Chapter -4

Synthesis of Pyrimidine derivatives from Coumarin moiety.
Pyrimidine itself is not found in nature but substituted pyrimidines and their derivatives containing pyrimidine moiety are widely distributed in nature. The six membered aromatic rings with two nitrogen atoms are called diazines. Using the terminology of benzenoid compounds, these may be ortho i.e. (1,2), meta (1,3), or para (1,4) each other. These three compounds known by their trivial names, pyridazine (1), pyrimidine (2) and pyrazine (3). Actually, in early systematic study of the ring was started with the work of Pinner\(^1\) in 1884, who named 1,3 diazine (2) as pyrimidine.

\[
\begin{array}{ccc}
1 & 2 & 3 \\
4 & 5 & 6
\end{array}
\]

Pyrimidine is the parent compound of a large group of heterocyclic compounds, which are having much attraction in the most important biological polymers such as RNA and DNA, and also in the pharmaceutical industries. The compounds belonging to this category are being known as breakdown products of uric acid at an early decade in the history of organic chemistry.

A research paper entitled "Synthesis, anti-microbial and cytotoxic activity of Pyrimidine-based compounds containing a coumarin moiety" has been communicated to Archiv der Pharmazie, 2009.
The pyrimidine entity is one of the most prominent structures found in nucleic acid chemistry. Pyrimidine derivatives including uracil, thymine, cytosine, adenine, and guanine are fundamental building blocks for deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). Vitamin B₁ (thiamine) (4) is a well known example of a naturally occurring pyrimidine that is encountered in our daily lives. Synthetic pyrimidine containing compounds also occupy a prominent place in the pharmaceutical arena. Pyrimethamine (5) and Trimethoprim (6) are two representative pyrimidine containing chemotherapeutics. Pyrimethamine is a dihydrofolate reductase inhibitor; effective for toxoplasmosis in combination with a sulfonamide; whereas Trimethoprim is an anti-malarial drug, widely used as a general systemic anti-bacterial agent in combination with sulfamethoxazole.

During the last two decades a great deal of research work in the drug development area has been focused on the development of several pyrimidine derivatives as chemotherapeutic agents and also found wide
clinical applications. The pyrimidine derivatives play a vital role in many biological processes. In the recent years much attention has been focused on the synthesis of pyrimidine scaffold, because of their biological and medicinal importance.

Kemnitzer et al., have synthesized a series of 4-anilino-N-methylthieno[3,2-d]pyrimidines and 4-anilino-N-methylthieno[2,3-d]pyrimidines as potent apoptosis inducers. Compounds (7) and (8) were most potent with EC\(_{50}\) values of 0.008 and 0.004 \(\mu\)M in T47D human breast cancer cells, respectively. Compound (7) was found to be highly active in the MX-1 breast cancer model. Functionally, compounds (7) and (8) both induced apoptosis through inhibition of tubulin polymerization.\(^2\)

![Chemical structures of compounds (7) and (8)](attachment)

A series of 2,4,6-trisubstituted pyrimidines have been synthesized and screened for their \textit{in vitro} and \textit{in vivo} anti-leishmanial activity against \textit{Leishmania donovani}. All the synthesized compounds have shown promising inhibition of 80-100\% at 10 \(\mu\)g/ml against promastigotes and IC\(_{50}\) in the range of 0.89-9.68 \(\mu\)g/ml against amastigotes. The compounds (9-11) have shown better selectivity index in comparison to pentamidine and sodium stibogluconate. As a consequence, these hybrid molecules can be
served as promising prototypes for the development of potent anti-leishmanial agents.³

Deshmukh et al., have developed a simple and efficient approach towards one step synthesis of 2-amino-5-cyano-6-hydroxy-4-aryl pyrimidines (12) using three component condensation of aromatic aldehydes, ethyl cyanoacetate and guanidine hydrochloride in alkaline ethanol. The synthesized compounds were evaluated for their anti-bacterial activity against Gram-positive and Gram-negative bacteria. The anti-bacterial study of the synthesized compounds showed good to excellent activity against tested Gram-positive and Gram-negative bacteria. Among these, interestingly, the 2-amino-5-cyano-6-hydroxy-4-phenyl pyrimidine found to be selectively active against Gram-positive bacteria.⁴
A series of novel thiazolidin-4-ones bearing a hydrophobic substituent at 5-position on the 4,6-dimethylpyrimidine ring at N-3 have been synthesized by Hua Chen et al., in good yields of 60.1-85.3% using microwave-assisted one pot protocol with the combination of dicyclohexylcarbonimide (DCC) as the promoter and evaluated as HIV-1 reverse transcriptase inhibitors. The results of *in vitro* HIV-1 RT kit assay showed that some of the newly synthesized compounds effectively inhibit RT activity. Among them, compounds (13) and (14) where ethyl group existed at 5-position on N-3 pyrimidine ring were the best ones with the IC$_{50}$ value of 0.26 μM and 0.23 μM, respectively.$^5$

![Chemical Structures](image)

Faizul Azam et al., have synthesized a series of 3-phenyl/ethyl-2-thioxo-2,3-dihydrothiazolo[4,5-d]pyrimidin-7-yl urea and thiourea derivatives (15). All the compounds have been evaluated for their anti-parkinsonian activity in catalepsy induced by haloperidol in mice. A majority of the compounds exhibited significant anti-parkinsonian activity after intraperitoneal administration. The most active compound carries methoxy group at 2-position of the phenyl ring. Some of the potent compounds were selected for biochemical estimations of malondialdehyde, glutathione, superoxide dismutase and glutathione peroxidase from brain homogenate to highlight the neuroprotective properties associated with them.$^6$
A series of thieno[3,2-\textit{d}]pyrimidine derivatives have been synthesized by Folkes \textit{et al.}, and evaluated as inhibitors of PI3K. Compound (16), which has been extensively profiled and shown to be a potent and highly selective inhibitor of members of Class I PI3K. The compound shows potent growth inhibitory activity \textit{in vitro} in a range of human tumor cell lines and exhibits a strong inhibitory effect on the growth of human U87MG glioblastoma xenografts in athymic mice. Compound (16) demonstrates an acceptable pharmaceutical profile and is currently being evaluated in human clinical trials for the treatment of cancer.\textsuperscript{7}

\begin{center}
\includegraphics[width=0.5\textwidth]{image.png}
\end{center}

Huang \textit{et al.}, have synthesized a series of pyrido[2,3-\textit{d}]pyrimidin-5-ones and evaluated as inhibitors of the kinase domain of macrophage colony-stimulating factor-1 receptor (FMS). FMS inhibitors may be useful in treating rheumatoid arthritis and other chronic inflammatory diseases. Structure based optimization of the lead amide analogue (17) led to hydroxamate analogue (18), which possessed excellent potency and an
improved pharmacokinetic profile. During the chronic phase of streptococcal cell wall-induced arthritis in rats, compound (18) (10, 3 and 1 mg/kg) was highly effective at reversing established joint swelling. In an adjuvant-induced arthritis model in rats, (18) prevented joint swelling partially at 10 mg/kg. In this model, osteoclastogenesis and bone erosion were prevented by low doses (1 or 0.33 mg/kg) that had minimal impact on inflammation. These data underscore the potential of FMS inhibitors to prevent erosions and reduce symptoms in rheumatoid arthritis.8

