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A Facile Synthesis of Face'd' Azaquinazolino Annulated Analogues of Benzazepinones Through the Corresponding Enol Ether Derivative

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ABSTRACT

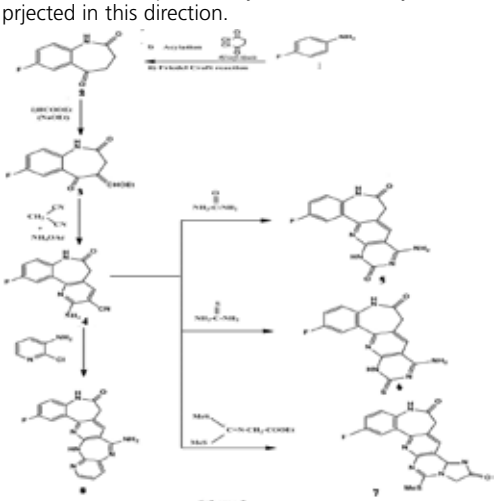
protocol to the synthesis of face 'd' azaquinazolino annulated analogues of benzazepinones 5-8 has been developed by reacting compound 2 with ethyl formate in presence of a base to give the corresponding enol ether derivative 3 which underwent cyclocondensation first with malononitrile, in presence of ammonium acetate to give 4 followed by the reaction of the later with urea, thiourea, ethyl glycinate dithioacetal and 2-chloro-3-amino pyridine to afford the corresponding azaquinazoilno annulated analogues 5-8 in acceptable yields. 2 resulted from the acylation of p-fluoro aniline 1 with succinyl chloride followed by cyclocondensation of the later with PPA.

KEYWORDS Benzazepinone-2,5-dione, enol ether, Friedel-Craft cyclocondensation with PPA

Introduction

Substituted azaquinazolines are useful antiviral agents, in particular against cytomegaloviruses[1-3]. Several 1,6-naphthyridine or 8-azaquinazoline derivatives have been found to be useful in the treatment of aldosteronism, hypertension, cardiac insufficiency, myocardial infarct sequelae, liver cirrhosis, renal insufficiency and stroke[4].Azaquinazoline EFGR (epidermal growth factor receptor) has entered into clinical trials for the treatment of cancer, demonstrating the competitive nature of this area[5].This discovery has stimulated a renewed interest in these molecules from yet another perspective. The biological potential of azaquinazoline nucleus prompted us to focus research on the synthesis and study of biological properties of newer series of heteroring annulated products containing this ring.

In view of the impressive pharmacological properties exhibited by this nucleus it was thought that, it could be worthwhile to incorporate the azaquinazoline ring to the benzazepinone nucleus to verify the assumption that incorporation of the pharmacophores which have previous history of being biologically active, could produce an additive effect on the overall potency in the parent molecule. Herein, in this communication we describe the preliminary results of our synthetic endeavour prjected in this direction.



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.

Preparation of 4 - (ethoxymethylene) -7- fluoro -3 ,4 – dihydro -1H- benzo [b]azepin-2,5-dione (3)

To a solution of 10% sodium ethoxide (1.09g ,0.016 mol) in dry benzene (50ml) at 0°C,a solution of ethyl formate (1.18g,0.016 mol) in dry benzene (25 ml) was added. To this mixture, 7-fluoro-3,4-dihydro-1H-benzo[b]azepin-2,5-dione **(2)** (3.25g, 0.016 mol) in dry benzene (25ml) was added.The mix-

