Synthesis of 1,3-Dihydro-3,3-dimethyl-2*H*-indol-2-one Derivatives as Possible Nonsteroidal Cardiotonics

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New substituted 1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one derivatives **19-29** and **34-43** were synthesized and examined for their inotropic activity in isolated dog ventricular tissues. Among them, compound **26** (2-(2,3-dimethoxybenzylamino)-*N*-(3,3,7-trimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)acetamide) showed very potent activity.

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Introduction.

In the past decade, inspired by the success of amrinone [1] and milrinone [2,3], studies of orally active nonsteroidal, noncatecholamine cardiotonics to manage congestive heart failure, a highly malignant and debilitating disease, have been directed toward the genesis of agents that modulate intracellular levels of cAMP. This has led to a variety of specific phosphodiesterase III (PDE III) inhibitors [4]. The majority of them possess both positive inotropic and peripheral vasodilatory activities. Such "inodilators" ameliorate the symptoms of congestive heart failure by simultaneously enhancing the cardiac output on the failing myocardia and depressing impedance to ventricular ejection. The nonsteroidal cardiotonics, in many cases, consist of a dihydropyridazinone moiety appended to a substituted aryl or heteroaryl nucleus, *e.g.* imazodan [5-8], CI-930 [5-8], MCI-154 [9], indolidan [10-12], pimobendan [13,14], bemoradan [15] and BM 50.0430 [16]. Although the pharmacological profiles of these compounds are similar in animal models, there exists a difference in the potency and relative balance of the cardiotonic and vasodilatation activities.

The very potent inotropic activity of indolidan found by Robertson [10-12] represents a new generation of nonsympathomimetic, noncardenolide cardiotonics of which the dihydropyridazinone moiety is attached to a benzo-fused heterocycle. The nature of this benzo-fused heterocyclic fragment of the molecule would seem to enjoy a beneficial effect on the pharmacodynamics as well as the pharmacokinetics of the compounds. However, indolidan and its related analogues are by no means free from adverse effects. They cause tachycardia in animals, which may also pose a risk for increasing heart rate in human beings.

In examining the influence of the structural variation of indolidan type cardiotonics, recent studies have emphasized the bioisosteric replacement on the nucleus of dihydropyridazinone [17-19]. We wish to report herein the synthesis of derivatives 1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one bearing at C(5) various *N*- and *O*-substituted chains instead of a dihydropyridazinone ring as a novel class of nonsteroidal cardiotonics and their preliminary results of inotropic effects. Our efforts have resulted in the discovery of several potent non-dihydropyridazinone type inotropes. The most promising compound was 2-(2,3-dimethoxybenzylamino)-*N*-(3,3,7-trimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)acetamide **26**.

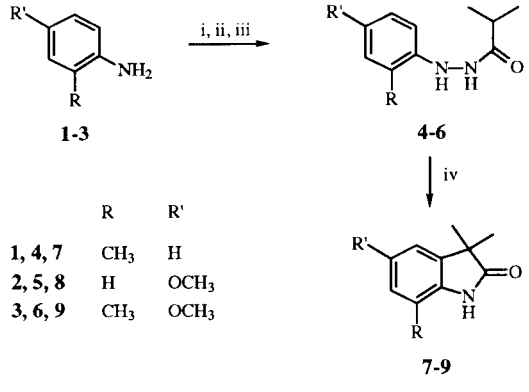
Results and Discussion.

Schemes 1 and 2 outline the two synthetic sequences employed in our laboratories for preparation of the key intermediates 1,3-dihydro-3,3-dimethyl-5,7-disubstituted-2*H*-indol-2-ones **7-9**.

The first approach (Scheme 1) was a modified method of Endler [20] and Robertson [10]. This procedure was most suitable for preparation of compounds of which C(7) were *nor*-substituted. In this manner, various anilines **1-3** were transformed into the corresponding acid hydrazides **4-6** by diazotization (sodium nitrite/hydrochloric acid) and subsequent reduction with tin(II) chloride dihydrate/hydrochloric acid under standard reaction conditions, and then condensation with equimolar isobutyryl chloride in triethylamine at 0° for 1-1.5 hours. Construction of the bicyclic intermediates **7-9** was completed by a base-induced [3,3] sigmatropic rearrangement for 0.5 hour followed by refluxing in concentrated hydrochloric acid, again for 0.5 hour. The uncyclized starting material was removed effortlessly by hydrolysis in hydrochloric acid solution and then filtration. The use of ground and predried calcium hydride decidedly increased the yields of cyclization. Although this procedure could be scaled-up without much difficulty, the rearrangement needed, however, extremely high temperature (>230°) to initiate the reaction. There occurred a sud-

den very exothermic reaction when reaching that temperature; it was extremely vigorous as the reaction began. An extensive charring was always observed during the reactions. However, mild conditions were achieved by dilution of the mixture with tetralin. The modified reactions were allowed to proceed smoothly at about 200° and fairly good yields (usually 60-90%) were obtained. Thus, variation of commercial starting materials enabled the synthesis of most derivatives of indolones. In the preparation of some C(7)-substituted analogues, there arose a rapid decomposition in aryl hydrazinium chlorides, notably 4-methoxy-2-methylphenyl hydrazinium chloride. Hunsberger converted those unstable aryl hydrazinium chlorides to the more stable hydrogen oxalates or neutral oxalates [21]. In our study, this problem was solved by a rapid removal of the residual water from the crude products under reduced pressure, kept strictly at 5° or below, and the freshly prepared materials were immediately subjected to isobutyrylation to form the very stable acid hydrazides.

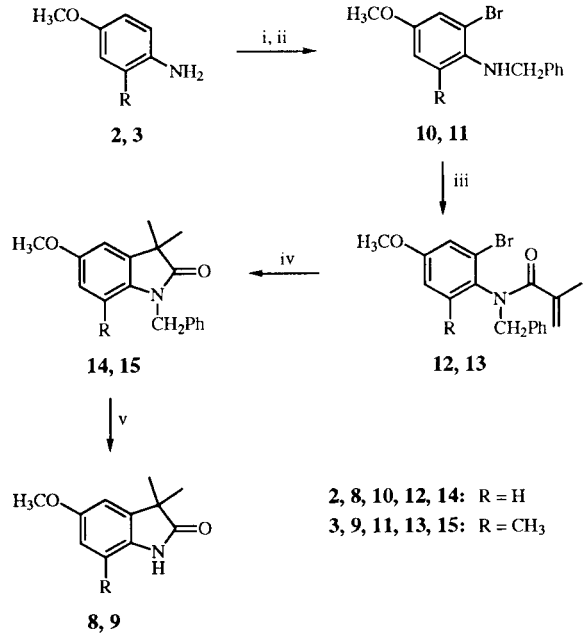
Scheme 1



i: $NaNO_2$/HCl, ii: $SnCl_2 \cdot 2H_2O$/HCl, iii: $(H_3C)_2CHCOCl/Et_3N$/MeOH, iv: CaH_2/200°

An alternative approach, suitable for the synthesis of 5-methoxyindolones **8** and **9**, recognizes the mild intramolecular annulation *via* a radical process in a regioselective manner (Scheme 2). In fact, this very efficient route enabled large-scale synthesis of the intermediates described in this paper and has become our choice of synthesis. Prior to bromination, protection of the amino group of anilines was indispensable. Among the protective groups used, the benzyl proved to be best. Excessive benzyl bromide and the dibenzylated side products (*ca.* 5%) were readily removed by column chromatography. Use of other protective groups such as acetyl, allyl or carbamates produced, in addition to the desired *o*-bromoanilines, a variety of unidentifiable products after bromination. Protection of **2** and **3** with an acetyl (*p*-methoxyacetanilides) greatly facilitated the unexpected *meta*-directing effect in the electrophilic aromatic brominations. Acylation of **10** and **11** with methacryloyl chloride in dry tetrahydrofuran at 0° in the presence of sodium hydride or triethylamine underwent smoothly to afford amines **12** and **13**, respectively. The ring closure was accomplished in an hour by intramolecular cyclization of the phenyl radicals, generated *in situ* by reactions of **12** and **13** with tributyltin hydride (TBTH) (1.2 equivalents) and catalytic azobisisobutyronitrile (AIBN) [22,23] in dry toluene, under reflux conditions. Hydrogenolysis over 10% palladium on activated carbon in methanol at ambient temperature gave exclusively 2-indolone derivatives **14** and **15**, respectively, in excellent yields. In our conditions no 2-quinolones, caused by a further [1,2]-acyl migration of the amide moiety [24], had ever been found as the side products. The compounds obtained according to Scheme 2 had the same physicochemical properties as those determined from Scheme 1. Similar approaches have elegantly been employed by Jones and colleagues in the total synthesis of horsfiline [25].

