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Original Article

Synthesis of novel 2,4-*bis*(substituted phenoxy)-6-(phenylthio) pyrimidine analogs and their antimicrobial activities

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ABSTRACT

Background/aims: Pyrimidines have a long and distinguished history extending from the days of their discovery as important constituents of nucleic acids to their current use in medicinal chemistry. As a part of project devoted to the development of pyrimidine analogs as antimicrobial agents we have focused our attention on synthesis of C_5/C_6 substituted pyrimidine derivatives, specifically C_6 substituted pyrimidine analogs which have emerged as potent molecule in recent years.

Methods: 2,4-*Bis*(substituted phenoxy)-6-(phenylthio)pyrimidines were prepared in five steps starting from barbituric acid. Initial reaction of barbituric acid **(1)** with $POCl_3$ in presence of *N*,*N*-dimethylaniline under reflux furnished 2,4,6-trichloropyrimidine **(2)**, which on hydrolysis with aq. NaOH under reflux yielded 6-chlorouracil **(3)**. 6-Chlorourail on treatment with thiophenol in dry pyridine generated 6-phenylthiouracil **(4)**, chlorination of **4** using excess $POCl_3$ under reflux afforded the key synthon 2,4-dichloro-6-(phenylthio) pyrimidine **(5)**. Aromatic nucleophillic substitution reaction of **5** with oxygen nucleophiles like sodium phenoxides provided the desired targeted compounds **6a**–**g** in 62–86% yield. Structural assignments of the synthesized compounds were based on their IR, ^{1}H NMR, mass and analytical data. The antimicrobial evaluation of newly synthesized compounds was carried out by cup–plate method.

Results: The investigation of antimicrobial screening reveals that the compounds **5**, **6b**, **6c** and **6f** showed good activity against fungal strains comparable to the standard drug Flucanazole. Remaining compounds exhibited moderate activity against bacterial and fungal strains compared to standard drug.

Conclusion: We have developed a facile methodology which avoids the use of moisture sensitive reagents like organolithiums, diphenyl disulphide, etc. The C_6 substituted pyrimidine analogs can be considered for further studies as potent antifungal agents.

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1. Introduction

Pyrimidines have a long and distinguished history extending from the days of their discovery as important constituents of nucleic acids. The presence of pyrimidine base in thymine, cytosine and uracil which are the essential building blocks of nucleic acids, DNA and RNA is one possible reason for their activity. Pyrimidine being an integral part of DNA and RNA, imparts to diverse pharmacological properties. The C_6 substituted pyrimidine analogs exhibited selective anti-tumor,[1] antiviral[2] and antibacterial activity[3–6] suggesting the importance of this class of compound as broad spectrum drugs. 6-Phenylselenyl acyclic pyrimidines were found to have potent anti-human-immunodeficiency-virus-type-1 (HIV-1) activity.[7,8] In addition, pyrimidine derivatives have been reported to possess analgesic,[9] anti-inflammatory[10] and acid pump antagonist[11] properties. Thus, the excellent biological activities exhibited by C_6 substituted pyrimidine derivatives and in continuation of our earlier research on pyrimidines[12,13] encouraged us to develop a novel methodology in order to generate a large number of various 2,4,6-trisubstituted pyrimidine analogs for biological evaluation. Herein, we report a facile methodology for the synthesis and antibacterial activities of various 2,4-*bis*(phenoxy)-6-(phenylthio)pyrimidines starting from barbituric acid.

2. Materials and methods

Barbituric acid, thiophenol, $POCl_3$ and substituted phenols were purchased from SISCO Research Laboratories Pvt. Ltd. Mumbai (India). All the solvents used were of analytical grade and were purified according to standard procedures. Melting points were recorded by using Thomas-Hoover melting point apparatus and were uncorrected. IR spectra in KBr disc were recorded on Perkin-Elmer-Spectrum-one FT IR spectrophotometer (ν_{max} in cm^{-1}) and ^1H NMR in DMSO-d_6 on amx 400, 400 MHz spectrophotometer using TMS as internal standard (chemical shift in δ or ppm). Mass spectra were recorded on a JEOL SX 102 mass spectrometer using argon/xenon (6 kv, 10 mA) as the FAB gas. Purity of the compounds was checked by TLC using silica gel 'G' plates obtained from Whatman Inc, and a fluorescent indicator.

