.10, 134.64, 136.50, and 148.18 (16C, Ar–C+allylic C=C), 160.39 (C=O), 168.56 (C=O), 195.47 (C=O); MS(ESI) *m/z* 474.0 $[M]^+$, 476.1 $[M+2]^+$; anal. calcd. for $C_{27}H_{24}ClN_3O_3$ (473.95 g/mol): C, 68.42; H, 5.10; N, 8.87; found: C, 68.33; H, 4.86; N, 9.03.

1-Allyl-7′,7′-dimethyl-1′-(phenylamino)-3′,4′,7′,8′-tetrahydro-3,4′-biquinoline-2,2′,5′(1H,1′H,6′H)-trione **(G21)** Yield: 79%; mp: 234–236 °C; IR (KBr, ν_{max}, cm^{-1}): 3256 (NH str.), 3040 (Ar C–H str.), 1697, 1643 and 1612 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.96 (s, 3H, CH_3 of dimedone ring), 1.02 (s, 3H, CH_3 of dimedone ring), 1.94–2.81 (m, 4H, 2 × CH_2 of dimedone ring), 3.04 (dd, 1H, $J_1 = 16.0$ Hz, $J_2 = 16.4$ Hz, H-3), 3.47 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 8.0$ Hz, H-3), 4.72 (t, 1H, $J_1 = 7.2$, $J_2 = 7.6$ Hz, C<u>H</u>, H-4), 4.86 (d, 2H, $J = 6.4$ Hz, N–C<u>H</u>$_2$–CH),

5.18 (d, 1H, $J = 17.2$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.40 (d, 1H, $J = 10.4$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 6.02 (m, 1H, C<u>H</u>=CH_2), 7.17–7.89 (m, 10H, Ar–H), 8.81 (s, 1H, NH); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 27.87, 28.61 ($2 \times CH_3$ of dimedone ring), 31.64 (quinolone C-4), 33.47 (CH_2), 35.81 (quinolone C-3), 39.89 (<u>C</u>(CH_3)$_2$), 45.21 (<u>C</u>H_2–CO), 49.92 (allylic N–<u>C</u>H_2–CH), 112.02, 113.32, 117.09, 123.71, 125.45, 126.21, 127.94, 128.50, 129.87, 132.96, 134.40, 136.05, 139.42, 144.78, 155.94, and 158.54 (16C, Ar–C+allylic C=C), 159.89 (C=O), 169.94 (C=O), 194.95 (C=O); MS (ESI) *m/z* 467.4 $[M]^+$; anal. calcd. for $C_{29}H_{29}N_3O_3$ (467.56 g/mol): C, 74.50; H, 6.25; N, 8.99; found: C, 74.40; H, 5.89; N, 9.30.

1-Allyl-6,7′,7′-trimethyl-1′-(phenylamino)-3′,4′,7′,8′-tetrahydro-3,4′-biquinoline-2,2′,5′(1H,1′H,6′H)-trione **(G22)** Yield: 77%; mp: 245–247 °C; IR (KBr, ν_{max}, cm^{-1}): 3248 (NH str.), 2924 (Ar C–H str.), 1697, 1642, and 1605 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.98 (s, 3H, CH_3 of dimedone ring), 1.03 (s, 3H, CH_3 of dimedone ring), 1.93–2.85 (m, 7H, $2 \times CH_2$ of dimedone ring+CH_3), 3.03 (dd, 1H, $J_1 = 14.8$ Hz, $J_2 = 15.2$ Hz, H-3), 3.45 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 8.0$ Hz, H-3), 4.73 (t, 1H, $J_1 = 7.2$, $J_2 = 7.6$ Hz, C<u>H</u>, H-4), 4.85 (d, 2H, $J = 6.4$ Hz, N–C<u>H</u>$_2$–CH), 5.17 (d, 1H, $J = 16.4$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.41 (d, 1H, $J = 10.4$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.99 (m, 1H, C<u>H</u>=CH_2), 7.16–7.89 (m, 9H, Ar–H), 8.82 (s, 1H, NH); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 27.81, 28.57 ($2 \times CH_3$ of dimedone ring), 29.14 (CH_3), 31.62 (quinolone C-4), 33.45 (CH_2), 35.78 (quinolone C-3), 39.84 (<u>C</u>(CH_3)$_2$), 45.26 (<u>C</u>H_2–CO), 49.91 (allylic N–<u>C</u>H_2–CH), 112.07, 113.36, 117.15, 123.74, 125.49, 126.26, 127.92, 128.51, 129.85, 132.94, 134.41, 136.08, 139.43, 144.75, 155.91, and 158.52 (16C, Ar–C+allylic C=C), 159.94 (C=O), 169.98 (C=O), 194.97 (C=O); MS (ESI) *m/z* 481.7 $[M]^+$; anal. calcd. for $C_{30}H_{31}N_3O_3$ (481.59 g/mol): C, 74.82; H, 6.49; N, 8.73; found: C, 74.93; H, 6.53; N, 8.52.

1-Allyl-6-methoxy-7′,7′-dimethyl-1′-(phenylamino)-3′,4′,7′,8′-tetrahydro-3,4′-biquinoline-2,2′,5′(1H,1′H,6′H)-trione **(G23)** Yield: 72%; mp: 252–254 °C; IR (KBr, ν_{max}, cm^{-1}): 3248 (NH str.), 2924 (Ar C–H str.), 1697, 1642, and 1612 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.94 (s, 3H, CH_3 of dimedone ring), 1.01 (s, 3H, CH_3 of dimedone ring), 1.96–2.84 (m, 4H, $2 \times CH_2$ of dimedone ring), 3.05 (dd, 1H, $J_1 = 15.6$ Hz, $J_2 = 16.0$ Hz, H-3), 3.48 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 8.4$ Hz, H-3), 3.83 (s, 3H, OCH_3), 4.74 (t, 1H, $J_1 = 7.2$, $J_2 = 7.6$ Hz, C<u>H</u>, H-4), 4.88 (d, 2H, $J = 5.6$ Hz, N–C<u>H</u>$_2$–CH), 5.21 (d, 1H, $J = 17.2$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.44 (d, 1H, $J = 10.8$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 6.09 (m, 1H, C<u>H</u>=CH_2), 7.18–7.90 (m, 9H, Ar–H), 8.83 (s, 1H, NH); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 28.21, 30.83 ($2 \times CH_3$ of dimedone ring), 31.81 (quinolone C-4), 33.52 (CH_2), 35.86 (quinolone C-3), 39.95 (<u>C</u>(CH_3)$_2$), 45.24 (<u>C</u>H_2–CO), 49.96 (allylic N–<u>C</u>H_2–CH), 57.18 (OCH_3), 111.93, 113.46, 117.13, 123.69, 125.49, 126.24, 127.90, 128.55, 129.91, 133.00, 134.46, 136.03, 139.46, 144.80, 156.01, and 158.60 (16C, Ar–C+allylic C=C), 159.85 (C=O), 169.88 (C=O), 194.87 (C=O); MS (ESI) *m/z* 497.4 $[M]^+$; anal. calcd. for $C_{30}H_{31}N_3O_4$ (497.58 g/mol): C, 72.41; H, 6.28; N, 8.44; found: C, 72.35; H, 6.45; N, 8.26.

1-Allyl-6-chloro-7′,7′-dimethyl-1′-(phenylamino)-3′,4′,7′,8′-tetrahydro-3,4′-biquinoline-2,2′,5′(1H,1′H,6′H)-trione **(G24)** Yield: 86%; mp: 258–260 °C; IR (KBr, ν_{max}, cm^{-1}): 3256 (NH str.), 3040 (Ar C–H str.), 1697, 1643, and 1605 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 0.97 (s, 3H, CH_3 of dimedone ring), 1.02 (s, 3H, CH_3 of dimedone ring), 1.95–2.82 (m, 4H, $2 \times CH_2$ of dimedone ring), 3.05 (dd, 1H, $J_1 = 14.8$ Hz, $J_2 = 15.2$ Hz, H-3), 3.45 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 8.4$ Hz, H-3), 4.75 (t, 1H, $J_1 = 7.6$, $J_2 = 8.0$ Hz, C<u>H</u>, H-4), 4.89 (d, 2H, $J = 5.2$ Hz, N–C<u>H</u>$_2$–CH), 5.20 (d, 1H, $J = 17.2$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.46 (d, 1H, $J = 10.8$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 6.08 (m, 1H, C<u>H</u>=CH_2), 7.20–7.91 (m, 9H, Ar–H), 8.86 (s, 1H, NH); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 27.81, 28.57 ($2 \times CH_3$ of dimedone ring), 31.65 (quinolone C-4), 33.45 (CH_2), 35.72 (quinolone C-3), 39.82 (<u>C</u>(CH_3)$_2$), 45.26 (<u>C</u>H_2–CO), 49.95 (allylic N–<u>C</u>H_2–CH), 112.14, 113.44, 117.23, 123.65, 125.48, 126.26, 127.95, 128.54, 129.81, 132.95, 134.48, 136.11, 139.40, 144.82, 155.96, and 158.58 (16C, Ar–C+allylic C=C), 160.01 (C=O), 170.04 (C=O), 195.03 (C=O); MS (ESI) *m/z* 502.1 $[M]^+$, 503.9 $[M+2]^+$; anal. calcd. for $C_{29}H_{28}ClN_3O_3$ (502.00 g/mol): C, 69.38; H, 5.62; N, 8.37; found: C, 69.59; H, 5.71; N, 8.38.

