

Synthesis of tetrahydrobenzo[*b*]pyran derivatives catalysed by Aliquat®336 in water under microwave irradiation

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A series of 4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran derivatives has been synthesised in excellent yield in a single pot using trioctylmethylammonium chloride (Aliquat®336) as phase-transfer catalyst in water under microwave irradiation. This method provides a clean access to the desired products. The structures of the products were confirmed by IR, ¹H NMR, ¹³C NMR in all cases and HRMS in several cases, and supported by single crystal X-ray diffraction analysis of 2-amino-4-(3-benzyloxy-4-methoxyphenyl)-3-cyano-7,7-dimethyl-5-oxo-4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran and 2-amino-3-cyano-4-(3-iodo-4-hydroxy-5-methoxyphenyl)-7,7-dimethyl-5-oxo-4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran.

Keywords: tetrahydrobenzo[*b*]pyrans, active methylene compounds, aliquat®336, aqueous media

Tetrahydrobenzo[*b*]pyran derivatives have distinguished themselves as heterocycles of profound biological and pharmacological significance such as anti-coagulant, anticancer, spasmolytic, diuretic, anti-anaphylactic agents, *etc.*¹ Furthermore, suitably functionalised 4*H*-pyrans also constitute the structural unit of a series of natural products.² Some of the 2-amino-4*H*-pyrans are also useful as photoactive materials.³ As a result, synthesising libraries of these types of small heterocyclic molecules with a high degree of structural diversity continues to be a target of both medicinal and synthetic chemists.^{4–8} Recently, multicomponent reaction strategy has attracted the attention of synthetic organic chemists for building up highly functionalised organic molecules and pharmacologically important heterocyclic compounds with maximum simplicity. Inclusion of environmentally benign water as solvent also represents a powerful green procedure.⁹ Aliquat®336 has already been used as a mild, inexpensive, environmentally friendly phase-transfer catalyst in a number of organic reactions.^{10–12} We have reported previously a high yield synthesis of 1*H*- and 4*H*-benzochromenes using this catalyst in an aqueous medium under microwave irradiation.¹³ However, the use of Aliquat®336 in the synthesis of 4*H*-benzo[*b*]pyran derivatives has not been reported previously. With the aim of developing a more efficient synthetic process, shortening the synthetic route, simplifying work-up procedures, maximising yields and increasing environmental friendliness we report here an excellent result of combination of multicomponent reaction strategy, phase-transfer catalysis by Aliquat®336

and microwave irradiation for the synthesis of a series of 4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran derivatives in water (Scheme 1).

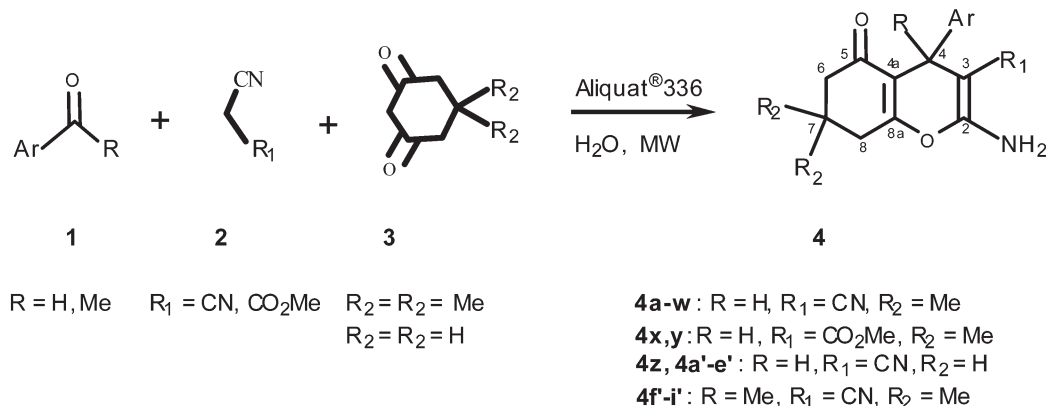
Results and discussion

The reaction was simply carried out by mixing an aromatic aldehyde or ketone **1**, an active methylene compound **2**, a cyclic 1,3-diketone **3** and the catalyst Aliquat®336 (15 mol%) in water and then subjecting the mixture to microwave irradiation. The corresponding 4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran derivatives **4** were obtained in excellent yields as summarised in Table 1.

All the aromatic aldehydes reacted smoothly and almost equally well to afford the desired products. The electronic nature of the substituents on the aromatic ring did not show a strong affect on rates of reaction and yields under these reaction conditions.

