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Synthesis and biological evaluation of some new N-fatty acyl derivatives of 4,5-dimethoxy tryptamine

Vijayendar Venepally[a,c], R B N Prasad[a,c], Y Poornachandra[b,c], C Ganesh Kumar[b,c] & Ram Chandra Reddy Jala*[a,c]

[a] Centre for Lipid Research, CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500 007, India

[b] Medicinal Chemistry and Pharmacology Division, CSIR-Indian Institute of Chemical Technology, Tarnaka, Hyderabad 500 007, India

[c] Academy of Scientific and Innovative Research, New Delhi, India

E-mail: jrcreddy10@gmail.com

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The aim of this study is to synthesize and examine the *in vitro* anticancer, antioxidant and antimicrobial activities of N-fatty acyl derivatives of 4,5-dimethoxy tryptamine. A series of new N-fatty acyl derivatives of 4,5-dimethoxy tryptamine compounds derived from 2,3-dimethoxy benzaldehyde have been prepared. The synthesized compounds have been characterized and screened for anticancer, antioxidant and antimicrobial activities. The synthesized derivatives have been evaluated for their cytotoxicity on various cell lines. Compounds **9a** and **9g** have shown promising cytotoxicity, while compounds **9c**, **9d** and **9e** have shown moderate activity for all the tested cancer cell lines. The antioxidant activities have been determined with regard to DPPH radical scavenging activity, superoxide free radical scavenging activity and inhibition of lipid peroxidation. Based on the results, it has been observed that N-fatty acyl derivatives of 4,5-dimethoxy tryptamine exhibit promising antioxidant activity. In particular, the undecenoic acid-based derivative **9d** shows good antioxidant activity in all the three assays. Further, the compound **9d** exhibits significant antimicrobial activity against *Bacillus subtilis* MTCC 121 with MIC value of 15.6 µg/mL.

Keywords: Anticancer, antioxidant, antimicrobial, tryptamine, DPPH radical scavenging, super oxide free radical scavenging, lipid peroxidation, BHT

Indole nucleus represents one of the privileged scaffolds in various biologically active natural and synthetic products. Indole derivatives are considered as one of the important family of heterocyclic compounds as they have attracted significant interest in medicinal chemistry and as a source of new and useful pharmaceuticals and bioactive compounds[1-4]. Numerous reports exist on a variety of biological activities of indoles and its derivatives such as antibacterial[5], antifungal[6], antiviral[7], antimalarial[8], anti-HIV[9], anticancer[10-12] and antioxidant properties[13,14]. It is also known that indole moiety containing several natural products have attracted significant interest in medicinal chemistry due to their potent biological activities especially anticancer properties[15-18] and also as effective antioxidants, protecting both lipids and proteins from peroxidation, and the indole structure mainly influences the antioxidant efficacy in biological systems[19]. Tryptamine derivatives containing various natural and synthetic compounds have received a renewed interest in the area of pharmaceutical chemistry. Most importantly, several tryptamine derivatives demonstrated cytotoxicity against various cell lines. Research reports indicated that tryptamine derivatives[20-22] including melatonin[23] have demonstrated antitumor activity. Considering the above facts, it was anticipated that tryptamine derivatives can exhibit significant anticancer activity.

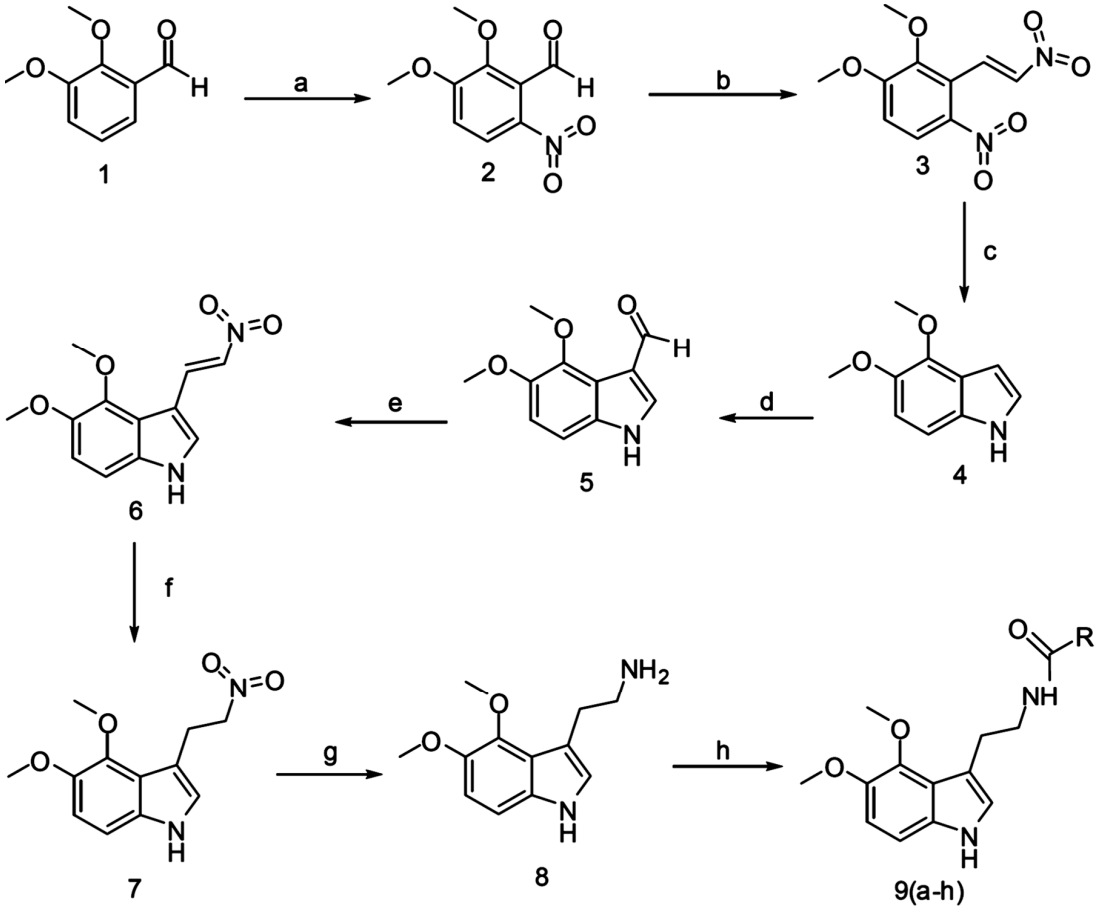
Indole ring containing tryptamine derivative such as melatonin (MLT) is a highly conserved molecule that acts as a free radical scavenger and a broad-spectrum antioxidant [24,25]. There are many studies reported on MLT; however, only a few of them relate to the *in vitro* antimicrobial activity[26-28]. On the other hand, fatty acids are prime constituents of dietary oils and natural fats and they play an important role as nutritional substances and metabolites in living organisms[29]. An earlier study demonstrated that fatty acids are known to possess various biological activities such as antibacterial and antifungal properties, since they have advantages of being derived from natural sources, they are biodegradable, and the hydrophobicity of final derivatives can be altered to meet the pharmacological requirements[30].