Motta et al., have prepared a number of pyrazolo[3,4-d]pyrimidin-4-ones bearing either alkyl or arylalkyl substituents in position 2 of the nucleus and tested for their ability to inhibit adenosine deaminase (ADA) from bovine spleen. The 2-arylalkyl derivatives exhibited excellent inhibitory activity, showing $K_i$ values in the nanomolar/subnanomolar range. The most active compound, 1-{4-[(4-oxo-4,5-dihydropyrazolo[3,4-d]pyrimidin-2-yl)methyl]phenyl}-3-(4-(trifluoromethyl)phenyl)urea (19), was tested in rats with colitis induced by 2,4-dinitrobenzenesulfonic acid to assess its efficacy to attenuate bowel inflammation. The treatment with (19) induced a significant amelioration of both systemic and intestinal inflammatory alterations in animals with experimental colitis. Thus prospectively guiding the design of novel ADA inhibitors.9
Chhabria et al., have designed novel imidazo[1,2-c]pyrimidines (20). The designed molecules were synthesized by nucleophilic displacement of chloro group of various substituted 4-chloropyrimidines by ethanolamine followed by cyclisation of these 4-(2-hydroxyethyl)aminopyrimidines to imidazo[1,2-c]pyrimidines in good yield. All the compounds were screened for their anti-mycobacterial activity on Mycobacterium tuberculosis H37Rv strain by 1% proportion method. Some of the synthesized compounds exhibited potent antimycobacterial activity with MIC values in the range of 2-20 μg/mL.\textsuperscript{10}

B-Raf kinase plays a critical role in the Raf-MEK-ERK signaling pathway and inhibitors of B-Raf could be used in the treatment of melanomas, colorectal cancer, and other Ras related human cancers. A. Gopalsamy et al., have identified novel small molecule pyrazolo[1,5-a]pyrimidine derivatives (21) as B-Raf kinase inhibitors.\textsuperscript{11}
Kubota et al., have prepared a series of phenothiazine carboxylic acid derivatives having 6-amino-pyrimidine-2,4 (1H,3H)-dione moiety via an appropriate linker and evaluated for their affinity toward human histamine H1 receptor and Caco-2 cell permeability. Selected compounds were further evaluated for their oral antihistaminic activity in mice and bioavailability in rats. Finally, promising compounds were examined for their anti-inflammatory potential in mice OVA-induced biphasic cutaneous reaction model. Among the compounds tested, compound (22) showed both histamine H1-receptor antagonistic activity and anti-inflammatory activity in vivo model.12

Ravi Kumar et al., have synthesized twelve new 3-aryl/heteroaryl-5,7-dimethyl-1,2,4-triazolo[4,3-c]pyrimidines by the oxidation of pyrimidinylhydrazones of various aryl/heteroaryl aldehydes using 1.1 equiv. of iodobenzene diacetate (IBD) in dichloromethane. All the compounds tested in vitro for their anti-bacterial activity against two Gram-positive bacteria namely, Bacillus subtilis, Bacillus stearothermophilus and two Gram-negative bacteria Pseudomonas putida, Escherichia coli. Two compounds, namely 3-(2,4-dichlorophenyl)-5,7-dimethyl-1,2,4-triazolo [4,3-c]pyrimidine (23) and 3-(4-hydroxy-2-methoxyphenyl)-5,7-dimethyl-
1,2,4-triazolo[4,3-c]pyrimidine (24) were found to be equipotent or more potent than the commercially available antibiotics (chloramphenicol and streptomycin).\textsuperscript{13}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{images/23_24.png}
\caption{Structures of 23 and 24.}
\end{figure}

Yijun Deng \textit{et al.}, have synthesized a series of seven 2-amino-4-oxo-6-substituted thieno[2,3-\textit{d}]pyrimidines with bridge length variations (from 2 to 8 carbon atoms) as selective folate receptor (FR) \(\alpha\) and \(\beta\) substrates and as antitumor agents. Compounds (25-28) were potent growth inhibitors (IC\textsubscript{50} 4.7-334 nM) of human tumor cells (KB and IGROV1) that express FRs. In addition, compounds (25-28) inhibited the growth of Chinese hamster ovary (CHO) cells that expressed FRs but not the reduced folate carrier (RFC) or proton-coupled folate transporter (PCFT).\textsuperscript{14}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{images/25_28.png}
\caption{Structures of 25-28.}
\end{figure}

Said \textit{et al.}, have synthesized a series of pyrimidines and their derivatives using 2-amino-6-methyl-4-phenylnicotinonitrile as starting materials. The newly synthesized compounds were then screened pharmacologically for their anti-inflammatory and analgesic activities. Compounds (29) show remarkable activity comparable with those of diclofenac potassium and valdecoxib drugs.\textsuperscript{15}
Ahmeda et al., have synthesized pyrazolo [1,5-a]pyrimidines from sodium 3-hydroxy-1-(2-naphthyl)prop-2-en-1-one with the appropriate 3-aminopyrazoles in the presence of piperidine acetate. The synthesized compounds were screened for anti-tumor cytotoxicity using four different human cancer cell lines namely HepG\textsubscript{2} (liver carcinoma cell line), MCF\textsubscript{7} (breast carcinoma cell line), HCT\textsubscript{116} (colon carcinoma cell line), and HeLa (cervix carcinoma cell line). Compound (30) was more potent in inducing cytotoxicity against hepatocellular carcinoma cell line.\textsuperscript{16}

