Unexpected Formation of 1,2-Dihydro-2-azolyl- and azinylisoquinolines by the Reduction of the Corresponding Isoquinolinium Salts with Sodium borohydride in Methanol

Ibolya Prauda, Mária Tóth-Lauritz and József Reiter

Egis Pharmaceuticals Ltd., P. O. Box 100, H-1475 Budapest, Hungary

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Dedicated to Professor Josef Michl on the occasion of his 65th birthday

The reduction of different 2-azolyl- and azinylisoquinolinium salts with sodium borohydride in methanol was studied. Surprisingly, contrary to what is found in the literature 1,2-dihydroisoquinoline derivatives were obtained. Their formation was attributed to the electron withdrawing character of the heterocyclic ring in position 2 of the isoquinolinium moiety. This was corroborated by synthesis and reduction of differently substituted 2-phenyl- and 2-methylisoquinolinium salts.

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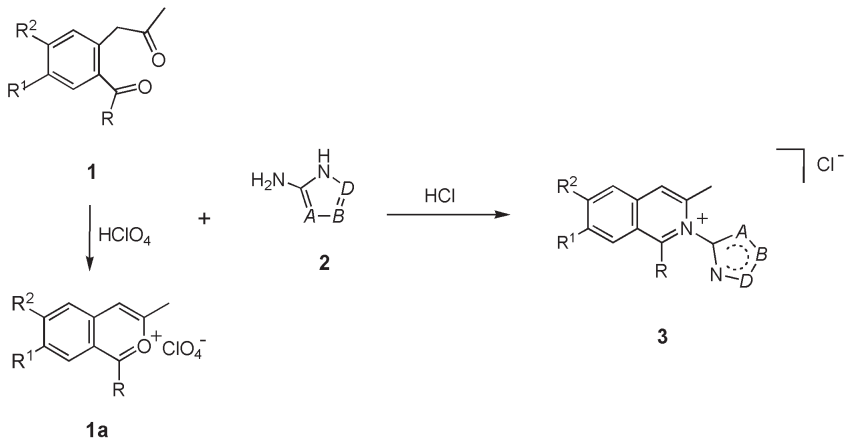
Recently, we have reported on the synthesis of 2-(pyrazol-3-yl)- [**3**, *A* = *B* = CH, *D* = NH], 2-(1,2,4-triazol-3-yl)- [**3**, *A* = N, *B* = C-R", *D* = NH], and 2-tetrazolyl- [**3**, *A* = *B* = N, *D* = NH] isoquionolinium salts [1,2] by the reaction of *ortho*-acylphenylacetones (**1**) or the pyrylium salts (**1a**) formed from them with perchloric acid and the corresponding aminoazoles (**2**) (Scheme 1).

Scheme 1



Some of these derivatives moderately but rather selectively inhibited the $5HT_7$ receptors showing promising CNS activity. To help them to penetrate through blood-brain barrier we decided to remove their ionic character by reduction.

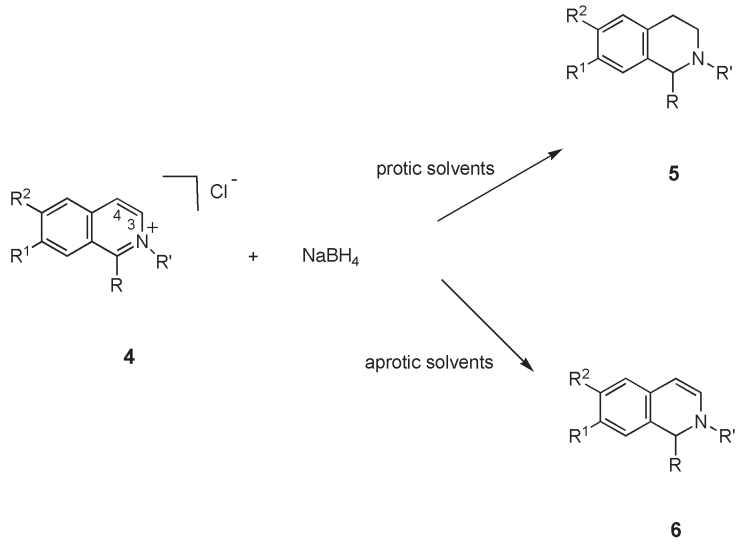
It was known [3,4] that the isoquinolinium salts (**4**) were reduced with sodium borohydride in protic solvents like water, methanol, ethanol, *etc*., to 1,2,3,4-tetrahydroisoquinolines (**5**) while in aprotic solvents like anhydrous pyridine or dimethylformamide to 1,2-dihydroisoquinolines (**6**) (Scheme 2). However, electron withdrawing groups in position 3 [5,6] or 4 [7,8] of the isoquionolinium moiety stopped the reduction at the 1,2-dihydroisoquinoline (**6**) stage even in protic solvents like methanol or ethanol.

Surprisingly, when reducing the 6,7-dialkoxy-3-methyl-1-R-2-(5-substituted-1,2,4-triazol-3-yl)isoquinolinium chlorides (**3a**, *A* = N, *B* = C-R", *D* = NH) with excess of sodium borohydride in methanol only the corresponding 1,2-dihydroisoquinolines **8a** (*A* = N, *B* = C-R", *D* = NH) were formed in good yield (see Table I, for their spectral data see Table II) (Scheme 3).

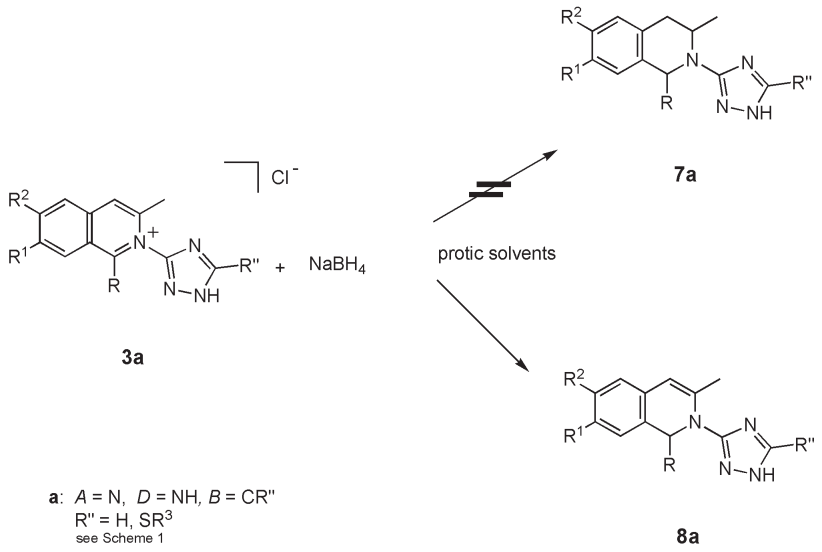
To study further this unexpected reaction it was performed also with 2-pyrazolyl- [**3b**, *A* = CH, *B* = C-R'", *D* = NH], 2-imidazolyl- [**3c**, *A* = NH, *B* = *D* = CH] and 2-tetrazolyl- [**3d**, *A* = *B* = N, *D* = NH] isoquinolinium salts prepared mostly for this purpose (see Table III, for their spectral data see Table IV) yielding again only the corresponding 1,2-dihydro-derivatives **8b** (*A* = CH, *B* = C-R'", *D* = NH), **8c** (*A* = NH, *B* = *D* = CH) and **8d** (*A* = *B* = N, *D* = NH), respectively (see Table I, for their spectral data see Table II) (Scheme 4).

To extend the scope of this unusual reduction it was performed also with azinyl-, namely the 3-pyridyl- (**9a**, *E* = *G*

Scheme 2



Scheme 3



= CH, *F* = N) and 2-pyridazinyl- (**9b**, *E* = N, *F* = NH, *G* = C=O) derivatives (Table V, for their spectral data see Table VI) having six membered heteroring in position 2 of the isoquinolinium moiety to yield again 1,2-dihydroisoquinolines **11a** (*E* = *G* = CH, *F* = N) and **11b** (*E* = N, *F* = NH, *G* = C=O) (Scheme 5).

It is worth mentioning that the 1-(3-chlorophenyl)-6,7-dimethoxy-3-methyl-2-(pyridazin-6(1*H*)-one-3-yl)isoquinolinium perchlorate (**9b)** was obtained in a very sluggish reaction of 1-(3-chlorophenyl)-6,7-dimethoxy-3-methylpyrrilium perchlorate (**1a**, R = 3-chlorophenyl, R^1 = R^2 = methoxy) and 3-amino-6-chloropyridazine carried out in acetic acid. From the reaction mixture besides **9b** and the unreacted **1a** (R = 3-chlorophenyl, R^1 = R^2 = methoxy) only the ring opened product of **1a**, namely the phenylacetone derivative **1** (R = 3-chlorophenyl, R^1 = R^2 = methoxy) could be isolated. However, the hydrolysis of the pyridazine chlorine atom to the corresponding hydroxy group in boiling acetic acid is not so surprising as it was known [9] that the 3-substituted-amino-6-chloropyridazines hydrolyses in acidic media to the corresponding 6-hydroxy derivatives appearing as amides.

As the positions 3 and 4 of the isoquinolinium moiety

Table I

Synthetical and' Analytical Data of the *N*-Azolyl-1,2-dihydroisoquinolines **8a-d**

Comp.	*A B D*	R	R^1	R^2	R"/R"'	Yield %	Method Temp. (°C)	Mp (°C) (cryst. from)	Molecular formula (MW)	Analysis % Calcd./Found C	H	N	S	Cl	Starting material
8a/1	N CR" NH	4-Methyl-phenyl	Methoxy	Methoxy	H	95	A 25	183-186 (EtOAc)	$C_{21}H_{22}N_4O_2$ (362.44)	69.59 69.64	6.12 6.21	15.46 15.27			**3a/1**
8a/2	N CR" NH	4-Methyl-phenyl	Methoxy	Methoxy	Ethylthio	70	A 25	172-173 (EtOAc)	$C_{23}H_{26}N_4O_2S$ (422.55)	65.38 65.06	6.20 6.28	13.26 13.03	7.59 7.61		**3a/2**
8a/3	N CR" NH	4-Methyl-phenyl	Methoxy	Methoxy	*3*-(*N*,*N*-dimethylamino) propylthio	83	A 25	178-180 (AcN/ MeOH)	$C_{26}H_{33}N_5O_2S$ (479.65)	65.11 64.87	6.93 7.08	14.60 14.38	6.68 6.79		**3a/3**
8a/4	N CR" NH	4-(2-Propyl)-phenyl	Methoxy	Methoxy	3-[4-(3-chloro-phenyl)-piperazin-1-yl]propylthio	68	B 0-10	99-101 (MeOH)	$C_{36}H_{43}ClN_6O_2S$ (659.30)	65.58 65.41	6.57 6.65	12.75 12.57	4.86 4.94	5.38 5.35	**3a/4**
8a/5	N CR" NH	4-Methyl-phenyl	Methoxy	Methoxy	3-[4-(2-pyrimidinyl)piperazin-1-yl]propylthio	70	A [a] 0-10	191-194 (MeOH)	$C_{32}H_{38}N_8O_2S$ (598.78)	64.19 63.88	6.40 6.52	18.71 18.54	5.35 5.21		**3a/5**
8a/6	N CR" NH	4-Nitrophenyl	Methoxy	Methoxy	2-[(2,3-dihydrobenzo-dioxan-5-yl) oxy]ethylthio	89	A [a] 0-10	182-185 (EtOAc/Di isopropyl ether)	$C_{30}H_{29}N_5O_7S$ (603.66)	59.69 59.50	4.84 5.01	11.60 11.57	5.31 5.18		**3a/6**
8a/7	N CR" NH	3,4-Dichloro-phenyl	Methoxy	Methoxy	3-[4-(3,4-dimethyl-phenyl)piperazin-1-yl]propylthio	63	B [a] 0-10	88-92 (EtOAc)	$C_{35}H_{40}Cl_2N_6O_2S$ •HCl (716.18)	58.70 58.52	5.77 5.41	11.73 11.57	4.48 4.34	14.85 14.91	**3a/7**
8a/8	N CR" NH	Methyl	Methoxy	Methoxy	Methylthio	75	A [a] 25	83-86 [b]	$C_{16}H_{20}N_4O_2S$ (332.43)	57.81 57.52	6.06 6.21	16.85 16.65	9.65 9.46		**3a/8** Lit. [2]
8b/1	CH CR"' NH	4-Methyl-phenyl	Methoxy	Methoxy	H	56	A 5-25	155-158 (2-PrOH)	$C_{22}H_{23}N_3O_2$ (361.45)	73.11 73.04	6.41 6.26	11.63 11.31			**3b/1** Lit. [1]
8b/2	CH CR"' NH	4-Nitrophenyl	Methoxy	Methoxy	H	59	A 5-25	175-178 (AcN)	$C_{21}H_{20}N_4O_4$ (392.42)	64.28 63.95	5.14 5.05	14.28 14.03			**3b/2** Lit. [1]
8b/3	CH CR"' NH	3-Chloro-phenyl	Methylenedioxy		Methyl	61	A 5-25	152-155 (2-PrOH)	$C_{21}H_{18}ClN_3O_2$ (379.85)	66.40 66.21	4.78 5.01	11.06 10.84		9.33 8.98	**3b/3** Lit. [1]
8c/1	NH CH CH	4-Nitrophenyl	Methoxy	Methoxy	H	53	A 5-25	225-228 (AcN)	$C_{21}H_{20}N_4O_4$ (392.42)	64.28 63.96	5.14 5.13	14.28 14.01			**3c/1**
8c/2	NH CH CH	3,4-Dichloro-phenyl	Methoxy	Methoxy	H	65	A 5-25	166-169 [b]	$C_{21}H_{19}Cl_2N_3O_2$ (416.31)	60.59 60.55	4.60 4.69	10.09 10.02		17.03 17.28	**3c/2**

