Bioorganic & Medicinal Chemistry 19 (2011) 3204–3215

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

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

Synthesis and evaluation of 1-(1*H*-indol-3-yl)ethanamine derivatives as new antibacterial agents

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ARTICLE INFO

Article history:
Received 12 November 2010
Revised 20 March 2011
Accepted 28 March 2011
Available online 2 April 2011

Keywords:
Indolic derivatives
Substituted hydroxylamines
Antibacterial activity

ABSTRACT

A collection of 3-substituted indole derivatives was prepared using nucleophilic addition of indoles to nitrones. The compounds were then tested for their antibacterial activity against almost thirty bacterial strains representative of common human pathogens. Two types of indolic molecules inhibit the growth of *Staphylococcus aureus*, including MRSA and VISA strains, with MIC values ranging from 8 to 16 mg/L.

1. Introduction

Antibiotics changed the history of mankind in the early forties. Frequent and often deadly diseases were successfully cured and for half a century, this revolution was considered as definitely acquired, occulting the extraordinary adaptability of the bacterial world.[1] Unfortunately, over the last 15 years, bacterial resistances have evolved much faster than innovation. The increased prevalence and worldwide dissemination of multidrug-resistant bacteria has resulted in a major decrease in therapeutic options, especially in the hospital setting.[2] Among the gram-positive bacteria, major antibiotic-resistant pathogens belong to the genera *Staphylococcus*, *Enterococcus* and *Streptococcus*. As for *Staphylococcus* sp., the widespread and long-term use of beta-lactam and glycopeptide antibiotics has led to the emergence of meticillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-intermediate *Staphylococcus aureus* (VISA) strains.[3] Resistance has also emerged to beta-lactams in *Streptococcus pneumoniae* and *Enterococcus* sp., and to glycopeptides in *Enterococcus* sp.[4] Multidrug-resistance also concern many gram-negative species such as *Escherichia coli*, *Pseudomonas aeruginosa*, and *Acinetobacter baumanii*.[5] The discovery of antibacterial agents that operate via novel modes of action and are thus not prone to currently existing resistance mechanisms, is now urgent.

The sources of antibacterial compounds are either natural products or synthetic molecules. Though most of the antibiotics on the market today originate from natural products or their semisynthetic derivatives,[6] research for new natural antibiotics is restricted due to their structural complexity, instability and limited availability as compared to synthetic chemicals. On the other hand, despite the ability of chemists to prepare libraries containing thousands of synthetic compounds, major discoveries relevant to infectious disease treatment remains rare and, arguably, serendipitous.[7] This could be explained by a weak structural diversity and poor physicochemical properties of available commercial compound libraries. Consequently, the creation of diverse collections of unique, highly potent bioactive small molecules could dramatically accelerate the rate of biochemical discoveries of new antibiotics.[8]

One approach to this problem is the creation of compound collections based on 'privileged scaffolds'.[7a] Due to their versatile binding properties, these frameworks (or substructures) are able to provide potent and selective ligands for a range of different biological targets. Our choice of indole scaffold[9] for a search of novel

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doi:10.1016/j.bmc.2011.03.060

antibiotics accounts for several reasons. Firstly, the indole nucleus is a widespread substructure found in molecules which exhibit a wide spectrum of pharmacological activities,[7a,10] including a significant antimicrobial one.[11] Furthermore, it has been shown that even nonsubstituted indole nucleus possesses a weak antibacterial activity.[12] Secondly, a versatile and efficient chemical approach towards 3-substituted indoles by the nucleophilic addition of indoles to nitrones has been developed by our research group (Fig. 1).[13] This method was successfully employed[14] to the total synthesis of marine sponge bis(indole) alkaloids of the hamacanthin, spongotine, and topsentin classes, exhibiting significant antibiotic activity.[11c]

In this Letter, we report the synthesis of a collection of differently substituted indolic derivatives and the results on their antibacterial activity against almost thirty bacterial strains. Some information about mechanism of action, as well as the cytotoxicity data of synthesized compounds, is also reported.

2. Results and discussion

2.1. Chemistry

The synthesis of the indole library is outlined in Scheme 1. Coupling reaction[13] in acidic conditions between three nitrones **1a–c**[15] and nine commercially available indoles **2a–i** efficiently provided the indolic *N*-hydroxylamines **3aa–ci** (Table 1). Then the latter compounds have been oxidized to aldonitrones **4aa–ci** by manganese dioxide in toluene.[16] A hydroxyaminolysis of indolic nitrones **4aa–ci** was performed yielding *N*-hydroxylamines **5aa–ci**, that have been subjected to Boc-cleavage reaction. A series of amino-*N*-hydroxylamines **6ca–ci** was obtained as stable solids. Finally, a collection of 66 indole derivatives was created, and all synthesized products possess *N*-(1-(1*H*-indol-3-yl)ethanamine substructure (Table 1). Moreover, using simple and efficient chemical transformations we have obtained four different sublibraries of indolic molecules: secondary *N*-hydroxylamines **3aa–ci**, aldonitrones **4aa–ci**, primary *N*-hydroxylamines **5aa–ci** and primary amines **6ca–ci**. The diversity of functional groups of library members enhances the possibility to discover biologically active molecules.

2.2. Biological activity

The indolic compounds were tested for their antimicrobial activity against a panel of 28 reference bacterial strains belonging to 17 different species representative of common human pathogens. The minimum inhibitory concentrations (MICs) of the tested compounds allowing complete inhibition of visual bacterial growth show that compounds from one of four sublibraries, namely the aldonitrones **4aa–ci**, are completely inactive (MIC >128 mg/L) towards gram-positive and gram-negative bacteria. In contrast, several primary and secondary *N*-hydroxylamine compounds belonging to the three other groups display a significant antibacterial activity against *Staphylococcus* sp. and a weak activity against *S. pneumoniae*. This indicates that the *N*-hydroxylamine function group plays an important role for antibacterial activity of *N*-(1-(1*H*-indole-3-yl)ethyl)hydroxyamines. It should be mentioned that inactivity of aldonitrones **4aa–ci** against bacterial

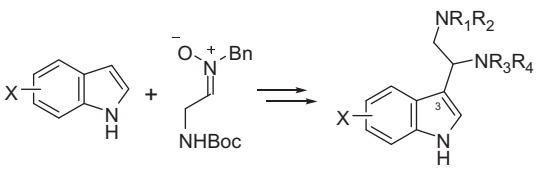
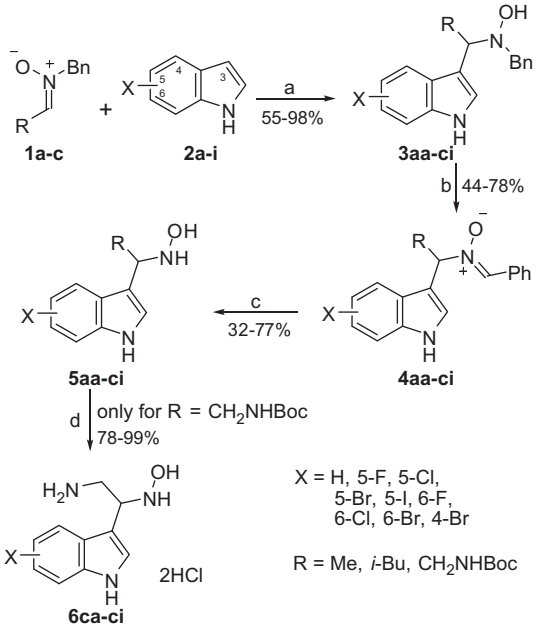


Figure 1. The chemical approach towards 3-substituted indoles.



Scheme 1. Synthesis of 3-substituted indoles. Reagents and conditions: (a) HCl, MeOH, 0 °C; (b) MnO_2, toluene, 100 °C; (c) $NH_2OH{\cdot}HCl$, MeOH, rt; (d) HCl, MeOH, 0 °C.

strains allowed us to test their inhibitory activity against bacterial efflux pumps. These results will be presented in a separate publication.

Disubstituted *N*-hydroxylamines **3aa–ci** provided six indolic molecules showing a significant antibacterial activity (Table 2). The *N*-hydroxylamines **3cc–ce** and **3cg–ch** are bacteriostatic against all tested *Staphylococcus* sp. strains with MIC values ranging from 8 to 16 mg/L. A weak antibacterial activity was also observed against *Streptococcus* sp. for compounds **3cc–ce**, with MIC values of 64–128 mg/L for *S. pneumoniae* and 32–64 μg/ml for *S. pyogenes* CIP 10422. Furthermore, compounds **3bb**, **3cc** and **3ce** were weakly active against *H. influenzae* with MIC values of 64 μg/ml. Structural diversity of the sublibrary members allowed us to draw some SAR observations. Growth of the side alkyl chain size of *N*-hydroxylamines **3aa–ci** from methyl to isobutyl and then to CH_2-NH-Boc increases the antibacterial activity. These results demonstrate that a bulky group at this position of disubstituted *N*-hydroxylamines is required for antibacterial activity. It can be hypothesized that CH_2-NH-Boc functional group can interact with bacterial target by means of hydrogen bonds of carbamate function. Furthermore, substitution at the C(5) or C(6) position of indole core by a halogen such as chlorine, bromine or iodine, is essential to improve antibacterial activity.

The monosubstituted *N*-hydroxylamines **5aa–ci** of the second sublibrary, obtained by benzyl cleavage reaction of disubstituted *N*-hydroxylamines **3aa–ci**, display a weak antibacterial activity against *Staphylococcus* strains with MIC values of 64–128 mg/L (Table 3). Two opposite observations were made for this group of indolic derivatives. (1) In the case of *N*-hydroxylamines **5aa–be** with simple aliphatic side chain (R = Me or *i*-Bu), the benzyl cleavage lead to an improvement of the antibacterial activity. It is especially true for the compounds **5ab–ae** and **5bb–be** substituted by a halogen at position C(5) of the indole core. (2) In contrast, in the case of monosubstituted *N*-hydroxylamines **5ca–ci** with carbamate side chain (R = CH_2NHBoc), the benzyl cleavage results in reduction of the antibacterial activity. This last observation demonstrates that benzyl and CH_2-NH-Boc functional groups may be simultaneously required for antibacterial activity of sublibrary **3ca–ci** compounds.

Table 1
Synthesis of 3-substituted indoles

Indole	R	X	Yield[a] (%)	Indole	R	X	Yield[a] (%)	Indole	R	X	Yield[a] (%)
3aa	Me	H	98	**4ad**	Me	5-Br	45	**5bb**	*i*-Bu	5-F	46
3ab	Me	5-F	85	**4ae**	Me	5-I	51	**5bc**	*i*-Bu	5-Cl	41
3ac	Me	5-Cl	85	**4ba**	*i*-Bu	H	59	**5bd**	*i*-Bu	5-Br	36
3ad	Me	5-Br	68	**4bb**	*i*-Bu	5-F	44	**5be**	*i*-Bu	5-I	32
3ae	Me	5-I	70	**4bc**	*i*-Bu	5-Cl	50	**5ca**	CH_2NHBoc	H	65
3ba	*i*-Bu	H	93	**4bd**	*i*-Bu	5-Br	52	**5cb**	CH_2NHBoc	5-F	58
3bb	*i*-Bu	5-F	79	**4be**	*i*-Bu	5-I	50	**5cc**	CH_2NHBoc	5-Cl	62
3bc	*i*-Bu	5-Cl	79	**4ca**	CH_2NHBoc	H	78	**5cd**	CH_2NHBoc	5-Br	56
3bd	*i*-Bu	5-Br	56	**4cb**	CH_2NHBoc	5-F	66	**5ce**	CH_2NHBoc	5-I	75
3be	*i*-Bu	5-I	55	**4cc**	CH_2NHBoc	5-Cl	66	**5cf**	CH_2NHBoc	6-F	40
3ca	CH_2NHBoc	H	90	**4cd**	CH_2NHBoc	5-Br	64	**5cg**	CH_2NHBoc	6-Cl	77
3cb	CH_2NHBoc	5-F	98	**4ce**	CH_2NHBoc	5-I	68	**5ch**	CH_2NHBoc	6-Br	57
3cc	CH_2NHBoc	5-Cl	87	**4cf**	CH_2NHBoc	6-F	72	**5ci**	CH_2NHBoc	4-Br	68
3cd	CH_2NHBoc	5-Br	84	**4cg**	CH_2NHBoc	6-Cl	71	**6ca**	CH_2NH_2	H	98
3ce	CH_2NHBoc	5-I	83	**4ch**	CH_2NHBoc	6-Br	72	**6cb**	CH_2NH_2	5-F	94
3cf	CH_2NHBoc	6-F	85	**4ci**	CH_2NHBoc	4-Br	52	**6cc**	CH_2NH_2	5-Cl	78
3cg	CH_2NHBoc	6-Cl	82	**5aa**	Me	H	66	**6cd**	CH_2NH_2	5-Br	98
3ch	CH_2NHBoc	6-Br	87	**5ab**	Me	5-F	60	**6ce**	CH_2NH_2	5-I	99
3ci	CH_2NHBoc	4-Br	80	**5ac**	Me	5-Cl	55	**6cf**	CH_2NH_2	6-F	89
4aa	Me	H	53	**5ad**	Me	5-Br	62	**6cg**	CH_2NH_2	6-Cl	95
4ab	Me	5-F	50	**5ae**	Me	5-I	58	**6ch**	CH_2NH_2	6-Br	89
4ac	Me	5-Cl	51	**5ba**	*i*-Bu	H	64	**6ci**	CH_2NH_2	4-Br	99

[a] Isolated and purified yield. All compounds gave correct IR, ^1H and ^{13}C NMR and LC-MS analyses.