Franciszek Herold et al., have synthesized several new derivatives of 4-aryl-pyrido[1,2-c]pyrimidine possessing 3-(4-piperidyl)-1H-indole group (31) or its 5-methoxy derivative. The synthesized compounds possessed high to moderate binding activity to the 5-HT\textsubscript{1A} receptor as well as to the 5-HT transporter.\textsuperscript{17}
Shi et al., have synthesized a series of 4H-[1,2,5]oxadiazolo[3,4-d]pyrimidine-5,7-dione-1-oxide nucleosides (32) evaluated against vesicular stomatitis virus (VSV) in Wish cell. The anti-viral activities of all compounds were stronger than those of acyclovir, while their toxicities were similar to those of acyclovir.\(^{18}\)

![Chemical structure of 4H-[1,2,5]oxadiazolo[3,4-d]pyrimidine-5,7-dione-1-oxide nucleosides (32)](image)

Alloxan (33) was the first pyrimidine derivative to be isolated in 1818 by Brugnatelli\(^{19}\) by the oxidation of uric acid with nitric acid, is known for its diabetogenic action in a number of animals.\(^{20}\) The derivatives of barbituric acid (34), i.e oxygenated pyrimidines are perhaps the most widely used in medicines for example, Veronal (35), Luminal (36) are being used in the pharmaceutical industries as hypnotics while pentothal (37) is used as anesthetic.\(^{21}\)

![Chemical structures of pyrimidine derivatives](image)
Several important sulfa drugs are pyrimidine derivatives namely sulfadiazine (38), sulfamerazine (39) and sulfadimidine (40) are superior to many other sulfonamides and are being used in the acute urinary tract infections, cerebrospinal meningitis and for patients allergic to penicillin. Sulfonamide-trimethoprim combinations are being used extensively for opportunistic infections in patients with AIDS. Sulfadoxime (41), a short and intermediate acting sulfonamide with a half-life of 7-9 days is used for malarial prophylaxis. Sulfisomidine (42) with a half-life of 7 hrs is used as a combination therapy in veterinary medicine. Sulfadiazine (38), sulfamerazine (39) and sulfadimidine (40) possess good water solubility and therefore carry minimum risk kidney damage, which makes them safe even for patients with impaired renal functions.

Three pyrimidines are of considerable biological importance because of their relation to the nucleic acids, these are uracil (43), thymine (44) and cytosine (45). The purine ring system (46) obtained by the fusion of
pyrimidine and imidazole nuclei also is important because certain of its
derivatives, in particular adenine (47) and guanidine (48) are building blocks
of RNA and DNA.26

A variety of natural products such as alkaloids also contain the
pyrimidine ring system, and are included hypoxanthine (49) and xanthine
(50), which occur in the tea and caffeine (51) and theophylline (52) are the
constituents of tea leaves. Theobromine (53) is found in cocoa beans.26
The pteridine (54) ring system is also widely distributed in nature. The important growth factor folic acid, vitamin B$_{20}$ (55) is constructed of a pteridine ring, p-aminobenzoic acid and glutamic acid, i.e. pteroylglutamic acid. It is widely distributed and has been isolated from liver and yeast.$^{26}$

![Chemical structures](image_url)

Recent addition to the class of anti-cancer agents containing pyrimidine nucleus are tegafur$^{27}$ (56), mopidamol$^{28}$ (57), nimustine$^{29}$ (58), uramustine$^{30}$ (59), raltitrexed$^{31}$ (60) and trimetrixate glucuronate (61).$^{32}$
Considering the extensive applications of pyrimidine derivatives in the pharmaceutical industries, we have explored the synthesis of pyrimidine derivatives from 4-bromo methyl coumarin, which exhibits the enhanced activities owing to the incorporation of different pharmacophores into their structures. The study of such fused heterocyclic compounds is an attractive field for both academic interest and diverse applications in various industries. Thus, pyrimidine derivatives play a very important intervention in the field of pharmaceutical chemistry.

The work carried out during the present investigation has been described in Scheme-1.

The required 4-bromomethylcoumarins (1a-e) were prepared by Pechmann cyclisation of phenol and 4-bromoethylacetoacetate at 0-5 °C. The 4-bromoethylacetoacetate in turn was obtained by the bromination of ethylacetoacetate in dry ether at 0-5 °C.

4-bromomethylcoumarins (1a-e) were reacted with equimolar quantity of p-hydroxy benzaldehyde in presence of dry acetone and anhydrous K₂CO₃ to obtain 4-(2-oxo-2H-chromen-4-ylmethoxy)-benzaldehydes (2a-e). Attempted condensation of (2a-e) with acetophenone with 40% NaOH did not result the formation of chalcones (4a-e). A plausible explanation for this could be competition between the activated C₄-CH₂ and COCH₃ group for carbanion formation. Compounds (4a-e) were
prepared by a different method, in which the chalcone (4), prepared separately by the reaction of \( p \)-hydroxy benzaldehyde and acetophenone in the presence of 20% alcoholic NaOH solution, was treated with 4-bromomethyl coumarins (1a-e) in the presence of anhydrous K\(_2\)CO\(_3\) in dry acetone at room temperature to give the corresponding cinnamoyl derivatives (4a-e). Further the compounds (4a-e) were treated with urea, thiourea and guanidine hydrochloride in DMF to yield the corresponding pyrimidine derivatives [5-7(a-e)].

SCHEME-1
All reagents and solvents were used as obtained from the supplier or recrystallized/redistilled as necessary. The melting points of the products were determined by open capillaries on a Buchi apparatus and are uncorrected. The IR spectra were recorded on a Nicolet Impact-410 FT-IR Spectrophotometer, using KBr pellets. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker AC-300F 300 MHz spectrometer in DMSO/CDCl$_3$ using TMSi as internal standard with $^1$H resonant frequency of 300 MHz and $^{13}$C resonant frequency of 75 MHz. D$_2$O exchange was applied to confirm the assignment of the signals of NH protons. The Mass spectra were recorded on an Autospec EI-MS. The elemental analysis was carried out using Heraus CHN rapid analyzer. All the compounds gave C, H and N analysis within ± 0.4% of the theoretical values. The homogeneity of the compounds was described by TLC on aluminum silica gel 60 F$_{254}$ (Merck) detected by U.V light (254 nm) and iodine vapours.

This part deals with preparation of following compounds.

