CHAPTER 1

INTRODUCTION

Heterocyclic compounds make up about 70% of the total organic molecules known of which majority of them possess potent biological properties. Heterocyclic compounds hold a special place in medicinal and pharmaceutical chemistry due to their biological activities and this has catalyzed the discovery and development of heterocyclic chemistry and synthetic methods. Drug industries have also exploited the heterocycles to a great extent on account of their ability to manifest substituents around a core scaffold in defined three dimensional representations. They have contributed to the development of society from a biological and industrial point of view as well as to the understanding of life processes and to the efforts to improve the quality of life. Almost all known organic compounds contain heterocycles of which sulfur and nitrogen-containing heterocyclic compounds have maintained the interest of researchers through decades of historical development of organic synthesis. N-Heterocyclic compounds are abundant in nature and are of great significance to life because of their structural subunits exist in many natural products such as vitamins, hormones, antibiotics, alkaloids, as well as pharmaceuticals, herbicides, and dyes.

Six membered heterocyclic compounds containing two nitrogen atoms such as pyridazines, pyrazines and pyrimidines are known to possess important biological properties. A few examples of pyrimidine based heterocycles are described hereunder.
1.1 PYRIMIDINE BASED HETEROCYCLIC COMPOUNDS

The pyrimidine nucleus is present in a wide range of bioactive natural products and its nucleus is also present in adenine, guanine, uracil, cytosine and thiamine, part of ribonucleic acid (RNA), deoxyribonucleic acid (DNA), vitamin B₂ and folic acid [1]. Pyrimidine has been subjected to a large number of modifications in order to obtain derivatives with different biological properties. Several groups have studied the chemistry and pharmacological properties of pyrimidine derivatives [2-7]. Pyrimidines are associated with various therapeutic activities such as antiviral [8], antitumor [9], antibacterial [10,11], antihypertensive [12], neuropeptide Y (NPY) antagonist activity [13], diuretics [14], antimalarial [15] etc. Several synthetic strategies have been reported for the preparation of the derivatives of pyrimidine [16-22]. Some of these are discussed in the following section.

1.1.1 A. K. Nezhad and coworkers reported [23,24] the synthesis of novel unsymmetrical 1,3-dialkylpyrimidine derivatives via N3-alkylation of 1-alkylpyrimidines with carbon electrophiles in the presence of catalytic amount of TBAB and Cs₂CO₃ in MeCN at room temperature (Scheme 1).

Some of the N3-alkylated N1substituted pyrimidine nucleobases synthesized by them are shown below.
These N1, N3-substituted pyrimidines possess necessary scaffold to be considered as intercalating and alkylating agents, which play a critical role in cancer chemotherapy.

1.1.2 S. Y. Ke and coworkers have reported [25] the synthesis of a series of o-fluorophenoxy acetylimino-2H-1,2,4-thiadiazolo[2,3-a]pyrimidine derivatives (10) from 9 using bromine as oxidant (Scheme 2).

![Scheme 2](image)

For example, 11 and 12. Some of these compounds showed good herbicidal activity.

![11](image) ![12](image)

1.1.3 Ana M. F. Oliveira-campos and coworkers reported [26] the synthesis of the 4-substituted pyrazolo[3,4-d]pyrimidines as shown below (Scheme 3, Scheme 4).
These compounds were tested for their antifungal activities.

1.1.4 N. A. Kheder used the versatile 6-bromomethylpyrimidine (22) as a building block for the synthesis of cyclopenta[d]pyrimidine, pyrido[4,3-d]pyrimidine and thiazolo[3,4-c]pyrimidine [27] as shown in (Scheme 5).
A versatile synthon, ethyl 6-(bromomethyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (22), was obtained by the bromination of ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (21) in acetic acid. Treatment of the compound 22 with malononitrile or with ethylcyanoacetate afforded the corresponding hexahydrocyclopentan[\v]pyrimidine derivatives 24. 6-bromomethylpyrimidine underwent nucleophilic substitution reaction on treatment with potassium cyanide to afford ethyl 6-cyanomethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate.
(25), which couples smoothly with 4-chlorobenzenediazoniumchloride to give the corresponding hydrazone 26. When the hydrazone was treated with hydrazine hydrate or phenyl hydrazine, it afforded the corresponding pyrido[4,3-\(d\)]pyrimidine derivatives 28. It also reacted with thiourea, thiosemicarbazide to afford the corresponding thiazolo[3,4-c]pyrimidine 30. The antimicrobial activity of selected samples of the synthesized compounds was tested and showed moderate activities.

