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Synthesis, antibacterial and anticancer evaluation of some new 2-chloro-3-hetarylquinolines

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Abstract *N*′-((2-Chloroquinolin-3-yl)methylene)-2-cyanoacetohydrazide (**3**) was synthesized then treated with aromatic aldehydes in basic medium to afford the arylidene derivatives **4a**–**e**. Reaction of **4a**–**c** with hydrazine hydrate in boiling ethanol gave the 3-aminopyrazoles **5a**–**c**. Base promoted Michael addition of **3** to arylidene malononitriles **6** afforded 2-pyridones **9a**–**d**. Cyclocondensation of **3** with some salicylaldehyde derivatives gave the iminocoumarins **10a**–**c**; these underwent acid-catalyzed hydrolysis to give coumarins **11a**–**c**. Coupling of **3** with arene diazonium chloride in pyridine afforded the arylhydrazononitriles **12a**–**c**. Heterocyclization of **12a** with formalin and piperidine in warm ethanol gave the 1,2,4-triazine derivative **13**. The mechanisms and the chemoselectively of these reactions are discussed. The newly synthesized compounds were tested for antibacterial and anticancer activity. Pyridone **9b** and coumarin **11c** had the most potent antibacterial activity against *S. aureus*. Acrylamide **4d**, pyridones **9a**, **c**, and 1,2,4-triazine **13** were the most active anticancer compounds, with a broad range of activity against most of the tumor cell lines tested.

Keywords Quinoline · Pyrazole · Pyridone · Coumarin · Anticancer activity

Introduction

Quinolines and their derivatives with specific substituents at appropriate positions have attracted much interest in synthetic and medicinal chemistry. They have a wide

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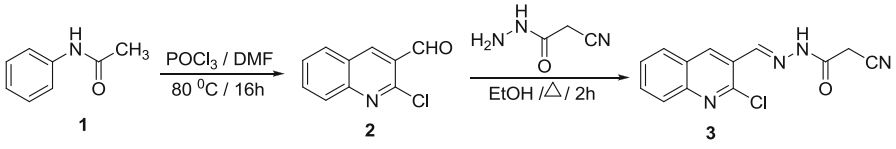
range of chemotherapeutic activity including antimicrobial [1, 2], antimalarial [3, 4], antitumor [5], anti-inflammatory [6, 7], and antiparasitic [8] activity. The 3-substituted quinolines are small molecules reported to be potent and selective inhibitors of platelet-derived growth factor receptor (PDGFr) tyrosine kinase and non-TZD selective peroxisome proliferator-activated receptor gamma (PPARγ) agonists for type 2 diabetes [9, 10]. Among quinolines, 2-chloro-3-formylquinolines are versatile precursors and have been used as building blocks for synthesis of annulated quinolines with potential biological activity [11–13]. Our recent work has involved synthesis of multifunctionalized heterocyclic compounds for evaluation as antimicrobial [14–21] and anticancer agents [22, 23]. As a part of this work, new 3-hetarylquinolines were required for antibacterial and anticancer evaluation. *N*′-((2-Chloroquinolin-3-yl)methylene)-2-cyanoacetohydrazide (**3**) seemed a good starting material to fulfill this objective.

Results and discussion

Chemistry

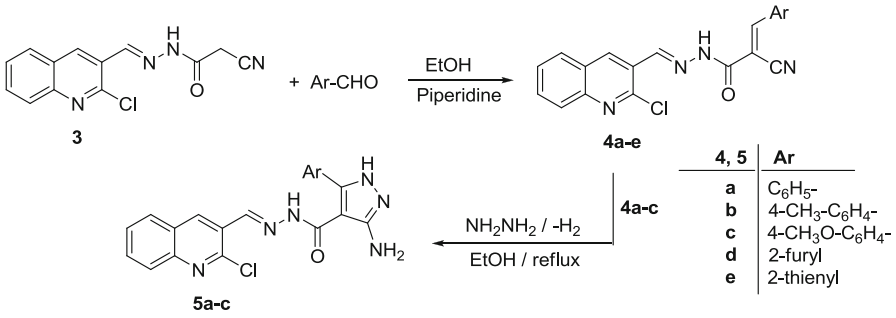
The synthetic strategy adopted to obtain the target compounds is depicted in Schemes 1, 2, 3, 4, and 5. The starting material *N*′-((2-chloroquinolin-3-yl)methylene)-2-cyanoacetohydrazide (**3**) was obtained in two steps by gentle heating of acetanilide (**1**) with $POCl_3$/DMF at 80 °C in the Vilsmeier–Haack reaction to afford 2-chloro-3-formylquinoline (**2**) [24]; this underwent condensation with 2-cyanoacetohydrazide in boiling ethanol to afford **3** as depicted in Scheme 1.

To show the synthetic potential of compound **3**, its reactivity with aromatic aldehydes was examined. Thus, Knoevenagel condensation of **3** with aromatic aldehydes (benzaldehyde, *p*-tolualdehyde and *p*-anisaldehyde) and heterocyclic aldehydes (furfural and 2-formylthiophene) in ethanol under reflux containing a catalytic amount of piperidine furnished the corresponding arylidene derivatives **4a**–**e**. The structure of compounds **4a**–**e** was confirmed on the basis of elemental analysis and spectral data. For example, the IR spectrum of **4c** contained absorption bands at 3,250, 2,208, 1,685, and 1,617 cm^{-1} ascribed to NH, nitrile, amidic C=O, and C=N functionaility, respectively. Its ^1H NMR spectrum contained five singlet signals at δ 3.89, 8.25, 8.61, 8.98, and 12.27 ppm, assignable to methoxy protons, olefinic CH=, quinoline-H_4, CH=N, and NH protons, respectively, and a multiplet in the region δ 7.18–8.08 ppm ascribed to eight aromatic protons. The ^{13}C NMR spectrum contained 21 signals; the most important, at δ 55.7, 115.2, and 162.9 ppm,

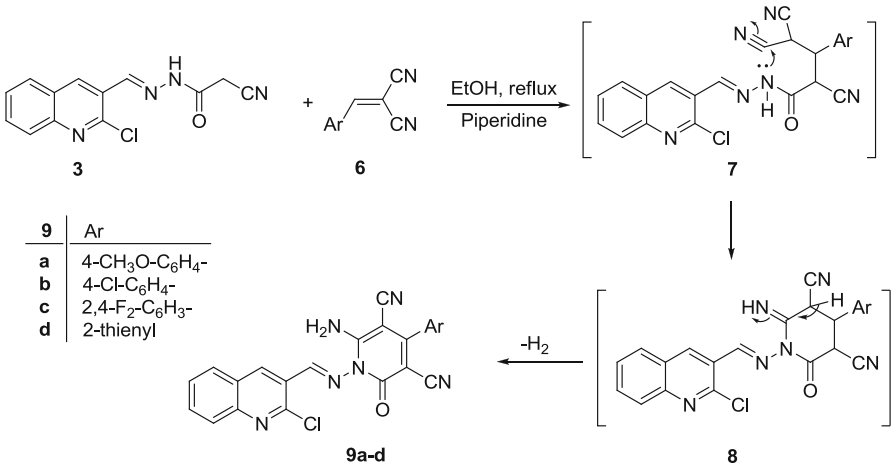


1 2 3

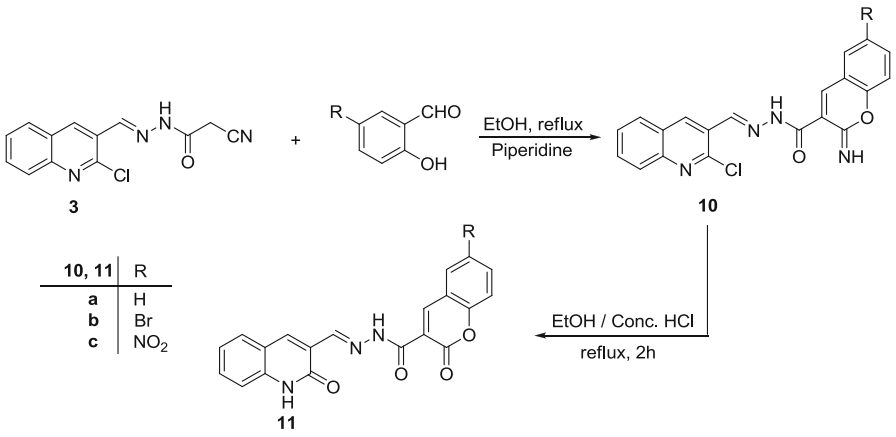
Scheme 1 Synthesis of *N*′-((2-chloroquinolin-3-yl)methylene)-2-cyanoacetohydrazide (**3**)



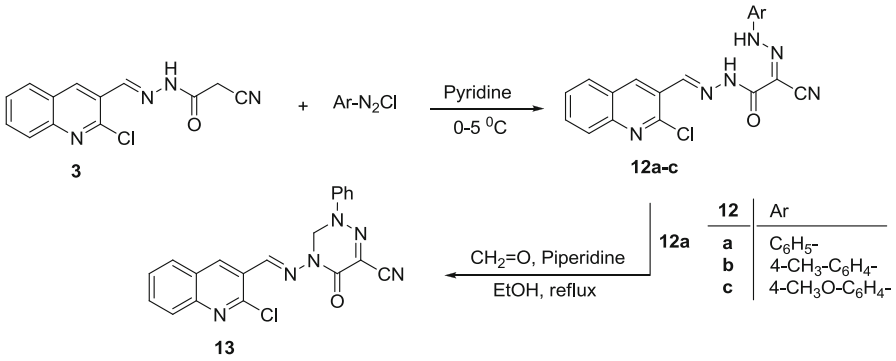
Scheme 2 Synthetic route to pyrazole derivatives **5a–c**



Scheme 3 Synthetic route to pyridone derivatives **9a–d**



Scheme 4 Synthetic route to coumarin derivatives **10a–c** and **11a–c**



Scheme 5 Synthetic route to 1,2,4-triazine derivative **13**

were ascribed to OCH_3, CN, and C=O carbon, respectively. The mass spectrum contained the molecular ion peak at $m/z = 390$ (M^+) corresponding to the molecular formula $C_{21}H_{15}ClN_4O_2$.

Treatment of **4a–c** with hydrazine hydrate in ethanol, under reflux, furnished the pyrazolylquinoline derivatives **5a–c**. The IR spectrum of compound **5b**, as representative example, contained absorption bands at 3,421, 3,329, 3,193, 3,141, and 1,636 cm^{-1} ascribed to NH_2, NH, amide-NH, and carbonyl functionality, respectively. The ^1H NMR spectrum of **5b** contained six singlet signals at δ 2.30, 6.50, 8.66, 9.10, 10.93, and 13.24 ppm assignable to CH_3, NH_2, quinoline-H_4, CH=N, and amide-NH, and pyrazole NH protons, respectively. Its mass spectrum contained a molecular ion peak at $m/z = 404$ (M^+) which corresponded to its molecular formula ($C_{21}H_{17}ClN_6O$). Formation of compounds **5a–c** is assumed to proceed via Michael addition of hydrazine hydrate to α,β-unsaturated nitrile **4a–c** and in-situ intramolecular 1,5-dipolar cyclization via addition of an amino group to a nitrile function to give dihydropyrazole, which underwent autooxidation to give the target pyrazoles.

