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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis of new quinoline-2-pyrazoline-based thiazolinone derivatives as potential antimicrobial agents

N. C. Desai · V. V. Joshi · K. M. Rajpara

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Abstract A series of 2-(5-(2-chloro-6-methylquinolin-3-yl)-3-(aryl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-4(5*H*)ones **(4a–l)** were synthesized and characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectra. All the synthesized compounds were tested for their in vitro antimicrobial activity against *Escherichia coli* (MTCC 443), *Pseudomonas aeruginosa* (MTCC 1688), *Staphylococcus aureus* (MTCC 96), *Streptococcus pyogenes* (MTCC 442), *Candida albicans* (MTCC 227), *Aspergillus niger* (MTCC 282), and *Aspergillus clavatus* (MTCC 1323) by serial broth dilution. Compounds **4e**, **4f**, **4g**, **4i**, **4j**, and **4l** were the most distinctive derivatives identified in present study because of their remarkable in vitro antimicrobial potency.

Keywords Quinoline · 2-Pyrazoline · Vilsmeier–Haack reaction · Thiazolinone · Cycloaddition reaction · Antimicrobial activity · MIC

Introduction

Resistance of pathogenic bacteria toward available antibiotics is rapidly becoming a major worldwide problem. Owing to this reason, the design of new compounds to deal with resistant bacteria has become one of the most important areas of antibacterial research today. In addition, primary and opportunistic fungal infections continue to increase rapidly because of the increased number of immunocompromised patients. As known, not only biochemical similarity of the human cell and fungi forms a handicap for selective activity but also the easily gained resistance is the main problem encountered in developing safe and efficient antifungal. Despite the development of several new antimicrobial agents, their clinical value is limited to treating an increasing array of life-threatening systemic infections because of their relatively high toxicity, emergence of drug resistant strains, pharmacokinetic differences, and/or insufficiencies in their activity (Brad *et al.,* 2004). Fascinating pharmacological activities associated with heterocyclic compounds (Krchnak and Holladay, 2002) are increasingly important in designing new class of structural entities of medicinal importance.

The current interest in the development of new antimicrobial agents can be partially ascribed both to the increasing emergence of bacterial resistance to antibiotic therapy and to newly emerging pathogens (Cohen 2000, Barrett and Barrett 2003). Over the past few years, we have been principally engrossed in the synthesis of quinoline incorporating structures for antimicrobial evaluations (Desai *et al.,* 2011, 2012a) on the premise that quinoline moiety is found in a large variety of naturally occurring compounds. In fact, introducing chloroquine into treatment of malaria more than 60 years ago triggered a new era of quickly developing antimicrobial drugs. Quinoline ring is endowed with various activities, such as antituberculosis (Lilienkampf *et al.*, 2009), antimalarial (Nasveld and Kitchener, 2005), anti-inflammatory (Bekhit *et al.,* 2004), anticancer (Shi *et al.,* 2008), antihypertensive (Muruganantham *et al.,* 2004), tyrokinase PDGF-RTK-inhibiting agents (Maguire *et al.,* 1994), and anti-HIV (Ahmed *et al.,* 2010).The design concepts have been drawn in Fig. 1, which explains the structural similarity of our new target compounds with renowned drug chloroquine. Moreover,

N. C. Desai (✉) · V. V. Joshi · K. M. Rajpara
Division of Medicinal Chemistry, Department of Chemistry, Maharaja Krishnakumarsinhji Bhavnagar University, Mahatma Gandhi Campus, Bhavnagar 364 002, India
e-mail: dnisheeth@rediffmail.com

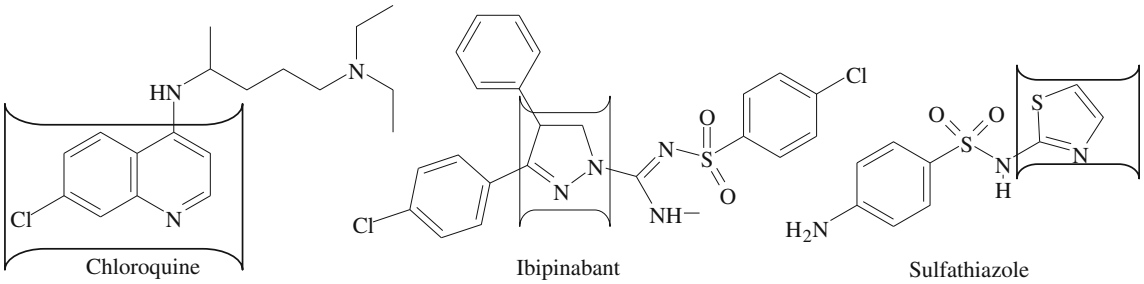


Fig. 1 Commercially available drugs containing quinoline, pyrazoline, and thiazole nucleus

2-pyrazoline derivatives have been reported to exhibit various pharmacological activities such as antimicrobial (Baraldi *et al*., 2003), anti-inflammatory (Barsoum *et al.,* 2006), and antihypertensive (Turan-Zitouni *et al.,* 2000). 1-Unsubstituted-3,5-diaryl-2-pyrazolines are reported to exhibit human Acyl CoA cholesterol acyltransferase activity (Jeong *et al.,* 2004a) as well as the activity of low-density lipoprotein oxidation inhibitors (Jeong *et al.,* 2004b). In addition, 1,3,5-triaryl-2-pyrazolines are reported to possess antidepressant properties (Palaska *et al.,* 1996) and monoamine oxidase (MAO) inhibitory activities (Soni *et al.,* 1987). Structurally relevant drug ibipinabantis CB_1 antagonists are shown in Fig. 1. Thiazole is a versatile bioactive heterocycle with biocidal S–C = N entity having its wide presence in many synthetic drugs such as sulfathiazole (antimicrobial), nizatidine (Antihistaminic), fanetizole (anti-inflammatory), ritonavir (anti-HIV), niridazole (schistosomicidal), abafungin (antifungal) with trade name: abasol cream, bleomycin (antineoplastic), and tiazofurin (antineoplastic) have been explored previously. Several physiologic activities of various thiazole derivatives have proved the efficacy in combating various diseases and are found to have good antitubercular activity (krainets *et al.,* 2002).

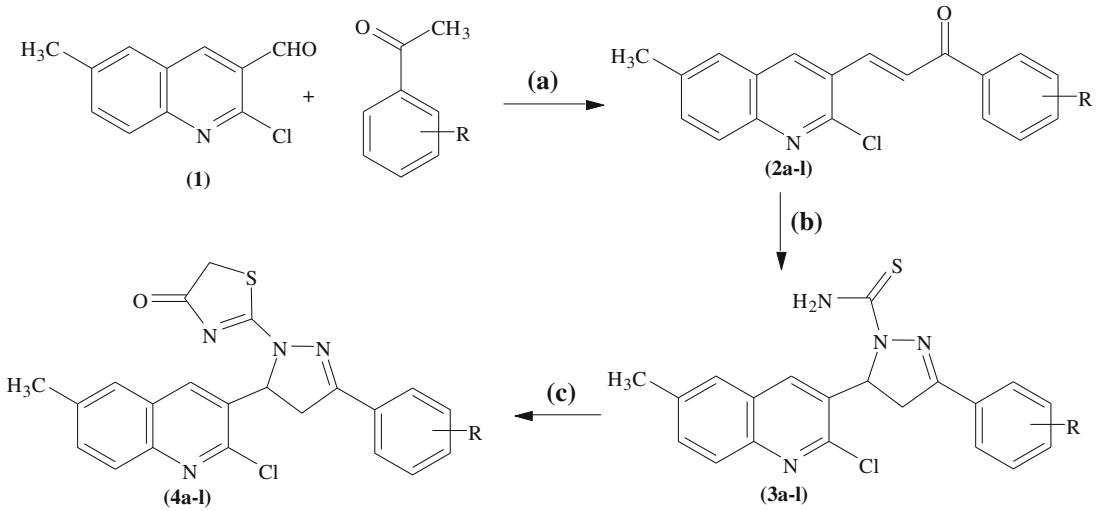
Prompted by the above-mentioned results, it was planned to construct some new antimicrobial derivatives bearing quinoline moiety attached to different substituted 2-thiazolyl-pyrazoline nucleus at 3rd position and study the structure activity relationship due to substituent variations. These combinations are suggested in an attempt to investigate the possible synergistic influence of such structure hybridizations on the antimicrobial activity, hoping to discover a new lead structure that would have a significant activity at a very small concentration. In continuation of our recent work aiming to synthesize heterocyclic systems with remarkable biologic importance (Desai *et al*. 2012a, 2012b, 2012c, 2012d, 2012e, 2012f), we report herein the utility of 2-(5-(2-chloro-6-methylquinolin-3-yl)-3-(aryl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)ones (**4a–l**) as building blocks to get new compounds that could be optimized as potent antimicrobial agents.

