SIMPLE AND EFFICIENT SYNTHESIS OF IMINO PYRIMIDO THIAZINE AND THEIR DERIVATIVES.

Sirsat Shivraj B, Jadhav Anilkumar G, Khansole Sandeep V, Ade Suraj B, Bobade Dnyaneshwar R, Kale Prashant S, Jadhav Madhav S.*
P.G. Research Centre, Department Of Chemistry,
Yeshwant Mahavidyalaya, Nanded-431602(MS) India.

Abstract : In this review we report simple and efficient synthesis of novel fused tricyclic heterocyclic compounds by heating 6-imino-2-(4-methoxyphenyl)-8-(methylthio)-4-phenyl-9,9a-dihydro-2H,6H-pyrimido[2,1-b][1,3]thiazine-7-carbonitrile with hydrazine, substituted phenyl hydrazine and substituted benzothiazole using potassium carbonate in DMF as solvent under reflux condition to give 4-imino-8-(4-methoxyphenyl)-2-substituted-6-phenyl-2,4,9a,10-tetrahydro-8H-pyrazolo[3',4':4,5]pyrimido[2,1-b][1,3]thiazin-3-amine.

Keywords: Addition-elimination reaction, pyrimido thiazine, hydrazine, substituted phenyl hydrazine, substituted benzothiazole.

I. INTRODUCTION

Thiazines are an important type of heterocyclic compounds. Heterocyclic compounds are abundant in nature and have acquired more importance because their structural subunits are exhibit in various natural products such as vitamins, hormones, antibiotics etc. Thiazine core having great interest in recent years especially in synthetic drug formulation owing to their biological activities that showed a wide variety of pharmacological properties. Some derivatives of thiazine are cannabinoid receptor agonists, also they can act as an antihypotensive, antitubercular and antibacterial agents. Moreover, thiazine derivatives can be used for gastrointestinal disorders or diabetes prevention[1-6]. Thiazine derivatives having N-C-S linkage have been used as antibacterial, antimicrobial, antitumor, insecticidal, fungicidal, herbicidal agents, tranquilizers and various dyes etc[7-16].
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 6-imino-2-(4-methoxyphenyl)-8-(methylthio)-4-phenyl-9,9a-dihydro-2H,6H-pyrimido[2,1-b][1,3]thiazine-7-carbonitrile by using 6-(4-methoxyphenyl)-4-phenyl-6H-1,3-thiazin-2-amine[17-18] and 2-bis(methylthio)methylene) malononitrile. Aminothiazines with amino group occupying the position in between two hetero atoms are important synthetic target as well as building block of various heterocycles. These substituted 2-amino-1,3-thiazines are proved to be very potent antimicrobial[19], antiinflammatory[20], antihypertensive[21], calcium channel blocker[22] etc. The amino thiazines are prepared by the reaction of chalcone with thiourea in the presence of ethanol and sodium hydroxide under reflux condition. The chalcones possess a wide range of biological activities such as antimicrobial, antibacterial, antiviral, analgesic[23-26] etc.

II. 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.

Synthesis of 6-imino-2-(4-methoxyphenyl)-8-(methylthio)-4-phenyl-9,9a-dihydro-2H,6H-pyrimido[2,1-b][1,3]thiazine-7-carbonitrile . (Scheme 1)

Step – I

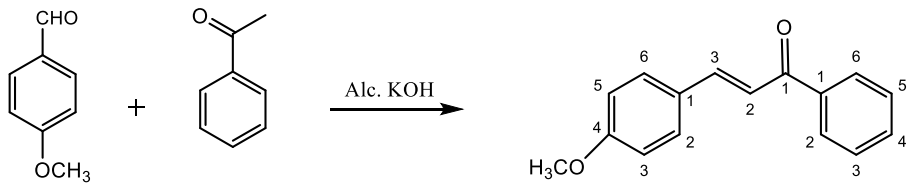
A solution of KOH 50 % is added to an equimolar solution of acetophenone (0.01mole) and 4-Methoxybenzaldehyde (0.01mole) in ethanol 95 %; the addition is performed under energetic stirring at room temperature. The reaction is left under stirring for one night and then diluted with water and acidified; the precipitate is separated by filtration and dried under vacuum. They are crystallized by ethanol compound.

