7.1. INTRODUCTION

The replacement of two CH units in benzene by nitrogen atoms to give pyrimidine (89) naturally results in reduced symmetry, so that all bonds are no longer of the same length and all bond angles no longer equal.\(^1\) Pyrimidine consists of a heterocyclic carbon-nitrogen and as such possesses strongly basic properties.\(^2\)

\[
\begin{array}{c}
\text{89}
\end{array}
\]

Pyrimidine does retain symmetry about the 2,5-axis so three differing pairs of equal bond lengths and three differing pairs of equal bond angles result. In addition, the nitrogen constitutes havens for \(\pi\)-electrons, which are equally distributed about the ring in benzene. There is considerable depletion of electron density at the 2- and 4/6-positions, a slight depletion at the 5-position and a greatly enhanced density at the nitrogen atoms. The depletion \(\alpha\) or \(\gamma\) to the ring-nitrogens are naturally more marked in pyrimidine. Indeed, on this depends the unique character of pyrimidine chemistry. Pyrimidine is much weaker base (\(pK_a = 1.31\)) than pyridine because the second nitrogen shares the available \(\pi\)-electrons with the first and the system. Formation of zwitterionic species seldom occurs and they react with mineral acids to form stable salts and its hydrochloride combines with the chlorides of gold and platinum to form relatively insoluble complex salts. Due to the electron-withdrawing effects of doubly-bound ring nitrogen atoms nucleophilic attack will take place C-2, C-4 and C-6 positions whereas electrophilic attack is confined to C-5 or ring nitrogen atoms. Pyrimidine oxidizes to give their N-oxides and the nuclear reduction may be done by hydrogenation over palladium or platinum catalysts, especially in acidic media.\(^1\)

7.2. APPLICATIONS

Pyrimidine derivatives comprise a diverse and interesting group of drugs\(^3\) and in general are extremely important for their biological activities. For example, some are antiviral agents,\(^4\) others are selective CCk1 receptor antagonists,\(^5\) platelet aggregation inhibitors\(^6\) and potential anti-RV inhibitors.\(^7\)

Considerable evidences have been accumulated to demonstrate the efficacy of pyrimidine derivatives including anticancer, anti-HIV,\(^8\) antibacterial,\(^9\) antifungal,\(^10\)
antitumor, anti-inflammatory, antileishmanial, analgesic, antimalarial, antihistaminic (H₁) antiparasitic and CNS depressant activity.

Various pyrimidine derivatives have been described with a wide range of pharmacological activities which are valuable for medicinal applications. For instance Gershon et al have prepared polychlorinated pyrimidines and screened for their anticancer activity. Brogden et al synthesized trimethoprim or 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine, which is active against gram-positive, gram-negative aerobic bacteria and also display different bactericidal effects against Escherichia coli and Mycobacteria. Recently Salmi et al studied the effect of brodioprim or 2,4-diamino-5-(4-methylthio-3,5-dimethoxybenzyl)pyrimidine for the treatment of bacterial respiratory tract infection. 2-substituted 5-(1,2-diethyl)-4,6-dichloropyrimidine derivatives 90a-b were active against the undesirable bacteria of both foot and the axilla, could be proposed for their deodorant properties. Compounds 90a-b also used for chemotherapy of cryptococcus in HIV-infected persons and as new antifungal agents for the inhibition of the growth of the yeasts.
Falcao et al\textsuperscript{25} have synthesized a series of phthalimidopyrimidines 91a-c, which showed quite satisfactory anti-inflammatory activity without any toxic effects and also studied cytotoxical evaluations of these compounds using neoplastic cells (NCI-H\textsubscript{292} and Hep-2) which presented 41\% of growth inhibition of neoplastic cells NCI-H\textsubscript{292}.\textsuperscript{26} Pyrimidine ring in an organic molecule shows prominent activity as anti-malarial,\textsuperscript{27} antimicrobial,\textsuperscript{28} anti-infectious agent\textsuperscript{29} analgesic, ulcerogenic index\textsuperscript{30} and pyridoxol antagonist disease.\textsuperscript{31}

![Chemical structure of compound 92](image)

Huang et al\textsuperscript{32} designed and synthesized new pyrimidine antitumor agent 92 by combining sulfadiazine and anticancer agent CBL in one molecule and investigated for their acute toxicity and antitumor activity in mice, which demonstrated high antitumor activity and low toxicity with a TI of 47.55 against murine S-180 sarcoma cells and is more potent and safer than its mother compound CBL.

