SYNTHESIS OF ISOQUINO[1,2-*b*]QUINAZOLINES BY CYCLOADDITION REACTION

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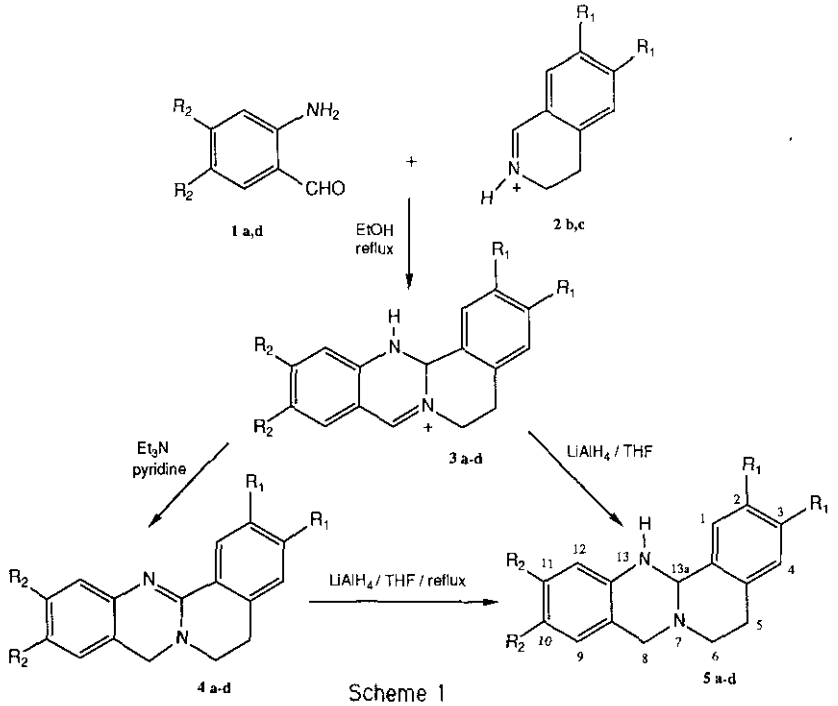
Abstract -*The cycloaddition reaction of 3,4-dihydroisoquinolinium salts* (**2c,d**) *with 2-aminobenzaldehydes* (**1a,b**) *was a convenient way to obtain 5,6,13,13a-tetrahydro-8* H*-isoquino[1,2-* b*]quinazolinium salts* (**3a-d**). *The reduction, transposition and oxidation of these compounds gave 8* H*-isoquino[1,2-* b*]quinazoline derivatives in good yields. The mechanism of the cycloaddition reaction is discussed. The cis and trans isomers of the tetrahydro derivative* (**5d**) *have been isolated and identified by an infrared spectroscopic study.*

During the course of our synthetic work on the berbine ring system,[1] our interest was focused in the preparation of isoquino[1,2-*b*]quinazolines (**5a-d**). As a matter of fact, these compounds possess a second nitrogen atom instead of the C-13 carbon atom of the berbine skeleton. We have considered this structural feature in order to enhance the pharmacological activity of the berbine heterocycles.[2,3]

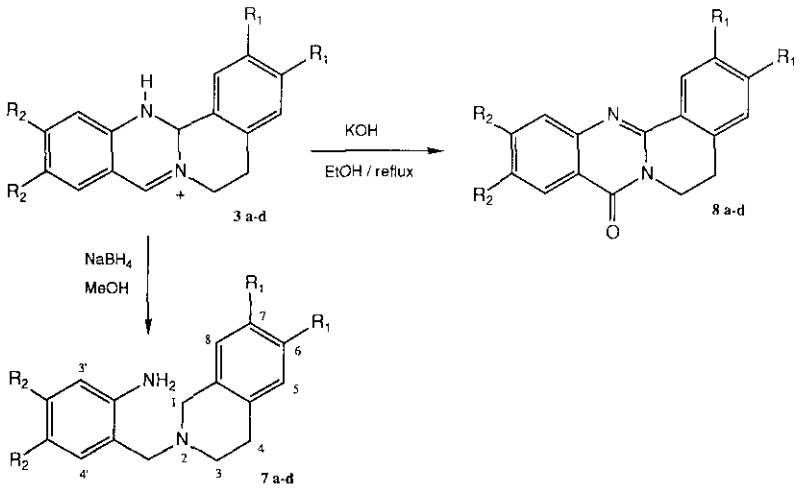


Scheme 1

A unique chemical pathway to the isoquino[1,2-*b*]quinazoline structure has been reported in the literature; the method consisted in a condensation of an isatoic anhydride with a 3,4-dihydroisoquinoline.[4] For our purpose, a new synthetic procedure was necessary for preparing further derivatives of this heterocycle.