Step – II

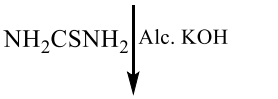
A mixture of chalcone i.e. (4-methoxyphenyl)-1-phenylprop-2-en-1-one (2.42 g, 0.01mole), and thiourea (0.60 g 0.01 mole) were dissolved in ethanolic potassium hydroxide solution (10 ml). It was heated for 4 hrs, then it was poured into cold ice obtain 6-(4-methoxyphenyl)-4-phenyl-6H-1, 3-thiazin-2-amine (2).

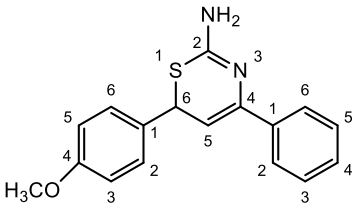
Step – III

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 hrs. The reaction was monitored by TLC. After completion, 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 (silica gel, n-hexane-ethyl acetate 8:2) to obtain pure solid compound 6-imino-2-(4-methoxyphenyl)-8-(methylthio)-4-phenyl-9,9a-dihydro-2H,6H-pyrimido[2,1-b][1,3]thiazine-7-carbonitrile (3). The compound (3) confirmed by IR, ^{1}H, C^{13} NMR and MS analytical data.

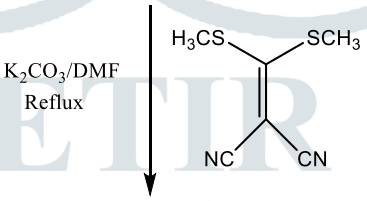


(4-methoxyphenyl)-1-phenylprop-2-en-1-one

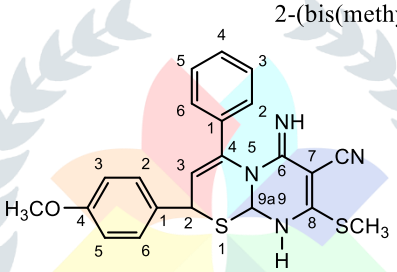




6-(4-methoxyphenyl)-4-phenyl-6*H*-1,3-thiazin-2-amine



2-(bis(methylthio)methylene)malononitrile



6-imino-2-(4-methoxyphenyl)-8-(methylthio)-4-phenyl-9,9a-dihydro-2*H*,6*H*-pyrimido[2,1-*b*][1,3]thiazine-7-carbonitrile