3. Results and discussion

We have reported earlier the synthesis of 2,4-*bis*(benzyloxy)-6-(phenylthio)pyrimidine starting from barbituric acid.[14] This reported method requires expensive reagents like organolithiums, diphenyl disulphide, etc. The key reaction in this method is the metal halogen exchange reaction under inert atmosphere followed by addition of electrophile at very low temperature (−80 °C). Hence, this method is not suitable to synthesize a series of 2,4-*bis*(substituted phenoxy)-6-(phenylthio)pyrimidines in normal laboratory conditions. The present methodology involves the synthesis of 2,4-*bis*(-substituted phenoxy)-6-(phenylthio)pyrimidines **6(a–g)** in five steps starting from barbituric acid **(1)** (Scheme 1). Reaction of compound **1** with $POCl_3$ in presence of a catalytic amount of *N,N*-dimethylaniline at refluxing temperature for 3 h gave 2,4,6-trichloropyrimidine **(2)** in 85% yield, which was subsequently hydrolyzed with aqueous NaOH at refluxing temperature for 1 h furnished 6-chlorouracil **(3)** in 82% yield, m.p 292–296 °C (decomp). Reaction of **3** with thiophenol in pyridine under reflux for 24 h furnished the desired 6-phenylthiouracil **(4)** in 65% yield, m.p 239–240 °C. ^1H NMR spectrum of compound **4** showed singlets at δ 11.4 & δ 7.9 corresponds to two NH protons of the pymimidine ring present at C_1 and C_3, multiplet at δ 7.0–7.4 for 5H of SC_6H_5 and a characteristic absorption of C_5 proton as a singlet of pyrimidine ring at δ 5.6 confirms the formation of compound **4**. Chlorination of compound **4** with $POCl_3$ yielded 2,4-dichloro-6-(phenylthio)pyrimidine **(5)** in 72% yield, m.p 65–67 °C. Formation of this compound **5** was confirmed by the presence of C–Cl stretching absorptions at 749 and 705 cm^{-1} in its IR spectrum. Further confirmation of compound **5** is by the presence of aromatic protons signal as a multiplet from δ 7.4–7.7, characteristic absorption of C_5 proton as a singlet of pyrimidine ring at δ 6.6 and absence of NH proton signal in its ^1H NMR spectrum. Final confirmation of compound **5** is by the appearance of molecular ion peak at $m/z = 257$ (M^+, 100%) in its mass spectrum.

Reaction of compound **5** with oxygen nucleophiles, such as sodium phenoxides in dry toluene under inert N_2 atmosphere for 48 h at room temperature furnished the desired targeted compounds **6(a–g)** in 62–86% yield. Compound **6a** was obtained in 86% yield m.p 130–132 °C. In support of the formation of the product by ^1H NMR signal at δ 7.0–7.5 as a multiplet corresponds to the 15 aromatic protons and appearance of a singlet at 5.9 ppm for C_5 proton of pyrimidine. Further the mass spectrum of compound **6a** shows molecular ion peak at $m/z = 374$ (M^+, 100%). Physical and spectral data of all the synthesized compounds are tabulated in Table 1.

