Bioorganic & Medicinal Chemistry 17 (2009) 94–110

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Alantrypinone and its derivatives: Synthesis and antagonist activity toward insect GABA receptors

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ARTICLE INFO

Article history:
Received 14 October 2008
Revised 6 November 2008
Accepted 7 November 2008
Available online 17 November 2008

Keyword:
Alantrypinone
Insect GABA receptors
Hetero Diels–Alder reaction

ABSTRACT

The γ-aminobutyric acid (GABA) receptor bears important sites of action for insecticides. Alantrypinone is an insecticidal alkaloid that acts as a selective antagonist for housefly (vs rat) GABA receptors, and is considered to be a lead compound for the development of a safer insecticide. In an attempt to obtain compounds with greater activity, a series of racemic alantrypinone derivatives were systematically synthesized using hetero Diels–Alder reactions, and a total of 34 compounds were examined for their ability to inhibit the specific binding of [^{3}H]4′-ethynyl-4-*n*-propylbicycloorthobenzoate, a high-affinity non-competitive antagonist, to housefly-head membranes. The assay results showed that (1) there is no significant difference between the potencies of natural (+)-alantrypinone and its synthetic racemate; (2) the amide NHs at the 2- and 18-positions are important for high activity; (3) there is a considerable drop in potency for compounds without an aromatic ring at the 16-position; and (4) a large substituent at the 3-position is detrimental to high activity.

1. Introduction

Ionotropic γ-aminobutyric acid (GABA) receptors are major neurotransmitter receptors that mediate fast inhibitory synaptic neurotransmission in the nervous system of invertebrates as well as vertebrates. Vertebrate ionotropic GABA receptors are classified into $GABA_A$-type and $GABA_C$-type receptors.[1] However, insect ionotropic GABA receptors do not easily fit into the vertebrate $GABA_A$/$GABA_C$ receptor classification. Insect GABA receptors are distinguished from $GABA_A$-type vertebrate receptors by their insensitivity to bicuculline, and differ from $GABA_C$ receptors in that insect receptors are subject to allosteric modulation, albeit weak, by benzodiazepines and barbiturates. These differences between insect and vertebrate GABA receptors might provide great opportunities for the development of safer insecticides. The *Drosophila melanogaster* GABA receptor subunit RDL (resistant to dieldrin) can be heterologously expressed to form functional homo-oligomeric receptors, the pharmacology of which closely resembles that of most native insect GABA receptors, and thus the RDL receptor has been shown to be useful for investigating its physiology and pharmacology.[2] Insect GABA receptors are the target of the important insecticide fipronil (Fig. 1).[3] Since fipronil-resistant insects have recently been reported, structurally different classes of novel insecticide are needed.

Alantrypinone[4] ((+)-**1**, Fig. 1), which is a polycyclic alkaloid that is biosynthetically derived from anthranilic acid and tryptophan, was isolated from *Penicillium thymicola* in 1998. Its biological activities were not known at the isolation stage. In 2004, one of the authors (Ozoe) and co-workers reported that (+)-**1** and (+)-serantrypinone[5] (Fig. 1), which were isolated through binding assay-based screening of fungal culture extracts, were insecticidal alkaloids that were highly selective for insect (vs mammalian) GABA receptors.[6] To the best of our knowledge, there has been no report on the structure–activity relationships of (+)-**1**.

To understand the interaction of (±)-**1** with GABA receptors, with the ultimate goal of contributing to the development of a novel insecticide, we designed alantrypinone derivatives ((±)-**3**–(±)-**33**) and synthesized (±)-**1**–(±)-**33** (Fig. 2). In this report, we describe the design, synthesis, and biological effects of (±)-**1** and these analogues.

2. Results and discussion

We designed the analogues shown in Figure 2, based on the structural features of (+)-**1**. (±)-**3**–(±)-**7** contain halogens and might

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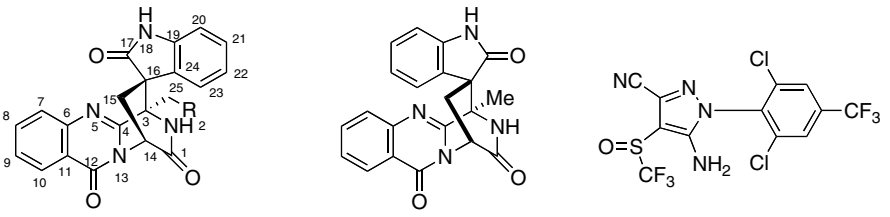
doi:10.1016/j.bmc.2008.11.017

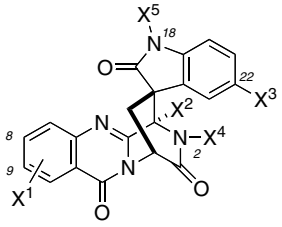


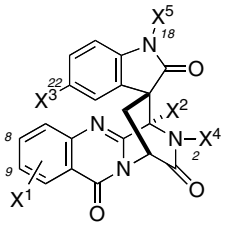
(+)-alantrypinone (**1**): R = H
(+)-serantrypinone: R = OH

(±)-*epi*-alantrypinone (**2**)

fipronil

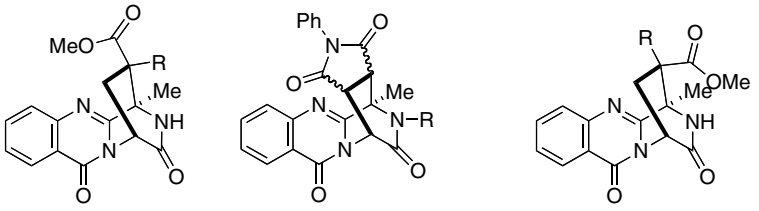
Figure 1. Structures of quinazolinones and fipronil.





(±)-**3** : X^1 = 9-Cl, X^2 = Me, X^3 = H, X^4 = H, X^5 = H
(±)-**4** : X^1 = 9-F, X^2 = Me, X^3 = H, X^4 = H, X^5 = H
(±)-**5**: X^1 = 8-Cl, X^2 = Me, X^3 = H, X^4 = H, X^5 = H
(±)-**6**: X^1 = H, X^2 = Me, X^3 = Cl, X^4 = H, X^5 = H
(±)-**7** : X^1 = 9-Cl, X^2 = Me, X^3 = Cl, X^4 = H, X^5 = H
(±)-**8** : X^1 = H, X^2 = Bn, X^3 = H, X^4 = H, X^5 = H
(±)-**9** : X^1 = H, X^2 = ^{i}Pr, X^3 = H, X^4 = H, X^5 = H
(±)-**10** : X^1 = H, X^2 = ^{i}Bu, X^3 = H, X^4 = H, X^5 = H
(±)-**11** : X^1 = H, X^2 = Me, X^3 = H, X^4 = Me, X^5 = H
(±)-**12**: X^1 = H, X^2 = Me, X^3 = H, X^4 = H, X^5 = Me
(±)-**13** : X^1 = H, X^2 = Me, X^3 = H, X^4 = Me, X^5 = Me
(±)-**14** : X^1 = H, X^2 = Me, X^3 = H, X^4 = H, X^5 = Bn
(±)-**15** : X^1 = H, X^2 = Me, X^3 = H, X^4 = Me, X^5 = Bn

(±)-**20** : X^1 = 9-Cl, X^2 = Me, X^3 = H, X^4 = H, X^5 = H
(±)-**21** : X^1 = 9-F, X^2 = Me, X^3 = H, X^4 = H, X^5 = H
(±)-**22**: X^1 = 8-Cl, X^2 = Me, X^3 = H, X^4 = H, X^5 = H
(±)-**23**: X^1 = H, X^2 = Me, X^3 = Cl, X^4 = H, X^5 = H
(±)-**24** : X^1 = 9-Cl, X^2 = Me, X^3 = Cl, X^4 = H, X^5 = H
(±)-**25** : X^1 = H, X^2 = Bn, X^3 = H, X^4 = H, X^5 = H
(±)-**26** : X^1 = H, X^2 = ^{i}Pr, X^3 = H, X^4 = H, X^5 = H
(±)-**27** : X^1 = H, X^2 = ^{i}Bu, X^3 = H, X^4 = H, X^5 = H
(±)-**28** : X^1 = H, X^2 = Me, X^3 = H, X^4 = H, X^5 = Me
(±)-**29** : X^1 = H, X^2 = Me, X^3 = H, X^4 = Me, X^5 = Me
(±)-**30** : X^1 = H, X^2 = Me, X^3 = H, X^4 = H, X^5 = Bn
(±)-**31** : X^1 = H, X^2 = Me, X^3 = H, X^4 = Me, X^5 = Bn



(±)-**16** : R = Ph
(±)-**17** : R = H

(±)-**18** : R = H
(±)-**19** : R = Me

(±)-**32** : R = Ph
(±)-**33** : R = H

Figure 2. Alantrypinone derivatives.

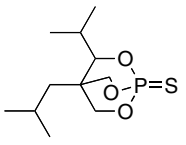
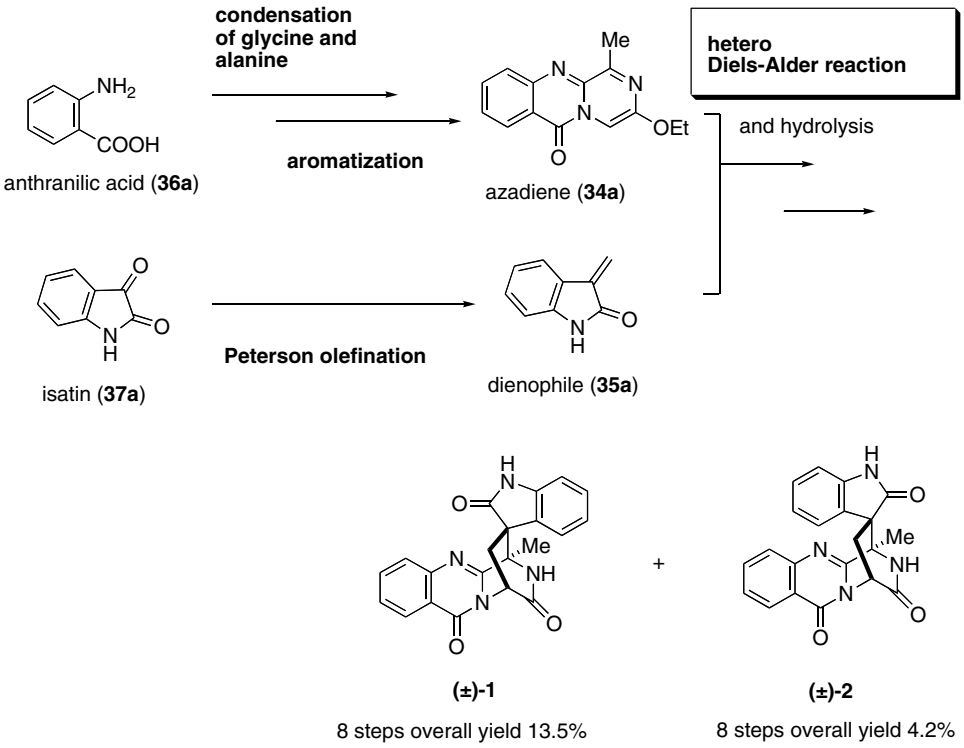


Figure 3. Structure of IBIPPS.

be easily absorbed into an insect body. (±)-**8**–(±)-**10** have a bulky substituent at the bridgehead of the bicycles and might have a desired conformational restriction, like the caged antagonist 4-isobutyl-3-isopropyl-2,6,7-trioxa-1-phosphabicyclo[2.2.2]octane 1-sulfide (IBIPPS) (Fig. 3).[6] (±)-**11**–(±)-**15** have an alkyl substituent(s) on the amide nitrogen at the 2- and/or 18-position, which confers lower polarity, so these compounds should highlight the necessity of an amide functional group for sufficient biological activity. Simplified analogues, (±)-**16**–(±)-**19**, (±)-**32**, and (±)-**33**, should clarify which part of (±)-**1** is necessary for a desired biological activity. Based on a consideration of the efficient and systematic synthesis of (±)-**1** and (±)-**3**–(±)-**19** in racemic form, we decided to use a procedure for the synthesis of (±)-**1** developed by Kende and co-workers.[4d,e] Their key reaction for the synthesis of (±)-**1** is a hetero Diels–Alder reaction between azadiene **34a** and dienophile **35a** (Scheme 1). Compounds **34a** and **35a** are prepared from anthranilic acid (**36a**) in 6 steps and isatin (**37a**) in 2 steps, respectively. This method is applicable to the synthesis of (±)-**3**–(±)-**19**. In this synthetic method, we can also obtain the epimers, (±)-**2** and (±)-**20**–(±)-**33**, and examine their biological activities.

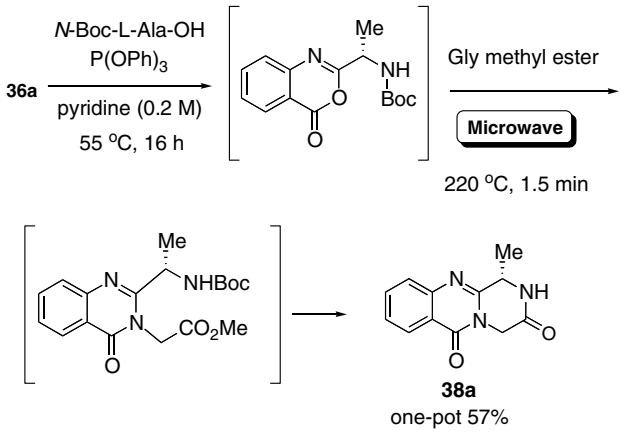
2.1. Synthesis of (±)-1 and (±)-2

Liu and co-workers reported stepwise condensations of anthranilic acid (**36a**) with two amino acids under microwave conditions and a one-pot synthesis of quinazolines (Scheme 2).[7] The use of

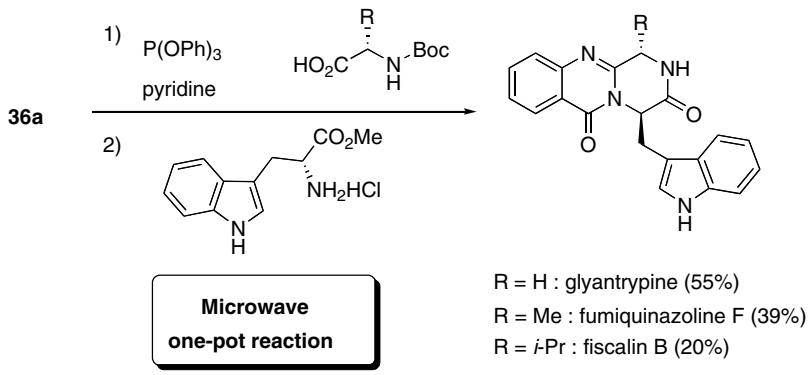


Scheme 1. Total synthesis of (±)-alantrypinone (**1**) by Kende group.

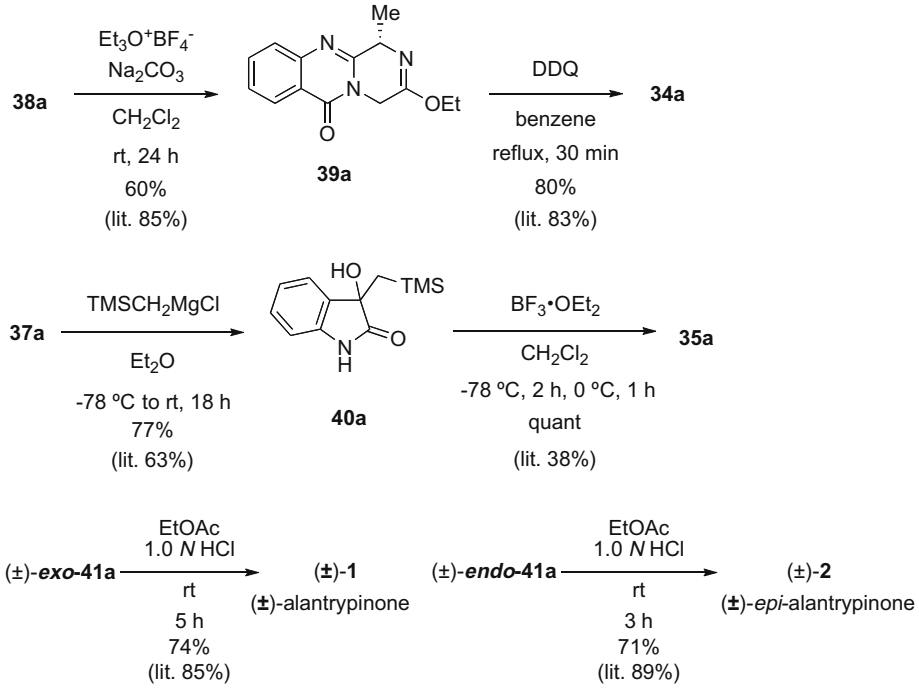
microwave conditions improved the synthesis of **34a** so that the yield of **38a** was increased from 31% (4 steps) to 57% (2 steps) (Scheme 3).[4e] According to Kende's method, **38a** was converted to **34a** (Scheme 4). Dienophile **35a** was prepared by the Peterson olefination of isatin (**37a**). The hetero Diels–Alder reaction of **34a** with **35a** proceeded regioselectively, and desired (±)-*exo*-**41a** and undesired (±)-*endo*-**41a** were obtained in respective yields of 52% and 18% (Table 1, entry 2). When the amount of **34a** in the reaction was reduced to 1.5 equiv, (±)-*endo*-**41a** was obtained in 43% yield together with 34% of (±)-*exo*-**41a** (entry 3). The same reactions under heated conditions (entries 4–6) gave (±)-*endo*-**41a** with greater stereoselectivity. These results indicate that (±)-*endo*-**41a** is a thermodynamically stable product. Since we needed both isomers, (±)-*exo*-**41a** and (±)-*endo*-**41a**, we adopted 'entry 3' for our standard hetero Diels–Alder reaction conditions. (±)-*exo*-**41a** and (±)-*endo*-**41a** were converted to (±)-**1** and (±)-**2**, respectively, as reported by Kende and co-workers. Our synthetic results are summarized in Scheme 4.



