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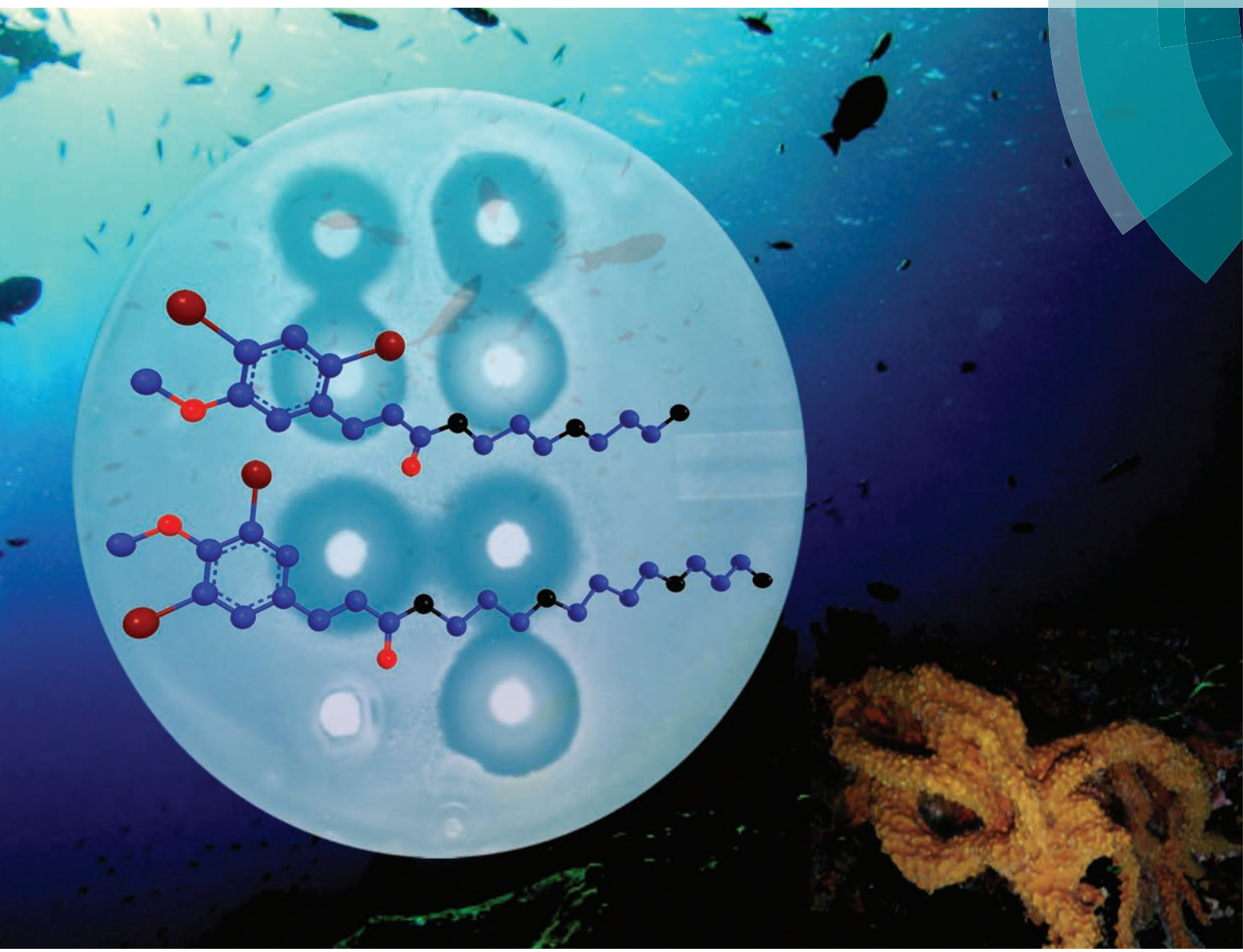

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Syntheses of a library of molecules on the marine natural product ianthelliformisamines platform and their biological evaluation†

Faiz Ahmed Khan,*[a] Saeed Ahmad,[a] Naveena Kodipelli,[b] Gururaj Shivange[b] and Roy Anindya*[b]

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Ianthelliformisamines A–C are a novel class of bromotyrosine-derived antibacterial agents isolated recently from the marine sponge *Suberea ianthelliformis*. We have synthesized ianthelliformisamines A–C straightforwardly by the condensation of (*E*)-3-(3,5-dibromo-4-methoxyphenyl)acrylic acid and the corresponding Boc-protected polyamine followed by Boc-deprotection with TFA. Further, using this reaction protocol, a library of their analogues (39 analogues) has been synthesized by employing 3-phenylacrylic acid derivatives and Boc-protected polyamine chains through various combinations of these two fragments differing in phenyl ring substitution, double bond geometry or chain length of the central spacer of the polyamine chain (shown in red color). All the synthesized compounds (ianthelliformisamines A–C and their analogues) were screened for antibacterial activity against both Gram-negative (*Escherichia coli*) and Gram-positive (*Staphylococcus aureus*) strains. All synthetic analogues of ianthelliformisamine A showed bacterial growth inhibition against both strains (*Escherichia coli* and *Staphylococcus aureus*), having MIC values in the range of 117.8–0.10 μM, while none of the synthetic analogues of ianthelliformisamine C as well as the parent compound showed any detectable antibacterial activity. Interestingly, some of the synthetic analogues of ianthelliformisamines A and B exerted a bactericidal effect against both *E. coli* and *S. aureus* strains, decreasing viable bacterial count by 99% at concentrations as low as 2 × MIC.

Introduction

The emergence of antibiotic resistant bacterial pathogens is a major public health concern worldwide and it has highlighted the need for the development of new antibiotics. Unfortunately, there have been only a few new classes of clinically important antibiotics discovered in recent years, emphasizing the need to develop antibiotics possessing new scaffolds with novel modes of action.[1] Natural and artificial polyamines offer a promising new group of antibacterial compounds and have been shown to increase the susceptibility of bacteria to several antibiotics.[2] Natural polyamines, like spermine and spermidine, are found in significant amounts in all organisms ranging from prokaryotic to eukaryotic cells and are considered as cell growth factors.[3,4] In bacteria, they regulate key cellular processes like DNA replication, transcription, and translation and influence the optimal cell growth and viability by protecting from various toxic conditions, *e.g.*, radiation, acidic pH, and oxidative stress.[5–11] Polyamine analogues, in contrast, completely lack any physiological function but, being structurally similar to natural polyamines, act as decoys and compete with natural polyamines, and affect major cellular processes. Not surprisingly, polyamine analogues were developed as potential antibiotics in treating several parasitic diseases.[12–18]

Natural medicinal ingredients have been used by mankind for thousands of years for the treatment of various diseases and ailments, and also in the current paradigm, isolated natural products have proven a rich source of potent biological activities in all therapeutic areas.[19–21] In the past few decades, natural products have remarkably influenced the area of drugs development. According to a report, in the last 30 years during the period 1981–2010, approximately half of the drugs approved by the US Food and Drug Administration (FDA) or by similar organizations are actually either natural products or

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† Electronic supplementary information (ESI) available: Copies of ^{1}H NMR and ^{13}C NMR spectra for products and biological evaluation test results. See DOI: 10.1039/c3ob42537a

their derivatives or molecules designed and synthesized on natural products platforms.[22] In the search for therapeutic agents against drug-resistant microbes with novel modes of actions, natural products can be considered as pre-validated leads and one can reckon on nature's ability to make biologically relevant chemical entities.[23] Even though many well-established techniques are available for the isolation and characterization of natural products, acquisition of new natural products is still a very tedious and laborious task in terms of difficulties associated with isolation, poor yield and structure elucidation.[24] In this aspect, synthesis of a library of molecules on the biologically potent natural products template is one of the worthwhile approaches for finding lead compounds.[25]

Recently, Quinn and co-workers isolated bromotyrosine-derived alkaloids, ianthelliformisamines A–C (**1–3**, Fig. 1), from the marine sponge *Suberea ianthelliformis*.[26] Based on extensive NMR experiments, the structures of ianthelliformisamines were assigned as a polyamine chain (spermine or spermidine) condensed with (*E*)-3-(3,5-dibromo-4-methoxyphenyl)-acrylic acid, forming amide linkage.[26] Previously isolated natural products spermatinamine,[27a] pseudoceramines A–C[27b] and tokaradine C[27c] also possess the same skeleton and are represented in Fig. 1 (**4–8**).

The isolated natural products ianthelliformisamines A–C (**1–3**) exhibited antibacterial activity, and out of them, ianthelliformisamine A (**1**) was found most active against the Gram-negative bacterium *Pseudomonas aeruginosa* with a MIC value of 35 μM.[26] The profound potent antibacterial activities of ianthelliformisamines A–C prompted us to design and synthesize a library of molecules on these platforms in order to explore more potent leads than the original natural products. We envisaged that bisecting the title molecules into two parts, *viz.*, a 3-phenylacrylic acid derivative and a polyamine chain, would provide a convenient handle to create a library through various combinations of the two parts differing in phenyl ring substitution, double bond geometry or chain length of the central spacer of the polyamine chain (shown in red color). For this purpose, we have used substituted aromatic aldehydes **9a–d** and Boc-protected polyamines (**12a–c**, **13a–c** and **14a–c**). Interestingly, the choice of phenyl ring substituents in aldehydes **9a–d** is inspired by the presence of these moieties in marine natural products like amathamides,[28] wilsoniamines,[28c] convolutamines,[29] and amathaspiramides.[30] Herein, we report a synthesis of natural products ianthelliformisamines A–C and a library built on their platform. All the synthetic analogues of ianthelliformisamines were screened for antibacterial activity. Our results revealed a set of synthetic

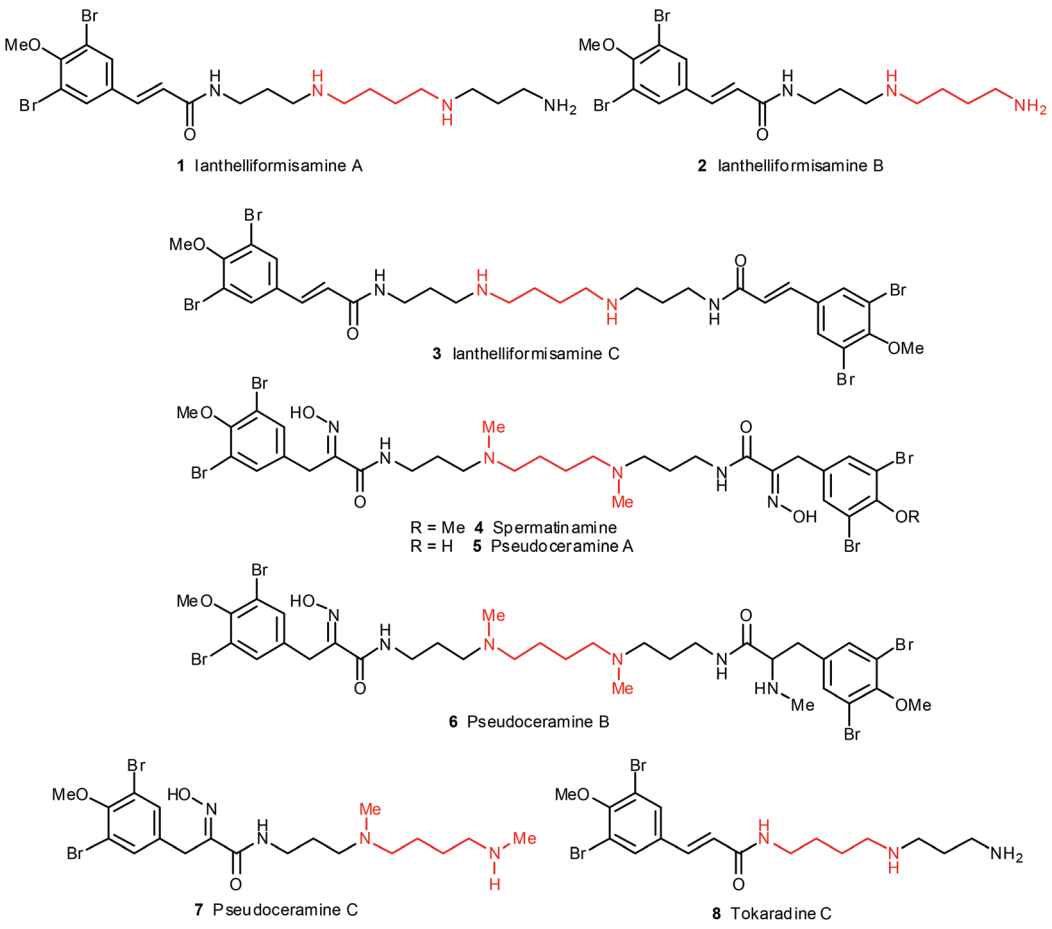


Fig. 1 Structures of naturally occurring bromotyrosine-derived alkaloids possessing polyamine chains.

ianthelliformisamine-mimicking analogues exhibiting enhanced antibacterial activity.

