Indian Journal of Chemistry
Vol. 60B, February 2021, pp. 261-266

2-Pyridone quinoline hybrids as potent antibacterial and antifungal agents

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Received 11 May 2020; accepted (revised) 4 September 2020

An efficient synthetic strategy for the synthesis of 6-amino-1-(((2-chloroquinolin-3-yl)methylene)amino)-2-oxo-4-(aryl)-1,2-dihydropyridine-3,5-dicarbonitriles is well described in this paper. Structures of synthesized compounds have been identified by standard spectroscopic techniques like ^{1}H NMR, ^{13}C NMR, IR and mass spectroscopy. Results of the biological activity reveals that electron withdrawing groups and presence of –OH group on *meta* position play a significant role for the increment in the antibacterial and antifungal activities respectively of **3a-j**. In the present study, it has been observed that compounds **3i** and **3e** are the most active antimicrobials.

Keywords: Quinoline, 2-pyridone,antimicrobial,structure activity relationship

In recent scenario, bacterial and fungal resistance are biggest challenges for the scientific community. Microbial infections are causing very harmful effect in human body. Due to this, it is necessary to develop new hybrid bioactive motifs which may not be resisted by microbial strains[1]. In order to achieve this goal, we have made different antimicrobial agents using quinoline and 2-pyridone skeleton. Quinoline is most potent lead structure among the other heterocyclic motifs. It is widely used for the treatment of microbial diseases[2-13]. Pyridone nucleus is present in many medicinally important alkaloids like "cytisin" which is a tricyclic alkaloid in which pyridone nucleus is bind with quinolizidine alkaloid[14-24]. Therefore, our research interest is to bind these two active scaffolds in one component and to create new set of compounds (**3a-j**, Scheme I) which may not resist by different microbes.

Results and Discussion

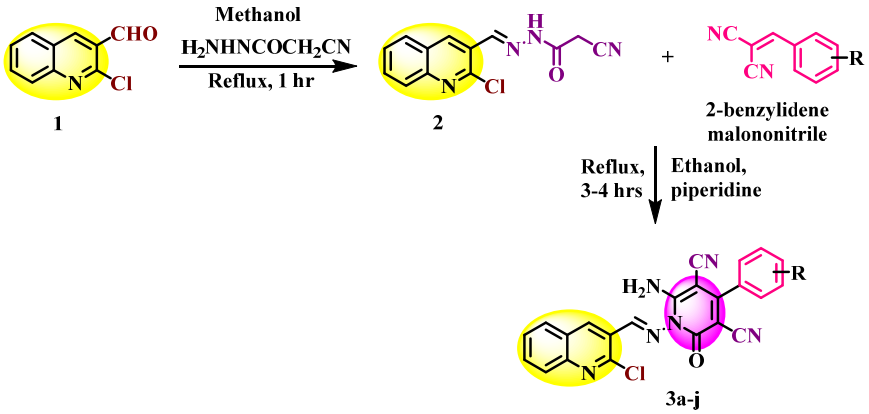
Antibacterial assay

"The newly synthesized compounds were screened for their antibacterial activity against Gram-positive bacteria (*Staphylococcus aureus* (MTCC-96), *Streptococcus pyogenes* (MTCC-442) and Gram-negative bacteria (*Escherichia coli* (MTCC-443), *Pseudomonas aeruginosa* (MTCC-1688). Antibacterial activity was measured as per National Committee for Clinical Laboratory Standards (NCCLS) protocol. For antibacterial evaluation of newly synthesized compounds "Broth dilution method" was used which is a widely used technique for *in vitro* antimicrobial evaluation. As a nutrient medium "Muller Hinton Broth" has been used to grow the strains and DMSO was used as a diluent/vehicle to get the required concentration of newly synthesized compounds to test against different standard bacterial strains. Ciprofloxacin was used as a standard drug for evaluating antibacterial activity, which showed 25, 25, 50 and 50 µg/mL MIC against *E. coli*, *P. aeruginosa*, *S. aureus* and *S. pyogenes* respectively.

Results of *in vitro* antibacterial screening of compounds **3a-j** are displayed in Table I. These screening results indicate that compound **3i** has excellent antibacterial potential against *E. coli*, *P. aeruginosa* and *S. aureus* bacterial strains with MIC of 12.5 µg/mL. Also compound **3i** possess very good antibacterial activity with MIC of 25 µg/mL against *S. pyogenes*. Compounds **3g**, **3h** and **3j** found to have moderate antibacterial efficacy against *E. coli* strain with MIC of 150 µg/mL while compound **3j** also possessed moderate antibacterial potential against *P. aeruginosa*[25].

