Bioorganic & Medicinal Chemistry 19 (2011) 3120–3127

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

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

Tryptamine derivatives as novel non-nucleosidic inhibitors against hepatitis B virus

Shi-Jin Qu [a,†], Gui-Feng Wang [b,†], Wen-Hu Duan [c], Shan-Yan Yao [c], Jian-Ping Zuo [b,*], Chang-Heng Tan [a,*], Da-Yuan Zhu [a]

[a] Department of Natural Medicinal Chemistry, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China
[b] State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China
[c] Synthetic Organic & Medicinal Chemistry Laboratory, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China

ARTICLE INFO

Article history:
Received 17 February 2011
Revised 30 March 2011
Accepted 1 April 2011
Available online 6 April 2011

Keywords:
Tryptamine derivatives
Anti-HBV activity
Non-nucleosidic inhibitors

ABSTRACT

A series of tryptamine derivatives were synthesized and evaluated for their anti-hepatitis B virus (HBV) activity and cytotoxicity in the HepG2.2.15 cell line. The preliminary SAR was discussed. Compounds **2e** and **4a** showed potent antiviral activity (IC_{50} = 0.4 and <1 μM, respectively) and low cytotoxicity (CC_{50} = 40.6 and >25 μM, respectively).

1. Introduction

Hepatitis B is a potentially life-threatening liver infection caused by the hepatitis B virus (HBV). It can cause chronic liver disease and puts people at high risk of death from cirrhosis of the liver and liver cancer. WHO estimated that 2 billion people worldwide had been infected by HBV with about 600,000 persons died each year due to the acute or chronic consequences of hepatitis B.[1] Current treatment regimens for the patients with chronic HBV relies mainly on the use of interferon-α (IFN), or nucleoside analogs, such as lamivudine, adefovir dipivoxil (ADV) or entecavir. However, the use of IFN and peg-IFN was limited by low sustained response rates (20–30%) and the numerous side effects.[2,3] On the other hand, nucleoside analogues are well tolerated and exhibit an early and potent antiviral effect which is limited by the selection of resistant mutants during long-term therapy and nephrotoxicity.[4–6] Therefore, new non-nucleoside anti-HBV agents with different mechanisms are desperately needed.

Natural compounds, due to their structural diversity, provide a large opportunity for screening anti-HBV agents possessing novel structures and mechanisms.[7–11] Our previous study disclosed that *N*,*N*-dimethyltryptamine N^{12}-oxide **3a** (Fig. 1), a natural alkaloid from liver-protective medicinal plant *Evodia fargesii* Dode (Rutaceae), had potent inhibitory effect on HBV DNA replication (IC_{50} = 17.6 μM, SI >5.7) in the HepG2.2.15 cell line.[12] Tryptamine analogues such as **3a** might be the ligands of 5-HT (5-hydroxytryptamine, a neurotransmitter) receptor, which possibly involve in obesity and certain neuropsychiatric disorders.[13,14] In order to search more potent inhibitors against HBV, we designed and synthesized a series of tryptamine derivatives to evaluate their anti-HBV activity. The strategies for structure modification of tryptamine (**1a**) were as following (Fig. 1): (1) introduction of different alkyls, cycloalkyls, aromatic or heteroaromatic ring groups in N-12 position, (2) introduction of *N*-oxide in N-12 position, (3) introduction of hydroxyl or halogens in C-5, to study the influence on anti-HBV activity and cytotoxicity. Further exploration based on the optimized compound **2e** was also carried out, which comprised, (4) introduction of single isopentyl, and isopentyl with another alkyls in N-12 position of **1a**, and (5) replacement of H with benzenesulfonyl in N-1 position of **2e**. In this paper, we report a series of novel tryptamine derivatives and their anti-HBV activity in vitro.

2. Results and discussion

2.1. Chemistry

A series of tryptamine derivatives were obtained through the general procedures as shown in Schemes 1–3. The structures of target compounds are listed in Tables 1–4, respectively. Tryptamine hydrochloride or 5-substituted tryptamine hydrochlorides

* Corresponding authors. Tel.: +86 21 50806728; fax: +86 21 50807088 (C.-H.T.).
E-mail addresses: jpzuo@mail.shcnc.ac.cn (J.-P. Zuo), chtan@mail.shcnc.ac.cn (C.-H. Tan).
† These two authors contributed equally to this work.

0968-0896/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2011.04.004

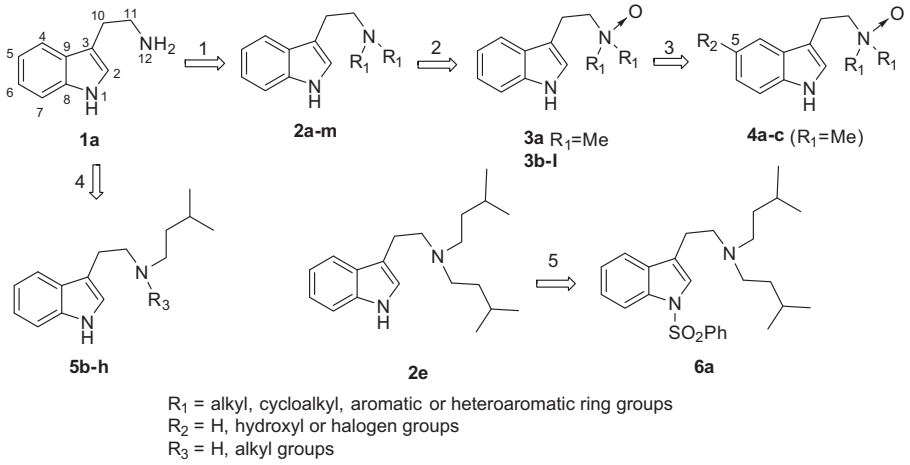
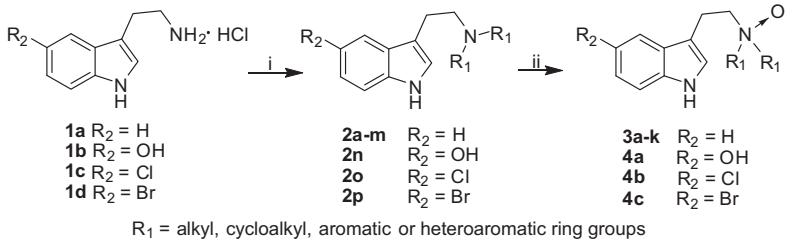
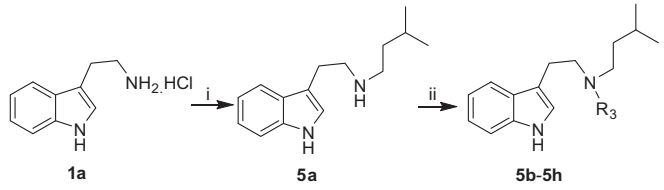


Figure 1. Synthesized strategies for tryptamine derivatives.



Scheme 1. Reagents and conditions: (i) NaOMe, MeOH, 30% CH_2O (aq) or other appropriate aldehydes, $NaCNBH_3$, AcOH, rt, 2–16 h; (ii) MCPBA, $CHCl_3$, 0 °C, 10 min.



Scheme 2. Reagents and conditions: (i) NaOMe, MeOH, isovaleraldehyde (ratio: 1:1), $NaCNBH_3$, AcOH, 0 °C, 0.5 h; (ii) appropriate aldehyde (ratio: 1:2.4), rt, overnight.

(**1a**–**d**), as started material, were commercially available. Neutralization of the hydrochlorides with sodium methoxide in dry methanol afforded the corresponding free primary amines. Subsequently the primary amine group was dialkylated by reductive alkylation with aqueous formaldehyde or other appropriate aldehydes in the presence of sodium cyanoborohydride under weak acidic condition to yield **2a**–**p**.[15] Oxidation was carried out on N-12 position of **2a**–**k** and **2n**–**p** with *m*-chloroperoxybenzoic acid (MCPBA) in $CHCl_3$ to give **3a**–**k** and **4a**–**c** (Scheme 1).[16]

Encouraged by the optimized compound **2e**, **5a**–**g** possessing one isopentyl and another alkyl in N-12 position of **1a** were prepared under moderate reductive alkylation reaction (Scheme 2). Furthermore, **2e** was treated with benzenesulfonyl chloride under basic condition to yield **6a** (Scheme 3).[17]

2.2. Biological activity test

All the synthesized tryptamine derivatives were evaluated for their cytotoxicity and anti-HBV activity with the antiviral drug lamivudine as reference control. Cytotoxicity data (CC_{50}) and inhibitory activity on HBV DNA replication (IC_{50}), along with the therapeutic selective index (SI) of each tested compound, are presented in Tables 1–4, in which half of the evaluated compounds exhibited inhibitory effect on HBV DNA replication and were superior to **3a**.

