Full Paper

Synthesis and Antimicrobial Activity of Some New *N*-Substituted Quinoline Derivatives of 1*H*-Pyrazole

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A new series of 32 derivatives of 4-pyrazolyl-*N*-(hetero)arylquinoline **5a–p** and **6a–p** were synthesized by a one-pot base-catalyzed cyclocondensation reaction of 1-phenyl-3-(hetero)aryl-pyrazole-4-carbaldehyde **1a–h**, malononitrile **2**, and 3-(hetero)aryl-5,5-disubstitutedcyclohex-2-enone **3a–b** or **4a–b**, respectively. All the synthesized compounds were characterized by elemental analysis, FT-IR, ^{1}H-NMR, and ^{13}C-NMR spectral data. All the synthesized compounds were screened, against six bacterial pathogens, namely *Bacillus subtilis*, *Clostridium tetani*, *Streptococcus pneumoniae*, *Salmonella typhi*, *Vibrio cholerae*, *Escherichia coli*, and antifungal activity, against two fungal pathogens *Aspergillus fumigatus* and *Candida albicans*, using broth microdilution MIC method. Some of the compounds were found to be more or equipotent against most of the employed strains than commercially available drugs as evident from the screening data.

Keywords: Antimicrobial activity / MCR / MIC / Pyrazole-4-carbaldehyde / Quinoline

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Introduction

Quinoline derivatives are known to exhibit a wide range of biological activities such as antibacterial, anticancer, antimalarial, and antiproliferative properties [1–8]. Recently, 4-functionally substituted 1,3-diaryl pyrazole derivatives have received considerable attention due to their wide range of useful biological properties [9–16].

Various routes for the synthesis of *N*-arylquinoline derivatives have been reported using two-component as well as three-component reactions. Yao and coworkers have reported fluoride-ion-catalyzed multicomponent reactions for the synthesis of *N*-arylquinoline derivatives in aqueous media. Tu and coworkers have carried out a clean synthesis of 1,4-diarylquinoline derivatives catalyzed by benzyl-triethyl ammonium chloride (TEBAC) in aqueous media. They have also reported a three-component green synthesis in ionic liquid [Bmim^{+}][BF$_4^{-}$] and under microwave irradiation.

A literature survey [17] reveals studies concerning *N*-substituted quinoline derivatives of aromatic aldehydes, but not a single reference has been found where 1,3-diaryl pyrazole-4-carbaldehydes and thiazole were used and evaluated for their biological profile. Several pyrazolylquinoline skeleton systems have been found to exhibit multiple pharmacological activities such as antibacterial, antimalarial, antifungal, and anticancer activity [18].

Thus, by considering that a modification at the 1- and 4-position of the quinoline nucleus could bring significant changes of the pharmacological activities and could provide new classes of therapeutically active compounds for biomedical screening, and as part of our ongoing approach in developing new antimicrobial agents containing quinoline [19, 20], thiazole [22], and pyrazole-4-carbaldehyde [20, 21] derivatives, herein, we report the synthesis of some new derivatives of 4-pyrazolyl-*N*-(hetero)arylquinoline **5a–p** and **6a–p** via a multi component reaction (MCR) approach. The constitution of all the products was characterized using elemental analysis, FT-IR, ^{1}H-NMR, ^{13}C-NMR; some selected compounds were also confirmed by mass spectrometry. All synthesized compounds were screened for their *in-vitro* antimicrobial activity against eight human pathogens, of which three were Gram-positive bacterial strains, namely *Streptococcus pneumoniae*, *Clostridium tetani*, and *Bacillus subtilis*, three Gram-negative bacterial strains *Salmonella typhi*, *Vibrio cholerae*, and *Escherichia coli*, and two fungal pathogens *Aspergillus fumigatus* and *Candida albicans*, using the broth

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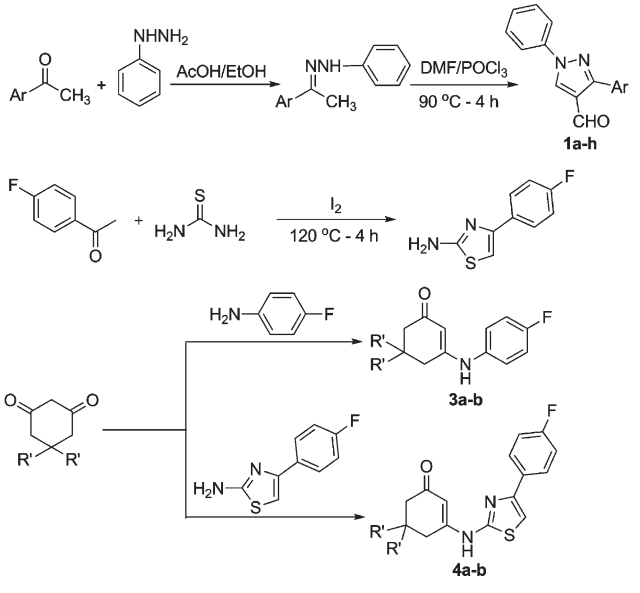
microdilution MIC (minimum inhibitory concentration) method [23].

Results and discussion

Chemistry

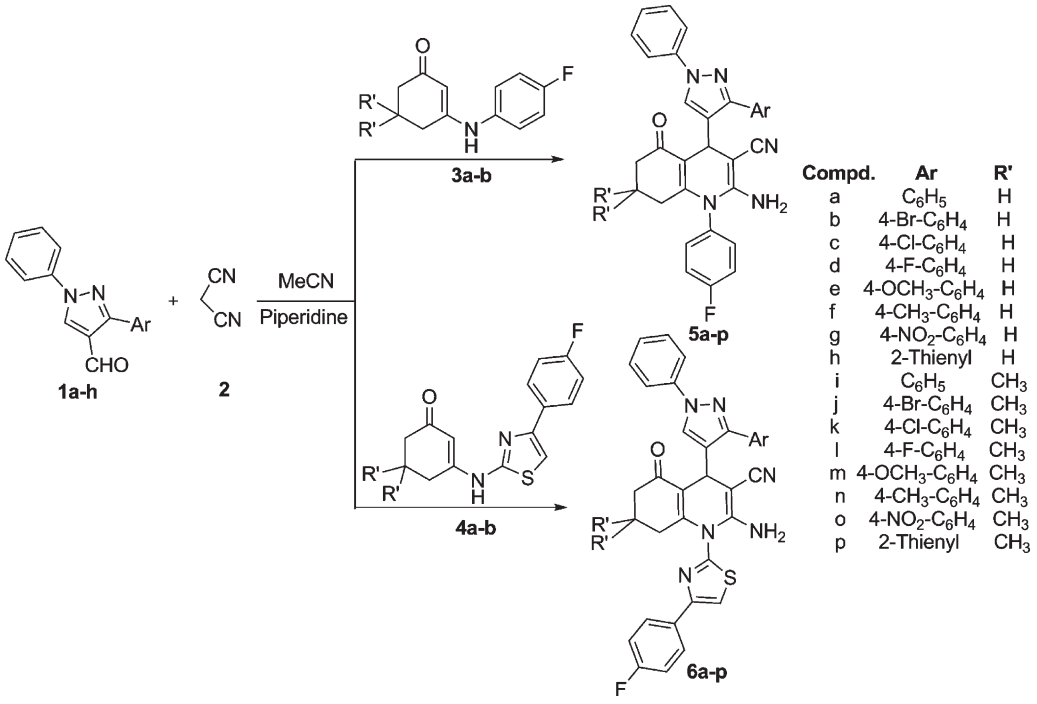
In continuation of our interest on synthesizing biologically potent antimicrobials [19–22], herein, we report a new series of 4-pyrazolyl-*N*-(4-fluorophenyl)-quinoline **5a–p** and 4-pyrazolyl-*N*-(4-(4-fluorophenyl)thiazol-2-yl)-quinoline **6a–p** derivatives, via an one-pot three-component cyclocondensation reaction of 1-phenyl-3-(hetero)aryl-pyrazole-4-carbaldehyde **1a–h**, malononitrile **2**, and 3-(4-fluorophenylamino)-5,5-disubstituted cyclohex-2-enone **3a–b** or 3-(4-(4-fluorophenyl)-thiazol-2-ylamino)-5,5-disubstituted cyclohex-2-enone **4a–b**, respectively. The required 1-phenyl-3-(hetero)aryl-pyrazole-4-carbaldehyde **1a–h** were synthesized by the Vilsmeier–Haack reaction of respective (hetero)arylhydrazone at 90°C for 4 h [24] (Scheme 1). The solid-phase reaction of 4-fluoroacetophenone, thiourea, and iodine (4 h at 120°C) afforded 2-amino-4-(4-fluorophenyl)thiazole [25]. The required β-enaminones were prepared by reacting β-diketone with 4-fluoroaniline under microwave irradiation [26] resulting in **3a–b** or with 2-amino-4-(4-fluorophenyl)thiazole in refluxing methanol in the presence of acetic acid to give **4a–b**. To obtain the title *N*-arylquinoline derivatives, we have tried to carry out the reaction in aqueous medium and under neutral conditions but failed to proceed even under prolonged refluxing. Similarly, microwave irradiation was unsuccessful. The reaction proceeded in ethanol, methanol, benzene, or DMF, under basic condition requiring prolonged refluxing and still resulted in a poor yield. The most optimal condition for the title derivatives is refluxing the mixture in acetonitrile for 3–4 h in the presence of piperidine as basic catalyst; this will lead to moderate to good yields (57–79%) (Scheme 2). A mechanism for the formation of the quinoline derivatives **5a–p** and **6a–p** 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, a Michael addition of **3** or **4** to the initially formed unsaturated nitrile, *i. e.* a nucleophilic attack of the enaminone at the cyano olefins affords the cyclized quinoline derivatives **5a–p** and **6a–p**. 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 some selected 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.



