SYNTHESIS OF NOVEL IMINO PYRIMIDO PYRIMIDINE AND THEIR DERIVATIVES

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ABSTRACT

Pyrimidine derivatives were synthesized to possess various pharmacological activities. In the present report 3-(4-chloro phenyl)-1-phenyl prop-2en-1-one (1) (chalcone) is synthesized by Claisen-Schmidt condensation reaction using 4-chlorobenzaldehyde and acetophenone in presence of ethanoic KOH. After purification and characterization by physical and spectral methods of synthesized chalcone have been converted into 6-(4-chlorophenyl)-4-phenyl-1, 6-dihydropyrimidin-2-amine(2) by treating with 3-(4-chloro phenyl)-1-phenyl prop-2en-1-one andguanidine nitrate in presence of alkali the structure (2) also confirmed by spectral Characterization. The synthesized (2) reacting with 2-(bis (methylthio) methylene) malononitrlein the presence of catalytic amount of potassium carbonate in DMF under reflux condition. Offered Novel 2-(4-chlorophenyl)-6-imino-8-(methylthio)-4-phenyl-1, 6, 9, 9a-tetrahydro-2H-pyrimido [1, 2-a] pyrimidine-7-carbonitrile (3) in good yields. The compound (3) possesses replaceable methylthio (-SCH_3) group at 8 position. The compound (3) reacting with various nucleophiles like substituted aromatic amines, aromatic phenols, heteryl amines, active methylene compounds to give 2-(4-chlorophenyl)-6-imino-8-(Substituted)-4-phenyl-1,6,9,9a-tetrahydro-2H-pyrimido[1,2-a]pyrimidine-7-carbonitrilein good yields.

Keywords: *Claisen-Schmidt Condensation, Michael addition reaction, 2-(bis (methylthio) methylene) Malononitrle, guanidine nitrate.*