To identify the effects of N-12-dialkylation and their N^{12}-oxides, two subseries of derivatives **2a**–**m** and **3a**–**k** were synthesized and assessed for anti-HBV activity (Scheme 1, Tables 1 and 2). Among compounds **2a**–**m**, the diisopentyl derivative **2e** showed dramatically increased antiviral activity (IC_{50} = 0.4 μM), which approached to lamivudine (IC_{50} = 0.33 μM) and about 44 times higher than **3a** (IC_{50} = 17.6 μM). The SI of **2e** was also the highest in all tested modified compounds. By contrast, whenever the chain of the alkyl substituted on N-12 position shortened or lengthened the inhibitory activity fell off correspondingly, which suggested that isopentyl group was an important determinant for the anti-HBV activity.

Although the introduction of aromatic or heteroaromatic rings in N-12 brought considerable antiviral activity, it resulted in a noticeable cytotoxicity (CC_{50}: 12.4–33.3 μM). Among them, electron-rich heteroaromatic groups such as furanyl and thiophenyl were more in favor of enhancing inhibitory activity than the electron-deficient groups. The similar results were also observed between **2l** with trimethoxybenzyl substituent and **2m** with nitrobenzyl substituent.

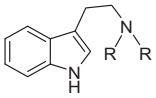
To our surprise, oxidation of N-12 in tryptamine derivatives did decrease the anti-HBV activity with the only exception of **3a**. Most of the N^{12}-oxide derivatives exhibited poor antiviral activities. N^{12}-oxides seemed to have a negative influence on antiviral activities in certain range.

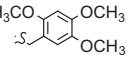
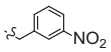
To identify the effects of electron donor/acceptor substituents in C-5 position, hydroxyl and halogen were introduced. All of them exhibited significant antiviral activities. The 5-hydroxyl derivative

4a showed the most potent inhibition efficacy on HBV with more than 50% inhibitory ratio at the concentration of 1 μM, which was another optimized compound. However, the certain IC_{50} value of **4a** could not be calculated, which might be related with **4a** being easily oxidated by exposure to the air. Compound **4c** with Cl substituent showed lower antiviral activity than those of **4a** (OH) and **4b** (Br), suggesting that the more capable of electron-withdrawing element was undesirable.

Continuous exploration based on **2e** was carried out as shown in Scheme 3. Replacement of one of the diisopentyl in N-12 position with hydrogen or other alkyl such as methyl, ethyl, propyl and isobutyl led to uniformly inferior activity in contrast with **2e**. Moreover, with the chain growth of the replaced alkyl, there appeared a comeback inhibition trend. Benzenesulfonyl substituted in N-1 position is detrimental to activity, which indicated that electron-withdrawing group in N-1 position might reduce the inhibitory activity.

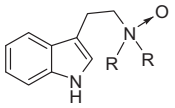
Table 1
Structures of compounds **2a**–**m** and their inhibitory activities on HBV replication[a]



Compound	R	CC_{50}[b]	IC_{50}[c]	SI[d]
2a	Me	>100	>100	—
2b	Et	>100	>100	—
2c	*n*-Pr	>100	>100	—
2d	*i*-Bu	>100	12.2	>8.2
2e	*i*-Pentyl	40.6	0.4	102
2f	$-CH_2$-cyclopropyl	>100	6	>16.7
2g	$-CH_2$-cyclohexyl	>33.3	>100	—
2h	$-CH_2Ph$	12.4	13	0.95
2i	$-CH_2$(2-pyridyl)	5.8	>25	—
2j	$-CH_2$(2-furyl)	27.3	3.5	7.8
2k	$-CH_2$(2-thiophyl)	>33.3	3.9	>8.5
2l		21	1.2	17.2
2m		>100	>100	—
Lamivudine		1174	0.33	3557

[a] The data shown here are from a representative experiment repeated three times with similar results.
[b] CC_{50}: 50% cytotoxic concentration (μM) in HepG2.2.15 cells.
[c] IC_{50}: 50% inhibitory concentration (μM).
[d] SI: selective index (= CC_{50}/IC_{50}); '—': The relevant SI cannot be calculated.

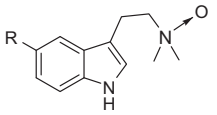
Table 2
Structures of compounds **3a**–**l** and their inhibitory activities on HBV replication[a]



Compound	R	CC_{50}[b]	IC_{50}[c]	SI[d]
3a	Me	>100	17.6	>5.7
3b	Et	>100	>100	—
3c	*n*-Pr	>100	>100	—
3d	*i*-Bu	>100	>100	—
3e	*i*-Pentyl	77.6	NC[e]	—
3f	$-CH_2$-cyclopropyl	>100	>100	—
3g	$-CH_2$-cyclohexyl	23.1	>100	—
3h	CH_2Ph	>100	>100	—
3i	CH_2(2-pyridyl)	56.5	>100	—
3j	CH_2(2-furyl)	>100	7.5	>13.3
3k	CH_2(2-thiophyl)	>100	9.4	>10.6

[a] The data shown here are from a representative experiment repeated three times with similar results.
[b] CC_{50}: 50% cytotoxic concentration (μM) in HepG2.2.15 cells.
[c] IC_{50}: 50% inhibitory concentration (μM).
[d] SI: selective index (= CC_{50}/IC_{50}), '—': The relevant SI cannot be calculated.
[e] NC: IC_{50} cannot be calculated.

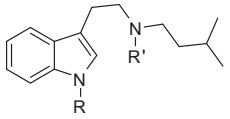
Table 3
Structures compounds **4a**–**c** and their inhibitory activities on HBV replication[a]



Compound	R	CC_{50}[b]	IC_{50}[c]	SI[d]
4a	OH	>25	<1	>25
4b	Br	>25	5.4	>4.6
4c	Cl	>25	8.4	>3

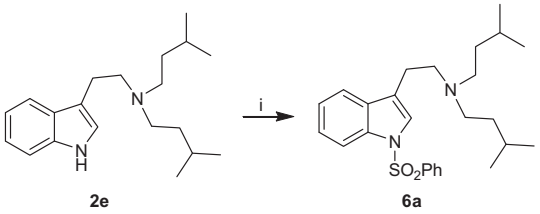
[a] The data shown here are from a representative experiment repeated three times with similar results.
[b] CC_{50}: 50% cytotoxic concentration (μM) in HepG2.2.15 cells.
[c] IC_{50}: 50% inhibitory concentration (μM).
[d] SI: selective index (= CC_{50}/IC_{50}).

Table 4
Structures of compounds **5a**–**g** and **6a** and their inhibitory activities on HBV replication[a]



Compound	R	R′	CC_{50}[b]	IC_{50}[c]	SI[d]
5a	H	H	>25	>25	—
5b	H	Me	>25	>25	—
5c	H	Et	>25	>25	—
5d	H	*n*-Pr	>25	20	>1.25
5e	H	*i*-Bu	>25	1.1	>23
5f	H	CH_2(2-furyl)	>25	5.3	>4.7
5g	H	CH_2(2-thiophyl)	>25	10.1	>2.5
6a	SO_2Ph	*i*-Pentyl	15	>25	—

[a] The data shown here are from a representative experiment repeated three times with similar results.
[b] CC_{50}: 50% cytotoxic concentration (μM) in HepG2.2.15 cells.
[c] IC_{50}: 50% inhibitory concentration (μM).
[d] SI: selective index (= CC_{50}/IC_{50}); '—': The relevant SI cannot be calculated.



Scheme 3. Reagents and conditions: (i) NaH, 110 °C, dry DMF, $PhSO_2Cl$, 0 °C, 10 min, rt, 3 h.

3. Conclusion

In summary, a series of novel tryptamine analogues were prepared and assessed for their anti-HBV activity and cytotoxicity in vitro. The preliminary SAR was discussed. Compounds **2e** and **4a** showed potent antiviral activities (IC_{50} = 0.4 and <1 μM, respectively) and high selectivity (SI = 102 and >25, respectively).

4. Materials and methods

4.1. General

^{1}H (400 MHz) and ^{13}C NMR (100 MHz) spectra were acquired on a Bruker AM-400 spectrometer with TMS as internal standard in $CDCl_3$, CD_3OD, D_2O or C_5D_5N. Chemical shifts (δ) are reported in parts per million (ppm). The ^{1}H NMR signals are described as s (singlet), d (doublet), t (triplet), q (quarter), m (multiple), and dd (doublet of doublet). Coupling constants (J values) are given in Hertz. The ^{13}C NMR signals are described as s (C), d (CH), t (CH_2), and q (CH_3). ESI-MS and HR-ESI-MS data were acquired on Finnigan LCQ-Deca and Waters/Micromass Q-Tof-Ultima mass spectrometers, respectively. Silica gel (200–300 meshes) was used for column chromatography (CC), and precoated plates of silica gel (HSGF254; Qingdao Haiyang Chemical Group Co., Qingdao, China) were used for TLC to monitor the reactions. Started materials **1a**–**d** were purchased from Alfa.

