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A Facile Synthesis And Microbial Screening Of Carbonitrile Motif Based Substituted Hexahydroquinoline Derivatives

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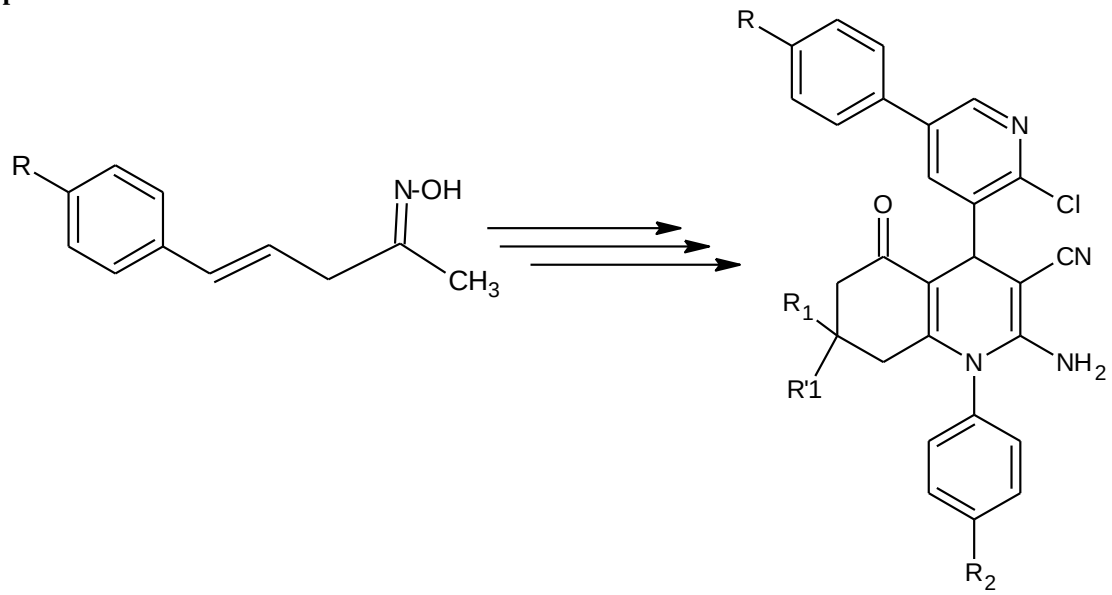
Abstract:
A series of 2-amino-4-(2-chloro-5-(4-substitutedphenyl) pyridin-3-yl)-1-(4-substitutedphenyl)-7,7-disubstituted-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carbonitrilehave been synthesized by the reaction of 5,5-disubstituted-1, 3-cyclohexanedione and 4- substituted aniline in the presence of ethanol and piperidine. The structure of synthesized compounds are established with the help of TLC, IR, [1]HNMR,[13]CNMR, Mass and elemental analysis. The synthesized compounds were screened for in Vitro antibacterial activity against various bacterial strains and antifungal activity against various fungal strains.

Keywords: *1,4,5,6,7,8-hexahydroquinolin-5-ones, Spectroscopy analysis, Microbial screening*

Graphical abstract:



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I. Introduction:

Hydroquinoline derivatives are an important heterocyclic compound to synthesis of organic and medicinal chemistry. Quinolines are the versatile nitrogen containing heterocyclic compounds. Due to its importance as substructures in a wide range of natural and designed products, still great efforts continue to be directed to the development of new quinoline-based structures. More than a century, heterocyclic compounds have attracted particular attention in the organic chemistry because they have an important place in biological and industrial applications. In addition, quinoline derivatives have received considerable attention because of their pivotal role in various biological processes and numerous derivatives of quinolines have been reported to have wide biological activities including the anticancer activity[1,2].anti-inflammatory [3,4].fungicides,

virucides, biocides, alkaloids,rubber chemical and flavouring and anti-malarial agents [5,6].anti-fungal [7]. Quinolines derivatives have several prominent effects and considerable antimicrobial activities [8-12].

