Synthesis, Characterization, and *In Vitro* Microbial Evaluation of Some New 4*H*-Chromene and Quinoline Derivatives of 1*H*-Pyrazole

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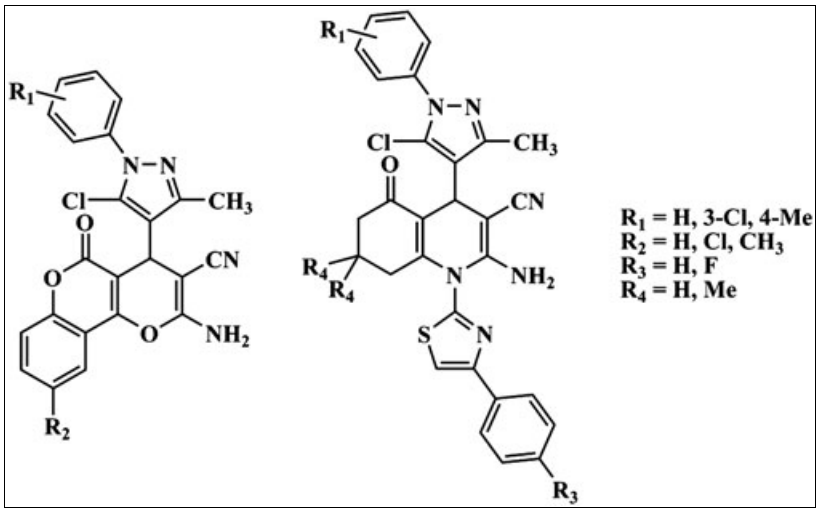

A new series of nine derivatives of 4*H*-pyrano[3,2-*c*]chromene and 12 derivatives of *N*-thiazolyl-4*H*-quinoline of 1*H*-pyrazole has been synthesized by one pot base catalyzed cyclocondensation reaction of 1*H*-pyrazole-4-carbaldehyde, malononitrile, and 4-hydroxy coumarin or β-enaminones, respectively. All the synthesized compounds were characterized by elemental analysis, FT-IR, ^{1}H NMR, ^{13}C NMR spectral data and were further screened, against a panel of pathogenic strains of bacteria and fungi.

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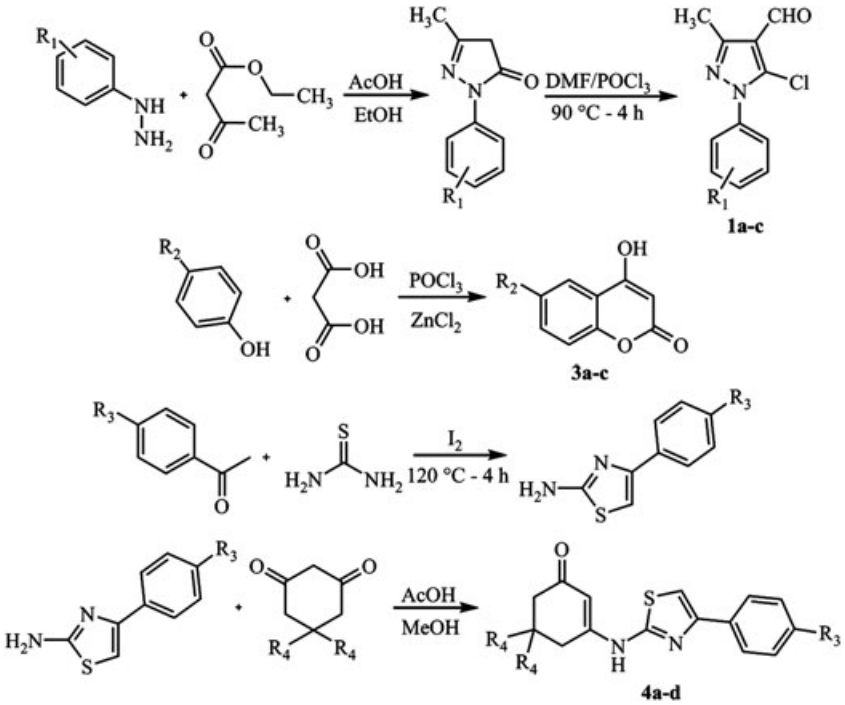
INTRODUCTION

The 4*H*-chromene nucleus is a fertile source of biologically important molecules possessing a wide spectrum of pharmacological activities, such as antimicrobial [1], antiviral [2], mutagenicity [3], antiproliferative [4], sex pheromone [5], antitumor [6], cancer therapy [7], and central nervous system activity [8]. Some of these compounds are widely employed as cosmetics and pigments and as potential biodegradable agrochemicals [9]. Moreover, Quinoline represent an important class of compounds being the main components of molecules possessing a wide spectrum of biological activities, such as antibacterial [10], anticancer [11], antimalarial [12], antiplasmodial [13], antiproliferative [14], antitumor [15], cytotoxic [16], and intrinsic activity [17]. Therefore, the synthesis of 4*H*-chromene and -quinoline derivatives has attracted us with strong interest.

In recent years, several 4 functionally substituted *N*-arylpyrazole derivatives identified as antimicrobial [18–20], anti-inflammatory (COX-2 inhibitor and ulcerogenic activity) [19], antitubercular [20], antitumor [21, 22], antiangiogenesis [22], anti-parasitic [23], antiviral [24], and also possesses analgesic and anxiolytic activity [25].

Despite their importance from pharmacological, industrial, and synthetic point of views, comparatively few studies on 4-aryl-4*H*-pyrano[3,2-*c*]chromene derivatives [26] have been reported in the presence of piperidine, morpholine, K_2CO_3, diammonium hydrogen phosphate, $H_6[P_2W_{18}O_{62}]\cdot 18H_2O$, tetrabutylammonium bromide, and water. Similarly, 1,4-diaryl-4*H*-quinoline derivatives [27] reported in the presence of piperidine, pyridine, DMAP, TBAF, TEBAC, [bmim$^+$][BF_4^-] and microwave irradiation, wherein not a single reference has been found for 4-heteryl-4*H*-pyrano[3,2-*c*]chromene or 1,4-diheteryl-4*H*-quinoline derivatives. In view of biological significance of 4*H*-chromene and -quinoline, a modification on the 4-position on 4*H*-pyrano[3,2-*c*]chromene by 1*H*-pyrazole-4-carbaldehydes and likewise modification on the 1 and 4-position on 4*H*-quinoline by thiazole and 1*H*-pyrazole-4-carbaldehydes, respectively may bring significant changes in pharmacological activities and may provide new classes of therapeutically active compounds, with this hope and as

Scheme 1. Synthetic pathway for the intermediates **1a-c**, **3a-c**, and **4a-d**.



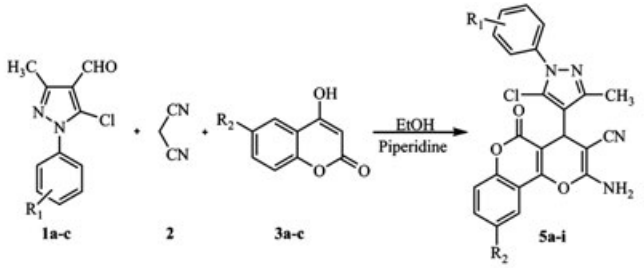
part of our current studies in developing new antimicrobial agents [27a, 27c, 28] containing 4*H*-chromene, *N*-aryl (heteryl)-4*H*-quinoline, thiazole, and 1*H*-pyrazole-4-carbaldehyde derivatives, we have prepared and report herein 4-pyrazolyl-4*H*-chromene **5a-i** and *N*-thiazolyl-4-pyrazolyl-4*H*-quinoline **6a-l** derivatives *via* MCR approach i.e., one pot base catalyzed cyclocondensation reaction of 1*H*-pyrazole-4-carbaldehydes, malononitrile, and 4-hydroxycoumarin or β-thiazolylenaminone. The constitution of all the products was characterized using elemental analysis, FT-IR, ^{1}H NMR, and ^{13}C NMR spectrometry and were subjected to *in vitro* antimicrobial study against eight human pathogens, of which three gram-positive bacterial pathogens *Streptococcus pneumoniae*, *Clostridium tetani*, *Bacillus subtilis*, three Gram-negative bacterial pathogens *Salmonella typhi*, *Vibrio cholerae*, *Escherichia coli* and two fungal pathogens *Aspergillus fumigatus* and *Candida albicans*, using broth microdilution MIC (Minimum Inhibitory Concentration) method [29].