Linking of the adamantyl moiety to pyrimidine rings leads to compound 93 of amphiphilic character. The crystallographic analysis revealed the high affinity of non-polar solvent to aliphatic part of the molecule, while the heterocyclic fragment exhibited significant polar properties. The introduction of such molecular architecture was very promising for medicinal applications, which exhibited potent antimicrobial activity, pronounced cytotoxicity against different human cancer cell lines, particularly against monocytic leukemia (U-937) and inhibitory activity against HIV-1(III\textsubscript{B}) and HIV-2(ROD)-induced cytopathicity in CEM cell cultures. From these observation indicates that the most promising compounds might be derivatives of adamantylaminopyrimidines with diverse 4-s- polar substituents as pharmacophoric groups.\textsuperscript{33}
2-[(3-pyridinmethyl)thio]pyrimidine 94 exhibit superior bronchosecretolytic property that change the viscoelasticity of the respiratory mucus resulting in an improvement of the clinical status and represent a new structural class of bronchosecretolytics drugs that are different from known structures of bronchosecretolytics and mucolytic agents.34

The pyrimidine ring system is present in a number of biologically active organic compounds which includes antitumor,35,36 antibacterial,37 anticonvulant,38 antipyretic,39 antiproliferative,40 antigenotoxic,41 herbicidal,42 anticytokinin activity.43 Besides pyrimidines were considered as inhibitors of Pneumocystis carinii (pc), Toxoplasma gondii (tg) of tumor cell lines in culture44 which is mainly due to inhibition of DHFR.45,46

Recently Chandra et al47 synthesized some N and O substituted pyrimidines 95a-c and screened for invitro antileishmanial activity. The pyrimidines attached to a suitable hydrophobic terpene handle form a unique pharmacophore and show antimicrobial and antileishmanial profile. The terpene plays a good hydrophobic handle and activity profile is displayed by the pyrimidine ring. The oxygen substituted pyrimidine 96a and 96b showed 99% inhibition at 5 µg ml⁻¹ concentration which might be acting through immunostimulation.48
Pyrimidine derivative 96a-b having TZD moiety were identified as novel potent glucose and lipid lowering agents which exhibit more potent antidiabetic activity than that of the reference compounds, pioglitazone and rosiglitazone, respectively.

Dicationic 2,4-diarylpyrimidines 97a-b were found to be potential new anti-PCP agents. These dicationic molecules which have the amidine unit incorporated in a five and six-membered ring system strongly bind to AT-rich DNA and inhibit DNA-related enzymes such as topoisomerase II, thus showing potent anti-PCP activity.

The pyrimidine scaffold has received extensive attention in medicinal chemistry, especially after the commercialization of the pyrimidine drugs. Most drugs in pyrimidine series fall into four categories: the barbiturates, the sulfonamides, the antimicrobials and the antitumor agents. Sulfadiazine 98 is an antibiotic used for acute urinary-tracttrimethamine infections and has chief advantage over earlier heterocyclic analogues such as sulfapyridine and sulfathiazole, due to its solubility in water and its bioacetylated product. This minimizes the risk of kidney blockage by precipitation and eliminates the need for an excessive water intake during therapy, even for patients with impaired renal function.
Pyrimethamine (Daraprim) \text{99} inhibits the enzyme, DHFR, thereby blocking the reduction of di- to tetra-hydrofolic acid, which is essential coenzyme in nucleic acid synthesis. It has a far higher affinity for protozoal than for mammalian DHFR, so that it may used for malarial prophylaxis without adversely affecting human DHFR. It is active against both \textit{Plasmodium falciparum} and \textit{P. vivax} in combination with an appropriate sulfonamide; it is affective for toxoplasmosis because the sulfonamide acts synergistically by arresting production of dihydrofolic acid from p-aminobenzoic acid, thus achieving a double (sequential) blockage of the folate pathway in the microorganism.\textsuperscript{2}

