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SYNTHESIS, CHARECTERIZATION AND BIOLOGICAL EVALUATION OF SOME NOVEL BENZOTHIAZOLE PYRAMIDINE ANALOGS AS POTENTIAL ANTITUBERCULAR AGENTS

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ABSTRACT

Benzthiazole, Pyramidines and their analogues have a good sort of biological activities like Neuro protective activity**,** anti helminthic, antifungal, antibacterial, antidiabetic, antitubercular, anti-inflammatory, anti-convulsant, herbicidal activity, Anti-malarial activity, Hypolipedimic activity etc., within the present research work, an attempt has been made to synthesize some new series of novel benzthiazole linked chalcones from 3-aminoacetophenone and potassium thiocyanate which were dissolved in glacial acetic acid at temperature 25±2.5°C and liquid bromine in glacial acetic acid was then added drop-wise, and eventually the reaction mass is quenched and basified with ammonia to get the specified Benzthiazole linked chalcone later the answer of benzothiazole linked chalcone in ethanol was condensed with guanidine hydrochloride within the presence of catalytic amount of pyridine in absolute ethanol at reflux temperature on a water bath to get the desired compound. The purity of the compounds was identified by TLC. The solvent was evaporated in vacuum and crushed ice was added to the residue while mixing thoroughly, a bright yellow solid separated out. This solid was filtered under vacuum, dried and purified by chromatography to offer light yellow solid. The structures were determined by IR, 1H NMR and Mass spectral data. The synthesized benthiazole linked pyramidine analogues were screened for anti-tubercular activity by use of MABA (Microplate Alamar Blue assay) analytical method on H37Rv strain of tubercle bacillus. The compounds containing electron withdrawing groups like chlorine, fluorine, nitrogen showed better activity than that of the opposite compounds within the series. The mechanism of action of the compounds can be assassinated for the activity on the cell membrane disruption by inhibiting the peptidoglycon synthesis as potential antitubercular agent.

KEYWORDS: Benzthiazoles, Pyramidines, antitubercular, MABA.

INTRODUCTION

Synthesis of hybrid drug technology paved way for development of innovative medicines which are a symbol of relief from several complex abnormalities/ diseases which incorporates tuberculosis, cancer and lots of other microbial infections. Single drug targets might not help within the treatment of complicated diseases which are difficult to diagnose or cure. a primary step toward this alteration is that the hybrid drug or, even better and cheaper , the dual-target strategy, where two targets at different key points within an equivalent or concurrent pathogenic pathways are carefully chosen for his or her potential additive effects or synergistic potentiating. In recent years, the chemistry of benzothiazoles captivated importance as these compounds are found to exhibit several biological activities, such as Anti-inflammatory, Analgesic, Antitumor, Anticonvulsant, Anti-diabetic, Antimicrobial, Antifungal, CNS depressant, Antimalarial, Anthelmintic, Anticancer Antiurease, Hypoglycemic agent, Anti-oxidant, Antihelmenthic, Anti-histaminic, Insecticidal, Anti-HIV, Antiprotozoal, Antitubercular.

Similarly, Pyramidines have also been found to exhibit several biological activities, such as Neuro protective activity,[1] anti-microbial,[2-5] antifungal,[6-8] antibacterial,[9-14] anti-cancer,[15-17] CDK2 & CDK4 inhibitor,[18] anti-tumour,[19-20] Dihydrofolate reductase,[21] anti-inflammatory,[22-23] COX-2

inhibitor,[24] herbicidal activity,[25-27] anti viral,[28-29] Selective human enterovirus inhibitor,[30] HSV-1 & HIV inhibitor,[31] HIV-I inhibitor,[32-33] anti-tubercular,[34-35] Anti-malarial activity,[36-40] Anti-Leishmanial activity,[41-42] Hypolipedimic activity,[43-44] In-addition, besides to benzothiazoles and substituted pyrimidines have also been reported to exhibit diverse biological activities, such as such as Antiretroviral, Anti-tubercular, Antitumor, Antineoplastic, Anti-inflammatory, Diuretic, Antimalarial, Cardiovascular, Cystic fibrosis transmembrane conductance regulator inhibitors, β-site APP-cleaving enzyme 1 inhibitors, A3 adenosine receptor antagonists, Inhibitors of heat shock protein 90, Adenosine kinase inhibitory activity, EGFr and C-erbB-2 inhibitory activity, Antibacterial, Phosphodiesterase 5 inhibitory activity, Antifungal, Antiviral, Antihypertensive and Hepatoprotective respectively.

Having such diverse range of pharmacological activities, these classes of compound have attracted medicinal chemists and consequently a number of strategies based on hybrid drug discovery and development have been originated to synthesize them.

In the present research, emerging drug discovery paradigm based on the selection of pharmacophore fragments with superior therapeutic value and safety has been chosen. This can be achieved by designing individual new chemical entities (hybrid drugs) by applying molecular hybridization techniques to the chosen bioactive fragment pharmacophores. The relevant work will discusses the synthetic methodology used to prepare the designed hybrid molecules and the ease by which it may be cleaved to form the independent components in vivo.

It is proved from the literature that the compounds containing either benzothiazole/pyramidine based on these observations, it was considered worthwhile to synthesize and characterize a series of benzothiazole-linked pyramidines in the present investigation. As a part of research program aimed at search for new hybrid pharmacophores as antitubercular agents, we are interested to have pyamidine conjugation to the benzothiazole basic nucleus to give a series of benzothiazole-linked pyramidines. Therefore, in the present study an attempt has been made to synthesize and characterize a series of benzothiazole analogs of the key intermediate 1-(2-aminobenzo[d]thiazol-5-yl)ethan-1-one as Fig. 1.