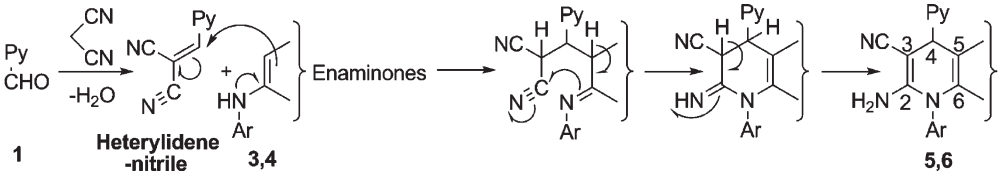
Scheme 1. Synthetic pathway for the intermediates **1a–h**, **3a–b**, and **4a–b**.

Antimicrobial screening

The examination of the data (Table 1) reveals that most of the compounds showed excellent antibacterial and antifungal activity when compared with the standard drugs ampicillin and griseofulvin. Against the Gram-positive pathogen *S. pneumoniae*, compounds **5i** and **6e** (MIC = 100 μg/mL) were found to exhibit comparable activity to that of ampicillin (MIC = 100 μg/mL). The compounds **5k**, **6a**, **6c**, **6l**, and **6n** (MIC < 250 μg/mL) were found to be more efficient, whereas, **5a**, **5d–e**, **5g–h**, **5l–o**, **6b**, **6d**, **6g**, **6i**, **6k**, **6m**, and **6p** (MIC = 250 μg/mL) were found equally potent to ampicillin (MIC = 250 μg/mL) towards *C. tetani*. Compounds **5f**, **5h**, **5i**, **5k**, **6a**, **6e**, **6g**, **6h**, **6i**, and **6l** (MIC < 250 μg/mL) show better activity, whereas **5b**, **5g**, **5j**, **5l**, **5o**, **6b**, **6f**, **6j**, and **6k** (MIC = 250 μg/mL) found equally potent to ampicillin (MIC = 250 μg/mL) against *B. subtilis*. Towards the Gram-negative strain *S. typhi*, compounds **5b**, **5f**, and **6l** (MIC = 100 μg/mL) were equally active compared to ampicillin (MIC = 100 μg/mL). Compounds **5m** and **6i** (MIC = 100 μg/mL) found to be equipotent towards ampicillin (MIC = 100 μg/mL) against *V. cholerae*. Compounds **5f** and **6a** (MIC < 100 μg/mL) show a better and **5k**, **5o**, **6c**, **6e**, **6g**, **6j**, and **6m** (MIC = 100 μg/mL) were found to exhibit a comparable activity compared to that of ampicillin (MIC = 100 μg/mL) towards *E. coli*. Against the fungal pathogen *C. albicans*, compounds **5g–h**, **5p**, **6a–b**, **6d**, and **6n** (MIC < 500 μg/mL) exhibited a better activity whereas, **5a**, **5c–f**, **5i–k**, **5m–n**, **6c**, **6g**, **6i**, **6k**, and **6o** (MIC = 500 μg/mL) were found to be equipotent compared to griseofulvin (MIC = 500 μg/mL). Only one of the tested compounds, **6a** (MIC = 100 μg/mL), was found to be



Scheme 2. Synthetic pathway for the compounds **5a–p** and **6–p**.



Scheme 3. Plausible mechanistic pathway of the synthesis of quinoline derivatives.

potent against the fungal strains *C. albicans* and *A. fumigatus*, compared to the standard drug nystatin (MIC = 100 μg/mL). The remaining compounds showed moderate to good activity inhibiting the growth of bacterial pathogens but are all less effective than the standard drugs.

The investigation of the structure-activity relationships (SAR) of antibacterial screening revealed that the compounds with *p*-methoxy or unsubstituted phenyl at the 3-position of the pyrazole nucleus gave better results against *V. cholerae* and *S. pneumoniae*. Similarly, towards *C. tetani* compounds with phenyl, thienyl, or *p*-chloro or fluorophenyl substituents at the 3-position of the pyrazole were found to be highly active. Against *B. subtilis*, thienyl, *p*-chloro, methyl, methoxy, nitro, fluoro, or unsubstituted phenyl-containing compounds were found to be more potent. Compounds containing *p*-bromo, fluoro, or methyl substituents exhibited a comparable activity against *S. typhi*. The antifungal evaluation showed that thienyl-, *p*-bromo-, fluoro-, methyl-, or nitrophenyl-containing compounds were found to be active against *C. albicans*, whereas the unsubstituted phenyl-ring-containing compound was found to be the most potent among all against both fungal species *C. albicans* and *A. fumigatus*. From the SAR study of the title derivatives, it is interesting to note that a minor alteration in the molecular configuration of the investigated compounds may have a pronounced effect on the antimicrobial activity.

Conclusion

Two new series of substituted 4-pyrazolyl-*N*-(4-fluorophenyl)-quinoline **5a–p** and 4-pyrazolyl-*N*-(4-(4-fluorophenyl)thiazol-2-yl)-quinoline **6a–p** derivatives have been synthesized via MCR approach; the compounds were characterized by elemental and spectral analysis. This synthetic strategy allows the construction of relatively complicated nitrogen-containing fused heterocyclic system as well as the introduction of various (hetero)aromatic substitutions into the 1- and 4-position of the quinoline system. It can be concluded from the

Table 1. Antimicrobial activity of compounds **5a–p** and **6a–p**.

Compound	Minimum Inhibitory Concentration (MIC, μg/mL)							
	Gram-positive bacteria			Gram-negative bacteria			Fungi	
	Streptococcus pneumoniae	*Clostridium tetani*	*Bacillus subtilis*	*Salmonella typhi*	*Vibrio cholerae*	*Escherichia coli*	*Aspergillus fumigatus*	*Candida albicans*
	MTCC 1936	MTCC 449	MTCC 441	MTCC 98	MTCC 3906	MTCC 443	MTCC 3008	MTCC 227
5a	500	**250**	500	250	250	250	1000	**500**
5b	250	1000	**250**	**100**	1000	150	1000	1000
5c	1000	1000	1000	250	1000	200	500	**500**
5d	500	**250**	500	250	500	200	1000	**500**
5e	500	**250**	500	1000	500	500	1000	**500**
5f	150	500	**150**	**100**	250	**62.5**	>1000	**500**
5g	200	**250**	**250**	200	1000	125	200	**100**
5h	150	**250**	**150**	250	500	250	500	**200**
5i	**100**	1000	**100**	250	500	250	>1000	**500**
5j	250	500	**250**	250	150	150	1000	**500**
5k	200	**200**	**200**	150	200	**100**	500	**500**
5l	250	**250**	**250**	500	150	500	>1000	>1000
5m	500	**250**	500	200	**100**	150	>1000	**500**
5n	500	**250**	500	250	250	250	1000	**500**
5o	250	**250**	**250**	150	200	**100**	500	1000
5p	500	500	500	250	250	500	>1000	**250**
6a	150	**200**	**200**	150	500	**62.5**	**100**	**100**
6b	250	**250**	**250**	500	500	500	500	**250**
6c	250	**150**	500	250	250	**100**	250	**500**
6d	500	**250**	500	500	500	500	1000	**250**
6e	**100**	500	**100**	250	150	**100**	500	1000
6f	500	500	**250**	500	250	500	500	1000
6g	250	**250**	**200**	250	250	**100**	1000	**500**
6h	200	500	**200**	125	500	250	1000	1000
6i	200	**250**	**200**	250	**100**	250	500	**500**
6j	250	500	**250**	150	500	**100**	1000	1000
6k	250	**250**	**250**	250	250	200	1000	**500**
6l	200	**125**	**200**	**100**	200	150	>1000	1000
6m	500	**250**	500	500	200	**100**	>1000	1000
6n	1000	**150**	1000	500	250	500	>1000	**250**
6o	1000	500	1000	500	500	250	500	**500**
6p	500	**250**	1000	500	500	500	>1000	1000
Ampi.	**100**	**250**	**250**	**100**	**100**	**100**	–	–
Chlorm.	**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; Chlorm.: Chloramphenicol; Cipro.: Ciprofloxacin; Genta.: Gentamicin; Grise.: Griseofulvin; Nyst.: Nystatin.