(a) 4-Bromoethylacetoacetate
(b) 4-Bromoethylcoumarins. (General method)
(c) (2-Oxo-2H-chromen-ylmethoxy)-benzaldehydes (3a-e). (General method)
(d) Preparation of 4-[4-3-Oxo-3-phenyl-propenyl]-phenoxyethyl]-chromen-2-one (4a-e). (General method)
(e) 4-[4-(6-phenyl-pyrimidin-4-yl)-phenoxyethyl]-chromen-2-one [5-7(a-e)]. (General method)
The preparation of 4- Bromoethylacetoacetate, 4-Bromoethylcoumarins and (2-Oxo-2H-chromen-ylmethoxy)-benzaldehydes (3a-e) are given Chapter 3.

(d) Preparation of 4-[4-3-Oxo-3-phenyl-propenyl)-phenoxymethyl]-chromen-2-one (4a-e).

Compound (4) (0.01 mol) and anhydrous K₂CO₃ (0.01 mol) were stirred in anhydrous acetone for half an hour, to this substituted 4-bromomethyl coumarins (2a-e) (0.01 mol) were added and the stirring was continued for 24 hours. The reaction mixture was added to the cursed ice and neutralized with 1:1 HCl. The solid separated was filtered and washed with water, dried and recrystallized from dioxane-ethanol mixture.

(e) Preparation of 4-[4-(6-phenyl-pyrimidin-4-yl)-phenoxymethyl]-chromen-2-one [5-7(a-e)].

Chalcones (0.01 mol) (4a-e) and urea, thiourea or guanidine hydrochloride (0.01 mol) were dissolved in DMF (20ml). Few drops of concentrated HCl were added and the reaction mixture was refluxed and the reaction was monitored by TLC. After completion of reaction, it was poured into 250ml of ice cold water and kept it for some time. The crude solid was filtered and subjected to column chromatography. Elution with solvent system ethyl acetate/petroleum ether (60-80 °C) gave pure compound.
The synthesis of chalcone and pyrimidine derivatives was performed as shown in Scheme-1. Synthesis of various 4-bromomethyl coumarins (1a-e) was brought about by the Pechmann cyclisation of phenols with 4-bromoacetoacetate. 4-bromomethyl coumarins (1a-e) were reacted with 4-hydroxy benzaldehyde in the presence of anhydrous K$_2$CO$_3$ in dry acetone at room temperature to give the corresponding ethers (2a-e). In the IR Spectrum of 4-(2-oxo-2H-chromen-4-yl-methoxy)-benzaldehyde (2a), the lactone carbonyl stretching frequency was observed at 1718 cm$^{-1}$, whereas the aldehydic carbonyl stretching appeared at 1690 cm$^{-1}$. In the $^1$H NMR spectrum of compound (2a), a singlet was observed at $\delta$ 2.38 ppm due to C$_6$-CH$_3$ protons. The C$_4$-CH$_2$ protons were observed downfield as a singlet at $\delta$ 5.31 ppm. The C$_3$-H of coumarin appeared at $\delta$ 6.64 ppm. The aldehydic proton appeared as a singlet in the downfield at $\delta$ 9.95 ppm. Attempted condensation of (2a-e) with acetophenone with 40% NaOH did not result the formation of chalcones (4a-e). A plausible explanation for this could be competition between the activated C$_4$-CH$_2$ and COCH$_3$ group for carbanion formation. Compounds (4a-e) were prepared by a different method, in which the chalcone (4), prepared separately by the reaction of p-hydroxy benzaldehyde and acetophenone in the presence of 20% alcoholic NaOH solution, was treated with 4-bromomethyl coumarins (1a-e) in the
presence of anhydrous K$_2$CO$_3$ in dry acetone at room temperature to give the corresponding cinnamoyl derivatives (4a-e). The IR Spectrum of 6-Methyl-4-[4-3-oxo-3-phenyl-propenyl]-phenoxyethyl]-chromem-2-one (4a), the lactone carbonyl stretching frequency was observed at 1721 cm$^{-1}$ and $\alpha, \beta$-unsaturated keto group at 1653 cm$^{-1}$. In the $^1$H NMR spectrum of compound (4a), a singlet was observed at $\delta$ 2.17 ppm due to C$_6$-CH$_3$ protons. The C$_4$-CH$_2$ protons were observed downfield as a singlet at $\delta$ 5.27 ppm. The C$_3$-H of coumarin appeared at $\delta$ 6.61 ppm. The olefinic protons were observed at 7.16 and 7.51 ppm as two separate doublets. Further the compounds (4a-e) were treated with urea, thiourea and guanidine hydrochloride in DMF to yield the corresponding pyrimidine derivatives. The IR Spectrum of 4-[4-2-Hydroxy-6-phenyl-pyrimidin-4-yl]-phenoxyethyl]-6-methyl-chromem-2-one (5a) shows the lactone carbonyl stretching frequency at 1718 cm$^{-1}$ and hydroxyl group of pyrimidine at 3498 cm$^{-1}$. In the PMR spectrum of compound (5a), a singlet was observed at $\delta$ 2.36 ppm due to C$_6$-CH$_3$ protons. The C$_4$-CH$_2$ protons were observed downfield as a singlet at $\delta$ 5.15 ppm. The C$_3$-H of coumarin appeared at $\delta$ 6.31 ppm. The pyrimidine proton was observed downfield as a singlet at $\delta$ 6.61 ppm and hydroxyl group proton is at $\delta$ 9.97 ppm. The aromatic protons resonated as multiplet in the region of 7.08 to 8.09 ppm. All the physical and analytical data of the synthesized compounds are presented in Table-1.
Table-1 Physical and Analytical Data of the Pyrimidine derivatives

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<th>R'</th>
<th>Yield (%)</th>
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<th>Mol. Formula/ Mol. Wt</th>
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<td>227-228</td>
<td>C&lt;sub&gt;27&lt;/sub&gt;H&lt;sub&gt;21&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>74.45</td>
<td>4.85</td>
</tr>
<tr>
<td>13</td>
<td>7c 6-Cl</td>
<td>NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>68.00</td>
<td>176-177</td>
<td>C&lt;sub&gt;26&lt;/sub&gt;H&lt;sub&gt;18&lt;/sub&gt;CIN&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>68.50</td>
<td>3.98</td>
</tr>
<tr>
<td>14</td>
<td>7d 5,6-Benzo</td>
<td>NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>67.00</td>
<td>142-144</td>
<td>C&lt;sub&gt;30&lt;/sub&gt;H&lt;sub&gt;22&lt;/sub&gt;CINO&lt;sub&gt;5&lt;/sub&gt;</td>
<td>70.42</td>
<td>4.49</td>
</tr>
<tr>
<td>15</td>
<td>7e 7,8-Benzo</td>
<td>NH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>59.13</td>
<td>227-229</td>
<td>C&lt;sub&gt;30&lt;/sub&gt;H&lt;sub&gt;22&lt;/sub&gt;CINO&lt;sub&gt;5&lt;/sub&gt;</td>
<td>70.46</td>
<td>4.50</td>
</tr>
</tbody>
</table>

