Original Research Paper Chemistry

A Facile Protocol to the Hetero- Annulation of Face 'A' of Pyridine Condensed Benzazepinone with Thiazolidine Nucleus

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ABSTRACT

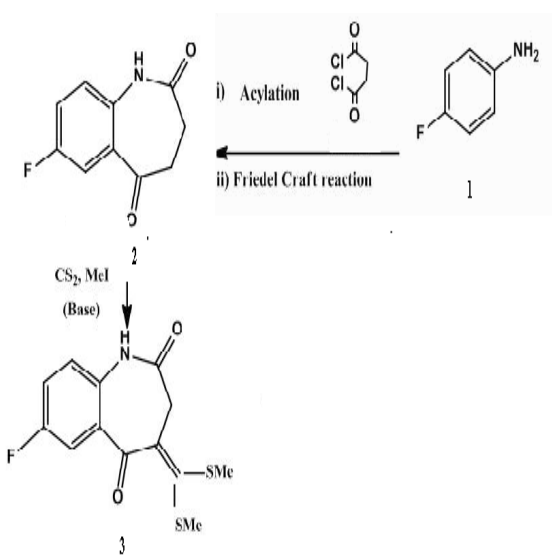
A Facile protocol to the hetero- annulation of face 'a' of pyridine condensed benzazepinone with thiazolidine nucleus through its 2-iminothiol function (6) has been described. The synthesis of thiazolidino annulated analogues 7-10 was achieved by exploiting the propensity of azomethine group containing a 2-thiomethylether function, in its nucleophilic displacement reactions with ethylchloroacetate, chloroacetone, 2-chlorocyclohexanone and N-phenyl-2-bromo-4-piperidone respectively [scheme-1,2]

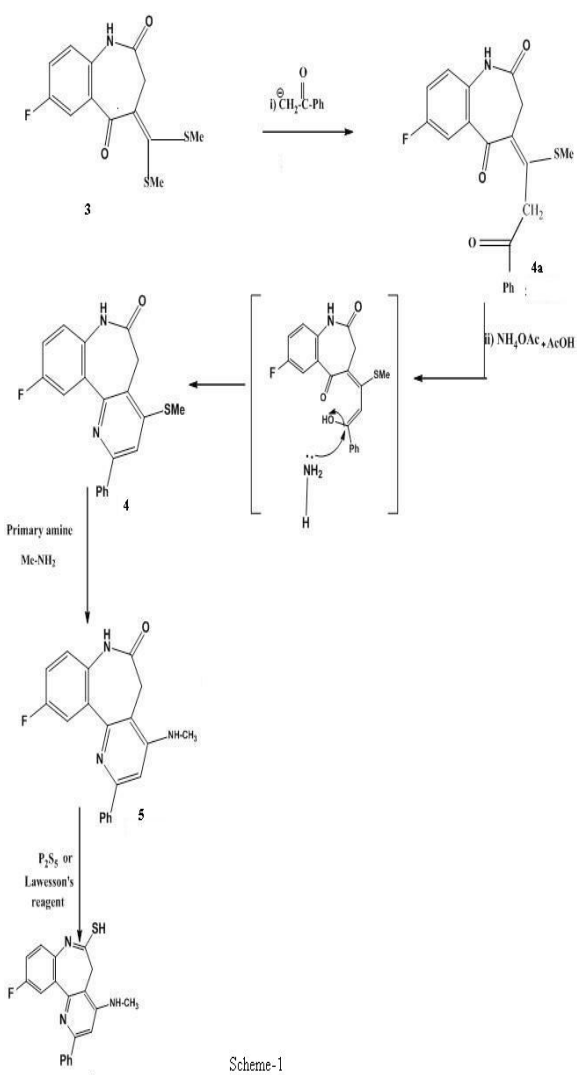
KEYWORDS :10-fluoro-4-(methylamino)-2-phenyl-5H-benzo[b]pyrido[2,3-d]azepin-6-thiol

