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REVIEW

# Quinolinyl-pyrazoles: synthesis and pharmacological evolution in the recent decennial

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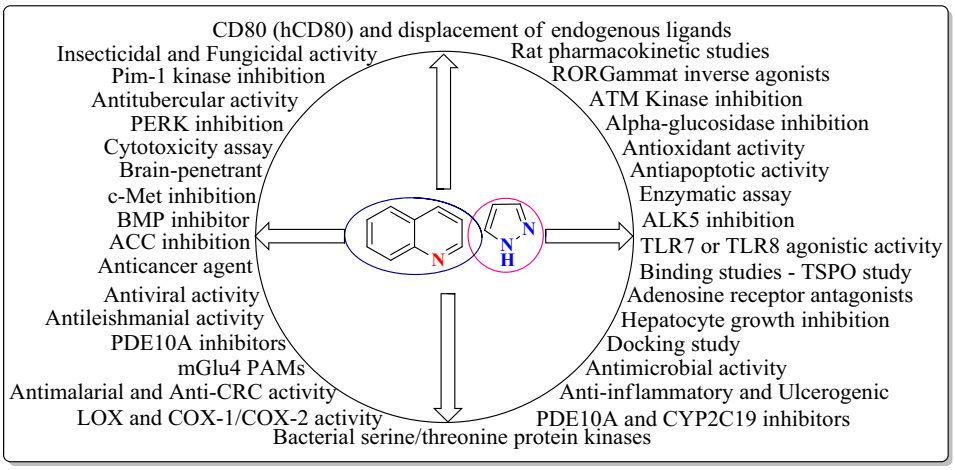
## Abstract

In the recent decade, the study on *N*-heterocycles has dramatically increased due to its versatility in many significant fields and because of its distinctive battle which is associated with the bioassay and its interaction with the cells. These novel heterocycles are designed and synthesized by chemists through new strategies on par with the reported methods. Subsequently, the synthesized molecules were screened for their efficacy against the typical drugs in the market. In this article, recently unveiled pharmacologically important quinoline allied pyrazoles have been reviewed. Moreover, this review gives a bird's-eye view of different methods adopted for synthesis in addition to the conventional approaches and also detailed study of the bioactive quinolinyl-pyrazole heterocycle when compared with standard drug-associated/having efficient molecule. We believe that this review will inspire synthetic as well as medicinal chemists who are in quest of less toxic and more potent quinolinyl-pyrazoles for the treatment of various health threats.

### Graphic abstract




**Keywords** Quinoline · Pyrazole · Quinolinyl-pyrazole · Synthetic strategy · Pharmacological screening

## Introduction

Quinoline also called as benzopyridine is a well-known nitrogenous tertiary base [1] containing a hetero nucleus with chemical formula $C_9H_7N$. Besides, it is a pungent hygroscopic colorless oily liquid with molecular weight of

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129.16 g/mol. In general, quinoline derivatives have been used since ancient times; however, the culture of quinine (**1**) and cinchonine (**2**), which were isolated from the bark of the cinchona tree for the treatment of malaria [2–4], started from 1820. Other important naturally occurring quinoline derivatives are mepacrine (**3**), camptothecin (**4**), hydroquinine (**5**), skimmianine (**6**), *d*-quinotoxine (**7**), sanguinarine (**8**) and dictamnine (**9**) (Fig. 1).

Chloroquine was first isolated [5] as a drug by Hans Andersag et al, in 1934 among the series of alkaloids. The quinoline scaffold was first extracted [6] in 1834 from coal tar by German analytical chemist Friedlieb Ferdinand Runge; subsequently, in 1842 it was synthesized [7] by French chemist Charles Gerhardt by dry distillation of quinine, strychnine or cinchonine in the presence of sodium hydroxide. There are also many conventional named reactions such as Skraup [8], Doebner-von Miller [9], Friedlander [10], Combes synthesis [11], Conrad-Limpach [12], Pictet Spengler [13] and many more [14, 15] to tailor quinoline core molecules. In recent years, the discovery of quinoline-bearing moieties has enhanced due to its wide range of applications in agrochemical [16], dye industry [17, 18] and in medicinal fields [19–23] as antimicrobial [24, 25], anti-HIV [26], antimalarial [27, 28], antiprotozoal [29, 30], antitubercular [31, 32], anticancer [33, 34], antipsychotics [35], antioxidant [36], antineurodegenerative [37] agents.

Pyrazole is a nitrogen-containing electron-rich heterocycle [38] which has received considerable attention from the last few decades due to its versatile synthetic approaches [39] and for showing bioactivity concerning anticancer [40], antifungal [41], antibacterial [42, 43], insecticidal [44], antitumor [45], anti-inflammatory [46], antidepressant [47–50], antitubercular [51], anticonvulsant [52, 53] and antidiabetic [54] properties.

Moreover, several review papers that are published in peer-reviewed journals have given complete details about the preparation and the biological evaluation of quinoline [14, 55–59] and pyrazole [60] derivatives over the past decade. This comprehensive review aims to recapitulate the recent approaches for the synthesis and pharmacological evolution

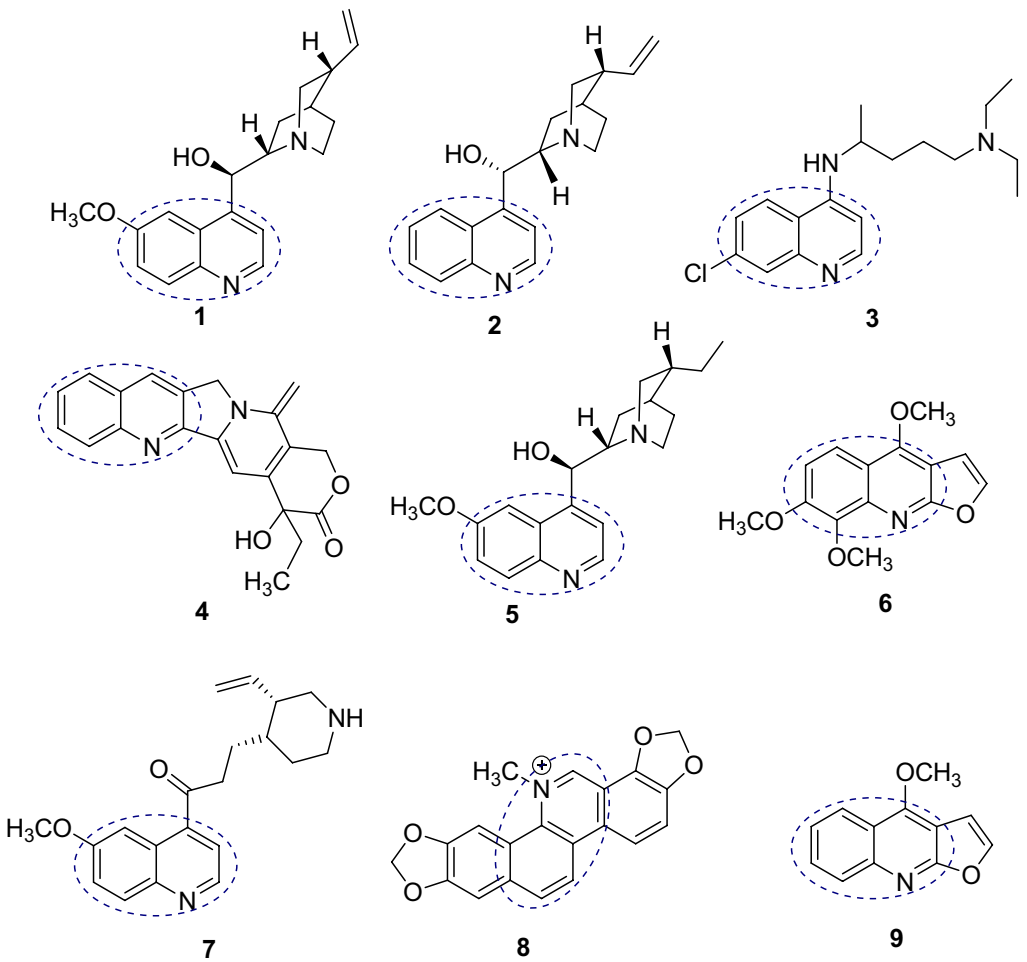
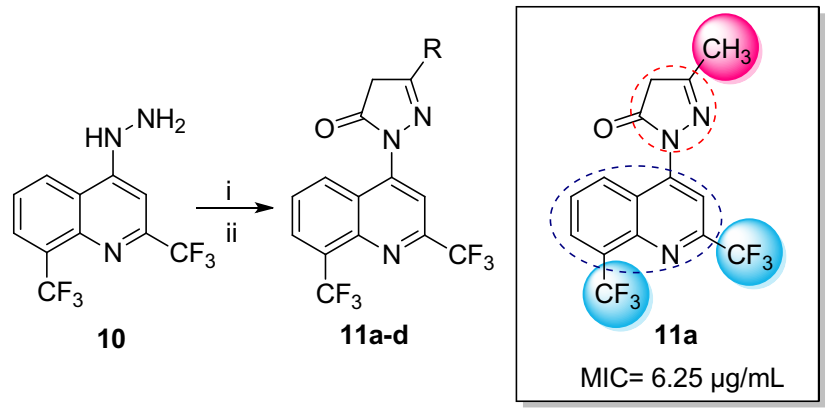



**Fig. 1** Some promising quinoline alkaloids

of quinoline-appended pyrazoles as potential therapeutic agents, and the structure–activity relationship (SAR) studies are also briefly explained.

Through a multi-step process, various quinoline-appended pyrazoles (Scheme 1) were synthesized from quinoline hydrazide **(10)** via cyclization reaction [61]. The target molecules (**11a–d**) were obtained by treating the hydrazide **(10)** with isocyanate, later with substituted isothiocyanate under the toluene medium. Final compounds **(11a–d)** obtained were tested for their in vitro antibacterial and antituberculosis activity, and the study revealed that the compound containing pyrazole moiety with a methyl group (**11a**) inhibits 99% growth of *M. tuberculosis*.

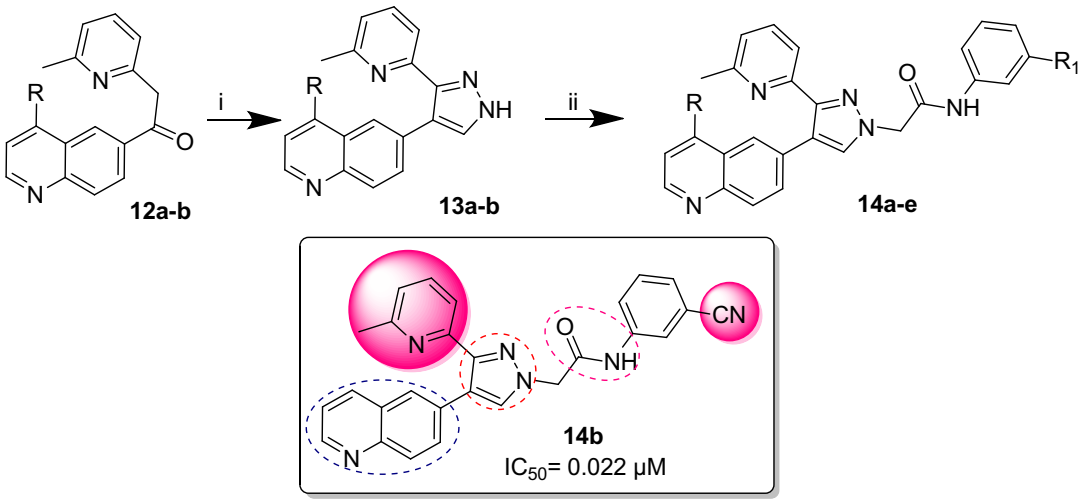
Cheng Hua Jin et al. in 2011 prepared various pyrazole-containing quinoline analogues, (Scheme 2) and assessed for their ALK5 inhibitory activity [62]. Here pyrazole-appended quinoline (**13a–b**) was obtained by treating 2-(6-methylpyridin-2-yl)-1-(quinolin-6-yl)ethanone (**12a–b**) with hydrazine hydrate via cyclization in the presence of dimethylacetamide and hydrazine hydrate under ethanol solvent system.




**11a-d = R=** Alkyl, Aryl,

**Reagents and conditions:** (i) Substituted isocyanate, toluene, 110 °C, 30 min, (ii) Substituted isothiocyanate, toluene, 110 °C, 30 min.

**Scheme 1** Synthesis of quinoline allied pyrazole with trifluoromethyl substituents




**12a = 13a** = R=H, **12b = 13b** = R=OMe, **14a** = R=$R_1$=H, **14b** = R=H, $R_1$=CN, **14c** = R=OMe, $R_1$=H, **14d** = R=OMe, $R_1$=CN, **14e** = R=H, $R_1$=$CONH_2$,

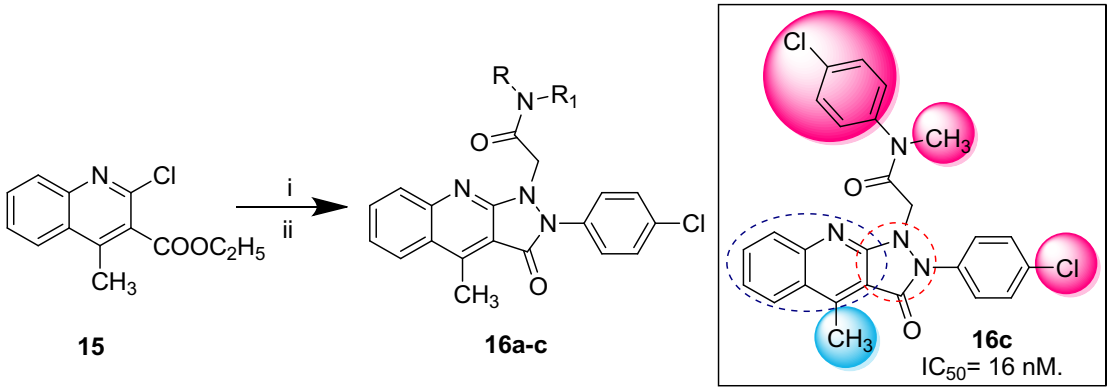
**Reagents and conditions:** (i) (a) DMF DMA, 90 °C, 4 h, (b) $N_2H_4$ $H_2O$, EtOH, reflux, 4 h, (ii) Substituted 2-chloro-N-phenylacetamide, NaH, NaI (cat.), DMF, rt, 30 min.

**Scheme 2** Synthesis of quinoline allied pyrazole with carbonitrile group and amide link

The final compounds **(14a–e)** as positional isomers were obtained through alkylation by treating with 2-chloro-*N*-phenylacetamide. A kinase assay was investigated toward ALK5 inhibitory activity in a luciferase reporter assay, and the scaffold containing carbonitrile group with amide linkage at the pyrazole part (**14b**) possessed significant ALK5 inhibitory activity which is much greater than other compounds obtained.

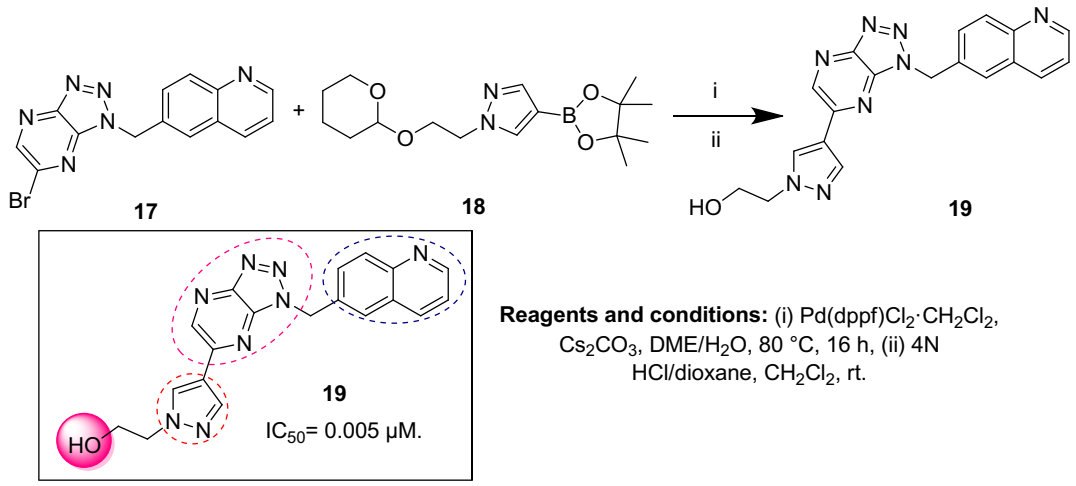
Series of novel pyrazolo[3,4-b]-quinoline with *N*-alkyl derivatives (Scheme 3) were designed and synthesized in a simple route by treating 2-chloroquinoline derivative **(15)** with phenylhydrazine in presence of 1-pentanol followed by *N*-alkylation in the presence of sodium carbonate [63]. Then all the synthesized compounds **(16a–c)** were subjected to in vitro binding studies where the compounds showed TSPO affinities based on structure affinity relationship. Moreover, the bioassay envisioned that the compound containing chloroaryl group at the pyrazole part **(16c)** exhibited noteworthy binding property in both light and dark box tests compared to other derivatives.

Novel candidate of pyrazole-bearing quinoline (Scheme 4) was synthesized by a multi-step procedure through the Suzuki coupling reaction followed by deprotection [64]. The quinoline affixed pyrazole analogue **(19)** with hydroxyl functionality was obtained by treating 6-((6-bromo-1*H*-[1,2,3]triazolo[4,5-b]pyrazin-1-yl)methyl)quinoline **(17)** with pyrazole boronic ester **(18)** followed by deprotection under hydrochloric acid medium. Finally, all the discovered molecules were screened as a potent inhibitor for c-MET in both in vitro and in vivo target modulation studies which revealed that the quinoline-containing pyrazole heterocycle with hydroxyl functional group **(19)** possessed excellent




**16a** = R=$CH_3$, $R_1$=$(CH_2)_3CH_3$, **16b** = R=$(CH_2)_2CH_3$, $R_1$=$(CH_2)_2CH_3$, **16c** = R=$CH_3$, $R_1$=p-Cl-$C_6H_4$,
**Reagents and conditions:** (i) $C_6H_4NHNH_2$, 1-pentanol, (or X-$C_6H_4NHNH_2$ .3HCl, $Na_2CO_3$, 1-pentanol), (ii) Bromoacetamide derivatives, $Na_2CO_3$, DMF.

**Scheme 3** Synthesis of quinoline allied pyrazole with chloroaryl group and amide link




**Reagents and conditions:** (i) $Pd(dppf)Cl_2 \cdot CH_2Cl_2$, $Cs_2CO_3$, $DME/H_2O$, 80 °C, 16 h, (ii) 4N HCl/dioxane, $CH_2Cl_2$, rt.

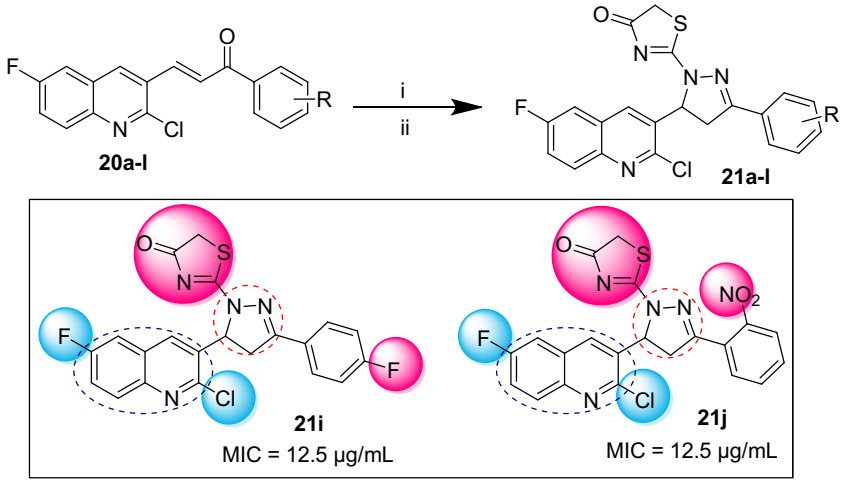
**Scheme 4** Synthesis of quinoline allied pyrazole linked with triazolo-pyrazine

tumor growth inhibition, oral PK and binding properties with 208 different protein kinases. In 2015, Minghui Dong et al. [65] screened the above-discovered quinoline allied heterocycles for hepatocyte growth inhibition and subjected for docking study which revealed that the same compound **(19)** emerged as a potent molecule favored by a hydrophilic hydroxyl group.

Some important pyrazole-containing quinolines (Scheme 5) were obtained through chalcones **(20a–l)** by treating it with thiosemicarbazide under alkaline condition followed by cyclization and screened for their antimicrobial activity [66]. Compounds containing fluoro **(21i)** and nitro aryl groups **(21j)** at the pyrazole part emerged as potent antimicrobial agents against *E. coli, S. pyogenes,* and *P. aeruginosa* with the highest inhibition.

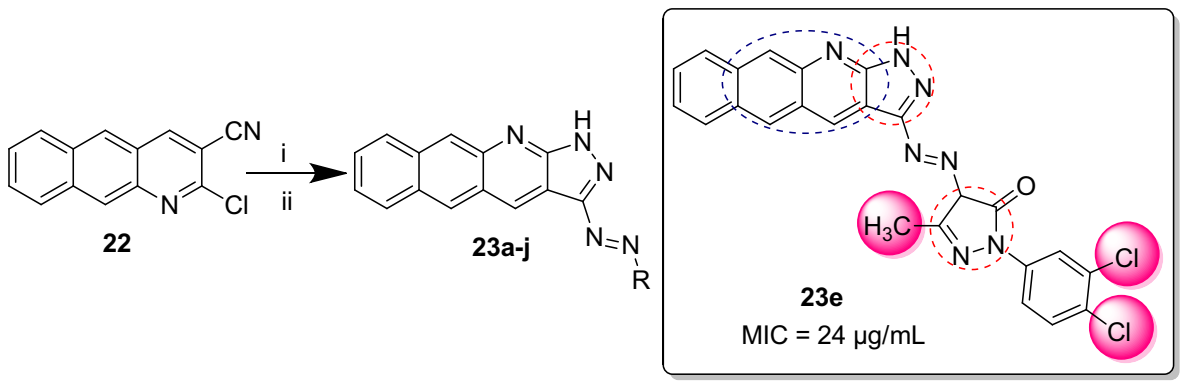
Series of quinoline-tethered pyrazoles (Scheme 6) were synthesized as a potent antimicrobial and antifungal agents [67]. The intermediate compound 2-chlorobenzo[g]quinoline-3-carbonitrile **(22)** was subjected to cyclization reaction with hydrazine hydrate followed by a diazotization reaction by using sodium nitrite and coupled with various amines to afford the compounds **(23a–j)**. The bioassay of the synthesized compounds showed that the dichloro-derivative **(23e)** exhibited excellent antimicrobial and antifungal activity.

Through conventional method and Suzuki reaction, various quinoline allied *N*-aryl-pyrazole heterocycles




**20a=21a** = R=H, **20b=21b** = R=2-OH, **20c=21c** = R=4-OH, **20d=21d** = R=4-$OCH_3$, **20e=21e** = R=2-Cl, **20f=21f** = R=4-Cl, **20g=21g** = R=2-F, **20h=21h** = R=3-F, **20i=21i** = R=4-F, **20j=21j** = R=2-$NO_2$, **20k=21k** = R=3-$NO_2$, **20l=21l** = R=4-$NO_2$,
**Reagents and conditions:** (i) $NH_2CSNHNH_2$, ethanol, reflux, 8 h, (ii) $BrCH_2COOC_2H_5$, ethanol, reflux, 1 h.

**Scheme 5** Synthesis of quinoline allied thiazole-substituted pyrazole heterocycle



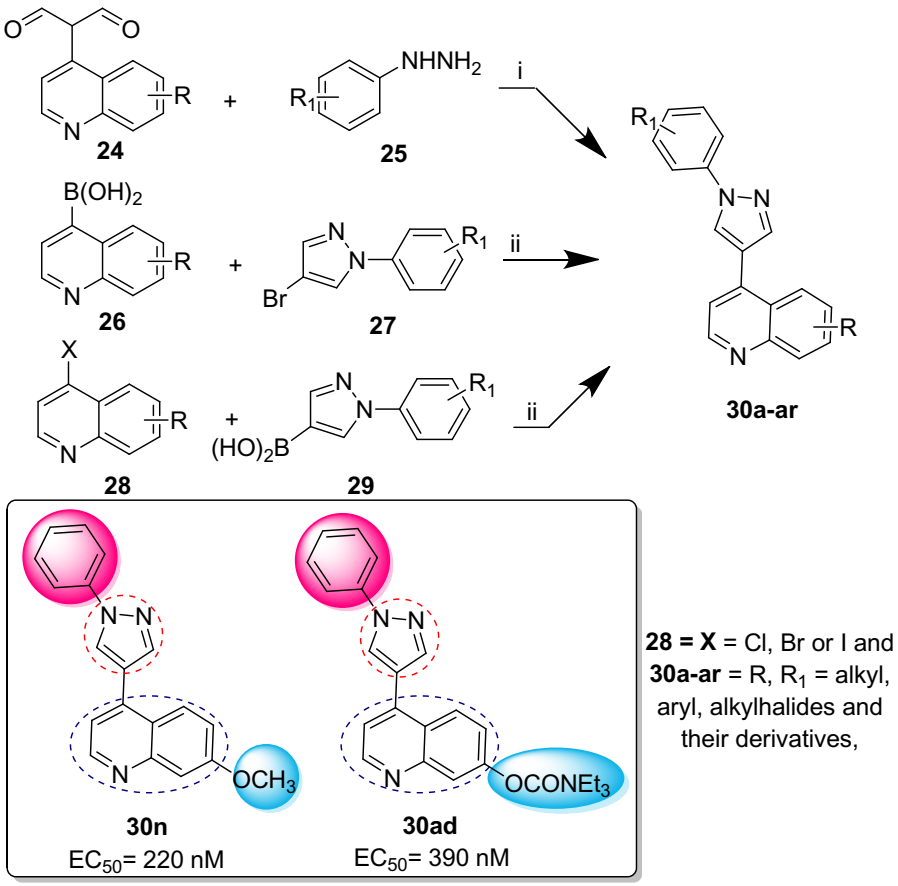

**23a-j** = R= various phenyl pyrazolone derivatives,
**Reagents and conditions:** (i) Hydrazine hydrate, ethanol, reflux, (ii) Sodium nitrite/HCl, 0 - 5 °C.

