Design and Synthesis of Opioid Receptor Type Selective Ligands with a Propellane Skeleton and Their Pharmacologies

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List of Abbreviations

Ac	acetyl
Bn	benzyl
CHO cell	Chinese hamster ovary cell
CSA	camphorsulfonic acid
DAMGO	[D-Ala^2, N-Me-Phe^4, Gly^5-ol]-enkephalin
DIAD	diisopropyl azodicarboxylate
DMAP	*N*,*N*-dimethyl-4-aminopyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DPDPE	[D-Phe^{2,5}]-enkephalin
EC_{50}	effective concentration 50%
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Et	ethyl
GDP	guanosine diphosphate
GTP	guanosine triphosphate
IR	infrared
IUPAC	International Union of Pure Applied Chemistry
Lys	lysine
Me	Methyl
Mp	melting point
Ms	methanesulfonyl
MS	mass spectra
NMR	nuclear magnetic resonance
nor-BNI	nor-binaltorphimine
NTB	naltriben
NTI	naltrindole
Ph	phenyl
PTSA	*p*-toluenesulfonic acid
quant.	quantitative
rt	room temperature
s.c.	subcutaneous
THF	tetrahydrofuran
TLC	thin layer chromatography

1. General Introduction

1.1 Opioid receptor

The term “opiate” was used extensively until the 1980s to describe any natural or synthetic agent that was derived from morphine (**1**) (**Fig. 1**). However, the discovery of endogenous peptides in the brain that had pharmacological effects similar to morphine led to a change in nomenclature. The peptides were not related morphine structurally; yet, their effects were like those produced by morphine (**1**). At this time, the term opioid, meaning opium- or morphine-like, in terms of the pharmacological action, was introduced. To be precise, the term “opioid” refers to the natural or synthetic peptides that act as in a similar way to morphine (**1**), the opium alkaloids, and their derivatives. The general term “opioid” is derived from the English name of the plant “opium”. Opium is a white powder obtained from drying of a milky liquid derived from immature pericarp of the opium poppy *Papaver somniferum*. Although the powder includes more than fifty kinds of alkaloids, it has been used as a medicine from ancient times as described by Teophrastus in the 3rd century B. C.

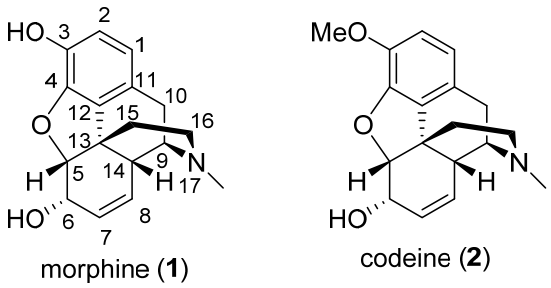


Fig. 1. The structures of morphine (**1**) and codeine (**2**)

The first isolated alkaloid from opium by Sertürner was morphine (**1**).[1] It was named after Morpheus, the principal god of dream or of sleep in Greek mythology. Afterward, codeine (**2**) was isolated by Robiquet in 1832 (**Fig. 1**). In the mid-1800s, the pure alkaloids began to be used instead of crude preparation of opium. However, it took more than a century to determine their correct structures because of the complexities of the structures of alkaloids. The correct structure of morphine (**1**) was proposed by Robinson and Gulland in 1925,[2] and it was determined by Schöpf in1927.[3] The structure had five asymmetric carbons, and the absolute configuration was determined through total synthesis[4] by Gate and Tschudi in 1952, and through X-ray crystal structural analysis[5] by Machay and Hodglein in 1955.

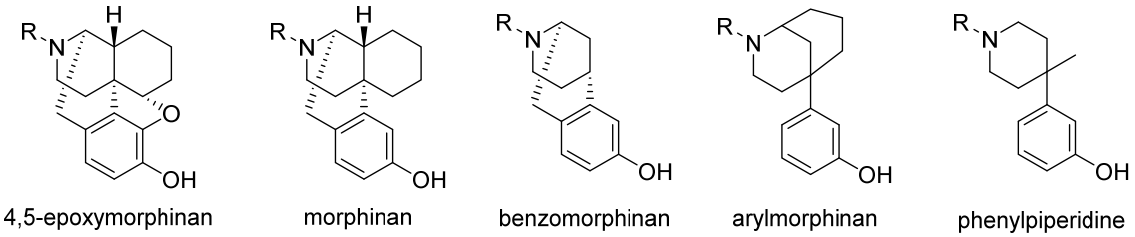


Fig. 2. The skeletons of opioid ligand

Morphine (**1**) has been well-known to have not only analgesic effect but also narcotic addiction for a long time. Hence, the development of strong analgesics without addiction started after the structure of morphine (**1**) was determined. The basic skeleton of morphine (**1**) was called 4,5-epoxymorphinan and synthesized as a prototype. However, the complexity of the 4,5-epoxy-morphinan skeleton made it difficult for its supply in large amounts by synthetic methods. To simplify the skeleton, morphinan, benzomorphane, arylmorphan and phenylpiperidine skeletons were synthesized (**Fig. 2**).[6] These derivatives possessing the indicated azapolycyclic skeletons showed agonistic or antagonistic activity for opioid receptor, and also became a powerful tool for elucidating the working mechanism of the compounds. After the pharmacological and biological investigations, using these derivatives and endogenous opioid peptides as opioid ligands, three types of opioid receptors (μ, δ, κ) were well established. The narcotic addiction derived from morphine (**1**) is believed to be derived from the μ receptor type.[7] Therefore, δ and κ receptor types are believed to be promising drug targets for analgesics without addiction, hence there has been a lot of effort to develop δ and κ selective agonists.

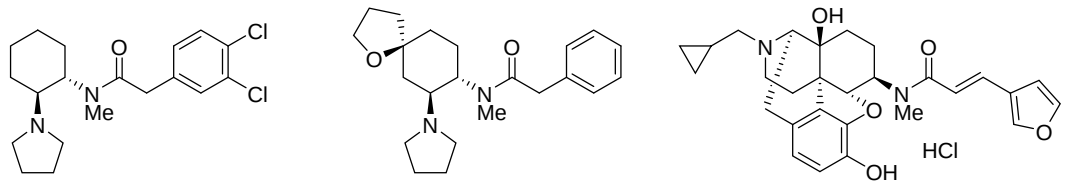
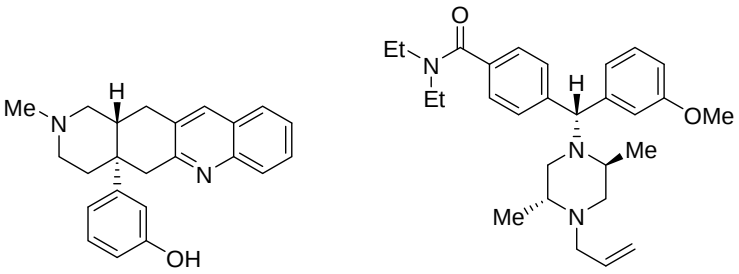


Fig. 3. The structures of U-50,488H (**3**), U-69,593 (**4**) and nalfurafine (**5**) hydrochloride

The Upjohn Company developed U-50,488H (**3**)[8] and U-69,593 (**4**),[9] which showed analgesic effect without addiction (**Fig. 3**). Nevertheless, these derivatives were not clinically tested because of severe aversion side effects, effects contrary to addiction.[10] On the other hand, nalfurafine (**5**) hydrochloride,[11] a κ selective agonist, was launched in Japan as an antipruritic drug for patients undergoing dialysis by Nagase *et al.* in 2009[12] (**Fig. 3**). Nalfurafine (**5**) showed neither addiction nor aversion[13] but it could not be used as an analgesic drug because of slightly inseparable sedative effect. So far, no κ agonist has been approved as an analgesic drug, and the research for developing κ agonist as an analgesic is continuing even now.



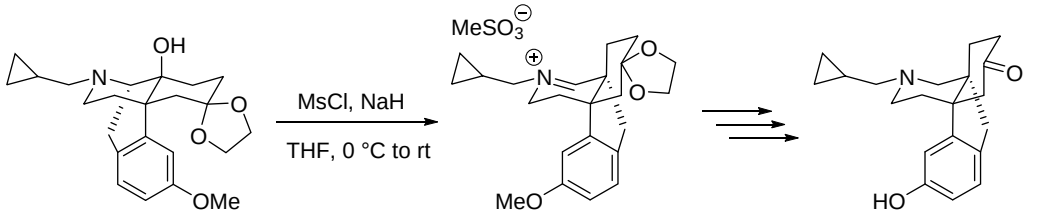
TAN-67 (**6**) SNC-80 (**7**)

Fig. 4. The structures of TAN-67 (**6**), SNC-80 (**7**)

Meanwhile, the research of δ selective ligands has not made much progress compared to that of κ selective ligands. Although TAN-67 (**6**)[14] and SNC-80 (**7**)[15] were developed as δ agonists and showed highly agonistic activities and selectivities for δ receptor *in vitro*, these compounds showed insufficient activity for δ receptor *in vivo*. Furthermore, the role of δ receptor in organisms is still unclear. Therefore, δ agonist is significantly desired not only as an analgesic but also as a biological tool for elucidating the role of δ receptor. Since X-ray crystal structures of three types of antagonist-bound opioid receptor (μ, δ, κ) were reported in 2012,[16] the three dimensional structures of the three receptor types were unveiled. Accordingly, the design and synthesis of opioid ligands were expected to progress based on these information.

Quite recently, Nagase *et al.* reported highly selective and potent δ agonist, KNT-127 which showed potent analgesic effect via systemic administration (ED_{50} =1.2 mg/kg).[17] The derivative has been developed as an antidepressant and an anti-anxiety drug.

1.2 Propellane skeleton



Scheme 1. Synthesis of propellane compound **10**

Recently, Nagase *et al.* reported that the treatment of 14-hydroxymorphinan **8** with MsCl and NaH furnished highly stable iminium salt **9** with propellane skeleton (**Scheme 1**). And the iminium **9** was reduced with $NaBH_4$ to afford a saturated compound, followed by hydrolysis of the acetal and *O*-demethylation to give propellane type compound **10**.[18] Propellane type compound is defined as a derivative which has three rings-fused one C-C bond.

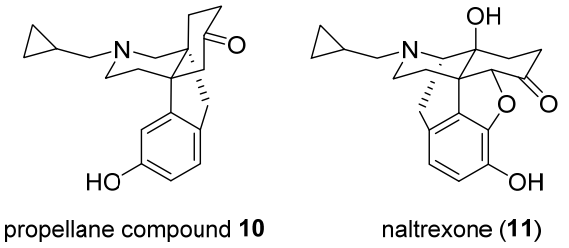


Fig. 5. The structures of propellane compound **10** and naltrexone (**11**)

Although naltrexone (**11**), as a starting material of many kinds of κ selective ligands like nalfurafine (**5**) showed undesired μ selectivity (μ/κ = 0.9), propellane type compound **10** showed κ selectivity (μ/κ = 3.3) (**Fig. 5**).[19] On the basis of the promising κ selectivity of the propellane skeleton, the author chose the skeleton for developing κ selective agonists.

The numbering of propellane derivatives and pentacyclic derivatives according to the IUPAC nomenclature is shown in **Fig. 6**. However, in this thesis the author used a tentative numbering to the propellane derivatives, which would make it easy to compare the relative positions between morphinan and propellane skeletons.

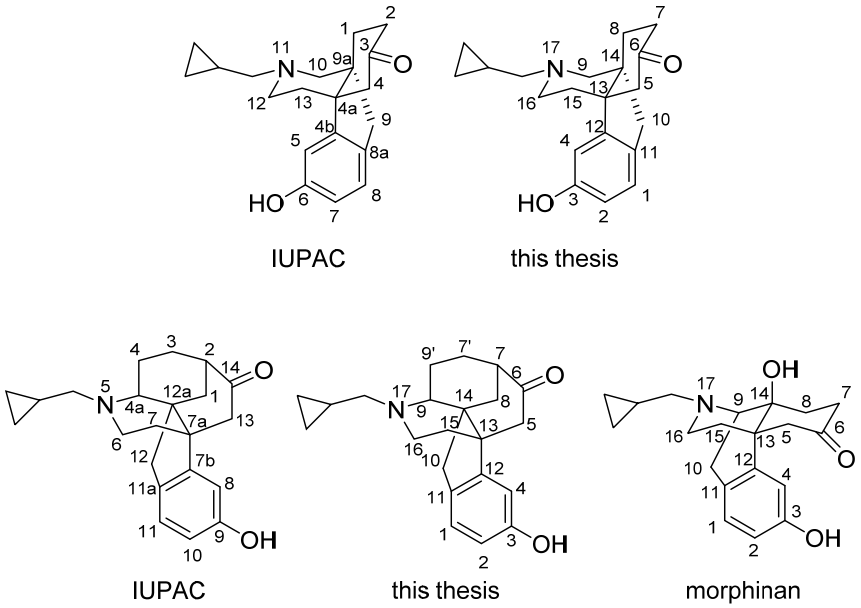


Fig. 6. The numbering of propellane, pentacyclic and morphinan derivatives

2. Design and Synthesis of κ Receptor Selective Propellane Derivatives with Pentacyclic Skeleton and Their Pharmacologies

2.1 Design of κ receptor selective propellane derivatives with pentacyclic skeleton

Nalfurafine (**5**) hydrochloride is garnering attention around the world as an opioid drug without addiction, and especially aversion.[13] Nalfurafine (**5**) is structurally different from the arylacetamide derivatives known as κ selective agonists, which have aversive effects.[10] The proposed active conformation of nalfurafine (**5**) for binding to the κ receptor is shown in **Fig. 7**.[20]

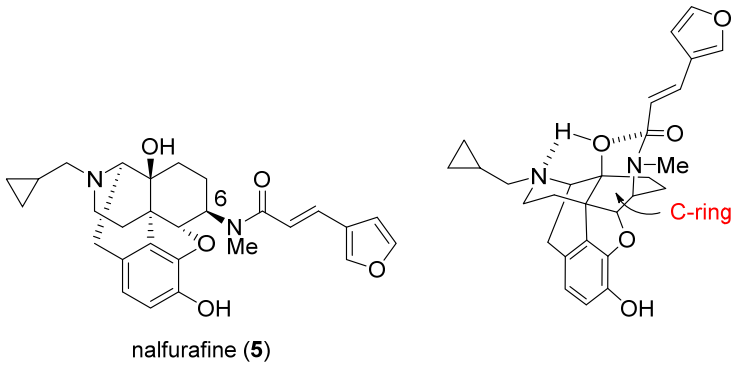


Fig. 7. The proposed active conformation of nalfurafine (**5**)

The C-ring of nalfurafine (**5**) would require the boat form to orient the 6-amide side chain toward the upper side of the C-ring. On the basis of the proposed active conformation, Nagase *et al.* investigated the essential structures for binding to the κ receptor.[21] As mentioned in Chapter **1.2**, propellane **10** showing κ selectivity was a promising skeleton for designing κ selective ligands. However, its affinity (K_i = 17.4 nM) for the κ receptor was much lower than that of nalfurafine (K_i = 0.178 nM).[19] The reason for its low affinity for κ receptor was postulated to be derived from its conformational flexibility. Propellane **10** could have two canonical conformation termed bent form and extended form (**Fig. 8**). Compared to the proposed active conformation of nalfurafine (**5**), the bent form of propellane **10** would be the active conformation for binding to the κ receptor. Accordingly, the author designed and synthesized pentacyclic compound **12**, in which C7 and C9 were connected with an ethylene bridge to fix the bent form of propellane **10** (**Fig. 8**).

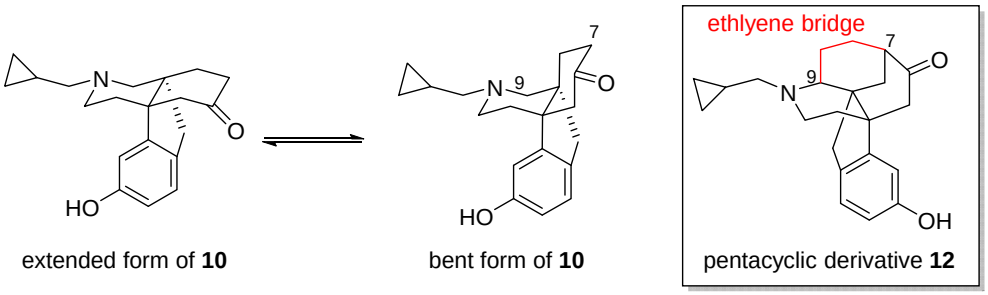
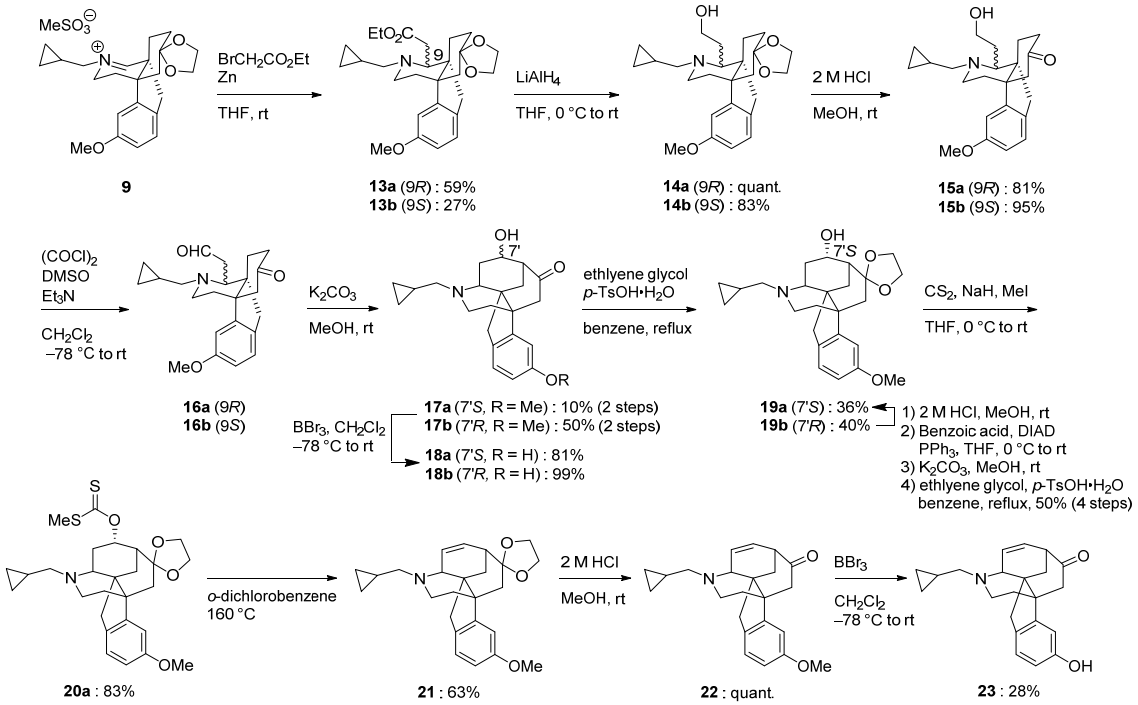


Fig. 8. Two conformers of propellane **10** and pentacyclic derivative **12** with the fixed bent form

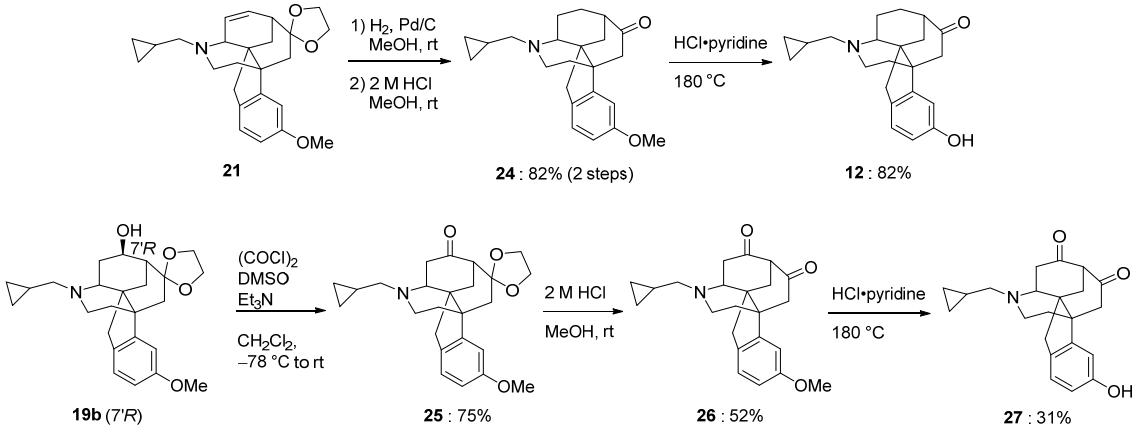
2.2 Synthesis of propellane derivatives with pentacyclic skeleton



Scheme 2. Synthetic route of propellane derivatives with pentacyclic skeleton

Synthetic route of propellane derivatives is shown in **Scheme 2**.[22] The reduction of iminium **9**[18] with $NaBH_4$ gave the corresponding saturated propellane derivative. Furthermore, iminium **9** also reacted with NaCN to afford a cyano adduct, and the trial of nucleophilic addition of Grignard reagents to iminium **9** resulted in complex mixtures.[18] These results suggest that a mild nucleophile may be an adequate reagent for addition to iminium **9**. After intensive efforts seeking for an appropriate nucleophile, the author found that a Reformatsky reaction involving iminium salt **9,** ethyl bromoacetate, and zinc gave adducts **13a** and **13b** as diastereoisomers[23] in 59% and 27% yield, respectively. Attempts at intramolecular cyclization of the ketoester, obtained from

13b by deacetalization, under basic conditions resulted in the recovery of the starting material because of insufficient electrophilicity of the ester group. An aldehyde is a stronger electrophile for the intramolecular cyclization. Therefore, the author attempted to convert the ester into the more electrophilic aldehyde group. Reduction of the ester **13a** and **13b** with $LiAlH_4$ provided alcohol **14a** and **14b** in quantitative and 83% yield, respectively. Before attempting the intramolecular aldol reaction, the author attempted the S_N2 type reaction for conversion of the hydroxyl group into leaving group that resulted in formation of azetidinium salt by nucleophilic addition of nitrogen to the leaving group. Deacetalization of alcohol **14a** and **14b** gave ketoalcohol **15a** and **15b**, followed by oxidation under Swern conditions to give aldehyde **16a** and **16b**. It was found that obtained aldehyde **16a** and **16b** were easily epimerized by retro-aza-Michael addition and recyclization at room temperature. Therefore, the crude material containing the diastereomeric mixture of **16a** and **16b** was used for the next intramolecular aldol step. The intramolecular aldol reaction of mixture of **16a** and **16b** successfully proceeded under mild basic condition to provide desired pentacyclic derivatives **17a** and **17b** in 10% and 50% yield, respectively.[24] The *o*-demethlylation of **17a** and **17b** with BBr_3 gave phenols **18a** and **18b** in 81% and 99% yield, respectively. The author next attempted to dehydrate the hydroxyl group at C7' of pentacyclic compounds **18a** and **18b**. Before the dehydration reaction, acetalization of the mixture of **18a** and **18b** furnished acetals **19a** and **19b** in 36% and 40% yield, respectively. Unfortunately, the conversion of the hydroxyl group into a strong leaving group such as mesylate resulted in cleavage of ethlylene bridge by participation of the lone electron pair on nitrogen to give a stable iminium salt. The cleavage reaction led the author to covert the hydroxyl group into a weak leaving group such as a xanthate. The removal of hydroxyl group of diastereomer **19a** (7'*S*) was achieved by Chugaev reaction of the obtained xanthate to give etheno-bridge compound **21** in 52% yield in two steps. On the other hand, Chugaev reaction of the xanthate with opposite configuration of **20a**, derived from diastereomer **19b** (7'*R*), resulted in cleavage of ethylene bridge. This cleavage would result from the highly fixed stereochemistry of the hydroxyl group by the rigid pentacyclic structure. In other words, the lone electron pair on nitrogen could easily participate with the cleavage reaction of the xanthate because of stereoelectronic effect. Accordingly, undesired **19b** was converted into **19a** by Mitsunobu reaction. Deacetalization of **21** afforded ketone **22** in quantitative yield, followed by *O*-demethlylation to give phenol **23** in 28% yield.



Scheme 3. Synthetic route of pentacyclic derivatives **12** and **27**

The synthesis of ethano-bridged compound **12** and diketo compound **27** is shown in **Scheme 3**. The obtained olefin **21** was catalytically hydrogenated and subsequently deacetalyzed to provide ethano-bridged compound **24**. Diketo compound **26** was obtained by Swern oxidation of **19b** with subsequent deacetalization. The methoxy groups in compounds **24** and **26** were demethylated with pyridinium chloride to give the corresponding phenols **12** and **27** in 82% and 31% yield, respectively.

2.3 Binding affinities and conformational analyses of pentacyclic derivatives

The binding affinities of the prepared pentacyclic propellane derivatives for the opioid receptors were evaluated with a competitive binding assay (**Table 1**).

Table 1. Binding affinities of **10**, **18a**, **18b**, **23**, **12** and **27** to opioid receptors[a]

Compound	K_i (nM)			Selectivity	
	μ[b]	δ[c]	κ[d]	μ/κ	δ/κ
10	58.2	448	17.4	3.34	25.7
18a	70.7	146	16.7	4.22	8.72
18b	13.1	67.9	7.63	1.72	8.90
23	17.6	52.2	1.92	9.17	27.2
12	3.21	43.6	0.84	3.82	52.0
27	187	410	56.5	3.31	7.26

[a] Binding assays were carried out in duplicate (k receptor: cerebellum of guinea pig, μ receptor and δ receptor: whole brain without cerebellum of mouse). [b] [^{3}H] DAMGO was used. [c] [^{3}H] DPDPE was used. [d] [^{3}H] U-69,593 was used.

As expected, the affinities of etheno- and ethano-bridged compounds **23** and **12** for opioid receptors were stronger than those of **10**. The increment of the affinity for the κ receptor was largest among the three types of opioid receptors. Compounds **23** and **12** also showed higher selectivity for κ receptor than **10**. These results support that the bent form would play an important role in binding to the κ receptor. Meanwhile, the affinity and selectivity of derivatives **18** and **27** for κ receptor, with hydroxyl and keto groups, respectively, were not high, despite being pentacyclic derivatives. The affinities of diketo compound **27** were especially lower for the μ and κ receptors compared to those of **10**, but similar for the δ receptor.

To clarify the reason why some pentacyclic propellane derivatives displayed higher affinity and selectivity for κ receptor, conformational analyses of these derivatives using the Conformational Analyzer with Molecular Dynamics And Sampling (CAMDAS) 2.1 program were carried out (**Fig. 9**).[25] The movement range of basic nitrogen in compound **10**, one of the important pharmacophores, was very wide (**Fig. 9A**). By contrast, the conformations of **23** and **12** (**Fig. 9B, C**) were rather fixed by introduction of the fifth additional ring. The more restricted range of basic nitrogens in **23** and **12** would result in improved affinities and selectivities for the κ receptor compared to **10**. Meanwhile, the nitrogens in compounds **18** and **27** are less basic because of the electron withdrawing hydroxyl and keto groups.[26] This phenomenon could account for compounds **18** and **27** not showing high affinities and selectivities for the κ receptor, although the possibility that the keto group in **27** or the hydroxyl group in **18** might interfere with the precise interaction of the compound with the κ receptor could not be ruled out. Keto compound **27**, which has the least basic nitrogen due to the inductive effect of the β-carbonyl group[26] among the three compounds (**18a**, **18b** and **27**), showed the weakest affinity for the opioid receptors. The basicity of the nitrogen may also influence the difference of binding affinities between **23** and **12**; the less basic nitrogen in **23**, which has the electron withdrawing olefin moiety,[27] may lower the binding affinities of **23** compared to those of **12**.

In summary, the author design and synthesized propellane derivatives with pentacyclic skeleton to fix the proposed active conformation of **10** and improve its affinity for the k receptor. Etheno- and ethano-bridged compounds **23** and **12**, respectively, showed high affinities and selectivities for the κ receptor. These results supported the hypothesis that the bent form of propellane **10** is important for binding to κ receptor. Compounds **23** and **12** may be useful skeletons for the development of the κ selective ligands.

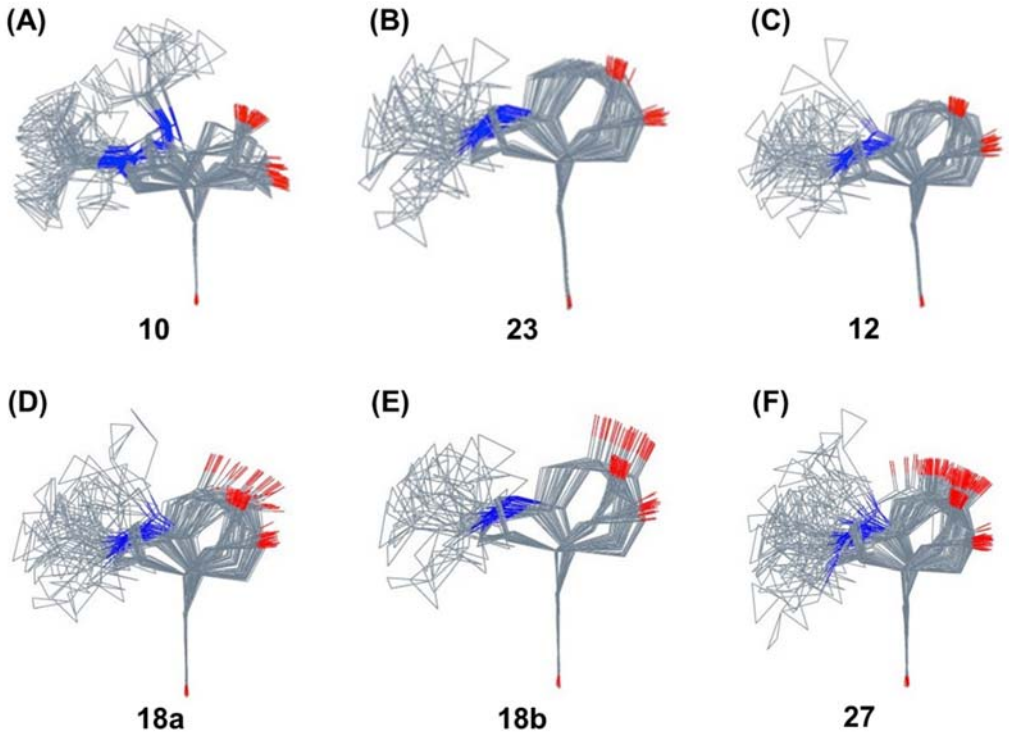


Fig. 9. Result of the conformational analysis of (A) parent propellane **10**, (B) etheno-bridged propellane **23**, (C) ethano-bridged propellane **12**, (D) 7'α-hydroxy propellane **18a**, (E) 7'β-hydroxy propellane **18b**, (F) 7'-keto propellane **27**. Structures within 10 kcal/mol of the most stable conformer were collected. The nitrogen, oxygen, and carbon atoms were indicated by blue, red, and gray colors, respectively. The hydrogen atoms were omitted for clarity.