Table 2
Antibiotic activity of disubsituted *N*-hydroxylamines **3aa–ci** against *Staphylococcus* sp. and *Streptococcus pneumoniae*[a]

Indole	MIC (mg/L)					Indole	MIC (mg/L)				
	S. aureus[b]	MRSA[c]	VISA ATCC 106414	*S. epidermidis*[d]	*S. pneumoniae*[e]		*S. aureus*	MRSA	VISA ATCC 106414	*S. epidermidis*	*S. pneumoniae*
Cip	0.5	0.125	32	0.25	0.5–1	**Gen**	0.125-0.25	0.25	>64	0.125	—
3aa	128	—	—	64	—	**Cfx**	—	—	—	—	0.125
3ab	>128	>128	>128	>128	>128	**3ca**	>128	>128	>128	>128	>128
3ac	>128	>128	>128	>128	>128	**3cb**	>128	>128	>128	>128	>128
3ad	>128	>128	>128	>128	>128	**3cc**	16	16	16	16	64
3ae	>128	>128	>128	>128	>128	**3cd**	8–16	16	8	16	128
3ba	32	—	—	16	—	**3ce**	8–16	8–16	8	8	64
3bb	64–128	128	128	64–128	128	**3cf**	>128	>128	>128	>128	>128
3bc	>128	>128	>128	>128	>128	**3cg**	16	16	16	16	>128
3bd	>128	>128	>128	>128	>128	**3ch**	8–16	16	16	16	>128
3be	>128	>128	>128	>128	>128	**3ci**	>128	>128	>128	>128	>128

[a] Cip, ciprofloxacin; Gen, gentamicin: Cfx, cefotaxime.
[b] MIC values of the following *S. aureus* strains: ATCC 25923, ATCC 29213, ATCC 9144, ATCC 6538, CIP 65.6 and CIP 103428.
[c] MIC values of meticillin-resistant *S. aureus* CIP 65.25 and ATCC 33592.
[d] MIC values of the following *S. epidermidis* strains: ATCC 12228, CIP 81.55 and CIP 103627.
[e] MIC values of *Streptococcus pneumoniae* ATCC 49619 and ATCC 6303.

Finally, Boc cleavage reaction, leading to the free amino-*N*-hydroxylamines **6ca–ci** sublibrary, induces an outstanding increase of antibacterial activity (Table 4), compared to sublibrary **5ca–ci**. Indeed, a significant activity was recorded for all the amino-*N*-hydroxylamines hydrochlorides **6ca–ci** against *Staphylococcus* sp., including MRSA and VISA strains. Moreover, a weak activity was also highlighted against *Streptococcus* sp., with MIC values ranging from 64 to 128 mg/L for *S. pneumoniae, Streptococcus agalactiae, S. pyogenes*, *S. mitis*, *E. faecium* and *E. faecalis* strains. Compounds **6cc**, **6ce** and **6cg** were also weakly active against *H. influenzae*, with MIC values of 64–128 mg/L. Lastly, the amino-*N*-hydroxylamines was the only sublibrary exhibiting a weak activity against other Gram negative bacilli. We recorded MIC values ranging from 16 to 128 mg/L against *E. coli*, *K. pneumoniae*, *E. cloacae*, *S. marcescens*, *P. aeruginosa* and *A. baumanii* strains. For this sublibrary, the important role of the halogen atom was also demonstrated. The fluorine, chlorine or bromine atoms at the C(5) or C(6) positions of the indole core increased the antibiotic activity of indolic derivatives **6cb–ch** against *Staphylococcus* sp., with MIC values ranging from 8 to 32 mg/L.

Table 3
Antibiotic activity of monosubstituted *N*-hydroxyl-amines **5aa–ci** against *Staphylococcus* sp.[a]

Indole	MIC (mg/L)		Indole	MIC (mg/L)	
	S. aureus[b]	*S. epidermidis*[c]		*S. aureus*	*S. epidermidis*
Cip	0.5	0.25	**Gen**	0.125–0.25	0.125
5aa	128	64	**5ca**	>128	>128
5ab	64	64	**5cb**	>128	>128
5ac	32	16	**5cc**	64	64
5ad	64	64	**5cd**	32-64	64
5ae	64	32	**5ce**	32	64
5ba	64	32	**5cf**	>128	>128
5bb	32–64	32	**5cg**	128	>128
5bc	16	32	**5ch**	64	64
5bd	32	16	**5ci**	128	128
5be	32	16			

[a] Cip, ciprofloxacin; Gen, gentamicin.
[b] MIC values of the following *S. aureus* strains: ATCC 25923, ATCC 29213, ATCC 9144, ATCC 6538, CIP 65.6 and CIP 103428.
[c] MIC values of the following *S. epidermidis* strains: ATCC 12228, CIP 81.55 and CIP 103627.

One relevant way to guide the synthesis work towards an increase of the potency of the synthesized molecules as antimicrobial compounds is to elucidate their mode of action. Based on the structure similarity between our *N*-hydroxylamines and indolic acetohydroxamic acids,[11a,b] peptide deformylase (PDF) was postulated to be a possible target inside the bacterial cell. The ability of several indolic derivatives including **5cd** and **6cd**, both displaying a 5-Br substitution, to inhibit the activity of *E. coli* PDF (*Ec*PDF) was tested in vitro. Compound **6cd** was chosen because it exhibits the lowest MIC value against *E. coli* among all the compounds tested in this study (Table 4), whereas the monosubstituted *N*-hydroxylamine **5cd** had no antibacterial activity (Table 3). In the presence of 1 μM concentration the tested compounds displayed only modest PDF inhibition capacity (25%). Complete inhibition of *Ec*PDF activity was observed at 500 μM of compound **6cd**, whereas at the same concentration inhibition by compound **5cd** reached only 54%. These data, indicating that **6cd** is more potent than **5cd**, are in keeping with the in vivo data showing that **5cd** antimicrobial activity against *E. coli* (MIC >128 mg/L) is weaker than that observed with **6cd** (MIC 16–32 mg/L). This evidences the role of the substitution at position 3 of indole unit in PDF inhibition, a feature already reported in SAR analysis of PDF.[11a,b] Hence, it should be stressed that the *N*-hydroxylamine compound **6cd** only showed a weak affinity for *Ec*PDF compared to other efficient PDF inhibitors reported in the literature such as actinonin. Indeed, by comparison, another 5-Br indole derivative substituted with an acetohydroxamic acid at position 3 (AB47) was reported to inhibit PDF with an IC_{50} of 0.035 μM[11a] whereas IC_{50} of compounds **5cd** and **6cd** is higher than 1 μM. However, AB47 is only a modest antimicrobial compound angainst *E. coli* as the associated MIC value is identical to that of **6cd** (16–32 mg/L). These data do not allow excluding that the target is PDF and might suggest that the permeability of *E. coli* to **6cd** is improved. Increasing the passive penetration of **6cd** in the bacterium is likely to compensate for the lower potency of the compound. In this context, it should be reminded that 5-Br indole binds weakly but specifically to PDF and that *N*-hydroxylamine derivatives display similar inhibition properties as **6cd**.

As a preliminary evaluation of their potential side effects in humans, in vitro cytotoxicity assays were performed for all indolic compounds possessing antibacterial activity (MIC <32–64 mg/L), that is, six molecules from the first sublibrary of secondary *N*-hydroxylamines (**3ba**, **3cc**, **3cd**, **3ce**, **3cg**, and **3ch**), nine molecules from the third group of primary *N*-hydroxylamines (**5ac**, **5ae**–**be**, **5cd**, and **5ce**), and all nine molecules from the last sublibrary of primary amines (**6ca**–**ci**). The indolic compounds were tested at 10 and 1 μM concentrations on three selected eukaryotic cell types: KB (oral carcinoma), HCT116 (colon cancer cell line) and MRC5 (human noncancerous cells in rapid proliferation). At 10 μM, only three indoles (**3cc**, **3ce**, **3cg**) out of the 24 tested compounds displayed a cytotoxic effect with a cell growth inhibition ranging from 72% to 98%. In contrast, none of these compounds had detectable cytotoxicity, at 1 μM. These data show that the members of our library have a moderate cytotoxic effect on human cells at concentrations where they are active as antimicrobial compounds, which is a positive for their future development as antibiotics.

3. Conclusions

In an attempt to find novel type of antibacterial agents, we have synthesized and fully characterized the collection of 3-substituted indole derivatives. The evaluation of the antibacterial activity of these compounds, using a large panel of human pathogens, allowed us to distinguish two types of indolic *N*-hydroxylamines **3ca–ci** and **6ca–ci** that inhibit predominantly the growth of *Staphylococcus* strains, including MRSA and VISA strains. (Fig. 2). The SAR studies demonstrated that the presence of a halogen at positions C(5) or C(6) of the indole core is essential for the antibacterial activity of indolic compounds. The presence of ethanamine substituent (R = CH_2NH_2 or R = CH_2NHBoc) at alkyl side chain is also

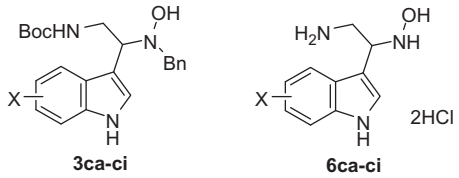


Figure 2. The chemical structures of the most active *N*-hydroxylamines **3ca–ci** and **6ca–ci**.

Table 4
Antibiotic activity of amino-*N*-hydroxylamines **6ca–ci** against gram-positive and gram-negative strains[a]

Indole	MIC (mg/L)									
	S. aureus[b]	MRSA[c]	VISA ATCC 106414	*S. epidermidis*[d]	*S. pneumoniae*[e]	*Streptococcus*[f]	*Enterococcus*[g]	*Gram-negative bacilli*[h]	*E. coli* ATCC 25922	*H. influenzae* ATCC 49766
Cip	0.5	0.125	32	0.25	0.5–1	0.25–2	1	0.016–2	0.064	0.5
Gen	0.125–0.25	0.25	>64	0.125	—	—	—	0.5–32	1	—
Cfx	—	—	—	—	0.125	0.016–0.063	0.5–2	—	—	0.032
6ca	32–64	64	32	32	>128	>128	>128	>128	>128	>128
6cb	8–16	16	8	8	64	32–128	64–128	32–128	32	>128
6cc	16	16	16	16	64–128	128	>128	128	64	128
6cd	16	16	16	8–16	64	64	128	64–128	16–32	—
6ce	16–32	32	16	16–32	64	128	128	64–128	32	64
6cf	16	16	16	16	64	64–128	128	64–128	64	>128
6cg	16	16–32	16	16	64	64–128	128	64–128	32	128
6ch	16–32	16	16	16	64	128	>128	64-128	32	—
6ci	32	32	32	32	128	128	>128	128->128	128	—

[a] Cip, ciprofloxacin; Gen, gentamicin: Cfx, cefotaxime.
[b] MIC values of the following *S. aureus* strains: ATCC 25923, ATCC 29213, ATCC 9144, ATCC 6538, CIP 65.6 and CIP 103428.
[c] MIC values of meticillin-resistant *S. aureus* CIP 65.25 and ATCC 33592.
[d] MIC values of the following *S. epidermidis* strains: ATCC 12228, CIP 81.55 and CIP 103627.
[e] MIC values of *Streptococcus pneumoniae* ATCC 49619 and ATCC 6303.
[f] MIC values of *Streptococcus agalactiae* ATCC 12400, *Streptococcus pyogenes* CIP 104226 and *S. mitis* CIP 103335.
[g] MIC values of *Enterococcus faecium* CIP 54.32 and *Enterococcus faecalis* ATCC 29212.
[h] MIC values of *K. pneumoniae* ATCC 35657, *E. cloacae* ATCC 13047, *S. marcescens* CIP 103551, *P. aeruginosa* CIP 5933 and *A. baumanii* ATCC 19606.

essential for the antibiotic activity of *N*-(1-(1*H*-indol-3-yl)ethyl)-hydroxylamines.

Our results represent a valuable starting point for the preparation a new series of 1-(1*H*-indol-3-yl)ethanamine derivatives with the aim of improving their antibacterial activity. Our attempts to identify possible intracellular targets of our compounds revealed one putative target is PDF. However, our data show that compounds such as **6cd** exhibits only weak affinity for PDF; at this stage, we cannot exclude therefore the existence of other intracellular targets. Thus, in depth investigation of the mode of action of our compounds including bacterial uptake is required. This microbiological approach could be associated to rationale design of further members of this indolic class of compounds in order to provide potent antibacterial agents.

4. Experimental part

4.1. Chemistry

Purchased reagents were used without purification. Reactions were monitored by thin layer chromatography (TLC) using commercial aluminum-backed silica gel plates (Merck G 60 F_{254}). TLC spots were viewed under ultraviolet light and by heating the plate after treatment with either a 0.5% solution of ninhydrine in 3% ethanolic acetic acid or a 2% solution of potassium permanganate in 7% aqueous sodium carbonate; *N*-hydroxylamines were detected with a 1% triphenyl tetrazolium chloride (TTC) in ethanol (red color). Product purification by gravity column chromatography was performed using Macherey–Nagel Silica Gel 60 (70–230 mesh). Infrared (IR) spectra were recorded on a Nicolet Magna-550 Fourier transform infrared spectrometer (FTIR) equipped with an ATR (Attenuated Total Reflection) device and the data are reported in reciprocal centimeters (cm^{-1}). ^1H NMR and ^{13}C NMR spectra were run on Bruker Advance300 spectrometer. Chemical shifts for ^1H spectra are values downfield from tetramethylsilane in $CDCl_3$ (δ 0.00), or CD_3OD (δ 3.31) and are reported as follows: chemical shift (ppm), multiplicity, coupling constants (Hz), and integration. Mass spectra (MS) were recorded on a ThermoFinnigan PolarisQ ion-trap spectrometer using DCI (ammonia/methane 63/37) or on a Bruker Esquire 3000 plus (ESI) in order to improve the bacterial activity of these compounds.

4.1.1. General procedure for the synthesis of indolic *N*-hydroxylamines 3aa–ci

A cold solution of hydrochloric acid was prepared by reaction of 143 μL (157 mg, 2.0 mmol) of freshly distilled acetyl chloride with 5 mL of dry methanol. This solution was stirred at 0 °C during 15 min and was added to a mixture of both nitrone (1.0 mmol) and indole (1.0 mmol) in 5 mL of dry methanol. The reaction mixture was stirred at 0 °C during 2 h to completion. A saturated aqueous solution of $NaHCO_3$ was then added. The mixture was extracted with DCM (3 × 10 mL), and the collected organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. Column chromatography using EtOAc–pentane (1/99—40/60) yielded pure products.