1.1.5 V. H. Shah and coworkers have reported [28] the synthesis of pyrimidine derivatives from their corresponding chalcones by reacting them with urea as shown in Scheme 6.

Some of these compounds exhibited promising antitubercular activities against mycobacterium tuberculosis. They also reported [29] the synthesis of some pyrimidine derivatives containing the phenothiazine nucleus of the type 35 (Scheme 7). These were also tested for their antitubercular activities.

\[
\begin{align*}
36 & \quad R^1 = \text{various substituents} \\
37 & \quad R' = \text{various substituents}
\end{align*}
\]

1.2 TETRAHYDROPYRIMIDINE BASED HETEROCYCLIC COMPOUNDS

Tetrahydropyrimidines (THPs) are one of the most important systems among the heterocycles. Since these compounds have been found to be of minimal toxicity to men, domesticated animals and fish and selectively display remarkable control on pests, they have been produced in large numbers. A few molecules with reference to their preparation and uses are described in the following sections.

1.2.1 Laurenz Gsell has reported [31] the synthesis of substituted pyridyl methyl cyanoiminotetrahydropyrimidines (40) by the reaction of compounds 38 and 39 in appropriate solvents (Scheme 8).

\[
\begin{align*}
n(\text{Halogen}) + R_3 & \quad \text{Benzene, toluene etc} \\
38 & \quad \text{R}^1 = \text{various substituents} \\
39 & \quad \text{R}^2 = \text{various substituents}
\end{align*}
\]

X = Halogen, n = 0, 1, 2 or 3

\[Y_1 = Y_2\] leaving groups such as \(-\text{SCH}_3, -\text{O-CH}_3, -\text{O-C}_6\text{H}_5\).
Similarly compounds 41, 42 and 43 have been synthesized by the above general method.

These compounds were found to be useful in controlling insects and pests of rice crops, while being well tolerated by plants and having low toxicity to warm blooded animals.

1.2.2 Bernardus A. Oude Alink has reported [32,33] the synthesis of substituted 2,3,4,5-tetrahydropyrimidines and their derivatives of the general formula 44.

\[ \text{R}_1 - \text{R}_6: \text{hydrogen, alkyl, aryl, aralkyl, cycloalkyl, heterocyclic substituted derivatives thereof.} \]

A few methods for the preparation of tetrahydropyrimidines are described below.

1.2.2.1 By the reaction of carbonyl compounds 45 (ketone and aldehyde) with NH$_3$/NH$_2$OH and a sulfur containing catalyst (e.g. CS$_2$) (Scheme 9).
1.2.2 The reaction of $\alpha$, $\beta$-unsaturated ketones 47, carbonyl compounds 48 and $\text{NH}_3/\text{NH}_4\text{OH}$ without a catalyst (Scheme 10).

![Scheme 10]

1.2.2.3 By the reaction of $\alpha$, $\beta$-unsaturated ketones 50, 1-aminoalcohol 51 and $\text{NH}_3/\text{NH}_4\text{OH}$ without a catalyst (Scheme 11).

![Scheme 11]

This tetrahydropyrimidine 52 was further used as intermediate for the preparation of N-dithiocarboxylates. Reaction of the substituted 2,3,4,5-tetrahydropyrimidines (52) with carbon disulfide yielded 1:1 adducts 53 (Scheme 12).

![Scheme 12]

![Scheme 13]
These adducts were efficient corrosion inhibitors in acid systems. Tetrahydropyrimidines, where \( R_6 \) was hydrogen were isomerised to obtain 1,4,5,6-tetrahydropyrimidines (54) (Scheme 13).