Fig. 1.General structures of rationally designed benzothiazole analogs

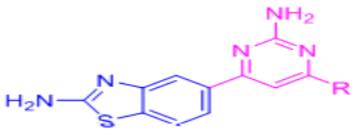


Fig-1: Benzthiazole Linked Pyramidine.

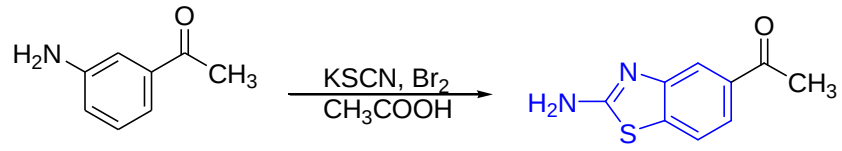
All the structures of the benzothiazole-linked pyramidines (APY1-APY14) were appropriately established by melting point, IR, NMR, mass spectroscopic and analytical data so as to evaluate the synthesized benzothiazole-linked pyramidines (APY1-APY14) for their in vitro antitubercular activity using Mycobacterium tuberculosis H37Rv strain.

MATERIALS AND METHODS

The reaction sequence employed in the synthesis of benzothiazole-linked pyramidines (APY1-APY14).

Synthesis of 1-(2-aminobenzo[d]thiazol-5-yl)ethan-1-one(I).

The key intermediate in the present investigation is 1-(2-aminobenzo[d]thiazol-5-yl)ethan-1-one (**I**) which was prepared as per the method reported earlier from 3-aminoacetophenone (2.0 g, 14.8 mmol), potassium thiocyanate (3.9 g, 52.0 mmol) were dissolved in glacial acetic acid at room temperature. Liquid bromine (2.6 g, 16.3 mmol) in glacial acetic acid was then added drop-wise, maintaining the reaction temperature below 10°C for a period of 90-180min. After the addition was complete, the reaction mixture was stirred, and the progress of the reaction was monitored by thin-layer chromatography (TLC). After completion of the reaction as indicated by the disappearance of starting material on TLC analysis, the solids were filtered off and then washed first with glacial acetic acid and then with water. The filtrate was diluted with 300 ml of warm water, neutralized to pH 7 to 7.5 by using liquor ammonia, and then cooled overnight in the refrigerator to allow the product to precipitate. The product was filtered, washed with cold water, and dried under vacuum. The product was recrystallized using Methanol. Compound **I**, analyzed for $C_9H_8N_2OS$, which possess m.p. 242-245^oC which was consistent with the literature reported m.p. 246 ^oC. The IR spectrum of compound **I** exhibited the characteristic absorption bands at 3356 cm^{-1} and 1647 cm^{-1} suggesting the presence of a primary amine group and carbonyl groups respectively. The characteristic band attributed to the presence of C=N stretch in the benzothiazole ring was observed at 1594 cm^{-1}. The 400 MHz ^{1}H-NMR spectrum of the compound **I** in DMSO-$d_6$with TMS as an internal standard exhibited characteristic peaks of primary amino (-NH) and acetyl protons (-$COCH_3$) as two singlets, one at δ 7.85 ppm (1H, s) and the other one at δ 2.50 ppm (1H,s). The aromatic protons of benzothiazole nucleus accounted in the range of δ 7.3 to 8.3. In the ^{13}C-NMR spectrum a carbonyl carbon appeared at δ 210 ppm. The ESI mass spectrum (negative ion mode) of compound **I** revealed a $(M-H)^-$ ion at *m/z*191. Eventually all the spectra of the compound are in keeping consistent with the literature reported characterization data. Based on the above spectral data and elemental analysis, the structure of the compound was confirmed as 1-(2-aminobenzo[d]thiazol-5-yl)ethan-1-one (**I**). The reaction procedure for the synthesis of intermediate is well illustrated in **Scheme-1.**



Scheme 1: Reaction scheme for the synthesis of intermediate (I).

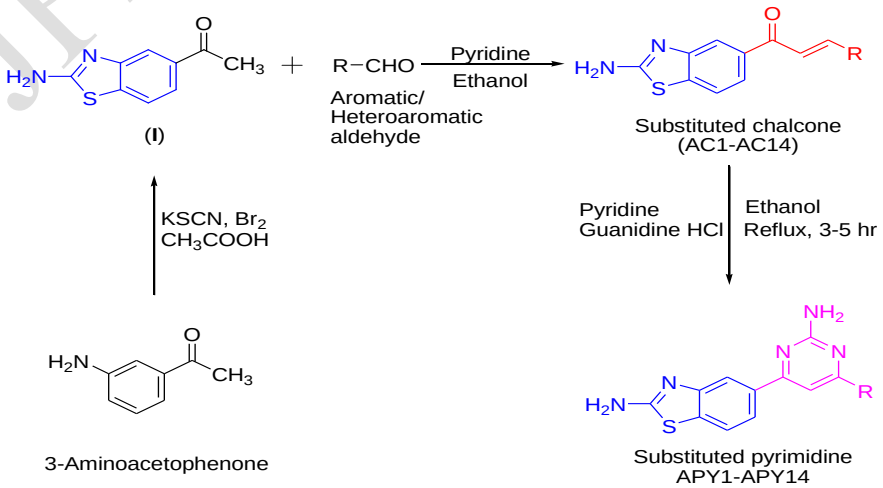
GENERAL PROCEDURE

Synthesis of *(E)*-1-(2-aminobenzo[d]thiazol-5-yl)-3-(substituted)prop-2-en-1-ones:

To a solution of 1-(2-aminobenzo[d]thiazol-5-yl)ethan-1-one (I) (0.005 M) and suitably substituted aldehydes (0.005 M) in ethanol (10 ml),catalytic amount of pyridine was added drop wise with continuous stirring at room temperature over a period of 15 min. The reaction mixture was then kept at room temperature for about 48 h with occasional shaking. After 48 h it was poured into ice-cold water, and then neutralized to pH 2 using 5 N hydrochloric acid. The yellow precipitate obtained was filtered, washed, dried, and recrystallized from dry ethanol. The substituted chalcones (AC1-AC14) were obtained in good yield. All the synthesized compounds characterized by spectroscopic methods such as FTIR, NMR and mass spectral analysis. The solution of *(E)*-1-(2-aminobenzo[d]thiazol-5-yl)-3-phenylprop-2-en-1-one (AC1) (0.005 mol) in ethanol was condensed with guanidine hydrochloride (0.005 mol) in the presence of catalytic amount of pyridine (5-6 drops) in absolute ethanol (30 ml) at reflux temperature on a water bath for 3 hrs. The solvent was evaporated in vacuum and crushed ice was added to the residue while mixing thoroughly, whereupon a bright yellow solid separated out. This solid was filtered under vacuum, dried and purified by column chromatography to give light yellow solid.

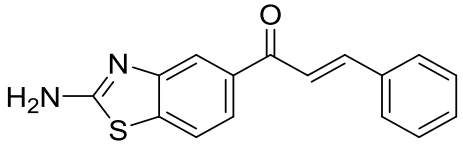
Compound **APY1**, analyzed for $C_{17}H_{13}N_5S$, m.p. 297-299^{o}C. The IR spectrum of compound **APY1** exhibited the characteristic absorption bands at 3355 cm^{-1} and 1595 cm^{-1} suggesting the presence of a primary amine group and C=N stretching bands respectively. The characteristic band attributed to the presence of C-S stretch in the benzothiazole ring was observed at 710 cm^{-1}. The 400 MHz ^{1}H-NMR spectrum of the compound **APY1** in DMSO-d_6 with TMS as an internal standard exhibited characteristic peaks of C-5-H of the pyrimidine at δ 8.26 as singlet and C-2-NH_2 at 5.21 as singlet. The spectrum also accounted for the other aromatic protons in between δ 7.52-8.30. In the ^{13}C-NMR spectrum of compound APY1 accounted for characteristic carbons whose resonances appeared at the δ values 164.29 (C-2) and 103.45 (C-5) respectively. The ESI mass spectrum (negative ion mode) of compound **APY1** revealed a $(M-H)^-$ ion at *m/z*318. Eventually all the spectra of the compound are in keeping consistent with the expected structure. The results of elemental analysis were also in close agreement with those of the calculated values. Based on the above spectral data and elemental analysis, the structure of the compound was confirmed as 5-(2-amino-6-phenylpyrimidin-4-yl)benzo[d]thiazol-2-amine (APY1).By adopting the above the synthetic procedure, benzothiazole-linked pyrimidines (**APY2-APY14)** were also been synthesized. The physical and spectral characterisation of all the compounds was presented individually as follows.

The reaction procedure for the synthesis of intermediate is well illustrated in **Scheme-2.**

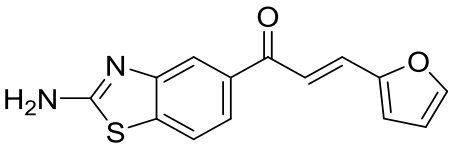


Scheme 2: Reaction scheme for the synthesis of substituted Pyramidine.

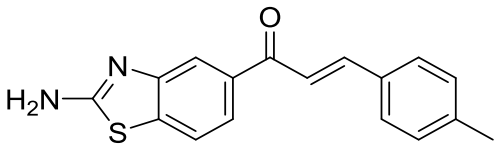
List of benzothiazole-linked chalcones**AC1-AC14**



