Indian Journal of Chemistry
Vol. 48B, November, 2009, pp. 1558-1564

Synthesis and antimicrobial screening of 4*H*-2-acetyl-3-acetyamido furo[3,2-*c*] benzopyran 4-one, 11*H* -2,4-dimethyl-3,4-dihydro-3-amino-4-hydroxy-pyrimido [3,2-*d*]furo [3,2-*c*] benzopyran-11-one and 4*H*-2-acetyl-3-(3′-methyl-1′,2′,4′-triazol-4′-yl) furo[3,2-*c*] benzopyran 4-one

V V Mulwad* & A S Hegde

Department of Chemistry, The Institute of Science, 15, Madam Cama Road, Mumbai 400 032, India

E-mail: vinata_mulwad@hotmail.com

Received 20 October 2008; accepted (revised) 08 April 2009

A suspension of 4*H*-2-acetyl-3-amino furo [3,2-*c*] benzopyran 4-one **5a-d** in aqueous sodium hydroxide is treated with acetyl chloride to give 4*H*-2-acetyl-3-acetylamido furo[3,2-*c*] benzopyran 4-one **6a-d**. The compounds **6a-d** and hydrazine hydrate in absolute alcohol is refluxed to give 11*H*-2,4-dimethyl-3,4-dihydro-3-amino-4-hydroxy-pyrimido[3,2-*d*] furo [3,2-*c*]benzopyran-11-one **7a-d** which in formic acid is refluxed for 5 hr to give 4*H*-2-acetyl-3-(3′-methyl-1′,2′,4′-triazol-4′-yl) furo[3,2-*c*] benzopyran 4-one **8a-d**. The structures of all these compounds have been established on the basis of the spectral and analytical data. All compounds have showed good antimicrobial activity.

Keywords: Acetyl chloride, formic acid, hydrazine hydrate, herbicidal, antimicrobial activity

Furobenzopyran is found in a variety of natural products exhibiting various herbicidal activity[1]. They have an excellent herbicidal activity on weeds and are completely selective to crops such as paddy rice, soyabeans and cotton. Furan derivatives have their own class of important drug and drug intermediate. Pyrimidine based heterocycles are of interest as potential bioactive molecules and exhibit antimicrobial, antiplatelet activities and also act as enzyme inhibitors[2-11]. A large number of heterocyclic compounds containing the 1,2,4-triazole ring are associated with diverse pharmacological properties, such as anti-inflammatory, antifungal, antimicrobial, anticonvulsants, antidepressant, antiviral and anti-tumor activity[12-26]. This initiated to synthesize biologically active new heterocyclic compounds in which furan ring is flanked between 4-hydroxy coumarin and 1,2, 4-triazole moiety.