4. Experimental

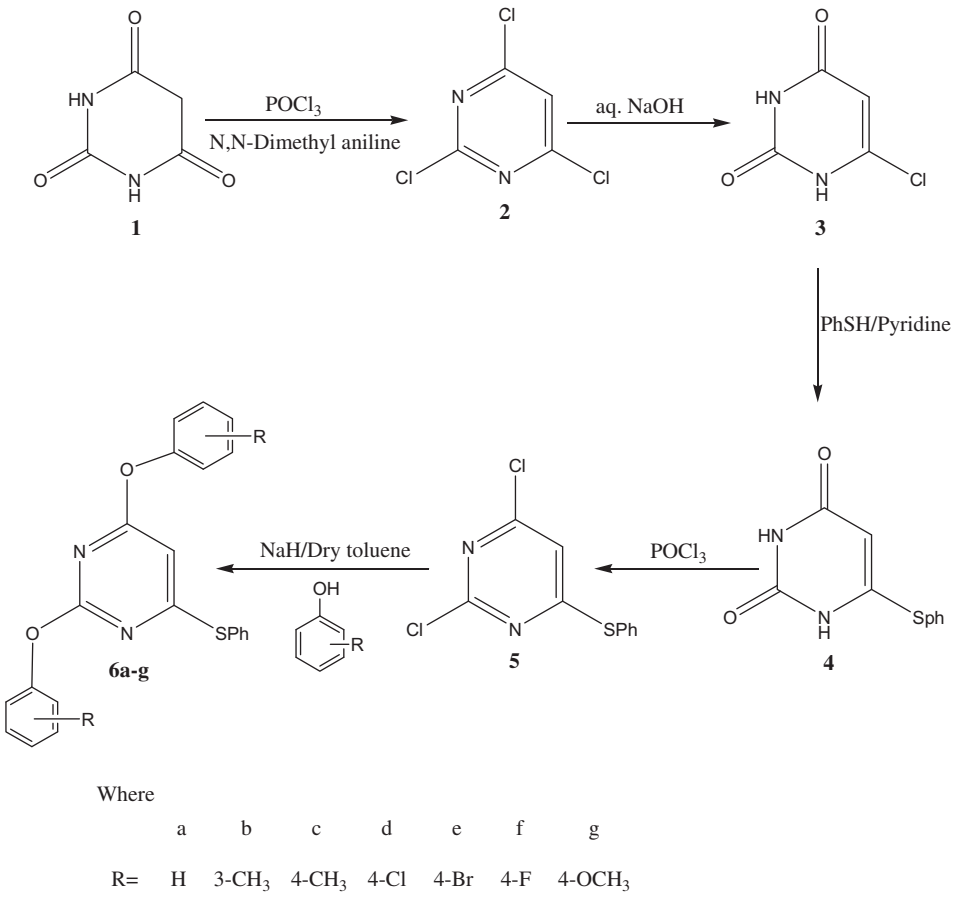
2,4,6-Trichloropyrimidine **(2)** and 6-chlorouracil **(3)** were prepared by adopting literature procedure.[15]

4.1. *Synthesis of 6-phenylthiouracil (4)*

A mixture of 6-chlorouracil **(3)** (2.92 g, 0.02 mol) and thiophenol (2.2 g, 0.02 mol) in dry pyridine (20 ml) was heated under reflux with stirring for 3 h and allowed to cool to room temperature. The mixture was then poured into ice water (500 ml) and the separated solid product was collected by filtration, washed with water, dried and crystallized from ethanol to afford compound **4**.

4.1.1. *Compound* **(4)**

Yield: 65%. M.P: 239–240 °C. ^1H NMR (DMSO-d_6): δ 11.4 (s, 1H, NH), 7.9 (s, 1H, NH), 7.0–7.4 (m, 5H, SC_6H_5), 5.6 (s, 1H, C_5H of pyrimidine). Anal Cacld for $C_{10}H_8N_2SO_2$: C, 54.54; H, 3.63; N, 12.72. Found: C, 54.52; H, 3.62; N, 12.70.



Scheme 1 – Synthetic scheme for the preparation of 2,4-bis(substituted phenoxy)-6-(phenylthio)pyrimidine analogs.

4.2. *Synthesis of 2,4-dichloro-6-(phenylthio)pyrimidine (5)*

A mixture of 6-phenylthiouracil **(4)** (3 g, 0.0125 mol) and $POCl_3$ (12.2 ml, 0.125 mol) was refluxed for 4–5 h. Excess of $POCl_3$ was removed under reduced pressure and the mixture was treated with ice/water. The separated solid was extracted with ether (3 × 50 ml) and washed with 5% aq. sodium bicarbonate solution (1 × 25 ml). Ether layer was collected and dried over

Table 1 – Physical and spectral data of synthesized compounds (2–5) and 6a–g.

