Synthesis of New 1,3,4-Oxadiazol, Thiadiazole, 1,2,4-Triazole, and Arylidene Hydrazide Derivatives of 4-Oxo-1,4-dihydroquinoline with Antimicrobial Evaluation

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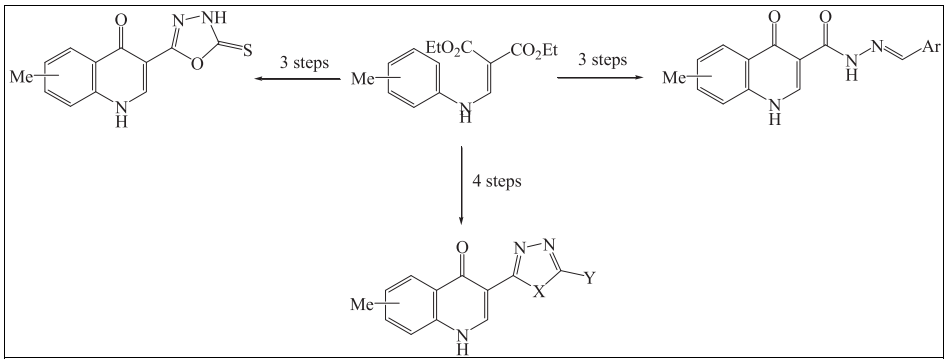
Received January 18, 2011
DOI 10.1002/jhet.1005
Published online 2 April 2013 in Wiley Online Library (wileyonlinelibrary.com).



A series of substituted 1,3,4-oxadiazole, 1,2,4-triazole, and 1,3,4-thiadiazole derivatives of the substituted 3-carboethoxy-1,4-dihydro-4-oxoquinoline have been synthesized through the reaction of the key intermediate thiosemicarbazide derivatives with different reagents. *N′*-Arylidene-4-oxo-1,4-dihydroquinoline-3-carbohydrazides were also synthesized through the condensation reaction of the corresponding hydrazides with the appropriate aldehydes. Antimicrobial activity of some of the synthesized compounds was evaluated.

J. Heterocyclic Chem., **50**, E1 (2013).

INTRODUCTION

Quinoline derivatives represent the major class of heterocycles, and a number of preparations have been known since the late 1800s. The quinoline ring system occurs in various natural products, especially in alkaloids. The quinoline skeleton is often used for the design of many synthetic compounds with diverse pharmacological properties [1]. Despite its relatively low efficacy and tolerability, quinine still plays an important role in the treatment of multiresistant malaria [2]. Nalidixic acid 1-ethyl-7-methyl-4-oxo-[1,8] naphthyridine-3-carboxylic acid was developed as an antibacterial for the treatment of urinary tract infections [3]. The presence of quinoline nucleus in the framework of various pharmacologically active compounds with antiasthmatic [4], antibacterial [5], antifungal [6], antimalarial [7], antiviral [8], antitumor [9], and anti-inflammatory [10] activities continues to promote their synthetic efforts. In addition, the hydrazones derived from the α-(*N*)-acetylquinolines inhibited *in vitro* antitumor activity, and other related compounds were effective inhibitors of leukemia, colon, and ovarian cancer cells [11]. The novel quinoline-quinone streptonigrin is an antitumor antibiotic that has activity against a broad range of tumors [12]. Furthermore, their synthesis is performed in the ordinary organic solvent. On the other hand, it has been reported that certain compounds bearing 1,3,4-oxa-, thiadiazole, and 1,2,4-triazole nuclei possess significant anti-inflammatory activity [13–22]. Recently, some 1,2,4-triazole derivatives incorporating Shiff base structure were synthesized as antitumor agents [23]. In view of these facts and in continuation of our research program on the synthesis of new heterocyclic compounds to shed some light on their biological studies [24–32], we report herein the synthesis of some newer heterocyclic systems containing 1,2,4-triazoles, 1,3,4-oxadiazoles, 1,3,4-thiadiazoles, and arylidene hydrazides linked with 3-carboethoxy-1,4-dihydro-4-oxoquinoline.