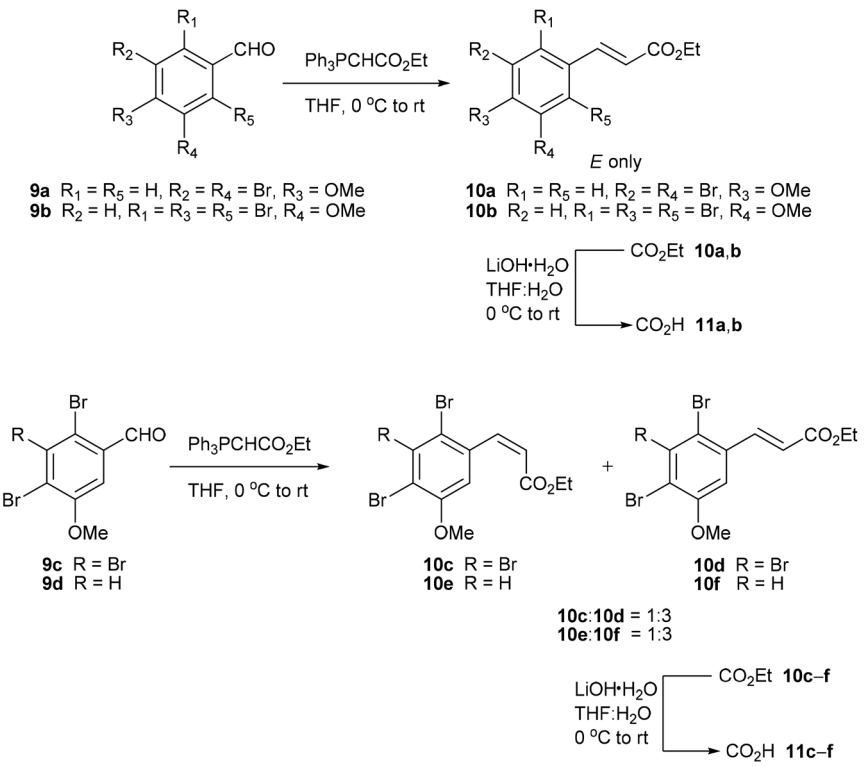
Results and discussion

Chemistry

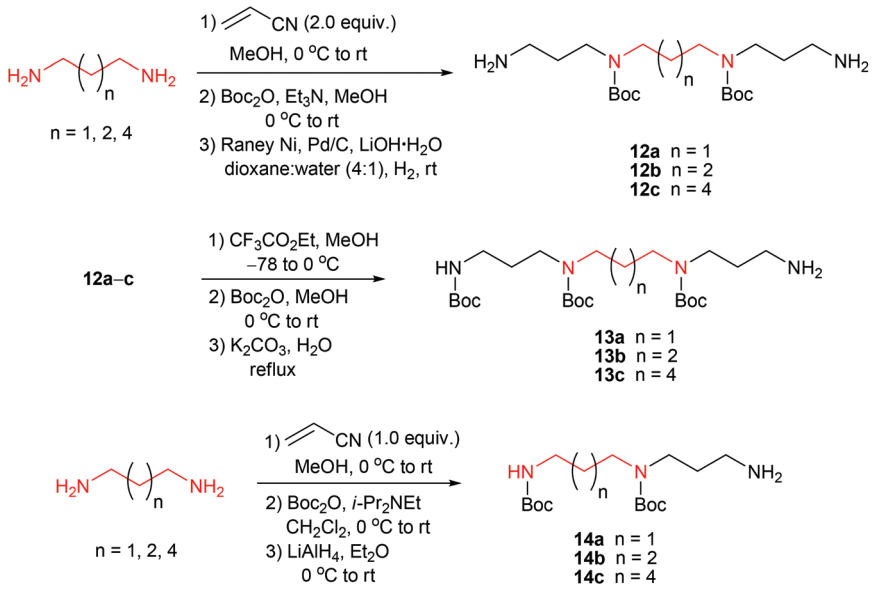
Ianthelliformisamines A–C (**1–3**) contain an (*E*)-3-(3,5-dibromo-4-methoxyphenyl)acrylic acid moiety which is connected with the polyamine chain spermine or spermidine *via* amide functionality. We commenced the preparation of (*E*)-3-(3,5-dibromo-4-methoxyphenyl)acrylic acid from 3,5-dibromo-4-methoxybenzaldehyde **9a** which was obtained from 4-hydroxybenzaldehyde by using the literature protocol *via* bromination with Br_2/AcOH/NH_4OAc[31a] followed by methylation of the hydroxyl group with MeI.[31b] To access a library of analogues, 2,4,6-tribromo-3-methoxybenzaldehyde **9b** and 2,4-dibromo-5-methoxybenzaldehyde **9d** were prepared from 3-hydroxybenzaldehyde by treating it with Br_2/H_2O[32] and $Br_2/CHCl_3$,[32] respectively, followed by methylation of the hydroxyl group with MeI.[32] 2,3,4-Tribromo-5-methoxybenzaldehyde **9c** is accessible from Grob-type fragmentation–aromatization reaction of 1,4,5,6-tetrabromo-7,7-dimethoxybicyclo[2.2.1]-hept-5-en-2-one followed by further functional group transformations.[33] The aldehydes **9a–d** were converted into α,β-unsaturated ethyl esters **10a–f** by Wittig reaction of ethoxycarbonylmethylenetriphenylphosphorane in THF (Scheme 1).[34] We found that aldehydes **9a** and **9b** gave exclusively *trans* products in excellent yields, while other aldehydes **9c** and **9d** gave a mixture of chromatographically separable *cis* and *trans* products in a ratio of 1 : 3, respectively. Further, α,β-unsaturated ethyl esters **10a–f** were hydrolyzed by lithium hydroxide monohydrate ($LiOH{\cdot}H_2O$)–THF–water[35] to get α,β-unsaturated carboxylic acids **11a–f** (Scheme 1).

Boc-protected spermines **12b** and **13b** were synthesized from 1,4-diaminobutane according to the literature protocol[36] (Scheme 2). Other Boc-protected spermine analogues (**12a**, **c** and **13a**, **c**) were also synthesized by using the same literature protocol from the corresponding diamines (Scheme 2).[36] In the reaction sequence, the corresponding diamines (n = 1, 2 and 4) on treatment with acrylonitrile (2.0 equiv.) gave the bis Michael adduct. Further, central amines were protected with the Boc-group and then nitrile groups were reduced by RANEY-Ni® to get Boc-protected amines **12a–c**.[36a] TriBoc-tetraamines **13a–c** were synthesized from amines **12a–c** *via* a three step one-pot protocol.[36] In the reaction sequence, first, amines **12a–c** were predominantly mono-trifluoroacetylated by treatment of ethyl trifluoroacetate at −78 °C and then the remaining amine group was protected with Boc by using Boc_2O. Further, *in situ* deprotection of the trifluoroacetate group with K_2CO_3 under reflux conditions gave triBoc-tertaamines **13a–c**.[36] Boc-protected spermidine **14b** and its analogues **14a,c** were synthesized from the corresponding diamines *via* selective mono-Michael addition to acrylonitrile and then Boc-protection of primary and secondary amines[37a] followed by reduction of the nitrile group with $LiAlH_4$.[37b]

Coupling of (*E*)-3-(3,5-dibromo-4-methoxyphenyl)acrylic acid **11a** and (N^1,N^4,N^9-tri-*tert*-butoxycarbonyl)-1,12-diamino-



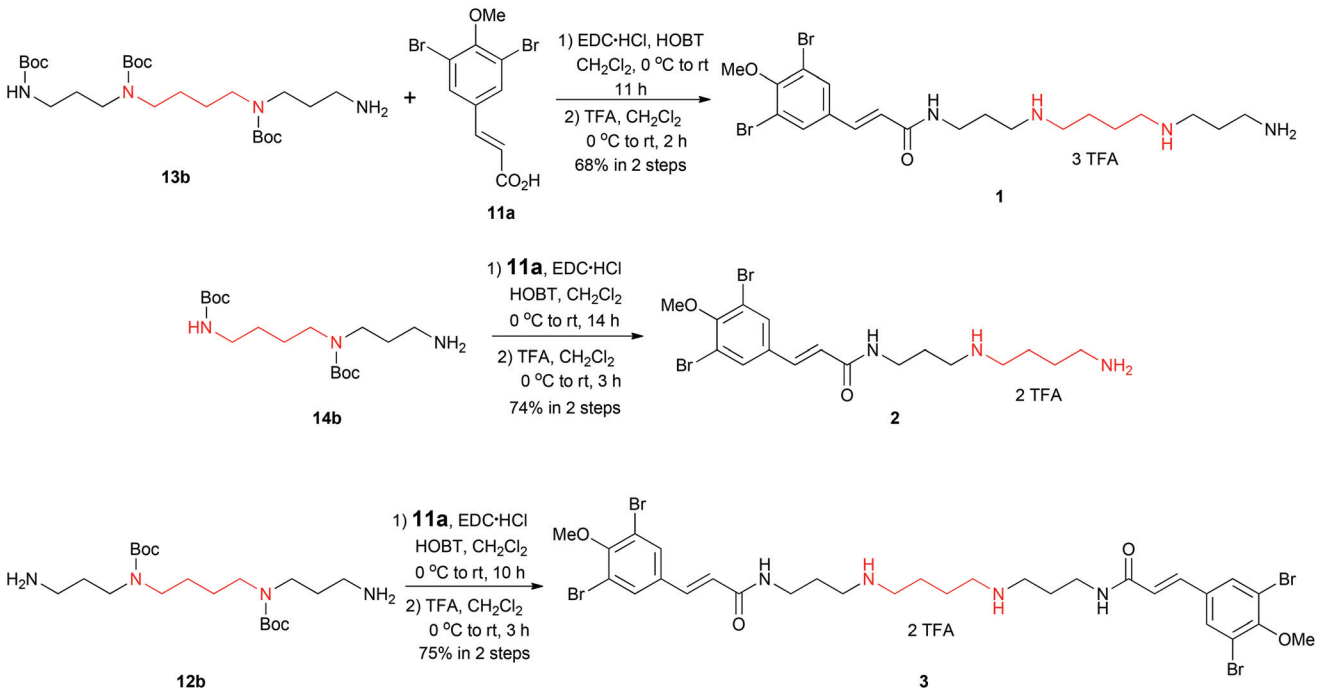
Scheme 1 Syntheses of 3-phenylacrylic acid derivatives.



Scheme 2 Syntheses of Boc-protected spermine, spermidine and their analogues.

4,9-diazadodecane **13b** by using EDC·HCl as a coupling reagent[38] gave the corresponding amide, which after Boc-deprotection with trifluoroacetic acid (TFA) in CH_2Cl_2 [38] at 0 °C yielded compound **1** as a TFA salt with 68% yield in 2 steps (Scheme 3). Synthetic **1** was confirmed as ianthelliformisamine A (**1**) by ^{1}H NMR, ^{13}C NMR and high-resolution mass spectrometry.

Coupling of (*E*)-3-(3,5-dibromo-4-methoxyphenyl)acrylic acid **11a** and Boc-protected spermidine **14b** by using EDC·HCl as a coupling reagent[38] followed by deprotection of the Boc-group with trifluoroacetic acid[38] yielded compound **2** as a TFA salt with 74% yield in 2 steps (Scheme 3). Synthetic compound **2** has all spectroscopic data in accordance with the literature reported values of ianthelliformisamine B. Coupling of (*E*)-3-(3,5-dibromo-4-methoxyphenyl)acrylic acid **11a** and N^1,N^4-di(*tert*-butyloxycarbonyl)-N^1,N^4-di(3-aminopropyl)-1,4-butanediamine **12b** gave the corresponding amide, which after Boc-deprotection with trifluoroacetic acid yielded compound **3** as a



Scheme 3 Synthesis of ianthelliformisamine A (**1**), ianthelliformisamine B (**2**) and ianthelliformisamine C (**3**).

TFA salt (Scheme 3). Synthetic **3** was confirmed to be identical to ianthelliformisamine C (**3**) by NMR (^{1}H and ^{13}C NMR) and high-resolution mass spectrometry. Further, a library of ianthelliformisamines A–C analogues **15–53** (a total of 39 analogues, Tables 1–3) were synthesized by employing various α,β-unsaturated carboxylic acids having differently substituted phenyl ring **11a–f** and Boc-protected polyamines (spermine, spermidine and their analogues) (**12a–c**, **13a–c**, **14a–c**) using the same reaction procedure as for ianthelliformisamines A–C.

Antibacterial activity

Synthetic analogues of ianthelliformisamines A–C were evaluated for their *in vitro* antibacterial activity against representative Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli*) strains using standard techniques. Minimum inhibitory concentration (MIC) was defined as the lowest concentration that inhibited bacterial growth and started the zone of inhibition as compared to the control, and MICs of the

Table 1 Antibacterial activities of ianthelliformisamine A (**1**) and its synthetic analogues

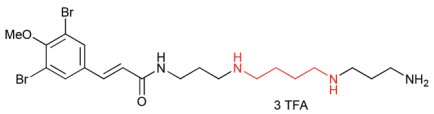
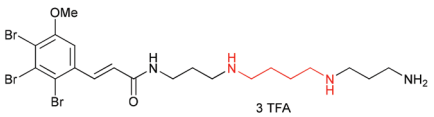
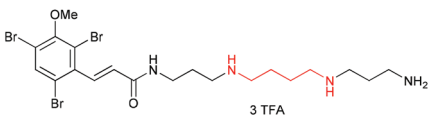
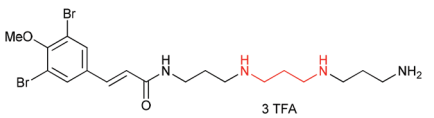
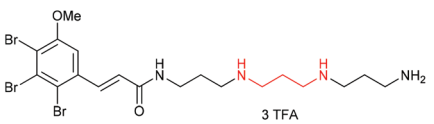
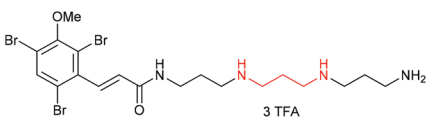
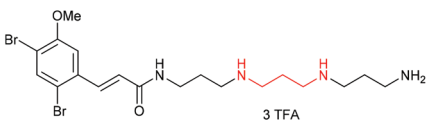
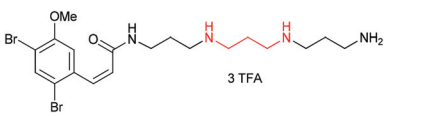
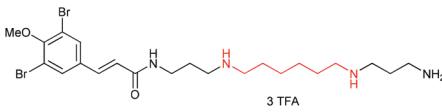
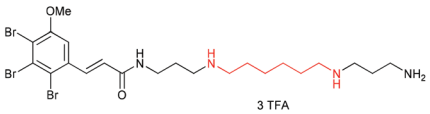
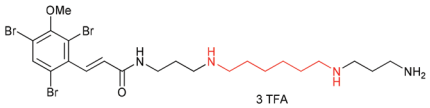
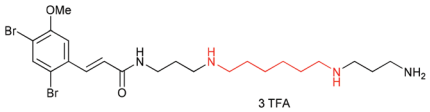
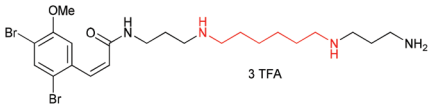
Compd.	Structure	Yield[a] (%)	Inhibition zone diameter against the microorganism[b]		MIC (μM)	
			E. coli	*S. aureus*	*E. coli*	*S. aureus*
1		68	++	++	11.04	11.04
15		70	++	++	11.04	11.04
16		73	+++	+++	1.1	1.6
17		89	+++	+++	1.2	0.12
18		74	+	+	107.8	107.8
19		68	+++	+++	1.1	1.1
20		71	+++	+++	1.2	1.2
21		72	+++	+	0.12	117.8
22		82	++	++	11.2	11.2

Table 1 *(Contd.)*

Compd.	Structure	Yield[a] (%)	Inhibition zone diameter against the microorganism[b]		MIC (μM)	
			E. coli	*S. aureus*	*E. coli*	*S. aureus*
23		80[c]	++	++	10.3	10.3
24		73	+++	+++	1.03	0.10
25		68[d]	+++	+++	0.11	0.11
26		66	+++	+	0.11	112

[a] All reactions were performed at 0.1 or 0.2 mmol scale. Yield in 2 steps. [b] Effectivity was classified into three zones based on the diameter of zone of inhibition; +++: most effective; ++: moderately effective; +: slightly effective. [c] Has a mixture of *E* and *Z* isomers (5 : 1). [d] Has a mixture of *E* and *Z* isomers (9 : 1).