Results and discussion

Chemistry

The Vilsmeier-Haack reaction on acetanilide provided a vital and efficient intermediate for the synthesis of several newer substituted heterocyclic compounds. The reaction was performed at 100 °C for 15–20 h using the typical Vilsmeiere-Haack reagent derived from phosphorus oxychloride-dimethylformamide yielded chloroquinoline aldehyde (Meth-Cohn, 1993). Although the reaction proceeded uneventfully, the products formed were isolated by silica gel column chromatography. The reaction sequences employed for synthesis of the target compounds (**4a–l**) are illustrated in Scheme 1. The key chalcone intermediates (**2a–l**) were synthesized through the Claisen–Schmidt condensation of equimolar amounts of acetophenone derivatives and chloroquinoline aldehyde **(1)** through stirring the reactants in aqueous ethanolic solution containing 20 % sodium hydroxide at room temperature for 24 h in accordance with the method described in the literature (Elgazwy, 2008).

The newly synthesized compounds 5-(2-chloro-6-methylquinolin-3-yl)-3-(aryl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamides (**3a–l**) were obtained by heating at reflux equimolar amounts of thiosemicarbazide and the corresponding α,β-unsaturated ketones (**2a–l**) in hot ethanolic sodium hydroxide solution for 8 h (Scheme 1). 1-Thiocarbamoyl pyrazole derivative (**3a**) was characterized by IR, NMR, and mass spectra. IR spectra showed strong absorption bands at 3440 and 3373 cm^{-1} due to primary amine group. The characteristic signals in ^{1}H NMR of 1-thiocarbamoyl pyrazole derivative (**3a**) of the three pyrazoline protons displayed doublet of doublet confirms the presence of 1-thiocarbamoyl pyrazole. The methine proton of pyrazolines displayed a signal at δ = 6.02 ppm as a doublet of doublet with coupling constants of nearly 11.12 and 3.08 Hz. The two methylene protons displayed two signals; a doublet of doublet at δ = 3.93 ppm with coupling constants of nearly 17.45 and 11.13 Hz and a doublet of doublet at δ = 3.18 ppm with coupling constants of nearly 17.44 and 3.08 Hz. Furthermore, ^{13}C NMR spectra



(a) Ethanol, NaOH, stirring, 24 h **(b)** $NH_2CSNHNH_2$, Ethanol, Reflux 8 h **(c)** $BrCH_2COOC_2H_5$, Ethanol, Reflux 1 h

Scheme 1 Synthetic route for compounds **4a–l**

displayed a signal at 176.3 ppm assignable to thiocarbamoyl carbon (C=S). The mass spectrum of (**3a**) showed a molecular ion peak at $m/z = 380$ (M^+) corresponding to a molecular formula $C_{20}H_{17}ClN_4S$. Moreover, the aforementioned 1-thiocarbamoyl pyrazole derivatives (**3a–l**) were cyclized to (**4a–l**) through their reaction with ethyl bromoacetate in hot ethanol for 1 h. Compound (**4a**) showed a strong absorption band at 1711 cm^{-1}due to the carbonyl group in IR spectra. ^{1}H NMR spectrum revealed the appearance of a singlet peak at $\delta = 4.01$ ppm integrating the two protons of the thiazolinone ring. ^{1}H NMR of 1-thiocarbamoyl pyrazoline derivative (**4a**) of the three pyrazoline protons displayed doublet of doublet confirms the presence of 1-thiocarbamoyl pyrazole. The methine proton of pyrazolines displayed a signal at $\delta = 6.02$ ppm as a doublet of doublet with coupling constants of nearly 11.17 and 3.00 Hz. The two methylene protons displayed two signals; a doublet of doublet at $\delta = 3.88$ ppm with coupling constants of nearly 17.48 and 11.18 Hz and a doublet of doublet at $\delta = 3.17$ ppm with coupling constants of nearly 17.48 Hz and 3.01 Hz. The two aromatic proton displayed a triplet at $\delta = 7.56$ ppm with coupling constants of nearly 8.2 Hz. The two aromatic proton displayed a doublet at $\delta = 7.76$ ppm with coupling constants of nearly 7.8 Hz. The one aromatic proton displayed a triplet at $\delta = 7.48$ ppm with coupling constants of nearly 8.2 Hz. ^{13}C NMR spectrum of **4a** displayed a signal at $\delta = 187.5$ ppm assignable to the carbonyl carbon (C=O) and the appearance of a signal around $\delta = 39.0$ ppm due to the presence of a methylene group of the thiazolinone ring. Compound **4a** displayed signals at $\delta = 42.2$ ppm, $\delta = 60.1$ ppm, and 159.5 ppm due to the presence of a pyrazoline ring. Compound showed signals at 124.7–143.7 due to the presence of aromatic carbons. Moreover, the mass spectrum of (**4a**) showed a molecular ion peak at $m/z = 420$ (M^+) corresponding to a molecular formula $C_{22}H_{17}ClN_4OS$.

Antimicrobial activity

Compounds **4a–l** were evaluated against Gram-positive, Gram-negative bacteria, and fungi strains. The intermediate compounds **3a-l** exhibited poor activity. The individual minimum inhibitory concentration (MIC, μg/mL) obtained for compounds **4a-l** is presented in (Table 1). It was observed that compounds **4e** (2-Cl), **4f** (4-Cl), **4g** (2-F), **4i** (4-F), **4j** (2-NO_2), and **4l** (4-NO_2) were most active. On the basis of antibacterial screening, it was observed that compounds **4e** (2-Cl), **4i** (4-F) and **4l** (4-NO_2) possessed very good activity against *E. coli*. When hydrogen of phenyl ring in **4a** was replaced by fluoro and nitro groups at 2nd position, i.e., **4g** (2-F) and **4j** (2-NO_2), activity increased and compounds displayed excellent activity against *E. coli*. Compounds **4e** (2-Cl) and **4i** (4-F) possessed very good activity against *P. aeruginosa.* When we replaced hydrogen of phenyl ring in **4a** by nitro group at 2nd position, we get compound **4j** which underwent enhancement in activity and possessed excellent activity against *P. aeruginosa.* Compounds **4g** (2-F)**, 4i** (4-F), and **4l** (4-NO_2) showed very good activity, while compound exhibiting chloro group substituent at 4th position of substituted benzene ring showed

excellent activity against *S. aureus.* Compounds **4e** (2-Cl), **4f** (4-Cl), and **4l** (4-NO_2) displayed very good activity, while compounds **4i** (4-F) and **4j** (2-NO_2) possessed excellent activity against *S. pyogenes.*

The intermediate compounds **3a-l** exhibited poor activity. Antifungal activity showed that compounds **4i** (4-F) and **4j** (2-NO_2) possessed very good activity against *C. albicans*. When we replace hydrogen of phenyl ring in **4a** by 2-Cl and 2-F groups, activity enhanced and showed excellent activity against *C. albicans*. Compounds **4e** (2-Cl), **4g** (2-F), and **4j** (2-NO_2) displayed very good activity against *A. niger*, whereas compounds **4l** bearing nitro group at the 4th position showed excellent activity against *A. niger*. Compounds **4f** (3-Cl) and **4 k** (3-NO_2) possessed very good activity against *A. clavatus*. When we have incorporated NO_2 group on the 2nd carbon of phenyl ring of compound **4a**, the activity enhanced and it displayed excellent activity against *A. clavatus*. The MIC (minimum inhibitory concentration) values were determined by comparison with ampicillin and griseofulvin as reference drugs.

Results clearly demonstrate in Table 1 that when compounds **3a–l** were converted to the corresponding final compounds **4a–l**, they exhibited significant antimicrobial activity. Most of the synthesized compounds **3a–l** exhibited poor antibacterial and antifungal activity. On the basis of MIC values, it is our observation that the presence of thiazol-4(5*H*)-one led to a significant increase in the antimicrobial activity.

Structure–activity relationship

Results of the biologic testing revealed that the activity was considerably affected by various substituents on the aromatic ring. For antibacterial activity, it was observed that the introduction of electron-withdrawing groups on the benzene ring showed considerable increase in the antibacterial potency of the compounds. It was observed from the screening data that the compounds **4g** and **4j** containing fluoro and nitro substituents showed significant potency against bacteria *E. coli*. Compound containing nitro group at 2-position of the substituted benzene ring showed maximum inhibition against *P. aeruginosa* at MIC 12.5 μg/mL. Chloro substitution at the 4th position on benzene ring showed excellent activity against *S. aureus.* Compounds **4i** and **4j** containing 4-F and 2-NO_2 groups on benzene ring showed maximum inhibition against *S. pyogenes* at MIC 25 μg/mL. On the basis of MIC results, it was clear that electron-withdrawing groups substituting the benzene ring showed higher potency than electron donating groups. All other compounds showed good to moderate activity. According to the MIC values of antifungal activity, compounds containing chloro and fluoro atoms **4e** and **4g** showed excellent activity