4.2. Synthesis

4.2.1. General procedure for the preparation of compounds 2a–m

A stirred solution of tryptamine (**1a**) (200 mg, 1.25 mmol) in anhydrous methanol (20 mL) was added glacial acetic acid (280 μL, 4.99 mmol) followed by sodium cyanoborohydride (157 mg, 2.50 mmol) under Ar_2 at 0 °C. A solution of formaldehyde (38%, 220 μL, 3.00 mmol) or other appropriate aldehydes (3.00 mmol) in anhydrous methanol (15 mL) was then added dropwise over 20 min, and the resulting solution was stirred at room temperature for 2–16 h. Aqueous Na_2CO_3 (2 N) was added to adjust pH to 8–9 and the methanol was removed under reduce pressure. The residue was partitioned between $CHCl_3$ and water. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuum. The crude product was purified by CC of silica gel with gradient $CHCl_3$/MeOH as eluant afforded compounds **2a**–**m**.

4.2.1.1. *N,N*-Dimethyltryptamine (2a). Colorless thick oil (223 mg, 95% yield). ^{1}H NMR ($CDCl_3$): δ 8.11 (br s, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.19 (t, J = 7.9 Hz, 1H), 7.12 (t, J = 7.8 Hz, 1H), 7.03 (s, 1H), 2.99 (m, 2H), 2.70 (m, 2H), 2.38 (s, 6H); ^{13}C NMR (DEPT) ($CDCl_3$): δ 136.3 (s), 127.4 (s), 121.8 (d), 121.6 (d), 119.1 (d), 118.7 (d), 113.9 (s), 111.1 (d), 60.2 (t), 45.2 (q × 2), 23.5 (t). ESI-MS: m/z 189 ([M+H]$^+$); HR-ESI-MS: calcd for $C_{12}H_{17}N_2$ ([M+H]$^+$) 189.1392, found 189.1393.

4.2.1.2. *N,N*-Diethyltryptamine (2b). Colorless thick oil (262 mg, 97% yield). ^{1}H NMR ($CDCl_3$): δ 8.00 (br s, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 7.04 (s, 1H), 2.96 (m, 2H), 2.88 (m, 2H), 2.58 (q, J = 8.3 Hz, 4H), 0.92 (t, J = 7.4 Hz, 6H); ^{13}C NMR (DEPT) ($CDCl_3$): δ 136.4 (s), 127.6 (s), 122.2 (d), 121.7 (d), 119.5 (d), 118.9 (d), 114.3 (s), 111.3 (d), 56.1 (t × 2), 54.8 (t), 22.6 (t), 12.1 (q × 2). ESI-MS: m/z 217 ([M+H]$^+$); HR-ESI-MS: calcd for $C_{14}H_{21}N_2$ ([M+H]$^+$) 217.1705, found 217.1702.

4.2.1.3. *N,N*-Dipropyltryptamine (2c). Colorless thick oil (287 mg, 94% yield). ^{1}H NMR ($CDCl_3$): δ 8.04 (br s, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 7.12 (t, J = 7.8 Hz, 1H), 7.02 (s, 1H), 2.93 (m, 2H), 2.82 (m, 2H), 2.53 (m, 4H), 1.54 (m, 4H), 0.91 (t, J = 7.4 Hz, 6H); ^{13}C NMR (DEPT) ($CDCl_3$): δ 136.2 (s), 127.4 (s), 121.9 (d), 121.5 (d), 119.2 (d), 118.7 (d), 114.4 (s), 111.1 (d), 56.0 (t × 2), 54.6 (t), 22.5 (t), 19.9 (t × 2), 12.0 (q × 2). ESI-MS: m/z 245 ([M+H]$^+$); HR-ESI-MS: calcd for $C_{16}H_{25}N_2$ ([M+H]$^+$) 245.2018, found 245.2017.

4.2.1.4. *N,N*-Diisobutyltryptamine (2d). Colorless thick oil (323 mg, 95% yield). ^{1}H NMR ($CDCl_3$): δ 7.93 (br s, 1H), 7.63 (d, J = 7.4 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.22 (t, J = 7.8 Hz, 1H), 7.15 (t, J = 7.4 Hz, 1H), 7.01 (s, 1H), 2.91 (m, 2H), 2.75 (m, 2H), 2.25 (d, J = 7.0 Hz, 4H), 1.78 (m, 2H), 0.94 (d, J = 6.4 Hz, 12H); ^{13}C NMR (DEPT) ($CDCl_3$): δ 136.4 (s), 127.7 (s), 121.9 (d), 121.7 (d), 119.2 (d), 118.9 (d), 114.9 (s), 111.3 (d), 63.8 (t × 2), 55.9 (t), 26.8 (d × 2), 22.9 (t), 21.2 (q × 4). ESI-MS: m/z 273 ([M+H]$^+$); HR-ESI-MS: calcd for $C_{18}H_{29}N_2$ ([M+H]$^+$) 273.2331, found 273.2328.

4.2.1.5. *N,N*-Diisopentyltryptamine (2e). Colorless thick oil (341 mg, 91% yield). ^{1}H NMR ($CDCl_3$): δ 8.19 (br s, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.31 (d, J = 7.5 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.14 (t, J = 7. 6 Hz, 1H), 7.01 (s, 1H), 2.94 (m, 2H), 2.82 (m, 2H), 2.59 (m, 4H), 1.62 (m, 4H), 1.44 (m, 2H), 0.93 (d, J = 6.6 Hz, 12H); ^{13}C NMR (DEPT) ($CDCl_3$): δ 136.4 (s), 126.5 (s), 123.4 (d), 122.2 (d), 119.7 (d), 118.0 (d), 112.0 (d), 108.9 (s), 53.2 (t), 51.8 (t × 2), 31.8 (t × 2), 26.2 (d × 2), 22.3 (q × 4), 20.4 (t). ESI-MS: m/z 301 ([M+H]$^+$); HR-ESI-MS: calcd for $C_{20}H_{33}N_2$ ([M+H]$^+$) 301.2644, found 301.2647.

4.2.1.6. *N,N*-Dicyclopropylmethyltryptamine (2f). Colorless thick oil (291 mg, 87% yield). ^{1}H NMR (CD_3OD): δ 10.37 (br s, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 7.20 (s, 1H), 7.12 (t, J = 7.0 Hz, 1H), 7.07 (t, J = 7.0 Hz, 1H), 3.49 (m, 2H), 3.10 (m, 6H), 0.94 (m, 2H), 0.71 (br s, 4H), 0.40 (br s, 4H); ^{13}C NMR (DEPT) (CD_3OD): δ 138.1 (s), 128.0 (s), 124.5 (d), 122.9 (d), 120.3 (d), 119.1 (d), 112.7 (d), 110.0 (s), 59.0 (t × 2), 53.9 (t), 21.3 (t), 6.7 (d × 2), 5.2 (t × 4). ESI-MS: m/z 269 ([M+H]$^+$); HR-ESI-MS: calcd for $C_{18}H_{25}N_2$ ([M+H]$^+$) 269.2018, found 269.2017.

4.2.1.7. *N,N*-Dicyclohexylmethyltryptamine (2g). Colorless thick oil (374 mg, 85% yield). ^{1}H NMR ($CDCl_3$): δ 8.09 (br s, 1H), 7.60 (d, J = 7.7 Hz, 1H), 7.36 (d, H, J = 8.0 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 7.12 (t, J = 7.7 Hz, 1H), 7.01 (s, 1H), 2.90 (m, 2H), 2.79 (m, 2H), 2.33 (d, J = 6.7 Hz, 4H), 1.76 (m, 8H), 1.45 (m, 2H), 1.22 (m, 4H), 0.88 (m, 8H); ^{13}C NMR (DEPT) ($CDCl_3$): δ 136.4 (s), 127.4 (s), 121.9 (d), 121.8 (d), 119.1 (d), 118.7 (d), 113.7 (s), 111.4 (d), 61.8 (t × 2), 55.3 (t), 35.8 (d × 2), 31.9 (t × 4) 26.8 (t × 2), 26.2 (t × 4), 22.3 (t). ESI-MS: m/z 353 ([M+H]$^+$); HR-ESI-MS: calcd for $C_{24}H_{37}N_2$ ([M+H]$^+$) 353.2957, found 353.2954.