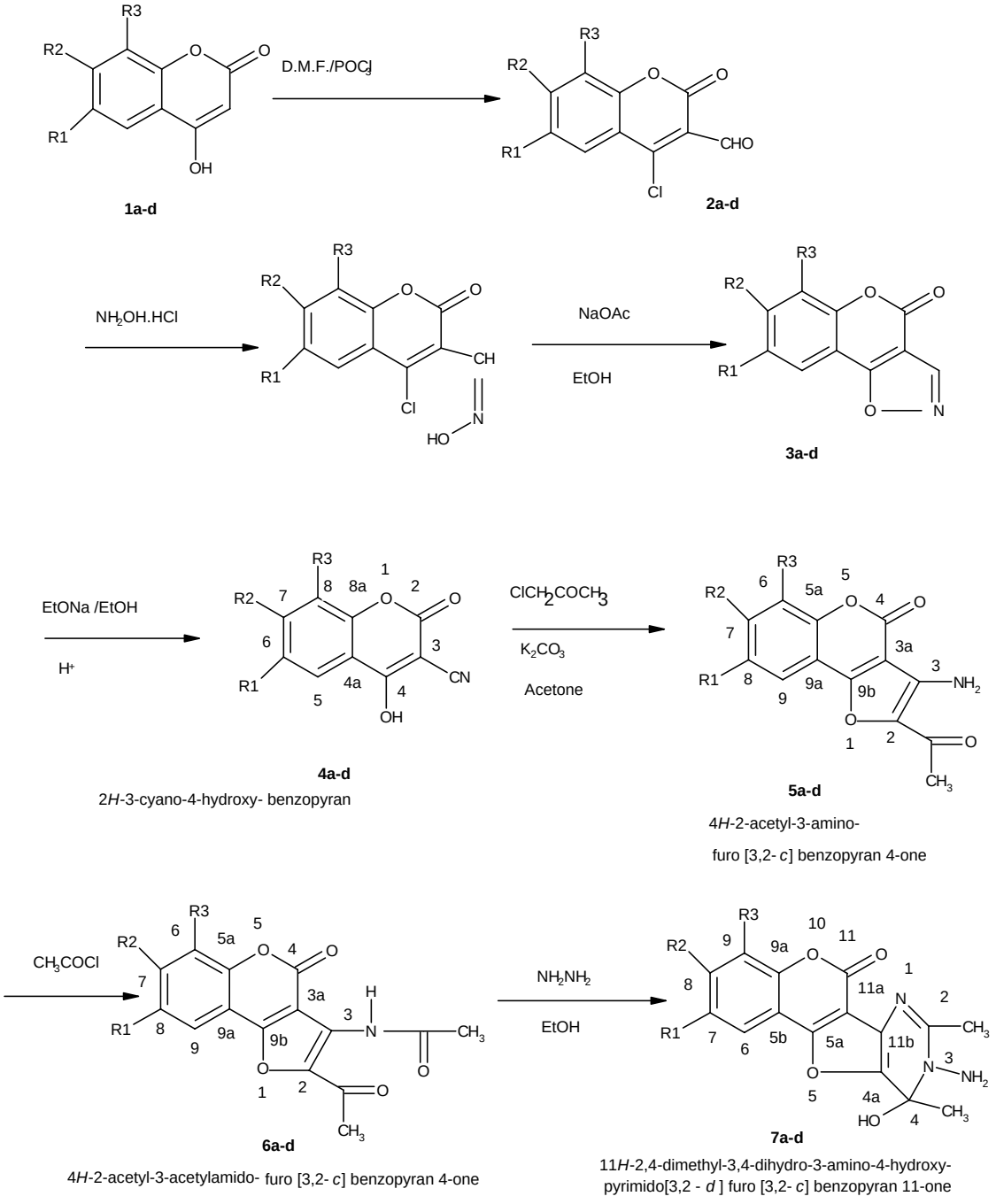
2*H*-[1] benzopyran [3, 4-*d*] isoxazoles- 2-one **3a-d** was prepared according to the method described by D. Heber *et al*[27]. and this was hydrolysed by freshly prepared sodium ethoxide to get 2*H*-[1] 3-cyano-4-hydroxy benzopyran 2-one **4a-d**[28].

2*H*-3-cyano-4-hydroxy benzopyran 2-one **4a-d** was treated with chloroacetone in dry acetone with anhydrous potassium carbonate to give 4*H*-2-acetyl-3-amino furo [3,2-*c*] benzopyran 4-one **5a-d**.

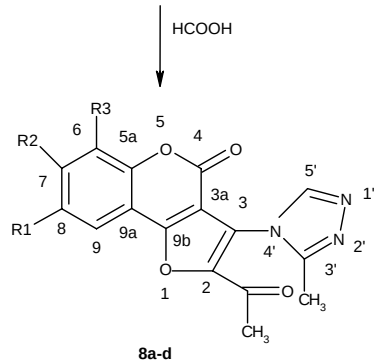
A suspension of 4*H*-2-acetyl-3-amino furo [3,2-*c*] benzopyran 4-one **5a-d** in aqueous sodium hydroxide was when treated with acetyl chloride gave 4*H*-2-acetyl-3-acetylamido furo[3,2-*c*] benzopyran 4-one **6a-d** (**Scheme I**, **Figure I**). The IR spectra of **6b** showed peak at 1619 cm^{-1} for >C=O stretching of acetyl group, 1700 cm^{-1} for >C=O stretching of coumarin, 3439 cm^{-1} for –NH stretching. The ^1H NMR of **6b** in DMSO-d_6 showed singlet at δ 2.20 for three protons of CH_3 of acetylamido at C_3, δ 2.25 for three protons of CH_3 group at C_8, δ 2.30 for three protons of CH_3 of acetyl group at C_2, doublet at δ 7.4 (J =7.5 Hz) for proton at C_6, doublet at δ 7.5 (J =7.5 Hz) for proton at C_7, singlet at δ 8.0 for proton at C_9. The –NH proton appeared as a singlet at δ 6.5 which was D_2O exchangeable. The ^{13}C NMR spectra displayed signals at δ 21 for methyl carbon at C_8, δ 27 for methyl carbon of acetyl group, δ 33 for methyl carbon of acetylamido group, signal appeared at δ 100 for C_{3a}, signal appeared at δ 112 for C_2, signal appeared at δ 117 for C_{9a}, signal appeared at δ 121 for C_6, signal appeared at δ 127 for C_9, signal appeared at δ 128 for C_7, signal appeared at δ 135 for C_8, signal appeared at δ 145 for C_{5a}, signal appeared at δ 155 for C_3, signal appeared at δ 156 for C_{9b}, signal appeared at δ 160, 196, 200 for carbonyl carbon of coumarin, acetyl group, acetylamido group respectively. The mass

spectrum gave molecular ion peak *m/z* (M^+) at 299 (70%) along with other peaks at 294, 261, 195, 160 (100%), 155, 135, 77, 58.