Introduction

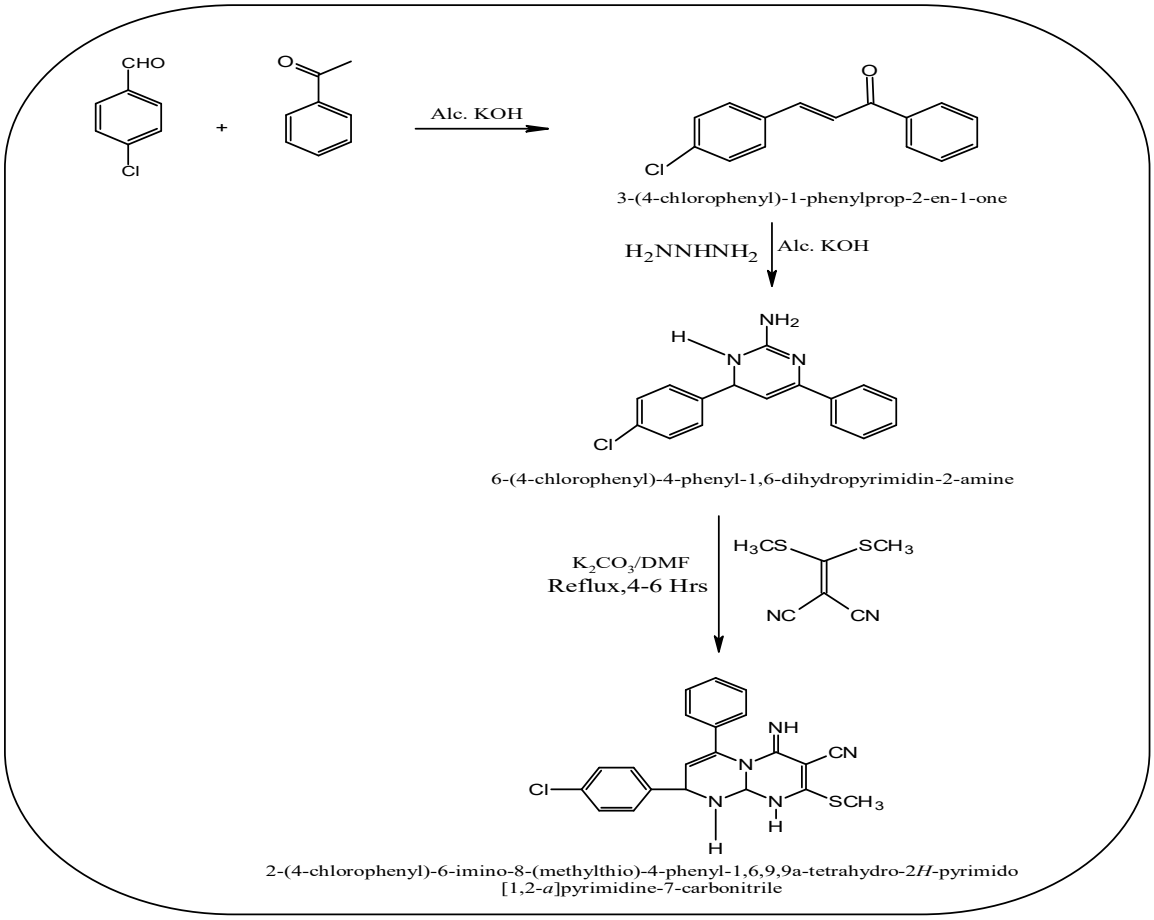
Pyrimidine is a heterocyclic aromatic organic compound containing two nitrogen atoms. It is the biologically important nitrogen-containing molecule called nitrogenous base. Basically pyrimidines are used in our body for the construction of genetic material i.e. deoxyribonucleic acid (DNA) and ribonucleic acid (RNA). In addition pyrimidines also possess antibacterial [1-3], antifungal [4-6],antileishmanial [6],anti-inflammatory [7],analgesic [8], antihypertensive [9], antipyretic [10], antiviral [11], ant diabetic [12], antiallergic [13], antioxidant[14] activities. In the same way pyrimido pyrimidine also have good biological importance. It also act as good pharmacophore. Recently some fused heterocyclic compounds containing nitrogen atom show a wide range of pharmacological activities. Pyrimido pyrimidines are annulated to uracil that have considerable interest in recent years [15-16].Derivatives of pyrimido pyrimidine display potent inhibitory properties regarding tyrosine kinase domain of epidermal growth factor receptor [17].Pyrimido [4, 5-d] pyrimidine fused system represent attractive pharmacological application such as antitumor [18],antiviral [19],antioxidant [20], antifungal [21] and hepatoprotective activities [22].Pyrimido pyrimidine have a ring system that can be found marine derived natural products such as crambescidin [23] alkaloid. Various compounds have been found which inhibit platelet aggregation and reduce adhesiveness one of them from which is trimorpholino pyrimidine is a synthetic analogue of dipyridamole, this analogue shows powerful inhibitor of platelet aggregation and adhesiveness [24].The above observations prompted us to synthesize an imino pyrimido pyrimidine and its derivatives. 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-chlorophenyl)-6-imino-8-(methylthio)-4-phenyl-1, 6, 9, 9a-tetrahydro-2H-pyrimido [1, 2-a] pyrimidine-7-carbonitrile by using 6-(4-chlorophenyl)-4-phenyl-1, 6-dihydropyrimidin-2-amine[25-26]and 2-bis (methylthio) methylene) malononitrle. The amino pyrimidine were prepared by the reaction of Chalcone [27-28] with guanidine nitrate in the presence of ethanol and potassium hydroxide under reflux condition.

Experimental

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.

General Procedure

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



Step – I

A solution of KOH 50% is added to an equimolar solution of acetophenone (0.01mole) and 4-chlorobenzaldehyde (0.01mole) 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 driedunder vacuum. They are crystallized by ethanol compound.