Scheme 3. One-pot microwave-promoted synthesis of quinazoline.

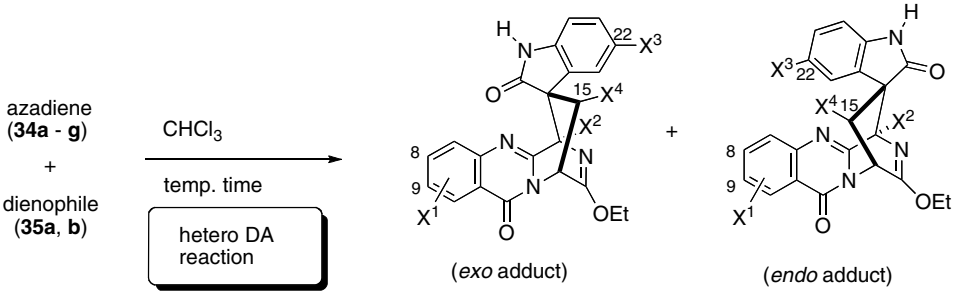


Scheme 2. Liu's one-pot synthesis of glyantrypine, fumiquinazoline F, and fiscalin B.



Scheme 4. Synthesis of (±)-**1** and (±)-**2**.

Table 1
Hetero DA reaction



(±)-**41a** : X^1 = H, X^2 = Me, X^3 = H, X^4 = H
(±)-**41b** : X^1 = 9-Cl, X^2 = Me, X^3 = H, X^4 = H
(±)-**41c** : X^1 = 9-F, X^2 = Me, X^3 = H, X^4 = H
(±)-**41d** : X^1 = 8-Cl, X^2 = Me, X^3 = H, X^4 = H
(±)-**41e** : X^1 = H, X^2 = Me, X^3 = Cl, X^4 = H
(±)-**41f** : X^1 = 9-Cl, X^2 = Me, X^3 = Cl, X^4 = H
(±)-**41g** : X^1 = H, X^2 = Bn, X^3 = H, X^4 = H
(±)-**41h** : X^1 = H, X^2 = ^{i}Pr, X^3 = H, X^4 = H
(±)-**41i** : X^1 = H, X^2 = ^{i}Bu, X^3 = Cl, X^4 = H

Entry	Azadiene	Dienophile (equiv)	Temperature (°C)	Time (h)	Product (yield, %)			Ratio
						exo	*endo*	*exo*:*endo*
1[a]	**34a**	**35a** (5.0)	rt	24	(±)-**41a**	55	18	3.1:1
2	**34a**	**35a** (5.0)	rt	24	(±)-**41a**	52	18	2.9:1
3	**34a**	**35a** (1.5)	rt	24	(±)-**41a**	34	43	1:1.3
4	**34a**	**35a** (5.0)	40	4.5	(±)-**41a**	31	37	1:1.2
5	**34a**	**35a** (1.5)	40	7	(±)-**41a**	30	39	1:1.3
6	**34a**	**35a** (1.5)	Reflux	3	(±)-**41a**	23	46	1:2
7	**34b**	**35a** (5.0)	rt	24	(±)-**41b**	34	25	1.4:1
8	**34c**	**35a** (1.5)	rt	8	(±)-**41c**	40	59	1:1.5
9	**34d**	**35a** (5.0)	rt	24	(±)-**41d**	40	36	1.1:1
10	**34a**	**35b** (5.0)	rt	24	(±)-**41e**	38	47	1:1.2
11	**34b**	**35b** (1.5)	rt	5	(±)-**41f**	31	38	1:1.5
12	**34e**	**35a** (1.5)	rt	9	(±)-**41g**	67		1:1.9[b]
13	**34f**	**35a** (1.5)	40	24	(±)-**41h**	Quant		1:2.5[b]
14	**34g**	**35a** (1.5)	rt	12	(±)-**41i**	26	38	1:1.5

[a] Kende's data.
[b] Inseparable mixture was obtained. The ratio was determined by ^{1}H NMR.

2.2. Synthesis of alantrypinone analogues

Based on the above method for the synthesis of (±)-**1** and (±)-**2**, other molecules (±)-**3**–(±)-**33** were also synthesized. Key synthons (**34b**–**34g**) were efficiently prepared by the one-pot synthesis of quinazolines (Scheme 5) and their conversion to the corresponding azadienes (Scheme 6). Dienophile **35b** was prepared from **37b** by Peterson olefination (Scheme 7). Hetero Diels–Alder reactions of these azadienes (**34a**–**34g**) with dienophiles (**35a**,**b**) were performed. Although the reactivities and *exo*–*endo* selectivities varied according to the substituent of the azadiene and dienophile, hetero Diels–Alder adducts **41b**–**41i** were obtained under similar conditions (Table 1, entries 7–14). Hydrolysis of *exo*-adduct and *endo*-adduct of **41b**–**41i** led to (±)-**3**–(±)-**10** and (±)-**20**–(±)-**27** in good to excellent yields, in the same manner as in the conversion of (±)-*exo*-**41a** to (±)-**1**. Hetero Diels–Alder reactions of azadiene **34a** with dienophiles, acrylates **35c** and **35d**, are summarized in Table 2. Compound **41j** was obtained as an inseparable mixture of an *endo*-adduct and an *exo*-adduct, which was subjected to hydrolysis to give a less polar product and a more polar product in respective yields of 10% and 13% (2 steps). Compound **41k** was obtained as separable stereoisomers, which were also subjected to the same hydrolysis to give the corresponding products in good yields, respectively (Scheme 8). Based on a comparison of the ^{1}H NMR chemical shifts of aromatic protons at the 23-position (Fig. 1) of these products ((±)-**16** and (±)-**32**) with the corresponding chemical shifts of (±)-**1**–(±)-**10** and (±)-**20**–(±)-**27**, we assumed that a less polar product from (±)-**41j** could be an *exo*-adduct ((±)-**16**) and a more polar product could be an *endo*-adduct ((±)-**32**) (Table 3), as Kende did.[4e] In the same manner, by comparing the ^{1}H NMR chemical shifts of the methoxy protons of (±)-**17** and (±)-**33** with those of (±)-**16** and (±)-**32**, we assumed that a less polar product from (±)-**41k-LP** could be an *endo*-adduct ((±)-**33**) and a more polar product could be an *exo*-adduct ((±)-**17**). The reaction of **34a** with *N*-phenylmaleimide (**35e**) yielded a less polar and a more polar adducts in respective yields of 77% and 3% (Scheme 9). Hydrolysis of these compounds gave the corresponding amides in respective yields of 82% and 65%. The nitrogen at the 2-position of (±)-**18** was methylated to give (±)-**19** in 94% yield. ^{1}H NMR analysis of (±)-**18** and (±)-**19** failed to give any information about the stereochemistry of these compounds. (±)-**11**–(±)-**15** and (±)-**28**–(±)-**31** were synthesized from (±)-*exo*-**41a** or (±)-*endo*-**41a** as shown in Scheme 10.

2.3. Inhibition of GABA-induced currents and [^{3}H]EBOB binding

We first examined whether (+)-**1** acts as an antagonist of insect GABA receptors. GABA-induced currents in American cockroach (*Periplaneta americana* L.) neurons were recorded by the whole-cell patch clamp method. Control inward currents were induced following the application of 100 μM GABA for 2 s at a holding potential of −80 mV, with symmetric chloride concentrations (188 mM) between internal and external solutions. As shown in Figure 4, GABA-induced inward currents were blocked (by 90.3 ± 1.6%, $n = 4$) after a 5-min application of 10 μM (+)-**1**, indicating that (+)-**1** is an antagonist of insect GABA receptors.

We next performed a series of competition assays to determine the potency of alantrypinone ((+)-**1**) and its synthetic racemate and analogues ((±)-**1**–(±)-**33**) at housefly (*Musca domestica* L.) GABA receptors, using the high-affinity non-competitive GABA receptor antagonist [^{3}H]4′-ethynyl-4-*n*-propylbicycloorthobenzoate ([^{3}H]EBOB). The results summarized in Figure 5 show that there is no significant difference between the potencies of alantrypinone ((+)-**1**) and its racemate ((±)-**1**). The potency of (±)-**1** (*exo*) was found to be higher than that of (±)-**2** (*endo*). Overall, *exo*-adducts had a higher potency than *endo*-adducts. These findings indicate that the housefly GABA receptor recognizes the stereochemistry of the bicycles. Among the compounds (±)-**1**–(±)-**7**, (±)-**1** and (±)-**3** were found to be the most potent, followed by (±)-**4** and (±)-**7**. Based on the assay results of (±)-**1** and (±)-**8**–(±)-**10**, high potency is retained with Me, ^{i}Pr, and Bn substitution at the bridgehead position, while ^{i}Bu substitution is detrimental to high potency. We initially hypothesized that bulkier substituents would lead to higher potency. However, docking studies of **3** using a human β3 GABA receptor homology model, which has been shown to be a good model of insect GABA receptors,[8] predict that large bridgehead substituents are not tolerated in the potential binding site within the channel pore (Fig. 6). Figure 6 also shows that 9-Cl of **3** is acceptable within the channel pore, and that a hydrogen bond between the carbonyl oxygen atom of the oxindole ring and the hydroxyl group of Thr281 is formed. (±)-**11**–(±)-**15** showed low activity, indicating that the amide NHs at the 2- and 18-positions are important for high activity. Alternatively, the Me groups introduced into these positions might hinder binding to the receptor. Synthetic intermediates and compounds without an aromatic ring at the 16-position showed low activity.

2.4. Conclusions

In the current study, we systematically synthesized a series of racemic alantrypinone derivatives, some of which inhibited specific [^{3}H]EBOB binding to housefly-head membranes. Generally, *exo*-adducts had higher activity than *endo*-adducts in [^{3}H]EBOB binding assays. However, there was no significant difference between the potencies of the native enantiomer (+)-**1** and its synthetic racemate ((±)-**1**). The inhibitory activities of several derivatives were found to be comparable to that of (+)-**1**, although none showed activity that was dramatically higher than that of (+)-**1**. Further modification of (±)-**1** based on structure-activity studies with receptor homology models may help to improve its potency.

3. Experimental

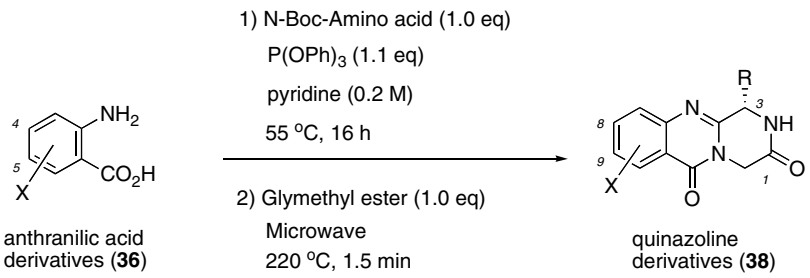
3.1. Synthesis

All melting points are uncorrected. Infrared absorption spectra were recorded using a JASCO FT/IR-230 spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$ at 25 °C unless otherwise noted, at 400 MHz, with TMS as an internal standard. ^{13}C NMR spectra were recorded in $CDCl_3$ at 25 °C unless otherwise noted, at 100 MHz. All moisture-sensitive reactions were performed under an Ar atmosphere. Flash column chromatography was performed with silica gel 60 N (spherical, neutral, 40–50 μm, Kanto Chemical Co., Inc.). Microwave irradiation experiment was performed in a CEM Discover system (NC, USA), operating at a frequency of 2.45 GHz with continuous irradiation power from 0 to 150 W. The reaction was carried out in an open 3 mL glass vial, which was cooled by air.

3.1.1. General procedure for synthesis of azadienes (34)

*Step 1: Synthesis of quinazolines (**38**) using microwave.*

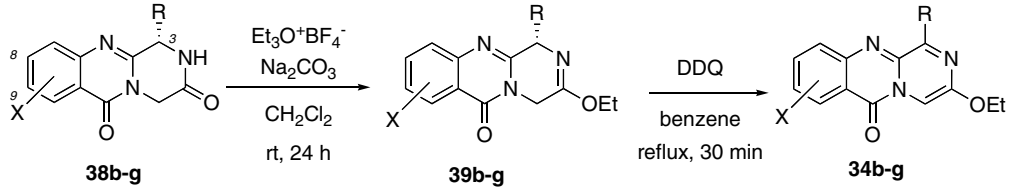
To a solution of anthranilic acid (**36**) and *N*-Boc-L-Ala-OH (1.0 equiv) in pyridine (2.0 M) was added $P(OPh_3)_3$ (1.2 equiv) and the mixture was stirred for 16 h at 55 °C. The whole was cooled to room temperature and to the mixture was added amino acid methyl ester (1.0 equiv). Microwave irradiation (150 W, 220 °C) was carried out for 1.5 min. After removal of the solvent, the residue was subjected to column chromatography to give the corresponding quinazolines **38**.



entry	**36** (SM)	amino acid	product	yield (%)
1	5-Cl	Ala	9-Cl (**38b**)	48[a]
2	5-F	Ala	9-F (**38c**)	56
3	4-Cl	Ala	8-Cl (**38d**)	52
4	H	Phe	3-Bn (**38e**)	51
5	H	Val	3-*i*Pr (**38f**)	40
6	H	Leu	3-*i*Bu (**38g**)	42

[a]) Overall yield was 22% by 4 steps precedures developed by Kende.

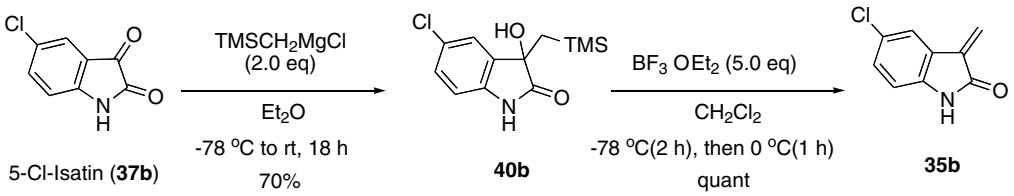
Scheme 5. One-pot microwave-promoted synthesis of various quinazolines.



entry	substrate	X	R	yield (%) **39**[a]), 1st step	**34**, 2nd step
1	**38b**	9-Cl	Me	83	76
2	**38c**	9-F	Me	60 (32)	78
3	**38d**	8-Cl	Me	41 (18)	79
4	**38e**	H	Bn	60 (40)	68
5	**38f**	H	*i*-Pr	48 (25)	69
6	**38g**	H	*i*-Bu	67 (33)	55

[a]) The numbers inparentheses indicate the yield of recovered **38**.

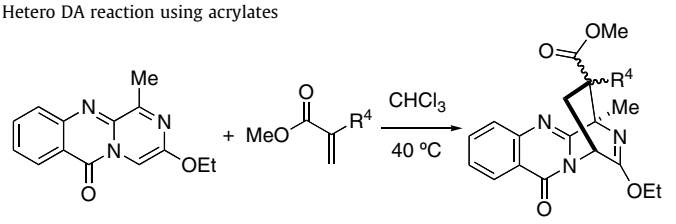
Scheme 6. Synthesis of various azadienes.



Scheme 7. Synthesis of **35b**.

38a[9]*:* 57% (2 steps) from **36a**, a white solid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.74 (d, J = 6.8 Hz, 3H), 4.68–4.75 (m, 1H), 4.76 (s, 2H), 6.72 (s, 1H), 7.52 (ddd, J = 0.8, 7.6, 7.6 Hz, 1H), 7.68 (dd, J = 0.6, 8.2 Hz, 1H), 7.79 (ddd, J = 1.4, 7.6, 7.6 Hz, 1H), 8.30 (dd, J = 1.6, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 20.2, 44.6, 51.4, 119.9, 126.8, 127.2, 127.3, 134.8, 147.1, 151.1, 160.6, 166.6; IR (neat) ν: 3256, 1668, 1597, 1467, 1380 cm^{-1}; LRMS (EI) m/z 229 $[M]^+$.

Table 2
Hetero DA reaction using acrylates



34a **35c:** R^4 = Ph; **35d**: R^4 = H (±)-**41j:** R^4 = Ph; (±)-**41k**: R^4 = H

Entry	Dienophile		Time (h)	Yield (%)	
		Equiv		LP	MP
1	**35c**	1.5	27		30
2	**35d**	3.0	10	21	63

LP, less polar isomer; MP, more polar isomer.

38b[4e]*:* 48% (2 steps) from **36b**, a purple solid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.72 (d, J = 6.8 Hz, 3H), 4.70 (dq, J = 2.4, 6.8 Hz, 1H), 4.73 (s, 1H), 4.76 (s, 1H), 6.59 (br s, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.71 (dd, J = 2.4, 8.8 Hz, 1H), 8.25 (d, J = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 20.0, 44.7, 51.3, 121.0, 126.1, 129.0, 133.1, 135.2, 145.6, 151.4, 159.6, 166.5; IR (neat) ν: 1679, 1597, 1330, 830, 784 cm^{-1}; LRMS (EI) m/z 263 $[M]^+$; HRMS (FAB) m/z Calcd for $C_{12}H_{11}{}^{37}ClN_3O_2$ $[M+H]^+$ 266.0514; found: 266.0503.

38c*:* 56% (2 steps) from **36c**, a purple solid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.73 (d, J = 6.8 Hz, 3H), 4.68 (dq, J = 2.4, 6.8 Hz, 1H), 4.75 (d, J = 9.2 Hz, 2H), 6.52 (br s, 1H), 7.50 (ddd, J = 2.8, 8.0, 8.8 Hz, 1H), 7.70 (dd, J = 4.8, 8.8 Hz, 1H), 7.92 (dd, J = 2.8, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 20.0, 44.7, 51.2, 111.6 (d, J = 23.9 Hz), 121.2 (d, J = 9 Hz), 123.4 (d, J = 24 Hz), 129.8 (d, J = 8.2 Hz), 143.8, 150.5, 159.9 (d, J = 15 Hz), 161.1 (d, J = 236 Hz), 166.7; IR (KBr) ν: 3415, 1691, 1610, 1485, 1345, 1141 cm^{-1}; LRMS (EI) m/z 247 $[M]^+$; HRMS (FAB) m/z Calcd for $C_{12}H_{11}FN_3O_2$ $[M+H]^+$ 248.0835; found: 248.0827.

