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Reinvestigation of the Nitration of Trichloroethene – Subsequent Reactions of the Products and Evaluation of Their Antimicrobial and Antifungal Activity[‡]

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The nitration reaction of trichloroethene (**1**) to main products trichloronitroethene (TCNiE **2**, up to 60.8 %, by GC), 1,1,2,2-tetrachloro-1-nitroethane (**8**, up to 25.1 %, by GC), and 1,2,2-trichloro-2-nitroethyl [chloro(nitro)methylene]azinate (**9**, up to 8.0 %, by GC) was comprehensively investigated and optimized. Different 1,1-diamino-2-chloro-2-nitroethenes, 2-nitroethoxyguanidines, and rare *O*-(1,2,2-trichloro-2-nitroethyl) oximes and carbimidoyl halides with unique formulas R–O–N=C(NO_2)NRR_1 and R–O–N=C(Hal)NRR_1, respectively, were obtained from these nitration products in yields up to 91 %. The structure of (*E*)-morpholino(nitro)methanone *O*-(1,2,2-trichloro-2-nitroethyl) oxime (**19**) was proven by single-crystal X-ray diffraction analysis. In addition, the antimicrobial and antifungal activity of the synthesized compounds was examined. Notably, *N*-(1,2,2-trichloro-2-nitroethoxy)-3,4-dihydroisoquinoline-2(1*H*)carbimidoyl chloride (**27**) inhibited the growth of methicillin-resistant and sensitive *Staphylococcus aureus* with minimum inhibitory concentrations of 1.3 μg mL^{-1}, and reduced the viability of the MCF-7 cancer cell line with an IC_{50} of 0.2 μg/mL.

Introduction

The chemistry of nitro compounds has been extensively studied over the years. Special interest in this class of compounds mainly arises from their versatility as precursors in the synthesis of various functionalized compounds. In particular, halonitroethenes are valuable building blocks, e.g. for the directed synthesis of four-, five-, and six-membered heterocycles with unique substitution patterns.[1] In addition, a multitude of known nitroethene and nitramide derivatives exhibit biological activity as drugs or as plant-protecting agents. For example, ranitidine (trade name *Zantac*, Figure 1) is a histamine H_2-receptor antagonist that inhibits stomach acid production. It is also used as an antiulcer drug and is found on the World Health Organization's List of Essential Medicines, which reflects the most important medication needed in a basic health care system.[2] In addition to this medical application, imidacloprid (Figure 1) is a systemic insecticide that acts as an insect neurotoxin. It has been one of the most widely used insecticides in the world.[3] Another neurotoxic, neonicotinoide, is the insecticide nitenpyram (Figure 1), which is used in agriculture and veterinary medicine to kill external parasites of livestock and pets.[4]

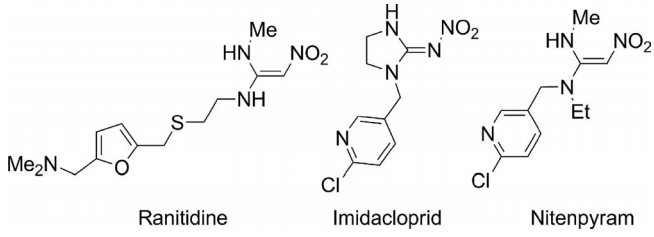

Figure 1. Nitroethene and nitramide derivatives as drugs and plant protectors.[2–4]

In contrast to haloalkenes, the introduction of an additional nitro substituent, to provide the corresponding halonitroalkenes, chemically qualifies the latter as powerful electrophiles that readily react with common nucleophiles.[1] In addition, some are useful dienophiles or even (aza)dienes for cycloaddition reactions.[5] Furthermore, such nitroalkenes may be selectively reduced to the corresponding amino derivatives, which themselves represent potent precursors for the synthesis of various functionalized heterocycles. The most studied halonitroethene is 1,1,2-trichloro-2-nitroeth-