2.4 Design of κ receptor selective pentacyclic propellane derivatives with a 6-amide side chain

As discussed in the previous section, etheno- and ethano-bridged pantacyclic propellane derivatives **23** and **12**, respectively, seemed to be promising lead compounds for development of the κ selective ligand.[22] Based on previous studies for development of the κ selective agonists,[20] the 6-amide side chain of morphinan derivatives such as nalfurafine (**5**) would be an important pharmacophore unit for binding to the κ receptor. However, the existing probability of the chair form of the C-ring in nalfurafine (**5**), considered to be disfavor conformation for the κ receptor, could not be ruled out. The author next attempted to introduce several kinds of amide side chain to pentacyclic derivatives **23** and **12** with the conformational fixed boat form by additional E-ring to improve affinities and selectivities for κ receptor.[28] Compared with the range of orientations of the amide side chain of nalfurafine (**5**), the one of designed 6β-amide derivatives with pentacyclic skeleton **33a** would be expected to show enhanced affinity and selectivity for κ receptor (**Fig. 10**).

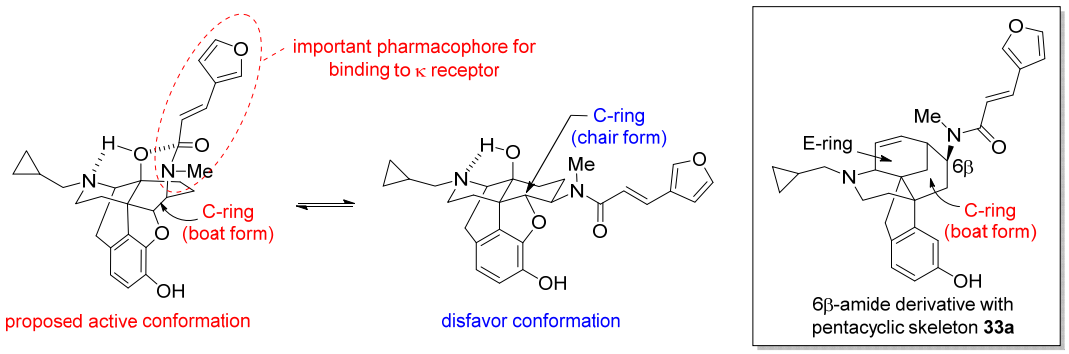
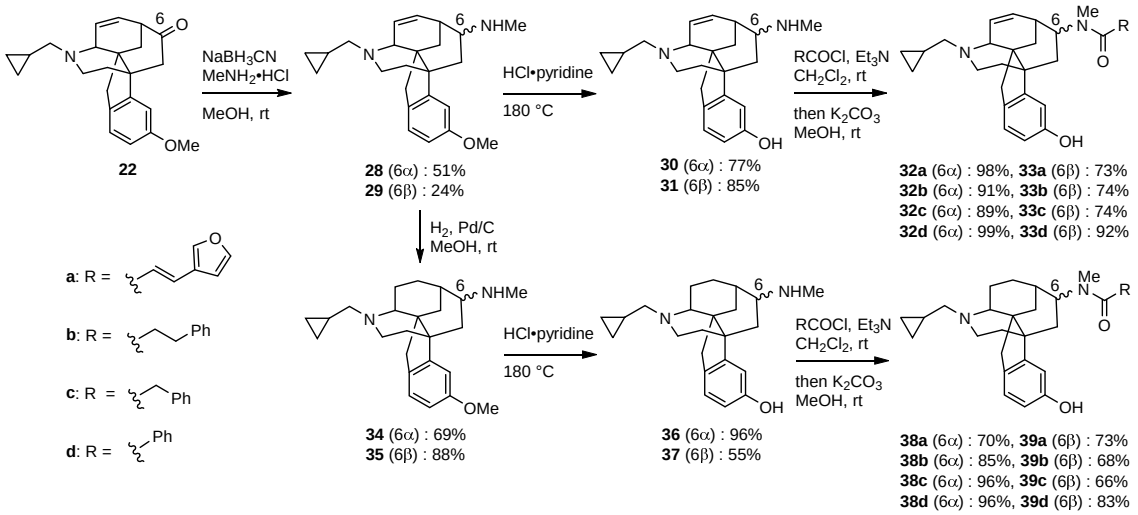


Fig. 10. Conformers of nalfurafine (**5**) and designed 6β-amide derivatives **33a**

2.5 Synthesis of pentacyclic propellane derivatives with a 6-amide side chain

All of the 6-amide derivatives **32a-d**, **33a-d**, **38a-d** and **39a-d** were synthesized from pentacyclic ketone **22**[22] (**Scheme 4**).[28] Reductive amination of **22** gave methylamines **28** and **29** in 51% and 24%, respectively.[29] At first, the author converted methylamines **28** and **29** to the corresponding amide derivatives by use of acyl chloride. However, the yields of the *O*-demethylation reaction in the obtained amide derivatives with boron tribromide were very low (0-28%), which may result from the decomposition of the sterically hindered amide group.[30] Therefore, the *O*-methyl groups in **28** and **29** were removed with pyridinium hydrochloride before acylation of the amine groups. The obtained phenolic compounds **30** and **31** were treated with acyl chlorides to successfully give the etheno-bridged amides **32a-d** and **33a-d**. The ethano-bridged compounds **34** and **35** were obtained by catalytic hydrogenation of **28** and **29** with Pd/C in MeOH. The demethylation of **34** and **35**, followed by amidation of the resulting phenols **36** and **37** afforded the amide derivatives **38a-d** and **39a-d**.



Scheme 4. Synthetic scheme of pentacyclic propellane derivatives with 6-amide side chain

2.6 Pharmacological effects of pentacyclic propellane derivatives with a 6-amide side chain

Table. 2. Binding affinities of nalfurafine, **23**, **12** and amide derivatives **32**, **33**, **38** and **39** to opioid receptors[a]

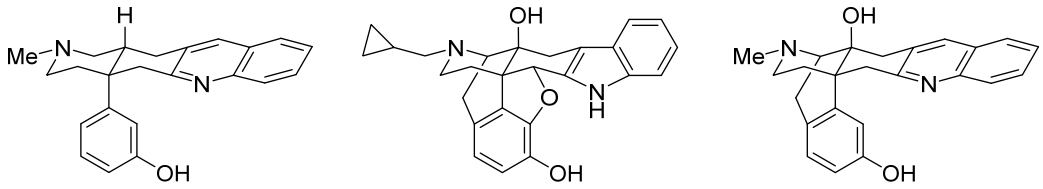
Compound	C(6)	R=	K_i (nM)			Selectivity	
			μ[b]	δ[c]	κ[d]	μ/κ	δ/κ
nalfurafine (**5**)	β	*trans*-(3-furyl)vinyl	0.431	51.3	0.178	2.42	288
23	–	-	17.6	52.2	1.92	9.17	27.2
12	–	-	3.21	43.6	0.84	3.82	52.0
32a	α	*trans*-(3-furyl)vinyl	0.570	3.98	0.230	2.48	17.3
32b	α	phenethyl	0.510	3.52	0.470	1.09	7.49
32c	α	benzyl	0.420	1.66	0.240	1.75	6.92
32d	α	phenyl	2.70	2.23	4.46	0.610	0.50
33a	β	*trans*-(3-furyl)vinyl	13.9	14.2	0.820	17.0	17.3
33b	β	phenethyl	4.36	10.7	1.86	2.34	5.75
33c	β	benzyl	12.2	4.50	1.73	7.05	2.60
33d	β	phenyl	47.6	6.46	13.1	3.63	0.493
38a	α	*trans*-(3-furyl)vinyl	0.232	0.182	0.204	1.14	0.89
38b	α	phenethyl	0.229	1.15	0.113	2.03	10.2
38c	α	benzyl	0.197	1.19	0.136	1.45	8.75
38d	α	phenyl	0.280	3.65	0.543	0.516	6.72
39a	β	*trans*-(3-furyl)vinyl	47.9	19.1	8.36	5.73	2.28
39b	β	phenethyl	11.5	32.4	11.9	0.966	2.72
39c	β	benzyl	59.6	15.0	11.0	5.42	1.36
39d	β	phenyl	56.0	1.27	13.8	4.06	0.092

[a] Binding assays were carried out in duplicate (κ receptor: cerebellum of guinea pig, μ and δ receptor: whole brain without cerebellum of mouse). [b][^{3}H] DAMGO was used. [c][^{3}H] DPDPE was used. [d][^{3}H] U-69,593 was used.

The results of binding assays of the obtained 6-amide derivatives for the opioid receptors are shown in **Table 2**. The affinities of the etheno- and ethano-bridged compounds **32** and **38**, respectively, with the 6α-amide side chain for the κ receptor were higher than those of **23** and **12** except for **32d**. However, selectivity of all 6α-isomers **32** and **38** for the κ receptor were lower than those of **23** and **12**. This result may occur from the improper orientation of the 6α-side chain toward the downward side of the C-ring. On the other hand, although ethano-bridged 6β-isomers **39** showed lower affinities for the κ receptor than did **12**, these 6β-amide derivatives showed higher μ/κ ratio than **12**, with the exception of **39b**. Meanwhile, both of the affinities and selectivities for the κ receptor of the etheno-bridged 6β-isomers **33b-d** were lower than those of etheno-bridged compound **23**. On the contrary, the etheno-bridged derivative **33a** with the same

amide side chain as in nalfurafine showed higher affinity for the κ receptor than did **23**, and furthermore, **33a** displayed the highest μ/κ ratio of all the previously reported propellane derivatives. Moreover, the μ/κ ratio of **33a** was seven times higher than that of nalfurafine (**5**). These outcomes indicated that not only the orientation of the amide side chain of **33a** toward the upper side of C-ring, but also the rigidity of the E-ring and the amide side chain could be important for interaction with the κ receptor.

Interestingly, the 6β-isomers **33d** and **39d** showed selectivity for the δ receptor, with the selectivity of **39d** for δ receptor being the highest of the compounds shown in **Table 2**. This selectivity may arise from the adequate orientation of the phenyl ring in **39d** for binding to the δ receptor in a manner similar to the orientation of the benzene ring in δ receptor selective ligands, TAN-67 (**6**),[14] NTI (**40**),[31] and KNT-127 (**41**)[17] (**Fig. 11**).



TAN-67 (**6**) NTI (**40**) KNT-127 (**41**)

Fig. 11. The structure of δ selective ligands, TAN-67 (**6**), NTI (**40**) and KNT-127 (**41**)

The agonist activity of **33a** for the κ receptor was evaluated by the [^{35}S]GTPγS binding assays (**Table 3**). The standard ligand U-69,593 (**4**) was also evaluated for comparison. **33a** showed full agonist activity corresponding to the standard κ agonist U-69,593 (**4**). Moreover, the EC_{50} value of **33a** was 2.3-fold lower than that of U-69,593 (**4**)

Table 3. The κ receptor-agonist activities of U-69,593 and **33a**[a]

Compound	EC_{50} (nM)	E_{max} (%)
U-69,593	28.1	100
33a	11.8	108

[a] Membranes were incubated with [^{35}S] GTPγS and GDP with the compound. The κ human recombinant cell membrane (CHO) was used in this assay. U-69,593 was used as the standard κ agonist. The data represent the means of four samples.

Next, antinociceptive effect induced with s.c.-administrated **33a** using the acetic acid writhing test (AAW test) was evaluated (**Fig. 12**). Compound **33a** showed a dose-dependent antinociceptive effect (ED_{50} = 0.589 mg/kg) in mice, which was antagonized by the κ selective antagonist nor-BNI (10 mg/kg). These results indicated that antinociceptive effect of **33a** in mice would be derived from the κ receptor.

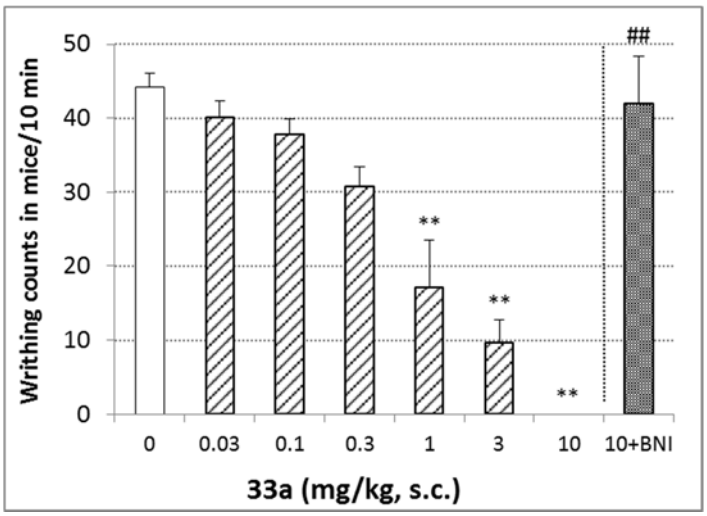


Fig. 12. Antinociceptive effect of **33a** in the acetic acid writhing test

Although nalfurafine (**5**) showed a strong antinociceptive effect (ED_{50} = 0.00622 mg/kg), the sedative effect was also strong in the clinical trial test for postoperative pain, which led us to give up nalfurafine (**5**) for this indication. The isolation of the sedation effect from the analgesic effect of **33a** and nalfurafine (**5**) were compared by evaluating their spontaneous locomotor activities (**Fig. 13**). Compound **33a** exhibited less sedative effect than did nalfurafine (**5**).

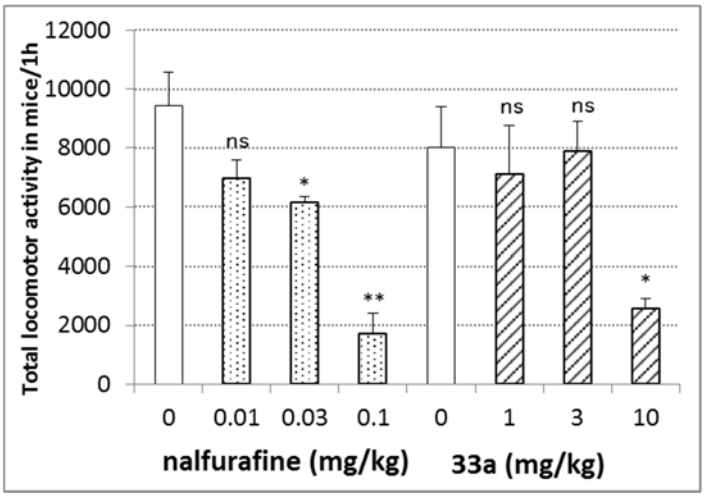


Fig. 13. Sedative effect of nalfurafine (**5**) and **33a** in the spontaneous locomotor activity test

The ED_{50} ratio between antinociceptive effect and sedation of YNT-854 was higher than that of nalfurafine (**Table. 4**), indicating that **33a** would be expected to act as an analgesic drug for postoperative pain with a lower sedative effect than nalfurafine.[28]

Table 4. The ED_{50} of antinociceptive effect and sedation effect and the ED_{50} ratio

Compound	%Antinociceptive ED_{50} (mg/kg)	%Sedation ED_{50} (mg/kg)	ED_{50} Ratio
nalfurafine (**5**)	0.00622	0.0344	5.5
33a	0.589	7.74	13.1

2.7 Conclusion

In conclusion, the author have designed and synthesized the pentacyclic derivatives with the amide side chain based on the proposed active conformation of nalfurafine (**5**). The obtained **33a** showed full agonist activity and the highest μ/κ ratio in all the reported propellane derivatives. Furthermore, the sedative effect of **33a** was notably separated from the analgesic effect, as compared to nalfurafine (**5**). Although the ED_{50} ratio of nalfurafine (**5**) is much higher than that of U-50,488H in mice, nalfurafine (**5**) showed a slightly narrow safety margin to be used for postoperative pain. Given the ED_{50} ratio of **33a** is 2.4 times higher than that of nalfurafine (**5**), **33a** would be applicable to postoperative pain. The fact that **33a** with the fixed amide chain toward the upper side of the C-ring showed higher μ/κ ratio than nalfurafine (**5**) supported the idea for an active conformation of the amide side chain in the nalfurafine (**5**) for binding to κ receptor (**Fig. 10**). Furthermore, the fact that **33a** showed a higher dose ratio between the sedative effect and the analgesic effect than nalfurafine (**5**) may provide a clue for the design of useful analgesics with weaker sedative effects than nalfurafine (**5**).

3. Design and Synthesis of δ Receptor Selective Quinolinopropellane Derivatives and Their Pharmacologies

3.1 The message-address concept and the δ receptor selective ligands

Portoghese successfully utilized the message-address concept as a useful guideline for design of type selective opioid ligands.[32] The message-address concept was advocated by Schwyzer to explain the organization of recognition elements in peptide hormones in 1977.[33] The concept termed the component of peptide responsible for receptor transduction "message", and the component of peptide providing additional binding affinity but not being essential for the transduction process "address". This concept was applied to endogenous opioid peptide by Goldstein *et al*,[34] and to general opioid ligands by Portoghese. In this concept of opioid ligands, message part is essential moiety for the intrinsic activities of opioid receptor and common structural part for binding to all three types of opioid receptors, and address part participates in selectivity for receptor types. It is known that ligands with smaller address part have selectivity for the μ receptor, ligands with bigger address part bind to the δ receptor and ligands with the biggest address moiety bind to the κ receptor. The several example of this concept for opioid receptor is shown in **Fig. 14**.

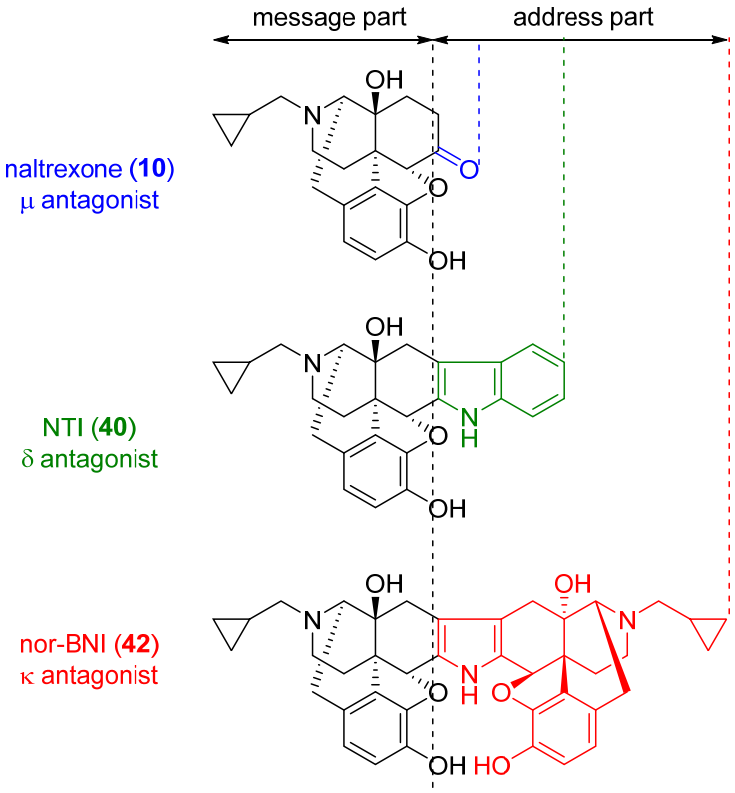


Fig. 14. Message-address moieties of selective antagonists for each opioid receptor types

Based on this concept, some δ selective ligands for opioid receptor types were developed. For instance, δ antagonists such as NTI (**40**),[31] NTB (**43**),[31] BNTX (**44**),[35] and SB-205588 (**45**),[36] δ agonists such as TAN-67 (**6**),[14] SB-219825 (**46**),[36] SN-28 (**47**),[37] and KNT-127 (**41**)[17] were designed and synthesized (**Fig. 15**). The δ receptor ligands possess various message structures, including 4,5-epoxymorphinan, morphinan, and 4a-phenyldecahydroisoquinoline structures.

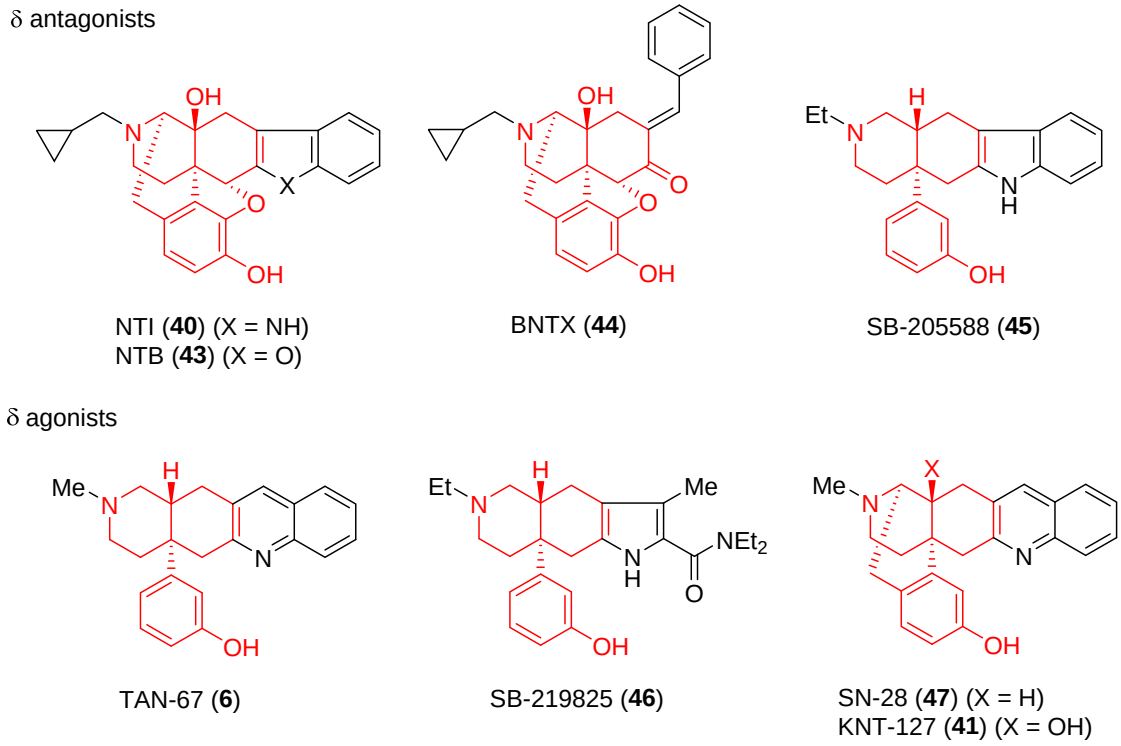


Fig. 15. The structure of δ antagonists and agonists (red line is message part)

3.2 Design of δ receptor selective propellane derivatives and *in silico* investigations

Recently, Li *et al*. reported that indolopropellane **48** (**Fig. 16**) exhibited almost no affinity for opioid receptors although Compound **48** has an indole moiety as a possible δ receptor address part like the selective δ antagonist NTI (**40**).[38] As mentioned in Chapter 2, indolopropellane **48** could have two canonical conformations, bent and extended forms (**Fig. 16**). The extended form, which resembles the stable conformation of NTI (**40**), could bind to the δ receptor. Indeed, the real binding conformation of NTI (**40**) unveiled by the X-ray crystallographic analysis of the NTI-δ receptor complex[16] is an extended form (**Fig. 17**). The lack of binding of indolopropellane **48** to the δ receptor may have ascribed that the bent conformer may be the most stable form.

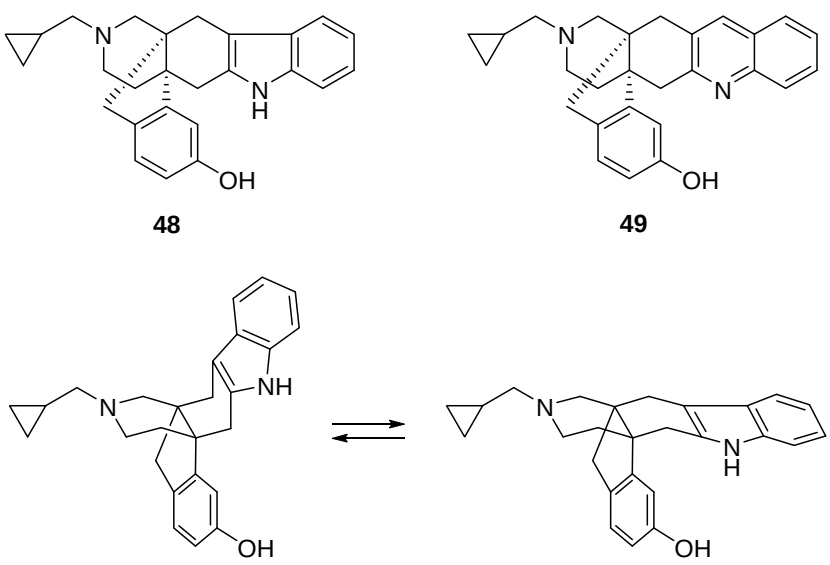


Fig. 16. Structure of indolopropellane **48**, quinolinopropellane **49**, and the bent and extended forms of **48**

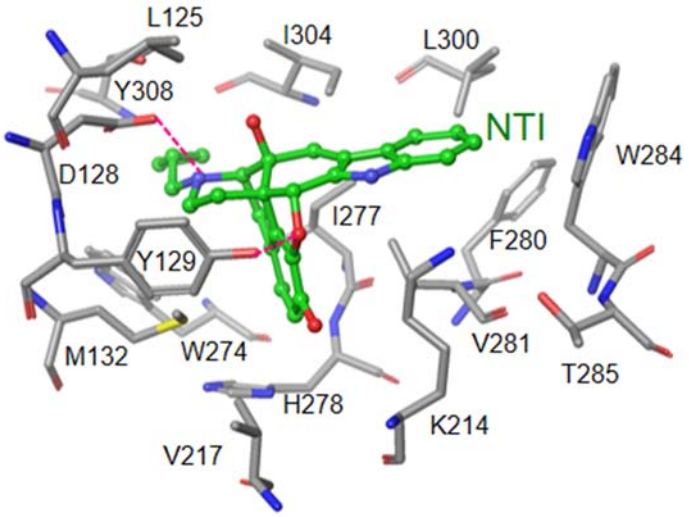


Fig. 17. The binding mode of NTI (**40**) observed in the X-ray structure of the NTI-δ receptor complex[16]

This working hypothesis suggests that the derivatives, which has stable extended conformation can interact with the δ receptor to stabilize the ligand-δ receptor complex, would enhance the binding affinity to the δ receptor. In the course of designing the selective δ agonist TAN-67 (**6**),[14] it is assumed that an hydrogen bond between the quinoline nitrogen and the δ receptor would lead to the δ agonistic activity. Based on the above discussion, quinolinopropellane **49** (**Fig. 16**) was designed to form the hydrogen bond with δ receptor, which would also need to stabilize the extended conformation for binding to the δ receptor.

First, the conformational analyses of NTI (**6**), indolo- and quinolinopropellane **48** and **49** using Conformational Analyzer with Molecular Dynamics And Sampling (CAMDAS) 2.1 program[25] were performed to confirm the above hypothesis related to the bent form and extended form conformers of **48** and **49**. When the low-energy conformers of NTI (**6**), **48** and **49** (those within 2.5 kcal/mol of global minimum) were superimposed (**Fig. 18**), the most lowest-energy conformers of both **48** and **49** were the bent form, while those of NTI (**6**), was the extended form as expected. The extended form of **48** and **49** appeared at the energy difference of 3-5 kcal/mol from the global minimum.

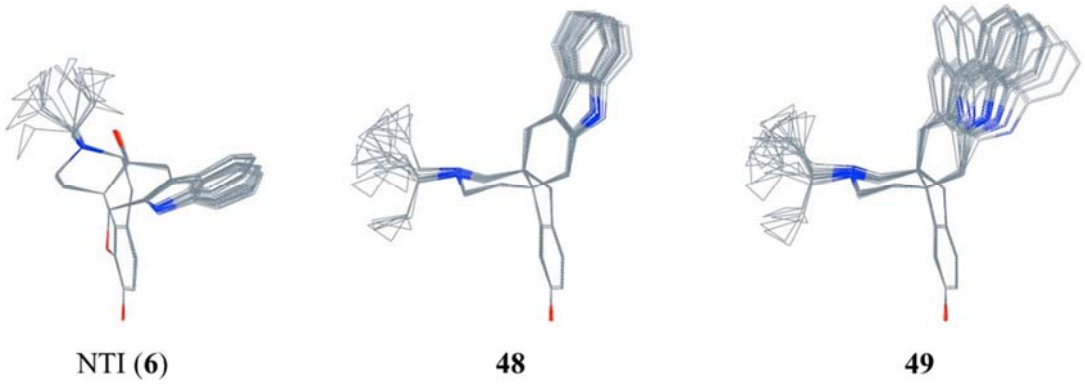


Fig. 18.The superposition of the low-energy conformers of NTI (**6**), **48** and **49**

Next, the binding modes of **48** and **49** with the δ receptor and their binding free energies (ΔG_{bind} values) were examined by using a combination method of the molecular-docking calculation[39] and the molecular mechanics Generalized-Born surface area (MM-GBSA) free energy analysis.[40] The resulting binding modes of **48** and **49** are shown in **Fig 19**, and their calculated ΔG_{bind} values are given in **Table 5**.