In the present study, an attempt was made to append the alkyl chain moiety of the fatty acid to the

4,5-dimethoxy tryptamine nucleus by amide coupling so as to equip with the beneficial effects to generate a hybrid molecule with expected biological activities. Till date there were no attempts being made on the synthesis and the biological evaluation of N-fatty acyl derivatives of 4,5-dimethoxy tryptamine for various activities. Considering this fact, we synthesized some hybrid molecules involving dimethoxy tryptamine in the present study and further evaluated these different fatty acid-based dimethoxy tryptamine derivatives for their anticancer, antioxidant and antimicrobial activities.

Results and Discussion

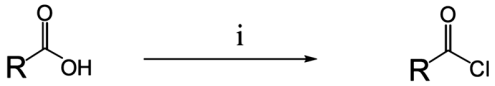
The synthesis of target compounds (**9a-h**) is described in Scheme I. N-fatty acyl derivatives of dimethoxy tryptamine were obtained *via* a synthetic route consisting of eight steps from 2,3-dimethoxy benzaldehyde (**1**) as the starting material. The compounds were separated by column chromatography to get the desired 2,3-dimethoxy-6-nitrobenzaldehyde (**2**)[31]. This was converted to 1, 2-dimethoxy-4-nitro-3-(2-nitrovinyl) (**3**) benzene by employing nitromethane, 18-crown ether in n-methyl morpholine as a solvent under inert atmosphere for 12 h at RT.



Scheme I — Synthesis of fatty amide based dimethoxy tryptamine derivatives. Reagents and conditions: (a) fuming HNO_3, glacial AcOH, RT for 4 h; (b) N-methyl morpholine, CH_3NO_2, KF, 18-crown-6-ether, 12 h, NaOAc, acetic anhydride, 60°C, 1 h; (c) Fe-powder, SiO_2, CH_3COOH, toluene, 90°C, 1 h; (d) $POCl_3$, DMF at 0°C, RT for 4 h; (e) CH_3COONH_4, CH_3NO_2, 90°C, 6 h; (f) $NaBH_4$, MeOH: DMF (1:1) at RT for 4 h; (g) Fe, NH_4Cl, MeOH: H_2O (5:1), reflux for 2 h; (h) Acid chloride, Et_3N, DCM, RT for 2 h.

Nitration of (**1**) in the presence of fuming nitric acid and glacial acetic acid afforded a mixture of 5-nitro and 6-nitro derivatives. After 12 h, this reaction mixture was poured in a mixture containing sodium acetate in acetic anhydride and heated for 1 h and poured in ice water and the mixture was filtered to collect the solid. Finally, the silica gel assisted reductive cyclization of (**3**) in the presence of iron and acetic acid afforded the required compound 4,5-dimethoxy-1*H*-indole (**4**)[32]. The 4,5-dimethoxy-1*H*-indole-3-carbaldehyde (**5**) was synthesized from compound 4 by Vills-Mayer Heck reaction with $POCl_3$ and DMF. Compound (**5**) was condensed with nitromethane and ammonium acetate based on the Henry reaction to form the corresponding 4,5-dimethoxy-3-(2-nitrovinyl)-1*H*-indole (**6**)[31]. Double bond in compound 6 was reduced by sodium borohydride in methanol and DMF at RT to give 4,5-dimethoxy-3-(2-nitroethyl)-1*H*-indole (**7**)[32].

Further, compound (**7**) was reduced by Fe powder and ammonium chloride in methanol and water at reflux temperature to yield 2-(4,5-dimethoxy-1*H*-indol-3-yl) ethanamine (**8**). On the other hand, fatty acids were converted to fatty acid chlorides (**11a-h**, Scheme II) by oxalyl chloride and catalytic.



10(a-h) 11(a-h)

R = $-(CH_2)_2-CH_3$, $-(CH_2)_4-CH_3$, $-(CH_2)_6-CH_3$, $-(CH_2)_8-CH=CH_2$, $-(CH_2)_{10}-CH_3$, $-(CH_2)_{12}-CH_3$, $-(CH_2)_7-CH=CH_2-(CH_2)_7-CH_3$, $-(CH_2)_{16}-CH_3$.

Scheme II — Synthesis of fatty acid chlorides. Reagents and conditions: (i) $COCl_2$, cat. DMF, DCM, 3 h

amount of DMF in DCM at RT for 3 h. Fatty acyl chlorides were treated with 8 in the presence of triethyl amine in DCM to form the corresponding amide derivatives (**9a-h**).

All the synthesized compounds (**9a-h**) along with doxorubicin as a reference compound were screened against a panel of different cancer cell lines such as A549, PC3, MDA-MB-231, HepG2 and HUVEC (normal cell line) using MTT assay[33]. The cytotoxicity results for all the synthesized compounds are depicted in Table I.

Most of the compounds showed significant cytotoxic effect. Among the tested compounds, the compounds **9a** and **9g** showed the promising cytotoxicity (IC_{50} <16 μM) as compared to other derivatives. In particular, the compounds **9a** and **9g** have an amide linkage with butyric acid and oleic acid, respectively. It was earlier reported that butyric acid functioned as a potent antitumor agent *in vitro*[34] and also a number of unsaturated fatty acids have been reported to inhibit cancer cell growth[35-39]. There are also reports on oleic acid exhibiting inhibition of tumour growth[40,41]. Oleic acid is generally regarded as non-toxic to normal cells. Our present study also revealed that these compounds showed no cytotoxicity against normal cell line (HUVEC). On the other hand, compounds **9c**, **9d** and **9f** showed significant cytotoxicity against all the tested cell lines (IC_{50} <40 μM).

