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Stereochemical course of the reaction of homophthalic anhydride and *N*-(1-methyl-1*H*-pyrrol-2-yl-methylidene)-phenethylamine was studied. Mixtures of the expected *trans*- and *cis*-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acids trans-**4** and cis-**4** were obtained along with by-products **5** and **6**. The ratios of all products and the diastereomers, obtained under different reaction conditions, were established by pmr. THF as a solvent and ultrasonic treatment are applied for the first time in the reaction of this type. The reaction was made diastereoselective towards any isomer. The carboxylic group of trans-**4** was transformed in four steps into various cyclic amino-methyl groups yielding numerous new tetrahydroisoquinolinones trans-**10a-i** incorporating a given fragment of pharmacological interest. Reduction of **10a-i** was studied.

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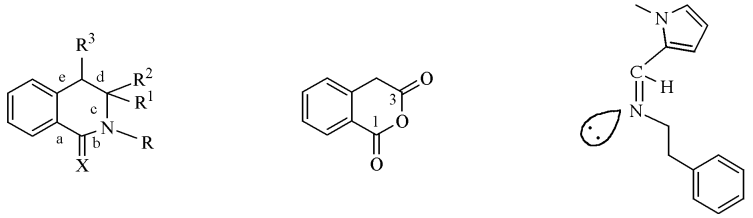
2,3,4-Trisubstituted 1,2,3,4-tetrahydroisoquinolines **1** are important from synthetic and pharmacological point of view [1-9]. Some of them have *cis* and *trans* forms if $C^3$ and $C^4$ are stereogenic centres. The synthesis of such tetrahydroisoquinolines is possible by reactions of different types where one or two bonds of piperidine ring are formed [10-19]. Compounds of type **1a** are prepared in one step, with the formation of **b** and **d** bonds, by a new reaction from homophthalic anhydride and an imine [20,21]. Haimova *et al*. [22,23] assume that bond **d** is formed before bond **b**. Chushman and Madaj [24] discuss this mechanism of the reaction, the alternative mechanism (**b** formed before **d**) and the concerted mechanism (**b** and **d** are formed simultaneously). On the basis of data from Hammett equation, they give preference of the alternative mechanism. In the first paper of this series [1], we have pointed out that some of the data of ref. 24 are in agreement with the concerted mechanism. Thus, this mechanism should be not excluded from consideration. A specific concerted mechanism being $2\pi + 4\sigma$ has been proposed [1]. Recently, a modification of this mechanism has been supported [25] by a MO and DFT theoretical study.

Since 1977, the reaction between a homophthalic anhydride and an imine has been widely applied [1,2,20-24,26-38] for preparation of substituted tetrahydroisoquinolinones and polycyclic heterocycles containing isoquinoline moiety. Although the reaction is of great synthetic importance, its stereochemical course varies from case to case and thus predictions are difficult to make.

The present paper deals with the chemical and stereochemical course of the reaction between homophathalic anhydride (**2**) and the acyclic imine **3** aiming at selection of conditions leading predominantly to either trans-**4** or cis-**4** (see Scheme 1). In general, *trans* and *cis* diastereomers, as racemates, have different properties including pharmacological activity. Thus, making a specific reaction diastereoselective is important. Compounds **2** and **3** have enantiotopic faces (*re*/*si*) as shown in the formula of compound **2**. Moreover, **3** exists in *E* and *Z* forms.

Till now, the reaction between homophthalic anhydride (**2**) and an imine has been performed in large scale in boiling benzene mainly affording the corresponding thermodinamically controlled acid (*trans* in the case of isoquinolines of type **1a** and *cis* in the case of compounds with a condensed heterocyclic system including isoquinoline moiety) [1,20-22,28,29,38,39]. At room temperature the reaction is considered as kinetically controlled and mixtures of *cis* and *trans* acids are obtained [2,22,24,40].




**1** (X = O or 2H)
**a**: X = O, $R^3$ = $CO_2H$

**2**
front side : si ($C^1$) - re ($C^3$)
rear side : re ($C^1$) - si ($C^3$)

**3**
Z: re and si
E: re and si

*Trans*/*cis* ratio depends [24] on the substituents in positions 2 and 3, solvent used (chloroform, methanol or formamide) and temperature, ranging from 22 °C to 61 °C. There are two different ways for preparation of the reaction mixture: a) the two reactants are mixed simultaneously [24,40] or b) solid **2** is added to a solution of an imine [2,22,24,39]. Treatment of reaction mixture with 10 % sodium hydroxide, to isolate the acidic products, is considered as a factor resulting in a change of the configuration of the kinetically controlled isomer [24].

To establish the *trans*/*cis* ratio, the reaction between anhydride **2** and imine **3** was done in small scale (by 0.5 mmole of any reactant) under different conditions. The aprotic solvents used were dichloroethane, benzene and tetrahydrofuran (THF) having different polarity. The solutions prepared are usually 0.1 *M* and 0.5 *M*. THF is used for the first time in such type of reaction. In some cases, ultrasonic treatment of the reaction mixture was applied. Such studies are not known for the reaction of **2** with an imine. Otherwise, ultrasonic treatment has significant influence in the chemical course of various reactions [41]. The reaction between **2** and an imine is usually highly exothermic. This was true in the case of imine **3** and it forced us to perform the reaction in wider temperature range (from –20 °C to 83 °C). Till now, the reaction of this type has not been performed at low temperature. In all cases studied, solution of imine **3** was added to solution of **2**. The opposite order of mixing, as stated above in item b, has a shortcoming (the solid **2** cannot be transferred quantitatively in the reaction mixture). In any case, a mixture of the expected trans-**4,** cis-**4** and additional products **5** and **6** was yielded. The latter two products were obtained regardless of the mixing order of **2** and **3**. It is worth mentioning that cis-**4** is the kinetically controlled isomer. Its heating with acetic acid, similarly to ref. 24, converted it into the thermodynamically more stable trans-**4**.

The ratios of products **4**-**6** and trans-**4**/cis-**4** ratios were determined by pmr from the integrals of relevant protons. The signals for the protons at C-3 and C-4 were used, as in refs. 20 and 21, for any isomer **4**. In the case of products **5** and **6**, a pyrrol signal was taken into account. The data observed for these ratios are summarized in Table 1. It is clear that the quantities of **4** (both isomers) vary from 74 % to 96 % when the absence of the starting compounds **2** and **3** was established at the end of the reaction. Thus, the latter proceeds rapidly not only at higher temperatures but

