International Journal for Pharmaceutical Research Scholars (IJPRS)

V-3, I-1, 2014 ISSN No: 2277 - 7873

RESEARCH ARTICLE

Synthesis and QSAR Study of 4-(6-methylquinolin-3-yl) – Dihydropyrimidines and their Antimicrobial and Antitubercular Activity

Ranjan Khunt[1], Vijay Khedkar[2], Evans Coutinho[2], Satishkumar Tala[1]

[1]*Chemical Research Laboratory, Department of Chemistry, Saurashtra University, Rajkot-360005, (Gujarat), India.*

[2]*Department of Pharmaceutical Chemistry, Bombay College of Pharmacy, Kalina, Santa Cruz (E), Mumbai- 400 098 (Maharashtra), India.*

Manuscript No: IJPRS/V3/I1/00104, Received On: 28/02/2014, Accepted On: 11/04/2014

ABSTRACT

A new series of quinolone pyrimidines were synthesized employing cyclo-condensation reaction of quinolinyl chalcones with either urea or thiourea and their anti-microbial and anti-tubercular properties were examined. The preliminary studies indicate significant inhibition against two gram positive bacteria (*Bacillus subtilis, Bacillus coccus*), two gram negative bacteria (*Escherichia coli, Proteus Vulgaris*), fungi (*Aspergillusniger*) and *Mycobacterium tuberculosis H37Rv*. This study reports compound **4e** as potential lead candidate for tuberculosis. The structural characteristics that affects the structure-activity relationship(SAR) was reported by implementing recursive partitioning (RP) analysis base classification model, which can be useful for further lead development.

KEYWORDS

Chalcones, Quinoline, Pyrimidine, Anti-microbial Activity, Anti-tubercular Activity, QSAR Study

INTRODUCTION

Among the infectious diseases, tuberculosis (TB) infection (Mycobacterium tuberculosis) is one of the most fatal infectious diseases claiming approximately three million lives eachyearglobally[1].In addition, the efficacy of TB-drug is limited due to the development of various multidrug resistant forms of TB. Therefore, the quest for novel anti-TB agents having high potency is the main mission for medicinal chemist. Pyrimidine is one of the most important members of all the diazines and it has great biological importance. Important member of the pyrimidine family are uracil, thymine and cytosine, which demonstrate diverse biological profile.

***Address for Correspondence:**
Ranjan Khunt
Chemical Research Laboratory, Department of Chemistry, Saurashtra University, Rajkot-360005 (Gujarat), India.
E-Mail Id: evans@bcpindia.org; drrckhunt12@yahoo.com

In the last decade, pyrimidine derivatives constitute displaying a variety of activities including immunotropic[2], anti- inflammatory[3], antitumor[4], antiviral[5] and antimycobacterial[6]. In addition, several pyrimidine derivatives are also reported to have anti-HIV activity[7], antitubercular[8] and IKKinhibitors[9].

On the other hand, quinoline derivatives are regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities including antibacterial[10], antimicrobial[11], antimycobacterial[12], antimalarial[13], anti-inflammatory[14] and anticancer activities[15]. Quinoline containing compounds have long been used for the treatment of malaria, beginning with quinine. Study by De Souzaetal.[16] showed that some7-chloro-4-amino-quinoline derivatives exhibited significant inhibitory activity against *M.*

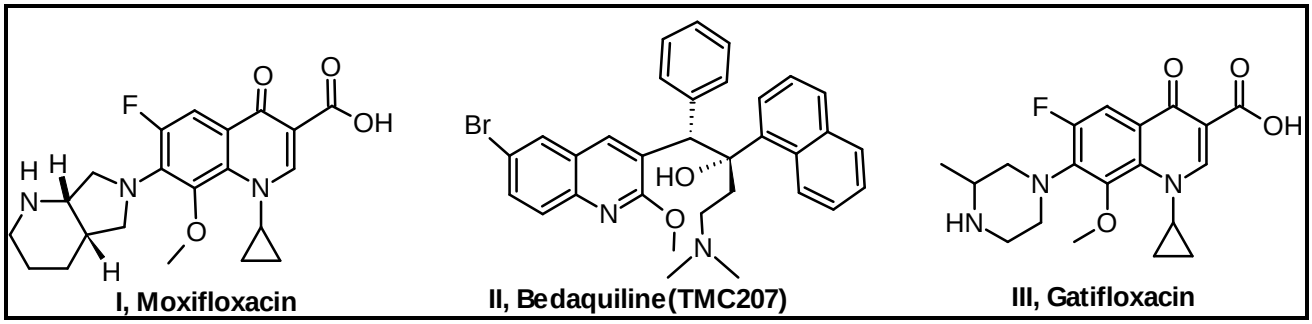


Figure 1: Structure of Molecules

Tuberculosis (MIC= 3.12–12.5µg/mL), when compared with first line drugs such as ethambutol (MIC=3.12µg/mL). Moreover, quinoline containing drugs Moxifloxacin(**I**) and Bedaquiline (TMC207,**II**)[17] are in phase-II, and Gatifloxacin (**III**) is in phase III clinical trial for the treatment of TB. Inspired with the biological profile of pyrimidine and quinoline derivatives, and in connection with our ongoing research on antitubercular agents a new series of pyrimidine derivatives bearing the quinolone scaffold have been prepared and their antibacterial and antitubercular activities have been reported herein.

A Recursive Partitioning (RP) based classification model was developed to classify the quinoline derivatives into their own activity class and for investigating structural characteristics responsible for different affinity profiles. Recursive partitioning is a classification method for statistically determining rules that classify structures into groups of molecules with similar potencies and seeks to decode the complex structure-activity relationships into their large complex datasets. It enables fast derivation of classification models for the prediction of activities or properties by employing a tree-structured set of queries about the descriptors to recursively partition the dataset into groups, wherein the response variable is homogeneous. The input space is recursively split into nodes of a tree using an algorithm that considers all possible binary splits for each descriptor and chooses the optimal criterion. This sequential partitioning continues recursively until the threshold value of the termination rule is reached.

The graphical output of the SAR in terms of decision tree derived from the classification model can qualitatively predict activities or activity classes in structure–activity relationship analysis and provides the essential decisive elements to split the dataset into groups of molecules with higher and lower responses.

EXPERIMENTAL SECTION

Chemistry

The chemicals and solvents were used for the synthesis was purchased from Spectrochem, Mumbai (India). Melting points of the synthesized product were determined in open capillary tubes in an Electro thermal 9200 melting point apparatus and are uncorrected. High-performance liquid chromatography was performed on Shimadzu instrument: Compounds were detected by UV at 260nm with flow rate of 1mL/min. The purity of all tested compounds was >95% based on analytical HPLC. ^{1}HNMR spectra were recorded on a Bruker Avance II 300 MHz spectrophotometer with $CDCl_3$ or DMSO-d_6 as solvents and tetramethylsilane (TMS) as the internal standard. Chemical shift (δ) are given in ppm relative to TMS and coupling constants (J) in Hz. Mass spectra were recorded on a Shimadzu GCMS-QP 2010 instrument.

Synthesis of (E)-3-(2-chloro-6-methylquinolin-3-yl)-1-aryl-prop-2- en-1-one (2)

To a stirring solution of 2-chloro-6-methylquinoline-3-carboxaldehyde (2.06g,0.01mol) in methanol (20mL) was added 40% NaOH and the mixture was stirred for 10min at room temperature (RT). A solution of

substituted acetophenone (0.01mol) in methanol (20 mL) was added dropwise. The resulting mixture was allowed to stir for 12h at RT. After the completion of reaction, the reaction mixture was poured onto crushed ice. The resulting solution was acidified using 5N HCl and the separated product was filter, and washed with water. The obtained crude product was purified by crystallization in methanol. Yield 67%, m.p. 137 °C[21].