N-(1-allyl-2,2′,5′-trioxo-1,2,3′,4′,5′,6′,7′,8′-octahydro-3,4′-biquinolin-1′(2′H)-yl)benzamide **(G25)** Yield: 81%; mp: 242–244 °C; IR (KBr, ν_{max}, cm^{-1}): 3271 (NH str.), 2962 (Ar C–H str.), 1720, 1636, and 1589 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.08–2.70 (m, 6H, $3 \times CH_2$ of cyclohexenone ring), 2.84 (dd, 1H, $J_1 = 16.0$ Hz, $J_2 = 16.4$ Hz, H-3), 3.16 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 8.0$ Hz, H-3), 4.43 (t, 1H, $J_1 = 7.2$, $J_2 = 7.6$ Hz, C<u>H</u>, H-4), 4.92 (d, 2H, $J = 6.4$ Hz, N–C<u>H</u>$_2$–CH), 5.02 (d, 1H, $J = 17.2$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.15 (d, 1H, $J = 9.6$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.93 (m, 1H, C<u>H</u>=CH_2), 7.25–8.08 (m, 10H, Ar–H), 11.07 (s, 1H, NH); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 21.64 (CH_2), 25.14 (CH_2), 29.58 (quinolone C-4), 35.71 (quinolone C-3), 36.33 (<u>C</u>H_2–CO), 44.64 (allylic N–<u>C</u>H_2–CH), 114.34, 115.35, 115.86, 120.10, 120.39, 128.17, 129.17, 130.26, 130.57, 130.75, 131.79, 131.89, 133.02, 136.00, 138.51, and 158.10 (16C, Ar–C+allylic C=C), 160.79 (C=O), 167.00 (C=O),

167.50 (C=O), 195.31 (C=O); MS (ESI) *m/z* 467.4 $[M]^+$; anal. calcd. for $C_{28}H_{25}N_3O_4$ (467.52 g/mol): C, 71.93; H, 5.39; N, 8.99; found: C, 72.20; H, 5.49; N, 8.91.

N-(1-allyl-6-methyl-2,2′,5′-trioxo-1,2,3′,4′,5′,6′,7′,8′-octahydro-3,4′-biquinolin-1′(2′H)-yl)benzamide **(G26)** Yield: 80%; mp: 247–249 °C; IR (KBr, ν_{max}, cm^{-1}): 3256 (NH str.), 2955 (Ar C–H str.), 1720, 1620 and 1582 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.07–2.73 (m, 9H, 3 × CH_2 of cyclohexenone ring+CH_3), 2.82 (dd, 1H, J_1 = 16.0 Hz, J_2 = 16.4 Hz, H-3), 3.15 (dd, 1H, J_1 = 8.0 Hz, J_2 = 8.0 Hz, H-3), 4.41 (t, 1H, J_1 = 7.2, J_2 = 7.6 Hz, C<u>H</u>, H-4), 4.93 (d, 2H, J = 6.4 Hz, N–C<u>H</u>$_2$–CH), 5.05 (d, 1H, J = 16.4 Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.12 (d, 1H, J = 9.6 Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.91 (m, 1H, C<u>H</u>=CH_2), 7.23–8.07 (m, 9H, Ar–H), 11.05 (s, 1H, NH); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 21.65 (CH_2), 25.18 (CH_2), 27.14 (CH_3), 29.57 (quinolone C-4), 35.72 (quinolone C-3), 36.35 (<u>C</u>H$_2$–CO), 44.62 (allylic N–<u>C</u>H$_2$–CH), 114.32, 115.37, 115.85, 120.11, 120.42, 128.18, 129.20, 130.28, 130.54, 130.74, 131.81, 131.92, 133.06, 136.07, 138.54, and 158.15 (16C, Ar–C+allylic C=C), 160.74 (C=O), 167.03 (C=O), 167.48 (C=O), 195.34 (C=O); MS (ESI) *m/z* 481.5 ($M^{+\cdot}$); anal. calcd. for $C_{29}H_{27}N_3O_4$ (481.54 g/mol): C, 72.33; H, 5.65; N, 8.73; found: C, 72.17; H, 5.57; N, 8.92.

N-(1-allyl-6-methoxy-2,2′,5′-trioxo-1,2,3′,4′,5′,6′,7′,8′-octahydro-3,4′-biquinolin-1′(2′H)-yl)benzamide **(G27)** Yield: 78%; mp: 257–259 °C; IR (KBr, ν_{max}, cm^{-1}): 3217 (NH str.), 2955 (Ar C–H str.), 1720, 1628, and 1597 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.06–2.71 (m, 6H, 3 × $CH_2$of cyclohexenone ring), 2.80 (dd, 1H, J_1 = 16.0 Hz, J_2 = 16.4 Hz, H-3), 3.12 (dd, 1H, J_1 = 8.0 Hz, J_2 = 8.0 Hz, H-3), 3.82 (s, 3H, OCH_3), 4.42 (t, 1H, J_1 = 7.2, J_2 = 7.6 Hz, C<u>H</u>, H-4), 4.91 (d, 2H, J = 6.4 Hz, N–C<u>H</u>$_2$–CH), 5.04 (d, 1H, J = 16.4 Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.10 (d, 1H, J = 9.6 Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.92 (m, 1H, C<u>H</u>=CH_2), 7.21–8.05 (m, 9H, Ar–H), 11.06 (s, 1H, NH); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 21.64 (CH_2), 25.16 (CH_2), 29.56 (quinolone C-4), 35.71 (quinolone C-3), 36.34 (<u>C</u>H$_2$–CO), 44.63 (allylic N–<u>C</u>H$_2$–CH), 55.90 (OCH_3), 114.30, 115.35, 115.86, 120.14, 120.40, 128.19, 129.25, 130.30, 130.51, 131.88, 132.02, 133.10, 136.08, 138.56, 154.24, and 158.17 (16C, Ar–C+allylic C=C), 160.72 (C=O), 167.02 (C=O), 167.47 (C=O), 195.32 (C=O); MS (ESI) *m/z* 497.6 ($M^{+\cdot}$); anal. calcd. for $C_{29}H_{27}N_3O_5$ (497.54 g/mol): C, 70.01; H, 5.47; N, 8.45; found: C, 70.03; H, 5.63; N, 8.70.

N-(1-allyl-6-chloro-2,2′,5′-trioxo-1,2,3′,4′,5′,6′,7′,8′-octahydro-3,4′-biquinolin-1′(2′H)-yl)benzamide **(G28)** Yield: 87%; mp: 264–266 °C; IR (KBr, ν_{max}, cm^{-1}): 3256 (NH str.), 2962 (Ar C–H str.), 1728, 1620, and 1589 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.07–2.71 (m, 6H, 3 × CH_2 of cyclohexenone ring), 2.83 (dd, 1H, J_1 = 16.0 Hz, J_2 = 16.4 Hz, H-3), 3.15 (dd, 1H, J_1 = 7.6 Hz, J_2 = 8.0 Hz, H-3), 4.45 (t, 1H, J_1 = 7.2, J_2 = 7.6 Hz, C<u>H</u>, H-4), 4.93 (d, 2H, J = 6.4 Hz, N–C<u>H</u>$_2$–CH), 5.03 (d, 1H, J = 17.2 Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.14 (d, 1H, J = 9.6 Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.92 (m, 1H, C<u>H</u>=CH_2), 7.24–8.07 (m, 9H, Ar–H), 11.08 (s, 1H, NH); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 21.65 (CH_2), 25.16 (CH_2), 29.57 (quinolone C-4), 35.72 (quinolone C-3), 36.35 (<u>C</u>H$_2$–CO), 44.65 (allylic N–<u>C</u>H$_2$–CH), 114.35, 115.38, 115.85, 120.11, 120.42, 128.18, 129.25, 130.28, 130.55, 130.72, 131.80, 131.84, 133.06, 136.08, 140.52, and 158.16 (16C, Ar–C+allylic C=C), 160.82 (C=O), 167.09 (C=O), 167.54 (C=O), 195.35 (C=O); MS (ESI) *m/z* 502.0 $[M]^+$, 504.1 $[M+2]^+$; anal. calcd. for $C_{28}H_{24}ClN_3O_4$ (501.96 g/mol): C, 67.00; H, 4.82; N, 8.37; found: C, 66.96; H, 4.63; N, 8.25.