Encouraged by these results, we extended the scope of the present protocol for condensation using aromatic ketones instead of aromatic aldehydes. The desired 2-amino-4-aryl-3-cyano-4-methyl-5-oxo-5,6,7,8-tetrahydrobenzo[*b*]pyran derivatives were also obtained in good yields. As expected, the result summarised in Table 1 indicate the lower reactivity of ketones than that of aldehydes in the concerned condensation process.

We have also investigated the significant effects of the solvent and the dosage of the catalyst. A comparison of water-mediated synthesis using catalyst with syntheses performed



Scheme 1

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Table 1 Microwave-assisted synthesis of polyfunctionalised 4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran derivatives using Aliquat®336 in water

Products	Ar	R	R ₁	R ₂	Time/min	Yield ^a /%	M.p./°C	
							Found	Reported
4a	C ₆ H ₅	H	CN	Me	2	90	227–228	228–230 ⁵
4b	2-NO ₂ C ₆ H ₄	H	CN	Me	2	87	223–225	222–223 ⁵
4c	3-NO ₂ C ₆ H ₄	H	CN	Me	3	90	211–212	212–214 ⁵
4d	4-NO ₂ C ₆ H ₄	H	CN	Me	5	95	178–179	179–180 ⁵
4e	4-ClC ₆ H ₄	H	CN	Me	5	95	216–218	215–217 ⁴
4f	3-HOC ₆ H ₄	H	CN	Me	3	95	235–237	236–238 ⁵
4g	4-HOC ₆ H ₄	H	CN	Me	8	92	204–206	204–205 ⁵
4h	4-Me ₂ NC ₆ H ₄	H	CN	Me	7	94	210–212	212–213 ⁵
4i	4-MeOC ₆ H ₄	H	CN	Me	2	93	195–197	194–196 ⁹
4j	4-HO-3-MeOC ₆ H ₃	H	CN	Me	6	93	238–239	239 ⁷
4k	3-HO-4-MeOC ₆ H ₃	H	CN	Me	8	92	236–237	237–238 ⁵
4l^b	4-HO-3,5(MeO) ₂ C ₆ H ₂	H	CN	Me	15	80	189–192	–
4m	4-BnOC ₆ H ₄	H	CN	Me	3	89	225–227	224–226 ¹⁶
4n^b	3-BnO-4-MeOC ₆ H ₃	H	CN	Me	3	95	173–176	–
4o	3,4(O-CH ₂ -O)C ₆ H ₃	H	CN	Me	3	85	219–221	220–222 ⁹
4p	2,3,4(MeO) ₃ C ₆ H ₂	H	CN	Me	6	82	201–203	200–202 ¹⁵
4q	3,4,5(MeO) ₃ C ₆ H ₂	H	CN	Me	2	85	155–158	^c
4r^b	2-Br-4,5-(MeO) ₂ C ₆ H ₂	H	CN	Me	8	83	184–186	–
4s^b	2-Br-4,5-(O-CH ₂ -O)C ₆ H ₂	H	CN	Me	10	81	194–197	–
4t^b	3-1-4-HO-5-MeOC ₆ H ₂	H	CN	Me	5	95	224–226	–
4u	3-BrC ₆ H ₄	H	CN	Me	5	87	189–192	188–190 ¹⁸
4v	4-BrC ₆ H ₄	H	CN	Me	10	83	200–203	203–205 ⁵
4w	CH=CHC ₆ H ₅	H	CN	Me	15	82	198–201	^c
4x	3-NO ₂ C ₆ H ₄	H	CO ₂ Me	Me	20	80	190–191	190–192 ⁵
4y	4-BrC ₆ H ₄	H	CO ₂ Me	Me	18	78	164–166	165–169 ¹⁷
4z	C ₆ H ₅	H	CN	H	3	87	235–237	238 ¹⁴
4a'	4-HOC ₆ H ₄	H	CN	H	8	85	234–236	^c
4b'	3-NO ₂ C ₆ H ₄	H	CN	H	10	89	201–202	202–204 ⁹
4c'	3-BrC ₆ H ₄	H	CN	H	10	82	241–242	243–244 ¹⁴
4d'	4-BrC ₆ H ₄	H	CN	H	15	80	220–224	^c
4e'	3-BrC ₆ H ₄	Me	CN	Me	18	80	221–223	222–224 ⁸
4f'	4-BrC ₆ H ₄	Me	CN	Me	20	79	211–213	213–214 ⁸
4g'^b	3-NO ₂ C ₆ H ₄	Me	CN	Me	17	82	199–202	–
4h'	4-MeC ₆ H ₄	Me	CN	Me	25	75	212–214	213–215 ⁸
4i'	4-MeOC ₆ H ₄	Me	CN	Me	20	83	241–244	243–245 ⁸