RESULTS AND DISCUSSION

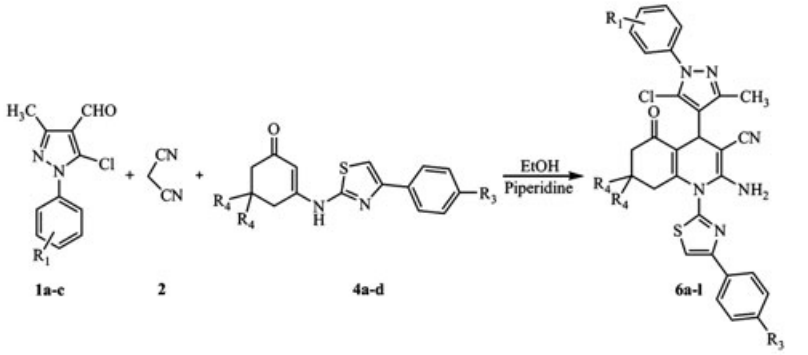
Chemistry. In continuation of our interest on synthesizing biologically active heterocyclic derivatives [27a, 27c, 28], we report herein series of 4-pyrazolyl-4*H*-chromene **5a-i** and *N*-thiazolyl-4-pyrazolyl-4*H*-quinoline **6a-l** derivatives synthesized by one pot three component cyclocondensation reaction of 1-aryl-5-chloro-3-methyl-1*H*-pyrazole-4-carbaldehyde **1a-c**, malononitrile **2** and 4-hydroxy-6-substituted-2*H*-chromen-2-one **3a-c** or 3-(4-arylthiazol-2-ylamino)-5,5-disubstitutedcyclohex-2-enone **4a-d**. Solid phase reaction of 4-substitutedacetophenone, thiourea and iodine for 4 h at 120°C afford to give 2-amino-4-arylthiazole [30]. The required β-enaminones **4a-d** were prepared [28a] by the reaction β-diketone with 2-amino-4-arylthiazole by refluxing in methanol in presence of catalytic amount of acetic acid. Moreover, Vilsmeier-Haack reaction of 1-aryl-3-methyl-1*H*-pyrazol-5(4*H*)-one lead to chloroformylation to give required 1-aryl-5-chloro-3-methyl-1*H*-pyrazole-4-carbaldehyde **1a-c** [31]**.** The 4-hydroxy-6-substituted-2*H*-chromen-2-ones **3a-c** [32] was prepared by solid phase reaction of malonic acid, phenol and phosphorous oxychloride, and zinc chloride (Scheme 1).

To obtain the title 4*H*-chromene and -quinoline derivatives **5a-i** and **6a-l**, according to literature survey, the reaction was carried out in aqueous media under neutral conditions but failed to proceed even on prolong refluxing. The reaction was tried under microwave irradiation, but not succeeded. The reaction proceeded under basic conditions such as pyridine, morpholine, K_2CO_3, and DMAP, but required prolong refluxing and resulted only in poor yield. Finally, upon refluxing the reaction mixture in ethanol for 6 h in the presence of piperidine as basic catalyst gave

Scheme 2. Synthesis of various substituted 4*H*-chromene **5a-i** and *N*-thiazolylquinoline **6a-l** derivatives of 1*H*-pyrazole.



Compd	5a	5b	5c	5d	5e	5f	5g	5h	5i
R_1	H	3-Cl	4-Me	H	3-Cl	4-Me	H	3-Cl	4-Me
R_2	H	H	H	Cl	Cl	Cl	Me	Me	Me



Compd	6a	6b	6c	6d	6e	6f	6g	6h	6i	6j	6k	6l
R_1	H	3-Cl	4-Me	H	3-Cl	4-Me	H	3-Cl	4-Me	H	3-Cl	4-Me
R_3	H	H	H	H	H	H	F	F	F	F	F	F
R_4	H	H	H	Me	Me	Me	H	H	H	Me	Me	Me

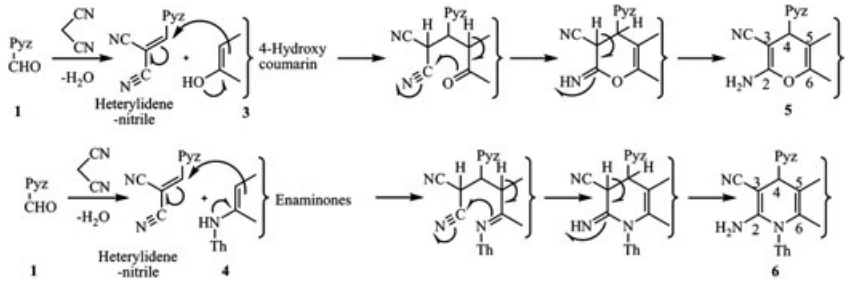
moderate to good yield (58–78%) (Scheme 2). Hence, these conditions were considered as the most optimized conditions for the synthesis of title derivatives 4*H*-chromene and -quinoline derivatives **5a-i** and **6a-l**.

A mechanism for the formation of the 4*H*-chromene and -quinoline derivatives **5a-i** and **6a-l** is outlined in Scheme 3. The reaction occurs *via* an *in situ* initial formation of the heterylidenenitrile, containing the electron-poor C C double bond, from the Knoevenagel condensation between pyrazole-4-carbaldehyde and malononitrile by loss of water molecules. Finally, Michael addition of **3** or **4** to the initially formed unsaturated nitrile, i.e., nucleophilic attack of hydroxyl moiety or enaminone to the cyano moiety affords cyclized 4*H*-chromene **5a-i** or 4*H*-quinoline derivatives **6a-l.**

The structures of all the new compounds were established by ^{1}H NMR, ^{13}C NMR, and FT-IR spectrometry. ^{1}H NMR (DMSO-d_6) spectrum of 4*H*-chromene derivatives **5a-i** exhibited a singlet around δ 4.52–4.64 for methine (H4) and 7.28–7.46 ppm for amine protons (NH_2), respectively. A singlet around 2.21–2.28 ppm stands for methyl of pyrazole ring. Aromatic protons resonate as multiplets appeared at around δ 7.31–8.05 ppm. ^{13}C NMR of **5a-i** exhibited a signal around δ 12.51–12.63 and 27.32–27.42 ppm stands for methyl of pyrazole (pyz-CH_3) and methine carbon (C4), respectively. All the aromatic carbons showed signals around δ 101.28–158.94 ppm and the distinctive peak around δ 160.00–160.10 ppm is of carbonyl carbon (C5) confirms the structure **5a-i**. The IR spectrum of compounds **5a-i** exhibited characteristic absorption band around 3460–3260 cm^{-1} (asym. and sym. str.) for amine, 2210–2190 cm^{-1} for cyanide (CN) and 1705–1680 cm^{-1} for carbonyl (C O) group, respectively supports the formation of **5a-i**.