38d*:* 52% (2 steps) from **36d**, a purple solid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.72 (d, J = 7.2 Hz, 3H), 4.68 (dq, J = 2.4, 6.6 Hz, 1H), 4.72 (s, 1H), 4.75 (s, 1H), 6.71 (br s, 1H), 7.46 (dd, J = 2.4, 12.6 Hz, 1H), 7.69 (d, J = 2.0 Hz, 1H), 8.21 (d, J = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 20.1, 44.6, 51.4, 118.5, 126.9, 128.0, 128.3, 141.1, 148.0, 152.4, 160.0, 166.2; IR (neat) ν: 1671, 1599, 1421, 1318, 1100, 786 cm^{-1}; LRMS (EI) m/z 263 $[M]^+$; HRMS (FAB) m/z Calcd for $C_{12}H_{11}{}^{37}ClN_3O_2$ $[M+H]^+$ 266.0514; found: 266.0526.

38e*:* 51% (2 steps) from **36a**, a white solid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.25 (dd, J = 7.6, 14.0 Hz, 1H), 3.42 (dd, J = 4.0, 14.0 Hz, 1H), 3.51 (d, J = 18.8 Hz, 1H), 4.66 (d, J = 18.8 Hz, 1H), 4.90 (qui, J = 3.6 Hz, 1H), 6.23 (br s, 1H), 7.10–7.13 (m, 2H), 7.28–7.34 (m, 3H), 7.54 (ddd, J = 1.2, 7.2, 7.8 Hz, 1H), 7.73–7.75 (m, 1H), 7.83 (ddd, J = 2.0, 7.2, 7.8 Hz, 1H), 8.29 (ddd, J = 0.4, 1.6, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 42.7, 44.2, 57.2, 119.8, 126.8, 127.1, 127.3, 127.9, 129.1 (2C), 129.8 (2C), 134.3, 134.9, 147.1, 149.9, 160.3, 166.4; IR (KBr) ν: 3062, 1672, 1595, 1473, 1428, 1341 cm^{-1}; LRMS (EI) m/z 305 $[M]^+$; HRMS (FAB) m/z Calcd for $C_{18}H_{16}N_3O_2$ $[M+H]^+$ 306.1243; found: 306.1226.

38f*:* 40% (2 steps) from **36a**, a white solid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.00 (d, J = 6.8 Hz, 3H), 1.12 (d, J = 7.2 Hz, 3H), 2.39–2.50 (m, 1H), 4.38 (d, J = 18.8 Hz, 1H), 4.42 (dd, J = 1.2, 4.8 Hz, 1H), 5.00 (d, J = 18.8 Hz, 1H), 7.50 (ddd, J = 1.2, 7.6, 7.8 Hz, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.78 (ddd, J = 1.6, 7.6, 7.6 Hz, 1H), 8.28 (dd, J = 1.2, 8.0 Hz, 1H), 8.37 (d, J = 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 17.0, 19.2, 35.1, 44.6, 61.7, 119.7, 126.6, 127.0, 127.1, 134.8, 147.0, 149.9, 160.7, 166.8; IR (KBr) ν: 2963, 1683, 1598, 1475, 1438, 1346 cm^{-1}; LRMS (EI) m/z 257 $[M]^+$; HRMS (FAB) m/z Calcd for $C_{14}H_{16}N_3O_2$ $[M+H]^+$ 258.1243; found: 258.1263.

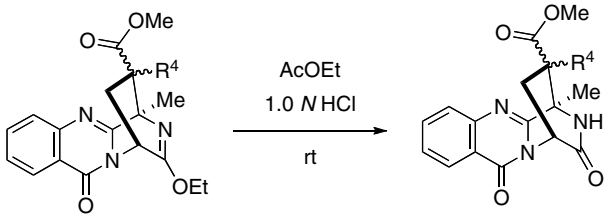
38g*:* 52% (2 steps) from **36a**, a colorless solid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.04 (d, J = 6.0 Hz, 3H), 1.05 (d, J = 6.0 Hz, 3H), 1.67–1.93 (m, 3H), 4.42 (d, J = 18.4 Hz, 1H), 4.58 (m, 1H), 5.03 (d, J = 18.4 Hz, 1H), 7.43 (br s, 1H), 7.51 (ddd, J = 0.8, 7.6, 8.0 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.78 (ddd, J = 1.6, 7.2, 7.6 Hz, 1H), 8.29 (dd, J = 0.8, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 21.4, 23.2, 24.6, 44.1, 44.6, 54.8, 120.6, 127.5, 127.90, 127.91, 135.5, 147.9, 151.7, 161.6, 167.4; IR (KBr) ν: 3200, 2961, 1700, 1593, 1472, 1324 cm^{-1}; LRMS (FAB) m/z 272 $[M+H]^+$; HRMS (FAB) m/z Calcd for $C_{15}H_{18}N_3O_2$ $[M+H]^+$ 272.1399; found: 272.1380.

*Step 2: Synthesis of **34** from **38**.*

A solution of **38**, $Et_3O^+{\cdot}BF_4^-$ (1.5 equiv) and Na_2CO_3 (6.0 equiv) in CH_2Cl_2 (20 mM) was stirred for 24 h at room temperature. The reaction was quenched by the addition of water and the organic compounds were extracted with CH_2Cl_2 and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography to give the corresponding ethyl enol ether. A solution of ethyl enol ether and DDQ (1.2 equiv) in benzene (18 mM) was refluxed for 30 min. The solution was filtered by basic alumina. After removal of the solvent, the residue was subjected to column chromatography to give the corresponding **34**.

34a[4e]*:* 48% (2 steps) from **38a**, a yellow solid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.13 (t, J = 6.8 Hz, 3H), 2.72 (s, 3H), 3.76 (q, J = 6.8 Hz, 2H), 7.08 (ddd, J = 1.2, 6.8, 7.6 Hz, 1H), 7.33 (ddd, J = 1.6, 7.6, 7.6 Hz, 1H), 7.81 (dd, J = 0.8, 8.4 Hz, 1H), 7.88 (s, 1H), 8.54 (dd, J = 0.8, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.6, 21.8, 64.3, 95.0, 116.9, 126.9, 127.0, 128.2, 134.6, 139.0, 147.1, 151.1, 158.0, 161.9; LRMS (EI) m/z 255 $[M]^+$.

34b[4e]*:* 63% (2 steps) from **38b**, a yellow solid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.52 (t, J = 6.8 Hz, 3H), 2.93 (s, 3H), 4.23 (q,



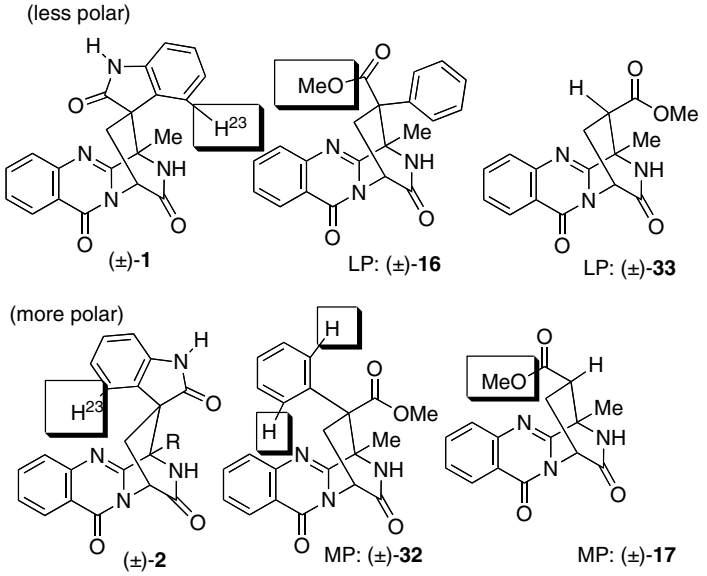
(±)-**41j** : R^4 = Ph

(±)-**41k** : R^4 = H

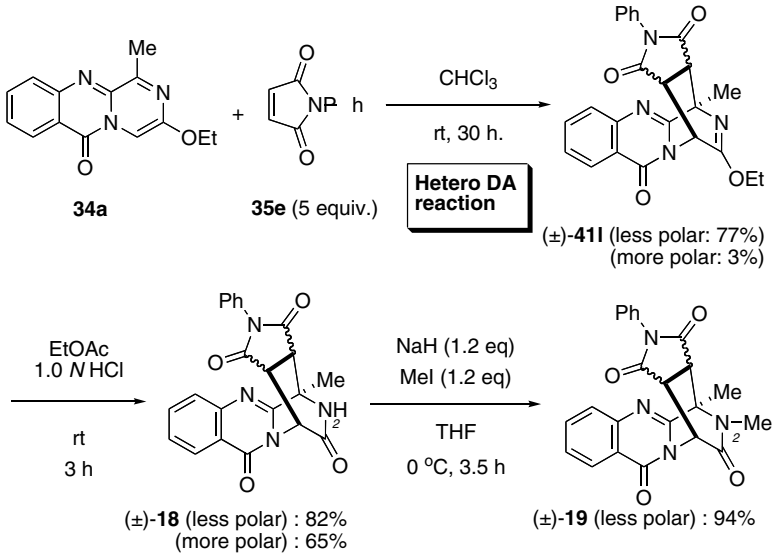
(±)-**16** (R^4 = Ph): 10% (2 steps), less polar isomer
(±)-**32** (R^4 = Ph): 13% (2 steps), more polar isomer
(±)-**17** (R^4 = H): 59% (from (±)-**41k-MP**), more polar isomer
(±)-**33** (R^4 = H): 67% (from (±)-**41k-LP**), less polar isomer

Scheme 8. Synthesis of simplified alantripinone derivatives (I).

Table 3
Chemical Shift of (±)-**1**, (±)-**2**, (±)-**16**, (±)-**17**, (±)-**32**, and (±)-**33** ($CDCl_3$, 400 MHz)



	Position	Less polar (ppm)	More polar (ppm)	Difference (ppm)
(±)-**1** (Alantrypinone)	H^{23}	6.81 (*exo*)	5.87 (*endo*)	0.94
(±)-**16** or (±)-**32**	Ph	7.19	6.71	0.48
	OMe	3.60	3.79	0.19
(±)-**17** or (±)-**33**	OMe	3.77	3.59	0.18

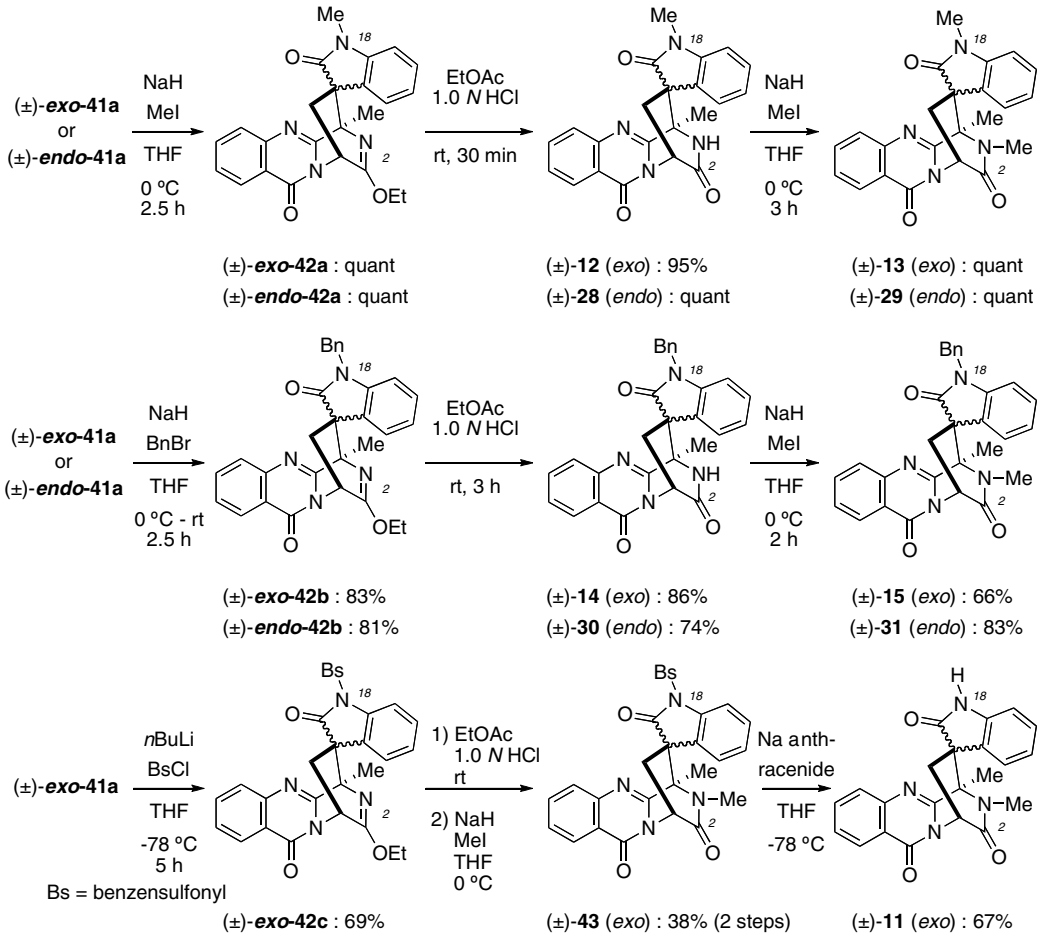


Scheme 9. Hetero DA reaction of N-phenylmaleimide and synthesis of simplified alantrypinone derivatives (II).

J = 7.2 Hz, 2H), 7.79 (dd, *J* = 2.4, 4.8 Hz, 1H) 7.87 (d, *J* = 8.8 Hz, 1H), 8.00 (s, 1H), 8.42 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.6, 21.7, 64.3, 95.1, 117.5, 125.8, 129.9, 132.5, 135.2, 138.8, 145.5, 151.4, 156.9, 161.9; IR (neat) *v*: 1681, 1629, 1462, 1149, 1073 cm^{-1}; LRMS (EI) *m/z* 289 $[M]^+$; HRMS (FAB) *m/z* Calcd for $C_{14}H_{12}{}^{35}ClN_3O_2$ $[M]^+$ 289.0618; found: 289.0630.

34c: 47% (2 steps) from **38c**, a yellow solid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.52 (t, *J* = 7.2 Hz, 3H), 2.93 (d, *J* = 0.8 Hz, 3H), 4.22 (q, *J* = 7.2 Hz, 2H), 7.62 (ddd, *J* = 2.8, 8.4, 8.8 Hz, 1H), 7.94 (dd, *J* = 5.2, 8.8 Hz, 1H), 7.95 (s, 1H), 8.06 (dd, *J* = 2.8, 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.6, 21.7, 64.3, 94.9, 110.9 (d, *J* = 24 Hz), 117.8 (d, *J* = 9.0 Hz), 124.1 (d, *J* = 26 Hz), 130.9 (d, *J* = 8.2 Hz), 138.4, 144.0, 151.4, 157.4 (d, *J* = 4.0 Hz), 160.8 (d, *J* = 244 Hz), 162.0; IR (KBr) *v*: 1700, 1670, 1636, 1535, 1483 cm^{-1}; LRMS (EI) *m/z* 273 $[M]^+$; HRMS (FAB) *m/z* Calcd for $C_{14}H_{13}FN_3O_2$ $[M+H]^+$ 274.0992; found: 274.0993.

34d: 32% (2 steps) from **38d**, a yellow solid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.52 (t, *J* = 7.2 Hz, 3H), 2.91 (s, 3H), 4.22 (q, *J* = 7.2 Hz, 2H), 7.50 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.90 (d, *J* = 1.6 Hz, 1H), 7.95 (br s, 1H), 8.36 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.6, 21.7, 64.3, 95.2, 115.0, 127.3, 127.6, 128.3, 139.5, 140.9, 147.9, 151.3, 157.4, 161.8; IR (KBr) *v*: 1690,



Scheme 10. Synthesis of alantrypinone derivatives ((±)-**11**–(±)-**15** and (±)-**28**–(±)-**31**).

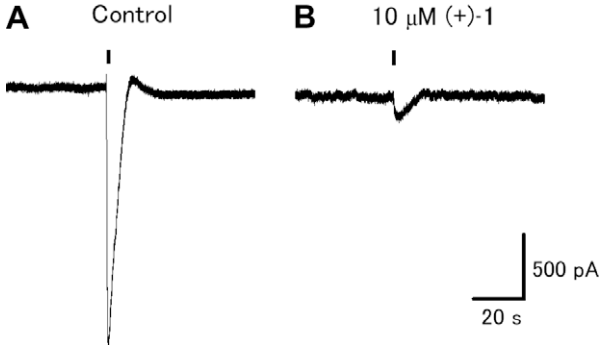


Figure 4. Inhibition of GABA-induced currents by (+)-**1** in cockroach neurons. GABA-evoked currents in cockroach neurons were recorded by the whole-cell patch–clamp method. (A) Control inward currents induced by 100 μM GABA. (B) Inward currents induced by 100 μM GABA after the 5-min application of 10 μM (+)-**1**. GABA was applied during the period indicated by the black bar. Recordings A and B were obtained from the same preparations.

1631, 1523, 1449, 1078 cm^{-1}; LRMS (EI) *m/z* 289 $[M]^+$; HRMS (FAB) *m/z* Calcd for $C_{14}H_{13}{}^{37}ClN_3O_2$ $[M+H]^+$ 292.0671; found: 292.0677.