Antifungal assay

Newly synthesized compounds which were evaluated against different fungal strains. Primary and secondary screening was done for antifungal evaluation. Primary



R = H, 4-CH_3, 4-OCH_3, 3,4,5-$(OCH_3)_3$, 3-OH, 4-OH, 3-NO_2, 4-NO_2, 4-F, 2-Cl

Scheme I — Synthetic scheme for the preparation of compounds **3a-j**

Table I — Results of antibacterial and antifungal activities of compounds **3a-j**

		Minimum inhibitory concentration (MIC) µg/mL						
Entry	-R	Gram-negative		Gram-positive		Fungi		
		Ec	*Pa*	*Sa*	*Sp*	*Ca*	*An*	*Ac*
3a	-H	250	250	250	250	500	500	500
3b	-4-CH_3	250	250	250	250	250	1000	1000
3c	-4-OCH_3	250	250	250	250	500	1000	1000
3d	-3,4,5-$(OCH_3)_3$	250	500	1000	1000	500	500	500
3e	-3-OH	250	250	500	500	25	50	50
3f	-4-OH	500	500	250	250	500	1000	1000
3g	-3-NO_2	150	500	500	1000	1000	500	500
3h	-4-NO_2	150	250	250	250	500	500	500
3i	-4-F	12.5	12.5	12.5	25	1000	1000	1000
3j	-2-Cl	150	150	250	250	1000	500	500
	Ciprofloxacin	25	25	50	50	–	–	–
	Griseofulvin	–	–	–	–	500	100	100

Escherichiacoli (E.c.) MTCC-443; *Pseudomonasaeruginosa(P.a.)* MTCC-1688; *Staphylococcusaureus (S.a.)* MTCC-96; *Staphylococcuspyogenes (S.p.)* MTCC-442; *Candidaalbicans (C.a.)* MTCC-227; *Aspergillusniger (A.n.)* MTCC-282; *Aspergillusclavatus (A.c.)* MTCC- 1323.

screening was performed against *Candida albicans*, *Aspergillus niger* and *Aspergillus clavatus* at various concentrations of 1000, 500, 200 and 100 µg/mL as shown in Table I. For stock solution the synthesized compounds were diluted up to 1000 µg/mL. Compounds which were found to be active in primary screening were tested for secondary screening. Griseofulvin was used as a standard drug for antifungal activity, which showed 500, 100 and 100 µg/mL MIC against *C. albicans*, *A. niger* and *A. clavatus* respectively"[25]. Outcome of antifungal activity suggested that compound **3e** exhibited excellent antifungal activity against *Candida albicans* with MIC of 25 µg/mL and moderate antibacterial activity against *Aspergillusniger* and *Aspergillusclavatus* with MIC of 50 µg/mL .Figure 1 displayed the comparison of the antimicrobial activity.

Structure Activity Relationship Study

Transparently elucidated from the results of antibacterial screening of compounds **3a-j**, presence of electron-withdrawing groups in compounds **3a-j** is responsible for enhancing the antibacterial potential. Among various functional groups with *–I* effect, presence of –F showed excellent activity against bacterial strains. However other electron-withdrawing groups *i.e.* –NO_2 and -Cl showed moderate activity against *Escherichia coli* species. As shown in Table I,

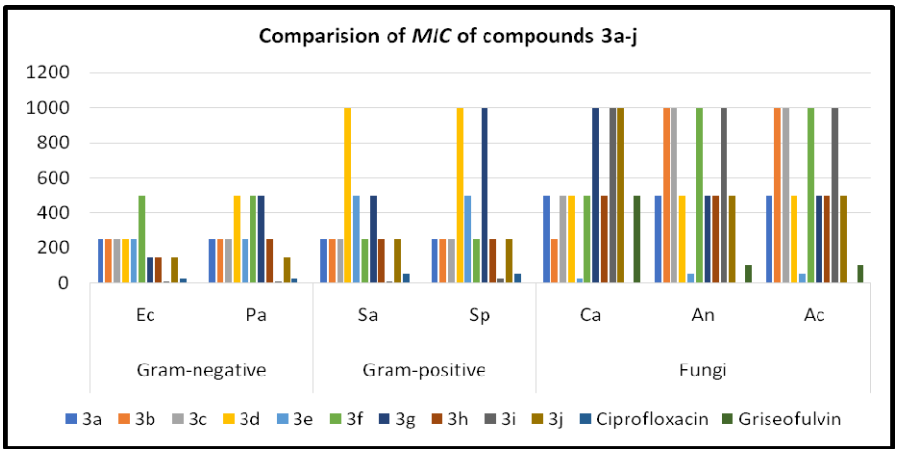


Figure 1 — Comparison of MIC of compounds **3a-j** against bacterial and fungal strains

