

Full Paper

## Synthesis of New *trans*-2-Benzyl-3-(furan-2-yl)-4-substituted-1,2,3,4-tetrahydroisoquinolinones

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**Abstract:** The reaction of homophthalic anhydride and N-(furan-2-yl-methylidene)-benzylamine in different solvents and varying temperatures was studied in detail. Mixtures of the expected *trans*- and *cis*-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acids *trans*-**5** and *cis*-**5**, alongwith by-products **6** and **7** were obtained in dichloroethane or benzene. In pyridine, used for the first time, the reaction became completely diastereoselective, giving only the *trans* isomer. The carboxylic acid group of *trans*-**5** was transformed in four steps into cyclic aminomethyl groups which yielded various new tetrahydroisoquinolinones *trans*-**11a-g**, incorporating both a known fragment of pharmacological interest and various pharmacophoric substituents.

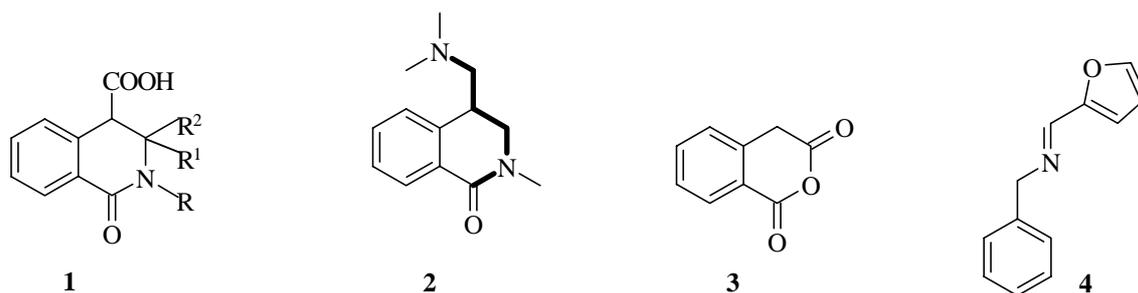
**Keywords:** Homophthalic anhydride, imine, tetrahydroisoquinolinones, stereochemistry.

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### Introduction

Substituted 1,2,3,4-tetrahydroisoquinolines are important because of their occurrence in nature [1,2] and their pharmacological properties [3-6]. Several methods have been described for preparation of tetrahydroisoquinolines [7-20]. The reaction between homophthalic anhydride and imines, developed in our laboratory [15], is nowadays a well known method for an one step preparation of acids of type **1** having two stereogenic centers and thus *cis* and *trans* forms if R<sup>1</sup> is different from R<sup>2</sup> [15-18, 20-22]. Depending of the conditions (solvent, temperature and catalyst if any), the reaction leads to mixtures

of *cis*- and *trans*-isomers or to one of these isomers [15-18, 21-26]. In some cases side reactions take place and by-products are isolated [20-22].

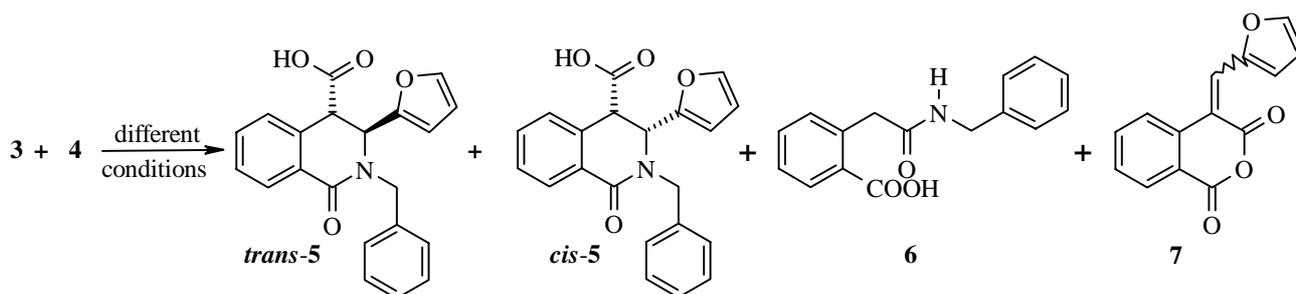


This paper continues our attempts [21,22] to further outline the scope and limitations of the reaction between homophthalic anhydride and imines and to study its stereochemistry. The latter is of interest because the effect of reaction conditions cannot be predicted in advance. Moreover, attention was paid to the transformation of the products of type **1** into various compounds of type **2** having a cyclic aminomethyl group in position 4 of the tetrahydroisoquinolinone ring. The presence of the fragment given in bold in **2** is the source of their potential biological activity [5] that can be modified by the presence of other pharmacophoric groups.

## Results and Discussion

Scheme 1 shows the products obtained from the reaction between homophthalic anhydride (**3**) and imine **4**.