A mixture of 4*H* -2-acetyl-3-acetylamido furo[3,2-*c*] benzopyran-4-one and hydrazine hydrate when refluxed in absolute alcohol gave 11*H* -2,4-dimethyl-3,4-dihydro-3-amino-4-hydroxy-pyrimido[3,2-*d*]furo [3,2-*c*] benzopyran-11-one **7a-d**. The IR spectra of **7b** showed peak at 1621 cm^{-1} for ›C=O stretching of acetyl group, 1700 cm^{-1} for >C=O stretching of coumarin, 3404 cm^{-1} for $–NH_2$ stretching, 3533 cm^{-1} for –OH stretching. The ^1H NMR of **7b** in DMSO-d_6 showed singlet at δ 2.20 for three protons of CH_3 group at C_2, δ 2.40 for three protons of CH_3 group at C_4, δ 2.45 for three protons of CH_3 group at C_7, doublet at δ 7.4 (J = 7.5 Hz) for proton at C_9, doublet at δ 7.5 (J = 7.5 Hz) for proton at C_8, singlet at δ 8.0 for proton at C_6. The –OH proton appeared as a singlet



Scheme I



8a-d

4*H*-2-acetyl-3-[3'-methyl-1',2',4'- triazol-4'yl]- furo [3,2- *c*] benzopyran 4-one

1a,2a,3a,4a R_1,R_2,R_3=H
1b,2b,3b,4b R_1=CH_3,R_2,R_3=H
1c,2c,3c,4c R_2=CH_3,R_1,R_3=H
1d,2d,3d,4d R_3=CH_3,R_1,R_2=H

Scheme I (*Contd*)

at δ 3.5 which was D_2O exchangeable. The $–NH_2$ proton appeared as a singlet at δ 6.4 which was D_2O exchangeable. The ^{13}C NMR spectra displayed signals at (δ) 20 for methyl carbon at C_2, signal appeared at *δ* 24 for methyl proton at C_4, signal appeared at 25 for methyl proton at C_7, signal appeared at 90 for C_4, signal appeared at 100 for C_{11b}, signal appeared at 123 for C_9, signal appeared at 125 for C_{11a}, signal appeared at 129 for C_8, signal appeared at 131 for C_6, signal appeared at 135 for C_7, signal appeared at 148 for C_{9a}, signal appeared at 157 for C_{5b}, signal appeared at 158 for C_{5a}, signal appeared at 159 for C_{4a}, 162 for carbonyl carbon of coumarin, signal appeared at 165 for C_2. The mass spectrum gave molecular ion peak *m/z* (M^+) at 297 (50%) along with other peaks at 266, 249, 224, 200 (100%), 108, 94, 66.

A suspension of 11*H*-2,4-dimethyl-3,4-dihydro-3-amino-4-hydroxy-pyrimido[3,2-*d*]furo[3,2-*c*] benzopyran-11-one in formic acid (30 mL) gave 4*H*-2-acetyl-3-(3′-methyl-1′,2′,4′-triazol-4′-yl)furo[3,2-*c*] benzopyran 4-one **8a-d** (**Table I**). This proceeds *via* formamide formation then opening of the pyrimidine ring and followed by cyclisation. The IR spectra of **8b** showed peak at 1691 cm^{-1} for ›C=O stretching of acetyl group, 1700 cm^{-1} for >C=O stretching of coumarin. The ^1H NMR of **8b** in DMSO-d_6 showed singlet at (*δ*) 2.00 for three protons of CH_3 group at $C_{3'}$, 2.20 for three protons of CH_3 group at C_2, 2.25 for three protons of CH_3 group at C_8, doublet at δ 7.4 (*J* =7.5 Hz) for proton at C_6, doublet at 7.5 (*J* =7.5 Hz) for proton at C_7, singlet at 7.8 for proton at C_9, singlet at 8.0 for proton at $C_{5'}$. The ^{13}C NMR spectra displayed signals at (δ) 20 for methyl carbon at $C_{3'}$, 21 for methyl carbon at C_8, signal appeared at 22 for methyl carbon at C_2, fused carbons at 100 for C_{3a}, 110 for C_2, signal appeared at 118 for C_{9a}, signal appeared at 121 for C_6, signal appeared at 128 for C_9, signal appeared at 129 for C_7, signal appeared at 134 for C_8, signal appeared at 148 for C_{5a}, signal appeared at 150 for $C_{5'}$, signal appeared at 155 for C_3, signal appeared at 158 for C_{9b}, 162 for carbonyl carbon of coumarin, 164 for $C_{3'}$, 196 for carbonyl carbon of acetyl group. The mass spectrum gave molecular ion peak *m/z* (M^+) at 323 (20%) along with other peaks at 242, 200,160 (100%), 108, 94, 82.

