Synthesis and Characterization of Novel Thiazole Substituted Pyridine and Piperidine Imidazole

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ABSTRACT:

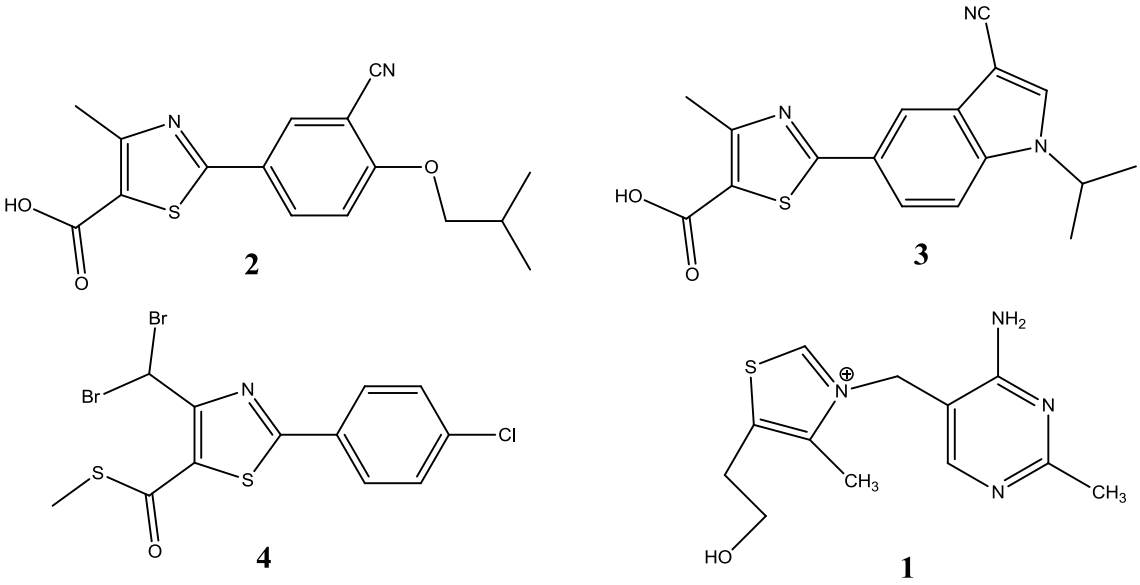
Thiazole substituted heterocyclic compounds find immense important due to wide range of biological activity covering various therapeutic targets.The synthesis of novel thiazole substituted pyridine and pipyridine imidazole was achive from staring with 2-iodo thiazole, this iodo displace by substituted piperidene and coupled with boronate ester of pyridine to got desire thiazole substituted piperidine and pyridine imidazole respectively. Structures of targeted compounds and their intermediates were confirmed by IR, NMR, Mass Spectroscopic.

Keyword : Thiazole, Pyridine, Piperidine, Imidazole.

INTRODUCTION:

Thiazole substituted heterocyclic compounds found to be important place in synthetic organic chemistry due to versatile industrial applications in pharmaceutical, Agricultural, Dyes industry. Thiazole is one of the very important and promising pharmacophore in medicinal chemistry research as there are number of medicine and biologically active compound's targeting various therapeutic targets.

Thiazole is found naturally in vitamin B1 (Thiamin), Thiamin **[1]** is water soluble vitamin that helps the body to release energy from Carbohydrates during metabolism. And it's enzyme play vital role in decaboxylation of alfa keto acid and as an electron sink respectively. It also helps in the normal functioning of the Nervous system by its role in the synthesis of the acetylcholine a neurotransmitter.



The medicine Febaxostat [**2]** acid of thiazole substituted phenyl nitrile, the xanthine oxidase inhibitoin in non competitive fashion it use as efficient treatment for hyperuricemia in gout. Also xanthase oxidase inhibitor **[3]**[1] use in acute inflammatory arthritis, containing benzo-pyrrol substituted acid of thaizole. And 4-Clphenyl substituted thiazole **[4]**[2] as inhibitor of flavivirus envelope protin act as antiviral agent.

