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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

New *N*-arylamino biquinoline derivatives: microwave-assisted synthesis and their antimicrobial activities

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Abstract A new series of *N*-arylamino biquinoline derivatives **5a–x** were synthesized under microwave irradiation technique in good yields compared with conventional method and screened for their antimicrobial activity. All the synthesized compounds have been established by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. In vitro antimicrobial activity was carried out against three Gram-positive bacteria (*Bacillus subtilis*, *Clostridium tetani*, *Streptococcus pneumoniae*), three Gram-negative bacteria (*Escherichia coli*, *Salmonella typhi*, *Vibrio cholerae*) and two fungal species (*Aspergillus fumigatus*, *Candida albicans*) using broth microdilution method. Of the compounds studied, compound **5u** exhibited promising antimicrobial activity against *Streptococcus pneumoniae* and *Salmonella typhi*.

Keywords Quinoline · Microwave irradiation · MIC · Antimicrobial activity

Introduction

Emerging infectious diseases and the increasing number of multi-drug resistant microbial pathogens still make the treatment of infectious diseases an important and pressing global problem. Therefore, a substantial research for the discovery and synthesis of new classes of antimicrobial agents is needed (Kaplancıklı *et al.*, 2008).

Quinoline derivatives have received considerable attention because of their pivotal role in various biological processes, and numerous derivatives of quinolines have been reported to have wide biological activities (Charris *et al.*, 2005; Bava and Kumar 2009; Shi *et al.*, 2008; Naik *et al.*, 2009), including the antimycobacterial (De Souza *et al.*, 2009) and antimicrobial (Eswaran *et al.*, 2009) activity. Because of the biological activities they exhibit, these compounds have distinguished themselves as heterocycles of profound chemical and biological significance. Thus, the synthesis of these molecules has attracted considerable attention.

Various routes for the synthesis of N-substituted quinoline derivatives have been reported using two-component as well as three-component reactions. Gao *et al.* (2008) have reported fluoride ion catalyzed multicomponent reactions for synthesis of N-substituted quinoline derivatives in aqueous media. Wang *et al.* (2007) have carried out clean synthesis of 1,4-diarylquinoline derivatives catalyzed by TEBAC in aqueous media. They have also reported a three-component green synthesis in ionic liquid [Bmim^{+}][BF$_4^{-}$] and under microwave irradiation. However, the synthesis of new heterocyclic compounds containing the N-substituted quinoline scaffold and the development of more rapid and efficient entry to these heterocycles are strongly desired.

Literature survey reveals studies concerning N-substituted quinoline, e.g., Alqasoumi *et al.* (2009) have reported synthesis of some novel quinoline derivatives bearing a trimethoxyphenyl moiety. Ghorab *et al.* (2010) have reported anticancer activity of some new quinoline derivatives bearing a free sulfonamide moiety. Heravi *et al.* (2010) have carried out synthesis of indeno[1,2-*b*]-quinoline catalyzed by heteropolyacid. However, after extensive literature search, it was observed that till date enough efforts have not been made to synthesize *N*-arylamino biquinoline scaffold and to study its antimicrobial activity. Consequently, prompted from the findings described

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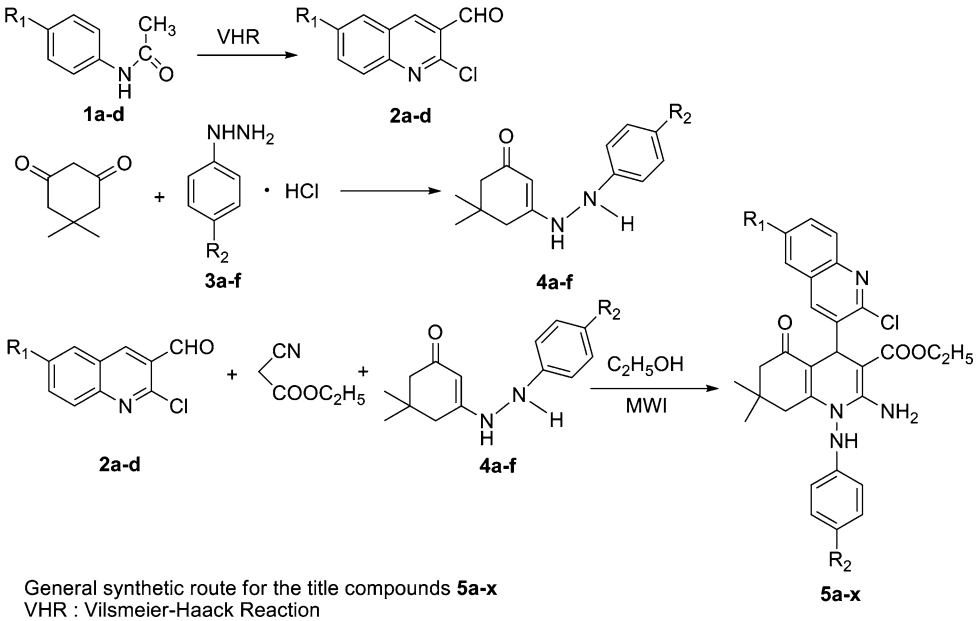
above, and as a part of our ongoing approach in developing new biologically active heterocycles containing quinoline (Shah *et al.*, 2011; Ladani et al. 2009a, b, 2010; Mungra et al. 2009, 2011; Nirmal *et al.*, 2009; Shah et al. 2009a, b; Makawana *et al.*, 2011; Thakor *et al.*, 2007; Thumar and Patel 2010), we here report synthesis and antimicrobial evaluation of some new *N*-arylamino biquinoline derivatives **5a–x** under microwave irradiation via Multi Component Reaction (MCR) approach.

Results and discussion

Chemistry

This study was undertaken to synthesize some new *N*-arylamino biquinoline derivatives and investigate their probable antimicrobial effects. The required 2-chloro-3-formyl quinoline **2a–d** was prepared by Vilsmeier-Haack reaction of acetanilide **1a–d** according to literature procedure (Meth-Cohn and Bramha 1978). The required enhydrazinoketones **4a–f** were prepared by the reaction of *β*-diketone with phenyl hydrazine according to literature procedure (Lichitsky *et al.* 2000).

In this work, a new series of *N*-arylamino biquinoline derivatives have been synthesized by one-pot three-component condensation reaction of 2-chloro-3-formyl quinolines **2a–d** with ethyl cyanoacetate and enhydrazinoketones **4a–f** in ethanol in the presence of piperidine as a catalyst both under conventional heating and microwave irradiation method. The *N*-arylamino quinoline **5a–x** were synthesized in ethanol as a solvent in conventional method, which took longer period for completion of reaction (3–3.5 h) with yields (60–78 %). The reactions



Scheme 1 General synthetic route for the title compounds **5a–x** VHR: Vilsmeier-Haack Reaction

General synthetic route for the title compounds **5a-x**
VHR : Vilsmeier-Haack Reaction

Compound	R_1	R_2	Compound	R_1	R_2
5a	H	H	**5m**	H	F
5b	CH_3	H	**5n**	CH_3	F
5c	OCH_3	H	**5o**	OCH_3	F
5d	Cl	H	**5p**	Cl	F
5e	H	Cl	**5q**	H	OCH_3
5f	CH_3	Cl	**5r**	CH_3	OCH_3
5g	OCH_3	Cl	**5s**	OCH_3	OCH_3
5h	Cl	Cl	**5t**	Cl	OCH_3
5i	H	CH_3	**5u**	H	Br
5j	CH_3	CH_3	**5v**	CH_3	Br
5k	OCH_3	CH_3	**5w**	OCH_3	Br
5l	Cl	CH_3	**5x**	Cl	Br

Table 1 Comparative study between microwave-assisted and conventional method for the synthesis of *N*-arylamino biquinoline derivatives **5a**–**x** in terms of yield and time

Compd.	Microwave		Conventional	
	Time (min)	Yield[a] %	Time (min)	Yield[a] %
5a	3	86	180	74
5b	3.5	81	190	67
5c	3.5	78	220	71
5d	3	83	180	75
5e	3	81	185	78
5f	4	77	200	70
5g	5	80	210	78
5h	3	78	190	62
5i	4.5	73	210	65
5j	5	72	200	69
5k	6	76	240	71
5l	3.5	81	200	73
5m	4	79	195	78
5n	4.5	77	200	73
5o	5	71	185	60
5p	4	73	215	62
5q	3.5	72	200	71
5r	3	74	190	70
5s	4	79	200	63
5t	4 5	83	185	79
5u	3	81	180	68
5v	3.5	84	185	77
5w	3.5	81	220	75
5x	3	87	180	71