Scheme 1



Preliminary experiments were carried out to ensure high yields and stereoselectivity. The reaction was performed using 1 mmol of each reactant under different conditions (Table 1). In general, the expected products obtained were *cis*-**5** and *trans*-**5** along with by-products **6** and **7**. The formation of the by-products can be attributed to decomposition of **4** to the corresponding parent aldehyde and amine in the course of the reaction [21,22]. The ratios between the acid products (containing **5** and **6**) and **7** were determined after work up of the reaction mixtures. Compound **7** is known, but was previously prepared in a different manner [27]. The ratios between *trans*-**5**, *cis*-**5** and **6** in the acid products were determined by <sup>1</sup>H-NMR spectroscopy from the integrals of relevant protons and are shown in Table 1. The signals for the protons at C-3 (5.07 ppm for *cis*-**5** and 5.29 ppm for *trans*-**5**) and

at C-4 (4.64 ppm for *cis*-**5** and 4.24 ppm for *trans*-**5**) were used for **5** [15,17]. In the case of product **6** the methylene protons (3.92 ppm) were taken into account. The configuration of each isomer of **5** was determined on the basis of  $J_{3,4}$ . By analogy to Refs. [15] and [17], a *trans* configuration was attributed to the isomer with the smaller  $J_{3,4}$  (0 Hz) and a *cis* configuration to the one with the greater  $J_{3,4}$  (5.75 Hz).

The data of Table 1 show that the reaction in aprotic solvents like dichloroethane and benzene (items 1-3) leads always to a mixture of *cis*-**5**, *trans*-**5** and by-products **6** and **7**. Independently of the great difference in temperature, the *trans* isomer of acid **5** is the preferred diastereoisomer. The use of pyridine as a solvent and eventually as a basic catalyst in reactions of this type is now reported for the first time. Both at 0 °C and boiling pyridine (items 4 and 5), the *trans* isomer of **5** was obtained in almost quantitative yields and the by-products **6** and **7** could not be isolated. Thus, these two experiments show that the use of pyridine ensures complete stereoselectivity of the reaction and the highest yield of the cyclic product with *trans* configuration.

**Table 1.** Ratios among Products of the Reaction of Homophthalic Anhydride (**3**) and Imine **4** under Different Conditions.<sup>a, b</sup>

No	Reaction conditions		Ratio (%)	
	Solvent	Temperature (°C)	Acidic residue/ <b>7</b> <sup>c</sup>	<i>cis</i> - <b>5</b> / <i>trans</i> - <b>5</b> / <b>6</b> <sup>d</sup>
1	Dichloroethane	83	83/17	19/41/40
2	Dichloroethane	0	88/12	15/32/53
3	Benzene	80	84/16	20/45/35
4	Pyridine	116	100/ -	traces/99/ -
5	Pyridine	0	100/ -	traces/99/ -

<sup>a</sup>The reaction time was 15 min and complete consumption of **3** was confirmed by TLC.

<sup>b</sup>The yield was 100% in all cases after work up of the reaction mixture.

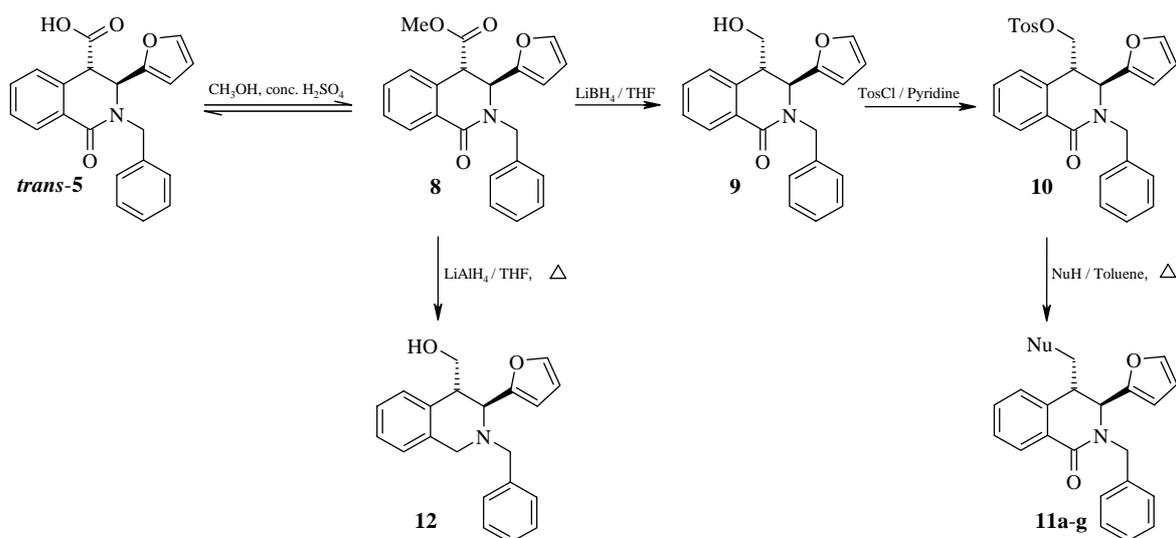
<sup>c</sup>Yields of the obtained acidic residue and **7** before recrystallisation.

