Studies on Novel *N*4-[4,6-Diaryl-2-pyrimidinyl]- 7-chloro-4-quinolinamine and their Microbicidal Efficacy

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Received 11 June 2009; Accepted 18 July 2009

Abstract: The required chalcones **1a-h** were prepared by reaction of substituted acetophenone with different aryl aldehyde, which in turn treated with guanidine nitrate, yielded 4-(substituted phenyl)-6-(substituted phenyl)-2-pyrimidinamine **2a-h**. Novel pyrimidine quinoline clubbed molecules **3a-h** have been prepared by reaction of **2a-h** with 4,7-dichloroquinoline. All the compounds were characterized by elemental analysis and spectral studies. The newly synthesized compounds were evaluated for their antibacterial and antifungal activity.

Keywords: 2-Aminopyrimidine derivatives, Quinoline derivatives, Antibacterial and Antifungal.

Introduction

Heterocycles are abundant in nature and are of great significance to life, because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics *etc*¹. Hence, they have attracted considerable attention in the design of biologically active molecules²⁻³. The classes of pyrimidines possess a broad spectrum of biological effectiveness such as antimicrobial³⁻⁴, calcium channel blockers⁵, antitubercular⁶, anticancer⁶, antibacterial⁷, antiinflammatory⁸ and many classes of chemotherapeutic agents containing pyrimidine nucleus are in clinical uses. Apart from these, chalcones have been reported to possess various biological activities⁹⁻¹³. Extensive work on synthesis of chalcones has been done by various routes¹⁴⁻¹⁶. Quinoline derivatives are also drugs of therapeutic importance showing wide spectrum of biological activities. Some 4-substituted quinoline derivatives have been found to possess enhanced antibacterial activity¹⁷⁻²⁰. Numerous processes for the preparation of chloroquinoline derivatives were reported in literature²¹⁻²². If pyrimidine and quinoline moieties clubbed into one molecule, the resultant molecule may enhance the pharmaceutical activity up to some extent. Hence, it was thought interesting to explore the study of such molecules. Thus the present paper describes the synthesis of *N*4-[4,6-diaryl substituted-2-pyrimidinyl]-7-chloro-4-quinolinamine derived from 2-amino-4,6-diaryl substituted pyrimidine derivatives and 4,7-dichloroquinoline. This work is shown in Scheme 1.

Experimental

All melting points were taken in open capillary tubes and are uncorrected. Thin layer chromatography was performed on precoated TLC plates with silica gel (Merck GF₂₅₄) and detection was done by UV lamp (254 nm). The IR spectra were obtained on a Perkin-Elmer BX series FTIR-5000 spectrophotometer using KBr pellets. The ¹H NMR spectra in DMSO-*d*₆ or CDCl₃ were recorded on Varian Gemini 400 MHz spectrometer and chemical shift were reported as parts per million (δ ppm) down field using TMS as internal standard.

Where

(a) $R_2=R_4=\text{Cl}$; $R'_4=R_5=\text{F}$; $R'_3=\text{H}$

(b) $R_2=R_5=R'_3=\text{H}$; $R_4=\text{OCH}_3$; $R'_4=\text{F}$

(c) $R_2=R_5=R'_3=\text{H}$; $R_4=\text{CH}_3$; $R'_4=\text{F}$

(d) $R_2=R_5=R'_4=\text{H}$; $R_4=\text{Cl}$; $R'_3=\text{Br}$

(e) $R_2=R_5=R'_4=\text{H}$; $R_4=\text{CH}_3$; $R'_3=\text{Br}$

(f) $R_2=R_5=R'_4=\text{H}$; $R_4=\text{OCH}_3$; $R'_3=\text{Br}$

(g) $R_2=R_5=R'_4=\text{H}$; $R_4=\text{Cl}$; $R'_3=\text{NO}_2$

(h) $R_2=R_5=R'_4=\text{H}$; $R_4=\text{OCH}_3$; $R'_3=\text{NO}_2$

Scheme 1

Preparation of 2-amino-4,6-diaryl substituted pyrimidine (2a-h)

A mixture of substituted chalcone **1a-h** (0.01 mol) and guanidine nitrate (0.01 mol) was dissolved in ethanol (30 mL). Aqueous sodium hydroxide (40%, 1 mL) was added and the reaction mixture was refluxed. Further installments of sodium hydroxide (4x1 mL) were added during two hours to the refluxing solution. Refluxing was continued (10-12 h) and the completion of the reaction was monitored by TLC. The resultant mixture was cooled at room temperature, diluted with water (3 x 100 mL) and neutralized with cold dilute HCl (10%). The product thus separated was filtered out, washed with water dried and crystallized from ethanol. Following the same procedure all the compounds of this series were prepared. Their characterization data are recorded in Table 1.