Introduction

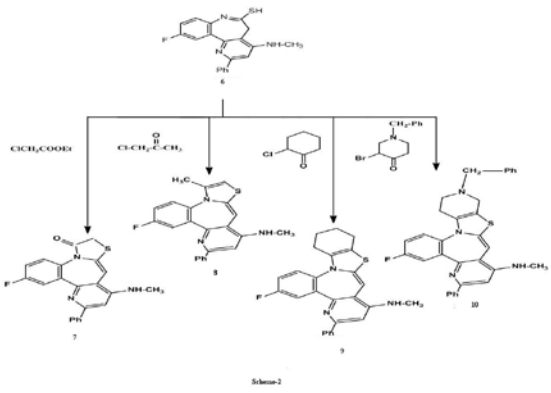
The thiazolidine template has emerged as one of the privileged structural fragments in medicinal chemistry due to their broad pharmacological [1-8] spectrum and its affinity to various biotargets. On account of its such features, the combination of thiazolidine nucleus to other heterocycles has been a well known approach to the 'drug like molecule build up' in medicinal chemistry. This aroused our interest in the heteroannulation of face 'a' of pyridine incorporated benzazepinone ring with thiazolidine nucleus. Development of chemotherapeutically useful materials from the privileged heterocyclic scaffolds is an emerging subject in medicinal chemistry.

Eversince, the benzazepinone nucleus has been recognized as a privileged template capable of providing ligands to a number of functionally and structurally discrete biological receptors, an intense global effort has been underway to discover medicinally potent materials from this class of compounds. Encouraged by the bioactive profiles of benzazepinones,we considered it worthwhile to explore the feasibility of the preparation of its novel analogues which were annulated with thiazolidine ring on face 'a' of its molecule.





Scheme-1



Scheme-2

Related work

Melting points were determined in open glass capillaries and are uncorrected. The purity of the compounds was checked by TLC on silica gel (G) plates.IR spectra were recorded on CE (Schimatzu) FTIR-9050 S.^{1}H- NMR spectra and ^{13}C NMR spectra were recorded on Sea 400 (Bruker) using $CDCl_3$ as solvent and TMS as an internal reference. Chemical shift are expressed in δ ppm. Mass spectra were recorded on Bosch Tech. X.

Experimental section

Synthesis of 7-fluoro-3,4-dihydro-1H-benzo[b]aze ine-2,5-dione (2)

p-Fluoroaniline **(1)** (3.60ml,0.03 mol) was mixed with succinyl chloride (4.92g, 0.03 mol) in dry pyridine (20.0 ml) and the mixture was refluxed for 15 min. Cold reaction mixture was poured slowly with stirring to 150-200ml ice cold water. The solid which settled was filtered, washed with cold water, recrystallized from methanol and water .PPA (25g) was mixed to 3.21 g (0.01 mol) of it and heated at 150-160°C for 4h (the progress of the reaction was monitored by TLC).The reaction mixture was cooled to 20°C and a concentrated aqueous solution of Na_2CO_3 was added to make it alkaline. The product was extracted with ethyl acetate (3x10 ml).The extract was dried over anhydrous Na_2SO_4 and concentrated in vaccum. The residue was purified by column chromatography on silica gel with $CHCl_3$ as an eluent to give **2** (2.85g, yield :79%); m.p.: 158-160 °C; IR (KBr) cm$^-$: 3240(N-H str.), 2990 (C-H str.), 2900, 1400 (-CH_2 next to C=O), 1712, 1704 (C=O), 1535 (C=Cstr.); ^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 8.0 (1H, s, NH), 7.26-7.78 (3H, m, Ar-H), 3.49 (4H, s, $(CH_2)_2$); ^{13}C-NMR (400MHz, $CDCl_3$) δ ppm: Ar-C [157.55 (CF), 120.24 (CH), 113.54 (CH), 112.44 (CH)], Ar-C [134.44 (C), 115.25 (C), azepinone], 27.6, 34.4 [$(CH_2)_2$ azepinone)], 176.75 (C of amide), 183.49 (C of carbonyl); MS: m/z 193.17(M$^+$); Anal. calcd. / found for $C_{10}H_8FNO_2$: C, 62.18 / 62.35; H, 4.17/4.11; N, 7.25/7.48.