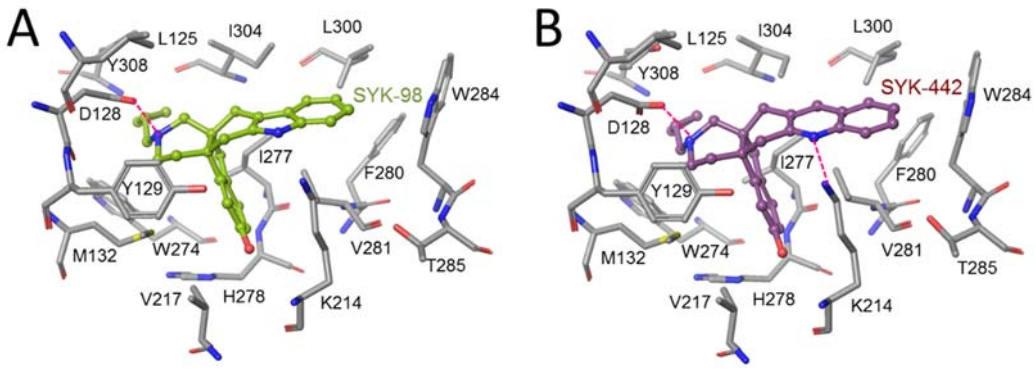


Fig. 19. The binding modes of **48** (A) and **49** (B) with the δ receptor determined by our docking procedure. Hydrogen-bonding interactions are indicated by red dashed lines.

Table 5. Energy contributions (kcal/mol) to the binding free energy of **48** and **49** to the δ receptor

Energy contribution	**48**	**49**	Energy difference[a]
ΔE_{int}[b]	3.19	2.80	0.39
ΔE_{VDW}[c]	–50.03	–48.59	–1.44
ΔE_{elec}[d]	–11.93	–25.47	13.54
ΔG_{GB}[e]	11.06	13.99	–2.93
ΔG_{SA}[f]	–6.28	–8.15	1.87
ΔG_{bind}[g]	–53.99	–65.42	11.43

[a] Differences of energy contributions of **48** and **49**

[b] Internal contributions from bond, angle, dihedral terms.

[c] Nonbonded van der Waals.

[d] Nonbonded electronstatics.

[e] Electrostatic component to solvation.

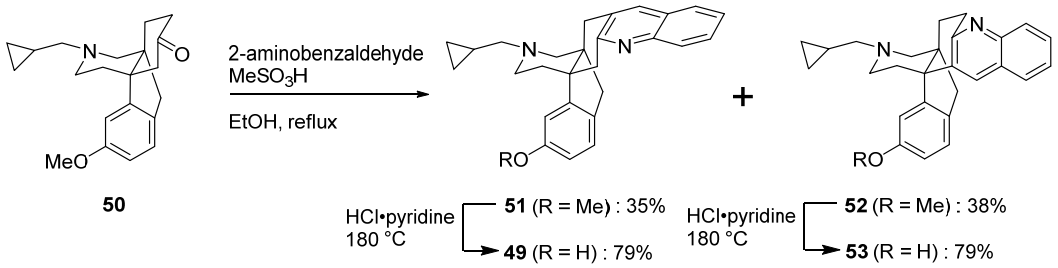
[f] Nonpolar component to solvation.

[g] Total change of free energy in binding

Indoropropellane **48** was shown to bind with the δ receptor in its extended form (**Fig. 19A**). This result strongly supported the working hypothesis that the extremely low affinity of **48** to the δ receptor may result from the fact that **48** could not bind to the δ receptor when the ligand existed in the low-energy bent form. In other words, the binding of **48** to the δ receptor would require a considerable energy penalty to adopt the high-energy extended form, which is suited to bind to the δ receptor as shown in the crystal structure of the NTI-δ receptor complex[16] (**Fig. 18**). On the other hand, the binding mode of quinolinopropellane **49** (**Fig. 20A**) proposed that the extended form of **49** could also bind to the δ receptor.[41] Interestingly, the lone electron pair on the nitrogen atom in the quinoline ring in **49** could form a hydrogen bonding interaction with the NH_3^+ of Lys^{214} residue. A similar hydrogen bond was not observed in the **48**-δ receptor complex, because **48** possessed the indole ring which lacks a lone electron pair. Owing to the additional hydrogen bonding interaction, the electrostatic interaction (ΔE_{elec}) of **49** with the δ receptor was suggested to be much greater than that of **48** (**Table 5**). This situation inevitably led to a much better ΔG_{bind} value for **49**. Taken together, the above observations suggest that the additional hydrogen bonding interaction in the 49-δ receptor complex might compensate for any energy penalty, allowing **49** to adopt the high-energy extended form upon binding. The obtained binding mode of quinolinopropellane **49** with the δ receptor included the hydrogen bonding with the Lys^{214} residue, whereas a corresponding interaction with Lys^{214} residue was not observed in the crystal structure of the NTI (**6**)-δ receptor complex.[16] In the course of δ agonist TAN-67 discovery, the hydrogen bonding with the δ receptor was proposed to be important in producing the δ agonist activity.[14] Therefore, quinolinopropellane **49** was expected to produce the δ receptor agonism. To confirm the *in silico* results, the author synthesized the quinolinopropellnae derivatives.

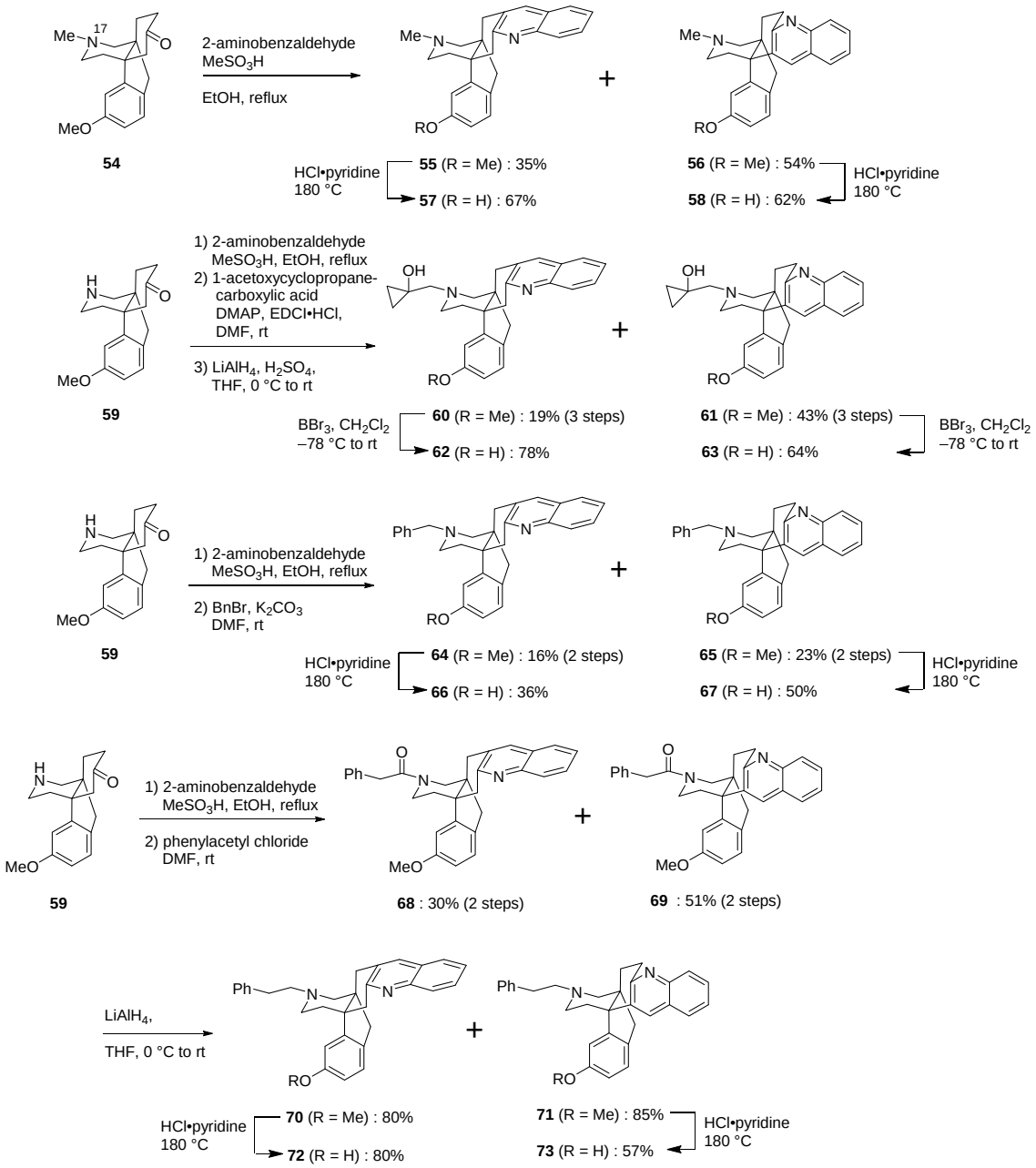
3.3 Synthesis of quinolinopropellane derivatives

Synthetic method of quinolinopropellane **49** and its regioisomer **53** is shown in **Scheme 5**.[42] A Friedländer quinoline synthesis[43] of **50**[18] with 2-aminobenzaldehyde provided desired quinolinopropellane **51** and its regioisomer **52** in 35% and 38% yield, respectively. *O*-Demethylation of **51** and **52** with pyridinium chloride to give the corresponding phenol **49** and **53** in 79% and 79% yield, respectively.



Scheme 5. Synthetic method of quinolonopropellane **49** and its regioisomer **53**

The author also synthesized 17-*N*-substituted quinolinopropellane derivatives to investigate the effects of *N*-substituents, considered to be important for selectivity for the opioid receptors (**Scheme 6**). *N*-Me quinolinopropellane **55** and its regioisomer **56** were obtained by Friedländer quinoline synthesis of **54**[18] in 35% and 54 % yield, respectively. The methoxy groups in compound **55** and **56** were demethylated with pyridinium chloride to afford phenol **57** and **58** in 67% and 62% yield, respectively. *N*-(1-OH-CPM) quinolinopropellane **60** and its regioisomer **61** were furnished by Friedländer quinoline synthesis of **59**, followed by amidation with 1-acetoxycyclopropanecarboxylic acid and reduction of the obtained amide by alane[44] in 19% and 43 % yield in three steps, respectively. A Friedländer quinoline synthesis of **59**, followed by S_N2 reaction with BnBr to afford *N*-Bn quinolinopropellane **64** and its regioisomer **65** in 16% and 23% yield in two steps, respectively. *O*-Demethylation of **64** and **65** with pyridinium chloride to give phenol **66** and **67** in 78% and 64% yield, respectively. Finally, A Friedländer quinoline synthesis of **59**, followed by amidation with phenylacetyl chloride to provide the corresponding amide **68** and its regioisomer **69** in 30% and 51% yield in two steps, respectively. *N*-Phenethyl quinolinopropellane **70** and **71** was obtained by reduction of amide **68** and **69** with $LiAlH_4$ in 80% and 85% yield in two steps, respectively. *O*-Demethylation of **70** and **71** with pyridinium chloride afforded phenol **72** and **73** in 80% and 57% yield in two steps, respectively.



Scheme 6. Synthesis of *N*-substituted quinolonopropellane derivatives and their regioisomers

3.4 Pharmacological effects of the obtained quinolinopropellane derivatives

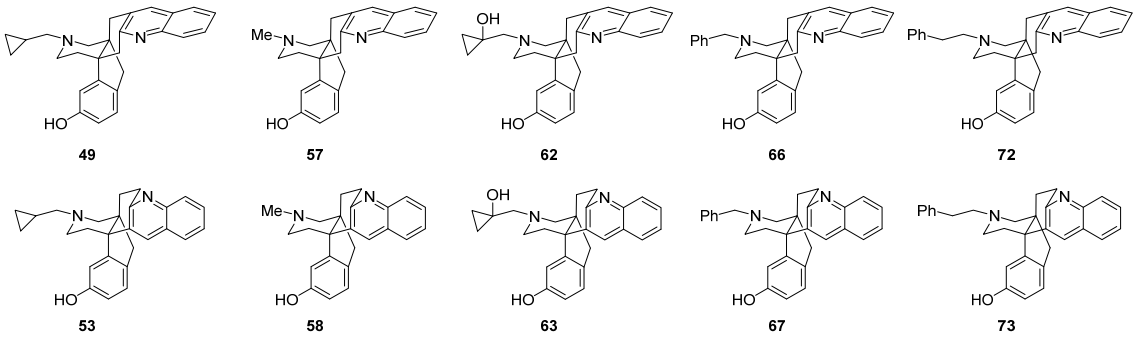


Fig. 20. The structure of the obtained quinolinopropellane derivatives

Table. 6. Binding affinities of quinolinopropellane derivatives **49**, **57**, **62**, **66** and **72** and those regioisomers **53**, **58**, **63**, **67** and **73** to the opioid receptors[a]

Compound	K_i (nM)			Selectivity	
	μ[b]	δ[c]	κ[d]	μ/δ	κ/δ
49	112	0.941	84.6	119	89.9
57	3.06	1.88	195	1.63	104
62	415	1.10	879	378	801
66	2.32	178	>1000	0.013	-
72	76.3	31.6	594	2.42	18.8
53	588	124	446	4.73	3.58
58	8.37	17.9	790	0.467	44.1
63	660	168	113	3.94	0.675
67	101	398	>1000	0.253	-
73	182	68.6	115	2.65	1.67

[a] Binding assays were carried out in duplicate (κ receptor: cerebellum of guinea pig, μ and δ receptor: whole brain without cerebellum of mouse). [b][^{3}H] DAMGO was used. [c][^{3}H] DPDPE was used. [d][^{3}H] U-69,593 was used.

The binding affinities of the synthesized quinolinopropellane derivatives **49**, **57**, **62**, **66** and **72** and those regioisomers **53**, **58**, **63**, **67** and **73** to the opioid receptors were evaluated by competitive assays (**Table 6**). As expected, quinolinopropellane derivatives **49**, **57** and **62** showed high binding affinities for the δ receptor. However, *N*-Me derivative **57** exhibited extremely low selectivity for the δ receptor compared to *N*-cyclopropylmethyl derivatives **49** and **62**, derived from its high affinity for the μ receptor. Quinolinopropellane **49** with *N*-cyclopropylmethyl group had the highest binding affinity for the δ receptor, while *N*-(1-hydroxycyclopropylmethyl) derivative **62** showed the highest selectivity for the δ receptor, although its binding affinity for

the δ receptor was slightly decreased compared with that of **49**. On the other hand, *N*-Bn and *N*-phenethyl derivatives **66** and **72** exhibited low binding affinities for the δ receptor, which may indicate that phenyl group of **66** and **72** would be inappropriate for binding to the δ receptor. Meanwhile, regioisomers **53**, **58**, **63**, **67** and **73** showed lower affinities for the δ receptor than did the corresponding isomers **49**, **57**, **62**, **66** and **72**. These results would be derived from inappropriate orientation of lone electron pair of quinoline ring, expected to be an important pharmacophore for the δ receptor in the proposed working hypothesis.

Table 7. The δ receptor-Agonist activities of **49** and **62**[a]

Compound	EC_{50} (nM)	E_{max} (%)
49	2.50	88
62	15.4	95

[a] Membranes were incubated with [^{35}S] GTPγS and GDP with the compound. The δ human recombinant cell membrane (CHO) was used in this assay. DPDPE was used as the standard δ agonist. The data represent the means of four samples.

To confirm the working hypothesis, the functional activities of selected compounds **49** and **62**, which exhibited high selectivities for the δ receptor, were evaluated by [^{35}S] GTPγS binding assays (**Table 7**). As expected, both of these quinolinopropellanes exhibited δ receptor full agonist activity. Compared to *N*-hydroxycyclopropylmethyl derivative **62**, *N*-cyclopropylmethyl derivative **49** showed lower EC_{50} value, indicating *N*-cyclopropylmethyl group would be suitable for binding to the δ receptor. The results of *in vitro* evaluations supported the working hypothesis and the *in silico* experimental results. Furthermore, these observations indicate that the hydrogen bonding interaction between a ligand and the Lys^{214} residue in the δ receptor plays a crucial role in not only obtaining strong binding ability but also exerting δ receptor agonist activity.

3.5 Conclusion

The working hypothesis have been developed, that almost no binding affinity of indolopropellane **48** to the δ receptor would be derived from its possibly extremely stable bent conformer. To enable the bent conformation of propellane skeleton to convert to the extended conformation, which could be expected to interact with the δ receptor, quinolinopropellanes derivatives were designed which had an additional pharmacophore, the quinoline nitrogen. The calculated binding free energies of ligand-δ receptor complexes supported the working hypothesis. The synthesized quinolinopropellane derivatives **49** and **62** showed selective δ receptor full agonist activities, confirming the working hypothesis and the outcomes of *in silico* investigations.

4. Conclusion

The author developed the working hypothesis that the bent form and the extended form of propellane compounds would be important for binding to the κ and δ receptors, respectively (**Fig. 21**). Based on this hypothesis, the author designed and synthesized pentacyclic propellane derivatives with fixed bent form to bind to κ receptor and quinolinopropellnane derivatives possessing lone electron pair of quinoline to stabilize the extend form of propellane by ligand-δ receptor interaction to bind to δ receptor. As expected, obtained pentacyclic propellane derivative **33a** with amide side chain and quinolinopropellane **49** exhibited high affinity and selectivity for the κ receptor and the δ receptor, respectively.

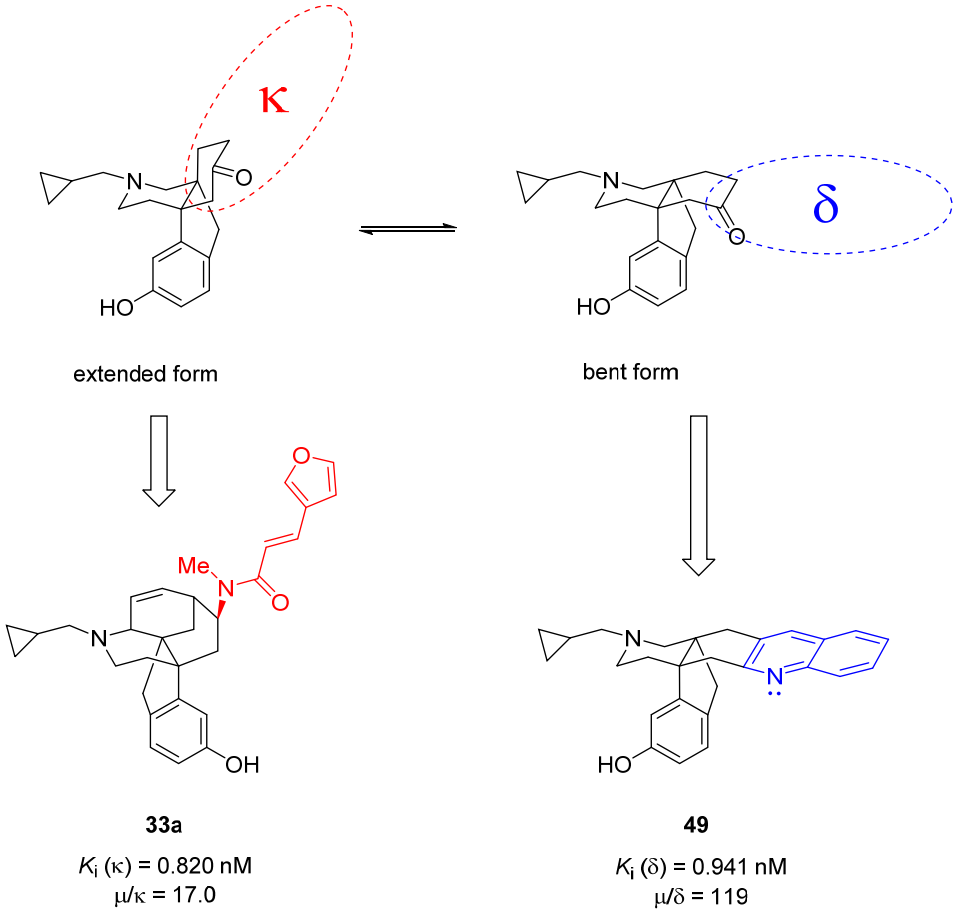


Fig. 21. The working hypothesis of propellane compounds and the structure of κ selective penatacyclic propellane derivative **33a** with amide side chain and δ selective quinolino-propellane **49**

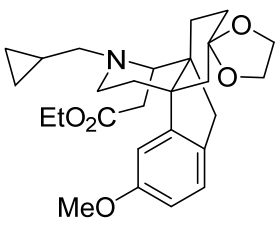
Experimental section

Chemistry

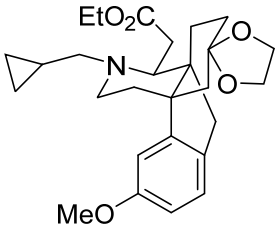
Melting points were determined on a Yanako MP-500P melting point apparatus and were uncorrected. Infrared (IR) spectra were recorded on a JASCO FT/IR-460Plus. Nuclear magnetic resonance (NMR) spectra were recorded on Agilent Technologies Mercury-300 at 300MHz for ^{1}H NMR and 75.5 MHz for ^{13}C NMR. NMR chemical shifts were reported in δ (ppm) using residual solvent peaks as standard ($CDCl_3$, 7.26 ppm (^{1}H), 77.0 ppm (^{13}C); THF-d_8, 3.58 ppm (^{1}H), 67.6 ppm (^{13}C); Pyridine-d_5, 8.74 ppm (^{1}H), 150.4 ppm (^{13}C)). Mass spectra (MS) were obtained on a JMS-AX505HA, JMS-700 MStation, or JMS-100LP instrument by applying an electron ionization (EI), a fast atom bombardment (FAB), or an electrospray ionization (ESI) method. Elemental analyses were determined with a Yanako MT-5 and JM10 for carbon, hydrogen, and nitrogen. The progress of the reaction was determined on Merck Silica Gel Art. 5715 (0.25 mm). Column chromatographies were carried out using Kanto Silica Gel 60N (neutral, spherical, 40–100 μm).

Ethyl 2-[(4a*R*,9a*R*,10*R*)-11-(cyclopropylmethyl)-6-methoxy-1,2,4,9-tetrahydrospiro[4a,9a-(ethanoiminomethano)fluorene-3,2'-[1,3] dioxolan]-10-yl]acetate (13a)

Ethyl 2-[(4aR,9aR,10S)-11-(cyclopropylmethyl)-6-methoxy- 1,2,4,9-tetrahydrospiro[4a,9a-(ethanoiminomethano)fluorene-3,2'-[1,3] dioxolan]-10-yl]acetate (13b)



13a



13b

To a suspension of Zn dust (6.77 g, 103 mmol) in THF (20 mL) was added a solution of **9** (4.82 g, 10.4 mmol) and ethyl bromoacetate (3.44 mL, 31.1 mmol) in THF (40 mL) at room temperature under an argon atmosphere. The reaction mixture was stirred at 60 °C for 1 h. The cooled reaction mixture was filtered through a Celite pad and the Celite pad was washed with AcOEt. After concentration of the filterate, the reaction mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/AcOEt = 3/1) to give **13a** (2.80 g, 59%) as a yellow oil and **13b** (1.28 g, 27%) as a yellow oil.

13a

IR (film) cm^{-1}: 3075, 2940, 2833, 1731, 1613, 1492, 1274, 1097, 1037, 801.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.01–0.13 (m, 2H), 0.40–0.55 (m, 2H), 0.74–0.90 (m, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.30–1.37 (m, 1H), 1.39–1.66 (m, 4H), 1.79–1.92 (m, 1H), 1.97 (dd, *J* = 14.5, 2.4 Hz, 1H), 2.08–2.18 (m, 1H), 2.22 (d, *J* = 8.5 Hz, 1H), 2.26–2.43 (m, 3H), 2.51 (dd, *J* = 13.1, 6.3 Hz, 1H), 2.61 (dd, *J* = 17.2, 1.9 Hz, 1H), 3.00 (dt, *J* = 12.1, 3.4 Hz, 1H), 3.09 (dd, *J* = 6.0, 2.0 Hz, 1H), 3.27 (d, *J* = 14.9 Hz, 1H), 3.76–3.99 (m, 4H), 3.79 (s, 3H), 4.08–4.25 (m, 2H), 6.63–6.70 (m, 2H), 7.08 (d, *J* = 7.8 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.5, 4.8, 8.1, 14.2, 29.3, 30.5, 35.1, 37.2, 37.4, 38.0, 48.0, 48.6, 48.7, 55.3, 57.8, 59.3, 60.6, 63.8, 64.2, 108.5, 109.1, 111.0, 126.1, 131.1, 152.9, 158.1, 173.6.

MS (ESI): *m/z* = 456$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{27}H_{38}NO_5$: 456.2750. Found: 456.2772.

13b

IR (film) cm^{-1}: 3075, 2939, 2833, 1733, 1611, 1489, 1282, 1489, 1282, 1157, 1036, 755.

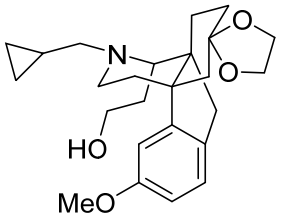
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) –0.14–0.03 (m, 2H), 0.29–0.47 (m, 2H), 0.60–0.74 (m, 1H), 1.19 (t, *J* = 7.1 Hz, 3H), 1.42–1.59 (m, 3H), 1.66–1.84 (m, 4H), 1.87–2.00 (m, 1H), 2.14–2.30 (m, 1H), 2.31–2.50 (m, 5H), 2.69 (td, *J* = 13.7, 4.5 Hz, 1H), 2.98 (d, *J* = 15.5 Hz, 1H), 3.03–3.12 (m, 1H), 3.77–3.91 (m, 2H), 3.78 (s, 3H), 3.95–4.17 (m, 4H), 6.57 (d, *J* = 2.4 Hz, 1H), 6.66 (dd, *J* = 8.1, 2.4 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.1, 5.1, 8.7, 14.1, 22.6, 27.4, 30.5, 35.3, 37.5, 45.5, 49.3, 50.1, 50.1, 55.4, 58.5, 60.4, 62.4, 63.4, 64.5, 107.9, 108.0, 111.2, 126.4, 133.1, 151.5, 158.8, 173.8.

MS (ESI): *m/z* = 456$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{27}H_{38}NO_5$: 456.2750. Found: 456.2751.

2-[(4a*R*,9a*R*,10*R*)-11-(Cyclopropylmethyl)-6-methoxy-1,2,4,9-tetrahydrospiro[4a,9a-(ethanoiminomethano)fluorene-3,2'-[1,3]dioxolan]-10-yl]ethanol (14a)



14a

To a suspension of $LiAlH_4$ (831 mg, 21.9 mmol) in THF (20 mL) was added a solution of **13a** (1.66 g, 3.65 mmol) in THF (20 mL) at 0 °C under an argon atmosphere. The reaction mixture was stirred at room temperature for 30 min. The reaction mixture was quenched with saturated $NaHCO_3$ aqueous solution dropwise at 0 °C and stirred for 30 min at the same temperature. After addition of anhydrous Na_2SO_4, the mixture was filtered through a Celite pad and the Celite pad was washed with AcOEt. After concentration of the filterate, the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH/25% ammonia aqueous solution = 100/1/0.1 to 100/5/0.5) to give **14a** (1.51 g, quant.) as a colorless amorphous solid.

14a

IR (KBr) cm^{-1}: 3423, 2935, 1492, 1272, 1097, 1034, 812, 669.

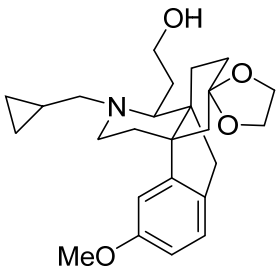
^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.06–0.17 (m, 2H), 0.43–0.58 (m, 2H), 0.75–0.89 (m, 1H), 1.24–1.81 (m, 6H), 1.84–2.28 (m, 5H), 2.28–2.47 (m, 3H), 2.48–2.53 (m, 1H), 2.72 (dd, *J* = 12.8, 6.2 Hz, 1H), 3.09 (dt, *J* = 12.6, 3.8 Hz, 1H), 3.27 (dd, *J* = 21.1, 15.1 Hz, 1H), 3.60–4.07 (m, 6H), 3.79 (s, 3H), 6.64 (d, *J* = 2.3 Hz, 1H), 6.68 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.6, 4.7, 8.7, 29.4, 29.7, 30.6, 32.3, 35.8, 37.9, 47.3, 48.6, 48.7, 55.3, 58.4, 62.7, 63.0, 63.8, 64.2, 108.5, 109.0, 111.0, 126.1, 131.6, 152.7, 158.1.

MS (ESI): *m/z* = 414$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{25}H_{36}NO_4$: 414.26443. Found: 414.2646.

2-[(4a*R*,9a*R*,10*S*)-11-(Cyclopropylmethyl)-6-methoxy-1,2,4,9-tetrahydrospiro[4a,9a-(ethanoiminomethano)fluorene-3,2'-[1,3]dioxolan]-10-yl]ethanol (14b)



14b

Compound **14b** was prepared from compound **13b** according to the procedure used to synthesize compound **14a**. Yield, 83%.; a yellow oil.

14b

IR (film) cm^{-1}: 3399, 3076, 2949, 2877, 1610, 1488, 1283, 1041, 754.