Table 1. Characterization data of compounds (**2a-h**).

Compd.	Mol formula (Mol.wt.)	M.P. °C	Yield %	Elemental analysis					
				%C		%H		%N	
				Found	Calcd.	Found	Calcd.	Found	Calcd.
2a	C ₁₆ H ₉ N ₃ Cl ₂ F ₂ (352.16)	153	70	54.50	54.57	2.51	2.58	11.87	11.93
2b	C ₁₇ H ₁₄ ON ₃ F(295.31)	149	68	69.10	69.14	4.69	4.78	14.16	14.23
2c	C ₁₇ H ₁₄ N ₃ F(279.31)	139	65	73.02	73.10	4.95	5.05	14.98	15.04
2d	C ₁₆ H ₁₁ N ₃ ClBr(360.63)	168	69	53.20	53.29	3.01	3.07	11.60	11.65
2e	C ₁₇ H ₁₄ N ₃ Br(340.21)	159	61	59.97	60.02	4.09	4.15	12.26	12.35
2f	C ₁₇ H ₁₄ ON ₃ Br(356.21)	171	66	57.27	57.32	3.89	3.96	11.75	11.80
2g	C ₁₆ H ₁₁ O ₂ N ₄ Cl(326.7)	191	60	58.78	58.82	3.30	3.39	17.10	17.15
2h	C ₁₇ H ₁₄ O ₃ N ₄ (322.31)	161	64	63.26	63.35	4.25	4.38	17.29	17.38

4-(2,4-Dichloro-5-fluorophenyl)-6-(4-fluorophenyl)-2-pyrimidinamine (2a)

IR [ν , cm⁻¹, KBr]: 3420 (-NH₂), 1257 (C-N), 1109 (C-F), 820 (C-Cl). ¹H NMR [400MHz, δ , ppm, CDCl₃]: 5.39 (2H,s,NH₂), 6.95-7.86 (7H,m,Ar-H).

4-(4-Methoxyphenyl)-6-(4-fluorophenyl)-2-pyrimidinamine (2b)

IR [ν , cm⁻¹, KBr]: 3433 (-NH₂), 1291 (C-N), 2826 (OCH₃), 1182 (C-F). ¹H NMR [400MHz, δ , ppm, CDCl₃]: 5.43 (2H, s, NH₂), 3.75 (3H, s, -OCH₃), 6.80-7.98 (9H, m, Ar-H).

4-(4-Methylphenyl)-6-(4-fluorophenyl)-2-pyrimidinamine (2c)

IR [ν , cm⁻¹, KBr]: 3449 (-NH₂), 1340 (C-N), 2919 (CH₃), 1161 (C-F). ¹H NMR [400MHz, δ , ppm, CDCl₃]: 5.35 (2H,s,NH₂), 2.39 (3H,s,-CH₃), 6.94-7.81 (9H,m,Ar-H)

4-(4-Chlorophenyl)-6-(3-bromophenyl)-2-pyrimidinamine (2d)

IR [ν , cm⁻¹, KBr]: 3460 (-NH₂), 1311 (C-N), 1019 (C-Br), 803 (C-Cl). ¹H NMR [400MHz, δ , ppm, CDCl₃]: 5.47 (2H,s,NH₂), 7.01-8.11 (9H,m,Ar-H).

4-(4-Methylphenyl)-6-(3-bromophenyl)-2-pyrimidinamine (2e)

IR [ν , cm⁻¹, KBr]: 3452 (-NH₂), 1296 (C-N), 2913 (CH₃), 1074 (C-Br). ¹H NMR [400MHz, δ , ppm, CDCl₃]: 5.39 (2H,s,NH₂), 2.48 (3H,s,-CH₃), 6.94-7.91 (9H,m,Ar-H).

4-(4-Methoxyphenyl)-6-(3-bromophenyl)-2-pyrimidinamine (2f)

IR [ν , cm⁻¹, KBr]: 3432 (-NH₂), 1287 (C-N), 2816 (OCH₃), 1069 (C-Br). ¹H NMR [400MHz, δ , ppm, CDCl₃]: 5.37 (2H, s, NH₂), 3.77 (3H,s,-OCH₃), 6.97-8.19 (9H,m,Ar-H).