<sup>d</sup>The ratio was determined by <sup>1</sup>H NMR integrals of the obtained acidic residue (see text).

To obtain *trans*-**5** in greater quantities for the subsequent transformations, the reaction was performed on a large scale (6-140 mmols) in dichloroethane or pyridine. The results obtained were in agreement with the data found for the small scale experiments.

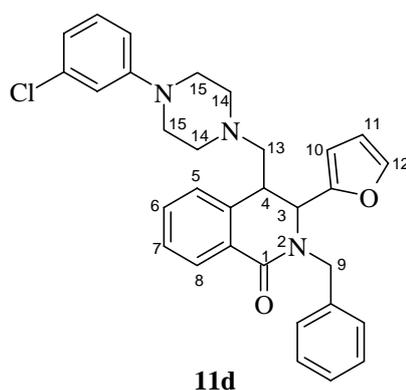
Scheme 2 shows the synthetic route to the target 4-aminomethyl-1,2,3,4-tetrahydroisoquinolin-1-ones (**11**). The direct esterification of acid *trans*-**5** leads to methyl ester **8**. The latter was reduced with lithium borohydride in tetrahydrofuran to the corresponding hydroxymethyl derivative **9**. The reduction did not affect the amide group. Alcohol **9** was converted to the corresponding tosylate **10**. Reaction of **10** with the secondary cyclic amines, denoted as NuH, yielded tetrahydroisoquinolinones **11a-g**. In all cases, the reaction mixture was refluxed until complete consumption of the tosylate as observed by TLC. Ester **8** was reduced completely with lithium aluminium hydride to tetrahydroisoquinoline alcohol **12**.

Scheme 2.



Comp	NuH	Comp	NuH
<b>11a</b>		<b>11e</b>	
<b>11b</b>		<b>11f</b>	
<b>11c</b>		<b>11g</b>	
<b>11d</b>			

The description of  $^1\text{H-NMR}$  spectra uses the arbitrary numbering given in formula **11d**. The  $^1\text{H-NMR}$  signals of **11d** were assigned by COSY experiments and these data were taken into account in the analysis of the other  $^1\text{H-NMR}$  spectra. On the basis of the value of  $J_{3,4}$ , all compounds **8-12** have *trans* configuration. The starting compound for their synthesis is *trans* acid **5**, *i.e.* all reactions performed are stereospecific. This conclusion is expected since the reactions do not affect the stereogenic centers but it is not trivial since it is known that epimerization can occur in some cases of esterification or reduction.



The target compounds **11a-g** contain not only the fragment given in bold in formula **2** but also other pharmacophores like furan and piperazine groups. Thus, different biological activity is expected for them and their screening is being carried out.

## Conclusions

The cycloaddition between homophthalic anhydride and an imine gave under different conditions the expected diastereomeric tetrahydroisoquinolinone carboxylic acids along with two by-products. The reaction proceeded in almost quantitative yields and stereoselectively in the presence of pyridine at different temperatures furnishing the acid with *trans* configuration. A four-step transformation of the carboxylic group of the *trans* acid resulted in stereospecific synthesis of seven tetrahydroisoquinolinones containing different pharmacophoric groups.

## Acknowledgements

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## Experimental

### General

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  $\text{cm}^{-1}$ . Nujol was used for *cis*-**5**, *trans*-**5**, **6** and **7** and chloroform for all other compounds. The  $^1\text{H-NMR}$  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 shifts are given in ppm ( $\delta$ ) relative to tetramethylsilane used as internal standard. Elemental analyses were performed in the analytical laboratory at the Faculty of Chemistry, University of Sofia. TLC was carried out on precoated 0.2 mm Merck silica gel 60F<sub>254</sub> plates. Merck silica gel 60 (0.040-0.063 mm) was used for chromatographic filtration and flash chromatography.

