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Synthesis of Pyrimidines Bearing Quinoline Motif Served as a Potential Antimicrobial Agents

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Research Article

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ABSTRACT

A facile and rapid protocol for the Synthesis of Pyrimidine derivatives have been undertaken by Biginelli typed multi-component reactions of diversely substituted Quinoline-3-carboxaldehyde, Ethyl-3-oxohexanonate and urea. The structure elucidation of the products 1a to 1j has been delineated by various spectral analyses. All the compounds 1a-1j was tested for their preliminary *in vitro* antifungal activities and antibacterial activities against a panel of fungal and bacterial and strains. From the tested series, five compounds 1h, 1d, 1e, 1f and 1i displayed significant antibacterial and antifungal activity. It is worthwhile noting here that the compounds 1h exhibited promising activity towards *Escherichia coli* MTCC 442 could be considered as the future leaders for the development of potent antimicrobial agents.

INTRODUCTION

The exploitation in the heterocyclic molecules with diverse functionalities is a worthwhile contribution in the medicinal chemistry [1]. Pyrimidines are key scaffold in various biological entities as well as serve as a building block of DNA and RNA skeleton [2]. The numerous analogues of Pyrimidines utilize for the treatment of cancer and also interfere in the synthesis and functionalities of nucleic acid. e.g., fluorouracil [3]. The class of compounds containing Pyrimidines such as Purines, Barbituric acid, Uric acid utilize in several medicinal applications [4]. Pyrimidine nucleus is an imperative class of nitrogen-bearing heterocyclic compounds extensively used as an important motif for pharmaceutical agents [5]. Pyrimidines exploited to a large number of diverse modifications to attain promising medicinal applications [6].

The several kinds of literature had been well reported on the chemistry and medicinal properties of pyrimidines. Including antitumor, [7] anti-inflammatory, [8] antiviral, [9] antihypertensive, [10] antibacterial, [11] cardiovascular, [12] calcium channel blockers [13]. The Nitrogen-containing Heteroaryl carboxamides have been comparatively limited exploration in the class of heterocyclic molecules possess promising biological activities [14]. Hence, the literature was recently published as antiplatelet, partial serotonin antagonists and antithrombotic agents [15]. The several 1,3,4-oxadiazole carboxamides bearing di□erent lipophilic functionalities (i.e., 1-naphthyl, 4-biphenyl-, n-hexyl and phenyl propyl substituents), moreover, basic groups, were generally amino alkyl and alkyl residues and have been recently reported as antithrombotic and antiplatelet compounds as well as serotonin inhibitors [16].

The most common pathway for the synthesis of pyrimidine is the reagent possesses N-C-N and C-C-C skeleton [17]. The C-C-C skeleton obtained from reagents containing 1,3-dicarbonyl functional groups and the N-C-N skeleton were obtained from nitrogen suppliers such as thiourea or urea or guanidine derivatives [18]. To develop a facile and rapid protocol for the synthesis of potent antimicrobial agents undertaken by diversely substituted Pyrimidines bearing Quinoline motif were

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synthesized utilizing one-pot, multi-component, Biginelli typed condensation, [19] of Urea, Quinoline-3-carboxaldehyde and Ethyl-3-oxohexanoate gives various pyrimidine 1a to 1j in moderate to better yield.

Keeping in mind the above facts and feature of Pyrimidines and to further explore the pharmaceutical profile of pyrimidine derivatives, our groups has developed some diversely substituted pyrimidine scaffolds containing Quinoline motif and their antibacterial as well as antifungal screening were carried out against a panel of bacterial and fungal strains at various concentrations which compared against reference standard drugs.