**Scheme 6** Synthesis of diazo linked quinoline allied pyrazole heterocycle

(Scheme 7) as promising brain-penetrant and fairly potent mGlu4 PAMs were prepared starting from malonic aldehyde **(24)**, aryl boronic acid **(26)** and halogenated quinoline **(28)** via cyclization and nucleophilic substitution reaction [68]. Among the series, compounds bearing the electron-donating group at the seventh position of quinoline core moiety **(30n)** and **(30ad)** emerged as a comparable functional efficacy with respect to a hit molecule 4-(1-phenyl-1*H*-pyrazol-4-yl) quinoline **(30a)** chemotype for mGlu4 PAM activity.

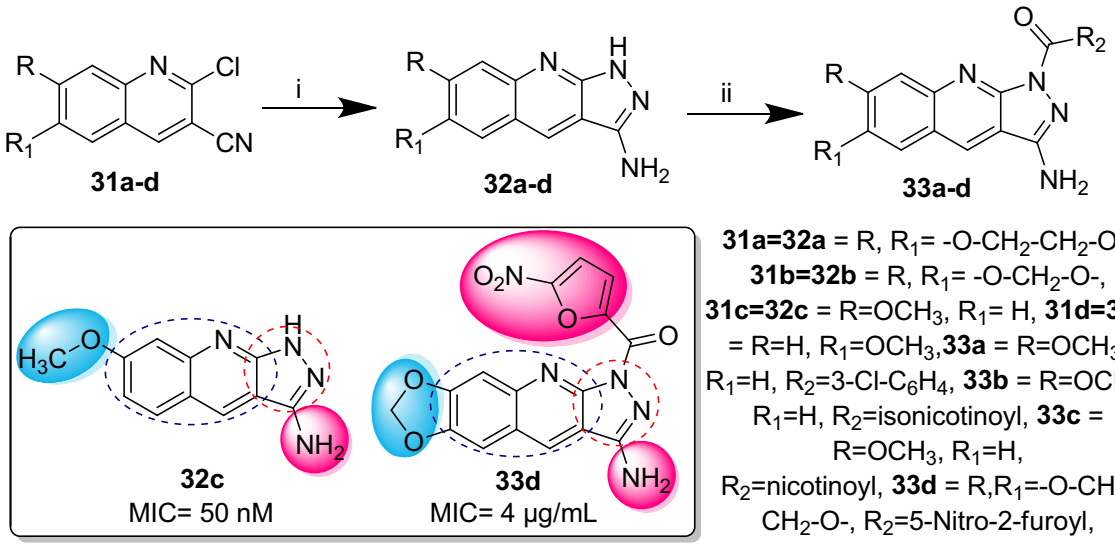
Some novel pyrazole affixed quinolines (Scheme 8) were synthesized as a promising antibacterial and bacterial serine/threonine protein kinases (BSTK) agent using 2-chloro-3-cyanoquinolines **(31a–d)** as precursor through *H*-pyrazolo[3,4-b]quinolines-3-amine **(32a–d)** intermediates which were initially obtained by treating the precursors **(31a–d)** with hydrazine hydrate in dimethylformamide [69]. Then the resultant intermediates **(32a–d)** were treated with substituted aryl chloride, aryl carbonic acid and isothiocyanate in a dimethylformamide-dioxane solvent to afford corresponding pyrazole containing quinolines with aryl substitution **(33a–d)**. Finally, the bioassay of the synthesized compound **(31a–d** to **33a–d)** revealed that the intermediate with 7-methoxy functionality **(32c)** exhibited significant inhibition activity against BSTK, whereas the compound containing nitrofuroyl functionality **(33d)** at pyrazole part showed moderate BSTK inhibition and antibacterial activity.

As emerging PDE10A inhibitors, some important aryl/heteroaryl-quinolino-pyrazoles (Scheme 9) were discovered through various 3-methyl-5-(o-tolylamino)-1*H*-pyrazole-4-carboxylic acid **(34a–b)** intermediates [70]. The corresponding acids upon condensation and hydrolysis followed by cyclization gave pyrazoloquinolines **(35a–b)** which upon substitution yielded the final compound **(36a–q)** with good yield under tetrahydrofuran solvent medium. Here, PDE10A inhibitory activity generally varies with nitrogen position at the core moiety, and it is observed with low efficacy when pyridine is replaced with an azole. So the methylpyrimidyl



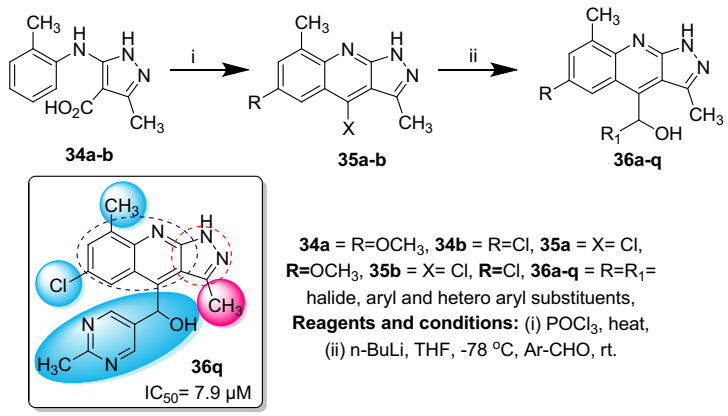

**Reagents and conditions:** (i) 2-Substituted malonic aldehyde, aryl hydrazine, ethanol, MW irradiation, 10–30 min at 110–140 °C, (ii) Arylboronic acid and haloheterocycle, dioxane, $PdCl_2(dppf)CH_2Cl_2$ or $Pd(PPh_3)_4$, $Na_2CO_3$, 14 h, reflux.

**Scheme 7** Synthesis of quinoline allied *N*-aryl-pyrazole heterocycle




**Scheme 8** Synthesis of quinoline allied pyrazole with amine and nitro-furyl substituents

**Scheme 9** Synthesis of aryl/heteroaryl-quinolino-pyrazoles with methyl substituents

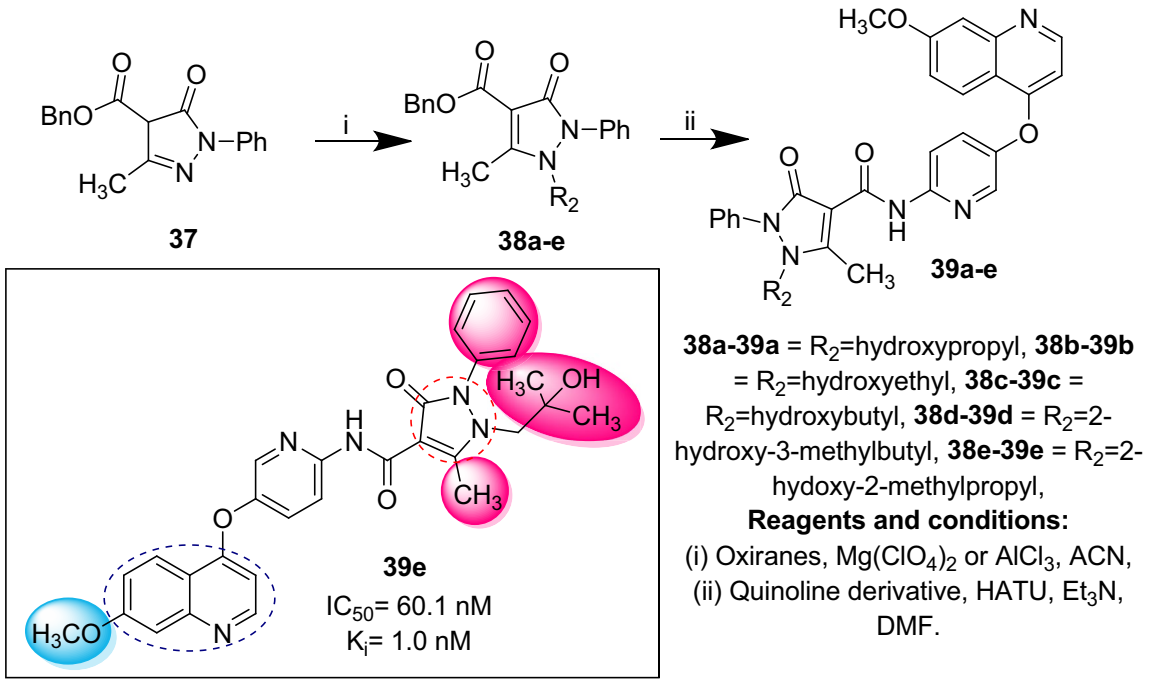



pyrazoloquinoline **(36q)** compound emerged as a potent PDE10A inhibitor for *schizophrenia*.

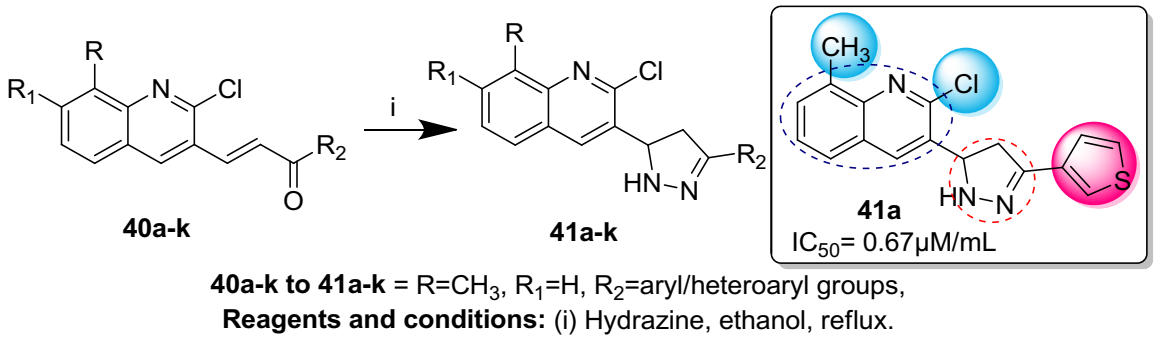
Several novel pyrazoles affixed quinolines with pyridinyl-amide links (Scheme 10) were synthesized and tested for their class II c-Met inhibition property [71]. Biologically significant analogues **(39a–e)** were synthesized by hydroxyethylation of pyrazolone **(37)** with oxiranes followed by coupling with quinoline derivative. Finally, all the synthesized compounds **(39a–e)** were screened for their class II c-Met inhibition activity which revealed that the compound-containing *N*-phenyl and hydroxydimethyl ethane functional group at pyrazole part **(39e)** exhibited the highest potency compared to other derivatives.

Series of pyrazole affixed quinoline scaffolds (Scheme 11) were synthesized by using substituted chalcones **(40a–k)** [72]. Initially, the chalcones **(40a–k)** were subjected to Claisen–Schmidt condensation reaction with acetyl thiophenes followed by cyclization with hydrazine hydrate to afford the title compound containing pyrazole and quinoline moieties **(41a–k)**. Finally, the synthesized compounds **(40a–k)** to **(41a–k)** were screened for their antileishmanial activity which revealed that the compound containing chloride at the quinoline part and plane thiophene ring at pyrazole part **(41a)** exhibited moderate potency whereas chalcones showed the highest efficiency.

Three different pyrazoles appended quinoline derivatives (Scheme 12) were conveniently synthesized by using 8-hydroxyquinoline-5-sulfonyl chloride **(42)** as starting material and was evaluated for their antimicrobial and antiviral activity [73]. Initially, the precursor **(42)** was refluxed with 2'-acetyl-2-cyanoacetohydrazide, 2-cyanoacetic acid hydrazide and 3-amino-5-pyrazolone in the presence of triethylamine under dioxane solvent media to afford 5-(2-acetyl-2-amino-5-oxo-1,2-dihydropyrazol-4-yl)




**Scheme 10** Synthesis of quinoline allied pyrazole with pyridinyl-amide linkage



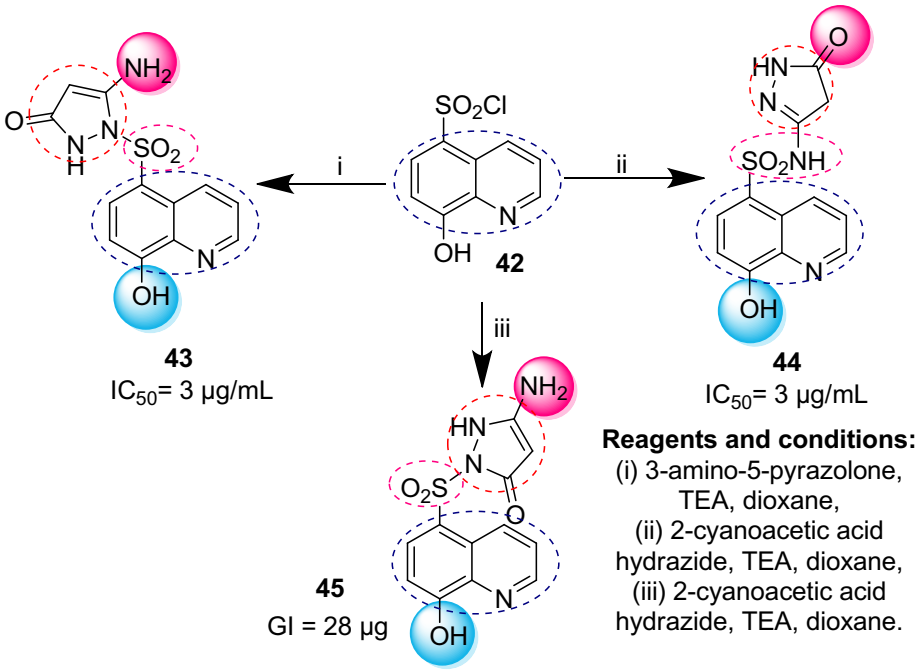

**Scheme 11** Synthesis of 2-chloroquinoline allied pyrazole heterocycle

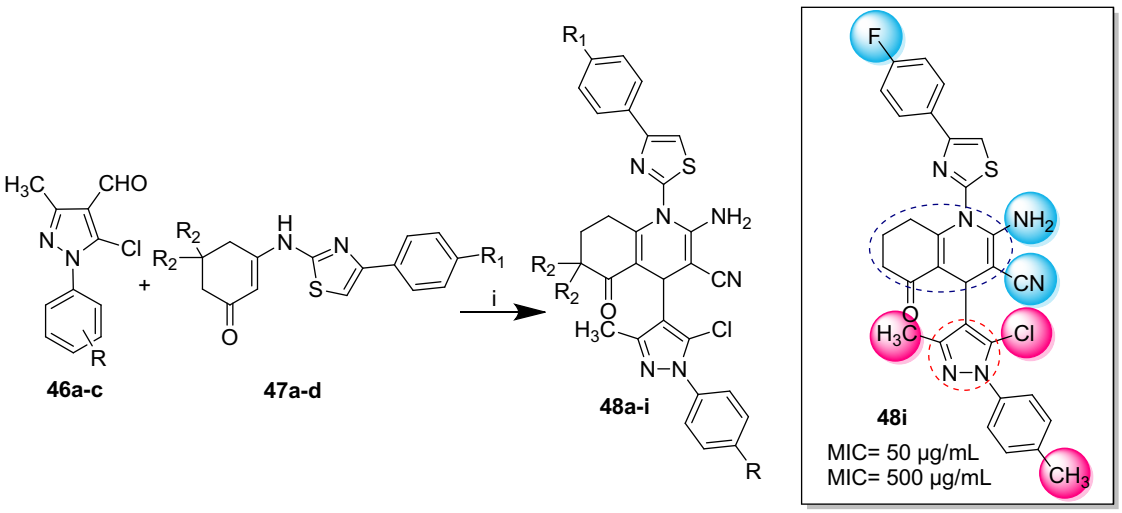
sulfonyl-8-hydroxyquinoline **(43)**, 4-aryl-5-carbonitrile-pyrano(2,3-c)pyrazol-3-yl)sulfonamido-8-hydroxyquinoline **(44)** and 5-(3-amino-5-oxo-1,2-dihydropyrazol-1-yl) sulfonyl-8-hydroxyquinoline **(45)**, respectively. The bioassay of the synthesized compounds envisioned that the intermediates **(43)** and **(44)** showed excellent antiviral and the compound (**45**) showed the highest antimicrobial activity compared to other derivatives.

In addition to other heterocycles, series of quinoline allied pyrazole derivatives (Scheme 13) were conveniently synthesized as potent antimicrobial and antifungal agents [74]. The target molecules **(47a–l)** were obtained by cyclization reaction of pyrazole-4-carbaldehyde **(46a–c)** with substituted cyclohex-2-enone **(47a–d)** in the presence of malononitrile under ethanol solvent medium. Finally, all the synthesized compounds were screened for their antimicrobial and antifungal activity which envisioned that the compound bearing fluoroaryl at the thiazole part and methylaryl at pyrazole part **(48i)** emerged as a potent heterocycle with highest inhibition value.

Several quinoline allied pyrazoles (Scheme 14) were prepared as a promising anticancer agent against HT29 cancer cell line and MDA-MB231 human breast cancer cell lines [75]. Initially, the hydrazide **(49)** was converted to quinoline appended pyrazole **(50)** and pyrazolone **(51)** by treating with acetylacetone and ethyl acetoacetate, respectively, in the presence of glacial acetic acid under reflux condition. The study of antiproliferative activity against cLog P, HT29 and MDA-MB231 breast cancer cell lines for pyrazole **(50)** and pyrazolone containing quinoline **(51)** was moderate against

**Scheme 12** Synthesis of quinoline allied pyrazole heterocycle with sulfonyl and sulfonamide linkage



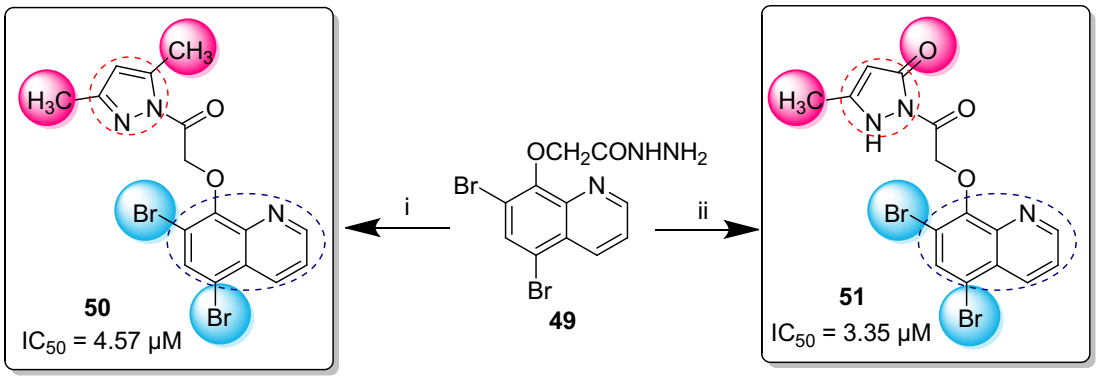

**48a** = R=H, $R_1$=H, $R_2$=H, **48b** = R=3-Cl, $R_1$=H, $R_2$=H, **48c** = R=4-Me, $R_1$=H, $R_2$=H, **48d** = R=H, $R_1$=H, $R_2$=Me, **48e** = R=3-Cl, $R_1$=H, $R_2$=Me, **48f** = R=4-Me, $R_1$=H, $R_2$=Me, **48g** = R=H, $R_1$=F, $R_2$=H, **48h** = R=3-Cl, $R_1$=F, $R_2$=H, **48i** = R=4-Me, $R_1$=F, $R_2$=H, **48j** = R=H, $R_1$=F, $R_2$=Me, **48k** = R=3-Cl, $R_1$=F, $R_2$=Me, **48l** = R=4-Me, $R_1$=F, $R_2$=Me,
**Reagents and conditions:** (i) Dinitrile, piperidine, ethanol.

**Scheme 13** Synthesis of quinoline allied pyrazole with thiazole moiety

cLog P cell lines compared to other less active molecules with hydrogen bond and electron-donating groups such as –OH, –SH and –NH, respectively.

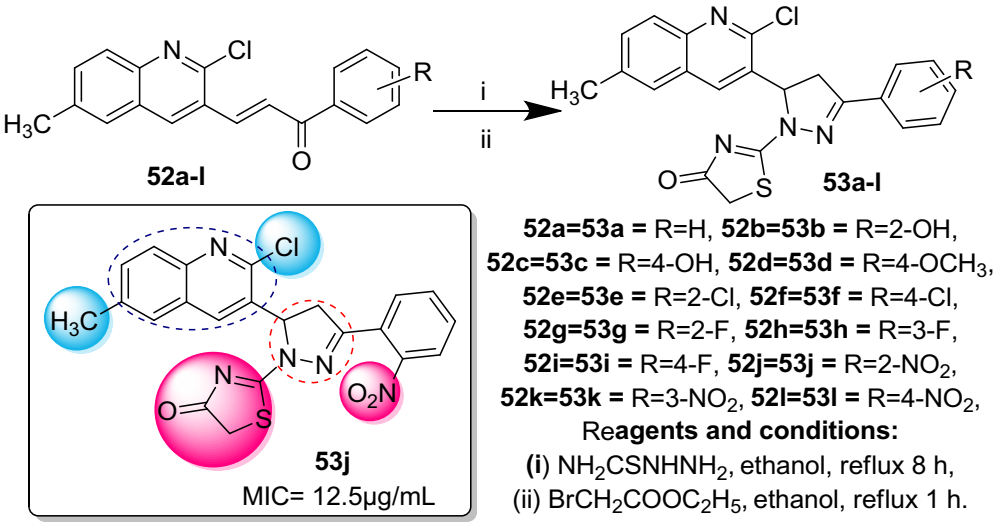
As a potent antimicrobial agent, some novel quinoline-based pyrazoles (Scheme 15) were synthesized through chalcones **(52a–l)** via cyclization reaction to afford pyrazole and thiazole with thiosemicarbazide and bromoacetoester, respectively [76]. Then all the prepared compounds **(53a–l)** were screened for their antimicrobial and antifungal activity which revealed that the compound containing 2-nitroaryl and thiazole at pyrazole part (**53j**) exhibits excellent activity against most of the microbes; *E. coli, P. aeruginosa, S. pyogenes, A. niger* and *A. clavatus* with MIC value from 12.5 to 50 µg/mL.

Series of novel pyrazole-appended quinolines (Scheme 16) were synthesized by coupling




**Reagents and conditions:** (i) Acetylacetone, gl. AcOH, 8h, reflux, (ii) Ethylacetoacetate, gl. AcOH, abs. EtOH, 6h, reflux.

**Scheme 14** Synthesis of quinoline allied 3-methyl-pyrazole heterocycle



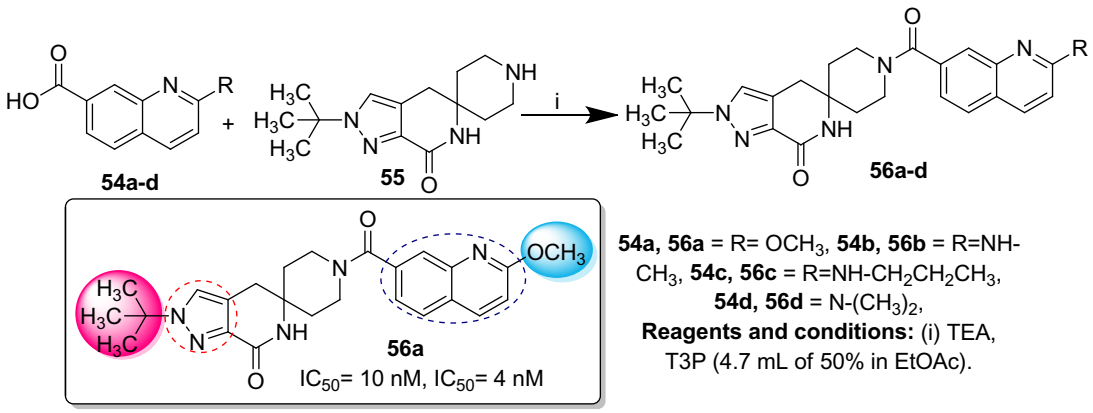

**52a=53a =** R=H, **52b=53b =** R=2-OH, **52c=53c =** R=4-OH, **52d=53d =** R=4-$OCH_3$, **52e=53e =** R=2-Cl, **52f=53f =** R=4-Cl, **52g=53g =** R=2-F, **52h=53h =** R=3-F, **52i=53i =** R=4-F, **52j=53j =** R=2-$NO_2$, **52k=53k =** R=3-$NO_2$, **52l=53l =** R=4-$NO_2$,

**Reagents and conditions:**

**(i)** $NH_2CSNHNH_2$, ethanol, reflux 8 h,

(ii) $BrCH_2COOC_2H_5$, ethanol, reflux 1 h.