In resent research updates find out that thiazole containing heterocyclic compounds are potent Bacterial DNA Gyrase inhibitors[3,4]. Along with that there are number of biologically active Thiazole containing heterocyclic compounds show extensive application in medicinal chemistry research as antimicrobial, anti-inflamatory, antiviral, anti-HIV, anticancer, antitumour, antidiabetic, anti-convulscant,anti-depressant[5-14] etc.

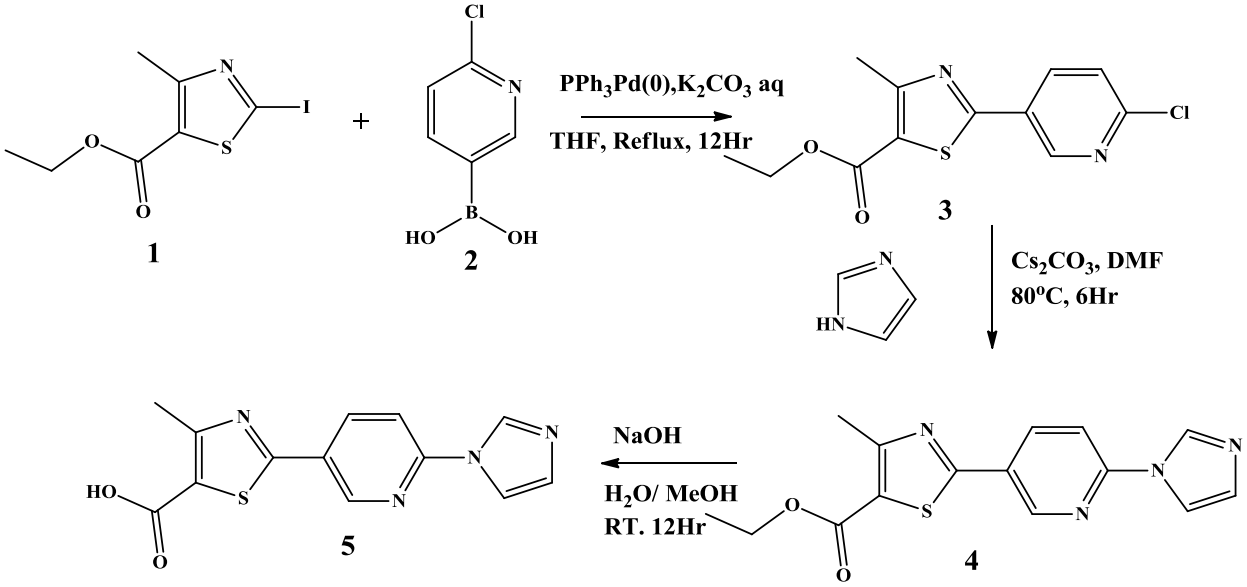
. Recently researcher observed that thiazole derivatives showed potential antimicrobial activity by SAR studies of different compounds. Also antibiotic cephalosporin contain thiazole ring.

Thiazole substituted imidazole, pyrazole, perimidine, pyridine, chacones and azo compounds show good antimicrobial activity and promising activity in bacterial DNA gyrase inhibitor. Literature search reveals that thiazole substituted heterocyclics compounds are important pharmacophoric scaffold due to their wide range of biological and industrial application. There derivatives showed as antimicrobial[5], anti-inflamatory[6], antiviral[7], anti-HIV[8], anticancer[9], antitumour[10], antidiabetic[11], anti-convulscant[12], auroprotective and antioxidant[13], diuratic activity[14] etc.