Step – II

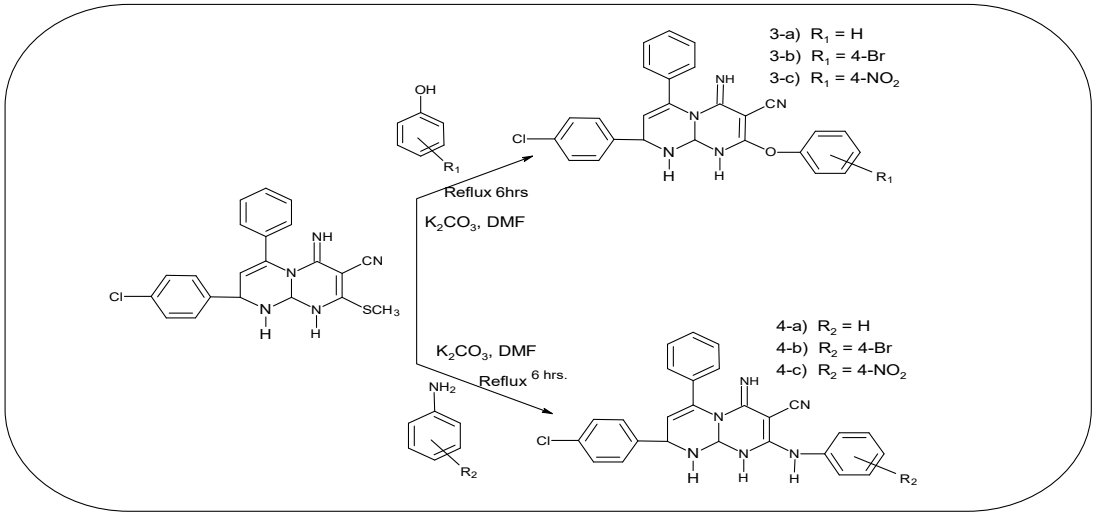
A mixture of chalcone i.e. 3-(4-chlorophenyl)-1-phenylprop-2-en-1-one (2.42 gm, 0.01mole), and guanidine nitrate (1.22 gm 0.01 mole) were dissolved in ethanolic potassium hydroxide solution (10 ml). It was heated for 4 hrs, then it was poured into cold ice obtain 6-(4-chlorophenyl)-4-phenyl-1, 6-dihydropyrimidin-2-amine (2).

