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Biomimetic synthesis of the metabolites of trequinsin

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Six metabolites of Trequinsin [9,10-dimethoxy-3-methyl-2-(2,4,6-trimethylphenylimino-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-a]isoquinolin-4-one. hydrochloride] are identified which have been synthesised from the parent molecule trequinsin **1**. A base-promoted selective demethylation of **1** at position 9 gives the metabolite **4.** An acid aided demethylation at position 10 furnishes the metabolite **7.** Treatment of compounds **1** and **4** with DDQ gives the 4'-DDQ complexes **10** and **14** respectively. These complexes on treatment with $ZnCl_2$–MeOH afford the 4'-methoxymethyl derivatives **11** and **15** respectively, which on subsequent demethylation with dil. HCl give the corresponding hydroxy derivatives **2** and **5.** When treated with two equivalents of DDQ, **1** gives the DDQ complex **12**, which on subsequent treatment with $Zn(OAc)_2$ yields the 4'-formyl derivative **13**. Oxidation of **13** with $AgNO_3$–NaOH gives the 4'-carboxy derivative **3**, which was subsequently selectively demethylated to give the metabolite **6**. Treatment of **13** with $NH_2OH.HCl$ produces the oxime **17**, which is then dehydrated to the nitrile **18** using $(Ac)_2O$. Alkaline hydrolysis of **18** gives **3.**

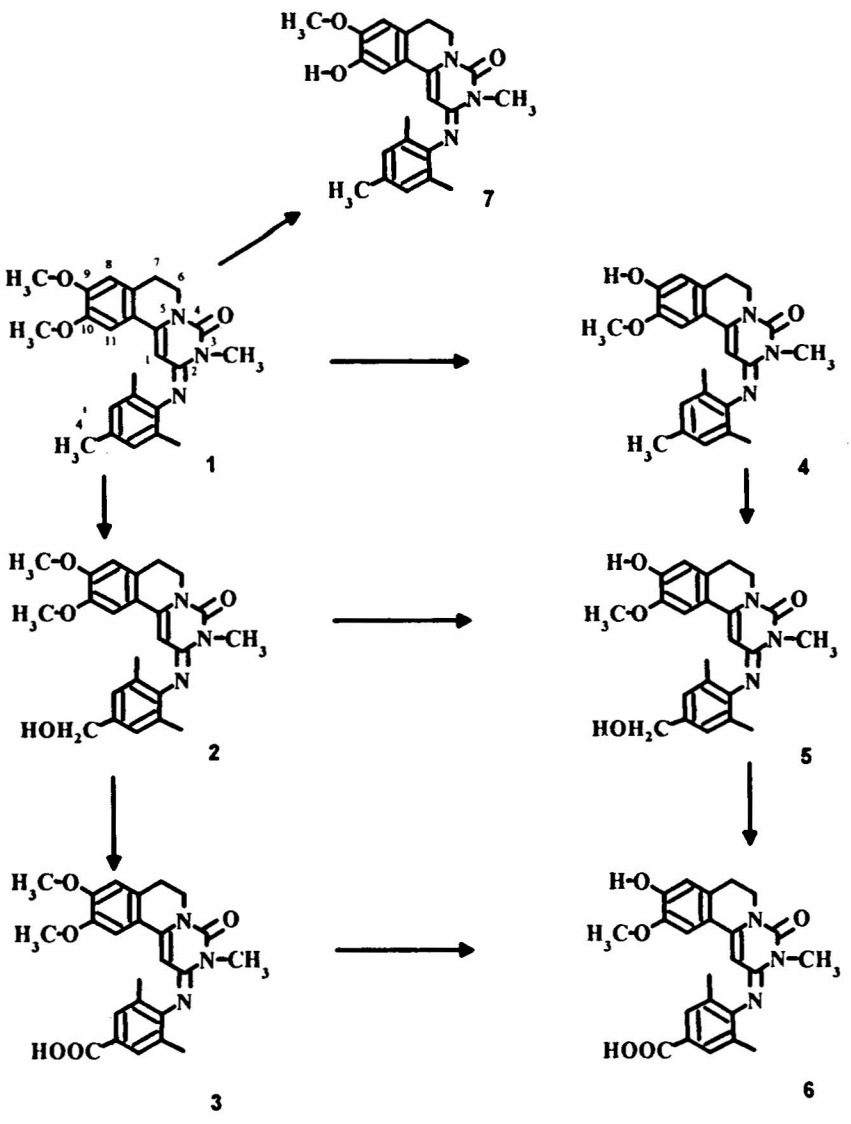
Trequinsin has been discovered by our group[1,2] as a powerful antihypertensive agent possessing excellent platelet antiaggregation properties and stands out as one of the most powerful phosphodiesterase inhibitors. Several papers and a review article[3] have appeared on the molecule. This compound reached the clinical trials [1] (phase 1). The isolation and identification of the six major metabolites (**2-7**) (Scheme I) of trequinsin **1** have been carried out at Hoechst Frankfurt[4].

Literature records several examples[5,6], where all the known (isolated) metabolites of a drug have been synthesised using the regular synthetic approaches. However, we have not come across any report in the literature, of a drug, where all the metabolites were prepared from the parent compound. The biomimetic synthesis of the Metabolites **2-7** has been carried out and forms the subject matter of this paper. The uniqueness of the synthesis is that all the metabolites were made from trequinsin in a manner mimicking chemically the biological pattern of metabolism. The individual metabolically vulnerable centres of the free base of trequinsin molecule **1** were targetted to chemical sequences using specific reagents. The substituents at positions 9 and 4' of **1** are the centres more vulnerable to metabolic attack followed by those at positions 10 and 3.