Generalmethodforthesynthesisof4-(2-chloro-6-methylquinolin-3-yl)-6-aryl-3, 4-dihydropyrimidin-2(1H)-one (3a-j and 4a-j)

To a stirring mixture of compound**2** (0.01mol), and urea/thiourea (0.01mol) in ethanol (25 mL), alcoholic KOH was added. The resulting reaction mixture was refluxed for 6h. After the completion of reaction, monitored by TLC, the solvent was evaporated to dryness under reduced pressure and the residue obtained was neutralized with 5N HCl solution. The product obtained was isolated by filtration, washed with water, followed by hexane. The crude product obtained was crystallized from dioxane.

4-(2-Chloro-6-methylquinolin-3-yl)-6-phenyl-3, 4-dihydropyrimidin-2(1H)-one (3a)

Yield 65%; m.p.124-126°C; IR(KBr):3380,3080,2975,1642,1523,713cm^{-1}; ^{1}HNMR(300MHz,$CDCl_3$)δ 2.51(s,3H, Ar-CH_3), 6.60(s,1H,Ar-H),6.81(s,1H,Ar-H), 7.26-7.48(m,5H,Ar-H),7.59 (d, J= 1.7Hz,1H, Ar-H),7.46(d, J= 8.3Hz,1H, Ar-H), 7.76(d, J= 8.3Hz,1H, Ar-H), 8.11(s,1H,Ar-H), 8.5(br,2H,NH); Mass: 349(M+),351(m+2); Ana Cald. for $C_{20}H_{16}ClN_3O$: C,68.67; H,4.61;N,12.01%; found:C,68.62; H,4.55; N, 11.96%.

4-(2-Chloro-6-methylquinolin-3-yl)-6-(p-tolyl)-3, 4- dihydropyrimidin-2(1H)-one (3b)

Yield 72%; m.p.98-100°C; IR(KBr):3421,3110,2942,1662,1560,732cm^{-1}; ^{1}HNMR(300MHz,$CDCl_3$)δ 2.35(s,3H,Ar-CH_3), 2.41(s,3H,Ar-CH_3), 6.71(s,1H,Ar-H), 6.83(s,1H,Ar-H), 7.05 (dd,J=8.6 and 1.3Hz, 2H,Ar-H), 7.49(d,J=1.9Hz, 1H,Ar-H), 7.52(dd,J=8.2 and 1.9Hz, 1H, Ar-H), 7.85 (d,J=8.2Hz,1H,Ar-H), 7.99 (dd,J=8.6 and 1.3Hz,2H,Ar-H), 8.10(s,1H,Ar-H), 8.61(br,2H,-NH); Mass 363(m+): Ana Cald. for $C_{21}H_{18}ClN_3O$: 363(m+);C, 69.32;H, 4.99; N, 11.55% found: C, 69.28; H, 4.92; N, 11.50%.

4-(2-Chloro-6-methylquinolin-3-yl)-6-(4-methoxyphenyl)-3, 4- dihydropyrimidin-2(1H)-one (3c)

Yield 75%; m.p. 90-93°C; IR(KBr): 3462,3118,2920,1653,1588,754cm^{-1}; ^{1}HNMR (300MHz,$CDCl_3$)δ 2.49(s,3H,Ar-CH_3), 3.89(s,3H,Ar-OCH_3), 6.81(s,1H,Ar-H), 6.94(s,1H,Ar-H), 6.98(dd, J=8.8 and 1.1Hz, 2H,Ar-H), 7.46(d,J=1.8Hz,1H,Ar-H), 7.49(dd, J=8.4 and 1.8Hz,1H,Ar-H), 7.72 (d,J=8.4Hz,1H,Ar-H), 8.05 (dd,J=8.8 and 1.9Hz,2H,Ar-H), 8.16(s,1H,Ar-H), 8.5(br,1H,-NH),8.8(br,1H,NH); Mass:379(m+); Ana. Calcd for $C_{21}H_{18}ClN_3O_2$: C,66.40; H,4.78;N,11.06% Found:C,66.36; H, 4.72; N, 11.01%.

4-(2-Chloro-6-methylquinolin-3-yl)-6-(4-chlorophenyl)-3, 4- dihydropyrimidin-2(1H)-one (3d)

Yield 69%; m.p.109-111°C; IR(KBr): 3442,3098,2962,1622,1561,769cm^{-1}; ^{1}HNMR (300MHz,$CDCl_3$)δ 2.38 (s,3H,Ar-CH_3), 6.52(s,1H,Ar-H), 6.79(s,1H,Ar-H), 7.01(dd,J=8.7 and 1.2Hz,2H,Ar-H), 7.35 (d,J=1.7Hz,1H,Ar-H), 7.41(dd,J=8.5 and 1.7Hz,1H,Ar-H), 7.62(d,J=8.5Hz,1H,Ar-H), 7.92 (dd, J=8.7 and 1.2Hz, 2H, ArH), 8.03(s,1H,ArH), 8.61(br,2H,NH; Mass: 384(m+); Anal. Calcd. for $C_{20}H_{15}Cl_2N_3O$: C, 62.51; H, 3.93; N, 10.94% found: C, 62.46; H, 3.88; N, 10.89%.

4-(2-Chloro-6-methylquinolin-3-yl)-6-(4-fluorophenyl)-3, 4- dihydropyrimidin-2(1H)-one (3e)

Yield 73%; m.p.207-209°C; IR(KBr): 3448,3091,2958,1638,1573,782cm^{-1}; ^{1}HNMR (300MHz,$CDCl_3$)δ 2.41(s,3H,Ar-CH_3), 6.54 (s,1H,Ar-H), 6.82(s,1H,Ar-H), 7.03(dd,J=8.8 and 1.1Hz,2H,Ar-H), 7.31 (d,J=1.8Hz,1H,Ar-H), 7.43 (dd,J=8.6 and 1.8Hz,1H,Ar-H), 7.59(d,J=8.7Hz,1H,Ar-H), 7.85 (dd,J=8.8 and 1.1Hz, 2H,Ar-H), 8.00(s,1H,Ar-H),8.52(br,2H,-

NH); Mass: 368(M+); Ana.Calcd.for $C_{20}H_{15}ClFN_3O$: C, 65.31; H, 4.11; N, 11.42% found: C, 65.26; H, 4.50; N, 11.36%.

4-(2-Chloro-6-methylquinolin-3-yl)-6-(4-hydroxyphenyl)-3, 4- dihydropyrimidin-2(1H)-one (3f)

Yield 59%; m.p.233-235°C; IR(KBr):3392,3018,2923,1649,1526,771cm^{-1}; ^{1}HNMR (300MHz,$CDCl_3$) δ2.51(s,3H,Ar-CH_3), 5.41(s,1H,-OH), 6.71(s,1H,Ar-H), 6.89(s,1H,Ar-H), 7.12(dd,J=8.8 and 1.5Hz, 2H, Ar-H), 7.25(d,J=1.9Hz,1H,Ar-H), 7.36(dd,J=8.5 and 1.9Hz,1H,Ar-H), 7.53(d,J=8.5Hz,1H,Ar-H), 7.79(dd, J= 8.8 and 1.5 Hz,2H, Ar-H), 7.86(s, 1H, Ar-H), 8.52 (br, 2H,-NH); Mass: 365 (m+); Anal. Calcd. for $C_{20}H_{16}ClN_3O_2$: C, 65.67; H, 4.41; N, 11.49% found: C, 65.62; H, 4.35; N,11.44%.