THPs, where \( C_2 \) position contains at least one hydrogen and one of the groups attached to \( C_4 \) has at least a methylene group could be converted to substituted pyrimidines (56) by the liberation of ammonia (Scheme 14). These compounds were useful as bactericides. In general the above series of compounds were found to be useful as biocides, antioxidants, oxygen-scavengers and corrosion inhibitors.

1.2.3 Oude Alink and coworkers reported [34] the reaction of tetrahydropyrimidines (57) with various stoichiometric quantities of formaldehyde leading to the formation of mixture of compounds called polyols of tetrahydropyrimidines (58) (Scheme 15).

When \( n \) is less than 4, a mixture of products with the –CH\(_2\)OH group located at one or more of the four possible sites 3, 5 and 6 were obtained.

For example, when 4,4,6-trimethyl-2,3,4,5-tetrahydropyrimidine was reacted with one third molar ratio of formaldehyde a mixture of products 60, 61 and 62 containing three methylol groups were obtained (Scheme 16).
When the same reaction was carried out with 0.5 molar ratio of formaldehyde the product obtained were 63, 64 and 65 (Scheme 17).

Similarly, when the reaction was carried out with 1 molar ratio of formaldehyde three possible products 66, 67 and 68 were obtained (Scheme 18).

These compounds when heated in the presence of Lewis acids such as FeCl₃, AlCl₃ etc. polymerized to form a compound having the general structure 70 with the liberation of ammonia (Scheme 19). The polyols of tetrahydropyrimidines and their respective polymers were found to be useful as corrosion inhibitors.
1.3 1,2,3,4-TETRAHYDROPYRIMIDINE BASED HETEROCYCLES

Our literature survey revealed that the synthesis of 1,2,3,4-tetrahydropyrimidines in particular has been extensively studied because of its wide range of biological activities. A few examples on the synthesis of 1,2,3,4-tetrahydropyrimidines are discussed in the following sections.

1.3.1 M. K. Mishra and coworkers have reported [35] the synthesis of 6-methyl-4-aryl-5-(5-phenyl-1,3,4-oxadiazol-2-y1)-1,2,3,4-tetrahydropyrimidine-2(1H)-one with anti-inflammatory property and synthesized compound 71 having significant effect against Streptococcus pneumonia (+ve) and 72 having significant activity against Escheria coli (-ve).
1.3.2 O. A. El-Fattah and coworkers synthesized [36] some new derivatives containing 5-acetyl-4-(3,4-dimethoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine moiety incorporating different biologically active heterocycles such as pyridon, iminopyridines, thiazolidinones derivatives and the antimicrobial activities were studied (Scheme 20).

![Scheme 20](image)

1.3.3 N. C. Desai and coworkers reported [37] the synthesis of several new substituted 1,2,3,4 tetrahydropyrimidine derivatives and evaluated for their in vitro anticancer activity on various cell lines (Scheme 21). Some of the molecules have exhibited significantly potent inhibition on several cell lines. To find out inter-correlation between anticancer activity and molecular descriptors, QSAR study was carried out. On the basis of the
results, significant correlation between anticancer activity on some of the cell lines and molecular descriptor was observed.

\[ \text{Comp} \quad R^1 \quad X \quad R^2 \]

\begin{align*}
\text{81a-81d} & \quad \text{Cl} \quad \text{S} \quad \text{(a) 2-Cl, (b) 3-OC}_6\text{H}_5 \\
\text{81e-81f} & \quad \text{Cl} \quad \text{O} \quad \text{(e) 2-OH, (f) 3-Cl} \\
\text{81g-81k} & \quad \text{F} \quad \text{S} \quad \text{(g) 2-Cl, (h) 3-Cl, (i) 3-OC}_6\text{H}_5 \\
\text{81l} & \quad \text{F} \quad \text{O} \quad \text{(l) 3-OC}_6\text{H}_5
\end{align*}

**Scheme 21**

1.3.4 R. L. Sawant and M. S. Bhatia reported [38] the preparation of 5-acyl-6-methyl-4-substituted-2-oxo-1,2,3,4-tetrahydropyrimidines (85) by cyclocondensation reaction between appropriate aldehyde, acetoacetates and urea using aluminium chloride and concentrated hydrochloric acid as catalyst.
These compounds (85) upon treatment with dimethylformamide and phosphorous oxychloride furnished 3-formyl-2-oxo-1,2,3,4-tetrahydropyrimidines (86) with antibacterial activity against *Staphylococcus aureus* (Scheme 22).

