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# Synthesis of Novel Oxo Pyrimido Pyrimidine and Their Derivatives

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***Abstract:****Pyrimidine derivatives are synthesized to possess various pharmacological and biological activities. In the present work, we havesynthesized 3-(4-methoxyphenyl)-1-phenyl prop-2-en-1-one (1) (chalcone) by using 4-methoxybenzaldehyde and acetophenone in the presence of alcoholic KOH by Claisen-Schmidt condensation reaction. After purification and characterization by physical and spectral methods, The synthesized chalcone have been converted into 6-(4-methoxyphenyl)-4-phenyl-1,6-dihydropyrimidin-2-amine (2) by treating with guanidine nitrate in the presence of alcoholic KOH. The structure (2) has been characterized by spectral analysis. The synthesized compound (2) is further reacted with ethyl 2-cyano-3, 3-bis (methylthio)acrylate in the presence of catalytic amount of potassium carbonate in DMFunderrefluxcondition to givenovel 2-(4-methoxyphenyl)-8-(methylthio)-6-oxo-4-phenyl-1,6,9,9a-tetrahydro-2H-pyrimido[1,2-a]pyrimidine-7-carbonitrile(3) in goodyields.Thecompound(3) possesses replaceable methylthio (-$SCH_3$) group at 8 position. The compound (3) is further reacted with various nucleophiles like substituted aromatic amines, aromatic phenols, hetryl amines and active methylene compounds to give 2-(4-methoxyphenyl)-8-substituted-6-oxo-4-phenyl-1,6,9,9a-tetrahydro-2H-pyrimido[1,2-a]pyrimidine-7-carbonitrile in good yields.*

***Keywords: Claisen-Schmidt Condensation, ethyl2-cyano-3,3-bis(methylthio)acrylate,Michaeladdition reaction,pyrimidopyrimidine.***

## I. INTRODUCTION

The pyrimidine nucleus is present in a broad range of bioactive natural products. In addition, the pharmacological and biological activities of pyrimidine derivatives are well documented [1-2],such as antiviral, antibacterial, antitumor, anti-inflammatory, antifungal, and anti-leishmanial agents[3].Several documents have been reported for the preparation of these fused heterocycles, derivatives of which are useful as bronchodilators [4],vasodilators [5],anti-allergic [6],anti-hypertensive [7] and anti-cancer agents[4]. The presence of a pyrimidine system In thymine, cytosine, and uracil, pyrimidine system is present which are the essential building blocks of nucleic acids and one possible reason for the activity [8]. Fused derivatives of pyrimidine with thiazole are bioactive. These derivatives are used as a potent and selective inhibitors of acetyl-coA carboxylase 2[9] and VEGF receptors I and II [10]. They have also shown potent and selective human adenosine A 3 receptor [11, 12] and vanilloid receptor I TRPVI antagonism [13]. Now a days, one pot multi component reactions are gaining more importance because of environmentally implication [14].MCRs are economically and environmentally very advantageous because multistep syntheses produce considerable amounts of waste mainly due to complex isolation procedures often involving expensive, toxic and hazardous solvents after each step. Due to these advantages these reactions are perfectly suited for combinatorial library synthesis, and thus are finding increasing use in the discovery process for new drugs and agrochemicals [15-16]. Most of the MCRs are based on condensation of carbonyl group [17]. The Biginelli reaction has been employed for the synthesis of pyrimido [4, 5-d] pyrimidine [18] by the one pot condensation of acetophenone, urea and aldehydes. And most of the methods involve modification of the Biginelli reaction by condensation of aldehydes, urea and alkyl aryl ketones in acetic acid using catalytic amounts of $KHSO_4$ [19]. Although Biginelli reaction is often employed for the synthesis of pyrimido [4, 5-d] pyrimidine by the use of base [20] and microwave assisted [21] synthesis. The other promising methods for the synthesis of pyrimido [4, 5-d] pyrimidines involve multistep syntheses starting from 1, 3-dsubstituted cyanouracils [22] polymer bound amino pyrimidine derivatives [23], aza-Wittig-type reaction [24] and reacting aminouracils with various heterocumulenes [25]. Synthetic alternatives are many, varied and have resorted to harsh conditions, example the use of PTSA (p-toluene sulphonic acid) as a catalyst, using $POCl_3$with DMF as a solvent [26]. Additionally, reagents for these procedures are not readily or commercially available. Considering all above facts and important of pyrimido [4,5-d] pyrimidine derivatives, it is considered worthwhile to find out new methodology for synthesizing these compounds utilizing green chemistry protocol like using eco-friendly reagents and catalysts, solvent free or reaction in non-hazardous solvent, because it offers enhanced chemical process economics concomitant with a reduced environmental burden.The structures of the various synthesized compounds were assigned on the basis of IR, $^1$H NMR, $^{13}$C NMR and Mass spectral data.