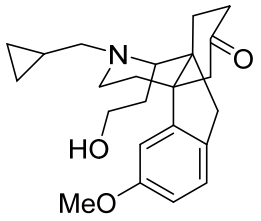
^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.00–0.18 (m, 2H), 0.42–0.59 (m, 2H), 0.71–0.88 (m, 1H), 1.52 (d, *J* = 14.3 Hz, 1H), 1.60 (dd, *J* = 14.1, 1.6 Hz, 1H), 1.66–2.15 (m, 10H), 2.18–2.33 (m, 1H), 2.49 (d, *J* = 15.8 Hz, 1H), 2.65–2.76 (m, 1H), 2.81 (dd, *J* = 13.7, 4.3 Hz, 1H), 3.00–3.10 (m, 1H), 3.18–3.29 (m, 1H), 3.84–4.25 (m, 5H), 3.86 (s, 3H), 6.65 (d, *J* = 2.4 Hz, 1H), 6.73 (dd, *J* = 8.1, 2.4 Hz, 1H), 7.16 (d, *J* = 8.1 Hz, 1H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.4, 4.9, 10.2, 22.6, 24.3, 28.0, 30.5, 36.3, 45.6, 46.9, 48.9, 50.4, 51.9, 55.3, 63.5, 64.1, 64.2, 64.4, 108.0, 108.0, 111.2, 126.1, 133.0, 151.8, 158.9.

MS (ESI): *m/z* = 414$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{25}H_{36}NO_4$: 414.2644. Found: 414.2638.

(4a*R*,9a*R*,10*R*)-11-(Cyclopropylmethyl)-10-(2-hydroxyethyl)-6-methoxy-4,9-dihydro-1*H*-4a,9a-(ethanoiminomethano)fluoren-3(2*H*)-one (15a)



15a

To a stirred solution of **14a** (1.73 g, 4.19 mmol) in MeOH (3 mL) was added 2 M HCl (3mL) at room temperature under an argon atmosphere. After 4 h with stirring, the reaction mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution at 0 °C and extracted with $CHCl_3$ three times. The combined organic extracts were dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH/25% ammonia aqueous solution = 100/1/0.1 to 100/5/0.5) to give **15a** (1.25 g, 81%) as a colorless amorphous solid.

15a

IR (film) cm^{-1}: 3412, 2936, 1611, 1588, 1491, 1463, 1286, 1033.

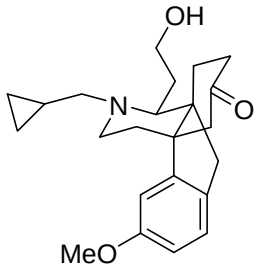
^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.10–0.17 (m, 2H), 0.47–0.56 (m, 2H), 0.82–0.89 (m, 1H), 1.51 (ddd, *J* = 13.8, 5.4, 2.4 Hz, 1H), 1.65 (ddd, *J* = 13.8, 10.8, 3.0 Hz, 1H), 1.72–1.81 (m, 2H), 1.86–1.96 (m, 2H), 1.99–2.05 (m, 1H), 2.26–2.36 (m, 2H), 2.50 (t, *J* = 12.0 Hz, 1H), 2.57 (d, *J* = 12.6 Hz, 1H), 2.59 (d, *J* = 12.6 Hz, 1H), 2.71 (br s, 1H), 2.75 (dd, *J* = 12.6, 6.0 Hz, 1H), 2.85 (d, *J* = 16.2 Hz, 1H), 3.05–3.10 (m, 1H), 3.49 (d, *J* = 15.6 Hz, 1H), 3.75 (s, 3H), 3.77–3.85 (m, 2H), 6.57 (d, *J* = 2.4 Hz, 1H), 6.68 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), a proton (OH) was not observed.

^{13}C NMR (150 MHz, $CDCl_3$): δ (ppm) 3.4, 4.8, 8.8, 31.2, 33.2, 35.2, 36.9, 39.0, 44.7, 46.6, 48.9, 51.2, 55.3, 57.9, 60.8, 62.4, 107.7, 112.6, 126.0, 132.2, 150.7, 159.1, 211.3.

MS (ESI): *m/z* = 370 $[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{23}H_{32}NO_3$: 370.2382. Found: 370.2376.

(4a*R*,9a*R*,10*S*)-11-(Cyclopropylmethyl)-10-(2-hydroxyethyl)-6-methoxy-4,9-dihydro-1*H*-4a,9a-(ethanoiminomethano)fluoren-3(2*H*)-one (15b)



15b

Compound **15b** was prepared from compound **14b** according to the procedure used to synthesize compound **15a**. Yield, 95%.; a yellow oil.

15b

IR (film) cm^{-1}: 3413, 2955, 1711, 1610, 1588, 1485, 1459, 1428, 1330, 1033.

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.00–0.09 (m, 2H), 0.41–0.50 (m, 2H), 0.65–0.75 (m, 1H), 1.68–1.87 (m, 3H), 1.88–2.01 (m, 2H), 2.16–2.24 (m, 2H), 2.24–2.38 (m, 4H), 2.43 (d, *J* = 13.6 Hz, 1H), 2.48–2.57 (m, 2H), 2.76 (d, *J* = 16.0 Hz, 1H), 3.12 (d, *J* = 15.6 Hz, 1H), 3.21 (td, *J* = 8.8, 4.0 Hz, 1H), 3.54–3.62 (m, 1H), 3.64–3.72 (m, 1H), 3.77 (s, 3H), 6.56 (d, *J* = 2.4 Hz, 1H), 6.70 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.12 (d, *J* = 8.0 Hz, 1H), a proton (OH) was not observed.

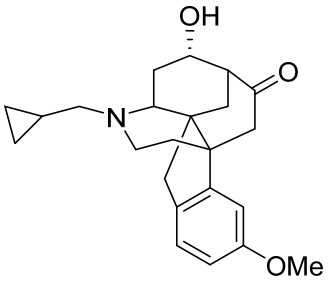
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 3.8, 4.1, 9.7, 27.2, 27.6, 31.6, 36.9, 37.6, 47.4, 49.9, 52.5, 53.6, 55.3, 56.5, 63.2, 63.3, 107.7, 112.0, 126.1, 132.7, 149.9, 159.1, 211.1.

MS (ESI): *m/z* = 370 $[M+H]^+$.

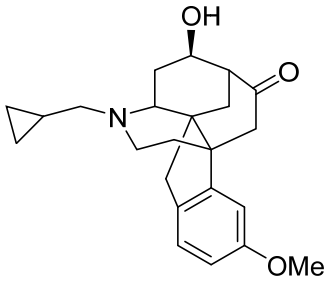
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{23}H_{32}NO_3$: 370.2382. Found: 370.2388.

(2*S*,3*S*,4a*S*,7a*R*,12a*R*)-5-(Cyclopropylmethyl)-3-hydroxy-9-methoxy-2,3,4,4a,5,6,7,12-octahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-one (17a)

(2*S*,3*R*,4a*S*,7a*R*,12a*R*)-5-(Cyclopropylmethyl)-3-hydroxy-9-methoxy-2,3,4,4a,5,6,7,12-octahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-one (17b)



17a



17b

To a solution of oxalyl chloride (246 μL, 2.84 mmol) in CH_2Cl_2 (3 mL) was added DMSO (402 μL, 5.68 mmol) dropwise at –78 °C and stirred for 15 min under an argon atmosphere. To the stirred reaction mixture was added a solution of mixture of **15a** and **15b** (500 mg, 1.35 mmol) in CH_2Cl_2 (4 mL) dropwise. After 1 h with stirring at the same temperature, to the stirred reaction mixture was added Et_3N (1.13 mL, 8.12 mmol) and then allowed to warm gradually to room temperature for 2 h. the reaction mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH/25% ammonia aqueous solution = 100/1/0.1 to 100/5/0.5) to give a yellow oil (431 mg). The oil (431 mg) was dissolved in MeOH (2 mL), and then K_2CO_3 (400 mg, 2.89 mmol) was added to the solution at room temperature. After 7 h with stirring at the same temperature, the reaction mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by preparative TLC (hexane/AcOEt/MeOH/25% ammonia aqueous solution = 200/100/100/1) to give **17a** (50.6 mg, 10% in two steps) as a colorless amorphous solid and **17b** (247 mg, 50% in two steps) as a colorless amorphous solid.

17a

IR (film) cm^{-1}: 3406, 2929, 1696, 1610, 1586, 1481, 1282, 1213.

^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.08–0.17 (m, 2H), 0.44–0.55 (m, 2H), 0.81–0.90 (m, 1H), 1.48 (d, *J* = 14.0 Hz, 1H), 1.53–1.74 (m, 1H), 1.80 (dd, *J* = 14.0, 2.8 Hz, 1H), 1.85–1.92 (m, 2H), 2.04 (dd, *J* = 14.0, 2.0 Hz, 1H), 2.29 (dd, *J* = 12.8, 6.8 Hz, 1H), 2.37 (d, *J* = 15.2 Hz, 1H), 2.45 (d, *J* = 2.0 Hz, 1H), 2.49–2.66 (m, 4H), 2.94 (d, *J* = 19.2 Hz, 1H), 3.44 (t, *J* = 8.8 Hz, 1H), 3.74 (d, *J* = 15.2 Hz, 1H), 3.78 (s, 3H), 4.20 (d, *J* = 2.4 Hz, 1H), 6.63 (d, *J* = 2.4 Hz, 1H), 6.69 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), a proton (OH) was not observed.

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 3.2, 4.1, 9.7, 26.1, 29.9, 38.5, 40.6, 41.4, 44.9, 46.4, 46.6, 52.6, 54.7, 55.4, 59.4, 68.2, 107.9, 111.7, 126.5, 132.9, 152.6, 158.7, 212.2.

MS (ESI): *m/z* = 368 $[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{23}H_{30}NO_3$: 368.2225. Found: 368.2224.

17b

IR (film) cm^{-1}: 3412, 2923, 1698, 1610, 1586, 1480, 1284, 1215.

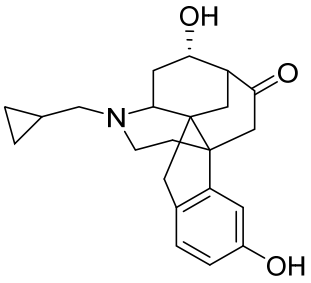
^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 0.08–0.18 (m, 2H), 0.42–0.56 (m, 2H), 0.80–0.92 (m, 1H), 1.35 (dd, *J* = 14.4, 2.0 Hz, 1H), 1.48 (dt, *J* = 14.0, 3.2 Hz, 1H), 1.58–1.75 (m, 2H), 2.02 (dd, *J* = 10.0, 4.0 Hz, 1H), 2.15 (td, *J* = 13.6, 6.0 Hz, 1H), 2.27 (d, *J* = 14.8 Hz, 1H), 2.32 (t, *J* = 6.0 Hz, 1H), 2.52–2.60 (m, 4H), 2.63 (d, *J* = 8.4 Hz, 1H), 2.96 (d, *J* = 18.8 Hz, 1H), 3.20 (dd, *J* = 12.0, 6.0 Hz, 1H), 3.73 (d, *J* = 15.2 Hz, 1H), 3.77 (s, 3H), 3.93 (dt, *J* = 11.6, 5.6 Hz, 1H), 6.63 (d, *J* = 2.4 Hz, 1H), 6.68 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), a proton (OH) was not observed.

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 3.3, 4.0, 9.7, 27.4, 34.7, 38.5, 39.9, 41.4, 45.5, 45.8, 47.2, 51.9, 55.4, 57.4, 59.2, 70.6, 107.8, 111.7, 126.4, 132.7, 152.3, 158.7, 213.2.

MS (ESI): *m/z* = 390 $[M+Na]^+$.

HR-MS (ESI): $[M+Na]^+$ Calcd for $C_{23}H_{29}NNaO_3$: 390.2045. Found: 390.2028.

(2*S*,3*S*,4a*S*,7a*R*,12a*R*)-5-(Cyclopropylmethyl)-3,9-dihydroxy-2,3,4,4a,5,6,7,12-octahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-one (18a)



18a

To a stirred solution of **17a** (37.9 mg, 0.103 mmol) in CH_2Cl_2 (2 mL) was added 1.0 M solution of BBr_3 in CH_2Cl_2 (515 μL, 0.515 mmol) dropwise at –78 °C under an argon atmosphere and stirred at room temperature for 1.5 h. To the reaction mixture was added 25% ammonia aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/AcOEt/MeOH/25% ammonia aqueous solution = 100/100/10/1) to give **18a** (29.6 mg, 81%) as a yellow amorphous solid.

To a solution of **18a** in MeOH was added 10% HCl•MeOH dropwise. After evaporation, to the residue was added AcOEt to give a colorless solid. Filtration followed by drying the solid gave **18a** •HCl as a colorless solid.

18a

IR (film) cm^{-1}: 3361, 2929, 1692, 1012, 756.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.06–0.16 (m, 2H), 0.41–0.54 (m, 2H), 0.78–0.92 (m, 1H), 1.38–1.52 (m, 1H), 1.55–1.71 (m, 1H), 1.71–1.92 (m, 3H), 1.96–2.08 (m, 1H), 2.26 (dd, *J* = 12.4, 7.0 Hz, 1H), 2.33 (d, *J* = 14.7 Hz, 1H), 2.40–2.68 (m, 5H), 2.90 (d, *J* = 19.0 Hz, 1H), 3.44 (t, *J* = 7.8 Hz, 1H), 3.70 (d, *J* = 15.4 Hz, 1H), 4.19 (d, *J* = 2.2 Hz, 1H), 6.55–6.67 (m, 2H), 7.05 (d, *J* = 7.8 Hz, 1H), two protons (OH) were not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.2, 4.2, 9.7, 26.0, 30.0, 38.4, 40.5, 41.3, 44.9, 46.3, 46.6, 52.7, 54.7, 59.4, 68.2, 109.1, 113.6, 126.7, 132.6, 152.6, 154.7, 213.7.

MS (ESI): *m/z* = 354$[M+H]^+$.

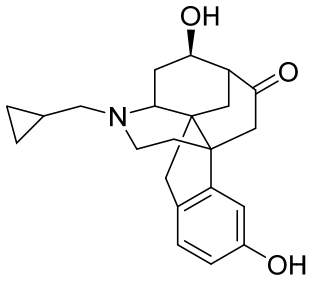
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{22}H_{28}NO_3$: 354.2069. Found: 354.2052.

18a•HCl

mp (dec.) 194–195 °C

Anal. Calcd for $C_{22}H_{27}NO_3 \cdot HCl \cdot 0.8H_2O$: C, 65.35; H, 7.38; N, 3.46. Found: C, 65.26; H, 7.42; N, 3.48.

(2*S*,3*R*,4a*S*,7a*R*,12a*R*)-5-(Cyclopropylmethyl)-3,9-dihydroxy-2,3,4,4a,5,6,7,12-octahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-one (18b)



18b

Compound **18b** was prepared from compound **17b** according to the procedure used to synthesize compound **18a**. Yield, 99%.; a yellow amorphous solid.

18a

IR (film) cm^{-1}: 3360, 2925, 1692, 1460, 1214, 1055, 755.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.05–0.17 (m, 2H), 0.40–0.55 (m, 2H), 0.76–0.92 (m, 1H), 1.19–1.47 (m, 2H), 1.52–1.82 (m, 2H), 1.95 (dd, *J* = 13.8, 3.2 Hz, 1H), 2.06–2.33 (m, 3H), 2.45–2.70 (m, 5H), 2.92 (d, *J* = 17.9 Hz, 1H), 3.12–3.26 (m, 1H), 3.68 (d, *J* = 15.5 Hz, 1H), 3.92–4.03 (m, 1H), 6.57–6.65 (m, 2H), 7.01 (d, *J* = 8.2 Hz, 1H), two protons (OH) were not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.3, 4.1, 9.6, 26.6, 34.8, 38.1, 39.6, 41.3, 45.4, 45.5, 47.4, 52.3, 57.3, 59.0, 70.4, 109.2, 113.6, 126.7, 132.3, 152.1, 154.9, 214.5.

MS (ESI): *m/z* = 354$[M+H]^+$.

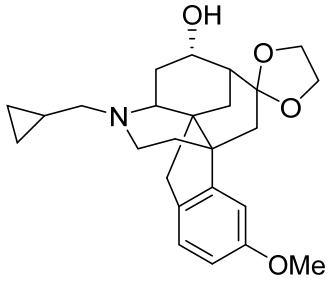
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{22}H_{28}NO_3$: 354.2069. Found: 354.2071.

18a•HCl

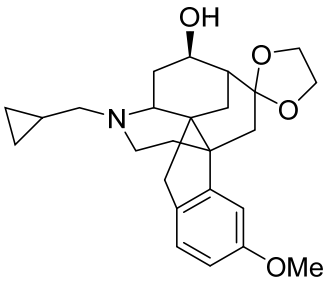
mp (dec.) 203–204 °C

Anal. Calcd for $C_{22}H_{27}NO_3 \cdot HCl \cdot 0.7H_2O$: C, 65.64; H, 7.36; N, 3.48. Found: C, 65.55; H, 7.36; N, 3.58.

(2*S*,3*S*,4a*S*,7a*R*,12a*R*)-5-(Cyclopropylmethyl)-9-methoxy-2,3,4,4a,5,6,7,12-octahydro-1*H*-spiro[2,7a-ethanoindeno[1,2-*d*]quinoline-14,2'-[1,3]dioxolan]-3-ol (19a)
(2*S*,3*R*,4a*S*,7a*R*,12a*R*)-5-(Cyclopropylmethyl)-9-methoxy-2,3,4,4a,5,6,7,12-octahydro-1*H*-spiro[2,7a-ethanoindeno[1,2-*d*]quinoline-14,2'-[1,3]dioxolan]-3-ol (19b)



19a



19b

To a solution of mixture of **17a** and **17b** (26.6 g, 72.3 mmol) in benzene (400 mL) were added ethylene glycol (36.0 mL, 645 mmol) and *p*-toluenesulfonic acid monohydrate (13.7 g, 72.0 mmol), and the mixture was refluxed under an argon atomosphere. After 11 h with stirring, the reaction mixture was evaporated and the residue was basified (pH 9) with K_2CO_3 and saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 100/0.2 to 100/6) to give **19a** (10.8 g, 36%) as a brown amorphous solid and **19b** (11.8 g, 40%) as a yellow amorphous solid.

19a

IR (film) cm^{-1}: 3406, 2922, 1611, 1585, 1480, 1096, 732.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.06–0.17 (m, 2H), 0.40–0.54 (m, 2H), 0.76–0.91 (m, 1H), 1.22–1.33 (m, 1H), 1.52 (dt, *J* = 12.5, 6.3 Hz, 1H), 1.63–1.79 (m, 4H), 2.04 (d, *J* = 15.4 Hz, 1H), 2.10–2.26 (m, 4H), 2.47–2.66 (m, 3H), 3.30 (dd, *J*= 11. 1, 6.6 Hz, 1H) 3.71 (d, *J* = 15.6 Hz, 1H), 3.78 (s, 3H), 3.80–4.01 (m, 4H), 4.26–4.33 (m, 1H), 6.62–6.68 (m, 2H), 7.10 (d, *J* = 8.6 Hz, 1H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.1, 4.2, 9.7, 23.9, 29.7, 35.9, 38.3, 39.6, 40.9, 44.8, 45.7, 46.0, 54.6, 55.3, 58.7, 64.0, 64.2, 67.7, 108.3, 109.4, 110.4, 126.3, 133.4, 152.9, 157.9.

MS (ESI): *m/z* = 412$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{25}H_{34}NO_4$: 412.2488. Found: 412.2478.

19b

IR (film) cm^{-1}: 3508, 2911, 1617, 1586, 1479, 1087, 1054.

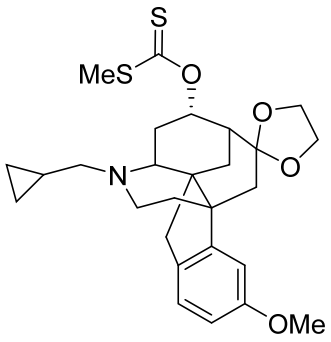
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.07–0.19 (m, 2H), 0.42–0.52 (m, 2H), 0.75–0.90 (m, 1H), 1.06 (dd, *J* = 13.6, 2.0 Hz, 1H), 1.22–1.35 (m, 1H), 1.43–1.62 (m, 1H), 1.72–1.99 (m, 4H), 2.02–2.33 (m, 4H), 2.45–2.68 (m, 3H), 2.99–3.14 (m, 1H), 3.67 (d, *J* = 15.0 Hz, 1H), 3.75–4.09 (m, 5H), 3.79 (s, 3H), 6.63–6.69 (m, 2H), 7.07–7.12 (m, 1H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.3, 3.9, 9.6, 26.8, 34.6, 37.3, 38.3, 39.2, 41.4, 41.5, 45.0, 46.5, 55.3, 57.4, 58.7, 63.8, 64.4, 71.3, 108.4, 110.4, 112.0, 126.3, 133.4, 152.6, 158.0.

MS (ESI): *m/z* = 412$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{25}H_{34}NO_4$: 412.2488. Found: 412.2503.

***O*-[(2*S*,3*S*,4a*S*,7a*R*,12a*R*)-5-(Cyclopropylmethyl)-9-methoxy-2,3,4,4a,5,6,7,12-octahydro-1*H*-spiro[2,7a-ethanoindeno[1,2-*d*]quinoline-14,2'-[1,3]dioxolan]-3-yl]*S*-methyl carbonodithioate (20a)**



20a

To a suspension of NaH (514 mg, 12.9 mmol) in THF (50 mL) was added a solution of **19a** (529 mg, 1.29 mmol) in THF (400 mL) at 0 °C under an argon atmosphere. After 10 min with stirring, to the reaction mixture was added freshly distilled CS_2 (232 μL, 3.86 mmol) at room temperature. After 1.5 h with stirring at the same temperature, to the reaction mixture was added MeI (96 μL, 1.54 mmol) at room temperature. After 3 h with stirring, the reaction mixture was quenched by saturated NH_4Cl aqueous solution at 0 °C, and then basified (pH 9) with saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/AcOEt = 6/1) to give **20a** (536 mg, 83%) as a yellow oil.

20a

IR (film) cm^{-1}: 2923, 1610, 1479, 1230, 1049.

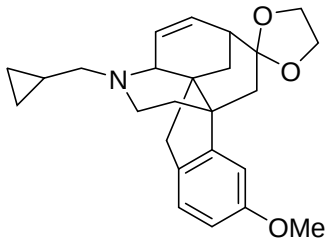
^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.06–0.16 (m, 2H), 0.42–0.53 (m, 2H), 0.75–0.89 (m, 1H), 1.24–1.36 (m, 1H), 1.47–1.63 (m, 2H), 1.73–1.84 (m, 1H), 1.96 (dd, *J* = 16.3, 6.7 Hz, 1H), 2.06–2.33 (m, 6H), 2.45 (dd, *J* = 12.7, 6.0 Hz, 1H), 2.52–2.67 (m, 2H), 2.55 (s, 3H), 3.30 (dd, *J* = 11.1, 6.7 Hz, 1H), 3.68–4.02 (m, 5H), 3.79 (s, 3H), 6.04–6.10 (m, 1H), 6.64–6.72 (m, 2H), 7.10 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.2, 3.8, 9.7, 18.8, 21.0, 30.6, 36.4, 38.2, 39.5, 40.2, 40.9, 45.3, 46.0, 55.0, 55.2, 58.6, 64.2, 64.3, 81.8, 108.4, 108.7, 110.5, 126.3, 133.2, 152.7, 158.0, 214.6.

MS (ESI): *m/z* = 502$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{27}H_{36}NO_4S_2$: 502.2086. Found: 502.2089.

(2*S*,4a*S*,7a*R*,12a*R*)-5-(Cyclopropylmethyl)-9-methoxy-2,4a,5,6,7,12-hexahydro-1*H*-spiro[2,7a-ethanoindeno[1,2-*d*]quinoline-14,2'-[1,3]dioxolane] (21)



21

A solution of **20a** (447 mg, 0.891 mmol) in *o*-dichlorobenzene (7 mL) was stirred at 160 °C under an argon atmosphere. After 2 h with stirring at the same temperature, the reaction mixture was passed through a short column of silica gel for removal of *o*-dichlorobenzene and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/AcOEt/MeOH/ 25% ammonia aqueous solution = 80/10/10/1) to give **21** (220 mg, 63%) as a brown amorphous solid.

21

IR (film) cm^{-1}: 2998, 2913, 1611, 1587, 1485, 1219, 947.

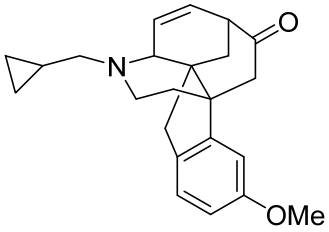
^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.11–0.18 (m, 2H), 0.44–0.53 (m, 2H), 0.78–0.92 (m, 1H), 1.20–1.30 (m, 1H), 1.42–1.55 (m, 2H), 1.88–1.99 (m, 2H), 2.11–2.20 (m, 1H), 2.16 (d, *J* = 14.6 Hz, 1H), 2.25 (d, *J* = 14.6 Hz, 1H), 2.40–2.64 (m, 4H), 3.55–3.60 (m, 1H), 3.60 (d, *J* = 14.0 Hz, 1H), 3.79 (s, 3H), 3.81–3.99 (m, 4H), 5.93–6.07 (m, 2H), 6.65–6.72 (m, 2H), 7.10 (d, *J* = 8.6 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.6, 3.7, 9.8, 34.3, 34.8, 39.3, 39.4, 39.8, 43.2, 44.7, 47.5, 55.3, 58.7, 59.8, 64.0, 64.4, 108.3, 110.6, 110.8, 126.1, 129.0, 132.5, 132.9, 152.8, 158.1.

MS (ESI): *m/z* = 394$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{25}H_{32}NO_3$: 394.2382. Found: 394.2372.

(2*S*,4a*S*,7a*R*,12a*R*)-5-(Cyclopropylmethyl)-9-methoxy-2,4a,5,6,7,12-hexahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-one (22)



22

Compound **22** was prepared from compound **21** according to the procedure used to synthesize compound **15a**. Yield, quant.; a colorless amorphous solid.

22

IR (film) cm^{-1}: 3076, 3001, 2922, 1713, 1483, 1284, 1219, 1034.

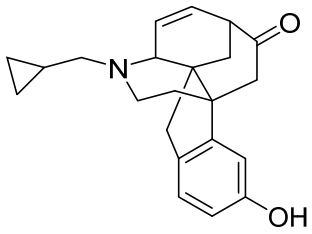
^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.14–0.20 (m, 2H), 0.45–0.58 (m, 2H), 0.81–0.95 (m, 1H), 1.32–1.41 (m, 1H), 1.61 (dt, *J* = 14.8, 4.5 Hz, 1H), 1.85 (dd, *J* = 13.6, 3.6 Hz, 1H), 1.97 (dt, *J* = 13.4, 2.1 Hz, 1H), 2.34 (d, *J* = 15.0 Hz, 1H), 2.44–2.70 (m, 5H), 2.79–2.86 (m, 1H), 2.98 (d, *J* = 16.1 Hz, 1H), 3.69 (d, *J* = 15.0 Hz, 1H), 3.75–3.80 (m, 1H), 3.78 (s, 3H), 5.90–5.99 (m, 1H), 6.21 (dd, *J* = 10.0, 1.5 Hz, 1H), 6.66–6.71 (m, 2H), 7.11 (d, *J* = 8.7 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.6, 3.8, 9.7, 37.3, 39.2, 39.6, 41.5, 43.2, 45.3, 48.7, 50.8, 55.3, 58.6, 59.5, 108.0, 111.9, 126.4, 130.3, 130.8, 132.5, 151.2, 158.7, 211.1.

MS (ESI): *m/z* = 350$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{23}H_{28}NO_2$: 350.2120. Found: 350.2128.

(2*S*,4a*S*,7a*R*,12a*R*)-5-(Cyclopropylmethyl)-9-hydroxy-2,4a,5,6,7,12-hexahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-one (23)



23

Compound **23** was prepared from compound **22** according to the procedure used to synthesize compound **18a**. Yield, 28%.; a colorless amorphous solid.

23

IR (film) cm^{-1}: 3349, 2924, 1704, 1462, 1218, 757.

^1H NMR (300 MHz, CD_3OD): δ (ppm) 0.12–0.27 (m, 2H), 0.46–0.61 (m, 2H), 0.80–0.99 (m, 1H), 1.22–1.42 (m, 2H), 1.54–1.76 (m, 1H), 1.86 (dd, *J* = 13.5, 3.4 Hz, 1H), 1.98 (d, *J* = 13.5 Hz, 1H), 2.32 (d, *J* = 15.1 Hz, 1H), 2.45–2.76 (m, 5H), 2.80–2.89 (br s, 1H), 2.98 (d, *J* = 16.1 Hz, 1H), 3.61–3.86 (m, 2H), 5.91–6.03 (m, 1H), 6.21 (dd, *J* = 10.0, 1.1 Hz, 1H), 6.60–6.67 (m, 2H), 7.06 (d, *J* = 8.6 Hz, 1H).

^{13}C NMR (75 MHz, CD_3OD): δ (ppm) 4.30, 4.34, 10.3, 38.9, 40.1, 40.4, 42.5, 44.6, 46.4, 50.1, 52.2, 59.7, 60.8, 110.0, 114.7, 127.6, 131.5, 131.7, 132.3, 152.2, 157.4, 213.6.

MS (ESI): *m/z* = 336$[M+H]^+$.

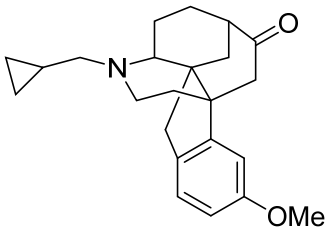
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{22}H_{26}NO_2$: 336.1966. Found: 336.1962.

23•HCl

mp (dec.) 168–170 °C

Anal. Calcd for $C_{22}H_{25}NO_2 \cdot HCl \cdot 2.4H_2O$: C, 63.65; H, 7.48; N, 3.37. Found: C, 63.81; H, 7.23; N, 3.53.

