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ORIGINAL ARTICLE

Syntheses and anti-microbial evaluation of new quinoline scaffold derived pyrimidine derivatives

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Abstract A series of diversely substituted chalcones derived from a quinoline scaffold, e.g. (E)-3-(2-chloroquinolin-3-yl)-1-(2-hydroxyphenyl) prop-2-en-1-one and its pyrimidine analogues e.g. 2-[2-amino-6-(2-chloroquinolin-3-yl)-5,6-dihydropyrimidin-4-yl]phenols have been prepared by condensation of 2-chloro-3-formyl quinoline with differently substituted 2-hydroxy acetophenones and further treatment with guanidine carbonate. All the newly synthesized compounds have been evaluated for their *in vitro* growth inhibitory activity against *Escherichia coli, Pseudomonas vulgaris, Bacillus subtilis, Staphylococcus aureus*, *Staphylococcus typhi*, *Candida albicans, Aspergillus niger and Pseudomonas chrysogenum*.

1. Introduction

Extensive research on diverse biological activities of heterocycles has confirmed their immense significance in the pathophysiology of diseases. The amalgamation of two pharmacologically important structural scaffolds leads to a new library of heterocycles, possessing a broad spectrum of activities against numerous pathogenic strains and also striking activities against cancer. We have developed an extensive research program on the synthesis (Pathan et al., 2011) and biological evaluations of Chemical Hybrids (as "Molecular Lego Sets") incorporating a diverse architecture of nuclei within their molecular framework and to explore synergistic therapeutic relevance as thrombin inhibitors, prostate specific antigen inhibitors, and anticancer drugs. We have exemplified the synthesis of an array of hybrid molecules: We combined substituted quinolines with pyrazoline residues in hybrid scaffolds in a single molecular framework to secure enhanced and systematically attenuated and accentuated biological activity (Dave and Rahatgaonkar, 2009). Synthesis of hybrid molecules is of interest as a way of synergistically increasing drug discovery portfolios.

Chalcone derivatives have demonstrated activity of pharmaceutical relevance: considerable attention has been lavished on these moieties. The compounds are of potential therapeutic relevance as anti-bacterial, antifungal, antiviral, anti-parasitic, anti-cancer, antileishmaniel and anti-tubercular agents (Peters and Musher, 1937; Crambie and Mistry, 1990; Bratt et al., 2003). Some chalcones are also known to possess anti-inflammatory and analgesic properties. Quinolines and their derivatives

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have been extensively explored for their biological (Gupta et al., 1998; Dube et al., 1998), anti-filarial (Tiwari et al., 2000; Mathew et al., 2010), anti-bacterial (Kidwai et al., 2000; Naik et al., 2009) and anti-malarial (Ziegler et al., 2001; Chauhan and Srivastava, 2001; Kaur et al., 2010) activities and additionally, for their cardiovascular (Dong et al., 1992), anti-neoplastic (Ferlin et al., 2000) and receptor agonist activities (Zhi et al., 1998).

The unique structural motif of pyrimidine has been used as a starting point for an elegant design of potential drugs and novel heterocycles. Pyrimidine containing heterocycles incorporating hydroxyl groups are found to play a vital role in biological processes (Kenner et al., 1944; Bhuiyan et al., 2005) as well as in synthetic drugs. Different pyrimidine heterocycles are reported to have various therapeutic activities like anti-HIV (Noriyuki et al., 2002), anti-tubercular (Jani et al., 1994), antitumor (Safonova et al., 1999) antineoplastic (Jean-Damien et al., 2002), anti-inflammatory (Nakaguti et al., 1986), diuretic (Papesh and Schroeder, 1956) and antimalarial (Tokutake, 1977). Fascinated by such properties, medicinal chemists expend considerable synthetic efforts to construct these fascinating scaffolds in a highly efficient fashion by employing a variety of new elegant strategies. Very few approaches have been directed at the synthesis of heterocycles containing both quinoline and pyrimidine nuclei within a single molecular framework. Our research encompasses the synthesis of quinoline–pyrimidine hybrids.