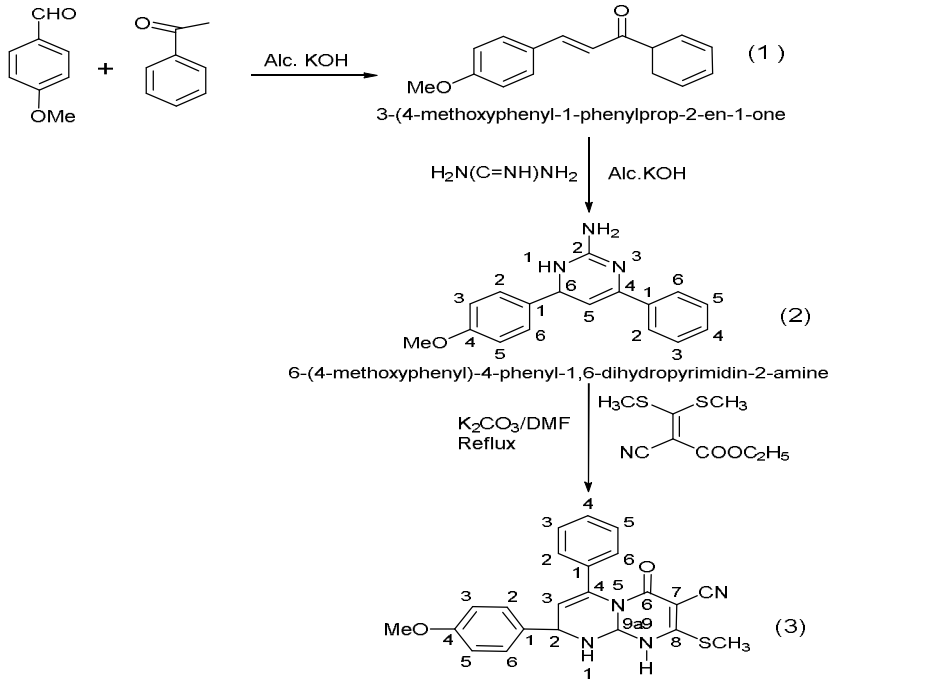
In the view of this observation and extension of earlier work, we have synthesized 2-(4-methoxyphenyl)-8-(methylthio)-6-oxo-4-phenyl-1,6,9,9a-tetrahydro-2H-pyrimido[1,2-a] pyrimidine-7-carbonitrile (3) by using6-(4-methoxyphenyl)-4-phenyl-1,6-dihydropyrimidin-2-amine (2) [27-28 ] and ethyl 2-cyano-3, 3-bis(methylthio)acrylate. 6-(4-methoxyphenyl)-4-phenyl-1,6-dihydropyrimidin-2-amine (2) is prepared by the reaction of 3-(4-methoxyphenyl)-1-phenyl prop-2-en-1-one (1)chalcone[29-30] with guanidine nitrate in the presence of alcoholic potassium hydroxide under reflux condition.

## II. METHODS

Melting points were determined in open capillary tubes and are uncorrected. The silica gel $F_{254}$ plates were used for thin layer chromatography (TLC); the spots were examined under UV light and then developed in an iodine vapor. Column chromatography was performed with silica gel (BDH 100-200 mesh). Solvents were purified according to standard procedures. The spectra were recorded as follows: IR, KBr pellets, a Perkin-Elmer RX1 FT-IR spectrophotometer; $^1$H NMR, $CDCl_3$, 200 MHz, a Varian Gemini 200 instrument. Elemental analysis was performed on a Heraeus CHN-O rapid analyzer.