[a] Isolated yield

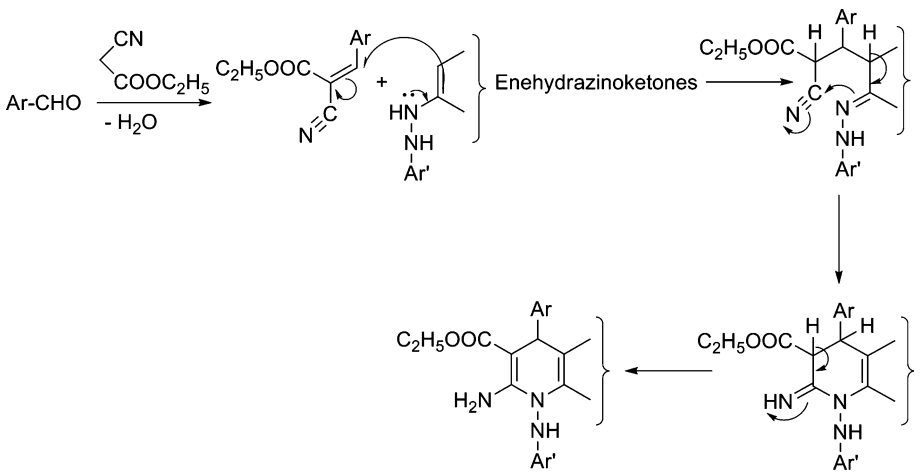
when carried out under microwave irradiation were completed within 3–6 min with substantial increase in yield of products (86 %).

To explore conditions of the reaction of 2-chloro-3-formyl quinolines **2a**–**d** with ethyl cyanoacetate and enhydrazinoketones **4a**–**f** in ethanol (Scheme 1) under MW, various reaction conditions were investigated, including solvent and base. To search for the optimal reaction solvent, the reaction was examined in ethylene glycol, DMF, glacial acetic acid and ethanol, respectively under MW at the maximum power of 350 Watt. The reaction in ethanol resulted in higher yields and shorter reaction time than others. So ethanol was chosen as the appropriate solvent. Furthermore, to further improve the reaction yields, different bases were examined for their ability to promote this reaction. The base piperidine afforded the target product **5a** in 86 % yield. Therefore, piperidine was chosen as the most suitable base for all further microwave-assisted reactions. A comparative study of all the compounds synthesized by conventional method and microwave method are provided in a Table 1.

A possible mechanism for the reaction is outlined in Scheme 2. The reaction occurs via an in situ initial formation of the heterylidenenitrile, containing the electron-poor C=C double bond, from the Knoevenagel condensation between 2-chloro-3-formyl quinolines **2a**–**d** and ethyl cyanoacetate by loss of water molecules. Michael addition of enhydrazinoketones **4a**–**f** to the ylidenic bond is forming an acyclic intermediate that cyclizes by nucleophilic attack of the NH group on the cyano carbon, followed by tautomerisation to the final products **5a–x**.

The structures of the obtained compounds were fully characterized by ^{1}H NMR, ^{13}C NMR and FT-IR spectral data and molecular weight of some selected compounds confirmed by mass spectrometry. ^{1}H NMR (DMSO-d_6) spectrum of *N*-arylamino biquinoline derivatives **5a**–**x** exhibited a singlet around δ 5.22–5.28 for methine (H4) and 8.91–9.20 ppm for –NH– proton, respectively. The

Scheme 2 Plausible mechanistic pathway of the synthesis of *N*-arylamino biquinoline derivatives



^{13}C NMR spectrum of **5a** is in good agreement with the structure assigned. The peaks at δ 14.78, 26.80 and 29.52 ppm are assigned to three methyl carbons, the peaks at δ 38.09 and 49.73 ppm are assigned to two methylene carbons. The peak at δ 77.29 ppm is assigned to carbon of carboxylate, peaks at δ 169.02 and 195.05 ppm are assigned to two carbonyl carbons. All compounds gave satisfactory elemental analyses. Mass spectra of the compound **5a** and **5h** showed $[M + H]^+$ peaks in agreement with their exact mass or molecular weight. All spectroscopic data have been given in experimental section.

Antimicrobial activity

All the glass apparatus used were sterilized before use. The MICs of all the synthesized compounds was carried out by broth microdilution method (NCCLS 2002). Mueller–Hinton broth was used as nutrient medium to grow and dilute the compound suspension for the test bacteria, and Sabouraud Dextrose broth was used for fungal nutrition. Inoculum size for test strain was adjusted to 10^8 colony forming unit (CFU) per milliliter by comparing the turbidity. The strains used for the activity were procured from (MTCC—microbial type culture collection) Institute of Microbial Technology, Chandigarh. DMSO was used as diluent to get desired concentration of compounds to test on standard bacterial strains. Serial dilutions were prepared in primary and secondary screening. The control tube containing no antibiotic was immediately subcultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37 °C overnight. The tubes were then incubated overnight. The MIC of the control organism was read to check the accuracy of the compound concentrations. The lowest concentration inhibiting growth of the organism was recorded as the MIC. All the tubes not showing visible growth (in the same manner as control tube described above) was subcultured and incubated overnight at 37 °C. The amount of growth from the control tube before incubation (which represents the original inoculum) was compared. Subcultures might show similar number of colonies indicating bacteriostatic; a reduced number of colonies indicating a partial or slow bactericidal activity and no growth if the whole inoculum has been killed. The test must include a second set of the same dilutions inoculated with an organism of known sensitivity. Each synthesized compound was diluted to 2,000 μg/mL concentration, as a stock solution. In primary screening, 500, 250 and 125 μg/mL concentrations of the synthesized compounds were taken. The active synthesized compounds found in this primary screening were further tested in a second set of dilution against all microorganisms. The compounds found active in primary screening were similarly diluted to obtain 200, 100, 50, 25, 12.5, 6.250, 3.125 and 1.5625 μg/mL concentrations. The highest dilution showing at least 99 % inhibition is taken as MIC. The protocols were summarized in Table 2.

Screening results displayed that compounds **5a–x** exhibited good-to-moderate activity for all the bacterial strains, compared with other standard drugs. An examination of the data (Table 1) reveals that against Gram-positive pathogen *Streptococcus pneumoniae*, compounds **5d** and **5k–l** (MIC 100 μg/ml) were found to exhibit comparable activity to ampicillin (MIC 100 μg/ml). Compound **5u** (MIC 25 μg/ml) possessed pronounced activity against *S. pneumoniae* compared with ampicillin (MIC 100 μg/ml), chloramphenicol (MIC 50 μg/ml) and ciprofloxacin (MIC 50 μg/ml). Compounds **5a**, **5c–e**, **5k**, **5m–o** and **5x** (MIC 200 μg/ml) show good activity compared with ampicillin (MIC 250 μg/ml) towards *Bacillus subtilis*. The compound **5v** (MIC 100 μg/ml) found equally potent, to norfloxacin (MIC 100 μg/ml) against *B. subtilis*. The compounds **5d–f**, **5k**, **5m–n**, **5q** and **5w** (MIC $<$ 250 μg/ml) found to be more efficient against *Clostridium tetani* compared with ampicillin (MIC 250 μg/ml). The compounds **5n** and **5q** (MIC 100 μg/ml) were found to exhibit comparable activity to ciprofloxacin (MIC 100 μg/ml) towards *C. tetani*. Towards Gram-negative strain, *Salmonella typhi*, compounds **5g**, **5m**, **5r** and **5x** (MIC 100 μg/ml) were found equally active to ampicillin (MIC 100 μg/ml), whereas compounds **5k** (MIC 62.5 μg/ml) and **5u** (MIC 50 μg/ml) were found more potent to ampicillin (MIC 100 μg/ml). Compound **5u** (MIC 50 μg/ml) was also found equally active to chloramphenicol (MIC 50 μg/ml) towards *S. typhi*. The compounds **5b**, **5d** and **5n** (MIC 100 μg/ml) were found equipotent than ampicillin (MIC 100 μg/ml) against *Vibrio cholerae*. The compounds **5a** (MIC 50 μg/ml), **5f** (MIC 62.5 μg/ml) and **5q** (MIC 50 μg/ml) show better and **5b**, **5g**, **5m–n** and **5u** (MIC 100 μg/ml) were equally active to ampicillin (MIC 100 μg/ml) towards *E. coli*. Against fungal pathogen *C. albicans*, compounds **5a**, **5l–m**, **5n** and **5q–r** were found to have better activity, whereas **5b**, **5f–g**, **5k**, **5v** and **5x** were found to be equipotent compared with Griseofulvin. Rest of the compounds showed less activity against all the microorganisms tested.