among various electron-donating functional groups, presence of –OH group on *meta* position is highly responsible for excellent activity against *Candida albicans*, *Aspergillus niger* and *Aspergillus clavatus*. Comparison of MIC values of compounds **3a-j** against bacterial and fungal strains using ciprofloxacin and griseofulvin as standard drugs are depicted in Figure 1.

Experimental Section

All reactions except those in aqueous media were carried out by standard techniques for the exclusion of moisture. Melting points were taken in open glass capillary tubes using a Toshniwal melting point apparatus and are uncorrected. TLC on silica gel plates (Merck, 60, F_{254}) was used for checking homogeneity and reaction monitoring. Column chromatography over silica gel (Merck, 70-230 mesh and 230-400 mesh ASTH for flash chromatography) was applied when necessary to isolate and purify the reaction products. Elemental analysis (% CHN) was carried out on a Perkin-Elmer 2400 CHN analyser. IR spectra of all compounds were recorded on a Perkin-Elmer FT-IR spectrophotometer in KBr. ^{1}H NMR spectra were recorded on a Bruker Advance II 400 MHz and ^{13}C NMR spectra on Varian Mercury 400 at 100 MHz in $CDCl_3$ as a solvent and tetramethylsilane (TMS) as an internal standard. Mass spectra were scanned on a Shimadzu LC-MS 2010 spectrometer. Anhydrous reactions were carried out in oven-dried glass wares in nitrogen atmosphere and Büchi Rotavapor instrument was used for distillation purpose.

Preparation of 2-chloroquinoline-3-carbaldehyde, 1

Synthesis of 2-chloroquinoline-3-carbaldehyde was achieved by reported literature[26].

Preparation of *N*'-((2-chloroquinolin-3-yl)methylene)-2-cyanoacetohydrazide, 2

The solution of compound **1** was prepared by using 1,4-dioxane as a solvent, 2-cyanoacetohydrazide was added in small portions with stirring in that solution. The resulting mixture was refluxed for 1 hour and cooled down at RT. The solid separated was filtered and recrystallized with the mixture of methanol and chloroform. Yield: 90%. m.p. 210°C. IR (KBr): 3435 (>N-H, stretching), 2243, 2211 (-C≡N, stretching), 1664 (>C=O, stretching), 756 (-C-Cl, stretching), 1504 cm^{-1} (>C=N, stretching); ^{1}H NMR (400 MHZ, $CDCl_3$): δ 3.12 (s, 9H, Ar-$(OCH_3)_3$, 6.72-8.77 (s, 7H, Ar-H), 8.27 (s, 2H, Ar-CH=N-), 8.96 (s, 2H, Ar-NH_2); LCMS: *m/z* 272.05 (M^+). Anal. Calcd for $C_{13}H_9ClN_4O$ C, 57.26; H, 3.33; Cl, 13.00; N, 20.55; O, 5.87. Found: C, 57.27; H, 3.34; Cl, 13.01; N, 20.57; O, 5.84%.

General procedure for the preparation of 6-amino-1-(((2-chloroquinolin-3-yl)methylene)amino)-2-oxo-4-(aryl)-1,2-dihydropyridine-3,5-dicarbonitriles, 3a-j

A mixture of compound **2** (0.01 mol), corresponding 2-benzylidenemalononitrile (0.01 mol) and 2 drops of piperidine in ethanol (99.9%, 50 mL) was refluxed for 2-3 h. The mixture was then cooled down to RT and the crystals formed were filtered, dried and purified by recrystallization from aqueous dimethylformamide.