RESULTS AND DISCUSSION:

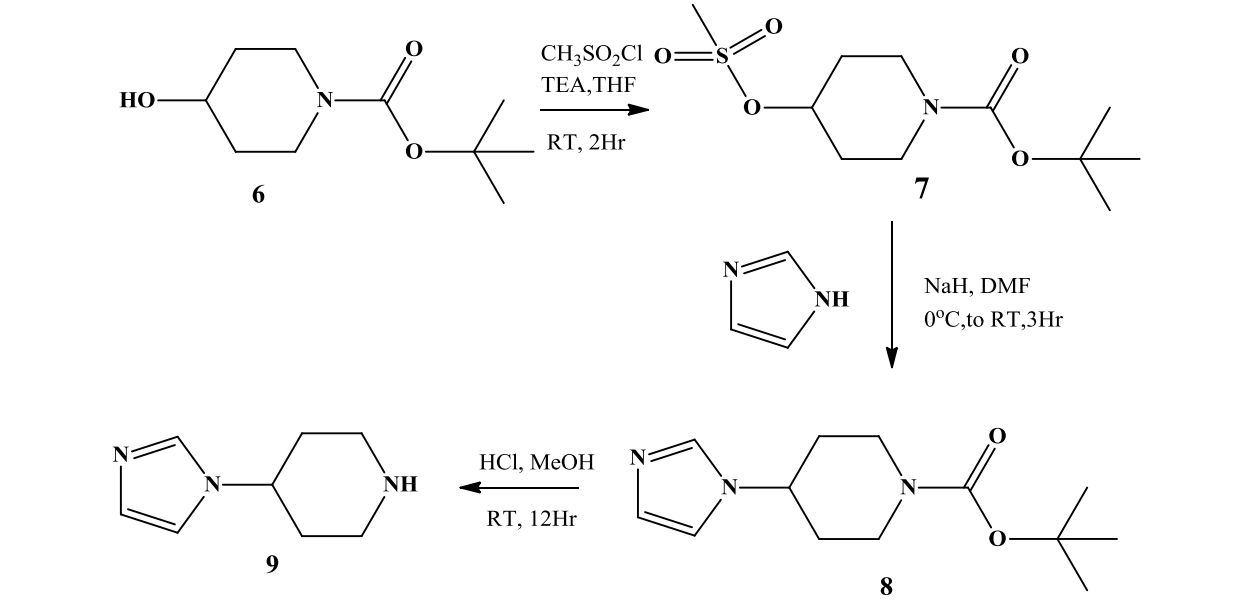
Chemistry:

Thiazole substituted pyridine and pieyridine imidazole synthesis described in (scheme 1-3) Acid of thiazole substituted imdazole pyridine **5** was achive to hydrolysis of ethyl ester in aq NaOH and methanol at rt. ester of thiazole substituted pyridine imidazole **4** it was synthesized from thiazole substituted ortho chloro pyridine where chloro substituted by imidazole in basic condition Cs_2CO_3 and DMF at 80^OC. Thiazole Chloro pyridine **3** is Suzuki coupled product of 2-iodo thiazole ester **1** and 2-Cl pyridine boronic acid **2.** The iodo thiazole obtained from amino thiazole in Sandmayer condition using $NaNO_2$ and KI in MeCN at rt. the consequent amine was synthesized from 2-Chloro ethylacetoacetate refluxing with thiourea in ethanol. .