ture was stirred for 4 h at room temperature and allowed to stand overnight.It was then diluted with cold water, acidified with dil.HCl and extracted with ether.The solvent was evaporated and the resultant compound was recrystallized with ethanol to give **3 (**2.85g, yield**:** 88%); m.p. **:** 298-300°C;IR (KBr) cm^{-} : 3240(N-H str.), 3000(C-H str.), 2980,1400 (-CH_2 next to C=O),1680,1700(C=O), 1590(C=C str.), 1250(C-O str. of ether); ^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 8.0 (1H,s, NH), 7.457.98(3H,m,Ar-H),7.12(1H,s,CH),4.49(2H,q,CH_2 of ethyl), 2.90 (2H ,s ,CH_2), 1.21(3H,t,CH_3 of ethyl); ^{13}C-NMR (400MHz, $CDCl_3$) δ ppm: Ar-C [164.56(CF),121.55(CH), 113.14 (CH), 112.16(CH)],168.19 (amidecarbon), 177.67(carbonylcarbon), 36.14 (CH_2 of azepi none), Ar-C [136.84(C), 128.32(C), 121.62(C), azepinone] ,162.64 (=CHOEt), 71.55,15.34 (C of ethyl); MS,m/z: 249.02 (M^+ 80.0%), 208.04 (100.0%), 152.29(9.6%); Anal. calcd. / found for $C_{13}H_{12}FNO_3$: C, 62.65 / 62.40; H, 4.85/4.89; N, 5.62/5.33.

Preparation of 2- amino- 10- fluoro-6-oxo -6,7-dihydro-5H-benzo[b]pyrido [2,3-d]-azepin-3-carbonitrile (4)

A mixture of 4 - (ethoxymethylene) -7- fluoro -3 ,4 – dihydro -1H- benzo [b]azepin-2,5-dione **(3)** (2.81g, 0.01mol),malononitrile (0.66g,0.01mol) and ammonium acetate (0.6g,0.08mol) dissolved in ethanol (25ml) was heated under reflux for 8h.The contents were poured into crushed ice,filtered and recrystallized with ethanol to give **4** (2.12g ,yield: 75%); m.p.:220-222°C; IR (KBr) cm^{-} : 3370(NH_2), 3210(N-H str.), 3010(C-H str.), 2975,1400 (CH_2 next to C=O), 2100(CN), 1680 (C=O), 1596(C=N),1580(C=C str.); ^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 8.24(1H,s,CH of pyridine ring),8.01(1H,s,NH), 7.24-7.88(3H,m,Ar-H),7.15(2H,s,NH_2),3.70(2H,s,CH_2);^{13}CNMR (400MHz, $CDCl_3$) δ ppm: Ar-C[163.78(CF),123.74(CH), 116.66 (CH), 114.55(CH)], 176.78(amide carbon),44.22(CH_2 azepinone),Ar-C[168.24(C) ,134.27(C), 129.23 (C) ,122.24(C), azepinone], 139.76 (CH ,pyridine),163.24(-CNH_2),102.09(-CCN) ,122.39(C of CN);MS,m/z: 268.15 (M^+65.0%), 260.07 (11.5 %),241.03(100.0%),141.12(1.5%); Anal. calcd. / found for $C_{14}H_9FN_4O$: C, 62.68 / 62.89; H, 3.38/3.31; N, 20.89/20.48.

Preparation of 9-amino-2-fluoro-5H-benzo[b]pyrimi o-[5',4': 5,6]-pyrido [2,3-d]azepin-6,11(7H,12H)-dione (5)

A mixture of 2- amino- 10- fluoro-6-oxo -6,7-dihydro-5H-benzo[b]pyrido [2,3-d]azepin-3-carbonitrile **(4)** (2.10g, 0.008mol) and urea (0.48g , 0.008 mol) was heated in an oil bath at 120°C for 4h with constant stirring.The temperature was raised to 180°C and finally the mixture was heated at 220°C for 4h. On cooling, the product solidified, which was recrystallised from DMF-EtOH mixture to give **5 (**1.54g, yield: 73%); m.p.**:** 248-252°C**;** IR (KBr) cm^{-} : 3370(NH_2) ,3210(N-H str.),3000(C-H str.) ,2970,1400(CH_2 next to C=O),1600(C=O),1540(C=C str.),1530(C=N); ^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 8.38 (1H,s,CH of pyridine ring), 8.13(1H,s, NH),7.64-8.64(3H,m, Ar-H) ,7.47(1H,s,NH of pyrimi dine ring), 7.17 (2H,s,NH_2), 3.70(2H,s, CH_2); ^{13}C-NMR (400MHz, $CDCl_3$) δ ppm: Ar-C[163.88(CF), 123.16(CH), 114.53(CH),1114.44(CH)],172.68(C of amide) ,Ar-C[167.50(C), 152.46(C), 130.57 (C), 113.13 (C) , azepinone],39.16(CH_2 azepinone) ,Ar-C[168.01(C),143.17(CH), 100.38 (C) ,pyridine) ;183.48(-CNH_2),170.43(C of carbonyl)**;** MS,m/z:311.27 (M+45%), 261.22% (100.0%),308.36(15%), 176.02(35%),110.75(20%); Anal. calcd. / found for $C_{15}H_{10}FN_5O_2$: C, 57.88 /57.65; H, 3.24/3.20; N, 22.50/22.68.