N-(1-allyl-7′,7′-dimethyl-2,2′,5′-trioxo-1,2,3′,4′,5′,6′,7′,8′-octahydro-3,4′-biquinolin-1′(2′H)-yl)benzamide **(G29)** Yield: 83%; mp: 245–247 °C; IR (KBr, ν_{max}, cm^{-1}): 3232 (NH str.), 2962 (Ar C–H str.), 1720, 1636, and 1582 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.08 (s, 3H, CH_3 of dimedone ring), 1.10 (s, 3H, CH_3 of dimedone ring), 2.21–2.75 (m, 4H, 2 × CH_2 of dimedone ring), 2.81 (dd, 1H, J_1 = 16.0 Hz, J_2 = 16.4 Hz, H-3), 3.14 (dd, 1H, J_1 = 8.0 Hz, J_2 = 8.0 Hz, H-3), 4.47 (t, 1H, J_1 = 8.0, J_2 = 8.4 Hz, C<u>H</u>, H-4), 4.92 (d, 2H, J = 6.4 Hz, N–C<u>H</u>$_2$–CH), 4.97 (d, 1H, J = 17.2 Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.12 (d, 1H, J = 10.4 Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.89 (m, 1H, C<u>H</u>=CH_2), 7.31–8.02 (m, 10H, Ar–H), 10.75 (s, 1H, NH); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 20.47, 20.68 (2 × CH_3 of dimedone ring), 29.32 (quinolone C-4), 32.94 (CH_2), 36.31 (quinolone C-3), 38.40 (<u>C</u>(CH_3)$_2$), 44.57 (<u>C</u>H$_2$–CO), 49.85 (allylic N–<u>C</u>H$_2$–CH), 113.41, 114.79, 115.26, 116.91, 120.35, 128.20, 128.75, 128.86, 129.24, 130.45, 131.54, 133.08, 134.81, 135.83, 136.54, and 156.06 (16C, Ar–C+allylic C=C), 160.56 (C=O), 167.05 (C=O), 167.52 (C=O), 195.24 (C=O); MS (ESI) *m/z* 495.4 $[M]^+$; anal. calcd. for $C_{30}H_{29}N_3O_4$ (495.57 g/mol): C, 72.71; H, 5.90; N, 8.48; found: C, 72.58; H, 5.81; N, 8.32.

N-(1-allyl-6,7′,7′-trimethyl-2,2′,5′-trioxo-1,2,3′,4′,5′,6′,7′,8′-octahydro-3,4′-biquinolin-1′(2′H)-yl)benzamide **(G30)** Yield: 84%; mp: 250–252 °C; IR (KBr, ν_{max}, cm^{-1}): 3217 (NH str.), 2955 (Ar C–H str.), 1728, 1628, and 1597 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.09 (s, 3H, CH_3 of dimedone ring), 1.11 (s, 3H, CH_3 of dimedone ring), 2.22–2.78 (m, 7H, 2 × CH_2 of dimedone ring+CH_3), 2.82 (dd, 1H, J_1 = 12.4 Hz, J_2 = 12.8 Hz, H-3), 3.19 (dd, 1H, J_1 = 8.4 Hz, J_2 = 8.4 Hz, H-3), 4.49 (t, 1H, J_1 = 8.0, J_2 = 8.4 Hz, C<u>H</u>, H-4), 4.90 (d, 2H, J = 6.4 Hz, N–C<u>H</u>$_2$–CH), 4.95

(d, 1H, $J = 17.6$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.14 (d, 1H, $J = 10.8$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.90 (m, 1H, C<u>H</u>=CH_2), 7.32–8.02 (m, 9H, Ar–H), 10.73 (s, 1H, NH); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 20.45, 20.66 ($2 \times CH_3$ of dimedone ring), 27.75 (CH_3), 29.29 (quinolone C-4), 32.92 (CH_2), 36.36 (quinolone C-3), 38.41 (<u>C</u>$(CH_3)_2$), 44.55 (<u>C</u>H_2–CO), 49.86 (allylic N–<u>C</u>H_2–CH), 113.43, 114.78, 115.25, 116.92, 120.31, 128.18, 128.74, 128.84, 129.22, 130.42, 131.53, 133.05, 134.79, 135.80, 136.56, and 156.02 (16C, Ar–C+allylic C=C), 160.58 (C=O), 167.02 (C=O), 167.50 (C=O), 195.20 (C=O); MS (ESI) *m/z* 509.5 $[M]^+$; anal. calcd. for $C_{31}H_{31}N_3O_4$ (509.60 g/mol): C, 73.06; H, 6.13; N, 8.25; found: C, 73.34; H, 6.35; N, 8.23.

N-(1-allyl-6-methoxy-7′,7′-dimethyl-2,2′,5′-trioxo-1,2,3′,4′,5′,6′,7′,8′-octahydro-3,4′-biquinolin-1′(2′H)-yl)benzamide **(G31)** Yield: 80%; mp: 263–265 °C; IR (KBr, ν_{max}, cm^{-1}): 3232 (NH str.), 2955 (Ar C–H str.), 1720, 1620, and 1582 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.08 (s, 3H, CH_3 of dimedone ring), 1.11 (s, 3H, CH_3 of dimedone ring), 2.21–2.69 (m, 4H, $2 \times CH_2$ of dimedone ring), 2.81 (dd, 1H, $J_1 = 15.6$ Hz, $J_2 = 16.0$ Hz, H-3), 3.20 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 8.0$ Hz, H-3), 3.82 (s, 3H, OCH_3), 4.52 (t, 1H, $J_1 = 7.2$, $J_2 = 7.6$ Hz, C<u>H</u>, H-4), 4.89 (d, 2H, $J = 6.4$ Hz, N–C<u>H</u>$_2$–CH), 4.95 (d, 1H, $J = 17.6$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.14 (d, 1H, $J = 10.0$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.90 (m, 1H, C<u>H</u>=CH_2), 7.16–8.08 (m, 9H, Ar–H), 11.10 (s, 1H, NH); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 27.45, 28.89 ($2 \times CH_3$ of dimedone ring), 29.43 (quinolone C-4), 33.01 (CH_2), 36.49 (quinolone C-3), 38.42 (<u>C</u>$(CH_3)_2$), 44.70 (<u>C</u>H_2–CO), 49.87 (allylic N–<u>C</u>H_2–CH), 56.14 (OCH_3), 111.16, 114.98, 116.96, 118.69, 121.17, 128.06, 128.28, 129.37, 130.88, 131.22, 131.74, 133.02, 133.20, 135.79, 154.61, and 156.07 (16C, Ar–C+allylic C=C), 160.28 (C=O), 166.92 (C=O), 167.56 (C=O), 195.21 (C=O); MS (ESI) *m/z* 525.3 $[M]^+$; anal. calcd. for $C_{31}H_{31}N_3O_5$ (525.59 g/mol): C, 70.84; H, 5.94; N, 7.99; found: C, 70.90; H, 6.09; N, 7.93.

N-(1-allyl-6-chloro-7′,7′-dimethyl-2,2′,5′-trioxo-1,2,3′,4′,5′,6′,7′,8′-octahydro-3,4′-biquinolin-1′(2′H)-yl)benzamide ***(G32)*** Yield: 88%; mp: 270–272 °C; IR (KBr, ν_{max}, cm^{-1}): 3271 (NH str.), 2962 (Ar C–H str.), 1728, 1636, and 1597 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.07 (s, 3H, CH_3 of dimedone ring), 1.11 (s, 3H, CH_3 of dimedone ring), 2.22–2.76 (m, 4H, $2 \times CH_2$ of dimedone ring), 2.83 (dd, 1H, $J_1 = 15.6$ Hz, $J_2 = 16.0$ Hz, H-3), 3.12 (dd, 1H, $J_1 = 8.4$ Hz, $J_2 = 8.4$ Hz, H-3), 4.48 (t, 1H, $J_1 = 8.0$, $J_2 = 8.4$ Hz, C<u>H</u>, H-4), 4.93 (d, 2H, $J = 6.4$ Hz, N–C<u>H</u>$_2$–CH), 4.99 (d, 1H, $J = 16.4$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.11 (d, 1H, $J = 10.4$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.92 (m, 1H, C<u>H</u>=CH_2), 7.32–8.04 (m, 9H, Ar–H), 10.78 (s, 1H, NH); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 20.49, 20.72 ($2 \times CH_3$ of dimedone ring), 29.38 (quinolone C-4), 32.96 (CH_2), 36.33 (quinolone C-3), 38.42 (<u>C</u>$(CH_3)_2$), 44.59 (<u>C</u>H_2–CO), 49.88 (allylic N–<u>C</u>H_2–CH), 113.42, 114.81, 115.28, 117.02, 120.38, 128.21, 128.73, 128.85, 129.29, 130.48, 131.51, 133.12, 134.87, 135.86, 136.50, and 156.10 (16C, Ar–C+allylic C=C), 160.58 (C=O), 167.07 (C=O), 167.54 (C=O), 195.26 (C=O); MS (ESI) *m/z* 529.9 $[M]^+$, 532.1 $[M+2]^+$; anal. calcd. for $C_{30}H_{28}ClN_3O_4$ (530.01 g/mol): C, 67.98; H, 5.32; N, 7.93; found: C, 68.24; H, 5.06; N, 7.61.