Scheme 1

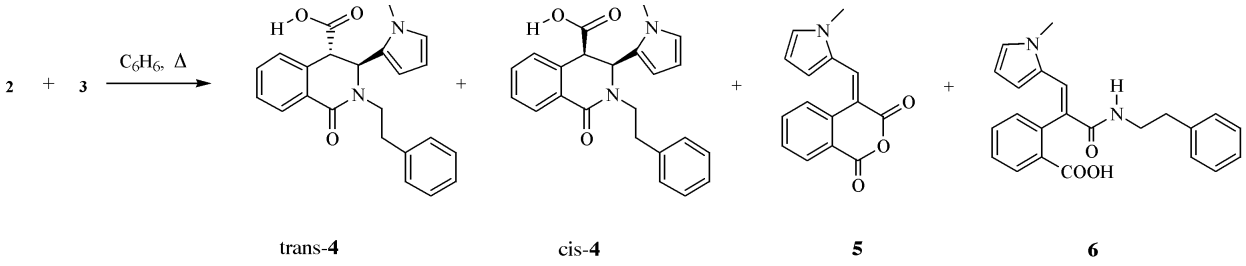


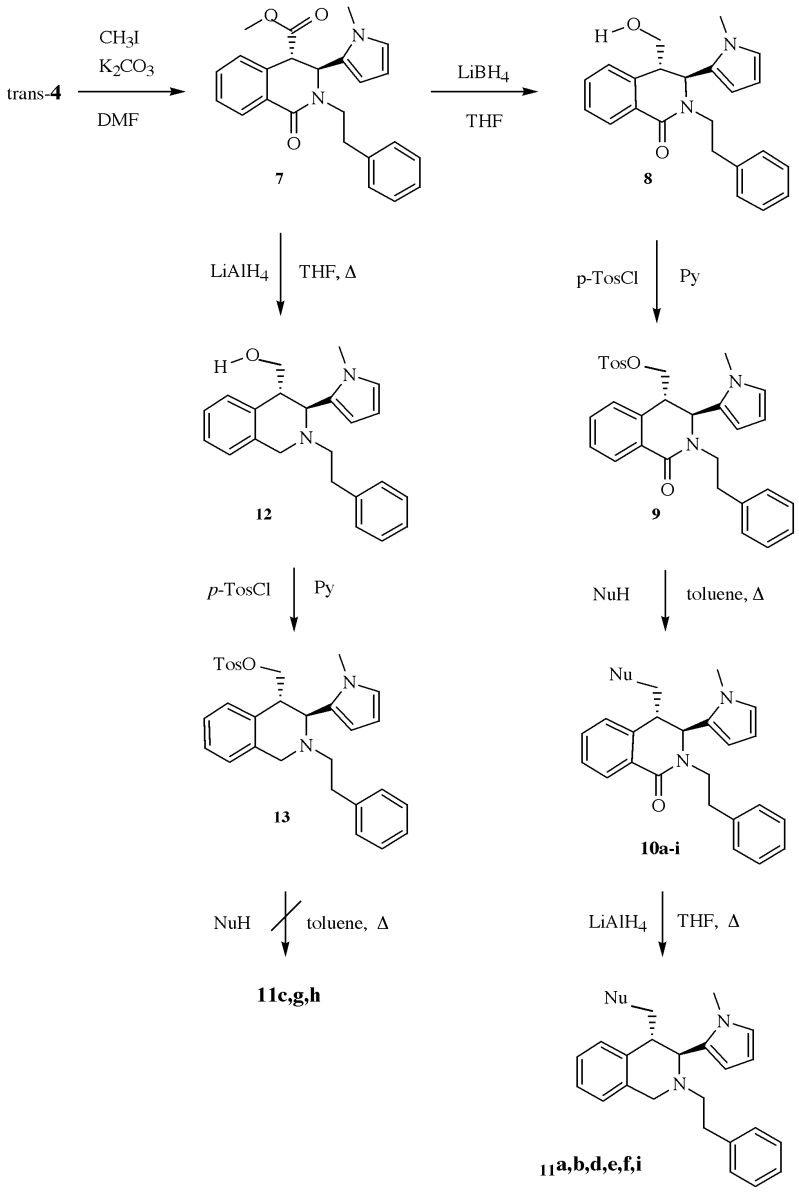

Table 1

Ratios among products in the Reaction of Homophthalic Anhydride (**2**) and Imine **3** under Different Conditions.

| No. | Reaction Conditions | | | | **4**/**5**/**6** Ratio [a] | Trans-**4**/cis-**4** ratio [a] |
|---|---|---|---|---|---|---|
| | Solvent [b] | Ultra sound | Tempe-rature ( °C) | Reaction time [c] (min) | | |
| 1 | Dichloroethane [d] | - | -20 | 10 | 96/traces/4 | 25/75 |
| 2 | Dichloroethane | - | -20 | 10 | 89/4/7 | 17/83 |
| 3 | Dichloroethane | - | 22 | 5 | 85/7/8 | 17/83 |
| 4 | Dichloroethane | Applied | 22 | 3 | 83/4/13 | 19/81 |
| 5 | Dichloroethane | - | 83 | 5 | 83/4/13 | 73/27 |
| 6 | Benzene | - | 22 | 10 | 88/5/7 | 32/68 |
| 7 | Benzene | Applied | 22 | 5 | 88/5/7 | 39/61 |
| 8 | Benzene | - | 80 | 5 | 85/6/9 | 73/27 |
| 9 | Tetrahydrofuran | - | -20 | 10 | 86/3/11 | 54/46 |
| 10 | Tetrahydrofuran | - | 22 | 5 | 81/5/14 | 43/57 |
| 11 | Tetrahydrofuran | Applied | 22 | 3 | 74/9/17 | 82/18 |
| 12 | Tetrahydrofuran | - | 65 | 5 | - [e] | 38/62 |

[a] The ratio was determined by pmr integrals (see text). [b] The concentration was 0.1 M, unless otherwise stated. [c] The reaction time was determined by the full consumption of compound **2** (tlc or pmr). [d] The concentratoin was 0.5 M. [e] This ratio was not established owing to proton overlap.

Scheme 2


trans-4
CH3I
K2CO3
DMF
7
LiBH4
THF
8
LiAlH4
THF, Δ
12
p-TosCl
Py
9
p-TosCl
Py
13
NuH
toluene, Δ
10a-i
NuH
toluene, Δ
11c,g,h
LiAlH4
THF, Δ
11a,b,d,e,f,i
Nu-
a
b
c
d
e
Nu-
f
g
h
i

also at –20 °C. As seen from items 1 and 2 at that temperature in $ClCH_2CH_2Cl$, the kinetically controlled *cis* isomer predominates. The reaction time is 10 minutes at different concentration of the solution.

Within items 2-12 (Table 1), comparisons are possible since the concentration is same while the solvent, ultrasonic treatment and temperature vary. The temperature effects for the non-polar $ClCH_2CH_2Cl$ and benzene are similar: cis-**4** is predominantly obtained at lower temperatures (items 2, 3 and 6) and trans-**4** is the major product at reflux of the reaction mixtures (items 5 and 8). Different results were obtained with the polar THF where both isomers were yielded in an almost 50:50 ratio at lower temperatures (items 9 and 10) and cis-**4** prevails at higher temperature (item 12). The effect of the ultrasonic treatment is seen from the comparisons of the experiments done at same temperature without application and with application of such a treatment (item 3 vs. item 4, item 6 vs. item 7 and item 10 vs. item 11). This treatment always decreases the reaction time. Its effect on the trans-**4**/cis-**4** ratios depends on the solvent. Practically no effect was observed for the two non-polar solvents and a profound effect was established for the polar THF leading for the first time, in the cases studied, to a high quantity (82%) of the thermodynamically more stable trans-**4** at room temperature.

In contrast to Cushman and Madaj [24], we do not consider the *trans*/*cis* ratio as a reliable criterion for the mechanism of the reaction of **2** and an imine. However, the smooth performance of the reaction in any kind of solvent (non-polar aprotic, polar aprotic or protic as used in ref. 24) is a fact in favor of the concerted mechanism. The most important, from practical point of view, result of Table 1 is the high diastereoselectivity in items 2 and 3 (83% *cis*) and in item 11 (82 % *trans*) showing that the reaction was directed towards any of both isomers.