Table 1 Results of antibacterial and antifungal screening of compounds **4a–l**

Entry	-R	Minimum inhibitory concentration for bacteria (μg/mL) ± SD				Minimum inhibitory concentration for fungi (μg/mL) ± SD		
		Gram-negative		Gram-positive				
		E. coli MTCC 443	*P. aeruginosa* MTCC 1688	*S. aureus* MTCC 96	*S. pyogenes* MTCC 442	*C. albicans* MTCC 227	*A. niger* MTCC 282	*A. clavatus* MTCC 1323
4a	-H	500 ± 3.05**	250 ± 1.00*	250 ± 2.04*	500 ± 3.46	1000 ± 4.61*	500 ± 3.70	500 ± 4.50*
4b	-2-OH	500 ± 1.00*	500 ± 1.50**	500 ± 3.21	250 ± 3.60**	1000 ± 2.88**	500 ± 1.60**	1000 ± 1.00**
4c	-4-OH	500 ± 1.52**	250 ± 2.04	500 ± 4.04***	250 ± 1.92***	1000 ± 4.06*	1000 ± 3.16***	1000 ± 2.04*
4d	-4-OCH_3	500 ± 1.00*	500 ± 1.60**	500 ± 2.04*	500 ± 2.05	1000 ± 2.64*	500 ± 1.60	500 ± 2.05*
4e	-2-Cl	50 ± 3.21**	50 ± 2.88*	250 ± 4.60	50 ± 1.69**	100 ± 1.52	50 ± 1.16*	100 ± 4.50
4f	-4-Cl	250 ± 1.20***	100 ± 4.04	50 ± 2.05**	50 ± 3.78*	500 ± 3.06	100 ± 1.20***	50 ± 4.72***
4g	-2-F	25 ± 1.78**	250 ± 4.16	100 ± 1.05*	500 ± 3.78**	100 ± 4.72*	50 ± 1.04***	500 ± 3.78**
4h	-3-F	500 ± 1.60*	100 ± 2.04**	500 ± 1.60***	100 ± 1.21***	1000 ± 1.52**	500 ± 4.16*	500 ± 3.46*
4i	-4-F	50 ± 3.60**	50 ± 3.21***	100 ± 3.16*	25 ± 4.16**	250 ± 2.18*	250 ± 1.18*	100 ± 4.04*
4j	-2-NO_2	25 ± 1.78*	12.5 ± 3.78**	250 ± 1.78**	25 ± 1.16*	250 ± 4.72**	50 ± 1.60**	12.5 ± 2.52***
4k	-3-NO_2	250 ± 3.61*	500 ± 1.60	500 ± 4.16***	500 ± 3.21**	500 ± 3.52	100 ± 1.58***	50 ± 1.00
4l	-4-NO_2	50 ± 1.40***	250 ± 3.26*	100 ± 2.04**	50 ± 1.61**	500 ± 2.32*	25 ± 1.60*	100 ± 3.60*
	Ampicillin	100 ± 2.05	100 ± 1.00	250 ± 1.52	100 ± 2.06	–	–	–
	Griseofulvin	–	–	–	–	500 ± 0.50	100 ± 1.10	100 ± 1.20

2 % DMSO used as control and its antibacterial activity is nil or zero

±*SD* Standard deviation

*** $P < 0.001$ extremely significant, ** $P < 0.01$ moderately significant, * $P < 0.05$ significant. All values are presented as mean of 6 experiments ($n = 6$). All significant differences are considered from control value (0.00)

against *C. albicans,* whereas compound **4j** containing nitro group showed excellent activity against *A. niger*. Compound **4j** containing nitro group exhibited maximum potency at MIC 12.5 μg/mL against *A. clavatus*. On the basis of SAR, it has been observed that there was strong correlation between antibacterial and antifungal activity.

Biologic screening

Antibacterial assay

The newly synthesized compounds (**4a–l**) were screened for their antibacterial activity against Gram-positive bacteria (*Staphylococcus aureus* (MTCC-96)—*Streptococcus pyogenes* (MTCC-442)) and Gram-negative (*Escherichia coli* (MTCC-443)—*Pseudomonas aeruginosa* (MTCC-1688)). All MTCC cultures were collected from the Institute of Microbial Technology, Chandigarh. The activity of compounds was determined as per the National Committee for Clinical Laboratory Standards (NCCLS) protocol using Mueller–Hinton Broth (Becton–Dickinson, USA) (Al-Bayati and Al-Mola, 2008, Finegold and Garrod, 1995). Compounds were screened for their antibacterial activity as primary screening in six sets against *E. coli*, *S. aureus*, *P. aeruginosa,* and *S. pyogenes* at different concentrations of 1000, 500, and 250 μg/mL. The compounds found to be active in primary screening were similarly diluted to obtain 200, 125, 100, 62.5, 50, 25, and 12.5 μg/mL concentrations for secondary screening to test in a second set of dilution against all microorganisms. Inoculum size for test strain is adjusted to 10^6 CFU/mL (Colony Forming Unit per milliliter) by comparing the turbidity (turbidimetric method). Mueller–Hinton Broth is used as nutrient medium to grow and dilute the compound suspension for test bacteria. 2 % DMSO was used as a diluent/vehicle to obtain the desired concentration of synthesized compounds and standard drugs to test upon standard microbial strains. Synthesized compounds were diluted to 1000 μg/mL concentration as a stock solution. The control tube containing no antibiotic was immediately subcultured [before inoculation] by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of test organisms. The tubes were then put for incubation at 37 °C for 24 h for bacteria. 10 μg/mL suspensions were further inoculated on an appropriate media and growth is noted after 24 and 48 h. The highest dilution (lowest concentration) preventing appearance of turbidity was considered as minimum inhibitory concentration (MIC, μg/mL), i.e., the amount of growth from the control tube before incubation (which represents the original inoculum) was compared. A set of tubes containing only seeded broth and solvent controls were maintained under identical conditions so as to make sure that the solvent had no influence on strain growth. The result of this was greatly affected by the size of the inoculum. The test mixture should contain 10^6 CFU/mL organisms. DMSO and sterilized distilled water was used as negative control, while ampicillin antibiotic (1 U strength) was used as positive control. Standard drug used in the present study was "ampicillin" for evaluating antibacterial activity which showed 100, 100, 250, and 100 μg/mL MIC against *E. coli, P. aeruginosa, S. aureus*, and *S. pyogenes*, respectively.

Antifungal assay

The same compounds (**4a–l**) were tested for their antifungal activity as primary screening in six sets against *C.albicans*, *A. niger*, and *A. clavatus* at various concentrations of 1000, 500, 250 μg/mL, respectively. The compounds found to be active in primary screening were similarly diluted to obtain 200, 125, 100, 62.5, 50, 25, and 12.5 μg/mL concentrations for secondary screening to test in a second set of dilution against all microorganisms. Griseofulvin was used as a standard drug for the antifungal activity, which showed 500, 100, and 100 μg/mL MIC against *C. albicans*, *A. niger*, and *A. clavatus*, respectively. DMSO and sterilized distilled water was used as negative control, while Griseofulvin (1 U strength) was used as positive control. For fungal growth, in the present protocol, we have used Sabourauds dextrose broth at 28 °C in an aerobic condition for 48 h.

Statistical analysis

Standard deviation value is expressed in terms of ±SD. On the basis of calculated value by one-way ANOVA method followed by independent two sample *t* test, it has been observed that differences below 0.001 level are considered as statistically significant.

Materials and methods

General

All reactions except those in aqueous media were carried out by standard techniques for the exclusion of moisture. Melting points were determined on an electro thermal melting point apparatus and were reported uncorrected. TLC on silica gel plates (Merck, 60, F_{254}) was used for purity checking and reaction monitoring. Column chromatography on silica gel (Merck, 70–230 mesh and 230–400 mesh ASTH for flash chromatography) was applied when necessary to isolate and purify the reaction products. Elemental analysis (% C, H, N) was carried out using a Perkin-Elmer 2400 CHN analyzer. IR spectra of all compounds were recorded on a Perkin-Elmer FT-IR spectrophotometer

in KBr. ^{1}H NMR spectra were obtained on Varian Gemini 300 MHz and ^{13}C NMR spectra on Varian Mercury-400 100 MHz in DMSO-d_6 as a solvent and tetramethylsilane (TMS) as an internal standard. Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer. Anhydrous reactions were carried out in oven-dried glassware in nitrogen atmosphere.

Experimental

*General procedure for the preparation of 5-(2-chloro-6-methylquinolin-3-yl)-3-(aryl)-4,5-dihydro-1H-pyrazole-1-carbothioamides (**3a–l**)*

To a suspension of chalcones (0.01 mol) and sodium hydroxide (0.025 mol) in ethanol (99.5 %) (50 mL), thiosemicarbazide (0.01 mol) was added and the mixture was refluxed for 8 h. The mixture was then poured onto crushed ice and the solid mass which separated out was filtered, dried, and crystallized from ethanol (95 %).

Physical constants and characterization of synthesized compounds (**3a-l**)

*5-(2-Chloro-6-methylquinolin-3-yl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3a**)*

Light brown crystals, yield: 75 %; m.p.: 137–139 °C; IR (KBr) ν_{max}/cm^{-1}: 3440, 3373 (NH_2), 3067 (C–H, aromatic), 1576 (C=N), 1511 (C=C), 1330 (C=S), 728 (C–Cl); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.35 (s, 3H, –CH_3), 3.18 (dd, 1H, J = 17.44 Hz, 3.08 Hz, C_4–H pyrazoline), 3.93 (dd, 1H, J = 17.45 Hz, 11.13 Hz, C_4-H pyrazoline), 6.02 (dd, 1H, J = 11.12 Hz, 3.08 Hz, C_5–H pyrazoline), 7.35 (d, 1H, J = 7.8 Hz, Ar–H), 7.48 (t, 1H, J = 8.2 Hz, Ar–H), 7.56 (t, 2H, J = 7.8 Hz, Ar–H),7.62 (s, 1H, Ar–H), 7.69 (d, 2H, J = 7.8 Hz, Ar–H), 7.90 (d, 1H, J = 8.0 Hz, Ar–H), 8.36 (s, 1H, Ar–H),8.52 (s, 2H, NH_2, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.4 (CH_3), 43.2 (C_4 of pyrazoline), 63.1 (C_5 of pyrazoline), 124.8–144.1 (Ar–C), 151.2 (C–Cl of quinoline), 156.7 (C=N of pyrazoline), 176.3 (C=S); LCMS *(m/z)*: 380(M^+), 382 (M^++2); Anal. Calcd. For $C_{20}H_{17}ClN_4S$: C-63.07, H-4.50, N-14.71; Found: C-63.13, H-4.57, N-14.77 %.