N-(1-allyl-2,2′,5′-trioxo-1,2,3′,4′,5′,6′,7′,8′-octahydro-3,4′-biquinolin-1′(2′H)-yl)isonicotinamide **(G33)** Yield: 82%; mp: 251–253 °C; IR (KBr, ν_{max}, cm^{-1}): 3456 (NH str.), 2962 (Ar C–H str.), 1728, 1682, and 1620 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.10–2.73 (m, 6H, $3 \times CH_2$ of cyclohexenone ring), 2.86 (dd, 1H, $J_1 = 15.2$ Hz, $J_2 = 15.6$ Hz, H-3), 3.14 (dd, 1H, $J_1 = 8.0$ Hz, $J_2 = 8.0$ Hz, H-3), 4.42 (t, 1H, $J_1 = 7.2$, $J_2 = 7.6$ Hz, C<u>H</u>, H-4), 4.91 (d, 2H, $J = 5.2$ Hz, N-C<u>H</u>$_2$–CH), 5.01 (d, 1H, $J = 16.4$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.13 (d, 1H, $J = 10.4$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.90 (m, 1H, C<u>H</u>=CH_2), 7.23–8.06 (m, 9H, Ar–H), 11.13 (s, 1H, NH); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 21.72 (CH_2), 25.28 (CH_2), 29.62 (quinolone C-4), 35.76 (quinolone C-3), 36.35 (<u>C</u>H_2–CO), 44.68 (allylic N–<u>C</u>H_2–CH), 114.38, 115.91, 120.23, 120.46, 128.25, 129.29, 130.31, 130.86, 131.81, 131.93, 133.14, 136.46, 138.51, 151.32, and 155.84 (15C, Ar–C+allylic C=C), 160.64 (C=O), 167.12 (C=O), 167.74 (C=O), 195.37 (C=O); MS (ESI) *m/z* 468.4 $[M]^+$; anal. calcd. for $C_{27}H_{24}N_4O_4$ (468.50 g/mol): C, 69.22; H, 5.16; N, 11.96; found: C, 69.11; H, 4.85; N, 12.17.

N-(1-allyl-6-methyl-2,2′,5′-trioxo-1,2,3′,4′,5′,6′,7′,8′-octahydro-3,4′-biquinolin-1′(2′H)-yl)isonicotinamide **(G34)** Yield: 81%; mp: 257–259 °C; IR (KBr, ν_{max}, cm^{-1}): 3402 (NH str.), 2962 (Ar C–H str.), 1720, 1690, and 1582 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.09–2.74 (m, 9H, $3 \times CH_2$ of cyclohexenone ring+CH_3), 2.84 (dd, 1H, $J_1 = 15.2$ Hz, $J_2 = 15.6$ Hz, H-3), 3.12 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 7.6$ Hz, H-3), 4.46 (t, 1H, $J_1 = 7.2$, $J_2 = 7.6$ Hz, C<u>H</u>, H-4), 4.92 (d, 2H, $J = 6.4$ Hz, N–C<u>H</u>$_2$–CH), 5.05 (d, 1H, $J = 17.4$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.11 (d, 1H, $J = 10.4$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.91 (m, 1H, C<u>H</u>=CH_2), 7.22–8.05 (m, 8H, Ar–H), 11.12 (s, 1H, NH); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 21.75 (CH_2), 25.28 (CH_2), 27.45 (CH_3), 29.63 (quinolone C-4), 35.75 (quinolone C-3), 36.38 (<u>C</u>H_2–CO), 44.65 (allylic N–<u>C</u>H_2–CH), 114.42, 115.88, 120.26, 120.52, 128.28, 129.31, 130.28, 130.80, 131.76, 131.90, 133.11, 136.48, 138.55, 151.34, and 155.85 (15C, Ar–C+allylic C=C), 160.63 (C=O), 167.12 (C=O), 167.75 (C=O), 195.36 (C=O); MS (ESI)

m/z 482.4 $[M]^+$; anal. calcd. for $C_{28}H_{26}N_4O_4$ (482.53 g/mol): C, 69.70; H, 5.43; N, 11.61; found: C, 69.90; H, 5.14; N, 11.32.

N-(1-allyl-6-methoxy-2,2′,5′-trioxo-1,2,3′,4′,5′,6′,7′,8′-octahydro-3,4′-biquinolin-1′(2′H)-yl)isonicotinamide **(G35)** Yield: 84%; mp: 263–265 °C; IR (KBr, ν_{max}, cm^{-1}): 3163 (NH str.), 2955 (Ar C–H str.), 1720, 1682, and 1620 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.09–2.71 (m, 6H, 3 × $CH_2$of cyclohexenone ring), 2.85 (dd, 1H, J_1 = 15.6 Hz, J_2 = 16.0 Hz, H-3), 3.14 (dd, 1H, J_1 = 8.0 Hz, J_2 = 8.0 Hz, H-3), 3.81 (s, 3H, OCH_3), 4.47 (t, 1H, J_1 = 7.6, J_2 = 8.0 Hz, C<u>H</u>, H-4), 4.94 (d, 2H, J = 6.4 Hz, N–C<u>H</u>$_2$–CH), 5.08 (d, 1H, J = 16.4 Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.15 (d, 1H, J = 10.4 Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.92 (m, 1H, C<u>H</u>=CH_2), 7.22–8.06 (m, 8H, Ar–H), 11.12 (s, 1H, NH); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 21.75 (CH_2), 25.27 (CH_2), 29.65 (quinolone C-4), 35.78 (quinolone C-3), 36.32 (<u>C</u>H$_2$–CO), 44.67 (allylic N–<u>C</u>H$_2$–CH), 55.87 (OCH_3), 114.36, 115.87, 120.21, 120.48, 128.26, 129.28, 130.30, 130.84, 131.79, 131.91, 133.17, 136.45, 138.52, 151.34, and 155.86 (15C, Ar–C+allylic C=C), 160.62 (C=O), 167.14 (C=O), 167.73 (C=O), 195.36 (C=O); MS (ESI) *m/z* 498.6 $[M]^+$; anal. calcd. for $C_{28}H_{26}N_4O_5$ (498.53 g/mol): C, 67.46; H, 5.26; N, 11.24; found: C, 67.18; H, 5.50; N, 11.15.

N-(1-allyl-6-chloro-2,2′,5′-trioxo-1,2,3′,4′,5′,6′,7′,8′-octahydro-3,4′-biquinolin-1′(2′H)-yl)isonicotinamide **(G36)** Yield: 87%; mp: 270–272 °C; IR (KBr, ν_{max}, cm^{-1}): 3456 (NH str.), 2962 (Ar C–H str.), 1720, 1690, and 1582 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 2.10–2.72 (m, 6H, 3 × CH_2 of cyclohexenone ring), 2.84 (dd, 1H, J_1 = 16.0 Hz, J_2 = 16.4 Hz, H-3), 3.10 (dd, 1H, J_1 = 8.4 Hz, J_2 = 8.4 Hz, H-3), 4.46 (t, 1H, J_1 = 7.6, J_2 = 8.0 Hz, C<u>H</u>, H-4), 4.92 (d, 2H, J = 6.4 Hz, N–C<u>H</u>$_2$–CH), 5.07 (d, 1H, J = 16.4 Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.12 (d, 1H, J = 10.4 Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.93 (m, 1H, C<u>H</u>=CH_2), 7.25–8.08 (m, 8H, Ar–H), 11.15 (s, 1H, NH); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 21.81 (CH_2), 25.32 (CH_2), 29.68 (quinolone C-4), 35.80 (quinolone C-3), 36.41 (<u>C</u>H$_2$–CO), 44.70 (allylic N–<u>C</u>H$_2$–CH), 115.01, 115.98, 120.21, 120.45, 128.20, 129.34, 130.38, 130.90, 131.95, 133.12, 136.45, 138.58, 150.14, 151.30, and 155.81 (15C, Ar–C +allylic C=C), 160.67 (C=O), 167.15 (C=O), 167.73 (C=O), 195.38 (C=O); MS (ESI) *m/z* 503.1 $[M]^+$, 504.9 $[M+2]^+$; anal. calcd. for $C_{27}H_{23}ClN_4O_4$ (502.95 g/mol): C, 64.48; H, 4.61; N, 11.14; found: C, 64.57; H, 4.69; N, 11.08.

