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Studies on molecular properties prediction, antitubercular and antimicrobial activities of novel quinoline based pyrimidine motifs

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Abstract

In the present study, a series of 3-((6-(2,6-dichloroquinolin-3-yl)-4-aryl-1,6-dihydro-pyrimidin-2-yl)thio)propanenitriles **5a-o** were synthesized and subjected to molecular properties prediction and drug-likeness model score by Molinspiration property calculation toolkit and MolSoft software, respectively. Compound **5m** (4-OCH_3) was found to be maximum drug-likeness model score (0.42). Among the screened compounds, **5m** showed the most promising antitubercular activity with MIC of 0.20 µg/mL, while compounds **5g**, **5k** and **5m** displayed broad spectrum antibacterial activity against all the bacterial strains. Moreover, compound **5k** was found to be the most potent antifungal agent. Further, the results of preliminary MTT cytotoxicity studies on HeLa cells suggested that potent antimicrobial activity of **5g**, **5k** and **5m** was escorted by low cytotoxicity.

Keywords: Antimicrobial; Antitubercular; Cytotoxicity; Lipinski 'Rule of five'; Molecular properties prediction;

The contributory driving force of tuberculosis (TB) is the pathogenic bacterium *Mycobacterium tuberculosis* (Mtb).[1] According to the global tuberculosis report 2013 published by World Health Organization (WHO), an estimated 8.6 million people developed TB and 1.3 million died from the disease (including 320,000 deaths among HIV-positive people) in 2012.[2] Furthermore, emergence of new virulent forms of TB such as multi drug resistant (MDR-TB) and extremely drug resistant (XDR-TB), and its synergy with human immunodeficiency virus (HIV) has fuelled its epidemic nature.[3,4] The development of antimicrobial resistance contributes greatly to the challenges occurring in the discovery of new therapies for combating life threatening infectious diseases.[5] These reasons mould a compelling case indicating an urgent need for novel and effective antimicrobial agents to fight against the MDR infections.

It has been established that heterocyclic moieties play an essential role in designing newer class of structural entities for medicinal applications. Among them, quinoline and its derivatives are significant because of their diverse biological activities and their presence in naturally occurring compounds. They are reported to possess antibiotic,[6] antimalarial,[7] anticancer,[8] anti-inflammatory,[9] antihypertensive,[10] tyrokinase PDGF-RTK inhibition[11] and anti-HIV[12] properties. Amongst the wide array of activities flaunted by quinoline derivatives, antimicrobial activity is noteworthy. Quinoline derivatives have been reported to exhibit substantial antitubercular activities and can be considered a promising area for the discovery of new antitubercular agents.[13-15] It is interesting to note that quinoline is a core pharmacophore in the recently developed antitubercular drugs, viz. bedaquiline (TMC207), a diarylquinoline,[16] mefloquine,[17,18] and moxifloxacin.[19] Bedaquiline is the first drug with a novel mechanism of action for TB in more than 40 years and the sole drug specifically indicated for MDR-TB. It works via inhibition of enzyme adenosine triphosphate (ATP) synthase, which is the energy source for the bacterium.[16] On the other hand, pyrimidines

occupy a distinct and unique place in medicinal chemistry due to their presence in several biologically active natural products.[20] In view of wide spectrum biological activities such as anti-allergic,[21] antitumor,[22] anti-inflammatory[23] and antiparasitic[24] activities, exhibited by synthetic pyrimidine based scaffolds, a number of analogues have garnered considerable amount of attention. In addition, pyrimidines are potential inhibitors of dihydrofolate reductase (DHFR), a promising drug target for the development of anti-infective agents. Although DHFR does not represent a novel target, there is still a large scope for the development of DHFR inhibitors, particularly with respect to mycobacteria.[25,26]

Keeping this in view and in continuation of our endeavors towards the development of anti-infective agents,[27-29] it was envisaged that the design and synthesis of new prototypes which include advantage of dual pharmacophores of quinoline and pyrimidine in single molecular framework is worth the attempt. In addition, all the title compounds **5a-o** were exposed to molecular properties prediction and drug-likeness model score by Molinspiration property calculation toolkit and MolSoft software in direction to filter the drugs for biological screenings.