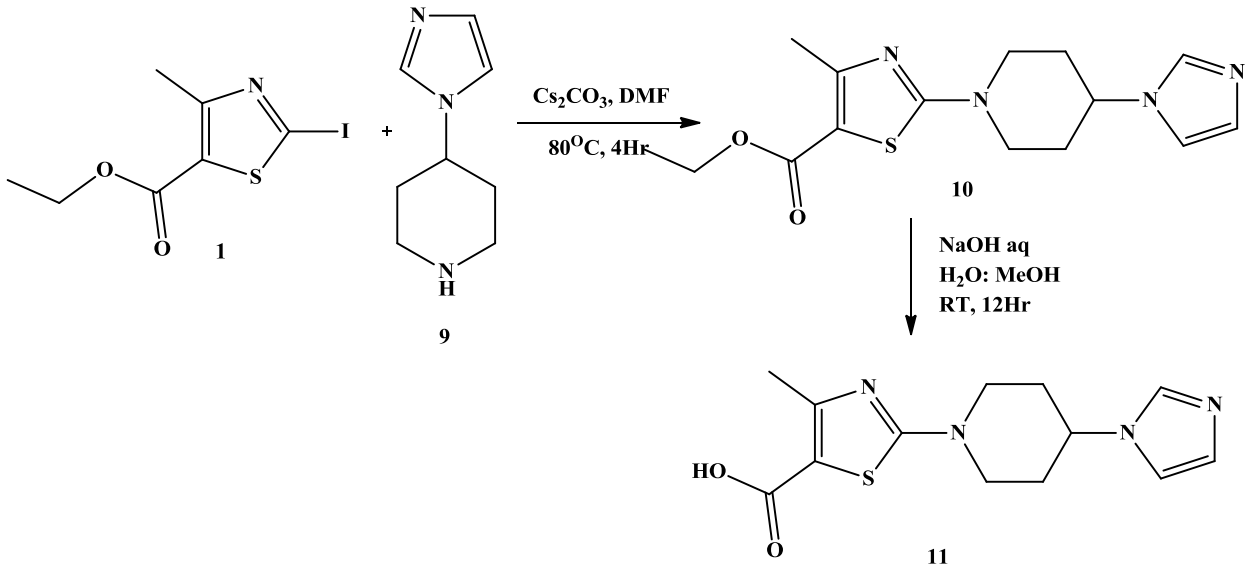


Scheme 1

Iodo of 2-iodo thaizole ethyl ester **1** describe above is displace by 4- imidazole piperidine in basic condition Cs_2CO_3 and DMF at 80^OC, to get thiazole ester of piperidine imidazole **10**. the synthesis of pipyridine-4-imidazole **9** fragment achieved from starting with 4-Hydroxy-N-Boc piperidine **6**, where hydroxy converted to good living group mesylate was replace by imidazole using NaH, DMF. the 4-imidazole piperidene **9** getting after boc deprotection in acidic condtion . finaly ester **10** hydrolyzed in basic condition using aq NaOH and methanol obtained acid of thiazole piperidine imidazole **11.**



Scheme 2



Scheme 3

EXPERIMENTAL SECTION:

All the chemicals and solvents used were dried and purified by standard literature procedures, and moisture was excluded from the glass apparatus using $CaCl_2$ drying tubes. The melting points were determined in open capillary tubes with Gallenkamp melting point apparatus and are uncorrected. FT-IR spectra were recorded on Bruker FTIR-TENSOR II spectrophotometer using Platinum ATR discs. ^{1}H NMR spectra of synthesized compounds were recorded on Varian Mercury 300 NMR spectrophotometer at 300 MHz frequency, and Bruker

400 NMR spectrophotometer at 500 MHz frequency in $CDCl_3$ or dimethyl sulfoxide (DMSO-d_6) using tetramethylsilane (TMS) as internal standard Chemical shifts were reported in δ ppm and multiplicities are given as s (singlet), bs (broad singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel 60 F_{254} (Merck) plates using UV light (254 and 366 nm) for detection. Common reagent grade chemicals were commercially available and used without further purification or prepared by standard literature procedures. All the compounds were prepared by conventional methods.

Synthesis of ethyl 2-amino-4-methylthiazole-5-carboxylate

2-Chloro ethylacetoacetate 1 (20gm, 0.125mol, 1eq) and thiourea (11.09gm,0.145mol, 1.2eq) was refluxed in EtOH (100ml) for 24hr (TLC check). The ethanol was vacuum out under reduced pressure and the residue was stirred in ice cold water. The fall out white solid was filtered off, washed with water, dried and recrystallized from ethanol offered white solid of ethyl 2-amino-4-methylthiazole-5-carboxylate.