Methoxy and acyl groups as essential substituents on MLT contribute to the antioxidant properties. This can be explained in terms of lipophilicity by the replacement of the acetyl group with the nonanoyl group which plays a significant role in increasing the antioxidant activity[42]. In the present study, we synthesized various fatty acid-based derivatives

Table I — Cytotoxic activity of compounds **9a-h**

Compd	IC_{50} values (μM) (Mean ± S.D.)				
	A549	PC3	MDA-MB-231	HepG2	HUVEC
9a	13.4 ± 0.12	12.5 ± 0.15	12.6 ± 0.22	14.2 ± 0.28	85.6 ± 0.24
9b	–[a]	–[a]	–[a]	–[a]	–[a]
9c	22.4 ± 0.18	20.2 ± 0.38	–	27.6 ± 0.26	93.2 ± 0.36
9d	25.3 ± 0.34	24.5 ± 0.36	22.2 ± 0.18	19.8 ± 0.20	100.4 ± 0.52
9e	–[a]	–[a]	–[a]	–[a]	–[a]
9f	25.6 ± 0.42	31.2 ± 0.18	22.1 ± 0.24	19.8 ± 0.32	91.5 ± 0.36
9g	14.8 ± 0.15	11.8 ± 0.26	12.8 ± 0.18	15.6 ± 0.14	89.6 ± 0.42
9h	–[a]	–[a]	34.2 ± 0.18	32.3 ± 0.26	99.2 ± 0.44
Doxorubicin (Control)	0.8 ± 0.12	0.6 ± 0.11	0.9 ± 0.07	0.8 ± 0.09	68.2 ± 0.22

[a] – = No activity, A549: human alveolar adenocarcinoma epithelial cells (ATCC No. CCL-185), PC3: human prostate cancer cells (ATCC No. CRL-1435), MDA-MB-231: human breast adenocarcinoma cells (ATCC No. HTB-26), HepG2 human liver adenocarcinoma cells (ATCC No HB-8065), HUVEC: normal human umbilical vein epithelial cells (ATCC No. CRL-1730).

of 4,5-dimethoxy tryptamine nucleus by amide coupling. The antioxidant activity of the newly prepared N-fatty acyl derivatives of 4,5-dimethoxy tryptamine was evaluated based on three *in vitro* assays such as DPPH radical scavenging activity[43], superoxide radical scavenging activity[44] and inhibition of lipid peroxidation[45] in comparison to BHT and α-tocopherol as standard antioxidants. The amount of compound required to inhibit the free radicals by 50% was estimated and the values are given as their effective concentration (EC_{50}) values. The results to this regard are shown in Table II. It was observed that all the compounds showed significant activities in case of all the three antioxidant assays. Among all the tested fatty acid-based dimethoxy tryptamine derivatives, undecenoic acid-based (**9d**) and stearic acid-based (**9h**) compounds selectively exhibited higher antioxidant activities as compared to the reference compounds. The EC_{50} values observed for BHT and α-tocopherol were 27.2 and 10.1 µg/mL, respectively.

The prepared fatty acid-based dimethoxy tryptamine derivatives were screened for antimicrobial activity against seven bacterial strains and one fungal strain[46]. The results to this regard are shown in Table III. Among the screened compounds, only undecenoic acid-based (**9d**) and octanoic acid-based (**9c**) derivatives exhibited promising activity against *Bacillus subtilis* MTCC 121 with MIC values of 15.6 and 31.2 µg/mL, respectively. While the other compounds exhibiting MIC values of >125 µg/mL were considered as less active compounds. All the compounds prepared in the present study possess a basic dimethoxy tryptamine scaffold with different fatty acids coupled with an amide linkage. It was earlier demonstrated that undecenoic acid-based derivatives exhibited promising antimicrobial activity[47] and our results corroborate well with these findings.

Table II — Antioxidant activity of prepared N-fatty acyl derivatives of 4,5-dimethoxy tryptamine

Compd	DPPH FRSA	Superoxide FRSA	Inhibition of lipid peroxidation
	EC_{50} (µg/mL) (Mean ± S.D.)		
9a	85.0 ± 0.35	74.2 ± 0.36	108.2 ± 0.54
9b	115.7 ± 0.44	102.6 ± 0.42	136.8 ± 0.52
9c	85.2 ± 0.42	79.2 ± 0.58	88.9 ± 0.44
9d	30.2 ± 0.38	25.6 ± 0.28	33.3 ± 0.32
9e	42.1 ± 0.18	38.8 ± 0.32	42.6 ± 0.22
9f	55.7 ± 0.22	60.2 ± 0.44	77.7 ± 0.28
9g	37.2 ± 0.28	39.8 ± 0.28	44.8 ± 0.34
9h	32.7 ± 0.32	29.6 ± 0.36	38.5 ± 0.38
BHT	27.2 ± 0.26	13.2 ± 0.12	41.1 ± 0.32
α-Tocopherol	10.1 ± 0.18	7.2 ± 0.14	19.2 ± 0.14

Based on the antibacterial activity results, the minimum bactericidal concentration was evaluated against *Bacillus subtilis* MTCC 121 for **9c** and **9d** and the results showed that the MBC values determined were 62.5 and 31.2 µg/mL, respectively, when compared with ciprofloxacin (1.9 µg/mL).

Experimental Section

All the chemicals used in the present study were obtained from different commercial sources and were used without any further purification. Reactions were monitored on micro TLC with UV detection. Final purification was carried out using silica gel 60-120 mesh (Rankem). All ^{1}H and ^{13}C NMR spectra were recorded on AVANCE-300 (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR). Chemical shifts are reported in ppm with reference to internal standard TMS. Molecular weights of unknown compounds were identified by ESI-MS and HRMS (Electron spray ionization technique). IR spectra were recorded in chloroform on a Perkin-Elmer Spectrum BX FT-IR instrument.