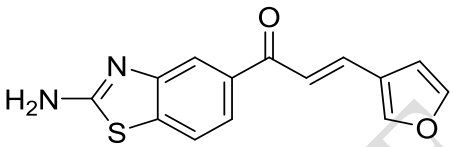
AC1



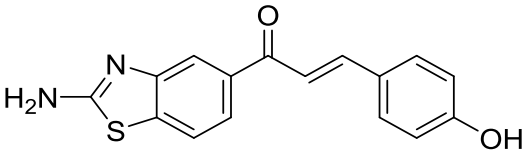
AC8



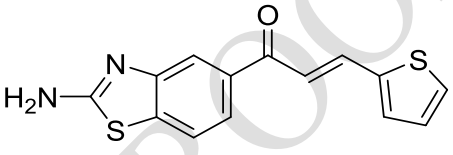
AC2



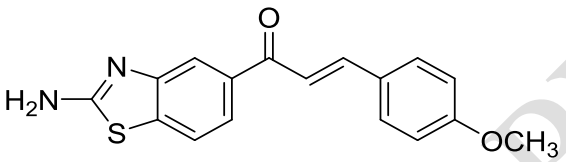
AC9



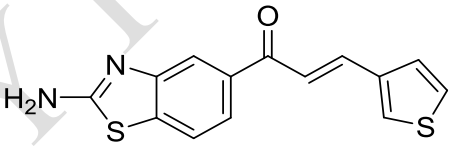
AC3



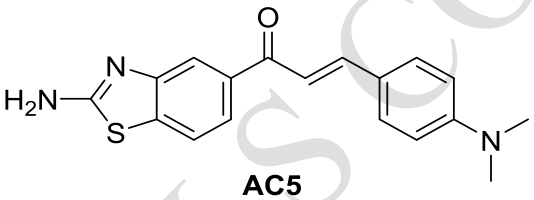
AC10



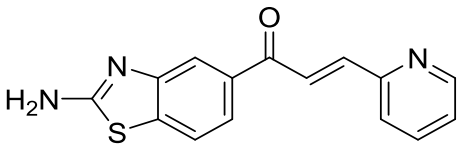
AC4



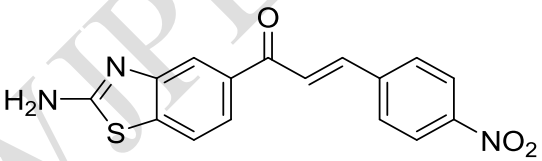
AC11



AC5



AC12



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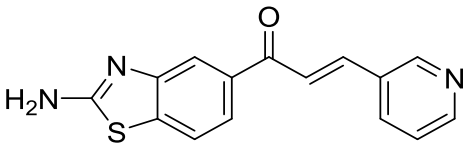
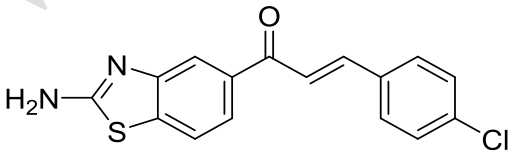


AC13



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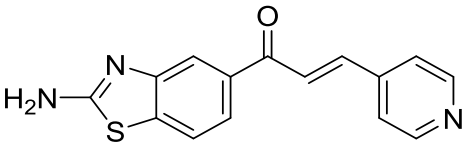
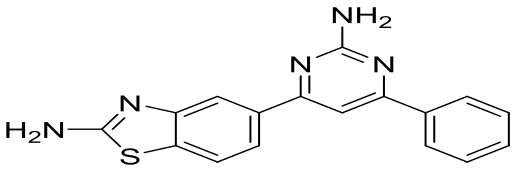
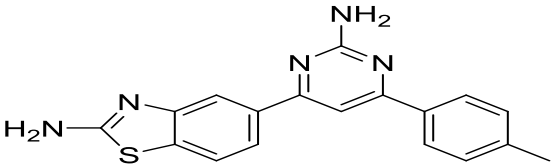


AC14

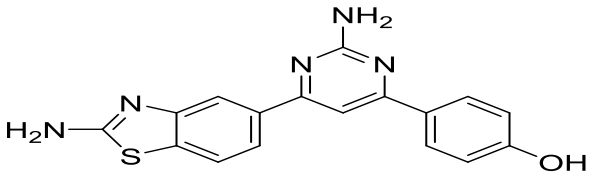
List of Benzothiazole-linked Pyramidines **APY1-APY14**



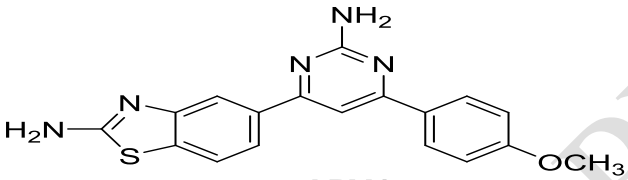
APY1



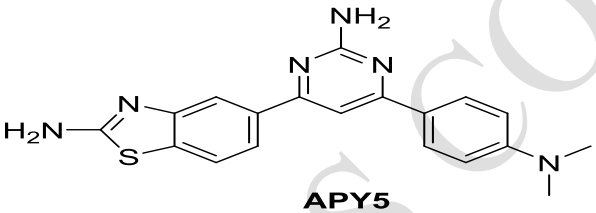
APY2



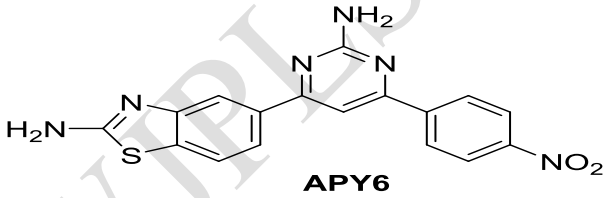
APY3



APY4



APY5



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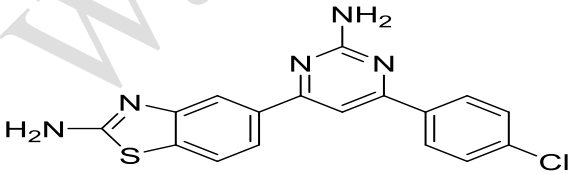

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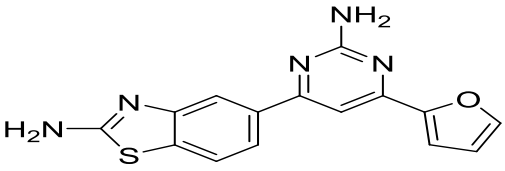

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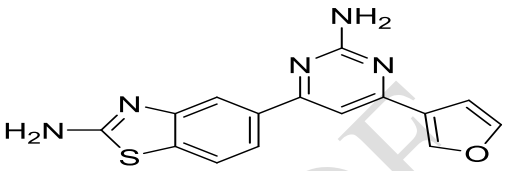

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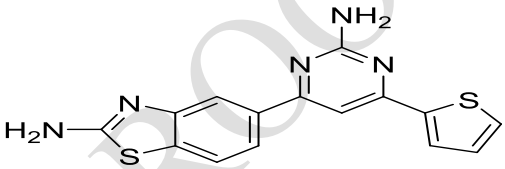
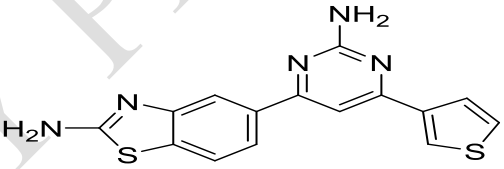
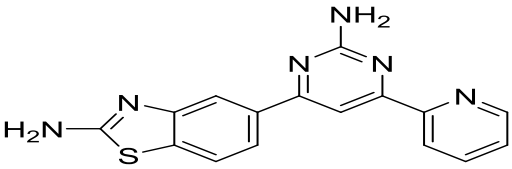