4-(4-Chlorophenyl)-6-(3-nitrophenyl)-2-pyrimidinamine (2g)

IR [ν , cm^{-1} , KBr]: 3428 (–NH₂), 1517 (NO₂), 1277 (C–N), 783 (C–Cl). ¹H NMR [400MHz, δ , ppm, CDCl₃]: 5.48 (2H, s, NH₂), 7.18–8.39 (9H, m, Ar–H).

4-(4-Methoxyphenyl)-6-(3-nitrophenyl)-2-pyrimidinamine (2h)

IR [ν , cm^{-1} , KBr]: 3458(–NH₂), 2826(OCH₃), 1545(NO₂), 1250(C–N). ¹H NMR [400MHz, δ , ppm, CDCl₃]: 5.44(2H,s,NH₂), 3.69(3H,s,–OCH₃), 7.09–8.33(9H,m,Ar–H).

Preparation of 4,7-dichloroquinoline

It was synthesized according to the method reported in the literature²².

General procedure for the preparation of (3a–h)

To a mixture of 2-amino-4,6-diaryl substituted pyrimidine (0.01 mol) **2a–h** and 4,7-dichloroquinoline (0.01 mol) in THF, anhydrous K₂CO₃ (0.11 mol) were added. The reaction mixture was refluxed. TLC [Toluene-ethyl acetate-acetone; 5:3:2] showed that reaction was complete after 8 h. The reaction mixture was poured in an ice water and the precipitate was filtered, washed with water, dried and recrystallized from ethanol. Their characterization data are recorded in Table 2.

Table 2. Characterization data of compounds (**3a–h**).

Compd.	Mol formula (Mol.wt.)	M.P. °C	Yield %	Elemental analysis					
				%C		%H		%N	
				Found	Calcd.	Found	Calcd.	Found	Calcd.
3a	C ₂₅ H ₁₃ N ₄ Cl ₃ F ₂ (513.75)	190	89	58.39	58.45	2.48	2.55	10.85	10.91
3b	C ₂₆ H ₁₈ ON ₄ ClF(456.89)	180	86	68.28	68.35	3.91	3.97	12.20	12.26
3c	C ₂₆ H ₁₈ N ₄ ClF(440.89)	179	90	70.78	70.83	4.07	4.11	12.64	12.71
3d	C ₂₅ H ₁₅ N ₄ Cl ₂ Br(522.22)	177	85	57.43	57.50	2.85	2.90	10.68	10.73
3e	C ₂₆ H ₁₈ N ₄ ClBr(501.80)	181	82	62.17	62.23	3.56	3.62	11.10	11.17
3f	C ₂₆ H ₁₈ ON ₄ ClBr(517.80)	178	87	60.26	60.31	3.43	3.50	10.78	10.82
3g	C ₂₅ H ₁₅ O ₂ N ₅ Cl ₂ (488.32)	186	80	61.40	61.49	3.07	3.10	14.29	14.34
3h	C ₂₆ H ₁₈ O ₃ N ₅ Cl(483.90)	173	81	64.48	64.53	3.71	3.75	14.41	14.47

N4-[4-(2,4-Dichloro-5-fluorophenyl)-6-(4-fluorophenyl)-2-pyrimidinyl]-7-chloro-4-quinolinamine (3a)

IR [ν , cm^{-1} , KBr]: 3365 (N–H), 1355 (C–N), 1116 (C–F), 820 (C–Cl). ¹H NMR [400 MHz, δ , ppm, DMSO-*d*₆]: 6.90 (1H,s,–NH), 6.99–8.61 (12H,m,Ar–H).

N4-[4-(4-Methoxyphenyl)-6-(4-fluorophenyl)-2-pyrimidinyl]-7-chloro-4-quinolinamine (3b)

IR [ν , cm^{-1} , KBr]: 3347 (N–H), 2836 (OCH₃), 1345 (C–N), 1157 (C–F), 809 (C–Cl). ¹H NMR [400 MHz, δ , ppm, DMSO-*d*₆]: 6.85 (1H,s,–NH), 3.67 (3H,S,–OCH₃), 7.08–8.59 (14H,m,Ar–H).