antimicrobial screening (Table 1), against a panel of human pathogens that most of the synthesized quinoline derivatives were found to be highly active, compared to standard drugs against bacterial pathogens. Among them, many compounds were found to be most active against *Clostridium tetani* and *Bacillus subtilis* compared to the rest of the investigated species. The antifungal activity of the new compounds shows that most of the compounds active against *C. albicans* compared to *A. fumigatus*. It is worth mentioning that a minor change in the molecular configuration of these compounds profoundly influences the activity.

Experimental

General procedures

Phenyl hydrazine was distilled before use; all other reagents are commercially available and were used without further purification. The 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 visualizing agents. Elemental analysis (% C, H, N) was carried out with a Perkin-Elmer 2400 series-II elemental analyzer (Perkin-Elmer, USA) and all compounds are within ±0.4% of theoretical value. 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}. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in DMSO-d_6 on a Bruker Avance 400F (MHz) spectrometer (Bruker Scientific Corporation Ltd., Switzerland) using the 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).

Chemistry

*General procedure for the synthesis of 3-aryl-1-phenylpyrazole-4-carbaldehyde **1a–h***

3-Aryl-1-phenylpyrazole-4-carbaldehydes **1a–h** were prepared according to the literature procedure [24] by Vilsmeier–Haack reaction of acetophenone (hetero)arylhydrazones (Scheme 1).

General procedure for the synthesis of 2-amino-4-(4-fluorophenyl)thiazole

2-(4-Fluorophenyl)thiazol-4-amine was synthesized according to the literature procedure [25] by the solid-phase reaction of thiourea, 1-(4-fluorophenyl)ethanone, and iodine (Scheme 1).

*General procedure for the synthesis of 3-(4-fluorophenylamino)- 5,5-(un)substituted cyclohex-2-enones **3a–b***

3-(4-Fluorophenylamino)-5,5-(un)substituted cyclohex-2-enones were synthesized according to the literature procedure [26] by the solid-phase reaction of the 1,3-dicarbonyl compound and 4-fluoroaniline under microwave irradiation (Scheme 1).

*General procedure for the synthesis of 3-(4-(4-fluorophenyl)- thiazol-2-ylamino)-5,5-(un)substituted cyclohex-2-enones **4a–b***

The 1,3-dicarbonyl compound (30 mmol), 2-amino-4-(4-fluorophenyl)thiazole (30 mmol), methanol (15 mL) and two drops of acetic acid were charged in a 100 mL round-bottom flask equipped with a refluxing condenser. The reaction mixture was slowly heated and refluxed for 1 h. On completion of reaction, monitored by TLC using 30% EtOAc in toluene as eluent, the reaction mixture was cooled to room temperature and the solid which separated was filtered and washed with methanol to obtain the pure compounds **4a–b**. Analytical and spectroscopic characterization data of the synthesized compounds **4a–b** are given below.

*3-(4-(4-Fluorophenyl)thiazol-2-ylamino)cyclohex-2-enone **4a***

Yield: 70%; m. p.: 199–201°C; IR (KBr, ν, cm^{-1}): 3430 (NH str.), 1655 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.92–2.33 (6H, m, 3 CH_2), 6.87–7.94 (m, 6H, Ar–H), 10.55 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 20.37 (CH_2), 27.60 (CH_2), 36.79 (CH_2–CO), 105.35, 106.78, 113.04, 127.93, 131.82, 148.63, 154.41, 159.30, 162.11 (9C, Ar–C), 197.49 (C=O). Anal. calcd. for $C_{15}H_{13}FN_2OS$ (288.34 g/mol): C, 62.48; H, 4.54; N, 9.72. Found: C, 62.63; H, 4.27; N, 9.87.

*3-(4-(4-Fluorophenyl)thiazol-2-ylamino)-5,5-dimethylcyclohex-2-enone **4b***

Yield: 72%; m. p.: 218–220°C; IR (KBr, ν, cm^{-1}): 3385 (NH str.), 1670 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.04 (s, 6H, CH_3), 2.14–2.43 (4H, m, 2 CH_2), 6.80–7.81 (m, 6H, Ar–H), 10.34 (s, 1H, NH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 28.33 (CH_3), 32.82 ($C(CH_3)_2$), 42.17 (CH_2), 50.65 (CH_2–CO), 104.78, 104.94, 114.65, 127.51, 130.73, 150.85, 155.37, 159.59, 161.29 (9C, Ar–C), 197.98 (C=O). Anal. calcd. for $C_{17}H_{17}FN_2OS$ (316.39 g/mol): C, 64.53; H, 5.42; N, 8.85. Found: C, 64.75; H, 5.27; N, 8.69.

*General procedure for the synthesis of 2-amino-4-(3-aryl-1-phenyl-1H-pyrazol-4-yl)-1-(hetero)aryl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile **5a–p** and **6a–p***

A mixture of 3-aryl-1-phenylpyrazole-4-carbaldehyde **1a–h** (30 mmol), malononitrile **2** (30 mmol), and appropriate β-enaminone **3a–b** or **4a–b** (30 mmol) in acetonitrile (20 mL) containing three drops of piperidine was slowly heated and refluxed for 3–4 h. On completion of the reaction, monitored by TLC (ethyl acetate/toluene, 3:7), the reaction mixture was cooled to room temperature and the solid separated was filtered and washed with a mixture of chloroform and methanol (1:1) to obtain the pure compounds **5a–p** and **6a–p**. Analytical and spectroscopic characterization data of the synthesized compounds **5a–p** and **6a–p** are given below.

*2-Amino-4-(1,3-diphenyl-1H-pyrazol-4-yl)-1-(4-fluorophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile **5a***

Yield: 76%; m. p.: 244–246°C; IR (KBr, ν, cm^{-1}): 3400 asym. & sym. str. of $-NH_2$), 2200 (–C≡N str.), 1675 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.81–2.34 (6H, m, 3 CH_2), 4.54 (s, 1H, quinoline H-4), 5.28 (s, 2H, NH_2), 7.06–7.97 (m, 14H, Ar–H), 8.28 (s, 1H, pyrazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 26.41 (C4), 20.87, 28.56 (2C, CH_2), 36.16 (CH_2–CO), 62.91 (C–CN), 112.55, 113.31, 114.22, 118.92, 121.39, 124.01, 126.09, 126.13, 127.87, 128.16, 131.72, 134.29, 135.77, 137.00, 145.63, 150.11, 152.67, 157.07, 159.86 (19C, Ar–C), 194.87 (C=O). Anal. calcd. for $C_{31}H_{24}FN_5O$ (501.55 g/mol): C, 74.24; H, 4.82; N, 13.96. Found: C, 74.09; H, 5.09; N, 14.15.

*2-Amino-4-(3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(4-fluorophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile **5b***

Yield: 62%; m. p.: 236–238°C; IR (KBr, ν, cm^{-1}): 3395 & 3360 (asym. & sym. str. of $-NH_2$), 2185 (–C≡N str.), 1680 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.97–2.41 (6H, m, 3 CH_2), 4.69 (s, 1H, quinoline H-4), 5.25 (s, 2H, NH_2), 7.01–8.07 (m, 13H, Ar–H), 8.36 (s, 1H, pyrazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 25.81 (C4), 21.45, 29.17 (2C, CH_2), 37.12 (CH_2–CO), 62.35 (C–CN), 111.08, 112.24, 112.32, 115.40, 120.84, 126.43, 127.71, 128.47, 128.52, 129.79, 131.30, 133.76, 135.27, 136.75, 147.04, 151.96,

154.36, 159.12, 161.50 (19C, Ar–C), 196.10 (C=O). Anal. calcd. for $C_{31}H_{23}BrFN_5O$ (580.45 g/mol): C, 64.15; H, 3.99; N, 12.07. Found: C, 63.91; H, 4.17; N, 11.88.