The reaction between anhydride **2** and imine **3** was done also in large scale (by 0.1 *M* of any reactant) in boiling benzene for a greater reaction time relative to item 8 of Table 1. This was necessary for complete consumption of the reactants. To avoid isomerisation [24] of *cis* isomer, the reaction mixture was treated with dilute sodium hydrogen carbonate instead of sodium hydroxide. Thus, trans-**4** was isolated as a main product in 66% yield along with 11 % of cis-**4,** 11 % of unsaturated anhydride **5** and 7% of acyclic amide acid **6**. Compound **5** is known [42] but is prepared in another way. Similarly to refs. 20,21,40 the configuration of any isomer was determined on the basis of $J^{3,4}$. *Trans* configuration was ascribed to the isomer with a smaller (1.4 Hz) $J^{3,4}$ and *cis* configuration to the isomer with a greater $J^{3,4}$ (5.5 Hz).

Concerning elucidation of the reaction mechanism, attention was paid to products **5** and **6**. It is worth noting that an unsaturated anhydride similar to **5** has not been isolated in ref. 1. Compounds **5** and **6** do not correspond to any intermediate in the two consequent mechanisms. Concluding, they are by-products resulting from competing reactions. When the mechanism of the reaction is further elucidated, the stereochemical course of the reaction should take into account the relevant orientation of *re* and *si* faces of **2** and **3** and the fact that imine **3** have *Z* and *E* forms.

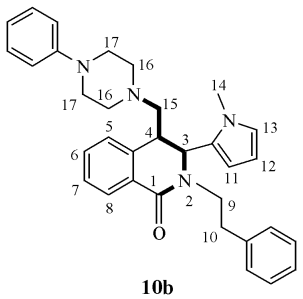
Scheme 2 gives the route from acid trans-**4** to the target compounds **10** and **11**. The pathway is similar to that used by us in ref. 1. Compounds **10** contain a fragment that is considered [2] as interesting from pharmacological point of view. This fragment is written in bold in formula **10b** below.

The conversion of acid trans-**4** into methyl ester **7** was done by treatment with iodomethane in the presence of potassium carbonate. The direct esterification of trans-**4** leads to a mixture of many products. Ester **7** was reduced with lithium borohydride in dry THF to the corresponding hydroxymethyl derivative **8**. The reduction did not affect the amide group. Alcohol **8** was converted to the corresponding tosylate **9**. Reaction of **9** with any of the secondary amines, denoted as NuH, yielded after a prolonged heating tetrahydroisoquinolinones **10a-i**. The course of the reaction was followed by tlc. Reaction time depends on the structure and size of the secondary amine. Reduction of **10a**,**b**,**d-f**,**i** with lithium aluminium hydride gave tetrahydroisoquinolines **11a**,**b**,**d-f**,**i**.

Ester **7** was reduced completely with lithium aluminum hydride to alcohol **12** that was converted to tosylate **13**. Unexpectedly, the reaction of **13** with three secondary amines (**c:** 1-(2-methoxyphenyl)-piperazine, **g:** morpholine, **h:** 2,6-dimethylmorpholine) did not give pure **11c**,**g**,**h** owing to the great number of products. Thus, this shorter path from **7** to **11** cannot be used (compare with ref. 1).

Starting from acid trans-**4**, compounds **7**-**11** obtained have trans configuration, *i.e.* all reactions done are stereospecific.

The description of the pmr spectra uses the arbitrary numbering given in formula **10b**. The signals in the pmr spectrum of **10d** were attributed by COSY experiments and these data were taken into account in the analysis of the other pmr spectra.



**10b**

The ir spectra of **10a-i** show CO (amide) at 1660 $cm^{-1}$. Such a signal was not observed in the ir spectra of compounds **11a,b,d,e,f,i**.

## EXPERIMENTAL

Melting points were determined on a Kofler hot stage and are uncorrected. The ir spectra were taken on a Specord 75 and are reported in reciprocal centimeters. Nujol was used for trans-**4**, cis-**4** and **6** and chloroform for all other compounds. The pmr spectra were obtained on a Bruker AM400 spectrometer at 400.13 MHz and Bruker Avance DRX-250 spectrometer at 250.1 MHz in deuteriochloroform as solvent, if not stated otherwise. The chemical shift is given in ppm (δ) relative to tetramethylsilane as internal standard. Mass spectra were recorded on a Hewlet Packard MS 5973 using electron impact of 30 eV. Elemental analyses were done in the relevant laboratories at the Faculty of Chemistry, University of Sofia and at the Institute of Organic Chemistry, Bulgarian Academy of Sciences. Tlc was done on precoated 0.2 mm Merck silica gel $60F_{254}$ plates. Mobile phases used are heptane-ethylacetate 2.8:2.2 and heptane-ethylacetate-ammonia 2.8:2.2:0.03 (see also ref. 43). Merck silica gel 60 (0.040-0.063 mm) was used for chromatographic filtration and flash-chromatography. The ultrasonic treatment in items 4, 7 and 11 of Table 1 was done by ultrasonic bath of 35 Hz.

*N*-(1-Methyl-1*H*-pyrrol-2-yl-methylidene)-phenethylamine (**3**).

A mixture of 1-methyl-1*H*-pyrrole-2-carbaldehyde (4.70 g, 0.043 mole) and phenethylamine (5.21 g, 0.043 mole) was stirred and heated at 100 °C for 0.5 h. The reaction mixture was distilled under reduced pressure. Bp 123.5-124.5°/2 mm. After spontaneous crystallization, imine **3** was obtained as white needles, 8.3 g (91 %), mp 44-45 °C (lit. [44] mp 44.7 °C); $^1$H nmr: δ, 2.87 (t, 2H, -$CH_2C_6H_5$, J = 7.4 Hz), 3.66 (td, 2H, -N$CH_2$-, J = 7.4, 1.0 Hz), 3.81 (s, 3H, -$CH_3$), 6.04 (m, 1H, pyrrol), 6.39 (m, 1H, pyrrol), 6.60 (m, 1H, pyrrol), 7.11-7.22 (m, 5H, phenyl protons), 7.95 (s, 1H, =CH).

*Anal*. Calcd. for $C_{14}H_{16}N_2$: C, 79.20; H, 7.60; N, 13.20. Found: C, 79.47; H, 7.34; N, 13.50.

(±)-*trans*- and (±)-*cis*-2-Phenethyl-3-(1-methyl-1*H*-pyrrol-2-yl)-1-oxo-1,2,3,4-tetrahydro-4-isoquinoline Carboxylic Acid (trans-**4**, cis-**4**) and by-products **5** and **6**.

General Procedure for Determination of the Ratios of the Products obtained form **2** and **3** in the Small Scale Experiments.

No Ultrasonic Treatment (items 1-3, 5, 6, 8-10, 12 of Table 1).

Solution of imine **3** (0.106 g, 0.5 mmole) in dry solvent was added dropwise for 5 min. to a suspension of homophthalic anhydride (**2**) (0.081 g, 0.5 mmole). The solution obtained was 0.1 *M* or 0.5 *M*. The reaction mixture was stirred at the corresponding temperature (see Table 1). At the end of the reaction, where the absence of **2** and **3** was established (tlc and nmr). The solvent was then evaporated, and the ratios of both/all products (**4**/**5**/**6**) and trans-**4**/cis-**4** were determined, as described above, by nmr integration (DMSO-$d_6$). The data obtained are summarised in Table 1.