[Insert Scheme 1 here]

The fifteen new 3-((6-(2,6-dichloroquinolin-3-yl)-4-aryl-1,6-dihydropyrimidin-2-yl)thio)propanenitriles **5a-o** presented in this work were prepared through the synthetic route illustrated in **Scheme 1**. The intermediate chalcones 3-(2,6-dichloroquinolin-3-yl)-1-(aryl)prop-2-en-1-ones **3a-o** were synthesized through the Claisen–Schmidt condensation of equimolar amounts of acetophenone derivatives **2a-o** and 2,6-dichloroquinoline-3-carbaldehyde **1** in accordance with the method described in the literature.[30] The starting 2,6-dichloroquinoline-3-carbaldehyde **1** was furnished through reported method.[31] Chalcones **3a-o** underwent cyclization reaction with thiourea in ethanolic potassium hydroxide under reflux condition to furnish quinolyl dihydropyrimidines identified as 6-(2,6-dichloroquinolin-

3-yl)-4-aryl-1,6-dihydropyrimidine-2-thiols **4a-o**. The structures of intermediates **4a-o** were established by IR spectra which showed the characteristic absorption bands at 2555-2569 and 3306-3318 cm^{-1} for S-H and N-H stretching respectively, beside disappearance of carbonyl group stretching due to its involvement in cyclization. ^{1}H NMR spectrum showed besides the expected aromatic signals, two singlets at δ 9.12-9.21, 11.25-1138 ppm and a doublet at δ 5.26-5.37 ppm for protons of NH, SH and the proton attached to asymmetric carbon respectively. In the final step, intermediates **4a-o** were treated with acrylonitrile in pyridine followed by the neutralized with hydrochloric acid well-appointed the respective targeted 3-((6-(2,6-dichloroquinolin-3-yl)-4-aryl-1,6-dihydropyrimidin-2-yl)thio)propanenitriles **5a-o**.[32]

The structures of the final compounds **5a-o** were established by IR spectrum which displayed disappearance of S-H stretching in intermediates **4a-o**. Moreover, absorption band appearing between 2241-2254 cm^{-1} was assigned to CN group and its ^{1}H NMR spectra revealed two triplets at δ 3.09-3.17 and 3.22-3.34 ppm for methylene protons attached to cyanide group and S atom respectively, along with the vanishing of SH group singlet. Furthermore, ^{13}C NMR spectrum of compound **5a** as a representative example displayed, besides the aromatic signals, four characteristic signals at δ 166.6, 119.2, 54.6 and 47.8 ppm due to carbon of pyrimidine ring attached to S, cyanide group carbon and two methylene carbons attached to cyanide group and S atom respectively. The mass spectrum of **5a** showed molecular ion peak at m/z = 438.07 [M^{+} 79%], in agreement with its proposed structure. Similarly, the spectral values for all the compounds and their C, H, N analysis is presented in the supplementary data.

[Insert Table 1 here]

In the development of drugs projected for oral use, good drug absorption and appropriate drug delivery are very important.[33] About 30% of oral drugs flop in development

due to poor pharmacokinetics.[34] Among the pharmacokinetic properties, a low and highly flexible bioavailability is definitely the main reason for stopping further development of the drug.[35] To qualify the compound as a drug candidate, the computed molecular properties are shown in **Table 1**. Lipophilicity (*mi*LogP), molecular weight (MW), number of rotatable bonds (NROTB), number of hydrogen bond donors (HBD) and number of hydrogen bond acceptors (HBA) of Lipinski's rule of five[36] were calculated using Molinspiration online property calculation toolkit.[37] The degree of absorption is expressed by the percentage of absorption (%ABS) and is calculated by using %ABS = 109 - (0.345 × TPSA).[38] Molecular polar surface area (TPSA) is a very valuable parameter for the prediction of drug transport properties.