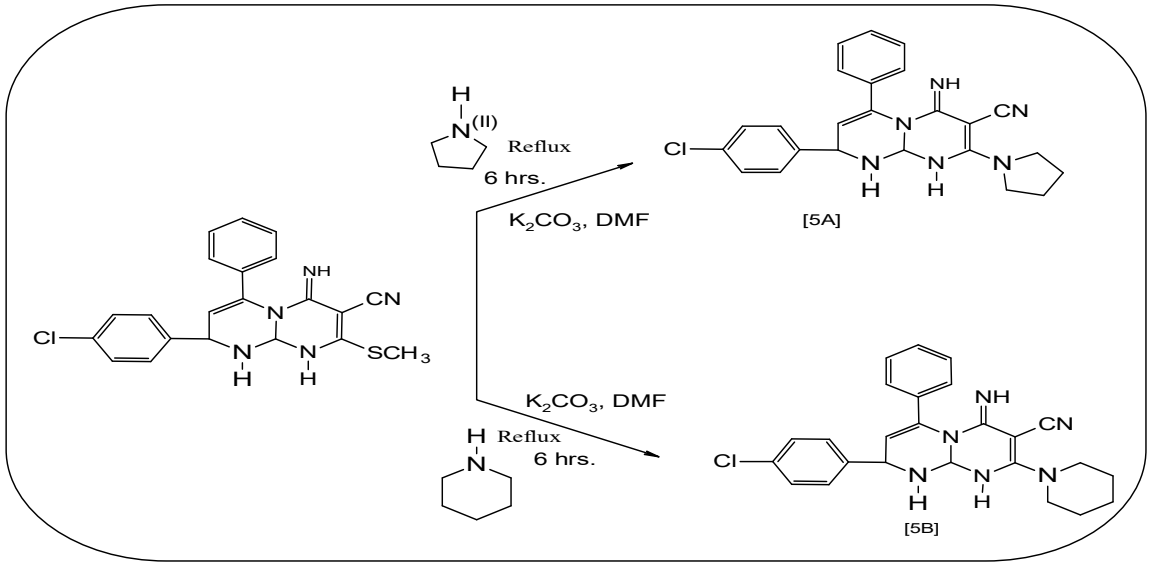
Step – III

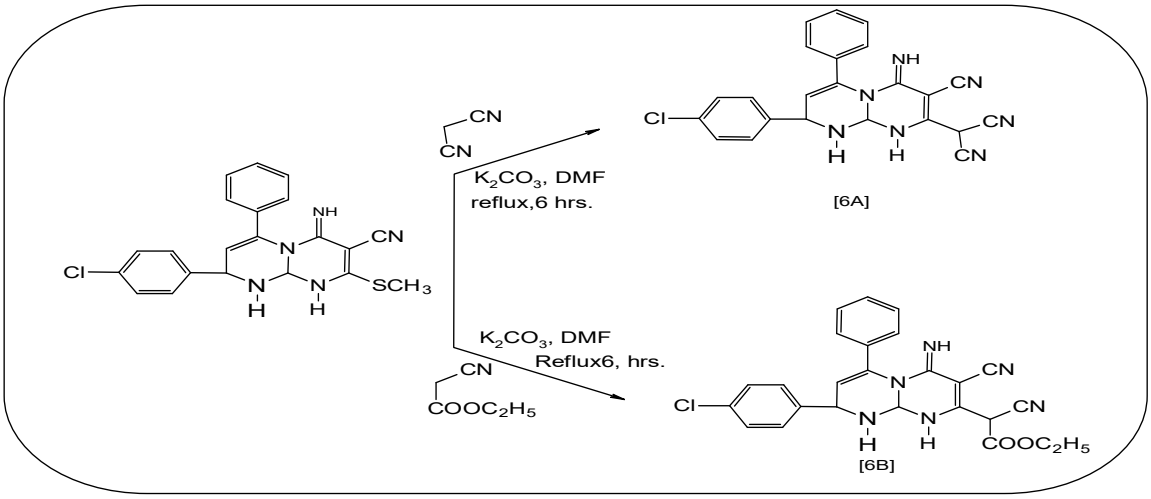
A mixture of 6-(4-chlorophenyl)-4-phenyl-1, 6-dihydropyrimidin-2-amine (2) and 2-(bis (methylthio) methylene) malononitrlein the presence of catalytic amount of potassium carbonate (10 mg) in DMF was refluxed for 6 hrs.The reaction was monitored by TLC. After complete ion, the reaction mixture was set to cool at room temperature.And washed with water the extracted with ethyl acetate. The extract was concentrated and the residue was subjected to column chromatography (silicagel,n-hexane-ethyl acetate 8:2) to obtain pure solid compound 2-(4-chlorophenyl)-6-imino-8-(methylthio)-4-phenyl-1, 6, 9, 9 a-tetrahydro-2H-pyrimido [1, 2-a] pyrimidine-7-carbonitrile(3). The compound (3) confirmed by IR, ^{1}H, C^{13}NMR and MS analytical data.

Synthesis of Derivatives

A mixture of (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 recrystallized using ethyl alcohol.







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Result and Discussion

The compound 2-(4-chlorophenyl)-6-imino-8-(methylthio)-4-phenyl-1, 6, 9, 9 a-tetrahydro-2H-pyrimido [1, 2-a] pyrimidine-7-carbonitrile(3) are synthesized by dissolving 6-(4-chlorophenyl)-4-phenyl-1,6-dihydropyrimidin-2-amine (2) and 2-(bis (methylthio) methylene) malononitrle (1) in presence of K_2CO_3 in DMF under reflux condition. The synthesized compound act as electrophilic species due to leaving nature reacting with various substituted aromatic amines, aromatic phenols, heteryl amines and active methylene compound give 2-(4-chlorophenyl)-6-imino-8-(substituted)-4-phenyl-1, 6, 9, 9 a-tetrahydro-2H-pyrimido [1, 2-a] pyrimidine-7-carbonitrile(3) in good yield.

3) 2-(4-chlorophenyl)-6-imino-8-(methylthio) -4-phenyl-1, 6, 9, 9 a-tetrahydro-2H-pyrimido [1, 2-a] pyrimidine-7-carbonitrile.
^{1}H NMR:2.39 (s, 3H, SCH_3), 5.04 (s, 1H N-H), 4.86 (s 1H CH),1.88 (s 1 H N-H),4.56 (d 1H CH),6.69 (d 1H =CH),7.65(s 5H Ar-H),9.32 (s, 1H =NH), 7.26 (dd, 2H Ar-H), 7.32 (dd, 2H Ar-H).**IR (KBr, cm^{-1}):** 3350, 2240, 1650,760 cm^{-1}; Mass (**ESI-MS):***m/z* ($M^{+)}$ 407 (M+2) 409. **Anal. Calcd for**$C_{21}H_{18}CLN_5S$: C, 61.83; H, 4.45; CL, 8.69; N, 17.17; S, 7.86.**Found:**C, 61.76; H, 4.48; CL, 8.73; N, 17.25; S, 7.78.**Mol. Formula:**$C_{21}H_{18}CLN_5S$.**Mol.Wt:**407 & 409.