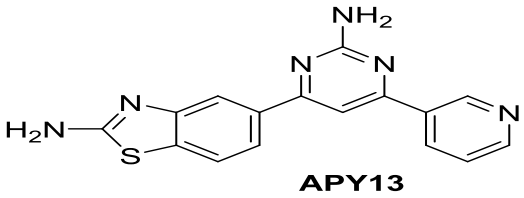
APY10



APY11



APY12



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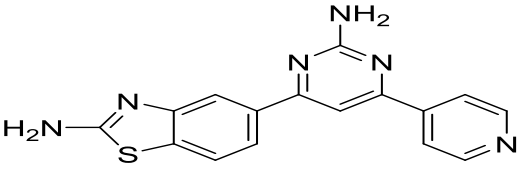


APY14

5-(2-amino-6-phenylpyrimidin-4-yl)benzo[d]thiazol-2-amine (APY1)

Yield: 61%, Yellow powder, Melting point (m.p.):297-299 ^{o}C, Chemical Formula: $C_{17}H_{13}N_5S$, Relative Molecular Mass: 319.39. Anal. Found. for $C_{17}H_{13}N_5S$, %: C, 63.93; H, 4.10; N, 21.93; S, 10.04, IR (KBr, ν_{max} cm^{-1}): 3355 (N−H), 1595 (C=N), 710 (C–S), ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): δ 7.21 (1H, s,),7.52-7.65 (3H, 7.57 (dddd, *J* = 7.7, 7.6, 1.3, 0.4 Hz), 7.60 (tdd, *J* = 7.7, 1.6, 1.5 Hz)), 7.97 (1H, dd, *J* = 8.3, 0.4 Hz), 8.04-8.16 (3H, 8.07 (dddd, *J* = 7.6, 1.6, 1.5, 0.4 Hz), 8.13

(dd, *J* = 8.3, 1.5 Hz)),8.26 (1H, s). ESI-MS (*m/z*, negative ion mode): 318 $[M–H]^-$

5-(2-amino-6-(p-tolyl)pyrimidin-4-yl)benzo[d]thiazol-2-amine (APY2)

Yield: 54%, Yellow powder, Melting point (m.p.):283-285 ^oC, Chemical Formula: $C_{18}H_{15}N_5S$

Relative Molecular Mass: 333.41, Anal. Found. for $C_{18}H_{15}N_5S$, %: C, 64.84; H, 4.53; N, 21.01; S, 9.62, IR (KBr, ν_{max} cm^{-1}): 3367 (N−H), 1659 (C=N), 704 (C–S), ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): δ 2.23 (3H, s), 7.35 (2H, ddd, *J* = 7.9, 1.2, 0.4 Hz), 7.74 (1H, dd, *J* = 8.3, 0.4 Hz), 7.88 (2H, ddd, *J* = 7.9, 1.6, 0.4 Hz), 8.05-8.12 (2H, 8.05 (s), 8.09 (dd, *J* = 8.3, 1.5 Hz)), 8.21 (1H, dd, *J* = 1.5, 0.4 Hz). ESI-MS (*m/z*, negative ion mode): 332 $[M–H]^-$

4-(2-amino-6-(2-aminobenzo [d] thiazol-5-yl) pyrimidin-4-yl) phenol (APY3)

Yield: 47%, Yellowish white powder, Melting point (m.p.):295-297 ^oC, Chemical Formula: $C_{17}H_{13}N_5OS$, Relative Molecular Mass: 335.39, Anal. Found. for $C_{17}H_{13}N_5OS$, %: C, 60.88; H, 3.91; N, 20.88; O, 4.77; S, 9.56, IR (KBr, ν_{max} cm^{-1}): 3367 (N−H), 1659 (C=N), 748 (C–S)

^1H NMR (400 MHz, DMSO-d_6) δ (ppm): δ 7.17 (2H, ddd, *J* = 8.4, 1.2, 0.4 Hz), 7.69-7.76 (3H, 7.72 (dd, *J* = 8.3, 0.4 Hz), 7.73 (ddd, *J* = 8.4, 1.7, 0.4 Hz)), 7.83 (1H, s), 8.13 (1H, dd, *J* = 8.3, 1.5 Hz), 8.20 (1H, dd, *J* = 1.5, 0.4 Hz). ESI-MS (*m/z*, negative ion mode): 332 $[M–H]^-$

5-(2-amino-6-(4-methoxyphenyl) pyrimidin-4-yl) benzo [d] thiazol-2-amine (APY4)

Yield: 63%, Yellow powder, Melting point (m.p.): 304-306 ^oC, Chemical Formula: $C_{18}H_{15}N_5OS$

Relative Molecular Mass: 349.41. Anal. Found. for $C_{18}H_{15}N_5OS$, %: C, 61.87; H, 4.33; N, 20.04; O, 4.58; S, 9.18. IR (KBr, ν_{max} cm^{-1}): 3460 (N−H), 1605 (C=N), 708 (C–S), ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): δ 3.87 (3H, s), 7.16 (2H, ddd, *J* = 8.9, 1.2, 0.4 Hz), 7.69-7.77 (4H, 7.75 (dd, *J* = 8.3, 0.4 Hz), 7.72 (ddd, *J* = 8.5, 1.7, 0.4 Hz), 7.69 (s)), 8.10 (1H, dd, *J* = 8.3, 1.5 Hz), 8.20 (1H, dd, *J* = 1.5, 0.4 Hz). ESI-MS (*m/z*, negative ion mode): 348 $[M–H]^-$

5-(2-amino-6-(4-(dimethylamino)phenyl) pyrimidin-4-yl) benzo[d]thiazol-2-amine (APY5)

