New *trans*/*cis* Tetrahydroisoquinolines. 3. [1,3]-Oxazolo-[3,2-*b*]-tetrahydroisoquinolinones Having an Angular Aryl Substituent

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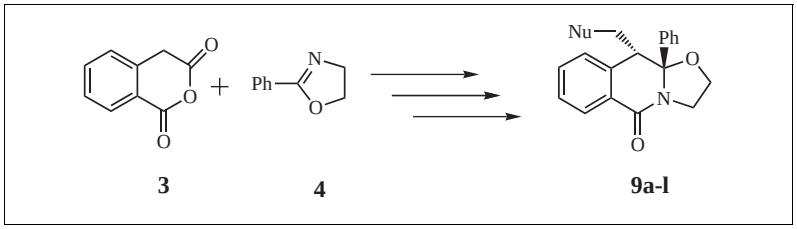

The parent compound 5-oxo-10a-phenyl-2,3,10,10a-tetrahydro-5*H*-[1,3]-oxazolo-[3,2-*b*]-isoquinoline-10-carboxylic acid (**5**) was prepared in large scale and a good yield by reaction between homophthalic anhydride (**3**) and 4,5-dihydro-2-phenyl-1,3-oxazole (**4**). Thus, the closure of the isoquinoline ring and fusion of the 1,3-oxazol ring occur in one step. *Trans* configuration was assumed for the product. The parent acid **5** was converted in four steps to the target aminomethyl derivatives **9a-l**. The latter contain four features that make them interesting from pharmaceutical point of view.

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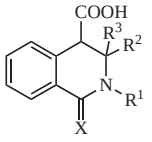
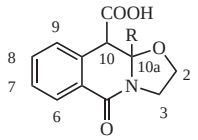
Introduction.

Tetrahydroisoquinoline acids of type **1** are important because they are used as starting compounds for the total synthesis of numerous natural compounds such as corydaline [1], 8-oxoberbines [2] and chelidonine [3]. In addition, some of these acids have shown different activities such as antiflamatory, anti-allergic, psychotropic, antitumor and estrogenic activity [4-6].



1

X = O or 2H
R^1 - R^3 : variuos



2

R : variuos

There are several approaches for synthesis of compounds of type **1**. Some of them are: a) cyclization by the Pictet-Spengler reaction [7], b) reaction of isocoumarins with imines [8] or aldehydes [9], c) reaction of homophthalic anhydrides with imines proposed almost simultaneously by Haimova *et al*. [2] and Cushman *et al*. [10], and recent modifications of this reaction [11,12] and d) (-)-sparteine mediated benzamide lateral metalation–imine addition [13]. The cyclization proceeds in one step but usually the starting compounds are not easy to prepare. The only exception is the reaction between homophthalic anhydride (commercial product) and an imine that is synthesised simply.