6-(4-Aminophenyl)-4-(2-chloro-6-methylquinolin-3-yl)-3, 4- dihydropyrimidin-2(1H)-one (3g)

Yield 68%;m.p.181-183°C; IR(KBr):3408,3101, 2968,1653,1586,773cm^{-1}; ^{1}HNMR(300MHz, $CDCl_3$)δ 2.47(s,3H,Ar-CH_3), 3.89(s,2H,-NH_2),6.47(s,1H,Ar-H), 6.58(s,1H,Ar-H), 6.72(dd,J=8.6 and 1.8Hz,2H,Ar-H), 6.98(d,J=1.8Hz,1H,Ar-H), 7.23(dd,J=8.6 and 1.7Hz,1H,Ar-H), 7.46(d,J=8.6Hz,1H,Ar-H),7.82 (dd,J=8.6 and 1.8Hz,2H,Ar-H), 7.86(s,1H,Ar-H), 8.52(br,2H,-NH); Mass:364(m+); Ana. Calcd. for $C_{20}H_{17}ClN_4O$: C,65.84; H,4.70;N,15.36%found:C,65.79; H,4.65; N,15.30%.

4-(2-Chloro-6-methylquinolin-3-yl)-6-(4-nitrophenyl)-3, 4- dihydropyrimidin-2(1H)-one (3h)

Yield, 79%; m.p.274-276°C; IR(KBr):3369, 3081, 2915, 1668, 1583,735cm^{-1}; ^{1}HNMR(300MHz,$CDCl_3$)δ 2.56(s,3H,Ar-CH_3), 6.65(s,1H,Ar-H), 6.73(s,1H,Ar-H), 7.06(dd,J=8.1 and 1.9Hz,2H,Ar-H), 7.23 (d,J=2.1Hz,1H,Ar-H), 7.45(dd,J=7.9 and 2.1Hz,1H,Ar-H), 7.76(d,J=7.9Hz,1H,Ar-H), 8.10 (dd,J=8.1 and 1.9Hz, 2H,Ar-H), 8.29(s,1H,Ar-H), 8.71(br,2H,-NH); Mass: 395(m+); Ana. Calcd. for $C_{20}H_{15}ClN_4O_3$: C, 60.84; H, 3.83; N,14.19% found: C, 60.80; H, 3.78; N, 14.15%.

4-(2-Chloro-6-methylquinolin-3-yl)-6-(3-nitrophenyl)-3, 4- dihydropyrimidin-2(1H)-one (3i)

Yield, 76%; m.p.264-266°C; IR(KBr):3365, 3076,2946,1654,1590,745cm^{-1}; ^{1}HNMR (300MHz,$CDCl_3$)δ 2.53(s,3H,Ar- CH_3), 6.64(s,1H,Ar-H),6.75(s,1H,Ar-H), 7.31-7.63(m,4H,Ar-H), 7.20 (d,J=2.0Hz,1H,Ar-H), 7.38(dd, J=7.6 and 2.0Hz,1H,Ar-H),7.58(d, J=7.6Hz, 1H, Ar-H), 8.12 (s,1H, Ar-H), 8.76(br, 2H,-NH); Mass:395 (m+); Ana. Calcd. for $C_{20}H_{15}ClN_4O_3$: C, 60.84; H, 3.83; N, 14.19%found: C, 60.80; H, 3.78; N, 14.15%

4-(2-Chloro-6-methylquinolin-3-yl)-6-(2-hydroxyphenyl)-3, 4- dihydropyrimidin-2(1H)-one (3j)

Yield, 63%; m.p.118-120°C; IR(KBr):3401, 3052,2963,1666,1575,756cm^{-1}; ^{1}HNMR (300MHz,$CDCl_3$)δ 2.49(s,3H,Ar- CH_3), 5.44(s,1H,-OH), 6.69 (s,1H,Ar-H), 6.91(s,1H,Ar-H), 7.49-7.83(m,4H,Ar-H), 7.23 (d,J=1.4Hz,1H,Ar-H), 7.42 (dd,J= 7.6 and 1.4Hz,1H, Ar- H), 7.76(d,J=7.6Hz,1H,Ar-H), 8.39(s,1H,Ar-H), 8.70(br,2H,-NH); Mass:366(m+); Ana. Calcd. for $C_{20}H_{16}ClN_3O_2$: C,65.67; H,4.41; N,11.49% found: C,65.60; H,4.38; N, 11.42%.

4-(2-Chloro-6-methylquinolin-3-yl)-6-phenyl-3, 4- dihydropyrimidine-2(1H)-thione (4a)

Yield, 60%; m.p.151-153°C; IR(KBr):3380, 3080,2975,1523,1114,713cm^{-1}; ^{1}HNMR (300MHz, $CDCl_3$)δ 2.42(s,3H,Ar- CH_3), 6.52(s,1H,Ar-H), 6.72(s,1H,Ar-H),7.06-7.23(m,5H,Ar-H), 7.41(d,J=1.8Hz,1H,Ar-H), 7.52(dd,J=8.1 and 1.6Hz,1H,Ar-H),7.63(d,J= 8.1Hz,1H, Ar-H),8.06(s, 1H, Ar-H),8.52(br,1H,-NH), 8.78(br,1H,-NH); Mass:366(m+); Ana. Calcd. For $C_{20}H_{16}ClN_3S$: C,65.65; H,4.41; N,11.48% found: C, 65.61; H, 4.36; N, 11.41%.

4-(2-Chloro-6-methylquinolin-3-yl)-6-(p-tolyl)-3, 4- dihydropyrimidine-2(1H)-thione (4b)

Yield 55%; m.p.150-152°C; IR (KBr):3398, 3089,2897,1125,1560,732cm^{-1}; ^{1}HNMR (300MHz, $CDCl_3$)δ 2.33(s,3H, Ar- CH_3), 2.37(s, 3H, Ar- CH_3), 6.61(s, 1H,Ar-H), 6.83(s, 1H, Ar-H),6.89 (dd,J=8.4 and 1.6Hz,2H,Ar-H), 7.13(d,J=1.7Hz,1H,Ar-H), 7.31(dd,J=8.1 and 1.7Hz,1H,Ar-H),7.56 (d,J=8.1Hz,1H,Ar-H), 7.85(dd,J=8.4 and 1.5Hz,2H,Ar-H), 7.95(s,1H,Ar-H), 8.41(br,1H,-NH), 8.71 (br,1H,-NH); Mass:380(M+); Anal. Calcd. For $C_{21}H_{18}ClN_3S$:C,66.39; H,4.78;N, 11.06% found: C, 66.32; H, 4.73; N, 11.01%.

4-(2-Chloro-6-methylquinolin-3-yl)-6-(4-methoxyphenyl)-3, 4-dihydropyrimidine-2(1H)-thione (4c)

Yield, 59%; m.p.107-109°C; IR(KBr):3410, 3138,2969,1549,1178,739cm^{-1}; ^{1}HNMR (300MHz, $CDCl_3$)δ 2.53(s,3H, Ar- CH_3), 3.84(s, 3H,Ar-O CH_3), 6.74(s, 1H,Ar-H),6.92(s, 1H, Ar-H), 7.13 (d, J=8.8 Hz, 2H, Ar-H), 7.55 (d, 1H, Ar-H), 7.58 (d,1H, Ar-H), 7.87(d,1H, Ar-H), 8.13(d,J=8.8Hz,2H,Ar-H), 8.34(s,1H,Ar-H), 8.59(br,1H,-NH), 8.83(br,1H,-NH); Mass:396(M+); Ana. calcd. for $C_{21}H_{18}ClN_3OS$: C,63.71;H,4.58; N, 10.61% found: C, 63.68;H,4.52;N,10.55%.

