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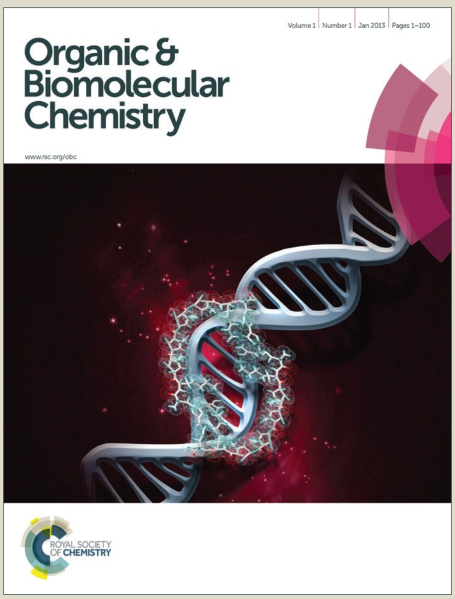

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Discovery, Stereospecific Characterization and Peripheral Modification of 1-(Pyrrolidin-1-ylmethyl)-2-[(6-chloro-3-oxo-indan)-formyl]-1,2,3,4-tetrahydroisoquinolines As Novel Selective κ Opioid Receptor Agonists

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INTRODUCTION

μ opioid receptor agonists are traditionally analgesic agents for the treatment of moderate to severe pain.[1] However, the over-activation of the μ receptor unnecessarily leads to some serious side effects, such as respiratory depression, dependence and tolerance, which significantly limit their clinical application.[2] Hence, considerable efforts have been transferred to the development of selective κ opioid receptor agonists which demonstrate some advantages over the widely used μ opioid analgesics.[3] For instance, the compound TRK-820,[4] a novel highly selective κ agonists, was first developed as an analgesic for postoperative pain.[5]

Despite the huge potential of currently selective κ opioid agonist, their therapeutic effects are still mediated by stimulating the central nervous system (CNS), and thus some CNS-related side effects, including dysphoria, sedation, and psychotomimetic effects are unavoidable.[6] However, the recently-developed peripherally selective κ receptor agonists represent a series of appealing candidates for improvement of drug safety. For example, clinical studies have proved that the activation of peripheral κ receptors could produce antinociceptive effects without centrally-mediated side effects.[7] Therefore, The discovery and development of peripherally acting κ-agonists is currently the focus of research interest.

The leading compound **2** (the restricted derivative of **1,** Figure 1), was reported to be a highly potent κ receptors agonist (Ki = 0.20 ± 0.02 nM). In this molecule, the isoquinoline appears to the key structural moiety in maintaining the high affinity for κ receptors. In order to further improve the κ-receptor affinity, here we designed and synthesized a novel series of

1-(pyrrolidin-1-ylmethyl)-2-[(3-oxo-indan)-formyl]-1,2,3,4-tetrahydroisoquinoline *κ* agonists *maj*-**3a-3u** by incorporating an indanone structure moiety.[8] The preliminary pharmacological studies revealed that the 24-Cl substituted compound *maj*-**3c** exhibited excellent affinity at *κ* receptor (Ki = 0.033 nM) and potent antinociceptive activity in Acetic acid writhing (AAW) and Mouse hot plate (MHP) tests. Additionally, Considering that the pharmacological activities of the novel agonists are largely dependent on their stereospecific structure as those published *κ* agonists[9, 10, 11], we separated the four stereoisomers of compound **3c** and their *in-vitro* affinity for κ receptor and *in-vivo* analgesic effects were evaluated independently. Compound (1*S*,18*S*)-**3c** displayed the highest *κ* affinity with the K_i value of 0.0059 nM.

Although *maj*-**3c** was a highly potent κ agonist, CNS side effects such as anxiety and sedation were also observed in the further pharmacological evaluations, which might reduce its druggability. A key factor to minimize or eliminate the CNS side effects was to introduce more polar substituents to reduce lipophilicity of molecules, thus rendering compounds with limited accessibility to the CNS.[12] Therefore, we employed a similar research strategy to improve the peripherally-targeting capability by introducing hydrophilic substituents such as hydroxyl group into the benzene ring of *maj*-**3c** (as shown in Scheme 2). A series of new compounds (*maj*-**11a-i**) were synthesized and their affinity for κ receptor was evaluated *in-vitro*. Compound *maj*-**11a** displayed potent κ-opioid receptor agonists (K_i = 35.13 nM), and antinociceptive ED_{50} values (0.392 mg·kg^{-1}, s.c.). More importantly, the dose of sedative effect (ED_{50} = 9.29 mg·kg^{-1}) of *maj*-**11a** was significantly higher than its analgesic dose (ED_{50} = 0.392 mg·kg^{-1}), which made it a promising analgesic candidate with weaker sedative side effects than its parental compound *maj*-**3c**.

CHEMISTRY

Synthesis of *maj*-3a-u and *maj*-11a-i

The desired compounds *maj*-**3a-u** were prepared by condensing different diamines **6a-h** with indan acids **10a-f**, and these intermediates were respectively obtained by convenient methods in advance. [13, 14, 15, 16]

The synthesis of diamines **6a-h** was carried out following the literature methods in two steps as depicted in Scheme 1. Non-aqueous treatment of solvent xylene, portion-wise addition of chloroacetamide **4** and nitrogen gas protection were required for good yields at the first step of preparing compounds **5a-h**.

Synthetic routes of another key intermediate indan acids **10a-f** were illustrated in Scheme 2. It should be noted that in the intramolecular cyclization step, replacement of the traditional nitrobenzene with dichloromethane as solvent has led the Friedel-Crafts acylation to be lower toxicity and higher yield (40% to 60%) in a mild reaction condition.

1-(Pyrrolidin-1-ylmethyl)-2-[(3-oxo-indan)-formyl]-1,2,3,4-tetrahydroisoquinoline derivatives *maj*-**3a-u** were synthesized in moderate yields (about 40%), from indan acids **10a-f** by condensation with diamines **6a-h** using dicyclohexylcarbodiimide (DCC) as coupling agent, and 4-(dimethylamino)-pyridine (DMAP) as catalyst shown in the Scheme 2. The demethylation of *maj*-**3f**, **3h, 3j**, **3p-u** to afford hydroxyl analogs *maj*-**11a-i** was obtained in 48% HBr under reflux condition in moderate yields. All the final novel compounds were purified by column chromatography, and well-characterized by spectral data (IR, ^{1}H NMR, MS) and elemental analyses or HRMS.

Synthesis of the four stereoisomers of 3c

Considering that the pharmacological activity is largely dependent on their stereospecific structure, thus the four stereoisomers of the most potent compound **3c** were prepared and their absolute configurations were determined.

Apparently, the reaction of **6a** with **10c** would form two pairs of enantiomers of **3c**，which can be readily separated by column chromatography. The pair of high R_f enantiomers obtained as major product was defined as *maj*-**3c** which consists of (1*S*,18*S*)**-3c** and (1*R*,18*R*)**-3c** according to the X-ray structure analysis of *maj*-**3c** (Figure 2), while the higher polar enantiomers in poor yield was appointed as *min*-**3c** which consists of (1*S*,18*R*)**-3c** and (1*R*,18*S*)**-3c** enantiomers.

Since the C-1 stereocentre keeps unaffected in the condensation, *S*-**6a** reacted with racemic acid **10c** affoted the diastereomers of (1*S*,18*S*)**-3c** and (1*S*,18*R*)**-3c**, which can be separated by column chromatography. Accordingly, the corresponding pair of diastereomers (1*R*,18*R*)**-3c** and (1*R*,18*S*)**-3c** were successfully prepared using *R*-**6a** as the starting material (Scheme 3).

S-**6a** and *R*-**6a** was further acquired according to the similar reported method (Scheme 3),[13] The absolute configuration of (+)**-6a** was confirmed via reacting with 2-(4-(trifluoromethyl)phenyl)acetic acid to synthesize the reported compound (*S*)-1-(pyrrolidin-1-ylmethyl)-2-[(4-trifluoromethyl)acetyl]-1,2,3,4–tetrahydroisoquinoline.[12] Based on the well-accordant $[\alpha]^{20}_{D}$ value between the experimental and the literature results[12] (–60.0 vs = –66.2 (*c* = 1, $CHCl_3$)), the (+)**-6a** was assigned as (*S*)-configuration, and relatively, (–)**-6a** was (*R*)-configuration.

In another approach, the four pure stereosiomers of **3c** can also be obtained by HPLC employing a Chiralcel OD-RH chiral column (Figure 3, for details to see Experimental Section).

PHARMACOLOGICAL RESULTS AND DISCUSSION

Affinity of the synthesized compounds

The binding affinity and selectivity of the new compounds for κ and μ receptors were evaluated by competition with [^{3}H]-diprenorphine binding prepared from Chinese hamster ovary (CHO) cell membranes stably expressing human κ and rat μ opioid receptors. The SAR research was started with the major pair of enantiomers of **3a-u** (*maj*-**3a-u**).

The effects of substitution in the phenyl rings of tetrahydroisoquinoline and indan moieties on the binding affinities at κ- and μ-opioid receptors were summarized in Table 1. The compounds with unsubstituted tetrahydroisoquinoline nucleus such as *maj*-**3a-e** exhibited high affinities for κ receptor (K_i = 0.033-1.37 nM), and showed varying degrees of affinity for μ receptor (K_i = 99.0- >10,000 nM). However, substitution of methoxy for H in tetrahydroisoquinoline nucleus drastically decreased the binding affinity of these compounds for κ receptor. For example, 7-methoxy or 6-methoxy substituted compounds *maj*-**3h** and *maj*-**3o** exhibited approximately 563- and 113-fold lower affinities for κ receptor than their corresponding unsubstituted compound *maj*-**3c** (K_i = 0.033 ± 0.008nM, the affinity curves of *maj*-**3c** was shown in Figure 4), respectively. Moreover, 6,7-dimethoxy substitution in tetrahydroisoquinoline nucleus completely abolished the affinity for κ receptor, as indicated by compounds *maj*-**3j-m**. In addition, of the nine compounds obtained by introducing a hydroxyl group in 6-, 7-, and 8- positions of the benzene ring in the tetrahydroisoquinoline moiety, the 7-substituted compound *maj*-**11a** was more active than the other compounds**.** Noteworthy, the strong electron-withdrawing group such as –NO_2, -CF_3 were barely investigated due to the poor synthetic yield in the cyclization step or the inaccessibility of the starting material. In conclusion**,** substitution in tetrahydroisoquinoline moiety strongly affects κ receptor affinity of these compounds, suggesting that this moiety may function as key pharmacophore elements in binding to κ receptor.

Compared to substitution in the phenyl rings of tetrahydroisoquinoline moiety affecting κ receptor affinity, substitution of the indan moiety appears to influencing the binding affinity to μ receptor. As shown in Table 1, substitution of methoxy, Cl or F for H in the indan moiety remarkably increased the affinity for μ receptor. For instance, dimethoxy, Cl, F and monomethoxy-substituted compounds *maj*-**3b**, *maj*-**3c**, *maj*-**3d** and *maj*-**3e** displayed relatively higher affinity for μ receptor with the K_i values of 99, 698, 486 and 140 nM, respectively, whereas unsubstituted *maj*-**3a** exhibited a negligible affinity for μ receptor with a K_i value >10,000 nM. However, substitution of methoxy, dimethoxy, methyl, or F for H in the indan moiety had no marked effect on the κ affinity. For instance, the K_i value of unsubstituted *maj*-**3a** was 0.452 nM, which was not significantly different from that of monomethoxy substituted *maj*-**3e** (K_i = 0.933 nM), dimethoxy substituted *maj*-**3b** (K_i = 1.37 nM), methyl substituted *maj*-**3r** (K_i = 69.57 nM) and F substituted *maj*-**3d** (K_i = 0.228 nM). Unexpectedly, substitution of Cl for H in the indan moiety (*maj*-**3c**) displayed the highest affinity at κ receptor in all of the *maj*-enantiomers, with the K_i value of 0.033 nM, which is much higher than that of unsubstituted *maj*-**3a** (14-fold), the parental compound BRL52580 (6-fold) and (-)U50488H (184-fold).

The effect of *min*-**3c**, the diastereoisomers of *maj*-**3c**, on the binding affinity to opioid receptors was further investigated. It was found that the κ affinity of the minor pair of enantiomers *min*-**3c** was 112-fold lower than that of the predominant enantiomers *maj*-**3c**, suggesting that the binding ability for κ receptor is strongly dependent on its enantiotropy. We then focused our attention on evaluation of *maj*-**3c** in vivo and the further stereo-SAR investigations on the four pure stereoisomers of **3c**.

In vivo studies of *maj*-3c

As shown in Table 2, *maj*-**3c** was evaluated in vivo for analgesic activity. Subcutaneous administration (s.c.) of *maj*-**3c** produced dose-dependent antinociceptive effects in the mouse hot plate (MHP) assay with the ED_{50} value of 2.061 μg/kg, which was about 12-, >39- and 2142-fold more potent than that of *min*-**3c**, BRL 52580 and U-50,488H, respectively. In the acetic acid writhing (AAW) assays, *maj*-**3c** produced antinociceptive effects with ED_{50} value of 0.406 μg/kg, which was 6-, 190- and 2180-fold lower than that of *min*-**3c,** *maj*-**11a** and U-50,488H, respectively.

Next, the potential of *maj*-**3c** to develop physical dependence and antinociceotive tolerance were determined in mice. As shown in Figure 5, an acute injection of naloxone (3.0mg·kg^{-1}, s.c.) resulted in a robust increase in withdrawal jumping and weight loss after a progressive treatment for morphine. However, treatment of mice with progressive dose of *maj*-**3c** did not produce any naloxone-precipitated jumping and weight loss, indicating that *maj*-**3c** may have less potential to develop physical dependence relative to morphine. We further evaluate the effect of *maj*-**3c** on the development of morphine physical dependence. As shown in Figure 6, chronic treatment of mice with morphine for 5 days followed by a single injection of naloxone induced a robust withdrawal jumping and it could be significantly suppressed by co-administration of *maj*-**3c** (300 μg·kg^{-1}, i.p.). The results demonstrated that *maj*-**3c** may have the potential to inhibit the physical dependence effects induced by morphine. On the other hands, with measured by MHP assay, Figure 7 showed that repeated administration of morphine led to a progressive decrease in antinociceptive effects. However, *maj*-**3c**

(25ug·kg^{-1}, s.c.) was shown to produce 90% antinociception after repeated injection for 9 days, suggested that *maj*-**3c** had lower potential to develop antinociceptive tolerance compared to morphine.

Stereochemistry studies on the Four Stereoisomers of 3c

The affinities of the four enantiomerically pure stereoisomers of **3c** at κ and μ receptors were determined. As shown in Table 3, all four stereoisomers exhibited low affinity for μ receptor but high affinity for κ receptor. (1*S*,18*S*)-**3c** displayed the highest κ affinity among these stereoisomers with the K_i value of 0.0059 nM (The affinity curves of (1*S*,18*S*)-3c was shown in Figure 4), which is 8.3-fold better than its 1*S*-diastereomer (1*S*,18*R*)-**3c** (0.049 nM). Compared to (1*S*,18*S*)- and (1*S*,18*R*)-**3c,** (1*R*,18*R*)- and (1*R*,18*S*)-**3c** have a relatively lower affinity for κ receptor with the K_i values of 18.2 and 17.5 nM, respectively. The (*S*,*S*)-stereoisomers seems to be the most compatible substrate for the binding site of the κ-receptor protein according to the results.

The four stereoisomers of **3c** were evaluated in vivo for analgesic activity by using mouse formalin (MF) test[17, 18]. As shown in Figure 8, in both the first and second phases, (1*S*,18*S*)-**3c (**20 ug/kg, s.c.) significantly blocked formalin-induced paw licking responses, and (1*S*,18*R*)-**3c** (20 ug/kg, s.c.) exhibited a trend to inhibit formalin-induced paw licking responses, but it did not reach statistical significance. In contrast, (1*R*,18*S*)-**3c** (20 ug/kg, s.c.) and (1*R*,18*R*)-**3c** (20 ug/kg, s.c.) did not show any effects on formalin-induced paw licking, indicating that two 1*R*-isomers had no effects on pain relief. These results suggested that (1*S*,18*S*)-configuration was uniquely required for the analgesic activity of this novel compound **3c**. It should be noted that (1*S*,18*S*)-**3c** is a potent biphasic analgesia, since it performed inhibitory effect not only on the acute pain responses for phase I, but also on the tonic pain responses for phase II in MF test.

Sedative and anxious studies on *maj*-3c and *maj*-11a

Sedative activity was evaluated in the mouse rotated test and the peripheral index was calculated. As shown in Table 4, the sedative ED_{50} value of the compound *maj*-**3c** was 0.568 $ug \cdot kg^{-1}$. The peripheral restriction index (the ED_{50} value of sedative effect to that of antinociceptive effect (AAW))was 1.4. In contrast, the sedative ED_{50} value of *maj*-**11a**, a *maj*-**3c** peripheral activated hydroxyl analog, was 9.29 $mg \cdot kg^{-1}$. The peripheral restriction index was found to be much greater for *maj*-**11a** (23.7) than that for its parental compound *maj*-**3c** (1.4) and (-)U50,488H (3.7), suggesting that *maj*-**11a** had a less sedative effect. These data revealed that introduction of one hydrophilic hydroxyl group at the 7-position largely minimized sedative activity.

Anxiety-related behavior was evaluated in the elevated plus maze test. As shown in Table 5, both *maj*-**3c** and *maj*-**11a** dose dependently increased time spent in the closed arms of the plus maze, suggesting that both compounds produced anxiety-related behavior. The high doses of *maj*-**3c** (5 $ug \cdot kg^{-1}$) and *maj*-**11a** (3.75 $mg \cdot kg^{-1}$) we chose were both almost 10-fold higher than their AAW ED_{50} values. Compared to *maj*-**3c** (5 $ug \cdot kg^{-1}$), the mice injected with *maj*-**11a** (3.75 $mg \cdot kg^{-1}$) spent more time in the open arm, suggested that *maj*-**11a** produce less anxiety-related behavior.