34e: 41% (2 steps) from **38e**, a yellow solid, ^1H NMR ($CDCl_3$, 400 MHz) *δ: 1.51 (t, J* = 6.8 Hz, 3H), 4.32 (q, *J* = 7.2 Hz, 2H), 4.68 (s, 2H), 7.18–7.32 (m, 3H), 7.52–7.61 (m, 3H), 7.89 (ddd, *J* = 1.6, 6.8, 7.6 Hz, 1H), 7.97 (d, *J* = 7.6 Hz, 1H), 7.98 (s, 1H), 8.44 (dd, *J* = 1.6, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 14.6, 40.0, 64.2, 95.6, 116.7, 126.7, 126.8, 126.9, 128.2, 128.3 (2C), 129.7 (2C), 134.5, 137.6, 138.3, 147.1, 151.2, 158.0, 162.7; IR (KBr) *ν*: 1685, 1629, 1527, 1454 cm^{-1}; LRMS (EI) *m/z* 331 $[M]^+$; HRMS (FAB) *m/z* Calcd for $C_{20}H_{18}N_3O_2$ $[M+H]^+$ 332.1352; found: 332.1376.

34f: 33% (2 steps) from **38f**, a yellow solid, ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 1.41 (s, 3H), 1.43 (s, 3H), 1.53 (t, *J* = 7.2 Hz, 3H), 4.26 (q, *J* = 7.2 Hz, 2H), 4.34 (qui, *J* = 6.8 Hz, 1H), 7.58 (ddd, *J* = 1.6, 7.2, 7.6 Hz, 1H), 7.87 (ddd, *J* = 1.6, 6.8, 7.6 Hz, 1H), 7.91 (ddd, *J* = 1.6, 7.6, 7.6 Hz, 1H), 7.99 (s, 1H), 8.46 (dd, *J* = 1.6, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 14.6, 20.9 (2C), 30.6, 64.1, 95.0, 116.9, 126.8, 126.9, 128.3, 134.5, 138.1, 147.2, 151.4, 158.2, 169.0; IR (KBr) *ν*: 1687, 1631, 1534, 1458 cm^{-1}; LRMS (EI) *m/z* 283 $[M]^+$; HRMS (FAB) *m/z* Calcd for $C_{16}H_{18}N_3O_2$ $[M+H]^+$ 284.1399; found: 284.1395.

34g: 37% (2 steps) from **38g**, a yellow solid, ^1H NMR ($CDCl_3$, 400 MHz) *δ*: 1.05 (d, *J* = 6.4 Hz, 6H), 1.52 (t, *J* = 6.8 Hz, 3H), 2.51 (m, 1H), 3.24 (d, *J* = 7.2 Hz, 2H), 4.25 (q, *J* = 6.8 Hz, 2H), 7.58 (ddd, *J* = 1.2, 7.2, 7.6 Hz, 1H), 7.87 (ddd, *J* = 1.6, 6.4, 7.6 Hz, 1H), 7.91 (ddd, *J* = 0.8, 8.0, 8.8 Hz, 1H), 8.00 (s, 1H), 8.45 (dd, *J* = 1.6, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 14.6, 22.7 (2C), 27.4, 42.5, 64.2, 95.1, 116.8, 126.8, 126.9, 128.3, 134.5, 138.9, 147.2, 151.2, 158.2, 164.3; IR (KBr) *ν*: 1678, 1631, 1531, 1454, 1105 cm^{-1}; LRMS (EI) *m/z* 297 $[M]^+$; HRMS (FAB) *m/z* Calcd for $C_{17}H_{20}N_3O_2$ $[M+H]^+$ 298.1556; found: 298.1549.

3.1.2. Synthesis of 3-methyleneoxindole

*Synthesis of 3-methyleneoxindole (**35a**):* To a solution of isatin (**37a**, 1 g, 6.80 mmol) in diethyl ether (70 mL) was added a solution of $TMSCH_2MgCl$ in diethyl ether (1.0 M, 13.6 mL, 13.6 mmol) at −78 °C and the mixture was stirred for 15 min at −78 °C then for

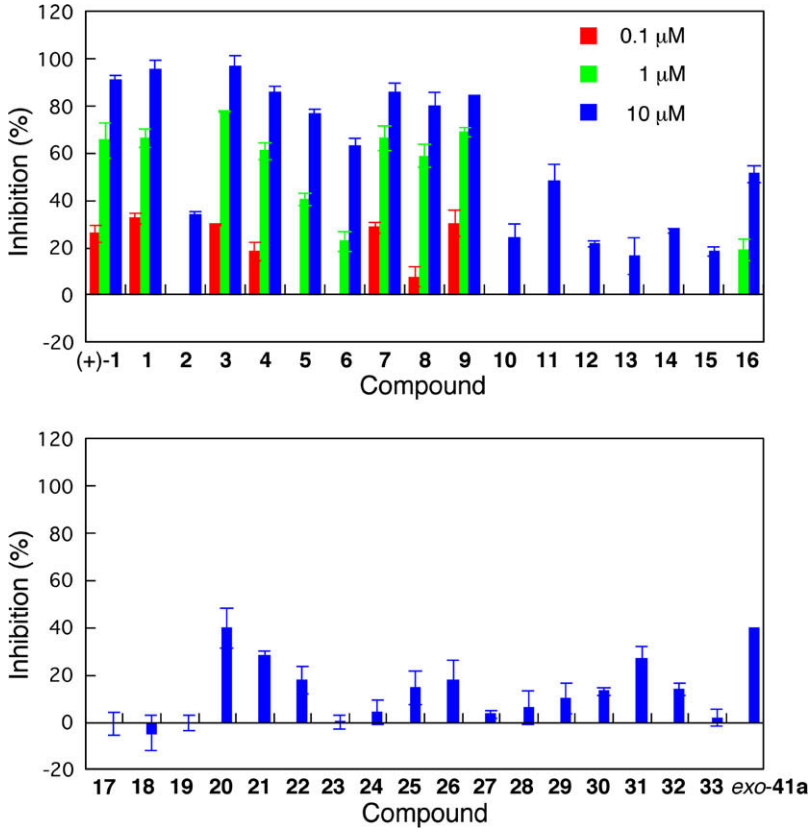


Figure 5. Potencies of alantrypinone derivatives in inhibiting specific [^{3}H]EBOB binding to housefly-head membranes. Compounds other than (+)-**1** were racemates. Data are means ± SD of at least three experiments, each performed in triplicate, except the data of *exo*-**41a** (n = 1). Data of (+)-**1** were taken from Ref. 6.

18 h at room temperature. The reaction was quenched by the addition of MeOH. After removal of the solvent, the residue was subjected to column chromatography (hexane/AcOEt = 1:1) to give 3-hydroxy-3-trimethylsilylmethyloxindole (1.23 g, 77%) as a yellow solid. To a solution of 3-hydroxy-3-trimethylsilylmethyloxindole (1.23 g, 5.23 mmol) in CH_2Cl_2 (90 mL) was added $BF_3{\cdot}OEt_2$ (3.3 mL, 26.1 mmol) at −78 °C and the mixture was stirred for 2 h at −78 °C then for 1 h at 0 °C. The reaction was quenched by the addition of satd aq $NaHCO_3$ and the organic compounds were extracted with CH_2Cl_2 and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, **35a**[10] (750 mg, quant.) was obtained as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.13 (s, 1H), 6.39 (s, 1H), 6.87 (d, J = 7.6 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 7.26 (t, J = 6.2 Hz, 1H), 7.47 (d, J = 7.6 Hz, 1H), 8.08 (s, 1H).

*Synthesis of 5-chloro-3-methyleneoxindole (**35b**):* To a solution of **37b** (500 mg, 2.75 mmol) in diethyl ether (30 mL) was added a solution of $TMSCH_2MgCl$ in diethyl ether (1.0 M, 5.5 mL, 5.5 mmol) at −78 °C and the mixture was stirred for 15 min at −78 °C then for 18 h at room temperature. The reaction was quenched by the addition of MeOH. After removal of the solvent, the residue was subjected to column chromatography (hexane/AcOEt = 1:1) to give 3-hydroxy-3-trimethylsilylmethyloxindole (520 mg, 70%) as a yellow solid. To a solution of 3-hydroxy-3-trimethylsilylmethyloxindole (100 mg, 373 μmol) in CH_2Cl_2 (10 mL) was added $BF_3{\cdot}OEt_2$ (240 μL, 1.87 mmol) at −78 °C and the mixture was stirred for 2 h at −78 °C then for 1 h at 0 °C. The reaction was quenched by the addition of satd aq $NaHCO_3$ and the organic compounds were extracted with CH_2Cl_2 and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, **35b** (68 mg, quant.) was obtained as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.15 (s, 1H), 6.45 (s, 1H), 6.79 (d, J = 8.4 Hz, 1H), 7.23 (dd, J = 2.0, 8.4 Hz, 1H), 7.44 (s, 1H), 7.75 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 111.0, 120.1, 121.7, 124.0, 127.8, 130.0, 135.0, 139.4, 168.2; IR (KBr) ν: 3410, 1719, 1677 cm^{-1}; LRMS (EI) m/z 179 [M]$^+$; HRMS (FAB) m/z Calcd for $C_9H_7{}^{37}ClNO$ [M+H]$^+$ 182.0189; found: 182.0188.

3.1.3. General procedure of hetero Diels–Alder reaction

A solution of **34** and **35** in $CHCl_3$ was stirred at the conditions in Table 1. After removal of the solvent, the residue was subjected to column chromatography to give the corresponding adducts.

*(±)-exo-**41a**[4e]:* 52% from **34a** and **35a**, a yellow amorphous, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.42 (t, J = 7.2 Hz, 3H), 1.56 (s, 3H), 2.25 (dd, J = 2.4, 14 Hz, 1H), 2.57 (dd, J = 3.2, 14 Hz, 1H), 4.32–4.40 (m, 2H), 6.05 (d, J = 2.8 Hz, 1H), 6.81 (d, J = 7.6 Hz, 1H), 7.02–7.09 (m, 2H), 7.23–7.26 (m, 1H), 7.46–7.56 (m, 1H), 7.63 (br s, 1H), 7.72–7.75 (m, 2H), 8.32 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.2, 16.8, 37.6, 47.6, 54.7, 63.7, 66.9, 110.1, 120.1, 122.7, 124.1, 126.6, 126.7, 127.8, 128.9, 130.7, 134.2, 141.4, 147.4, 154.2, 159.4, 172.6, 178.6; LRMS (EI) m/z 400 [M]$^+$.

*(±)-endo-**41a**[4e]:* 18% from **34a** and **35a**, a yellow amorphous, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.40 (t, J = 7.2Hz, 3H), 1.60 (s, 3H), 2.25 (dd, J = 3.2, 13.8 Hz, 1H), 2.58 (dd, J = 2.0, 13.8 Hz, 1H), 4.13–4.31 (m, 1H), 4.38–4.45 (m, 1H), 5.84 (d, J = 7.6 Hz, 1H), 6.06 (br s, 1H), 6.76–6.74 (m, 1H), 6.85 (d, J = 8.0Hz, 1H), 7.15 (t, J = 8.0, 1H), 7.55 (t, J = 7.2 Hz, 1H), 7.66 (br s, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.79 (ddd, J = 1.2, 7.2, 7.4 Hz, 1H), 8.38 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.1, 17.0, 37.1, 48.0, 53.1, 63.8, 67.1, 109.7, 120.1, 122.7, 123.2, 126.9, 127.2, 128.2, 128.8, 130.1, 134.6, 141.1, 147.2, 153.8, 159.1, 171.5, 178.5; LRMS (EI) m/z 400 [M]$^+$.

*(±)-exo-**41b**:* 34% from **34b** and **35a**, a yellow amorphous, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.43 (t, J = 7.2 Hz, 3H), 1.60 (s, 3H),

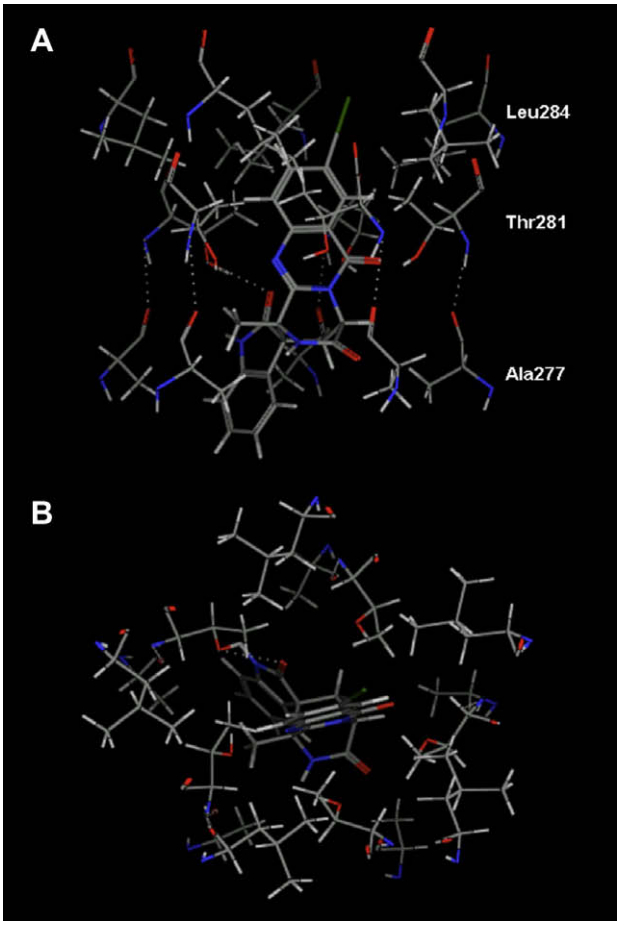


Figure 6. A homopentameric β3 GABA receptor channel model with **3** docked into the putative binding site. A **3** isomer having the same stereochemistry as that of (+)-**1** was docked into the model. Only the pore-facing region surrounded by five Ala277s, five Thr281s, and five Leu284s from five subunits, which is thought to be the antagonist-binding site,[8] is shown. (A) Side view. (B) Top view of the channel.

2.25 (dd, *J* = 2.4, 14 Hz, 1H), 2.55 (dd, *J* = 3.2, 14 Hz, 1H), 4.32–4.40 (m, 2H), 6.02 (s, 1H), 6.75–6.81 (m, 1H), 7.04–7.13 (m, 3H), 7.67 (s, 2H), 7.90 (s, 1H), 8.28 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 14.2, 16.8, 37.7, 47.8, 54.7, 63.9, 66.9, 110.1, 121.3, 123.0, 124.2, 126.1, 129.1, 129.6, 130.6, 132.4, 134.6, 141.3, 146.0, 154.6, 158.4, 172.6, 178.5; IR (neat) *ν*: 1700, 1654, 1472, 1027, 991 cm^{-1}; LRMS (EI) *m*/*z* 434 [M]$^+$; HRMS (FAB) *m*/*z* Calcd for $C_{23}H_{20}{}^{35}ClN_4O_3$ [M+H]$^+$ 435.1224; found: 435.1220.

*(±)-endo-**41b**:* 25% from **34b** and **35a**, a yellow amorphous, ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 1.41 (t, *J* = 7.2 Hz, 3H), 1.58 (s, 3H), 2.24 (dd, *J* = 3.2, 13.8 Hz, 1H), 2.58 (dd, *J* = 2.0, 13.6 Hz, 1H), 4.23–4.31 (m, 1H), 4.39–4.47 (m, 1H), 5.80 (d, *J* = 7.2 Hz, 1H), 6.04 (d, *J* = 5.6 Hz, 1H), 6.73 (t, *J* = 6.8 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 7.17 (t, *J* = 6.8 Hz, 1H), 7.65–7.77 (m, 3H), 8.34 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 14.1, 16.9, 37.1, 48.3, 53.2, 63.9, 67.2, 109.8, 121.2, 122.7, 123.1, 126.3, 129.0, 129.8, 130.0, 133.1, 135.1, 141.2, 145.7, 154.1, 158.2, 171.4, 178.5; IR (neat) *ν*: 1655, 1560, 1473, 1025, 993 cm^{-1}; LRMS (EI) *m*/*z* 434 [M]$^+$; HRMS (FAB) *m*/*z* Calcd for $C_{23}H_{20}{}^{35}ClN_4O_3$ [M+H]$^+$ 435.1224; found: 435.1192.

*(±)-exo-**41c**:* 40% from **34c** and **35a**, a yellow amorphous, ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 1.42 (t, *J* = 7.2 Hz, 3H), 1.51 (s, 3H), 2.24 (dd, *J* = 2.0, 14.0 Hz, 1H), 2.55 (dd, *J* = 3.2, 14.0 Hz, 1H), 4.29–4.41 (m, 2H), 6.03 (br s, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 7.01–7.07 (m, 2H), 7.21 (ddd, *J* = 1.6, 7.6, 7.6 Hz, 1H), 7.44 (ddd, *J* = 2.8, 8.4, 8.6 Hz, 1H), 7.72 (dd, *J* = 4.8, 8.6 Hz, 1H), 7.94 (dd, *J* = 2.8, 8.4 Hz, 1H), 8.38 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 14.2, 16.8, 37.7, 47.7, 54.6, 63.8, 66.9, 110.0, 111.6 (d, *J* = 24 Hz), 121.4 (d, *J* = 8 Hz), 122.7 (d, *J* = 24 Hz), 122.9, 124.3, 129.0, 130.3 (d, *J* = 8 Hz), 130.6, 141.3, 144.2, 153.6, 158.7 (d, *J* = 3 Hz), 160.9 (d, *J* = 247 Hz), 172.5, 178.2; IR (KBr) *ν*: 3214, 1722, 1685, 1655, 1632, 1487 cm^{-1}; LRMS (EI) *m*/*z* 418 [M]$^+$; HRMS (FAB) *m*/*z* Calcd for $C_{23}H_{20}FN_4O_3$ [M+H]$^+$ 419.1519; found: 419.1488.