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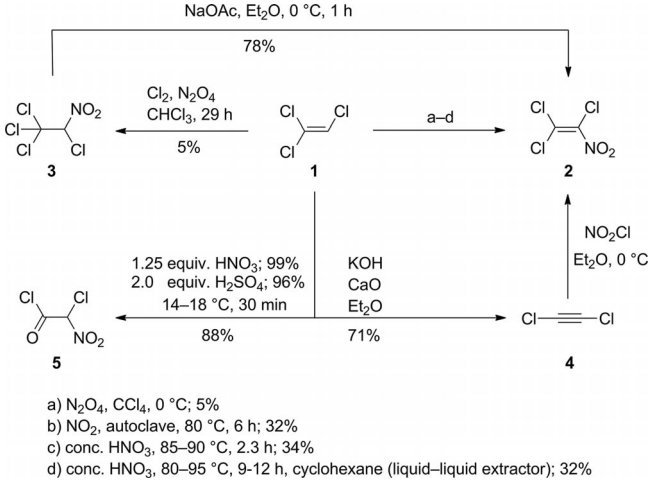
ene (TCNiE; **2**), a perchlorovinylogue of nitryl chloride. The first attempt to synthesize this useful C_2-building block was carried out already in 1873 by treatment of tetrachloroethene with a mixture of concentrated sulfuric and red fuming nitric acid.[6a] Use of this experimental protocol in 1902 exclusively led to isolation of trichloroacetic acid.[6b] However in 1960 a successful synthesis of **2** in 77.5% yield was achieved by conducting the dehydrochlorination of 1,1,1,2-tetrachloro-2-nitroethane (**3**) with sodium acetate in diethyl ether at 0 °C for 1 h.[7,8] Starting material **3** was accessible through halonitration of **1** with chlorine gas and N_2O_4 in chloroform for 29 h, but in only 5% yield. An alternative formation of **2** was possible by reaction of **1** with N_2O_4 in CCl_4 at 0 °C, but again in only 5% yield.[7] TCNiE (**2**) was also formed through addition of nitryl chloride to dichloroacetylene (**4**) in diethyl ether at 0 °C (no yield given).[9] Acetylenic precursor **4** was obtained by dehydrochlorination of **1** with KOH in the presence of CaO. Furthermore, by heating **1** with nitrogen dioxide (3 equiv.) in an autoclave at 80 °C for 6 h resulted in **2** with 32% yield.[10]

The current synthesis of **2** is based upon an electrophilic nitration of inexpensive industrial solvent **1** with nitric acid.[11,12] Recently, we developed the synthesis of **2** on a laboratory scale (100 g and above) through nitration of a solution of **1** in cyclohexane (placed in a liquid-liquid extractor) with 65% nitric acid under mild temperature conditions, which suppress oxidative destruction and finally leads to pure **2** in 32% yield. In contrast to previous attempts, careful temperature control of the reaction and subsequent distillation conditions allowed the synthesis of 1,1,2-trichloro-2-nitroethene (**2**) with high purity.[1i] Interestingly, treatment of **1** with concentrated sulfuric acid and fuming nitric acid exclusively leads to the formation of chloronitroacetyl chloride (**5**) in 88% yield (Scheme 1).[13]



Scheme 1. Synthetic pathways to trichloronitroethene (**2**).

Aside from these synthetic aspects, TCNiE (**2**) shows fungicidal activity against different aquatic weeds[11] and *Fusarium oxysporum*.[14] In addition, **2** is used to control diseases of upland crops[15] and in other agricultural compositions.[16]

Result and Discussion

In the present work we studied the nitration of **1** with different reagents to increase the chemical yield of pure nitroethene **2**. In addition, we explored the byproducts of this reaction, which result from unfavorable reaction pathways, e.g. oxidation or chlorination. In Table 1, Entries 1–3, describes how we applied different amounts of nitric acid, in Table 1, Entries 4–9, are combination with sulfuric or phosphoric acid, and Table 1, Entry 10, with oleum. In Table 1, Entries 11 and 12, nitronium tetrafluoroborate was used. Table 1, Entries 13 and 14 correspond to mixtures of nitric acid and acetic acid, respectively, and Table 1, Entries 15 and 16 with trifluoroacetic acid. Next, we made a solution of 1,2,4,5-tetrachlorobenzene (**6**; 5% w/w; internal standard) in trichloroethene (**1**). Determined by gas chromatography with flame ionization detection, this initial ratio corresponds to a GC peak ratio of 1.0:8.1 (whereby the deviation is caused by the high heteroatom content of these two compounds). Because the relative amount of **6** remains unchanged during this reaction, we determined the relation of compounds **2** and **6**. The highest content of **2** was achieved upon treatment of **1** with a 10:1 mixture of concd. HNO_3 and concd. H_2SO_4 (61.3% yield as measured by GC, Table 1, Entry 4), whereas the highest ratio of **2** to **6** with a value of 6.7:1 was observed with a 60.8% content of **2** (in Table 1, Entry 8). As byproducts, trichloronitromethane (chloropicrin) (**7**, 0.4–3.4%), 1,1,2,2-tetrachloro-1-nitroethane (**8**, 9.0–25.1%), and 1,2,2-trichloro-2-nitroethyl [chloro(nitro)methylene]azinate (**9**, 0–8.0%) were isolated and characterized (Scheme 2, Table 1).

Structurally interesting azinate **9** is formed as a 95:5 mixture of two isomers. In some cases, additional byproducts were found in very small amounts (1–4% by GC), but could not be isolated by purification of the reaction mixture by means of a Fischer Spaltrohr® column HMC 500 C. Nitroethane **8** is a known sterilizer, insecticide, herbicide, and nematocide[17] It is accessible by condensation of nitrosyl chloride with ethane **1** after 14 d at room temp. in a yield of 88%,[18] or by nitration of **1** with a mixture of 98% H_2SO_4 and 98% HNO_3 (15:11 ratio) at 50–55 °C after 6 h,[17] or by nitration of **1** with 98% HNO_3 and P_2O_5 at 90 °C after 2 h.[17]