Table I (continued)

Comp.	A	R	R^1	R^2	R''/R'''	Yield %	Method Temp. (°C)	Mp (°C) (cryst. from)	Molecular formula (MW)	Analysis % Calcd./Found C	H	N	S	Cl	Starting material
	B														
	D														
8d/1	N	4-Chloro-	Methoxy	Methoxy	-	91	C	209-212	$C_{19}H_{18}ClN_5O_2$	59.45	4.73	18.25		9.24	**3d/1**
	N	phenyl						(EtOAc)	(383.84)	59.33	4.65	18.12		9.31	Lit. [1]
	NH						60								
8d/2	N	3,4-Dichloro-	Methoxy	Methoxy	-	88	C	200-203	$C_{19}H_{17}Cl_2N_5O_2$	54.56	4.10	16.74		16.95	**3d/2**
	N	phenyl						(EtOAc/Di	(418.29)	54.43	4.17	16.50		17.11	Lit. [1]
	NH						60	isopropyl ether)							
8d/3	N	4-Methoxy-	Methoxy	Methoxy	-	49	C	206-209	$C_{20}H_{21}N_5O_3$	63.31	5.58	18.46			**3d/3**
	N	phenyl						(AcN)	(379.42)	63.09	5.52	18.64			Lit. [1]
	NH						60								

[a] The reaction mixture was diluted with a mixture of water and 0.1 *M* hydrochloric acid; [b] Raw product that was analitically pure enough.

were in our derivatives **3a-d** and **9a-b** not substituted with electron withdrawing substituents, moreover the methyl group in position 3 is rather electron donating one of the reason for stopping the reductions in the 1,2-dihydroisoquinoline stage should be the electron withdrawing character of the azole or azine rings in position 2 stabilising through the conjugated double bond the 1,2-dihydroisoquinoline moiety.

To test this idea the corresponding 2-phenylisoquinolines (**12a-e**) having both, electron withdrawing and donating groups on the phenyl moiety were synthesised by route shown on Scheme 1 (see Table V, for their spectral data see Table VI) and subjected to sodium borohydride reduction in methanol (Scheme 6). As expected, those derivatives that had strong electron withdrawing groups on the phenyl moiety (**12a**, R^4= 4-chloro, **12b,** R^4 = 3-nitro) even using excess of sodium borohydride were reduced again to 1,2-dihydroisoquinolines **14a** and **14b** while those derivatives that had electron donating groups on the phenyl moiety (**12d**, R^4 = 2-hydroxy, **12e**, R^4 = 3-methoxy, R^5 = 4-methoxy) were reduced to the diastereomeric mixtures of the 1,2,3,4-tetrahydro-isoquinoline derivatives **13d** and **13e**. The differentiation between *cis* and *trans* configurations was made by irradiating the proton at position 1 of the isoquinoline ring causing a DNOE enhancement in case of *cis* derivatives (both phenyl and methyl groups are equatorial) on the proton 3, while in case of *trans* arrangement (phenyl group is equatorial and methyl group is axial) at 3-methyl protons. This is in agreement with the proposal of Mirza [10] and discussed also by A. Pelter and K. Smith [11], assuming protonation of the 1,2-dihydroisoquinoline moiety by the protic solvent at position 4 yielding 1,4-dihydroisoquinolinium salts **15** that could be further reduced by sodium borohydride (Scheme 7). Protonation at position 4 should be enabled by electron donating groups in position 2 while the electron withdrawing groups should prevent it.

Derivative **12c** (R^4 = 4-methyl, R^5 = H) having a *para*-methyl group on the phenyl ring most probably balancing its electron withdrawing character depending on the reaction time, yields both the 1,2,3,4-tetrahydroisoquinoline (**13c**) and the 1,2-dihydroisoquinoline (**14c**) derivatives. The rate of the reduction of **12c** was monitored by HPLC-MS which showed that the reduction to 1,2-dihydroisoquinoline (**14c)** is very rapid. It is complete within 1-3 minutes. On the other hand the further reduction of **14c** to the 1,2,3,4-tetrahydroisoquinoline (**13c**) is slow and requires hours. This is again in agreement with the Mirza's proposal [10] which requires protonation at position 4 accompanied by a shift of the double bond to yield intermediate **15**.

The final proof of the electron withdrawing requirement of the substituent in position 2 of the isoquinolinium salts to stop their reduction at the 1,2-dihydro stage was pro-

Table II

Pmr and cmr Spectral Data of Derivatives **8a-d**

Comp.	H-1 H-4	H-5 H-8	R	R"/R"'	CH_3-3 R^1, R^2 other	C-1 C-3	C-4 C-4a	C-5 C-6	C-7 C-8	C-8a R^1, R^2	R	R"	other
8a/1	6.33 s 5.89 s [a]	6.64 s 6.73 s	2.29 (s, 3H) 7.05 (d, 2H, J = 8.1 Hz) 7.17 (d, 2H, J = 8.1 Hz)	7.89 (s, 3H)	2.21 (d, J = 0.7 Hz) 3.85 s 3.88 s	62.5 134.3 [a]	110.2 125.2	107.4 148.4	147.3 111.2	123.4 55.9 56.1	20.0 126.5, 128.9 136.9, 138.8	-	21.0 143.8 160.8
8a/2	6.34 s 5.87 s [a]	6.63 s 6.71 s	2.28 (s, 3H) 7.05 (d, 2H, J = 8.2 Hz) 7.18 (d, 2H, J = 8.3 Hz)	1.40 (t, 3H, J = 7.3 Hz) 3.12 (q, 2H, J = 7.3 Hz)	2.19 s 3.85 s 3.87 s	62.0 134.1 [a]	110.3 125.2	107.5 148.4	147.3 111.0	123.5 55.9 56.1	21.0 126.8, 128.7 136.7, 139.0	15.0, 27.1	20.2 153.7 160.1
8a/3	6.35 s 5.82 s [a]	6.61 s 6.73 s	2.27 (s, 3H) 7.03 (d, 2H, J = 8.0 Hz) 7.17 (d, 2H, J = 8.0 Hz)	1.97 (m, 2H) 2.31 (s, 6H) 2.55 (m, 2H) 3.17 (m, 2H)	2.21 s 3.84 s 3.86 s	61.8 135.3 [a]	110.3 125.6	107.4 148.3	147.1 110.5	123.5 55.8 56.0	21.0 125.6, 126.9 128.6, 135.3 136.4, 139.5	20.2, 20.9 27.6, 29.9	20.4 153.2 162.9
8a/4	6.33 s 5.81 s [a]	6.61 s 6.73 s	1.18 (d, 6H J = 6.4 Hz) 2.82 (h, 1H, J = 6.4 Hz) 7.07 (d, 2H, J = 8.4 Hz) 7.16 (d, 2H, J = 8.4 Hz)	2.09 (m, 2H) 2.63-2.68 (m, 6H) 3.08-3.19 (m, 2H) 3.31 (t, 4H, J = 4.8 Hz) 6.83 (dd, 1H, J = 2.0 and 6.0 Hz), 6.87 (dd, 1H, J = 2.0 and 6.4 Hz), 6.89 (d, 1H, J = 2.0 Hz), 7.19 (dd, 1H, J = 6.0 and 6.4 Hz)	2.21 s 3.82 s 3.85 s	61.9 135.0 [a]	110.3 122.8	104.7 147.4	147.1 107.3	123.5 56.1 57.1	23.6, 23.9 33.6 125.4, 126.0 130.0, 139.7	26.9, 29.9 48.3, 52.4 55.9 113.8, 115.7 119.6, 130.0 134.9, 148.3	20.5 152.0 162.9
8a/5	6.35 s 5.82 s [a]	6.62 s 6.74 s	2.27 (s, 3H) 7.03 (d, 2H, J = 8.2 Hz) 7.16 (d, 2H, J = 8.0 Hz)	2.13 (m, 2H), 2.75 (m, 6H), 3.16 (m, 2H) 4.08 (m, 4H), 6.55 (t, 1H, J = 4.7 Hz), 8.33 (d, 2H, J = 4.8 Hz)	2.22 s 3.85 s 3.86 s	61.8 135.1 [a]	110.5 123.6	107.5 148.4	147.3 110.3	123.6 56.0 56.1	21.1 125.6, 127.1 128.8, 139.6	26.7, 30.0 43.1, 52.5 54.4, 136.6 157.9, 161.7	20.5 153.2 161.7
8a/6	6.48 s 5.83 s [a]	6.65 s 6.75 s	7.45 (dd, 2H, J = 8.9 and 0.6 Hz) 8.08 (d, 2H, J = 8.9 Hz)	3.39 (t, 2H, J = 5.4 Hz), 4.31 (m, 2H) 4.36 (m, 2H), 4.44 (m, 2H), 6.49 (dd, 1H, J = 1.3 and 6.8 Hz), 6.61 (dd, 1H, J = 1.3 and 8.4 Hz), 6.80 (m, 1H)	2.21 s 3.87 s 3.89 s	61.6 135.1 [a]	110.3 125.6	107.6 147.5	147.1 111.0	123.2 56.0 56.2	121.7, 128.0 147.1, 148.9	33.5, 64.3 64.8, 68.9 104.2, 110.2 120.6, 132.8 144.4, 148.9	20.4 150.3 162.3
8a/7	6.32 s 5.79 s [a]	6.62 s 6.66 s	7.09 (dd, 1H, J = 2.0 and 8.8 Hz) 7.24 (d, 1H, J = 8.8 Hz) 7.37 (d, 1H, J = 2.0 Hz)	2.05 (m, 2H), 2.20 (s, 3H), 2.24 (s, 3H), 2.67-2.72 (m, 6H), 3.15 (m, 2H), 3.31-3.33 (m 4H), 6.65 (dd, 1H, J = 2.4 and 8.4 Hz), 6.78 (d, 1H, J = 2.4 Hz), 7.04 (d, 1H, J = 8.4 Hz)	2.19 s 3.83 s 3.87 s	61.0 135.1 [a]	110.0 125.6	107.4 147.3	148.6 110.1	121.9 55.9 56.1	129.3, 129.8 130.2, 130.8 131.8, 143.1	18.8, 20.2 26.8, 29.9 49.3, 52.5 53.8, 114.1 118.3, 126.8 128.6, 137.2	20.5 152.9 162.6
8a/8	5.30 (q, 1H, J = 6.6 Hz) 5.87 bs [a]	6.57 s 6.59 s	1.37 (d, 3H, J = 6.6 Hz)	2.60 (s, 3H)	2.23 s 3.84 s 3.85 s	56.5 132.4 [a]	110.4 123.8	107.3 148.0	147.5 108.4	126.7 55.9 56.0	19.9	14.8	20.1 155.8 158.3
8b/1	5.92 s 5.68 s [a]	6.59 s 6.68 s	7.06 (d, 2H, J = 8.1 Hz) 7.21 (d, 2H, J = 8.1 Hz)	5.91(d, 1H, J = 2.4 Hz) 7.37 (d, 1H, J = 2.4 Hz)	2.10 s 3.84 s 3.87 s	65.2 136.5 [a]	105.2 125.5	106.8 146.8	148.3 110.3	122.7 55.9 56.2	21.0 126.3, 128.9 136.8, 140.4	-	20.0 98.0 129.6 153.8
8b/2	6.08 s 5.72 s [a]	6.62 s 6.71 s	7.50 (d, 2H, J = 8.2 Hz) 8.10 (d, 2H, J = 8.9 Hz)	5.91(d, 1H, J = 2.4 Hz) 7.40 (d, 1H, J = 2.4 Hz)	2.11 s 3.87 s 3.88 s	64.4 136.2 [a]	106.6 125.6	106.9 147.1	147.0 110.0	121.0 55.9 56.2	123.4 127.6 147.0 148.8	-	20.0 98.1 129.4 154.8