*5-(2-Chloro-6-methylquinolin-3-yl)-3-(2-hydroxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3b**)*

Light yellow crystals, yield: 72 %; m.p.: 158–160 °C; IR (KBr) ν_{max}/cm^{-1}: 3452, 3361 (NH_2), 3414 (OH), 3067 (C–H, aromatic), 1584 (C=N), 1513 (C=C), 1326 (C=S), 722 (C–Cl); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.31 (s, 3H, –CH_3), 3.09 (dd, 1H, J = 17.34 Hz, 3.01 Hz, C_4–H pyrazoline), 3.86 (dd, 1H, J = 17.35 Hz, 11.04 Hz, C_4–H pyrazoline), 6.11 (dd, 1H, J = 11.04 Hz, 3.01 Hz, C_5–H pyrazoline), 6.92 (d, 1H, J = 8.4 Hz, Ar–H), 7.00 (d, 1H, J = 7.8 Hz, Ar–H), 7.36 (d, 1H, J = 7.6 Hz, Ar–H), 7.43 (t, 1H, J = 8.0 Hz, Ar–H), 7.58 (d, 1H, J = 7.4 Hz, Ar–H), 7.67 (s, 1H, Ar–H), 7.94 (d, 1H, J = 8.2 Hz, Ar–H), 8.33 (s, 1H, Ar–H), 8.47 (s, 2H, NH_2, D_2O exch.), 9.19 (s, 1H, OH, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.0 (CH_3), 43.3 (C_4 of pyrazoline), 62.9 (C_5 of pyrazoline), 117.3–143.6 (Ar–C), 151.3 (C–Cl of quinoline), 156.4 (C=N of pyrazoline), 162.3 (C –OH), 176.0 (C=S); LCMS *(m/z)*: 396(M^+), 398 (M^++2); Anal. Calcd. For $C_{20}H_{17}ClN_4OS$: C-60.52, H-4.32, N-14.12; Found: C-60.60, H-4.38, N-14.20 %.

*5-(2-Chloro-6-methylquinolin-3-yl)-3-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3c**)*

Dark yellow crystals, yield: 74 %; m.p.: 192-194 °C; IR (KBr) ν_{max}/cm^{-1}: 3442, 3366 (NH_2), 3415 (OH), 3073 (C–H, aromatic), 1575 (C=N), 1525 (C=C), 1327 (C=S), 734 (C–Cl); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.33 (s, 3H, –CH_3), 3.14 (dd, 1H, J = 17.48 Hz, 3.07 Hz, C_4–H pyrazoline), 3.83 (dd, 1H, J = 17.48 Hz, 11.12 Hz, C_4-H pyrazoline), 6.07 (dd, 1H, J = 11.11 Hz, 3.07 Hz, C_5–H pyrazoline), 6.81 (d, 2H, J = 8.0 Hz, A_2B_2, *p*-chlorophenyl), 7.32 (d, 1H, J = 7.6 Hz, Ar–H), 7.65 (s, 1H, Ar–H), 7.83 (d, 2H, J = 8.0 Hz, A_2B_2, *p*-chlorophenyl), 7.95 (d, 1H, J = 8.0 Hz, Ar–H), 8.32 (s, 1H, Ar–H), 8.52 (s, 2H, NH_2, D_2O exch.), 9.21 (s, 1H, OH, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.1 (CH_3), 43.3 (C_4 of pyrazoline), 62.9 (C_5 of pyrazoline), 115.9–143.2 (Ar–C), 151.3 (C–Cl of quinoline), 156.6 (C=N of pyrazoline), 160.7 (C–OH), 176.3 (C=S); LCMS *(m/z)*: 396 (M^+), 398 (M^++2); Anal. Calcd. For $C_{20}H_{17}ClN_4OS$: C-60.52, H-4.32, N-14.12; Found: C-60.47, H-4.27, N-14.05 %.

*5-(2-Chloro-6-methylquinolin-3-yl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3d**)*

Light pink crystals, yield: 72 %; m.p.: 205–207 °C; IR (KBr) ν_{max}/cm^{-1}: 3454, 3368 (NH_2), 3073 (C–H, aromatic), 1585 (C=N), 1523 (C=C), 1324 (C=S), 1215 (C–O–C), 740 (C–Cl); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.36 (s, 3H, –CH_3), 3.18 (dd, 1H, J = 17.52 Hz, 3.02 Hz, C_4–H pyrazoline), 3.67 (s, 3H, –OCH_3), 3.87 (dd, 1H, J = 17.52 Hz, 11.16 Hz, C_4–H pyrazoline), 6.04 (dd, 1H, J = 11.16 Hz, 3.03 Hz, C_5–H pyrazoline), 7.03 (d, 2H, J = 8.2 Hz, A_2B_2, *p*-methoxyphenyl), 7.36 (d, 1H, J = 8.2 Hz, Ar–H), 7.61 (s, 1H, Ar–H), 7.95 (d, 1H, J = 7.8 Hz, Ar–H), 8.03 (d, 2H, J = 8.2 Hz, A_2B_2, *p*-methoxyphenyl), 8.38 (s, 1H, Ar–H), 8.44 (s, 2H, NH_2, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.2 (CH_3), 43.5 (C_4 of pyrazoline), 54.4 (OCH_3), 62.7 (C_5 of pyrazoline), 114.5–144.6 (Ar–C), 151.5 (C–Cl of quinoline), 156.2 (C=N of pyrazoline), 176.7

(C=S); LCMS *(m/z)*: 410(M^+), 412 (M^++2); Anal. Calcd. For $C_{21}H_{19}ClN_4OS$: C-61.38, H-4.66, N-13.63; Found: C-61.44, H-4.73, N-13.72 %.

*5-(2-Chloro-6-methylquinolin-3-yl)-3-(2-chlorophenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3e**)*

Light gray crystals, yield: 75 %; m.p.: 182–184 °C; IR (KBr) ν_{max}/cm^{-1}: 3454, 3373 (NH_2), 3071 (C–H, aromatic), 1573 (C=N), 1515 (C=C), 1338 (C=S), 745 (C–Cl); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.35 (s, 3H, –CH_3), 3.23 (dd, 1H, J = 17.44, 3.10 Hz, C_4–H pyrazoline), 3.90 (dd, 1H, J = 17.44 Hz, 11.12 Hz, C_4–H pyrazoline), 6.10 (dd, 1H, J = 11.12, 3.09 Hz, C_5–H pyrazoline), 7.38 (d, 1H, J = 8.4 Hz, Ar–H), 7.42 (t, 1H, J = 8.2 Hz, Ar–H), 7.54 (t, 1H, J = 8.2 Hz, Ar–H), 7.59 (d, 1H, J = 8.4 Hz, Ar–H), 7.62 (s, 1H, Ar–H), 7.79 (d, 1H, J = 8.4 Hz, Ar–H), 7.92 (d, 1H, J = 8.2 Hz, Ar–H), 8.34 (s, 1H, Ar–H), 8.51 (s, 2H, NH_2, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.5 (CH_3), 43.2 (C_4 of pyrazoline), 62.6 (C_5 of pyrazoline), 128.8 (C–Cl of chlorophenyl), 124.6–143.8 (Ar–C), 151.5 (C–Cl of quinoline), 156.1 (C=N of pyrazoline), 176.5 (C=S); LCMS *(m/z)*: 414(M^+), 416 (M^++2); Anal. Calcd. For $C_{20}H_{16}Cl_2N_4S$: C-57.84, H-3.88, N-13.49; Found: C-57.78, H-3.83, N-13.55 %.

*5-(2-Chloro-6-methylquinolin-3-yl)-3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3f**)*

Dark gray crystals, yield: 71 %; m.p.: 177–179 °C; IR (KBr) ν_{max}/cm^{-1}: 3448, 3380 (NH_2), 3067 (C–H, aromatic), 1577 (C=N), 1514 (C=C), 1337 (C=S), 753 (C–Cl); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.34 (s, 3H, –CH_3), 3.19 (dd, 1H, J = 17.48, 3.13 Hz, C_4–H pyrazoline), 3.93 (dd, 1H, J = 17.47 Hz, 11.18 Hz, C_4-H pyrazoline), 6.07 (dd, 1H, J = 11.18 Hz, 3.12 Hz, C_5-H pyrazoline),7.35 (d, 1H, J = 7.8 Hz, Ar–H), 7.52 (d, 2H, J = 8.2 Hz, A_2B_2, *p*-chlorophenyl), 7.67 (s, 1H, Ar–H), 7.95 (d, 1H, J = 8.4 Hz, Ar–H), 8.01 (2H, d, J = 8.2 Hz, A_2B_2, *p*-chlorophenyl), 8.37 (s, 1H, Ar–H), 8.55 (s, 2H, NH_2, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.7 (CH_3), 43.5 (C_4 of pyrazoline), 62.3 (C_5 of pyrazoline), 124.2–143.5 (Ar–C), 132.5 (C–Cl of chlorophenyl), 151.3 (C–Cl of quinoline), 156.7 (C=N of pyrazoline), 176.8 (C=S); LCMS *(m/z)*: 414 (M^+), 416 (M^++2); Anal. Calcd. For $C_{20}H_{16}Cl_2N_4S$: C-57.84, H-3.88, N-13.49; Found: C-57.90, H-3.94, N-13.44 %.