Calculated Physicochemical Indicators of *maj*-3r, *maj*-3c, *maj*-11a, *maj*-11g

Lipophilic efficiency indices (LLE) and the ligand efficiency-dependent lipophilicity index (LELP) are the crucial parameters suggested to support balanced optimization of potency and ADMET profile[19]. Thus, physicochemical indicators such as clogP, LLE, LELP of *maj*-**3r**, *maj*-**3c**, *maj*-**11a**, *maj*-**11g** were determined. As shown in table 6, the ranking of clogP values was: *maj*-**3c**, 3.52, *maj*-**11a**, 2.76, *maj*-**3r**, 2.44, and *maj*-**11g** 1.3. Compound *maj*-**3c** with the favorable clogP value seems to be more readily to penetrate into CNS, it can be perceived that the high BBB permeability may lead to more serious centrally mediated side effect of sedation and anxiety compared to the other compounds. On the other hand, the hydroxy substituted compound *maj*-**11g** gave lower clogP value compared to methoxy substituted compound *maj*-**3r** and *maj*-**3c**. This result may support that the hydrophilic substituent hydroxyl would decrease the BBB penetration. In addition, the comparison between *maj*-**11g** and *maj*-**11a** recognizes the halogen in indanone ring as the major contributor to the lipophilicity indices. Furthermore, the calculated LLE values were: *maj*-**3r**, 4.72, *maj*-**3c**, 6.96, *maj*-**11a**, 4.7, *maj*-**11g**, 6.08, respectively. These values are basically constant with the Ki affinity. However, the LELP value are not agreed with the LLE value, *maj*-**11g** displayed the unexpected lowest LELP value 3.78.

The peripheral antinociceptive effects studies on *maj*-11a

To determine whether the antinociceptive effect of *maj*-**11a** was via a local, peripheral mechanism of action, 1.6 mg/kg *maj*-**11a** was administered s.c. into the plantar surface of the left hind paw (contralateral). The result had demonstrated that local ipsilateral, but not contralateral, intraplantar administration of *maj*-**11a** (0.8, 1.6 mg/kg; 20 μl/paw) significantly inhibited flinching behavior during the second phase (Figure 9). One-way ANOVA tests ($F_{2,15} = 11.41$, $P < 0.001$) and the following post hoc comparison using Dunnett's tests ($P < 0.001$) revealed a significant effect of 1.6 mg/kg *maj*-**11a** to inhibit formalin-induced pain in second phase (Figure 9). We found that intraplantar injection of *maj*-**11a** to the same paw in which formalin was given generated significant antinociceptive effects in second phase as measured by a reduction in flinching behavior; however, when the drug was given to the paw contralateral to the formalin injection, there were no antinociceptive effects, indicating that the antinociceptive effects of *maj*-**11a** in the formalin test occur through a peripheral mechanism.

Acute toxicity studies and bioavailability tests in vivo on *maj*-11a

Acute toxicity studies were carried out to test the medium lethal dose (LD_{50}) of *maj*-**11a**, the results in table 6 indicated that the LD_{50} of *maj*-**11a** was 29.6 $mg{\cdot}kg^{-1}$, while the antinociceptive ED_{50} in AAW was 0.392$mg{\cdot}kg^{-1}$. The therapeutic index (TI) calculated according to the LD_{50} and ED_{50} is 75.5. The bioavailability data of *maj*-**11a** was also determined. As shown in table 7，the bioavailability of *maj*-**11a** was 40.6% in p.o manner, and other results were indicated as follows: T_{max} was 1.00h, C_{max} was 214.4ng/mL, $t_{1/2}$ was 4.16h, $AUC_{0\text{-}t}$ was 1083.9μg·h/L, $AUC_{0\text{-}\infty}$ was 1099.9μg·h/L.

CONCLUSION

In the present study, a novel series of isoquinoline κ receptor agonists were synthesized and evaluated. The SAR exploration on their major pair of enantiomers indicates that the introduction of electron-withdrawing substituents at phenyl ring of indan moiety would increase κ binding ability, while increase the number of methoxy substituent in that of tetrahydroisoquinoline moiety tends to progressively decrease κ affinity. 24-Cl substituted compound *maj*-**3c,** the most potent selective κ agonist among the racemic novel compounds, displayed much higher analgesic effects than U-50,488H and original BRL 52580 in MHP tests. Moreover, it may have the potential to inhibit the physical dependence effects induced by morphine. A further stereo-SAR probe into the four stereoisomers of **3c** has identified the key role of stereochemistry played in κ affinity and efficacy of this new scaffold. We also found that peripheralization of *maj*-**3c** was able to significantly minimize central nervous system side effects. *maj*-**11a** containing hydroxyl group produced potent analgesic effect with less sedative and anxiety side effects. Thus, *maj*-**11a** has been identified as a promising analgesic candidate compound with acceptable TI (75.5) and bioavailability (40.6%) in p.o manner.

EXPERIMENTAL SECTION

General. Melting points were recorded on a RY-1 melting point apparatus and were uncorrected. The IR spectra (in KBr pellets) were recorded on a Nicolet Impact 410 spectrometer. The NMR spectra were recorded on a BRUKER AV-300 NMR spectrometer using TMS as the internal standard. MS spectra were acquired on an Agilent 1100 series LC/MSD Tarp (SL). The HRMS spectra were acquired on waters Micros Q-TOF apparatus. Elemental analyses were determined by an Elementar Vario EL Ш instrument. Optical rotations were taken with a Jasco P-1020 polarimeter. The X-ray analysis was run on a X'TRA X-ray diffractometer. Agilent 1100 (ChemStation for LC, Version Rev.A.09.01) was employed to the HPLC resolution. Compound **6** and **10** were prepared as described previously.[13,15]

General procedure for preparation of compounds 3a-u

A solution of DCC (1.3 g, 6.3 mmol) in CH_2Cl_2 (10 ml) was added over 30 min under N_2 to an ice-cold stirred solution of diamine **6** (4.5 mmol) and 1.2 equiv of indan acid **10** (5.4 mmol) in the same solvent (20 ml) in the presence of DMAP (catalytic amount). After stirred at room temperature overnight, the reaction mixture was filtered, concentrated and purified by silica gel column chromatography, using a mixture of petroleum ether/EtOAc/triethylamine as eluent, to afford the target compound as main product.

General procedure for preparation of compounds 11a-i

The methoxy-substituted diamines **3** (4.5 mmol) were heated for 2 h at 130^{o}C with 48% HBr (20 mL). The solution was evaporated and to the residue was added 10% Na_2CO_3 solution (50ml), which was exhaustively extracted with CH_2C1_2 (3×75ml). The organic solution was washed with saturated NaCl solution (2×30ml), dried over Na_2SO_4, and evaporated to yield the free bases which were purified by silica gel flash column chromatography using CH_2C1_2-MeOH=40:1 as eluent to afford the target compound. Treatment of the free base with HCl/EtOAc in acetone at room temperature gave the hydrochloride salt.

Stereoselective Synthesis of the Four Stereoisomers of 3c (Method A)

(+)-1-(Pyrrolidin-1-ylmethyl)-1,2,3,4-tetrahydroisoquinoline (*S*-(+)-6a). To a thoroughly stirred solution of the racemic compound (8.9 g, 0.0254 mol) in absolute ether (50 ml), D-(+)-di-*p*-toluoyltartaric acid (D-(+)-DTTA) (9.8 g, 0.0254 mol) in absolute ether (50 ml) was added dropwise, and the mixture was filtered and the resulting solid was dissolved in the solvent of isopropanol/isopropyl ether (8.5:5, 13.5 ml/g) for recrystallization. The solution was left at –10 ~ –5 ^{o}C for 12 h and then filtered to give the solid, which was stirred and washed with a mixture of ether and acetone (4:2.5, 6.5 ml/g) and then recrystallized from acetone (10 ml/g, –10 ~ –5 ^{o}C) to afford the D-(+)-DTTA salt as white crystals (1.88 g, 0.00255mol, 10 %, mp.145~147 ^{o}C). Treatment of the crystals with NaOH solution and removal of the N-protecting group as published procedure,[16] gave the title compound as a pale yellow oil in an overall 5 % yield, $[\alpha]^{20}_{D}$ = + 35.5 (c = 1, MeOH).

(–)-1-(Pyrrolidin-1-ylmethyl)-1,2,3,4-tetrahydroisoquinoline (*R*-(–)-6a). The enantiomeric compound *R*-(–)-**6a** was prepared in a similar procedure to *S*-(+)-**6a** using L-(-)-DTTA as resolving agent and isopropanol/isopropyl ether (9:5) as solvents for the first recrystallization, to obtain a pale yellow oil (4.5 %), $[\alpha]^{20}_{D}$ = – 37.8 (c = 1, MeOH).

Spectroscopic Data of Enantiomers *S*-(+)-6a and *R*-(–)-6a. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.07-7.25 (m, 4H, ArH), 4.07 (dd, *J* = 3.2, 10.1 Hz, 1H, H_1), 3.17-3.22 (m, 1H, H_3), 2.92-3.00 (m, 2H, $H_{3',9}$), 2.80-2.82 (m, 2H, $H_{9',4}$), 2.70 (bs, 1H, NH), 2.65-2.67 (m, 2H, $H_{11,14}$), 2.57-2.60 (m, 1H, $H_{4'}$), 2.48-2.50 (m, 2H, $H_{11',14'}$), 1.75-1.79 (m, 4H, $H_{12,12',13,13'}$). ESI-MS: 217.2 ($[M+H]^+$, base peak).

The target diastereomers (1*S*,18*S*)-**3c** and (1*S*,18*R*)-**3c** were synthesized from *S*-(+)-**6a** and indan acid **10c** using general procedure described above and separated by column chromatography, eluting with a mixture of CH_2Cl_2/MeOH/$NH_3 \cdot H_2O$ (70:1:0.2) to afford the pure (1*S*,18*S*)-**3c** (35%) and (1*S*,18*R*)-**3c** (8%) as white solids. The pure separated diastereomers (1*R*,18*R*)-**3c** and (1*R*,18*S*)-**3c** were obtained successfully (33% and 9%, respectively) by a same method from *R*-(–)-**6a** and indan acid **10c**.

Chiral HPLC resolution of the Four Stereoisomers of 3c (Method B) The resolution of stereoisomers of **3c** was carried out using a Chiralcel OD-RH chiral column (150mm, Column No: ODRH CD-KK030), with the conditions: eluent, 0.05M KH_2PO_4/MeCN 70:30; flow rate, 1.0 mL/min; injection volume, 20 μl; UV detector λ, 254nm; column temperature, 30 °C.

1-(Pyrrolidin-1-ylmethyl)-2-[(3-oxo-indan)-formyl]-1,2,3,4-tetrahydroisoquinoline (*maj*-3a). Compound *maj*-**3a** was synthesized from **6a** and **10a** using general procedure described above to obtain 0.67 g (40%) of white solid, mp.120-122 °C. The ^{1}H NMR signals were doubled due to the rotamers, using number underlined to differentiate the two series of spectra. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.00-7.75 (m, 16H, $H_{22,\underline{22},23,\underline{23},24,\underline{24},25,\underline{25},5,\underline{5},6,\underline{6},7,\underline{7},8,\underline{8}}$), 5.85-5.87/<u>5.47-5.49</u> (m/m, 2H, $H_{1,\underline{1}}$),

<u>4.99-5.01</u>/4.72-4.74 (m/m, 2H, $H_{\underline{18},18}$), <u>4.75-4.78</u>/4.27-4.31 (m/m, 2H, $H_{\underline{3},3}$), 3.92-3.98 (m, 1H, $H_{3'}$), 2.37-3.35 (m, 21H, $H_{\underline{3'},11,\underline{11},11',\underline{11'},13,\underline{13},13',\underline{13'},16,\underline{16},16',\underline{16'},19,\underline{19},19',\underline{19'},4,\underline{4},4',\underline{4'}}$), 1.67-1.81 (m, 8H, $H_{14,\underline{14},14',\underline{14'},15,\underline{15},15',\underline{15'}}$). Ratio of rotamers = 9:<u>10</u>. IR (KBr): 3415, 2962, 2929, 2790, 1712 (C=O), 1641 (C=O), 1604, 1434, 1284, 1238, 1043, 761 cm^{-1}; ESI-MS: 375.2 ($[M+H]^+$, base peak). Anal. Calcd. for $C_{24}H_{26}N_2O_2$: C 76.98, H 7.00, N 7.48, found: C 76.88, H 7.07, N 7.43.

1-(Pyrrolidin-1-ylmethyl)-2-[(5,6-dimethoxy-3-oxo-indan)-formyl]-1,2,3,4-tetrahydroisoquinoline (*maj*-3b). Compound *maj*-**3b** was synthesized from **6a** and **10b** using general procedure described above to obtain 0.68 g (35%) of white solid, mp.124-125 ^oC. ^1H NMR (500 MHz, $CDCl_3$): δ6.95-7.27 (m, 10H, $H_{25,\underline{25},5,\underline{5},6,\underline{6},7,\underline{7},8,\underline{8}}$), 6.30/<u>6.95</u> (s/s, 2H, $H_{22,\underline{22}}$), 5.80-5.82/<u>5.51-5.53</u> (m/m, 2H, $H_{1,\underline{1}}$), <u>4.85-4.88</u>/4.55-4.57 (m/m, 2H, $H_{\underline{18},18}$), <u>4.82-4.83</u>/4.21-4.25 (m, 2H, $H_{\underline{3},3}$), 3.09, 3.84, 3.91, 3.95 (s/s/s/s, 12H, $(OCH_3)_2$, $(OCH_{\underline{3}})_2$), 2.45-3.43 (m, 22H, $H_{3',\underline{3'},11,\underline{11},11',\underline{11'},13,\underline{13},13',\underline{13'},16,\underline{16},16',\underline{16},19,\underline{19},19',\underline{19'},4,\underline{4},4',\underline{4'}}$), 1.62-1.81 (m, 8H, $H_{14,\underline{14},14',\underline{14'},15,\underline{15},15',\underline{15'}}$). Ratio of rotamers = 3:<u>10</u>. IR (KBr): 3493, 2961, 2924, 2805, 2794, 1673 (C=O), 1635 (C=O), 1594, 1503, 1442, 1311, 1266, 1218, 1191, 1119, 1044, 854, 771 cm^{-1}; ESI-MS: 435.2 ($[M+H]^+$, base peak). Anal. Calcd. for $C_{26}H_{30}N_2O_4 \cdot H_2O$: C 69.01, H 7.13, N 6.19, found: C 68.94, H 7.08, N 6.14.

(1*S*,18*S*)/(1*R*,18*R*) 1-(Pyrrolidin-1-ylmethyl)-2-[(6-chloro-3-oxo-indan)-formyl]-1,2,3,4–tetra-hydroisoquinoline (*maj*-3c). The title compound was synthesized from **6a** and **10c** using general procedure described above to obtain 0.70 g (38%) of white solid as main product (*maj*-**3c**), mp.120-121^{o}C. ^1H NMR (500 MHz, $CDCl_3$): δ6.98-7.70 (m, 14H, $H_{22,\underline{22},23,\underline{23},25,\underline{25},5,\underline{5},6,\underline{6},7,\underline{7},8,\underline{8}}$), 5.80-5.83/<u>5.37-5.40</u> (m/m, 2H, $H_{\underline{1},1}$), <u>4.91-4.93</u>/4.63-4.65 (m/m, 2H, $H_{\underline{18},18}$), <u>4.74-4.78</u>/4.25-4.28 (m/m, 2H, $H_{\underline{3},3}$), 3.94-4.00 (m, 1H, $H_{3'}$), 2.44-3.31 (m/m, 21H,

$H_{\underline{3'},11,\underline{11},11',\underline{11'},13,\underline{13},13',\underline{13'},16,\underline{16},16',\underline{16'},19,\underline{19},19',\underline{19'},4,\underline{4},4',\underline{4'}}$), 1.54-1.79 (m, 8H, $H_{14,\underline{14},14',\underline{14'},15,\underline{15},15',\underline{15'}}$)**.** Ratio of rotamers = 10:$\underline{7}$. IR (KBr): 3471, 3413, 2964, 2929, 2790, 1716 (C=O), 1639 (C=O), 1596, 1440, 825, 744 cm^{-1}; HRMS(ESI) m/z $[M+H]^+$ Calcd for $C_{24}H_{26}ClN_2O_2$ 409.1683 Found 409.1685 PPM error 5.0. Anal. Calcd. for $C_{24}H_{25}ClN_2O_2$: C 70.49, H 6.16, N 6.85, found: C 70.63, H 6.31, N 6.74**.**

(1*S*,18*R*)/(1*R*,18*S*) 1-(Pyrrolidin-1-ylmethyl)-2-[(6-chloro-3-oxo-indan)-formyl]-1,2,3,4–tetra -hydroisoquinoline (*min*-3c). The title compound was synthesized from **6a** and **10c** using general procedure described above to obtain 0.16 g (8%) of white solid as secondary product (*min*-**3c**), mp.134-135°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ7.13-7.71 (m, 14H, $H_{22,\underline{22},23,\underline{23},25,\underline{25},5,\underline{5},6,\underline{6},7,\underline{7},8,\underline{8}}$), 5.68-5.80/$\underline{5.13\text{-}5.15}$ (m/m, 2H, $H_{\underline{1},1}$), $\underline{4.80\text{-}4.87}$/4.52-4.59 (m/m, 2H, $H_{\underline{18},18}$), $\underline{4.72\text{-}4.80}$/4.01-4.12 (m/m, 2H, $H_{\underline{3},3}$), 3.60-3.72 (m, 1H, $H_{3'}$), 2.38-3.18 (m/m, 21H, $H_{\underline{3'},11,\underline{11},11',\underline{11'},13,\underline{13},13',\underline{13'},16,\underline{16},16',\underline{16'},19,\underline{19},19',\underline{19'},4,\underline{4},4',\underline{4'}}$), 1.67-1.88 (m, 8H, $H_{14,\underline{14},14',\underline{14'},15,\underline{15},15',\underline{15'}}$)**.** Ratio of rotamers = 7:$\underline{10}$. IR (KBr): 3376, 2950, 1714 (C=O), 1633 (C=O), 1596, 1434, 834, 768 cm^{-1}; HRMS(ESI) m/z $[M+H]^+$ Calcd for $C_{24}H_{26}ClN_2O_2$ 409.1683 Found 409.1689 PPM error 5.0.

1-(Pyrrolidin-1-ylmethyl)-2-[(6-fluoro-3-oxo-indan)-formyl]-1,2,3,4-tetrahydroisoquinoline (*maj*-3d). Compound *maj*-**3d** was synthesized from **6a** and **10d** using general procedure described above to obtain 0.67 g (38%) of white solid, mp.147-148°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ6.80~7.77(m, 14H, $H_{22,\underline{22},23,\underline{23},25,\underline{25},5,\underline{5},6,\underline{6},7,\underline{7},8,\underline{8}}$), 5.79/$\underline{5.36}$(m/m, 2H, $H_{1,\underline{1}}$), $\underline{4.93}$/4.77 (m/m, 2H, $H_{\underline{18},18}$), $\underline{4.64}$/4.24 (m/m, 2H, $H_{\underline{3},3}$), 3.94-4.00 (m, 2H, $H_{11,\underline{11}}$), 3.29-3.33/$\underline{3.22\text{-}3.26}$ (m/m, 2H, $H_{3',\underline{3'}}$), 2.44-3.20 (m, 14H, $H_{11',\underline{11'},13,\underline{13},13',\underline{13'},16,\underline{16},16',\underline{16'},19,19',4,4'}$), $\underline{2.42\text{-}2.45}$/$\underline{2.59\text{-}2.62}$ (m, 4H, $H_{\underline{19},\underline{19'},\underline{4},\underline{4'}}$), 1.54-1.79 (m, 8H, $H_{14,\underline{14},14',\underline{14'},15,\underline{15},15',\underline{15'}}$). Ratio of rotamers = 10:$\underline{9}$. IR (KBr): 3457, 3003, 2929, 2787, 1712 (C=O), 1639 (C=O), 1440, 825, 744 cm^{-1}; ESI-MS: 393.2 ($[M+H]^+$, base peak).