Scheme 2

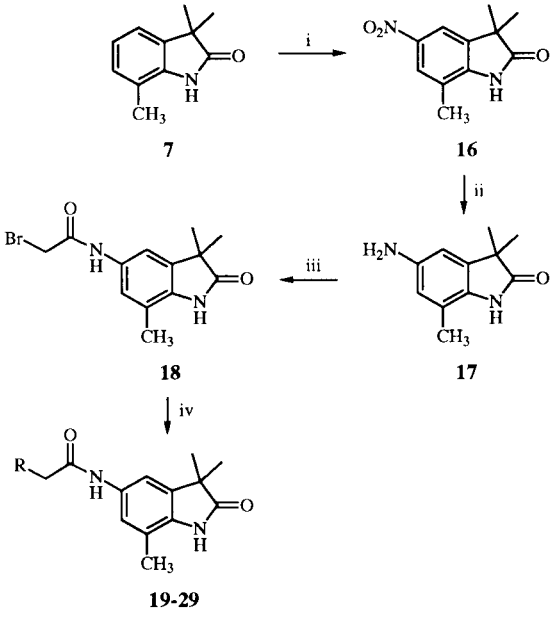


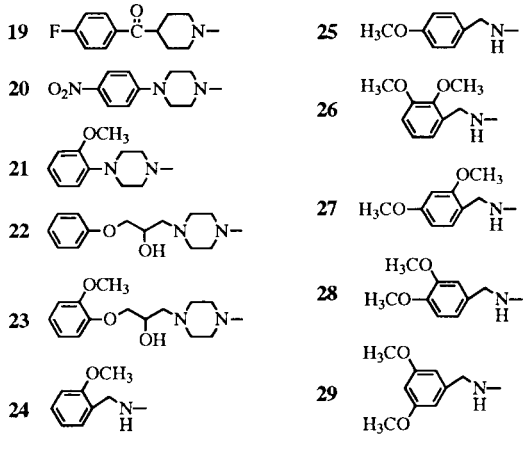
i: BnBr/$NaHCO_3/H_2O$, ii: Br_2/HOAc, iii: NaH/CH_3CH_2COCl/THF, iv: TBTH/AIBN/toluene, v: $Pd/C/H_2$/MeOH

Scheme 3 summarizes the chain extension for aminoindolone **17**. Specific nitration at C(5) of indolone **7** was affected with nitric acid/85% sulfuric acid [26] at ambient temperature and furnished only the desired product **16** in 72% yield. The 5-nitro-3,3,7-trimethylindolone **16** was easily identified by its pmr spectra, in which the aromatic protons appeared as two broad singlets of equal intensity at δ 7.97 and 8.07, respectively. Reduction of the nitro

compound **16** to **17** was best achieved (75% yield) by hydrogenation (50 psi) over 10% palladium on activated carbon in ethanol at 25°. Alternatively, conversion of **16** to **17** could also be conducted by reduction with either zinc or tin(II) chloride dihydrate in concentrated hydrochloric acid. However, the yields were constantly much lower. Subsequent reaction of **17** with bromoacetyl bromide in refluxing acetonitrile afforded **18**. Finally, upon treatment of **18** with appropriate amines, in the presence of triethylamine, gave target C(5)-*N*-substituted compounds **19-29**.

Scheme 3

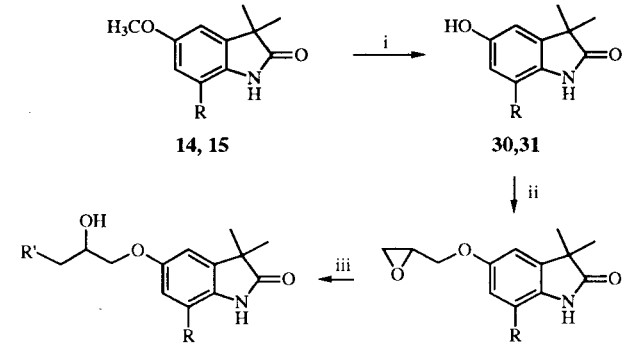




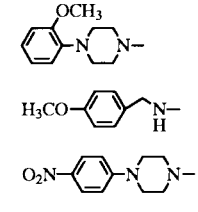
i: HNO_3/85% H_2SO_4, ii: Pd/C/H_2/EtOH, iii: $BrCH_2COBr/CH_3CN$, iv: amines/Et_3N/propanol

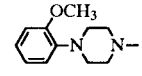
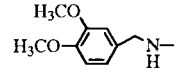
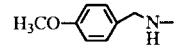
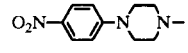
The chain extension of **14** and **15** was straightforward and is illustrated in Scheme 4. Hydrolysis of **14** and **15** using 47% hydrobromic acid readily produced the corresponding phenolic derivatives **30** and **31**. Further manipulations with the standard sequence led to the isolation of title compounds with the common structures of aryloxypropanolamine. Thus, alkylation of **30** and **31** with epichlorohydrin or epibromohydrin in methanol, in the presence of potassium carbonate, yielded the requisite epoxides **32** and **33**, respectively, which were coupled with various amines in methanol after reflux for 3 hours to provide the desired products **34-43**.

Scheme 4



	R	R'
14	H	
15	CH_3	
30	H	
31	CH_3	
32	H	
33	CH_3	



	R	R'
37	CH_3	
38	CH_3	$CH_3(CH_2)_3NH$—
39	CH_3	
40	CH_3	$(CH_3)_2CHNH$—
41	CH_3	
42	CH_3	
43	CH_3	

i: 47% HBr, ii: epichlorohydrin/K_2CO_3/MeOH, iii: amines/MeOH

All the target compounds were isolated as free bases. In most cases, crystallization or chromatography was necessary for purification. The structures of synthetic intermediates and products were established by spectroscopy and the specific data of elemental analyses.

Compounds **19-43** were evaluated *in vitro* for their possible cardiotonic activities in isolated dog ventricular tissues as described in Experimental protocols. The percent increase in contractile force over 10 is considered positive. Most compounds displayed significant positive inotropic activities (Table 1). Of the 1,3-dihydro-3,3-dimethyl-2*H*-indol-2-one derivatives tested, the C(5)-*N*-

substituted derivatives were generally more active than the C(5)-*O*-substituted derivatives. In the former series, compounds **24-29** were the derivatives with the simplest structure. Substitution of a methoxy group in the phenyl ring, especially at the *para* position, led to an only trivial improvement. Substitution with two methoxy residues, on the contrary, seemed to be advantageous in general. The presence and appropriately positioning of these methoxy residues appeared to be critical determinants of inotropic potency. Compound **26**, the most potent inotrope in this study, proved to be the case. The influence of the electron-releasing or electron-withdrawing groups in the aromatic rings of the chains of C(5)-*N*-substituted derivatives of indolones is apparent and complex but nevertheless not very clear. Further studies revealed that **26** did not affect the relaxation phase of ventricular myocytes of the dog, which was indicative of a potentially advantageous effect for the treatment of congestive heart failure, while exerting a very potent inotropic activity even at a concentration as low as 1 μ*M*. A logical explanation of this fact was the better interactions with the receptor site. Compared with the derivatives substituted with secondary amines at the α-carbon of acetamido group (**24-29**), tertiary amines (piperidine or piperazine) in **19-23** demonstrated a striking effectiveness, except for **23**, of which activity vanished. Replacement of the methylene bridge in **24-29** with a piperazinyl (**20,21**) was notably instrumental in increasing inotropic activity. Insertion of a (racemic) oxypropanol moiety between the phenyl and piperazinyl in **20** and **21**, however, resulted in quite a discrepancy. While **21** revealed a modest enhancement in the potency of cardiotonic activity, **23** showed a significant effect of depression. Removal of the methoxy group from **23**, to afford the *nor*-substituted compound **22**, led to a dramatic increase in potency.

In the case of C(5)-*O*-substituted series, the biological data showed that introduction of a methyl residue at C(7) gave a particularly favorable positive inotropic effect only to **37** where C(5) is appended with a 2-hydroxy-3-[4-(2-methoxyphenyl)piperazin-1-yl]propoxy chain. Surprisingly, a completely reverse situation was observed in our result by removal of a small hydrophobic methyl from C(7) of **37**. Compound **34**, even though possessing exactly the same chain as that of **37**, proved to be a depressant on the dog ventricular fibers. The molecular basis for this disparity is unknown. All the C(5)-*O*-substituted compounds directly bearing a 3-alkylamino-2-hydroxypropoxy group (**38-40**) showed mediocre activity, irrespective of the nature of the alkyl residues. Once again the *para* substitution, either electron-releasing (**35,42**) or electron-withdrawing (**36,43**), in either benzylamino or piperazinyl groups did not facilitate much inotropism. Interestingly, transposition of the *p*-methoxy to the *o*-methoxy (**37**) or by anchoring an additional methoxy adjacent to the *p*-methoxy (**41**) exhibited significant activity. It is interesting that compound **41** possesses the same 2-hydroxy-3-(3,4-dimethoxybenzylamino)propoxy chain as OPC-18790, a very promising digitalis replacement recently reported by Fujioka and coworkers [27]. Our data also showed that **41** elicited a prominent inotropic activity.

Table 1

Inotropic Activities of 1,3-Dihydro-3,3-dimethyl-2*H*-indol-2-ones in Isolated Dog Ventricular Tissues

Compound	Dose (μ*M*)	% Change in contractile force
19	10	60
20	10	85
21	10	12
22	10	33
23	10	-37
24	10	25
25	10	<10
26	10	162
27	10	15
28	10	53
29	10	71
34	10	-10
35	10	<10
36	10	15
37	5	32
	10	50
38	10	15
39	10	13
40	10	13
41	10	39
42	10	<10
43	10	10

In summary, we have successfully prepared several new 1,3-dihydro-3,3-dimethyl-2*H*-indol-2-ones and demonstrated that certain members of these non-dihydropyridazinone derivatives possess potent inotropic activity. The role of substituents in the aromatic rings of the appended chains, however, is to be clarified. Among the products obtained, **26** is the most potent and might be useful in the management of congestive heart failure. The results gleaned from this study have provided further information for the development of new cardiotonics. At the present time, there is thought to be a possible mechanism for the positive inotropic effect: inhibition of cardiac PDE III. Several products possess a single chiral center, and therefore more detailed *in vivo* pharmacological and biochemical studies of the racemic mixtures and the resolution and biological properties of the optical isomers are in progress and will be reported subsequently.