*(±)-trans- and (±)-cis-2-Benzyl-3-(furan-2-yl)-1-oxo-1,2,3,4-tetrahydro-4-isoquinoline Carboxylic Acid (trans-5 and cis-5) and By-products 6 and 7: General Procedure for Determination of the Ratios of the Products Obtained from 3 and 4 on a Small Scale Experiments*

A solution of imine **4** (0.185 g, 1 mmol) in dry solvent (0.7 mL) was added dropwise over 5 min. to a suspension of homophthalic anhydride (**3**, 0.162 g, 1 mmol) in dry solvent (1 mL). The reaction mixture was stirred at the corresponding temperature (see Table 1) for 15 min. The absence of **3** was confirmed by TLC. The reaction mixture was diluted with dichloromethane (5 mL, entries 1 and 2 of Table 1) or with toluene (5 mL, entry 3 of Table 1), when non-polar solvents were used. In the cases when pyridine was used as a polar solvent (entries 4 and 5 of Table 1), the reaction mixture was diluted with water (50 mL), extracted three times with dichloromethane and the organic layers were

washed once with aqueous HCl (1:1). For all cases, the organic layers obtained were washed three times with 10 % sodium hydroxide. The amount of the product **7** was determined after evaporation of the relevant organic solvents (entries 1 to 3 of Table 1). The alkaline solutions were acidified, extracted three times with ethyl acetate, the combined organic layers were washed twice with water, dried (sodium sulfate) and evaporated under reduced pressure leaving a brown oil containing the acid products **5** and **6**. The *cis*-**5**/*trans*-**5**/**6** ratios were determined from the <sup>1</sup>H-NMR integration (DMSO-d<sub>6</sub>), as described above. The data obtained are summarised in Table 1. The characterisation of the products is given below.

*Reaction between 3 and 4 Performed on a Large Scale in Dichloroethane.*

A solution of imine **4** (1.110 g, 6 mmol) in dry dichloroethane (5 mL) was added dropwise to a hot and stirred suspension of homophthalic anhydride (**3**, 0.972 g, 6 mmol) in dry dichloroethane (5 mL). The reaction mixture was boiled at 83 °C and stirred for 45 min. The absence of **3** was established by TLC. The reaction mixture was left overnight. The yellow crystals of **7** were collected by filtration (0.124 g, 9 %). The filtrate was extracted three times with 10 % sodium hydroxide and the alkaline solutions were acidified and then extracted three times with ethyl acetate. The organic layers were washed twice with water and dried over sodium sulfate. The solvent was evaporated under reduced pressure leaving a dark brown oil (1.68 g). The acid products *cis*-**5**, *trans*-**5** and **6** were separated by flash chromatography (toluene-ethyl acetate 4.7:0.3) in yields of 9 %, 19 % and 10 %, respectively. A mixed fraction containing both *cis*-**5** and *trans*-**5** was also obtained (7 %).

*(±)-cis-2-Benzyl-3-(furan-2-yl)-1-oxo-1,2,3,4-tetrahydro-4-isoquinoline Carboxylic Acid (cis-5).*

White crystals, mp 172-174 °C; *Anal.* Calc. For C<sub>21</sub>H<sub>17</sub>NO<sub>4</sub>: C, 72.61; H, 4.93. Found: C, 72.58; H, 5.15; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 4.02 (d, 1H, -CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, J = 15.5 Hz), 4.64 (d, 1H, 4-H, J = 5.5 Hz), 5.07 (d, 1H, 3-H, J=5.75 Hz), 5.26 (d, 1H, -CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, J =15.5 Hz), 5.99-6.01 (m, 1H, 11-H), 6.25-6.27 (m, 1H, 10-H), 7.27-7.34 (m, 5H, phenyl protons), 7.42-7.48 (m, 2H, 5,12-H), 7.52-7.59 (m, 1H, 6-H), 7.64-7.67 (m, 1H, 7-H), 8.00-8.04 (m, 1H, 8-H); IR: 1730 (CO<sub>2</sub>H, dimer), 1630 (CO).

*(±)-trans-2-Benzyl-3-(furan-2-yl)-1-oxo-1,2,3,4-tetrahydro-4-isoquinoline Carboxylic Acid (trans-5).*

White crystals, mp 195-197 °C. *Anal.* Calc. For C<sub>21</sub>H<sub>17</sub>NO<sub>4</sub>: C, 72.61; H, 4.93. Found: C, 72.59; H, 4.92; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 4.16 (d, 1H, -CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, J = 15.04 Hz), 4.24 (s, 1H, 4-H), 5.18 (d, 1H, -CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, J = 15.0 Hz), 5.29 (s, 1H, 3-H), 5.94-6.00 (m, 1H, 11-H), 6.21-6.27 (m, 1H, 10-H), 7.22-7.29 (m, 5H, phenyl protons), 7.34-7.36 (m, 1H, 5-H), 7.40-7.44 (m, 1H, 12-H), 7.48-7.54 (m, 2H, 6,7-H), 7.87-7.94 (m, 1H, 8-H); IR: 1720 (CO<sub>2</sub>H, dimer), 1700 (CO<sub>2</sub>H, monomer), 1630 (CO).