^a Isolated yields; ^b newly synthesised compounds; ^c m.p. not found in the literature.

under solvent-free condition using catalyst, and in pure water in the absence of catalyst is drawn in Table 2. The condensation of benzaldehyde, dimedone and malononitrile in the presence of 15 mol % of Aliquat®336 under solvent-free condition afforded 83% of **4a** in 7 min, whereas the same product was obtained in 90% yield in 2 min in the presence of 15 mol % of Aliquat®336 in 3 mL of water. Table 2 also showed that non-catalysed reaction (without Aliquat®336) in water afforded only poor yields (20–35%) of the cyclised products in some cases and in a few cases no yields of cyclised products at all. Thus it can be inferred that the catalyst in water through

phase-transfer catalysis actually enhances the activity of the tandem reaction in terms of reaction time and yields of the products.

In the reaction involving vanillin, dimedone and malononitrile in the presence of 5 mol % of Aliquat®336, **4j** was obtained in 75% yield. We then examined the same reaction for optimisation by increasing the amount of catalyst from 5 mol % to 10 mol % and 15 mol % keeping the amount of reactants and the irradiation period the same. It was found that use of 15 mol % of catalyst leads to the optimum yield of product (Table 3). No significant yield improvement was observed for

Table 2 Microwave-assisted synthesis of polyfunctionalised 4*H*-5,6,7,8-tetrahydrobenzo[*b*]pyran derivatives using Aliquat®336 (15 mol %)

Products	Method A		Method B		Method C	
	Time/min	Yield/%	Time/min	Yield/%	Time/min	Yield/%
4a	2	90	7	83	2	30
4b	2	87	5	80	2	35
4e	5	95	10	87	5	25
4f	3	95	8	89	3	35
4i	2	93	6	86	2	30
4m	3	89	9	83	3	20
4s	10	81	15	55	10	20
4y	18	78	25	45	18	–
4f'	20	79	28	50	20	–

Method A: Reaction carried out using Aliquat®336 in water.

Method B: Reaction carried out using Aliquat®336 under solvent-free conditions.

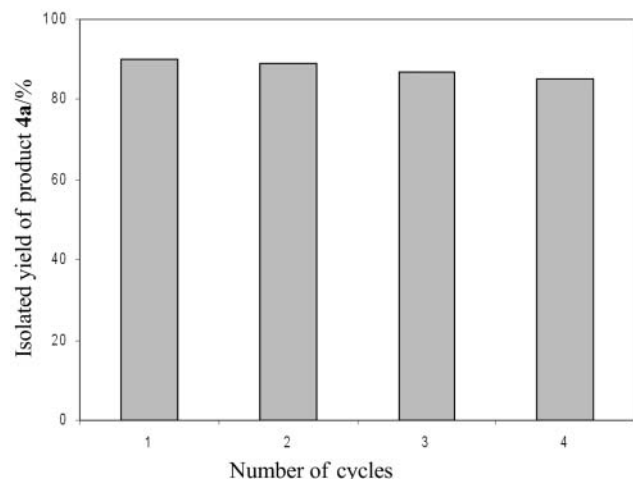
Method C: Reaction carried out in water without catalyst.

Table 3 Standardisation of the amount of Aliquat®336 for the optimisation of yield of the product

No. of observations	Amount of catalyst used/mol %	Isolated yield of product 4j /%
1	5	75
2	10	85
3	15	93
4	20	94

further increase of the amount of catalyst. Finally, Aliquat®336 can be recycled easily for the next 3–4 runs with little decrease in catalytic activity (Fig. 1). The recycling study was done with benzaldehyde (1 mmol), malononitrile (1 mmol), dime-done (1 mmol) and Aliquat®336 (15 mol %). After each run, the reaction mixture was titrated with diethyl ether. Then the solid product was filtered out and the filtrate was freed from ether by evaporation on a water bath. The aqueous part containing the entire Aliquat®336 was then reused easily for the next run.

