Some Pharamaceutically Important Pyrimido Molecules: Synthesis And Characterisation

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ABSTRACT

This paper describes the synthesis of pyrimido annulated analogues of carbazolo and azacarbazolo condensed aza-acridines respectively by the cyclocondensation of corresponding enol ether,chalcone, oxoketene dithioacetal and dimethyl aminomethylene ketone derivatives withurea, thiourea, acetamidine and guanidine respectively. The structures of all the compounds have been established on the basis of their elemental analysis and (IR, ^{1}HNMR and MS) spectral data.

Key words: Carbazolo, azacarbazolo, aza-acridines, pyrimido, enol ether,chalcone,Oxoketene dithioacetal and dimethyl aminomethylene ketone, IR, ^{1}HNMR and MS.

INTRODUCTION

The present research work includes to incorporate six membered rings viz; hydroxyl pyrimidine, mercapto pyrimidine, amino pyrimidine, methyl pyrimidine on the carbazole ,azacarbazole and condensed aza-acridine nucleus . The strategy adopted to incorporate these bioactive pharmacophores to this nucleus involves the corresponding enol ethers, chalcones, oxoketenedithioacetals and dimethylamino-methylene ketones respectively. Pyrimidine forms heterocyclic core of DNA and RNA, and has been associated with diverse biological activities[1].

Pyrimidines also play a vital role in many biological processes since this ring system is present in several vitamins, coenzymes, nucleic acids etc. therefore Pyrimidines and their derivatives are considered to be important for drugs and agricultural chemicals[2,3]. This ring system is incorporated into drugs is widely used as anti – viral and for the treatment of AIDS, Cancer[4-9].

The synthesis of this series of heterocyclics was undertaken on this assumption that incorporation of one or more than one bioactive heterocyclic moiety into the pyrimidine framework may result heterocycles with enhanced biological activity.

Pyrimidine is a promising structural moiety (fig-4.1)for drug designing. Pyrimidine derivatives form a component in a number of useful drugs and

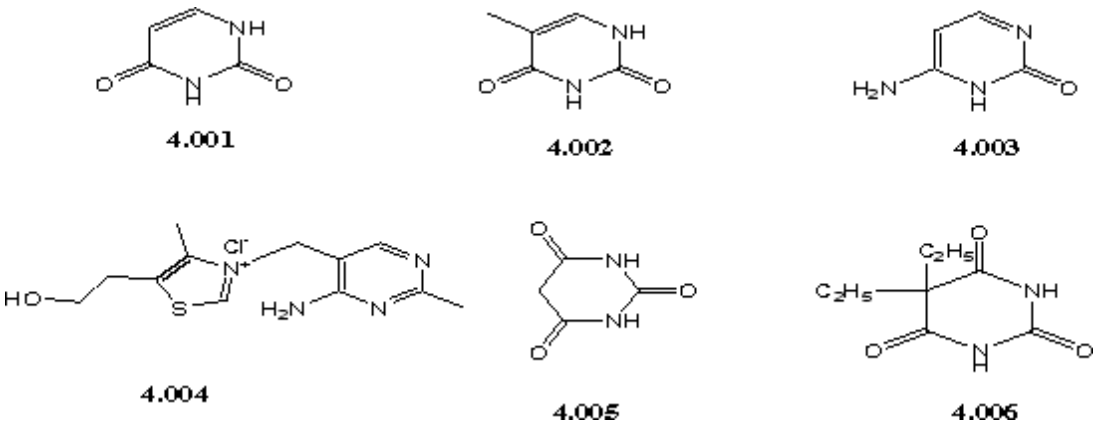


Fig. 1:

are associated with many biological, pharmaceutical and therapeutically activities [15].Condensed pyrimidine derivatives have been reported as anti-microbial[16],anti-inflammatory[17], anti-HIV[18], anti-tubercular[19], anti-tumor [20], analgesic[21], anti-malarial[22], diuretic [23], cardiovascular [24] agents. Pyrimidine compounds are also used as hypnotic drugs for the nervous system [25], calcium-sensing receptor antagonists[26] and also for antagonists of the human A2A adenosine receptor[27]. Drugs such as 5-thiouracil (, gemcitabine , 2-thiouracil , brodimoprin , 5-hydroxymethyl-2-methoxypyrimidine-4-amine , flucystosine , luminal , ritaserin and azidothiamidine(AZT) comprise pharmacological properties such as antineoplastic[28], antitumour[29], hyperthyroidism[30], antibacterial[31], antibiotic[32], antifungal[33], hypnotic[34] and anxiolytic[35] respectively

EXPERIMENTAL

Melting points were determined on an open capillary and are uncorrected. The IR spectra were recorded on Schimadzu

FTIR-8400S. 1H NMR spectra were recorded in DMSO-d6 and CDCl3 on Brukar 500 spectrometer using TMS as reference, expressed in ´ ppm. and Mass spectra were taken on a Bosch Tech – X 600 mass spectrometer at 70 eV.