Results and Discussions

Methoxyl group at position 9 froms a part of the highly extended conjugated system in **1** as compared to the 10-methoxyl group. The 2'- and 6'-methyl groups are sterically more crowded than the 4'-methyl group, which makes position 4', more vulnerable to a chemical transformation. When the 10-methoxy group is converted to the 10-hydroxy group, position 7 of the molecule becomes electron rich. However, no metabolite involving position 7 has been isolated from among the minor unidentified metabolites of **1**. After mapping out the apparent differences in the electronic and stereochemical centres of **1**, a selection of the correct reagents and reaction conditions led to the synthesis of the desired metabolites.

Demethylation of **1** using 65% AcOH–35% HBr (48% aqueous)[7] gave the metabolites **7** and **4** (trace amounts) together with the dihydroxy compound **9** (Scheme II). The structure of **7**, was confirmed by an unambiguous synthesis of the benzylated

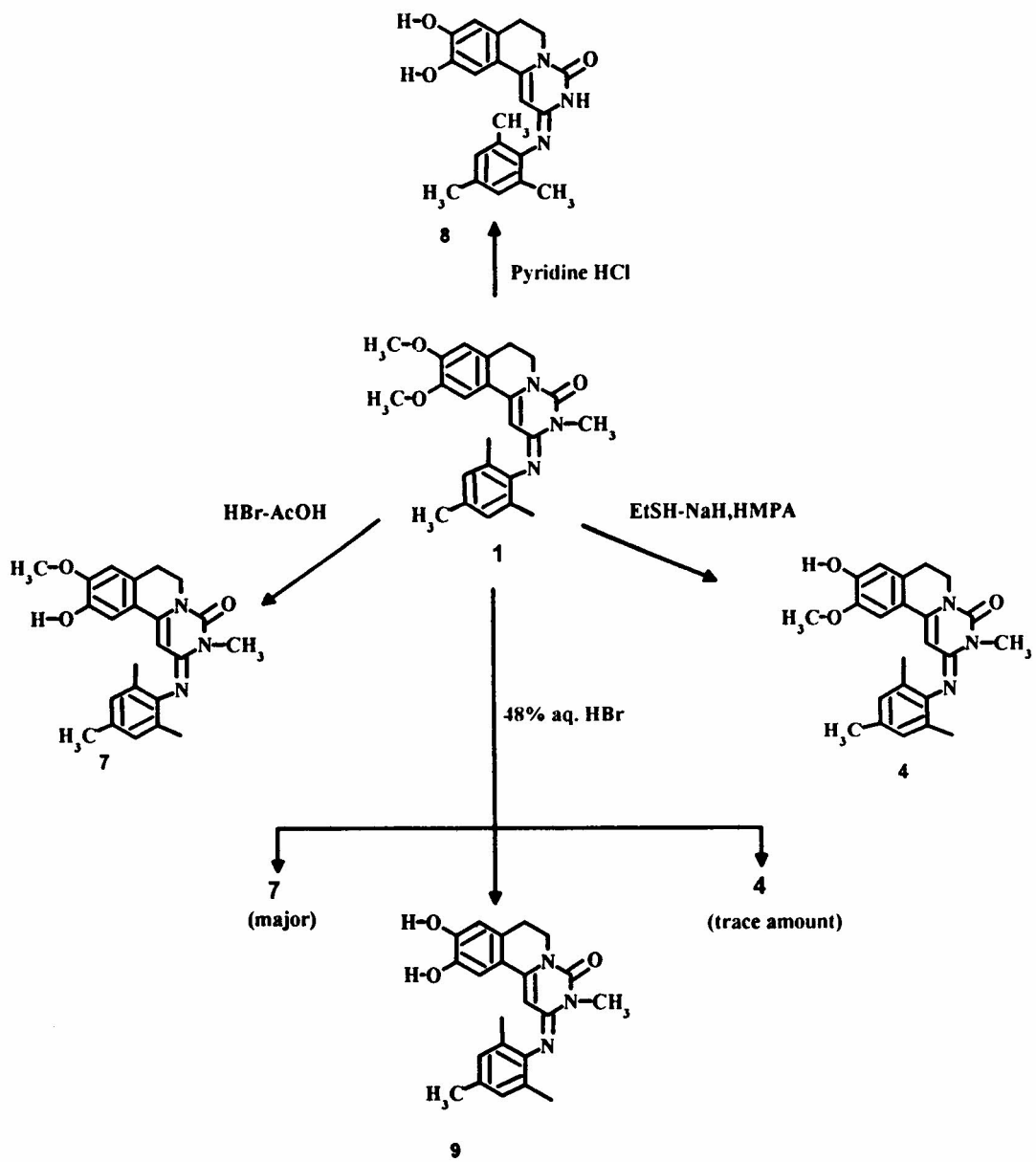


Scheme I

product of **7** viz compound **25** (Scheme III). The 10-hydroxy compound **7** was benzylated to give a compound identical in all respects to compound **25** proving that the assignment of 9-OH and 10-OH groups to compounds **4** and **7** respectively is correct.

Demethylation of **1** using pyridine hydrochloride gave **8** in 65% yield. The 9-OCH_3 group, which has a lower electron density as compared to the 10-OCH_3 group, was demethylated to **4**, using a basic reagent ethylmercaptan-NaH-DMF[8a,b] , in low yields. A replacement of DMF with HMPA gave **4** in 54% yield. An extension of this reaction to metabolite **3**, gave selectively the demethylated metabolite **6** in 48% yield. Trequinsin **1** was also demethylated without affecting the *N*-methyl group using 48% HBr to give **9**. Metabolite **2** was obtained by the selective demethylation of compound **11** (4'-methoxymethyl derivative) using 2*N*-HCl, the rest of the methoxyls and methyl groups remained unaffected.