N4-[4-(4-Methylphenyl)-6-(4-fluorophenyl)-2-pyrimidinyl]-7-chloro-4-quinolinamine (3c)

IR [ν , cm^{-1} , KBr]: 3326 (N–H), 2930 (CH₃), 1348 (C–N), 1159 (C–F), 812 (C–Cl). ¹H NMR [400 MHz, δ , ppm, DMSO-*d*₆]: 6.86 (1H,s,–NH), 2.38 (3H,S,–CH₃), 7.00–8.61 (14H,m,Ar–H).

N4-[4-(4-Chlorophenyl)-6-(3-bromophenyl)-2-pyrimidinyl]-7-chloro-4-quinolinamine (3d)

IR [ν , cm^{-1} , KBr]: 3367 (N-H), 1340 (C-N), 1024 (C-Br), 814 (C-Cl). ^1H NMR [400 MHz, δ , ppm, DMSO- d_6]: 6.88 (1H, s, -NH), 7.03-8.58 (14H, m, Ar-H).

N4-[4-(4-Methylphenyl)-6-(3-bromophenyl)-2-pyrimidinyl]-7-chloro-4-quinolinamine (3e)

IR [ν , cm^{-1} , KBr]: 3392 (N-H), 2937 (CH_3), 1326 (C-N), 1071 (C-Br), 811 (C-Cl). ^1H NMR [400 MHz, δ , ppm, DMSO- d_6]: 6.89 (1H, s, -NH), 2.36 (3H, s, - CH_3), 7.01-8.62 (14H, m, Ar-H).

N4-[4-(4-Methoxyphenyl)-6-(3-bromophenyl)-2-pyrimidinyl]-7-chloro-4-quinolinamine (3f)

IR [ν , cm^{-1} , KBr]: 3359 (N-H), 2973 (CH_3), 2812 (OCH_3), 1319 (C-N), 1057 (C-Br), 799 (C-Cl). ^1H NMR [400 MHz, δ , ppm, DMSO- d_6]: 6.90 (1H, s, -NH), 3.71 (3H, s, - OCH_3), 7.00-8.61 (14H, m, Ar-H).

N4-[4-(4-Chlorophenyl)-6-(3-nitrophenyl)-2-pyrimidinyl]-7-chloro-4-quinolinamine (3g)

IR [ν , cm^{-1} , KBr]: 3344 (N-H), 2961 (CH_3), 1515 (NO_2), 1396 (C-N), 785 (C-Cl). ^1H NMR [400 MHz, δ , ppm, DMSO- d_6]: 6.86 (1H, s, -NH), 7.05-8.69 (14H, m, Ar-H).

N4-[4-(4-Methoxyphenyl)-6-(3-nitrophenyl)-2-pyrimidinyl]-7-chloro-4-quinolinamine (3h)

IR [ν , cm^{-1} , KBr]: 3349 (N-H), 2944 (CH_3), 2845 (OCH_3), 1538 (NO_2), 1379 (C-N), 795 (C-Cl). ^1H NMR [400 MHz, δ , ppm, DMSO- d_6]: 6.89 (1H, s, -NH), 3.72 (3H, s, - OCH_3), 7.09-8.66 (14H, m, Ar-H).

Results and Discussion

Chalcones **1a-h** were prepared by the condensation of substituted acetophenone with substituted aldehydes and were cyclized with guanidine nitrate to give 4-6-diaryl substituted-2-pyrimidinamine **2a-h** and further reacted with 4-7-dichloroquinoline to get corresponding compound **3a-h**.

Formation of compounds **2a-h** and **3a-h** was confirmed on the basis of elemental analysis and spectroscopic investigation. IR spectrum of **2a-h** revealed characteristic bands at $3460\text{--}3300\text{cm}^{-1}$ (-NH $_2$), $1340\text{--}1250\text{cm}^{-1}$ (C-N) and confirmatory by ^1H NMR signal at 5.4 (2H, s, -NH $_2$). Further, IR spectroscopic investigation of **3a-h** revealed bands at $3375\text{--}3329\text{cm}^{-1}$ (N-H str.) and 1608 (N-H def.) while additional peak appears due to substitution in the aromatic ring showing absorption band at ~ 2953 (-CH $_3$), ~ 2810 (-OCH $_3$), ~ 1528 (-NO $_2$), ~ 1100 (C-F), ~ 1050 (C-Br), ~ 810 (C-Cl). ^1H NMR signal at 6.8 (1H, s, -NH) and additional signal appears due to substitution in aromatic ring showing common signals at 2.3 (3H, s, -CH $_3$), δ 3.7 (3H, s, -OCH $_3$) and m 6.9-8.0 (aromatic proton) which confirmed its structure.