Preparation of 10-benzyl-5-amino-3-mercapto-3,5,6,9,10,11,12,15-octahydro-2H-[1,6] naphthyridino[3,2-*h*]quinazolino[4,5a]carbazole-8-carboxylic acid (4.077a)

A mixture of **4.075** (1.92g, 004mole), malanonitrile(0.264g,0.004mole) and ammonium acetate(3.08g,0.04mole) in ethanol (10ml) was refluxed on a water bath for 16-18h, cooled, acidified with AcOH and precipitate which settled was collected. It was washed with 30% of aqueous ethanol and solid mass (1.7g) and thiourea (0.25g) was heated on an oil bath at 120°C for 4 hr with constant stirring. The temperature was raised to 180°C and finally the mixture was heated at 220°C for 2 h. On cooling the product solidified, which was recrystallized from DMF-EtOH mixture (1 :2) to give 4.077a 1.49 g Yield 67% m.pt. 295-96°C Similarly 4.077b, 4.077c, 4.077d were prepared from the reaction 4.075b with thiourea and by the reaction 4.075a,4.075b with urea respectively.

Preparation of 10-benzyl-2-mercapto-4-phenyl-3,5,6,9,10,11,12,15-octahydro-2H-[1,6] naphthyridino[3,2-*h*]pyrimido[4,5a] carbazole-8-carboxylic acid (4.080a)

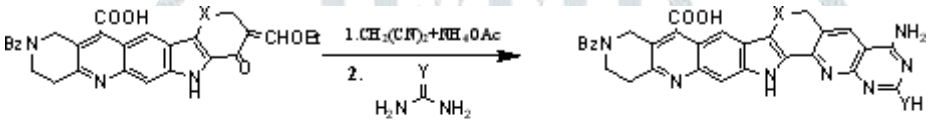
A mixture of 4.078(0.513g,.001mol), thiourea(0.01g,0.0051mol) and 0.1g NaOH in 25ml of 80% dil.ethanol was refluxed for 1.5h, then concentrated and cooled, the precipitated 4.080a was filtered off and recrystallized from ethanol. 0.379g. Yield 71% m.pt.245-46°C

Preparation of 10-benzyl-4-ethoxy-2-mercapto-3,5,6,9,10,11,12,15-octahydro-2*H*-[1,6] naphthyridino[3,2- *h*]pyrimido[4,5a]carbazole-8-carboxylic acid(4.083a)

To a mixture a thiourea (0.152g,0.002mol), sodium ethoxide(1.36g,0.02mol) and ethanol(25-30ml) was added 4.081a(1.058g,.002mol) and the reaction mixture was refluxed for 14 h. The solvent was removed by distillation and residue was treated with glacial acetic acid (7-10ml just enough to dissolved sodium salt of the pyrimidine) and refluxed for 15 minutes. The reaction mixture was acidified with AcOH and precipitate was collected and purified by crystallization with ethanol to give 4.083a 0.789g Yield 76% m.pt. 274-75^{0}C.Similarly 4.083b, 4.083c, 4.084d were prepared from reaction of 4.081b on its reaction with thiourea and 4.081a, 4.081b on its reaction with urea respectively.

Preparation of 10-benzyl-2-methyl-6,9,10, 11,12,15-hexahydro-5H-[1,6] naphthyridino [3,2h]pyrimido[4,5a]carbazole-8 carboxylic acid(4.086a)

To a solution of 4.084a (0.480g,1mmol) in ethanol (1000 ml) were added acetamidine hydrochloride (0.158g,1.67mmol) and Et_3N (2.35ml, 1.69mmol) and the solution was heated under reflux for 42 h and concentrated.The residue was extracted with AcOH and was dried over anhydrous $MgSO_4$.The residue was purified by column chromatography eluting with hexane:AcOEt(1:2) to give a brown powder.The solid 4.086a was recrystallized with ethanol to give 0.361g Yield 76% m.pt 224-25^{0}C.Similarly 4.086b,4.086c,4.086d were prepared from the reaction of 4.084b with acetamidine and 4.084a,4.084b with guanidine respectively.