EXPERIMENTAL

Melting points were taken in open capillary tubes on a Buchi-530 melting point apparatus and are uncorrected. Infrared spec-

tra were recorded on a Perkin-Elmer 983G infrared spectrophotometer. The ^1H and ^{13}C nmr were determined on a Varian Gemini-300 NMR instrument in DMSO-d_6 unless otherwise noted. The chemical shifts were reported as parts per million (ppm) downfield from tetramethylsilane as the internal standard (δ 0.00) and signals were described as s (singlet), d (doublet), t (triplet), and m (multiplet). Electron-impact mass spectra were accomplished at 70 eV using an HP 5985B mass spectrometer. Only peaks of significant relative intensity or of diagnostic importance are presented in the form of m/z (intensity relative to base peak). Microanalyses (C, H and N) were performed on a Perkin-Elmer 240C elemental analyzer and were within ± 0.4% of the theoretical values.

All reactions were followed by tlc on Merck F254 silica gel plates. Merck silica gel (70-230 mesh) was used for column chromatography. Evaporations were carried out under reduced pressure with the bath temperature not more than 45°. All solvents and reagents were obtained from commercial sources and purified before use if necessary.

Isobutyric Acid 2-(2-Methylphenyl)hydrazide **4**.

To a solution of *o*-toluidine (53.4 g, 0.500 mole) in aqueous 3 *N* hydrochloric acid (700 ml) at ice-salt bath temperature was added dropwise (0.5-1 ml/minute) a solution of sodium nitrite (35.0 g, 0.510 mole) in water (100 ml). The resultant mixture was stirred for an additional 30 minutes after the addition was complete. To this solution was added dropwise (0.5-1 ml/minute) a solution of tin(II) chloride dihydrate (280.0 g, 1.24 moles) in concentrated hydrochloric acid (200 ml). After addition, the resultant mixture was stirred for a further 1 hour at ice-salt bath temperature and then filtered. The precipitate was washed with cold brine and 2 *N* hydrochloric acid in succession and then dried under reduced pressure at 0-5° overnight. The white solid (64.8 g, 0.414 mole) was dissolved in methanol (350 ml) and cooled to 0-5°. To this solution was added dropwise (1 ml/minute) triethylamine (106.3 g, 1.05 moles). After sirring at 0-5° for 30 minutes isobutyryl chloride (57.2 g, 0.537 mole) was added dropwise (0.5 ml/minute). The resultant mixture was stirred for an additional 1 hour and then concentrated to dryness under reduced pressure. The residue was taken up with water (500 ml) and extracted in ethyl acetate (2 x 500 ml). The combined organic layers were washed with water (2 x 250 ml), dried over anhydrous sodium sulfate. Filtration and elimination of the solvent afforded a residue which was recrystallized from ethyl acetate to give 61.5 g (65%) of the analytically pure hydrazide **4** as white crystals, mp 94°; ir (potassium bromide): 3294, 3219 (NH), 1608 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.96 (d, 6H, J = 7.1 Hz, 2 x C*H*$_3$-CH), 2.13 (s, 3H, Ar-C*H*$_3$), 2.50 (m, 1H, *H*CCO), 6.59-6.67 (m, 2H, 2 x Ar-*H*), 6.95-7.03 (m, 2H, 2 x Ar-*H*), 9.61 (s, 2H, N*H*); ^{13}C nmr (DMSO-d_6): δ 17.2, 19.4, 32.2, 110.7, 118.5, 121.7, 126.3, 129.9, 146.8, 175.7; ms: m/z 192 (M^+, 57), 122 (100), 105 (25), 71 (14).

Anal. Calcd. for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.76; H, 8.39; N, 14.63.

Isobutyric Acid *N'*-(4-Methoxyphenyl)hydrazide **5**.

Starting from *p*-anisidine **2** and using the method described for **4** afforded, after recrystallization from tetrahydrofuran/dichloromethane, the desired product **5** was obtained in an overall yield of 61%, mp 120°; ir (potassium bromide): 3290 (NH), 1680 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.04 (s, 6H, 2 x C*H*$_3$-CH), 2.52 (m, 1H, *H*CCO), 3.64 (s, 3H, O-C*H*$_3$), 6.64 (d, 2H, J = 8.6 Hz, 2 x Ar-*H*), 6.74 (d, 2H, J = 8.6 Hz, 2 x Ar-*H*), 9.54 (s, 2H, 2 x N*H*); ms: m/z 208 (M^+, 100), 138 (94), 122 (59).

Anal. Calcd. for $C_{11}H_{16}N_2O_2$: C, 63.44; H, 7.74; N, 13.45. Found: C, 63.56; H, 7.76; N, 13.44.

Isobutyric Acid 2-(2-Methyl-4-methoxyphenyl)hydrazide **6**.

Starting from 4-methoxy-2-methylaniline **3** and using the method described for **4** afforded, after recrystallization from tetrahydrofuran/dichloromethane, the desired product **6** was obtained in an overall yield of 58%, mp 77°; ir (potassium bromide): 3591 (NH), 1710 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.06 (d, 6H, J = 6.8 Hz, 2 x C*H*$_3$-CH), 2.13 (s, 3H, Ar-C*H*$_3$), 2.50 (m, 1H, *H*CCO), 3.64 (s, 3H, O-C*H*$_3$), 6.54-6.67 (m, 3H, 3 x Ar-*H*), 9.59 (s, 1H, N*H*), 9.60 (s, 1H, N*H*); ms: m/z 222 (M^+, 100), 152 (25), 136 (36).

Anal. Calcd. for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.51; H, 8.07; N, 12.50.

1,3-Dihydro-3,3,7-trimethyl-2*H*-indol-2-one **7**.

Ground, predried calcium hydride (11.0 g, 0.260 mole) was added to a mixture of **4** (25.0 g, 0.130 mole) in tetralin (500 ml) in a 1000-ml round bottom flask. The mixture was slowly heated over 2 hours to about 200° and then maintained at this temperature for 30 minutes. The reaction was slowly cooled to room temperature. A solution of water (50 ml) and methanol (50 ml) was slowly added at 0-5°. After hydrogen evolution ceased, the *p*H of the mixture was adjusted to 1 with concentrated hydrochloric acid. The mixture was heated to reflux for 1 hour and then 3 *N* sodium hydroxide was added until the mixture had a *p*H of 5. The precipitate was filtered, dried to give 20.1 g (89%) of **7** as a white solid, mp 151° (lit 150° [28]); ir (potassium bromide): 3457 (NH), 1700 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.21 (s, 6H, 2 x C*H*$_3$-C), 2.19 (s, 3H, Ar-C*H*$_3$), 6.85 (t, 1H, J = 7.4 Hz, Ar-*H*), 6.95 (d, 1H, J = 7.4 Hz, Ar-*H*), 7.05 (d, 1H, J = 7.4 Hz, Ar-*H*), 10.31 (s, 1H, N*H*); ^{13}C nmr (DMSO-d_6): δ 16.4, 24.4, 43.8, 118.6, 119.8, 121.4, 128.7, 135.7, 139.4, 182.6; ms: m/z 175 (M^+, 73), 160 (100), 91 (4).

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.35; H, 7.47; N, 7.68.

1,3-Dihydro-3,3-dimethyl-5-methoxy-2*H*-indol-2-one **8**.

Starting from **5** and using the method described for **7** afforded, after recrystallization from methanol/dichloromethane, the desired product **8** in 62% yield, mp 126°; ir (potassium bromide): 3190 (NH), 1690 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.23 (s, 6H, 2 x C*H*$_3$-C), 3.70 (s, 3H, O-C*H*$_3$), 6.72 (s, 1H, Ar-*H*), 6.73 (s, 1H, Ar-*H*), 6.94 (s, 1H, Ar-*H*), 10.12 (s, 1, N*H*); ms: m/z 191 (M^+, 100), 176 (83).

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 68.89; H, 6.85; N, 7.38.

1,3-Dihydro-3,3,7-trimethyl-5-methoxy-2*H*-indol-2-one **9**.

Starting from **6** and using the methods described for **7** afforded, after recrystallization from methanol/dichloromethane, the desired product **9** in 66% yield, mp 155°; ir (potassium bromide): 3163 (NH), 1695 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.21 (s, 6H, 2 x C*H*$_3$-C), 2.17 (s, 3H, Ar-C*H*$_3$), 3.67 (s, 3H, O-C*H*$_3$), 6.54 (d, 1H, J = 2.1 Hz, Ar-*H*), 6.74 (d, 1H, J = 2.1 Hz, Ar-*H*), 10.16 (s, 1H, N*H*); ms: m/z 205 (M^+, 90), 190 (100).

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.33; H, 7.39; N, 6.78.

N-Benzyl-2-bromo-4-methoxyaniline **10**.