On the basis of the synthesis of the rutecarpine,[5] we have shown that the salts (picrate or hydrochloride) of 3,4-dihydroisoquinolines (**2c,d**) could react directly with 2-aminobenzaldehydes (**1a,b**) in boiling ethanol. Following this method we isolated isoquino[1,2-*b*]quinazolinium salts (**3a-d**) in good yields (Scheme 1). As expected, the immonium double bond was easily reduced with lithium aluminum hydride to obtain the desired 5,6,13,13a-tetrahydro-8*H*-isoquino[1,2-*b*]quinazolines (**5a-d**).

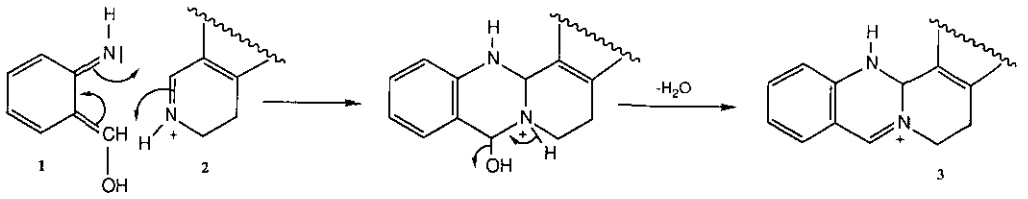
We observed that the migration of the immonium double bond of compounds (**3a-d**), in anhydrous basic medium using triethylamine in pyridine afforded the 5,6-dihydro-8*H*-isoquino[1,2-*b*]quinazolines (**4a-d**). We reduced the imino double bond with lithium aluminum hydride in refluxing tetrahydrofuran to form (**5a-d**). In contrast, the isoquinoquinazolinium salts (**3a-d**), in aqueous basic solution did not afford any transposition products (**4a-d**). But an addition of the hydroxide anion to the immonium double bond took place, followed by an oxidation of the intermediate carbinolamine to give 5,6-dihydro-8*H*-isoquino[1,2-*b*]quinazoline-8-ones (**6a-d**) (Scheme 2). When, however, the immonium salts (**3a-d**) were reduced with a large excess of sodium borohydride in a polar solvent, such as methanol, an opening of the ring occurred and 2-(2-aminobenzyl)-1,2,3,4-tetrahydroisoquinolines (**7a-d**) were isolated in good yields.



Scheme 2

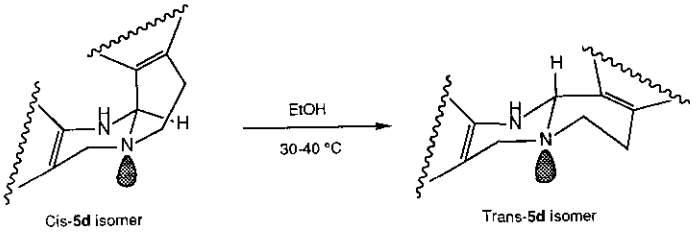
The starting material 2-aminobenzaldehydes (**1a,b**) and 3,4-dihydroisoquinolines (**2c,d**) were prepared according to the literature.[6-9]

We investigated the mechanism of the cycloaddition reaction of 3,4-dihydroisoquinolinium salts (**2c,d**) with 2-aminobenzaldehydes (**1a,b**). The formyl group and the amino function were alternatively removed in compounds (**1a,b**). Thus, 3,4-dimethoxyaniline and 3,4-dimethoxybenzaldehyde were attempted to react directly with the 3,4-dihydroisoquinoline hydrochloride (**2d**). In agreement with our previsions, no reaction products were formed. These results suggested that the amino and aldehyde groups should be adjacent to give compounds (**3a-d**). Actually, the resonance structure of the imino enol (**1**) should represent the active diene, whereas the imino double bond, activated as a salt, should be the dienophile, as described in the Diels-Alder reaction (Scheme 3).