6-amino-1-(((2-chloroquinolin-3-yl)methylene)amino)-2-oxo-4-phenyl-1,2-dihydropyridine-3,5-dicarbonitrile, 3a: Yield: 59%. m.p. 242°C. IR (KBr): 3436 (>N-H, stretching), 2244,

2212 (-C≡N, stretching), 1666 (>C=O, stretching), 757 (-C-Cl, stretching), 1506 cm^{-1} (>C=N, stretching); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.71-8.75 (s, 9H, Ar-H), 8.25 (s, 2H, Ar-CH=N-), 8.94 (s, 2H, Ar-NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.4, 160.0, 159.5, 149.7, 143.2, 137.7, 132.3, 131.2, 128.9, 128.7 (2), 128.5, 128.2, 127.9, 127.6, 127.1, 126.9, 125.7, 124.1, 115.6(2), 115.5, 76.5; LCMS: *m/z* 424.85 (M^+). Anal. Calcd for $C_{23}H_{13}ClN_6O$ C, 65.02; H, 3.08; Cl, 13.00; N, 19.78; O, 3.77. Found: C, 64.87; H, 2.89; Cl, 13.01; N, 19.66; O, 3.35%.

6-amino-1-(((2-chloroquinolin-3-yl)methylene)amino)-2-oxo-4-(*p*-tolyl)-1,2-dihydropyridine-3,5-dicarbonitrile, 3b: Yield: 57%. m.p. 249°C. IR (KBr): 3436 (>N-H, stretching), 2244, 2212 (-C≡N, stretching), 1666 (>C=O, stretching), 757 (-C-Cl,stretching), 1506 cm^{-1} (>C=N, stretching); ^{1}H NMR (400 MHZ, $CDCl_3$): δ, 6.71-8.75 (s, 9H, Ar-H), 8.25 (s, 2H, Ar-CH=N-), 8.94 (s, 2H, Ar-NH_2), 2.41(s, 2H, Ar-CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.6, 160.2, 159.4, 152.9, 149.5, 143.4, 137.6, 137.4, 134.3 (3), 131.2, 129.7, 128.7 (3), 128.2, 127.4, 127.4, 126.7, 124.9, 115.4 (2), 115.5, 76.7, 21.5; LCMS: *m/z* 438.10 (M^+). Anal. Calcd for $C_{24}H_{15}ClN_6O$ C, 65.68; H, 3.45; Cl, 13.00; N, 19.15; O, 5.06. Found: C, 65.45; H, 3.22; Cl, 13.01; N, 19.00; O, 5.04%.

6-amino-1-(((2-chloroquinolin-3-yl)methylene)amino)-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile, 3c: Yield: 59%. m.p. 255°C. IR (KBr): 3436 (>N-H,stretching), 2244, 2212 (-C≡N, stretching), 1130,1048 (-C-O-C-, stretching) 1666 (>C=O, stretching), 757 (-C-Cl, stretching), 1506 cm^{-1} (>C=N, stretching); ^{1}H NMR (400 MHZ, $CDCl_3$): δ, 6.71-8.75 (s, 9H, Ar-H), 8.25 (s, 1H, Ar-CH=N-), 8.94 (s, 2H, Ar-NH_2), 3.86 (s, 3H, Ar-OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.4, 160.0, 159.8, 159.5, 152.7, 149.7, 143.3, 137.8, 130.1 (2), 131.0, 128.1, 127.8, 127.2, 126.8, 124.8, 124.3, 115.8(2), 115.3, 114.2 (2), 76.5, 55.8; LCMS: *m/z* 454.87 (M^+). Anal. Calcd for $C_{24}H_{15}ClN_6O_2$ C, 63.37; H, 3.32; Cl, 13.00; N, 18.48; O, 7.03. Found: C, 63.31; H, 3.15; Cl, 13.01; N, 18.33; O, 7.04%.

6-amino-1-(((2-chloroquinolin-3-yl)methylene)amino)-2-oxo-4-(3,4,5-trimethoxyphenyl)-1,2-dihydropyridine-3,5-dicarbonitrile, 3d: Yield: 60%. m.p. 259°C. IR (KBr): 3436 (>N-H, stretching), 2244, 2212 (-C≡N, stretching), 1130, 1048 (-C-O-C-, stretching) 1666 (>C=O, stretching), 757 (-C-Cl, stretching), 1506 cm^{-1} (>C=N, stretching); ^{1}H NMR (400 MHZ, $CDCl_3$): δ, 6.71-8.75 (s, 7H, Ar-H), 8.50 (s, 1H, Ar-CH=N-), 6.49 (s, 2H, Ar-NH_2), 3.83 (s, 9H, Ar-OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.3, 160.2, 159.6, 153.1 (2), 152.5, 149.5, 143.2, 138.5, 137.7, 131.2, 128.2, 127.3, 126.7, 124.4, 115.9 (2), 115.2, 105.2, 76.6, 56.2 (2), 60.7; LCMS: *m/z* 514.93 (M^+). Anal. Calcd for $C_{26}H_{19}ClN_6O_4$ C, 60.65; H, 3.72; Cl, 13.00; N, 16.32; O, 12.43. Found: C, 60.51; H, 3.55; Cl, 13.01; N, 16.21; O, 12.46%.

