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Article

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KEYWORDS general anesthetics, benzocyclobutene derivatives, hydrogen bond acceptor substituent, $GABA_A$ receptor

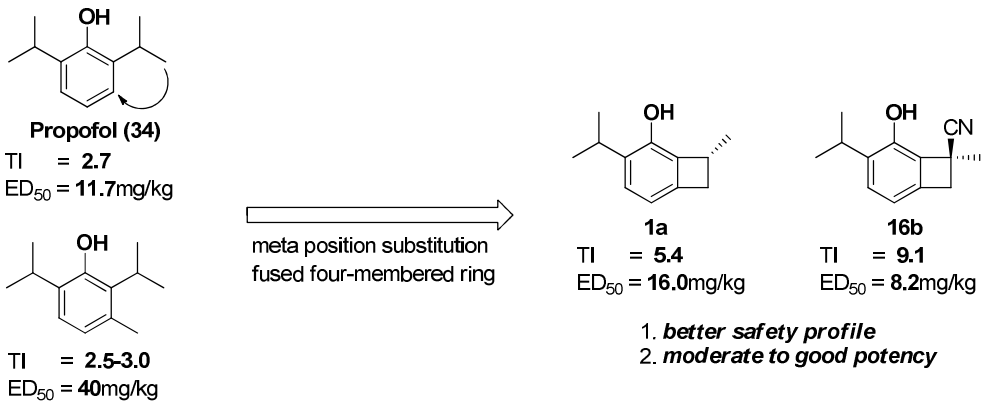
ABSTRACT In the present work, a series of structurally novel benzocyclobutene derivatives was identified as general anesthetics through the loss of righting reflex (LORR) experiment on mice. Our initial efforts found compound **1a** with a fused four-membered ring on the 2,3-position of the phenol ring could significantly improve the safety profile. Further SAR study revealed that small hydrogen bond acceptor (HBA) groups are optimal for good ED_{50} along with much broader therapeutic windows, such as compounds **16b** and **17**. Present work demonstrates the superiority of this novel benzocyclobutene scaffold.

INTRODUCTION

Propofol (2,6-diisopropylphenol, compound **34**), which was first discovered in 1977 by Kay and Rolly,[1] is now the most widely used intravenous general anesthetic in current clinical use. It

is a short-acting medication with rapid onset and offset effects,[2-3] which can be clinically used for induction and maintenance of general anesthesia, sedation for mechanically ventilated adults, and procedural sedation. Therefore, it is on the WHO Model List of Essential Medicines.[4] Despite being the most important medication needed in a health system, it is associated with side effects including pain on injection, low blood pressure related to vasodilation, respiratory depression, and propofol infusion syndrome.[5-8] Thus, the administration of compound **34** is contraindicated in multiple clinical settings. Subsequently, many existing anesthetics have been modified to improve the overall profile of compound **34**.[9-11]

Scheme 1. Design of novel anesthetics with a benzocyclobutene scaffold



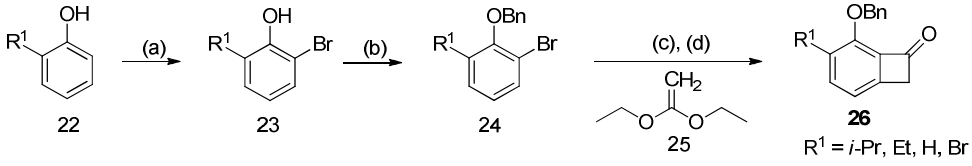
We herein report our effort on the design, synthesis and evaluation of a series of novel chemical scaffolds with improved potency and safety profiles as compared with compound **34**. A number of literature documents have reported on the structural modification of compound **34**,[3,9] among which we noticed that the meta position of the phenol ring was a suitable position for modification, for instance, methyl group substitution afforded a good therapeutic index along with acceptable potency(**Scheme 1**).[3] Reasonably, a novel benzocyclobutene scaffold was designed by fusing the isopropyl to the meta position of the phenyl ring (**Scheme 1**). Many drug molecule containing cyclobutane moiety such as ivabradine, sibutramine, butorphanol,

carboplatin, and apalutamide etc. have been launched or in late-stage clinical trial, which indicates cyclobutane moiety possesses sufficient *in vivo* stability. This modification not only reduced the molecule weight but also increased the rigidity as compared with the scaffold of compound **34**.[12] Such benzocyclobutene derivatives provided a chiral benzylic center for various substituents. Through medicinal chemistry efforts, compounds **1a** & **16b** were identified as optimal general anesthetics with much larger therapeutic windows than compound **34**.

RESULTS AND DISCUSSION

Chemistry. The synthesis of benzocyclobutene derivatives is now becoming more attractive for the synthetic community.[13-14] Drug candidates containing the benzocyclobutene scaffold have emerged.[15] Because benzocyclobutenone is an unique building block with rich reactivity,[14] it was chosen as an ideal intermediate for the quick assembly of various benzocyclobutene derivatives. As shown in **Scheme 2**, ortho-substituted phenols were brominated using NBS and then protected with a benzyl group to prepare compound **24.** This was then reacted with $NaNH_2$ and 1,1-diethoxyethene **25** followed by treatment with acid to afford benzocyclobutenone intermediate **26**.

Scheme 2. Synthesis of key intermediate 26[a]

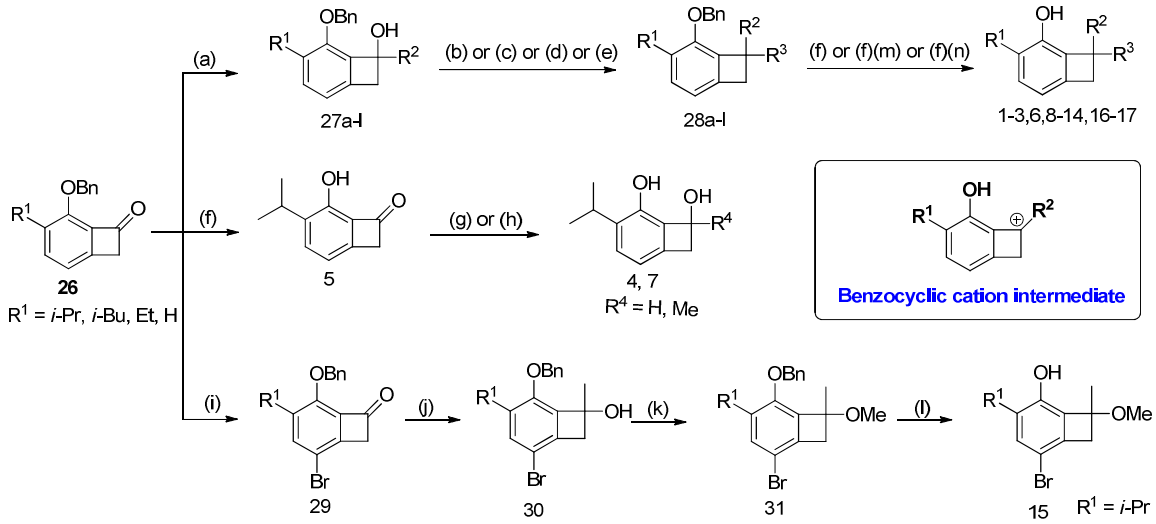


[a]Reagents and conditions: (a) NBS, $(i\text{-Pr})_2NH$, DCM; (b) BnBr, K_2CO_3, DMF; (c) $NaNH_2$, THF; (d) HCl, H_2O.