Scheme 3

The conformation of the tetrahydroisoquinoquinolizine (**5d**) was studied by ir spectroscopy. This compound, isolated after lithium aluminum hydride reduction of (**4d**), did not show any Bohlmann bands in the 2800-2600 cm^{-1} region. This suggested that the junction of the B/C rings was cis.[10, 11] The heating of the cis isomer at 30-40°C for a few minutes in ethanolic solution, involved the conversion into the trans isomer, as proved by the appearance of Bohlmann bands (Scheme 4). We observed also a shift of the NH absorption from 3365 cm^{-1} (cis) to 3325 cm^{-1} (trans).



Scheme 4

Based on the data presented above, the cycloaddition reaction of 2-aminobenzaldehydes with 3,4-dihydroisoquinolinium salts, followed by lithium aluminum hydride reduction may be concluded to serve as an adequate means for obtaining isoquino[1,2-*b*]quinazoline derivatives.

EXPERIMENTAL

Melting points (uncorrected) were determined on a KOFFLER hot-stage apparatus. Spectral data were obtained with a Beckman IR 4230 spectrophotometer and a Brucker AC 200 NMR spectrometer. Analyses were performed by Cent. Sci. Microan., Vernaison. All tlcs were performed on Merck Silica Gel F-254 plates ($CHCl_3$-AcOEt-Et_3N, 25: 25: 1).

General procedure for preparing the 5,6,13,13a-tetrahydroisoquino[1,2-*b*]quinolizinium salts (picrate or chloride) (3a-d) - A mixture of 3,4-dihydroisoquinoline (**2c**) (picrate) or (**2d**) (hydrochloride) (2.78 mmol) and 2-aminobenzaldehyde (**1a**) or (**1b**) (2.78 mmol) in absolute ethanol(50 ml), was refluxed under stirring for 1 h. After cooling and addition of ether, the compounds (**3a-d**) precipitated , were filtered, washed with ether and dried. The yellow crude product was recrystallized from ethanol.

5,6,13,13a-Tetrahydroisoquino[1,2-*b*]quinazolinium picrate (3a) -yield 62%; mp 198°C; ir (KBr) (cm^{-1}): 3340 (NH), 1640 (C=N$^+$); ^{1}H-nmr (DMSO-d_6) δ: 3.10 (m, 2H, H_5); 4.20 (m, 2H, H_6); 6.18 (s, 1H, H_{13a}); 7.40 - 7.88 (m, 8H, arom.); 9.62 (s, 1H, NH). Anal. Calcd for $C_{22}H_{17}N_5O_7$: C, 57.02; H, 3.70; N, 15.11. Found: C, 56.98; H, 3.72; N, 15.07.

2,3-Dimethoxy-5,6,13,13a-tetrahydroisoquino[1,2-*b*]quinazolinium chloride (3b) -yield 79%; mp 260°C; ir (KBr) (cm^{-1}): 3380 (NH), 1630 (C=N$^+$); ^{1}H-nmr (DMSO-d_6) δ: 3.00 (m, 4H, 2xH_5 and 2xH_6); 3.85 (s, 3H, CH_3O at C_3); 3.90 (s, 3H, CH_3O at C_2); 6.15 (s, 1H, H_{13a}); 7.10 (s, 1H, H_4); 7.25 (s, 1H, H_1); 7.50 (m, 4 H, H_9-H_{12}); 8.80 (s, 1H, H_8); 9.80 (s, 1H, NH). Anal. Calcd for $C_{18}H_{19}N_2O_2Cl$: C, 65.54; H, 5.81; N, 8.49. Found: C, 65.57; H, 5.77; N, 8.51.

10,11-Dimethoxy-5,6,13,13a-tetrahydroisoquino[1,2-*b*]quinazolinium picrate (3c) -yield 82%; mp 210°C; ir (KBr) (cm^{-1}): 3400 (NH), 1640 cm^{-1}; ^{1}H-nmr (DMSO-d_6) δ: 3.08 (m, 2H, H_5); 3.72 (s, 3H, CH_3O at C_{10}); 3.85 (s, 3H, CH_3O at C_{11}); 4.14 (m, 2H, H_6); 6.03 (s, 1H, H_{13a}); 6.52 (s, 1H, H_{12}); 7.06 (s, 1H, H_9); 7.42 (m, 4H, H_1-H_4); 8.00 (s, 1H, NH) 8.54 (s, 2H, arom. of picrate); 8.75 (s, 1H, H_8). Anal. Calcd for $C_{24}H_{21}N_5O_9$: C, 55.07; H, 4.04; N, 13.38. Found: C, 55.09; H, 4.09; N, 13.42.