*2-[2-(Benzylamino)-2-oxoethyl]benzenecarboxylic Acid (6).*

White crystals, mp 141-143 °C; *Anal.* Calc. For C<sub>16</sub>H<sub>15</sub>NO<sub>3</sub>: C, 71.36; H, 5.61. Found: C, 71.00; H, 5.77; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): 3.92 (s, 2H, -CH<sub>2</sub>CO-), 4.27 (d, 2H, -CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, J = 5.9 Hz), 7.22-7.51 (m,

8H, phenyl protons), 7.82-7.85 (m, 1H, phenyl proton), 8.38 (t, 1H, NH,  $J = 5.9$  Hz); IR: 3300 (NH), 1710 and 1610 (CO).

*4-(Furan-2-yl)methylidene-1H-isochromene-1,3-dione (7).*

Yellow crystals, mp. 209-215 °C (lit. [27] mp 212 °C); *Anal.* Calc. For  $C_{14}H_8O_4$ : C, 70.00; H, 3.36. Found: C, 70.14; H, 3.16;  $^1H$ -NMR: 6.61-6.63 (m, 1H, furan), 7.28-7.43 (m, 2H, furan), 7.67-7.77 (m, 2H, phenyl protons), 7.85 (s, 1H, methyne proton), 8.13-8.16 (m, 2H, phenyl protons); IR: 3300 (NH), 1710 and 1610 (CO).

*Reaction between 3 and 4 Performed on a Large Scale in Pyridine.*

A solution of imine **4** (25.9 g, 0.14 mol) in dry pyridine (100 mL) was added dropwise over 30 min to a solution of homophthalic anhydride (**3**, 22.68 g, 0.14 mol) in dry pyridine (150 mL). The reaction mixture was boiled at 116 °C and stirred for 15 min., until the absence of **3** was established by TLC. The reaction mixture was diluted with water (300 mL) and extracted three times with dichloromethane. The organic layers were washed once with HCl (1:1) and three times with 10 % sodium hydroxide. The alkaline solutions were acidified, extracted three times with ethyl acetate. The combined organic layers were washed twice with water, dried (sodium sulfate) and evaporated affording crystals of *trans*-**5** (39.2 g, 80 %).

*(±)-trans-Methyl-2-Benzyl-3-(furan-2-yl)-1-oxo-1,2,3,4-tetrahydro-4-isoquinoline Carboxylate (8).*

Concentrated sulfuric acid (14.7 mL, 26.95 g, 0.28 mol) was added dropwise upon stirring to a hot solution of *trans*-**5** (39.20 g, 0.11 mol) in a mixture of methanol (148 mL, 140.80 g, 4.4 mol) and toluene (200 mL). The reaction mixture was refluxed for 3.5 h. Then the reaction mixture was cooled, diluted with toluene (200-250 mL) and washed three times with water and twice with 10 % sodium carbonate. The organic layer was dried (sodium sulfate) and toluene was evaporated under reduced pressure affording crystals of **8** in 76 % yield, mp 124-126 °C; *Anal.* Calc. For  $C_{22}H_{19}NO_4$ : C, 73.12; H, 5.30. Found: C, 73.15; H, 5.12;  $^1H$ -NMR: 3.13 (s, 3H,  $-COCH_3$ ), 3.69 (d, 1H,  $-CH_2C_6H_5$ ,  $J = 14.6$  Hz), 3.88 (s, 1H, 4-H), 5.04 (s, 1H, 3-H), 5.42 (m, 1H,  $-CH_2C_6H_5$ ), 5.63-5.69 (m, 1H, 11-H), 5.90-5.95 (m, 1H, 10-H), 6.93-6.95 (m, 1H, 5-H), 7.04-7.11 (m, 6H, 12-H, phenyl protons), 7.22-7.23 (m, 2H, 6,7-H), 7.96-7.98 (m, 1H, 8-H); IR: 1740 and 1650 (CO).

*(±)-trans-2-Benzyl-3-(furan-2-yl)-4-hydroxymethyl-1,2,3,4-tetrahydroisoquinolin-1-one (9).*

To a stirred suspension of potassium borohydride (10.8 g, 0.2 mol) and lithium chloride (8.5 g, 0.2 mol) in dry tetrahydrofuran (100 mL), solution of ester **8** (29.7 g, 0.08 mol) in dry tetrahydrofuran (70 mL) was added dropwise. The reaction mixture was stirred at room temperature for 15 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 **9** as an oil. The latter was crystallized from ethyl acetate giving white crystals, (23.9 g, 90%), mp 105-106 °C. *Anal.* Calc. For  $C_{21}H_{19}NO_3$ : C, 75.66; H, 5.74; N, 4.20. Found: C, 75.30; H, 5.43; N, 4.54;  $^1H$ -NMR:

3.20-3.34 (m, 2H,  $-CH_2OH$ ), 3.43-3.52 (m, 1H,  $-OH$ ), 3.81 (d, 1H,  $-CH_2C_6H_5$ ,  $J = 14.3$  Hz), 4.85 (s, 1H, 4-H), 5.85 (d, 1H,  $-CH_2C_6H_5$ ,  $J = 14.3$  Hz), 5.90 (s, 1H, 3-H), 5.91-5.95 (m, 1H, 11-H), 6.16-6.19 (m, 1H, 10-H), 7.09-7.16 (m, 1H, 5-H), 7.25-7.28 (m, 1H, 12-H), 7.28-7.46 (m, 7H, 6,7-H, phenyl protons), 8.13-8.17 (m, 1H, 8-H); IR: 3610 (OH), 1640 (CO).