*(±)-endo-**41c**:* 59% from **34c** and **35a**, a yellow amorphous, ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 1.41 (t, *J* = 7.2 Hz, 3H), 1.58 (s, 3H), 2.24 (dd, *J* = 3.2, 13.6 Hz, 1H), 2.58 (dd, *J* = 2.0, 13.6 Hz, 1H), 4.23–4.31 (m, 1H), 4.39–4.47 (m, 1H), 5.80 (d, *J* = 7.6 Hz, 1H), 6.04 (dd, *J* = 2.0, 3.2 Hz, 1H), 6.73 (t, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.51 (ddd, *J* = 2.8, 8.0, 8.4 Hz, 1H), 7.56 (s, 1H), 7.72 (dd, *J* = 4.8, 8.4 Hz, 1H), 8.00 (dd, *J* = 2.8, 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 14.1, 16.9, 37.0, 48.2, 53.2, 63.9, 67.1, 109.9, 111.8 (d, *J* = 24 Hz), 121.3 (d, *J* = 9 Hz), 122.6, 123.0, 123.2 (d, *J* = 24 Hz), 128.9, 130.1, 130.5 (d, *J* = 8 Hz), 141.3, 143.8, 153.2, 158.4 (d, *J* = 3 Hz), 161.1 (d, *J* = 248 Hz), 171.3, 178.9; IR (KBr) *ν*: 3239, 1646, 1475, 1382, 1343 cm^{-1}; LRMS (EI) *m*/*z* 418 [M]$^+$; HRMS (FAB) *m*/*z* Calcd for $C_{23}H_{20}FN_4O_3$ [M+H]$^+$ 419.1519; found: 419.1484.

*(±)-exo-**41d**:* 40% from **34d** and **35a**, a yellow amorphous, ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 1.43 (t, *J* = 7.2 Hz, 3H), 1.52 (s, 3H), 2.25 (dd, *J* = 2.0, 14 Hz, 1H), 2.55 (dd, *J* = 3.2, 14 Hz, 1H), 4.36 (dq, *J* = 4.0, 7.2 Hz, 2H), 6.02 (t, *J* = 2.8 Hz, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 7.00–7.08 (m, 2H), 7.24–7.26 (m, 1H), 7.43 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.74 (d, *J* = 1.2 Hz, 1H), 8.03 (br s, 1H), 8.24 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 14.2, 16.8, 37.7, 47.7, 54.7, 63.8, 67.1, 110.0, 118.8, 123.0, 124.3, 125.6, 127.2, 127.6, 128.3, 129.1, 130.6, 141.3, 148.5, 155.6, 158.8, 172.6, 178.2; IR (KBr) *ν*: 1687, 1600, 1471, 1422, 1330 cm^{-1}; LRMS (EI) *m*/*z* 434 [M]$^+$; HRMS (FAB) *m*/*z* Calcd for $C_{23}H_{20}{}^{35}ClN_4O_3$ [M+H]$^+$ 435.1224; found: 435.1232.

*(±)-endo-**41d**:* 36% from **34d** and **35a**, a yellow amorphous, ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 1.41 (t, *J* = 7.2 Hz, 3H), 1.53 (s, 3H), 2.24 (dd, *J* = 3.2, 13.6 Hz, 1H), 2.57 (dd, *J* = 2.4, 13.6 Hz, 1H), 4.24–4.31 (m, 1H), 4.39–4.45 (m, 1H), 5.83 (d, *J* = 7.6 Hz, 1H), 6.04 (t, *J* = 2.8 Hz, 1H), 6.75 (t, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.50 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.72 (d, *J* = 2.0 Hz, 1H), 8.30 (d, *J* = 8.4 Hz, 1H), 8.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 14.1, 16.9, 37.1, 48.2, 53.1, 64.0, 67.2, 109.7, 118.6, 122.8, 123.1, 127.7, 127.8, 128.3, 129.0, 129.9, 140.9, 141.1, 148.1, 155.2, 158.5, 171.4, 178.2; IR (KBr) *ν*: 1722, 1643, 1471, 1343, 1179 cm^{-1}; LRMS (EI) *m*/*z* 434 [M]$^+$; HRMS (FAB) *m*/*z* Calcd for $C_{23}H_{20}{}^{37}ClN_4O_3$ [M+H]$^+$ 437.1205; found: 437.1218.

*(±)-exo-**41e**:* 38% from **34a** and **35b**, a yellow amorphous, ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 1.44 (t, *J* = 7.2 Hz, 3H), 1.57 (s, 3H), 2.23 (dd, *J* = 2.0, 14 Hz, 1H), 2.57 (dd, *J* = 3.2, 14 Hz, 1H), 4.33–4.41 (m, 2H), 6.05 (dd, *J* = 2.0, 3.2 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 2.0 Hz, 1H), 7.23 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.49 (m, 1H), 7.74 (d, *J* = 4.0 Hz, 3H), 8.32 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 14.2, 16.9, 37.7, 47.5, 55.0, 63.9, 66.9, 111.0, 120.2, 124.8, 126.8, 127.9, 128.1, 128.9, 132.0, 132.4, 134.3, 139.9, 147.5, 153.8, 159.3, 172.8, 178.1; IR (KBr) *ν*: 3261, 1632, 1477, 1385, 1300, 1192, 1155 cm^{-1}; LRMS (EI) *m*/*z* 434 [M]$^+$; HRMS (FAB) *m*/*z* Calcd for $C_{23}H_{20}{}^{35}ClN_4O_3$ [M+H]$^+$ 435.1224; found: 435.1191.

*(±)-endo-**41e**:* 48% from **34a** and **35b**, a yellow amorphous, ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 1.42 (t, *J* = 7.6 Hz, 3H), 1.60 (s, 3H), 2.24 (dd, *J* = 3.6, 14 Hz, 1H), 2.57 (dd, *J* = 2.2, 14 Hz, 1H), 4.24–4.32 (m, 1H), 4.38–4.46 (m, 1H), 5.76 (d, *J* = 2.0 Hz, 1H), 6.08 (t, *J* = 2.8 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 7.13 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.57 (ddd, *J* = 0.8, 7.5, 8.0 Hz, 1H), 7.74 (dd, *J* = 0.8, 8.0 Hz, 1H), 7.81 (ddd, *J* = 1.2, 7.2, 7.7 Hz, 1H), 8.38 (dd, *J* = 1.6, 8.0 Hz, 1H), 9.70 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 14.2, 17.1, 37.1, 48.0, 53.7, 64.0, 67.2, 110.9, 120.1, 124.0, 126.9, 127.5, 128.0,

128.2, 128.9, 131.9, 134.9, 139.9, 147.1, 153.3, 159.2, 171.6, 178.7; IR (KBr) ν: 3218, 1719, 1642, 1609, 1473, 1176 cm^{-1}; LRMS (EI) m/z 434 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{23}H_{20}{}^{37}ClN_4O_3$ [M+H]$^+$ 437.1205; found: 437.1199.

*(±)-exo-**41f***: 31% from **34b** and **35b**, a colorless amorphous, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.45 (t, J = 7.2 Hz, 3H), 1.54 (s, 3H), 2.23 (dd, J = 2.4, 14 Hz, 1H), 2.55 (dd, J = 3.2, 14 Hz, 1H), 4.35–4.39 (m, 2H), 6.03 (dd, J = 2.4, 3.2 Hz, 1H), 6.72 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 1.6 Hz, 1H), 7.23 (dd, J = 2.0, 8.0 Hz, 1H), 7.66-7.67 (m, 2H), 8.07 (s, 1H), 8.28 (dd, J = 1.6, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.2, 16.8, 37.7, 47.6, 54.9, 64.0, 66.8, 110.9, 121.3, 125.0, 126.2, 128.3, 129.0, 129.6, 132.2, 132.6, 134.7, 139.6, 146.0, 154.1, 158.3, 172.7, 177.5; IR (KBr) ν: 1720, 1628, 1475, 1383, 1192 cm^{-1}; LRMS (FAB) m/z 469 [M+H]$^+$; HRMS (FAB) m/z Calcd for $C_{23}H_{19}{}^{35}Cl_2N_4O_3$ [M+H]$^+$ 469.0834; found: 469.0846.

*(±)-endo-**41f***: 48% from **34b** and **35b**, a colorless amorphous, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.40 (t, J = 7.2 Hz, 3H), 1.57 (s, 3H), 2.20 (dd, J = 3.2, 14 Hz, 1H), 2.57 (dd, J = 2.0, 14 Hz, 1H), 4.23–4.31 (m, 1H), 4.38–4.46 (m, 1H), 5.73 (d, J = 2.0 Hz, 1H), 6.04 (dd, J = 2.0, 3.2 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 7.15 (dd, J = 2.0, 8.4 Hz, 1H), 7.54 (br s, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.74 (dd, J = 2.4, 8.8 Hz, 1H), 8.34 (dd, J = 0.4, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.0, 16.9, 36.9, 48.0, 53.5, 64.0, 67.1, 110.8, 121.1, 123.8, 126.2, 128.0, 128.9, 129.7, 131.6, 133.3, 135.3, 139.7, 145.5, 153.6, 158.1, 171.4, 178.3; IR (KBr) ν: 1687, 1473, 1387, 1281, 1174 cm^{-1}; LRMS (FAB) m/z 469 [M+H]$^+$; HRMS (FAB) m/z Calcd for $C_{23}H_{19}{}^{35}Cl_2N_4O_3$ [M+H]$^+$ 469.0834; found: 469.0846.

(±)-*exo*-**41g** and (±)-*endo*-**41g** were obtained as an inseparable mixture (67%) from **34e** and **35a**.

(±)-*exo*-**41h** and (±)-*endo*-**41h** were obtained as an inseparable mixture (quant.) from **34f** and **35a**.

*(±)-exo-**41i***: 26% from **34g** and **35a**, a yellow amorphous, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.89 (d, J = 6.8 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H), 1.13 (dd, J = 6.8, 13.2 Hz, 1H), 1.42 (t, J = 7.2 Hz, 3H), 2.00 (dq, J = 2.8, 6.8 Hz, 1H), 2.21 (dd, J = 2.0, 14.0 Hz, 1H), 2.32 (dd, J = 2.8, 13.6 Hz, 1H), 2.48 (dd, J = 2.8, 13.6 Hz, 1H), 4.37 (dq, J = 0.8, 6.8 Hz, 2H), 6.03 (dd, J = 2.8, 2.8 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 7.00–7.09 (m, 2H), 7.23 (ddd, J = 1.6, 7.2, 7.2 Hz, 1H), 7.48 (ddd, J = 3.2, 5.6, 7.6 Hz, 1H), 7.71–7.76 (m, 2H), 7.88 (br s, 1H), 8.32 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.2, 24.4, 24.8, 25.6, 36.1, 38.6, 47.0, 55.2, 63.4, 70.4, 109.7, 120.2, 122.7, 124.4, 126.5, 126.7, 128.2, 128.7, 131.3, 134.1, 141.3, 147.6, 153.4, 159.6, 171.9, 178.1; IR (KBr) ν: 3226, 1715, 1645, 1472, 1338, 1193 cm^{-1}; LRMS (EI) m/z 442 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{26}H_{27}N_4O_3$ [M+H]$^+$ 443.2083; found: 443.2089.

*(±)-endo-**41i***: 38% from **34g** and **35a**, a yellow amorphous, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.97 (d, J = 6.8 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H), 1.40 (t, J = 7.2 Hz, 3H), 1.54 (dd, J = 6.8, 13.6 Hz, 1H), 1.97 (dd, J = 4.0, 14.0 Hz, 1H), 2.09 (dq, J = 2.4, 6.8 Hz, 1H), 2.14 (dd, J = 3.2, 13.6 Hz, 1H), 2.53 (dd, J = 2.0, 13.6 Hz, 1H), 4.15–4.45 (m, 2H), 5.77 (d, J = 6.8 Hz, 1H), 6.04 (dd, J = 2.4, 3.2 Hz, 1H), 6.70 (ddd, J = 0.8, 7.6, 7.6 Hz, 1H), 6.83 (d, J = 7.6 Hz, 1H), 7.15 (ddd, J = 0.8, 7.6, 7.6 Hz, 1H), 7.55 (ddd, J = 1.2, 7.6, 7.6 Hz, 1H), 7.58 (br s, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.78 (ddd, J = 1.2, 7.6, 7.6 Hz, 1H), 8.37 (dd, J = 1.2, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.1, 24.6, 24.8, 25.4, 36.6, 38.1, 47.4, 53.8, 63.6, 70.3, 109.4, 120.1, 122.6, 123.5, 126.8, 127.0, 128.3, 128.7, 130.2, 134.5, 140.8, 147.1, 153.2, 159.2, 170.5, 178.3; IR (KBr) ν: 3193, 1702, 1605, 1467, 1335 cm^{-1}; LRMS (EI) m/z 442 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{26}H_{27}N_4O_3$ [M+H]$^+$ 443.2083; found: 443.2089.

(±)-*exo*-**41j** and (±)-*endo*-**41j** were obtained as an inseparable mixture (30%) from **34a** and **35c**.

*(±)-41k-**LP**:* 21% from **34a** and **35d**, a colorless amorphous, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.34 (t, J = 7.2 Hz, 3H), 1.96 (s, 3H), 2.12–2.19 (m, 1H), 2.35 (td, J = 2.8, 13.6 Hz, 1H), 2.84 (dd, J = 4.0, 13.6 Hz, 1H), 3.77 (s, 3H), 4.12–4.30 (m, 2H), 5.89 (s, 1H), 7.47–7.50 (m, 1H), 7.75–7.78 (m, 2H), 8.27 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.9, 20.8, 30.0, 45.0, 47.5, 52.2, 63.4, 63.6, 120.1, 126.7, 126.9, 127.8, 134.4, 147.5, 155.7, 159.0, 170.6, 171.9; IR (KBr) ν: 1674, 1641, 1473, 1431, 1373 cm^{-1}; LRMS (EI) m/z 341 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{18}H_{20}N_3O_4$ [M+H]$^+$ 342.1454; found: 342.1451.

*(±)-41k-**MP**:* 63% from **34a** and **35d**, a colorless amorphous, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.31 (t, J = 7.2 Hz, 3H), 1.89 (s, 3H), 2.19–2.22 (m, 2H), 2.86 (dd, J = 7.2, 9.2 Hz, 1H), 3.59 (s, 3H), 4.11–4.22 (m, 2H), 5.87 (t, J = 6.8 Hz, 1H), 7.45–7.49 (m, 1H), 7.73 (d, J = 3.6 Hz, 2H), 8.29 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.9, 20.8, 29.8, 46.7, 47.5, 52.3, 63.4, 63.8, 120.2, 126.6, 126.7, 127.9, 134.2, 147.6, 154.4, 159.2, 171.5, 172.2; IR (KBr) ν: 1720, 1655, 1637, 1508, 1475 cm^{-1}; LRMS (EI) m/z 341 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{18}H_{20}N_3O_4$ [M+H]$^+$ 342.1454; found: 342.1469.

*(±)-41l-**LP**:* 77% from **34a** and **35d**, a colorless amorphous, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.29 (t, J = 7.2 Hz, 3H), 2.26 (s, 3H), 3.17 (d, J = 8.0 Hz, 1H), 3.57 (dd, J = 4.0, 8.0 Hz, 1H), 4.12–4.26 (m, 2H), 6.34 (d, J = 4.0 Hz, 1H), 7.21–7.24 (m, 2H), 7.41–7.45 (m, 1H), 7.49 (ddd, J = 1.6, 6.2, 6.7 Hz, 2H), 7.54 (ddd, J = 2.4, 5.5, 5.8 Hz, 1H), 7.78–7.83 (m, 2H), 8.32 (dd, J = 1.2, 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.9, 19.3, 45.3, 46.2, 48.1, 64.0, 64.1, 120.0, 126.0 (2C), 126.9, 127.5, 128.0, 129.1, 129.3 (2C), 131.2, 134.9, 147.2, 154.3, 158.8, 168.7, 171.5, 172.2; IR (KBr) ν: 1721, 1686, 1624, 1384 cm^{-1}; LRMS (EI) m/z 428 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{24}H_{21}N_4O_4$ [M+H]$^+$ 429.1563; found: 429.1595.

*(±)-41l-**MP**:* 3% from **34a** and **35d**, a colorless amorphous, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.36 (t, J = 3.2 Hz, 3H), 2.21 (s, 3H), 3.32 (d, J = 8.8 Hz, 1H), 3.60 (dd, J = 3.2, 8.8 Hz, 1H), 4.20–4.32 (m, 2H), 6.37 (d, J = 2.8 Hz, 1H), 6.62–6.66 (m, 2H), 7.17–7.23 (m, 3H), 7.49 (ddd, J = 2.4, 3.0, 10.9 Hz, 1H), 7.74-7.79 (m, 2H), 8.26 (dd, J = 1.2, 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.9, 20.4, 44.9, 47.8, 49.1, 64.2, 64.3, 119.7, 126.0 (2C), 127.1, 127.5, 128.1, 129.0, 129.1 (2C), 130.7, 134.8, 147.0, 152.9, 158.5, 170.5, 171.5, 171.9; IR (KBr) ν: 1718, 1685, 1638, 1381 cm^{-1}; LRMS (EI) m/z 428 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{24}H_{21}N_4O_4$ [M+H]$^+$ 429.1563; found: 429.1530.

3.1.4. General procedure: hydrolysis of 41 to (±)-1–(±)-10, (±)-16–(±)-18, (±)-20–(±)-27, (±)-32, and (±)-33

A solution of **41** in AcOEt (15 μM) and 1.0 N HCl (1.5 μM) was stirred at room temperature. After removal of the solvent, the residue was washed with MeOH to give the corresponding hydrolyzed product.

*(±)-**1***[4e]*:* 74% from (±)-*exo*-**41a**, a white solid, ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.16 (s, 3H), 2.39 (s, 2H), 5.56 (d, J = 2.0Hz, 1H), 6.91 (d, J = 7.6Hz, 1H), 7.10 (t, J = 7.2Hz, 1H), 7.17 (d, J = 6.8Hz, 1H), 7.31 (t, J = 6.8Hz, 1H), 7.59 (t, J = 7.2, 1H), 7.69 (d, J = 8.0Hz, 1H), 7.86 (ddd, J = 1.2, 6.8, 7.2Hz, 1H), 8.20 (d, J = 6.8Hz, 1H), 9.56 (s, 1H), 10.65 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 13.4, 35.9, 51.9, 54.7, 61.8, 109.8, 120.0, 122.3, 123.7, 126.3, 127.2, 127.7, 129.1, 129.9, 134.7, 142.5, 146.8, 152.9, 158.3, 169.6, 176.6; IR (KBr) ν: 3176, 1680, 1627, 1469 cm^{-1}; LRMS (EI) m/z 372 [M]$^+$.