As shown in **Scheme 3**, Grignard reactions of ketone **26** led to benzocyclobutanols **27a-l**. Compounds 27a-l underwent acid-catalyzed reactions with various reagents via the benzocyclic cation intermediates to access different types of substituted benzocyclobutene derivatives

(**Scheme 3**). For example, tertiary benzocyclic cation intermediates derived from **27a-d** can be intercepted by triethylsilane to give compounds **28a-d**. Similarly, compounds **27e-k** reacted with different alcohols $R^{3'}OH$ in the presence of TsOH to form compounds **28e-k**. Compound **27l** formed the corresponding tertiary benzocyclic cation in the presence of $BF_3{\cdot}Et_2O$, following by the treatment of TMSCN to produce compound **28l**. Debenzylation reactions of compounds **28a-m** provided compounds **1-3**,**6**,**8-16**. Utilizing the tertiary benzocyclic cation intermediate again, compound **8** was successfully transformed to compound **17** using NaN_3 in the presence of CF_3COOH.

Scheme 3. Synthesis of benzocyclobutene derivatives[a]



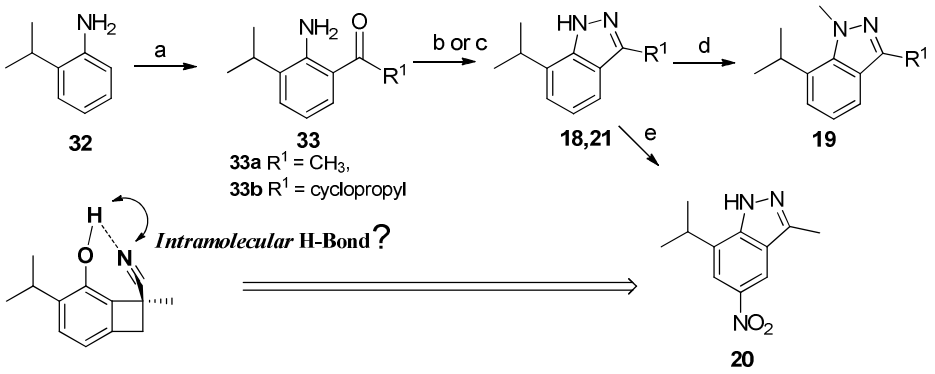
[a]Reagents and conditions: (a)R^2MgBr, THF; (b)Et_3SiH, BF_3,Et_2O, DCM; (c)TsOH, $R^{3'}OH$; (d)TMSCN, $BF_3.Et_2O$, DCM; (e)NaN_3, CF_3COOH; (f)H_2, 10% Pd/C, EtOH; (g)$NaBH_4$, MeOH; (h)R^4MgBr, THF; (i)$BnNMe_3Br_3$, HCOOH; (j)CH_3MgBr, THF; (k)TsOH, MeOH; (l)BBr_3, DCM; (m)NBS, $(i\text{-}Pr)_2NH$, DCM ; (n)NaN_3, CF_3COOH.

Debenzylation of intermediate **26** via Pd/C catalyzed hydrogenolysis provided ketone **5**, followed by reduction using $NaBH_4$ to give compound **4** or Grignard reaction with R^4MgBr to yield compound **7**. Bromination of ketone **26** afforded compound **29** which was treated with Grignard reagents to give tertiary alcohol **30**. Tertiary alcohol **30** reacted with TsOH in methanol

to furnish compound **31**, followed by debenzylation using BBr_3 in DCM to generate compound **15**.

Another set of compounds featuring an indazole-based chemical structure were prepared (**Scheme 4**, compounds **18-20**). 2-Isopropylaniline **32** was treated with BCl_3, $AlCl_3$, and alkyl nitriles to produce ketones **33**. Ketone **33a** reacted with hydroxylamine chloride and sodium hydroxide, and then treated with Et3N and MsCl to generate compound **18**. Compound **21** was generated from compound **33b** using concentrated hydrochloric acid, sodium nitrite and tin(II) chloride dehydrate. Methylation of compound **18** provided compound **19** using NaH and CH_3I. Nitration reaction transformed compound **18** into compound **20** using concentrated sulphuric acid and sodium nitrate.

Scheme 4. Synthesis of indazole derivatives[a]



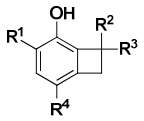
[a]Reagents and conditions: (a) BCl_3, $AlCl_3$, R^1CN; (b) NH_2OHHCl, NaOH, CH_3SO_2Cl, Et_3N; (c) $NaNO_2$, conc. HCl, $SnCl_2$; (d) NaH, CH_3I,THF; (e) H_2SO_4, $NaNO_3$.

Biological Evaluation. When the isopropyl group of compound **34** was fused to the phenyl ring, benzocyclobutene compound **1** exhibited a 2-fold broader therapeutic index with a comparable ED_{50} to compound **34** through the loss of righting reflex experiment on mice (**as explained in the experimental section**). Meanwhile, compound **1** took effect during the injection (within 10s) with an anesthesia duration over 5mins. This finding encouraged us to

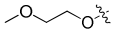
explore more of the chemistry space around this benzocyclobutene scaffold, which led to the discovery a series of novel compounds with fast on-set effect and moderate duration time (**Table 1**). Similarly, these benzocyclobutene derivatives may still associate with aforementioned side effects of compound **34** such as low blood pressure related to vasodilation and respiratory depression, which could be lethal in high dose.

Initial efforts were focused on the modification of the R^2 group in order to improve the potency, while keeping a tertiary benzylic carbon center. However, changing R^2 from methyl group to ethyl, cyclopropyl, hydroxyl or oxo groups did not enhance potencies or increase therapeutic index values (compound **2**-**5**), and the *ortho*-bromo substitution significantly reduced the potency (compound **6**).