(±)-*trans*-2-Benzyl-1-oxo-3-(furan-2-yl)-4-tosyloxymethyl-1,2,3,4-tetrahydroisoquinolin-1-one (**10**).

*p*-Toluenesulfonyl chloride (30.5 g, 0.16 mol) was added in portions to a solution of **9** (26.4 g, 0.08 mol) in pyridine (150 mL) maintained at  $-5$  °C. The reaction mixture was stirred at room temperature for 15 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 **10** was obtained as a red oil, (36.6 g, 94%). Tosylate **10** was used in the next stage of the reaction scheme without any preliminary purification. The NMR-spectra of compound **10** is similar to that of the starting alcohol **9** and shows a singlet for the methyl group of the *p*-toluenesulfonyl group, signals for four additional aromatic protons and the signal for the hydroxylic proton was absent.

*General Procedure for the Preparation of (±)-trans*-2-Benzyl-1-oxo-3-(furan-2-yl)-4-(*N,N*-disubstitutedaminomethyl)-1,2,3,4-tetrahydroisoquinolin-1-ones (**11a-g**).

The secondary amine NuH (Scheme 2, 18 mmol) was added to a solution of tosylate **10** (3.0 g, 6 mmol) in toluene (15 mL). The reaction mixture was refluxed (20-49 hrs) until **10** was no longer present, as indicated by TLC. Ethyl acetate 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 (4.8:0.2 dichloromethane-ethyl acetate) and/or flash chromatography (4.5:0.5 hexane-ethyl acetate) and subsequent recrystallisation (from 4:1 hexane-ethyl acetate).

(±)-*trans*-2-Benzyl-1-oxo-3-(furan-2-yl)-4-[(piperidin-1-yl)methyl]-1,2,3,4-tetrahydroisoquinolin-1-one (**11a**).

This compound was obtained from **10** and piperidine as white crystals (0.580 g, 24 %) after flash chromatography and recrystallisation mp 124-126 °C; *Anal.* Calc. For  $C_{26}H_{28}N_2O_2$ : C, 77.97; H, 7.05. Found: C, 77.91; H, 7.28;  $^1H$ -NMR: 1.54-1.63 (m, 6H, 15-H), 1.96-2.00 (m, 2H, 14-H), 2.48-2.54 (m, 1H, 4-H), 2.59-2.61 (m, 2H, 14-H), 3.49 (dd, 1H, 13-H,  $J = 15.5$ , 8 Hz), 4.05 (d, 1H, 9-H,  $J = 14.3$  Hz), 5.46 (s, 1H, 3-H), 5.99 (d, 1H, 9-H,  $J = 14.3$  Hz), 6.18-6.19 (m, 1H, 11-H), 6.45-6.46 (m, 1H, 10-H), 7.26-7.33 (m, 1H, 5-H), 7.48-7.79 (m, 8H, 6,7,12-H, phenyl protons), 8.41-8.49 (m, 1H, 8-H); IR: 1660 (CO).

(±)-*trans*-2-Benzyl-1-oxo-3-(furan-2-yl)-4-[(4-phenylpiperazin-1-yl)methyl]-1,2,3,4-tetrahydroisoquinolin-1-one (**11b**).

This compound was obtained from **10** and *N*-phenylpiperazine as white crystals (1.1 g, 38 %) after chromatographic filtration, flash chromatography and recrystallisation; mp 189 °C; *Anal.* Calc. For

$C_{31}H_{31}N_3O_2$ : C, 77.96; H, 6.54; N, 8.80. Found: C, 78.22; H, 6.68; N, 8.55;  $^1H$ -NMR: 1.83-1.88 (m, 2H, 14-H), 2.09 (dd, 1H, 13-H,  $J = 16.0$ , 8 Hz), 2.28-2.34 (m, 1H, 4-H), 2.50-2.55 (m, 2H, 14-H), 2.91-3.09 (m, 4H, 15-H), 3.22 (dd, 1H, 13-H,  $J = 16.0$ , 8 Hz), 3.69 (d, 1H, 9-H,  $J = 14.3$  Hz), 5.16 (s, 1H, 3-H), 5.77 (d, 1H, 9-H,  $J = 14.3$  Hz), 5.90-5.91 (m, 1H, 11-H), 6.16-6.17 (m, 1H, 10-H), 6.80-6.85 (m, 3H, 5,6,7-H), 7.03-7.05 (m, 1H, 12-H), 7.20-7.48 (m, 10H, phenyl protons), 8.13-8.15 (m, 1H, 8-H); IR: 1660 (CO).