Diaveridine \text{100} is used prophylactically against coccidiosis in poultry and in combination with sulfaquinoxaline as a curative agent for the same disease. Dimpylate \text{101} is a powerful insecticide, which is used in veterinary medicine, in particular for topical application, with or without added DDT, in cases of blowfly strike in sheep.\textsuperscript{2}

7.3. PLAN OF SYNTHESIS OF 2-(2-AROYLAROXY)-4,6-DIMETHOXY PYRIMIDINES (\text{107a-e})

Condensation of thiourea \text{102} with diethylmalonate \text{103}, generated the starting material, 2-mercapto-pyrimidine-4,6-diol \text{104}. Alkylation with methyl iodide gave 2-methylmercapto-4,6-dimethoxypyrimidine \text{105} which further on perborate oxidation converted the methyl-mercapto group of \text{105} to a sulfone \text{106}, which on nucleophilic displacement by (2-hydroxaryl) aryl methanones \text{46a-e} in presence of potassium carbonate afforded 2-(2-arylaroxy)-4,6-dimethoxy pyrimidines \text{107a-e, scheme-10}.
3. Discussion on the Experiment Leading to the Synthesis of 2-Methylsulfonyl-4,6-Dimethoxypyrimidine (106)

The synthesis of pyrimidines has attracted considerable interest in the scientific community, as this skeleton is present in many natural products and a variety of biologically active substances. Although various procedures for the synthesis of pyrimidines have been reported, most have been restricted to methodologies involving a Pinner synthesis (3,4- and 1,6-bond formation reactions). The more commonly utilized methods for the preparation of pyrimidine derivatives involve interaction of ureas with malonic esters or β-diketones and amidines with β-ketoesters or cyanoacetates. Construction of pyrimidine skeleton using guanidine and 1,3-diaryl-propenones have been reported by various authors. Recently synthesis of pyrimidines using thiourea and malonic ester has been reported. On the basis of previous reports 2-methylsulfonyl-4,6-dimethoxy-pyrimidine (106) was synthesized in good yield. In a typical procedure the condensation of thiourea 102 with

\[
\text{NH}_2 \quad \text{O} \quad \text{O} \quad \text{Et} \\
\text{O} \quad \text{OEt} \quad \text{Et} \quad \text{NH}_2
\]

and

\[
\text{NaOC}_2\text{H}_5 \quad \text{NaBO}_3
\]

in the presence of Anhy. K_2CO_3/Acetone and MIBK led to the formation of pyrimidine 106. The reaction was monitored by TLC and the product was isolated by column chromatography. The structure of the product was confirmed by spectral analysis. The yield of the reaction was found to be good and the product was纯天然
diethylmalonate 103, generated the starting material, 2-mercapto-pyrimidine-4,6-diol 104. Alkylation with methyl iodide gave 2-methylmercapto-4,6-dimethoxy-pyrimidine 105 which further on perborate oxidation converted the methylmercapto group of 105 to a sulfone 106, a better leaving group for displacement by nucleophiles.