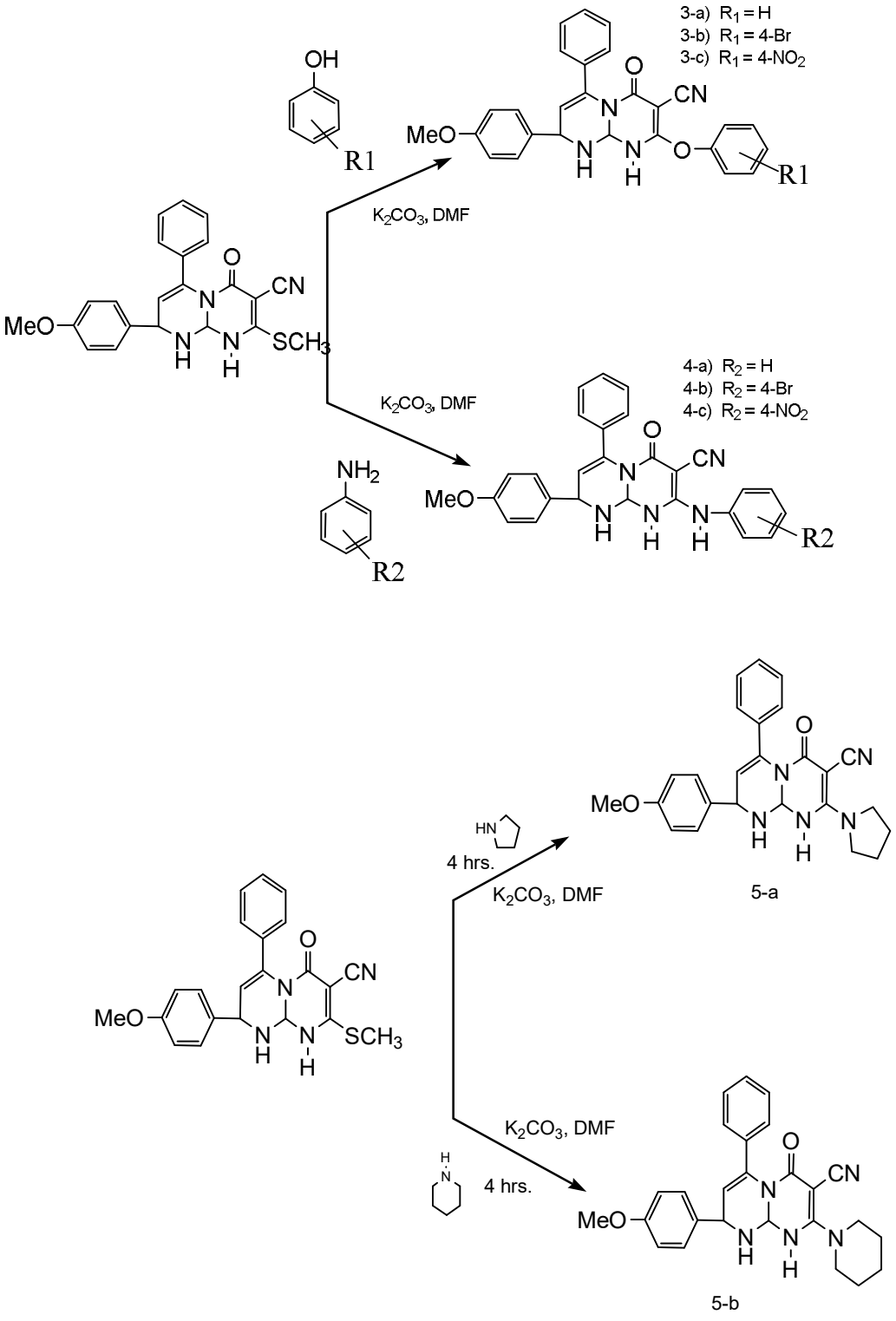
*A. 2-(4-methoxyphenyl)-8-(methylthio)-6-oxo-4-phenyl-1,6,9,9a-tetrahydro-2H-pyrimido[1,2-a]pyrimidine-7-carbonitrile..*