1.3.5 D. Lokwani and coworkers presented [39] the energetic pharmacophore model representing complementary features of the 1,2,3,4-tetrahydropyrimidine for selective cyclooxygenase-2 (COX-2) inhibition. Some new 4,5,6-triphenyl-1,2,3,4-tetrahydropyrimidine derivatives were synthesized using one pot Biginelli reaction of 1-(4-(methylthio)phenyl)-2-phenylethanone, substituted aldehyde and urea/thiourea/guanidine hydrochloride in the presence of potassium carbonate and ethanol as solvent and assessed for selective COX-2 inhibitory activity where compounds 87 and 88 were found to be potent and selective COX-2 inhibitors.

1.3.6 S. Gaffar and coworkers synthesized [40] a series of (Z)-N’-(benzyldiene/ylmethylene)-4-(1H-indole-3-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbohydrazide (93a) by refluxing 1H-indole-3-carbaldehyde with thiourea/guanidine and ethyl acetoacetate in presence of acid catalyst and ethanol and (Z)-N’-(benzyldiene/ylmethylene)-2-imino-4-(1H-indol-3-yl)-6-methyl-1,2,3,4 tetrahydropyrimidine-5-carbohydrazide (93b) by refluxing ethyl-2-(thioxo/imino)-4-(1H-indol-3-yl)-6-methyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate and hydrazine hydrate in presence of acid catalyst and ethanol and their antifungal activity was studied against *Candida albicans*, *A. Niger*, and *A. clavatus*. Some of the synthesized compounds were found to be equally potent as to the standard drug Griseofulvin and Nystatin (Scheme 23).
1.3.7 N. Chauhan and coworkers reported [41] the synthesis of novel N-[2-chloro-4-(trifluoromethyl)phenyl]-4-(substituted phenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidines-5-carboxamide (95) by acid catalysed cyclocondensation of N-(2-chloro-4-(trifluoromethyl)phenyl)-3-oxobutanamide, thiourea and substituted benzaldehydes. The synthesized compounds were screened for antimicrobial activity (Scheme 24).

1.3.8 M. Mansouri and coworkers reported [42] the synthesis of 4-(furan-2-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate esters by refluxing furan-2-carbaldehyde, appropriate acetoacetate ester and thiourea (1.3 mmole) in absolute ethanol. Ferric chloride (0.2 mmole) was used as a Lewis acid. The antioxidant activity of the synthesized compounds was determined. Compound 98c was found to be the most potent
antioxidant with the IC\textsubscript{50} of 0.6 mg/ml. The results of reducing power assays proved 98d and 98e as the moderate reducing agents. All of the studied compounds were very weak compared with gallic acid in scavenging hydrogen peroxide (Scheme 25).

Scheme 25

1.3.9 A. Baldev and coworkers reported [43] the synthesis of novel 1,2,3,4-tetrahydro-N

Scheme 26

(substituted phenyl)- 6-methyl-2-oxo-[(4-(phenoxy)-methyl) phenyl] pyrimidine-5-carboxamide using N-(substituted phenyl)-3-oxobutanamides, 4-(phenoxy methyl)benzaldehydes, urea and catalytic amount of conc. hydrochloric acid (HCl) in ethanol (Scheme 26). By the antimicrobial study of the compounds, it was found that most of the compounds were good antimicrobial agents.
1.3.10 Synthesis of 1,2,3,4-tetrahydropyrimidine have also been carried out under microwave and ultrasound irradiations. A few of them are cited herein.

1.3.10.1 N. I. Singh et al. have developed [44] a simple and efficient method for the synthesis of ethyl-1-(2-hydrazone-2-oxoethyl)-6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives prepared from urea and substituted aldehydes using microwave irradiation technique and evaluated for their calcium channel inhibition using nifedipine as a analog (Scheme 27).