Antimicrobial activity

The compounds **6-8a-d** were screened for their antibacterial activity against *S.aureus*, *S.typhi* and *E.coli* and antifungal activity against *A. niger and C. albicans.* The minimum inhibitory concentration (MIC) was determined using tube dilution method according to the standard procedure[29]. DMSO-d_6 was used as a blank and ciprofloxacin (MIC: 5μg/mL) and miconazole (MIC: 5μg/mL) were used as antibacterial and antifungal standards respectively. An examination of the data shows that all the compounds had antimicrobial activity ranging from 21 to 90 μg/mL (**Table II**).

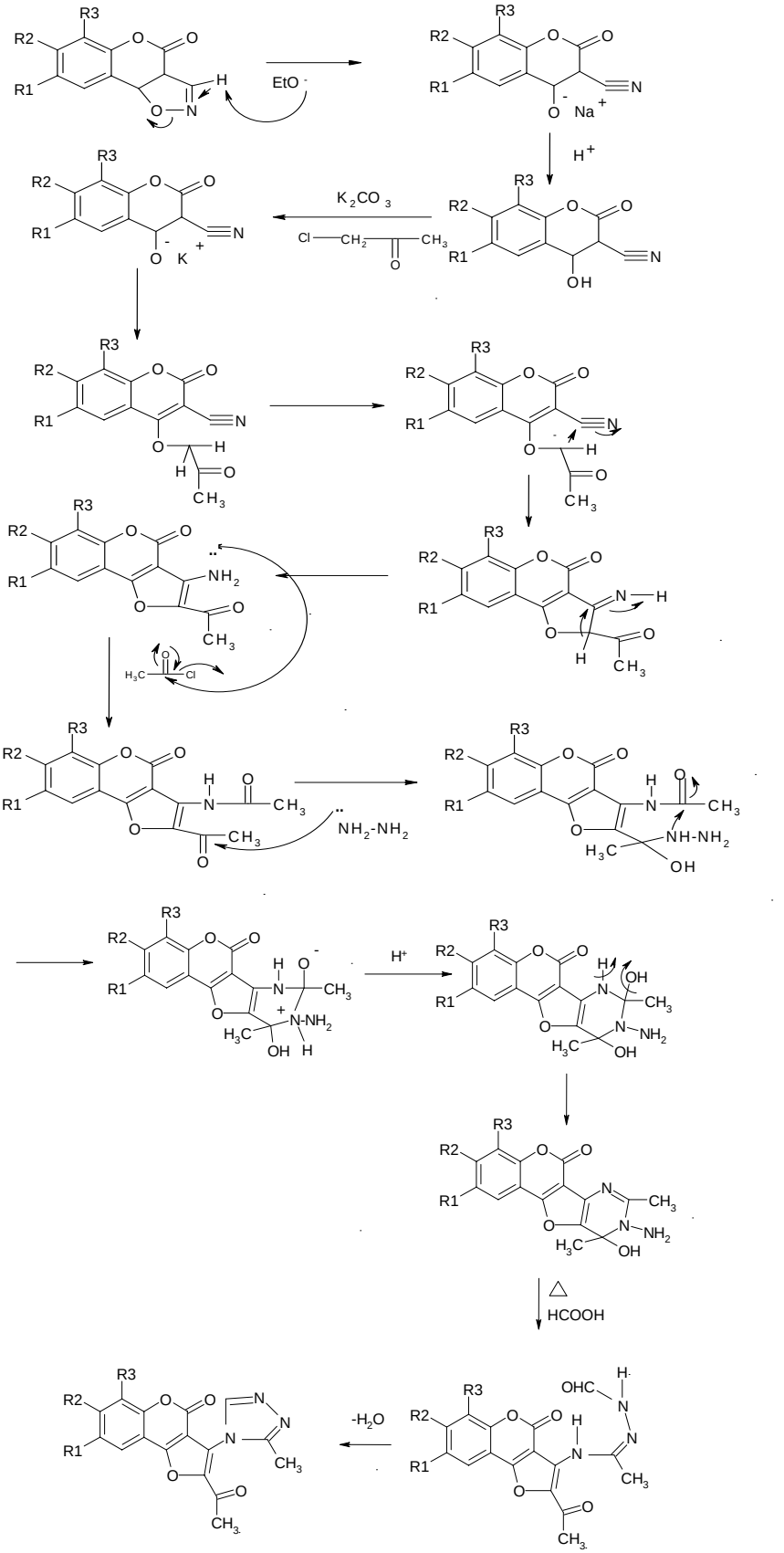

R3
R2
R1
O
H
N
EtO -
Na +
H+
K2CO3
Cl—CH2—C(=O)—CH3
K +
OH
NH2
CH3
H3C—C(=O)—Cl
NH2-NH2
NH-NH2
OH H
HCOOH
OHC
-H2O

Figure 1

Table I — Characterization data of compounds **6-8a-d**

Compd	Mol Formula	m.p. °C	Yield (%)	Found (Calcd) (%) C	H	N
6a	$C_{15}H_{11}NO_5$	130-32	50	63.10 (63.15	3.84 3.85	4.90 4.91)
6b	$C_{16}H_{13}NO_5$	141-43	50	64.15 (64.21	4.33 4.34	4.67 4.68)
6c	$C_{16}H_{13}NO_5$	153-55	45	64.10 (64.21	4.32 4.34	4.66 4.68)
6d	$C_{16}H_{13}NO_5$	182-83	40	64.09 (64.21	4.30 4.34	4.65 (4.68)
7a	$C_{15}H_{11}N_2O_4$	193-95	45	63.59 (63.60	3.80 3.88	9.87 9.89)
7b	$C_{16}H_{13}N_2O_4$	182-84	40	64.60 (64.64	4.30 4.37	9.40 9.42)
7c	$C_{16}H_{13}N_2O_4$	200-02	50	64.61 (64.64	4.35 4.37	9.41 9.42)
7d	$C_{16}H_{13}N_2O_4$	220-22	60	64.58 (64.64	4.31 4.37	9.39 9.42)
8a	$C_{16}H_{11}N_3O_4$	211-12	50	62.11 (62.13	3.51 3.55	13.58 13.59)
8b	$C_{17}H_{13}N_3O_4$	230-33	55	63.14 (63.15	4.01 4.02	12.59 13.00)
