Chapter-II

Synthesis and Characterization of ethyl 2-(1-aminocyclobutyl)-5-(benzoyloxy)-6-hydroxyl pyrimidine-4-carboxylate sulfonamide, carboxamide and 2-amino pyrimidine derivatives
2.0. Introduction to synthesis of pyrimidines

Pyrimidine is a π-deficient heterocycle because of the presence of two electronegative nitrogen atoms. Electron densities at the 2, 4 and 6 positions are depleted, making these positions strongly electrophilic. However, electron density at the 5-position is only slightly depleted, and this position retains benzenoid properties. Hydroxy, thiol, and amino groups in pyrimidine exist in tautomeric equilibria with their oxo, thioxo and imino forms. An amino group in an electrophilic position exists predominantly and the compound is named as an amine. Pyrimidines with a hydroxy or thiol group in an electrophilic position, are dominated by the oxo or thioxo forms and are named as such, or with -one or -thione suffixes, if they are the principal groups. Thermally promoted Claisen rearrangement of simple allyloxy pyrimidines is ineffective [1], an attempted amino-Claisen rearrangement of a 4-allylaminopyrimidine was unsuccessful [2]. Pyrimidine derivative leads to pyrimidinium salts which are powerful acylating agents. Primary and secondary pyrimidinamines undergo acylation at the amino group. Simple alkylations of pyrimidines with nontautomerizable substituents are largely controlled by steric factors. Alkylation of 2-hydroxy and 4-hydroxy pyrimidines is largely governed by the nature of the alkylating agent and by steric and electronic effects from adjacent substituents, N-alkylation is sterically more demanding than O-alkylation. The rate of reaction at nitrogen decreases relative to that of oxygen as the bulk of the alkylating reagent increases. Alkylation of a primary or secondary 2-, 4- or 6-aminopyrimidine usually takes place on ring nitrogen to afford a 1-alkyl or 3-alkyl iminopyrimidine, which subsequently undergo a Dimroth rearrangement to its alkylamino isomer [3]. Pyrimidine is also found in meteorites, although scientists still do not know its origin,
pyrimidine also photolytically decomposes into uracil under UV light [6]. N-amino pyrimidines can be acylated and sulfonylated to give amide and sulfonamide derivatives, and also reacts with isocyanates to give ureas, and with aldehydes and ketones to give imines. They can also participate in cyclization reactions to form fused pyrimidines heterocycles. Pyrimidines have been obtained after transformation of other mono heterocycles in reactions in which the pyrimidine ring is set free in ring-opening or elimination reactions. A wide variety of synthetic routes to pyrimidine derivatives have been described in this chapter. While ring synthesis has traditionally been the major synthetic route in metal-catalyzed amination and cross-coupling chemistry, the modification of existing substrates has become a much more feasible approach. Therefore, the best choice of synthetic route to any particular compound or class of compound is not straightforward and depends upon a number of different factors that are continually changing. The cost of raw materials and reagents, the number of synthetic steps, the stability, toxicity, and ease of manipulation of intermediates are all factors that must be considered. For example, while Stille cross-coupling reactions often proceed in good yield with pyrimidine substrates, toxicity issues mean that other cross-coupling procedures are often much more favored. The purpose of the synthesis also has a bearing on the type of procedure chosen. Thus, in medicinal chemistry, synthetic procedures that allow for the greatest compound diversity as late as possible in the synthesis are desirable, but these may not be the optimum procedures once the final drug candidate is identified. Additionally, procedures that require chromatography for product purification may be perfectly acceptable on a laboratory scale, but are often undesirable on an industrial scale. Legal issues can also influence the choice of synthetic procedure, if the preferred route is covered by a competitor’s patent. Therefore, it is not possible to say
categorically that one synthetic route is superior to another until all the various factors have been fully assessed, and even then the result is only valid for that point in time, as a new or improved procedure may appear at any time. Factors influencing the choice of synthetic routes to pyrimidines depend very much upon the substitution pattern of the desired product. The best example is the displacement of the amino group in 2-aminopyrimidine by chlorine [4] and its reverse [5]. Pyrimidines can also be prepared within the laboratory by organic synthesis. One method is the classic Bignelli reaction. There are many methods on condensation of carbonyls with amines, for instance the synthesis of 2-thio-6-methyluracil from thiourea and ethyl acetate [7] or the synthesis of 4-methylpyrimidine with 4,4-dimethoxy-2-butanone and formamide [8]. A novel method is by reaction of certain amides with carbonitriles under electrophilic activation of the amide with 2-chloro-pyridine and trifluromethanesulfonic anhydride [9]. There are several synthetic routes to synthesize pyrimidine and we would like to expose some important synthesis of pyrimidine from different heterocycles.

2.0.1. Synthesis of the pyrimidine ring from other heterocycles

It is possible to prepare pyrimidines from other heteromonocyclic compounds by a variety of processes, or from fused heterobicyclic systems which already contain pyrimidine ring by preferentially degrading the unwanted second ring. In the latter case, the bicyclic system may best be made from a pyrimidine in the first place, occasionally even from the selfsame pyrimidine to which it reverts on degradation. Such synthesis may be of interest but are certainly not of any utility.

A. Pyrimidines from pyrroles

Pyrimidines can be synthesized from pyrroles. One of the best example is, when oxime of 2,4,5-triphenylpyrrol-3(2H)-one (135) is treated with phosphorus...
pentachloride, two acyclic products (136; $X=\text{O}$ or $\text{NOH}$) are formed. The first of the products on heating gives rise to 2,5,6-triphenylpyrimidin-4(3H)-one (137) and the second on reduction with zinc / acetic acid gives the triphenylpyrimidin-4-amine (138), and the reaction is done in chloroform, the product (137) is obtained directly [10]. An unrelated ring expansion occurs when 2,3,5-triphenylpyrrole is irradiated in alcoholic ammonial open to air to give 2,4,6-triphenylpyrimidine, it is evident that the second nitrogen atom is inserted between the two adjacent phenyl substituents of the pyrrole [11].

![Chemical structures](image1)

B. Pyrimidines from imidazoles

Hydantoins, i.e., imidazole-2,4(3H,5H)-diones, sometimes arise in reactions designed to make pyrimidines. However, they can be usually converted into the desired pyrimidines, often under hydrolytic conditions. For example, diethyl oxalacetate and urea under the usual conditions do not give the expected uracilcarboxylic acid. But the hydantoin (139) may be converted into the acyclic intermediate (140) and then into orotic acid (141) [12]. The reaction is not confined entirely to substituted orotic acids, for example, diethyl methylxalacetate and guanidine give the imidazole (142) and then the pyrimidine (143) [13]. A different approach is the condensation of acetylenedicarboxylic acid and thiourea to give the thiohydantoin (144) which yield 2-thioorotic acid (145) on alkaline treatment [14].
C. Pyrimidines from isoxazoles and oxazoles

Pyrimidines can also synthesize from isoxazoles and oxazoles. 3,4-dimethyl isoxazol-5-amine (146) is easily acylated to its formyl derivative on catalytic hydrogenation, which undergoes ring cleavage and recyclization to yield 5,6-dimethylpyrimidin-4(3H)-one (147) and the other acyl derivatives gives 2-substituted pyrimidines. A similar result achieved by ring cleavage followed by acylation and final reclosure [15] of the oxazole (148) treated with ammonia converts into 5-hydroxy-4,6-dimethyl-pyrimidine(149) [16].

D. Pyrimidines from pyridines, pyrazines and triazines

Although not a practical method of preparing pyrimidines, but also certain halogenopyridines undergo amination with sodium amide in liquid ammonia to give poor to moderate yields of pyrimidines. For example, 2,6-dibromopyridine (150) gives 2-methylpyrimidin-4-amine (151) along with pyridine-2,6-diamine, 2,6-dichloro-pyridine gives similar products but not 2,6-difluoropyridine [17]. Several
other derivatives of 2-bromopyridine behave similarly as a result 2-bromo-6-phenoxypyridine (152) gives 2-methyl-4-phenoxypyrimidine (153) [18].

The pyrolysis of pyrazine at $1000^0C/2$ mmHg gives pyrimidine with fewer yields. The photolysis of pyrazine at 254nm gives a little pyrimidine. In addition, 2-methylpyrazine gives both 4- and 5-methylpyrimidine, 2,6-dimethylpyrazine gives 4,5-dimethylpyrimidine and 2,5-dimethylpyrazine gives both 4,6,5-dimethyl pyrimidine, all in minute yield [19].

1,3,5-Triazine reacts with 2-ethoxycarbonylacetamidinium chloride (154) or with ethyl 5-ethoxycarbonylacetic imidate (155) in acetonitrile to give ethyl 4-aminopyrimidine-5-carboxylate (156; R=NH$_2$) in good yield and it reacts with the same acetimidate hydrochloride to give ethyl 4-ethoxypyrimidine-5-carboxylate (156; R=OEt) [20]. This reaction can be modified to give a variety of 4,5-disubstituted pyrimidines, e.g. malononitrile gives 4-aminopyrimidine-5-carbonitrile, while malondiamide gives 5-carbamoylpyrimidin-4(3H)-one [21]. In a rather different way, triazine reacts with propane-1,3-diamine to give 1,4,5,6-tetrahydropyrimidine [22].

Several triazinyl ketones isomerizes to 4-acetamidopyrimidines. This is seen in the C-acylation of 2,4,6-trimethyl-1,3,5-triazine (157) with benzoyl chloride in the presence of sodium amide to give the ketone (158) which undergoes Dimroth like...
rearrangement in boiling water to afford N-(2-methyl-6-phenylpyrimidine-4-yl)acetamide (159) [23].

\begin{center}
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\end{center}

**E. Pyrimidines from oxazines and thiazines**

Both 1,3-oxazines and 1,3-thiazines may be converted into pyrimidines by treating with ammonia or primary amines. Thus 2,5-diphenyl-1,3-oxazin-6-one (160) with ammonia or aniline yields 2,5-diphenylpyrimidin-4(3H)-one (161; R=H) or its 2,3,5-triphenyl analogue (161; R=Ph), respectively [24], and the 6-(hydroxymethyl)-2-thioxo-2H-1,3-thiazin-4(3H)-one (162) in warm aqueous ammonia gives 6-hydroxymethyl-2-thiouracil (163; R=H) or with methylamine gives the 1-methyl derivative (163; R=Me) [25]. It is evident that such oxazine or thiazine substrates must carry an oxo or thioxo substituent as well as two double bonds in the ring to yield a fully aromatic pyrimidine or a dihydropyrimidine. For example, ethyl 2-anilino-1,3-thiazine-5-carboxylate undergoes rearrangement in hot formic acid to give the dihydropyrimidine thione (164) [26].

\begin{center}
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F. Pyrimidines from benzofurans and other O-heterocycles

The Pyrimidine synthesis from benzofurans is specialized only to 5-(o-hydroxyphenyl)pyrimidines. One of the best examples is the treatment of 3-acetyl-2-ethyl-6-nitrobenzofuran (165) with guanidine, acetamidine, thiourea or urea to give 4-ethyl-5-(2-hydroxy-4-nitropheno-1)-6-methylpyrimidin-2-amine (166; R=NH$_2$), the 2-methyl analogue (166; R=Me) and the corresponding pyrimidin-2(1H)-thione and pyrimidinone respectively [27]. A similar result is obtained on treatment of chromones with sulfaguanidine. The substrate and sulfaguanidine in alcoholic alkoxide gives sulfonamide. Single ring O-heterocycles behave similarly, 2,6-dimethylpyran-4-one and urea in ethanolic sodium ethoxide give 4-acetonyl-1,6-methyl-pyrimidin-2(1H)-one [28].