4.1.1.1. *N*-Benzyl-*N*-(1-(1*H*-indol-3-yl)ethyl)hydroxylamine 3aa. Compound **3aa** (260 mg, 98%) was obtained from nitrone **1a** (149 mg, 1.0 mmol) and indole **2a** (117 mg, 1.0 mmol) as a white solid. IR (neat): 695, 740, 750, 920, 1010, 1095, 1120, 1345, 1370, 1420, 1460, 1495, 2900, 2930, 2965, 3045, 3410 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$–CD_3OD): δ = 1.60 (d, J = 6.7 Hz, 3H), 3.65 (d, J = 13.3 Hz, 1H), 3.81 (d, J = 13.3 Hz, 1H), 4.25 (q, J = 6.7 Hz, 1H), 7.08–7.28 (m, 8H), 7.33–7.36 (m, 1H), 7.75–7.78 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$–CD_3OD): δ = 18.5, 59.2, 61.0, 111.1, 118.9, 119.7, 121.5, 122.7, 126.6, 126.7, 127.8 (2 C), 129.3 (2 C), 136.2, 138.5 (2 C). MS (ES^+): m/z (%) = 289 (9) $[M+Na]^+$, 267 (1) $[M+H]^+$, 144 (100) $[M+H-N(OH)Bn]^+$.

4.1.1.2. *N*-Benzyl-*N*-(1-(5-fluoro-1*H*-indol-3-yl)ethyl)hydroxylami-ne 3ab. Compound **3ab** (240 mg, 85%) was obtained from nitrone **1a** (149 mg, 1.0 mmol) and 5-fluoroindole **2b** (135 mg, 1.0 mmol) as a white solid. IR (neat): 695, 740, 920, 1170, 1455, 1485, 1580, 2900, 2970, 3415 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$–CD_3OD): δ = 1.61 (d, J = 6.7 Hz, 3H), 3.60 (d, J = 13.5 Hz, 1H), 3.81 (d, J = 13.5 Hz, 1H), 4.18 (q, J = 6.7 Hz, 1H), 6.89 (dt, J_1 = 9.3 Hz, J_2 = 2.5 Hz, 1H), 7.18–7.32 (m, 7H), 7.44 (dd, J_1 = 10.2 Hz, J_2 = 2.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$–CD_3OD): δ = 18.0, 59.4, 60.5, 104.1 (d, J = 23.7 Hz), 109.2 (d, J = 26.5 Hz), 111.4 (d, J = 9.7 Hz), 124.3, 126.2, 127.4 (2 C), 128.8 (2 C), 132.7, 138.4 (2 C), 157.1 (d, J = 232.7 Hz). ^{19}F NMR (282 MHz, $CDCl_3$–CD_3OD): δ = −126.2 (dt, J_1 = 9.5 Hz, J_2 = 4.5 Hz, 1F). MS (ES^+): m/z (%) = 307 (15) $[M+Na]^+$, 285 (10) $[M+H]^+$, 162 (100) $[M+H-N(OH)Bn]^+$.

4.1.1.3. *N*-Benzyl-*N*-(1-(5-chloro-1*H*-indol-3-yl)ethyl)hydroxylami-ne 3ac. Compound **3ac** (255 mg, 85%) was obtained from nitrone **1a** (149 mg, 1.0 mmol) and 5-chloroindole **2c** (152 mg, 1.0 mmol) as a white solid. IR (neat): 695, 740, 805, 905, 1100, 1230, 1375, 1455, 2875, 3415 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$–CD_3OD): δ = 1.61 (d, J = 6.7 Hz, 3H), 3.61 (d, J = 13.5 Hz, 1H), 3.80 (d, J = 13.5 Hz, 1H), 4.19 (q, J = 6.7 Hz, 1H), 7.09 (dd, J_1 = 8.6 Hz, J_2 = 2.0 Hz, 1H), 7.18–7.46 (m, 7H), 7.76 (d, J = 2.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$–CD_3OD): δ = 18.1, 59.0, 60.6, 111.9, 118.9, 121.2, 124.0, 124.1 (2 C), 126.4, 127.5 (2 C), 128.9 (2 C), 134.6, 138.3 (2 C). MS (ES^+): m/z (%) = 323 (9) $[M+Na]^+$, 301 (12) $[M+H]^+$, 178 (100) $[M+H-N(OH)Bn]^+$.

4.1.1.4. *N*-Benzyl-*N*-(1-(5-bromo-1*H*-indol-3-yl)ethyl)hydroxylami-ne 3ad. Compound **3ad** (235 mg, 68%) was obtained from nitrone **1a** (149 mg, 1.0 mmol) and 5-bromoindole **2d** (196 mg, 1.0 mmol) as a white solid. IR (neat): 695, 740, 802, 885, 1045, 1100, 1375, 1455, 2965, 3415 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$–CD_3OD): δ = 1.60 (d, J = 6.7 Hz, 3H), 3.60 (d, J = 13.5 Hz, 1H), 3.80 (d, J = 13.5 Hz, 1H), 4.19 (q, J = 6.7 Hz, 1H), 7.17–7.34 (m, 8H), 7.93 (d, J = 1.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$–CD_3OD): δ = 18.0, 59.4, 60.5, 111.5, 112.3, 122.0, 123.6, 123.9, 126.2, 127.4 (2 C), 128.8 (2 C), 134.8, 138.3 (2 C). MS (ES^+): m/z (%) = 367 (14) $[M+Na]^+$, 245 (8) $[M+H]^+$, 222 (100) $[M+H-N(OH)Bn]^+$.

4.1.1.5. *N*-Benzyl-*N*-(1-(5-iodo-1*H*-indol-3-yl)ethyl)hydroxylamine 3ae. Compound **3ae** (274 mg, 70%) was obtained from nitrone **1a** (149 mg, 1.0 mmol) and 5-iodoindole **2e** (243 mg, 1.0 mmol) as a white solid. IR (neat): 700, 750, 795, 880, 1040, 1115, 1230, 1370, 1435, 1455, 2970, 3310 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$–CD_3OD): δ = 1.60 (d, J = 6.7 Hz, 3H), 3.60 (d, J = 13.4 Hz, 1H), 3.80 (d, J = 13.4 Hz, 1H), 4.19 (q, J = 6.7 Hz, 1H), 7.16–7.28 (m, 7H), 7.38 (dd, J_1 = 8.6 Hz, J_2 = 1.4 Hz, 1H), 8.14 (d, J = 1.3 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$–CD_3OD): δ = 18.1, 58.8, 60.5, 81.6, 112.9, 123.3, 126.3, 127.4 (2 C), 128.4, 128.8 (2 C), 129.2, 135.2, 138.3 (2 C). MS (ES^+): m/z (%) = 415 (10) $[M+Na]^+$, 393 (10) $[M+H]^+$, 267 (100).

4.1.1.6. *N*-Benzyl-*N*-(1-(1*H*-indol-3-yl)-3-methylbutyl)hydroxylamine 3ba. Compound **3ba** (286 mg, 93%) was obtained from nitrone **1b** (191 mg, 1.0 mmol) and indole **2a** (117 mg, 1.0 mmol) as a white solid. IR (neat): 700, 740, 810, 1010, 1095, 1230, 1340, 1455, 1495, 2865, 2955, 3060, 3410 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (d, J = 6.6 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H), 1.47–1.56 (m, 1H), 1.88–2.08 (m, 2H), 3.61 (d, J = 13.4 Hz, 1H), 3.71 (d, J = 13.4 Hz, 1H), 4.18 (dd, J_1 = 9.3 Hz, J_2 = 5.6 Hz, 1H), 5.29 (br s, 1H), 7.10–7.25 (m, 8H), 7.30–7.32 (m, 1H), 7.71 (d, J = 7.7 Hz,

1H), 8.12 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1, 23.5, 25.3, 42.3, 61.6, 61.9, 111.1, 119.5, 120.0, 121.9, 123.5, 126.9, 127.7, 128.1 (2 C), 129.3 (2 C), 136.2, 138.6 (2 C). MS (ES^+): *m/z* (%) = 240 (100) $[M+Na-Bn]^+$, 186 (71) $[M+H-N(OH)Bn]^+$.

4.1.1.7. *N*-Benzyl-*N*-(1-(5-fluoro-1*H*-indol-3-yl)-3-methylbutyl)-hydroxylamine 3bb. Compound **3bb** (258 mg, 79%) was obtained from nitrone **1b** (191 mg, 1.0 mmol) and 5-fluoroindole **2b** (135 mg, 1.0 mmol) as a white solid. IR (neat): 695, 740, 790, 930, 1055, 1175, 1350, 1365, 1455, 1485, 1575, 2950, 3355 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$–CD_3OD): δ = 0.85 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H), 1.42–1.56 (m, 1H), 1.88–2.05 (m, 2H), 3.60 (d, *J* = 13.4 Hz, 1H), 3.73 (d, *J* = 13.4 Hz, 1H), 4.09 (dd, J_1 = 9.5 Hz, J_2 = 5.5 Hz, 1H), 6.91 (dt, J_1 = 9.1 Hz, J_2 = 2.4 Hz, 1H), 7.17–7.31 (m, 7H), 7.37 (dd, J_1 = 10.2 Hz, J_2 = 2.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$–CD_3OD): δ = 21.7, 23.2, 25.1, 41.9, 61.4, 62.1, 104.4 (d, *J* = 23.7 Hz), 109.6 (d, *J* = 26.5 Hz), 111.6 (d, *J* = 9.7 Hz), 125.4, 126.7, 127.8 (2 C), 129.1 (2 C), 132.8, 138.5 (2 C), 157.5 (d, *J* = 233.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$–CD_3OD): δ = −121.6 (dt, J_1 = 9.8 Hz, J_2 = 4.6 Hz, 1F). MS (ES^+): *m/z* (%) = 349 (11) $[M+Na]^+$, 327 (2) $[M+H]^+$, 258 (14), 204 (100), 148 (48), 91 (13).

4.1.1.8. *N*-Benzyl-*N*-(1-(5-chloro-1*H*-indol-3-yl)-3-methylbutyl)-hydroxylamine 3bc. Compound **3bc** (270 mg, 79%) was obtained from nitrone **1b** (191 mg, 1.0 mmol) and 5-chloroindole **2c** (157 mg, 1.0 mmol) as a white solid. IR (neat): 695, 740, 795, 890, 1055, 1110, 1435, 1465, 2960, 3295 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$–CD_3OD): δ = 0.85 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 1.42–1.57 (m, 1H), 1.85–2.05 (m, 2H), 3.60 (d, *J* = 13.3 Hz, 1H), 3.72 (d, *J* = 13.3 Hz, 1H), 4.11 (dd, J_1 = 9.4 Hz, J_2 = 5.4 Hz, 1H), 7.11 (dd, J_1 = 8.6 Hz, J_2 = 1.9 Hz, 1H), 7.21–7.34 (m, 7H), 7.68 (d, *J* = 1.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$–CD_3OD): δ = 21.8, 23.2, 25.1, 42.0, 61.4, 61.8, 112.1, 119.1, 121.6, 124.6, 125.1, 126.7, 127.8 (2 C), 129.1 (2 C), 134.6, 138.4 (2 C). MS (ES^+): *m/z* (%) = 365 (11) $[M+Na]^+$, 343 (3) $[M+H]^+$, 220 (100), 164 (43).

4.1.1.9. *N*-Benzyl-*N*-(1-(5-bromo-1*H*-indol-3-yl)-3-methylbutyl)-hydroxylamine 3bd. Compound **3bd** (217 mg, 56%) was obtained from nitrone **1b** (191 mg, 1.0 mmol) and 5-bromoindole **2d** (196 mg, 1.0 mmol) as a white solid. IR (neat): 700, 745, 795, 935, 1050, 1110, 1435, 1455, 1595, 2865, 2960, 3300 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$–CD_3OD): δ = 0.85 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 1.43–1.57 (m, 1H), 1.85–2.05 (m, 2H), 3.60 (d, *J* = 13.4 Hz, 1H), 3.72 (d, *J* = 13.4 Hz, 1H), 4.10 (dd, J_1 = 9.5 Hz, J_2 = 5.5 Hz, 1H), 7.21–7.28 (m, 8H), 7.84 (d, *J* = 0.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$–CD_3OD): δ = 21.7, 23.2, 25.0, 42.0, 61.3, 61.8, 112.1, 112.6, 122.1, 124.0, 124.9, 126.7, 127.8 (2 C), 129.1 (2 C), 134.8, 138.4 (2 C). MS (ES^+): *m/z* (%) = 409 (10) $[M+Na]^+$, 387 (3) $[M+H]^+$, 360 (12), 266 (100), 208 (34).

4.1.1.10. *N*-Benzyl-*N*-(1-(5-iodo-1*H*-indol-3-yl)-3-methylbutyl)-hyd-roxylamine 3be. Compound **3be** (240 mg, 55%) was obtained from nitrone **1b** (191 mg, 1.0 mmol) and 5-iodoindole **2e** (243 mg, 1.0 mmol) as a white solid. IR (neat): 700, 685, 745, 795, 855, 935, 1055, 1110, 1365, 1435, 1455, 2960, 3295 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$–CD_3OD): δ = 0.85 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H), 1.43–1.55 (m, 1H), 1.84–2.06 (m, 2H), 3.57 (d, *J* = 13.4 Hz, 1H), 3.74 (d, *J* = 13.4 Hz, 1H), 4.08 (dd, J_1 = 9.5 Hz, J_2 = 5.3 Hz, 1H), 7.19–7.28 (m, 7H), 7.38–7.41 (m, 1H), 8.04 (d, *J* = 1.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$–CD_3OD): δ = 21.4, 22.9, 24.8, 42.0, 61.1, 62.3, 81.8, 113.0, 124.1, 126.4, 127.5 (2 C), 128.3, 128.9 (2 C), 129.2, 135.0, 138.4 (2 C). MS (ES^+): *m/z* (%) = 457 (6) $[M+Na]^+$, 435 (1) $[M+H]^+$, 312 (100), 256 (17).