Table 2 Antibacterial activities of ianthelliformisamine B (**2**) and its synthetic analogues

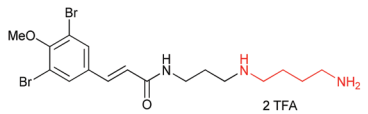
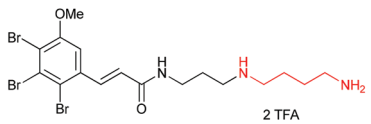
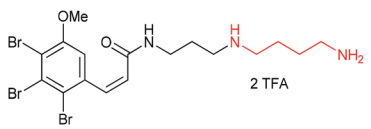
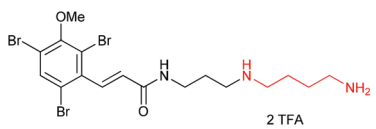
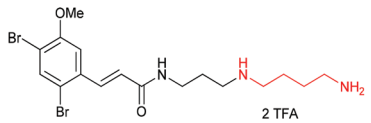
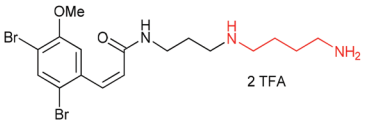
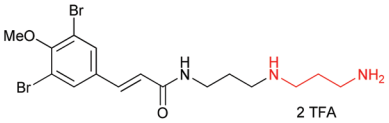
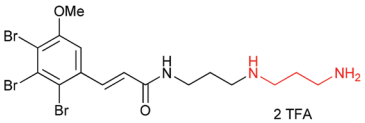
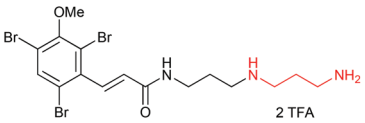
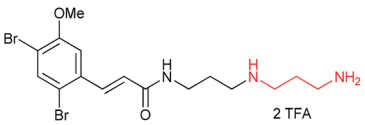
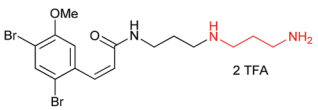
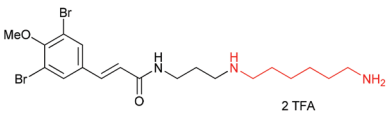
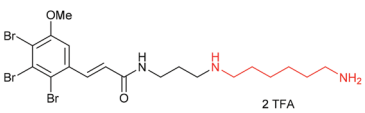
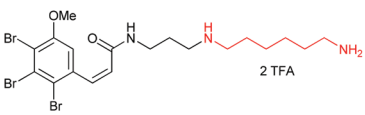
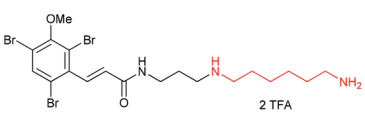
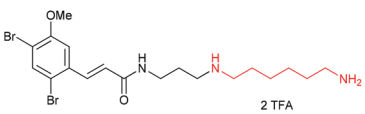
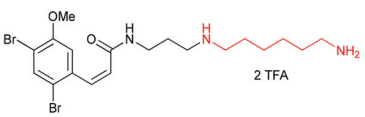
Compd.	Structure	Yield[a] (%)	Inhibition zone diameter against the microorganism[b]		MIC (μM)	
			E. coli	*S. aureus*	*E. coli*	*S. aureus*
2		74	++	+	14.5	144.7
27		85	+	+	129.8	129.8
28		78	+	+	129.8	129.8
29		78	+	+	129.8	129.8
30		84	++	+	14.5	144.7

Table 2 *(Contd.)*

Compd.	Structure	Yield[a] (%)	Inhibition zone diameter against the microorganism[b]		MIC (μM)	
			E. coli	*S. aureus*	*E. coli*	*S. aureus*
31		75	+++	+	1.47	144.7
32		88	+++	+++	1.47	1.47
33		90	++	+	13.2	132.2
34		94	++	+	13.2	132.2
35		83[c]	+++	+++	0.15	0.15
36		83[d]	+++	—	0.15	1476
37		82	+++	—	1.46	1464
38		66	+	+	125.3	125.3
39		63	+++	+++	1.3	1.3
40		74	—	—	NA	NA
41		77	+	+	773.5	773.5
42		79	+++	+	1.39	139

[a] All reactions were performed at 0.1 or 0.2 mmol scale. Yield in 2 steps. [b] Effectivity was classified into three zones based on the diameter of zone of inhibition; +++: most effective; ++: moderately effective; +: slightly effective; —: not effective. NA: no activity. [c] Has a mixture of *E* and *Z* isomers (18 : 1). [d] Has a mixture of *Z* and *E* isomers (15 : 1).

Table 3 Antibacterial activities of ianthelliformisamine C (**3**) and its synthetic analogues

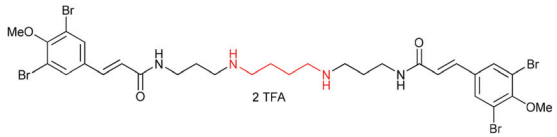
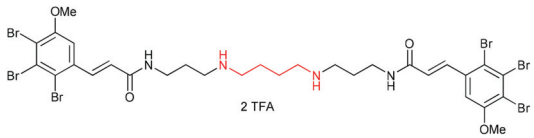
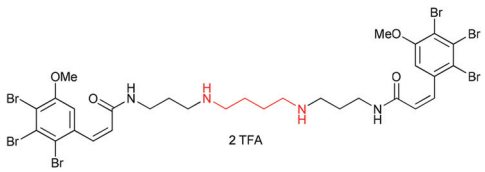
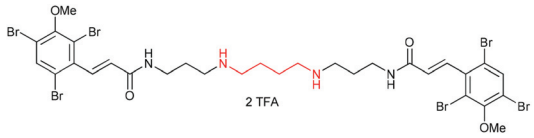
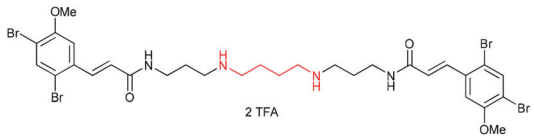
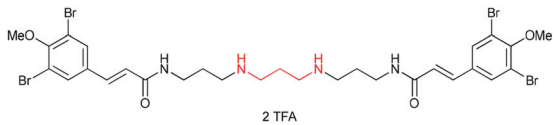
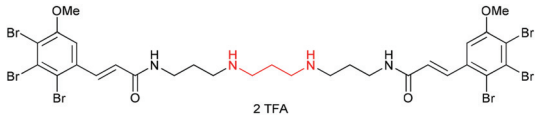
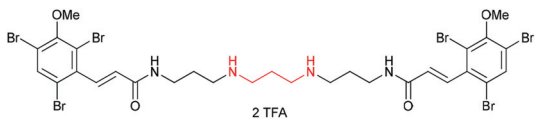
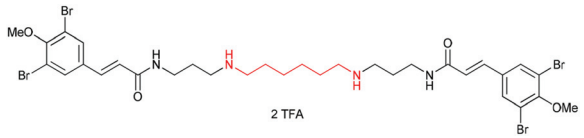
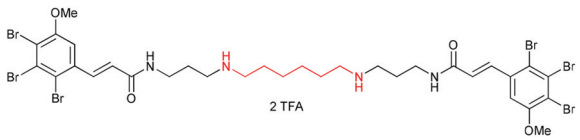
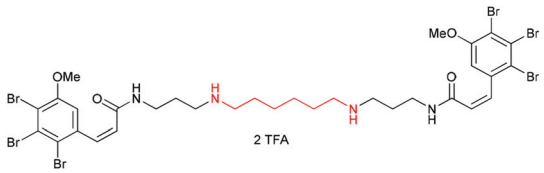
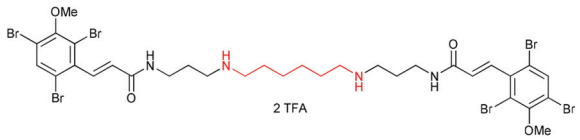
Compd.	Structure	Yield[a] (%)	Inhibition zone diameter against the microorganism[b]		MIC (μM)	
			E. coli	*S. aureus*	*E. coli*	*S. aureus*
3		75	—	—	NA	NA
43		85	—	—	NA	NA
44		73	—	—	NA	NA
45		89	—	—	NA	NA
46		88	—	—	NA	NA
47		83	—	—	NA	NA
48		77	—	—	NA	NA
49		81	—	—	NA	NA
50		84	—	—	NA	NA
51		81	—	—	NA	NA

Table 3 *(Contd.)*

Compd.	Structure	Yield[a] (%)	Inhibition zone diameter against the microorganism[b]		MIC (μM)	
			E. coli	*S. aureus*	*E. coli*	*S. aureus*
52		87	—	—	NA	NA
53		88	—	—	NA	NA

[a] All reactions were performed at 0.1 or 0.2 mmol scale. Yield in 2 steps. [b] Effectivity was classified into zones based on the diameter of zone of inhibition; —: not effective; NA: no activity.

synthesized compounds are reported in Tables 1–3 and ESI Fig. A.† These compounds did not belong to the PAINS (pan assay interference compounds) category.[39]

The results indicate that in comparison with the natural product ianthelliformisamine A (**1**), when the phenyl ring is substituted with 2,3,4-tribromo-5-methoxy (compd. **15**, Table 1), there was no change in antibacterial activity, while when the phenyl ring is substituted with 2,4,6-tribromo-5-methoxy (compd. **16**, Table 1), antibacterial activity increased up to 10-fold in both strains. After decreasing the middle carbon chain of spermine from four to three (represented in red color) antibacterial activity increased up to 10-fold in *E. coli* and up to 100-fold in *S. aureus* (compd. **17**, Table 1), while by increasing the middle carbon chain of spermine from four to six there was no effect on antibacterial activity (compd. **22**, Table 1). In conclusion, *cis* analogues are more or equally active in *E. coli*, but less active in *S. aureus* in comparison with their *trans* counterparts (compd. **20**, **21** and **25**, **26**, Table 1). Among the synthetic analogues of ianthelliformisamine A, antibacterial activities of compounds **16**, **17**, **19**, **20** and **24** were found highly potent against both Gram-positive and Gram-negative bacteria with MIC value less than 2 μM. In particular, compound **25** (MIC value 0.11 μM, against both *E. coli* and *S. aureus*) was found to be the most potent antibacterial agent in this series and has 100-fold less MIC value than the parent compound ianthelliformisamine A (**1**) (MIC value 11.04 μM, against both *E. coli* and *S. aureus*) (Table 1).

In the series of ianthelliformisamine B (**2**) analogues, on changing the substituents on the phenyl ring, antibacterial activity slightly changed in *E. coli*, but there was no change of antibacterial activity in *S. aureus* (compd. **27–31**, Table 2). In comparison with ianthelliformisamine B (**2**), on decreasing the terminal carbon chain of spermidine from four to three (represented in red color), antibacterial activity increased up to 10-fold in *E. coli* and 100-fold in *S. aureus* (compd. **32**, Table 2), while on increasing the terminal carbon chain of spermidine from four to six, antibacterial activity increased 10-fold in *E. coli* and decreased 10-fold in *S. aureus* (compd. **37**, Table 2). Among the synthetic analogues of ianthelliformisamine B (**2**), compounds **32**, **35** and **39** (MIC values 1.47, 0.15 and 1.3 μM, respectively, against both *E. coli* and *S. aureus*) were found to be far better than the parent compound, ianthelliformisamine B (**2**) (MIC values 14.5 and 144.7 μM against *E. coli* and *S. aureus*, respectively) (Table 2). In this series the most efficient synthetic analogue is **35** (MIC values 0.15 μM in both strains). In the series of synthetic analogues of ianthelliformisamines A and B, our finding was that substituted phenyl rings as well as polyamines are both equally responsible for antibacterial activity. Unfortunately, the series of ianthelliformisamine C analogues (compd. **43–53**) as well as parent compound **3** did not show any significant antibacterial activity against both *E. coli* and *S. aureus* (Table 3), and there was no effect of substituted phenyl rings, size of polyamine chains and double bond geometry.

To further investigate the antibiotic activity, we conducted time-kill assays where cultures of *E. coli* and *S. aureus* were exposed to the test compounds and at subsequent times samples were recovered, diluted and plated for counting to differentiate between bacteriostatic and bactericidal effects. Interestingly, among the ianthelliformisamine A (**1**) analogues, compounds **15**, **18**, **20**, **23**, and among the ianthelliformisamine B (**2**) analogues, compounds **33**, **34**, **38** exerted a bactericidal effect against *E. coli* and *S. aureus* reducing viable bacterial cfu by 99% within 4 h at concentrations as low as 2 × MIC (ESI Fig. B†). Ianthelliformisamine A (**1**) analogues, compounds **22**, **24**, **25**, and ianthelliformisamine B (**2**) analogues, compounds **27**, **28**, **41**, showed bactericidal activity against Gram-negative *E. coli* but partial activity to Gram-positive *S. aureus*.

Conclusion

In conclusion, we have synthesized natural products ianthelliformisamines A–C by condensation of (*E*)-3-(3,5-dibromo-4-methoxyphenyl)acrylic acid and Boc-protected polyamine (spermine or spermidine) followed by Boc-deprotection with TFA. Further, a variety of synthetic analogues (39 analogues) of ianthelliformisamines A–C, varying in substitution on the phenyl ring, size of the polyamine chain and double bond geometry, were prepared by using 3-phenylacrylic acid derivatives and Boc-protected polyamines (spermine, spermidine and their analogues). All the synthesized compounds (ianthelliformisamines A–C and their 39 synthetic analogues) were screened for antibacterial activity. In the series of analogues of ianthelliformisamines A and B, the change in the substitution of the phenyl ring as well as the change in the size of polyamine chains are both equally responsible for antibacterial activity. Our results revealed that synthetic analogues of ianthelliformisamines A and B are more potent against both Gram-negative and Gram-positive bacteria than the parent natural products.

Experimental section

General methods

All reactions were performed in oven dried apparatus and under an argon atmosphere. Commercial grade solvents were distilled before use. Melting points were obtained in open capillary tubes and are uncorrected. ^{1}H NMR spectra were recorded at 400 MHz or 500 MHz and proton decoupled ^{13}C NMR spectra were recorded at 100 MHz or 125 MHz. Infrared spectra were recorded as KBr pellets or as thin films. High-resolution mass spectra (HRMS) were recorded using electron spray ionization (ESI) or atmospheric pressure chemical ionization (APCI) mode. The purity of all compounds (**1–3** and **15–53**), tested for biological activity, was determined by high-pressure liquid chromatography (HPLC) and it was found >95% pure. The HPLC method utilized for purity: Waters HPLC with C18 column (5.0 μm, 4.6 × 250 mm^2); flow rate = 0.1 mL min^{-1}; solvent 0.1% TFA–MeOH; pressure 135–140 psi; wavelength 254 nm.

General experimental procedure for the preparation of 10a–f by Wittig reaction

To a cooled (0 °C) solution of ethoxycarbonylmethylenetriphenylphosphorane (Ph_3PCHCO_2Et, 1.1 mmol, 1.1 equiv.) in THF (4 mL) was added an appropriate aromatic aldehyde (1.0 mmol, 1.0 equiv.) and then it was allowed to warm to room temperature with stirring. After complete consumption of the starting material (monitored by TLC), all volatiles were removed under reduced pressure, and the residue was purified by silica gel column chromatography (3–8% EtOAc–hexane) to get the Wittig products **10a–f**.

(*E*)-Ethyl 3-(3,5-dibromo-4-methoxyphenyl)acrylate (10a). The product was obtained as a white solid (1.84 g, 99%); Mp 139–141 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (s, 2H), 7.48 (d, 1H, J = 15.9 Hz), 6.34 (d, 1H, J = 16.2 Hz), 4.25 (q, 2H, J = 7.2 Hz), 3.90 (s, 3H), 1.32 (t, 3H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 155.5, 141.0, 133.2, 132.0, 120.2, 118.8, 60.9, 14.3; IR (KBr) 3065, 2977, 1719, 1638, 1476, 1175, 991, 855 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{13}Br_2O_3$ (M + H), 362.9231; found, 362.9238.

(*E*)-Ethyl 3-(2,4,6-tribromo-3-methoxyphenyl)acrylate (10b). The product was obtained as a white solid (2.27 g, 96%); Mp 83–85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.56 (d, 1H, J = 16.3 Hz), 6.35 (d, 1H, J = 16.3 Hz), 4.30 (q, 2H, J = 7.1 Hz), 3.88 (s, 3H), 1.36 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.7, 154.2, 141.7, 136.6, 136.0, 127.4, 120.3, 118.3, 118.1, 61.0, 60.6, 14.3; IR (neat) 3068, 2934, 1719, 1644, 1449, 1268, 1171, 938, 744 cm^{-1}; HRMS (APCI) calcd for $C_{12}H_{12}Br_3O_3$ (M + H), 440.8337; found, 440.8333.

