NEW 4-RING FUSED HETEROCYCLIC SYSTEMS DERIVED FROM PYRIMIDO[6,1-a]ISOQUINOLIN-4-ONES. POTENT c-AMP PHOSPHODIESTERASE INHIBITORS

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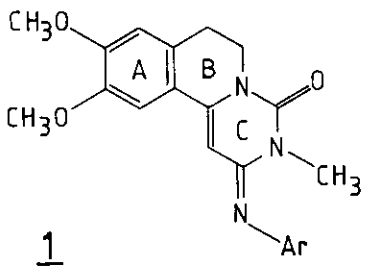
Abstract-The pyrimido[6,1-a]isoquinolin-4-one ring system has been annelated to form new 4-ring fused heterocyclic systems of interest as c-AMP phosphodiesterase inhibitors. The new ring systems prepared represent derivatives of triazolo[4,5-d]pyrimido[6,1-a]isoquinolin-5-one, imidazo[4,5-d]pyrimido[6,1-a]isoquinolin-5-one and thiazolo-[5,4-d]pyrimido[6,1-a]isoquinolin-5-one.

Arylimino-pyrimido[6,1-a]isoquinolin-4-ones 1 are potent inhibitors of c-AMP phosphodiesterase and possess antihypertensive and platelet aggregation inhibitor properties[1,2]. Greatest potency is observed when the arylimino group is substituted in the two ortho positions, as in Trequinsin[R].[2] 1a suggesting that spatial constraint on the interaction of the mesityl group with the c-AMP phosphodiesterase plays an important role. In order to test this hypothesis analogues 2 and 3 of pyrimido-isoquinolinone 1 have been synthesised. These tetracyclic heterocycles where the exocyclic nitrogen atom of 1 has been annelated to the pyrimido-isoquinoline system and the related thio analogue 4 are reported for the first time (Scheme 1).

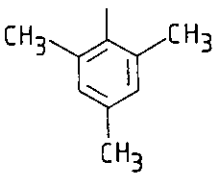
Homoveratrylurea 5[3] was condensed with diethyl acetamidomalonate to give disubstituted barbituric acid 6 in 66% yield. Completion of the B-ring by cyclisation in refluxing phosphoryl chloride gave the key acetamido-chloro-pyrimido-isoquinolinone 7 in 68% yield. Displacement of the chlorine by mesidine followed by removal of the acetyl group gave diamine hydrochloride 8 as monohydrate. Ring closure of 8 to the imidazo[4,5-d]pyrimido[6,1-a]-isoquinolin-5-ones 3 was achieved on heating with orthoesters; whilst diazotisation of 8 afforded to the triazolo[4,5-d]pyrimido[6,1-a]isoquinolin-5-one 2 (Scheme 2).

Scheme 1.

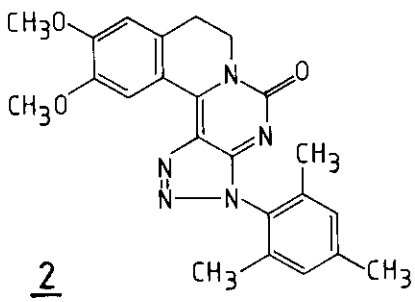


1

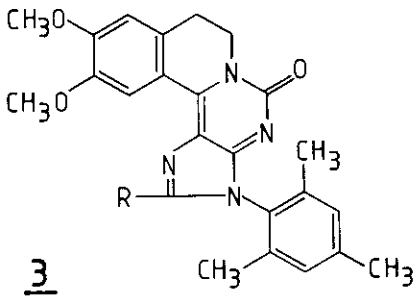
Ar =



(1a):

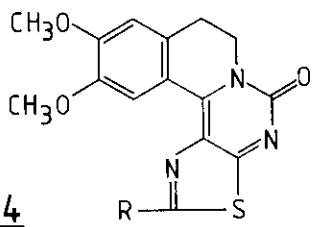


2



3

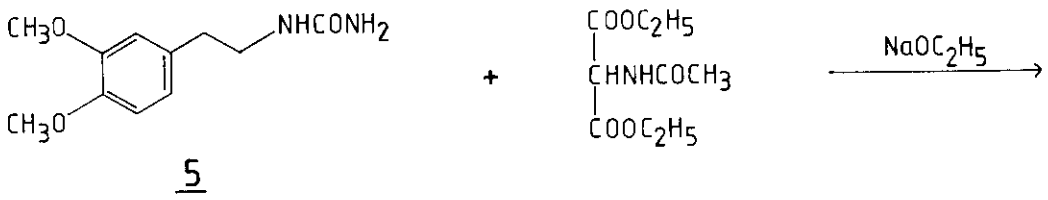
	R
a	H
b	CH_3
c	C_2H_5
d	CF_3



4

	R
a	CH_3
b	CF_3

Scheme 2.