4-(2-Chloro-6-methylquinolin-3-yl)-6-(4-chlorophenyl)-3, 4-dihydropyrimidine-2(1H)-thione (4d)

Yield, 58%;m.p.159-161°C; IR(KBr): 3458,3026,2915,1518,1198,769cm^{-1}; ^{1}HNMR (300MHz,$CDCl_3$) δ2.19(s,3H, Ar- CH_3), 6.56(s, 1H, Ar-H),6.70(s, 1H,Ar-H),6.78(d, J= 8.4Hz,2H, Ar- H), 6.93(d,J= 1.1Hz,1H,Ar-H),7.08(dd,J=8.9and1.1Hz,1H,Ar-H), 7.42(d,J=8.8Hz,1H,Ar-H),7.82(d, J= 8.5Hz,2H,Ar-H), 8.03(s,1H,Ar-H),8.42(br,1H,-NH), 8.54(br,1H,-NH); Mass: 400(M+) ; Ana. Calcd. for $C_{20}H_{15}Cl_2N_3S$: C, 60.00; H, 3.78; N, 10.50% found: C, 59.91; H, 3.74; N, 10.46%.

4-(2-Chloro-6-methylquinolin-3-yl)-6-(4-fluorophenyl)-3, 4-dihydropyrimidine-2(1H)-thione (4e)

Yield 58%; m.p.134-136°C; IR(KBr):3418, 3135,2989,1573,1149,782cm^{-1}; ^{1}HNMR (300MHz,$CDCl_3$)δ 2.35(s,3H,Ar- CH_3), 6.59(s,1H,Ar-H), 6.68(s,1H,Ar-H), 7.10 (dd,J=8.8 and 1.1Hz,2H,Ar-H),7.23 (d,J=1.8Hz,1H,Ar-H), 7.38(d,J=8.6 and 1.8Hz,1H,Ar-H), 7.56(d,J=8.7Hz,1H,Ar-H), 7.88 (d,J=8.8 and 1.1Hz,2H,Ar-H), 8.08(s,1H,Ar-H), 8.35(br, 1H,-NH), 8.47(br,1H, -NH); Mass:384(M+); Ana. calcd. for $C_{20}H_{15}ClFN_3S$: C,62.58;H,3.94;N, 10.95% found:C,62.51;H,3.90;N,10.89%.

4-(2-Chloro-6-methylquinolin-3-yl)-6-(4-hydroxyphenyl)-3, 4-dihydropyrimidine-2(1H)-thione(4f)

Yield,65%; m.p.84-86°C; IR(KBr):3329, 3057,2964,1576,1157,771cm^{-1}; ^{1}HNMR (300MHz,$CDCl_3$) δ:2.49(s,3H,Ar- CH_3), 5.59(s,1H,-OH), 6.73(s,1H,Ar-H), 6.91(s,1H,Ar-H),6.99 (dd,J=8.6 and 1.3Hz, 2H,Ar-H), 7.08(d,J=1.7Hz,1H,Ar-H), 7.21(dd,J=8.7and1.6Hz,1H,Ar-H), 7.63(dd, J=8.7Hz,1H,Ar-H), 7.98(dd,J=8.6 and 1.4Hz,2H,Ar-H), 8.16(s,1H,Ar-H), 8.47(br,1H,-NH), 8.62(br,1H,-NH);Mass: 381(M+); Ana. calcd. for $C_{20}H_{16}ClN_3OS$:C,62.90;H,4.22; N,11.00%found:C,62.85; H, 4.17; N, 10.93%.

6-(4-Aminophenyl)-4-(2-chloro-6-methylquinolin-3-yl)-3, 4-dihydropyrimidine-2(1H)-thione (4g)

Yield, 60%; m.p.213-215°C; IR(KBr):3398, 3056,2913,1586,1198,719cm^{-1}; ^{1}HNMR (300MHz,$CDCl_3$)δ 2.47(s,3H,Ar- CH_3), 4.01(s,2H,NH2), 6.42(s,1H,Ar-H), 6.54(s,1H,Ar-H), 6.71(dd, J=8.6 and 1.8Hz, 2H, Ar-H), 6.97(d,J=1.8Hz,1H,Ar-H), 7.13(dd,J=8.6 and 1.7Hz,1H,Ar-H), 7.53(d,J=8.6Hz,1H,Ar-H),7.93 (dd,J=8.6 and 1.8Hz,2H,Ar-H), 8.21(s,1H,Ar-H), 8.58(br,1H,-NH), 8.83(br,1H,-NH); Mass:381(M+); Ana. Calcd. for $C_{20}H_{17}ClN_4S$:C,63.07;H,4.50;N,14.71% found:, 63.02; H, 4.45; N, 14.66%.

4-(2-Chloro-6-methylquinolin-3-yl)-6-(4-nitrophenyl)-3, 4-dihydropyrimidine-2(1H)-thione(4h)

Yield, 67%; m.p.119-221°C; IR(KBr):3346, 3021, 2986, 1545, 1161, 735cm^{-1}; ^{1}HNMR (300MHz, $CDCl_3$) δ2.29(s, 3H,Ar- CH_3),6.56(s, 1H,Ar-H),6.79(s,1H,Ar-H), 7.22(dd,J=7.9 and 1.2Hz, 2H, Ar-H), 7.29 (d,J=2.0Hz,1H,Ar-H), 7.58(dd,J=7.6 and 1.9Hz,1H,Ar-H), 7.84(d,J=7.7Hz,1H,Ar-H), 8.35(dd,J=7.8 and 1.1Hz, 2H,Ar-H), 8.46(s,1H,Ar-H), 8.63(br,1H,-NH), 8.96(br,1H,-NH); Mass: 411(M+); Ana. calcd. for $C_{20}H_{15}ClN_4O_2S$:C,58.46;H,3.68; N,13.64% found:C,58.41;H, 3.61;N, 13.61%.

4-(2-Chloro-6-methylquinolin-3-yl)-6-(3-nitrophenyl)-3, 4- dihydropyrimidine-2(1H)-thione(4i)

Yield, 62%; m.p.157-159°C; IR(KBr):3410, 3116,2997,1590,1186,796cm^{-1}; ^{1}HNMR (300MHz, $CDCl_3$)δ 2.35(s,3H,Ar- CH_3), 6.59(s,1H,Ar-H), 6.84(s,1H,Ar-H), 7.23-7.89(m,4H,Ar-H), 7.36(d,J=1.3Hz,1H,Ar-H), 7.49(dd,J=7.8 and 1.3Hz,1H,Ar-H), 7.82(d,J= 7.8Hz,1H, Ar-H), 8.38(s, 1H, Ar-H), 8.57(br,1H,-NH), 8.82(br,1H,-NH); Mass: 410(M+); Ana. Calcd. for $C_{20}H_{15}ClN_4O_2S$:C,58.46;H,3.68; N,13.64% found: C, 58.40; H, 3.61; N, 13.59%.

4-(2-Chloro-6-methylquinolin-3-yl)-6-(2-hydroxyphenyl)-3, 4-dihydropyrimidine-2(1H)-thione (4j)

Yield, 60%; m.p.198-200°C; IR(KBr):3356, 3098, 2912, 1575, 1168,756cm^{-1}; ^{1}HNMR (300MHz,$CDCl_3$)δ 2.36(s,3H, Ar- CH_3), 5.64(s, 1H,-OH), 6.57(s, 1H, Ar-H),6.78(s, 1H, Ar-H), 6.91-7.82 (m,m2H,Ar-Hm), 7.09(d,J=1.5Hz,1H,Ar-H), 7.37(dd,J=7.8 and 1.5Hz,1H,Ar-H), 7.61(d,J=7.8Hz,1H,Ar-H),8.04 (s,1H,Ar-H), 8.42(br,1H,-NH), 8.69(br,1H,-NH); Mass:381(M+); Ana. calcd. for $C_{20}H_{16}ClN_3OS$:C, 62.90; H,4.22; N, 11.00% found: C, 62.85; H, 4.17; N, 10.97%.