4.2.1.8. *N,N*-Dibenzyltryptamine (2h). Colorless thick oil (348 mg, 82% yield). ^{1}H NMR ($CDCl_3$): δ 7.87 (br s, 1H), 7.39–7.43 (overlapped, 5H), 7.31–7.35 (overlapped, 5H), 7.24–7.28 (overlapped, 2H), 7.18 (t, J = 8.0 Hz, 1H), 7.06 (t, J = 7.8 Hz, 1H), 6.91 (s, 1H), 3.72 (br s, 4H), 3.01 (m, 2H), 2.84 (m, 2H); ^{13}C NMR (DEPT) ($CDCl_3$): δ 139.8 (s × 2), 136.1 (s), 128.7 (d × 4), 128.1 (d × 4), 127.5 (s), 126.7 (d × 2), 121.8 (d), 121.4 (d), 119.0 (d), 118.8 (d), 114.5 (s), 110.9 (d), 58.3 (t × 2), 53.8 (t), 23.0 (t). ESI-MS: m/z 341 ([M+H]$^+$); HR-ESI-MS: calcd for $C_{24}H_{25}N_2$ ([M+H]$^+$) 341.2018, found 341.2019.

4.2.1.9. *N,N*-Bis(pyridin-2-yl-methyl)tryptamine (2i). Colorless thick oil (355 mg, 83% yield). ^{1}H NMR ($CDCl_3$): δ 8.63 (br s, 1H), 8.52 (d, J = 4.8 Hz, 2H), 7.57 (dt, J = 7.2, 1.2 Hz, 2H), 7.47 (d, J = 7.2 Hz, 2H), 7.42 (d, J = 8.1 Hz, 1H), 7.28 (t, J = 7.2 Hz, 1H), 7.11 (m, 3H), 7.02 (t, J = 8.1 Hz, 1H), 6.89 (s, 1H), 3.95 (s, 4H), 3.01 (m, 2H), 2.93 (m, 2H); ^{13}C NMR (DEPT) ($CDCl_3$): δ 159.8 (s × 2), 148.9 (d × 2), 136.3 (d × 2), 136.2 (s), 127.5 (s), 122.8 (d × 2), 121.9 (d × 2), 121.8 (d), 121.5 (d), 119.0 (d), 118.8 (d), 114.3 (s), 110.9 (d), 60.4 (t × 2), 54.8 (t), 22.7 (t). ESI-MS: m/z 343 ([M+H]$^+$); HR-ESI-MS: calcd for $C_{22}H_{23}N_4$ ([M+H]$^+$) 343.1923, found 343.1926.

4.2.1.10. *N,N*-Bis(furan-2-yl-methyl)tryptamine (2j). Colorless thick oil (325 mg, 81% yield). ^{1}H NMR ($CDCl_3$): δ 7.81 (br s, 1H),

7.41 (d, J = 7.8 Hz, 1H), 7.25 (d, J = 1.5 Hz, 2H,), 7.18 (d, J = 8.1 Hz, 1H), 7.02 (t, J = 8.1 Hz, 1H), 6.94 (t, J = 7.8 Hz, 1H), 6.84 (s, 1H), 6.19 (dd, J = 1.5, 3.0 Hz, 2H), 6.09 (d, J = 3.0 Hz, 2H), 3.64 (s, 4H), 2.86 (m, 2H), 2.67 (m, 2H); ^{13}C NMR (DEPT) ($CDCl_3$): δ 152.5 (s × 2), 142.6 (d × 2), 136.7 (s), 127.9 (s), 122.4 (d), 122.1 (d), 119.4 (d), 119.2 (d), 114.1 (s), 111.7 (d), 110.6 (d × 2), 109.6 (d × 2), 54.4 (t), 50.1 (t × 2), 23.8 (t). ESI-MS: m/z 321 ($[M+H]^+$); HR-ESI-MS: calcd for $C_{20}H_{21}N_2O_2$ ($[M+H]^+$) 321.1603, found 321.1602.

4.2.1.11. *N,N*-Bis(thiophen-2-yl-methyl)tryptamine (2k). Colorless thick oil (362 mg, 82% yield). ^{1}H NMR ($CDCl_3$): δ 7.50 (br s, 1H), 7.12 (d, J = 7.7 Hz, 1H), 6.94 (d, J = 8.2 Hz, 1H), 6.86 (dd, J = 4.2, 2.0 Hz, 2H), 6.79 (t, J = 8.2 Hz, 1H), 6.70 (t, J = 7.7 Hz, 1H), 6.62 (s, 1H), 6.56–6.59 (m, 4H), 3.57 (s, 4H), 2.64 (m, 2H), 2.51 (m, 2H); ^{13}C NMR (DEPT) ($CDCl_3$): δ 142.8 (s × 2), 136.2 (s), 127.6 (s), 126.6 (d × 2), 125.9 (d × 2), 124.9 (d × 2) 121.9 (d), 121.8 (d), 119.2 (d), 118.9 (d), 114.2 (s), 111.2 (d), 53.6 (t), 52.2 (t × 2), 23.6 (t). ESI-MS: m/z 353 ($[M+H]^+$); HR-ESI-MS: calcd for $C_{20}H_{21}N_2S_2$ ($[M+H]^+$) 353.1146, found 353.1143.

4.2.1.12. *N,N*-Bis(2,4,5-trimethoxybenzyl)tryptamine (2l). Colorless thick oil (545 mg, 84% yield). ^{1}H NMR (C_5D_5N): δ 12.2 (br s, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.44 (s, 1H), 7.34 (s, 2H), 7.31 (t, J = 7.5 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 6.60 (s, 2H), 3.84 (s, 6H), 3.82 (s, 6H), 3.79 (m, 4H), 3.57 (s, 6H), 3.57 (m, 2H), 3.46 (m, 2H); ^{13}C NMR (DEPT) (C_5D_5N): δ 153.1 (d × 4), 144.4 (s × 2), 138.1 (s), 128.1 (s), 124.8 (d), 122.5 (d), 119.8 (d), 119.2 (d), 116.9 (s × 2), 116.9 (d × 2), 112.6 (d), 110.1 (s), 98.4 (d × 2), 57.2 (t × 2), 56.6 (t × 2), 56.4 (t × 2), 54.7 (t), 53.9 (t × 2), 22.5 (t). ESI-MS: m/z 521 ($[M+H]^+$); HR-ESI-MS: calcd for $C_{30}H_{37}N_2O_6$ ($[M+H]^+$) 521.2652, found 521.2651.

4.2.1.13. *N,N*-Bis(3-nitrobenzyl)tryptamine (2m). Colorless thick oil (430 mg, 80% yield). ^{1}H NMR ($CDCl_3$): δ 8.16 (br s, 2H), 8.04 (d, J = 8.4 Hz, 2H), 7.99 (br s, 1H), 7.61 (d, J = 7.5 Hz, 2H), 7.41 (d, J = 7.5 Hz, 1H), 7.38 (d, J = 7.5 Hz, 1H), 7.29 (t, J = 8.4 Hz, 2H), 7.15 (t, J = 6.9 Hz, 1H), 6.98 (s, 1H), 6.97 (t, J = 6.9 Hz, 1H), 3.75 (br s, 4H), 2.99 (m, 2H), 2.85 (m, 2H); ^{13}C NMR (DEPT) ($CDCl_3$): δ 148.1 (s × 2), 141.5 (s × 2), 136.2 (s), 134.6 (d × 2), 129.2 (d × 2), 127.1 (s), 123.4 (d × 2), 122.1 (d × 2), 121.9 (d), 121.7 (d), 119.1 (d),118.4 (d), 113.7 (s), 111.2 (d), 57.7 (t × 2), 53.9 (t), 23.3 (t). ESI-MS: m/z 431 ($[M+H]^+$); HR-ESI-MS: calcd for $C_{24}H_{23}N_4O_4$ ($[M+H]^+$) 431.1719, found 431.1718.

4.2.2. General procedure for the preparation of compounds 3a–k

m-Chloroperoxybenzoic acid (138 mg, 0.80 mmol) in $CHCl_3$ (10 mL) was added at 0 °C to a stirred solution of *N,N*-dimethyltryptamine (**2a**) (100 mg, 0.53 mmol) or other *N,N*-dialkyltryptamine derivatives (0.53 mmol) in $CHCl_3$ under argon. After 10 min, the reaction mixture was poured into a saturated solution of Na_2CO_3 and the N^{12}-oxides were extracted with $CHCl_3$. The organic layer was washed with water and brine, dried over Na_2SO4, and concentrated in vacuum. The crude product was purified by CC of silica gel with gradient $CHCl_3$/MeOH as eluant afforded compounds 3a–**k**.