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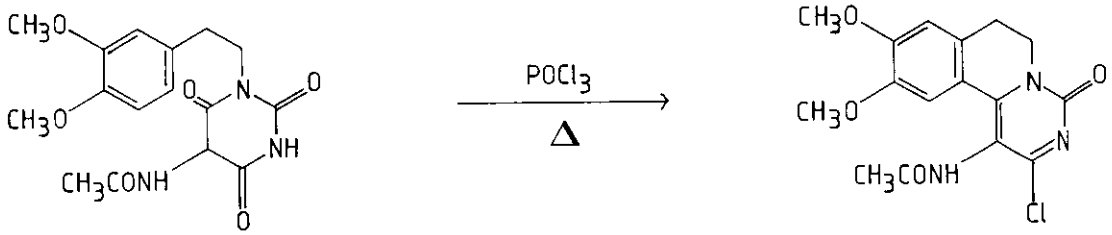
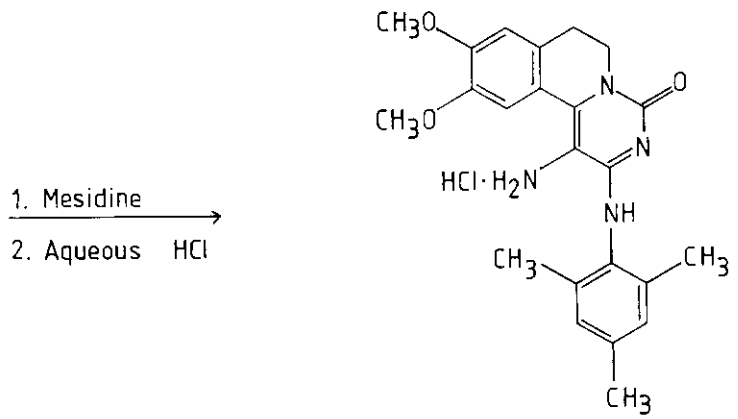


6 7



8

2

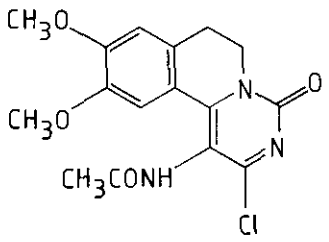
3a

3b

3c

A different strategy was used to introduce the trifluoromethyl group. Hydrolysis of the acetamido-dione 9a and re-acylation with trifluoroacetic anhydride gave 9b, which on conversion to a chloro-intemediate and subsequent reaction with mesidine, cyclised spontaneously to the desired product 3d (Scheme 3). Pyrimido-isoquinolinediones 9a and 9b readily formed the corresponding new thiazolopyrimido-isoquinolines 4a and 4b on treatment with P_2S_5.

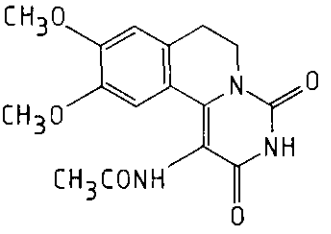
Scheme 3



7

H_2O / room temp

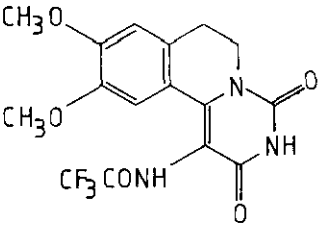
Standing several days



9a

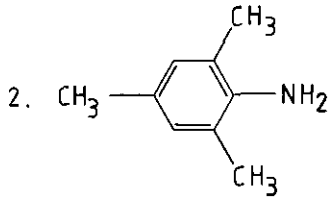
1. conc HCl, 1 h, reflux

2. $(CF_3CO)_2O$, 100°C, 30 min



9b

1. $POCl_3$, 1 h, reflux

2. 

, 180°C, 6 h

3d

Imidazopyrimidoisoquinolinones 3 inhibit human platelet aggregation and are potent inhibitors of c-AMP phosphodiesterase. These biological findings will be reported elsewhere.

EXPERIMENTAL

Melting points (uncorrected) were determined using a Büchi Schmelzpunkt-bestimmungapparat. Tlc was carried out on Merck (5719) silica gel $60F_{254}$ *pre-coated plates (10 x 5 cm) and were viewed under uv light (short wave).* Flash chromatography was carried out using silica gel 60 (70-230 mesh ASTM) (Merck). Ir spectra were determined on a Perkin-Elmer 881 Infrared spectrophotometer. Nmr spectra were determined on a JEOL FX-90Q spectrometer; chemical shifts are reported in ppm with positive values being downfield from the reference. Microanalyses were made on a Perkin-Elmer 240 Elemental Analyser. Yields were not optimised.