G. Pyrimidines from purines and related fused systems

Purin-2(3H)-one (167), the corresponding thione and its S-methyl derivative all undergo facile hydrolytic degradation to 4,5-diaminopyrimidin-2(1H)-one (168), the analogue thione or the 2-methylthio analogue, respectively. Similarly 9-methylpurine gives 4-methyl-aminopyrimidin-5-amine [29]. 7-methylpurine (169) can be made easily from aliphatic intermediates and can subsequently undergo
alkaline degradation to 5-methylaminopyrimidin-4-amine (170) [30]. A variation
of these procedures produce 4,5-bis(alkylamino) pyrimidines [31].

2-Phenylpyrazolo (3,4-d) pyrimidin-3(2H)-one (171) may be made easily from
an available pyrazole and then degraded by catalytic hydrogenation to give 4-amino-
N-phenyl pyrimidine-5-carboxamide (172; R=NHPH) and then by alkaline hydrolysis
to the carboxylic acid (172; R=OH) [32], oxidative degradations are also possible
[33]. Isoxazolopyrimidines may be made from isoxazole intermediates and then
degraded to pyrimidines. For illustration, hydrogenation of 3-methylisoxazolo (5,4-d)
pyrimidin-4-amine (173) followed by boiling water yields 5-acetyl-6-
aminopyrimidin-4(3H)-one (174) [34]. Thienopyrimidines are prepared from
thiophenes. For example, 5-methylthieno (2,3-d) pyrimidin-4-amine (175) undergoes
desulfurization by Raney nickel to give a mixture of 5-isopropenyl- (176) and 5-
isopropyl-pyrimidin-4-amine [35]. Thiazolo[4,5-d] pyrimidine (177), is made from
thiazole intermediates, which is boiled with aqueous alkali in the absence of air, 6-
anilino 5-mercaptopyrimidin-4(3H)-one (178) is formed in good yield. And in the
presence of air, the product is naturally the corresponding disulfide [36].
H. Pyrimidines from pteridines and related fused systems:

Most pteridines when degraded to pyrazines yield pyrimidines. However, some useful preparations of pyrimidines from pteridines are known. Thus, reduction of pteridin-7(8H)-one (179) and subsequent hydrolysis yields N-(4-aminopyrimidin-5-yl) glycine (180) [37] and hydrolysis of 5,8-dimethylpteridine-6,7(5H, 8H)-dione (181) gives $N,N$-dimethyl-pyrimidine-4,5-diamine (182) [38].
Pyrimido (4,5-d) pyrimidines may be used as pyrimidine precursors. Thus, the dihydro derivative (183) undergoes alkaline hydrolysis to the amide (184; R=PrCO) which may be deacylated in ethanolic hydrogen chloride to give 5-aminomethyl 1-2 propylpyrimidin-4-amine (184; R=H) [39]. Similarly, pyrimidopyrimidinedione (185) reacts with amines to give 6-amino-5-benzyliminomethyl-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (186; R=CH₂Ph) or the hydrazone (186; R=NH₂) [40]. The oxidation of quinazoline with alkaline permanganate is the preferred route to pyrimidine-4,5-dicarboxylic acid [41]. The pyrano[2,3-d]pyrimidine (187) on easy alcoholyis yields the pyrimidine (188; R=CO₂Et) and 2-thio analogue may also be made similarly [42].

2.0.2. Preferred synthetic routes to pyrimidines

I. Synthesis of pyrimidine

The best way to make pyrimidine from 1,1,3,3-tetraethoxypropane and formmaide, is by a continuous process [43,44]. Other practical ways to make small
amounts in the laboratory are thermal decarboxylation of pyrimidine-4,6-dicarboxylic acid (189), prepared by oxidation of 4,6-dimethylpyrimidine [45], or hydrogenolysis of 2,4-dichloropyrimidine over palladium/charcoal in the presence of magnesium oxide [46].

The best route to 1,4,5,6-tetrahydropyrimidine (191) is treatment of propane-1,3-diamine with ethyl formate to give the formyl derivative (190) which is heated at 150°C/20 mm Hg to give the tetrahydropyrimidine. It also made by hydrogenation of pyrimidine in aqueous hydrochloric acid over palladium or by hydrogenolysis of 2-chloro-, 2,4-dichloro-, or 4,6-dichloro-pyrimidine (192) in aqueous ether over palladium [47]. Hexahydropyrimidine is made by treatment of propane-1,3-diamine with aqueous formaldehyde [48].

A. Primary synthesis of the pyrimidine Ring

Considerable localization of π-electrons at the nitrogen atoms of pyrimidine ring system is still sufficiently aromatic to possess substantial stability. This is great advantage in the primary synthesis of pyrimidines from the breakdown or modification of other heterocyclic systems and in the myriad of metatheses required to synthesize specifically substituted pyrimidines. The first primary synthesis of a pyrimidine from aliphatic fragments was carried out by Frankland and Kolbe in 1848.

B. Primary synthesis involving formation of one bond

In many pyrimidine ring synthesis, it is possible or even desirable to isolate an intermediate for ring-closure by the formation of one bond. For example, ethyl 3-aminocrotonate (193) reacts with methyl isocyanate to give the ureido ester (194),
which may be isolated and subsequently converted into 3,6-dimethyluracil (195) by the completion of one bond. However, the whole synthesis involves the formation of two bonds and therefore only two pyrimidine synthesis is involve in the formation of one bond.

\[ \text{Rinkes synthesis of uracil} \] is brought about by treating malediame (196) with sodium hypochlorite, one of the amide group appears to undergo first stages of Hofmann reaction to give isocyanate intermediate (197), then cyclizes with the other amide to give uracil (198). The reaction does not seem to have been extended within the pyrimidine series but there are even earlier examples of such procedures giving quinazoline-2,4 (1H,3H)-dione (200) from phthaladiame (199) and 5,6-dihydrouracil (202) from succindiamide (201; R=H) [50]. The last reaction can be extended by using 2-phenylsuccindiamide (201; R=Ph) to afford 6-phenyl-5,6 dihydouracil.
C. Primary synthesis involving formation of two bonds

The Remfry-Hull synthesis is illustrated by the condensation of \(\alpha\)-butylmalondiamide (203) and ethyl formate in ethanolic sodium ethoxide to give 5-butyl-6-hydroxypyrimidin-4(3H)-one (204) [51]. The diamide may be replaced by a monothiodiamide and the ester by an acid chloride 2-ethyl-2-thiocarbamoylbutyramide (205) and acetyl chloride gives pyrimidinethione (206). Other variations include the use of diethyl oxalate to give malondiamide, the pyrimidine-2-carboxylic acid (207) [52] and replacement of the ester by a simple amide such as formamide which reacts with \(\alpha\)-methoxymalondiamide to give 6-hydroxy-5-methoxypyrimidin-4(3H)-one (208) [53]. When homologues of formide or ethyl formate are used, the reaction is slowed and hence allows time for the self-condensation of malondiamide to yield the by-product [54].
Pyrimidine-4,6-diamines are obtained from similar condensation of malondiamidine with esters or amides. For example, malondiamidine (209) and ethyl benzoate give 2-phenylpyrimidine-4,6-diamine (210). Similarly diethyl carbonate or ethyl chloroformate yields 4,6-diaminopyrimidin-2(1H)-one (211) [55]. The use of \( N \)-substituted malondiamidines is seen in the condensation of symmetrical \( N,N' \)-diallyl-malondiamidine with ethyl formate to give \( N,N' \)-diallylpyrimidine-4,6-diamine (212).

D. Primary synthesis involving formation of three bonds:

The Frankland-Kolbe synthesis was pioneered in 1848, and its subsequent history is fascinating [56]. The synthesis involves the trimerization of three simple nitriles (213) by heating with potassium alkoxide to give a di- or tri-alkylprimidin-4-amine.
(214) in which the 5-alkyl group has one methylene less than those in the 2- and 6-positions. This places a severe restrictions on its scope but it is still used as a convenient route to 2,6-dimethylpyrimidin-4-amine (214; R=H) from acetonitrile (213; R=H) and potassium ethoxide [57] or to 5-ethyl-2,6-dipropylpyrimidin-4-amine (214; R=Et) [58]. The mechanism is not understood and it may be because a 1,3,5-triazine intermediate is involved. Thus, propionitrile trimerizes when heated under pressure without any catalyst give 2,4,6-triethyl-1,3,5-triazine (215) and this can be converted subsequently into 2,5-diethyl-5-methylpyrimidin-4-amine (214; R=Me) [59] by use of alkali mixtures of nitriles. For example, p-chlorophenylacetonitrile (1 mol) and pyridine-4-carbonitrile (2 mol) in butanolic butoxide at 115 ºC give 5-p-chlorophenyl-2,6-di(pyridine-4yl)pyrimidin-4-amine in excellent yield [60].

The formamide or active methylene synthesis is illustrated by the condensation of acetophenone with two molecules of formamide to give 4-phenylpyrimidin (217), via the intermediate (216). Similarly phenyl acetonitrile and formamide gives 5-phenyl pyrimidin-4-amine (219), via the intermediate (218). The synthesis may be used more effectively by combining the molecules of formamide as trisformamidomethane, which may then furnish N-formylformamidine. Thus, acetone and this reagent with toluenesulfonic acid catalyst yield 4-methylpyrimidine (220).
E. Primary synthesis involving formation of four or more bonds

The synthesis of tetrahydropyrimidines from carbonyl compounds and ammonia or an amine is usually known as the acetonin synthesis. Thus, acetone reacts with liquid ammonia in the presence of calcium chloride to give a compound ‘acetonin’ which is now known as 2,2,4,4,6-pentamethyl-2,3,4,5-tetrahydropyrimidine (221) [61]. The mechanism involves three molecules of acetone and two of ammonia, with mesityl oxide (222) and diacetonamin (223) as the only definite intermediates. The reaction is capable of considerable variation, for example, in the conversion of diacetonin into the thione (224) [62].
A synthesis involving an aldehyde, ammonia and a β-dicarbonyl compound which has inbuilt capacity for prototropy or oxidation leads first to a dihydropyrimidine, which subsequently becomes a pyrimidine [63]. Thus, α-benzylideneacetylacetone, benzaldehyde and ammonia gives benzylidenePyrimidine (225) which rearranges to 5-benzyl-4,6-dimethyl-2-phenylpyrimidine (226). For example, a similar condensation using dibenzoylbromomethane as the dicarbonyl compound yields the intermediate (227) which spontaneously loses HBr to give 2,4,6-triphenylpyrimidine (228). The practical route is the condensation of N-phenacylpyridinium bromide with ammonia and p-nitrobenzaldehyde to give the notional tetrahydro intermediate which loses the quaternary group as a pyridine salt and is further oxidized by excess of aldehyde to give 2,4-di(p-nitrophenyl)-6-phenylpyrimidine.

These are some of the preferred synthetic routes for the synthesis of pyrimidines [64]. There are several published syntheses of both the parent compound and analogs using Biginelli reaction chemistry [65-69], and this has continued with a number of recent examples [70-72]. Dihydropyrimidinethiones have been used as a source of 2-amino-4-arylpyrimidine-5-carboxylic acid
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derivatives [73]. The synthetic procedure involves initial S-alkylation of the dihydropyrimidinethione with methyl iodide, aromatization with manganese dioxide and then oxidation of the thiomethyl group with oxone to provide 2-methylsulfonylpyrimidines, which are then reacted with amines and other nucleophiles. The synthesis of related dihydropyrimidinones has also received recent attention [74-79], and the 1,2- or 1,4-addition of nucleophiles to 2(1H)-pyrimidinones has given access to compounds not readily available by the Biginelli reaction route [80,81]. We have constructed pyrimidine from hydroxylamine group using diethyl acetylene dicorboxylate.