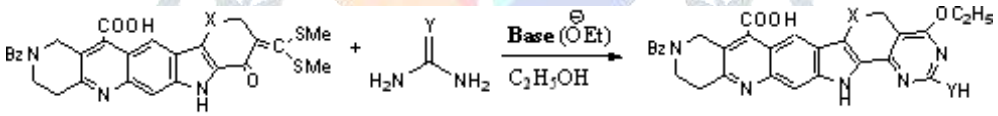


4.075a, X=CH$_2$
4.075b,X=N-Bz

4.076a,Y=S
4.076b,Y=O

4.077a,X=CH$_2$,Y=S
4.077b,X=N-Bz,Y=S
4.077c,X=CH$_2$,Y=O
4.077d,X=N-Bz,Y=O

Scheme 1:



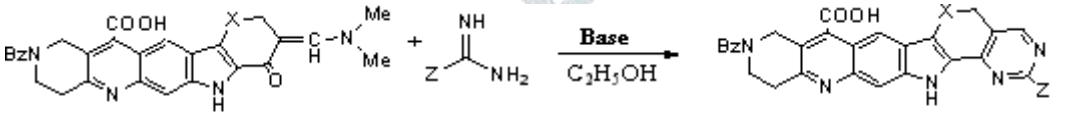
4.081a, X=CH$_2$
4.081b,X=N-Bz

4.082a,Y=S
4.082b,Y=O

4.083a,X=CH$_2$,Y=S
4.083b,X=N-Bz,Y=S
4.083c,X=CH$_2$,Y=O
4.083d,X=N-Bz,Y=O

Scheme:4.22

Scheme 2:



4.084a, X=CH$_2$
4.084b,X=N-Bz

4.085a,Z=CH$_3$
4.085b,Z=NH$_2$

4.086a, X=CH$_2$ Z=CH$_3$
4.086b,X=N-Bz,Z=CH$_3$
4.086c,X=CH$_2$,Z=NH$_2$
4.086d,X=N-Bz,Z=NH$_2$

Scheme 3:

10-benzyl-5-amino-3-mercapto-3,5,6,9, 10,11,12,15-octahydro-2H-[1,6] naphthyridino [3,2-*h*]quinazolino[4,5a]carbazole-8-carboxylic acid (4.077a).

The compound 4.077a was obtained by applying the general procedure mentioned above. Yield: 67%; m.p. 294–295^0 C; IR (KBr) cm-1: 3350.3200,3130,2530,1710,1580,1550,1530, 1020; 1H NMR (300 MHz, CDCl3+DMSO-d6) δ ppm:12.0(1H,s, SH), 11.9 (1H, s, OH), 11.2 (1H,s, NH), 7.35 (asymmetric)[5H,m,ArH]), 6.0(2H,s, NH_2],], 3.7 [2H,s,CH_2], 3.62[2H,s,,CH_2] 3.1[2H,t,J=6.4 CH_2], 2.45[2H,t,J=6.4CH_2],2.82[2H,t,J=6.4 CH_2],2.76[2H,t,J=6.4CH_2] 13C NMR (´ ppm): C (141.2, 124.8, 122.2, 122.0 for indazole ring), CH (128.9, 121.1, 112.0 for indazole ring), C (133.6, 124.1 for indole ring), C (183.0 for carbonyl carbon), CH2 (37.2, 26.4, 24.3 for aliphatic carbons); MS: *m/z* 559.64 [M+]; Anal. calcd./found for C31H25N7O2S : N, 18.52/18.46.

10-benzyl-2-mercapto-4-phenyl-3,5,6,9, 10,11,12,15-octahydro-2H-[1,6]naphthyridino [3,2-*h*] pyrimido [4,5a]carbazole-8-carboxylicacid (4.080a).