![Scheme 27](image)

1.3.10.2 Q. Chen and coworkers reported [45] the synthesis of methyl 6-methyl-1-(4-methylphenyl)-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate via the modified Biginelli reaction from benzaldehyde, p-tolylurea, and methyl acetoacetate, promoted with microwave irradiation and catalyzed by TsOH under solvent-free conditions in high yield as shown in Scheme 28.

![Scheme 28](image)
1.3.10.3 P. K. Chaudhari and coworkers reported [46] the synthesis of 1,2,3,4-tetrahydropyrimidine derivatives via a multicomponent reaction of aldehyde derivative, urea or thiourea and 1,3-dicarbonyl compounds using Biginelli Reaction and microwave irradiation catalyzed by HCl and evaluated for their antiviral, antibiotic, anticarcinogenic, antihypertensive, antitubercular, antimycobacterial or anticancer activity (Scheme 29).

![Scheme 29](image)

1.3.10.4 N. R. Chatterjee and coworkers reported [47] an efficient synthesis of some 5-ethoxycarbonyl-4-(2 or 4-substituted phenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-2(1H)-carboxylic acids (115). The ultrasonic assisted Vilsmeier-Haack reaction of 5-ethoxycarbonyl-4-(4-substituted phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-ones (113) gave N-1-formyl derivative (114) using silica gel as catalyst. The N-1 carboxylic acids (115) obtained were converted to their amide derivatives (116) in very good yield by classical reactions (Scheme 30).

![Scheme 30](image)

\[a, Ar = C_6H_5 \quad b, Ar = 4-(OCH_3) \quad C_6H_4 \quad c, Ar = 2-(NO_2) \quad C_6H_4 \quad d, Ar = 2-(Cl) \quad C_6H_4\]
Preliminary pharmacological screening of these novel carboxamides indicated that they possessed significant antiplatelet activity and moderate anticardiac activity.

1.3.11 Keeping in view the biological importance of these molecules, our lab. also has made significant contribution towards the synthesis of novel 1,2,3,4-tetrahydropyrimidines and developed new facile synthetic strategies, some of which are discussed in the following sections.

1.3.11.1 E. Karim and coworkers reported [48] a facile one-pot synthesis of 5-benzoyl-6-methylthio-1,2,3,4-tetrahydropyrimidines in good yields using primary amine and formaldehyde in methanol (Scheme 31).

\[ R_1 = \text{aryl, } R_2 = \text{aryl, aralkyl} \]

\[ R_1 = \text{aryl, } R_2 = \text{aryl, aralkyl, alkyl} \]

Scheme 31

1.3.11.2 K. Chanda and coworkers synthesized [49] 1-(aralkyl/aryl)-3-(alkyl/aralkyl)-5-aroyl-1,2,3,4-tetrahydropyrimidines (121) by dethiomethylation of 5-aroyl-6-methylthio-1,2,3,4-tetrahydropyrimidines and also to achieve the tetrahydropyrimidine (121) in a single step, an alternative synthetic strategy using enamiones of type 122, primary amine and formaldehyde has been developed (Scheme 32).
1.3.11.3 M. C. Dutta and coworkers reported [50] the synthesis of [alkanediylbis(3-alkyl/aralkyl/aryl-3,6-dihydropyrimidine-1,5-(2H)-diyl)]bis(arylmethanones) and [1,4-phenylenebis(3-alkyl/aralkyl/aryl-3,6-dihydropyrimidine-1,5(2H)diyl)]bis(phenylmethanone) envisaging the fact that molecules with two tetrahydropyrimidine rings linked through flexible aliphatic chains or through rigid aromatic chains could have enhanced biological activities (Scheme 33).