4.2.2.1. *N,N*-Dimethyltryptamine N^{12}-oxide (3a). White solid (105 mg, 98% yield). ^{1}H NMR (CD_3OD): δ 8.50 (br s, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.15 (s, 1H), 7.11 (t, J = 8.0 Hz, 1H), 7.03 (t, J = 7.7 Hz, 1H), 3.72 (m, 2H), 3.34 (s, 6H), 3.28 (m, 2H); ^{13}C NMR (DEPT) (CD_3OD): δ 138.7 (s), 128.8 (s), 124.3 (d), 123.1 (d), 120.4 (d), 119.6 (d), 112.9 (d), 111.2 (s), 72.4 (t), 58.9 (q × 2), 21.1 (t). ESI-MS: m/z 205 ($[M+H]^+$); HR-ESI-MS: calcd for $C_{12}H_{17}N_2O$ ($[M+H]^+$) 205.1341, found 205.1343.

4.2.2.2. *N,N*-Diethyltryptamine N^{12}-oxide (3b). Colorless thick oil (117 mg, 95% yield). ^{1}H NMR (CD_3OD): δ 7.59 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 8.1 Hz, 1H), 7.14 (s, 1H), 7.10 (t, J = 8.1 Hz, 1H), 7.03 (t, J = 7.8 Hz, 1H), 3.42 (m, 2H), 3.34 (m, J = 8.3 Hz, 4H), 3.25 (m, 2H), 1.28 (m, 6H); ^{13}C NMR (DEPT) (CD_3OD): δ 138.2 (s), 128.3 (s), 124.1 (d), 122.8 (d), 120.1 (d), 119.0 (d), 112.6 (d), 110.4 (s), 65.4 (t), 60.6 (t × 2), 20.0 (t), 8.7 (q × 2). ESI-MS: m/z 233 ($[M+H]^+$); HR-ESI-MS: calcd for $C_{14}H_{21}N_2O$ ($[M+H]^+$) 233.1654, found 233.1653.

4.2.2.3. *N,N*-Dipropyltryptamine N^{12}-oxide (3c). Colorless thick oil (117 mg, 85% yield). ^{1}H NMR ($CDCl_3$): δ 10.22 (br s, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.06 (t, J = 7.8 Hz, 1H), 6.95 (s, 1H), 3.40 (m, 2H), 3.24 (m, 2H), 3.18 (m, 4H), 1.80 (m, 4H), 0.94 (t, J = 7.5 Hz, 6H); ^{13}C NMR (DEPT) ($CDCl_3$): δ 136.7 (s), 127.1 (s), 123.0 (d), 121.9 (d), 119.2 (d), 118.1 (d), 112.0 (d), 110.1 (s), 67.6 (t × 2), 66.0 (t), 19.4 (t), 16.8 (t × 2), 11.3 (q × 2). ESI-MS: m/z 261 ($[M+H]^+$); HR-ESI-MS: calcd for $C_{16}H_{25}N_2O$ ($[M+H]^+$) 261.1967, found 261.1970.

4.2.2.4. *N,N*-Diisobutyltryptamine N^{12}-oxide (3d). Colorless thick oil (130 mg, 85% yield). ^{1}H NMR ($CDCl_3$): δ 7.49 (d, J = 7.7 Hz, 1H), 7.42 (d, J = 7.7 Hz, 1H), 7.13 (t, J = 7.7 Hz, 1H), 7.05 (t, J = 7.7 Hz, 1H), 6.93 (s, 1H), 3.52 (m, 2H), 3.22 (m, 2H), 3.19 (d, J = 5.2 Hz, 4H), 2.28 (m, 2H), 1.13 (d, J = 6.5 Hz, 6H), 1.11 (d, J = 6.5 Hz, 6H); ^{13}C NMR (DEPT) ($CDCl_3$): δ 136.5 (s), 126.7 (s), 122.8 (d), 121.1 (d), 118.4 (d), 117.5 (d), 111.8 (d), 108.7 (s), 73.7 (t × 2), 66.0 (t), 49.2 (d × 2), 23.9 (q × 2), 22.7 (q × 2) 19.6 (t). ESI-MS: m/z 289 ($[M+H]^+$), 577 ($[2M+H]^+$); HR-ESI-MS: calcd for $C_{18}H_{29}N_2O$ ($[M+H]^+$) 289.2280, found 289.2281.

4.2.2.5. *N,N*-Diisopentyltryptamine N^{12}-oxide (3e). Colorless thick oil (139 mg, 83% yield). ^{1}H NMR ($CDCl_3$): δ 10.14 (br s, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.41 (d, J = 7.6 Hz, 1H), 7.16 (t, J = 7.8 Hz, 1H), 7.09 (t, J = 7.8 Hz, 1H), 6.99 (s, 1H), 3.42 (m, 2H), 3.29 (m, 2H), 3.24 (m, 4H), 1.72 (m, 4H), 1.61 (m, 2H), 0.93 (br d, J = 6.3 Hz, 12H); ^{13}C NMR (DEPT) ($CDCl_3$): 136.9 (s), 127.1 (s), 123.2 (d), 109.8 (s), 121.6 (d), 118.9 (d), 118.0 (d), 112.1 (d), 64.9 (t × 2), 66.1 (t), 31.9 (t × 2), 26.6 (d × 2), 22.7 (q × 4), 19.4 (t). ESI-MS: m/z 317 ($[M+H]^+$), 633 ($[2M+H]^+$); HR-ESI-MS: calcd for $C_{20}H_{33}N_2O$ ($[M+H]^+$) 317.2593, found 317.2590.

4.2.2.6. *N,N*-Dicyclopropylmethyltryptamine N^{12}-oxide (3f). Colorless thick oil (123 mg, 82% yield). ^{1}H NMR ($CDCl_3$): δ 10.29 (br s, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.12 (t, J = 7.0 Hz, 1H), 7.07 (t, J = 7.0 Hz, 1H), 7.00 (s, 1H), 3.67 (m, 2H), 3.32 (m, 2H), 3.25 (m, 4H), 1.34 (m, 2H), 0.71 (m, 4H), 0.35 (m, 4H); ^{13}C NMR (DEPT) ($CDCl_3$): δ 136.8 (s), 127.2 (s), 123.1 (d), 121.5 (d), 118.8 (d), 118.1 (d), 112.0 (d), 109.9 (s), 71.1 (t × 2), 64.8 (t), 19.3 (t), 5.7 (d × 2), 4.8 (t × 2), 4.3 (t × 2). ESI-MS: m/z 285 ($[M+H]^+$), 569 ($[2M+H]^+$); HR-ESI-MS: calcd for $C_{18}H_{25}N_2O$ ($[M+H]^+$) 285.1967, found 285.1965.

4.2.2.7. *N,N*-Dicyclohexylmethyltryptamine N^{12}-oxide (3g). Colorless thick oil (160 mg, 82% yield). ^{1}H NMR ($CDCl_3$): δ 10.56 (br s, 1H), 7.49 (d, J = 7.6 Hz, 1H), 7.43 (d, J = 7.6 Hz, 1H), 7.14 (d, J = 7.7 Hz, 1H), 7.06 (t, J = 7.7 Hz, 1H), 6.93 (s, 1H), 3.52 (m, 2H), 3.22 (m, 2H), 3.16 (m, 4H), 1.93–1.99 (m, 6H, overlapped), 1.60–1.71 (m, 6H, overlapped), 1.05–1.30 (m, 10H, overlapped); ^{13}C NMR (DEPT) ($CDCl_3$, 100 MHz): δ 136.6 (s), 126.8 (s), 122.8 (d), 121.4 (d), 118.7 (d), 117.6 (d), 112.0 (d), 108.8 (s), 73.1 (t × 2), 65.8 (t), 33.3 (t × 4), 33.2 (t × 4), 32.9 (d × 2), 25.6 (t × 2), 19.8 (t). ESI-MS: m/z 369 ($[M+H]^+$), 737 ($[2M+H]^+$); HR-ESI-MS: calcd for $C_{24}H_{37}N_2O$ ($[M+H]^+$) 369.2906, found 369.2905.

4.2.2.8. *N,N*-Dibenzyltryptamine N^{12}-oxide (3h). Colorless thick oil (157 mg, 83% yield). ^{1}H NMR (CD_3OD): δ 7.72 (m, 4H), 7.40–7.53 (m, 6H, overlapped), 7.29 (d, J = 7.8 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 7.08 (t, J = 7.7 Hz, 1H), 6.96 (s, 1H), 6.92 (t, J = 7.7 Hz, 1H), 4.63 (d, J = 12.7 Hz, 2H), 4.51 (d, J = 12.7 Hz, 2H), 3.34 (m, 2H), 3.20 (m, 2H); ^{13}C NMR (DEPT) (CD_3OD): δ 138.1 (s), 133.9 (d × 4), 131.7 (s × 2), 130.8 (d × 2), 129.7 (d × 4), 128.3 (s), 123.6 (d), 122.6 (d), 119.8 (d), 119.2 (d), 112.4 (d), 110.7 (s), 71.4 (t × 2), 65.0 (t), 21.1 (t). ESI-MS: m/z 357 ([M+H]$^+$); HR-ESI-MS: calcd for $C_{24}H_{25}N_2O$ ([M+H]$^+$) 357.1967, found 357.1964.