With Ultrasonic Treatment (items 4, 7 and 11 of Table 1).

The flask with the solution of anhydride **2** (0.081 g, 0.5 mmole) was placed in ultrasonic bath. The addition of imine **3** (0.5 mmole) and work up of reaction mixture were the same as described for the previous case.

Reaction Between **2** and **3** Performed in Large Scale.

To a hot and stirred solution of homophthalic anhydride (16.2 g, 0.1 mole) in 150 mL dry benzene, *N*-(1-methyl-1*H*-pyrrol-2-yl-methylidene)-phenethylamine (**3**) (21.23 g, 0.1 mole) in 50 mL dry benzene was added dropwise for 20 min. The reaction mixture was refluxed for 15 min and left overnight. The orange crystals were collected by filtration and washed with toluene yielding 3.4 g (9 %) of **5**. The filtrate was extracted three times with 10 % sodium hydrogen carbonate and the alkaline solutions were acidified, extracted three times with ethyl acetate. The combined organic layers were washed twice with water and were dried (sodium sulfate) and evaporated under reduced pressure leaving a brown oil (32.2 g). Its chromatographic filtration yielded acid trans-**4** (24.7 g, 66 %), cis-**4** (4.1 g, 11 %) along with 0.75 g (2 %) of **5** and 2.6 g (7 %) of **6**.The total yield of **5** was 11 %.

Compound trans-**4** was obtained as white crystals (from ethyl acetate), mp 148-150°; ir (Nujol): 1720 ($CO_2H$, dimer), 1680 ($CO_2H$, monomer), 1630 (CON) $cm^{-1}$; $^1$H nmr (DMSO-$d_6$): δ 2.71-2.74 (m, 1H, 9-H), 2.86-2.88 (m, 1H, 10-H), 2.99-3.05 (m, 1H, 10-H), 3.68 (s, 3H, 14-H), 4.02-4.06 (m, 1H, 9-H), 4.13 (s, 1H, 4-H), 5.26 (d, 1H, 11-H, J = 1.7 Hz), 5.48 (d, 1H, 3-H, J = 1.4 Hz), 5.68-5.69 (m, 1H, 12-H), 6.63 (s, 1H, 13-H), 7.17-7.32 (m, 6H, phenyl protons), 7.37-7.46 (m, 2H, phenyl protons), 7.92 (d, 1H, 8-H, J = 7.4 Hz), 12.90 (broad s, 1H, $CO_2H$).

*Anal*. Calcd. for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92. Found: C, 73.61; H, 5.67.

Compound cis-**4** was obtained as colourless needles (from ethyl acetate), mp 180-181°; ir (Nujol): 1720 ($CO_2H$, dimer), 1700 ($CO_2H$, monomer), 1640 (CON) $cm^{-1}$; $^1$H nmr (DMSO-$d_6$): δ 2.64-2.75 (m, 1H, 9-H), 2.81-2.93 (m, 1H, 10-H), 2.97-3.09 (m, 1H, 10-H), 3.42 (s, 3H, 14-H), 3.96-4.03 (m, 1H, 9-H), 4.27 (d, 1H, 4-H, J = 5.5 Hz), 4.90 (d, 1H, 3-H, J = 5.5 Hz), 5.35 (m, 1H, 11-H), 5.71 (m, 1H, 12-H), 6.36-6.38 (m, 1H, 13-H), 7.10-7.63 (m, 8H, phenyl protons), 8.03 (d, 1H, 8-H, J = 7.3 Hz), 12.40 (broad s, 1H, $CO_2H$).

*Anal*. Calcd. for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92. Found: C, 73.68; H, 5.96.

4-(1-Methyl-1*H*-pyrrol-2-yl)methylidene-1*H*-isochromene-1,3-dione (**5**).

This by-product was obtained as orange needles (from toluene), mp 174-175° (lit. [42] mp 175°); ir: CO 1740, 1770 $cm^{-1}$ (similar to ref. 42); $^1$H nmr: δ, 3.79 (s, 3H, -$CH_3$), 6.30-6.32 (m, 1H, pyrrol), 6.98-6.99 (m, 1H, pyrrol), 7.33-7.37 (m, 1H, pyrrol), 7.60-7.66 (m, 2H, phenyl protons), 7.71 (s, 1H, =CH-), 8.10-8.15 (m, 2H, phenyl protons).

*Anal.* Calcd. for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38. Found: C, 71.02; H, 4.24.

2-[1-[(Phenethylamino)carbonyl]-2-(1-methyl-1*H*-pyrrol-2-yl)ethenyl]benzenecarboxylic Acid (**6**).

This by-product was obtained as white crystals (from ethyl acetate-methanol), mp 209-210°; ir (Nujol): CO 1710, 1630 $cm^{-1}$; $^1$H nmr (DMSO-$d_6$): δ 2.59-2.73 (m, 2H, -$CH_2C_6H_5$), 3.30-3.41 (m, 2H, -N$CH_2$-) 3.64 (s, 3H, -$CH_3$), 4.72 (dd, 1H, pyrrol, J = 3.9, 1.5 Hz), 5.74 (dd, 1H, pyrrol, J = 3.5, 2.6 Hz), 6.79 (dd, 1H, pyrrol, J = 2.4, 1.7 Hz), 6.89 (t, 1H, -NH, J = 5.7 Hz), 7.12-7.21 (m, 6H, phenyl protons), 7.41 (s, 1H, =CH-), 7.50-7.65 (m,

2H, phenyl protons), 8.04 (dd, 1H, phenyl proton, J = 7.5, 1.4 Hz), 12.71 (broad s, 1H, -$CO_2H$).

*Anal*. Calcd. for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92. Found: C, 73.87; H, 6.22.

(±)-*trans*-Methyl-2-Phenethyl-3-(1-methyl-1*H*-pyrrol-2-yl)-1-oxo-1,2,3,4-tetrahydro-4-isoquinoline Carboxylate (**7**).

To a mixture of potassium carbonate (8.28 g, 0.06 mole) and acid trans-**4** (22.44 g, 0.06 mole) in dimethylformamide (300 mL), iodomethane (17.04 g, 0.12 mole) was added dropwise for 1 hour. The reaction mixture was stirred for 1.5 hours, added to water and extracted twice with ethyl acetate. The organic layer was dried (sodium sulfate) and evaporated. An oil was obtained. It afforded **7** as colourless crystals (from tetrahydrofuran), 20.02 g (86 %), mp 86-89 °C; ir: CO 1740, 1650 $cm^{-1}$; $^1H$ nmr: δ 3.20-3.30 (m, 1H, 9-H), 3.45-3.85 (m, 2H, 10-H), 3.77 (s, 3H, $CO_2CH_3$), 3.80 (s, 3H, 14-H), 4.03 (d, 1H, 4-H, J = 2.0 Hz), 4.33-4.41 (m, 1H, 9-H), 5.48 (d, 1H, 3-H, J = 2.0 Hz), 5.73-5.74 (m, 1H, 11-H), 5.97-6.01 (m, 1H, 12-H, 6.63-6.66 (m, 1H, 13-H), 7.25-7.43 (m, 6H, phenyl protons), 7.53-7.58 (m, 2H, phenyl protons), 8.27-8.33 (m, 1H, 8-H); ms: m/z 388 (molecular ion).

*Anal*. Calcd. for $C_{24}H_{24}N_2O_3$: C, 74.20; H, 6.22; N, 7.21. Found: C, 74.45; H, 5.90; N,7.50.