II. Materials and Method:

Experimental section: All the melting points are uncorrected and expressed in ^{O}C. The monitoring of the progress of all reactions and homogeneity of the synthesized compounds was carried out by TLC. TLC was runned using TLC aluminium sheet silica gel 60 F_{254} (Merck) and visualization was done using iodine/UV lamp for detection of the spots. Elemental analysis (% C, H, N) was carried out by Perkin Elmer 2400 CHN analyser. IR spectra of all the compounds have been recorded on a Shimadzu FT-IR 8401 spectrophotometer in KBr disks. The ^{1}H-NMR spectra have been recorded on a Bruker AC 400F (400MHz) instrument using TMS as internal standard in DMSO-d6 as a solvent, chemical shifts in δ ppm. Mass spectra; JEOL-JMS 600 spectrometer. The solvent was removed under reduced pressure using Buchi rotary evaporator. Chemicals were purchased from AR grade and substituted anilines, malononitrile are commercial products and were used without further purification. All the solvents were distilled before use.

III. Methodology:

Synthesis of 2-amino-4-(2-chloro-5-(4-substitutedphenyl) pyridin-3-yl)-1-(4-substitutedphenyl)-7, 7-disubstituted-5-oxo-1, 4, 5, 6, 7, 8-hexahydroquinoline-3-carbonitrilederivatives.

Synthesis of 5-(4-substitutedphenyl)-2-chloro-3-formyl pyridine [I].

Charged Dimethylformamide (9.66 mL, 60 mmoles) and N-(2-arylethenyl) acetamide (5 mmoles) in a three-necked round-bottomed flask equipped with a thermometer pocket, reflux condenser, guard tube and mechanical stirrer. Reaction mixture cooled to 0^{0}C. To it phosphorous oxychloride (40 mmoles) was added drop wise with stirring over a period of 30-40 minutes at 0-5^{0}C. Stirred the reaction mixture for 1 hour at room temperature and then stirred at 90^{0}C for 4 hours.

After the completion of the reaction the reaction mass cooled to room temperature and poured in crushed ice and neutralized with sodium acetate. The crude solid was filtered and washed with water, mother liquid extracted with chloroform and evaporated to dryness. The resulting crude solid was crystallized from Diethyl ether to give a compound.

Synthesis of {[2-chloro-5-(4-substitutedphenyl) pyridin-3-yl] methylidene} propanedinitrile [II].

5-phenyl-2-chloro-3-formyl pyridine (0.01mole), malononitrile (0.01mole) and ethanol (10 ml) were charged in R.B. flask with mechanical stirrer, thermometer pocket and reflux condenser. The reaction mixture was slowly heated. When the entire compound was dissolved in mixture, 2-3 drops of triethylamine was added to mixture and refluxed for 0.5 to 1 hr. After the completion of reaction (checked by TLC), the product was filtered and washed with chilled ethanol. The product was recrystallized with methanol. All the other compounds (II a-c) were synthesized by above procedure.