4.2.2.9. *N,N*-Bis(pyridin-2-yl-methyl)tryptamine N^{12}-oxide (3i). Colorless thick oil (154 mg, 81% yield). ^{1}H NMR ($CDCl_3$): δ 10.06 (br s, 1H), 8.58 (d, J = 4.4 Hz, 2H), 7.79 (d, J = 7.6 Hz, 2H), 7.63 (m, 2H), 7.54 (d, J = 7.5 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H), 7.25 (m, 2H), 7.07 (t, J = 7.0 Hz, 1H), 6.99 (t, J = 7.0 Hz, 1H), 6.81 (s, 1H), 4.95 (d, 2H), 4.84 (d, 2H), 3.56 (m, 4H); ^{13}C NMR (DEPT) ($CDCl_3$): δ 149.5 (s × 2), 149.2 (d × 2), 136.7 (d × 2), 136.3 (s), 128.2 (d × 2), 127.0 (s), 124.2 (d × 2), 123.2 (d), 121.3 (d), 118.6 (d), 118.2 (d), 111.6 (d), 108.8 (s), 69.1 (t × 2), 64.4 (t), 19.2 (t). ESI-MS: m/z 359 ([M+H]$^+$), 739 ([2M+Na]$^+$); HR-ESI-MS: calcd for $C_{22}H_{23}N_4O$ ([M+H]$^+$) 359.1872, found 359.1873.

4.2.2.10. *N,N*-Bis(furan-2-yl-methyl)tryptamine N^{12}-oxide (3j). Colorless thick oil (142 mg, 80% yield). ^{1}H NMR ($CDCl_3$): δ 10.70 (br s, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 1.5 Hz, 2H), 7.38 (d, J = 8.1 Hz, 1H), 7.12 (t, J = 8.1 Hz, 1H), 7.04 (t, J = 7.6 Hz, 1H), 6.90 (s, 1H), 6.74 (d, J = 3.1 Hz, 2H), 6.43 (dd, J = 3.1, 1.5 Hz, 2H), 4.49 (d, J = 14.1 Hz, 2H), 4.36 (d, J = 14.1 Hz, 2H), 3.57 (m, 2H), 3.34 (m, 2H); ^{13}C NMR (DEPT) ($CDCl_3$): δ 144.7 (s × 2), 143.8 (d × 2), 136.5 (s), 126.9 (s), 123.1 (d), 120.9 (d), 118.3 (d), 117.8 (d), 114.7 (d × 2), 111.7 (d), 110.9 (d × 2), 109.1 (s), 65.7 (t), 62.2 (t × 2), 18.7 (t). ESI-MS: m/z 337 ([M+H]$^+$), 673 ([2M+H]$^+$); HR-ESI-MS: calcd for $C_{20}H_{21}N_2O_3$ ([M+H]$^+$) 337.1552, found 337.1555.

4.2.2.11. *N,N*-Bis(thiophen-2-yl-methyl)tryptamine N^{12}-oxide (3k). Colorless thick oil (162 mg, 83% yield). ^{1}H NMR ($CDCl_3$): δ 9.95 (br s, 1H), 7.43 (d, J = 7.7 Hz, 1H), 7.42 (dd, J = 4.1, 1.1 Hz, 2H), 7.35 (d, J = 8.1 Hz, 1H), 7.18 (d, J = 2.5 Hz, 2H), 7.10 (t, J = 8.1 Hz, 1H), 7.03 (m, 3H), 6.86 (s, 1H), 4.64 (d, J = 14.0 Hz, 2H), 4.59 (d, J = 14.0 Hz, 2H), 2.64 (m, 4H); ^{13}C NMR (DEPT) ($CDCl_3$): δ 136.7 (s), 131.2 (s × 2), 131.1 (d × 2), 129.5 (d × 2), 127.1 (s), 126.4 (d × 2), 123.2 (d), 121.6 (d), 118.9 (d), 118.2 (d), 112.0 (d), 109.3 (s), 64.0 (t × 3), 19.8 (t). ESI-MS: m/z 369 ([M+H]$^+$), 737 ([2M+H]$^+$); HR-ESI-MS: calcd for $C_{20}H_{21}N_2OS_2$ ([M+H]$^+$) 369.1095, found 369.1094.

4.2.3. General procedure for the preparation of compounds 4a–c

Starting from compounds **1b–d** (1.25 mmol), **4a–c** were prepared according to the same procedure as preparing **3a**.

4.2.3.1. 5-Hydroxy-*N,N*-dimethyltryptamine N^{12}-oxide (4a). White solid (198 mg, 72% yield). ^{1}H NMR (D_2O): δ 7.18 (d, J = 8.5 Hz, 1H), 7.11 (s, 1H), 6.93 (d, J = 2.4 Hz, 1H), 6.68 (dd, J = 8.5, 2.4 2.4 Hz, 1H), 3.53 (m, 2H), 3.26 (s, 6H), 3.20 (m, 2H); ^{13}C NMR (DEPT) (D_2O): δ 151.4 (s), 134.0 (s), 129.7 (s), 127.3 (d), 115.4 (d), 114.4 (d), 111.3 (s), 105.0 (d), 72.5 (t), 59.8 (q × 2), 21.6 (t). ESI-MS: m/z 221 ([M+H]$^+$); HR-ESI-MS: calcd for $C_{12}H_{17}N_2O_2$ ([M+H]$^+$) 221.1290, found 221.1293.

4.2.3.2. 5-Chloro-*N,N*-dimethyltryptamine N^{12}-oxide (4b). White solid (223 mg, 75% yield). ^{1}H NMR (CD_3OD): δ 7.64 (s, 1H), 7.30 (d, J = 8.7 Hz, 1H), 7.17 (s, 1H), 7.05 (d, J = 8.7 Hz, 1H), 3.49 (m, 2H), 3.25 (m, 2H), 3.20 (s, 6H); ^{13}C NMR (DEPT) (CD_3OD): δ 136.6 (s), 129.6 (s), 125.8 (d), 122.9 (d), 118.8 (d), 113.7 (d × 2), 110.8 (s), 71.7 (t), 58.6 (q × 2), 20.4 (t). ESI-MS: m/z 239 ([M+H]$^+$), 477.0 ([2M+H]$^+$); HR-ESI-MS: calcd for $C_{12}H_{16}{}^{35}ClN_2O$ ([M+H]$^+$) 239.0951, found 239.0950.

4.2.3.3. 5-Bromo-*N,N*-dimethyltryptamine N^{12}-oxide (4c). White solid (257 mg, 73% yield). ^{1}H NMR (CD_3OD): δ 7.80 (s, 1H), 7.26 (d, J = 8.1 Hz, 1H), 7.18 (d, J = 8.1 Hz, 1H), 7.16 (s, 1H), 3.49 (m, 2H), 3.22 (m, 2H), 3.20 (s, 6H); ^{13}C NMR (DEPT) (CD_3OD): δ 136.9 (s), 130.3 (s), 125.7 (d), 125.5 (d), 121.9 (d), 114.2 (d), 113.3 (s), 110.8 (s), 71.8 (t), 58.7 (q × 2), 20.4 (t). ESI-MS: m/z 283/285 [M+H$^+$], 565/567/569 ([2M+H]$^+$); HR-ESI-MS: calcd for $C_{12}H_{16}{}^{79}BrN_2O$ ([M+H]$^+$) 283.0446, found 283.0443.

4.2.4. General procedure for the preparation of compounds 5a–g

A stirred solution of tryptamine (**1a**) (100 mg, 0.62 mmol) in dry methanol (20 mL) was added glacial acetic acid (140 μL, 2.48 mmol) followed by sodium cyanoborohydride (78 mg, 1.24 mmol) under Ar_2 at 0 °C. A solution of isovaleraldehyde (67 μL, 0.62 mmol) in methanol (20 mL) was then added dropwise over 1 h, and the resulting solution was stirred at 0 °C for 0.5 h to afford **5a**. And then excessive appropriate aldehyde (1.5 mmol) in methanol (10 mL) was added dropwise over 20 min, and stirring was continued overnight. Aqueous Na_2CO_3 (2 N) was added to adjust pH to 8 and the methanol was removed under vacuum. The residue was partitioned between $CHCl_3$ and water. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuum. The crude product was purified by CC of silica gel with gradient $CHCl_3$/MeOH as eluant afforded compounds **5b–g**.