2-Pyridones are important heterocycles with great applicability in medicinal chemistry; this core structure can be found in compounds with diverse biological and medicinal applications [25]. Literature survey revealed that reaction of *N*-hetaryl-2-cyanoacetamides with either β-diketones or arylidene malononitriles is an efficient method for synthesis of 2-pyridones [26]. In this context, we investigated reaction of the active methylene group of compound **3** with a variety of arylidene malononitriles. Thus, treatment of **3** with a series of arylidene malononitriles **6** in boiling ethanol containing a catalytic amount of piperidine afforded the 2-pyridone derivatives **9a–d** (Scheme 3).

Elemental analysis and spectroscopic data confirmed the proposed structures of products **9a–d**. The IR spectrum of compound **9a**, as example, contained absorption bands at 3,350, 3,243, 2,212, 1,647, and 1,608 cm^{-1}, ascribed to NH_2, CN, C=O, and C=N functionality, respectively. Its ^1H NMR spectrum contained four singlet signals at δ 3.84, 6.87, 8.76, and 9.00 ppm assignable to methoxy, NH_2 proton, quinoline-H_4, and CH=N protons, respectively, and a multiplet in the region δ

7.08–8.12 ppm ascribed to eight aromatic protons. The ^{13}C NMR spectrum contained 24 signals, the most important of which at δ 117.3, 117.5, and 161.9 ppm were ascribed to two unsymmetrical CN and C=O carbon atoms, respectively. The mass spectrum of **9a** contained the molecular ion peak at *m/z* = 454 (M^+), corresponding to the molecular formula $C_{24}H_{15}ClN_6O_2$. The mass fragmentation pattern of pyridone **9a**, shown in Fig. 1, confirmed its chemical structure.

The mechanism of formation of pyridones **9a–d** is depicted in Scheme 3. Presumably, the reaction path includes the Michael addition of CH acid **3** to the β-carbon of the arylidene malononitriles **6** with formation of intermediate **7** which undergoes chemoselective heterocyclization via nucleophilic addition of the amidic NH to a nitrile function affording intermediate **8** which subsequently undergoes tautomerism with elimination of a hydrogen molecule to give the substituted 2-pyridones **9a–d**.

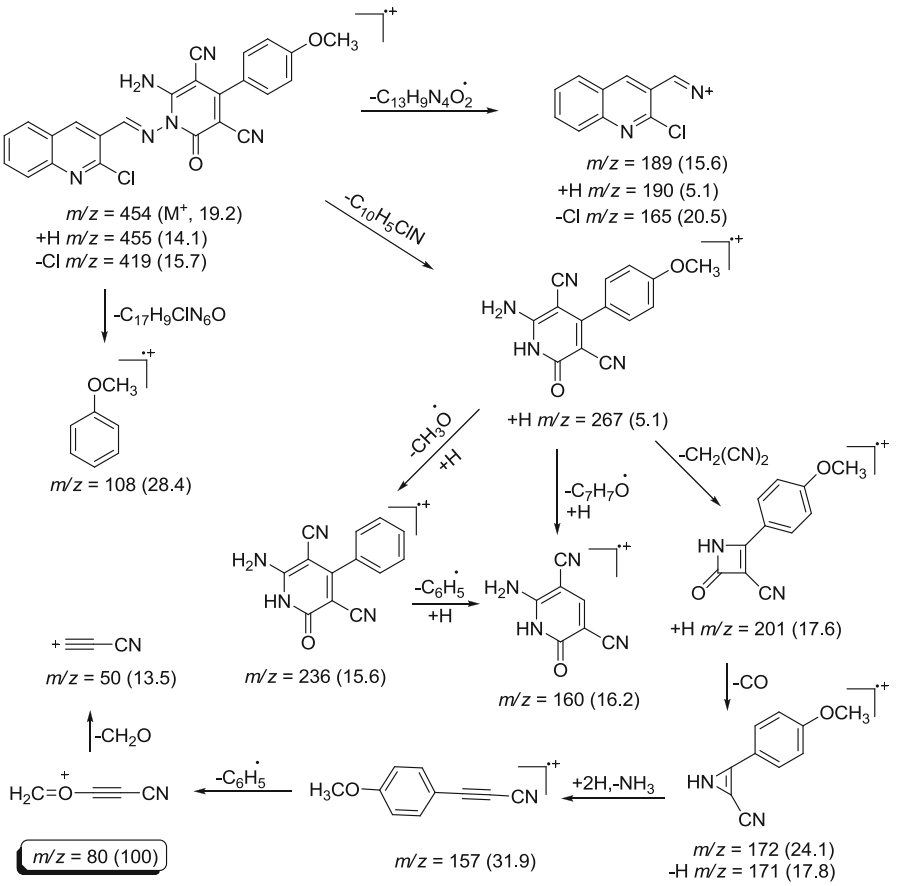


Fig. 1 Mass fragmentation pattern of compound **9a**

As an extension of this study, the behavior of **3** toward 2-hydroxybenzaldehydes as a convenient synthetic route to some new coumarins incorporating the quinoline structure was also investigated. Thus, condensation of **3** with salicylaldehyde, 5-bromosalicylaldehyde, and 5-nitrosalicylaldehyde in boiling ethanolic piperidine solution furnished the 2-iminocoumarin derivatives **10a–c**. The structures of these products were confirmed by IR spectroscopy which revealed the absence of a nitrile function and the appearance of absorption bands in the regions 3,354–3,284, 1,662–1,654, and 1,615–1,610 cm^{-1} characteristic of NH, C=O, and C=N functionality, respectively. Their ^{1}H NMR spectra revealed a coumarin-H_4 proton as a singlet signal resonating at approximately δ 7.96 ppm, and the other signals expected (Scheme 4). The iminocoumarins **10a–c** were converted to coumarins **11a–c** upon warming in ethanol containing a catalytic amount of conc. HCl. Surprisingly, chemical testing of the isolated products revealed the absence of chlorine atoms, and the IR spectrum of **11b** contained five strong absorption bands at 3,448, 3,258, 1,717, 1,670, and 1,655 cm^{-1} assignable to two amidic NH, C=O, and amidic carbonyl functionality, respectively. Its ^{1}H NMR spectrum contained four singlets at δ 8.26, 8.34, 8.85, and 9.07 ppm assignable to coumarin-H_5, coumarin-H_4, quinoline-H_4, and CH=N protons, respectively, and two singlets, exchangeable with D_2O, at δ 10.18 and 12.10 ppm, assigned to two amidic NH protons, and the multiplet signal centered around δ 7.35–8.09 ppm which integrated to six aromatic protons. The ^{13}C NMR spectrum of compound **11b** contained 20 signals, the most important of which at δ 157.9, 165.4, and 177.2 ppm were characteristic of three carbonyl carbons. The mass spectra of coumarins **11a–c** contained molecular ion peaks (M^+) in agreement with their molecular formulas. This analysis proved the structures of **11a–c** as the reaction products.

A plausible mechanism for formation of coumarins **10a–c** and **11a–c** may be initial Knoevenagel condensation of the active methylene nitrile of **3** with carbonyl groups of the salicylaldehyde derivatives followed by intramolecular 1,6-dipolar cyclization via addition of a phenolic OH group to the nitrile function to give the isolated iminocoumarins **10a–c**; these underwent acid-catalyzed hydrolysis to afford the target coumarins **11a–c**.

The behavior of compound **3** toward diazotized aromatic amines as potential precursors for hydrazonyl nitriles was also investigated. Thus, coupling of compound **3** with a series of diazotized aromatic amines in pyridine at 0–5 °C furnished the arylhydrazones **12a–c** in excellent yields (Scheme 5). Formation of arylhydrazones, rather than arylazo derivatives (CH–azo), was established from their IR spectra, which contained absorption bands in the regions 2,215–2,209 and 1,700–1,696 cm^{-1}, ascribed to conjugated CN and C=O functionality, respectively. In addition, their ^{1}H NMR spectra contained no singlet peak at δ 5.72 ppm, characteristic of the CH proton of the CH–azo compounds [27]. It is important to mention that arylhydrazones **12a–c** can occur as two geometric structures, the *E* and *Z* configurations. Predominant formation of the *Z* configuration was apparent from their ^{1}H NMR spectra which contained the hydrazone proton (C=N–NH) signal at δ = 11.90–11.94 ppm, which agrees with previous reports for similar hydrazones [28].

We next investigated the heterocyclization of hydrazonyl nitrile **12a** with formalin. Thus, treatment of **12a** with formalin in ethanol under reflux containing a

catalytic amount of piperidine afforded, as sole product, in moderate yield, the 1,2,4-triazin-5-one derivative **13**. The IR spectrum of **13** contained absorption bands at 2,212, 1,701, and 1,617 cm^{-1} ascribed to CN, C=O, and C=N functionality, respectively. The ^{1}H NMR spectrum contained three sharp singlets at δ 4.50, 8.65, and 9.70 ppm, ascribed to CH_2, quinoline-H_4, and CH=N protons, and multiplet at δ 7.26–7.86 ppm region ascribed to nine aromatic protons. The ^{13}C NMR spectrum contained signals from 18 types of carbon atom; the most important signals at δ 76.6 and 163.9 ppm were characteristic of methylene and cyclic amidic carbonyl carbon atoms, respectively. Moreover, the mass spectrum of **13** contained a molecular ion peak at $m/z = 388$ (M^+) corresponding to the molecular formula $C_{20}H_{13}ClN_6O$. The mass fragmentation pattern depicted in Fig. 2 confirms its chemical structure.

Pharmacology

Antibacterial evaluation

Antibacterial screening of the compounds studied, to determine minimum inhibitory concentrations, was performed at the Microanalytical Center, Faculty of Science, Cairo University, Egypt. The compounds were tested to determine their in-vitro

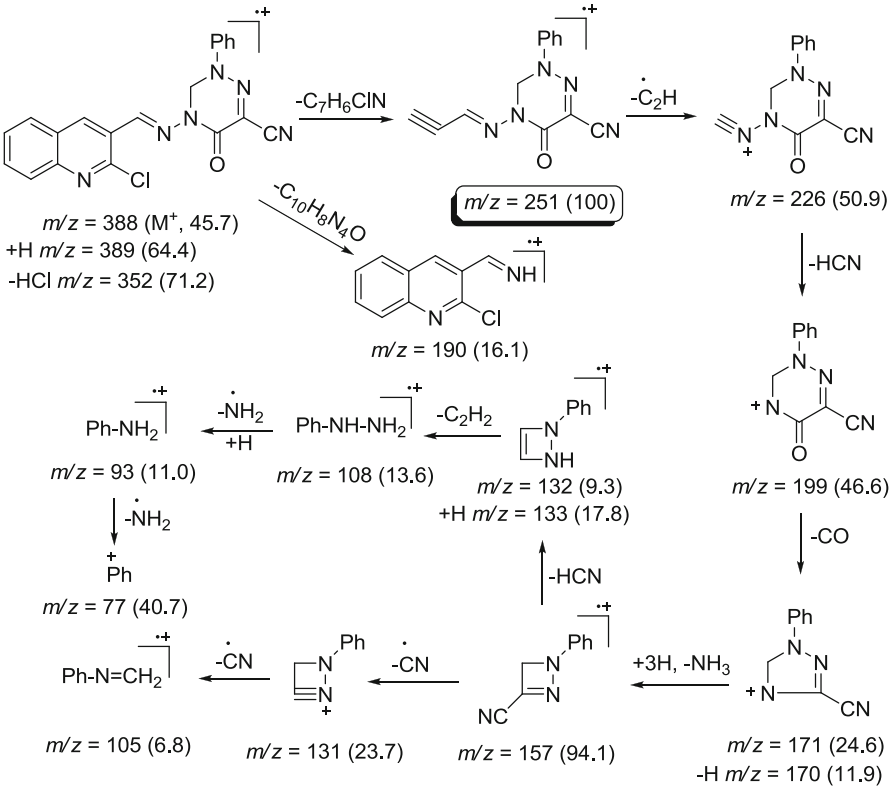


Fig. 2 Mass fragmentation pattern of compound **13**

antibacterial activity against the human pathogens *Bacillus subtilis*, *Streptococcus faecalis*, and *Pseudomonas aeruginosa*, as examples of Gram-positive bacteria, and *Staphylococcus aureus*, *Escherichia coli*, and *Neisseria gonorrhoeae*, as examples of Gram-negative bacteria. Preliminary screening for antibacterial activity was performed by the disk-diffusion method [29]. The results are recorded in Table 1 as the average diameter of zones of inhibition (IZ) of microbial growth around the disks (mm). The concentration tested was 5 mg/mL and ampicillin was used as reference drug.