*Products were characterized by IR, NMR, MS and elemental analysis.*

*Isolated yields.*

*Melting points are uncorrected.*
6-Methyl-4-[4-(3-Oxo-3-phenyl-propenyl)-phenoxymethyl]-chromen-2-one (4a)

Colourless shiny crystals, Yield 70%, m.p. 232-233 °C, IR (KBr, \(\nu\) cm\(^{-1}\)): 3055 (\(=\text{CH}\)), 1721 (C=O of coumarin), 1653 (\(\alpha\), \(\beta\)-unsaturated keto group), 1513 (C=C) cm\(^{-1}\);

\(^1\)H NMR (300MHz, \(\delta\) ppm, CDCl\(_3\)): 2.17 (s, 3H, CH\(_3\)), 5.27 (s, 2H, CH\(_2\)O), 6.61 (s, 1H, C\(_3\)H), 7.51 (d, \(J=2.35\) Hz, 1H, -CH=CH), 7.16 (d, \(J=1.33\) Hz, 1H, -CH=CH), 7.05-8.03 (m, 12H, Ar-H); \(^1^3\)C NMR (75 MHz, \(\delta\) ppm, CDCl\(_3\)): 20.0, 74.6, 103.8, 112.6, 119.2, 122.5, 126.5, 127.6, 129.8, 132.9, 135.0, 140.1, 147.2, 157.7, 160.2, 162.3, 179.0; ESI-MS: 396 (M\(^+\)); Anal. Calcd for C\(_{26}\)H\(_{20}\)O\(_4\): C, 78.77; H, 5.09; Found C, 78.74; H, 5.12 %.

7-Methyl-4-[4-(3-Oxo-3-phenyl-propenyl)-phenoxymethyl]-chromen-2-one (4b)

Colourless shiny crystals, Yield 58 %, m.p. 205-206 °C, IR (KBr, \(\nu\) cm\(^{-1}\)): 3079 (\(=\text{CH}\)), 1717 (C=O of coumarin), 1655 (\(\alpha\), \(\beta\)-unsaturated keto group), 1520 (C=C) cm\(^{-1}\);

\(^1\)H NMR (300MHz, \(\delta\) ppm, CDCl\(_3\)): 2.15 (s, 3H, CH\(_3\)), 5.33 (s, 2H, CH\(_2\)O), 6.67 (s, 1H, C\(_3\)H), 7.47 (d, \(J=7.65\) Hz, 1H, -CH=CH), 7.87 (d, \(J=7.47\) Hz, 1H, -CH=CH), 6.88-8.13 (m, 12H, Ar-H); \(^1^3\)C NMR (75 MHz, \(\delta\) ppm, CDCl\(_3\)): 22.6, 79.3, 106.3, 110.3, 117.8, 120.7, 125.9, 126.9, 128.3, 134.0, 135.8, 139.8, 145.6, 159.1, 162.3, 165.1, 175.7; ESI-MS: 396 (M\(^+\)); Anal. Calcd for C\(_{26}\)H\(_{20}\)O\(_4\): C, 78.77; H, 5.09; Found C, 78.80; H, 5.10 %.
6-Chloro-4-[4-(3-Oxo-3-phenyl-propenyl)-phenoxymethyl]-chromen-2-one (4c)

Pale yellow shiny crystals, Yield 63%, m.p. 145-147 °C, IR (KBr, \nu \text{ cm}^{-1}): 3088 (=\text{CH}-), 1715 (\text{C=O of coumarin}), 1647 (\alpha, \beta\text{-unsaturated keto group}), 1532 (\text{C=C}) \text{ cm}^{-1}; \text{^1}H \text{ NMR (300 MHz, } \delta \text{ ppm, CDCl}_3): 5.38 (s, 2H, CH\text{=O}), 6.53 (s, 1H, C\text{=H}), 7.32 (d, J=7.64 Hz, 1H, -CH=CH), 7.72 (d, J=7.76 Hz, 1H, -CH=CH), 6.76-7.98 (m, 12H, Ar-H); \text{^13}C \text{ NMR (75 MHz, } \delta \text{ ppm, CDCl}_3): 75.8, 104.6, 112.6, 119.4, 122.0, 123.6, 125.3, 129.6, 135.2, 136.3, 141.2, 148.3, 156.8, 159.1, 161.5, 184.4; ESI-MS: 418 (M+1); Anal. Calcd for C\text{_{26}H\text{_{17}}ClO}_4: C, 72.03; H, 4.11; Found C, 72.00; H, 4.14 %.

1-[4-(3-Oxo-3-phenyl-propenyl)-phenoxymethyl]-benzo[\text{f}]chromen-3-one (4d)

Yellow crystals, Yield 73%, m.p. 242-243 °C, IR (KBr, \nu \text{ cm}^{-1}): 3103 (=\text{CH}-), 1728 (\text{C=O of coumarin}), 1664 (\alpha,\beta\text{-unsaturated keto group}), 1542 (\text{C=C}) \text{ cm}^{-1}; \text{^1}H \text{ NMR (300MHz, } \delta \text{ ppm, CDCl}_3): 5.13 (s, 2H, CH\text{=O}), 6.37 (s, 1H, C\text{=H}), 7.54 (d, J=7.32 Hz, 1H, -CH=CH), 7.83 (d, J=7.43Hz, 1H, -CH=CH), 7.02-8.41 (m, 15H, Ar-H); \text{^13}C \text{ NMR (75 MHz, } \delta \text{ ppm, CDCl}_3): 83.5, 106.3, 113.3, 115.2, 116.7, 121.6, 123.3, 124.7, 126.5, 128.3, 129.3, 133.1, 136.5, 140.8, 150.2, 158.3, 160.4, 163.3, 177.2; ESI-MS: 433 (M+1); Anal. Calcd for C\text{_{29}H\text{_{20}}O}_4: C, 80.54; H, 4.66; Found C, 80.50; H, 4.62 %.
4-[4-(3-Oxo-3-phenyl-propenyl)-phenoxymethyl]-benzo[h]chromen-2-one (4e)