1-(Pyrrolidin-1-ylmethyl)-2-[(6-methoxy-3-oxo-indan)-formyl]-1,2,3,4-tetrahydroisoquinoline (*maj*-3e). Compound *maj*-**3e** was synthesized from **6a** and **10e** using general procedure described above to obtain 0.67 g (37%) of white solid, mp.143-144 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ7.73-7.75/<u>7.62-7.64</u> (d/d, J = 8.5 Hz / J = <u>8.5</u> Hz, 2H, $H_{25,\underline{25}}$), 6.35-7.25 (m, 12H, $H_{22,\underline{22},23,\underline{23},5,\underline{5},6,\underline{6},7,\underline{7},8,\underline{8}}$), 5.75-5.78/<u>5.46-5.49</u> (m/m, 2H, $H_{1,\underline{1}}$), <u>4.89-4.92</u>/4.60-4.73 (m/m, 2H, $H_{\underline{18},18}$), <u>4.80-4.84</u>/4.20-4.24 (m, 2H, $H_{\underline{3},3}$), 3.20, 3.87 (s/s, 6H, OCH_3, $OCH_{\underline{3}}$), 2.37-3.40 (m, 22H, $H_{3'\underline{3'},11,\underline{11},11',\underline{11'},13,\underline{13},13',\underline{13'},16,\underline{16},16',\underline{16'},19,19'\underline{19},\underline{19'},4,4'\underline{4},\underline{4'}}$), 1.66-1.90 (m, 8H, $H_{14,\underline{14},14',\underline{14'},15,\underline{15},15',\underline{15'}}$). Ratio of rotamers = 1:<u>2</u>. IR (KBr): 3463, 3419, 2931, 2819, 1701 (C=O), 1643 (C=O), 1596, 1433, 1286, 1244, 1087, 831, 748 cm^{-1}; ESI-MS: 405.1 ($[M+H]^+$, base peak). Anal. Calcd. for $C_{25}H_{28}N_2O_3$: C 74.23, H 6.98, N 6.93, found: C 73.73, H 7.41, N 7.35.

1-(Pyrrolidin-1-ylmethyl)-2-[(3-oxo-indan)-formyl]-7-methoxy-1,2,3,4-tetrahydroisoquinoline (*maj*-3f). Compound *maj*-**3f** was synthesized from **6b** and **10a** using general procedure described above to obtain 0.76 g (42%) of white solid, mp.135-136 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ6.73-7.77 (m, 14H, $H_{22,\underline{22},23,\underline{23},24,\underline{24},25,\underline{25},5,\underline{5},6,\underline{6},8,\underline{8}}$), 5.77-5.80/<u>5.37-5.40</u> (m/m, 2H, $H_{1,\underline{1}}$), <u>4.97-5.00</u>/4.74-4.76 (m/m, 2H, $H_{\underline{18},18}$), <u>4.77-4.78</u>/4.26-4.30 (m/m, 2H, $H_{\underline{3},3}$), 3.88-3.92 (m, 1H, $H_{3'}$), 3.78, 3.83 (s/s, 6H, OCH_3, $OCH_{\underline{3}}$), 2.65-3.90(m, 21H, $H_{\underline{3'},11,\underline{11},11',\underline{11'},13,\underline{13},13',\underline{13'},16,\underline{16},\underline{16'},16',19,\underline{19},19',\underline{19'},4,\underline{4},4',\underline{4'}}$), 1.69-1.81 (m, 8H, $H_{14,\underline{14},14',\underline{14'},15,\underline{15},15',\underline{15'}}$). Ratio of rotamers = 1:<u>1</u>. IR (KBr): 3456, 3417, 2929, 2806, 1714 (C=O), 1639 (C=O), 1610, 1502, 1442, 1249, 1153, 1037, 765, 811, 765 cm^{-1}; ESI-MS: 405.2 ($[M+H]^+$, base peak). Anal. Calcd. for $C_{25}H_{28}N_2O_3$: C 74.23, H 6.98, N 6.93, found: C 74.13, H 6.88, N 6.89.

1-(Pyrrolidin-1-ylmethyl)-2-[(5,6-dimethoxy-3-oxo-indan)-formyl]-7-methoxy-1,2,3,4-tetrahydroisoquinoline (*maj*-3g). Compound *maj*-**3g** was synthesized from **6b** and **10b** using general procedure described above to obtain 0.82 g (39%) of white solid, mp.122-124 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ6.34-7.20 (m, 10H, $H_{22,\underline{22},25,\underline{25},5,\underline{5},6,\underline{6},8,\underline{8}}$), 5.76-5.79/$\underline{5.46\text{-}5.48}$ (m/m, 2H, $H_{1,\underline{1}}$), $\underline{4.84\text{-}4.86}$/4.54-4.57 (m/m, 2H, $H_{\underline{18},18}$), $\underline{4.80\text{-}4.83}$/4.21-4.24 (m/m, 2H, $H_{\underline{3},3}$), 3.17, 3.78, 3.80, 3.85, 3.91, 3.96 (s/s/s/s/s/s, 18H, $(OCH_3)_3$, $(OCH_{\underline{3}})_3$), 2.40-3.42 (m, 22H, $H_{3',\underline{3'},11,\underline{11},11',\underline{11'},13,\underline{13},13',\underline{13'},16,\underline{16},16',\underline{16'},19,19',\underline{19},\underline{19'},4,4',\underline{4},\underline{4'}}$), 1.63-1.80 (m, 8H, $H_{14,\underline{14},14',\underline{14'},15,\underline{15},15',\underline{15'}}$). Ratio of rotamers = 4:$\underline{10}$. IR (KBr): 3460, 2960, 2794, 1701 (C=O), 1639 (C=O), 1500, 1440, 1296, 1253, 1215, 1039, 856, 819 cm^{-1}; ESI-MS: 465.5 ($[M+H]^+$, base peak). Anal. Calcd. for $C_{27}H_{32}N_2O_5 \cdot 1/2\ H_2O$): C 68.48, H 7.02, N 5.92, found: C 68.95, H 7.15, N 5.46.

1-(Pyrrolidin-1-ylmethyl)-2-[(6-chloro-3-oxo-indan)-formyl]-7-methoxy-1,2,3,4-tetrahydroisoquinoline (*maj*-3h). Compound *maj*-**3h** was synthesized from **6b** and **10c** using general procedure described above to obtain 0.79 g (40%) of white solid, mp.151-153 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ6.74-7.70 (m, 12H, $H_{22,\underline{22},23,\underline{23},25,\underline{25},5,\underline{5},6,\underline{6},8,\underline{8}}$), $\underline{5.75\text{-}5.76}$/5.31-5.32 (m/m, 2H, $H_{\underline{1},1}$), $\underline{4.89\text{-}4.90}$/4.62-4.63 (m/m, 2H, $H_{\underline{18},18}$), $\underline{4.69\text{-}4.73}$/4.21-4.24 (m/m, 2H, $H_{\underline{3},3}$), 3.91-3.95 (m, 1H, $H_{3'}$), 3.78, 3.82 (s/s, 6H, OCH_3, $OCH_{\underline{3}}$), 2.46-3.32 (m, 21H, $H_{\underline{3'},11,\underline{11},11',\underline{11'},13,\underline{13},13',\underline{13'},16,\underline{16},16',\underline{16'},19,19',\underline{19},\underline{19'},4,4',\underline{4},\underline{4'}}$), 1.64-1.77 (m, 8H, $H_{14,\underline{14},14',\underline{14'},15,\underline{15},15',\underline{15'}}$). Ratio of rotamers = 10:$\underline{7}$. IR (KBr): 3469, 3411, 2956, 2794, 1708 (C=O), 1641 (C=O), 1600, 1436, 1311, 1242, 1161, 1035, 881, 835, 806 cm^{-1}; ESI-MS: 439.2 ($[M+H]^+$, base peak). Anal. Calcd. for $C_{25}H_{27}ClN_2O_3$: C 68.41, H 6.20, N 6.38, found: C 68.08, H 6.32, N 6.11.

1-(Pyrrolidin-1-ylmethyl)-2-[(6-methoxy-3-oxo-indan)-formyl]-7-methoxy-1,2,3,4-tetrahydroisoquinoline (*maj*-3i). Compound *maj*-**3i** was synthesized from **6b** and **10e** using general procedure described above to obtain 0.66 g (34%) of white solid, mp.144-145 °C. ^{1}H NMR (500 MHz, $CDCl_3$):

δ7.71-7.73/$\underline{7.63\text{-}7.65}$ (d/d, J = 8.5 Hz / J = $\underline{8.5}$ Hz, 2H, $H_{25,\underline{25}}$), 6.36-7.14 (m, 10H, $H_{22,\underline{22},23,\underline{23},5,\underline{5},6,\underline{6},8,\underline{8}}$), 5.75-5.78/$\underline{5.43\text{-}5.45}$ (m/m, 2H, $H_{1,\underline{1}}$), $\underline{4.88\text{-}4.90}$/4.58-4.60 (m/m, 2H, $H_{\underline{18},18}$), $\underline{4.80\text{-}4.83}$/4.21-4.25 (m/m, 2H, $H_{\underline{3},3}$), 3.24, 3.78, 3.81, 3.87, (s/s/s/s/, 12H, $(OCH_3)_2$, $(OCH_{\underline{3}})_2$), 2.37-3.42 (m, 22H, $H_{3'\underline{3'},11,\underline{11},11',\underline{11'},13,\underline{13},13',\underline{13'},16,\underline{16},16',\underline{16'},19,19',\underline{19},\underline{19'},4,4'\underline{4},\underline{4'}}$), 1.60-1.80 (m, 8H, $H_{14,\underline{14},14',\underline{14'},15,\underline{15},15',\underline{15'}}$). Ratio of rotamers = 6:$\underline{10}$. IR (KBr): 3475, 3415, 2960, 2921, 2804, 1704 (C=O), 1645 (C=O), 1598, 1498, 1436, 1284, 1249, 1037, 827, 775 cm^{-1}; ESI-MS: 435.2 ($[M+H]^+$, base peak). Anal. Calcd. for $C_{26}H_{30}N_2O_4 \cdot 1/2\ H_2O$): C 70.41, H 7.04, N 6.32, found: C 70.71, H 7.04, N 6.62.

1-(Pyrrolidin-1-ylmethyl)-2-[(3-oxo-indan)-formyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (*maj*-3j). Compound *maj*-**3j** was synthesized from **6c** and **10a** using general procedure described above to obtain 0.82 g (42%) of white solid, mp.174-175 °C. ^1H NMR (500 MHz, $CDCl_3$): δ6.61-7.78 (m, 12H, $H_{22,\underline{22},23,\underline{23},24,\underline{24},25,\underline{25},5,\underline{5},8,\underline{8}}$), 5.72-5.75/$\underline{5.37\text{-}5.40}$ (m/m, 2H, $H_{1,\underline{1}}$), $\underline{4.97\text{-}4.98}$/4.75-4.76 (m/m, 2H, $H_{\underline{18},18}$), $\underline{4.78\text{-}4.82}$/4.27-4.31 (m/m, 2H, $H_{\underline{3},3}$), 3.85, 3.90 (s/s, 12H, $(OCH_3)_2$, $(OCH_{\underline{3}})_2$), 2.47-3.38 (m, 22H, $H_{3'\underline{3'},11,\underline{11},11',\underline{11'},13,\underline{13},13',\underline{13'},16,\underline{16},16',\underline{16'},19,19'\underline{19},\underline{19'},4,4',\underline{4},\underline{4'}}$), 1.65-1.78 (m, 8H, $H_{14,\underline{14},14',\underline{14'},15,\underline{15},15',\underline{15'}}$). Ratio of rotamers = 9:$\underline{10}$. IR (KBr): 3448, 3406, 2958, 2790, 1708 (C=O), 1639 (C=O), 1515, 1436, 1257, 1234, 1120, 1024, 883, 837, 775 cm^{-1}; ESI-MS: 435.5 ($[M+H]^+$, base peak). Anal. Calcd. for $C_{26}H_{30}N_2O_4$: C 71.87, H 6.96, N 6.45, found: C 72.19, H 6.87, N 6.38.

1-(Pyrrolidin-1-ylmethyl)-2-[(5,6-dimethoxy-3-oxo-indan)-formyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (*maj*-3k). Compound *maj*-**3k** was synthesized from **6c** and **10b** using general procedure described above to obtain 0.73 g (33%) of white solid, mp.125-127 °C. ^1H NMR (500 MHz, $CDCl_3$): 7.19/$\underline{7.15}$ (s/s, 2H, $H_{25,\underline{25}}$), 6.94/$\underline{6.75}$ (s/s, 2H, $H_{22,\underline{22}}$), 6.73/$\underline{6.67}$ (s/s, 2H, $H_{8,\underline{8}}$), 6.59/$\underline{6.36}$ (s/s, 2H, $H_{5,\underline{5}}$), 5.70-5.73/$\underline{5.40\text{-}5.43}$ (m/m, 2H, $H_{1,\underline{1}}$), $\underline{4.84\text{-}4.85}$/4.54-4.56 (m/m, 2H, $H_{\underline{18},18}$), $\underline{4.81\text{-}4.83}$/4.20-4.25 (m/m, 2H, $H_{\underline{3},3}$), 3.20, 3.85-3.95 (s/m, 24H, $(OCH_3)_4$, $(OCH_{\underline{3}})_4$), 2.40-3.42 (m, 22H, $H_{3'\underline{3'},11,\underline{11},11',\underline{11'},13,\underline{13},13',\underline{13'},16,\underline{16},16',\underline{16'},19,\underline{19},19'\underline{19'},4,\underline{4},4',\underline{4}}$), 1.58-1.80 (m, 8H, $H_{14,\underline{14},14',\underline{14'},15,\underline{15},15',\underline{15'}}$). Ratio of rotamers = 4:$\underline{10}$. IR (KBr): 3415, 2947, 2800, 1695 (C=O), 1633 (C=O), 1500, 1442, 1307, 1269, 1251, 1215, 1116, 1043, 864, 775 cm^{-1}; ESI-MS: 495.5 ($[M+H]^+$, base peak). Anal. Calcd. for $C_{28}H_{34}N_2O_6 \cdot H_2O$: C 65.61, H 7.08, N 5.47, found: C 65.79, H 6.86, N 5.23.

1-(Pyrrolidin-1-ylmethyl)-2-[(6-chloro-3-oxo-indan)-formyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (*maj*-3*l*). Compound *maj*-**3*l*** was synthesized from **6c** and **10c** using general procedure described above to obtain 0.74 g (35%) of white solid, mp.178-179 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ6.62-7.70 (m, 10H, $H_{22,\underline{22},23,\underline{23},25,\underline{25},5,\underline{5},8,\underline{8}}$), 5.72-5.74/$\underline{5.30\text{-}5.32}$ (m/m, 2H, $H_{1,\underline{1}}$), $\underline{4.90\text{-}4.92}$/4.64-4.66 (m/m, 2H, $H_{\underline{18},18}$), $\underline{4.73\text{-}4.77}$/4.24-4.28 (m/m, 2H, $H_{\underline{3},3}$), 3.86, 3.90 (s/s, 12H, $(OCH_3)_2$, $(OCH_{\underline{3}})_2$), 2.46-3.50 (m, 22H, $H_{3',\underline{3'},11,\underline{11},11',\underline{11'},13,\underline{13},13',\underline{13'},16,\underline{16},16',\underline{16'},19,\underline{19},19'\underline{19'},4,\underline{4},4',\underline{4}}$), 1.56-1.90(m, 8H, $H_{14,\underline{14},14',\underline{14'},15,\underline{15},15',\underline{15}}$). Ratio of rotamers = 13:$\underline{10}$. IR (KBr): 3456, 3413, 3328, 2927, 2796, 1712 (C=O), 1637 (C=O), 1591, 1517, 1438, 1313, 1261, 1238, 1118, 887, 840, 777 cm^{-1}; ESI-MS: 469.2 ($[M+H]^+$, base peak). Anal. Calcd. for $C_{26}H_{29}ClN_2O_4$: C 66.59, H 6.23, N 5.97, found: C 66.48, H 6.67, N 5.93.

1-(Pyrrolidin-1-ylmethyl)-2-[(6-methoxy-3-oxo-indan)-formyl]-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (*maj*-3m). Compound *maj*-**3m** was synthesized from **6c** and **10e** using general procedure described above to obtain 0.92 g (44%) of white solid, mp.193-195 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δδ 7.70-7.72/$\underline{7.63\text{-}7.65}$ (d/d, *J* = 8.5 Hz, *J* = $\underline{8.5}$ Hz, 2H, $H_{25,\underline{25}}$), 7.02/$\underline{6.73}$ (s/s, 2H, $H_{22,\underline{22}}$), 6.90-6.92/$\underline{6.83\text{-}6.85}$ (dd/dd, *J* = 1.8, 8.5 Hz, 2H, $H_{23,\underline{23}}$), 6.73/$\underline{6.67}$(s/s, 2H, $H_{8,\underline{8}}$), 6.60/$\underline{6.39}$(s/s, 2H,

$H_{5,\underline{5}}$), 5.70-5.80/$\underline{5.45\text{-}5.35}$ (m/m, 2H, $H_{1,\underline{1}}$), $\underline{4.87\text{-}4.90}$/4.57-4.60 (m/m, 2H, $H_{\underline{18},18}$), $\underline{4.81\text{-}4.84}$/4.22-4.26 (m/m, 2H, $H_{\underline{3},3}$), 3.28, 3.85-3.88 (s/m, 18H, $(OCH_3)_3$, $(OCH_{\underline{3}})_3$), 2.64-3.41 (m, 22H, $H_{3',\underline{3'},11,\underline{11},11',\underline{11'},13,\underline{13},13',\underline{13'},16,\underline{16},16',\underline{16'},19,\underline{19},19'\underline{19'},4,\underline{4},4',\underline{4'}}$), 1.61-1.78 (m, 8H, $H_{14,\underline{14},14',\underline{14'},15,\underline{15},15',\underline{15'}}$)**.** Ratio of rotamers = 6:$\underline{10}$. IR (KBr): 3446, 2960, 2933, 2796, 1701 (C=O), 1637 (C=O), 1596, 1515, 1442, 1282, 1253, 1114, 1022, 837, 775 cm^{-1}; ESI-MS: 465.2 ($[M+H]^+$, base peak). Anal. Calcd. for $C_{27}H_{32}N_2O_5$: C 69.81, H 6.94, N 6.03, found: C 70.04, H 6.96, N 5.90.