Table 1. *In vivo* study of benzocyclobutene derivatives



Compound[a]	R^1	R^2	R^3	R^4	On-set (Sec)	Duration (Sec)	ED_{50} (mg/kg)	TI[b]
1	*i*-Pr	Me	H	H	<10	319.7±158.4	16.3	5.2
2	*i*-Pr	Et	H	H	20.2±7.0	744.3±389.3	14.3	2.4
3	*i*-Pr	▷⧘	H	H	14.9±4.8	126.6±84.4	18.5	3.6
4	*i*-Pr	OH	H	H	<10	212.3±113.7	24.5	ND
5	*i*-Pr	=O	-	H	14.9±9.9	105.6±119.02	36.9	ND
6	Br	Me	H	H	<10	124.4±51.3	39.0	ND
7	*i*-Pr	Me	OH	H	<10	401.2±315.3	27.5	ND
8	*i*-Pr	Me	OMe	H	12.8±14.5	324.8±140.7	5.8	3.8
9	*i*-Pr	Me	OEt	H	30.8±17.7	367.4±123.6	6.0	3.7

10	*i*-Pr	Me	O*i*-Pr	H	19.4±5.8	ND	ND[c]	ND
11	*i*-Pr	Me		H	20.2±7.0	ND	ND[c]	ND
12	*i*-Pr	Et	OMe	H	<10	221.0±117.1	10.0	5.8
13	*i*-Bu	Me	OMe	H	<10	343.0±21.8	5.0	ND
14	Et	Me	OMe	H	<10	211.3±145.7	16.2	>5
15	*i*-Pr	Me	OMe	Br	11.6±2.9	407.8±140.7	42.5	ND
16	*i*-Pr	Me	CN	H	<10	340.8±180.0	7.7	7.4
17	*i*-Pr	Me	N_3	H	<10	381.7±131.6	9.4	5.9

compound **34**: ED_{50} = 11.7mg/kg, TI = 2.7; ND: not determined;

a: racemic; b: TI(Therapeutic index)=LD_{50}/ED_{50}

c: unable to find a safe dosage from righting reflex experiment on mice

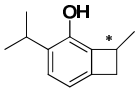
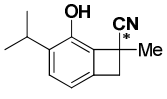
Next, benzocyclobutene derivatives with a quaternary benzylic carbon center were evaluated with various R^1 and R^3 substituents (compound **7**-**17**). Hydroxyl substitution at the R^3 position did not benefit the activity (compound **7**), however, when the hydroxyl group was alkylated to methoxyl or ethoxyl groups, these compounds showed both good potencies and TI values (compound **8**, **9**). Further, increasing the size of R^3 to the even bulkier isopropoxy or methoxy-ethoxyl (compound **10**, **11**) significantly increase the toxicity, in which the safe and effective dosage in mice could not be found. Compared to compound **8**, compound **12** was less effective when modifying R^2 from methyl to ethyl. Substitution at R^1 with isobutyl (compound **13**) has minor effects on potency, while an ethyl group as R^1 greatly decreased potency (compound **14**). Furthermore, the *para* halogen substitution decreased the potency significantly (compound **15**).

These results suggested that R^3 may favor a small hydrogen bond acceptor (HBA) to maintain a good overall profile. Subsequently, two other small HBA groups were built on the R^3 position while keeping R^1 as isopropyl. Satisfactorily, compound **16**, with a benzylic cyanide group on R^3, demonstrated a much better therapeutic index (TI=7.4) as well as a strong potency

(7.7mg/kg). Similarly, the azido group at the R^3 position (compound **17**) also showed a good potency (9.4mg/kg) and an improved TI value (TI=5.9). Herein, we have successfully discovered a series of structurally unique benzocyclobutene derivatives, featuring small HBA group on R^3, as potent and safe candidates of general anesthetics.

Furthermore, we suspected that a small HBA on R^3, like the cyano group, might have an intramolecular hydrogen bond interaction with the phenolic hydroxyl group, which could benefit both the higher potency and safety profiles (**Scheme 4**). Thus, compounds **18-20** featuring by an indazole-based chemical structure were assessed, in which case an aniline group was utilized to mimic the phenolic hydroxyl group. However, insufficient activities were detected in these cases, which indicated the importance of a phenolic hydroxyl group to maintain a good activity. Therefore the intramolecular interaction may not contribute to the better potency and safety profile.

Table 2. Chiral resolution and evaluation of compounds **1** and **16**

Compound		On-set (Sec)	Duration (Sec)	ED_{50} (mg/kg)	TI	$GABA_A$ receptor binding assay (% inh.)
Propofol	**34**	<10	303.2±97.8	11.7	2.7	IC_{50} =10 μ M[16]
	Racemic	<10	319.7±158.4	16.3±1.4	5.2±1.7	-
	**1a** (*R*)	<10	373.5±98.2	16.0±5.9	5.4±0.3	33 (10 μ M)
	1b (*S*)	<10	332.1±198.5	18.3±2.2	4.1±0.6	19 (10 μ M)
	Racemic	<10	340.8±180.0	7.7±0.1	7.4±0.5	-
	**16a** (*S*)	<10	521.4±180.6	14.3±0.1	3.7±0.2	35 (10 μ M)
	16b (*R*)	13.8±4.2	364.8±110.4	8.2±1.7	9.1±1.9	19 (10 μ M)

To further investigate the lead Compounds **1** and **16**, enantiopure compounds (Compounds **1a**, **1b**, **16a**, and **16b**) were obtained through preparative chiral HPLC, and the absolute configurations of compounds **1a** and **16b** were determined by the X-Ray crystallography of their ester derivatives of (*1S,4R*)-camphanic acid chloride. **Table 2** are summarizes the ED_{50}, TI values and $GABA_A$ receptor binding assays of these compounds. Compound **1a** was more active than its enantiomer compound **1b** along with a better TI value. The binding assay of compound **1a** was also stronger than compound **1b**, which corresponds well with their efficacies. Remarkably, compound **16b** possessed a four-fold broader therapeutic window and was more active than compound **34**. However, compound **16a** showed a better binding affinity than **16b**, which is contrary to their ED_{50} values. Although these compounds all exhibited binding affinity to $GABA_A$,[17] the mismatches of efficacies and binding assays in the case of compounds **16a** vs. **16b** or **16b** vs. **34** suggested that these compounds might also interact with other effective targets, which needs further exploration and mechanistic study.

The pharmacokinetic profiles of **1a** and **1b** were evaluated in rats owing to their good *in vivo* profile. As shown in **Table 3**, compound **1a** and **1b** demonstrated similar half-lives to compound **34**, with $t_{1/2}$ = 38 mins for **1a** and $t_{1/2}$ = 41 mins for **1b**, respectively. Compared with compound **34**, relatively low systemic clearances were observed, with Cl=77 mL/kg·min for **1a** and Cl=67 mL/kg·min for **1b**. However, the relatively low volume of distribution of each target compound resulted in an overall half-life similar to compound **34**, with V_{dss} = 2.14 L/kg for **1a** and V_{dss} = 2.53 L/kg for **1b**, respectively. Both the AUC values of **1a** and **1b** are almost 3-fold more than compound **34**, which suggests a lower dose for further clinical use.