The results listed in Table 1 reveal that nine of the 22 compounds tested had obvious inhibitory effect against the growth of Gram-positive and Gram-negative bacteria. All the compounds tested had moderate to high activity against the Gram-positive microorganisms (*B. subtilis*, *S. faecalis*, *S. aureus*; inhibition zones varied from 9 to 16 mm compared with 18–20 for ampicillin) and against the Gram-negative bacteria (*P. aeruginosa*, *E. coli*, *N. gonorrhoeae*; inhibition zones varied from 9 to 16 mm).

Compounds **9a–c** had the most potent effects against the Gram-positive bacteria (*B. subtilis*, *S. faecalis*, *S. aureus*) and compounds **9b** and **c** were very potent against the Gram-positive bacteria *B. subtilis* and *S. faecalis* with inhibition zones of 15 mm, compared with 20 mm for ampicillin. Compound **9b** had an effect against *S. aureus* close to that of ampicillin. The other compounds had a wide range of activity against all the Gram-positive bacteria tested, with weak to moderate potency.

The antibacterial activity of the compounds against Gram-negative bacteria are also listed in Table 1. Compounds **9a–c** resulted in the largest inhibition zones, 15, 16, and 15 mm, respectively, against *P. aeruginosa*, compared with 17 mm for ampicillin. Compounds **9b** and **c** were, moreover, very potent against *E. coli* with inhibition zones of 16 and 14 mm, respectively, compared with 22 mm for ampicillin. Compounds **9b** and **c** had relatively high growth inhibitory activity against *N. gonorrhoeae* (IZ 14 mm). The other compounds had moderate to weak

Table 1 Mean diameter of inhibition zone (mm) as indicator of the antibacterial activity of the newly synthesized compounds

Compounds	**5b**	**9a**	**9b**	**9c**	**9d**	**11a**	**11c**	**12c**	**13**	AMPI
Gram-positive bacteria										
B. subtilis	10	13	15	15	12	9	10	–[a]	12	20
S. faecalis	12	12	15	15	12	9	9	9	11	20
S. aureus	9	13	16	15	12	–	12	–	12	18
Gram-negative bacteria										
P. aeruginosa	11	15	16	15	11	–	9	–	11	17
E. coli	–	12	16	14	10	–	11	9	10	22
N. gonorrhoeae	11	12	14	14	11	10	10	11	11	20

AMPI ampicillin

[a] No activity

activity against growth of the different Gram-negative bacteria, with inhibition zones varying from 9 to 12 mm.

Study of the structures of the active compounds revealed they were mainly pyridones (**9a–d**) or coumarins (**11a** and **c**). Among the pyridones (**9a–d**), the nature of the substituent at position 4 on the phenyl ring seems to affect antibacterial activity. In this regard, the presence of such electron-withdrawing groups as Cl or F in pyridones **9b** or **9c** enhanced their antibacterial activity whereas the presence of the electron-donating group OCH_3 in pyridone **9a** reduced its antimicrobial activity. With regard to the second series, coumarins **11a** and **c** had moderate antibacterial activity against *S. aureus*. Substituting the hydrogen atom at position 6 of the coumarin ring with an electron-withdrawing NO_2 group (**11c**), resulted in dramatic enhancement of activity against all the organisms tested.

Anticancer evaluation

The cytotoxic effects of the newly synthesized compounds against four human tumor cell lines, breast cancer (MCF-7), non-small cell lung (NCI-H460), central nervous system (SF-268), and lung fibroblasts WI-38, were evaluated at the National Institute of Cancer, Cairo, Egypt. Doxorubicin was used as reference drug.

The results revealed that the compounds in Table 2 had variable inhibitory activity against the cell lines. With regard to activity against MCF-7, NCI-H460, and SF-268, the highest cytotoxic activity was observed for compounds **4a**, **d**, **9a**, **c**, **10c**, **11c**, **12c**, and **13**. The other compounds had weak to moderate inhibitory activity. Interestingly, compound **4d** was more active than doxorubicin against MCF-7 and NCI-H460, with IC_{50} of 0.01 and 0.02 μg/mL, respectively.

Compounds **9a**, **c**, and **13** had the highest IC_{50} of 0.04, 0.07, and 0.02 μg/mL, respectively, against NCI-H460 compared with 0.09 μg/mL for doxorubicin. Similarly, compounds **9a**, **12c**, and **13** had higher activity (0.021, 0.02, and 0.01 μg/mL) than doxorubicin (IC_{50} 0.09 μg/mL) against SF-268. The other compounds had a wide range of activity against the three cell lines MCF-7, NCI-H460, and SF-268. Some of the compounds tested had high growth-inhibitory activity against WI-38. The best activity was that of **10b** and **12c**.

With regard to structure–activity relationships (SAR) for the compounds, the acrylamide **4d** and the pyridones **9a** and **c** were the most active against cell lines MCF-7 and NCI-H460. The 1,2,4-triazine **13** was most active against NCI-H460 and SF-268. Cyclization of arylhydrazononitrile **12** to the 1,2,4-triazine resulted in enhanced anticancer activity. Conversion of acrylamides **4** to aminopyrazoles **5** resulted in reduced anticancer activity. Among the coumarin series, coumarin **11c**, with the powerful electron-withdrawing NO_2 group, was most active against MCF-7. The sensitivity of the cell lines to 3-hetarylquinolines was in the descending order NCI-H460 > SF-268 > MCF-7 > WI-38.

Table 2 Cytotoxicity (IC_{50}) of the tested compounds against different cell lines

Compounds	IC_{50} (μg/mL)[a]			
	MCF-7	NCI-H460	SF-268	WI-38
3	20.45 ± 2.18	6.30 ± 1.09	1.80 ± 1.08	38.58 ± 2.25
4a	6.67 ± 1.18	5.93 ± 3.16	4.26 ± 1.81	>100
4d	0.010 ± 0.006	0.020 ± 0.006	0.10 ± 0.06	48.50 ± 5.81
5b	22.05 ± 10.22	18.72 ± 4.70	12.69 ± 3.80	>100
5c	33.60 ± 4.60	26.73 ± 6.60	22.65 ± 4.80	>100
9a	0.050 ± 0.008	0.040 ± 0.009	0.021 ± 0.006	>100
9c	0.80 ± 0.03	0.070 ± 0.002	20.41 ± 2.08	66.12 ± 8.20
10b	28.26 ± 8.22	18.59 ± 4.18	16.22 ± 4.18	26.16 ± 4.22
10c	4.20 ± 1.42	0.89 ± 0.08	2.08 ± 1.06	68.08 ± 4.88
11a	22.05 ± 10.22	18.72 ± 4.70	12.69 ± 3.80	>100
11c	0.66 ± 0.02	1.41 ± 0.02	2.060 ± 0.008	>100
12b	20.82 ± 6.32	31.27 ± 8.32	52.21 ± 6.22	>100
12c	0.20 ± 0.01	0.60 ± 0.04	0.020 ± 0.006	18.40 ± 0.68
13	0.080 ± 0.004	0.020 ± 0.006	0.010 ± 0.004	77.80 ± 8.67
Doxorubicin	0.040 ± 0.008	0.090 ± 0.008	0.090 ± 0.007	>100

[a] Results (mean ± SEM from three independent experiments performed in duplicate) are the concentrations which inhibited cell growth by 50 % (IC_{50}) after continuous exposure for 48 h

Conclusion

The purpose of this study was to synthesize new 3-hetarylquinolines and to investigate their antibacterial and anticancer activity, in the hope of discovering new structures which might lead to the development of potent antibacterial and anticancer agents. We synthesized four different groups of compounds with hybrid structures containing, basically, the quinoline group linked to pyrazole, pyridone, coumarin, or 1,2,4-triazine groups. The results obtained clearly showed that compounds derived from coumarins and pyridones had better antibacterial activity and that compounds derived from pyridones and 1,2,4-triazine had excellent anticancer activity.

Experimental

The chemicals used for synthesis were obtained from Aldrich and Sigma, and were used without further purification. The solvents used were of analytical-grade. Melting points were determined by use of a Stuart SMP11 apparatus and are uncorrected. Elemental analysis was performed at the Central Laboratories, Faculty of Science, King Saud University; the results were in satisfactory agreement with calculated values. IR spectra were acquired (KBr) by use of a Thermo Scientific Smart Omni-Transmission spectrophotometer at the Faculty of Science, King

Khalid University. ^{1}H NMR and ^{13}C NMR spectra were acquired by use of Bruker NMR 500 MHz Ultra Shield, in DMSO-d_6 and CF_3COOD as solvents, at the Faculty of Science, King Khalid University, Saudi Arabia. Mass spectra were acquired with a Finnegan MAT 212 instrument, at the Microanalytical Unit, Faculty of Science, Cairo University. 2-Chloro-3-formylquinoline (**2**) and *N*′-((2-chloroquinolin-3-yl)methylene)-2-cyanoacetohydrazide (**3**) were prepared as reported elsewhere [7, 24].

General procedure for synthesis of acrylohydrazide derivatives **4a**–**e**

A mixture of compound **3** (0.79 g, 0.002 mol) and an aromatic aldehyde (0.002 mol) in absolute ethanol (30 mL) containing piperidine (three drops) was heated under reflux for 4 h. The precipitate obtained was isolated by filtration, dried well, and recrystallized from 1:2 EtOH–DMF to give compounds **4a**–**e**.