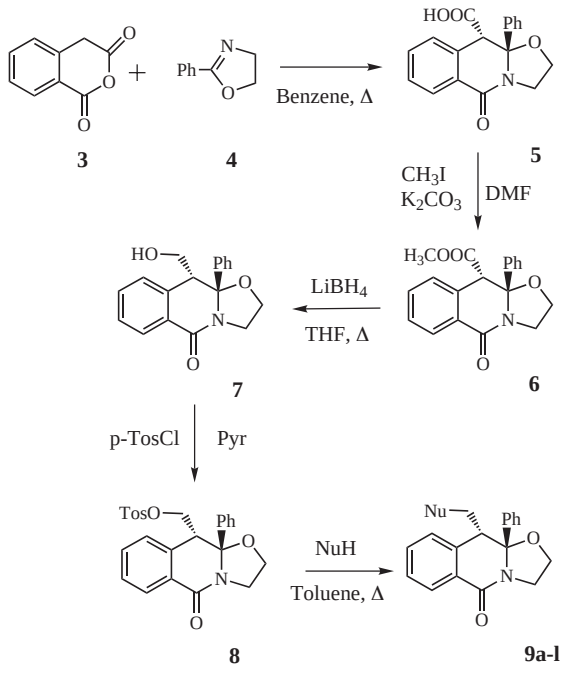
This third paper of the current series continues our attempts [14,15] to specify further the scope and limitation of the reaction between homophthalic anhydride and imines and to transform the acids obtained to compounds with expected pharmaceutical activity. Our attention was attracted by the naturally occurring antibiotics cervinomycines A_1 and A_2 containing the moiety of oxazolotetrahydroisoquinoline **2** [16-18]. Note the presence of an angular alkyl group in this structure. The synthesis of this moiety is performed in four [18] to seven [16-17] steps where the last of them is the reaction of an isocoumarin with an amine. The synthesis of structure **2** without an angular group (R = H) or with such a group is done by a radical-mediated cyclization [19] or by reaction of homophthalic anhydride and a cyclic imine [20-22]. The last reaction does not proceed smoothly [21]. Moreover, when the cyclic imine contains a substituent that should occupy the angular position, the reaction does not occur in that direction in boiling toluene owing to elimination of the substituent (R = $CO_2C_2H_5$) [20]. This made us to study the reaction of homophthalic anhydride with a specific cyclic imine that should lead in one step to a tetrahydroisoquinolinone **2** with three fused rings and an angular aryl group (R = C_6H_5).

Results and Discussion.

The reaction between equimolar quantities of homophthalic anhydride (**3**) and 4,5-dihydro-2-phenyl-1,3-oxazole (**4**) [23,24] was performed in different ways varying the solvent, temperature and applying ultra sound as in Ref. 15. When the reaction was done in boiling

benzene (in large scale), only one product was isolated in good yield. It was identified as the expected acid **5** having an angular phenyl group (Scheme 1). The reason that we succeeded to keep the angular group contrary to the case of Ref. 21 is probably the difference in the electronic structures of the groups and the lower by 30 °C reaction temperature. Thus, this is the first case when the reaction between homophthalic anhydride and a substituted oxazole proceeds smoothly. In general this approach can be extended to the synthesis of other compounds having different angular aryl groups and also to the synthesis of the cervinomycines. The stereochemistry of tetrahydroisoquinolinone acids of type **2** (R = H) can be defined on the basis of the value of the vicinal J constant between the protons at C10 and C10a [2,10]. The acid **5** obtained does not possess a proton at C10a, which makes the determination of its configuration only possible through X-ray analysis. Such results will be published in a subsequent paper.

Scheme 1

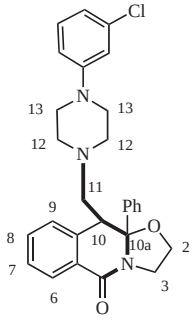


3 **4** **5** **6** **7** **8** **9a-l**

The conversion of the parent acid **5** to the target compounds **9a-l** was performed in analogy to Refs. 15, 16. To this end, **5** was reacted with methyl iodide and potassium carbonate in DMF to form ester **6** that was selectively reduced with $LiBH_4$ in dry THF to yield 4-hydroxymethyl derivative **7**.

The ^1H nmr spectra of the acid **5**, its ester **6** and alcohol **7** were very similar suggesting, that there were no changes in the stereochemistry of these compounds during the relevant reactions. Alcohol **7** was converted into tosylate **8** by reaction with tosyl chloride in dry pyridine. Tosylate **8** was reacted with different secondary cyclic amines to give rise to the target compounds **9a-l** in good to high yields (Table 1). *Trans* configuration is assumed for compounds **5-9** since the thermodynamically more stable *trans* acid is obtained in boiling benzene and the ^1H nmr signal for the ester CH_3 of **6** is in the region established for *trans* isomers of type **1** [2,10].

These compounds are of significant interest because they contain the fragment (given in bold below in **9g**) of inverse amide of γ-aminobutyric acid [4], which is believed to play a key role in the state of anxiety and the appearance of epilepsy [25-27]. The description of the nmr spectra of compounds **5-8** and **9a-l** uses the arbitrary numbering shown in the formula of **9g**.