4.1.1.11. *tert*-Butyl 2-(benzyl(hydroxy)amino)-2-(1*H*-indol-3-yl)-ethylcarbamate 3ca. Compound **3ca** (343 mg, 90%) was obtained from nitrone **1c** (264 mg, 1.0 mmol) and indole **2a** (117 mg, 1.0 mmol) as a white solid.[12a]

4.1.1.12. *tert*-Butyl 2-(benzyl(hydroxy)amino)-2-(5-fluoro-1*H*-indol-3-yl)ethylcarbamate 3cb. Compound **3cb** (390 mg, 98%) was obtained from nitrone **1c** (264 mg, 1.0 mmol) and 5-fluoroindole **2b** (135 mg, 1.0 mmol) as a white solid. IR (neat): 695, 745, 845, 935, 1165, 1290, 1455, 1490, 1540, 1655, 2890, 2975, 3300, 3410 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD): δ = 1.43 (s, 9H), 3.49–3.81 (m, 4H), 4.13 (t, *J* = 5.4 Hz, 1H), 6.90 (dt, J_1 = 9.1 Hz, J_2 = 2.4 Hz, 1H), 7.20–7.40 (m, 8H). ^{13}C NMR (75 MHz, CD_3OD): δ = 28.8 (3C), 44.2, 60.9, 62.4, 78.2, 103.2 (d, *J* = 24.8 Hz), 110.6 (d, *J* = 26.4 Hz), 113.0 (d, *J* = 9.4 Hz), 124.3, 127.3, 127.8, 129.0 (2 C), 130.2 (2 C), 132.9, 136.7, 140.3, 156.7, 159.3 (d, *J* = 236.1 Hz). ^{19}F NMR (282 MHz, CD_3OD): δ = −124.2 (dt, J_1 = 9.8 Hz, J_2 = 4.8 Hz, 1F). MS (ES^+): *m/z* (%) = 422 (21) $[M+Na]^+$, 400 (97) $[M+H]^+$, 277 (17), 221 (100), 177 (20).

4.1.1.13. *tert*-Butyl 2-(benzyl(hydroxy)amino)-2-(5-chloro-1*H*-indol-3-yl)ethylcarbamate 3cc. Compound **3cc** (360 mg, 87%) was obtained from nitrone **1c** (264 mg, 1.0 mmol) and 5-chloroindole **2c** (152 mg, 1.0 mmol) as a white solid. IR (neat): 695, 735, 790, 895, 910, 1165, 1295, 1520, 1655, 2970, 3315 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$–CD_3OD): δ = 1.48 (s, 9H), 3.58–3.63 (m, 2H), 3.60 (d, *J* = 13.7 Hz, 1H), 3.81 (d, *J* = 13.7 Hz, 1H), 4.07 (t, *J* = 5.4 Hz, 1H), 5.37 (t, *J* = 6.2 Hz, 1H), 7.11 (dd, J_1 = 8.6 Hz, J_2 = 2.0 Hz, 1H), 7.20–7.37 (m, 8H), 7.68 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$–CD_3OD): δ = 29.8 (3C), 45.3, 59.0, 63.7, 81.3, 113.9 (2 C), 120.7, 123.5 (2 C), 126.4 (2 C), 126.8, 128.4, 129.5 (2 C), 130.3, 136.4, 139.7, 158.0. MS (ES^+): *m/z* (%) = 438 (22) $[M+Na]^+$, 416 (100) $[M+H]^+$, 293 (18), 237 (89), 193 (16).

4.1.1.14. *tert*-Butyl 2-(benzyl(hydroxy)amino)-2-(5-bromo-1*H*-indol-3-yl)ethylcarbamate 3cd. Compound **3cd** (385 mg, 84%) was obtained from nitrone **1c** (264 mg, 1.0 mmol) and 5-bromoindole **2d** (196 mg, 1.0 mmol) as a white solid.[14a]

4.1.1.15. *tert*-Butyl 2-(benzyl(hydroxy)amino)-2-(5-iodo-1*H*-indol-3-yl)ethylcarbamate 3ce. Compound **3ce** (420 mg, 83%) was obtained from nitrone **1c** (264 mg, 1.0 mmol) and 5-iodoindole **2e** (243 mg, 1.0 mmol) as a white solid. IR (neat): 695, 740, 790, 880, 910, 1165, 1295, 1365, 1390, 1455, 1525, 1660, 2960, 3315 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$–CD_3OD): δ = 1.48 (s, 9H), 3.57–3.61 (m, 2H), 3.59 (d, *J* = 14.0 Hz, 1H), 3.83 (d, *J* = 14.0 Hz, 1H), 4.07 (t, *J* = 5.8 Hz, 1H), 5.47 (br s, 1H), 7.18–7.30 (m, 7H), 7.41 (dd, J_1 = 8.5 Hz, J_2 = 1.6 Hz, 1H), 8.03 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$–CD_3OD): δ = 29.9 (3C), 44.3, 59.1, 63.6, 84.2, 97.8, 115.1 (2 C), 123.7, 124.5, 126.4, 126.8, 128.2, 129.6 (2 C), 130.4, 131.5, 132.4, 134.9, 138.2, 157.5. MS (ES^+): *m/z* (%) = 530 (33) $[M+Na]^+$, 508 (100) $[M+H]^+$, 329 (63).

4.1.1.16. *tert*-Butyl 2-(benzyl(hydroxy)amino)-2-(6-fluoro-1*H*-indol-3-yl)ethylcarbamate 3cf. Compound **3cf** (340 mg, 85%) was obtained from nitrone **1c** (264 mg, 1.0 mmol) and 6-fluoroindole **2f** (135 mg, 1.0 mmol) as a white solid. IR (neat): 695, 735, 800, 830, 910, 1095, 1140, 1165, 1290, 1520, 1625, 1655, 2875, 2975, 3365, 3410 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (s, 9H), 3.54–3.63 (m, 2H), 3.62 (d, *J* = 14.0 Hz, 1H), 3.83 (d, *J* = 14.0 Hz, 1H), 4.08 (t, *J* = 5.7 Hz, 1H), 4.92 (t, *J* = 6.8 Hz, 1H), 6.50 (br s, 1H), 6.88 (dt, J_1 = 9.4 Hz, J_2 = 2.3 Hz, 1H), 7.02 (dd, J_1 = 9.6 Hz, J_2 = 2.0 Hz, 1H), 7.18–7.27 (m, 6H), 7.56 (dd, J_1 = 8.7 Hz, J_2 = 5.3 Hz, 1H), 8.42 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.7 (3C), 44.0, 60.9, 64.0, 80.1, 97.7 (d, *J* = 26.2 Hz), 108.7 (d, *J* = 24.4 Hz), 120.7 (d, *J* = 10.4 Hz), 123.9, 124.0, 127.1,

128.3 (2 C), 128.8 (2 C), 132.3, 136.3, 138.9, 158.7, 160.3 (d, J = 238.1 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −125.0 (dt, J_1 = 9.6 Hz, J_2 = 4.7 Hz, 1F). MS (ES^+): m/z (%) = 422 (58) $[M+Na]^+$, 400 (94) $[M+H]^+$, 277 (20), 221 (100), 173 (12).

4.1.1.17. *tert*-Butyl 2-(benzyl(hydroxy)amino)-2-(6-chloro-1*H*-indol-3-yl)ethylcarbamate 3cg. Compound **3cg** (340 mg, 82%) was obtained from nitrone **1c** (264 mg, 1.0 mmol) and 6-chloroindole **2g** (152 mg, 1.0 mmol) as a white solid. IR (neat): 695, 735, 800, 905, 1105, 1160, 1290, 1365, 1455, 1520, 1655, 2850, 2975, 3360, 3405 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (s, 9H), 3.54–3.63 (m, 2H), 3.62 (d, J = 14.0 Hz, 1H), 3.80 (d, J = 14.0 Hz, 1H), 4.07 (t, J = 5.6 Hz, 1H), 4.92 (t, J = 6.2 Hz, 1H), 6.52 (br s, 1H), 7.08 (dd, J_1 = 8.5 Hz, J_2 = 1.7 Hz, 1H), 7.18–7.26 (m, 6H), 7.33 (d, J = 1.4 Hz, 1H), 7.55 (d, J = 8.6 Hz, 1H), 8.45 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.5 (3C), 43.7, 60.6, 64.7, 79.9, 111.2 (2 C), 120.4 (2 C), 120.5, 124.2, 125.7, 126.8, 128.1 (2 C), 128.6, 136.3, 138.7, 157.7. MS (ES^+): m/z (%) = 438 (17) $[M+Na]^+$, 416 (97) $[M+H]^+$, 293 (17), 237 (100), 193 (9).

4.1.1.18. *tert*-Butyl 2-(benzyl(hydroxy)amino)-2-(6-bromo-1*H*-indol-3-yl)ethylcarbamate 3ch. Compound **3ch** (400 mg, 87%) was obtained from nitrone **1c** (264 mg, 1.0 mmol) and 6-bromoindole **2h** (196 mg, 1.0 mmol) as a white solid.[14a]

4.1.1.19. *tert*-Butyl 2-(benzyl(hydroxy)amino)-2-(4-bromo-1*H*-indol-3-yl)ethylcarbamate 3ci. Compound **3ci** (370 mg, 80%) was obtained from nitrone **1c** (264 mg, 1.0 mmol) and 4-bromoindole **2i** (196 mg, 1.0 mmol) as a white solid. IR (neat): 695, 730, 910, 1120, 1165, 1290, 1330, 1455, 1560, 1655, 2830, 2980, 3290, 3375 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD): δ = 1.43 (s, 9H), 3.51–3.69 (m, 2H), 3.69 (d, J = 14.3 Hz, 1H), 3.88 (d, J = 14.3 Hz, 1H), 5.29 (t, J = 6.0 Hz, 1H), 7.00 (t, J = 7.8 Hz, 1H), 7.19–7.31 (m, 6H), 7.42 (d, J = 8.1 Hz, 1H), 7.60 (s, 1H). ^{13}C NMR (75 MHz, CD_3OD): δ = 28.9 (3C), 42.7, 62.2, 64.1, 80.2, 112.1, 114.3, 123.0, 125.1, 125.7, 126.6, 126.9, 127.3, 129.0 (2 C), 130.0, 132.8, 135.8, 138.9, 156.4. MS (ES^+): m/z (%) = 482 (26) $[M+Na]^+$, 460 (100) $[M+H]^+$, 281 (37).

4.1.2. General procedure for the synthesis of indolic nitrones 4aa–ci

A stirred solution of indolic *N*-hydroxylamine **3aa–ci** in toluene was warmed to 100 °C. Five equiv. of manganese dioxide were then added. The resulting heterogeneous mixture was then stirred at 100 °C during 5 min. It was then cooled and filtered on celite. Resulted solution was concentrated under vacuum. The crude extract was purified by column chromatography on silica gel (treated by 2.5% of trietylamine) using EtOAc–pentane (5/95—90/10) yielded pure products.

4.1.2.1. (*Z*)-*N*-Benzylidene-1-(1*H*-indol-3-yl)ethanamine oxide 4aa. Compound **4aa** (250 mg, 53%) was obtained from *N*-hydroxylamine **3aa** (479 mg, 1.80 mmol) and MnO_2 (783 mg, 9.00 mmol) as a beige foam. IR (neat): 685, 730, 750, 825, 1040, 1120, 1135, 1290, 1435, 1455, 1580, 3175 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.96 (d, J = 6.4 Hz, 3H), 5.46 (q, J = 6.4 Hz, 1H), 7.03–7.15 (m, 3H), 7.26–7.35 (m, 4H), 7.52 (s, 1H), 7.59 (d, J = 7.8 Hz, 1H), 8.17–8.21 (m, 2H), 9.28 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 69.1, 111.8, 112.7, 118.5, 120.0, 122.3, 124.3, 125.9, 128.4 (2 C), 128.8 (2 C), 130.3, 130.5, 132.6, 136.5. MS (ES^+): m/z (%) = 287 (21) $[M+Na]^+$, 265 (3) $[M+H]^+$, 144 (100).

4.1.2.2. (*Z*)-*N*-Benzylidene-1-(5-fluoro-1*H*-indol-3-yl)ethanamine oxide 4ab. Compound **4ab** (210 mg, 50%) was obtained from *N*-hydroxylamine **3ab** (426 mg, 1.50 mmol) and MnO_2 (653 mg, 7.50 mmol) as a beige foam. IR (neat): 690, 755, 800, 930, 1115, 1175, 1285, 1445, 1490, 1580, 1630, 2870, 2905, 3185 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.91 (d, J = 6.8 Hz, 3H), 5.38 (q, J = 6.8 Hz, 1H), 6.78 (dt, J_1 = 9.0 Hz, J_2 = 2.3 Hz, 1H), 7.03–7.07 (m, 2H), 7.19 (dd, J_1 = 9.6 Hz, J_2 = 2.3 Hz, 1H), 7.33–7.35 (m, 3H), 7.59 (s, 1H), 8.20–8.23 (m, 2H), 9.63 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.9, 68.9, 103.2 (d, J = 23.8 Hz), 110.5 (d, J = 26.2 Hz), 112.4 (d, J = 4.7 Hz), 112.5 (d, J = 9.8 Hz), 126.0 (d, J = 9.8 Hz), 126.1, 128.5 (2 C), 128.9 (2 C), 130.1, 130.6, 133.0, 133.3, 157.9 (d, J = 235.2 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −123.4 (dt, J_1 = 9.4 Hz, J_2 = 4.4 Hz, 1F). MS (ES^+): m/z (%) = 305 (100) $[M+Na]^+$, 283 $[M+H]^+$, 216 (34), 162 (45).

4.1.2.3. (*Z*)-*N*-Benzylidene-1-(5-chloro-1*H*-indol-3-yl)ethanamine oxide 4ac. Compound **4ac** (230 mg, 51%) was obtained from *N*-hydroxylamine **3ac** (451 mg, 1.50 mmol) and MnO_2 (653 mg, 7.50 mmol) as a beige foam. IR (neat): 690, 750, 795, 890, 1030, 1110, 1230, 1290, 1370, 1450, 1520, 2880, 3130 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.90 (d, J = 6.8 Hz, 3H), 5.37 (q, J = 6.8 Hz, 1H), 6.95–7.07 (m, 3H), 7.33–7.36 (m, 3H), 7.51 (d, J = 1.6 Hz, 1H), 7.60 (s, 1H), 8.20–8.23 (m, 2H), 9.77 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.0, 68.7, 111.9, 112.9, 117.7, 122.4, 125.5, 125.9, 126.8, 128.5 (2 C), 128.9 (2 C), 130.1, 130.7, 133.4, 134.8. MS (ES^+): m/z (%) = 321 (100) $[M+Na]^+$, 299 (17) $[M+H]^+$, 216 (13), 178 (54).