(±)-*trans*-2-Benzyl-1-oxo-3-(furan-2-yl)-4-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl)methyl]-1,2,3,4-tetrahydroisoquinolin-1-one (**11c**).

This compound was obtained from **10** and 3-(trifluoromethyl)-N-phenylpiperazine as white crystals (1.3 g, 40 %) after chromatographic filtration, flash chromatography and recrystallisation; mp 170-172.5 °C; *Anal.* Calc. For  $C_{32}H_{30}N_3O_2F_3$ : C, 70.43; H, 5.55; N, 7.70. Found: C, 70.50; H, 5.40; N, 7.38;  $^1H$ -NMR: 1.66-1.71 (m, 2H, 14-H), 1.93 (dd, 1H, 13-H,  $J = 17.0$ , 7.4 Hz), 2.11-2.17 (m, 1H, 4-H), 2.35-2.38 (m, 2H, 14-H), 2.75-2.83 (m, 4H, 15-H), 3.05 (dd, 1H, 13-H,  $J = 15.4$ , 8.2 Hz), 3.51 (d, 1H, 9-H,  $J = 14.3$  Hz), 4.97 (s, 1H, 3-H), 5.61 (d, 1H, 9-H,  $J = 14.3$  Hz), 5.73-5.74 (m, 1H, 11-H), 5.99-6.00 (m, 1H, 10-H), 6.79-6.81 (m, 1H, 5-H), 6.85-6.88 (m, 3H, 6,7,12-H), 7.07-7.31 (m, 9H, phenyl protons), 7.96-7.98 (m, 1H, 8-H); IR: 1660 (CO).

(±)-*trans*-2-Benzyl-1-oxo-3-(furan-2-yl)-4-[4-(3-chlorophenyl)-piperazin-1-yl)methyl]-1,2,3,4-tetrahydroisoquinolin-1-one (**11d**).

This compound was obtained from **10** and 1-(3-chlorophenyl)-piperazine as white crystals (0.82 g, 23 %) after chromatographic filtration, flash chromatography and recrystallisation; mp 187-189 °C; *Anal.* Calc. For  $C_{31}H_{30}ClN_3O_2$ : C, 72.72; H, 5.91. Found: C, 72.49; H, 5.78;  $^1H$ -NMR: 1.62-1.67 (m, 2H, 14-H), 1.90 (dd, 1H, 13-H,  $J = 16.7$ , 8.8 Hz), 2.09-2.15 (m, 1H, 4-H), 2.31-2.34 (m, 2H, 14-H), 2.75-2.83 (m, 4H, 15-H), 3.03 (dd, 1H, 13-H,  $J = 15.6$ , 8.3 Hz), 3.50 (d, 1H, 9-H,  $J = 14.3$  Hz), 4.96 (s, 1H, 3-H), 5.60 (d, 1H, 9-H,  $J = 14.3$  Hz), 5.72-5.73 (m, 1H, 11-H), 5.97-5.99 (m, 1H, 10-H), 6.52-6.93 (m, 4H, 5,6,7,12-H), 7.03-7.29 (m, 9H, phenyl protons), 7.94-8.04 (m, 1H, 8-H); IR: 1660 (CO).

(±)-*trans*-2-Benzyl-1-oxo-3-(furan-2-yl)-4-[4-fluorophenylpiperazin-1-yl)methyl]-1,2,3,4-tetrahydroisoquinolin-1-one (**11e**).

This compound was obtained from **10** and 1-(4-fluorophenyl)piperazine as white crystals (1.2 g, 40 %) after chromatographic filtration, flash chromatography and recrystallisation; mp 150-152 °C; *Anal.* Calc. For  $C_{31}H_{30}FN_3O_2$ : C, 75.13; H, 6.10. Found: C, 74.85; H, 5.67;  $^1H$ -NMR: 1.89-1.94 (m, 2H, 14-H), 1.87 (dd, 1H, 13-H,  $J = 16.7$ , 8.9 Hz), 2.34-2.40 (m, 1H, 4-H), 2.58-2.61 (m, 2H, 14-H), 2.86-2.95 (m, 4H, 15-H), 3.28 (dd, 1H, 13-H,  $J = 16.8$ , 8.9 Hz), 3.75 (d, 1H, 9-H,  $J = 14.3$  Hz), 5.21 (s, 1H, 3-H), 5.83 (d, 1H, 9-H,  $J = 14.3$  Hz), 5.96-5.97 (m, 1H, 11-H), 6.22-6.23 (m, 1H, 10-H), 6.83-7.00 (m, 3H, 5,6,7-H), 7.09-7.11 (m, 1H, 12-H), 7.28-7.47 (m, 9H, phenyl protons), 8.19-8.21 (m, 1H, 8-H); IR: 1660 (CO).