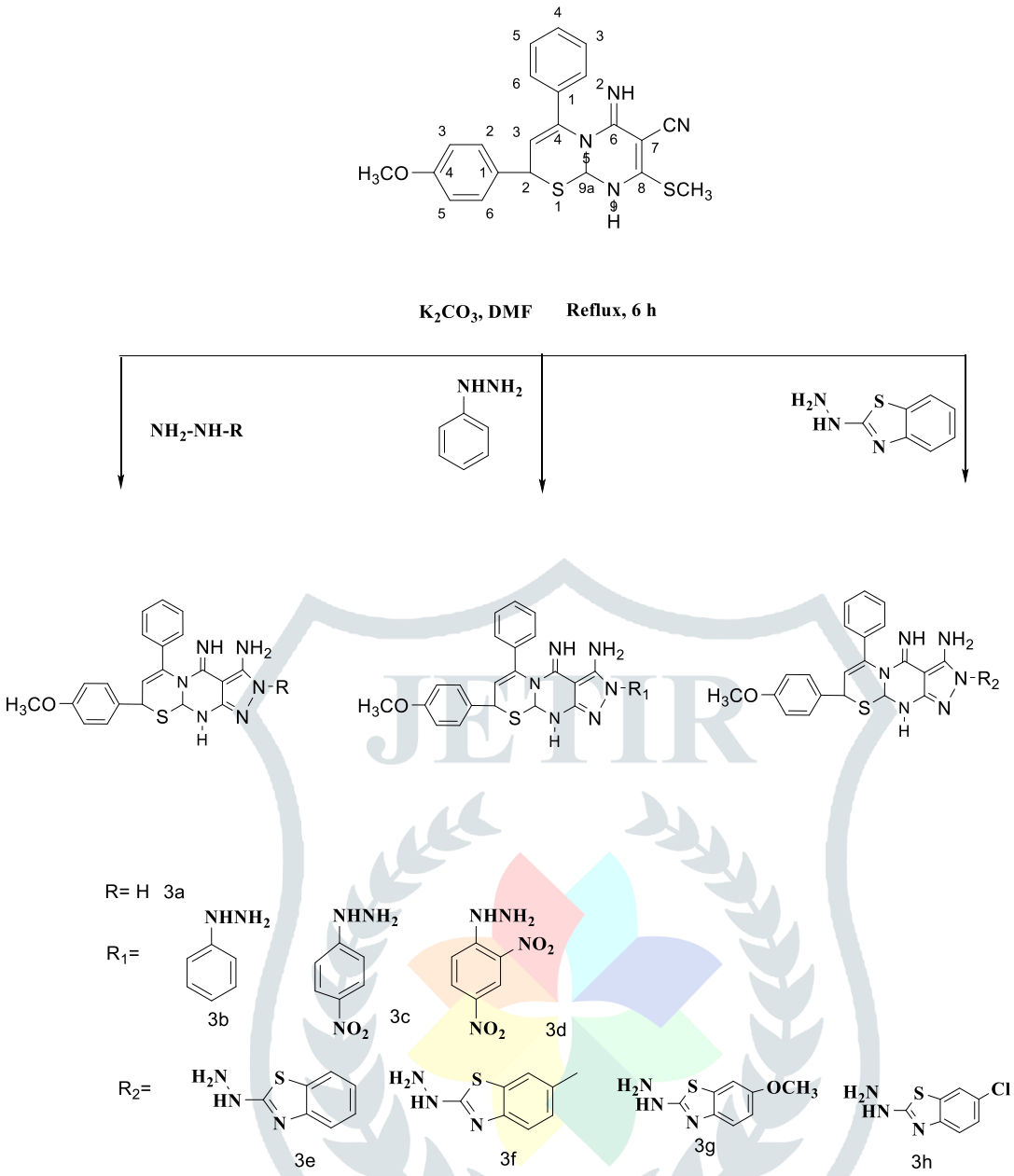
Scheme 1

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

IR : 3360, 2250, 1660, 1060 cm^{-1};
^{1}H NMR : δ2.51(s,3H,SCH_3),5.72(s,1H,NH),8.22(s,1H=NH),5.42 (s, 1H=CH) 4.54(s,1H,CH), 4.76(s,1H,CH), 7.24(s,5H,Ar-H), 7.22(dd, 2H, Ar-H) ,6.92 (dd,2H, Ar-H),3.79 (s,3H,OCH_3).
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.

Synthesis of Derivatives (Scheme 2)

A mixture of (3) (1mmol) and independently, various hydrazine, substituted hydrazine, substituted benzothiazole (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.



Scheme 2

3-a) 4-imino-8-(4-methoxyphenyl)-6-phenyl-2,4,9a,10-tetrahydro-8H-pyrazolo [3',4':4,5]pyrimido[2,1-b][1,3]thiazin-3-amine.

IR : 3320,1645,1610, 1310,1080 cm^{-1};

1H NMR : δ 7.67 (s,5H, Ar-H), 7.39(dd,2H, Ar-H),6.78(dd,2H, Ar-H),6.68(s,1H, N-H),12.58(s,1H,N-H),10.61(s,1H,=NH),6.19(s,2H,NH2),6.68(d,1H,=CH),4.44(d,1H,CH),4.73 (s,1H, CH), 3.79(s,3H).