Drug-likeness model score (a combined outcome of physicochemical properties, pharmacokinetics and pharmacodynamics of a compound and is represented by a numerical value) was computed by MolSoft[39] software for the fifteen molecules under study. Computed drug-likeness scores are presented in **Table 1**. Compounds having zero or negative value should not be considered as drug-like candidate. Compounds **5l** (3-OCH_3) and **5m** (4-OCH_3) possessed maximum drug-likeness score of 0.26 and 0.42.

[Insert Table 2 here]

All the compounds were initially screened for their *in vitro* antimycobacterial activity against *M. tuberculosis* H_{37}Rv strain by using Lowenstein-Jensen slope method exactly as described previously.[40] The results of the antitubercular studies are presented in **Table 2.** Compounds exhibiting ≥90% inhibition in the initial screen were retested at lower concentration (MIC) in Lowenstein-Jensen medium to determine the actual MIC. In the preliminary screening, compounds **5g** and **5j-m** inhibited Mtb by 90-100%. In the secondary level, compounds **5g** and **5k** inhibited Mtb with MIC of 3.12 µg/mL and compound **5m** with

MIC of 0.20 µg/mL. Among all the screen compounds, compound **5m** having 4-OCH_3 substituent at the phenyl ring of pyrimidine substitution was found to be the most potent compound of the series with MIC equivalent to the standard drug isoniazid. The preliminary *in vitro* results provide an excellent lead for further development of these molecules as novel antitubercular agents. It is interesting to note that substituents with electron donating groups such as methoxy, methyl and hydroxy at *para* position of phenyl ring demonstrated high inhibitory activity against Mtb as compared *meta* substituted derivatives, indicating that the electronic properties of the substituents have major influence on the antimycobacterial activity.

[Insert Table 3 here]

All the tested compounds were evaluated for their *in vitro* antibacterial and antifungal activity (MIC) by conventional broth microdilution method.[41] Bacterial strains *Staphylococcus aureus* MTCC 96 and *Streptococcus pyogenes* MTCC 442 as Gram-positive, *Escherichia coli* MTCC 443 and *Pseudomonas aeruginosa* MTCC 1688 as Gram-negative and *Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282 and *Aspergillus clavatus* MTCC 1323 as fungal strains were used. Ciprofloxacin and Griseofulvin were used as standard drugs. As indicated in **Table 3**, compounds **5g, 5k** and **5m** displayed broad spectrum antibacterial activity against both gram-positive and gram-negative bacteria as compared with ciprofloxacin. Compounds **5m** and **5k** were found to be 4-fold more active against *S. aureus* and *S. pyogens* (MIC = 12.5 µg/mL) and compound **5g** exhibited 2-fold more potency against *S. aureus* and *S. pyogens* (MIC = 25 µg/mL) compared to the standard drug. While, compound **5m** showed equivalent activity against *E. coli* and *P. aeruginosa* and 2-fold more activity against *S. pyogens* (MIC = 25 µg/mL). Moreover, compound **5k** exhibited 2-fold inhibition against *S. aureus* and equivalent inhibition against *P. aeruginosa*. As observed

with antitubercular activity, high antibacterial potency of **5g, 5k** and **5m** may be attributed to the presence of electron donating substituents such as methoxy, methyl and hydroxy at 4th position of phenyl ring of pyrimidine substitution. In comparison to the standard drug griseofulvin, the *in vitro* antifungal activity results indicated that compound **5k** substituted with hydroxy group at 4th position of phenyl ring was found to be the most potent with 4 and 2-fold higher activity against *A. niger*, *A. clavatus* (MIC = 25 µg/mL) and *C. albicans* (MIC = 250 µg/mL) respectively.

