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Synthesis, molecular properties and evaluation of anthelmintic activity of new thiazolopyrimidine derivatives

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ABSTRACT

In order to develop a better bioactive molecules with good efficacy, we synthesized a new series of Thiazolo [3,2-a] pyrimidine derivatives with good yield and studied their anthelmintic properties, structure- activity relationships (SARs). A new series of Thiazolo[3,2-a]pyrimidines have been synthesized through duff formylation, 'One pot' Biginelli reaction, cyclization followed by knoevenagel condensation and were characterized by IR, ^{1}H NMR, ^{13}C NMR, Mass spectra and elemental analysis. New molecules were screened for their in-vitro anthelmintic activity against Indian earthworm Pheretima posthuma and studied their physico-chemical properties. Effect of substitution at arylidene part on anthelmintic property was studied. Compounds 3j and 3s with electron withdrawing groups were found to be highly potent among the series and were also supported by ADME parameters.

Keywords: Heterocycles, Cyclizations, Structure-activity relationships, Anthelmintic activity

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INTRODUCTION

Helminthiasis is a macroparasitic disease found in humans due to parasitic worms, such as Nematodes or Cestodes which are exist in skin, liver, brain, lungs, lymph, eye, muscles and other tissues of the body [1]. The wide varieties of anthelmintics or anthelmintic drugs are available in market to expel such parasitic worms from the body by either stunning or killing them without causing any significant damage to the host cell. Especially, well known marketing pyrimidine derived drugs pyrantel and morantel, are commonly used as anthelmintic agents which has broad spectrum activity and high cure rates due to the sustainability of the periodic emergence of resistance. But some existing infectious diseases cannot be eliminated completely from human body by using presently available drugs [2]. Particularly, filariasis diagnosis is helpful for its cure only in its earlier stage. After the advancement of parasitic infection, it cannot be cured completely. It is unevenly distributed disease in low income countries which affected badly and showing the highest risk of morbidity day by day. Currently, the development of multicomponent reactions (MCRs) are integral part of numerous research efforts around the world which are involved in the drug development programs to achieve the synthetic targets in an expeditious manner. The Biginelli reaction is the one such reaction, which involves simple one pot three-component condensation of an aldehyde, *β*-ketoester, and urea or thiourea in the presence of a catalytic amount of acid to produce 3,4-dihydropyrimidin- 2-(1H)-ones (DHPMs) [3-4]. In order to bring about synthetic advancement, variations were introduced in different ways. The reaction was carried out by varying all the three building blocks i.e. biginelli scaffolds [5], catalyst [6-8], carried out asymmetric synthesis [9] and also rate enhancement reactions such as sonication [10] and microwave irradiation [11], which

lead to extension of scope of the original multi-component reaction resulting in large molecular diversity of biginelli product, dihydropyrimidine. The presence of pyrimidine in cellular processes has made them valuable leads in drug discovery strategy. In 2-mercaptopyrimidine ring sulfur atom serves as an attractive replacement for the existing oxygen atom bonded to C-2 in uridine base [12]. They found widely use as cardiotonic drugs [13] and anti-TB drugs [14]. Also, 2-mercaptopyrimidine and their derivatives are important intermediates in organic synthesis; because of N-3 position and the exocyclic sulfur atom are nucleophilic in nature and are readily susceptible to attack by electrophilic agents. Pyrimidines in association with thiazole have also occupied a prominent place in medicinal chemistry because of their significant properties as therapeutics in clinical applications. A recent survey of literature on thiazolopyrimidines revealed that, these bioactive molecules have received much attention on account of their extensive utilization as antitumor [15-16], antiproliferative [17], Fungicidal [18], anti-HIV [19] and anti-inflammatory agents [20]. They also have been of interest due to their ability to inhibit the 2-methylerythritol-2,4-cyclodiphosphate synthase [21], act as modulators of Transient Receptor Potential Vanilloid–receptor 1 (TRPV1) [22], inhibit thymidylate synthase and dihydrofolate reductase [23], angiogenesis inhibiting [24] and inhibitory action on cyclin-dependent kinase [25]. In the view from above biological profiles of 2-mercapto pyrimidine and thiazolopyrimidines, we carefully optimized structure for new target compounds. We envisioned that the bicyclic thiazolepyrimidine, by virtue of its structural features might serve as a prototype for the search of new drugs that could be used in anthelmintic research.

EXPERIMENTAL SECTION

Melting points were determined in open capillaries and uncorrected (melting point apparatus: Sewell instruments Inc., India). All solvents used were of analytical grade and the reagents were purchased from commercial vendors. The purity of the compounds was checked by thin layer chromatography on a silica coated aluminum sheet (silica gel F_{254}). IR spectra were recorded on a Shimadzu ATR-IR 157-spectrophotometer. The ^{1}H-NMR spectra were recorded on a Bruker Avance III, (400 MHz) spectrometer using TMS as internal standard. The splitting pattern is designated as follows; s (singlet), d (doublet), t (triplet), m (multiplet), bs (broad singlet). The ^{13}C-NMR was recorded in 400 MHz Joel resonance-delta 2-NMR refractometer. The mass spectra were recorded on an MDS SCIEX/API4000 spectrophotometer. Elemental analysis was carried out using Flash EA 1112 Series, CHNSO Analyzer (Thermo). Thin layer chromatography (TLC) analysis was done on pre-coated silica gel G plates using a mixture of ethyl acetate and n-hexane as mobile phase. 3,5-dimethyl-4-hydroxy benzaldehyde (**1**) was prepared by Duff formylation procedure [26].

*General procedure for the preparation of ethyl-4-(4-hydroxy-3,5-dimethylphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (**2**)*

A mixture of substituted aldehyde **1** (5 mmol), ethyl acetoacetate (7.5 mmol), thiourea (6.5 mmol) in 35ml of ethanol and con.HCl was stirred at 50-55 ^{o}C for 10 hrs. One drop of Con. HCl was added for every 2 hrs. After completion of the reaction, the reaction mixture was allowed to stand for overnight at 0^{o}C. The same reaction was also carried out under microwave irradiation for 6 mins at 100 ^{o}C (power 90 W) in a sealed tube. Then it was treated with water to remove the catalyst and the unreacted thiourea and was extracted with ethylacetate (3 x 5 mL). The combined extract was dried (anhydrous Na_2SO_4) and the solvent was evaporated to get the crude product and was purified by recrystallisation from ethanol.

Yellow solid; yield: 90%; m.p.: 143-145 ^{O}C; IR (KBr): *v* 3275 (N-H), 3040 (Ar-H), 2989, 2938 (C-H), 1749 (C=O), 1590 (C=C), 1261 (O-C)cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.11 (t, 3H, *J* = 6.8 Hz), 2.11 (s, 6H, -2CH_3), 2.27 (s, 3H), 3.99 (q, 2H, -CH_2-CH_3, *J* = 6.8 Hz), 5.01 (s, 1H, pyrimidine-H), 6.73 (s, 2H, Ar-H), 7.84 (s, 1H, exocyclic CH), 9.50 (s, 1H, NH), 10.19 (s, 1H, OH); MS (m/z, %): 321.82 (M^{+}+1); Anal. calcd. For $C_{16}H_{20}N_2O_3S$: C 59.98, H 6.29, N 8.74, S 10.01; found C 59.99, H 6.28, N 8.75, S 10.02.

*General procedure for the preparation of thiazolopyrimidine derivatives **(3a-t)***

A mixture of biginelli pyrimidine **2** (10 mmol), monochloroacetic acid (15 mmol), anhydrous sodium acetate (2 g), glacial acetic acid (20 ml), acetic anhydride (15 ml), and aromatic aldehyde (10 mmol) were heated to reflux, and temperature was maintained at 140–142 ^{0}C for 6 h. After completion of the reaction (monitored by TLC hexane: ethyl acetate (7: 3, v/v)), resulting solution was cooled to room temperature and poured the reaction mixture into the ice water (150 ml). The precipitate was separated by filtration and dissolved by dichloromethane. The organic layer

was washed using 6 % $NaHCO_3$ and brine, dried over sodium sulphate and the solvent evaporated. The product obtained was recrystallized from suitable solvent.