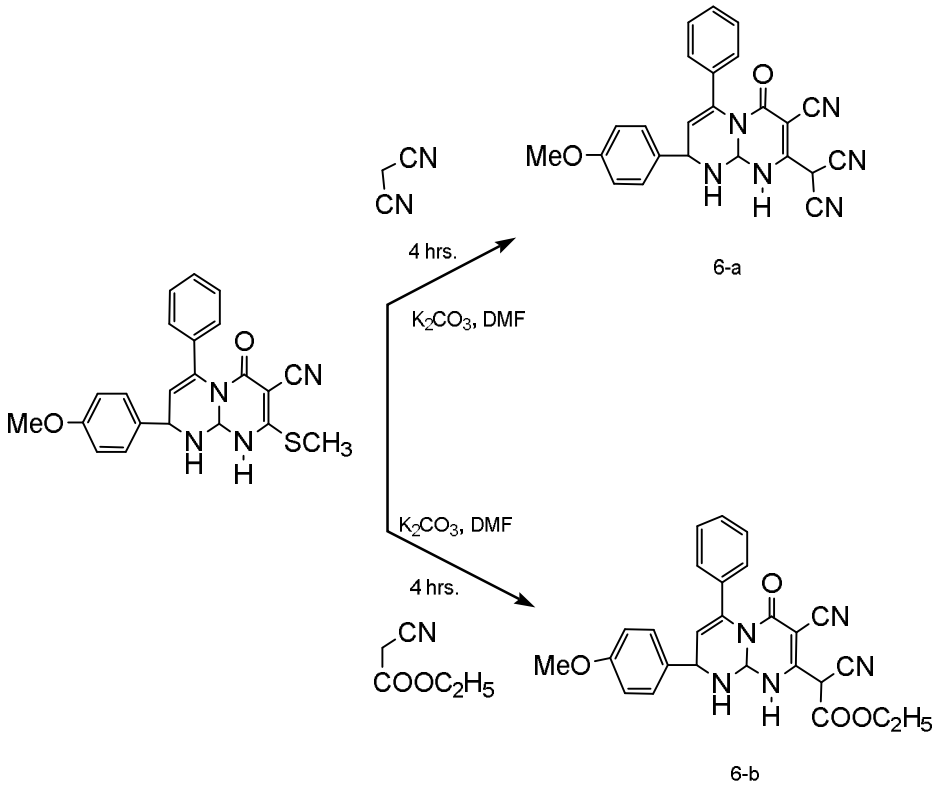
1) *Step – I:*A solution of KOH 50% is added to an equimolar solution of acetophenone (0.01mole) and 4-methoxybenzaldehyde (0.01 mole) in ethanol 95%; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. They are crystallized by ethanol compound.
2) *Step – II:*A mixture of chalcone i.e. 3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (2.38 gm,0.01mole ), and guanidine nitrate (1.20 g 0.01 mole ) were dissolved in alcoholic potassium hydroxide solution (10 ml ) was heated for 4 hrs., then it was poured into cold ice obtained 6-(4-methoxyphenyl)-4-phenyl-1,6-dihydropyrimidin-2-amine.
3) *Step – III:*A mixture of 6-(4-methoxyphenyl)-4-phenyl-1,6-dihydropyrimidin-2-amine (2) and ethyl 2-cyano-3,3-bis(methylthio)acrylate in the presence of catalytic amount of potassium carbonate (10 mg) in DMF was refluxed for 4 hours, the reaction was monitored by TLC. After completion, the reaction mixture was cooled at room temperature then wash with water and extracted with ethyl acetate. The extract was concentrated and the residue was subjected to column chromatography (silica gel, n-hexane-ethyl acetate 8:2) to obtain pure solid compound 2-(4-methoxyphenyl)-8-(methylthio)-6-oxo-4-phenyl-1,6,9,9a-tetrahydro-2H-pyrimido[1,2-a]pyrimidine-7-carbonitrile (3). The compound (3) is confirmed by IR, $^1$H NMR, $C^{13}$ NMR and MS analytical data.



*B. Synthesis of Derivatives*

A mixture of compound (3) (1mmol) and independently, various substituted aromatic amines, aromatic phenols, hetryl amines and active methylene compounds (1mmol) in DMF (10 ml) and anhydrous potassium carbonate (10 mg ) was reflux for 4 to 6 hrs. The reaction mixture cooled to room temperature and poured into ice cold water. The separated solid product was filtered, washed with water and recrystllized by using ethyl alcohol.