1-(Pyrrolidin-1-ylmethyl)-2-[(6-chloro-3-oxo-indan)-formyl]-6-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride salt (*maj*-3n). Compound *maj*-**3n** was synthesized from **6d** and **10c** using general procedure described above to obtain white solid. Treatment of the free base with HCl/EtOAc in acetone at room temperature gave the hydrochloride salt of ***maj*-3n** as white solid (35.2%), mp.244-246°C. The doubled ^{1}H NMR signals were disappeared after transferring into hydrochloride salt. ^{1}H-NMR(300MHz, DMSO-d_6), δ(ppm): 8.21~8.25(m, 1H, ArH), 7.61 (d, J = 8.1Hz, 1H, ArH), 7.50 (d, J = 8.2 Hz, 1H, ArH), 7.30 (d, J = 8.2 Hz, 1H, ArH), 6.78~6.81(m, 2H, ArH), 5.86 (d, J = 10.5 Hz, 1H, CH), 4.95~5.05(m, 1H, CH), 4.23 (d, J = 12.4 Hz, 1H, 1/2CH_2), 3.77(s, 3H, OCH_3), 3.34~3.85(m, 6H, 2×CH_2, 2×1/2CH_2), 3.17~3.19(m, 1H, 1/2CH_2), 2.82~3.19(m, 3H, 1/2CH_2, CH_2), 2.50~2.53(m, 1H, 1/2CH_2), 1.98~2.08(m, 4H, 2×CH_2). ^{13}C-NMR(75MHz, DMSO-d_6), δ(ppm): 203.2, 172.3, 158.3, 156.3, 139.0, 135.6, 135.3, 129.1, 128.6, 128.3, 124.7, 123.8, 113.6, 112.6, 55.5, 55.0, 54.7, 52.2, 47.8, 41.3, 40.5, 28.7, 23.0, 22.4. IR(KBr): 2930, 2817, 1714, 1642, 1595, 1461, 1283, 1157, 1042, 922, 836, 809 cm^{-1}; ESI-MS: 439.3($[M+H]^+$,base peak). Anal. Calcd. for $C_{25}H_{27}ClN_2O_3$: C 68.41, H 6.20, N 6.38; Found: C 68.26, H 6.39, N 6.15

1-(Pyrrolidin-1-ylmethyl)-2-[(6-fuloro-3-oxo-indan)-formyl]-6-methoxy-1,2,3,4-tetrahydrois

oquinoline hydrochloride salt (*maj*-3o). Compound *maj*-**3o** was synthesized from **6d** and **10d** using general procedure described above to obtain white solid. Treatment of the free base with HCl/EtOAc in acetone at room temperature gave the hydrochloride salt of ***maj*-3o** as white solid (37.9%), mp.238-240°C. ^{1}H-NMR(300MHz, DMSO-d_6), δ(ppm): 7.85 (d, *J* = 9.1 Hz, 1H, ArH), 7.67~7.72(dd, *J* = 5.6 Hz, 8.0 Hz, 1H, ArH), 7.29~7.34(m, 2H, ArH), 6.79~6.83(m, 2H, ArH), 5.85 (d, *J* = 9.5 Hz, 1H, CH), 4.95~5.05(m, 1H, CH), 4.24 (d, *J* = 11.9 Hz, 1H, 1/2CH_2), 3.73(s, 3H, OCH_3), 3.34~3.85(m, 6H, 2×CH_2, 2×1/2CH_2), 3.00~3.15(m, 1H, 1/2CH_2), 2.88~2.98(m, 3H, 1/2CH_2, CH_2), 2.50~2.54(m, 1H, 1/2CH_2), 1.97~2.08(m, 4H, 2×CH_2). ^{13}C-NMR(75MHz, DMSO-d_6), δ(ppm): 202.3, 172.3, 167.8, 164.1, 158.3, 157.7, 157.6, 135.7, 133.2, 128.6, 124.8, 124.7, 113.6, 112.6, 55.7, 55.1, 54.8, 52.3, 47.8, 41.2, 28.7, 23.0, 22.4. IR(KBr):2964, 1706, 1643, 1489, 1432, 1261, 1146, 1088, 965, 831, 707 cm^{-1}; HRMS(ESI): m/z $[M+H]^+$ Calcd for $C_{25}H_{28}FN_2O_3$: 423.2078; Found: 423.2081.

1-(Pyrrolidin-1-ylmethyl)-2-[(3-oxo-indan)-formyl]-5-chloro-8-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride salt (*maj*-3p). Compound *maj*-**3p** was synthesized from **6f** and **10a** using general procedure described above to obtain white solid. Treatment of the free base with HCl/EtOAc in acetone at room temperature gave the hydrochloride salt of ***maj*-3p** as white solid (32.3%), mp.268-270°C. ^{1}H-NMR(300MHz, DMSO-d_6), δ(ppm): 8.04 (d, *J* = 7.6 Hz, 1H, ArH), 7.67 (t, *J* = 7.2 Hz, 1H, ArH), 7.60 (d, *J* = 7.5 Hz, 1H, ArH), 7.40~7.49(m, 2H, ArH), 6.95 (d, *J* = 8.8 Hz, 1H, ArH), 6.00 (d, *J* = 9.9Hz, 1H, CH), 4.98 (d, *J* = 4.3 Hz, 1H, CH), 4.38 (d, *J* = 9.2 Hz, 1H, 1/2CH_2), 3.86(s, 3H, OCH_3), 3.77~3.86(m, 3H, CH_2, 1/2CH_2), 3.55~3.62(m, 1H, 1/2CH_2), 3.18~3.30(m, 2H, CH_2), 3.08~3.17(m, 2H, 2×1/2CH_2), 2.78~2.93(m, 2H, CH_2), 2.52~2.58(m, 1H, 1/2CH_2), 1.91~2.08(4H, m, 2×CH_2). ^{13}C-NMR(75MHz, DMSO-d_6), δ(ppm): 204.0, 172.6, 154.2, 154.0, 135.2, 134.2, 133.2, 129.2, 128.6, 127.8, 124.9, 122.9, 122.1, 110.0, 56.0, 54.5, 52.9, 52.4, 44.3, 41.2, 26.9, 22.9, 22.3. ESI-MS:: 439.1([M+H]$^+$,base peak). IR(KBr): 2976, 1717, 1647, 1427, 1258, 1197, 1085, 826, 784, 660 cm^{-1}; HRMS(ESI): m/z [M+H]$^+$ Calcd for $C_{25}H_{27}ClN_2O_3$: 439.1785; Found: 439.1781.

1-(Pyrrolidin-1-ylmethyl)-2-[(6-chloro-3-oxo-indan)-formyl]-5-chloro-8-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride salt (*maj*-3q). Compound *maj*-**3q** was synthesized from **6f** and **10c** using general procedure described above to obtain white solid. Treatment of the free base with HCl/EtOAc in acetone at room temperature gave the hydrochloride salt of ***maj*-3q** as white solid (34.7%), mp.282-284^{o}C. ^{1}H-NMR(300MHz, DMSO-d$_6$), δ(ppm): 8.12(s, 1H, ArH), 7.41~7.62(m, 3H, ArH), 6.96 (d, *J* = 7.8 Hz, 1H, ArH), 5.96 (d, *J* = 10.1Hz, 1H, CH), 4.98~5.00(m, 1H, CH), 4.34~4.42(m, 1H, 1/2CH_2), 3.86(s, 3H, OCH_3), 3.20~3.95(m, 6H, 2×CH_2, 2×1/2CH_2), 3.12~3.20(m, 2H, 2×1/2CH_2), 2.73~2.95(m, 2H, CH_2), 2.50~2.62(m, 1H, 1/2CH_2), 1.85~2.10(4H, m, 2×CH_2). ^{13}C-NMR(75MHz, DMSO-d$_6$), δ(ppm): 203.4, 169.8, 155.7, 154.2, 139.5, 134.8, 132.5, 128.6, 127.7, 126.1, 124.7, 124.4, 109.9, 55.8, 54.3, 53.6, 46.3, 40.7, 27.3, 24.3, 23.1. IR(KBr):2976, 1721, 1644, 1466, 1400, 1109, 1087, 838, 822, 720 cm^{-1}; HRMS(ESI): m/z [M+H]$^+$ Calcd for $C_{25}H_{27}Cl_2N_2O_3$: 473.1393; Found: 473.1400.

1-(Pyrrolidin-1-ylmethyl)-2-[(5-methyl-3-oxo-indan)-formyl]-7-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride salt (*maj*-3r). Compound *maj*-**3r** was synthesized from **6b** and **10f** using general procedure described above to obtain white solid. Treatment of the free base with HCl/EtOAc in acetone at room temperature gave the hydrochloride salt of ***maj*-3r** as white solid (42.7%), mp.232-234^{o}C. ^{1}H-NMR(300MHz, DMSO-d$_6$), δ(ppm): 7.82~7.85(m, 1H, ArH), 7.50 (d, *J* = 7.9 Hz, 1H, ArH), 7.42(s, 1H, ArH), 7.10 (d, *J* = 8.5 Hz, 1H, ArH), 7.04(s, 1H, ArH), 6.82~6.85(m, 1H, ArH), 5.85 (d, J = 10.2 Hz, 1H, CH), 4.85~4.95(m, 1H, CH), 4.24~4.38(m, 1H, 1/2CH_2), 3.74(s, 3H, OCH_3), 3.34~3.85(m, 6H, 2×CH_2, 2×1/2CH_2), 2.97~3.15(m, 2H, 2×1/2CH_2), 2.81~2.96(m, 2H, CH_2), 2.50~2.60(m, 1H, 1/2CH_2), 2.39(s, 3H, CH_3), 1.91~2.10(m, 4H, 2×CH_2). ^{13}C-NMR(75MHz, DMSO-d_6), δ(ppm): 204.1. 172.9, 157.5, 151.9, 137.4, 136.6, 135.4, 133.9, 130.1, 128.5, 125.9, 122.0, 114.0, 112.3, 55.5, 55.2, 54.5, 52.2, 48.4, 40.9, 27.7, 22.9, 22.5, 20.6. IR(KBr):2951, 1731, 1624, 1507, 1401, 1258, 1158, 1029, 833, 749, 641 cm^{-1}; HRMS(ESI): m/z $[M+H]^+$ Calcd for $C_{26}H_{31}N_2O_3$: 419.2329; Found: 419.2333.

1-(Pyrrolidin-1-ylmethyl)-2-[(6-meothoxy-3-oxo-indan)-formyl]-7-fuluro-1,2,3,4-tetrahydroisoquinoline hydrochloride salt (*maj*-3s). Compound *maj*-**3s** was synthesized from **6e** and **10e** using general procedure described above to obtain white solid. Treatment of the free base with HCl/EtOAc in acetone at room temperature gave the hydrochloride salt of ***maj*-3s** as white solid (35.1%), mp.264-266°C. ^{1}H-NMR(300MHz, DMSO-d_6), δ(ppm): 7.64~7.65(m, 1H, ArH), 7.54 (d, J = 8.5Hz, 1H, ArH), 7.35 (d, J = 9.5 Hz, 1H, ArH), 7.24~7.26(m, 1H, ArH), 7.10~7.12(m, 1H, ArH), 7.00 (d, J = 8.4 Hz, 1H, ArH), 5.96 (d, J = 9.4 Hz, 1H, CH), 4.92 (d, J = 4.7 Hz, 1H, CH), 4.34~4.46(m, 1H, 1/2CH_2), 3.85(s, 3H, OCH_3), 3.35~3.85(m, 6H, 2×CH_2, 2×1/2CH_2), 3.04~3.12(m, 2H, 2×1/2CH_2), 2.87~2.95(m, 2H, CH_2), 2.40~2.50(m, 1H, 1/2CH_2), 1.91~2.08(m, 4H, 2×CH_2). ^{13}C-NMR(75MHz, DMSO-d_6), δ(ppm): 202.0, 173.1, 164.4, 157.4, 134.8, 131.1, 130.4, 129.8, 123.9, 115.7, 114.7, 114.4, 114.2, 112.3, 55.8, 55.1, 54.7, 52.3, 48.1, 40.8, 27.9, 23.0, 22.4. IR(KBr):2976, 1721, 1644, 1466, 1400, 1109, 1087, 838, 822, 720 cm^{-1}; HRMS(ESI): m/z $[M+H]^+$ Calcd for $C_{25}H_{28}FN_2O_3$: 423.2078; Found: 423.2084.

1-(Pyrrolidin-1-ylmethyl)-2-[(3-oxo-indan)-formyl]-5-bromo-8-methoxy-1,2,3,4-tetrahydrois

oquinoline hydrochloride salt (*maj*-3t). Compound *maj*-**3t** was synthesized from **6g** and **10a** using general procedure described above to obtain white solid. Treatment of the free base with HCl/EtOAc in acetone at room temperature gave the hydrochloride salt of ***maj*-3t** as white solid (35.1%), mp.260-262^{o}C. ^{1}H-NMR(300MHz, DMSO-d_6), δ(ppm): 8.02~8.04(m, 1H, ArH), 7.67 (t, *J* = 7.4 Hz, 1H, ArH), 7.56~7.63(m, 2H, ArH), 7.44~7.49(m, 1H, ArH), 6.90(d, *J* = 8.9 Hz, 1H, ArH), 5.99 (d, *J* = 10.1 Hz, 1H, CH), 4.96~5.00(m, 1H, CH), 4.38~4.44(m, 1H, 1/2CH_2), 3.86(s, 3H, OCH_3), 3.77~3.95(m, 3H, CH_2, 1/2CH_2), 3.54~3.59(m, 1H, 1/2CH_2), 3.24~3.35(m, 2H, CH_2), 2.95~3.17(m, 2H, 2×1/2CH_2), 2.75~2.84(m, 2H, CH_2), 2.52~2.58(m, 1H, 1/2CH_2), 1.91~2.08(m, 4H, 2×CH_2). ^{13}C-NMR(75MHz, DMSO-d_6), δ(ppm): 204.1, 172.5, 154.6, 154.2, 136.4, 134.6, 134.2, 131.9, 129.2, 127.8, 123.5, 122.1, 115.2, 110.6, 56.0, 54.5, 52.9, 52.4, 44.3, 41.2, 29.7, 22.9,22.3. R(KBr):3453, 1718, 1649, 1430, 1401, 1255, 1196, 1084, 990, 815, 784 cm^{-1}; HRMS(ESI): m/z $[M+H]^+$ Calcd for $C_{25}H_{27}BrN_2O_3$: 483.1278; Found: 483.1280.

1-(Pyrrolidin-1-ylmethyl)-2-[(6-chloro-3-oxo-indan)-formyl]-6-bromo-7-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride salt (*maj*-3u). Compound *maj*-**3u** was synthesized from **6h** and **10c** using general procedure described above to obtain white solid. Treatment of the free base with HCl/EtOAc in acetone at room temperature gave the hydrochloride salt of ***maj*-3u** as white solid (28.8%), mp.246-248^{o}C. ^{1}H-NMR(300MHz, DMSO-d_6), δ(ppm): 7.76(s, 1H,ArH), 7.66 (d, *J* = 8.2 Hz, 1H,ArH), 7.54 (t, *J* = 8.2 Hz, 1H, ArH), 7.47(s, 1H, ArH), 7.19(s, 1H, ArH), 5.89 (d, *J* = 9.8 Hz, 1H, CH), 4.89~4.90(m, 1H, CH), 4.28~4.33(m, 1H, 1/2CH_2), 3.85(s, 3H, OCH_3), 3.57~3.90(m, 4H, CH_2, 2×1/2CH_2), 3.32~3.57(m, 2H, CH_2), 3.11~3.20(m, 2H, CH_2), 2.82~2.86(m, 2H, CH_2), 2.56~2.63(m, 1H, 1/2CH_2), 1.94~2.10(m, 4H, 2×CH_2).^{13}C-NMR(75MHz, DMSO-d_6), δ(ppm): 203.4, 169.6, 155.7, 139.5, 136.6, 132.7, 129.3, 128.6, 127.4, 126.1, 125.7, 124.4, 111.4, 59.0, 56.2, 54.4, 53.7, 50.8, 40.7, 27.8, 23.5, 23.2. IR(KBr):3446, 1712, 1636, 1597, 1435, 1400, 1290, 1040, 979, 825, 729 cm^{-1}; HRMS(ESI): m/z $[M+H]^+$ Calcd for $C_{25}H_{26}BrClN_2O_3$: 517.0888; Found: 517.0889.

1-(Pyrrolidin-1-ylmethyl)-2-[(6-chloro-3-oxo-indan)-formyl]-7-hydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride salt (*maj*-11a). Compound *maj*-**11a** was synthesized from *maj*-**3h** using general procedure described above to obtain white solid (38.8%), mp.194-196°C. ^{1}H-NMR(500MHz, DMSO-d_6), δ(ppm): 9.36(1H, brs, OH), 8.13(1H, s, ArH), 7.62 (d, *J* = 8.1 Hz, 1H, ArH), 7.51 (d, *J* = 8.1 Hz, 1H, ArH), 7.00(d, *J* = 8.2 Hz, 1H, ArH), 6.76(s, 1H, ArH), 6.69 (d, *J* = 8.2 Hz, 1H, ArH), 5.81 (d, *J* = 10.5 Hz, 1H, CH), 5.00 (d, *J* = 4.7 Hz, 1H, CH), 4.22~4.24(d, *J* = 10.1 Hz, 1H, 1/2CH_2), 3.34~3.82(m, 6H, 2×CH_2,2×1/2CH_2), 3.02~3.25(m, 2H, 2×1/2CH_2), 2.52~2.85(m, 3H, CH_2, 1/2CH_2), 1.93~2.07(m, 4H, 2×CH_2). ^{13}C-NMR(75MHz, DMSO-d_6), δ(ppm): 203.4, 172.9, 156.8, 156.0, 139.7, 135.8, 134.0, 130.5, 129.3, 128.9, 124.6, 124.4, 115.6, 114.4, 56.1, 55.2, 53.0, 49.0, 41.6, 28.1, 23.4, 22.9. ESI-MS: 425.2($[M+H]^+$,base peak). IR(KBr):3425, 2966, 2790, 1708, 1696, 1629, 1461, 1238, 1161, 1024, 893, 820, 730 cm^{-1}; Anal. Calcd. for $C_{24}H_{25}N_2O_3Cl$: C 67.84, H 5.93, N 6.59; Found: C 67.72, H 5.87, N6.56.