Table 3. Pharmacokinetic Profiles of Compounds compound **34**, **1a** & **1b**

	ED_{50}	TI	$t_{1/2}$	Cl	V_{dss}	C_{max}	AUC

	(mL/kg)		(min)	(mL/kg ·min)	(L/kg)	(ng/mL)	(ng·h/mL)
34	11.7	2.7	42±13	204±9	5.23±0.67	384±56	77±4
1a	16.0±5.9	5.4±0.3	38±14	77±6	2.14±0.21	861±57	205±12
1b	18.3±2.2	4.1±0.6	41±6	67±4	2.53±0.41	728±81	227±10

CONCLUSION

We have developed a novel series of benzocyclobutene derivatives as general anesthetics, with potent anesthetic effect and much better therapeutic index than compound **34**, such as compounds **1a** and **16b**. In addition to much better pharmacokinetic profiles, these candidates predicted lower human dosage and broader therapeutic window. Subsequent results from our laboratories will detail further mechanistic studies in this series that address enhancing potency and safety window for general anesthesia.

EXPERIMENTAL SECTION

***In vivo* loss of righting reflex (LORR) assays on mice**. The on-set and duration time of anesthesia effect of benzocyclobutene derivatives was evaluated through the experiment of loss of righting reflex (LORR) using a validated rodent model of general anesthesia.[18] The tested compounds were formulated with 5% of dimethyl sulfoxide, 5-10% of Solutol HS-15 and 85-90% of saline. The fasted ICR mice were randomly divided into 7-9 dosage groups, and each dosage group has 10 ICR mice, then were administered a single intravenous bolus injection in clear or emulsion solution in the lateral tail vein, which took approximately 10 seconds. Anesthetic effects were assessed using: (1) onset of LORR, as measured by the time from dosing to LORR, (2) LORR duration as measured by the time from dosing to recovery of fighting reflex. Non-linear fitting using GraphPad Prism5 was applied to calculated ED_{50} and LD_{50} values.

Therapeutic Index (TI) was calculated by LD_{50} divided by ED_{50}. A high TI is preferable to have a favorable safety profile. The duration time of the tested compounds is corresponding to the dosage which could produce 100% LORR of the mice.

Binding assay A radioligand binding assay method was utilized to evaluate the $GABA_A$ receptor binding ability of compounds **1a**, **1b**, **16a**, and **16b**. According to Maksay and Simonyi[19], crude synaptosomal membranes of cerebral cortex of male Wistar rats were prepared for this study, and then, membrane suspension in 20 mM Tris-HCl (pH 7.4) containing 200 mM NaCl were pre-incubated with 2.0 nM [^{35}S]TBPS at 25℃. After 3 hours, the suspension was filtered under reduced pressure and washed with ice-cold buffer (3 x 3 mL). The radioactivity of the filters was measured in a scintillation counter. Nonspecific binding of the test compound was measured with 200 μM picrotoxin. $GABA_A$ receptor binding assays of the tested compounds were obtained and expressed as the percent inhibition of control specific TBPS binding.

Animals Male and female ICR mice (18-22g) and Sprague–Dawley rats (180-220g) were purchased from Vital River Laboratory Animal Technology Co., Ltd, Beijing, China. Male and female beagle dogs (7-8kg) were supplied by Dossy Experimental Animals Co., Ltd, Chengdu, China. The animals were group-housed and maintained in a controlled environment of constant temperature of 24 ± 1 ℃ and 58% humidity with a 12 h light-dark cycle and were allowed free access to food and water. Food was withdrawn 12 h prior to study. Animal facilities, animal care and study programs were in accordance with in-house guidelines of Institute of Laboratory Animal Resources, Commission on Life Science, National Research Council (National Academy Press, Washington, D.C., 2010).

General procedures All purchased starting materials were used without further purification. ^{1}H NMR spectra were acquired on a Bruker Avance-400 spectrometer (400 MHz) or a Bruker

Avance-300 spectrometer (300 MHz), with tetramethylsilane (TMS) as an internal standard; chemical shifts are expressed in parts per million (ppm, δunits). Data are reported as app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, hept = heptet, m = multiplet, br = broad, coupling constant(s) in Hz. Proton-decoupled carbon nuclear magnetic resonance spectra (^{13}C-NMR) spectra were recorded on a Bruker Avance-400 spectrometer (400 MHz) or a Bruker Avance-300 spectrometer (300 MHz), with tetramethylsilane (TMS) as an internal standard; chemical shifts are expressed in parts per million (ppm, δunits). Melting points were recorded on an OptiMelt automated melting point system and are uncorrected. Mass spectra were obtained on a FinniganLCQAd instrument (ESI). Most masses were reported as those of the protonated parent ions. Preparative column chromatography was performed using YantaiHuanghai 200-300mesh silica. CLogP values of the title compounds were calculated by Chemdraw/CLogP(Biobyte). Purities of title compounds were ≥95% by HPLC.

4-Isopropyl-7-methyl-bicyclo[4.2.0]octa-1,3,5-trien-5-ol (1). To a stirred solution of 6-(benzyloxy)-5-isopropyl-1-methyl-1,2-dihydrocyclobutabenzene (**28a**, 1.80 g，6.75 mmol) in 100 mL of methanol was added Pd/C (0.14 g, 10wt%). The mixture was stirred under a hydrogen atmosphere at room temperature for 4 hrs. The resulting solution was filtered. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (1:20 ethyl acetate/hexanes). The title compound was obtained as colorless oil (1.04 g) in 87.3% yield. $cLogP_{compound1}$=3.675. R_f=0.20 (1:20 ethyl acetate/hexanes, TLC). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (d, J = 7.4 Hz, 1H), 6.65 (d, J = 7.4 Hz, 1H), 4.42 (br s, 1H), 3.65 – 3.47 (m, 1H), 3.28 (dd, J = 13.8, 5.3 Hz, 1H), 3.18(hept, J = 6.9 Hz, 1H), 2.58 (dd, J = 13.7, 2.4 Hz, 1H), 1.41 (d, J = 7.0 Hz, 3H), 1.25 (d, J = 6.9 Hz, 3H), 1.23 (d, J = 6.9 Hz, 3H).^{13}C NMR (101 MHz,

$CDCl_3$) δ 145.18, 140.23, 132.03, 131.13, 123.87, 114.44, 35.33, 34.12, 25.29, 21.42, 21.26, 17.45. MS m/z (ESI): Calcd. for $C_{12}H_{17}O$ $[M+H]^+$ 177.1. Found: 177.1.