N-(1-allyl-7′,7′-dimethyl-2,2′,5′-trioxo-1,2,3′,4′,5′,6′,7′,8′-octahydro-3,4′-biquinolin-1′(2′H)-yl)isonicotinamide **(G37)** Yield: 84%; mp: 255–257 °C; IR (KBr, ν_{max}, cm^{-1}): 3402 (NH str.), 2955 (Ar C–H str.), 1728, 1690, and 1589 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.08 (s, 3H, CH_3 of dimedone ring), 1.11 (s, 3H, CH_3 of dimedone ring), 2.23–2.78 (m, 4H, 2 × CH_2 of dimedone ring), 2.80 (dd, 1H, J_1 = 16.8 Hz, J_2 = 17.2 Hz, H-3), 3.22 (dd, 1H, J_1 = 8.0 Hz, J_2 = 8.0 Hz, H-3), 4.51 (t, 1H, J_1 = 7.2, J_2 = 7.6 Hz, C<u>H</u>, H-4), 4.91 (d, 2H, J = 7.2 Hz, N–C<u>H</u>$_2$–CH), 4.98 (d, 1H, J = 16.2 Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.15 (d, 1H, J = 10.0 Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.93 (m, 1H, C<u>H</u>=CH_2), 7.25–8.84 (m, 9H, Ar–H), 11.39 (s, 1H, NH); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 19.77, 20.08 (2 × CH_3 of dimedone ring), 28.83 (quinolone C-4), 33.02 (CH_2), 36.37 (quinolone C-3), 38.29 (<u>C</u>$(CH_3)_2$), 44.68 (<u>C</u>H$_2$–CO), 49.86 (allylic N–<u>C</u>H$_2$–CH), 113.31, 115.01, 117.12, 120.05, 120.35, 121.81, 122.06, 122.61, 130.36, 133.04, 135.95, 138.54, 138.86, 151.21, and 155.75 (15C, Ar–C+allylic C=C), 160.72 (C=O), 165.74 (C=O), 167.39 (C=O), 195.25 (C=O); MS (ESI) *m/z* 496.8 $[M]^+$; anal. calcd. for $C_{29}H_{28}N_4O_4$ (496.56 g/mol): C, 70.15; H, 5.68; N, 11.28; Found: C, 70.30; H, 5.85; N, 11.41.

N-(1-allyl-6,7′,7′-trimethyl-2,2′,5′-trioxo-1,2,3′,4′,5′,6′,7′,8′-octahydro-3,4′-biquinolin-1′(2′H)-yl)isonicotinamide **(G38)** Yield: 83%; mp: 258–260 °C; IR (KBr, ν_{max}, cm^{-1}): 3456 (NH str.), 2955 (Ar C–H str.), 1720, 1690, and 1589 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.06 (s, 3H, CH_3 of dimedone ring), 1.09 (s, 3H, CH_3 of dimedone ring), 2.21–2.78 (m, 7H, 2 × CH_2 of dimedone ring+CH_3), 2.81 (dd, 1H, J_1 = 16.8 Hz, J_2 = 17.2 Hz, H-3), 3.21 (dd, 1H, J_1 = 8.0 Hz, J_2 = 8.0 Hz, H-3), 4.52 (t, 1H, J_1 = 7.2, J_2 = 7.6 Hz, C<u>H</u>, H-4), 4.93 (d, 2H, J = 7.2 Hz, N–C<u>H</u>$_2$–CH), 4.99 (d, 1H, J = 16.2 Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.16 (d, 1H, J = 10.0 Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.92 (m, 1H, C<u>H</u>=CH_2), 7.24–8.83 (m, 8H, Ar–H), 11.40 (s, 1H, NH); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 19.78, 20.10 (2 × CH_3 of dimedone ring), 27.12 (CH_3), 28.84 (quinolone C-4), 33.05 (CH_2), 36.38 (quinolone C-3), 38.31 (<u>C</u>$(CH_3)_2$), 44.67 (<u>C</u>H$_2$–CO), 49.85 (allylic N–<u>C</u>H$_2$–CH), 113.32, 115.04, 117.15, 120.07, 120.36, 121.86, 122.09, 122.62, 130.38, 133.02, 135.91, 138.55, 138.83, 151.25, and 155.77 (15C, Ar–C+allylic C=C), 160.76 (C=O), 165.78 (C=O), 167.45 (C=O), 195.28 (C=O); MS (ESI) *m/z* 510.8 $[M]^+$; anal. calcd. for $C_{30}H_{30}N_4O_4$ (510.58 g/mol): C, 70.57; H, 5.92; N, 10.97; found: C, 70.47; H, 5.89; N, 10.83.

N-(1-allyl-6-methoxy-7′,7′-dimethyl-2,2′,5′-trioxo-1,2,3′,4′,5′,6′,7′,8′-octahydro-3,4′-biquinolin-1′(2′H)-yl)isonicotinamide **(G39)** Yield: 86%; mp: 266–268 °C; IR (KBr, ν_{max}, cm^{-1}): 3163 (NH str.), 2962 (Ar C–H str.), 1728, 1682, and 1582 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.08 (s, 3H, CH_3 of dimedone ring), 1.12 (s, 3H, CH_3 of dimedone ring), 2.21–2.69 (m, 4H, 2 × CH_2

of dimedone ring), 2.80 (dd, 1H, $J_1 = 17.2$ Hz, $J_2 = 17.6$ Hz, H-3), 3.22 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 7.6$ Hz, H-3), 3.82 (s, 3H, OCH_3), 4.49 (t, 1H, $J_1 = 7.6$, $J_2 = 8.0$ Hz, C<u>H</u>, H-4), 4.91 (d, 2H, $J = 8.0$ Hz, N–C<u>H</u>$_2$–CH), 4.95 (d, 1H, $J =$ 18.8 Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.14 (d, 1H, $J = 11.2$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.91 (m, 1H, C<u>H</u>=CH_2), 7.13–8.84 (m, 8H, Ar–H), 11.43 (s, 1H, NH); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 26.94, 28.39 (2 × CH_3 of dimedone ring), 28.93 (quinolone C-4), 32.56 (CH_2), 35.81 (quinolone C-3), 37.77 (<u>C</u>(CH_3)$_2$), 44.20 (<u>C</u>H$_2$–CO), 49.33 (allylic N–<u>C</u>H$_2$–CH), 55.45 (OCH_3), 110.61, 114.56, 116.24, 116.42, 118.28, 120.58, 122.39, 130.24, 132.51, 132.61, 135.07, 138.24, 150.61, 154.09, and 155.43 (15C, Ar–C+allylic C=C), 159.71 (C=O), 165.10 (C=O), 166.90 (C=O), 194.72 (C=O); MS (ESI) *m/z* 526.4 $[M]^+$; anal. calcd. for $C_{30}H_{30}N_4O_5$ (526.58 g/mol): C, 68.43; H, 5.74; N, 10.64; found: C, 68.52; H, 6.05; N, 10.80.

N-(1-allyl-6-chloro-7′,7′-dimethyl-2,2′,5′-trioxo-1,2,3′,4′,5′,6′,7′,8′-octahydro-3,4′-biquinolin-1′(2′H)-yl)isonicotinamide **(G40)** Yield: 89%; mp: 276–278 °C; IR (KBr, ν_{max}, cm^{-1}): 3456 (NH str.), 2962 (Ar C–H str.), 1720, 1682, and 1620 (C=O str.); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 1.08 (s, 3H, CH_3 of dimedone ring), 1.12 (s, 3H, CH_3 of dimedone ring), 2.20–2.70 (m, 4H, 2 × CH_2 of dimedone ring), 2.85 (dd, 1H, $J_1 = 17.2$ Hz, $J_2 = 17.6$ Hz, H-3), 3.24 (dd, 1H, $J_1 = 7.6$ Hz, $J_2 = 8.4$ Hz, H-3), 4.48 (t, 1H, $J_1 = 7.2$, $J_2 = 7.6$ Hz, C<u>H</u>, H-4), 4.88 (d, 2H, $J = 8.0$ Hz, N–C<u>H</u>$_2$–CH), 5.09 (d, 1H, $J = 18.8$ Hz, N–CH_2CH=C<u>H</u>-*trans*), 5.15 (d, 1H, $J = 11.2$ Hz, N–CH_2CH=C<u>H</u>-*cis*), 5.91 (m, 1H, C<u>H</u>=CH_2), 7.46–8.29 (m, 8H, Ar–H), 11.40 (s, 1H, NH); ^{13}C NMR (APT) (100 MHz, DMSO-d_6) δ ppm: 26.99, 28.45 (2 × CH_3 of dimedone ring), 28.97 (quinolone C-4), 32.48 (CH_2), 35.56 (quinolone C-3), 37.76 (<u>C</u>(CH_3)$_2$), 44.34 (<u>C</u>H$_2$-CO), 49.27 (allylic N-<u>C</u>H$_2$-CH), 114.25, 116.61, 117.03, 121.03, 121.40, 126.06, 127.30, 129.76, 131.21, 132.28, 134.55, 136.78, 138.27, 150.66, 155.30 (15C, Ar-C+allylic C=C), 159.96 (C=O), 165.24 (C=O), 166.76 (C=O), 194.71 (C=O); MS (ESI) *m/z* 530.9 $[M]^+$, 533.2 $[M+2]^+$; anal. calcd. for $C_{29}H_{27}ClN_4O_4$ (531.00 g/mol): C, 65.59; H, 5.13; N, 10.55; found: C, 65.71; H, 5.06; N, 10.54.