2-Amino-4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(4-fluorophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile ***5c***

Yield: 75%; m. p.: 277–280°C; IR (KBr, ν, cm^{-1}): 3450 asym. & sym. str. of $-NH_2$), 2210 ($-C\equiv N$ str.), 1685 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.80–2.32 (6H, m, 3 CH_2), 4.68 (s, 1H, quinoline H-4), 5.38 (s, 2H, NH_2), 7.09–7.85 (m, 13H, Ar–H), 8.49 (s, 1H, pyrazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 26.52 (C4), 20.90, 28.24 (2C, CH_2), 36.78 (CH_2–CO), 59.08 (*C*–CN), 113.20, 113.97, 114.14, 115.18, 120.42, 125.34, 126.63, 127.21, 127.37, 128.58, 132.56, 134.90, 136.57, 138.65, 149.54, 151.69, 153.88, 156.43, 159.68 (19C, Ar–C), 195.02 (C=O). Anal. calcd. for $C_{31}H_{23}ClFN_5O$ (536.00 g/mol): C, 69.47; H, 4.33; N, 13.07. Found: C, 69.31; H, 4.17; N, 12.85.

2-Amino-1-(4-fluorophenyl)-4-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile ***5d***

Yield: 60%; m. p.: 190–191°C; IR (KBr, ν, cm^{-1}): 3455 & 3370 (asym. & sym. str. of $-NH_2$), 2190 ($-C\equiv N$ str.), 1675 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.76–2.20 (6H, m, 3 CH_2), 4.73 (s, 1H, quinoline H-4), 5.27 (s, 2H, NH_2), 6.96–7.92 (m, 13H, Ar–H), 8.43 (s, 1H, pyrazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 26.73 (C4), 20.97, 29.33 (2C, CH_2), 35.88 (CH_2–CO), 61.56 (*C*–CN), 112.79, 113.05, 114.54, 116.00, 118.86, 120.45, 125.97, 126.03, 128.30, 128.73, 130.91, 135.53, 137.17, 139.37, 146.75, 153.44, 155.93, 156.62, 160.83 (19C, Ar–C), 195.19 (C=O). Anal. calcd. for $C_{31}H_{23}F_2N_5O$ (519.54 g/mol): C, 71.67; H, 4.46; N, 13.48. Found: C, 71.49; H, 4.27; N, 13.72.

2-Amino-1-(4-fluorophenyl)-4-(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile ***5e***

Yield: 66%; m. p.: 267–270°C; IR (KBr, ν, cm^{-1}): 3460 asym. & sym. str. of $-NH_2$), 2175 ($-C\equiv N$ str.), 1650 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.71–2.17 (6H, m, 3 CH_2), 3.84 (s, 3H, OCH_3), 4.76 (s, 1H, quinoline H-4), 5.25 (s, 2H, NH_2), 7.04–7.90 (m, 13H, Ar–H), 8.27 (s, 1H, pyrazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 26.88 (C4), 21.00, 28.50 (2C, CH_2), 36.50 (CH_2–CO), 55.60 (OCH_3), 61.77 (*C*–CN), 113.13, 114.09, 118.60, 121.79, 123.45, 126.28, 126.78, 127.47, 128.90, 129.82, 130.35, 133.06, 133.25, 136.04, 140.11, 150.67, 150.88, 152.16, 159.46 (19C, Ar–C), 195.71 (C=O); MS *m/z*: 532.2 $[M + 1]^+$. Anal. calcd. for $C_{32}H_{26}FN_5O_2$ (531.58 g/mol): C, 72.30; H, 4.93; N, 13.17. Found: C, 71.99; H, 5.14; N, 12.88.

2-Amino-1-(4-fluorophenyl)-5-oxo-4-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile ***5f***

Yield: 68%; m. p.: 237–239°C; IR (KBr, ν, cm^{-1}): 3395 & 3335 (asym. & sym. str. of $-NH_2$), 2195 ($-C\equiv N$ str.), 1675 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.86–2.25 (6H, m, 3 CH_2), 2.34 (s, 3H, tolyl-CH_3), 4.65 (s, 1H, quinoline H-4), 5.49 (s, 2H, NH_2), 6.88–7.95 (m, 13H, Ar–H), 8.39 (s, 1H, pyrazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 21.29 (tolyl-CH_3), 25.92 (C4), 21.73, 29.20 (2C, CH_2), 36.85 (CH_2–CO), 62.29 (*C*–CN), 113.49, 114.33, 114.85, 115.19, 118.15, 120.26, 124.06, 126.48, 126.59, 127.17, 130.70, 134.81, 137.66, 138.99, 145.02, 152.38, 153.20, 157.80, 158.82 (19C, Ar–C), 196.35 (C=O). Anal. calcd. for $C_{32}H_{26}FN_5O$ (515.58 g/mol): C, 74.55; H, 5.08; N, 13.58. Found: C, 74.78; H, 4.81; N, 13.39.

2-Amino-1-(4-fluorophenyl)-4-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile ***5g***

Yield: 74%; m. p.: 281–283°C; IR (KBr, ν, cm^{-1}): 3420 asym. & sym. str. of $-NH_2$), 2200 ($-C\equiv N$ str.), 1685 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.89–2.31 (6H, m, 3 CH_2), 4.53 (s, 1H, quinoline H-4), 5.36 (s, 2H, NH_2), 7.13–8.14 (m, 13H, Ar–H), 8.25 (s, 1H, pyrazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 25.79 (C4), 21.54, 28.12 (2C, CH_2), 36.56 (CH_2–CO), 60.17 (*C*–CN), 112.64, 112.95, 114.98, 115.23, 118.60, 120.46, 123.35, 126.04, 127.74, 127.94, 131.51, 135.28, 137.68, 139.78, 144.61, 151.05, 152.41, 155.89, 161.25 (19C, Ar–C), 194.92 (C=O). Anal. calcd. for $C_{31}H_{23}FN_6O_3$ (546.55 g/mol): C, 68.12; H, 4.24; N, 15.38. Found: C, 67.91; H, 3.98; N, 15.63.

2-Amino-1-(4-fluorophenyl)-5-oxo-4-(1-phenyl-3-(thiophen-2-yl)-1H-pyrazol-4-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile ***5h***

Yield: 69%; m. p.: 225–227°C; IR (KBr, ν, cm^{-1}): 3440 asym. & sym. str. of $-NH_2$), 2180 ($-C\equiv N$ str.), 1650 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.73–2.22 (6H, m, 3 CH_2), 4.49 (s, 1H, quinoline H-4), 5.31 (s, 2H, NH_2), 7.20–7.90 (m, 12H, Ar–H), 8.32 (s, 1H, pyrazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 26.73 (C4), 20.99, 28.50 (2C, CH_2), 36.45 (CH_2–CO), 60.92 (*C*–CN), 112.87, 117.07, 117.29, 118.77, 126.64, 127.93, 128.26, 129.10, 129.89, 133.13, 133.23, 135.73, 139.77, 144.94, 151.17, 152.63, 161.58, 164.03 (19C, Ar–C), 195.57 (C=O). Anal. calcd. for $C_{29}H_{22}FN_5OS$ (507.58 g/mol): C, 68.62; H, 4.37; N, 13.80. Found: C, 68.79; H, 4.28; N, 14.07.

2-Amino-4-(1,3-diphenyl-1H-pyrazol-4-yl)-1-(4-fluorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile ***5i***

Yield: 79%; m. p.: 239–241°C; IR (KBr, ν, cm^{-1}): 3430 asym. & sym. str. of $-NH_2$), 2190 ($-C\equiv N$ str.), 1685 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 0.80 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 2.19–2.47 (4H, m, 2 CH_2), 4.66 (s, 1H, quinoline H-4), 5.38 (s, 2H, NH_2), 7.14–7.90 (m, 14H, Ar–H), 8.32 (s, 1H, pyrazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 26.21, 27.87 (2C, CH_3), 28.39 (C4), 33.36 ($C(CH_3)_2$), 40.14 (CH_2), 51.05 (CH_2–CO), 63.61 (*C*–CN), 112.85, 114.52, 115.11, 116.60, 118.24, 120.38, 122.94, 126.21, 126.38, 127.93, 132.30, 134.20, 135.02, 137.79, 146.12, 152.38, 155.67, 160.32, 163.44 (19C, Ar–C), 196.48 (C=O). Anal. calcd. for $C_{33}H_{28}FN_5O$ (529.61 g/mol): C, 74.84; H, 5.33; N, 13.22. Found: C, 75.05; H, 5.56; N, 12.98.