3-a) 2-(4-chlorophenyl)-6-imino-8-phenoxy-4-phenyl-1,6,9,9a-tetrahydro-2H-pyrimido[1,2-a]pyrimidine-7-carbonitrile .
^{1}H NMR: 5.02(s, 1H N-H), 4.82 (s 1H CH), 1.86 (s1H N-H), 4.51 (d 1H CH), 6.70 (d 1H =CH), 7.60 (s 5H Ar-H), 9.30 (s, 1H =NH), 7.25 (dd, 2H Ar-H), 7.30 (dd, 2H Ar-H), 7.10(s 5H Ar-H).**IR (KBr, cm^{-1}):**3350, 2240, 650,760cm^{-1}; **Mass (ESI-MS):***m/z* ($M^{+)}$ 453. (M+2) 455. **Anal. Calcd for**$C_{26}H_{20}ClN_5O$: C, 68.80; H, 4.44; Cl, 7.81;N, 15.43; O, 3.52. **Found:** C, 68.74; H, 4.49; Cl, 7.85; N, 15.47; O, 3.45.**Mol. Formula:**$C_{26}H_{20}ClN_5O$.**Mol.Wt:**453 & 455.

3-b) 8-(4-bromophenoxy)-2-(4-chlorophenyl) -6-imino-4-phenyl-1,6,9,9a-tetrahydro-2H-pyrimido[1,2-a]pyrimidine-7-carbonitrile.
^{1}H NMR: 5.05 (s, 1H N-H), 4.83 (s 1H CH), 1.95 (s 1 H N-H), 4.54 (d 1H CH), 6.69 (d 1H =CH), 7.65(s 5H Ar-H), 9.32 (s, 1H =NH), 7.24 (dd, 2HAr-H), 7.29 (dd, 2H Ar-H).6.81 (dd 2H Ar-H),
7.38 (dd 2H Ar-H).**IR (KBr, cm^{-1}):**3350, 2240, 650,760cm^{-1}; **Mass (ESI-MS):***m/z* ($M^{+)}$ 531 (M+2) 533.**Anal. Calcd for**$C_{26}H_{19}BrClN_5O$: C,61.53; H, 3.93; Cl , 8.65 ; N, 10.25; O, 7.81;S,7.83;
Found C, 61.45; H, 3.97; Cl ,8.69 ; N, 10.35; O, 7.86; S,7.86; **Mol. Formula:**$C_{26}H_{19}BrClN_5O$. **Mol.Wt:**531 &533.

3-c) 2-(4-chlorophenyl)-6-imino-8-(4-nitrophenoxy)-4-phenyl-1,6,9,9a-tetrahydro-2H- pyrimido[1,2-a]pyrimidine-7-carbonitrile.
^{1}H NMR: 5.02 (s, 1H N-H), 4.83 (s 1H CH),1.94 (s 1 H N-H),4.54 (d 1H CH),6.70 (d 1H =CH) ,7.62(s 5H Ar-H),9.31 (s, 1H =NH),

7.25 (dd, 2H Ar-H), 7.30 (dd, 2H Ar-H),7.15 (dd 2H Ar-H),8.12 (dd 2H Ar-H).**IR (KBr, cm^{-1}):**3350, 2260, 1650, 760, 1510 cm^{-1}. **Mass (ESI-MS):***m/z* (M^+) 498 (M+2) 500. **Anal. Calcd for**$C_{26}H_{19}ClN_6O_3$:C, 62.59; H, 3.84; Cl, 7.11; N, 16.84; O, 9.62; **Found**C, 62.69; H, 3.80; Cl, 7.14; N, 16.78; O, 9.59; **Mol. Formula:**$C_{26}H_{19}ClN_6O_3$.**Mol.Wt:** 498 & 500.