We embarked on the synthesis of appropriately substituted 2-[2-amino-6-(2-chloroquinolin-3-yl)-5,6-dihydropyrimidin-4-yl] phenols by conventional method and synthesized a library of new quinoline–pyrimidine hybrids **3a–j**.

2. Experimental

2.1. General

Melting points were determined by open capillary method and are uncorrected. All solvents were distilled and dried prior to use. TLC was performed on silica gel G and the spots were exposed to iodine vapour for visualization. A mixture of benzene and ethylacetate (7:3) was used as an eluent. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Brucker AC 400 (MHz) instrument. Chemical shifts are reported in ppm using TMS as the internal standard. IR spectra were obtained on a Perkin Elmer 1800 spectrophotometer using KBr discs and mass spectra were measured with Shimadzu gas chromatograph coupled with QP5050 Spectrometer at 1–1.5 eV.

2.2. Microbiology

2.2.1. In vitro antibacterial and antifungal activities

All the newly synthesized compounds were evaluated for their efficacy against the clinically isolated microorganisms like *Escherichia coli, Pseudomonas vulgaris, Bacillus subtilis, Staphylococcus aureus, Staphylococcus typhi, Candida albicans, Aspergillus niger* and *Pseudomonas chrysogenum*.

The preliminary antimicrobial activities of the compounds **3a–j** were tested using the cup-plate (Collins, 1967) method. For compounds **3a–j**, the nutrient agar broth was prepared by aseptic inoculation with 0.5 mL of 24-h-old subcultures of all the above said microorganisms, in separate flasks at 40–50 °C and mixing well by gentle shaking. About 25 mL of the contents of the flask was poured, evenly spread in a Petri dish (13 cm in diameter) and allowed to set for 2 h. Cups (6 mm in diameter) were made with the help of borer in an agar medium. The compounds to be tested were dissolved in DMSO at different concentrations viz. 10 ug/mL, 100 ug/mL, 200 ug/mL and 500 ug/mL; and were filled in the well made in Petri dishes with 1 mL of the respective solution.

The plates were incubated at 37 °C for 24 h, the control was similarly maintained with 1 mL of DMSO and the zones of inhibition of the bacterial and fungal growth were measured in mm.

The test compounds under investigation were incorporated into agar, which had previously been inoculated with the test organisms.

Ampicillin and amphotericin B were used as the standard drugs. The inoculated plates were incubated at 37 °C for 24 h in the case of bacteria and 48 h in the case of fungus. The zone of inhibition was compared with the standard drugs (Tables 2 and 3).

The minimum inhibitory concentration (MIC) (Murray et al., 1995) of the compounds was tested using the microdilution susceptibility method. The chemical stock solutions of all the compounds and reference drugs were prepared by dissolving 1000 ug in 5 mL DMSO. A series of dilutions was prepared as 500, 200, 100, 10 ug/mL. The culture of microorganism was inoculated in each dilution. The dilutions were incubated at

Table 1 Physical and analytical data of the newly synthesized compounds **3a–j**.

Compound	R^1	R^2	R^3	M.P. (°C)	Yield (%)	Mol. formula	Analysis% found (calculated)		
							C	H	N
3a	Cl	H	H	165	82	$C_{19}H_{14}Cl_2N_4O$	59.06 (59.24)	3.68 (3.66)	14.13 (14.54)
3b	CH_3	H	H	205	78	$C_{20}H_{17}ClN_4O$	65.86 (65.84)	4.48 (4.70)	15.23 (15.36)
3c	Cl	H	Br	210	84	$C_{19}H_{13}BrCl_2N_4O$	49.16 (49.17)	2.66 (2.82)	12.11 (12.07)
3d	CH_3	H	Br	152	78	$C_{20}H_{16}BrClN_4O$	54.09 (54.14)	3.57 (3.63)	13.17 (12.63)
3e	Cl	H	I	238	85	$C_{19}H_{13}Cl_2IN_4O$	44.04 (44.65)	2.32 (2.56)	10.13 (10.96)
3f	CH_3	H	I	168	80	$C_{20}H_{16}ClIN_4O$	48.92 (48.95)	3.45 (3.29)	11.56 (11.42)
3g	Cl	H	NO_2	288	81	$C_{19}H_{13}Cl_2N_5O_3$	52.06 (53.04)	3.05 (3.05)	16.10 (16.28)
3h	CH_3	H	NO_2	250	73	$C_{20}H_{16}ClN_5O_3$	57.88 (58.61)	3.34 (3.94)	17.09 (17.09)
3i	Br	OCH_3	H	130	78	$C_{20}H_{16}BrClN_4O_2$	52.57 (52.25)	3.19 (3.51)	12.21 (12.19)
3j	I	OCH_3	H	132	81	$C_{20}H_{16}ClIN_4O_2$	47.89 (47.41)	3.12 (3.18)	11.17 (11.06)