2-Amino-4-(3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(4-fluorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile ***5j***

Yield: 74%; m. p.: 260–262°C; IR (KBr, ν, cm^{-1}): 3435 & 3360 (asym. & sym. str. of $-NH_2$), 2205 ($-C\equiv N$ str.), 1680 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 0.88 (s, 3H, CH_3), 0.96 (s, 3H, CH_3),

2.12–2.40 (4H, m, 2 CH_2), 4.69 (s, 1H, quinoline H-4), 5.22 (s, 2H, NH_2), 6.92–7.99 (m, 13H, Ar–H), 8.24 (s, 1H, pyrazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 25.37, 26.05 (2C, CH_3), 29.16 (C4), 32.09 (*C*(CH_3)$_2$), 39.97 (CH_2), 52.20 (*C*H_2–CO), 64.29 (*C*–CN), 111.85, 114.50, 115.49, 117.23, 121.19, 122.04, 126.35, 127.51, 128.48, 128.59, 133.28, 133.68, 136.66, 138.70, 147.17, 154.81, 157.99, 160.25, 162.51 (19C, Ar–C), 196.91 (C=O). Anal. calcd. for $C_{33}H_{27}BrFN_5O$ (608.50 g/mol): C, 65.14; H, 4.47; N, 11.51. Found: C, 64.97; H, 4.26; N, 11.69.

2-Amino-4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(4-fluorophenyl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile ***5k***

Yield: 71%; m. p.: 243–245°C; IR (KBr, ν, cm^{-1}): 3430 asym. & sym. str. of –NH_2), 2205 (–C≡N str.), 1690 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 0.84 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 1.80–2.16 (4H, m, 2 CH_2), 4.75 (s, 1H, quinoline H-4), 5.29 (s, 2H, NH_2), 7.30–7.94 (m, 13H, Ar–H), 8.29 (s, 1H, pyrazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 27.05, 27.45 (2C, CH_3), 29.12 (C4), 32.44 (*C*(CH_3)$_2$), 41.58 (CH_2), 49.82 (*C*H_2–CO), 61.23 (*C*–CN), 111.78, 117.23, 117.46, 118.81, 121.83, 126.68, 127.73, 128.78, 129.28, 129.94, 130.82, 132.77, 133.21, 139.92, 149.86, 150.40, 150.92, 161.58, 164.03 (19C, Ar–C), 195.65 (C=O). Anal. calcd. for $C_{33}H_{27}ClFN_5O$ (564.05 g/mol): C, 70.27; H, 4.82; N, 12.42. Found: C, 69.96; H, 5.11; N, 12.63.

2-Amino-1-(4-fluorophenyl)-4-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile ***5l***

Yield: 69%; m. p.: 210–211°C; IR (KBr, ν, cm^{-1}): 3390 asym. & sym. str. of –NH_2), 2180 (–C≡N str.), 1670 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.03 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 2.02–2.36 (4H, m, 2 CH_2), 4.71 (s, 1H, quinoline H-4), 5.40 (s, 2H, NH_2), 7.12–8.16 (m, 13H, Ar–H), 8.40 (s, 1H, pyrazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 26.62, 27.42 (2C, CH_3), 28.74 (C4), 33.21 (*C*(CH_3)$_2$), 41.88 (CH_2), 50.01 (*C*H_2–CO), 62.32 (*C*–CN), 113.88, 114.26, 115.64, 117.00, 119.15, 120.98, 124.46, 126.33, 126.74, 128.06, 131.39, 133.77, 134.89, 138.57, 148.78, 151.41, 156.05, 159.61, 162.82 (19C, Ar–C), 195.87 (C=O). Anal. calcd. for $C_{33}H_{27}F_2N_5O$ (547.60 g/mol): C, 72.38; H, 4.97; N, 12.79. Found: C, 72.55; H, 5.20; N, 12.54.

2-Amino-1-(4-fluorophenyl)-4-(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile ***5m***

Yield: 78%; m. p.: 255–258°C; IR (KBr, ν, cm^{-1}): 3380 asym. & sym. str. of –NH_2), 2210 (–C≡N str.), 1680 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 0.89 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 2.06–2.39 (4H, m, 2 CH_2), 3.81 (s, 3H, OCH_3), 4.67 (s, 1H, quinoline H-4), 5.35 (s, 2H, NH_2), 7.00–7.90 (m, 13H, Ar–H), 8.28 (s, 1H, pyrazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 25.13, 26.25 (2C, CH_3), 29.94 (C4), 32.97 (*C*(CH_3)$_2$), 42.20 (CH_2), 50.33 (*C*H_2–CO), 54.83 (OCH_3), 62.11 (*C*–CN), 112.73, 114.42, 115.54, 116.71, 119.01, 120.03, 124.40, 126.58, 127.76, 131.80, 135.27, 135.65, 136.16, 139.75, 149.09, 154.13, 155.32, 160.29, 164.56 (19C, Ar–C), 195.69 (C=O). Anal. calcd. for $C_{34}H_{30}FN_5O_2$ (559.63 g/mol): C, 72.97; H, 5.40; N, 12.51. Found: C, 73.19; H, 5.24; N, 12.73.

2-Amino-1-(4-fluorophenyl)-7,7-dimethyl-5-oxo-4-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile ***5n***

Yield: 75%; m. p.: 272–274°C; IR (KBr, ν, cm^{-1}): 3400 asym. & sym. str. of –NH_2), 2200 (–C≡N str.), 1660 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 0.94 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.13–2.37 (4H, m, 2 CH_2), 2.40 (s, 3H, tolyl-CH_3), 4.76 (s, 1H, quinoline H-4), 5.24 (s, 2H, NH_2), 6.81–7.84 (m, 13H, Ar–H), 8.32 (s, 1H, pyrazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 21.38 (tolyl-CH_3), 25.09, 26.45 (2C, CH_3), 28.87 (C4), 32.68 (*C*(CH_3)$_2$), 40.75 (CH_2), 50.67 (*C*H_2–CO), 60.72 (*C*–CN), 111.63, 113.84, 114.14, 116.97, 118.18, 121.34, 125.56, 125.69, 126.24, 127.87, 132.47, 133.36, 133.90, 136.00, 147.96, 153.22, 158.50, 160.62, 163.83 (19C, Ar–C), 194.90 (C=O). Anal. calcd. for $C_{34}H_{30}FN_5O$ (543.63 g/mol): C, 75.12; H, 5.56; N, 12.88. Found: C, 74.90; H, 5.39; N, 13.15.

2-Amino-1-(4-fluorophenyl)-7,7-dimethyl-4-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile ***5o***

Yield: 70%; m. p.: 210–212°C; IR (KBr, ν, cm^{-1}): 3430 asym. & sym. str. of –NH_2), 2175 (–C≡N str.), 1660 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.02 (s, 3H, CH_3), 1.09 (s, 3H, CH_3), 2.05–2.35 (4H, m, 2 CH_2), 4.70 (s, 1H, quinoline H-4), 5.42 (s, 2H, NH_2), 7.27–8.26 (m, 13H, Ar–H), 8.34 (s, 1H, pyrazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 25.65, 26.76 (2C, CH_3), 28.20 (C4), 32.05 (*C*(CH_3)$_2$), 40.01 (CH_2), 51.68 (*C*H_2–CO), 63.43 (*C*–CN), 111.46, 112.95, 114.21, 115.73, 118.55, 120.71, 124.45, 125.30, 127.53, 132.37, 133.32, 134.72, 134.87, 136.91, 148.86, 156.39, 158.62, 159.07, 163.09 (19C, Ar–C), 195.83 (C=O). Anal. calcd. for $C_{33}H_{27}FN_6O_3$ (574.60 g/mol): C, 68.98; H, 4.74; N, 14.63. Found: C, 69.21; H, 4.88; N, 14.46.