N′-*((2-Chloroquinolin-3-yl)methylene)-2-cyano-3-phenylacrylohydrazide (**4a**)*

Yellow powder; yield 63 %; mp = 229–230 °C; IR (KBr) υ_{max}/cm^{-1} = 3,175 (NH), 2,220 (CN), 1,673 (C=O, amidic), 1,617 (C=N), 1,595 (C=C, conjugated), 750 (C–Cl); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 7.62 (t, J = 7.5 Hz, 1H, Ar–H_4), 7.63 (t, J = 7.5 Hz, 2H, $Ar_{3,5}$), 7.71 (t, J = 7.5 Hz, 1H, quinoline-H_6), 7.89 (t, J = 7.5 Hz, 1H, quinoline-H_6), 8.00 (d, J = 7.5 Hz, 2H, Ar–$H_{2,6}$), 8.03 (d, J = 6 Hz, 1H, quinoline-H_8), 8.25 (d, J = 6 Hz, 1H, quinoline-H_5), 8.36 (s, 1H, quinoline-H_4), 8.95 (s, 1H, CH=, olefinic), 8.98 (s, 1H, CH=N), 12.37 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ_{ppm} = 105.2 (C= CN), 115.9 (CN), 125.8 (quinoline-C_3), 126.8 (quinoline-C_{4a}), 127.6 (quinoline-C_6), 127.9 (Ar–C_4), 129.1 (quinoline-C_8), 130.2 (Ar–$C_{3,5}$), 131.8 (quinoline-C_7), 131.9 (Ar–$C_{2,6}$), 132.8 (Ar-C_1), 136.0 (quinoline-C_7), 144.6 (C=N), 147.3 (quinoline-C_{8a}), 148.5 (C–Ar), 151.9 (quinoline-C_2), 158.5 (C=O); MS *m*/*z* (%) = 360 (M^+, 1.7), 283 (1.2), 232 (4.2), 204 (1.8), 205 (0.5),190 (3.0), 189(11.1), 172 (26.6), 171 (100), 162 (0.5), 156 (38.55),122 (0.1),120 (0.2); Anal. Calcd. for $C_{20}H_{13}ClN_4O$ (360.79): C, 66.58; H, 3.63; N, 15.53 %, Found: C, 66.55; H, 3.60; N, 15.50 %.

N′-*((2-Chloroquinolin-3-yl)methylene)-2-cyano-3-p-tolylacrylohydrazide (**4b**)*

Yellow powder; yield 58 %; mp = 209–210 °C; IR (KBr) υ_{max}/cm^{-1} = 3,284 (NH), 2,212 (CN), 1,692 (C=O, amidic), 1,617 (C=N), 1,589 (C=C, conjugated), 757 (C–Cl); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.42 (s, 3H, CH_3),7.43 (d, J = 8 Hz, 2H, Ar–$H_{3,5}$), 7.72 (t, J = 7.5 *Hz*, 1H, quinoline-H_6), 7.89 (t, J = 7.5 Hz, 1H, quinoline-H_7), 7.95 (t, J = 7.5 *Hz*, 2H, Ar–$H_{2,6}$), 7.98 (d, J = 8.5 Hz, 1H, quinoline-H_5), 8.27 (d, J = 8.5 Hz, 1H, quinoline-H_8), 8.31 (s, 1H, quinoline-H_4), 8.95 (s, 1H, CH=, olefinic), 8.98 (s, 1H, CH=N), 12.32 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ_{ppm} = 21.3 (CH_3), 104.9(C–CN),116.7(CN), 125.8 (quinoline-C_3), 126.8 (quinoline-C_{4a}), 127.7 (quinoline-C_6), 127.9 (quinoline-C_8), 129.1 (quinoline-C_5), 129.9 (Ar–$C_{2,6}$), 130.4 (Ar–$C_{3,5}$), 131.9 (Ar–C_1), 132.7 (quinoline-C_7), 136.0 (Ar–C4), 139.9 (quinoline-C_4), 147.3 (quinoline-C_{8a}), 148.8 (C–Ar),151.8 (quinoline-C_2), 168.9 (C=O); MS *m*/*z* (%) = 374 (M^+, 1.2),

359 (8.1), 283 (0.9), 232 (10.1), 204 (1.6), 205 (0.4),190 (11.1), 189 (2.7), 186 (25.9), 185 (100),162 (1.1), 142 (19.2); Anal. Calcd. for $C_{21}H_{15}ClN_4O$ (374.82): C, 67.29; H, 4.03; N, 14.95 %, Found: C, 67.25; H, 4.00; N, 14.91 %.

*N′-((2-Chloroquinolin-3-yl)methylene)-2-cyano-3-(4-methoxyphenyl) acrylohydrazide (**4c**)*

Yellow powder; yield 42 %; mp = 191–192 °C; IR (KBr) υ_{max}/cm^{-1} = 3,250 (NH), 2,208 (CN), 1,685 (C=O, amidic), 1,617 (C=N), 1,585 (C=C, conjugated), 757 (C–Cl); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 3.89 (s, 3H, OCH_3), 7.18 (d, J = 8.5 Hz, 2H, Ar–$H_{3,5}$), 7.71 (t, J = 7 Hz, 1H, quinoline-H_6), 7.89 (t, J = 7 *Hz*, 1H, quinoline-H_7), 7.96 (d, J = 9.5 Hz, 1H, quinoline-H_8), 8.00 (d, J = 8.5 Hz, 2H, Ar–$H_{2,6}$), 8.08 (d, J = 9.5 Hz, 1H, quinoline-H_5), 8.25 (s, 1H, quinoline-H_4), 8.61 (s, 1H, CH=, olefinic), 8.98 (s, 1H, CH=N), 12.27 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ_{ppm} = 55.7 (OCH_3), 104.5 (C–CN), 114.9 (Ar–$C_{3,5}$), 115.2 (CN), 123.6 (quinoline-C_3), 124.5 (Ar–C_1), 126.8 (quinoline-C_{4a}), 127.6 (quinoline-C_6), 127.9 (quinoline-C_8), 129.1 (quinoline-C_5), 131.9 (Ar–$C_{2,6}$), 132.9 (quinoline-C_7), 135.9 (quinoline-C_4), 143.7(CH=N), 147.2 (quinoline-C_{8a}),149.5 (C–Ar), 152.7 (quinoline-C_2), 161.7(Ar–C_4), 162.9(C=O); MS *m/z* (%) = 390 (M^+, 1.2), 283 (6.9), 257 (7.9), 204 (8.6), 205 (7.3), 201 (92.5), 189 (10.2), 186 (100), 177 (17.4), 158 (51.8), 107 (8.9), 77 (46.7); Anal. Calcd. for $C_{21}H_{15}ClN_4O_2$ (390.82): C, 64.54; H, 3.87; N, 14.34 %, Found: C, 64.51; H, 3.84; N, 14.30 %.

*N′-((2-Chloroquinolin-3-yl)methylene)-2-cyano-3-(furan-2-yl)acrylohydrazide (**4d**)*

Green crystals; yield 78 %; mp > 300 °C; IR (KBr) υ_{max}/cm^{-1} = 3,251 (NH), 2,201 (CN), 1,654 (C=O, amidic), 1,617 (C=N), 1,577 (C=C, conjugated),777 (C–Cl); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 6.95 (t, J = 4.5 Hz, 1H, furan-H_4), 7.66 (t, J = 7.5 Hz, 1H, quinoline-H_6), 7.68 (d, J = 6 Hz, 1H, furan-H_3), 7.74 (t, J = 7.5 Hz, 1H, quinoline-H_7), 7.90 (d, J = 8 Hz, 1H, quinoline-H_5), 8.08 (d, J = 8 Hz, 1H, quinoline-H_8), 8.22 (s, 1H, quinoline-H_4), 8.26 (d, J = 6 Hz, 1H, furan-H_5), 8.76 (s, 1H, CH=, olefinic), 9.02 (s, 1H, CH = N), 12.15 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ_{ppm}=110.9 (furan-C_3), 112.2 (furan-C_4), 113.8 (C–CN), 115.1 (CN), 124.2 (quinoline-C_3), 126.5 (quinoline-C_{4a}), 127.0 (quinoline-C_6), 127.9 (quinoline-C_8), 128.4 (quinoline-C_5), 131.8 (quinoline-C_7), 136.3 (quinoline-C_4), 144.2 (CH=N), 145.7 (furan-C_4), 149.1 (quinoline-C_{8a}), 150.0 (furan-C_2), 152.7 (quinoline-C_2), 154.7 (=C-Furan), 166.9 (C = O); MS *m/z* (%) = 350 (M^+, 61.8), 283 (79.8), 204 (11.2), 175 (58.4), 171 (100), 147 (67.4), 118 (51.7), 67 (6.7); Anal. Calcd. for $C_{18}H_{11}ClN_4O_2$ (350.76): C, 61.64; H, 3.16; N, 15.97 %, Found: C, 61.60; H, 3.12; N, 15.94 %.

*N′-((2-Chloroquinolin-3-yl)methylene)-2-cyano-3-(thiophen-2yl)acrylohydrazide (**4e**)*

Yellow powder; yield 62 %; mp = 216–217 °C; IR (KBr) υ_{max}/cm^{-1} = 3,190 (NH), 2,208 (CN), 1,661 (C=O, amidic), 1,618 (C=N), 1,577 (C=C, conjugated), 787 (C–Cl); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 7.37 (t, J = 4.5 Hz, 1H, thiophene-H_4), 7.71 (t, J = 7 Hz, 1H, quinoline-H_6), 7.88 (t, J = 7.0 Hz, 1H, quinoline-H7), 8.00

(d, $J = 8.5$ Hz, 1H, quinoline-H_5), 8.01(d, $J = 5$ Hz, 1H, thiophene-H_3), 8.18 (d, $J = 5$ Hz, 1H, thiophene-H_5), 8.25 (d, $J = 8.5$ Hz, 1H, quinoline-H_8), 8.60 (s, 1H, quinoline-H_4), 8.97 (s, 1H, CH=,olefinic), 8.98 (s, 1H, CH=N), 12.27 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): $\delta_{ppm} = 98.8$ (C–CN), 114.5 (CN), 126.8 (quinoline-C_3), 127.7 (quinoline-C_{4a}), 127.9 (quinoline-C_6), 128.7 (quinoline-C_8), 129.1 (quinoline-C_5), 131.9 (thiophene-C_4), 135.8 (thiophene-C_3), 135.9 (thiophene-C_5), 139.5 (quinoline-C_7), 142.2 (quinoline-C_4), 143.6 (thiophene-C_2), 147.2 (CH=N), 148.4 (quinoline-C_{8a}), 149.3 (quinoline-C_2), 151.2 (=C-Thiophene), 168.1 (C=O); MS *m/z* (%) = 366 (M^+, 0.8), 283 (0.2), 257 (10.02), 232 (0.2), 205 (0.5), 204 (2.3), 190 (1.0), 189 (2.1), 178 (30.6), 177 (100), 162 (79.2), 134 (61.3), 82 (2.4); Anal. Calcd. for $C_{18}H_{11}ClN_4OS$ (366.82): C, 58.94; H, 3.02; N, 15.27 %, Found: C, 58.90; H, 3.00; N, 15.23 %.

General procedure for the synthesis of pyrazolylquinoline derivatives **5a–c**

A mixture of compound **4a**, **b**, or **c** (0.001 mol) and hydrazine hydrate (1 mL, 0.002 mol) in ethanol (30 mL) was heated under reflux for 4 h. The reaction mixture was left to cool to room temperature then poured on to ice-cold water (25 mL). The solid product obtained was collected by filtration, washed with water, dried, and recrystallized from 1:4 DMF–EtOH to give compounds **5a–c**.