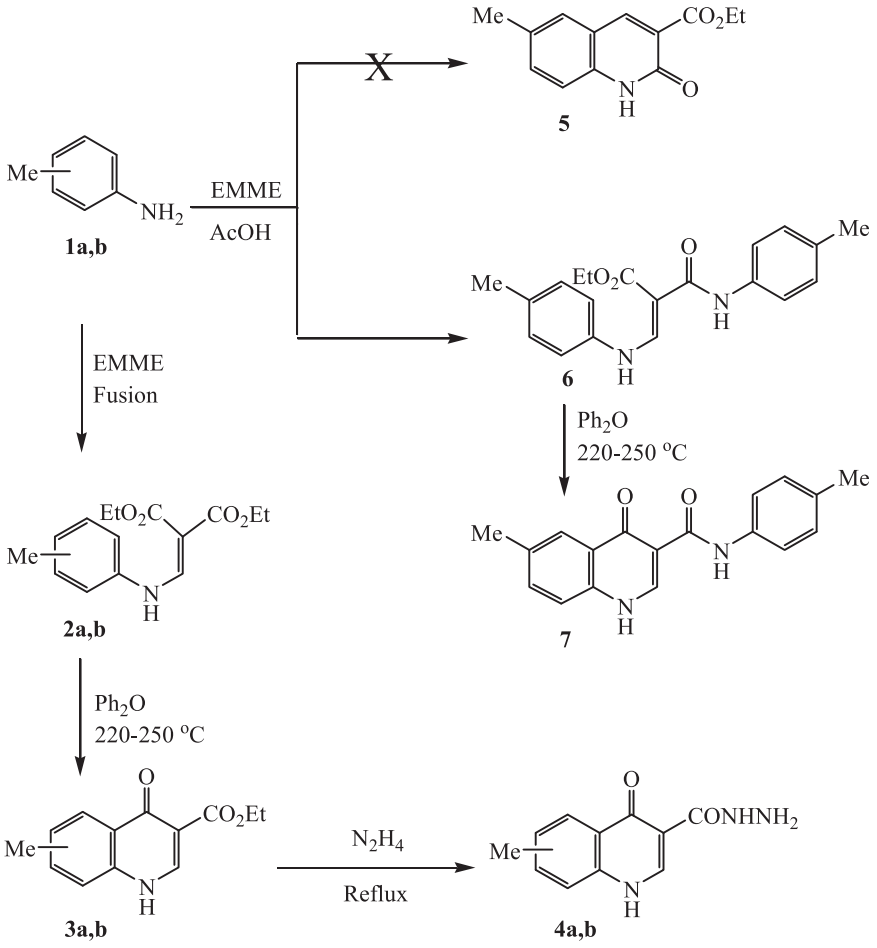
RESULTS AND DISCUSSION

The starting materials quinolone derivatives **3a**,**b** were synthesized by the treatment of commercially available *o*-toluidines and *p*-toluidines with diethyl ethoxymethylene malonate (EMME), according to the reported method [33], to afford diethyl methylanilinomethylenemalonates **2a**,**b**, which were then subjected to cyclization in refluxing diphenylether affording 3-carboethoxy-8-methyl-1,4-dihydro-4-oxoquinoline (**3a**) and 3-carboethoxy-6-methyl-1,4-dihydro-4-oxoquinoline (**3b**) in 90% and 80% yields, respectively. The respective hydrazides **4a**,**b** were obtained by refluxing quinolone esters **3a**,**b** with hydrazine in ethanol. Their IR spectra showed a characteristic C═O absorption at 1642–1669 cm^{-1}, and their ^1H NMR spectra agree with the structures that showed a characteristic broad band

for NHNH_2 at δ 4.58 and 4.56 ppm for **4a** and **4b**, respectively. On the other hand, treating of **1b** with EMME in AcOH at reflux temperature afforded ethyl 3-[(4-methylphenyl)amino]-2-{[(4-methylphenyl)amino]carbonyl}acrylate (**6**), and the expected product **5**, according to the report of Anderson [34], was not obtained at all on the basis of the spectral data. The structural assignment of **6** is based on ^{1}H NMR spectroscopy and its conversion to 6-methyl-*N*-(4-methylphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide (**7**) through its thermal cyclization in refluxing diphenyl ether. The ^{1}H NMR spectrum of **6** revealed two singlet signals at δ 2.24 and 2.26 ppm corresponding to the two methyl groups of tolyl groups, a triplet at δ 1.39 and quartet at 4.31 ppm indicating the presence of only one ester group, a doublet at δ 8.55 indicative of the vinylic proton (Hβ) adjacent to NH, a singlet at δ 12.31 corresponding to the CONH, and a doublet at δ 10.88 ppm, indicative of the typical NH adjacent to the vinylic proton. Also, the structural assignment of **7** is based on its ^{1}H NMR spectrum, which revealed the disappearance of the ethyl group and the presence of a singlet at δ 2.24 and 2.29 ppm corresponding to the two methyl groups. Besides, the MS spectrum revealed the molecular ion peak at 292, indicating the molecular weight of the derivative **7** (Scheme 1).

On treatment of hydrazides **4a**,**b** with phenyl isothiocyanate in absolute ethanol, under reflux, the thiosemicarbazide derivatives **8a**,**b** were obtained in 88% and 89% yields, respectively. The latter thiosemicarbazides **8a**,**b** showed a characteristic absorption band for C═S at 1193–1153 cm^{-1}. Oxidative cyclization of **8a**,**b** by elimination of H_2S using I_2 and KI in ethanolic NaOH afforded 3-[2-phenylamino-1,3,4-oxadiazoles]-8 and/or 6-methylquinoline-4(1*H*)-one (**9a**,**b**), respectively. The ^{1}H NMR spectra of compounds **9a**,**b** showed a singlet at δ 10.55 and 10.56 ppm for N*H*Ph proton and a broad singlet at δ 12.41 and 11.76 ppm for the NH of quinoline. On heating

Scheme 1



1-4	1a	1b	2a	2b	3a	3b	4a	4b
Me	*O*	*P*	*O*	*P*	8-	6-	8-	6-

of **8a**,**b** with 2*N* NaOH in ethanol, they underwent smooth cyclization through dehydration to afford (4,5-dihydro-4-phenyl-5-thioxo-1*H*-1,2,4-triazol-3-yl)-8-methylquinolin-4(1*H*)-one and/or (4,5-dihydro-4-phenyl-5-thioxo-1*H*-1,2,4-triazol-3-yl)-6-methylquinolin-4(1*H*)-one (**10a**,**b**), respectively. Their ^{1}H NMR spectra showed a singlet at δ 11.05–12.97 ppm for the NH groups. 3-[5-Phenylamino-1,3,4-thiadiazole]-8-methylquinoline-4(1*H*)-one and/or 3-[5-phenylamino-1,3,4-thiadiazole]-6-methylquinoline-4(1*H*)-one (**11a**,**b**) were obtained by cyclization of **8a**,**b** after its treatment with cold concentrated H_2SO_4. The IR data of compounds **11a**,**b** showed carbonyl frequencies at 1631–1635 cm^{-1} and a broad NH absorption in the region 3336–3366 cm^{-1}. Their ^{1}H NMR spectra showed broad singlets at δ 10.65 and 10.66 ppm corresponding to the N*H*Ph proton (Scheme 2).