5-Acetamido-1-(3,4-dimethoxyphenylethyl)barbituric acid (6)

To a solution of sodium (4.6 g, 0.2 mol) in absolute ethanol (100 ml) was added a solution of homoveratrylurea[3] (44.8 g; 0.2 mol) in absolute ethanol (500 ml) followed by a solution of diethyl acetamidomalonate (43.4 g, 0.2 mol) in absolute ethanol (400 ml) and the mixture was heated under reflux with stirring for 11 h. Ethanol was then removed by distillation using oil-bath heating. Reduced pressure was applied in the final stages of distillation with the bath temperature raised to 120°C to ensure complete removal of ethanol. The solid residue, after cooling, was dissolved in water (600 ml) and a small amount of insoluble material was removed by filtration. The solution was then acidified to pH 1 by the slow addition of concentrated hydrochloric acid with stirring, and the precipitated product was collected by filtration, washed well with water and dried to constant weight at 90°C in an air-oven : yield: 46.1g (66% crude); *mp* 215-216°C. For characterisation a sample of the crude material was recrystallised from aqueous 60% dimethylformamide with charcoal clarification treatment. Amorphous prisms, mp 219-220°C were obtained. Anal. Calcd for $C_{16}H_{19}N_3O_6$: C, 55.01; H, 5.48; N, 12.03. Found: C, 55.03; H, 5.49; N, 12.01. Ir (nujol mull): νmax 3140; 1725; 1665; 1590; 1500; 1340; 1265; 1250; 1160; 1140; 1035; 845; 795; 760 cm^{-1}. ^{1}H-Nmr (89.55 MHz, DMSO-d_6/TMS) δ 11.48 (s, 1H, replaceable with D_2O); 9.48 (s, 1H, replaceable with D_2O); 6.92 (m, 3H, aromatic-H); 5.04 (s, 1H,

replaceable with D_2O); 3.91 (t, J=6 Hz, 2H, $-CH_2N$); 3.76 (s, 3H, OCH_3); 3.74 (s, 3H, OCH_3); 2.76 (t, J=6 Hz, 2H, $-CH_2$-arom.); 2.00 ppm (s, 3H, CH_3CO-).

1-Acetamido-2-chloro-6,7-dihydro-9,10-dimethoxy-4H-pyrimido[6,1-a]isoquinolin-4-one (7)

A mixture of the barbituric acid 6 (5 g, 0.014 mol, crude material) and phosphoryl chloride (50 ml, excess as solvent) was heated under reflux with stirring for 1 h. After allowing to cool, phosphoryl chloride was removed under vacuum distillation at bath 30-40°C and the residue was treated with ice/water (95 ml). The oily mixture was extracted with chloroform (3 x 25 ml) and the combined chloroform extract was washed with water (2 x 25 ml) and dried over $MgSO_4$. Chloroform was removed under vacuum distillation and the residue was triturated with ether to give a yellow solid which was collected by filtration, washed well with ether and dried: yield: 3.4 g (68% crude), mp 232°C. For characterisation a sample of the crude material was crystallised from a mixture of chloroform and ethyl acetate (1:1) by dissolving in cold $CHCl_3$, filtering, adding EtOAc and allowing to stand overnight. Yellow prisms, mp 237°C were obtained. Anal. Calcd for $C_{16}H_{16}ClN_3O_4$: C, 54.94; H, 4.61; N, 12.01. Found: C, 54.62; H, 4.61; N, 11.80. Ir (nujol mull): ν max 3200; 1660; 1585; 1565; 1500; 1430; 1370; 1310; 1275; 1090; 1010 cm^{-1}. ^{1}H-Nmr (89.55 MHz, $CDCl_3$/TMS) δ 7.77 (s, 1H, aromatic-H); 7.59 (s, 1H, replaceable with D_2O); 6.75 (s, 1H, aromatic-H); 4.28 (t, J=6 Hz, 2H, $-CH_2N$); 3.97 (s, 3H, OCH_3); 3.88 (s, 3H, OCH_3); 2.99 (t, J=6 Hz, 2H, $-CH_2$-arom.); 2.19 ppm (s, 3H, CH_3CO-).