## III. RESULT AND DISCUSSION

Thecompound2-(4-methoxyphenyl)-8-(methylthio)-6-oxo-4-phenyl-1,6,9,9a-tetrahydro-2H-pyrimido[1,2-a]pyrimidine-7-carbonitrile are synthesized by dissolving 6-(4-methoxyphenyl)-4-phenyl-1,6-dihydropyrimidin-2-amine (2) and ethyl 2-cyano-3-3-bis(methylthio)acrylate in the presence of $K_2CO_3$ in DMF under reflux condition. The synthesized compound acts as electrophilic species reacting with various substituted aromatic amines, aromatic phenols, hetryl amines and active methylene compound gives 2-(4-methoxyphenyl)-8-(methylthio)-6-oxo-4-phenyl-1,6,9,9a-tetrahydro-2H-pyrimido[1,2-a]pyrimidine-7-carbonitrile in good yields.

## IV. CONCLUSION

A new different 2-(4-methoxyphenyl)-8-(methylthio)-6-oxo-4-phenyl-1,6,9,9a-tetrahydro-2H-pyrimido[1,2-a]pyrimidine-7-carbonitrilearesynthesized by using simple and efficient chemistry and this synthesized compounds possesses methylthio group at 8-position which is best leaving group therefore synthesized compound (3) act as an electrophilic species and it reacts with various nucleophiles.

3) 2-(4-methoxyphenyl)-8-(methylthio)-6-oxo-4-phenyl-1,6,9,9a-tetrahydro-2H-pyrimido[1,2-a]pyrimidine-7-carbonitrile.

IR : 3360, 2260,1715, 1630, 1030 $cm^{-1}$;

$^1$HNMR : δ 2.38 (s,3H,$SCH_3$), 5.10 (s,1H,NH), 4.92 (s,1H,NH), 5.86(s,1H,=CH), 4.51 (s,1H,CH), 5.82 (s,1H,CH), 7.65 (s,5H,Ar-H), 7.12 (dd,2H,Ar-H), 6.69 (dd,2H,Ar-H), 3.79 (s,3H,$OCH_3$).

ESI-MS : 404.

Anal.Calcd for $C_{22}H_{20}N_4O_2S$: C, 65.33; H,4.98; N,13.85;O,7.91;S, 7.93

Found : C,62.63;H,4.52;N, 9.96;O,7.63;S,15.26.

Mol. Formula : $C_{22}H_{20}N_4O_2S$

Mol.Wt. : 404.

3-a) 2-(4-methoxyphenyl)-6-0xo-8-phenoxy-4-phenyl-1,6,9,9a-tetrahydro-2H-pyrimido[1,2-a]pyrimidine-7-carbonitrile.

IR : 3390, 2220, 1700, 1620, 1050, $cm^{-1}$;

$^1$H NMR : δ 5.10 (s,1H,NH), 6.47 (s,1H,=CH) 5.75 (s,1H,CH), 4.32 (s,1H,NH), 5.52 (s,1H,CH), 7.24 (s,5H,Ar-H), 6.90 (dd,2H,Ar-H), 7.21 (dd,2H,Ar-H), 7.05 (s,5H,Ar-H), 3.80 (s,3H,$OCH_3$)

ESI-MS : 450.

Anal. Calcd. : $C_{27}H_{22}N_4O_3$C,71.99;H,4.92;N,12.44;O,10.65
Found : C, 69.34; H, 4.52; N, 8.98; O, 10.28; S, 6.88.
Mol. Formula : $C_{27}H_{22}N_4O_3$
Mol.Wt. : 450.

3-b) 8-(4-bromophenoxy)-2-(4-methoxyphenyl)-6-oxo-4-phenyl-1,6,9,9a-tetra-hydro-2H-pyrimido[1,2-a]pyrimidine-7-carbonitrile.

IR : 3370, 2260, 1705, 1640, 1020,670 $cm^{-1}$;
$^1$H NMR : δ 5.11 (s,1H,NH), 6.46 (s,1H,=CH) 5.73 (s,1H,CH), 4.66 (s,1H,NH), 5.54 (s,1H,CH), 7.19 (s,5H,Ar-H), 6.94 (dd,2H,Ar-H),7.23 (dd,2H,Ar-H),6.88 (dd,2H,Ar-H),7.24 (dd,2H,Ar-H),3.78 (s,3H,$OCH_3$)
ESI-MS : 529.
Anal. Calcd : $C_{27}H_{21}BrN_4O_3$:C,61.26; H,4.00; Br,15.09; N,10.58; O,9.07
Found : C,59.31; H, 3.62; Br,14.60; N,7.71; O,8.83; S,5.93.
Mol. Formula : $C_{27}H_{21}BrN_4O_3$
Mol.Wt : 529.