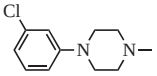
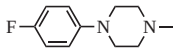
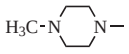
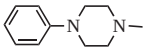
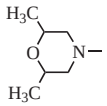
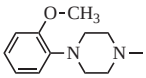
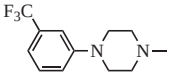
9g

The presence of the fused oxazole ring, the angular phenyl group at C10a and various amine groups arising from pharmacophoric secondary cyclic amines are additional points that can evoke activity. Pharmacological screening of **9a-l** is in course.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage and are uncorrected. The ir spectra were acquired in chloroform, if not stated otherwise, on a Specord 75 and are reported in reciprocal centimeters. The ^1H nmr spectra were obtained on a Bruker AM400 NMR spectrometer at 400.13 MHz in deuterochlorofom as solvent, if not stated otherwise. The chemical shift is given in ppm (δ) relative to tetramethylsilane as internal standard. Elemental analyses were obtained in the relevant laboratories at the Faculty of Chemistry, University of Sofia or at the Institute of Organic Chemistry, Bulgarian Academy of Sciences. The TLC was done on precoated 0.2 mm Merck silica gel $60F_{254}$ plates. Merck silica gel 60 (0.040-0.063 mm) was used for chromatographic filtration and flash chromatography.

Table 1
Structures of the Nu group in compounds **9a-l** and the yields of the latter.

	Nu	Yield (%)		Nu	Yield (%)
a		76	g		48
b		68	h		52
c		78	i		83
d		87	j		78
e		63	k		78
f		88	l		48

(±)-*trans*-5-Oxo-10a-phenyl-2,3,10,10a-tetrahydro-5*H*-[1,3]-oxazolo-[3,2-*b*]-isoquinoline-10-carboxylic acid (**5**).

Homophthalic anhydride (**3**) (47.74 g, 0.27 mol) was dissolved by heating in 250 ml of dry benzene. After all the anhydride was dissolved, the heating was stopped and the solution cooled to ambient temperature. 4,5-Dihydro-2-phenyl-1,3-oxazole (**4**) [23, 24] (39.69 g, 0.27 mol), dissolved in 100 ml of dry benzene, was dropwise added within 15 min. The reaction mixture was refluxed for 2 h and afterwards was left overnight at room temperature. The crystals were collected by filtration to give 30 g of pure acid **5**. The filtrate was extracted with 10% NaOH (3x50 ml), the alkaline solution was acidified and extracted with ethyl acetate (3x50 ml). The combined organic layers were dried with sodium sulfate and evaporated under reduced pressure to give additionally 11.71 g of pure acid **5** (total yield 50%), mp 185-187°; ^{1}H nmr (DMSO-d6): δ 3.54-3.60 (m, 2H, H-3), 3.77-3.82 (m, 1H, H-2), 4.15-4.21 (m, 1H, H-2), 4.35 (s, 1H, H-10), 7.26-7.44 (m, 1H, H-7), 7.05-7.44 (m, 7H, H-8, H-9, Ph), 7.81-7.90 (dd, 1H, H-6, J = 6.7 Hz, 2.0 Hz), 12.81 (broad s, 1H, COOH); ir (nujol): 1590-1620 cm^{-1} (ArH), 1675 cm^{-1} (C=O), 1730cm^{-1} (C=O), 2500-3400 cm^{-1} (OH).

Anal. Calcd. for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.95; H, 4.91; N, 4.49.

Methyl ester of (±)-*trans*-5-oxo-10a-phenyl-2,3,10,10a-tetrahydro-5*H*-[1,3]-oxazolo-[3,2-*b*]-isoquinoline-10-carboxylic acid (**6**).