*(±)-**2***[4e]*:* 71% from (±)-*endo*-**41a**, a white solid, ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.22 (s, 3H), 2.31 (dd, J = 4.0, 14.4Hz, 1H), 2.54 (d, J = 14.0, 1H), 5.56 (s, 1H), 5.86 (d, J = 7.2Hz, 1H), 6.65 (t, J = 7.6Hz, 1H), 6.86 (d, J = 7.6Hz, 1H), 7.14 (t, J = 7.6Hz, 1H), 7.61–7.69 (m, 2H), 7.87 (t, J = 8.4Hz, 1H), 8.25 (d, J = 8.0Hz, 1H), 9.28 (s, 1H), 10.73 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 13.3, 35.2, 52.2, 52.6, 61.9, 109.5, 120.1, 121.6, 123.3, 126.6, 127.7, 127.8, 128.9, 129.2, 135.0, 142.3, 146.3, 152.4, 158.2, 168.9, 177.1; IR (KBr) ν: 3192, 1691, 1620, 1469 cm^{-1}; LRMS (EI) m/z 372 [M]$^+$.

*(±)-**3**:* 62% from (±)-*exo*-**41b**, a white solid, mp >300 °C (MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.16 (s, 3H), 2.40 (s, 2H), 5.55 (s, 1H), 6.91 (d, J = 7.6 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 7.17 (d, J = 6.8 Hz, 1H), 7.31 (t, J = 7.2 Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.89 (d, J = 8.8 Hz, 1H), 8.15 (s, 1H), 9.60 (s, 1H), 10.66 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 13.3, 35.9, 52.2, 54.7, 61.8, 109.9, 121.4, 122.4, 123.8, 125.3, 129.2, 129.8, 129.9, 131.5, 134.8, 142.6, 145.6, 153.5, 157.4, 169.4, 176.6; IR (KBr) ν: 3217, 1726, 1619, 1470 cm^{-1}; LRMS (EI) m/z 406 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{21}H_{16}{}^{35}ClN_4O_3$ [M+H]$^+$ 407.0911; found: 407.0920.

*(±)-**4**:* 90% from (±)-*exo*-**41c**, a white solid, mp >300 °C (MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.18 (s, 3H), 2.41 (s, 2H), 5.57 (d, J = 2.0 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 7.19 (d, J = 6.8 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H), 7.76–7.80 (m, 2H), 7.90 (dd, J = 2.4, 8.8 Hz, 1H), 9.58 (s, 1H), 10.65 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 13.3, 35.8, 52.1, 54.6, 61.7, 109.8, 111.0 (d, J = 23 Hz), 121.3 (d, J = 8.0 Hz), 122.3, 123.0, 123.7, 129.1, 129.8, 130.4 (d, J = 9 Hz), 142.5, 143.6, 152.4, 157.6 (d, J = 3 Hz), 160.2 (d, J = 244 Hz), 169.4, 176.6; IR (KBr) ν: 3252, 1705, 1629, 1486, 1334 cm^{-1}; LRMS (EI) m/z 390 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{21}H_{16}FN_4O_3$ [M+H]$^+$ 391.1206; found: 391.1202.

*(±)-**5**:* 60% from (±)-*exo*-**41d**, a white solid, mp >300 °C (MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.15 (s, 3H), 2.40 (d, J = 2.4 Hz, 2H), 5.55 (d, J = 2.4 Hz, 1H), 6.91 (d, J = 7.6 Hz, 1H), 7.10 (ddd, J = 1.2, 7.5, 7.6 Hz, 1H), 7.17 (d, J = 6.8 Hz, 1H), 7.31 (ddd, J = 1.2, 7.6, 7.8 Hz, 1H), 7.63 (dd, J = 2.0, 8.4 Hz, 1H), 7.77 (d, J = 2.0 Hz, 1H), 8.20 (d, J = 8.8 Hz, 1H), 9.59 (d, J = 1.6 Hz, 1H), 10.67 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 13.3, 35.8, 52.0, 54.7, 61.8, 109.9, 118.9, 121.4, 122.4, 123.8, 126.9, 127.5, 128.4, 129.2, 129.8, 139.3, 142.6, 147.9, 154.4, 169.4, 176.6; IR (KBr) ν: 3199, 1712, 1662, 1599 cm^{-1}; LRMS (EI) m/z 406 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{21}H_{15}{}^{37}ClN_4O_3$ [M+H]$^+$ 409.0890; found: 409.0902.

*(±)-**6**:* 72% from (±)-*exo*-**41e**, a white solid, ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.21 (s, 3H), 2.41 (dd, J = 3.6, 14.4 Hz, 1H), 2.50 (d, J = 14.4 Hz, 1H), 5.58 (s, 1H), 6.95 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 2.0 Hz, 1H), 7.39 (dd, J = 2.0, 8.0 Hz, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.88 (ddd, J = 1.2, 7.8, 8.4 Hz, 1H), 8.21 (dd, J = 1.2, 8.0 Hz, 1H), 9.69 (d, J = 1.2 Hz, 1H), 10.81 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 13.3, 35.6, 51.7, 55.0, 61.7, 111.2, 119.9, 123.9, 126.0, 126.3, 127.2, 127.6, 129.0, 131.7, 134.6, 141.5, 146.7, 152.5, 158.2, 169.5, 176.2; IR (KBr) ν: 1719, 1686, 1624, 1475 cm^{-1}; LRMS (FAB) m/z 407 [M+H]$^+$; HRMS (FAB) m/z Calcd for $C_{21}H_{16}{}^{35}ClN_4O_3$ [M+H]$^+$ 407.0911; found: 407.0887.

*(±)-**7**:* 90% from (±)-*exo*-**41f**, a white solid, mp >300 °C (MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.20 (s, 3H), 2.41 (dd, J = 3.2, 14.8 Hz, 1H), 2.49 (d, J = 14.8 Hz, 1H), 5.57 (s, 1H), 6.95 (d, J = 8.4 Hz, 1H), 7.17 (s, 1H), 7.40 (ddd, J = 0.8, 2.4, 8.4 Hz, 1H), 7.73 (dd, J = 0.8, 8.4 Hz, 1H), 7.90 (ddd, J = 1.6, 2.4, 8.4 Hz, 1H), 8.15 (dd, J = 1.2, 2.4 Hz, 1H), 9.71 (s, 1H), 10.82 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 13.2, 35.5, 51.9, 55.0, 61.6, 111.3, 121.3, 123.9, 125.3, 126.1, 129.0, 129.8, 131.5, 131.6, 134.8, 141.5, 145.4, 153.0, 157.3, 169.3, 176.2; IR (KBr) ν: 1672, 1626, 1464, 1319 cm^{-1}; LRMS (EI) m/z 440 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{21}H_{15}{}^{35}Cl_2N_4O_3$ [M+H]$^+$ 441.0521; found: 441.0509.

*(±)-**8**:* 17% (2 steps) from from **34e** and **35a**, a colorless solid, mp >300 °C (MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.37–2.47 (m, 2H), 2.71 (d, J = 14.8 Hz, 1H), 3.45 (d, J = 14.8 Hz, 1H), 5.60 (br s, 1H), 6.87 (d, J = 7.6 Hz, 1H), 7.12–7.15 (m, 4H), 7.27 (d, J = 7.6 Hz, 1H), 7.28 (d, J = 7.6 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.89 (t, J = 8.0 Hz, 1H), 8.22 (d, J = 8.0 Hz, 1H), 9.11 (s, 1H), 10.51 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 32.4, 37.5, 51.8, 55.3, 65.2, 110.0, 120.0, 122.4, 124.3, 126.4, 126.6, 127.4, 127.5 (2C), 127.7, 129.3, 129.7, 131.3 (2C), 134.0, 134.8, 142.8, 146.5, 151.5, 158.4, 169.7, 170.4; IR (KBr) ν: 3264, 1701, 1628, 1473 cm^{-1}; LRMS (EI) m/z 448 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{27}H_{21}N_4O_3$ [M+H]$^+$ 449.1614; found: 449.1570.

*(±)-**9**:* 27% (2 steps) from **34f** and **35a**, a white solid, mp >300 °C (MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.14 (d, J = 6.8 Hz, 3H), 1.22 (d, J = 6.4 Hz, 3H), 2.01 (qui, J = 6.8 Hz, 1H), 2.24 (d, J = 14.0 Hz, 1H), 2.43 (dd, J = 4.0, 14.0 Hz, 1H), 5.56 (br s, 1H), 6.92 (d, J = 7.6 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 7.6 Hz, 1H), 7.33 (d, J = 6.8 Hz, 1H), 7.61 (t, J = 7.6 Hz, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.88 (t, J = 7.6 Hz, 1H), 8.21 (d, J = 8.0 Hz, 1H), 9.52 (br s, 1H), 10.65 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 16.4, 18.3, 30.7, 48.5, 51.2, 54.1, 66.9, 110.1, 119.9, 122.2, 123.9, 126.1, 127.1, 127.8, 129.0, 130.2, 134.5, 141.7, 146.5, 150.9, 158.5, 169.7, 177.8; IR (KBr) ν: 3183, 1709, 1617, 1471, 1370, 1331 cm^{-1}; LRMS (EI) m/z 400 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{23}H_{21}N_4O_3$ [M+H]$^+$ 401.1614; found: 401.1637.

*(±)-**10**:* quant. from (±)-*exo*-**41i**, a colorless solid, mp >300 °C (MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.81 (d, J = 6.4 Hz, 3H), 0.88 (d, J = 6.4 Hz, 3H), 1.02 (dd, J = 5.2, 14.0 Hz, 1H), 2.07–2.18 (m, 2H), 2.34 (s, 2H), 5.59 (s, 1H), 6.91 (d, J = 7.6 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 7.23 (d, J = 7.6 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.61 (t, J = 7.6 Hz, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.88 (t, J = 7.6 Hz, 1H), 8.22 (d, J = 7.6 Hz, 1H), 9.17 (s, 1H), 10.61 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 23.1, 23.9 (2C), 33.6, 37.0, 51.5, 55.9, 65.3, 109.6, 119.9, 122.3, 124.6, 126.2, 127.1, 127.7, 129.1, 129.9, 134.6, 142.5, 146.5, 151.4, 158.3, 170.0, 176.4; IR (KBr) ν: 3318, 1700, 1665, 1619, 1467 cm^{-1}; LRMS (EI) m/z 414 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{24}H_{23}N_4O_3$ [M+H]$^+$ 415.1770; found: 415.1751.

*(±)-**16**:* 10% (2 steps) from from **34a** and **35c**, a colorless solid, mp 275-277 °C (MeOH);^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.72 (s, 3H), 2.94–3.02 (m, 2H), 3.60 (s, 3H), 5.84 (d, J = 2.4 Hz, 1H), 6.45 (s, 1H), 7.19 (d, J = 6.8 Hz, 2H), 7.30–7.39 (m, 3H), 7.52 (ddd, J = 1.2, 7.4, 7.4 Hz, 1H), 7.78 (ddd, J = 1.2, 7.4, 7.6 Hz, 1H), 7.82 (t, J = 7.6 Hz, 1H), 8.30 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 16.3, 37.8, 52.1, 52.7, 58.5, 62.6, 120.3, 126.9, 127.4, 128.1 (2C), 128.2, 128.3, 128.5 (2C), 134.6, 137.0, 147.4, 153.2, 159.1, 169.7, 172.7; IR (KBr) ν: 1739, 1626, 1458, 1389, 1331, 1242 cm^{-1}; LRMS (EI) m/z 389 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{22}H_{20}N_3O_4$ [M+H]$^+$ 390.1454; found: 390.1436.

*(±)-**17**:* 59% from (±)-**41j-MP**, a colorless amorphus solid, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.34 (t, J = 7.2 Hz, 3H), 1.96 (s, 3H), 2.12–2.19 (m, 1H), 2.35 (td, J = 2.8, 13.6 Hz, 1H), 2.84 (dd, J = 4.0, 13.6 Hz, 1H), 3.77 (s, 3H), 4.12–4.30 (m, 2H), 5.89 (s, 1H), 7.47–7.50 (m, 1H), 7.75–7.78 (m, 2H), 8.27 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.9, 20.8, 30.0, 45.0, 47.5, 52.2, 63.4, 63.6, 120.1, 126.7, 126.9, 127.8, 134.4, 147.5, 155.7, 159.0, 170.6, 171.9; IR (KBr) ν: 1674, 1641, 1473, 1431, 1373 cm^{-1}; LRMS (EI) m/z 341 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{18}H_{20}N_3O_4$ [M+H]$^+$ 342.1454; found: 342.1451.

*(±)-**18**:* 82% from (±)-*exo*-**41l-LP**, a colorless solid, mp >300 °C (MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.94 (s, 3H), 3.42 (d, J = 8.4 Hz, 1H), 4.02 (dd, J = 4.0, 8.0 Hz, 1H), 5.62 (dd, J = 2.0, 4.0 Hz, 1H), 7.21 (d, J = 7.6 Hz, 2H), 7.48 (t, J = 7.6 Hz, 1H), 7.56 (t, J = 7.6 Hz, 2H), 7.63 (t, J = 7.6 Hz, 1H), 7.78 (d, J = 7.6 Hz, 1H), 7.90 (ddd, J = 1.2, 7.2, 7.6 Hz, 1H), 8.21 (d, J = 8.0 Hz, 1H), 9.64 (d, J = 1.2 Hz, 1H); ^{13}C NMR (DMSO-d_6, 150 MHz) δ: 16.4, 44.6, 48.3, 53.1, 59.1, 121.0, 127.0, 127.4 (2C), 128.2, 128.3, 129.5, 129.7 (2C), 132.4, 135.4, 147.3, 154.1, 158.9, 166.8, 173.3, 173.8; IR (KBr) ν: 1717, 1623, 1468, 1389, 1182 cm^{-1}; LRMS (FAB) m/z 401 [M+H]$^+$; HRMS (FAB) m/z Calcd for $C_{22}H_{17}N_4O_4$ [M+H]$^+$ 401.1250; found: 401.1221.

*(±)-**20**:* 60% from (±)-*endo*-**41b**, a white solid, mp >300 °C (MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.22, (s, 3H), 2.31 (dd, J = 3.6, 14. Hz, 1H), 2.55 (d, J = 14 Hz, 1H), 5.55 (s, 1H), 5.92 (d, J = 7.6 Hz, 1H), 6.68 (t, J = 7.6 Hz, 1H), 6.86 (t, J = 7.6 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.72 (t, J = 8.8 Hz, 1H), 7.90 (dd, J = 2.8, 8.8 Hz,

1H), 8.20 (d, J = 2.4 Hz, 1H), 9.34 (s, 1H), 10.95 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 12.3, 35.1, 52.4, 52.6, 62.0, 109.5, 121.7, 122.2, 123.5, 125.6, 128.9, 129.1, 130.0, 131.9, 135.0, 142.4, 145.1, 152.9, 157.3, 168.7, 177.1; IR (KBr) ν: 3202, 1739, 1622, 1469 cm^{-1}; LRMS (EI) m/z 406 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{21}H_{16}{}^{37}ClN_4O_3$ [M+H]$^+$ 409.0890; found: 409.0889.

*(±)-**21**:* 67% from (±)-*endo*-**41c**, a white solid, mp >300 °C (MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.23 (s, 3H), 2.32 (dd, J = 3.2, 14 Hz, 1H), 2.56 (d, J = 14 Hz, 1H), 5.56 (s, 1H), 5.90 (d, J = 7.6 Hz, 1H), 6.67 (t, J = 7.6 Hz, 1H), 6.87 (d, J = 7.6 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.77 (d, J = 6.0 Hz, 2H), 7.94 (d, J = 8.4 Hz, 1H), 9.31 (s, 1H), 10.75 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 13.3, 35.1, 52.3, 52.6, 61.9, 109.5, 111.3 (d, J =29 Hz), 121.5 (d, J = 8 Hz), 121.6, 123.3 (d, J = 24 Hz), 123.4, 128.9, 129.2, 130.7 (d, J = 9 Hz), 142.4, 143.2, 151.9, 157.6 (d, J = 3 Hz), 160.5 (d, J = 245 Hz), 168.7, 177.1; IR (KBr) ν: 3188, 1740, 1709, 1626, 1484 cm^{-1}; LRMS (EI) m/z 390 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{21}H_{16}FN_4O_3$ [M+H]$^+$ 391.1206; found: 391.1220.

*(±)-**22**:* 86% from (±)-*endo*-**41d**, a white solid, mp >300 °C (MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.20 (s, 3H), 2.31 (dd, J = 3.6, 14.4 Hz, 1H), 2.53 (dd, J = 1.6, 14.4 Hz, 1H), 5.53–5.54 (m, 1H), 5.93 (d, J = 7.2 Hz, 1H), 6.69 (ddd, J = 0.8, 7.6, 7.7 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 7.14 (ddd, J = 0.8, 7.8, 8.0 Hz, 1H), 7.66 (dd, J = 2.0, 8.8 Hz, 1H), 7.77 (d, J = 2.0 Hz, 1H), 8.24 (d, J = 8.8 Hz, 1H), 9.32 (d, J = 1.6 Hz, 1H), 10.77 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 13.3, 35.0, 52.2, 52.5, 62.0, 109.5, 119.1, 121.7, 123.4, 127.0, 128.0, 128.6, 128.9, 129.0, 139.5, 142.3, 147.5, 153.8, 157.6, 168.7, 177.0; IR (KBr) ν: 3445, 1735, 1707, 1603 cm^{-1}; LRMS (EI) m/z 406 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{21}H_{16}{}^{37}ClN_4O_3$ [M+H]$^+$ 409.0890; found: 409.0873.