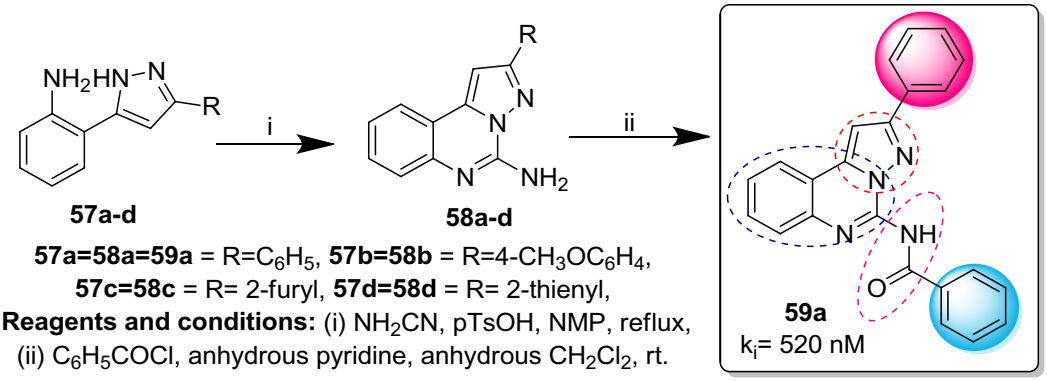
**Scheme 15** Synthesis of quinoline allied thiazole-substituted pyrazole




**54a, 56a** = R= $OCH_3$, **54b, 56b** = R=NH-$CH_3$, **54c, 56c** = R=NH-$CH_2CH_2CH_3$, **54d, 56d** = N-$(CH_3)_2$,

**Reagents and conditions:** (i) TEA, T3P (4.7 mL of 50% in EtOAc).

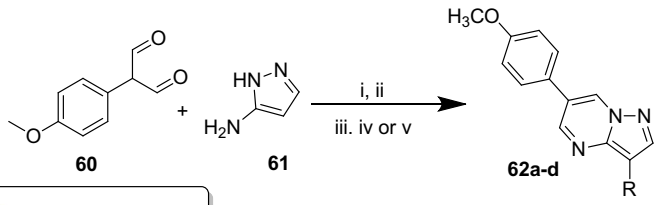
**Scheme 16** Synthesis of quinoline allied pyrazole heterocycle with alkyl and amine groups

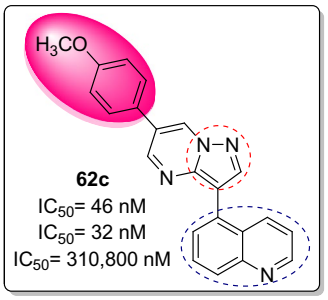



**57a=58a=59a** = R=$C_6H_5$, **57b=58b** = R=4-$CH_3OC_6H_4$,
**57c=58c** = R= 2-furyl, **57d=58d** = R= 2-thienyl,
**Reagents and conditions:** (i) $NH_2CN$, pTsOH, NMP, reflux,
(ii) $C_6H_5COCl$, anhydrous pyridine, anhydrous $CH_2Cl_2$, rt.

**Scheme 17** Synthesis of quinoline allied pyrazole heterocycle with aryl, heteroaryl and amide functional group

**Scheme 18** Synthesis of quinoline allied pyrazolopyrimidines with aryl and heteroaryl substituents

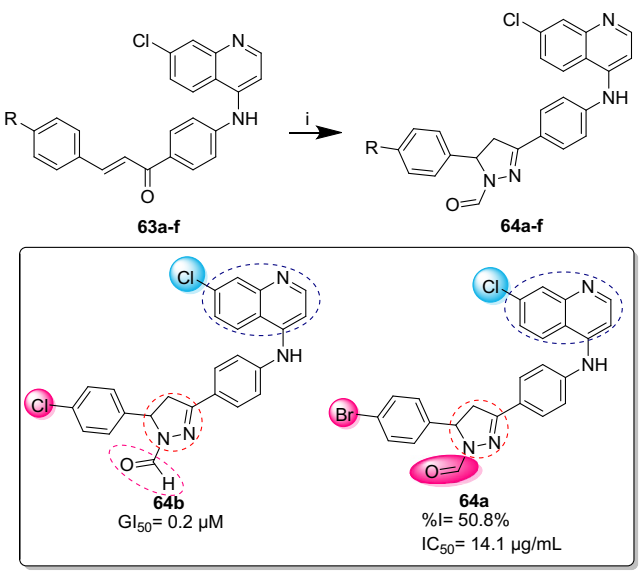



**62a-d** = R= Quinoline linked at = **(62a)** =8th position, **(62b)** =3rd position, **(62c)** =5th position and **(62d)** =4th position,
**Reagents and conditions:** (i) AcOH, EtOH, 170°C, 10 min, microwave, (ii) NIS, DMF, (iii) diboronpinacol ester, $Pd(dppf)Cl_2$ DCM, KOAc, DMF, 100°C, 16 h, (iv) $R_1X$, $Pd(dppf)Cl_2$, DCM, $K_3PO_4$, 1,4-dioxane, $H_2O$, 120°C, 30 min, microwave, (v) $R_1B(OH)_2$, $Pd(dppf)Cl_2$, DCM, $K_3PO_4$, 1,4-dioxane, $H_2O$, 120°C, 30 min, microwave.

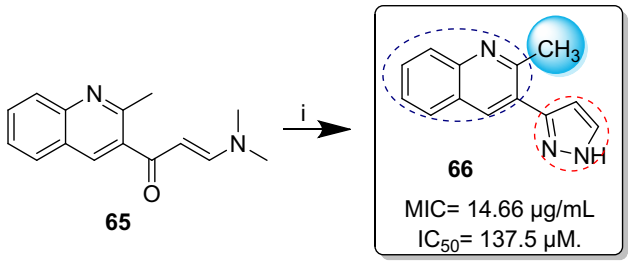
2-chloroquinoline-7-carboxylic acid **(54a–d)** with pyrazole amine derivative **(55)** using EDC.HCl coupling reagent in dichloromethane solvent followed by a substitution reaction of chlorine with the amine in a sealed vial [77]. Then all the synthesized compounds **(56a–d)** were screened for their acetyl-CoA carboxylase (ACC) inhibition activity which revealed that the compound containing alkyl group at pyrazole part and methoxy group at quinoline part (**56a**) exhibited excellent activity towards inhibition of both ACC1 and ACC2.

Some simple pyrazole-tethered quinolones (Scheme 17), as promising adenosine receptor antagonists, were synthesized from 2-(1*H*-pyrazol-5-yl)aniline **(57a–d)** through cyclization and coupling reactions [78]. Then the scaffolds were tested for their binding efficiency with $hA_1$, $hA_{2A}$, and $hA_3$ adenosine receptors in the $\mu$-molar range. The amount of protein was measured according to the Bio-Rad method, and the inhibitory constant ($k_i$) was calculated using the Cheng and Prusoff equation. Finally, the study revealed that the quinoline-tethered pyrazole-bearing *N*-benzoyl group **(59a)** emerged as a potent molecule with the highest $k_i$ value in the $\mu$-molar range against $hA_3$ AR subtype.




**63a=64a** = R=Br, **63b=64b** = R=Cl, **63c=64c** = R=H, **63d=64d** = R=$OCH_3$, **63e=64e** = R=3,4,5-$(OCH_3)_3$, **63f=64f** = R=$CH_3$,
**Reagents and conditions:** (i) Hydrazine hydrate, formic acid, reflux.

**Scheme 19** Synthesis of aminophenyl-substituted quinoline allied pyrazole-carbaldehyde




**Reagents and conditions:** (i) $NH_2NH_2$, EtOH, reflux,

**Scheme 20** Synthesis of quinolinyl-pyrazole with methyl group

Two series of pyrazole-containing quinolones (Scheme 18) were synthesized using 2-(4-methoxyphenyl) malonaldehyde **(60)** and 1*H*-pyrazol-5-amine **(61)** as precursors through condensation followed by Suzuki–Miyaura cross-coupling method [79]. The obtained compounds were subjected to iodination and Suzuki–Miyaura cross-coupling reaction to yield efficient pyrazole bearing quinolines **(62a–d)** as a potent bone morphogenetic protein receptor (BMP) inhibitor for ALK2 versus ALK3. The study inferred that the molecule containing quinoline-tethered pyrazole with methoxy group **(62c)** emerged as a potent molecule with greater than 300-fold selectivity for ALK3 and comparable selectivity against ALK1, ALK2 with respect to the standard drug.

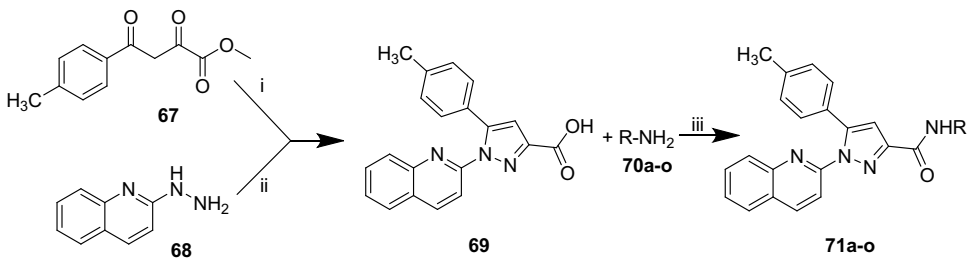
Various quinoline allied pyrazoles (Scheme 19) were obtained as promising antitumor and antimalarial agents [80]. The corresponding chalcones **(63a–f)** were converted to pyrazole-appended quinolines **(64a–f)** by treating with hydrazine hydrate in the presence of formic acid. The biological study has revealed that pyrazole appended quinoline scaffolds bearing chloro **(64b)** and bromo **(64a)** functionality displayed the highest activity towards 60 types of cancer cell lines and also against the growth of *P. falciparum* parasites respectively.

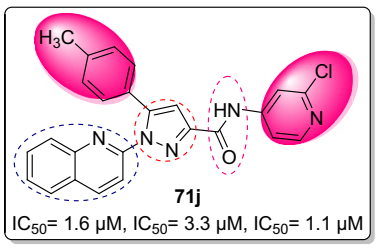
A new quinoline allied pyrazole analogue (Scheme 20) was designed using 3-(dimethylamino)-1-(2-methylquinoline-3-yl)prop-2-one **(65)** intermediate [81]. The key intermediate **(65)** was converted to 2-methyl-3-(1*H*-pyrazol-3-yl)quinoline **(66)** by adding hydrazine hydrate in ethanol. Finally, derived compound was evaluated for their antimycobacterial and cytotoxicity assay. The study evidenced that quinoline-containing acylated pyrazole **(66)** emerged as a potent antimycobacterial agent compared to other quinolinyl-pyrazolines.

In 2014, Seyma Cankara Pirol et al. synthesized a class of amide derivatives of pyrazole-appended quinolines (Scheme 21) in two novel ways to assess their efficiency against human cancer cell lines; Huh7, MCF7, and HCT116 [82]. The precursors **(67)** and **(68)** upon cyclization gave pyrazole ring with a carboxylic group **(69)** and on coupling the same with various amines **(70a–o)** resulted in amide derivatives of pyrazole allied quinoline **(71a–o)**. The biostudy has revealed that the compound containing a 2-chloropyridinyl group with an amide bond at the pyrazole part **(71j)** displayed excellent cytotoxicity against all three cell lines.

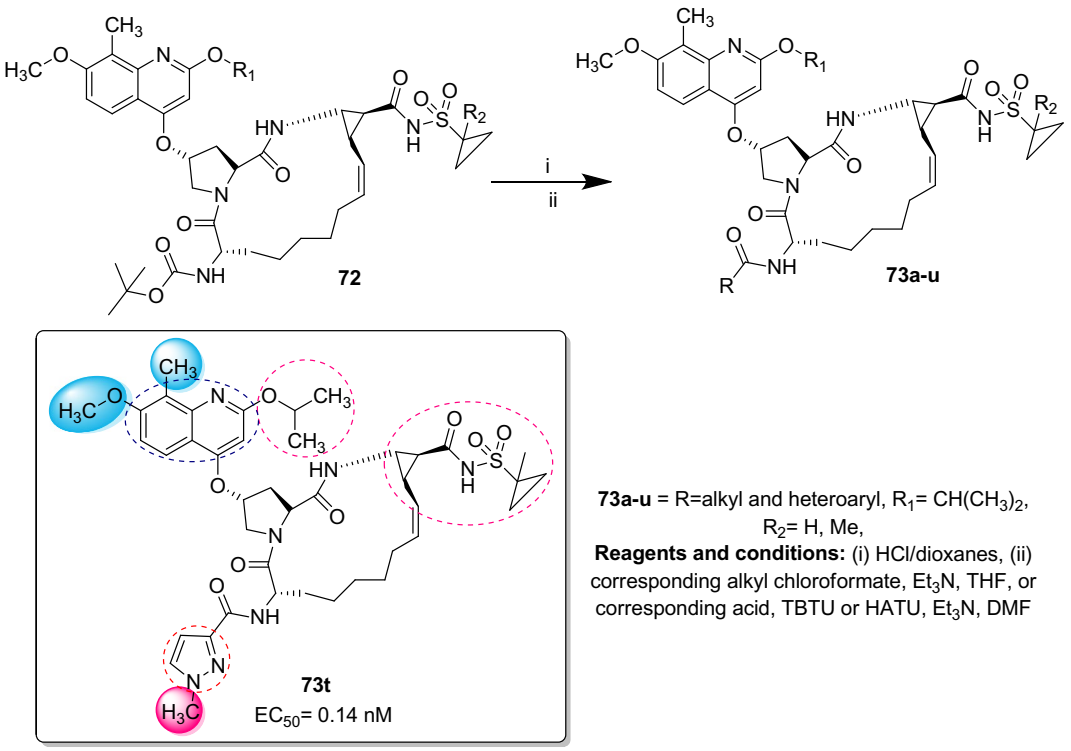
Series of novel quinoline allied pyrazoles (Scheme 22) were synthesized as hepatitis C virus NS3-4A protease inhibitor [83]. The macrocyclic compound **(72)** was subjected to a coupling reaction with pyrazole chloroformate or pyrazole acid in the presence of triethylamine or TBTU, respectively, to afford pyrazole affixed quinoline macromolecules **(73a–u)**. Finally, the bioassay of the synthesized compounds revealed that the macromolecule containing *N*-methyl functional group **(73t)** at the pyrazole part

**Scheme 21** Synthesis of quinoline-substituted pyrazoles




**70a-o to 71a-o = R=** N-containing heterocycles,
**Reagents and conditions:** (i) MeOH, HCl, reflux, 10 h, (ii) LiOH, THF:$H_2O$ (1:1), 70°C, 3 h, (iii) EDC, DMAP, $CH_2Cl_2$, rt for (a-i) and (n-o) or oxalyl chloride, DIEA, $CH_2Cl_2$, rt for (j-m).



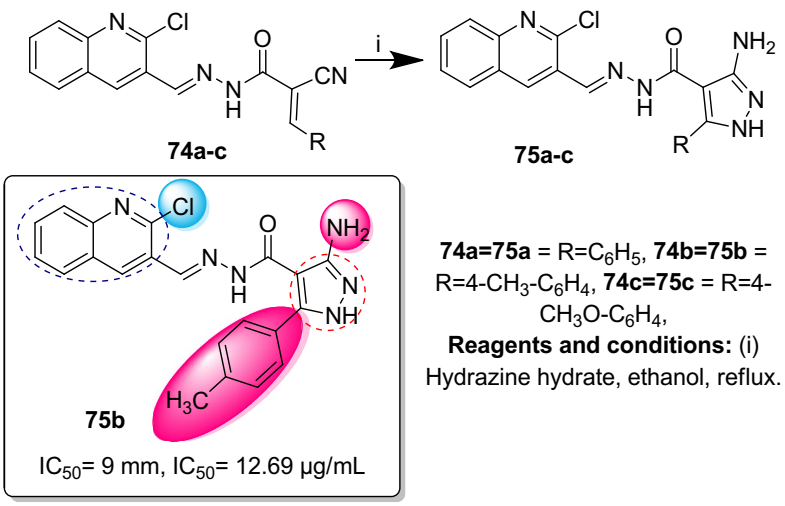

**Scheme 22** Synthesis of a macromolecule with quinoline and pyrazole heterocycles

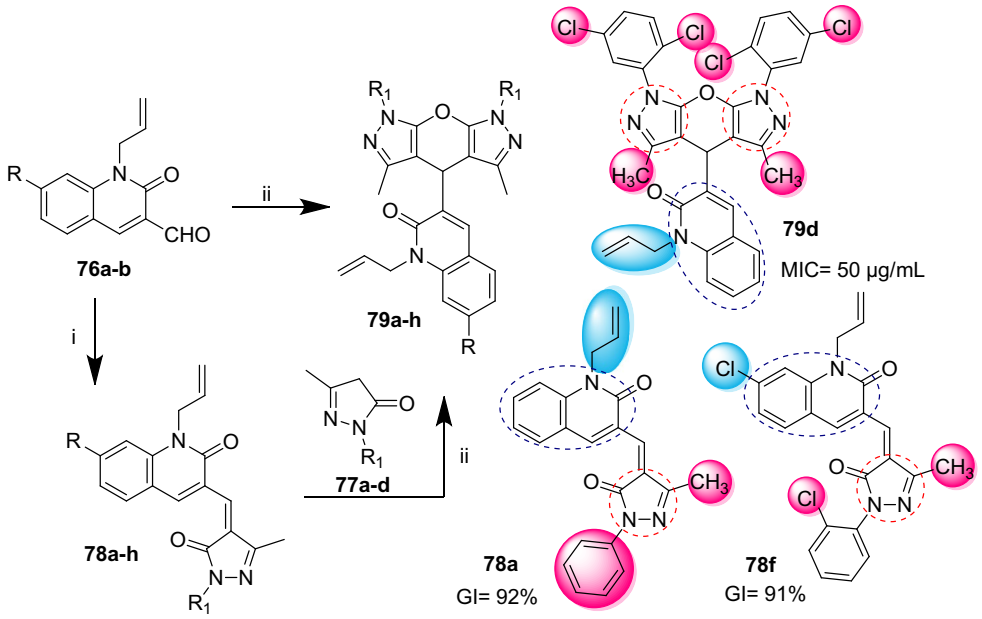
exhibited excellent hepatitis C virus NS3-4A protease inhibition activity compared to other macromolecules.

Series of quinoline allied pyrazoles (Scheme 23) in addition to other heterocycles were synthesized as potent antibacterial and anticancer agents [84]. The arylidene **(74a–c)** derivatives on cyclization reaction with hydrazine hydrate afforded the compounds containing pyrazole and quinoline heterocycle **(75a–c)**. Finally, the compounds **(75a–c)** were screened for their antibacterial and anticancer activity. The compound containing methylaryl **(75b)** group at pyrazole part with amide linkage showed moderate antimicrobial activity against *S. aureus* and anticancer activity against SF-268 cell line.

Three new quinoline allied pyrazole families (Scheme 24) were synthesized through *N*-allyl-2-quinolone-3-carbaldehyde **(76)** intermediate [85]. Initially, the key intermediate **(76)** was subjected to Knoevenagel–Michael's reaction with pyrazolones **(77a–d)** followed by Knoevenagel–Michael cyclization at 120 °C yielding the target compounds containing quinoline and pyrazole scaffolds **(78a–h)** to **(79a–h)**.

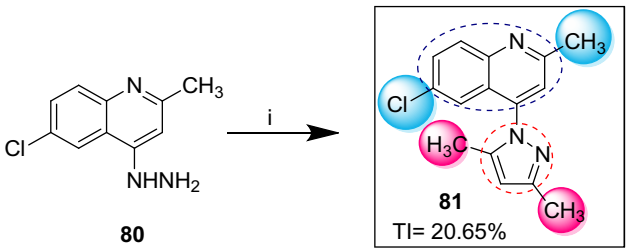
**Scheme 23** Synthesis of quinoline allied 3-amino-5-aryl-pyrazole heterocycle






**76a** = R= H, **76b** = R= Cl, **77a** = $R_1$ = Ph, **77b** = $R_1$=2-Cl-Ph, **77c** = $R_1$=3-Cl-Ph, **77d** = $R_1$=2,5-$Cl_2$Ph,
**78a-h to 79a-h=** R= H, Cl, $R_1$= Ph, 2-Cl-Ph, 3-Cl-Ph, 2,5-$Cl_2$-Ph
**Reagents and conditions:** (i) TBA–HS (20 %), solvent-free 100 °C, (ii) TBA–HS (20 %), solvent-free, 120 °C.

**Scheme 24** Synthesis of quinoline allied pyrazole with alkyl and haloaryl group




**Reagents and conditions:** (i) Acetylacetone, EtOH, reflux.

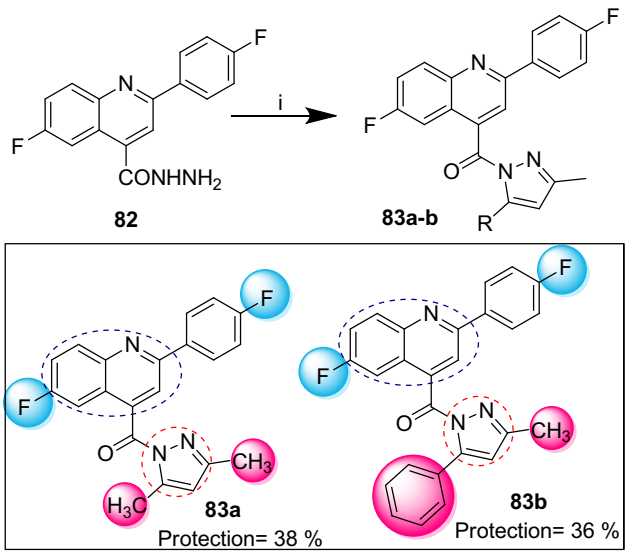
**Scheme 25** Synthesis of quinoline allied pyrazole with alkyl and halo functional group

Finally, the synthesized compounds were screened for their antimicrobial and antitubercular activity which revealed that the compound containing bis-2,5-dichloro aryl functionality at pyrazole part **(79d)** exhibited excellent antimicrobial activity against *Streptococcus pneumoniae*, whereas the compounds containing aryl **(78a)** and 2-chloroaryl **(78f)** functionality at pyrazole part exhibited highest antitubercular activity compared to other compounds.

In addition to novel quinoline allied heterocycles, few novel pyrazoles containing quinolones (Scheme 25) were synthesized through cyclo-condensation reaction by treating quinoline hydrazine **(80)** with acetylacetone and ethyl acetoacetate, respectively [86]. Then all the heterocycles were screened for insecticidal and fungicidal activity against *Fusarium oxysporum* and *Rhynchophorus ferrugineus* pathogens. Compared to the other heterocycles, quinoline-appended pyrazole **(81)** exhibited moderate fungicidal and insecticidal activity against *Rhynchophorus ferrugineus*.

In addition to other hetero analogues, pyrazoloquinoline-based derivatives (Scheme 26) were successfully synthesized and verified for their anti-inflammatory and ulcerogenic effect [87]. The hydrazide **(82)** was subjected to cyclization reaction with acetylacetone and benzoyl acetone to yield the corresponding final compounds **(83a–b)**. Finally, they were screened for anti-inflammatory and ulcerogenic activity, and compounds containing methyl **(83a)** and phenyl **(83b)** groups at the pyrazole part showed moderate activity with respect to other analogues.

A new group of pyrazoloquinolines (Scheme 27) was successfully synthesized through 1-aryl-5-chloro-3-methyl-1*H*-pyrazole-4-carbaldehydes **(84a–c)** and 3-(pyridin-3-ylamino)cyclohex-2-enones **(85a–b)** intermediates [88]. The key intermediates were subjected to three-component cyclo-condensation reaction with malononitrile/ethylcyanoacetate **(86a–b)** to afford quinoline allied pyrazole **(87a–l)** in the presence of piperidine as a catalyst. All molecules were tested for in vitro antibacterial and anticancer activities against *E. coli* and A549 cell lines, respectively. Among the series, a compound containing methyl **(87k)** and chloro **(87f)** functional group at the pyrazole part possessed the highest efficiency against epidermal growth factor receptor (EGFR), A549 and HepG2 cell line, respectively. In addition to that, the compound containing methyl group at the




**83a** = R=$CH_3$, **83b** = R=$C_6H_5$,
**Reagents and conditions:** (i) Acetylacetone or benzoylacetone/AcOH, rt.

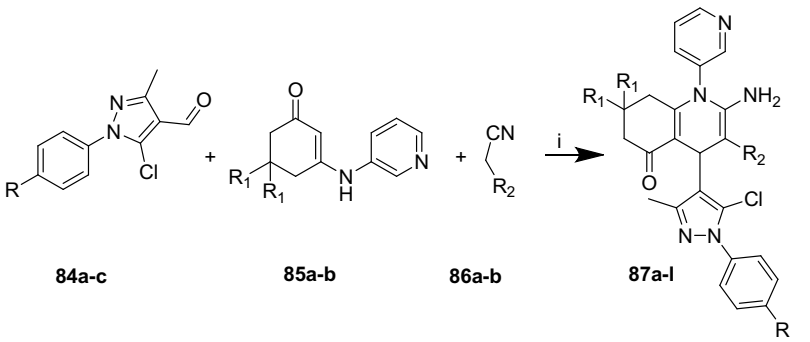
**Scheme 26** Synthesis of quinoline allied pyrazole with alkyl, aryl and haloaryl groups

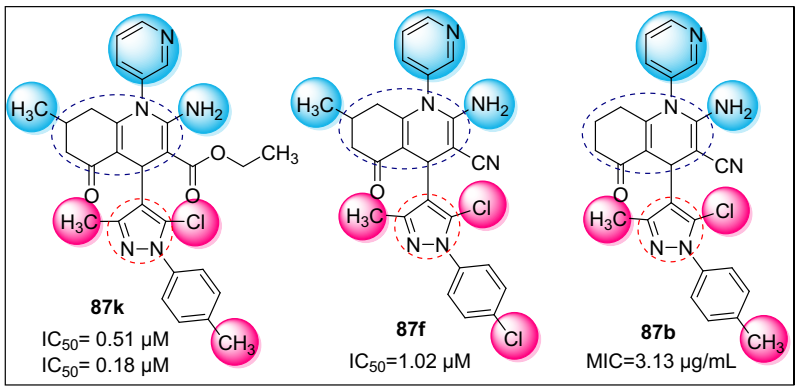
pyrazole part and nitrile group at the quinoline part (**87b**) possessed more potency than penicillin G and, also when compared to Kanamycin B against gram-negative bacteria *E. coli*.

In addition to other heterocycles, some novel pyrazole-containing quinolones (Scheme 28) were synthesized through pyrano[3,2-c]quinoline-3-carboxaldehyde intermediate (**88**) and were tested for their antimicrobial activity [89]. The key intermediate compound (**88**) was treated with hydrazine hydrate (**89a**), phenylhydrazine (**89b**), 7-chloro-4-hydrazinoquinoline (**89c**) and 3-hydrazino-5,6-diphenyl-1,2,4-triazine (**89d**), respectively, to afford corresponding title compounds containing pyrazole and quinoline heterocycles (**90a-d**). All the synthesized compounds were screened for their antimicrobial and antifungal activities which revealed that the compound containing two quinoline moiety bridged with pyrazole heterocycle (**90c**) exhibited moderate potency against *E. coli* and *A. fumigatus* compared to other heterocycles.