The chief advantage over earlier heterocyclic analogues such as sulfapyridine and sulfathiazole is the good water solubility of both the drugs 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. Today, sulfadiazine is widely used, however sulfamerazine is no longer used for chemotherapy of infections. A third homologue, sulfadimidine, which is the 4,6-dimethyl derivative of sulfadiazine, is also used in little amount although it is still found in most pharmacopoeias. Other pyrimidine sulfonamides currently in clinical use include sulfametoxydiazine, sulfasomidine which is an isomer of sulfadimidine and sulfametomidine. Sulfonamide-trimethoprim combinations are used extensively for opportunistic infections in patients with AIDS. Sulfadoxine [82], a short and intermediate acting sulfonamide with a half-life of 7-9 days is used for malarial prophylaxis. Sulfisomidine with a half-life of 7 h is used as a combination of sulfa therapy in veterinary medicine [83]. Sulfadiazine, sulfamerzine and sulfadimidine possess good water solubility and therefore carry minimum risk of kidney damage, which makes them safe even for patients with impaired renal
functions. Sulfonamides remain the drugs of choice in well-defined areas such as acute urinary-tract infections, cerebrospinal meningitis, or the numerous patients sensitive to penicillins [84]. In addition, most sulfonamides have excellent therapeutic indices and their side effects disappear quickly on discontinuance of the drug. Based on these, we have synthesized substituted ethyl 2-(1-aminocyclobutyl)-5-(benzoyloxy)-6-hydroxy pyrimidine-4-carboxylate sulfonamide derivatives, substituted ethyl 2-(1 aminocyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate carboxamide derivatives and 2-aminopyrimidine derivatives.
2.1. Synthesis and characterization of substituted ethyl 2-(1-aminocyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate sulfonamide derivatives (VIIIa-i):

2.1.1. Materials and methods

A brief description of purification of solvents, the analytical procedure followed in the different physico-chemical techniques for the characterization of the synthesized compounds and experiments are presented here.

2.1.2. Purification of organic Solvents

The organic solvents such as methanol, chloroform, diethyl ether, dichloromethane, N,N-dimethyl formamide, hexane, benzene, toluene, isopropyl alcohol, acetonitrile, ethyl acetate, tetrahydrofuran, ethanol, acetone, acetic acid, dimethyl Sulphoxide etc are purchased from various companies such as Merck, Ranbaxy, Qualigens, Sigma, Rankem and S. D. fine. Distilled water–Double distilled water, distilled by quartz distillation unit.

2.1.3. Reagents

Different amines, sulfonyl chlorides, alkyl halides, aryl halides, triethylamine, sodium sulphate, sodium hydroxide, sodium bicarbonate, N-methyl morpholine, sodium ethoxide, sodium acetate, potassium hydroxide, hydroxyl amine hydrochloride, ammonium chloride, ammonium carbonate, potassium carbonate, isobutylchloroformate, sodium chloride etc., all these chemicals were obtained from standard commercial sources.

2.1.4. Analytical techniques

A. Thin-Layer chromatography (TLC)

For TLC, Analtech silica gel GF 254 performed with 0.2mm silica gel (E-merck, reagent No.017) with fluorescent indication and Merck made TLC plates. The
following mobile phases were employed for TLC hexane: ethyl acetate, chloroform: methanol, dichloromethane: methanol in different ratio.

B. Column chromatography

For column chromatography silica gel (Merck Grade 60-120 mesh) was used.

C. Determination of melting point

Melting points were determined using SELACO-650 and Veego VMP-III model hot stage melting point apparatus and were uncorrected.

2.1.5. Instrumentation

The instrumental techniques employed for the characterization of the synthesized compound include Ultra-Violet, Infrared, $^1$H NMR and elemental analysis. The details of instrumentation are briefly given below.

A. Infrared spectra

The Infrared spectra on KBr Pellets in the range of 4000-400 cm$^{-1}$ were recorded on a Shimadzu 8300 and Jasco FT-IR 4100 series. FTIR Fourier transform spectrophotometer provided with KBr optics. The observed infrared bands were calibrated with standard frequencies of polystyrene.

B. $^1$H NMR spectrometer.

$^1$H NMR (400 MHz) spectra was recorded on CDCl$_3$, D$_2$O, DMSO solution in a 5 mm tube on a BRUKER amx 400 Fourier transform spectrophotometer (at SIF, Indian Institute of Science, Bangalore, India) with Tetramethylsilane (TMS) as internal standard. Chemical shifts were recorded in ppm relative to TMS.

C. Elemental analysis

Elemental analysis was carried out on elemental Vario EL III. Oxygen was used for combustion and Helium as the mobile phase. The combustion chamber temperature was set at 1150$^\circ$C and the reduction chamber temperature was at 850$^\circ$C.
Delelten used for thermal conductance and the liberated SO₂ was detected at 140 °C. The CO₂, N₂ and H₂O were detected at room temperature.

2.2. Procedure for the synthesis of ethyl 2-(1-aminocyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate.

For the synthesis of the target key intermediate VII the reaction sequences outlined in Scheme 1, were followed. 1-isocyanocyclobutanamine II was prepared by treating cyclobutanone I with ammonium chloride and sodium cyanide in methanol. Amine group of compound II was protected by using benzyl chloroformate in the presence of mild base sodium carbonate, followed by the oxime formation by using hydroxylamine hydrochloride in presence of base potassium hydroxide and methanol as a solvent gives compound IV. Benzyl 1-(4-(ethoxycarbonyl)-5,6-dihydroxypyrimidin-2-yl)cyclobutylcarbamate V was prepared by cyclisation of compound IV with diethyl acetylene dicarboxylate in chloroform using triethylamine as a base for 5 hr followed by evaporation of chloroform and reflux in xylene at 145 °C for 48 hr. Then the alkylated product VI was obtained by treating with benzoic anhydride in pyridine. Final intermediate VII was obtained by deprotection of amine group of compound VI by using Pd/C in ethyl acetate.

The nucleophilic substitution reaction of ethyl 2-(1-aminocyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate VII with different substituted aromatic sulfonyl chlorides (R-SO₂-Cl) were carried out in the presence of triethyl amine and dichloromethane as solvent with good yield ranging from 75-86%. The absence of -NH₂ proton peak and the presence of amide -NH peak in synthesized derivatives VIII(a-i) in proton NMR and IR spectra confirms the formation of our products. It is also confirmed by IR data, which shows asymmetric stretching frequency of -SO₂- at 1350 cm⁻¹ and symmetric structure frequency at 1280 cm⁻¹.
products obtained were purified by column chromatography using hexane:ethyl acetate (8:2) as eluent. All the synthesized compound VIII(a-i) were characterized by IR, $^1$H-NMR, LC/MS and elemental analysis.

2.2.1. Synthesis of 1-isocyano-cyclobutanamine (II)

A filtered solution of ammonium chloride (100 g, 1.87 mol) in 250 ml of water was taken and cooled to 5-10 °C. A solution of cyclobutanone I (87.5 g, 1.25 mol) in 250 ml of ether was then added with stirring. A solution of sodium cyanide (80 g, 1.63 mol) in water (175 ml) was added with stirring, at such a rate that the temperature never exceeded 10 °C. The reaction mixture was stirred for 1 hr after all the cyanide has been added and then was allowed to stand overnight. The ether layer was separated and the aqueous layer was extracted twice with ether (100 ml). The
ether extract were combined and the ether was removed by evaporation through vacuum pump (rotavapour). The residue which consists mainly of cyclobutane cyanohydrin was diluted with 400 mL of methanol. The mixture was cooled and saturated with ammonia gas. The reaction mixture was allowed to stand for two days, and the excess ammonia was expelled by a current of air. The methanol was removed by distillation. The crude product obtained was purified by column chromatography over silica gel (60-120 mesh) using dichloromethane and methanol as eluent. Yield = 99.3 g, 83%. IR (KBr, cm\(^{-1}\)): 3303, 2850, 2223, 1245. \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\): 3.1 (br s, 2H, -NH\(_2\)), 2.5 (m, 2H, -CH\(_2\)), 2.2 (m, 2H, CH\(_2\)), 2.0 (m, 2H, -CH\(_2\)). MS(M+1) m/z: 97.07. Anal. Calcd. for C\(_5\)H\(_8\)N\(_2\): C - 62.47, H - 8.39, N - 29.14. Found C - 62.51, H - 8.43, N - 29.11.

2.2.2. **Synthesis of benzyl 1-cyanocyclobutylcarbamate (III)**

To a suspension of compound II (54.8 g, 0.57 mol) in water (500 ml), Na\(_2\)CO\(_3\) (60.63 g, 0.57 mol) and benzyl chloroformate (97.68 g, 0.57 mol) were added, with an external cooling. The reaction mixture was stirred for 12 hr at room temperature. The progress of the reaction was monitored by TLC. Upon completion, water was added to the reaction mixture and extracted with ethyl acetate and organic layer was washed with NaHCO\(_3\) (saturated solution) dried over Na\(_2\)SO\(_4\). The solvent was removed by vacuum, a white solid was obtained, which was further purified by column chromatography over silica gel (60-120 mesh) using dichloromethane and methanol as eluent. Yield = (112.35 g, 85.7%). IR (KBr, cm\(^{-1}\)): 3100, 2968, 2223, 1695, 1261, 796. \(^1\)H NMR (CDCl\(_3\), 400 MHz) \(\delta\): 7.38-7.32 (m, 5H, Ar-H), 5.31 (br s, 1H, -NH), 5.16 (br s, 2H, -CH\(_2\)), 2.75 (m, 2H, -CH\(_2\)), 2.36 (t, 2H, -CH\(_2\)), 2.15 (m, 2H, -CH\(_2\)). MS
Synthesis-\textit{Pyrimidine derivatives}  

**Chapter-II**

(M+1) m/z: 231.26. Anal. Calcd. for C_{13}H_{14}N_{2}O_{2}(\%): C-67.81, H-6.13, N-12.17. 


2.2.3. **Synthesis of benzyl 1-amidinocyclobutylcarbamate (IV)**

Hydroxylamine hydrochloride (18.20 g, 0.26 mol) in methanol was added to an equimolar stirred solution of KOH (15.36 g, 0.26 mol) in methanol. The reaction mixture was stirred for 15 min and the precipitated KCl was removed by filtration. The filtrate was added to an equimolar amount of the nitrile compound III (59.86 g, 0.26 mol) and the solution was stirred for 12 hr at 40^\circ C. The progress of the reaction was monitored by TLC. Then the reaction mixture was cooled to room temperature and concentrated. The resulting residue was treated with water, and a white solid was obtained after drying under vacuum. The crude product obtained was purified by column chromatography over silica gel (60-120 mesh) using dichloromethane and methanol as eluent. Yield = (58.0 g, 84.5\%). IR (KBr, cm^{-1}): 3357, 3150, 2965, 1693, 1264, 795. \textsuperscript{1}H NMR (DMSO-\textit{d}_{6}, 400 MHz) \(\delta\): 9.14 (br s, 1H, -OH), 7.62 (br s, 1H, -NH), 7.35-7.30 (br s, 5H, Ar-H), 5.15 (br s, 2H, -NH\textsubscript{2}), 5.05 (s, 2H, -CH\textsubscript{2}), 2.5 (m, 2H, -CH\textsubscript{2}), 2.15 (t, 2H, -CH\textsubscript{2}), 1.83-1.7, (m, 2H, -CH\textsubscript{2}). MS(M+1) m/z: 265. Anal. Calcd. for C_{13}H_{17}N_{3}O_{3}(\%): C-59.30, H-6.51, N-15.96. Found C-59.36, H-6.55, N-15.91.