2,3,10,11-Tetramethoxy-5,6,13,13a-tetrahydroisoquino[1,2-*b*]quinazolinium chloride (3d) -yield 85%; mp 264°C; ir (KBr) (cm^{-1}): 3360 (NH), 1640 (C = N$^+$); ^{1}H-nmr (DMSO-d_6) δ: 2.70 (m, 2H, H_5); 3.75 (s, 6H, 2xCH_3O at C_2, C_3); 3.90 (s, 3H, CH_3O at C_{10}); 3.95 (s, 3H, CH_3O at C_{11}); 5.60 (s, 1H, H_{13a}); 6.40 (s, 1H, H_{12}); 6.70 (s, 1H, H_9); 7.10 (s, 1H, H_4); 7.25 (s, 1H, H_1); 8.75 (s, 1H, H_8); 9.05 (s, 1H, NH). Anal. Calcd for $C_{20}H_{23}N_2O_4Cl$: C, 67.59 H, 6.52; N, 7.88. Found: C, 67.52; H, 6.47; N, 7.85.

General procedure for preparing the 5,6-dihydro-8*H*- isoquino[1,2-*b*]quinazoline (4a-d) - A mixture of isoquinoquinazolinium salt (**3**) (2.16 mmol), triethylamine (dried over KOH) (10 ml) and dry pyridine (50 ml) was refluxed for 30 min, under stirring. Then the solvent was removed and the residue was triturated in ether. The resulting solid was filtered, washed with ether, dried, and recrystallized from isopropanol.

5,6-Dihydro-8*H*- isoquino[1,2-*b*]quinazoline (4a) -yield 66%; mp 158°C; ir ($CHCl_3$) (cm^{-1}): 1605 (C = N); ^{1}H-nmr ($CDCl_3$) δ: 3.01 (t, $J_{5,6}$=6.3Hz, 2H, H_5); 3.26 (t, $J_{5,6}$=6.3Hz, 2H, H_6); 4.52 (s, 2H, H_8); 7.25-7.36 (m, 7H, arom.); 8.28 (d, $J_{1,2}$=7.9 Hz, 1H, H_1). Anal. Calcd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 81.98; H, 5.96; N, 12.03.

5,6-Dihydro-2,3-dimethoxy-8*H*-isoquino[1,2-*b*]quinazoline (4b) -yield 71%; mp 180°C; ir ($CHCl_3$)(cm^{-1}): 1605 (C = N); ^{1}H-nmr ($CDCl_3$) δ: 2.97 (t, $J_{5,6}$=6.2Hz, 2H, H_5); 3.23 (t, $J_{5,6}$=6.2Hz, 2H, H_6); 3.87 (s, 3H, CH_3O at C_3); 4.50 (s, 2H, H_8); 6.40 (s, 1H, H_4); 7.24-7.35 (m, 4H, H_{9-12}); 7.62 (s, 1H, H_1). Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found : C, 73.49; H, 6.10; N, 9.58.

5,6-Dihydro-10,11-dimethoxy-8*H*- isoquino[1,2-*b*]quinazoline (4c) -yield 63%; mp 161°C; ir ($CHCl_3$) (cm^{-1}): 1610 (C=N); ^{1}H-nmr ($CDCl_3$) δ: 3.00 (t, $J_{5,6}$=6.3Hz, 2H, H_5); 3.25 (t, $J_{5,6}$=6.3Hz, 2H, H_6); 3.85 (s, 6H,2xCH_3O); 4.50 (s, 2H, H_8); 6.35 (s, 1H, H_9); 6.80 (s, 1H, H_{12}); 7.25 (m, 3H, H_{2-4}); 8.30 (d, $J_{1,2}$=7.9 Hz, 1H, H_1). Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.48; H, 6.19; N, 9.53.