The antimicrobial activity of **1a-h**, **2a-h** and **3a-h** was carried out against some strain bacteria. The results show that the synthesized compounds were toxic against the bacteria. The comparison of the antibacterial and antifungal activity of these compounds with standard drugs shows that the presence of methoxy and halogen (-Cl, -Br, -F) groups in the phenyl ring increases the activity.

Biological Screening

Antibacterial activities

Antibacterial activities of all the compounds were studied against gram-positive bacteria [*Staphylococcus aureus* (MTCC96), *Streptococcus pyogenes* (MTCC442)] and gram-negative bacteria [*Escherichia coli* (MTCC443), *Pseudomonas aeruginosa* (MTCC424)] at a concentration of 100 µg/mL by agar cup plate method. DMF system was used as control in this method. Under similar condition using chloramphenicol, ciprofloxacin and norfloxacin as a standard for comparison control experiment was carried out. The area of inhibition of zone measured in mm.

An examination of the data reveals that all compounds showed antibacterial activity. The compounds **3a**, **3b**, **3d**, **3f** were highly active against all four organisms employed. The compounds **1a**, **1b**, **1d**, **1f**, **2a**, **2b**, **2d**, **2f**, **3a**, **3b**, **3d** and **3f** were highly active against *Escherichia coli* (MTCC443) and *Staphylococcus aureus* (MTCC96). Results are presented in Table 3.

Antifungal activities

The compounds **1a-h**, **2a-h** and **3a-h** were also screened for their antifungal activity against *Candida albicans* (MTCC227), *Aspergillus niger* (MTCC282) and *Aspergillus clavatus* (MTCC1323) at 100 µg/mL concentration using agar cup plate technique. The antifungal activity was compared with the known standard drugs greseofulvin, nystatin and the results are presented in Table 3.

Table 3. Antimicrobial activity (100 µg/mL) of compounds **2a-h** and **3a-h**.

Compound.	Antibacterial activity				Antifungal activity		
	<i>S.a</i> ^a	<i>S.p</i> ^b	<i>E.c</i> ^c	<i>P.a</i> ^d	<i>A.n</i> ^e	<i>A.c</i> ^f	<i>C.a</i> ^g
2a	18	15	19	16	21	20	17
2b	16	15	18	14	20	19	17
2c	11	10	13	10	19	18	19
2d	17	16	20	15	20	21	19
2e	10	11	14	11	19	18	18
2f	17	17	20	18	22	20	20
2g	10	10	12	11	18	16	17
2h	11	11	13	10	18	19	18
3a	19	19	21	17	22	23	19
3b	17	18	20	18	23	21	20
3c	15	14	15	14	20	20	19
3d	18	17	21	17	23	23	20
3e	15	14	18	15	21	19	19
3f	18	19	20	17	23	22	21
3g	16	15	18	17	20	21	18
3h	15	16	19	16	21	20	19
Chloramphenicol	20	20	23	19	-	-	-
Ciprofloxacin	22	21	28	26	-	-	-
Norfloxacin	26	21	27	23	-	-	-
Greseofulvin	-	-	-	-	25	25	22
Nystatin	-	-	-	-	29	28	55

S.a^a - *Staphylococcus Aureus* (MTCC96), *S.p*^b - *Streptococcus Pyogenes* (MTCC442), *E.c*^c - *Escherichia coli* (MTCC443), *P.a*^d - *Pseudomonas aeruginosa* (MTCC424), *A.n*^e - *Aspergillus Niger* (MTCC282), *A.c*^f - *Aspergillus Clavatus* (MTCC1323), *C.a*^g - *Candida albicans* (MTCC227).

Conclusions

The clubbing of 2-amino-4,6-diaryl substituted pyrimidine derivatives and 4,7-dichloroquinoline has been done successfully into one molecule. Both the moieties have important applications in medicinal use; the synthesized compounds may act as good biological compounds.

Acknowledgements

Authors are thankful to the Principal, Sir P.T. Sarvajanik College of Science, Surat for providing research facilities. Authors are also thankful to Swadev Chemicals, Vapi and Navin Fluorine International Ltd., Surat for providing chemicals. Thanks are also due to Centre of excellence, Vapi for providing spectral data and elemental analysis.

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