(*Z*)-Ethyl 3-(2,3,4-tribromo-5-methoxyphenyl)acrylate (10c) and (*E*)-ethyl 3-(2,3,4-tribromo-5-methoxyphenyl)acrylate (10d). After column purification *Z*-product **10c** was obtained as a white puffy solid (0.58 g, 24%) and *E*-product **10d** was obtained as a white crystalline solid (1.74 g, 73%). Data for *Z*-product **10c**: Mp 132–134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 1H), 7.01 (d, 1H, J = 12.2 Hz), 6.06 (d, 1H, J = 12.2 Hz), 4.11 (q, 2H, J = 7.1 Hz), 3.87 (s, 3H), 1.20 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 155.5, 142.8, 137.0, 129.0, 122.2, 116.7, 116.2, 112.5, 60.6, 56.9, 14.1; IR (neat) 2979, 1716, 1530, 1364, 1203, 1063, 864 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{12}Br_3O_3$ (M + H), 440.8337; found, 440.8350. Data for *E*-product **10d**: Mp 162–164 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, 1H, J = 15.8 Hz), 6.99 (s, 1H), 6.31 (d, 1H, J = 15.8 Hz), 4.27 (q, 2H, J = 7.1 Hz), 3.91 (s, 3H), 1.33 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 156.2, 144.0, 136.1, 130.4, 122.5, 119.0, 118.1, 108.6, 61.0, 56.9, 14.3; IR (neat) 2981, 1714, 1634, 1410, 1187, 1069, 965, 837 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{12}Br_3O_3$ (M + H), 440.8337; found, 440.8331.

(*Z*)-Ethyl 3-(2,4-dibromo-5-methoxyphenyl)acrylate (10e) and (*E*)-ethyl 3-(2,4-dibromo-5-methoxyphenyl)acrylate (10f). After column purification *Z*-product **10e** was obtained as a white solid (1.29 g, 24%) and *E*-product **10f** was obtained as a white puffy solid (4.02 g, 74%). Data for *Z*-product **10e**: Mp 83–85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.21 (s, 1H), 6.99 (d, 1H, J = 12.3 Hz), 6.08 (d, 1H, J = 12.3 Hz), 4.13 (q, 2H, J = 7.1 Hz), 3.88 (s, 3H), 1.21 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.4, 154.7, 141.5, 135.7, 135.4, 122.2, 114.2, 114.0, 112.7, 60.5, 56.5, 14.1; IR (neat) 2981, 2849, 1713, 1469, 1369, 1189, 1039, 874 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{13}Br_2O_3$ (M + H), 362.9231; found, 362.9210. Data for *E*-product **10f**: Mp 141–143 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, 1H, J = 15.8 Hz), 7.77 (s, 1H), 7.06 (s, 1H), 6.39 (d, 1H, J = 16.0 Hz), 4.29 (q, 2H, J = 7.1 Hz), 3.92 (s, 3H), 1.35 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 155.5, 142.3, 136.9, 134.4, 121.4, 116.0, 114.6, 109.9, 60.9, 56.5, 14.3; IR (neat) 2979, 2899, 1706, 1369, 1233, 1041, 871 cm^{-1}; HRMS (APCI) calcd for $C_{12}H_{13}Br_2O_3$ (M + H), 362.9231; found, 362.9243.

General experimental procedure for alkaline hydrolysis of ethylesters 10a–f. Preparation of compounds 11a–f

To a cooled (0 °C) solution of an appropriate α,β-unsaturated ethyl ester (1.0 mmol, 1.0 equiv.) in THF–H_2O (5 mL : 1 mL) was added lithium hydroxide monohydrate ($LiOH{\cdot}H_2O$, 1.5 mmol, 1.5 equiv.) and then it was allowed to warm to room temperature with stirring. After complete consumption of the starting material (monitored by TLC), all volatiles were removed under reduced pressure, and the residue was diluted with water (1 mL) and made acidic up to pH 2–3 with 10% HCl. The aqueous layer was extracted with EtOAc (4 × 5 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to get the carboxylic acid **11a–f**.

(*E*)-3-(3,5-Dibromo-4-methoxyphenyl)acrylic acid (11a). The product **11a** was obtained as a white puffy solid (5.0 g, 98%); Mp 202–205 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.52 (br s, 1H), 8.04 (s, 2H), 7.50 (d, 1H, J = 16.1 Hz), 6.62 (d, 1H, J = 15.6 Hz), 3.81 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.2, 154.4, 140.4, 133.6, 132.3, 121.4, 118.0, 60.5; IR (neat) 2803, 1695, 1631, 1422, 1214, 975, 850, 745 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_9Br_2O_3$ (M + H), 334.8918; found, 334.8917.

(*E*)-3-(2,4,6-Tribromo-3-methoxyphenyl)acrylic acid (11b). The product **11b** was obtained as a white solid (2.66 g, 97%); Mp 200–203 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.90 (br s, 1H), 8.09 (s, 1H), 7.41 (d, 1H, J = 16.2 Hz), 6.26 (d, 1H, J = 16.3 Hz), 3.81 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.3, 153.6, 141.2, 136.6, 135.6, 128.1, 119.8, 117.85, 117.80, 60.3; IR (neat) 2977, 2845, 1691, 1417, 1288, 1037, 873, 741 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_8Br_3O_3$ (M + H), 412.8024; found, 412.8018.

(*Z*)-3-(2,3,4-Tribromo-5-methoxyphenyl)acrylic acid (11c). The product **11c** was obtained as a white solid (0.34 g, 96%); Mp 250–253 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.50 (br s, 1H), 7.18 (s, 1H), 7.04 (d, 1H, J = 11.7 Hz), 6.12 (d, 1H, J = 12.2 Hz), 3.83 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.2, 155.2, 141.0, 138.2, 127.8, 124.0, 115.5, 114.5, 112.9, 57.0; IR (neat) 3051, 2963, 1701, 1632, 1469, 1376, 1235, 1071, 855 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_8Br_3O_3$ (M + H), 412.8024; found, 412.8032.

(*E*)-3-(2,3,4-Tribromo-5-methoxyphenyl)acrylic acid (11d). The product **11d** was obtained as a white solid (1.53 g, 98%); Mp 250–255 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.75 (br s, 1H), 7.80 (d, 1H, J = 15.8 Hz), 7.48 (s, 1H), 6.72 (d, 1H, J = 15.8 Hz), 3.95 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.9, 156.1, 142.3, 135.7, 129.1, 124.4, 117.9, 117.0, 110.1, 57.3; IR (neat) 2807, 1680, 1626, 1455, 1362, 1228, 1065, 940, 727 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_8Br_3O_3$ (M + H), 412.8024; found, 412.8010.

(*Z*)-3-(2,4-Dibromo-5-methoxyphenyl)acrylic acid (11e). The product **11e** was obtained as a white solid (0.82 g, 92%); Mp 227–230 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.63 (br s, 1H), 7.84 (s, 1H), 7.23 (s, 1H), 6.95 (d, 1H, J = 12.2 Hz), 6.14 (d, 1H, J = 12.2 Hz), 3.81 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 166.4, 154.2, 139.6, 136.2, 134.8, 123.9, 114.3, 112.9, 111.3, 56.4; IR (neat) 2919, 2849, 1695, 1432, 1366, 1248, 1058, 872, 664 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_9Br_2O_3$ (M + H), 334.8918; found, 334.8911.

(*E*)-3-(2,4-Dibromo-5-methoxyphenyl)acrylic acid (11f). The product **11f** was obtained as a white solid (2.43 g, 96%); Mp 215–218 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.73 (br s, 1H), 7.91 (s, 1H), 7.73 (d, 1H, J = 15.7 Hz), 7.51 (s, 1H), 6.78 (d, 1H, J = 15.7 Hz), 3.93 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.1, 155.2, 140.6, 135.9, 133.9, 123.3, 115.1, 113.7, 111.2, 56.8; IR (neat) 2848, 1690, 1625, 1469, 1369, 1210, 1054, 973, 699 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_9Br_2O_3$ (M + H), 334.8918; found, 334.8910.

General procedure for the synthesis of Boc-protected tetraamines 12a–c

To a cooled (0 °C) solution of diamine (11.8 mmol, 1.0 equiv.) in anhydrous MeOH (5 mL) was added a solution of acrylonitrile (1.25 g, 23.6 mmol, 2.0 equiv.) in anhydrous MeOH (25 mL) dropwise over a period of 30 min. The resulting reaction solution was allowed to warm to room temperature and stirred for 22–24 h at room temperature. All volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography (10–40% MeOH–$CHCl_3$) to get both side Michael addition products.

To a cooled (0 °C) solution of the above obtained product (11.8 mmol, 1.0 equiv.) in anhydrous MeOH (50 mL) was added Et_3N (2.61 g, 25.8 mmol, 2.2 equiv.) and then a solution of Boc_2O (5.38 g, 24.7 mmol, 2.1 equiv.) in anhydrous MeOH (55 mL) was added dropwise. The resulting reaction solution was allowed to warm to room temperature and stirred for 24 h at room temperature. All volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography (30–60% EtOAc–hexane or 2% MeOH–CH_2Cl_2) to get the Boc-protected compound.

To a solution of the above obtained Boc-protected compound in a mixture of dioxane–water 4 : 1 (250 mL) were added RANEY® nickel (7.5 g, 50% aqueous suspension), Pd/C (250 mg) and lithium hydroxide monohydrate (940 mg, 22.4 mmol). The resulting solution was stirred at room temperature under a hydrogen atmosphere for 2–10 h (monitored by TLC). The reaction solution was filtered and washed with MeOH (2 × 50 mL). The filtrate was concentrated under reduced pressure and the residue was taken in CH_2Cl_2 (60 mL) and water (60 mL). The organic layer was separated and aqueous layer again extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated. The residue was pure enough to proceed further or it can be purified by silica gel column chromatography (2–10% Et_3N–MeOH) to get the product.

General procedure for the synthesis of Boc-protected tetraamines 13a–c

To a cooled (−78 °C) solution of appropriate amines **12a–c** (1.0 mmol, 1.0 equiv.) in anhydrous MeOH (16 mL) was added CF_3CO_2Et (1.0 mmol, 1.0 equiv.) dropwise over a period of 10 min and stirred for 30 min at the same temperature. The reaction solution was slowly allowed to warm to 0 °C. Then a

solution of Boc_2O (1.5 mmol, 1.5 equiv.) in MeOH (4 mL) was added dropwise at 0 °C. The resulting reaction solution was allowed to warm to room temperature and stirred for 10–15 h. Then K_2CO_3 (5.0 mmol, 5.0 equiv.) and water (1.2 mL) were added, and then the reaction solution was refluxed for 2–3 h. After that, all volatiles were removed under reduced pressure and the residue was taken in water (10 mL) and extracted with $CHCl_3$ (4 × 8 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to get the Boc-protected tetraamines **13a–c**.

(N^1,N^4,N^{11}-Tri-*tert*-butyloxycarbonyl)-1,14-diamino-4,11-diazatetradecane 13c. The product **13c** was obtained as a colorless viscous liquid (1.14 g, 57%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30 and 4.75 (br s, 1H), 3.23–3.08 (m, 10H), 2.72–2.68 (m, 2H), 2.38 (br s, 2H), 1.72–1.58 (m, 4H), 1.52–1.42 (m, 31H), 1.28–1.23 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 155.5, 79.4, 78.9, 77.3, 50.4, 46.9, 44.1, 43.6, 39.4, 38.7, 37.4, 32.4, 30.9, 28.4, 28.3, 28.2, 26.6; IR (neat) 3356, 2975, 2931, 1678, 1417, 1249, 1156, 733 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{55}N_4O_6$ (M + H), 531.4122; found, 531.4123.

General procedure for the synthesis of Boc-protected triamines 14a–c

To a cooled (0 °C) solution of an appropriate diamine (34.9 mmol, 1.1 equiv.) in anhydrous MeOH (25 mL) was added acrylonitrile (1.69 g, 31.8 mmol, 1.0 equiv.) dropwise over a period of 2 h. The resulting reaction solution was allowed to warm to room temperature and stirred for 22–24 h at room temperature. All volatiles were removed under reduced pressure and the residue was co-evaporated with anhydrous toluene (3 × 25 mL).

In the case of 1,3-diaminopropane, all volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography (10–50% MeOH–$CHCl_3$) to get both side Michael addition products (618 mg, 36%) and (10 : 90 : 1–40 : 60 : 1 MeOH–$CHCl_3$–25% aqueous NH_3) to get one side Michael addition product (1.36 g, 57%).

To a cooled (0 °C) solution of the above obtained one side Michael addition product (1.0 equiv.) in anhydrous CH_2Cl_2 (50 mL) was added Boc_2O (13.0 g, 24.7 mmol, 2.1 equiv.) in portions. The resulting solution was stirred for 10 min and then ice was removed. *i*-Pr_2NEt (11.0 mL, 25.8 mmol, 2.2 equiv.) was added dropwise over 1 h and then the reaction mixture was stirred for 24 h at room temperature. All volatiles were removed under reduced pressure and the residue was purified by silica gel column chromatography (30–60% EtOAc–hexane) to get the Boc-protected compound.

To a cooled (0 °C) suspension of $LiAlH_4$ (3.5 g, 93.0 mmol, 3.6 equiv.) in anhydrous Et_2O (400 mL) was added a solution of the above obtained Boc-protected compound (8.8 g, 25.8 mmol, 1.0 equiv.) in anhydrous Et_2O (115 mL) dropwise *via* cannula. The resulting reaction solution was allowed to warm to room temperature and stirred for 7–16 h at room temperature. The reaction was quenched by the dropwise addition of NaOH (1.0 N aq. solution, 50 mL) at 0 °C, and then it was filtered through a celite pad. The filtrate was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (3 : 96 : 1–10 : 89 : 1 MeOH–CH_2Cl_2–25% aqueous NH_3) to get the amine product (4.8 g, 54%).

{6-[(3-Amino-propyl)-*tert*-butoxycarbonyl-amino]-hexyl}-carbamic acid *tert*-butyl ester 14c. The product **14c** was obtained as a colorless viscous liquid (3.16 g, 56%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 (br s, 1H), 3.26–3.06 (m, 6H), 2.94 (br s, 2H), 2.71 (br s, 2H), 1.69 (br s, 2H), 1.51–1.43 (m, 4H), 1.41 (s, 9H), 1.40 (s, 9H), 1.33–1.19 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 156.0, 155.5, 79.6, 79.3, 79.0, 77.3, 47.0, 46.6, 44.4, 43.6, 41.7, 40.4, 39.3, 38.4, 32.3, 30.3, 30.0, 28.43, 28.41, 28.0, 26.5; IR (neat) 3350, 2974, 2930, 2861, 1678, 1365, 1248, 1162, 871, 734 cm^{-1}; HRMS (APCI) calcd for $C_{19}H_{40}N_3O_4$ (M + H), 374.3019; found, 374.3019.

General procedure for amide synthesis

To a cooled (0 °C) solution of an appropriate α,β-unsaturated carboxylic acid (0.42 mmol) in anhydrous CH_2Cl_2 (1.5 mL) were added EDC·HCl (85 mg, 0.44 mmol) and HOBT (62 mg, 0.46 mmol). The resulting solution was stirred at 0 °C for 10 min, and then a solution of amine (0.2 mmol) in anhydrous CH_2Cl_2 (1.5 mL) was added at 0 °C. The reaction solution was allowed to warm to room temperature and stirred at room temperature until complete consumption of the starting material (monitored by TLC). CH_2Cl_2 (20 mL) was added and washed with saturated aqueous $NaHCO_3$ solution (3 mL), water (3 mL), and brine (5 mL), dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (30–80% EtOAc–hexane) to get the coupled product.

Boc deprotection of the coupled product

To a cooled (0 °C) solution of the coupled product (obtained above) in anhydrous CH_2Cl_2 (10 mL) was added TFA (1 mL). The resulting solution was allowed to warm to room temperature until complete consumption of the starting material (~1–3 h, monitored by TLC). All volatiles were removed under reduced pressure till dryness and then it was co-evaporated with CH_2Cl_2 (3 × 15 mL) to get the white amorphous solid or the residue was purified by silica gel column chromatography (MeOH–CH_2Cl_2–TFA, 30 : 70 : 1–60 : 40 : 1).