ESI-MS : *m/z* (M^{+}) 404

Anal. Calcd for $C_{21}H_{20}N_6OS$:C, 62.36; H, 4.98; N, 20.78; O, 3.96; S, 7.93

Found : C, 62.30; H, 4.94; N, 20.84; O, 3.98; S, 7.94.

Mol. Formula : $C_{21}H_{20}N_6OS$.

Mol.Wt : 404.

3-b) 4-imino-8-(4-methoxyphenyl)-2,6-diphenyl-2,4,9a,10-tetrahydro-8H-pyrazolo [3',4':4,5]pyrimido[2,1-b][1,3] thiazin-3-amine.

IR : 3310, 1660,1600, 1290,1110 cm^{-1};

1H NMR : δ 7.62 (s, 5H, Ar-H), 7.41(dd,2H, Ar-H),7.78(dd,2H, Ar-H),6.67(s,1H, N-H),10.63(s,1H,=NH),6.39(s,2H,NH_2),6.66(d,1H, =CH),4.43(d,1H, CH),4.75(s,1H CH),7.55(s,5H Ar-H),3.78(s,3H).

ESI-MS : *m/z* (M^{+})480.

Anal. Calcd for $C_{21}H_{20}N_6OS$:C, 67.48; H, 5.03; N, 17.49; O, 3.33; S, 6.67

Found : C, 67.40; H, 5.06; N, 17.52; O, 3.30; S, 6.72

Mol. Formula: $C_{27}H_{24}N_6OS$

Mol.Wt : 480.

3-c) 4-imino-8-(4-methoxyphenyl)-2-(4-nitrophenyl)-6-phenyl-2,4,9a,10-tetrahydro-8H-pyrazolo[3',4':4,5]pyrimido [2,1-b][1,3]thiazin-3-amine .

IR : 3330, 1670,1620, 1280,1120,815cm^{-1};

1H NMR : δ 7.64 (s, 5H, Ar-H), 6.37(dd,2H, Ar-H),6.81(dd,2H, Ar-H),6.68(s,1H ,N-H), 10.62(s,1H, =NH),6.63(s,2H, NH_2),6.69(d,1H, =CH),4.48(d,1H, CH),4.72(s,1H, CH), 8.10(dd,2H, Ar-H),8.30(dd,2H, Ar-H),3.80(s,3H).

ESI-MS : *m/z* (M^+) 525.
Anal. Calcd for $C_{27}H_{23}N_7O_3S$:C, 61.70; H, 4.41; N, 18.66; O, 9.13; S, 6.10.
Found : C, 61.65; H, 4.36; N, 18.71; O, 9.15; S, 6.13.
Mol. Formula: $C_{27}H_{23}N_7O_3S$.
Mol.Wt : 525.

3-d)2-(2,4-dinitrophenyl)-4-imino-8-(4-methoxyphenyl)-6-phenyl-2,4,9a,10-tetrahydro-8H-pyrazolo[3',4':4,5]pyrimido[2,1-b][1,3]thiazin-3-amine.

IR : 3320, 1660,1610, 1290,1130,875,cm^{-1};
^{1}H NMR : δ 7.67 (s, 5H, Ar-H), 6.43(dd,2H, Ar-H),6.83(dd,2H, Ar-H),6.69(s,1H, N-H),10.59(s,1H,=NH),6.37(s,2H,NH_2),6.68(d,1H,=CH),4.39(d,1H,CH),4.75(s,1H, CH),8.79(s,1H, Ar-H),8.09(d,1H, Ar-H),8.70(d,1H, Ar-H),3.76(s,3H).
ESI-MS : *m/z* (M^+) 570.
Anal. Calcd for $C_{27}H_{22}N_8O_5S$:C, 56.84; H, 3.89; N, 19.64; O, 14.02; S, 5.62.
Found : C, 56.80; H, 3.83; N, 19.69; O, 14.04; S, 5.64.
Mol. Formula: $C_{27}H_{22}N_8O_5S$.
Mol.Wt : 570.