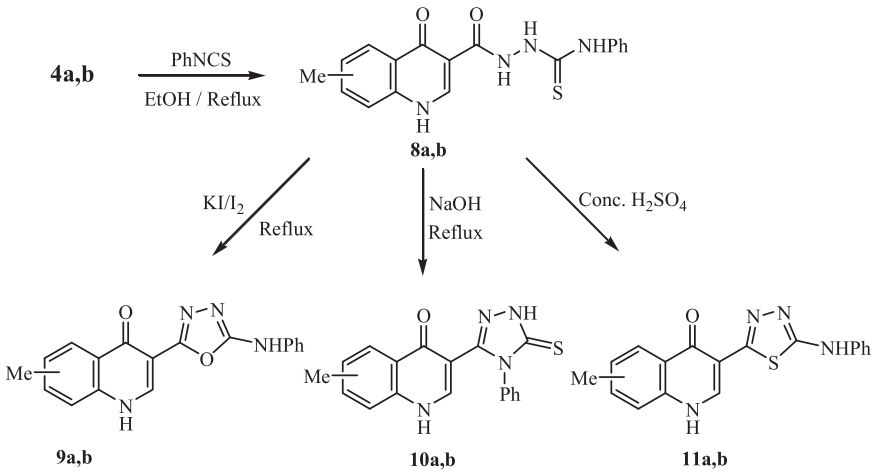
Reaction of the hydrazides **4a**,**b** with CS_2 in alcoholic KOH at reflux temperature afforded the corresponding substituted oxadiazole derivatives **12a**,**b**. The ^{1}H NMR spectra showed a broad singlet at δ 11.68–13.49 ppm for the NH groups. Treatment of the acid hydrazides **4a**,**b** with CS_2 in the presence of alc. KOH solution at room temperature gave the crude potassium salts **13a**,**b**. Their cyclization upon treatment with equivalent amount of $N_2H_4.H_2O$ at reflux temperature afforded 3-(4-amino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-8-methylquinolin-4(1*H*)-one and/or 3-(4-amino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)-6-methylquinolin-4(1*H*)-one (**14a**,**b**) after neutralization by 3*N* HCl. The ^{1}H NMR spectra of the substituted 1,2,4-triazoles **14a**,**b** showed broad singlets at δ 5.80 and 5.90 ppm corresponding to the NH_2 and a singlet at δ 10.68–13.58 ppm for the NH groups. Also, the acid hydrazides **4a**,**b** were condensed with different aldehydes under reflux to afford the corresponding arylidene carbohydrazide derivatives **15a–d**. In the ^{1}H NMR and ^{13}C NMR spectra of compounds **15a–d**, the signals corresponding to benzylidene group were observed at aromatic region, whereas the signals of the –NH_2 disappeared. Additionally, the ^{1}H NMR spectra confirmed the presence of N=CH proton in the range δ 8.67–8.80 ppm, besides the increase of aromatic protons as a result of the insertion of aryl group of the appropriate aldehydes at the range δ 7.42–8.51 ppm. The signal corresponding to the amide proton became downfield at the range δ 13.17–13.35 ppm (Scheme 3).

Antimicrobial activity. The synthesized compounds were evaluated for their antimicrobial action against three different bacterial species, namely, *Pseudomonas* sp. (Gram-negative bacterium), *Bacillus subtilis* (Gram-positive bacterium), and *Streptomyces* sp. (one of the important actinomycetes). All the tested compounds exhibited different degrees of antibacterial activities or inhibitory actions. The most susceptible organisms were the two Gram-positive and Gram-negative bacteria (*B. subtilis* and *Pseudomonas* sp.) followed by *Streptomyces* sp., whereas the lowest inhibitory effect was encountered in the case of *Pseudomonas* sp. The highest degrees of inhibition were recorded for compounds **9a**, **11b**, and **14a** followed by **8a**, **9b**, **11a**, **12b**, **14b**, and **15c**, whereas the lowest degree of inhibition was recorded for **4a**, **4b**, **8b**, **10a**, **10b**, and **12a** (Table 1).

EXPERIMENTAL

Melting points were recorded using Kofter block instrument. TLC was performed on plastic plates Silica Gel 60F254 (E. Merck, Darmstadt, Germany; layer thickness 0.2 mm). NMR spectra were recorded on a Bruker AC 250 FT NMR spectrometer

Scheme 2



4, 8-11	Me
a	-8
b	-6

Scheme 3

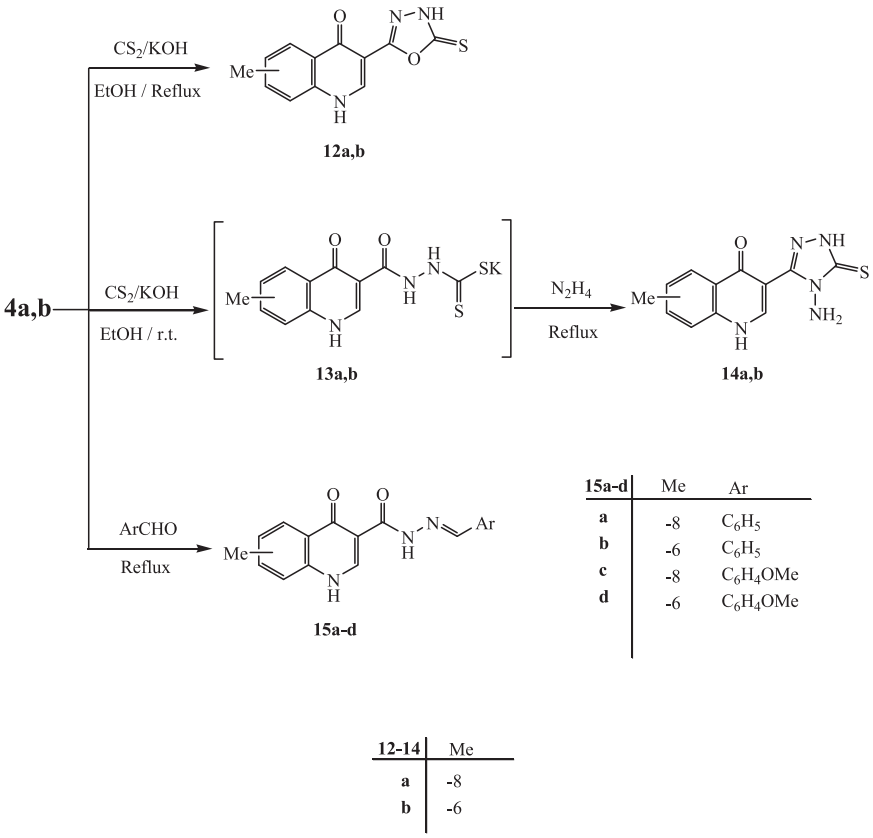


Table 1

Antimicrobial activity of the tested compounds.

Compound	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Streptomyces* sp.
4a	–	–	+
4b	–	–	–
8a	+++	–	++
8b	–	–	–
9a	++++	+	+++
9b	+++	+	+
10a	–	–	++
10b	–	–	–
11a	+++	–	++
11b	++++	+	+++
12a	–	+	–
12b	+++	–	++
14a	++++	+	+++
14b	+++	+	+
15c	++	+	–

– No antimicrobial effect; + low antimicrobial effect (4 mm); ++ moderate antimicrobial effect (8–10 mm); +++ high antimicrobial effect (12–18 mm); ++++ potent antimicrobial effect (20–22 mm).