To a mixture of potassium carbonate (15 g) and acid **5** (41.77 g, 0.135 mol) in dry dimethylformamide, iodomethane (16.8 ml) was drop wise added for 1 h. After stirring at rt for 2.5 h the mixture was poured into 500 ml of cold water. The water was extracted with ethyl acetate (4x150 ml), the organic layers were dried with sodium sulfate and evaporated in vacuum to give the crude ester. The ester was recrystalized from ethyl acetate/ petroleum ether to give 34.93 g (80%) of **6**, mp 170-171°; ^{1}H nmr: δ 3.66-3.76 (m, 5H, OCH_3, H-3), 4.05-4.07 (m, 1H, H-2), 4.21-4.24 (m, 1H, H-2), 4.24-4.35 (m, 1H, H-10), 7.26-7.44 (m, 1H, H-7), 7.22-7.54 (m, 7H, H-8, H-9, Ph), 8.15-8.17 (m, 1H, H-6); ir (nujol): 1590-1620 (ArH), 1650 cm^{-1} (C=O), 1735 cm^{-1} (C=O), 1750cm^{-1} (C-O).

Anal. Calcd. for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.34; H, 5.44; N, 4.34.

(±)-*trans*-10-Hydroxymethyl-10a-phenyl-2,3,10,10a-tetrahydro-5*H*-[1,3]-oxazolo-[3,2-*b*]-isoquinolin-5-one (**7**).

To a stirred suspension of potassium borohydride (11.66 g) and lithium chloride (9.16 g) in dry tetrahydrofuran (80 ml), ester **6** (34.93 g, 0.108 mol) was dissolved in tetrahydrofuran (100 ml) and dropwise added for a period of 30 min. The reaction mixture was refluxed for 2 h, concentrated under reduced pressure, poured into water (300 ml) and extracted with ethyl acetate (4x130 ml). The combined organic layers were dried with sodium sulfate and evaporated under reduced pressure to afford the crude alcohol, which after flash purification gave 27.68 g (86%) of pure product **7**, mp 180-182°; ^{1}H nmr: δ 3.39-3.40 (m, 1H, H-11), 3.48-3.51 (m, 1H, H-3), 3.59-3.62 (m, 1H, H-11), 3.80-3.86 (m, 2H, H-2, H-10), 4.14-4.16 (m, 1H, H-2), 4.35-4.38 (m, 1H, H-3), 6.90-7.28 (m, 8H, H-7, H-8, H-9, Ph), 7.79-7.81 (m, 1H, H-6); ir: 1590-1620 (ArH), 1650 cm^{-1} (C=O), 1050 cm^{-1} (C-O), 3300-3600cm^{-1} (OH).

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.34; H, 5.93; N, 5.01.

(±)-*trans*-5-Oxo-10a-phenyl-2,3,10,10a-tetrahydro-5*H*-[1,3]-oxazolo-[3,2-*b*]-isoquinoline-10-methylene-toluene-4-sulfonate (**8**).

Alcohol **7** (27.60 g, 0.093 mol) was dissolved in dry pyridine (150 ml). The mixture was cooled at –5°C and *p*-toluensulfonyl chloride (35.24 g, 0.186 mol) was added in portions. After stirring at room temperature for 20 h, the mixture was poured into cold water (1l) with intensive stirring. The tosylate **8** precipitated as amorphous solid and was collected by filtration, washed

extensively with cold water and dried at high vacuum to give 41 g of pure product (99%), mp 146-148°; ^{1}H nmr: δ 3.05 (s, 3H, OCH_3), 3.60-3.69 (m, 3H, H-2, H-3), 3.87 (m, 1H, H-2), 4.06-4.14 (m, 2H, H-11), 4.58-4.62 (m, 1H, H-10), 6.95-7.02 (m, 1H, H-7), 7.16-7.42 (m, 7H, H-8, H-9, Ph), 7.99-8.08 (m, 1H, H-6).

General Procedure for the Synthesis of Compounds **9a-l**.

