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Multistep synthesis and nematicidal activity of 2-(8-azabicyclo[3.2.1]octan-3-yl)-3-imino-2,3-dihydro-1*H*-isoindol-1-one derivatives

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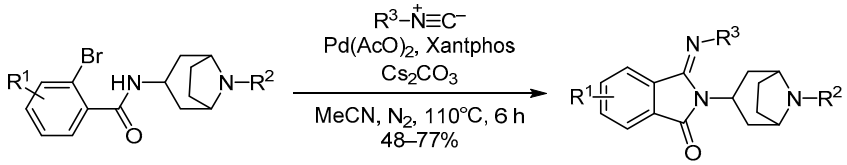


Novel 2-(8-azabicyclo[3.2.1]octan-3-yl)-3-imino-2,3-dihydro-1*H*-isoindol-1-ones derived from 5-HT_3 receptor antagonists hexahydro-azepinylbenzamides were designed and synthesized through isocyanide insertion reaction. All target compounds were evaluated against pinewood nematodes *B. xylophilus* and root-knot nematodes *M. incognita.* Good lethal rate (75%) for 3-(*tert*-butylimino)-5-chloro-2-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-2,3-dihydro-1*H*-isoindol-1-one and serious nervous curl effect against pinewood nematodes *B. xylophilus* for 3-(*tert*-butylimino)-2-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-2,3-dihydro-1*H*-isoindol-1-one were observed at 10 mg/l. The inhibition activities of 3-[(4-methoxyphenyl)imino]-2-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-2,3-dihydro-1*H*-isoindol-1-one against root-knot nematodes *M. incognita* were 84% at 160 mg/l and 60% at 20 mg/l for *in vitro* test and test tube test, respectively.

Keywords: azabicyclo, iminoisoindoline, isocyanide insertion, nematicidal activity.

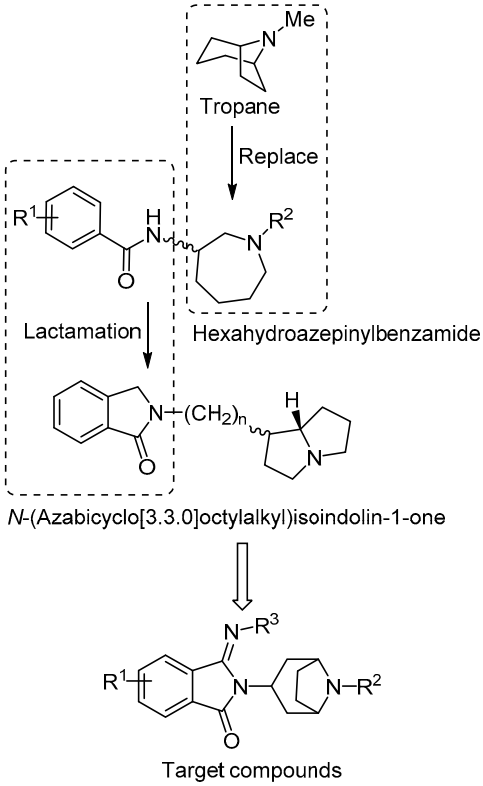
It has been reported that the annual crop loss caused by plant-parasitic nematodes is approximately $125 billion globally.[1] Phytonematodes can also seriously endanger the health of pinewood forest.[2] While great success has been achieved for synthetic nematicides in eliminating the damage of nematodes, a large part of synthetic nematicides such as halogenated hydrocarbons (methyl bromide), carbamates (aldicarb), organophosphates (fenamiphos) are restrictedly used or weeded out recently because of their toxicity to environment or mammals.[3] More recently, biological source nematicides such as avermectins received extensive attention. But they still suffer from some shortages such as complex using method, soil adsorption, and long effective time.[4] Thus, the development of novel environmentally friendly, efficient, and less toxic nematicides has become one of the actual research topics in pesticide discovery and has a huge market prospect.

Serotonin (5-hydroxytryptamine, 5-HT) is a significant monoamine neurotransmitter which exists widely in both vertebrates and invertebrates. It is widely distributed in both central and peripheral nervous system of vertebrates, and participate in various physiological activities like intestinal movements, mood, appetite, and sleeping.[5] It is also found in the central nervous, digestive, and reproductive systems of nematodes and influence various biological behaviors like eating, movement, and reproduction.[6]

Because of the homology between the 5-HT receptors of nonmammalian and mammals, some classical mammalian 5-HT receptor ligands show certain nematicidal activity. In 2003, Trowell and coworkers found that the selective mammalian 5-HT_3 receptor antagonist MDL 72222 could bind to the 5-HT_{3Ce} receptor in *C. elegans* and, in turn, inhibit the pharyngeal pumping contraction and even kill the nematode under a certain level of concentration.[7]

According to the pharmacophoric requirements for 5-HT_3 receptor antagonists proposed by Hibert et al., the pharmacophore consists of three components: an aromatic/heteroaromatic ring, a carbonyl-containing linking moiety, and a basic center in a specific spatial arrangement (Scheme 1).[8] Inspecting the structures of classical 5-HT_3 receptor antagonists, tropane is often used as an effective basic center. Besides, tropane exhibits a broad spectrum of biological activities[9] and has been proven to be an effective functional group in some active nematicidal compounds.[10] On the other hand, in 1998, substituted hexahydroazepinyl-benzamides were reported with high affinity for 5-HT_3 receptor.[11] In 1991, Zabrowski et al. reported *N*-azabicyclo-[3.3.0]octaneisoindolin-1-one derivatives to be mammalian 5-HT_3 receptor antagonists and exhibited prokinetic

Scheme 1. Molecular design of the target compounds



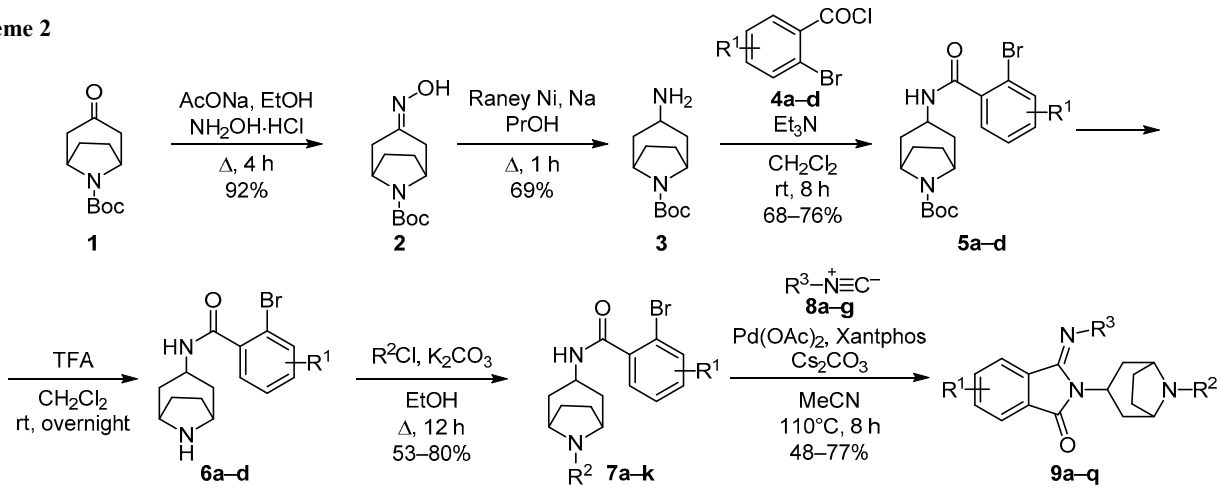
activity.[12] As a continuous effort of searching for novel pesticides potentially targeted on the 5-HT receptors of pests,[13] herein, we propose a new structure based on our previous works and literature reports based on the following considerations: 1) tropane is employed according to its excellent performance as a 5-HT_3 receptor antagonist pharmacophore and our previous works, 2) lactam is introduced to increase the stability of target compounds, since benzolactam derivatives were reported to have nematicidal activity,[14] and 3) the introduction of imine is aimed to improve the nematicidal activity in view of the fact that imine is often used as an effective active fragment in pesticides.[15] A series of novel compounds combining tropane, lactam, and imine moieties were thus synthesized and screened against the root-knot nematodes *M. incognita* and pinewood nematodes *B. xylophilus*.

An efficient Pd-catalyzed isocyanide insertion pathway was adopted to synthesize the target compounds (Scheme 2).[16] *tert*-Butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (**1**) was treated with $NH_2OH·HCl$ to afford *tert*-butyl 3-(hydroxyimino)-8-azabicyclo[3.2.1]octane-8-carboxylate (**2**). *tert*-Butyl 3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (**3**) was obtained *via* reduction of compound **2** by Na and catalytic amount of Raney Ni. Furthermore, amidation of compound **3** with substituted 2-bromobenzoyl chlorides **4a**–**d** afforded the respective substituted *tert*-butyl 3-[(2-bromobenzoyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylates **5a**–**d**. Boc removal with TFA (compounds **6a**–**d**) followed by substitution reaction with alkyl halides leads to intermediate substituted *N*-(8-azabicyclo[3.2.1]octan-3-yl)-2-bromobenzamides **7a**–**k**. Finally, target compounds **9a**–**q** were obtained *via* isocyanide **8a**–**g** insertion reaction from compounds **7a**–**k** and the respective isocyanides **8a**–**g** in the presence of $Pd(OAc)_2$ as catalyst.

All target compounds were evaluated against the pinewood nematodes *B. xylophilus* and the root-knot nematodes *M. incognita*. In the *in vitro* test, 96-well plates were used to investigate the contact toxicity of the compounds against nematodes. Apart from the *in vitro* test, the target compounds were also tested against the infection of *M. incognita* in cucumber plants. In the root-knot nematode test, the inhibitory effect of the nematode infection of plant roots and the compound's phytotoxic effects on plants could be observed by a test tube test.