(Bruker UK, Coventry) at 300 MHz for ^{1}H NMR and at 75.5 and 62.5 MHz for ^{13}C NMR with TMS as an internal standard. IR spectra were recorded on a Nicolet FTIR spectrophotometer (Nicolet, Madison, WI). Mass spectra were measured on a Kratos 50 TC spectrometer (Kratos, Manchester, UK). The microanalyses were performed at the microanalytical unit, Cairo University, Egypt, and were found to agree favorably with the calculated values. Antimicrobial activity of the synthesized compounds was evaluated at the Botany Department, Faculty of Science, Menoufia University, Shebin El-Koam, Egypt.

General procedure for the synthesis of compounds 3a,b. A suspension of methylenemalonates **2a,b** (1.11 g, 4 mmol) in diphenyl ether (10 mL) was heated in an oil bath for 5–10 min at 220–250°C using a short air condenser to remove the liberated ethanol. After cooling, the reaction mixture was digested with diethyl ether, and the obtained precipitate was filtered, washed with diethyl ether, and recrystallized from ethanol to give compounds **3a,b**.

Ethyl 8-methyl-4-oxo-1,4-dihydroquinolin-3-carboxylate (3a). White crystal (0.84 g, 90%). mp 259–260°C; IR (KBr) ν: 3246 (NH), 1726 (C=O), 1644 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.28 (t, J = 7.2 Hz, 3H, CH_3CH$_2$O), 2.21 (s, 3H, CH$_3$), 4.22 (q, J = 7.2 Hz, 2H, CH$_3$CH_2O), 7.30 (t, J = 7.2 Hz, 1H, ArH-6), 7.55 (d, J = 6.0 Hz, 1H, ArH-7), 8.03 (d, J = 6.9 Hz, 1H, ArH-5), 8.39 (s, 1H, ArH-2), 11.62 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 15.25 (*C*H$_3$CH$_2$O), 19.82 (CH$_3$), 60.57 (OCH$_2$CH$_3$), 110.16, 124.54, 125.23, 127.09, 128.41, 134.21, 138.34, 145.45 (C–Ar), 165.67, 174.5 (2 CO). MS *m/z* (*I*, %): 231 (M$^+$, 45), 185 (100), 159 (10), 129 (41). *Anal*. Calcd for C$_{13}$H$_{13}$NO$_3$: C, 67.52; H 5.67; N 6.06. Found: C 67.61; H 5.72; N 6.12.

Ethyl 6-methyl-4-oxo-1,4-dihydroquinolin-3-carboxylate (3b). White crystals (0.74 g, 80%). mp 268–270°C; IR (KBr) ν: 3152–2981 (OH/NH), 1724 (C=O), 1641 (C=O) cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.27 (t, J = 7.2 Hz, 3H, CH_3CH$_2$O), 2.23 (s, 3H,

CH_3), 4.21 (q, J = 7.2 Hz, 2H, CH_3CH_2O), 7.52 (m, 2H, ArH-7,8), 7.95 (s, 1H, ArH-5), 8.49 (s, 1H, ArH-2), 12.20 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 16.12 (CH_3CH_2O), 19.08 (CH_3), 62.07(OCH_2CH_3), 112.12, 125.12, 126.24, 129.55, 129.94, 136.31, 139.24, 147.56 (C–Ar), 168.04, 174.5 (2 CO). MS *m/z* (*I*, %): 231 (M^+, 42), 186 (100), 159 (30); *Anal*. Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.56; H, 5.55; N, 5.98.

General procedure for the synthesis of compounds 4a,**b**. A mixture of quinolone esters **3a**,**b** (1.50 g, 6.5 mmol) and $N_2H_4 \cdot H_2O$ (1.25 g, 25 mmol) in ethanol (20 mL) was heated under reflux for 4–6 h. The excess of ethanol was removed under reduced pressure, and the resulting precipitate was filtered off, washed with ethanol, and recrystallized from DMF.

8-Methyl-4-oxo-1,4-dihydroquinoline-3-carbohydrazide (4a). White crystals (1.28 g, 91%). mp >330°C; IR (KBr) ν: 3295–3067 ($NHNH_2$), 1667 (C═O), 1644 (C═O) cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.28 (s, 3H, CH_3), 4.58 (bs, 2H, NH_2), 7.34–7.39 (m, 1H, ArH-6), 7.60–762 (m, 1H, ArH-7), 8.11–814 (d, J = 7.8 Hz, 1H, ArH-5), 8.60 (s, 1H, ArH-2), 10.68 (s, 1H, CONH), 11.97 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 19.51 (CH_3), 114.77, 122.44, 124.98, 125.15, 126.42, 131.66, 137.33 143.18 (ArC), 165.77, 175.61 (2 CO). MS *m/z* (*I*, %): 217 (M^+, 100), 202 (30), 188(10), 161 (15); *Anal*. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.87; H, 5.18; N, 19.45.

6-Methyl-4-oxo-1,4-dihydroquinoline-3-carbohydrazide (4b). White crystals (1.14 g, 81%). mp >300°C; IR (KBr) ν: 3316–3043 ($NHNH_2$), 1669 (C═O), 1642 (C═O). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.24 (s, 3H, CH_3), 4.56 (bs, 2H, NH_2), 7.59 (m, 2H, ArH-7,8), 8.04 (s, 1H, ArH-5), 8.68 (s, 1H, ArH-2), 10.74 (s, 1H, CONH), 12.13 (bs, 1H, NH). MS *m/z* (*I*, %): 217 (M^+, 100), 202 (18), 188 (21), 161 (33), 131 (50). *Anal*. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.64; H, 5.16; N, 19.52.