(±)-*trans*-2-Benzyl-1-oxo-3-(furan-2-yl)-4-[4-(morpholin-4-yl)methyl]-1,2,3,4-tetrahydroisoquinolin-1-one (**11f**).

This compound was obtained from **10** and morpholine as white crystals (0.89 g, 37 %) after chromatographic filtration, flash chromatography and recrystallisation; mp 135-137 °C; *Anal. Calc.* For C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>3</sub>: C, 74.60; H, 6.51. Found: C, 74.82; H, 6.62; <sup>1</sup>H-NMR: 1.38-1.49 (m, 2H, 14-H), 1.87 (dd, 1H, 13-H, J = 16.7, 8.7 Hz), 1.98-2.07 (m, 1H, 4-H), 2.11-2.16 (m, 2H, 14-H), 3.00 (dd, 1H, 13-H, J = 15, 8.6 Hz), 3.24-3.28 (m, 4H, 15-H) 3.50 (d, 1H, 9-H, J = 14.3 Hz), 4.96 (s, 1H, 3-H), 5.60 (d, 1H, 9-H, J = 14.3 Hz), 5.71-5.72 (m, 1H, 11-H), 5.97-5.98 (m, 1H, 10-H), 6.77-6.84 (m, 1H, H-5), 6.93-7.41 (m, 8H, 6,7,12-H, phenyl protons), 7.93-7.96 (m, 1H, 8-H); IR: 1660 (CO).

(±)-*trans*-2-Benzyl-1-oxo-3-(furan-2-yl)-4-[4-(thiomorpholin-4-yl)methyl]-1,2,3,4-tetrahydroisoquinolin-1-one (**11g**).

This compound was obtained from **10** and thiomorpholine as white crystals (1.26 g, 50 %) after chromatographic filtration, flash chromatography and recrystallisation; mp 162-164 °C; *Anal. Calc.* For C<sub>25</sub>H<sub>26</sub>N<sub>2</sub>O<sub>2</sub>S: C, 71.73; H, 6.26; N, 6.69. Found: C, 71.90; H, 6.17; N, 6.68; <sup>1</sup>H-NMR: 1.73 -1.78 (m, 2H, 14-H), 2.17-2.20(m, 4H, 13-, 15-H), 2.39-2.44 (m, 2H, 15-H), 2.96-2.98 (m, 1H, 4-H), 2.11-2.16 (m, 2H, 14-H), 3.48 (d, 1H, 9-H, J = 14.3 Hz), 4.87 (s, 1H, 3-H), 5.59 (d, 1H, 9-H, J = 14.3 Hz), 5.71-5.72 (m, 1H, 11-H), 5.97-5.98 (m, 1H, 10-H), 6.82-6.83 (m, 1H, H-5), 7.04-7.30 (m, 8H, 6,7,12-, H, phenyl protons), 7.93-7.96 (m, 1H, 8-H); IR: 1660 (CO).

(±)-*trans*-2-Benzyl-3-(furan-2-yl)-4-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (**12**).

The completely reduced alcohol **12** was prepared from **8** (0.824 g, 2.3 mmol) following literature procedures [21, 22] with a reaction time of 2 hours. It was obtained as colorless crystals (from ethyl acetate), (0.520 g, 71 %); mp 103-105 °C; *Anal. Calc.* For C<sub>21</sub>H<sub>21</sub>NO<sub>2</sub>: C, 78.97; H, 6.63. Found: C, 78.99; H, 6.71; <sup>1</sup>H-NMR: 3.31 (br s, 1H, -OH), 3.55 (d, 1H, -CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, J = 15.5 Hz), 3.86 (d, 1H, 13-H, J = 13 Hz), 4.01 (d, 1H, -CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, J = 15.5 Hz), 4.14 (d, 1H, 13-H, J = 13 Hz), 4.15 (d, 1H, 1-H, J = 10 Hz), 4.30 (d, 1H, 1-H, J = 10 Hz), 4.34-4.36 (m, 1H, 4-H), 4.61 (s, 1H, 3-H), 5.94-5.95 (m, 1H, 11-H), 6.43-6.44 (m, 1H, 10-H), 7.17-7.20 (m, 1H, 5-H), 7.31-7.40 (m, 1H, 12-H), 7.44-7.61 (m, 7H, 6,7-H, phenyl protons), 7.63-7.67 (m, 1H, 8-H); IR: 3640 (OH).

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*Sample Availability:* Compounds ***cis*-5**, ***trans*-5,6-9**, ***trans*-11a-e**, and ***trans*-11g** are available in 20 mg amounts from the authors.