*3-Amino-N′-((2-chloroquinolin-3-yl)methylene)-5-phenyl-1H-pyrazole-4-carbohydrazide (**5a**)*

Yellow crystals; yield 55 %; mp > 300 °C; IR(KBr) $\upsilon_{max}/cm^{-1} = 3{,}421$, 3,329 ($NH_2$), 3,193 (NH), 3,141(NH, amidic), 1,636 (C=O, amidic), 1,616 (C=N), 1,596 (C=C, conjugated), 751 (C–Cl); ^{1}H NMR (DMSO-d_6): $\delta_{ppm} = 6.45$ (s, 1H, NH_2), 7.37 (t, $J = 6$ Hz, 1H, Ar–H_4), 7.43 (t, $J = 7.5$ Hz, 2H, Ar–$H_{3,5}$), 7.55 (t, $J = 7$ Hz, 1H, quinoline-H_6), 7.62 (t, $J = 7$ *Hz*, 1H, quinoline-H_7), 7.77 (d, $J = 7.5$ Hz, 2H, Ar–$H_{2,6}$), 7.80 (d, $J = 6.5$ Hz, 1H, quinoline-H_8), 7.98 (d, $J = 6.5$ Hz, 1H, quinoline-H_5), 8.20 (s, 1H, quinoline-H_4), 9.00 (s, 1H, CH=N), 10.90 (s, 1H, NH), 13.00 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): $\delta_{ppm} = 93.4$ (pyrazole-C_4), 123.9 (quinoline-C_3), 124.6 (pyrazole-C_5), 126.0 (quinoline-C_{4a}), 127.1 (quinoline-C_6), 127.7 (Ar-$C_{2,6}$), 127.9 (quinoline-C_8), 128.0 (quinoline-C_5), 128.6 (Ar–C_4), 129.4 (Ar–$C_{3,5}$), 131.5 (quinoline-C_7), 132.8 (Ar–C_1), 138.1 (quinoline-C_4), 143.6 (CH=N), 149.0 (quinoline-C_{8a}), 151.9 (quinoline-C_2), 153.0 (pyrazole-C_3), 162.7 (C=O); MS *m/z* (%) = 390 (M^+, 61.7), 355 (65.9), 280 (30.9), 264 (89.4), 229 (2.1), 223 (55.3), 219 (100), 159 (3.2),158 (25.5),152 (20.2); Anal. Calcd. for $C_{20}H_{15}ClN_6O$ (390.83): C, 61.46; H, 3.87; N, 21.50 %, Found: C, 61.43; H, 3.83; N, 21.54 %.

*3-Amino-N′-((2-chloroquinolin-3-yl)methylene)-5-p-tolyl-1H-pyrazole-4-carbohydrazide (**5b**)*

Yellow powder; yield 70 %; mp = 126–127 °C; IR (KBr) υ_{max}/cm^{-1}: 3,421,3,329 (NH_2), 3,193 (NH), 3,141(NH, amidic), 1,636 (C=O, amidic), 1,594 (C=C, conjugated), 751 (C–Cl); ^{1}H NMR (DMSO-d_6): $\delta_{ppm} = 2.30$ (s, 3H, CH_3), 6.50

(s, 1H, NH_2), 7.23 (d, $J = 6$ Hz, 2H, Ar–$H_{3,5}$), 7.62 (t, $J = 7$ Hz, 1H, quinoline-H_6), 7.67 (d, $J = 6$ Hz, 2H, Ar–$H_{2,6}$), 7.70 (t, $J = 7$ Hz, 1H, quinoline-H_7), 7.88 (d, $J = 6.5$ Hz, 1H, quinoline-H_8), 8.00 (d, $J = 6.5$ Hz, 1H, quinoline-H_5), 8.66 (s, 1H, quinoline-H_4), 9.10 (s, 1H, CH=N), 10.93 (s, 1H, NH), 13.24 (s, 1H, NH, Pyrazole); ^{13}C NMR (DMSO-d_6): $\delta_{ppm} = 22.1$ (CH_3), 90.9 (pyrazole-C_4), 124.0 (quinoline-C_3), 125.3 (pyrazole-C_5), 126.5 (quinoline-C_{4a}), 127.0 (quinoline-C_6), 127.5 (quinoline-C_8), 128.0 (quinoline-C_5), 128.7 (Ar–$C_{2,6}$), 129.1 (Ar–$C_{3,5}$), 130.3 (Ar–C_1), 131.2 (quinoline-C_7), 132.0 (Ar–C_4), 137.7 (quinoline-C_4), 143.4 (CH=N), 148.9 (quinoline-C_{8a}), 152.0 (quinoline-C_2), 154.5 (pyrazole-C_3), 163.3 (C=O); MS *m/z* (%) = 404 (M^+, 10.2), 389 (0.2), 347 (0.9), 314 (4.9), 313 (0.7), 309 (4.7), 307 (100), 216 (5.6), 190 (1.9), 189 (3.6), 162 (7.4); Anal. Calcd. for $C_{21}H_{17}ClN_6O$ (404.85): C, 62.30; H, 4.23; N, 20.76 %, Found: C, 62.34; H, 4.20; N, 20.72 %.

*3-Amino-N′-((2-chloroquinolin-3-yl)methylene)-5-(4-methoxyphenyl)-1H-pyrazole-4-carbohydrazide (**5c**)*

Yellow powder; yield 55 %; mp = 151–152 °C; IR (KBr) $\upsilon_{max}/cm^{-1} = 3{,}420, 3{,}329$ (NH_2), 3,193 (NH), 3,141(NH, amidic) 1,636 (C=O, amidic),1,604 (C=N), 1,583 (C=C, conjugated), 750 (C–Cl); ^{1}H NMR (DMSO-d_6): $\delta_{ppm} = 3.80$ (s, 3H, CH_3), 6.51 (s, 1H, NH_2), 7.13 (d, $J = 6$ Hz, 2H, Ar–$H_{3,5}$), 7.60 (t, $J = 7.5$ Hz, 1H, quinoline-H_6), 7.64 (d, $J = 6$ Hz, 2H, Ar–$H_{2,6}$), 7.71 (t, $J = 7.5$ Hz, 1H, quinoline-H_7), 7.85 (d, $J = 7$ Hz, 1H, quinoline-H_8), 8.06 (d, $J = 7$ Hz, 1H, quinoline-H_5), 8.71 (s, 1H, quinoline-H_4), 9.22 (s, 1H, CH=N), 10.88 (s, 1H, NH), 13.17 (s, 1H, NH, Pyrazole); ^{13}C NMR (DMSO-d_6): $\delta_{ppm} = 53.7$ (OCH_3), 91.0 (pyrazole-C_4), 115.1 (Ar–$C_{3,5}$), 124.2 (quinoline-C_3), 125.6 (pyrazole-C_5), 126.0 (Ar–C_1), 126.4 (quinoline-C_{4a}), 127.3 (quinoline-C_7), 127.8 (quinoline-C_8), 128.1 (quinoline-C_5), 128.4 (Ar–$C_{2,6}$), 131.0 (quinoline-C_7), 137.5 (quinoline-C_4), 143.4 (CH=N), 149.1 (quinoline-C_{8a}), 152.0 (quinoline-C_2), 154.5 (pyrazole-C_3), 160.0 (Ar–C_4), 163.1 (C=O); MS *m/z* (%) = 420 (M^+, 39.5), 405 (33.7), 385 (33.1), 355 (42.4), 341 (41.3), 144 (33.1), 143 (33.7), 78 (10.5), 77 (100), 68 (36.6); Anal. Calcd. for $C_{21}H_{17}ClN_6O_2$ (420.85): C, 59.93; H, 4.07; N, 19.97 %, Found: C, 59.90; H, 4.03; N, 19.94 %.

General procedure for the synthesis of 2-pyridone derivatives **9a–d**

Arylidene malononitriles **6** (0.004 mol) were added to a solution of compound **3** (1 g, 0.004 mol) in absolute ethanol (30 mL) containing three drops of piperidine. The reaction mixture was heated under reflux for 6 h, then left to cool to room temperature. The solid product formed upon pouring on to ice–water (20 mL) was collected by filtration, dried, and recrystallized from 4:1 EtOH–DMF to give compounds **9a–d**.

*6-Amino-1-((2-chloroquinolin-3-yl)methylene-amino)-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**9a**)*

Yellow powder; yield 78 %; mp = 246–247 °C; IR (KBr) $\upsilon_{max}/cm^{-1} = 3{,}350, 3{,}243$ (NH_2), 2,212 (CN), 1,647 (C=O, amidic), 1,608 (C=N), 1,559 (C=C, conjugated), 1,387 (CH_3), 757 (C–Cl); ^{1}H NMR (DMSO-d_6): $\delta_{ppm} = 3.84$ (s, 3H, OCH_3), 6.87 (s, 2H,

NH_2), 7.08 (d, $J = 9$ Hz, 2H, Ar–$H_{3,5}$), 7.10 (d, $J = 9$ Hz, 2H, Ar–$H_{2,6}$), 7.48 (t, $J = 7.5$ Hz, 1H, quinoline-H_6), 7.51 (t, $J = 7.5$ Hz, 1H, quinoline-H_7), 8.10 (d, $J = 6.5$ Hz, 1H, quinoline-H_8), 8.12 (d, $J = 6.5$ Hz, 1H, quinoline-H_5), 8.76 (s, 1H, quinoline-H_4), 9.00 (s, 1H, CH=N); ^{13}C NMR (DMSO-d_6): $\delta_{ppm} = 55.2$ (CH_3), 78.1 (pyridine-C_5), 114.2 (Ar–$C_{3,5}$), 116.9 (pyridine-C_3), 117.3 (2CN), 123.2 (quinoline-C_3), 125.7 (Ar–C_1), 126.3 (quinoline-C_{4a}), 127.8 (quinoline-C_6), 128.1 (quinoline-C_8), 128.4 (quinoline-C_5), 129.2 (Ar–$C_{2,6}$), 130.2 (quinoline-C_7), 138.3 (quinoline-C_4), 142.9 (CH=N), 147.6 (quinoline-C_{8a}), 154.1 (quinoline-C_2), 156.7 (pyridine-C_6), 160.6 (Ar-C_4), 161.9 (C=O, pyridine-C_2), 162.3 (pyridine-C_4); MS *m/z* (%) = 455 (M^++1, 14.1), 454 (M^+, 19.2), 429 (16.2), 419 (15.7), 414 (6.8),398 (15.4), 190 (5.1),189 (15.7), 187 (0.27), 80 (100); Anal. Calcd. for $C_{24}H_{15}ClN_6O_2$ (454.87): C, 63.37; H, 3.32; N, 18.48 %, Found: C, 63.34; H, 3.29; N, 18.44 %.

*6-Amino-4-(4-chlorophenyl)-1-((2-chloroquinolin-3-yl)methyleneamino)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**9b**)*

Yellow powder; yield 89 %; mp = 141–142 °C; IR (KBr) υ_{max}/cm^{-1} = 3,356, 3,240 (NH_2), 2,214 (CN), 1,654 (C=O, amidic), 1,559 (C=C, conjugated), 756 (C–Cl); ^{1}H NMR (DMSO-d_6): $\delta_{ppm} = 6.73$ (s, 2H, NH_2), 7.54 (d, $J = 8.5$ Hz, 2H, Ar–$H_{2,6}$), 7.60 (d, $J = 8.5$ Hz, 2H, Ar–$H_{3,5}$), 7.62 (t, $J = 6.5$ Hz, 1H, quinoline-H_6), 7.63 (t, $J = 6.5$ Hz, 1H, quinoline-H_7), 7.95 (d, $J = 8$ Hz, 1H, quinoline-H_8), 8.15 (d, $J = 8$ *Hz*, 1H, quinoline-H_5), 8.75 (s, 1H, CH=N), 9.00 (s, 1H, quinoline-H_4); ^{13}C NMR (DMSO-d^6): $\delta_{ppm} = 77.4$ (pyridine-C_5), 116.1 (pyridine-C_3), 117.3, 117.6 (2CN), 125.4 (quinoline-C_3), 127.5 (quinoline-C_{4a}), 127.8 (quinoline-C_6), 128.1 (quinoline-C_8), 128.3 (quinoline-C_5), 128.6 (Ar–$C_{3,5}$), 129.4 (Ar–$C_{2,6}$), 130.5 (Ar–C_1), 131.2 (quinoline-C_7), 134.3 (Ar–C_4), 134.7 (quinoline-C_4), 144.8 (CH=N), 148.3 (quinoline-C_{8a}), 153.5 (quinoline-C_2), 156.1 (pyridine-C_6), 163.8 (C=O, pyridine-C_2), 165.9 (pyridine-C_4); MS *m/z* (%) = 458 (M^+, 23.9), 394 (16.3), 204 (18.7), 191 (17.5), 190 (3.9), 155 (1.5),111(2.42), 80 (100), 66 (4.2);Anal. Calcd. for $C_{23}H_{12}C_{l2}N_6O$ (459.29): C, 60.15; H, 2.63; N, 18.30 %, Found: C, 60.11; H, 2.60; N, 18.34 %.