1-(Pyrrolidin-1-ylmethyl)-2-[(3-oxo-indan)-formyl]-7-hydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride salt (*maj*-11b). Compound *maj*-**11b** was synthesized from *maj*-**3f** using general procedure described above to obtain white solid (36.6%), mp.252-254°C. ^{1}H-NMR(300MHz, DMSO-d_6), δ(ppm): 9.39(s,1H, OH), 7.95 (d, *J* = 7.7 Hz, 1H, ArH), 7.61~7.71(m, 2H, ArH), 7.44 (t, *J* = 7.4 Hz, 1H, ArH), 6.98 (d, *J* = 8.3 Hz, 1H, ArH), 6.77(s, 1H, ArH), 6.69 (d, *J* = 8.3Hz, 1H, ArH), 5.83 (d, *J* = 8.9 Hz, 1H, CH), 4.98 (dd, *J* = 3.5 Hz, 8.1 Hz, 1H, CH), 4.28~4.35(m, 1H, 1/2CH_2), 3.35~3.85(m, 6H, 2×CH_2, 2×1/2CH_2), 2.95~3.15(m, 2H, 2×1/2CH_2), 2.71~2.94(m, 2H, CH_2), 2.50~2.60(m, 1H, 1/2CH_2), 1.85~2.10(m, 4H, 2×CH_2). ^{13}C-NMR(75MHz, DMSO-d_6), δ(ppm): 204.0, 172.7,155.5, 154.0, 136.4, 134.3, 133.5, 130.0, 128.4, 127.9, 124.0, 122.4, 115.1, 113.8, 55.8, 54.5, 52.9, 48.6, 41.1, 27.6, 22.8, 22.5. IR(KBr):3399, 3103, 2966, 1713, 1639, 1430, 1257, 1048, 814, 773, 673 cm^{-1}; HRMS(ESI): m/z $[M+H]^+$ Calcd for $C_{24}H_{27}N_2O_3$: 391.2016; Found: 391.2023.

1-(Pyrrolidin-1-ylmethyl)-2-[(3-oxo-indan)-formyl]-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride salt (*maj*-11c). Compound *maj*-**11c** was synthesized from *maj*-**3j** using general procedure described above to obtain white solid (28.1%), mp.248-250^{o}C. ^{1}H-NMR(300MHz, DMSO-d_6), δ(ppm): 9.15(brs, 1H, OH), 8.70(brs, 1H, OH), 7.63~7.78(m, 3H, ArH), 7.45~7.50(m, 1H, ArH), 6.69(s, 1H, ArH), 6.56(s, 1H, ArH), 5.68(d, *J* = 9.0 Hz, 1H, CH), 4.92(d, *J* = 4.0Hz, 1H,CH), 4.28 (d, *J* = 10.5 Hz, 1H, 1/2CH_2), 3.61~3.78(m, 2H, 2×1/2CH_2), 3.06~3.50(m, 4H, 2×CH_2), 2.88~3.15(m, 2H, 2×1/2CH_2), 2.65~2.85(m, 2H, CH_2), 2.50~2.60(m, 1H, 1/2CH_2), 1.75~2.09(m, 4H, 2×CH_2).^{13}C-NMR(75MHz, DMSO-d_6), δ(ppm): 204.3, 172.4, 154.1, 144.9, 143.9, 136.4, 134.5, 126.7, 125.0, 124.5, 123.0, 122.6, 115.5, 114.3, 56.5, 54.5, 53.8, 48.6, 40.1, 27.9, 23.3, 22.7. IR(KBr):3362, 2962, 1708, 1631, 1433, 1262, 1110, 872, 765, 617 cm^{-1}; HRMS(ESI) m/z $[M+H]^+$ Calcd for $C_{24}H_{27}N_2O_4$: 407.1965; Found: 407.1967.

1-(Pyrrolidin-1-ylmethyl)-2-[(3-oxo-indan)-formyl]-5-chloro-8-hydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride salt (*maj*-11d). Compound *maj*-**11d** was synthesized from *maj*-**3p** using general procedure described above to obtain white solid (31.7%), mp.260-262^{o}C. ^{1}H-NMR(300MHz, DMSO-d_6), δ(ppm): 7.99(d, *J* = 7.6 Hz, 1H,ArH). 7.61~7.72(m, 2H, ArH), 7.44(t, *J* = 7.3 Hz, 1H, ArH), 7.22(d, *J* = 8.6Hz, 1H, ArH), 6.82(d, *J* = 8.6 Hz, 1H, ArH), 5.97(d, *J* = 9.8 Hz, 1H, CH), 4.98~5.00(m, 1H, CH), 4.38(d, *J* = 9.1 Hz, 1H, 1/2CH_2), 3.72~3.90(m, 3H, CH_2, 1/2CH_2), 3.54~3.62(m, 1H, 1/2CH_2), 3.18~3.30(m, 2H, CH_2), 2.95~3.17(m, 2H, 2×1/2CH_2), 2.68~2.99(m, 2H, CH_2), 2.52~2.58(m, 1H, 1/2CH_2), 1.85~2.10(m, 4H, 2×CH_2). ^{13}C-NMR(75MHz, DMSO-d_6), δ(ppm): 204.0, 172.5, 154.0, 152.4, 136.4, 134.2, 133.0, 128.8, 128.5, 127.8, 123.1, 122.2, 121.7, 114.0, 54.6, 52.9, 44.6, 41.1, 26.9, 22.8, 22.3. IR(KBr):3104, 2955, 2681, 1715, 1644, 1476, 1288, 1198, 1042, 823, 768, 717 cm^{-1};. HRMS(ESI): m/z $[M+H]^+$ Calcd for $C_{24}H_{26}ClN_2O_3$: 425.1626; Found: 425.1635.

1-(Pyrrolidin-1-ylmethyl)-2-[(6-chloro-3-oxo-indan)-formyl]-5-chloro-8-hydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride salt (*maj*-11e). Compound *maj*-**11e** was synthesized from *maj*-**3q** using general procedure described above to obtain white solid (24.7%), mp.198-200^{o}C. ^{1}H-NMR(300MHz, DMSO-d_6), δ(ppm): 8.13(s, 1H, ArH), 7.62(d, *J* = 8.1Hz, 1H, ArH), 7.51(d, *J* = 8.1 Hz, 1H, ArH), 7.22(d, *J* = 8.6Hz, 1H, ArH), 6.80(d, *J* = 8.6 Hz, 1H, ArH), 5.97(d, *J* = 10.1 Hz, 1H, CH), 4.95~5.05(m, 1H, CH), 4.26~4.42(m, 1H, 1/2CH_2), 3.72~3.95(m, 3H, CH_2, 1/2CH_2), 3.51~3.62(m, 1H, 1/2CH_2), 3.18~3.30(m, 2H, CH_2), 2.95~3.17(m, 2H, 2×1/2CH_2), 2.69~2.95(m, 2H, CH_2), 2.48~2.53(m, 1H, 1/2CH_2), 1.85~2.15(m, 4H, 2×CH_2). ^{13}C-NMR(75MHz, DMSO-d_6), δ(ppm): 204.1, 172.5, 154.2, 152.4, 136.4, 134.2, 133.0, 129.0, 128.4, 127.8, 123.1, 122.7, 121.7, 114.1, 59.7, 54.5, 52.8, 52.6, 44.5, 41.1, 26.9, 22.5, 22.3. IR(KBr):3421, 2957, 1713, 1642, 1599, 1439, 1199, 1069, 1042, 823, 658 cm^{-1}; HRMS(ESI): m/z $[M+H]^+$ Calcd for $C_{24}H_{25}Cl_2N_2O_3$: 459.1237; Found: 459.1247.

1-(Pyrrolidin-1-ylmethyl)-2-[(3-oxo-indan)-formyl]-5-bromo-8-hydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride salt (*maj*-11f). Compound *maj*-**11f** was synthesized from *maj*-**3t** using general procedure described above to obtain white solid (34.2%), mp.276-278^{o}C. ^{1}H-NMR(300MHz, DMSO-d_6), δ(ppm): 9.62(brs, 1H, OH). 7.63~7.79(m, 3H, ArH), 7.46~7.51(m, 1H, ArH), 7.39 (d, *J* = 8.6 Hz, 1H, ArH), 6.74(d, *J* = 8.6Hz, 1H, ArH), 5.95(d, *J* = 9.6 Hz, 1H, CH), 4.90~4.92(m, 1H, CH), 4.42~4.45(m, 1H, 1/2CH_2), 3.72~3.90(m, 3H, CH_2, 1/2CH_2), 3.50~3.54(m, 1H, 1/2CH_2), 3.32~3.37(m, 1H, CH_2), 2.95~3.17(m, 3H, 1/2CH_2, CH_2), 2.75~2.88(m, 2H, CH_2), 2.52~2.58(m, 1H, 1/2CH_2), 1.91~2.08(4H, m, 2×CH_2). ^{13}C-NMR(75MHz, DMSO-d_6), δ(ppm): 204.0, 172.5, 153.7, 153.0, 136.4, 134.5, 134.4, 131.7, 128.5, 128.0, 122.4, 122.0, 114.7, 113.2, 54.5, 53.3, 44.9, 40.9, 40.6, 38.1, 29.6, 22.5, 22.3. IR(KBr):3420, 2958, 2705, 1705, 1638, 1435, 1286, 1198, 1041, 817, 766 cm^{-1}; HRMS(ESI): m/z $[M+H]^+$ Calcd for $C_{24}H_{26}BrN_2O_3$: 469.1121; Found: 469.1127.

1-(Pyrrolidin-1-ylmethyl)-2-[(5-methyl-3-oxo-indan)-formyl]-7-hydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride salt (*maj*-11g). Compound *maj*-**11g** was synthesized from *maj*-**3r** using general procedure described above to obtain white solid (48.0%), mp.238-240°C. ^{1}H-NMR(300MHz, DMSO-d_6), δ(ppm): 9.35(brs, 1H, OH), 7.67 (d, *J* = 7.9Hz, 1H, ArH), 7.51(d, *J* = 8.0Hz, 1H, ArH), 7.44(s, 1H, ArH), 6.99(d, *J* = 8.3Hz, 1H,ArH), 6.76(s, 1H, ArH), 6.69(d, *J* = 7.8Hz, 1H, ArH), 5.82(d, *J* = 9.5Hz, 1H, CH), 4.88~4.89(m, 1H, CH), 4.31(d, *J* = 11.9Hz, 1H, 1/2CH_2), 3.34~3.90(m, 6H, 2×CH_2, 2×1/2CH_2), 3.00~3.15(m, 2H, 2×1/2CH_2), 2.73~2.94(m, 2H, CH_2), 2.50~2.60(m, 1H, 1/2CH_2), 2.39(s, 3H, CH_3), 1.85~2.10(m, 4H, 2×CH_2).^{13}C-NMR(75MHz, DMSO-d_6), δ(ppm): 204.0, 172.9, 155.5, 151.4, 137.5, 136.6, 135.5, 133.5, 130.0, 128.0, 124.1, 122.2, 115.1, 113.8, 55.8, 54.4, 53.0, 48.6,41.0, 27.6, 22.7, 22.4, 20.5. IR(KBr):3411, 2959, 2694, 1709, 1639, 1430, 1257, 1114, 1042, 817, 737 cm^{-1}; HRMS(ESI) m/z $[M+H]^+$ Calcd for $C_{25}H_{28}N_2O_3$: 405.2173; Found: 405.2181.

1-(Pyrrolidin-1-ylmethyl)-2-[(6-hydroxy-3-oxo-indan)-formyl]-7-fuluro-1,2,3,4-tetrahydroisoquinoline hydrochloride salt (*maj*-11h). Compound *maj*-**11h** was synthesized from *maj*-**3s** using general procedure described above to obtain white solid (38.9%), mp.218-220^{o}C. ^{1}H-NMR(300MHz, DMSO-d_6), δ(ppm): 9.73(brs, 1H, OH), 7.47(d, *J* = 8.4Hz, 1H, ArH), 7.35(dd, *J* = 2.3Hz, 9.9Hz, 1H, ArH), 7.25~7.27(m, 1H, ArH), 7.11~7.15(m, 2H, ArH), 6.86(dd, *J* = 1.7Hz, 8.4Hz, 1H, ArH), 5.96(d, *J* = 9.4Hz, 1H, CH), 4.82(d, *J* = 4.3Hz, 1H, CH), 4.28~4.30(m, 1H, 1/2CH_2), 3.30~3.83(m, 6H, 2×CH_2, 2×1/2CH_2), 2.88~3.16(m, 4H, 2×1/2CH_2, CH_2), 2.50~2.55(m, 1H, 1/2CH_2), 1.95~2.08(m, 4H, 2×CH_2). ^{13}C-NMR(75MHz, DMSO-d_6), δ(ppm): 201.5, 172.8, 163.3, 156.8, 134.7, 131.1, 130.3, 128.5, 124.3, 116.4, 114.7, 114.4, 114.2, 113.8, 55.4, 54.6, 52.9, 48.2, 40.9, 27.7, 22.8, 22.5. ESI-MS: 409.2($[M+H]^+$,base peak). IR(KBr):3357, 2956, 2682, 1703, 1623, 1584, 1439, 1237, 1095, 826, 737, 643 cm^{-1}; HRMS(ESI) m/z $[M+H]^+$ Calcd for $C_{24}H_{26}FN_2O_3$: 409.1922; Found: 409.1928.

1-(Pyrrolidin-1-ylmethyl)-2-[(6-chloro-3-oxo-indan)-formyl]-6-bromo-7-hydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride salt (*maj*-11i). Compound *maj*-**11i** was synthesized from *maj*-**3u** using general procedure described above to obtain white solid (28.2%), mp.256-258^{o}C. ^{1}H-NMR(300MHz, DMSO-d_6), δ(ppm): 10.14(brs, 1H, OH), 8.01(s, 1H, ArH), 7.63(d, *J* = 6.6Hz, 1H, ArH), 7.52(d, *J* = 6.6Hz, 1H, ArH), 7.37(s, 1H, ArH), 6.92(s, 1H, ArH), 5.82(d, *J* = 8.9Hz, 1H, CH), 4.99~5.00(m, 1H, CH), 4.24~4.28(m, 1H, 1/2CH_2), 3.32~3.90(m, 6H, 2×CH_2, 2×1/2CH_2), 3.01~3.17(m, 2H, CH_2), 2.82~2.88(m, 2H, CH_2), 2.52~2.58(m, 1H, 1/2CH_2), 1.91~2.08(m, 4H, 2×CH_2). ^{13}C-NMR(75MHz, DMSO-d_6), δ(ppm): 202.7, 172.5, 156.0, 152.1, 139.1, 135.3, 133.1, 132.9, 128.4, 126.4, 123.9, 115.0, 109.2, 55.3, 54.6, 52.8, 48.1, 41.1, 27.2, 22.8, 22.3. IR(KBr):3398, 2956, 1705, 1642, 1598, 1432, 1293, 1199, 1069, 823, 760 IR(KBr):3411, 2959, 2694, 1709, 1639, 1430, 1257, 1114, 1042, 817, 737 cm^{-1}; HRMS(ESI): m/z $[M+H]^+$ Calcd for $C_{24}H_{25}BrClN_2O_3$: 503.0732; Found: 503.0720.

(1*S*,18*S*)-1-(pyrrolidin-1-ylmethyl)-2-[(6-chloro-3-oxo-indan)-formyl]-1,2,3,4-tetrahydroisoquinoline ((1*S*,18*S*)-3c) Mesylate. According to the method A or B described above, the title compound was obtained as a white solid free base: $[\alpha]^{20}_{D}$ = -38.3 (c = 1, MeOH), mp.120-122 °C, chiral HPLC 100 % (t_R = 3.523 min). ^{1}H NMR (500 MHz, CD_3OD): δ 7.71 (s, 1H, H_{25}), 7.62-7.67 (d/d, *J* = 8.2 Hz / *J* = $\underline{8.2}$ Hz, 2H, $H_{22,\underline{22}}$), 7.16-7.48 (m, 10H, $H_{23,\underline{23},5,\underline{5},6,\underline{6},7,\underline{7},8,\underline{8}}$), $\underline{6.95}$ (s, 1H, $H_{\underline{25}}$), 5.76-5.79/$\underline{5.66\text{-}5.68}$ (dd/dd, *J* = 8.6, 4.2 Hz / *J* = $\underline{7.1}$, $\underline{3.4}$ Hz, 2H, $H_{1,\underline{1}}$), $\underline{5.09}$/4.91 (s/s, 2H, $H_{\underline{18},18}$), $\underline{4.55\text{-}4.59}$/4.39-4.43 (m/dd, *J* = 13.9, 4.7 Hz, 2H, $H_{\underline{3},3}$), $\underline{4.05\text{-}4.11}$/3.88-3.94 (m, 2H, $H_{\underline{11},11}$), 2.59-3.30 (m, 20H, $H_{3',\underline{3'},11',\underline{11'},13,\underline{13},13',\underline{13'},16,\underline{16},16',\underline{16'},19,\underline{19},19',\underline{19'},4,\underline{4},4',\underline{4'}}$), 1.69-1.83 (m, 8H, $H_{14,\underline{14},14',\underline{14'},15,\underline{15},15',\underline{15'}}$). Ratio of rotamers = 10:$\underline{4}$. Anal. Calcd. for $C_{24}H_{25}ClN_2O_2$: C 70.49, H 6.16, N 6.85, found: C 70.07, H 6.50, N 6.89. Treatment of the free base with 1:1 equiv of methanesulfonic acid in acetone at room temperature gave the CH_3SO_3H salt of (1*S*,18*S*)-**3c** as white solid (81%), mp.220-222 °C.