2.2.4. **Synthesis of benzyl 1-(4-(ethoxycarbonyl)-5,6-dihydroxypyrimidin-2-yl)cyclobutylcarbamate (V)**

Compound IV (52.60 g, 0.20 mol) was treated with diethyl acetylene dicarboxylate (40.8 g, 0.24 mol) in chloroform and triethylamine (20.20 g, 0.40 mol), and the reaction mixture was stirred at room temperature for 5 hr. Then the chloroform was removed by vacuum finally the residue was dissolved in xylene (10 volumes) and heated at 145^\circ C for 48 hr. The progress of the reaction was monitored.
by TLC. The reaction mixture was stirred at room temperature overnight to allow the precipitation, a brown solid was obtained. This solid was collected by filtration and washed with ether. The solid obtained was purified by column chromatography over silica gel (60-120 mesh) using dichloromethane and methanol as eluent. Yield = (66.3 g, 85.7%). IR (KBr, cm\(^{-1}\)): 3248, 3096, 1690, 1252, 790. \(^1\)H NMR (DMSO-\(d_6\), 400 MHz) \(\delta\): 12.54 (s, 1H, -OH), 10.21 (s, 1H, -OH), 7.83 (br s, 1H, -NH), 7.21 (br s, 5H, Ar-H), 4.98 (s, 2H, -CH\(_2\)), 4.29 (q, 2H, -CH\(_2\)), 2.65 (q, 2H, -CH\(_2\)), 2.20 (q, 2H, -CH\(_2\)), 1.95 (m, 1H, -CH) 1.91 (t, 1H, -CH), 1.22 (t, 3H, -CH\(_3\)). MS (M+1) m/z: 388.42.

Anal. Calcd. for C\(_{19}\)H\(_{21}\)N\(_3\)O\(_6\) (%): C - 58.91, H - 5.46, N - 10.85. Found C - 58.95, H - 5.48, N - 10.81.

2.2.5. Synthesis of benzyl 1-(4-(ethoxycarbonyl)-5-(benzoyloxy)-6-hydroxy pyrimidin-2-yl)cyclobutyl carbamate (VI)

A solution of compound V (65.80 g, 0.17 mol) and benzoic anhydride (42.26 g, 0.187 mol) in pyridine were taken and stirred for 12 hr at room temperature. The progress of the reaction was monitored by TLC. After completion, Pyridine was evaporated and residue was taken in ethyl acetate and washed with 1N HCl and brine solution. Organic layer was dried over Na\(_2\)SO\(_4\), filtered and concentrated by rotary evaporation and residue was stirred with ether and filtered off the white solid. The crude product obtained was purified by column chromatography over silica gel (60-120 mesh) using dichloromethane and methanol as eluent. Yield = (66.9 g, 80%). IR (KBr, cm\(^{-1}\)): 3340, 3058, 1562, 1294, 791. \(^1\)H NMR (DMSO-\(d_6\), 400 MHz) \(\delta\): 12.68 (s, 1H, -OH), 8.1 (d, 1H, Ar-H), 8.08 (br s, 1H, -NH), 7.6 (t, 3H, Ar-H), 7.2 (br s, 5H, Ar-H), 5.02 (s, 2H, -CH\(_2\)), 4.26 (q, 2H, -CH\(_2\)), 2.75 (q, 2H, -CH\(_2\)), 2.29 (q, 2H, -CH\(_2\)),
1.98 (m, 1H, -CH), 1.8 (t, 1H, -CH), 1.06 (t, 3H, -CH3). MS(M+1) m/z: 492.17. Anal. Calcd. for C25H25N3O7 (%): C-63.54, H-5.13, N-8.55. Found C-63.59, H-5.18, N-8.51.

2.2.6. Synthesis of ethyl 2-(1-aminocyclobutyl)-5-(benzoyloxy)-6-hydroxy pyrimidine-4-carboxylate (VII)

Compound VI (72 g, 0.146 mol) was treated with Pd/C in presence of solvent ethyl acetate, the reaction mixture is stirred for 12 hr at room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was filtered, the solvent was removed under reduced pressure and the residue was stirred with ether and filtered off the white solid. The crude product obtained was purified by column chromatography over silica gel (60-120 mesh) using dichloromethane and methanol as eluent. Yield = (43.5 g, 83%). IR (KBr, cm⁻¹): 3440, 3066, 1630, 1300, 1087, 755. ¹H NMR (DMSO-d6, 400 MHz) δ: 12.72 (s, 1H, -OH), 8.1 (d, 2H, Ar-H), 7.6 (t, 3H, Ar-H), 4.26 (q, 2H, -CH2), 2.75 (q, 2H, -CH2), 2.5 (br s, 2H, -NH2) 2.29 (q, 2H, -CH2), 1.98 (m, 1H, -CH), 1.8 (t, 1H, -CH), 1.06 (t, 3H, -CH3). MS (M+1) m/z: 358.36. Anal. Calcd. for C18H19N3O5 (%): C-60.50, H-5.36, N-11.76. Found C-60.56, H-5.40, N-11.70.

2.2.7. General procedure for the synthesis of ethyl 2(1-aminocyclobutyl)-5-(benzoyloxy)-6-hydroxy pyrimidine-4-carboxylate derivatives VIII(a-i).

A solution of ethyl 2-(1-aminocyclobutyl)-5-(benzoyloxy)-6-hydroxy pyrimidine-4-carboxylate VII (1.0 eq) in dichloromethane was taken and cooled to 0-5 °C in ice bath. Triethyl amine (3.0 eq) was added to the cold mixture and stirred for 10 min and respective sulfonyl chlorides (1.0 eq) were added, the mixture was stirred and allowed at room temperature for 5 hr. The progress of the reaction was monitored by TLC. Upon completion, water was added to reaction mixture and extracted with ethyl acetate. The organic layer was washed with 10% ammonium chloride solution.
followed by water wash and dried with anhydrous sodium sulphate. The solvent was evaporated and the crude product obtained was purified by column chromatography over silica gel (60-120 mesh) using dichloromethane: methanol (9:1) as eluent.

Table 1. Chemical structure, yield molecular weight and melting point of the synthesized compounds VIII(a-i)

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Mol. wt</th>
<th>Yield</th>
<th>M.P (°C)</th>
</tr>
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<tbody>
<tr>
<td>VIIIa</td>
<td>O₂N</td>
<td>542</td>
<td>83%</td>
<td>180-182</td>
</tr>
<tr>
<td>VIIIb</td>
<td>O₂N</td>
<td>542</td>
<td>85%</td>
<td>186-188</td>
</tr>
<tr>
<td>VIIIc</td>
<td>ClCl</td>
<td>566</td>
<td>78%</td>
<td>197-199</td>
</tr>
<tr>
<td>VIIIId</td>
<td>Cl</td>
<td>531</td>
<td>80%</td>
<td>194-196</td>
</tr>
<tr>
<td>VIIIe</td>
<td>NO₂</td>
<td>542</td>
<td>86%</td>
<td>190-192</td>
</tr>
<tr>
<td>VIIIIf</td>
<td>H₃C[CH₃]</td>
<td>553</td>
<td>79%</td>
<td>208-210</td>
</tr>
<tr>
<td>VIIIg</td>
<td></td>
<td>497</td>
<td>75%</td>
<td>200-202</td>
</tr>
<tr>
<td>VIIIh</td>
<td>H₂C</td>
<td>435</td>
<td>76%</td>
<td>210-212</td>
</tr>
<tr>
<td>VIIIi</td>
<td>H₃C[H₂C]</td>
<td>511</td>
<td>75%</td>
<td>204-206</td>
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2.2.8. Synthesis of ethyl 2-(1-(4-nitrobenzenesulfonylamino)cyclobutyl)-5-(benzoyloxy)-6-hydroxy pyrimidine-4-carboxylate (VIIIa)

The product obtained was white solid from ethyl 2(1-aminocyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate VII (0.1 g, 0.28 mmol), 4-nitrobenzene sulfonyl chloride (0.062 g, 0.28 mmol) and triethyl amine (0.085 g, 0.84 mmol). IR (KBr, cm\(^{-1}\)): 3442, 3108, 2780, 2371, 1475, 1352, 1286, 1039. \(^1\)H NMR (DMSO-\(d_6\), 400 MHz) \(\delta\): 13.08 (s, 1H, -OH), 8.83 (s, 1H, -NH), 8.35 (d, 2H, \(J=8.6\) Hz, Ar-H), 8.18 (dd, 2H, \(J=8.5\) Hz, Ar-H), 7.95 (dd, 2H, \(J=8.6\) Hz, Ar-H), 7.8 (t, 1H, \(J=7.4\) Hz, 7.2 Hz, Ar-H), 7.64 (t, 2H, \(J=7.7\) Hz, 7.5 Hz, Ar-H), 4.17 (q, 2H, \(J=6.8, 7.1, 6.9\) Hz, -CH\(_2\)), 2.2 (m, 2H, -CH\(_2\)), 1.05 (t, 3H, \(J=7.1\) Hz, 7.0 Hz, -CH\(_3\)), 1.76 (m, 2H, -CH\(_2\)), 1.63 (m, 2H, -CH\(_2\)). MS (M+1) m/z: 543.11. Anal. Calcd. for C\(_{24}\)H\(_{22}\)N\(_4\)O\(_9\)S (\%): C\(-\)53.13, H\(-\)4.09, N\(-\)10.33, S\(-\)5.91. Found C\(-\)53.18, H\(-\)4.13, N\(-\)10.27, S\(-\)5.85.

2.2.9. Synthesis of ethyl 2-(1-(3-nitrobenzenesulfonylamino)cyclobutyl)-5-(benzoyloxy)-6-hydroxy pyrimidine-4-carboxylate (VIIIb)

The product obtained was white solid from ethyl 2(1-aminocyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate VII (0.1 g, 0.28 mmol), 3-nitrobenzene sulfonyl chloride (0.062 g, 0.28 mmol) and triethyl amine (0.085 g, 0.84 mmol). IR (KBr, cm\(^{-1}\)): 3436, 2789, 2369, 1455, 1355, 1276, 1048. \(^1\)H NMR (DMSO-\(d_6\), 400 MHz) \(\delta\): 13.14 (s, 1H, -OH), 8.7 (s, 1H, -NH), 8.45 (d, 1H, \(J=7.2\) Hz, Ar-H), 8.38 (s, 1H, Ar-H), 8.1 (t, 3H, \(J=11.8, 7.2\) Hz, Ar-H), 7.8 (m, 2H, Ar-H), 7.76 (t, 2H, \(J=7.8, 7.5\) Hz, Ar-H), 4.19 (q, 2H, \(J=6.9, 7.1, 7.0\) Hz, -CH\(_2\)), 2.23 (m, 2H, -CH\(_2\)), 1.08 (t, 3H, \(J=7.1, 7.0\) Hz, -CH\(_3\)), 1.75 (m, 2H, -CH\(_2\)), 1.62 (m, 2H, -CH\(_3\)). MS (M+1) m/z: 543.12. Anal. Calcd. For C\(_{24}\)H\(_{22}\)N\(_4\)O\(_9\)S (\%): C\(-\)53.13, H\(-\)4.09, N\(-\)10.33, S\(-\)5.91. Found C\(-\)53.18, H\(-\)4.13, N\(-\)10.27, S\(-\)5.85.
2.2.10. Synthesis of ethyl 2-(1-(3,5-dichlorobenzenesulfonylamino)cyclobutyl)-5-(benzoyloxy)-6-hydroxy pyrimidine-4-carboxylate (VIIIc)

The product obtained was white solid from ethyl 2-(aminocyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate VII (0.1 g, 0.28 mmol), 3,5-dichlorobenzene sulfonyl chloride (0.068 g, 0.28 mmol) and triethyl amine (0.085 g, 0.84 mmol). IR (KBr, cm⁻¹): 3446, 3084, 1470, 1358, 975, 1279, 722. ¹H NMR (DMSO-d₆, 400 MHz) δ: 13.1 (s, 1H, -OH), 8.65 (s, 1H, -NH), 8.0 (m, 3H, Ar-H), 7.65 (m, 5H, Ar-H), 4.2 (q, 2H, J=7.3, 6.9, 7.2 Hz, -CH₂), 2.1 (m, 2H, -CH₂), 1.05 (t, 3H, J=7.1, 7.0 Hz, -CH₃), 1.78 (m, 2H, -CH₂), 1.65 (m, 2H, -CH₂). MS (M+1) m/z: 567.06. Anal. Calcd. for C₂₄H₂₁Cl₂N₃O₇S (%): C-50.89, H-3.74, N-7.42, S-5.66. Found C-53.94, H-3.81, N-7.36, S-5.61.