EXPERIMENTAL CRITERIA

All chemicals utilized in the research were purchased from Merck. Solvents were dried (except Laboratory-grade) and purified according to the standard method when it necessary. The reactions were monitored by pre-coated silica gel GF254 plates (thin-layer chromatography) from E-Merck Co and molecules visualized by UV exposure. The determination of melting points has been carried out by open capillaries method and is calibrated. The IR spectra were recorded on IR spectrophotometer (Nicolet Impact 410 FTIR) using KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on FT NMR spectrometer (Bruker 300-MHz FTNMR) in $CDCl_3$ and DMSO-d6 with TMS act as an internal standard. The Mass spectral analysis was recorded on Thermo-Finnigan-MAT, Bremen (Model MAT8200) spectrometer and CHN analysis were taken out using Heraeus CHN rapid analyzer.

General Procedure for the Synthesis

Ethyl 4-(aryl-2-chloroquinolin-3-yl)-1,2,3,4-tetrahydro-2-oxo-6-propylpyrimidin e-5-carboxylate (1a-1j)

A mixture of urea (0.03 mol), substituted 2-chloro-quinoline-3-carbaldehyde (I) (0.01 mol) and ethyl-3-oxo-hexanoate (0.01 mol) in ethanol (25 mL) containing Conc. hydrochloric acid (0.01 mol) were refluxed for four hours. The reaction conditions were monitored by TLC. After the completion of reaction, mixture was dumped into the ice water. The solid mass were filtered out, washed with plenty of water, dried and recrystallized using ethanol to affording the desired compound 1a to 1j with the yield of 66-87%.

Ethyl 4-(2-chloroquinolin-3-yl)-2-oxo-6-propyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1a)

Yield: 84%; mp: 168-170°C; IR (KBr, cm-1): 3387 (N-H stretching of amine), 1742 (C=O stretching of ester), 1496 (C-C stretching of aromatic ring), 1440 (-CH_3 bending of alkane), 1350 (C-N stretching of aromatic ring), 966 (=C-H stretching of alkene), 823 (C-H bending two adjacent H atoms of aromatic ring), 809 (stretching of C-Cl); ^{1}H NMR (400 MHz, DMSO-d6) d: 0.69 (s, 3H, -CH_3), 0.94 (s, 3H, -CH_3), 1.39-1.52 (m, 2H, -CH_2), 2.61-2.89 (m, 2H, -CH_2), 4.08 (s, 2H, -CH_2), 5.61 (s, Ar-1H), 6.72-6.80 (m, Ar-1H); 6.95-7.01 (m, Ar-1H), 7.15-7.31 (m, Ar-^{1}H), 7.48-7.52 (m, Ar-1H), 7.83 (s, Ar-1H), 8.70 (s, -NH), 10.48 (s, -NH); MS: m/z373. Anal Calcd for $C_{19}H_{20}ClN_3O_3$: C, 61.04; H, 5.39; N, 9.48%. Found: C, 61.18; H, 5.24; N, 9.35%.

Ethyl-4- (2-chloro-7-methoxyquinolin-3-yl)-2-oxo-6-propyl-1,2,3,4-tetrahy dropyr i midi ne-5-carboxylate (1b)

Yield: 82%; mp: 149-151°C; IR (KBr, cm^{-1}): 3487 (N-H stretching of amine), 1746 (C=O stretching of ester), 1498 (C-C stretching of aromatic ring), 1477 (-CH_3 bending of alkane), 1388 (C-N stretching of aromatic ring), 825 (C-H bending two adjacent H atoms of aromatic ring), 779 (stretching of C-Cl); ^{1}H NMR (400 MHz, DMSO-d6) d: ^{1}H NMR (400 MHz, DMSO-d6) d: 0.87-0.93 (m, 6H,-CH_3), 1.45-1.47 (m, 2H, -CH_2), 2.24 (m, ^{1}H, -CH_2), 2.66-2.68 (m, 1H, -CH_2), 3.77 (s, 3H, -CH_3), 3.86-3.88 (m, 2H, -CH_2), 5.25 (s, Ar-1H), 7.00-7.09 (m, Ar-^{1}H); 7.29 (s, Ar-1H), 7.39-7.48 (m, Ar-1H), 7.80 (s, Ar-1H), 8.96 (s, -NH), 10.18 (s, -NH); MS: m/z403. Anal. Calcd for $C_{20}H_{22}Cl$-N_3O_4: C, 59.48; H, 5.49; N, 10.40%. Found: C, 59.96; H, 5.51; N, 10.12%.