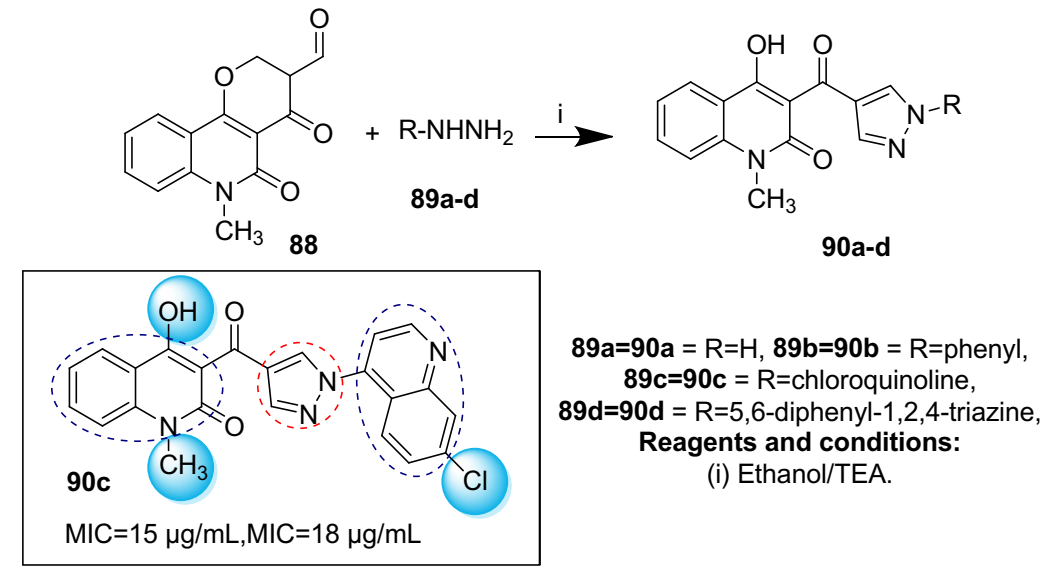
Variety of pyrazolo[3,4-h]quinolones (Scheme 29) were conveniently synthesized and screened against human cancer cell lines such as JURKAT, HL-60, MCF-7, A-549, and LoVo by MTT test [90]. Initially, the key intermediates (**91a–h**) were cyclized to compound (**92a–j**) by reacting with phenylsulfonylacetonitrile followed by oxidation using

**Scheme 27** Synthesis of quinoline allied pyrazole heterocycle with pyridine heterocycle

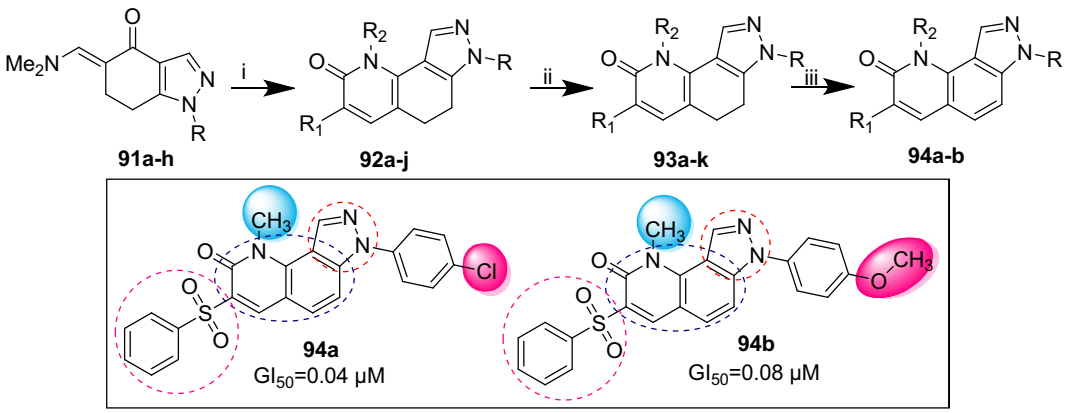



**87a** = R=H, $R_1$=H, $R_2$=CN, **87b** = R=$CH_3$, $R_1$=H, $R_2$=CN, **87c** = R=Cl, $R_1$=H, $R_2$=CN, **87d** = R=H, $R_1$=$CH_3$, $R_2$=CN, **87e** = R=$CH_3$, $R_1$=$CH_3$, $R_2$=CN, **87f** = R=Cl, $R_1$=$CH_3$,, $R_2$=CN, **87g** = R=H, $R_1$=H, $R_2$=COOEt, **87h** = R=$CH_3$, $R_1$=H, $R_2$=COOEt, **87i** = R=Cl, $R_1$=H, $R_2$=COOEt, **87j** = R=H, $R_1$=$CH_3$, $R_2$=COOEt, **87k** = R=$CH_3$, $R_1$=$CH_3$, $R_2$=COOEt, **87l** = R=Cl, $R_1$=$CH_3$,, $R_2$=COOEt,
**Reagents and conditions:** (i) EtOH, piperidine, reflux.




**Scheme 28** Synthesis of pyrazole bridged biquinoline



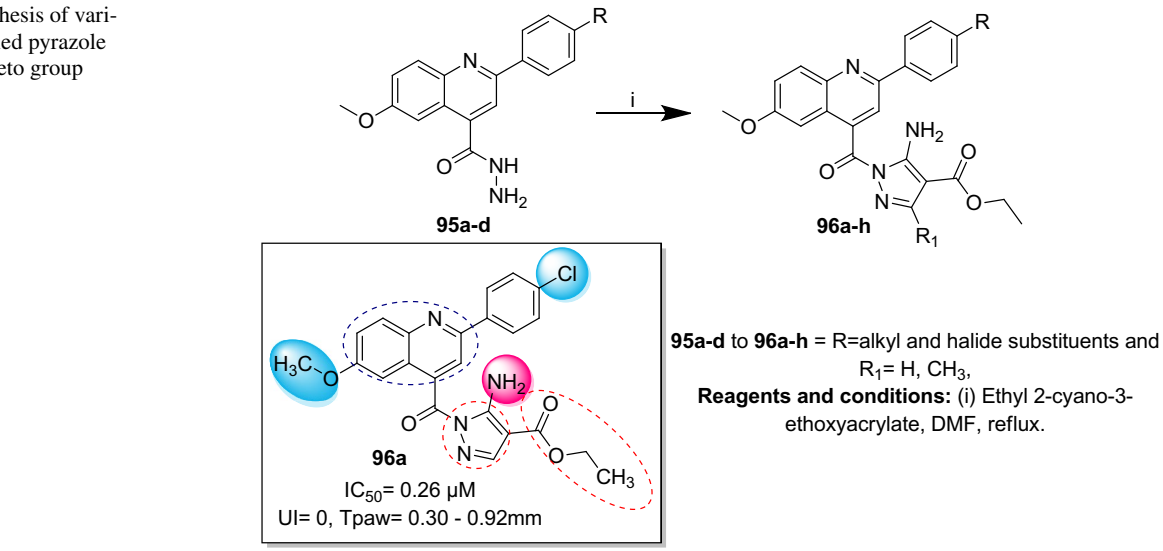

**Scheme 29** Synthesis of quinoline allied pyrazole with an aryl-sulfonyl group

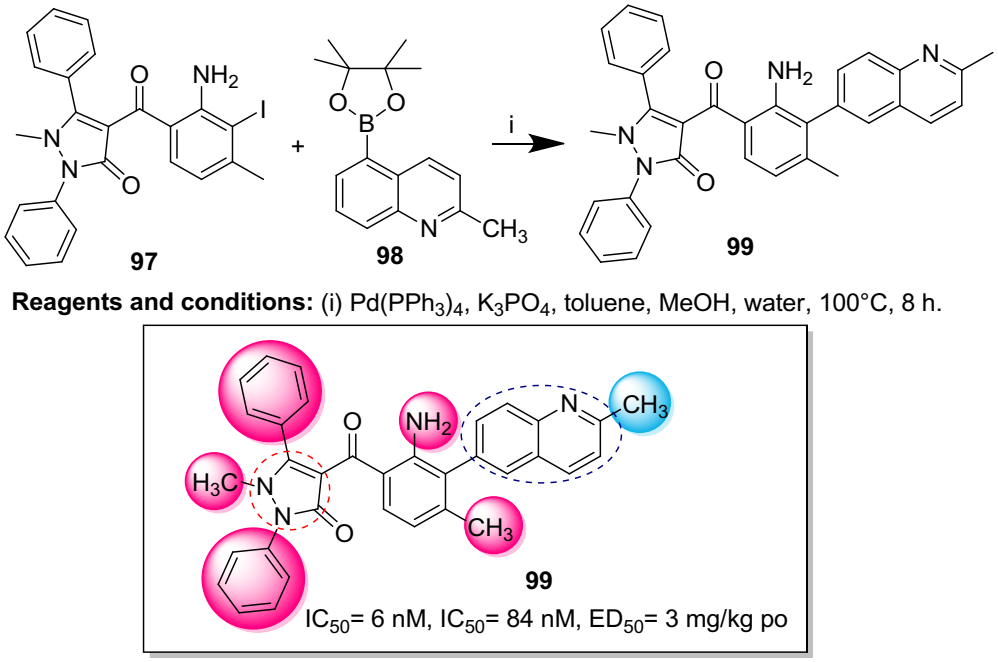
DDQ in dioxane solvent yielding pyrazolo[3,4-h]quinolines **(94a–b)** with good yield. Moreover, the cytotoxic investigation revealed that the compounds containing chloro **(94a)** and methoxy **(94b)** at the fourth position of the phenyl part emerged as potent molecules against all five types of cancer cell lines.

Series of quinolines containing pyrazoles (Scheme 30) were prepared through versatile Pfitzinger reaction and screened for in vitro COX-1/COX-2 enzyme inhibition assay, anti-inflammatory activity, analgesic activity and ulcerogenic effect [91]. The biologically active quinoline affixed pyrazoles **(96a–h)** were prepared through cyclocondensation of carbohydrazide **(95a–d)** with appropriate *β*-dicarbonyl compounds under reflux condition. Scaffolds containing methoxy, chloroaryl groups at the quinoline part and amine and ester groups at the pyrazole part **(96a)** exhibited the best anti-inflammatory, analgesic, ulcerogenic activity and binding property into the COX-2 binding pocket.

Some important class of pyrazole containing quinolines (Scheme 31) were conveniently synthesized as an effective and selective inhibitor of protein kinase R-like endoplasmic reticulum kinase (PERK) through benzoyl-1*H*-pyrazol-3(2*H*)-one **(97)** intermediates [92]. Initially, the intermediate **(97)** was subjected to the Suzuki–Miyaura coupling reaction with the commercially available 2-methyl-6-quinolylboronate ester **(98)** to afford the compounds, pyrazolyl-quinoline

**Scheme 30** Synthesis of various quinoline allied pyrazole linked with the keto group



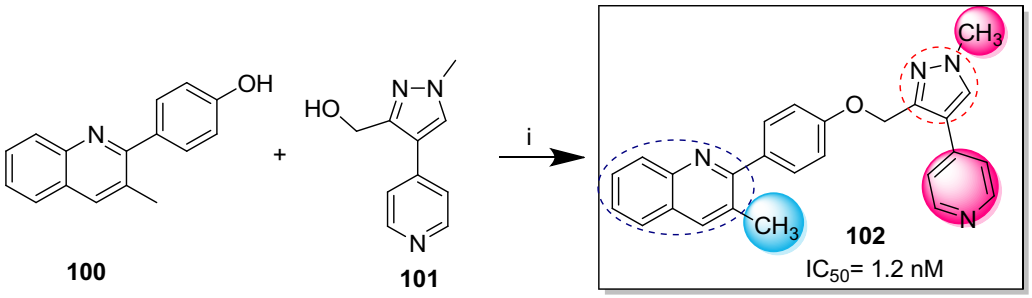




**Scheme 31** Synthesis of quinoline allied pyrazole with keto and amide link

**(99)**. All the synthesized compounds were tested for their efficiency against PERK, Cell pPERK and Mouse PD ED inhibition which shows that the compound containing pyrazole and quinoline scaffold **(99)** exhibited excellent inhibition compared to other heterocycles.

In addition to other significant heterocycles, quinoline affixed pyrazole (Scheme 32) was successfully synthesized and screened for their PDE10A inhibition property [93]. The biologically active analogue of quinolone **(102)** was obtained by treating the 3-methylquinolin derivative **(100)** with hydroxypyrazole **(101)** through the reported method [94]. The synthesized compounds were tested for their PDE10A inhibition property which envisioned that the compound containing methyl at quinoline and pyrazole moieties **(102)** showed best [95] and moderate activity compared to other hetero analogues.

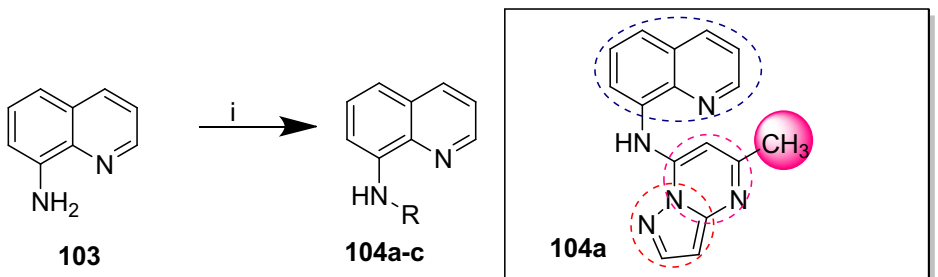
As an effective antimalarial agent, 8-aminoquinoline–pyrazolopyrimidines (Scheme 33) was conveniently synthesized through a simple aromatic nucleophilic substitution reaction [96]. Initially, 8-aminoquinoline **(103)** was used as a precursor to prepare novel compounds containing pyrazole-appended quinoline. Later, upon microwave




**Reagents and conditions:** (i) $SOCl_2$, $CH_2Cl_2$.

**Scheme 32** Synthesis of various quinoline allied pyridinyl-pyrazoles

**Scheme 33** Synthesis of quinoline allied pyrazole heterocycle with pyrimidine ring




**104a-c** = R=aromatic hetero cycles,

**Reagents and conditions:** (i) Pd/C, TEA, $H_2$ gas, DCM/MeOH (1:2), rt, 6–12 h.

irradiation of the compound aminopyrazoles with *N,N*-dimethylformamide dimethyl acetal followed by cyclization with malononitrile yielded intermediate which was subsequently converted to quinoline allied pyrazole with amine linkage. Then the obtained compounds **(104a-c)** were tested for antimalarial activity against *Plasmodium falciparum* (*Pf*_ NF54) and resistant strain (*Pf*_K1) which revealed that quinoline containing pyrazolopyrimidine with a methyl group **(104a)** showed very good potency compared to other series of novel compounds.

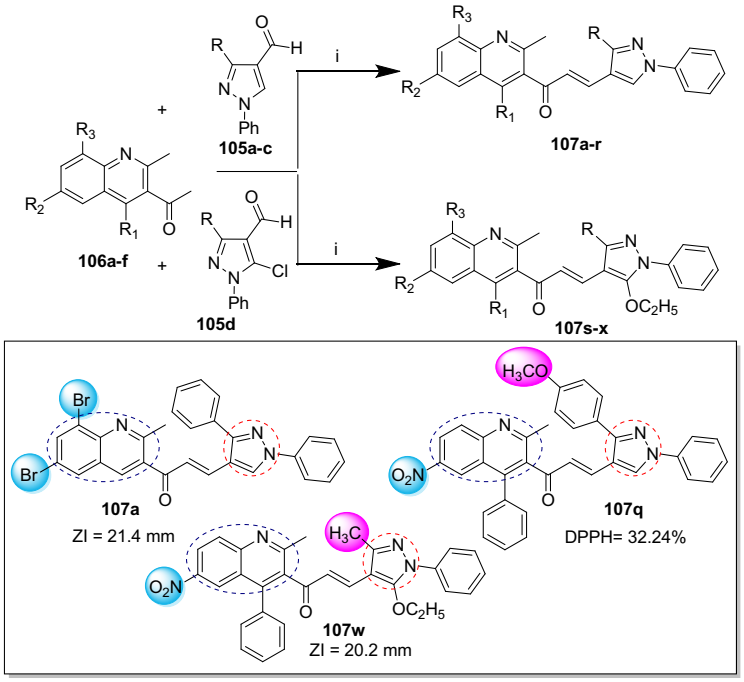
Through Claisen–Schmidt condensation reaction, two series of pyrazole affixed quinolinyl chalcones (Scheme 34) were synthesized and subjected for their antimicrobial and antioxidant activities [97]. Series of quinoline allied pyrazole **(107a–x)** compounds were prepared by treating substituted 1,3-diphenyl-1*H*-pyrazole-4-carbaldehyde **(105a–c)** or 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbaldehyde **(105d)** with 2-methyl-3-acetylquinoline **(106a–f)** from conventional and ultrasonic methods, respectively. Then the antimicrobial and antioxidant activity study revealed that the analogue containing two bromo groups at the quinoline ring **(107a)** showed the highest antimicrobial efficacy against *E.coli*; analogue containing methyl group at pyrazole part with a nitro group at quinoline part **(107w)** showed best antifungal activity against *C.albicans* and analogue containing methoxy group at pyrazole ring **(107q)** showed significant efficacy for the antioxidant property.

Novel series of quinoline appended pyrazoles (Scheme 35) were obtained through [3 + 2] cyclo-condensation reaction and were tested for cytotoxicity [98]. The key intermediate hydrazide **(108a–d)** upon cyclo-condensation with 4-methoxy-1,1,1-trifluorobut-3-en-2-ones **(109a–d)** yielded quinoline allied pyrazoles **(110a–p)**. Then the bioassay of the compounds with human leukocytes revealed that aromatic ring at the quinoline part and a methyl group at the pyrazole part **(110e)** showed very good cytotoxicity.

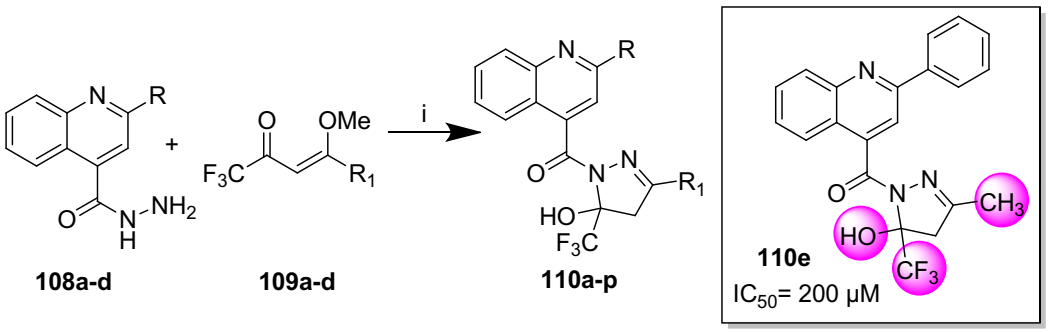
An antimicrobial pyrazole-tethered quinolines (Scheme 36) were prepared through (*E*)-1-(2-chloro-6-methoxyquinolin-3-yl)-3-(4-methoxyphenyl)prop-2-en-1-one **(111)** intermediate [99]. Initially, the compound **(111)** was treated with hydrazine to yield corresponding novel quinoline-appended pyrazoles **(112)**. Then the resultant compound **(112)** was screened for antimicrobial activity, which revealed that the compound **(112)** containing methoxy group exhibited significant efficacy, whereas other heterocycles showed moderate efficacy against most of the microbes.

Novel morpholinoquinoline-appended pyrazoles (Scheme 37) were designed by Vilsmeier–Haack reaction and screened for their antibacterial, antitubercular and antimalarial activities [100]. The key components **(113a–d)** were subjected to microwave irradiation with

**Scheme 34** Synthesis of quinoline allied pyrazole with chalcone functional group




**107a,s** = R=$C_6H_5$, $R_1$= H, $R_2$=Br, $R_3$=Br, **107b,t** = R=$C_6H_5$, $R_1$=$CH_3$, $R_2$=H, $R_3$=H, **107c,u** = R=$C_6H_5$, $R_1$=$C_6H_5$, $R_2$=H, $R_3$=H, **107d,v** = R=$C_6H_5$, $R_1$=$C_6H_5$, $R_2$=Cl, $R_3$=H, **107e,w** = R=$C_6H_5$, $R_1$=$C_6H_5$, $R_2$=$NO_2$, $R_3$=H, **107f,x** = R=$C_6H_5$, $R_1$=2-Cl$C_6H_4$, $R_2$=Cl, $R_3$=H, **107g** = R=$C_6H_4$4-Br, $R_1$=H; $R_2$=Br, $R_3$=Br, **107h** = R=$C_6H_4$4-Br, $R_1$=$CH_3$, $R_2$=H, $R_3$=H, **107i** = R=$C_6H_4$4-Br, $R_1$=$C_6H_5$, $R_2$=H, $R_3$=H, **107j** = R=$C_6H_4$4-Br, $R_1$=$C_6H_5$, $R_2$=Cl, $R_3$=H, **107k** = R=$C_6H_4$4-Br, $R_1$=$C_6H_5$, $R_2$=$NO_2$, $R_3$=H, **107l** = R=$C_6H_4$4-Br, $R_1$=2-Cl$C_6H_4$, $R_2$=Cl, $R_3$=H, **107m** = R=$C_6H_4$4-$OCH_3$, $R_1$=H, $R_2$=Br, $R_3$=Br, **107n** = R=$C_6H_4$4-$OCH_3$, $R_1$=$CH_3$, $R_2$=H, $R_3$=H, **107o** = R=$C_6H_4$4-$OCH_3$, $R_1$=$C_6H_5$, $R_2$=H, $R_3$=H, **107p** = R=$C_6H_4$4-$OCH_3$, $R_1$=$C_6H_5$, $R_2$=Cl, $R_3$=H, **107q** = R=$C_6H_4$4-$OCH_3$, $R_1$=$C_6H_5$, $R_2$=$NO_2$, $R_3$=H, **107r** = R=$C_6H_4$4-$OCH_3$, $R_1$=2-Cl$C_6H_4$, $R_2$=Cl, $R_3$=H,
**Reagents and conditions:** (i) KOH, EtOH.

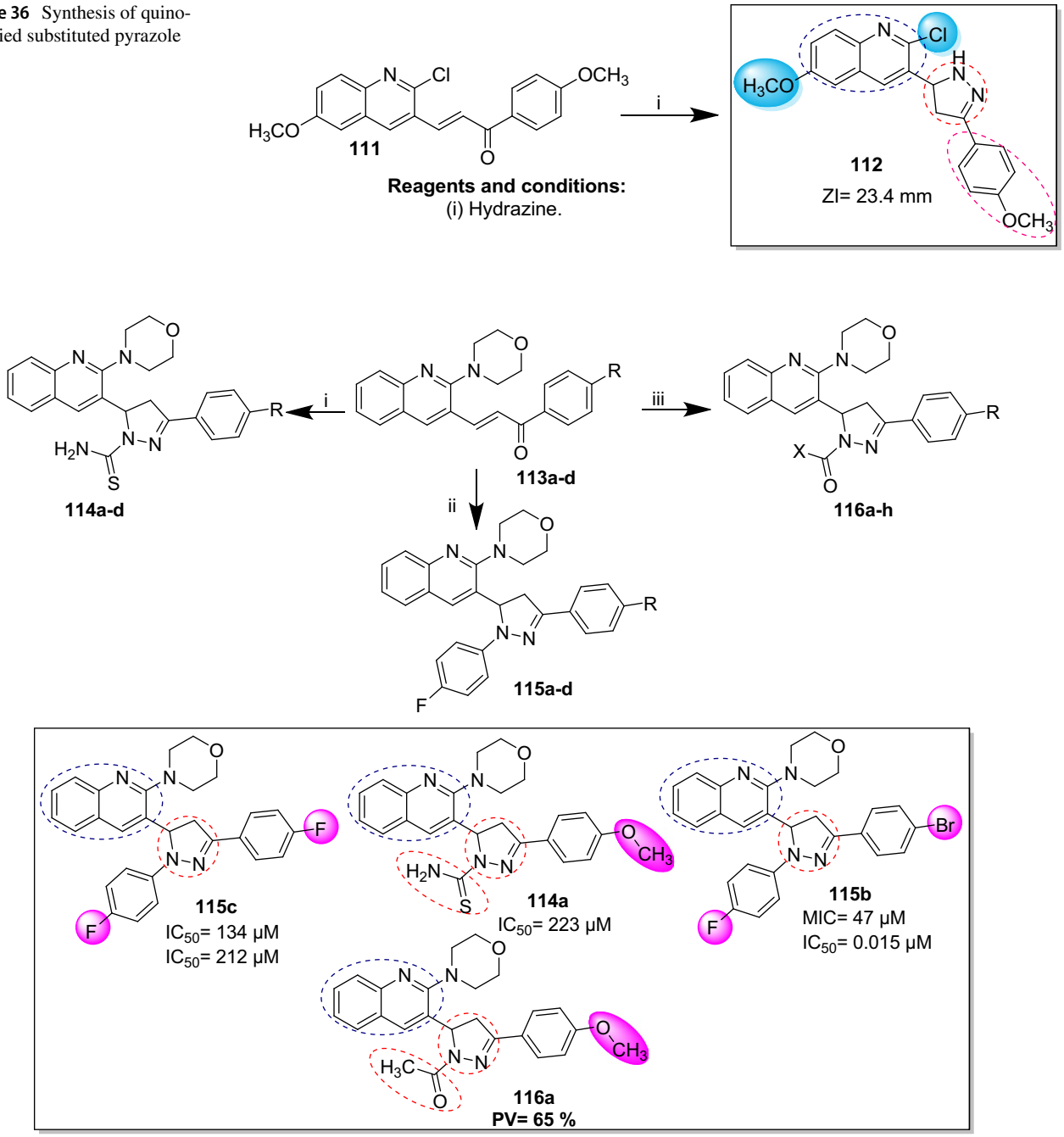



**110a** = R=Me, $R_1$=Me, **110b** = R=Me, $R_2$=Ph, **110c** =R=Me, $R_1$=4F$C_6H_4$, **110d** = R=Me, $R_1$=2-thienyl, **110e** = R=Ph, $R_1$=Me, **110f** = R=Ph, $R_1$=Ph, **110g** = R=Ph, $R_1$=4F$C_6H_4$, **110h** = R=Ph, $R_1$=2-thienyl, **110i** = R=4F$C_6H_4$, $R_1$=Me, **110j** = R=4F$C_6H_4$, $R_1$=Ph, **110k** = R=4F$C_6H_4$, $R_1$=4F$C_6H_4$, **110l** = R=4F$C_6H_4$, $R_1$=2-thienyl, **110m** = R=2-thienyl, $R_1$=Me, **110n** = R=2-thienyl, $R_1$=Ph, **110o** = R=2-thienyl, $R_1$=4F$C_6H_4$, **110p** = R=2-thienyl, $R_1$=2-thienyl,
**Reagents and conditions:** (i) EtOH, reflux, 16h.

