SYNTHESIS OF NOVEL IMINO PYRIMIDO THIAZINE AND THEIR DERIVATIVES

S.B. Sirsat[1], A.G. Jadhav[2], M.S. Jadhav[3*], H.J. Bhosale[4] and P.S kale[5]
[1,5]Post Graduate Research Centre, Dept. of Chemistry, Yeshwant Mahavidyalaya, Nanded, MS, India
[2]Department of Chemistry, Mahatma Gandhi Mahavidyalaya Ahmadpur
[3]Department of Chemistry, Shri Shivaji College Parbhani, MS, India
[4]School of Life Sciences, Swami Ramanand Teerth Marathwada University Nanded, MS, India
[1]sbs.igm@gmail.com, [2*]madhavj7778@gmail.com

ABSTRACT

In present report we have synthesized a novel 6-imino-2-(4-methoxyphenyl)-8-(methylthio)-4-phenyl-2,6,9,9a-tetrahydropyrimido[2,1-b][1,3]thiazine-7-carbonitrile by the reaction 6-(4-methoxyphenyl) 4-phenyl-6H-1,3-thiazin-2amine with 2-(bis (methylthio) methylene) malononitrile in the presence of catalytic amount of potassium carbonate in DMF under reflux condition. The amino thiazine are prepared by the reaction of chalcone with thiourea in the presence of ethanoic KOH under reflux condition. The synthesized compounds were characterized by spectral methods. The synthesized compound possesses replaceable methylthio (-SCH_3) group at 8 position. The synthesized compound { 6-imino-2-(4-methoxyphenyl)-8-(methylthio)-4-phenyl-2,6,9,9a-tetrahydropyrimido[2,1-b][1,3]thiazine-7-carbonitrile} react with various nucleophiles like substituted aromatic amines, aromatic phenols, hetryl amines and active methylene compounds to give novel 6-imino-2-(4-methoxyphenyl)-8-(Substituted)-4-phenyl-2,6,9,9a-tetrahydropyrimido [2,1-b][1,3]thiazine-7-carbonitrile (3) in good yields.

Keywords: *Claisen-Schmidt Condensation, 2-(bis (methylthio) methylene malononitrile, Michael addition reaction, Thiourea.*

Introduction

Thiazines are six membered heterocycles that contain a nitrogen atom and sulphur atoms in their structure .Thiazine are very useful units in field of medicinal and pharmaceutical chemistry and have been reported to exhibit variety of biological activities [1]. 1, 3-thiazine core moieties have remarkable potential of anti-radiation agents [2]. 1, 3-thiazines are used in various organic synthesis and transformations as reaction intermediates [2-3].Thiazine derivatives having N-C-S linkage exhibit a variety of biological activities. Like, antitubercular, antibacterial, antimicrobial, antitumor, insecticidal, fungicidal and herbicidal agents [3-12]. Some derivatives of thiazine are cannabinoid receptor agonists, also they can act as an anti-hypotensive. Moreover, thiazine derivatives can be used for gastrointestinal disorders or diabetes prevention [13-18]. In the view of this observation and extension of earlier work, we have synthesized novel 6-imino-2-(4-methoxyphenyl)-8-(methylthio)-4-phenyl-2,6,9,9a-tetrahydro pyri- mido[2,1 - b][1,3]thiazine-7-carbonitrile by using 3-(4-methoxyphenyl)-1-phenyl prop-2-en-1-one [19-20] and 6-(4-methoxyphenyl) 4-phenyl-6H-1,3-thiazin-2-amine[21-22].

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

6-imino-2-(4-methoxyphenyl)-8-(methylthio)-4-phenyl-2,6,9,9a-tetrahydropyrimido[2,1-b][1,3]thiazine-7-carbonitrile.