[Insert Table 4 here]

In vitro cytotoxicity of most active antitubercular and antimicrobial compounds **5g**, **5k** and **5m** were evaluated against human cervical cancer cell line (HeLa) by MTT colorimetric assay.[42,43] The IC_{50} values obtained for these compounds are shown in **Table 4**. As seen from **Table 4**, none of the tested compounds exhibited any significant cytotoxic effect on HeLa cells, suggesting a great potential for their *in vivo* use as antimicrobial agents.

In summary, we have conveniently synthesized a novel series of quinoline bearing pyrimidines and evaluated them for prediction of their molecular properties and drug-likeness model score by different softwares in order to find suitable molecules for the antitubercular, antimicrobial and cytotoxic activities with anticipation of generating new structural leads serving as potent anti-infective agents. Among the screened compounds, compounds **5g**, **5k** and **5m** with electron donating group/atoms such as methoxy, methyl and hydroxy at fourth position of phenyl ring attached to pyrimidine ring showed the most promising antitubercular and antibacterial activity. While, compound **5k** with electron donating hydroxyl group at fourth position was identified as the most promising antifungal agent. The potent antitubercular and antimicrobial activity of compounds **5g**, **5k** and **5m** were accompanied with relatively low level of cytotoxicity, which reflect their therapeutic potential for their

growth in the field of anti-infective agents. The work reported herein provides an insight into the development of novel antimicrobial and antitubercular agents effective over a wide range of pathogenic strains.

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Captions

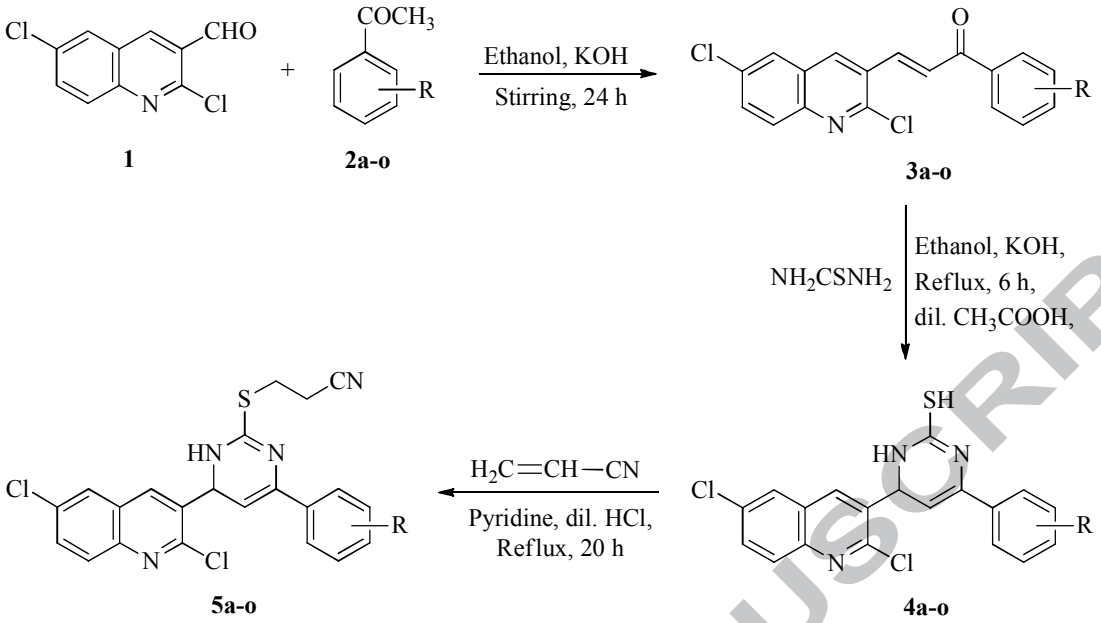
Scheme 1 Synthetic route for the preparation of title compounds **5a-o**