Synthesis of 4-(bis (methylthio) methylene) - 7-fluoro-3, 4-dihydro-1H-benzo [b]azepine-2, 5-dione (3)

A mixture of 7-fluoro-3,4-dihydro-1H-benzo[b]azepine-2,5-dione **(2)** (2.82g, 0.01 mol) and CS_2 (1.6 ml,0.01mol) was added to a well stirred and cold suspension of t-BuOK (2.23g,0.02 mol) in dry benzene (7.0ml) and DMF (3.0ml) and the reaction mixture was allowed to stand for 4h. Methyl iodide (3.3ml, 0.02mol) was gradually added with stirring and external cooling (exothermic reaction) and the reaction mixture was allowed to stand for 4 h. at room temperature with occasional shaking and then refluxed on a water bath for 3 h. The mixture was poured on crushed ice and the benzene layer was separated. The aqueous portion was extracted with benzene and the combined extracts were washed with water, dried over anhydrous sodium sulphate and the solvent was removed by distillation. The product thus obtained was purified by crystallization with ethanol to give **3** (1.7g, yield: 60%); m.p.:155-157°C ; IR (KBr) cm$^-$: 3240 (N-H str.), 3000 (C-H str.), 2900, 1400 (-CH_2 next to C=O), 1640, 1685 (C=O), 1620 (C=C of α, β–unsaturated ketone), 1535 (C=C str.), 680 (C-S str.); ^{1}H- NMR (400 MHz, $CDCl_3$) δ ppm: 8.0(1H, s, NH), 7.45-7.98 (3H, m, Ar-H), 3.53 (2H, s, CH_2), 2.80 (6H, s, $(CH_3)_2$ of $(SMe)_2$); ^{13}C-NMR (400MHz, $CDCl_3$) δ ppm : Ar-C [164.5 (CF), 121.5 (CH), 113.1 (CH), 112.6 (CH)] , Ar-C [136.8 (C), 136.0 (C), 108.7 (C), azepinone] ,28.60 (CH_2 azepinone), 168.7 (C of amide), 187.0 (C of carbonyl),155.3 [-C-$(SMe)_2$] , 18.0 [2C of $(CH_3)_2$]; MS: m/z 297.37 (M$^+$); Anal. calcd. / found for $C_{13}H_{12}FNO_2S_2$: C, 52.51/ 52.32; H, 4.07/4.01; N, 14.71/14.48; S, 21.57/ 21.38.

Preparation of 10-fluoro-4-(methylthio)-2-phenyl-5H-benzo[b]pyrido[2,3-d]azepin-6(7H)-one (4)

To a mixture of **(3)** (3.95g, 0.01mol) in dry THF was added a solution of acetophenone (1.2g,0.01mol) and potassium t-BuOK (2.2g,0.02mol) in dry THF (15 ml).The solution was stirred at room temperature overnight, then glacial acetic acid (15ml) and ammonium acetate (1.6g,0.02mol) were added to the above solution which was then refluxed for 4h with constant removal of THF. The solution was then cooled to 20°C, poured in ice (50 g), neutralized the excess acetic acid with NH_4OH and allowed to stand for 1 h, water was added and the precipitate was collected and recrystallized with petroleum ether to give **4** (3.50g, yield: 89%); m.p.:145-147°C; IR (KBr) cm$^-$: 3180 (N-H str.),3010(C-H str.),2990,1400(-CH_2 next to C=O),1660(C=O),1580 (C=C str.),685(C-S str.); ^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 8.01(1H,s,NH),7.43-8.48 (5H,m,Ar-H),7.24-8.34(3H,m,Ar-H),6.97(1H,s,CH), 3.49(2H,s,CH_2) ,2.53 (3H,s,CH_3); ^{13}C-NMR (400MHz, $CDCl_3$) δ ppm: Ar-C[157.62(CF),123.71(CH), 116.22(CH),114.31(CH)], Ar-C[158.94 (C), 134.72(C), 125.13(C),122.22(C),azepinone],168.23(C of amide) ,41.44 (CH_2 azepinone),152.64 (pyridine C,-CPh),153.15 (pyridine C,-CSMe),109.11(pyridine C),15.12 (C of CH_3),Ar-C[139.24(C), 129.23 (two CH), 127.64(two CH), 127.32 (CH), phenyl];MS,m/z:350.24(M$^+$60.0%), 338.09 (13.2%), 294.58(100%), 232.10 (22.3%);Anal. calcd. / found for $C_{20}H_{15}FN_2OS$:C, 68.55 / 68.38; H, 4.31/4.24; N, 7.99/7.74;S,9.15/9.32.