The assumed mechanism for the formation of nitration products **2** and **7**–**9** is given in Scheme 3. Starting material **1** reacts with a nitronium cation to form highly substituted ethyl cations **A** and **B**. Subsequent elimination of a proton from **A** leads to nitroethene **2**, which is then hydrated to aliphatic alcohol **C**. Afterwards, dehydrochlorination of **C** provides acetyl chloride derivative **D**, which readily reacts with water to form free acid **E**. Successive thermal decarboxylation of **E** provides chloronitromethane **F**, which is then converted into chlorodinitromethane **G** by means of a second nitronium cation. In contrast, addition of water to trichloronitroethane **B** gives alcohol **I**, which reacts with *aci*-form **H** of chlorodinitromethane **G**, mentioned above, to form azinate **9**. In addition, formation of nitroethane **8** is conceivable by treatment of ethane derivative **B** with in-situ

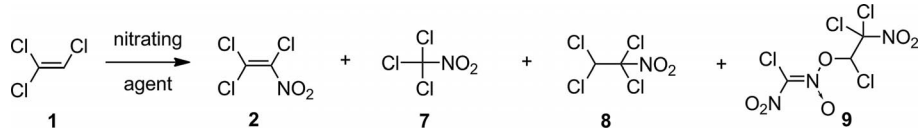
Table 1. Nitration of trichloroethene (**1**).

Entry	Yield (GC) [%]					Ratio **2/6**[a]
	1	**2**	**7**	**8**	**9**	
1	17.4	44.0	2.0	22.3	5.3	4.0
2	1.0	55.6	1.7	25.1	6.9	4.5
3	0.0	52.5	1.8	23.3	4.2	3.4
4	0.0	61.3	2.4	22.8	7.3	3.9
5	0.0	49.2	3.4	18.0	8.0	4.5
6	0.0	60.6	3.3	18.2	4.4	6.3
7	0.0	59.6	2.7	22.4	4.1	6.6
8	0.0	60.8	2.8	19.1	4.5	6.7
9	0.3	55.8	1.3	21.5	5.1	4.9
10	100	no reaction				
11	100	no reaction				
12	54.3	salt-like unstable compounds				
13	21.8	39.3	2.4	24.7	0	3.1
14	1.5	38.8	2.6	20.0	0	1.6
15	10.6	28.1	0.4	18.6	5.3	2.6
16	0	41.6	2.3	9.0	2.0	1.8

Experimental details on the nitration of trichloroethene

Entry	For Entries 1–10: nitration mixture for 40 mL of aliquot (5.0% w/w solution of **6** in **1**), 6 h at 100–105 °C
1	50 mL of 65% HNO_3
2	100 mL of 65% HNO_3
3	150 mL of 65% HNO_3
4	150 mL of 65% HNO_3 + 15 mL concd. H_2SO_4
5	120 mL of 65% HNO_3 + 30 mL concd. H_2SO_4
6	150 mL of 65% HNO_3 + 15 mL concd. H_3PO_4
7	120 mL of 65% HNO_3 + 30 mL concd. H_3PO_4
8	130 mL of 65% HNO_3 + 20 mL concd. H_3PO_4
9	150 mL of 65% HNO_3 + 2.8 mL concd. H_2SO_4
10[b]	300 mL oleum (20% SO_3) + 96 g $NaNO_3$
11[b]	Suspension of NO_2BF_4 (0.47 g, 3.54 mmol) in **1** (4.20 g, 32.0 mmol), 8 h at reflux temperatures.
12[b]	Addition of a solution of **1** (0.42 g, 3.20 mmol) in MeCN (1 mL) within 5 min to a solution of NO_2BF_4 (0.47 g, 3.54 mmol) in MeCN (3 mL) at 0 °C, mixture kept for further 2 h at 0 °C, then at room temp. for 12 h.
13	Dropwise addition of **1** (0.65 g, 5.00 mmol) to a mixture of HNO_3 (65%, 1.45 g, 15.0 mmol) and HOAc (100%, 4 mL) at 0 °C, stirring for 1 h at 0 °C, then for 1 h at r.t., and additionally 8 h at 85–90 °C.
14	As described for **13**, with heating for 20 h at 85–90 °C.
15[c]	Dropwise addition of **1** (0.65 g, 5.00 mmol) to a mixture of HNO_3 (65%, 0.73 g, 7.5 mmol) and CF_3CO_2H (4.05 mL, 6.00 g) at 0 °C, stirring for 1 h at 0 °C, 1 h at r.t., and 8 h at 55–60 °C.
16[c]	Dropwise addition of **1** (0.65 g, 5.00 mmol) to a mixture of HNO_3 (65%, 1.45 g, 15.0 mmol) and CF_3CO_2H (4.05 mL, 6.00 g) at 0 °C, stirring for 1 h at 0 °C, 1 h at r.t., and 16 h at 55–60 °C.