Ethyl (3-[(4-methylphenyl)amino]-2-{[(4-methylphenyl)amino]-carbonyl}acrylate (6). A mixture of *p*-toluidine (0.54 g, 5 mmol) and EMME (1.18 g, 5.5 mmol) was refluxed for 7 h in glacial acetic acid (30 mL). The solvent was removed under reduced pressure, and the residue was co-evaporated with anhydrous toluene (3 × 10 mL). The residue was triturated with diethyl ether (30 mL), and the separated solid product was collected by filtration, dried, and recrystallized from ethanol to afford the pale yellow crystals of **6** (1.45 g, 85%). mp 139–140°C; IR (KBr) ν: 3289–3150 (NH), 1726 (C═O), 1641 (C═O) cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.39 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 2.24 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 4.31 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 7.06 (d, J = 8.5 Hz, 2H, ArH-3,5), 7.27 (d, J = 8.2 HZ, 2H, ArH-3′,5′), 7.51 (d, J = 8.5 Hz, 2H, ArH-2,6), 8.55 (d, J = 8.2 Hz, 2H, ArH-2′,6′), 10.88 (s, 1H, CONH), 12.31 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 12.89 (CH_3CH_2), 19.21, 19.81 (2 CH_3), 49.51 (CH_2CH_3), 116.18, 120.55, 120.91, 124.61, 125.20, 132.13, 135.19, 137.09, 138.51, 140.12, 141.83, 142.44, 143.55, 163.89 (C–Ar), 165.51, 177.54 (2 CO). MS *m/z* (*I*, %): 338 (M^+, 5), 232 (60), 186 (80), 187 (25), 107 (100). *Anal*. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28. Found: C, 71.08; H, 6.71; N, 8.33.

6-Methyl-*N*-(4-methylphenyl)-4-oxo-1,4-dihydroquinoline-3-carboxamide (7). A suspension of compound **6** (1.35 g, 4 mmol) in diphenyl ether (10 mL) was heated in an oil bath for 5–10 min at 220–250°C using a short air condenser to remove the liberated ethanol. After cooling, the reaction mixture was digested with diethyl ether; the obtained precipitate was filtered, washed with diethyl ether, and recrystallized from methanol to afford a white crystal of compound **7** (0.85 g, 73%). mp 220–222°C; IR (KBr) ν: 3315–3264 (NH), 1661 (C═O), 1640 (C═O) cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.24 (s, 3H, *p*-CH_3), 2.29 (s, 3H, CH_3), 7.16 (d, J = 8.1 Hz, 2H, ArH-3′,5′), 7.21 (d, 2H, J = 8.1 Hz, H–Ar-2′,6′), 7.44 (m, 2H, ArH-7,8), 8.11 (s, 1H, ArH-5), 8.81 (s, 1H, ArH-2), 12.43 (s, 1H, CONH), 12.93 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 21.13, 21.25 (2 CH_3), 116.09, 118.58, 120.85, 121.33, 123.55, 126.22, 130.66, 135.07, 136.33, 136.78, 138.66, 139.36, 140.43, 163.17 (C–Ar), 165.51, 170.89 (2 CO). MS *m/z* (*I*, %): 292 (M^+, 60), 277 (100), 185 (30), 158 (20), 143 (15). *Anal*. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.98; H, 5.64; N, 9.67.

General procedure for the synthesis of compounds 8a,**b**. To a solution of acid hydrazides **4a**,**b** (2.17 g, 10 mmol) in absolute ethanol (15 mL), phenyl isothocyanate (1.35 g, 10 mmol) was added. The reaction mixture was heated under reflux for 3–5 h. The product that separated on cooling was filtered off, washed with ethanol, and dried well to afford thiosemicarbazides **8a**,**b**, which were recrystallized from methanol.

2-[(8-Methyl-4-oxo-1,4-dihydroquinolin-3-yl)carbonyl]-N-phenyl thiosemicarbazide (8a). White crystals (3.11 g, 88%). mp 220–222°C; IR (KBr) ν: 3316–3225 (NH), 1660 (C═O), 1641 (C═O), 1193 (C═S) cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.54 (s, 3H, CH_3), 6.54–6.91 (m, 3H, ArH), 7.55–7.92 (m, 4H, ArH), 8.41 (m, 2H, ArH), 9.45 (bs, 1H, PhNH), 9.71 (bs, 1H, CSNH), 10.65 (bs, 1H, CONH), 12.12 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 21.03 (CH_3), 109.08, 118.56, 118.99, 121.32, 122.36, 124.08, 130.89, 134.66, 135.15, 135.91, 136.04, 137.18, 139.41, 159.43 (C–Ar), 166.03, 175.05 (2 CO), 181.33 (C═S). MS *m/z* (*I*, %): 353 (M^+, 10), 352 (M^+, 5), 217 (45), 186 (41), 135 (96), 103 (32), 51 (100). *Anal*. Calcd for $C_{18}H_{16}N_4O_2S$: C, 61.35; H, 4.58; N, 15.90. Found: C, 61.44; H, 4.66; N, 15.97

2-[(6-Methyl-4-oxo-1,4-dihydroquinolin-3-yl)carbonyl]-N-phenyl thiosemicarbazide (8b). White crystals (3.14 g, 89%). mp 238–240°C; IR (KBr) ν: 267–3169 (NH), 1661 (C═O), 1640 (C═O), 1153 (C═S) cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.50 (s, 3H, CH_3), 6.53–6.91 (m, 3H, ArH), 7.55–7.92 (m, 4H, ArH), 8.40 (m, 2H, ArH), 9.60 (bs, 1H, PhNH), 9.83 (bs, 1H, CSNH), 10.65 (bs, 1H, CONH), 12.63 (bs, 1H, NH). MS *m/z* (*I*, %): 352 (M^+, 3), 217 (42), 185 (36), 136 (13), 93 (45), 50 (100). *Anal*. Calcd for $C_{18}H_{16}N_4O_2S$: C, 61.35; H, 4.58; N, 15.90. Found: C, 61.51; H, 4.62; N, 15.95.

General procedure for the synthesis of compounds 9a,**b**. A suspension of thiosemicarbazides **8a**,**b** (1.41 g, 4 mmol) in absolute ethanol (50 mL) was dissolved in 5*N* aqueous NaOH with cooling and stirring, resulting in the formation of a clear solution. To this, 5% I_2 in KI solution was added dropwise with stirring till the color of iodine persisted at room temperature. The reaction mixture was then refluxed for 7 h on water bath. It was then concentrated and cooled, and the solid separated out was filtered, dried, and recrystallized with methanol to afford the oxadiazole derivatives **9a**,**b**.