Yield 18g, 84%, m.p.175 ^oC, IR (KBr): $\bar{\upsilon}$ = 3373.24 cm^{-1} (NH), 1673.46cm^{-1} (C=O, Ester), ^1H NMR (DMSO-d_6), δ 7.70 (bs, 2H, NH_2), 4.17- 4.10(q, J= 7.1Hz, 2H, CH_2), 2.37(s,3H, CH_3), 1.24-1.19(t, J= 7.1Hz, 3H, CH_3,). MS: m/z 185.43 $(M-H)^-$ Anal, Clacd Molecular Formula: $C_7H_{10}N_2O_2S$, Exact Mass: 186.05, Molecular Weight: 186.23,m/z: 186.05 (100.0%), 187.05 (8.6%), 188.04 (4.5%),elemental Analysis: C, 45.15; H, 5.41; N, 15.04; O, 17.18; S, 17.22.

Synthesis of ethyl 2-iodo-4-methylthiazole-5-carboxylate (1)

In the solution of ethyl 2-amino-4-methylthiazole-5-carboxylate, (10gm, 0.05mol, 1eq) in acetonitrile (100ml), p-toluenesulphonic acid monohydrate (20.4gm, 0.107mol, 2eq) was added and the reaction mixture was stirred at room temperature for 4 hours. After cooling this resultant reaction mixture to 0^oC aqueous solution of $NaNO_2$ (5.5gm, 0.080mol, 1.5eq) and KI (13.36gm, 0.080mol, 1.5eq) in 25 ml water was added by maintaining temperature below 0^oC. After complete addition, the reaction mixture was stirred for 24 hrs at room temperature. Then it was quench by adding aqueous sodium meta bisulphate and was extracted with ethyl acetate (5x100ml). The organic layer was dried over anhydrous Na_2SO_4, concentrate under vacuum to get pale yellow solid ethyl 2-iodo-4-methylthiazole-5-carboxylate, **3**. Yield 11.5gm, 72%, m.p. 175 ^oC. IR (KBr): $\bar{\upsilon}$ = 1711cm^{-1} (C=O), 1524 cm^{-1} (Ar C=C). ^1H NMR (DMSO-d_6), δ 4.29-4.22(q, J= 7.1Hz, 2H,CH_2) 2.62(s,3H,CH_3), 1.29-1.24(t, J= 7.1Hz, 3H,CH_3). MS: m/z 297$(M)^+$ Anal, Clacd, Molecular Formula:$C_7H_8INO_2S$ Exact Mass: 296.93, Molecular Weight: 297.11,m/z: 296.93 (100.0%), 297.94 (7.7%), 298.93 (4.6%), 297.93 (1.2%),Elemental Analysis: C, 28.30; H, 2.71; I, 42.71; N, 4.71; O, 10.77; S, 10.79.

Synthesis of ethyl 2-(6-chloropyridin-3-yl)-4-methylthiazole-5-carboxylate (3)

Ethyl-2-iodo-4-methylthiazole-5-carboxylate **1**, (9.3gm,0.03mol,1eq) and (2-chloropyridin)-5-boronic acid **2**, (5.87gm,0.037mol,1.1eq) in dry THF, under nitrogen atmosphere was added Tetrakisstriphenylphosphin Pd(0) (903mg, 25 mol%), stir it at room temperature for 30 minutes, then add aqueous Na_2CO_3 (10% aq., 6.63gm,0.06mol,2eq), and heated to reflux for 12Hr .THF was removed at reduced pressure, add water and extracted by ethyl acetate, dry ethyl acetate layer over anhydrous Na_2SO_4, concentrate the organic layer to obtain crud product which was purified by silica gel column chromatography eluting with 2% EtOAc and pet ether. Get white solid (6.2gm), yield 70%, m.p. 113 ^oC. ^1H NMR (DMSO-d_6), δ 9.034(s,1H,Pyr-H), 8.441-8.420(d, J=8.4Hz, 1H,Ar-H), 7.715-7.694(d,J=8.4Hz,1H,Ar-H), 4.318(q,2H,CH_2), 2.722 (s,3H,CH_3), 1.320(t,3H,CH_3). MS: m/z 282.99 $(M)^+$ Anal, Clacd, Molecular Formula: $C_{12}H_{11}ClN_2O_2S$, Exact Mass: 282.02,Molecular Weight: 282.75, m/z: 282.02 (100.0%), 284.02 (36.6%), 283.03 (13.2%), 285.02 (5.3%), 286.02 (1.7%), 283.02 (1.5%), 284.03 (1.3%). Elemental Analysis: C, 50.97; H, 3.92; Cl, 12.54; N, 9.91; O, 11.32; S, 11.34.