Ethyl 4- (2-chloro-7-methylquinolin-3-yl)-2-oxo-6-propyl-1,2,3,4-tetrahydropyri midine-5-carboxylate (1c)

Yield: 71%; mp: 145-147°C; IR (KBr, cm^{-1}): 3420 (N-H stretching of amine), 1743 (C=O stretching of ester), 1480 (C-C stretching of aromatic ring), 1468 (-CH_3 bending of alkane), 1374 (C-N stretching of aromatic ring), 831 (C-H bending two adjacent H atoms of aromatic ring), 750 (stretching of C-Cl); ^{1}H NMR (400 MHz, DMSO-d6) d: ^{1}H NMR (400 MHz, DMSO-d6) d: 0.86-0.90 (m,6H, -CH_3), 1.44-1.46 (m, 2H, -CH_2), 2.25-2.29 (m, ^{1}H, -CH), 2.34 (s, 3H, CH_3), 2.66-2.68 (m, ^{1}H, -CH), 3.86-3.89 (m, 2H, Hf), 5.40 (s, Ar-1H), 6.98-7.02 (m, Ar-^{1}H); 7.30 (s, Ar-^{1}H), 7.39-7.48 (m, Ar-1H), 7.82 (s, Ar-^{1}H), 8.99 (s, -NH), 10.50 (s, -NH); MS: 387 m/z. Anal. Calcd for $C_{20}H_{22}ClN_3O_3$: C, 61.93; H, 5.72; N, 10.83%. Found: C, 61.97; H, 5.81; N, 10.12%.

Ethyl-4- (2-chloro-7-chloroquinolin-3-yl)-2-oxo-6-propyl-1,2,3,4-tetrahydro pyr imidine-5-carboxylate (1d)

Yield: 72%; mp: 123-125°C; IR (KBr, cm^{-1}): 3444 (N-H stretching of amine), 1458 (C=O stretching of ester), 1479 (C-C stretching of aromatic ring), 1466 (-CH_3 bending of alkane), 1378 (C-N stretching of aromatic ring), 839 (C-H bending two adjacent H atoms of aromatic ring), 761 (stretching of C-Cl); ^{1}H NMR (400 MHz, DMSO-d6) d: 1H NMR (400 MHz, DMSO-d6) d: 0.90-0.94 (m, 6H, -CH_3), 1.44-1.47 (m, 2H, -CH_2),1.96-1.97 (m, ^{1}H, -CH), 2.66-2.68 (m, ^{1}H, -CH), 4.20-4.23 (m, 2H, Hf),

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5.13 (s, Ar-^{1}H), 7.63-7.65 (d, Ar-^{1}H); 7.74 (s, Ar-^{1}H), 7.94-7.96 (m, Ar-^{1}H), 7.98 (s, Ar-^{1} H), 8.27 (s, -NH), 10.29 (s, -NH); MS: 408 m/z. Anal. Calcd for $C_{19}H_{19}Cl_2N_3O_3$: C, 55.89; H,4.69; N, 10.29%. Found: C, 55.87; H, 4.61; N, 10.22%.

Ethyl-4- (2-chloro-7-bromoquinolin-3-yl)-2-oxo-6-propyl-1,2,3,4-tetrahydropyr imi dine-5-carboxylate (1e)