3-[2-Phenylamino-1,3,4-oxadiazoles]-8-methylquinoline-4(1H)-one (9a). Pale yellow powder (1.17 g, 92%). mp 270–272°C; IR (KBr) ν: 3211 (NH), 1638 (C═O), 1608 (C═N) cm^{-1}. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.32 (s, 3H, CH_3), 6.99 (t, J = 7.4 Hz, 1H, Ar–H), 7.31–7.54 (m, 5H, Ar–H), 7.59 (m, 1H, Ar–H), 8.10 (d, J = 8.1 Hz, 1H, ArH), 8.38 (s, 1H, ArH-2), 10.55 (s, 1H, N*H*Ph), 11.76 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 19.89 (CH_3), 105.26, 116.08, 116.73, 121.09, 121.44, 123.20, 124.04, 126.90, 128.86, 128.99, 133.10, 134.15, 138.85, 140.37, (C–Ar), 165.50 (oxadiazolyl C-5), 168.55 (oxadiazolyl C-2), 174.22 (CO). MS *m/z*

(*I*, %): 319 ($M^+ + 1$, 25), 318 (M^+, 98), 317 (31), 262 (3), 186 (28), 184 (51), 118 (26), 77 (100). *Anal*. Calcd for $C_{18}H_{14}N_4O_2$: C, 67.91; H, 4.43; N, 17.60. Found: C, 67.99; H, 4.71; N, 17.75.

3-[2-Phenylamino-1,3,4-oxadiazoles]-6-methylquinoline-4(1H)-one (9b). Pale yellow powder (1.10 g, 85%). mp 240–243°C; IR (KBr) ν: 3212 (NH), 1635 (C═O), 1610 (C═N) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 2.28 (s, 3H, CH_3), 6.99 (m, 1H, Ar–H), 7.32–7.37 (m, 2H, ArH), 7.57–7.63 (m, 4H, ArH), 8.01 (s, 1H, ArH), 8.50 (s, 1H, ArH), 10.56 (s, 1H, N*H*Ph), 12.41 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 19.75 (CH_3), 104.06, 116.78, 116.12, 121.01, 121.31, 123.19, 123.54, 126.71, 128.43, 128.78, 132.65, 134.20, 137.81, 139.85, 163.15 (Ar + oxadiazolyl C-5), 165.71 (oxadiazolyl C-2), 173.61 (CO). MS *m/z* (*I*, %): 319 ($M^+ + 1$, 22), 318 (M^+, 98), 184 (54), 118 (20), 77 (100). *Anal*. Calcd for $C_{18}H_{14}N_4O_2$: C, 67.91; H, 4.43; N, 17.60. Found: C, 67.88; H, 4.31; N, 17.38.

General procedure for the synthesis of compounds 10a,b. A suspension of thiosemicarbazides **8a,b** (1.76 g, 5 mmol) in absolute ethanol (50 mL) was dissolved in 2*N* NaOH resulting in the formation of a clear solution. The reaction mixture was refluxed for 6 h on water bath, concentrated, cooled, and filtered. The pH of the filtrate was adjusted at 5–6 with AcOH and kept aside for 1–2 h. The solid separated out was filtered, washed with water, dried, and recrystallized with methanol to give the 1,2,4-triazole derivatives **10a,b**.

3-(4,5-Dihydro-4-phenyl-5-thioxo-1H-1,2,4-triazol-3-yl)-8-methylquinolin-4(1H)-one (10a). Yellow powder (1.59 g, 95%). mp 202–203°C; IR (KBr) ν: 3485–3318 (NH), 1639 (C═O), 1605 (C═N) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 2.29 (s, 3H, CH_3), 7.19 (m, 1H, ArH), 7.30–7.36 (m, 3H, ArH), 7.51 (d, J = 7.5 Hz, 1H, ArH), 7.74 (m, 2H, ArH), 7.81 (d, J = 7.5 Hz, 1H, ArH), 8.47 (s, 1H, ArH), 11.05 (bs, 1H, NH), 12.97 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 19.19 (CH_3), 107.19, 122.81, 123.73, 125.26, 126.79, 127.79, 128.27, 128.86, 129.05, 133.05, 134.49, 137.99, 141.61, 141.86 (ArC), 166.48 (triazolyl C-2), 174.02 (C═O), 181.05 (C═S). MS *m/z* (*I*, %): 335 ($M^+ + 1$, 29), 334 (M^+, 46), 333 (26), 185 (20), 184 (20), 149 (26), 103 (51), 51 (100). *Anal*. Calcd for $C_{18}H_{14}N_4OS$: C, 64.65; H, 4.22; N, 16.75. Found: C, 64.43; H, 4.13; N, 16.58.

3-(4,5-Dihydro-4-phenyl-5-thioxo-1H-1,2,4-triazol-3-yl)-6-methylquinolin-4(1H)-one (10b). Yellow powder (1.50 g, 90%). mp 292–293°C; IR (KBr) ν: 3436–3300 (NH), 1641 (C═O), 1610 (C═N) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 2.29 (s, 3H, CH_3), 7.24–7.38 (m, 4H, ArH), 7.42 (m, 1H, ArH), 7.46–7.58 (m, 2H, ArH), 7.73 (1H, s, ArH-5), 8.24 (1H, s, ArH-2), 11.26 (bs, 1H, NH), 12.96 (bs, 1H, NH). MS *m/z* (*I*, %): 334 (M^+, 55), 185 (43), 149 (25), 125 (23), 103 (55), 51 (100). *Anal*. Calcd for $C_{18}H_{14}N_4OS$: C, 64.65; H, 4.22; N, 16.75. Found: C, 64.71; H 4.41; N, 16.61.

General procedure for the synthesis of compounds 11a,b. The thiosemicarbazides **8a,b** (1.76 g, 5 mmol) was added gradually with stirring to cooled concentrated H_2SO_4 (10 mL) during 10 min. The mixture was further stirred for another 5 h in an ice bath. It was then poured over crushed ice with stirring. The solid separated out was filtered, washed with water, dried, and recrystallized from methanol to afford the thiadiazole derivatives **11a,b**.