*6-Amino-1-((2-chloroquinolin-3-yl)methyleneamino)-4-(2,4-difluorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (**9c**)*

Red powder; yield 82 %; mp = 115–116 °C; IR (KBr) υ_{max}/cm^{-1}: 3,353, 3,247 (NH_2), 2,216 (CN), 1,654 (C=O, amidic), 1,618 (C=N), 1,560 (C=C, conjugated), 756 (C–Cl); ^{1}H NMR (DMSO-d_6): $\delta_{ppm} = 6.75$ (s, 2H, NH_2), 6.70 (s, 1H, Ar–H_3), 6.87 (d, $J = 7$ Hz, 1H, Ar–H_5), 7.20 (d, $J = 7$ Hz, 1H, Ar–H_6), 7.35 (t, $J = 7.5$ Hz, 1H, quinoline-H_7), 7.53 (t, $J = 7.5$ Hz, 1H, quinoline-H_6), 7.70 (d, $J = 7$ Hz, 1H, quinoline-H_8), 7.81 (d, $J = 7$ Hz, 1H, quinoline-H_5), 8.12 (s, 1H, CH=N), 9.00 (s, 1H, quinoline-H_4); ^{13}C NMR (DMSO-d_6): $\delta_{ppm} = 75.4$ (pyridine-C_5), 109.9 (Ar–C_5), 113.7 (Ar–C_3), 115.5 (pyridine-C_3), 116.3, 116.9 (2CN), 118.1 (Ar–C_1), 126.3 (quinoline-C_3), 127.5 (quinoline-C_{4a}), 127.7 (quinoline-C_6), 128.1 (quinoline-C_8), 128.6 (quinoline-C_5), 129.4 (Ar–C_6), 131.8 (quinoline-C_7), 132.4 (quinoline-C_4), 141.2 (CH=N), 147.1 (quinoline-C_{8a}), 155.9 (quinoline-C_2), 158.5 (Ar–C_2), 159.3

(pyridine-C_6), 162.3 (Ar–C_4), 163.6 (C=O, pyridine-C_2), 165.3 (pyridine-C_4); MS *m/z* (%) = 460 (M^+, 27.9), 347 (24.3), 190 (0.4), 189 (16.9), 162 (8.8), 161 (3.7), 160 (1.8),159 (22.1), 127 (100), 113 (4.0), 94 (27.94), 80 (87.5); Anal. Calcd. for $C_{23}H_{11}ClF_2N_6O$ (460.82): C, 59.95; H, 2.41;N, 18.24 %, Found: C, 59.92; H, 2.46;N, 18.20 %.

*6-Amino-1-((2-chloroquinolin-3-yl)methyleneamino)-2-oxo-4-(thiophen-2-yl)-1,2-dihydropyridine-3,5-dicarbonitrile (**9d**)*

Orange powder; yield 80 %; mp > 300 °C; IR (KBr) υ_{max}/cm^{-1} = 3,350, 3,244(NH_2), 2,210 (CN), 1,654 (C=O, amidic), 1,610 (C=N), 1,559 (C=C, conjugated), 757(C–Cl); ^{1}H NMR (DMSO-d^6): δ_{ppm} = 6.96 (s, 2H, NH_2), 7.64-8.70 (m, 8H, Ar–H), 8.84 (s, 1H, CH=N); ^{13}C NMR (DMSO-d^6): δ_{ppm} = 63.6 (pyridine-C_5), 117.1, 117.4 (2CN), 120.1 (pyridine-C_3), 123.5 (quinoline-C_3), 124.3 (quinoline-C_{4a}), 126.1 (thiophen-C_3), 127.6 (quinoline-C_6), 128.1 (quinoline-C_8), 129.2 (quinoline-C_5), 129.8 (thiophen-C_4), 130.4 (thiophen-C_5), 132.2 (quinoline-C_7), 134.3 (thiophen-C_2), 136.2 (quinoline-C_4), 142.0 (CH=N), 145.6 (quinoline-C_{8a}), 151.2 (quinoline-C_2), 157.5 (pyridine-C_6), 163.8 (C=O, pyridine-C_2), 168.3 (pyridine-C_4); MS *m/z* (%) = 430 (M^+, 4.4), 348 (9.9), 289 (21.0), 269 (20.3), 268 (10.5), 213 (13.4), 211 (10.2), 162 (17.6), 105 (10.5), 80 (100); Anal. Calcd. for $C_{21}H_{11}ClN_6OS$ (430.87): C, 58.54; H, 2.57; N, 19.50 %, Found: C, 58.50; H, 2.53; N, 19.55 %.

General procedure for the synthesis of iminocoumarin derivatives **10a–c**

The substituted salicylaldehdye (0.002 mol) was added to a solution of compound **10** (0.79 g, 0.002 mol) in absolute ethanol (30 mL) containing three drops of piperidine. The reaction mixture was heated under reflux for 1 h, then left to cool to room temperature. The precipitate obtained was isolated by filtration, washed with ethanol, dried, and recrystallized from EtOH to afford compounds **10a–c**.

*N′-((2-Chloroquinolin-3-yl)methylene)-2-imino-2H-chromene-3-carbohydrazide (**10a**)*

Yellow powder; yield 60 %; mp = 225–227 °C; IR (KBr) ν_{max}/cm^{-1} = 3,354 (NH), 3,228 (NH), 1,662 (C=O, amidic), 1,611 (C=N), 1,583 (C=C, conjugated), 756 (C–Cl); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 7.04 (t, *J* = 8 Hz, 1H, (iminocoumarin-H_6), 7.29 (t, *J* = 8 Hz, 1H, (iminocoumarin-H_7), 7.49 (t, *J* = 8 Hz, 1H, quinoline-H_6), 7.56 (d, *J* = 8.5 Hz, 1H, (iminocoumarin-H_8), 7.72 (d, *J* = 8.5 Hz, 1H, (iminocoumarin-H_5), 7.96 (s, 1H, (iminocoumarin-H_4), 8.01 (d, *J* = 7.5 Hz, 1H, quinoline-H_8), 8.27 (d, *J* = 7.5 Hz, 1H, quinoline-H_5), 8.58 (s, 1H, quinoline-H_4), 8.91 (s, 1H, CH=N), 12.14 (s, 1H, NH), 13.87 (s, 1H, NH, Iminocoumarin); ^{13}C NMR (DMSO-d_6): δ_{ppm} = 109.7 (iminocoumarin-C_{4a}), 115.5 (iminocoumarin-C_8), 120.1 (iminocoumarin-C_3), 123.5 (iminocoumarin-C_6), 125.6 (quinoline-C_3), 126.9 (quinoline-C_{4a}), 127.6 (quinoline-C_6), 127.9 (quinoline-C_8), 129.1 (quinoline-C_5), 130.2 (iminocoumarin-C_4), 131.9 (iminocoumarin-C_5), 133,5 (iminocoumarin-C_7), 134.9 (quinoline-C_7), 136.2 (quinoline-C_4), 144.2 (CH=N), 147.3 (quinoline-

C_{8a}), 152.5 (quinoline-C_2), 154.7 (iminocoumarin-C_{8a}), 158.5 (iminocoumarin-C_2), 162.3 (C=O); MS *m/z* (%) = 376 (M^+, 0.9), 324 (0.8), 307 (100), 257 (1.1), 232 (0.7), 205 (1.7), 204 (3.4), 189 (65.4), 162 (7.4), 145 (62.2), 144 (5.3); Anal. Calcd. for $C_{20}H_{13}ClN_4O_2$ (376.79): C, 63.75; H, 3.48; N, 14.87 %, Found: C, 63.71; H, 3.44; N, 14.85 %.

*7-Bromo-N′-((2-chloroquinolin-3-yl)methylene)-2-imino-2H-chromene-3-carbohydrazide (**10b**)*

Orange powder; yield 69 %; mp = 198–199 °C; IR (KBr) ν_{max}/cm^{-1} = 3,354 (NH), 3,284 (NH) 1,654 (C=O, amidic), 1,614 (C=N), 1,599 (C=C, conjugated),750 (C–Cl); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 7.72 (t, *J* = 7 Hz, 1H, quinoline-H_6),7.88 (t, *J* = 7 Hz, 1H, quinoline-H_7), 7.96 (s, 1H, (iminocoumarin-H_5), 7.98 (d, *J* = 7.5 Hz, 1H, (iminocoumarin-H_4), 8.02 (d, *J* = 7.5 Hz, 1H, (iminocoumarin-H_8), 8.10 (d, *J* = 8.5 Hz, 1H, quinoline-H_8), 8.23 (d, *J* = 8.5 Hz, 1H, quinoline-H_5), 8.45(s, 1H, (iminocoumarin-H_8), 8.92 (s, 1H, quinoline-H_4), 9.01 (s, 1H, CH=N), 9.36 (s, 1H, NH, Iminocoumarin) 12.13 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ_{ppm} = 113.5 (iminocoumarin-C_8), 115.9 (iminocoumarin-C_{4a}), 120.9 (iminocoumarin-C_3), 125.7 (quinoline-C_3), 126.8 (quinoline-C_{4a}), 127.7 (quinoline-C_6), 127.9 (quinoline-C_8), 128.6 (iminocoumarin-C_5), 129.7 (quinoline-C_5), 131.6 (iminocoumarin-C_4), 131.8 (quinoline-C_7), 135.9 (iminocoumarin-C_6), 139.4(iminocoumarin-C_7), 147.1 (quinoline-C_4), 148.2 (CH=N), 152.3 (quinoline-C_{8a}), 155.7 (iminocoumarin-C_{8a}), 162.3 (quinoline-C_2), 165.3 (iminocoumarin-C_2, C=NH), 168.5 (C=O); MS *m/z* (%) = 455 (M^+, 9.7), 375 (2.2), 265 (2.6), 232 (0.8), 221 (6.4), 205 (4.5), 204 (4.5), 197 (8.9), 196 (3.5), 189 (14.6),169 (100), 162 (4.9); Anal. Calcd. for $C_{20}H_{12}BrClN_4O_2$ (455.69): C, 52.71; H, 2.65;N, 12.29 %, Found: C, 52.67; H, 2.61; N, 12.26 %.