Synthesis of 2,3-dimethoxy-6-nitrobenzaldehyde, 2

A solution of 2,3-dimethoxybenzaldehyde (5 g, 3.14 mmol) in glacial acetic acid (20 mL) was cooled to 0°C and treated with fuming nitric acid (5 mL), after being stirred at RT for 4 h. Progress of the reaction was monitored by TLC. After complete consumption of raw materials, the reaction mixture was poured over ice and kept under cold conditions until an abundant yellow precipitate was formed. Then the reaction mixture was filtered and washed with water several times to afford the crude solid compound. The compound was purified by column chromatography using ethyl acetate:hexane (5:95, v/v) solvent system to yield pure 2,3-dimethoxy-6-nitrobenzaldehyde (26%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.30 (s, 1H, Ald-H), 7.91 (d, J = 9.1 Hz, 1H, Ar-H), 6.98 (d, J = 9.1 Hz, 1H, Ar-H), 3.94 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.35, 153.15, 145.66, 143.33, 121.53, 114.91, 112.77, 111.69, 62.46, 56.58; IR ($CHCl_3$): 3687, 3317, 3020, 2400, 1662, 1215, 760, 669 cm^{-1}; ESI-MS: *m/z* $[M+H]^+$ 212; ESI-HRMS: *m/z* $[M+Na^+]$. Calcd for $C_9H_{10}NO_5$: 212.05535. Found: 212.05488 ($C_9H_{10}NO_5$).

Table III — Antimicrobial activity evaluation of the prepared N-fatty acyl derivatives of 4,5-dimethoxy tryptamine

Compd	Minimum inhibitory concentration (μg/mL)							
	S. aureus MTCC 96	*B. subtilis* MTCC 121	*S. aureus* MLS16 MTCC 2940	*M. luteus* MTCC 2470	*K. planticola* MTCC 530	*E. coli* MTCC 739	*P. aeruginosa* MTCC 2453	*C. albicans* MTCC 3017
9a	>125	>125	>125	>125	>125	>125	>125	–
9b	>125	>125	>125	>125	>125	>125	>125	–
9c	>125	31.2	>125	>125	>125	>125	>125	–
9d	>125	15.6	>125	>125	>125	>125	>125	–
9e	>125	>125	>125	>125	>125	>125	>125	–
9f	>125	>125	>125	>125	>125	>125	>125	–
9g	>125	>125	>125	>125	>125	>125	>125	–
9h	>125	>125	>125	>125	>125	>125	>125	–
Miconazole (Standard control)	–	–	–	–	–	–	–	7.8
Ciprofloxacin (Standard control)	0.9	0.9	0.9	0.9	0.9	0.9	0.9	–

Synthesis of 1, 2-dimethoxy-4-nitro-3-(2-nitrovinyl) benzene, 3

2,3-Dimethoxy-6-nitrobenzaldehyde (900 mg, 7.93 mmol) was stirred for 12 h under nitrogen at RT with N-methyl morpholine (8 mL), KF (150 mg), 18-crown-6 (50 mg) and nitromethane (5 mL, 40 mmol). The mixture was then poured into acetic anhydride (10 mL) containing sodium acetate (450 mg), and warmed to 60°C. After 1 h, the reaction mixture was poured over ice and stirred until a fine powder was formed. The mixture was filtered and extracted with ethyl acetate and washed with water. Then the organic layer was dried over anhyd. Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography over silica gel using ethyl acetate:hexane (10:90, v/v) solvent system to afford **1**, 2-dimethoxy-4-nitro-3-(2-nitrovinyl) benzene (65%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (d, *J* = 13.6 Hz, 1H, =CH), 7.90 (d, *J* = 9.1 Hz, 1H, Ar-H), 7.62 (d, *J* = 13.6 Hz, 1H, =CH), 6.99 (d, *J* = 9.1 Hz, 1H, Ar-H), 3.95 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.35, 147.99, 142.05, 141.92, 129.66, 122.38, 120.55, 112.41, 60.86, 56.48; IR ($CHCl_3$): 3318, 2935, 1663, 1513, 1344, 1277, 1091, 821, 736 cm^{-1}.

Synthesis of 4,5-dimethoxy-1*H*-indole, 4

A mixture of 1,2-dimethoxy-4-nitro-3-(2-nitrovinyl) benzene (600 mg), silica gel (1.20 g), reduced iron powder (800 mg), glacial AcOH (5 mL), and toluene (10 mL) was heated to 90°C under nitrogen with efficient mechanical stirring for 1 h. The progress of reaction was monitored by TLC. Then the reaction mixture was filtered and the solids were washed with ethyl acetate and water. The organic layer was dried over anhyd. Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography over silica gel using ethyl acetate: hexane (20:80, v/v) solvent system to afford 4,5-dimethoxy-1*H*-indole (70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11 (s, 1H, NH), 7.15 (t, *J* = 3.0 Hz, 1H, Ar-H), 7.05 (d, *J* = 9.0 Hz, 1H, Ar-H), 6.93 (d, *J* = 9.0 Hz, 1H, Ar-H), 6.69 – 6.58 (m, 1H, Ar-H), 4.07 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 188.35, 153.15, 145.66, 143.33, 121.53, 114.91, 112.77, 111.69, 62.46, 56.58; IR ($CHCl_3$): 3483, 3020, 2400, 1663, 1518, 1215, 928, 760, 669 cm^{-1}; ESI-MS: *m/z* $[M+H]^+$ 178; ESI-HRMS: *m/z* $[M+Na^+]$: Calcd for $C_{10}H_{12}NO_2$ is 178.08626. Found 178.08575 ($C_{10}H_{12}NO_2$).

Synthesis of 4,5-dimethoxy-1*H*-indole-3-carbaldehyde, 5

$POCl_3$ (1 mL) was added slowly to a stirred solution of DMF (5 mL) at 0°C and then stirred continuously at the same temperature for 30 min. Then the compound 4,5-dimethoxy-1*H*-indole (300 mg) was taken in DMF, and then added slowly to the reaction mixture and stirred at RT for 4 h. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was quenched with 2N NaOH (10 mL) slowly and the reaction mixture was refluxed for 2 h. The crude product was extracted using ethyl acetate and dried over anhyd. Na_2SO_4 and then concentrated under reduced pressure. The product was further purified by column chromatography using ethyl acetate:hexane

(40:60, v/v) solvent system to elute the desired 4,5-dimethoxy-1*H*-indole-3-carbaldehyde compound (85%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.36 (s, 1H, Ald-H), 10.28 (s, 1H, NH), 7.96 (d, *J* = 3.2 Hz, 1H, Ar-H), 7.18 (d, *J* = 8.8 Hz, 1H, Ar-H), 6.98 (d, *J* = 8.8Hz, 1H, Ar-H), 4.01 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 188.35, 153.15, 145.66, 143.33, 121.53, 114.91, 112.77, 111.69, 62.46, 56.58; IR ($CHCl_3$): 3686, 3312,3020, 2400, 1662, 1520, 1427, 1216, 928, 763, 669 cm^{-1}; ESI-MS: *m/z* $[M+Na]^+$ 228. ESI-HRMS: *m/z* [M+Na$^+$]: Calcd for $C_{11}H_{11}NO_3Na$ is 228.06311. Found 228.06243 ($C_{11}H_{11}NO_3Na$).