5,6-Dihydro-2,3,10,11-tetramethoxy-8*H*- isoquino[1,2-*b*]quinazoline (4d) -yield 79%; mp 187°C; ir ($CHCl_3$) (cm^{-1}): 1605 (C = N); ^{1}H-nmr ($CDCl_3$) δ: 2.97 (t, $J_{5,6}$=6.2Hz, 2H, H_5); 3.23 (t, $J_{5,6}$=6.2Hz, 2H, H_6); 3.86 (s, 3H, CH_3O at C_3); 3.90 (s, 6H, 2xCH_3O at C_{10},C_{11}); 4.00 (s, 3H, CH_3O at C_2); 4.45 (s, 2H, H_8); 7.43 (s, 1H, H_4); 7.56 (s, 1H, H_9); 7.80 (s, 1H, H_{12}); 7.99 (s, 1H, H_1). Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.49; H, 6.10; N, 9.58.

General procedures for reduction of compounds (3 and 4) to cis-5,6,13,13a-tetrahydro-8*H*-isoquino[1,2-*b*]quinazolines (5a-d)

Method A - In a three-necked flask was suspensed excess $LiAlH_4$ (1g) in dry THF (20 ml). The mixture was cooled at -15°C in a salt ice bath. A solution of compound (**3**) (2.0 mmol) in dry THF (25 ml) was added dropwise for a period of 25 min under strirring. After addition was complete, the mixture was allowed to stand at room temperature for 1 h. Then water(1 ml), 15 % sodium hydroxide solution(1 ml) and water (3 ml) were respectively added in order to hydrolyze the resulting complex. The lithium and aluminum hydroxides were filtered, washed thoroughly with THF. The filtrate and washing were evaporated under

reduced pressure at room temperature. The resulting product was triturated in ether, filtered, and dried. Purification was realised by dissolution in ethanol and precipitation with ether.

Method B - The reduction of the compounds (**4**) to tetrahydro-derivatives (**5**) was achieved with $LiAlH_4$ in THF under reflux for 40 h. The isolation and purification procedures were the same as described above (method A).

cis-5,6,13,13a-Tetrahydro-8*H*-isoquino[1,2-*b*]quinazoline (5a) -yields 40%(A), 36%(B); mp 168°C; ir (KBr) (cm^{-1}): 3365 (NH), 2905-2840 (CH alkanes); ^{1}H-Nmr ($CDCl_3$) δ: 2.96 (m, 2H, H_5); 3.48 (m, 2H, H_6); 3.90 (d, $J_{8a,8b}$=15.3 Hz,1H, H_8); 3.99 (d, $J_{8a,8b}$=15.3 Hz, 1H, H_8); 7.28 (m, 8H, arom.). Anal. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 81.27; H, 6.88; N, 11.89.

cis-2,3-Dimethoxy-5,6,13,13a-tetrahydro-8*H*-isoquino[1,2-*b*]quinazoline (5b) -yields 35%(A), 32%(B); mp 173°C; ir (KBr) (cm^{-1}): 3360 (NH), 2905-2840 (CH alkanes); ^{1}H-nmr ($CDCl_3$) δ: 2.94 (m, 2H, H_5); 3.45 (m, 2H, H_6); 3.65 (s, 1H, NH); 3.85 (s, 6H, 2xCH_3O); 3.98 (d, $J_{8a,8b}$=15.3 Hz,1H, H_8); 4.78 (s, 1H, H_{13a}); 6.61 (s, 2H, H_{14}); 7.25 (m, 4H, H_{9-12}). Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.90; H, 6.75; N, 9.48.

cis-10,11-Dimethoxy-5,6,13,13a-tetrahydro-8*H* -isoquino[1,2-*b*]quinazoline (5c)- yields 35%(A), 38%(B); mp 182°C; ir (KBr) (cm^{-1}) : 3360 (NH), 2910-2840 (CH alkanes); ^{1}H-nmr($CDCl_3$) δ: 2.95 (m, 2H, H_5); 3.46 (m, 2H, H_6); 3.55 (s, 1H, NH); 3.89 (s, 3H, CH_3O at C_{10}); 3.91 (s, 3H, CH_3O at C_{11}); 3.99 (d, $J_{8a,8b}$=15.1 Hz,1H, H_8); 4.81 (s, 1H, H_{13a}); 6.60 (s, 2H, $H_{9,12}$); 7.26 (m, 4H, H_{1-4}). Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.91; H, 6.78; N, 9.40.