A mixture of *p*-anisidine **2** (4.92 g, 40.0 mmoles) and sodium bicarbonate (1.01 g, 12.0 mmoles) in water (10 ml) was heated to 90-95° and then benzyl bromide (1.17 g, 10.0 mmoles) was slowly added. The mixture was stirred for àn additional 6 hours and then cooled to room temperature. The oily organic portion was taken up in chloroform (200 ml) and washed with brine (3 x 50 ml). The organic layer was dried over anhydrous sodium sulfate. Filtration and elimination of the solvent under reduced pressure yielded an oil residue. The crude mixture was purified by column chromatography (silica gel, *n*-hexane/acetone, 40:1 and then 20:1) to give 1.63 g of *N*-benzylanisidine, mp 48°; ^{1}H nmr (deuteriochloroform): δ 3.76 (s, 3H, O-C*H*$_3$), 4.31 (s, 2H, N-C*H*$_2$-Ar), 4.33 (br s, 1H, N*H*), 6.62 (d, 2H, J = 8.9 Hz, 2 x Ar-*H*), 6.80 (d, 2H, J = 8.9 Hz, 2 x Ar-*H*), 7.27-7.41 (m, 5H, 5 x Ar-*H*); ms: m/z 213 (M$^+$, 100), 198 (9), 122 (54). The *N*-monoblocked product was dissolved in acetic acid (20 ml). A solution of bromine (1.24 g, 7.73 mmoles) in acetic acid (20 ml) was added dropwise at 10-15°. The resultant mixture was stirred for an additional 2 hours and then partitioned in ethyl acetate (100 ml) and water (100 ml). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give after recrystallization from ether/petroleum ether 1.96 g (90%) of **10**, mp 79°; ir (potassium bromide): 3288 (NH) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 3.73 (s, 3H, O-C*H*$_3$), 4.28 (s, 2H, C*H*$_2$N), 4.31 (br s, 1H, N*H*), 6.80-7.23 (m, 8H, 8 x Ar-*H*); ms: m/z 291, 293 (M$^+$, 1:1, 52), 200, 202 (1:1, 43), 91 (100).

N-Benzyl-2-bromo-4-methoxy-6-methylaniline **11**.

Starting from 4-methoxy-2-methylaniline **3** and using the method described for **10** afforded, after recrystallization from ether/petroleum ether, the desired compound **11** was obtained in an overall yield of 62%, mp 188°; ir (potassium bromide): 3284 (NH) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 2.17 (s, 3H, Ar-C*H*$_3$), 3.70 (s, 3H, O-C*H*$_3$), 4.27 (s, 2H, C*H*$_2$-N), 4.37 (br s, 1H, N*H*), 6.77-7.24 (m, 7H, 7 x Ar-*H*); ms: m/z 305, 307 (M$^+$, 1:1, 57), 214, 216 (1:1, 44), 91 (100).

N-Benzyl-*N*-(2-bromo-4-methoxyphenyl)-2-methylacrylamide **12**.

To a stirred, cooled (0-5°) suspension of washed (dry benzene, 3 times) sodium hydride-mineral oil dispersion (300 mg, 7.50 mmoles) in dry tetrahydrofuran (10 ml) under argon was added dropwise a solution of **10** (1.45 g, 5.00 mmoles) in dry tetrahydrofuran (10 ml). After stirring at 0-5° for 30 minutes, a solution of distilled methacryloyl chloride (0.57 g, 5.50 mmoles) in dry tetrahydrofuran (5 ml) was added dropwise. The resultant mixture was stirred at 0-5° for an additional 1 hour after the addition was complete. The mixture was concentrated under reduced pressure and then partitioned between dichloromethane (200 ml) and water (200 ml). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield, after recrystallization from acetonitrile, 1.40 g (78%) of amide **12** as brown crystals, mp 141°; ir (potassium bromide): 1367 (C=O) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 1.84 (s, 3H, C*H*$_3$-C), 3.73 (s, 3H, O-C*H*$_3$), 3.78 (s, 2H, C*H*$_2$-N), 4.36 (s, 2H, C*H*$_2$ =C), 6.58 (d, 1H, J = 8.8 Hz, Ar-*H*,), 6.76 (d, 1H, J = 8.8 Hz, Ar-*H*), 7.10 (s, 1H, Ar-*H*), 7.31-7.37 (m, 5H, 5 x Ar-*H*); ms: m/z 359, 361 (M$^+$, 1:1, 11), 280 (28), 91 (100).

N-Benzyl-*N*-(2-bromo-4-methoxy-6-methylphenyl)-2-methylacrylamide **13**.

Starting from **11** and using the method described for **12** afforded, after recrystallization from acetonitrile, the desired compound **13** was obtained in 73% yield, mp 147°; ir (potassium bromide): 1634 (C=O) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 1.83 (s, 3H, C*H*$_3$-C), 2.13 (s, 3H, Ar-C*H*$_3$), 3.70 (s, 3H, O-C*H*$_3$), 3.76 (s, 2H, C*H*$_2$-N), 4.35 (s, 2H, C*H*$_2$ =C), 6.39 (s, 1H, Ar-*H*), 6.88 (s, 1H, Ar-*H*), 7.20-7.35 (m, 5H, 5 x Ar-*H*); ms: m/z 373, 375, (M$^+$, 1:1, 13), 294 (29), 91 (100).

1,3-Dihydro-3,3-dimethyl-5-methoxy-1-benzyl-2*H*-indol-2-one **14**.

To a solution of **12** (1.08 g, 3.00 mmoles) and azobisisobutyronitrile (30 mg, 0.18 mmole) in dry toluene (50 ml) under argon was added over 30 minutes a solution of tributyltin hydride (1.02 g, 3.50 mmoles) in dry toluene (20 ml). After addition was complete the mixture was stirred for an additional 15 minutes and then heated to reflux for 1 hour. The mixture was cooled to room temperature and concentrated under reduced pressure to dryness. The residue was partitioned between ether (100 ml) and water (100 ml). The ether layer was dried over anhydrous sodium sulfate and filtered to give, after recrystallization from acetonitrile/*n*-hexane, 0.73 g (87%) of **14** as white crystals, mp 179°; ir (potassium bromide): 1634 (NH) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.22 (s, 6H, 2 x C*H*$_3$-C), 3.73 (s, 3H, O-C*H*$_3$), 4.01 (s, 2H, C*H*$_2$-N), 6.65 (s, 1H, Ar-*H*), 6.67 (s, 1H, Ar-*H*), 6.88 (s, 1H, Ar-*H*), 7.01-7.31 (m, 5H, 5 x Ar-*H*); ms: m/z 281 (M$^+$, 24), 91 (100).

1,3-Dihydro-3,3,7-trimethyl-5-methoxy-1-benzyl-2*H*-indol-2-one **15**.

Starting from **13** and using the method described for **14** afforded, after recrystallization from acetonitrile/*n*-hexane, the desired compound **15** was obtained in 68% yield, mp 184°; ir (potassium bromide): 1635 (NH) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.21 (s, 6H, 2 x C*H*$_3$-C), 2.17 (s, 3H, Ar-C*H*$_3$), 3.68 (s, 3H, O-C*H*$_3$), 4.04 (s, 2H, C*H*$_2$-N), 6.45 (s, 2H, 2 x Ar-*H*), 6.99-7.31 (m, 5H, 5 x Ar-*H*); ms: m/z 295 (M$^+$, 22), 91 (100).

1,3-Dihydro-3,3-dimethyl-5-methoxy-2*H*-indol-2-one **8**.

A mixture of **14** (0.73 g, 2.50 mmoles) and 10% palladium on activated carbon (2 mg) in methanol (25 ml) under a hydrogen environment (50 psi) was shaken in a hydrogenator at room temperature until the reaction was complete. Filtration and concentration under reduced pressure yielded, after recrystallization from methanol/dichloromethane, 0.48 g (93%) of **8**. The physical properties were identical with those obtained by Scheme 1.

1,3-Dihydro-3,3,7-trimethyl-5-methoxy-2*H*-indol-2-one **9**.

Starting from **13** and using the hydrogenolysis conditions described for **8** afforded, after recrystallization from methanol/dichloromethane, the desired compound **9** in 92% yield. The physical properties were identical with those obtained by Scheme 1.

1,3-Dihydro-3,3,7-trimethyl-5-nitro-2*H*-indol-2-one **16**.

To a well stirred solution of **7** (19.5 g, 0.110 mole) in 85% sulfuric acid (15 ml) was added dropwise (1-2 ml/minute) a solution of nitric acid (12.0 ml) in 85% sulfuric acid (12.0 ml) at 0-5°. The resultant mixture was vigorously stirred for an additional 1.5 hours after the addition was complete and then poured into 700 ml of ice water. The mixture was stirred for 30 minutes. Filtration, washing with water and drying afforded 17.5 g (72%)

of the nitro compound **16** as a yellow solid, mp 243-245°; ir (potassium bromide): 3179 (NH), 1717 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.30 (s, 6H, 2 x CH_3-C), 2.30 (s, 3H, Ar-CH_3), 7.97 (br s, 1H, Ar-*H*), 8.07 (br s, 1H, Ar-*H*), 11.04 (br s, 1H, N*H*); ^{13}C nmr (DMSO-d_6): δ 16.3, 23.5, 44.2, 116.2, 119.7, 125.4, 136.4, 142.2, 146.4, 182.9; ms: m/z 220 (M^+, 100), 205 (84), 174 (4).

1,3-Dihydro-3,3,7-trimethyl-5-amino-2*H*-indol-2-one **17**.

A solution of **16** (4.00 g, 18.0 mmoles) and 10% palladium on activated carbon (0.6 g) in ethanol (50 ml) was shaken at room temperature under a hydrogen environment (50 psi) until the absorption of hydrogen ceased. The catalyst was filtered off and the filtrate was concentrated under reduced pressure to give after recrystallization from ethanol 2.60 g (75%) of **17**, mp 280°; ir (potassium bromide): 3485, 3285 (NH), 1675 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.24 (s, 6H, 2 x CH_3-C), 2.23 (s, 3H, Ar-CH_3), 7.01 (d, 1H, J = 1.7 Hz, Ar-*H*), 7.10 (d, 1H, J = 1.7 Hz, Ar-*H*), 10.23 (br s, 2H, NH_2), 10.56 (s, 1H, N*H*); ^{13}C nmr (DMSO-d_6): δ 16.5, 23.9, 44.2, 115.2, 119.9, 123.5, 125.5, 136.9, 139.2, 182.4; ms: m/z 190 (M^+, 100), 175 (59), 162 (34).