Preparation of 9-amino-2-fluoro-11-thioxo-11,12-dihydro-5H-benzo[b] pyri mido[5',4':5,6]- pyrido-[2,3-d]azepin-6,11(7H)-one (6)

A mixture of 2- amino- 10- fluoro-6-oxo -6,7-dihydro-5H-benzo[b]pyrido [2,3-d]azepin-3-carbonitrile **(5)** (2.10g, 0.008 mol) and thiourea (0.60g,0.008 mol) was heated in an oil bath at 120°C for 4h with constant stirring.The temperature was raised to 180°C and finally the mixture was heated at 220°C for 4h. On cooling the product solidified, which was recrystallised from DMF-EtOH mixture to give **6 (**1.64g , yield:78%); m.p.: 246-248°C; IR (KBr) cm^{-} : 3350(NH_2),3230(N-H str.),3010(C-H str.),2975,1400(CH_2 next to C=O),1620 (C=O),1570(C=N),1530(C=C str.),780(C=S); ^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 8.36 (1H,s, CH of pyridine ring),8.1(1H,s,NH),7.68-8.69(3H,m, Ar-H),7.15(2H,s,NH_2) ,4.0(1H ,s,NH of pyrimidine ring),3.70(2H,s, CH_2); ^{13}C-NMR (400MHz, $CDCl_3$) δ ppm: Ar-C[163.78(C),123.22(C),114.58 (C),114.48(C)]172.16(C of amide),39.18(CH_2 azepinone),Ar-C[167.55(C),152.48(C),130.57(C),113.13 (C),azepinone],Ar-C[167.22(C),143.24(CH),100.34 (C), pyridine] ,180.4(C of C=S),182.44(-CNH_2) ;MS,m/z:327.18(M+70%),272.23(100%),318.34(15%),180.04 (32.5%);Anal. calcd. / found for $C_{15}H_{10}FN_5OS$: C, 55.04/55.25; H, 3.08/3.02; N, 21.39/21.63;S,9.80/9.57.

Preparation of 9-fluoro-5(methylthio)-12,14-dihydro-2H-benzo [b] imidazo [1", 2":1',6'-]pyrimido-[5',4':5,6]-pyrido[2,3-d]azepin-2,13 (3H)-dione (7)

A mixture of 2- amino- 10- fluoro-6-oxo -6,7-dihydro-5H- benzo[b]pyrido [2,3-d]azepin-3-carbonitrile **(5)** (2.10g,0.008 mol) ,and ethylglycinate dithioacetal (1.66 g,0.008 mol) in glacial acetic acid (20 ml) was heated under reflux for 4 h.The reaction mixture was allowed to cool, poured on ice and neutralized with sodium carbonate. The precipitate was filtered off and recrystallized with ethanol to give **7** (1.5g, yield: 71%);m.p.:390-392°C; IR (KBr) cm^{-} : 3240(N-H str.),3000(C-H str.) ,2985,1400(CH_2 next to C=O),1610,1800(C=O) ,1570(C=N str.),1535(C=C str.),680(C-S str.); ^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 8.35(1H,s, CH of pyridine ring),8.03(1H,s,NH),7.62-8.58(3H,m, Ar-H) ,3.76(2H,s,CH_2 of pyrrole ring),3.70(2H,s,CH_2),2.55(3H,s,CH_3); ^{13}C-NMR (400MHz, $CDCl_3$) δ ppm: Ar-C[163.78(CF),123.22(CH), 115.55 (CH),115.42(CH)] ,171.56(C of amide) ,Ar-C[167.47(C),152.52(C),129.67(C),114.15(C) azepinone],44.24(CH_2azepinone),Ar-C[167.58(C),141.27(CH),100.38 (C) pyridine],Ar-C[168.34(C),155.39(C), pyrimidine],59.39(CH_2 pyrrole),170.83(C of carbonyl),14.1(1C of CH_3) **;**MS,m/z: 381.15(M^+85.0%),313.07(100.0%),246.42(15.5%), 183.08(21.8%);Anal. calcd. / found for $C_{18}H_{12}FN_5O_2S$:C, 59.69/59.43; H, 3.17/3.11; N, 18.36/18.14;S, 8.41/8.62.