(1*R*,18*R*)-1-(pyrrolidin-1-ylmethyl)-2-[(6-chloro-3-oxo-indan)-formyl]-1,2,3,4-tetrahydroisoquinoline ((1*R*,18*R*)-3c) Mesylate. According to the method A or B described above, the title compound was obtained as a white solid free base: $[\alpha]^{20}_{D}$ = +35.9 (c = 1, MeOH), mp.120-122 °C, chiral HPLC 95.2 % (t_R = 4.764 min). ^{1}H NMR (500 MHz, CD_3OD): δ 7.72 (s, 1H, H_{25}), 7.60-7.66 (d/d, *J* = 8.2 Hz / *J* = $\underline{8.2}$ Hz, 2H, $H_{22,\underline{22}}$), 7.15-7.46 (m, 10H, $H_{23,\underline{23},5,\underline{5},6,\underline{6},7,\underline{7},8,\underline{8}}$), $\underline{6.94}$ (s, 1H, $H_{\underline{25}}$), 5.77-5.80/$\underline{5.66\text{-}5.69}$ (dd/dd, *J* = 10.2, 4.3 Hz / *J* = $\underline{9.9}$, $\underline{3.5}$ Hz, 2H, $H_{1,\underline{1}}$), $\underline{5.08}$/4.88 (s/s, 2H, $H_{\underline{18},18}$), $\underline{4.54\text{-}4.58}$/4.37-4.40 (m/dd, *J* = 13.9, 4.7 Hz, 2H, $H_{\underline{3},3}$), $\underline{4.03\text{-}4.11}$/3.87-3.92 (m, 2H, $H_{\underline{11},11}$), 2.62-3.29 (m/m, 20H, $H_{3',\underline{3'},11',\underline{11'},13,\underline{13},13',\underline{13'},16,\underline{16},16',\underline{16'},19,\underline{19},19',\underline{19'},4,\underline{4},4',\underline{4'}}$), 1.73-1.82 (m, 8H, $H_{14,\underline{14},14',\underline{14'},15,\underline{15},15',\underline{15'}}$). Ratio of rotamers = 10:$\underline{4}$. Anal. Calcd. for $C_{24}H_{25}ClN_2O_2$: C 70.49, H 6.16, N 6.85, found: C 70.29, H 6.49, N 6.75. The CH_3SO_3H salt of (1*R*,18*R*)-**3c** was similarly prepared as a white solid (80%), mp.220-222 ^{o}C.

(1*S*,18*R*)-1-(pyrrolidin-1-ylmethyl)-2-[(6-chloro-3-oxo-indan)-formyl]-1,2,3,4-tetrahydroisoquinoline ((1*S*,18*R*)-3c) Mesylate. According to the method A or B described above, the title compound was obtained as a white solid free base: $[\alpha]^{20}_{D}$ = -52.3 (c = 1, MeOH), mp. 132-135 ^{o}C, chiral HPLC 100 % (t_R = 4.132 min). ^{1}H NMR (500 MHz, CD_3OD): δ $\underline{7.79}$ (s, 1H, $H_{\underline{25}}$), 7.68-7.70 (d/d, *J* = 4.0 Hz / *J* = $\underline{4.0}$ Hz, 2H, $H_{22,\underline{22}}$), 7.45-7.50 (m, 3H, $H_{25,23,\underline{23}}$), 7.16-7.25 (m, 8H, $H_{5,\underline{5},6,\underline{6},7,\underline{7},8,\underline{8}}$), 5.70-5.73/$\underline{5.39\text{-}5.41}$ (dd/d, *J* = 9.7, 4.6 Hz / *J* = $\underline{10.1}$ Hz, 2H, $H_{1,\underline{1}}$), $\underline{5.00}$/4.84 (s/s, 2H, $H_{\underline{18},18}$), $\underline{4.60\text{-}4.64}$/4.26-4.29 (dd/dd, *J* = $\underline{13.1}$, $\underline{5.1}$ Hz / *J* = 13.9, 3.4 Hz, 2H, $H_{\underline{3},3}$), $\underline{4.06\text{-}4.12}$/3.78-3.84 (m, 2H, $H_{\underline{11},11}$), 2.52-3.30 (m/m, 20H, $H_{3',\underline{3'},11',\underline{11'},13,\underline{13},13',\underline{13'},16,\underline{16},16',\underline{16'},19,\underline{19},19',\underline{19'},4,\underline{4},4',\underline{4'}}$), 1.71-1.92 (m, 8H, $H_{14,\underline{14},14',\underline{14'},15,\underline{15},15',\underline{15'}}$). Ratio of rotamers = 10:$\underline{8}$. The CH_3SO_3H salt of (1*S*,18*R*)-**3c** was similarly prepared as a white solid (77%), mp. 194-196 ^{o}C.

(1*R*,18*S*)-1-(pyrrolidin-1-ylmethyl)-2-[(6-chloro-3-oxo-indan)-formyl]-1,2,3,4-tetrahydroisoquinoline ((1*R*,18*S*)-3c) Mesylate. According to the method A or B described above, the title compound was obtained as a white solid free base: $[\alpha]^{20}_{D}$ = +54.3 (c = 1, MeOH), mp. 132-135 ^{o}C, chiral HPLC 100 % (t_R = 6.326 min). ^{1}H NMR (500 MHz, CD_3OD): δ $\underline{7.78}$ (s, 1H, $H_{\underline{25}}$), 7.64-7.66 (d/d, *J* = 3.3 Hz / *J* = $\underline{2.7}$ Hz, 2H, $H_{22,\underline{22}}$), 7.42-7.46 (m, 3H, $H_{25,23,\underline{23}}$), 7.14-7.24 (m, 8H, $H_{5,\underline{5},6,\underline{6},7,\underline{7},8,\underline{8}}$), 5.69-5.72/$\underline{5.38\text{-}5.40}$ (dd/d, *J* = 9.7, 4.6 Hz / *J* = $\underline{10.1}$ Hz, 2H, $H_{1,\underline{1}}$), $\underline{4.98}$/4.80 (s/s, 2H, $H_{\underline{18},18}$), $\underline{4.58\text{-}4.62}$/4.24-4.27 (dd/m, *J* = $\underline{13.3}$, $\underline{5.0}$ Hz, 2H, $H_{\underline{3},3}$), $\underline{4.05\text{-}4.11}$/3.75-3.81 (m, 2H, $H_{\underline{11},11}$), 2.51-3.30 (m/m, 20H, $H_{3',\underline{3'},11',\underline{11'},13,\underline{13},13',\underline{13'},16,\underline{16},16',\underline{16'},19,\underline{19},19',\underline{19'},4,\underline{4},4',\underline{4'}}$), 1.69-1.91 (m, 8H, $H_{14,\underline{14},14',\underline{14'},15,\underline{15},15',\underline{15'}}$). Ratio of rotamers = 10:$\underline{8}$. The CH_3SO_3H salt of (1*R*,18*S*)-**3c** was similarly prepared as a white solid (75%), mp. 194-196 ^{o}C.

Receptor binding assays Radioligand binding assay were carried out with [^{3}H]diprenorphine for opioid receptors. Saturation assays were conducted using 0.5 nM [^{3}H]diprenorphine, correspondingly 1 μM Naloxone (Sigma) was used in addition to define nonspecific binding. Incubations were performed in triple at 30 ℃ for 30 min with varying concentrations of test drug in 50 mM Tris–HCl buffer (pH 7.4) in the presence of [^{3}H]diprenorphine at a final volume of 100 μl with 20 μg of membrane protein. Incubation was terminated by cooling in an ice bath, rapid filtrated under vacuum pressure through Whatman GF/B filters and washed. Radioactivity on filters was determined by liquid scintillation counting (Beckman LS6500). The in vivo studies were performed as described previously.[20]

Mouse hot plate (MHP) tests Animals: Kunming strain male mice (about 20 g) were obtained from the Laboratory Animal Center, Chinese Academy of Sciences (Shanghai, China). Mice were housed in groups and maintained a 12 h light/dark cycle (lights-on at 8:00a.m.) in temperature controlled environment with free access to food and water. 10 to 15 mice were used per treatment group. All animal treatments were strictly in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Hot plate tests were used at temperature 55 ℃. Mice were placed on the heated smooth surface, and the latency to licking, shaking of the limbs or jumping was measured. Prior to drug administration, the nociceptive response of each mouse was measured three times. The first measurement was omitted and the mean of the 2nd and 3rd responses was used as pre-drug latency for each mouse. The cut-off time of 60 s for the temperature 55 ℃ hot plate test was used in the tests to minimize tissue damage.

Acetic acid writhing (AAW) assays Abdominal constriction was induced by the injection of 0.6% of acetic acid (10 ml·kg^{-1} body weight, i.p.). An abdominal constriction was defined as a wave of contraction of the abdominal musculature followed by extension of the hind limbs. Acetic acid solution was injected i.p. 15 min after the administration of the opioid drug being studied and the number of abdominal constriction was counted for 15 min after acetic acid administration. Percent analgesia was expressed as: 100×(No. of mean control abdominal constriction−No. of test abdominal constriction) /No. of mean control abdominal constriction. In all experiments with mice, compounds were given s.c. route before acetic acid administration.

Physical dependence assay Animals: Kunming strain male mice (about 20 g) were obtained from the Laboratory Animal Center, Chinese Academy of Sciences (Shanghai, China). Mice were treated with progressively increasing doses of either morphine (from 20 to 100 mg·kg^{-1}, s.c., over a period of 5 days, and remained a dose of 100 mg·kg^{-1} for 5 days) or *maj*-**3c** (from 50 to 300 μg·kg^{-1}, s.c., over a period of 5 days, and remained a dose of 300 μg·kg^{-1} for 5 days). Withdrawal jumping was precipitated by subcutaneous injection of naloxone (3.0 mg·kg^{-1}). 20 min after naloxone challenge, mice were immediately placed on a circular platform (30 cm diameter and 70 cm height). The jumping frequency of each mouse and the number of mice that jump in each group within 30 min were recorded (The positive jumping response was defined as jumping more than 4 times in 30 min). Body weight was measured initially and 30, 60 min after the naloxone injection either.

The Mouse Rotated Test Animals: Kunming strain male mice (about 20 g) were obtained from the Laboratory Animal Center, Chinese Academy of Sciences (Shanghai, China). Sedation was measured by the latency of a mouse to completely step off a slightly raised platform. Prior to treatment, mice were tested once for baseline latencies. Mice with baseline latencies >60s were not used. Mice were injected s.c. with U50,488H, *maj*-**3c** and *maj*-**11a**, 20 min later tested for the latency to step off the platform.

Plus Maze Test Animals: Kunming strain male mice (about 20 g) were obtained from the Laboratory Animal Center, Chinese Academy of Sciences (Shanghai, China). Male mice were injected s.c with different doses of *maj*-**3c** and *maj*-**11a**. Fifteen minutes later, mice were put into the elevated plus maze. The time that the mice spent in the open arm and closed arm is measured in 5 min. The percentage of closed arm time/total time indicates the anxious action.

Acute toxicity test Animals: ICR strain male and female mice (about 18~22 g) were obtained from the Laboratory Animal Center, China pharmaceutical university (Nanjing, China). Mice were housed in groups and maintained a 12h light/dark cycle (lights-on at 8:00a.m.) in temperature controlled environment with free access to food and water. Animals were fasted 12 h prior to dosing. The animals were randomly divided into five groups each containing ten mice, which were treated with *maj*-**11a** at a dose of 21.7 $mg{\cdot}kg^{-1}$、25.5 $mg{\cdot}kg^{-1}$、30 $mg{\cdot}kg^{-1}$、35.3 $mg{\cdot}kg^{-1}$ and 41.5$mg{\cdot}kg^{-1}$ (s.c). After the administration, animals were observed individually daily for a total of 7 days with the purpose of recording any symptoms of ill-health, behavioural changes or death. Data were calculated using Bliss method. $P< 0.05$ was considered as the level statistical significance.

Pharmacokinetic studies in rats Animals: SD male mice (about 200~300 g) were obtained from the Laboratory Animal Center. All the rats were acclimatized in an environmentally controlled breeding room for at least 3 days before experiments with free access to standard laboratory food and water. *maj*-**11a** was administered via a single p.o. administration to rats at the dose of 2.5 $mg{\cdot}kg^{-1}$. Blood samples were collected from retinal venous plexus before and after 5, 15, and 30 min, and 1, 2, 3, 4, 6, 8, 12, and 24 h of dosing, plasma samples were prepared and stored at −70 ◦C until analysis. The samples were analyzed on a LC–MS/MS system that consisted a Shimadzu LC system (Shimadzu Corporation, Kyoto, Japan) coupled to an API 4000 mass spectrometer (ABSCIEX, Concord, ON). An aliquot 0.5μl of sample was injected into an Synergi, 4 μm Hydro-RP (72 mm×2.0 mm) column for separation with a flow rate at 600 μl/min at 40 ◦C. The LC linear gradient was increased from 25% B to 75% B in 0.8 min (A, water with 0.1% formic acid; B, Acetonitrile with 0.1% formic acid), hold at 45% B for 1 min, and then restored to 25% B over 2 min. The resolved results were analyzed on the API 4000 with an ESI probe (ABSCIEX). The peak area ratio of *maj*-**11a** to the warfarin and quetiapine was used for the quantification of *maj*-**11a** in plasma samples.

The studies of peripheral antinociceptive effects of *maj*-11a The peripheral antinociceptive effects of *maj*-11a were measured according to the method described previously[21]. *maj*-**11a** (0.8 mg/kg, 1.6 mg/kg; 20 μl/paw) was injected subcutaneously (s.c.) into the plantar surface of the right hind paw (ipsilateral) 15 min before local injection of 1% formalin. To determine whether the effect was via a local, peripheral mechanism of action, 1.6 mg/kg *maj*-**11a** was administered s.c. into the plantar surface of the left hind paw (contralateral).

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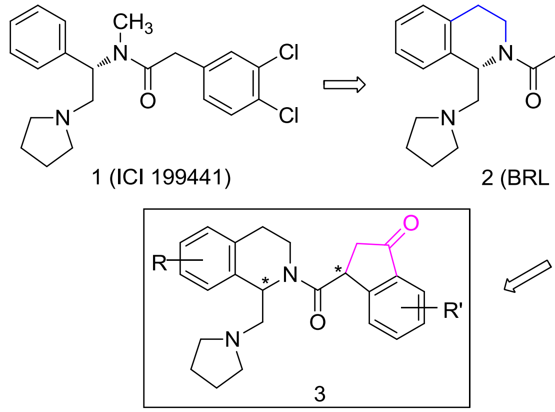
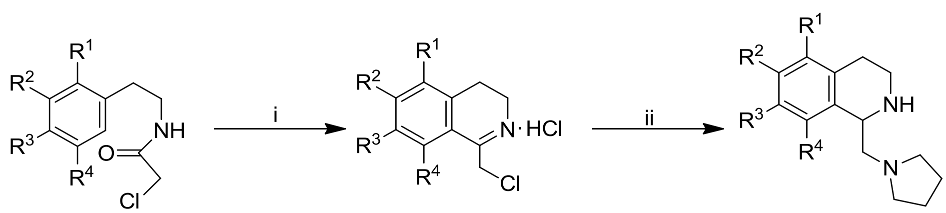
Figure 1. Structural design of 1-(Pyrrolidin-1-ylmethyl)-2-[(3-oxo-indan)-formyl]-1,2,3,4-tetrahydroisoquinoline selective κ opioid receptor agonists



Scheme 1. Synthesis of intermediate diamines 6a-h [a]



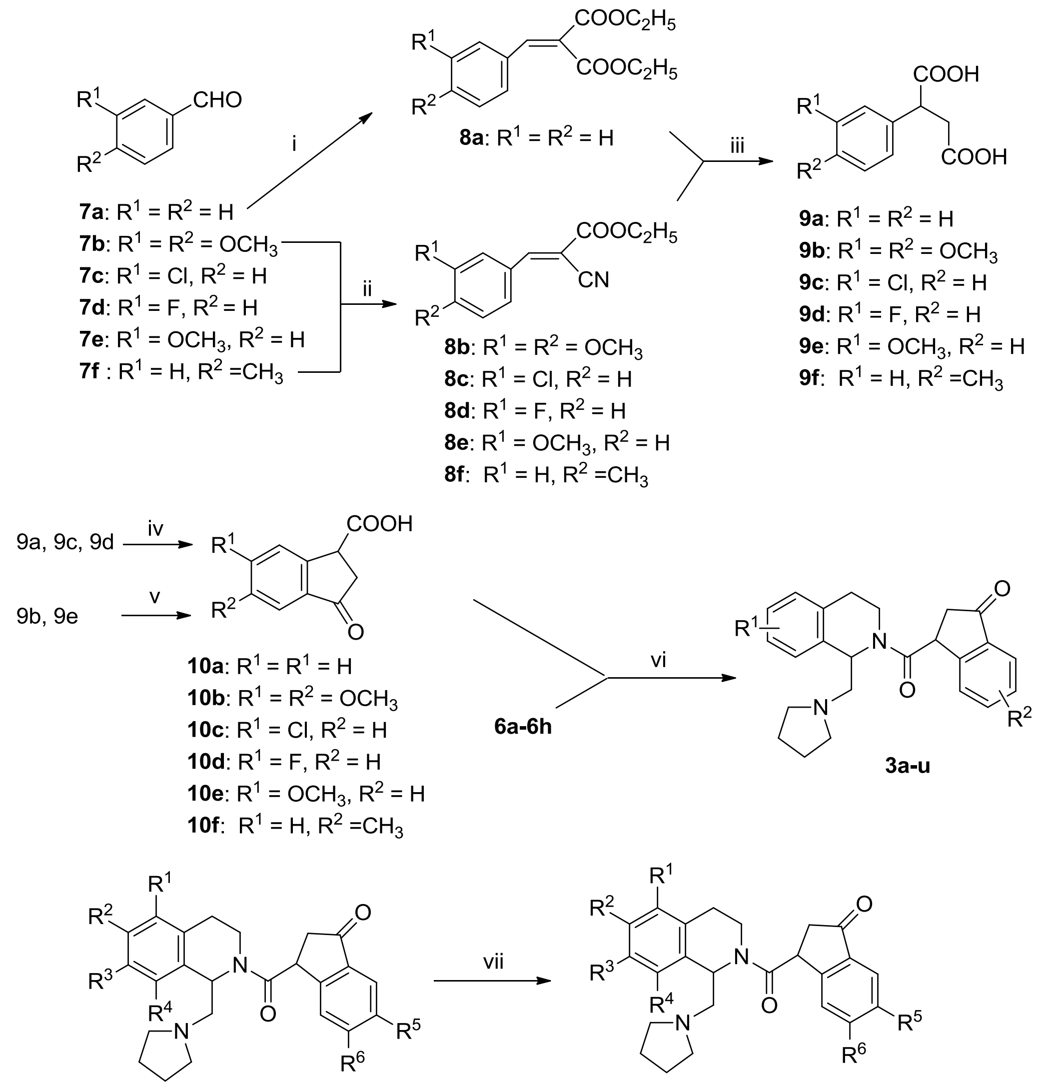
4a: $R^1 = R^2 = R^3 = R^4 = H$
4b: $R^1 = R^2 = R^4 = H$, $R^3 = OCH_3$
4c: $R^1 = R^4 = H$, $R^2 = R^3 = OCH_3$
4d: $R^1 = R^3 = R^4 = H$, $R^2 = OCH_3$
4e: $R^1 = R^2 = R^4 = H$, $R^3 = F$
4f: $R^1 = Cl$, $R^2 = R^3 = H$, $R^4 = OCH_3$
4g: $R^1 = Br$, $R^2 = R^3 = H$, $R^4 = OCH_3$
4h: $R^1 = R^4 = H$, $R^2 = Br$, $R^3 = OCH_3$

5a: $R^1 = R^2 = R^3 = R^4 = H$
5b: $R^1 = R^2 = R^4 = H$, $R^3 = OCH_3$
5c: $R^1 = R^4 = H$, $R^2 = R^3 = OCH_3$
5d: $R^1 = R^3 = R^4 = H$, $R^2 = OCH_3$
5e: $R^1 = R^2 = R^4 = H$, $R^3 = F$
5f: $R^1 = Cl$, $R^2 = R^3 = H$, $R^4 = OCH_3$
5g: $R^1 = Br$, $R^2 = R^3 = H$, $R^4 = OCH_3$
5h: $R^1 = R^4 = H$, $R^2 = Br$, $R^3 = OCH_3$

6a: $R^1 = R^2 = R^3 = R^4 = H$
6b: $R^1 = R^2 = R^4 = H$, $R^3 = OCH_3$
6c: $R^1 = R^4 = H$, $R^2 = R^3 = OCH_3$
6d: $R^1 = R^3 = R^4 = H$, $R^2 = OCH_3$
6e: $R^1 = R^2 = R^4 = H$, $R^3 = F$
6f: $R^1 = Cl$, $R^2 = R^3 = H$, $R^4 = OCH_3$
6g: $R^1 = Br$, $R^2 = R^3 = H$, $R^4 = OCH_3$
6h: $R^1 = R^4 = H$, $R^2 = Br$, $R^3 = OCH_3$

[a] Reagents and conditions: (i) a.P_2O_5, xylene, reflux, N_2 b. $HCl/C_2H_5OC_2H_5$; (ii) a.pyrrolidine, CH_3OH, 0 °C, N_2 b.$NaBH_4$, CH_3OH, 0 °C.