Reddish crystals, Yield 58%, m.p.221-222 °C, IR (KBr, v cm⁻¹):
3093 (C=CH-), 1725 (C=O of coumarin), 1655 (α,β-unsaturated keto group), 1526 (C=C) cm⁻¹; ¹H NMR (300MHz, δ ppm, CDCl₃): 5.36 (s, 2H, CH₂O), 6.42 (s, 1H, C₃H), 7.36 (d, J=7.78 Hz, 1H, -CH=CH), 7.92 (d, J=7.69 Hz, 1H, -CH=CH), 6.89-8.23 (m, 15H, Ar-H); ¹³C NMR (75 MHz, δ ppm, CDCl₃): 81.6, 104.8, 114.5, 115.6, 118.3, 120.4, 122.3, 123.6, 125.9, 128.1, 130.5, 132.3, 135.3, 138.7, 148.7, 160.0, 161.3, 162.8, 180.0; ESI-MS: 433 (M+1); Anal. Calcd for C₂₉H₂₀O₄: C, 80.54; H, 4.66; Found, C, 80.57; H, 4.69 %.

4-[4-(2-hydroxy-6-phenyl-pyrimidin-4-yl)-phenoxymethyl]-6-methyl-chromen-2-one (5a)

Colourless shiny crystals, IR (KBr, v cm⁻¹): 3426 (-OH), 3062 (Ar-H), 1729 (C=O of coumarin), 1595 (C=N) cm⁻¹; ¹H NMR (300MHz, δ ppm, CDCl₃): 2.36 (s, 3H, C₆-CH₃), 5.15 (s, 2H, CH₂O), 6.31 (s, 1H, C₃H), 6.61 (s, 1H, pyrimidine proton), 7.08-8.09 (m, 12H, Ar-H), 9.97 (s, OH, D₂O exchangeable); ¹³C NMR (75 MHz, δ ppm, CDCl₃): 17.8, 73.3, 98.8, 103.4, 109.2, 111.2, 113.5, 114.76, 116.3, 119.43, 129.0, 130.4, 145.0, 161.3, 166.6, 171.3, 177.65; ESI-MS: 436 (M)⁺.
4-[4-(2-hydroxy-6-phenyl-pyrimidin-4-yl)-phenoxy methyl]-7-methylchromen-2-one (5b)

Colourless shiny crystals, IR (KBr, $\nu$ cm$^{-1}$): 3486 (-OH), 3073 (Ar-H), 1721 (C=O of coumarin), 1589 (C=N) cm$^{-1}$; $^1$H NMR (300MHz, $\delta$ ppm, CDCl$_3$): 2.25 (s, 3H, C$_7$-CH$_3$), 5.53 (s, 2H, CH$_2$O), 6.33 (s, 1H, C$_3$H), 6.67 (s, 1H, pyrimidine proton), 7.05-8.44 (m, 12H, Ar-H), 11.6 (s, OH, D$_2$O exchangeable); $^{13}$C NMR (75 MHz, $\delta$ ppm, CDCl$_3$): 19.4, 80.3, 104.6, 108.5, 115.8, 121.7, 125.3, 127.7, 128.9, 130.4, 132.9, 138.7, 147.6, 150.5, 157.3, 159.2, 161.7, 176.8; ESI-MS: 436 (M$^+$).

6-Chloro-4-[4-(2-hydroxy-6-phenyl-pyrimidin-4-yl)-phenoxy methyl]-chromen-2-one (5c)

Colourless shiny crystals, IR (KBr, $\nu$ cm$^{-1}$): 3508 (-OH), 3067 (Ar-H), 1725 (C=O of coumarin), 1612 (C=N) cm$^{-1}$; $^1$H NMR (300MHz, $\delta$ ppm, CDCl$_3$): 5.53 (s, 2H, CH$_2$O), 6.41 (s, 1H, C$_3$H), 6.68 (s, 1H, pyrimidine proton), 6.91-8.33 (m, 12H, Ar-H), 10.87 (s, OH, D$_2$O exchangeable); $^{13}$C NMR (75 MHz, $\delta$ ppm, CDCl$_3$): 77.7, 103.6, 109.3, 113.1, 119.3, 125.7, 126.8, 128.9, 134.2, 135.5, 146.3, 147.9, 155.8, 160.1, 163.8 176.2; ESI-MS: 458 (M+1).

1-[4-(2-Hydroxy-6-phenyl-pyrimidin-4-yl)-phenoxy methyl]-benzo[ff]chromen-3-one (5d)

Yellow shiny crystals, IR (KBr, $\nu$ cm$^{-1}$): 3517 (-OH), 3088 (Ar-H), 1731 (C=O of coumarin), 1606
Tyrimidine 'Derivatives
(C=N) cm\(^{-1}\); \(^1\)H NMR (300MHz, \(\delta\) ppm, CDCl\(_3\)): 5.43 (s, 2H, CH\(_2\)O), 6.35 (s, 1H, C\(_3\)H), 6.71 (s, 1H, pyrimidine proton), 7.03-8.42 (m, 15H, Ar-H), 11.04 (s, OH, D\(_2\)O exchangeable); \(^13\)C NMR (75 MHz, \(\delta\) ppm, CDCl\(_3\)): 80.8, 102.3, 108.0, 114.8, 117.3, 120.1,122.3, 124.5, 126.3, 127.7, 128.3, 129.2, 135.3, 136.9, 151.3, 156.9,162.3, 164.2 172.1; ESI-MS: 473 (M+1).

4-[4-(2-Hydroxy-6-phenyl-pyrimidin-4-yl)-phenoxy-methyl]-benzo
[h]chromen-2-one (5e)

Red shiny crystals, IR (KBr, \(\nu\) cm\(^{-1}\)): 3503 (-OH), 3065 (Ar, C=O of coumarin), 1726 (C=O of coumarin), 1589 (C=N) cm\(^{-1}\);
\(^1\)H NMR (300MHz, \(\delta\) ppm, CDCl\(_3\)): 5.53 (s, 2H, CH\(_2\)O), 6.35 (s, 1H,C\(_3\)-H), 6.88 (s, 1H, pyrimidine proton), 6.97-8.13 (m, 15H, Ar-H), 10.65 (s, OH, D\(_2\)O exchangeable); \(^13\)C NMR (75 MHz, \(\delta\) ppm, CDCl\(_3\)): 77.5, 101.8, 111.0, 113.4, 116.7, 119.6, 122.0, 124.1, 126.3, 127.3, 128.8, 130.5, 134.6, 138.5, 147.7, 154.3, 159.5, 161.6, 175.5; ESI-MS: 473 (M+1).