Similarly, ^{1}H NMR (DMSO-d_6) spectrum of 4*H*-quinoline derivatives **6a-l** exhibited a singlet around δ 4.56–4.64 for methine and 5.94–6.10 ppm for amine, respectively. A singlet around δ 2.31–2.38 ppm stands for methyl of pyrazole ring. Aromatic protons resonate as multiplets appeared at around δ 7.29–8.10 ppm and a deshielded singlet, apart from aromatic multiplets, around δ 8.27–8.42 ppm is of H5 of thiazole ring. ^{13}C NMR of **6a-l** exhibited a

Scheme 3. Plausible mechanistic pathway for the 4*H*-chromene **5a-i** and *N*-thiazolylquinoline **6a-l** derivatives of 1*H*-pyrazole.



signal around δ 12.82–13.04 and 25.01–29.72 ppm stands for methyl of pyrazole (pyz-CH_3) and methine carbon (C4), respectively. All the aromatic carbons showed signals around δ 111.67–166.18 ppm and the distinctive peak around δ 195.51–196.48 ppm is of carbonyl carbon (C5) confirms the structure **6a-l**. The IR spectrum of compounds **6a-l** exhibited characteristic absorption band around 3455–3320 cm^{-1} (asym. and sym. str.) for amine, 2210–2175 cm^{-1} for cyanide (CN) and 1695–1660 cm^{-1} for carbonyl (C O) group, respectively supports the formation of **6a-l**.

The obtained elemental analyses of **5a-i** and **6a-l** values are in good agreement with theoretical data. The structures of all new synthesized compounds were well supported by ^{1}H NMR, ^{13}C NMR, and FT-IR spectral data and the molecular weight of compounds was confirmed by mass spectrometry. All spectroscopic data are provided in the Experimental section. In addition, all compounds were screened for their antibacterial and antifungal activity.

Antimicrobial screening. The *in vitro* antimicrobial activity of all the compounds and standard drugs were assessed against three representative of Gram-positive bacteria *viz*. *Streptococcus pneumoniae* (MTCC 1936), *Clostridium tetani* (MTCC 449), *Bacillus subtilis* (MTCC 441), three Gram-negative bacteria *viz*. *Salmonella typhi* (MTCC 98), *Vibrio cholerae* (MTCC 3906), *Escherichia coli* (MTCC 443) and two fungi *viz*. *Aspergillus fumigatus* (MTCC 3008) *and Candida albicans* (MTCC 227) by the Broth Microdilution MIC method recommended by National Committee for Clinical Laboratory Standards (NCCLS). The strains employed for the activity were procured from (MTCC—micro type culture collection) Institute of Microbial Technology, Chandigarh. Inoculum size for test strain was adjusted to 10^8 CFU mL^{-1} (Colony Forming Unit per milliliter) by comparing the turbidity (turbidimetric method). Mueller Hinton Broth was used as nutrient medium to grow and dilute the compound suspension for the test bacteria and Sabouraud Dextrose Broth used for fungal nutrition. Ampicillin, Chloramphenicol, Ciprofloxacin, Gentamicin, and Norfloxacin were used as standard antibacterial drugs, whereas griseofulvin and nystatin was used as standard antifungal drugs. DMSO was used as diluents/vehicle to get desired concentration of synthesized compounds and standard drugs to test upon standard microbial strains. Serial dilutions were prepared in primary and secondary screening. Each compound and standard drugs were diluted obtaining 2000 μg mL^{-1} concentration, as a stock solution. In primary screening 1000, 500, and 250 μg mL^{-1} concentrations of the synthesized compounds were taken. The active compounds found in this primary screening were further diluted to obtain 200, 100, 62.5, 50, 25, 12.5, and 6.250 μg mL^{-1} concentrations for secondary screening to test in a second set of dilution against all microorganisms. The control tube containing no antibiotic is immediately sub cultured [before inoculation] by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism. The tubes are then put for incubation at 37°C for 24 h for bacteria and 48 h for fungi. The highest dilution (lowest concentration) preventing appearance of turbidity is considered as minimal inhibitory concentration (MIC, μg mL^{-1}) i.e., the amount of growth from the control tube before incubation (which represents the original inoculum) is compared. A set of tubes containing only seeded broth and the solvent controls were maintained under identical conditions so as to make sure that the solvent had no influence on strain growth. The result of this is much affected by the size of the inoculum. The test mixture should contain 10^8 CFU mL^{-1} organisms. The protocols were summarized in Table 1 as the minimal inhibitory concentration (MIC, μg mL^{-1}).

The examination of the data (Table 1) reveals that majority of the compounds showed antibacterial and antifungal activity when compared with standard drugs ampicillin and griseofulvin. Compounds **5d** (R_1 = H, R_2 = Cl), **5e** (R_1 = 3-Cl, R_2 = Cl), **6i** (R_1 = 4-Me, R_3 = F, R_4 = H), and **6j** (R_1 = H, R_3 = F, R_4 = Me) were found to be highly potent against most of the employed strains to inhibit the growth of organism. In particular, Against Gram-positive

Table 1

Antimicrobial activity of the compounds **5a-i** and **6a-l**.

	Minimum inhibitory concentration (MIC, μg mL^{-1})							
	Gram-positive bacteria			Gram-negative bacteria			Fungi	
	S. p.	*C. t.*	*B. s.*	*S. t.*	*V. c.*	*E. c.*	*A. f.*	*C. a.*
Compds	MTCC (1936)	MTCC (449)	MTCC (441)	MTCC (98)	MTCC (3906)	MTCC (443)	MTCC (3008)	MTCC (227)
5a	500	500	500	200	500	500	500	**500**
5b	500	**250**	**250**	200	250	250	1000	**500**
5c	250	500	500	500	200	500	>1000	**250**
5d	500	**200**	**250**	**100**	250	**100**	>1000	**500**
5e	150	**100**	**62.5**	**100**	200	150	100	**100**
5f	500	**250**	500	200	500	250	500	1000
5g	500	**250**	500	250	500	500	1000	**500**
5h	1000	**250**	**250**	500	250	1000	>1000	1000
5i	500	**250**	**250**	1000	200	500	500	**500**
6a	1000	**250**	1000	500	250	1000	1000	1000
6b	**100**	500	**50**	200	1000	500	1000	1000
6c	**100**	**250**	500	500	250	**100**	>1000	>1000
6d	200	**250**	500	**100**	250	500	>1000	>1000
6e	500	500	500	500	500	500	500	**500**
6f	500	**100**	1000	200	**100**	500	500	1000
6g	**100**	500	**150**	250	250	**100**	>1000	>1000
6h	500	**200**	500	500	200	500	500	**500**
6i	200	1000	**100**	**100**	1000	**50**	>1000	**500**
6j	500	1000	**100**	**100**	1000	**100**	>1000	**500**
6k	500	**250**	**100**	500	500	1000	1000	1000
6l	500	500	1000	500	1000	500	1000	1000
Ampi.	**100**	**250**	**250**	**100**	**100**	**100**	–	–
Chlora.	**50**	**50**	**50**	**50**	**50**	**50**	–	–
Cipro.	**50**	**100**	**50**	**25**	**25**	**25**	–	–
Genta.	**0.5**	**5**	**1**	**5**	**5**	**0.05**	–	–
Grise.	–	–	–	–	–	–	**100**	**500**
Nyst.	–	–	–	–	–	–	**100**	**100**

Ampi.: Ampicillin, Chlora.: Chloramphenicol, Cipro.: Ciprofloxacin, Genta.: Gentamicin, Grise.: Griseofulvin, Nyst.: Nystatin, *S. p.: Streptococcus pneumoniae, C. t.: Clostridium tetani, B. s.: Bacillus subtilis, S. t.: Salmonella typhi, V. c.: Vibrio cholerae, E. c.: Escherichia coli, A. f.: Aspergillus fumigatus, C. a.: Candida albicans*.