A close examination of the structures of the active compounds in Table 2 revealed that, substituents at the quinoline-C_6, together with the substituent linked to the arylamino part of the structure influence the antimicrobial activities. Thus, in the case of *C. tetani*, compounds with R_1 = H/CH_3/OCH_3/Cl and R_2 = Cl/F/CH_3 showed good activity, whereas analogs with R_1 = H/CH_3 and R_2 = H/CH_3/Br lacked any activity against the same organism. However, the same trend is not observed for the other bacterial strains. Compound **5u** without a substituent in the

Table 2 Antimicrobial activity of the compounds **5a–x**

Compounds	Minimum inhibitory concentration (MIC, μg/mL)							
	Gram-positive bacteria			Gram-negative bacteria			Fungi	
	S.P. MTCC 1936	C.T. MTCC 449	B.S. MTCC 441	S.T. MTCC 98	V.C. MTCC 3906	E.C. MTCC 443	A.F. MTCC 3008	C.A. MTCC 227
5a	200	500	**200**	200	500	**50**	>1000	**250**
5b	250	500	500	250	**100**	100	>1000	**500**
5c	200	**250**	**200**	250	250	250	>1000	>1000
5d	**100**	**200**	**200**	250	**100**	125	250	1000
5e	200	**125**	**200**	250	250	200	250	1000
5f	500	**200**	500	200	250	**62.5**	>1000	**500**
5g	250	**250**	**250**	**100**	250	**100**	>1000	**500**
5h	500	**250**	500	250	250	250	500	1000
5i	250	500	500	250	**125**	250	>1000	>1000
5j	250	500	**250**	500	500	250	>1000	1000
5k	**100**	**125**	**200**	**62.5**	500	125	>1000	**500**
5l	**100**	500	**250**	500	500	500	>1000	**250**
5m	200	**200**	**200**	**100**	**200**	**100**	500	**250**
5n	200	**100**	**200**	200	**100**	**100**	>1000	**100**
5o	250	**250**	**200**	200	250	125	>1000	1000
5p	500	**250**	500	250	500	200	>1000	1000
5q	200	**100**	**250**	200	200	**50**	500	**250**
5r	125	**250**	**250**	**100**	250	250	500	**250**
5s	250	**250**	**250**	200	250	200	500	1000
5t	500	**250**	500	250	250	250	>1000	1000
5u	**25**	500	**250**	**50**	500	**100**	>1000	>1000
5v	250	500	**100**	500	500	500	1000	**500**
5w	250	**200**	**250**	200	200	200	500	>1000
5x	200	**250**	**200**	**100**	250	200	1000	500
Ampicillin	100	250	250	100	100	100	–	–
Chloramphencol	50	50	50	50	50	50	–	–
Ciprofloxacin	50	100	50	25	25	25	–	–
Gentamicin	0.5	5	1	5	5	0.05	–	–
Norfloxacin	10	50	100	10	10	10	–	–
Griseofulvin	–	–	–	–	–	–	100	500
Nystatin	–	–	–	–	–	–	100	100

E.C. *Escherichia coli*, S.T. *Salmonella typhi*, V.C. *Vibrio* cholerae, A.F. *Aspergillus fumigatus*, C.A. *Candida albicans*

Bold entries indicate that the compounds are found equipotent or more potent compared to the standard drugs used

quinoline-C_6 and arylamino ring containing a bromo substituent shows greater activity against *S. pneumonia* and *S. typhi* compared with the other compounds studied. Introduction of a methyl/methoxy/chlorine atom to the structure as in compounds **5v**, **5w** and **5x** resulted in reduction in the antibacterial activity against both the organism. Replacement of the bromo substituent on arylamino ring with H/Cl/CH_3/F/OCH_3 (compounds **5a**, **5e**, **5i**, **5m** and **5q**) also decreased antibacterial potency against both the organism. On the same grounds, the analogs **5a** without a substituent in the quinoline-C_6 and arylamino ring and compound **5q** without a substituent in the quinoline-C_6 and arylamino ring containing a methoxy substituent are the most active compounds against *E. coli*. It is worthy to mention that the biological activity of the target compounds depends not only on the bicyclic heteroaromatic pharmacophore but also on the nature of the substituents and may also on their spatial relationships.

Experimental

All the reagents were obtained commercially and used with further purification. Solvents used were of analytical grade.

All melting points were taken in open capillaries and are uncorrected. Thin-layer chromatography (TLC, on aluminium plates coated with silica gel 60 F_{254}, 0.25-mm thickness, Merck) was used for monitoring the progress of all reactions, purity and homogeneity of the synthesized compounds. Elemental analysis (% C, H, N) was carried out by Perkin-Elmer 2400 series-II elemental analyzer and all compounds are within ±0.4 % of theory specified. The IR spectra were recorded on a Shimadzu FTIR 8401 spectrophotometer using KBr discs and only the characteristic peaks are reported in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker Avance 400F (MHz) spectrometer using solvent peak as internal standard at 400 and 100 MHz, respectively. Chemical shifts are reported in parts per million (ppm). Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer. Mode of ionization employed was ESI (electrospray ionization). The microwave oven used was specially modified by RAGA's Electromagnetic systems.

General procedure for the synthesis of ethyl 2-amino-4-(2-chloro-6-(un)substituted (3-quinolyl))-7,7-dimehyl-5-oxo-1-arylamino-1,4,6,7,8,-pentahydro quinoline-3-carboxylate

Conventional synthesis

2-Chloro-3-formyl quinoline **2a**–**d** (1 mmol), ethyl cyanoacetate (1 mmol) and enhydrazinoketones **4a**–**f** (1 mmol) in absolute ethanol containing catalytic amount of piperidine were charged in round bottom flask. Then, the reaction mixture was refluxed for 3–3.5 h. The completion of reaction was monitored by the TLC. The solid product **5a**–**x** separated was filtered off and purified using chloroform–methanol.

Microwave-induced synthesis

2-Chloro-3-formyl quinoline **2a**–**d** (1 mmol), ethyl cyanoacetate (1 mmol) and enhydrazinoketones **4a**–**f** (1 mmol) in absolute ethanol containing catalytic amount of piperidine were charged in round bottom flask. The mixture was irradiated for 3–6 min at power of 350 W. On completion of the reaction as indicated by TLC monitoring, the reaction mixture was cooled to room temperature. The solid product **5a**–**x** was filtered and washed with EtOH (95 %), and subsequently dried and purified using chloroform–methanol. The physicochemical and spectral properties of all the newly synthesized compounds **5a**–**x** are presented below.

Ethyl 2-amino-4-(2-chloro(3-quinolyl))-7,7-dimethyl-5-oxo-1-phenylamino-1,4,6,7,8-pentahydro quinoline 3-carboxylate (**5a**): yield 86 %, m.p. 269–271 °C, Anal. Calcd. for $C_{29}H_{29}ClN_4O_3$ (517.02 g/mol): C 67.37, H 5.65, N 10.84 % Found: C 67.51, H 5.47, N 10.76 %. IR (KBr, cm^{-1}): 3360 and 3250 (asym. and sym. stretching of $-NH_2$), 1660 (C=O), 1640 (C=O), 750 (C–Cl). ^1H NMR (400 MHz, DMSO-d_6): δ 0.82 (s, 3H, CH_3), 0.96 (t, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.87–2.75 (m, 4H, 2 × CH_2), 3.90 (q, 2H, OCH_2), 5.26 (s, 1H, quinoline H4), 6.87–8.25 (m, 12H, Ar–H and NH_2), 8.97 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.78 (CH_3), 26.80, 29.52 (2C, CH_3), 32.01 ($\underline{C}(CH_3)_2$), 34.22 (C4), 38.09 (CH_2), 49.73 ($\underline{C}H_2$–CO), 58.75 (OCH_2), 77.29 ($\underline{C}$–COOEt), 112.67, 113.65, 120.51, 127.72, 127.90, 130.02, 130.11, 130.30, 138.57, 145.78, 147.11, 147.50, 150.61, 151.22, 153.70, 154.24 (16C, Ar–C), 169.02 (C=OOC_2H_5), 195.05 (C=O), MS: 517.2 $[M + H]^+$, 519.2 $[M + 2+H]^+$.