3-c) 2-(4-methoxyphenyl)-8-(4-nitrophenoxy)-6-oxo-4-phenyl-1,6,9,9a-tetrahydro-2H-pyrimido[1,2-a]pyrimidine-7-carbonitrile.

IR : 3365, 2275, 1710, 1650, 1070,1570 $cm^{-1}$;
$^1$H NMR : δ 5.09 (s,1H,NH), 6.49 (s,1H,=CH) 5.76 (s,1H,CH), 4.08 (s,1H,NH), 5.53 (s,1H,CH), 7.22 (s,5H,Ar-H), 6.92 (dd,2H,Ar- H),7.23 (dd,2H,Ar-H), 7.18 (dd,2H,Ar-H),7.96 (dd,2H,Ar-H), 3.76 (s,3H,$OCH_3$)
ESI-MS : 495.
Anal. Calcd : $C_{27}H_{21}N_5O_5$: C,65.45; H,4.27; N,14.13; O,16.14
Found : C,63.29; H,3.91; N,10.91; O,15.62, S,6.27.
Mol. Formula : $C_{27}H_{21}N_5O_5$
Mol.Wt. : 495.

4-a) 2-(4-Methoxyphenyl)-6-oxo-4-phenyl-8-(phenylamino)-1,6,9,9a-tetrahydro-2H-pyrimido[1,2-a]pyrimidine-7-carbonitrile.

IR : 3365, 2285, 1700, 1650, 1050, $cm^{-1}$;
$^1$H NMR : δ 5.10 (s,1H,NH), 4.10 (s,1H,NH), 6.43 (s,1H,=CH) 5.75 (s,1H,CH), 4.33 (s,1H,NH), 5.54 (s,1H,CH), 7.20 (s,5H,Ar-H), 6.89 (dd,2H,Ar-H),7.25 (dd,2H,Ar-H), 7.01 (s,5H,Ar-H), 3.80 (s,3H,$OCH_3$).
ESI-MS : 449.
Anal. Calcd : $C_{27}H_{23}N_5O_2$: C,72.14; H,5.16; N,15.58; O,7.12
Found : C, 69.48; H,4.81;N,12.03; O,6.83;S,6.85
Mol. Formula : $C_{27}H_{23}N_5O_2$
Mol.Wt. : 449.

4-b) 8-((4-bromophenyl)amino)-2-(4-methoxyphenyl)-6-oxo-4-phenyl-1,6,9,9a-tetrahydro-2H-pyrimido[1,2-a]pyrimidine-7-carbonitrile.

IR : 3320, 2260, 1710, 1630, 1050,660 $cm^{-1}$;
$^1$H NMR : δ 5.08 (s,1H,NH), 4.13 (s,1H,NH), 6.46 (s,1H,=CH) 5.76 (s,1H,CH), 4.63 (s, 1H, NH), 5.50 (s,1H,CH), 7.22 (s,5H,Ar-H), 6.92 (dd,2H,Ar-H), 7.23 (dd,2H,Ar-H), 6.49(dd,2H,Ar-H), 7.32 (dd,2H,Ar-H), 3.78 (s,3H,$OCH_3$)
ESI-MS : 528
Anal. Calcd : $C_{27}H_{22}BrN_5O_2$: C, 61.37; H,4.20;Br,15.12;N, 13.25; O, 6.06
Found : C,59.42; H,3.91; Br,14.58; N,10.32; O,5.89; S,5.88
Mol. Formula : $C_{27}H_{22}BrN_5O_2$
Mol.Wt. : 528.

4-c) 2-(4-methoxyphenyl)-8-((4-nitrophenyl)amino)-6-oxo-4-phenyl-1,6,9,9a-tetrahydro-2H-pyrimido[1,2-a]pyrimidine-7-carbonitrile.

IR : 3370, 2280, 1705, 1670, 1050, $cm^{-1}$;

$^1$H NMR : δ 5.11 (s,1H,NH), 4.09 (s,1H,NH), 6.44 (s,1H,=CH) 5.72 (s,1H,CH), 4.09 (s,1H,NH), 5.56 (s,1H,CH), 7.21 (s,5H,Ar-H), 6.88 (dd,2H,Ar-H),7.25 (dd,2H,Ar-H), 6.63 (dd,2H,Ar-H), 7.98 (dd, 2H,Ar-H), 3.80(s,3H,$OCH_3$)
ESI-MS : 494.
Anal. Calcd : $C_{27}H_{22}N_6O_4$: C,65.58; H,4.48; N,16.99; O,12.94
Found : C,63.45; H,4.13; N,13.67; O,12.48; S,6.27.
Mol. Formula : $C_{27}H_{22}N_6O_4$
Mol.Wt. : 494.