The structures of the newly synthesised compounds received support from extensive NMR studies. The noise-decoupled ¹³C NMR spectrum of **4r** displayed the presence of 20 carbon signals, the DEPT-135 spectrum having established nine of them as protonated and the remaining eleven as nonprotonated. Furthermore, an HSQC experiment allowed identification of the signal of a protonated carbon and the signal of the proton directly linked with it, while an HMBC spectrum

**Fig. 1** Recycling study.

permitted complete carbon spectroscopic assignments through three-bond and some two-bond ¹³C–¹H correlation. Thus, multiple bond correlation of 3'-H identified non-protonated carbon resonances for C-1', C-2', C-4' and C-5' (where -1', -2' etc. refer to positions in the benzene rings). Incidentally, the 4-H signal displayed multiple bond correlations with several close-by carbons viz., C-1', C-2', C-6', C-2, C-3, C-4a, C-8a, CN and C-5. Furthermore, from correlation of carbon resonances at δ 195.6 and 112.2 for C-5 and C-4a, respectively, with geminal ¹H resonances at δ 2.04 d and 2.21 d the latter signals were related to 6-H_aH_b. Consequently, the other geminal ¹H resonances at δ 2.53 and 2.43 were associated with 8-H_aH_b. Again, 8-H_aH_b resonances exhibited multiple-bond correlation with non-protonated carbon resonances at δ 163.0 and 112.2, and the NH₂ signal displayed two-bond correlation with the non-protonated carbon resonance at δ 158.6. Thus carbon signals at δ 158.6 and 163.0 were assignable to C-2 and C-8a, respectively. Again, in the NOESY spectrum, the proximity of 3'-H and 6'-H signals to methoxy signals at δ 3.71 and 3.63, respectively were confirmed. Further, an HSQC experiment allowed the identification of the corresponding carbon resonances. Thus, proton signals at δ 3.71 and 3.63 were assignable to 4'-OMe and 5'-OMe, respectively, with corresponding carbon resonances at δ 56.0 and 55.8.

Compounds **4n** and **4t** were subject to X-ray crystallographic analyses and the structures are given in Figs 2 and 3, respectively.

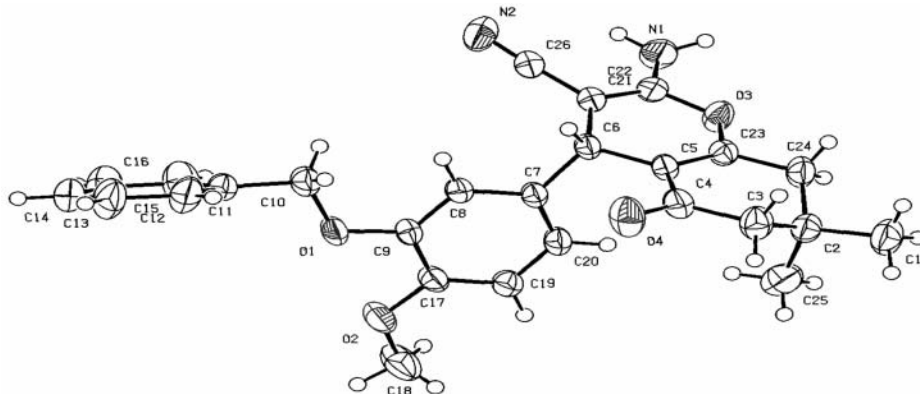
This method has the advantages of a short synthetic route, operational simplicity, increased safety for small scale high speed synthesis and minimal environmental impact. Moreover, the applicability of this procedure is not restricted to aromatic aldehydes but includes aromatic ketones too, which makes it a useful and attractive process for the synthesis of their derivatives.

Experimental

Melting points (uncorrected) were recorded on a Toshniwal apparatus and were compared with those reported in the literature. IR spectra were recorded on a Perkin-Elmer FT IR-RXI Spectrophotometer using KBr pellets. ¹H (300 MHz) and ¹³C (75 MHz) NMR spectra were recorded on a Bruker AV 300 supercon NMR spectrometer in a 5 mm BBO probe in *d*₆-DMSO as solvent and mass spectra on a Qtof Micro YA 263 spectrometer. This work involved the use of a domestic microwave oven. It should be noted that when others attempt the procedure the microwave conditions may have to be modified to obtain similar results.

Preparation of **4a–i**; general procedure

A mixture of aromatic aldehyde/ketone (1 mmol), malononitrile/methyl cyanoacetate (1 mmol), dime-done/1,3-cyclohexanedione (1 mmol) and Aliquat®336 (15 mol %) in water (3 mL) was placed

**Fig. 2** X-ray crystal structure of 2-amino-4-(3-benzyloxy-4-methoxyphenyl)-3-cyano-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (**4n**).