3-e) 2-(benzo[d]thiazol-2-yl)-4-imino-8-(4-methoxyphenyl)-6-phenyl-2,4,9a,10-tetrahydro-8H-pyrazolo[3',4':4,5]pyrimido [2,1-b][1,3]thiazin-3-amine..

IR : 3300, 1640,1590, 1270,1110,670,1610.cm^{-1};
^{1}H NMR : δ 7.67 (s,5H, Ar-H), 7.39(dd,2H,Ar-H),6.82(dd,2H, Ar-H),6.67(s,1H, N-H),10.62(s,1H,=NH),6.38(s,2H,NH_2),6.69(d,1H,=CH),4.42(d,1H,CH),4.74(s,1H,CH),7.49 (dd,1H, Ar-H),7.51(dd,1H, Ar-H),8.00(d,1H, Ar-H),8.10(d,1H, Ar-H),3.77(s,3H).
ESI-MS : *m/z* (M^+)537.
Anal. Calcd for $C_{28}H_{23}N_7OS_2$:C, 62.55; H, 4.31; N, 18.24; O, 2.98; S, 11.93.
Found : C, 62.61; H, 4.35; N, 18.19; O, 2.95; S, 11.90.
Mol. Formula: $C_{28}H_{23}N_7OS_2$.
Mol.Wt : 537.

3-f) 4-imino-8-(4-methoxyphenyl)-2-(6-methylbenzo[d]thiazol-2-yl)-6-phenyl-2,4,9a,10-tetrahydro-8H-pyrazolo[3',4':4,5]pyrimido[2,1-b][1,3]thiazin-3-amine.

IR : 3310, 1630,1580, 1250,1120,675,1627.cm^{-1};
^{1}H NMR : δ 7.69 (s, 5H, Ar-H), 7.36(dd,2H, Ar-H),6.84(dd,2H, Ar-H),6.68(s,1H, N-H),10.63(s,1H,=NH),6.39(s,2H,NH_2),6.68(d,1H,=CH),4.46(d,1H,CH),4.79(s,1H, CH),7.12(s,1H, Ar-H),7.41(d,1H, Ar-H),7.82(d,1H, Ar-H),2.41(s, 3H) 3.79,(s,3H).
ESI-MS : *m/z* ($M^{+)}$ 551
Anal. Calcd for $C_{29}H_{25}N_7OS_2$: C, 63.14; H, 4.57; N, 17.77; O, 2.90; S, 11.62
Found : C, 63.20; H, 4.61; N, 17.80; O, 2.82; S, 11.57.
Mol. Formula: $C_{29}H_{25}N_7OS_2$.
Mol.Wt : 551 .

3-g) 4-imino-2-(6-methoxybenzo[d]thiazol-2-yl)-8-(4-methoxyphenyl)-6-phenyl-2,4,9a,10-tetrahydro-8H-pyrazolo[3',4':4,5]pyrimido[2,1-b][1,3]thiazin-3-amine.

IR : 3330, 1610,1560, 1245,1110,670,1618.cm^{-1};
^{1}H NMR : δ 7.65(s,5H,Ar-H),7.41(dd,2H,Ar-H),6.82(dd,2H,Ar-H),6.67(s,1H,N-H), 10.59(s,1H,=NH),6.38(s,2H,NH_2),6.69(d,1H,=CH),4.49(d,1H,CH),4.72(s,1H,CH),7.02(d,1H, Ar-H),7.48(d,1H, Ar-H),7.49 (s,1H, Ar-H),3.82(s,3H).3.78(s,3H).
ESI-MS : *m/z* (M^+)567.
Anal. Calcd for $C_{29}H_{25}N_7O_2S_2$: C, 61.36; H, 4.44; N, 17.27; O, 5.64; S, 11.29.
Found : C, 61.40; H, 4.50; N, 17.23; O, 5.62; S, 11.25.
Mol. Formula : $C_{29}H_{25}N_7O_2S_2$.
Mol.Wt : 567.