cis-5,6,13,13a-Tetrahydro-2,3,10,11-tetramethoxy-8*H*-isoquino[1,2-*b*]quinazoline (5d) -yields 33%(A), 40%(B); mp 186°C; ir (KBr) (cm^{-1}): 3365 (NH), 2905-2840 (CH alkanes); ^{1}H-nmr ($CDCl_3$) δ: 2.92 (m, 2H, H_5); 3.44 (m, 2H, H_6); 3.60 (s, 1H, NH); 3.82 (s, 6H, 2xCH_3O at C_2, C_3); 3.89 (s, 3H, CH_3O at C_{10}); 3.91 (s, 3H, CH_3O at C_{11}); 3.99 (d, $J_{8a,8b}$=15.1 Hz,1H, H_8); 4.80 (s, 1H, H_{13a}); 6.60 (m, 4H, arom.). Anal. Calcd for $C_{20}H_{24}N_2O_4$: C, 67.59; H, 6.52; N, 7.88. Found: C, 67.64; H, 6.48; N, 7.90.

General procedure for oxidation of compounds (3a-d) to 5,6-dihydro-8*H*-isoquino[1,2-*b*]quinazolin-8-ones (6a-d) - To an ethanolic solution (50 ml) of the corresponding isoquinoquinazolinium salt (4.30 mmol) was added potassium hydroxide (6.80 mmol). The mixture was heated under reflux for 1.5h. After cooling, the solvent was evaporated and the residue was recrystallized from ethanol to give 6a-d.

5,6-Dihydro-8*H*-isoquino[1,2-*b*]quinazolin-8-one (6a) -yield 30%; mp 196°C; ir ($CHCl_3$) (cm^{-1}): 1660 (C = O); 1615 (C = N); ^{1}H-nmr ($CDCl_3$) δ: 3.05 (t, $J_{5,6}$=6.5 Hz, 2H, H_5); 4.35 (t, $J_{5,6}$=6.5 Hz, 2H, H_6); 7.15 (d, $J_{11,12}$=8.1 Hz,1H, H_{12}); 7.65 (d, $J_{9,10}$=8.0 Hz,1H, H_9); 8.45 (d, $J_{1,2}$=7.9 Hz,1H, H_1). Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.44; H, 4.90; N, 11.23.

5,6-Dihydro-2,3-dimethoxy-8*H*-isoquino[1,2-*b*]quinazolin-8-one (6b) -yield 38%; mp 208°C; ir ($CHCl_3$) (cm^{-1}): 1665 (C = O); 1605 (C = N); ^{1}H-nmr ($CDCl_3$) δ: 3.01 (t, $J_{5,6}$=6.5 Hz, 2H, H_5); 3.95 (s, 6H, 2xCH_3O at $C_{2,3}$); 4.40 (t, $J_{5,6}$=6.5 Hz, 2H, H_6); 6.75 (s, 1H, H_4); 7.65 (m, 4H, H_{9-12}); 8.25 (s, 1H, H_1). Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.10; H, 5.23; N, 9.09. Found: C, 70.05; H, 5.27; N, 9.12.

5,6-Dihydro-10,11-dimethoxy-8*H*-isoquino[1,2-*b*]quinazolin-8-one (6c) -yield 42 %; mp 212°C; ir ($CHCl_3$) (cm^{-1}): 1650 (C = O); 1605 (C = N); ^{1}H-nmr ($CDCl_3$) δ: 3.05 (t, $J_{5,6}$=6.5 Hz, 2H, H_5); 4.00 (s, 6H, 2xCH_3O at $C_{10,11}$); 4.40 (t, $J_{5,6}$=6.5 Hz, 2H, H_6); 7.15 (s, 1H, H_{12}); 7.35 (m, 3H, H_{2-4}); 7.69 (s, 1H, H_3); 8.45 (d, $J_{1,2}$=7.9 Hz, 1H, H_1). Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.10; H, 5.23; N, 9.09. Found: C, 70.08; H, 5.19; N, 9.06.

