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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)

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