3-h) 2-(6-chlorobenzo[d]thiazol-2-yl)-4-imino-8-(4-methoxyphenyl)-6-phenyl-2,4,9a,10-tetrahydro-8H-pyrazolo[3',4':4,5]pyrimido[2,1-b][1,3]thiazin-3-amine

IR : 3315, 1620, 1570, 1255, 1130, 665, 1615 cm^{-1};
^{1}H NMR : δ 7.68 (s,5H ,Ar-H), 7.41(dd,2H,Ar-H),6.84(dd,2H, Ar-H),6.62(s,1H, N-H), 10.63(s,1H =NH),6.41(s,2H,NH_2),6.67(d,1H,=CH),4.47(d,1H,CH),4.73(s,1H,CH), 7.52(d,1H, Ar-H),7.58(d,1H, Ar-H),8.08 (s,1H, Ar-H),3.78(s,3H).
ESI-MS : *m/z* ($M^{+)}$572.
Anal. Calcd for $C_{28}H_{22}ClN_7OS_2$:C, 58.78; H, 3.88; Cl, 6.20; N, 17.14; O, 2.80; S, 11.21.
Found : C, 58.73; H, 3.84; Cl, 6.19; N, 17.20; O, 2.82; S, 11.22
Mol. Formula: $C_{28}H_{22}ClN_7OS_2$.
Mol.Wt : 572.

III. RESULT AND DISCUSSION

The compound 6-imino-2-(4-methoxyphenyl)-8-(methylthio)-4-phenyl-9,9a-dihydro-2H,6H-pyrimido[2,1-b][1,3]thiazine-7-carbonitrile (3) are synthesized by dissolving 6-(4-methoxy- phenyl)-4-phenyl-6H-1,3-thiazin-2-amine and 2(bis(methylthio)methylene) malononitrile in presence of K_2CO_3 in DMF under reflux condition. The synthesized compound acts as electrophilic species due to leaving nature of thiomethyl group reacts with various hydrazine, substituted

phenyl hydrazine, substituted benzothiazole to give 4-imino-8-(4-methoxyphenyl)-2-substituted-6-phenyl-2,4,9a,10-tetrahydro-8H-pyrazolo[3',4':4,5]pyrimido[2,1-b][1,3]thiazin-3-amine in good yield.

IV. CONCLUSION

A new different 4-imino-8-(4-methoxyphenyl)-2-substituted-6-phenyl-2,4,9a,10-tetrahydro-8H-pyrazolo[3',4':4,5]pyrimido[2,1-b][1,3]thiazin-3-amine 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.

V. ACKNOWLEDGMENT

The authors are grateful to Dr. G.N. Shinde, Principal, Yeshwant Mahavidyalaya, Nanded, for providing laboratory facilities &Vishnu Chemicals Ltd., Hyderabad. For providing spectral data.