**Scheme 35** Synthesis of quinoline allied pyrazole heterocycle with a hydroxyl group

hydrazine hydrate, thiosemicarbazide, 4-fluorophenyl hydrazine hydrochlorides, in glacial acetic acid and hydrazine hydrate in formic acid medium, respectively, to afford series of quinoline allied pyrazoles (**114a–d** to **116a–d**). Then the bioassay revealed that the compounds containing methoxy (**114a**) and fluoro (**115c**) functional group at the pyrazole part emerged as a potent antibacterial and antifungal agent. In addition to that, molecules containing

**Scheme 36** Synthesis of quinoline allied substituted pyrazole



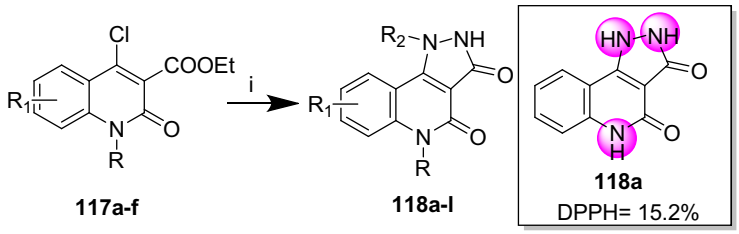

**113a-116a,e** = R=$OCH_3$, **113b-116b,f** = R= Br, **113c-116c,g** = R=F, **113d-116d,h** = R=Cl,
**116a-d** = X=$CH_3$, **116e-h** = X=H,
**Reagents and conditions:** (i) Sodium hydroxide, thiosemicarbazide, (ii) 4-fluoro phenyl hydrazine hydrochloride, (iii) Hydrazine hydrate,glacial acetic acid.

**Scheme 37** Synthesis of morpholine-bearing quinolinyl-pyrazole

bromo and fluoro at the pyrazole part **(115b)** showed the highest efficacy for antitubercular and antimalarial activity. The compound containing methoxy group at the pyrazole part **(116a)** showed the highest cytotoxicity compared to other molecules.

Series of pyrazolo[4,3-c]quinolin-3,4-dione regioisomers (Scheme 38) were synthesized through simple and convenient condensation reaction by treating ethyl 4-chloro-2-oxo-1,2-dihydroquinoline-3-carboxylate **(117a–f)** with substituted hydrazine [101]. All the synthesized compounds

**Scheme 38** Synthesis of quinoline fused pyrazole heterocycle

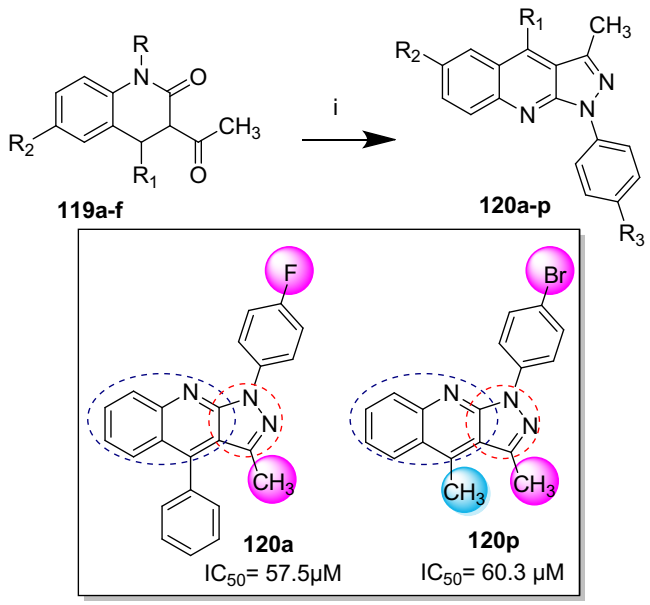



**118a** = R=H, $R_1$=H, $R_2$= H, **118b** = R=H, $R_1$=H, $R_2$= Me, **118c** = R=H, $R_1$=H, $R_2$= Ph, **118d** = R=H, $R_1$=Me, $R_2$= H, **118e** = R=H, $R_1$=Me, $R_2$= Me, **118f** = R=H, $R_1$=Me, $R_2$= Ph, **118g** = R=H, $R_1$=Bn, $R_2$= H, **118h** = R=H, $R_1$=Bn, $R_2$= Me, **118i** = R=H, $R_1$=Bn, $R_2$= Ph, **118j** = R=9-Cl, $R_1$=H, $R_2$= Me, **118k** = R=9-Cl, $R_1$=Me, $R_2$= Me, **118l** = R=9-Cl, $R_1$=Bn, $R_2$= Me,
**Reagents and conditions:** (i) $NH_2NHR_2$, $EtOCH_2CH_2OH$, reflux, 2h.

**(118a–l)** were tested for their antioxidant activity which envisioned that the unsubstituted pyrazolo[4,3-c]quinolin-3,4-diones **(118a)** possessed better scavenging effect on DPPH radicals.

As a potential α-glucosidase inhibiting agents, two series of pyrazole tethered quinolines (Scheme 39) were synthesized by conventional and microwave irradiation methods in the presence of indium(III) chloride catalyst by treating 3-acyl-quinolin-2-one and 4-hydroxy-3-acyl-quinolin-2-one **(119a–f)** with substituted phenylhydrazine [102]. Then the resultant compounds **(120a–p)** were screened for their *α*-glucosidase inhibition activity, which revealed that the compounds containing fluoro aryl **(120a)** and bromo aryl group **(120p)** at pyrazole part tethered to quinoline heterocycle exhibited excellent bioactivity compared to other derivatives.

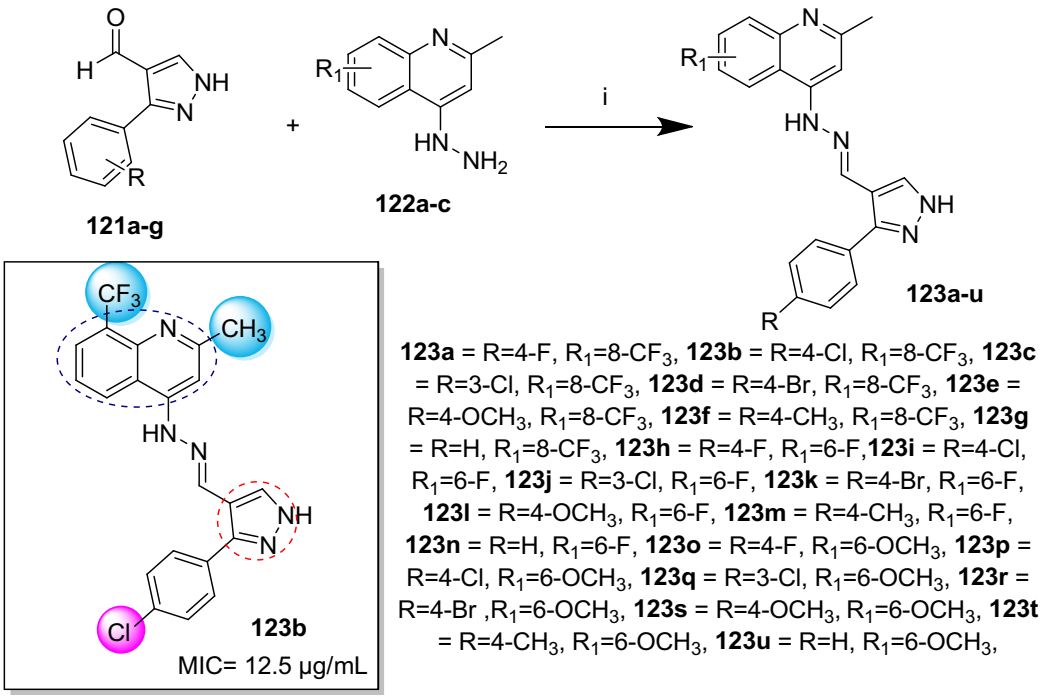
Novel trifluoro methyl-containing quinolino-pyrazoles (Scheme 40) were synthesized by using 3-aryl-1*H*-pyrazole-4-carbaldehydes **(121a–g)** and 1-(2-methyl-substituted)quinolin-4-yl)hydrazines **(122a–c)** intermediates and were screened for their antitubercular and antibacterial activity [103]. The target compound, quinolinyl-pyrazoles **(123a–u)** were obtained by refluxing the above-obtained intermediates **(121a–g** and **122a–c)** in the presence of




**120a** = $R_1$=Ph, $R_2$=H, $R_3$=F, **120b** = $R_1$=Ph, $R_2$=H, $R_3$=Cl, **120c** = $R_1$=Ph, $R_2$=H, $R_3$=$OCH_3$, **120d** = $R_1$=Ph, $R_2$=H, $R_3$=Br, **120e** = $R_1$=Ph, $R_2$=Cl, $R_3$=Br, **120f** = $R_1$=Ph, $R_2$=Cl, $R_3$=Cl, **120g** = $R_1$=Ph, $R_2$=Cl, $R_3$=$CF_3$, **120h** = $R_1$=Ph, $R_2$=Cl, $R_3$=H, **120i** = $R_1$=Ph, $R_2$=Cl, $R_3$=F, **120j** = $R_1$=Ph, $R_2$=$NO_2$, $R_3$=Br, **120k** = $R_1$=Ph, $R_2$=$NO_2$, $R_3$=H, **120l** = $R_1$=Ph, $R_2$=$NO_2$, $R_3$=$OCH_3$, **120m** = $R_1$=Ph, $R_2$=$NO_2$, $R_3$=$CF_3$, **120n** = $R_1$=Ph, $R_2$=$NO_2$, $R_3$=F, **120o** = $R_1$=$CH_3$, $R_2$=H, $R_3$=$OCH_3$, **120p** = $R_1$=$CH_3$, $R_2$=H, $R_3$=Br,

**Reagents and conditions:** (i) Substituted phenylhydrazine, $InCl_3$, ethanol.

**Scheme 39** Synthesis of quinoline allied *N*-aryl-pyrazole heterocycle with the methyl group



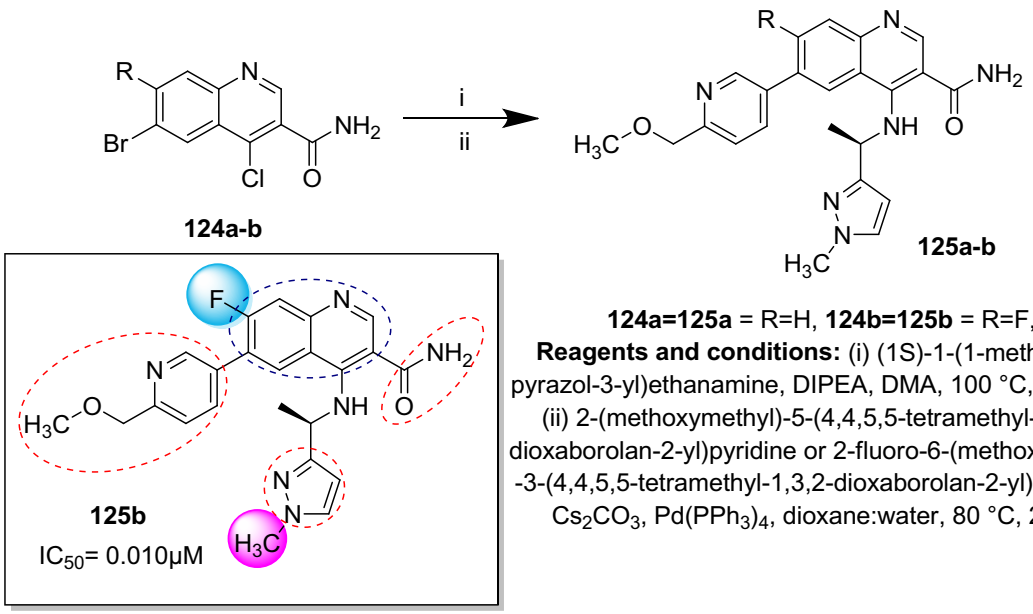

**123a** = R=4-F, $R_1$=8-$CF_3$, **123b** = R=4-Cl, $R_1$=8-$CF_3$, **123c** = R=3-Cl, $R_1$=8-$CF_3$, **123d** = R=4-Br, $R_1$=8-$CF_3$, **123e** = R=4-$OCH_3$, $R_1$=8-$CF_3$, **123f** = R=4-$CH_3$, $R_1$=8-$CF_3$, **123g** = R=H, $R_1$=8-$CF_3$, **123h** = R=4-F, $R_1$=6-F,**123i** = R=4-Cl, $R_1$=6-F, **123j** = R=3-Cl, $R_1$=6-F, **123k** = R=4-Br, $R_1$=6-F, **123l** = R=4-$OCH_3$, $R_1$=6-F, **123m** = R=4-$CH_3$, $R_1$=6-F, **123n** = R=H, $R_1$=6-F, **123o** = R=4-F, $R_1$=6-$OCH_3$, **123p** = R=4-Cl, $R_1$=6-$OCH_3$, **123q** = R=3-Cl, $R_1$=6-$OCH_3$, **123r** = R=4-Br ,$R_1$=6-$OCH_3$, **123s** = R=4-$OCH_3$, $R_1$=6-$OCH_3$, **123t** = R=4-$CH_3$, $R_1$=6-$OCH_3$, **123u** = R=H, $R_1$=6-$OCH_3$,

**Reagents and conditions:** (i) Ethanol, cat. sulfuric acid, 80 °C, 4 h.

**Scheme 40** Synthesis of quinoline allied pyrazole heterocycle with the methyl group

sulfuric acid. The biological study has revealed that the compound containing trifluoromethyl functional group at the quinoline part and chloro functional group at the pyrazole part **(123b)** exhibited excellent antitubercular and antibacterial activity.

Three series of orally bioactive pyrazole-containing quinoline derivatives (Scheme 41) were conveniently synthesized by treating 6-bromo-4-chloroquinoline-3-carboxamide **(124a–b)** with 1-methyl-4-BPin-1*H*-pyrazole, (1S)-1-(1-methyl-1*H*-pyrazol-3-yl)ethanamine, fluoro-pyrazole and



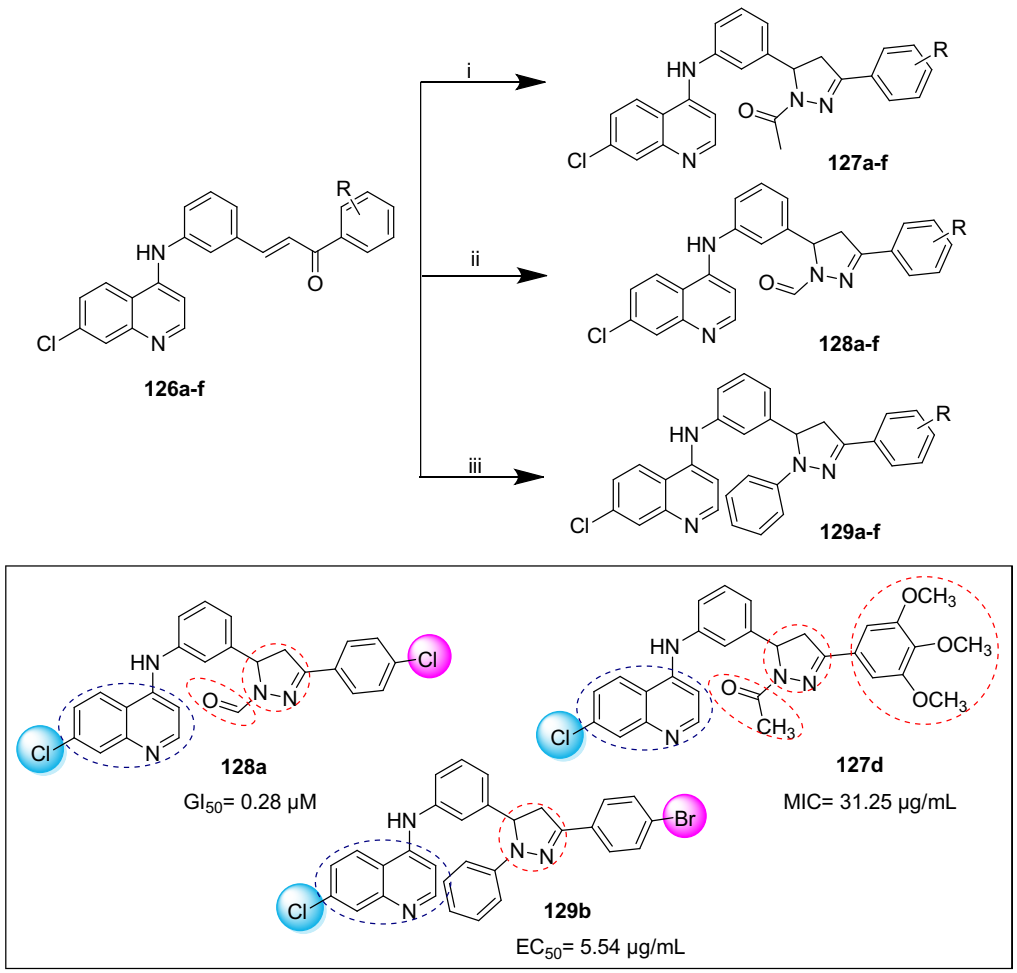

**124a=125a** = R=H, **124b=125b** = R=F,
**Reagents and conditions:** (i) (1S)-1-(1-methyl-1H-pyrazol-3-yl)ethanamine, DIPEA, DMA, 100 °C, 10-18 h, (ii) 2-(methoxymethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine or 2-fluoro-6-(methoxymethyl)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine, $Cs_2CO_3$, $Pd(PPh_3)_4$, dioxane:water, 80 °C, 2.5 h.

**Scheme 41** Synthesis of quinoline allied *N*-methyl-pyrazole heterocycle

methyl-pyrazole [104]. Then the compounds were screened for their ataxia telangiectasia mutated (ATM) kinase inhibition activity which envisioned that the derivative containing amide and pyrazole ring with amine linkage **(125b)** showed the highest inhibition activity against ATM.

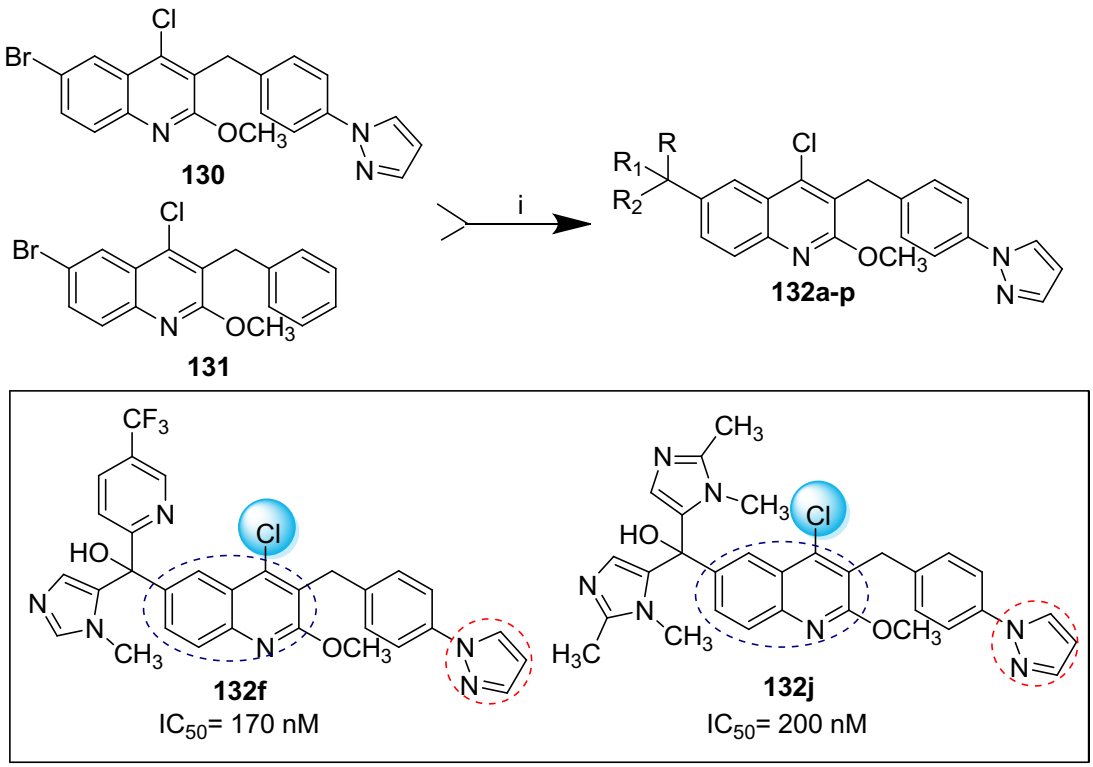
Novel quinoline allied pyrazoles were synthesized (Scheme 42) through chalcone intermediate **(126a–f)** followed by Claisen–Schmidt condensation reaction [105]. The chalcones **(126a–f)** were converted to three series of pyrazole affixed quinolines **(127a–f)** to **(129a–f)** by treating with hydrazine hydrate, phenylhydrazine in the presence of acetic anhydride and formic acid. All the synthesized compounds were screened for their anticancer, antifungal, antibacterial, antiplasmodial and antileishmanial activities. Concerning antifungal and antileishmanial activity, quinoline allied pyrazoles showed moderate efficacy, whereas compounds containing trimethoxy **(127d)**, chloro **(128a)** and bromo **(129b)** exhibited excellent anticancer, antimicrobial and antiplasmodial activities.

Novel quinoline allied pyrazoles-bearing hydroxyl/amine groups at the benzylic position (Scheme 43) were synthesized as RORγt inverse agonists by treating previously synthesized 2-methoxy-3-(1-pyrazole-benzyl)-quinolines **(130)** through reported method [106] or 3-benzyl-6-bromo-4-chloro-2-methoxyquinoline **(131)**. Then the key intermediates **(130 or 131)** were treated with diaryl ketones in the presence of *n*-butyllithium in tetrahydrofuran solvent medium followed by acetylation and subsequently treating it with methanolic ammonia or methylamine [107]. Finally, the binding property of the synthesized compounds was tested, and the study revealed that the compound containing 1-methylimidazol-5-yl and pyridine ring at the quinoline




**126a-129a** = R=Cl, **126b-129b** = R=Br, **126c-129c** = R=$OCH_3$, **126d-129d** = R=3,4,5-$(OCH_3)_3$, **126e-129e** = R=$CH_3$, **126f-129f** = R=H,
**Reagents and conditions:** (i) $NH_2NH_2{\cdot}H_2O$, $Ac_2O$, EtOH, reflux, 10 min, rt, 10 min, (ii) $NH_2NH_2{\cdot}H_2O$, HCOOH, EtOH, reflux, 10 min.

**Scheme 42** Synthesis of quinoline allied pyrazole heterocycle with amine bridge

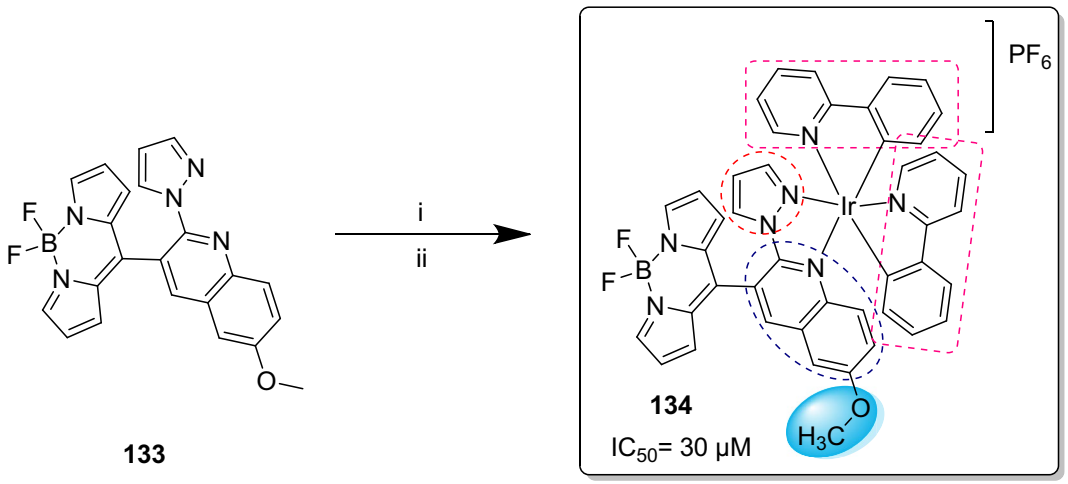



**132a-p** = R=$R_2$=various heterocycles, $R_1$=OH, $NH_2$ and NHMe,
**Reagents and conditions:** (i) Diarylketones, n-BuLi, THF.

**Scheme 43** Synthesis of quinolinyl-pyrazole with imidazole moiety

part **(132f)** possessed 57-fold increased potency, whereas the compound with bis-1,2-dimethylimidazole moiety at quinoline part **(132j)** possessed the highest potency in binding to nuclear hormone receptor RORγt.

Novel iridium(III)-based quinoline clubbed pyrazole complex (Scheme 44) was conveniently synthesized as a potent anticancer agent starting from *p*-methoxy aniline [108]. The ligand **(133)** was treated with chloro-bridged




**Reagents and conditions:** (i) $[(PPy)_2Ir(\mu\text{-}Cl)]_2$, 1:1 DCM/Methanol, 12h, stirring, (ii) $NH_4PF_6$, 4h, stirring.