(2*S*,4a*S*,7a*R*,12a*R*)-5-(Cyclopropylmethyl)-9-methoxy-2,3,4,4a,5,6,7,12-octahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-one (24)



24

Under an argon atmosphere, To a solution of **21** (100 mg, 0.254 mmol) in MeOH (5 mL) was added 10% Pd on carbon (110 mg), and after exchange of argon for H_2, the reaction mixture was stirred at room temperature for 28 h. The reaction mixture was filtered through a Celite pad and the Celite Pad was washed with MeOH. The filtrate was concentrated *in vacuo* to give a colorless amorphous solid (90.0 mg). To a stirred solution of the residue was added 2 M HCl (3 mL) at room temperature under an argon atmosphere. After 7 h with stirring, the reaction mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by preparative TLC (hexane/AcOEt = 2/1) to give **24** (64.7 mg, 82% in two steps) as a colorless oil.

24

IR (film) cm^{-1}: 3076, 3001, 2929, 1703, 1609, 1481, 1286, 1217, 1055, 753.

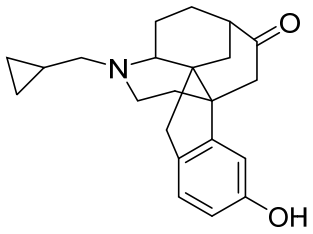
^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.08–0.21 (m, 2H), 0.42–0.57 (m, 2H), 0.79–0.96 (m, 1H), 1.32–1.84 (m, 6H), 1.91–2.07 (m, 2H), 2.22–2.42 (m, 3H), 2.48–2.74 (m, 3H), 2.55 (d, *J* = 18.8 Hz, 1H), 2.94 (d, *J* = 18.8 Hz, 1H), 3.06–3.24 (m, 1H), 3.70–3.86 (m, 1H), 3.78 (s, 3H), 6.62–6.71 (m, 2H), 7.11 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.2, 4.1, 9.8, 17.5, 28.3, 37.3, 38.5, 40.4, 41.4, 44.9, 45.5, 46.3, 47.4, 55.3, 58.4, 59.3, 107.8, 111.5, 126.5, 133.0, 152.7, 158.6, 215.2.

MS (ESI): *m/z* = 352$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{23}H_{30}NO_2$: 352.2277. Found: 352.2290.

(2*S*,4a*S*,7a*R*,12a*R*)-5-(Cyclopropylmethyl)-9-hydroxy-2,3,4,4a,5,6,7,12-octahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-one (12)



12

A mixture of **24** (223 mg, 0.635 mmol) and pyridinium chloride (8.5 g, 73.6 mmol) were stirred at 180 °C for 3 h. The cooled reaction mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by preparative TLC (hexane/AcOEt/MeOH/25% ammonia aqueous solution = 40/10/10/1) to give **12** (176 mg, 82%) as a colorless oil.

To a solution of **12** in MeOH was added a solution of CSA in AcOEt. After evaporation, to the residue was added Et_2O to give a colorless solid. Filtration followed by drying the solid gave **12** •CSA as a colorless solid.

12

IR (film) cm^{-1}: 3347, 2927, 1695, 1613, 1461, 1216, 755.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.10–0.18 (m, 2H), 0.43–0.57 (m, 2H), 0.80–0.94 (m, 1H), 1.38 (dd, *J* = 13.6, 2.1 Hz, 1H), 1.46 (dt, *J* = 14.0, 3.0 Hz, 1H), 1.47–1.90 (m, 4H), 1.90–2.07 (m, 2H), 2.26 (d, *J* = 15.0 Hz, 1H), 2.29–2.42 (m, 2H), 2.50–2.69 (m, 4H), 2.91 (d, *J* = 18.7 Hz, 1H), 3.15 (t, *J* = 8.7 Hz, 1H), 3.76 (d, *J* = 15.0 Hz, 1H), 6.57–6.64 (m, 2H), 7.04 (d, *J* = 7.8 Hz, 1H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.3, 4.1, 9.7, 17.5, 28.2, 37.4, 38.4, 40.4, 41.4, 44.9, 45.5, 46.3, 47.5, 58.4, 59.3, 109.1, 113.3, 126.7, 132.7, 152.7, 154.7, 216.0.

MS (ESI): *m/z* = 338$[M+H]^+$.

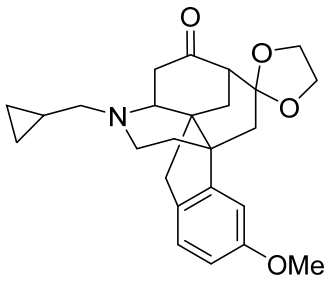
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{22}H_{28}NO_2$: 338.2120. Found: 338.2112.

12 •CSA

mp (dec.) 159–160 °C

Anal. Calcd for $C_{22}H_{27}NO_2 \cdot CSA \cdot 2.5H_2O$: C, 62.52; H, 7.87; N, 2.28. Found: C, 62.34; H, 7.50; N, 2.36.

(2*S*,4a*S*,7a*R*,12a*R*)-5-(Cyclopropylmethyl)-9-methoxy-4,4a,5,6,7,12-hexahydro-1*H*-spiro[2,7a-ethanoindeno[1,2-*d*]quinoline-14,2'-[1,3]dioxolan]-3(2*H*)-one (25)



25

To a solution of oxalyl chloride (1.26 mL, 14.6 mmol) in CH_2Cl_2 (20 mL) was added DMSO (2.07 mL g, 29.2 mmol) dropwise at –78 °C and stirred for 1 h under an argon atmosphere. To the stirred reaction mixture was added a solution of **19b** (2.00 g, 4.86 mmol) in CH_2Cl_2 (20 mL) dropwise. After 1 h with stirring, to the stirred reaction mixture was added Et_3N (1.50 mL, 10.8 mmol) and then allowed to warm gradually to room temperature for 3 h. the reaction mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were dried over Na_2SO_4, and evaporated i*n vacuo*. The residue was purified by silica gel column chromatography (hexane/AcOEt = 3/1) to give **25** (1.49 g, 75%) as a yellow amorphous solid.

25

IR (film) cm^{-1}: 3076, 3001, 2935, 1703, 1618, 1481, 1215, 1092, 947, 755.

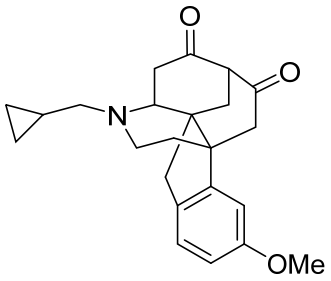
^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.09–0.16 (m, 2H), 0.43–0.54 (m, 2H), 0.73–0.90 (m, 1H), 1.34–1.42 (m, 1H), 1.46 (dd, *J* = 14.1, 1.9 Hz, 1H), 1.61 (td, *J* = 15.9, 5.5 Hz, 1H), 2.08–2.26 (m, 4H), 2.30 (br s, 1H), 2.39–2.60 (m, 4H), 2.63–2.72 (m, 1H), 2.80 (dd, *J* = 17.7, 8.2 Hz, 1H), 3.39–3.47 (m, 1H), 3.73 (d, *J* = 14.8 Hz, 1H), 3.77–3.84 (m, 1H), 3.80 (s, 3H), 3.88–4.00 (m, 3H), 6.67–6.73 (m, 2H), 7.10–7.16 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.4, 3.9, 9.4, 34.2, 34.9, 36.0, 38.3, 39.4, 40.9, 45.0, 46.5, 54.5, 55.3, 58.6, 58.6, 64.2, 64.6, 107.7, 108.6, 110.9, 126.3, 132.7, 151.9, 158.2, 210.3.

MS (ESI): *m/z* = 410$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{25}H_{32}NO_4$: 410.2331. Found: 410.2342.

(2*S*,4a*S*,7a*R*,12a*R*)-5-(Cyclopropylmethyl)-9-methoxy-4,4a,5,6,7,12-hexahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinoline-3,14(2*H*)-dione (26)



26

Compound **26** was prepared from compound **25** according to the procedure used to synthesize compound **15a**. Yield, 52%.; a colorless amorphous solid.

26

IR (film) cm^{-1}: 3077, 3001, 2923, 1695, 1610, 1482, 1212, 1035, 732.

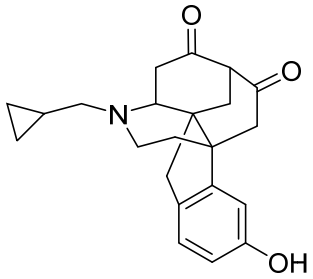
^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.10–0.18 (m, 2H), 0.46–0.56 (m, 2H), 0.76–0.92 (m, 1H), 1.45–1.54 (m, 1H), 1.67–1.86 (m, 2H), 2.18–2.31 (m, 2H), 2.37 (d, *J* = 15.0 Hz, 1H), 2.46–2.93 (m, 6H), 2.97 (d, *J* = 17.8 Hz, 1H), 3.27 (br s, 1H), 3.63 (dd, *J* = 9.3, 7.7 Hz, 1H), 3.75–3.86 (m, 1H), 3.78 (s, 3H), 6.66–6.74 (m, 2H), 7.15 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.4, 4.0, 9.4, 35.4, 37.1, 38.2, 39.5, 40.9, 43.3, 45.7, 48.5, 55.4, 58.7, 58.9, 65.1, 107.9, 112.0, 126.7, 132.3, 150.7, 158.9, 203.1, 204.0.

MS (ESI): *m/z* = 366$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{23}H_{28}NO_3$: 366.2069. Found: 366.2079.

(2*S*,4a*S*,7a*R*,12a*R*)-5-(Cyclopropylmethyl)-9-hydroxy-4,4a,5,6,7,12-hexahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinoline-3,14(2*H*)-dione (27)



27

Compound **27** was prepared from compound **26** according to the procedure used to synthesize compound **12**. Yield, 31%.; a colorless amorphous solid.

27

IR (film) cm^{-1}: 3382, 2924, 1717, 1693, 1614, 1209, 756.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.11–0.18 (m, 2H), 0.46–0.59 (m, 2H), 0.78–0.91 (m, 1H), 1.49 (dt, *J* = 16.3, 2.3 Hz, 1H), 1.68–1.86 (m, 3H), 2.20–2.30 (m, 2H), 2.36 (d, *J* = 15.0 Hz, 1H), 2.47–2.98 (m, 7H), 3.25–3.31 (br s, 1H), 3.62 (dd, *J* = 9.1, 7.8 Hz, 1H), 3.80 (d, *J* = 14.9 Hz, 1H), 6.60–6.67 (m, 2H), 7.10 (d, *J* = 7.7 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.4, 4.1, 9.4, 35.4, 37.2, 38.1, 39.5, 40.9, 43.4, 45.8, 48.6, 58.7, 58.8, 65.1, 109.2, 113.8, 126.9, 132.3, 150.9, 154.7, 203.3, 204.1.

MS (ESI): *m/z* = 352$[M+H]^+$.

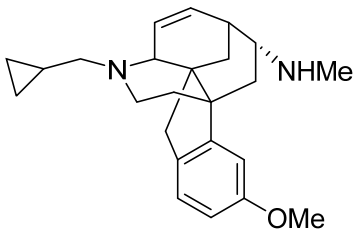
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{22}H_{26}NO_3$: 352.1913. Found: 352.1907.

27 •CSA

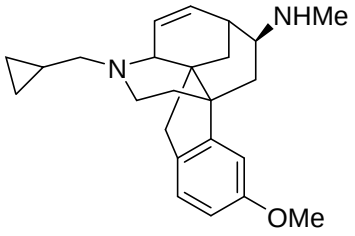
mp (dec.) 156–157 °C

Anal. Calcd for $C_{22}H_{25}NO_3 \cdot CSA \cdot 4.5H_2O$: C, 57.81; H, 7.58; N, 2.11. Found: C, 57.79; H, 7.50; N, 2.27.

(2*S*,4a*S*,7a*R*,12a*R*,14*R*)-5-(Cyclopropylmethyl)-9-methoxy-*N*-methyl-2,4a,5,6,7,12-hexahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-amine (28)
(2*S*,4a*S*,7a*R*,12a*R*,14*S*)-5-(Cyclopropylmethyl)-9-methoxy-*N*-methyl-2,4a,5,6,7,12-hexahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-amine (29)



28



29

To a stirred solution of **22** (759 mg, 2.17 mmol) in MeOH (15 mL) were added methylamine hydrochloride (1.47 g, 21.7 mmol) and sodium cyanoborohydride (150 mg, 2.39 mmol) at room temperature under an argon atmosphere. After 13 h with stirring at the same temperature, the reaction mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (CHCl3/MeOH/25% ammonia aqueous solution = 100/2/0.2) to give **28** (404 mg, 51%) as a colorless oil and **29** (193 mg, 24%) as a colorless oil.

28

IR (film) cm^{-1}: 3347, 3075, 3011, 2912, 2845, 2793, 1608, 1481, 1282, 1221, 1036.
^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.09–0.17 (m, 2H), 0.43–0.51 (m, 2H), 0.77–0.90 (m, 1H), 1.17–1.25 (m, 1H), 1.30 (dd, *J* = 13.4, 3.6 Hz, 1H), 1.37–1.50 (m, 1H), 1.62–1.80 (m, 2H), 1.93 (d, *J* = 15.1 Hz, 1H), 2.06 (dd, *J* = 15.1, 5.5 Hz, 1H), 2.20 (d, *J* = 15.0 Hz, 1H), 2.29 (s, 3H), 2.33–2.61 (m, 5H), 2.65–2.71 (m, 1H), 3.55–3.62 (m, 2H), 3.78 (s, 3H), 5.86–6.01 (m, 2H), 6.67 (dd, *J* = 8.1, 2.5 Hz, 1H), 6.77 (d, *J* = 2.5 Hz, 1H), 7.11 (d, *J* = 8.1 Hz, 1H).
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.6, 3.7, 9.7, 28.4, 30.1, 33.7, 39.5, 40.5, 43.4, 44.8, 45.5, 55.3, 56.9, 58.6, 60.0, 76.6, 107.1, 111.7, 126.6, 127.7, 133.3, 134.4, 153.6, 158.4.
MS (ESI): *m/z* = 365$[M+H]^+$.
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{24}H_{33}N_2O$: 365.2593. Found: 365.2578.

29

IR (film) cm^{-1}: 3326, 3075, 3001, 2915, 2848, 2796, 1609, 1482, 1282, 1220, 1037, 727.

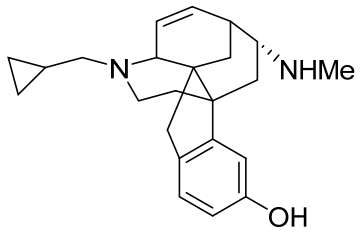
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.09–0.18 (m, 2H), 0.42–0.53 (m, 2H), 0.78–0.92 (m, 1H), 1.22–1.33 (m, 1H), 1.41–1.62 (m, 3H), 1.64–1.75 (m, 1H), 1.84–2.09 (m, 1H), 2.03 (dd, *J* = 13.6, 4.5 Hz, 1H), 2.20 (d, *J* = 15.0 Hz, 1H), 2.39–2.64 (m, 6H), 2.46 (s, 3H), 3.56–3.64 (m, 2H), 3.80 (s, 3H), 5.85–5.95 (m, 1H), 6.08 (dd, *J* = 10.2, 1.6 Hz, 1H), 6.68 (dd, *J* = 8.1, 2.4 Hz, 1H), 6.73 (d, *J* = 2.4 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.6, 3.7, 9.7, 32.6, 33.5, 33.6, 36.7, 38.8, 39.8, 43.3, 45.2, 47.3, 55.3, 58.0, 58.7, 60.2, 107.5, 110.8, 126.3, 129.4, 130.3, 133.6, 152.7, 158.5.

MS (ESI): *m/z* = 365$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{24}H_{33}N_2O$: 365.2593. Found: 365.2577.

(2*S*,4a*S*,7a*R*,12a*R*,14*R*)-5-(Cyclopropylmethyl)-14-(methylamino)-2,4a,5,6,7,12-hexahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-9-ol (30)



30

Compound **30** was prepared from compound **28** according to the procedure used to synthesize compound **12**. Yield, 77%.; a colorless amorphous solid.

30

IR (KBr) cm^{-1}: 3434, 2920, 1608, 1471, 1269, 1081, 817.

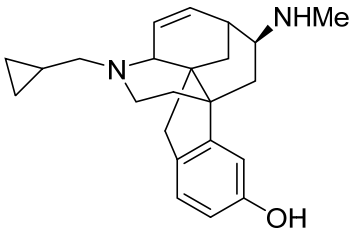
^1H NMR (300 MHz, Pyridine-d_8): δ (ppm) 0.12–0.19 (m, 2H), 0.39–0.52 (m, 2H), 0.80–0.94 (m, 1H), 1.20–1.37 (m, 2H), 1.51–1.67 (m, 1H), 1.93–2.12 (m, 3H), 2.18 (s, 3H), 2.28 (d, *J* = 15.2 Hz, 1H), 2.33–2.51 (m, 4H), 2.56 (dd, *J* = 12.6, 6.1 Hz, 1H), 2.64–2.70 (m, 1H), 3.58–3.63 (m, 1H), 3.80 (d, *J* = 15.2 Hz, 1H), 5.89–6.02 (m, 2H), 7.02 (dd, *J* = 7.9, 2.3 Hz, 1H), 7.17–7.28 (m, 2H), 11.01–11.29 (m, 1H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, Pyridine-d_8): δ (ppm) 4.0, 4.5, 10.4, 29.7, 30.9, 34.4, 34.4, 40.4, 41.2, 43.7, 45.4, 46.0, 57.8, 59.0, 60.9, 110.2, 114.1, 127.1, 128.2, 131.7, 135.0, 155.1, 157.7.

MS (ESI): *m/z* = 351$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{23}H_{31}N_2O$: 351.2436. Found: 351.2422.

(2*S*,4a*S*,7a*R*,12a*R*,14*S*)-5-(Cyclopropylmethyl)-14-(methylamino)-2,4a,5,6,7,12-hexahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-9-ol (31)



31

Compound **31** was prepared from compound **29** according to the procedure used to synthesize compound **12**. Yield, 85%.; a colorless oil.

31

IR (film) cm^{-1}: 3287, 3076, 3009, 2918, 2850, 2808, 1611, 1471, 1370, 1278, 807, 756.

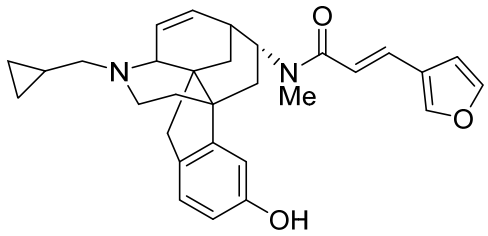
^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.10–0.17 (m, 2H), 0.44–0.52 (m, 2H), 0.78–0.90 (m, 1H), 1.19–1.32 (m, 1H), 1.41–1.76 (m, 4H), 2.06 (dd, *J* = 13.6, 4.3 Hz, 1H), 2.16 (d, *J* = 15.0 Hz, 1H), 2.38–2.64 (m, 6H), 2.45 (s, 3H), 3.51–3.62 (m, 2H), 4.42–4.81 (m, 1H), 5.82–5.91 (m, 1H), 6.07 (dd, *J* = 10.2, 1.4 Hz, 1H), 6.59 (dd, *J* = 7.9, 2.3 Hz, 1H), 6.68 (d, *J* = 2.2 Hz, 1H), 7.03 (d, *J* = 7.9 Hz, 1H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.6, 3.8, 9.7, 32.4, 32.9, 33.0, 36.7, 38.7, 39.8, 43.4, 45.1, 47.3, 57.8, 58.7, 60.2, 109.0, 113.5, 126.5, 129.7, 130.1, 132.4, 152.5, 155.5.

MS (ESI): *m/z* = 351$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{23}H_{31}N_2O$: 351.2436. Found: 351.2442.

(*E*)-*N*-[(2*S*,4a*S*,7a*R*,12a*R*,14*R*)-5-(Cyclopropylmethyl)-9-hydroxy-2,4a,5,6,7,12-hexahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-yl]-3-(furan-3-yl)-*N*-methyl-acrylamide (32a)



32a

To a stirred solution of **30** (20.0 mg, 0.0571 mmol) in CH_2Cl_2 (1 mL) were added triethylamine (23.8 μL, 0.171 mmol) and *trans*-3-(3-furyl)acryloyl chloride (10.7 mg, 0.0685 mmol) at room temperature under an argon atmosphere. After 30 min with stirring at the same temperature, the reaction mixture was concentrated and the residue was dissolved in MeOH (1 mL). To the stirred reaction mixture was added K_2CO_3 (23.7 mg, 0.171 mmol) at room temperature. After 2 h with stirring at the same temperature, the reaction was quenched with saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by preparative TLC ($CHCl_3$/MeOH = 100:3) to give **32a** (26.4 mg, 98%) as a colorless oil.

32a

IR (KBr) cm^{-1}: 3362, 2919, 2810, 1654, 1600, 1410, 1160, 1020, 974, 870, 792.

^1H NMR (300 MHz, THF-d_8): δ (ppm) 0.13–0.23 (m, 2H), 0.45–0.55 (m, 2H), 0.83–0.99 (m, 1H), 1.32–1.65 (m, 4H), 1.97–2.77 (m, 8H), 2.66 (s, 3H), 3.55–3.70 (m, 2H), 4.49–4.62 (m, 1H), 6.02–6.10 (m, 2H), 6.54–6.60 (m, 2H), 6.70–6.82 (m, 2H), 7.04 (br d, *J* = 7.7 Hz, 1H), 7.48–7.57 (m, 2H), 7.81 (s, 1H), 8.00 (s, 1H).

^{13}C NMR (75 MHz, THF-d_8): δ (ppm) 4.1, 4.4, 10.8, 31.0, 32.5, 33.9, 35.8, 40.2, 42.8, 44.4, 45.0, 46.4, 52.0, 60.0, 61.7, 108.5, 110.1, 114.2, 120.0, 124.8, 126.9, 129.0, 132.1, 132.2, 135.0, 144.9, 145.1, 154.1, 157.7, 167.0.

MS (ESI): *m/z* = 471$[M+H]^+$.

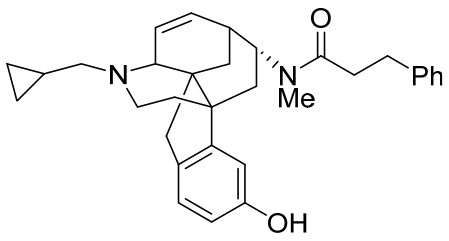
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{30}H_{35}N_2O_3$: 471.2648. Found: 471.2664.

32a•HCl

mp (dec.) 172–173 °C

Anal. Calcd for $C_{30}H_{34}N_2O_3 \cdot HCl \cdot 2.3H_2O$: C, 65.69; H, 7.28; N, 5.11. Found: C, 65.71; H, 7.03; N, 5.05.

***N*-[(2*S*,4a*S*,7a*R*,12a*R*,14*R*)-5-(Cyclopropylmethyl)-9-hydroxy-2,4a,5,6,7,12-hexahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-yl]-*N*-methyl-3-phenylpropanamide (32b)**



32b

To a stirred solution of **30** (20.0 mg, 0.0571 mmol) in CH_2Cl_2 (1 mL) were added triethylamine (23.8 μL, 0.171 mmol) and hydrocinnamoyl chloride (10.1 μL, 0.0685 mmol) at room temperature under an argon atmosphere. After 30 min with stirring at the same temperature, the reaction mixture was concentrated and the residue was dissolved in MeOH (1 mL). To the stirred reaction mixture was added K_2CO_3 (23.7 mg, 0.171 mmol) at room temperature. After 2 h with stirring at the same temperature, the reaction was quenched with saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by preparative TLC ($CHCl_3$/MeOH/25% ammonia aqueous solution = 100/3/0.3) to give **32b** (25.0 mg, 91%) as a colorless oil.

32b

IR (film) cm^{-1}: 3200, 3062, 3021, 2923, 2852, 1667, 1613, 1454, 1282, 1218, 754, 700.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.07–0.27 (m, 2H), 0.43–0.61 (m, 2H), 0.78–0.99 (m, 1H), 1.20–2.81 (m, 16H), 2.84–3.10 (m, 3H), 3.38–3.91 (m, 2.2H), 4.49–4.62 (m, 0.8H), 5.77–6.18 (m, 2H), 6.32–6.52 (m, 1H), 6.57–6.71 (m, 1H), 6.97–7.08 (m, 1H), 7.16–7.37 (m, 5H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.8, 3.8, 9.5, 29.7, 31.2, 31.4, 31.9, 32.7, 33.9, 36.4, 37.4, 41.7, 43.8, 45.1, 53.0, 58.8, 59.9, 108.9, 109.1, 113.5, 126.3, 126.5, 128.3, 128.5, 128.6, 128.7, 129.2, 132.6, 140.6, 141.8, 155.1, 172.6.

MS (ESI): *m/z* = 483$[M+H]^+$.

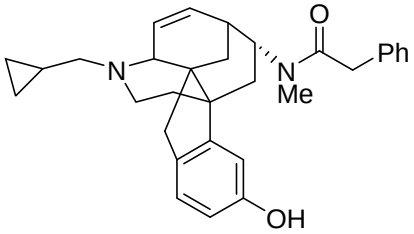
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{32}H_{39}N_2O_2$: 483.3012. Found: 483.3023.

32b•HCl

mp (dec.) 176–177 °C

Anal. Calcd for $C_{32}H_{38}N_2O_2 \cdot HCl \cdot 1.5H_2O$: C, 70.37; H, 7.75; N, 5.13. Found: C, 70.50; H, 7.56; N, 4.97.

***N*-[(2*S*,4a*S*,7a*R*,12a*R*,14*R*)-5-(Cyclopropylmethyl)-9-hydroxy-2,4a,5,6,7,12-hexahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-yl]-*N*-methyl-2-phenylacetamide (32c)**



32c

To a stirred solution of **30** (14.0 mg, 0.0456 mmol) in CH_2Cl_2 (1 mL) were added triethylamine (23.8 μL, 0.171 mmol) and phenylacetyl chloride (12.1 μL, 0.0913 mmol) at room temperature under an Ar atmosphere. After 30 min with stirring, the reaction mixture was concentrated and the residue was dissolved in MeOH (1 mL). To the stirred reaction mixture was added K_2CO_3 (22.0 mg, 0.159 mmol) at room temperature. After 2 h with stirring, the reaction was quenched with saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by preparative TLC ($CHCl_3$/MeOH/25% ammonia aqueous solution = 100/2.5/0.25) to give **32c** (19.0 mg, 89%) as a colorless oil.

32c

IR (film) cm^{-1}: 3261, 3013, 2919, 1614, 1455, 1282, 1218, 921, 755.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.04–0.22 (m, 2H), 0.40–0.54 (m, 2H), 0.73–0.94 (m, 1H), 1.17–1.61 (m, 3.4H), 1.66–2.66 (m, 11.6H), 3.31–3.84 (m, 4H), 3.91–4.04 (m, 0.4H), 4.53–4.64 (m, 0.6H), 5.76–6.07 (m, 2H), 6.29–6.69 (m, 2H), 7.02 (d, *J* = 8.0 Hz, 1H) 7.19–7.39 (m, 5H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ(ppm) 3.7, 3.7, 9.6, 18.8, 29.4, 32.3, 32.6, 33.3, 33.8, 39.4, 41.6, 41.9, 43.9, 45.1, 50.1, 58.8, 108.2, 109.0, 113.5, 126.7, 128.7, 128.8, 128.8, 128.9, 132.9, 134.1, 135.2, 144.9, 153.1, 154.9, 171.3.

MS (ESI): *m/z* = 469$[M+H]^+$.

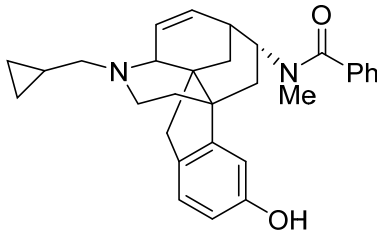
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{31}H_{37}N_2O_2$: 469.2855. Found: 469.2854.

32c•HCl

mp (dec.) 136–136 °C

Anal. Calcd for $C_{31}H_{36}N_2O_2 \cdot 1.0CSA \cdot 2.2H_2O$: C, 66.50; H, 7.68; N, 3.78. Found: C, 66.42; H, 7.50; N, 3.78.

***N*-[(2*S*,4a*S*,7a*R*,12a*R*,14*R*)-5-(Cyclopropylmethyl)-9-hydroxy-2,4a,5,6,7,12-hexahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-yl]-*N*-methylbenzamide (32d)**



32d

To a stirred solution of **30** (20.0 mg, 0.0571 mmol) in CH_2Cl_2 (1 mL) were added triethylamine (23.8 μL, 0.171 mmol) and benzoyl chloride (8.0 μL, 0.0685 mmol) at room temperature under an argon atmosphere. After 30 min with stirring, the reaction mixture was concentrated and the residue was dissolved in MeOH (1 mL). To the stirred reaction mixture was added K_2CO_3 (23.7 mg, 0.171 mmol) at room temperature. After 2 h with stirring, the reaction was quenched with saturated $NaHCO_3$ aqueous solution and extracted with $CHCl_3$ three times. The combined organic extracts were dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by preparative TLC ($CHCl_3$/MeOH = 100/3 to 100/7) to give **32d** (25.6 mg, 99%) as a colorless oil.

32d

IR (film) cm^{-1}: 3267, 3076, 3017, 2919, 2847, 2812, 1607, 1456, 1281, 1063, 910, 733.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.08–0.21 (m, 2H), 0.42–0.56 (m, 2H), 0.77–0.94 (m, 1H), 1.29–1.40 (m, 1H), 1.44–1.66 (m, 2H), 1.90–2.00 (m, 1H), 2.12–2.65 (m, 11H), 3.50–3.69 (m, 2H), 4.24–4.54 (m, 1H), 5.84–6.06 (m, 2H), 6.65 (dd, *J* = 7.9, 2.3 Hz, 1H), 6.72 (d, *J* = 2.3 Hz, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 7.18–7.32 (m, 5H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.8, 3.8, 9.6, 15.7, 29.9, 32.8, 33.5, 38.5, 41.3, 43.5, 44.0, 45.2, 51.5, 58.9, 60.0, 109.4, 109.4, 113.7, 126.6, 126.7, 128.4, 128.4, 129. 0, 129.4, 132.2, 133.3, 137.0, 152.7, 155.5, 172.9.