2.2.11. Synthesis of ethyl 2-(1-(4-chlorobenzenesulfonylamino)cyclobutyl)-5-(benzoyloxy)-6-hydroxy pyrimidine-4-carboxylate (VIIIId)

The product obtained was white solid from ethyl 2-(aminocyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate VII (0.1 g, 0.28 mmol), 4-chlorobenzene sulfonyl chloride (0.059 g, 0.28 mmol) and triethyl amine (0.085 g, 0.84 mmol). IR (KBr, cm⁻¹): 3456, 3095, 1476, 1352, 1283, 973, 726. ¹H NMR (DMSO-d₆, 400 MHz) δ: 13.1 (s, 1H, -OH), 8.44 (s, 1H, -NH), 8.1 (d, 2H, J=7.9, 11.4, 7.3 Hz, Ar-H), 7.8 (dd, 2H, J=18.9, 6.9, 7.8 Hz, Ar-H), 7.6-7.7 (m, 5H, Ar-H), 4.2 (q, 2H, J=7.2, 7.1, 7.0 Hz, -CH₂), 2.12 (m, 2H, -CH₂), 1.75 (m, 2H, -CH₂), 1.6 (m, 2H, -CH₂), 1.08 (t, 3H, J=7.1, 7.0 Hz, -CH₃). MS (M+1) m/z: 532.09. Anal. Calcd. for C₂₄H₂₂ClN₃O₇S (%): C-54.19, H-4.17, N-7.90, S-6.03. Found C-54.25, H-4.22, N-7.86, S-6.00.
2.2.12. Synthesis of ethyl 2-(1-(2-nitrobenzenesulfonylamino)cyclobutyl)-5-(benzoyloxy)-6-hydroxy pyrimidine-4-carboxylate (VIIIe)

The product obtained was white solid from ethyl 2-(aminocyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate VII (0.1 g, 0.28 mmol), 2-nitrobenzene sulfonyl chloride (0.062 g, 0.28 mmol) and triethyl amine (0.085 g, 0.84 mmol). IR (KBr, cm\(^{-1}\)): 3426, 2781, 2357, 1460, 1351, 1281, 849, 756. \(^1\)H NMR (DMSO-\(d_6\), 400 MHz) \(\delta\): 13.12 (S, 1H, -OH), 8.5 (S, 1H, -NH), 8.13 (d, 2H, J=7.5 Hz, Ar-H), 7.95 (m, 2H, Ar-H), 7.65 (m, 2H, Ar-H), 7.55 (d, 1H, J=8.4 Hz, Ar-H), 7.46 (m, 2H, Ar-H), 4.16 (q, 2H, J=7.0 Hz, Ar-H), 1.6 (m, 2H, -CH\(_2\)), 1.25 (s, 9H, CH\(_3\)), 1.05 (t, 3H, J=7.0 Hz, -CH\(_3\)). MS (M+1) m/z: 543.13. Anal. Calcd. for C\(_{24}\)H\(_{22}\)N\(_4\)O\(_9\)S (%): C -53.13, H -4.09, N -10.33, S -5.91. Found C -53.19, H -4.14, N -10.27, S -5.86.

2.2.13. Synthesis of ethyl 2-(1-(4-tert-butylbenzenesulfonylamino)cyclobutyl)-5-(benzoyloxy)-6-hydroxy pyrimidine-4-carboxylate (VIIIf)

The product obtained was white solid from ethyl 2-(aminocyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate VII (0.1 g, 0.28 mmol), 4-tert-butyl benzene sulfonyl chloride (0.065 g, 0.28 mmol) and triethyl amine (0.085 g, 0.84 mmol). IR (KBr, cm\(^{-1}\)): 3438, 2779, 2360, 1453, 1392, 1340, 1256, 1041. \(^1\)H NMR (DMSO-\(d_6\), 400 MHz) \(\delta\): 12.95 (s, 1H, -OH), 8.18(s, 1H, -NH), 8.06 (m, 4H, Ar-H), 7.65 (m, 2H, Ar-H), 7.55 (d, 1H, J=8.4 Hz, Ar-H), 7.46 (d, 2H, J=8.5 Hz, Ar-H), 4.16 (q, 2H, J=7.0 Hz, Ar-H), 1.6 (m, 2H, -CH\(_2\)), 1.25 (s, 9H, CH\(_3\)), 1.05 (t, 3H, J=7.0 Hz, -CH\(_3\)). MS (M+1) m/z: 554.19. Anal. Calcd. For C\(_{28}\)H\(_{31}\)N\(_3\)O\(_7\)S (%): C -60.74, H -5.64, N -7.59, S -5.79. Found C -60.79, H -5.69, N -7.53, 18, S -5.72.
2.2.14. Synthesis of ethyl 2-(1-(benzenesulfonylamino)cyclobutyl)-5-(benzoyloxy)-6-hydroxy pyrimidine-4-carboxylate (VIIIg).

The product obtained was white solid from ethyl 2-(aminocyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate VII (0.1 g, 0.28 mmol), benzenesulfonyl chloride (0.049 g, 0.28 mmol) and triethyl amine (0.085 g, 0.24 mmol). IR (KBr, cm\(^{-1}\)):
3420, 3084, 1470, 1391, 1350, 1280. \(^1\)H NMR (DMSO-\(d_6\), 400 MHz) \(\delta\): 13.1 (s, 1H, -OH), 8.33 (s, 1H, -NH), 8.097 (d, 2H, J=7.3 Hz, Ar-H), 7.76 (m, 4H, Ar-H), 7.5 (m, 4H, Ar-H), 4.25 (q, 2H, J=6.9, 7.1, 7.0 Hz, -CH\(_2\)), 2.12 (m, 2H, -CH\(_2\)), 1.75 (m, 2H, -CH\(_2\)), 1.6 (m, 2H, -CH\(_2\)), 1.02 (t, 3H, J=7.1, 7.0 Hz, -CH\(_3\)). MS (M+1) m/z: 498.13. Anal. Calcd. for C\(_{24}\)H\(_{23}\)N\(_3\)O\(_7\)S (%): C-57.94, H-4.66, N-8.45, S-6.44. Found C-57.99, H-4.71, N-8.40, S-6.39.

2.2.15. Synthesis of ethyl 2-(1-(methanesulfonylamino)cyclobutyl)-5-(benzoyloxy)-6-hydroxy pyrimidine-4-carboxylate (VIIIh)

The product obtained was white solid from ethyl 2-(aminocyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate VII (0.1 g, 0.28 mmol), methane sulfonyl chloride (0.032 g, 0.28 mmol) and triethyl amine (0.085 g, 0.84 mmol). IR (KBr, cm\(^{-1}\)):
3420, 3084, 1470, 1391, 1350, 1280. \(^1\)H NMR (DMSO-\(d_6\), 400 MHz) \(\delta\):
13.1 (s, 1H, OH), 8.0 (d, 2H, J=7.2 Hz, Ar-H), 7.89 (s, 1H, -NH), 7.77 (m, 1H, Ar-H), 7.6 (m, 2H, Ar-H), 4.22 (q, 2H, J=7.0, 7.1, 7.0 Hz, -CH\(_2\)), 2.93 (s, 3H -CH\(_3\)), 2.16(m, 2H, -CH\(_2\)), 1.9 (m, 2H, -CH\(_2\)), 1.73 (m, 2H, -CH\(_2\)), 1.0 (t, 3H, J=7.1, 7.1 Hz, -CH\(_3\)). MS (M+1) m/z: 436.11. Anal. Calcd. for C\(_{19}\)H\(_{21}\)N\(_3\)O\(_7\)S (%): C-52.41, H-4.86, N-9.65, S-7.36. Found C-52.46, H-4.89, N-9.61, S-7.31.
2.2.16. Synthesis of ethyl 2-(1-(4-toluylsulfonylamino)cyclobutyl)-5-(benzoyloxy)-6-hydroxy pyrimidine-4-carboxylate (VIII).

The product obtained was white solid from ethyl 2-(aminocyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate VII (0.1 g, 0.28 mmol), toluol-4-sulfonyl chloride (0.053 g, 0.28 mmol) and triethyl amine (0.085 g, 0.84 mmol). IR (KBr, cm$^{-1}$): 3430, 3091, 1482, 1386, 1352, 1288. $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$: 12.96 (s, 1H, -OH), 8.14 (s, 1H, -NH), 8.0 (d, 2H, J=7.0 Hz, Ar-H), 7.78 (m, 1H, Ar-H), 7.65 (m, 2H, Ar-H), 7.58 (d, 2H, J=8.1 Hz, Ar-H), 7.3 (d, 2H, J=7.9 Hz, Ar-H), 4.23 (q, 2H, -CH$_2$), 2.36 (s, 3H, -CH$_3$), 2.1 (m, 2H, -CH$_2$), 1.72 (m, 2H, -CH$_2$), 1.59 (m, 2H, -CH$_2$), 1.05 (t, 3H, J=7.1, 7.0 Hz, -CH$_3$). MS (M+1) m/z: 512.14. Anal. Caled. For C$_{25}$H$_{25}$N$_3$O$_7$S (%): C-58.70, H-4.93, N-8.21, S-6.27. Found C-58.75, H-4.97, N-8.17, S-6.22.
2.3. Synthesis and characterization of ethyl 2-(1-aminocyclobutyl)-5-(benzoyloxy)-6-hydroxy-pyrimidine-4-carboxylate derivatives IX(a-j):

2.3.1. General procedure for the synthesis of ethyl 2-(1-aminocyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate derivatives IX(a-j).

A solution of ethyl 2-(1-aminocyclobutyl)-5-(benzoyloxy)-6-hydroxy pyrimidine-4-carboxylate VII (1.0 eq) in dichloromethane was taken and cooled to 0-5 °C in ice bath. Triethyl amine (3.0 eq) was added to the cold mixture and stirred for 10 min and respective aryl carbonyl chlorides (1.0 eq) were added. The mixture was stirred and allowed at room temperature for 5 hr. The progress of the reaction was monitored by TLC. Upon completion, water was added to reaction mixture and extracted with ethyl acetate. The organic layer was washed with 10% ammonium chloride solution followed by water wash and dried with anhydrous sodium sulphate. The solvent was evaporated and the crude product obtained was purified by column chromatography over silica gel (60-120 mesh) using dichloromethane: methanol (9:1) as eluent.

Where (R-CO-Cl):

IXa)=3,5-dinitrobenzoyl chloride                     (IXf)=3-bromo benzoyl chloride
IXb)=2-methoxybenzoyl chloride                     (IXg)=4-chloro benzoyl chloride
IXc)=2-fluoro benzoyl chloride                     (IXh)=benzoyl chloride
IXd)=2,6-difluorobenzoyl chloride                  (IXi)=3-nitrobenzoyl chloride
IXe)=4-tert-butyl benzoyl chloride                 (IXj)=2,4-chloro benzoyl chloride
Table 2. Chemical structure, yield molecular weight and melting point of the synthesized compounds IX(a-j)

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Mol. wt</th>
<th>Yield</th>
<th>M.P (°C)</th>
</tr>
</thead>
</table>
| IXa      | O2N  
            | NO2  
            | 522   | 83%     | 210-212  |
| IXb      | Me  
            | OMe  | 491   | 85%     | 186-188  |
| IXc      | F  
            | 479   | 86%   | 190-192 |
| IXd      | F  
            | 497   | 78%   | 197-199 |
| IXe      | 517   | 80%   | 194-196 |
| IXf      | Br  | 540   | 75%   | 200-202 |
| IXg      | Cl  | 495   | 75%   | 204-206 |
| IXh      | 461   | 76%   | 180-182 |
| IXi      | NO2  | 477   | 78%   | 212-214 |
| IXj      | Cl  
            | Cl  | 530   | 79%     | 208-210 |
2.3.2. Synthesis of ethyl 2-(1-(3,5-dinitrobenzamido)cyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate (IXa)

The product obtained was white solid from ethyl 2-(1-aminocyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate VII (0.1 g, 0.28 mmol), 3,5-dinitrobenzoyl chloride (0.064 g, 0.28 mmol) and triethylamine (0.085 g, 0.84 mmol).