4-[4-(2-Mercapto-6-phenyl-pyrimidin-4-yl)-phenoxy-methyl]-6-methyl-
chromen-2-one (6a)

Colourless shiny crystals, IR (KBr, \(\nu\) cm\(^{-1}\)): 3048 (Ar-H), 1719 (C=O of coumarin), 1609 (C=N), 824 (SH) cm\(^{-1}\); \(^1\)H NMR (300MHz, DMSO-d\(_6\), \(\delta\) ppm): 2.22 (s, 3H, C\(_6\)-CH\(_3\)), 5.52 (s, 2H, CH\(_2\)O), 6.38 (s, 1H, C\(_3\)-H), 6.70 (s, 1H, pyrimidine proton), 6.76-8.04 (m, 12H, Ar-H), 12.02 (s, SH, D\(_2\)O exchangeable); \(^13\)C NMR (75 MHz, DMSO-d\(_6\), \(\delta\) ppm,): 20.1, 79.7, 103.5, 109.3, 112.7, 122.3, 125.8, 127.5, 128.8, 130.5, 132.7, 135.7, 146.0, 148.7, 158.1, 159.8, 162.3, 187.5; ESI-MS: 453 (M+1).
4-[4-(2-Mercapto-6-phenyl-pyrimidin-4-yl)-phenoxy-methyl]-7-methyl-chromen-2-one (6b)

Colourless shiny crystals, IR (KBr, \( \nu \text{ cm}^{-1} \)): 3053 (Ar-H), 1722 (C=O of coumarin), 1613 (C=N), 819 (SH) cm\(^{-1}\); \(^1\)H NMR (300MHz, DMSO-\(d_6\), \( \delta \) ppm): 2.13 (s, 3H, C\(_6\)-CH\(_3\)), 5.46 (s, 2H, CH\(_2\)O), 6.43 (s, 1H, C\(_3\)-H), 6.65 (s, 1H, pyrimidine proton), 7.06-8.34 (m, 12H, Ar-H), 11.87 (s, SH, D\(_2\)O exchangeable); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\), \( \delta \) ppm): 17.9, 81.2, 104.6, 110.6, 114.6, 121.7, 126.5, 127.9, 129.2, 130.7, 133.7, 138.3, 145.8, 149.7, 157.8, 158.9, 161.7, 184.3; ESI-MS: 453 (M\(^+\)).

6-Chloro-4-[4-(2-mercepto-6-phenyl-pyrimidin-4-yl)-phenoxy-methyl]-chromen-2-one (6c)

Colourless shiny crystals, IR (KBr, \( \nu \text{ cm}^{-1} \)): 3078 (Ar-H), 1719 (C=O of coumarin), 1609 (C=N), 823 (SH) cm\(^{-1}\); \(^1\)H NMR (300MHz, \( \delta \) ppm, CDCl\(_3\)): 5.29 (s, 2H, CH\(_2\)O), 6.36 (s, 1H, C\(_3\)H), 6.89 (s, 1H, pyrimidine proton), 7.04-8.43 (m, 12H, Ar-H), 11.78 (s, 1H, SH, D\(_2\)O exchangeable); \(^{13}\)C NMR (75 MHz, \( \delta \) ppm, CDCl\(_3\)): 82.1, 104.6, 107.1, 115.6, 118.2, 123.6, 125.8, 127.5, 128.6, 132.8, 136.9, 144.9, 146.7, 157.8, 159.7, 162.4, 179.6; ESI-MS: 474 (M\(^+\)).

1-[4-(2-Mercapto-6-phenyl-pyrimidin-4-yl)-phenoxy-methyl]-benzo[ff]chromen-3-one (6d)

Yellow shiny crystals, IR (KBr, \( \nu \text{ cm}^{-1} \)): 3093 (Ar-H), 1726 (C=O of coumarin), 1603 (C=N), 816 (SH) cm\(^{-1}\); \(^1\)H NMR
(300MHz, δ ppm, CDCl₃): 4.88 (s, 2H, CH₂O), 6.27 (s, 1H, C₃-H), 6.88 (s, 1H, pyrimidine proton), 7.12-8.51 (m, 15H, Ar-H), 12.13 (s, 1H, SH, D₂O exchangeable); ¹³C NMR (75 MHz, δ ppm, CDCl₃): 79.3, 106.7, 113.2, 121.6, 123.6, 126.2, 127.4, 128.0, 129.8, 134.9, 136.9, 149.4, 157.4, 161.7, 163.0, 165.1, 184.6; ESI-MS: 489 (M⁺).

4-[4-(2-Mercpto-6-phenyl-pyrimidin-4-yl)-phenoxymethyl]-benzo[h]chromen-2-one (6e) 
Red shiny crystals, IR (KBr, ν cm⁻¹): 3087 (Ar-H), 1732 (C=O of coumarin), 1596 (C=N), 820 (SH) cm⁻¹; ¹H NMR (300MHz, δ ppm, CDCl₃): 5.12 (s, 2H, CH₂O), 6.42 (s, 1H, C₃-H), 6.79 (s, 1H, pyrimidine proton), 7.07-8.36 (m, 15H, Ar-H), 11.76 (s, 1H, SH, D₂O exchangeable); ¹³C NMR (75 MHz, δ ppm, CDCl₃): 80.0, 107.5, 112.8, 119.9, 122.9, 125.9, 125.9, 127.8, 129.3, 135.2, 138.7, 150.1, 159.2, 160.6, 164.2, 166.6, 182.2; ESI-MS: 489 (M⁺).