Preliminary nematicidal activity of the target compounds against *B. xylophilus* is shown in Table 1. Most compounds

Scheme 2



4–7 a R^1 = H, **b** R^1 = 5-Cl, **c** R^1 = 5-F, **d** R^1 = 6-OMe;
8 a R^3 = *t*-Bu, **b** R^3 = Bn, **c** R^3 = Cy, **d** R^3 = *n*-Bu, **e** R^3 = *i*-Pr, **f** R^3 = Ph, **g** R^3 = 4-$MeOC_6H_4$;
9 a R^1 = H, R^2 = Bn, R^3 = *t*-Bu; **b** R^1 = H, R^2 =4-$MeC_6H_4CH_2$, R^3 = *t*-Bu; **c** R^1 = H, R^2 = 4-$F_3CC_6H_4CH_2$, R^3 = *t*-Bu;
d R^1 = H, R^2 = 3-$ClC_6H_4CH_2$, R^3 = *t*-Bu; **e** R^1 = H, R^2 = 4-$ClC_6H_4CH_2$, R^3 = *t*-Bu; **f** R^1 = H, R^2 = 2-$ClC_6H_4CH_2$, R^3 = *t*-Bu;
g R^1 = H, R^2 = Me, R^3 = *t*-Bu; **h** R^1 = 5-F, R^2 = Me, R^3 = *t*-Bu; **i** R^1 = 6-OMe, R^2 = Me,R^3 = *t*-Bu; **j** R^1 = 5-Cl, R^2 = Me, R^3 = *t*-Bu;
k R^1 = H, R^2 = Me, R^3 = Bn; **l** R^1 = H, R^2 = Me, R^3 = Cy; **m** R^1 = H, R^2 = Me, R^3 = *n*-Bu; **n** R^1 = H, R^2 = Me, R^3 = *i*-Pr;
o R^1 = H, R^2 = Me, R^3 = Ph; **p** R^1 = H, R^2 = Me, R^3 = 4-$MeOC_6H_4$; **q** R^1 = H, R^2 = Et, R^3 = *t*-Bu

Table 1. Nematicidal activity of target compounds **9a–q** against *B. xylophilus* in 72 h as fatality rate, %

Compound	R^1	R^2	R^3	Concentration of compound, mg/l			
				80	40	20	10
9a	H	Bn	*t*-Bu	66	67	–	–
9b	H	4-$MeC_6H_4CH_2$	*t*-Bu	69	71	–	–
9c	H	4-$F_3CC_6H_4CH_2$	*t*-Bu	72	73	–	–
9d	H	3-$ClC_6H_4CH_2$	*t*-Bu	53	65	–	–
9e	H	4-$ClC_6H_4CH_2$	*t*-Bu	10**	<10**	–	–
9f	H	2-$ClC_6H_4CH_2$	*t*-Bu	48	51	–	–
9g	H	Me	*t*-Bu	86**	82**	61**	60**
9h	5-F	Me	*t*-Bu	85**	73**	53	70
9i	6-OMe	Me	*t*-Bu	67	73	–	–
9j	5-Cl	Me	*t*-Bu	77**	76**	75	75
9k	H	Me	Bn	82	74	–	–
9l	H	Me	Cy	73	55	–	–
9m	H	Me	*n*-Bu	51**	45**	–	–
9n	H	Me	*i*-Pr	48**	36**	–	–
9o	H	Me	Ph	69**	64**	38	38
9p	H	Me	4-$MeOC_6H_4$	36**	24**	–	–
9q	H	Et	*t*-Bu	74**	54**	59	54
Fenamiphos*						28	
Avermectin*						100	

* Positive control experiments were performed with fenamiphos and avermectin at 5 mg/l.
** Nematodes showed neurogenic curvature at this concentration.

Table 2. Nematicidal activity of target compounds **9a–q** against *M. incognita* in 72 h as fatality rate, %

Compound	R^1	R^2	R^3	Concentration of compound, mg/l			Test tube test at 20 mg/l
				160	80	40	
9a	H	Bn	*t*-Bu	74	70	33	33
9b	H	4-$MeC_6H_4CH_2$	*t*-Bu	60	54	29	57
9c	H	4-$F_3CC_6H_4CH_2$	*t*-Bu	32	38	30	33
9d	H	3-$ClC_6H_4CH_2$	*t*-Bu	18	52	23	30
9e	H	4-$ClC_6H_4CH_2$	*t*-Bu	22	20	23	45
9f	H	2-$ClC_6H_4CH_2$	*t*-Bu	30	22	28	40
9g	H	Me	*t*-Bu	49	66	29	28
9h	5-F	Me	*t*-Bu	70	57	19	<10
9i	6-OMe	Me	*t*-Bu	41	39	10	60
9j	5-Cl	Me	*t*-Bu	67	67	30	15
9k	H	Me	Bn	60	32	16	28
9l	H	Me	Cy	58	42	13	43
9m	H	Me	*n*-Bu	50	42	10	62
9n	H	Me	*i*-Pr	73	43	11	35
9o	H	Me	Ph	51	39	18	32
9p	H	Me	4-$MeOC_6H_4$	84	27	20	60
9q	H	Et	*t*-Bu	45	36	23	36
Avermectin*					99		100

* Positive control experiments were performed with avermectin at 1 mg/l.

show certain nematicidal activity. Among these derivatives, compounds **9g**,**h**,**k** exhibited good nematicidal activities with the fatality rate over 80% at 80 mg/l. Compounds **9a–d**,**i**,**j**,**l**,**m**,**o**,**q** showed certain activities with the fatality rate ranging from 51 to 77%. It is worth mentioning that when an alkyl group was employed as R^2 substituent, the nematicidal activity of the compound could be improved (compare compounds **9g**,**q** with compounds **9a–f**). In terms of the R^1 substituent, employment of a halogen atom (compounds **9h**,**j**) or electron-donating group (compound **9i**) did not cause much influence on nematicidal activity. Besides, the employ of large sterically demanding *tert*-butyl group (compound **9g**) or benzyl group (compound **9k**) as R^3 could slightly increase the activity (compare with compounds **9l–p**).

Apart from the lethal activity, part of the target compounds could cause nematodes to display neurogenic curvature of varying degrees. For example, after contacting with the solution of compound **9g** (80 mg/l), almost all nematodes curled up within 1 h. After 24 h, parts of nematodes were dead and the remaining kept curved. Based on this phenomenon, a further gradient experiment was carried out to select compounds **9g**,**h**,**j**,**o**,**q** which exhibited both good nematicidal activity and visible curl phenomenon. As the result in Table 1 indicates, compounds **9h**,**j** remained over 70% nematicidal activity even at 10 mg/l. Meanwhile, obvious neurogenic curl phenomenon was observed for nematodes treated with a solution of compound **9g** at a concentration level of 10 mg/l.

Preliminary nematicidal activity of the target compounds against *M. incognita* is shown in Table 2. In the *in vitro* test, some compounds exhibited moderate nematicidal activities at a concentration of 160 mg/l. Among these derivatives, compound **9p** exhibited the highest nematicidal activity of 84% fatality rate. Unfortunately, all the target compounds exhibited poor nematicidal activities at the concentration of 40 mg/l. In the test tube tests, compounds **9b**,**i**,**m**,**p** showed moderate inhibition activities ranging from 57 to 62%.

In conclusion, 17 novel 2-(8-azabicyclo[3.2.1]octan-3-yl)-3-imino-2,3-dihydro-1*H*-isoindol-1-ones derived from 5-HT_3 receptor antagonists hexahydroazepinylbenzamides were synthesized. Part of the target compounds exhibited certain lethal activities and curl effect against pinewood nematodes *B. xylophilus*. Among them, 3-(*tert*-butylimino)-5-fluoro-2-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-2,3-dihydro-1*H*-isoindol-1-one and 3-(*tert*-butylimino)-5-chloro-2-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-2,3-dihydro-1*H*-isoindol-1-one were highlighted due to their good nematicidal activities (over 70% at 10 mg/l). 3-(*tert*-Butylimino)-2-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-2,3-dihydro-1*H*-isoindol-1-one was also worth noting because of its obvious neurogenic curl effect against pinewood nematodes *B. xylophilus* at 10 mg/l.

The common inhibitory effects against root-knot nematodes *M. incognita* were not as good as *B. xylophilus*. 3-[(4-Methoxyphenyl)imino]-2-(8-methyl-8-azabicyclo-[3.2.1]octan-3-yl)-2,3-dihydro-1*H*-isoindol-1-one was highlighted because of its relatively higher activities both in the *in vitro* test (84% at 160 mg/l) and in the test tube test (60% at 20 mg/l). Further studies are still in progress and will be reported in due course.

Experimental

^{1}H and ^{13}C NMR spectra were acquired on a Bruker AM-400 spectrometer (400 and 101 MHz, respectively) using $CDCl_3$ as the solvent and TMS as internal standard. High-resolution mass spectra were recorded on a Waters GCT Premier mass spectrometer with electron impact ion source or a Thermo Fisher Q Exactive Plus instrument using electrospray ionization source. Melting points were determined on an EZ-Melt 120 automated melting point apparatus and are uncorrected. Flash chromatography was performed using Merck silica gel 60 (230–400 mesh).

***tert*-Butyl 3-(hydroxyimino)-8-azabicyclo[3.2.1]octane-8-carboxylate (2)**. A 100-ml round-bottomed flask equipped with a magnetic stirrer was charged with *tert*-butyl 3-oxo-8-azabicyclo[3.2.1]octane-8-carboxylate (**1**) (2.25 g, 10 mmol), $HONH_2{\cdot}HCl$ (834 mg, 12 mmol), AcONa (984 mg, 12 mmol), and EtOH (40 ml). After stirring at refluxing temperature for 4 h, the reaction mixture was distilled to a solid residue by using a rotary evaporator. The residue was extracted with EtOAc (2×30 ml). The combined organic extracts were dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure. Yield 2.2 g (92%), white solid, mp 113–115°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm: 1.48 (9H, s, $C(CH_3)_3$); 1.54–1.69 (2H, m, $CHC\underline{H_2}C\underline{H_2}CH$); 1.93–2.03 (2H, m, $CHC\underline{H_2}C\underline{H_2}CH$); 2.16–2.27 (2H, m, $CHC\underline{H_2}CC\underline{H_2}CH$); 2.52–2.61 (1H, m, $CHC\underline{H_2}CCH_2CH$); 3.11–3.15 (1H, m, $CHCH_2CC\underline{H_2}CH$); 4.32–4.38 (2H, m, CHNCH). ^{13}C NMR spectrum, δ, ppm: 27.6; 28.5; 29.2; 31.6; 37.7; 52.5; 53.2; 79.9; 153.4; 155.6. Found, *m*/*z*: 241.1536 $[M+H]^+$. $C_{12}H_{21}N_2O_3$. Calculated, *m*/*z*: 241.1547.