Table 2 Minimum inhibitory concentration of **3a–j** in ug/mL against clinically isolated *S. aureus* and *P. vulgaris*.

Entry	*S. aureus*					*P. vulgaris*				
	10	100	200	500	App.MIC	10	100	200	500	App. MIC
3a	−−	–	+	++	500	−−	++	++	++	100
3b	−−	++	++	++	100	−−	++	++	++	100
3c	−−	–	+	++	500	−−	++	++	++	100
3d	−−	++	++	++	100	−−	++	++	++	100
3e	−−	−−	+	++	500	−−	++	++	++	100
3f	−−	−−	+	++	500	−−	–	+	++	500
3g	−−	++	++	++	100	−−	–	+	++	500
3h	−−	–	++	++	200	−−	++	++	++	100
3i	−−	++	++	++	100	−−	++	++	++	100
3j	−−	++	++	++	100	−−	++	++	++	100
Ampicillin	+++	+++	+++	+++	10	+++	+++	+++	+++	10

Symbols: (–) = confluent growth (no inhibition), Inactive (< 10 mm); (+) = weakly active (10–15 mm); (++) = moderately active (16–21 mm); (+++) = highly active (22–28 mm).

Table 3 Minimum inhibitory concentration of **3a–j** at 200 ug/mL against clinically isolated C. *albicans, A. niger* and *P. chrysogenum*.

Entry	*C. albicans*	*A. niger*	*P. chrysogenum*
3a	–	–	–
3b	–	–	–
3c	–	–	–
3d	–	++	+
3e	–	–	+
3f	–	–	–
3g	–	–	–
3h	–	–	–
3i	–	–	–
3j	+	+	–
Amphotericin B	++++	++++	++++

Symbols: zone diameter of growth inhibition: (–) = inactive (< 10 mm); (+) = weakly active (10–15 mm); (++) = moderately active (16–21 mm); (+++) = highly active (22–28 mm).

37 °C for 24 h and 48 h for bacteria and fungus, respectively. The solutions with no turbidity were considered as MIC for tested compounds.

3. General procedure for synthesis of a novel series of differently substituted 2-[2-amino-6-(2-chloroquinolin-3-yl)-5,6-dihydropyrimidin-4-yl]phenol (3a–j)

Major precursors of the reaction, i.e. appropriately substituted (E)-3-(2-chloroquinolin-3-yl)-1-(2-hydroxyphenyl) prop-2-en-1-ones **2a–j** were synthesized as per the reported procedures (Rahatgaonkar et al., 2009).

To 0.01 mol of chalcone was added 12 mL of EtOH. To the above reaction mixture was added 0.02 mol of Guanidine carbonate and the reaction was further basified by adding 0.56 g KOH. The solution was refluxed for 4–5 h. After the reaction when inferred through TLC, was quenched with water, and the organic compound obtained was then successively washed with 10 mL 5% solution of HCl and finally with 25 mL of water. The organic compound was filtered, washed, dried and recrystallized to furnish the corresponding pyrimidines.