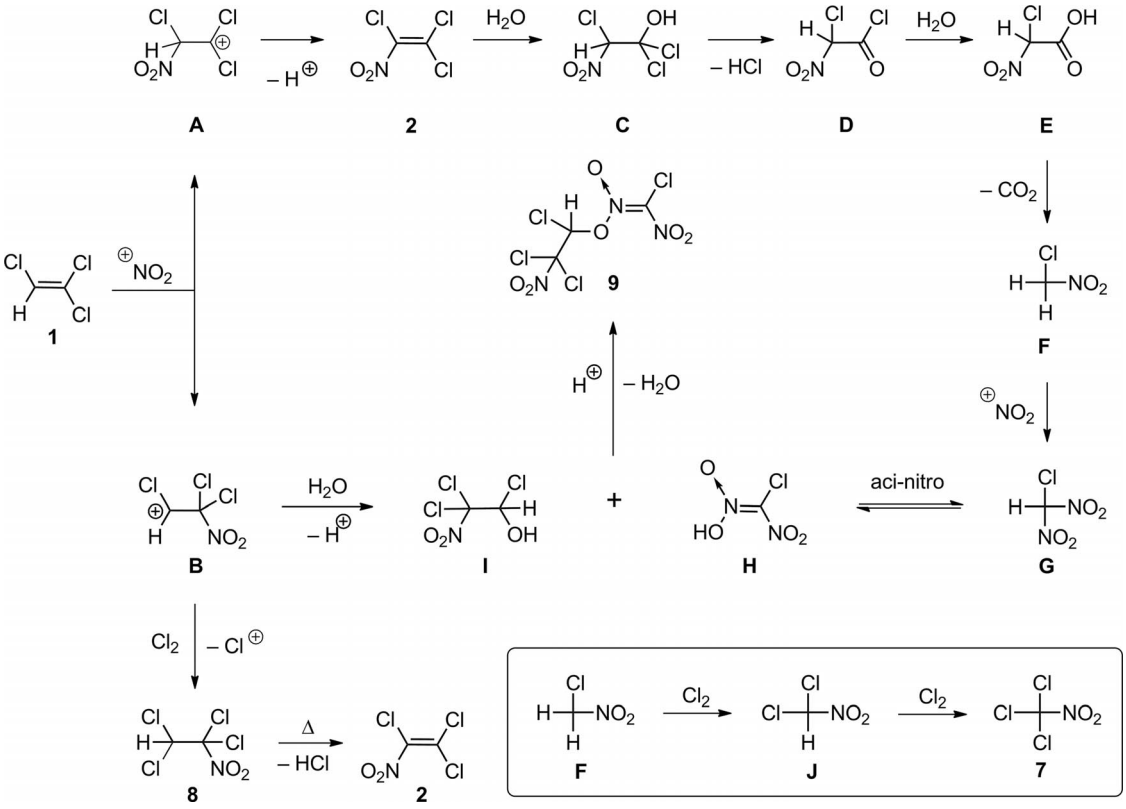
[a] A solution of **6** in **2** (5.0% w/w) gives a GC response of 6.67:93.33%, respectively. [b] For Table 1, Entries 10–12 pure **1** was applied instead of a mixture with **6**. [c] For Table 1, Entries 15 and 16 we observed the additional formation of unassigned byproducts in 10 and 17% yield (GC), respectively.



Scheme 2. Nitration products of trichloroethene (**1**) with varying yields given in Table 1.

formed molecular chlorine (derived from thermal decomposition of chlorinated starting material as previously observed[19]). It represents an additional source for main product **2** through a dehydrochlorination reaction. Byproduct chloropicrin **7** is formed by chlorination of intermediate **F** through derivative **J**.

After optimization of the nitration reaction of trichloroethene (**1**) and improvement of the separation of the main products by applying a Fischer Spaltrohr® column (HMC 500 C) we studied the suitability of these structurally unusual compounds in organic syntheses. Nitroethene **2** readily reacts with secondary aliphatic amines, such as morph-

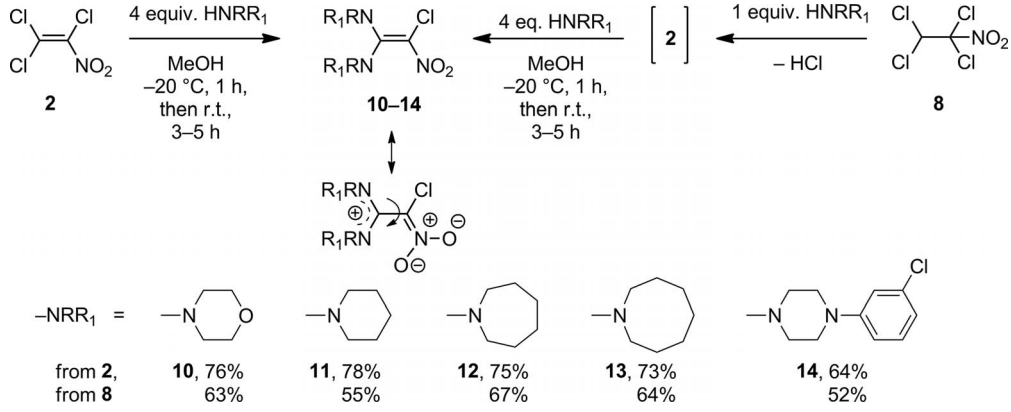


Scheme 3. Assumed mechanism for the formation of nitration products **2** and **7**–**9**.