In an earlier paper[9] the synthesis of an intermediate of one of the major metabolites of **1** using DDQ has been reported. In continuation, herein, the synthesis and reactions of some of the other metabolites are reported. It should be noted that the positions 7 and 4' of the trequinsin molecule are the most likely to be oxidised. The important prerequisite for benzylic oxidation postulated[10], was the formation, with proper orientation, of a charge transfer complex. In order to oxidise position 7 of trequinsin, it was necessary

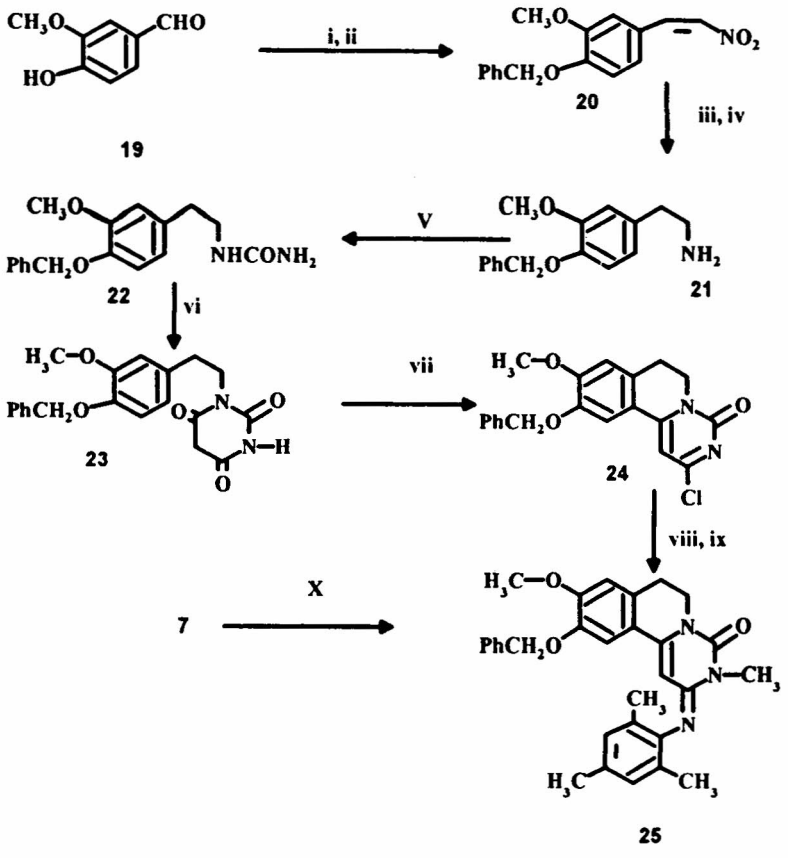


Scheme II

to demethylate 10-methoxy group to the 10-hydroxy metabolite **7**.

As reported in the literature[11], dihydro-isoquinoline undergoes benzylic oxidation using DDQ-MeOH via a methoxylate intermediate, which on thermolytic elimination yields isoquinoline. Extension of this observation to metabolite **7**, using benzene instead of MeOH gave us **16** directly, involving no methoxylated intermediate. In **1** the 4'-methyl group is activated due to the effect of extended conjugation and is susceptible to oxidation using DDQ. On investigating this reaction, it was found that the 4'-methyl group was selectively oxidised, using 1 equivalent of DDQ, to benzylic alcohol **2** (a major metabolite) in low yields, the major product being the DDQ complex **10**. Cleavage of the complex **10** using $ZnCl_2$-MeOH gave the 4'-methoxy methyl compound **11**[9] in 33% yield, which was then selectively demethylated using 2*N* HCl to obtain **2.** To increase the yields of **2**, an attempt was first made to breakup the complex **10** using PTSA-methanol, however **11** and traces of the aldehyde **13** were obtained. BF_3-etherate, silica gel, HCl and sulfuric acid were also used to breakup **10**, but the anhydrous $ZnCl_2$-methanol combination proved to be the most effective agent (Scheme IV).

It was postulated that with two equivalents of



i. $PhCH_2Br,CH_3ONa$ ii, CH_3NO_2, CH_3COONH_4, CH_3COOH iii, $NaBH_4$,aq MeOH,RT.
iv. Al/Hg, THF-H_2O-MeOH. v. KCNO,AcOH, vi. $CH_2(COOEt)_2$,EtONa. vii. $POCl_3$.
viii. mesitylamine ix. CH_3I,K_2CO_3,CH_3COCH_3. x. $PHCH_2Br,K_2CO_3,CH_3COCH_3$.