*N′-((2-Chloroquinolin-3-yl)methylene)-2-imino-7-nitro-2H-chromene-3-carbohydrazide (**10c**)*

Yellow powder; yield 80 %; mp > 300 °C; IR (KBr) ν_{max}/cm^{-1} = 3,350 (NH), 3,285 (NH), 1,661 (C=O, amidic), 1,613 (C=N), 1,593 (C=C, conjugated), 762 (C–Cl), 1,348–1,529 (NO_2); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 7.39 (d, *J* = 7.5 Hz, 1H, (iminocoumarin-H_8), 7.52 (s, 1H, (iminocoumarin-H_4), 7.64 (t, *J* = 7 Hz, 1H, quinoline-H_6), 7.70 (s, 1H, (iminocoumarin-H_5), 7.85 (t, *J* = 7 Hz, 1H, quinoline-H_7), 8.52 (d, *J* = 7.5 Hz, 1H, (iminocoumarin-H_7), 8.54 (d, *J* = 8 Hz, 1H, quinoline-H_8), 8.65 (d, *J* = 8 Hz, 1H, quinoline-H_5), 8.83 (s, 1H, CH=N), 9.19 (s, 1H, quinoline-H_4), 10.24 (s, 1H, NH, Iminocoumarin), 12.23 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ_{ppm} = 110.9 (iminocoumarin-C_8), 112.7 (Iminocoumarin -C_{4a}), 112.9 (iminocoumarin-C_3), 113.1 (quinoline-C_3), 113.4 (iminocoumarin-C_5), 113.5 (iminocoumarin-C_7), 115.0 (quinoline-C_{4a}), 115.4 (quinoline-C_6), 115.6 (quinoline-C_8), 115.8 (quinoline-C_5), 124.7 (iminocoumarin-C_4), 125.9 (quinoline-C_7), 136.4 (quinoline-C_4), 141.1 (iminocoumarin-C_6), 143.6 (CH=N), 145.4 (quinoline-C_{8a}), 151.8 (quinoline-C_2), 158.1 (Iminocoumarin -C_{8a}), 162.3 (iminocoumarin-C_2), 168.5 (C=O); MS *m/z* (%) = 421(M^+, 7.3), 307 (100), 218 (6.1), 204

(3.9), 189 (0.2), 163 (5.9), 162(0.8), 144 (0.2), 128 (16.9); Anal. Calcd. for $C_{20}H_{12}ClN_5O_4$ (421.79): C, 56.95; H, 2.87; N, 16.60 %, Found: C, 56.91; H, 2.83; N, 16.57 %.

General procedure for synthesis of coumarin derivatives **11a–c**

A solution of compound **10a–c** (0.001 mol) in absolute ethanol (15 mL) containing conc. HCl (4 M, 5 mL) was heated under reflux for 1 h. The mixture was left to cool, and the precipitate was isolated by filtration, washed with water, dried, and recrystallized from acetic acid to afford compounds **11a–c**.

*N′-((2-Oxo-1,2-dihydroquinolin-3-yl)methylene)-2-oxo-2H-chromene-3-carbohydrazide (**11a**)*

Yellow powder; yield 69 %; mp > 300 °C; IR (KBr) ν_{max}/cm^{-1} = 3,443 (NH), 3,256 (NH), 1,716 (C=O), 1,664, 1,655 (2C=O, amidic), 1,610 (C=N), 1,560 (C=C, conjugated); ^{1}H NMR (CF_3COOD): δ_{ppm} = 7.16 (d, J = 7.5 Hz, 1H, coumarin-H_8), 7.18 (t, J = 7 Hz, 1H, coumarin-H_6), 7.31 (t, J = 6.5 Hz, 1H, quinoline-H_6), 7.39 (d, J = 7.5 Hz, 1H, coumarin-H_5), 7.48 (d, J = 8.5 Hz, 1H, quinoline-H_8), 7.51 (t, J = 7 Hz, 1H, coumarin-H_7), 7.64 (t, J = 6.5 Hz, 1H, quinoline-H_7), 7.69 (d, J = 8.5 Hz, 1H, quinoline-H_5), 8.59 (s, 1H, CH=N), 8.77 (s, 1H, coumarin-H_4), 8.87 (s, 1H, quinoline-H_4), 9.8 (s, 1H, NH), 12.66 (s, 1H, NH); ^{13}C NMR (CF_3COOD): δ_{ppm} = 115.4 (coumarin-C_3), 115.8 (quinoline-C_3), 116.3 (coumarin-C_8), 117.3 (coumarin-C_{4a}), 118.6 (coumarin-C_4), 122.9 (quinoline-C_{4a}), 123.1 (quinoline-C_6), 126.1 (coumarin-C_6), 126.8 (coumarin-C_8), 127.5 (coumarin-C_5), 127.8 (quinoline-C_5), 128.6 (coumarin-C_7), 130.8 (quinoline-C_7), 136.3 (quinoline-C_4), 144.2 (CH=N), 149.1 (quinoline-C_{8a}), 153.8 (coumarin-C_{8a}), 160.8 (C=O, coumarin-C_2), 167.2 (C=O), 178.5 (quinoline-C_2, C=O); MS m/z (%) = 359 (M^+, 14.5), 307 (29.0), 214 (3.9), 190 (100), 172 (15.6), 156 (8.4),128 (24.0); Anal. Calcd. for $C_{20}H_{13}N_3O_4$ (359.33): C, 66.85; H, 3.65; N, 11.69 %, Found: C, 66.81; H, 3.62; N, 11.66 %.

*6-Bromo-N′-((2-oxo-1,2-dihydroquinolin-3-yl)methylene)-2-oxo-2H-chromene-3-carbohydrazide (**11b**)*

Orange powder; yield 71 %; mp > 300 °C; IR (KBr) ν_{max}/cm^{-1} = 3,448 (NH), 3,258 (NH), 1,717(C=O), 1,670, 1,655 (2C=O, amidic), 1,611 (C=N), 1,559 (C=C, conjugated); ^{1}H NMR (CF_3COOD): δ_{ppm} = 7.35 (d, J = 6.5 Hz, 1H, coumarin-H_8), 7.41 (t, J = 7.5 Hz, 1H, quinoline-H_6), 7.59 (d, J = 6.5 Hz, 1H, coumarin-H_7), 7.63 (t, J = 6.5 Hz, 1H, quinoline-H_7), 7.84 (d, J = 8.5 Hz, 1H, quinoline-H_8), 8.09 (d, J = 8.5 Hz, 1H, quinoline-H_5), 8.26 (s, 1H, coumarin-H_5), 8.34 (s, 1H, coumarin-H_4), 8.85 (s, 1H, quinoline-H_4), 9.07 (s, 1H, CH=N), 10.18 (s, 1H, NH), 12.10 (s, 1H, NH); ^{13}C NMR (CF_3COOD): δ_{ppm} = 113.2 (coumarin-C_3), 114.5 (quinoline-C_3), 119.4 (coumarin-C_8), 119.9 (coumarin-C_4), 120.6 (coumarin-C_6), 123.9 (quinoline-C_{4a}), 124.2 (coumarin-C_{4a}), 125.0 (quinoline-C_6), 127.8 (quinoline-C_8), 128.5 (quinoline-C_5), 129.9 (coumarin-C_5), 130.5 (quinoline-C_7), 137.7

(quinoline-C_4), 143.8 (CH=N), 149.5 (quinoline-C_{8a}), 152.1 (coumarin-C_{8a}), 157.9 (C=O, coumarin-C_2), 165.4 (C=O), 177.2 (quinoline-C_2, C=O); MS *m/z* (%) = 437 (M^+, 0.3), 420 (0.2), 251 (100), 223 (6.6), 222 (0.1), 188 (0.2), 171 (0.9), 144 (0.3); Anal. Calcd. for $C_{20}H_{12}BrN_3O_4$ (438.23): C, 54.81; H, 2.76; N, 9.59 %, Found: C, 54.78; H, 2.73; N, 9.55 %.

*N′-((2-Oxo-1,2-dihydroquinolin-3-yl)methylene)-6-nitro-2-oxo-2H-chromene-3-carbohydrazide (**11c**)*

Yellow powder; yield 97 %; mp > 300 °C; IR (KBr) ν_{max}/cm^{-1} = 3,422 (NH), 3,256 (NH), 1,724 (C=O), 1,670, 1,654 (2C=O, amidic), 1,618 (C=N), 1,559 (C=C, conjugated), 1,517, 1,346 (NO_2); ^{1}H NMR (CF_3COOD): δ_{ppm} = 7.69 (t, *J* = 7 Hz, 1H, quinoline-H_6), 7.98 (t, *J* = 7 Hz, 1H, quinoline-H_7), 8.45 (d, *J* = 7.5 Hz, 1H, coumarin-H_8), 8.47 (d, *J* = 7.5 Hz, 1H, quinoline-H_8), 8.63 (d, *J* = 7.5 Hz, 1H, quinoline-H_5), 8.86 (d, *J* = 7.5 Hz, 1H, coumarin-H_7), 8.90 (s, 1H, coumarin-H_4), 9.50 (s, 1H, coumarin-H_5), 9.28 (s, 1H, quinoline-H_4), 9.32 (s, 1H, CH=N), 10.01 (s, 1H, NH), 10.37 (s, 1H, NH); ^{13}C NMR (CF_3COOD): δ_{ppm} = 115.7 (coumarin-C_3), 117.4 (quinoline-C_3), 118.6 (coumarin-C_8), 119.5 (coumarin-C_4), 122.9 (coumarin-C_{4a}), 125.8 (quinoline-C_{4a}), 125.9 (coumarin-C_5), 126.2 (coumarin-C_7), 127.7 (quinoline-C_6), 127.9 (quinoline-C_8), 129.6 (quinoline-C_5), 132.7 (quinoline-C_7), 137.9 (quinoline-C_4), 144.3 (CH=N), 146.1 (coumarin-C_6), 148.3 (quinoline-C_{8a}), 158.8 (coumarin-C_{8a}), 159.4 (C=O, coumarin-C_2), 168.2 (C=O), 180.0 (quinoline-C_2, C=O); MS *m/z* (%) = 404 (M^+, 55.2), 218 (55.2), 187 (54.5), 186 (41.0), 172 (54.5), 171 (41.0), 144 (44.8), 121 (52.2), 78 (100), 77 (0.8); Anal. Calcd. for $C_{20}H_{12}N_4O_6$ (404.33): C, 59.41; H, 2.99; N, 13.86 %, Found: C, 59.44; H, 2.96; N, 13.82 %.

General procedure for synthesis of arylhydrazone derivatives **12a–c**

A cold solution of aryl diazonium salt solution (prepared by addition of a solution of sodium nitrite (0.2 g, 0.025 mol) in water (5 mL) to aromatic amines (0.002 mol) in concentrated HCl (0.5 ml)) was added, in small portions, with stirring, over 30 min, to an ice-cold solution of compound **3** (0.79 g, 0.002 mol) in pyridine (10 mL). The solution was stirred for a further 2 h at 0 °C then diluted with cold water (10 mL). The precipitate formed was isolated by filtration, washed with water, dried well, and recrystallized from 3:1 EtOH–DMF to give compounds **12a–c**.