4.1.2.4. (*Z*)-*N*-Benzylidene-1-(5-bromo-1*H*-indol-3-yl)ethanamine oxide 4ad. Compound **4ad** (140 mg, 45%) was obtained from *N*-hydroxylamine **3ad** (311 mg, 0.90 mmol) and MnO_2 (392 mg, 4.50 mmol) as a beige foam. IR (neat): 690, 750, 795, 1030, 1110, 1230, 1285, 1445, 2870, 3150 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.93 (d, J = 6.8 Hz, 3H), 5.40 (q, J = 6.8 Hz, 1H), 6.98 (d, J = 8.6 Hz, 1H), 7.06–7.14 (m, 2H), 7.36–7.39 (m, 3H), 7.61 (s, 1H), 7.68 (d, J = 1.7 Hz, 1H), 8.22–8.25 (m, 2H), 9.45 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 68.7, 112.1, 113.2, 113.3, 120.8, 125.1, 125.7, 127.5, 128.5 (2 C), 128.9 (2 C), 130.2, 130.7, 133.2, 135.1. MS (ES^+): m/z (%) = 365 (100) $[M+Na]^+$, 343 (38) $[M]^+$, 222 (98).

4.1.2.5. (*Z*)-*N*-Benzylidene-1-(5-iodo-1*H*-indol-3-yl)ethanamine oxide 4ae. Compound **4ae** (180 mg, 51%) was obtained from *N*-hydroxylamine **3ae** (353 mg, 0.90 mmol) and MnO_2 (392 mg, 4.50 mmol) as a beige foam. IR (neat): 690, 750, 795, 880, 1030, 1110, 1230, 1285, 1320, 1370, 1445, 2840, 3120 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.91 (d, J = 6.8 Hz, 3H), 5.38 (q, J = 6.8 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 6.98 (d, J = 2.4 Hz, 1H), 7.26 (dd, J_1 = 8.6 Hz, J_2 = 1.5 Hz, 1H), 7.36–7.38 (m, 3H), 7.60 (s, 1H), 7.88 (d, J = 1.0 Hz, 1H), 8.21–8.24 (m, 2H), 9.58 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 68.6, 83.6, 111.6, 113.8, 125.4, 127.0, 128.3, 128.5 (2 C), 128.9 (2 C), 130.1, 130.4, 130.7, 133.3, 135.5. MS (ES^+): m/z (%) = 413 (86) $[M+Na]^+$, 391 (25) $[M+H]^+$, 324 (21), 267 (100).

4.1.2.6. (*Z*)-*N*-Benzylidene-1-(1*H*-indol-3-yl)-3-methylbutane-1-amine oxide 4ba. Compound **4ba** (325 mg, 59%) was obtained from *N*-hydroxylamine **3ba** (554 mg, 1.80 mmol) and MnO_2 (783 mg, 9.00 mmol) as a orange foam. IR (neat): 690, 740, 925, 1010, 1105, 1220, 1295, 1340, 1450, 1580, 2865, 2955, 3055, 3210, 3405 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95 (d, J = 6.6 Hz, 3H), 0.99 (d, J = 6.6 Hz, 3H), 1.61–1.75 (m, 1H), 1.96–2.06 (m, 1H), 2.45–2.55 (m, 1H), 5.40 (t, J = 7.5 Hz, 1H), 7.04–7.09 (m, 3H), 7.19–7.23 (m, 1H), 7.33–7.35 (m, 3H), 7.62 (s, 1H), 7.63–7.67 (m, 1H), 8.21–8.24 (m, 2H), 9.23 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.4, 22.6, 25.2, 41.6, 71.9, 111.7, 111.8, 118.2, 119.8, 122.0, 124.6, 126.1, 128.4 (2 C), 128.7 (2 C), 130.2, 130.5, 133.2, 136.3. MS (ES^+): m/z (%) = 329 (81) $[M+Na]^+$, 307 (100) $[M+H]^+$.

4.1.2.7. (*Z*)-*N*-Benzylidene-1-(5-fluoro-1*H*-indol-3-yl)-3-methylbutane-1-amine oxide 4bb. Compound **4bb** (200 mg, 44%) was obtained from *N*-hydroxylamine **3bb** (456 mg, 1.40 mmol) and MnO_2 (609 mg, 7.00 mmol) as a beige foam. IR (neat): 690, 750, 795, 940, 1120, 1175, 1455, 1490, 1580, 2955, 3185 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.97 (d, J = 6.6 Hz, 3H), 1.01 (d, J = 6.6 Hz, 3H), 1.62–1.73 (m, 1H), 1.93–2.04 (m, 1H), 2.44–2.54 (m, 1H), 5.31 (dd, J_1 = 8.5 Hz, J_2 = 6.4 Hz, 1H), 6.73 (dt, J_1 = 9.1 Hz, J_2 = 2.4 Hz, 1H), 6.94 (dd, J_1 = 8.8 Hz, J_2 = 4.5 Hz, 1H), 7.10 (d, J = 2.6 Hz, 1H), 7.25 (dd, J_1 = 9.3 Hz, J_2 = 2.4 Hz, 1H), 7.36–7.40 (m, 3H), 7.68 (s, 1H), 8.26–8.29 (m, 2H), 9.32 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.3, 22.7, 25.1, 41.2, 71.7, 102.9 (d, J = 23.8 Hz), 110.3 (d, J = 26.3 Hz), 111.7 (d, J = 4.8 Hz), 112.4 (d, J = 9.8 Hz), 126.2 (d, J = 9.8 Hz), 126.5, 128.5 (2 C), 128.8 (2 C), 130.3, 130.5, 132.8, 133.6, 157.9 (d, J = 234.8 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −123.9 (dt, J_1 = 9.5 Hz, J_2 = 4.5 Hz, 1F). MS (ES^+): *m/z* (%) = 347 (100) $[M+Na]^+$, 325 (10) $[M+H]^+$, 258 (28), 204 (68), 148 (57).

4.1.2.8. (*Z*)-*N*-Benzylidene-1-(5-chloro-1*H*-indol-3-yl)-3-methylbutane-1-amine oxide 4bc. Compound **4bc** (240 mg, 50%) was obtained from *N*-hydroxylamine **3bc** (480 mg, 1.40 mmol) and MnO_2 (609 mg, 7.00 mmol) as a beige foam. IR (neat): 690, 750, 795, 890, 1110, 1130, 1215, 1450, 2870, 2955, 3170 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.96 (d, J = 6.6 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H), 1.59–1.75 (m, 1H), 1.90–1.99 (m, 1H), 2.43–2.52 (m, 1H), 5.33 (dd, J_1 = 8.6 Hz, J_2 = 6.3 Hz, 1H), 6.86–6.94 (m, 2H), 7.02 (d, J = 2.6 Hz, 1H), 7.37–7.40 (m, 3H), 7.56 (d, J = 1.7 Hz, 1H), 7.70 (s, 1H), 8.26–8.30 (m, 2H), 9.52 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2, 22.7, 25.1, 41.2, 71.5, 111.1, 112.8, 117.4, 122.1, 125.4, 126.3, 127.0, 128.6 (2 C), 128.9 (2 C), 130.2, 130.6, 133.8, 134.6. MS (ES^+): *m/z* (%) = 363 (78) $[M+Na]^+$, 341 (29) $[M+H]^+$, 220 (100), 164 (72).

4.1.2.9. (*Z*)-*N*-Benzylidene-1-(5-bromo-1*H*-indol-3-yl)-3-methylbutane-1-amine oxide 4bd. Compound **4bd** (130 mg, 52%) was obtained from *N*-hydroxylamine **3bd** (252 mg, 0.65 mmol) and MnO_2 (283 mg, 3.25 mmol) as a beige foam. IR (neat): 690, 750, 795, 885, 1110, 1130, 1215, 1450, 2870, 2955, 3165 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.96 (d, J = 6.6 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H), 1.59–1.72 (m, 1H), 1.89–1.98 (m, 1H), 2.42–2.52 (m, 1H), 5.32 (dd, J_1 = 8.5 Hz, J_2 = 6.2 Hz, 1H), 6.80 (d, J = 8.7 Hz, 1H), 6.98–7.05 (m, 2H), 7.38–7.40 (m, 3H), 7.70 (d, J = 1.5 Hz, 1H), 7.71 (s, 1H), 8.27–8.30 (m, 2H), 9.59 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2, 22.8, 25.1, 41.2, 71.4, 110.9, 113.0, 113.3, 120.4, 124.6, 126.1, 127.6, 128.6 (2 C), 128.9 (2 C), 130.2, 130.6, 133.9, 134.8. MS (ES^+): *m/z* (%) = 407 (84) $[M+Na]^+$, 385 (21) $[M+H]^+$, 266 (100), 208 (39).

4.1.2.10. (*Z*)-*N*-Benzylidene-1-(5-iodo-1*H*-indol-3-yl)-3-methylbutane-1-amine oxide 4be. Compound **4be** (150 mg, 50%) was obtained from *N*-hydroxylamine **3be** (304 mg, 0.70 mmol) and MnO_2 (305 mg, 3.50 mmol) as a beige foam. IR (neat): 690, 750, 795, 880, 1110, 1135, 1320, 1450, 2870, 2955, 3195 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.97 (d, J = 6.6 Hz, 3H), 1.01 (d, J = 6.6 Hz, 3H), 1.60–1.73 (m, 1H), 1.89–1.98 (m, 1H), 2.43–2.52 (m, 1H), 5.32 (dd, J_1 = 8.6 Hz, J_2 = 6.1 Hz, 1H), 6.71 (d, J = 8.5 Hz, 1H), 7.01 (d, J = 2.5 Hz, 1H), 7.20 (dd, J_1 = 8.6 Hz, J_2 = 1.6 Hz, 1H), 7.38–7.41 (m, 3H), 7.70 (s, 1H), 7.90 (d, J = 1.5 Hz, 1H), 8.27–8.31 (m, 2H), 9.41 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.3, 22.8, 25.1, 41.3, 71.3, 83.5, 110.8, 113.8, 125.7, 126.6, 128.5, 128.6 (2 C), 128.9 (2 C), 130.2, 130.3, 130.6, 133.8, 135.2. MS (ES^+): *m/z* (%) = 455 (58) $[M+Na]^+$, 433 (13) $[M+H]^+$, 312 (100).

4.1.2.11. (*Z*)-*N*-Benzylidene-2-(*tert*-butoxycarbonylamino)-1-(1*H*-indol-3-yl)ethanamine oxide 4ca. Compound **4ca** (560 mg, 78%) was obtained from N-hydroxylamine 3ca (724 mg, 1.90 mmol) and MnO2 (827 mg, 9.50 mmol) as a beige foam.14a

4.1.2.12. (*Z*)-*N*-Benzylidene-2-(*tert*-butoxycarbonylamino)-1-(5-fluoro-1*H*-indol-3-yl)ethanamine oxide 4cb. Compound **4cb** (210 mg, 66%) was obtained from *N*-hydroxylamine **3cb** (320 mg, 0.80 mmol) and MnO_2 (348 mg, 4.00 mmol) as a beige foam. IR (neat): 670, 695, 785, 940, 1130, 1150, 1175, 1240, 1370, 1455, 1505, 1685, 2970, 3060, 3295, 3465 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 9H), 3.78-3.87 (m, 1H), 3.98–4.07 (m, 1H), 5.22–5.29 (m, 1H), 5.52–5.57 (m, 1H), 6.88 (dt, J_1 = 9.1 Hz, J_2 = 2.5 Hz, 1H), 7.18 (dd, J_1 = 9.0 Hz, J_2 = 4.4 Hz, 1H), 7.34–7.42 (m, 5H), 8.22–8.25 (m, 2H), 8.86 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$–CD_3OD): δ = 27.9 (3C), 42.2, 71.4, 79.6, 103.0 (d, J = 23.1 Hz), 110.2 (d, J = 26.3 Hz), 112.1 (d, J = 9.6 Hz), 125.7, 128.2 (2 C), 128.9 (2 C), 129.6, 130.8, 132.4, 136.2, 156.7, 157.7 (d, J = 234.7 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −123.3 (dt, J_1 = 9.3 Hz, J_2 = 4.3 Hz, 1F). MS (ES^+): *m/z* (%) = 420 (47) $[M+Na]^+$, 398 (28) $[M+H]^+$, 277 (15), 221 (100), 177 (15).

4.1.2.13. (*Z*)-*N*-Benzylidene-2-(*tert*-butoxycarbonylamino)-1-(5-chloro-1*H*-indol-3-yl)ethanamine oxide 4cc. Compound **4cc** (190 mg, 66%) was obtained from *N*-hydroxylamine **3cc** (290 mg, 0.70 mmol) and MnO_2 (305 mg, 3.50 mmol) as a beige foam. IR (neat): 690, 750, 795, 895, 1130, 1160, 1250, 1365, 1450, 1505, 1695, 2980, 3265 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9H), 3.71–3.76 (m, 1H), 3.95–4.03 (m, 1H), 5.39–5.55 (m, 2H), 6.90–6.98 (m, 2H), 7.02–7.10 (m, 1H), 7.30–7.39 (m, 3H), 7.59–7.62 (m, 2H), 8.20–8.24 (m, 2H), 9.70 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.2 (3C), 42.7, 71.5, 79.8, 108.9, 112.7, 117.8, 122.4, 125.6, 125.7, 126.9, 128.5 (2 C), 128.9 (2 C), 129.9, 130.8, 134.4, 135.3, 156.2. MS (ES^+): *m/z* (%) = 436 (40) $[M+Na]^+$, 414 (34) $[M+H]^+$, 293 (12), 237 (100), 193 (12).