Results and discussion

Chemistry

For the better exploration of SAR, a library comprises forty 3,4′-bicarbostyrilderivatives **G(1–40)** was derived using DOS. The structural diversity at *N*-1, C-4 and C-7 positions was obtained through variations in synthons. The key precursors 1-allyl-2-oxo-1,2-dihydroquinoline-3-carbaldehydes **B(1–4)** were synthesized by electrophilic favoured *N*-allylation of **A(1–4)** in the presence of K_2CO_3 in DMF at room temperature (Jardosh and Patel 2012). To insert the variety of spacers at the *N*-1 position, various β-enaminones **E(1–10)** were synthesized by nucleophilic addition reaction of 1,3-cyclohexanedione/dimedone **C(1–2)** with aniline **D1**/ benzyl amine **D2**/BHZ **D3**/ INH**D4** at 120 °C for 30 min under solvent free condition and β-enaminones of PHZ **E5** were prepared by a reported procedure of Fatiadi (Fatiadi 1970) (Scheme 1).

A general synthetic protocol has been established for the synthesis of 3,4′-bicarbostyril derivatives **G (1–40)** and depicted in (Scheme 1). These title derivatives were prepared via one-pot three component cyclo-condensation reaction between **B(1–4)**, Meldrum's acid **F** and β-enaminones **E(1–10)** in ethanol containing a catalytic amount of piperidine in good to excellent yields (61–89%). The key features of this protocol are, ease to afford complex and hybrid heterocyclic scaffolds without isolating any intermediates, and exemption from the tedious purification procedure.

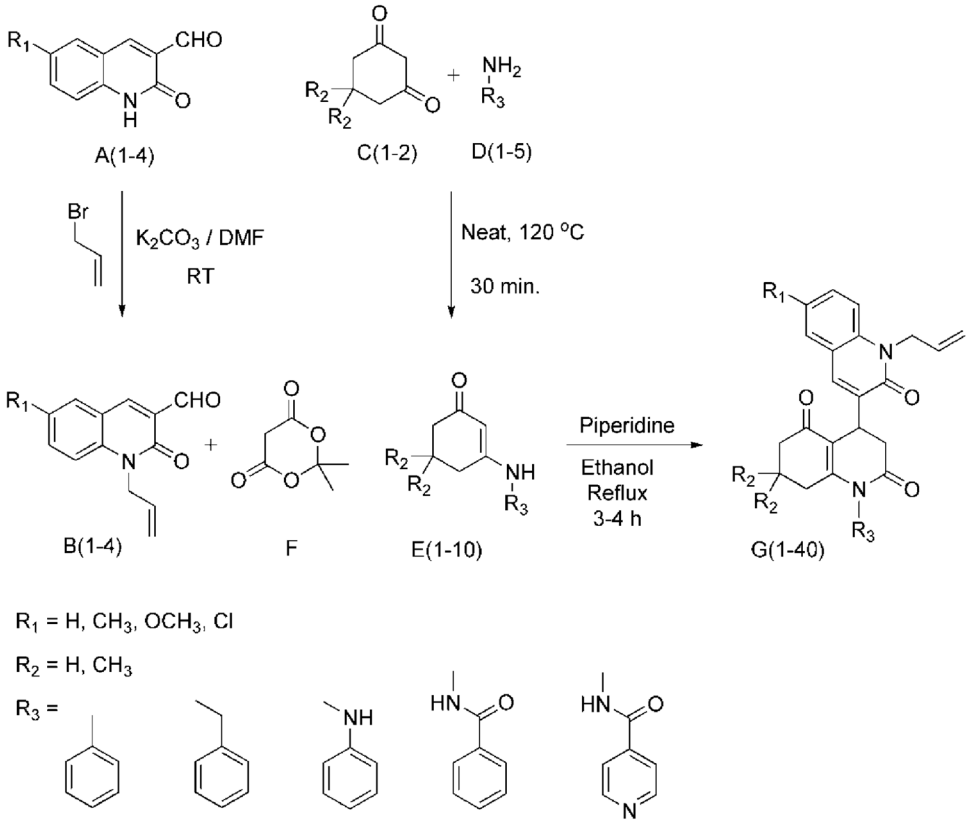
Biological activity

Antimicrobial activity

The in vitro antimicrobial activity of synthesized compounds was carried out against three Gram-positive and negative bacteria as well as two fungi as per guidelines of the National Committee for Clinical Laboratory Standards (NCCLS 2002) (See supplementary material) and the results are tabulated in (Table 1).

Upon exploration of antimicrobial activity data, it has been observed that against *P. aeruginosa*, compound **G37** (MIC = 25 µg/mL) found to have fabulous activity compared to chloramphenicol and equal to that of ciprofloxacin. Compound **G8** (MIC = 50 µg/mL) showed comparable activity to that of chloramphenicol. Against *S. typhi*, compound **G38** (MIC = 50 µg/mL) was found to be more potent than ampicillin and equipotent to chloramphenicol (MIC = 50 µg/mL). Compounds **G1**, **G6**, **G13**, and **G34** (MIC = 100 µg/mL) were found equally potent to ampicillin. Against *E. coli*, compounds **G18** (MIC = 50 µg/mL) and **G4**, **G6**, **G13**, and **G34** (MIC = 62.5 µg/mL) were found to have magnificent activity while compounds **G10**, **G16**, **G22**, **G23**, **G25**, and **G37** (MIC = 100 µg/mL) were found to have equivalent activity compared to ampicillin. Against *B. subtillis*, compound **G37** (MIC = 50 µg/mL) showed remarkable potency as compared to norfloxacin (MIC = 100 µg/mL), ciprofloxacin (MIC = 50 µg/mL) and chloramphenicol (MIC = 50 µg/mL). Compounds **G27** (MIC = 100 µg/mL); **G7**, **G8**, **G9**, **G10**, **G29**, **G31**, **G34**, and **G38** (MIC = 200 µg/mL) were found to be more effective as

Scheme 1 Synthesis of intermediates and 3,4′-bicarbostyril derivatives



compared to ampicillin (MIC = 250 μg/mL). Against *C. tetani*, compounds **G6** and **G35** (MIC = 62.5 μg/mL); **G10**, **G13**, **G31**, and **G38** (MIC = 100 μg/mL) exhibited significant potency as compared to ciprofloxacin (MIC = 100 μg/mL). Compounds **G8**, **G14**, **G17**, **G25**, **G32**, and **G37** (MIC = 125 μg/mL); **G5**, **G19**, **G27**, **G29**, **G30**, and **G40** (MIC = 200 μg/mL) were found to be more potent compared to ampicillin (MIC = 250 μg/mL). Against *S. aureus*, compounds **G6** and **G14** (MIC = 100 μg/mL); **G8**, **G10**, **G13**, **G17**, **G32**, **G35**, and **G38** (MIC = 125 μg/mL); **G5**, **G12**, **G19**, **G25**, **G30**, **G31**, and **G37** (MIC = 200 μg/mL) were found to have more potency compared with ampicillin (MIC = 250 μg/mL).

The antifungal screening data (Table 1) revealed that against *C. albicans*, compounds **G16**, **G19** and **G36** (MIC = 100 μg/mL) exhibited marvelous activity compared to griseofulvin (MIC = 500 μg/mL) and equally potent to nystatin (MIC = 100 μg/mL). Compounds **G1**, **G6**, **G12**, **G15**, **G20**, and **G27** (MIC = 200 μg/mL); **G3**, **G4**, **G7**, **G23**, **G24**, **G25**, **G28**, **G38**, and **G39** (MIC = 250 μg/mL) were showing significant activity compared to griseofulvin. Against *T. rubrum* compounds **G24** and **G40** (MIC = 100 μg/mL) were found to be equally potent to nystatin (MIC = 100 μg/mL) as well as griseofulvin (MIC = 100 μg/mL).