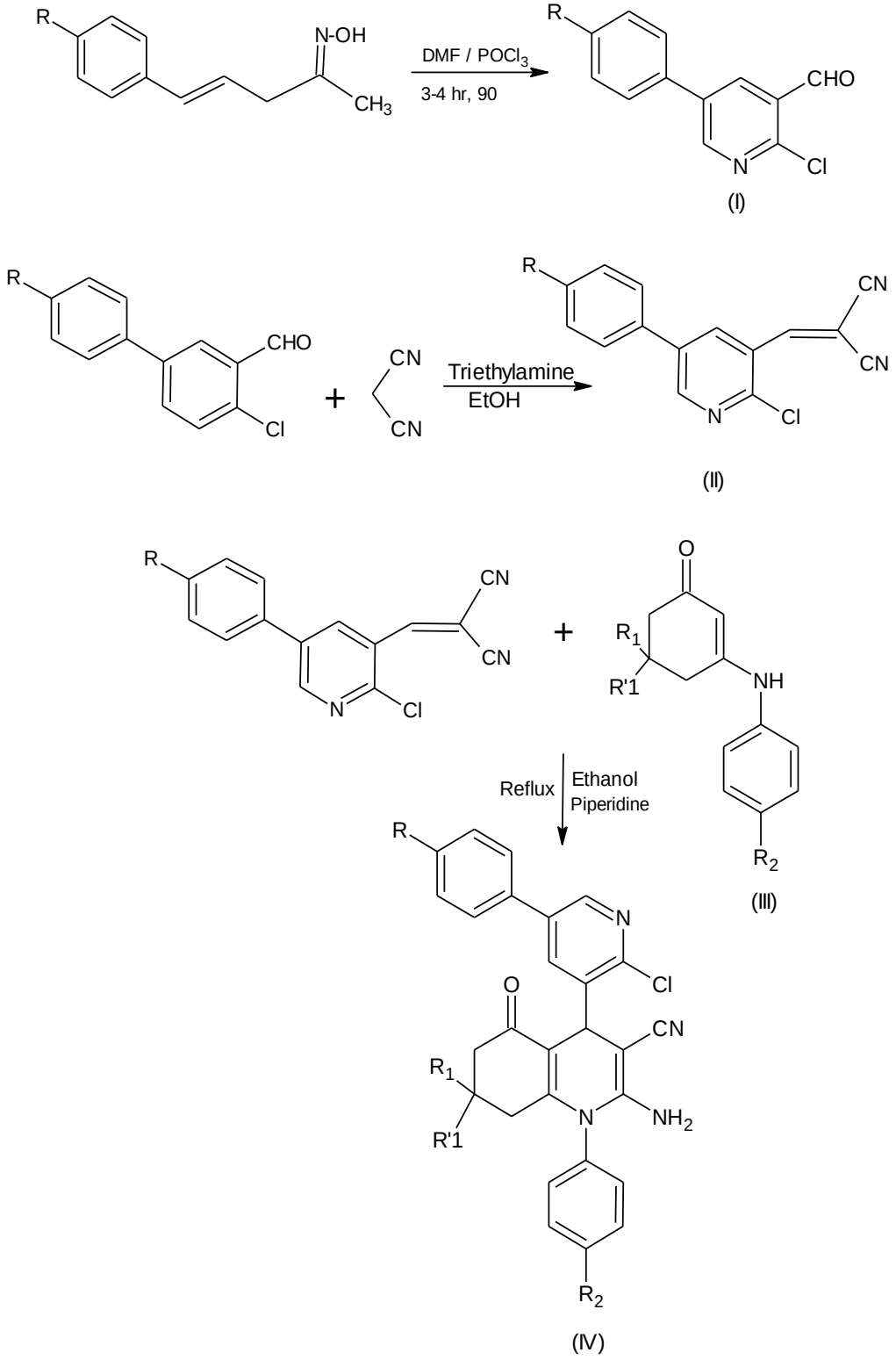
Synthesis of enaminone (III)

A mixture of 5, 5-disubstituted-1, 3-cyclohexanedione (0.01 mole) and 4- substituted aniline (0.01 mole) was heated in oil bath for 1 hr. and cooled to room temperature. The separated solid mass was filtered and washed with ether and dried.

Synthesis of 2-amino-4-(2-chloro-5-(4-substitutedphenyl) pyridin-3- yl)-1-(4-substitutedphenyl)-7, 7-disubstituted-5-oxo-1, 4, 5, 6, 7, 8- hexahydroquinoline-3-carbonitrile derivatives (Q-1 toQ-10) (IV)

Charged enaminone (0.01mole), {[2-chloro-5-(4-substitutedphenyl) pyridin-3-yl] methylidene} propanedinitrile (0.01mole), piperidine (3-4 drops) and ethanol (10 ml) in a three-necked round-bottomed flask equipped with a thermometer pocket, reflux condenser and mechanical stirrer. Reaction mass was refluxed with continuous stirring. The reaction was monitored by TLC, after the completion of reaction, it was cooled to room temperature and stirred for 10-15 min; the resulting solid mass was filtered, washed with small amount of ethanol and dried. The crude product was purified by leaching in equimolar mixture of chloroform and methanol to obtain the pure solid sample.