7-Ethyl-4-isopropyl-bicyclo[4.2.0]octa-1,3,5-trien-5-ol (2). Yellow oil; yield 67.0% (1.50 g, 7.9 mmol), $cLogP_{compound2}$=4.204. R_f =0.21 (1:30 ethyl acetate/hexanes, TLC). ^1H NMR (400 MHz, $CDCl_3$): δ7.07 (d, *J* = 7.4 Hz, 1H), 6.68 (d, *J* = 7.4 Hz, 1H), 4.58 (br s, 1H), 3.52 – 3.35 (m, 1H), 3.33 – 3.12 (m, 2H), 2.72 – 2.60 (m, 1H), 1.90 – 1.81 (m, 1H), 1.77-1.68 (m, 1H), 1.25 (app, t, *J* = 6.9 Hz, 6H), 1.09 (t, *J* = 7.3 Hz, 3H). MS m/z (ESI): Calcd. for $C_{13}H_{17}O$ $[M-H]^-$ 189.1. Found: 189.1.

8-Cyclopropyl-3-isopropylbicyclo[4.2.0]octa-1,3,5-trien-2-ol (3). Yellow solid; yield 85% (265 mg, 1.31 mmol), $cLogP_{compound3}$=4.029. R_f =0.22 (1:60 ethyl acetate/hexanes, TLC). mp: 44–46℃; ^1H NMR (400 MHz, $CDCl_3$) δ7.08 (d, *J* = 7.4 Hz, 1H), 6.67 (d, *J* = 7.4 Hz, 1H), 4.52 (s, 1H), 3.28-3.16 (m, 2H), 2.97 – 2.90 (m, 1H), 2.84 (dd, *J* = 13.8, 2.5 Hz, 1H), 1.25 (d, *J* = 6.9 Hz, 3H), 1.23 (d, *J* = 6.9 Hz, 3H), 1.12 – 1.01 (m, 1H), 0.62 – 0.54 (m, 2H), 0.40 – 0.34 (m, 1H), 0.28 – 0.21 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.08, 142.22, 132.79, 131.58, 125.93, 116.09, 45.86, 35.32, 27.14, 23.09, 22.85, 14.20, 4.42, 3.61. MS m/z (ESI): Calcd. for $C_{14}H_{17}O$ $[M-H]^-$ 201.1. Found: 201.0.

5-Isopropyl-1,2-dihydrocyclobutabenzene-1,6-diol (4). To a stirred solution of 5-hydroxy-4-isopropyl-bicyclo[4.2.0]octa-1,3,5-trien-7-one (**5**, 0.58 g, 3.29 mmol) in 15 mL of methanol was added sodium borohydride (0.25 g, 6.41 mmol). The mixture was stirred at room temperature for 0.5 hr. The reaction mixture was quenched with a saturated solution of ammonium chloride (4.0 mL), extracted with dichloromethane (50 mL×2), and dried with sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (1:15 ethyl acetate/hexanes). The title compound was obtained as white solid (350 mg) in 59.7%

yield. cLogP$_{compound4}$=1.669. R_f =0.18 (1:15 ethyl acetate/hexanes, TLC). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.22(s, 1H), 7.02 (d, J = 7.3 Hz, 1H), 6.55 (d, J = 7.3 Hz, 1H), 5.31 (d, J = 6.5 Hz, 1H), 5.08 (ddd, J = 6.5, 4.5, 1.8 Hz, 1H), 3.28 (dd, J = 13.6, 4.5 Hz, 1H), 3.17 (hept, J = 7.0 Hz, 1H), 2.72 (dd, J = 13.6, 1.8 Hz, 1H), 1.12 (d, J = 7.0 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.60, 139.94, 134.38, 130.35, 128.66, 115.76, 69.53, 41.22, 26.84, 22.95, 22.92. MS m/z (ESI): Calcd. for $C_{11}H_{13}O_2$ $[M-H]^-$ 177.1. Found: 177.0.

5-Hydroxy-4-isopropyl-bicyclo[4.2.0]octa-1,3,5-trien-7-one (5). To a stirred solution of 5-benzyloxy-4-isopropyl-bicyclo[4.2.0]octa-1,3,5-trien-7-one (**26a**, 3.50g, 13.14 mmol) in 70 mL of methanol was added Pd/C (2.1 g, 10wt%). The mixture was stirred under a hydrogen atmosphere at room temperature for 1.5 hrs. The resulting solution was filtered. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (1:15 ethyl acetate/hexanes). The title compound was obtained as white solid (1.23 g) in 53.1% yield. mp: 45–46℃, cLogP$_{compound5}$=2.918. R_f =0.25 (1:15 ethyl acetate/hexanes, TLC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (s, 1H), 7.42 (d, J = 7.3 Hz, 1H), 7.00 (d, J = 7.3 Hz, 1H), 3.87 (s, 2H), 3.31 (hept, J = 6.9 Hz, 1H), 1.23 (d, J = 6.9 Hz, 6H). MS m/z (ESI): Calcd. for $C_{11}H_{11}O_2$ $[M-H]^-$ 175.1. Found: 175.0.

4-Bromo-7-methyl-bicyclo[4.2.0]octa-1,3,5-trien-5-ol (6). White solid; yield 63% (1.6 g, 7.5 mmol). mp: 58–62℃, cLogP$_{compound6}$=3.328. R_f =0.63 (40:1 hexanes/ethyl acetate, TLC). ^{1}H NMR (400 MHz, $CDCl_3$): δ7.37-7.27 (m, 1H), 6.66 -6.44(m, 1H), 5.44 (s, 1H), 3.75-3.50 (m, 1H), 3.35 -3.15(m, 1H), 2.60 (d, J = 13.9 Hz, 1H), 1.50-1.35 (m, 3H). MS m/z (ESI): Calcd. for $C_9H_{10}BrO$ $[M+H]^+$ 213.0. Found: 212.9.

4-Isopropyl-7-methyl-bicyclo[4.2.0]octa-1,3,5-triene-5,7-diol (7). To a stirred solution of 5-hydroxy-4-isopropyl-bicyclo[4.2.0]octa-1,3,5-trien-7-one (**Compound 5**, 0.27 g, 1.40 mmol) in

10 mL of dry THF was added dropwise methylmagnesium bromide (3.0 M, 4.66 mL, 13.98 mmol) under nitrogen at -78℃. Subsequent to the addition, the reaction mixture was allowed to warm to room temperature and stirred for 10 hrs. The reaction mixture was quenched with a saturated solution of ammonium chloride (10 mL), extracted with ethyl acetate (10 mL×2), and dried with sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (1:15 ethyl acetate/hexanes). The title compound was obtained as yellow solid (130 mg) in 48% yield. $cLogP_{compound7}$=2.188. R_f =0.19 (1:15 ethyl acetate/hexanes, TLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.95 (s, 1H), 6.99 (d, J = 7.3 Hz, 1H), 6.56 (d, J = 7.3 Hz, 1H), 5.39 (s, 1H), 3.19 (hept, J = 6.9 Hz, 1H), 3.01-2.91 (m, 2H), 1.57 (s, 3H), 1.13 (d, J = 6.9 Hz, 3H), 1.12(d, J = 6.9 Hz, 3H).^{13}C NMR (100 MHz, DMSO-d_6) δ 147.4, 139.2, 135.9, 133.5, 126.7, 115.1, 76.5, 46.6, 26.8,26.7, 23.5, 23.2. MS m/z (ESI): Calcd. for $C_{12}H_{15}O_2$ $[M-H]^-$ 191.1. Found: 190.9.