5,6-Dihydro-2,3,10,11-tetramethoxy-8*H*-isoquino[1,2-*b*]quinazolin-8-one (6d) -yield 30%; mp 243°C; ir ($CHCl_3$) (cm^{-1}): 1650 (C = O); 1605 (C = N); ^{1}H-nmr ($CDCl_3$) δ: 3.00 (t, $J_{5,6}$=6.3 Hz, 2H, H_5); 3.95 (s, 12H, 4xCH_3O); 4.35 (t, $J_{5,6}$=6.3 Hz, 2H, H_6), 6.70 (s, 1H, H_4); 7.15 (s, 1H, H_{12}); 7.60 (s, 1H, H_9); 7.90 (s, 1H, H_1). Anal. Calcd for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 65.17; H, 5.52; N, 7.63.

General procedure for opening ring of compounds(3a-d) to 2-(2-aminobenzyl)-1,2,3,4-tetrahydroisoquinolines (7a-d) - To a methanolic solution (50 ml) of isoquinoquinazolinium salt (3) (3.78 mmol) was added sodium borohydride (7.96 mmol) in small portions under continuous stirring. After 30 min, the solvent was removed in vaccuo. The resulting oil was dissolved in ether and then compound (7) crystallized slowly, which was recrystallised from ethanol/ether.

2-(2-Aminobenzyl)-1,2,3,4-tetrahydroisoquinoline (7a) -oil, purified by chromatography on silica gel,elution was performed with $CHCl_3$: CH_3OH(80:20); yield 67%; mp 208°C; ir ($CHCl_3$) (cm^{-1}): 3440 and 3300 (NH_2), ^{1}H-nmr ($CDCl_3$) δ: 2.80 (m, 4H, $H_{3,4}$); 3.60 (s, 2H, benzylic CH_2); 3.61 (s, 2H, H_1); 4.85 (s, 2H, NH_2); 7.10 (m, 8H, arom.). Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.75. Found: C, 80.70; H, 7.58; N, 11.71.

2-(2-Aminobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (7b) -yield 65%; mp 155 °C; ir ($CHCl_3$) (cm^{-1}): 3425 and 3230 (NH_2); ^{1}H-nmr ($CDCl_3$) δ: 2.78 (m, 4H, $H_{3,4}$); 3.65 (s, 2H, benzylic CH_2); 3.75 (s, 2H, H_1); 3.80(s, 3H,CH_3O at $C_{6\ or\ 7}$); 3.85(s, 3H,CH_3O at $C_{7\ or\ 6}$); 4.60 (s, 2H, NH_2); 6.95 (m, 6H, arom.). Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.99; H, 6.75; N, 8.94. Found: C, 68.95; H, 6.78; N, 8.91.

2-(2-Amino-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline (7c) -yield 90%; mp 106 °C; ir ($CHCl_3$) (cm^{-1}): 3340 and 3240 (NH_2); ^{1}H-nmr ($CDCl_3$) δ: 2.80 (m, 4H, $H_{3,4}$); 3.25 (s, 2H, NH_2); 3.65 (s, 2H, benzylic CH_2); 3.75 (s, 2H, H_1); 3.80 (s, 6H, 2xCH_3O); 6.25 (s, 1H, H_3'); 6.60 (s, 1H, H_6'); 7.15 (m, 4H, H_{5-8}). Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.99; H, 6.75; N, 8.94. Found: C, 69.02; H, 6.71; N, 8.96.

2-(2-Amino-4,5-dimethoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (7d) -yield 88%; mp 154 °C; ir ($CHCl_3$) (cm^{-1}): 3430 and 3300 (NH_2); ^1H-nmr ($CDCl_3$) δ: 2.75 (s, 4H, $H_{3,4}$); 3.50 (s, 2H, benzylic CH_2); 3.65 (s, 2H, H_1); 3.80 (s, 12H, 4xCH_3O); 4.55 (s, 2H, NH_2); 6.30 (s, 1H, $H_{3'}$); 6.50 (s, 1H, $H_{6'}$); 6.65 (s, H, $H_{5 \text{ or } 8}$); 6.70 (s, H, $H_{8 \text{ or } 5}$). Anal. Calcd for $C_{20}H_{26}N_2O_4$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.98; H, 7.28; N, 7.85.

Isomerisation of compound (cis-5d) to (trans-5d) - A mixture of (cis-5d)(1g) and ethanol(20 ml) was refluxed for 10 min. The solvent was evaporated and the crude compound was crystallized from ether: yield 98 % (0.983g); mp 189°C; ir (KBr) (cm^{-1}): 3325 (NH); 2905-2840 (CH alkanes); 2820-2700 (Bohlmann bands).

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