Synthesis of 2-amino-4-(2-chloro-5-(4-substitutedphenyl) pyridin-3- yl)-1-(4-substitutedphenyl)-7, 7-disubstituted-5-oxo-1, 4, 5, 6, 7, 8- hexahydroquinoline-3-carbonitrile derivatives

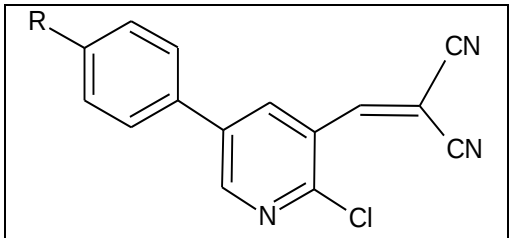


Reaction Scheme

Scheme-1: Synthesis of 2-Amino-4-(2-Chloro-5-(4-Substitutedphenyl) Pyridin-3- Yl)-1-(4-Substitutedphenyl)-7, 7- Disubstituted-5-Oxo-1, 4, 5, 6, 7, 8- Hexahydroquinoline-3-Carbonitrile Derivatives
[Where R = H, Me, Cl; R_1, R'_1 = H, CH_3; R_2 = H, CH_3, OCH_3, Cl, Br_2, NO_2]

IV. Results and Discussion:

Spectroscopic Analysis of YlidenemalononitrileDerivatives



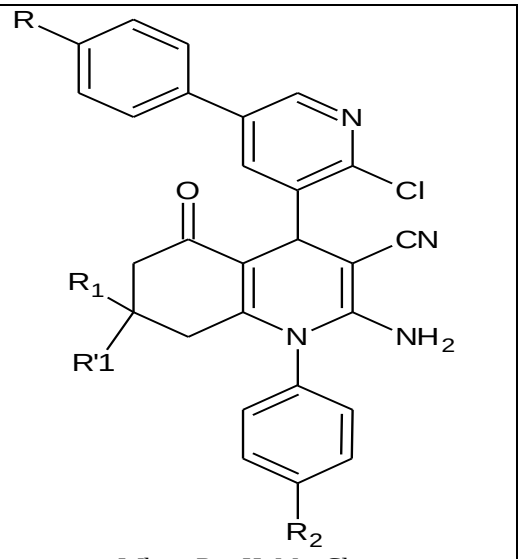
Where R = H, Me, Cl

Comp (II - a) R = H, M.P 122-126 C^0, Yield 87%, **IR cm^{-1}** 3040 (C-H str of =CH-), 2240 (C≡N str.), 1570 & 1480 (C=C str. of aromatic ring), 745(C-Cl str.) **^{1}H NMR $\delta_H$ppm** 7.18-8.93(1H, s, -CH=C-and 7H, m, Ar-H)

Comp (II - b) R = -Me, M.P 195-200 C^0, Yield 85%, **IR cm^{-1}** 3048 (C-H str. of =CH-),2889 (C-H str. of –CH_3),2245(C≡N str.),1575&1485 (C=C str. of aromatic ring), 737(C-Cl str.)**^{1}H NMR $\delta_H$ppm** 2.40 (3H, s, -CH_3), 7.18-8.93 (1H, s, -CH=C- and 6H, m, ArH)

Comp (II - c) R = -Cl, M.P 215-217 C^0, Yield 75%, **IR cm^{-1}** 3046 (C-H str. of =CH-), 2250 (C≡N str.), 1570 & 1465 (C=C str. of aromatic ring), 732 (C-Cl str.) **^{1}H NMR $\delta_H$ppm** 7.25-8.82 (1H, s, -CH=C- and 6H, m, Ar- H)

Spectroscopic Analysis and analytical data of Synthesis of 2-amino-4-(2-chloro-5-(4-substitutedphenyl) pyridin-3- yl)-1-(4-substitutedphenyl)-7, 7-disubstituted-5-oxo-1, 4, 5, 6, 7, 8- hexahydroquinoline-3-carbonitrile derivatives



Where R = H, Me, Cl
R_1 R'_1 = H, CH_3
R_2 = H, CH_3, OCH_3, Cl, Br, NO_2

Q1: M.P. 265-268^{0}C, Yield 81%, **IRcm^{-1}** 3475 (asym N-H str.), 3345 (sym N-H str), 3025 (aromatic C-H str), 2180 (-CN str), 1660 (C=O str), 1570 & 1460 (C=C str of aromatic ring), 712 (C-Cl str),**^{1}H NMR $\delta_H$ppm** 1.80-2.46 (m, 6H, 3xCH_2), 4.60 (s,1H, CH), 5.45 (s, 2H, NH_2), 7.29-7.60 (m, 12H, Ar-H), **Mol. For**. $C_{27}H_{21}ClN_4O$, **Mol. Wt**. 452, **Anal. data**. (Cal/Found) C%71.60/70.45, H% 4.67/4.59, N% 12.37/13.08. (where R, R_1/ R'_1, R_2, = -H, -H, -H).