oline, piperidine, azepane, azocane, and 1-(3-chlorophenyl)-piperazine, under mild temperature conditions (MeOH, –20 °C to room temp., fourfold excess of amine). Thus, corresponding 1,1-diamino-2-chloro-2-nitroethenes **10**–**14** were obtained in a twofold S_NVin-reaction in moderate to good chemical yields (64–78%). Both amino groups of enamines **10**–**14** are chemically equivalent as a result of the possibility to form intramolecular salts of the *aci*-nitro group with free rotation along the C–C single bond. By starting from nitroethane **8**, treatment with one equivalent of a secondary aliphatic amine led to elimination of HCl and formation of trichloronitroethene (**2**). On application of a fivefold excess of an amine, again the first equivalent enabled dehydrochlorination to give **2**, but two further equivalents formed diamino derivatives **10**–**14** (52–67%, Scheme 4), and the remaining two equivalents of amine trapped the HCl formed.

Recently, we published the synthesis of bisazolylnitroethene **15** and its useful application in a monoamination reaction and in the formation of tetrazole derivatives.[20] Structurally similar products from the reaction of **2** with aniline, *o*-phenylendiamine, and 1,8-diaminonaphthalene are also known.[21] Some 1,1-diamino-2-chloro-2-nitroethenes (**16**–**18**) are bioactive and exhibit distinct insecticidal activity (Figure 2).[22]

The reaction of azinate **9** with secondary aliphatic amines, such as morpholine, 1,2,3,4-tetrahydroisoquinoline, 1-(3-chlorophenyl)piperazine, and piperazine, led to 2-nitroethyl oximes **19**–**22** in good yields (71–88%). The best re-



Scheme 4. Synthesis of 1,1-diamino-2-chloro-2-nitroethenes **10**–**14** from **2** or **8**.

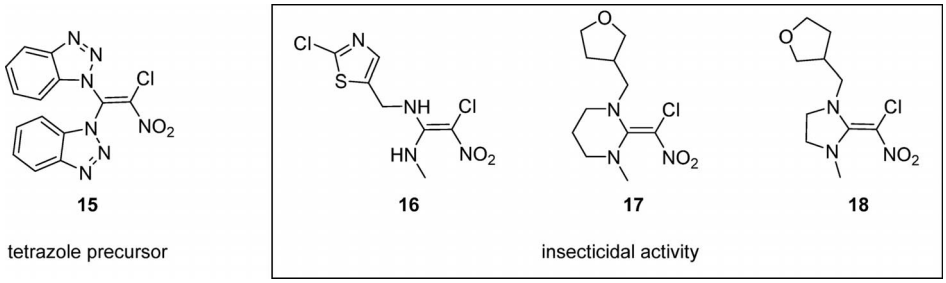


Figure 2. Structurally and physiologically interesting 1,1-diamino-2-chloro-2-nitroethenes.

sults were achieved with methanol as solvent and with two equivalents of amine (for bisoxime **22** only one equivalent of piperazine is needed). The amidation of **9** is accompanied by the reduction of the *N*-oxide group in the presence of amine. Oximes **19**–**22** were formed as a mixture of isomers (*E*:*Z* = 95:5 as determined by ^{1}H NMR spectroscopy). The chemistry of this extraordinary structural unit that is represented by the formula R–O–N=C(NO_2)NRR_1 is virtually unknown in the literature. To the best of our knowledge, only two papers that deal with this class of organic compounds have been published.[23] In this case, the structure of (*E*)-morpholino-(nitro)methanone *O*-(1,2,2-trichloro-2-nitroethyl) oxime (**19**) was determined by single-crystal X-ray diffraction analysis (Figure 3).