**Scheme 44** Synthesis of quinoline allied pyrazole-Ir-complex

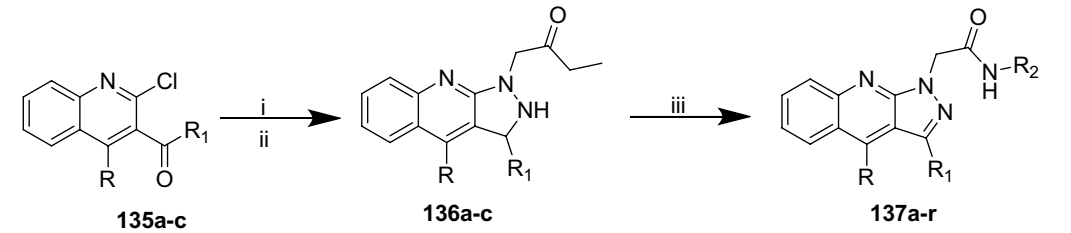
dimeric iridium in ethanol/dichloromethane solvent to afford the final complex **(134)**. Finally, the synthesized compound was screened for anticancer activity and subjected for a docking study which envisioned that the complex coordinated with two additional 2-phenyl pyridine ring **(134)** exhibited excellent anticancer and binding potency.

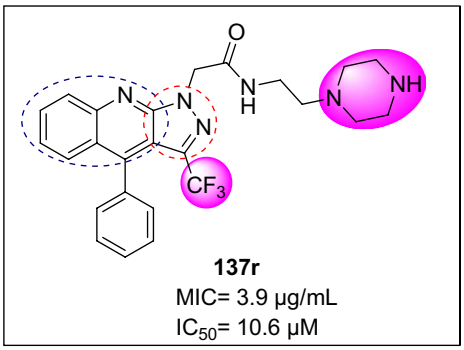
Series of alkyl amide-appended pyrazoloquinolines (Scheme 45) were prepared as potent anticancer and antimicrobial agents [109]. Initially, chloroquinoline derivatives **(135a–c)** were converted to pyrazole-tethered quinoline **(135a–c)** through cyclization by refluxing with hydrazine hydrate followed by *N*-alkylation and later treated with primary and secondary amines to afford respective alkyl amide appended pyrazoloquinoline derivatives **(137a–r)**. Further bioassay of prepared compounds revealed that the compound containing trifluoromethyl and piperazine moieties at the pyrazole part **(137r)** emerged as a promising antibacterial and anticancer lead with favorable cytotoxicity.

Novel series of quinoline and coumarin appended thiazole-substituted pyrazoles (Scheme 46) were synthesized by using various 3-(2-bromoacetyl)-6-*H*/halo-2*H*-chromen-2-ones **(138a–e)** and 3-(2-chlorophenyl)-5-(2-chloroquinolin-3-yl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamide **(139a–e)** intermediates which were previously synthesized according to the reported methods [110]. The resultant compounds were subjected to cyclization by refluxing in ethanol to afford the target compounds; 3-(2-(5-(2-chloroquinolin-3-yl)-3-substituted-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl) thiazol-4-yl)-6-*H*/halo-2*H*-chromen-2-ones **(140a–y)**. The bioassay of the obtained compounds envisioned that the compounds containing fluoro-coumarin ring along with the fluoroaryl ring **(140q–s)** exhibited the highest antimicrobial and antifungal activity compared to the standard drug.

Novel quinoline-appended aminopyridazine-substituted pyrazoles (Scheme 47) were synthesized in a multi-step reaction [111]. Initially, the pinacol boronic ester **(141)** was subjected to Suzuki coupling with quinoline-8-boronic acid **(142)** followed by the deprotection of Boc to afford the title compound: quinoline allied pyrazole **(143)**. The synthesized compounds were screened for in vitro profiling and rat pharmacokinetic studies against 5-$HT_{2C}$ receptor agonists, (one of the clinically proven mechanisms for pharmacological weight reduction) which envisioned that the compound containing aminopyridazine at pyrazole part (**143**) emerged as a potent agonist of the 5-$HT_{2C}$ receptor.

A powerful anti-dengue viral agent, novel diaryl-pyrazolyl-quinolines (Scheme 48) were synthesized through chalcone **(144a–c)** intermediates [112]. Initially, the chalcones **(144a–c)** were refluxed with various phenylhydrazine hydrochloride and DDQ to yield various diaryl-pyrazolyl-quinolines **(145a–c)** with good yield. Finally, the bioassay revealed that the compound containing sulfonamide and methoxy functional group at the pyrazole part **(145c)** exhibited excellent antiviral activity against DENV-2 compared to the standard drug ribavirin and cytotoxicity against Huh-7 cell line.

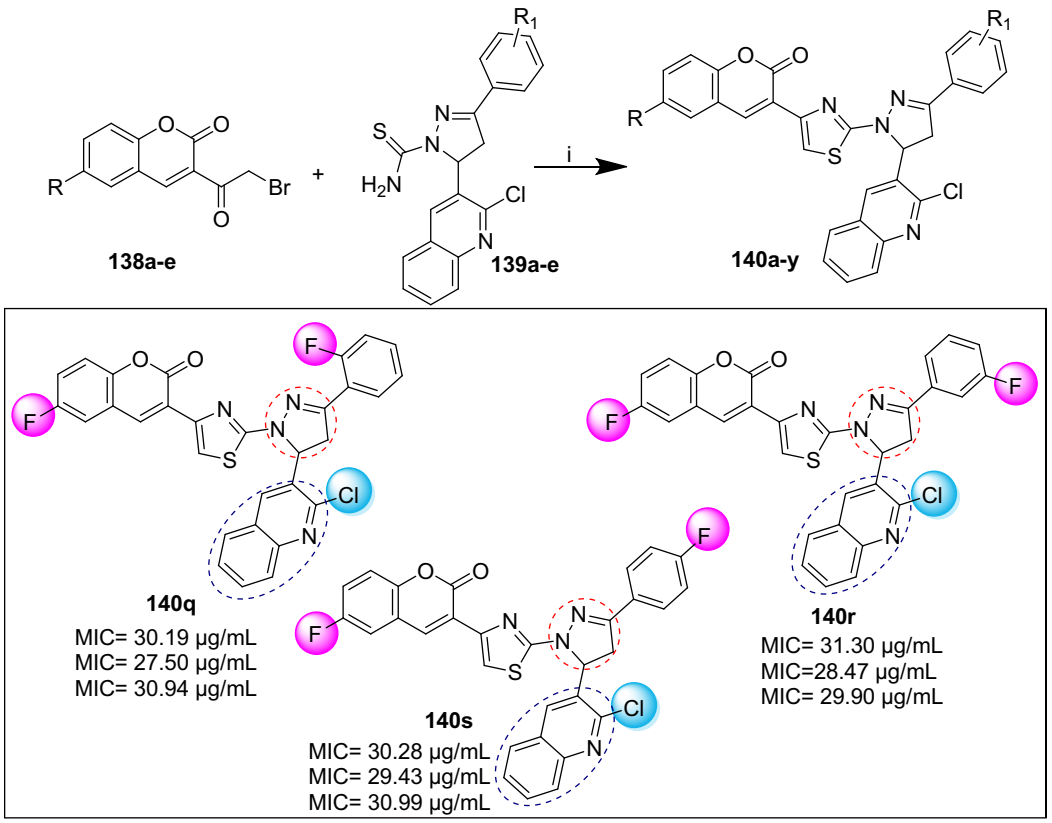



**137a** = R=$CH_3$, $R_1$=$CH_3$, $R_2$=methyl, **137b** = R=$CH_3$, $R_1$=$CH_3$, $R_2$=cyclo propyl, **137c** = R=$CH_3$, $R_1$=$CH_3$, $R_2$=cyclo hexyl, **137d** = R=$CH_3$, $R_1$=$CH_3$, $R_2$=2-furfuryl, **137e** = R=$CH_3$, $R_1$=$CF_3$, $R_2$=methyl, **137f** =R=$CH_3$, $R_1$=$CF_3$, $R_2$=ethyl, **137g** = R=$CH_3$, $R_1$=$CF_3$, $R_2$=n-hexyl, **137h** = R=$CH_3$, $R_1$=$CF_3$, $R_2$=cyclo propyl, **137i** =R=$CH_3$, $R_1$=$CF_3$, $R_2$=cyclopentyl, **137j** = R=$CH_3$, $R_1$=$CF_3$, $R_2$=cyclo hexyl, **137k** = R=$CH_3$, $R_1$=$CF_3$, $R_2$=2-furfuryl, **137l** = R=$C_6H_5$, $R_1$=$CF_3$, $R_2$=methyl, **137m** = R=$C_6H_5$, $R_1$=$CF_3$, $R_2$=ethyl, **137n** = R=$C_6H_5$, $R_1$=$CF_3$, $R_2$=n-propyl, **137o** = R=$C_6H_5$, $R_1$=$CF_3$, $R_2$=cyclo propyl, **137p** = R=$C_6H_5$, $R_1$=$CF_3$, $R_2$=cyclo hexyl, **137q** = R=$C_6H_5$, $R_1$=$CF_3$, $R_2$=2-furfuryl, **137r** = R=$C_6H_5$, $R_1$=$CF_3$, $R_2$=piperazine

**Reagents and conditions:** (i) Hydrazine hydrate, ethanol, reflux 2-3 h, (ii) Bromoethyl acetate, potassium iodide, acetone, reflux 8-10 h, (iii) Pimary amine, 50-80 °C, sealed tube, 8-10h.

**Scheme 45** Synthesis of alkyl amide appended pyrazoloquinolines

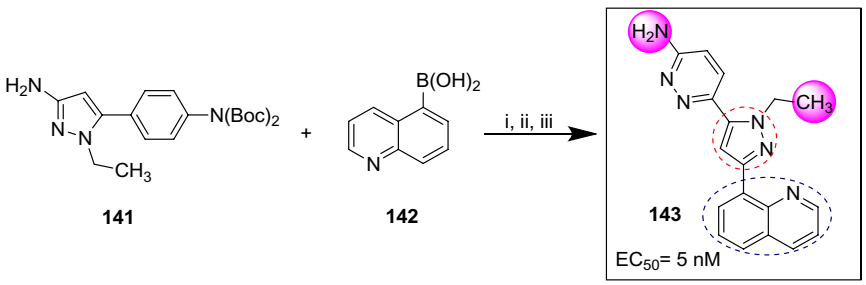



**138a** = R=H, **138b** = R=Cl, **138c** = R=Br, **138d** = R=F, **138e** = R=I,**139a** = R=2Cl, **139b** = R=2F, **139c** = R=3F, **139d =** R=4F, **139e** = R=4$NO_2$, **140a** = R=H, $R_1$=2-Cl, **140b** = R=H, $R_1$=2-F, **140c** = R=H, $R_1$=3F, **140d** = R=H, $R_1$=4-F, **140e** = R=H, $R_1$=4$NO_2$, **140f** = R=Cl, $R_1$=2-Cl, **140g** = R=Cl, $R_1$=2-F, **140h** = R=Cl, $R_1$=3F, **140i** = R=Cl, $R_1$=4-F, **140j** = R=Cl, $R_1$=4$NO_2$,**140k** = R=Br, $R_1$=2-Cl, **140l** = R=Br, $R_1$=2-F, **140m** = R=Br, $R_1$=3F, **140n** = R=Br, $R_1$=4-F, **140o** = R=Br, $R_1$=4$NO_2$,**140p** = R=F, $R_1$=2-Cl, **140q** = R=F, $R_1$=2-F, **140r** = R=F, $R_1$=3F, **140s** = R=F, $R_1$=4-F, **140t** = R=F, $R_1$=4$NO_2$, **140u** = R=I, $R_1$=2-Cl, **140v** = R=I, $R_1$=2-F, **140w** = R=I, $R_1$=3F, **140x** = R=I, $R_1$=4-F, **140y** = R=I, $R_1$=4$NO_2$,

**Reagents and conditions:** (i) Ethanol.

**Scheme 46** Synthesis of quinoline and coumarin appended thiazole-substituted pyrazole

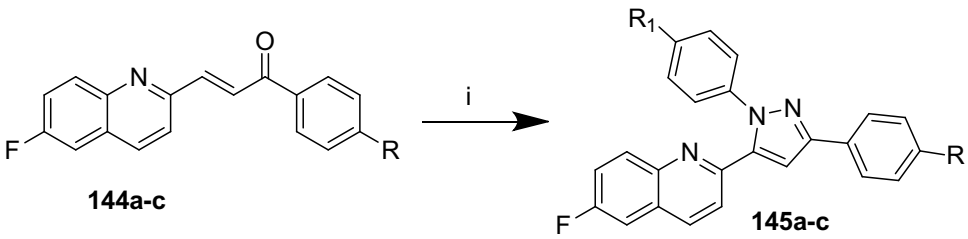
**Scheme 47** Synthesis of quinoline allied pyrazole heterocycle with aminopyridazine

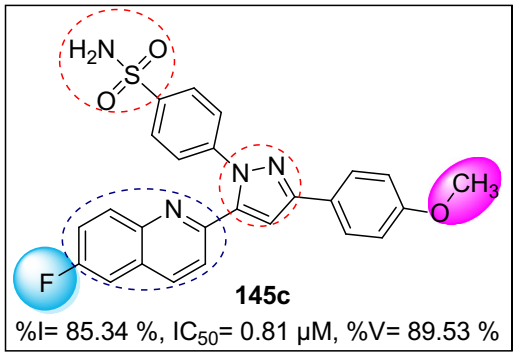



**Reagents and conditions:** (i) t-BuONO,Cu(I)Br, LiBr, acetonitrile, 50 °C, (ii) $PdCl_2(dppf)_2$, $Cs_2CO_3$, dioxane, 90-100 °C, sealed tube, (iii) TFA, rt.

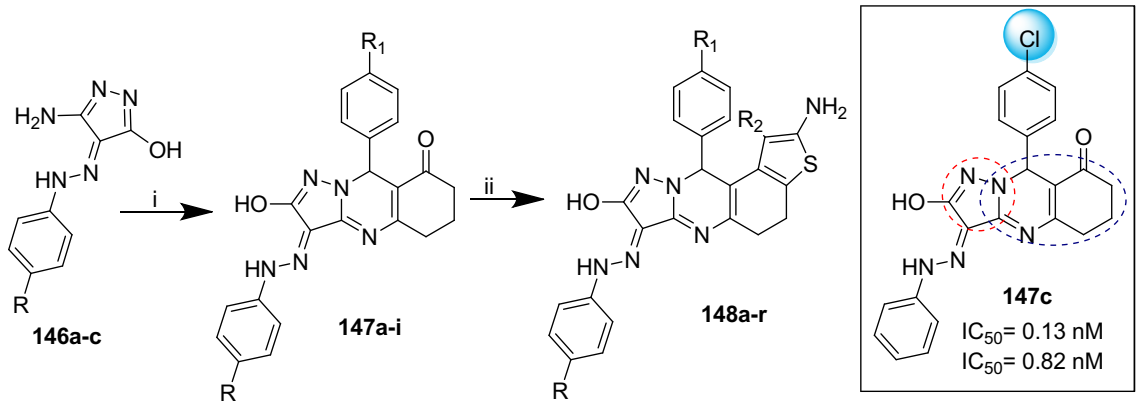
Novel quinoline allied pyrazole heterocycle with thiophene ring (Scheme 49) was obtained as a potent Pim-1 kinase inhibitor [113]. Initially, the pyrazole moiety with an aryl hydrazone group **(146a–c)** was converted to pyrazole allied quinolines **(147a–i)** by treating with aromatic aldehydes and cyclohexane-1,3-dione. Then the resultant compound **(147a–i)** was treated with phenylhydrazine and malononitrile or ethylcyanoacetate in the presence of elemental sulfur to afford the series of quinoline compounds **(148a–r)**. Finally, the synthesized compounds were screened

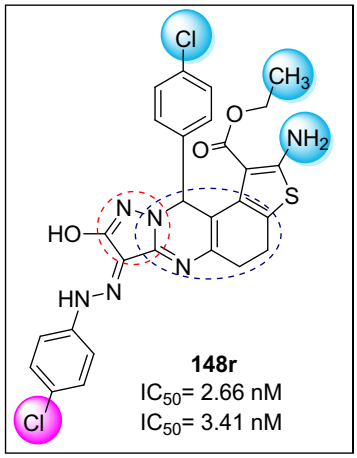
**Scheme 48** Synthesis of fluoro-quinoline allied pyrazole heterocycle




**144a** = R=H, **144b** = R=F, **144c** = R=OMe,**145a** = R=H, $R_1$=$SO_2NH_2$, **145b** = R=F, $R_1$=$SO_2NH_2$, **145c** =R=OMe, $R_1$=$SO_2NH_2$,
**Reagents and conditions:**
(i) 4-Substituted phenylhydrazine hydrochloride, reflux, 24h.




**146a** = R=H, **146b** = R=$CH_3$, **146c** = R=Cl,
**147a** = R=H, $R_1$=H, **147b** = R=H, $R_1$=$OCH_3$, **147c** = R=H, $R_1$=Cl,
**147d** =R=$CH_3$, $R_1$=H, **147e** = R=$CH_3$, $R_1$=$OCH_3$, **147f** = R=$CH_3$, $R_1$=Cl,
**147g** = R=Cl, $R_1$=H, **147h** = R=Cl, $R_1$=$OCH_3$, **147i** = R=Cl, $R_1$=Cl,
**148a** = R=H, $R_1$=H, $R_2$=CN, **148b** = R=H, $R_1$=H, $R_2$=COOEt,
**148c** = R=H, $R_1$=$OCH_3$, $R_2$=CN, **148d** = R=H, $R_1$=$OCH_3$, $R_2$=COOEt,
**148e** = R=H, $R_1$=Cl, $R_2$=CN, **148f** = R=H, $R_1$=Cl, $R_2$=COOEt,
**148g** = R=$CH_3$, $R_1$=H, $R_2$=CN, **148h** = R=$CH_3$, $R_1$=H, $R_2$=COOEt,
**148i** = R=$CH_3$, $R_1$=$OCH_3$, $R_2$=CN, **148j** = R=$CH_3$, $R_1$=$OCH_3$, $R_2$=COOEt,
**148k** = R=$CH_3$, $R_1$=Cl, $R_2$=CN, **148l** = R=$CH_3$, $R_1$=Cl, $R_2$=COOEt,
**148m** = R=Cl, $R_1$=H, $R_2$=CN, **148n** = R=Cl, $R_1$=H, $R_2$=COOEt,
**148o** = R=Cl, $R_1$=$OCH_3$, $R_2$=CN, **148p** = R=Cl, $R_1$=$OCH_3$, $R_2$=COOEt,
**148q** = R=Cl, $R_1$=Cl, $R_2$=CN, **148r** = R=Cl, $R_1$=Cl, $R_2$=COOEt,
**Reagents and conditions:** (i) Substituted aldehydes, cyclohexadione, TEA, dioxane. (ii) Malononitrile, sulphur, 1,4-dioxane, TEA.

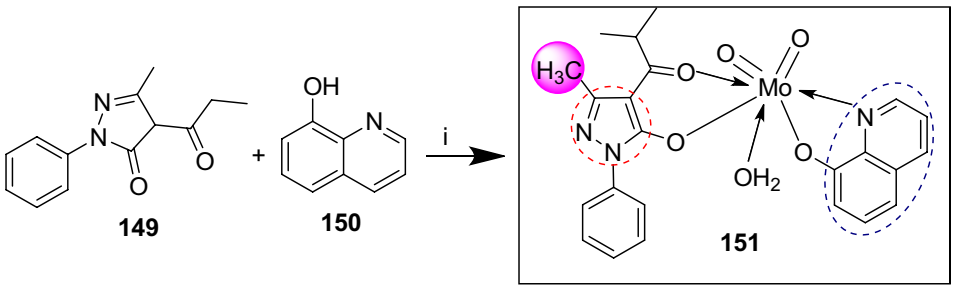
**Scheme 49** Synthesis of quinoline allied pyrazole heterocycle with a thiophene ring

for their Pim-1 kinase inhibition which envisioned that the compound containing chloroaryl and thiophene ring tethered to quinoline ring **(148r)** exhibited excellent potency compared to other scaffolds. Moreover, the compound containing the chloroaryl group at the quinoline part **(147c)** exhibited excellent c-MET enzymatic activity and anticancer activity against the PC3 cell line.

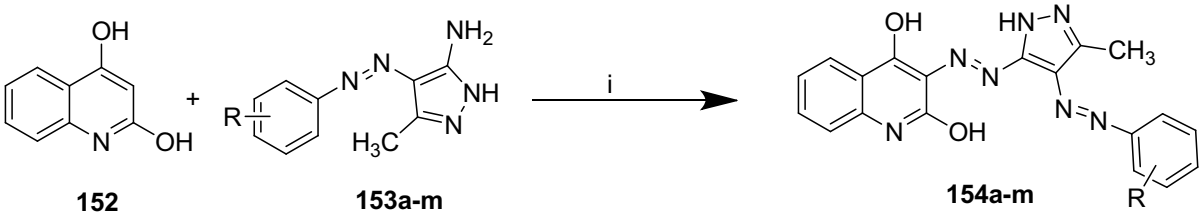
Series of molybdenum metal complexes containing pyrazole and quinoline moieties (Scheme 50) were conveniently prepared [114] by treating previously synthesized pyrazole **(149)** derivatives [115, 116] with 8-hydroxyquinoline **(150)** followed by bis(acetylacetonato)dioxomolybdenum(VI) in ethanol. Then the obtained complexes were tested for their antibacterial activity which revealed that the complex **(151)** showed significant activity against *E. coli*.

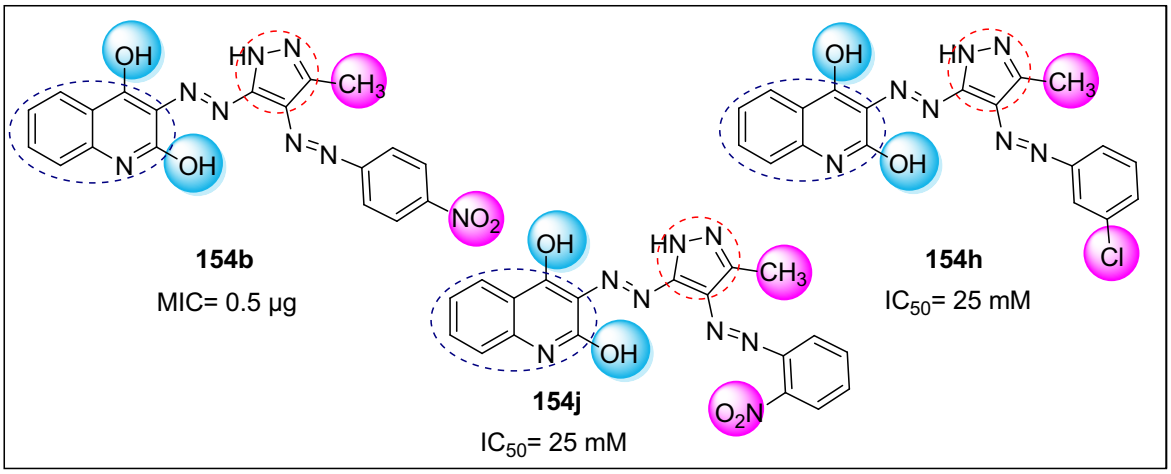
New series of pyrazole allied quinolines (Scheme 51) was synthesized by treating 2,4-dihydroxyquinoline **(152)** with various 5-amino-4-phenylazo-3-methyl-1*H*-pyrazoles **(153a–m)** intermediates [117]. Then the resultant compounds **(154a–m)** were screened for antimicrobial and anticancer activity which revealed that the compound containing nitro aryl group at pyrazole part **(154b)** exhibited excellent antimicrobial activity and compounds containing chloro at the third position **(154 h)** and nitro at

**Scheme 50** Synthesis of Mo-complex with quinoline and pyrazole




**Reagents and conditions:** (i) Bis(acetylacetonato)dioxomolybdenum(VI), ethanol (95%), reflux.

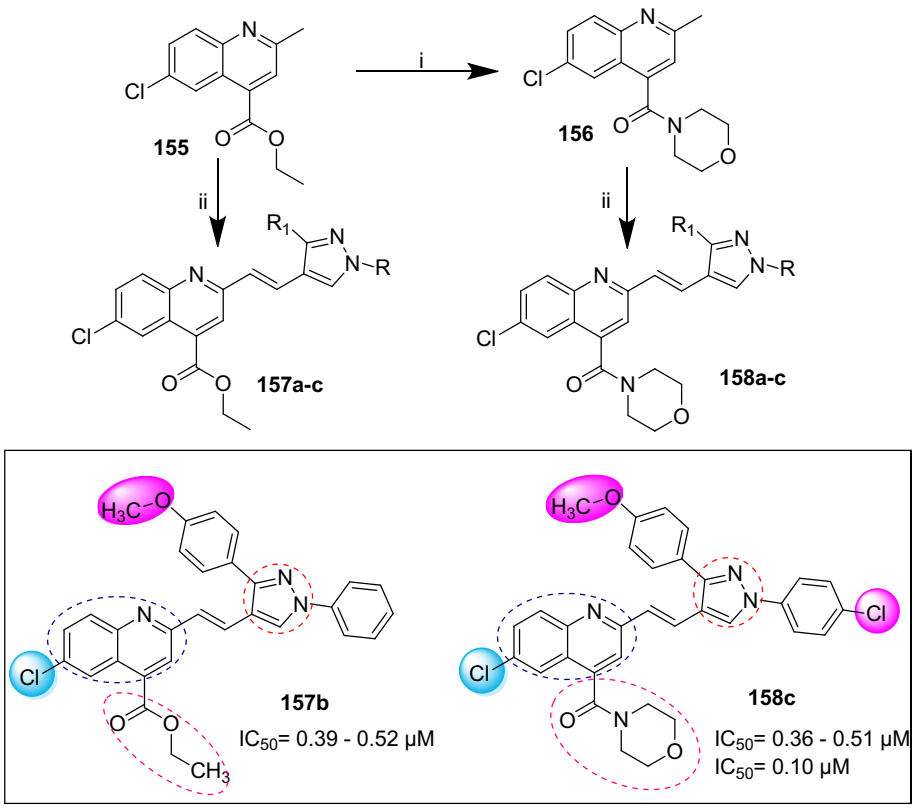



**153a-154a** = R=H, **153b-154b** = R=4-$NO_2$, **153c-154c** = R=4-$OCH_3$, **153d-154d** = R=4-Cl, **153e-154e** = R=4-$CH_3$, **153f-154f** = R=2-$NO_2$, **153g-154g** = R=3-$OCH_3$, **153h-154h** = R=3-Cl, **153i-154i** = R=3-$CH_3$, **153j-154j** = R=2-$NO_2$, **153k-154k** = R= 2-$OCH_3$, **153l-154l** = R=2-Cl, **153m-154m** = R=2-$CH_3$,
**Reagents and conditions:** (i) Acetic acid/HCl/$NaNO_2$.