IR (KBr, cm⁻¹): 3460, 2930, 2859, 2371, 1681, 1059. ¹H NMR (DMSO-δ6, 400 MHz) δ: 12.85 (s, 1H, -OH), 9.85 (s, 1H, -NH), 9.65 (s, 1H, Ar-H), 9.15 (m, 2H, Ar-H), 7.22 (m, 5H, Ar-H), 4.24 (q, 2H, -CH₂), 2.82 (t, 2H, -CH₂), 2.45 (t, 2H, -CH₂), 1.97 (m, 2H, -CH₂), 1.10 (t, 3H, -CH₃). MS (M⁺1) m/z: 523.17. Anal. Calcd. for C₂₅H₂₁N₅O₁₀ (%): C-54.45; H-3.84, N-12.70, O-29.01. Found C-54.48; H-3.87, N-12.66, O-29.00.

2.3.3. Synthesis of ethyl 2-(1-(2-methoxybenzamido)cyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate (IXb)

The product obtained was white solid from ethyl 2-(1-aminocyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate VII (0.1 g, 0.28 mmol), 2-methoxybenzoyl chloride (0.048 g, 0.28 mmol) and triethylamine (0.085 g, 0.84 mmol). IR (KBr, cm⁻¹): 3459, 2941, 2848, 2365, 1679, and 1065. ¹H NMR (DMSO-δ6, 400 MHz) δ: 13.08 (s, 1H, -OH), 9.01 (s, 1H, -NH), 8.08 (t, 2H, Ar-H), 7.78 (d, 1H, Ar-H), 7.63 (m, 1H, Ar-H), 7.12 (m, 5H, Ar-H), 4.24 (q, 2H, -CH₂), 3.84 (s, 3H, -OCH₃), 2.82 (t, 2H, -CH₂), 2.45 (t, 2H, -CH₂), 1.97 (m, 2H, -CH₂), 1.10 (t, 3H, -CH₃). MS (M⁺1) m/z: 492.17. Anal. Calcd. for C₂₆H₂₅N₃O₇(%): C-63.54, H-5.13, N-8.55, O-22.79. Found C-63.59, H-5.18, N-8.50, O-22.73.
2.3.4. Synthesis of ethyl 2-(1-(2-fluorobenzamido)cyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate (IXc)

The product obtained was white solid from ethyl 2-(1-aminocyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate VII (0.1 g, 0.28 mmol), 2-fluoro benzoyl chloride (0.044 g, 0.28 mmol) and triethylamine (0.085 g, 0.84 mmol).

IR (KBr, cm\(^{-1}\)): 3450, 2959, 2855, 2360, 1665, 1079, 790. \(^1\)H NMR (DMSO-\(d_6\), 400 MHz) \(\delta\): 12.89 (s, 1H, -OH), 9.80 (s, 1H, -NH), 7.78 (t, 1H, Ar-H), 7.38 (t, 1H, Ar-H), 7.85 (d, 1H, Ar-H), 7.58 (d, 1H, Ar-H), 7.17 (m, 5H, Ar-H), 4.22 (q, 2H, -CH\(_2\)), 2.75 (t, 2H, -CH\(_2\)), 2.42 (t, 2H, -CH\(_2\)), 1.91 (m, 2H, -CH\(_2\)), 1.12 (t, 3H, -CH\(_3\)). MS (M+1) m/z: 480.46. Anal. Calcd. for C\(_{25}\)H\(_{22}\)FN\(_3\)O\(_6\) (%): C-62.63, H-4.62, F-3.96, N-8.76, O-20.02. Found C-62.68, H-4.66, F-3.91, N-8.72, O-20.01.

2.3.5. Synthesis of ethyl 2-(1-(2,6-difluorobenzamido)cyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate (IXd)

The product obtained was white solid from ethyl 2-(1-aminocyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate VII (0.1 g, 0.28 mmol), 2,6-difluorobenzoyl chloride (0.049 g, 0.28 mmol) and triethylamine (0.085 g, 0.84 mmol). IR (KBr, cm\(^{-1}\)): 3434, 2927, 2360, 1666, 1105, 794. \(^1\)H NMR (DMSO-\(d_6\), 400 MHz) \(\delta\): 12.52 (s, 1H, -OH), 9.85 (s, 1H, -NH), 7.91 (dd, 2H, Ar-H), 7.75 (m, 1H, Ar-H), 7.23 (m,5H, Ar-H), 4.25 (q, 2H, -CH\(_2\)), 2.76 (t, 2H, -CH\(_2\)), 2.53 (t, 2H, -CH\(_2\)), 1.94 (m, 2H, -CH\(_2\)), 1.1 (t, 3H, -CH\(_3\)). MS (M+1) m/z: 498.14. Anal. Calcd. for C\(_{25}\)H\(_{21}\)F\(_2\)N\(_3\)O\(_6\) (%): C-60.36, H-4.26, F-7.64, N-8.45, O-9.30. Found C-60.38, H-4.29, F-7.60, N-8.41, O-9.27.
2.3.6. Synthesis of ethyl 2-(1-(4-tert-butylbenzamido)cyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate (IXe)

The product obtained was white solid from ethyl 2-(1-aminocyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate VII (0.1 g, 0.28 mmol), 4-tert-butyl benzoyl chloride (0.055 g, 0.28 mmol) and triethylamine (0.085 g, 0.84 mmol). IR (KBr, cm⁻¹): 3462, 2955, 2848, 2358, 1669, and 1045. ¹H NMR (DMSO-d₆, 400 MHz) δ: 12.56 (s, 1H, -OH), 10.25 (s, 1H, -NH), 8.88 (d, 2H, Ar-H), 7.87 (d, 2H, Ar-H), 7.44-7.50 (m, 5H, Ar-H), 4.22 (q, 2H, -CH₂), 2.79 (t, 2H, -CH₂), 2.50 (t, 2H, -CH₂), 1.96 (m, 2H, CH₂), 1.29 (s, 9H, -(CH₃)₃), 1.07 (t, 3H, -CH₃). MS (M+1) m/z: 518.22. Anal. Calcd. for C₂₉H₃₁N₃O₆ (%): C-67.30, H-6.30, N-8.12, O-18.55. Found C-67.47, H-3.35, N-8.9, O-18.52.

2.3.7. Synthesis of ethyl 2-(1-(3-bromobenzamido)cyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate (IXf)

The product obtained was white solid from ethyl 2-(1-aminocyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate VII (0.1 g, 0.28 mmol), 3-bromo benzoyl chloride (0.061 g, 0.28 mmol) and triethylamine (0.085 g, 0.84 mmol). IR (KBr, cm⁻¹): 3451, 2956, 2854, 2362, 1672, 1046, 763. ¹H NMR (DMSO-d₆, 400 MHz) δ: 12.95 (s, 1H, -OH), 9.20 (s, 1H, -NH), 8.24 (s, 1H, Ar-H), 8.06 (d, 1H, Ar-H), 7.88 (t, 1H, Ar-H), 7.61 (m, 5H, Ar-H), 7.48 (d, 1H, Ar-H), 4.21 (q, 2H, -CH₂), 2.78 (t, 2H, -CH₂), 2.48 (t, 2H, -CH₂), 1.95 (m, 2H, -CH₂), 1.01 (t, 3H, -CH₃). MS (M+1) m/z: 541.07. Anal. Calcd. for C₂₅H₂₂BrN₃O₆ (%): C-55.57, H-4.10, Br-14.79, N-7.78, O-17.77. Found C-55.63, H-4.15, Br-14.74, N-7.75, O-17.71.
2.3.8. Synthesis of ethyl 2-((1-(4-chlorobenzamido)cyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate (IXg)

The product obtained was white solid from ethyl 2-(1-aminocyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate VII (0.1 g, 0.28 mmol), 4-chlorobenzoyl chloride (0.049 g, 0.28 mmol) and triethylamine (0.085 g, 0.84 mmol). IR (KBr, cm\(^{-1}\)): 3458, 2951, 2836, 2355, 1668, 723. \(^1\)H NMR (DMSO-\(d_6\), 400 MHz) \(\delta\) : 12.43 (s, 1H, -OH), 10.21 (s, 1H, -NH), 8.91 (d, 2H, Ar-H), 7.93 (d, 2H, Ar-H), 7.44-7.56 (m, 5H, Ar-H), 4.29 (q, 2H, -CH\(_2\)), 2.73 (t, 2H, -CH\(_2\)), 2.48 (t, 2H, -CH\(_2\)), 1.94 (m, 2H, -CH\(_2\)), 1.05 (t, 3H, -CH\(_3\)). MS (M+1) m/z: 496.89. Anal. Calcd. for C\(_{25}\)H\(_{22}\)ClN\(_3\)O\(_6\) (%): C-60.55, H-4.47, Cl-7.15, N-8.47, O-19.36. Found C-60.59, H-4.50, Cl-7.11, N-8.42, O-19.32.

2.3.9. Synthesis of ethyl 2-(1-(benzamido)cyclobutyl)-5-(benzoyloxy)-6-hydroxy pyrimidine-4-carboxylate (IXh)

The product obtained was white solid from ethyl 2-(1-aminocyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate VII (0.1 g, 0.28 mmol), benzoyl chloride (0.039 g, 0.28 mmol) and triethylamine (0.085 g, 0.84 mmol). IR (KBr, cm\(^{-1}\)): 3450, 2960, 2849, 2356, 1679. \(^1\)H NMR (DMSO-\(d_6\), 400 MHz) \(\delta\) : 12.79 (s, 1H, -OH), 9.31 (s, 1H, -NH), 7.52-7.85 (m, 10H, Ar-H), 4.25 (q, 2H, -CH\(_2\)), 2.80 (t, 2H, -CH\(_2\)), 2.49 (t, 2H, -CH\(_2\)), 2.02 (m, 2H, -CH\(_2\)), 1.06 (t, 3H, -CH\(_3\)). MS (M+1) m/z: 462.26. Anal. Calcd. for C\(_{25}\)H\(_{23}\)N\(_3\)O\(_6\) (%): C-65.07, H-5.02, N-9.11, O-20.80. Found C-65.12, H-5.07, N-9.08, O-20.76.
2.3.10. Synthesis of ethyl 2-(1-(3-nitrobenzamido)cyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate (IXi)

The product obtained was white solid from ethyl 2-(1-aminocyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate VII (0.1 g, 0.28 mmol), 3-nitrobenzoyl chloride (0.052 g, 0.28 mmol) and triethylamine (0.085 g, 0.84 mmol). IR (KBr, cm⁻¹): 3462, 2941, 2863, 2358, 1685, and 1061. ¹H NMR (DMSO-d6, 400 MHz) δ: 12.70 (s, 1H, -OH), 9.25 (s, 1H, -NH), 8.22 (s, 1H, Ar-H), 8.12 (d, 1H, Ar-H), 7.91 (t, 1H, Ar-H), 7.63 (m, 5H, Ar-H), 7.43 (d, 1H, Ar-H), 4.24 (q, 2H, -CH₂), 2.81 (t, 2H, -CH₂), 2.50 (t, 2H, -CH₂), 1.98 (m, 2H, -CH₂), 1.12 (m, 3H, -CH₃). MS (M+1) m/z: 478.34. Anal. Calcd. for C₂₅H₂₂N₄O₈ (%): C-59.29, H-4.38, N-11.06, O-25.27. Found C-59.33, H-4.42, N-11.01, O-25.22.