*3.1. 2-[2-Amino-6-(2-chloroquinolin-3-yl)-5,6-dihydropyrimidin-4-yl]-4-chlorophenol (**3a**)*

IR (KBr) λ_{max} (cm^{-1}): 3430, 3350; ^1H NMR (400 MHz, DMSO-d_6) (δ): 6.93 (s, 2H, N<u>H</u>$_2$), 7.21 (m, 3H, C<u>H</u>–C<u>H</u>), 11.97 (s, 1H, O<u>H</u>), 7.43–8.92 (br m, 8H, aromatic region.); ^{13}C NMR (DMSO-d_6) (δ: 38.6 (<u>C</u>H$_2$ pyrimidine ring carbon), 41.8 (<u>C</u>H pyrimidine ring carbon), 116.7, 120.1, 126.3, 127.2, 127.4, 128.3, 128.6, 129.8, 132.4, 132.8, 136.5, 138.7, 145.2 (phenyl carbons), 152.2 (C–Cl quinoline ring), 159.3 (<u>C</u>–OH), 163.1 (<u>C</u>–NH$_2$), 165.1 (pyrimidine ring carbon). Mass spectrum (GC–MS), *m/z* 384.

*3.2. 2-[2-Amino-6-(2-chloroquinolin-3-yl)-5,6-dihydropyrimidin-4-yl]-4-methylphenol (**3b**)*

IR (KBr) λ_{max} (cm^{-1}): 3432, 3354; ^1H NMR (400 MHz, DMSO-d_6) (δ): 2.36 (s, 3H, C<u>H</u>$_3$), 6.82 (s, 2H, N$_{H2}$), 7.10 (m, 3H, C<u>H</u>$_2$–C<u>H</u>), 11.86 (s, 1H, O<u>H</u>), 7.32–8.81 (br m, 8H, aromatic region.); ^{13}C NMR (DMSO-d_6) (δ: 24.4 (<u>C</u>H$_3$), 38.4 (<u>C</u>H$_2$ pyrimidine ring carbon), 41.8 (<u>C</u>H pyrimidine ring carbon), 115.2, 119.5, 126.7, 128, 128, 128.1, 128.8, 131.2, 131.5, 132.8, 135.8, 139.2, 144.9 (phenyl carbons), 151.7 (C–Cl quinoline ring), 159.2 (<u>C</u>–OH), 163.3 (<u>C</u>–NH$_2$), 165.2 (pyrimidine ring carbon). Mass spectrum (GC–MS), *m/z* 364.

*3.3. 2-[2-Amino-6-(2-chloroquinolin-3-yl)-5,6-dihydropyrimidin-4-yl]-6-bromo-4-chlorophenol (**3c**)*

IR (KBr) λ_{max} (cm^{-1}): 3430, 3357; ^1H NMR (400 MHz, DMSO-d_6) (δ): 7.02 (s, 2H, N<u>H</u>$_2$), 7.31 (m, 3H, C<u>H</u>$_2$–C<u>H</u>), 12.00 (s, 1H, O<u>H</u>), 7.54–8.93 (br m, 7H, aromatic region.); ^{13}C NMR (DMSO-d_6) (δ: 38.3 (<u>C</u>H$_2$ pyrimidine ring carbon), 42.2 (<u>C</u>H pyrimidine ring carbon), 115.9, 119.8, 127.4, 128, 128.2, 128.4, 129.7, 129.9, 131.2, 133.3, 137.1, 139, 144.2 (phenyl carbons), 151.6 (C–Cl quinoline ring), 159.3 (<u>C</u>–OH),

163.4, (C–NH_2) 166.5 (pyrimidine ring carbon). Mass spectrum (GC–MS), *m*/*z* 464.

*3.4. 2-[2-Amino-6-(2-chloroquinolin-3-yl)-5,6-dihydropyrimidin-4-yl]-6-bromo-4-methylphenol (**3d**)*

IR (KBr) λ_{max} (cm^{-1}): 3435, 3362; ^{1}H NMR (400 MHz, DMSO-d_6) (δ): 2.36(s, 3H, CH_3), 6.90 (s, 2H, NH_2), 7.18 (m, 3H, CH_2–CH), 11.97 (s, 1H, OH), 7.32–8.81 (br m, 7H, aromatic region.); ^{13}C NMR (DMSO-d_6) (δ: 23.5 (CH_3), 39.2 (CH_2 pyrimidine ring carbon), 40.7 (CH pyrimidine ring carbon), 116.4, 120.4, 126.7, 127.5, 127.9, 128.1, 129.4, 129.5, 131.3, 133.3, 135.8, 138.4, 145.2 (phenyl carbons), 152.1 (C–Cl quinoline ring), 159.5 (C–OH), 162.8 (C–NH_2), 164.6 (pyrimidine ring carbon). Mass spectrum (GC–MS), *m*/*z* 442.