Structure–activity relationship (SAR) for antimicrobial activity

Antimicrobial activity results revealed that against *S. aureus*, compounds **G6** and **G14** having lipophilic –CH_3 group at R_1 and R_2 position as well as –Ph and –Bn at R_3 position improved solubility and gave significant potency compared to ampicillin. While compounds carrying –PHZ spacer at R_3position reduced the inhibitory action. Against *B. subtilis*, increment of spacer length to amide linkage enhanced the potency and showed excellent activity compared to ampicillin, e.g. compounds **G37** and **G27**. It can be seen that antibacterial effectiveness becomes double when a Ph ring of –BHZ replace with pyridyl ring. However, compounds having R_3 = –BHZ and –INH displayed better activity compared to other spacers with reference to ampicillin, e.g. **G27**, **G29**, **G31**, **G34**, **G37**, and **G38**. Against *C. tetani*, extension of spacer length from –Ph to –Bn reduced the potency by two-fold, but further increment from –Bn to –INH improved the power of bacterial growth inhibition by 3.2-fold and showed significant activity to ciprofloxacin and ampicillin, e.g. **G6** and **G35**. Also, compounds **G31** and **G38** displayed comparable activity to ciprofloxacin. In case of *E. coli*, reverse trend was observed compared to Gram-positive bacteria, because compounds containing shorter length spacers *viz*., R_3 = –PHZ, –Ph, and

Table 1 In vitro antimicrobial activity of title compounds (MIC, μg/mL)

				Minimum inhibitory concentration (MIC) in μg/mL							
				Gram-positive bacteria			Gram-negative bacteria			Fungi	
Entry	R_1	R_2	R_3	SA	BS	CT	EC	ST	PA	CA	TR
G1	H	H	Ph	250	500	250	500	100	250	200	500
G2	CH_3	H	Ph	250	500	250	250	250	200	500	1000
G3	OCH_3	H	Ph	250	500	500	500	500	250	250	1000
G4	Cl	H	Ph	250	500	500	62.5	200	500	250	500
G5	H	CH_3	Ph	200	250	200	500	250	250	1000	1000
G6	CH_3	CH_3	Ph	100	500	62.5	62.5	100	500	200	1000
G7	OCH_3	CH_3	Ph	250	200	500	250	250	250	250	500
G8	Cl	CH_3	Ph	125	200	125	500	500	50	500	>1000
G9	H	H	Bn	250	200	500	250	500	100	1000	500
G10	CH_3	H	Bn	125	200	100	100	200	500	1000	500
G11	OCH_3	H	Bn	500	250	500	200	250	200	500	1000
G12	Cl	H	Bn	200	500	250	200	250	250	200	>1000
G13	H	CH_3	Bn	125	250	100	62.5	100	500	500	250
G14	CH_3	CH_3	Bn	100	250	125	200	250	250	>1000	>1000
G15	OCH_3	CH_3	Bn	250	500	250	250	500	500	200	1000
G16	Cl	CH_3	Bn	250	500	250	100	200	100	100	500
G17	H	H	PHZ	125	250	125	200	250	500	1000	1000
G18	CH_3	H	PHZ	500	250	500	50	200	500	>1000	>1000
G19	OCH_3	H	PHZ	200	500	200	250	250	250	100	500
G20	Cl	H	PHZ	500	500	500	500	500	500	200	500
G21	H	CH_3	PHZ	500	250	500	250	250	250	1000	1000
G22	CH_3	CH_3	PHZ	500	250	500	100	250	500	500	500
G23	OCH_3	CH_3	PHZ	500	500	500	100	200	250	250	>1000
G24	Cl	CH_3	PHZ	500	500	500	250	500	100	250	100
G25	H	H	BHZ	200	250	125	100	200	500	250	500
G26	CH_3	H	BHZ	250	500	250	200	200	500	1000	>1000
G27	OCH_3	H	BHZ	250	100	200	500	250	200	200	>1000
G28	Cl	H	BHZ	500	500	500	500	500	100	250	>1000
G29	H	CH_3	BHZ	250	200	200	200	200	200	500	500
G30	CH_3	CH_3	BHZ	200	250	200	500	500	500	1000	>1000
G31	OCH_3	CH_3	BHZ	200	200	100	500	250	200	500	1000
G32	Cl	CH_3	BHZ	125	500	125	500	500	100	500	>1000
G33	H	H	INH	500	500	500	250	200	500	1000	1000
G34	CH_3	H	INH	500	200	500	62.5	100	250	500	>1000
G35	OCH_3	H	INH	125	500	62.5	125	125	500	500	1000
G36	Cl	H	INH	500	500	500	125	200	200	100	1000
G37	H	CH_3	INH	200	50	125	100	125	25	1000	>1000
G38	CH_3	CH_3	INH	125	200	100	250	50	200	250	1000
G39	OCH_3	CH_3	INH	250	250	250	200	250	250	250	1000
G40	Cl	CH_3	INH	250	250	200	200	200	250	1000	100
Ampicillin				250	250	250	100	100	nd[a]	–	–
Ciprofloxacin				50	50	100	25	25	25	–	–
Chloramphenicol				50	50	50	50	50	50	–	–
Norfloxacin				10	100	50	10	10	10	–	–

Table 1 continued

Entry	R_1	R_2	R_3	Minimum inhibitory concentration (MIC) in μg/mL							
				Gram-positive bacteria			Gram-negative bacteria			Fungi	
				SA	BS	CT	EC	ST	PA	CA	TR
Griseofulvin				–	–	–	–	–	–	500	100
Nystatin				–	–	–	–	–	–	100	100

nd not determine, *SA Staphylococcus aureus* (MTCC 96), *BS Bacillus subtilis* (MTCC 441), *CT Clostridium tetani* (MTCC 449), *EC Escherichia coli* (MTCC 443), *ST Salmonella typhi* (MTCC 98), *PA Pseudomonas aeruginosa* (MTCC 1688), *CA Candida albicans* (MTCC 227), *TR Trichophyton rubrum*(MTCC 296)

–Bn displayed magnificent results, e.g. **G18** demonstrated equal potency to chloramphenicol; while **G4**, **G6**, and **G13** except **G34** showed higher potential than ampicillin. Both EDG $–CH_3$ and EWG –Cl at R_1 along with $–CH_3$ at R_2 position took part in the enhancement of potency of title compounds. Against *S. typhi*, only compound **G38** having $–CH_3$ group at R_1 and R_2 position increased the lipophilicity (ClogP 3.34) and became equipotent to chloramphenicol. Further, it carries drug-like spacer –INH (amide linkage) at R_3 position which provides more flexibility to facilitate molecule to transport through the cell membrane of the bacteria (Waterbeemd 2007). Against *P. aeruginosa*, the increment of spacer length –Ph to –INH increased activity by two-fold, e.g. compound **G37** found to have remarkable activity; while **G8** possessed comparable activity with chloramphenicol. These compounds possessed lipophilic $–CH_3$ group at R_2 position and found equipotent to ciprofloxacin and chloramphenicol, respectively. Eventually, the bactericidal effect is increased in the order of INH > Ph > PHZ > BHZ > Bn.

Against fungi *C. albicans*, both the EDG-OCH_3 and EWG -Cl containing compounds **G16**, **G19**, and **G36** exhibited marvelous inhibition of growth of fungi compared to nystatin and griseofulvin. Compounds **G1**, **G6**, **G12**, **G15**, and **G27** exhibited excellent potency than griseofulvin. Against *T. rubrum,* only the compounds **G24** and **G40** having –Cl group at R_1 position and $–CH_3$ group at R_2 position exhibited excellent antifungal effectiveness and became equally potent to griseofulvin and nystatin. The antifungal potency is increased in order of PHZ > Bn > Ph > INH > BHZ. By reviewing the antimicrobial activity results it can be seen that compounds those exhibited MIC ≤ 100 μg/mL displayed excellent CLogP values (1.97–4.79) less than 5 and polar surface area (PSA) (57.69–108.38 $Å^2$) less than 140 Å (Waterbeemd 2007; Ertl 2007). Consequently, it may be expected that the molecules should be transferred through the bacterial cells.

Antitubercular activity

Some excellent results from the antimicrobial studies encouraged us to go to the preliminary screening of the title compounds for their antitubercular activity. In vitro antitubercular activity of all the newly synthesized compounds was carried out against *M. tuberculosis* H37Rv strain by Loweinstein-Jensen (Rattan 2000) (L. J. slope) method (Rattan 2000) (See supplementary material) and the biological results are shown in (Table 2).