Table II (continued)

Comp.	H-1 H-4	H-5 H-8	R	R"/R"'	CH_3-3 R^1, R^2 other	C-1 C-3	C-4 C-4a	C-5 C-6	C-7 C-8	C-8a R^1, R^2	R	R"	other
8b/3	5.90 s 5.63 s [a]	6.54 s 6.66 s	7.17-7.18 (m, 3H) 7.29 (m, 1H)	2.11 (d, 3H, J = 0.7 Hz)	2.23 s 5.65 (d, 1H, J = 0.7 Hz) 5.92 (m, 2H)	64.6 136.5 [a]	104.0 124.7	106.4 145.3	147.0 107.1	122.7 100.7	126.5, 126.7 127.7, 129.3 134.0, 145.1	11.4	20.0 97.2 129.4 154.1
8c/1	6.20 s 5.83 s [a]	6.65 s 6.68 s	7.51(d, 2H, J = 9.1 Hz) 8.09 (d, 2H, J = 8.9 Hz)	-	2.02 s 3.86 s 3.89 s 6.76 bs 6.91 bs	63.7 133.4 [a]	109.8 124.9	107.3 149.8	148.9 110.0	121.3 56.0 56.2	123.3 128.0 147.2 147.8	-	19.6 113.1 127.4 146.4
8c/2	6.00 s 5.77 s [a]	6.60 s 6.75 s	6.59 (dd, 1H, J = 2.1 and 8.4 Hz) 7.17 (d, 1H, J = 8.4 Hz) 7.28 (d, 1H, J = 2.2 Hz)	-	1.97 s 3.81 s 3.86 s 6.75 s 7.30 s	63.4 133.9 [a]	109.1 125.0	107.3 148.7	147.5 110.0	121.4 55.9 56.1	126.6, 129.0 130.0, 131.1 132.1, 142.7	-	19.6 111.2 126.6 146.3
8d/1	6.21 s 5.53 s [a]	6.63 s 6.94 s	7.26 (d, 2H, J = 9.2 Hz) 7.30 (d, 2H, J = 9.5 Hz)	-	2.16 s 3.72 (bs, 6H)	62.5 137.4 [a]	111.1 126.0	104.0 148.2	146.6 106.8	121.8 55.7 56.0	127.7 128.8 131.1 143.1	-	20.8 164.5
8d/2	6.20 s 5.54 s [b]	6.64 s 6.98 s	7.22 (dd, 1H, J = 1.2 and 8.5 Hz) 7.47 (d, 1H, J = 8.2 Hz) 7.50 (bs,1H)	-	2.14 s 3.72 s 3.73 s	62.1 137.0 [b]	112.3 125.8	106.6 148.2	146.4 110.9	120.8 55.4 55.8	127.2, 128.6 128.9, 129.8 130.2, 145.2	-	20.5 164.0
8d/3	6.17 s 5.50 s [b]	6.61 s 6.85 s	3.67 (s, 3H) 6.75 (d, 2H, J = 8.6 Hz) 7.18 (d, 2H, J = 8.5 Hz)	-	2.14 s 3.71 s 3.72 s	62.5 136.1 [b]	111.0 126.1	106.7 148.0	146.4 110.9	122.6 55.7 56.0	55.1 113.1, 128.0 137.4, 158.0	-	20.9 164.6

[a] Taken in deuteriochloroform; [b] Taken in DMSO-d_6.

Scheme 4

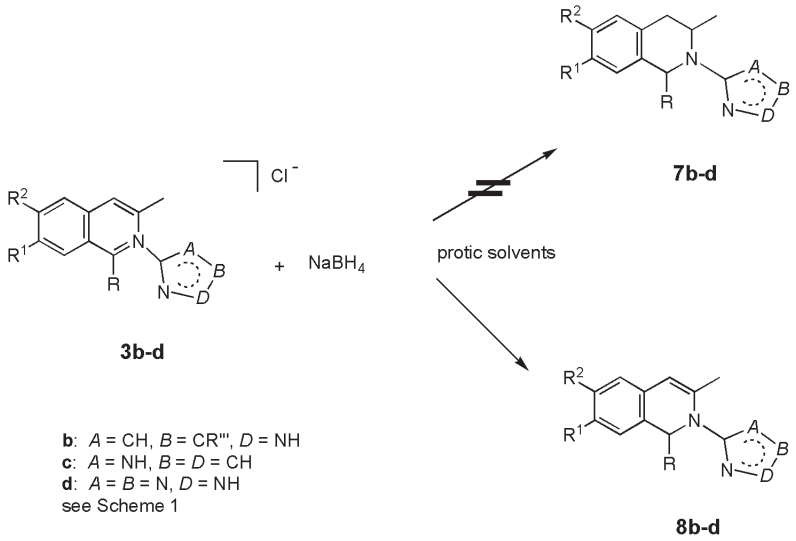


Table III

Synthetical and Analytical Data of the *N*-azolyl-isoquinolinium Salts **3a-c**

Comp.	*A* *B* *D*	R	R^1	R^2	R"	Yield %	Method	Mp (°C) (cryst. from)	Molecular formula (MW)	Analysis % Calcd./Found C	H	N	S	Cl	Starting amino-azole 2
3a/1	N CR" NH	4-Methyl-phenyl	Methoxy	Methoxy	H	59	A	200-203 (CH_3CN)	$C_{21}H_{20}N_4O_2$ •HCl (396.88)	63.55 63.41	5.33 5.59	14.12 14.08		8.93 9.11	**2a/1** [a]
3a/2	N CR" NH	4-Methyl-phenyl	Methoxy	Methoxy	Ethylthio	70	A [b]	140-142 (CH_3CN)	$C_{23}H_{24}N_4O_2S$ (420.54) [c]	65.69 65.42	5.75 5.79	13.32 13.13	7.62 7.70		**2a/2** [14]
3a/3	N CR" NH	4-Methyl-phenyl	Methoxy	Methoxy	*3*-(*N*,*N*-dimethylamino) propylthio	57	B	112-115 (CH_3CN / EtOAc)	$C_{26}H_{31}N_5O_2S$ (477.63) [c]	65.38 65.31	6.54 6.49	14.66 14.83	6.71 6.55		**2a/3** [15]
3a/4	N CR" NH	4-(2-Propyl)-phenyl	Methoxy	Methoxy	3-[4-(3-chlorophenyl) piperazin-1-yl]propylthio	58	B	119-122 (CH_3CN)	$C_{36}H_{41}ClN_6O_2S$ (657.28) [c]	65.79 65.84	6.29 6.36	12.79 12.60	4.88 4.71	5.39 5.44	**2a/4** [18]
3a/5	N CR" NH	4-Methyl-phenyl	Methoxy	Methoxy	3-[4-(2-pyrimidinyl)-piperazin-1-yl]propylthio	56	B	124-127 (CH_3CN)	$C_{32}H_{36}N_8O_2S$ (596.76) [c]	64.41 64.29	6.08 6.09	18.78 18.87	5.37 5.31		**2a/5** [19]
3a/6	N CR" NH	4-Nitrophenyl	Methoxy	Methoxy	2-[(2,3-dihydrobenzo-dioxan-5-yl) oxy]ethylthio	9	B [d]	197-200 (CH_3CN)	$C_{30}H_{27}N_5O_7S$ (601.64) [c]	59.89 59.73	4.52 4.45	11.64 11.47	5.33 5.46		**2a/6** [20]
3a/7	N CR" NH	3,4-Dichloro-phenyl	Methoxy	Methoxy	3-[4-(3,4-dimethylphenyl) piperazin-1-yl]propylthio	68	B [d]	112-114 (EtOH)	$C_{35}H_{38}Cl_2N_6O_2S$ (677.70) [c]	62.03 62.10	5.65 5.61	12.40 12.27	4.73 4.59	10.46 10.60	**2a/7** [21]
3c/1	NH CH CH	4-Nitrophenyl	Methoxy	Methoxy	H	70	A	212-214 (CH_3CN)	$C_{21}H_{18}N_4O_4$ •HCl (426.86)	59.09 58.88	4.49 4.53	13.13 13.06		8.31 8.39	**2c/1** [a]
3c/2	NH CH CH	3,4-Dichloro-phenyl	Methoxy	Methoxy	H	72	A	185-189 (EtOAc/ 2-propanol)	$C_{21}H_{17}Cl_2N_3O_2$ .HCl (450.76)	55.96 55.84	4.03 4.08	9.32 9.50		23.60 23.54	**2c/2** [a]

[a] Fluka; [b] Extraction with 5 *N* sodium hydroxide solution; [c] Zwitter Ion; [d] Chromatography.