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

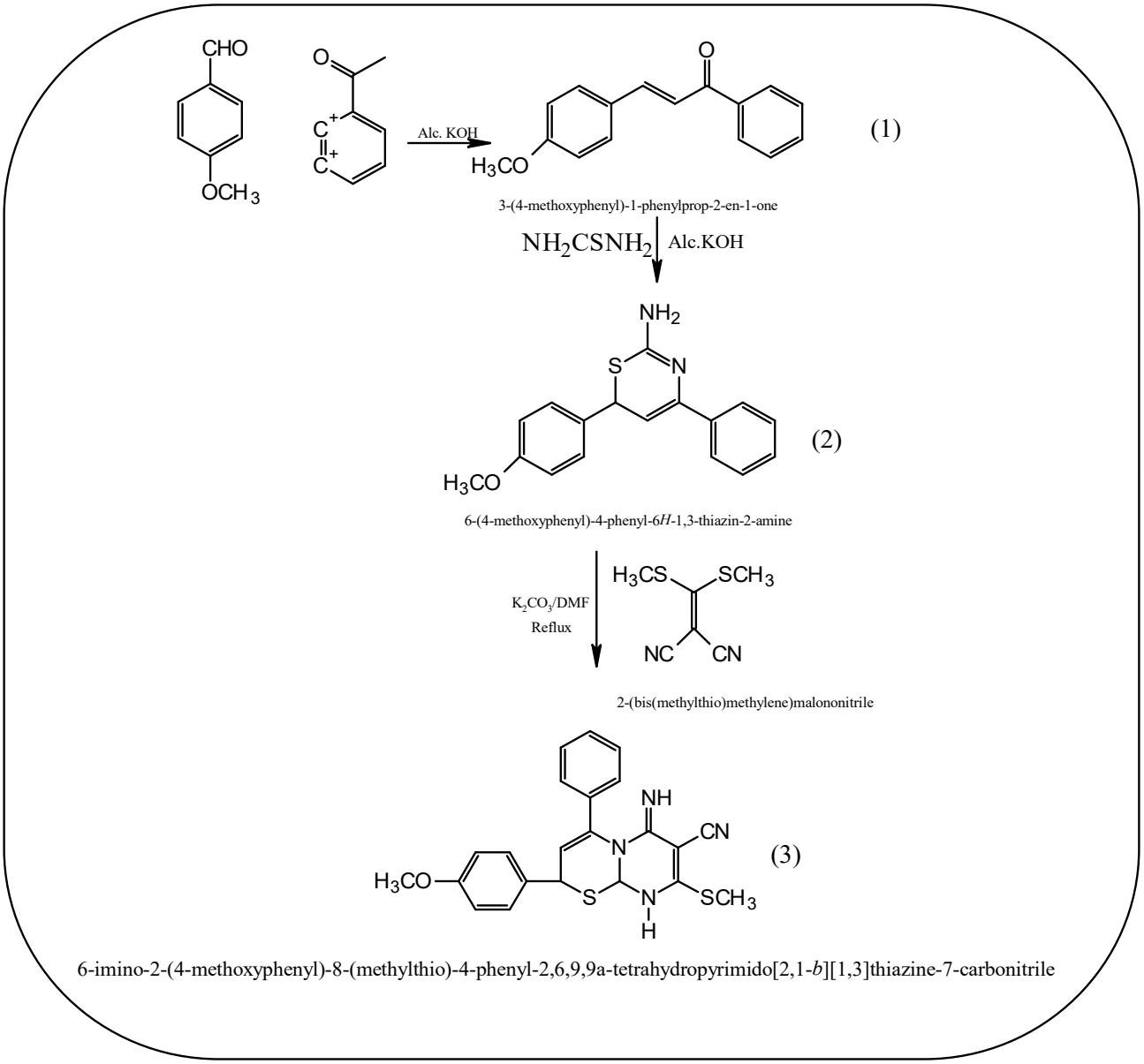
then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. They are crystallized by ethanol compound.

Step – II

A mixture of chalcone i.e. 3-(4-methoxyphenyl)-1-phenylprop-2-en-1-one (2.38 gm,0.01mole), and thiourea (0.76 gm., 0.01 mole) were dissolved in ethanoic potassium hydroxide solution (10 ml) was heated for 4 hrs., then it was poured into cold ice obtained 6-(4-methoxyphenyl)-4-phenyl-6H-1,3-thiazin-2-amine (2).