2-Bromo-*N*-(3,3,7-trimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)acetamide **18**.

To a stirred solution of **17** (2.85 g, 15.0 mmoles) in acetonitrile (30 ml) was added dropwise bromoacetyl bromide (4.54 g, 22.5 mmoles). The mixture was heated at reflux for 3 hours and then slowly cooled to room temperature, then allowed to stand at 0° overnight. The precipitate was collected and washed thoroughly with water to yield 2.28 g (74%) of pure product **18**, mp 234-235°; ir (potassium bromide): 3298, 3181 (NH), 1696, 1660 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.22 (s, 6H, 2 x CH_3-C), 2.19 (s, 3H, Ar-CH_3), 3.99 (s, 2H, CH_2-Br), 7.14 (d, 1H, J = 1.8 Hz, Ar-*H*), 7.34 (d, 1H, J = 1.8 Hz, Ar-*H*), 10.19 (br s, 1H, N*H*), 10.36 (br s, 1H, N*H*); ^{13}C nmr (DMSO-d_6): δ 16.6, 24.2, 44.1, 61.7, 85.6, 112.6, 120.4, 132.8, 135.3, 170.2, 182.4; ms: m/z 310, 312 (M^+, 100), 295, 297 (1:1, 25), 189 (40).

Anal. Calcd. for $C_{13}H_{15}N_2O_2Br$: C, 50.18; H, 4.86; N, 9.00. Found: C, 49.89; H, 4.60; N, 8.74.

General Procedure for the Preparation of 2-Substituted *N*-(3,3,7-Trimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)acetamide **19-29**.

To a stirred solution containing 4.50 mmoles of each of the substituted amine hydrochlorides in propanol (10 ml) and triethylamine (0.91 g, 9.0 mmoles; or 0.46 g, 4.5 mmoles for free amines) was added dropwise a solution of **18** in propanol (10 ml). The resultant mixture was heated at reflux for 5-10 hours until the reaction was complete (monitored by tlc) and then cooled to room temperature. The mixture was concentrated under reduced pressure to dryness. The residue was taken up in ethyl acetate (100 ml) and washed with water (2 x 50 ml). The organic layer was dried over anhydrous sodium sulfate. Filtration and removal of the solvent under reduced pressure gave, after column chromatography (silica gel, dichloromethane/acetonitrile: 2:1 for **24**, **25**; 5:1 for **19**; 10:1 for **20**, **21**, **26-29**; and 20:1 for **22**, **23**, respectively), desired products **19-29**.

2-[4-(4-Fluorobenzoyl)piperidin-1-yl]-*N*-(3,3,7-trimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)acetmide **19**.

The yield was 81%, mp 205-207°; ir (potassium bromide): 3328, 3149 (NH), 1694, 1626 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.38 (s, 6H, 2 x CH_3-C), 1.90-1.94 (m, 4H, 2 x CH_2-CH), 2.36-2.45 (m, 2H, 2 x CH_{ax}-N), 3.00-3.04 (m, 2H, 2 x CH_{eq}-N) 3.16 (s, 2H, N-CH_2-CO), 3.24-3.29 (m, 1H, CHCO), 7.14 (s, 1H, Ar-*H*), 7.14 (t, 2H, J = 8.7 Hz, 2 x Ar-*H*), 7.36 (s, 1H, Ar-*H*), 7.97 (dd, 2H, J = 8.7 Hz, 5.4 Hz, 2 x Ar-*H*), 8.32 (br s, 1H, N*H*), 9.02 (br s, 1H, N*H*); ms: m/z 437 (M^+, 13), 232 (38), 205 (63), 200 (100).

Anal. Calcd. for $C_{25}H_{28}N_3O_3F$: C, 68.63; H, 6.45; N, 9.60. Found: C, 68.39; H, 6.44; N, 9.29.

2-[4-(4-Nitrobenzoyl)piperidin-1-yl]-*N*-(3,3,7-trimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)acetamide **20**.

The yield was 27%, mp 275°; ir (potassium bromide): 3271 (NH), 1709 (C=O), 1539, 1384 (NO_2) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.21 (s, 6H, 2 x CH_3-C), 2.17 (s, 3H, Ar-CH_3), 2.64 (br s, 4H, 2 x CH_2-NCH_2CO), 3.15 (s, 2H, CH_2-CO), 3.53 (br s, 4H, 2 x CH_2-NAr), 7.03 (d, 2H, J = 9.4 Hz, 2 x Ar-*H*), 7.23 (s, 1H, Ar-*H*), 7.38 (s, 1H, Ar-*H*), 8.03 (d, 2H, J = 9.4 Hz, 2 x Ar-*H*), 9.55 (s, 1H, Ar-*H*); ^{13}C nmr (DMSO-d_6): δ 16.5, 24.2, 44.1, 46.3, 52.2, 112.5, 112.6, 125.7, 132.6, 177.7; ms: m/z 437 (M^+, 9), 232 (10), 205 (100).

Anal. Calcd. for $C_{23}H_{27}N_5O_4$: C, 63.14; H, 6.22; N, 16.01. Found: C, 63.47; H, 6.41; N, 16.39.

2-[4-(2-Methoxyphenyl)piperazin-1-yl]-*N*-(3,3,7-trimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)acetamide **21**.

The yield was 98%, mp 191°; ir (potassium bromide): 3270 (NH), 1711, 1718 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.38 (s, 6H, 2 x CH_3-C), 2.25 (s, 3H, Ar-CH_3) 2.81-2.84 (m, 4H, 2 x CH_2-NCH_2CO), 3.15-3.19 (m, 4H, 2 x CH_2-NAr), 3.20 (s, 2H, CH_2-CO), 3.86 (s, 3H, O-CH_3), 6.86-7.04 (m, 4H, 4 x Ar-*H*), 7.12 (d, 1H, J = 1.5 Hz, Ar-*H*), 7.38 (d, 1H, J = 1.5 Hz, Ar-*H*), 8.16 (br s, 1H, N*H*), 9.07 (br s, 1H, N*H*); ^{13}C nmr (deuteriochloroform): δ 16.5, 24.4, 50.8, 53.7, 55.4, 62.0, 88.2, 111.4, 112.6, 118.2, 120.3, 120.9, 123.3, 132.8, 136.5, 183.6; ms: m/z 422 (M^+, 11), 273 (37), 205 (100), 190 (25).

Anal. Calcd. for $C_{24}H_{30}N_4O_3$: C, 68.22; H, 7.16; N, 13.26. Found: C, 68.16; H, 7.23; N, 13.04.

2-[4-(2-Hydroxy-3-phenoxypropyl)piperazin-1-yl]-*N*-(3,3,7-trimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)acetamide **22**.

The yield was 84%, mp 98°; ir (potassium bromide): 3253 (NH), 1695 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.38 (s, 6H, 2 x CH_3-C), 2.27 (s, 3H, Ar-CH_3), 2.59-2.75 (m, 11H, 5 x CH_2-N + O*H*), 3.13 (s, 2H, CH_2-CO), 3.99 (d, 2H, J = 4.9 Hz, CH_2-O), 4.08-4.13 (m, 1H, C*H*-OH), 6.69-6.89 (m, 3H, 3 x Ar-*H*), 7.09 (br s, 1H, Ar-*H*), 7.27 (t, 2H, J = 7.6 Hz, 2 x Ar-*H*), 7.37 (s, 1H, Ar-*H*), 8.54 (br s, 1H, N*H*), 8.94 (br s, 1H, N*H*); ^{13}C nmr (deuteriochloroform): δ 16.5, 24.3, 45.3, 53.5, 60.5, 61.8, 65.8, 70.1, 112.5, 114.5, 120.3, 121.1, 129.5, 132.6, 136.6, 167.9; ms: m/z 466 (M^+, 13), 329 (100), 355 (17).

Anal. Calcd. for $C_{26}H_{34}N_4O_4$: C, 66.93; H, 7.34; N, 12.01. Found: C, 66.55; H, 7.34; N, 12.20.

2-[4-[2-Hydroxy-3-(2-methoxy)phenoxypropyl]piperazin-1-yl]-*N*-(3,3,7-trimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)acetamide **23**.

The yield was 64%, mp 90°; ir (potassium bromide): 3281 (NH), 1702 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.38 (s, 6H, 2 x CH_3-C), 2.24 (s, 3H, Ar-CH_3), 2.59-2.74 (m, 11H, 5 x CH_2-N + O*H*), 3.12 (s, 2H, CH_2-CO), 3.84 (s, 3H, O-CH_3), 4.03 (m, 1H, CH_2-O), 4.12-4.14 (m, 1H, C*H*-OH), 6.86-6.95 (m, 4H, 4 x Ar-*H*), 7.10 (d, 1H, J = 2.8 Hz, Ar-*H*), 7.38 (d, 1H, J =

2.8 Hz, Ar-*H*), 7.83 (br s, 1H, N*H*), 8.95 (br s, 1H, N*H*); ^{13}C nmr (deuteriochloroform): δ 16.9, 24.5, 24.8, 30.8, 44.5, 53.3, 55.8, 61.5, 62.1, 67.0, 72.4, 112.8, 114.1, 119.0, 121.3, 133.0, 135.7, 136.5, 148.7, 149.6, 168.1, 182.8; ms: m/z 496 (M^+, 5), 355 (22), 329 (100), 355 (17).