pathogen *S. pneumoniae*, compounds **6b** (R_1 = 3-Cl, R_3 = H, R_4 = H)**, 6c** (R_1 = 4-Me, R_3 = H, R_4 = H) and **6g** (R_1 = H, R_3 = F, R_4 = H) were found to exhibit comparable activity, to ampicillin (MIC = 100 μg mL^{-1}). The compounds **5d** (R_1 = H, R_2 = Cl)**, 5e** (R_1 = 3-Cl, R_2 = Cl)**, 6f** (R_1 = 4-Me, R_3 = H, R_4 = Me), and **6h** (R_1 = 3-Cl, R_3 = F, R_4 = H) found to be more efficient (MIC < 250 μg mL^{-1}) whereas, **5b** (R_1 = 3-Cl, R_2 = H)**, 5f** (R_1 = 4-Me, R_2 = Cl)**, 5g** (R_1 = H, R_2 = Me)**, 5h** (R_1 = 3-Cl, R_2 = Me)**, 5i** (R_1 = 4-Me, R_2 = Me)**, 6a** (R_1 = H, R_3 = H, R_4 = H)**, 6c** (R_1 = 4-Me, R_3 = H, R_4 = H)**, 6d** (R_1 = H, R_3 = H, R_4 = Me) and **6k** (R_1 = 3-Cl, R_3 = F, R_4 = Me) was found equally potent to ampicillin (MIC = 250 μg mL^{-1}), toward *C. tetani*. The compounds **5e** (R_1 = 3-Cl, R_2 = Cl)**, 6b** (R_1 = 3-Cl, R_3 = H, R_4 = H)**, 6g** (R_1 = H, R_3 = F, R_4 = H)**, 6i** (R_1 = 4-Me, R_3 = F, R_4 = H)**, 6j** (R_1 = H, R_3 = F, R_4 = Me), and **6k** (R_1 = 3-Cl, R_3 = F, R_4 = Me) shows better activity (MIC < 250 μg mL^{-1}) where as, **5b** (R_1 = 3-Cl, R_2 = H)**, 5d** (R_1 = H, R_2 = Cl)**, 5h** (R_1 = 3-Cl, R_2 = Me), and **5i** (R_1 = 4-Me, R_2 = Me) found equally potent (MIC = 250 μg mL^{-1}), to ampicillin, against *B. subtilis*. Toward Gram-negative strain *S. typhi*, compounds **5d** (R_1 = H, R_2 = Cl)**, 5e** (R_1 = 3-Cl, R_2 = Cl)**, 6d** (R_1 = H, R_3 = H, R_4 = Me)**, 6i** (R_1 = 4-Me, R_3 = F, R_4 = H), and **6j** (R_1 = H, R_3 = F, R_4 = Me) were equally active to ampicillin (MIC = 100 μg mL^{-1}). The only Compound **6f** (R_1 = 4-Me, R_3 = H, R_4 = Me) found equipotent to ampicillin (MIC = 100 μg mL^{-1}) against *V. cholerae*. The compound **6i** (R_1 = 4-Me, R_3 = F, R_4 = H) shows better (MIC < 100 μg mL^{-1}) and **5d** (R_1 = H, R_2 = Cl)**, 6c** (R_1 = 4-Me, R_3 = H, R_4 = H)**, 6g** (R_1 = H, R_3 = F, R_4 = H), and **6j** (R_1 = H, R_3 = F, R_4 = Me) were found to exhibit comparable activity to ampicillin (MIC = 100 μg mL^{-1}) toward *E. coli*.

Against fungal pathogen *C. albicans*, compound **5c** (R_1 = 4-Me, R_2 = H) and **5e** (R_1 = 3-Cl, R_2 = Cl) found better

active (MIC < 500 μg mL^{-1}) where as, **5a** (R_1 = H, R_2 = H), **5b** (R_1 = 3-Cl, R_2 = H), **5d** (R_1 = H, R_2 = Cl), **5g** (R_1 = H, R_2 = Me), **5i** (R_1 = 4-Me, R_2 = Me), **6e** (R_1 = 3-Cl, R_3 = H, R_4 = Me), **6h** (R_1 = 3-Cl, R_3 = F, R_4 = H), **6i** (R_1 = 4-Me, R_3 = F, R_4 = H) and **6j** (R_1 = H, R_3 = F, R_4 = Me) were found to be equipotent compared to the standard griseofulvin (MIC = 500 μg mL^{-1}). None of the tested compounds found to be potent against fungal strain, *A. fumigatus*, compared to the standard drug griseofulvin. The remaining compounds showed moderate to good activity to inhibit the growth of bacterial pathogens and are all less effective than standard drugs.

The investigation of the structure–activity relationship of antibacterial screening revealed that the chloro substituted compounds (5b, 5d, 5e, 5f, 5h, 6h, 6k) gave better results against *C. tetani*, *B. subtilis*, and *E. coli*. Similarly, toward *B. subtilis*, compound (6b) containing chloro substituted phenyl ring in pyrazole were found to be most potent. Moreover, compounds (5h, 5i, 6f, 6i, 6j, 6k) with methyl substituted phenyl ring in pyrazole have exhibited better activity against *C. tetani* and *B. subtilis*. Antifungal evaluation results revealed none of the effect of the presence of particular group.

From antimicrobial screening results, it is interesting to note that a minor alteration in the molecular configuration of the investigated compounds may have a pronounced effect on antimicrobial activity.

CONCLUSION

A new series of substituted 4-pyrazolyl-pyrano[3,2-*c*] chromene **5a-i** and 4-pyrazolyl-*N*-thiazolylquinoline **6a-l** derivatives has been synthesized *via* MCR approach and characterized through elemental and spectral analysis. This synthetic strategy allows the construction of relatively complicated nitrogen and oxygen containing fused heterocyclic system as well as the introduction of various heteryl substitutions into 1 and 4-position of chromene and quinoline system. It can be concluded from antimicrobial screening (Table 1), against panel of human pathogens, that most of the synthesized chromene and quinoline derivatives was found to be highly active, compared to the standard drugs, against bacterial pathogens. Among them, many compounds were found to be the most active against *Bacillus subtilis* and *Clostridium tetani* compared to rest of the employed species. Antifungal activity of the compounds shows that most of the compounds found to be potent against *C. albicans* compared to *A. fumigatus*. It is worth mentioning that minor changes in molecular configuration of these compounds profoundly influence the antimicrobial activity. Further, synthetic work to intensify the potency of these derivatives by changing molecular configuration is in progress at our laboratory. The present study throws light on the identification of this new structural class as antimicrobials which can be of interest for further detailed preclinical investigations.

EXPERIMENTAL

Phenyl hydrazine was distilled before used; all other reagents were commercially available used without further purification. Solvents used were of analytical grade. All melting points were taken in open capillaries and are uncorrected. Thin-layer chromatography (TLC, on aluminum plates precoated with silica gel, $^{60}F_{254}$, 0.25 mm thickness) (Merck, Darmstadt, Germany) was used for monitoring the progress of all reactions, purity, and homogeneity of the synthesized compounds; eluent-toluene:ethyl acetate = 7:3. UV radiation and/or iodine were used as the visualizing agents. Elemental analysis (% C, H, N) was carried out by Perkin-Elmer 2400 series-II elemental analyzer (Perkin-Elmer, USA) and all compounds are within ±0.4% of theory specified. The IR spectra were recorded in KBr on a Perkin-Elmer Spectrum GX FT-IR Spectrophotometer (Perkin-Elmer, USA) and only the characteristic peaks are reported in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker Avance 400F (MHz) spectrometer (Bruker Scientific Corporation, Switzerland) using solvent peak as internal standard at 400 and 100 MHz, respectively. Chemical shifts are reported in parts per million (ppm). Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer (Shimadzu, Tokyo, Japan). Required 1-aryl-5-chloro-3-methyl-1*H*-pyrazole-4-carbaldehyde **1a-c** was prepared, according to literature procedure [31], by Vilsmeier–Haack reaction of 1-aryl-3-methyl-1*H*-pyrazol-5(4*H*)-one lead to chloroformylation to give 1-aryl-5-chloro-3-methyl-1*H*-pyrazole-4-carbaldehyde **1a-c** (Scheme 1). The 4-hydroxycoumarin (4-hydroxy-6-substituted-2*H*-chromen-2-one) **3a-c** was synthesized, according to literature method [32], by solid phase reaction of malonic acid, phenol and phosphorous oxychloride, and zinc chloride (Scheme 1). Solid phase reaction of 4-substitutedacetophenone, thiourea, and iodine for 4 h at 120°C afford to give 2-amino-4-arylthiazole [30]. The 3-(4-Arylthiazol-2-ylamino)-5,5-disubstitutedcyclohex-2-enone **4a-d** were synthesized by the reaction β-diketone with 2-amino-4-arylthiazole by refluxing in methanol in presence of catalytic amount of acetic acid [28a].