Q2: M.P. 276-279^{0}C, Yield 79%, **IRcm^{-1}** 3488 (asym N-H str.), 3340 (sym N-H str), 3017 (aromatic C-H str), 2185 (-CN str), 1635 (C=O str), 1575 & 1455 (C=C str of aromatic ring), 709 (C-Cl str),**^{1}H NMR $\delta_H$ppm** 1.89 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 1.80-2.46 (m, 6H, 3xCH_2), 4.60 (s, 1H, CH), 5.45 (s, 2H, NH_2), 7.29-7.60 (m, 11H, Ar-H), **Mol. For**. $C_{28}H_{23}ClN_4O$, **Mol. Wt**. 466, **Anal. data**. (Cal/Found) C% 72.02/73.04, H% 4.96/5.20, N% 12.00/11.86. (where R, R_1/ R'$_1$, R_2, = -H, -H, -CH_3).

Q3: M.P. 280-283^{0}C, Yield 71%, **IRcm^{-1}**3452 (asym N-H str.), 3388 (sym N-H str), 3025 (aromatic C-H str), 2182 (-CN str), 1628 (C=O str), 1572 & 1464 (C=C str of aromatic ring), 1248 & 1022 (C-O-C asym&sym str of –OCH_3), 710 (C-Cl str), **^{1}H NMR $\delta_H$ppm** 3.83(s, 3H, OCH_3), 2.28(s, 3H, CH_3), 1.85-2.48 (m, 6H, 3xCH_2), 4.58 (s, 1H, CH), 5.40 (s, 2H, NH_2), 7.30-7.62 (m, 11H, Ar-H), **Mol. For**. $C_{28}H_{23}ClN_4O_2$, **Mol. Wt**. 482, **Anal. data**. (Cal/Found) C%69.63/68.71, H% 4.80/3.94, N% 11.60/12.04. (where R, R_1/ R'$_1$, R_2, = -H, -H, OMe).

Q4: M.P. 283-286^{0}C, Yield 70%, **IRcm^{-1}** 3462 (asym N-H str.), 3330 (sym N-H str), 3020 (aromatic C-H str), 2186 (-CN str), 1630 (C=O str), 1570 & 1450 (C=C str of aromatic ring), 718 (C-Cl str), **^{1}H NMR $\delta_H$ppm** 2.20 (s, 3H, CH_3), 1.85-2.50 (m, 6H, 3xCH_2), 4.49 (s, 1H, CH), 5.52 (s, 2H, NH_2), 7.30-7.60 (m, 11H, Ar-H), **Mol. For**. $C_{27}H_{20}Cl_2N_4O$, **Mol. Wt**. 487, **Anal. data**. (Cal/Found) C%66.54/65.72, H% 4.14/4.30, N% 11.50/10.75. (where R, R_1/ R'$_1$, R_2, = -H, -H, -Cl).

Q5: M.P. 281-284^{0}C, Yield 80%, **IRcm^{-1}** 3465 (asym N-H str.), 3333 (sym N-H str.), 3028 (aromatic C-H str.), 2189 (-CN str.), 1639 (C=O str.), 1572 & 1464 (C=C str. of aromatic ring), 710 (C-Cl str.), 565 (C-Br str.), **^{1}H NMR $\delta_H$ppm** 2.17 (s, 3H, CH_3), 1.78-2.48 (m, 6H, 3xCH_2), 4.35 (s, 1H, CH), 5.54 (s, 2H, NH_2), 7.30-7.55 (m, 11H, Ar-H), **Mol. For**. $C_{27}H_{20}BrClN_4O$, **Mol. Wt**. 531, **Anal. data**. (Cal/Found) C%60.98/61.41, H% 3.79/3.25, N% 10.53/14.04. (where R, R_1/ R'$_1$, R_2, = -H, -H, -Br).