7.3.2. DISCUSSION ON THE EXPERIMENT LEADING TO THE SYNTHESIS
OF 2-(2-AROYLAROXY)-4,6-DIMETHOXY PYRIMIDINES (107a-e)

Phenols are important scaffolds for the preparation of a wide variety of pharmaceutically interesting and naturally occurring compounds.60 The development and design of a reliable and efficient method for the construction of the C(aryl)-O bond has attracted the attention of many chemists during the last century.61 This important transformation has been developed to include a wide range of compounds. Since the pioneering works by Ullmann and Goldberg, the copper-mediated cross-coupling reactions have become a powerful tool for the synthesis of complex molecules.62 In addition classical conditions, by the reaction of phenol with aryl donor, the scope of the copper-promoted methodology was extended mainly to other organometalloids such as organobismuth,63 organotrifluoroborate reagents64 and arylboronic acids.65 Nevertheless, the applicability is limited due to the synthesis of the boronic acids is troublesome or complicated. O-arylation of phenols with arylstannanes in presence of copper acetate under mild condition was reported.66 Recently nucleophilic aromatic substitution (NAS)of pyrimidines with phenolates have been described.67 On the basis of previous reports 2-(2-aroylaroxy)-4,6-dimethoxy pyrimidines (107a-e) were synthesized by nucleophilic aromatic substitution 2-methyl-sulfonyl-4, 6-dimethoxy-pyrimidine 103 with (2-hydroxyaryl) aryl methanones (46a-e). In a typical example 107a was synthesized by refluxing 46a (2 mmol) in MIBK with 106 (2 mmol) and anhydrous potassium carbonate (4 mmol) for 8 h. The structure of the compounds was elucidated by IR, 1H NMR and mass spectral analysis. Compound 68a is taken as a representative example of the acetamide series to discuss the spectral studies. The IR spectrum of 107a showed the absorption band in the region 1569 and 1663 attributed to pyrimidin-skeletal and aromatic stretching frequencies, respectively. In the 1H NMR spectrum, it showed three singlets, two at the range δ 2.36, 2.41, and one at 5.64 attributed to two aromatic methyl and pyrimidine ring protons respectively. The signals due to seven aromatic protons appeared as two sets of doublets in A2 B2 pattern centered at δ 7.32 (J = 8.3 Hz) and 7.58 (J = 8.5 Hz) and a multiplet in the range 7.15-7.52. In mass
spectrum, 107a did not show M+ peak, instead showed an ion peak corresponding to M+1 peak, at m/z 365 with 95% of relative abundance. The M+1 peak at mass 365 should have been formed by the abstraction of a hydrogen atom by the M+ ion from the neutral molecule. Compounds 107b and 107c-e also showed M+1 at m/z 385, 406, 369, and 389 respectively, with relative abundance in the range 93-96%.

7.4. EXPERIMENTAL SECTION

7.4.1. GENERAL PROCEDURE FOR THE SYNTHESIS OF 2-METHYL-SULFONYL-4, 6-DIMETHOXYPYRIMIDINE (106)

A typical procedure is described for the synthesis of 2-mercaptopyrimidine-4,6-diol (104): Thiourea 102 (10 g, 131.4 mmol) and diethylmalonate 103 (20 g, 124.8 mmol) were added to a mechanically stirred solution of sodium ethoxide formed from sodium (5 g, 217.4 mmol) in absolute ethanol (300 ml). A thick paste formed immediately; this was heated for 3 h at reflux, cooled to room temperature and the solid was collected by filtration through Whatman No. 2 paper. The solid material is dissolved in a minimum amount of water and decanted to remove traces of insoluble impurities. Acidification with concentrated hydrochloric acid precipitated a solid that was filtered through Whatman No. 2 paper and washed successively with water, ethanol and diethylether, which on drying gave 104. Yield 7.92 g (88%). IR (Nujol): 3510-3645 cm⁻¹ (OH); ¹H NMR: δ 6.05 (s, H, Ar-H), 6.20 (bs, 2H, OH).

A typical procedure is described for the synthesis of 2-methyl-mercapto-4,6-dimethoxypyrimidine (105): To a solution of 104 (6 g, 41.6 mmol) in acetone (100 ml) was added anhydrous potassium carbonate (11.5 g, 83.2 mmol) and methyl iodide (12 g, 84.5 mmol) was added slowly. The mixture was heated at reflux with stirring for 3 h. The reaction solution was diluted with ethyl acetate, washed with water, dried over anhydrous sodium sulfate and concentrated in vacuo to give the solid material 105. Yield 5.65 g (73%). ¹H NMR: δ 2.43 (s, 3H, SCH₃), 3.92 (s, 6H, 2-OCH₃), 6.15 (s, H, Ar-H).