2-Amino-1-(4-fluorophenyl)-7,7-dimethyl-5-oxo-4-(1-phenyl-3-(thiophen-2-yl)-1H-pyrazol-4-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile ***5p***

Yield: 67%; m. p.: 231–234°C; IR (KBr, ν, cm^{-1}): 3395 & 3320 (asym. & sym. str. of –NH_2), 2190 (–C≡N str.), 1690 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 0.90 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.18–2.44 (4H, m, 2 CH_2), 4.61 (s, 1H, quinoline H-4), 5.36 (s, 2H, NH_2), 6.80–7.89 (m, 12H, Ar–H), 8.26 (s, 1H, pyrazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 26.33, 26.48 (2C, CH_3), 28.82 (C4), 32.74 (*C*(CH_3)$_2$), 39.68 (CH_2), 50.94 (*C*H_2–CO), 64.57 (*C*–CN), 112.13, 114.07, 115.25, 116.11, 119.64, 120.89, 123.92, 126.77, 127.11, 130.08, 132.31, 133.93, 135.44, 137.57, 149.34, 153.12, 157.41, 160.48, 162.28 (19C, Ar–C), 196.31 (C=O); MS *m/z*: 536.1 $[M + 1]^+$. Anal. calcd. for $C_{31}H_{26}FN_5OS$ (535.63 g/mol): C, 69.51; H, 4.89; N, 13.07. Found: C, 69.36; H, 5.14; N, 12.88.

2-Amino-4-(1,3-diphenyl-1H-pyrazol-4-yl)-1-(4-(4-fluorophenyl)thiazol-2-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile ***6a***

Yield: 67%; m. p.: 228–229°C; IR (KBr, ν, cm^{-1}): 3430 asym. & sym. str. of –NH_2), 2210 (–C≡N str.), 1695 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.82–2.34 (6H, m, 3 CH_2), 4.84 (s, 1H, quinoline H-4), 6.11 (s, 2H, NH_2), 7.11–7.98 (m, 14H, Ar–H), 8.32 (s, 1H, pyrazole H-5), 8.39 (s, 1H, thiazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C

(ppm): 26.88 (C4), 21.34, 28.48 (2C, CH_2), 36.44 (CH_2–CO), 62.53 (*C*–CN), 112.91, 116.58, 117.47, 118.40, 120.01, 122.55, 124.70, 125.71, 126.11, 126.85, 128.78, 132.87, 139.13, 142.92, 144.07, 151.31, 153.69, 155.32, 156.08, 160.29, 162.00, 164.60 (22C, Ar-C), 196.07 (C=O). Anal. calcd. for $C_{34}H_{25}FN_6OS$ (584.67 g/mol): C, 69.85; H, 4.31; N, 14.37. Found: C, 70.03; H, 4.45; N, 14.22.

2-Amino-4-(3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(4-(4-fluorophenyl)thiazol-2-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile **6b**

Yield: 62%; m. p.: 245–248°C; IR (KBr, ν, cm^{-1}): 3450 asym. & sym. str. of –NH_2), 2170 (–C≡N str.), 1670 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.77–2.26 (6H, m, 3 CH_2), 4.98 (s, 1H, quinoline H-4), 6.04 (s, 2H, NH_2), 7.12–8.09 (m, 13H, Ar–H), 8.28 (s, 1H, pyrazole H-5), 8.33 (s, 1H, thiazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 25.93 (C4), 22.03, 28.59 (2C, CH_2), 36.90 (CH_2–CO), 59.24 (*C*–CN), 111.19, 113.84, 115.42, 118.54, 119.97, 121.73, 123.76, 124.34, 124.58, 126.56, 131.91, 137.03, 140.65, 146.53, 147.29, 152.90, 153.22, 154.09, 155.16, 158.36, 163.83, 166.74 (22C, Ar–C), 195.22 (C=O). Anal. calcd. for $C_{34}H_{24}BrFN_6OS$ (663.56 g/mol): C, 61.54; H, 3.65; N, 12.67. Found: C, 61.42; H, 3.78; N, 12.48.

2-Amino-4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(4-(4-fluorophenyl)thiazol-2-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile **6c**

Yield: 64%; m. p.: 208–210°C; IR (KBr, ν, cm^{-1}): 3440 asym. & sym. str. of –NH_2), 2185 (–C≡N str.), 1685 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.70–2.12 (6H, m, 3 CH_2), 4.72 (s, 1H, quinoline H-4), 6.09 (s, 2H, NH_2), 7.29–7.92 (m, 13H, Ar–H), 8.41 (s, 1H, pyrazole H-5), 8.46 (s, 1H, thiazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 26.34 (C4), 21.69, 28.90 (2C, CH_2), 35.94 (CH_2–CO), 61.66 (*C*–CN), 112.83, 115.63, 118.14, 118.95, 120.21, 123.40, 125.45, 128.27, 128.47, 129.12, 134.37, 136.75, 140.72, 142.43, 145.50, 150.00, 151.08, 152.30, 156.07, 159.16, 161.55, 163.23 (22C, Ar–C), 195.40 (C=O). Anal. calcd. for $C_{34}H_{24}ClFN_6OS$ (619.11 g/mol): C, 65.96; H, 3.91; N, 13.57. Found: C, 66.13; H, 4.09; N, 13.30.

2-Amino-4-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-1-(4-(4-fluorophenyl)thiazol-2-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile **6d**

Yield: 65%; m. p.: 200–201°C; IR (KBr, ν, cm^{-1}): 3385 & 3340 (asym. & sym. str. of –NH_2), 2205 (–C≡N str.), 1680 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.84–2.25 (6H, m, 3 CH_2), 4.77 (s, 1H, quinoline H-4), 5.94 (s, 2H, NH_2), 7.19–8.10 (m, 13H, Ar–H), 8.36 (s, 1H, pyrazole H-5), 8.39 (s, 1H, thiazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 26.27 (C4), 20.85, 29.15 (2C, CH_2), 36.23 (CH_2–CO), 62.82 (*C*–CN), 113.59, 114.18, 116.63, 118.79, 120.66, 124.39, 126.46, 126.52, 128.00, 128.69, 129.57, 133.80, 134.76, 144.50, 145.44, 153.96, 155.86, 157.90, 158.62, 158.84, 160.53, 164.80 (22C, Ar–C), 194.82 (C=O). Anal. calcd. for $C_{34}H_{24}F_2N_6OS$ (602.66 g/mol): C, 67.76; H, 4.01; N, 13.94. Found: C, 67.92; H, 3.87; N, 14.13.

2-Amino-1-(4-(4-fluorophenyl)thiazol-2-yl)-4-(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile **6e**

Yield: 63%; m. p.: 211–213°C; IR (KBr, ν, cm^{-1}): 3430 asym. & sym. str. of –NH_2), 2200 (–C≡N str.), 1670 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.93–2.37 (6H, m, 3 CH_2), 3.78 (s, 3H, OCH_3), 4.81 (s, 1H, quinoline H-4), 6.16 (s, 2H, NH_2), 7.21–8.08 (m, 13H, Ar–H), 8.25 (s, 1H, pyrazole H-5), 8.31 (s, 1H, thiazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 25.84 (C4), 21.22, 28.76 (2C, CH_2), 36.56 (CH_2–CO), 54.04 (OCH_3), 59.75 (*C*–CN), 112.85, 117.98, 118.06, 118.74, 120.59, 124.35, 126.24, 126.95, 128.28, 129.15, 135.04, 136.48, 140.89, 143.78, 147.17, 152.81, 155.02, 155.41, 156.82, 158.36, 161.62, 163.30 (22C, Ar–C), 194.94 (C=O). Anal. calcd. for $C_{35}H_{27}FN_6O_2S$ (614.69 g/mol): C, 68.39; H, 4.43; N, 13.67. Found: C, 68.52; H, 4.59; N, 13.52.

2-Amino-1-(4-(4-fluorophenyl)thiazol-2-yl)-5-oxo-4-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile **6f**

Yield: 57%; m. p.: 234–237°C; IR (KBr, ν, cm^{-1}): 3440 asym. & sym. str. of –NH_2), 2180 (–C≡N str.), 1660 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.95–2.33 (6H, m, 3 CH_2), 2.38 (s, 3H, tolyl-CH_3), 4.98 (s, 1H, quinoline H-4), 6.13 (s, 2H, NH_2), 7.03–7.96 (m, 13H, Ar–H), 8.34 (s, 1H, pyrazole H-5), 8.39 (s, 1H, thiazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 20.96 (tolyl-CH_3), 26.95 (C4), 20.82, 29.17 (2C, CH_2), 37.26 (CH_2–CO), 60.64 (*C*–CN), 112.07, 116.50, 118.32, 119.19, 121.60, 122.12, 123.79, 124.29, 126.11, 126.23, 129.66, 137.32, 139.53, 146.38, 148.27, 150.05, 151.67, 154.08, 155.61, 157.45, 161.67, 164.92 (22C, Ar–C), 195.43 (C=O); MS *m/z*: 599.2 $[M + 1]^+$. Anal. calcd. for $C_{35}H_{27}FN_6OS$ (598.69 g/mol): C, 70.22; H, 4.55; N, 14.04. Found: C, 69.97; H, 4.72; N, 13.90.