MS (ESI): *m/z* = 455$[M+H]^+$.

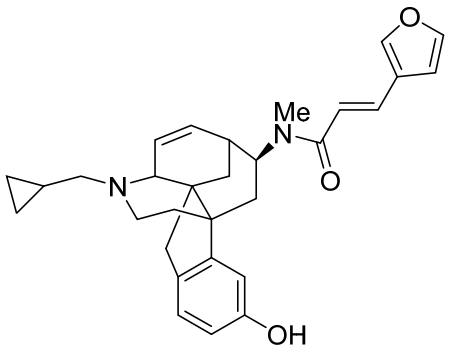
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{30}H_{35}N_2O_2$: 455.2699. Found: 455.2685.

32d•HCl

mp (dec.) 186–187 °C

Anal. Calcd for $C_{30}H_{34}N_2O_2 \cdot HCl \cdot 1.2H_2O$: C, 70.28; H, 7.35; N, 5.46. Found: C, 70.20; H, 7.23; N, 5.44.

(*E*)-*N*-[(2*S*,4a*S*,7a*R*,12a*R*,14*S*)-5-(Cyclopropylmethyl)-9-hydroxy-2,4a,5,6,7,12-hexahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-yl]-3-(furan-2-yl)-*N*-methylacrylamide (33a)



33a

Compound **33a** was prepared from compound **31** according to the procedure used to synthesize compound **32a**. Yield, 73%.; a colorless amorphous solid.

33a

IR (KBr) cm^{-1}: 2935, 1639, 1561, 1459, 1372, 1160, 1090, 980, 802.

^{1}H NMR (300 MHz, THF-d_8): δ (ppm) 0.15–0.27 (m, 2H), 0.47–0.60 (m, 2H), 0.87–1.00 (m, 1H), 1.32–1.43 (m, 1H), 1.52–1.70 (m, 2H), 1.72–1.92 (m, 2H), 2.19 (br d, *J* = 14.6 Hz, 1H), 2.33–2.79 (m, 6H), 2.99–3.14 (m, 3H), 3.58–3.73 (m, 2.2H), 4.26–4.83 (m, 0.8H), 5.96–6.10 (m, 1H), 6.12–6.21 (m, 1H), 6.53–6.84 (m, 4H), 6.99–7.09 (m, 1H), 7.46–7.60 (m, 2H), 7.80 (br s, 1H), 7.88–8.05 (m, 1H).

^{13}C NMR (75 MHz, THF-d_8): δ (ppm) 3.6, 4.3, 10.4, 26.6, 30.5, 39.0, 39.9, 40.4, 44.0, 45.7, 48.3, 52.7, 56.7, 59.6, 61.7, 108.3, 109.0, 114.3, 119.3, 124.8, 127.2, 130.0, 132.5, 132.8, 145.1, 145.1, 145.2, 153.0, 157.8, 166.6.

MS (ESI): *m/z* = 471[M+H]$^+$.

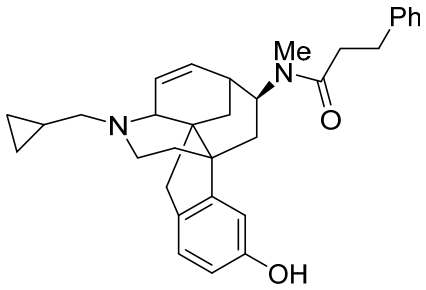
HR-MS (ESI): [M+H]$^+$ Calcd for $C_{30}H_{35}N_2O_3$: 471.2648. Found: 471.2637.

33a•HCl

mp (dec.) 191–192 °C

Anal. Calcd for $C_{30}H_{34}N_2O_3 \cdot HCl \cdot 1.5H_2O$: C, 67.47; H, 7.17; N, 5.25. Found: C, 67.59; H, 7.17; N, 5.07.

***N*-[(2*S*,4a*S*,7a*R*,12a*R*,14*S*)-5-(Cyclopropylmethyl)-9-hydroxy-2,4a,5,6,7,12-hexahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-yl]-*N*-methyl-3-phenylpropanamide (33b)**



33b

Compound **33b** was prepared from compound **31** according to the procedure used to synthesize compound **32b**. Yield, 74%.; a colorless oil.

33b

IR (film) cm^{-1}: 3249, 3019, 2917, 1614, 1455, 1217, 1074, 809, 754, 700.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.10–0.21 (m, 2H), 0.43–0.57 (m, 2H), 0.78–0.94 (m, 1H), 1.21–1.34 (m, 1H), 1.41–1.76 (m, 4H), 2.04–2.22 (m, 2H), 2.27–2.68 (m, 7H), 2.72–3.02 (m, 5H), 3.49–3.68 (m, 2.5H), 4.35–4.47 (m, 0.5H), 5.76–5.94 (m, 1H), 5.99–6.10 (m, 1H), 6.61–6.71 (m, 2H), 6.91–7.32 (m, 6H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.7, 3.9, 9.6, 28.0, 29.4, 31.6, 35.8, 36.3, 37.5, 38.7, 39.6, 43.4, 44.9, 47.6, 51.9, 55.7, 58.7, 107,9, 108.9, 113.6, 126.1, 126.4, 126.9, 128.3, 128.5, 128.5, 128.5, 129.3, 132.5, 141.2, 155.5, 173.0.

MS (ESI): *m/z* = 483$[M+H]^+$.

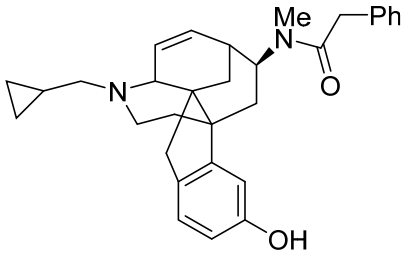
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{32}H_{39}N_2O_2$: 483.3012. Found: 483.2997.

33b•HCl

mp (dec.) 143–144 °C

Anal. Calcd for $C_{32}H_{38}N_2O_2 \cdot CSA \cdot 2.8H_2O$: C, 65.91; H, 7.85; N, 3.66. Found: C, 65.73; H, 7.56; N, 3.65.

***N*-[(2*S*,4a*S*,7a*R*,12a*R*,14*S*)-5-(Cyclopropylmethyl)-9-hydroxy-2,4a,5,6,7,12-hexahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-yl]-*N*-methyl-2-phenylacetamide (33c)**



33c

Compound **33c** was prepared from compound **31** according to the procedure used to synthesize compound **32c**. Yield, 74%.; a colorless amorphous solid.

33c

IR (film) cm^{-1}: 3261, 3013, 2919, 1614, 1455, 1282, 1218, 921, 755.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.06–0.22 (m, 2H), 0.41–0.55 (m, 2H), 0.76–0.94 (m, 1H), 1.14–1.90 (m, 6H), 2.04–2.31 (m, 2H), 2.33–2.68 (m, 4H), 2.87 (s, 3H), 3.45–3.77 (m, 4.5H), 4.39–4.50 (m, 0.5H), 5.74–5.93 (m, 1H), 5.98–6.06 (m, 1H), 6.35–6.41 (m, 0.5H), 6.55–6.71 (m, 1.5H), 6.93–7.00 (m, 1H), 7.04 (d, J = 8.0 Hz, 1H), 7.11–7.36 (m, 4H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.7, 3.9, 9.5, 28.1, 29.5, 31.9, 35.6, 37.3, 38.4, 39.6, 42.0, 44.9, 47.5, 52.3, 55.7, 58.7, 107.9, 108.8, 113.5, 126.5, 126.7, 128.3, 128.5, 128.7, 128.7, 128.8, 132.5, 134.9, 151.2, 155.2, 171.8.

MS (ESI): m/z = 469$[M+H]^+$.

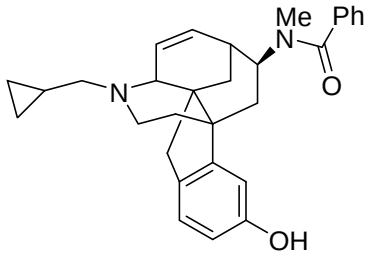
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{31}H_{37}N_2O_2$: 469.2855. Found: 469.2844.

33c •CSA

mp (dec.) 245–246 °C

Anal. Calcd for $C_{31}H_{36}N_2O_2 \cdot 1.0CSA \cdot 1.8H_2O$: C, 67.15; H, 7.64; N, 3.82. Found: C, 67.25; H, 7.48; N, 3.787.

***N*-[(2*S*,4a*S*,7a*R*,12a*R*,14*S*)-5-(Cyclopropylmethyl)-9-hydroxy-2,4a,5,6,7,12-hexahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-yl]-*N*-methylbenzamide (33d)**



33d

Compound **33d** was prepared from compound **31** according to the procedure used to synthesize compound **32d**. Yield, 92%.; a colorless oil.

33d

IR (film) cm^{-1}: 3274, 3017, 2918, 1608, 1446, 1370, 1221, 1072, 755.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.07–0.23 (m, 2H), 0.40–0.58 (m, 2H), 0.77–0.94 (m, 1H), 0.97–2.35 (m, 8H), 2.39–2.72 (m, 4H), 2.84–3.07 (m, 3H), 3.37–3.71 (m, 2.6H), 4.25–4.60 (m, 0.4H), 5.88–6.13 (m, 2H), 6.25–7.04 (m, 3H), 7.09–7.49 (m, 5H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.7, 3.9, 9.6, 29.0, 29.7, 35.5, 38.6, 39.6, 40.7, 43.6, 44.9, 47.4, 53.1, 57.5, 58.7, 108.2, 108.6, 113.4, 115.6, 126.4, 128.5, 128.5, 129.4, 131.0, 132.2, 136.7, 145.4, 151.0, 155.0, 172.8.

MS (ESI): *m/z* = 455$[M+H]^+$.

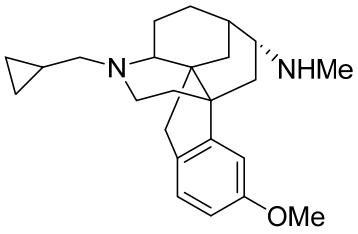
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{30}H_{35}N_2O_2$: 455.2699. Found: 455.2699.

33d•HCl

mp (dec.) 174–175 °C

Anal. Calcd for $C_{30}H_{34}N_2O_2 \cdot HCl \cdot 1.2H_2O$: C, 70.28; H, 7.35; N, 5.46. Found: C, 70.03; H, 7.06; N, 5.20.

(2*S*,4a*S*,7a*R*,12a*R*,14*R*)-5-(Cyclopropylmethyl)-9-methoxy-*N*-methyl-2,3,4,4a,5,6,7,12-octahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-amine (34)



34

Under an argon atmosphere, to a solution of **28** (59.8 mg, 0.164 mmol) in MeOH (2 mL) was added 10% Pd on carbon (52.0 mg), and after exchange of argon for H_2, the reaction mixture was stirred at room temperature for 19 h. The reaction mixture was filtered through a Celite pad and the Celite pad was washed with MeOH. After concentration of the filtrate, the residue was purified by preparative TLC ($CHCl_3$/MeOH/25% ammonia aqueous solution = 100/5/0.5) to give **34** (41.5 mg, 69%) as a colorless oil.

34

IR (film) cm^{-1}: 3075, 2998, 2912, 2848, 1608, 1586, 1478, 1282, 1037, 916, 728.

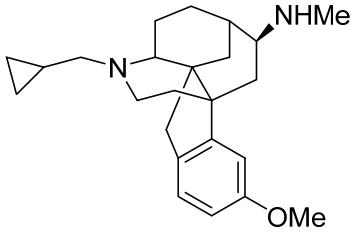
^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.06–0.17 (m, 2H), 0.40–0.53 (m, 2H), 0.76–0.89 (m, 1H), 0.96 (dd, *J* = 13.7, 2.5 Hz, 1H), 1.27–1.37 (m, 1H), 1.44–2.14 (m, 10H), 2.22 (dd, *J* = 12.6, 6.8 Hz, 1H), 2.34 (s, 3H), 2.47–2.70 (m, 4H), 3.01 (dd, *J* = 11.1, 6.8 Hz, 1H), 3.70 (d, *J* = 15.1 Hz, 1H), 3.79 (s, 3H), 6.65 (dd, *J* = 8.1, 2.5 Hz, 1H), 6.75 (d, *J* = 2.5 Hz, 1H), 7.10 (d, *J* = 8.1 Hz, 1H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.2, 4.1, 9.8, 16.3, 28.8, 30.6, 31.6, 32.8, 33.9, 38.7, 40.8, 41.5, 45.3, 45.9, 55.4, 58.5, 59.0, 60.3, 107.1, 111.1, 126.7, 134.1, 154.4, 158.3.

MS (ESI): *m/z* = 367$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{24}H_{35}N_2O$: 367.2749. Found: 367.2749.

(2*S*,4a*S*,7a*R*,12a*R*,14*S*)-5-(Cyclopropylmethyl)-9-methoxy-*N*-methyl-2,3,4,4a,5,6,7,12-octahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-amine (35)



35

Compound **35** was prepared from compound **29** according to the procedure used to synthesize compound **34**. Yield, 88%.; a colorless oil.

35

IR (film) cm^{-1}: 3075, 2918, 2850, 1609, 1586, 1479, 1284, 1216, 1033, 799, 727.

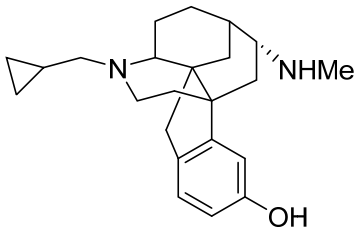
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.06–0.17 (m, 2H), 0.40–0.54 (m, 2H), 0.75–0.91 (m, 1H), 1.22 (dd, *J* = 13.4, 3.4 Hz, 1H), 1.26–1.35 (m, 1H), 1.40–1.66 (m, 4H), 1.68–2.14 (m, 5H), 2.15–2.26 (m, 2H), 2.40–2.69 (m, 4H), 2.45 (s, 3H), 2.97–3.09 (m, 1H), 3.74 (d, *J* = 14.7 Hz, 1H), 3.79 (s, 3H), 6.65 (dd, *J* = 8.0, 2.5 Hz, 1H), 6.70 (d, *J* = 2.5 Hz, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.2, 4.1, 9.8, 16.3, 23.6, 30.5, 33.4, 33.8, 38.1, 38.3, 40.0, 41.4, 46.2, 46.7, 55.3, 58.3, 58.6, 58.8, 107.4, 110.2, 126.6, 134.4, 153.5, 158.3.

MS (ESI): *m/z* = 367$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{24}H_{35}N_2O$: 367.2749. Found: 367.2737.

(2*S*,4a*S*,7a*R*,12a*R*,14*R*)-5-(Cyclopropylmethyl)-14-(methylamino)-2,3,4,4a,5,6,7,12-octahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-9-ol (36)



36

Compound **36** was prepared from compound **34** according to the procedure used to synthesize compound **12**. Yield, 96%.; a colorless amorphous solid.

36

IR (KBr) cm^{-1}: 3312, 2935, 2848, 1608, 1467, 1248, 1039, 816.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.06–0.16 (m, 2H), 0.40–0.54 (m, 2H), 0.74–0.92 (m, 1H), 0.96–1.06 (m, 1H), 1.22–1.39 (m, 1H), 1.46–2.01 (m, 7H), 2.13 (d, *J* = 13.3 Hz, 1H), 2.14–2.41 (m, 3H), 2.37 (s, 3H), 2.47–2.66 (m, 3H), 2.83–2.92 (m, 1H), 3.03 (dd, *J* = 10.8, 7.3 Hz, 1H), 3.69 (d, *J* = 14.9 Hz, 1H), 3.78–4.32 (m, 1H), 6.57 (dd, *J* = 8.0, 2.1 Hz, 1H), 6.81 (d, *J* = 2.1 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.2, 4.1, 9.7, 16.5, 28.5, 29.1, 31.1, 32.4, 33.1, 38.4, 40.8, 41.5, 45.1, 45.7, 58.3, 59.1, 60.4, 109.0, 113.8, 127.2, 132.9, 153.4, 155.5.

MS (ESI): *m/z* = 353$[M+H]^+$.

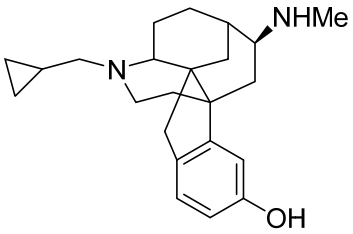
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{23}H_{33}N_2O$: 353.2593. Found: 353.2603.

36•HCl

mp (dec.) 205–206 °C

Anal. Calcd for $C_{23}H_{32}N_2O \cdot 2.0HCl \cdot 2.0H_2O$: C, 59.86; H, 8.30; N, 6.07. Found: C, 60.02; H, 8.31; N, 5.98.

(2*S*,4a*S*,7a*R*,12a*R*,14*S*)-5-(Cyclopropylmethyl)-14-(methylamino)-2,3,4,4a,5,6,7,12-octahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-9-ol (37)



37

Compound **37** was prepared from compound **35** according to the procedure used to synthesize compound **12**. Yield, 55%.; a colorless oil.

37

IR (film) cm^{-1}: 2919, 1611, 1471, 1373, 910, 732.

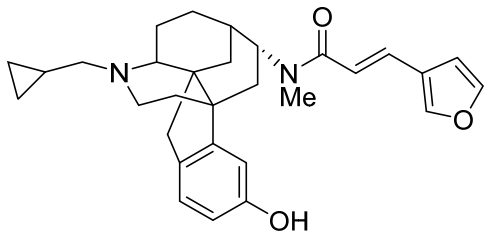
^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.04–0.15 (m, 2H), 0.38–0.52 (m, 2H), 0.73–0.90 (m, 1H), 1.16–1.34 (m, 2H), 1.40–1.66 (m, 3H), 1.68–2.12 (m, 4H), 2.07 (d, *J* = 14.8 Hz, 1H), 2.13–2.30 (m, 2H), 2.38–2.73 (m, 4H), 2.44 (s, 3H), 3.03 (dd, *J* = 10.7, 6.5 Hz, 1H), 3.71 (d, *J* = 14.8 Hz, 1H), 3.90–4.46 (m, 1H), 4.15 (br s, 1H), 6.58 (dd, *J* = 7.9, 2.3 Hz, 1H), 6.66 (d, *J* = 2.3 Hz, 1H), 7.03 (d, *J* = 7.9 Hz, 1H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.2, 4.1, 9.7, 16.4, 23.5, 29.9, 32.9, 33.6, 38.1, 38.2, 39.9, 41.3, 46.0, 46.6, 58.3, 58.5, 58.8, 108.6, 113.0, 126.8, 133.4, 153.2, 155.1.

MS (ESI): *m/z* = 353$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{23}H_{33}N_2O$: 353.25929. Found: 353.26031.

(*E*)-*N*-[(2*S*,4a*S*,7a*R*,12a*R*,14*R*)-5-(Cyclopropylmethyl)-9-hydroxy-2,3,4,4a,5,6,7,12-octahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-yl]-3-(furan-2-yl)-*N*-methylacrylamide (38a)



38a

Compound **38a** was prepared from compound **36** according to the procedure used to synthesize compound **32a**. Yield, 70%.; a colorless oil.

38a

IR (film) cm^{-1}: 3225, 3002, 2924, 2855, 1650, 1586, 1281, 1159, 870, 754.

^1H NMR (300 MHz, THF-d_8): δ (ppm) 0.04–0.19 (m, 2H), 0.38–0.57 (m, 2H), 0.80–0.97 (m, 1H), 1.14 (d, J = 12.5 Hz, 1H), 1.23–2.10 (m, 9H), 2.14–2.67 (m, 5H), 2.71–2.95 (m, 5H), 3.07–3.31 (m, 1H), 4.15–4.29 (m, 0.4H), 4.95–5.11 (m, 0.6H), 6.47–6.79 (m, 4H), 6.98 (d, J = 8.1 Hz, 1H), 7.40 (br s, 1H), 7.53–7.63 (m, 2H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, THF-d_8): δ (ppm) 3.6, 3.9, 10.2, 28.4, 29.9, 30.6, 31.2, 32.0, 35.1, 36.5, 38.1, 45.5, 46.2, 50.4, 53.8, 60.3, 63.9, 107.3, 109.7, 114.5, 116.5, 117.3, 123.0, 125.3, 131.1, 133.2, 144.1, 153.5, 156.2, 166.6.

MS (ESI): m/z = 473$[M+H]^+$.

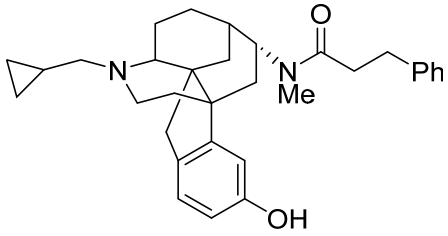
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{30}H_{37}N_2O_3$: 473.2804. Found: 473.2803.

38a•HCl

mp (dec.) 198–199 °C

Anal. Calcd for $C_{30}H_{36}N_2O_3 \cdot HCl \cdot 1.3H_2O$: C, 67.67; H, 7.50; N, 5.26. Found: C, 67.78; H, 7.51; N, 5.35.

***N*-[(2*S*,4a*S*,7a*R*,12a*R*,14*R*)-5-(Cyclopropylmethyl)-9-hydroxy-2,3,4,4a,5,6,7,12-octahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-yl]-*N*-methyl-3-phenylpropanamide (38b)**



38b

Compound **38b** was prepared from compound **36** according to the procedure used to synthesize compound **32b**. Yield, 85%.; a colorless oil.

38b

IR (film) cm^{-1}: 3249, 2924, 1614, 1454, 1286, 1215, 1073, 909.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.05–0.21 (m, 2H), 0.40–0.57 (m, 2H), 0.80–0.99 (m, 1H), 1.04–1.17 (m, 1H), 1.31–1.50 (m, 1H), 1.53–2.18 (m, 8H), 2.24–3.04 (m, 14H), 3.08–3.29 (m, 1H), 3.93–4.03 (m, 0.4H), 4.83–4.94 (m, 0.6H), 6.59 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.74 (dd, *J* = 8.1, 2.2 Hz, 1H), 6.93–7.00 (m, 1H), 7.14–7.33 (m, 5H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.6, 3.9, 9.9, 28.9, 30.1, 30.4, 30.9, 31.7, 31.9, 35.2, 35.9, 38.0, 45.3, 45.7, 46.2, 50.1, 53.8, 60.4, 63.8, 109.5, 114.7, 125.3, 126.2, 128.4, 128.5, 128.5, 128.6, 130.8, 141.0, 153.3, 156.4, 172.6.

MS (ESI): *m/z* = 485$[M+H]^+$.

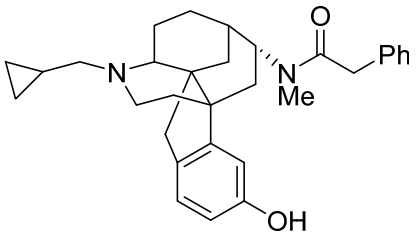
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{32}H_{41}N_2O_2$: 485.31680. Found: 485.31583.

38b•HCl

mp (dec.) 158–159 °C

Anal. Calcd for $C_{32}H_{40}N_2O_2 \cdot HCl \cdot 1.2H_2O$: C, 70.81; H, 8.06; N, 5.16. Found: C, 70.54; H, 7.95; N, 5.25.

***N*-[(2*S*,4a*S*,7a*R*,12a*R*,14*R*)-5-(Cyclopropylmethyl)-9-hydroxy-2,3,4,4a,5,6,7,12-octahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-yl]-*N*-methyl-2-phenylacetamide (38c)**



38c

Compound **38c** was prepared from compound **36** according to the procedure used to synthesize compound **32c**. Yield, 96%.; a colorless oil.

38c

IR (film) cm^{-1}: 3236, 2925, 2856, 1615, 1454, 1286, 909, 729.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.05–0.19 (m, 2H), 0.39–0.57 (m, 2H), 0.80–0.99 (m, 1H), 1.02–1.15 (m, 1.5H), 1.19–2.05 (m, 9.5H), 2.12–2.94 (m, 9H), 3.01–3.31 (m, 1H), 3.69 (s, 1H), 3.84 (d, *J* = 2.7 Hz, 1H), 3.88–3.98 (m, 0.5H), 4.90 (br s, 0.5H), 6.49 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.69 (dd, *J* = 8.0, 2.2 Hz, 1H), 6.91–6.93 (m, 1H), 7.18–7.36 (m, 5H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.5, 3.6, 9.8, 28.9, 30.5, 31.1, 34.7, 36.1, 38.2, 41.6, 42.2, 45.2, 45.8, 46.0, 50.4, 54.4, 60.2, 63.8, 109.6, 114.5, 125.1, 125.4, 127.0, 128.3, 128.3, 128.7, 128.7, 129.0, 135.1, 156.0, 171.0.

MS (ESI): *m/z* = 471$[M+H]^+$.

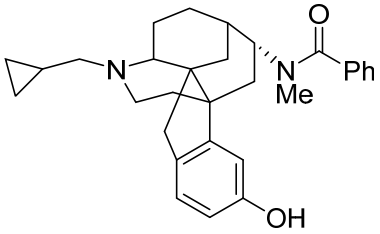
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{31}H_{39}N_2O_2$: 471.3012. Found: 471.3010.

38c•HCl

mp (dec.) 182–183 °C

Anal. Calcd for $C_{31}H_{38}N_2O_2 \cdot HCl \cdot 1.2H_2O$: C, 70.81; H, 8.06; N, 5.16. Found: C, 70.54; H, 7.95; N, 5.25.

***N*-[(2*S*,4a*S*,7a*R*,12a*R*,14*R*)-5-(Cyclopropylmethyl)-9-hydroxy-2,3,4,4a,5,6,7,12-octahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-yl]-*N*-methylbenzamide (38d)**



38d

Compound **38d** was prepared from compound **36** according to the procedure used to synthesize compound **32d**. Yield, 96%.; a colorless oil.

38d

IR (film) cm^{-1}: 3267, 2925, 2855, 1613, 1448, 1286, 1068, 910, 731.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.01–0.24 (m, 2H), 0.35–0.58 (m, 2H), 0.69–2.27 (m, 12H), 2.31–3.44 (m, 6H), 2.38 (d, *J* = 15.9 Hz, 1H), 2.88 (s, 3H), 3.92 (br s, 0.6H), 4.92 (br s, 0.4H), 6.53–6.70 (m, 2H), 6.88–6.98 (m, 1H), 7.41 (br s, 5H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.5, 3.9, 10.2, 23.5, 28.6, 29.6, 29.8, 31.5, 35.1, 36.3, 38.1, 45.6, 46.3, 51.1, 55.5, 59.8, 63.7, 109.7, 114.8, 125.2, 125.6, 125.9, 126.8, 128.7, 129.6, 130.9, 136.6, 153.1, 156.1, 172.0.

MS (ESI): *m/z* = 471$[M+H]^+$.

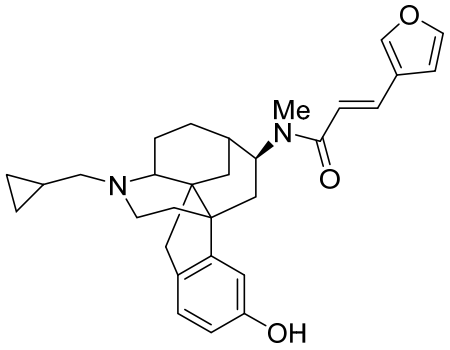
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{30}H_{37}N_2O_2$: 457.2855. Found: 457.2835.

38d•HCl

mp (dec.) 184–185 °C

Anal. Calcd for $C_{30}H_{36}N_2O_2 \cdot HCl \cdot 1.3H_2O$: C, 69.76; H, 7.73; N, 5.42. Found: C, 70.00; H, 7.68; N, 5.47.

(*E*)-*N*-[(2*S*,4a*S*,7a*R*,12a*R*,14*S*)-5-(Cyclopropylmethyl)-9-hydroxy-2,3,4,4a,5,6,7,12-octahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-yl]-3-(furan-2-yl)-*N*-methylacrylamide (39a)



39a

Compound **39a** was prepared from compound **37** according to the procedure used to synthesize compound **32a**. Yield, 73%.; a colorless oil.

39a

IR (film) cm^{-1}: 3231, 2921, 1650, 1584, 1463, 1159, 1021, 870, 755.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.06–0.22 (m, 2H), 0.41–0.56 (m, 2H), 0.79–0.94 (m, 1H), 1.06–1.38 (m, 2H), 1.52–1.74 (m, 4H), 1.78–2.78 (m, 10H), 3.01–3.28 (m, 4H), 3.65–3.79 (m, 1H), 3.96 (br s, 0.5H), 4.55 (br s, 0.5H), 6.27–6.73 (m, 4H), 6.94–7.10 (m, 1H), 7.28–7.44 (m, 1H), 7.45–7.60 (m, 2H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.2, 4.2, 9.7, 16.5, 26.3, 30.6, 32.6, 34.9, 38.2, 39.9, 41.5, 45.7, 46.8, 54.3, 56.9, 58.4, 58.8, 107.6, 113.2, 116.8, 123.0, 127.0, 129.2, 133.0, 133.1, 144.0, 144.0, 152.3, 153.7, 167.1.

MS (ESI): *m/z* = 473$[M+H]^+$.

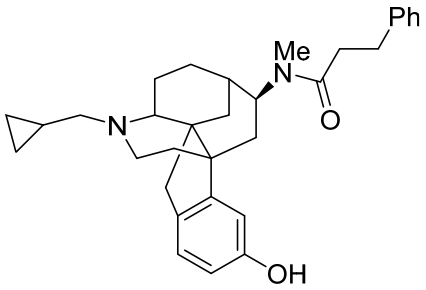
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{30}H_{37}N_2O_3$: 473.2804. Found: 473.2781.