4.1.2.14. (*Z*)-*N*-Benzylidene-2-(*tert*-butoxycarbonylamino)-1-(5-bromo-1*H*-indol-3-yl)ethanamine oxide 4cd. Compound **4cd** (365 mg, 64%) was obtained from *N*-hydroxylamine **3cd** (575 mg, 1.25 mmol) and MnO_2 (544 mg, 6.25 mmol) as a beige foam.[14a]

4.1.2.15. (*Z*)-*N*-benzylidene-2-(*tert*-butoxycarbonylamino)-1-(5-iodo-1*H*-indol-3-yl)ethanamine oxide 4ce. Compound **4ce** (240 mg, 68%) was obtained from *N*-hydroxylamine **3ce** (355 mg, 0.70 mmol) and MnO_2 (305 mg, 3.50 mmol) as a beige foam. IR (neat): 690, 750, 795, 880, 1160, 1250, 1365, 1450, 1505, 1695, 2930, 2970, 3275 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9H), 3.71–3.81 (m, 1H), 3.94–4.05 (m, 1H), 5.29–5.40 (m, 1H), 5.48–5.55 (m, 1H), 6.87 (d, J = 9.5 Hz, 1H), 7.10 (d, J = 2.3 Hz, 1H), 7.28 (dd, J_1 = 8.6 Hz, J_2 = 1.4 Hz, 1H), 7.36–7.41 (m, 3H), 7.61 (s, 1H), 7.97 (s, 1H), 8.21–8.25 (m, 2H), 9.50 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3 (3C), 42.8, 71.3, 80.0, 83.7, 108.7, 113.6, 125.1, 127.1, 128.4, 128.6 (2 C), 128.9 (2 C), 130.0, 130.6, 130.8, 135.1, 135.3, 156.2. MS (ES^+): *m/z* (%) = 528 (100) $[M+Na]^+$, 506 (40) $[M+H]^+$, 439 (6), 329 (86).

4.1.2.16. (*Z*)-*N*-Benzylidene-2-(*tert*-butoxycarbonylamino)-1-(6-fluoro-1*H*-indol-3-yl)ethanamine oxide 4cf. Compound **4cf** (200 mg, 72%) was obtained from *N*-hydroxylamine **3cf** (280 mg, 0.70 mmol) and MnO_2 (305 mg, 3.50 mmol) as a beige foam. IR (neat): 675, 685, 835, 950, 1135, 1270, 1320, 1455, 1530, 1685, 2910, 2985, 3160, 3370 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 9H), 3.80–3.88 (m, 1H), 3.98–4.07 (m, 1H), 5.22–5.29 (m, 1H), 5.56–5.60 (m, 1H), 6.87 (dt, J_1 = 9.4 Hz, J_2 = 2.3 Hz, 1H), 6.95 (dd, J_1 = 9.4 Hz, J_2 = 2.1 Hz, 1H), 7.28 (dd, J = 2.3 Hz, 1H), 7.39–7.42 (m, 3H), 7.57 (s, 1H), 7.62–7.67 (m, 1H), 8.21–8.25 (m, 2H), 8.80 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$–CD_3OD): δ = 27.6 (3C), 42.0, 71.4, 79.3, 97.3 (d, J = 23.8 Hz), 108.0 (d, J = 25.0 Hz), 108.7, 118.7

(d, J = 8.7 Hz), 122.3, 124.2 (d, J = 3.4 Hz), 128.1 (2 C), 128.9 (2 C), 129.5, 130.6, 135.9 (d, J = 12.6 Hz), 136.4, 156.6, 159.5 (d, J = 237.2 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −120.4 (m, 1F). MS (ES^+): m/z (%) = 420 (100) $[M+Na]^+$, 398 (12) $[M+H]^+$, 331 (8), 277 (6), 221 (36), 177 (5).

4.1.2.17. (*Z*)-*N*-Benzylidene-2-(*tert*-butoxycarbonylamino)-1-(6-chloro-1*H*-indol-3-yl)ethanamine oxide 4cg. Compound **4cg** (205 mg, 71%) was obtained from *N*-hydroxylamine **3cg** (290 mg, 0.70 mmol) and MnO_2 (305 mg, 3.50 mmol) as a beige foam. IR (neat): 690, 750, 800, 905, 1130, 1160, 1250, 1365, 1450, 1505, 1685, 2970, 3275 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9H), 3.67–3.80 (m, 1H), 3.94–4.06 (m, 1H), 5.43–5.58 (m, 2H), 6.93–7.07 (m, 3H), 7.33–7.38 (m, 3H), 7.48–7.53 (m, 1H), 7.61 (s, 1H), 8.20–8.24 (m, 2H), 9.65 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.2 (3C), 42.6, 71.7, 79.8, 109.3, 111.6, 119.2, 120.5, 124.4, 124.9, 127.9, 128.5 (2 C), 128.9 (2 C), 129.9, 130.8, 135.4, 136.4, 156.3. MS (ES^+): m/z (%) = 436 (81) $[M+Na]^+$, 414 (33) $[M+H]^+$, 293 (16), 237 (100), 193 (14).

4.1.2.18. (*Z*)-*N*-Benzylidene-2-(*tert*-butoxycarbonylamino)-1-(6-bromo-1*H*-indol-3-yl)ethanamine oxide 4ch. Compound **4ch** (430 mg, 72%) was obtained from *N*-hydroxylamine **3ch** (598 mg, 1.30 mmol) and MnO_2 (566 mg, 6.50 mmol) as a beige foam.[14a]

4.1.2.19. (*Z*)-*N*-Benzylidene-2-(*tert*-butoxycarbonylamino)-1-(4-bromo-1*H*-indol-3-yl)ethanamine oxide 4ci. Compound **4ci** (155 mg, 52%) was obtained from *N*-hydroxylamine **3ci** (299 mg, 0.65 mmol) and MnO_2 (283 mg, 3.25 mmol) as a beige foam. IR (neat): 690, 750, 780, 1125, 1165, 1270, 1365, 1430, 1500, 1525, 1690, 2865, 2975, 3440 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (s, 9H), 3.64–3.84 (m, 1H), 3.89–4.10 (m, 1H), 5.27–5.52 (m, 1H), 6.38–6.55 (m, 1H), 6.65–6.84 (m, 1H), 6.91–7.20 (m, 2H), 7.27–7.53 (m, 4H), 7.85 (s, 1H), 8.17–8.36 (m, 2H), 10.08 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3 (3C), 43.3, 69.6, 79.7, 109.0, 111.1, 112.5, 122.7, 123.8, 124.5, 127.0, 128.5 (2 C), 129.1 (2 C), 130.2, 130.7, 136.2, 137.3, 156.0. MS (ES^+): m/z (%) = 482 (100) $[M+Na]^+$, 458 (63) $[M+H]^+$, 339 (15), 283 (61), 239 (17).

4.1.3. General procedure for the synthesis of indolic *N*-hydroxylamines 5aa–ci

To a stirred solution of indolic nitrone **4aa–ci** in methanol three equiv. of hydroxylamine hydrochloride were added. The resulting mixture was stirred during 1 h at room temperature and then solution was concentrated under vacuum. A saturated aqueous solution of $NaHCO_3$ was added. The mixture was then extracted with Et_2O (3x10 mL), and the collected organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. Column chromatography using EtOAc–pentane (10/90—99/1) yielded pure products.

4.1.3.1. *N*-(1-(1*H*-Indol-3-yl)ethyl)hydroxylamine 5aa. Compound **5aa** (105 mg, 66%) was obtained from nitrone **4aa** (238 mg, 0.90 mmol) and $NH_2OH.HCl$ (188 mg, 2.70 mmol) as a brown foam. IR (neat): 740, 850, 915, 980, 1010, 1095, 1230, 1340, 1365, 1455, 1550, 1620, 2865, 2975, 3055, 3405 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (d, J = 6.6 Hz, 3H), 4.40 (q, J = 6.6 Hz, 1H), 6.83 (d, J = 1.6 Hz, 1H), 7.04–7.21 (m, 3H), 7.63 (d, J = 7.8 Hz, 1H), 8.18 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5, 54.0, 111.3, 116.1, 118.9, 119.5, 122.0, 122.2, 126.2, 136.1. MS (ES^+): m/z (%) = 199 (6) $[M+Na]^+$, 144 (100) $[M+H-NH_2OH]^+$.

4.1.3.2. *N*-(1-(5-Fluoro-1*H*-indol-3-yl)ethyl)hydroxylamine 5ab. Compound **5ab** (75 mg, 60%) was obtained from nitrone **4ab** (183 mg, 0.65 mmol) and $NH_2OH.HCl$ (136 mg, 1.95 mmol) as a brown foam. IR (neat): 795, 850, 935, 1175, 1225, 1455, 1485, 1580, 2850, 2920, 3250, 3415 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (d, J = 6.6 Hz, 3H), 4.25 (q, J = 6.6 Hz, 1H), 6.78 (td, J_1 = 9.1 Hz, J_2 = 2.2 Hz, 1H), 6.93 (s, 1H), 7.03–7.20 (m, 4H), 8.52 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.8, 53.9, 103.9 (d, J = 23.8 Hz), 110.5 (d, J = 26.3 Hz), 112.0 (d, J = 9.7 Hz), 115.4 (d, J = 4.8 Hz), 126.5 (d, J = 9.8 Hz), 132.7, 157.8 (d, J = 234.7 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −124.0 (dt, J_1 = 9.5 Hz, J_2 = 4.4 Hz, 1F). MS (ES^+): m/z (%) = 217 (5) $[M+Na]^+$, 162 $[M+H-NH_2OH]^+$.

4.1.3.3. *N*-(1-(5-Chloro-1*H*-indol-3-yl)ethyl)hydroxylamine 5ac. Compound **5ac** (75 mg, 55%) was obtained from nitrone **4ac** (194 mg, 0.65 mmol) and $NH_2OH.HCl$ (136 mg, 1.95 mmol) as a beige foam. IR (neat): 670, 795, 890, 1105, 1225, 1340, 1370, 1420, 1460, 3260, 3420 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.38 (d, J = 6.6 Hz, 3H), 4.24 (q, J = 6.6 Hz, 1H), 6.58 (br s, 2H), 6.89 (s, 1H), 6.97–7.07 (m, 2H), 7.52 (s, 1H), 8.50 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.0, 53.8, 112.4, 115.4, 118.5, 122.4, 123.8, 125.3, 127.3, 134.5. MS (ES^+): m/z (%) = 233 (6) $[M+Na]^+$, 178 $[M+H-NH_2OH]^+$.

4.1.3.4. *N*-(1-(5-Bromo-1*H*-indol-3-yl)ethyl)hydroxylamine 5ad. Compound **5ad** (110 mg, 62%) was obtained from nitrone **4ad** (240 mg, 0.70 mmol) and $NH_2OH.HCl$ (146 mg, 2.10 mmol) as a beige solid. IR (neat): 795, 865, 885, 1085, 1225, 1245, 1330, 1375, 1435, 1455, 2805, 3120, 3405 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD): δ = 1.50 (d, J = 6.6 Hz, 3H), 4.35 (q, J = 6.6 Hz, 1H), 7.15–7.26 (m, 3H), 7.83 (dd, J_1 = 1.9 Hz, J_2 = 0.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2, 55.3, 113.0, 113.9, 116.8, 122.5, 125.0, 125.2, 129.6, 136.7. MS (ES^+): m/z (%) = 277 (7) $[M+Na]^+$, 224 $[M+H-NH_2OH]^+$.

4.1.3.5. *N*-(1-(5-Iodo-1*H*-indol-3-yl)ethyl)hydroxylamine 5ae. Compound **5ae** (70 mg, 58%) was obtained from nitrone **4ae** (156 mg, 0.40 mmol) and $NH_2OH.HCl$ (83 mg, 1.20 mmol) as a beige foam. IR (neat): 755, 795, 875, 980, 1100, 1225, 1320, 1370, 1450, 3250, 3415 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$–CD_3OD): δ = 1.44 (d, J = 6.6 Hz, 3H), 4.30 (q, J = 6.6 Hz, 1H), 7.03–7.07 (m, 2H), 7.27–7.32 (m, 1H), 7.94 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5, 54.1, 82.7, 113.6, 115.1, 123.4, 127.8, 129.0, 130.1, 135.6. MS (ES^+): m/z (%) = 325 (8) $[M+Na]^+$, 270 $[M+H-NH_2OH]^+$.

4.1.3.6. *N*-(1-(1*H*-Indol-3-yl)-3-methylbutyl)hydroxylamine 5ba. Compound **5ba** (125 mg, 64%) was obtained from nitrone **4ba** (275 mg, 0.90 mmol) and $NH_2OH.HCl$ (188 mg, 2.70 mmol) as a orange foam. IR (neat): 740, 1010, 1045, 1095, 1230, 1340, 1455, 2865, 2955, 3410 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H), 1.43–1.56 (m, 1H), 1.73–1.89 (m, 2H), 4.35 (dd, J_1 = 8.9 Hz, J_2 = 5.8 Hz, 1H), 6.91 (d, J = 1.9 Hz, 1H), 7.06–7.28 (m, 3H), 7.67 (d, J = 7.7 Hz, 1H), 8.23 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1, 23.5, 25.2, 41.6, 57.6, 111.3, 115.1, 119.1, 119.5, 122.0, 122.9, 126.6, 136.2. MS (ES^+): m/z (%) = 241 (15) $[M+Na]^+$, 186 (100) $[M+H-NH_2OH]^+$.

4.1.3.7. *N*-(1-(5-Fluoro-1*H*-indol-3-yl)-3-methylbutyl)hydroxylamine 5bb. Compound **5bb** (60 mg, 46%) was obtained from nitrone **4bb** (178 mg, 0.55 mmol) and $NH_2OH.HCl$ (115 mg, 1.65 mmol) as a yellow foam. IR (neat): 795, 935, 1095, 1175, 1365, 1455, 1485, 1580, 1630, 2890, 2955, 3270, 3420 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.78 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 6.8 Hz, 3H), 1.35–1.48 (m, 1H), 1.60–1.76 (m, 2H), 4.17 (dd, J_1 = 8.7 Hz, J_2 = 6.0 Hz, 1H), 5.30 (br s, 2H), 6.82 (td, J_1 = 9.1 Hz, J_2 = 2.5 Hz, 1H), 6.97 (s, 1H), 7.12 (dd, J_1 = 8.8 Hz, J_2 = 4.4 Hz, 1H), 7.25 (dd, J_1 = 9.8 Hz, J_2 = 2.4 Hz, 1H), 8.24 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.2, 23.4, 25.2, 41.4, 57.6, 104.2 (d, J = 23.7 Hz), 110.5 (d, J = 26.4 Hz), 111.9 (d, J = 9.7 Hz), 115.7,

124.6, 127.0 (d, J = 9.8 Hz), 132.8, 157.7 (d, J = 234.6 Hz). MS (ES^+): m/z (%) = 259 (11) $[M+Na]^+$, 204 (100) $[M+H-NH_2OH]^+$.