Synthesis of 4,5-dimethoxy-3-(2-nitrovinyl)-1*H*-indole, 6

To a stirred solution of 4,5-dimethoxy-1*H*-indole-3-carbaldehyde compound (250 mg) in nitromethane, sodium acetate was added and the reaction mixture stirred at 90°C for 6 h. Progress of the reaction was monitored by TLC. Excess nitromethane in the reaction mixture was removed under reduced pressure and the crude product was extracted with ethyl acetate, washed with water and dried over anhyd. Na_2SO_4. The organic layer was concentrated, and purified by column chromatography using ethyl acetate:hexane (50:50, v/v) solvent system to get the desired 4,5-dimethoxy-3-(2-nitrovinyl)-1*H*-indole (81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, *J* = 13.2 Hz, 1H, =CH), 7.94 (m, 2H, =CH, NH), 7.76 (s, 1H, Ar-H), 6.95-6.96 (d, *J* = 8.6 Hz, 1H, Ar-H), 6.84-6.89 (d, *J* = 8.6 Hz, 1H, Ar-H), 3.93 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.41-3.44 (m, 2H, =CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.57, 140.50, 133.30, 132.69, 130.60, 118.16, 110.55, 106.22, 59.18, 55.85; IR ($CHCl_3$): 3325, 3020, 2400, 1662, 1522, 1215, 928, 764, 669 cm^{-1}; ESI-MS: *m/z* $[M+Na]^+$ 271; ESI-HRMS: *m/z* [M+H$^+$]: Calcd for $C_{12}H_{13}O_4N_2$ is 249.08698. Found 249.08644 ($C_{12}H_{13}O_4N_2$).

Synthesis of 4,5-dimethoxy-3-(2-nitroethyl)-1*H*-indole, 7

To a stirred solution of 5-dimethoxy-3-(2-nitrovinyl)-1*H*-indole (200 mg, 5 mmol) in methanol and DMF (5 mL : 5 mL), sodium borohydride (100 mg) was added at 0°C and stirred at RT for 4 h. Progress of reaction was monitored by TLC. Then cold water (1 mL) was added to quench excess sodium borohydride and solvents were evaporated under reduced pressure. The crude product was extracted with ethyl acetate and washed with water and then dried over anhyd. Na_2SO_4 and purified by column chromatography to get the desired 4,5-dimethoxy-3-(2-nitroethyl)-1*H*-indole (78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.30 (s, 1H, NH), 6.96 (d, *J* = 8.6 Hz, 1H, Ar-H), 6.89 (s, 1H, Ar-H), 6.85 (d, *J* = 8.6 Hz, 1H, Ar-H), δ 4.66 (t, *J* = 7.1 Hz, 2H, CH_2), 3.93 (s, 3H, OCH_3), 3.84 (s, 3H, OCH_3), 3.43 (t, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.35, 153.15, 145.66, 143.33, 121.53, 114.91, 112.77, 111.69, 62.46, 56.58; IR ($CHCl_3$): 3685, 3327, 3020, 2400, 1662, 1521, 1426, 1384, 1215, 928, 761, 669 cm^{-1}; ESI-MS: *m/z* $[M+Na]^+$ 273.

Synthesis of 2-(4,5-dimethoxy-1*H*-indol-3-yl) ethanamine, 8

To a stirred solution of 4,5-dimethoxy-3-(2-nitroethyl)-1*H*-indole (150 mg, 1 mmol) in methanol and water (5 mL : 1 mL), iron powder (100 mg) and ammonium chloride (90 mg) were added and reaction mixture was refluxed for 2 h. Progress of reaction was monitored by TLC. After conversion of the starting materials, reaction mixture was filtered using celite pad and methanol was evaporated under reduced pressure. Crude product was extracted with ethyl acetate and washed with water and then dried over anhyd. Na_2SO_4. Ethyl acetate was removed under reduced pressure and the product was used for the next step without purification. IR ($CHCl_3$): 3684, 3305, 3020, 2400, 1662, 1522, 1427, 1384, 1215, 928, 763, 669 cm^{-1}; ESI-MS: *m/z* $[M+H]^+$ 221.

General procedure for the synthesis of fatty acid chlorides 10a–h

To a stirred solution of fatty acid in DCM, catalytic amount of DMF was added and the contents were stirred at 0°C and oxalyl chloride was added under nitrogen atmosphere. The reaction mixture was further stirred at 0°C for 3 h. Later the reaction mixture was concentrated under reduced pressure to remove DCM and excess oxalyl chloride. Then the crude acid chloride dissolved in DCM was used for the next step directly under nitrogen atmosphere.

General procedure for the synthesis of target compounds 8a-h

To a stirred solution of 2-(4,5-dimethoxy-1*H*-indol-3-yl) ethanamine (60 mg, 2 mmol) in DCM (5 mL), triethyl amine (0.1 mL) followed by acid chlorides (0.1 mL) were added and stirring was continued at RT for 2 h. The crude product was extracted with DCM, washed with water, dried over anhyd. Na_2SO_4 and purified by column chromatography.

N-(2-(4,5-Dimethoxy-1*H*-indol-3-yl) ethyl) butyramide, 9a: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.42 (s, 1H, NH), 7.04 (d, *J* = 8.7 Hz, 1H, Ar-H), 6.90-6.92 (m, 2H,

Ar-H), 6.35 (s, 1H, Ar-H), 3.98 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.54-3.58 (m, 2H, CH_2), 3.01 (t, J = 6.4 Hz, 2H, CH_2), 2.04-2.06 (t, 2H, CH_2), 1.52-1.56 (m, 2H, CH_2), 1.24-1.27 (m, 2H, CH_2), 0.80 (t, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.38, 145.19, 142.27, 133.85, 123.85, 121.61, 112.49, 111.71, 106.77, 61.37, 58.14, 41.32, 38.70, 29.68, 25.87, 19.09, 13.64; IR ($CHCl_3$): 3356, 3019, 2928, 2400, 1657, 1498, 1215, 1065, 761, 669 cm^{-1}; ESI-MS: *m/z* $[M+Na]^+$ 313; ESI-HRMS: *m/z* $[M+H^+]$: Calcd for $C_{16}H_{23}O_3N_2$ is 291.17032. Found: 291.1732 ($C_{16}H_{23}O_3N_2$).