General procedure. ***2-Amino-4-(5-chloro-3-methyl-1-aryl-1H-pyrazol-4-yl)-9-(un)substituted-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (5a-i).*** A mixture of appropriate 1H-pyrazole-4-carbaldehyde 1a-c (30 mmol), malononitrile 2 (30 mmol), and 2H-chromen-2-ones 3a-c (30 mmol) in ethanol (20 mL) containing three drops of piperidine was slowly heated and refluxed with stirring for 3–4 h. On completion of reaction, monitored by TLC (ethyl acetate:toluene = 3:7), the reaction mixture was cooled to room temperature and the solid was collected by suction filtration and washed with mixture of chloroform and methanol (1:1) to obtain the pure compounds 5a-i. Physical, analytical and spectroscopic characterization data of the compounds 5a-i are given hereafter:

2-Amino-4-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (5a). This compound was obtained as colorless solid, 980 mg (76 %), Mp 217–219 °C; IR (KBr): 3405 and 3290 (NH_2), 2195 (CN), 1680 (CO); ^1H NMR (400 MHz, DMSO-d_6): δ 2.28 (s, 3H, CH_3), 4.53 (s, 1H, H4), 7.29 (s, 2H, NH_2), 7.32–8.01 (m, 9H, aromatic protons); ^{13}C NMR (100 MHz, DMSO-d_6): 12.54 (CH_3), 27.40 (C4), 55.35 (C3), 119.54 (CN), 102.10, 114.80, 117.99, 121.71,

123.78, 124.27, 125.62, 126.06, 130.13, 132.34, 133.45, 135.21, 148.43, 153.52, 155.64 (aromatic carbons), 158.83 (C2), 160.08 (C5); MS *m/z*: 430.7 $[M]^+$, 432.7 $[M+2]^+$; *Anal*. Calcd. for $C_{23}H_{15}ClN_4O_3$: C, 64.12; H, 3.51; N, 8.23. Found: C, 63.90; H, 3.79; N, 7.96.

2-Amino-4-(5-chloro-1-(3-chlorophenyl)-3-methyl-1H-pyrazol-4-yl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (5b). This compound was obtained as colorless solid, 960 mg (69 %), Mp 256–258°C; IR (KBr): 3390 and 3320 (NH_2), 2200 (CN), 1700 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.25 (s, 3H, CH_3), 4.62 (s, 1H, H4), 7.46 (s, 2H, NH_2), 7.49–7.91 (m, 8H, aromatic protons); ^{13}C NMR (100 MHz, DMSO-d_6): 12.56 (CH_3), 27.32 (C4), 55.27 (C3), 119.59 (CN), 101.87, 113.10, 117.15, 118.96, 122.98, 123.52, 124.70, 125.25, 125.67, 128.48, 131.31, 133.55, 133.87, 139.17, 149.20, 152.62, 154.00 (aromatic carbons), 158.91 (C2), 160.00 (C5); MS *m/z*: 464.8 $[M]^+$, 466.6 $[M+2]^+$; *Anal*. Calcd. for $C_{23}H_{14}Cl_2N_4O_3$: C, 59.37; H, 3.03; N, 12.04. Found: C, 59.61; H, 2.83; N, 11.87.

2-Amino-4-(5-chloro-3-methyl-1-p-tolyl-1H-pyrazol-4-yl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (5c). This compound was obtained as colorless solid, 840 mg (63%), Mp 228–230°C; IR (KBr): 3415 and 3325 (NH_2), 2190 (CN), 1690 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H, pyz-CH_3), 2.34 (tolyl-CH_3), 4.64 (s, 1H, H4), 7.40 (s, 2H, NH_2), 7.46–7.89 (m, 8H, aromatic protons); ^{13}C NMR (100 MHz, DMSO-d_6): 12.57 (pyz-CH_3), 20.54 (tolyl-CH_3), 27.39 (C4), 55.24 (C3), 119.52 (CN), 101.28, 112.19, 114.23, 115.40, 117.65, 123.10, 125.28, 126.73, 127.15, 130.56, 132.83, 135.19, 148.00, 153.69, 155.49 (aromatic carbons), 158.82 (C2), 160.10 (C5); MS *m/z*: 444.9 $[M]^+$, 446.8 $[M+2]^+$; *Anal*. Calcd. for $C_{24}H_{17}ClN_4O_3$: C, 64.80; H, 3.85; N, 12.59. Found: C, 65.12; H, 4.05; N, 12.33.

2-Amino-9-chloro-4-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (5d). This compound was obtained as pale yellow solid, 935 mg (67%), Mp 254–256°C; IR (KBr): 3420 and 3305 (NH_2), 2205 (CN), 1690 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.27 (s, 3H, CH_3), 4.55 (s, 1H, H4), 7.36 (s, 2H, NH_2), 7.41–7.93 (m, 8H, aromatic protons); ^{13}C NMR (100 MHz, DMSO-d_6): 12.60 (CH_3), 27.32 (C4), 55.41 (C3), 119.49 (CN), 101.69, 111.12, 114.09, 115.75, 116.85, 124.77, 125.45, 126.59, 129.00, 132.92, 134.63, 137.53, 148.84, 152.05, 155.25 (aromatic carbons), 158.81 (C2), 160.05 (C5); MS *m/z*: 464.6 $[M]^+$, 466.6 $[M+2]^+$; *Anal*. Calcd. for $C_{23}H_{14}Cl_2N_4O_3$: C, 59.37; H, 3.03; N, 12.04. Found: C, 59.59; H, 2.87; N, 11.80.

2-Amino-9-chloro-4-(5-chloro-1-(3-chlorophenyl)-3-methyl-1H-pyrazol-4-yl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (5e). This compound was obtained as pale yellow solid, 1095 mg (73%), Mp 237–239°C; IR (KBr): 3390 and 3295 (NH_2), 2190 (CN), 1705 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.24 (s, 3H, CH_3), 4.57 (s, 1H, H4), 7.28 (s, 2H, NH_2), 7.35–8.05 (m, 7H, aromatic protons); ^{13}C NMR (400 MHz, DMSO-d_6): 12.51 (CH_3), 27.38 (C4), 55.57 (C3), 119.47 (CN), 102.18, 115.75, 117.29, 119.44, 122.94, 124.64, 125.01, 127.87, 128.24, 130.86, 131.16, 134.47, 136.69, 139.57, 149.72, 153.21, 154.12 (aromatic carbons), 158.92 (C2), 160.02 (C5); MS *m/z*: 500.5 $[M]^+$, 502.5 $[M+2]^+$; *Anal*. Calcd. for $C_{23}H_{13}Cl_3N_4O_3$: C, 55.28; H, 2.62; N, 11.21. Found: C, 54.95; H, 2.82; N, 11.42.