1-Amino-9,10-dimethoxy-2-mesitylamino-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-4-one hydrochloride monohydrate (8)

a) Reaction of 7 with mesidine: A mixture of the chloro-intermediate 7 (10 g, 0.029 mol, crude material) and mesidine (20 g, excess as solvent) was heated with stirring for 3.5 h in a silicone oil bath at 180°C and then allowed to cool. The mixture was then treated with chloroform (300 ml) and filtered to remove mesidine hydrochloride. The chloroform filtrate was then given charcoal clarification treatment and filtered again to remove charcoal. The filtrate was then evaporated to an oil, which on trituration with ether afforded a light brown solid. The solid was collected by filtration, washed with ether and dried at 90°C in an air-oven. The product was 1-acetamido-9,10-dimethoxy-2-mesitylamino-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-4-one: yield 9.6 g (75% crude);

mp 202-204°C (decomp.); tlc (EtOAc/EtOH 3:1) R_f 0.29. For characterisation a sample of the crude material was recrystallised from aqueous ethanol with charcoal clarification treatment to afford prisms, mp 246-247°C (decomp.). Anal. Calcd for $C_{25}H_{28}N_4O_4$: C, 66.95; H, 6.29; N, 12.41. Found C, 66.74; H, 6.28; N, 12.29. Ir (nujol mull): ν max 3300; 3260; 1680; 1660; 1610; 1550; 1520; 1490; 1400; 1355; 1330; 1300; 1285; 1270; 1210; 1175; 1160; 1130; 1035; 980; 875; 850; 840; 800; 780; 750; 700 cm^{-1}. ^{1}H-Nmr (89.55 MHz, $CDCl_3$/TMS) δ 8.23 (s, 1H, replaceable with D_2O); 7.91 (s, 1H, replaceable with D_2O); 7.23 (s, 1H, aromatic-H); 6.89 (s, 2H, aromatic-H); 6.66 (s, 1H, aromatic-H); 4.23 (t, J=6 Hz, 2H, $-CH_2N$); 3.89 (s, 3H, OCH_3); 3.63 (s, 3H, OCH_3); 2.97 (t, J=6 Hz, 2H, $-CH_2$-arom.); 2.33 (s, 3H, 4-CH_3); 2.29 (s, 3H, CH_3CO); 2.24 ppm (s, 6H, 2-CH_3 and 6-CH_3).

b) Hydrolysis of acetamido group: 1-Acetamido-9,10-dimethoxy-2-mesitylamino-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-4-one (39 g, 0.087 mol, crude material) was slurried with concentrated hydrochloric acid (200 ml) at room temperature for 5 min and the mixture was then extracted with chloroform (3 x 100 ml). This treatment conveniently removed tarry impurities present in the crude material. The chloroform extracts were discarded; the aqueous phase was heated at reflux with stirring for 30 min during which time, after 10 min, the mixture was diluted by addition of hot water (200 ml) and reflux continued. At the end of the reflux period, the mixture was quickly cooled and solid which had formed was collected, washed well with water and dried in an air-oven at 90°C. (Drying in vacuo was avoided as monohydrate material is required for the next stage). Yield: 11.3 g (28% crude). Tlc (EtOAc/EtOH 3:1) R_f 0.49. For characterisation a sample of the crude material was recrystallised from a mixture of aqueous 4% HCl and ethanol (1:1) with charcoal clarification treatment. Amorphous pale brown solid was obtained, decomp. >215°C (darkening >160°C). Anal. Calcd for $C_{23}H_{26}N_4O_3.HCl.H_2O$: C, 59.93; H, 6.34; N, 12.16. Found C, 60.42; H, 6.41; N, 12.18. Ir (nujol mull): ν max 3280; 3200; 2600; 1640; 1580; 1510; 1400; 1340; 1290; 1215; 1160; 1040; 880; 860; 800; 780 cm^{-1}. ^{1}H-Nmr (89.55 MHz, DMSO-d_6/TMS) δ 9.28 (s, 1H, replaceable with D_2O); 6.92 (m, 4H, aromatic-H); 4.10 (t, J=6 Hz, 2H, $-CH_2N$); 3.82 (s, 3H, OCH_3); 3.48 (s, 3H, OCH_3); 2.98 (t, J=6 Hz, 2H, $-CH_2$-arom.); 2.24 (s, 3H, 4-CH_3); 2.18 ppm (s, 6H, 2-CH_3 and 6-CH_3).