Anal. Calcd. for $C_{27}H_{36}N_4O_5$: C, 65.30; H, 7.31; N, 11.28. Found: C, 65.66; H, 7.12; O, 10.98.

2-(2-Methoxybenzylamino)-*N*-(3,3,7-trimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)acetamide **24**.

The yield was 44%, mp 128°; ir (potassium bromide): 3433 (NH), 1717 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.21 (s, 6H, 2 x C*H*$_3$-C), 2.17 (s, 3H, Ar-C*H*$_3$), 3.21 (s, 2H, C*H*$_2$-CO), 3.68 (s, 2H, Ar-C*H*$_2$-N), 3.76 (s, 3H, O-C*H*$_3$), 6.61-6.97 (m, 2H, 2 x Ar-*H*), 7.18-7.33 (m, 4H, 4 x Ar-*H*), 9.60 (br s 1H, N*H*), 10.29 (br s, 1H, N*H*); ^{13}C nmr (deuteriochloroform): δ 17.1, 24.9, 30.9, 45.9, 52.7, 54.0, 55.8, 113.1, 114.7, 121.0, 126.0, 130.1, 133.1, 137.1, 184.6; ms: m/z 367 (M^+, 50), 232 (34), 136 (65), 121 (100).

Anal. Calcd. for $C_{21}H_{25}N_3O_3$: C, 68.64; H, 6.86; N, 11.44. Found: C, 68.76; H, 7.14; O, 11.28.

2-(4-Methoxybenzylamino)-*N*-(3,3,7-trimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)acetamide **25**.

The yield was 71%, mp 128°; ir (potassium bromide): 3257 (NH), 1707 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.38 (s, 3H, C*H*$_3$-C), 1.44 (s, 3H, C*H*$_3$-C), 2.28 (s, 3H, Ar-C*H*$_3$), 2.56 (br s, 1H, N*H*), 3.48 (s, 2H, C*H*$_2$-CO), 3.80 (s, 3H, O-C*H*$_3$), 3.83 (s, 2H, Ar-C*H*$_2$-N), 6.90 (d, 2H, J = 8.5 Hz, 2 x Ar-*H*), 7.12 (s, 1H, Ar-*H*), 7.28 (d, 2H, J = 8.5 Hz, 2 x Ar-*H*), 7.37 (s, 1H, Ar-*H*), 8.84 (br s, 1H, N*H*), 9.28 (br s, 1H, N*H*); ^{13}C nmr (deuteriochloroform): δ 16.9, 24.5, 24.8, 30.8, 44.5, 53.5, 55.8, 61.4, 62.1, 67.0, 72.4, 112.8, 114.1, 119.0, 121.3, 133.3, 135.7, 136.2, 148.7, 149.6, 168.1, 182.8; ms: m/z 367 (M^+, 5), 232 (7), 136 (42), 121 (100).

Anal. Calcd. for $C_{21}H_{25}N_3O_3$: C, 68.64; H, 6.86; N, 11.44. Found: C, 68.78; H, 6.97; N, 11.48.

2-(2,3-Dimethoxybenzylamino)-*N*-(3,3,7-trimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)acetamide **26**.

The yield was 26%, mp 150°; ir (potassium bromide): 3276 (NH), 1700 (C=O) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 1.22 (s, 6H, 2 x C*H*$_3$-C), 2.18 (s, 3H, Ar-C*H*$_3$), 3.23 (s, 2H, C*H*$_2$-CO), 3.71 (s, 2H, Ar-C*H*$_2$-N), 3.74 (s, 3H, O-C*H*$_3$), 3.79 (s, 3H, O-C*H*$_3$), 6.94-7.07 (m, 3H, 3 x Ar-*H*), 7.19 (s, 1H, Ar-*H*), 7.35 (s, 1H, Ar-*H*), 9.63 (br s, 1H, N*H*), 10.32 (br s, 1H, N*H*); ^{13}C nmr (DMSO-d$_6$): δ 17.1, 24.6, 44.5, 47.5, 52.3, 52.4, 56.0, 60.6, 106.6, 112.5, 119.0, 120.3, 121.5, 127.7, 135.6, 136.3, 169.8; ms: m/z 397 (M^+, 26), 232 (12), 190 (32), 151 (100).

Anal. Calcd. for $C_{22}H_{27}N_3O_4$: C, 66.48; H, 6.85; N, 10.57. Found: C, 66.78; H, 6.89; N, 10.80.

2-(2,4-Dimethoxybenzylamino)-*N*-(3,3,7-trimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)acetamide **27**.

The yield was 21%, mp 65°; ir (potassium bromide): 3267 (NH), 1705 (C=O) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 1.22 (s, 6H, C*H*$_3$-C), 1.35 (s, 3H, C*H*$_3$-C), 2.18 (s, 3H, Ar-C*H*$_3$), 3.19 (s, 2H, C*H*$_2$-CO), 3.61 (s, 2H, Ar-C*H*$_2$-N), 3.73 (s, 3H, O-C*H*$_3$), 3.75 (s, 3H, O-C*H*$_3$), 6.47 (d, 1H, J = 7.4 Hz, Ar-*H*), 6.53 (s, 1H, Ar-*H*), 6.86 (s, 1H, Ar-*H*), 7.19 (d, 1H, J = 7.4 Hz, Ar-*H*), 7.33 (s, 1H, Ar-*H*), 9.60 (br s, 1H, N*H*), 10.31 (br s, 1H, N*H*); ^{13}C nmr (DMSO-d$_6$): δ 16.9, 21.4, 24.7, 44.5, 47.6, 52.3, 55.6, 98.7, 104.6, 112.5, 119.0, 120.4, 125.3, 130.3, 133.4, 135.6, 139.5, 158.6, 160.1, 169.9, 182.8; ms: m/z 397 (M^+, 50), 232 (34), 205 (100).

Anal. Calcd. for $C_{22}H_{27}N_3O_4$: C, 66.48; H, 6.85; N, 10.57. Found: C, 66.67; H, 6.98; N, 10.46.

2-(3,4-Dimethoxybenzylamino)-*N*-(3,3,7-trimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)acetamide **28**.

The yield was 38%, mp 213°; ir (potassium bromide): 3168 (NH), 1694 (C=O) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 1.40 (s, 6H, 2 x C*H*$_3$-C), 2.29 (s, 3H, Ar-C*H*$_3$), 3.40 (s, 2H, C*H*$_2$-CO), 3.81 (s, 2H, Ar-C*H*$_2$-N), 3.86 (s, 3H, O-C*H*$_3$), 3.89 (s, 3H, O-C*H*$_3$), 6.84-6.92 (m, 2H, 2 x Ar-*H*), 7.02-7.05 (br s, 1H, Ar-*H*), 7.23 (s, 1H, Ar-*H*), 7.42 (s, 1H, Ar-*H*), 8.47 (br s, 1H, N*H*), 9.44 (br s, 1H, N*H*); ^{13}C nmr (DMSO-d$_6$): δ 17.1, 25.2, 45.9, 50.2, 52.9, 56.3, 61.3, 68.5, 113.0, 119.8, 122.5, 124.7, 133.7, 135.3, 137.1, 170.1; ms: m/z 397 (M^+, 7), 232 (7), 190 (25), 151 (100).

Anal. Calcd. for $C_{22}H_{27}N_3O_4$: C, 66.48; H, 6.85; N, 10.57. Found: C, 66.59; H, 6.80; N, 10.25.

2-(3,5-Dimethoxybenzylamino)-*N*-(3,3,7-trimethyl-2-oxo-2,3-dihydro-1*H*-indol-5-yl)acetamide **29**.

The yield was 36%, mp 203°; ir (potassium bromide): 3268 (NH), 1704 (C=O) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 1.20 (s, 6H, 2 x C*H*$_3$-C), 2.17 (s, 3H, Ar-C*H*$_3$), 3.21 (s, 2H, C*H*$_2$-CO), 3.66 (s, 2H, Ar-C*H*$_2$-N), 3.71 (s, 3H, O-C*H*$_3$), 3.74 (s, 3H, O-C*H*$_3$), 6.52 (d, 1H, J = 2.1 Hz, Ar-*H*), 6.62 (d, 1H, J = 2.1 Hz, Ar-*H*), 6.47 (t, 1H, J = 2.1 Hz, Ar-*H*), 7.19 (d, 1H, J = 1.6 Hz, Ar-*H*), 7.33 (d, 1H, J = 1.6 Hz, Ar-*H*), 9.59 (br s, 1H, N*H*), 10.28 (s, 1H, N*H*); ms: m/z 397 (M^+, 38), 232 (27), 190 (26), 180 (37), 166 (23), 151 (100).

Anal. Calcd. for $C_{22}H_{27}N_3O_4$: C, 66.48; H, 6.85; N, 10.57. Found: C, 66.47; H, 6.91; N, 10.18.

1,3-Dihydro-3,3-dimethyl-5-hydroxy-2*H*-indol-2-one **30**.

To a solution of oxindole **14** (19.1 g, 0.100 mole) in acetic acid (30 ml) was added 47% hydrobromic acid (300 ml). The resultant solution was heated at reflux for 5 hours under argon and then cooled to room temperature. The mixture was concentrated under reduced pressure and then partitioned between ether (300 ml) and water (200 ml). The organic layer was dried over anhydrous sodium sulfate. Concentration under reduced pressure and recrystallization from acetonitrile/dichloromethane afforded 11.7 g (66%) of **30**, mp 208°; ir (potassium bromide): 3239 (NH), 1680 (C=O) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 1.20 (s, 6H, 2 x C*H*$_3$-C), 6.54 (dd, 1H, J = 8.2, 2.3 Hz, Ar-*H*), 6.62 (d, 1H, J = 8.2 Hz, Ar-*H*), 6.68 (d, 1H, J = 2.3 Hz, Ar-*H*), 8.92 (br s, 1H, O*H*), 9.97 (br s, 1H, N*H*); ms: m/z 177 (M^+, 100), 162 (73).