***tert*-Butyl 3-amino-8-azabicyclo[3.2.1]octane-8-carboxylate (3)**. A 100-ml three-necked round-bottomed flask was equipped with a magnetic stirrer and a condenser pipe sealed with an empty balloon. Metallic Na (2.30 g, 100 mmol) was added to a mixture of compound **2** (2.41 g, 10 mmol) and Raney Ni (30 mg, 0.5 mmol) in PrOH (30 ml) over 10 min under reflux. The mixture was then maintained refluxing for 1 h. After cooling down to room temperature, H_2O (20 ml) was added and the solvent was evaporated using a rotary evaporator. The residue was extracted with CH_2Cl_2 (3×50 ml). The resulting organic phase was concentrated and purified by flash chromatography on silica gel (CH_2Cl_2–MeOH, 20:1). Yield 1.56 g (69%), white solid, mp 97–99°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm: 1.42–1.46 (11H, m, $C(CH_3)_3$, $CHC\underline{H_2}C\underline{H_2}CH$); 1.61 (2H, br. s, $CHC\underline{H_2}C\underline{H_2}CH$); 1.95–1.96 (2H, m, $CHC\underline{H_2}CHC\underline{H_2}CH$); 2.09–2.17 (4H, m, $CHC\underline{H_2}CHC\underline{H_2}CH$, NH_2); 3.31–3.33 (1H, m, $C\underline{H}NH_2$); 4.12–4.21 (2H, m, CHNCH). ^{13}C NMR spectrum, δ, ppm: 28.3; 28.5; 28.9; 37.5; 38.1; 43.5; 52.2; 53.0; 79.0; 153.4. Found, *m*/*z*: 227.1745 $[M+H]^+$. $C_{12}H_{23}N_2O_2$. Calculated, *m*/*z*: 227.1754.

Synthesis of *tert*-butyl 3-[(2-bromobenzoyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylates 5a–d (General method). Substituted 2-bromobenzoic acid (10 mmol) was added to $SOCl_2$ (15 ml). The mixture was stirred at reflux for 4 h. After cooling down to room temperature, the solvent was evaporated using a rotary evaporator. 2-Bromobenzoyl chloride **4a–d** was obtained as colorless oily residue. Solution of compound **4a–d** in CH_2Cl_2 (10 ml) was added dropwise to a solution of compound **3** (2.26 g, 10 mmol) and Et_3N (3.03 g, 30 mmol) in CH_2Cl_2 (30 ml) at 0°C. After the mixture was stirred at room temperature for 8 h, it was washed with brine and extracted with CH_2Cl_2 (3×50 ml). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was evaporated under reduced pressure. The solid residue was washed with solvent mixture petroleum ether – CH_2Cl_2, 10:1 (2×100 ml). The residue was filtered off to give the crude product as a white solid which was purified by flash chromatography on silica gel (eluent cyclohexane–EtOAc, 3:1).

***tert*-Butyl 3-[(2-bromobenzoyl)amino]-8-azabicyclo-[3.2.1]octane-8-carboxylate (5a)**. Yield 2.86 g (75%), white solid, mp 213–215°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.47 (9H, s, $C(CH_3)_3$); 1.56–1.61 (2H, m, $CHC\underline{H_2}C\underline{H_2}CH$); 1.80–1.85 (2H, m, $CHC\underline{H_2}C\underline{H_2}CH$); 2.00–2.07 (4H, m, $CHC\underline{H_2}CHC\underline{H_2}CH$); 4.28 (2H, br. s, CHNCH); 4.51–4.61 (1H, m, $C\underline{H}NH$); 5.73 (1H, d, J = 8.0, NH); 7.24–7.28 (1H, m, H-5 Ph); 7.33–7.37 (1H, m, H-4 Ph); 7.49 (1H, dd, J = 7.6, J = 1.4, H-3 Ph); 7.57 (1H, d, J = 8.0, H-6 Ph). ^{13}C NMR spectrum, δ, ppm: 28.0; 28.5; 37.6; 42.1; 53.0; 79.4; 119.2; 127.6; 129.4; 131.2; 133.3; 137.9; 153.2; 166.9. Found, *m*/*z*: 409.1104 $[M+H]^+$. $C_{19}H_{26}{}^{79}BrN_2O_3$. Calculated, *m*/*z*: 409.1121. Found, *m*/*z*: 411.1081 $[M+H]^+$. $C_{19}H_{26}{}^{81}BrN_2O_3$. Calculated, *m*/*z*: 411.1101.

***tert*-Butyl 3-[(2-bromo-4-chlorobenzoyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (5b)**. Yield 3.37 g (76%), white solid, mp 196–198°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.46 (9H, s, $C(CH_3)_3$); 1.55–1.61 (2H, m, $CHC\underline{H_2}C\underline{H_2}CH$); 1.79–1.84 (2H, m, $CHC\underline{H_2}C\underline{H_2}CH$); 2.00–2.05 (4H, m, $CHC\underline{H_2}CHC\underline{H_2}CH$); 4.27 (2H, br. s, CHNCH); 4.48–4.59 (1H, m, $C\underline{H}NH$); 5.78 (1H, d, J = 8.2, NH); 7.33 (1H, dd, J = 8.2, J = 1.9, H-5 Ph); 7.44 (1H, d, J = 8.3, H-6 Ph); 7.59 (1H, d, J = 1.9, H-3 Ph). ^{13}C NMR spectrum, δ, ppm: 28.0; 28.5; 37.5; 42.2; 53.0; 79.5; 119.8; 127.9; 130.4; 132.9; 136.2; 136.5; 153.2; 166.0. Found, *m*/*z*: 443.0727 $[M+H]^+$. $C_{19}H_{25}{}^{79}Br{}^{35}ClN_2O_3$. Calculated, *m*/*z*: 443.0732. Found, *m*/*z*: 445.0704 $[M+H]^+$. $C_{19}H_{25}{}^{81}Br{}^{35}ClN_2O_3$. Calculated, *m*/*z*: 445.0711.

***tert*-Butyl 3-[(2-bromo-4-fluorobenzoyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (5c)**. Yield 2.89 g (68%), white solid, mp 199–201°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.46 (9H, s, $C(CH_3)_3$); 1.58–1.62 (2H, m, $CHC\underline{H_2}C\underline{H_2}CH$); 1.79–1.85 (2H, m, $CHC\underline{H_2}C\underline{H_2}CH$); 2.00–2.02 (4H, m, $CHC\underline{H_2}CHC\underline{H_2}CH$); 4.27 (2H, br. s, CHNCH); 4.48–4.59 (1H, m, $C\underline{H}NH$); 5.85 (1H, d, J = 8.2, NH); 7.06 (1H, td, J = 8.3, J = 2.5, H-5 Ph); 7.31 (1H, dd, J = 8.2, J = 2.4, H-6 Ph); 7.50 (1H, dd, J = 8.6, J = 5.9, H-3 Ph). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 28.0; 28.5; 37.6; 42.2; 52.9; 79.5; 114.9 (d, $^2J_{CF}$ = 21.3, C-5 Ph); 119.9 (d, $^3J_{CF}$ = 9.7, C-2 Ph); 120.6 (d, $^2J_{CF}$ = 24.7, C-3 Ph); 131.1 (d, $^3J_{CF}$ = 8.9, C-6 Ph); 134.1; 153.2; 162.8 (d, $^1J_{CF}$ = 254.5, C-4 Ph); 166.0. Found, *m*/*z*: 427.1023 $[M+H]^+$. $C_{19}H_{25}{}^{79}BrFN_2O_3$. Calculated, *m*/*z*: 427.1027. Found, *m*/*z*: 429.1002 $[M+H]^+$. $C_{19}H_{25}{}^{81}BrFN_2O_3$. Calculated, *m*/*z*: 429.1007.

***tert*-Butyl 3-[(2-bromo-5-methoxybenzoyl)amino]-8-azabicyclo[3.2.1]octane-8-carboxylate (5d)**. Yield 3.15 g (72%), white solid, mp 172–174°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.48 (9H, s, $C(CH_3)_3$); 1.79–1.83 (2H, m, $CHC\underline{H_2}C\underline{H_2}CH$); 1.89–1.91 (2H, m,

CHC$\underline{H}_2$C$\underline{H}_2$CH); 2.07–2.09 (2H, m, CHC$\underline{H}_2$CHC$\underline{H}_2$CH); 2.29–2.32 (2H, m, CHC$\underline{H}_2$CHC$\underline{H}_2$CH); 3.82 (3H, s, OCH_3); 4.26 (2H, br. s, CHNCH); 4.38–4.40 (1H, m, C$\underline{H}$NH); 6.57 (1H, d, *J* = 6.8, NH); 6.85 (1H, dd, *J* = 8.8, *J* = 2.4, H-4 Ph); 7.15–7.16 (1H, m, H-3 Ph); 7.45 (1H, d, *J* = 8.9, H-6 Ph). ^{13}C NMR spectrum, δ, ppm: 27.9; 28.5; 35.3; 42.7; 52.5; 55.7; 79.5; 109.2; 115.1; 118.1; 134.3; 138.0; 153.3; 159.1; 166.3. Found, *m*/*z*: 439.1223 $[M+H]^+$. $C_{20}H_{28}{}^{79}BrN_2O_4$. Calculated, *m*/*z*: 439.1227. Found, *m*/*z*: 441.1201 $[M+H]^+$. $C_{20}H_{28}{}^{81}BrN_2O_4$. Calculated, *m*/*z*: 441.1206.

Synthesis of *N*-(8-azabicyclo[3.2.1]octan-3-yl)-2-bromobenzamides 6a–d (General method). Compound **5a–d** (10 mmol) was dissolved in CH_2Cl_2 (30 ml), and TFA (5.07 g, 50 mmol) was added. The mixture was stirred overnight at room temperature. The solvent and excess TFA were distilled off using a rotary evaporator. The residue was dissolved in CH_2Cl_2 (20 ml) and washed with brine (3× 0 ml). The organic phase was dried over anhydrous $MgSO_4$ and concentrated to afford crude product which was used directly without further purification.