N-(2-(4,5-Dimethoxy-1*H*-indol-3-yl) ethyl) hexanamide, 9b: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.44 (s, 1H, NH), 7.04 (d, J = 8.7 Hz, 1H, Ar-H), 6.90-6.92 (m, 2H, Ar-H), 6.35 (s, 1H, Ar-H), 3.98 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.54-3.58 (m, 2H, CH_2), 3.01 (t, J = 6.4 Hz, 2H, CH_2), 2.05-2.08 (t, 2H, CH_2), 1.52-1.56 (m, 2H, CH_2), 1.24-1.27 (m, 6H, $(CH_2)_3$), 0.80 (t, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.71, 145.46, 142.51, 134.25, 123.98, 121.95, 112.70, 111.92, 107.20, 61.70, 58.43, 41.72, 37.13, 36.26, 31.72, 25.58, 26.18, 22.72, 14.26; IR ($CHCl_3$): 3684, 3531, 3413, 3020, 2931, 2400, 1678, 1520, 1426, 1215, 928, 759, 669 cm^{-1}; ESI-MS: *m/z* $[M+Na]^+$ 341; ESI-HRMS: *m/z* $[M+H^+]$: Calcd for $C_{18}H_{27}O_3N_2$ is 319.20162. Found: 319.20069 ($C_{18}H_{27}O_3N_2$).

N-(2-(4,5-Dimethoxy-1*H*-indol-3-yl) ethyl) octanamide, 9c: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.17 (s, 1H, NH), 7.04 (d, J = 8.7 Hz, 1H, Ar-H), 6.90-6.92 (m, 2H, Ar-H), 6.35 (s, 1H, Ar-H), 3.98 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.54-3.58 (m, 2H, CH_2), 3.01 (t, J = 6.4 Hz, 2H, CH_2), 2.04-2.06 (t, 2H, CH_2), 1.52-1.56 (m, 2H, CH_2), 1.24-1.27 (m, 10H, $(CH_2)_5$), 0.80 (t, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.00, 147.79, 144.82, 140.46, 133.34, 122.98, 122.06, 112.31, 111.32, 106.22, 60.91, 57.66, 40.80, 39.12, 36.43, 35.97, 31.22, 29.25, 28.55, 25.30, 22.15, 13.62; IR ($CHCl_3$): 3355, 2926, 2855, 1642, 1425, 1256, 1065, 769 cm^{-1}; ESI-MS: *m/z* $[M+Na]^+$ 369; ESI-HRMS: *m/z* $[M+H^+]$: Calcd for $C_{20}H_{31}O_3N_2$ is 347.23292. Found: 347.23283($C_{20}H_{31}O_3N_2$).

N-(2-(4,5-Dimethoxy-1*H*-indol-3-yl) ethyl) undec-10-enamide, 9d: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (s, 1H, NH), 7.04 (d, J = 8.7 Hz, 1H, Ar-H), 6.90-6.92 (m, 2H, Ar-H), 6.35 (s, 1H, Ar-H), 5.76-5.84 (m, 1H, =CH), 4.91-5.01 (m, 2H, $=CH_2$), 3.98 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.54-3.58 (m, 2H, CH_2), 3.01 (t, J = 6.4 Hz, 2H, CH_2), 2.04-2.06 (t, 2H, CH_2), 1.52-1.56 (m, 2H, CH_2), 1.24-1.27 (m, 10H, $(CH_2)_5$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.98, 144.76, 141.82, 138.74, 133.35, 123.02, 121.19, 113.66, 112.18, 114.24, 106.25, 60.90, 57.64, 40.82, 36.40, 33.33, 24.73; IR ($CHCl_3$): 3685, 3479, 3020, 2929, 2400, 1654, 1517, 1215, 1066, 927, 760, 669 cm^{-1}; ESI-MS: *m/z* $[M+Na]^+$ 409; ESI-HRMS: *m/z* $[M+H^+]$: Calcd for $C_{23}H_{35}O_3N_2$ is 387.26422. Found 387.26301 ($C_{23}H_{35}O_3N_2$).

N-(2-(4,5-Dimethoxy-1*H*-indol-3-yl) ethyl) dodecanamide, 9e: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.22 (s, 1H, NH), 7.04 (d, J = 8.7 Hz, 1H, Ar-H), 6.90-6.92 (m, 2H, Ar-H), 6.35 (s, 1H, Ar-H), 3.98 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.54-3.58 (m, 2H, CH_2), 3.01 (t, J = 6.4 Hz, 2H, CH_2), 2.04-2.06 (t, 2H, CH_2), 1.52-1.56 (m, 2H, CH_2), 1.24-1.27 (m, 18H, $(CH_2)_9$), 0.83 (t, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.01, 147.97, 144.80, 133.34, 122.99, 121.20, 112.25, 111.29, 106.22, 60.90, 57.65, 40.81, 37.29, 36.43, 35.51, 31.43, 25.43, 22.24, 13.67; IR ($CHCl_3$): 3686, 3413, 3020, 2928, 2400, 1679, 1521, 1425, 1215, 1021, 928, 759, 669 cm^{-1}; ESI-MS: *m/z* $[M+Na]^+$ 425.

N-(2-(4,5-Dimethoxy-1*H*-indol-3-yl) ethyl) palmitamide, 9f: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (s, 1H, NH), 7.04 (d, J = 8.7 Hz, 1H, Ar-H), 6.90-6.92 (m, 2H, Ar-H), 6.35 (s, 1H, Ar-H), 3.98 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.54-3.58 (m, 2H, CH_2), 3.01 (t, J = 6.4 Hz, 2H, CH_2), 2.04-2.06 (t, 2H, CH_2), 1.52-1.56 (m, 2H, CH_2), 1.24-1.27 (m, 26H, $(CH_2)_{13}$), 0.87 (t, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.83, 144.22, 141.36, 133.14, 129.91, 122.61, 110.74, 110.22, 105.87, 60.15, 57.07, 39.29, 35.45, 34.71, 30.77, 28.20, 24.54, 21.55, 13.14; IR ($CHCl_3$): 3685, 3531, 3413, 3020, 2927, 2400, 1678, 1520, 1427, 1215, 1024, 928, 761, 669 cm^{-1}; ESI-MS: *m/z* $[M+Na]^+$ 481; ESI-HRMS: *m/z* $[M+H^+]$: Calcd for $C_{28}H_{47}O_3N_2$ is 459.35812. Found 459.35494 ($C_{28}H_{47}O_3N_2$).