*3.5. 2-[2-Amino-6-(2-chloroquinolin-3-yl)-5,6-dihydropyrimidin-4-yl]-4-chloro-6-iodophenol (**3e**)*

IR (KBr) λ_{max} (cm^{-1}): 3435, 3352; ^{1}H NMR (400 MHz, DMSO-d_6) (δ): 6.93 (s, 2H, NH_2), 7.21 (m, 3H, CH_2–CH), 12.27 (s, 1H, OH), 7.43–8.92 (br m, 7H, aromatic region.); ^{13}C NMR (DMSO-d_6) (δ:39.5 (CH_2 pyrimidine ring carbon), 40.7 (CH pyrimidine ring carbon), 88.9, 120.2, 126.5, 128.1, 128.4, 128.5, 129.4, 131.2, 133.2, 135.8, 139.2, 143.6, 147.6 (phenyl carbons), 152.3 (C–Cl quinoline ring), 158.6 (C–OH), 163 (C–NH_2), 164.5 (pyrimidine ring carbon). Mass spectrum (GC–MS), *m*/*z* 508.

*3.6. 2-[2-Amino-6-(2-chloroquinolin-3-yl)-5,6-dihydropyrimidin-4-yl]-6-iodo-4-methylphenol (**3f**)*

IR (KBr) λ_{max} (cm^{-1}): 3437, 3352; ^{1}H NMR (400 MHz, DMSO-d_6) (δ): 2.36 (s, 3H, CH_3), 6.85(s, 2H, NH_2), 7.13 (m, 3H, CH_2–CH), 12.16 (s, 1H, OH), 7.32–8.81 (br m, 7H, aromatic region.); ^{13}C NMR (DMSO-d_6) (δ:23.5 (CH_3), 39.6 (CH_2 pyrimidine ring carbon), 40.4 (CH pyrimidine ring carbon), 87.6, 120.1, 125.8, 127.5, 127.9, 128.1, 129.4, 131.2, 133.4, 135.2, 138.8, 144.9, 146.7 (phenyl carbons), 154.1 (C–Cl quinoline ring), 159.3 (C–OH), 162.7 (C–NH_2), 165.2 (pyrimidine ring carbon). Mass spectrum (GC–MS), *m*/*z* 488.

*3.7. 2-[2-Amino-6-(2-chloroquinolin-3-yl)-5,6-dihydropyrimidin-4-yl]-4-chloro-6-nitrophenol (**3g**)*

IR (KBr) λ_{max} (cm^{-1}): 3433, 3355; ^{1}H NMR (400 MHz, DMSO-d_6) (δ): 6.99 (s, 2H, NH_2), 7.31 (m, 3H, CH_2–CH), 13.58 (s, 1H, OH), 7.54–8.92 (br m, 7H, aromatic region.); ^{13}C NMR (DMSO-d_6) (δ:39.3 (CH_2 pyrimidine ring carbon), 40.3 (CH pyrimidine ring carbon), 120.8, 122.4, 124.4, 124.8, 125.2, 127.2, 127.8, 128.9, 132.1 (phenyl carbons), 137.5 (C–NO_2), 138.2, 139.8, 144.4 (phenyl carbons), 150.8 (C–OH), 152.7 (C–Cl quinoline ring), 162.8 (C–NH_2), 164.5 (pyrimidine ring carbon). Mass spectrum (GC–MS), *m*/*z* 429.