Synthesis of substituted *N*-(8-azabicyclo[3.2.1]octan-3-yl)-2-bromobenzamides 7a–k (General method). Compound **6a–d** (2.0 mmol), K_2CO_3 (331 mg, 2.4 mmol), and alkyl halide (2.4 mmol) were added to EtOH (30 ml). The mixture was stirred under reflux for 12 h, and the solvent was distilled using a rotary evaporator. The residue was extracted with CH_2Cl_2 (3×20 ml). The resulting organic phase was concentrated and purified by flash chromatography on silica gel (CH_2Cl_2–MeOH, 20:1).

***N*-(8-Benzyl-8-azabicyclo[3.2.1]octan-3-yl)-2-bromobenzamide (7a)**. Yield 517 mg (65%), white solid, mp 144–146°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.67–1.73 (2H, m, CHC$\underline{H}_2$C$\underline{H}_2$CH); 1.78–1.83 (2H, m, CHC$\underline{H}_2$C$\underline{H}_2$CH); 1.94–1.97 (2H, m, CHC$\underline{H}_2$CHC$\underline{H}_2$CH); 2.08–2.11 (2H, m, CHC$\underline{H}_2$CHC$\underline{H}_2$CH); 3.29 (2H, br. s, CHNCH); 3.58 (2H, s, NC$\underline{H}_2$Ph); 4.33–4.44 (1H, m, C$\underline{H}$NH); 5.79 (1H, d, *J* = 8.0, NH); 7.25–7.27 (2H, m, $CH_2\underline{Ph}$); 7.30–7.36 (3H, m, $CH_2\underline{Ph}$); 7.38–7.40 (2H, m, H-3,4 COPh); 7.48 (1H, dd, *J* = 7.6, *J* = 1.7, H-3 COPh); 7.56 (1H, dd, *J* = 8.0, *J* = 1.0, H-6 COPh). ^{13}C NMR spectrum, δ, ppm: 26.4; 38.2; 42.3; 56.3; 58.9; 119.2; 127.0; 127.5; 128.3; 128.7; 129.5; 131.1; 133.3; 138.1; 139.5; 166.9. Found, *m*/*z*: 399.1048 $[M+H]^+$. $C_{21}H_{24}{}^{79}BrN_2O$. Calculated, *m*/*z*: 399.1067. Found, *m*/*z*: 401.1026 $[M+H]^+$. $C_{21}H_{24}{}^{81}BrN_2O$. Calculated, *m*/*z*: 401.1046.

2-Bromo-*N*-{8-[(4-methylphenyl)methyl]-8-azabicyclo-[3.2.1]octan-3-yl}benzamide (7b). Yield 593 mg (72%), white solid, mp 156–158°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.65–1.71 (2H, m, CHC$\underline{H}_2$C$\underline{H}_2$CH); 1.77–1.82 (2H, m, CHC$\underline{H}_2$C$\underline{H}_2$CH); 1.93–1.98 (2H, m, CHC$\underline{H}_2$CHC$\underline{H}_2$CH); 2.07–2.10 (2H, m, CHC$\underline{H}_2$CHC$\underline{H}_2$CH); 2.34 (3H, s, PhC$\underline{H}_3$); 3.28 (2H, br. s, CHNCH); 3.53 (2H, s, NC$\underline{H}_2$Ph); 4.32–4.43 (1H, m, C$\underline{H}$NH); 5.75 (1H, d, *J* = 7.8, NH); 7.12–7.14 (2H, m, $CH_2\underline{Ph}$); 7.25–7.28 (3H, m, $CH_2\underline{Ph}$, COPh); 7.34 (1H, td, *J* = 7.5, *J* = 1.0, COPh); 7.49 (1H, dd, *J* = 7.6, *J* = 1.7, H-3 COPh); 7.57 (1H, dd, *J* = 8.0, *J* = 0.8, H-6 COPh). ^{13}C NMR spectrum, δ, ppm: 21.1; 26.4; 38.3; 42.4; 56.0; 58.7; 119.2; 127.5; 128.6; 128.9; 131.1; 133.3; 136.4; 136.7; 138.1; 166.9. Found, *m*/*z*: 413.1205 $[M+H]^+$. $C_{22}H_{26}{}^{79}BrN_2O$. Calculated, *m*/*z*: 413.1223. Found, *m*/*z*: 415.1183 $[M+H]^+$. $C_{22}H_{26}{}^{81}BrN_2O$. Calculated, *m*/*z*: 415.1203.

2-Bromo-*N*-(8-{[4-(trifluoromethyl)phenyl]methyl}-8-azabicyclo[3.2.1]octan-3-yl)benzamide (7c). Yield 494 mg (53%), white solid, mp 140–141°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.64–1.72 (2H, m, CHC$\underline{H}_2$C$\underline{H}_2$CH); 1.82–1.84 (2H, m, CHC$\underline{H}_2$C$\underline{H}_2$CH); 1.96–2.01 (2H, m, CHC$\underline{H}_2$CHC$\underline{H}_2$CH); 2.07–2.10 (2H, m, CHC$\underline{H}_2$CHC$\underline{H}_2$CH); 3.26 (2H, br. s, CHNCH); 3.62 (2H, s, NC$\underline{H}_2$Ph); 4.33–4.44 (1H, m, C$\underline{H}$NH); 5.77 (1H, d, *J* = 7.0, NH); 7.24–7.28 (1H, m, $CF_3\underline{Ph}$); 7.33–7.37 (1H, m, $CF_3\underline{Ph}$); 7.47–7.53 (3H, m, $CF_3\underline{Ph}$, COPh); 7.57–7.58 (3H, m, COPh). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 26.5; 38.3; 42.3; 56.0; 59.0; 119.2; 124.3 (q, $^1J_{CF}$ = 272.9, CF_3); 125.1 (q, $^3J_{CF}$ = 3.8, C-3,5 $CH_2\underline{Ph}$); 127.5; 128.6; 129.1 (q, $^2J_{CF}$ = 32.3, C-4 Ph); 129.4; 131.1; 133.3; 138.0; 166.9. Found, *m*/*z*: 467.0938 $[M+H]^+$. $C_{22}H_{23}{}^{79}BrF_3N_2O$. Calculated, *m*/*z*: 467.0940. Found, *m*/*z*: 469.0916 $[M+H]^+$. $C_{22}H_{23}{}^{81}BrF_3N_2O$. Calculated, *m*/*z*: 469.0920.

2-Bromo-*N*-{8-[(3-chlorophenyl)methyl]-8-azabicyclo-[3.2.1]octan-3-yl}benzamide (7d). Yield 689 mg (80%), white solid, mp 145–147°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.68–1.78 (4H, m, CHC$\underline{H}_2$C$\underline{H}_2$CH); 1.89–1.94 (2H, m, CHC$\underline{H}_2$CHC$\underline{H}_2$CH); 2.01–2.03 (2H, m, CHC$\underline{H}_2$CHC$\underline{H}_2$CH); 3.23 (2H, br. s, CHNCH); 3.51 (2H, s, NC$\underline{H}_2$Ph); 4.27–4.38 (1H, m, C$\underline{H}$NH); 5.79 (1H, d, *J* = 7.6, NH); 7.16–7.20 (3H, m, $CH_2\underline{Ph}$); 7.24–7.29 (2H, m, $CH_2\underline{Ph}$, COPh); 7.36 (1H, br. s, COPh); 7.40 (1H, dd, *J* = 7.6, *J* = 1.7, H-3 COPh); 7.49 (1H, dd, *J* = 8.0, *J* = 0.7, H-6 COPh). ^{13}C NMR spectrum, δ, ppm: 26.5; 38.3; 42.3; 55.9; 59.0; 119.2; 126.6; 127.0; 127.5; 128.5; 129.4; 129.5; 131.1; 133.3; 134.2; 138.0; 142.2; 166.9. Found, *m*/*z*: 433.0658 $[M+H]^+$. $C_{21}H_{23}{}^{79}Br{}^{35}ClN_2O$. Calculated, *m*/*z*: 433.0677. Found, *m*/*z*: 435.0633 $[M+H]^+$. $C_{21}H_{23}{}^{81}Br{}^{35}ClN_2O$. Calculated, *m*/*z*: 435.0656.

2-Bromo-*N*-{8-[(4-chlorophenyl)methyl]-8-azabicyclo-[3.2.1]octan-3-yl}benzamide (7e). Yield 536 mg (62%), white solid, mp 153–155°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.83–1.93 (6H, m, CHC$\underline{H}_2$C$\underline{H}_2$CH, CHC$\underline{H}_2$CHC$\underline{H}_2$CH); 2.05–2.07 (2H, m, CHC$\underline{H}_2$CHC$\underline{H}_2$CH); 3.23 (2H, br. s, CHNCH); 3.59 (2H, s, NC$\underline{H}_2$Ph); 4.30–4.41 (1H, m, C$\underline{H}$NH); 5.88 (1H, d, *J* = 6.1, NH); 7.17–7.21 (1H, m, $CH_2\underline{Ph}$); 7.24–7.29 (3H, m, $CH_2\underline{Ph}$); 7.36–7.41 (3H, m, COPh); 7.50 (1H, dd, *J* = 7.9, *J* = 0.7, H-6 COPh). ^{13}C NMR spectrum, δ, ppm: 26.4; 38.3; 42.3; 55.7; 58.9; 119.2; 127.6; 128.4; 129.5; 129.8; 131.1; 132.5; 133.3; 138.0; 138.4; 166.9. Found, *m*/*z*: 433.0661 $[M+H]^+$. $C_{21}H_{23}{}^{79}Br{}^{35}ClN_2O$. Calculated, *m*/*z*: 433.0677. Found, *m*/*z*: 435.0637 $[M+H]^+$. $C_{21}H_{23}{}^{81}Br{}^{35}ClN_2O$. Calculated, *m*/*z*: 435.0656.