A typical procedure is described for the synthesis of 2-methylsulfonyl-4,6-dimethoxypyrimidine (106): Compound 105 (2.48 g, 13.3 mmol) was added in one portion to a well stirred suspension of NaBO₃ x H₂O (5 g, 55 mmol) in glacial acetic acid (100 ml) preheated to 65 °C (oil bath temperature). The suspension was stirred for 3 h at that temperature, diluted with water (300 ml) and the compound was collected by filtration through Whatman No. 2 paper. The solid obtained was dried and kept in a...
dessicator. Yield 2.46 g (85%). M.p. 97-99°C; \(^1\)H NMR (CDCl\(_3\)):\( \delta: \) 3.33 (s, 3H, SO\(_2\)CH\(_3\)), 4.04 (s, 6H, 2-OCH\(_3\)), 6.18 (s, H, Ar-H). \(^{13}\)C NMR (CDCl\(_3\)):\( \delta \) 38.80 (q), 55.09 (q), 93.05 (d), 164.37 (s), 171.87 (s). Anal. Calcd. for C\(_7\)H\(_{10}\)N\(_2\)O\(_4\)S: C, 38.53; H, 4.62; N, 12.84; S, 14.69. Found: C, 38.47; H, 4.56; N, 12.76; S, 14.61%.
IR Spectrum of compound 107a
$^1$H NMR Spectrum of compound 107a
LC-Mass Spectrum of compound 107a
7.4.2. GENERAL PROCEDURE FOR THE SYNTHESIS OF 2-(2-AROYL-AROXY)-4,6-DIMETHOXY PYRIMIDINES (107a-e)

A typical procedure is described for the synthesis of 2-[2-(4-methylbenzoyl)-4-methylphenoxy]-4,6-dimethoxy pyrimidine (107a): A mixture of 46a (0.45 g, 2 mmol), 2-methylsulfonyl-4,6-dimethoxypyrimidine 106 (0.43 g, 0.028 mmol) in MIBK(10 ml) and anhydrous potassium carbonate (0.55 g, 4 mmol) was refluxed for 8 h then cooled and the solvent removed under reduced pressure. The residual mass was triturated with ice water to remove potassium carbonate and extracted with dichloromethane (3x10 ml) and the ether layer was washed with 10% sodium hydroxide solution (3x10 ml) followed by distilled water (3x10 ml) and then dried over anhydrous sodium sulfate and evaporated to dryness to get crude solid, which on recrystallization with ethanol gave white crystalline solid of 107a. Yield 0.59 g (82%). M.p. 124-126°C; IR (Nujol): 1569 (pyrimidin-skeletal), 1663 cm\(^{-1}\) (C=O); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 2.36 (s, 3H, CH\(_3\)), 2.41 (s, 3H, CH\(_3\)), 3.7 (s, 6H, 2OCH\(_3\)), 5.64 (s, 1H), 7.15-7.52 (m, 3H, Ar-H), 7.32 (d, J = 8.3 Hz, 2H, Ar-H), 7.58 (d, J = 8.5 Hz, 2H, Ar-H); LC-MS: m/z 365 (M\(^+\)+1, 95); Anal. Calcd. for C\(_{21}\)H\(_{20}\)N\(_2\)O\(_4\): C, 69.21; H, 5.53; N, 7.69. Found: C, 69.17; H, 5.48; N, 7.65%.