Preparation of 10-fluoro-4-(methylamino)-2-phenyl-5H-benzo[b]pyrido[2,3-d]azepin-6(7H) -one (5)

To the solution of 10-fluoro-4-(methylthio)-2-phenyl-5H-benzo[b] pyrido[2,3-d]azepin-6(7H)-one **(4)** (3.50g,0.01 mol), the aqueous solution of methyl amine (0.04 mol) was added and the mixture was stirred at room temperature for 15h. The solvent was then evaporated to afford a viscous crude product which was purified by column chromatography (silica gel: EtOAc), (1:1) to give **5** (2.54g, yield:73%); m.p.:152-154°C; IR (KBr) cm$^-$: 3170 (N-H str.),2990(C-Hstr.), 2980,1400(-CH_2 next to C=O),2950(C-H str.in CH_3) ,1660(C=O),1590(C=N imine),1580(C=C str.); ^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 8.01(1H,s,NH),7.43-8.48(5H,m,Ar-H),7.24-8.34(3H,m, Ar-H),6.31(1H,s,CH) ,4.0(1H,m,NH),3.49(2H,s,CH_2),2.63(3H ,d,CH_3); ^{13}C-NMR (400MHz, $CDCl_3$) δ ppm: Ar-C[157.62(CF),123.71CH), 116.22(CH),114.31(CH)],Ar-C[159.74(C),134.72(C), 122.21(C),114.52(C), azepinone], 168.23 (C of amide),39.92 (CH_2 azepinone),157.92(pyridine C,-CPh),153.43 (pyridine C,-CNH-),105.92(pyridine C),34.70 (C of CH_3) ,Ar-C[139.24(C),129.23(two CH),127.64(two CH), 127.32 (CH),phenyl]; MS,m/Z:333.16(M$^+$40.0%),320.12(11.1%)278.33(100%),235.13(15.5%);Anal. calcd. / found for $C_{20}H_{16}FN_3O$: C, 72.06/72.23; H, 4.84/4.89; N, 12.61/12.48.

Preparation of (E)-10-fluoro-4-(methylamino)-2-phenyl-5H-benzo [b]pyrido[2,3-d]azepin-6-thiol (6)

A suspension of 10-fluoro-4-(methylamino)-2-phenyl-5H-benzo[b] pyrido[2,3-d]azepin-6(7H)-one **(5)** (2.52g,0.007 mol) and Lawesson's reagent(1.4g,0.007 mol) in CH_2Cl_2 /toulene (1:1), (30ml) was heated under reflux for 17h.After this, the reaction mixture was concenterated to dryness under reduced pressure and the residue was recrystallized from ethanol to give **6 (**1.78g, yield:71%); m.p.:106-108°C; IR (KBr) cm$^-$: 3180 (N-H str.),3010(C-H str.),2975,1425(-CH_2 next to SH),2960(C-H str.in CH_3), 1612,1415(C=N) ,1570(C=C str.) ,685(C-S); ^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 7.43-8.48(5H,m,Ar-H),7.23-8.34(3H,m,Ar-H),6.31(1H,s,CH),4.0(1H,m,NH),2.63(3H,d,CH_3), 2.62(2H,s, CH_2), 1.5(1H,s,SH); ^{13}C-NMR (400MHz, $CDCl_3$) δ ppm: Ar-C[160.50(CF),124.42(CH),117.32(CH),115.41(CH)],Ar-C[159.72(C),143.22(C),128.41(C),114.52(C) ,azepine],31.94 (CH_2 azepine),164.52 (C,-CSH) ,157.92(pyridine C,-CPh),153.43 (pyridine C,-CNH-),105.92(pyridine C),Ar-C[139.24(C), 129.26 (two CH), 127.64(two CH),127.32 (CH),phenyl] ,34.72(C of CH_3);MS.m/z:349.23(M$^+$35.0%), 337.10(11.9%), 294.31 (100%),221.10(24.5%);Anal. calcd. / found for $C_{20}H_{16}FN_3S$: C, 68.75/68.63; H, 4.62/4.68; N, 12.03/12.26;S,9.18/9.36.