5-a) 2-(4-methoxyphenyl)-6-oxo-4-phenyl-8-(pyrrolidin-1-yl)-1,6,9,9a-tetrahydro-2H-pyrimido[1,2-a]pyrimidine-7-carbonitrile.
IR : 3380, 2265, 1715, 1650, 1050, $cm^{-1}$;
$^1$H NMR : δ 5.10 (s,1H,NH), 6.45 (s,1H,=CH) 5.76 (s,1H,CH), 4.32 (s,1H,NH), 5.52 (s,1H,CH), 7.22 (s,5H,Ar-H), 6.90(dd,2H,Ar-H),7.23 (dd,2H,Ar-H), 3.81 (s,3H,$OCH_3$), 2.60 (t,4H), 1.65 (m,4H)
ESI-MS : 427.
Anal. Calcd : $C_{25}H_{25}N_5O_2$, C,70.24; H,5.89; N,16.38; O,7.48
Found : C,67.57; H,5.41; N, 12.56; O,7.23; S,7.23
Mol. Formula : $C_{25}H_{25}N_5O_2$
Mol.Wt. : 427

5-b) 2-(4-methoxyphenyl)-6-oxo-4-phenyl-8-(piperidin-1-yl)-1,6,9,9a-tetrahydro-2H-pyrimido[1,2-a]pyrimidine-7-carbonitrile.
IR : 3360, 2240, 1715, 1630, 1070, $cm^{-1}$;
$^1$H NMR : δ 5.13 (s,1H,NH), 6.48 (s,1H,=CH) 5.72 (s,1H,CH), 4.54 (s,1H,NH), 5.54 (s,1H,CH),7.20 (s,5H,Ar-H), 6.86 (dd,2H,Ar-H),7.23 (dd,2H,Ar-H), 3.77 (s,3H,$OCH_3$), 3.13 (t,4H), 1.53 (m,6H)
ESI-MS : 441.
Anal. Calcd : $C_{26}H_{27}N_5O_2$, C,70.73; H,6.16; N,15.86; O,7.25
Found : C,68.18; H, 5.69; N,12.22; O,6.94; S,6.97.
Mol. Formula : $C_{26}H_{27}N_5O_2$
Mol.Wt. : 441.

6-a) 2-(7-cyano-2-(4-methoxyphenyl)-6-oxo-4-phenyl-1,6,9,9a-tetrahydro-2H-pyrimido[1,2-a]pyrimidin-8-yl)malononitrile.
IR : 3335, 2970, 2270, 1720, 1640, 1030 $cm^{-1}$;
$^1$H NMR : δ 5.10 (s,1H,NH), 6.49 (s,1H,=CH) 5.73 (s,1H,CH), 4.67 (s,1H,NH), 5.51 (s,1H,CH), 7.23 (s,5H,Ar-H), 6.91 (dd,2H,Ar-H), 7.22 (dd,2H,Ar-H), 4.16 (s,1H,act.-CH), 3.81 (s,3H,$OCH_3$)
ESI-MS : 422.
Anal. Calcd : $C_{24}H_{18}N_6O_2$,C,68.24; H,4.29; N,19.89; O,7.57
Found : C,65.55; H,3.92; N,15.92; O,7.30; S,7.31.
Mol. Formula : $C_{24}H_{18}N_6O_2$
Mol.Wt. : 422.

6-b) ethyl 2-cyano-2-(7-cyano-2-(4-methoxyphenyl)-6-oxo-4-phenyl-1,6,9,9a-tetrahydro-2H-pyrimido[1,2-a]pyrimidin-8-yl)acetate.
IR : 3355, 2265, 1715, 1625, 1050,2910,1760$cm^{-1}$;
$^1$H NMR : δ 5.08 (s,1H,NH), 6.44 (s,1H,=CH), 5.76 (s,1H,CH), 4.33 (s,1H,NH), 5.51 (s,1H,CH), 7.27 (s,5H,Ar-H), 6.89(dd,2H,Ar-H),7.22(dd,2H,Ar-H), 3.98 (s,1H,act.-CH),3.79 (s,3H,$OCH_3$), 4.19 (q,2H), 1.22 (t,3H).
ESI-MS : 469.
Anal. Calcd : $C_{26}H_{23}N_5O_4$: C,66.51; H,4.94; N,14.92; O,13.63
Found : C, 65.74; H,4.44; N,12.28; O,10.53; S,7.01.
Mol. Formula : $C_{26}H_{23}N_5O_4$
Mol.Wt. : 469.