Table IV

Pmr and cmr Spectral Data of Derivatives **3a-c**

Comp.	H-4	H-5 H-8	R	R"	CH_3-3 R^1, R^2 other	C-1 C-3	C-4 C-4a	C-5 C-6	C-7 C-8	C-8a R^1, R^2	R	R"	other
3a/1	8.38 s	7.79 s	2.35 (s, 3H)	8.61 (bs, 1H)	2.43 s	155.4	122.9	105.9	152.4	122.4	21.2	-	19.9
		6.84 s	7.28 (d, 2H, J = 8.1Hz)		3.71 s	145.9	138.6	156.9	106.9	56.1	126.7, 129.0		143.5
	[b]		7.35 (d, 2H, J = 8.1Hz)		4.14 s	[b]				57.5	130.2, 140.8		159.1
3a/2	7.83 s	7.25 s	2.35 (s, 3H)	1.12 (t, 3H, J = 7.3 Hz)	2.58 s	155.1	122.8	104.5	152.3	121.6	21.4	15.0, 28.0	20.5
		6.94s	7.18 (d, 2H, J = 8.4 Hz)	2.88 (q, 2H, J = 7.3 Hz)	3.79 s	145.6	137.6	157.7	107.3	56.2	127.0, 128.8		157.2
	[a]		7.28 (d, 2H, J = 8.4 Hz)		4.16 s	[a]				57.0	129.9, 140.7		158.3
3a/3	8.26 s	6.84 s	2.34 (s, 3H)	1.51 (m, 2H)	2.40 s	155.3	122.3	105.7	152.0	122.2	21.2	25.1, 27.5	19.9
		7.72 s	7.24 (d, 2H, J = 7.8 Hz)	2.09 (s, 6H)	3.69 s	144.4	137.5	156.4	106.9	55.9	127.6, 128.5	31.0, 45.4	155.3
	[b]		7.31 (d, 2H, J = 8.2 Hz)	2.20 (t, 2H, J = 7.1 Hz) 2.73 (t, 2H, J = 7.1 Hz)	4.11 s	[b]				57.1	130.3, 139.8		158.0
3a/4	7.82 s	7.24 s	1.25 (d, 6H, J = 7.0	1.74 (m, 2H), 2.49 (t, 2H, J = 7.1	2.58 s	155.3	123.0	104.6	152.4	121.8	23.8, 34.1	26.9, 32.0	20.7
		6.93 s	Hz), 2.95 (h, 1H,	Hz), 2.55-2.57 (m, 6H), 3.18 (t,	3.78 s	145.8	137.7	158.4	107.6	56.3	125.4, 127.5	48.7, 53.1	157.5
	[a]		J = 7.0 Hz), 7.25 (d,	4H, J = 5.0 Hz), 6.76-6.79 (m,	4.15 s					57.2	130.1, 151.4	57.2	157.9
			2H, J = 9.2 Hz)	2H), 6.86 (d, 1H, J = 2.2 Hz),		[a]						113.9, 115.8	
			7.38 (bs, 2H)	7.14 (dd, 1H, J = 8.1 and 8.2 Hz)								119.2, 130.1	
												135.0, 152.6	
3a/5	7.91 s	7.22 s	2.38 (s, 3H)	1.77 (m, 2H), 2.52-2.55 (m, 6H),	2.57 s	155.1	122.8	104.6	152.3	121.7	21.4	26.5, 31.6	20.3
		6.91 s	7.20 (d, 2H, J = 8.3 Hz)	3.01 (t, 2H, J = 7.0 Hz), 3.85 (t,	3.79 s	145.5	137.7	157.7	107.2	56.1	127.0, 128.9	43.5, 52.9	157.2
	[a]		7.32 (d, 2H, J = 8.3 Hz)	4H, J = 5.1 Hz), 6.47 (t, 1H, J = 4.8	4.17 s	[a]				57.0	129.9, 140.7	54.1, 136.6	158.4
				Hz), 8.29 (d, 2H, J = 4.8 Hz)								157.7, 161.7	
3a/6	8.04 s	7.40 s	7.65 (d, 2H, J = 8.4 Hz)	3.29 (t, 2H, J = 7.5 Hz), 4.14 (t,	2.63 s	154.8	122.5	105.0	152.3	123.0	121.7, 128.0	31.8, 64.3	20.5
		6.65 s	8.20 (d, 2H, J = 8.8 Hz)	2H, J = 7.5 Hz), 4.22-4.35 (m, 4H),	3.78 s	146.1	138.4	157.4	105.7	56.5	147.1, 148.9	64.5, 68.5	154.1
	[a]			6.47 (dd, 1H, J = 1.5 and 6.9 Hz),	4.20 s	[a]				57.4		106.3, 110.4	159.2
				6.53 (dd, 1H, J =1.5 and 8.7 Hz),								120.2, 133.9	
				6.72 (dd, 1H, J = 6.9 and 8.7 Hz)								144.5, 148.1	
3a/7	7.97 s	6.80 s	7.35 (dd, 1H, J = 2.0	1.85 (m, 2H), 2.18 (s, 3H), 2.22 (s,	2.61 s	154.7	122.5	104.8	152.9	128.0	129.3, 129.6	18.6, 20.1	20.4
		6.36 s	and 8.1 Hz)	3H), 2.66 (t, 2H, J = 7.2 Hz) 2.73	3.84 s	146.0	138.1	157.9	106.0	56.8	130.1, 130.5	26.4, 31.7	153.9
	[a]		7.53 (d, 1H, J = 8.2 Hz)	(m 4H), 3.02 (t, 2H, J = 7.3 Hz),	4.18 s	[a]				57.2	131.9, 149.6	49.4, 53.0	158.9
			7.57 (d, 1H, J = 2.0 Hz)	3.22 (m, 4H), 6.68 (dd, 1H, J =								56.4, 113.8	
				2.4 and 8.0 Hz) 6.74 (d, 1H, J =								118.1, 132.8	
				2.4 Hz), 7.01 (d, 1H, J = 8.0 Hz)								135.3, 137.1	
3c/1	8.45 s	6.74 s	7.82 (d, 2H, J = 8.6 Hz)	-	2.46 s	154.6	122.1	106.0	152.7	123.1	123.4	-	19.4
		7.83 s	8.34 (d, 2H, J = 8.6 Hz)		3.74 s	144.8	138.9	159.3	106.2	56.4	132.0		123.4
	[b]				4.16 s	[b]				57.5	136.7		132.0
					7.10 (bs, 2H)						148.6		135.8
3c/2	8.43 s	6.85 s	7.14 (d, 2H, J = 1.4 Hz)	-	2.44 s	154.1	122.3	106.0	152.7	123.1	129.9, 130.6	-	19.5
		7.91 s	7.58 (dd, 1H, J = 1.3		3.79 s	144.7	138.9	159.3	106.5	56.5	130.8, 131.4		129.9
	[b]		and 8.4 Hz)		4.15 s	[b]				57.6	132.2, 147.3		133.9
			7.78 (d, 1H, J = 8.3 Hz)		6.85 (bs, 2H)								136.8

[a] Taken in deuteriochloroform; [b] Taken in DMSO-d_6.

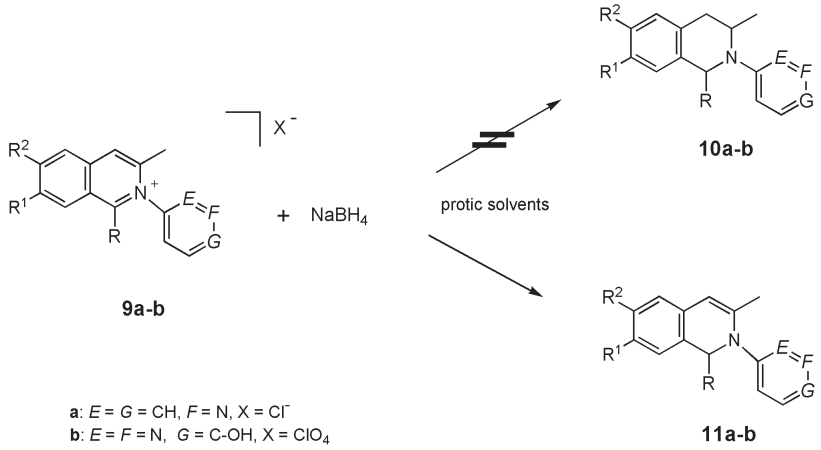
Table V

Synthetical and Analytical Data of the 2-Hetaryl-(**9a-b**) and 2-Aryl-(**12a-e**) isoquinolinium Salts

Comp.	R	R^1	R^2	*E* *F* *G*	R^4 R^5	Yield %	Mp (°C) (cryst. from)	Molecular formula (MW)	Analysis % Calcd./Found C	H	N	Cl
9a	4-Methyl-phenyl	Methoxy	Methoxy	CH N CH	-	98	278-282 (EtOAc)	$C_{24}H_{23}ClN_2O_2$ (406.92) (chloride)	70.84 70.68	5.70 5.74	6.88 6.75	8.71 8.79
9b	3-Chloro-phenyl	Methoxy	Methoxy	N NH CO	-	9 [a]	121-124 (EtOAc)	$C_{22}H_{19}Cl_2N_3O_7$ (508.32) (perchlorate)	51.98 52.06	3.77 3.81	8.27 8.11	13.95 13.87
12a	4-Methyl-phenyl	Methoxy	Methoxy	-	4-Chloro H	80	295-299 (EtOAc)	$C_{25}H_{23}Cl_2NO_2$ (440.37) (chloride)	68.19 68.02	5.26 5.14	3.18 3.23	16.10 15.95
12b	4-(2-Propyl)-phenyl	Methoxy	Methoxy	-	3-Nitro H	96	298-301 (CH_3CN/ EtOAc)	$C_{27}H_{27}ClN_2O_4$ (478.98) (chloride)	67.71 67.61	5.68 5.65	5.85 5.69	7.40 7.55
12c	4-Methyl-phenyl	Methoxy	Methoxy	-	4-Methyl H	93	270-275 (EtOAc)	$C_{26}H_{26}ClNO_2$ (419.96) (chloride)	74.36 74.21	6.24 6.29	3.34 3.31	8.44 8.57
12d	4-(2-Propyl)-phenyl	Methoxy	Methoxy	-	2-Hydroxy H	98	251-255 (CH_3CN/ EtOAc)	$C_{27}H_{28}ClNO_3$ (449.98) (chloride)	72.07 72.18	6.27 6.34	3.11 3.20	7.88 7.69
12e	4-(2-Propyl)-phenyl	Methoxy	Methoxy	-	3,4-Dimethoxy H	65	202-204 (CH_3CN/ EtOAc)	$C_{29}H_{32}ClNO_4$ (494.04) (chloride)	70.51 70.32	6.53 6.41	2.84 2.68	7.18 7.25

[a] For its preparation see Experimental.

Scheme 5



vided by the synthesis of 2-methylisoquinolinium salts (**16a-b** R = 3-chlorophenyl and 4-fluorophenyl, respectively) and the reduction of these salts to the corresponding diastereomeric mixtures of 1,2,3,4-tetrahydroisoquinolines (**17a-b**) (Scheme 8). In these reaction mixtures the presence of the corresponding 1,2-dihydroisoquinolines (**18a-b**) could not be detected.

It is worth mentioning that, as expected, the reactions leading to 1,2-dihydroisoquinolines were not influenced by the nature of substituents in position 1 which were varied over a broad range (alkyl, differently substituted aryl) on the isoquinolinium moiety.

EXPERIMENTAL

Melting points were determined on a Kofler-Boëtius micro apparatus and are not corrected. The pmr and cmr measurements were performed using Varian Gemini-2000 and Varian Unity