4-Isopropyl-7-methoxy-7-methyl-bicyclo[4.2.0]octa-1,3,5-trien-5-ol (8). White solid; yield 41.1% (0.6 g, 3 mmol). $cLogP_{compound8}$=3.024. mp: 125–128 ℃, R_f =0.20 (1:20 ethyl acetate/hexanes, TLC). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, J = 7.4 Hz, 1H), 6.71 (d, J = 7.4 Hz, 1H), 5.14 (s, 1H), 3.36 (d, J = 14.0 Hz, 1H), 3.33 (s, 3H), 3.23 (hept, J = 6.9 Hz, 1H), 2.95 (d, J = 14.0 Hz, 1H), 1.70 (s, 3H), 1.25 (d, J = 6.9 Hz, 3H), 1.23 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.35, 139.03, 133.79, 131.44, 127.89, 116.01, 82.68, 52.17, 40.68, 26.82, 24.24, 23.03, 22.96. MS m/z (ESI): Calcd. for $C_{13}H_{17}O_2$ $[M-H]^-$ 205.1. Found: 205.1.

8-Ethoxy-3-isopropyl-8-methylbicyclo[4.2.0]octa-1,3,5-trien-2-ol (9). Yellow solid; yield 54% (0.44 g, 2 mmol). $cLogP_{compound9}$=3.413. mp: 80–84℃, R_f =0.25 (1:15 ethyl acetate/hexanes, TLC). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 7.4 Hz, 1H), 6.71 (d, J = 7.4 Hz, 1H), 5.70 (s, 1H), 3.63 – 3.52 (dq, J = 9.1, 7.0 Hz,1H), 3.51 – 3.41 (dq, J = 9.1, 7.0 Hz, 1H), 3.34 (d, J = 14.0

Hz, 1H), 3.23 (hept, *J* = 6.9 Hz, 1H), 2.98 (d, *J* = 14.0 Hz, 1H), 1.71 (s, 3H), 1.27 – 1.19 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.19, 138.91, 133.55, 132.26, 127.70, 115.97, 81.81, 60.09, 41.65, 26.82, 24.55, 22.96, 22.94, 15.75. MS m/z (ESI): Calcd. for $C_{14}H_{19}O_2$ $[M-H]^-$ 219.1. Found: 219.2.

8-Isopropoxy-3-isopropyl-8-methylbicyclo[4.2.0]octa-1,3,5-trien-2-ol (10). Yellow oil; yield 75% (0.21 g, 0.9 mmol), $cLogP_{compound\ 10}$=3.722. R_f =0.21 (1:30 ethyl acetate/hexanes, TLC). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 7.4 Hz, 1H), 6.70 (d, *J* = 7.4 Hz, 1H), 5.28 (s, 1H), 3.77 (hept, *J* = 6.2 Hz,1H), 3.28 (d, *J* = 14.0 Hz, 1H), 3.21 (hept, *J* = 6.9 Hz, 1H), 3.01 (d, *J* = 14.0 Hz, 1H), 1.68 (s, 3H), 1.26-1.21 (m, 6H), 1.19 (d, *J* = 6.2 Hz,3H), 1.13 (d, *J* = 6.2 Hz,3H). MS m/z (ESI): Calcd. for $C_{15}H_{21}O_2$ $[M-H]^-$ 233.2. Found: 233.3.

3-Isopropyl-8-(2-methoxyethoxy)-8-methylbicyclo[4.2.0]octa-1,3,5-trien-2-ol (11). Yellow oil; yield 65% (0.25 g, 1 mmol), $cLogP_{compound\ 11}$=2.779. R_f =0.22 (1:100 ethyl acetate/hexanes, TLC). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 1H), 7.15 (d, *J* = 7.4 Hz, 1H), 6.69 (d, *J* = 7.4 Hz, 1H), 3.74 – 3.62 (m, 3H), 3.53 – 3.47 (m, 1H), 3.45 (s, 3H), 3.30 (hept, *J* = 6.9 Hz,1H), 3.22 (d, *J* = 13.6 Hz, 1H), 2.99 (d, *J* = 13.6 Hz,1H), 1.68 (s, 3H), 1.228 (d, *J* = 6.9 Hz, 3H), 1,225 (d, *J* = 6.9 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 147.98, 138.72, 134.36, 131.96, 127.83, 115.63, 83.03, 73.27, 64.54, 58.96, 43.12, 26.75, 25.31, 23.01, 22.98. MS m/z (ESI): Calcd. for $C_{15}H_{21}O_3$ $[M-H]^-$ 249.1. Found: 249.3.

8-Ethyl-3-isopropyl-8-methoxybicyclo[4.2.0]octa-1,3,5-trien-2-ol (12). Yellow solid; yield 41% (0.42 g, 0.9 mmol). $cLogP_{compound\ 12}$=3.553. mp: 62–66 ℃ , R_f =0.23 (1:60 ethyl acetate/hexanes, TLC). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 7.4 Hz, 1H), 5.34 (s, 1H), 3.32 (s, 3H), 3.27 (d, *J* = 14.1 Hz, 1H), 3.24-3.17 (m, 1H), 2.95 (d, *J* = 14.1 Hz, 1H), 1.99 (q, *J* = 7.3 Hz, 2H), 1.240 (d, *J* = 6.9 Hz, 3H), 1,233 (d, *J* = 6.9 Hz, 3H), 1.06

– 1.01 (t, J = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.50, 139.55, 133.39, 130.95, 127.72, 115.96, 86.19, 52.10, 38.52, 30.66, 26.86, 22.97, 22.90, 9.51. MS m/z (ESI): Calcd. for $C_{14}H_{19}O_2$ $[M-H]^-$ 219.1. Found: 219.0.

3-(Sec-butyl)-8-methoxy-8-methylbicyclo[4.2.0]octa-1,3,5-trien-2-ol (13). Yellow oil; yield 39.4% (0.28 g, 1.3 mmol), $cLogP_{compound\mathbf{13}}$=3.553. R_f =0.18 (1:40 ethyl acetate/Petroleum ether, TLC). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (app dd, J = 7.4, 2.1 Hz, 1H), 6.71 (app dd, J = 7.4, 2.3 Hz,1H), 5.38 (s, 1H), 3.36 (d, J = 14.0 Hz, 1H), 3.32 (s, 3H), 3.02-2.91 (m, 2H), 1.70 (s, 3H), 1.68-1.54 (m, 2H), 1.22 (app dd, J = 7.0, 1.6 Hz,3H), 0.86 (app td, J = 7.4, 5.0 Hz, 3H) MS m/z (ESI): Calcd. for $C_{14}H_{19}O_2$ $[M-H]^-$ 219.1. Found: 218.9.