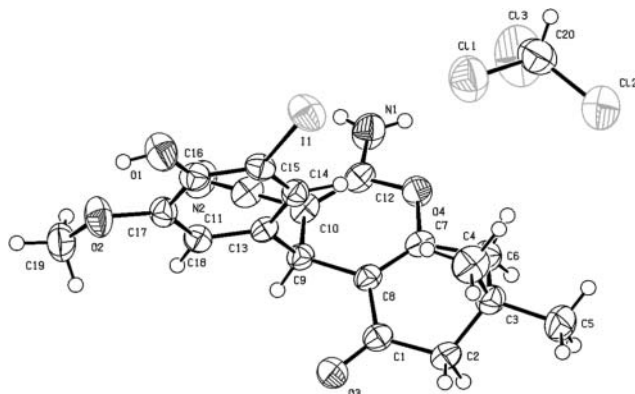


Fig. 3 X-ray crystal structure of 2-amino-3-cyano-4-(3-iodo-4-hydroxy-5-methoxyphenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b] pyran (**4t**).

inside a BPL-SANYO, 700T domestic microwave oven and was irradiated for a specified time (Table 1) at 720 W. After completion of reaction (indicated by solidification), the reaction mixture was titrated with diethyl ether. The solid thus separated out was filtered and finally purification by crystallisation from dichloromethane and methanol mixture afforded products (**4a-i**) in 75–95% yield. Spectroscopic data of the newly synthesised compounds are as follows:

2-Amino-3-cyano-4-(4-hydroxy-3,5-dimethoxyphenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (4l): Solid; amorphous; m.p. 189–192 °C; ν_{\max} (cm⁻¹): 1518, 1646, 2188, 3311, 3395; δ_{H} : 0.96 (s, 3H, 7-Me₍₁₎), 1.00 (s, 3H, 7-Me₍₂₎), 2.08 (d, $J = 16.1$ Hz, 1H, 6-H_a), 2.24 (d, $J = 16.1$ Hz, 1H, 6-H_b), 2.43 (d, $J = 16.5$ Hz, 1H, 8-H_a), 2.52 (d, $J = 16.5$ Hz, 1H, 8-H_b), 3.66 (s, 6H, 3'-OMe and 5'-OMe), 4.04 (s, 1H, 4-H), 6.30 (s, 2H, 2'-H and 6'-H), 6.89 (bs, 2H, NH₂), 8.20 (bs, 1H, OH); δ_{C} : 26.6 (7-Me₍₁₎), 28.7 (7-Me₍₂₎), 31.8 (C-7), 35.4 (C-4), 39.8 (C-8), 50.1 (C-6), 56.1 (3'-OMe and 5'-OMe), 58.8 (C-3), 104.7 (2C, C-2' and C-6'), 112.9 (C-4a), 119.9 (CN), 134.5 (C-4'), 135.1 (C-1'), 147.9 (2C, C-3' and C-5'), 158.4 (C-2), 162.5 (C-8a), 195.8 (C-5); m/z , M⁺Na (%), Found: 393.1426 (100). Calcd for C₂₀H₂₂N₂O₅Na: 393.1426.

2-Amino-4-(3-benzyloxy-4-methoxyphenyl)-3-cyano-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (4n): Solid; crystalline; m.p. 173–176 °C; ν_{\max} (cm⁻¹): 1588, 1652, 2189, 3320, 3476; δ_{H} : 0.92 (s, 3H, 7-Me₍₁₎), 0.99 (s, 3H, 7-Me₍₂₎), 2.03 (d, $J = 16.0$ Hz, 1H, 6-H_a), 2.20 (d, $J = 16.0$ Hz, 1H, 6-H_b), 2.44 (d, $J = 17.7$ Hz, 1H, 8-H_a), 2.48 (d, $J = 17.7$ Hz, 1H, 8-H_b), 3.70 (s, 3H, 4'-OMe), 4.11 (s, 1H, 4-H), 4.94 (d, $J = 11.8$ Hz, 1H, OCH₂), 5.00 (d, $J = 11.8$ Hz, 1H, OCH₂), 6.67 (dd, $J = 8.2$ Hz and 1.7 Hz, 1H, 6'-H), 6.76 (d, $J = 1.7$ Hz, 1H, 2'-H), 6.86 (d, $J = 8.3$ Hz, 1H, 5'-H), 6.91 (bs, 2H, NH₂), 7.29–7.42 (m, 5H, 2''-H, 3''-H, 4''-H, 5''-H and 6''-H); δ_{C} : 27.0 (7-Me₍₁₎), $^{1}J_{\text{C-H}} = 123.2$ Hz), 28.4 (7-Me₍₂₎), $^{1}J_{\text{C-H}} = 123.7$ Hz), 31.8 (C-7), 35.1 (C-4), $^{1}J_{\text{C-H}} = 137.1$ Hz), 39.8 (C-8), $^{1}J_{\text{C-H}} = 130.3$ Hz), 50.1 (C-6), $^{1}J_{\text{C-H}} = 127.5$ Hz), 55.7 (4'-OMe), $^{1}J_{\text{C-H}} = 144.3$ Hz), 58.7 (C-3), 70.4 (OCH₂), $^{1}J_{\text{C-H}} = 144.7$ Hz), 112.2 (C-5'), $^{1}J_{\text{C-H}} = 159.4$ Hz), 113.0 (C-4a), 113.2 (C-2'), $^{1}J_{\text{C-H}} = 160.4$ Hz, $^3J_{\text{C-H}} = 5.5$ Hz), 119.9 (CN), 120.0 (C-6'), $^{1}J_{\text{C-H}} = 159.8$ Hz, $^3J_{\text{C-H}} = 5.5$ Hz), 127.9 (3C, C-2'', C-4'' and C-6''), $^{1}J_{\text{C-H}} = 159.6$, 160.9 Hz), 128.5 (2C, C-3'' and C-5''), $^{1}J_{\text{C-H}} = 160.2$ Hz), 137.2 (C-1'), 137.4 (C-1'), 147.8 (C-3'), 148.2 (C-4'), 158.6 (C-2), 162.3 (C-8a), 195.7 (C-5); m/z , M⁺Na (%), Found: 453.1793 (100). Calcd for C₂₆H₂₆N₂O₄Na: 453.1790.