2.3.11. Synthesis of ethyl 2-(1-(2,4-dichlorobenzamido)cyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate (IXj)

The product obtained was white solid from ethyl-2(1-aminocyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate VII (0.1 g, 0.28 mmol), 2,4-dichloro benzoyl chloride (0.06 g, 0.28 mmol) and triethyl amine (0.08 g, 0.28 mmol). IR (KBr, cm⁻¹): 3461, 2965, 2842, 2349, 1460, 720. ¹H NMR (DMSO-d6, 400 MHz) δ: 12.90 (s, 1H, -OH), 9.9 (s, 1H, -NH), 8.03 (s, 1H, Ar-H), 7.92 (d, 1H, Ar-H), 7.71 (d, 1H, Ar-H), 7.35 (m, 5H, Ar-H), 4.31 (q, 2H, -CH₂), 2.71 (t, 2H, -CH₂), 2.57 (t, 2H, -CH₂), 1.95 (m, 2H, -CH₂), 1.08 (t, 3H, -CH₃). MS (M+1) m/z: 530.14. Anal. Calcd. for C₂₅H₂₂N₄O₈ (%): C-59.29, H-4.38, N-11.06. Found C-59.33, H-4.42, N-11.02.
2.4. Synthesis and characterization of a novel class of 2-amino pyrimidine derivatives

2.4.1. General procedure for the synthesis of 2-aminopyrimidine derivatives XII(a-j)

A solution of 2-aminopyrimidine X (1.0 eq) in tetrahydrofuran was taken and cooled to 0-5 °C in ice bath. Isobutyl chloroformate (1.5 eq) was added and stirred for 10 min. Triethyl amine (3.0 eq) was added to the cold mixture and stirred for 10 min and then the respective acid derivatives (1.0 eq) were added, the mixture was stirred for 5-6 hr. The progress of the reaction was monitored by TLC. Upon completion, water was added to reaction mixture and extracted with ethyl acetate. The combined organic layer was washed with 10% ammonium chloride solution followed by water wash and dried with anhydrous sodium sulphate. The solvent was evaporated and the crude product obtained was purified by column chromatography over silica gel (60-120 mesh) using dichloromethane: methanol (9:1) as eluent.

Reagents and conditions:

i) Isobutyl chloroformate, triethylamine, 0 °C-rt, 5 h.
2.4.2. Synthesis of \( N'\)-Fmoc-2-amino-3-(4'-ethyl-2'-methyl-biphenyl-4-yl)-N-(pyrimidin-2-yl)propanamide (XIIa)

The product obtained was cream white solid from 2-amino pyrimidine X (0.10 g, 1.05 mmol), \( N'\)-Fmoc-2-amino-3-(4'-ethyl-2'-methyl-biphenyl-4-yl)propanoic acid (0.53 g, 1.05 mmol), isobutyl chloroformate (0.22 g, 1.58 mmol), triethyl amine (0.32 g, 3.16 mmol) and tetrahydrofuran (2 ml). IR (KBr, cm\(^{-1}\)): 3467, 2965, 2245, 1687, 899. \(^1\)H NMR (DMSO-\(d_6\), 300 MHz) \( \delta \): 9.95 (br s, 1H, -NH), 9.85 (br s, 1H, -NH), 7.92 (m, 2H, Ar-H), 7.84 (m, 3H, Ar-H), 7.74 (t, 2H, Ar-H), 7.45 (m, 5H, Ar-H), 7.35 (m, 3H, Ar-H), 7.05 (m, 3H, Ar-H), 4.95 (d, 2H, -CH\(_2\)), 4.41 (d, 2H, -CH\(_2\)), 3.47 (s, 3H, -OCH\(_3\)), 3.25 (t, 1H, -CH), 3.15 (s, 1H, -CH), 3.05 (q, 2H, -CH\(_2\)), 2.05 (t, 3H, -CH\(_3\)). MS (M+1) m/z: 543.4. Anal. Calcd. for C\(_{37}\)H\(_{34}\)N\(_4\)O\(_3\) (%): C-76.27, H-5.88, N-9.62, O-8.24. Found C-76.32, H-5.91, N-9.57, O-8.21.
2.4.3. Synthesis of 6-fluoro-3,4-dihydro-N-(pyrimidin-2-yl)-2H-chromene-2-carboxamide (XIIb)

The product obtained was light yellow solid from 2-amino pyrimidine X (0.10 g, 1.05 mmol), 6-fluoro-3,4-dihydro-2H-chromene-2-carboxylic acid (0.20 g, 1.05 mmol), isobutyl chloroformate (0.22 g, 1.58 mmol), triethyl amine (0.32 g, 3.16 mmol) and tetrahydrofuran (2 ml). IR (KBr, cm\(^{-1}\)): 3477, 2955, 2345, 1690, 801. \(^1\)H NMR (DMSO-\(d_6\), 300 MHz) \(\delta\): 10.1 (br s, 1H, -NH), 8.12 (d, 1H, Ar-H), 6.92 (m, 3H, Ar-H), 6.88 (t, 1H, Ar-H), 4.76 (t, 1H, -CH), 2.78 (m, 2H, CH\(_2\)), 2.1 (t, 2H, CH\(_2\)). MS (M+1) m/z: 543.3. Anal. Calcd. for C\(_{14}\)H\(_{12}\)FN\(_3\)O\(_2\) (%): C - 61.53, H - 4.43, F - 6.95, N - 15.38, O - 11.71. Found C - 61.56, H - 4.47, F - 6.92, N - 15.33, O - 11.68.

2.4.4. Synthesis of 2-((Z)-5-((5-(4-chlorophenyl) furan-2-yl) methylene)-4-oxo-2-thioxothiazolidin-3-yl)-N-(pyrimidin-2-yl) acetamide (XIIc)

The product obtained was white solid from 2-amino pyrimidine X (0.10 g, 1.05 mmol), 2-((3-(5-(4-chlorophenyl) furan-2-yl)-2-oxo-5-thioxopyrrolidin-1-yl) acetic acid (0.36 g, 1.05 mmol), isobutyl chloroformate (0.22 g, 1.58 mmol), triethyl amine (0.32 g, 3.16 mmol) and tetrahydrofuran (2 ml). IR (KBr, cm\(^{-1}\)): 3427, 2925, 2245, 1677, 790. \(^1\)H NMR (DMSO-\(d_6\), 300 MHz) \(\delta\): 9.86 (br s, 1H, -NH), 7.76 (d, 2H, Ar-H), 7.75 (d, 2H, Ar-H), 7.05 (s, 1H, -CH), 7.03 (m, 3H, Ar-H), 6.97 (d, 1H, Ar-H), 6.88 (d, 1H, Ar-H), 4.51 (s, 2H, CH\(_2\)). MS (M+1) m/z: 566.4. Anal. Calcd. for C\(_{20}\)H\(_{13}\)ClN\(_4\)O\(_3\)S\(_2\) (%): C - 52.57, H - 2.87, Cl - 7.76, N - 12.26, O - 10.50, S - 14.04. Found C - 52.61, H - 2.92, Cl - 7.71, N - 12.22, O - 10.46, S - 14.01.

2.4.5. Synthesis of 2-(4-oxo-2-thioxothiazolidin-3-yl)-N-(pyrimidin-2-yl) acetamide (XIIId)

The product obtained was white solid from 2-amino pyrimidine X (0.10 g, 1.05 mmol), 2-(4-oxo-2-thioxothiazolidin-3-yl) acetic acid (0.20 g, 1.05 mmol),
isobutyl chloroformate (0.22 g, 1.58 mmol), triethyl amine (0.32 g, 3.16 mmol) and
tetrahydrofuran (2 ml). IR (KBr, cm⁻¹): 3407, 2935, 2145, 1677, 759.¹H NMR
(DMSO-d₆, 300 MHz) δ: 9.55 (br s, 1H, -NH), 7.45 (m, 2H, Ar-H), 7.35 (d, 1H, Ar-
H), 4.52 (s, 2H, -CH₂), 3.1 (s, 2H, -CH₂). MS (M+1) m/z: 532.6. Anal. Calcd. for
C₉H₈N₄O₂S₂ (%): C - 40.29, H - 3.01, N - 20.88, O - 11.93, S - 23.90.

2.4.6. Synthesis of 5-formyl-2-methoxy-N-(pyrimidin-2-yl) benzamide (XIIe)

The product obtained was white solid from 2-amino pyrimidine X (0.10 g, 1.05 mmol), 5-formyl-2-methoxybenzoic acid (0.18 g, 1.05 mmol), isobutyl chloroformate (0.22 g, 1.58 mmol), triethyl amine (0.32 g, 3.16 mmol) and
tetrahydrofuran (2 ml). IR (KBr, cm⁻¹): 3457, 2905, 2345, 1697, 992.¹H NMR
(DMSO-d₆, 300 MHz) δ: 9.58 (br s, 1H, -NH), 9.3 (s, 1H, -CHO), 7.78 (d, 1H, Ar-H), 7.75 (d, 1H, Ar-H), 7.50 (m, 2H, Ar-H), 7.32 (d, 1H, Ar-H), 7.05 (d, 1H, Ar-H), 3.2 (s, 3H, -OCH₃). MS (M+1) m/z: 543.2. Anal. Calcd. for C₁₃H₁₁N₃O₃ (%): C - 60.70, H - 4.31, N - 16.33, O - 18.66. Found C - 60.75, H - 4.36, N - 16.29, O - 18.61.

2.4.7. Synthesis of tert-butyl 1-(pyrimidin-2-ylcarbamoyl)-2-(4-hydroxyphenyl)
ethylcarbamate (XIIf)

The product obtained was white solid from 2-amino pyrimidine X (0.10 g, 1.05 mmol), N-Boc-2-amino-3-(4-hydroxyphenyl)propanoic acid (0.29 g, 1.05 mmol), isobutyl chloroformate (0.22 g, 1.58 mmol), triethyl amine (0.32 g, 3.16 mmol) and
tetrahydrofuran (2 ml). IR (KBr, cm⁻¹): 3437, 2925, 2545, 1677, 769.¹H NMR
(DMSO-d₆, 300 MHz) δ: 9.92 (br s, 1H, -NH), 9.53 (br s, 1H, -NH), 7.88 (s, 1H, - OH), 7.78 (d, 2H, Ar-H), 7.52 (d, 1H, Ar-H), 7.22 (d, 2H, Ar-H), 7.10 (d, 2H, Ar-H), 4.55 (d, 2H, -CH₂), 3.22 (t, 1H, -CH), 1.48 (s, 9H, -(CH₃)₃). MS (M+1) m/z: 554.5.
2.4.8. Synthesis of tert-butyl 2-(pyrimidin-2-ylcarbamoyl)-1H-pyrrole-1-carboxylate (XIIg)

The product obtained was white solid from 2-amino pyrimidine X (0.10 g, 1.05 mmol), N-Bocpyrrole 2-carboxylic acid (0.22 g, 1.05 mmol), isobutyl chloroformate (0.22 g, 1.58 mmol), triethyl amine (0.32 g, 3.16 mmol) and tetrahydrofuran (2 ml). IR (KBr, cm\(^{-1}\)): 3447, 2965, 2545, 1687, 1224, 788. \(^1\)H NMR (DMSO-\(d_6\), 300 MHz) \(\delta\): 9.45 (br s, 1H, -NH), 7.76 (d, 2H, Ar-H), 7.45 (d, 1H, Ar-H), 7.02 (d, 1H, Ar-H), 6.92 (d, 1H, Ar-H), 1.49 (s, 9H, (CH\(_3\))\(_3\)). MS (M+1) m/z: 498.6. Anal. Calcd. for C\(_{18}\)H\(_{22}\)N\(_4\)O\(_4\) (%): C-60.32, H-6.19, N-15.63, O-17.86. Found C-60.36, H-6.23, N-15.59, O-17.81.