Preparation of 2-fluoro-10-(methylamino)-12-phenylbenzo[f] pyrido[3,2-d] thiazolo[3,2-a]azepin-6(7H)-one (7)

A mixture of (E)-10-fluoro-4-(methylamino)-2-phenyl-5H-benzo[b]

pyrido[2,3-d]azepin-6-thiol **(6)** (0.70g,0.002 mol) and ethyl chloroacetate (0.48g,0.004 mol) in 50 ml ethanol was heated slowly to 90°C when vigorous foaming and solidification took place. Heating was continued for 3h to a maximum 120°C.After the completion of reaction (monitored by TLC) ,the reaction mixture was cooled, diluted with ether and the precipitate obtained was collected by filtration and recrystallized from ethanol to give **7** (0..45g, yield: 64%); m.p.:118-121°C; IR (KBr) cm^- : 3170 (N-H str.),3000(C-Hstr.),1600(C=O) ,1550(C=C),1410(C=N imine),710(C-S-C); ^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 7.43-8.48(5H,m,Ar-H),7.23-8.34(3H,m, Ar-H),6.39(1H,s,CH),5.50(1H,s,CH of azepine), 4.99(2H, s, CH_2 of thiazolidine ring) ,4.0(1H,m,NH),2.63(3H,d,CH_3); ^{13}C-NMR (400MHz, $CDCl_3$) δ ppm: Ar-C[157.44(CF),123.11 (CH),114.55(CH), 114.45(CH)],Ar-C [158.37 (C), 143.13(C), 130.71 (C), 125.36 (C),113.71 (C), 88.42(CH),azepine) ,163.83(thiazolidine C,-C=O) ,35.44(CH_2 thiazolidine),152.39(pyridine C,-CPh),153.65(pyridine C,-CNH-),108.56(pyridine C), Ar-C[141.51(C),129.11(two CH),127.56(two CH), 127.45 (CH),phenyl] ,34.72(C of CH_2); MS ,m/Z: 389.12(M^+26%),335.65(100%),293.25(33.7%),263.30(83.1%);Anal. calcd. / found for $C_{22}H_{16}FN_3OS$: C, 67.50/67.39; H, 4.63/4.69; N, 10.73/10.42;S,8.19/8.36.

Preparation of 2-fluoro-N,6-dimethyl-12-phenylbenzo[f] pyrido[3,2-d]thia zolo[3,2-a]azepin-10-amine (8)