Biological Assay

Antibacterial Activity

The antimicrobial activity was assayed by using the cup-plate agar diffusion method[22] in triplicate by measuring the zone of inhibition in mm. Newly synthesized compounds were screened *in-vitro* for the in antimicrobial activity against variety of bacterial strains such as *Bacillus subtilis* (ATCC6051), *Bacillus coccus* (ATCC53968), *Escherichiacoli* (ATCC25922), *Proteus Vulgaris* (ATCC 8427) and fungi *Aspergillus niger (*ATCC 9029) at 40 µg/mL concentration. DMSO was used as a control solvent and antimicrobial data were compared with standard drug such as ampicillin, amoxicillin, norfloxacin, penicillin and greseofulvin. After 24h incubation at 37ºC, the zone of inhibition was measured in mm. The results are depicted in Table 1.

Antitubercular Activity

In vitro antitubercular activity against *Mycobacterium tuberculosis H37Rv* of all the newly synthesized derivatives was determined in BACTEC 12B medium using the modified BACTEC460 radiometric system. The antitubercular evaluation so the compounds were carried out at Tuberculosis Antimicrobial Acquisition and Co-coordinating Facility (TAACF), USA. Primary screening of the compounds for antitubercular activity have been conducted at 6.25 µg/ml. In which stock solutions for test molecules was prepared in dimethylsulfoxide (DMSO) and sterilized by passage through 0.22µ MPFTE filters (Millex-FG, Millepore, Bedford MA)[23].Thedatawere compared with standard drug Rifampicin at 0.25µg/ml concentration which showed 98% inhibition.

Computational Study

Recursive partitioning (RP)[24-28] analysis was performed by using the CSAR methodology. Numerical descriptors that encode topological, thermodynamic, geometrical/structural and electronic properties were calculated using Cerius2 molecular modeling software[29]. The correlation matrices were obtained for these descriptor properties and those descriptors which showed zero variance or contain 95% of zero values were eliminated from the study table.

The quinoline derivatives were split into two classes, less active (0) and active (1). The class 1 contained molecules which showed less than

70% inhibition (less active) while the class 2 contained 5 molecules showing more than 70% inhibition (active). The activity classes were equally weighted (which allows you to adjust the cost of misclassifications between classes) and the Twoing rule scoring function was applied to split the dataset. This rule tends to split the dataset into two nodes with approximately the same number of samples, so that the trees look more balanced. The pruning factor was varied between 0 (no pruning) and 10 (heavy pruning) until the split was observed. Recursive partitioning does not stop splitting at the right moment; instead, it is designed to "oversplit" and then prune the tree backwards. Pruning factor provides a control over the amount of pruning to be performed. Also the maximum tree depth which specifies the maximum number of node splits that can yield to a terminal node was varied from 5 till 10 while the default values were set for maximum number of generic splits (30) and the number of knots per variable (20). A *knot* signifies a value in the column that is used to split. The decision tree model, derived with the CARTTM (classification and regression trees) method, was internally validated using cross-validation with the number of cross-validation groups set to10. The classification model was derived by variation of above discussed parameters trying to improve the following parameters:

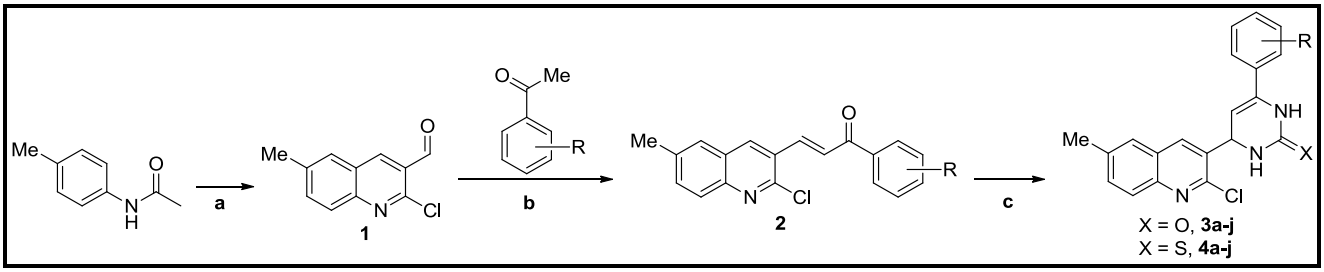
"Class% Observed Correct" (intra class prediction) which is the measure of the number of compounds correctly predicted to belong to a class as a percentage of the total number of compounds observed to be each class;

"Overall % Predicted Correct" (overall prediction), a measure of the total number of compounds correctly classified divided by the number of compounds predicted to belong to each class and "the enrichment factor" for a specific class which is the ratio of the "Overall% Predicted Correct" to the original percentage of compounds belonging to that class.

RESULTS AND DISCUSSION

Chemistry

The synthesis of quinolinyl pyrimidine derivatives (**3a-j**) and (**4a-j**) was carried out by following the steps as depicted in Reaction Scheme-1.The 2-chloro-6- methylquinolin-3-carbaldehyde (**1**) scaffold was prepared by Vilsmeier-Haack reaction of *N*-(p-tolyl) acetamide with DMF and $POCl_3$ as described in literature procedure[18]. The condensationof2-chloro-6-methylquinolin-3-carbaldehyde (**1**) with different aromatic ketones in the presence of alkali afforded the stable chalcones intermediate 2[19]. The syntheses of Oxo- and thiopyrimidine derivatives (3a-j and 4a-j) were carried out by cyclo-condensation reaction between chalcones **2** with either urea or thiourea, respectively, in the presence of alcoholic potassium hydroxide as a catalyst by following the literature method[20]. All the compounds synthesized were purified either by column chromatography or by recrystallization methods. The purity of novel compounds was confirmed by HPLC and clean ^{1}H NMR spectrum.



Scheme: 1 Synthetic pathway for compounds 3a-j and 4a-j.

Reagents and reaction conditions: (a) $POCl_3$, DMF; (b) 40% NaOH; (c) urea/thiourea, alcoholic KOH.

Biology

Antimicrobial and Antifungal Activity

Newly synthesized quinolinyl pyrimidine derivatives (3a–j and4a–j) were screened for the antimicrobial and antifungal activity against different stains such as *B.subtilis*, *B.coccus*, *E.coli*, *P.Vulgaris* and A.niger. Amoxicillin, benzyl penicillin, ciprofloxacin, and erythromycin were used as a standard drug for antibacterial and greseofulvin was used for antifungal studies. The antibacterial activity study revealed that compounds 3j, 4a, 4b, and 4e possessed significant inhibitory activity against *B.Coccus*, while compounds 3a, 3h, 4i, and 4e exhibited significant inhibitory effects against *B.Subtilis*. Compounds 3a, 3h, 4c, 4h, and 4e portrayed good activity against *E.coli*. The most promising compounds against *P. Vulgaris* are 3i, 4b, and 4e. Antifungal activity data showed that compounds 3i and 4e have good potential to inhibit *A.Niger* stain. Remaining compounds exhibited moderate to low activity compared to standard drugs.