*5-(2-Chloro-6-methylquinolin-3-yl)-3-(2-fluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3g**)*

Light brown crystals, yield: 74 %; m.p.: 179–181 °C; IR (KBr) ν_{max}/cm^{-1}: 3463, 3376 (NH_2), 3061 (C–H, aromatic), 1580 (C=N), 1528 (C=C), 1334 (C=S), 1145 (C–F), 738 (C–Cl); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.38 (s, 3H, –CH_3), 3.36 (dd, 1H, J = 17.40, 3.01 Hz, C_4–H pyrazoline), 3.89 (dd, 1H, J = 17.41 Hz, 11.14 Hz, C_4–H pyrazoline), 6.10 (dd, 1H, J = 11.14 Hz, 3.00 Hz, C_5–H pyrazoline),7.29 (t, 1H, J = 8.0 Hz, Ar–H), 7.37 (d, 1H, J = 8.4 Hz, Ar–H), 7.42 (d, 1H, J = 8.2 Hz, Ar–H), 7.50 (t, 1H, J = 8.6 Hz, Ar–H), 7.62 (s, 1H, Ar–H), 7.84 (d, 1H, J = 8.4 Hz, Ar–H), 7.93 (d, 1H, J = 8.4 Hz, Ar–H), 8.33 (s, 1H, Ar–H), 8.61 (s, 2H, NH_2, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.4 (CH_3), 43.6 (C_4 of pyrazoline), 62.2 (C_5 of pyrazoline), 118.3–144.7 (Ar–C), 151.6 (C–Cl of quinoline), 156.4 (C=N of pyrazoline), 160.1 (C–F of fluorophenyl), 176.4 (C=S); LCMS *(m/z)*: 398(M^+), 400 (M^++2); Anal. Calcd. For $C_{20}H_{16}ClFN_4S$: C-60.22, H-4.04, N-14.05; Found: C-60.30, H-4.10, N-14.11 %.

*5-(2-Chloro-6-methylquinolin-3-yl)-3-(3-fluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3h**)*

Light brown crystals, yield: 78 %; m.p.: 167–169 °C; IR (KBr) ν_{max}/cm^{-1}: 3469, 3361 (NH_2), 3075 (C–H, aromatic), 1585 (C=N), 1528 (C=C), 1330 (C=S), 1146 (C–F), 748 (C–Cl); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.36 (s, 3H, CH_3), 3.43 (dd, 1H, J = 17.38, 3.06 Hz, C_4–H pyrazoline), 3.92 (dd, 1H, J = 17.39 Hz, 11.29 Hz, C_4–H pyrazoline), 6.09 (dd, 1H, J = 11.28 Hz, 3.06 Hz, C_5–H pyrazoline), 7.35(d, 1H, J = 7.8 Hz, Ar–H), 7.44 (d, 1H, J = 8.2 Hz, Ar–H), 7.62 (t, 1H, J = 8.2 Hz, Ar–H), 7.67 (s, 1H, Ar–H), 7.75 (d, 1H, J = 8.4 Hz, Ar–H), 7.80 (s, 1H, Ar–H), 7.94 (d, 1H, J = 8.1 Hz, Ar–H), 8.34 (s, 1H, Ar–H), 8.62 (s, 2H, NH_2, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.5 (CH_3), 43.8 (C_4 of pyrazoline), 62.1 (C_5 of pyrazoline), 113.5–144.5 (Ar–C), 151.8 (C–Cl of quinoline), 156.3 (C=N of pyrazoline), 163.6 (C–F of fluorophenyl), 176.8 (C=S); LCMS *(m/z)*: 398 (M^+), 400 (M^++2); Anal. Calcd. For $C_{20}H_{16}ClFN_4S$: C-60.22, H-4.04, N-14.05; Found: C-60.17, H-4.01, N-14.00 %.

*5-(2-Chloro-6-methylquinolin-3-yl)-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3i**)*

Light reddish brown crystals, yield: 72 %; m.p.: 208–210 °C; IR (KBr) ν_{max}/cm^{-1}: 3471, 3384 (NH_2), 3066 (C–H, aromatic), 1584 (C=N), 1527 (C=C), 1333 (C=S), 1154 (C–F), 733 (C–Cl); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.34 (s, 3H, –CH_3), 3.38 (dd, 1H, J = 17.40, 3.00 Hz, C_4-H pyrazoline), 3.88 (dd, 1H, J = 17.41, 11.20 Hz, C_4–H pyrazoline), 6.09 (dd, 1H, J = 11.19 Hz, 3.00 Hz, C_5–H pyrazoline), 7.32 (d, 1H, J = 8.4 Hz, Ar–H), 7.41 (d, 2H, J = 8.4 Hz, A_2B_2, *p*-fluorophenyl), 7.66 (s, 1H, Ar–H), 7.81 (d, 2H, J = 8.4 Hz, A_2B_2, *p*-fluorophenyl), 7.95 (d, 1H,

$J = 8.4$ Hz, Ar–H), 8.36 (s, 1H, Ar–H), 8.57 (s, 2H, NH_2, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.5 (CH_3), 43.8 (C_4 of pyrazoline), 62.1 (C_5 of pyrazoline), 113.5–144.5 (Ar–C), 151.7 (C–Cl of quinoline), 156.7 (C=N of pyrazoline), 162.4 (C–F of fluorophenyl), 176.5 (C=S); LCMS *(m/z)*: 398 (M^+), 400 (M^++2); Anal. Calcd. For $C_{20}H_{16}ClFN_4S$: C-60.22, H-4.04, N-14.05; Found: C-60.28, H-4.10, N-14.12 %.

*5-(2-Chloro-6-methylquinolin-3-yl)-3-(2-nitrophenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3j**)*

Light orange yellow crystals, yield: 79 %; m.p.: 169–171 °C; IR (KBr) ν_{max}/cm^{-1}: 3452, 3364 (NH_2), 3053 (C–H, aromatic), 1584 (C=N), 1520 (C=C), 1485, 1354 (NO_2), 1333 (C=S), 730 (C–Cl); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.38 (s, 3H, CH_3), 3.45 (dd, 1H, $J = 17.36$, 3.13 Hz, C_4–H pyrazoline), 3.97 (dd, 1H, $J = 17.36$, 11.17 Hz, C_4-H pyrazoline), 6.08 (dd, 1H, $J = 11.16$ Hz, 3.12 Hz, C_5–H pyrazoline), 7.36 (d, 1H, $J = 8.2$ Hz, Ar–H), 7.53 (t, 1H, $J = 8.2$ Hz, Ar–H), 7.62 (s, 1H, Ar–H), 7.84 (t, 1H, $J = 7.8$ Hz, Ar–H), 7.92 (d, 1H, $J = 7.4$ Hz, Ar–H), 7.98 (d, 1H, $J = 7.6$ Hz, Ar–H), 8.09 (d, 1H, $J = 7.6$ Hz, Ar–H), 8.35 (s, 1H, Ar–H), 8.68 (s, 2H, NH_2, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.6 (CH_3), 43.6 (C_4 of pyrazoline), 62.3 (C_5 of pyrazoline), 125.2–143.3 (Ar–C), 134.6 (C–NO_2), 151.8 (C–Cl of quinoline), 156.6 (C=N of pyrazoline), 176.7 (C=S); LCMS *(m/z)*: 425(M^+), 427 (M^++2); Anal. Calcd. For $C_{20}H_{16}ClN_5O_2S$: C-56.40, H-3.79, N-16.44; Found: C-56.47, H-3.73, N-16.52 %.

*5-(2-Chloro-6-methylquinolin-3-yl)-3-(3-nitrophenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3k**)*

Dark yellow crystals, yield: 74 %; m.p.: 201–203 °C; IR (KBr) ν_{max}/cm^{-1}: 3475, 3353 (NH_2), 3068 (C–H, aromatic), 1583 (C=N), 1526 (C=C), 1484, 1348 (NO_2), 1327 (C=S), 750 (C–Cl); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.36 (s, 3H, –CH_3), 3.39 (dd, 1H, $J = 17.45$, 3.10 Hz, C_4–H pyrazoline), 3.80 (dd, 1H, $J = 17.45$ Hz, 11.16 Hz, C_4-H pyrazoline), 6.05 (dd, 1H, $J = 11.15$ Hz, 3.10 Hz, C_5-H pyrazoline), 7.32 (d, 1H, $J = 8.0$ Hz, Ar–H), 7.62 (s, 1H, Ar–H), 7.76 (t, 1H, $J = 8.0$ Hz, Ar–H), 7.93 (d, 1H, $J = 7.6$ Hz, Ar–H), 8.14 (d, 1H, $J = 8.2$ Hz, Ar–H), 8.28 (d, 1H, $J = 7.6$ Hz, Ar–H), 8.34 (s, 1H, Ar–H),8.53 (s, 1H, Ar–H), 8.62 (s, 2H, NH_2, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.4 (CH_3), 43.9 (C_4 of pyrazoline), 62.1 (C_5 of pyrazoline), 124.8–144.9 (Ar–C), 132.7 (C–NO_2), 151.6 (C–Cl of quinoline), 156.7 (C=N of pyrazoline), 176.5 (C=S); LCMS *(m/z)*: 425 (M^+), 427 (M^++2);Anal. Calcd. For $C_{20}H_{16}ClN_5O_2S$: C-56.40, H-3.79, N-16.44; Found: C-56.48, H-3.75, N-16.36 %.