6-amino-1-(((2-chloroquinolin-3-yl)methylene)amino)-4-(3-hydroxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile, 3e: Yield: 60%. m.p. 262°C. IR (KBr): 3436 (>N-H, stretching), 2244, 2212 (-C≡N, stretching), 3515 (-O-H, stretching), 1666 (>C=O, stretching), 757 (-C-Cl, stretching), 1506 cm^{-1} (>C=N, stretching); ^{1}H NMR (400 MHZ, $CDCl_3$): δ, 6.83-9.04 (s, 9H, Ar-H), 8.49 (s, 1H, Ar-CH=N-), 6.50 (s, 2H, Ar-NH_2), 9.45 (s, 1H, Ar-OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.3, 160.2, 159.4, 158.3, 152.6, 149.8, 137.9, 133.8, 131.2, 130.1, 128.3, 127.7, 127.3, 126.9, 124.4, 121.6, 112.2, 115.6 (2), 115.4, 115.2, 143.4, 76.6; LCMS: *m/z* 440.85 (M^+). Anal. Calcd for $C_{23}H_{13}ClN_6O_2$ C, 62.66; H, 2.97; Cl, 13.00; N, 16.32; O, 7.26. Found: C, 62.40; H, 2.84; Cl, 13.01; N, 16.21; O, 7.21%.

6-amino-1-(((2-chloroquinolin-3-yl)methylene)amino)-4-(4-hydroxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile, 3f: Yield: 59%. m.p. 245°C. IR (KBr): 3436 (>N-H, stretching), 2244, 2212 (-C≡N,stretching), 3515 (O-H, stretching), 1666 (>C=O, stretching), 757 (-C-Cl, stretching), 1506 cm^{-1} (>C=N, stretching); ^{1}H NMR (400 MHZ, $CDCl_3$): δ, 6.83-9.68 (s, 9H, Ar-H), 8.54 (s, 1H, Ar-CH=N-), 6.48 (s, 2H, Ar-NH_2), 9.67 (s, 1H, Ar-OH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.3, 160.2, 159.3, 158.5, 152.6, 149.8, 143.2, 137.9, 133.7, 131.1, 130.2, 128.2, 127.7, 127.3, 126.5, 124.4, 121.6, 112.3, 115.7 (2), 115.2, 115.3, 76.4; LCMS: *m/z* 440.08 (M^+). Anal. Calcd for $C_{23}H_{13}ClN_6O_2$ C, 62.66; H, 2.97; Cl, 13.00; N, 19.06; O, 7.26. Found: C, 62.42; H, 2.82; Cl, 13.01; N, 18.91; O, 7.27%.

6-amino-1-(((2-chloroquinolin-3-yl)methylene)amino)-4-(3-nitrophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile, 3g: Yield: 61%. m.p. 240°C. IR (KBr): 3436 (>N-H, stretching), 2244, 2212 (-C≡N, stretching), 1350,1550 (-NO_2, stretching), 1666 (>C=O, stretching), 757 (-C-Cl,

stretching), 1506 cm^{-1} (>C=N, stretching); ^{1}H NMR (400 MHZ, $CDCl_3$): δ, 6.83-9.68 (s, 9H, Ar-H), 9.04 (s, 1H, Ar-CH=N-), 6.49 (s, 2H, Ar-NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.5, 160.2, 159.3, 152.8, 149.9, 147.9, 143.2, 137.9, 135.1, 133.3, 131.2, 129.4, 128.2, 127.9, 127.1, 126.7, 124.2, 123.3, 120.2, 115.9 (2), 115.2, 76.5; LCMS: *m/z* 469.85 (M^+). Anal. Calcd for $C_{23}H_{12}ClN_7O_3$ C, 58.80; H, 2.57; Cl, 13.00; N, 20.87; O, 10.22. Found: C, 58.69; H, 2.43; Cl, 13.01; N, 20.75; O, 10.26%.