4.1.3.8. *N*-(1-(5-Chloro-1*H*-indol-3-yl)-3-methylbutyl)hydroxylamine 5bc. Compound **5bc** (65 mg, 41%) was obtained from nitrone **4bc** (215 mg, 0.63 mmol) and $NH_2OH.HCl$ (131 mg, 1.89 mmol) as a yellow foam. IR (neat): 800, 885, 1040, 1070, 1100, 1220, 1330, 1460, 2870, 2915, 2955, 3120, 3265 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$–CD_3OD): δ = 0.78 (d, J = 6.6 Hz, 3H), 0.82 (d, J = 6.6 Hz, 3H), 1.36–1.49 (m, 1H), 1.68–1.74 (m, 2H), 4.20 (dd, J_1 = 8.4 Hz, J_2 = 6.2 Hz, 1H), 6.99–7.07 (m, 2H), 7.16–7.25 (m, 1H), 7.57 (d, J = 1.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$–CD_3OD): δ = 21.8, 23.2, 25.0, 41.2, 57.3, 112.3, 113.9, 118.2, 121.8, 124.4, 124.7, 127.6, 134.6. MS (ES^+): m/z (%) = 275 (10) $[M+Na]^+$, 220 (100) $[M+H-NH_2OH]^+$.

4.1.3.9. *N*-(1-(5-Bromo-1*H*-indol-3-yl)-3-methylbutyl)hydroxylamine 5bd. Compound **5bd** (75 mg, 36%) was obtained from nitrone **4bd** (270 mg, 0.70 mmol) and $NH_2OH.HCl$ (146 mg, 2.10 mmol) as a yellow foam. IR (neat): 755, 795, 880, 1100, 1365, 1455, 2865, 2955, 3265, 3420 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$–CD_3OD): δ = 0.79 (d, J = 6.7 Hz, 3H), 0.82 (d, J = 6.7 Hz, 3H), 1.39–1.48 (m, 1H), 1.67–1.73 (m, 2H), 4.19 (dd, J_1 = 8.7 Hz, J_2 = 6.0 Hz, 1H), 7.03 (s, 1H), 7.13–7.14 (m, 2H), 7.74–7.75 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$–CD_3OD): δ = 21.9, 23.2, 25.0, 41.3, 57.3, 112.3, 112.7, 114.2, 121.3, 124.2, 124.4, 128.3, 134.9. MS (ES^+): m/z (%) = 319 (12) $[M+Na]^+$, 266 (100) $[M+H-NH_2OH]^+$.

4.1.3.10. *N*-(1-(5-Iodo-1*H*-indol-3-yl)-3-methylbutyl)hydroxylamine 5be. Compound **5be** (65 mg, 32%) was obtained from nitrone **4be** (260 mg, 0.60 mmol) and $NH_2OH.HCl$ (125 mg, 1.80 mmol) as a yellow foam. IR (neat): 755, 795, 875, 1100, 1365, 1455, 2865, 2955, 3260, 3415 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (d, J = 6.8 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H), 1.43-1.57 (m, 1H), 1.66–1.82 (m, 2H), 4.25 (dd, J_1 = 8.7 Hz, J_2 = 5.9 Hz, 1H), 6.96 (d, J = 1.9 Hz, 1H), 7.01 (d, J = 8.5 Hz, 1H), 7.40 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1H), 8.04 (d, J = 1.3 Hz, 1H), 8.33 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.3, 23.3, 25.2, 41.5, 57.4, 83.2, 113.3, 115.2, 123.5, 128.2, 129.3, 130.4, 135.4. MS (ES^+): m/z (%) = 367 (10) $[M+Na]^+$, 312 (100) $[M+H-NH_2OH]^+$.

4.1.3.11. *tert*-Butyl 2-(1*H*-indol-3-yl)-2-(hydroxyamino)ethylcarba-mate 5ca. Compound **5ca** (265 mg, 65%) was obtained from nitrone **4ca** (531 mg, 1.40 mmol) and $NH_2OH.HCl$ (292 mg, 4.20 mmol) as a beige foam.[14a]

4.1.3.12. *tert*-Butyl 2-(5-fluoro-1*H*-indol-3-yl)-2-(hydroxyamino)-ethylcarbamate 5cb. Compound **5cb** (80 mg, 58%) was obtained from nitrone **4cb** (179 mg, 0.45 mmol) and $NH_2OH.HCl$ (94 mg, 1.35 mmol) as a beige foam. IR (neat): 795, 850, 935, 1160, 1250, 1365, 1455, 1490, 1510, 1685, 2925, 2975, 3300, 3415 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9H), 3.43–3.50 (m, 1H), 3.55–3.68 (m, 1H), 4.28 (t, J = 5.3 Hz, 1H), 5.04 (br s, 1H), 6.88 (dt, J_1 = 9.0 Hz, J_2 = 2.4 Hz, 1H), 7.07 (s, H), 7.19 (dd, J_1 = 8.8 Hz, J_2 = 4.4 Hz, 1H), 7.21–7.30 (m, 1H), 8.79 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3 (3C), 42.4, 58.7, 79.9, 104.1 (d, J = 23.2 Hz), 110.6 (d, J = 26.5 Hz), 112.0 (d, J = 9.2 Hz), 124.4, 126.6 (d, J = 10.2 Hz), 132.6 (2 C), 157.2, 157.8 (d, J = 236.7 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −124.1 (m, 1F). MS (ES^+): m/z (%) = 332 (49) $[M+Na]^+$, 310 (7) $[M+H]^+$, 239 (44), 221 (100).

4.1.3.13. *tert*-Butyl 2-(5-chloro-1*H*-indol-3-yl)-2-(hydroxyamino)-ethylcarbamate 5cc. Compound **5cc** (80 mg, 62%) was obtained from nitrone **4cc** (165 mg, 0.40 mmol) and $NH_2OH.HCl$ (83 mg, 1.20 mmol) as a beige foam. IR (neat): 795, 860, 895, 1160, 1250, 1365, 1455, 1515, 1685, 2925, 2975, 3290, 3410 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 9H), 3.40–3.45 (m, 1H), 3.56–3.70 (m, 1H), 4.29 (t, J = 5.3 Hz, 1H), 5.03 (br s, 1H), 7.05–7.10 (m, 2H), 7.20 (d, J = 9.0 Hz, 1H), 7.59 (s, 1H), 8.84 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3 (3C), 42.5, 58.7, 79.9, 112.4, 118.7, 122.5, 124.1, 125.3, 127.3, 134.5 (2 C), 157.1. MS (ES^+): m/z (%) = 348 (14) $[M+Na]^+$, 326 (16) $[M+H]^+$, 237 (100), 193 (12).

4.1.3.14. *tert*-Butyl 2-(5-bromo-1*H*-indol-3-yl)-2-(hydroxyamino)-ethylcarbamate 5cd. Compound **5cd** (145 mg, 56%) was obtained from nitrone **4cd** (320 mg, 0.70 mmol) and $NH_2OH.HCl$ (146 mg, 2.10 mmol) as a beige foam.[14a]

4.1.3.15. *tert*-Butyl 2-(5-iodo-1*H*-indol-3-yl)-2-(hydroxyamino)-ethylcarbamate 5ce. Compound **5ce** (125 mg, 75%) was obtained from nitrone **4ce** (202 mg, 0.40 mmol) and $NH_2OH.HCl$ (83 mg, 1.20 mmol) as a beige foam. IR (neat): 750, 795, 1160, 1250, 1365, 1455, 1510, 1685, 2925, 2975, 3280, 3410 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 9H), 3.40–3.49 (m, 1H), 3.50–3.61 (m, 1H), 4.26 (t, J = 5.2 Hz, 1H), 5.08 (br s, 1H), 6.95 (s, 1H), 7.04 (d, J = 8.5 Hz, 1H), 7.35 (dd, J_1 = 8.5 Hz, J_2 = 1.4 Hz, 1H), 7.94 (s, 1H), 8.96 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3 (3C), 42.5, 58.5, 79.9, 83.0, 112.1, 113.4, 123.5, 127.9, 128.8, 130.3, 135.1, 157.0. MS (ES^+): m/z (%) = 440 (18) $[M+Na]^+$, 418 (56) $[M+H]^+$, 376 (100).

4.1.3.16. *tert*-Butyl 2-(6-fluoro-1*H*-indol-3-yl)-2-(hydroxyamino)-ethylcarbamate 5cf. Compound **5cf** (50 mg, 40%) was obtained from nitrone **4cf** (159 mg, 0.40 mmol) and $NH_2OH.HCl$ (83 mg, 1.20 mmol) as a beige foam. IR (neat): 800, 950, 1140, 1160, 1250, 1365, 1455, 1500, 1685, 2920, 2975, 3290, 3415 cm $^{-1}$. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.43 (s, 9H), 3.45–3.51 (m, 1H), 3.60–3.65 (m, 1H), 4.34 (t, J = 5.3 Hz, 1H), 5.02 (br s, 1H), 6.83 (dt, J_1 = 9.6 Hz, J_2 = 2.3 Hz, 1H), 6.97 (dd, J_1 = 9.6 Hz, J_2 = 2.3 Hz, 1H), 7.03 (s, H), 7.49 (dd, J_1 = 8.7 Hz, J_2 = 5.3 Hz, 1H), 8.74 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.4 (3C), 42.4, 58.6, 79.9, 97.6 (d, J = 26.2 Hz), 108.4 (d, J = 24.5 Hz), 122.8, 122.9, 128.8 (d, J = 12.2 Hz), 136.0, 136.1, 158.4, 160.0 (d, J = 238.5 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −120.7 (m, 1F). MS (ES^+): m/z (%) = 332 (43) $[M+Na]^+$, 310 (6) $[M+H]^+$, 239 (100), 221 (75).

4.1.3.17. *tert*-Butyl 2-(6-chloro-1*H*-indol-3-yl)-2-(hydroxyamino)-ethylcarbamate 5cg. Compound **5cg** (100 mg, 77%) was obtained from nitrone **4cg** (165 mg, 0.40 mmol) and $NH_2OH.HCl$ (83 mg, 1.20 mmol) as a beige foam. IR (neat): 800, 905, 1160, 1250, 1365, 1455, 1510, 1685, 2925, 2975, 3280, 3415 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.43 (s, 9H), 3.40–3.62 (m, 2H), 4.30 (t, J = 5.4 Hz, 1H), 5.06 (br s, 1H), 6.98–7.03 (m, 2H), 7.24–7.26 (m, 1H), 7.45 (d, J = 9.0 Hz, 1H), 8.87 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3 (3C), 42.4, 58.5, 79.9, 111.3, 119.8, 120.3, 123.3, 124.8, 128.0, 136.4 (2 C), 157.1. MS (ES^+): m/z (%) = 348 (18) $[M+Na]^+$, 326 (14) $[M+H]^+$, 301 (12), 237 (100), 193 (11).

4.1.3.18. *tert*-Butyl 2-(6-bromo-1*H*-indol-3-yl)-2-(hydroxyamino)-ethylcarbamate 5ch. Compound **5ch** (170 mg, 57%) was obtained from nitrone **4ch** (366 mg, 0.80 mmol) and $NH_2OH.HCl$ (167 mg, 2.40 mmol) as a beige foam.[14a]

4.1.3.19. *tert*-Butyl 2-(4-bromo-1*H*-indol-3-yl)-2-(hydroxyamino)-ethylcarbamate 5ci. Compound **5ci** (75 mg, 68%) was obtained from nitrone **4ci** (137 mg, 0.30 mmol) and $NH_2OH.HCl$ (63 mg, 0.90 mmol) as a beige foam. IR (neat): 735, 775, 1160, 1250, 1335, 1365, 1510, 1685, 2925, 2975, 3275, 3415 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.43 (s, 9H), 3.57–3.75 (m, 2H), 5.06–5.16 (m, 2H), 6.93 (t, J = 7.8 Hz, 1H), 7.18–7.25 (m, 3H), 9.18

(br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.3 (3C), 42.2, 57.2, 79.8, 110.9, 112.9, 113.3, 122.8, 124.2, 124.4, 124.5, 137.5, 157.4. MS (ES^+): *m/z* (%) = 384 (28) $[M+Na]^+$, 372 (14) $[M+H]^+$, 360 (11), 328 (100), 293 (23).

4.1.4. General procedure for the synthesis of indolic *N*-hydroxylamines 6ca–ci

A cold solution of hydrochloric acid was prepared by reaction of ten equiv. (compare to *N*-hydroxylamine quantity) of freshly distilled acetyl chloride with 3 mL of dry methanol. This solution was stirred at 0 °C during 15 min and was then added to a solution of indolic *N*-hydroxylamine **5ca–ci** in 1 mL of dry methanol. The resulting mixture was stirred during 2 h at 0 °C. Methanol was then slowly evaporated under vacuum (t<20 °C). The indolic 1,2-diamine salts **6ca–ci** was obtained as light brown solids.

4.1.4.1. 2-(1*H*-Indol-3-yl)-2-(hydroxyamino)ethanamine dihydro-chloride 6ca. Compound **6ca** (155 mg, 98%) was obtained from *N*-hydroxylamine **5ca** (175 mg, 0.60 mmol) as a light brown solid. IR (neat): 740, 1000, 1105, 1235, 1340, 1460, 1595, 2975, 3050, 3185, 3385 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD): δ = 3.81 (dd, J_1 = 13.1 Hz, J_2 = 8.9 Hz, 1H), 3.98 (dd, J_1 = 13.1 Hz, J_2 = 5.6 Hz, 1H), 5.28 (dd, J_1 = 8.9 Hz, J_2 = 5.6 Hz, 1H), 7.17–7.28 (m, 2H), 7.50 (dt, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.77 (s, 1H), 7.81 (d, J = 8.0 Hz). ^{13}C NMR (75 MHz, CD_3OD): δ = 40.2, 57.1, 103.3, 113.2, 119.2, 121.7, 124.0, 127.4, 128.1, 138.2. MS (ES^+): *m/z* (%) = 214 (19) $[M+Na]^+$, 192 (5) $[M+H]^+$, 159 (100).