Antimycobacterial Activity

The antitubercular activity of the newly synthesized quinolinyl pyrimidine (**3a-j** and**4a-j**) against *M.Tuberculosis* is shown in Table 1. The screening data indicated that thiopyrimidine derivatives (**4a-j**) are slightly more potent than the corresponding oxopyrimidine derivatives (**3a-j**).SAR study of oxopyrimidine derivatives (**3a-j**) shows that compounds containing 4-Cl-Ph (**3d**) and 4-F-Ph (**3e**) are more potent than compounds with other substituent(s). In addition, compound having-Me substitution (**3b**) at the 4-position of phenyl ring also shows moderate inhibitory activity. Remaining derivatives such as phenyl, hydroxyl phenyl, nitrophenyl and aminophenyl derivatives showed less inhibitory active against *M. Tuberculosis*. SAR study of thiopyrimidine derivatives (**4a-j**) reveals that the pattern of potency is almost similar to that of oxopyrimidines. Compounds having halogen substitution (**4e**), and 4-Me substitution (**4b**) shows potent antitubercular activity. In addition, 4-amino (**4g**) and 4-nitro (**4h**) derivatives also shows moderate activity against *M.Tuberculosis*. In conclusion, compound **4e** (4-F-Ph) showed most potent inhibitory effect (95% inhibition) against M.Tuberculosis and was most active compound amongst all compounds tested.

Computational Studies

The statistical results of the RP analysis and activity predictions are summarized in Table 2 and 3, respectively. The classification model was found to be statistically significant, correctly classifying 15 out of 15 compounds inclass1 i.e. the class of "less active". The enrichment factor for this class was found to be 1.33. Even for the class 2 i.e. the class of "actives", the prediction was found to be 100% classifying all the 5 out of 5 compounds correctly with an enrichment factor of 4.00."Overall% Predicted Correct" is the number of true positives among the predictions in each activity class and its value for both the classes was found to be 100% (Table 2). These statistical results indicate that the recursive partitioning model derived from this study could be fruitfully utilized for classifying new library of molecules.

The result of recursive partitioning analysis is represented by a decision tree, which is derived from CARTTM- classification and regression trees method. The entire dataset was split into smaller subsets (nodes) according to the particular cutoff value. All the descriptor variables were examined at each non-terminal node to identify the best criterion for further splitting of the dataset into "active" or "less active" class.

A 5-leaf decision tree (Figure 2) was obtained for the quinoline derivatives with 5 terminal and 4non-terminal nodes. Radius of gyration, molecular weight, density and principle moment of inertia (PMI) served as the decisive elements in the decision tree (Table 3). The terminal nodes 2 and 5 represent class 2 (active) while the class1 (less active) is represented by terminalnodes 1, 3 and 4. At each decision point, molecules were split into two categories, higher and lower responses, according to their

Table 1: Anti mycobacterial and antimicrobial activity data of the compounds 3a-j and 4a-j

Comp. No.	R	Antibacterial Activity[a]				Antifungal Activity[a]	Antitubercular Activity (%)
		B. Coccus	*B. Subtilis*	*E. Coli*	*P. Vulgaris*	*A. Niger*	*M. Tuberculosis*
3a	H	12.21 ± 0.30	20.34 ± 0.16	19.11 ± 0.78	17.49 ± 0.88	16.08 ± 0.03	39
3b	4-CH_3	12.62 ± 0.27	11.89 ± 0.78	13.17 ± 0.06	16.58 ± 0.12	11.24 ± 0.15	72
3c	4-OCH_3	18.15 ± 0.02	18.75 ± 0.17	16.27 ± 0.61	14.44 ± 0.87	14.52 ± 0.38	46
3d	4-Cl	17.06 ± 0.32	9.68 ± 0.91	11.02 ± 0.87	14.75 ± 0.35	17.09 ± 0.53	68
3e	4-F	15.66 ± 0.28	13.64 ± 0.49	13.28 ± 0.31	12.83 ± 0.43	16.15 ± 0.56	84
3f	4-OH	15.23 ± 0.62	11.46 ± 0.59	15.73 ± 0.83	10.09 ± 0.25	18.18 ± 0.46	45
3g	4-NH_2	13.54 ± 0.67	18.78 ± 0.53	16.33 ± 0.71	11.97 ± 0.24	13.67 ± 0.97	36
3h	4-NO_2	11.83 ± 0.11	20.21 ± 0.43	19.56 ± 0.04	18.14 ± 0.71	11.29 ± 0.12	41
3i	3-NO_2	10.57 ± 0.37	15.34 ± 0.64	17.28 ± 0.26	19.72 ± 0.44	21.19 ± 0.38	34
3j	2-OH	21.35 ± 0.86	18.27 ± 0.78	12.89 ± 0.04	17.55 ± 0.61	12.37 ± 0.88	38
4a	H	20.23 ± 0.13	17.10 ± 0.19	12.61 ± 0.43	14.39 ± 0.07	17.73 ± 0.11	37
4b	4-CH_3	19.04 ± 0.09	14.46 ± 0.72	9.89 ± 0.45	19.75 ± 0.37	14.91 ± 0.07	79
4c	4-OCH_3	18.68 ± 0.21	12.34 ± 0.09	19.45 ± 0.23	17.41 ± 0.06	12.37 ± 0.04	39
4d	4-Cl	12.37 ± 0.14	18.74 ± 0.21	17.32 ± 0.56	16.55 ± 0.74	13.46 ± 0.28	34
4e	4-F	20.77 ± 0.41	23.68 ± 0.06	19.89 ± 0.82	20.56 ± 0.72	24.91± 0.08	95
4f	4-OH	13.25 ± 0.12	17.37 ± 0.02	11.78 ± 0.56	13.72 ± 0.04	17.43 ± 0.17	20
4g	4-NH_2	9.12 ± 0.13	13.46 ± 0.32	16.82 ± 0.75	12.46 ± 0.18	15.72 ± 0.61	74
4h	4-NO_2	10.23 ± 0.77	15.33 ± 0.46	19.74 ± 0.09	11.51 ± 0.65	12.87 ± 0.54	64
4i	3-NO_2	7.36 ± 0.79	19.31 ± 0.08	13.49 ± 0.21	10.37 ± 0.28	17.81 ± 0.46	34
4j	2-OH	17.72 ± 0.57	18.97 ± 0.42	17.64 ± 0.13	18.48 ± 0.64	10.48 ± 0.71	37
Amoxicillin		17.76 ± 0.13	15.58 ± 0.46	19.25 ± 0.74	16.28 ± 0.62	ND[b]	ND
Benzylpenicillin		21.04 ± 0.03	21.45 ± 0.72	18.52 ± 0.34	19.31 ± 0.87	ND	ND
Ciprofloxacin		15.32 ± 0.09	20.59 ± 0.46	22.47 ± 0.31	16.12 ± 0.56	ND	ND
Erythromycin		23.57 ± 0.82	19.34 ± 0.28	22.23 ± 0.45	21.51 ± 0.48	ND	ND
Griseofulvin		ND	ND	ND	ND	26.23 ± 0.84	ND
Rifampicin		ND	ND	ND	ND	ND	98

[a]Zone of inhibition in mm, each value represents the average and the standard error of three independent experiments; [b]ND: Not Determine.

properties. It should be noted here that a false response to any decisive element follow the branch to the upside while a true response to any given split follows the branch to the downside. Class1 (less actives) has been plotted using red color while Class2 (active) using green color in the decision tree. Each split is guided by a descriptor value which partitions the dataset to separate active from less active compounds.

The first primary split was observed on the basis of density, which is a spatial descriptor defined as the ratio of molecular weight to molecular volume. It reflects the types of atoms and how closely they are packed in a molecule. It can also be related to transport and melt behavior of a molecule. The terminal node 6 contain 2 molecules with density less than 1.18 (3b and 4b) and they belong to class2 (active) while the remaining18 molecules formed the non-terminal node for further splitting.