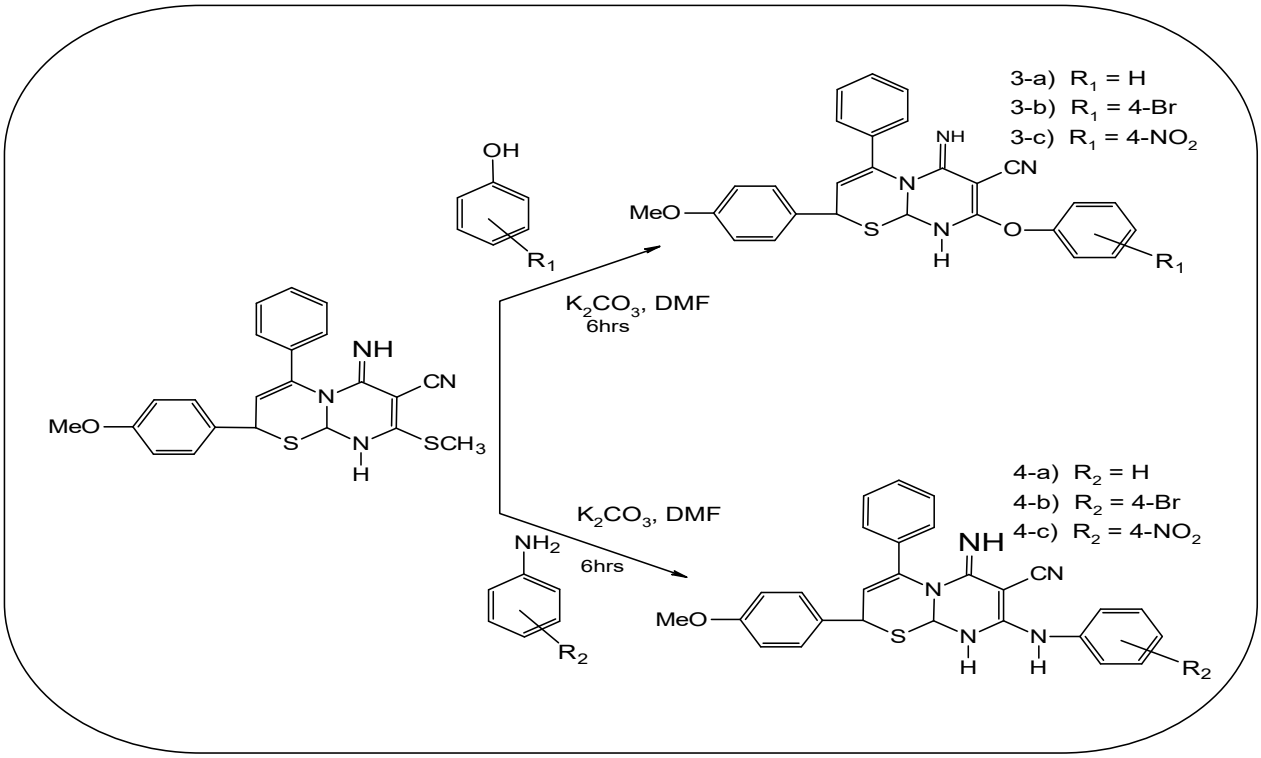
Step – III

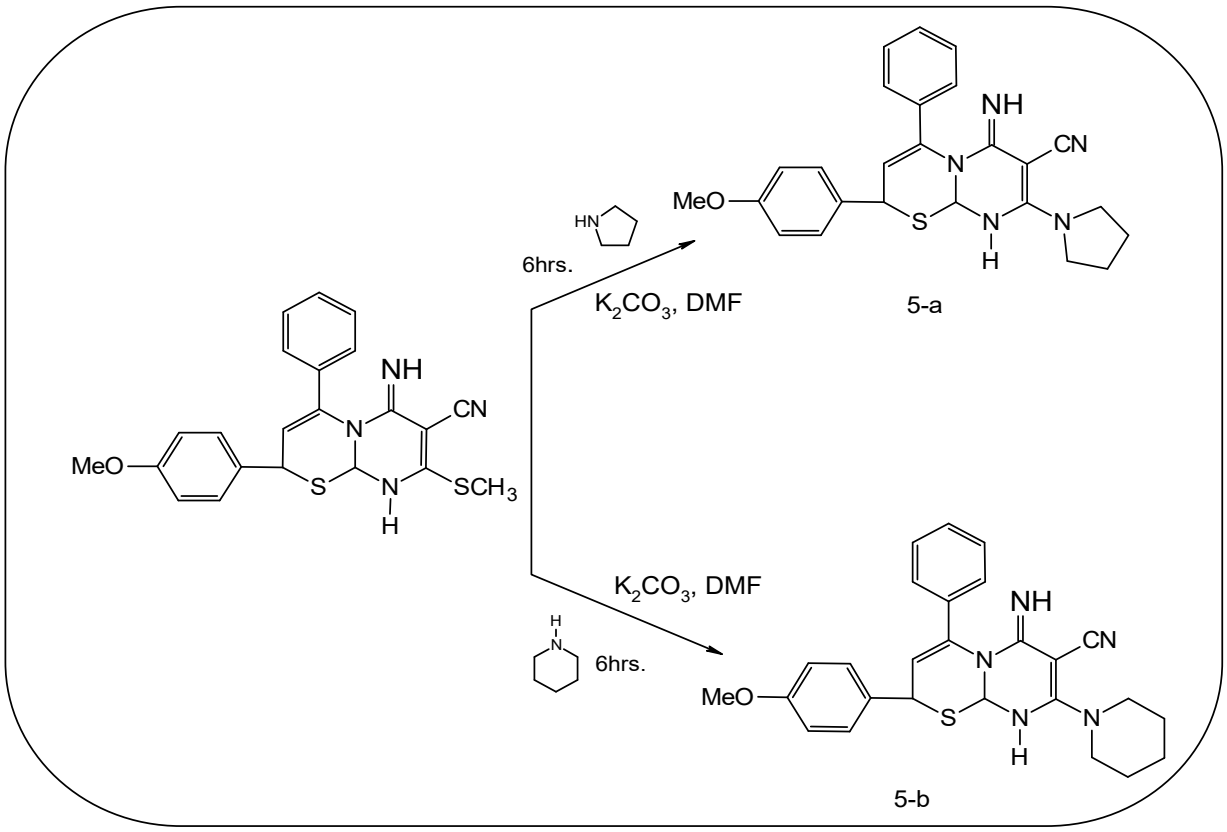
A mixture of 6-(4-methoxyphenyl)-4-phenyl-6H-1, 3-thiazin-2-amine (2) and 2-(bis (methylthio) methylene) malononitrile in the presence of catalytic amount of potassium carbonate (10 mg) in DMF was refluxed for 6 hours, the reaction was monitored by TLC. After completion, the reaction mixture was cooled at room temperature then wash with water the 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 6-imino-2-(4-methoxyphenyl)-8-(methylthio)-4-phenyl-2,6,9,9a-tetrahydropyrimido[2,1-b] [1,3]thiazine-7-carbonitrile (3). The compound (3) confirmed by IR, ^{1}H and C^{13} NMR and MS analytical data.