Anal. Calcd. for $C_{10}H_{11}NO_2 \cdot 1/3H_2O$: C, 65.56; H, 6.42; N, 7.65. Found: C, 65.40; H, 6.15; N, 7.65.

1,3-Dihydro-3,3,7-trimethyl-5-hydroxy-2*H*-indol-2-one **31**.

Starting from oxindole **15** and using the hydrolysis condition described for **30** gave, after recrystallization from acetonitrile/dichloromethane, the desired compound **31** in 70% yield, mp 241°; ir (potassium bromide): 3205 (NH), 1665 (C=O) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 1.17 (s, 6H, 2 x C*H*$_3$-C), 2.10 (s, 3H, Ar-C*H*$_3$), 6.36 (d, 1H, J = 1.7 Hz, Ar-*H*), 6.49 (d, 1H, J = 1.7 Hz, Ar-*H*), 8.81 (br s, 1H, O*H*), 10.05 (br s, 1H, N*H*); ms: m/z 191 (M^+, 100), 176 (68).

Anal. Calcd. for $C_{11}H_{13}NO_2 \cdot 1/3H_2O$: C, 66.99; H, 6.98; N, 7.10. Found: C, 67.21; H, 6.93; N, 7.13.

3,3-Dimethyl-5-(oxiran-2-ylmethoxy)-1,3-dihydroindol-2-one **32**.

To a stirred solution of **30** (3.98 g, 22.5 mmoles) and potassium carbonate (3.73 g, 27.0 mmoles) in methanol (250 ml) epichlorohydrin (20.8 g, 225 mmoles) was added dropwise. The resulting mixture was heated at reflux for 2 hours and then cooled to room temperature. The solution was concentrated under reduced pressure to dryness and then partitioned between dichloromethane (150 ml) and water (450 ml). The organic layer was dried over anhydrous sodium sulfate. Filtration, concentration under reduced pressure and recrystallization from methanol yielded 2.20 g (42%) of epoxide **32**, mp 118°; ir (potassium bromide): 3144 (NH), 1721 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.22 (s, 3H, CH_3-C), 1.25 (s, 3H, CH_3-C), 2.68 (dd, 1H, J = 5.1, 2.7 Hz, 1 of CHO-CH_2), 2.83 (dd, 1H, J = 5.1, 1.8 Hz, 1 of CHO-CH_2), 3.30 (m, 1H, CHO), 3.76 (dd, 1H, J = 11.2, 6.5 Hz, 1 of Ar-OCH_2-CH), 4.25 (dd, 1H, J = 11.2, 2.7 Hz, 1 of ArO-CH_2-CH), 6.74 (s, 2H, Ar-*H*), 6.99 (s, 1H, Ar-*H*), 10.15 (br s, 1H, N*H*); ms: m/z 233 (M^+, 100), 218 (5), 176 (36).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.58; H, 6.37; N, 5.68.

3,3,7-Trimethyl-5-(oxiran-2-ylmethoxy)-1,3-dihydroindol-2-one **33**.

Starting from **31** and using the condition described for **32** afforded, after recrystallization from methanol, the desired compound **33** in 51% yield, mp 147°; ir (potassium bromide): 3170 (NH), 1709 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.20 (s, 6H, 2 x CH_3-C), 2.16 (s, 3H, Ar-CH_3), 2.66 (br s, 1H, 1 of CHO-CH_2), 2.80 (br s, 1H, 1 of CHO-CH_2), 3.30 (m, 1H, CHO), 3.74 (dd, 1H, J = 11.5, 6.3 Hz, 1 of Ar-OCH_2), 4.21 (dd, 1H, J = 11.5, 3.4 Hz, 1 of Ar-OCH_2), 6.57 (s, 1H, Ar-*H*), 6.78 (s, 1H, Ar-*H*), 10.19 (br s, 1H, N*H*); ms: m/z 247 (M^+, 60), 232 (30), 190 (100).

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.67; H, 6.78; N, 5.39.

General Procedure for the Preparation of 5-(2-Hydroxy-3-substituted Propoxy)-3,3-dimethyl-7-substituted-1,3-dihydroindol-2-ones **34-43**.

A solution of **32** (652 mg, 2.80 mmoles) or **33** (692 mg, 2.80 mmoles) and 3.5 mmoles of each of the substituted amines in methanol (30 ml) was heated at reflux for 3 hours and then cooled to room temperature. The mixture was concentrated under reduced pressure and taken up in ethyl acetate (100 ml) and washed with water (3 x 50 ml). The organic layer was dried over anhydrous sodium sulfate. Filtration and removal of the solvent under reduced pressure gave the crude products. Compounds **38** and **39** precipitated out at the end of reactions and thus were purified by crystallization (ethyl acetate/*n*-hexane). The balance of the material was purified by column chromatography (silica gel, dichloromethane/tetrahydrofuran/methanol: 25:0.5:0.5 for **34**, **37**; 12:1:1 for **35** and 18:1:1 for **36**; 8:1:1 for **41**; 5:1:1 for **42**; 10:1:0.5 for **43**, and dichloromethane/methanol, 5:1 for **40**, respectively). Recrystallization yielded analytically pure compounds.

5-[2-Hydroxy-3-[4-(2-methoxyphenyl)piperazin-1-yl]propoxy]-3,3-dimethyl-1,3-dihydroindol-2-one **34**.

The yield was 35%, mp 120° (ethyl acetate/*n*-hexane); ir (potassium bromide): 3165 (NH), 1713 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.23 (s, 6H, 2 x CH_3-C), 2.59-2.60 (m, 4H, 2 x CH_2-NCH_2), 2.95 (m, 4H, 2 x CH_2-NAr), 3.30 (m, 2H, HOCH-CH_2-N), 3.76 (s, 3H, O-CH_3), 3.84 (m, 1H, *H*C-OH), 3.93 (m, 2H, CH_2O), 4.81 (d, 1H, J = 4.6 Hz, O*H*), 6.74 (s, 2H, 2 x Ar-*H*), 6.85-6.96 (m, 5H, 5 x Ar-*H*), 10.11 (br s, 1H, N*H*); ms: m/z 425 (M^+, 8), 205 (100), 177 (5).

Anal. Calcd. for $C_{24}H_{31}N_3O_4$: C, 67.74; H, 7.34; N, 9.87. Found: C, 67.86; H, 7.62; N, 9.95.

5-[2-Hydroxy-3-(4-methoxybenzyl)aminopropoxy]-3,3-dimethyl-1,3-dihydroindol-2-one **35**.

The yield was 48%, mp 174° (dichloromethane); ir (potassium bromide): 3175 (NH), 1697 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.21 (s, 6H, 2 x CH_3-C), 3.30 (m, 2H, HOCH-CH_2-N), 3.69 (s, 2H, Ar-CH_2), 3.72 (s, 3H, O-CH_3), 3.80-3.88 (m, 3H, O-CH_2-*CH*OH), 4.98 (br s, 1H, OH), 6.70 (s, 2H, 2 x Ar-*H*), 6.85 (d, 2H, J = 8.5 Hz, 2 x Ar-*H*), 6.92 (s, 1H, Ar-*H*), 7.24 (d, 2H, J = 8.5 Hz, 2 x Ar-*H*), 10.11 (br s, 1H, N*H*); ms: m/z 370 (M^+, 25), 177 (10), 150 (23), 121 (100).

Anal. Calcd. for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found: C, 68.33; H, 7.24; N, 7.88.

5-[2-Hydroxy-3-[4-(4-nitrophenyl)piperazin-1-yl]propoxy]-3,3-dimethyl-1,3-dihydroindol-2-one **36**.

The yield was 47%, mp 176° (methanol); ir (potassium bromide): 3505 (NH), 1694 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.23 (s, 6H, 2 x CH_3-C), 2.54-2.60 (m, 4H, 2 x CH_2-NCH_2), 3.28 (m, 2H, N-CH_2-CHOH), 3.42-3.46 (m, 4H, 2 x CH_2-NAr), 3.80-4.05 (m, 3H, O-CH_2-*CH*-OH), 4.86 (d, 1H, J = 4.8 Hz, O*H*), 6.73 (s, 2H, 2 x Ar-*H*), 6.95 (s, 1H, Ar-*H*), 7.02 (d, 2H, J = 9.3 Hz, 2 x Ar-*H*), 8.02 (d, 2H, J = 9.3 Hz, 2 x Ar-*H*), 10.10 (br s, 1H, N*H*); ms: m/z 440 (M^+, 5), 268 (8), 220 (100).

Anal. Calcd. for $C_{23}H_{28}N_4O_5$: C, 62.71; H, 6.41; N, 12.72. Found: C, 62.32; H, 6.44; N, 12.82.

5-[2-Hydroxy-3-[4-(2-methoxyphenyl)piperazin-1-yl]propoxy]-3,3,7-trimethyl-1,3-dihydroindol-2-one **37**.