Tosylate **8** (3 g, 0.0066 mol) was dissolved in toluene (15 ml) at heating. After cooling to room temperature, the corresponding secondary cyclic amine NuH (0.0018 mol) was added. The mixture was refluxed until the complete consumption of the tosylate. The reaction mixture was cooled down and ethyl acetate (100 ml) was added. The organic layer was washed with water (10x100 ml) and dried with sodium sulfate. Ethyl acetate was removed under reduced pressure to give the crude product, which was subject to flash chromatography to give the pure compound.

(±)-*trans*-10-[(Pyrolidin-1-yl)-methyl]-10a-phenyl-2,3,10,10a-tetrahydro-5*H*-[1,3]-oxazolo-[3,2-*b*]-isoquinolin-5-one (**9a**).

NuH: pyrolidine; yield: 2.00 g (76%); mp 121-123°; ^{1}H nmr: δ 1.54-1.58 (m, 4H, H-13), 2.24-2.34 (m, 4H, H-12), 2.55-2.60 (m, 1H, H-11), 3.31 (m, 1H, H-11), 3.38 (m, 1H, H-10), 3.58-3.64 (m, 2H, H-3) 3.85-3.89 (m, 1H, H-2), 4.14-4.18 (m, 1H, H-2), 6.84-6.96 (m, 1H, H-7), 7.10-7.23 (m, 7H, H-8, H-9, Ph), 7.94-7.97 (dd, 1H, H-6, J = 7.0 Hz, 2.1 Hz); ir:1590-1620 cm^{-1} (ArH), 1650 cm^{-1} (C=O).

Anal. Calcd. for $C_{22}H_{24}O_2$: C, 75.83; H, 6.94. Found: C, 75.88; H, 7.00.

(±)-*trans*-10-[(Piperidin-1-yl)-methyl]-10a-phenyl-2,3,10,10a-tetrahydro-5*H*-[1,3]-oxazolo-[3,2-*b*]-isoquinolin-5-one (**9b**).

NuH: piperidine; yield: 1.73 g (68%); mp 121-123°; ^{1}H nmr: δ 1.37-1.48 (m, 6H, H-13, H-14), 2.17-2.20 (m, 4H, H-12), 2.62-2.64 (m, 1H, H-11), 2.97-3.31 (m, 1H, H-11), 3.43-3.45 (m, 1H, H-10), 3.71-3.75 (m, 2H, H-3) 4.04 (m, 1H, H-2), 4.27-4.28 (m, 1H, H-2), 7.01-7.09 (m, 1H, H-7), 7.08-7.37 (m, 7H, H-8, H-9, Ph), 8.10-8.12 (m, 1H, H-6); ir: 1590-1620 cm^{-1} (ArH), 1650 cm^{-1} (C=O).

Anal. Calcd. for $C_{23}H_{26}N_2O_2$: C, 76.21; H, 7.23. Found: C, 76.31; H, 7.24

(±)-*trans*-10-[(4-Methyl)piperazin-1-yl)-methyl]-10a-phenyl-2,3,10,10a-tetrahydro-5*H*-[1,3]-oxazolo-[3,2-*b*]-isoquinolin-5-one (**9c**).

NuH: 1-methylpiperazine; yield: 2.20 g (78%); mp 104-106°; ^{1}H nmr: δ 2.01-2.42 (m, 4H, H-12), 2.21 (s, 3H, H-14), 2.61-2.83 (m, 4H, H-13), 3.22-3.41 (m, 2H, H-11), 3.42-3.61 (m, 4H, H-3, H-2), 3.82-4.12 (m, 1H, H-10), 6.52-7.22 (m, 8H, H-7, H-8, H-9, Ph), 7.32-7.61 (m, 1H, H-6); ir: 1590-1620 cm^{-1} (ArH), 1650 cm^{-1} (C=O).

Anal. Calcd. for $C_{23}H_{27}N_3O_2$: C, 73.18; H, 7.21. Found: C, 73.22; H, 7.23.

(±)-*trans*-10-[(4-Phenylpiperazin-1-yl)-methyl]-10a-phenyl-2,3,10,10a-tetrahydro-5*H*-[1,3]-oxazolo-[3,2-*b*]-isoquinolin-5-one (**9d**).