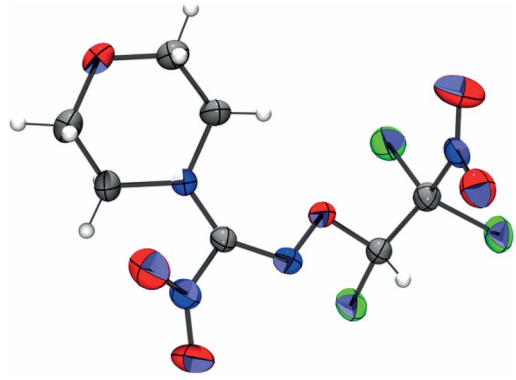
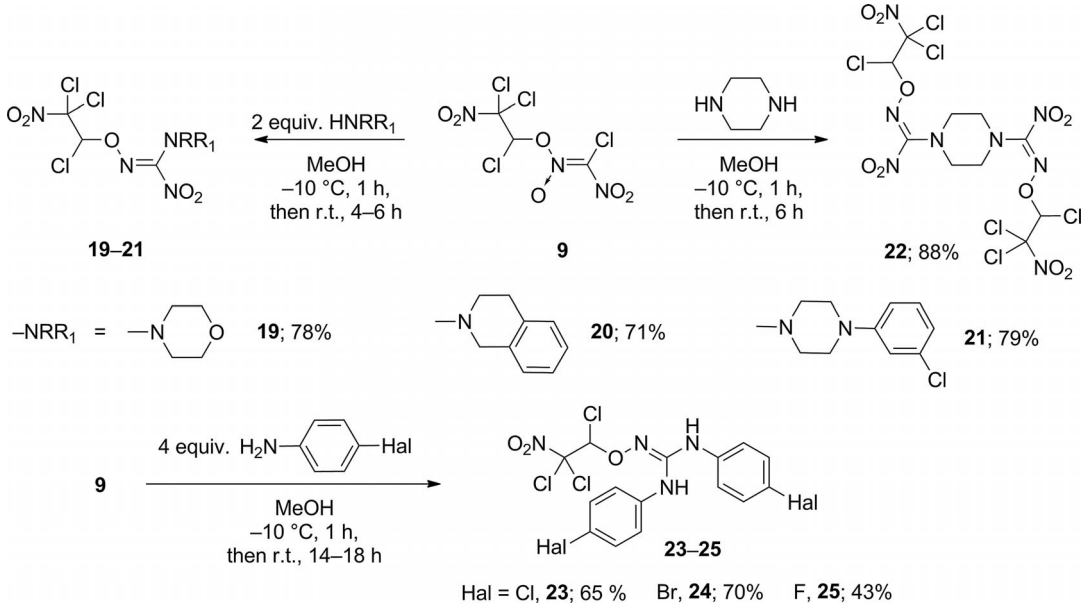


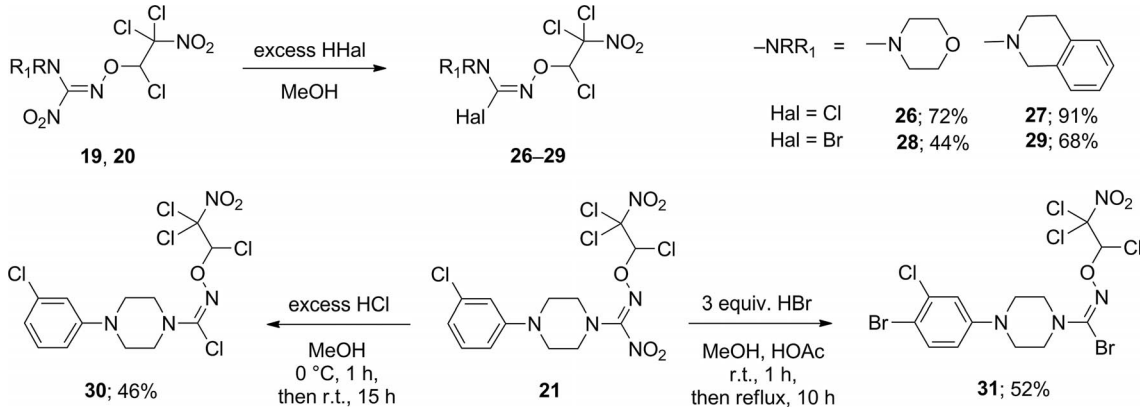
Figure 3. X-ray analysis of oxime ether **19**.

In contrast to oxime formation from aliphatic amine derivatives, the reaction of azinate **9** with aniline derivatives, such as 4-chloro-, 4-bromo-, and 4-fluoroaniline, allowed for twofold nucleophilic substitution. Replacement of both the chlorine substituent and the nitro group resulted in the unexpected formation of corresponding guanidines **23**–**25** in moderate to good yields (43–70%; Scheme 5). Interestingly, several 1,3-diaryl-2-organyloxyguanidines are known as potent inhibitors of inosine monophosphate dehydrogenase[24a,24b] or as immunosuppressants, as anti-cancer, anti-inflammatory, anti-psoriatic, and anti-viral agents.[24b]

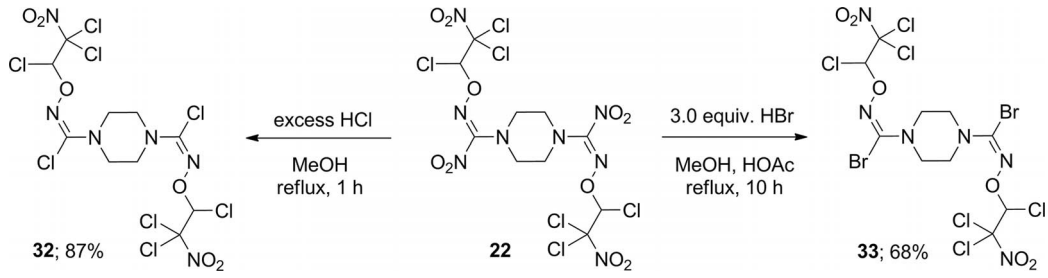
Subsequent treatment of oximes **19**–**21** with aqueous hydrogen chloride (37% HCl), or an acetic acid solution of hydrogen bromide (33% HBr) in the case of **19** and **20**, led to substitution of the methanone nitro-group and formation of corresponding carbimidoyl halides **26**–**30** in moderate to very good yields of 44–91%. The nitro group of the



Scheme 5. Formation of oximes **19**–**22** and guanidines **23**–**25** derived from azinate **9**.