(±)-*trans*-2-Phenethyl-3-(1-methyl-1*H*-pyrrol-2-yl)-4-hydroxymethyl-1,2,3,4-tetrahydroisoquinolin-1-one (**8**).

To a stirred suspension of potassium borohydride (5.61 g, 0.104 mole) and lithium chloride (4.41 g, 0.104 mole) in dry tetrahydrofuran (80 mL), solution of ester **7** (20.18 g, 0.052 mole) in dry tetrahydrofuran (60 mL) was added dropwise. The reaction mixture was stirred at room temperature for 2.5 hours, concentrated under reduced pressure, poured into water and extracted with ethyl acetate. The organic layer was washed with water, dried (sodium sulfate) and evaporated to yield compound **8** as an oil. The latter was crystallized from chloroform giving white crystals, 16.47 g (88 %), mp 120-123 °C; ir: OH 3650, CO 1660, OH 1050 $cm^{-1}$; $^1H$ nmr: δ 2.98-3.13 (m, 3H, 10-, 4-H), 3.16-3.24 (m, 1H, 9-H), 3.33-3.38 (m, 1H, 15-H), 3.49-3.52 (m, 1H, 15-H), 3.58 (s, 3H, 14- H), 4.48-4.55 (m, 1H, 9-H), 4.81 (s, 1H, 3-H), 5.58-5.60 (m, 1H, 11-H), 5.88-5.89 (m, 1H, 12-H), 6.51-6.52 (m, 1H, 13-H), 7.28-7.39 (m, 8H, phenyl protons), 8.18-8.20 (m, 1H, 8-H); ms: m/z 360 (molecular ion).

*Anal*. Calcd. for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77. Found: C, 76.79; H, 6.97; N, 7.94.

(±)-*trans*-2-Phenethyl-1-oxo-3-(1-methyl-1*H*-pyrrol-2-yl)-4-tosyloxymethyl-1,2,3,4-tetrahydroisoquinolin-1-one (**9**).

To a solution of **8** (18.72 g, 0.052 mole) in pyridine (120 mL) kept at –5 °C, *p*-toluenesulfonyl chloride (19.81 g, 0.104 mole) was added in portions. The reaction mixture was stirred at room temperature for 12 hours, poured into water and extracted with ethyl acetate. The organic layer was thoroughly washed with water, dried (sodium sulfate) and evaporated to dryness. Compound **9** was obtained as a brown oil, 25.66 g (96 %). $^1H$ nmr: δ 2.34 (s, 3H, 16-H), 2.62-2.88 (m, 3H, 10-, 15-H), 2.90-3.06 (m, 1H, 9-H), 3.16-3.24 (m, 1H, 4-H), 3.69-3.84 (m, 1H, 15-H), 3.94 (s, 3H, 14-H), 4.26-4.41 (m, 1H, 9-H), 4.90 (s, 1H, 3-H), 5.25-5.30 (m, 1H,11-H), 5.70-5.72 (m, 1H, 12-H), 6.66-6.70 (m, 1H, 13-H), 7.26-7.72 (m, 12H, phenyl protons), 7.96-7.98 (m, 1H, 8-H).

General Procedure for the Preparation of (±)-*trans*-2-Benzyl-3-(1-methyl-1*H*-pyrrol-2-yl)-4-(*N*,*N*-disubstitutedaminomethyl)-1,2,3,4-tetrahydroisoquinolin-1-ones (**10**).

A relevant secondary amine NuH (20 mmoles) was added to a solution of tosylate **8** (3.0 g, 5.8 mmoles) in 15-20 mL toluene. The reaction mixture was refluxed (12-30 hrs) until **8** was no longer present as indicated by tlc. Ethyl acetate (180 mL) was added after cooling. The organic layer was thoroughly washed with water and dried (sodium sulfate). The solvents were removed under reduced pressure and the resulting brown oil was purified by chromatographic filtration or flash chromatography and subsequent recrystallisation.

(±)-*trans*-2-Phenethyl-3-(1-methyl-1*H*-pyrrol-2-yl)-4-[(piperidin-1-yl)methyl]-1,2,3,4-tetrahydroisoquinolin-1-one (**10a**).

This compound was obtained from **9** and piperidine as white crystals (from hexane-ethyl acetate), 1.96 g (79 %), mp 68-70 °C; $^1H$ nmr: δ 1.67-1.92 (m, 7H, 17-, 15-H), 2.49-2.66 (m, 2H, 16-H), 2.82-2.88 (m, 3H, 16-,15-H), 3.15-3.25 (m, 3H, 9-,10-H), 3.31 (dd, 1H, 4-H, J = 12.0, 3.5 Hz), 3.88 (s, 3H, 14-H), 4.57-4.66 (m, 1H, 9-H), 5.63 (s, 1H, 3-H), 5.77-5.78 (m, 1H, 11-H), 6.07-6.09 (m, 1H, 12-H), 6.71-6.72 (m, 1H, 13-H,), 7.24-7.26 (m, 1H, phenyl proton), 7.43-7.63 (m, 7H, phenyl protons), 8.39 (dd, 1H, 8-H, J = 7.1, 2.0 Hz); ms: m/z 427 (molecular ion).

*Anal*. Calcd. for $C_{28}H_{33}N_3O$: C, 78.65; H, 7.77. Found: C, 78.91; H, 7.53.

(±)-*trans*-2-Phenethyl-3-(1-methyl-1*H*-pyrrol-2-yl)-4-[(4-phenyl-pyperazin-1-yl)methyl]-1,2,3,4-tetrahydroisoquinolin-1-one (**10b**).

This compound was obtained from **9** and *N*-phenylpiperazine as colourless prisms (from hexane-ethyl acetate), 1.81 g (62 %), mp 122-124 °C; $^1H$ nmr: δ 2.20 (dd, 1H, 15-H, J = 12.9, 3.9 Hz), 2.36-2.40 (m, 2H, 16-H) 2.55 (t, 1H, 15-H, J = 12.9 Hz), 2.65-2.69 (m, 2H, 16-H), 2.78-2.85 (m, 3H, 10-,9-H), 2.92 (dd, 1H, 4-H, J = 11.9, 3.6 Hz), 3.03-3.11 (m, 4H, 17-H), 3.44 (s, 3H, 14-H), 4.13-4.22 (m, 1H, 9-H), 5.17 (s, 1H, 3-H), 5.34-5.37 (m, 1H, 11-H), 5.64-5.68 (m, 1H, 12-H), 6.29-6.30 (m, 1H, 13-H), 6.70-6.87 (m, 4H, phenyl protons), 7.01-7.32 (m, 9H, phenyl protons), 7.99 (dd, 1H, 8-H, J = 7.0, 2.0 Hz); ms: m/z 504 (molecular ion).

*Anal*. Calcd. for $C_{33}H_{36}N_4O$: C, 78.54; H, 7.19. Found: C, 78.94; H, 7.30.

(±)-*trans*-2-Phenethyl-3-(1-methyl-1*H*-pyrrol-2-yl)-4-[(4-(2-methoxyphenyl)pyperazin-1-yl)methyl]-1,2,3,4-tetrahydroisoquinolin-1-one (**10c**).