Scheme 2. Synthesis of intermediate indan acids 10a-f and the target 1-(Pyrrolidin-1-ylmethyl)-2-[(3-oxo-indan)-formyl]-1,2,3,4-tetrahydroisoquinoline analogues 3a-u and 11a-i [a]



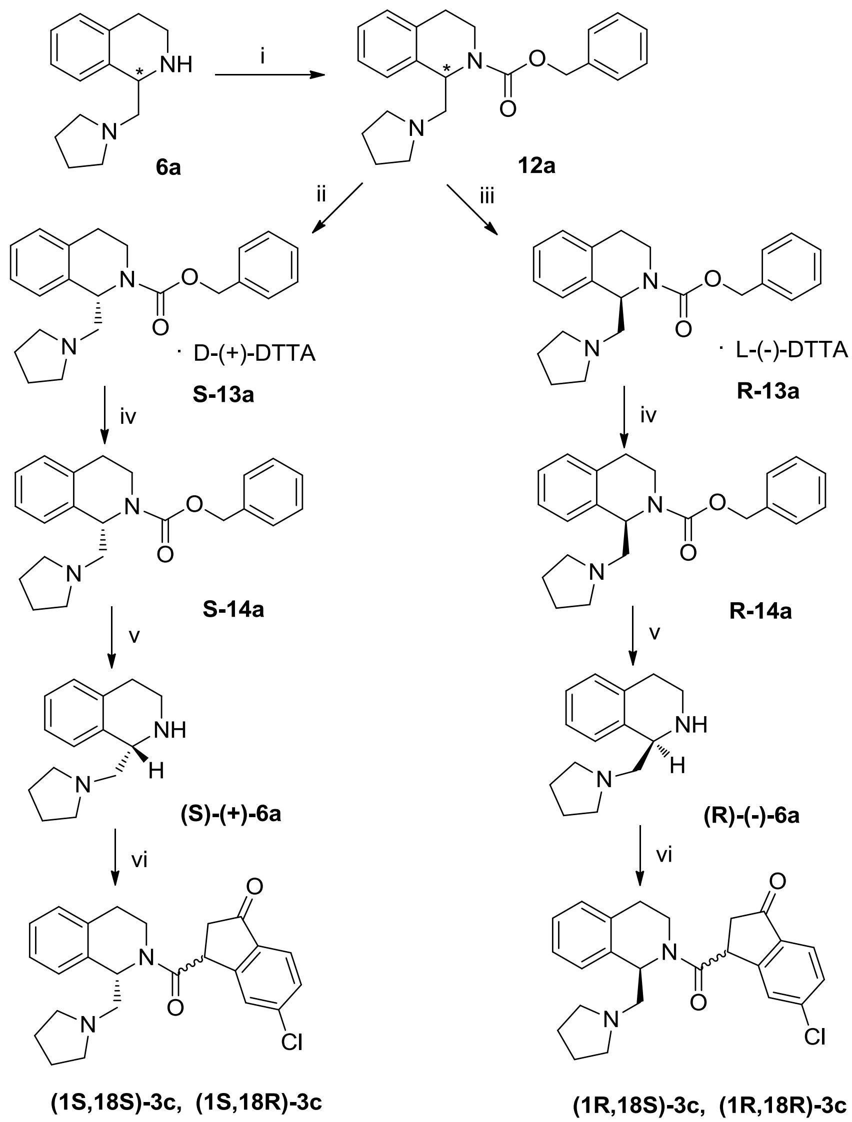
3h: $R^1 = R^2 = R^4 = H$, $R^3 = OCH_3$, $R^5 = H$, $R^6 = Cl$
3f: $R^1 = R^2 = R^4 = H$, $R^3 = OCH_3$, $R^5 = R^6 = H$
3j: $R^1 = R^4 = H$, $R^2 = R^3 = OCH_3$, $R^5 = R^6 = H$
3p: $R^1 = Cl$, $R^2 = R^3 = H$, $R^4 = OCH_3$, $R^5 = R^6 = H$
3q: $R^1 = Cl$, $R^2 = R^3 = H$, $R^4 = OCH_3$, $R^5 = H$, $R^6 = Cl$
3t: $R^1 = Br$, $R^2 = R^3 = H$, $R^4 = OCH_3$, $R^5 = R^6 = H$
3r: $R^1 = R^2 = R^4 = H$, $R^3 = OCH_3$, $R^5 = CH_3$, $R^6 = H$
3s: $R^1 = R^2 = R^4 = H$, $R^3 = F$, $R^5 = H$, $R^6 = OCH_3$
3u: $R^1 = R^4 = H$, $R^2 = Br$, $R^3 = OCH_3$, $R^5 = H$, $R^6 = Cl$

11a: $R^1 = R^2 = R^4 = H$, $R^3 = OH$, $R^5 = H$, $R^6 = Cl$
11b: $R^1 = R^2 = R^4 = H$, $R^3 = OH$, $R^5 = R^6 = H$
11c: $R^1 = R^4 = H$, $R^2 = R^3 = OH$, $R^5 = R^6 = H$
11d: $R^1 = Cl$, $R^2 = R^3 = H$, $R^4 = OH$, $R^5 = R^6 = H$
11e: $R^1 = Cl$, $R^2 = R^3 = H$, $R^4 = OH$, $R^5 = H$, $R^6 = Cl$
11f: $R^1 = Br$, $R^2 = R^3 = H$, $R^4 = OH$, $R^5 = R^6 = H$
11g: $R^1 = R^2 = R^4 = H$, $R^3 = OH$, $R^5 = CH_3$, $R^6 = H$
11h: $R^1 = R^2 = R^4 = H$, $R^3 = F$, $R^5 = H$, $R^6 = OH$
11i: $R^1 = R^4 = H$, $R^2 = Br$, $R^3 = OH$, $R^5 = H$, $R^6 = Cl$

[a] Reagents and conditions: (i) $CH_2(CO_2C_2H_5)_2$, piperidine, benzoic acid, methylbenzene, reflux; (ii)

$CNCH_2COOC_2H_5$, piperidine, glacial acetic acid, methylbenzene, reflux; (iii) a.KCN, C_2H_5OH, H_2O, reflux or. r.t. b.HCl, reflux; (iv) a.$SOCl_2$, reflux b.anhydrous $AlCl_3$, CH_2Cl_2, r.t.; (v) PPA, 90 ^{o}C; (vi) **6a-h**, DCC, DMAP, CH_2Cl_2, r.t.; (vii) 48% HBr, reflux.

Scheme 3. Synthesis of the four stereoisomers of 3c [a]



[a]Reagents and conditions: (i) Cbz-Cl, K_2CO_3, acetone, r.t; (ii) D-(+)-DTTA, isopropanol/isopropyl ether, reflux; (iii) L-(-)-DTTA, isopropanol/isopropyl ether, reflux; (iv) NaOH, H_2O, r.t; (v) H_2, Pd/C, CH_3OH, r.t; (vi) DCC, DMAP, **10c**, CH_2Cl_2

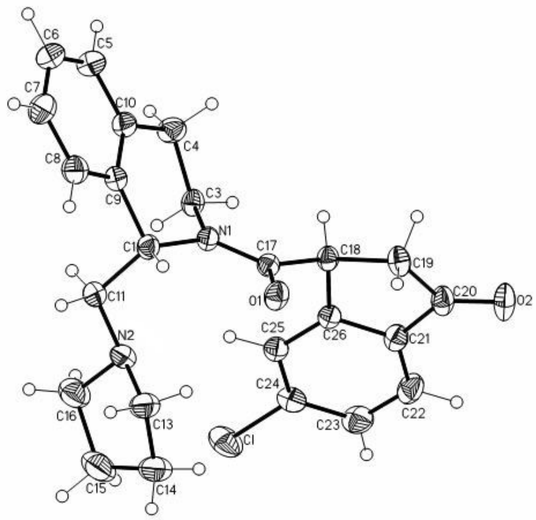


Figure 2. X-ray crystal structure of enantiomeric mixtures (1*S*,18*S*)-1-(pyrrolidin-1-ylmethyl) -2-[(6-chloro-3-oxo-indan)-formyl]-1,2,3,4-tetrahydroisoquinoline ((1*S*,18*S*)-3c) and (1*R*,18*R*)-1 -(pyrrolidin-1-ylmethyl)-2-[(6-chloro-3-oxo-indan)-formyl]-1,2,3,4-tetrahydroisoquinoline ((1*R*,18*R*)-3c)

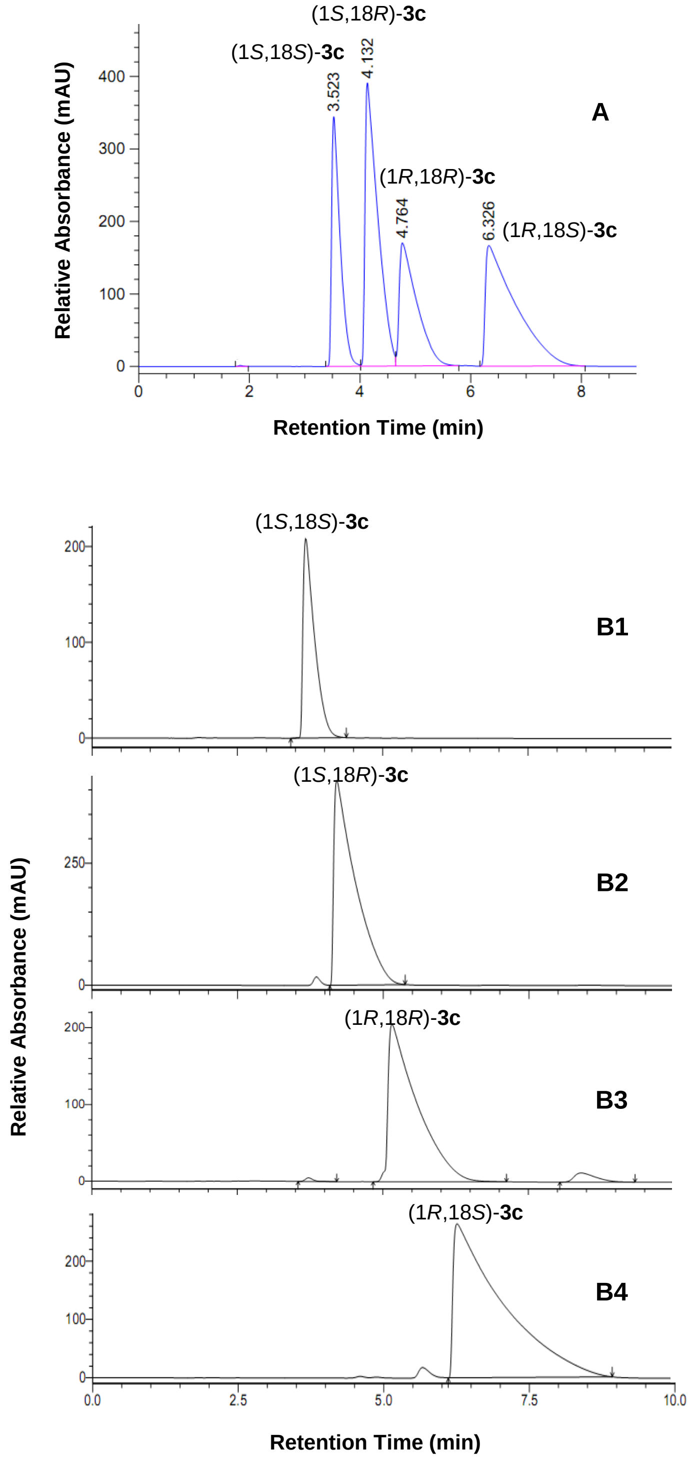


Figure 3. Chiral HPLC chromatogram of the four stereoisomers of 3c

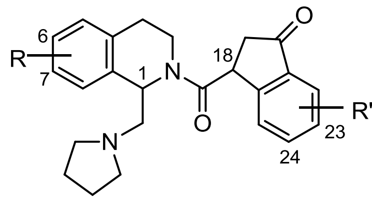


Table 1. ***K*$_i$ values for the inhibition of *κ*- and *μ*-opioid receptor binding to CHO membranes by novel compounds**

Cmpd.	R	R'	[^{3}H]diprenorphine binding K_i (nM) [a]	
			κ	*μ*
maj-**3a**	H	H	0.452 ± 0.083	>10,000
maj-**3b**	H	23,24-(OCH_3)$_2$	1.37 ± 0.09	99.0 ± 0.5
maj-**3c**	H	24-Cl	0.033 ± 0.008	698 ± 92
min-**3c**	H	24-Cl	3.7 ± 0.2	>10,000
maj-**3d**	H	24-F	0.228 ± 0.026	486 ± 81.4
maj-**3e**	H	24-OCH_3	0.933 ± 0.094	140 ± 11
maj-**3f**	7-OCH_3	H	270 ± 28	>10,000
maj-**3g**	7-OCH_3	23,24-(OCH_3)$_2$	>10,000	>10,000
maj-**3h**	7-OCH_3	24-Cl	16.9 ± 2.8	>10,000
maj-**3i**	7-OCH_3	24-OCH_3	1548 ± 14	NT [e]
maj-**3j**	6,7-(OCH_3)$_2$	H	>10,000	NT [e]
maj-**3k**	6,7-(OCH_3)$_2$	23,24-(OCH_3)$_2$	NB [d]	NT [e]
maj-**3*l***	6,7-(OCH_3)$_2$	24-Cl	>10,000	NT [e]
maj-**3m**	6,7-(OCH_3)$_2$	24-OCH_3	NB [d]	NT [e]
maj-**3n**[f]	6-OCH_3	24-Cl	3.73 ± 0.06	>10,000
maj-**3o**[f]	6-OCH_3	24-F	56.35 ± 5.71	>10,000
maj-**3p**[f]	5-Cl, 8-OCH_3	H	>10,000	>10,000
maj-**3q**[f]	5-Cl, 8-OCH_3	24-Cl	121.4 ± 13.0	>10,000
maj-**3r**[f]	7-OCH_3	23-CH_3	69.57 ± 1.49	>10,000
maj-**3s**[f]	7-F	24-OCH_3	1.57 ± 0.04	>10,000
maj-**3t**[f]	5-Br, 8-OCH_3	H	>10,000	>10,000
maj-**3u**[f]	6-Br, 7-OCH_3	24-Cl	221.5 ± 3.40	>10,000

maj-**11a**[f]	7-OH	24-Cl	35.13±1.74	N.B[d]
maj-**11b**[f]	7-OH	H	>10,000	N.B[d]
maj-**11c**[f]	6,7-$(OH)_2$	H	>10,000	N.B[d]
maj-**11d**[f]	5-Cl,8-OH	H	>10,000	N.B[d]
maj-**11e**[f]	5-Cl,8-OH	24-Cl	41.29±3.33	N.B[d]
maj-**11f**[f]	5-Br,8-OH	H	>10,000	N.B[d]
maj-**11g**[f]	7-OH	23-CH_3	42.00±0.23	N.B[d]
maj-**11h**[f]	7-F	24-OH	58.43±0.14	N.B[d]
maj-**11i**[f]	6-Br,7-OH	24-Cl	99.90±0.25	N.B[d]
BRL 52580[b]	–	–	0.20 ±0.02	30.2 ±6.4
U-50,488H[c]	–	–	6.08 ±0.10	1,397 ±488

[a] Data were expressed as the mean ± S.E.M. for six to eight independent experiments performed in triplicate.

[b] Data were from Ref.13.

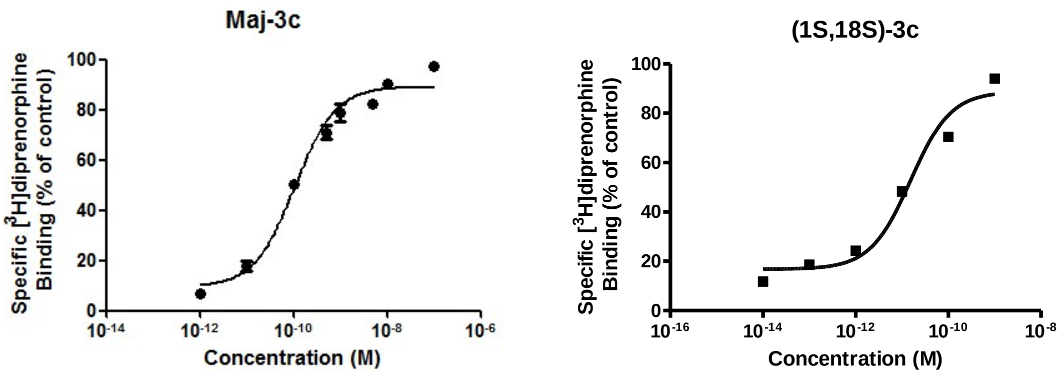
[c] Data were from Ref.19.