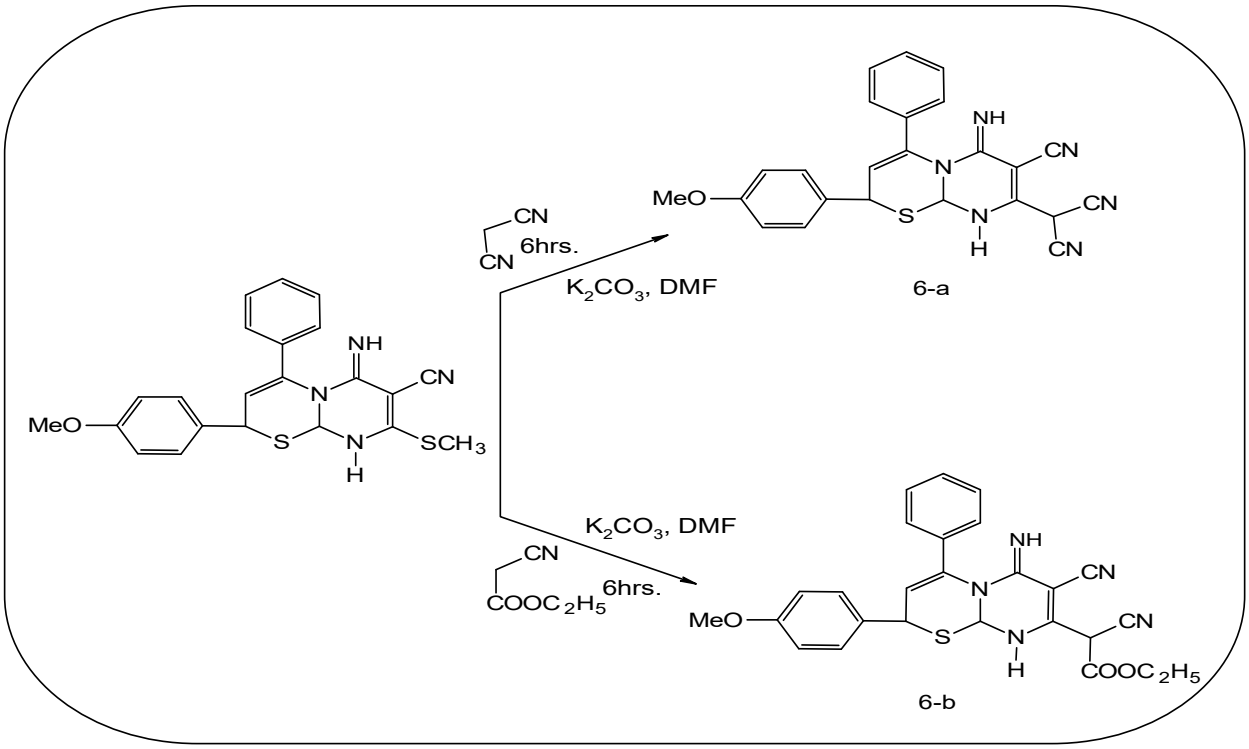


Synthesis of Derivatives

A mixture of (3) (1mmol) and independently, various substituted aromatic amines, substituted 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.







Result and Discussion

The compound 6-imino-2-(4-methoxyphenyl)-8-(methylthio)-4-phenyl-2,6,9,9a-tetrahy dropyrimido[2,1-b][1,3]thiazine-7-carbonitrile are synthesized by dissolving 6-(4-methoxy phenyl)4-phenyl-6H-1,3-thiazine-2-amine (2) and 2(bis(methylthio)methylene) malononitrle 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 6-imino-2-(4-methoxyphenyl)-8-(substituted)-4-phenyl-2,6,9,9a-tetrahydropyrimido[2,1-b] [1,3] thiazine-7-carbonitrile in good yields.

3)6-imino-2-(4-methoxyphenyl)-8-(methylthio)-4-phenyl-2,6,9,9 a tetrahydropyrimido[2,1b][1, 3] thiazine-7-carbonitrile.

IR : 3360, 2250, 1660, 1060 cm^{-1};
^{1}H NMR :
δ 2.51(s,3H,SCH_3), 5.72(s,1H,NH),8.22(s 1H = NH), 5.42(s, 1H =CH) 4.54 (s1HCH), 4.76(s, 1HCH), 7.24(s, 5HAr-H), 7.22(dd, 2HAr H)
6.92 (dd, 2H Ar-H), 3.79 (s, 3H).
ESI-MS : 420.
Anal.Calcd for $C_{22}H_{20}N_4OS_2$: C, 62.83; H, 4.79; N, 13.32; O, 3.80; S, 15.25
Found : C,62.63; H, 4.52; N,12.96; O, 4.63; S, 15.26.
Mol. Formula: $C_{22}H_{20}N_4OS_2$
Mol.Wt. : 420.