2-Bromo-*N*-{8-[(2-chlorophenyl)methyl]-8-azabicyclo-[3.2.1]octan-3-yl}benzamide (7f). Yield 657 mg (76%), white solid, mp 161–162°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.67–1.72 (2H, m, CHC$\underline{H}_2$C$\underline{H}_2$CH); 1.80–1.85 (2H, m, CHC$\underline{H}_2$C$\underline{H}_2$CH); 1.97–2.02 (2H, m, CHC$\underline{H}_2$CHC$\underline{H}_2$CH); 2.11–2.14 (2H, m, CHC$\underline{H}_2$CHC$\underline{H}_2$CH); 3.29 (2H, br. s, CHNCH); 3.65 (2H, s, NC$\underline{H}_2$Ph); 4.31–4.45 (1H, m, C$\underline{H}$NH); 5.76 (1H, d, *J* = 7.9, NH); 7.15–7.19 (1H, m, $CH_2\underline{Ph}$); 7.24–7.28 (2H, m, $CH_2\underline{Ph}$,); 7.32–7.36 (2H, m, COPh); 7.49 (1H, dd, *J* = 7.6, *J* = 1.7, H-3 $CH_2\underline{Ph}$); 7.57 (1H, dd, *J* = 8.0, *J* = 0.9, H-3 COPh); 7.65 (1H, d, *J* = 7.4,

H-6 COPh). ^{13}C NMR spectrum, δ, ppm: 26.7; 38.4; 42.3; 53.3; 59.5; 119.2; 126.7; 127.6; 127.8; 129.2; 129.5; 129.9; 131.1; 133.3; 133.7; 137.6; 138.1; 166.9. Found, *m/z*: 433.0659 $[M+H]^+$. $C_{21}H_{23}{}^{79}Br^{35}ClN_2O$. Calculated, *m/z*: 433.0677. Found, *m/z*: 435.0635 $[M+H]^+$. $C_{21}H_{23}{}^{81}Br^{35}ClN_2O$. Calculated, *m/z*: 435.0656.

2-Bromo-*N*-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-benzamide (7g). Yield 380 mg (59%), white solid, mp 160–162°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.66–1.72 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 1.75–1.80 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 1.97–2.01 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 2.07–2.10 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 2.32 (3H, s, NCH_3); 3.24 (2H, br. s, CHNCH); 4.29–4.40 (1H, m, C$\underline{H}$NH); 5.77 (1H, d, *J* = 6.5, NH); 7.23–7.27 (1H, m, H-5 Ph); 7.32–7.36 (1H, t, *J* = 7.5, H-4 Ph); 7.50 (1H, dd, *J* = 7.6, *J* = 1.4, H-3 Ph); 7.56 (1H, d, *J* = 8.0, H-6 Ph). ^{13}C NMR spectrum, δ, ppm: 25.9; 37.6; 39.8; 41.5; 61.1; 119.2; 127.5; 129.4; 131.1; 133.3; 137.9; 167.0. Found, *m/z*: 323.0746 $[M+H]^+$. $C_{15}H_{20}{}^{79}BrN_2O$. Calculated, *m/z*: 323.0754. Found, *m/z*: 325.0725 $[M+H]^+$. $C_{15}H_{20}{}^{81}BrN_2O$. Calculated, *m/z*: 325.0733.

2-Bromo-4-fluoro-*N*-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)benzamide (7h). Yield 374 mg (55%), white solid, mp 163–165°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.92–1.98 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 2.01–2.07 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 2.09–2.20 (4H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 2.49 (3H, s, NCH_3); 3.48 (2H, br. s, CHNCH); 4.35–4.48 (1H, m, C$\underline{H}$NH); 6.28 (1H, d, *J* = 6.5, NH); 7.06 (1H, td, *J* = 8.3, *J* = 2.5, H-5 Ph); 7.32 (1H, dd, *J* = 8.2, *J* = 2.4, H-6 Ph); 7.50 (1H, dd, *J* = 8.6, *J* = 5.9, H-3 Ph). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 25.4; 36.5; 39.4; 40.6; 62.1; 114.8 (d, $^2J_{CF}$ = 21.3, C-5 Ph); 120.0 (d, $^3J_{CF}$ = 9.7, C-2 Ph); 120.6 (d, $^2J_{CF}$ = 24.6, C-3 Ph); 130.9 (d, $^3J_{CF}$ = 8.9, C-6 Ph); 133.9 (d, $^4J_{CF}$ = 3.6, C-1 Ph); 162.8 (d, $^1J_{CF}$ = 254.3, C-4 Ph); 166.4. Found, *m/z*: 341.0657 $[M+H]^+$. $C_{15}H_{19}{}^{79}BrFN_2O$. Calculated, *m/z*: 341.0659. Found, *m/z*: 343.0635 $[M+H]^+$. $C_{15}H_{19}{}^{81}BrFN_2O$. Calculated, *m/z*: 343.0639.

2-Bromo-5-methoxy-*N*-(8-methyl-8-azabicyclo[3.2.1]-octan-3-yl)benzamide (7i). Yield 436 mg (62%), white solid, mp 136–139°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.74–1.82 (4H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 1.96–2.00 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 2.07–2.10 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 2.33 (3H, s, NCH_3); 3.27 (2H, br. s, CHNCH); 3.78 (3H, s, OCH_3); 4.28–4.39 (1H, m, C$\underline{H}$NH); 5.96 (1H, d, *J* = 8.1, NH); 6.79 (1H, dd, *J* = 8.8, *J* = 3.1, H-4 Ph); 7.03 (1H, d, *J* = 3.1, H-6 Ph); 7.41 (1H, d, *J* = 8.8, H-3 Ph). ^{13}C NMR spectrum, δ, ppm: 26.0; 37.9; 40.0; 41.8; 55.6; 61.0; 109.3; 114.7; 117.7; 134.1; 138.4; 158.9; 166.6. Found, *m/z*: 353.0850 $[M+H]^+$. $C_{16}H_{22}{}^{79}BrN_2O_2$. Calculated, *m/z*: 353.0859. Found, *m/z*: 355.0829 $[M+H]^+$. $C_{16}H_{22}{}^{81}BrN_2O_2$. Calculated, *m/z*: 355.0839.

2-Bromo-4-chloro-*N*-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)benzamide (7j). Yield 434 mg (61%), white solid, mp 167–168°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.69–1.81 (4H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 1.95–2.01 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 2.08–2.11 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 2.33 (3H, s, NCH_3); 3.26 (2H, br. s, CHNCH); 4.28–4.38 (1H, m, C$\underline{H}$NH); 5.87 (1H, d, *J* = 7.6, NH); 6.33 (1H, dd, *J* = 8.3, *J* = 2.0, H-5 Ph); 7.45 (1H, d, *J* = 8.3, H-6 Ph); 7.58 (1H, d, *J* = 2.0, H-3 Ph). ^{13}C NMR spectrum, δ, ppm: 25.9; 37.8; 40.0; 41.7; 61.1; 119.8; 127.9; 130.5; 132.9; 136.2; 136.4; 166.0. Found, *m/z*: 357.0356 $[M+H]^+$. $C_{15}H_{19}{}^{79}Br^{35}ClN_2O$. Calculated, *m/z*: 357.0364. Found, *m/z*: 359.0343 $[M+H]^+$. $C_{15}H_{19}{}^{81}Br^{35}ClN_2O$. Calculated, *m/z*: 359.0343.

2-Bromo-*N*-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)benzamide (7k). Yield 477 mg (71%), white solid, mp 134–136°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.12 (3H, t, *J* = 7.1, $CH_2C\underline{H_3}$); 1.67–1.79 (4H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 1.97–2.00 (4H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 2.47 (2H, q, *J* = 7.1, C$\underline{H_2}$CH$_3$); 3.38 (2H, br. s, CHNCH); 4.33–4.44 (1H, m, C$\underline{H}$NH); 5.78 (1H, d, *J* = 6.8, NH); 7.24–7.26 (1H, m, H-5 Ph); 7.34 (1H, t, *J* = 7.4, H-4 Ph); 7.49 (1H, dd, *J* = 7.5, *J* = 1.1, H-3 Ph); 7.56 (1H, d, *J* = 7.9, H-6 Ph). ^{13}C NMR spectrum, δ, ppm: 13.6; 26.3; 37.5; 42.2; 45.4; 58.4; 119.2; 127.5; 129.5; 131.1; 133.3; 137.9; 166.9. Found, *m/z*: 337.0900 $[M+H]^+$. $C_{16}H_{22}{}^{79}BrN_2O$. Calculated, *m/z*: 337.0910. Found, *m/z*: 339.0880 $[M+H]^+$. $C_{16}H_{22}{}^{81}BrN_2O$. Calculated, *m/z*: 339.0890.

Synthesis of 2-(8-azabicyclo[3.2.1]octan-3-yl)-3-imino-2,3-dihydro-1*H*-isoindol-1-ones 9a–q (General method). Compound **7a–k** (1 mmol), $Pd(OAc)_2$ (11.2mg, 0.05 mmol), Xantphos (29.0 mg, 0.05 mmol), Cs_2CO_3 (489 mg, 1.5 mmol), isocyanide **8a–g** (1.5 mmol), and MeCN (2 ml) were added to an oven-dried 10-ml screw cap vial equipped with a stir bar. The mixture was stirred under N_2 atmosphere at 110°C for 8 h. The resulting reaction mixture was cooled to ambient temperature, diluted with EtOAc (5 ml), and passed through a small bed of Celite. The filtrate was extracted with EtOAc (3×10 ml), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated under vacuum to provide crude imine which was further purified by flash chromatography on silica gel (cyclohexane–EtOAc, 3:1).

2-(8-Benzyl-8-azabicyclo[3.2.1]octan-3-yl)-3-(*tert*-butylimino)-2,3-dihydro-1*H*-isoindol-1-one (9a). Yield 268 mg (67%), white solid, mp 127–130°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.30–1.34 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 1.58 (9H, s, $C(CH_3)_3$); 1.72–1.78 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 2.04–2.08 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 2.82–2.85 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 3.32 (2H, br. s, CHNCH); 3.95 (2H, s, NCH_2Ph); 4.89 (1H, tt, *J* = 12.2, *J* = 6.0, CONCH); 7.23 (1H, t, *J* = 7.3, H-4 Ph); 7.32 (2H, t, *J* = 7.4, H-3,5 Ph); 7.50 (2H, d, *J* = 7.3, H-2,6 Ph); 7.56–7.64 (2H, m, H-5,6 isoindoline); 7.87 (1H, d, *J* = 6.8, H-4 isoindoline); 7.98 (1H, d, *J* = 7.2, H-7 isoindoline). ^{13}C NMR spectrum, δ, ppm: 27.5; 30.2; 30.9; 42.6; 53.2; 53.8; 57.7; 123.0; 126.6; 127.1; 128.2; 128.6; 128.7; 130.9; 131.7; 134.4; 146.1; 167.5. Found, *m/z*: 401.2464 $[M]^+$. $C_{26}H_{31}N_3O$. Calculated, *m/z*: 401.2462.