A solution of 1-chloropropan-2-one (0.45g,0.02 mol) in 2-methoxyethanol (50 ml), was added dropwise to a solution of (E)-10-fluoro-4-(methylamino)-2-phenyl-5H-benzo[b]pyrido[2,3-d]azepin-6-thiol **(6)** (1.75g,0.005 mol) in 2-methoxyethanol (100 ml).After heating under reflux for 5h,the solvent was removed and the residue obtained was recrystallized from ethanol to give **8 (**1.38g, yield :79%); m.p.: 248-250°C; IR (KBr) cm^- : 3180 (N-H str.),3010(C-Hstr.) ,1560 (C=Cstr.),1470(C-H str.in CH_3) ,1415(C=Nimine) ,710(C-S-C); ^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 7.43-8.48 (5H,m,Ar-H),7.23-8.34(3H,s, Ar-H),6.82(1H,s,CH of pyridine),5.34(1H,s,CH of azepine), 5.04(1H,m,CH of thiazole), 4.0(1H,m,NH), 2.63 (3H,d,CH_3) ,2.26(3H,s,$CH_3$of thiazole); ^{13}C-NMR (400MHz, $CDCl_3$) δ ppm: Ar-C[157.42(CF),123.12(CH) 114.54 (CH), 114.44 (CH)],Ar-C[158.24(C),143.13, 135.33 (CH),121.22(C), 114.15(C) ,108.57(C), azepine],157.39(pyridine C,-CPh),153.62 (pyridine C,-CNH-),108.63(pyridine C) ,34.70(C of CH_3,-NH-CH_3),Ar-C[141.51(C),129.11(two CH),127.56(two CH), 127.45 (CH),phenyl] ,131.62 (thiazole,-CCH_3) ,104.93 (thiazole,C),18.64 (C of CH_3 ,-CCH_3, thiazole);MS,m/z: 387.32(M^+60.0%), 375.13(21.1%),332.44 (100%), 260.13(14.5%);Anal. calcd. / found for $C_{23}H_{18}FN_3S$:C, 70.93/70.76; H, 5.18/5.11; N, 10.79/10.46;S,8.23/8.45.

Preparation of 3-fluoro-N-methyl-6-pheyl-11,12,13,14-tetrahydrobenzo[f] benzo[4,5] thiazolo[3,2-a]pyri[3,2-d] azepin-8-amine (9)

A solution of 2-chlorocyclohexanone (0.66g,0.01 mol) in 2-methoxyethanol (50 ml) , was added dropwise to a solution of (E)-10-fluoro-4-(methylamino)-2-phenyl-5H-benzo[b]pyrido[2,3-d]azepin-6-thiol **(6)** (1.75g,0.005 mol) in 2-methoxyethanol (100 ml). After heating under reflux for 3h, an additional (2.0g) of 2-chlorocyclohexanone was added and again heating was continued for 5h.After the completion of reaction (monitored by TLC) ,the solvent was removed and the residue obtained was recrystallized from ethyl acetate to give **9 (**1.32g, yield: 75%), m.p.: 267-270°C; IR (KBr) cm^- : 3180 (N-H str.),3010(C-Hstr.) ,1560(C=Cstr.), 1415(C=Nimine), 710(C-S-C); ^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 7.43-8.48(5H,m,Ar-H),7.23-8.34(3H,m, Ar-H),6.44(1H,s,CH),5.28(1H,s,CH of azepine), 4.0(1H,m,NH),2.63(3H,d,CH_3),1.74-1.96(8H, m,CH_2 ofcyclohexene); ^{13}C-NMR (400MHz, $CDCl_3$) δ ppm: Ar-C[157.43(CF),123.11(CH), 114.55(CH),114.45(CH)],Ar-C[158.24(C),143.13,135.33(CH), 121.22(C),114.15(C), 108.57(C), azepine] ,152.37(pyridine C,-CPh),153.63 (pyridine C,-CNH-),108.54(pyridine C),34.70(C of CH_3),Ar-C[141.51(C),129.11(two CH),127.56 (two CH), 127.45 (CH),phenyl] ,Ar-C[150.61(C),128.73(C), 25.31(CH_2), 21.90 (CH_2),21.12(CH_2),22.60(CH_2) ,cyclohexene]; MS,m/z:427.28 (M^+45.0%),407.16 (11.1%),371.37(100 %),329.16(24.5%);Anal. calcd. / found for $C_{26}H_{22}FN_3S$: C, 72.70/72.59; H, 5.63/5.58; N, 9.78/9.55;S,7.46/7.18.