*(±)-**23**:* 83% from (±)-*endo*-**41e**, a white solid, ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.24 (s, 3H), 2.43 (dd, J = 4.0, 10.0 Hz, 1H), 2.52 (d, J = 10.0 Hz, 1H), 5.55 (s, 1H), 5.93 (d, J = 1.6 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 7.21 (dd, J = 2.0, 8.4 Hz, 1H), 7.66 (t, J = 7.6 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.90 (ddd, J = 1.2, 7.2, 7.6 Hz, 1H), 8.27 (d, J = 8.0 Hz, 1H), 9.35 (s, 1H), 10.92 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 13.9, 34.7, 52.6, 53.6, 55.5, 62.6, 111.4, 120.8, 124.7, 125.9, 127.1, 128.3, 129.3, 131.6, 135.5, 141.9, 146.8, 152.7, 158.7, 169.4, 177.3; IR (KBr) ν: 1734, 1690, 1626, 1468, 1375, 1311 cm^{-1}; LRMS (FAB) m/z 407 [M+H]$^+$; HRMS (FAB) m/z Calcd for $C_{21}H_{16}{}^{35}ClN_4O_3$ [M+H]$^+$ 407.0911; found: 407.0887.

*(±)-**24**:* 92% from (±)-*endo*-**41f**, a white solid, mp >300 °C (MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 1.23 (s, 3H), 2.45 (dd, J = 3.6, 14.4 Hz, 1H), 2.53 (d, J = 14.4 Hz, 1H), 5.54 (s, 1H), 6.03 (d, J = 1.6 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 7.23 (dd, J = 1.6, 8.4 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.91 (dd, J = 2.4, 8.8 Hz, 1H), 8.17 (d, J = 2.4 Hz, 1H), 9.36 (s, 1H), 10.92 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 13.3, 34.5, 52.3, 53.1, 62.1, 110.9, 121.7, 124.2, 125.5, 125.6, 128.8, 129.9, 130.9, 131.9, 135.0, 141.4, 145.1, 152.6, 157.3, 168.7, 176.8; IR (KBr) ν: 1693, 1626, 1475, 1373 cm^{-1}; LRMS (EI) m/z 440 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{21}H_{15}{}^{35}Cl_2N_4O_3$ [M+H]$^+$ 441.0521; found: 441.0509.

*(±)-**25**:* 32% (2 steps) from **34e** and **35a**, a colorless solid, mp >300 °C (MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 2.31 (dd, J = 3.6, 14.0 Hz, 1H), 2.58 (d, J = 14.0 Hz, 1H), 2.97 (d, J = 14.8 Hz, 1H), 3.18 (d, J = 14.8 Hz, 1H), 5.59 (br s, 1H), 5.89 (d, J = 7.6 Hz, 1H), 6.70 (t, J = 7.6 Hz, 1H), 6.89 (d, J = 7.6 Hz, 1H), 7.13 (t, J = 7.6 Hz, 2H), 7.19 (t, J = 7.6 Hz, 2H), 7.40 (d, J = 7.2 Hz, 2H), 7.65 (t, J = 7.6 Hz, 2H), 7.88 (t, J = 7.6 Hz, 1H), 8.25 (d, J = 7.2 Hz, 1H), 8.71 (br s, 1H), 10.82 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 32.0, 36.5, 51.9, 53.7, 65.1, 109.7, 120.1, 121.6, 123.7, 126.3, 126.5, 127.5 (2C), 127.6, 127.8, 128.9, 129.1, 131.2 (2C), 134.3, 135.0, 142.4, 145.9, 150.5, 158.1, 169.0, 179.1; IR (KBr) ν: 3229, 1686, 1625, 1471 cm^{-1}; LRMS (EI) m/z 448 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{27}H_{21}N_4O_3$ [M+H]$^+$ 449.1614; found: 449.1580.

*(±)-**26**:* 68% (2 steps) from **34f** and **35a**, a colorless solid, mp >300 °C (MeOH); ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 0.98 (d, J = 6.8 Hz, 3H), 1.06 (d, J = 6.8 Hz, 3H), 2.12 (dd, J = 3.2, 14.0 Hz, 1H), 2.44 (qui, J = 6.8 Hz, 1H), 2.53 (dd, J = 2.4, 14.0 Hz, 1H), 5.52 (br s, 1H), 5.97 (d, J = 7.2 Hz, 1H), 6.70 (t, J = 7.6 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.67 (t, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.93 (t, J = 8.0 Hz, 1H), 8.27 (d, J = 8.0 Hz, 1H), 9.20 (br s, 1H), 10.77 (br s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 17.1, 18.4, 28.9, 51.6, 51.9 (2C), 67.9, 109.7, 120.1, 121.7, 123.5, 126.5, 127.8, 128.0, 128.8, 130.2, 135.1, 141.7, 146.2, 151.5, 158.2, 169.3, 178.3; IR (KBr) ν: 3206, 1709, 1616, 1468, 1373, 1333 cm^{-1}; LRMS (EI) m/z 400 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{23}H_{21}N_4O_3$ [M+H]$^+$ 401.1614; found: 401.1617.

*(±)-**27**:* 91% from (±)-*endo*-**41i**, a colorless solid, mp >300 °C (MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 0.99 (d, J = 6.8 Hz, 6H), 1.47 (dd, J = 6.8, 14.8 Hz, 1H), 2.03 (dd, J = 4.8, 14.8 Hz, 1H), 2.16–2.22 (m, 1H), 2.29 (dd, J = 4.0, 14.4 Hz, 1H), 2.77 (dd, J = 1.6, 14.4 Hz, 1H), 5.85 (d, J = 7.2 Hz, 1H), 5.95 (dd, J = 1.6, 1.6 Hz, 1H), 6.60 (s, 1H), 6.75 (t, J = 8.0 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.61 (t, J = 7.2 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.83 (ddd, J = 1.2, 7.6, 7.6 Hz, 1H), 7.93 (s, 1H), 8.41 (dd, J = 1.2, 8.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 23.1, 23.6, 23.8, 33.6, 36.2, 54.0, 57.8, 65.3, 109.5, 120.0, 121.5, 123.5, 126.4, 127.6, 127.8, 128.8, 129.1, 134.9, 147.2, 145.9, 151.0, 158.1, 169.3, 177.2; IR (KBr) ν: 2920, 1700, 1619, 1560, 1467 cm^{-1}; LRMS (EI) m/z 414 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{24}H_{23}N_4O_3$ [M+H]$^+$ 415.1770; found: 415.1786.

*(±)-**32**:* 13% (2 steps) from **34a** and **35c**, a colorless solid, mp 257–259 °C (MeOH);^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.87 (s, 3H), 2.98 (dd, J = 2.4, 15.6 Hz, 1H), 3.04 (dd, J = 3.2, 15.6 Hz, 1H), 3.79 (s, 3H), 5.88 (d, J = 2.4 Hz, 1H), 6.51 (s, 1H), 6.71 (d, J = 7.6 Hz, 2H), 7.11 (t, J = 7.6 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 7.2 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.53 (t, J = 8.0 Hz, 1H), 7.72 (ddd, J = 1.2, 7.6, 7.6 Hz, 1H), 8.35 (dd, J = 1.2, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.4, 37.6, 51.7, 52.8, 59.0, 63.6, 120.3, 126.9 (2C), 127.0, 127.5, 128.0, 128.2, 128.4 (2C), 134.6, 137.4, 146.9, 152.2, 159.0, 169.0, 173.0; IR (KBr) ν: 1697, 1604, 1560, 1450, 1369 cm^{-1}; LRMS (EI) m/z 389 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{22}H_{20}N_3O_4$ [M+H]$^+$ 390.1454; found: 390.1417.

*(±)-**33**:* 67% from (±)-**41j-LP**, a colorless solid, mp 214–218 °C (MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.25 (s, 3H), 1.84 (s, 3H), 2.38–2.52 (m, 2H), 2.88 (dd, J = 5.2, 9.6 Hz, 1H), 5.77–5.79 (m, 1H), 6.38 (br s, 1H), 7.53 (ddd, J = 1.2, 7.4, 7.4 Hz, 1H), 7.72 (d, J = 7.2 Hz, 1H), 7.78 (ddd, J = 1.2, 7.6, 9.5 Hz, 1H), 8.30 (dd, J = 1.6, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 17.2, 29.3, 45.7, 52.0, 52.6, 59.1, 120.7, 127.0, 127.6, 127.9, 134.7, 147.1, 153.4, 158.9, 169.0, 171.3; IR (KBr) ν: 1709, 1626, 1367, 1213, 1176 cm^{-1}; LRMS (EI) m/z 313 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{16}H_{16}N_3O_4$ [M+H]$^+$ 314.1141; found: 314.1139.

3.1.5. Synthesis of 2-methyl-alantrypinone ((±)-11)

To a solution of (±)-*exo*-**41e** (80 mg, 200 μmol) in THF (1 mL) was added a solution of *n*-BuLi (210 μmol) at −78 °C and the mixture was stirred for 30 min at −78 °C. To the mixture was added benzenesulfonyl chloride (130 μL, 210 μmol) for 5 h at −78 °C. The reaction was quenched by the addition of satd aq NH_4Cl and the organic compounds were extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography (hexane/AcOEt = 2:1) to give (±)-*exo*-**42c** (75 mg, 69%) as a colorless amorphous solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.15 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H), 2.16 (dd, J = 2.0, 14 Hz, 1H), 2.47 (dd, J = 3.2, 14 Hz, 1H), 4.25–4.27 (m, 2H), 5.98 (t, J = 2.8 Hz, 1H), 7.05 (dd, J = 0.4, 7.6 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 7.41 (ddd, J = 1.2, 8.0, 8.2 Hz, 1H), 7.49 (ddd, J = 1.2, 6.8, 7.6 Hz, 1H), 7.53 (t, J = 7.6 Hz, 2H), 7.68 (t, J = 7.6 Hz, 2H), 7.76

(ddd, J = 1.2, 7.6, 8.0 Hz, 1H), 7.99 (t, J = 7.6 Hz, 3H), 8.30 (dd, J = 1.2, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.1, 16.6, 38.6, 47.2, 54.6, 63.8, 67.5, 113.6, 120.2, 124.3, 125.3, 126.7, 126.8, 127.9 (2C), 128.1, 129.0, 129.2 (2C), 129.7, 134.3, 134.7, 137.7, 139.6, 147.5, 152.8, 159.2, 172.6, 174.6; IR (KBr) ν: 1751, 1687, 1628, 1460, 1389 cm^{-1}; LRMS (EI) m/z 540 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{29}H_{25}N_4O_5S$ [M+H]$^+$ 541.1546; found: 541.1502.

A solution of (±)-*exo*-**42c** (75 mg, 139 μmol) in AcOEt (5 mL) and 1.0 N HCl (0.5 mL) was stirred at room temperature for 3 h. After removal of the solvent, the residue was washed with MeOH to give 18-benzenesulfonyl-alantrypinone (70 mg, 98%) as a colorless solid. To a solution of 18-benzenesulfonyl-alantrypinone (70 mg, 137 μmol) and NaH (4 mg, 165 μmol) in THF (1.0 mL) was added MeI (10 μL, 165 μmol) at 0 °C and the mixture was stirred for 2 h at 0 °C. The reaction was quenched by the addition of satd aq NH_4Cl and the organic compounds were extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography (hexane/AcOEt = 1:1) to give **43** (28 mg, 39%) as a colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.25 (s, 3H), 2.34 (dd, J = 2.4, 14.4 Hz, 1H), 2.53 (dd, J = 3.2, 14.4 Hz, 1H), 2.88 (s, 3H), 5.94 (dd, J = 2.4, 3.2 Hz, 1H), 7.05 (dd, J = 1.2, 7.6 Hz, 1H), 7.26–7.30 (m, 1H), 7.48 (ddd, J = 1.2, 7.6, 8.0 Hz, 1H), 7.52–7.56 (m, 3H), 7.67–7.72 (m, 2H), 7.79 (ddd, J = 1.6, 7.2, 7.6 Hz, 1H), 8.00–8.04 (m, 3H), 8.32 (dd, J = 1.6, 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.7, 28.6, 36.4, 50.9, 55.8, 66.5, 114.1, 120.8, 123.9, 126.0, 127.0, 127.4, 127.9 (2C), 128.0, 128.2, 129.3 (2C), 130.5, 134.5, 134.9, 137.4, 139.7, 147.1, 150.4, 158.9, 168.8, 173.6; IR (KBr) ν: 1687, 1624, 1459, 1374, 1232, 1185, 1154, 1084, 957, 755 cm^{-1}; LRMS (EI) m/z 526 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{28}H_{22}N_4O_5S$ [M+H]$^+$ 527.1389; found: 527.1385.

To a solution of **43** (25 mg, 47 μmol) in THF (1.0 mL) was added 0.4 M solution of Na-anthracenide in THF (0.7 mL, 280 μmol) at −78 °C and the mixture was stirred for 30 min at −78 °C. The reaction was quenched by the addition of satd aq NH_4Cl and the organic compounds were extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography (hexane/AcOEt = 1:1) to give **11** (12 mg, 67%) as a colorless solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.54 (s, 3H), 2.43 (dd, J = 2.0, 14.0 Hz, 1H), 2.65 (dd, J = 3.2, 14 Hz, 1H), 2.97 (s, 3H), 6.00 (dd, J = 2.4, 2.8 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 7.07 (t, J = 7.2 Hz, 1H), 7.10 (t, J = 7.2 Hz, 1H), 7.28 (t, J = 7.6 Hz, 1H), 7.52 (t, J = 7.2 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.76 (t, J = 7.2 Hz, 1H), 8.24 (br s, 1H), 8.34 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.7, 28.7, 35.7, 51.2, 55.9, 65.9, 110.3, 120.9, 123.6, 123.9, 127.1, 127.2, 127.9, 129.6, 129.7, 134.3, 141.3, 147.2, 151.6, 159.0, 169.1, 177.0; IR (KBr) ν: 1687, 1610, 1469, 1385, 1329 cm^{-1}; LRMS (EI) m/z 386 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{22}H_{19}N_4O_3$ [M+H]$^+$ 387.1457; found: 387.1443.

3.1.6. Synthesis of (±)-12 and (±)-13

To a solution of (±)-*exo*-**41a** (10 mg, 25 μmol) and NaH (0.7 mg, 30 μmol) in THF (1.0 mL) was added MeI (1.9 μL, 30 μmol) at 0 °C and the mixture was stirred for 1.5 h at 0 °C. The reaction was quenched by the addition of satd aq NH_4Cl and the organic compounds were extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography (hexane/AcOEt = 2:3) to give (±)-*exo*-**42a** (10.4 mg, quant.) as a colorless amorphous solid. A solution of (±)-*exo*-**42a** (10 mg, 24 μmol) in AcOEt (1 mL) and 1.0 N HCl (0.5 mL) was stirred at room temperature for 30 min. After removal of the solvent, the residue was washed with MeOH to give (±)-**12** (8.8 mg, 95%) as a colorless solid. Mp >300 °C (MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.35 (s, 3H), 2.48 (dd, J = 2.0, 14.4 Hz, 1H), 2.69 (dd, J = 3.6, 14.4 Hz, 1H), 3.17 (s, 3H), 5.95 (br s, 1H), 6.39 (br s, 1H), 6.91 (d, J = 7.6 Hz, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.52 (ddd, J = 2.4, 6.8, 7.6 Hz, 1H), 7.73–7.79 (m, 2H), 8.34 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.2, 26.7, 30.4, 36.6, 54.9, 62.7, 108.7, 120.7, 123.6, 127.1, 127.2, 127.3, 128.1, 129.1, 129.7, 134.4, 144.2, 147.1, 151.7, 159.1, 170.2, 175.0; IR (KBr) ν: 3186, 1706, 1656, 1610, 1468, 1350 cm^{-1}; LRMS (EI) m/z 386 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{22}H_{19}N_4O_3$ [M+H]$^+$ 387.1457; found: 387.1440.

To a solution of (±)-**12** (6 mg, 15.5 μmol) and NaH (0.7 mg, 18.6 μmol) in THF (1.0 mL) was added MeI (1.2 μL, 18.6 μmol) at 0 °C and the mixture was stirred for 2 hours at 0 °C. The reaction was quenched by the addition of satd aq NH_4Cl and the organic compounds were extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography (hexane/AcOEt = 1:1) to give (±)-**13** (6.2 mg, quant.) as a colorless solid. Mp 294–296 °C (AcOEt); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.47 (s, 3H), 2.43 (dd, J = 2.4, 14.0 Hz, 1H), 2.64 (dd, J = 3.6, 14.0 Hz, 1H), 2.98 (s, 3H), 3.17 (s, 3H), 6.01 (dd, J = 2.8, 2.8 Hz, 1H), 6.91 (d, J = 8.0 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.40 (ddd, J = 0.8, 7.6, 8.0 Hz, 1H), 7.51 (ddd, J = 2.4, 7.6, 8.0 Hz, 1H), 7.70–7.78 (m, 2H), 8.34 (dd, J = 0.8, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.7, 26.6, 28.7, 35.7, 51.2, 55.5, 65.8, 108.7, 120.8, 123.5, 123.6, 127.0, 127.2, 128.0, 129.3, 129.7, 134.3, 144.2, 147.1, 151.6, 159.0, 169.2, 175.1; IR (KBr) ν: 1697, 1610, 1467, 1378 cm^{-1}; LRMS (EI) m/z 400 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{23}H_{21}N_4O_3$ [M+H]$^+$ 401.1614; found: 401.1584.