Table 1 Drug likeness calculations and Lipinski parameters of compounds **5a-o**

Table 2 *In vitro* antitubercular activity of compounds **5a-o** against *M. tuberculosis* $H_{37}Rv$

Table 3 Results of antibacterial and antifungal screening of compounds **5a-o**

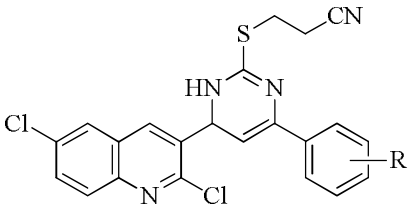
Table 4 Levels of cytotoxicity induced by selected compounds on HeLa cells



	-R		-R		-R
5a	-H	**5f**	-3-CH_3	**5k**	-4-OH
5b	-3-Cl	**5g**	-4-CH_3	**5l**	-3-OCH_3
5c	-4-Cl	**5h**	-3-NO_2	**5m**	-4-OCH_3
5d	-3-F	**5i**	-4-NO_2	**5n**	-3-Br
5e	-4-F	**5j**	-3-OH	**5o**	-4-Br

Scheme 1. Synthetic route for the preparation of title compounds **5a-o**

Table 1 Drug likeness calculations and Lipinski parameters of compounds **5a-o**



5a-o

Entry	R	MW[a]	Volume[b]	%ABS[c]	TPSA[d]	NROTB[e]	*n*ON[f]	*n*OHNH[g]	*mi*log*P*[h]	*n*violations[i]	Drug-likeness model score
Rule	--	>500	--	--	--	--	≥10	≥5	≥5.0	≥1	--
5a	H	439.371	360.016	87.92	61.075	5	4	1	4.884	0	0.06
5b	3-Cl	473.816	373.552	87.92	61.075	5	4	1	5.538	1	-0.02
5c	4-Cl	473.816	373.552	87.92	61.075	5	4	1	5.562	1	0.07
5d	3-F	457.361	364.947	87.92	61.075	5	4	1	5.024	1	-0.02
5e	4-F	457.361	364.947	87.92	61.075	5	4	1	5.048	1	0.06
5f	3-CH_3	453.398	376.577	87.92	61.075	5	4	1	5.308	1	0.02
5g	4-CH_3	453.398	376.577	87.92	61.075	5	4	1	5.332	1	0.10
5h	3-NO_2	484.368	383.35	72.11	106.899	6	7	1	4.819	0	-0.31
5i	4-NO_2	484.368	383.35	72.11	106.899	6	7	1	4.843	0	-0.25
5j	3-OH	455.37	368.034	80.95	81.303	5	5	2	4.381	0	0.13
5k	4-OH	455.37	368.034	80.95	81.303	5	5	2	4.405	0	0.18
5l	3-OCH_3	469.397	385.562	84.74	70.309	6	5	1	4.917	0	0.26
5m	4-OCH_3	469.397	385.562	84.74	70.309	6	5	1	4.941	0	0.42
5n	3-Br	518.267	377.902	87.92	61.075	5	4	1	5.669	2	-0.22
5o	4-Br	518.267	377.902	87.92	61.075	5	4	1	5.693	2	-0.14

[a] Molecular weight; [b] Molecular volume; [c] Percentage absorption; [d] Topological polar surface area; [e] Number of rotatable bonds; [f] Number of hydrogen bond acceptors;
[g] Number of hydrogen bond donors; [h] Lipophilicity; [i] Number of violations.