39a•HCl

mp (dec.) 204–205 °C

Anal. Calcd for $C_{30}H_{36}N_2O_3 \cdot HCl \cdot 1.4H_2O$: C, 67.44; H, 7.51; N, 5.24. Found: C, 67.29; H, 7.49; N, 5.31.

***N*-[(2*S*,4a*S*,7a*R*,12a*R*,14*S*)-5-(Cyclopropylmethyl)-9-hydroxy-2,3,4,4a,5,6,7,12-octahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-yl]-*N*-methyl-3-phenylpropanamide (39b)**



39b

Compound **39b** was prepared from compound **37** according to the procedure used to synthesize compound **32b**. Yield, 68%.; a colorless oil.

39b

IR (film) cm^{-1}: 3250, 2923, 1613, 1455, 1241, 1072, 911, 731.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.05–0.20 (m, 2H), 0.39–0.55 (m, 2H), 0.76–0.94 (m, 1H), 1.02–1.20 (m, 1H), 1.23–1.38 (m, 1H), 1.49–1.72 (m, 5H), 1.77–2.11 (m, 5H), 2.16–2.73 (m, 6H), 2.77–2.89 (m, 1H), 2.91–3.13 (m, 5H), 3.63–3.85 (m, 1.5H), 4.48 (br s, 0.5H), 6.58–6.67 (m, 2H), 6.95–7.35 (m, 6H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.2, 4.2, 9.7, 16.3, 26.2, 29.3, 30.1, 31.6, 32.1, 34.6, 35.8, 39.1, 39.9, 41.3. 45.7, 46.8, 56.9, 58.5, 58.8, 107.8, 113.1, 126.0, 126.1, 126.7, 127.1, 128.0, 128.4, 128.5, 133.3, 141.3, 155.2, 172.8.

MS (ESI): *m/z* = 485$[M+H]^+$.

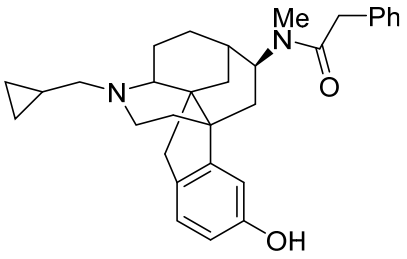
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{32}H_{41}N_2O_2$: 485.3168. Found: 485.3159.

39b•HCl

mp (dec.) 172–173 °C

Anal. Calcd for $C_{32}H_{40}N_2O_2 \cdot HCl \cdot 1.5H_2O$: C, 70.12; H, 8.09; N, 5.11. Found: C, 69.85; H, 8.00; N, 5.17.

***N*-[(2*S*,4a*S*,7a*R*,12a*R*,14*S*)-5-(Cyclopropylmethyl)-9-hydroxy-2,3,4,4a,5,6,7,12-octahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-yl]-*N*-methyl-2-phenylacetamide (39c)**



39c

Compound **39c** was prepared from compound **37** according to the procedure used to synthesize compound **32d**. Yield, 66%.; a colorless oil.

39c

IR (film) cm^{-1}: 3280, 2920, 1615, 1456, 1241, 911, 729.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.05–0.18 (m, 2H), 0.39–0.55 (m, 2H), 0.74–0.93 (m, 1H), 1.01–1.33 (m, 2H), 1.39–1.73 (m, 5H), 1.79–2.11 (m, 4H), 2.15–2.41 (m, 2H), 2.47–2.75 (m, 2H), 2.94–3.13 (m, 4H), 3.50–3.89 (m, 4.5H), 4.49 (br s, 0.5H), 6.11–6.18 (m, 0.5H), 6.55–6.65 (m, 1.5H), 6.93–7.08 (m, 2H), 7.16–7.36 (m, 4H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.2, 4.1, 9.6, 16.4, 26.4, 30.2, 32.0, 34.4, 37.9, 39.2, 39.8, 41.6, 42.2, 45.7, 46.7, 57.0, 58.3, 58.8, 107.8, 113.0, 126.5, 126.7, 128.4, 128.5, 128.7, 128.8, 133.2, 135.1, 152.1, 154.8, 171.9.

MS (ESI): *m/z* = 471$[M+H]^+$.

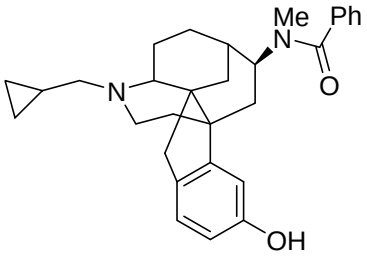
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{31}H_{39}N_2O_2$: 471.3012. Found: 471.2992.

39c•HCl

mp (dec.) 190–191 °C

Anal. Calcd for $C_{31}H_{38}N_2O_2 \cdot HCl \cdot 1.5H_2O$: C, 69.71; H, 7.93; N, 5.24. Found: C, 69.82; H, 7.85; N, 5.35.

***N*-[(2*S*,4a*S*,7a*R*,12a*R*,14*S*)-5-(Cyclopropylmethyl)-9-hydroxy-2,3,4,4a,5,6,7,12-octahydro-1*H*-2,7a-ethanoindeno[1,2-*d*]quinolin-14-yl]-*N*-methylbenzamide (39d)**



39d

Compound **39d** was prepared from compound **37** according to the procedure used to synthesize compound **32d**. Yield, 83%.; a colorless oil.

39d

IR (film) cm^{-1}: 3267, 3076, 2923, 1608, 1445, 1371, 1240, 1066, 912, 732.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.08–0.19 (m, 2H), 0.41–0.56 (m, 2H), 0.78–1.36 (m, 3H), 1.47–2.78 (m, 14H), 2.94–3.29 (m, 4H), 3.52–3.80 (m, 1.7H), 4.55 (br s, 0.3H), 6.27–6.61 (m, 2H), 6.78–6.96 (m, 1H), 7.04–7.48 (m, 5H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.2, 4.2, 9.4, 16.6, 26.6, 30.1, 31.4, 31.9, 34.5, 37.8, 39.7, 40.5, 41.5, 45.7, 46.6, 58.4, 58.7, 108.1, 112.9, 125.6, 126.6, 126.6, 128.4, 128.5, 129.3, 132.6, 139.0, 151.7, 155.1, 172.4.

MS (ESI): *m/z* = 457$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{30}H_{37}N_2O_2$: 457.2855. Found: 457.2854.

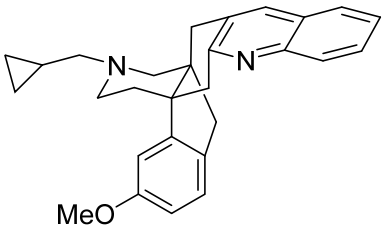
39d•HCl

mp (dec.) 208–209 °C

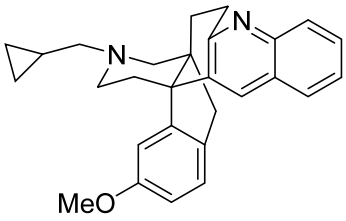
Anal. Calcd for $C_{30}H_{36}N_2O_2 \cdot HCl \cdot 1.5H_2O$: C, 69.28; H, 7.75; N, 5.39. Found: C, 69.21; H, 7.70; N, 5.48.

(6a*R*,11a*S*)-15-(Cyclopropylmethyl)-8-methoxy-11,12-dihydro-6*H*-6a,11a-(ethanoimino-methano)indeno[2,1-*b*]acridine (51)

(7a*R*,12b*R*)-16-(Cyclopropylmethyl)-11-methoxy-7,8-dihydro-6*H*-12b,7a-(ethanoimino-methano)indeno[1,2-*a*]acridine (52)



51



52

To a stirred solution of **50** (61.1 mg, 0.188 mmol) in ethanol (10 mL) were added methanesulfonic acid (48.7 μL, 0.751 mmol) and 2-aminobenzaldehyde (91.0 mg, 0.751 mmol) and refluxed under an argon atmosphere. After 12 h with stirring at the same temperature, the reaction mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution, and extracted with $CHCl_3$ three times. The combined organic extracts were dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by preparative TLC (Hexane/AcOEt/MeOH/25% ammonia aqueous solution = 300/100/10/1) to give **51** (27.0 mg, 35%) as a yellow oil and **52** (29.5 mg, 38%) as a yellow oil.

51

IR (film) cm^{-1}: 3075, 3001, 2915, 2832, 1714, 1609, 1490, 1284, 1221, 1033, 752.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.01–0.09 (m, 2H), 0.42–0.52 (m, 2H), 0.74–0.89 (m, 1H), 1.70–1.86 (m, 1H), 1.93–2.04 (m, 1H), 2.07–2.25 (m, 2H), 2.27–2.69 (m, 5H), 2.80 (d, *J* = 15.2 Hz, 1H), 2.97 (d, *J* = 15.2 Hz, 1H), 3.08 (d, *J* = 17.0 Hz, 1H), 3.20–3.36 (m, 1H), 3.24 (d, *J* = 9.9 Hz, 1H), 3.79 (s, 3H), 6.69 (dd, *J* = 8.1, 2.4 Hz, 1H), 6.77 (d, *J* = 2.4 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 7.40–7.47 (m, 1H), 7.57–7.64 (m, 1H), 7.68–7.73 (m, 1H), 7.84 (s, 1H), 7.97 (d, *J* = 8.3 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.7, 4.1, 8.4, 33.4, 36.8, 41.7, 42.6, 45.6, 47.3, 50.1, 55.4, 60.2, 63.4, 108.3, 111.6, 125.6, 126.2, 126.9, 127.4, 128.3, 128.5, 129.7, 133.1, 134.7, 146.6, 151.7, 158.2, 159.0.

MS (ESI): *m/z* = 411$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{28}H_{31}N_2O$: 411.2436. Found: 411.2423.

52

IR (film) cm^{-1}: 3000, 2921, 1587, 1488, 1283, 1223, 1031, 907, 732.

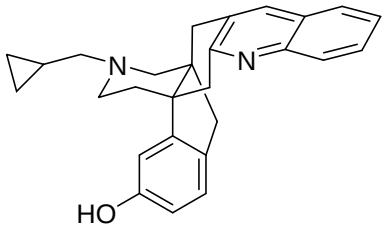
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.03–0.10 (m, 2H), 0.44–0.54 (m, 2H), 0.78–0.91 (m, 1H), 1.94–2.05 (m, 1H), 2.08–2.36 (m, 6H), 2.43–2.78 (m, 4H), 2.91 (d, *J* = 15.2 Hz, 1H), 3.26–3.38 (m, 2H), 3.81 (s, 3H), 6.69 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.77 (br s, 1H), 7.10 (d, *J* = 8.2 Hz, 1H), 7.39–7.46 (m, 1H), 7.57–7.65 (m, 1H), 7.69–7.75 (m, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 8.10 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.8, 4.2, 8.3, 27.9, 30.3, 35.4, 38.8, 46.1, 50.9, 51.6, 55.5, 60.8, 63.6, 110.8, 110.9, 125.5, 126.3, 127.2, 127.4, 128.0, 128.0, 129.1, 134.0, 135.6, 146.3, 149.5, 157.2, 158.7.

MS (ESI): *m/z* = 411$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{28}H_{31}N_2O$: 411.2436. Found: 411.2426.

(6a*R*,11a*S*)-15-(Cyclopropylmethyl)-11,12-dihydro-6*H*-6a,11a-(ethanoiminomethano)-indeno[2,1-*b*]acridin-8-ol (49)



49

Compound **49** was prepared from compound **51** according to the procedure used to synthesize compound **12**. Yield, 79%.; a colorless amorphous solid.

49

IR (film) cm^{-1}: 3007, 2918, 2816, 1613, 1494, 1465, 1238, 1217, 753.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.01–0.09 (m, 2H), 0.39–0.53 (m, 2H), 0.72–0.88 (m, 1H), 1.68–1.82 (m, 1H), 1.92–2.03 (m, 1H), 2.05–2.28 (m, 4H), 2.54–2.66 (m, 2H), 2.72 (d, *J* = 15.3 Hz, 1H), 2.85 (d, *J* = 15.3 Hz, 1H), 3.06–3.22 (m, 3H), 3.50 (d, *J* = 17.7 Hz, 1H), 6.60 (dd, *J* = 8.0, 2.2 Hz, 1H), 6.84 (d, *J* = 2.2 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 7.42–7.49 (m, 1H), 7.57–7.65 (m, 1H), 7.69–7.75 (m, 1H), 7.91 (s, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.7, 4.2, 8.4, 31.7, 36.1, 42.0, 43.3, 45.2, 47.3, 50.3, 60.9, 63.5, 109.9, 114.3, 125.9, 126.4, 127.0, 127.5, 127.6, 128.9, 129.9, 131.8, 135.7, 145.9, 151.0, 156.3, 158.3.

MS (ESI): *m/z* = 397$[M+H]^+$.

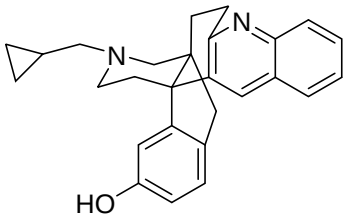
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{27}H_{29}N_2O$: 397.2280. Found: 397.2263.

49•HCl

mp (dec.) 186–187 °C

Anal. Calcd for $C_{27}H_{28}N_2O \cdot 2.0HCl \cdot 2.8H_2O$: C, 62.38; H, 6.90; N, 5.39. Found: C, 62.59; H, 7.08; N, 5.38.

(7a*R*,12b*R*)-16-(Cyclopropylmethyl)-7,8-dihydro-6*H*-12b,7a-(ethanoiminomethano)-indeno[1,2-*a*]acridin-11-ol (53)



53

Compound **53** was prepared from compound **52** according to the procedure used to synthesize compound **12**. Yield, 79%.; a colorless amorphous solid.

53

IR (film) cm^{-1}: 3006, 2923, 2814, 1613, 1590, 1491, 1464, 1282, 1220, 1052, 752.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.01–0.08 (m, 2H), 0.42–0.51 (m, 2H), 0.74–0.90 (m, 1H), 1.88–2.00 (m, 1H), 2.07–2.52 (m, 8H), 2.55–2.88 (m, 3H), 3.15–3.38 (m, 2H), 6.64 (dd, *J* = 8.0, 2.3 Hz, 1H), 6.83 (br s, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 7.34–7.42 (m, 1H), 7.53–7.65 (m, 2H), 7.96 (d, *J* = 8.4 Hz, 1H), 8.08 (s, 1H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 3.8, 4.2, 8.1, 28.0, 29.8, 35.3, 39.0, 46.0, 50.7, 51.4, 60.6, 63.6, 111.3, 114.0, 125.7, 126.5, 127.2, 127.4, 127.4, 127.9, 129.4, 132.8, 136.0, 145.7, 149.4, 155.6, 157.3.

MS (ESI): *m/z* = 397$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{27}H_{29}N_2O$: 397.2280. Found: 397.2275.

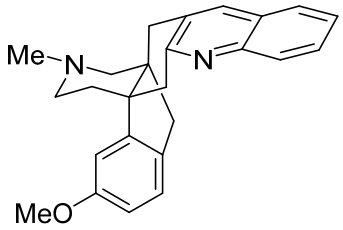
53•HCl

mp (dec.) 198–199 °C

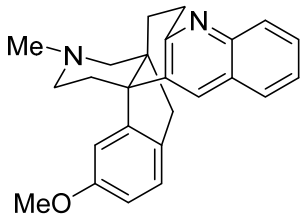
Anal. Calcd for $C_{27}H_{28}N_2O \cdot 2.0HCl \cdot 1.4H_2O$: C, 65.56; H, 6.68; N, 5.66. Found: C, 65.44; H, 7.03; N, 5.65.

(6a*R*,11a*S*)-8-Methoxy-15-methyl-11,12-dihydro-6*H*-6a,11a-(ethanoiminomethano)-indeno[2,1-*b*]acridine (55)

(7a*R*,12b*R*)-11-Methoxy-16-methyl-7,8-dihydro-6*H*-12b,7a-(ethanoiminomethano)-indeno[1,2-*a*]acridine (56)



55



56

Compound **55** and **56** was prepared from compound **54** according to the procedure used to synthesize compound **51** and **52**. Yield, **55**: 35%.; a colorless amorphous solid and **56**: 54%.; a colorless oil.

55

IR (film) cm^{-1}: 2933, 2840, 2790, 1714, 1609, 1491, 1284, 1034, 732.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.69–2.10 (m, 2H), 2.13–2.29 (m, 3H), 2.17 (s, 3H), 2.30–2.50 (m, 2H), 2.79 (d, *J* = 15.3 Hz, 1H), 2.94 (d, *J* = 15.3 Hz, 1H), 3.02–3.12 (m, 1H), 3.19 (d, *J* = 17.7 Hz, 1H), 3.30 (d, *J* = 17.7 Hz, 1H), 3.79 (s, 3H), 6.69 (dd, *J* = 8.1, 2.5 Hz, 1H), 6.77 (d, *J* = 2.5 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 1H), 7.40–7.47 (m, 1H), 7.57–7.64 (m, 1H), 7.67–7.72 (m, 1H), 7.82 (s, 1H), 7.97 (d, *J* = 8.4 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 33.5, 36.7, 41.6, 42.4, 45.6, 46.4, 46.5, 52.0, 55.3, 62.7, 108.4, 111.7, 125.6, 126.2, 126.9, 127.4, 128.3, 128.5, 129.5, 133.0, 134.7, 146.6, 151.6, 158.0, 159.0.

MS (ESI): *m/z* = 371$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{25}H_{27}N_2O$: 371.2123. Found: 371.2141.

56

IR (film) cm^{-1}: 2934, 2841, 2790, 1615, 1587, 1488, 1284, 1227, 1032, 751.

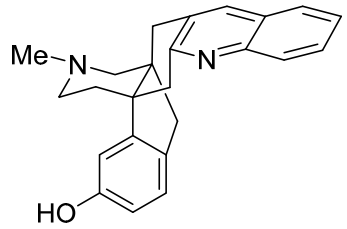
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.95–2.07 (m, 1H), 2.13–2.32 (m, 4H), 2.19 (s, 3H), 2.37–2.72 (m, 4H), 2.93 (d, *J* = 15.2 Hz, 1H), 3.28–3.39 (m, 2H), 3.84 (s, 3H), 6.72 (dd, *J* = 8.1, 2.4 Hz, 1H), 6.95 (br s, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 7.39–7.47 (m, 1H), 7.59–7.67 (m, 1H), 7.73 (d, *J* = 8.1 Hz, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 8.11 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 27.7, 30.3, 35.4, 38.6, 46.1, 46.4, 51.0, 52.8, 55.4, 63.2, 110.8, 111.0, 125.5, 126.3, 127.1, 127.3, 128.0, 129.1, 133.9, 135.1, 135.7, 146.3, 149.2, 157.0, 158.7.

MS (ESI): *m/z* = 371$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{25}H_{27}N_2O$: 371.2123. Found: 371.2114.

(6a*R*,11a*S*)-15-Methyl-11,12-dihydro-6*H*-6a,11a-(ethanoiminomethano)indeno[2,1-*b*]acridin-8-ol (57)



57

Compound **57** was prepared from compound **55** according to the procedure used to synthesize compound **12**. Yield, 67%.; a colorless amorphous solid.

57

IR (film) cm^{-1}: 3389, 2924, 2796, 1613, 1495, 1465, 1050, 752.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.70–1.84 (m, 1H), 1.92–2.04 (m, 1H), 2.12–2.29 (m, 2H), 2.20 (s, 3H), 2.37–2.55 (m, 2H), 2.75 (d, *J* = 15.2 Hz, 1H), 2.84 (d, *J* = 15.2 Hz, 1H), 3.08–3.21 (m, 3H), 3.43 (d, *J* = 17.8 Hz, 1H), 6.61 (dd, *J* = 8.0, 2.2 Hz, 1H), 6.81 (d, *J* = 2.2 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H), 7.43–7.50 (m, 1H), 7.59–7.66 (m, 1H), 7.70–7.76 (m, 1H), 7.91 (s, 1H), 8.08 (d, *J* = 8.5 Hz, 1H), a proton (OH) was not observed.

MS (ESI): *m/z* = 357$[M+H]^+$.

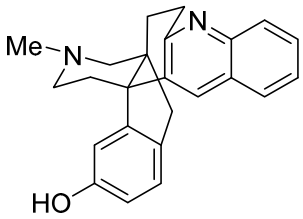
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{24}H_{25}N_2O$: 357.1967. Found: 357.1953.

57•HCl

mp (dec.) 202–203 °C

Anal. Calcd for $C_{24}H_{24}N_2O \cdot 2.0HCl \cdot 1.2H_2O$: C, 63.92; H, 6.35; N, 6.21. Found: C, 63.75; H, 6.53; N, 6.22.

(7a*R*,12b*R*)-16-Methyl-7,8-dihydro-6*H*-12b,7a-(ethanoiminomethano)indeno[1,2-*a*]acridin-11-ol (58)



58

Compound **58** was prepared from compound **56** according to the procedure used to synthesize compound **12**. Yield, 62%.; a colorless amorphous solid.

58

IR (film) cm^{-1}: 3365, 2925, 2796, 1590, 1464, 1226, 751.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.89–2.01 (m, 1H), 2.13–2.49 (m, 7H), 2.17 (s, 3H), 2.56–2.73 (m, 1H), 2.83 (d, *J* = 15.1 Hz, 1H), 3.23–3.36 (m, 2H), 6.63 (dd, *J* = 2.3, 8.0 Hz, 1H), 6.85 (br s, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 7.34–7.42 (m, 1H), 7.53–7.63 (m, 2H), 7.96 (d, *J* = 8.4 Hz, 1H), 8.09 (s, 1H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 27.7, 29.8, 35.2, 38.7, 46.0, 46.4, 50.8, 52.7, 63.0, 111.4, 114.1, 125.7, 126.6, 127.2, 127.4, 127.4, 129.4, 132.6, 135.1, 136.1, 145.8, 149.2, 155.9, 157.1.

MS (ESI): *m/z* = 357$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{24}H_{25}N_2O$: 357.1967. Found: 357.1984.

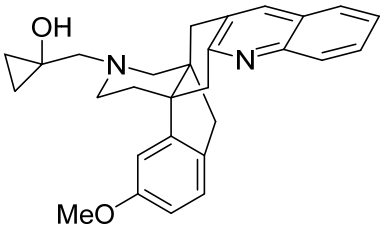
58•HCl

mp (dec.) 219–220 °C

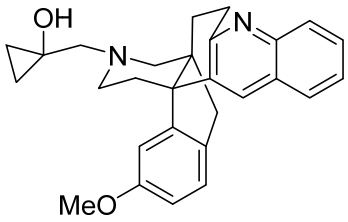
Anal. Calcd for $C_{24}H_{24}N_2O \cdot 2.0HCl \cdot 1.4H_2O$: C, 63.41; H, 6.39; N, 6.16. Found: C, 63.52; H, 6.71; N, 6.13.

1-{[(6a*R*,11a*S*)-8-Methoxy-11,12-dihydro-6*H*-6a,11a-(ethanoiminomethano)indeno[2,1-*b*]acridin-15-yl]methyl}cyclopropanol (60)

1-{[(7a*R*,12b*R*)-11-Methoxy-7,8-dihydro-6*H*-12b,7a-(ethanoiminomethano)indeno[1,2-*a*]acridin-16-yl]methyl}cyclopropanol (61)



60



61

To a stirred solution of **59** (329 mg, 1.21 mmol) in ethanol (10 mL) were added methanesulfonic acid (315 μL, 4.85 mmol) and 2-aminobenzaldehyde (588 mg, 4.85 mmol) and refluxed under an argon atmosphere. After 12 h with stirring at the same temperature, the reaction mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution, and extracted with $CHCl_3$ three times. The combined organic extracts were dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 100/1 to 100/10) to give an inseparable diastereomeric mixture (380 mg, 88%) as a colorless amorphous solid. The resulting diastereomeric mixture was used for the next reaction without further purification. To a stirred solution of the diastreomeric mixture (113 mg, 0.376 mmol) in DMF (10 mL) were added 4-dimethylaminopyridine (19 mg, 0.47 mmol), 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (303 mg, 1.58 mmol) and 1-acetoxycyclopropanecarboxylic acid (228 mg, 1.58 mmol), and stirred under an argon atmosphere at rt. After 6 h with stirring, the reaction mixture was evaporated *in vacuo*. The residue was basified (pH 9) with saturated $NaHCO_3$ aqueous solution, and extracted with $CHCl_3$ three times. The combined organic extracts were dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography (hexane/AcOEt/MeOH/25% ammonia aqueous solution = 200/100/10/1) to give an inseparable diastereomeric mixture (180 mg) as a colorless amorphous solid. but could not be purified completely. The resulting compound was used for the next reaction without further purification. To a stirred suspension of $LiAlH_4$ (120 mg, 3.16 mmol) in THF (3.2 mL) was added a solution of H_2SO_4 (84.2 μL, 1.58 mmol) at 0 °C under an argon atmosphere and stirred at room temperature. After 15 min with stirring, the diastereomeric mixture (180 mg) in THF (1.5 mL) was added to a reaction mixture and stirred at room temperature under an argon atmosphere. After 1 h with stirring, THF/H_2O = 1:1 and 25% NH_3 aqueous solution were added to the solution. The obtained solid was removed by filtration and the filtrate was evaporated *in vacuo*. The residue was purified

by preparative TLC (hexane/AcOEt/MeOH/25% ammonia aqueous solution = 200/100/10/1) to give **60** (29.1 mg, 22% in two steps) as a colorless amorphous solid and **61** (66.5 mg, 49% in two steps) as a colorless amorphous solid.

60

IR (film) cm^{-1}: 3000, 2917, 2831, 1609, 1491, 1285, 1033, 910, 732.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.29–0.38 (m, 2H), 0.75–0.84 (m, 2H), 1.69–1.82 (m, 1H), 1.94–2.06 (m, 1H), 2.37–2.50 (m, 1H), 2.39 (d, *J* = 2.1 Hz, 1H), 2.47 (d, *J* = 11.8 Hz, 1H), 2.53–2.63 (m, 1H), 2.57 (d, *J* = 11.5 Hz, 1H), 2.86 (d, *J* = 15.4 Hz, 1H), 2.98 (d, *J* = 15.4 Hz, 1H), 3.06–3.35 (m, 3H), 3.19 (d, *J* = 17.3 Hz, 1H), 3.30 (d, *J* = 17.3 Hz, 1H), 3.78–3.83 (m, 1H), 3.79 (s, 3H), 6.71 (dd, *J* = 8.1, 2.5 Hz, 1H), 6.77 (d, *J* = 2.5 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 1H), 7.41–7.49 (m, 1H), 7.58–7.66 (m, 1H), 7.69–7.74 (m, 1H), 7.84 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 10.9, 11.1, 33.3, 37.2, 42.1, 42.8, 46.0, 47.5, 50.0, 52.2, 55.4, 60.8, 64.4, 108.4, 111.9, 125.7, 126.1, 126.9, 127.4, 128.3, 128.6, 129.5, 132.9, 134.5, 146.7, 151.2, 158.2, 159.1.

MS (ESI): *m/z* = 427$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{28}H_{31}N_2O_2$: 427.2386. Found: 427.2364.

61

IR (film) cm^{-1}: 3002, 2924, 2832, 1587, 1488, 1285, 1032, 909, 732.

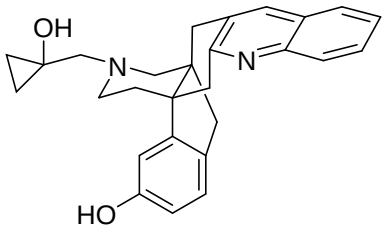
^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.31–0.38 (m, 2H), 0.78–0.85 (m, 2H), 2.02 (dt, *J* = 14.1, 5.9 Hz, 1H), 2.24–2.54 (m, 4H), 2.33 (d, *J* = 12.5 Hz, 1H), 2.43 (d, *J* = 12.5 Hz, 1H), 2.57–2.77 (m, 2H), 2.71 (d, *J* = 11.8 Hz, 1H), 2.93 (d, *J* = 15.2 Hz, 1H), 3.27–3.37 (m, 3H), 3.82 (s, 3H), 6.71 (dd, *J* = 8.1, 2.4 Hz, 1H), 6.90–6.97 (m, 1H), 7.11 (d, *J* = 8.1 Hz, 1H), 7.39–7.46 (m, 1H), 7.58–7.65 (m, 1H), 7.69–7.74 (m, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 8.09 (s, 1H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 10.8, 11.3, 27.7, 30.1, 35.5, 38.5, 46.3, 50.9, 51.5, 52.2, 55.5, 61.0, 64.5, 110.8, 111.0, 125.6, 125.7, 126.4, 127.1, 127.4, 128.0, 129.2, 133.8, 135.7, 146.3, 149.2, 156.9, 158.8.

MS (ESI): *m/z* = 427$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{28}H_{31}N_2O_2$: 427.2386. Found: 427.2391.

(6a*R*,11a*S*)-15-[(1-Hydroxycyclopropyl)methyl]-11,12-dihydro-6*H*-6a,11a-(ethanoimino-methano)indeno[2,1-*b*]acridin-8-ol (62)



62

Compound **62** was prepared from compound **60** according to the procedure used to synthesize compound **18a**. Yield, 78%.; a colorless oil.

62

IR (film) cm^{-1}: 2920, 2819, 1613, 1495, 1465, 1288, 908, 732.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.26–0.40 (m, 2H), 0.71–0.86 (m, 2H), 1.65–1.77 (m, 1H), 1.91–2.03 (m, 1H), 2.25–2.39 (m, 4H), 2.60–2.71 (m, 2H), 2.78 (d, *J* = 15.5 Hz, 1H), 2.89 (d, *J* = 15.5 Hz, 1H), 3.10–3.21 (m, 3H), 3.37 (d, *J* = 17.4 Hz, 1H), 6.63 (dd, *J* = 8.0, 2.2 Hz, 1H), 6.81 (d, *J* = 2.2 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 1H), 7.43–7.51 (m, 1H), 7.58–7.67 (m, 1H), 7.71–7.77 (m, 1H), 7.92 (s, 1H), 8.10 (d, *J* = 8.5 Hz, 1H), two proton (OH) were not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 11.0, 11.1, 31.9, 36.6, 42.3, 43.2, 45.6, 47.4, 50.1, 52.2, 61.3, 64.3, 109.8, 114.4, 126.1, 126.4, 127.0, 127.4, 127.6, 129.1, 129.8, 131.7, 135.4, 145.9, 150.5, 156.4, 158.3.