8c	$C_{17}H_{13}N_3O_4$	243-245	60	63.12 (63.15	4.00 4.02	12.57 13.00)
8d	$C_{17}H_{13}N_3O_4$	233-34	50	63.10 (63.15	4.01 4.02	12.56 13.00)

Table II — Antimicrobial activity of compounds **6-8a-d**

Compd	Antibacterial activity µg/mL			Antifungal activity µg/mL	
	E.coli	*S.typhi*	*S.aureus*	*A. niger*	*C. albicans*
6a	21	31	21	55	60
6b	23	33	22	60	55
6c	21	34	25	50	50
6d	22	33	25	55	55
7a	31	41	21	65	70
7b	34	44	22	70	75
7c	30	40	25	75	80
7d	31	46	25	70	90
8a	41	44	25	60	65
8b	30	40	25	55	60
8c	35	45	20	60	55
8d	50	50	25	65	60
Ciprofloxacin	5	5	5	-	-
Miconazole	-	-	-	5	5

The compounds **6-8a-d** showed good antibacterial activity for *S.aureus* as compared to *E.coli and S.typhi.*

Experimental Section

General: Melting points were recorded in open capillaries and are uncorrected. Homogenity of the compounds was checked on TLC. IR spectra were recorded on a Perkin-Elmer FT-IR instrument and ^{1}H and ^{13}C NMR on JEOL 300 MHz instrument using TMS as standard and mass spectra were recorded on a Shimadzu GC-MS QP-2010. Biological testing were carried out at Padmaja Aerobiologicals (P) Ltd.

General procedure for the preparation of 4*H*-2-acetyl-3-acetylamido furo[3,2-*c*] benzopyran 4-one, 6a-d

A stirred suspension of 4*H*-2-acetyl-3-amino furo [3,2-*c*] benzopyran 4-one **5a-d** (0.01 mole) in aqueous sodium hydroxide (10%, 30 mL) was treated with acetyl chloride (10 mL) in portions. After stirring the reaction-mixture for 20 minutes, the solid separated was collected and washed with water. Pure sample was obtained by crystallization from ethanol **6a-d**.