3-[5-Phenylamino-1,3,4-thiadiazole]-8-methylquinoline-4(1H)-one (11a). Yellow crystal (1.47 g, 88%). mp >300°C; IR (KBr) ν: 3336–3353 (NH), 1631 (C═O), 1607 (C═N) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 2.24 (s, 3H, CH_3), 7.42–7.59 (m, 4H, Ar–H), 7.68–7.94 (m, 3H, Ar–H), 8.10–8.15 (m, 1H, ArH-5), 8.83 (s, 1H, ArH-2), 10.65 (bs, 1H, N*H*Ph), 12.18 (bs, 1H, NH). MS *m/z* (*I*, %): 334 (M^+, 12), 332 (36), 159 (100). *Anal*. Calcd for $C_{18}H_{14}N_4OS$: C, 64.65; H, 4.22; N, 16.75. Found: C, 64.77; H, 4.50; N, 16.81.

3-[5-Phenylamino-1,3,4-thiadiazole]-6-methylquinoline-4(1H)-one (11b). Yellow crystal (1.17 g, 70%). mp >300°C; IR (KBr) ν: 3366 (NH), 1635 (C═O), 1604 (C═N) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 2.30 (s, 3H, CH_3), 7.37–7.56 (m, 4H, Ar–H), 7.62–7.86 (m, 3H, Ar–H), 8.05 (s, 1H, ArH-5), 8.88 (s, 1H, ArH-2), 10.66 (bs, 1H, N*H*Ph), 12.79 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 20.60 (CH_3), 107.18, 112.39, 123.22, 123.21 125.40, 125.86, 126.09, 129.55, 128.45, 128.79, 133.33, 138.07, 139.16, 146.55 (C–Ar), 160.31 (thiadiazolyl C-2), 169.89 (thiadiazolyl C-5), 174.60 (CO). MS *m/z* (*I*, %): 334 (M^+, 30), 243 (25), 210 (26), 159 (100). *Anal*. Calcd for $C_{18}H_{14}N_4OS$: C, 64.65; H, 4.22; N, 16.75. Found: C, 64.69; H, 4.31; N, 16.55.

General procedure for the synthesis of compounds 12a,b. A mixture of acid hydrazides **4a,b** (2.17 g, 10 mmol) and CS_2 (0.6 mL, 10 mmol) was added to a solution of KOH (0.56 g, 10 mmol) in H_2O (50 mL) and ethanol (50 mL). The reaction mixture was heated under reflux for 6 h. After evaporating the reaction to dryness *in vacuo*, a solid was obtained, which was then dissolved in H_2O (50 mL) and acidified with concentrated HCl. The precipitate was filtered off, washed with H_2O, and recrystallized from methanol to afford the oxadiazole derivatives **12a,b**.

3-(4,5-Dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)-8-methylquinolin-4(1H)-one (12b). White crystal (1.74 g, 67%). mp 160–163°C; IR (KBr) ν: 3424–3254 (NH), 1641 (C═O), 1609 (C═N) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 2.26 (s, 3H, CH_3), 7.35 (t, J = 7.5 Hz, 1H, ArH-6), 7.60 (d, J = 6.9 Hz, 1H, ArH-7), 8.04 (d, J = 7.5 Hz, 1H, ArH-5), 8.31 (s, 1H, ArH-2), 11.88 (bs, 1H, NH), 13.18 (bs, 1H, NH). MS *m/z* (*I*, %): 260 ($M^+ + 1$, 15), 259 (M^+, 36), 186 (100). *Anal*. Calcd for $C_{12}H_9N_3O_2S$: C 55.59; H 3.50; N, 16.21. Found: C, 55.64; H, 3.62; N, 16.31.

3-(4,5-Dihydro-5-thioxo-1,3,4-oxadiazol-2-yl)-6-methylquinolin-4(1H)-one (12a). White crystal (2.20 g, 85%). mp 139–141°C; IR (KBr) ν: 3431–3081 (NH), 1639 (C═O), 1605 (C═N) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 2.31 (s, 3H, CH_3), 7.53–7.67 (m, 2H, ArH-6,7), 7.97 (s, 1H, ArH-5), 8.49 (s, 1H, ArH-2), 11.68 (bs, 1H, NH), 13.49 (bs, 1H, SH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 19.23 (CH_3), 105.05, 117.64, 123.55, 125.93, 133.78, 134.44, 136.97, 141.12 (C–Ar), 159.20 (oxadiazolyl C-2), 171.65 (CO), 180.16 (C═S). MS *m/z* (*I*, %): 260 ($M^+ + 1$), 259 (M^+, 33) 186 (70), 88 (55), 77 (100). *Anal*. Calcd for $C_{12}H_9N_3O_2S$: C, 55.59; H, 3.50; N, 16.21. Found: C, 55.63; H, 3.57; N, 16.09.

General procedure for the synthesis of compounds 14a,b. Potassium hydroxide (0.84 g, 15 mmol) in absolute ethanol (10 mL) and acid hydrazides **4a,b** (2.17 g, 10 mmol) were mixed together until the solution became clear. To the clear solution, CS_2 (1.32 g, 30 mmol) was added. The solution was stirred for 3 h at 25°C, and then diethyl ether (30 mL) was added to form a precipitate. The precipitate was mixed with $N_2H_4{\cdot}H_2O$ (1.6 g, 32 mmol) and H_2O (1 mL). The solution was refluxed for 2 h until the color of the solution became clear green. After cooling to room temperature, ice water (10 mL) was added to the reaction mixture, which was then neutralized with 3*N* HCl to form a precipitate. The precipitate was isolated by filtration and purified by recrystallization from methanol to afford the triazole derivatives **14a,b**.

3-(4-Amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-8-methylquinolin-4(1H)-one (14a). Pale yellow crystals (1.99 g, 73%). mp 165–168°C; IR (KBr) ν: 3422–3154 (NH, NH_2), 1637 (C═O),

1608 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 2.25 (s, 3H, CH_3), 5.80 (bs, 2H, NH_2), 7.33–7.39 (m, 1H, Ar–H6), 6.61 (d, J = 7.5 Hz, 1H, ArH-7), 8.12 (d, J = 7.5 Hz, 1H, ArH-5), 8.59 (s, 1H, ArH-2), 10.68 (bs, 1H, NH), 12.57 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 19.15 (CH_3), 116.81, 122.13, 125.22, 126.30, 128.19, 133.14, 140.10, 141.32 (C–Ar), 160.15 (triazolyl C-2), 175.08 (CO), 180.14 (C=S). MS *m/z* (*I*, %): 273 (M^+, 12), 217 (45), 186 (100). *Anal*. Calcd for $C_{12}H_{11}N_5OS$: C, 52.73; H, 4.06; N, 25.62. Found: C, 52.61; H, 3.98; N, 25.51.