**Scheme 51** Synthesis of azo-linked-quinolinyl-pyrazoles

**Scheme 52** Synthesis of quinoline allied 1,3-diaryl-pyrazoles




**157a=158a** = R=$R_1$=4-ClC$_6$H$_4$, **157b=158b** = R=C$_6$H$_5$, $R_1$=4-OCH$_3$C$_6$H$_4$, **157c=158c** =R=4-ClC$_6$H$_4$, $R_1$=4-OCH$_3$C$_6$H$_4$,

**Reagents and conditions:** (i) Excess morpholine, reflux, (ii) 1,3-Diaryl-1H-pyrazole--carbaldehydes, Ac$_2$O, reflux.

the second position **(154j)** exhibited excellent anticancer activity against HeLa and PC3 cancer cell line with highest cytotoxic effects.

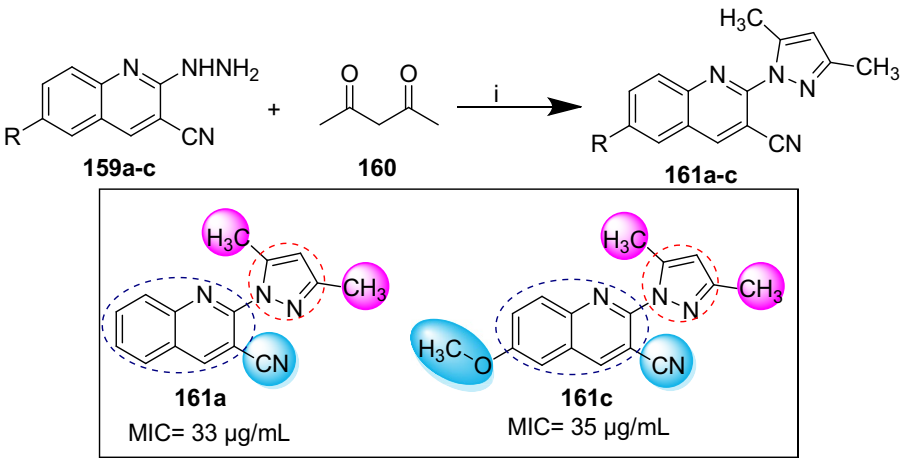
Novel variety pyrazole appended quinolines (Scheme 52) were obtained and screened for anti-inflammatory, ulcerogenic, in vitro LOX and COX-1/COX-2 activities [118]. Initially, the series of compounds **(157a–c)** were synthesized by treating ethyl-6-chloro-2-methylquinoline-4-carboxylate **(155)** with pyrazole-4-carboxaldehydes. The compound **(155)** was treated with morpholine followed by pyrazole-4-carboxaldehydes to afford the next series of compounds **(158a–c)**. The study of anti-inflammatory activity showed that the compound containing chloro aryl and methoxy aryl functional group at the pyrazole part and ester group at the quinoline part (**157c**) was found to be more effective for anti-inflammatory activity. Also, a compound containing chloro aryl and methoxy aryl functional group at pyrazole part with morpholine ring at the quinoline part (**158c**) was found to be more selective towards an anti-inflammatory and in vitro LOX COX-1/COX-2 activities.

New series of quinoline-3-carbonitrile-appended pyrazole (Scheme 53) were synthesized using 6-substituted-2-hydrazinyl quinoline-3-carbonitrile **(159a–c)** as an intermediate [119]. The key intermediate **(159a–c)** was treated with urea, active methylene compound **(160)** to obtain respective pyrazole appended quinolines **(161a–c)**. Then the final compounds obtained were screened for their antibacterial and antifungal activities which showed that the plane **(161a)** and a compound containing methoxy functional group at the quinoline part **(161c)** exhibited excellent antibacterial and moderate antifungal activities.

The series of pyrazole-bearing quinoline derivatives (Scheme 54) were prepared and screened for antibacterial and antifungal activities [120]. The corresponding quinoline-bearing pyrazoles **(163a–b)** were prepared by the treatment of 2-hydrazinylquinoline **(162)** with ethoxyethylidene, dithioacetal and arylidene derivatives. All the synthesized compounds were screened for antibacterial and antifungal activity. In addition, the compounds containing dichloro aryl, nitrile and amine groups at the pyrazole part **(163b)** showed fourfold potency compared to the standard drug in inhibiting the growth of microbes.

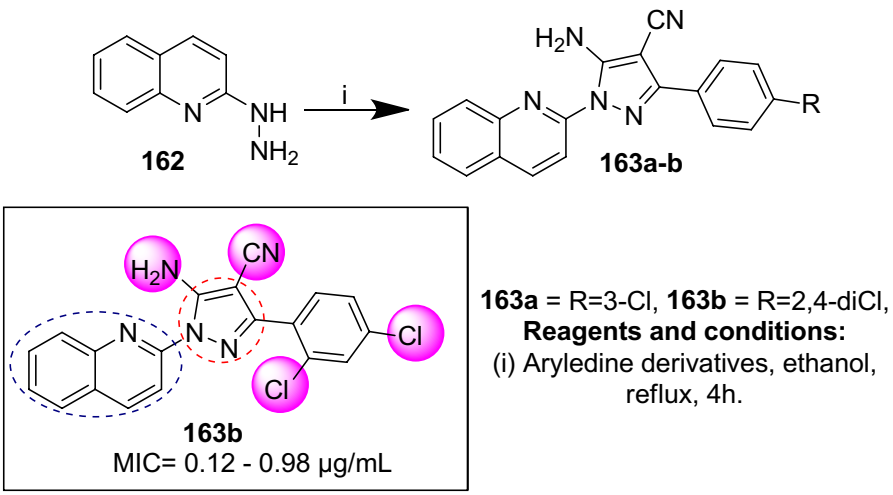
As anticancer agents, a series of novel 1*H*-pyrazolo[3,4-b] quinolin-3-amines (Scheme 55) were synthesized to inhibit the growth of colon cancer cells [121]. First, the starting materials **(164a–h)** were cyclized with hydrazine hydrate to

**Scheme 53** Synthesis of nitrile-substituted-quinolinyl-pyrazoles

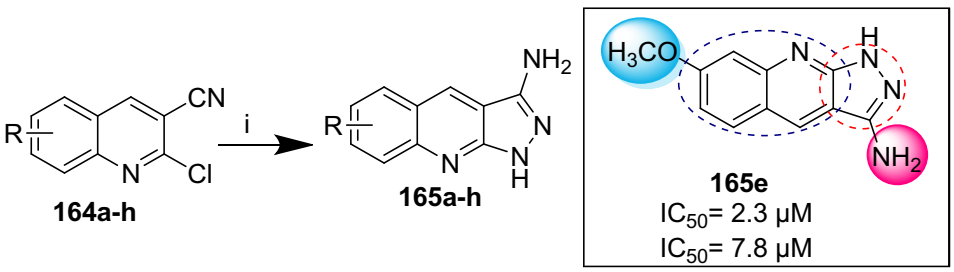



**159a, 161a** = R=H, **159b, 161b** = R=$CH_3$, **159c, 161c** = R=$OCH_3$,
**Reagents and conditions:** (i) Gl. acetic acid, reflux, 5h.

**Scheme 54** Synthesis of quinoline allied 3-aryl-pyrazole heterocycles




**163a** = R=3-Cl, **163b** = R=2,4-diCl,
**Reagents and conditions:**
(i) Aryledine derivatives, ethanol, reflux, 4h.



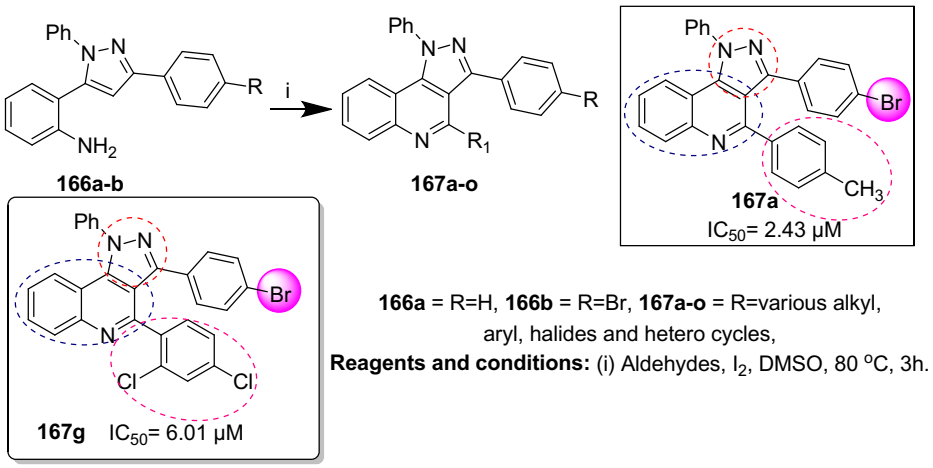

**164a-165a** = R=H, **164b-165b** = R=5-Me, **164c-165c=** R=5,6 diMe, **164d-165d** = R=5-O-$CH_3$, **164e-165e** = R=7-O-$CH_3$, **164f-165f** = R=5,6 diO-$CH_3$, **164g-165g** = R=6Cl, **164h-165h** = R=phenyl,
**Reagents and conditions:** (i) $NH_2NH_2.H_2O$, reflux.

**Scheme 55** Synthesis of quinoline allied aminopyrazoles

yield 1*H*-pyrazolo[3,4-b]quinolin-3-amines **(165a–h)** under reflux condition with good yield. Finally, the compounds obtained were tested for their anticancer activity against ten cancer cell lines, and the study revealed that the compound-containing methoxy functional group at the quinoline part **(165e)** exhibited excellent activity against most of the cancerous and non-cancerous cell lines such as breast, prostate, brain, ovarian, colon and normal cell lines with the highest cytotoxicity.

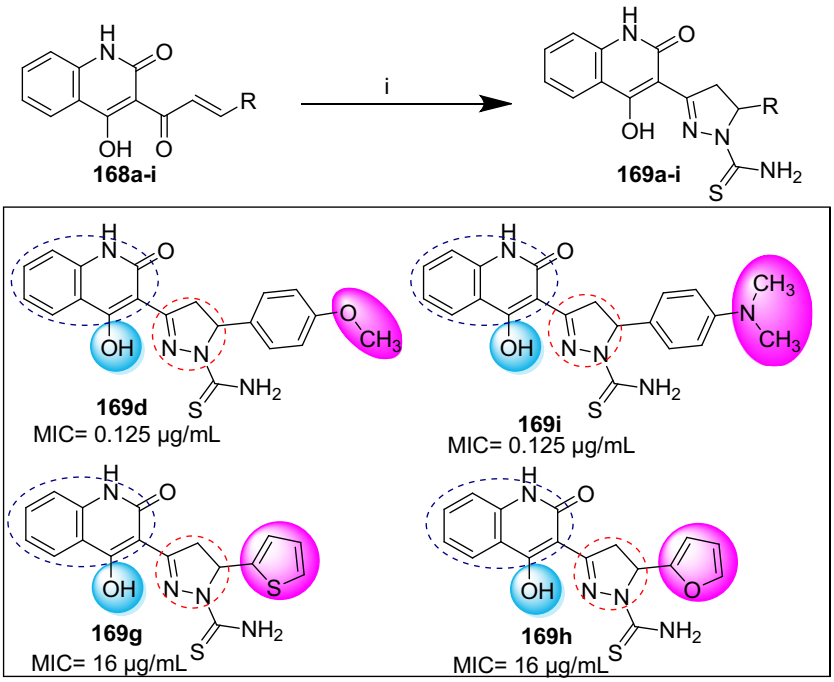
Series of pyrazole tethered quinolines (Scheme 56) were synthesized as antiproliferative agents through 2-(1,3-diphenyl-1*H*-pyrazol-5-yl)aniline **(166a–b)** intermediate [122]. Initially, compounds **(166a–b)** which upon condensation with various aldehydes mediated by iodine in DMSO solvent medium yielded desired quinoline allied pyrazoles **(167a–o)**. Also, the synthesized compounds were screened for their anticancer activity against human cancer cell lines and the study revealed that the compound containing the methylaryl group **(167a)** and dichloro aryl group **(167g)** at quinoline

**Scheme 56** Synthesis of quinoline allied *N*-phenyl-pyrazole heterocycle




**166a** = R=H, **166b** = R=Br, **167a-o** = R=various alkyl, aryl, halides and hetero cycles,
**Reagents and conditions:** (i) Aldehydes, $I_2$, DMSO, 80 °C, 3h.

**Scheme 57** Synthesis of quinoline allied *N*-thioamide-substituted pyrazole heterocycle

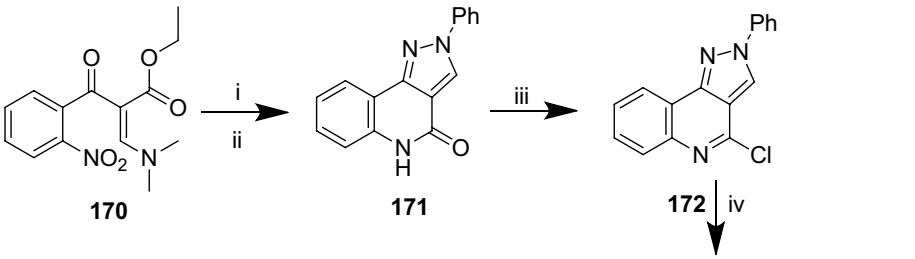



**168a=169a** = R=H-Ph, **168b=169b** = R=3-$NO_2$-Ph, **168c=169c** = R=4-$NO_2$-Ph, **168d=169d** = R=4-OMe-Ph, **168e=169e** = R=4-Cl-Ph, **168f=169f** = R=3-Cl-Ph, **168g=169g** = R=thiophen, **168h=169h** = R=furan, **168i=169i** = R=4-$N(CH_3)_2$-Ph,
**Reagents and conditions:** (i) Thiosemicarbazide, DMF/$H^+$, reflux.

part exhibited excellent anticancer activity against A549 and MCF7 cell lines, respectively.

Series of pyrazole-based quinolines (Scheme 57) were designed and screened for their antitubercular, antibacterial and antifungal activities [123]. First, the starting material 4-hydroxyquinolin-2(1*H*)-one chalcone **(168a–i)** was conveniently converted to quinoline allied pyrazole **(169a–i)** through cyclization reaction with thiosemicarbazide by microwave and conventional methods under acidic medium. Further, the bioassay revealed that the compounds containing methoxy **(169d)** and *N,N*-dimethyl aryl group at the pyrazole part **(169i)** exhibited excellent antitubercular and antibacterial activity, whereas compounds containing thiophene ring **(169g)** and furan ring **(169h)** exhibited significant antifungal activity compared to other synthesized compounds.

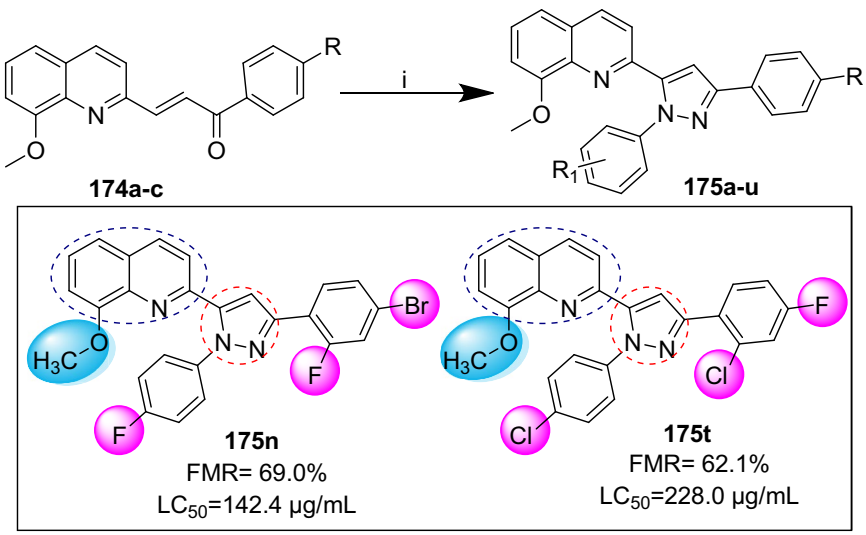
Novel quinoline allied pyrazoles (Scheme 58) were prepared as an anticancer prodrug using (*Z*)-ethyl-3-(dimethylamino)-2-(2-nitrobenzoyl)acrylate **(170)** as a precursor [124]. Initially, the quinolino-pyrazole **(171)** ring was achieved by treating the precursor with phenylhydrazine under reflux condition followed by cyclization catalyzed by the iron for quinolone formation. Then the resultant compound **(171)** was subjected to chlorination using phosphoryl chloride to get the chloroquinoline **(172)**, followed by a nucleophilic substitution reaction with 2-(3-fluorobenzyl)-2*H*-indazol-5-amine in the presence of concentrated hydrochloric acid which affords the desired pyrazole appended




**Reagents and conditions:** (i) Phenylhydrazine, n-butanol, reflux, 3 h, (ii) Fe, AcOH, 80 °C, 6 h, (iii) $POCl_3$, DMF, reflux, 3 h, (iv) 2-(3-fluorobenzyl)-2H-indazol-5 -amine, concentrated HCl, isopropanol, reflux, 4 h.

**Scheme 58** Synthesis of indazole linked quinoline allied *N*-phenyl pyrazole

**Scheme 59** Synthesis of methoxyquinoline allied *N*-aryl-pyrazole heterocycle

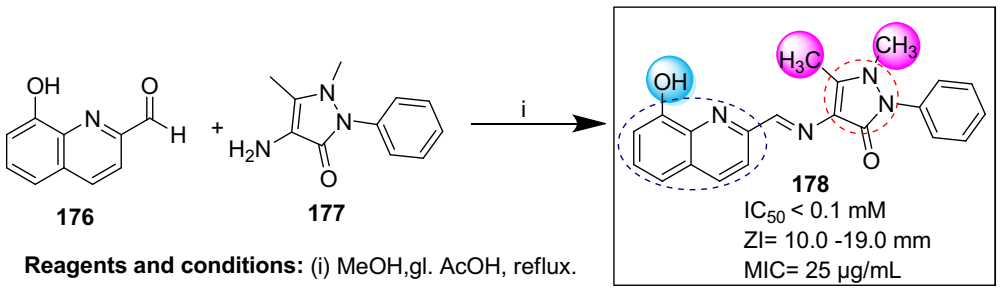



**174a-c to 175a-u** = R=$R_1$=alkyl and halo substituents,
**Reagents and conditions:** (i) Substituted phenyl hydrazine hydrochloride, $I_2$/EtOH,reflux.

quinolines **(173)**. All the newly synthesized compounds were screened for their anticancer activity which revealed that the synthesized compound **(173)** emerged as a significant pH-sensitive anticancer agent.

Novel *N*–phenylpyrazole appended 8-hydroxyquinaldines (Scheme 59) were synthesized through chalcones **(174a–c)** and tested for their insecticidal activity [125]. Initially, the chalcones **(174a–c)** were subjected to cyclization reaction by refluxing with various phenylhydrazine hydrochlorides mediated by iodine under ethanol solvent medium to get the target compound **(175a–u)** with good yield. Then all the synthesized compounds were tested for their bioassay and revealed that the compounds containing *N*-fluoroaryl, 2-fluoro-4-bromoaryl **(175n)**, and *N*-chloroaryl, 2-chloro-4-fluoroaryl **(175t)** at pyrazole part showed excellent insecticidal activity against *Mythimna separata Walker* and *Plutella xylostella Linnaeus*.

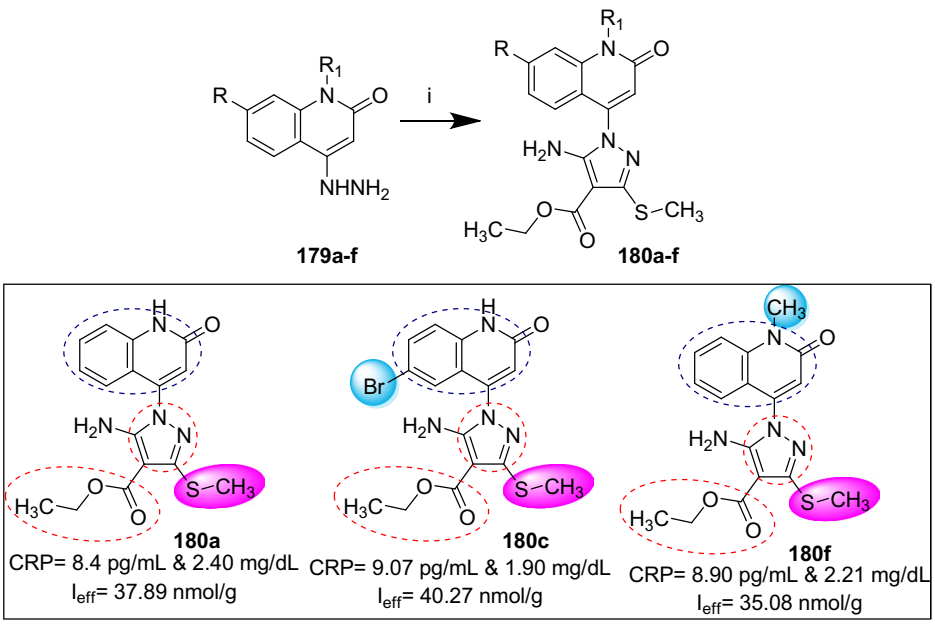
New pyrazole affixed quinoline Schiff bases (Scheme 60) were synthesized by condensing 8-hydroxyquinoline-2-carbaldehyde **(176)** with 4-aminoantipyrine **(177)** catalyzed by glacial acetic acid by using methanol as solvent [126]. Then the resultant compound was screened for antimicrobial, antioxidant and anticancer activities against MCF-7 human breast cancer cell line. The antibacterial and antifungal assay of the synthesized compound revealed that the compound **(178)** exhibited the highest activity against *M. Luteus, S. aureus, K. Pneumoniae,* and fungi *A. Niger* compared to Ampicillin and Nystatin standards. The cytotoxic effect of pyrazole appended quinoline against the MCF-7 cell line revealed that the same compound **(178)** exhibited significant inhibition. Moreover, the antioxidant property of pyrazole affixed quinoline Schiff base was studied using DPPH radical scavenging assay which showed that the compound **(178)** is




**Reagents and conditions:** (i) MeOH,gl. AcOH, reflux.

**Scheme 60** Synthesis of quinoline allied pyrazole Schiff base

**Scheme 61** Synthesis of quinoline allied *S*-methylthio-pyrazole




**179a=180a** = R=H, $R_1$=H, **179b=180b** = R=Cl, $R_1$=H, **179c=180c** = R=Br, $R_1$=H, **179d=180d** = R=$OCH_3$, $R_1$=H, **179e=180e** = R=$CH_3$, $R_1$=H, **179f=180f** = R=H, $R_1$=$CH_3$,
**Reagents and conditions:** (i) Ethyl-2-cyano-3,3-bis(methylthio)propenoate, EtOH, reflux, 10-15 h.

potent due to the presence of hydrogen transferrable phenolic group.

New series of pyrazole affixed quinolones (Scheme 61) were synthesized and tested for their antiapoptotic activity [127]. Initially, quinolones **(179a–f)** were subjected to cyclization by refluxing with 2-cyano-3,3-bis(methylthio) propenoate in ethanol solvent, yielding the target compound **(180a–f)**. Finally, the bioassay of the synthesized compounds revealed that the plane **(180a)**, bromo **(180c)** and *N*-methyl **(180f)** substituted quinolines containing pyrazole heterocycle showed the highest antiapoptotic, anti-inflammatory and antioxidant properties.

Series of quinolone-pyrazole with nitrile functional group (Scheme 62) were synthesized and tested for their cytotoxic activity against 60 cancer cell lines [128] through intermediate **(231a–f)** which was initially synthesized by the reported method [129]. The key intermediates **(231a–f)** were refluxed with ethene-1,1,2,2-tetracarbonitrile to afford the compound 1-(2-oxo-1,2-dihydroquinolin-4-yl)-1*H*-pyrazoles **(232a–f)**. Then, the bioassay of the synthesized compounds envisioned that the heterocycle containing chloro **(232e)** and bromo **(232f)** at the quinoline part exhibiting outstanding inhibitory activity against most of the cancer cell lines.

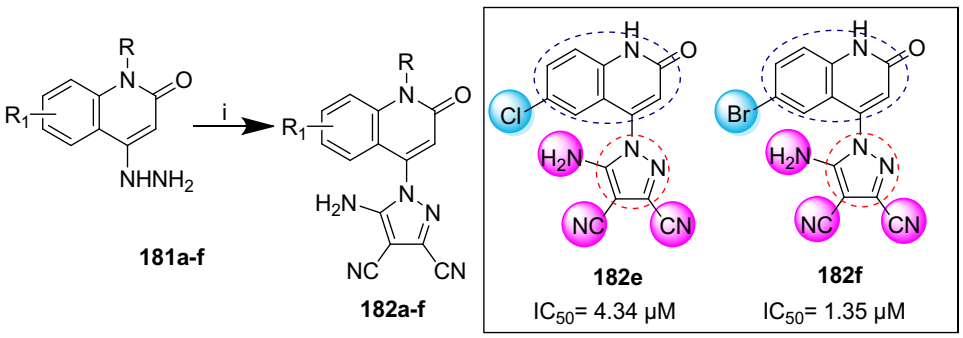
Series of quinoline affixed pyrazoles (Scheme 63) were synthesized and tested for their anticancer activity against MCF-7, HeLa and DLD1 cancer cell lines as well as normal fibroblast WI-38 [130]. Initially, the key intermediate, chalcones **(183)** were subjected to cyclization with thiosemicarbazide and hydrazine hydrate to afford the corresponding pyrazole appended quinolines **(184)**. Then the carbothioamide so obtained was further cyclized with phenacyl bromide, 3-chloropentane-2,4-diol and 2-oxo-*N*-aryl-propanehydrazonoyl chloride to afford corresponding compounds **(185a–d)** and **(186a–d)**, respectively. Finally, the compounds containing aryl group **(185a)**, electron-withdrawing fluoro **(185b)** and aryl group **(186a)** exhibited the highest antiproliferation activity compared to the other compounds.