This compound was obtained from **9** and 1-(2-methoxyphenyl)-piperazine as colourless prisms (from hexane-ethyl acetate), 1.64 g (53 %), mp 125-127 °C; $^1H$ nmr: δ 2.64 (dd, 1H, 15-H, J = 12.9, 3.8 Hz), 2.82-2.86 (m, 2H, 16-H), 2.97 (t, 1H, 15-H, J = 12.9 Hz), 3.09-3.16 (m, 2H, 16-H), 3.17-3.29 (m, 3H, 10-,9-H), 3.34 (dd, 1H, 4-H, J = 11.5, 3.6 Hz), 3.38-3.48 (m, 4H, 17-H), 3.87 (s, 3H, 14-H), 4.10 (s, 3H, 18-H), 4.58-4.64 (m, 1H, 9-H), 5.61 (s, 1H, 3-H), 5.78-5.79 (m, 1H,11-H), 6.08-6.09 (m, 1H, 12-H), 6.71-6.72(m, 1H, 13-H), 7.10-7.28 (m, 4H, phenyl protons), 7.42-7.66 (m, 8H, phenyl protons), 8.40 (dd, 1H, 8-H, J = 7.2, 1.5 Hz); ms: m/z 534 (molecular ion).

*Anal*. Calcd. for $C_{34}H_{38}N_4O_2$: C, 76.37; H, 7.16. Found: C, 76.26; H, 7.10.

(±)-*trans*-2-Phenethyl-3-(1-methyl-1*H*-pyrrol-2-yl)-4-[(4-(3-trifluoromethyl-phenyl)pyperazin-1-yl)methyl]-1,2,3,4-tetrahydroisoquinolin-1-one (**10d**).

This compound was obtained from **9** and 3-(trifluoromethyl)-*N*-phenylpiperazine as white crystals (from ethyl acetate), 1.56 g (47 %), mp 169-172 °C; $^1$H nmr: δ 2.46 (dd, 1H, 15-H, J = 12.8, 4.0 Hz), 2.62-2.66 (m, 2H, 16-H), 2.82 (t, 1H, 15-H, J = 12.8 Hz), 2.91-2.95 (m, 2H, 16-H), 3.04-3.15 (m, 3H, 10-, 9-H), 3.18 (dd, 1H, 4-H, J = 12.0, 3.6 Hz), 3.33-3.40 (m, 4H, 17-H), 3.71 (s, 3H, 14-H), 4.41-4.48 (m, 1H, 9-H), 5.4 (s, 1H, 3-H), 5.62-5.63 (m, 1H, 11-H), 5.92-5.94 (m, 1H, 12-H), 6.56-6.57 (m, 1H, 13-H), 7.11-7.58 (m, 12H, phenyl protons), 8.25 (dd, 1H, 8-H, J = 7.0, 2.0 Hz); ms: m/z 572 (molecular ion).

*Anal*. Calcd. for $C_{34}H_{35}F_3N_4O$: C, 71.30; H, 6.16; N, 9.78. Found: C, 71.29; H, 5.90; N, 9.75

(±)-*trans*-2-Phenethyl-3-(1-methyl-1*H*-pyrrol-2-yl)-4-[(4-(3-chlorophenyl)piperazin-1-yl)methyl]-1,2,3,4-tetrahydroisoquinolin-1-one (**10e**).

This compound was obtained from **9** and 1-(3-chlorophenyl)-piperazine as white crystals (from ethyl acetate), 1.62 g (52 %), mp 188-191 °C; $^1$H nmr: δ 2.20 (dd, 1H, 15-H, J = 12.8, 3.9 Hz), 2.35-2.38 (m, 2H, 16-H), 2.58 (t, 1H, 15-H, J = 12.8 Hz) 2.63-2.67 (m, 2H, 16-H), 2.78-2.84 (m, 3H, 10-, 9-H), 2.92 (dd, 1H, 4-H, J = 11.8, 3.8 Hz), 2.98-3.11 (m, 4H, 17-H), 3.45 (s, 3H, 14-H), 4.16-4.23 (m, 1H, 9-H), 5.15 (s, 1H, 3-H), 5.36-5.38 (m, 1H, 11-H), 5.67-6.68 (m, 1H, 12-H), 6.30-6.31 (m, 1H, 13-H), 6.61-6.72 (m, 3H, phenyl protons), 6.87-7.22 (m, 9H, phenyl protons), 8.00 (dd, 1H, 8-H, J = 7.0, 2.0 Hz); ms: m/z 538 (molecular ion).

*Anal*. Calcd. for $C_{33}H_{35}ClN_4O$: C, 75.71; H, 6.69; N, 9.38. Found: C, 75.99; H, 6.40; N, 9.68.

(±)-*trans*-2-Phenethyl-3-(1-methyl-1*H*-pyrrol-2-yl)-4-[(4-fluorophenyl)-piperazin-1-yl)methyl]-1,2,3,4-tetrahydroisoquinolin-1-one (**10f**).

This compound was obtained from **9** and 1-(4-fluorophenyl)-piperazine as colourless prisms (from hexane-ethyl acetate), 2.18 g (72 %), mp 114-116 °C; $^1$H nmr: δ 2.17 (dd, 1H, 15-H, J = 12.8, 3.9 Hz), 2.33-2.36 (m, 2H, 16-H), 2.55 (t, 1H, 15-H, J = 12.8 Hz), 2.62-2.65 (m, 2H, 16-H), 2.74-2.81 (m, 3H, 10-, 9-H), 2.89 (dd, 1H, 4-H, J = 12.0, 3.9 Hz), 2.92-3.01 (m, 4H, 17-H), 3.41 (s, 3H, 14-H), 4.12-4.19 (m, 1H, 9-H), 5.12 (s, 1H, 3-H), 5.33-5.34 (m, 1H, 11-H), 5.63-5.65 (m, 1H, 12-H), 6.26-6.27 (m, 1H, 13-H), 6.67-6.98 (m, 5H, phenyl protons), 7.02-7.19 (m, 7H, phenyl protons), 7.96 (m, 1H, 8-H, J = 7.0, 2.1 Hz); ms: m/z 522 (molecular ion).

*Anal*. Calcd. for $C_{33}H_{35}FN_4O$: C, 75.83; H, 6.75. Found: C, 75.75; H, 6.83.

(±)-*trans*-2-Phenethyl-3-(1-methyl-1*H*-pyrrol-2-yl)-4-[(morpholin-4-yl)methyl]-1,2,3,4-tetrahydroisoquinolin-1-one (**10g**).

This compound was obtained from **9** and morpholine as white crystals (from hexane-ethyl acetate), 1.57 g (63 %), mp 127-129 °C; $^1$H nmr: δ 2.34-2.43 (m, 3H, 16- 15-H), 2.65-2.71 (m, 3H, 16-, 15-H), 2.93-3.11 (m, 4H, 10-, 4-, 9-H), 3.65 (s, 3H, 14-H), 3.73-3.93 (m, 4H, 17-H), 4.35-4.42 (m, 1H, 9-H), 5.31 (s, 1H, 3-H), 5.57-5.58 (m, 1H, 11-H), 5.87-5.89 (m, 1H, 12-H), 6.50-6.51 (m, 1H, 13-H), 7.02-7.05 (m, 1H, phenyl proton), 7.21-7.47 (m, 7H, phenyl protons), 8.20 (d, 1H, 8-H, J = 7.3 Hz); ms: m/z 429 (molecular ion).

*Anal*. Calcd. for $C_{27}H_{31}N_3O_2$: C, 75.50; H, 7.27. Found: C, 75.51; H, 7.40.