Synthesis of ethyl 2-(6-(1H-imidazol-1-yl)pyridin-3-yl)-4-methylthiazole-5-carboxylate(4):

ethyl 2-(6-chloropyridin-3-yl)-4-methylthiazole-5-carboxylate **3** **(**1gm,0.0035mol,1eq) and imidazole(265mg, 0.0038mol, 1.1eq), taken in dry DMF. and add dry powderd Cs_2CO_3(1.70gm,0.00525mol,1.5eq), and heat reaction mixture at 100^{o}C, for 6Hr. quench the reaction to adding in ice cold water. Obtain solid was filtered and drying by vacuum to gating required product whie solid(810mg), yield 72%, m.p. 165^{o}C, IR (KBr): $\bar{\upsilon}$ = 1694.19cm^{-1} (C=O), 15282.37,1594.09 cm^{-1} (Ar C=C). ^1H NMR (DMSO-d_6), δ 9.103(s,1H,Imidazole-H), 8.650(s,1H,Imidazole-H),8.560-8.539(d, J=8.4Hz, 1H, Pyr-H),8.058(s,1H,Imidazole-H), 8.016-7.995(d, J=8.4Hz, 1H, Pyr-H), 7.186(s,1H,Imidazole-H), 4.345(q,2H,CH_2), 2.738 (s,3H,CH_3), 1.333(t,3H,CH_3). MS: m/z 315.42$(M+1)^+$ Anal, Clacd, Molecular Formula: $C_{15}H_{14}N_4O_2S$, Exact Mass: 314.08. Molecular Weight: 314.36, m/z: 314.08 (100.0%), 315.09 (16.5%), 316.08 (4.8%), 315.08 (2.3%), 316.09 (1.8%), Elemental Analysis: C, 57.31; H, 4.49; N, 17.82; O, 10.18; S, 10.20.

Synthesis of 2-(6-(1H-imidazol-1-yl)pyridin-3-yl)-4-methylthiazole-5-carboxylic acid(5):

ethyl 2-(6-(1H-imidazol-1-yl)pyridin-3-yl)-4-methylthiazole-5-carboxylate **4** **(**0.500gm,0.0015mol,1eq) take in MeOH(5ml), add aq saturated NaOH **(**0.254gm,0.0063mol,4eq) 5ml solution and stir the reaction mixture at room temperature for 12Hr. add 10 ml water wash by DCM, take aq layer and acidifying using aq $KHSO_4$ to obtain solid precipitate filter and dry to get white solid of acid(350mg). yield 87%, m.p. 240^{o}C, IR (KBr): $\bar{\upsilon}$ = 3421.94cm^{-1} (COOH), 1678.09cm^{-1} (C=O), 1594.79cm^{-1} (Ar C=C). ^1H NMR (DMSO-d_6), δ 13.592(bs.1H,-COOH), 9.073(s,1H,Imidazole-H), 8.643(s,1H,Imidazole-H),8.545-8.523(d, J=8.8Hz, 1H, Pyr-H),8.054(s,1H,Imidazole-H), 8.002-7.980(d, J=8.8Hz, 1H, Pyr-H),

7.180(s,1H,Imidazole-H), 2.750 (s,3H,CH_3). MS: m/z 287.39$(M+1)^+$ Anal, Clacd, Molecular Formula: $C_{13}H_{10}N_4O_2S$,Exact Mass: 286.05, Molecular Weight: 286.31, m/z: 286.05 (100.0%), 287.06 (14.3%), 288.05 (4.7%), 287.05 (2.3%), 288.06 (1.5%), Elemental Analysis: C, 54.54; H, 3.52; N, 19.57; O, 11.18; S, 11.20.