2-Amino-4-(2-bromo-4,5-dimethoxyphenyl)-3-cyano-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (4r): Solid; crystalline; m.p. 184–186 °C; ν_{\max} (cm⁻¹): 1599, 1666, 2188, 3205, 3321; δ_{H} : 0.96 (s, 3H, 7-Me₍₁₎), 1.00 (s, 3H, 7-Me₍₂₎), 2.04 (d, $J = 16.0$ Hz, 1H, 6-H_a), 2.21 (d, $J = 16.0$ Hz, 1H, 6-H_b), 2.43 (d, $J = 17.9$ Hz, 1H, 8-H_a), 2.53 (d, $J = 17.9$ Hz, 1H, 8-H_b), 3.63 (s, 3H, 5'-OMe), 3.71 (s, 3H, 4'-OMe), 4.58 (s, 1H, 4-H), 6.53 (s, 1H, 6'-H), 6.92 (bs, 2H, NH₂), 7.00 (s, 1H, 3'-H); δ_{C} : 26.8 (7-Me₍₁₎), $^{1}J_{\text{C-H}} = 125.0$ Hz), 28.7 (7-Me₍₂₎), $^{1}J_{\text{C-H}} = 126.2$ Hz), 31.8 (C-7), 35.0 (C-4), $^{1}J_{\text{C-H}} = 137.3$ Hz), 39.8 (C-8), $^{1}J_{\text{C-H}} = 129.1$ Hz), 50.1 (C-6), $^{1}J_{\text{C-H}} = 128.0$ Hz), 55.8 (5'-OMe), $^{1}J_{\text{C-H}} = 144.6$ Hz), 56.0 (4'-OMe), $^{1}J_{\text{C-H}} = 144.8$ Hz), 57.4 (C-3), $^2J_{\text{C-H}} = 5.8$ Hz), 112.2 (C-4a), 112.5 (C-6'), $^{1}J_{\text{C-H}} = 157.6$ Hz), 112.9 (C-2'), 115.6

(C-3'), $^{1}J_{\text{C-H}} = 163.8$ Hz), 119.3 (CN), 135.1 (C-1'), 148.4 and 148.6 (C-4', C-5'), 158.6 (C-2), $^2J_{\text{C-H}} = 3.3$ Hz), 163.0 (C-8a), 195.6 (C-5); m/z , M⁺Na (%), Found: 455.0584 (84, for Br⁷⁹), 457.0555 (100, for Br⁸¹). Calcd for C₂₀H₂₁BrN₂O₄Na: 455.0582 (for Br⁷⁹), 457.0565 (for Br⁸¹).