*3.8. 2-[2-Amino-6-(2-chloroquinolin-3-yl)-5,6-dihydropyrimidin-4-yl]-4-methyl-6-nitrophenol (**3h**)*

IR (KBr) λ_{max} (cm^{-1}): 3433, 3350; ^{1}H NMR (400 MHz, DMSO-d_6) (δ): 2.58 (s, 3H, CH_3), 6.92 (s, 2H, NH_2), 7.20 (m, 3H, CH_2–CH), 12.98 (s, 1H, OH), 7.43–8.92 (br m, 7H, aromatic region.); ^{13}C NMR (DMSO-d_6) (δ:23.6 (CH_3), 39 (CH_2 pyrimidine ring carbon), 40.3 (CH pyrimidine ring carbon), 119.6, 122.4, 124.5, 124.8, 126.4, 127.4, 130.2, 131.8, 133.1, 136.5 (phenyl carbons), 137.4 (C–NO_2), 138.8, 145.4 (phenyl carbons), 148.9 (C–OH), 152.6 (C–Cl quinoline ring), 162.7 (C–NH_2), 164.5 (pyrimidine ring carbon). Mass spectrum (GC–MS), *m*/*z* 409.

*3.9. 2-[2-amino-6-(2-chloroquinolin-3-yl)-5,6-dihydropyrimidin-4-yl]-4-bromo-5-methoxy phenol (**3i**)*

IR (KBr) λ_{max} (cm^{-1}): 3430, 3351; ^{1}H NMR (400 MHz, DMSO-d_6) (δ): 3.75 (s, 3H, OCH_3), 6.79 (s, 2H, NH_2), 7.07 (m, 3H, CH_2–CH), 11.98 (s, 1H, OH), 7.29–8.78 (br m, 7H, aromatic region.); ^{13}C NMR (DMSO-d_6) (δ: 39.2 (CH_2 pyrimidine ring carbon), 40.2 (CH pyrimidine ring carbon), 56.7 (OCH_3), 104.2, 105.2, 113.1, 123.4, 125.2, 125.6, 125.8, 127.4, 130.4, 135.1, 137, 145.1, 152.7 (C–Cl quinoline ring), 160.6 (C–OCH_3), 161.8 (C–OH), 163.5 (C–NH_2), 166.2 (pyrimidine ring carbon). Mass spectrum (GC–MS), *m*/*z* 458.

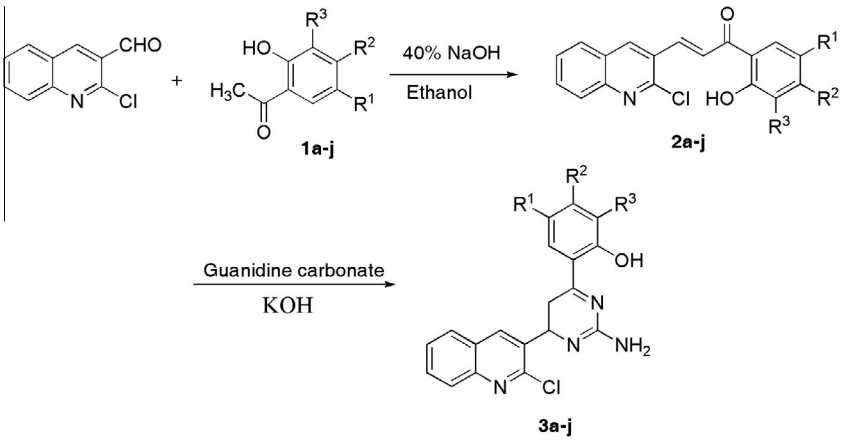
*3.10. 2-[2-Amino-6-(2-chloroquinolin-3-yl)-5,6-dihydropyrimidin-4-yl]-4-iodo-5-methoxyphenol (**3j**)*

IR (KBr) λ_{max} (cm^{-1}): 3430, 3356; ^{1}H NMR (400 MHz, DMSO-d_6) (δ): 3.74 (s, 3H, OCH_3), 6.82 (s, 2H, NH_2), 7.11 (m, 3H, CH_2–CH), 11.97 (s, 1H, OH), 7.17–8.82 (br m, 7H, aromatic region.); ^{13}C NMR (DMSO-d_6) (δ: 39.4 (CH_2 pyrimidine ring carbon), 40.5 (CH pyrimidine ring carbon), 56.5 (OCH_3), 78.5, 101.8, 114.5, 123.1, 125.2, 127.6, 128.2, 129.7, 130.5, 134.4, 138.8, 143.3, 152.4 (C–Cl quinoline ring), 160.7 (C–OCH_3), 162.5 (C–OH), 163.9 (C–NH_2), 165.7. Mass spectrum (GC–MS), *m*/*z* 504.