The compound 4.080a was obtained by applying the general procedure mentioned above. Yield: 65%; m.p. 245–246^{0}C; IR (KBr)cm"1:3300.3400,3010,2600,1600 ,1710,1570,1360; 1H NMR (300 MHz, CDCl3+DMSO-d6) ´ ppm:12.9(1H,s, SH), 11.1 (1H, s, OH), 11.9 (1H,s, NH), 8.9[1H,s,ArH],8.27[1H,s,ArH],7.9(asymmetric)[5H,m,ArH],7.25[5H,m,ArH],], 3.7 [2H,s,CH_2], 3.62[2H,s,CH_2]3.1 [2H,t,J=6.5CH_2], 2.45[2H,tJ=6.5 ,CH_2],2.82[2H,t, J=6.5CH_2],2.76[2H, TJ=6.5,CH_2] 13C NMR (´ ppm): C (142.4, 126.3, 124.8, 122.1 indazolering), CH (128.1, 123.1, 112.8 indazole ring), C (186.5,135.3, 113.9 indole ring), CH2 (53.6, 37.8, 33.9 foraliphatic carbon), C (137.4 for 1-benzene), CH (129.1,128.8, 127.9 for benzene ring)MS: *m/z* 569.19 [M+]; Anal. calcd./found for $C_{34}H_{27}N_5O_2S$: 17.71/17.62.

10-benzyl-4-ethoxy-2-mercapto-3,5 ,6,9,10,11, 12,15-octahydro-2*H*-[1,6] naphthyridino[3,2-*h*]pyrimido [4,5a]carbazole-8-carboxylic acid (4.083a)

The compound 4.083 a was obtained by applying the general procedure mentioned above. Yield: 66%; m.p. 274–274^{0}C; IR (KBr) cm"1: 3400.3100,3010,2500,1710,1610,1550,1320; 1H NMR (300 MHz, CDCl3+DMSO-d6) δppm: 12.5[H,s,SH],11.9[1H,s,OH], 11.2[1H,s,NH], 8.9[1H,s,ArH],8 .27[1H,s,ArH], 8.1(asymmetric) [5H,m,j=6.7ArH], 4.3[2H,m.j=6.7CH_2] , 3.7 [2H,sJ=6.7,CH_2], 3.62[2H,s,J=6.7CH_2] 3.1[2H,t,CH_2], 2.45 [2H,t,CH_2], 2.82 [2H,t,CH_2],2.76 [2H,t,CH_2], 1.33, [3H,t,CH_3] 13C NMR (´ ppm):C (143.4, 126.1, 123.7, 121.3 for indazole),CH (128.8, 121.5, 113.1 for indazole), C (132.2,116.1 for indole), CH2 (24.8, 23.3 for aliphatic carbon),128.8, 127.9 for benzene ring)MS: *m/z* 537.63 [M+]; Anal. calcd./found for $C_{36}H_{32}N_6O_3S$: 14.92/14.84...

10-benzyl-2-methyl-6,9,10,11,12,15-hexahydro-5H-[1,6] naphthyridino [3,2-h]pyrimido [4,5a] carbazole-8-carboxylic acid(4.086a)

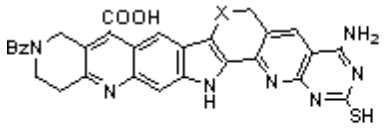
The compound 4.086 a was obtained by applying the general procedure mentioned above. Yield: 76%; m.p. 224-225^{0}C; IR (KBr)cm-1:3300, 3100,3010,1710,1580 ,1550; 1H NMR (300 MHz, CDCl3+DMSO-d6) δppm: 12.1[1H,s,OH], 11.8 [1H,s,NH],9.5[1H,s,ArH], 9.2[1H,s,CH], 8.27 [1H,s,ArH], 7.25[5H,m,ArH],]3.7 [2H,s,CH_2] 3.62 [2H,s,C H $_2$] 3.1 [2H, *t J = 6 . 5 C H* $_2$] , 2 . 4 5[2H,tJ=6.5,CH_2],2.82[2H,t,J=6 .5CH_2],2.76 [2H,t, J=6.5CH_2]2.35[3H,s,CH_3] 13C NMR (δ ppm): C(141.8, 124.6, 123.7, 121.2 for indazole), CH (128.3,

121.3, 112.1 for indazole), CH2 (56.2, 53.8 foraliphatic carbon), C (137.4 for 1-benzene), CH (128.8,128.5, 128.3, 128.1 127.8 for benzene), C (169.9 for1-carboxyl)MS: *m/z* 475.54 [M+]; Anal. calcd./found for $C_{29}H_{25}N_5O_2$: 14.92/14.84.