REFERENCES

1. (a)Kai, H., Morioka, Y., Tomida, M., Takahashi, T., Hattori, M., Hanasaki, K., Koike, K., Chiba, H., Shinohara, S., Kanemasa, T., Iwamoto, Y., Takahashi, K., Yamaguchi, Y., Baba, T., Yoshikawa, T., Takenaka, H., 2-Arylimino-5, 6-dihydro-4 H -1,3-thiazines as a new class of cannabinoid receptor agonists. Part 2: Orally bioavailable compounds.,BioOrg. &Med.Chem.Lett, **2007**, 17 (14), 3925.doi.org/10.1016/j.bmcl.2007.04.099 . (b)Kai, H., Morioka, Y., Murashi, T., Morita, K., Shinonome, S., Nakazato, H., Kawamoto, K., Hanasaki, K., Takahashi, F., Mihara, S., Morita, K., Shinonone, S., Nakazato, H., Kaomoto, K., Hanasaki, F., Arai, T., Abe, K., Okabe, H., Baba, T., Yoshikawa, T., Takenaka, H., 2-Arylimino-5,6-dihydro-4 H -1,3-thiazines as a new class of cannabinoid receptor agonists. Part 1: discovery of CB2 receptor selective compounds.,BioOrg. &Med.Chem.Lett.,**2007**, Vol. 17 (14), 4030.doi.org/10.1016/j.bmcl.2007.04.093 .
2. Trofimova, T. P., Zefirova, O. N., Mandrugin, A. A.,Fedoseev, V. M., Peregud, D. I., Onufriev, M. V., Gulycaeva, N. V., Proskuryakov, S. Y., Synthesis and Study of NOS-Inhibiting Activity of 2-N-Acylamino-5,6-dihydro-4H-1,3-thiazine., Moscow University Chem.Bull, **2008**, 63,274.doi.org/10.3103/s0027131408050088
3. Koketsu, M., Tanaka, K., Takenaka, Y., Kwong, C. D., Ishihara, H., Synthesis of 1,3-thiazine derivatives and their evaluation as potential antimycobacterial agents., Eur. J. Pharm. Sci, **2002**, Vol.15 (3), 307-310.doi.org/10.1016/s0928-0987(02)00014-3
4. Dabholkar, V. V., Gawande, R. P., RasayanJ.Chem, **2010**, 3 (4), 655.
5. Bourzet, J. D., Cotrel, C., Guyon, C., Pitchen, Ph.US Patent 4994569. doi.org/ 10.1002/jhet.2690
6. Beauchamp, J., Benardeau, A., Hilpert, H., Migliorini, C., Riboulet, W., Wang, H., 2-Aminodihydro [1, 3] Thiazines as Bace 2 Inhibitors For the Treatment of Diabetes.,**2011**, Patent Scope. WIPO, 165. doi.org/10.5958/0974-4150.2018.00026.3
7. Rai, V. K., Yadav, B. S., and Yadav, L. D. S., The first ionic liquid- promoted one-pot diastereoselective synthesis of 2,5-diamino-/2-amino-5-mercapto-1,3-thiazin-4-ones using masked amino/mercapto acids., Tetrahedron, **2009**, Vol. 38, 981.
8. Fu, L., Li, Y., Ye, D., and Yin, S.Synthesis and calming activity of 6H-2-amino-4-aryl-6-(4-β-D-Allopyranosyloxyphenyl)-1,3-thiazine.,Chem Nat Compd, **2010**, Vol. 46 (2), 169-172.doi.org/10.1007/s10600-010-9559-8
9. Haider, F. H. Z., Synthesis and antimicrobial screening of some 1,3-thiazines., J Chem Pharm Res, **2012** , Vol. 4(4), 2263-2267.
10. Dighade, A. S., and Dighade, S. R., Synthesis of substituted-4,6-diaryl-2-imino-diphenyl-6H-1,3-thiazines., Der PharmaChemica, **2012**, Vol. 4 (5), 1863-1867.
11. Biehl, E. D., and Sathunuru, Facile synthesis of 4H-naphtho [2,3-e] derivatives of 1,3- thiazines and 1,3-selenazines and naphtha [2',3':4,5] derivatives of selenolo[2,3-b]pyridines and thieno[2,3-b]pyridines via 2,3-didehydronaphthalene., ARKIVOK, **2004**, Vol. 12, 51-60.doi.org/10.3998/ark.5550190.0005.e05 .
12. Hossaini, Z., Nematpour, M., and Yavari I., Ph_3P-mediated one-pot synthesis of functionalized 3,4-dihydro-2H-1,3-thiazines from N,N'-dialkylthioureas and activated acetylenes in water., Monatsh Chem, **2010**, Vol. 141, 229-232. doi.org/10.1002/chin.20102 7160
13. Fedoseev, V. M., Mandrugin, A. A., Trofimova, T. P., Zefirova.,Synthesis and Study of NOS-Inhibiting Activity of 2-N-Acylamino-5,6-dihydro-4H-1,3-thiazine, Moscow Uni. Chem. Bull., **2008**, Vol. 63 (5), 274-277. doi.org/10.3103/s0027131408050088 .
14. Batra, S., Bhowmik, S., and Mishra, A., A novel stereoselective one-pot synthesis of 2-substituted amino-5,6-dihydro-4H-1,3-thiazines via primary allylamines afforded from Morita-Baylis-Hillman acetates., RSC Adv., **2011**, Vol. 1 (7), 1237-1244.doi.org/10.1039/c1ra00399b
15. Sambhaji, P. V., and Shivraj, B. S., Simple and Efficient Synthesis of Novel Fused Bicyclic Heterocycles Pyrimido-Thiazine and Their Derivatives., Organic ChemCurr Res, **2012**, Vol. 1 (5), 1-3.doi.org/10.4172/2161-0401.1000110
16. Nagaraj, A., and Reddy, C. S., Synthesis and biological study of novel bis-chalcones, bis-thiazines and bis-pyrimidines.,J Iran Chem Soc., **2008**, Vol. 5 (2), 262-267.doi.org/10.1007/bf03246116
17. SimerPreet, S., Damanjit, C. S., Synthesis and biological evaluation of 1,3-thiazines-A review., Pharmacophore (An Int. Nat. J.), **2014**, 45 (14), 70-88.doi.org/10.1002/chin.201414252
18. Didwagh, S.S., Piste, P. B., Green synthesis of thiazine and oxazine derivatives-A short review. Int. J. Pharm. Sci. Res. **2013**, 4, 2045-2061.doi.org/10.1002/chin.201347214
19. Kokestu M., Tanaka K., Takenaka Y., Kwong C.D. and Ishihara H., Synthesis of 1,3-thiazine derivatives and their evaluation as potential antimycobacterial agents, Eur. J. Pharm. Sci., **2002**, 15,307-310.
20. Bozsing D., Sohar P., Gigler G. and Kovacs G., Synthesis and pharmacological study of new 3,4 dihydro-2H, 6H-PYRIMIDO-[2,1-b][1,3] thiazines, Eur. J. Med. Chem., **1996**,31, 663-668.