4.2.4.1. N^{12}-Isopentyltryptamine (5a). Colorless thick oil (135 mg, 95% yield). ^{1}H NMR (CD_3OD): δ 7.55 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.09 (s, 1H), 7.08 (t, J = 7.5 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 3.01 (br s, 4H), 2.72 (m, 2H), 1.55 (m, 2H), 1.42 (m, 1H), 0.87 (d, J = 6.6 Hz, 6H); ^{13}C NMR (DEPT) (CD_3OD): δ 138.7 (s), 128.9 (s), 124.2 (d), 123.0 (d), 120.3 (d), 119.7 (d), 113.0 (d), 112.7 (s), 50.8 (t), 48.7 (t), 38.6 (t), 27.8 (d), 25.6 (t), 23.4 (q × 2); ESI-MS: m/z 231 ([M+H]$^+$); HR-ESI-MS: calcd for $C_{15}H_{23}N_2$ ([M+H]$^+$) 231.1861, found 231.1863.

4.2.4.2. N^{12}-Methyl-N^{12}-isopentyltryptamine (5b). Colorless thick oil (136 mg, 90% yield). ^{1}H NMR ($CDCl_3$): δ 8.24 (br s, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 7.12 (t, J = 7.6 Hz, 1H), 7.01 (s, 1H), 2.98 (m, 2H), 2.75 (m, 2H), 2.50 (m, 2H), 2.39 (s, 3H), 1.60 (m, 1H), 1.44 (m, 2H), 0.92 (d, J = 6.5 Hz, 6H); ^{13}C NMR (DEPT) ($CDCl_3$): δ 136.2 (s), 127.3 (s), 121.7 (d), 121.6 (d), 118.9 (d), 118.6 (d), 113.8 (s), 111.2 (d), 58.1 (t), 55.8 (t), 41.9 (q), 35.7 (t), 26.5 (d), 22.8 (q × 2), 22.6 (t). ESI-MS: m/z 245 ([M+H]$^+$); HR-ESI-MS: calcd for $C_{16}H_{25}N_2$ ([M+H]$^+$) 245.2018, found 245.2017.

4.2.4.3. N^{12}-Ethyl-N^{12}-isopentyltryptamine (5c). Colorless thick oil (131 mg, 82% yield). ^{1}H NMR ($CDCl_3$): δ 8.28 (br s, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.19 (t, J = 7.0 Hz, 1H), 7.12 (t, J = 7.0 Hz, 1H), 7.01 (s, 1H), 2.98 (m, 2H), 2.86 (m, 2H), 2.73 (q, J = 7.1 Hz, 2H), 2.64 (m, 2H), 1.60 (m, 1H), 1.45 (m, 2H), 1.14 (t, J = 7.1 Hz, 3H), 0.92 (d, J = 6.6 Hz, 6H); ^{13}C NMR (DEPT) ($CDCl_3$): δ 136.2 (s), 127.3 (s), 121.7 (d), 121.6 (d), 118.9 (d), 118.5 (d), 113.5 (s), 111.2 (d), 53.7 (t), 51.2 (t), 47.2 (t), 34.9 (t), 26.5 (d), 22.6 (q × 2), 22.2 (t), 11.1 (q). ESI-MS: m/z 259 ([M+H]$^+$); HR-ESI-MS: calcd for $C_{17}H_{27}N_2$ ([M+H]$^+$) 259.2174, found 259.2175.

4.2.4.4. N^{12}-Propyl-N^{12}-isopentyltryptamine (5d). Colorless thick oil (135 mg, 80% yield). ^{1}H NMR ($CDCl_3$): δ 8.25 (br s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 7.1 Hz, 1H), 7.19 (t, J = 7.1 Hz,

1H), 7.12 (t, J = 8.0 Hz, 1H), 7.01 (s, 1H), 2.95 (m, 2H), 2.85 (m, 2H), 2.60 (m, 4H), 1.59 (m, 3H), 1.43 (m, 2H), 0.95 (m, 9H); ^{13}C NMR (DEPT) ($CDCl_3$): δ 136.2 (s), 127.4 (s), 121.8 (d), 121.6 (d), 119.1 (d), 118.6 (d), 114.0 (s), 110.2 (d), 55.9 (t), 54.4 (t), 52.0 (t), 35.2 (t), 26.6 (d), 22.7 (q × 2), 22.4 (t), 19.8 (t), 11.9 (q). ESI-MS: *m/z* 273 ($[M+H]^+$); HR-ESI-MS: calcd for $C_{18}H_{29}N_2$ ($[M+H]^+$) 273.2331, found 273.2334.

4.2.4.5. N^{12}-Isobutyl-N^{12}-isopentyltryptamine (5e). Colorless thick oil (144 mg, 81% yield). ^{1}H NMR ($CDCl_3$): δ 7.95 (br s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 7.1 Hz, 1H), 7.19 (t, J = 7.1 Hz, 1H), 7.12 (t, J = 8.0 Hz, 1H), 7.02 (s, 1H), 2.90 (m, 2H), 2.77 (m, 2H), 2.53 (m, 2H), 2.26 (d, J = 7.2 Hz, 1H), 1.77 (m, 1H) 1.61 (m, 2H), 1.38 (m, 2H), 0.95 (d, J = 6.5 Hz, 12H); ^{13}C NMR (DEPT) ($CDCl_3$): δ 136.2 (s), 127.6 (s), 121.8 (d), 121.4 (d), 119.1 (d), 118.8 (d), 114.9 (s), 110.0 (d), 63.0 (t), 55.3 (t), 52.9 (t), 36.0 (t), 26.8 (d), 26.4 (d), 22.8 (q × 2), 22.7 (t), 21.1 (q × 2). ESI-MS: *m/z* 287 ($[M+H]^+$); HR-ESI-MS: calcd for $C_{19}H_{31}N_2$ ($[M+H]^+$) 287.2487, found 287.2486.

4.2.4.6. N^{12}-Furan-2-yl-methyl-N^{12}-isopentyltryptamine (5f). Colorless thick oil (165 mg, 86% yield). ^{1}H NMR ($CDCl_3$): δ 8.02 (br s, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.40 (d, J = 0.9 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.20 (t, J = 7.0 Hz, 1H), 7.12 (t, J = 7.0 Hz, 1H), 7.00 (s, 1H), 6.34 (dd, J = 3.3, 0.9 Hz, 1H), 6.22 (d, J = 3.3 Hz, 1H), 3.80 (s, 2H), 2.97 (m, 2H), 2.83 (m, 2H), 2.59 (m, 2H), 1.61 (m, 1H), 1.46 (m, 2H), 0.91 (d, J = 6.6 Hz, 6H); ^{13}C NMR (DEPT) ($CDCl_3$): δ 152.5 (s), 141.8 (d), 136.2 (s), 127.4 (s), 121.7 (d), 121.5 (d), 119.0 (d), 118.7 (d), 114.2 (s), 111.0 (d × 2), 108.5 (d), 54.4 (t), 51.9 (t), 49.9 (t), 35.8 (t), 26.4 (d), 22.9 (t), 22.7 (q × 2). ESI-MS: *m/z* 311 ($[M+H]^+$); HR-ESI-MS: calcd for $C_{20}H_{27}N_2O$ ($[M+H]^+$) 311.2123, found 311.2124.

4.2.4.7. N^{12}-Thiophen-2-yl-methyl-N^{12}-isopentyltryptamine (5g). Colorless thick oil (162 mg, 80% yield). ^{1}H NMR ($CDCl_3$): δ 7.96 (br s, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.24 (dd, J = 4.8, 1.2 Hz, 1H), 7.19 (t, J = 7.9 Hz, 1H), 7.12 (t, J = 7.9 Hz, 1H), 7.01 (s, 1H), 6.93–6.98 (m, 2H, overlapped), 3.95 (s, 2H), 2.98 (m, 2H), 2.84 (m, 2H), 2.62 (m, 2H), 1.64 (m, 1H), 1.46 (m, 2H), 0.90 (d, J = 6.6 Hz, 6H); ^{13}C NMR (DEPT) ($CDCl_3$): δ 142.9 (s), 136.1 (s), 127.5 (s), 126.3 (d), 125.5 (d), 124.5 (d), 121.8 (d), 121.5 (d), 119.1 (d), 118.8 (d), 114.4 (s), 111.0 (d), 54.1 (t), 52.5 (t), 51.7 (t), 36.0 (t), 26.3 (d), 23.2 (t), 22.7 (q × 2). ESI-MS: *m/z* 327 ($[M+H]^+$); HR-ESI-MS: calcd for $C_{20}H_{27}N_2S$ ($[M+H]^+$) 327.1895, found 327.1898.