10,11-Dimethoxy-3-mesityl-7,8-dihydro-3H,5H-triazolo[4,5-d]pyrimido[6,1-a]isoquinolin-5-one (2)

A suspension of crude 8 (2.8 g, 0.006 mol) in concentrated hydrochloric acid (16 ml) was cooled in an ice/water bath. At 0°C to 5°C with stirring, a solution of sodium nitrite (3 g, excess, in 20 ml water) was added dropwise during 30 min and after stirring for a further 1 h, the mixture was left to stand. After dilution with water, the solid precipitate was collected, washed well with water and recrystallised from aqueous dimethylformamide with charcoal clarification treatment. The crystalline product was collected, washed with ethanol and dried: yield 1.3 g (50%); mp 285°C; tlc (EtOAc/EtOH 3:1) R_f 0.71. Anal. Calcd for $C_{23}H_{23}N_5O_3$: C, 66.17; H, 5.55; N, 16.78. Found: C, 66.39; H, 5.47; N, 16.65. Ir (nujol mull): ν max 1710; 1280; 1205; 1160; 1020 cm^{-1}. ^{1}H-Nmr (89.55 MHz, $CDCl_3$/TMS) δ 7.67 (s, 1H, aromatic-H); 7.05 (s, 2H, aromatic-mesityl H); 6.72 (s, 1H, aromatic-H); 4.46 (t, J=6 Hz, 2H, $-CH_2N$); 3.94 (s, 3H, OCH_3); 3.84 (s, 3H, OCH_3); 3.03 (t, J=6 Hz, 2H, $-CH_2$-arom.); 2.40 (s, 3H, 4-CH_3); 2.00 ppm (s, 6H, 2-CH_3 and 6-CH_3).

General procedure for preparation of 7,8-dihydro-5H-imidazo[4,5-d]pyrimido-[6,1-a]isoquinolin-5-ones (3a-c)

A mixture of the crude amine hydrochloride monohydrate 8 (0.01 mol) and the appropriate triethyl orthoester (5 ml per g of 8) was heated and stirred in an oil-bath at 110°C for up to 4 h as indicated from tlc monitoring (EtOAc/EtOH 3:1) until reaction was complete. After cooling, the mixture was slurried with cyclohexane and the solid product was collected by filtration, washed with cyclohexane and dried. Purification by flash chromatography on silica gel eluting with EtOAc/EtOH (3:1) was carried out to afford the product (3).

10,11-Dimethoxy-3-mesityl-7,8-dihydro-5H-imidazo[4,5-d]pyrimido[6,1-a]isoquinolin-5-one (3a)

Prisms, mp 238-239°C. Yield 62%. Tlc (EtOAc) R_f 0.14. Anal. Calcd for $C_{24}H_{24}N_4O_3$ + 1/2 H_2O: C, 67.77; H, 5.92; N, 13.17. Found: C, 67.38; H, 5.90; N, 13.14. Ir (nujol mull): ν max 1690; 1610; 1600; 1540; 1500; 1340; 1280; 1240; 1220; 1205; 1160; 1100; 1080; 1055; 1025; 995; 970; 900; 880; 840; 795; 780; 670 cm^{-1}. ^{1}H-Nmr (89.55 MHz, $CDCl_3$/TMS) δ 7.67 (s, 1H, imidazole H at 2 pos.); 7.62 (s, 1H, aromatic-H); 7.03 (s, 2H, aromatic-mesityl H); 6.79 (s, 1H, aromatic-H); 4.46 (t, J=6 Hz, 2H, $-CH_2N$); 3.94 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3);

3.04 (t, J=6 Hz, 2H, -$C\underline{H}_2$-arom.); 2.39 (3H, 4-CH_3 of mesityl); 2.03 ppm (s, 6H, 2-CH_3 and 6-CH_3 of mesityl).

10,11-Dimethoxy-3-mesityl-2-methyl-7,8-dihydro-5H-imidazo[4,5-d]pyrimido-[6,1-a]isoquinolin-5-one (3b)

Prisms, mp 231-232°C. Yield 64 %. Tlc (EtOAc/EtOH 3:1) R_f 0.43. Anal. Calcd for $C_{25}H_{26}N_4O_3$ + 1/2 H_2O: C, 68.35; H, 6.19; N, 12.75. Found: C, 68.34; H, 6.10; N, 12.76. Ir (nujol mull): ν max 1690; 1610; 1540; 1510; 1350; 1280; 1210; 1160; 1140; 1090; 1040; 1000; 905; 870; 810; 785; 695; 670 cm^{-1}. ^{1}H-Nmr (89.55 MHz, $CDCl_3$/TMS) δ 7.59 (s, 1H, aromatic-H); 7.06 (s, 1H, aromatic mesityl H); 6.71 (s, 1H, aromatic-H); 4.46 (t, J=6 Hz, 2H, -CH_2N); 3.93 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3); 3.01 (t, J=6 Hz, 2H, -$C\underline{H}_2$-arom.); 2.41 (s, 3H, 4-CH_3 of mesityl); 2.03 (s, 3H, 2-CH_3); 2.16 (s, 1H, replaceable with D_2O, 1/2 H_2O); 1.96 ppm (s, 6H, 2-CH_3 and 6-CH_3 of mesityl).