General procedure for the preparation of 11*H*-2, 4-dimethyl-3,4-dihydro-3-amino-4-hydroxy-pyrimido[3,2-*d*]furo [3,2-*c*] benzopyran-11-one, 7a-d

A mixture of 4*H*-2-acetyl-3-acetylamido furo[3,2-*c*] benzopyran 4-one **6a-d** (0.01 mole) and hydrazine hydrate (0.01 mole) in absolute ethanol (50 mL) was refluxed for 8 hr on a water-bath, The resulting reaction-mixture was poured into ice water and the solid thus separated on washing with water gave the product which was recrystallised from ethanol **7a-d**.

General procedure for the preparation of 4*H*-2-acetyl-3-(3´-methyl-1´,2´,4´-triazol-4´-yl) furo[3,2-*c*] benzopyran 4-one, 8a-d

A suspension of 11*H* -2,4-dimethyl-3,4-dihydro-3-amino-4-hydroxy-pyrimido[3,2-*d*]furo[3,2-*c*]benzopyran-11-one **7a-d** in formic acid (30 mL) was refluxed for 5 hr and the reaction-mixture was allowed to cool for 2 hr, then poured into ice-cold water. The crude product was filtered and recrystallized from ethanol **8a-d**.

6a: IR(KBr): 3438 (-NH), 1710 (>C=O),1618 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.21 (s, 3H, C_3-CH_3), 2.26 (s, 3H, C_8-CH_3), 2.31 (s, 3H, C_2-CH_3), 6.4 (s, 1H,-NH, D_2O exchangeable), 7.1-8.25 (m, 3H, Ar-H).

6b: IR(KBr): 3439 (-NH), 1700 (>C=O),1619 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.20 (s, 3H, C_3-CH_3), 2.25 (s, 3H, C_8-CH_3), 2.30 (s, 3H, C_2-CH_3), 6.5 (s, 1H,-NH, D_2O exchangeable), 7.4 (d, 1H,C_6-H, J = 7.5Hz), 7.5 (d,1H,C_7-H, J = 7.5Hz), 8.0 (s, 1H, C_9-H); ^{13}C NMR

(DMSO-d_6): δ 21 (C_8-CH_3), 27 (C_2-CH_3), 33 (C_3-CH_3),100 (C_{3a}), 112 (C_2), 117 (C_{9a}), 121 (C_6), 127 (C_9), 128 (C_7), 135 (C_8), 145 (C_{5a}), 155 (C_3) , 156 (C_{9b}) , 160 (>C=O), 196 (C_2 ,>C=O), 200 (C_3, >C=O); MS: *m/z* (%) M^+ 299 (70%), 294, 261, 195, 160 (100%), 155, 135, 77, 58.

6c: IR(KBr): 3437 (-NH), 1711 (>C=O), 1615 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.22 (s, 3H, C_3-CH_3), 2.26 (s, 3H, C_8-CH_3), 2.32 (s, 3H, C_2-CH_3), 6.6 (s, 1H,-NH, D_2O exchangeable), 7.74 (d, 1H, C_8-H, *J*=7.5Hz), 8.0 (d, 1H, C_9-H, *J* = 7.5Hz), 8.25 (s, 1H, C_6-H).

6d: IR(KBr): 3436 (-NH), 1708 (>C=O), 1620 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.25 (s, 3H, C_3-CH_3), 2.27 (s, 3H, C_8-CH_3), 2.33 (s, 3H, C_2-CH_3), 6.6 (s, 1H,-NH, D_2O exchangeable), 7.78 (d, 1H, C_7-H, *J* = 7. 5), 8.26 (d, 1H, C_9-H, *J* = 7. 5), 8.3 (t, 1H, C_8-H).

7a: IR(KBr): 3532 (-OH), 3403 (-NH_2),1712 (>C=O), 1620, 1574, 1491 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.1 (s, 3H, C_2-CH_3), 2.26 (s, 3H, C_4-CH_3), 2.28 (s, 3H, C_7-CH_3), 3.6 (s, 1H, -OH, D_2O exchangeable), 6.5 (s, 2H, -NH_2, D_2O exchangeable), 7.0-7.90 (m, 4H, Ar-H).