1.3.11.4 M. C. Dutta and coworkers described [51] facile syntheses of novel bis-tetrahydropyrimidines, bis-pyrazolotetrahydropyrimidines and bis-pyrazolotetrahydrotriazines (Scheme 34).
J. N. Vishwakarma and coworkers reported [52] the synthesis of novel 5-isonicotinoyl-1,2,3,4-tetrahydropyrimidines 132 and 134 by the reaction of enaminoles 131a-c, primary amines and formaldehyde and screened for their antibacterial properties. Enaminones 131a-c have also been reacted with diamines and formaldehyde to give hitherto unreported bis-tetrahydropyrimidines 133 and 135 in good yields shown in Scheme 35. Some of the synthesized compounds were found to possess anti-bacterial activity on four gram-positive bacteria used in the study. However, variations in anti-bacterial activity, as indicated by mean zones of inhibition, were observed.
Recently S. P. Waghamele and P. B. Piste reported [53] the synthesis of a series of different 6-methyl-4-aryl-5-(5-aryl-1,3,4-oxadiazole-2-yl)-1,2,3,4-tetrahydropyrimidin-2-(1H)-one/thione (138) from ethyl-6-methyl-2-oxo/thioxo-4-substituted phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (136) followed by reaction with hydrazine hydrate in ethanol by means of Microwave irradiation for 2-4 mins with excellent yield in short reaction time (Scheme 36).
1.3.13 S. S. Kshirsagar and P. Shanmugasundaram [54] have most recently studied the calcium channel blocking activity of some synthesized 1,2,3,4-tetrahydropyrimidine derivatives (139, 140 & 141) containing carbamates and car bamides.

1.3.14 K. Elumalai and coworkers have recently presented [55] a new series of some novel isoniazid cyclocondensed 1,2,3,4-tetrahydropyrimidine derivatives by N’-acetoacetylisonicotinohydrazide, urea/thiourea and appropriate aldehyde with catalytic amount of benzenesulphonic acid in ethanol under microwave irradiation (300 W) for 8 minutes at the interval of 10 seconds (Scheme 37). The synthesized compounds were
subjected to *in vitro* antimicrobial activity against gram-positive bacteria *B. subtilis*, gram-negative bacteria *E. coli* and antimycobacterial activity against *M. tuberculosis* CIP and H37RV strain where almost all the synthesized compounds exhibited weak, moderate, or high antimicrobial and antimycobacterial activity.

1.4 MOLECULAR HYBRIDS
The design of new drugs with better physiochemical properties, adequate absorption, distribution, metabolism, and excretion, effective pharmacologic potency and lacking toxicity remains is still a challenge for researchers. Molecular hybridization is a molecular modification approach to obtain multiple-ligands/compounds with pharmacokinetic advantages over concomitant administration of two different drugs [56]. Hybrid molecules are defined as chemical entities with two or more structural domains having different biological functions and dual activity, indicating that a hybrid molecule acts as two distinct pharmacophores. In designing new bioactive agents, besides the development of completely new agents, there is another approach involving the synthesis of hybrid molecules. Combination of different pharmacophores each with a different mode of action in the same structure may lead to compounds having more efficiency in biological activity [57]. A few examples of hybrid molecules with their biological properties are shown below.
Literature survey at this stage revealed that only limited works on the hybrids of tetrahydropyrimidines with other molecules have been reported and so their biological properties remain unexplored. A few reported works on the synthesis and biological activities of hybrids of tetrahydropyrimidines are discussed in the following sections.

1.5.1 T. N. Akhaja and J. P. Raval synthesized [60] a series of 5-substitued-3-(5-(4-(furan-2-yl)-6-methyl-2-oxo/thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-1,3,4-thiadiazol-2-ylimino)indolin-2-one derivatives, tetrahydropyrimidine–isatin hybrids as potential antimalarial and anti-tubercular agents. Some of these synthesized compounds have remarkable improvement in antimalarial and anti-tubercular potency.
S. Acharjee and coworkers reported [61] the synthesis and pharmacological profile of a series of hybrid compounds bearing the 1,2,3,4-tetrahydropyrimidine moiety and substituted phenylthioureas joined via typical β-blocker aryloxypropanolamine group. Most of the synthesized novel compounds exhibited hypotensive as well as antihypertensive effects which could be attributed to the blockade of Ca\(^{2+}\) entry and β-adrenoreceptor blocking activities due to the introduction of aryloxypropanolamine as a linker between substituted phenyl thioureas and 1,4-dihydropyrimidine 2-thiones (Scheme 38).
These compounds obtained their antihypertensive action by binding to β-receptors and calcium channel receptors and can be considered as promising hits in the development of hybrid cardiovascular agents especially in situations like long term hypertension where a single drug is not effective in normalizing elevated blood pressure in hypertensive patients.