4. Result and discussion

The appropriately substituted 2-[2-amino-6-(2-chloroquinolin-3-yl)-5,6 dihydropyrimidin-4-yl]phenol **3a–j** were prepared by condensing differently substituted (E)-3-(2-chloroquinolin-3-yl)-1-(2-hydroxyphenyl) prop-2-en-1-ones **2a–j** with guanidine carbonate in the presence of ethanolic potassium hydroxide as depicted in Scheme 1. Table 1.

Our initial efforts focused on delineating a one pot Claisen Schmidt condensation of the series of (E)-3-(2-chloroquinolin-3-yl)-1-(2-hydroxyphenyl) prop-2-en-1-ones **2a–j** via cyclocondensation of differently substituted 2-hydroxy acetophenones with 2-chloro-3-formyl quinoline (Meth-Cohn and Taylor, 1995) in ethanol. All permutations generated by varying parameters, such as concentration of NaOH (1–3 equivalents), reaction time for cyclocondensation (10–24 h), stirring after the addition of strong base to reaction mixture (1–4 h), reaction temperature (Room temperature to boiling hot ethanol) did not lead to higher yields. Numerous experiments aimed at efficient synthesis of (E)-3-(2-chloroquinolin-3-yl)-1-(2-hydroxyphenyl) prop-2-en-1-ones **2a–j** were frustratingly unsuccessful. The yields were drastically low and the isolation procedures were tedious and cumbersome. After extensive experimentation, we developed an efficient synthesis of (E)-3-(2-chloroquinolin-3-yl)-1-(2-hydroxyphenyl) prop-2-en-1-ones



Scheme 1 Synthesis of Quinoline scaffold derived chalcones **2a**–**j** and their pyrimidine derivatives **3a**–**j**.

2a–j that overcame the drawbacks of the initial method (extended reaction times, difficulties in product isolation). The reaction, after suitable modifications has been fairly well optimized at 4 °C.

The formation of **2a–j** could be explained by simple unsubstituted 2-chloro-3-formyl quinoline showing less reactivity as compared to other aromatic aldehydes. Generally different aromatic aldehydes undergo Claisen Schmidt involving nucleophilic addition reaction; in the present case the quinoline moiety constitutes an electron rich nucleus with a slightly deactivated –CHO centre, making the molecule more stable but less reactive. The directly attached chlorine atom helps the reaction. Under such conditions, acetophenones having electron donating substituents encounter many reactivity problems while those with electron withdrawing groups like nitro, chloro, bromo, iodo attenuate the reaction efficiently in the forward direction with high yields.

To obtain the desired compounds **3a–j** in optimal yields, various conditions were tried for the condensation of appropriately substituted substrates 2-[2-amino-6-(2-chloroquinolin-3-yl)-5,6-dihydropyrimidin-4-yl] phenol **3a–j** with guanidine carbonate in DMF, ethylene glycol and ethanol/KOH. Ethanol was found to be the most suitable solvent to secure the highest yields.

4.1. Compound characterization

The IR spectra of compounds **3a–j** showed two peaks: one broad and another sharp at 3430 and 3350 cm^{-1} due to $–NH_2$ function and phenolic OH respectively. Absence of characteristic absorption bands for C═O in **3a** and appearance of other peaks at 1541, 1581 and 1664 supported the assigned structure.

The ^1H NMR spectra of compounds **3a–j** displayed an additional signal at 6.89 ppm due to two protons derived from $–NH_2$ attached to the pyrimidine moiety. Interestingly, a uniform pattern of multiplets ranging from 7.2 to 8.9 ppm was observed in the ^1H NMR spectra of all the compounds **3a–j** assigned the protons of aromatic rings, strongly supported the structures.