*5-(2-Chloro-6-methylquinolin-3-yl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazole-1-carbothioamide (**3l**)*

Orange crystals, yield: 76 %; m.p.: 220–222 °C; IR (KBr, cm^{-1}): IR (KBr) ν_{max}/cm^{-1}: 3466, 3362 (NH_2), 3077 (C–H, aromatic), 1585 (C=N), 1511 (C=C), 1480, 1349 (NO_2), 1326 (C=S), 739 (C–Cl); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.35 (s, 3H, –CH_3), 3.42 (dd, 1H, $J = 17.50$ Hz, 3.08 Hz, C_4–H pyrazoline), 3.88 (dd, 1H, $J = 17.50$ Hz, 11.18 Hz, C_4–H pyrazoline), 6.11 (dd, 1H, $J = 11.18$ Hz,3.08 Hz, C_5–H pyrazoline), 7.35 (d, 1H, $J = 8.4$ Hz, Ar–H), 7.66 (s, 1H, Ar–H), 7.95 (d, 1H, $J = 8.1$ Hz, Ar–H), 8.04 (d, 2H, $J = 8.2$ Hz, A_2B_2, *p*-nitrophenyl), 8.28 (2H, d, $J = 8.2$ Hz, A_2B_2, *p*-nitrophenyl), 8.37 (s, 1H, Ar–H), 8.58 (s, 2H, NH_2, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.6 (CH_3), 43.5 (C_4 of pyrazoline), 62.6 (C_5 of pyrazoline), 124.8–145.4 (Ar–C), 150.3 (C–NO_2), 151.8 (C–Cl of quinoline),156.9 (C=N of pyrazoline), 176.2 (C=S); LCMS *(m/z)*: 425 (M^+), 427 (M^++2); Anal. Calcd. For $C_{20}H_{16}ClN_5O_2S$: C-56.40, H-3.79, N-16.44; Found: C-56.34, H-3.84, N-16.50 %.

*General procedure for the preparation of 2-(5-(2-chloro-6-methylquinolin-3-yl)-3-(aryl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)ones (**4a–l**)*

To a suspension of compounds (**3a–l**) (0.01 mol) in ethanol (99.9 %), ethyl bromoacetate (0.01 mol) was added and heated at reflux for 1 h. After cooling, the separated product was filtered and washed. The product was crystallized from DMF.

Physical constants and characterization of synthesized compounds (**4a–l**)

*2-(5-(2-Chloro-6-methylquinolin-3-yl)-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4a**)*

Light brown crystals, yield: 60 %; m.p.: 188-190 °C; IR (KBr) ν_{max}/cm^{-1}: 3076 (C–H, aromatic), 1711 (C=O), 1578 (C=N), 1535 (C=C), 748 (C–Cl); ^1H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.35 (s, 3H, –CH_3), 3.17 (dd, 1H, $J = 17.48$ Hz, 3.01 Hz, C_4–H pyrazoline), 3.88 (dd, 1H, $J = 17.48$ Hz, 11.18 Hz, C_4–H pyrazoline), 4.01 (s, 2H, C_5–H thiazolinone), 6.02 (dd, 1H, $J = 11.17$ Hz, 3.00 Hz, C_5–H pyrazoline), 7.37 (d, 1H, $J = 8.4$ Hz, Ar–H), 7.48 (t, 1H, $J = 8.2$ Hz, Ar–H), 7.56 (t, 2H, $J = 7.8$ Hz, Ar–H),7.67 (s, 1H, Ar–H), 7.76 (d, 2H, $J = 7.8$ Hz, Ar–H), 7.92 (d, 1H, $J = 7.8$ Hz, Ar–H), 8.35 (s, 1H, Ar–H);^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.3 (CH_3), 39.0 (C_5 of thiazolinone), 42.2 (C_4 of pyrazoline), 60.1 (C_5 of pyrazoline), 124.7–143.7 (Ar–C), 151.4 (C–Cl of quinoline), 159.5 (C=N of pyrazoline), 178.1 (C=N of thiazolinone), 187.5 (C=O of

thiazolinone); LCMS *(m/z)*: 420(M^+), 422 (M^++2); Anal. Calcd. For $C_{22}H_{17}ClN_4OS$: C-62.78, H-4.07, N-13.31; Found: C-62.84, H-4.16, N-13.22 %.

*2-(5-(2-Chloro-6-methylquinolin-3-yl)-3-(2-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4b**)*

Light yellow crystals, yield: 58 %; m.p.: 175–177 °C; IR (KBr) ν_{max}/cm^{-1}: 3414 (OH, Ar-OH), 3068 (C–H, aromatic), 1701 (C=O), 1573 (C=N), 1530 (C=C), 748 (C–Cl); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.30 (s, 3H, $-CH_3$), 3.06 (dd, 1H, J = 17.44 Hz, 3.09 Hz, C_4–H pyrazoline), 3.84 (dd, 1H, J = 17.44 Hz, 11.12 Hz, C_4–H pyrazoline), 3.98 (s, 2H, C_5–H thiazolinone), 6.11 (dd, 1H, J = 11.12 Hz, 3.08 Hz, C_5–H pyrazoline), 6.92 (d, 1H, J = 8.2 Hz, Ar–H), 7.00 (d, 1H, J = 8.1 Hz, Ar–H), 7.38 (d, 1H, J = 8.0 Hz, Ar–H), 7.43 (t, 1H, J = 7.8 Hz, Ar–H), 7.58 (t, 1H, J = 7.4 Hz, Ar–H), 7.66 (s, 1H, Ar–H), 7.97 (d, 1H, J = 8.0 Hz, Ar–H), 8.38 (s, 1H, Ar–H), 9.19 (s, 1H, OH, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.1 (CH_3), 39.4 (C_5 of thiazolinone), 42.4 (C_4 of pyrazoline), 60.2 (C_5 of pyrazoline), 117.3–143.8 (Ar–C), 151.6 (C–Cl of quinoline), 159.1 (C=N of pyrazoline), 162.3 (C–OH), 178.6 (C=N of thiazolinone), 187.4 (C=O of thiazolinone); LCMS *(m/z)*: 436(M^+), 438 (M^++2); Anal. Calcd. For $C_{22}H_{17}ClN_4O_2S$: C-60.48, H-3.92, N-12.82; Found: C-60.55, H-3.85, N-12.89 %.

*2-(5-(2-Chloro-6-methylquinolin-3-yl)-3-(4-hydroxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4c**)*

Light brown crystals, yield: 58 %; m.p.: 185–187 °C; IR (KBr) ν_{max}/cm^{-1}: 3413 (OH), 3065 (C–H, aromatic), 1705 (C=O), 1572 (C=N), 1524 (C=C), 737 (C–Cl); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.35 (s, 3H, $-CH_3$), 3.17 (dd, 1H, J = 17.52, 3.12 Hz, C_4–H pyrazoline), 3.81 (dd, 1H, J = 17.51, 11.18 Hz, C_4–H pyrazoline), 4.00 (s, 2H, C_5–H thiazolinone), 6.11 (dd, 1H, J = 11.18, 3.12 Hz, C_5–H pyrazoline), 6.82 (d, 2H, J = 8.0 Hz, Ar–H),7.31 (d, 1H, J = 8.0 Hz, Ar–H), 7.62 (s, 1H, Ar–H), 7.82 (d, 2H, J = 7.8 Hz, Ar–H), 7.93 (d, 1H, J = 8.2 Hz, Ar–H), 8.36 (s, 1H, Ar–H), 9.21 (s, 1H, OH, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.4 (CH_3), 39.6 (C_5 of thiazolinone), 42.1 (C_4 of pyrazoline), 60.7 (C_5 of pyrazoline), 115.7–143.6 (Ar–C), 151.6 (C–Cl of quinoline), 159.3 (C=N of pyrazoline), 160.4 (C–OH), 178.2 (C=N of thiazolinone), 187.7 (C=O of thiazolinone); LCMS *(m/z)*: 436 (M^+), 438 (M^++2); Anal. Calcd. For $C_{22}H_{17}ClN_4O_2S$: C-60.48, H-3.92, N-12.82; Found: C-60.55, H-3.85, N-12.89 %.