Synthesis of tert-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate (7) :

tert-butyl 4-hydroxypiperidine-1-carboxylate 6(5gm,0.0248mol,1eq) take in dry THF add Triethylamine (6.91ml,0.0496mol,2eq), cool reaction at 0^oC and add Methane sulphonyl chloride dropwise. Further stir reaction at rt for 2Hr. diluted the reaction mixture by adding water, extrcted in ethyl acetate separate out ethyl acetate layer washed by aq $NaHCO_3$, organic layer dry over sodium sulphate concentrate to get oily product(5.8gm), yield 84%. ^{1}H NMR (DMSO-d_6), δ 4.838(m,1H,CH), 3.621-3.576(m,2H,CH_2), 3.201(s,3H,CH_3), 3.077-3.059 (m,2H,CH_2), 1.890(m,2H,CH_2), 1.622-1.582(m,2H,CH_2), 1.393(s,9H,Boc). MS: m/z 279$(M)^+$ Anal, Clacd, Molecular Formula: $C_{11}H_{21}NO_5S$,Exact Mass: 279.11,Molecular Weight: 279.35, m/z: 279.11 (100.0%), 280.12 (12.3%), 281.11 (4.6%), 281.12 (1.8%), 280.11 (1.2%),. Elemental Analysis: C, 47.29; H, 7.58; N, 5.01; O, 28.64; S, 11.48.

Syntesis of tert-butyl 4-(1H-imidazol-1-yl)piperidine-1-carboxylate (8) :

tert-butyl 4-((methylsulfonyl)oxy)piperidine-1-carboxylate **7** (5.8gm, 0.020mol,1eq), take in dry DMF add Imidazole(1.55gm,0.022mol,1.1eq), and NaH 60% in mineral oil (1.19gm, 0.0310mol,1.5eq). and stir at ambient temperature for 3Hr. then quench the reaction mixture to adding in ice cold water. Extracted by DCM, dry and concentrate dcm to get thick oil (4.5gm), yield 74%. ^{1}H NMR (DMSO-d_6), δ 7.717(s,1H, imidazole-H), 7.280(s,1H, imidazole-H), 6.880(s,1H, imidazole-H), 4.253(m,1H,CH), 4.080-4.051(m,2H,CH_2), 2.840 (m,2H,CH_2), 1.890(m,2H,CH_2), 1.958-1.923(m,2H,CH_2), 1.782-1.709(m,2H,CH_2), 1.390(s,9H,Boc). MS: m/z 252.24$(M+1)^+$ Anal, Clacd, Molecular Formula: $C_{13}H_{21}N_3O_2$, Exact Mass: 251.16, Molecular Weight: 251.32, m/z: 251.16 (100.0%), 252.17 (14.4%), 253.17 (1.4%), 252.16 (1.1%). Elemental Analysis: C, 62.13; H, 8.42; N, 16.72; O, 12.73.

Synthesis of 4-(1H-imidazol-1-yl)piperidin-1-ium chloride (9) :

tert-butyl 4-(1H-imidazol-1-yl)piperidine-1-carboxylate **8** (2gm) take in Methanolic HCl (10ml), at 0^oC further stir at ambident temperature for 12Hr, vacuum out solvent completely, and wash by n-pentane to obtain HCl salt of piperidine 1.3gm.(white solid), yield 86%. ^{1}H NMR (DMSO-d_6), δ 9.51(bs,2H,NH_2), 9.30(s,1H, imidazole-H), 7.86(s,1H, imidazole-H), 7.77(s,1H, imidazole-H), 4.67(m,1H,CH), 3.46-3.42(m,2H,CH_2), 3.09-3.02(m,2H,CH_2), 2.33-2.30(m,2H,CH_2), 2.14-2.04(m,2H,CH_2), MS: m/z 152$(M)^+$ Anal, Clacd, Molecular Formula: $C_8H_{14}ClN_3$,Exact Mass: 187.09(free base), Molecular Weight: 187.67. m/z: 187.09 (100.0%),

189.08 (32.0%), 188.09 (8.8%), 190.09 (2.8%), 188.08 (1.1%). Elemental Analysis: C, 51.20; H, 7.52; Cl, 18.89; N, 22.39.