Ethyl 2-amino-4-(2-chloro-6-methyl(3-quinolyl))-7,7-dimethyl-5-oxo-1-phenylamino-1,4,6,7,8-pentahydro quinoline-3-carboxylate (**5b**): yield 81 %, m.p. 241–243 °C, Anal. Calcd. for $C_{30}H_{31}ClN_4O_3$ (531.05 g/mol): C 67.85, H 5.88, N 10.55 % Found: C 68.03, H 5.63, N 10.41 %. IR (KBr, cm^{-1}): 3400 and 3355 (asym. and sym. str. of $-NH_2$), 1665 (C=O), 1640 (C=O), 750 (C–Cl). ^1H NMR (400 MHz, DMSO-d_6): δ 0.84 (s, 3H, CH_3), 0.97 (t, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.83–2.73 (m, 4H, 2 × CH_2), 2.46 (s, 3H, Ar–CH_3), 3.93 (q, 2H, OCH_2), 5.28 (s, 1H, quinoline H4), 6.96–8.29 (m, 11H, Ar–H and NH_2), 8.99 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.76 (CH_3), 21.58 (Ar–CH_3), 26.84, 29.25 (2C, CH_3), 32.12 ($\underline{C}(CH_3)_2$), 34.68 (C4), 38.05 (CH_2), 49.84 ($\underline{C}H_2$–CO), 58.91 (OCH_2), 77.57 ($\underline{C}$–COOEt), 112.27, 113.81, 120.12, 126.42, 126.95, 127.32, 130.02, 131.36, 132.55, 134.72, 138.26. 142.46, 144.26, 148.73, 150.38, 154.31 (16C, Ar–C), 168.94 (C=OOC_2H_5), 195.08 (C=O), MS: 531.2 $[M + H]^+$, 533.2 $[M + 2+H]^+$.

Ethyl 2-amino-4-(2-chloro-6-methoxy(3-quinolyl))-7,7-dimethyl-5-oxo-1-phenylamino-1,4,6,7,8,-pentahydro quinoline-3-carboxylate (**5c**): yield 78 %, m.p. 257–259 °C, Anal. Calcd. for $C_{30}H_{31}ClN_4O_4$ (547.04 g/mol): C 65.87, H 5.71, N 10.24 % Found: C 65.73, H 5.82, N 10.38 %. IR (KBr, cm^{-1}): 3395 and 3360 (asym. and sym. str. of $-NH_2$), 1665 (C=O), 1645 (C=O), 745 (C–Cl). ^1H NMR (400 MHz, DMSO-d_6): δ 0.82 (s, 3H, CH_3), 0.98 (t, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.87–2.77 (m, 4H, 2 × CH_2), 3.86 (s, 3H, Ar–OCH_3), 3.92 (q, 2H, OCH_2), 5.22 (s, 1H, quinoline H4), 6.71–8.14 (m, 11H, Ar–H and NH_2), 8.95 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.80 (CH_3), 27.01, 29.45 (2C, CH_3), 32.01 ($\underline{C}(CH_3)_2$), 34.12 (C4), 38.10 (CH_2), 49.77 ($\underline{C}H_2$–CO), 55.95 (OCH_3), 58.72 (OCH_2), 77.35 ($\underline{C}$–COOEt), 105.63, 112.87, 113.54, 120.52, 122.69, 128.48, 129.71, 130.01, 141.75, 147.14, 147.48, 148.02, 153.67, 154.10, 154.50, 157.92 (16C, Ar–C), 169.04 (C=OOC_2H_5), 194.99 (C=O), MS: 547.2 $[M + H]^+$, 549.2 $[M + 2+H]^+$.

Ethyl 2-amino-4-(2,6-dichloro(3-quinolyl))-7,7-dimethyl-5-oxo-1-phenylamino-1,4,6,7,8,-pentahydro quinoline-3-carboxylate (**5d**): yield 83 %, m.p. 219–221 °C, Anal. Calcd. for $C_{29}H_{28}Cl_2N_4O_3$ (551.46 g/mole): C 63.16, H 5.12, N 10.16 % Found: C 63.29, H 4.94, N 10.30 %. IR (KBr, cm^{-1}): 3410 and 3350 (asym. and sym. str. of $–NH_2$), 1660 (C=O), 1645 (C=O), 755 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.83 (s, 3H, CH_3), 0.95 (t, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.88–2.73 (m, 4H, m, 2 × CH_2), 3.92 (q, 2H, OCH_2), 5.25 (s, 1H, quinoline H4), 6.93–8.24 (m, 11H, Ar–H and NH_2), 8.94 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.76 (CH_3), 27.03, 29.46 (2C, CH_3), 32.03 ($\underline{C}(CH_3)_2$), 34.12 (C4), 38.02 (CH_2), 49.72 ($\underline{C}H_2$–CO), 58.74 (OCH_2), 77.23 ($\underline{C}$–COOEt), 112.14, 113.41, 120.26, 126.48, 128.20, 129.78, 130.52, 131.23, 134.06, 144.42, 147.23, 147.66, 151.39, 153.62, 154.11, 154.56 (16C, Ar–C), 168.98 (C=OOC_2H_5), 195.52 (C=O), MS: 551.2 $[M + H]^+$, 553.2 $[M + 2+H]^+$, 555.2 $[M + 4+H]^+$.

Ethyl 2-amino-4-(2-chloro-(3-quinolyl))-7,7-dimethyl-5-oxo-1-(4-chlorophenylamino)-1,4,6,7,8-pentahydro quinoline-3-carboxylate (**5e**): yield 81 %, m.p. 233–235 °C, Anal. Calcd. for $C_{29}H_{28}Cl_2N_4O_3$ (551.46 g/mole): C 63.16, H 5.12, N 10.16 % Found: C 63.03, H 5.01, N 10.33 %. IR (KBr, cm^{-1}): 3455 and 3370 (asym. and sym. str. of $–NH_2$), 1665 (C=O), 1640 (C=O), 740 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.84 (s, 3H, CH_3), 0.96 (t, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.88–2.76 (m, 4H, 2 × CH_2), 3.89 (q, 2H, q, OCH_2), 5.24 (s, 1H, quinoline H4), 6.84–8.22 (m, 11H, Ar–H and NH_2), 9.00 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.79 (CH_3), 26.95, 29.42 (2C, CH_3), 32.02 ($\underline{C}(CH_3)_2$), 34.16 (C4), 37.98 (CH_2), 49.74 ($\underline{C}H_2$–CO), 58.77 (OCH_2), 77.32 ($\underline{C}$–COOEt), 111.32, 113.47, 120.44, 126.14, 127.69, 128.28, 129.46, 130.78, 131.70, 134.28, 144.34, 147.16, 151.61, 153.36, 154.08, 154.54 (16C, Ar–C), 168.78 (C=OOC_2H_5), 195.24 (C=O), MS: 551.2 $[M + H]^+$, 553.2 $[M + 2+H]^+$, 555.2 $[M + 4+H]^+$.

Ethyl 2-amino-4-(2-chloro-6-methyl(3-quinolyl))-7,7-dimethyl-5-oxo-1-(4-chlorophenylamino)-1,4,6,7,8-pentahydro quinoline-3-carboxylate (**5f**): yield 77 %, m.p. 281–283 °C, Anal. Calcd. for $C_{30}H_{30}Cl_2N_4O_3$ (565.49 g/mole): C 63.72, H 5.35, N 9.91 % Found: C 63.87, H 5.21, N 10.05 %. IR (KBr, cm^{-1}): 3460 and 3350 (asym. and sym. str. of $–NH_2$), 1655 (C=O), 1640 (C=O), 760 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.86 (s, 3H, CH_3), 0.96 (t, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.87–2.74 (m, 4H, 2 × CH_2), 2.48 (s, 3H, Ar–CH_3), 3.92 (q, 2H, OCH_2), 5.23 (s, 1H, quinoline H4), 6.66–8.13 (m, 10H, Ar–H and NH_2), 9.20 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.76 (CH_3), 21.51 (Ar–CH_3), 26.99, 29.44 (2C, CH_3), 32.06 ($\underline{C}(CH_3)_2$), 34.19 (C4), 37.93 (CH_2), 49.71 ($\underline{C}H_2$–CO), 58.78 (OCH_2), 77.47 ($\underline{C}$–COOEt), 111.57, 113.68, 120.33, 126.07, 126.47, 127.46, 131.77, 132.46, 134.43, 138.02, 141.63, 144.42, 149.03, 150.14, 153.31, 154.18 (16C, Ar–C), 169.03 (C=OOC_2H_5), 194.98 (C=O), MS: 565.2 $[M + H]^+$, 567.2 $[M + 2+H]^+$, 569.2 $[M + 4+H]^+$.