Ianthelliformisamine A (1) tris-TFA salt

The product **1** was obtained as a white solid (118.2 mg, 68% in two steps); Mp 206–209 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.89 (br s, 2H), 8.74 (br s, 2H), 8.36 (t, 1H, J = 5.7 Hz), 8.02 (br s, 3H), 7.88 (s, 2H), 7.35 (d, 1H, J = 15.8 Hz), 6.68 (d, 1H, J = 15.8 Hz), 3.81 (s, 3H), 3.25 (q, 2H, J = 6.3 Hz), 2.98–2.92 (m, 10H), 1.90 (quintet, 2H, J = 7.6 Hz), 1.80 (quintet, 2H, J = 7.1 Hz), 1.69–1.57 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.8, 153.9, 135.3, 134.3, 131.5, 124.2, 118.0, 60.5, 46.1, 46.0, 44.6, 43.8, 36.1, 35.9, 25.9, 23.7, 22.6, 22.6; IR (neat) 3051, 2928, 2854, 1664, 1472, 1192, 1131, 978, 720 cm^{-1}; HRMS (APCI) calcd for $C_{20}H_{33}Br_2N_4O_2$ (M + H − 3TFA), 519.0970; found, 519.0955. HPLC purity 97.3%, RT = 15.100 min.

Ianthelliformisamine B (2) bis-TFA salt

The product **2** was obtained as a colorless oil (114 mg, 74% in two steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (br s, 2H), 8.36 (t, 1H, J = 5.8 Hz), 7.91 (br s, 3H), 7.89 (s, 2H), 7.36 (d, 1H, J = 15.8 Hz), 6.69 (d, 1H, J = 15.8 Hz), 3.82 (s, 3H), 3.25 (q, 2H, J = 6.4 Hz), 2.93 (m, 4H), 2.85–2.80 (m, 2H), 1.84–1.77 (m, 2H), 1.62–1.60 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.8, 153.9, 135.4, 134.3, 131.5, 124.1, 118.0, 60.5, 46.0, 44.6, 38.2, 35.9, 25.9, 24.1, 22.5; IR (neat) 3390, 3068, 1671, 1425, 1182, 1135, 979, 723 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{26}Br_2N_3O_2$ (M + H − 2TFA), 462.0392; found, 462.0381. HPLC purity 100%, RT = 14.948 min.

Ianthelliformisamine C (3) bis-TFA salt

The product **3** was obtained as a colorless oil (199.3 mg, 75% in two steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (br s, 4H), 8.40 (t, 2H, J = 5.8 Hz), 7.89 (s, 4H), 7.35 (d, 2H, J = 15.8 Hz), 6.69 (d, 2H, J = 15.8 Hz), 3.81 (s, 6H), 3.25 (q, 4H, J = 6.4 Hz), 2.94 (m, 8H), 1.84–1.77 (m, 4H), 1.65 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.8, 153.9, 135.3, 134.3, 131.5, 124.2, 118.0, 60.5, 46.0, 44.6, 35.9, 25.9, 22.6; IR (neat) 3372, 3041, 2830, 1667, 1439, 1179, 1127, 977, 722 cm^{-1}; HRMS (APCI) calcd for $C_{30}H_{39}Br_4N_4O_4$ (M + H − 2TFA), 834.9705; found, 834.9711. HPLC purity 100%, RT = 15.375 min.

(*E*)-*N*-(3-(4-(3-Aminopropylamino)butylamino)propyl)-3-(2,3,4-tribromo-5-methoxyphenyl)acrylamide tris trifluoroacetate 15. The product **15** was obtained as a white solid (131.4 mg, 70% in two steps); Mp 214–218 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.90 (br s, 2H), 8.75 (br s, 2H), 8.64 (t, 1H, J = 5.4 Hz), 8.03 (br s, 3H), 7.68 (d, 1H, J = 15.6 Hz), 7.37 (s, 1H), 6.82 (d, 1H, J = 15.6 Hz), 3.94 (s, 3H), 3.27 (q, 2H, J = 6.2 Hz), 2.93 (m, 10H), 1.90 (quintet, 2H, J = 7.6 Hz), 1.80 (quintet, 2H, J = 7.1 Hz), 1.64 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.5, 156.0, 137.6, 136.6, 129.1, 127.2, 117.7, 116.2, 109.5, 57.0, 46.1, 46.0, 44.7, 43.8, 36.1, 36.0, 25.9, 23.7, 22.6, 22.6; IR (neat) 3044, 2873, 1671, 1414, 1196, 1139, 837, 721 cm^{-1}; HRMS (APCI) calcd for $C_{20}H_{32}Br_3N_4O_2$ (M + H − 3TFA), 597.0075; found, 597.0060. HPLC purity 99.6%, RT = 14.833 min.

(*E*)-*N*-(3-(4-(3-Aminopropylamino)butylamino)propyl)-3-(2,4,6-tribromo-3-methoxyphenyl)acrylamide tris trifluoroacetate 16. The product **16** was obtained as a white solid (137.3 mg, 73% in two steps); Mp 218–221 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (t, 1H, J = 5.7 Hz), 8.45 (br s, 6H), 8.10 (s, 1H), 7.28 (d, 1H, J = 16.0 Hz), 6.44 (d, 1H, J = 15.9 Hz), 3.81 (s, 3H), 3.29–3.26 (m, 2H), 2.98–2.87 (m, 10H), 1.90 (quintet, 2H, J = 7.6 Hz), 1.80 (quintet, 2H, J = 7.1 Hz), 1.64 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.9, 153.6, 137.2, 136.5, 135.6, 130.3, 119.8, 117.8, 117.4, 60.3, 46.0, 46.0, 44.7, 43.8, 36.1, 25.8, 23.8, 22.6, 22.5; IR (neat) 3067, 2850, 1670, 1418, 1197, 1131, 835, 721 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{32}Br_3N_4O_2$ (M + H − 3TFA), 597.0075; found, 597.0053. HPLC purity 99.5%, RT = 14.788 min.

(*E*)-*N*-(3-(3-(3-Aminopropylamino)propylamino)propyl)-3-(3,5-dibromo-4-methoxyphenyl)acrylamide tris trifluoroacetate 17. The product **17** was obtained as a white solid (301.4 mg, 89% in two steps); Mp 214–217 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (br s, 2H), 8.87 (br s, 2H), 8.38 (t, 1H, J = 5.7 Hz), 8.04 (br s, 3H), 7.88 (s, 2H), 7.35 (d, 1H, J = 15.8 Hz), 6.68 (d, 1H, J = 15.8 Hz), 3.81 (s, 3H), 3.28–3.23 (m, 2H), 2.99–2.90 (m, 10H), 1.97–1.89 (m, 4H); 1.82–1.78 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.8, 153.9, 135.3, 134.3, 131.5, 124.2, 118.0, 60.5, 44.8, 44.0, 43.9, 36.1, 35.9, 27.9, 25.9, 23.8, 22.4; IR (neat) 3071, 2862, 1665, 1616, 1421, 1196, 1127, 987, 720 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{31}Br_2N_4O_2$ (M + H − 3TFA), 505.0814; found, 505.0812. HPLC purity 100%, RT = 16.045 min.

(*E*)-*N*-(3-(3-(3-Aminopropylamino)propylamino)propyl)-3-(2,3,4-tribromo-5-methoxyphenyl)acrylamide tris trifluoroacetate 18. The product **18** was obtained as a white solid (136.5 mg, 74% in two steps); Mp 210–214 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (br s, 2H), 8.83 (br s, 2H), 8.62 (t, 1H, J = 5.7 Hz), 8.01 (br s, 3H), 7.68 (d, 1H, J = 15.6 Hz), 7.36 (s, 1H), 6.80 (d, 1H, J = 15.5 Hz), 3.94 (s, 3H), 3.30–3.25 (m, 2H), 2.99–2.88 (m, 10H), 1.97–1.88 (m, 4H); 1.83–1.80 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.5, 156.0, 137.6, 136.6, 129.1, 127.2, 117.7, 116.2, 109.5, 57.0, 44.8, 44.0, 43.9, 36.1, 36.0, 25.9, 23.8, 22.4; IR (neat) 3074, 2942, 2869, 1667, 1422, 1367, 1197, 1161, 1132, 835, 721 cm^{-1}; HRMS (APCI) calcd for $C_{19}H_{30}Br_3N_4O_2$ (M + H − 3TFA), 582.9919; found, 582.9893. HPLC purity 98.1%, RT = 15.204 min.

(*E*)-*N*-(3-(3-(3-Aminopropylamino)propylamino)propyl)-3-(2,4,6-tribromo-3-methoxyphenyl)acrylamide tris trifluoroacetate 19. The product **19** was obtained as a white solid (126.5 mg, 68% in two steps); Mp 228–231 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (br s, 2H), 8.85 (br s, 2H), 8.60 (t, 1H, J = 5.6 Hz), 8.11 (s, 1H), 8.02 (br s, 3H), 7.29 (d, 1H, J = 16.0 Hz), 6.45 (d, 1H, J = 16.0 Hz), 3.81 (s, 3H), 3.27 (q, 2H, J = 6.4 Hz), 3.00–2.89 (m, 10H), 2.00–1.87 (m, 4H); 1.86–1.79 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.9, 153.6, 137.2, 136.5, 135.6, 130.3, 119.8, 117.9, 117.4, 60.3, 44.8, 44.0, 43.9, 36.1, 25.9, 23.8, 22.4; IR (neat) 3071, 2942, 2877, 1665, 1418, 1195, 1163, 835, 721 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{30}Br_3N_4O_2$ (M + H − 3TFA), 582.9919; found, 582.9902. HPLC purity 97.0%, RT = 15.426 min.

(*E*)-*N*-(3-(3-(3-Aminopropylamino)propylamino)propyl)-3-(2,4-dibromo-5-methoxyphenyl)acrylamide tris trifluoroacetate 20. The product **20** was obtained as a white solid (119.8 mg, 71% in two steps); Mp 219–223 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (br s, 2H), 8.83 (br s, 2H), 8.59 (t, 1H, J = 5.7 Hz), 8.02 (br s, 3H), 7.92 (s, 1H), 7.60 (d, 1H, J = 15.6 Hz), 7.37 (s, 1H), 6.85 (d, 1H, J = 15.6 Hz), 3.92 (s, 3H), 3.27 (q, 2H, J = 6.4 Hz), 3.00–2.87 (m, 10H), 1.98–1.89 (m, 4H); 1.84–1.80 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7, 155.2, 136.0, 135.9, 134.8, 126.1, 114.8, 112.8, 110.5, 56.5, 44.8, 44.0, 43.9, 36.1, 36.0, 27.9, 25.9, 23.8, 22.4; IR (neat) 3068, 2876, 1666, 1465, 1195, 1128, 835, 720 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{31}Br_2N_4O_2$ (M + H − 3TFA), 505.0814; found, 505.0813. HPLC purity 99.9%, RT = 15.222 min.

(*Z*)-*N*-(3-(3-(3-Aminopropylamino)propylamino)propyl)-3-(2,4-dibromo-5-methoxyphenyl)acrylamide tris trifluoroacetate

21. The product **21** was obtained as a white solid (122.1 mg, 72% in two steps); Mp 220–223 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (br s, 4H), 8.42 (t, 1H, J = 5.6 Hz), 8.03 (br s, 3H), 7.81 (s, 1H), 7.36 (s, 1H), 6.74 (d, 1H, J = 12.2 Hz), 6.20 (d, 1H, J = 12.2 Hz), 3.79 (s, 3H), 3.14 (q, 2H, J = 6.4 Hz), 3.00–2.94 (m, 6H), 2.88 (t, 4H, J = 7.3 Hz), 1.95–1.89 (m, 4H); 1.76–1.72 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.9, 154.0, 136.3, 135.4, 134.7, 126.4, 114.5, 113.4, 110.9, 56.3, 44.8, 44.0, 43.9, 36.1, 35.7, 25.8, 23.8, 22.4; IR (neat) 3078, 2851, 1669, 1422, 1197, 1164, 835, 721 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{31}Br_2N_4O_2$ (M + H − 3TFA), 505.0814; found, 505.0814. HPLC purity 99.8%, RT = 15.262 min.

(*E*)-*N*-(3-(6-(3-Aminopropylamino)hexylamino)propyl)-3-(3,5-dibromo-4-methoxyphenyl)acrylamide tris trifluoroacetate 22. The product **22** was obtained as a white solid (292.4 mg, 82% in two steps); Mp 157–160 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (br s, 2H), 8.65 (br s, 2H), 8.36 (t, 1H, J = 5.7 Hz), 8.05 (br s, 3H), 7.88 (s, 2H), 7.35 (d, 1H, J = 15.8 Hz), 6.68 (d, 1H, J = 15.8 Hz), 3.81 (s, 3H), 3.27–3.22 (m, 2H), 2.98–2.88 (m, 10H), 1.94–1.88 (m, 2H); 1.81–1.77 (m, 2H), 1.57 (m, 4H), 1.31 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.8, 153.9, 135.3, 134.3, 131.5, 124.2, 118.0, 60.5, 46.6, 44.7, 43.8, 36.1, 35.9, 25.9, 25.4, 25.3, 25.2, 23.7; IR (neat) 3048, 2935, 2866, 1687, 1420, 1195, 1138, 834, 720 cm^{-1}; HRMS (APCI) calcd for $C_{22}H_{37}Br_2N_4O_2$ (M + H − 3TFA), 547.1283; found, 547.1272. HPLC purity 99.3%, RT = 15.051 min.

***N*-(3-(6-(3-Aminopropylamino)hexylamino)propyl)-3-(2,3,4-tribromo-5-methoxyphenyl)acrylamide tris trifluoroacetate 23.** The product **23** was obtained along with the *Z*-isomer (*E* : *Z* ratio 5 : 1) as a white solid (155 mg, 80% in two steps); Mp 197–200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.78 (br s, 2H), 8.60 and 8.45 (m and t, respectively, 3H, J = 5.4 Hz for t), 7.99 (br s, 3H), 7.68 and 6.82 (each d, 1H, J = 15.7 Hz and 11.9 Hz), 7.37 and 7.19 (each s, 1H), 6.80 and 6.18 (each d, 1H, J = 15.6 Hz and 11.7 Hz), 3.94 and 3.81 (each s, 3H), 3.27 and 3.13 (each q, 2H, J = 6.4 Hz), 2.97–2.86 (m, 10H), 1.90 (quintet, 2H, J = 7.6 Hz); 1.81 and 1.71 (each quintet, 2H, J = 7.1 Hz and 7.0 Hz); 1.57 (m, 4H), 1.31 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7, 164.5, 156.0, 155.1, 138.7, 137.6, 137.4, 136.6, 129.1, 127.6, 127.2, 126.1, 117.7, 116.2, 109.6, 57.0, 56.9, 46.6, 44.7, 43.8, 36.1, 36.0, 25.9, 25.5, 25.3, 25.2, 23.7; IR (neat) 3325, 3062, 2935, 2843, 1658, 1458, 1190, 1137, 837, 707 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{36}Br_3N_4O_2$ (M + H − 3TFA), 625.0388; found, 625.0360. HPLC purity 99.3%, RT = 15.033 min.