[d] Did not bind at 10 μM.

[e] Not tested.

[f] Tested as hydrochloride salt.

Figure 4. Competitive inhibition by Maj-3c and (1S,18S)-3c of [3H]diprenorphine binding to human κ-opioid receptors [a]



[a] Membranes from CHO cells stably expressing κ-opioid receptor were incubated with varying concentrations of compounds in the presence of [^{3}H]diprenorphine (0.5 nM) as described in the methods. Each data point represents the mean±S.E.M. of at least three independent experiments conducted in triplicate.

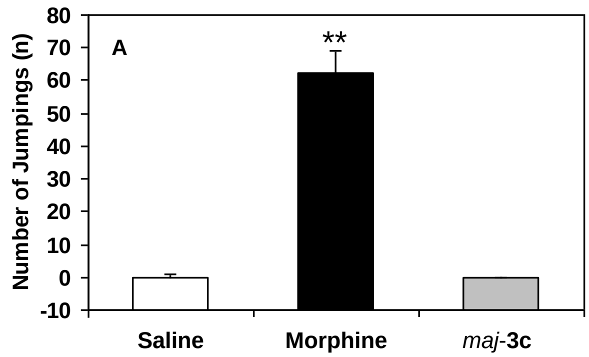
Table 2. ED_{50} values of the antinociception produced by s.c. injection of *maj*-, *min*-3c, *maj*-11a, BRL 52580， and U-50,488H evaluated with MHP and AAW Assays

cmpd	MHP 55 °C [a] ED$_{50}$ μg·kg^{-1}, s.c.	AAW [a] ED$_{50}$ μg·kg^{-1}, s.c.
maj-**3c**	2.061 (1.466–2.899)	0.406 (0.255–0.647)
min-**3c**	25.000 (16.733–37.352)	2.345 (1.158–4.746)
maj-**11a**	–	392 (235—655)
BRL 52580 [b]	> 80.6	–
U-50,488H [c]	4415 (2513–7754)	885 (541–1447)

[a] The antinociceptive ED_{50} value of each drug was calculated from concentration-effect curves with five concentrations and the data were obtained at 30 min after the drug administration. Parentheses: 95% confidence limits.

[b] Data were from Ref.13.

[c] Data were from Ref.19.



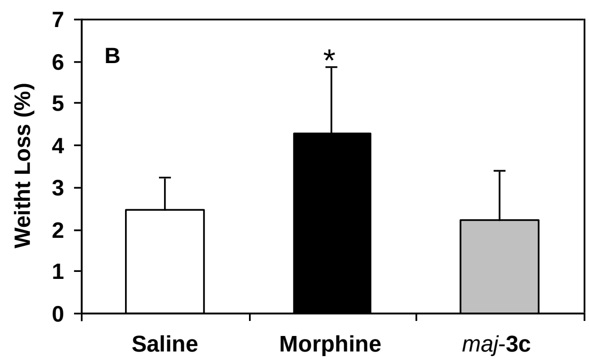


Figure 5. Naloxone-precipitated jumping and body weight loss in mice treated chronically with morphine and *maj*-3c.

(A) The number of jumpings was measured for 20 min after naloxone injection. (B) Body weight loss was measured initially and 30 min after the naloxone injection. Data were presented as the mean ± S.E.M from six animals. [*] $P < 0.05$ vs control group (saline). [**] $P < 0.01$ vs control group.

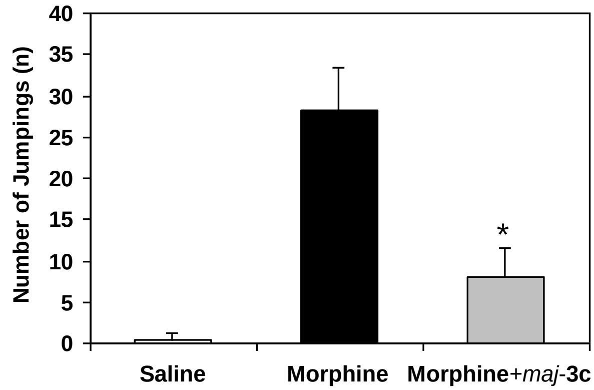


Figure 6. Inhibitory effects of *maj*-3c on naloxone-precipitaed jumping in mice treated chronically with morphine.

maj-**3c** (300 μg·kg^{-1}, i.p.) was coadministrated with morphine. A single injection of naloxone (3.0 mg·kg^{-1}, i.p.) was given 2 hours after the last administration of morphine. The number of jumping was measured for 20 min. Data were presented as the mean ± S.E.M from six animals. * $P < 0.05$ vs control group (saline).

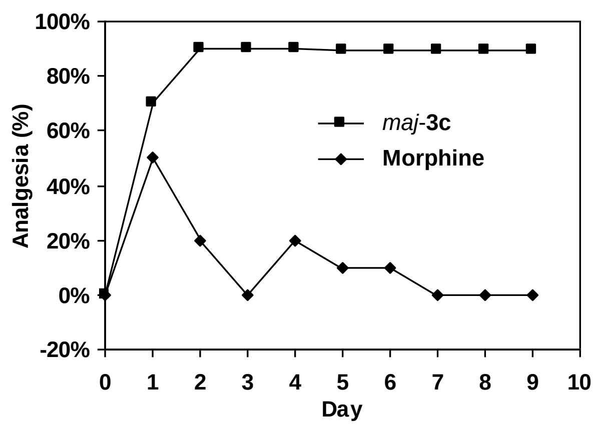


Figure 7. Development of tolerance to *maj*-3c and morphine induced antinociception in the mouse MHP assay.

Mice were treated with morphine (day 1-3: 7mg·kg^{-1}; day 4-7: 10mg·kg^{-1}; day 8-9: 15mg·kg^{-1}) and *maj*-**3c** (25 ug·kg^{-1}) for 9 days. Data were presented as the mean ± S.E.M from six animals.

Table 3. K_i values for the inhibition of κ- and μ-opioid receptor binding to CHO membranes by the four stereoisomers of 3c

cmpd [a]	[^{3}H]diprenorphine binding K_i (nM) [b]	
	κ	μ
(1*S*,18*S*)-**3c**	0.0059 ± 0.001	205.1 ± 7.7
(1*R*,18*R*)-**3c**	18.20 ± 4.72	> 10,000
(1*S*,18R)-**3c**	0.049 ± 0.007	486.0 ± 38.3
(1*R*,18*S*)-**3c**	17.50 ± 2.30	> 10,000

[a] Tested as mesylates.

[b] Data were expressed as the mean ± S.E.M. for six to eight independent experiments performed in triplicate.

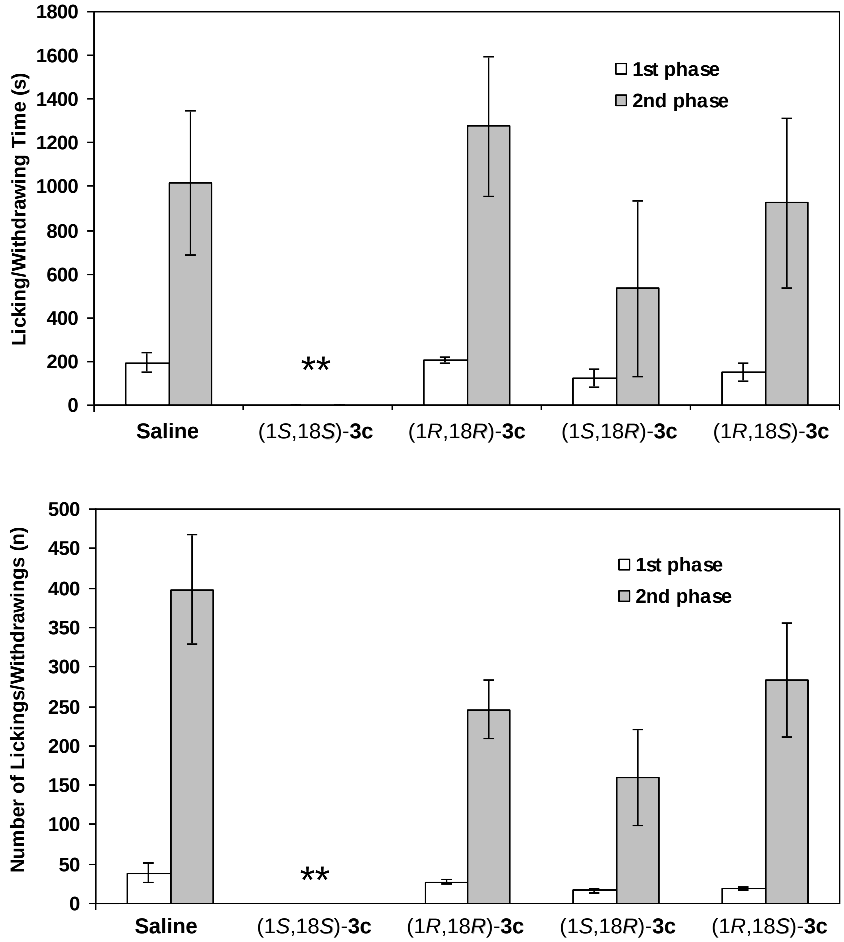


Figure 8. Effects of the four stereoisomers of 3c in the mouse MF test.

Formalin solution 5% (50 μl) was injected to the right hind paw of rats. The first phase occurred immediately after formalin injection and lasted 5 min. Second phase occurred form 10 min after the injection and lasted to 60 min. The antinociceptive effects of the compounds (mesylate, 20 ug·kg^{-1}, s.c.) were measured in both first and second phase. Data were presented as the mean ± S.E.M from six animals. $^{**}P < 0.01$ vs control group (saline).

Table. 4 The sedative effects of *maj*-3c and *maj*-11a in the Mouse Rotated Test

Cmpd	Sedative ED_{50} Values (mg · kg^{-1})	peripheral restriction index[a]
maj-**3c**	0.000568	1.4
maj-**11a**	9.29	23.7
(-)U50,488H	3.32	3.7

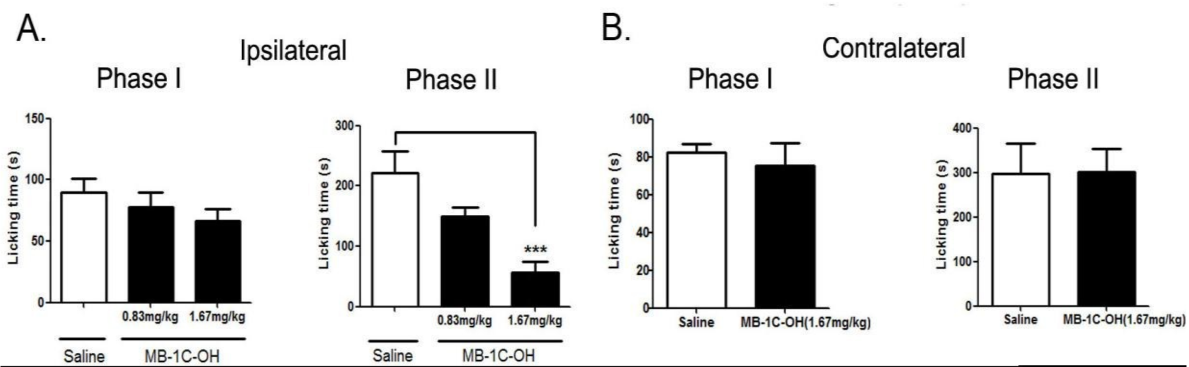
[a] Peripheral restriction index = platform sedation ED_{50}/AAW writhing ED_{50}.

Table 5. The effects of *maj*-3c and *maj*-11a on responses to the Elevated Plus Maze [a]

Entry	Cmpd.	Open arm time /total time(%)	Closed arm time/total time(%)
1	Control (saline)	39	61
2	*maj*-3c (1μg·kg^{-1})	34	66
3	*maj*-3c (2.5μg·kg^{-1})	17*	83*
4	*maj*-3c (5μg·kg^{-1})	3*	97*
5	*maj*-11a (1.25mg·kg^{-1})	35	65
6	*maj*-11a (2.5mg·kg^{-1})	23	77
7	*maj*-11a (3.75mg·kg^{-1})	14*	86*

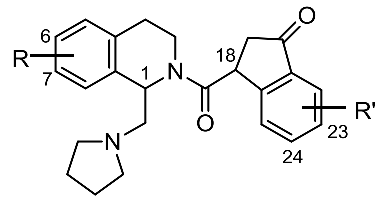
[a] Male mice were injected s.c with different doses of *maj*-**3c** and *maj*-**11a**. * $P < 0.05$ vs control group (saline).

Figure 9. Peripheral antinociceptive effects of *maj*-11a in formalin test.



The animals were pretreated with *maj*-11a into right hind paw (ipsilateral, IL) (A) or left hind paw (contralateral, CL) (B). After 15 minutes, the animals were injected with formalin (20 μl/paw). The Licking or flinching time of Phase I and Phase II were recorded. All data are expressed as mean ± S.E.M. (number of animals in each group is at least five). $^{**}P < 0.01$, $^{***}P < 0.001$ compared with vehicle group (one-way ANOVA with Dunnettæs test).

Table 6. Calculated Physicochemical Indicators of *maj*-3c, *maj*-3r, *maj*-11a, *maj*-11g.



Compd	R	R'	clogP [a]	Ki (nM)	LLE [b]	LELP [c]
***maj*-3c**	H	24-Cl	3.52	0.033 ± 0.008	6.96	6.95
***maj*-3r**	7-OCH_3	23-CH_3	2.44	69.57 ± 1.49	4.72	7.54
***maj*-11a**	7-OH	24-Cl	2.76	35.13±1.74	4.7	7.93
***maj*-11g**	7-OH	23-CH_3	1.3	42.00±0.23	6.08	3.78

[a] Measured by the method of Avdeef and Tsinman[22] on a Gemini Profiler instrument (pION) by the 'goldstandard' Av-deef- Bucher potentiometric titration method[23]. [b] LLE = pKi - clogP. [c] LELP = clogP/LE, LE =ΔG/N, N = number of non-hydrogen atoms, ΔG = -RTlnKi or -1.4(logKi)

Table 7. The LD_{50} Value of *maj*-11a

Dose (mg·kg)	logarithmic dose	Overall number (n)	Death number (n)	Percentage mortality (%)	Experimental probability Unit(Y)	Regression probability Unit(Y)	LD_{50} value [a] （95% confidence limits）
21.7	1.3365	10	0	0	---	3.0266	
25.5	1.4065	10	2	20	4.1585	4.0508	
30	1.4771	10	6	60	5.2529	5.0823	29.6 $mg{\cdot}kg^{-1}$ (27.2~32.2)
35.5	1.5502	10	8	80	5.8415	6.1508	
41.5	1.618	10	10	100	---	7.142	

[a] Data were expressed as the mean ±S.E.M. Parentheses: 95% confidence limits.

Table 8. The main pharmacokinetic parameter estimated by non-compartmental model following a p.o. administration of *maj*-11a to Sprague-Dawley rats [a]

route of administration (Dose)	$t_{1/2}$	T_{max}	C_{max}	$AUC_{(0\text{-}t)}$	$AUC_{(0\text{-}\infty)}$	$MRT_{(0\text{-}\infty)}$	F [b]
	hr	**hr**	**$\mu g \cdot L^{-1}$**	**$\mu g \cdot L^{-1} \cdot hr^{-1}$**	**$\mu g \cdot L^{-1} \cdot hr^{-1}$**	**hr**	**%**
i.v. (2mg/kg)	1.37	0.083	455.54	536.87	541.57	1.35	-
p.o. (10 mg/kg)	4.16	1.00	214.41	1083.97	1099.93	4.44	40.6

[a] Data were analyzed by software WinNonlin version 5.2

[b] F (%) = $(Dose_{iv} \times AUC_{oral(0\text{-}\infty)}) / (Dose_{oral} \times AUC_{iv(0\text{-}\infty)}) \times 100\%$

Legends

Figure 1. Structural Design of 1-(Pyrrolidin-1-ylmethyl)-2-[(3-oxo-indan)-formyl]-1,2,3,4-tetrahy-droisoquinoline Selective κ Receptor Agonists

Scheme 1. Synthesis of Intermediate Diamines 6a-h

Scheme 2. Synthesis of Intermediate Indan Acids 10a-e and the Target 1-(Pyrrolidin-1-ylmethyl)-2-[(3-oxo-indan)-formyl]-1,2,3,4-tetrahydroisoquinoline Analogues 3a-u and 11a-i

Scheme 3. Synthesis of the Four Stereoisomers of 3c

Figure 2. X-ray Crystal Structure of Enantiomeric Mixtures (1S,18S)-1-(pyrrolidin-1-ylmethyl)-2-[(6-chloro-3-oxo-indan)-formyl]-1,2,3,4-tetrahydroisoquinoline ((1S,18S)-3c) and (1R,18R)-1-(pyrrolidin-1-ylmethyl)-2-[(6-chloro-3-oxo-indan)-formyl]-1,2,3,4-tetrahydroisoquinoline ((1R,18R)-3c)

Figure 3. Chiral HPLC Chromatogram of the Four Stereoisomers of 3c

Table 1. Ki values for the inhibition of κ- and μ-opioid receptor binding to CHO membranes by novel compounds

Figure 4. Competitive inhibition by maj-3c and (1S,18S)-3c of [3H]diprenorphine binding to human κ-opioid receptors

Table 2. ED_{50} values of the antinociception produced by s.c. injection of *maj-*, *min-3c*, *maj-11a*, BRL 52580， and U-50,488H evaluated with MHP and AAW Assays

Table 3. Ki values for the inhibition of κ- and μ-opioid receptor binding to CHO membranes by the four stereoisomers of 3c

Figure 5. Dependence Potential of Morphine and *maj*-3c on Naloxone-precipitated Mice Withdrawal Jumping and Body Weight Loss Assays

Figure 6. Inhibitory Effects of *maj*-3c on the Development of Morphine Dependence Assay

Figure 7. Analgesic Tolerance Tests of Morphine and *maj*-3c in MHP Assay

Figure 8. Comparison of the Four Stereoisomers of 3c on MF Assay

Table. 4 The Sedative Effects of *maj*-3c and *maj*-11a in Mouse Rotated Test

Table 5. The Effects of *maj*-3c and *maj*-11a on Responses to the Elevated Plus Maze

Figure 9. Peripheral antinociceptive effects of *maj*-11a in formalin test

Table 6. Calculated Physicochemical Indicators of *maj*-3r, *maj*-3c, *maj*-11a, *maj*-11g

Table 7. The LD_{50} Value of *maj*-11a

Table 8. The main pharmacokinetic parameter estimated by non-compartmental model following a p.o. administration of *maj*-11a to Sprague-Dawley rats