Ethyl 2-amino-4-(2-chloro-6-methoxy(3-quinolyl))-7,7-dimethyl-5-oxo-1-(4-chlorophenylamino)-1,4,6,7,8-pentahydro quinoline-3-carboxylate (**5g**): yield 80 %, m.p. 263–265 °C, Anal. Calcd. for $C_{30}H_{30}Cl_2N_4O_4$ (581.49 g/mole): C 61.97, H 5.20, N 9.64 % Found: C 62.09, H 5.29, N 9.49 %. IR (KBr, cm^{-1}): 3395 and 3335 (asym. and sym. str. of $–NH_2$), 1665 (C=O), 1640 (C=O), 750 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.84 (s, 3H, CH_3), 0.97 (t, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.86–2.75 (m, 4H, 2 × CH_2), 3.87 (s, 3H, Ar–OCH_3), 3.92 (q, 2H, OCH_2), 5.26 (s, 1H, quinoline H4), 6.69–8.16 (m, 10H, Ar–H and NH_2), 8.95 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.78 (CH_3), 27.01, 29.42 (2C, CH_3), 32.04 ($\underline{C}(CH_3)_2$), 34.48 (C4), 38.06 (CH_2), 49.83 ($\underline{C}H_2$–CO), 55.59 (Ar–OCH_3), 58.79 (OCH_2), 77.59 ($\underline{C}$–COOEt), 105.27, 112.16, 113.63, 122.31, 128.72, 129.40, 130.51, 134.19, 138.88, 141.02, 145.36, 149.20, 150.42, 154.25, 154.73, 157.69 (16C, Ar–C), 169.07 (C=OOC_2H_5), 194.68 (C=O), MS: 581.1 $[M + H]^+$, 583.2 $[M + 2+H]^+$, 585.2 $[M + 4+H]^+$.

Ethyl 2-amino-4-(2,6-dichloro(3-quinolyl))-7,7-dimethyl-5-oxo-1-(4-chlorophenylamino)-1,4,6,7,8-pentahydro quinoline-3-carboxylate (**5h**): yield 78 %, m.p. 250–252 °C, Anal. Calcd. for $C_{29}H_{27}Cl_3N_4O_3$ (585.91 g/mole): C 59.45, H 4.64, N 9.56 % Found: C 59.57, H 4.53, N 9.71 %. IR (KBr, cm^{-1}): 3450 and 3250 (asym. and sym. stretching of $–NH_2$), 1660 (C=O), 1630 (C=O), 740 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.83 (s, 3H, CH_3), 0.96 (t, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.88–2.71 (m, 4H, 2 × CH_2), 3.89 (q, 2H, OCH_2), 5.24 (s, 1H, quinoline H4), 6.91–8.29 (m, 10H, Ar–H and NH_2), 9.18 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.77 (CH_3), 27.05, 29.40 (2C, CH_3), 32.05 ($\underline{C}(CH_3)_2$), 34.76 (C4), 37.94 (CH_2), 49.68 ($\underline{C}H_2$–CO), 58.80 (OCH_2), 76.90 ($\underline{C}$–COOEt), 111.71, 113.19, 120.10, 126.25, 126.62, 128.13, 129.84, 130.83, 131.70, 134.46, 144.18, 148.67, 151.64, 153.65, 154.05, 154.30 (16C, Ar–C), 168.91 (C=OOC_2H_5), 195.14 (C=O), MS: 585.1 $[M + H]^+$, 587.2 $[M + 2+H]^+$, 589.2 $[M + 4+H]^+$, 591.2 $[M + 6+H]^+$.

Ethyl 2-amino-4-(2-chloro-(3-quinolyl))-7,7-dimethyl-5-oxo-1-(4-methylphenylamino)-1,4,6,7,8-pentahydro quinoline-3-carboxylate (**5i**): yield 73 %, m.p. 220–222 °C, Anal. Calcd. for $C_{30}H_{31}ClN_4O_3$ (531.05 g/mole): C 67.85, H 5.88, N 10.55 % Found: C 68.04, H 5.97, N 10.36 %. IR (KBr, cm^{-1}): 3420 and 3330 (asym. and sym. str. of $–NH_2$), 1670 (C=O), 1640 (C=O), 765 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.85 (s, 3H, CH_3), 0.97 (t, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.87–2.75 (m, 4H, 2 × CH_2), 2.47

(s, 3H, Ar–CH_3), 3.91 (q, 2H, OCH_2), 5.26 (s, 1H, quinoline H4), 6.79–8.19 (m, 11H, Ar–H and NH_2), 9.10 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.78 (CH_3), 21.28 (Ar–CH_3), 26.93, 29.17 (2C, CH_3), 32.03 ($\underline{C}(CH_3)_2$), 34.37 (C4), 38.04 (CH_2), 49.81 ($\underline{C}H_2$–CO), 58.47 (OCH_2), 77.08 ($\underline{C}$–COOEt), 111.65, 113.24, 120.42. 126.39, 126.67, 128.18, 130.55, 131.31, 138.78, 144.34, 147.42, 148.59, 150.43, 153.12, 154.78, 157.05 (16C, Ar–C), 169.05 (C=OOC_2H_5), 194.93 (C=O), MS: 531.2 $[M + H]^+$, 533.2 $[M + 2+H]^+$.

Ethyl 2-amino-4-(2-chloro-6-methyl(3-quinolyl))-7,7-dimethyl-5-oxo-1-(4-methylphenylamino)-1,4,6,7,8-pentahydro quinoline-3-carboxylate (**5j**): yield 72 %, m.p. 244–246 °C, Anal. Calcd. for $C_{31}H_{33}ClN_4O_3$ (545.07 g/mole): C 68.31, H 6.10, N 10.28 % Found: C 68.14, H 5.99, N 10.12 %. IR (KBr, cm^{-1}): 3440 and 3350 (asym. and sym. str. of –NH_2), 1665 (C=O), 1645 (C=O), 745 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.87 (s, 3H, CH_3), 0.96 (t, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.85–2.75 (m, 4H, 2 × CH_2), 2.45 (s, 3H, Ar–CH_3), 2.47 (s, 3H, Ar–CH_3), 3.90 (q, 2H, OCH_2), 5.23 (s, 1H, quinoline H4), 6.73–8.16 (m, 10H, Ar–H and NH_2), 9.14 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.76 (CH_3), 21.33 (Ar–CH_3), 21.54 (Ar–CH_3), 27.04, 29.38 (2C, CH_3), 32.06 ($\underline{C}(CH_3)_2$), 34.53 (C4), 37.98 (CH_2), 49.63 ($\underline{C}H_2$–CO), 58.67 (OCH_2), 77.21 ($\underline{C}$–COOEt), 112.05, 113.42, 125.52, 126.34, 128.73, 130.06, 131.27. 132.65, 134.88, 138.35, 141.22, 144.61, 147.13, 150.01, 153.56, 154.23 (16C, Ar–C), 168.88 (C=OOC_2H_5), 194.97 (C=O), MS: 545.2 $[M + H]^+$, 547.2 $[M + 2+H]^+$.