Yield: 76%; mp: 112-114°C; IR (KBr, cm^{-1}): 3458 (N-H stretching of amine), 1460 (C=O stretching of ester), 1471 (C-C stretching of aromatic ring), 1454 (-CH_3 bending of alkane), 1379 (C-N stretching of aromatic ring), 841 (C-H bending two adjacent H atoms of aromatic ring), 775 (stretching of C-Cl); ^{1}H NMR (400 MHz, DMSO-d6) d: ^{1}H NMR (400 MHz, DMSO-d6) d: 0.90-0.94 (m, 6H, -CH_3), 1.45-1.48 (m, 2H, -CH_2), 1.95-1.97 (m, ^{1}H, -CH), 2.66-2.67 (m, ^{1}H, -CH), 4.21-4.24 (m, 2H, Hf), 5.20 (s, Ar-1H), 7.71-7.73 (d, Ar-1H); 7.82 (s, Ar-^{1}H), 7.94-7.96 (m, Ar-1H), 8.10 (s, Ar-^{1}H), 8.24 (s, -NH), 10.18 (s, -NH); MS: 408 m/z. Anal. Calcd for $C_{19}H_{19}BrClN_3O_3$: C, 50.41; H, 4.23; N, 9.28%. Found: C, 50.17; H, 4.21; N, 9.22%.

RESULTS AND DISCUSSION

Chemistry

In 1893 Pietro Biginelli reported the first syntheses of 3,4-dihydropyrimidin-2 (l/-&ones of type 1 by a very simple one-pot condensation reaction of an aromatic aldehyde, urea and ethyl acetoacetate in ethanolic solution. This efficient approach to partly reduced pyrrmidines, termed the n Bigrnelli reaction or condensation, was largely ignored in the following years, and therefore, also the synthetic potential of these multi-functionalized dihydropyrimidines (henceforth denoted as Biginelli compounds) remained unexplored.

In recent years, however, interest in these compounds has increased rapidly, and the scope of the original cyclo-condensation reaction has been widely extended by variation of all three components. Currently, the number of publications and patents dealing with the synthesis, properties and applications of Biginelli compounds has reached approximately 120. The present popularity of these dihydropynmidines is mainly due to their close structural relationship to the clinically important dihydropyridine calcium channel blockers of the nifedipine-type. Although the Biginelli reaction was first described 100 years ago no review has appeared on this subject. Furthermore, in most organic monographs and treatises the Biginelli reaction is touched upon only briefly and in these few cases only a very limited number of references and Information is provided. It is therefore not surprising that this dihydropyrimidine synthesis and its considerable scope and potential is unknown to a great number of organic chemists.

These non-planar heterocyclic compounds have interesting multifaceted pharmacological profile such as calcium channel modulators, α1a-adrenergic receptor antagonists, mitotic kinesin inhibitors, hepatitis B virus replication inhibitors etc.

In view of these observations, we synthesized a small library of Dihydropyrimidines 1a-j containing quinoline-3-carboxaldehyde precursor condensed with Ethyl-3-oxohexanoate in order to form arylidine followed by cyclisation with nitrogen supplier (Urea) to form Pyrimidines 1a-j in the presence of hydrochloride at reflux temperature. The purity and structural elucidation of the compounds was determined by TLC, Mass, NMR IR, and elemental analysis. The reported compounds 1a-1j was in fully supported with reported scaffolds **(Figure 1).**

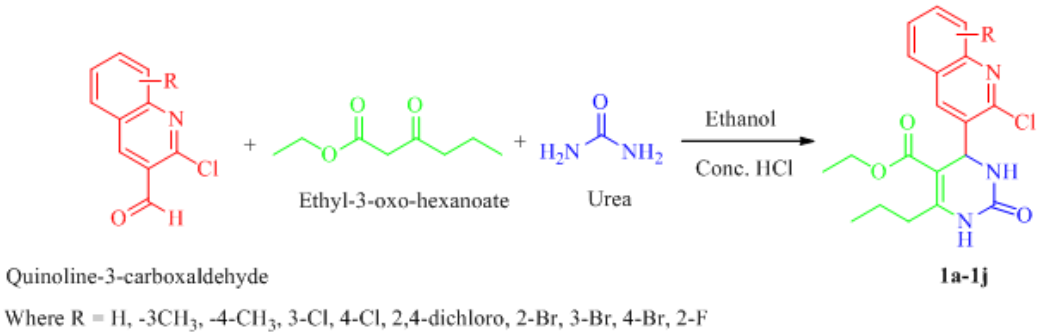

Figure 1. Quinoline-3-carboxaldehyde treated with ethanol in presence of Conc. HCL to convert to Ia-IJ compound.