3-Ethyl-8-methoxy-8-methylbicyclo[4.2.0]octa-1,3,5-trien-2-ol (14). White solid; yield 77% (0.97 g, 5 mmol). $cLogP_{compound\mathbf{14}}$=2.775. mp: 77–83℃, R_f =0.25 (1:20 ethyl acetate/hexanes, TLC) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (d, J = 7.2 Hz, 1H), 6.69 (d, J = 7.2 Hz, 1H), 5.75-5.45 (br, 1H), 3.38 (d, J = 14.0 Hz, 1H), 3.34 (s, 3H), 2.95 (d, J = 14.0 Hz, 1H), 2.62 (q, J = 7.6 Hz, 2H), 1.70 (s, 3H), 1.22 (t, J = 7.6 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 148.01, 139.25, 131.34, 130.90, 129.16, 115.86, 82.42, 52.13, 40.75, 24.17, 23.17, 14.53. MS m/z (ESI): Calcd. for $C_{12}H_{15}O_2$ $[M-H]^-$ 191.1. Found: 191.0.

5-Bromo-3-isopropyl-8-methoxy-8-methylbicyclo[4.2.0]octa-1,3,5-trien-2-ol (15). To a stirred solution of 2-(benzyloxy)-5-bromo-3-isopropyl-8-methoxy-8-methylbicyclo [4.2.0]octa-1,3,5-triene (**31**, 0.55 g, 1.44 mmol) in 15 mL of dichloromethane was added dropwise a solution of boron tribromide (0.3 mL, 2.93 mmol) in 3 mL of dichloromethane at -15℃. Subsequent to the addition, the reaction mixture was allowed to warm to 0℃ and stirred for 0.5 hr. The reaction mixture was quenched with methane (3 mL), extracted with dichloromethane (15 mL×3), and dried with sodium sulfate. The solvent was removed under reduced pressure. The residue was

purified by flash column chromatography (1:20 ethyl acetate/hexanes, TLC). The title compound was obtained as yellow solid (0.22 g) in 53.6% yield. $cLogP_{compound\ 15}$=4.184. mp: 118–126℃; R_f =0.23 (1:20 ethyl acetate/hexanes). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.47 (s, 1H), 7.11 (s, 1H), 3.24-3.11 (m, 5H), 2.78 (d, J = 13.9 Hz, 1H), 1.61 (s, 3H), 1.130 (d, J = 6.9 Hz, 3H), 1.126(d, J = 6.9 Hz, 3H). MS m/z (ESI): Calcd. for $C_{13}H_{16}BrO_2$ $[M-H]^-$ 285.0. Found: 284.8.

5-Hydroxy-4-isopropyl-7-methyl-bicyclo[4.2.0]octa-1,3,5-triene-7-carbonitrile (16). White solid; yield 56% (0.36g, 1.8 mmol). $cLogP_{compound\ 16}$=2.648. mp: 125–128 ℃, R_f =0.24 (1:40 ethyl acetate/hexanes, TLC). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 7.5 Hz, 1H), 6.69 (d, J = 7.5 Hz, 1H), 6.14 (br s, 1H), 3.69 (d, J = 13.7 Hz, 1H), 3.22 (hept, J = 6.9 Hz, 1H), 3.15 (d, J = 13.7 Hz, 1H), 1.85 (s, 3H), 1.227 (d, J = 6.9 Hz, 3H), 1.221 (d, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 147.93, 139.57, 134.82, 127.93, 127.92, 123.46, 115.23, 43.61, 36.91, 26.81, 23.30, 23.28, 22.92. MS m/z (ESI): Calcd. for $C_{13}H_{16}NO$ $[M+H]^+$ 202.1. Found: 202.1.

8-Azido-3-isopropyl-8-methylbicyclo[4.2.0]octa-1,3,5-trien-2-ol (17). To a stirred solution of 4-isopropyl-7-methoxy-7-methyl-bicyclo[4.2.0]octa-1,3,5-trien-5-ol (**8**, 1.5 g, 7.27 mmol) and sodium amide (1.6 g, 23.27 mmol) in 180 mL of dichloromethane was added dropwisetrifluoroacetic acid (3.6 mL, 46 mmol) under nitrogen at 0℃. Subsequent to the addition, the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched with a saturated solution of sodium bicarbonate (80 mL), extracted with dichloromethane (80 mL×2), and dried with sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (1:100 ethyl acetate/hexanes). The title compound was obtained as a yellow solid (1.33 g) in 84.0% yield. $cLogP_{compound\ 17}$=4.348. R_f =0.30 (1:100 ethyl acetate/hexanes, TLC). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 7.7 Hz, 1H), 6.73 (d, J = 7.7 Hz, 1H), 5.70 (br s, 1H), 3.36 (d, J = 14.0 Hz,

1H), 3.25 – 3.11 (m, 2H), 1.73 (s, 3H), 1.25 (d, J = 6.8 Hz, 6H).^{13}C NMR (101 MHz, DMSO-d_6) δ 148.27, 139.03, 134.50, 130.43, 128.21, 115.15, 67.26, 44.67, 26.66, 23.65, 23.35, 23.30. MS m/z (ESI): Calcd. for $C_{12}H_{15}O$ $[M\text{-}N_3]^+$ 175.1. Found: 175.1.

7-Isopropyl-3-methyl-1H-indazole (18). To a stirred solution of 1-(2-amino-3-isopropylphenyl) ethanone **(33a** 20.0 g, 0.11 mol) and hydroxylamine hydrochloride (23.4 g, 0.34 mol) in distilled water (17.0 mL) and ethanol (93.0 mL) was added sodium hydroxide (35.2 g, 0.88 mol) under nitrogen at 0℃. Subsequent to the addition, the mixture was refluxed at 80℃ for 1 hr. The mixture was transferred to a 1-L, single-necked round-bottomed flask and concentrated. The solid residue was dissolved in distilled water (140 mL) and extracted with ethyl acetate (200 mL×2), dried over anhydrous $MgSO_4$, and concentrated *in vacuo* .The residue was dissolved in dichloromethane 100 ml. Triethylamine (22.0 g, 0.23 mol) was added *via* syringe, and the reaction mixture was stirred for 15 min at ambient temperature before being cooled to 0–5℃ in an ice/water bath. Methanesulfonyl chloride (15.5 g, 0.14 mol) was added to 300 mL dichloromethane, and the resulting solution was cooled to 0–5℃ in an ice/water bath. The cold solution of methanesulfonyl chloride was added *via* cannula to the colorless oxime mixture over 30 min. The resulting yellow solution was stirred at 0–5℃ for 1.5 h. Silica gel was added, and the green/brown solution was concentrated by rotary evaporation. The residue was purified by flash column chromatography (1:4 ethyl acetate/hexanes) to give the title compound **18** (6.3 g, 36 %) as white solid. $cLogP_{compound\,18}$=3.321. mp: 114–116℃; R_f =0.30 (1:40 ethyl acetate/hexanes, TLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.64 (s, 1H), 7.49 (d, J = 7.9 Hz, 1H), 7.15 (d, J = 7.0 Hz,1H), 7.02 (m, 1H), 3.34 (hept, J = 6.8 Hz, 1H), 2.47 (s, 3H), 1.30 (d, J = 6.8 Hz, 6H). MS m/z (ESI): Calcd. for $C_{11}H_{15}N_2$ $[M+H]^+$ 175.1. Found: 175.3.