Ethyl 2-amino-4-(2-chloro-6-methoxy(3-quinolyl))-7,7-dimethyl-5-oxo-1-(4-methylphenylamino)-1,4,6,7,8-pentahydro quinoline-3-carboxylate (**5k**): yield 76 %, m.p. 207–209 °C, Anal. Calcd. for $C_{31}H_{33}ClN_4O_4$ (561.07 g/mole): C 66.36, H 5.93, N 9.99 % Found: C 66.50, H 6.09, N 10.16 %. IR (KBr, cm^{-1}): 3430 and 3355 (asym. and sym. str. of –NH_2), 1660 (C=O), 1640 (C=O), 740 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.88 (s, 3H, CH_3), 0.95 (t, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.84–2.76 (m, 4H, 2 × CH_2), 2.45 (s, 3H, Ar–CH_3), 3.87 (s, 3H, Ar–OCH_3), 3.89 (q, 2H, OCH_2), 5.25 (s, 1H, quinoline H4), 6.73–8.18 (m, 10H, Ar–H and NH_2), 9.11 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.72 (CH_3), 21.25 (Ar–CH_3), 27.02, 29.09 (2C, CH_3), 32.01 ($\underline{C}(CH_3)_2$), 34.32 (C4), 38.06 (CH_2), 49.79 ($\underline{C}H_2$–CO), 55.16 (Ar–OCH_3), 58.64 (OCH_2), 77.08 ($\underline{C}$–COOEt), 105.77, 111.75, 113.21, 120.69, 128.25, 129.41, 130.52, 131.54, 134.11, 138.74, 141.03, 144.52, 147.25, 148.35, 154.85, 157.12 (16C, Ar–C), 168.23 (C=OOC_2H_5), 194.87 (C=O), MS: 561.2 $[M + H]^+$, 563.2 $[M + 2+H]^+$.

Ethyl 2-amino-4-(2,6-dichloro(3-quinolyl))-7,7-dimethyl-5-oxo-1-(4-methylphenylamino)-1,4,6,7,8-pentahydro quinoline-3-carboxylate (**5l**): yield 81 %, m.p. 268–270 °C, Anal. Calcd. for $C_{30}H_{30}Cl_2N_4O_3$ (565.49 g/mole): C 63.72, H 5.35, N 9.91 % Found: C 63.91, H 5.60, N 9.67 %. IR (KBr, cm^{-1}): 3435 and 3360 (asym. and sym. str. of –NH_2), 1660 (C=O), 1645 (C=O), 765 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.89 (s, 3H, CH_3), 0.97 (t, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.86–2.77 (m, 4H, 2 × CH_2), 2.44 (s, 3H, Ar–CH_3), 3.91 (q, 2H, OCH_2), 5.23 (s, 1H, quinoline H4), 6.76–8.28 (m, 10H, Ar–H and NH_2), 9.03 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.75 (CH_3), 21.22 (Ar–CH_3), 26.95, 29.07 (2C, CH_3), 32.05 ($\underline{C}(CH_3)_2$), 34.42 (C4), 38.10 (CH_2), 49.73 ($\underline{C}H_2$–CO), 58.78 (OCH_2), 77.36 ($\underline{C}$–COOEt), 111.65, 113.24, 122.25, 127.54, 128.64, 130.15, 131.27, 134.57, 135.65, 143.74, 145.70, 148.06, 150.86, 153.29, 154.37, 154.93 (16C, Ar–C), 168.64 (C=OOC_2H_5), 195.07 (C=O), MS: 565.2 $[M + H]^+$, 567.2 $[M + 2+H]^+$, 569.2 $[M + 4+H]^+$.

Ethyl 2-amino-4-(2-chloro-(3-quinolyl))-7,7-dimethyl-5-oxo-1-(4-fluorophenylamino)-1,4,6,7,8-pentahydro quinoline-3-carboxylate (**5m**): yield 79 %, m.p. 228–230 °C, Anal. Calcd. for $C_{29}H_{28}ClFN_4O_3$ (535.01 g/mole): C 65.10, H 5.28, N 10.47 % Found: C 64.94, H 5.40, N 10.63 %. IR (KBr, cm^{-1}): 3430 and 3325 (asym. and sym. str. of –NH_2), 1665 (C=O), 1640 (C=O), 745 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.87 (s, 3H, CH_3), 0.95 (t, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.84–2.75 (m, 4H, 2 × CH_2), 3.98 (q, 2H, OCH_2), 5.27 (s, 1H, quinoline H4), 6.74–8.29 (m, 11H, Ar–H and NH_2), 9.13 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.77 (CH_3), 27.06, 29.22 (2C, CH_3), 32.10 ($\underline{C}(CH_3)_2$), 34.28 (C4), 38.10 (CH_2), 49.81 ($\underline{C}H_2$–CO), 58.62 (OCH_2), 77.47 ($\underline{C}$–COOEt), 111.34, 113.65, 119.75, 120.54, 127.25, 127.88, 130.05, 130.27, 138.43, 145.60, 147.35, 147.86, 150.24, 153.11, 154.52, 157.34 (16C, Ar–C), 168.25 (C=OOC_2H_5), 194.85 (C=O), MS: 535.2 $[M + H]^+$, 537.2 $[M + 2+H]^+$.

Ethyl 2-amino-4-(2-chloro–6-methyl(3-quinolyl))-7,7-dimethyl-5-oxo-1-(4-fluorophenylamino)-1,4,6,7,8-pentahydro quinoline-3-carboxylate (**5n**): yield 77 %, m.p. 284–286 °C, Anal. Calcd. for $C_{30}H_{30}ClFN_4O_3$ (549.04 g/mole): C 65.63, H 5.51, N 10.20 % Found: C 65.31, H 5.28, N 10.42 %. IR (KBr, cm^{-1}): 3390 and 3320 (asym. and sym. str. of –NH_2), 1670 (C=O), 1645 (C=O), 750 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.86 (s, 3H, CH_3), 0.96 (t, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.82–2.75 (m, 4H, 2 × CH_2), 2.44 (s, 3H, Ar–CH_3), 3.95 (q, 2H, OCH_2), 5.22 (s, 1H, quinoline H4), 6.76–8.19 (m, 10H, Ar–H and NH_2), 9.16 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.72 (CH_3), 21.43 (Ar–CH_3), 26.92, 29.04 (2C, CH_3), 32.06 ($\underline{C}(CH_3)_2$), 34.25 (C4), 38.01 (CH_2), 49.77 ($\underline{C}H_2$–CO), 58.59 (OCH_2), 77.53 ($\underline{C}$–COOEt), 112.07, 113.56, 118.92, 126.16, 126.41, 127.68, 131.05, 132.63, 134.66, 138.52, 141.21, 144.35, 148.12, 150.32, 154.88, 157.02 (16C, Ar–C), 169.12 (C=OOC_2H_5), 194.89 (C=O), MS: 549.2 $[M + H]^+$, 551.2 $[M + 2+H]^+$.

Ethyl 2-amino-4-(2-chloro–6-methoxy(3-quinolyl))-7,7-dimethyl-5-oxo-1-(4-fluorophenylamino)-1,4,6,7,8-pentahydro quinoline-3-carboxylate (**5o**): yield 71 %, m.p. 245–247 °C, Anal. Calcd. for $C_{30}H_{30}ClFN_4O_4$ (565.04 g/mole): C 63.77, H 5.35, N 9.92 % Found: C 63.92, H 5.59, N 9.65 %. IR (KBr, cm^{-1}): 3380 and 3345 (asym. and sym. str. of $–NH_2$), 1665 (C=O), 1645 (C=O), 765 (C–Cl). ^1H NMR (400 MHz, DMSO-d_6): δ 0.87 (s, 3H, CH_3), 0.97 (t, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.84–2.77 (m, 4H, 2 × CH_2), 3.87 (s, 3H, Ar–OCH_3), 3.91 (q, 2H, OCH_2), 5.27 (s, 1H, quinoline H4), 6.79–8.23 (m, 10H, Ar–H and NH_2), 8.98 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.78 (CH_3), 26.96, 29.09 (2C, CH_3), 32.08 ($\underline{C}(CH_3)_2$), 34.33 (C4), 38.07 (CH_2), 49.88 ($\underline{C}H_2$–CO), 55.82 (OCH_3), 58.69 (OCH_2), 77.57 ($\underline{C}$–COOEt), 105.24, 111.25, 113.64, 118.12, 122.57, 128.37, 130.28, 134.78, 138.22, 141.85, 144.02, 147.58, 148.75, 154.17, 157.02, 157.34 (16C, Ar–C), 168.92 (C=OOC_2H_5), 194.78 (C=O), MS: 565.2 $[M + H]^+$, 567.2 $[M + 2+H]^+$.