(*Z)-ethyl-2-(4-methoxybenzylidene)-7-methyl-3-oxo-5-(4-hydroxy-3,5-dimethylphenyl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3a**)*
Light yellow solid; yield: 83%; m.p.: 203-205 ^{O}C; IR (KBr) *ν* 3099 (Ar-H), 2976, 2927 (aliphatic C-H), 1759 (C=O), 1595 (C=C), 1224 (O-C) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* ppm 1.20 (t, 3H, -CH_3, *J* = 6.8 Hz), 2.11 (s, 6H, -2CH_3), 2.29 (s, 3H, -CH_3), 3.81 (s, 3H, -OCH_3), 4.07-4.09 (q, 2H, -CH_2-CH_3, *J* = 6.8 Hz and 3.6 Hz), 6.12 (s, 1H, pyrimidine-H), 6.97 (d, 2H, Ar-H), 7.07(s, 2H, Ar-H), 7.43 (d, 2H, Ar-H), 7.71 (s, 1H, exocyclic CH), 7.95(s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* ppm 14.04 (CH_3), 16.43 (CH_3), 22.83 (CH_3), 54.22 (pyrimidine C-H), 55.56 (-OCH_3), 60.48 (ester CH_2), 108.72, 114.88, 117.22, 125.84, 128.22, 130.29, 132.07, 133.56, 148.32 (exocyclic C-H), 152.54, 156.68, 161.40 (ring C=O), 165.52(ester C=O); MS (ESI): (m/z, %) 477.1(M^+-H); Anal. calcd. for $C_{26}H_{26}N_2O_5S$: C 65.25, H 5.48, N 5.85, S 6.70; found C 65.26, H 5.48, N 5.86, S 6.71.

*(Z)-ethyl-2-(3,4,5-trimethoxybenzylidene)-7-methyl-3-oxo-5-(4-hydroxy-3,5-dimethylphenyl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3b**)*
Creamy yellow solid; yield: 84%; m.p.: 232-234 ^{O}C; IR (KBr) *ν* cm^{-1} 3053 (Ar-H), 2940, 2890 (C-H), 1752(C=O), 1597 (C=C), 1223 (O-C); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm 1.16 (t, 3H, -CH_3, *J* = 6.8 Hz), 2.08 (s, 6H, -2CH_3), 2.46 (s, 3H, -CH_3), 3.73 (s, 9H, -3OCH_3), 3.99 (q, 2H, -CH_2-CH_3), 6.20 (s, 1H, pyrimidine-H), 6.98 (s, 2H, Ar-H), 7.01(s, 2H, Ar-H), 7.76 (s, 1H, exocyclic CH), 8.08(s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* ppm 14.06 (CH_3), 16.46 (CH_3), 22.87 (CH_3), 54.25 (pyrimidine C-H), 55.56(-OCH_3), 56.43 (OCH_3), 60.48 (ester CH_2), 108.72, 114.88, 117.22, 125.84, 128.22, 130.29, 132.07, 133.56, 138.40, 149.32 (exocyclic C-H), 152.54, 156.68, 162.40 (ring C=O), 166.52 (ester C=O); MS (ESI) (m/z, %): 539.2 (M^++H); Anal. Calcd. for $C_{28}H_{30}N_2O_7S$: C 62.44, H 5.61, N 5.20, S 5.95; found C 62.45, H 5.62, N 5.20, S 5.96.

*(Z)-ethyl-2-(2-chloro-6-fluorobenzylidene)-7-methyl-3-oxo-5-(4-hydroxy-3,5-dimethylphenyl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3c**)*
Light brown solid; yield: 82%; m.p.: 201-203 ^{O}C; IR (KBr) *ν* cm^{-1} 3084 (Ar-H), 2978, 2924 (C-H), 1759(C=O), 1597 (C=C), 1233 (O-C); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm 1.12 (t, 3H, -CH_3, *J* = 6.8 Hz), 2.05 (s, 6H, -2CH_3), 2.43 (s, 3H, -CH_3), 3.98 (q, 2H, -CH_2-CH_3, *J* = 6.8 Hz and 3.6 Hz), 6.04 (s, 1H, pyrimidine-H), 7.01(s, 2H, Ar-H), 7.19-7.27 (m, 3H, Ar-H), 7.74 (s, 1H, exocyclic CH), 8.05 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* ppm 14.01 (CH_3), 16.45(CH_3), 22.76 (CH_3), 54.94 (pyrimidine C-H), 60.56 (ester CH_2), 109.18, 114.90, 124.69, 125.93, 127.80, 128.40, 130.41, 131.65, 136.89, 148.40 (exocyclic C-H), 152.09, 155.73, 158.69, 160.71, 164.27, 165.37 (ring C=O), and 168.60 (ester C=O); MS (ESI) (m/z, %): 501.2 (M^++1); Anal. Calcd. for $C_{25}H_{22}ClFN_2O_4S$: C 59.94, H 4.43, N 5.59, S 6.40; found C 59.95, H 4.42, N 5.60, S 6.41.

*(Z)-ethyl-2-(2,4-dichlorobenzylidene)-7-methyl-3-oxo-5-(4-hydroxy-3,5-dimethylphenyl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3d**)*
Creamy white solid; yield: 78%; m.p. 211-213 ^{O}C; IR (KBr) *ν* cm^{-1} 3042 (Ar-H), 2987, 2939 (C-H), 1748 (C=O), 1587 (C=C), 1233 (O-C), 988 (C-Cl) cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* ppm 1.19 (t, 3H, -CH_3, *J* = 6.8 Hz), 2.15 (s, 6H, -2CH_3), 2.43 (s, 3H, -CH_3), 3.96 (q, 2H, -CH_2-CH_3), 6.21 (s, 1H, pyrimidine-H), 7.26 (s, 2H, Ar-H), 7.15-7.23 (m, 3H, Ar-H), 7.74 (s, 1H, exocyclic CH), 7.98 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* ppm 14.43 (CH_3), 16.46 (CH_3), 22.87(CH_3), 54.56 (pyrimidine C-H), 60.41(ester CH_2), 109.72, 114.88, 116.34, 118.22, 125.84, 128.22, 130.29, 132.07, 133.56, 134.21, 148.62 (exocyclic C-H), 152.54, 156.68, 162.40 (ring C=O), 166.52 (ester C=O); MS (ESI) (m/z, %): 516.07 (M^+-H); Anal. Calcd. for $C_{25}H_{22}Cl_2N_2O_4S$: C 58.03, H 4.29, N 5.41, S 6.20; found C 58.04, H 4.30, N 5.42, S 6.21.

*(Z)-ethyl-2-(2,3-dichlorobenzylidene)-7-methyl-3-oxo-5-(4-hydroxy-3,5-dimethylphenyl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3e**)*
White solid; yield: 86%, m.p.: 243-245 ^{O}C; IR (KBr) *ν* 3044 (Ar-H), 2989, 2939 (C-H), 1740 (C=O), 1584 (C=C), 1236 (O-C), 989 (C-Cl) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm 1.21 (t, 3H, -CH_3, *J* = 6.8 Hz), 2.17 (s, 6H, -2CH_3), 2.49 (s, 3H, -CH_3), 3.94 (q, 2H, -CH_2-CH_3), 6.20 (s, 1H, pyrimidine-H), 7.28(s, 2H, Ar-H), 7.19-7.25 (m, 3H, Ar-H), 7.83 (s, 1H, exocyclic CH), 8.05(s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* ppm 14.42 (CH_3), 16.36 (CH_3), 22.86 (CH_3), 54.46 (pyrimidine C-H), 60.45(ester CH_2), 109.73, 114.48, 116.34, 118.52, 125.82, 128.21, 130.39, 132.17, 133.52, 134.21, 148.61 (exocyclic C-H), 152.51, 156.68, 162.43 (ring C=O), 166.55 (ester C=O);

MS (ESI) (m/z, %): 516.17 (M^+-H); Anal. Calcd. for $C_{25}H_{22}Cl_2N_2O_4S$: C 58.03, H 4.29, N 5.41, S 6.20; found C 58.03, H 4.30, N 5.42, S 6.20.