Table VI

Pmr and cmr Spectral Data of Derivatives **9** and **12**

Comp.	H-4	H-5 H-8	R	Het/Ar	CH_3-3 R^1, R^2	C-1 C-3	C-4 C-4a	C-5 C-6	C-7 C-8	CH_3-3 C-8a R^1, R^2	R	Het/Ar
9a	8.45 s	6.71 s	2.29 (s, 3H)	7.53 (dd, 1H, J = 4.8 and	2.40 s	156.6	123.0	106.6	152.2	21.8	21.1	124.4, 129.3
		7.82 s	7.21-7.40	8.8 Hz), 8.09 (dd, 1H,	3.69 s	143.6	137.8	158.3	105.6	122.9	127.9, 129.2	136.0, 137.2
	[b]		(m, 4H)	J = 2.1 and 8.8 Hz), 8.59	4.14s					56.1	130.1, 140.2	147.9, 150.9
				(dd, 1H, J = 2.1 and 4.8 Hz)		[b]				57.4		
				8.76 (d, 1H, J = 2.1 Hz)								
9b	8.13 s	6.67 s	6.76-6.85	5.20 (bs, 1H)	6.61 s	153.3	123.5	105.5	152.8	21.9	128.3, 129.4	130.4, 130.7
		7.49 s	(m, 2H)	7.65 (d, 1H, J = 9.1 Hz)	3.79 s	142.9	138.6	159.2	105.1	122.6	129.8, 130.3	130.9, 131.2
	[a]		7.16-7.46	7.75 (d, 1H, J = 8.9 Hz)	4.15 s					55.9	131.5, 134.6	
			(m, 2H)			[b]				57.1		
12a	8.58 s	6.69 s	2.37 (s, 3H)	7.36 (d, 2H, J = 8.8 Hz)	2.55 s	155.8	124.1	106.3	152.3	21.9	21.3	129.2, 129.8
		6.82 s	7.17 (d, 2H	7.64 (d, 2H, J = 8.8 Hz)	3.74 s	143.2	138.2	158.2	106.0	123.3	127.5, 128.9	136.0, 138.0
	[a]		J = 7.8 Hz)		4.13 s					55.9	129.8, 140.6	
			7.35 (d, 2H,			[a]				57.4		
			J = 7.8 Hz)									
12b	8.44 s	6.74 s	1.12 (d, 6H	7.76 (dd, 1H, J = 7.9 and	2.44 s	156.4	123.5	106.6	152.2	21.7	23.5, 33.2	122.8, 126.4
		7.82 s	J = 6.7 Hz)	8.2 Hz), 8.05 (ddd, 1H,	3.69 s	143.4	137.8	158.3	105.9	122.9	124.9, 126.4	130.3, 134.5
	[b]		2.86 (h, 1H,	J =0.9, 1.8 and 7.8 Hz)	4.14 s					56.0	128.2, 130.2	140.5, 147.9
			J = 6.7 Hz)	8.27 (ddd, 1H, J = 0.9, 1.2		[b]				57.3	131.1, 150.9	
			7.23-7.44	and 7.0 Hz), 8.59 (dd, 1H,								
			(m, 4H)	J = 1.8 and 2.1 Hz)								
12c	8.80 s	6.67 s	2.36 (s, 3H)	2.36 (s, 3H)	2.53 s	155.6	124.4	106.2	152.4	21.9	21.3	21.0
		8.03 s	7.19 (bs, 2H)	7.19 (bs, 2H)	3.74 s	143.4	138.1	158.2	106.1	123.2	126.7, 129.1	127.5, 129.6
	[a]		7.21 (bs, 2H)	7.21 (bs, 2H)	4.22 s					55.9	130.2, 140.4	130.2, 136.8
						[a]				57.6		
12d	8.40 s	6.71 s	1.15 (d, 6H	6.79 (ddd, 1H,	2.40 s	156.9	122.9	106.7	152.0	20.6	23.6, 33.3	116.9, 119.6
		6.76 s	J = 7.0 Hz)	J = 1.2, 6.4 and 7.6 Hz)	3.67 s	143.9	137.5	158.1	105.5	122.9	126.2, 128.2	127.5, 128.0
	[b]		2.90 (h, 1H,	7.00 (d, 1H, J = 7.0 Hz)	4.12 s					55.9	130.3, 150.8	131.9, 151.2
			J = 7.0 Hz)	7.27-7.34 (m, 1H)		[b]				57.2		
			7.27-7.34	7.40 (ddd, 1H,								
			(m, 4H)	J = 1.5, 6.4 and 7.2 Hz)								
12e	8.54 s	7.70 s	1.22 (d, 6H	3.73 (s, 3H, OCH_3)	2.60 s	156.1	124.1	106.4	152.4	21.9	23.4, 33.7	55.9, 56.0
		7.80 s	J = 6.9 Hz)	3.84 (s, 3H, OCH_3)	3.85 s	144.0	138.1	158.1	106.0	123.2	126.3, 126.4	110.6, 111.0
	[a]		2.82 (h, 1H,	7.27 (d, 2H, J = 8.2 Hz)	4.16 s					56.7	128.1, 129.8	119.5, 130.0
			J = 6.9 Hz)	7.30 (d, 2H, J = 1.5 Hz)		[a]				57.5	132.2, 149.5	149.7, 151.1
			6.80 (m, 2H)	7.48 (dd, 2H, J = 1.5 and								
			7.18 (m, 2H)	8.2 Hz)								

[a] Taken in deuteriochloroform; [b] Taken in DMSO-d_6.

Inova instruments. Standard Varian HSQC and HMBC programs were used. As adsorbent of dry-column flash chromatographies, Kieselgel 60H (Merck 7736 for thin layer chromatography) was used. As eluents, different mixtures of petroleum ether, dichloromethane and methanol of continuously increasing polarities were used.

General Methods for the Synthesis of *N*-Azolylisoquinolinium Salts (**3a-e**).

Method A.

A mixture of 10 mmole of the corresponding phenylacetone (**1**) [12], 10 mmole of the corresponding aminoazole (Fluka), 15 ml of acetonitrile and 1.0 ml of concentrated hydrochloric acid was heated at reflux with stirring for 3 hours. After cooling the crystals that precipitated were collected by filtration and recrystallised from an appropriate solvent (see Table III, for their spectral data see Table IV).

Method B.

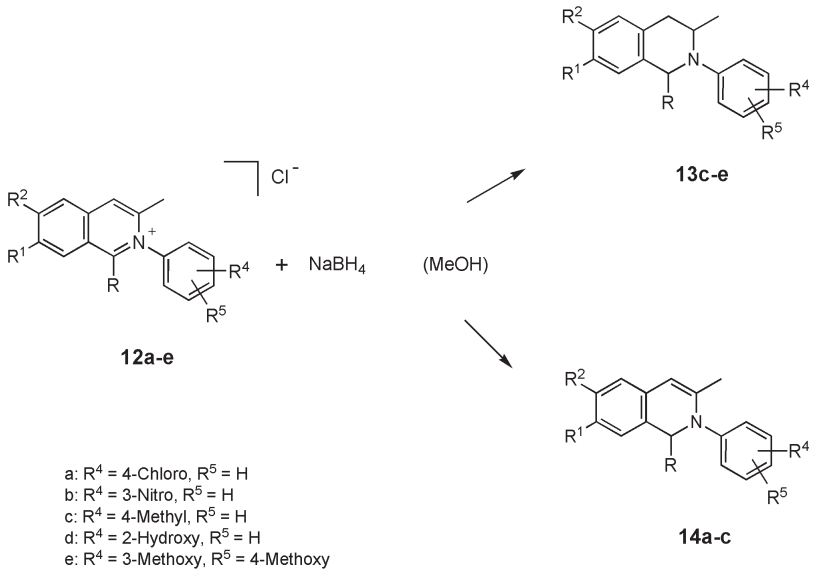
A mixture of 10 mmole of the corresponding phenylacetone (**1**) [12], 10 mmole of the corresponding aminoazole (Fluka) and 15 ml of acetic acid was heated at reflux with stirring for 3 hours. After cooling 50 ml of water was added to the reaction mixture and it was made alkaline with 40 ml of 5 *N* sodium hydroxide solution. The mixture was extracted with 2 x 50 ml of dichloromethane, the collected organic phases were dried over anhydrous sodium sulphate, filtered, and evaporated *in vacuo* to dryness. The residue was recrystallized from an appropriate solvent (see Table III, for their spectral data see Table IV).

General Methods for the Synthesis of *N*-Azolyl-1,2-dihydroisoquinolines **8a-d**.

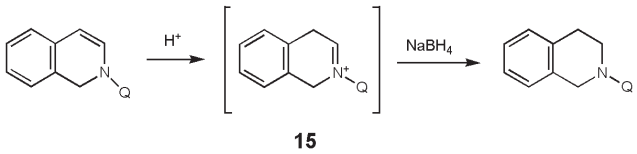
Method A.

To a solution of 10 mmole of the corresponding isoquinolinium salt (**3a-d**) [1-2] in 30 ml of dry methanol, 0.45 g (12 mmole) of

Scheme 6



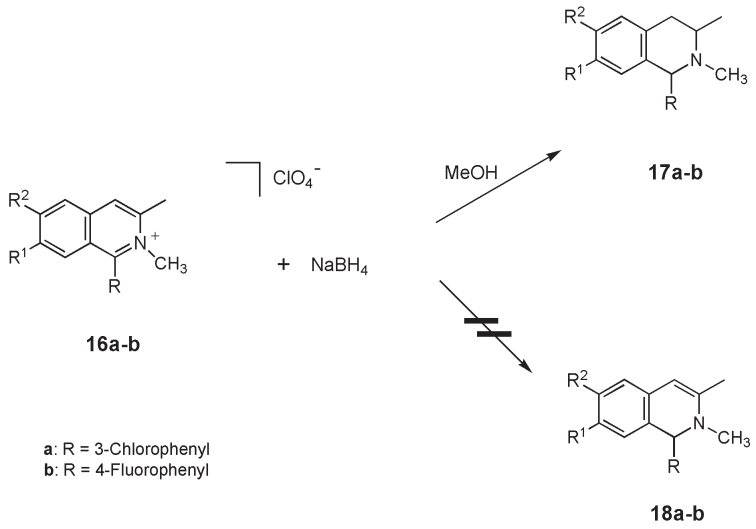
Scheme 7



Method B.

To a solution of 10 mmole of the corresponding isoquinolinium salt (**3a**) [2] in 30 ml of dry methanol was added 0.45 g (12 mmole) of sodium borohydride in portions, with stirring, at a temperature given in Table I. The stirring was continued for an additional 1 hour. The reaction mixture was diluted with 40 ml of water stirred overnight and extracted with 2 x 50 ml of dichloromethane. The combined organic phases were dried over anhydrous sodium sulphate, filtered and evaporated *in vacuo* to dryness. The residue was dry-column flash chromatographed on Kieselgel 60 H, as eluents different mixtures of petroleum ether, dichloromethane and methanol of continuously increasing polarities were used. After

Scheme 8



sodium borohydride was added in portions, with stirring, at a temperature given in Table I. The stirring was continued for an additional 1 hour. The reaction mixture was diluted with 40 ml of water and stirred overnight. The crystals that precipitated were collected by filtration, washed with a small amount of water and recrystallized from an appropriate solvent (see Table I, for their spectral data see Table II).

evaporating the appropriate fractions *in vacuo* to dryness the residue was recrystallized from an appropriate solvent (see Table I, for their spectral data see Table II).

Method C.

A mixture of 1.5 mmole of the corresponding isoquinolinium salt (**3d**) [1] and 50 ml of dry methanol was heated to 60°. To the resulting solution, 1.70 g (45 mmole) of sodium borohydride was added in portions, and the mixture was heated at reflux for 1 hour. After cooling, the reaction mixture was diluted with 20 ml of water and stirred overnight. The methanol was evaporated *in vacuo*. The crystals that precipitated were collected by filtration, washed with a small amount of water and recrystallized from an appropriate solvent (see Table I, for their spectral data see Table II).

General Method for the Synthesis of 2-Hetaryl- (**9a-b**)- and 2-Aryl- (**12a-e**) isoquinolinium Salts

A mixture of 10 mmole of the corresponding phenylacetone (**1**) [12], 10 mmole of the 3-aminopyridine (Fluka), or the corresponding aniline (Fluka), 15 ml of acetonitrile and 1.0 ml of concentrated hydrochloric acid was heated at reflux with stirring for 3 hours. After cooling, the reaction mixture was evaporated *in vacuo* to dryness, diluted with 10 ml of water, and extracted with 2 x 15 ml of dichloromethane. The combined organic phases were dried over anhydrous sodium sulphate, filtered, and evaporated *in vacuo* to dryness. The residue was recrystallised from an appropriate solvent (see Table V, for their spectral data see Table VI).

1-(3-Chlorophenyl)-6,7-dimethoxy-3-methyl-2-(pyridazin-6(1*H*)-one-3-yl)-isoquinolinium Perchlorate (**9b**).

A mixture of 1.25 g (3.0 mmol) of 6,7-dimethoxy-3-methyl-1-(3-chlorophenyl)pyrilium perchlorate (**1a**, R = 3-chlorophenyl, R^1 = R^2 = methoxy) [12], 0.43 g (3.3 mmol) of 3-amino-6-chloropyridazine [13] and 6 ml of acetic acid was heated at reflux, with stirring, for 12 hours. After cooling, the crystals that precipitated were collected by filtration to obtain 0.45 g (30 %) of unreacted **1a** (R = 3-chlorophenyl, R^1 = R^2 = methoxy), mp 215-221°. To the mother liquor 20 ml of water was added and the product allowed to crystallize. After collection by filtration 0.32 g (21 %) of 6-(3-chlorobenzoyl)-3,4-dimethoxy-phenylacetone (**1**, R = 3-chlorophenyl, R^1 = R^2 = methoxy) was obtained, mp 130-134°. The pH of the mother liquor was adjusted to 5 with 5 *N* sodium hydroxide solution and the water layer was decanted and extracted with 50 ml of dichloromethane. The organic phase was dried over anhydrous sodium sulphate, filtered and evaporated *in vacuo* to dryness. The residue was recrystallized from 5 ml ethyl acetate to yield 0.13 g (9 %) of 1-(3-chlorophenyl)-6,7-dimethoxy-3-methyl-2-(pyridazin-6(1*H*)-one-3-yl)-isoquinolinium perchlorate (**9b**), mp 121-124° (see Table V, for its spectral data see Table VI).