Biological Evaluation

The numerous diverse biological applications of pyrimidines encourage us to biologically evaluate the synthesized molecules. There are several antimicrobial agents have been reported for therapy; even though still the field much needs key efforts to develop new anti-microbial agents to overcome the Multidrug resistance. The synthesized molecules 1a-1j

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were tested for their *in vitro* (MIC) anti-fungal activity and antibacterial activity by using the standard broth dilution method [20,21] with three fungal strains *Aspergillus niger*-MTCC 282, *Candida albicans*-MTCC 227, *Aspergillus clavatus*-MTCC 1323, two Gram-negative bacteria *Pseudomonas aeruginosa*-MTCC 441, *Escherichia coli*-MTCC 442, two Gram-positive bacteria *Streptococcus pyogenes*-MTCC 443, *Staphylococcus aureus*-MTCC-96 and taking griseofulvin, nystatin norfloxacin, chloramphenicol, ampicillin and ciprofloxacin as a standard drugs. The fungal and bacterial strains were procured from the Microbial Type Culture Collection (MTCC) and Gene Bank, IMT, Chandigarh, India.

The evaluated results of antimicrobial susceptibility screening are depicted in **Table 1.** The results indicate that some molecules were potent. It is worth noting here that compound 1h exhibited significant antibacterial activity against *Escherichia coli* MTCC 442 whereas the compounds 1d, 1e, 1f and 1i also possess promising antibacterial activity against both the bacterial strains compared to reference standard drug Ampicillin. The other compounds exhibit moderate to low activity.

Table 1. Antibacterial and antifungal activity of synthesized compounds 1a-1j.

Compounds	R	Minimum inhibition concentration (µg mL-1)						
		Gram-positive		Gram-negative		Fungal species		
		S. a.	S. p.	E. c.	P. a.	C. a.	A. n.	A. c.
1a	-H	1000	500	500	500	>1000	>1000	>1000
1b	-3-CH_3	500	500	250	250	500	500	1000
1c	-4-CH_3	250	125	125	250	500	500	250
1d	-3-Cl	250	250	100	100	250	500	500
1e	-4-Cl	100	250	500	500	250	250	500
1f	-2, 4-dichloro	100	125	100	100	250	500	500
1g	-2-Br	250	250	500	500	500	250	250
1h	-3-Br	100	100	62.5	100	100	100	250
1i	-4-Br	250	250	100	125	250	250	125
1j	-2-F	500	500	250	250	500	500	500
Ampicillin		250	100	100	100	-	-	-
Chloramphenicol		50	50	50	50	-	-	-
Ciprofloxacin		50	50	25	25	-	-	-
Norfloxacin		10	10	10	10	-	-	-
Nystatin		-	-	-	-	100	100	100
Griseofulvin		-	-	-	-	500	100	100

The compound 1h exhibit the most significant activity against *Aspergillus niger* MTCC 282 and *Candida albicans* MTCC 227 compared to reference standard drugs Griseofulvin and Nystatin whereas the other molecules exhibit moderate to low activity.

CONCLUSION

In the present context, the synthesis of Pyrimidines bearing Quinoline motif was elaborated to the development of new lead for antimicrobial agents to overcome the Multidrug resistance. The results of *in vitro* biological screening of the titled compounds ethyl 4- (aryl-2-chloroquinolin-3-yl)-1,2,3,4-tetrahydro-2-oxo-6-propylpyrimidine-5-carboxylate (1a-j) show that compounds 1h, 1d, 1f, and 1i exhibited significant (maximum) antimicrobial activities, could be considered as the future leaders for the development of potent antimicrobial agents.

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