2-Amino-1-(4-(4-fluorophenyl)thiazol-2-yl)-4-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile **6g**

Yield: 59%; m. p.: 260–262°C; IR (KBr, ν, cm^{-1}): 3435 & 3375 (asym. & sym. str. of –NH_2), 2210 (–C≡N str.), 1665 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.86–2.38 (6H, m, 3 CH_2), 4.86 (s, 1H, quinoline H-4), 5.97 (s, 2H, NH_2), 7.32–8.35 (m, 13H, Ar–H), 8.40 (s, 1H, pyrazole H-5), 8.42 (s, 1H, thiazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 27.24 (C4), 21.09, 27.44 (2C, CH_2), 36.43 (CH_2–CO), 63.09 (*C*–CN), 115.35, 116.07, 116.29, 118.80, 120.84, 124.14, 127.10, 128.25, 128.42, 128.77, 129.86, 130.68, 139.71, 140.92, 147.37, 148.78, 150.62, 151.30, 152.18, 157.23, 161.44, 163.88 (22C, Ar–C), 196.01 (C=O). Anal. calcd. for $C_{34}H_{24}FN_7O_3S$ (629.66 g/mol): C, 64.85; H, 3.84; N, 15.57. Found: C, 65.01; H, 3.69; N, 15.69.

2-Amino-1-(4-(4-fluorophenyl)thiazol-2-yl)-5-oxo-4-(1-phenyl-3-(thiophen-2-yl)-1H-pyrazol-4-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile **6h**

Yield: 65%; m. p.: 255–256°C; IR (KBr, ν, cm^{-1}): 3390 asym. & sym. str. of –NH_2), 2205 (–C≡N str.), 1680 (–C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.72–2.31 (6H, m, 3 CH_2), 4.72 (s, 1H, quinoline H-4), 5.98 (s, 2H, NH_2), 7.15–7.84 (m, 12H, Ar–H), 8.27 (s, 1H, pyrazole H-5), 8.34 (s, 1H, thiazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 25.88 (C4), 21.19, 28.68 (2C, CH_2), 36.10 (CH_2–CO), 61.85 (*C*–CN), 112.49, 115.64, 116.51, 118.00, 118.33, 120.29, 122.46, 124.26, 124.93, 127.12, 128.68, 134.20, 138.77, 142.25, 146.47, 152.99, 153.88, 154.70, 154.96, 157.02, 162.13, 163.54 (22C, Ar–C), 195.47 (C=O). Anal. calcd. for $C_{32}H_{23}FN_6OS_2$ (590.69 g/mol): C, 65.07; H, 3.92; N, 14.23. Found: C, 65.22; H, 4.11; N, 14.02.

2-Amino-4-(1,3-diphenyl-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 ***6i***

Yield: 70%; m. p.: 241–242°C; IR (KBr, ν, cm^{-1}): 3395 & 3320 (asym. & sym. str. of $-NH_2$), 2195 ($-C\equiv N$ str.), 1665 (−C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 0.96 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.01–2.38 (4H, m, 2 CH_2), 4.83 (s, 1H, quinoline H-4), 6.02 (s, 2H, NH_2), 7.16–8.03 (m, 14H, Ar–H), 8.35 (s, 1H, pyrazole H-5), 8.39 (s, 1H, thiazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 26.57, 27.42 (2C, CH_3), 29.46 (C4), 33.59 ($C(CH_3)_2$), 41.29 (CH_2), 51.83 (CH_2–CO), 60.93 (*C*–CN), 112.04, 114.12, 116.32, 117.81, 120.72, 125.95, 126.17, 126.28, 127.14, 127.35, 128.79, 129.33, 130.82, 132.65, 136.49, 139.61, 149.38, 151.15, 157.99, 159.01, 161.72, 162.06 (22C, Ar–C), 195.56 (C=O). Anal. calcd. for $C_{36}H_{29}FN_6OS$ (612.72 g/mol): C, 70.57; H, 4.77; N, 13.72. Found: C, 70.29; H, 4.56; N, 13.89.

2-Amino-4-(3-(4-bromophenyl)-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***

Yield: 77%; m. p.: 216–218°C; IR (KBr, ν, cm^{-1}): 3425 & 3355 (asym. & sym. str. of $-NH_2$), 2180 ($-C\equiv N$ str.), 1685 (−C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.04 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 2.18–2.41 (4H, m, 2 CH_2), 4.73 (s, 1H, quinoline H-4), 6.15 (s, 2H, NH_2), 7.25–8.17 (m, 13H, Ar–H), 8.37 (s, 1H, pyrazole H-5), 8.44 (s, 1H, thiazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 25.32, 26.17 (2C, CH_3), 28.93 (C4), 31.17 ($C(CH_3)_2$), 40.49 (CH_2), 52.24 (CH_2–CO), 62.78 (*C*–CN), 111.31, 112.85, 115.98, 116.74, 118.49, 121.94, 125.35, 126.28, 126.59, 127.51, 128.04, 128.66, 128.81, 131.29, 136.20, 137.02, 148.52, 152.25, 158.06, 158.35, 162.73, 163.88 (22C, Ar–C), 196.29 (C=O). Anal. calcd. for $C_{36}H_{28}BrFN_6OS$ (691.61 g/mol): C, 62.52; H, 4.08; N, 12.15. Found: C, 62.70; H, 3.94; N, 12.31.

2-Amino-4-(3-(4-chlorophenyl)-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 ***6k***

Yield: 75%; m. p.: 273–274°C; IR (KBr, ν, cm^{-1}): 3390 asym. & sym. str. of $-NH_2$), 2195 ($-C\equiv N$ str.), 1670 (−C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 0.97 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.15–2.36 (4H, m, 2 CH_2), 4.99 (s, 1H, quinoline H-4), 5.99 (s, 2H, NH_2), 7.17–7.94 (m, 13H, Ar–H), 8.42 (s, 1H, pyrazole H-5), 8.47 (s, 1H, thiazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 26.06, 26.84 (2C, CH_3), 29.52 (C4), 32.73 ($C(CH_3)_2$), 40.67 (CH_2), 51.01 (CH_2–CO), 59.46 (*C*–CN), 113.27, 114.18, 115.49, 118.33, 120.64, 122.24, 126.06, 126.22, 127.23, 128.48, 129.50, 130.93, 131.78, 135.32, 136.17, 136.67, 147.70, 151.50, 156.82, 159.52, 161.02, 163.36 (22C, Ar–C), 196.78 (C=O). Anal. calcd. for $C_{36}H_{28}ClFN_6OS$ (647.16 g/mol): C, 66.81; H, 4.36; N, 12.99. Found: C, 67.02; H, 4.61; N, 12.76.

2-Amino-4-(3-(4-fluorophenyl)-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 ***6l***

Yield: 69%; m. p.: 182–184°C; IR (KBr, ν, cm^{-1}): 3400 asym. & sym. str. of $-NH_2$), 2170 ($-C\equiv N$ str.), 1650 (−C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 0.85 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 2.04–2.32 (4H, m, 2 CH_2), 4.88 (s, 1H, quinoline H-4), 6.04 (s, 2H, NH_2), 7.28–8.26 (m, 13H, Ar–H), 8.24 (s, 1H, pyrazole H-5), 8.31 (s, 1H, thiazole H-5); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 26.42, 27.75 (2C, CH_3), 29.49 (C4), 32.02 ($C(CH_3)_2$), 41.10 (CH_2), 51.56 (CH_2–CO), 64.90 (*C*–CN), 112.26, 113.90, 116.96, 117.03, 121.42, 125.95, 126.57, 127.15, 127.83, 128.99, 129.89, 130.68, 131.94, 134.80, 137.31, 138.05, 149.88, 152.30, 159.51, 158.61, 160.49, 162.98 (22C, Ar–C), 197.02 (C=O). Anal. calcd. for $C_{36}H_{28}F_2N_6OS$ (630.71 g/mol): C, 68.56; H, 4.47; N, 13.32. Found: C, 68.39; H, 4.33; N, 13.48.