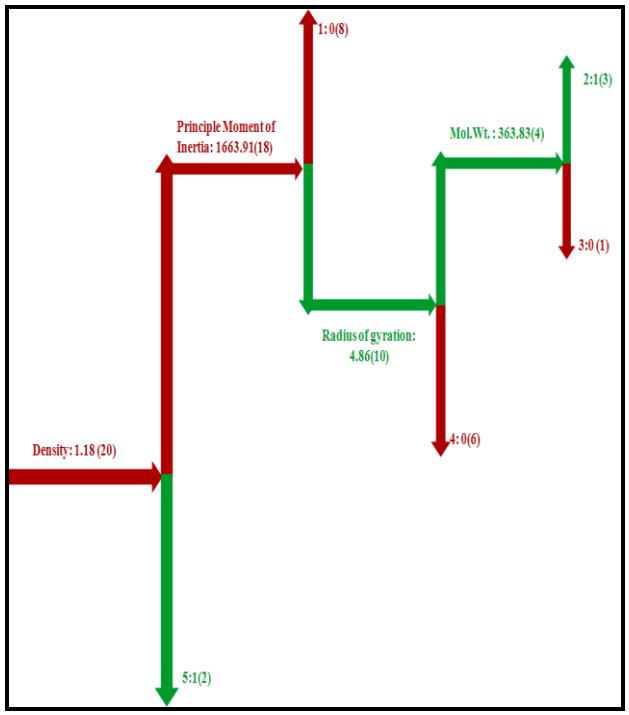


Figure 2: Decision tree for the Recursive Partitioning model: 1:0, 2:1, 3:0, 4:0, and 5:1correspond to terminal nodes1-5 and each terminal node corresponds to the value of 0 (less active) or1 (active).

The second split was seen on principle moment of inertia (a spatial descriptor) with a cut-off value of 1663.91. The terminal node 1 contains eight molecules (**3c**, **3d**, **3h**, **3i**, **4c**, **4d**, **4h** and **4i**) with principle moment of inertia value more than 1663.91 and they belongs to class1 (less active) while the remaining 10 molecules have the values below 1663.91 forming the non-terminal node.

The next split was observed on radius of gyration, which is a measure of the size of a molecule. The terminal node 4 contains six molecules (**3a**, **3f**, **3j**, **4a**, **4f** and **4j**) with radius of gyration below 4.86 and they belong to class1 (less active) while the remaining 4 molecules having the values above 4.86 formed the non-terminal node.

The fourth split was observed on the molecular weight with a cut-off value 363.83. The terminal node 2 contains 3 molecules (**3e**, **4e** and **4g**) with molecular weight greater than 363.83 and they belong to class 2 (active), while the remaining one molecule (**3g**) with molecular weight below 363.83 formed the terminal node 3 and is correctly classified as class1 (less active). It could be suggested that modulation of these properties would help in designing of molecules with enhanced potency.

A close appraisal of the model suggests that if we follow the path upside in the decision tree for 4-(6-methylquinolin-3-yl)-dihydrpyrimidine scaffold to arrive at a better molecule, it should have a molecular weight greater that 363.83 with radius of gyration also more than 4.86. Furthermore the candidate should have a principle moment of inertia below 1663.91 and density value more than 1.18.

Cross-Validation Test

In order to avoid over fitting of the data and to improve generalization of the classification model, 5-fold cross-validation was performed as a measure of internal validation. A 5-fold cross-validation leaves out (neglects) 5% of molecules from the set. The model is derived using rest of the molecules in the dataset and then it is used to predict the property of those 5% molecules which were left out. The statistical data of cross-validation is summarized in Table 4.

Table 2: Statistical results of recursive partitioning

Class	Number of Compound	%	Class % Observed Correct	Overall % Predicted Correct	Enrichment
1	15	75	100	100	1.33
2	5	25	100	100	4.00

Table 3: Activity Prediction by Recursive Partitioning

	Activity	RP Predicted Activity	Radius of Gyration	Molecular weight (MW)	Density	Principle moment of Inertia
3a	0	0	4.73	347.80	1.18	1264.19
3b	1	1	5.02	361.83	1.16	1449.79
3c	0	0	5.37	377.83	1.18	1757.99
3d	0	0	4.89	382.25	1.25	1775.42
3e	1	1	4.88	365.79	1.22	1546.52
3f	0	0	4.82	363.80	1.21	1451.13
3g	0	0	4.92	362.82	1.19	1447.404
3h	0	0	4.98	392.80	1.24	1924.82
3i	0	0	4.94	392.80	1.23	1850.88
3j	0	0	4.80	363.80	1.20	1343.92
4a	0	0	4.74	363.86	1.19	1340.64
4b	1	1	5.02	377.89	1.18	1520.82
4c	0	0	5.17	393.89	1.19	1723.57
4d	0	0	4.89	398.31	1.25	1830.80
4e	1	1	4.89	381.85	1.23	1604.26
4f	0	0	4.83	379.86	1.22	1525.66
4g	1	1	4.91	378.88	1.19	1509.65
4h	0	0	4.99	408.86	1.25	1991.49
4i	0	0	4.96	408.86	1.24	1912.03
4j	0	0	4.73	379.86	1.22	1404.95

Table 4: Statistical Results of Recursive Partitioning

Class	Number of Compounds	%	Class % Observed Correct	Overall % Predicted Correct	Enrichment
1	15	75	66.67	76.92	1.03
2	5	25	40.00	28.57	1.14

An acceptable classification percentage observed for the training and test sets suggests reasonably good predictability. This prediction rate is acceptable considering the size of the dataset and other limitations associated with it. The key descriptors determined in the total set were consistently observed in the test set as well. These predictive parameters signify the stability of the model to classify and predict the activity class of new candidates.

CONCLUSION

In continuation of our on-going research work and therapeutic interest of both pyrimidine and quinoline scaffolds, a new series of quinolinyl pyrimidine derivatives have been synthesized. A variety of substitutions were introduced to the phenylringatthe 6-position of pyrimidine moiety to study their structure activity relationships. The structure of all synthesized compounds was confirmed by spectroscopic analysis. Newly synthesized compounds were evaluated for their antimicrobial, antifungal as well as anti-mycobacterial activity. The recursive partitioning model was also generated and showed considerable discriminative power in spite of high degree of structural similarity and the limited size of the dataset. The decision tree derived from the RP model encodes the useful information regarding chemical environment around important functional groups that could serve as a guideline for the design of molecules with better affinity and selectivity. This model will be continuously refined by enlarging the dataset with the hope to end up with a molecule fulfilling the requirements of an ideal drug candidate. The computational study predictions (compounds 3e, 4e and 4g were active) were also matched with anti-mycobacterial activity data. The results of the present study have identified compound 4e as a potential candidate for tuberculosis. Further lead optimization and detailed biological study will be reported in due course.

ACKNOWLEDGEMENT

Dr. Ranjan Khunt thanks Saurashtra University for infrastructure facilities. We also thank Dr. CecilK wong, TAACF, USA, for the antitubercular screening. Special thanks are due to "National Facility for Drug Discovery through New Chemical Entities (NCE's) Development & Instrumentation Support to Small Manufacturing Pharma Enterprises" Programme under Drug & Pharma Research Support (DPRS) jointly funded by Department of Science & Technology, New Delhi, Government of Gujarat Industries Commissionerate & Saurashtra University, Rajkot.