6,7-Dimethoxy-3-methyl-1-(4-methylphenyl)-2-(3-pyridyl)-1,2-dihydroisoquinoline (**11a**)

To a solution of 0.81 g (2 mmole) of 6,7-dimethoxy-3-methyl-1-(4-methylphenyl)-2-(3-pyridyl)isoquinolinium chloride (**9a**) in 5 ml of dry methanol was added 0.10 g (2.7 mmole) of sodium borohydride in portions with stirring at 0°. The mixture was allowed to warm to room temperature, and stirred for an additional 1 hour, after which it was diluted with 10 ml of water and stirred overnight. The crystals that precipitated were collected by filtration and washed with a small amount of water to yield 0.60 g (81 %) of 6,7-dimethoxy-3-methyl-1-(4-methylphenyl)-2-(3-pyridyl)-1,2-dihydroisoquinoline (**11a**), mp 102-105°; pmr (deuteriochloroform): δ, ppm 2.01 (s, 3H, CH_3-3), 2.31 (s, 3H, CH_3-4'), 3.85 (s, 3H, OCH_3-7), 3.87 (s, 3H, OCH_3-6), 5.63 (s, 1H, H-4), 5.82 (s, 1H, H-1), 6.58 (s, 1H, H-5), 6.67 (s, 1H, H-8), 7.01 [d (J = 8.1 Hz), 2H, H-3', 5'], 7.08 [d (J = 8.1 Hz), 2H, H-2', 6'], 7.14 (m, 1H, H-5"), 7.31 (m, 1H, H-4"), 8.26 [dd (J = 0.8 and 4.7 Hz), 1H, H-6"], 8.39 [d (J = 2.7 Hz), 1H, H-2"]; cmr (deuteriochloroform): δ, ppm 19.9 (CH_3-3), 21.0 (CH_3-4'), 55.9 (OCH_3-7), 56.1 (OCH_3-6), 66.8 (C-1), 107.0 (C-5), 109.8 (C-4), 110.2 (C-8), 122.5 (C-8a), 124.9 (C-4a), 135.6 (C-3), 147.2 (C-7), 148.4 (C-6), 123.3, 125.9, 129.1, 129.2, 136.9, 139.7, 142.5, 143.5, 144.6 (ArC).

Anal. Calcd. for $C_{24}H_{24}N_2O_2$ (MW 372.47): C, 77.39; H, 6.49; N, 7.52. Found: C, 77.18; H, 6.51; N, 7.47.

1-(3-Chlorophenyl)-6,7-dimethoxy-3-methyl-2-(pyridazin-6(1*H*)-one-3-yl)-1,2-dihydroisoquinoline (**11b**)

To a solution of 70 mg (0.13 mmole) of 1-(3-chlorophenyl)-6,7-dimethoxy-3-methyl-2-[pyridazin-6(1*H*)-one-3-yl]isoquinolinium perchlorate (**9b**) in 2 ml of dry methanol 6.4 mg (0.17 mmole) of sodium borohydride was added in portions with stirring at 0°. The mixture was allowed to warm to room temperature, stirred for an additional 1 hour, diluted with 5 ml of water and stirred overnight. The methanol was evaporated *in vacuo*, the crystals which precipitated were collected by filtration and washed with a small amount of water to yield 45 mg (85 %) of 1-(3-chlorophenyl)-6,7-dimethoxy-3-methyl-2-(pyridazin-6(1*H*)-one-3-yl)-1,2-dihydroisoquinoline (**11b**), mp 195-197°; pmr (deuteriochloroform): δ, ppm 2.01 (s, 3H, CH_3-3), 3.88 (s, 3H, OCH_3-7), 3.89 (s, 3H, OCH_3-6), 5.11 (s, 1H, H-1), 6.02 (s, 1H, H-4), 6.67 (s, 1H, H-5), 6.71 (s, 1H, H-8), 6.92 [d (J = 9.9 Hz), 1H, H-4"], 7.09 [d (J = 9.9 Hz), 1H, H-5"], 7.13-7.19 (m, 4H, Ar'H), 11.80 (bs, 1H, NH-1") cmr (deuteriochloroform): δ, ppm 20.5 (CH_3-3), 55.9 (OCH_3-7), 56.1 (OCH_3-6), 62.4 (C-1), 107.6 (C-5), 110.0 (C-4), 113.4 (C-8), 122.7 (C-8a), 124.7 (C-4a), 134.1 (C-3), 147.8 (C-7), 148.7 (C-6), 160.5 (C=O), 125.1, 127.0, 127.5, 129.3, 129.8, 130.6, 132.6, 143.8, 146.6, (ArC).

Anal. Calcd. for $C_{22}H_{20}ClN_3O_3$ (MW 409.88): C, 64.47; H, 4.92; Cl, 8.65; N, 10.25. Found: C, 64.22; H, 5.21; Cl, 8.59; N, 10.08.

2-(4-Chlorophenyl)-6,7-dimethoxy-3-methyl-1-(4-methylphenyl)-1,2-dihydroisoquinoline (**14a**).

To a solution of 1.32 g (3 mmole) of 2-(4-chlorophenyl)-6,7-dimethoxy-3-methyl-1-(4-methylphenyl)isoquinolinium chloride (**12a**) in 5 ml of dry methanol, 0.15 g (4 mmole) of sodium borohydride was added in portions with stirring at 0°. The mixture was allowed to warm to room temperature, stirred for an additional 1 hour, diluted with 15 ml of water and the stirring was continued overnight. The crystals that precipitated were collected by filtration and washed with a small amount of water to obtain 1.2 g of impure product, which was recrystallized from 12 ml acetonitile to yield 1.01 g (83 %) of 2-(4-chlorophenyl)-6,7-dimethoxy-3-methyl-1-(4-methylphenyl)-1,2-dihydroisoquinoline (**14a)**, mp 114-117°; pmr (deuteriochloroform): δ, ppm 1.99 (s, 3H, CH_3-3), 2.30 (s, 3H, CH_3-4'), 3.85 (s, 3H, OCH_3-7), 3.86 (s, 3H, OCH_3-6), 5.63 (s, 1H, H-4), 5.82 (s, 1H, H-1), 6.58 (s, 1H, H-5), 6.67 (s, 1H, H-8), 6.95 [d (J = 8.8 Hz), 2H, H-3', 5'], 7.08 [d (J = 8.8 Hz), 2H, H-2', 6'], 7.20 [d (J = 8.0 Hz), 2H, H-2", 6"], 7.22 [d (J = 8.0 Hz), 2H, H-3", 5"]; cmr (deuteriochloroform): δ,

ppm 20.0 (CH_3-3), 21.0 (CH_3-4'), 55.9 (OCH_3-7), 56.2 (OCH_3-6), 67.1 (C-1), 106.9 (C-5), 108.9 (C-4), 110.4 (C-8), 122.5 (C-8a), 125.2 (C-4a), 136.4 (C-3), 147.1 (C-7), 148.5 (C-6), 125.9, 128.6, 128.8, 128.9, 129.0, 136.8 (two peaks), 140.1 (ArC).

Anal. Calcd. for $C_{25}H_{24}ClNO_2$ (MW 405.93): C, 73.97; H, 5.96; Cl, 8.73; N, 3.45. Found: C, 73.72; H, 5.71; Cl, 8.99; N, 3.41.

6,7-Dimethoxy-3-methyl-2-(3-nitrophenyl)-1-[4-(2-propyl)-phenyl]-1,2-dihydroisoquinoline (**14b**).

To a mixture of 0.96 g (2 mmole) of 6,7-dimethoxy-3-methyl-2-(3-nitrophenyl)-1-[4-(2-propyl)phenyl]isoquinolinium chloride (**12b**) and 10 ml of dry methanol was added 0.10 g (2.7 mmole) of sodium borohydride in portions with stirring at 0°. The mixture was allowed to warm to room temperature and stirred for an additional 1 hour, after which it was diluted with 10 ml of water and stirred overnight. The crystals, which precipitated were collected by filtration and washed with a small amount of water to yield 0.80 g (90 %) of 6,7-dimethoxy-3-methyl-2-(3-nitrophenyl)-1-[4-(2-propyl)phenyl]-1,2-dihydroisoquinoline (**14b**), mp 137-140°; pmr (deuteriochloroform): δ, ppm 1.23 [d (J = 7.0 Hz), 6H, CH-C*H*$_3$], 2.05 [d (J = 1.1 Hz), 3H, CH_3-3], 2.88 [h (J = 7.0 Hz), 1H, C*H*-CH_3], 3.86 (s, 3H, OCH_3-7), 3.87 (s, 3H, OCH_3-6), 5.73 (s, 1H, H-1), 6.01 (s, 1H, H-4), 6.64 (s, 1H, H-5), 6.72 (s, 1H, H-8), 7.13-7.86 (m, 8H, ArH); cmr (deuteriochloroform): δ, ppm 19.7 (CH_3-3), 23.9 (CH-*C*H$_3$), 33.6 (*C*H-CH_3), 55.9 (OCH_3-7), 56.2 (OCH_3-6), 66.8 (C-1), 107.4 (C-5), 110.4 (C-4), 112.5 (C-8), 122.9 (C-8a), 124.7 (C-4a), 134.9 (C-3), 147.5 (C-6), 148.0 (C-7), 116.1, 116.5, 125.8 (two peaks), 126.5, 127.2, 129.5, 139.5, 148.6, 148.9 (ArC).

Anal. Calcd. for $C_{27}H_{28}N_2O_4$ (MW 444.54): C, 72.95; H, 6.35; N, 6.30. Found: C, 72.68 H, 6.45; N, 5.99.

6,7-Dimethoxy-3-methyl-1-(4-methylphenyl)-2-(4-methyl-phenyl)-1,2-dihydroisoquinoline (**14c**) and *cis-trans* 6,7-Dimethoxy-3-methyl-1-(4-methylphenyl)-2-(4-methylphenyl)-1,2,3,4-tetrahydroisoquinoline (**13c**).

To a solution of 0.84 g (2 mmole) of 6,7-dimethoxy-3-methyl-1-(4-methylphenyl)-2-(4-methylphenyl)isoquinolinium chloride (**12c**) in 30 ml of dry methanol was added 0.09 g (2.4 mmole) of sodium borohydride in portions at room temperature with stirring. The mixture was stirred for 5 minutes, diluted with 10 ml of water and stirred for an additional 1 hour. The crystals which precipitated were collected by filtration and washed with a small amount of water to obtain 0.57 g of impure product, which was recrystallized from 15 ml 2-propanol to yield 0.41 g (53 %) of 6,7-dimethoxy-3-methyl-1-(4-methylphenyl)-2-(4-methyl-phenyl)-1,2-dihydroisoquinoline (**14c**) mp 115-118°; pmr (deuteriochloroform): δ, ppm 2.00 (s, 3H, CH_3-3), 2.30 (s, 6H, CH_3-4' and CH_3-4"), 3.84 (s, 3H, OCH_3-7), 3.86 (s, 3H, OCH_3-6), 5.65 (s, 1H, H-4), 5.74 (s, 1H, H-1), 6.58 (s, 1H, H-5), 6.66 (s, 1H, H-8), 6.93 [d (J = 8.1 Hz), 2H, H-3', 5'], 7.07 [d (J = 8.4 Hz), 2H, H-3", 5"], 7.08 [d (J = 8.4 Hz), 2H, H-2", 6"], 7.20 [d (J = 8.1 Hz), 2H, H-2', 6']; cmr (deuteriochloroform): δ, ppm 20.2 (CH_3-3), 20.7 (CH_3-4'), 21.0 (CH_3-4"), 55.8 (OCH_3-7), 56.2 (OCH_3-6), 67.2 (C-1), 106.6 (C-5), 106.9 (C-4), 110.3 (C-8), 122.2 (C-8a), 123.4 (C-4a), 136.6 (C-3), 146.7 (C-6), 148.3 (C-7), 125.5, 126.0, 128.9, 129.3, 132.6, 137.3, 140.7, 143.9 (ArC).