4.1.4.2. 2-(5-Fluoro-1*H*-indol-3-yl)-2-(hydroxyamino)ethanamine dihydrochloride 6cb. Compound **6cb** (50 mg, 94%) was obtained from *N*-hydroxylamine **5cb** (62 mg, 0.2 mmol) as a light brown solid. IR (neat): 800, 935, 1155, 1185, 1455, 1490, 1585, 2690, 2865 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD): δ = 3.31 (dd, J_1 = 13.2 Hz, J_2 = 9.0 Hz, 1H), 3.80 (dd, J_1 = 13.2 Hz, J_2 = 5.6 Hz, 1H), 5.26 (dd, J_1 = 9.0 Hz, J_2 = 5.6 Hz, 1H), 7.02 (dt, J_1 = 9.0 Hz, J_2 = 2.4 Hz, 1H), 7.47 (dd, J_1 = 9.0 Hz, J_2 = 4.5 Hz, 1H), 7.52 (dd, J_1 = 9.6 Hz, J_2 = 2.4 Hz, 1H), 7.83 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.0, 56.9, 103.6 (d, J = 9.2 Hz), 104.4 (d, J = 23.7 Hz), 112.3 (d, J = 26.7 Hz), 114.2 (d, J = 9.8 Hz), 127.9 (d, J = 10.7 Hz), 130.0, 134.7, 159.8 (d, J = 238.7 Hz). ^{19}F NMR (282 MHz, CD_3OD): δ = −124.9 (dt, J_1 = 9.4 Hz, J_2 = 4.5 Hz, 1F). MS (ES^+): *m/z* (%) = 194 (100) $[M+H]^+$.

4.1.4.3. 2-(5-Chloro-1*H*-indol-3-yl)-2-(hydroxyamino)ethanamine dihydrochloride 6cc. Compound **6cc** (40 mg, 78%) was obtained from *N*-hydroxylamine **5cc** (55 mg, 0.17 mmol) as a light brown solid. IR (neat): 800, 895, 1000, 1110, 1405, 1455, 2690, 2920 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD): δ = 3.80 (dd, J_1 = 13.1 Hz, J_2 = 8.9 Hz, 1H), 3.96 (dd, J_1 = 13.1 Hz, J_2 = 5.6 Hz, 1H), 5.25 (dd, J_1 = 8.9 Hz, J_2 = 5.6 Hz, 1H), 7.22 (dd, J_1 = 8.7 Hz, J_2 = 1.9 Hz, 1H), 7.48 (d, J = 8.7 Hz, 1H), 7.83 (s, 1H), 7.84 (d, J = 1.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.1, 56.7, 103.3, 114.6, 119.0, 124.2, 127.5, 128.6, 129.9, 136.8. MS (ES^+): *m/z* (%) = 226 (100) $[M+H]^+$.

4.1.4.4. 2-(5-Bromo-1*H*-indol-3-yl)-2-(hydroxyamino)ethanamine dihydrochloride 6cd. Compound **6cd** (135 mg, 98%) was obtained from *N*-hydroxylamine **5cd** (148 mg, 0.4 mmol) as a light brown solid. IR (neat): 795, 885, 995, 1110, 1155, 1230, 1455, 2675, 2870 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD): δ = 3.79 (dd, J_1 = 13.1 Hz, J_2 = 8.8 Hz, 1H), 3.95 (dd, J_1 = 13.1 Hz, J_2 = 5.5 Hz, 1H), 5.25 (dd, J_1 = 8.8 Hz, J_2 = 5.5 Hz, 1H), 7.33–7.36 (m, 1H), 7.42–7.45 (m, 1H), 7.81 (d, J = 2.0 Hz, 1H), 7.98 (d, J = 1.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.1, 56.7, 103.2, 114.8, 114.9, 122.1, 126.9, 129.2, 129.6, 136.9. MS (ES^+): *m/z* (%) = 270 (100).

4.1.4.5. 2-(5-Iodo-1*H*-indol-3-yl)-2-(hydroxyamino)ethanamine dihydrochloride 6ce. Compound **6ce** (100 mg, 99%) was obtained from *N*-hydroxylamine **5cfe** (104 mg, 0.25 mmol) as a light brown solid. IR (neat): 795, 880, 1000, 1110, 1230, 1450, 2690, 2865, 3100 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD): δ = 3.79 (dd, J_1 = 13.2 Hz, J_2 = 8.7 Hz, 1H), 3.97 (dd, J_1 = 13.2 Hz, J_2 = 5.5 Hz, 1H), 5.26 (dd, J_1 = 8.7 Hz, J_2 = 5.5 Hz, 1H), 7.33 (d, J = 8.6 Hz, 1H), 7.51 (dd, J_1 = 8.6 Hz, J_2 = 1.5 Hz, 1H), 7.78 (s, 1H), 8.19 (d, J = 1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.1, 56.6, 84.7, 102.8, 115.3, 128.4, 129.2, 130.0, 132.4, 137.2. MS (ES^+): *m/z* (%) = 318 (100) $[M+H]^+$.

4.1.4.6. 2-(6-Fluoro-1*H*-indol-3-yl)-2-(hydroxyamino)ethanamine dihydrochloride 6cf. Compound **6cf** (25 mg, 89%) was obtained from *N*-hydroxylamine **5cf** (31 mg, 0.1 mmol) as a light brown solid. IR (neat): 815, 850, 950, 980, 1100, 1135, 1230, 1450, 1500, 2670, 2900, 3290 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD): δ = 3.79 (dd, J_1 = 13.1 Hz, J_2 = 8.8 Hz, 1H), 3.97 (dd, J_1 = 13.1 Hz, J_2 = 5.5 Hz, 1H), 5.28 (dd, J_1 = 8.8 Hz, J_2 = 5.5 Hz, 1H), 6.99 (dt, J_1 = 9.0 Hz, J_2 = 2.3 Hz, 1H), 7.20 (dd, J_1 = 9.0 Hz, J_2 = 2.3 Hz, 1H), 7.77 (s, 1H), 7.79 (dd, J_1 = 9.0 Hz, J_2 = 5.1 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD): δ = 40.1, 56.9, 99.1 (d, J = 25.5 Hz), 103.7, 110.2 (d, J = 24.7 Hz), 120.5 (d, J = 10.8 Hz), 124.0, 128.8 (d, J = 8.7 Hz), 138.3, 161.8 (d, J = 236.7 Hz). ^{19}F NMR (282 MHz, $CDCl_3$): δ = −122.1 (dt, J_1 = 9.6 Hz, J_2 = 5.1 Hz, 1F). MS (ES^+): *m/z* (%) = 210 (100) $[M+H]^+$.

4.1.4.7. 2-(6-Chloro-1*H*-indol-3-yl)-2-(hydroxyamino)ethanamine dihydrochloride 6cg. Compound **6cg** (80 mg, 95%) was obtained from *N*-hydroxylamine **5cg** (91 mg, 0.28 mmol) as a light brown solid. IR (neat): 810, 980, 1060, 1400, 1485, 2705, 2970, 3410 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD): δ = 3.80 (dd, J_1 = 13.2 Hz, J_2 = 8.8 Hz, 1H), 3.98 (dd, J_1 = 13.2 Hz, J_2 = 5.6 Hz, 1H), 5.30 (dd, J_1 = 8.8 Hz, J_2 = 5.6 Hz, 1H), 7.18 (dd, J_1 = 8.5 Hz, J_2 = 1.8 Hz, 1H), 7.52 (d, J = 1.8 Hz, 1H), 7.80 (d, J = 8.5 Hz, 1H), 7.81 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.1, 56.7, 103.8, 113.0, 120.7, 122.2, 126.1, 129.2, 129.9, 138.5. MS (ES^+): *m/z* (%) = 226 (100) $[M+H]^+$.

4.1.4.8. 2-(6-Bromo-1*H*-indol-3-yl)-2-(hydroxyamino)ethanamine dihydrochloride 6ch. Compound **6ch** (120 mg, 89%) was obtained from *N*-hydroxylamine **5ch** (148 mg, 0.4 mmol) as a light brown solid. IR (neat): 800, 895, 985, 1050, 1110, 1300, 1335, 1405, 1445, 1495, 2695, 2895, 3105 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD): δ = 3.79 (dd, J_1 = 13.2 Hz, J_2 = 8.9 Hz, 1H), 3.96 (dd, J_1 = 13.2 Hz, J_2 = 5.5 Hz, 1H), 5.26 (dd, J_1 = 8.9 Hz, J_2 = 5.5 Hz, 1H), 7.31 (dd, J_1 = 8.6 Hz, J_2 = 1.8 Hz, 1H), 7.68–7.78 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.1, 56.7, 103.8, 116.1, 117.3, 121.0, 124.8, 126.4, 129.1, 139.0. MS (ES^+): *m/z* (%) = 270 (100) $[M+H]^+$.

4.1.4.9. 2-(4-Bromo-1*H*-indol-3-yl)-2-(hydroxyamino)ethanamine dihydrochloride 6ci. Compound **6ci** (55 mg, 99%) was obtained from *N*-hydroxylamine **5ci** (59 mg, 0.16 mmol) as a light brown solid. IR (neat): 730, 770, 810, 915, 990, 1165, 1195, 1425, 1485, 2675, 2890, 2965 cm^{-1}. ^{1}H NMR (300 MHz, CD_3OD): δ = 3.85 (dd, J_1 = 13.4 Hz, J_2 = 8.2 Hz, 1H), 4.00 (dd, J_1 = 13.4 Hz, J_2 = 6.0 Hz, 1H), 6.16 (dd, J_1 = 8.2 Hz, J_2 = 6.0 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.37 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H), 7.52 (dd, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H), 7.94 (d, J = 2.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 40.4, 56.4, 104.0, 113.1, 113.9, 124.9, 125.3, 126.3, 129.8, 139.7. MS (ES^+): *m/z* (%) = 270 (100) $[M+H]^+$.

4.2. Microbiology

Stock solutions of the indolic compounds were prepared in dimethylsulfoxide (DMSO, Sigma-Aldrich, France) at a concentration of 25.6 mg/mL. These stock solutions were further 1:20 diluted in sterile 10% DMSO solution. Working solutions of the indolic compounds contained less than 5% DMSO which was verified to be nontoxic for all bacterial strains tested. The antibacterial activity of indolic compounds was evaluated against 28 gram-positive or gram-negative reference strains belonging to 17 different species, obtained from the American Type Culture Collection (Mannasas VA, USA) or from the Institut Pasteur Collection (Paris, France): six methicillin-susceptible *S. aureus* strains (ATCC 25923, ATCC 29213, ATCC 9144, ATCC 6538, CIP 65.6 and CIP 103428), two methicillin-resistant *S. aureus* (MRSA) strains (CIP 65.25 and ATCC 33592), one vancomycin-intermediate *S. aureus* (VISA) strain (ATCC 106414), three *S. epidermidis* strains (ATCC 12228, CIP 81.55 and CIP 103627), two *S. pneumoniae* strains (ATCC 49619, ATCC 6303), and one strain each for the species *S. agalactiae* (ATCC 12400), *S. pyogenes* (CIP 104226), *S. mitis* (CIP 103335), *Enterococcus faecium* (CIP 54.32), *E. faecalis* (ATCC 29212), *Listeria innocua* (CIP 80.11), *Bacillus subtilis* (CIP 5262), *E. coli* (ATCC 25922), *Klebsiella pneumoniae* (ATCC 35657), *Enterobacter cloacae* (ATCC 13047), *Serratia marcescens* (CIP 103551), *P. aeruginosa* (CIP 5933), *A. baumanii* (ATCC 19606) and *Haemophilus influenzae* (ATCC 49766). The minimal inhibitory concentrations (MICs) of the indolic compounds against previously mentioned bacterial strains were determined using a broth microdilution method according to the international standard reference method ISO/FDIS 20776-1:2006(E) and the method recommended by the Clinical and Laboratory Standards Institute (CLSI; M07-A8 Vol. 29, N°2). Briefly, for each microorganism, two rows of a 96-well microtiter plate were filled with a 10^6 cfu/ml bacterial inoculum (180 μL per well) and serial dilutions of the indolic compound to be tested (20 μL per well), at ten-fold the desired final concentration, ranging from 2 to 128 μg/ml. The bacterial growth medium was Mueller–Hinton broth (AES Chemunex, France), supplemented with 5% sheep blood (BioMérieux, France) for the fastidious species *S. pneumoniae*, *S. mitis*, and *H. influenzae*. One well that did not receive any antibiotic served as a growth control. Experiments were made at least twice for each indolic compound to confirm results. MICs were read after 18 h incubation of the plates at 37 °C. They corresponded to the minimal indolic compound concentration allowing complete inhibition of visible growth. MIC values were also determined for the three antibiotics ciprofloxacin, gentamicin and cefotaxime, taken as controls. Deformylase activity was determined in HEPES buffer at pH 7.5 and at 37 °C by a PDF–formate dehydrogenase coupled assay.[17] Deformylation rate of Formyl-Met-Ala-Ser (1 mM) in the presence of *Ec*PDF (20 nM; purified in the presence of $NiCl_2$) was assayed by coupling with formate dehydrogenase (Sigma) and was directly proportional to the rate of production of NADH. Formation of NADH was monitored using UV spectroscopy at 340 nm. All inhibitors were diluted in dimethylsulfoxide, and the final assay buffer contained 10% of this solvent. For the determination of inhibition potency of *Ec*PDF, to prevent the effects associated with slow binding,[11a] each inhibitor was incubated with the enzyme for 10 min at 25 °C before kinetic analysis, which was initiated by adding the peptide substrate.

Acknowledgments

This work was supported by the grant ANR-08-EBIO-012 from the Agence Nationale de la Recherche (ANR, France). The authors wish to thank Karim Hamiche (UPR 2355 CNRS, Gif-sur-Yvette) for the tests of PDF inhibition and Dr. Thierry Cresteil (UPR 2301 CRNS, Gif-sur-Yvette) for the tests of cytotoxicity.

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