Products	R	Mol. formula	m.p. (°C)	Yield (%)	Spectral data IR (cm^{-1}), ^1H NMR (δ), mass (m/z)
2	–	$C_4HN_2Cl_3$	28–30	85	–
3	–	$C_4H_3N_2O_2Cl$	296–300	81	–
4	–	$C_{10}H_8N_2SO_2$	239–240	65	^1H NMR (DMSO-d_6): δ 11.4 (s, 1H, NH), 7.9 (s, 1H, NH), 7.0–7.4 (m, 5H, SC_6H_5), 5.6 (s, 1H, C_5H of pyrimidine)
5	–	$C_{10}H_6N_2SCl_2$	48–50	72	IR (cm^{-1}): 749 & 705 (C–Cl). ^1H NMR (DMSO-d_6): δ 7.2–7.6 (m, 5H, SC_6H_5), 5.9 (s, 1H, C_5H of pyrimidine). Mass: $m/z = 257$ (M^+, 100%)
6a	H	$C_{22}H_{16}N_2O_2S$	130–132	86	^1HNMR (DMSO-d_6): δ 7.0–7.5 (m, 15H, ArH), 5.9 (s, 1H, C_5H of pyrimidine). Mass: $m/z = 374$ (M^+, 100%)
6b	4-CH_3	$C_{24}H_{20}O_2N_2S$	79–80	70	^1HNMR (DMSO-d_6): δ 6.8–7.5 (m, 13H, ArH), 5.9 (s, 1H, C_5H of pyrimidine), 2.3 (s, 6H, CH_3)
6c	3-CH_3	$C_{24}H_{20}O_2N_2S$	80–82	63	^1HNMR (DMSO-*d6*): δ 6.9–7.5 (m, 13H, ArH), 6.4 (s, 1H, C_5H of pyrimidine), 2.3 (s, 6H, CH_3)
6d	4-Cl	$C_{24}H_{14}O_2N_2SCl_2$	112–114	68	^1HNMR (DMSO-d_6): δ 7.1–7.4 (m, 13H, ArH), 6.5 (s, 1H, C_5H of pyrimidine)
6e	4-Br	$C_{22}H_{14}O_2N_2SCBr_2$	92–94	65	^1HNMR (DMSO-d_6): δ 7.2–7.6 (m, 13H, ArH), 7.09 (s, 1H, C_5H of pyrimidine). Mass: $m/z = 530$ (M^+, 100%)
6f	4-F	$C_{22}H_{14}O_2N_2SCF_2$	124–126	62	^1HNMR (DMSO-d_6): δ 7.1–7.5 (m, 13H, ArH), 6.0 (s, 1H, C_5H of pyrimidine). Mass: $m/z = 408$ (M^+, 100%)
6g	4-OCH_3	$C_{24}H_{20}O_4N_2S$	88–90	74	^1HNMR (DMSO-d_6): δ 7.2–7.5 (m, 13H, ArH), 6.9 (s, 1H, C_5H of pyrimidine), 3.74 (s, 6H, OCH_3). Mass: $m/z = 432$ (M^+, 100%)

Table 2 – Antimicrobial activity of synthesized compounds (2–5) and 6a–g.

Compd. No	Dose (μg/ml)	Antibacterial activity			Antifungal activity		
		Zone of inhibition (mm)			Zone of inhibition (mm)		
		S. aureus	*K. pneumonia*	*P. aeruginosa*	*A. niger*	*A. flavus*	*A. terrus*
2	1000	06	06	06	06	06	06
3	1000	06	06	06	06	06	06
4	1000	14	06	12	06	06	06
5	1000	19	14	10	23	19	22
6a	1000	17	11	10	13	08	13
6b	1000	13	15	10	22	11	11
6c	1000	13	13	10	24	24	10
6d	1000	15	15	12	19	19	19
6e	1000	14	13	14	18	15	16
6f	1000	14	12	12	20	19	20
6g	1000	12	10	10	16	17	18
Gentamycine	1000	23	23	23	–	–	–
Flucanazole	1000	–	–	–	24	26	23

anhydrous sodium sulfate. Evaporation of the solvent furnished the title compound **5**.