The yield was 81%, mp 115° (ethyl acetate/*n*-hexane); ir (potassium bromide): 3181 (NH), 1708 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.22 (s, 6H, 2 x CH_3-C), 2.18 (s, 3H, Ar-CH_3), 2.60 (m, 4H, 2 x CH_2-NCH_2), 2.96 (m, 4H, 2 x CH_2-NAr), 3.30 (m, 2H, N-CH_2-CHOH), 3.76 (s, 3H, O-CH_3), 3.91 (m, 2H, O-CH_2-CHOH), 4.02 (m, 1H, C*H*-OH), 4.81 (d, 1H, J = 4.5 Hz, O*H*), 6.58 (d, 1H, J = 2.3 Hz, Ar-*H*), 6.77 (d, 1H, J = 2.3 Hz, Ar-*H*), 6.85-6.92 (m, 4H, 4 x Ar-*H*), 10.19 (br s, 1H, N*H*); ms: m/z 439 (M^+, 8), 205 (100), 190 (15).

Anal. Calcd. for $C_{25}H_{33}N_3O_4$: C, 68.31; H, 7.57; N, 9.56. Found: C, 68.69; H, 7.54; N, 9.32.

5-(2-Hydroxy-3-butylaminopropoxy)-3,3,7-trimethyl-1,3-dihydroindol-2-one **38**.

The yield was 67%, mp 145° (ethyl acetate/*n*-hexane); ir (potassium bromide): 3207 (NH), 1704 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.86 (t, 3H, J = 7.1 Hz, CH_3-CH_2), 1.21 (s, 6H, 2 x CH_3-C), 1.25-1.42 (m, 4H, CH_2-CH_2-CH_3), 2.17 (s, 3H, Ar-CH_3), 2.54 (m, 2H, CH_2-CH_2-N), 2.65 (m, 2H, N-CH_2-CHOH), 3.83-3.84 (m, 3H, O-CH_2-*CH*-OH), 4.98 (br s, 1H, O*H*), 6.56 (s, 1H, Ar-*H*), 6.76 (s, 1H, Ar-*H*), 10.18 (br s, 1H, N*H*); ms: m/z 320 (M^+, 12), 191 (82), 130 (45), 86 (100).

Anal. Calcd. for $C_{18}H_{28}N_2O_3$: C, 67.47; H, 8.81; N, 8.74. Found: C, 67.63; H, 9.04; N, 8.78.

5-(2-Hydroxy-3-cyclohexylaminopropoxy)-3,3,7-trimethyl-1,3-dihydroindol-2-one **39**.

The yield was 48%, mp 125° (ethyl acetate/*n*-hexane); ir (potassium bromide): 3181 (NH), 1701 (C=O) cm^{-1}; ^1H nmr (methanol-d_4): δ 1.10-1.36 (m, 5H, 5 x cyclohexyl-*H*), 1.30 (s, 6H, 2 x CH_3-C), 1.63-1.95 (m, 5H, 5 x cyclohexyl-*H*), 2.23 (s, 3H, Ar-CH_3), 2.44-2.49 (m, 1H, C*H*-N), 2.68 (dd, 1H, J = 12.1, 8.3 Hz, 1 of N-CH_2-CHOH) 2.72 (s, 1H, N*H*), 2.87 (dd, 1H, J = 12.1, 3.7 Hz, 1 of N-CH_2-CHOH), 3.89 (m, 2H, O-CH_2-CHOH), 3.90 (br s, 1H, O*H*), 3.98-4.03 (m, 1H, C*H*-OH), 6.62 (d, 1H, J = 2.3 Hz, Ar-*H*), 6.73 (d, 1H, J = 2.3 Hz, Ar-*H*), 10.08 (br s, 1H, N*H*); ms: m/z 346 (M^+, 18), 205 (12), 191 (44), 112 (100).

Anal. Calcd. for $C_{20}H_{30}N_2O_3$: C, 69.33; H, 8.73; N, 8.09. Found: C, 69.52; H, 8.84; N, 7.69.

5-(2-Hydroxy-3-isopropylaminopropoxy)-3,3,7-trimethyl-1,3-dihydroindol-2-one **40**.

The yield was 31%, mp 137°; ir (potassium bromide): 3165 (NH), 1713 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.12 (d, 6H, J = 6.5 Hz, 2 x CH_3-CH), 1.33 (s, 6H, 2 x CH_3-C), 2.04 (s, 1H, N*H*), 2.22 (s, 3H, Ar-CH_3), 2.76 (dd, 1H, J = 12.1, 8.3 Hz, 1 of CH_2-N), 2.85-2.91 (m, 2H, C*H*-NH-CH_2 (x 1/2)-CHOH), 2.94 (s, 1H, O*H*), 3.92 (d, 2H, J = 5.0 Hz, O-CH_2-CHOH), 4.01-4.08 (m, 1H, C*H*-OH), 6.56 (s, 1H, Ar-*H*), 6.62 (s, 1H, Ar-*H*), 10.10 (br s, 1H, N*H*); ms: m/z 306 (M^+, 15), 205 (8), 191 (40), 116 (26), 72 (100).

Anal. Calcd. for $C_{17}H_{26}N_2O_3$: C, 66.64; H, 8.55; N, 9.14. Found: C, 66.80; H, 8.68; N, 9.02.

5-[2-Hydroxy-3-(3,4-dimethoxybenzylamino)propoxy]-3,3,7-trimethyl-1,3-dihydroindol-2-one **41**.

The yield was 34%, mp 144° (dichloromethane); ir (potassium bromide): 3429 (NH), 1701 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.17 (s, 6H, 2 x CH_3-C), 2.10 (s, 3H, Ar-CH_3), 2.16 (s, 1H, N*H*), 2.51-2.69 (m, 2H, CH_2-CHOH), 3.62-3.64 (m, 2H, O-CH_2-CHOH), 3.70 (s, 3H, O-CH_3), 3.72 (s, 3H, O-CH_3), 3.81 (s, 2H, CH_2-Ar), 3.89 (m, 1H, C*H*-OH), 4.82 (s, 1H, O*H*), 6.44 (d, 1H, J = 10.2 Hz, Ar-*H*), 6.64 (d, 1H, J = 10.2 Hz, Ar-*H*), 6.81-6.93 (m, 3H, 3 x Ar-*H*), 10.15 (br s, 1H, N*H*); ms: m/z 414 (M^+, 10), 205 (5), 191 (20), 151 (100).

Anal. Calcd. for $C_{23}H_{30}N_2O_5$: C, 66.65; H, 7.30; N, 6.76. Found: C, 66.94; H, 7.32; N, 6.89.

5-[2-Hydroxy-3-(4-methoxybenzylamino)propoxy]-3,3,7-trimethyl-1,3-dihydroindol-2-one **42**.

The yield was 51%, mp 223°; ir (potassium bromide): 3160 (NH), 1699 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.21 (s, 6H, 2 x CH_3-C), 2.17 (s, 3H, Ar-CH_3), 3.30 (m, 2H, N-CH_2-CHOH), 3.76 (s, 3H, O-CH_3), 3.86-3.88 (m, 3H, O-CH_2-CHOH), 4.09 (s, 2H, CH_2-Ar), 4.14 (m, 1H, C*H*-OH), 5.78 (br s, 1H, O*H*), 6.55 (d, 1H, J = 2.3 Hz, Ar-*H*), 6.76 (d, 1H, J = 2.3 Hz, Ar-*H*), 7.47 (d, 2H, J = 8.7 Hz, 2 x Ar-*H*), 7.97 (d, 2H, J = 8.7 Hz, 2 x Ar-*H*), 10.23 (br s, 1H, N*H*); ms: m/z 384 (M^+, 10), 191 (34), 150 (15), 121 (100).

Anal. Calcd. for $C_{22}H_{28}N_2O_4$: C, 68.73; H, 7.34; N, 7.29. Found: C, 69.03; H, 7.01; N, 7.28.

5-[2-Hydroxy-3-[4-(4-nitrophenyl)piperazin-1-yl]propoxy]-3,3,7-trimethyl-1,3-dihydroindol-2-one **43**.

The yield was 76%, mp 215°; ir (potassium bromide): 3180 (NH), 1710 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.22 (s, 6H, 2 x CH_3-C), 2.17 (s, 3H, Ar-CH_3), 2.34-2.44 (m, 4H, 2 x CH_2-NCH_2CHOH), 2.49-2.51 (m, 4H, 2 x CH_2-NAr), 3.45 (d, 2H, J = 5.0 Hz, N-CH_2-CHOH), 3.82 (dd, 1H, J = 9.9, 5.8 Hz, 1 of O-CH_2-CHOH), 3.90 (dd, 1H, J = 9.9, 3.8 Hz, 1 of O-CH_2-CHOH), 3.93-4.04 (m, 1H, C*H*-OH), 4.85 (d, 1H, J = 4.7 Hz, O*H*), 6.57 (d, 1H, J = 2.3 Hz, Ar-*H*), 6.76 (d, 1H, J = 2.3 Hz, Ar-*H*) 7.02 (d, 2H, J = 9.5 Hz, 2 x Ar-*H*), 8.04 (d, 2H, J = 9.5 Hz, 2 x Ar-*H*), 10.17 (br s, 1H, N*H*); ms: m/z 454 (M^+, 10), 220 (100), 177 (12).

Anal. Calcd. for $C_{24}H_{30}N_4O_5$: C, 63.42; H, 6.65; N, 12.33. Found: C, 63.73; H, 6.63; N, 12.47.

Determination of Cardiotonic Activity.

The cardiotonic activity of **19-43** in isolated ventricular tissues of Mongrel dogs were determined by following the method reported previously [29]. The test compounds **19-43** were administered at a dose of 10 μ*M* for 10 minutes to evaluate their ability to increase contractile force. Inotropism was expressed as the ratio of percent change of maximum response to each compound to the maximum response to control.

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