2-Amino-1-(4-(4-fluorophenyl)thiazol-2-yl)-4-(3-(4-methoxyphenyl)-1-phenyl-1H-pyrazol-4-yl)-7,7-dimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile ***6m***

Yield: 72%; m. p.: 265–268°C; IR (KBr, ν, cm^{-1}): 3390 asym. & sym. str. of $-NH_2$), 2200 ($-C\equiv N$ str.), 1665 (−C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 0.97 (s, 3H, CH_3), 1.05 (s, 3H, CH_3), 2.10–2.49 (4H, m, 2 CH_2), 3.90 (s, 3H, OCH_3), 4.79 (s, 1H, quinoline H-4), 6.06 (s, 2H, NH_2), 7.11–8.17 (m, 13H, Ar–H), 8.37 (s, 1H, pyrazole H-5), 8.45 (s, 1H, thiazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 25.69, 26.88 (2C, CH_3), 28.02 (C4), 33.21 ($C(CH_3)_2$), 40.79 (CH_2), 50.72 (CH_2–CO), 56.67 (OCH_3), 63.09 (*C*–CN), 112.84, 113.73, 115.39, 116.79, 117.27, 120.34, 126.18, 126.58, 127.03, 127.47, 128.65, 128.72, 128.87, 131.75, 134.09, 139.31, 148.22, 151.71, 157.53, 158.69, 160.32, 161.29 (22C, Ar–C), 195.91 (C=O). Anal. calcd. for $C_{37}H_{31}FN_6O_2S$ (642.74 g/mol): C, 69.14; H, 4.86; N, 13.08. Found: C, 68.97; H, 5.03; N, 12.89.

2-Amino-1-(4-(4-fluorophenyl)thiazol-2-yl)-7,7-dimethyl-5-oxo-4-(1-phenyl-3-p-tolyl-1H-pyrazol-4-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile ***6n***

Yield: 76%; m. p.: 292–293°C; IR (KBr, ν, cm^{-1}): 3420 asym. & sym. str. of $-NH_2$), 2185 ($-C\equiv N$ str.), 1685 (−C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 0.89 (s, 3H, CH_3), 0.94 (s, 3H, CH_3), 2.08–2.31 (4H, m, 2 CH_2), 2.40 (s, 3H, tolyl-CH_3), 4.76 (s, 1H, quinoline H-4), 5.99 (s, 2H, NH_2), 7.33–8.05 (m, 13H, Ar–H), 8.25 (s, 1H, pyrazole H-5), 8.34 (s, 1H, thiazole H-5); ^{13}*C*-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 21.44 (tolyl-CH_3), 26.94, 27.71 (2C, CH_3), 28.49 (C4), 32.90 ($C(CH_3)_2$), 40.41 (CH_2), 49.99 (CH_2–CO), 64.43 (*C*–CN), 116.07, 116.15, 116.36, 118.51, 120.85, 126.62, 127.22, 128.68, 128.81, 129.42, 130.00, 130.63, 130.69, 131.07, 137.55, 139.89, 149.80, 150.91, 151.22, 157.93, 161.47, 163.90 (22C, Ar–C), 195.74 (C=O). Anal. calcd. for $C_{37}H_{31}FN_6OS$ (626.75 g/mol): C, 70.91; H, 4.99; N, 13.41. Found: C, 71.10; H, 5.23; N, 13.25.

2-Amino-1-(4-(4-fluorophenyl)thiazol-2-yl)-7,7-dimethyl-4-(3-(4-nitrophenyl)-1-phenyl-1H-pyrazol-4-yl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile ***6o***

Yield: 74%; m. p.: 287–289°C; IR (KBr, ν, cm^{-1}): 3385 & 3325 (asym. & sym. str. of $-NH_2$), 2200 ($-C\equiv N$ str.), 1685 (−C=O str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 0.91 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 2.12–2.40 (4H, m, 2 CH_2), 4.85 (s, 1H, quinoline H-4), 6.19 (s, 2H, NH_2), 7.13–8.24 (m, 13H, Ar–H), 8.33 (s, 1H, pyrazole H-5), 8.37 (s, 1H, thiazole H-5); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 26.21, 27.39 (2C, CH_3), 29.51 (C4), 31.72 ($C(CH_3)_2$), 39.31 (CH_2), 52.08 (CH_2–CO), 63.80 (*C*–CN), 114.63, 115.40, 117.42, 118.00, 120.92, 122.56, 126.01, 126.76, 127.37, 127.90, 128.96, 130.77, 131.16, 133.45, 136.91, 139.83, 149.13, 152.00, 158.86, 159.54, 162.62, 163.43 (22C, Ar–C), 195.25 (C=O). Anal. calcd. for $C_{36}H_{28}FN_7O_3S$

(657.72 g/mol): C, 65.74; H, 4.29; N, 14.91. Found: C, 65.88; H, 4.42; N, 14.76.

2-Amino-1-(4-(4-fluorophenyl)thiazol-2-yl)-7,7-dimethyl-5-oxo-4-(1-phenyl-3-(thiophen-2-yl)-1H-pyrazol-4-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrile ***6p***

Yield: 72%; m. p.: 227–229°C; IR (KBr, ν, cm^{-1}): 3435 & 3340 (asym. & sym. str. of $-NH_2$), 2190 ($-C\equiv N$ str.), 1650 ($-C=O$ str.); ^{1}H-NMR (400 MHz, DMSO-d_6) δ_H (ppm): 0.89 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 2.14–2.33 (4H, m, 2 CH_2), 4.88 (s, 1H, quinoline H-4), 6.03 (s, 2H, NH_2), 7.22–8.06 (m, 12H, Ar–H), 8.27 (s, 1H, pyrazole H-5), 8.33 (s, 1H, thiazole H-5); ^{13}C-NMR (100 MHz, DMSO-d_6) δ_C (ppm): 26.99, 27.64 (2C, CH_3), 28.58 (C4), 32.89 ($C(CH_3)_2$), 40.07 (CH_2), 50.01 (CH_2–CO), 64.10 (*C*–CN), 115.91, 116.13, 116.34, 118.44, 118.63, 120.95, 126.41, 126.56, 126.88, 127.02, 127.91, 128.08, 128.79, 130.04, 130.65, 135.39, 139.63, 145.15, 149.88, 151.10, 151.30, 157.92 (22C, Ar–C), 195.57 (C=O); MS *m/z*: 619.2 $[M + 1]^+$. Anal. calcd. for $C_{34}H_{27}FN_6OS_2$ (618.75 g/mol): C, 66.00; H, 4.40; N, 13.58. Found: C, 65.83; H, 4.23; N, 13.67.

Methodology for *in-vitro* antimicrobial screening or Minimal Inhibitory Concentration (MIC) measurement

The *in-vitro* antimicrobial activities of all the synthesized compounds and the standard drugs were assessed against three representatives 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 the National Committee for Clinical Laboratory Standards (NCCLS) [23]. The strains employed for the activity were procured from the Institute of Microbial Technology, Chandigarh (MTCC – micro type culture collection). The inoculum size for the 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 suspensions for the test bacteria and Sabouraud Dextrose broth was used as fungal nutrition. Ampicillin, chloramphenicol, ciprofloxacin, gentamicin, and norfloxacin were used as standard antibacterial drugs, whereas griseofulvin and nystatin were used as standard antifungal drugs. DMSO was used as diluent/vehicle to get the desired concentrations of the synthesized compounds and standard drugs for testing the standard microbial strains. Serial dilutions were prepared for primary and secondary screening. Each synthesized compound and the standard drugs were diluted ob $\mu g\ mL^{-1}$ concentrations of the synthesized drugs were taken. The active synthesized compounds found in this primary screening were further diluted to obtain 200, 100, 62.5, 50, 25, 12.5, and 6.25 $\mu g\ mL^{-1}$ concentrations for a secondary screening to test all microorganisms. The control tube containing no antibiotic was immediately subcultured (before inoculation) by spreading a loopful evenly over a quarter of a plate of medium suitable for the growth of the test organism. The tubes were then incubated at 37°C for 24 h for bacteria and 48 h for fungi. The highest dilution (lowest concentration) preventing the appearance of turbidity was considered as minimal inhibitory concentration (MIC, in $\mu g\ mL^{-1}$), *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 are summarized in Table 1 as the minimal inhibitory concentration (MIC, $\mu g\ mL^{-1}$).

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