(±)-*trans*-2-Phenethyl-3-(1-methyl-1*H*-pyrrol-2-yl)-4-[(2,6-dimethyl-morpholin-4-yl)methyl]-1,2,3,4-tetrahydroisoquinolin-1-one (**10h**).

This compound was obtained from **9** and 2,6-dimethylmorpholine as amorphous compound, 1.85 g (70 %), mp 46-48 °C; $^1$H nmr: δ 0.98-1.05 (m, 6H, 18-H), 1.67 (t, 1H, 16-H, J = 10.7 Hz), 1.79 (t, 1H, 16-H, J = 10.7 Hz), 2.10 (dd, 1H, 15-H, J = 12.8, 3.9 Hz), 2.33 (d, 1H, 15-H, J = 12.8 Hz), 2.43-2.49 (m, 2H, 16-H), 2.76-2.93 (m, 4H, 10-, 4-, 9-H), 3.44 (s, 3H, 14-H), 3.47-3.55 (m, 2H, 17-H), 4.13-4.22 (m, 1H, 9-H), 5.10 (s, 1H, 3-H), 5.36-5.38 (m, 1H, 11-H), 5.67-5.69 (m, 1H, 12-H), 6.30-6.32 (m, 1H, 13-H), 6.84-7.25 (m, 8H, phenyl protons), 8.00 (dd, 1H, 8-H, J = 7.1, 2.0); ms: m/z 457 (molecular ion).

*Anal*. Calcd. for $C_{29}H_{35}N_3O_2$: C, 76.11, H, 7.71. Found: C, 75.91; H, 7.82.

(±)-*trans*-2-Phenethyl-3-(1-methyl-1*H*-pyrrol-2-yl)-4-[(thiomorpholin-4-yl)methyl]-1,2,3,4-tetrahydroisoquinolin-1-one (**10i**).

This compound was obtained from **9** and thiomorpholine as colourless prisms (from ethyl acetate), 1.6 g (62 %), mp 149-150 °C; $^1$H nmr: δ 2.53 (dd, 1H, 15-H, J = 13.0, 4.0 Hz), 2.70 (t, 1H, 15-H, J = 13.0 Hz), 2.78-2.91 (m, 6H, 16-, 17-H), 3.04-3.20 (m, 6H, 16-, 10-, 4-H), 3.75 (s, 3H, 14-H), 4.43-4.50 (m, 1H, 9-H), 5.37 (s, 1H, 3-H), 5.66-5.67 (m, 1H, 11-H), 5.97-5.98 (m, 1H, 12-H), 6.60-6.61 (m, 1H, 13-H), 7.12-7.53 (m, 8H, phenyl protons), 8.29 (m, 1H, 8-H, J = 7.1, 2.0 Hz); ms: m/z 445 (molecular ion).

*Anal*. Calcd. for $C_{27}H_{31}N_3OS$: C, 72.77; H, 7.01. Found: C, 72.74; H, 6.99.

General Procedure for the Preparation of (±)-*trans*-2-Benzyl-3-(1-methyl-1*H*-pyrrol-2-yl)-4-(*N*,*N*-disubstituted-aminomethyl)-1,2,3,4-tetrahydroisoquinolines (**11**).

Lithium aluminium hydride (2.4 mmoles) was added in portions to a solution of **10** (2 mmoles) in 10 mL dry tetrahydrofuran and the reaction mixture was refluxed 1-2 hours. After cooling, water (9.6 mmoles) was added. The reaction mixture was stirred for 30 min and dried (magnesium sulfate). The inorganic precipitate was filtered and washed with dichloromethane. The solvent was removed from the filtrate and the product was purified by chromatographic filtration or recrystallisation.

(±)-*trans*-2-Phenethyl-3-(1-methyl-1*H*-pyrrol-2-yl)-4-[(piperidin-1-yl)methyl]-1,2,3,4-tetrahydroisoquinoline (**11a**).

This compound was obtained from **10a** as white crystals (from hexane), 0.47 g (57 %), mp 92.5-94 °C; $^1$H nmr: δ 1.34-1.42 (m, 6H, 17-H), 2.05 (dd, 1H, 15-H, J = 12.0, 3.6 Hz), 2.08 (broad s, 2H, 16-H), 2.35 (broad s, 2H, 16-H), 2.41-2.48 (m, 1H, 9-H), 2.57-2.63 (m, 1H, 9-H), 2.66-2.78 (m, 4H, 10-, 4-, 15-H), 3.51 (s, 3H, 14-H), 3.60 (d, 1H, 1-H, J = 15.5 Hz), 3.73 (d, 1H, 1-H, J = 15.5 Hz), 4.53 (s, 1H, 3-H), 5.25-5.29 (m, 1H, 11-H), 5.75-5.77 (m, 1H, 12-H), 6.34 (s, 1H, 13-H), 6.80-7.09 (m, 9H, phenyl protons); ms: m/z 413 (molecular ion).

*Anal*. Calcd. for $C_{28}H_{35}N_3$: C, 81.31; H, 8.53. Found: C, 81.31; H, 8.59.

(±)-*trans*-2-Phenethyl-3-(1-methyl-1*H*-pyrrol-2-yl)-4-[(4-phenyl-pyperazin-1-yl)methyl]-1,2,3,4-tetrahydroisoquinoline(**11b**).

This compound was obtained from **10b** as white crystals (from ethyl acetate), 0.45 g (46 %), mp 137-139 °C; $^1$H nmr: δ 2.16 (d,

1H, 15-H, J = 8.6 Hz), 2.28-2.30 (m, 2H, 16-H), 2.42-2.49 (m, 1H, 9-H), 2.55-2.78 (m, 5H, 16-, 4-, 15-, 9-H), 2.80 (s, 2H, 10-H), 2.97-3.05 (m, 4H, 17-H), 3.49 (s, 3H, 14-H), 3.60 (d, 1H, 1-H, J = 15.5 Hz), 3.76 (d, 1H, 1-H, J = 15.5 Hz), 4.51 (s, 1H, 3-H), 5.29-5.30 (m, 1H, 11-H), 5.76-5.78 (m, 1H, 12-H), 6.34-6.35 (m, 1H, 13-H), 6.67-6.78 (m, 3H, phenyl protons), 6.95-7.12 (m, 11H, phenyl protons); ms: m/z 490 (molecular ion).

*Anal*. Calcd. for $C_{33}H_{38}N_4$: C, 80.78; H, 7.80. Found: C, 80.69; H, 7.83.

(±)-*trans*-2-Phenethyl-3-(1-methyl-1*H*-pyrrol-2-yl)-4-[(4-(3-trifluoromethyl-phenyl)pyperazin-1-yl)methyl]-1,2,3,4-tetrahydroisoquinoline (**11d**).

This compound was obtained from **10d** as white crystals (from hexane-ethyl acetate), 0.59 g (53 %), mp122-124 °C; $^1$H nmr: δ 2.25 (d, 1H, 15-H, J = 8.6 Hz), 2.34-2.39 (m, 2H, 16-H), 2.53-2.87 (m, 6H, 9-, 16-, 4-, 15-H), 3.09-3.18 (m, 4H, 17-H), 3.58 (s, 3H, 14-H), 3.69 (d, 1H, 1-H, J = 15.6 Hz), 3.85 (d, 1H, 1-H, J = 15.6 Hz), 4.57 (s, 1H, 3-H), 5.39-5.40 (m, 1H, 11-H), 5.86-5.87 (m, 1H, 12-H), 6.43-6.44 (m, 1H, 13-H), 6.92-7.18 (m, 13H, phenyl protons); ms: m/z 558 (molecular ion).