Yield: 71%, Yellowish orange powder, Melting point (m.p.): 289-291 ^oC ,Chemical Formula: $C_{19}H_{18}N_6S$, Relative Molecular Mass: 362.46. Anal. Found. for $C_{19}H_{18}N_6S$, %: C, 62.96; H, 5.01; N, 23.19; S, 8.85 IR (KBr, ν_{max} cm^{-1}): 3445 (N−H), 1642 (C=N), 727 (C–S), ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): δ 2.85 (6H, s), 6.96 (2H, ddd, *J* = 8.4, 1.3, 0.4 Hz), 7.56 (1H, s), 7.64-7.72 (3H, 7.69 (dd, *J* = 8.3, 0.4 Hz), 7.67 (ddd, *J* = 8.4, 1.5, 0.4 Hz)), 8.13-8.20 (2H, 8.19 (dd, *J* = 1.5, 0.4 Hz), 8.16 (dd, *J* = 8.3, 1.5 Hz)). ESI-MS (*m/z*, negative ion mode): 361 $[M–H]^-$

5-(2-amino-6-(4-nitrophenyl) pyrimidin-4-yl) benzo [d] thiazol-2-amine (APY6)

Yield: 64%, Yellow powder,Melting point (m.p.): 292-294 ^oC , Chemical Formula: $C_{17}H_{12}N_6O_2S$

Relative Molecular Mass: 364.38, Anal. Found. for $C_{17}H_{12}N_6O_2S$, %: C, 56.04; H, 3.32; N, 23.06; O, 8.78; S, 8.80, IR (KBr, ν_{max} cm^{-1}): 3354 (N−H), 1675 (C=N), 705 (C–S), ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): δ 7.79 (1H, s), 8.09 (1H, dd, *J* = 7.7, 0.4 Hz), 8.19 (2H, ddd, *J* = 8.7, 1.7, 0.5 Hz), 8.20-8.27 (4H, 8.23 (ddd, *J* = 8.7, 1.7, 0.5 Hz), 8.24 (dd, *J* = 7.7, 1.9 Hz), 8.21 (dd, *J* = 1.9, 0.4 Hz)). ESI-MS (*m/z*, negative ion mode): 363 $[M–H]^-$

5-(2-amino-6-(4-chlorophenyl) pyrimidin-4-yl) benzo [d] thiazol-2-amine (APY7)

Yield: 74%, Yellow powder, Melting point (m.p.): 262-264 ^oC , Chemical Formula: $C_{17}H_{12}ClN_5S$

Relative Molecular Mass: 353.83, Anal. Found. for $C_{17}H_{12}ClN_5S$, %: C, 57.71; H, 3.42; Cl, 10.02; N, 19.79; S, 9.06. IR (KBr, ν_{max} cm^{-1}): 3481 (N−H), 1616 (C=N), 668 (C–S), ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): δ 7.77 (2H, ddd, *J* = 8.2, 1.4, 0.4 Hz), 7.82-7.90 (3H, 7.87 (dd, *J* = 8.3, 0.4 Hz), 7.85 (ddd, *J* = 8.2, 1.6, 0.4 Hz)), 7.96 (1H, s), 8.15 (1H, dd, *J* = 8.3, 1.5 Hz), 8.20 (1H, dd, *J* = 1.5, 0.4 Hz). ESI-MS (*m/z*, negative ion mode): 352 $[M–H]^-$

5-(2-amino-6-(furan-2-yl) pyrimidin-4-yl) benzo [d] thiazol-2-amine (APY8)

Yield: 68%, Yellow powder, Melting point (m.p.): 237-239 ^oC, Chemical Formula: $C_{15}H_{11}N_5OS$

Relative Molecular Mass: 309.35, Anal. Found. for $C_{15}H_{11}N_5OS$, %: C, 58.24; H, 3.58; N, 22.64; O, 5.17; S, 10.36, IR (KBr, ν_{max} cm^{-1}): 3412 (N−H), 1597 (C=N), 735 (C–S), ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): δ 6.67 (1H, dd, *J* = 3.5, 1.8 Hz), 7.15 (1H, dd, *J* = 3.5, 0.9 Hz), 7.42 (1H, dd, *J* = 8.2, 0.4 Hz), 7.84 (1H, s), 7.99 (1H, dd, *J* = 1.8, 0.9 Hz), 8.18-8.24 (2H, 8.21 (dd, *J* = 1.6, 0.4 Hz), 8.21 (dd, *J* = 8.2, 1.6 Hz)). ESI-MS (*m/z*, negative ion mode): 308 $[M–H]^-$

5- (2-amino-6-(furan-3-yl) pyrimidin-4-yl) benzo [d] thiazol-2-amine (APY9)

Yield: 68%, Yellow powder, Melting point (m.p.):241-243 ^oC, Chemical Formula: $C_{15}H_{11}N_5OS$

Relative Molecular Mass: 309.35, Anal. Found. for $C_{15}H_{11}N_5OS$, %: C, 58.24; H, 3.58; N, 22.64; O, 5.17; S, 10.36, IR (KBr, ν_{max} cm^{-1}): 3381 (N−H), 1664 (C=N), 708 (C–S), ^1H NMR (400 MHz, DMSO-d_6) δ (ppm): δ 7.08 (1H, dd, *J* = 1.8, 1.4 Hz), 7.42 (1H, dd, *J* = 8.2, 0.4 Hz), 7.74 (1H, dd, *J* = 1.8, 1.4 Hz), 7.83-7.85 (2H, 7.85 (s), 7.84 (t, *J* = 1.4 Hz)), 8.18-8.24 (2H, 8.21 (dd, *J* = 1.6,

0.4 Hz), 8.21 (dd, *J* = 8.2, 1.6 Hz)). ESI-MS (*m/z*, negative ion mode): 308 $[M–H]^-$

5-(2-amino-6-(thiophen-2-yl) pyrimidin-4-yl) benzo [d] thiazol-2-amine (APY10)
Yield: 55%, Yellow powder, Melting point (m.p.): 261-263 °C, Chemical Formula: $C_{15}H_{11}N_5S_2$