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

^{1}H NMR: 5.02 (s, 1H N-H), 4.84 (s 1H CH), 1.88 (s 1 H N-H), 4.56 (d 1H CH), 6.69 (d 1H =CH), 7.58 (s 5H Ar-H), 9.36 (s, 1H =NH), 7.29 (dd, 2H Ar-H), 7.34 (dd, 2H Ar-H), 10.74 (s 1H N-H), 6.80 (s 5H Ar-H).**IR (KBr, cm^{-1}):**3350, 2240, 1650, 760, 3250 cm^{-1}; **Mass (ESI-MS):***m/z*(M^+) 452 (M+2) 454. **Anal. Calcd for**$C_{26}H_{21}ClN_6$:C, 68.95; H, 4.67; Cl ,7.83 ; N, 18.55; **Found**:C, 68.83; H, 4.71; Cl, 7.87; N, 18.59;**Mol. Formula:**$C_{26}H_{21}ClN_6$.**Mol.Wt :** 452 & 454.

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

^{1}H NMR:5.03 (s, 1H N-H), 4.84 (s 1H CH),1.85 (s 1 H N-H),4.56 (d 1H CH),6.70 (d 1H =CH),7.54(s 5H Ar-H),9.32 (s, 1H =NH),7.26 (dd, 2H Ar-H), 7.32 (dd, 2H Ar-H), 10.70 (s 1H N-H) ,6.78 (dd 2H Ar-H),7.24 (dd 2H Ar-H).**IR (KBr, cm^{-1}):**3350, 2240, 1650, 3250, 640, 760 cm^{-1} ;**Mass (ESI-MS):***m/z* ($M^{+)}$ 530 (M+2) 532. **Anal. Calcd for**$C_{26}H_{20}BrClN_6$:C, 58.72; H, 3.79; Br, 15.02; Cl, 6.67; N, 15.80; **Found**: C, 58.80; H, 3.75; Br, 15.06; Cl, 6.63; N, 15.76.**Mol. Formula:**$C_{26}H_{20}BrClN_6$. **Mol.Wt :** 530 &532

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

^{1}H NMR: 5.04 (s, 1H N-H), 4.83 (s 1H CH),1.86 (s 1 H N-H),4.55 (d 1H CH),6.69 (d 1H CH) , 7.64(s 5H Ar-H),9.34 (s, 1H =NH),7.24 (dd, 2H Ar-H), 7.29 (dd, 2H Ar-H),11.26 (s 1H N-H),6.90 (dd 2H Ar-H),7.86 (dd 2H Ar-H).**IR (KBr, cm^{-1}):**3350, 2240, 1650, 3250, 1480, 760 cm^{-1}. **Mass (ESI-MS):***m/z* (M^+) 497 (M+2) 499.**Anal. Calcd for**$C_{26}H_{20}ClN_7O_2$:C, 62.72; H, 4.05; Cl, 7.12; N, 19.69; O, 6.43; **Found**: C, 62.64; H, 4.09; Cl, 7.06; N, 19.73; O, 6.48. **Mol. Formula:**$C_{26}H_{20}ClN_7O_2$. **Mol.Wt:**497 & 499.

5-a) 2-(4-chlorophenyl)-6-imino-4-phenyl-8-(pyrrolidin-1-yl)-1, 6, 9,9a-tetrahydro-2H-Pyrimido [1, 2-a] pyrimidine-7-carbonitrile.

^{1}H NMR: 5.06 (s, 1H N-H), 4.79 (s 1H CH),1.81 (s 1 H N-H),4.52 (d 1H CH),6.64 (d 1H =CH),7.66(s 5H Ar-H),9.30 (s, 1H =NH),7.22 (dd, 2H Ar-H), 7.27 (dd, 2H Ar-H), 2.50 (t 4H), 1.50 (quintet 4H).**IR (KBr, cm^{-1}):**3350, 2240, 1650, 760 cm^{-1}; **Mass (ESI-MS):***m/z* ($M^{+)}$ 430 (M+2) 432. **Anal. Calcd for**$C_{24}H_{23}ClN_6$: C, 66.89; H, 5.38; Cl , 8.23 ; N, 19.50;**Found**C, 66.83; H, 5.43; Cl , 8.29 ; N, 19.45;**Mol.Formula:**$C_{24}H_{23}ClN_6$. **Mol.Wt:**430 & 432.