*Anal*. Calcd. for $C_{34}H_{37}F_3N_4$: C, 73.09; H, 6.67. Found: C, 73.17; H, 6.71.

(±)-*trans*-2-Phenethyl-3-(1-methyl-1*H*-pyrrol-2-yl)-4-[(4-(3-chlorophenyl)pyperazin-1-yl)methyl]-1,2,3,4-tetrahydroisoquinoline (**11e**).

This compound was obtained from **10e** as white crystals (from ethyl acetate), 0.52 g (49 %), mp 145-146.5 °C; $^1$H nmr: δ 2.34 (d, 1H, 15-H, J = 9.7 Hz), 2.41-2.45 (m, 2H, 16-H), 2.69-2.90 (m, 6H, 9-, 16-, 4-, 15-H), 2.96 (s, 2H, 10-H), 3.14-3.21 (m, 4H, 17-H), 3.68 (s, 3H, 14-H), 3.78 (d, 1H, 1-H, J = 15.5 Hz), 3.95 (d, 1H, 1-H, J = 15.5 Hz), 4.67 (s, 1H, 3-H), 5.48 -5.49 (m, 1H, 11-H), 5.95-5.97 (m, 1H, 12-H), 6.54 (s, 1H, 13-H), 6.80-6.95 (m, 3H, phenyl protons), 7.13-7.30 (m, 10H, phenyl protons); ms: m/z 524 (molecular ion).

*Anal*. Calcd. for $C_{33}H_{37}ClN_4$: C, 75.48; H, 7.10. Found: C, 75.37; H, 7.09.

(±)-*Trans*-2-phenethyl-3-(1-methyl-1*H*-pyrrol-2-yl)-4-[(4-fluorophenyl)pyperazin-1-yl)methyl]-1,2,3,4-tetrahydroisoquinoline (**11f**).

This compound was obtained from **10f** as white crystals (from ethyl acetate), 0.47 g (46 %), mp 145.5-146.5 °C; $^1$H nmr: δ 2.32 (d, 1H, 15-H, J = 8.8 Hz), 2.42-2.46 (m, 2H, 16-H), 2.61-2.67 (m, 1H, 9-H), 2.71-2.77 (m, 2H, 16-H), 2.78-2.94 (m, 3H, 9-, 4-, 15-H), 2.97 (s, 2H, 10-H), 3.66 (s, 3H, 14-H), 3.76 and 3.92 (d, each 1H, 1-H, J = 15.5 Hz), 4.66 (s, 1H, 3-H), 5.46 -5.47 (m, 1H, 11-H), 5.93-5.94 (m, 1H, 12-H), 6.51 (s, 1H, 13-H), 6.86-6.99 (m, 4H, phenyl protons), 7.12-7.26 (m, 9H, phenyl protons); ms: m/z 508 (molecular ion).

*Anal*. Calcd. for $C_{33}H_{37}FN_4$: C, 77.92; H, 7.33. Found: C, 77.78; H, 7.32.

(±)-*trans*-2-Phenethyl-3-(1-methyl-1*H*-pyrrol-2-yl)-4-[(thiomorpholin-4-yl)methyl]-1,2,3,4-tetrahydroisoquinoline (**11i**).

This compound was obtained from **10i** as white crystals (from ethyl acetate), 0.45 g (52 %), mp 120-122 °C; $^1$H nmr: δ 2.57 (dd, 1H, 15-H, J = 12.0, 3.6 Hz), 2.76-2.90 (m, 6H, 9-H, 15-, 16-H), 2.97-3.32 (m, 8H, 4-, 9-H, 10-H, 17-H), 3.92 (s, 3H, 15-H), 3.98 (d, 1H, 1-H, J = 15.6 Hz), 4.18 (d, 1H, 1-H, J = 15,6 Hz), 4.82 (d, 1H, 3-H, J = 1.5 Hz), 5.68-5.69 (m, 1H, 11-H), 6.17-6.18 (m, 1H, 12-H), 6.76-6.77 (m, 1H, 13-H), 7.24-7.50 (m, 9H, phenyl protons); ms: m/z 431 (molecular ion).

*Anal*. Calcd. for $C_{27}H_{33}N_3S$: C, 75.13; H, 7.70. Found: C, 75.37; H, 7.74.

(±)-*trans*-2-Phenethyl-3-(1-methyl-1*H*-pyrrol-2-yl)-4-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (**12**).

The completely reduced alcohol **12** was prepared from **7** (7.8 g, 0.02 mole) in analogy to ref. 1 at reaction time 2 hours. It was obtained as colourless crystals (from ethyl acetate), 4.65 g (67 %), mp 104-105 °C; ir: (OH) 3650 cm$^{-1}$; $^1$H nmr: δ 1.56 (broad s, 1H, -OH), 2.48-2.55 (m, 1H, 9-H), 2,76-2.85 (m, 3H, 9-, 10-H), 2.93 (d, 1H, 4-H, J = 2.2 Hz), 3.58 (s, 3H, 14-H), 3.62 (d, 1H, 1-H , J = 15.4 Hz), 3.82 (dd, 1H, 15-H, J = 10.3, 3.5 Hz), 3.97 (d, 1H, 1-H, J = 15.4 Hz), 4.04 (dd, 1H, 15-H, J = 10.3, 3.2 Hz), 4.29 (d, 1H, 3-H, J = 2.2 Hz), 5.40-5.41 (m, 1H, 11-H), 5.85-5.86 (m, 1H, 12-H), 6.44-6.45 (m, 1H, 13-H), 7.01-7.23 (m, 9H, phenyl protons); ms: m/z 346 (molecular ion).

*Anal*. Calcd. for $C_{23}H_{26}N_2O$: C, 79.73; H, 7.56. Found: C, 79.51; H, 7.47.

(±)-*trans*-2-Phenethyl-3-(1-methyl-1*H*-pyrrol-2-yl)-4-tosyloxymethyl-1,2,3,4-tetrahydroisoquinoline (**13**).

The synthesis of tosylate **13** from the parent alcohol **12** (4.6 g, 0.013 mole) was done similarly to the preparation of **9**. The product was obtained as white crystals (from ethyl acetate) 4.2 g (63 %), mp 104-105 °C; $^1$H nmr: δ 2.41 (s, 3H, 16-H), 2.53-2.59 (m, 1H, 9-H), 2.69-2.74 (m, 3H, 10-, 9- H), 3.24-3.26 (m, 1H, 4-H), 3.63 (s, 3H, 14-H) 3.73 (d, 1H, 1-H, J = 15.8 Hz), 3.87 (d, 1H, 1-H, J = 15.8 Hz), 4.10 (dd, 1H, 15-H, J = 9.6, 3.7 Hz), 4.30 (d, 1H, 3-H, J = 2.5 Hz), 4.51 (t, 1H, 15-H, J = 9.6 Hz), 5.42-5.43 (m, 1H, 11-H), 5.91-5.93 (m, 1H, 12-H), 6.52-6.53 (m, 1H, 13-H), 7.08-7.33 (m, 11H, phenyl protons), 7.76-7.78 (m, 2H, phenyl protons).

*Anal*. Calcd. for $C_{30}H_{32}N_2O_3S$: C, 71.97; H, 6.44. Found: C, 72.07; H, 6.59.

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