3-a) 6-imino-2-(4-methoxyphenyl)-8-phenoxy-4-phenyl-2,6,9,9a-tetrahydropyrimido[2,1-b][1,3]thiazine-7-carbonitrile.

IR : 3340, 2240, 1670, 1050, cm^{-1};
^{1}H NMR : 5.74 (s, 1H NH), 8.27(s 1H =NH), 5.39 (s, 1H=CH) 4.51 (s, 1H CH), 4.79
(s, 1H CH), 7.18 (s, 5H Ar-H), 6.88 (dd, 2H Ar-H), 7.23 (dd, 2H Ar-H),
6.99 (s 5H Ar-H), 3.78 (s, 3H)
ESI-MS : 466.
Anal. Calcd. : $C_{27}H_{22}N_4O_2S$ C, 69.51; H, 4.75; N, 12.01; O, 6.86; S, 6.87
Found : C, 69.34; H, 4.52; N, 12.15; O, 7.21; S, 6.78.
Mol. Formula: $C_{27}H_{22}N_4O_2S$
Mol.Wt. : 466.

3-b) 8-(4-bromophenoxy)-6-imino-2-(4-methoxyphenyl)-4-phenyl-2,6,9,9a-tetrahydropyrimido[2,1-b][1,3]thiazine-7-carbonitrile.

IR : 3330, 2210, 1650, 1050, 660 cm^{-1};
^{1}H NMR : 5.78 (s, 1H NH), 8.29(s 1H =NH,), 6.40 (s, 1H =CH) 4.50 (s, 1H CH), 4.82 (s, 1H CH), 7.23 (s, 5H Ar-H), 6.91 (dd, 2H Ar-H), 7.25 (dd, 2H Ar- H), 6.89 (dd 2H Ar-H), 7.40 (dd 2 H Ar-H), 3.76(s, 3H)
ESI-MS : 545.
Anal. Calcd : $C_{27}H_{21}BrN_4O_2S$: C, 59.45; H, 3.88; Br, 14.65; N, 10.27; O, 5.87; S, 5.88.
Found : C, 59.31; H, 3.62; Br,14.60; N,10.71; O,5.91; S,5.85.
Mol. Formula: $C_{27}H_{21}BrN_4O_2S$
Mol.Wt : 545.

3-c) 6-imino-2-(4-methoxyphenyl)-8-(4-nitrophenoxy)-4-phenyl-2,6,9,9a-tetrahydropyrimido[2,1-b][1,3]thiazine-7-carbonitrile.
IR : 3330, 2210, 1650, 1050, 1510 cm^{-1};
^{1}H NMR : 5.79 (s, 1H NH), 8.32(s 1H =NH), 6.44 (s, 1H =CH) 4.59 (s, 1H CH), 4.78 (s, 1H CH), 7.24 (s, 5H Ar-H), 6.92 (dd, 2H Ar-H), 7.24 (dd, 2H Ar-H), 7.19 (dd 2 H Ar-H), 7.98 (dd 2 H Ar-H), 3.80 (s, 3H)
ESI-MS : 511.
Anal. Calcd : $C_{27}H_{21}N_5O_4S$: C, 63.39; H, 4.14; N, 13.69; O, 12.51; S, 6.27.
Found : C, 63.29; H, 3.91; N, 13.85; O, 12.67, S, 6.28.
Mol. Formula: $C_{27}H_{21}N_5O_4S$
Mol.Wt. : 511.