5-b) 2-(4-chlorophenyl)-6-imino-4-phenyl-8-(piperidin-1-yl)-1, 6, 9,9a-tetrahydro-2H-Pyrimido [1, 2-a] pyrimidine-7-carbonitrile.

^{1}H NMR: 5.04 (s, 1H N-H), 4.81 (s 1H CH), 1.84 (s 1 H N-H), 4.52 (d 1H CH), 6.68 (d 1H =CH), 7.68(s 5H Ar-H), 9.29 (s, 1H =NH), 7.24 (dd, 2H Ar-H), 7.29 (dd, 2H Ar-H), 3.12 (t 4H), 1.50 (m 6H).**IR (KBr, cm^{-1}):**3350, 2240, 1650, 760cm^{-1}; **Mass (ESI-MS):** *m/z* ($M^{+)}$ 444 (M+2) 446.**Anal. Calcd for**$C_{25}H_{25}ClN_6$: C, 67.48; H, 5.66; Cl , 7.97 ; N, 18.89;.**Found**C, 67.55; H, 5.60; Cl, 7.90; N, 18.95.**Mol. Formula:**$C_{25}H_{25}ClN_6$.**Mol.Wt:** 444 & 446.

6-a) 2-(2-(4-chlorophenyl)-7-cyano-6-imino-4-phenyl-1,6, 9, 9a-tetrahydro-2H-Pyrimido[1, 2-a] pyrimidin-8-yl)malononitrle.

^{1}H NMR:5.02 (s, 1H N-H), 4.83 (s 1H CH), 1.87 (s 1 H N-H), 4.53 (d 1H CH), 6.67 (d 1H =CH), 7.70 (s 5H Ar-H), 9.30 (s, 1H =NH),7.23 (dd, 2H Ar-H), 7.30 (dd, 2H Ar-H), 4.14 (s 1H act-CH).**IR (KBr, cm^{-1}):**3350, 2240, 1650, 2950, 760 cm^{-1}; **Mass (ESI-MS):** *m/z* ($M^{+)}$ 425 (M+2) 427. **Anal. Calcd for**$C_{23}H_{16}ClN_7$: C, 64.87; H, 3.79; Cl , 8.32 ; N, 23.02; **Found**C, 64.75; H, 3.85; Cl , 8.35 ; N, 23.05.**Mol. Formula:**$C_{23}H_{16}ClN_7$.**Mol.Wt:** 425 & 427.

6-b) ethyl 2-(2-(4-chlorophenyl)-7-cyano-6-imino-4-phenyl-1,6,9,9a-tetrahydro-2H-Pyrimido[1,2-a]pyrimidin-8-yl)-2-cyanoacetate.

^{1}H NMR:5.05 (s, 1H N-H), 4.83 (s 1H CH), 1.85 (s 1 H N-H), 4.50 (d 1H CH), 6.71 (d 1H =CH) , 7.60(s 5H Ar-H), 9.31 (s, 1H =NH), 7.25 (dd, 2H Ar-H), 7.28 (dd, 2H Ar-H), 4.05(s 1H act-CH) , 4.16(quartet 2H),1.16 (t 3H).**IR (KBr, cm^{-1}):**3350,2240, 1650,1950,1710, 760 cm^{-1} ; **Mass(ESI-MS) :***m/z* ($M^{+)}$ 472 (M+2) 474.**Anal. Calcd for**$C_{25}H_{21}ClN_6O_2$: C, 63.49; H, 4.48; Cl , 7.50 ; N, 17.77; O, 6.77; **Found**C, 63.39; H, 4.58; Cl , 7.42 ; N, 17.88; O, 6.73; **Mol. Formula:**$C_{25}H_{21}ClN_6O_2$.**Mol.Wt:** 472 & 474.

Conclusion

A new different 2-(4-chlorophenyl)-6-imino-8-(substituted)-4-phenyl-1, 6, 9, 9 a-tetrahydro-2H-pyrimido [1, 2-a] pyrimidine-7-carbonitrileare synthesized by using simple and efficient chemistry and this synthesized compounds possesses methylthio group at 8-position which is best leaving group therefore synthesized compound act as an electrophilic species and reacting with various nucleophiles. In compound (3) cyano and thiomethyl groupsare at adjacent positionit also undergo cyclization to give polycyclic heterocyclic compound.

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