6-amino-1-(((2-chloroquinolin-3-yl)methylene)amino)-4-(4-nitrophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile, 3h: Yield: 61%. m.p. 240°C. IR (KBr): 3436 (>N-H, stretching), 2244, 2212 (-C≡N, stretching), 1350,1550 (-NO_2, stretching), 1666 (>C=O, stretching), 757 (-C-Cl Stretching), 1506 cm^{-1} (>C=N, stretching); ^{1}H NMR (400 MHZ, $CDCl_3$): δ, 6.83-9.68 (s, 9H, Ar-H), 9.04 (s, 1H, Ar-CH=N-), 6.49 (s, 2H, Ar-NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.3, 160.2, 159.3, 152.5, 149.6, 147.9, 143.2, 137.9, 135.1, 133.5, 131.1, 129.6, 128.3, 127.7, 127.3, 126.9, 124.4, 123.2, 120.1, 115.9 (2), 115.4, 76.4; LCMS: *m/z* 469.85 (M^+). Anal. Calcd for $C_{23}H_{12}ClN_7O_3$ C, 58.80; H, 2.57; Cl, 13.00; N, 20.87; O, 10.22. Found: C, 58.67; H, 2.42; Cl, 13.01; N, 20.72; O, 10.23%.

6-amino-1-(((2-chloroquinolin-3-yl)methylene)amino)-4-(4-fluorophenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile, 3i: Yield: 62%. m.p. 251°C. IR (KBr): 3436 (>N-H, stretching), 2244, 2212 (-C≡N,stretching), 945 (-C-F, stretching), 757 (-C-Cl, stretching), 1666 (>C=O, stretching), 1506 cm^{-1} (>C=N, stretching); ^{1}H NMR (400 MHZ, $CDCl_3$): δ, 6.83-9.68 (s, 9H, Ar-H), 9.02 (s, 1H, Ar-CH=N-), 6.55 (s, 2H, Ar-NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.3, 160.1, 159.4, 156.7, 152.9, 149.8, 137.9, 131.2, 129.6, 128.2, 128.1, 127.9, 127.3, 126.9, 124.4, 124.3, 121.8, 115.7 (2), 115.2, 115.4, 143.5, 76.6; LCMS: *m/z* 442.84 (M^+). Anal. Calcd for $C_{23}H_{12}ClFN_6O$ C, 62.38; H, 2.73; Cl, 13.00; N, 18.98; O, 3.61. Found: C, 62.21; H, 2.64; Cl, 13.01; N, 18.77; O, 3.58%.

6-amino-4-(2-chlorophenyl)-1-(((2-chloroquinolin-3-yl)methylene)amino)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile, 3j: Yield: 60%. m.p. 247°C. IR (KBr): 3436 (>N-H, stretching), 2244, 2212 (-C≡N,stretching), 757 (-C-Cl, stretching), 1666 (>C=O, stretching), 1506 cm^{-1} (>C=N, stretching); ^{1}H NMR (400 MHZ, $CDCl_3$): δ, 6.83-9.68 (s, 9H, Ar-H), 8.51 (s, 1H, Ar-CH=N-), 6.48 (s, 2H, Ar-NH_2); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.3, 160.0, 159.6, 156.7, 152.8, 149.6, 137.6, 131.0, 129.6, 128.2, 128.1, 127.9, 127.3, 126.9, 124.2, 124.3, 121.8, 115.9 (2), 115.3, 115.4, 143.5, 76.6; LCMS: *m/z* 459.29 (M^+). Anal. Calcd for $C_{23}H_{12}Cl_2N_6O$ C, 60.15; H, 2.63; Cl, 13.00; N, 18.30; O, 3.48. Found: C,60.04; H, 2.45; Cl, 13.01; N, 18.20; O, 3.44%.

Conclusion

Discussion presented over here indicates that compounds **3a-j** can be synthesized by a simple synthetic path without formation of any side products. Further, among these newly synthesized molecules, compound **3i** exhibited excellent antibacterial potential and compound **3e** is found to have excellent antifungal capacity. Aforesaid structure activity relationship studyrecommends that presence of electron-donating functional groups and presence of –OH group on *meta* position as substituents in compounds **3a-j** is responsible for prominent antibacterial and antifungal potential respectively. Hence further modification of these novel molecules (**3i** and **3e**) constructed by bridging quinoline and 2-pyridone molecules may be useful to identify lead in order to invent new drug resistant antimicrobial candidates.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

Acknowledgement

Authors are thankful to the University Grants Commission, New Delhi and Department of Science and Technology, New Delhi for financial support under the NON-SAP and DST-FIST programs respectively. One of the authors Prof. Nisheeth C. Desai is thankful to the University Grant Commission, New Delhi for awarding BSR Faculty-Fellowship 2019 [No. F 18-1/2011 (BSR)] and financial assistance.

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