2-Amino-4-(2-bromo-4,5-methylenedioxyphenyl)-3-cyano-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (4s): Solid; amorphous; m.p. 194–197 °C; ν_{\max} (cm⁻¹): 1477, 1681, 2194, 3332, 3474; δ_{H} : 0.95 (s, 3H, 7-Me₍₁₎), 0.99 (s, 3H, 7-Me₍₂₎), 2.06 (d, $J = 15.9$ Hz, 1H, 6-H_a), 2.18 (d, $J = 15.9$ Hz, 1H, 6-H_b), 2.43 (d, $J = 17.6$ Hz, 1H, 8-H_a), 2.52 (d, $J = 17.6$ Hz, 1H, 8-H_b), 4.59 (s, 1H, 4-H), 5.94 (d, $J = 16.0$ Hz, 1H, O-CH₂-O), 6.04 (d, $J = 16.0$ Hz, 1H, O-CH₂-O), 6.59 (s, 1H, 6'-H), 6.94 (bs, 2H, NH₂), 7.05 (s, 1H, 3'-H); δ_{C} : 27.3 (7-Me₍₁₎), $^{1}J_{\text{C-H}} = 124.2$ Hz), 28.3 (7-Me₍₂₎), $^{1}J_{\text{C-H}} = 126.1$ Hz), 31.9 (C-7), 35.0 (C-4), $^{1}J_{\text{C-H}} = 138.2$ Hz), 39.8 (C-8), $^{1}J_{\text{C-H}} = 131.3$ Hz), 50.2 (C-6), $^{1}J_{\text{C-H}} = 128.4$ Hz), 57.3 (C-3), 102.0 (O-CH₂-O), $^{1}J_{\text{C-H}} = 176.1$ Hz), 108.8 (C-6'), $^{1}J_{\text{C-H}} = 166.1$ Hz), 112.1 (C-3'), $^{1}J_{\text{C-H}} = 170.1$ Hz), 113.0 (2C, C-2', C-4a), 119.2 (CN), $^3J_{\text{C-H}} = 2.3$ Hz), 136.7 (C-1'), 147.0 (C-4'), 147.6 (C-5'), 158.6 (C-2), 163.2 (C-8a), $^2J_{\text{C-H}} = 4.0$ Hz), 195.7 (C-5); m/z , M⁺Na (%), Found: 439.0268 (100, for Br⁷⁹), 441.0226 (94, for Br⁸¹). Calcd for C₁₉H₁₇BrN₂O₄Na: 439.0269 (for Br⁷⁹), 441.0251 (for Br⁸¹).

2-Amino-3-cyano-4-(3-iodo-4-hydroxy-5-methoxyphenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (4t): Solid; crystalline; m.p. 224–226 °C; ν_{\max} (cm⁻¹): 1594, 1671, 2190, 3324, 3446; δ_{H} : 0.94 (s, 3H, 7-Me₍₁₎), 0.99 (s, 3H, 7-Me₍₂₎), 2.07 (d, $J = 16.1$ Hz, 1H, 6-H_a), 2.23 (d, $J = 16.1$ Hz, 1H, 6-H_b), 2.48 (d, $J = 18.9$ Hz, 1H, 8-H_a), 2.50 (d, $J = 18.9$ Hz, 1H, 8-H_b), 3.71 (s, 3H, OMe), 4.05 (s, 1H, 4-H), 6.67 (bs, 1H, 6'-H), 6.92 (bs, 1H, 2'-H), 6.94 (bs, 2H, NH₂), 9.37 (bs, 1H, OH); δ_{C} : 26.6 (7-Me₍₁₎), $^{1}J_{\text{C-H}} = 125.9$ Hz), 28.7 (7-Me₍₂₎), $^{1}J_{\text{C-H}} = 126.0$ Hz), 31.9 (C-7), 34.8 (C-4), $^{1}J_{\text{C-H}} = 137.7$ Hz), 39.6 (C-8), $^{1}J_{\text{C-H}} = 129.2$ Hz), 50.1 (C-6), $^{1}J_{\text{C-H}} = 129.4$ Hz), 56.2 (5'-OMe), $^{1}J_{\text{C-H}} = 144.9$ Hz), 58.5 (C-3), 84.5 (C-3'), $^2J_{\text{C-H}} = 8.0$ Hz), 111.3 (C-6'), $^{1}J_{\text{C-H}} = 164.2$ Hz, $^3J_{\text{C-H}} = 5.0$ Hz), 112.6 (C-4a), $^2J_{\text{C-H}} = 7.0$ Hz), 119.8 (CN), 128.4 (C-2'), $^{1}J_{\text{C-H}} = 163.9$ Hz, $^3J_{\text{C-H}} = 5.8$ Hz), 137.8 (C-1'), $^2J_{\text{C-H}} = 5.2$ Hz), 145.1 (C-4'), 147.0 (C-5'), 158.5 (C-2), $^2J_{\text{C-H}} = 4.0$ Hz), 162.6 (C-8a), $^2J_{\text{C-H}} = 6.4$ Hz), 195.9 (C-5). m/z , M⁺Na (%), Found: 489.0287 (100). Calcd for C₁₉H₁₉I₂N₂O₄Na: 489.0287.