NuH: 1-phenylpiperazine; yield: 2.15 g (87%); mp 117-119°; ^{1}H nmr: δ 2.26-2.33 (m, 2H, H-12), 2.42-2.44 (m, 2H, H-12), 2.59-2.61 (m, 1H, H-11), 2.94-2.97 (m, 5H, H-11, H-13), 3.34-3.36 (m, 1H, H-10), 3.58-3.63 (m, 2H, H-3), 3.61-3.91 (m, 1H, H-2), 4.14-4.16 (m, 1H, H-2), 6.73-6.79 (m, 3H, N-Ph), 7.92-7.96 (m, 1H, H-7), 7.11-7.24 (m, 9H, H-8, H-9, Ph, N-Ph), 7.97-7.99 (dd, 1H, H-6, J = 6.8 Hz, 1.3 Hz); ir: 1590-1620 cm^{-1} (ArH), 1650 cm^{-1} (C=O).

Anal. Calcd. for $C_{28}H_{29}N_3O_2$: C, 76.51, H, 6.64, N, 9.55. Found: C, 76.26; H, 6.92; N, 9.32.

(±)-*trans*-10-[(4-(2-Methoxy)phenyl-piperazin-1-yl)-methyl]-10a-phenyl-2,3,10,10a-tetrahydro-5*H*-[1,3]-oxazolo-[3,2-*b*]-isoquinolin-5-one (**9e**).

NuH: 1-(2-methoxyphenyl)-piperazine; yield: 1.64 g (63%); mp 150-152°; ^{1}H nmr: δ 2.38-2.42 (m, 2H, H-12), 2.53-2.63 (m, 2H, H-12), 2.64-2.66 (m, 1H, H-11), 3.05-3.09 (m, 1H, H-11), 2.66 (m, 4H, H-13), 3.43-3.44 (m, 1H, H-10), 3.65-3.69 (m, 2H, H-3), 2.66 (s, 3H, OCH_3), 3.98 (m, 1H, H-2), 4.22 (m, 1H, H-2), 6.66 (m, 1H, N-Ph), 6.79-6.88 (m, 3H, N-Ph), 7.04 (m, 1H, H-7), 7.18-7.30 (m, 7H, H-8, H-9, Ph), 8.03 (dd, 1H, H-6, J = 7.0 Hz, 1.8 Hz); ir: 1230 cm^{-1} (CH_3O), 1590-1620 cm^{-1} (ArH), 1650 cm^{-1} (C=O).

Anal. Calcd. for $C_{29}H_{31}N_3O_3$: C, 74.18; H, 6.65. Found: C, 74.22; H, 6.70.

(±)-*trans*-10-[(4-(3-Trifluoromethyl)phenyl-piperazin-1-yl)-methyl]-10a-phenyl-2,3,10,10a-tetrahydro-5*H*-[1,3]-oxazolo-[3,2-*b*]-isoquinolin-5-one (**9f**).

NuH: 1-(3-trifluoromethyl)phenylpiperazine; yield: 2.20 g (88%); mp 85-87°; ^{1}H nmr: δ 2.16-2.50 (m, 4H, H-12), 2.67-2.84 (m, 1H, H-11), 2.92-3.08 (m, 5H, H-11, H-13), 3.41-3.63 (m, 1H, H-10), 3.63-3.71 (m, 2H, H-3), 3.94-4.03 (m, 1H, H-2), 4.20-4.27 (m, 1H, H-2), 7.00-7.04 (m, 4H, N-Ph), 7.22-7.60 (m, 8H, H-7, H-8, H-9, Ph), 7.99-8.12 (dd, 1H, H-6, J = 7.0 Hz, 2 Hz); ir: 1590-1620 cm^{-1} (ArH), 1650 cm^{-1} (C=O).

Anal. Calcd. for $C_{29}H_{28}F_3N_3O_2$: C, 68.63; H, 5.56. Found: C, 68.95; H 5.53.