Ethyl 2-amino-4-(2,6-dichloro(3-quinolyl))-7,7-dimethyl-5-oxo-1-(4-fluorophenylamino)-1,4,6,7,8-pentahydro quinoline-3-carboxylate (**5p**): yield 73 %, m.p. 261–263 °C, Anal. Calcd. for $C_{29}H_{27}Cl_2FN_4O_3$ (569.45 g/mole): C 61.17, H 4.78, N 9.84 % Found: C 61.40, H 4.54, N 9.61 %. IR (KBr, cm^{-1}): 3400 and 3350 (asym. and sym. str. of $–NH_2$), 1675 (C=O), 1640 (C=O), 750 (C–Cl). ^1H NMR (400 MHz, DMSO-d_6): δ 0.89 (s, 3H, CH_3), 0.96 (t, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.86–2.76 (m, 4H, 2 × CH_2), 3.93 (q, 2H, OCH_2), 5.26 (s, 1H, quinoline H4), 6.89–8.27 (m, 10H, Ar–H and NH_2), 8.91 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.77 (CH_3), 27.00, 29.03 (2C, CH_3), 32.02 ($\underline{C}(CH_3)_2$), 34.49 (C4), 37.98 (CH_2), 49.61 ($\underline{C}H_2$–CO), 58.74 (OCH_2), 77.75 ($\underline{C}$–COOEt), 112.09, 113.21, 120.25, 124.11, 126.87, 129.52, 130.67, 131.44, 134.62, 135.33, 141.35, 144.71, 148.31, 151.41, 154.34, 156.59 (16C, Ar–C), 169.02 (C=OOC_2H_5), 195.18 (C=O), MS: 569.2 $[M + H]^+$, 571.2 $[M + 2+H]^+$, 573.2 $[M + 4+H]^+$.

Ethyl 2-amino-4-(2-chloro-(3-quinolyl))-7,7-dimethyl-5-oxo-1-(4-methoxyphenylamino)-1,4,6,7,8-pentahydro quinoline-3-carboxylate (**5q**): yield 72 %, m.p. 273–275 °C, Anal. Calcd. for $C_{30}H_{31}ClN_4O_4$ (547.04 g/mole): C 65.87, H 5.71, N 10.24 % Found: C 66.07, H 5.96, N 9.96 %. IR (KBr, cm^{-1}): 3430 and 3340 (asym. and sym. str. of $–NH_2$), 1670 (C=O), 1645 (C=O), 760 (C–Cl). ^1H NMR (400 MHz, DMSO-d_6): δ 0.88 (s, 3H, CH_3), 0.96 (t, 3H, CH_3), 0.99 (s, 3H, CH_3) 1.86–2.77 (m, 4H, 2 × CH_2), 3.89 (s, 3H, Ar–OCH_3), 3.95 (q, 2H, OCH_2), 5.27 (s, 1H, quinoline H4), 6.84–8.23 (m, 11H, Ar–H and NH_2), 9.09 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.72 (CH_3), 26.92, 29.01 (2C, CH_3), 32.05 ($\underline{C}(CH_3)_2$), 34.27 (C4), 38.01 (CH_2), 49.55 ($\underline{C}H_2$–CO), 55.80 (OCH_3), 58.79 (OCH_2), 77.50 ($\underline{C}$–COOEt), 111.88, 113.15, 120.44, 127.26, 127.83, 128.22, 130.02, 130.11, 131.54, 138.36, 141.58, 147.43, 147.51, 150.61, 153.24, 154.85 (16C, Ar–C), 168.90 (C=OOC_2H_5), 194.88 (C=O), MS: 547.2 $[M + H]^+$, 549.2 $[M + 2+H]^+$.

Ethyl 2-amino-4-(2-chloro-6-methyl(3-quinolyl))-7,7-dimethyl-5-oxo-1-(4-methoxyphenylamino)-1,4,6,7,8-pentahydro quinoline-3-carboxylate (**5r**): yield 74 %, m.p. 231–233 °C, Anal. Calcd. for $C_{31}H_{33}ClN_4O_4$ (561.07 g/mole): C 66.36, H 5.93, N 9.99 % Found: C 66.11, H 5.71, N 10.24 %. IR (KBr, cm^{-1}): 3395 and 3320 (asym. and sym. str. of $–NH_2$), 1665 (C=O), 1640 (C=O), 760 (C–Cl). ^1H NMR (400 MHz, DMSO-d_6): δ 0.89 (s, 3H, CH_3), 0.95 (t, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.87–2.75 (m, 4H, 2 × CH_2), 2.47 (s, 3H, Ar–CH_3), 3.89 (s, 3H, Ar–OCH_3), 3.97 (q, 2H, OCH_2), 5.22 (s, 1H, quinoline H4), 6.89–8.29 (m, 10H, Ar–H and NH_2), 9.16 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.79 (CH_3), 21.47 (Ar–CH_3), 26.96, 28.03 (2C, CH_3), 32.08 ($\underline{C}(CH_3)_2$), 34.64 (C4), 37.98 (CH_2), 49.72 ($\underline{C}H_2$–CO), 55.73 (OCH_3), 58.70 (OCH_2), 77.22 ($\underline{C}$–COOEt), 112.08, 113.45, 118.21, 126.45, 127.14, 127.85, 130.20, 132.55, 134.64, 138.46, 141.31, 144.26, 149.75, 150.43, 153.25, 154.46 (16C, Ar–C), 168.92 (C=OOC_2H_5), 195.03 (C=O), MS: 561.2 $[M + H]^+$, 563.2 $[M + 2+H]^+$.

Ethyl 2-amino-4-(2-chloro-6-methoxy(3-quinolyl))-7,7-dimethyl-5-oxo-1-(4-methoxyphenylamino)-1,4,6,7,8-pentahydro quinoline-3-carboxylate (**5s**): yield 79 %, m.p. 210–212 °C, Anal. Calcd. for $C_{31}H_{33}ClN_4O_5$ (577.07 g/mole): C 64.52, H 5.76, N 9.71 % Found: C 64.79, H 5.43, N 10.46 %. IR (KBr, cm^{-1}): 3430 and 3365 (asym. and sym. str. of $–NH_2$), 1665 (C=O), 1640 (C=O), 755 (C–Cl). ^1H NMR (400 MHz, DMSO-d_6): δ 0.85 (s, 3H, CH_3), 0.96 (t, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.86–2.77 (m, 4H, 2 × CH_2), 3.84 (s, 3H, Ar–OCH_3), 3.88 (s, 3H, Ar–OCH_3), 3.95 (q, 2H, OCH_2), 5.25 (s, 1H, quinoline H4), 6.90–8.28 (m, 10H, Ar–H and NH_2), 9.09 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.73 (CH_3), 26.92, 28.07 (2C, CH_3), 32.05 ($\underline{C}(CH_3)_2$), 34.55 (C4), 37.91 (CH_2), 49.84 ($\underline{C}H_2$–CO), 55.73 (Ar–OCH_3), 55.78 (Ar–OCH_3), 58.72 (OCH_2), 77.46 ($\underline{C}$–COOEt), 105.25, 111.68, 113.61, 118.41, 122.42, 129.38, 130.29, 134.62, 138.33, 140.28, 141.25, 147.46, 148.53, 153.12, 154.65, 157.49 (16C, Ar–C), 169.01 (C=OOC_2H_5), 194.91 (C=O), MS: 577.2 $[M + H]^+$, 579.2 $[M + 2+H]^+$.

Ethyl 2-amino-4-(2,6-dichloro(3-quinolyl))-7,7-dimethyl-5-oxo-1-(4- methoxyphenylamino)-1,4,6,7,8-pentahydro quinoline-3-carboxylate (**5t**): yield 83 %, m.p. 247–249 °C, Anal. Calcd. for $C_{30}H_{30}Cl_2N_4O_4$ (581.49 g/mole): C 61.97, H 5.20, N 9.64 % Found: C 62.27, H 5.38, N 9.49 %. IR (KBr, cm^{-1}): 3450 and 3370 (asym. and sym. str. of $–NH_2$), 1675 (C=O), 1645 (C=O), 745 (C–Cl). ^1H NMR (400 MHz, DMSO-d_6): δ 0.83 (s, 3H, CH_3), 0.97 (t, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.85–2.77 (m, 4H, 2 × CH_2),

3.84 (s, 3H, Ar–OCH_3), 3.99 (q, 2H, OCH_2), 5.28 (s, 1H, quinoline H4), 6.93–8.29 (m, 10H, Ar–H and NH_2), 9.13 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.71 (CH_3), 26.99, 28.05 (2C, CH_3), 32.01 ($\underline{C}(CH_3)_2$), 34.28 (C4), 37.95 (CH_2), 49.89 ($\underline{C}H_2$–CO), 55.75 (Ar–OCH_3), 58.76 (OCH_2), 77.35 ($\underline{C}$–COOEt), 111.20, 113.35, 118.41, 126.32, 126.83, 127.06, 130.25, 131.64, 134.79, 135.27, 140.02, 144.15, 148.61, 151.46, 153.74, 154.85 (16C, Ar–C), 168.97 (C=OOC_2H_5), 194.96 (C=O), MS: 581.2 $[M + H]^+$, 583.2 $[M + 2+H]^+$, 585.2 $[M + 4+H]^+$.