Anal. Calcd. for $C_{26}H_{27}NO_2$ (MW 385.51): C, 81.01; H, 7.06; N, 3.63. Found: C, 80.88; H, 6.95; N, 3.79.

The wet mother liquor crystallised after standing overnight again. The crystals which precipitated were collected by filtration and washed with a small amount of water yielding 0.14 g of impure product, which was recrystallized from 6 ml 2-propanol to yield 78 mg (10 %) of a 9:1 mixture of *cis-trans* 6,7-dimethoxy-3-methyl-1-(4-methylphenyl)-2-(4-methylphenyl)-1,2,3,4-tetrahydroisoquinoline (**13c**) mp 94-96 °; pmr (deuteriochloroform): δ, ppm *trans* 1.02 (d, (J = 6.2 Hz), 3H, CH_3-3), *cis* 1.27 [d (J = 5.9 Hz), 3H, CH_3-3], *cis* 2.24 (s, 3H, CH_3-4'), *cis* 2.29 (s, 3H, CH_3-4"), *cis* 2.56 [dd (J = 11.0 and 14.9 Hz), 1H, H-4], *cis* 2.76 [dd (J = 4.3 and 14.9 Hz), 1H, H-4], *cis* 3.73 (m, 1H, H-3), *cis* 3.80 (s, 3H, OCH_3-7), *cis* 3.87 (s, 3H, OCH_3-6), *cis* 5.49 (s, 1H, H-1), *trans* 5.52 (s, 1H, H-1), *cis* 6.63 (s, 1H, H-8), *cis* 6.68 (s, 1H, H-5), *cis* 6.79 [d (J = 8.2 Hz), 2H, H-3', 5'], *cis* 7.01 [d (J = 8.1 Hz), 2H, H-3", 5"], *cis* 7.04 [d (J = 8.1 Hz), 2H, H-2", 6"], *cis* 7.16 [d (J = 8.2 Hz), 2H, H-2', 6']; cmr (deuteriochloroform) *cis* **13c**: δ, ppm 20.4 (CH_3-3), 21.0 (CH_3-4'), 21.4 (CH_3-4"), 36.8 (C-4), 51.0 (C-3), 55.9 (OCH_3-7), 56.0 (OCH_3-6), 66.6 (C-1), 110.7 (C-5), 111.3 (C-8), 127.8 (C-4a), 128.1 (C-8a), 147.8 (C-7), 147.9 (C-6), 117.7, 127.2, 128.7, 129.3, 131.2, 136.1, 141.5, 147.0 (ArC), (chemical shifts of the *trans* derivative were not detected).

Anal. Calcd. for $C_{26}H_{29}NO_2$ (MW 387.53): C, 80.59; H, 7.54; N, 3.61. Found: C, 80.63; H, 7.40; N, 3.68.

cis-trans 6,7-Dimethoxy-2-(2-hydroxyphenyl)-3-methyl-1-[4-(2-propylphenyl)]-1,2,3,4-tetrahydroisoquinoline (**13d**).

To a mixture of 0.90 g (2 mmole) of 6,7-dimethoxy-2-(2-hydroxyphenyl)-3-methyl-1-[4-(2-propyl)phenyl]isoquinolinium chloride (**12d**) and 6 ml of dry methanol was added 0.10 g (2.7 mmole) of sodium borohydride in portions with stirring at 0°. The mixture was allowed to warm to room temperature, and stirred for 1 hour. Then 10 ml of water was added and the solution stirred overnight. The crystals which precipitated were isolated by filtration and washed with a small amount of water to obtain 0.80 g of impure product, which was recrystallized from a mixture of 3 ml cyclohexane and 3 ml of *n*-hexane to yield 0.44 g (52 %) of a 1:10 mixture of *cis-trans* 6,7-dimethoxy-2-(2-hydroxyphenyl)-3-methyl-1-[4-(2-propylphenyl)]-1,2,3,4-tetrahydroisoquinoline (**13d**), mp 114-117°; pmr (deuteriochloroform): δ, ppm *trans* 0.90 [d (J = 6.2 Hz), 3H, CH_3-3], *cis* 1.13 [d (J = 6.7 Hz), 6H, CH-C*H*$_3$], *trans* 1.15 [d (J = 6.6 Hz), 6H, CH-C*H*$_3$], *cis* 1.23 [d (J = 6.7 Hz), 3H, CH_3-3], *trans* 2.77 [q (J = 6.7 Hz), 1H, H-3], *trans* 2.89 [dd (J = 3.7 and 15.8 Hz), 1H, H-4], *trans* 3.05 [dd (J = 10.1 and 15.8 Hz), 1H, H-4], *trans* 3.40 (m, 1H, C*H*-CH_3), *trans* 3.57 (s, 3H, OCH_3-7), *cis* 3.70 (s, 3H, OCH_3-7), *trans* 3.89 (s, 3H, OCH_3-6), *cis* 3.92 (s, 3H, OCH_3-6), *cis* 5.08 (s, 1H, H-1), *trans* 5.16 (s, 1H, H-1), *trans* 6.10 (s, 1H, H-5), *cis* 6.35 (s, 1H, H-5), *trans* 6.63 [dd (J = 1.6 and 7.9 Hz), 1H, Ar"H], *trans* 6.65 (s, 1H, H-8), *cis* 6.70 (s, 1H, H-8), *trans* 6.81-7.02 (m, 6H, Ar'H and Ar"H), *trans* 7.31 [dd (J = 1.6 and 7.9 Hz), 1H, Ar"H]; cmr (deuteriochloroform) *trans* **13d**: δ, ppm 20.2 (CH_3-3), 23.7 (CH-*C*H$_3$), 23.9 (CH-*C*H$_3$), 33.5 (*C*H-CH_3), 39.1 (C-4), 55.3 (C-3), 55.8 (two peaks) (OCH_3-6 and OCH_3-7), 70.0 (C-1), 110.3 (C-5), 111.3 (C-8), 126.8 (C-4a), 130.7 (C-8a), 147.2 (C-7), 147.7 (C-6), 113.4, 119.7, 124.5, 125.9, 127.0, 129.0, 135.4, 140.3, 147.6, 154.1 (ArC) (chemical shifts of the *cis* derivative were not detected)

Anal. Calcd. for $C_{27}H_{31}NO_3$ (MW 417.55): C, 77.67; H, 7.48; N, 3.35. Found: C, 77.50; H, 7.32; N, 3.46.

cis 6,7-Dimethoxy-2-(3,4-dimethoxyphenyl)-3-methyl-1-[4-(2-propyl)phenyl]-1,2,3,4-tetrahydroisoquinoline (**13e**)

To a solution of 0.99 g (2 mmole) of 6,7-dimethoxy-2-(3,4-

dimethoxyphenyl)-3-methyl-1-(4-(2-propyl)phenyl)isoquinolinium chloride (**12e**) in 6 ml of dry methanol was added 0.10 g (2.7 mmole) of sodium borohydride in portions with stirring at 0°. The mixture was allowed to warm to room temperature, stirred for an additional 1 hour, diluted with 10 ml of water and the stirring continued overnight. The crystals that precipitated were collected by filtration and washed with a small amount of water to obtain 0.88 g of impure product, which was recrystallized from 12 ml of diisopropylether to yield 0.67 g (73 %) of *cis* 6,7-dimethoxy-2-(3,4-dimethoxyphenyl)-3-methyl-1-[4-(2-propyl)phenyl]-1,2,3,4-tetrahydroisoquinoline (**13e**), mp 89-92°; pmr (deuteriochloroform): δ, ppm 1.20 [d (J = 6.2 Hz), 6H, CH-C*H*$_3$], 1.23 [d (J = 6.7 Hz), 3H, CH_3-3], 2.73-2.77 [m, 2H, H-3 and H-4], 2.84 [dd (J = 4.0 and 14.0 Hz), 1H, H-4], 3.62 (m, 1H, C*H*-CH_3), 3.67 (s, 3H, OCH_3''), 3.71 (s, 3H, OCH_3''), 3.82 (s, 3H, OCH_3-7), 3.87 (s, 3H, OCH_3-6), 5.24 (s, 1H, H-1), 6.37 [d (J = 2.6 Hz), 1H, H-2''], 6.44 (s, 1H, H-5), 6.54 [dd (J = 2.6 and 8.8 Hz), 1H, H-6''], 6.67 (s, 1H, H-8), 6.74 [d (J = 8.8 Hz), 1H, H-5''], 7.03 [d (J = 8.4 Hz), 1H, H-3',5'], 7.09 [d (J = 8.4 Hz), 1H, H-2',6']; cmr (deuteriochloroform): δ, ppm 21.3 (CH_3-3), 23.9 (CH-CH_3), 24.0 (CH-*C*H$_3$), 33.6 (*C*H-CH_3), 52.3 (OCH_3''), 55.7 (OCH_3-7), 55.9 (OCH_3-6), 56.0 (C-3), 56.2 (OCH_3''), 68.9 (C-1), 107.6 (C-5), 110.6 (C-4), 111.4 (C-8), 125.9 (C-8a), 126.3 (C-4a), 142.2 (C-3), 147.1 (C-6), 147.7 (C-7), 111.7, 113.2, 126.2, 127.5, 128.2, 131.2, 144.0, 144.7, 147.1, 148.8 (ArC).

Anal. Calcd. for $C_{29}H_{35}NO_4$ (MW 461.61): C, 75.46; H, 7.64; N, 3.03. Found: C, 75.21; H, 7.72; N, 3.29.

1-(3-Chlorophenyl)-6,7-dimethoxy-2,3-dimethylisoquinolinium Perchlorate (**16a**).

To a mixture of 4.15 g (10 mmol) of 1-(3-chlorophenyl)-6,7-dimethoxy-3-methyl-benzo[*c*]pyrilium perchlorate (**1a**, R = 3-chlorophenyl) [12] and 15 ml of ethanol 1.24 ml (0.94 g, 10 mmol) of 8.03 *M* methylamine solution (Fluka) was added with stirring at room temperature and the stirring was continued for additional 3 hours. The crystals which precipitated were collected by filtration, washed with a small amount of ethanol to obtain 3.70 g of impure product, which was recrystallized from a mixture of 9 ml ethylacetate and 1 ml of acetonitrile to yield 3.56 g (83 %) of 1-(3-chlorophenyl)-6,7-dimethoxy-2,3-dimethylisoquinolinium perchlorate (**16a**) mp 205-208°; pmr (deuteriochloroform): δ, ppm 2.89 (s, 3H, CH_3-3), 3.75 (s, 3H, CH_3-2), 4.00 (s, 3H, OCH_3-7), 4.09 (s, 3H, OCH_3-6), 6.51 (s, 1H, H-8), 7.36 (s, 1H, H-5), 7.55-7.68 (m, 4H, ArH), 8.27 (s, 1H, H-4), cmr (deuteriochloroform): δ, ppm 21.1 (CH_3-3), 42.6 (CH_3-2), 56.0 (OCH_3-7), 57.1 (OCH_3-6), 105.0 (C-5), 105.7 (C-8), 123.4 (C-8a), 124.5 (C-4), 135.7 (C-4a), 144.2 (C-3), 152.3 (C-6), 153.2 (C-1), 157.6 (C-7), 127.5, 128.8, 131.3, 131.4, 132.8, 137.1 (ArC).