2.4.9. Synthesis of N-(pyrimidin-2-yl) benzofuran-2-carboxamide (XIIh)

The product obtained was white solid from 2-amino pyrimidine X (0.10 g, 1.05 mmol), benzofuran-2-carboxylic acid (0.17 g, 1.05 mmol), isobutyl chloroformate (0.22 g, 1.58 mmol), triethyl amine (0.32 g, 3.16 mmol) and tetrahydrofuran (2 ml). IR (KBr, cm\(^{-1}\)): 3457, 2925, 2245, 1687, 790. \(^1\)H NMR (DMSO-\(d_6\), 300 MHz) \(\delta\): 9.52 (br s, 1H, -NH), 7.55 (d, 2H, Ar-H), 7.46 (d, 2H, Ar-H), 7.35 (d, 2H, Ar-H), 7.22 (d, 1H, Ar-H), 7.02 (d, 1H, Ar-H). MS (M+1) m/z: 436.1. Anal. Calcd. for C\(_{14}\)H\(_{16}\)N\(_3\)O\(_2\) (%): C-65.27, H-3.79, N-17.56, O-13.38. Found C-65.30, H-3.82, N-17.51, O-13.33.
2.4.10. Synthesis of tert-butyl 4-(pyrimidin-2-ylcarbamoyl)piperidine-1-carboxylate (XIIi)

The product obtained was white solid from 2-amino pyrimidine X (0.10 g, 1.05 mmol), 1-(tert-butoxycarbonyl) piperidine-4-carboxylic acid (0.24 g, 1.05 mmol), isobutyl chloroformate (0.22 g, 1.58 mmol), triethyl amine (0.32 g, 3.16 mmol) and tetrahydrofuran (2 ml). IR (KBr, cm\(^{-1}\)): 3367, 2965, 2245, 1677, 1223, 994. \(^1\)H NMR (DMSO-\(d_6\), 300 MHz) \(\delta\): 9.55 (br s, 1H, -NH), 7.47 (d, 2H, Ar-H), 7.30 (d, 1H, Ar-H), 3.1 (m, 1H, -CH), 2.50 (m, 4H, -(CH\(_2\))\(_2\)), 2.25 (m, 4H, -(CH\(_2\))\(_2\)) 1.49(s, 9H, -(CH\(_3\))\(_3\)). MS (M+1) m/z: 512.2. Anal. Calcd. for C\(_{15}\)H\(_{22}\)N\(_4\)O\(_3\) (%): C-58.81, H-7.24, N-18.29, O-15.67. Found C-58.85, H-7.28, N-18.24, O-15.63.

2.4.11. Synthesis of tert-butyl 5-(pyrimidin-2-ylcarbamoyl)-1H-indole-1-carboxylate (XIIj)

The product obtained was white solid from 2-amino pyrimidine X (0.10 g, 1.05 mmol), 1-(tert-butoxycarbonyl)-1H-indole-5-carboxylic acid (0.27 g, 1.05 mmol), isobutyl chloroformate (0.22 g, 1.58 mmol), triethyl amine (0.32 g, 3.16 mmol) and tetrahydrofuran (2 ml). IR (KBr, cm\(^{-1}\)): 3387, 2965, 2545, 1647, 1223, 804. \(^1\)H NMR (DMSO-\(d_6\), 300 MHz) \(\delta\): 9.49 (br s, 1H, -NH), 7.67 (d, 1H, Ar-H), 7.63 (s, 1H, Ar-H), 7.55 (m, 2H, Ar-H), 7.45 (d, 1H, Ar-H), 7.35 (1H, d, Ar-H), 7.05 (d, 2H, Ar-H), 1.45(s, 9H, -(CH\(_3\))\(_3\)). MS (M+1) m/z: 339.5. Anal. Calcd. for C\(_{18}\)H\(_{18}\)N\(_4\)O\(_3\) (%): C-63.89, H-5.36, N-16.56, O-14.19.
Table 3. Chemical structure, yield molecular weight and melting point of the synthesized compounds XII(a-j)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Structure</th>
<th>Mol. wt</th>
<th>Yield</th>
<th>M.P (°C)</th>
</tr>
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<tr>
<td>XIIa</td>
<td><img src="image" alt="Structure XIIa" /></td>
<td>542</td>
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<td>180-182</td>
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<tr>
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<td><img src="image" alt="Structure XIIb" /></td>
<td>542</td>
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<td>186-188</td>
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<tr>
<td>XIIc</td>
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<td>566</td>
<td>86%</td>
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</tr>
<tr>
<td>XIId</td>
<td><img src="image" alt="Structure XIId" /></td>
<td>531</td>
<td>80%</td>
<td>194-196</td>
</tr>
<tr>
<td>XIIe</td>
<td><img src="image" alt="Structure XIIe" /></td>
<td>542</td>
<td>78%</td>
<td>197-199</td>
</tr>
<tr>
<td>XIIf</td>
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<td>75%</td>
<td>200-202</td>
</tr>
<tr>
<td>XIIg</td>
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<td>497</td>
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<td>204-206</td>
</tr>
<tr>
<td>XIIh</td>
<td><img src="image" alt="Structure XIIh" /></td>
<td>435</td>
<td>79%</td>
<td>208-210</td>
</tr>
<tr>
<td>XIIi</td>
<td><img src="image" alt="Structure XIIi" /></td>
<td>511</td>
<td>76%</td>
<td>210-212</td>
</tr>
<tr>
<td>XIIj</td>
<td><img src="image" alt="Structure XIIj" /></td>
<td>338</td>
<td>78%</td>
<td>212-214</td>
</tr>
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</table>
2.5. Results and discussion

Synthesis of $N$-substituted ethyl 2-(1-aminocyclobutyl)-5-(benzoyloxy)-6-hydroxypyrimidine-4-carboxylate begins with the commercially available cyclobutanone, followed by cyanation and amination using cheap chemicals. $N$-amino protection was done by commonly using protecting group benzyloxy carbonyl, one pot oximation and amination on nitrile was done by well known method using hydroxylamine hydrochloride and cyclisation of pyrimidine ring was performed by novel method. The present report is focused on several derivatives of bio-applicable substituted pyrimidines. The cycloaddition with sulfonyl chlorides and acid chlorides gave exclusively 2-substituted pyrimidine consisting of regioselectivity as major products. In the synthesis of another series of pyrimidine amides, activation acid group done by commonly using coupling reagent isobutyrylchloroformate to form incit anhydride, then anhydride was made to react with amine to form amide. All the compounds were purified through column chromatography by using dichloromethane and methanol as solvent systems. Series of substituted pyrimidines were obtained in very good yields in the ratio of 65-85% with a purity of 80-85%. In the present work, all the synthesized compounds were characterized by the spectral analysis (IR, $^1$H NMR), and finally by elemental analysis.

2.5.1. IR spectral data

Absorption in the region is confirmed to molecular species for which small energy differences exit between the vibrational and rotational states. Majority of applications of IR measurements have been confined in the region between 400-4000 cm$^{-1}$. Skeletal vibration covers in the region of 1400-700 cm$^{-1}$ and the bonds in this region are referred to as ‘fingerprint band’. This region is very sensitive to slight
changes in the structure of compound. A given structural moiety is often recognized merely by the appearance of the spot of the spectrum. This region forms an excellent region for the identification of compounds with the help of spectra-structure correlation charts.

The IR spectra of all pyrimidine derivatives were recorded on KBr pellets in the range of 4000-400 cm\(^{-1}\) and spectral data were given. Peak observed at 3303 cm\(^{-1}\) for primary amine and absence of peak at 1650 cm\(^{-1}\) in the product IR spectra confirms the formation of isocyanocyclobutanamine. A broad band in the region of 3300-3200 cm\(^{-1}\) was observed for the -OH group stretching in case of oximes. And also, we observed a peak in the region of 1660-1690 cm\(^{-1}\) i.e., for CH=N stretching, which confirms the formation of oxime. For substituted pyrimidine, the bands in the range of 3075-2865 cm\(^{-1}\) might be assigned to the -CH stretching of the aromatic ring system. The bands observed at 1392-1256 cm\(^{-1}\) might be assigned for C-N aromatic stretching vibrations. The signals in the range of 1605-1456 cm\(^{-1}\) might be assigned to the ring stretching mode of -C=N of the pyrimidine moiety.

2.5.2. \(^1\)H NMR Spectral Analysis

\(^1\)H NMR spectra of the sulfonamide and amide derivatives of pyrimidines bearing multifunctional moieties such as methyl, benzyl, nitrobenzyl, tertiary butyl, phenoxy, halobenzyl, tolyl etc, showed a very good spectral values. A sharp singlet was observed for -O-CH\(_3\) (methoxy) group between the range of 2.70-3.20 ppm and an important bond for the formation of amide that is -NH, a sharp singlet between the range of 9.2-10.7 ppm was noted. The NMR values we noticed for all the synthesized compounds were in good agreement with their respective standard values.
2.6. Conclusion

In conclusion, we have synthesized and characterized all the substituted pyrimidine derivatives with high purity and good yield. In addition to this, we have followed feasible, cheaper and environmentally benign protocol for the synthesis of pyrimidine substituted amides, sulfonamides, benzamides, acetamides and other substituted amides bearing potent bioactive heterocycles. All the synthesized compounds were characterized by IR, $^1$H NMR, Mass spectrometer and elemental analysis.
$^1$H NMR Spectrum of the Synthesized Compounds

$^1$H NMR Spectrum of Benzyl 1-cyanocyclobutylcarbamate (III)

$^1$H NMR Spectrum of Benzyl 1-amidinocyclobutylcarbamate (IV)
1H NMR Spectrum of benzyl 1-(4-ethoxycarbonyl)-5,6-dihydroxy pyrimidin-2-yl)cyclobutylcarbamate (V)

1H NMR Spectrum of benzyl 1-(4-ethoxycarbonyl)-5-(benzoyloxy)-6-hydroxy pyrimidin-2-yl(cyclobutyl carbamate (VI)
$^1$H NMR Spectrum of ethyl 2-((1-4-nitrobenzenesulfonylamino) cyclobutyl)-5-(benzoyloxy)-6-hydroxy pyrimidine-4-carboxylate (VIIIa)

$^1$H NMR Spectrum of ethyl 2-((1-3-nitrobenzenesulfonylamino) cyclobutyl)-5-(benzoyloxy)-6-hydroxy pyrimidine-4-carboxylate (VIIIb)
$^1$H NMR Spectrum of ethyl 2-(1-nitrobenzenesulfonylamino)cyclobutyl) - 5-(benzoyloxy)-6-hydroxy pyrimidine-4-carboxylate (VIIIc)

$^1$H NMR Spectrum of ethyl 2-(1-(3,5-dichlorobenzenesulfonylamino)cyclobutyl)-5-(benzoyloxy)-6-hydroxy pyrimidine-4-carboxylate (VIIIe)
1H NMR Spectrum of ethyl 2-(1-benzensulfonylamino)cyclobutyl)-5-(benzoyloxy)-6-hydroxy pyrimidine-4-carboxylate (VIIIf).

1H NMR Spectrum of ethyl 2-(1-toluylsulfonylamino) cyclobutyl)-5-(benzoyloxy)-6-hydroxy pyrimidine-4-carboxylate (VIIIg).
$^1$H NMR Spectrum of ethyl 2-(1-tert-butylbenzenesulfonylamino) cyclobutyl-5- (benzoyloxy)-6- hydroxyl pyrimidine-4-carboxylate (VIIIh).

$^1$H NMR Spectrum of ethyl 2-(1-methanesulfonylamino) cyclobutyl)-5- (benzoyloxy)-6-hydroxy pyrimidine-4-carboxylate (VIIIi).
2.7. Reference:

41. S. Gabriel, J. Colman, *Ber.*, 1904, 37, 3643.