3-(4-Amino-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)-6-methylquinolin-4(1H)-one (14b). Pale yellow crystals (2.18 g, 80%). mp 140–143°C; IR (KBr) ν: 3460–3215 (NH, NH_2), 1641 (C=O), 1612 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 2.24 (s, 3H, CH_3), 5.90 (bs, 2H, NH_2), 7.34–8.61 (m, 4H, ArH), 11.40 (brs, 1H, NH), 13.58 (bs, 1H, NH). MS *m/z* (*I*, %): 274 (M^+, 45), 273 (M^+, 25), 218 (17), 217 (66), 186 (100). *Anal.* Calcd for $C_{12}H_{11}N_5OS$: C, 52.73; H, 4.06; N, 25.62. Found, %: C, 52.78; H, 4.14; N, 25.44.

General procedure for the synthesis of compounds 15a–d. A solution of the acid hydrazides **4a**,**b** (1.08 g, 5 mmol) in absolute ethanol (15 mL) was treated with appropriate aldehydes (10 mmol) in presence of a few drops of piperidine. The mixture was boiled under reflux for 3–5 h (TLC). The excess of ethanol was removed under reduced pressure, and the solid separated was collected by filtration, washed with ethanol, dried, and recrystallized from methanol to afford the arylidene derivatives **15a–d**.

N′-Benzylidene-8-methyl-4-oxo-1,4-dihydroquinoline-3-carbohydrazide (15a). White crystals (1.31 g, 86%). mp 310–313°C; IR (KBr) ν: 3172 (NH), 1665 (C=O), 1642 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz): δ 2.24 (s, 3H, CH_3), 7.42–7.50 (m, 3H, ArH)), 7.70–7.94 (m, 3H, (ArH)), 8.22–8.51 (m, 3H, ArH), 8.78 (s, 1H, N=CH), 12.30 (bs, 1H, NH), 13.21 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 19.81 (CH_3), 110.15, 123.41, 125.07, 126.10, 127.13, 127.26, 128.83, 129.12, 130.31, 133.91, 134.15, 143.19, 147.90, 154.33 (C–Ar), 160.24 (C=N), 162.99, 171.33 (2 CO). MS *m/z* (*I*, %): 306 (M^+ + 1, 18), 305 (M^+, 55), 228 (62), 186 (100). *Anal*. Calcd. for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76. Found: C, 70.93; H, 5.03; N, 13.81.

N′-Benzylidene-6-methyl-4-oxo-1,4-dihydroquinoline-3-carbohydrazide (15b). White crystals (1.23 g, 81%). mp 323–325°C; IR (KBr) ν: 3210 (NH), 1650 (C=O), 1641 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 2.25 (s, 3H, CH_3), 7.42–7.46 (m, 3H, ArH), 7.61–7.77 (m, 4H, ArH), 8.15–8.41 (m, 2H, ArH), 8.80 (s, 1H, N=CH), 12.33 (bs, 1H, NH), 13.35 (bs, 1H, NH). MS *m/z* (*I*, %): 305 (M^+, 40), 228 (30), 186 (100), 158 (42), 143 (52), 131 (12). *Anal*. Calcd. For $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76. Found: C, 70.90; H, 5.01; N, 13.45.

N′-(4-Methoxybenzylidene)-8-methyl-4-oxo-1,4-dihydroquinoline-3-carbohydrazide (15c). White crystals (1.40 g, 84%). mp >330°C; IR (KBr) ν: 3250 (NH), 1666 (C=O), 1642 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 2.26 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.99–7.01 (d, J = 8.6 Hz, 2H, ArH), 7.41 (m, 1H, ArH), 7.63 (d, J = 8.7 Hz, 1H, ArH-7), 7.69 (d, J = 8.6 Hz, 2H, ArH), 8.15 (d, J = 8.6 Hz, 1H, ArH-5), 8.35 (s, 1H, ArH-2), 8.67 (s, 1H, N=CH), 12.15 (bs, 1H, NH), 13.17 (bs, 1H, NH). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 21.07 (CH_3), 55.67 (OCH_3), 110.99, 117.22, 123.15, 126.14, 127.23, 127.76, 128.14, 128.85, 129.07, 131.63, 132.53, 141.11, 144.44, 155.09 (C–Ar), 160.14 (C=N) 166.45, 176.61 (2 CO). MS *m/z* (*I*, %): 336 (M^+ + 1, 45), 335 (M^+, 33), 228 (62), 185 (60), 158 (25), 103 (22), 51 (100). *Anal*. Calcd. For $C_{19}H_{17}N_3O_3$: C, 65.05; H, 5.11; N, 12.53. Found: C, 65.13; H, 5.17; N, 12.61.

N′-(4-Methoxybenzylidene)-6-methyl-4-oxo-1,4-dihydroquinoline-3-carbohydrazide (15d). White crystals (1.60 g, 96%). mp: 290–291°C; IR (KBr) ν: 3272 (NH), 1670 (C=O), 1638 (C=O) cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 2.24 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.70 (d, J = 8.6 Hz, 2H, ArH), 7.61–7.70 (m, 4H, ArH), 8.05 (m, 1H, ArH,), 8.33 (s, 1H, ArH-2), 8.78 (s, 1H, N=CH), 12.30 (bs, 1H, NH), 13.25 (s, 1H, CONH). MS *m/z* (*I*, %): 336 (M^+ + 1, 11), 335 (M^+, 30), 185 (35), 158 (25), 129 (26), 115 (12), 107 (100). *Anal*. Calcd. For $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 68.10; H, 5.14; N, 12.41.

Antimicrobial testing. The inhibition zones were measured using the agar cup diffusion technique [35]. Nutritive agar plates seeded with the test organisms (three plates for each organism) were allowed to solidify, and then 5-mm-diameter holes were formed in the plates using a cork borer. Each hole was filled with one drop of the DMF of the tested compound, whereas the hole in the center of the plate was filled with one drop of DMF. The plates were separately incubated at 30°C for 24 h. Inhibition zones (zones with no growth) around the holes were measured.

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