1.5.3 K. V. Sashidhara and coworkers discovered [62] coumarin-monastrol hybrid as potential anti-breast tumor-specific agent, which selectively induce apoptosis in both primary and metastatic breast cancer cell lines. The detailed reaction conditions for the synthesis of coumarin-monastrol hybrids are illustrated in Scheme 39. The synthesis of intermediate compounds (161) was achieved by the Duff formylation reaction of o-substituted phenols in the presence of hexamethylenetetramine (HMTA) and trifluoroacetic acid (TFA) at 120 °C. Reaction of compounds (161) with different substituted phenyl acetic acids in the presence of cyanuric chloride and N-methyl morpholine (NMM) in DMF for 1 h afforded the respective 3-aryl coumarin aldehydes (162) in excellent yield. Finally, the target compounds were synthesized via the Biginelli reaction involving 3-aryl coumarin aldehydes, ethylacetoacetate and thiourea/urea in ethanol in the presence of catalytic amount of pTSA to afford coumarin-monastrol hybrid compounds (158). So, in this study the latent ability of coumarin-monastrol hybrid as a new class of selective anti breast cancer agent has been observed.

![Scheme 39](image-url)
1.6 Adamantane derivatives

Adamantane derivatives have attracted a great deal of interest among researchers due to their wide applications in the field of pharmaceuticals. Inclusion of adamantane moiety into several molecules results in compounds with relatively high lipophilicity, which in turn can modify the biological availability of these molecules [63]. After the discovery of amantadine in 1960 as antiviral and antiparkinsonian drug, adamantane derivatives attracted the attention of several scientists as potential chemotherapeutic agents. As a result of this intensive search, thousands of adamantane derivatives were synthesized and tested for several biological activities. This resulted in the discovery of several drugs which are now available in market. Among the major biological activities displayed by adamantane derivatives, the antiviral, antibacterial, antifungal, anti-inflammatory, central nervous and 11β-HSD1 inhibitory activities are the most important ones.

1.6.1 Antiviral Adamantane Derivatives

Amantadine hydrochloride \(163\) (1-adamantanamine hydrochloride) was the first adamantane derivative to be introduced in medicine as effective therapy against Asian A\(_2\) influenza viruses [64]. The pronounced central nervous stimulant and cardiovascular effects of amantadine necessitated the search for newer, more potent and less toxic agents for the control of pandemic influenza viruses. Rimantadine \(164\) (α-methyl-1-adamantanemethylamine hydrochloride) [65] was further developed as more potent and less toxic alternative to amantadine [66].

![Chemical structures of amantadine and rimantadine](https://example.com/structures.png)

The 1-(1-adamantyl)thiourea derivatives \(165\) were found to possess good activity against Herpes Simplex viruses (HSV-1) [67]. Danilenko et al. reported [68] the synthesis and antiviral activity of a series of arylamides of adamantane carboxylic acids \(166\). The derivative \((n = 0, R = 3\text{-OCH}_3)\) was the most effective against A\(_2\) influenza virus.
Potent anti-HIV-1 activity was recently observed with a series of (±)-2-(1-adamanthyl-3-alkyl- or arylthiazolidin-4-ones 167 [69]. The derivative with R = 4,6-dimethyl-2-pyridyl substituent produced the optimal activity and behaved as typical non-nucleoside reverse transcriptase inhibitor [70]. In addition to the activity of adamantane derivatives against influenza, herpes and HIV viruses, adamantane derivatives are recently attracting the attention of several hepatologists after the exploration of the role of amantadine in improving the clinical therapeutic efficacy of interferon/ribavirin combination against hepatitis C viruses (HCV) [71].