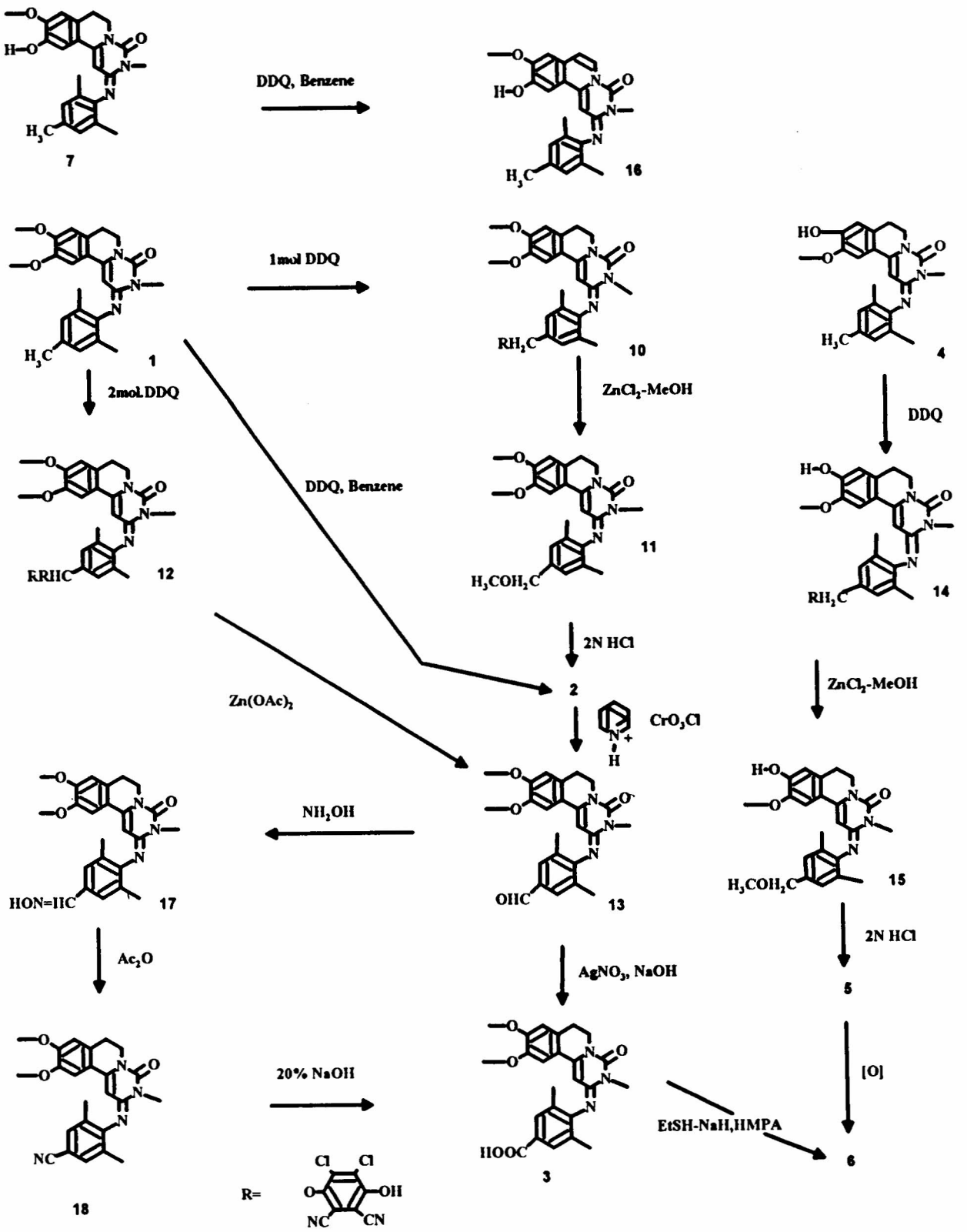
Scheme III

DDQ, **1** should get oxidised to the aldehyde **13**. On investigating the reaction, it was found that the complex **12** was obtained, which was subsequently cleaved using zinc acetate-dioxane to obtain **13**. However, oxidation of the metabolite **2** using pyridinium chlorochromate gave **13** in higher yields. Oxidation of the 9-hydroxy metabolite **4** with two equivalents of DDQ resulted in the formation of the complex **14**, which was subsequently cleaved with $ZnCl_2$-MeOH to obtain the methyl ether **15** and not an aldehyde. The cleavage of the methoxyl group in **15** was achieved using 2*N* HCl to give **5**.

Among the many methods[12-20] reported in the literature, the one using $AgNO_3$[20] in 50% aqueous ethanol and NaOH as oxidising agent helped in the conversion of **13** into the metabolite **3** in 28% yield. Alternatively **13** was first converted into its aldoxime **17** using hydroxylamine hydrochloride[21] in pyridine-ethanol. The aldoxime **17** was then easily dehydrated to the nitrile **18** with acetic anhydride. Hydrolysis of **18** with 20% NaOH–rectified spirit gave **3** (Scheme IV).

Conclusion

We have succeeded in generating "*chemometabolites*" (degradation) of Trequinsin, which parallels the actual metabolites in the biological systems (*All the metabolites of trequinsin have been successfully synthesised from the parent molecule trequinsin itself*); and in the process discovered (i) that the DDQ complex of the metabolites can be broken using $ZnCl_2$–MeOH to the methyl ethers, and (ii) that the bis complex


DDQ, Benzene
1mol DDQ
2mol DDQ
DDQ, Benzene
ZnCl2-MeOH
DDQ
2N HCl
ZnCl2-MeOH
Zn(OAc)2
CrO3Cl
NH2OH
Ac2O
AgNO3, NaOH
2N HCl
20% NaOH
[O]
EtSH-NaH,HMPA
R=
7
16
1
10
4
12
11
14
2
13
17
15
5
18
3
6

Scheme IV

of DDQ could be cleaved using $Zn(OAc)_2$ to obtain an aldehyde.

Experimental Section

General. Melting points were determined using a Kofler hot stage apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian T-60 or JEOL FX-90Q spectrometers, IR spectra on a Perkin-Elmer 157 spectrophotometer using KBr discs, and UV spectra on a Carl Zeiss Specord spectrophotometer using MeOH and MeOH-NaOAc (λ_{max} in nanometers).