*(Z)-ethyl-2-(2-fluoro3-methoxybenzylidene)-7-methyl-3-oxo-5-(4-hydroxy-3,5-dimethylphenyl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3f**)*
Brown solid; yield: 86%, m.p.: 243-245 ^{O}C; IR (KBr) *ν* 3049 (Ar-H), 2984, 2939 (C-H), 1747 (C=O), 1588 (C=C), 1236 (O-C)cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm 1.28 (t, 3H, -CH_3, *J* = 6.8 Hz), 2.20 (s, 6H, -2CH_3), 2.50 (s, 3H, -CH_3), 3.82 (s, 3H, OCH_3), 3.94 (q, 2H, -CH_2-CH_3), 6.22 (s, 1H, pyrimidine-H), 7.20(s, 2H, Ar-H), 7.25-7.31 (m, 3H, Ar-H), 7.89 (s, 1H, exocyclic CH), 7.90 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* ppm 14.24 (CH_3), 14.79 (CH_3), 16.40 (CH_3), 22.74 (CH_3), 54.95 (pyrimidine C-H), 55.53 (-OCH_3), 60.57 (ester CH_2), 115.49, 125.62, 128.22, 130.41, 132.39, 137.10, 148.40 (exocyclic C-H), 152.32, 155.73, 158.69, 160.71, 164.28, 166.37 (ring C=O), 167.72 (ester C=O); MS (ESI): (m/z, %) 495.05 (M^+-H); Anal. Calcd. for $C_{26}H_{25}FN_2O_5S$: C 62.89, H 5.07, N 5.64, S 6.46; found C 62.90, H 5.08, N 5.63, S 6.47.

*(Z)-ethyl-2-(3-bromobenzylidene)-7-methyl-3-oxo-5-(4-hydroxy-3,5-dimethylphenyl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate(**3g**)*
Dark brown solid; yield: 76%; m.p.: 218-220 ^{O}C; IR (KBr) *ν* 3054 (Ar-H), 2987, 2934 (C-H), 1749 (C=O), 1588 (C=C), 1231 (O-C) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm 1.30 (t, 3H, -CH_3, *J* = 6.8 Hz), 2.23 (s, 6H, -2CH_3), 2.50 (s, 3H, -CH_3), 3.94 (q, 2H, -CH_2-CH_3), 6.20 (s, 1H, pyrimidine-H), 7.29 (s, 2H, Ar-H), 7.31 (t, 1H, Ar-H, *J* = 8.6 Hz), 7.35 (d, 1H, Ar-H, *J* = 8.6 Hz), 7.42 (d, 1H, Ar-H, *J* = 8.4 Hz), 7.62 (s, 1H, Ar-H), 7.89 (s, 1H, exocyclic CH), 8.10 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* ppm 14.54 (CH_3), 14.59 (CH_3), 16.43 (CH_3), 54.98 (pyrimidine C-H), 60.67 (ester CH_2), 117.49, 125.62, 128.22, 130.41, 132.83, 137.10, 146.40 (exocyclic C-H), 152.32, 155.73, 158.69, 160.71, 163.28, 167.37 (ring C=O), 169.72 (ester C=O); MS (ESI): (m/z, %) 526.35 (M^+-H); Anal. Calcd. for $C_{25}H_{23}BrN_2O_5S$: C 56.93, H 4.40, N 5.31, S 6.06; found C 56.94, H 4.41, N 5.32, S 6.07.

*(Z)-ethyl-2-(3-fluoro-4-methylbenzylidene)-7-methyl-3-oxo-5-(4-hydroxy-3,5-dimethylphenyl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3h**)*
Creamy solid; yield: 76%; m.p.: 231-233 ^{O}C; IR (KBr) *ν* 3039 (Ar-H), 2970, 2943 (C-H), 1757 (C=O), 1597 (C=C), 1236 (O-C) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm1.20 (t, 3H, -CH_3, *J* = 6.8 Hz), 2.12 (s, 6H, -2CH_3), 2.30 (s, 3H, CH3), 2.52 (s, 3H, -CH_3), 4.08-4.14 (q, 2H, -CH_2-CH_3, *J* = 6.8 Hz and 3.6 Hz), 6.12 (s, 1H, pyrimidine-H), 7.07-7.18 (m, 5H, Ar-H), 7. 61(s, 1H, exocyclic CH), 7.87 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* ppm 14.08 (CH_3), 14.78 (CH_3), 16.49 (CH_3), 22.73 (CH_3), 54.94 (pyrimidine C-H), 61.59 (ester CH_2), 107.49, 125.62, 128.22, 130.41, 132.39, 137.10, 149.40 (exocyclic C-H), 152.52, 155.73, 158.69, 160.71, 164.28, 167.39 (ring C=O), 169.75 (ester C=O); MS (ESI) (m/z, %) 480.55 (M^+); Anal. Calcd. for $C_{26}H_{25}FN_2O_4S$: C 64.98, H 5.24, N 5.83, S 6.67; found C 64.98, H 5.25, N 5.84, S 6.68.

*(Z)-ethyl-2-(2-fluoro-3-chlorobenzylidene)-7-methyl-3-oxo-5-(4-hydroxy-3,5-dimethylphenyl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3i**)*
White solids; yield: 87%; m.p.: 234-236 ^{O}C; IR (KBr) *ν* 3040 (Ar-H), 2980, 2933 (C-H), 1753 (C=O), 1589 (C=C), 1234 (O-C) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm 1.21 (t, 3H, -CH_3, *J* = 6.8 Hz), 2.28 (s, 6H, -2CH_3), 2.56 (s, 3H, -CH_3), 3.90 (q, 2H, -CH_2-CH_3), 6.27 (s, 1H, pyrimidine-H), 7.23-7.27 (m, 3H, Ar-H), 7.39 (s, 1H, Ar-H), 7.83 (s, 1H, exocyclic CH), 7.95(s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* ppm 14.08 (CH_3), 14.78 (CH_3), 16.49 (CH_3), 54.44 (pyrimidine C-H), 60.59 (ester CH_2), 107.49, 124.62, 128.62, 131.41, 132.29, 139.10, 146.40 (exocyclic C-H), 153.52, 156.73, 158.69, 160.71, 164.28, 167.30 (ring C=O), 169.71 (ester C=O); MS (ESI) (m/z, %) 514.21 (M^+-H); Anal. Calcd. for $C_{26}H_{24}ClFN_2O_4S$: C 60.64, H 4.70, N 5.44, S 6.63; found C 60.64, H 4.70, N 5.45, S 6.24.

*(Z)-ethyl-2-(4-cyanobenzylidene)-7-methyl-3-oxo-5-(4-hydroxy-3,5-dimethyl phenyl) -3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3j**)*
White solid; yield: 87%; m.p.: 231-233 ^{O}C; IR (KBr) *ν* 3048 (Ar-H), 2989, 2930 (C-H), 2240 (C≡N), 1748 (C=O), 1598 (C=C), 1236 (O-C) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm 1.30 (t, 3H, -CH_3, *J* = 6.8 Hz), 2.23 (s, 6H, -2CH_3), 2.50 (s, 3H, -CH_3), 3.94 (q, 2H, -CH_2-CH_3), 6.23 (s, 1H, pyrimidine-H), 7.29 (s, 2H, Ar-H), 7.35 (d, 2H, Ar-H, *J* = 8.6 Hz), 7.44 (d, 2H, Ar-H, *J* = 8.4 Hz), 7.89 (s, 1H, exocyclic CH), 7.95(s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* ppm 14.14 (CH_3), 16.44 (CH_3), 22.84 (CH_3), 55.22 (pyrimidine C-H), 60.48 (ester CH_2), 108.72, 114.88, 115.3, 117.22, 125.84, 128.22, 130.29, 132.07, 133.56, 148.38 (exocyclic C-H), 152.56, 156.78, 161.48 (ring C=O),

165.58 (ester C=O); MS (ESI): (m/z, %) 490.52 (M^+-H); Anal. Calcd. for $C_{26}H_{24}ClFN_2O_4S$: C 63.53, H 4.51, N 8.55, S 6.52; found C 63.54, H 4.52, N 8.55, S 6.53.