Q6: M.P. 270-273^{0}C, Yield 70%, **IRcm^{-1}** 3485 (asym N-H str.), 3360 (sym N-H str.), 3020 (aromatic C-H str.), 2170 (-CN str.), 1640 (C=O str.), 1561 & 1475 (C=C str. of aromatic ring), 720 (C-Cl str.), **^{1}H NMR $\delta_H$ppm** 1.63(s, 3H, CH_3), 2.19(s, 3H, CH_3), 1.80-2.50 (m, 6H, 3xCH_2), 4.62 (s, 1H, CH), 5.49 (s, 2H, NH_2), 7.31-7.62 (m, 10H, Ar-H), **Mol. For**. $C_{28}H_{22}Cl_2N_4O$, **Mol. Wt**. 501, **Anal. data**. (Cal/Found) C%67.07/66.27, H% 4.42/3.95, N% 11.17/11.84. (where R, R_1/ R'$_1$, R_2, = -CH_3, -H, -Cl).

Q7: M.P. 273-277^{0}C, Yield 60%, **IRcm^{-1}** 3467 (asym N-H str.), 3318 (sym N-H str.), 3025 (aromatic C-H str.), 2163 (-CN str.), 1670 (C=O str.), 1548 & 1352 (N=O str. of Ar=NO_2), 1577 & 1455 (C=C str. of aromatic ring), 710 (C-Cl str.), **^{1}H NMR $\delta_H$ppm** 1.60(s, 3H, CH_3), 2.10(s, 3H, CH_3), 1.83-2.53 (m, 6H, 3xCH_2), 4.60 (s, 1H, CH), 5.50 (s, 2H, NH_2), 7.30-7.80 (m, 10H, Ar-H), **Mol. For**. $C_{28}H_{22}ClN_5O_3$, **Mol. Wt**. 511, **Anal. data**. (Cal/Found) C% 65.69/65.90, H% 4.33/4.54, N% 13.65/14.28. (where R, R_1/ R'$_1$, R_2, = - CH_3, -H, -NO_2).

Q8: M.P. 276-280^{0}C, Yield 72%, **IRcm^{-1}**3480 (asym N-H str.), 3333 (sym N-H str.), 3018 (aromatic C-H str.), 2155 (-CN str.), 1667 (C=O str.), 1582 & 1451 (C=C str. of aromatic ring), 703 (C-Cl str.), **^{1}H NMR $\delta_H$ppm** 2.17 (s, 3H, CH_3),2.20 (s, 3H, CH_3),1.58-2.30 (m, 6H, 3xCH_2), 4.64 (s, 1H, CH), 5.32 (s, 2H, NH_2), 7.15-7.71 (m, 10H, Ar-H), **Mol. For**. $C_{28}H_{22}Cl_2N_4O$, **Mol. Wt**. 501, **Anal. data**. (Cal/Found) C% 67.07/66.76, H% 4.42/4.55, N% 11.57/10.81. (where R, R_1/ R'$_1$, R_2, = -Cl, -H, -CH_3).

Q9: M.P. 266-269^{0}C, Yield 73%, **IRcm^{-1}** 3472 (asym N-H str.), 3318 (sym N-H str.), 3019 (aromatic C-H str.), 2185 (-CN str.), 1660 (C=O str.), 1568& 1472 (C=C str. of aromatic ring), 723 (C-Cl str.), **^{1}H NMR $\delta_H$ppm** 2.19(s, 3H, CH_3), 1.64-2.36 (m, 6H, 3xCH_2), 4.60 (s, 1H, CH), 5.35 (s, 2H, NH_2), 7.10-7.55 (m, 10H, Ar-H), **Mol. For**. $C_{27}H_{19}Cl_3N_4O$, **Mol. Wt**. 521, **Anal. data**. (Cal/Found) C% 62.15/61.52, H% 3.67/3.80, N% 10.74/11.13. (where R, R_1/ R'$_1$, R_2, = -Cl, -H, -Cl).