9,10-Dimethoxy-2- (2,6-dimethyl-4-hydroxymethyl-phenylimino-3-methyl-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-4-one 2. A solution of trequinsin **1** (free base) (6.06 g, 15 mmoles) and DDQ (3.41 g, 15 mmoles) in benzene (200 mL) was refluxed for 39 hr. Benzene was removed under vacuo and the solid (10 g) obtained was purified over a column of neutral alumina to obtain 0.8 g of a mixture of three compounds. This mixture was rechromatographed to obtain the desired product, which was crystallised from $CHCl_3$-pet. ether (60-80°), yield 0.166 g (2%), m.p. 246-48°;. IR(KBr): 3333, 1692 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.07 (s, 6H, 2'-, and 6'-CH_3), 1.93 (s, 1H, OH), 2.9 (t, *J*=6 Hz, 2H, -CH_2CH_2N), 3.6 (s, 3H, NCH_3), 3.4 (s, 3H, 10-OCH_3), 3.9 (s, 3H, 9-OCH_3); 4.07 (t, *J*=6 Hz, 2H, $-CH_2CH_2N$), 4.6 (s, 2H, 4'$-CH_2O-$), 5.5 (s, 1H, H-1), 6.73, (d, *J*=4 Hz, 2H, Ar–H). Anal. Found: C, 68.25; H, 5.97; N, 10.09. Calcd for $C_{24}H_{27}N_3O_4$: C, 69.39; H, 6.46; N, 9.97%.

9,10-Dimethoxy-2-(2,6-dimethyl-4-carboxy)-phenylimino-3-methyl-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-4-one 3. Procedure A: Compound **13** (0.5 g, 1.19 mmoles) was added to a mixture of $AgNO_3$ (1.8 g, 10.6 mmoles) and NaOH (0.8 g, 20 mmoles) in 30% aqueous C_2H_5OH(30 mL) and the reaction mixture refluxed for 45 hr and neutralised with CH_3COOH. The organic solvent was removed under vacuo, and the residue obtained purified by chromatography over a silica gel column to give **3**, yield: 0.146 g (28%).

Procedure B: Compound **18** (1.1 g, 2.7 mmoles was refluxed in a mixture of 20% aqueous NaOH (2 mL, 0.1 mole) and rectified spirit (40 mL) for 39 hr. The organic solvent was removed under vacuo, water added, the solution chilled, neutralised with AcOH and extracted with EtOAc. The organic extract was washed with water, dried (Na_2SO_4) and the solvent removed under vacuo to obtain the desired solid product which was crystallised from chloroform-pet. Ether (60-80°), yield 0.620 g (53.91%), m.p. 248-50°; IR(KBr): 3570, 2700-2500, 1692, 1639 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.15 (s, 6H, 2'- and 6'-CH_3), 2.87 (t, *J*=6 Hz, 2H, $-CH_2CH_2N$), 3.6 (s, 3H, NCH_3), 3.73 (s, 3H, 10-OCH_3), 3.87 (s, 3H, 9-OCH_3), 4.07 (t, *J*=6 Hz, 2H, $-CH_2CH_2N$), 5.33 (s, 1H, H-1), 6.63 (d, 2H, Ar-H), 7.77 (s, 2H, Ar-H), 7.2-7.4 (1H, br, hump, OH, exchangeable with D_2O), Anal. Found: C, 66.53; H, 6.28; N, 9.78. Calcd for $C_{24}H_{25}N_3O_5$: C, 66.20; H, 5.79; N, 9.65%.

9-Hydroxy-10-methoxy-2-mesitylimino-3-methyl-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-4-one 4. Sodium hydride (2g; 60% dispersion in oil, 50.0 mmoles) was washed with dry benzene, then taken in HMPA (5 mL) in an atmosphere of nitrogen, and chilled. Ethanethiol (10.8 mL, 10.8 mmoles) was added dropwise, and the mixture stirred for 5 min. Compound **1** (1.0 g, 2.5 mmoles) was then added and the mixture stirred at room temperature for 1.5 hr. The reaction mixture was chilled, treated with methanol, water, extracted with EtOAc, dried and concentrated to obtain 678 mg of the crude product, which was purified over a column of basic alumina and crystallised from EtOAc. Yield: 522 mg (54%) m.p. 256-58°. UV (MeOH): 230 and 350 nm, UV (MeOH-NaOAc): 350nm; IR(KBr): 3448, 1678 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.03 (s, 6 H, 2'-,6'-CH_3), 2.27(s, 3H, 4'-CH_3), 2.8 (t, *J*=6 Hz, 2H, $-CH_2CH_2N$), 3.57 (s, 3H, NCH_3), 3.73 (s, 3 H, O-CH_3), 4.0 (*t*, *J*=6 Hz, 2H, CH_2CH_2N), 5.4 (s, 1H, H-1), 6.67 (s, 2H, Ar-H), 6.8 (s, 2H, Ar-H). Anal. Found: C, 70.61; H, 6.25; N, 10.49.Calcd for $C_{23}H_{25}N_3O_3$: C, 70.57; H, 6.44; N, 10.73%.

9-Hydroxy-10-methoxy-2-(2,6-dimethyl-4-hydroxymethyl)phenylimino-3-methyl-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-4-one 5. Compound **15** (1.112 g, 2.6 mmoles) was heated in 2*N* HCl (56 mL) at 90-100°C for 93 hr. The reaction mixture was chilled, basified with liquor NH_3, filtered and the filtrate extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried

(Na_2SO_4) and concentrated under vacuo to obtain a crude solid, which was purified over a column of silica gel and crystallised from EtOH, yield: 0.56 g (52.9%). m.p. 246-48°; IR(KBr): 3175-2985, 1721 cm^{-1}; ^1H NMR (DMSO-d_6): δ 2.03 (s, 6H, 2'-and 6'-CH_3), 2.83 (*t*, *J*=6 Hz, 2H, –CH_2CH_2N), 3.47 (s, 3H, NCH_3), 3.65 (s, 3H, 10 –OCH_3), 3.92 (*t*, *J*=6 Hz, 2H, –CH_2CH_2N), 4.43 (s, 2H, CH_2OH), 5.32 (s, 1H, H-1), 6.70 (d, 2H, Ar-H), 6.98 (s, 2H, Ar-H). Anal Found: C, 67.43; H, 6.06; N, 10.33. Calcd for $C_{23}H_{25}N_3O_4$: C, 67.80; H, 6.19; N, 10.33%.