4.2.1. *Compound* ***(5)***
Yield: 72%. M.P: 48–50 °C. IR (cm^{-1}): 749 & 705 (C–Cl). ^1H NMR (DMSO-d_6): δ 7.2–7.6 (m, 5H, SC_6H_5), 5.9 (s, 1H, C_5H of pyrimidine). Mass: m/z = 257 (M^+, 100%). Anal Cacld for $C_{10}H_6N_2SCl_2$: C, 46.91; H, 2.43; N, 10.94. Found: C, 46.45; H, 2.36; N, 10.60.

4.3. *General procedure for the preparation of 2,4-bis(substituted phenoxy)-6-phenylthio-pyrimidines (6a–g)*

To a solution of appropriate phenol (0.004 mol) in dry toluene (10 ml) was treated with 60% w/v sodium hydride (0.004 mol) in oil under an inert atmosphere. The mixture was warmed to 50–60 °C for 30 min to facilitate the formation of sodium salt. After all the sodium hydride had reacted, the suspension was cooled and a solution of 2,4-dichloro-6-(phenylthio)pyrimidine (**5**) (0.001 mol) in toluene (10 ml) was added slowly at room temperature. After stirring the reaction mixture at 75–80 °C overnight, it was allowed to cool and the mixture was treated with water (25 ml). The separated solid was extracted with ether (3 × 25 ml) and washed with 10% aq. sodium hydroxide (3 × 25 ml). Ether layer was collected, dried over anhydrous sodium sulfate and evaporation of the solvent furnished the crude compounds, which were recrystallized from spirit yielded the title compounds **6a–g** in 62–86% yield.

4.3.1. *2,4-diphenoxy-6-(phenylthio)pyrimidine* ***(6a)***
Yield: 86%. M.P: 130–132 °C. ^1H NMR (DMSO-d_6): δ 7.0–7.5 (m, 15H, ArH), 5.9 (s, 1H, C_5H of pyrimidine). Mass: molecular ion peak at m/z = 374 (M^+, 100%). Anal Cacld for $C_{22}H_{16}O_2N_2S$: C, 70.96; H, 4.30; N, 7.52. Found: C, 70.89; H, 4.28; N, 7.50.

4.3.2. *4-(phenylthio)-2,6-bis(m-tolyloxy)pyrimidine* ***(6b)***
Yield: 70%. M.P: 79–80 °C. ^1H NMR (DMSO-d_6): δ 6.8–7.5 (m, 13H, ArH), 5.9 (s, 1H, C_5H of pyrimidine), 2.3 (s, 6H, CH_3). Anal Cacld for $C_{24}H_{20}O_2N_2S$: C, 72.00; H, 5.00; N, 7.00. Found: C, 71.96; H, 4.97; N, 7.06.

4.3.3. *4-(phenylthio)-2,6-bis(p-tolyloxy)pyrimidine* ***(6c)***
Yield: 63%. M.P: 80–82 °C ^1H NMR (DMSO-d6): δ 6.9–7.5 (m, 13H, ArH), 6.4 (s, 1H, C_5H of pyrimidine), 2.3 (s, 6H, CH_3). Anal Cacld for $C_{24}H_{20}O_2N_2S$: C, 72.00; H, 5.00; N, 7.00. Found: C, 71.46; H, 4.96; N, 6.94.

4.3.4. *2,4-bis(4-chlorophenoxy)-6-(phenylthio)pyrimidine* ***(6d)***
Yield: 68%. M.P: 112–114 °C ^1H NMR (DMSO-d_6): δ 7.1–7.4 (m, 13H, ArH), 6.5 (s, 1H, C_5H of pyrimidine). Anal Cacld for $C_{24}H_{14}O_2N_2SCl_2$: C, 59.86; H, 3.17; N, 6.34. Found: C, 59.72; H, 3.16; N, 6.33.