10,11-Dimethoxy-2-ethyl-3-mesityl-7,8-dihydro-5H-imidazo[4,5-d]pyrimido[6,1-a]-isoquinolin-5-one (3c)

Prisms, mp 225-227°C. Yield 60%. Tlc (EtOAc/EtOH 3:1) R_f 0.51. Anal. Calcd for $C_{26}H_{28}N_4O_3$: C, 70.25; H, 6.35; N, 12.60. Found: C, 69.96; H, 6.13; N, 12.57. Ir (nujol mull): ν max 1695; 1540; 1510; 1350; 1280; 1270; 1210; 1160; 1140; 1090; 1070; 1050; 1000; 905; 870; 805; 780 720, 690 cm^{-1}. ^{1}H-Nmr (89.55 MHz, $CDCl_3$/TMS) δ 7.57 (s, 1H, aromatic-H); 7.04 (s, 2H, aromatic-mesityl H); 6.70 (s, 1H, aromatic-H); 4.46 (t, J=6 Hz, 2H, -CH_2N); 3.94 (s, 3H, OCH_3); 3.81 (s, 3H, OCH_3); 3.00 (t, J=6 Hz, 2H, -$C\underline{H}_2$-arom.); 2.51 (q, J=8 Hz, 2H, $CH_3C\underline{H}_2$-); 2.43 (s, 3H, 4-CH_3 of mesityl); 1.97 (s, 6H, 2-CH_3 and 6-CH_3 of mesityl); 1.27 ppm (t, J=8 Hz, 3H, $C\underline{H}_3CH_2$-).

1-Acetamido-9,10-dimethoxy-3,4,6,7-tetrahydro-2H-pyrimido[6,1-a]isoquinoline-2,4-dione (9a)

The dione 9a was obtained as a by-product from prolonged standing of aqueous liquors for several days after chloroform extraction of the chloro intermediate 7. Solid which had formed in the liquors was collected by filtration, washed with water and dried. Recrystallisation was achieved by dissolving the solid (10 g) in cold concentrated hydrochloric acid (100 ml) and stirring with charcoal. After removal of charcoal by filtration the solution was diluted by addition of water (400 ml) and allowed to stand. Crystals which formed were collected, washed first with water, then ethanol and then dried :

recovery 8.0 g (80 %) mp >300°C. Anal. Calcd for $C_{16}H_{17}N_3O_4$: C, 58.00; H, 5.17; N, 12.68. Found: C, 57.74; H, 5.29; N, 12.62. Ir (nujol mull): ν max 3300; 3160; 1700; 1670; 1600; 1510; 1350; 1280; 1220; 1160; 1140; 1080; 990; 870; 820; 780 720, 650 cm^{-1}. ^{1}H-Nmr (89.55 MHz, DMSO-d_6/TMS) δ 11.49 (s, 1H, replaceable with D_2O); 9.14 (s, 1H, replaceable with D_2O); 7.54 (s, 1H, aromatic-H); 7.00 (s, 1H, aromatic-H); 3.97 (t, J=6 Hz, 2H, $-CH_2N$); 3.83 (s, 3H, OCH_3); 3.71 (s, 3H, OCH_3); 2.85 (t, J=6 Hz, 2H, $-C\underline{H}_2$-arom.); 1.94 ppm (s, 3H, CH_3CO-).

9,10-Dimethoxy-1-trifluoroacetamido-3,4,6,7-tetrahydro-2H-pyrimido[6,1-a]-isoquinoline-2,4-dione (9b)

a) Hydrolysis of 9a to 1-amino derivative: A mixture of 9a (20 g, 0.06 mol) and concentrated hydrochloric acid (200 ml) was heated under reflux with stirring for 1 h and then allowed to cool. Crystals which formed were collected by filtration, washed well with water and the damp solid was then recrystallised from dimethylformamide with charcoal clarification treatment to afford 1-amino-9,10-dimethoxy-3,4,6,7-tetrahydro-2H-pyrimido[6,1-a]isoquinoline-2,4-dione: yield 16.3 g (93 %); mp 292-293°C. Anal. Calcd for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.53. Found:C, 57.89; H, 5.43; N, 14.47. Ir (nujol mull): ν max 3400; 3300; 1690; 1590; 1510; 1490; 1360; 1290; 1260; 1210; 1160; 1080; 980; 840; 780 cm^{-1}. ^{1}H-Nmr (89.55 MHz, DMSO-d_6/TMS) δ 11.49 (s, 1H, replaceable with D_2O); 7.83 (s, 1H, aromatic-H); 6.94 (s, 1H, aromatic-H); 4.37 (s, 2H, replaceable with D_2O); 3.87 (t, J=6 Hz, 2H, $-CH_2N$); 3.85 (s, 3H, OCH_3); 3.79 (s, 3H, OCH_3); 2.83 ppm (t, J=6 Hz, 2H, $-C\underline{H}_2$-arom.).