2-[2-(4-Chlorobenzoyl)-4-methylphenoxy]-4,6-dimethoxypyrimidine (107b):

Obtained from 46b (0.49 g, 2 mmol), 2-methylsulfonyl-4,6-dimethoxypyrimidine 106 (0.43 g, 2 mmol) and anhydrous potassium carbonate (0.55 g, 4 mmol) in presence of MIBK as white crystalline solid. Yield 0.6 g (79%). M.p. 114-116°C; IR (Nujol): 1560 (pyrimidin-skeletal), 1665 cm\(^{-1}\) (C=O); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 2.36 (s, 3H, CH\(_3\)), 2.41 (s, 3H, CH\(_3\)), 3.7 (s, 6H, 2OCH\(_3\)), 5.7 (s, 1H), 7.16-7.62 (m, 7H, Ar-H); LC-MS: m/z 385 (M\(^+\)+1, 93); Anal. Calcd. for C\(_{20}\)H\(_{17}\)ClN\(_2\)O\(_4\): C, 62.42; H, 4.45; Cl, 9.21; N, 7.25. Found: C, 62.37; H, 4.40; Cl, 9.17; N, 7.21%.

2-[2-(4-Chlorobenzoyl)-4-chlorophenoxy]-4,6-dimethoxypyrimidine (107c):

Obtained from 46c (0.49 g, 2 mmol), 2-methylsulfonyl-4,6-dimethoxypyrimidine 106 (0.53 g, 2 mmol) and anhydrous potassium carbonate (0.55 g, 4 mmol) in presence of MIBK as white crystalline solid. Yield 0.63 g (78%). M.p. 99-101°C; IR (Nujol): 1567 (pyrimidin-skeletal), 1670 cm\(^{-1}\) (C=O); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 3.72 (s, 6H, 2OCH\(_3\)), 5.68 (s, 1H), 7.21-7.64 (m, 7H, Ar-H); LC-MS: m/z 406 (M\(^+\)+1, 96); Anal. Calcd. for C\(_{19}\)H\(_{14}\)Cl\(_2\)N\(_2\)O\(_4\): C, 56.30; H, 3.48; Cl, 17.50; N, 6.90. Found: C, 56.27; H, 3.42; Cl, 17.46; N, 6.86%.
2-[2-(4-Methylbenzoyl)-4-fluorophenoxy]-4,6-dimethoxy pyrimidine (107d):
 Obtained from 46d (0.46 g, 2 mmol), 2-methylsulfonyl-4,6-dimethoxypyrimidine 106 (0.53 g, 2 mmol) and anhydrous potassium carbonate (0.55 g, 4 mmol) in presence of MIBK as white crystalline solid. Yield 0.6 g (82%). M.p. 105-107°C; IR (Nujol): 1559 (pyrimidin-skeletal), 1660 cm\(^{-1}\) (C=O); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 2.42 (s, 3H, CH\(_3\)), 3.71 (s, 6H, 2OCH\(_3\)), 5.72 (s, 1H), 7.18-7.62 (m, 7H, Ar-H); LC-MS: m/z 369 (M\(^+\)+1, 95); Anal. Calcd. for C\(_{20}\)H\(_{17}\)FN\(_2\)O\(_4\): C, 65.20; H, 4.65; F, 5.16; N, 7.60. Found: C, 65.16; H, 4.60; F, 5.12; N, 7.54%.

2-[2-(4-Chlorobenzoyl)-4-fluorophenoxy]-4,6-dimethoxy pyrimidine (107e):
 Obtained from 46e (0.50 g, 2 mmol), 2-methylsulfonyl-4,6-dimethoxypyrimidine 106 (0.43 g, 2 mmol) and anhydrous potassium carbonate (0.55 g, 4 mmol) in presence of toluene as white crystalline solid. Yield 0.61 g (79%). M.p. 89-91°C; IR (Nujol): 1565 (pyrimidin-skeletal), 1668 cm\(^{-1}\) (C=O); \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 3.72 (s, 6H, 2OCH\(_3\)), 5.75 (s, 1H), 7.2-7.65 (m, 7H, Ar-H); LC-MS: m/z 389 (M\(^+\)+1, 96); Anal. Calcd. for C\(_{19}\)H\(_{14}\)ClFN\(_2\)O\(_4\): C, 58.70; H, 3.62; Cl, 9.12; F, 4.89; N, 7.20. Found: C, 58.65; H, 3.57; Cl, 9.08; F, 4.82; N, 7.14%.

7.5. BIBLIOGRAPHY


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