4.2.5. Preparation of compound 6a

A mixture of *N*,*N*-diisopentyltryptamine (**2e**) (100 mg, 0.33 mmol) and 60% NaH (15 mg, 0.37 mmol) was heated at 110 °C under Ar_2 until the evolution of the H_2 gas ceased. The resultant mass was dissolved in anhydrous DMF (3 mL) and benzenesulfonyl chloride (51 μL, 0.4 mmol) in anhydrous DMF (2 mL) was added in a dropwise manner at 0 °C over 10 min. The reaction mixture was allowed to stir at room temperature for 3 h. At 0 °C ice was added to the reaction mixture to decompose the excess NaH followed by H_2O (15 mL); the crude mixture was dissolved in $CHCl_3$ (30 mL) and washed with H_2O (2 × 50 mL). The organic portion was dried (Na_2SO_4) and solvent was removed under vacuum. The crude product was purified through CC of silica gel with petrol ether/acetone (3:1) as eluant to afford a colorless thick oil **6a** (123 mg, 85% yield). ^{1}H NMR ($CDCl_3$): δ 7.98 (d, J = 8.3 Hz, 1H), 7.86 (d, J = 8.3 Hz, 2H), 7.40–7.54 (m, 4H), 7.39 (s, 1H), 7.31 (t, J = 7.3 Hz, 1H), 7.24 (t, J = 7.3 Hz, 1H), 2.79 (m, 2H), 2.74 (m, 2H), 2.51 (m, 4H), 1.57 (m, 2H), 1.36 (m, 4H), 0.88 (t, 12H); ^{13}C NMR (DEPT) ($CDCl_3$): δ 138.2 (s), 135.1 (s), 133.5 (d), 131.1 (s), 129.1 (d × 2), 126.6 (d × 2), 124.6 (d), 123.0 (d), 122.8 (d), 121.6 (s), 119.4 (d), 113.6 (d), 53.4 (t), 52.1 (t × 2), 35.9 (t × 2), 29.6 (t), 26.4 (d × 2), 22.7 (q × 4). ESI-MS: *m/z* 441 ($[M+H]^+$); HR-ESI-MS: calcd for $C_{26}H_{37}N_2O_2S$ ($[M+H]^+$) 441.2576, found 441.2575.

4.3. Biological assays

4.3.1. In vitro anti-HBV assays

The antiviral activities of these tryptamine derivatives against HBV in HepG2.2.15 cells were evaluated by methods reported previously.[18–20] For the antiviral analyses, confluent cultures of HepG 2.2.15 cells were maintained in 96-well flat-bottomed tissue culture plates in minimal essential medium (MEM) supplemented with 10% fetal bovine serum. Cultures were treated with various doses of antiviral compounds and lamivudine (purchased from Glaxo & Welcome Co.). Fresh MEM with the same concentration of tested compounds and positive control was replaced at day 4, and the supernatants were harvested at day 8, then the extracellular (virion) HBV DNA were measured by real time fluorescent PCR.

4.3.2. Toxicity measurements

Cytotoxicity induced by the tested compounds to HepG2.2.15 cells were assessed by MTT assay as previously described.[19–21] Briefly, HepG2.2.15 cells were cultured in triplicate of 96-well tissue culture plates for 8 days with various doses of tested compounds. Untreated cells with media alone were used as controls. MTT (5 g/L) reagent was added 4 h before the end of culture, and then cells were lysed with 10% sodium dodecyl sulfate (SDS), 50% DMF, pH 7.2. OD absorbance values at 570 nm were collected by microplate reader (Bio-Rad, model 550) and the cell death percent was calculated.

4.3.3. Real time fluorescent PCR

The supernatants of HepG2.2.15 cells were collected from 8 days culture after the compounds added. The HBV DNA in the supernatants was quantified by using fluorescent PCR.[21] Briefly, 50 μL of the supernatants were added into the extraction buffer, boiled for 10 min and centrifuged for 5 min, and then proper aliquots were used for the fluorescent PCR. PCR primers were:

P1: 5′-ATCCTGCTGCTATGCCTCATCTT-3′,
P2: 5′-ACAGTGGGGAAAGCCCTACGAA-3′.

The probe was 5′-TGGCTAGTTTACTAGTGCCATTTTG-3′. PCR reaction was run at MJ Research PTC-200, and results were analyzed by software OPTICONMONITOR v2.01.

Acknowledgments

This study was financial supported by grants from the National Science & Technology Major Project 'Key New Drug Creation and Manufacturing Program' (Nos. 2009ZX09301-001 and 2008ZXJ09002-011), the National Science Foundation of China (No. 81072545), '863' Project (No. 2007AA021504), and Shanghai Commission of Science and Technology (No. 083958012).

References and notes

1. World Health Organization. Hepatitis B. World Health Organization Fact Sheet 204 (Revised August 2008). (http://www.who.int/mediacentre/factsheets/fs204/en/index.html.).
2. Piratvisuth, T. *Hepatol. Int.* **2008**, *2*, 140.
3. Wong, D. K.; Cheung, A. M.; O'Rourke, K.; Naylor, C. D.; Detsky, A. S.; Heathcote, J. *Ann. Intern. Med.* **1993**, *119*, 312.
4. Zoulim, F. *Antiviral Res.* **2004**, *64*, 1.
5. Zoulim, F. *Hepatology* **2006**, *44*, 1404.
6. Tanji, N.; Tanji, K.; Kambham, N.; Markowitz, G. S.; Bell, A.; D'Agati, V. D. *Hum. Pathol.* **2001**, *32*, 734.

7. Ding, P.; Liao, Z.; Huang, H.; Zhou, P.; Chen, D. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1231.
8. Zhou, Z.; Zhang, Y.; Ding, X.; Chen, S.; Yang, J.; Wang, X.; Jia, G.; Chen, H.; Bo, X.; Wang, S. *Antiviral Res.* **2007**, *74*, 59.
9. Xu, B. X.; Huang, Z. M.; Liu, C. X.; Cai, Z. G.; Pan, W. D.; Cao, P. X.; Hao, X. J.; Liang, G. Y. *Bioorg. Med. Chem.* **2009**, *17*, 3118.
10. Su, C. R.; Yeh, S. F.; Liu, C. M.; Damua, A. G.; Kuo, T. H.; Chiang, P. C.; Bastow, K. F.; Lee, K. H.; Wua, T. S.; Yeh, S. F. *Bioorg. Med. Chem.* **2009**, *17*, 6137.
11. Janmanchi, D.; Tseng, Y. P.; Wang, K. C.; Huang, R. L.; Lin, C. H. *Bioorg. Med. Chem.* **2010**, *18*, 1213.
12. Qu, S. J.; Liu, Q. W.; Tan, C. H.; Jiang, S. H.; Zhu, D. Y. *Planta Med.* **2006**, *72*, 264.
13. Glennon, R. A. *J. Med. Chem.* **2003**, *46*, 2795.
14. Holenz, J.; Pauwels, P. J.; Díaz, J. L.; Merce, R.; Codony, X.; Buschmann, H. *Drug Discovery Today* **2006**, *11*, 283.
15. Russell, M. G. N.; Baker, R. J.; Barden, L.; Beer, M. S.; Bristow, L.; Broughton, H. B.; Knowles, M.; McAllister, G.; Patel, S.; Castro, J. L. *J. Med. Chem.* **2001**, *44*, 3881.
16. GuBritte, F.; Langlois, N.; Langlois, Y.; Sundberg, R. J.; Bloom, J. D. *J. Org. Chem.* **1981**, *46*, 5393.
17. Pullagurla, M. R.; Dukat, M.; Setola, V.; Rothb, B.; Glennona, R. A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3355.
18. Suzuki, S.; Lee, B.; Luo, W.; Tovell, D.; Robins, M. J.; Tyrrell, D. L. *Biochem. Biophys. Res. Commun.* **1988**, *156*, 1144.
19. Yang, Z. S.; Zhou, W. L.; Sui, Y.; Wang, J. X.; Wu, J. M.; Zhou, Y.; Zhang, Y.; He, P. L.; Han, J. Y.; Tang, W.; Li, Y.; Zuo, J. P. *J. Med. Chem.* **2005**, *48*, 4608.
20. Luo, Y.; Yao, J. P.; Yang, L.; Feng, C. L.; Tang, W.; Wang, G. F.; Zuo, J. P.; Lu, W. *Bioorg. Med. Chem.* **2010**, *18*, 5048.
21. Li, Y. F.; Wang, G. F.; He, P. L.; Huang, W. G.; Zhu, F. H.; Gao, H. Y.; Tang, W.; Luo, Y.; Feng, C. L.; Shi, L. P.; Ren, Y. D.; Lu, W.; Zuo, J. P. *J. Med. Chem.* **2006**, *49*, 4790.