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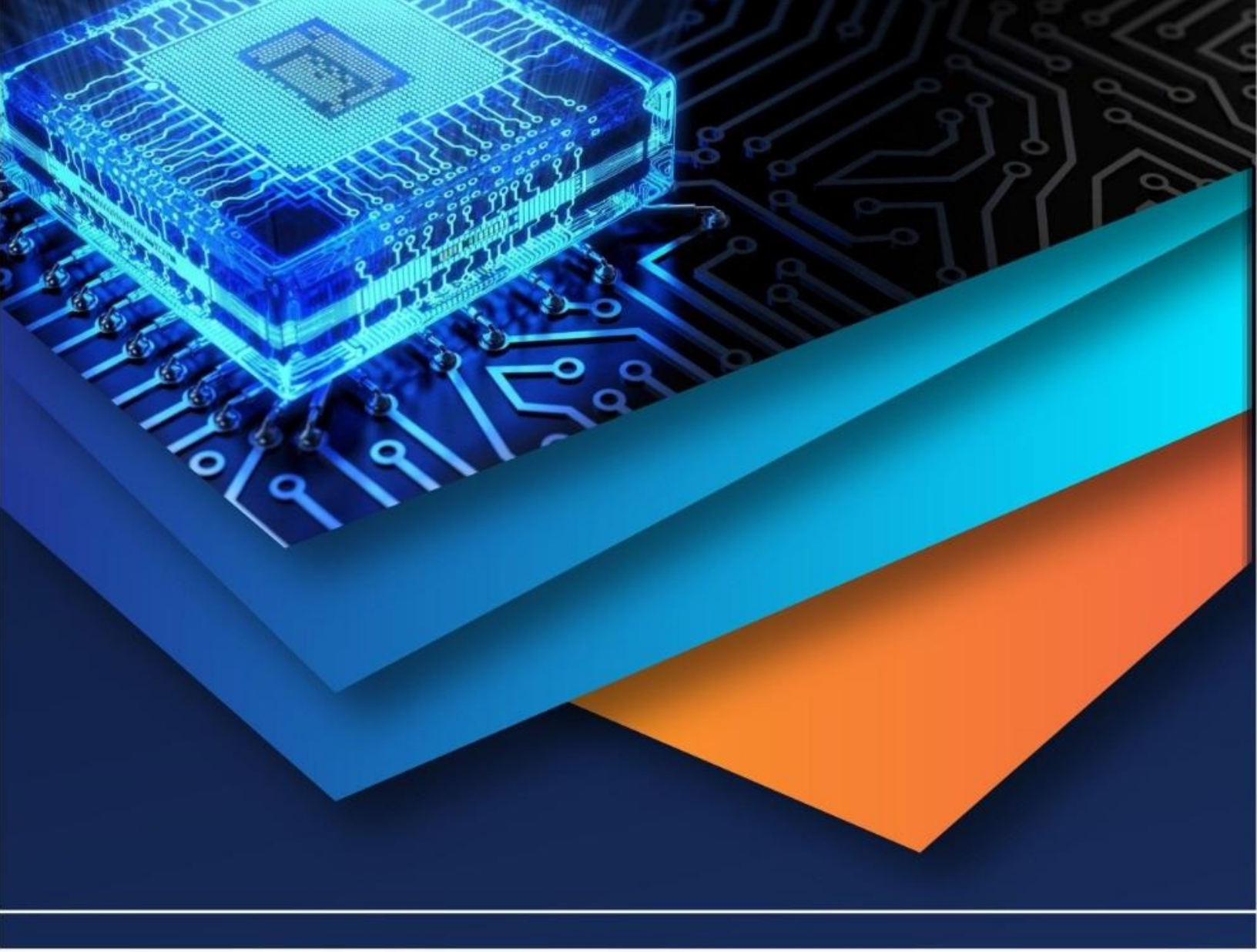

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