9-Hydroxy-10-methoxy-2-(2,6-dimethyl-4-carboxy)phenylimino-3-methyl-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-4-one 6. NaH (2 g, 50 mmoles, 60% dispersion in oil) was washed with dry benzene and taken in HMPA (5 mL) in an atmosphere of nitrogen and chilled. Ethanethiol (10 mL, 0.135 moles) was added dropwise and the mixture stirred for 5 min. Compound **3** (1.0 g, 2.3 mmoles) was then added in one lot and the mixture stirred at room temperature for 23 hr. After usual workup, the crude obtained was purified over a column of silica gel, yield 0.472 g (48.76%). m.p. 314-15°. IR(KBr): 3448, 1695, 1639 cm^{-1}; ^1H NMR (Pyridine-d_5) δ 2.25 (s, 6H, 2'- and 6'-CH_3), 2.73 (*t*, *J*=6 Hz, 2H, –CH_2CH_2N), 3.38 (3 H, s, NCH_3), (s, 3H, 10-OCH_3), 4.07 (2H, t, J=6 Hz, -CH_2CH_2N), 5.73 (s, 1H, H-1), 7.13 (s, 2H, Ar-H), 7.48 (s, 1H, Ar-8H), 8.17 (s, 1H, Ar-11H); Anal. Found: C, 65.26; H, 5.29; N, 10.34. Calcd for $C_{23}H_{23}N_3O_5$: C, 65.55; H, 5.50; N, 9.97%.

10-Hydroxy-9-methoxy-2-mesitylimino-3-methyl-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-4-one 7. Compound **1** (52.98 g, 12 moles) was heated in a solution of acetic acid (693 mL, 12.12 moles) and 47% HBr (375 mL, 3.22 moles) at 115°C for 3 hr. Acetic acid was distilled off under vacuo and the residue obtained was chilled, and basified with liquor NH_3 to obtain a yellow solid, which in turn was washed with water, dried (Na_2SO_4) and purified by chromatography over florisil to obtain a solid, which was crystallised from $CHCl_3$-pet. Ether (60-80°), yield 22.8 g (48.59%), m.p. 245-47°; UV λ(MeOH): 230 and 350 nm, UV(MeOH-NaOAc): 230 and 350 nm; IR(KBr): 3390, 1667 cm^{-1}; ^1H NMR ($CDCl_3$): δ2.0 (s, 6H, 2'- and 6'-CH_3), 2.27 (s, 3H, 4'-CH_3), 2.83 (t, *J*=6 Hz, 2H, -CH_2CH_2N), 3.57 (s, 3H, NCH_3), 3.87 (s, 3H, O-CH_3), 4.03 (t, *J*=6 Hz, 2H, -CH_2CH_2N), 5.47 (s, 1H, H-1), 6.6 (s, 1H, Ar-H), 6.83 (s, 3H, Ar-H). Anal. Found: C, 70.29; H, 6.39; N, 10.8. Calcd for $C_{23}H_{25}N_3O_3$ C, 70.57; H, 6.44; N, 10.73%.

9-10-Dihydroxy-2-mesitylimino-6,7-dihydro-4*H*-pyrimido[6,1-*a*]isoquinolin-4-one 8. Trequinsin **1** (1.0 g, 2.47 mmoles) was refluxed with pyridine hydrochloride (10g, 87 mmoles) for 20 min. The reaction mixture was cooled, and treated with chilled water to obtain a clear solution. The desired product that separated out was crystallised from DMF-H_2O, yield 0.59 g (65.85%). m.p. 280° (dec); IR(KBr): 3333, 3030, 1639, and 1282 cm^{-1} ; ^1H NMR (DMSO): δ 2.13 (s, 6H, 2'- and 6'-CH_3), 2.27 (s, 3H, 4'-CH_3), 2.8(t, *J*=6 Hz, 2H, -CH_2CH_2N), 3.87(t, *J*=6 Hz, 2H, -CH_2CH_2N), 5.2 (s, 1H, H-1), 6.57-7 (m, 4H, Ar-H); Anal. Found: C, 68.01; H, 5.93; N, 11.94. Calcd for $C_{21}H_{21}N_3O_3$: C, 67.73; H, 5.95; N, 11.28%.

9-10-Dihydroxy-2-mesitylimino-3-methyl-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-4-one 9. Tequinsin **1** (0.5 g, 1.23 mmoles) was refluxed in 48% aqueous HBr (5 mL) for 2 hr to obtain colorless crystals, which were filtered, washed with water, dried (Na_2SO_4) and crystallised from methanol to give 9, yield 0.356 g (63.01%). m.p. 300-302°;. IR(KBr): 3125, 1721 cm^{-1}; ^1H NMR (DMSO): δ 1.9 (s, 6H, 2'- and 6'-CH_3), 2.17 (s, 3H, 4'-CH_3), 2.67 (*t*, *J*=6 Hz, 2H, -CH_2CH_2N), 3.33 (s, 3H, NCH_3), 3.77 (t, *J*=6 Hz, 2H, -CH_2CH_2N), 5.03 (s, 1H, H-1), 6.38 (s, 2H Ar-H), 6.57 (s, 2H, Ar-H). Anal. Found: C, 57.70; H, 5.09; N, 9.31; Br, 17.25. Calcd. for $C_{22}H_{24}N_3O_3Br$: C, 57.64; H, 5.28; N, 9.16, Br, 17.45%.