N-(2-(4,5-Dimethoxy-1*H*-indol-3-yl) ethyl) oleamide, 9g: ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (s, 1H, NH), 7.04 (d, J = 8.7 Hz, 1H, Ar-H), 6.90-6.92 (m, 2H, Ar-H), 6.35 (s, 1H, Ar-H), 5.32–5.36 (m, 2H, $(=CH)_2$), 3.98 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 2.47 – 2.52 (t, 2H, CH_2), 1.97 – 2.01 (m, 6H, $(CH_2)_3$), 1.55– 1.59 (t, 2H, CH_2), 1.25–1.43 (m, 20H, $(CH_2)_{10}$), 0.85 – 0.89 (t, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$):

δ 176.18, 173.80, 145.60, 142.67, 134.21, 130.37, 123.87, 122.03, 113.00, 112.08, 107.11, 61.73, 58.48, 41.68, 37.23, 32.29, 30.15, 27.60, 25.92, 23.07, 14.50; IR ($CHCl_3$): 3445, 3686, 3320, 3020, 2928, 2400, 1665, 1521, 1428, 1384, 1215, 1023, 928, 761, 669 cm^{-1}; ESI-MS: *m/z* $[M+Na]^+$ 507; ESI-HRMS: *m/z* $[M+H^+]$: Calcd for $C_{30}H_{49}O_3N_2$ is 485.37377. Found 485.37067 ($C_{30}H_{49}O_3N_2$).

N-(2-(4,5-Dimethoxy-1*H*-indol-3-yl) ethyl) stearamide, 9h: ^1H NMR (300 MHz, $CDCl_3$): δ 7.95 (s, 1H, NH), 7.04 (d, *J* = 8.7 Hz, 1H, Ar-H), 6.90-6.92 (m, 2H, Ar-H), 6.35 (s, 1H, Ar-H), 3.98 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 3.54-3.58 (m, 2H, CH_2), 3.01 (t, *J* = 6.4 Hz, 2H, CH_2), 2.20-2.23 (m, 2H, CH_2), 1.52-1.56 (m, 2H, CH_2), 1.24-1.27 (m, 30H, $(CH_2)_{15}$), 0.89 (t, *J* = 7.3 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.86, 148.82, 145.65, 134.19, 123.84, 122.06, 113.11, 112.14, 107.08, 61.76, 58.51, 41.66, 37.29, 36.36, 32.32, 30.10, 25.94, 23.10, 14.52; IR ($CHCl_3$): 3685, 3531, 3413, 3020, 2927, 2400, 1678, 1520, 1427, 1335, 1215, 1024, 928, 762, 669, 497 cm^{-1}; ESI-MS: *m/z* $[M+Na]^+$ 509; ESI-HRMS: *m/z* $[M+H^+]$: Calcd for $C_{30}H_{51}O_3N_2$ is 487.38942. Found 487.38623 ($C_{30}H_{51}O_3N_2$).

In vitro cytotoxicity assay

All the synthesized fatty acid-based dimethoxy tryptamine derivatives were screened for *in vitro* cytotoxicity on a panel of four different cancer cell lines such as A549 derived from human alveolar adenocarcinoma epithelial cells (ATCC No. CCL-185), PC3 derived from human prostate cancer cells (ATCC No. CRL-1435), MDA-MB-231 derived from human breast adenocarcinoma cells (ATCC No. HTB-26), HepG2 derived from human liver adenocarcinoma cells (ATCC No HB-8065), and HUVEC derived from normal human umbilical vein epithelial cells (ATCC No. CRL-1730) which were obtained from the American Type Culture Collection, Manassas, VA, USA. The cytotoxicity was determined using MTT assay (Mosmann, 1983). The effects of the different synthesized compounds on the viability of the tumour cell lines were measured at 540 nm using a multimode reader (Infinite® M200Pro, Tecan, Switzerland). The IC50 values (50% inhibitory concentration) were calculated from the plotted absorbance data of the dose–response curves. The assay was performed using doxorubicin as positive controls and 1% DMSO as a vehicle control. In order to account for the toxicity of DMSO, the values obtained for the DMSO control were subtracted from those of the test compounds. Statistical analysis was performed using GraphPad PRISM software version 3.0 (GraphPad Software, Inc, La Jolla, CA, USA). All experimental data were compared using Student's t-test. In all comparisons, $p < 0.05$ was considered statistically significant. The IC50 values (in mM) are expressed as means ± standard deviation (SD), (n = 3) of three independent experiments performed in triplicates.

Antioxidant activities

DPPH radical scavenging activity

Antioxidant activity of prepared N-fatty acyl derivatives of 4,5-dimethoxy tryptamine was assessed on the basis of the free radical scavenging effect on the stable 1, 1-diphenyl-2-picrylhydrazyl (DPPH) by a modified method of Moon and Terao2 and the DPPH radical scavenging activity was calculated using the formula of Bors *et al*. Radical scavenging potential was expressed as EC50 value, which represents the test compound concentration at which 50% of the DPPH radicals were scavenged. BHT and α-tocopherol were run in parallel as positive controls. All tests were performed in triplicate and values are represented as mean.

DPPH radical scavenging activity (%) = [(Absorbance of control – Absorbance of test sample) / (Absorbance of control)] × 100

Superoxide radical scavenging assay

The superoxide radical scavenging activity of prepared N-fatty acyl derivatives of 4,5-dimethoxy tryptamine was performed according to the protocol described by Liu *et al*. The superoxide radical was generated by phenazine methosulfate - nicotinamide adenine dinucleotide (PMS/NADH) system, which reduces nitro blue tetrazolium (NBT) forming a purple colored formazan. The reaction mixture consisted of 3.0 mL of 16 mM Tris-HCl buffer (*p*H 8.0) containing 78 mM NADH, 50 µM NBT, 10 µM PMS and various concentrations of test compound and incubated for 5 min at RT. After incubation the absorbance was read at 560 nm. BHT and α-tocopherol were run in parallel as positive controls. The scavenging activity of superoxide radical (%) was calculated using the equation:

$[(A_{560}$ of control $- A_{560}$ of sample$)/A_{560}$ of control$] \times 100$

Inhibition of lipid peroxidation

The inhibition of lipid peroxidation was assayed by measuring the lipid peroxide decomposition product

malondialdehyde (MDA) based on reaction with thiobarbituric acid using egg yolk as oxidizable substrate by Zang *et al*. The yolk was taken out from an egg and same volume of PBS (0.1 M, *p*H 7.45) was added and stirred vigorously. The yolk suspension was mixed with 0.5 mL different concentrations of prepared N-fatty acyl derivatives of 4,5-dimethoxy tryptamine, 0.2 mL 25 mM $FeSO_4$ and 1.3 mL PBS and incubated at 37°C for 15 min. And the reaction was stopped by adding 0.5 mL 20% trichloroacetic acid and 1 mL of 0.8% thiobarbituric acid and then the mixture was heated at 100°C for 15 min. The absorbance of all the samples was recorded at 532 nm. BHT and α-tocopherol were run in parallel as positive controls. The inhibition of lipid peroxidation was calculated from the following equation:

$$\text{Inhibition effect (\%)} = A_{control} - A_{sample}/A_{control} \times 100\%$$

General statistical analysis for all the antioxidant assays

Statistical analysis was performed using GraphPad PRISM software version 3.0 (GraphPad Software, Inc, La Jolla, CA, USA). All experimental data were compared using Student's t-test. In all comparisons, $p < 0.05$ was considered statistically significant. The EC_{50} (µg/ mL) are expressed as means ± standard deviation (SD), (n = 3) of three independent experiments performed in triplicates.

Antibacterial and antifungal assays

Antimicrobial activity of the prepared N-fatty acyl derivatives of 4,5-dimethoxy tryptamine was screened using well diffusion method against a panel of pathogenic bacterial strains, including *Micrococcus luteus* MTCC 2470, *Staphylococcus aureus* MTCC 96, *Staphylococcus aureus* MLS16 MTCC 2940, *Bacillus subtilis* MTCC 121, *Escherichia coli* MTCC 739, *Klebsiella planticola* MTCC 530, *Pseudomonas aeruginosa* MTCC 2453 and *Candida albicans* MTCC 3017 which were procured from the Microbial Type Culture Collection (MTCC), CSIR-Institute of Microbial Technology, Chandigarh, India. The pathogenic reference strains were seeded on the surface of the media Petri plates, containing Muller-Hinton agar with 0.1 mL of previously prepared microbial suspensions individually containing 1.5×10^8 cfu mL^{-1} (equal to 0.5 McFarland). Wells of 6.0 mm diameter were prepared in the media plates using a cork borer and the prepared molecules at a dose range of 125 - 0.48 µg $well^{-1}$ were added in each well under sterile conditions in a laminar air flow chamber. Standard antibiotic solution of ciprofloxacin and miconazole at a dose range of 125-0.48 µg $well^{-1}$ and the well containing methanol served as positive and negative controls, respectively. The plates were incubated for 24 h at 37°C for bacterial and 30°C for *Candida albicans* and the well containing the least concentration showing the inhibition zone was considered as the minimum inhibitory concentration. All experiments were carried out in duplicates and mean values are represented.

Minimum bactericidal concentration

Minimum bactericidal concentration assay (NCCLS, 2000) were performed in sterile 2.0 mL microfuge tubes against *Bacillus subtilis* MTCC 121 which were procured from the Microbial Type Culture Collection (MTCC), CSIR-Institute of Microbial Technology, Chandigarh, India[5]. The pathogenic *Bacillus subtilis* strain was cultured overnight in Mueller Hinton broth. Serial dilutions of prepared N-fatty acyl derivatives of 4,5-dimethoxy tryptamine were prepared in Mueller Hinton broth with different concentrations ranging from 0 to150 µg/mL. To the serially diluted N-fatty acyl derivatives of 4,5-dimethoxy tryptamine, 100 µL of overnight cultured bacterial suspension was added to reach a final concentration of 1.5×10^8 cfu mL^{-1} (equal to 0.5 McFarland) and incubated at 37°C for 24 h. After 24 h of incubation, the minimum bactericidal concentration (MBC) was determined by sampling 10 µL of suspension from the tubes onto Mueller Hinton agar plates and were incubated for 24 h at 37°C to observe the growth of test organisms. MBC is the lowest concentration of prepared N-fatty acyl derivatives of 4,5-dimethoxy tryptamine required to kill a particular bacterium. All the experiments were carried in duplicates.

Biofilm inhibition assay

The N-fatty acyl derivatives of 4,5-dimethoxy tryptamine were screened in sterile 96 well polystyrene microtiter plates using the modified biofilm inhibition assay, against *Bacillus subtilis* MTCC 121, which were cultured overnight in tryptone soy broth (supplemented with 0.5% glucose). The test compounds of predetermined concentrations ranging from 0 to 250 µg/mL were mixed with the bacterial suspension having an initial inoculum concentration of 5×10^5 CFU/mL. Aliquots of 100 µL were distributed in each well and then incubated at 37°C for 24 h under static conditions. The medium was then discarded and washed with phosphate buffered saline to remove the

non-adherent bacteria. Each well of the microtiter plate was stained with 100 µL of 0.1% crystal violet solution followed by 30 min incubation at RT. Later the crystal violet solution from the plates was discarded, thoroughly washed with distilled water for 3 to 4 times and air dried at RT. The crystal violet stained biofilm was solubilised in 95% ethanol (100 µL) and the absorbance was recorded at 540 nm using TRIAD multimode reader (Dynex Technologies, Inc, Chantilly, VA, USA). Blank wells were employed as background check. The inhibition data were interpreted from the dose-response curves, where IC_{50} value is defined as the concentration of inhibitor required to inhibit 50% of biofilm formation under the above assay conditions. All the experiments were carried out in triplicate and the values are indicated as mean ± S.D.

Conclusions

In conclusion, a series of novel N-fatty acyl derivatives of 4,5-dimethoxy tryptamine were synthesized and screened for *in vitro* anticancer, antioxidant and antimicrobial activities. The results revealed that short chain saturated (butyric) and long chain unsaturated (oleic) derivatives exhibited the highest anticancer activities. It was also observed that dimethoxy tryptamine derivative of undecenoic acid exhibited promising antibacterial and antioxidant activities. The antioxidant results also suggested that undecenoic and stearic acid derivatives exhibited significant lipid peroxidation inhibition as compared to BHT.

Supplementary Information

Supplementary information is available in the website http://nopr.niscair.res.in/handle/123456789/60.

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