Scheme 6. Synthesis of carbimidoyl halides **26**–**31** from oximes **19**–**21**.



Scheme 7. Synthesis of piperazinyl derivatives **32** and **33** from bisoxime **22**.

dichloronitromethyl moiety did not react under the selected reaction conditions. Reactions with HCl and an 8–10-fold excess of hydrogen chloride was necessary (MeOH, 0 °C to r.t.). The processes of applying HBr required only a 1.5-fold excess of this acid (0 °C then r.t., or then 30–35 °C for bromide **28**). The reaction of oxime **21** with HBr was very slow at room temp., but at increased temperature upon application of a threefold excess of hydrogen bromide product **31** was formed. Thereby, in addition to the expected nitro group replacement, the 4-position of the phenyl ring was brominated to give **31** in 52% yield (Scheme 6) probably as a result of previous oxidation of the bromide anion to bromine by nitrogen dioxide.

The reaction of bisoxime ether **22** with hydrogen halides was found to give corresponding carbimidoyl halides **32** (87%) and **33** (68%). In both cases, is was essential that the reaction mixtures were heated at reflux temperatures. The accordant products of a single substitution were not observed (Scheme 7). Also structurally unique products **26**–**33** belong to a very rare class of compounds that contain fragment R–O–N=C(Hal)NRR$_1$. To the best of our knowledge only three publications about these carbimidoyl halides are known.[23a,25]

Biological Assays

A selection of twelve compounds was tested in growth inhibitory assays against a panel of bacterial pathogens that includes the so-called ESKAPE panel that comprises the

Table 2. Minimal inhibitory concentrations in μg/mL of selected compounds against bacterial and fungal pathogens.

	A. baumannii	*E. cloacae*	*E. faecium*	*K. pneumoniae*	*P. aeruginosa PA7*	*E. coli*	*M. luteus*	*S. aureus MRSA*	*S. aureus MSSA*	*C. albicans*
19	20.0	n.a.[a]	20.0	>20	n.a.	n.a.	n.a.	n.a.	5.0	1.3
20	n.a.	n.a.	5.0	n.a.	n.a.	n.a.	10.0	10.0	1.3	1.3
21	n.a.	n.a.	20.0	n.a.	n.a.	n.a.	10.0	10.0	20.0	>20.0
22	n.a.	n.a.	20.0	n.a.	n.a.	n.a.	10.0	10.0	20.0	n.a.
23	n.a.	n.a.	10.0	n.a.	n.a.	n.a.	5.0	5.0	10.0	>20.0
24	n.a.	n.a.	20.0	n.a.	n.a.	n.a.	5.0	5.0	10.0	n.a.
25	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	20.0	n.a.
27	n.a.	n.a.	5.0	n.a.	n.a.	n.a.	1.3	1.3	1.3	1.3
29	n.a.	n.a.	10.0	n.a.	n.a.	n.a.	1.3	5.0	5.0	10.0
30	n.a.	n.a.	20.0	n.a.	n.a.	n.a.	2.5	5.0	20.0	n.a.
32	n.a.	n.a.	20.0	n.a.	n.a.	n.a.	10.0	20.0	20.0	n.a.
33	n.a.	n.a.	20.0	n.a.	n.a.	n.a.	>10.0	10.0	20.0	n.a.

[a] n.a.: not active at maximum tested concentration of 20 μg/mL.

clinically relevant Gram-negative and Gram-positive bacterial pathogens *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter Sp.* (Table 2). Most compounds displayed activity against Methicillin-sensitive *S. aureus* (MSSA), Methicillin-resistant *S. aureus* (MRSA), *M. luteus*, and *E. faecium*. The best profile was obtained for compound **27** that displayed activities of 1.3, 1.3, 1.3, and 5.0 μg/mL, respectively, against these four bacterial pathogens. In contrast, a minimal inhibitory concentration (MIC) against Gram-negative strains was not observed at concentrations up to 20 μg/mL.

To probe whether the compounds also affected eukaryotic cells, they were tested in a growth assay with fungus *C. albicans* and in viability assays with four mammalian cell lines (Tables 2 and 3). Although compounds **23**–**25** were inactive, all other compounds affected fungal growth and/or the viability of cells. High activities were observed for compounds **19**, **20**, **27**, **29**, and **30**. For example, **27** was able to achieve a 50% reduction of viability of MCF-7, L929, KB-31, or FS4 cells at concentrations of 0.2, 2.7, 3.9, and 12 μM, respectively. The compounds do not display selectivity, but there is some coherence in the level of activity towards prokaryotic versus eukaryotic cells. The molecular mechanisms behind these activities remain to be elucidated.

Table 3. Effect of compounds on cell viability in the WST-1 test. IC_{50} and IC_{90} values are given in μg/mL.