4-a) 6-imino-2-(4-methoxyphenyl)-4-phenyl-8-(phenylamino)-2,6,9,9a-tetrahydropyrimido[2,1-b][1,3]thiazine-7-carbonitrile.
IR : 3330, 2210, 1650, 1050, 1590 cm^{-1};
^{1}H NMR : 7.89 (s, 1H NH), 8.36(s 1H =NH) 4.45 (s, 1NH), 6.40 (s, 1H =CH), 4.62 (s,1H CH), 4.82 (s, 1H CH), 7.27 (s, 5H Ar-H), 6.87 (dd, 2H Ar-H), 7.24 (dd, 2H Ar-H), 7.05 (s 5H Ar-H), 3.77 (s, 3H).
ESI-MS : 465.
Anal. Calcd : $C_{27}H_{23}N_5OS$: C, 69.65; H, 4.98; N, 15.04; O, 3.44; S, 6.89
Found : C, 69.48; H, 4.81; N, 15.13; O, 3.73; S, 6.85
Mol. Formula: $C_{27}H_{23}N_5OS$
Mol.Wt. : 465.

4-b) 8-((4-bromophenyl)amino)-6-imino-2-(4-methoxyphenyl)-4-phenyl-2,6,9,9a-tetrahydropyrimido[2,1-b][1,3]thiazine-7-carbonitrile.
IR : 3330, 2210, 1650, 1050, 660 cm^{-1};
^{1}H NMR : 7.82 (s, 1H NH), 4.52 (s, 1H NH), 8.38, (s 1H =NH) 6.38 (s, 1H =CH) 4.49 (s, 1H CH), 4.84 (s 1H CH), 7.23 (s, 5H Ar-H), 6.90 (dd, 2H Ar-H), 7.24 (dd, 2H Ar-H), 6.48 (dd 2H Ar-H), 7.32 (dd 2 H Ar-H), 3.75 (s, 3H)
ESI-MS : 544.
Anal. Calcd for $C_{27}H_{22}BrN5OS$: C, 59.56; H, 4.07; Br, 14.68; N, 12.86; O, 2.94; S, 5.89
Found : C,59.42; H,3.91; Br,14.58; N,13.02; O,3.19; S,5.88
Mol. Formula: $C_{27}H_{22}BrN_5OS$,
Mol.Wt. : 544.

4-c) 6-imino-2-(4-methoxyphenyl)-8-((4-nitrophenyl)amino)-4-phenyl-2,6,9,9a-tetrahydropyrimido[2,1-b][1,3]thiazine-7-carbonitrile.
IR : 3330, 2210, 1650, 1050, 1580 cm^{-1};
^{1}H NMR : 7.84 (s, 1H NH), 4.49 (s, 1NH), 8.40 (s 1H =NH), 6.42 (s, 1H = CH), 4.54 (s, 1H CH), 4.80 (s, 1H CH), 7.22 (s, 5H Ar-H), 6.90 (dd, 2H Ar-H), 7.23 (dd, 2H Ar-H), 6.48 (dd 2H Ar- H), 7.90 (dd 2H ArH), 3.74(s, 3H)
ESI-MS : 510.
Anal. Calcd : $C_{27}H_{22}N_6O_3S$: C, 63.52; H, 4.34; N, 16.46; O, 9.40; S, 6.28
Found : C, 63.45; H, 4.13; N, 16.67; O, 9.48; S, 6.27.
Mol. Formula: $C_{27}H_{22}N_6O_3S$.
Mol.Wt. : 510.

5-a) 6-imino-2-(4-methoxyphenyl)-4-phenyl-8-(pyrrolidin-1-yl)-2,6,9,9a-tetrahydropyrimido [2, 1-b][1, 3]thiazine-7-carbonitrile.

IR : 3330, 2210, 1650, 1050, 1580 cm^{-1};

^{1}H NMR : 7.82 (s, 1H NH), 8.45 (s 1H =NH), 6.47 (s, 1H=CH) 4.49 (s, 1H CH), 4.78 (s, 1H CH), 7.25 (s, 5H Ar-H), 6.87 (dd, 2H Ar-H), 7.19 (dd, 2H Ar-H), 3.78 (s, 3H), 2.58 (t, 4H), 1.59 (m, 4H)

ESI-MS : 443.