(*E*)-*N*-(3-(6-(3-Aminopropylamino)hexylamino)propyl)-3-(2,4,6-tribromo-3-methoxyphenyl)acrylamide tris trifluoroacetate 24. The product **24** was obtained as a white solid (140.8 mg, 73% in two steps); Mp 190–194 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (t, 1H, J = 5.6 Hz), 8.52 (br s, 7H), 8.11 (s, 1H), 7.28 (d, 1H, J = 16.0 Hz), 6.45 (d, 1H, J = 16.0 Hz), 3.81 (s, 3H), 3.26 (q, 2H, J = 6.4 Hz), 3.01–2.86 (m, 10H), 1.95–1.87 (m, 2H); 1.86–1.80 (m, 2H), 1.58 (m, 4H), 1.32 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.9, 153.6, 137.3, 136.5, 135.6, 130.4, 119.8, 117.9, 117.4, 60.3, 46.6, 46.6, 44.7, 43.8, 36.1, 25.8, 25.5, 25.3, 25.2, 23.7; IR (neat) 3260, 2940, 2849, 1672, 1471, 1198, 1055, 836, 721 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{36}Br_3N_4O_2$ (M + H − 3TFA), 625.0388; found, 625.0360. HPLC purity 99.6%, RT = 14.389 min.

***N*-(3-(6-(3-Aminopropylamino)hexylamino)propyl)-3-(2,4-dibromo-5-methoxyphenyl)acrylamide tris trifluoroacetate 25.** The product **25** was obtained along with the *Z*-isomer (*E* : *Z* ratio 9 : 1) as a white solid (120.3 mg, 68% in two steps); Mp 184–187 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.83 (br s, 2H), 8.68 (br s, 2H), 8.61 and 8.45 (each t, 1H, J = 5.6 Hz), 8.04 (br s, 3H), 7.92 and 7.81 (each s, 1H), 7.60 and 6.75 (each d, 1H, J = 15.6 Hz and 12.2 Hz), 7.38 and 7.34 (each s, 1H), 6.87 and 6.20 (each d, 1H, J = 15.6 Hz and 12. 2 Hz), 3.93 and 3.79 (each s, 3H), 3.27 and 3.14 (each q, 2H, J = 5.9 Hz), 2.98–2.89 (m, 10H), 1.90 (quintet, 2H, J = 7.6 Hz); 1.81 and 1.73 (each m, 2H), 1.58 (m, 4H), 1.32 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.0, 164.7, 155.2, 154.1, 136.0, 135.9, 134.8, 126.1, 114.8, 112.8, 110.6, 56.5, 56.4, 46.6, 44.7, 43.8, 36.1, 36.0, 25.9, 25.5, 25.3, 25.2, 23.7; IR (neat) 3064, 2937, 2866, 1667, 1467, 1193, 1056, 835, 720 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{37}Br_2N_4O_2$ (M + H − 3TFA), 547.1283; found, 547.1248. HPLC purity 100%, RT = 15.148 min.

(*Z*)-*N*-(3-(6-(3-Aminopropylamino)hexylamino)propyl)-3-(2,4-dibromo-5-methoxyphenyl)acrylamide tris trifluoroacetate 26. The product **26** was obtained as a white solid (117.2 mg, 66% in two steps); Mp 157–160 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.88 (br s, 2H), 8.68 (br s, 2H), 8.47 (t, 1H, J = 5.6 Hz), 8.07 (br s, 3H), 7.82 (s, 1H), 7.35 (s, 1H), 6.75 (d, 1H, J = 12.2 Hz), 6.21 (d, 1H, J = 12.3 Hz), 3.80 (s, 3H), 3.14 (q, 2H, J = 6.4 Hz), 2.99–2.87 (m, 10H), 1.96–1.88 (m, 2H); 1.77–1.70 (m, 2H), 1.58–1.55 (m, 4H), 1.30 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.0, 154.1, 136.5, 135.6, 134.7, 126.4, 114.5, 113.4, 110.8, 56.4, 46.6, 44.6, 43.8, 36.1, 35.6, 25.8, 25.5, 25.3, 25.2, 23.7; IR (neat) 3065, 2937, 2867, 1667, 1471, 1194, 1056, 835, 720 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{37}Br_2N_4O_2$ (M + H − 3TFA), 547.1283; found, 547.1281. HPLC purity 100%, RT = 15.037 min.

(*E*)-*N*-(3-(4-Aminobutylamino)propyl)-3-(2,3,4-tribromo-5-methoxyphenyl)acrylamide bis trifluoroacetate 27. The product **27** was obtained as a white sticky solid (106.8 mg, 85% in two steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (br s, 2H), 8.64 (t, 1H, J = 5.9 Hz), 7.94 (br s, 3H), 7.68 (d, 1H, J = 15.6 Hz), 7.37 (s, 1H), 6.82 (d, 1H, J = 15.6 Hz), 3.94 (s, 3H), 3.29–3.24 (m, 2H), 2.93 (m, 4H), 2.84–2.79 (m, 2H), 1.85–1.77 (m, 2H), 1.61 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.5, 156.0, 137.6, 136.6, 129.1, 127.2, 117.7, 116.2, 109.5, 57.0, 46.0, 44.6, 38.1, 36.0, 25.9, 24.1, 22.5; IR (neat) 3395, 1661, 1048, 993, 762 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{25}Br_3N_3O_2$ (M + H − 2TFA), 539.9497; found, 539.9493. HPLC purity 100%, RT = 14.856 min.

(*Z*)-*N*-(3-(4-Aminobutylamino)propyl)-3-(2,3,4-tribromo-5-methoxyphenyl)acrylamide bis trifluoroacetate 28. The product **28** was obtained as a white solid (60.1 mg, 78% in two steps); Mp 138–140 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (br s, 2H), 8.46 (t, 1H, J = 5.6 Hz), 7.95 (br s, 3H), 7.20 (s, 1H), 6.81 (d, 1H, J = 12.2 Hz), 6.18 (d, 1H, J = 12.2 Hz), 3.81 (s, 3H), 3.14–3.09 (m, 2H), 2.87–2.79 (m, 6H), 1.75–1.68 (m, 2H),

1.59–1.57 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.6, 155.0, 138.6, 137.2, 127.6, 126.2, 115.9, 114.1, 113.0, 56.9, 46.1, 44.6, 38.2, 35.7, 25.9, 24.1, 22.5; IR (neat) 3289, 3027, 2841, 1670, 1558, 1186, 1129, 841, 722 cm^{-1}; HRMS (APCI) calcd for $C_{17}H_{25}Br_3N_3O_2$ (M + H − 2TFA), 539.9497; found, 539.9500. HPLC purity 100%, RT = 15.230 min.

(*E*)-*N*-(3-(4-Aminobutylamino)propyl)-3-(2,4,6-tribromo-3-methoxyphenyl)acrylamide bis trifluoroacetate 29. The product **29** was obtained as a white solid (134.3 mg, 78% in two steps); Mp 182–185 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (br s, 2H), 8.61 (t, 1H, J = 5.7 Hz), 8.10 (s, 1H), 7.96 (br s, 3H), 7.28 (d, 1H, J = 15.9 Hz), 6.44 (d, 1H, J = 16.0 Hz), 3.80 (s, 3H), 3.26 (q, 2H, J = 6.4 Hz), 2.93 (m, 4H), 2.82–2.81 (m, 2H), 1.85–1.78 (m, 2H), 1.61 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.9, 153.6, 137.3, 136.5, 135.6, 130.3, 119.8, 117.9, 117.4, 60.3, 46.0, 44.6, 38.1, 36.1, 25.8, 24.1, 22.5; IR (neat) 3419, 3235, 3066, 2879, 1662, 1352, 1174, 1044, 949, 718 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{25}Br_3N_3O_2$ (M + H − 2TFA), 539.9497; found, 539.9487. HPLC purity 99.5%, RT = 15.376 min.

(*E*)-*N*-(3-(4-Aminobutylamino)propyl)-3-(2,4-dibromo-5-methoxyphenyl)acrylamide bis trifluoroacetate 30. The product **30** was obtained as a white sticky solid (129.5 mg, 84% in two steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (br s, 2H), 8.62 (t, 1H, J = 5.7 Hz), 7.96 (br s, 3H), 7.91 (s, 1H), 7.60 (d, 1H, J = 15.6 Hz), 7.38 (s, 1H), 6.88 (d, 1H, J = 15.6 Hz), 3.92 (s, 3H), 3.27 (q, 2H, J = 6.3 Hz), 2.94 (m, 4H), 2.85–2.80 (m, 2H), 1.86–1.79 (m, 2H), 1.66–1.59 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7, 155.2, 136.0, 135.9, 134.8, 126.1, 114.8, 112.8, 110.6, 56.5, 46.0, 44.7, 38.1, 36.0, 25.9, 24.1, 22.5; IR (neat) 3276, 3029, 2850, 1673, 1468, 1179, 1129, 1056, 970, 723 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{26}Br_2N_3O_2$ (M + H − 2TFA), 462.0392; found, 462.0381. HPLC purity 99.9%, RT = 14.924 min.

(*Z*)-*N*-(3-(4-Aminobutylamino)propyl)-3-(2,4-dibromo-5-methoxyphenyl)acrylamide bis trifluoroacetate 31. The product **31** was obtained as a white solid (103.6 mg, 75% in two steps); Mp 114–117 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (br s, 2H), 8.44 (t, 1H, J = 5.6 Hz), 7.95 (br s, 3H), 7.81 (s, 1H), 7.35 (s, 1H), 6.74 (d, 1H, J = 12.2 Hz), 6.20 (d, 1H, J = 12.2 Hz), 3.79 (s, 3H), 3.16–3.11 (m, 2H), 2.87–2.80 (m, 6H), 1.77–1.70 (m, 2H), 1.60–1.58 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.9, 154.0, 136.4, 135.4, 134.7, 126.4, 114.5, 113.4, 110.9, 56.4, 46.0, 44.6, 38.1, 35.7, 25.8, 24.1, 22.5; IR (neat) 3399, 3064, 1672, 1196, 1130, 838, 720 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{26}Br_2N_3O_2$ (M + H − 2TFA), 462.0392; found, 462.0366. HPLC purity 99.1%, RT = 15.198 min.

(*E*)-*N*-(3-(3-Aminopropylamino)propyl)-3-(3,5-dibromo-4-methoxyphenyl)acrylamide bis trifluoroacetate 32. The product **32** was obtained as a white solid (239 mg, 88% in two steps); Mp 119–121 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.81 (br s, 2H), 8.38 (t, 1H, J = 5.6 Hz), 8.03 (br s, 3H), 7.88 (s, 2H), 7.35 (d, 1H, J = 15.6 Hz), 6.68 (d, 1H, J = 15.6 Hz), 3.81 (s, 3H), 3.25 (q, 2H, J = 6.4 Hz), 3.00–2.91 (m, 6H), 1.94–1.86 (m, 2H), 1.83–1.76 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.8, 153.9, 135.4, 134.3, 131.5, 124.1, 118.0, 60.5, 44.8, 43.9, 36.1, 35.9, 25.9, 23.8; IR (neat) 3037, 2930, 1666, 1264, 1166, 1132, 975, 721 cm^{-1}; HRMS (APCI) calcd for $C_{16}H_{24}Br_2N_3O_2$ (M + H − 2TFA), 448.0235; found, 448.0237. HPLC purity 100%, RT = 14.913 min.

(*E*)-*N*-(3-(3-Aminopropylamino)propyl)-3-(2,3,4-tribromo-5-methoxyphenyl)acrylamide bis trifluoroacetate 33. The product **33** was obtained as a white solid (135.5 mg, 90% in two steps); Mp 170–173 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (br s, 2H), 8.61 (t, 1H, J = 5.6 Hz), 7.98 (br s, 3H), 7.68 (d, 1H, J = 15.6 Hz), 7.36 (s, 1H), 6.80 (d, 1H, J = 15.6 Hz), 3.94 (s, 3H), 3.27 (q, 2H, J = 6.4 Hz), 3.00–2.87 (m, 6H), 1.94–1.86 (m, 2H), 1.83–1.78 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.5, 156.0, 137.6, 136.6, 129.1, 127.2, 117.7, 116.2, 109.5, 57.0, 44.8, 43.9, 36.1, 36.0, 25.9, 23.8; IR (neat) 3038, 2848, 1670, 1568, 1368, 1139, 969, 723 cm^{-1}; HRMS (APCI) calcd for $C_{16}H_{23}Br_3N_3O_2$ (M + H − 2TFA), 525.9340; found, 525.9339. HPLC purity 97.3%, RT = 15.100 min. HPLC purity 100%, RT = 14.825 min.

(*E*)-*N*-(3-(3-Aminopropylamino)propyl)-3-(2,4,6-tribromo-3-methoxyphenyl)acrylamide bis trifluoroacetate 34. The product **34** was obtained as a white solid (284.9 mg, 94% in two steps); Mp 208–210 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.77 (br s, 2H), 8.59 (t, 1H, J = 5.6 Hz), 8.10 (s, 1H), 7.99 (br s, 3H), 7.28 (d, 1H, J = 16.1 Hz), 6.44 (d, 1H, J = 16.1 Hz), 3.81 (s, 3H), 3.29–3.24 (m, 2H), 3.00–2.89 (m, 6H), 1.93–1.86 (m, 2H), 1.85–1.79 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.9, 153.6, 137.2, 136.5, 135.6, 130.3, 119.8, 117.9, 117.4, 60.3, 44.8, 43.9, 36.1, 36.1, 25.9, 23.8; IR (neat) 3062, 2932, 1671, 1351, 1173, 1131, 968, 720 cm^{-1}; HRMS (APCI) calcd for $C_{16}H_{23}Br_3N_3O_2$ (M + H − 2TFA), 525.9340; found, 525.9341. HPLC purity 99.6%, RT = 15.124 min.

(*E*)-*N*-(3-(3-Aminopropylamino)propyl)-3-(2,4-dibromo-5-methoxyphenyl)acrylamide bis trifluoroacetate 35. The product **35** was obtained along with the *Z*-isomer (*E* : *Z* ratio 18 : 1) as a white solid (112.5 mg, 83% in two steps); Mp 174–177 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (br s, 2H), 8.58 and 8.42 (each t, 1H, J = 5.6 Hz), 7.99 (br s, 3H), 7.91 and 7.81 (each s, 1H), 7.59 and 6.74 (each d, 1H, J = 15.6 Hz and 12.2 Hz), 7.37 and 7.36 (each s, 1H), 6.85 and 6.20 (each d, 1H, J = 15.6 Hz and 12.2 Hz), 3.92 and 3.79 (each s, 3H), 3.27 and 3.14 (each q, 2H, J = 6.4 Hz), 3.00–2.89 (m, 6H), 1.94–1.87 (m, 2H), 1.85–1.78 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7, 155.2, 136.0, 135.9, 134.8, 126.1, 114.8, 112.8, 110.6, 56.5, 44.8, 43.9, 36.1, 36.0, 25.9, 23.8; IR (neat) 3278, 3066, 2850, 1671, 1464, 1131, 970, 722 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{24}Br_2N_3O_2$ (M + H − 2TFA), 448.0235; found, 448.0218. HPLC purity 99.8%, RT = 15.510 min.