Ethyl 2-amino-4-(2-chloro-(3-quinolyl))-7,7-dimethyl-5-oxo-1-(4-bromophenylamino)-1,4,6,7,8-pentahydro quinoline-3-carboxylate (**5u**): yield 81 %, m.p. 266–268 °C, Anal. Calcd. for $C_{29}H_{28}BrClN_4O_3$ (595.91 g/mole): C 58.45, H 4.74, N 9.40 % Found: C 58.16, H 4.42, N 9.63 %. IR (KBr, cm^{-1}): 3440 and 3385 (asym. and sym. str. of –NH_2), 1660 (C=O), 1640 (C=O), 770 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.87 (s, 3H, CH_3), 0.95 (t, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.83–2.74 (m, 4H, 2 × CH_2), 3.91 (q, 2H, OCH_2), 5.26 (s, 1H, quinoline H4), 6.87–8.23 (m, 11H, Ar–H and NH_2), 9.16 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.77 (CH_3), 26.92, 28.01 (2C, CH_3), 32.04 ($\underline{C}(CH_3)_2$), 34.52 (C4), 37.90 (CH_2), 49.67 ($\underline{C}H_2$–CO), 58.72 (OCH_2), 77.51 ($\underline{C}$–COOEt), 111.39, 113.47, 120.12, 124.03, 127.08, 127.56, 130.20, 130.87, 131.45, 134.75, 138.43, 145.21, 145.88, 147.63, 150.14, 154.57 (16C, Ar–C), 169.01 (C=OOC_2H_5), 194.93 (C=O), MS: 595.1 $[M + H]^+$, 597.1 $[M + 2+H]^+$, 599.2 $[M + 4+H]^+$.

Ethyl 2-amino-4-(2-chloro-6-methyl(3-quinolyl))-7,7-dimethyl-5-oxo-1-(4-bromophenylamino)-1,4,6,7,8-pentahydro quinoline-3-carboxylate (**5v**): yield 84 %, m.p. 203–205 °C, Anal. Calcd. for $C_{30}H_{30}BrClN_4O_3$ (609.94 g/mole): C 59.07, H 4.96, N 9.19 % Found: C 59.22, H 5.27, N 9.01 %. IR (KBr, cm^{-1}): 3385 and 3340 (asym. and sym. str. of –NH_2), 1665 (C=O), 1640 (C=O), 750 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.89 (s, 3H, CH_3), 0.97 (t, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.85–2.76 (m, 4H, 2 × CH_2), 2.48 (s, 3H, Ar–CH_3), 3.95 (q, 2H, OCH_2), 5.24 (s, 1H, quinoline H4), 6.77–8.25 (m, 10H, Ar–H and NH_2), 9.06 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.74 (CH_3), 21.43 (Ar–CH_3), 26.99, 28.07 (2C, CH_3), 32.05 ($\underline{C}(CH_3)_2$), 34.71 (C4), 37.95 (CH_2), 49.85 ($\underline{C}H_2$–CO), 58.75 (OCH_2), 77.44 ($\underline{C}$–COOEt), 111.54, 113.70, 120.04, 126.21, 126.93, 127.42, 131.02, 132.65, 134.24, 138.66, 141.88, 144.52, 148.23, 150.03, 153.41, 154.33 (16C, Ar–C), 169.10 (C=OOC_2H_5), 194.95 (C=O), MS: 609.1 $[M + H]^+$, 611.1 $[M + 2+H]^+$, 613.1 $[M + 4+H]^+$.

Ethyl 2-amino-4-(2-chloro-6-methoxy(3-quinolyl))-7,7-dimethyl-5-oxo-1-(4-bromophenylamino)-1,4,6,7,8-pentahydro quinoline-3-carboxylate (**5w**): yield 81 %, m.p. 255–257 °C, Anal. Calcd. for $C_{30}H_{30}BrClN_4O_4$ (625.94 g/mole): C 57.56, H 4.83, N 8.95 % Found: C 57.79, H 5.07, N 9.11 %. IR (KBr, cm^{-1}): 3430 and 3365 (asym. and sym. str. of –NH_2), 1660 (C=O), 1645 (C=O), 765 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.87 (s, 3H, CH_3), 0.96 (t, 3H, CH_3), 1.00 (s, 3H, CH_3), 1.86–2.77 (m, 4H, 2 × CH_2), 3.82 (s, 3H, Ar–OCH_3), 3.94 (q, 2H, OCH_2), 5.23 (s, 1H, quinoline H4), 6.75–8.27 (m, 10H, Ar–H and NH_2), 9.10 (s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.77 (CH_3), 26.95, 28.05 (2C, CH_3), 32.07 ($\underline{C}(CH_3)_2$), 34.40 (C4), 37.90 (CH_2), 49.89 ($\underline{C}H_2$–CO), 55.75 (Ar–OCH_3), 58.71 (OCH_2), 77.31 ($\underline{C}$–COOEt), 105.28, 112.20, 113.64, 120.37, 122.46, 128.74, 129.14, 130.55, 135.24, 137.37, 141.62, 146.37, 147.16, 148.18, 152.22, 157.63 (16C, Ar–C), 169.02 (C=OOC_2H_5), 195.09 (C=O), MS: 625.1 $[M + H]^+$, 627.1 $[M + 2+H]^+$, 629.1 $[M + 4+H]^+$.

Ethyl 2-amino-4-(2,6-dichloro(3-quinolyl))-7,7-dimethyl-5-oxo-1-(4-bromophenylamino)-1,4,6,7,8-pentahydro quinoline-3-carboxylate (**5x**): yield 87 %, m.p. 273–275 °C, Anal. Calcd. for $C_{29}H_{27}BrCl_2N_4O_3$ (630.36 g/mole): C 55.26, H 4.32, N 8.89 % Found: C 54.98, H 4.64, N 9.01 %. IR (KBr, cm^{-1}): 3440 and 3360 (asym. and sym. str. of –NH_2), 1670 (C=O), 1645 (C=O), 755 (C–Cl). ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.89 (s, 3H, CH_3), 0.97 (t, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.85–2.77 (m, 4H, 2 × CH_2), 3.98 (q, 2H, OCH_2), 5.25 (s, 1H, quinoline H4), 6.79–8.21 (m, 10H, Ar–H and NH_2), 9.15 (s,1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.77 (CH_3), 26.94, 28.07 (2C, CH_3), 32.04 ($\underline{C}(CH_3)_2$), 34.28 (C4), 37.92 (CH_2), 49.71 ($\underline{C}H_2$–CO), 58.75 (OCH_2), 77.51 ($\underline{C}$–COOEt), 111.41, 113.75, 120.01, 126.41, 127.05, 128.14, 129.25, 130.44, 131.61, 132.08, 134.34, 135.20, 144.52, 148.26, 151.23, 154.77 (16C, Ar–C), 169.00 (C=OOC_2H_5), 194.99 (C=O), MS: 629.1 $[M + H]^+$, 631.1 $[M + 2+H]^+$, 633.1 $[M + 4+H]^+$.

Conclusions

In conclusion, we have developed an efficient procedure for the synthesis of *N*-arylamino biquinoline derivatives, which are often encountered in molecules of biologically active compounds. Particularly, valuable features of this method achieved by both microwave irradiation and conventional heating include high yields, broad substrate scope and convenient operation. The antimicrobial results revealed that numbers of compounds were found to be the most active against *C. tetani* and *B. subtilis* compared with rest of the employed species. Among all the compounds, **5a**, **5f** and **5q** exhibited good inhibition against *E. coli*. Compounds **5k** and **5u** showed superior activity against *S. typhi*. Compound **5u** also exhibited excellent activity against *S. pneumoniae*. Antifungal activity of the compounds shows that many compounds are found to be potent against *C. albicans.* Finally, these compounds represent

new structure scaffolds that could be further optimized for future development of more potent and selective antimicrobial agents.

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