*(Z)-ethyl-2-(4-ethoxybenzylidene)-7-methyl-3-oxo-5-(4-hydroxy-3, 5-dimethyl phenyl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3k**)*

Creamy white solid; yield: 79%; m.p.: 199-201 ^{O}C; IR (KBr) *ν* 3048 (Ar-H), 2989, 2930 (C-H), 1748 (C=O), 1598 (C=C), 1236 (O-C)cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* - 1.37 (t, 6H, -2CH_3, *J* = 6.2 Hz), 2.24 (s, 6H, -2CH_3), 2.53 (s, 3H, -CH_3), 3.94 (q, 4H, (-CH_2-CH_3)$_2$), 6.24 (s, 1H, pyrimidine-H), 7.37 (s, 2H, Ar-H), 7.38 (d, 2H, Ar-H, *J* = 8.8 Hz), 7.47 (d, 2H, Ar-H, *J* = 8.8 Hz), 7.92 (s, 1H, exocyclic CH), 7.95(s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* ppm 14.14 (CH_3), 14.80 (CH_3), 16.44 (CH_3), 22.84 (CH_3), 55.22 (pyrimidine C-H), 60.48 (ester CH_2), 64.7 (CH2), 109.72, 114.88, 118.22, 125.84, 128.22, 130.29, 132.07, 133.59, 146.38 (exocyclic C-H), 152.56, 156.78, 162.48 (ring C=O), and 166.58 (ester C=O); MS (ESI): (m/z, %) 509.52 (M^+-H); Anal. Calcd. for $C_{27}H_{27}FN_2O_4S$: C 63.51, H 5.33, N 5.49, S 6.28; found C 63.52, H 5.34, N 5.50, S 6.29.

*(Z)-ethyl-2-(6-methoxynaphthalen-2-yl)methylene-7-methyl-3-oxo-5-(4-hydroxy-3,5-dimethylphenyl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3l**)*

White solid; yield: 83%; m.p.: 237-239 ^{O}C; IR (KBr) *ν* cm^{-1} 3042 (Ar-H), 2980, 2926 (C-H), 1749 (C=O), 1594 (C=C), 1258 (O-C); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm 1.30 (t, 3H, -CH_3, *J* = 6.8 Hz), 2.28 (s, 6H, -2CH_3), 3.92 (q, 2H, -CH_2-CH_3), 3.98 (s, 3H, -OCH_3), 6.26 (s, 1H, pyrimidine-H), 7.34 (s, 2H, Ar-H), 7.40-7.62 (m, 6H, aryl), 7.90 (s, 1H, exocyclic CH), 7.95(s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* = 14.15 (CH_3), 14.80 (CH_3), 16.44 (CH_3), 22.84 (CH_3), 55.22 (pyrimidine C-H), 60.48 (ester CH_2), 64.7 (CH2), 109.72, 114.88, 118.22, 125.84, 126.93, 128.22, 129.34, 130.29, 132.07, 132.97, 133.59, 136.39, 136.97, 137.20, 142.46, 146.38 (exocyclic C-H), 152.56, 154.21, 156.78, 162.48 (ring C=O), 167.50 (ester C=O); MS (ESI) - m/z 527.17 (M^+-H); Anal. Calcd. for $C_{30}H_{28}N_2O_5S$: C 68.16, H 5.34, N 5.30, S 6.07; found C 68.17, H 5.34, N 5.30, S 6.07.

*(Z)-ethyl-2-(3-chlorobenzylidene)-7-methyl-3-oxo-5-(4-hydroxy-3,5-dimethylphenyl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3m**)*

Creamy white solid; yield: 80%; m.p.: 205-207 ^{O}C; IR (KBr) *ν* 3040 (Ar-H), 2990, 2936 (C-H), 1759 (C=O), 1593 (C=C), 1258 (O-C), 958 (C-Cl) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm 1.36 (t, 3H, -CH_3, *J* = 6.8 Hz), 2.29 (s, 6H, -2CH_3), 2.55 (s, 3H, -CH_3), 3.96 (q, 2H, -CH_2-CH_3), 6.23 (s, Ar-H), 7.31 (s, 2H, Ar-H), 7.38 (t, 1H, Ar-H, *J* = 8.6 Hz), 7.35 (d, 1H, Ar-H, *J* = 8.6 Hz), 7.42 (d, 1H, Ar-H, *J* = 8.4 Hz), 7.62 (s, 1H, Ar-H), 7.89 (s, 1H, exocyclic CH), 7.95(s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* ppm 14.52 (CH_3), 14.59 (CH_3), 16.43 (CH_3), 54.98 (pyrimidine C-H), 60.67 (ester CH_2), 117.49, 125.62, 128.22, 130.41, 132.83, 137.10, 148.40 (exocyclic C-H), 152.32, 155.73, 159.69, 160.71, 163.28, 167.37 (ring C=O), 168.72 (ester C=O); MS (ESI): (m/z, %) 483.80 (M^++1); Anal. Calcd. for $C_{25}H_{23}ClN_2O_4S$: C 62.17, H 4.80, N 5.80, S 6.64; found C 62.18, H 4.80, N 5.80, S 6.64.

*Ethyl-2-(4-chlorobenzylidene)-7-methyl-3-oxo-5-(4-hydroxy-3,5-dimethylphenyl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3n**)*

Light yellow solid; yield: 83%; m.p.: 237-239 ^{O}C; IR (KBr) *ν* 3042 (Ar-H), 2980, 2926 (C-H), 1749 (C=O), 1594 (C=C), 1258 (O-C)cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm 1.34 (t, 3H, -CH_3, *J* = 6.8 Hz), 2.29 (s, 6H, -2CH_3), 2.50 (s, 3H, -CH_3), 3.92 (q, 2H, -CH_2-CH_3), 6.26 (s, 1H, pyrimidine-H), 7.36 (s, 2H, Ar-H), 7.45 (d, 2H, Ar-H, *J* = 8.6 Hz), 7.58 (d, 2H, Ar-H, *J* = 8.4 Hz), 7.89 (s, 1H, exocyclic CH), 7.98 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* ppm 14.11 (CH_3), 16.44 (CH_3), 22.84 (CH_3), 55.22 (pyrimidine C-H), 60.48(ester CH_2), 108.72, 114.88, 117.22, 125.84, 128.22, 130.29, 132.07, 133.56, 148.38 (exocyclic C-H), 154.56, 156.78, 161.90 (ring C=O), 165.58 (ester C=O); MS (ESI): (m/z, %) 483.80 (M^++1); Anal. Calcd. for $C_{25}H_{23}ClN_2O_4S$: C 62.17, H 4.80, N 5.80, S 6.64; found C 62.18, H 4.80, N 5.80, S 6.64.

*(Z)-ethyl-2-(4-N,N-dimethylaminobenzylidene)-7-methyl-3-oxo-5-(4-hydroxy-3,5-dimethylphenyl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3o**)*

Brownish solid; yield: 80%; m.p.: 198-200 ^{O}C; IR (KBr) *ν* 3040 (Ar-H), 2985, 2928 (C-H), 1743 (C=O), 1595 (C=C), 1260 (O-C)cm^{-1}; 1H NMR (400 MHz, $CDCl_3$) *δ* ppm 1.30 (t, 3H, -CH_3, *J* = 6.8 Hz), 2.23 (s, 12H, -4CH_3), 2.50 (s, 3H, -CH_3), 3.92 (q, 2H, -CH_2-CH_3), 6.26 (s, 1H, pyrimidine-H), 6.76 (d, 2H, Ar-H, *J* = 9.0 Hz)7.29 (s, 2H, Ar-H), , 7.50 (d, 2H, Ar-H, *J* = 9.0 Hz), 7.99 (s, 1H, exocyclic CH), 7.91(s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* ppm 14.21 (CH_3), 16.44 (CH_3), 22.84 (CH_3), 40.3 (CH_3), 55.29 (pyrimidine C-H), 60.48 (ester CH_2), 108.72, 115.88, 117.22, 125.84, 129.22, 130.29, 132.07, 133.56, 149.38 (exocyclic C-H), 153.56, 156.78, 162.90 (ring

C=O), 166.58 (ester C=O); MS (ESI): (m/z, %) 492.62 (M^++1); Anal. Calcd. for $C_{27}H_{29}N_3O_4S$: C 65.97, H 5.95, N 8.55, S 6.52; found C 65.98, H 5.96, N 8.56, S 6.53.