Preparation of 9-amino-2-fluoro-7,15-dihydrobenzo[6',7'] azepino [4',5':5,6] pyrido[2,3-e] pyrido[3,2-b] [1,4]diazepin-6(5H)-one(8)

2- Amino- 10- fluoro-6-oxo -6 ,7-dihydro-5H- benzo[b]pyrido [2,3-d] azepin-3 -carbonitrile **(5)** (2.10g,0.008 mol) was fused with 2-chloro -3-amino- pyridine (1.02 g,0.01 mol) to form a homogenous solution.Then anhydrous $AlCl_3$ (0.008 mol) was added, and the reaction mixture was heated at 170-180°C for 20 min . 10%aq. HCl solution was added, and mixture was heated for 5min.The resulting solution was filtered while hot into a conical flask containing 10% NaOH solution.The precipitates that formed was collected by filtration under sunction,washed with water until the filtrate was neutral,and left to dry at room temperature overnight to give **8 (**1.42g,yield: 68%);m.p.:149-151°C.;IR (KBr) cm^{-} : 3360(NH_2),3230(N-H str.),3010(C-H),2975,1400(CH_2 next to C=O),1680 (C=O),1575(C=N),1530(C=C str.);^{1}H-NMR (400MHz, $CDCl_3$) δ ppm: 8.34(1H,s,CH of pyridine ring),8.01(1H,s,NH),7.54-8.54(3H,m, Ar-H) ,7.62-8.77(3H,m,CH of pyridine ring),7.13(2H,s,NH_2 of diazepine) ,4.0(1H,s,NH of diazepine),3.70(2H,s,CH_2); ^{13}C-NMR (400MHz, $CDCl_3$) δ ppm: Ar-C[163.46(CF),124.32(CH), 115.51(CH),114.46(CH)],172.45(C of amide), 44.22(CH_2 azepinone); Ar-C[168.2(C),134.47(C),129.34(C), 122.22 (C), azepinone]Ar-C[167.58(C),141.27(CH),100.38(C),pyridine],164.0(-CNH_2),Ar-C[149.7(C),108.3(C), diazepine] ,Ar-C[146.54(CH),132.45(CH), 113.43 (CH) , pyridine]**;**MS,m/z: 360.12(M^+70.0,%),311.12(100.0%),226.11(22.2%),160.32(15.2%);Anal. calcd. / found for $C_{19}H_{13}FN_6O$: C, 63.33 / 63.57; H, 3.64/3.60; N, 23.32/23.11.

Results

The synthesis of compounds **5-8** wherein one can easily discern the presence of a variety of bioactive pharmacophores in their molecules was conceived in the present communication from enol ether following the strategy shown in **Scheme-1**. The synthesis consisted of reacting compound **2** with ethyl formate in presence of a base to give **3** which underwent

reaction with malononitrile and ammonium acetate formed the corresponding amino benzonitrile derivative **4** , which on treatment with urea[6], thiourea[6] , ethyl glycinate dithioacetal [7-8] and 2-chloro-3-amino pyridine[9,10] generated the azaquinazoline annulated analogues of benzazepinone **5-8** .

Conclusion

In summary, a facile protocol has been developed to provide the annulation of face 'd' of the benzazepinone nucleus with azaquinazolino ring by exploring the unprecendented potential of enol ether in this venture.

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