Table 2 *In vitro* antitubercular activity of compounds **5a-o** against *M. tuberculosis* $H_{37}Rv$

Entry	% Inhibition	MIC (μg/mL)
5a	62	--
5b	62	--
5c	42	--
5d	41	--
5e	69	--
5f	81	--
5g	98	3.12
5h	38	--
5i	56	--
5j	98	100
5k	99	3.12
5l	97	12.5
5m	99	0.20
5n	66	--
5o	58	--
Isoniazid	99	0.20

Table 3 Results of antibacterial and antifungal screening of compounds **5a-o**

Entry	-R	Minimum inhibitory concentration (MIC) µg/mL						
		Gram positive bacteria[a]		Gram negative bacteria[b]		Fungi[c]		
		Sa	Sp	Ec	Pa	Ca	An	Ac
5a	-H	100	250	500	250	1000	1000	500
5b	-3-Cl	250	500	1000	500	>1000	500	1000
5c	-4-Cl	250	500	1000	500	>1000	500	1000
5d	-3-F	125	250	500	500	1000	>1000	500
5e	-4-F	500	500	1000	>1000	1000	1000	500
5f	-3-CH_3	100	100	250	100	1000	500	500
5g	-4-CH_3	25	25	50	50	500	500	250
5h	-3-NO_2	500	1000	>1000	1000	>1000	500	>1000
5i	-4-NO_2	1000	500	500	1000	>1000	>1000	1000
5j	-3-OH	100	100	125	250	500	250	250
5k	-4-OH	25	12.5	50	25	250	25	25
5l	-3-OCH_3	50	100	100	250	500	500	100
5m	-4-OCH_3	12.5	25	25	25	1000	250	250
5n	-3-Br	500	1000	>1000	1000	>1000	500	1000
5o	-4-Br	250	500	1000	500	500	1000	500
Ciprofloxacin		50	50	25	25	--	--	--
Griseofulvin		--	--	--	--	500	100	100

[a] Sa: *Staphylococcus aureus* MTCC 96; Sp: *Staphylococcus pyogenes* MTCC 442;

[b] Ec: *Escherichia coli* MTCC 443; Pa: *Pseudomonas aeruginosa* MTCC 1688;

[c] Ca: *Candida albicans* MTCC 227; An: *Aspergillus niger* MTCC 282; Ac: *Aspergillus clavatus* MTCC 1323.

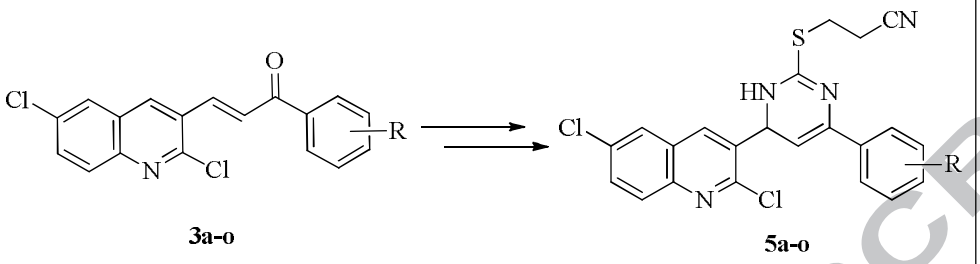
Table 4 Levels of cytotoxicity induced by selected compounds on HeLa cells

Compounds	IC_{50} (μM)
5g	94.20
5k	>100
5m	>100
Doxorubicin	3.24

The known numbers of cells (1.0×10^4) were incubated for 24 h in a 5% CO_2 incubator at 37 ºC in the presence of different concentrations of test compounds. After 24 h of drug incubation the MTT solution was added and supernatant was discarded and 100 ml DMSO was added in each well and absorbance was recorded at 540 nm by ELISA reader.

Studies on molecular properties prediction, antitubercular and antimicrobial activities of novel quinoline based pyrimidine motifs

N C Desai*, G M Kotadiya, A R Trivedi



3a-o **5a-o**

Where R = -H, -3-Cl, -4-Cl, -3-F, -4-F, -3-CH_3, -4-CH_3, -3-NO_2, -4-NO_2, -3-OH, -4-OH, -3-OCH_3, -4-OCH_3, -3-Br, -4-Br