2-Amino-3-cyano-4-methyl-4-(3-nitrophenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (4g): Solid; amorphous; m.p. 199–202 °C; ν_{\max} (cm⁻¹): 1526, 1664, 2193, 3329, 3395; δ_{H} : 0.95 (s, 3H, 7-Me₍₁₎), 0.98 (s, 3H, 7-Me₍₂₎), 1.76 (s, 3H, 4-Me), 2.04 (d, $J = 15.7$ Hz, 1H, 6-H_a), 2.16 (d, $J = 15.7$ Hz, 1H, 6-H_b), 2.51 (bs, 2H, 8-H_a, 8-H_b), 6.97 (bs, 2H, NH₂), 7.56 (t, $J = 8.4$ Hz, 1H, 5'-H), 7.73 (br.d, $J = 7.9$ Hz, 1H, 6'-H), 7.99 (bs, 1H, 2'-H), 8.00 (br.d, 1H, 4'-H); δ_{C} : 25.6 (4-Me), 27.3 (7-Me₍₁₎), 27.7 (7-Me₍₂₎), 31.6 (C-7), 38.2 (C-4), 40.2 (C-8), 51.2 (C-6), 64.7 (C-3), 115.3 (C-4a), 118.6 (CN), 120.8 (C-2'), 121.0 (C-4'), 129.5 (C-5'), 133.4 (C-6'), 147.6 (C-1'), 150.4 (C-3'), 156.9 (C-2), 162.3 (C-8a), 195.9 (C-5). m/z , M⁺Na (%), Found: 376.1273 (100). Calcd for C₁₉H₁₉N₃O₄Na: 376.1273.

Crystallographic data were collected using a Bruker APEX-II CCD diffractometer. Structures were solved by direct methods and refined using SHELXL-97 (Sheldrick, 2008). The drawings used ORTEP-3 for Windows. The CCDC numbers given below contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from the Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/data_request.cif.

Crystallographic data for **2-amino-4-(3-benzyloxy-4-methoxyphenyl)-3-cyano-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (4n)**: C₂₆H₂₆N₂O₄, Mr 430.49, monoclinic, space group P-1 (No. 2), $a = 8.1144(7)$, $b = 15.5357(13)$, $c = 18.0853(15)$ Å, $\alpha = \gamma = 90^\circ$, $\beta = 99.728(3)^\circ$, $V = 2247.1(3)$ Å³, $Z = 4$, $D_{\text{calc}} = 1.273$ g cm⁻³, μ (mm⁻¹) = 0.086, $F(000) = 912.0$, crystal size 0.20 × 0.18 × 0.15 mm. Radiation type MoK α , 0.71073 Å. A total number of 31351 reflections were collected for $1.74 < \theta < 30.22^\circ$ and $-11 \leq h \leq 10$, $-20 \leq k \leq 21$ and $-25 \leq l \leq 24$. There were 6598 independent reflections and 4187 reflections with $I > 2\sigma(I)$ were used in the refinement. The final R indices were $R^1 = 0.0501$, $wR^2 = 0.1576$. The largest difference peak and hole were 0.279 eÅ⁻³ and -0.181 eÅ⁻³. CCDC No. 790155.

Crystallographic data for **2-Amino-3-cyano-4-(3-iodo-4-hydroxy-5-methoxyphenyl)-7,7-dimethyl-5-oxo-4H-5,6,7,8-tetrahydrobenzo[b]pyran (4t)**: C₂₀H₂₀Cl₃I₂N₂O₄, Mr 601.63, Triclinic, space group P-1 (No. 2), $a = 8.000(5)$, $b = 11.876(5)$, $c = 13.306(5)$ Å, $\alpha = 81.937(5)^\circ$, $\beta = 81.616(5)^\circ$, $\gamma = 76.124(5)^\circ$, $V = 1206.8(10)$ Å³, $Z = 2$, $D_{\text{calc}} = 1.656$ g cm⁻³, μ (mm⁻¹) = 1.692, $F(000) = 831.0$, crystal size

0.08 × 0.12 × 0.14 mm. Radiation type MoK α , 0.71073 Å. A total number of 12050 reflections were collected for 1.56 < θ < 24.74° and -9 ≤ h ≤ 9, -13 ≤ k ≤ 13 and -15 ≤ l ≤ 14. There were 4109 independent reflections and 3750 reflections with I > 2 σ (I) were used in the refinement. The final R indices were R¹ = 0.0284, wR² = 0.0793. The largest difference peak and hole were 0.51 eÅ⁻³ and -0.41 eÅ⁻³. CCDC No. 790156.

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