*(Z)-ethyl-2-(3,5-dimethyl-4-hydroxybenzylidene)-7-methyl-3-oxo-5-(4-hydroxy-3,5-dimethylphenyl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3p**)*
White solid; yield : 79%; m.p.: 194-196 ^{O}C; IR (KBr) *ν* 3304 (O-H), 3045 (Ar-H), 2989, 2938 (C-H), 1746 (C=O), 1590 (C=C), 1261 (O-C)cm^{-1}; 1H NMR (400 MHz, $CDCl_3$) *δ* ppm 1.38 (t, 3H, -CH_3, *J* = 6.8 Hz), 2.31 (s, 12H, -4CH_3), 2.54 (s, 3H, -CH_3), 3.86 (q, 2H, -CH_2-CH_3), 6.20 (s, 1H, pyrimidine-H), 7.36 (s, 4H, Ar-H), 7.90 (s, 1H, exocyclic CH), and 7.95(s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* ppm14.11 (CH_3), 14.7 (CH_3), 16.44 (CH_3), 22.94 (CH_3), 55.29 (pyrimidine C-H), 61.48 (ester CH_2), 109.72, 114.68, 117.22, 125.82, 125.96, 128.22, 130.29, 132.07, 133.56, 148.38 (exocyclic C-H), 154.56, 154.86, 156.78, 161.90 (ring C=O), and 165.58 (ester C=O); MS (ESI): (m/z, %) 493.60 (M^++1); Anal. Calcd. For $C_{27}H_{28}N_2O_5S$: C 65.83, H 5.73, N 5.69, S 6.51; found C 65.84, H 5.74, N 5.70, S 6.52.

*(Z)-ethyl-2-(pyridene-3-yl)methylidene-7-methyl-3-oxo-5-(4-hydroxy-3,5-dimethylphenyl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3q**)*
Brown solid; yield: 84%; m.p.: 200-202 ^{O}C; IR (KBr) *ν* 3045 (Ar-H), 2989, 2938 (C-H), 1746 (C=O), 1590 (C=C), 1261 (O-C) cm^{-1}; 1H NMR (400 MHz, $CDCl_3$) *δ* ppm 1.32 (t, 3H, -CH_3, *J* = 6.8 Hz), 2.34 (s, 6H, -2CH_3), 2.53 (s, 3H, -CH_3), 3.90 (q, 2H, -CH_2-CH_3), 6.20 (s, 1H, pyrimidine-H), 7.36 (s, 2H, Ar-H), 7.45 (d, 2H, Ar-H, *J* = 8.8 Hz), 7.58 (d, 2H, Ar-H, *J* = 8.8 Hz), 7.75 (t, 1H, Ar-H, *J* = 8.6 Hz), 7.89 (s, 1H, exocyclic CH), 7.95(s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* ppm 14.24 (CH_3), 14.69 (CH_3), 17.43 (CH_3), 54.88 (pyrimidine C-H), 60.77 (ester CH_2), 125.82, 128.22, 130.45, 131.41, 132.80, 137.30,138.42, 147.40 (exocyclic C-H), 150.41, 152.32, 156.73, 158.69, 160.71, 163.28, 167.37 (ring C=O), 169.72 (ester C=O); MS (ESI): (m/z, %) 450.52 (M^++1); Anal. Calcd. for $C_{24}H_{23}N_3O_4S$: C 64.13, H 5.16, N 9.35, S 7.13; found C 64.14, H 5.17, N 9.36, S 7.14.

*(Z)-ethyl-2-(thiophen-2-ylmethylidene)-7-methyl-3-oxo-5-(4-hydroxy-3,5-dimethylphenyl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3r**)*
Brown solid; Yield: 74%; m.p.: 192-194 ^{O}C; IR (KBr) *ν* 3050 (Ar-H), 2989, 2938 (C-H), 1746 (C=O), 1590 (C=C), 1261 (O-C)cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm 1.37 (t, 3H, -CH_3, *J* = 6.8 Hz), 2.32 (s, 6H, -2CH_3), 2.60 (s, 3H, -CH_3), 3.90 (q, 2H, -CH_2-CH_3), 6.20 (s, 1H, pyrimidine-H), 7.38 (s, 2H, Ar-H), 7.53 (d, 2H, Ar-H, *J* = 8.4 Hz), 7.60 (d, 2H, Ar-H, *J* = 8.4 Hz), 7.78 (t, 1H, Ar-H, *J* = 8.6 Hz), 7.92 (s, 1H, exocyclic CH), 7.95(s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* ppm 14.14 (CH_3), 15.43 (CH_3), 22.53 (CH_3), 54.29 (pyrimidine C-H), 61.48 (ester CH_2), 121.5, 122.96, 125.84, 126.43, 127.32, 128.22, 130.29, 132.07, 133.56, 135.52, 148.32 (exocyclic C-H), 152.54, 156.68, 161.40 (ring C=O), 165.52(ester C=O); MS (ESI): (m/z, %) 454.12 (M^+); Anal. Calcd. For $C_{23}H_{22}N_2O_4S_2$: C 60.77, H 4.88, N 6.16, S 14.11; found C 60.78, H 4.87, N 6.16, S 14.12.

*(Z)-ethyl-2-(5-(4-nitrophenylfuran-2-yl)-methylidene)-7-methyl-3-oxo-5-(4-hydroxy-3,5-dimethylphenyl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3s**)*
Dark yellow solid; yield: 79%; m.p.: 196-198 ^{O}C; IR (KBr) *ν* 3040 (Ar-H), 2989, 2938 (C-H), 1749 (C=O), 1590 (C=C), 1261 (O-C), 1258, 1226 (NO_2) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm 1.31 (t, 3H, -CH_3, *J* = 6.8 Hz), 2.31 (s, 6H, -2CH_3), 2.58 (s, 3H, -CH_3), 3.94 (q, 2H, -CH_2-CH_3), 6.25 (s, 1H, pyrimidine-H), 7.04 (d, 1H, β-protons of furan ring, *J* = 3.7 Hz), 7.32 (s, 2H, Ar-H), 7.36 (d, 1H, β-protons of furan ring, *J* = 3.7 Hz), 7.89 (s, 1H, exocyclic CH), 7.98 (d, 2H, 4-NO_2-Ar-H, *J* = 7.8 Hz), 8.31 (d, 2H, 4-NO_2-Ar-H, *J* = 7.8 Hz), 8.47 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* ppm 14.04 (CH_3), 16.46 (CH_3), 21.83 (CH_3), 54.29 (pyrimidine C-H), 60.42 (ester CH_2), 106.5, 108.72, 110.45, 114.88, 117.22, 121.45, 125.84, 128.22, 128.60, 130.29, 132.07, 133.56, 145.20, 148.32 (exocyclic C-H), 152.54, 156.68, 157.38, 161.40(ring C=O), 165.52(ester C=O); MS (ESI): (m/z, %) 558.34 (M^+-H); $C_{29}H_{25}N_3O_7S$: C 62.24, H 4.50, N 7.51, S 5.73; found C 62.25, H 4.51, N 7.51, S 5.72.

*(Z)-ethyl-2-(5-(2,4,5-trichlorophenylfuran-2-yl)-methylidene)-7-methyl-3-oxo-5-(4-hydroxy-3,5-dimethylphenyl)-3,5-dihydro-2H-thiazolo[3,2-a]pyrimidine-6-carboxylate (**3t**)*
Creamy white solid; yield: 81%; m.p.: 202-204 ^{O}C; IR (KBr) *ν* 3040 (Ar-H), 2989, 2938 (C-H), 1749 (C=O), 1590 (C=C), 1261 (O-C), 798 (C-Cl) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm 1.33 (t, 3H, -CH_3, *J* = 6.8 Hz), 2.11 (s, 6H, -2CH_3), 2.52 (s, 3H, -CH_3), 3.92 (q, 2H, -CH_2-CH_3), 6.23 (s, 1H, pyrimidine-H), 7.07 (d, 1H, β-protons of furan ring, *J* = 3.7 Hz), 7.30 (s, 2H, Ar-H), 7.37 (d, 1H, β-protons of furan ring, *J* = 3.7 Hz), 7.81 (s, 1H, exocyclic CH), 8.03 (s, 2H, 2,4,5-Cl_3-Ar-H, *J* = 7.8 Hz), 8.23 (s, 1H, OH); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* ppm 14.04 (CH_3), 16.46 (CH_3), 21.83 (CH_3), 54.29 (pyrimidine C-H), 60.42 (ester CH_2), 106.5, 108.72, 110.45, 114.88, 117.22, 125.84,

128.22, 128.60, 130.29, 132.07, 133.56,134.52, 135.60, 149.47 (exocyclic C-H), 152.54, 156.68, 157.38, 162.40 (ring C=O), 166.52 (ester C=O); MS (ESI): (m/z, %) 616.82 (M^+-H); Anal. Calcd. For $C_{29}H_{23}Cl_3N_2O_5S$: calcd. C 56.37, H 3.75, N 4.53, S 5.19; found C 56.38, H 3.76, N 4.54, S 5.20.