7-Isopropyl-1,3-dimethyl-1H-indazole (19). To a stirred solution of 7-isopropyl-3-methyl-1H -indazole (**18,** 3.6 g, 20.70 mmol) in 250 mL of THF was added sodium hydride (1.65 g, 41.38 mmol) under nitrogen. The reaction mixture was stirred for 15 min at 0–5℃ in an ice/water bath, then methyl iodide (3.87 ml, 62.07 mmol) was added. The mixture was stirred at 30℃ for 3 h. The reaction mixture was poured into ice-water (100 mL), extracted with ethyl acetate (200 mL×2), and dried with sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (1:5 ethyl acetate/hexanes)to give the title compound **19** (1.1 g, 28 %) as light yellow solid. $cLogP_{compound\mathbf{19}}$=3.337. mp: 55–58℃; R_f =0.40 (1:5 ethyl acetate/hexanes, TLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.49 (d, J = 8.0 Hz,1H), 7.24 (d, J = 7.2 Hz,1H), 7.04 (t, J = 7.6 Hz,1H), 4.16 (s, 3H), 3.73 (hept, J = 6.8 Hz, 1H), 2.42 (s, 3H), 1.31 (d, J = 6.8 Hz, 6H). MS m/z (ESI): Calcd. for $C_{12}H_{17}N_2$ $[M+H]^+$ 189.1. Found: 189.2.

7-Isopropyl-3-methyl-5-nitro-1H-indazole (20). To a stirred solution of 7-isopropyl-3-methyl-1H -indazole (**18,** 1.5 g, 8.60 mmol) in 10 mL of concentrated sulfuric acid was added sodium nitrate (806 mg, 9.48 mmol) under nitrogen. The reaction mixture was stirred for 4 hrs at ambient temperature. The reaction mixture was poured into ice-water (100 mL), extracted with ethyl acetate (200 mL×2), and dried with sodium sulfate. The solvent was removed under reduced pressure. The residue was purified by flash column chromatography (1:4 ethyl acetate/hexanes) to give the title compound **20** (1.5 g, 80 %) as light yellow solid. $cLogP_{compound\mathbf{20}}$=3.424. R_f =0.40 (1:4 ethyl acetate/hexanes, TLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.42 (s, 1H), 8.62 (d, J = 2.0 Hz,1H), 7.98 (d, J = 2.0 Hz,1H), 3.42 (hept, J = 6.9 Hz, 1H), 2.58 (s, 3H), 1.35 (d, J = 6.9 Hz, 6H). MS m/z (ESI): Calcd. for $C_{11}H_{14}N_3O_2$ $[M+H]^+$ 220.1. Found: 220.1.

3-Cyclopropyl-7-isopropyl-1H-indazole (21). To a stirred solution of (2-amino-3-isopropylphenyl)(cyclopropyl)methanone (**33b**, 400 mg, 1.97 mmol) in concentrated hydrochloric acid (2 ml) was added dropwise a solution of sodium nitrite (273 mg, 3.94 mmol) in 3 ml of water with stirring at 0℃, and the mixed solution was further stirred at 0℃ for 1h. To the reaction solution was added dropwise tin (II) chloride dihydrate (823 mg, 4.33 mmol) dissolved in concentrated hydrochloric acid (2 ml), and the solution was stirred at 0℃ for 2 hours. The reaction solution was extracted with dichloromethane, the organic layer was washed with brine, dried over sodium sulfate and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by silica-gel chromatography (developing solvent: hexane / ethyl acetate = 2:1) to give the title compound **21** (280 mg, 71%) as a white solid. $cLogP_{compound\mathbf{21}}$=3.765. R_f =0.30 (1:2 ethyl acetate/hexanes, TLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.56 (s, 1H), 7.56 (d, J = 8.0 Hz,1H), 7.14 (d, J = 7.0 Hz, 1H), 7.01 (dd, J = 8.0, 7.0 Hz, 1H), 3.38-3.26 (m, 1H), 2.28-2.20 (m, 1H), 1.30 (d, J = 6.9 Hz, 6H), 0.98-0.92 (m, 4H). MS m/z (ESI): Calcd. for $C_{13}H_{17}N_2$ $[M+H]^+$ 201.1. Found: 201.2.

ASSOCIATED CONTENT

Supporting Information Available: Characterization data for compounds **1-21.** This material is available free of charge via the internet at http://pubs.acs.org.

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ABBREVIATIONS USED

DMF, N,N-dimethylformamide; NBS, *N*-bromosuccinimide; DCM, dichloromethane; BCl_3, boron trichloride; BBr_3, boron tribromide; $AlCl_3$, aluminium chloride; NaH, sodium hydride; $NaNH_2$, sodium amide; BnBr, benzyl bromide; Et_3SiH, triethylsilane; CH_3I, iodomethane; THF, tetrahydrofuran; TMSCN, cyanotrimethylsilane; MeOH, methanol; EtOH, ethanol; DMSO, dimethyl sulfoxide; Et_3N, triethylamine; p-TsOH, toluene-p-sulfonic acid; K_2CO_3, potassium carbonate.

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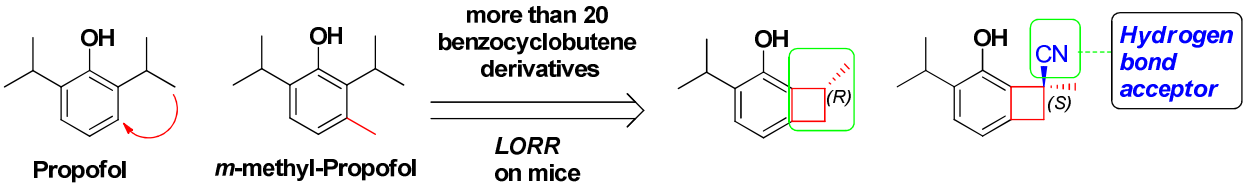
Table of Contents Graphic.



Propofol

TI = **2.7**
ED_{50} = **11.7**mg/kg

***m*-methyl-Propofol**

TI = **2.5-3.0**
ED_{50} = **40**mg/kg

TI = **5.4**
ED_{50} = **16.0**mg/kg

TI = **9.1**
ED_{50} = **8.2**mg/kg

much broader safety windows along with moderate to good potencies