(*Z*)-*N*-(3-(3-Aminopropylamino)propyl)-3-(2,4-dibromo-5-methoxyphenyl)acrylamide bis trifluoroacetate 36. The product **36** was obtained along with the *E*-isomer (*Z* : *E* ratio 15 : 1) as a white solid (111.6 mg, 83% in two steps); Mp 154–157 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (br s, 2H), 8.44 and 8.61 (each t, 1H, J = 5.6 Hz), 8.03 (br s, 3H), 7.81 and 7.91 (each s, 1H), 7.36 and 7.37 (each s, 1H), 6.74 and 7.59 (each d, 1H, J = 12.2 Hz and 15.6 Hz), 6.20 and 6.86 (each d, 1H, J = 12.3 Hz and 15.7 Hz), 3.79 and 3.92 (each s, 3H), 3.14 and 3.27 (each q,

2H, J = 6.4 Hz), 2.95–2.87 (m, 6H), 1.92–1.85 (m, 2H), 1.77–1.70 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.9, 154.1, 136.3, 135.4, 134.7, 126.4, 114.6, 113.4, 110.9, 56.4, 44.8, 43.9, 36.1, 35.7, 25.8, 23.8; IR (neat) 3264, 3065, 2848, 1671, 1467, 1169, 1056, 722 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{24}Br_2N_3O_2$ (M + H − 2TFA), 448.0235; found, 448.0220. HPLC purity 100%, RT = 15.841 min.

(*E*)-*N*-(3-(6-Aminohexylamino)propyl)-3-(3,5-dibromo-4-methoxyphenyl)acrylamide bis trifluoroacetate 37. The product **37** was obtained as a colorless oil (118.3 mg, 82% in two steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (br s, 2H), 8.38 (t, 1H, J = 5.8 Hz), 7.89 (s, 5H, br s merged with s of aromatic H), 7.35 (d, 1H, J = 15.7 Hz), 6.70 (d, 1H, J = 15.7 Hz), 3.82 (s, 3H), 3.26 (q, 2H, J = 6.4 Hz), 2.93–2.86 (m, 4H), 2.81–2.75 (m, 2H), 1.82–1.79 (m, 2H), 1.57–1.52 (m, 4H), 1.33–1.31 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.8, 153.9, 135.3, 134.3, 131.5, 124.2, 118.0, 60.5, 46.6, 44.7, 38.6, 35.9, 26.7, 25.9, 25.4, 25.3; IR (neat) 2948, 2867, 1668, 1472, 1131, 977, 722 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{30}Br_2N_3O_2$ (M + H − 2TFA), 490.0705; found, 490.0697. HPLC purity 100%, RT = 15.130 min.

(*E*)-*N*-(3-(6-Aminohexylamino)propyl)-3-(2,3,4-tribromo-5-methoxyphenyl)acrylamide bis trifluoroacetate 38. The product **38** was obtained as a white solid (105 mg, 66% in two steps); Mp 98–100 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (t, 3H, J = 5.4 Hz), 7.85 (br s, 3H), 7.68 (d, 1H, J = 15.6 Hz), 7.37 (s, 1H), 6.80 (d, 1H, J = 15.7 Hz), 3.94 (s, 3H), 3.27 (q, 2H, J = 6.4 Hz), 2.93–2.86 (m, 4H), 2.80–2.75 (m, 2H), 1.83–1.78 (m, 2H), 1.57–1.51 (m, 4H), 1.31 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.5, 156.1, 137.6, 136.6, 129.1, 127.2, 117.7, 116.2, 109.6, 57.0, 46.7, 44.7, 38.6, 36.1, 26.8, 25.9, 25.4, 25.3; IR (neat) 3335, 3057, 2965, 2860, 1691, 1542, 1361, 1182, 1128, 974, 799 cm^{-1}; HRMS (APCI) calcd for $C_{19}H_{29}Br_3N_3O_2$ (M + H − 2TFA), 567.9810; found, 567.9824. HPLC purity 100%, RT = 15.376 min.

(*Z*)-*N*-(3-(6-Aminohexylamino)propyl)-3-(2,3,4-tribromo-5-methoxyphenyl)acrylamide bis trifluoroacetate 39. The product **39** was obtained as a white sticky solid (50.2 mg, 63% in two steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.67 (br s, 2H), 8.50 (t, 1H, J = 5.4 Hz), 7.92 (br s, 3H), 7.19 (s, 1H), 6.81 (d, 1H, J = 11.7 Hz), 6.19 (d, 1H, J = 11.7 Hz), 3.81 (s, 3H), 3.12 (q, 2H, J = 6.4 Hz), 2.83–2.76 (m, 6H), 1.72 (quintet, 2H, J = 7.0 Hz), 1.52 (m, 4H), 1.29–1.28 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7, 155.1, 138.7, 137.4, 127.6, 126.2, 115.8, 114.0, 113.0, 56.9, 47.0, 44.6, 38.6, 35.6, 26.8, 25.9, 25.4, 25.3, 25.3; IR (neat) 3416, 3055, 2942, 2866, 1670, 1435, 1194, 1131, 839, 721 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{29}Br_3N_3O_2$ (M + H − 2TFA), 567.9810; found, 567.9810. HPLC purity 99.7%, RT = 15.214 min.

(*E*)-*N*-(3-(6-Aminohexylamino)propyl)-3-(2,4,6-tribromo-3-methoxyphenyl)acrylamide bis trifluoroacetate 40. The product **40** was obtained as a white sticky solid (117.8 mg, 74% in two steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (br s, 2H), 8.67 (t, 1H, J = 5.6 Hz), 8.09 (s, 1H), 7.98 (br s, 3H), 7.27 (d, 1H, J = 16.1 Hz), 6.45 (d, 1H, J = 16.1 Hz), 3.80 (s, 3H), 3.26 (q, 2H, J = 6.4 Hz), 2.91–2.89 (m, 4H), 2.79–2.74 (m, 2H), 1.86–1.79 (m, 2H), 1.59–1.54 (m, 4H), 1.31 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.9, 153.7, 137.3, 136.5, 135.6, 130.4, 119.9, 117.9, 117.4, 60.3, 46.6, 44.7, 38.6, 36.2, 26.8, 25.8, 25.5, 25.3, 25.3; IR (neat) 3397, 3078, 1673, 1444, 1202, 1133, 843, 724 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{29}Br_3N_3O_2$ (M + H − 2TFA), 567.9810; found, 567.9815. HPLC purity 99.7%, RT = 14.937 min.

(*E*)-*N*-(3-(6-Aminohexylamino)propyl)-3-(2,4-dibromo-5-methoxyphenyl)acrylamide bis trifluoroacetate 41. The product **41** was obtained as a white solid (165.5 mg, 77% in two steps); Mp 128–130 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (t merged with br s, 3H, J = 5.9 Hz), 7.91 (s, 1H), 7.84 (br s, 3H), 7.59 (d, 1H, J = 15.6 Hz), 7.36 (s, 1H), 6.84 (d, 1H, J = 15.6 Hz), 3.92 (s, 3H), 3.27 (q, 2H, J = 6.2 Hz), 2.92–2.90 (m, 4H), 2.80–2.75 (m, 2H), 1.84–1.77 (m, 2H), 1.56–1.53 (m, 4H), 1.31 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7, 155.2, 136.0, 135.9, 134.8, 126.1, 114.8, 112.8, 110.5, 56.5, 46.6, 44.7, 38.6, 36.0, 26.8, 25.9, 25.4, 25.3; IR (neat) 3255, 2939, 2852, 1667, 1462, 1129, 1056, 836, 721 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{30}Br_2N_3O_2$ (M + H − 2TFA), 490.0705; found, 490.0703. HPLC purity 99.9%, RT = 15.030 min.

(*Z*)-*N*-(3-(6-Aminohexylamino)propyl)-3-(2,4-dibromo-5-methoxyphenyl)acrylamide bis trifluoroacetate 42. The product **42** was obtained as a white sticky solid (113.8 mg, 79% in two steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (br s, 2H), 8.46 (t, 1H, J = 5.6 Hz), 7.90 (br s, 3H), 7.81 (s, 1H), 7.34 (s, 1H), 6.75 (d, 1H, J = 12.2 Hz), 6.20 (d, 1H, J = 12.2 Hz), 3.79 (s, 3H), 3.14 (q, 2H, J = 6.4 Hz), 2.84–2.75 (m, 6H), 1.73 (quintet, 2H, J = 7.1 Hz), 1.55–1.52 (m, 4H), 1.30–1.29 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 165.0, 154.1, 136.5, 135.6, 134.7, 126.4, 114.5, 113.4, 110.8, 56.4, 46.6, 44.6, 38.6, 35.6, 26.8, 25.8, 25.4, 25.3, 25.3; IR (neat) 3283, 2946, 2845, 1677, 1465, 1126, 1054, 840, 722 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{30}Br_2N_3O_2$ (M + H − 2TFA), 490.0705; found, 490.0705. HPLC purity 100%, RT = 15.115 min.

(2*E*,2′*E*)-*N*,*N*′-(3,3′-(Butane-1,4-diylbis(azanediyl))bis(propane-3,1-diyl))bis(3-(2,3,4-tribromo-5-methoxyphenyl)acrylamide) bis trifluoroacetate 43. The product **43** was obtained as a white sticky solid (103.6 mg, 85% in two steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (br s, 4H), 8.64 (t, 2H, J = 5.6 Hz), 7.68 (d, 2H, J = 15.7 Hz), 7.37 (s, 2H), 6.82 (d, 2H, J = 15.2 Hz), 3.94 (s, 6H), 3.28–3.26 (m, 4H), 2.94 (m, 8H), 1.83–1.80 (m, 4H), 1.64 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.5, 156.0, 137.6, 136.6, 129.1, 127.2, 117.7, 116.2, 109.5, 57.0, 46.0, 44.7, 36.0, 25.9, 22.6; IR (neat) 3403, 3068, 2848, 1667, 1413, 1193, 1129, 835, 718 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{37}Br_6N_4O_4$ (M + H − 2TFA), 990.7915; found, 990.7904. HPLC purity 100%, RT = 15.119 min.

(2*Z*,2′*Z*)-*N*,*N*′-(3,3′-(Butane-1,4-diylbis(azanediyl))bis(propane-3,1-diyl))bis(3-(2,3,4-tribromo-5-methoxyphenyl)acrylamide) bis trifluoroacetate 44. The product **44** was obtained as a white solid (89.3 mg, 73% in two steps); Mp 160–162 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (br s, 4H), 8.48 (t, 2H, J = 5.6 Hz), 7.19 (s, 2H), 6.80 (d, 2H, J = 12.2 Hz), 6.18 (d, 2H, J = 12.2 Hz), 3.80 (s, 6H), 3.12 (q, 4H, J = 6.4 Hz), 2.86 (m, 8H), 1.72 (quintet, 4H, J = 7.0 Hz), 1.59 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.6, 155.1, 138.7, 137.3, 127.6, 126.2, 115.9,

114.1, 113.1, 56.9, 46.1, 44.6, 35.7, 25.9, 22.6; IR (neat) 3264, 3078, 2839, 1670, 1532, 1129, 1066, 842, 723 cm^{-1}; HRMS (APCI) calcd for $C_{30}H_{37}Br_6N_4O_4$ (M + H − 2TFA), 990.7915; found, 990.7933. HPLC purity 99.5%, RT = 15.137 min.

(2*E*,2′*E*)-*N*,*N*′-(3,3′-(Butane-1,4-diylbis(azanediyl))bis(propane-3,1-diyl))bis(3-(2,4,6-tribromo-3-methoxyphenyl)acrylamide) bis trifluoroacetate 45. The product **45** was obtained as a white solid (135.6 mg, 89% in two steps); Mp 190–193 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (br s, 4H), 8.60 (t, 2H, J = 5.6 Hz), 8.09 (s, 2H), 7.28 (d, 2H, J = 16.1 Hz), 6.44 (d, 2H, J = 15.7 Hz), 3.81 (s, 6H), 3.26 (q, 4H, J = 6.4 Hz), 2.94 (m, 8H), 1.82 (quintet, 4H, J = 7.1 Hz), 1.64 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.9, 153.6, 137.2, 136.5, 135.6, 130.3, 119.8, 117.9, 117.4, 60.3, 46.0, 44.7, 36.1, 25.8, 22.6; IR (neat) 3397, 3235, 3065, 1673, 1415, 1194, 1133, 965, 720 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{37}Br_6N_4O_4$ (M + H − 2TFA), 990.7915; found, 990.7908. HPLC purity 100%, RT = 14.804 min.

(2*E*,2′*E*)-*N*,*N*′-(3,3′-(Butane-1,4-diylbis(azanediyl))bis(propane-3,1-diyl))bis(3-(2,4-dibromo-5-methoxyphenyl)acrylamide) bis trifluoroacetate 46. The product **46** was obtained as a white sticky solid (116.7 mg, 88% in two steps); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (br s, 4H), 8.64 (t, 2H, J = 5.7 Hz), 7.90 (s, 2H), 7.59 (d, 2H, J = 15.6 Hz), 7.37 (s, 2H), 6.89 (d, 2H, J = 15.6 Hz), 3.92 (s, 6H), 3.27 (q, 4H, J = 6.3 Hz), 2.95 (m, 8H), 1.86–1.79 (m, 4H), 1.66 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7, 155.2, 136.0, 135.8, 134.8, 126.2, 114.8, 112.8, 110.6, 56.5, 46.0, 44.7, 36.0, 25.9, 22.6; IR (neat) 3395, 1678, 1444, 1202, 1137, 846, 725 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{39}Br_4N_4O_4$ (M + H − 2TFA), 834.9705; found, 834.9703. HPLC purity 98.6%, RT = 15.775 min.

(2*E*,2′*E*)-*N*,*N*′-(3,3′-(Propane-1,3-diylbis(azanediyl))bis(propane-3,1-diyl))bis(3-(3,5-dibromo-4-methoxyphenyl)acrylamide) bis trifluoroacetate 47. The product **47** was obtained as a white solid (174.1 mg, 83% in two steps); Mp 208–210 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (br s, 4H), 8.35 (t, 2H, J = 5.6 Hz), 7.87 (s, 4H), 7.35 (d, 2H, J = 15.7 Hz), 6.67 (d, 2H, J = 15.7 Hz), 3.81 (s, 6H), 3.26 (q, 4H, J = 6.4 Hz), 3.00–2.94 (m, 8H), 1.95 (quintet, 2H, J = 7.3 Hz), 1.80 (quintet, 4H, J = 7.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.8, 153.9, 135.4, 134.3, 131.5, 124.1, 118.0, 60.5, 44.8, 43.9, 35.9, 26.0, 22.4; IR (neat) 3082, 2865, 1664, 1472, 1196, 1132, 979, 743 cm^{-1}; HRMS (APCI) calcd for $C_{29}H_{37}Br_4N_4O_4$ (M + H − 2TFA), 820.9548; found, 820.9547. HPLC purity 100%, RT = 14.648 min.

(2*E*,2′*E*)-*N*,*N*′-(3,3′-(Propane-1,3-diylbis(azanediyl))bis(propane-3,1-diyl))bis(3-(2,3,4-tribromo-5-methoxyphenyl)acrylamide) bis trifluoroacetate 48. The product **48** was obtained as a white solid (94 mg, 77% in two steps); Mp 216–218 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.74 (br s, 4H), 8.59 (t, 2H, J = 5.6 Hz), 7.68 (d, 2H, J = 15.2 Hz), 7.35 (s, 2H), 6.77 (d, 2H, J = 15.7 Hz), 3.94 (s, 6H), 3.28 (q, 4H, J = 6.4 Hz), 3.00–2.95 (m, 8H), 1.98–1.93 (m, 2H), 1.85–1.79 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.5, 156.0, 137.7, 136.6, 129.1, 127.1, 117.7, 116.2, 109.5, 57.0, 44.8, 43.9, 36.0, 26.0, 22.5; IR (neat) 3278, 3077, 2862, 1665, 1367, 1197, 1134, 970, 719 cm^{-1}; HRMS (ESI) calcd for $C_{29}H_{35}Br_6N_4O_4$ (M + H − 2TFA), 976.7759; found, 976.7781. HPLC purity 99.0%, RT = 15.191 min.