b) Trifluoroacetylation of 1-amino derivative: 1-Amino-9,10-dimethoxy-3,4,6,7-tetrahydro-2H-pyrimido[6,1-a]isoquinoline-2,4-dione (10 g, 0.035 mol) and trifluoroacetic anhydride (15 g, excess) were heated together at 100°C on a steam-bath for 30 min. After allowing to cool, water was added and the mixture was allowed to stand. The crystalline solid which formed was collected, washed well with water and dried to constant weight in a vacuum oven at 90°C: yield: 11.5 g. (86 %); mp 287-289°C decomp. Ir (nujol mull): ν max 3240; 3160; 1730; 1700; 1660; 1590; 1510; 1360; 1295; 1270; 1230; 1200; 1170; 1090; 1000; 885; 785; 690 cm^{-1}. ^{1}H-Nmr (89.55 MHz, DMSO-d_6/TMS) δ 11.74 (s, 1H, replaceable with D_2O); 10.83 (s, 1H, replaceable with D_2O); 7.42 (s, 1H, aromatic-H); 7.06 (s, 1H, aromatic-H); 3.83 (s, 3H, OCH_3); 3.77 (t, J=6 Hz, 2H, $-CH_2N$); 3.71 (s, 3H, OCH_3);

2.91 ppm (t, J=6 Hz, 2H, -C<u>H</u>$_2$-arom.). ^{19}F-Nmr (84.25 MHz DMSO-d_6/$CFCl_3$ external ref.) δ -73.74 ppm (s, CF_3).

10,11-Dimethoxy-3-mesityl-2-trifluoromethyl-7,8-dihydro-5H-imidazo[4,5-d]-pyrimido[6,1-a]isoquinolin-5-one (3d)

a) Chloro-derivative of 9b: A mixture of the crude dione 9b (11.0 g, 0.028 mol) and phosphoryl chloride (110 ml, excess) was heated under reflux with stirring for 1 h. After allowing to cool, excess of phosphoryl chloride was removed by distillation under reduced pressure at bath temperature 30-40°C. The resulting oily residue was treated with ice/water (250 ml) and the mixture was extracted with chloroform (600 ml). The chloroform extract was washed with water (2 x 150 ml) and dried over $MgSO_4$. Chloroform was removed under vacuum distillation and the residue was triturated with ether to give a solid which was collected by filtration, washed well with ether and dried : yield 6.3 g (55% crude). Tlc (EtOAc/dioxan 3:1) R_f 0.48 (main component) + impurities. Flash column chromatography was carried out on the above material using 90 g silica gel, eluting with EtOAc/dioxan (3:1) to obtain the main component (R_f 0.48) which was 2-chloro-9,10-dimethoxy-trifluoroacetamido-6,7-dihydro-4H-pyrimido[6,1-a]-isoquinolin-4-one; recovery 1.6 g (25%), yellow prisms, mp >300°C. Ir (nujol mull): ν max 3250; 3180; 1735; 1710; 1670; 1625; 1590; 1520; 1470; 1300; 1275; 1240; 1210; 1170; 1085; 890; 790; 700 cm^{-1}. ^{1}H-Nmr (89.55 MHz, DMSO-d_6/TMS) δ 8.21 (s, 1H, aromatic-H); 7.17 (s, 1H, aromatic-H); 4.24 (t, J=6 Hz, 2H, -CH_2N); 3.84 (s, 3H, OCH_3); 3.31 (s, 3H, OCH_3); 3.09 ppm (t, J=6 Hz, 2H, -C<u>H</u>$_2$-arom.). NH not detected. ^{19}F-Nmr (84.25 MHz $CDCl_3$/$CFCl_3$ external ref.) δ -75.30 ppm (s, CF_3).

b) Ring-closure of chloro-derivative with mesidine: A mixture of 2-chloro-9,10-dimethoxy-1-trifluoroacetamido-6,7-dihydro-4H-pyrimido[6,1-a]isoquinolin-4-one (5.8 g, 0.014 mol) and mesidine (11.6 g, excess as solvent) was heated with stirring for 6 h in a silicone oil-bath at 180°C and then allowed to cool. The mixture was then treated with chloroform (150 ml) and filtered to remove mesidine hydrochloride. The chloroform filtrate was evaporated to an oil, which on trituration with ether afforded a brown solid. The solid was collected by filtration, washed with ether and dried: yield 4.8 g (69 % crude). Tlc (EtOAc/dioxan 3:1) R_f 0.40 (Main component) + impurities. Flash column chromatography was carried out on the above material using 90g silica gel,