2-Amino-9-chloro-4-(5-chloro-3-methyl-1-p-tolyl-1H-pyrazol-4-yl)-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (5f). This compound was obtained as pale yellow solid, 1020 mg (71%), Mp >300°C; IR (KBr): 3385 and 3300 (NH_2), 2210 (CN), 1695 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.22 (s, 3H, pyz-CH_3), 2.38 (tolyl-CH_3), 4.52 (s, 1H, H4), 7.42 (s, 2H, NH_2), 7.45–7.95 (m, 7H, aromatic protons); ^{13}C NMR (400 MHz, DMSO-d_6): 12.62 (pyz-CH_3), 20.62 (tolyl-CH_3), 27.42 (C4), 55.33 (C3), 119.56 (CN), 103.82, 112.55, 115.02, 116.42, 117.58, 123.68, 125.62, 126.11, 128.79, 131.61, 133.20, 136.89, 149.06, 152.30, 154.25 (aromatic carbons), 158.82 (C2), 160.07 (C5); MS *m/z*: 478.8 $[M]^+$, 480.8 $[M+2]^+$; *Anal*. Calcd. for $C_{24}H_{16}Cl_2N_4O_3$: C, 60.14; H 3.36, N 11.69. Found: C, 59.87; H, 3.16; N, 11.91.

2-Amino-4-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-9-methyl-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (5g). This compound was obtained as colorless solid, 1040 mg (78 %), Mp 230–232°C; IR (KBr): 3460 and 3310 (NH_2), 2205 (CN), 1685 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.26 (s, 3H, pyz-CH_3), 2.31 (Ar-CH_3), 4.63 (s, 1H, H4), 7.35 (s, 2H, NH_2), 7.39–7.90 (m, 8H, aromatic protons); ^{13}C NMR (400 MHz, DMSO-d_6): 12.63 (pyz-CH_3), 20.73 (Ar-CH_3), 27.34 (C4), 55.62 (C3), 119.48 (CN), 102.52, 112.66, 114.08, 117.74, 123.73, 125.04, 126.51, 128.76, 130.22, 132.41, 135,14, 137.46, 149.81, 151.98, 154.27 (aromatic carbons), 158.94 (C2), 160.04 (C5); MS *m/z*: 444.7 $[M]^+$, 446.7 $[M+2]^+$; *Anal*. Calcd. for $C_{24}H_{17}ClN_4O_3$: C, 64.80; H 3.85, N 12.59. Found: C, 65.18; H, 4.11; N, 12.38.

2-Amino-4-(5-chloro-1-(3-chlorophenyl)-3-methyl-1H-pyrazol-4-yl)-9-methyl-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (5h). This compound was obtained as colorless solid, 875 mg (61%), Mp 210–212°C; IR (KBr): 3380 and 3280 (NH_2), 2190 (CN), 1680 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.25 (s, 3H, pyz-CH_3), 2.37 (Ar-CH_3), 4.64 (s, 1H, H4), 7.36 (s, 2H, NH_2), 7.40–7.88 (m, 7H, aromatic protons); ^{13}C NMR (400 MHz, DMSO-d_6): 12.53 (pyz-CH_3), 20.89 (Ar-CH_3), 27.40 (C4), 55.56 (C3), 119.55 (CN), 103.96, 113.14, 114.43, 116.38, 119.88, 122.26, 124.54, 125.48, 127.71, 129.03, 132.78, 133.56, 135.68, 136.13, 148.83, 152.17, 154.07 (aromatic carbons), 158.85 (C2), 160.06 (C5); MS *m/z*: 478.6 $[M]^+$, 480.5 $[M+2]^+$; *Anal*. Calcd. for $C_{24}H_{16}Cl_2N_4O_3$: C, 60.14; H, 3.36; N, 11.69. Found: C, 59.84; H, 3.59; N, 11.44.

2-Amino-4-(5-chloro-3-methyl-1-p-tolyl-1H-pyrazol-4-yl)-9-methyl-5-oxo-4,5-dihydropyrano[3,2-c]chromene-3-carbonitrile (5i). This compound was obtained as colorless solid, 990 mg (72%), Mp 229–231°C; IR (KBr): 3420 and 3260 (NH_2), 2200 (CN), 1695 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.21 (s, 3H, pyz-CH_3), 2.35 (Ar-CH_3), 2.42 (tolyl-CH_3), 4.58 (s, 1H, H4), 7.29 (s, 2H, NH_2), 7.31–7.70 (m, 7H, aromatic protons); ^{13}C NMR (400 MHz, DMSO-d_6): 12.51 (pyz-CH_3), 20.94 (Ar-CH_3), 21.02 (tolyl-CH_3), 27.37 (C4), 55.62 (C3), 119.58 (CN), 101.81, 112.75, 116.86, 118.22, 122.45, 124.93, 125.31, 130.01, 132.77, 134.62, 135.75, 138.17, 148.26, 150.79, 153.89 (aromatic carbons), 158.84 (C2), 160.02 (C5); MS *m/z*: 458.9 $[M]^+$, 460.8 $[M+2]^+$; *Anal*. Calcd. for $C_{25}H_{19}ClN_4O_3$: C, 65.43; H, 4.17; N, 12.21. Found: C, 65.68; H, 3.80; N, 11.99.

General procedure. ***2-Amino-4-(5-chloro-3-methyl-1-aryl-1H-pyrazol-4-yl)-1-(4-arylthiazol-2-yl)-7,7-di(un)substituted-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (6a-l).*** A mixture of appropriate 1*H*-pyrazole-4-carbaldehyde **1a-c** (30 mmol), malononitrile **2** (30 mmol), and β-enaminone **3a-c** (30 mmol) in ethanol (20 mL) containing three drops of piperidine was slowly heated and refluxed with stirring for 3–4 h. On completion of reaction, monitored by TLC (ethyl acetate: toluene = 3:7), the reaction mixture was cooled to room temperature and the solid was collected by suction filtration

and washed with mixture of chloroform and methanol (1:1) to obtain the pure compounds **6a-l.** Physical, analytical and spectroscopic characterization data of the compounds **6a-l** are given hereafter.

2-Amino-4-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-5-oxo-1-(4-phenylthiazol-2-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (6a). This compound was obtained as colorless solid, 1210 mg (75 %), Mp 250–253°C; IR (KBr): 3455 and 3350 (NH_2), 2205 (CN), 1685 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.84–2.27 (m, 6H, 3×CH_2), 2.37 (s, 3H, CH_3), 4.64 (s, 1H, H4), 5.97 (s, 2H, NH_2), 7.34–7.94 (m, 10H, aromatic protons), 8.27 (s, 1H, thiazole H5); ^{13}C NMR (400 MHz, DMSO-d_6): 12.88 (CH_3), 21.44 (C8), 25.14 (C4), 29.81 (C7), 36.28 (C6), 62.94 (C3), 120.03 (CN), 114.70, 115.61, 117.10, 122.80, 126.96, 127.49, 128.09, 131.38, 133.26, 136.28, 139.25, 149.08, 152.40, 158.29, 159.98, 162.18, 163.02 (aromatic carbons), 195.72 (C5); MS *m/z*: 539.3 $[M]^+$, 541.2 $[M+2]^+$; *Anal*. Calcd. for $C_{29}H_{23}ClN_6OS$: C, 64.62; H, 4.30; N, 15.59. Found: C, 64.41; H, 3.94; N, 15.76.