(2*E*,2′*E*)-*N*,*N*′-(3,3′-(Propane-1,3-diylbis(azanediyl))bis(propane-3,1-diyl))bis(3-(2,4,6-tribromo-3-methoxyphenyl)acrylamide) bis trifluoroacetate 49. The product **49** was obtained as a white solid (195.4 mg, 81% in two steps); Mp 222–224 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.82 (br s, 4H), 8.60 (t, 2H, J = 5.4 Hz), 8.09 (s, 2H), 7.28 (d, 2H, J = 16.1 Hz), 6.44 (d, 2H, J = 16.1 Hz), 3.80 (s, 6H), 3.27 (q, 4H, J = 6.4 Hz), 3.01–2.95 (m, 8H), 1.99–1.92 (m, 2H), 1.82 (quintet, 4H, J = 7.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.9, 153.6, 137.2, 136.5, 135.6, 130.3, 119.8, 117.9, 117.4, 60.3, 44.8, 43.9, 36.1, 25.9, 22.5; IR (neat) 3253, 3072, 2869, 1665, 1558, 1196, 1135, 1043, 832, 718 cm^{-1}; HRMS (APCI) calcd for $C_{29}H_{35}Br_6N_4O_4$ (M + H − 2TFA), 976.7759; found, 976.7747. HPLC purity 100%, RT = 15.174 min.

(2*E*,2′*E*)-*N*,*N*′-(3,3′-(Hexane-1,6-diylbis(azanediyl))bis(propane-3,1-diyl))bis(3-(3,5-dibromo-4-methoxyphenyl)acrylamide) bis trifluoroacetate 50. The product **50** was obtained as a white solid (184.3 mg, 84% in two steps); Mp 56–58 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.64 (br s, 4H), 8.36 (t, 2H, J = 5.6 Hz), 7.88 (s, 4H), 7.35 (d, 2H, J = 15.7 Hz), 6.68 (d, 2H, J = 16.1 Hz), 3.81 (s, 6H), 3.25 (q, 4H, J = 6.4 Hz), 2.92–2.89 (m, 8H), 1.79 (quintet, 4H, J = 7.1 Hz), 1.57 (m, 4H), 1.31 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.8, 153.9, 135.4, 134.3, 131.6, 124.2, 118.0, 115.2, 60.5, 46.6, 44.7, 36.0, 26.0, 25.4, 25.3; IR (neat) 3290, 2944, 2864, 1660, 1471, 1200, 1177, 1133, 982, 721 cm^{-1}; HRMS (APCI) calcd for $C_{32}H_{43}Br_4N_4O_4$ (M + H − 2TFA), 863.0018; found, 863.0023. HPLC purity 100%, RT = 14.871 min.

(2*E*,2′*E*)-*N*,*N*′-(3,3′-(Hexane-1,6-diylbis(azanediyl))bis(propane-3,1-diyl))bis(3-(2,3,4-tribromo-5-methoxyphenyl)acrylamide) bis trifluoroacetate 51. The product **51** was obtained as a white solid (101.3 mg, 81% in two steps); Mp 122–124 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.62 (m, 6H), 7.67 (d, 2H, J = 15.7 Hz), 7.36 (s, 2H), 6.80 (d, 2H, J = 15.2 Hz), 3.94 (s, 6H), 3.27 (m, 4H), 2.92–2.90 (m, 8H), 1.81 (quintet, 4H, J = 7.1 Hz), 1.57 (m, 4H), 1.31 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.5, 156.0, 137.7, 136.6, 129.1, 127.2, 117.7, 116.2, 109.5, 57.0, 46.6, 44.7, 36.1, 25.9, 25.4, 25.3; IR (neat) 3326, 3062, 2842, 1657, 1361, 1188, 975, 707 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{41}Br_6N_4O_4$ (M + H − 2TFA), 1018.8228; found, 1018.8222. HPLC purity 100%, RT = 14.803 min.

(2*Z*,2′*Z*)-*N*,*N*′-(3,3′-(Hexane-1,6-diylbis(azanediyl))bis(propane-3,1-diyl))bis(3-(2,3,4-tribromo-5-methoxyphenyl)acrylamide) bis trifluoroacetate 52. The product **52** was obtained as a white solid (108.7 mg, 87% in two steps); Mp 138–141 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (br s, 4H), 8.49 (t, 2H, J = 5.9 Hz), 7.19 (s, 2H), 6.81 (d, 2H, J = 12.2 Hz), 6.19 (d, 2H, J = 12.2 Hz), 3.81 (s, 6H), 3.12 (q, 4H, J = 6.4 Hz), 2.84–2.81 (m, 8H), 1.72 (quintet, 4H, J = 7.0 Hz), 1.52 (m, 4H), 1.26 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.7, 155.1, 138.7, 137.4, 127.6, 126.1, 115.8, 114.0, 113.0, 56.9, 46.7, 44.6, 35.6, 25.9, 25.5, 25.3; IR (neat) 3270, 3072, 2838, 1672, 1358, 1134, 839, 722 cm^{-1}; HRMS (APCI) calcd for $C_{32}H_{41}Br_6N_4O_4$ (M + H − 2TFA), 1018.8228; found, 1018.8204. HPLC purity 99.9%, RT = 15.304 min.

(2*E*,2′*E*)-*N*,*N*′-(3,3′-(Hexane-1,6-diylbis(azanediyl))bis(propane-3,1-diyl))bis(3-(2,4,6-tribromo-3-methoxyphenyl)acrylamide) bis trifluoroacetate 53. The product **53** was obtained as a white solid (220.4 mg, 88% in two steps); Mp 186–188 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.66 (br s, 4H), 8.60 (t, 2H, J = 5.6 Hz), 8.08 (s, 2H), 7.28 (d, 2H, J = 15.7 Hz), 6.44 (d, 2H, J = 15.6 Hz), 3.80 (s, 6H), 3.26 (q, 4H, J = 6.4 Hz), 2.92–2.90 (m, 8H), 1.81 (quintet, 4H, J = 7.1 Hz), 1.58 (m, 4H), 1.32 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0, 153.7, 137.3, 136.5, 135.6, 130.4, 119.9, 117.9, 117.5, 60.3, 46.6, 44.7, 36.1, 25.9, 25.5, 25.3; IR (neat) 3283, 3065, 2843, 1778, 1659, 1414, 1150, 970, 708 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{41}Br_6N_4O_4$ (M + H − 2TFA), 1018.8228; found, 1018.8210. HPLC purity 99.8%, RT = 14.646 min.

Antibacterial activity test

Test-bacteria. The antibacterial activity of various compounds was assessed against two bacterial species: Gram-positive *Staphylococcus aureus* ATCC 25923 and Gram-negative *Escherichia coli* ATCC 25922, maintained at −70 °C.

Disc-diffusion assay. Overnight cultures of cells of either *Staphylococcus aureus* or *Escherichia coli* were uniformly smeared on to Luria broth agar medium (Hi-Media) in Petri plates, and sterile discs (5 mm diameter) containing 50 μg of the different synthesized compounds dissolved in dimethyl sulfoxide (DMSO) were placed on to these plates to allow each compound to diffuse into the surrounding areas and inhibit bacterial growth. Production of such zones of growth inhibition would indicate sensitivity of the bacteria to the specific compound. For each treatment, 3 replicates were maintained. The plates were then incubated at 37 °C for 12 h and the size of the resulting zone of inhibition, if any, was determined.

Determination of the Minimum Inhibitory Concentration (MIC): For the determination of MIC, bacterial strains were exposed to 10-fold dilution series of the compounds ranging from 0.1 to 15 000 μM at 37 °C for 24 h. MIC was defined as the lowest concentration of the agent that resulted in the zone of growth inhibition in the disc diffusion assay.

Time-kill assay. To determine cell viability, a single bacterial colony was inoculated into Luria broth. Following overnight growth the bacterial cultures were diluted 1 : 100 and further grown for 2 h to allow exponential growth. *E. coli* and *S. aureus* cultures were then treated with serial dilution of each of the compounds at 37 °C for 4 h. At times 0 and 4 h post-treatment, 10 μL cultures were withdrawn and spotted on to Luria broth agar medium and grown overnight at 37 °C.

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Notes and references

1 M. A. Fischbach and C. T. Walsh, *Science*, 2009, **325**, 1089.
2 D. H. Kwon and C. D. Lu, *Antimicrob. Agents Chemother.*, 2007, **51**, 2070.
3 R. A. Casero Jr. and P. M. Woster, *J. Med. Chem.*, 2009, **52**, 4551.
4 H. M. Wallace and K. Niiranen, *Amino Acids*, 2007, **33**, 261.
5 K. Igarashi and K. Kashiwagi, *Biochem. Biophys. Res. Commun.*, 2000, **271**, 559.
6 M. Yoshida, K. Kashiwagi, A. Shigemasa, S. Taniguchi, K. Yamamoto, H. Makinoshima, A. Ishihama and K. Igarashi, *J. Biol. Chem.*, 2004, **279**, 46008.
7 M. K. Chattopadhyay, C. W. Tabor and H. Tabor, *Proc. Natl. Acad. Sci. U. S. A.*, 2003, **100**, 2261.
8 I. L. Jung, T. J. Oh and I. G. Kim, *Arch. Biochem. Biophys.*, 2003, **418**, 125.
9 I. G. Kim and T. J. Oh, *Toxicol. Lett.*, 2000, **116**, 143.
10 H. Samartzidou, M. Mehrazin, Z. Xu, M. J. Benedik and A. H. Delcour, *J. Bacteriol.*, 2003, **185**, 13.
11 K. W. Minton, H. Tabor and C. W. Tabor, *Proc. Natl. Acad. Sci. U. S. A.*, 1990, **87**, 2851.
12 K. Higashi, K. Yoshida, K. Nishimura, E. Momiyama, K. Kashiwagi, S. Matsufuji, A. Shirahata and K. Igarashi, *J. Biochem.*, 2004, **136**, 533.
13 C. M. Holst, B. Frydman, L. J. Marton and S. M. Oredsson, *Toxicology*, 2006, **223**, 71.
14 R. M. Reguera, B. L. Tekwani and R. Balana-Fouce, *Comp. Biochem. Physiol., C: Toxicol. Pharmacol.*, 2005, **140**, 151.
15 Y. Zou, Z. Wu, N. Sirisoma, P. M. Woster, R. A. Casero Jr., L. M. Weiss, D. Rattendi, S. Lane and C. J. Bacchi, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1613.
16 X. Bi, C. Lopez, C. J. Bacchi, D. Rattendi and P. M. Woster, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 3229.
17 B. K. Verlinden, J. Niemand, J. Snyman, S. K. Sharma, R. J. Beattie, P. M. Woster and L.-M. Birkholtz, *J. Med. Chem.*, 2011, **54**, 6624.
18 V. Choomuenwai, B. D. Schwartz, K. D. Beattie, K. T. Andrews, S. Khokhar and R. A. Davis, *Tetrahedron Lett.*, 2013, **54**, 5188.
19 S. A. Pomponi, *Oceanography*, 2001, **14**, 78.
20 F. E. Koehn and G. T. Carter, *Nat. Rev. Drug Discovery*, 2005, **4**, 206.
21 J. Clardy and C. Walsh, *Nature*, 2004, **432**, 829.
22 D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2012, **75**, 311.
23 D. J. Newman, *J. Med. Chem.*, 2008, **51**, 2589.
24 S. D. Sarker, Z. Latif and A. I. Gray, *Natural products isolation*, Humana Press Inc., New Jersey, 2nd edn, 2005.
25 A. M. Boldi, *Curr. Opin. Chem. Biol.*, 2004, **8**, 281.
26 M. Xu, R. A. Davis, Y. Feng, M. L. Sykes, T. Shelper, V. M. Avery, D. Camp and R. J. Quinn, *J. Nat. Prod.*, 2012, **75**, 1001.
27 (*a*) M. S. Buchanan, A. R. Carroll, G. A. Fechner, A. Boyle, M. M. Simpson, R. Addepalli, V. M. Avery, J. N. A. Hooper, N. Su, H. Chen and R. J. Quinn, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 6860; (*b*) S. Yin, R. A. Davis, T. Shelper,

M. L. Sykes, V. M. Avery, M. Elofsson, C. Sundin and R. J. Quinn, *Org. Biomol. Chem.*, 2011, **9**, 6755; (*c*) N. Fusetani, Y. Masuda, Y. Nakao, S. Matsunaga and R. W. M. van Soest, *Tetrahedron*, 2001, **57**, 7507.

28 (*a*) A. J. Blackman and D. J. Matthews, *Heterocycles*, 1985, **23**, 2829; (*b*) A. J. Blackman and R. D. Green, *Aust. J. Chem.*, 1987, **40**, 1655; (*c*) A. R. Carroll, S. Duffy, M. Sykes and V. M. Avery, *Org. Biomol. Chem.*, 2011, **9**, 604.

29 (*a*) H. P. Zhang, Y. Kamano, H. Kizu, H. Itokawa, G. R. Pettit and C. L. Herald, *Chem. Lett.*, 1994, 2271; (*b*) Y. Kamano, A. Kotake, H. Hashima, I. Hayakawa, H. Hiraide, H. P. Zhang, H. Kizu, K. Komiyama, M. Hayashi and G. R. Pettit, *Collect. Czech. Chem. Commun.*, 1999, **64**, 1147; (*c*) R. A. Davis, M. Sykes, V. M. Avery, D. Camp and R. J. Quinn, *Bioorg. Med. Chem.*, 2011, **19**, 6615.

30 B. D. Morris and M. R. Prinsep, *J. Nat. Prod.*, 1999, **62**, 688.

31 (*a*) G. Zhu, F. Yang, R. Balachandran, P. Hook, R. B. Vallee, D. P. Curran and B. W. Day, *J. Med. Chem.*, 2006, **49**, 2063; (*b*) M. Takahashi, A. Yamamoto, T. Inuzuka, T. Sengoku and H. Yoda, *Tetrahedron*, 2011, **67**, 9484.

32 M. R. Osuna, G. Aguirre, R. Somanathan and E. Molins, *Tetrahedron: Asymmetry*, 2002, **13**, 2261.

33 F. A. Khan and S. Ahmad, *J. Org. Chem.*, 2012, **77**, 2389.

34 R. Córdoba, N. S. Tormo, A. F. Medarde and J. Plumet, *Bioorg. Med. Chem.*, 2007, **15**, 5300.

35 P. Xu, G.-S. Liu, J. Xi, S. Wang and Z.-J. Yao, *Tetrahedron*, 2011, **67**, 5455.

36 (*a*) P. Singh, C. Samorì, F. M. Toma, C. Bussy, A. Nunes, K. T. Al-Jamal, C. Ménard-Moyon, M. Prato, K. Kostarelos and A. Bianco, *J. Mater. Chem.*, 2011, **21**, 4850; (*b*) A. J. Geall, R. J. Taylor, M. E. Earll, M. A. W. Eaton and I. S. Blagbrough, *Bioconjugate Chem.*, 2000, **11**, 314.

37 (*a*) C. J. Thomas, A. O. Chizhov, C. J. Leitheiser, M. J. Rishel, K. Konishi, Z.-F. Tao and S. M. Hecht, *J. Am. Chem. Soc.*, 2002, **124**, 12926; (*b*) P. Chen, X. Bao, L.-F. Zhang, M. Ding, X.-J. Han, J. Li, G.-B. Zhang, Y.-Q. Tu and C.-A. Fan, *Angew. Chem., Int. Ed.*, 2011, **50**, 8161.

38 V. R. Espejo and J. D. Rainier, *Org. Lett.*, 2010, **12**, 2154.

39 J. B. Baell and G. A. Holloway, *J. Med. Chem.*, 2010, **53**, 2719.