4.3.5. *2,4-bis(4-bromophenoxy)-6-(phenylthio)pyrimidine* ***(6e)***
Yield: 65%. M.P: 92–94 °C. ^1H NMR (DMSO-d_6): δ 7.2–7.6 (m, 13H, ArH), 7.09 (s, 1H, C_5H of pyrimidine). Mass: molecular ion peak at m/z = 530 (M^+, 100%). Anal Cacld for $C_{22}H_{14}O_2N_2SCBr_2$: C, 49.83; H, 2.66; N, 5.28. Found: C, 49.79; H, 2.60; N, 5.23.

4.3.6. *2,4-bis(4-fluorophenoxy)-6-(phenylthio)pyrimidine* ***(6f)***
Yield: 62%. M.P: 124–126 °C. ^1H NMR (DMSO-d_6): δ 7.1–7.5 (m, 13H, ArH), 6.0 (s, 1H, C_5H of pyrimidine). Mass: molecular ion peak at m/z = 408 (M^+, 100%). Anal Cacld for $C_{22}H_{14}O_2N_2SCF_2$: C, 64.70; H, 3.46; N, 6.86. Found: C, 64.66; H, 3.43; N, 6.82.

4.3.7. *2,4-bis(4-methoxyphenoxy)-6-(phenylthio)pyrimidine* ***(6g)***
Yield: 74%. M.P: 88–90 °C. ^1H NMR (DMSO-d_6): δ 7.2–7.5 (m, 13H, ArH), 6.9 (s, 1H, C_5H of pyrimidine), 3.74 (s, 6H, OCH_3 of pyrimidine). Mass: molecular ion peak at m/z = 432 (M^+, 100%). Anal Cacld for $C_{24}H_{20}O_4N_2S$: C, 66.65; H, 4.66; N, 6.48. Found: C, 66.56; H, 4.62; N, 6.46.

5. Antimicrobial activity

The antimicrobial activities were performed by cup–plate method.[16] The sample was dissolved in DMF at the concentration of 1000 μg/ml. Antibacterial activity screened against 1 g positive organism (*Staphylococcus aureus*) and 2 g negative

organisms (*Klebsiella pneumonia* and *Pseudomonas aeruginosa*). Antifungal activity was carried out against (*Aspergillus flavus*, *Aspergillus terrus* and *Aspergillus niger*) under aseptic conditions. Gentamycine and fluconazole were used as standard drug for antibacterial and antifungal activities respectively. The zone of inhibition was compared with standard drug after 24 h of incubation at 25 °C for antibacterial activity and 48 h at 30 °C for antifungal activity. The antibacterial activity revealed that all the synthesized compounds exhibited moderate to good activity against all the bacterial strains used for evaluation (Table 2). The antifungal activity revealed that compound **5** exhibited good antifungal activity against *A. terrus* and *A. niger*. Compounds **6b** and **6f** exhibited good antifungal activity against *A. flavus*, *A. terrus* and *A. niger*. Compound **6c** exhibited good antifungal activity against *A. flavus* and *A. niger*. Remaining compounds exhibited moderate to good activity against all the fungal strains used for evaluation Table 2.

6. Conclusion

The present work reports the synthesis of 2,4-*bis*(substituted phenoxy)-6-(phenylthio)pyrimidines in normal laboratory conditions. We have developed a facile methodology which avoids the use of expensive reagents like organolithiums, diphenyl disulphide, etc. and addition of electrophile at very low temperature (−80 °C). The investigation of antimicrobial screening reveals that the compounds **5**, **6b**, **6c** and **6f** showed good activity against fungal strains comparable to the standard drug Flucanazole. Remaining compounds exhibited moderate activity against bacterial and fungal strains compared to standard drug.

Conflicts of interest

All authors have none to declare.

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