4-[4-(2-Amino-6-phenyl-pyrimidin-4-yl)-phenoxymethyl]-6-methyl-chromen-2-one (7a) 
Colourless crystals, IR (KBr, ν cm⁻¹): 3433, 3378 (NH₂), 3065 (Ar-H), (C=O of coumarin), 1601 (C=N) cm⁻¹; ¹H NMR (300MHz, DMSO-d₆, δ ppm): 2.31 (s, 3H, C₆-CH₃), 5.07 (s, 2H, CH₂O), 5.75 (s, 2H, NH₂, D₂O exchangeable), 6.88 (s, 1H, pyrimidine proton), 7.09-8.32 (m, 12H, Ar-H); ¹³C NMR (75 MHz, DMSO-d₆, δ ppm): 17.9, 80.3, 107.3, 112.8, 120.3, 125.7, 126.8, 128.4, 134.8, 135.3, 147.6, 158.0, 160.3, 161.3, 167.7, 170.3; ESI-MS: 436 (M⁺).
4-[4-(2-Amino-6-phenyl-pyrimidin-4-yl)-phenoxy-methyl]-7-methyl-
chromen-2-one (7b)

Colourless crystals, IR (KBr, $\nu$ cm$^{-1}$):
3427, 3367 (NH$_2$), 3042 (Ar-H), 1719
(C=O of coumarin), 1597 (C=N) cm$^{-1}$;

$^1$H NMR (300MHz, DMSO-d$_6$, $\delta$ ppm): 2.25 (s, 3H, C$_7$-CH$_3$), 5.56 (s, 2H, CH$_2$O), 5.85 (s, 2H, NH$_2$, D$_2$O exchangeable), 6.76 (s, 1H, pyrimidine proton), 7.01-8.42 (m, 12H, Ar-H); $^{13}$C NMR (75 MHz, DMSO-d$_6$, $\delta$ ppm.):
18.6, 78.5, 106.8, 114.3, 119.6, 124.3, 127.0, 129.1, 134.0, 137.7, 145.3,
160.1, 161.7, 164.3, 168.1, 169.2; ESI-MS: 436 (M+1).

4-[4-(2-Amino-6-phenyl-pyrimidin-4-yl)-phenoxy-methyl]-6-chloro-
chromen-2-one (7c)

Colourless crystals, IR (KBr, $\nu$ cm$^{-1}$):
3408, 3345 (NH$_2$), 3032 (Ar-H), 1726
(C=O of coumarin), 1614(C=N) cm$^{-1}$;

$^1$H NMR (300MHz, DMSO-d$_6$, $\delta$ ppm): 5.21 (s, 2H, CH$_2$O), 5.47 (s, 2H, NH$_2$, D$_2$O exchangeable), 6.57 (s, 1H, pyrimidine proton), 6.97-8.24 (m, 12H, Ar-H); $^{13}$C NMR (75 MHz, DMSO-d$_6$, $\delta$ ppm): 82.6, 107.2, 113.4,
121.8, 127.1, 128.6, 129.8, 131.5, 135.9, 147.3, 157.8, 162.6, 167.4, 168.1;
ESI-MS: 457 (M+1).

1-[4-(2-Amino-6-phenyl-pyrimidin-4-yl)-phenoxy-methyl]-
benzof[\alpha]chromen-3-one (7d)

Yellow shiny crystals, IR (KBr, $\nu$
$\nu$ cm$^{-1}$): 3423, 3309 (NH$_2$), 3025 (Ar-
H), 1731 (C=O of coumarin), 1607

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Pyrimidine Derivatives

(C=N) cm$^{-1}$; $^1$H NMR (300MHz, DMSO-d$_6$, $\delta$ ppm): 5.43 (s, 2H, CH$_2$O), 5.68 (s, 2H, NH$_2$, D$_2$O exchangeable), 6.75 (s, 1H, pyrimidine proton), 7.07-8.36 (m, 15H, Ar-H); $^{13}$C NMR (75 MHz, $\delta$ ppm, CDCl$_3$): 81.7, 107.2, 115.6, 116.0, 117.7, 121.0, 123.9, 126.0, 127.2, 128.5, 129.4, 135.3, 150.2, 159.2, 162.1, 163.1, 166.6, 168.1; ESI-MS: 472 (M$^+$).

4-[4-(2-Amino-6-phenyl-pyrimidin-4-yl)-phenoxymethyl]-benzo[h]chromen-2-one (7e)

Red shiny crystals, IR (KBr, $\nu$ cm$^{-1}$): 3417, 3325 (NH$_2$), 3020 (Ar-H), 1726 (C=O of coumarin), 1600 (C=N) cm$^{-1}$;

$^1$H NMR (300MHz, DMSO-d$_6$, $\delta$ ppm): 5.31 (s, 2H, CH$_2$O), 5.54 (s, 2H, NH$_2$, D$_2$O exchangeable), 6.69 (s, 1H, pyrimidine proton), 6.92-8.26 (m, 15H, Ar-H); $^{13}$C NMR (75 MHz, $\delta$ ppm, CDCl$_3$): 78.9, 106.7, 113.2, 115.7, 118.4, 120.7, 122.4, 125.7, 126.8, 127.9, 128.7, 134.6, 148.7, 157.9, 160.3, 162.4, 165.1, 166.3; ESI-MS: 472 (M$^+$).
Pyrimidine Derivatives

Spectrum 1: IR Spectrum of compound (4a)

Spectrum 2: $^1$H NMR (300MHz) Spectrum of compound (4a) in CDCl₃.
Spectrum 3: IR Spectrum of compound (5a)

Spectrum 4: $^1$H NMR (300MHz) Spectrum of compound (5a) in CDCl$_3$. 

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Spectrum 5: $^{13}$C NMR (75MHz) Spectrum of compound (5a)

Spectrum 6: Mass Spectra of compound (5a)
1. Pinner, 
*Ber.*, 1884, **17**, 2519.

2. W. Kemnitzer, N. Sirisoma, C. May, B. Tseng, J. Drewe and S.X. Cai, 

3. N. Sunduru, Nishi, S. Palne, P. M.S. Chauhan and S. Gupta, 


5. Hua Chen, Jie Bai, Lingling Jiao, Zaihong Guo, Qingmei Yin and Xiaoliu Li, 

6. Faizul Azam, Ismail A. Alkskas and M.A. Ahmedb, 

7. A.J. Folkes, K. Ahmadi and W.K. Alderton, 

8. H. Huang, D.A. Hutta, J.M. Rinker and Huaping Hu, 

9. C.L. Motta, S. Sartini, L. Mugnaini, S. Salerno, F. Simorini, S. Taliani, 
A.M. Marini, F.D. Settimo, A. Lavecchia, E. Novellino, L. Antonioli, 
M. Fornai, C. Blandizzi and M.D. Tacca, 

10. M.T. Chhabria and M.H. Jani, 

11. A. Gopalsamy, G. Ciszewski, Y. Hu, F. Lee, L. Feldberg, E. Frommer, 
S. Kim, K. Collins, D. Wojciechowicz and R. Mallon, 

12. K. Kubota, H. Kurebayashi, H. Miyachi, M. Tobe, M. Onishi and Y. Isobe, 