Anal. Calcd. for $C_{19}H_{19}Cl_2NO_6$ (MW 428.27): C, 53.29; H, 4.47; Cl, 16.56; N, 3.27. Found: C, 52.98; H, 4.51; Cl, 16.38; N, 3.18.

cis-trans 1-(3-Chlorophenyl)-6,7-dimethoxy-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (**17a**).

To a solution of 0.86 g (2 mmole) of 1-(3-chlorophenyl)-6,7-dimethoxy-2,3-dimethylisoquinolinium chloride (**16a**) in 6 ml of dry methanol was added 0.10 g (2.7 mmole) of sodium borohydride in portions with stirring at room temperature. The mixture was heated to 50° and stirred for additional 6 hours. After cooling the reaction mixture was diluted with a mixture of 8 ml of water and 3 ml of 10 % hydrochloric acid and stirred overnight. The crystals that precipitated were collected by filtration and washed with a small amount of water to yield 0.58 g (88 %) of a 9:1 mixture of *cis-trans* 1-(3-chlorophenyl)-6,7-dimethoxy-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (**17a**), mp 83-87°; pmr (deuteriochloroform): δ, ppm *trans* 1.03 [d (J = 6.6 Hz), 3H, CH_3-3], *cis* 1.27 [d (J = 6.2 Hz), 3H, CH_3-3], *cis* 2.16 (s, 3H, CH_3-2), *trans* 2.27 (s, 3H, CH_3-2), 2.58 (m, 1H, H-3), *cis* 2.68 [dd (J = 2.9 and 15.6 Hz), 1H, H-4], *cis* 2.87 [dd (J = 11.1 and 15.6 Hz), 1H, H-4], *cis* 3.58 (s, 3H, OCH_3-7), *trans* 3.65 (s, 3H, OCH_3-7), *cis* 3.84 (s, 3H, OCH_3-6), *trans* 3.86 (s, 3H, OCH_3-6), *cis* 4.19 (s, 1H, H-1), *trans* 4.45 (s, 1H, H-1), *cis* 6.04 (s, 1H, H-8), *trans* 6.20 (s, 1H, H-8), *cis* 6.55 (s, 1H, H-8), *trans* 6.59 (s, 1H, H-8), 7.23 (m, 4H, ArH); cmr (deuteriochloroform): δ, ppm *trans* 12.8 (CH_3-3), *cis* 20.9 (CH_3-3), *trans* 34.7 (C-4), *cis* 38.1 (C-4), *trans* 39.3 (CH_3-2), *cis* 39.6 (CH_3-2), *trans* 51.5 (C-3), *cis* 55.6 (C-3), 55.8 (two peaks) (OCH_3-6 and OCH_3-7), *trans* 66.0 (C-1), *cis* 71.9 (C-1), *cis* 110.3 (C-5), *trans* 111.2 (C-5), *cis* 111.3 (C-8), *trans* 111.4 (C-8), *cis* 127.0 (C-4a), *cis* 129.8 (C-8a), *cis* 147.1 (C-7), *cis* 147.7 (C-6), 127.4, 127.6, 129.3, 129.5, 134.2, 147.5 (ArC).

Anal. Calcd. for $C_{19}H_{22}ClNO_2$ (MW 331.85): C, 68.77; H, 6.68; Cl, 10.68; N, 4.22. Found: C, 68.55; H, 6.84; Cl, 10.70; N, 4.12.

6,7-Dimethoxy-2,3-dimethyl-1-(4-fluorophenyl)isoquinolinium Perchlorate (**16b**).

To a mixture of 4.00 g (10 mmol) of 6,7-dimethoxy-3-methyl-1-(4-fluorophenyl)benzo[*c*]pyrilium perchlorate (**1a**, R = 4-fluorophenyl) [12] and 15 ml of ethanol was added 1.24 ml (0.94 g, 10 mmol) of 8.03 *M* methylamine solution (Fluka) with stirring at room temperature and stirred for additional 3 hours. The crystals that precipitated were collected by filtration, washed with a small amount of ethanol to yield 2.70 g (66 %) of 6,7-dimethoxy-2,3-dimethyl-1-(4-fluorophenyl)isoquinolinium perchlorate (**16b**) mp 212-214°; pmr (DMSO-d_6): δ, ppm 2.85 (s, 3H, CH_3-3), 3.68 (s, 3H, CH_3-2), 3.87 (s, 3H, OCH_3-7), 4.07 (s, 3H, OCH_3-6), 6.57 (s, 1H, H-8), 7.63-7.75 (m, 4H, ArH), 7.64 (s, 1H, H-5), 8.27 (s, 1H, H-4), cmr (DMSO-d_6): δ, ppm 20.8 (CH_3-3), 42.8 (CH_3-2), 55.9 (OCH_3-7), 57.0 (OCH_3-6), 105.1 (C-5), 106.1 (C-8), 117.0 [d (J = 22.1 Hz), C-3''], 123.1 (C-8a), 123.4 (C-4), 127.6 [d (J = 3.4 Hz), C-1''], 131.9 [d (J = 8.8 Hz), C-2''], 136.2 (C-4a), 144.2 (C-3), 151.9 (C-6), 154.4 (C-1), 157.2 (C-7), 163.5 [d (J = 249.5 Hz), C-4''].

Anal. Calcd. for $C_{19}H_{19}ClFNO_6$ (MW 411.82): C, 55.42; H, 4.65; Cl, 8.61; N, 3.40. Found: C, 55.09; H, 4.66; Cl, 8.49; N, 3.31.

cis-trans 6,7-Dimethoxy-2,3-dimethyl-1-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (**17b**).

To a mixture of 0.82 g (2 mmole) of 6,7-dimethoxy-2,3-dimethyl-1-(4-fluorophenyl)isoquinolinium chloride (**16b**) and 6 ml of dry methanol was added 0.10 g (2.7 mmole) of sodium borohydride in portions with stirring at room temperature. The mixture was heated to 50° and stirred for additional 2 hours. Then it was diluted with 15 ml of water and stirred overnight. The crystals which precipitated were collected by filtration and washed with a small amount of water to yield 0.50 g (79 %) of an 8:1 mixture of *cis-trans* 6,7-dimethoxy-2,3-dimethyl-1-(4-fluorophenyl)-1,2,3,4-tetrahydroisoquinoline (**17b**) mp 104-107°; pmr (deuteriochloroform): δ, ppm *trans* 1.03 [d (J = 6.6 Hz), 3H,

CH_3-3], *cis* 1.27 [d (J = 5.9 Hz), 3H, CH_3-3], *trans* 2.15 (s, 3H, CH_3-2), *cis* 2.25 (s, 3H, CH_3-2), 2.58 (m, 1H, H-3), *cis* 2.68 [dd (J = 2.9 and 15.3 Hz), 1H, H-4], *cis* 2.88 [dd (J = 11.4 and 15.4 Hz), 1H, H-4], *cis* 3.56 (s, 3H, OCH_3-7), *trans* 3.64 (s, 3H, OCH_3-7), *cis* 3.84 (s, 3H, OCH_3-6), *trans* 3.86 (s, 3H, OCH_3-6), *cis* 4.18 (s, 1H, H-1), *trans* 4.45 (s, 1H, H-1), *cis* 6.01 (s, 1H, H-8), *trans* 6.18 (s, 1H, H-8), *cis* 6.55 (s, 1H, H-8), *trans* 6.59 (s, 1H, H-8), 6.93-7.32 (m, 4H, ArH); cmr (deuteriochloroform): δ, ppm *trans* 12.6 (CH_3-3), *cis* 20.9 (CH_3-3), *trans* 34.9 (C-4), *cis* 38.4 (C-4), *trans* 39.3 (CH_3-2), *cis* 39.4 (CH_3-2), *trans* 51.2 (C-3), *cis* 55.7 (C-3), 55.8 (two peaks) (OCH_3-6 and OCH_3-7), *trans* 65.6 (C-1), *cis* 71.6 (C-1), *cis* 110.3 (C-5), *trans* 111.2 (C-5), *cis* 111.3 (C-8), *trans* 111.4 (C-8), *trans* 114.8 [d (J = 21.0 Hz), C-3'], *cis* 115.1 [d (J = 21.0 Hz), C-3'], *cis* 126.5 [d (J = 3.3 Hz), C-1'], 127.0 (C-4a), 130.5 (C-8a), *cis* 130.8 [d (J = 8.0 Hz), C-2'], *cis* 147.0, (C-7), *cis* 147.4 (C-6), *cis* 161.9 [d (J = 244.9 Hz), C-4'].

Anal. Calcd. for $C_{19}H_{22}FNO_2$ (MW 315.39): C, 72.36; H, 7.03; N, 4.44. Found: C, 72.14; H, 7.04; N, 4.41.

Conditions of Liquid Chromatography/Mass Spectroscopy (HPLC/MS).

(1) MS measuring conditions: Instrument: Micromass LC-TOF, Ionization mode: ES+, Capillary: 3500 V, MCP Detector 2700 V, Desolvation temperature 300 °C, Source temperature: 150 °C, MS_1: Cone Voltage: 20 eV, Mass Range: 100.0 – 1000.0, MS_2: Cone Voltage: 50 eV, Mass Range: 100.0 – 1000.0

(2) LC measuring conditions: Instrument: Waters 2790 HPLC System, Pump: 2790, Detector: Photodiode Array Detector 996, Autosampler: 2790, Chromatographic Conditions (HPLC-MS): Column: Xterra MS C_8, 3.5 µm, 150 x 4.6 mm I.D. (Waters) Flow rate: 1.0 ml per minute, Detection (UV): 240 nm (220 – 360 nm DAD) Injected volume: 10 µl, Column temperature: 40°C, Mobile phase: (A) 95% water 5% acetonitrile, (B) 100% acetonitrile, (C) 0.1M Ammonium-acetate solution in water (contains 5% acetonitrile) Gradient program: Time: 0.0 (min.): A: 90.0 (%), B: 0.0 (%), C: 10.0 (%); Time: 10.0 (min.): A: 0.0 (%), B: 90.0 (%), C: 10.0 (%); Time: 15.0 (min.): A: 0.0 (%), B: 90.0 (%), C: 10.0 (%); Time: 15.1 (min.): A: 90.0 (%), B: 0.0 (%), C: 10.0 (%); Time: 20.0 (min.): A: 90.0 (%), B: 0.0 (%), C: 10.0 (%).

Retention times: **12c**: 8.92 min., **13c**: 12.19 min., **14c**: 11.94 min.

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[15] Compound **2a/3** was prepared by alkylation of 5-amino-2,3-dihydro-1*H*-1,2,4-triazole-3-thione [16] with 3,3-dimethylaminopropylchloride according to [17], Yield 64 %, mp. 128-130° (acetonitrile).

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[18] Compound **2a/4** was prepared by alkylation of 5-amino-2,3-dihydro-1*H*-1,2,4-triazole-3-thione [16] with 3-[4-(3-chlorophenyl)piperazin-1-yl]propylchloride according to [17], Yield 54 %, mp. 157-160° (ethanol).

[19] Compound **2a/5** was prepared by alkylation of 5-amino-2,3-dihydro-1*H*-1,2,4-triazole-3-thione [16] with 3-[4-(2-pyrimidinyl)piperazin-1-yl]propylchloride according to [17], Yield 56 %, mp. 128-131° (acetonitrile).

[20] Compound **2a/6** was prepared by alkylation of 5-amino-2,3-dihydro-1*H*-1,2,4-triazole-3-thione [16] with 2-[(2,3-dihydrobenzodioxan-5-yl)oxy]ethylbromide according to [17], Yield 59 %, mp. 167-169° (acetonitrile/methanol).

[21] Compound **2a/7** was prepared by alkylation of 5-amino-2,3-dihydro-1*H*-1,2,4-triazole-3-thione [16] with 3-[4-(3,4-dimethylphenyl)piperazin-1-yl]propylchloride according to [17], Yield 72 %, mp. 85-87° (acetonitrile).