REFERENCES

1. World HealthOrganization. Global tuberculosiscontrol. WHO 2011 report: http://www.who.int/mediacentre/news/releases/2011/tb_20111011/en/index.html
2. Krivonogov, V. P., Tolstikov, G. A., Murinov, Y. I., Zarudii, F. S., Davydova, V. A., Ismagilova, A. F., & Spirikhin, L. V. (1997). Synthesis and immunotropic activity of pyrimidine derivatives. Part. IV. Synthesis and immunotropic and antiinflammatory activity of pyrimidine acyclonucleosides. *Pharmaceutical chemistry Journal*, *31*(6), 298-302.
3. Panda, S. S., & Chowdary, P. V. R. (2008). Synthesis of novel indolyl-pyrimidine antiinflammatory, antioxidant and antibacterial agents. *Indian Journal of Pharmaceutical Sciences*, *70*(2), 208 –215.
4. Cozzi, M., Giorgi, F., Marcelli, E., Pentimalli, F., Forte, I. M., Schenone, S., & Indovina, P. (2012). Antitumor activity of new pyrazolo [3, 4-d] pyrimidine SRC kinase inhibitors in Burkitt lymphoma cell lines and its enhancement by WEE1 inhibition. *Cell Cycle*, *11*(5), 1029-1039.
5. Ramiz M. M. M., El-Sayed W. A., Hagag E., & Abdel-Rahman A. A. H. (2011). Synthesis and antiviral activity of new substituted pyrimidine glycosides, *J. Het. Chem., 48*, 1028–1038.
6. Zalavadiya, P., Tala, S., Akbari, J., Joshi, H. (2009). Multi- component synthesis of dihydro pyrimidines by iodine catalystat ambient temperature and *in-vitro* anti

mycobacterial activity, *Arch. Pharm. (Weinheim), 342,* 469–475.

7. Lather, V., & Madan, A. K. (2005). Topological models for the prediction of anti-HIV activity of dihydro (alkylthio) (naphthyl methyl) oxopyrimidines. *Bioorganic & Medicinal Chemistry*, *13*(5), 1599-1604.
8. Paghdar, D. J., Akbari, J. D., Tala S. D., Dhaduk, M. F., & Joshi, H. S. (2007). Synthesis of some new thiopyrimidine and oxopyrimidine heterocycles bearing 4-(methylsulfonyl) phenylnucleus as potent ant-tubercular and antimicrobial agents, *Indian J. Het. Chem.*, 17, 113–116.
9. Waelchli R., Bollbuck B., Bruns C., EderJ., Feifel, R., Hersperger, R., Janser, P., Revesz L., Zerwes, H. G., Schlapbach, A. (2006). Design and preparation of 2-benzamido-pyrimidines as inhibitors o IKK, *Bioorg.Med.Chem. Lett., 16,* 108–112.
10. Kalluraya, B., Nayak, J., Adhikari, A., Shetty, N. S., & winter, M. (2008). Synthesis and characterization of some novel quinolinothiazines of biological interest. *Phosphorus, Sulfur, and Silicon, 183*(8), 1870-1883.
11. Rana, P. B., Mistry, B. D., & Desai, K. R. (2008). Green chemistry: microwaveand conventional induced synthesis of various thiazolidinone derivatives from 3-{[(1E)-(2'-chloro-7'-methoxy quinoline-3'-yl) methylene] amino}-4-(substituted Phenyl diazenyl) phenol and their antimicrobial screening, *Arkivoc, 15,* 262–279.
12. Mital, A., Negi, V. S., & Ramachandran, U., Synthesis and antimycobacterial activities of certain tri fluoro methyl-amino quinoline derivatives, *Arkivoc, 10,* 220–227.
13. Charris, J. E., Domınguez ,J. N., Gamboa, N., Rodrigues, J. R., & Angel, J. E. (2005). Synthesis and anti-malarial activity of E-2-quinolinyl benzo cyclo alcanones, *Eur. J. Med. Chem., 40,* 875–881.
14. Bawa, S., & Kumar, S. (2009). Synthesis of Schiff's bases of 8-methyltetrazolo (1, 5-a) quinoline as potential anti-inflammatory and antimicrobial agents. *Indian Journal of Chemistry. Section B, Organic including medicinal*, *48(1)*, 142.
15. Shi, A., Nguyen, T. A., Battina, S. K., Rana, S., Takemoto, D. J., Chiang, P. K., & Hua, D. H. (2008). Synthesis and anti-breast cancer activities of substituted quinolines. *Bioorganic & medicinal chemistry letters*, *18*(11), 3364-3368.
16. De Souza, M. V., Pais, K. C., Kaiser, C. R., Peralta, M. A., de L Ferreira, M., & Lourenço, M. (2009). Synthesis and in vitro antitubercular activity of a series of quinoline derivatives. *Bioorganic & medicinal chemistry*, *17*(4), 1474-1480.
17. Rustomjee, R., Diacon, A. H., Allen, J., Venter, A., Reddy, C., Patientia, R. F., & McNeeley, D. F. (2008). Early bactericidal activity and pharmacokinetics of the diarylquinoline TMC207 in treatment of pulmonary tuberculosis. *Antimicrobial agents and chemotherapy*, *52*(8), 2831-2835.
18. Srivastava, A., Singh, M. K., Singh, R. M. (2006). Pyrazolo-fused quinolineanalogues: Synthesis of 1H-pyrazolo[3,4-b]quinolinesand 3-amino-1H- pyrazolo[3,4-b]quinolinesfrom 3-formyland 3-cyano-2-chloroquinolines. *Indian J. Chem., 45B,* 292–296.
19. Mistry, B. D., Desai, K. R., Patel, J. A., & Patel, N. I. (2012). Conventional and microwave-assisted synthesis of pyrazole derivatives and screening of their antibacterial and antifungal activities. *Ind J Chem B*, *51*, 746-751.
20. Bharmal, F. M., Kaneriya, D. J., & Parekh, H. H. (2001). Synthesis of some pyrazoline derivatives as biologically active agents. *Indian Journal of Heterocyclic Chemistry*, *10*(3), 189-192.
21. Hemasri,Y. (2009). Microwave assisted synthesis of substituted l,2,3,4- tetrahydro-

2-pyrimidinones and 1,2,3,4 tetrahydro-2-pyrimidine thiones from quinoline chalcones, *Het. Comm.*, *15*, 423–427.

22. Barry, A. L. (1977). *The antimicrobial Susceptibility test*, Principle and practices. Lea & Febiger; *Biol Abstr*, 64, 25183
23. Collins, L., & Franzblau, S. G. (1997). Microplate alamar blue assay versus BACTEC 460 system for high-throughput screening of compounds against Mycobacterium tuberculosis and Mycobacterium avium. *Antimicrobial Agents and Chemotherapy*, *41*(5), 1004-1009.
24. Blower, P., Fligner M., & Verducci, J., Bjoraker, J. (2002). On combining recursive partitioning and simulated an nealing to detect groups of biologically active compounds. *J. Chem. Inf. Comput. Sci.*, *42*, 393–404.
25. Strobl, C., Malley, J., & Tutz, G. (2009). An introduction to recursive partitioning: rationale, application, and characteristics of classification and regression trees, bagging, and random forests, *Psychol. Methods*, *14*, 323–348.
26. Choi S. Y., Shin, J. H., Ryu, C. K., Nam K. Y., No, K. T., & ParkChoo, H. Y. (2006). The development of 3D-QSAR study and recursive partitioning of heterocyclic quinone derivatives with antifungal activity, *Bioorg.Med. Chem.*, *14*, 1608–1617.
27. Nakata, K., Honda T. N., Weiden, M., & Keicho N. (2000). Tuberculosis in patients with acquired immune deficiency syndrome. *Kekkaku*, *75*, 547–556.
28. Young, S. S., Hawkins, D. M. (2004). Using recursive partitioning analysis to evaluate compound selection methods. *Methods Mol. Biol.*, *275*, 317–334.
29. ccelrys,Inc. Cerius2, version 4.8; San Diego, CA, USA, 1998