3-(*tert*-Butylimino)-2-{8-[(4-methylphenyl)methyl]-8-azabicyclo[3.2.1]octan-3-yl}-2,3-dihydro-1*H*-isoindol-1-one (9b). Yield 299 mg (72%), white solid, mp 179–182°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.29–1.34 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 1.57 (9H, s, $C(CH_3)_3$); 1.73–1.78 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 2.08–2.18 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 2.34 (3H, s, $PhCH_3$); 2.83–2.89 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 3.39 (2H, br. s, CHNCH); 4.02 (2H, s, NCH_2Ph); 4.91 (1H, tt, *J* = 12.1, *J* = 5.9, CONCH);

7.15 (2H, d, *J* = 7.7, H-3,5 Ph); 7.44 (2H, d, *J* = 7.4, H-2,6 Ph); 7.57–7.65 (2H, m, H-5,6 isoindoline); 7.88 (1H, d, *J* = 6.9, H-4 isoindoline); 7.99 (1H, d, *J* = 7.6, H-7 isoindoline). ^{13}C NMR spectrum, δ, ppm: 21.2; 27.1; 27.4; 30.5; 37.7; 49.9; 55.2; 58.5; 122.7; 123.0; 128.7; 129.0; 131.9; 132.0; 132.9; 134.8; 136.4; 148.3; 152.0. Found, *m/z*: 415.2630 $[M]^+$. $C_{27}H_{33}N_3O$. Calculated, *m/z*: 415.2618.

3-(*tert*-Butylimino)-2-(8-{[4-(trifluoromethyl)phenyl]-methyl}-8-azabicyclo[3.2.1]octan-3-yl)-2,3-dihydro-1*H*-isoindol-1-one (9c). Yield 351 mg (75%), white solid, mp 122–124°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.28–1.33 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 1.58 (9H, s, C(CH$_3$)$_3$); 1.74–1.79 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 2.04–2.07 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 2.79–2.86 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 3.29 (2H, br. s, CHNCH); 3.99 (2H, s, NCH$_2$Ph); 4.89 (1H, tt, *J* = 12.2, *J* = 6.1, CONCH); 7.56–7.63 (6H, m, H Ph, H-5,6 isoindoline); 7.88 (1H, d, *J* = 6.8, H-4 isoindoline); 7.98 (1H, d, *J* = 7.4, H-7 isoindoline). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 27.5; 30.3; 30.9; 42.5; 53.0; 53.8; 57.8; 123.0; 124.4 (q, $^1J_{CF}$ = 271.7, CF$_3$); 125.1 (q, $^3J_{CF}$ = 3.7, C-3,5 Ph); 127.2; 128.5; 128.7; 128.8 (q, $^2J_{CF}$ = 32.1, C-4 Ph); 131.0; 131.8; 134.4; 144.8; 146.1; 167.6. Found, *m/z*: 469.2343 $[M]^+$. $C_{27}H_{30}F_3N_3O$. Calculated, *m/z*: 469.2335.

3-(*tert*-Butylimino)-2-{8-[(3-chlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-yl}-2,3-dihydro-1*H*-isoindol-1-one (9d). Yield 328 mg (75%), white solid, mp 138–141°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.30–1.32 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 1.58 (9H, s, C(CH$_3$)$_3$); 1.75–1.77 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 2.04–2.06 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 2.79–2.85 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 3.29 (2H, br. s, CHNCH); 3.91 (2H, s, NCH$_2$Ph); 4.89 (1H, tt, *J* = 12.0, *J* = 5.9, CONCH); 7.17–7.25 (2H, m, H-5,6 Ph); 7.37 (1H, d, *J* = 7.2, H-4 Ph); 7.49 (1H, s, H-2 Ph); 7.56–7.64 (2H, m, H-5,6 isoindoline); 7.87 (1H, d, *J* = 6.7, H-4 isoindoline); 7.98 (1H, d, *J* = 7.5, H-7 isoindoline). ^{13}C NMR spectrum, δ, ppm: 27.5; 30.3; 30.9; 42.6; 52.9; 53.8; 57.8; 123.0; 126.7; 126.8; 127.1; 128.6; 129.4; 131.0; 131.8; 134.1; 134.4; 142.7; 146.1; 167.5. Found, *m/z*: 435.2087 $[M]^+$. $C_{26}H_{30}{}^{35}ClN_3O$. Calculated, *m/z*: 435.2072. Found, *m/z*: 437.2042 $[M]^+$. $C_{26}H_{30}{}^{37}ClN_3O$. Calculated, *m/z*: 437.2042.

3-(*tert*-Butylimino)-2-{8-[(4-chlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-yl}-2,3-dihydro-1*H*-isoindol-1-one (9e). Yield 302 mg (69%), white solid, mp 136–138°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.28–1.33 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 1.57 (9H, s, C(CH$_3$)$_3$); 1.74–1.79 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 2.03–2.06 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 2.77–2.82 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 3.28 (2H, br. s, CHNCH); 3.89 (2H, s, NC$\underline{H_2}$Ph); 4.88 (1H, tt, *J* = 12.1, *J* = 6.0, CONCH); 7.28 (2H, d, *J* = 8.4, H-3,5 Ph); 7.43 (2H, d, *J* = 8.3, H-2,6 Ph); 7.56–7.64 (2H, m, H-5,6 isoindoline); 7.87 (1H, d, *J* = 6.8, H-4 isoindoline); 7.98 (1H, d, *J* = 7.3, H-7 isoindoline). ^{13}C NMR spectrum, δ, ppm: 27.4; 30.4; 30.9; 42.5; 52.8; 53.8; 57.7; 123.0; 127.1; 128.3; 128.5; 130.0; 131.0; 131.8; 132.2; 134.4; 138.9; 146.1; 167.5. Found, *m/z*: 435.2069 $[M]^+$. $C_{26}H_{30}{}^{35}ClN_3O$. Calculated, *m/z*: 435.2072. Found, *m/z*: 437.2047 $[M]^+$. $C_{26}H_{30}{}^{37}ClN_3O$. Calculated, *m/z*: 437.2042.

3-(*tert*-Butylimino)-2-{8-[(2-chlorophenyl)methyl]-8-azabicyclo[3.2.1]octan-3-yl}-2,3-dihydro-1*H*-isoindol-1-one (9f). Yield 251 mg (58%), white solid, mp 139–144°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.47 (9H, s, C(CH$_3$)$_3$); 1.74–1.80 (4H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 1.98–2.03 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 2.14–2.16 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 3.31 (2H, br. s, CHNCH); 3.71 (2H, s, NCH$_2$Ph); 4.27 (1H, tt, *J* = 12.1, *J* = 6.0, CONCH); 7.14–7.28 (2H, m, H-4,5 Ph); 7.32 (1H, d, *J* = 7.9, H-6 Ph); 7.53–7.58 (2H, m, H-5,6 isoindoline); 7.76 (1H, d, *J* = 7.5, H-3 Ph); 7.81–7.87 (2H, m, H-4,7 isoindoline). ^{13}C NMR spectrum, δ, ppm: 27.4; 30.4; 38.5; 49.7; 53.0; 55.1; 59.5; 122.6; 122.9; 126.7; 127.5; 129.0; 129.9; 131.8; 131.9; 132.7; 133.5; 134.7; 138.2; 148.1; 151.9. Found, *m/z*: 435.2082 $[M]^+$. $C_{26}H_{30}{}^{35}ClN_3O$. Calculated, *m/z*: 435.2072. Found, *m/z*: 437.2052 $[M]^+$. $C_{26}H_{30}{}^{37}ClN_3O$. Calculated, *m/z*: 437.2042.

3-(*tert*-Butylimino)-2-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-2,3-dihydro-1*H*-isoindol-1-one (9g). Yield 181 mg (56%), white solid, mp 107–111°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.26–1.31 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 1.56 (9H, s, C(CH$_3$)$_3$); 1.72–1.79 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 2.05–2.10 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 2.60 (3H, s, NCH$_3$); 2.74–2.80 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 3.30 (2H, br. s, CHNCH); 4.87 (1H, tt, *J* = 12.0, *J* = 5.9, CONCH); 7.56–7.64 (2H, m, H-5,6 isoindoline); 7.86 (1H, d, *J* = 6.8, H-4 isoindoline); 7.98 (1H, d, *J* = 7.5, H-7 isoindoline). ^{13}C NMR spectrum, δ, ppm: 27.6; 29.1; 30.9; 36.1; 42.1; 53.7; 59.4; 123.0; 127.1; 128.5; 131.0; 131.8; 134.4; 146.1; 167.4. Found, *m/z*: 325.2155 $[M]^+$. $C_{20}H_{27}N_3O$. Calculated, *m/z*: 325.2149.

3-(*tert*-Butylimino)-5-fluoro-2-(8-methyl-8-azabicyclo-[3.2.1]octan-3-yl)-2,3-dihydro-1*H*-isoindol-1-one (9h). Yield 202 mg (59%), white solid, mp 152–154°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.23–1.26 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 1.52 (9H, s, C(CH$_3$)$_3$); 1.68–1.73 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 2.04–2.06 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 2.56 (3H, s, NCH$_3$); 2.69–2.76 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 3.26 (2H, br. s, CHNCH); 4.81 (1H, tt, *J* = 12.1, *J* = 5.9, CONCH); 7.25 (1H, td, *J* = 8.3, *J* = 5.2, H-6 isoindoline); 7.63 (1H, dd, *J* = 9.3, *J* = 2.1, H-7 isoindoline); 7.82 (1H, dd, *J* = 8.3, *J* = 5.2, H-4 isoindoline). ^{13}C NMR spectrum, δ, ppm (*J*, Hz): 27.7; 29.1; 30.9; 36.2; 42.6; 53.8; 59.4; 114.8 (d, $^2J_{CF}$ = 26.3, C-4 isoindoline); 118.1 (d, $^2J_{CF}$ = 23.3, C-6 isoindoline); 124.9 (d, $^3J_{CF}$ = 9.5, COC$\underline{C}$H); 130.3 (d, $^4J_{CF}$ = 2.2, NCO$\underline{C}$); 130.5 (d, $^3J_{CF}$ = 8.9, FCCH$\underline{C}$CN); 144.9; 164.7 (d, $^1J_{CF}$ = 251.1, CF); 166.41. Found, *m/z*: 343.2061 $[M]^+$. $C_{20}H_{26}FN_3O$. Calculated, *m/z*: 343.2054.