9,10-Dimethoxy-2-(2,6-dimethyl-4-methoxymethyl)phenylimino-3-methyl-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-4-one 11. Compound **1** (20 g, 0.049 moles) was taken in benzene (600 mL) and DDQ (11.3 g, 0.049 mole) added to it slowly with stirring. The reaction mixture was refluxed for 20 hr and the organic solvent removed **10** (30.56 g) under vacuo to obtain a crude solid. Titration of the solid with pet. ether yielded a 1:1 complex of **1**-DDQ (30.56 g). This complex (0.048 moles) was taken in dry methanol (1 L) to which was added fused and powdered $ZnCl_2$ (52g, 0.382 mole), and the mixture refluxed for 43 hr.

The solvent was removed under vacuo and the residue obtained was treated with chilled water, basified with 30% NaOH and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4)and the organic solvent removed under vacuo to obtain the desired product which was purified over a column of silica gel and crystallised from EtOH-pet. ether, yield: 6.95 g (32.3%), m.p. 160-62°; IR(KBr): 1700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.1 (s, 6H, 2'- and 6'-CH_3), 2.88 (t, *J*=6 Hz, 2H, -CH_2CH_2N), 3.37(s, 3H, -CH_2OCH_3), 3.6(s, 3H, NCH_3), 3.73(s, 3H, 10-OCH_3), 3.87(s, 3H, 9-OCH_3), 4.07(t, *J*=6 Hz, 2H, -CH_2CH_2N), 4.37 (s, 2H, CH_2OCH_3), 5.43 (s, 1H, H-1), 6.67 (d, *J*=4 Hz, 1H, Ar-H), 7.02 (s, 2H, Ar-H); Anal. Found: C, 65.26; H, 5.29; N, 10.34. Calcd. For $C_{25}H_{29}N_3O_4$: C, 65.55; H, 5.50; N, 9.97%.

9,10-dimethoxy-2-(2,6-dimethyl-4-formyl)-phenylimino-3-methyl-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-4-one 13. Procedure A. Compound **1** (6.06 g, 0.015 mole) was taken in benzene (200 mL) and DDQ (6.81 g, 0.03 mole) added to it slowly with stirring. The reaction mixture was refluxed for 43 hr and the organic solvent subsequently removed under vacuo to obtain a crude solid. Trituration of the solid with pet. ether yielded a 1:2 complex **12** (12.8 g) of **1**-DDQ. This complex (5 g, 0.005 mole) was taken in dioxane (200 mL) to which was added $Zn(OAc)_2$ (10.0 g, 0.05 mole), and the mixture refluxed for 43 hr. and filtered.The filtrate was removed under vacuo to obtain the desired product which was purified over a column of silica gel and crystallised from CH_2Cl_2-EtOH, yield 0.5 g (8.3%). m.p. 241-43°C. IR(KBr): 2941, 2857, 2717, 1709-1695, 1642 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.13 (s, 6H, 2' and 6'-CH_3), 2.88 (*t*, *J*=6 Hz, 2H, -CH_2CH_2N), 3.57 (s, 3H, NCH_3), 3.72 (s, 3H, 10-OCH_3), 3.85 (s, 3H, 9-OCH_3), 4.05 (*t*, *J*=6 Hz, 2H, -CH_2CH_2N), 5.28 (s, 1H, H-1), 6.62 (s, 2H, Ar-H), 7.52 (s, 2H, Ar-H), 9.0 (s, 1H, CHO); Anal. Found: C, 69.32; H, 6.42; N, 10.25. Calcd for $C_{24}H_{25}N_3O_4$: C, 68.73; H, 6.01; N, 10.02%.

Procedure B: To a suspension of pyridinium chlorochromate(4.025 g, 18.7 mmoles) in CH_2Cl_2 was added a CH_2Cl_2 solution of **2** (5.25 g, 12.47 mmoles) in one lot and the reaction mixture stirred at room temperature for 2 hr. The organic solvent was removed under vacuo and the crude obtained was purified over a column of silica gel, yield 3.26 g (62.33%)%.

9-Hydroxy-10-methoxy-2-(2,6-dimethyl-4-methoxymethyl)phenylimino-3-methyl-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-4-one 15. Compound **4** (5.055 g, 0.013 mole) was taken in benzene (300 mL) and DDQ (5.68 g, 0.025 mole) added to it slowly with stirring. The reaction mixture was refluxed for 20 hr and the organic solvent removed under vacuo to obtain a crude solid. Trituration of the solid with pet. ether yielded a 1:2 complex **14** (30.56 g) of **4**-DDQ. This complex (2.47 g, 0.0029 mole) was taken in dry methanol (80 mL) to which were added fused and powdered $ZnCl_2$ (2.72 g, 0.02 mol), and the mixture was refluxed for 20 hr. The solvent was removed under vacuo, and the residue obtained was treated with chilled water, basified with liquor NH_3 and extracted with EtOAc. The extract was washed with water, dried (Na_2SO_4) and the organic solvent removed under vacuo to obtain the desired product which was purified over a column of silica gel, yield: 0.51 g (8.9%). m.p. 220-22° (dec, of hydrochloride); IR(KBr): 3571-3125 , 1695 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.08 (s, 6H, 2' and 6'-CH_3), 2.83 (*t*, *J*=6 Hz, 2H, -CH_2CH_2N), 3.37 (s, 3H, -CH_2OCH_3), 3.58 (s, 3H, NCH_3), 3.75 (s, 3H, 10-OCH_3), 4.0 (*t*, *J*=6 Hz, 2H, -CH_2CH_2N), 4.37 (s, 2H, CH_2OCH_3), 5.40 (s, 1H, H-1), 6.67 (s, 2H, Ar-H), 7.0 (s, 2H, Ar-H). Anal. Found: C, 62.58; H, 6.4; N, 9.38; Cl, 7.91. Calcd. for $C_{24}H_{28}N_3O_4Cl$: C, 62.94; H, 6.16; N, 9.18; Cl, 7.74%.