(±)-*trans*-10-[(4-(3-Chlorophenyl)piperazine-1-yl)-methyl]-10a-phenyl-2,3,10,10a-tetrahydro-5*H*-[1,3]-oxazolo-[3,2-*b*]-isoquinolin-5-one (**9g**).

NuH: 1-(3-chlorophenyl)piperazine; yield: 1.32 g (48%); mp 133-135°; ^{1}H nmr: δ 2.32-2.34 (m, 2H, H-12), 2.44-2.47 (m, 2H, H-12), 2.71-2.73 (m, 1H, H-11), 3.00-3.03 (m, 3H, H-11, H-13), 2.66 (m, 2H, H-13), 3.42 (m, 1H, H-10), 3.66-3.69 (m, 2H, H-3), 3.69 (m, 1H, H-2), 3.98-4.24 (m, 1H, H-2), 6.77-6.79 (m, 3H, N-Ph), 7.02-7.04 (m, 1H, H-7), 7.09-7.11 (m, 1H, N-Ph), 7.18-7.33 (m, 7H, H-8, H-9, Ph), 8.05-8.07 (dd, 1H, H-6, J = 6.9 Hz, 1.9 Hz); ir: 1590-1620 cm^{-1} (ArH), 1650 cm^{-1} (C=O).

Anal. Calcd. for $C_{28}H_{28}ClN_3O_2$: C, 70.95; H, 5.95. Found: C, 70.98; H, 6.03.

(±)-*trans*-10-[(4-Fluorophenyl-piperazin-1yl)-methyl]-10a-phenyl-2,3,10,10a-tetrahydro-5*H*-[1,3]-oxazolo-[3,2-*b*]-isoquinolin-5-one (**9h**).

NuH: 1-(4-fluorophenyl)piperazine; yield: 1.06 g (52%); mp 146-148°; ^{1}H nmr: δ 2.34-2.50 (m, 4H, H-12), 2.67-2.84 (m, 1H, H-11), 2.94-2.98 (m, 4H, H-13), 3.00-3.06 (m, 1H, H-11), 3.41-3.47 (m, 1H, H-10), 3.57-3.73 (m, 2H, H-3), 3.95-4.02 (m, 1H, H-2), 4.20-4.26 (m, 1H, H-2), 6.76-6.82 (m, 2H, N-Ph), 6.89-6.94 (m, 1H, N-Ph), 7.02-7.04 (m, 1H, N-Ph), 7.19-7.55 (m, 7H, H-8, H-9, Ph), 8.05-8.07 (m, 1H, H-6); ir: 1590-1620 cm^{-1} (ArH), 1650 cm^{-1} (C=O).

Anal. Calcd. for $C_{28}H_{28}FN_3O_2$: C, 73.50; H, 6.17. Found: C, 73.62; H, 6.20.

(±)-*trans*-10-[(Morpholin-4-yl)-methyl]-10a-phenyl-2,3,10,10a-tetrahydro-5*H*-[1,3]-oxazolo-[3,2-*b*]-isoquinolin-5-one (**9i**).

NuH: morpholine; yield: 2.00 g (83%); mp 118-120°; ^{1}H nmr: δ 2.26-2.31 (m, 2H, H-12), 2.38-2.43 (m, 2H, H-12), 2.70-2.75 (m, 1H, H-11), 3.05-3.09 (m, 1H, H-11), 3.42 -3.62 (m, 1H, H-10), 3.62-3.74 (m, 4H, H-13), 3.74-3.81 (m, 2H, H-3), 4.02-4.06 (m, 1H, H-2), 4.30-4.34 (m, 1H, H-2), 7.04-7.12 (m, 1H, H-7), 7.18-7.44 (m, 7H, H-8, H-9, Ph), 8.07-8.25 (dd, 1H, H-6, J = 7.0 Hz, 2.2 Hz); ir: 1590-1620 cm^{-1} (ArH), 1650 cm^{-1} (C=O).