Of the compounds screened for antitubercular activity, eleven compounds were found to exhibit >90% inhibition of *M. tuberculosis* bacteria. Compounds **G22** (MIC = 12.5 μg/mL) and **G38** (MIC = 25 μg/mL) found to possess the highest potency against *M. tuberculosis* with 99% inhibition. These two compounds found to have fabulous activity as compared to rifampicin (MIC = 40 μg/mL). Compounds **G24** (MIC = 50 μg/mL); **G10** and **G40** (MIC = 62.5 μg/mL) exhibited better inhibition of 98%. Compounds **G20** (MIC = 62.5 μg/mL) and **G30** (MIC = 50 μg/mL) were found to have 97 and 96% inhibition of *M. tuberculosis* bacteria, respectively. Also, compounds **G3** (MIC = 62.5 μg/mL); **G14** and **G32** (MIC = 100 μg/mL); **G7** (MIC = 125 μg/mL) displayed moderate inhibition of 94, 93, 92, and 91%, respectively. Compounds **G22** and **G38** ($R_1 = CH_3$, $R_2 = CH_3$) were emerging out as the most potent member of the series and opens up a new door to optimize this series for new a class of antitubercular agents.

Structure–activity relationship (SAR) for antitubercular activity

Compounds **G38** and **G22** carrying $–CH_3$ group at R_1 and R_2 position and exhibited highest potency against MTB when compared with rifampicin. These molecules may be considered as good hits, in terms of MIC values, good lipophilicity (ClogP 4.48, 3.34) and PSA (69.72, 99.15 $Å^2$), respectively. Moreover, compounds **G24**, **G10** and **G40**, **G20** and **G30** bearing $R_1 = –Cl/–CH_3$ and long spacer length showed >95% inhibition. The order of antitubercular activity was found to be PHZ > INH > Bn > BHZ > Ph.

Antimalarial activity

In vitro antimalarial activity of all the newly synthesized compounds were carried out against *Plasmodium*

Table 2 In vitro antitubercular activity of title compounds at 250 µg/mL (% Inhibition and MIC, µg/mL)

Entry	*M. tuberculosis* (H37Rv)		ClogP[a]	PSA (Å^2)[a]	Entry	*M. tuberculosis* (H37Rv)		ClogP[a]	PSA (Å^2)[a]
	% Inhibition	MIC (µg/mL)				% Inhibition	MIC (µg/mL)		
G1	21	nd[b]	2.77	57.69	**G22**	99	12.5	4.48	69.72
G2	66	nd	3.27	57.69	**G23**	51	nd	4.15	78.95
G3	94	62.5	2.94	66.92	**G24**	98	50	4.79	69.72
G4	54	nd	3.58	57.69	**G25**	56	nd	2.61	86.79
G5	16	nd	3.81	57.69	**G26**	12	nd	3.11	86.79
G6	70	nd	4.31	57.69	**G27**	20	nd	2.77	96.02
G7	91	125	3.98	66.92	**G28**	38	nd	3.42	86.79
G8	46	nd	4.62	57.69	**G29**	16	nd	3.65	86.79
G9	54	nd	2.65	57.69	**G30**	96	50	4.15	86.79
G10	98	62.5	3.15	57.69	**G31**	61	nd	3.81	96.02
G11	45	nd	2.81	66.92	**G32**	92	100	4.45	86.79
G12	31	nd	3.45	57.69	**G33**	56	nd	1.80	99.15
G13	84	nd	3.69	57.69	**G34**	48	nd	2.30	99.15
G14	93	100	4.19	57.69	**G35**	32	nd	1.97	108.38
G15	63	nd	3.85	66.92	**G36**	24	nd	2.61	99.15
G16	23	nd	4.49	57.69	**G37**	46	nd	2.84	99.15
G17	12	nd	2.94	69.72	**G38**	99	25	3.34	99.15
G18	69	nd	3.44	69.72	**G39**	65	nd	3.00	108.38
G19	74	nd	3.11	78.95	**G40**	98	62.5	3.65	99.15
G20	97	62.5	3.75	69.72	**RIF**	98	40	–	–
G21	45	nd	3.98	69.72	**INH**	99	0.20	–	–

[a] CLogP and PSA (Polar surface area) calculated using the Chem Bio Draw Ultra, version 11.0, software by Cambridge Soft

[b] *nd* not determine, *RIF* Rifampicin, *INH* Isoniazid

falciparum (3D7) strain employing the microassay protocol of Rieckmann (1978), and the biological results are shown in (Table 3).

Of the compounds screened for antimalarial activity, thirteen compounds gave better results than the standard drugs employed. Compounds **G40** ($IC_{50} = 0.019$ µg/mL) elicited fabulous activity compared to chloroquine ($IC_{50} = 0.020$ µg/ml)and quinine ($IC_{50} = 0.268$ µg/ml). Compounds **G20** ($IC_{50} = 0.028$ µg/mL), **G31** ($IC_{50} = 0.042$ µg/mL), **G3** ($IC_{50} = 0.056$ µg/mL), **G32** ($IC_{50} = 0.068$ µg/mL), **G14** ($IC_{50} = 0.079$ µg/mL), **G9** ($IC_{50} = 0.081$ µg/mL), **G7** ($IC_{50} = 0.084$ µg/mL), **G24** ($IC_{50} = 0.089$ µg/mL), **G21** ($IC_{50} = 0.113$ µg/mL), **G28** ($IC_{50} = 0.135$ µg/mL), **G38** ($IC_{50} = 0.148$ µg/mL) and **G36** ($IC_{50} = 0.256$ µg/mL) displayed significant activity when compared with the quinine.

Structure–activity relationship (SAR) for antimalarial activity

Compounds **G40**, **G20**, **G32**, **G24**, **G28**, and **G36** carrying EWG -Cl demonstrated better inhibition of *P. falciparum* compared to quinine. The replacement of BHZ with INH at R_3 position improved the antiplasmodial characteristic by 3.5 fold. Moreover, hybrids possessed EDGs -CH_3 and –OCH_3, elicited good to moderate inhibitory action against *P. falciparum* e.g., **G31, G3, G14, G7**, and **G38**. Exceptionally, parent hybrids **G9** and **G21** displayed significant activity. Only compound **G40** showed marvelous efficacy than chloroquine and quinine. This derivative may be considered as a good hit. From the antimalarial activity data, it can be observed that the inhibitory action against *P. falciparum* is increased in the order of INH > PHZ > BHZ > Ph > Bn.

Conclusion

A diversity-oriented synthesis approach has been adopted for the synthesis of novel 3,4′-bicarbostyril library which yields skeletally diverse molecules and hence provide better explanations about SAR. The satisfactory biological activity results verify a proposed hypothesis of the present work. Compounds **G37**,**G8**, **G38**, and**G18** were found to be most efficient antibacterial members; while compounds **G16**,

Table 3 In vitro antimalarial activity of title compounds (IC_{50}, μg/mL)

Entry	*P. falciparum* (3D7) IC_{50} (μg/mL)	Entry	*P. falciparum* (3D7) IC_{50} (μg/mL)
G1	0.871	**G22**	1.159
G2	0.865	**G23**	0.454
G3	0.056	**G24**	0.089
G4	1.473	**G25**	1.104
G5	0.790	**G26**	1.207
G6	0.746	**G27**	0.830
G7	0.084	**G28**	0.135
G8	1.325	**G29**	1.401
G9	0.081	**G30**	1.546
G10	1.294	**G31**	0.042
G11	0.946	**G32**	0.068
G12	0.845	**G33**	0.428
G13	1.402	**G34**	1.477
G14	0.079	**G35**	1.322
G15	1.734	**G36**	0.256
G16	0.653	**G37**	0.650
G17	1.127	**G38**	0.148
G18	0.977	**G39**	0.891
G19	0.564	**G40**	0.019
G20	0.028	**CLQ**	0.020
G21	0.113	**QUIN**	0.268

CLQ chloroquine, *QUIN* quinine

G19, **G24**, **G36**, and **G40** were found to be excellent antifungal members of the library. Compounds **G22** and **G38** were found to be promising antitubercular members and compounds **G20** and **G40** found most remarkable antimalarial members of the series. The SAR results revealed that the EDG and EWG at R_1 position, lipophilic $-CH_3$ at R_2 position and flexibility and length of diverse spacers at the $N-1$ position of carbostyril take part in the enhancement of biological activities. Especially, compounds carrying $R_2 = CH_3$ and $R_3 =$ PHZ and INH showed marvelous potency and hence plays pivotal roles in the construction of a library containing 3,4′-bicarbostyril derivatives as potent antimicrobial, antitubercular and antimalarial agents. On the basis of activity data and drug-like physicochemical properties, we can say that the 3,4′-bicarbostyril derivatives can be potential leads for the further preclinical investigations.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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