*2-(5-(2-Chloro-6-methylquinolin-3-yl)-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4d**)*

Light pink crystals, yield: 55 %; m.p.: 198–200 °C; IR (KBr) ν_{max}/cm^{-1}: 3073 (C–H, aromatic), 1698 (C=O), 1580 (C=N), 1525 (C=C), 1234 (C–O–C), 748 (C–Cl); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.33 (s, 3H, $-CH_3$), 3.14 (dd, 1H, J = 17.45 Hz, 3.11 Hz, C_4–H pyrazoline), 3.66 (s, 3H, $-OCH_3$), 3.88 (dd, 1H, J = 17.46 Hz, 11.13 Hz, C_4–H pyrazoline), 4.03 (s, 2H, C_5–H thiazolinone), 6.04 (dd, 1H, J = 11.14, 3.10 Hz, C_5–H pyrazoline), 7.02 (d, 2H, J = 8.0 Hz, A_2B_2, *p*-methoxyphenyl), 7.34 (d, 1H, J = 8.2 Hz, Ar–H), 7.64 (s, 1H, Ar–H), 7.95 (d, 1H, J = 8.4 Hz, Ar–H), 8.03 (d, 2H, J = 8.0 Hz, A_2B_2, *p*-methoxyphenyl), 8.32 (s, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.5 (CH_3), 39.7 (C_5 of thiazolinone), 42.2 (C_4 of pyrazoline), 54.8 (OCH_3), 62.0 (C_5 of pyrazoline), 114.7–143.7 (Ar–C), 151.5 (C–Cl of quinoline), 159.7 (C=N of pyrazoline), 178.3 (C=N of thiazolinone), 187.4 (C=O of thiazolinone); LCMS *(m/z)*: 450(M^+), 452 (M^++2); Anal. Calcd. For $C_{23}H_{19}ClN_4O_2S$: C-61.26, H-4.25, N-12.42; Found: C-61.20, H-4.31, N-12.35 %.

*2-(5-(2-Chloro-6-methylquinolin-3-yl)-3-(2-chlorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4e**)*

Light yellow crystals, yield: 59 %; m.p.: 226–228 °C; IR (KBr) ν_{max}/cm^{-1}: 3065 (C–H, aromatic), 1695 (C=O), 1573 (C=N), 1529 (C=C), 745 (C–Cl); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.35 (s, 3H, $-CH_3$), 3.24 (dd, 1H, J = 17.48 Hz, 3.10 Hz, C_4–H pyrazoline), 3.94 (dd, 1H, J = 17.48 Hz, 11.18 Hz, C_4–H pyrazoline), 4.04 (s, 2H, C_5–H thiazolinone), 6.08 (dd, 1H, J = 11.17 Hz, 3.09 Hz, C_5–H pyrazoline),7.37 (d, 1H, J = 7.8 Hz, Ar–H), 7.42 (t, 1H, J = 7.4 Hz, Ar–H), 7.54 (t, 1H, J = 8.2 Hz, Ar–H), 7.59 (d, 1H, J = 8.4 Hz, Ar–H), 7.61 (s, 1H, Ar–H), 7.79 (d, 1H, J = 8.4 Hz, Ar–H), 7.94 (d, 1H, J = 8.4 Hz, Ar–H), 8.36 (s, 1H, Ar–H);^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.6 (CH_3), 39.6 (C_5 of thiazolinone), 42.2 (C_4 of pyrazoline), 62.8 (C_5 of pyrazoline), 128.4 (C–Cl of chlorophenyl), 124.3–143.4 (Ar–C), 151.6 (C–Cl of quinoline), 159.5 (C=N of pyrazoline), 178.5 (C=N of thiazolinone), 187.3 (C=O of thiazolinone); LCMS *(m/z)*: 454(M^+), 456 (M^++2); Anal. Calcd. For $C_{22}H_{16}Cl_2N_4OS$: C-58.03, H-3.54, N-12.30; Found: C-58.11, H-3.61, N-12.37 %.

*2-(5-(2-Chloro-6-methylquinolin-3-yl)-3-(4-chlorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4f**)*

Light brown crystals, yield: 55 %; m.p.: 164–166 °C; IR (KBr) ν_{max}/cm^{-1}: 3061 (C–H, aromatic), 1690 (C=O),

1582 (C=N), 1527 (C=C), 738 (C–Cl); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.34 (s, 3H, –CH_3), 3.17 (dd, 1H, $J = 17.36$, 3.02 Hz, C_4–H pyrazoline), 3.97 (dd, 1H, $J = 17.36$ Hz, 11.17 Hz, C_4–H pyrazoline), 4.08 (s, 2H, C_5–H thiazolinone), 6.10 (dd, 1H, $J = 11.16$, 3.01 Hz, C_5–H pyrazoline), 7.33 (d, 1H, $J = 7.6$ Hz, Ar–H), 7.54 (d, 2H, $J = 8.0$ Hz, A_2B_2, *p*-chlorophenyl), 7.63 (s, 1H, Ar–H), 7.91 (d, 1H, $J = 8.1$ Hz, Ar–H), 8.01 (d, 2H, $J = 8.0$ Hz, A_2B_2, *p*-chlorophenyl), 8.38 (s, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.6 (CH_3), 39.7 (C_5 of thiazolinone), 42.4 (C_4 of pyrazoline), 62.5 (C_5 of pyrazoline), 132.3 (C–Cl of chlorophenyl), 124.6–143.8 (Ar–C), 151.6 (C–Cl of quinoline), 159.4 (C=N of pyrazoline), 178.4 (C=N of thiazolinone), 187.8 (C=O of thiazolinone); LCMS *(m/z)*: 454 (M^+), 456 (M^++2); Anal. Calcd. For $C_{22}H_{16}Cl_2N_4OS$: C-58.03, H-3.54, N-12.30; Found: C-57.96, H-3.49, N-12.23 %.

*2-(5-(2-Chloro-6-methylquinolin-3-yl)-3-(2-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4g**)*

Light yellow crystals, yield: 53 %; m.p.: 173–175 °C; IR (KBr) ν_{max}/cm^{-1}: 3072 (C–H, aromatic), 1698 (C=O), 1583 (C=N), 1524 (C=C), 1147 (C–F); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.37 (s, 3H, –CH_3), 3.33 (dd, 1H, $J = 17.42$ Hz, 3.10 Hz, C_4–H pyrazoline), 3.89 (dd, 1H, $J = 17.41$ Hz, 11.29 Hz, C_4–H pyrazoline), 4.02 (s, 2H, C_5–H thiazolinone), 6.11 (dd, 1H, $J = 11.28$ Hz, 3.10 Hz, C_5–H pyrazoline),7.29 (t, 1H, $J = 8.0$, Ar–H), 7.35 (d, 1H, $J = 8.4$, Ar–H), 7.42 (d, 1H, $J = 8.2$, Ar–H), 7.50 (t, 1H, $J = 8.4$, Ar–H), 7.62 (s, 1H, Ar–H), 7.84 (d, 1H, $J = 8.6$, Ar–H), 7.94 (d, 1H, $J = 8.3$ Hz, Ar–H), 8.33 (s, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.8 (CH_3), 39.8 (C_5 of thiazolinone), 42.5 (C_4 of pyrazoline), 62.2 (C_5 of pyrazoline), 114.7–144.1 (Ar–C), 151.9 (C–Cl of quinoline), 159.4 (C=N of pyrazoline), 159.8 (C–F), 178.3 (C=N of thiazolinone), 187.4 (C=O of thiazolinone); LCMS *(m/z)*: 438(M^+), 440 (M^++2); Anal. Calcd. For $C_{22}H_{16}ClFN_4OS$: C-60.20, H-3.67, N-12.77; Found: C-60.28, H-3.73, N-12.70 %.

*2-(5-(2-Chloro-6-methylquinolin-3-yl)-3-(3-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4h**)*

Light brown crystals, yield: 61 %; m.p.: 163–165 °C; IR (KBr) ν_{max}/cm^{-1}: 3070 (C–H, aromatic), 1704 (C=O), 1572 (C=N), 1501 (C=C), 1152 (C–F); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.35 (s, 3H, –CH_3), 3.46 (dd, 1H, $J = 17.45$, 3.18 Hz, C_4–H pyrazoline), 3.90 (dd, 1H, $J = 17.44$ Hz, 11.19 Hz, C_4–H pyrazoline), 4.10 (s, 2H, C_5–H thiazolinone), 6.03 (dd, 1H, $J = 11.18$, 3.18 Hz, C_5–H pyrazoline),7.34 (d, 1H, $J = 8.2$ Hz, Ar–H), 7.44 (d, 1H, $J = 7.8$ Hz, Ar–H), 7.63 (t, 1H, $J = 8.2$ Hz, Ar–H), 7.68 (s, 1H, Ar–H), 7.75 (d, 1H, $J = 8.4$ Hz, Ar–H), 7.80 (s, 1H, Ar–H), 7.91 (d, 1H, $J = 8.0$ Hz, Ar–H), 8.36 (s, 1H, Ar–H);^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.7 (CH_3), 39.8 (C_5 of thiazolinone), 42.2 (C_4 of pyrazoline), 62.4 (C_5 of pyrazoline), 113.8–144.2 (Ar–C), 151.7 (C–Cl of quinoline), 159.6 (C=N of pyrazoline), 162.4 (C–F), 178.7 (C=N of thiazolinone), 187.5 (C=O of thiazolinone); LCMS *(m/z)*: 438 (M^+), 440 (M^++2); Anal. Calcd. For $C_{22}H_{16}ClFN_4OS$: C-60.20, H-3.67, N-12.77; Found: C-60.13, H-3.60, N-12.84 %.