In-vivo anthelmintic activity:

Indian adult earthworms (*pheretima posthuma*) were used to study the anthelmintic activity, due to its anatomical resemblance with the intestinal roundworm parasites of human beings [27]. It is found in the wet soil which is rich in organic matter. They may damage the plants and cause soil erosion. They also act as an intermediate host for certain parasites. They belong to the class oligochaeta. The earthworms (collected from krishikendra, dharmasthala, Dakshina Kannada) were washed with normal saline to remove all fecal materials. The earthworms in 5-6 cm. in length and 0.1 - 0.2 cm in width were used for all experimental protocols. All the chemicals were used of IP/BP specifications. Anthelmintic activity is evaluated by using Albendazole as a standard drug. A suspension of 2.5% (w/v) and 1% (w/v) of test compounds were prepared in 1% (w/v) of gum acacia. A standard solution of 1.0% (w/v) of Albendazole was prepared in 1% (w/v) gum acacia. Six worms of approximately same size were placed in each petridish containing 50 mL of the suspension of the test compounds and standard drug at the 20 µg/mL concentration. The control test having six worms in 50 mL of 1% (w/v) of gum-acacia solution was also carried out simultaneously. The average time required for the paralysis and death of worms was recorded. The paralysis time of worms was the time when the worms show no movement after the drug administration but become active on transferring them into a beaker containing hot water at 40 ^oC. The death of worms was ascertained by the absence of movements of the worms in hot water.

***Lipinski's rule of Five*:**

For the any bioactive compound to be drug candidate it should satisfy lipinski's rule [28]. However, violation of one rule doesn't affect much [29]. According to this rule, active compound should have molecular weight ≤500, partition coefficient (logP) should be ≤5, number of hydrogen bond donors should be ≤5 and number of hydrogen bond acceptors ≤10. Along with this rule, number of rotatable bonds in a molecule should be ≤10 and Tropical polar surface area (TPSA) should be ≤ 140 A^0 for a effective orally bioactive compound [30].

RESULTS AND DISCUSSION

Chemistry

The reaction sequences are displayed in **Scheme.1**. The synthesis of core moiety dihydropyrimidine was done by well known three component one pot Biginelli reaction of a substituted aldehyde, 1,3-dicarbonyl compound and thiourea. The Biginelli product ethyl-4-(4-hydroxy-3,5-dimethylphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5 carboxylate (**2**) was obtained by refluxing 4-hydroxy-3,5-dimethyl benzaldehyde, ethyl acetoacetate and thiourea in the presence of catalytic amount of con. hydrochloric acid for 12h. The obtained yield was less (54%). The same reaction was tried with microwave irradiation for 6 min. Product obtained with excellent yield (90%) and purity with short reaction time. 4-hydroxy-3,5-dimethyl benzaldehyde was synthesized by a Duff formylation of 2,4-xylenol by HMTA in trifluoroacetic acid. The Biginelli compound (**2**) was then cyclized with different substituted aromatic/heterocyclic aldehydes in presence of anhydrous sodium acetate in buffer medium to afford the new series of thiazolopyrimidines (**3**). All the newly synthesized compounds were characterized by IR, 1H-NMR, LCMS and elemental analysis.

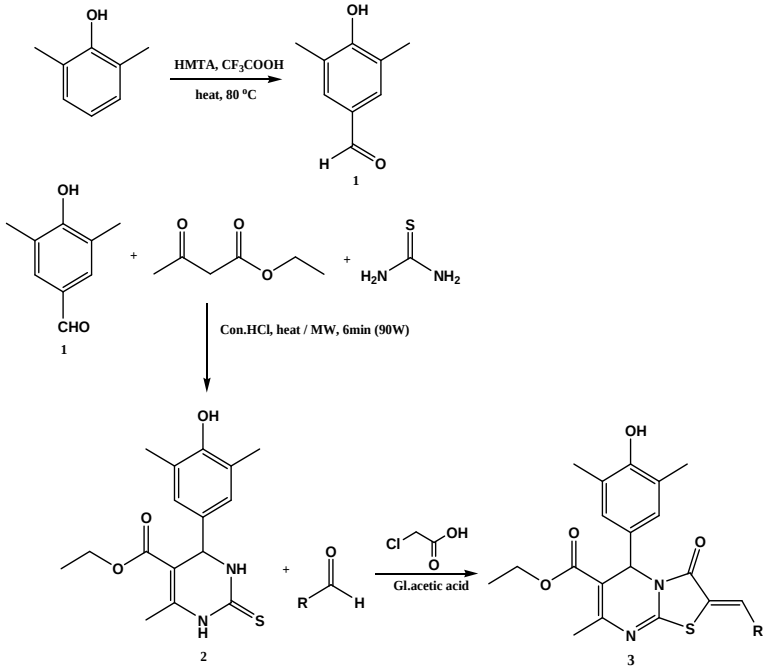
The IR spectrum of the compound (**2**) showed a broad absorption band at 3275 cm^{-1} corresponding to NH/SH tautomer stretching. In the 1H-NMR spectra of the same compound, the phenolic proton was seen as a sharp singlet at δ 10.19. The NH/SH protons were observed at δ 8.25 and δ 9.50 integrating for one proton each. The methane proton of pyrimidine ring was observed at δ 5.01 integrating for one proton as a sharp singlet, which confirms the formation of the biginelli intermediate (**2**). The ESI-MS of (**2**) showed protonated molecular ion peak (base peak) at m/z 321.8, consistent with its molecular formula, $C_{16}H_{20}N_2O_3S$.

Further, in IR spectrum of the **3a**, the disappearance of characteristic broad –NH peak confirms the cyclization reaction. The ester carbonyl group showed an absorption peak at 1759 cm^{-1} and O-C-O stretching observed at 1224 cm^{-1}. Formation of **3a** was confirmed by 400 MHz 1H-NMR, where methyl and methylene protons of ester side chain resonated as a triplet and a quartet at δ 1.20 and δ 4.09 respectively with J = 6.8 Hz and 3.6 Hz. A sharp singlet peak was observed at δ 6.12 integrating for one proton corresponding to methane proton of thiazolopyrimidone skeleton. Instead of signal for NH/SH tautomeric protons of pyrimidine ring, a new singal for

alkenyl proton of benzylidene ring was appeared at δ 7.71 as a sharp singlet. This was strongly evidenced the cyclization of pyrimidine thione into thiazolo pyrimidine. The ortho and meta protons of 4-methoxy phenyl ring gave two doublets centered at δ 6.97 and δ 7.43 integrating for two protons respectively. Two protons of 4-hydroxy-2,5-dimethyl phenyl ring resonated as a singlet at δ 7.07. The phenolic proton appeared as a singlet at δ 7.95. The 125 MHz ^{13}C-NMR showed characteristic signal for carbons of one ester methyl group, two methyl groups attached to the phenyl ring and one methyl group on pyrimidine ring were found at 14.04, 16.43 and 22.83 ppm respectively. The signal for saturated carbon of pyrimidine and methoxy carbon were found at 54.22 and 55.56 ppm respectively. Two carbonyl groups of ester and thiazolinone ring were appeared as two distinct downfield signals at 165.52 and 161.40 ppm. Presence of exocyclic carbon of benzylidene ring at 148.32 ppm evidenced the formation of above compound. Further, ESI-MS spectrum of the same compound showed intense deprotonated molecular ion (M^+-H) peak (base peak) at m/z 477 along with (M^++H) peak at m/z 479, consistent with its molecular formula $C_{26}H_{26}N_2O_5S$. Further, on elemental analyses, results found were in good agreement (±0.2) with the calculated values.