Anal. Calcd : $C_{25}H_{25}N_5OS$, C, 67.69; H, 5.68; N, 15.79; O, 3.61; S,7.23.

Found : C, 67.67; H, 5.63; N, 15.76; O, 3.73; S, 7.21

Mol. Formula: $C_{25}H_{25}N_5OS$

Mol.Wt. : 443

5-b) 6-imino-2-(4-methoxyphenyl)-4-phenyl-8-(piperidin-1-yl)-2,6,9,9a-tetrahydropyrimido[2,1-b][1,3]thiazine-7-carbonitrile.

IR : 3330, 2210, 1650, 1050, 1580 cm^{-1};

^{1}H NMR : 7.88 (s, 1H NH), 8.49 (s 1H =NH), 6.38 (s, 1H=CH) 4.66 (s, 1H CH), 4.82 (s, 1H CH), 7.26 (s, 5H Ar-H), 6.85 (dd, 2H Ar-H), 7.20 (dd, 2H Ar-H), 3.74 (s, 3H), 3.09 (t, 4H), 1.52 (m, 6H).

ESI-MS : 457.

Anal. Calcd : $C_{26}H_{27}N_5OS$, C, 68.24; H, 5.95; N, 15.30; O, 3.50; S, 7.01.

Found : C, 68.28; H, 5.79; N, 15.32; O, 3.64; S, 6.97.

Mol. Formula: $C_{26}H_{27}N_5OS$.

Mol.Wt. : 457.

6-a) 2-(7-cyano-6-imino-2-(4-methoxyphenyl)-4-phenyl-2,6,9,9a-tetrahydropyrimido[2,1-b][1,3]thiazin-8-yl)malononitrile:

IR : 3330, 2210, 1650, 1050 cm^{-1};

^{1}H NMR : 7.89 (s, 1H NH), 8.46 (s 1H =NH), 6.41 (s, 1H=CH) 4.50 (s, 1H CH), 4.69 (s, 1H CH), 7.19 (s, 5H Ar-H), 6.87 (dd, 2H Ar-H), 7.21 (dd, 2H Ar-H), 4.09 (s 1H act.-CH), 3.71 (s, 3H).

ESI-MS : 438.

Anal. Calcd : $C_{24}H_{18}N_6OS$, C, 65.74; H, 4.14; N, 19.17; O, 3.65; S, 7.31.

Found : C, 65.83; H, 4.11; N,19.15; O, 3.62; S, 7.29.

Mol. Formula: $C_{24}H_{18}N_6OS$

Mol.Wt. : 438.

6-b) ethyl2-cyano-2-(7-cyano-6-imino-2-(4-methoxyphenyl)-4-phenyl-2,6,9,9a-tetrahydropyrimido[2,1-b][1,3]thiazin-8-yl)acetate:

IR : 3330, 2210, 1650, 1050, 2910, 1710 cm^{-1};

^{1}H NMR : 7.80 (s, 1H NH), 8.47 (s 1H =NH), 6.38 (s, 1H=CH), 4.46 (s, 1H CH), 4.71 (s, 1H CH), 7.22 (s, 5H Ar-H), 6.90 (dd, 2H Ar-H), 7.20 (dd, 2H Ar-H), 3.97 (s, 1H act.-CH), 3.76 (s, 3H), 4.16 (q, 2H), 1.17 (t, 3H).

ESI-MS : 485.

Anal. Calcd : $C_{26}H_{23}N_5O_3S$: C,64.31; H,4.77; N,14.42; O,9.89; S,6.60

Found : C, 64.14; H, 4.47; N, 14.88; O, 9.32; S, 7.19.

Mol. Formula: $C_{26}H_{23}N_5O_3S$.

Mol.Wt. : 485.

Conclusion

A new different 6-imino-2-(4-methoxyphenyl)-8-(methylthio)-4-phenyl-2,6,9,9 a-tetrahydropyrimido[2,1-b][1,3]thiazine-7-carbonitrile are 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 groups are at adjacent position it also undergo cyclization to give polycyclic heterocyclic compound.

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