3-(*tert*-Butylimino)-6-methoxy-2-(8-methyl-8-aza-bicyclo[3.2.1]octan-3-yl)-2,3-dihydro-1*H*-isoindol-1-one (9i). Yield 234 mg (66%), white solid, mp 166–169°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.23–1.28 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 1.53 (9H, s, C(CH$_3$)$_3$); 1.70–1.76 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 2.05–2.10 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 2.60 (3H, s, NCH$_3$); 2.73–2.79 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 3.28 (2H, br. s, CHNCH); 3.90 (3H, s, OCH$_3$); 4.84 (1H, tt, *J* = 12.1, *J* = 5.9, CONCH); 7.10 (1H, dd, *J* = 8.6, *J* = 2.5, H-5 isoindoline); 7.33 (1H, d, *J* = 2.3, H-4 isoindoline); 7.86 (1H, d, *J* = 8.6, H-7 isoindoline). ^{13}C NMR spectrum, δ, ppm: 27.7; 29.0; 30.8; 36.1; 42.2; 53.5; 55.8; 59.4; 106.4; 118.7; 121.0; 128.5; 136.9; 146.0; 161.9; 167.2 Found, *m/z*: 355.2263 $[M]^+$. $C_{21}H_{29}N_3O_2$. Calculated, *m/z*: 355.2254.

3-(*tert*-Butylimino)-5-chloro-2-(8-methyl-8-azabicyclo-[3.2.1]octan-3-yl)-2,3-dihydro-1*H*-isoindol-1-one (9j). Yield 275 mg (77%), white solid, mp 173–176°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.34–1.39 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 1.55 (9H, s, C(CH$_3$)$_3$); 1.79–1.84 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 2.22–2.25 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 2.73 (3H, s, NCH$_3$); 2.76–2.83 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 3.45 (2H, br. s, CHNCH); 4.87 (1H, tt, *J* = 12.1, *J* = 6.0, CONCH); 7.58 (1H, d, *J* = 8.0, H-6 isoindoline); 7.80 (1H, d, *J* = 8.0, H-7 isoindoline); 7.94 (1H, s, H-4 isoindoline). ^{13}C NMR spectrum, δ, ppm: 27.2; 28.3; 31.0; 35.3; 41.7; 54.1; 59.6; 124.2; 127.5; 129.9; 131.3; 132.4; 138.3; 144.6; 166.4. Found, *m*/*z*: 359.1763 [M]$^+$. $C_{20}H_{26}{}^{35}ClN_3O$. Calculated, *m*/*z*: 359.1759. Found, *m*/*z*: 361.1727 [M]$^+$. $C_{20}H_{26}{}^{37}ClN_3O$. Calculated, *m*/*z*: 361.1729.

3-(Benzylimino)-2-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-2,3-dihydro-1*H*-isoindol-1-one (9k). Yield 226 mg (63%), white solid, mp 124–127°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.34–1.39 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 1.75–1.81 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 2.07–2.12 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 2.51 (3H, s, NCH$_3$); 2.80–2.87 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 3.29 (2H, br. s, CHNCH); 4.91 (1H, tt, *J* = 12.0, *J* = 6.1, CONCH); 5.25 (2H, s, NCH$_2$Ph); 7.29 (1H, t, *J* = 7.3, H-4 Ph); 7.39 (2H, t, *J* = 7.6, H-3,5 Ph); 7.46 (2H, d, *J* = 7.4, H-2,6 Ph); 7.61–7.65 (2H, m, H-5,6 isoindoline); 7.88–7.90 (1H, m, H-4 isoindoline); 7.95–7.97 (1H, m, H-7 isoindoline). ^{13}C NMR spectrum, δ, ppm: 27.6; 29.4; 36.2; 42.8; 53.7; 59.4; 123.4; 125.6; 126.9; 127.2; 128.5; 129.6; 131.6; 132.8; 133.1; 140.2; 151.1; 167.6. Found, *m*/*z*: 359.1997 [M]$^+$. $C_{23}H_{25}N_3O$. Calculated, *m*/*z*: 359.1992.

3-(Cyclohexylimino)-2-(8-methyl-8-azabicyclo[3.2.1]-octan-3-yl)-2,3-dihydro-1*H*-isoindol-1-one (9l). Yield 234 mg (67%), white solid, mp 140–142°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.25–1.28 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 1.37–1.47 (3H, m, H cyclohexane); 1.60–1.62 (2H, m, H cyclohexane); 1.69–1.73 (1H, m, H cyclohexane); 1.75–1.77 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 1.86–1.92 (4H, m, H cyclohexane); 2.06–2.10 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 2.64 (3H, s, NCH$_3$); 2.79–2.85 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 3.28 (2H, br. s, CHNCH); 4.21–4.26 (1H, m, 1-CH cyclohexane); 4.81 (1H, tt, *J* = 12.1, *J* = 6.0, CONCH); 7.55–7.63 (2H, m, H isoindoline); 7.82–7.87 (2H, m, H isoindoline). ^{13}C NMR spectrum, δ, ppm: 24.6; 25.7; 27.9; 28.4; 34.5; 35.5; 42.7; 57.5; 59.0; 123.2; 125.3; 129.5; 131.1; 132.6; 133.2; 148.0; 167.4. Found, *m*/*z*: 351.2314 [M]$^+$. $C_{22}H_{29}N_3O$. Calculated, *m*/*z*: 351.2305.

3-(Butylimino)-2-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-2,3-dihydro-1*H*-isoindol-1-one (9m). Yield 168 mg (52%), white solid, mp 123–126°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.00 (3H, t, *J* = 7.4, NCH$_2$CH$_2$CH$_2$C$\underline{H_3}$); 1.25–1.31 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 1.48–1.57 (2H, m, NCH$_2$C$\underline{H_2}$CH$_2$CH$_3$); 1.75–1.83 (4H, m, NCH$_2$CH$_2$C$\underline{H_2}$CH$_3$, CHC$\underline{H_2}$C$\underline{H_2}$CH); 2.07–2.10 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 2.62 (3H, s, NCH$_3$); 2.78–2.85 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 3.29 (2H, br. s, CHNCH); 3.97 (2H, t, *J* = 6.8, NC$\underline{H_2}$CH$_2$CH$_2$CH$_3$); 4.81 (1H, tt, *J* = 12.1, *J* = 6.0, CONCH); 7.57–7.64 (2H, m, H-5,6 isoindoline); 7.86 (1H, d, *J* = 6.6, H-4 isoindoline); 7.92 (1H, d, *J* = 6.8, H-7 isoindoline). ^{13}C NMR spectrum, δ, ppm: 14.0; 20.7; 27.7; 28.9; 34.0; 35.8; 42.5; 50.0; 59.1; 123.2; 125.6; 129.6; 131.2; 132.5; 133.0; 149.8; 167.5. Found, *m*/*z*: 325.2153 [M]$^+$. $C_{20}H_{27}N_3O$. Calculated, *m*/*z*: 325.2149.

3-(Isopropylimino)-2-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-2,3-dihydro-1*H*-isoindol-1-one (9n). Yield 176 mg (57%), white solid, mp 109–111°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.37 (6H, d, *J* = 6.2, CH(C$\underline{H_3}$)$_2$); 1.66–1.71 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 2.07–2.13 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 2.69–2.71 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 3.01–3.07 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 3.19 (3H, s, NCH$_3$); 3.92 (2H, br. s, CHNCH); 4.59–4.69 (1H, m, NC$\underline{H}$(CH$_3$)$_2$); 4.94 (1H, tt, *J* = 12.0, *J* = 6.1, CONCH); 7.64–7.72 (2H, m, H-5,6 isoindoline); 7.80 (1H, d, *J* = 6.5, H-4 isoindoline); 7.95 (1H, d, *J* = 7.4, H-7 isoindoline). ^{13}C NMR spectrum, δ, ppm: 24.5; 25.9; 26.4; 29.7; 39.7; 49.8; 60.0; 123.7; 125.9; 129.2; 131.9; 132.3; 133.5; 148.0; 167.2. Found, *m*/*z*: 311.1996 [M]$^+$. $C_{19}H_{25}N_3O$. Calculated, *m*/*z*: 311.1992.

2-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-3-(phenylimino)-2,3-dihydro-1*H*-isoindol-1-one (9o). Yield 164 mg (48%), yellow solid, mp 131–133°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.44–1.49 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 1.78–1.83 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 2.11–2.13 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 2.58 (3H, s, NCH$_3$); 2.85–2.92 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 3.34 (2H, br. s, CHNCH); 4.85 (1H, tt, *J* = 12.1, *J* = 6.1, CONCH); 6.57 (1H, d, *J* = 7.8, H isoindoline); 6.94–6.97 (2H, m, H Ph); 7.20 (1H, t, *J* = 7.4, H-4 Ph); 7.25–7.29 (1H, m, H isoindoline); 7.37–7.41 (2H, m, H Ph); 7.50 (1H, t, *J* = 7.5, H-4 isoindoline); 7.81 (1H, d, *J* = 7.5, H-7 isoindoline). ^{13}C NMR spectrum, δ, ppm: 27.3; 29.7; 36.5; 43.2; 59.5; 119.7; 123.1; 124.0; 125.4; 129.4; 129.5; 131.7; 132.4; 132.7; 148.9; 150.4; 167.8. Found, *m*/*z*: 345.1843 [M]$^+$. $C_{22}H_{23}N_3O$. Calculated, *m*/*z*: 345.1836.