In this case two isomeric products of **3a-t** were expected from nucleophilic attack at N-1 and N-3 position of biginelli pyrimidine. However, it was well documented that N-3 position of pyrimidine ring is more susceptible to nucleophilic attack than N-1 position, which was due to the conjugation with the ester group at 5-position of the pyrimidine ring [31-32]. The low field shift of 1H-NMR signal of only pyrimidine proton in compounds **3a-t** (at > δ 5.01) was observed when compared with its biginelli pyrimidine (at δ 5.01). This was due to the deshielding effect of neighbouring carbonyl group, which well supports attack at N-3 position of pyrimidine ring. Further, the *E/Z* configuration of the exocyclic C=C bond present in the compounds **3a-3t** could be assigned on the basis of ^{1}H NMR spectroscopy results. The -CH= proton of **3a-3t** are resonated at higher chemical shift values i.e. in the region δ 7.70-7.95 representing *Z*-configuration of the compounds, which was in agreement with the reported literature [33-34].

Scheme. 1: Synthetic route for the synthesis of thiazolopyrimidines



3a:R =4-OCH_3-C_6H_4, 3b: 3,4,5-$(OCH_3)_3$-C_6H_2, 3c: 2-Cl-6-F- C_6H_3, 3d: 2,4-Cl_2-C_6H_3, 3e: 2,3-Cl_2-C_6H_3, 3f: 2-F-3-OCH_3-C_6H_3, 3g: 3-Br-C_6H_4, 3h: 3-F-4-CH_3-C_6H_3, 3i: 3-Cl-2-F-C_6H_3, 3j: 4-CN-C_6H_4, 3k: 4-OC_2H_5-C_6H_4, 3l: 4-OCH_3-$C_{10}H_7$, 3m: 3-Cl-C_6H_4, 3n: 4-Cl-C_6H_4, 3o:4-N$(CH_3)_2$-C_6H_4, 3p: 3,5-$(CH_3)_2$-4-OH-C_6H_2, 3q: C_5H_4N, 3r: C_4H_3S, 3s: 2-(4-nitrophenyl)furyl, 3t: 2-(2,4,5-trichlorophenyl)furyl

Table. 1: In-vivo antihelmithic activity of the synthesized compounds 3a-t

S.No.	Compound	Conc. in µg/mL	*Pheretima posthuma earthworm*	
			Time for paralysis(P) in min.	Time for death(D) in min.
1	3a	20	76.23 ± 2.62	138.68 ± 4.32
2	3b	20	69.54 ± 4.54	125.54 ± 3.62
3	3c	20	45.22 ± 3.54	87.30 ± 2.72
4	3d	20	46.54 ± 2.62	88.18 ± 4.08
5	3e	20	47.57 ± 2.62	90.18 ± 3.08
6	3f	20	53.18 ± 4.12	97.64 ± 3.16
7	**3g**	**20**	**43.32 ± 3.66**	**88.68 ± 4.18**
8	3h	20	54.36 ± 2.60	105.43 ± 3.82
9	3i	20	44.54 ± 2.62	88.18 ± 4.08
10	**3j**	**20**	**38.54 ± 3.55**	**65.32 ± 4.62**
11	3k	20	81.22 ± 8.46	130.22 ± 4.62
12	3l	20	68.15± 4.08	115.32 ± 3.66
13	**3m**	**20**	**42.16 ± 3.62**	**85.24 ± 4.96**
14	**3n**	**20**	**41.42 ± 2.59**	**75.11 ± 2.54**
15	3o	20	56.14 ± 2.36	109.28 ± 4.62
16	3p	20	72.54 ± 3.84	123.55 ± 3.23
17	3q	20	81.22 ± 8.46	130.22 ± 6.05
18	3r	20	88.48 ± 6.33	135.45 ± 8.08
19	**3s**	**20**	**39.43 ± 2.58**	**72.08 ± 2.54**
20	3t	20	56.54 ± 3.55	106.55 ± 3.23
control		**0.2% CMC**	-	-
Standard drug Albendazole		**20**	**38.54 ± 2.62**	**64.68 ± 3.18**

All Values represent Mean of triplicate values ±SEM; n=6 in each group. Comparisons made between standard versus treated groups, P<0.05 was considered significant.

In order to identify the potential anthelmintic activity of the newly synthesized compounds, we introduced different substitutions at benzylidene end with different functionality. The anthelmintic study data of **3a-t** are depicted in **Table.1**. From the results it was clear that, compounds exhibited excellent to moderate anti-helmintic activity. Out of twenty newly synthesized derivatives compound **3j** (4-CN) bearing strongly deactivating group at the para position of benzylidene ring was found to be very potent in paralyzing the worms and causing their death among the compounds in the series, when compared with the standard drug Albendazole. This excellent activity of the compound may be due to the effective interfering of active site of the compound with metabolic processes or neuromuscular physiology of the worms. Another compound **3s** also displayed excellent inhibition, which possesses p-Nitro arylfurylidene substitution in place of benzylidene ring. Whereas, 2,4,5-trichloro arylfurylidene substituted derivative (**3t**) showed reduced activity. When monohalo and dihalo substitutions were introduced to benzylidine moiety, there was slightly increase in the time for paralysis and death was observed i.e. inhibition slightly reduced. Compounds **3g** (3-Br), **3m** (3-Cl) and **3n** (4-Cl) with monohalo benzylidene derivatives showed pronounced inhibition than dihalo derivatives **3c** (2-Cl-6-F), **3d** (2,4-diCl), **3e** (2,3-diCl) and **3i** (3Cl-2-F). Further, in mono halo derivatives, para chloro derivative showed more inhibition than its meta derivative. The order of reactivity of monohalo derivatives in the decreasing sequence is **3n**>**3m**>**3g**. A larger bromine atom in the benzylidene ring showed slightly reduced activity when compared with chlorine atoms. Further, with increasing number of halo substitutions at benzylidene ring, time to attain paralysis and time for death again extended, which indicates depletion in the activity. We can also observe better inhibition of hetero dihalo derivatives (**3c**, **3i**) over homo dihalo compounds (**3d**, **3e**). Moreover, in addition to fluorine substitution, presence of another electron releasing group i.e. in the compounds **3f** (2-F-3-OCH_3) and **3h** (3-F-4-CH_3), further reduction in the activity was observed. Furthermore, in case of compounds with highly electron releasing groups like 4-OCH_3 (**3a**), 3,4,5-trimethoxy (**3b**), 6-OCH_3-naphthyl (**3l**) and moderately activating groups like 4-ethoxy (**3k**), 4-OH-3,5-DiCH_3 (**3p**) showed weaker inhibition. When benzylidene ring was replaced with unsubstituted heterocyclic ring i.e. in **3q** (3-pyridinyl) and **3r** (2-thiophenyl), poor inhibition was observed. Hence, from anthelmintic data of **3a-3t**, it is clear that mono substituted electron withdrawing and halo derivatives showed pronounced activity, but inhibition substantially reduced by the introduction of more number of substitutions, electron releasing groups or unsubstitution at benzylidene part. Thus, only mono electron withdrawing groups and monohalo substituted compounds were found to be potent anthelmintic agents which contributed in accelerating the inhibition.

The physicochemical descriptor provides a useful tool for evaluating drug candidate or the drug likeliness nature of the drug candidate [35]. In our present study, physico-chemical descriptors of potent compounds **3g**, **3j**, **3m**, **3n** and

3s were assessed by using molinspiration online property calculation toolkit to check the bioavailability of the bioactive molecules. The results are summarized in **Table. 2.** To develop a bioactive molecule as therapeutic agents it should satisfy Lipinski's Rule of Five along with high oral bioavailability, which is decided by ADME (Absorption, Distribution, Metabolism and Elimination) profile. For the compound to be a potent drug agent, it should not violate more than one Lipinski's rule. The compounds **3j**, **3m**, **3n** obeys all the parameters except log p value which was quite high for these compounds. Compounds **3g** and **3s** violate two parameters i.e. molecular mass and log p value. All the compounds showed good passive oral absorption (i.e.>75%). Numbers of rotatable bonds were less than 10 for all the potent compounds which determine the molecular flexibility in turn decides the binding of receptors. TPSA for all the compounds was ≤ 140 A^o which is the main requirement for oral bioavailability.