21. Florio S. and Leng J. L., Synthesis and reactivity of 4 substituted-2,3-dihydrobenzo-1,4-thiazines, J. Het. Chem., **1982**, 19, 237-240.
22. Suarez M., Novoa H., Verdecia Y., Ochoa E., Alvarez A., Roberto R., Alvarez M., Dolores M., Seone C., Norbert M. B., Ostwald M.P., Nazario M., A straight forward synthesis and structure of unprecedented iminium salts of dihydropyrido[3,2-E][1,3]thiazines, Tetrahedron, **2006**, 62, 1365-1371.
23. Prasad, Y. R., Rao, A. L., and Rambabu, R., Synthesis and Antimicrobial Activity of some Chalcone Derivatives., E-Journal of Chemistry, **2008**, Vol. 5 (3), 461-466.doi.org/10.1155/2008/876257
24. Won, S. J., Liu, C. T.,, Tso, L. T., Ko, H. H., Wang, J. P., Lin, C. N., Synthetic Chalcones as potential anti-inflammatory and cancer chemoprevantive agents., European Journal of Medicinal Chemistry, **2005**, 40 (1), 103-112.doi.org/10.1016/j.ejmech.2004.09.006
25. Bhanat K., Parashar B., and Sharma V.K., Microwave induced synthesis and antimicrobial activities of various substituted pyrazolidines from chalcones, Res. J. Chem. Sci., **2014**, 4(2), 68-74.
26. Bhale P.S., Dongare S.B., and Chanshetti U.B., Synthesis and antimicrobial screening of chalcones containing imidazo[1,2-a]pyridine nucles, Res. J. Chem. Sci., **2013**, 3(12), 38-42.