Relative Molecular Mass: 325.41, Anal. Found. for $C_{15}H_{11}N_5S_2$, %: C, 55.37; H, 3.41; N, 21.52; S, 19.70, IR (KBr, ν_{max} cm^{-1}): 3412 (N−H), 1597 (C=N), 735 (C–S), ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): δ 7.12 (1H, dd, *J* = 8.0, 6.1 Hz), 7.42 (1H, dd, *J* = 8.2, 0.4 Hz), 7.53 (1H, dd, *J* = 8.0, 1.2 Hz), 7.86 (1H, dd, *J* = 6.1, 1.2 Hz), 7.90 (1H, s), 8.18-8.24 (2H, 8.21 (dd, *J* = 1.6, 0.4 Hz), 8.21 (dd, *J* = 8.2, 1.6 Hz)). ESI-MS (*m/z*, negative ion mode): 324 $[M–H]^-$

5-(2-amino-6-(thiophen-3-yl) pyrimidin-4-yl) benzo [d] thiazol-2-amine (APY11)
Yield: 61%, Yellow powder, Melting point (m.p.): 284-286 °C, Chemical Formula: $C_{15}H_{11}N_5S_2$

Relative Molecular Mass: 325.4, Anal. Found. for $C_{15}H_{11}N_5S_2$, %: C, 55.37; H, 3.41; N, 21.52; S, 19.70, IR (KBr, ν_{max} cm^{-1}): 3349 (N−H), 1654 (C=N), 737 (C–S), ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): δ 7.42 (1H, dd, *J* = 8.2, 0.4 Hz), 7.73 (1H, dd, *J* = 7.0, 1.2 Hz), 7.80 (1H, dd, *J* = 7.0, 1.4 Hz), 7.88 (1H, s), 8.19-8.24 (2H, 8.21 (dd, *J* = 1.6, 0.4 Hz), 8.21 (dd, *J* = 8.2, 1.6 Hz)), 8.27 (1H, dd, *J* = 1.4, 1.2 Hz). ESI-MS (*m/z*, negative ion mode): 324 $[M–H]^-$

5-(2-amino-6-(pyridin-2-yl) pyrimidin-4-yl) benzo [d] thiazol-2-amine (APY12)
Yield: 54%, Yellow powder, Melting point (m.p.): 290-292 °C, Chemical Formula: $C_{16}H_{12}N_6S$

Relative Molecular Mass: 320.37, Anal. Found. for $C_{16}H_{12}N_6S$, %: C, 59.98; H, 3.78; N, 26.23; S, 10.01, IR (KBr, ν_{max} cm^{-1}): 3383 (N−H), 1671 (C=N), 711 (C–S), ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): δ 7.58 (1H, ddd, *J* = 7.8, 6.1, 1.7 Hz), 7.85-7.95 (2H, 7.92 (dd, *J* = 8.3, 0.4 Hz), 7.90 (ddd, *J* = 7.8, 7.6, 1.8 Hz)), 8.00 (1H, ddd, *J* = 7.6, 1.7, 0.5 Hz), 8.16 (1H, dd, *J* = 8.3, 1.6 Hz), 8.22 (1H, dd, *J* = 1.6, 0.4 Hz), 8.33 (1H, s), 8.72 (1H, ddd, *J* = 6.1, 1.8, 0.5 Hz). ESI-MS (*m/z*, negative ion mode): 319 $[M–H]^-$

5-(2-amino-6-(pyridin-3-yl)pyrimidin-4-yl) benzo [d] thiazol-2-amine (APY13)
Yield: 47%, Yellow powder, Melting point (m.p.): 307-309 °C, Chemical Formula: $C_{16}H_{12}N_6S$

Relative Molecular Mass: 320.37, Anal. Found. for $C_{16}H_{12}N_6S$, %: C, 59.98; H, 3.78; N, 26.23; S, 10.01, IR (KBr, ν_{max} cm^{-1}): 3346 (N−H), 1599 (C=N), 782 (C–S), ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): δ 7.58 (1H, ddd, *J* = 7.8, 5.2, 0.5 Hz), 7.72 (1H, s), 7.92 (1H, dd, *J* = 8.3, 0.4 Hz), 8.20-8.26 (2H, 8.21 (dd, *J* = 1.6, 0.4 Hz), 8.23 (dd, *J* = 8.3, 1.6 Hz)), 8.57 (1H, dt, *J* = 5.2, 1.9 Hz), 8.87 (1H, ddd, *J* = 7.8, 1.9, 1.8 Hz), 9.15 (1H, ddd, *J* = 1.9, 1.8, 0.5 Hz). ESI-MS (*m/z*, negative ion mode): 319 $[M–H]^-$

5-(2-amino-6-(pyridin-4-yl) pyrimidin-4-yl) benzo [d] thiazol-2-amine (APY14)
Yield: 51%, Yellow powder, Melting point (m.p.): 314-316 °C, Chemical Formula: $C_{16}H_{12}N_6S$

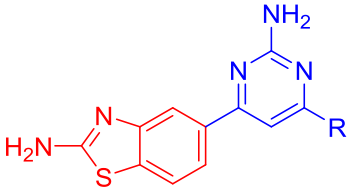
Relative Molecular Mass: 320.37, Anal. Found. for $C_{16}H_{12}N_6S$, %: C, 59.98; H, 3.78; N, 26.23; S, 10.01. IR (KBr, ν_{max} cm^{-1}): 3382 (N−H), 1672 (C=N), 711 (C–S), ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): δ 7.92 (1H, dd, *J* = 8.3, 0.4 Hz), 8.10 (2H, ddd, *J* = 5.6, 2.2, 0.4 Hz), 8.15 (1H, dd, *J* = 8.3, 1.6 Hz), 8.22 (1H, dd, *J* = 1.6, 0.4 Hz), 8.37 (1H, s), 8.75 (2H, ddd, *J* = 5.6, 2.0, 0.4 Hz). ESI-MS (*m/z*, negative ion mode): 319 $[M–H]^-$