MS (ESI): *m/z* = 413$[M+H]^+$.

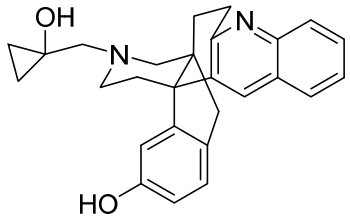
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{27}H_{29}N_2O_2$: 413.2229. Found: 413.2237.

62•HCl

mp (dec.) 177–178 °C

Anal. Calcd for $C_{27}H_{28}N_2O_2 \cdot 1.0HCl \cdot 3.5H_2O$: C, 63.33; H, 7.09; N, 5.47. Found: C, 63.50; H, 7.06; N, 5.50.

(7a*R*,12b*R*)-16-[(1-Hydroxycyclopropyl)methyl]-7,8-dihydro-6*H*-12b,7a-(ethanoimino-methano)indeno[1,2-*a*]acridin-11-ol (63)



63

Compound **63** was prepared from compound **61** according to the procedure used to synthesize compound **18a**. Yield, 64%.; a colorless oil.

63

IR (film) cm^{-1}: 2923, 1590, 1464, 1285, 1125, 908, 732.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.29–0.38 (m, 2H), 0.76–0.86 (m, 2H), 1.89–2.06 (m, 1H), 2.12–2.75 (m, 11H), 2.85 (d, *J* = 15.1 Hz, 1H), 3.20–3.40 (m, 2H), 6.67 (dd, *J* = 8.0, 2.2 Hz, 1H), 6.89 (br s, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 7.34–7.41 (m, 1H), 7.52–7.62 (m, 2H), 7.97 (d, *J* = 8.4 Hz, 1H), 8.08 (s, 1H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 10.8, 11.4, 27.6, 29.6, 35.4, 38.7, 46.1, 50.9, 51.4, 52.2, 60.8, 64.4, 111.3, 114.1, 125.8, 126.6, 127.2, 127.2, 127.5, 129.5, 132.5, 135.2, 136.3, 145.6, 149.1, 155.9, 157.0.

MS (ESI): *m/z* = 413$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{27}H_{29}N_2O_2$: 413.2229. Found: 413.2210.

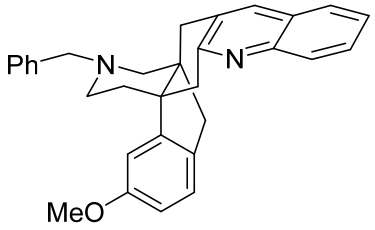
63•HCl

mp (dec.) 195–196 °C

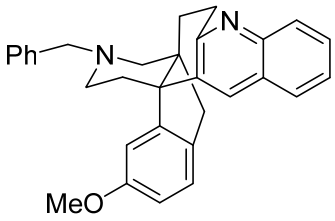
Anal. Calcd for $C_{27}H_{28}N_2O_2 \cdot 2.0HCl \cdot 1.0H_2O$: C, 64.41; H, 6.41; N, 5.56. Found: C, 64.61; H, 6.55; N, 5.60.

(6a*R*,11a*S*)-15-Benzyl-8-methoxy-11,12-dihydro-6*H*-6a,11a-(ethanoiminomethano)-indeno[2,1-*b*]acridine (64)

(7a*R*,12b*R*)-16-Benzyl-11-methoxy-7,8-dihydro-6*H*-12b,7a-(ethanoiminomethano)-indeno[1,2-*a*]acridine (65)



64



65

To a stirred solution of **59** (329 mg, 1.21 mmol) in ethanol (10 mL) were added methanesulfonic acid (315 μL, 4.85 mmol) and 2-aminobenzaldehyde (588 mg, 4.85 mmol) and refluxed under an argon atmosphere. After 12 h with stirring at the same temperature, the reaction mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution, and extracted with $CHCl_3$ three times. The combined organic extracts were dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 100/1 to 100/10) to give an inseparable diastereomeric mixture (380 mg, 88%) as a colorless amorphous solid. The resulting diastereomeric mixture was used for the next reaction without further purification.

To a stirred solution of the diastreomeric mixture (98.7 mg, 0.277 mmol) in DMF (2 mL) were added K_2CO_3 (153 mg, 1.11 mmol) and benzyl bromide (98.7 μL, 0.831 mmol) at room temperature under an argon atmosphere. After 4 h with stirring at the same temperature, the reaction mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution, and extracted with $CHCl_3$ three times. The combined organic extracts were dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by preparative TLC ($CHCl_3$/Et_2O = 4/0.1) to give **64** (21.8 mg, 18%) as a colorless amorphous solid and **65** (31.7 mg, 26%) as a colorless amorphous solid.

64

IR (film) cm^{-1}: 3025, 2913, 2807, 1609, 1493, 1284, 1220, 1030, 752, 699.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.69–1.81 (m, 1H), 1.91–2.03 (m, 1H), 2.21–2.38 (m, 3H), 2.39–2.51 (m, 1H), 2.75 (d, *J* = 15.2 Hz, 1H), 2.95 (d, *J* = 15.0 Hz, 1H), 2.99 (d, *J* = 17.2 Hz, 1H), 3.15–3.49 (m, 2H), 3.25 (d, *J* = 8.6 Hz, 1H), 3.39 (d, *J* = 6.5 Hz, 1H), 3.79 (s, 3H), 6.69 (dd, *J* = 8.1, 2.4 Hz, 1H), 6.77 (d, *J* = 2.4 Hz, 1H), 7.12 (d, *J* = 8.1 Hz, 1H), 7.21–7.34 (m, 5H), 7.35–7.40 (m, 1H), 7.41–7.48 (m, 1H), 7.57–7.65 (m, 1H), 7.69–7.74 (m, 1H), 7.82 (s, 1H), 7.98 (d, *J* = 8.5 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 33.7, 36.7, 41.5, 42.5, 45.9, 47.3, 50.3, 55.4, 60.0, 62.7, 108.3, 111.7, 125.6, 126.1, 126.8, 126.9, 127.4, 127.6, 128.1, 128.2, 128.3, 128.5, 128.7, 129.8, 133.2, 134.5, 139.1, 146.6, 151.8, 158.3, 159.0.

MS (ESI): *m/z* = 447$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{31}H_{31}N_2O$: 447.2436. Found: 447.2432.

65

IR (film) cm^{-1}: 2932, 2806, 1587, 1489, 1283, 1028, 752.

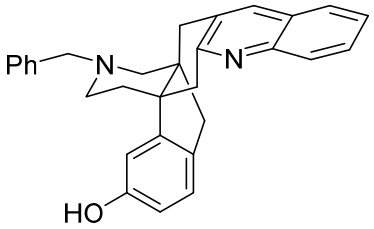
^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.90 (td, *J* = 14.2, 5.8 Hz, 1H), 2.13–2.32 (m, 4H), 2.38–2.70 (m, 4H), 2.86 (d, *J* = 15.1 Hz, 1H), 3.17–3.41 (m, 3H), 3.46 (d, *J* = 13.4 Hz, 1H), 3.82 (s, 3H), 6.70 (dd, *J* = 8.2, 2.4 Hz, 1H), 6.91–6.96 (m, 1H), 7.09 (d, *J* = 8.2 Hz, 1H), 7.20–7.36 (m, 5H), 7.38–7.45 (m, 1H), 7.57–7.64 (m, 1H), 7.67–7.74 (m, 1H), 7.96 (d, *J* = 8.5 Hz, 1H), 8.08 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 27.6, 30.2, 35.6, 38.5, 46.4, 51.1, 51.7, 55.5, 60.6, 62.8, 110.8, 110.9, 125.5, 126.3, 126.9, 127.2, 127.4, 127.4, 128.0, 128.2, 128.2, 128.6, 128.6, 129.1, 134.1, 135.6, 139.0, 146.3, 149.5, 157.3, 158.7.

MS (ESI): *m/z* = 447$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{31}H_{31}N_2O$: 447.2436. Found: 447.2424.

(6a*R*,11a*S*)-15-Benzyl-11,12-dihydro-6*H*-6a,11a-(ethanoiminomethano)indeno[2,1-*b*]-acridin-8-ol (66)



66

Compound **66** was prepared from compound **64** according to the procedure used to synthesize compound **12**. Yield, 36%.; a colorless amorphous solid.

66

IR (film) cm^{-1}: 3024, 2923, 2809, 1613, 1495, 1347, 1217, 907, 751.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.37–1.84 (m, 3H), 1.93–2.04 (m, 1H), 2.18 (d, *J* = 11.4 Hz, 1H), 2.35 (d, *J* = 11.4 Hz, 1H), 2.45–2.56 (m, 1H), 2.70–2.83 (m, 2H), 3.02 (d, *J* = 17.8 Hz, 1H), 3.12–3.26 (m, 2H), 3.29–3.47 (m, 2H), 6.61 (dd, *J* = 8.0, 2.2 Hz, 1H), 6.82 (d, *J* = 2.2 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 7.22–7.34 (m, 5H), 7.44–7.51 (m, 1H), 7.59–7.67 (m, 1H), 7.72–7.78 (m, 1H), 7.90 (s, 1H), 8.08 (d, *J* = 8.4 Hz, 1H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 32.2, 36.0, 41.7, 43.2, 45.6, 47.3, 50.5, 60.6, 62.7, 109.8, 114.1, 125.9, 126.4, 126.9, 126.9, 127.6, 127.6, 128.2, 128.2, 128.7, 128.7, 128.9, 130.0, 132.2, 135.4, 139.1, 146.0, 151.2, 156.0, 158.4.

MS (ESI): *m/z* = 433$[M+H]^+$.

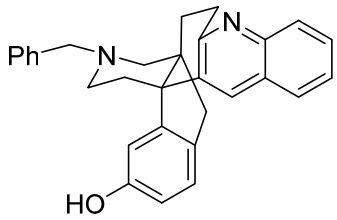
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{30}H_{29}N_2O$: 433.2280. Found: 433.2270.

66•HCl

mp (dec.) 172–173 °C

Anal. Calcd for $C_{30}H_{28}N_2O \cdot 1.0HCl \cdot 2.7H_2O$: C, 69.61; H, 6.70; N, 5.41. Found: C, 69.42; H, 6.81; N, 5.67.

(7a*R*,12b*R*)-16-Benzyl-7,8-dihydro-6*H*-12b,7a-(ethanoiminomethano)indeno[1,2-*a*]acridin-11-ol (67)



67

Compound **67** was prepared from compound **65** according to the procedure used to synthesize compound **12**. Yield, 50%.; a colorless amorphous solid.

67

IR (film) cm^{-1}: 3026, 2926, 2806, 1590, 1493, 1454, 1282, 908, 733.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.87 (td, *J* = 14.0, 6.0 Hz, 1H), 2.11–2.32 (m, 4H), 2.33–2.51 (m, 2H), 2.42 (d, *J* = 11.6 Hz, 1H), 2.57–2.85 (m, 1H), 2.79 (d, *J* = 14.9 Hz, 1H), 3.14–3.50 (m, 2H), 3.32 (d, *J* = 13.6 Hz, 1H), 3.44 (d, *J* = 13.3 Hz, 1H), 6.65 (dd, *J* = 8.0, 2.3 Hz, 1H), 6.83 (br s, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 7.19–7.34 (m, 5H), 7.36–7.44 (m, 1H), 7.55–7.65 (m, 2H), 7.98 (d, *J* = 8.4 Hz, 1H), 8.06 (s, 1H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 27.8, 29.9, 35.7, 38.8, 46.3, 51.0, 51.6, 60.5, 62.8, 102.3, 111.2, 113.9, 125.7, 126.5, 126.9, 127.2, 127.5, 127.5, 128.2, 128.6, 128.7, 129.3, 129.4, 133.3, 136.0, 139.0, 145.8, 149.7, 155.3, 157.4.

MS (ESI): *m/z* = 433$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{30}H_{29}N_2O$: 433.22799. Found: 433.22903.

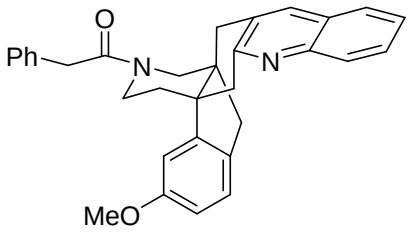
67•HCl

mp (dec.) 188–189 °C

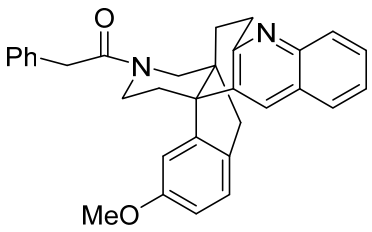
Anal. Calcd for $C_{30}H_{28}N_2O \cdot 1.0HCl \cdot 2.2H_2O$: C, 70.89; H, 6.62; N, 5.51. Found: C, 70.87; H, 6.37; N, 5.51.

1-[(6a*R*,11a*S*)-8-Methoxy-11,12-dihydro-6*H*-6a,11a-(ethanoiminomethano)indeno[2,1-*b*]acridin-15-yl]-2-phenylethanone (68)

1-[(7a*R*,12b*R*)-11-Methoxy-7,8-dihydro-6*H*-12b,7a-(ethanoiminomethano)indeno[1,2-*a*]acridin-16-yl]-2-phenylethanone (69)



68



69

To a stirred solution of **59** (329 mg, 1.21 mmol) in ethanol (10 mL) were added methanesulfonic acid (315 μL, 4.85 mmol) and 2-aminobenzaldehyde (588 mg, 4.85 mmol) and refluxed under an argon atmosphere. After 12 h with stirring at the same temperature, the reaction mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution, and extracted with $CHCl_3$ three times. The combined organic extracts were dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 100/1 to 100/10) to give an inseparable diastereomeric mixture (380 mg, 88%) as a colorless amorphous solid. The resulting diastereomeric mixture was used for the next reaction without further purification.

To a stirred solution of the diastreomeric mixture (99.0 mg, 0.278 mmol) in DMF (3 mL) was added phenylacetyl chloride (73.5 mg, 0.556 mmol) at room temperature under an argon atmosphere. After 2 h with stirring at the same temperature, the reaction mixture was basified (pH 9) with saturated $NaHCO_3$ aqueous solution, and extracted with $CHCl_3$ three times. The combined organic extracts were dried over Na_2SO_4, and evaporated *in vacuo*. The residue was purified by preparative TLC (hexane/AcOEt/MeOH/25% ammonia aqueous solution = 100/100/10/1) to give **68** (44.6 mg, 34%) as a colorless oil and **69** (76.8 mg 58%) as a colorless oil.

68

IR (film) cm^{-1}: 2934, 1635, 1496, 1420, 1285, 1032, 910, 728.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.80–2.07 (m, 2H), 2.63 (s, 0.5H), 2.75 (s, 0.5H), 2.85 (d, *J* = 16.8 Hz, 1H), 2.92–3.10 (m, 4H), 3.18–3.28 (m, 2H), 3.31–3.40 (m, 1H), 3.44–3.59 (m, 2H), 3.70–3.83 (m, 0.3H), 3.77 (s, 1.5H), 3.79 (s, 1.5H), 4.13 (d, *J* = 13.5 Hz, 0.7H), 6.62–6.74 (m, 2H), 6.84 (d, *J* = 8.2 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 0.7H), 7.01–7.07 (m, 1.3H), 7.11–7.21 (m, 2H), 7.24–7.38 (m, 1H), 7.43–7.51 (m, 1H), 7.59–7.67 (m, 1H), 7.70–7.78 (m, 1.3H), 7.85 (br s, 0.7H), 7.96–8.04 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 33.7, 39.6, 40.7, 41.6, 43.2, 44.7, 46.6, 47.0, 50.3, 55.4, 108.2, 113.6, 125.2, 126.0, 126.6, 127.2, 127.7, 128.5, 128.6, 128.6, 128.7, 128.8, 129.5, 129.9, 132.9, 133.7, 134.5, 146.8, 148.3, 159.0, 159.3, 171.5.

MS (ESI): *m/z* = 475$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{32}H_{31}N_2O_2$: 475.2386. Found: 475.2379.

69

IR (film) cm^{-1}: 2923, 1634, 1490, 1284, 1153, 1033, 909, 730.

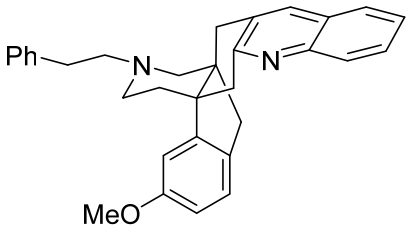
^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.82–2.04 (m, 1H), 2.05–2.35 (m, 3H), 2.49 (d, *J* = 15.6 Hz, 0.4H), 2.64 (d, *J* = 15.8 Hz, 0.6H), 2.91 (d, *J* = 15.6 Hz, 0.4H), 3.00 (d, *J* = 15.6 Hz, 0.6H), 2.99–3.11 (m, 1H), 3.12–3.33 (m, 3H), 3.49–3.62 (m, 1H), 3.71–3.87 (m, 2H), 3.80 (s, 1.8H), 3.81 (s, 1.2H), 3.97–4.15 (m, 1H), 6.69–6.77 (m, 1H), 6.86 (dd, *J* = 18.9, 2.3 Hz, 1H), 7.05–7.20 (m, 1.5H), 7.21–7.39 (m, 4.5H), 7.42–7.51 (m, 1H), 7.60–7.79 (m, 2H), 7.98 (d, *J* = 8.5 Hz, 1H), 8.04 (s, 0.6H), 8.11 (s, 0.4H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 27.7, 29.9, 34.4, 38.4, 40.8, 43.2, 46.9, 48.0, 52.0, 55.4, 110.6, 111.5, 125.7, 126.3, 126.8, 127.1, 127.3, 128.0, 128.3, 128.7, 128.7, 129.3, 133.0, 133.6, 134.4, 134.9, 135.2, 146.2, 147.8, 157.2, 158.9, 170.0.

MS (ESI): *m/z* = 475$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{32}H_{31}N_2O_2$: 475.2386. Found: 475.2383.

(6a*R*,11a*S*)-8-Methoxy-15-phenethyl-11,12-dihydro-6*H*-6a,11a-(ethanoiminomethano)-indeno[2,1-*b*]acridine (70)



70

To a stirred suspension of $LiAlH_4$ (21.4 mg, 0.564 mmol) in THF (5 mL) was added a solution of **68** (44.6 mg, 0.094 mmol) in THF (5 mL) at 0 °C and then the reaction mixture was allowed to warm to room temperature under an argon atmosphere. After 1 h with stirring at the same temperature, AcOEt (5 mL) and saturated Na_2SO_4 aqueous solution were added to the solution. The obtained solid was removed by filtration and the filtrate was evaporated *in vacuo*. The residue was purified by preparative TLC (hexane/AcOEt/MeOH/25% ammonia aqueous solution = 100/100/10/1) to give **70** (34.5 mg, 80%) as a yellow oil.

70

IR (film) cm^{-1}: 3025, 2931, 2806, 1607, 1492, 1284, 1032, 750.

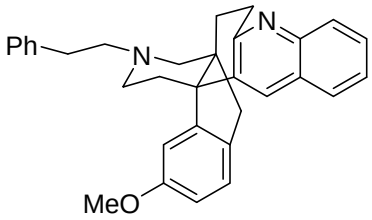
^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.67–1.80 (m, 1H), 1.91–2.02 (m, 1H), 2.26–2.57 (m, 6H), 2.68–2.84 (m, 3H), 2.93 (d, *J* = 15.2 Hz, 1H), 3.05 (d, *J* = 17.3 Hz, 1H), 3.14–3.32 (m, 3H), 3.79 (s, 3H), 6.70 (dd, *J* = 8.1, 2.4 Hz, 1H), 6.77 (d, *J* = 2.4 Hz, 1H), 7.09–7.28 (m, 6H), 7.41–7.48 (m, 1H), 7.57–7.64 (m, 1H), 7.68–7.74 (m, 1H), 7.80 (s, 1H), 7.98 (d, *J* = 8.4 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 33.5, 33.6, 36.9, 41.8, 42.7, 45.8, 47.4, 50.2, 55.4, 60.1, 60.4, 108.4, 111.7, 125.6, 125.6, 125.8, 126.1, 126.9, 127.4, 128.2, 128.2, 128.3, 128.5, 128.7, 129.7, 133.2, 134.6, 140.6, 146.6, 151.6, 158.3, 159.0.

MS (ESI): *m/z* = 461$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{32}H_{33}N_2O$: 461.2593. Found: 461.2573.

(7a*R*,12b*R*)-11-Methoxy-16-phenethyl-7,8-dihydro-6*H*-12b,7a-(ethanoiminomethano)-indeno[1,2-*a*]acridine (71)



71

Compound **71** was prepared from compound **69** according to the procedure used to synthesize compound **70**. Yield, 85%.; a yellow oil.

71

IR (film) cm^{-1}: 2934, 2806, 1587, 1488, 1283, 1225, 1033, 908.

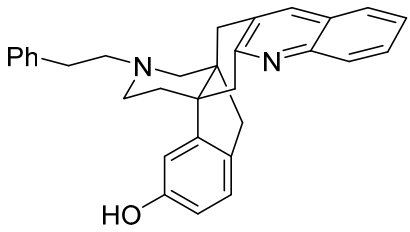
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.97 (dt, *J* = 14.2, 5.9 Hz, 1H), 2.19–2.33 (m, 4H), 2.39–2.80 (m, 8H), 2.90 (d, *J* = 15.2 Hz, 1H), 3.26–3.37 (m, 2H), 3.81 (s, 3H), 6.70 (dd, *J* = 8.1, 2.4 Hz, 1H), 6.89–6.96 (m, 1H), 7.10 (d, *J* = 8.1 Hz, 1H), 7.13–7.21 (m, 3H), 7.22–7.30 (m, 2H), 7.37–7.45 (m, 1H), 7.57–7.64 (m, 1H), 7.68–7.74 (m, 1H), 7.96 (d, *J* = 8.4 Hz, 1H), 8.09 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 27.9, 30.3, 33.7, 35.6, 38.8, 46.3, 51.1, 51.7, 55.5, 60.3, 60.9, 110.8, 111.0, 125.5, 125.9, 126.3, 127.2, 127.4, 128.0, 128.2, 128.3, 128.7, 128.7, 129.1, 134.1, 135.2, 135.6, 140.6, 146.3, 149.4, 157.2, 158.7.

MS (ESI): *m/z* = 461$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{32}H_{33}N_2O$: 461.25929. Found: 461.26084.

(6a*R*,11a*S*)-15-Phenethyl-11,12-dihydro-6*H*-6a,11a-(ethanoiminomethano)indeno[2,1-*b*]acridin-8-ol (72)



72

Compound **72** was prepared from compound **70** according to the procedure used to synthesize compound **12**. Yield, 80%.; a colorless oil.

72

IR (film) cm^{-1}: 3025, 2923, 2812, 1614, 1495, 1350, 1239, 907, 731, 700.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.66–1.80 (m, 1H), 1.94–2.04 (m, 1H), 2.16–2.29 (m, 2H), 2.39–2.63 (m, 4H), 2.66–2.79 (m, 3H), 2.86 (d, *J* = 15.4 Hz, 1H), 3.04–3.23 (m, 3H), 3.41 (d, *J* = 17.7 Hz, 1H), 6.62 (dd, *J* = 8.0, 2.3 Hz, 1H), 6.87 (d, *J* = 2.3 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 7.12–7.29 (m, 5H), 7.44–7.52 (m, 1H), 7.59–7.67 (m, 1H), 7.72–7.78 (m, 1H), 7.89 (s, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 31.8, 33.6, 36.1, 42.0, 43.4, 45.4, 47.4, 50.4, 59.9, 61.0, 109.8, 114.3, 125.8, 125.8, 125.9, 126.5, 126.9, 127.5, 127.6, 128.2, 128.7, 128.8, 129.0, 129.9, 132.0, 135.6, 140.6, 145.9, 150.9, 156.2, 158.4.

MS (ESI): *m/z* = 447$[M+H]^+$.

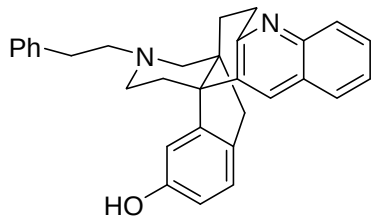
HR-MS (ESI): $[M+H]^+$ Calcd for $C_{31}H_{31}N_2O$: 447.24364. Found: 447.24245.

72•HCl

mp (dec.) 168–169 °C

Anal. Calcd for $C_{31}H_{30}N_2O \cdot 2.0HCl \cdot 0.2H_2O$: C, 71.18; H, 6.24; N, 5.36. Found: C, 71.25; H, 6.47; N, 5.27.

(7a*R*,12b*R*)-16-Phenethyl-7,8-dihydro-6*H*-12b,7a-(ethanoiminomethano)indeno[1,2-*a*]acridin-11-ol (73)



73

Compound **73** was prepared from compound **71** according to the procedure used to synthesize compound **12**. Yield, 57%.; a colorless amorphous solid.

73

IR (film) cm^{-1}: 3025, 2925, 2807, 1589, 1493, 1283, 1225, 908, 731.

^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.86–1.99 (m, 1H), 2.11–2.89 (m, 13H), 3.17–3.39 (m, 2H), 6.66 (dd, *J* = 8.0, 2.2 Hz, 1H), 6.87 (br s, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 7.11–7.28 (m, 5H), 7.33–7.41 (m, 1H), 7.52–7.62 (m, 2H), 7.97 (d, *J* = 8.4 Hz, 1H), 8.07 (s, 1H), a proton (OH) was not observed.

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 27.8, 29.7, 33.4, 35.5, 38.8, 46.1, 51.0, 51.5, 60.3, 60.8, 111.3, 114.1, 125.7, 125.9, 126.5, 127.2, 127.3, 127.5, 128.3, 128.3, 128.7, 128.7, 129.4, 132.8, 135.3, 136.1, 140.4, 145.6, 149.3, 155.7, 157.3.

MS (ESI): *m/z* = 447$[M+H]^+$.

HR-MS (ESI): $[M+H]^+$ Calcd for $C_{31}H_{31}N_2O$: 447.24364. Found: 447.24210.

73•HCl

mp (dec.) 190–191 °C

Anal. Calcd for $C_{31}H_{30}N_2O \cdot 2.0HCl \cdot 0.1H_2O$: C, 71.42; H, 6.23; N, 5.37. Found: C, 71.44; H, 6.43; N, 5.33.

Pharmacology

Opioid receptor binding assay

Membrane tissue obtained from mouse whole brain without cerebellum and guinea pig cerebellum wes prepared as described previously.[45] The μ, δ or κ opioid receptor binding assays were performed with 2.0 nM [^{3}H]DAMGO ([D-Ala^2, N-Me-Phe^4, Gly^5-ol]-Enkephalin), [^{3}H]DPDPE ([D-Pen^{2,5}]-Enkephalin) or [^{3}H]U-69,593. Nonspecific binding was measured in the presence of 1 μM unlabeled DAMGO, DPDPE or U-69,593. K_i value was calculated according to the Cheng–Prusoff equation.[46]

GTPγS binding assay

Membrane suspension from κ or δ human recombinant cell (CHO cell) was incubated in 0.25 mL of assay buffer (50 mM Tris, 1 mM EDTA, 5 mM $MgCl_2$, 100 mM NaCl) with various concentrations of the tested compound, 30 μM GDP and 0.1 nM [^{35}S]GTPγS (PerkinElmer). Nonspecific binding was measured in the presence of 10 μM unlabeled GTPγS.

Material and Methods for antinociceptive assay and Spontaneous locomotor activity test

1. Animals

Male ICR mice weighing 35–45 g were purchased from Japan SLC, Inc. and housed in standard polycarbonate mouse cages for at least 2 weeks prior to the experimental procedures.

2. Antinociceptive assay

An antinociceptive assay was performed using the acetic acid-abdominal constriction (writhing) test based on previous method.[47] Briefly, each mouse was injected intraperitoneally (i.p.) with 0.6 % acetic acid at a dose of 10 mL/kg 15 min after s.c. administration of drugs. After a 10 min delay, the animals were observed for an additional 10 min, during which the number of abdominal constrictions was counted. Percent inhibition was calculated and compared with the number of writhing movements in the control group. To block κ opioid receptor, nor-binaltorphimine (nor-BNI) was administered s.c. 24 h before drug administration. The doses and administration schedules were determined according to our previous methods.[48]

3. Spontaneous locomotor activity test

The spontaneous locomotor activity apparatus consisted of a square area (24 cm × 24 cm × 30 cm) placed in indirect light (200 lux). Animals were kept in the test apparatus 30 min for adaptation before drug administration. The mice were allowed to freely explore the apparatus for 3 h. Spontaneous locomotor activity was tracked and recorded via an overhead video camera. After the test period, the movement data were analyzed with a computerized image analysis system (CompACT AMS DI-064W Muromachi Kikai Co., Ltd., Tokyo, Japan).

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List of publications

(1) Nakajima, R.; Yamamoto, N.; Hirayama, S.; Iwai, T.; Saitoh, A.; Nagumo, Y.; Fujii, H.; Nagase, H. *Bioorg. Med. Chem*., **2015**, *23*, 6271.

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Supplementary list of publications

(1) Kutsumura, N.; Nakajima, R.; Koyama, Y.; Miyata, Y.; Saitoh, T.; Yamamoto, N.; Iwata, S.; Fujii, H.; Nagase, H. *Bioorg. Med. Chem. Lett*. **2015**, *25*, 4890.

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