2-Amino-4-(5-chloro-1-(3-chlorophenyl)-3-methyl-1H-pyrazol-4-yl)-5-oxo-1-(4-phenylthiazol-2-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (6b). This compound was obtained as colorless solid, 1170 mg (66%), Mp 254–257°C; IR (KBr): 3380 and 3355 (NH_2), 2210 (CN), 1690 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.75–2.25 (m, 6H, 3×CH_2), 2.36 (s, 3H, CH_3), 4.59 (s, 1H, H4), 6.04 (s, 2H, NH_2), 7.35–8.02 (m, 9H, aromatic protons), 8.35 (s, 1H, thiazole H5); ^{13}C NMR (400 MHz, DMSO-d_6): 12.83 (CH_3), 20.16 (C8), 26.97 (C4), 29.03 (C7), 37.17 (C6), 60.25 (C3), 120.33 (CN), 116.58, 116.73, 116.86, 126.07, 127.12, 128.41, 129.37, 130.28, 130.42, 130.65, 131.19, 137.41, 139.57, 149.60, 150.17, 151.39, 157.71, 161.19, 163.22 (aromatic carbons), 195.51 (C5); MS *m/z*: 574.0 $[M]^+$, 576.0 $[M+2]^+$; *Anal.* Calcd. for $C_{29}H_{22}Cl_2N_6OS$: C, 60.73; H, 3.87; N, 14.65. Found: C, 61.05; H, 4.03; N, 14.45.

2-Amino-4-(5-chloro-3-methyl-1-p-tolyl-1H-pyrazol-4-yl)-5-oxo-1-(4-phenylthiazol-2-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (6c). This compound was obtained as colorless solid, 960 mg (58%), Mp 244–246°C; IR (KBr): 3445 and 3370 (NH_2), 2175 (CN), 1670 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.74–2.27 (m, 6H, 3×CH_2), 2.35 (s, 3H, pyz-CH_3), 2.36 (s, 3H, tolyl-CH_3), 4.62 (s, 1H, H4), 6.01 (s, 2H, NH_2), 7.32-7.99 (m, 9H, aromatic protons), 8.38 (s, 1H, thiazole H5); ^{13}C NMR (400 MHz, DMSO-d_6): 12.91 (pyz-CH_3), 20.46 (tolyl-CH_3), 21.38 (C8), 25.01 (C4), 29.43 (C7), 37.32 (C6), 62.76 (C3), 120.95 (CN), 112.62, 113.78, 115.09, 117.79, 126.27, 127.72, 128.05, 128.99, 131.85, 134.82, 139.24, 148.40, 151.53, 157.11, 158.64, 160.97, 161.47 (aromatic carbons), 195.75 (C5); MS *m/z*: 553.5 $[M]^+$, 555.5 $[M+2]^+$; *Anal*. Calcd. for $C_{30}H_{25}ClN_6OS$: C, 65.15; H, 4.56; N, 15.20. Found: C, 64.94; H, 4.72; N, 14.96.

2-Amino-4-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-7,7-dimethyl-5-oxo-1-(4-phenylthiazol-2-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (6d). This compound was obtained as colorless solid, 1105 mg (65%), Mp 229–231°C; IR (KBr): 3395 and 3325 (NH_2), 2195 (CN), 1670 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.94 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 1.92–2.34 (m, 4H, 2×CH_2), 2.37 (s, 3H, pyz-CH_3), 4.62 (s, 1H, H4), 6.02 (s, 2H, NH_2), 7.35–8.07 (m, 10H, aromatic protons), 8.40 (s, 1H, thiazole H5); ^{13}C NMR (400 MHz, DMSO-d_6): 12.93 (pyz-CH_3), 26.75, 27.36 (CH_3), 28.12 (C4), 32.00 (C7), 40.08 (C8), 49.83 (C6), 64.31 (C3), 121.50 (CN), 112.20, 113.06, 116.59, 125.48, 126.85, 127.16, 128.72, 129.36, 131.73, 134.42, 137.10, 149.98, 152.18, 159.20, 158.56, 160.01, 162.90 (aromatic carbons), 196.20 (C5); MS *m/z*: 567.3 $[M]^+$, 569.2 $[M+2]^+$; *Anal*. Calcd. for $C_{31}H_{27}ClN_6OS$: C, 65.65; H, 4.80; N, 14.82. Found: C, 65.41; H, 5.03; N, 15.06.

2-Amino-4-(5-chloro-1-(3-chlorophenyl)-3-methyl-1H-pyrazol-4-yl)-7,7-dimethyl-5-oxo-1-(4-phenylthiazol-2-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (6e). This compound was obtained as colorless solid, 1265 mg (70 %), Mp 238–241°C; IR (KBr): 3440 and 3355 (NH_2), 2180 (CN), 1685 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.90 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 1.93–2.29 (m, 4H, 2×CH_2), 2.34 (s, 3H, pyz-CH_3), 4.56 (s, 1H, H4), 5.94 (s, 2H, NH_2), 7.29–7.92 (m, 9H, aromatic protons), 8.37 (s, 1H, thiazole H5); ^{13}C NMR (400 MHz, DMSO-d_6): 12.97 (pyz-CH_3), 25.63, 26.98 (CH_3), 28.47 (C4), 32.90 (C7), 40.49 (C8), 51.04 (C6), 63.87 (C3), 121.74 (CN), 111.81, 112.77, 115.59, 116.01, 118.46, 125.94, 126.91, 127.00, 128.29, 128.27, 131.34, 136.52, 137.81, 148.06, 152.30, 158.35, 158.13, 162.17, 163.14 (aromatic carbons), 196.39 (C5); MS *m/z*: 602.0 $[M]^+$, 604.0 $[M+2]^+$; *Anal*. Calcd. for $C_{31}H_{26}Cl_2N_6OS$: C, 61.90; H, 4.36; N, 13.97. Found: C, 62.15; H, 4.19; N, 14.12.

2-Amino-4-(5-chloro-3-methyl-1-p-tolyl-1H-pyrazol-4-yl)-7,7-dimethyl-5-oxo-1-(4-phenylthiazol-2-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (6f). This compound was obtained as colorless solid, 1255 mg (72 %), Mp 263–265°C; IR (KBr): 3395 and 3340 (NH_2), 2190 (CN), 1685 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.85 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), (m, 4H, 2×CH_2), 2.30 (s, 3H, tolyl-CH_3), 2.32 (s, 3H, pyz-CH_3), 4.60 (s, 1H, H4), 6.00 (s, 2H, NH_2), 7.33–8.01 (m, 9H, aromatic protons), 8.38 (s, 1H, thiazole H5); ^{13}C NMR (400 MHz, DMSO-d_6): 13.04 (pyz-CH_3), 21.02 (tolyl-CH_3), 26.06, 26.21 (CH_3), 28.15 (C4), 32.41 (C7), 39.40 (C8), 50.66 (C6), 64.42 (C3), 120.82 (CN), 112.87, 114.51, 116.13, 125.89, 126.68, 127.07, 128.35, 129.43, 130.05, 132.45, 139.04, 149.89, 151.30, 157.12, 159.47, 161.02, 162.08 (aromatic carbons), 196.48 (C5); MS *m/z*: 581.4 $[M]^+$, 583.4 $[M+2]^+$; *Anal*. Calcd. for $C_{32}H_{29}ClN_6OS$: C 66.14, H 5.03, N 14.46. Found: C 65.87, H 4.86, N 14.68.

2-Amino-4-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-(4-(4-fluorophenyl)thiazol-2-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (6g). This compound was obtained as colorless solid, 1135 mg (68 %), Mp 281–282°C; IR (KBr): 3440 and 3375 (NH_2), 2185 (CN), 1660 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.82–2.31 (m, 6H, 3×CH_2), 2.38 (s, 3H, CH_3), 4.61 (s, 1H, H4), 6.10 (s, 2H, NH_2), 7.29–8.04 (m, 9H, aromatic protons), 8.42 (s, 1H, thiazole H5); ^{13}C NMR (400 MHz, DMSO-d_6): 12.85 (CH_3), 20.22 (C8), 26.39 (C4), 28.02 (C7), 36.24 (C6), 62.11 (C3), 120.99 (CN), 112.43, 115.63, 118.80, 122.64, 124.01, 127.36, 128.88, 138.25, 142.11, 146.95, 152.76, 153.60, 154.23, 154.21, 157.61, 162.55, 163.15 (aromatic carbons), 195.83 (C5); MS *m/z*: 557.2 $[M]^+$, 559.1 $[M+2]^+$; *Anal*. Calcd. for $C_{29}H_{22}ClFN_6OS$: C, 62.53; H, 3.98; N, 15.09. Found: C, 62.72; H, 4.27; N, 14.83.