*2-(2-((2-Chloroquinolin-3-yl)methylene)-hydrazinyl)-2-oxo-N′-phenylacetohydrazonoyl cyanide (**12a**)*

Orange crystals; yield 99 %; mp = 216–217 °C; IR (KBr) ν_{max}/cm^{-1} = 3,205, 3,197 (2NH), 2,215 (CN), 1,667 (C=O, amidic), 1,616 (C=N), 1,559 (C=C, conjugated), 751 (C–Cl); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 7.27 (t, *J* = 6.5 Hz, 1H, Ar–H_4), 7.30 (d, *J* = 8 Hz, 2H, Ar–$H_{3,5}$), 7.40 (d, *J* = 8 Hz, 2H, Ar–$H_{2,6}$), 7.48 (t, *J* = 8 Hz, 1H, quinoline-H_6), 7.64 (t, *J* = 8 Hz, 1H, quinoline-H_7), 7.82 (d, *J* = 7.5 Hz, 1H, quinoline-H_8), 7.86 (d, *J* = 7.5 Hz, 1H, quinoline-H_5), 8.60 (s, 1H,

quinoline-H_4), 9.29 (s, 1H, CH=N), 11.92 (s, 1H, NH-Ar), 12.23 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ_{ppm} = 110.9 (C–CN), 113.0 (CN), 113.6 (Ar–$C_{2,6}$), 124.0 (Ar–C_4), 124.8 (quinoline-C_3), 125.8 (quinoline-C_{4a}), 125.9 (quinoline-C_6), 127.4 (quinoline-C_8), 127.6 (quinoline-C_5), 128.9 (Ar–$C_{3,5}$), 129.0 (quinoline-C_7), 129.9 (Ar-C_1), 142.5 (CH=N), 148.9 (quinoline-C_{8a}), 150.1 (quinoline-C_2), 163.9 (C=O); MS *m/z* (%) = 376 (M^+, 19.0), 351 (3.7), 307 (100), 299 (2.8), 274 (14.2), 162 (14.6); Anal. Calcd. for $C_{19}H_{13}ClN_6O$ (376.08): C, 60.56; H, 3.48; N, 22.30 %, Found: C, 60.53; H, 3.44; N, 22.27 %.

*2-(2-((2-Chloroquinolin-3-yl)methylene)-hydrazinyl)-2-oxo-N′-p-tolylacetohydrazonoyl cyanide (**12b**)*

Orange powder; yield 87 %; mp = 209–210 °C; IR (KBr) ν_{max}/cm^{-1} = 3,198, 3,101 (2NH), 2,209 (CN), 1,660 (C=O, amidic), 1,615 (C=N), 1,559 (C=C, conjugated),760 (C–Cl); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 2.32 (s, 3H, CH_3),7.24 (d, *J* = 8 Hz, 2H, Ar–$H_{2,6}$), 7.62 (d, *J* = 8 Hz, 2H, Ar–$H_{3,5}$), 7.71 (t, *J* = 7 Hz, 1H, quinoline-H_6), 7.88 (t, *J* = 7 Hz, 1H, quinoline-H_7), 8.12 (d, *J* = 8 *Hz*, 1H, quinoline-H_8), 8.24 (d, *J* = 8 Hz, 1H, quinoline-H_5), 8.45 (s, 1H, quinoline-H_4), 9.00 (s, 1H, CH=N), 11.94 (s, 1H, NH-Ar), 12.16 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ_{ppm} = 20.5 (CH_3), 106.2 (C–CN), 111.3 (CN), 116.4 (Ar–$C_{2,6}$), 125.7 (quinoline-C_8), 126.8 (quinoline-C_{4a}), 127.6 (quinoline-C_6), 127.8 (quinoline-C_6), 128.6 (quinoline-C_5),129.6 (Ar–$C_{3,5}$),131.8 (quinoline-C_7), 131.9(Ar–C_4), 135.7(quinoline-C_4), 139.6(Ar–C_1), 142.9 (CH=N), 148.5 (quinoline-C_{8a}), 159.1 (quinoline-C_2), 162.3 (C=O); MS *m/z* (%) = 390 (M^+, 85.4), 324 (60.0), 285 (76.4), 229 (59.1), 228 (52.8), 188 (54.55), 162 (57.3),154 (100); Anal. Calcd. for $C_{20}H_{15}ClN_6O$ (390.09): C, 61.46; H, 3.87; N, 21.50 %, Found: C, 61.42; H, 3.84; N, 21.54 %.

*2-(2-((2-Chloroquinolin-3-yl)methylene)-hydrazinyl)-N′-(4-methoxyphenyl)-2-oxoacetohydrazonoyl cyanide (**12c**)*

Orange powder; yield 88 %; mp = 181–182 °C; IR (KBr) ν_{max}/cm^{-1} = 3,208, 3,143 (2NH), 2,213 (CN), 1,664 (C=O, amidic), 1,616 (C=N), 1,559 (C=C, conjugated), 761 (C–Cl); ^{1}H NMR (DMSO-d_6): δ_{ppm} = 3.78 (s, 3H, CH_3), 7.01(d, *J* = 9 Hz, 2H, Ar–$H_{3,5}$), 7.69 (d, *J* = 9 Hz, 2H, Ar–$H_{2,6}$), 7.72 (t, *J* = 5.5 Hz, 1H, quinoline-H_6), 7.86 (t, *J* = 6 Hz, 1H, quinoline-H_7), 8.09 (d, *J* = 8 Hz, 1H, quinoline-H_8), 8.22 (d, *J* = 8 Hz, 1H, quinoline-H_5), 8.61 (s, 1H, quinoline-H_4), 8.93(s, 1H, CH=N), 11.90 (s, 1H, N–NH–Ar), 12.22 (s, 1H, NH–C=O); ^{13}C NMR (DMSO-d_6) δ_{ppm} = 55.3 (CH_3), 105.3(C–CN), 114.4(CN), 115.9(Ar–$C_{3,5}$), 117.9 (Ar-$C_{3,5}$), 125.7 (quinoline-C_3), 126.8 (quinoline-C_{4a}), 127.6 (quinoline-C_6), 127.8 (quinoline-C_8), 127.9 (quinoline-C_5), 131.8 (quinoline-C_7), 135.6 (Ar-C_1), 135.9 (quinoline-C_4), 143.0 (CH=N), 148.5 (quinoline-C_{8a}), 156.6 (quinoline-C_2), 158.9 (Ar–C_4), 162.3 (C=O); MS *m/z* (%) = 406 (M^+, 10.7), 376 (2.62), 375 (0.6), 299 (2.6), 232 (2.6), 205 (4.5), 204 (5.9), 189 (13.3), 162 (8.3), 122 (100); Anal. Calcd. for $C_{20}H_{15}ClN_6O_2$(406.09): C, 59.05; H, 3.72; N, 20.66 %, Found: C, 59.01; H, 3.69; N, 20.63 %.

Synthesis of 4-((2-chloroquinolin-3-yl)methyleneamino)-5-oxo-2-phenyl-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile (**13**)

To a mixture of compound **12a** (0.8 g, 0.002 mol) and formalin (0.06 mL, 0.002 mol) in absolute ethanol (25 mL), piperidine (0.2 mL) was added. The reaction mixture was heated under reflux for 6 h, and then allowed to cool down. The formed precipitate was filtered off, dried and recrystallized from ethanol to give compound **13**.

Brown powder; yield 62 %; mp > 300 °C; IR (KBr) ν_{max}/cm^{-1} = 2,989 (C–H, SP^3), 2,212 (CN), 1,701 (C=O), 1,617 (C=N), 1,560 (C=C, conjugated), 760 (C–Cl); ^1H NMR (CF_3COOD): δ_{ppm} = 4.50 (s, 2H, CH_2), 7.26–7.86 (m, 9H, Aromatic-H), 8.65 (s, 1H, quinoline-H_4), 9.70 (s, 1H, CH=N); ^{13}C NMR (CF_3COOD): δ_{ppm} = 76.6 (CH_2), 110.7 (CN), 117.5 (Ar–$C_{2,6}$), 121.7 (Ar–C_4), 125.8 (quinoline-C_3), 126.7 (quinoline-C_6), 127.0 (quinoline-C_8), 127.8 (quinoline-C_5), 129.5 (Ar–$C_{3,5}$), 130.3 (quinoline-C_7), 136.8 (quinoline-C_4), 144.1 (CH=N), 146.4 (Ar–C_1), 149.7 (quinoline-C_{8a}), 154.3 (quinoline-C_{8a}), 156.9 (triazine-C_6), 163.9 (C=O, triazine-C_6); MS *m/z* (%) = 388 (M^+, 45.8), 353 (5.1), 328 (6.8), 311 (44.1), 286 (5.1), 257 (2.5), 251 (100), 233 (69.5), 204 (48.3), 205 (52.5), 190 (16.1); Anal. Calcd. for $C_{20}H_{13}ClN_6O$ (388.08): C, 61.78; H, 3.37; N, 21.61 %, Found: C, 61.75; H, 3.33; N, 21.64 %.

Antibacterial screening

Whatman filter paper disks of standard size (6.0 mm diameter) were prepared and placed in 1.0-oz screw-capped wide-mouthed containers for sterilization in a hot air oven at 150 °C. The disks, impregnated with a solution of the test compound in DMSO (100 ml, 5 mg/mL), were then placed on nutrient agar plates seeded with the appropriate test organism. Experiments were performed in triplicate. A standard concentration of 10^6 CFU/mL (colony-forming units/mL) was used for antibacterial assay.

Pyrex glass Petri dishes (9 cm in diameter) were used, and each plate contained two impregnated filter paper disks. *B. subtilis*, *S. faecalis*, and *P. aeruginosa* were used as examples of Gram-positive bacteria and *S. aureus*, *E. coli*, and *N. gonorrhoeae* as Gram-negative bacteria. Ampicillin was used as standard antibacterial agent. DMSO alone was used as control and resulted in no visible change in bacterial growth. The plates were incubated at 37 °C for 24 h. The mean zone of inhibition was measured in mm.

Anticancer screening

Fetal bovine serum (FBS) and L-glutamine, were from Gibco Invitrogen (Scotland, UK). RPMI-1640 medium was from Cambrex (New Jersey, USA). DMSO was used as solvent and doxorubicin was used as reference anticancer agent. Penicillin, streptomycin, and sulforhodamine B (SRB) were purchased from Sigma Chemical (Saint Louis, USA).

Four human tumor cell lines, breast cancer (MCF-7), non-small cell lung (NCI-H460), central nervous system (SF-268), and lung fibroblasts (WI-38), were obtained from the European Collection of Cell Cultures (ECACC, Salisbury, UK) and National Cancer institute (NCI, Cairo, Egypt).

They were grown as monolayers and routinely maintained in RPMI-1640 medium supplemented with 5 % heat-inactivated FBS, 2 mM glutamine and antibiotics (penicillin 100 U/mL, streptomycin 100 μg/mL), at 37 °C, in a humidified atmosphere containing 5 % CO_2.

Exponentially growing cells were obtained by plating 1.5×10^5 cells/mL for MCF-7 and SF-268 and 0.75×10^4 cells/mL for NCI-H460, then incubated for 24 h. The effect of the solvent (DMSO) on the growth of these cell lines was evaluated in all experiments by exposing untreated control cells to the maximum concentration (0.5 %) of DMSO used in each assay.

The effect of the compounds on the in-vitro growth of the cell lines was evaluated in accordance with the procedure adopted by the National Cancer Institute (NCI, USA) and as reported in the publication "In vitro Anticancer Drug Discovery Screen" that uses the protein-binding dye sulforhodamine B to assess cell growth [30, 31]. Briefly, exponentially growing cells in 96-well plates were exposed for 48 h to five serial concentrations of each compound; the maximum concentrations was 150 μM. After this exposure period, adherent cells were fixed, washed, and stained. The bound stain was solubilized and the absorbance was measured at 492 nm by use of a plate reader (PowerWave XS; Bio-Tek Instruments, Winooski, USA). For each test compound and cell line, a dose–response curve was obtained and the concentration which inhibited cell growth by 50 % (IC_{50}) was calculated as described elsewhere. Doxorubicin was used as positive control and was tested in the same manner.

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