Preparation of 12-benzyl-N-meyl-6-pheyl-11,12,13,14-tetrahydrobenzo[f] pyrido [3,2 -d] pyrido [4',3':4,5] thiazolo [3,2-a] azepin-8-amine (10)

A solution of 3-bromo-1-methylpiperidin-4-one (1.09g,0.002 mol) and (E)-10-fluoro-4-(methylamino)-2-phenyl-5H-benzo[b]pyrido[2,3-d] azepin-6-thiol **(6)** (0.70g,0.002mol) in N,N-dimethylformamide (100 ml) was heated under reflux for 7h.After the completion of reaction (monitored by TLC) ,the reaction mixture was cooled, diluted with water and the precipitate obtained was collected by filtration and recrystallized from methanol to give **10 (** 0.45g, yield :64%), m.p.:278-280°C; IR (KBr) cm^- : 3170 (N-H str.),3010(C-Hstr.) ,1560(C=C-str.) ,1415(C=Nimine) ,710(C-S-C); ^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 7.43-8.48(5H,m,Ar-H),7.23-8.34(3H,m, Ar-H),7.26-7.36(5H,m, Ar-H),6.80(1H,s,CH),5.54(1H,s,CH of azepine) ,4.0(1H,m,NH) ,3.66 (2H,s, CH_2), 3.74(2H,s,CH_2 of piperidine),2.63(3H,d,CH_3),2.85(2H,t,CH_2 of piperidine), 2.82(2H,t,CH_2 of piperidine); ^{13}C-NMR (400MHz, $CDCl_3$) δ ppm: Ar-C[157.43(CF),123.11(CH), 114.55 (CH), 114.45(CH)] ,Ar-C[158.24(C),143.13,135.33 (CH),121.22(C), 114.15(C), 108.57(C), azepine], 152.37(pyridine C,-CPh),153.63 (pyridine C,-CNH-), 108.34 (pyridine C) ,Ar-C[141.51(C),129.11(two CH),127.56(two CH), 127.45 (CH),phenyl],34.70 (C of CH_3),Ar-C[127.84(C),115.11(C), 59.32(CH_2), 46.82 (CH_2),19.42 (CH_2),piperidine], 63.72 (CH_2 ,-CH_2-Ph) ,Ar-C[141.51(C), 129.11(two CH),127.56(two CH), 127.45 (CH),phenyl] ;MS,m/z: 518.49 (M^+35%),506.21(36.9%),462.21(100%),422.22(15.9 %);Anal. calcd. / found for $C_{33}H_{27}FN_4S$: C, 73.82/73.68; H, 5.61/5.56; N, 10.76/1054;S,6.16/6.42.

Experimental Results

In view of the impressive biological activities shown by thiazolidine nucleus, it was thought of interest to construct a system ,which carried benzazepinone fused with thiazolidine nucleus in the same molecular framework. The idea behind building such a system was to incorporate the biological activities of this well established molecule in a single molecular framework. The synthetic plan conceived to achieve this goal required the preparation of **6** which was used as key intermediate in the synthesis of the compounds outlined in **[Schemes 2]** respectively. The synthesis propelled forward with the reaction of anion of acetophenone with **3** to furnish the dione **4a,**whose reaction in the subsequent step with NH_4OAc in AcOH led to the incorporation of pyridine ring on face d of benzazepinone nucleus to give **4.** The literature is replete with examples showing the participation of the lactim thioethers in nucleophilic displacement reactions. This propensity of SMe group attached to an azomethine function was utilized in the reaction of **4** with methyl amine to give **5**. Preparation of **6** took place from **5** on its reaction with P_2S_5 (or Lawesson's reagent)[9] to give **6 [Scheme-1].**

The versatility of azomethine function (bearing an SH group on 2-position) in nucleophilic displacements[10] was elegantly exploited in reaction of compound **6** with ethylchlorocetate,chloroacetone,2-chlorocyclohexanone and N-phenyl-2-bromo-4-piperidone to give face 'a 'thiazolidino annulated analogues **7-10** in good yield [**Scheme**-**2**].

Conclusion

In summary, the unprecedented potential of 2-iminothiol function in synthesis, was exploited to provide an easy access to face 'a' thiazolidine annulated analogues of pyridine condensed benzazepinone **7-10** respectively, from 10-fluoro-4-(methylamino)-2-phenyl-5H-benzo [b]pyrido[2,3-d]azepin -6-thiol **6.**The process is characterized by mild reaction condition and easy work-up procedure.

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