Anal. Calcd. for: $C_{22}H_{24}N_2O_3$: C, 77.49; H, 6.65; N, 7.68. Found: C, 77.68; H, 6.98; N, 7.53.

(±)-*trans*-10-[(2,6-Dimethylmorpholin-4-yl)-methyl]-10a-phenyl-2,3,10,10a-tetrahydro-5*H*-[1,3]-oxazolo-[3,2-*b*]-isoquinolin-5-one (**9j**).

NuH: 2,6-dimethylmorpholine; yield: 2.06 g (78%); mp 165-168°; ^{1}H nmr: δ 0.92-1.05 (m, 6H, 2CH_3), 1.70 (t, 2H, H-12, J = 10.1 Hz)), 2.27 (t, 2H, H-12, J = 10.1 Hz), 2.49-2.54 (m, 1H, H-11), 2.84-2.88 (m, 1H, H-11), 3.57 (m, 1H, H-10), 3.30-3.44 (m, 2H, H-13), 3.87-3.88 (m, 2H, H-3), 4.02-4.06 (m, 1H, H-2), 4.13-4.16 (m, 1H, H-2), 6.81-6.91 (m, 1H, H-7), 7.13-7.24 (m, 7H, H-8, H-9, Ph), 7.98-7.99 (dd, 1H, H-6, J = 6.8 Hz, 1.8 Hz); ir: 1590-1620 cm^{-1} (ArH), 1650 cm^{-1} (C=O).

Anal. Calcd. for: $C_{24}H_{28}N_2O_3$: C, 73.44; H, 7.19. Found: C, 73.24; H, 7.20.

(±)-*trans*-10-[(Thiomorpholin-4-yl)-methyl]-10a-phenyl-2,3,10, 10a-tetrahydro-5*H*-[1,3]-oxazolo-[3,2-*b*]-isoquinolin-5-one (**9k**).

NuH: thiomorpholine; yield: 1.98 g (78%); mp 149-151°; ^{1}H nmr: δ 2.54-2.72 (m, 8H, H-12, H-13), 2.73-2.75 (m, 1H, H-11), 3.10-3.15 (m, 1H, H-11), 3.45-3.48 (m, 1H, H-10), 3.74-3.82 (m, 2H, H-3), 4.02-4.12 (m, 1H, H-2), 4.30-4.36 (m, 1H, H-2), 7.11-7.18 (m, 1H, H-7), 7.22-7.54 (m, 7H, H-8, H-9, Ph), 8.14-8.23 (dd, 1H, H-6, J = 7.0 Hz, 2.0 Hz); ir: 1590-1620 cm^{-1} (ArH), 1650 cm^{-1} (C=O).

Anal. Calcd. for: $C_{24}H_{28}N_2O_2S$: C, 70.55; H, 6.91. Found: C, 70.57; H, 6.93.

(±)-*trans*-10-[(1,2,4-Triazol-4-yl)-methyl]-10a-phenyl-2,3,10, 10a-tetrahydro-5*H*-[1,3]-oxazolo-[3,2-*b*]-isoquinolin-5-one (**9l**).

NuH: 1,2,4-triazole; yield: 1.20 g (48%); mp 171-174°; ^{1}H nmr: δ 3.71-3.75 (m, 2H, H-3), 3.97-4.11 (m, 3H, H-2, H-11), 4.13-4.37 (m, 1H, H-2), 5.00-5.05 (m, 1H, H-10), 6.29-6.31 (m, 1H, H-12), 6.99-7.15 (m, 1H, H-7), 7.18-7.26 (m, 7H, H-8, H-9, Ph), 7.32-7.43 (m, 1H, H-12), 8.08-8.10 (m, 1H, H-6); ir: 1590-1620 cm^{-1} (ArH), 1650 cm^{-1} (C=O).

Anal. Calcd. for: $C_{20}H_{18}N_4O_2$: C, 69.35; H, 5.24. Found: C, 69.38; H, 5.28.

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