*2-(5-(2-Chloro-6-methylquinolin-3-yl)-3-(4-fluorophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4i**)*

Light reddish brown crystals, yield: 59 %; m.p.: 180–182 °C; IR (KBr) ν_{max}/cm^{-1}: 3071 (C–H, aromatic), 1696 (C=O), 1582 (C=N), 1521 (C=C), 1148 (C–F); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.37 (s, 3H, –CH_3), 3.35 (dd, 1H, $J = 17.52$ Hz, 3.10 Hz, C_4–H pyrazoline), 3.87 (dd, 1H, $J = 17.51$ Hz, 11.12 Hz, C_4–H pyrazoline), 4.07 (s, 2H, C_5–H thiazolinone), 6.14 (dd, 1H, $J = 11.12$ Hz, 3.11 Hz, C_5–H pyrazoline), 7.32 (d, 1H, $J = 7.8$, Ar–H), 7.40 (d, 2H, $J = 8.4$ Hz, A_2B_2, *p*-fluorophenyl), 7.67 (s, 1H, Ar–H), 7.81 (d, 2H, $J = 8.4$ Hz, A_2B_2, *p*-fluorophenyl), 7.90 (d, 1H, $J = 8.2$ Hz, Ar–H), 8.32 (s, 1H, Ar–H);^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.4 (CH_3), 39.3 (C_5 of thiazolinone), 42.1 (C_4 of pyrazoline), 62.6 (C_5 of pyrazoline), 115.1–143.7 (Ar–C), 151.5 (C–Cl of quinoline), 159.8 (C=N of pyrazoline), 164.3 (C–F), 178.4 (C=N of thiazolinone), 187.9 (C=O of thiazolinone); LCMS *(m/z)*: 438 (M^+), 440 (M^++2); Anal. Calcd. For $C_{22}H_{16}ClFN_4OS$: C-60.20, H-3.67, N-12.77; Found: C-60.28, H-3.73, N-12.82 %.

*2-(5-(2-Chloro-6-methylquinolin-3-yl)-3-(2-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4j**)*

Dark yellow crystals, yield: 53 %; m.p.: 194–196 °C; IR (KBr) ν_{max}/cm^{-1}: 3060 (C–H, aromatic), 1700 (C=O), 1582 (C=N), 1528 (C=C), 1486, 1357 (NO_2); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.38 (s, 3H, –CH_3), 3.40 (dd, 1H, $J = 17.34$ Hz, 3.03 Hz, C_4–H pyrazoline), 3.95 (dd, 1H, $J = 17.34$ Hz, 11.19 Hz, C_4–H pyrazoline), 4.05 (s, 2H, C_5–H thiazolinone), 6.02 (dd, 1H, $J = 11.18$ Hz, 3.03 Hz, C_5–H pyrazoline), 7.36 (d, 1H, $J = 8.2$, Ar–H),7.53 (t, 1H, $J = 8.2$ Hz, Ar–H), 7.64 (s, 1H, Ar–H), 7.84 (t, 1H, $J = 8.4$ Hz, Ar–H), 7.93 (d, 1H,$J = 7.8$ Hz, Ar–H), 7.98 (d, 1H, $J = 7.8$ Hz, Ar–H), 8.07 (d, 1H, $J = 7.8$ Hz, Ar–H), 8.35 (s, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.8 (CH_3), 39.2 (C_5 of thiazolinone), 42.3 (C_4 of pyrazoline), 62.8 (C_5 of pyrazoline), 124.4–143.6 (Ar–C), 134.8 (C-NO_2), 151.6 (C–Cl of quinoline), 159.2 (C=N of pyrazoline), 178.4 (C=N of thiazolinone), 187.7 (C=O of thiazolinone); LCMS *(m/z)*: 465(M^+), 467 (M^++2); Anal.

Calcd. For $C_{22}H_{16}ClN_5O_3S$: C-56.71, H-3.46, N-15.03; Found: C-56.78, H-3.52, N-15.11 %.

*2-(5-(2-Chloro-6-methylquinolin-3-yl)-3-(3-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4k**)*

Light yellowish brown crystals, yield: 54 %; m.p.: 158–160 °C; IR (KBr) ν_{max}/cm^{-1}: 3078 (C–H, aromatic), 1697 (C=O), 1579 (C=N), 1518 (C=C), 1488, 1359 (NO_2); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.36 (s, 3H, –CH_3), 3.44 (dd, 1H, $J = 17.48$ Hz, 3.13 Hz, C_4–H pyrazoline), 3.89 (dd, 1H, $J = 17.48$ Hz, 11.04 Hz, C_4–H pyrazoline), 4.11 (s, 2H, C_5–H thiazolinone), 6.18 (dd, 1H, $J = 11.04$ Hz, 3.12 Hz, C_5–H pyrazoline), 7.34 (d, 1H, $J = 7.8$, Ar–H), 7.63 (s, 1H, Ar–H), 7.74 (t, 1H, $J = 8.0$ Hz, Ar–H), 7.89 (d, 1H, $J = 8.0$ Hz, Ar–H), 8.14 (d, 1H, $J = 8.4$ Hz, Ar–H), 8.28 (d, 1H, $J = 8.2$ Hz, Ar–H), 8.34 (s, 1H, Ar–H), 8.52 (s, 1H, Ar–H); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.6 (CH_3), 39.7 (C_5 of thiazolinone), 42.8 (C_4 of pyrazoline), 62.4 (C_5 of pyrazoline), 124.5–144.1 (Ar–C), 132.3 (C-NO_2),151.8 (C–Cl of quinoline), 159.6 (C=N of pyrazoline), 178.3 (C=N of thiazolinone), 187.6 (C=O of thiazolinone); LCMS *(m/z)*: 465 (M^+), 467 (M^++2); Anal. Calcd. For $C_{22}H_{16}ClN_5O_3S$: C-56.71, H-3.46, N-15.03; Found: C-56.66, H-3.40, N-14.95 %.

*2-(5-(2-Chloro-6-methylquinolin-3-yl)-3-(4-nitrophenyl)-4,5-dihydro-1H-pyrazol-1-yl)thiazol-4(5H)-one (**4l**)*

Orange crystals, yield: 52 %; m.p.: 170–172 °C; IR (KBr) ν_{max}/cm^{-1}: 3073 (C–H, aromatic), 1705 (C=O), 1580 (C=N), 1513 (C=C), 1487, 1354 (NO_2); ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.38 (s, 3H, –CH_3), 3.47 (dd, 1H, $J = 17.42$ Hz, 3.10 Hz, C_4–H pyrazoline), 3.88 (dd, 1H, $J = 17.43$, 11.14 Hz, C_4–H pyrazoline), 4.07 (s, 2H, C_5–H thiazolinone), 6.14 (dd, 1H, $J = 11.15$, 3.10 Hz, C_5–H pyrazoline), 7.32 (d, 1H, $J = 7.8$, Ar–H), 7.60 (s, 1H, Ar–H), 7.92 (d, 1H, Ar–H), 8.06 (d, 2H, $J = 8.6$ Hz, A_2B_2, *p*-nitrophenyl), 8.29 (d, 2H, $J = 8.6$ Hz, A_2B_2, *p*-nitrophenyl), 8.37 (s, 1H, Ar–H), 8.32 (s, 1H, Ar–H), 8.58 (s, 2H, NH_2, D_2O exch.); ^{13}C NMR (100 MHz, DMSO-d_6, δ, ppm): 21.8 (CH_3), 39.8 (C_5 of thiazolinone), 42.3 (C_4 of pyrazoline), 62.1 (C_5 of pyrazoline), 124.1–145.1 (Ar–C), 150.1 (C–NO_2),151.6 (C–Cl of quinoline), 159.3 (C=N of pyrazoline), 178.4 (C=N of thiazolinone), 187.4 (C=O of thiazolinone); LCMS *(m/z)*: 465 (M^+), 467 (M^++2);Anal. Calcd. For $C_{22}H_{16}ClN_5O_3S$: C-56.71, H-3.46, N-15.03; Found: C-56.76, H-3.52, N-15.08 %.

Conclusion

The preliminary in vitro antibacterial and antifungal screening results of novel quinoline-2-pyrazoline-based thiazolinone derivatives exhibited remarkable antimicrobial potency. Results of antimicrobial activity clearly demonstrated that the presence of thiazolinone heterocycle is essential for enhancing biologic activity along with the variation on different groups/atom on the phenyl ring at 3rd position of pyrazoline heterocycle. It is a very well-known fact that halogen atom (chloro/fluoro) is hydrophobic in nature; due to this reason, it will influence as substituent group's physicochemical properties on the activity of compounds. This property is useful to a compound to diffuse through the biologic membranes and reach to its site of action. Owing to this reason, hydrophobicity was found to be directly related to the antimicrobial activity. The presence of hydrophobic substituent at 2nd position of phenyl ring provides a positive influence on antimicrobial activity. The presence of chloro, fluoro, and nitro substituents conjugated to the aromatic ring has increased the activity of the compounds compared to those with electron donating substituents. It may be considered as a promising lead for further design and development of new lead molecules. SAR studies have encouraged us to make further modifications on basic structures of the synthesized compounds to achieve more selective and more potential antimicrobial derivatives in ongoing program. In addition, further investigations of these findings can have good effects on medicinal chemists to synthesize similar compounds selectively bearing chloro, fluoro, and nitro substituents.

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