9-Methoxy-10-hydroxy-2-mesitylimino-3-methyl-3,4-dihydro-2*H*-pyrimido[6,1-*a*]isoquinolin-4-one 16. Compound **7** (3.9 g, 0.01 mole) was taken in benzene (200 mL) and DDQ (2.27 g, 0.01 mole) added to it slowly with stirring. The reaction mixture was refluxed for 3 hr and the organic solvent removed under vacuo to obtain a crude solid, which was treated with chilled water and acidified with 2*N* HCl. This acidic solution was extracted with EtOAc. The aqueous portion was basified with 15% aqueous NaOH and extracted with $CHCl_3$. The organic extract was washed with water, dried (Na_2SO_4) and the solvent removed under vacuo to obtain the desired product which was purified over a column of basic alumina, yield 0.628 g. The free base was converted into the

hydrochloride and crystallised from ethanol-ether, yield 0.605 g (14.2%). m.p. 268-70°. IR(KBr): 1727 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.28 (s, 6H, 2'- and 6'-CH_3), 2.45 (s, 3H, 4'-CH_3), 3.88 (s, 3H, NCH_3), 4.02 (s, 3H, 9-OCH_3), 5.8 (s, 1H, H-1), 7.03 (d, *J*=7 Hz, 1H, H-7), 7.2 (d, *J*=7 Hz, 4H, Ar-H), 8.27 (d, *J*=7 Hz, 1H, H-6). Anal. Found: C, 63.16; H, 5.43; N, 9.61; Cl, 8.07. Calcd. for $C_{23}H_{24}N_3O_3Cl.1/2H_2O$: C, 63.66; H, 5.76; N, 9.68; Cl, 8.17%.

9,10-Dimethoxy-2-(2,6-dimethyl-4-aldehyde oxime)phenylimino-3-methyl-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-4-one 17. A mixture of aldehyde **13** (2.5 g, 0.006 mole) and hydroxylamine hydrochloride (2.5 g, 0.036 mole) taken in ethanol (25 mL) and pyridine (2.5 mL, 0.031 mole) was refluxed for 16 hr. The mixture was stripped off ethanol under vacuo and treated with water to obtain the desired product which was filtered, washed with water and dried(Na_2SO_4), yield 2.53 g (97.68%). m.p. 231-33°. IR(KBr): 3448, 3226, 1724, 1695, 1653cm^{-1}; ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 2.18 (s, 6H, 2' and 6'-CH_3), 2.98 (t, *J*=6 Hz, 2H, -CH_2CH_2N), 3.72 (s, 3H, NCH_3), 3.80 (s, 3H, 10-OCH_3), 3.90 (s, 3H, 9-OCH_3), 4.13 (*t*, *J*=6 Hz, 2H, -CH_2CH_2N), 5.45 (s, 1H, H-1), 6.70 (d, 2H, Ar-H), 7.4 (s, 2H, Ar-H), 8.0 (s, 1H, CH of aldoxime)

9,10-Dimethoxy-2-(2,6-dimethyl-4-cyano)phenylimino)-3-methyl-3,4,6,7-tetrahydro-2*H*-pyrimido[6, 1-*a*] isoquinolin-4- one 18. A solution of oxime **17** (2.5 g, 0.0058 mole) in acetic anhydride (30 mL, 0.318 mole) was refluxed for 2 hr. On cooling the desired product crystallised out. It was filtered and washed with ethanol, yield: 2.06g (85.83%). m.p. 273-75°. IR(KBr): 2227, 1698 cm^{-1}; ^1H NMR (DMSO-d_6): δ 1.85 (s, 6H, 2' and 6'-CH_3), 2.73 (t, *J*=6 Hz, 2H, -CH_2CH_2N), 3.28 (s, 3H, NCH_3), 3.47 (s, 3H, 10-OCH_3), 3.63 (s, 3H, 9-OCH_3), 3.76 (t, *J*=6 Hz, 2H, -CH_2CH_2N), 5.18 (s, 1H, H-1), 6.75 (d, 2H, Ar-H), 7.38 (s, 2H, Ar-H).

10-Benzyloxy-9-methoxy-2-mesitylimino-3-methyl-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinolin-4-one 25. A mixture of **7** (0.15 g, 0.38 mmole), benzylbromide (0.06 mL, 0.5 mmole) and K_2CO_3 (0.08 g, 0.57 mmole) taken in acetone was refluxed for 2hr. The mixture was cooled treated with water and extracted with $CHCl_3$ to obtain the desired product, which was crystallised from acetone-pet.ether in the form of yellow needles, yield 0.12 g (65.2%). m.p. 144-46o; IR(KBr): 1640, 1685 cm^{-1}; ^1H NMR($CDCl_3$): δ2.05 (s, 6H, 2' and 6'-CH_3), 2.35 (s, 3H, 4'-CH_3), 2.85 (t, *J*=6 Hz, 2H, -CH_2CH_2N), 3.57 (s, 3H, NCH_3), 3.9 (s, 3H, O-CH_3), 4.03(t, J=6 Hz, 2H, -CH_2CH_2N), 5.05 (s, 2H, OCH_2), 5.47 (s, 1H, H-1), 6.7 (s, 1H, Ar-H), 6.95 (s, 3H, Ar-H), 7.27 (m, 5H, Ar-H). Anal. Found: C, 75.27; H, 6.59; N, 8.48. Calcd. for $C_{30}H_{31}N_3O_3$: C, 74.84; H, 6.44; N, 8.73%.

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