Mycobacterium Tuberculosis H37rv (Mtb H37rv) Inhibitory Activity (In-Vitro antitubercular Activity).
The Mycobacterium *tuberculosis* H37Rv (*Mtb* H37Rv) inhibitory activity for the synthesized benzothiazole-linked Pyramidines (**APY1-APY14**) are assessed by using micro plate Alamar Blue assay (MABA) described by Maria et al [23]. This methodology is non-toxic, uses a thermally stable reagent and shows good correlation with proportional and BACTEC radiometric method. Briefly, 200 µL of sterile deionzed water was added to all outer perimeter wells of sterile 96 wells plate to minimized evaporation of medium in the test wells during incubation. The 96 wells plate received 100 µL of the Middle brook 7H9 broth and serial dilution of compounds was made directly on plate. The final drug concentrations tested were 100 to 0.2 µg/mL. Plates were covered and sealed with parafilm and incubated at 37 °C for five days. After this time, 25 µL of freshly prepared 1:1 mixture of Alamar Blue reagent and 10% tween 80 was added to the plate and incubated for 24 h. A blue color in the well was interpreted as no bacterial growth, and pink color was scored as growth. The IC_{50}value, which prevented the color change from blue to pink. The results of *Mtb* H37Rv inhibitory activity studies are given in **Table 1**.

RESULTS

Benzothiazole-Linked Pyramidine

Table 1. Mycobacterium *tuberculosis* H37Rv inhibitory activity data of benzothiazole-linked Pyramidine APY1-APY14



S.No	Compound Code	R	MIC values (µg/mL) of M. tuberculosis $H_{37}Rv$
1	APY1	C6H5	100
2	APY2	4-MeC6H4	50
3	APY3	4-OHC6H4	100
4	APY4	4-OMeC6H4	25
5	APY5	4-NMe2C6H4	50
6	APY6	4-NO2C6H4	6.25
7	APY7	4-ClC6H4	50
8	APY8	Furan-2-yl	12.5
9	APY9	Furan-3-yl	100
10	APY10	Thiophen-2-yl	50
11	APY11	Thiophen-3-yl	100
12	APY12	Pyridin-2-yl	12.5
13	APY13	Pyridin-3-yl	100
14	APY14	Pyridin-4-yl	100
15	Pyrazinamide	--	3.125

DISCUSSION ON THE RESULTS

In vitro Mycobacterium tuberculosis H37Rv inhibitory activity screening data revealed that the compound APY6 demonstrated comparatively the potent inhibitory activity, with MIC value of 6.25 µg/mL. Compounds APY12 and APY8 also showed appreciable inhibitory activity with MIC values of 12.5µg/mL respectively. Compounds such as APY2, APY4, APY5, APY7 and APY10 showed moderate level of activity at concentrations MIC ranging from 25 to 50µg/mL. Compounds APY1, APY3, APY9, APY11, APY13 and APY14 exhibited comparatively less activity with MIC value 100 µg/mL in comparison with the standard drug (Pyrazinamide, MIC : 3.125 µg/mL). Structure-Activity Relationship (SAR) of these compounds clearly exhibited the intrinsic phenomenon of *Mycobacterium tuberculosis* H37Rv inhibitory activity associated with the basic nucleus consisting of benzothiazole and pyrimidine moieties as seen in case of the compounds APY1- APY14. In some cases, the activity was enhanced by the influence of some substituent's and decreased by some other substituent's, APY6 (4-$NO_2C_6H_4$)>APY12 (Pyridin-2-yl)>APY8 (Furan-2-yl)>APY4 (4-$OMeC_6H_4$)>APY5 (4-$NMe_2C_6H_4$)>APY10 (Thiophen-2-yl)>APY2 (4-MeC_6H_4)>APY7 (4-ClC_6H_4)>APY14 (Pyridin-4-yl)>APY1 (C_6H_5)>APY9 (Furan-3-yl)>APY11 (Thiophen-3-yl)>APY13 (Pyridin-3-yl)>APY3 (4-OHC_6H_4).

CONCLUSION

Benzthiazole and Benzthiazole linked pyramidines play a crucial role within the treatment of the many disorders like tuberculosis at the present the envy to synthesize anti-tubercular moiety by synthesis of Benzthiazole linked pyramidines has paved thanks to many of the researcher to synthesize the molecules of this type . The main activity of the Benzthiazole linked pyramidine could also be attributed to inhibition of cell membrane synthesis and a few of the bioactive groups present within the molecule like hydroxyl may increase the penetration through a number of the specialized channels (polar porin channels) present in gram negative bacteria. So both electron withdrawing and electron donating groups are equally important in these synthesized schiff bases. Compounds with electron withdrawing groups on aryl aldehyde showed challenging activity as antifungal agents. Anti-tubercular activity of the compound could also be attributed to inhibition of cell membrane component which is mostly assumed to inhibit Mycolic acid synthesis which is an important part in the cell wall synthesis.

FUTURE PROSPECTIVE

Benzthiazole is that the order of interest to several of the researcher within the recent days. Still many of the pharmacological investigations to be administered on the various hybrid molecules which are to synthesized within the near future. Benzthiazole may be a high multifaceted molecule which provides platform for the cure of the many of the disorders present during this world. The researchers within the future has got to consider the modification of the free versatile amino to synthesize schiff bases or sulphonyl urease to urge different pharmacological interest molecules and their derivatives.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

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