3.1.7. Synthesis of (±)-14 and (±)-15

To a solution of (±)-*exo*-**41a** (20 mg, 50 μmol) and NaH (2.4 mg, 100 μmol) in THF (1.0 mL) was added benzyl bromide (12 μL, 100 μmol) at 0 °C and the mixture was stirred for 3.5 h at 0 °C. The reaction was quenched by the addition of satd aq NH_4Cl and the organic compounds were extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography (hexane/AcOEt = 2:3) to give (±)-*exo*-**42b** (20.4 mg, 83%) as a colorless amorphous solid. A solution of (±)-*exo*-**42b** (20 mg, 41 μmol) in AcOEt (5 mL) and 1.0 N HCl (0.5 mL) was stirred at room temperature for 3.5 h. After removal of the solvent, the residue was washed with MeOH to give (±)-**14** (16.4 mg, 86%) as a colorless solid. Mp >300 °C (MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.38 (s, 3H), 2.51 (dd, J = 2.0, 14 Hz, 1H), 2.75 (dd, J = 3.6, 14 Hz, 1H), 4.78 (d, J = 15.6 Hz, 1H), 4.88 (d, J = 15.6 Hz, 1H), 5.97 (ddd, J = 1.6, 1.6, 2.8 Hz, 1H), 6.43 (br s, 1H), 6.83 (d, J = 8.0 Hz, 1H), 7.10 (t, J = 7.6 Hz, 1H), 7.25–7.35 (m, 7H), 7.52 (ddd, J = 3.2, 5.2, 8.0 Hz, 1H), 7.75–7.80 (m, 2H), 8.35 (dd, J = 0.4, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.2, 36.9, 44.3, 52.1, 54.8, 62.8, 109.7, 120.7, 123.6, 123.7, 127.1, 127.3, 127.5 (2C), 127.9, 128.1, 128.9 (2C), 129.2, 129.6, 134.5, 135.3, 143.3, 147.2, 151.7, 159.2, 170.7, 175.2; IR (KBr) ν: 3434, 1710, 1629, 1466, 1362 cm^{-1}; LRMS (EI) m/z 462 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{28}H_{23}N_4O_3$ [M+H]$^+$ 463.1770; found: 463.1783.

To a solution of (±)-**14** (15 mg, 32 μmol) and NaH (1.0 mg, 39 μmol) in THF (1.0 mL) was added MeI (2.4 μL, 39 μmol) at 0 °C and the mixture was stirred for 2 h at room temperature. The reaction was quenched by the addition of satd aq NH_4Cl and the organic compounds were extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography (hexane/AcOEt = 1:1) to give (±)-**15** (10.5 mg, 69%) as a colorless solid. Mp 290–291 °C (AcOEt); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.51 (s, 3H), 2.46 (dd, J = 2.0, 14 Hz,

1H), 2.70 (dd, J = 3.6, 14 Hz, 1H), 2.99 (s, 3H), 4.77 (d, J = 15.6 Hz, 1H), 4.89 (d, J = 15.6 Hz, 1H), 6.03 (dd, J = 2.0, 3.6 Hz, 1H), 6.83 (d, J = 8.0, Hz, 1H), 7.08–7.13 (m, 2H), 7.25–7.35 (m, 6H), 7.52 (ddd, J = 2.8, 6.0, 6.8 Hz, 1H), 7.74–7.79 (m, 2H), 8.35 (dd, J = 2.8, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.0, 28.7, 36.1, 44.3, 51.2, 55.4, 65.9, 109.8, 120.9, 123.65, 123.69, 127.1, 127.3, 127.5 (2C), 128.0, 128.1, 128.9 (2C), 129.4, 129.6, 134.4, 135.3, 143.4, 147.2, 151.6, 159.0, 169.2, 175.3; IR (KBr) ν: 1687, 1604, 1469, 1375cm^{-1}; LRMS (EI) m/z 476 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{29}H_{25}N_4O_3$ [M+H]$^+$ 477.1927; found: 477.1927.

3.1.8. Synthesis of 12,13-Dimethyl-2-phenyl-3a,4,12, 12a-tetrahydro-12,4-iminomethano-5-azaphthalimido[2,1, *b*]-quinazoline-6,14-dione (19)

To a solution of **18** (20 mg, 50.0 μmol) and NaH (1.5 mg, 60.0 μmol) in diethyl ether (1.0 mL) was added MeI (3 μL, 60.0 μmol) at 0 °C and the mixture was stirred for 3.5 h at 0 °C. The reaction was quenched by the addition of satd aq NH_4Cl and the organic compounds were extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was washed with hexane to give **19** (19 mg, 94%) as a colorless solid. Mp 287–289 °C (Hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.29 (s, 3H), 3.00 (s, 3H), 3.24 (d, J = 8.4 Hz, 1H), 3.65 (dd, J = 4.0, 8.4 Hz, 1H), 6.26 (d, J = 4.0 Hz, 1H), 7.20 (d, J = 7.6 Hz, 2H), 7.44 (t, J = 7.6 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.57 (t, J = 8.0 Hz, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.82 (t, J = 8.0 Hz, 1H), 8.32 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.5, 27.8, 44.3, 48.2, 52.3, 62.5, 86.5, 120.7, 126.5 (2C), 127.3, 128.1, 129.4, 129.5 (2C), 131.0, 135.0, 146.9, 152.0, 158.4, 165.1, 170.8, 172.3; IR (KBr) ν: 1730, 1619, 1499, 1370, 1164 cm^{-1}; LRMS (EI) m/z 414 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{23}H_{19}N_4O_4$ [M+H]$^+$ 415.1406; found: 415.1416.

3.1.9. Synthesis of (±)-28 and (±)-29

To a solution of (±)-*endo*-**41a** (20 mg, 250 μmol) and NaH (1.4 mg, 60 μmol) in THF (1.0 mL) was added MeI (3.7 μL, 60 μmol) at 0 °C and the mixture was stirred for 1.5 h at 0 °C. The reaction was quenched by the addition of satd aq NH_4Cl and the organic compounds were extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography (hexane/AcOEt = 2:3) to give (±)-*endo*-**42a** (10.4 mg, quant.) as a colorless amorphous solid. A solution of (±)-*endo*-**42a** (20 mg, 48 μmol) in AcOEt (1.5 mL) and 1.0 N HCl (0.5 mL) was stirred at room temperature for 30 min. After removal of the solvent, the residue was washed with MeOH to give (±)-**28** (18.6 mg, quant.) as a colorless solid. Mp 295–298 °C (MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.40 (s, 3H), 2.37 (dd, J = 3.2, 14.4 Hz, 1H), 2.77 (d, J = 14.4 Hz, 1H), 3.29 (s, 3H), 5.93 (d, J = 7.6 Hz, 1H), 5.94 (s, 1H), 6.71 (br s, 1H), 6.77 (t, J = 7.6 Hz, 1H), 6.86 (d, J = 7.6 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.81 (t, J = 7.6 Hz, 1H), 8.41 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.9, 26.7, 36.4, 52.4, 53.0, 62.7, 108.4, 123.1, 123.3, 127.2, 127.7, 128.2, 128.6, 129.4, 134.8, 140.0, 143.8, 146.8, 151.7, 158.9, 169.4, 176.1; IR (KBr) ν: 3232, 1718, 1675, 1619, 1468, 1375 cm^{-1}; LRMS (EI) m/z 386 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{22}H_{19}N_4O_3$ [M+H]$^+$ 387.1457; found: 387.1440.

To a solution of (±)-**28** (20 mg, 52 μmol) and NaH (1.5 mg, 62 μmol) in THF (1.0 mL) was added MeI (3.9 μL, 62 μmol) at 0 °C and the mixture was stirred for 2 h at 0 °C. The reaction was quenched by the addition of satd aq NH_4Cl and the organic compounds were extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography (hexane/AcOEt = 1:1) to give (±)-**29** (20.8 mg, quant.) as a colorless solid. Mp 285–288 °C (AcOEt); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.47 (s, 3H), 2.33 (dd, J = 4.0, 14.4 Hz, 1H), 2.74 (dd, J = 1.6, 14.4 Hz, 1H), 3.07 (s, 3H), 3.27 (s, 3H), 5.87 (d, J = 7.6 Hz, 1H), 6.00 (dd, J = 4.0, 7.6 Hz, 1H), 6.75 (t, J = 7.6 Hz, 1H), 6.85 (d, J = 7.6 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.80 (ddd, J = 1.6, 8.0, 8.0 Hz, 1H), 8.40 (dd, J = 1.6, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.8, 26.6, 29.0, 35.6, 51.5, 53.1, 65.9, 108.3, 120.7, 123.1, 123.2, 127.2, 127.7, 128.1, 128.9, 129.3, 134.7, 143.8, 146.8, 151.7, 158.8, 168.2, 176.2; IR (KBr) ν: 2926, 1685, 1610, 1468, 1376 cm^{-1}; LRMS (EI) m/z 400 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{23}H_{21}N_4O_3$ [M+H]$^+$ 401.1614; found: 401.1595.

3.1.10. Synthesis of (±)-30 and (±)-31

To a solution of (±)-*endo*-**41a** (30 mg, 75 μmol) and NaH (4.0 mg, 150 μmol) in THF (1.0 mL) was added benzyl bromide (18 μL, 150 μmol) at 0 °C and the mixture was stirred for 3.5 h at 0 °C. The reaction was quenched by the addition of satd aq NH_4Cl and the organic compounds were extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography (hexane/AcOEt = 2:3) to give (±)-*endo*-**42b** (31 mg, 84%) as a colorless amorphous solid. A solution of (±)-*endo*-**42b** (44 mg, 90 μmol) in AcOEt (3 mL) and 1.0 N HCl (0.5 mL) was stirred at room temperature for 3.5 h. After removal of the solvent, the residue was washed with MeOH to give (±)-**30** (29 mg, 74%) as a colorless solid. Mp >300 °C (MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.38 (s, 3H), 2.40 (dd, J = 3.6, 13.6 Hz, 1H), 2.83 (d, J = 13.6 Hz, 1H), 4.83 (d, J = 15.6 Hz, 1H), 5.07 (d, J = 15.6 Hz, 1H), 5.91 (d, J = 7.6 Hz, 1H), 5.96 (br s, 1H), 6.28 (s, 1H), 6.74 (t, J = 7.6 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 7.16 (t, J = 8.0 Hz, 1H), 7.30-7.35 (m, 5H), 7.59 (t, J = 8.0 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H), 7.80 (t, J = 8.0 Hz, 1H), 8.40 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 13.6, 35.5, 43.3, 52.2, 52.4, 62.2, 109.3, 120.2, 122.4, 123.4, 126.7, 127.6 (2C), 127.7, 127.8, 127.9, 128.5, 128.8 (2C), 129.1, 135.1, 136.3, 143.0, 146.4, 152.3, 158.2, 168.9, 175.7; IR (KBr) ν: 3229, 1716, 1677, 1618, 1468, 1371 cm^{-1}; LRMS (EI) m/z 462 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{28}H_{23}N_4O_3$ [M+H]$^+$ 463.1770; found: 463.1747.

To a solution of (±)-**30** (20 mg, 43 μmol) and NaH (1.2 mg, 52 μmol) in THF (1.0 mL) was added MeI (3.9 μL, 52 μmol) at 0 °C and the mixture was stirred for 2 h at room temperature. The reaction was quenched by the addition of satd aq NH_4Cl and the organic compounds were extracted with AcOEt and the combined organic layers were washed with brine and dried over Na_2SO_4. After removal of the solvent, the residue was subjected to column chromatography (hexane/AcOEt = 1:1) to give (±)-**31** (17 mg, 83%) as a colorless solid. Mp 138–140 °C (AcOEt); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.47 (s, 3H), 2.36 (dd, J = 4.0, 14 Hz, 1H), 2.78 (dd, J = 2.0, 14 Hz, 1H), 3.07 (s, 3H), 4.81 (d, J = 15.2 Hz, 1H), 5.07 (d, J = 15.2 Hz, 1H), 5.86 (d, J = 7.6 Hz, 1H), 6.02 (dd, J = 2.0, 4.0 Hz, 1H), 6.72 (t, J = 7.6 Hz, 1H), 6.80 (d, J = 8.0 Hz, 1H), 7.15 (ddd, J = 0.8, 7.6, 7.6 Hz, 1H), 7.29–7.38 (m, 5H), 7.58 (ddd, J = 0.8, 7.6, 7.6 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.80 (ddd, J = 1.6, 7.6, 7.6 Hz, 1H), 8.39 (dd, J = 0.8, 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 12.9, 29.0, 35.9, 44.3, 51.5, 53.0, 66.1, 109.3, 120.7, 123.1, 123.2, 127.2, 127.5 (2C), 127.7, 128.0, 128.1, 128.87, 128.90 (2C), 129.2, 134.7, 135.4, 143.0, 146.7, 151.7, 158.8, 168.1, 176.4; IR (KBr) ν: 1718, 1610, 1473, 1375 cm^{-1}; LRMS (EI) m/z 476 [M]$^+$; HRMS (FAB) m/z Calcd for $C_{29}H_{25}N_4O_3$ [M+H]$^+$ 477.1927; found: 477.1946.

3.2. Patch–clamp recording procedures

The thoracic and the sixth abdominal ganglia were excised from male adult American cockroaches (*P. americana* L.) and incubated

for 60 min at room temperature in a cockroach saline solution containing collagenase (0.5 mg/mL; Sigma–Aldrich) and trypsin (0.5 mg/mL; Sigma–Aldrich) without Ca^{2+} and Mg^{2+}. The ganglia were then rinsed twice in a normal saline solution (in mM): 167 NaCl, 3.1 KCl, 5 $CaCl_2$, 4 $MgCl_2$, 10 Hepes, 10 glucose, and 10 ppm phenol red (pH adjusted to 7.4 with NaOH), and mechanically dissociated by gentle repeated trituration through a fire-polished Pasteur pipette.

Membrane currents were recorded with the whole-cell recording configuration[11] using a patch–clamp amplifier (EPC-8; HEKA, Lambrecht/Pfalz, Germany) linked to a computer. Recording procedures were controlled by pCLAMP software (Axon Instruments, Sunnyvale, CA). Data were low-pass filtered with a cutoff frequency of 1 kHz and then digitized at 2 kHz by an analog-to-digital interface. Fast and slow capacitative transients were canceled by the compensation circuitry of EPC-8. Cells were voltage-clamped at a membrane potential of −80 mV. Patch pipettes were pulled from borosilicate glass capillaries (Warner Instruments, Hamden, CT) on a puller (P-97; Sutter Instrument, Novato, CA) and had a resistance of 5 MΩ when filled with a pipette solution, which contained (in mM): 15 NaCl, 170 KCl, 0.5 $CaCl_2$, 1 $MgCl_2$, 10 EGTA, 10 Hepes, 5 ATP–Tris, and 20 sodium pyruvate (pH adjusted to 7.4 with KOH). GABA was dissolved in the cockroach saline solution and ejected through the hole of the polyethylene tubing that was located close to the cell (≈100 μm). (+)-**1** dissolved in dimethyl sulfoxide (DMSO) was diluted with the saline solution at final DMSO concentrations of 0.1% (v/v) or less. Solutions of control and (+)-**1** were applied by perfusion using a VC-6M valve control system (Warner Instruments) at a flow rate of 1 mL/min.

3.3. [^{3}H]EBOB binding assays using housefly-head membranes

The heads of adult houseflies (*Musca domestica* L.) were homogenized in 10 mM Tris–HCl buffer, pH 7.5, containing 0.25 M sucrose (buffer A) with a glass-Teflon homogenizer; then, the homogenate was filtered through two layers of 64-μm mesh nylon screen and centrifuged at 500*g* for 5 min. The supernatant was filtered through two layers of 64-μm mesh nylon screen and centrifuged at 25,000*g* for 30 min. The pellets were suspended in buffer A and were kept on an ice bath for 30 min. The suspension was centrifuged at 25,000*g* for 30 min. The pellets were suspended in 10 mM sodium phosphate buffer, pH 7.5, containing 0.3 M NaCl (buffer B) and were used immediately for the binding assays.

The homogenates containing housefly-head membranes (200 μg as protein) were incubated with various concentrations of test compounds and 0.5 nM [^{3}H]EBOB in 1 mL of buffer B at 22 °C for 70 min. Test compounds were added as DMSO solutions (4 μL) in buffer B. The protein content was measured by the method of Bradford.[12] After the incubation, the mixture was filtered through Whatman GF/B filters and rapidly rinsed twice with 5 mL of cold buffer B using a Brandel M-24 cell harvester. The radioactivity of [^{3}H]EBOB on the filters was measured with a liquid scintillation counter. Nonspecific binding was determined in the presence of 1 μM α-endosulfan. Experiments were repeated at least three times.

3.4. Homology modeling and docking

The transmembrane segments of the human β3 GABA receptor were modeled using the cryo-electron microscopy structure of the nicotinic acetylcholine receptor of *Torpedo marmorata* obtained at 4 Å resolution (PDB entry 1OED).[13] The multiple sequence alignment of both receptor subunits was performed with the MOE 2006.08 program (Chemical Computing Group, Montreal) using the PAM250 substitution matrix, and the long loop between TM3 and TM4 was deleted because of the lack of structure data in the template. About 20 intermediary models were generated by MOE, and the raw model with the best packing quality was further refined until the root mean square gradient became 0.01, according to the molecular mechanics minimization protocol using the Merck molecular field force MMFF94x[14] in MOE. The validation tests of stereochemical quality were conducted using MOE. Only three residues from the constructed model fell outside of the acceptable regions of the Ramachandran plot (data not shown). All bond angles, bond lengths, and C_α chiralities were also found to be adequate. The structure of **3** having the same stereochemisty as that of (+)-**1** was built using the molecular modeling software SYBYL ver. 7.1 (Tripos, St. Louis, MO) and was fully optimized by the semi-empirical molecular orbital method AM1. Compound **3** was automatically docked into the potential binding site[8] of the β3 receptor model using the dock program in MOE. Compound **3** was subjected to conformational analysis, placement, and pharmacophore filtering, and was scored in terms of hydrophobic, ionic, and hydrogen bond contacts, which were generally favorable interactions. A final representation of the potential binding mode of (+)-**3** was chosen based on selection of the compound that possessed the best docking score within the most populated cluster with the lowest docking energy.

Acknowledgment

This research was partially supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan. We thank Professors T. Ishikawa and T. Kumamoto for their help with microwave irradiation experiments.

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