7b: IR(KBr): 3533 (-OH), 3404 (-NH_2),1700 (>C=O), 1621,1575, 1490 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.20 (s, 3H, C_2-CH_3), 2.40 (s, 3H, C_4-CH_3), 2.45 (s, 3H, C_7-CH_3), 3.5 (s, 1H, -OH, D_2O exchangeable), 6.4 (s, 2H, -NH_2, D_2O exchangeable), 7.4 (d, 1H, C_9-H, *J* = 7.5Hz), 7.5 (d, 1H, C_8-H, *J* = 7.5Hz), 8.0 (s, 1H, C_6-H). ^{13}C NMR (DMSO-d_6): δ 20 (C_2-CH_3), 24 (C_4), 25 (C_7), 90 (C_4), 100 (C_{11b}), 123 (C_9), 125 (C_{11a}), 129 (C_8),131 (C_6), 135 (C_7), 148 (C_{9a}),157 (C_{5b}), 158 (C_{5a}), 159 (C_{4a}), 162 (>C=O), 165 (C_2); MS: *m/z* (%) M^+ 297 (50%), 249, 266, 224, 200 (100%), 160, 108, 94, 66.

7c: IR(KBr): 3534 (-OH), 3405 (-NH_2),1704 (>C=O), 1623,1573,1482 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.21 (s, 3H, C_2-CH_3), 2.24 (s, 3H, C_4-CH_3), 2.28 (s, 3H, C_7-CH_3), 3.8 (s, 1H, -OH, D_2O exchangeable), 6.8 (s, 2H, -NH_2, D_2O exchangeable), 7.78 (d, 1H, C_8-H, *J* = 7.5Hz), 8.1 (d, 1H, C_9-H, *J* = 7.5Hz), 8.26 (s, 1H, C_6-H).

7d: IR(KBr): 3538 (-OH), 3406 (-NH_2),1708 (>C=O), 1624,1572, 1483 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.20 (s, 3H, C_2-CH_3), 2.22 (s, 3H, C_4-CH_3), 2.27 (s, 3H, C_7-CH_3), 3.8 (s, 1H, -OH, D_2O exchangeable), 6.7 (s, 2H, -NH_2, D_2O exchangeable), 7.77 (d, 1H, C_8-H, *J* = 7.5 Hz), 8.2 (t,1H, C_7-H), 8.25 (d,1H, C_6-H, *J* = 7.5 Hz).

8a: IR(KBr):1701 (>C=O), 1690, 1573, 1488 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.01 (s, 3H, $C_{3'}$-CH_3), 2.21 (s, 3H, C_2-CH_3), 2.26 (s, 3H, C_8-CH_3), 7.1-8.24 (m, 4H, Ar-H), 8.3(s, 1H, $C_{5'}$-H).

8b: IR(KBr): 1700 (>C=O),1691, 1574, 1491 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.00 (s, 3H, $C_{3'}$-CH_3), 2.20 (s, 3H, C_2-CH_3), 2.25 (s, 3H, C_8-CH_3), 7.4 (d,1H, C_6-H, *J* = 7.5Hz), 7.5 (d, 1H, C_7-H, *J* = 7.5Hz), 7.8 (s, 1H, C_9-H), 8.0(s, 1H, $C_{5'}$-H). ^{13}C NMR (DMSO-d_6): δ 20 ($C_{3'}$-CH_3), 21 (C_8-CH_3), 22 (C_2-CH_3), 100 (C_{3a}), 110 (C_2), 118 (C_{9a}), 121 (C_6), 128 (C_9), 129 (C_7), 134 (C_8), 148 (C_{5a}), 150 ($C_{5'}$), 155 (C_3), 158 (C_{9b}), 162 (>C=O), 164 ($C_{3'}$), 196 (C_2, >C=O); MS: *m/z* (%) M^+ 323 (20%), 242, 200, 160 (100%), 108, 94, 82.

8c: IR(KBr): 1703 (>C=O), 1693,1571,1492 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.02 (s, 3H, $C_{3'}$-CH_3), 2.24 (s, 3H, C_2-CH_3), 2.27 (s, 3H, C_8-CH_3), 7.74 (d, 1H, C_8-H, *J* = 7.5Hz), 8.0 (d, 1H, C_9-H, *J* = 7.5Hz), 8.1 (s, 1H, C_6-H), 8.2 (s, 1H, $C_{5'}$-H).

8d: IR(KBr): 1704 (>C=O), 1694,1572, 1490 cm^{-1}; ^{1}H NMR (DMSO-d_6): δ 2.04 (s, 3H, $C_{3'}$-CH_3), 2.25 (s, 3H, C_2-CH_3), 2.28 (s, 3H, C_8-CH_3), 7.79 (d, 1H, C_7-H, *J* = 7. 5), 8.1 (t, 1H, C_8-H), 8.28 (d, 1H, C_9-H), 8.3 (s, 1H, $C_{5'}$-H).