2-Amino-4-(5-chloro-1-(3-chlorophenyl)-3-methyl-1H-pyrazol-4-yl)-1-(4-(4-fluorophenyl)thiazol-2-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (6h). This compound was obtained as colorless solid, 1295 mg (73 %), Mp 274–276°C; IR (KBr): 3430 and 3355 (NH_2), 2190 (CN), 1670 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.79–2.25 (m, 6H, 3×CH_2), 2.35 (s, 3H, CH_3), 4.57 (s, 1H, H4), 5.98 (s, 2H, NH_2), 7.31–8.02 (m, 8H, aromatic protons), 8.39 (s, 1H, thiazole

H5); ^{13}C NMR (400 MHz, DMSO-d_6): 12.92 (CH_3), 20.27 (C8), 26.09 (C4), 28.78 (C7), 36.89 (C6), 60.07 (C3), 120.15 (CN), 115.08, 116.31, 116.52, 118.69, 124.02, 127.55, 128.34, 129.23, 130.73, 139.84, 140.58, 147.13, 148.75, 150.16, 151.92, 152.44, 157.48, 161.73, 163.11 (aromatic carbons), 196.12 (C5); MS *m/z*: 591.9 $[M]^+$, 593.7 $[M+2]^+$; *Anal*. Calcd. for $C_{29}H_{21}Cl_2FN_6OS$: C, 58.89; H, 3.58; N, 14.21. Found: C, 59.20; H, 3.31; N, 13.99.

2-Amino-4-(5-chloro-3-methyl-1-p-tolyl-1H-pyrazol-4-yl)-1-(4-(4-fluorophenyl)thiazol-2-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (6i). This compound was obtained as colorless solid, 1295 mg (60%), Mp 259–261°C; IR (KBr): 3405 and 3320 (NH_2), 2185 (CN), 1675 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.96–2.25 (m, 6H, 3×CH_2), 2.31 (s, 3H, pyz-CH_3), 2.35 (s, 3H, tolyl-CH_3), 4.56 (s, 1H, H4), 5.98 (s, 2H, NH_2), 7.34–8.10 (m, 8H, aromatic protons), 8.36 (s, 1H, thiazole H5); ^{13}C NMR (400 MHz, DMSO-d_6): 12.82 (pyz-CH_3), 21.34 (C8), 21.80 (tolyl-CH_3), 25.86 (C4), 28.99 (C7), 36.48 (C6), 59.33 (C3), 120.83 (CN), 112.06, 117.93, 118.03, 124.21, 126.46, 128.65, 129.12, 135.78, 140.51, 143.31, 147.86, 152.06, 155.87, 156.54, 158.03, 161.94, 163.15 (aromatic carbons), 196.24 (C5); MS *m/z*: 571.5 $[M]^+$, 573.5 $[M+2]^+$; *Anal*. Calcd. for $C_{30}H_{24}ClFN_6OS$: C, 63.10; H, 4.24; N, 14.72. Found: C, 62.80; H, 3.94; N, 15.08.

2-Amino-4-(5-chloro-3-methyl-1-phenyl-1H-pyrazol-4-yl)-1-(4-(4-fluorophenyl)thiazol-2-yl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (6j). This compound was obtained as colorless solid, 1230 mg (70 %), Mp 281–283°C; IR (KBr): 3430 and 3370 (NH_2), 2200 (CN), 1695 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.95 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 1.94–2.31 (m, 4H, 2×CH_2), 2.33 (s, 3H, pyz-CH_3), 4.57 (s, 1H, H4), 6.07 (s, 2H, NH_2), 7.36–8.05 (m, 9H, aromatic protons), 8.39 (s, 1H, thiazole H5); ^{13}C NMR (400 MHz, DMSO-d_6): 13.03 (pyz-CH_3), 26.20, 27.05 (CH_3), 28.91 (C4), 33.45 (C7), 41.84 (C8), 50.29 (C6), 62.32 (C3), 120.57 (CN), 113.19, 114.39, 118.44, 124.32, 126.93, 128.04, 129.14, 133.71, 144.53, 145.92, 153.49, 155.90, 157.76, 158.70, 158.91, 160.74, 164.62 (aromatic carbons), 195.95 (C5); MS *m/z*: 585.6 $[M]^+$, 587.4 $[M+2]^+$; *Anal*. Calcd. for $C_{31}H_{26}ClFN_6OS$: C, 63.64; H, 4.48; N, 14.36. Found: C, 63.82; H, 4.63; N, 14.11.

2-Amino-4-(5-chloro-1-(3-chlorophenyl)-3-methyl-1H-pyrazol-4-yl)-1-(4-(4-fluorophenyl)thiazol-2-yl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (6k). This compound was obtained as colorless solid, 1245 mg (67%), Mp 269–270°C; IR (KBr): 3415 and 3320 (NH_2), 2205 (CN), 1680 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.85 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 1.96–2.32 (m, 4H, 2×CH_2), 2.38 (s, 3H, pyz-CH_3), 4.59 (s, 1H, H4), 6.03 (s, 2H, NH_2), 7.31–8.05 (m, 8H, aromatic protons), 8.37 (s, 1H, thiazole H5); ^{13}C NMR (400 MHz, DMSO-d_6): 12.85 (pyz-CH_3), 26.37, 27.73 (CH_3), 29.72 (C4), 33.23 (C7), 41.69 (C8), 51.18 (C6), 60.19 (C3), 120.22 (CN), 112.21, 115.14, 118.32, 118.96, 123.67, 125.63, 128.66, 129.09, 134.56, 140.38, 142.97, 145.68, 150.75, 151.16, 152.77, 156.22, 159.79, 161.20, 163.67 (aromatic carbons), 195.72 (C5); MS *m/z*: 620.1 $[M]^+$, 622.1 $[M+2]^+$; *Anal*. Calcd. for $C_{31}H_{25}Cl_2FN_6OS$: C, 60.10; H, 4.07; N, 13.56. Found: C, 59.80; H, 3.88; N, 13.77.

2-Amino-4-(5-chloro-3-methyl-1-p-tolyl-1H-pyrazol-4-yl)-1-(4-(4-fluorophenyl)thiazol-2-yl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile (6l). This compound was obtained as colorless solid, 1115 mg (62 %), Mp 286–288°C; IR (KBr): 3435 and 3360 (NH_2), 2185 (CN), 1690 (CO); ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.98 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 1.92-2.27 (m, 4H, 2×CH_2), 2.32 (s, 3H, pyz-CH_3), 2.36 (s, 3H, tolyl-CH_3), 4.57 (s, 1H, H4), 5.95 (s, 2H, NH_2), 7.29–7.90 (m, 8H, aromatic protons), 8.42 (s, 1H, thiazole H5); ^{13}C NMR (400 MHz, DMSO-d_6): 12.96 (pyz-CH_3), 21.77 (tolyl-CH_3), 25.26, 26.85 (CH_3), 29.35 (C4), 32.13 (C7), 39.30 (C8), 52.93 (C6), 64.10 (C3), 121.07 (CN), 111.67, 113.54, 115.45, 119.04, 123.84, 124.24, 126.05, 140.26, 146.69, 147.88, 152.50, 153.10, 154.66, 155.37, 158.33, 163.56, 166.18 (aromatic carbons), 196.46 (C5); MS *m/z*: 599.6 $[M]^+$, 601.5 $[M+2]^+$; *Anal*. Calcd. for $C_{32}H_{28}ClFN_6OS$: C, 64.15; H, 4.71; N, 14.03. Found: C, 63.85; H, 5.04; N, 13.89.

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