Table.2. In silico physico-chemical properties (ADME) of potent compounds 3g, 3j, 3m, 3n and 3s

Compd.	MV	MW	mi LogP	n-ON	n-OHNH	n-ROTB	%ABS	TPSA (A2)	n-Violtn
3g	414.50	527.40	6.95	6	1	5	81.90	80.90	2
3j	414.48	473.55	5.92	7	1	5	77.90	90.14	1
3m	411.15	482.99	6.82	6	1	5	81.08	80.90	1
3n	411.15	482.99	6.85	6	1	5	81.08	80.90	1
3s	460.28	513.60	6.47	7	1	6	76.55	94.04	2

MV: molecular volume, MW: molecular weight, miLogP: logarithm of partition coefficient between n-octanol and water, nON: number of hydrogen bond donors, nOHNH: number of hydrogen bond donors, n-ROTB: number of rotatable bonds, TPSA: topological polar surface area, %ABS: percentage absorption, nVioltn: number of violations.

CONCLUSION

In an attempt of developing a new class of anthelmintic agents, a new series of thiazolo pyrimidines efficiently synthesized with good yield. The anthelmintic activity study revealed that some derivatives came out to be very good anthelmintics. Compounds **3j** and **3s** emerged as excellent anthelmintic agents. Structural activity relationship revealed that incorporation of electron withdrawing groups at benzylidene ring enhanced the activity. This might be due to the presence of electron withdrawing groups at benzylidene ring which is successful in effectively interfere with metabolic processes or neuromuscular physiology of the worms, thereby causing depletion of its energy level and finally leads to paralysis which is followed by death. Also, ADME parameters showed good bioavailability of the potent compounds. Mono and hetero halo derivatives showed medium activity whereas; electron donating group derivative contributed less activity. Further structural modifications are underway to get its newer analogues with better efficacy. Hence, we can conclude that, there is ample scope for the further study.

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REFERENCES

[1] RO McCracken; WH Stillwell, *Inte.r J. Parasitol*., **1991**, 21(1), 99-104.
[2] L Mottier; L Alvarez; L Ceballos; C Lanusse, *Exp. Parasitol.*, **2006**, 113(1), 49-57.
[3] CO Kappe, *Tetrahedron*, **1993**, 49(32), 6937-6963.
[4] Kappe CO, *Acc. Chem. Res.*, **2000**, 33(12), 879-888.
[5] M Phukan; MK Kalita; R Borah, *Green Chem. Lett. Rev*., **2010**, 3, 329-334.
[6] S Tu; F Fang; C Miao; H Jiang; Y Feng; D Shi; X Wang, *Tetrahedron Lett*., **2003**, 44(32), 6153-6155.
[7] A Stadler; BH Yousefi; D Dallinger; P Walla; E Van der Eycken; N Kaval; CO Kappe, ***Org. Proc. Res. Dev.*, 2003, 7(5), 707-716.**
[8] YT Reddy; B Rajitha; PN Reddy; BS Kumar; VPG Rao, *Synth. Commun*., **2004**, 34(20), 3821-3825.
[9] RS Bhosale; AM Hashmi; PK Zubaidha; MK Dongre, *Heterocycl. Commun.*, **2005**, 11(5), 399-402.
[10] R Gedye, F Smith, K Westaway, H Ali, L Baldisera, L Laberge, J Rousell, *Tetrahedron Lett*., **1986**, 27(3), 279-282.
[11] HL Luo; W Yang; Y Li; SF Yin, *Chem. Natural Comp.*, **2010**, 46, 412.
[12] E Sochacka; I Fratczak, *Tetrahedron Lett.*, **2004**, 45(36), 6729-6731.
[13] ZG Hajos; RM Kanojia, JB Press, Eur Pat Appl. EP 458459 A2, **1991**; Chem Abstr. **1991**, 116, 83701

[14] AK Pathak; V Pathak; LE Seit; WJ Sulng; RCJ Reynolds, *J. Med. Chem.*, **2004**, 47(1), 273-276.
[15] R Lin; SG Johnson; PG Connolly; SK Wetter; E Binnun; TV Hughes; WV Murray; NB Pandey; SJ Moreno-Mazza; M Adams; AR Fuentes-Pesquera; SA Middleton, *Bioorg. Med. Chem. Lett.*, **2009**, 19(8), 2333-2337.
[16] FAM Al-Omary; GS Hassan; SM El-Messery; HI El-Subbagh, *Eur. J. Med. Chem.*, **2012**, 47(1), 65-72.
[17] B Singh; SK Guru; S Kour; SK Jain; R Sharma; PR Sharma; SK Singh; S Bhushan; SB Bharate; RA Vishwakarma, *Eur J Med Chem.*, **2013**, 70, 864-874.
[18] S Pandey; P Pandey; J Singh, *Der Pharma Chemica.*, **2014,** 6(1), 170-175.
[19] K Danel; EB Pedersen; Nielsen C, *J. Med. Chem.*, **1998**, 41(2), 191-198.
[20] B Tozkoparan; N Gökhan; G Aktay; ES Ilada; Ertan M, *Eur. J. Med. Chem.*, **2000**, 35(7-8), 743-750.
[21] JG Geist; S Lauw; V Illarinova; M Fischer; T Gwawert; F Rohdich; W Eisenreich; J Kaise;, M Groll; Scheurer C, *Chem Med Chem*, **2010**, 5(7), 1092-1101.
[22] BJ Branstetter; JG Breitenbucher; AD Lebsack; Xiao W, Thiaolopyrimidine Modulators of TRPV1. **2008**; *US Patent*, WO 005,303.
[23] A Gangjee; HD Jain; J Phan; X Lin, *J. Med. Chem.*, **2006**, 49(3), 1055-1065.
[24] A Gangjee; Y Zeng; M Ihnat; LA Warnke, *Bioorg. Med. Chem.*, **2005**, 13(18), 5475-5491.
[25] S Verma; D Nagarathnam; J Shao; L Zhang, *Bioorg Med Chem Lett.*, **2005**, 15(8), 1973-1977.
[26] WE Smith, *J. Org. Chem.*, **1972**, 37(24), 3972-3973.
[27] UK Patil; S Saraf; VK Dixit, *J. Ethnopharmacology*, **2004**, 90(2), 249-252.
[28] AD Headley; SD Starnes; LY Wilson; GR Famini, *J. Org. Chem.*, **1994**, 59(26), 8040-8046.
[29] CA Lipinski; F Lombardo; BW Dominy; Feeney PJ, *Adv. Drug Deli. Rev.*, **2001**, 46(1-3), 3-25.
[30] DF Veber; SR Johnson; HY Cheng; BR Smith; KW Ward; KD Kapple, *J. Med. Chem.*, **2002**, 45(12), 2615-2623.
[31] N Foroughifar; A Mobinikhaledi; F Goodarzi, *Phosphorus Sulfur Silicon Relat Elem.*, **2003**, 178, 2539-2544.
[32] A Mobinikhaledi; N Foroughifar; FB Ahmadi, *Phosphorus Sulfur Silicon Relat. Elem.*, **2005**, 180; 339-345.
[33] R Ottana; Maccari R; Barreca ML; Bruno G; Rotondo A; Rossi A; Chiricosta G; Paola RD; Sautebin L; Cuzzocrea S; Vigorita MG, *Bioorg. Med. Chem.*, **2005**, 13(13), 4243-4252.
[34] G Bruno; L Costantino; C Curinga; R Maccari; F Monforte; F Nicolo; R Ottana; Vigorita MG, *Bioorg. Med. Chem.*, **2002**, 10(4), 1077-1084.
[35] J Xu; Stevenson J, *J. Chem. Inf. Comput. Sci.*, **2000**, 40(5), 1177-1187.