In addition, $–CH_3$ group of compounds **3b, 3d, 3f, 3h** resonated at 2.3 ppm integrating for three protons as a singlet in the ^1H NMR spectrum of each compound, respectively. Moreover, the signals derived from $–OCH_3$ group in compound **3i** and **3j** were recorded at 3.75 ppm integrating three protons, respectively. The singlets ranging from 11.97 to 13.58 ppm were observed for the phenolic –OH group of the respective compounds **3a–j**.

^{13}C NMR spectrum of compound **3a** showed aromatic resonances at 38.6, 41.8 ppm for pyrimidine carbon atoms. The peak corresponding to the $–OCH_3$ at 56.5 ppm of **3i** and **3j** supported the assigned structure. The compounds **3a–j** revealed peaks at 163 ppm suggesting the presence of $–C–NH_2$ of pyrimidine ring.

The elemental analysis and molecular ion peaks of compounds **3a–j** were consistent with the assigned structure.

4.2. Biological activity

4.2.1. In vitro antibacterial and antifungal activities

All the newly synthesized compounds **3a–j** were screened *in vitro* for their antimicrobial activities against clinically isolated bacterial strains such as *S. aureus*, *S. typhi*, *E. coli*, *P. vulgaris*, and *B. subtilis* by the cup-plate method. Ampicillin was used as a reference standard drug. The noteworthy antibacterial screening results of compounds **3a–j** are depicted in the Table 2. Compounds **3b**, **3d**, **3g**, **3h–j** displayed moderate activity at 200 ug/mL against *S. aureus* whereas **3a**, **3c**, **3e** and **3f** exhibited negligible activity. Among all the compounds, **3f** and **3g** showed insignificant activity at 100 ug/mL, 200 ug/mL and moderate activity at concentration 500 ug/mL against *P. vulgaris*. Surprisingly, the microorganisms, *E. coli*, *B. subtilis*, *S. typhi* displayed confluent growth with no inhibition, this implies the possibility that these microorganisms may possess strong resistivity against **3a–j**.

The compounds **3a–j** tested against clinically isolated*C. albicans, A. niger* and *P.* chrysogenum strains, amphotericin B was used as the standard drug. Compound 3d showed inhibition of growth of microorganism at 200 ug/mL against *A. niger and P. chrysogenum*, however, *C. albicans* displayed strong resistivity towards 3a–j. No significant activity was observed at the concentration of 10–100 ug/mL against all fungal strains, while results obtained at 200 ug/mL are summarized in Table 3.

The study reveals that most of the synthesized compounds possess low to moderate antimicrobial activities against *P. vulgaris, A. niger* and *P.* chrysogenum suggesting that the presence

of electron withdrawing groups like (–Cl, –Br, –NO_2) as substituents at the *meta* and *para* positions in phenolic ring may attenuate the anti-microbial activity wherein MIC has been shifted to higher concentration up to 500 ug/mL. Additionally, it should be noted that these hybrid scaffolds when incorporated with subunits like methyl and methoxy showed activity against *S. aureus*. However, nitro group when amalgamated with halogen in 3 g shows its virtue of activity against the strains *S. aureus*. On the other hand, the same molecule couldn't inhibit the growth of *P. vulgaris*. Thus the selective antimicrobial behaviour of all the above said microorganisms towards the synthesized molecules remains unexplored and the efficacy of **3a–g** is proved to be independent of the nature of the substituents.

5. Conclusions

We have synthesized substituted 2-[2-amino-6-(2-chloroquinolin-3-yl)-5,6-dihydropyrimidin-4-yl]phenols **(3a–j)** with high yields. All the synthesized compounds were evaluated for their antibacterial and antifungal activities at conc 10–500 ug/mL. These heterocycles accommodating both subunits i.e. quinoline and pyrimidine are expected to prove the therapeutic relevance and its utility in medicinal chemistry and drug development. Ongoing research focuses on the same molecular hybrid template with the incorporation of more effective substituents in search of new specific and effective antimicrobial agents.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.arabjc.2011.06.009.

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