As colorectal cancer agents, novel pyrazole appended quinolines (Scheme 64) were synthesized in a convenient method with noteworthy yield [131]. The series of novel compounds **(189a–p)** were synthesized by the coupling reaction of pyrazole acid **(188a–p)** with various quinoline amines **(187)**. Then the anti-CRC activity of the obtained compounds envisioned that the compound containing the *N*-arylbromo group at pyrazole part with amide linkage **(189c)** exhibited promising dual activity such as Wnt inhibition and AMPK activation.

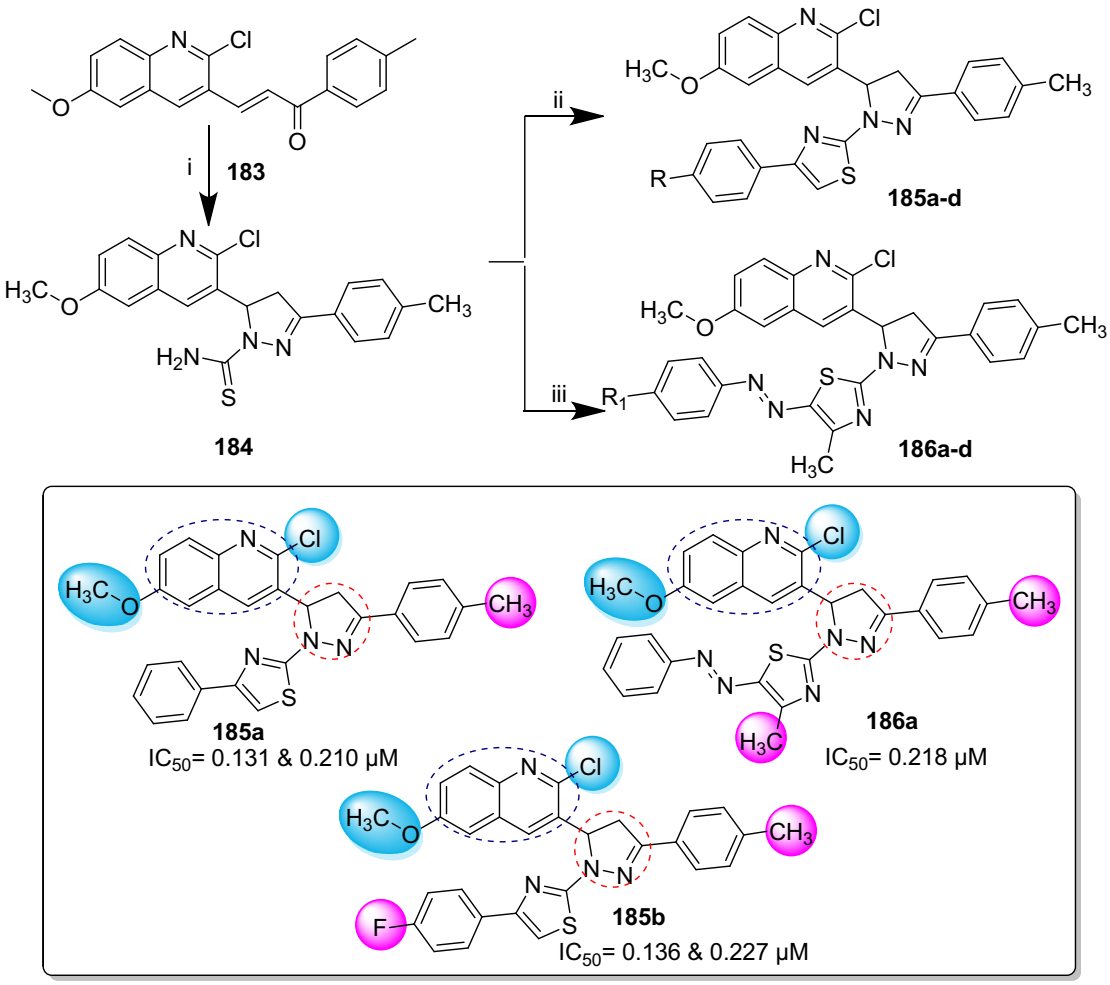
Novel pyrazole tethered quinolones (Scheme 65) were synthesized with addition to other heterocycles and screened for their TLR7 or TLR8 agonistic and antagonistic activities [132]. Initially, the key intermediate **(190a–d)** was treated with sodium hydride, phosphorus oxychloride and *N,N*-diethylaniline followed by displacement of chlorine with an amine group on treatment with ammonia to obtain the title compound containing pyrazole-tethered quinoline **(193a–d)**. Then all the synthesized compounds were tested for their TLR7 or TLR8 agonistic and antagonistic activities which envisioned that the greatest activity was shown by the compound containing butyl **(193a)** and isobutyl chain **(193b)**.

Series of novel pyrazole-appended quinoline scaffolds (Scheme 66) were synthesized as potent antimicrobial, antimalarial and antitubercular agents through Doebner reaction [133]. At first, the key intermediates **(194a–g)** were subjected to three-component one-pot synthesis with substituted aniline and pyruvic acid to afford quinoline allied pyrazoles with a carboxylic acid group **(195a–n)**, later, converted to acid chloride **(196a–g)** by treating with thionyl chloride. Then quinoline-affixed pyrazole with acid chloride **(196a–g)** functional group was subjected to a coupling reaction with *N,N*-dimethylaminoethylamine to afford the corresponding final compounds **(197a–g)**. The bioassay of the synthesized compounds envisioned that the compound containing 4-fluoro aryl at pyrazole part **(195d)** possessed excellent antibacterial and antifungal activities, whereas the compound containing 4-chlorophenyl **(197f)** possessed

**Scheme 62** Synthesis of quinolone-pyrazole with nitrile functional group



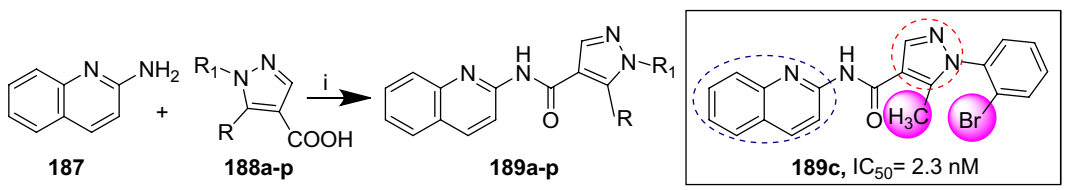

**181a=182a** = R=$R_1$=H, **181b=182b** = R=H, $R_1$=5-$CH_3$, **181c=182c** = R=H, $R_1$=6-$CH_3$, **181d=182d** = R=H, $R_1$=6-$OCH_3$, **181e=182e** = R=H, $R_1$=6-Cl, **181f=182f** = R=H, $R_1$=6-Br,
**Reagents and conditions:** (i) TCNE in ethanol, reflux, 20–24 h.




**185a** = R=H, **185b** = R=F, **185c** = R=Cl, **185d** = R=$CH_3$, **186a** = $R_1$=H, **186b** = $R_1$=Cl, **186c** = $R_1$=$CH_3$, **186d** = $R_1$=$OCH_3$,

**Reagents and conditions:** (i) Thiosemicarbazide, NaOH, EtOH, reflux, 12 h, (ii) Appropriate phenylacyl bromide, EtOH, reflux, 4h. (iii) Appropriate 2-oxo-N-arylpropanehydrazonoyl chloride, EtOH, reflux,4h.

**Scheme 63** Synthesis of quinoline allied thiazole-substituted pyrazole

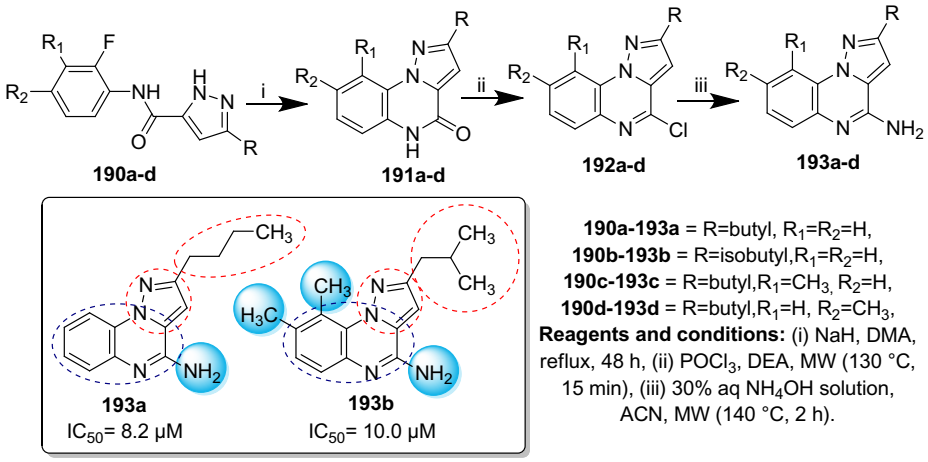



**188a=189a** = R=Me, $R_1$=Ph, **188b=189b** = R=Me, $R_1$=2-F-Ph, **188c=189c** = R=Me, $R_1$=2-Br-Ph, **188d=189d** = R=Me, $R_1$=2-Et-Ph, **188e=189e** = R=Me, $R_1$=2,6-diF-Ph, **188f=189f** = R=Me, $R_1$=2-F-6Br-Ph, **188g=189g** = R=Me, $R_1$=2,4-diF-Ph, **188h=189h** = R=Me, $R_1$=2-F-3Cl-Ph, **188i=189i** = R=Me, $R_1$=2,5-diMe-Ph, **188j=189j** = R=Me, $R_1$=2,6-diMe-Ph, **188k=189k** = R=Me, $R_1$=3-Me-Py, **188l=189l** = R=Cl, $R_1$=Ph, **188m=189m** = R=Br, $R_1$=Ph, **188n=189n** = R=Et, $R_1$=Ph, **188o=189o** = R=Pr, $R_1$=Ph, **188p=189p** = R=$MeN(CH_3)_3$, $R_1$=Ph,

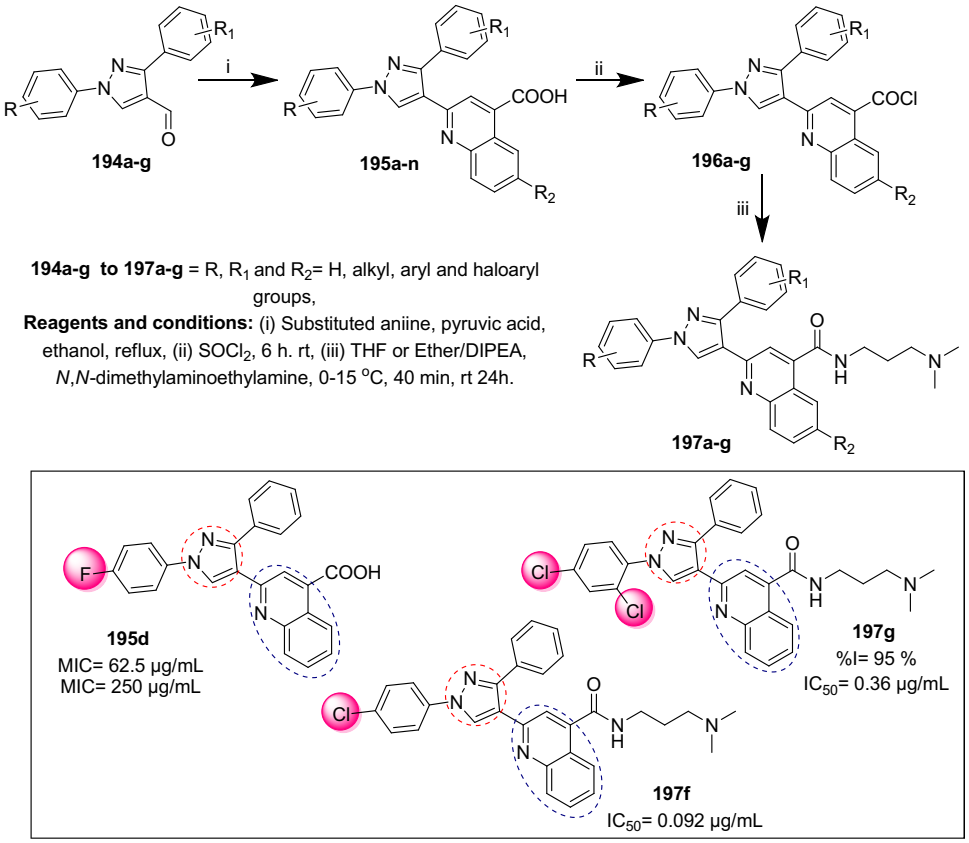
**Reagents and conditions:** (i) PyClU, DIPEA, DCE, 80 °C.

**Scheme 64** Synthesis of amide linked quinolinyl-pyrazole

**Scheme 65** Synthesis of 2-aminoquinoline allied pyrazole heterocycle



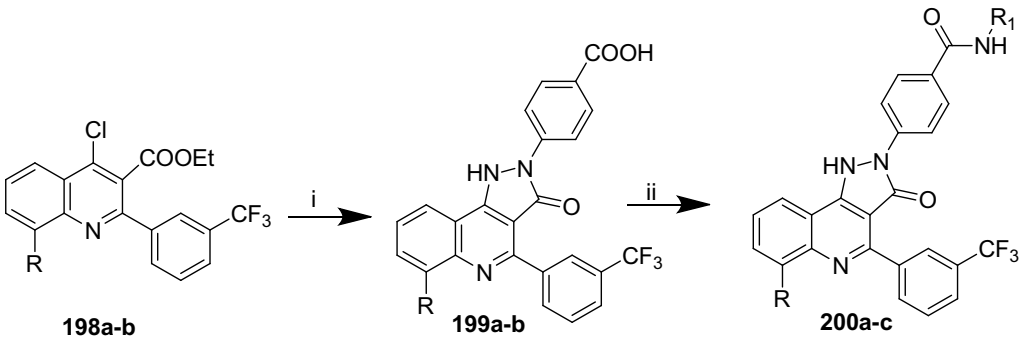

**Scheme 66** Synthesis of hydroxyl/amide-substituted quinoline allied 1,3-diaryl-pyrazole

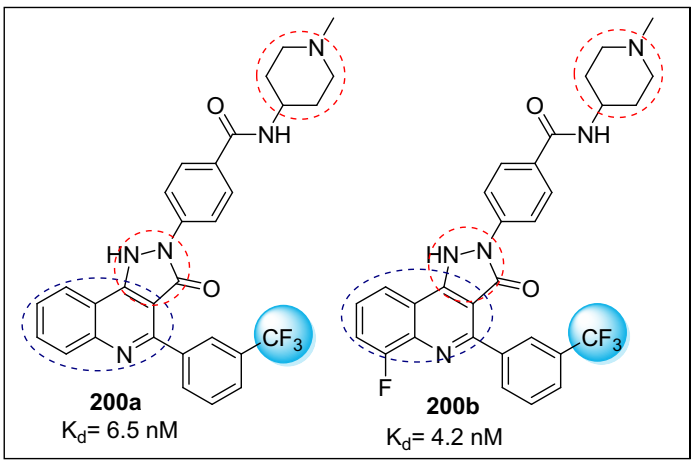



significant antimalarial activity and also the compound with 2,4-dichlorophenyl **(197g)** showed promising antituberculosis and antimalarial activities compared to other derivatives.

Series of heterocycles including quinoline-appended pyrazole (Scheme 67) were synthesized and tested for their affinity to human CD80 (hCD80) cell line and displacement of endogenous ligands [134]. Pyrazole containing quinolines were conveniently synthesized by Knorr pyrazole ring formation of the compounds **(198a–b)** with hydrazinyl benzoic acid to get **(199a–b)** derivatives and finally coupling reaction with substituted amines using EDC.HCl or HATU to get the compounds **(200a–c)**. Finally, the bioassay of the synthesized compounds **(200a–c)** through positron emission tomography (PET) revealed that the unsubstituted (**200a**) and fluoro substituted (**200b**) quinoline with pyrazole heterocycle showed excellent affinity in binding to hCD80.

Novel anticancer agents quinoline allied pyrazole positional isomers (Scheme 68) were designed through a convenient method [135]. To obtain the quinoline allied pyrazole intermediate **(202)**,




**198a=199a** = R=H, **198b=199b** = R=F, **200a** = R=H, $R_1$=piperidine derivative, **200b** = R=F, $R_1$=piperidine derivative, **200c** = R=F, $R_1$=phenyl derivative,
**Reagents and conditions:** (i) 4-Hydrazinylbenzoic acid, NaOtBu, 100 °C, ethylene glycol, 18 h, (ii) R-$NH_2$, HATU, DIPEA, rt, DMF, 30 min.

**Scheme 67** Synthesis of quinoline allied pyrazole heterocycle with piperidine ring

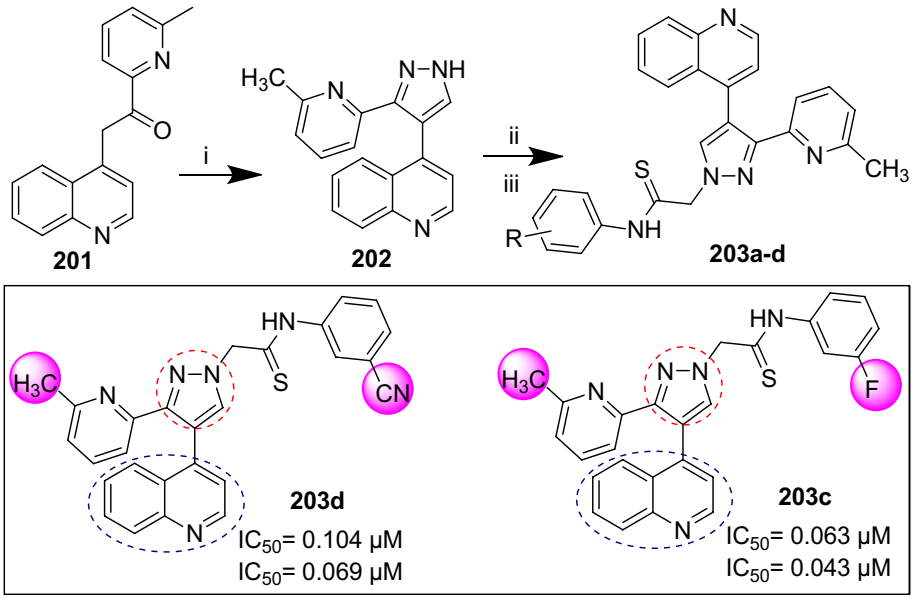
1-(6-methylpyridin-2-yl)-2-(quinolin-4-yl)ethanone **(201)** was subjected to cyclization reaction with hydrazine hydrate under dimethylformamide solvent. Then the resultant pyrazole-appended quinoline **(202)** was further subjected to *N*-alkylamidation using chlorophenylacetamides in the presence of sodium hydride, catalyzed by sodium iodide followed by thionation using Lawesson's reagent to afford the quinoline allied pyrazoles **(203a–d)** as positional isomers. All the synthesized compounds were tested for their activity against ALK5 and HIF-1α enzyme assay which revealed that the compound containing benzonitrile group attached to pyrazole ring with thioamide linkage **(203d)** effectively inhibited the activation of HIF-1α without disturbing the protein and endorsed apoptosis of HCT116 cells, whereas the compound containing fluoro aryl group **(203c)** inhibited ALK5 phosphorylation.

Novel pyrazole fused quinolines (Scheme 69) were synthesized through a one-pot three-component reaction by microwave irradiation using pyrazole amine **(204)**, aromatic aldehyde **(206a–h)** and dione **(205)** as precursors followed by dehydrogenation [136]. All the synthesized compounds **(207a–h)** were screened for antimycobacterial activity which envisioned that the plane compound **(207a)** showed excellent inhibition activity compared to other derivatives.

Conveniently, a series of quinolinyl-pyrazoles (Scheme 70) were synthesized and screened for their anti-breast cancer activity starting from 8-hydroxyquinoline **(208a–d)** and benzaldehyde hydrazone **(210a–d)**, respectively, through cyclization and *O*-alkylation [137]. Bioassay of the synthesized compounds **(209a–i)** showed that the compound holding chloro **(209b)** and bromo **(209c)** derivatives emerged as the best anticancer agents against MCF7 cell line.

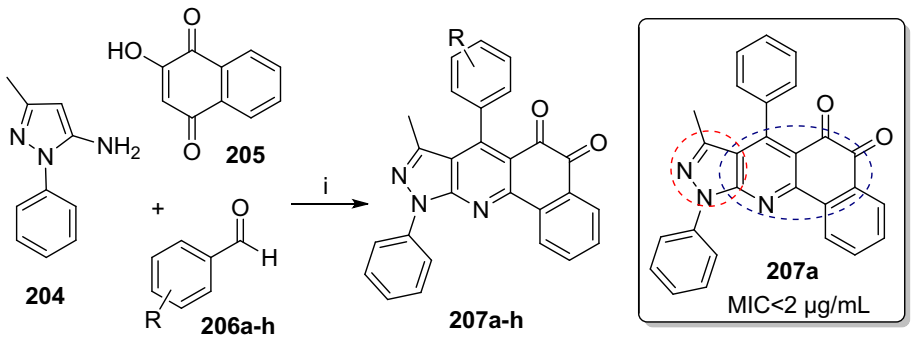
## Conclusion

Quinoline and pyrazole are mono and di-nitrogen heterocyclic ring systems, which play an important role in biological and pharmacological activities. The hybrid molecules have shown the advantage over the non-hybrid




**203a** = R=H, **203b** = R=2-F, **203c** = R=3-F, **203d=** R=3-CN,
**Reagents and conditions:** (i) (a) DMF•DMA, DMF, 80 °C, 4 h, (b) $N_2H_4$•$H_2O$, EtOH, reflux, 4 h, (ii) Substituted chlorophenylacetamides, NaI (cat.), NaH, DMF, rt, 2 h.
(iii) Lawesson's reagent, 85 °C, 4–12 h.

**Scheme 68** Synthesis of quinoline allied pyrazole heterocycle with the thioamide group

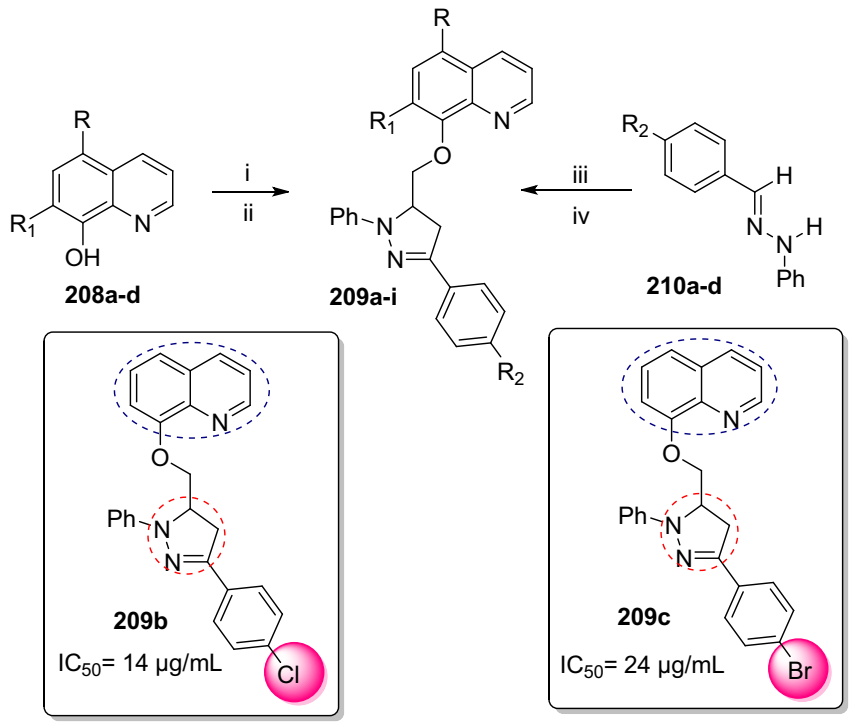



**206a=207a** = R=H, **206b=207b** = R=4$CH_3$, **206c=207c** = R=4$OCH_3$, **206d=207d** = R=3,4,5-$OCH_3$,
**206e=207e** =4-Cl, **206f=207f** =4-Br, **206g=207g** =4-F, **206h=207h** =4-$NO_2$.
**Reagents and conditions:** (i) Microwave irradiation, 3 min.

**Scheme 69** Synthesis of quinoline tethered pyrazole heterocycles

molecules and emerged as promising drug-able candidates. This review is mainly documenting the recent decennial effort in the synthesis of quinolinyl-pyrazole scaffolds, their pharmacological advantages and structure–activity relationship. This wealth of chemical and biological knowledge exhibited by the compounds will be very useful for the researcher working on these scaffolds, and it would help them to develop an innovative template in drug discovery and other pharmaceutical developments.

**Scheme 70** Synthesis of quinoline allied pyrazole heterocycles




**209a**= R=H, $R_1$=H, $R_2$= H, **209b**= R=H, $R_1$=H, $R_2$= Cl, **209c**= R=H, $R_1$=H, $R_2$=Br , **209d**= R=H, $R_1$=H, $R_2$= $OCH_3$, **209e**= R=Cl, $R_1$=H, $R_2$= H, **209f**= R=H, $R_1$=Cl, $R_2$=H, **209g**= R=Cl, $R_1$=Cl, $R_2$=H , **209h**= R=Cl, $R_1$=Cl, $R_2$= Cl, **209i**= R=Cl, $R_1$=Cl, $R_2$=$OCH_3$.

**Reagents and conditions:** (i) Allyl chloride, $K_2CO_3$, ethanol, (ii) Benzaldehyde hydrazone, CAT, (iii) Allyl chloride, CAT, ethanol, (iv) 8-Hydroxyquinoline, $K_2CO_3$, acetone.

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## Compliance with ethical standards

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

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