eluting with EtOAc/dioxan (3:1) to obtain the main component (R_f 0.40) which was 10,11-dimethoxy-3-mesityl-2-trifluoromethyl-7,8-dihydro-5H-imidazo[4,5-d]-pyrimido[6,1-a]isoquinolin-5-one, (3d): recovery 0.6 g (12 %) mp >300°C. Anal. Calcd for $C_{25}H_{23}F_3N_4O_3$: C, 61.98; H, 4.79; N, 11.57. Found: C, 61.88; H, 4.97; N, 11.29. Ir (nujol mull): ν max 1660; 1560; 1265; 1175; 1110; 1055; 990; 870; 780; 705 cm^{-1}. ^{1}H-Nmr (89.55 MHz, $CDCl_3$/TMS) δ 8.81 (s, 1H, aromatic-H); 7.00 (s, 2H, aromatic-mesityl-H); 6.83 (s, 1H, aromatic-H); 4.43 (t, J=6 Hz, 2H, $-CH_2N$); 4.04 (s, 3H, OCH_3); 4.00 (s, 3H, OCH_3); 3.07 (t, J=6 Hz, 2H, $-CH_2$-arom.); 2.34 (s, 3H, 4-CH_3 of mesityl); 2.00 ppm (s, 6H, 2-CH_3 and 6-CH_3 of mesityl). ^{19}F-Nmr (84.25 MHz $CDCl_3/CFCl_3$ external ref.) δ -65.49 ppm (s, CF_3).

General procedure for preparation of 10,11-dimethoxy-7,8-dihydro-5H-thiazolo-[5,4-d]pyrimido[6,1-a]isoquinolin-5-ones (4a-b)

A mixture of the appropriate dione (9a-b) (0.072 mol) and phosphorus pentasulphide (18.0 g, 0.08 mol) in dioxan (800 ml) was heated at 100°C under reflux with stirring for 4 h and then allowed to cool. The dioxan solution was decanted from the solid reaction residue, which was then extracted with chloroform (2 x 200 ml). The dioxan and chloroform extracts were evaporated and the residues obtained therefrom were combined and purified by flash chromatography on silica gel, eluting with EtOAc/dioxan (3:1) to afford the product 4.

10,11-Dimethoxy-2-methyl-7,8-dihydro-5H-thiazolo[5,4-d]pyrimido[6,1-a]isoquinolin-5-one (4a)

Yellow prisms, mp 187-188°C. Yield 34 %. Tlc (EtOAc/dioxan 3:1) R_f 0.12. Anal. Calcd for $C_{16}H_{15}N_3O_3S$: C, 58.34; H, 4.59; N, 12.76; S, 9.73. Found: C, 58.04; H, 4.90; N, 12.44; S, 9.82. Ir (nujol mull): ν max 1650; 1590; 1485; 1360; 1295; 1270; 1230; 1160; 1070; 1045; 1000; 775 cm^{-1}. ^{1}H-Nmr (89.55 MHz, $CDCl_3$/TMS) δ 8.72 (s, 1H, aromatic-H); 6.81 (s, 1H, aromatic-H); 4.37 (t, J=6 Hz, 2H, $-CH_2N$); 4.00 (s, 3H, OCH_3); 3.98 (s, 3H, OCH_3); 3.03 (t, J=6 Hz, 2H, CH_2-arom.); 2.74 ppm (s, 3H, 2-methyl).

10,11-Dimethoxy-2-trifluoromethyl-7,8-dihydro-5H-thiazolo[5,4-d]pyrimido-[6,1-a]isoquinolin-5-one (4b)

Yellow prisms, mp 254-255°C. Yield 30 %. Tlc (EtOAc/EtOH) R_f 0.52. Anal. Calcd for $C_{16}H_{12}F_3N_3O_3S$: C, 50.13; H, 3.16; N, 10.93, S, 8.36. Found: C, 49.99; H, 3.23; N, 10.98 ; S, 8.59. Ir (nujol mull): ν max 1685; 1590; 1530; 1520; 1485; 1470; 1370; 1330; 1300; 1270; 1210; 1140; 1075; 1055; 1010; 880; 845; 770; 745 cm^{-1}. ^{1}H-Nmr (89.55 MHz, $CDCl_3$/TMS) δ 8.64 (s, 1H, aromatic-H); 6.83 (s, 1H,

aromatic-H); 4.41 (t, J=6 Hz, 2H, $-CH_2N$); 4.01 (s, 3H, OCH_3); 3.94 (s, 3H, OCH_3); 3.07 ppm (t, J=6 Hz, 2H, $C\underline{H}_2$-arom.). ^{19}F-Nmr (84.25 MHz $CDCl_3/CFCl_3$ external ref.) δ -63.66 ppm (s, CF_3).

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