Synthesis of ethyl 2-(4-(1H-imidazol-1-yl)piperidin-1-yl)-4-methylthiazole-5-carboxylate

(10): take ethyl 2-iodo-4-methylthiazole-5-carboxylate 1 (0.5gm,0.00168mol,1eq) and 4-(1H-imidazol-1-yl)piperidin-1-ium chloride **9** (0.346gm,0.00185mol,1.1eq) in Dry DMF add Cs_2CO_3 (0.821gm,0.00252mol,1.5eq) and heat the reaction at 80^oC for 4Hr. cool reaction mixture at rt then add it on ice cold water, solid precipitate is filtered and dry by vacuum to get required product **10**, 360mg, yield 67%, faint yellow solid**, m.p.** 109^oC. IR (KBr): $\bar{\upsilon}$ = 1688.75cm^{-1} (C=O), 1513.16cm^{-1} (Ar C=C). ^{1}H NMR (DMSO-d_6), δ 7.74(s,1H, imidazole-H), 7.30(s,1H, imidazole-H), 6.89(s,1H, imidazole-H), 4.40(m,1H,CH), 4.22(q, J= 7.1Hz, 2H,CH2) 3.27-3.24(m,2H,CH_2), 2.45(s,3H,CH_3), 2.06-2.04(m,2H,CH_2), 1.95-1.91(m,2H,CH_2), 1.26-1.24(t, J= 7.1Hz, 3H,CH_3). MS: m/z 321.04$(M+1)^+$ Anal. Clacd, Molecular Formula: $C_{15}H_{20}N_4O_2S$,Exact Mass: 320.13, Molecular Weight: 320.41, m/z: 320.13 (100.0%), 321.13 (18.6%), 322.13 (5.3%), 322.14 (1.3%),Elemental Analysis: C, 56.23; H, 6.29; N, 17.49; O, 9.99; S, 10.01.

Synthesis of 2-(4-(1H-imidazol-1-yl)piperidin-1-yl)-4-methylthiazole-5-carboxylic acid (11):

ethyl 2-(4-(1H-imidazol-1-yl)piperidin-1-yl)-4-methylthiazole-5-carboxylate **10** (350mg,0.001mol, 1eq) hydrolyzed in aq NaOH(174mg,0.004mol, 4eq) 2ml, and MeOH 5ml, stir at ambient temperature for 12Hr. add 10 ml water wash by DCM, take aq layer and acidifying using aq $KHSO_4$ to obtain solid precipitate filter and dry to get white solid of acid (175mg) yield 56%, m.p. 185^oC, IR (KBr): $\bar{\upsilon}$ = 3429.14cm^{-1} (COOH), 1643.07cm^{-1} (C=O), 1561.47cm^{-1} (Ar C=C). ^{1}H NMR (DMSO-d_6), δ 14.9(bs.1H,-COOH), 9.26(s,1H,Imidazole-H), 7.94(s,1H,Imidazole-H), 7.69(s,1H,Imidazole-H), 2.750 (s,3H,CH_3). 4.75-4.73(m,1H,CH), 4.05(m,2H,CH_2), 3.55-3.49(m,2H,CH_2), 2.27-2.25(m,2H,CH_2), 2.19(s,3H,CH_3) 2.12-2.06(m,2H,CH_2), MS: m/z 292$(M)^+$ Anal, Clacd, Molecular Formula: $C_{13}H_{16}N_4O_2S$, Exact Mass: 292.10, Molecular Weight: 292.36, m/z: 292.10 (100.0%), 293.10 (16.4%), 294.10 (5.3%), Elemental Analysis: C, 53.41; H, 5.52; N, 19.16; O, 10.95; S, 10.97.

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