Acknowledgment

Authors are thankful to RSIC, IIT, Powai for ^{1}H and ^{13}C NMR spectral analysis and elemental analysis and Padmaja Aerobiologicals (P) Ltd for biological testing.

References

1 Arai K, Ooka M, Koizumi F, Koda S, Iwasaki Y & Kanemoto Y,*US patent*, Japan, **1994**, 5,356,866.

2 Holla B S, Padmaja M T, Shivananda M K & Akbarali P M, *Indian J Chem*, 37B, **1998**, 280.

3 Chaurasia M R & Sharma A K, *Indian J Chem*, 24B, **1985**, 308.

4 Tiwari L, Chaturvedi B & Nizamuddin, *Indian J Chem*, 28B, **989**, 200.

5 Mukherji D D, Nautiyal S R, Prasad C R & Dhawal B N, *Indian J Med Res*, 71, **1980**, 400.

6 Rinaldi M, Pecorari P, Costantino L, Provvisionato A, Malagoli M & Cermelli C, *Il Farmaco*, 47(10)**, 1992**,1315.

7 Itoh F, Yukishige K, Wajima M, Dotsu K & Akimoto H, *Chem Pharm Bull*, 43(2), **1995**, 230.

8 Gangjee-Aleem, Elzein-Elfaith, Queener-Sherry F & Meguire-John J, *J Med Chem*, 41(9), **1998**, 1409.

9 Bruno O, Schenone S, Ranise A, Bondavalli F, Barocelli E, Ballabeni V, Chiavarini M, Bertoni S, Tognolini M & Impicciatore M, *Bioorg Med Chem*, 9(3)**, 2001**, 629.

10 Crespo M I, Pages L, Vega A, Segarra V, Lopez M, Domenech T, Moorty S R, Sundaramurthy V & Subba Rao N V, *Indian J Chem*, 11, **1973**, 854.

11 Mulwad V V & Mayekar S, *Indian J Chem*, 46B, **2007**, 1869

12 Holla B S, Gonsalves R & Shenoy S, *Il Farmaco*, 53, **1998**, 773.

13 Milcent R & Vicart P, *Eur J Med Chem-chim Ther*, 18**, 1983**, 215.

14 Papakonstanttinou-Garoufalias S, Pouli N, Marakos P & Chytyroglou-Ladas A, *Il Farmaco*, 57**, 2002**, 973.

15 Bhat A R, Bhat G V & Shenoy G G, *J Pharm Pharmcol*, 53**, 2001**, 267.

16 Kücükgüzel I, Kücükgüzel S G, Rollas S, Ötük S G, Özedmir O, Bayrak I, Altug T & Stables J B, *Il Farmaco*, 59**, 2004**, 893.

17 Srivastava S K, Srivastava S & Srivastava S D, *Indian J Chem*, 41B**, 2002**, 2357.

18 Muhi-Eldeen Z, Nadir M, Aljobory N R, Husseen F & Stohs S J, *Eur J Med Chem*, 26**, 1991**, 237.

19 Ulusoy N, Gürsoy A & Ötük G, *Il Farmaco*, 56**, 2001**, 947.

20 Demirbas N, Karaoglu S A, Demirbas A & Sancak K, *Eur J Med Chem*, 39, **2004**, 793.

21 Collin X, Sauleau A & Coulon J, *Bioorg Med Chem*, 13**, 2003**, 2601.

22 Ikizler A A, Johansson C B, Bekirean O & Celik C, *Acta Pol Pharm Drug Res*, 56, **1999**, 283.

23 Kahveci B & Ikizler A A, *Acta Pol Pharm Drug Res*, 57, **2000**, 119.

24 Demirbas N, Ugurrluoglu R & Demirbas A, *Bioorg Med Chem*, 10, **2002**, 3717.

25 Kahveci B, Bekirean O, Serdar M & Ikizler A A, *Indian J Chem*, 42B**, 2003**, 1527.

26 Demirbas N & Ugurrluoglu R, *Turk J Chem*, 28**, 2004**, 559.

27 Heber D, Ivanov I C & Karagiosov S K, *J Hetrocyc Chem*, 32, **1995**, 505.

28 Moorty S R, Sundaramurthy V & Subba Rao N V, *Indian J Chem*, 11, **1973**, 854.

29 Frankel S, Reitman & Sonnenwirth A C, *Gradwol's Clinical Laboratory Methods and Diagnosis*, A textbook on laboratory procedure and their interpretation, Vol.2, 7th edn, (C V Mosby Company, Germany), **1970,** 1406.