Q10: M.P. 284-287^{0}C, Yield 73%, **IRcm^{-1}**3455 (asym N-H str.), 3348 (sym N-H str.), 3025 (aromatic C-H str.), 2210 (-CN str.), 1668 (C=O str.), 1560& 1472 (C=C str. of aromatic ring), 697 (C-Cl str.), 1375 (*gem*-dimethyl str.)**^{1}H NMR $\delta_H$ppm** 0.81(s, 3H, CH_3), 0.83 (s, 3H, CH_3), 1.72-2.39 (m, 4H, 2xCH_2), 4.60 (s, 1H, CH), 5.38 (s, 2H, NH_2), 7.10-7.63 (m, 12H, Ar-H), **Mol. For**. $C_{29}H_{25}ClN_4O$, **Mol. Wt**. 480, **Anal. data**. (Cal/Found) C% 72.42/73.02, H% 5.24/5.18, N% 11.65/12.09. (where R, R_1/ R'$_1$, R_2, = -H, - CH_3 -H).

Scheme-I and Scheme-II outline the synthesis of intermediates used for the preparation of final compounds. Scheme-III outlines the synthesis of new quinoline derivatives (Q-1 to Q-10). The structures of the compounds were confirmed on the basis of elemental analysis and spectral data. As an example, the IR spectra shows band at 3485 cm^{-1} for asym N-H str., 3360 cm^{-1} for sym. N-H str., 3020 cm^{-1} for aromatic C-H

stretching, 2170 cm^{-1} for CN stretching, 1640 cm^{-1} for C=O stretching carbonyl, 1561&1475$cm^{-1}$for C=C stretching of aromatic ring and 720$cm^{-1}$for C-Cl stretching.^{1}H-NMR spectra showed signal at δ 1.63 and 2.19 for two methyl group, a multiplate at δ1.80-for three methylene group, two singlet at δ 4.62 and δ 5.49 for methine group and amine group respectively and a multiplate due to the aromatic protons around at δ 7.31-7.62.

Table - 1: Antimicrobial Activity of Synthesis of 2-amino-4-(2-chloro-5-(4-substitutedphenyl) pyridin-3-yl)-1-(4-substitutedphenyl)-7, 7-disubstituted-5-oxo-1, 4, 5, 6, 7, 8- hexahydroquinoline-3-carbonitrile derivatives

Compound Name	Inhibiton zone (in mm) against					
	E.coli	***B.substilis***	***S.aureus***	***F.oxyporum***	***A.niger***	***R.oryzae***
Q_1	21	20	18	20	19	21
Q_2	18	17	19	19	22	18
Q_3	20	19	17	20	17	20
Q_4	17	16	19	21	20	19
Q_5	22	18	21	18	21	23
Q_6	19	16	21	20	21	19
Q_7	17	18	22	17	21	20
Q_8	19	17	15	19	18	21
Q_9	24	18	20	18	22	19
Q_{10}	18	20	19	19	18	21
Ciprofloxacin	35	34	33	---	---	---
Ampicillin	28	30	30	---	---	---
Griseofulvin	---	---	---	28	26	30

V. Result of antimicrobial activity:

All the synthesized compounds Q-1 to Q-10 were tested against microorganism species at 1000 ppm concentration. The observed results of antibacterial screening reported in above table indicate that methyl group containing compounds Q_1, Q_5, and Q_9, are active against bacterial spices *E.coli*, NO_2 group containing compound Q_3 and methoxy group containing compound Q_3 are found active against *B.substilis*and Br group containing compound Q_5 and NO_2 group containing compound Q_3 active against *E.coli, S.aureus*spices.

From the antifungal assay it has been also observed that compounds Q_1, Q_3, Q_4, and Q_6 are found to be active against *F.oxysporium*, Compound Q_2, Q_5, Q_6, Q_7, and Q_9 having methyl substituents show the good activity against *A.niger* and halogen containing compound Q_5shows good activity against *R.oryzae*. Rest of the compounds show significant activity but it could not reach the effectiveness of the conventional fungicidal Griseofulvin.

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