1.6.2 Antimicrobial Adamantane Derivatives
Several adamantane derivatives have long been known to possess bactericidal and fungicidal activities. Orzeszko et al. reported the synthesis and potent antibacterial activity of series of 4-(1- or 2-adamantyloxy carbonyl)-N-substituted phthalimides 168 [72] and 4-(1-adamantylalkyloxy-carbonyl)-N-substituted phthalimides 169 [73].

Al-Deeb et al. reported [74] the synthesis, antimicrobial and anti-inflammatory activities of novel series of 2-[3-(1-adamantyl)-4-substituted-5-thioxo-1,2,4-triazolin-1-yl]acetic acids 170, 2-[3-(1-adamantyl)-4-substituted-5-thioxo-1,2,4-triazolin-1-yl]propionic acids 171, and 2-[2-(1-adamantyl)-1,3,4-oxadiazol-5-ylthio]acetic acid 172. These compounds produced good antibacterial activity against Bacillus subtilis and Escherichia coli, and
moderate activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Candida albicans*. Some members of these series also exhibited potent, dose-dependent anti-inflammatory activity. Newer series of 2-(1-adamantyl)-5-substituted-1,3,4-oxadiazoles 173 and 2-(1-adamantylamino)-5-substituted-1,3,4-thiadiazoles 174 were recently reported [75] to possess good antimicrobial activity particularly against the tested Gram-positive bacteria *Bacillus subtilis* and moderate activity against the yeast-like pathogenic fungus *Candida albicans*. Some members of these derivatives particularly the oxadiazoles 173 displayed good, dose-dependent anti-inflammatory activity.

1.6.3 Anti-inflammatory Adamantane Derivatives

Anti-inflammatory activities of several adamantane-containing molecules have been reported [76] in the literature. A series of 3-(1-adamantyl)-4-substituted-5-mercapto-1,2,4-triazoles of the general structure 175, 176 and 177 were prepared and tested for anti-inflammatory and analgesic activities. The derivatives 175 were found to be the most potent among these derivatives. The activity of the derivatives 175 with a methyl, ethyl or benzyl substituents was found comparable to the activity of Indomethacin. The analgesic activity of these compounds correlated to their anti-inflammatory activity.
1.6.4 Adamantane Derivatives as 11β-HSD1 Inhibitors

11β-Hydroxysteroid dehydrogenase type 1 (11β-HSD1) is an endoplasmic reticulum associated enzyme that acts as NADPH-dependent reductase which converts inactive cortisone to the active glucocorticoid cortisol. The invention of selective 11 β-HSD1 inhibitors would be an important therapy for controlling non-insulin-dependent diabetes, hyperglycemia, obesity, insulin resistance, hyperlipidemia, hypertension and other symptoms associated with excessive body cortisol.

In the late 2003, adamantyl 1,2,4-triazoles of the structures 178 and the related compound 179 have been discovered [77], as potent inhibitors of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1).

To improve the selectivity, potency and pharmacodynamic profile, amide function was introduced into the adamantane structure and adamantane amide ether 180 was found to possess potent and selective inhibitory activity against human and mouse 11β-HSD1 [78]. Then compound 180 was modified by replacing the amide function with carboxy alkyl group 181 or a heterocyclic nucleus 182 [79].
Later, the highly potent, 11β-HSD1-selective inhibitor N-(2-adamantyl)acetamide derivative 183, and its (±)-methyl derivative 184 were discovered [80]. The methyl analogue 184 has excellent potency, 11β-HSD1 selectivity and improved microsomal stability in both in vitro studies on human and mouse 11β-HSD1 and in vivo studies on mouse and rats.

1.7 Adamantane-Tetrahydropyrimidine hybrids
The above reports clearly show that derivatives of both adamantane and 1,2,3,4-tetrahydropyrimidine are well documented in the literature. However, 1,2,3,4-tetrahydropyrimidines containing adamantane moiety are unknown in the literature and hence their synthesis and biological properties remain unexplored. Prompted by these literature findings, we decided to develop synthetic protocols for 1,2,3,4-tetrahydropyrimidine-adamantane hybrids with a view to studying the biological activities of this class of compounds. The results of our studies are presented in this thesis.