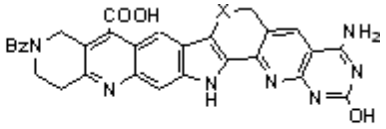
RESULTS AND DISCUSSION

In the present work, the synthesis of incorporated six membered rings viz; hydroxyl pyrimidine, mercapto pyrimidine, amino pyrimidine, methyl pyrimidine on the carbazole and azacarbazole fused aza-acridine nucleus carried out by the cyclocondensation of corresponding enol ethers, chalcones, oxoketene dithioacetals, and dimethyl aminomethylene ketones with urea, thiourea, acetamide, and guanidine respectively. The enol ethers, chalcones, oxoketene dithioacetals, and dimethyl aminomethylene ketones were synthesized in accordance to the

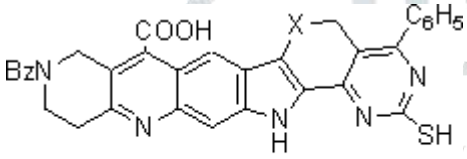
sequence of reaction shown under the heading of the synthesis of starting materials. When enol ethers (4.075a,b), were reacted with malononitrile in the presence of ammonium acetate[66] and the resulting o-amino pyridonitrile derivatives were treated with thiourea (4.076a) and urea (4.076b) ,formed the corresponding pyrimidine derivative (4.077a,b,c,d) respectively (Scheme:4.21). Treatment of chalcones (4.078a,b) and oxoketenedithioacetals (4.081a,b) with thiourea and urea, formed the corresponding pyrimidines derivatives (4.080a,b,c,d;4.083a,b,c,d) respectively (Scheme:4.21,Scheme4.22). Reaction of dimethyl aminomethylene derivatives (4.084a,b) with acetamidine (4.085a) and guanidine nitrate(4.085b) hydrochloride, produced the pyrimidine derivatives (4.086a,b,c,d) respectively (Scheme:4.23).



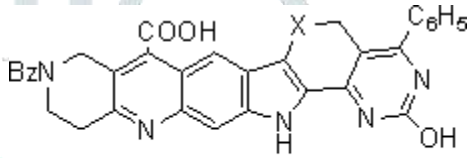
4.077a, X=CH_2
4.077b,X=N-Bz



4.077c, X=CH_2
4.077d,X=N-Bz



4.080a, X=CH_2
4.080b,X=N-Bz



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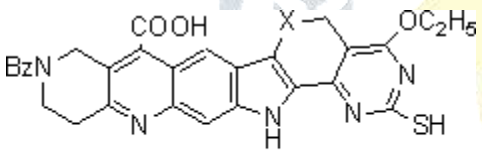
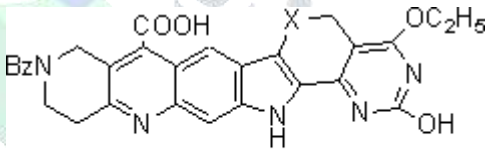
4.080d,X=N-Bz



4.083a, X=CH_2
4.083b,X=N-Bz



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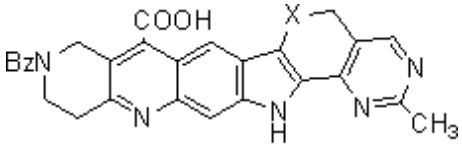
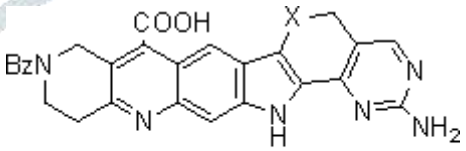
4.083d,X=N-Bz



4.086a, X=CH_2
4.086b,X=N-Bz



4.086a, X=CH_2
4.086b,X=N-Bz

CONCLUSION

In conclusion, an efficient methodology for the synthesis of pyrimido condensed oxocarbazoles and oxoazacarbazoles and their one-pot conversion to corresponding carbazolo and azacarbazolo fused quinoline carboxylic acids was developed. Heterocyclic scaffolds bearing these structures have been widely studied because of their impressive pharmacological activities. It was, therefore, reasoned that the presence of pyrimidine, carbazole or azacarbazole and quinoline carboxylic acid in tandem with the same molecular framework could produce the novel heterocyclic scaffolds with interesting biological activities

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