3-[(4-Methoxyphenyl)imino]-2-(8-methyl-8-azabicyclo-[3.2.1]octan-3-yl)-2,3-dihydro-1*H*-isoindol-1-one (9p). Yield 251 mg (67%), white solid, mp 142–147°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.41–1.45 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 1.77–1.82 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 2.06–2.12 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 2.58 (3H, s, NCH$_3$); 2.84–2.91 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 3.32 (2H, br. s, CHNCH); 3.86 (3H, s, OCH$_3$); 4.84 (1H, tt, *J* = 12.1, *J* = 6.0, CONCH); 6.69 (1H, d, *J* = 7.8, H isoindoline); 6.87–6.95 (4H, m, H Ph); 7.27–7.31 (1H, m, H isoindoline); 7.50 (1H, t, *J* = 7.5, H-4 isoindoline); 7.81 (1H, d, *J* = 7.5, H-7 isoindoline). ^{13}C NMR spectrum, δ, ppm: 27.5; 29.6; 36.5; 43.3; 55.6; 59.4; 114.6; 120.8; 123.1; 125.4; 129.3; 131.6; 132.4; 132.7; 142.1; 150.9; 156.5; 167.8. Found, *m*/*z*: 375.1951 [M]$^+$. $C_{23}H_{25}N_3O_2$. Calculated, *m*/*z*: 375.1941.

3-(*tert*-Butylimino)-2-(8-ethyl-8-azabicyclo[3.2.1]octan-3-yl)-2,3-dihydro-1*H*-isoindol-1-one (9q). Yield 254 mg (75%), white solid, mp 85–86°C (cyclohexane–EtOAc). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.08 (3H, t, *J* = 7.2, CH$_2$C$\underline{H_3}$); 1.11–1.16 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 1.47 (9H, s, C(CH$_3$)$_3$); 1.63–1.66 (2H, m, CHC$\underline{H_2}$C$\underline{H_2}$CH); 1.94–1.96 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 2.63–2.69 (2H, m, CHC$\underline{H_2}$CHC$\underline{H_2}$CH); 2.85 (2H, q, *J* = 6.8, C$\underline{H_2}$CH$_3$); 3.32 (2H, br. s, CHNCH); 4.80 (1H, tt, *J* = 12.1, *J* = 6.0, CONCH); 7.46–7.55 (2H, m, H-5,6 isoindoline); 7.75 (1H, d, *J* = 7.2, H-4 isoindoline); 7.89 (1H, d, *J* = 7.7, H-7

isoindoline). ^{13}C NMR spectrum, δ, ppm: 13.5; 27.7; 28.2; 30.8; 41.5; 42.2; 53.7; 56.5; 122.9; 127.1; 128.4; 130.9; 131.7; 134.3; 146.2; 167.3. Found, *m*/*z*: 339.2313 $[M]^+$. $C_{21}H_{29}N_3O$. Calculated, *m*/*z*: 339.2305.

In vitro* test against nematodes *B. xylophilus* and *M. incognita. All target compounds were dissolved in DMSO and diluted to required concentration with 0.1% aqueous solution of Triton X-100. The sample solution was added to 96-well plates (50 μl each well), and then nematodes (about 60 pieces) were added. The plates were capped and placed in the observation room at 22 ± 1°C. Distilled H_2O containing Triton X-100 and DMSO was used as blank control. The positive control was run with a solution of fenamiphos or avermectin.[17] For each sample, the bioassay was repeated twice, and the nematicidal activity is indicated by the average inhibition ratio on nematode of two trials.

Test against the infestation of *M. incognita* in cucumber plants. The germinant cucumber seedlings were planted in a test tube containing a substrate soil. Sample solution (3 ml) and around 2000 root-knot nematodes *M. incognita* second-instar larvae were added to each tube. Distilled H_2O containing Triton X-100 (0.1 mg/l) and DMSO was used as blank control. The positive control was run with a solution of avermectin. All test tubes were placed in the observation room at 22 ± 1°C. After 2 weeks, the plant roots were washed out with H_2O and the number of root knots was counted, graded, and scored. For each sample, the bioassay was repeated three times with four replicates in each trial. The nematicidal activity is indicated by the average inhibition ratio on root knots of three trials.

Inhibition ratio (%) = (1 – Treat score/Blank control score) × 100%.

Supplementary information file containing neurogenic curvature photos of *B. xylophilus*, as well as ^{1}H and ^{13}C NMR spectra of all synthesized compounds, is available at the journal website at http://link.springer.com/journal/10593.

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References

1. Sasser, J. N.; Freckman, D. W. In *Vistas on Nematology: A Commemoration of the Twenty-fifth Anniversary of the Society of Nematologists*; Veech, J. A.; Freckman, D. W., Eds.; Society of Nematologists: Maryland, 1987, p. 7.
2. Jones, J. T.; Haegeman, A.; Danchin, E. G. J.; Gaur, H. S.; Helder, J.; Jones, M. G. K.; Kikuchi, T.; Manzanilla-López, R.; Palomares-Rius, J. E.; Wesemael, W. M. L.; Perry, R. N. *Mol. Plant. Pathol.* **2013**, *14*, 946.
3. (a) de Souza, A.; Narvencar, K. P. S.; Sindhoora, K. V. *J. Neurol. Sci.* **2013**, *335*, 36. (b) Arnot, L. F.; Steyl, J. C. A.; Myburgh, J. G.; Veale, D. J. H. J. S. *Afr. Vet. Assoc.* **2011**, *82*, 232. (c) Qin, S.; Gan, J.; Liu, W.; Becker, J. O. *J. Agric. Food Chem.* **2004**, *52*, 6239. (d) Sánchez-Moreno, S.; Alonso-Prados, E.; Alonso-Prados, J. L.; García-Baudin, J. M. *Pest Manage. Sci.* **2009**, *65*, 82.
4. (a) Pitterna, T.; Cassayre, J.; Hüter, O. F.; Jung, P. M. J.; Maienfisch, P.; Kessabi, F. M.; Quaranta, L.; Tobler, H. *Bioorg. Med. Chem.* **2009**, *17*, 4085. (b) Mushtaq, M.; Feely, W. F.; Syintsakos, L. R.; Wislocki, P. G. *J. Agric. Food Chem.* **1996**, *44*, 940.
5. (a) Young, S. N. *J. Psychiatr. Neurosci.* **2007**, *32*, 394. (b) Berger, M.; Gray, J. A.; Roth, B. L. *Annu. Rev. Med.* **2009**, *60*, 355. (c) Yano, J. M.; Yu, K.; Donaldson, G. P.; Shastri, G. G.; Ann, P.; Ma, L.; Nagler, C. R.; Ismagilov, R. F.; Mazmanian, S. K.; Hsiao, E. Y. *Cell* **2015**, *161*, 264.
6. (a) Srinivasan, S.; Sadegh, L.; Elle, I. C.; Christensen, A. G. L.; Faergeman, N. J.; Ashrafi, K. *Cell Metab.* **2008**, *7*, 533. (b) Heusser, S. A.; Yoluk, Ö.; Klement, G.; Riederer, E. A.; Lindahl, E.; Howard, R. J. *J. Neurochem.* **2016**, *138*, 243. (c) Sawin, E. R.; Ranganathan, R.; Horvitz, H. R. *Neuron* **2000**, *26*, 619. (d) Shea-Donohue, T.; Sun, R.; Bohl, J. A.; McLean, L. P.; Zhao, A. *Cytokine* **2015**, *75*, 62.
7. Trowell, S. C.; Dumancic, M.; Llao, C.; Easr, P. US Patent 20030186370.
8. (a) Hibert, M. F.; Hoffmann, R.; Miller, R. C.; Carr, A. A. *J. Med. Chem.* **1990**, *33*, 1594. (b) Thompson, A. J.; Lummis, S. C. R. *Curr. Pharm. Des.* **2006**, *12*, 3615.
9. Kostochka, L. M.; Lezina, V. P.; Kostochka, M. L. *Chem. Heterocycl. Compd.* **2003**, *39*, 1227. [*Khim. Geterotsikl. Soedin.* **2003**, 1227.]
10. (a) Cui, J.-L.; Fu, X.-G.; Lu Q.; Song G.-H; Sun L.; Wang, J.-Y.; Xu, B.-L.; Xu, J.; Zheng, Y.-T.; Zhou, X.-Y.; Zhu, J.-P. CN Patent 105294674. (b) Lu, Q.; Shen, Q.-Y.; Song, G.-H.; Sun, L.; Wang, J.-Y. CN Patent 105315279.
11. Hirokawa, Y.; Morie, T.; Yamazaki, H.; Yoshida, N.; Kato, S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 619.
12. Zabrowski, D. L.; Flynn, D. L. US Patent 4992461.
13. (a) Cai, M.; Li, Z.; Fan, F.; Huang, Q.; Shao, X.; Song, G. H. *J. Agric. Food Chem.* **2010**, *58*, 2624. (b) Shen, Y.; Wang, J.-Y.; Song, G.-H. *Mol. Diversity* **2014**, *18*, 195. (c) Lu, Q.; Shen, Q.; Sun, L.; Wang, J.; Song, G. *Chin. J. Org. Chem.* **2016**, *36*, 760 [In Chinese]. (d) Sun, H.; Li, H.; Wang, J.; Song, G. *Chin. Chem. Lett.* **2018**, *29*, 977.
14. (a) Huang, M.-Z.; Huang, K.-L.; Ren, Y.-G.; Lei, M.-X.; Huang, L.; Hou, Z.-K.; Liu, A.-P.; Ou, X.-M. *J. Agric. Food Chem.* **2005**, *53*, 7908. (b) Chen, X.-L.; Li, Z.; Shao, X.-S.; Wang, G.-L.; Xu, X.-Y.; Xu, Z.-P.; Zhang, J.-W. WO Patent 2016116058.
15. Crouse, G. D.; Sparks, T. C. WO Patent 2013019824.
16. Sharma, U. K.; Sharma, N.; Xu, J.; Song, G.; Van der Eycken, E. V. *Chem.–Eur. J.* **2015**, *21*, 4908.
17. Huang, J.; Chen, A.-L.; Zhang, H.; Yu, Z.; Li, M.-H.; Li, N.; Lin, J.-T.; Bai, H.; Wang, J.-D.; Zheng, Y.-G. *Appl. Environ. Microbiol.* **2015**, *81*, 5326.