	L929		KB-31		MCF-7		FS4-LTM	
	IC_{50}	IC_{90}	IC_{50}	IC_{90}	IC_{50}	IC_{90}	IC_{50}	IC_{90}
19	1.1	2.2	4.0	6.7	0.3	0.5	5.0	>6.7
20	1.5	6.7	n.a.[a]	n.a	0.7	1.3	n.a.	n.a.
21	3.0	10.0	10.0	31.0	6	9.2	10.0	31.0
22	1.1	3.0	n.a.	n.a.	2.2	4.0	n.a.	n.a.
23	n.a.	n.a.	n.a.	n.a	n.a.	n.a.	n.a.	n.a.
24	n.a.	n.a.	n.a.	n.a	n.a.	n.a.	n.a.	n.a.
25	n.a.	n.a.	n.a.	n.a	n.a.	n.a.	n.a.	n.a.
27	2.7	8.5	3.9	8.5	0.2	0.6	12.0	26.0
29	1.1	3.0	8.6	29.0	0.3	0.9	13.0	29.0
30	0.5	2.2	2.2	6.7	0.2	0.5	n.a.	n.a.
32	1.5	4.0	1.8	4.2	1.0	1.2	4.0	13.0
33	1.7	5.0	2.2	4.8	1.1	1.4	5.0	15.0

[a] n.a.: not active at tested concentration of 6.7 μg/mL.

Conclusions

The reaction of trichloroethene (**1**) with different nitration agents was studied and optimized. It was shown that the use of a mixture of concd. HNO_3 and concd. H_3PO_4 (6.5:1) and a 5:1 ratio of the nitration mixture to the olefinic substrate leads to the best yield of trichloronitroethene (**2**, 60.8% by GC). Side-products trichloronitromethane (**7**), in up to 3.4% (by GC), 1,1,2,2-tetrachloro-1-nitroethane (**8**) in up to 25.1% (by GC), and 1,2,2-trichloro-2-nitroethyl [chloro(nitro)methylene]azinate (**9**) in up to 8.0% (by GC) were isolated and characterized. Reactions of **2** or **8** with secondary aliphatic amines gave 1,1-diamino-2-chloro-2-nitroethenes **10**–**14** in 52–78% yield. Treatment of azinate **9** with secondary amines led to unique products. The use of aliphatic amines resulted in the formation of 2-nitroethyl oximes **19**–**22** (71–88%), whereas aniline derivatives formed guanidines **23**–**25** (43–70%). On application of oximes **19**–**22** in subsequent reactions, use of hydrogen halides provided carbimidoyl halides **26**–**33** (44–91%). The structure of the (*E*)-morpholino(nitro)methanone *O*-(1,2,2-trichloro-2-nitroethyl) oxime (**19**) was determined by single-crystal X-ray diffraction analysis. Products with unique formulas R–O–N=C(NO_2)NRR_1 and R–O–N=C(Hal)NRR_1 belong to very rare classes of organic compounds. The antimicrobial activity of the synthesized compounds against Gram-positive bacteria was examined. In particular, compound *N*-(1,2,2-trichloro-2-nitroethoxy)-3,4-dihydroisoquinoline-2(1*H*)-carbimidoyl chloride (**27**) displayed potent biological activity with MICs of 1.3 and 5 μg/mL against MRSA and *E. faecium*, respectively, and an IC_{50} of 0.2 μg/mL against MCF-7 viability.

Experimental Section

General Remarks: Solvents and reagents were used as received from commercial sources without further purification. TLC was performed with Merck aluminum-backed TLC plates with silica gel 60, F254. Flash column chromatography was performed with Macherey–Nagel silica gel 60 M (0.040–0.063 mm) with appropriate mixtures of petroleum ether (PE, boiling range 60–70 °C) and ethyl acetate as eluents. Analytical separation of the nitration products and their determination of purity was accomplished by means of gas chromatography ("GC 3900", Varian) with split/splitless injector, flame ionization detector and a 30 m capillary column "CP-Sil 8 CB". Melting points were determined in capillary tubes with a Büchi B-520. FTIR spectra were recorded with a Bruker "Alpha-T" spectrometer with solid compounds measured as KBr pellets. ATR-IR spectra were measured on the same instrument with a Bruker "Alpha Platinum ATR" single reflection diamond ATR module. ^{1}H NMR and ^{13}C NMR spectra at 600 and 150 MHz, respectively, were recorded with an "Avance III" 600 MHz FT-NMR spectrometer (Bruker, Rheinstetten, Germany). ^{1}H NMR and ^{13}C NMR spectra at 400 and 100 MHz, respectively, were recorded with an "Avance" 400 MHz FT-NMR spectrometer (also Bruker). ^{14}N and ^{15}N NMR spectra were measured at their appropriate resonance frequency on the aforementioned spectrometers; ^{15}N measurements were taken as gs-^{1}H,^{15}N-HSQC or -HMBC experiments with inverse detection. ^{1}H and ^{13}C NMR spectra were referenced to the residual solvent peak: $CDCl_3$, δ = 7.26 (^{1}H) and 77.0 ppm (^{13}C); [D_6]DMSO, δ = 2.50 (^{1}H), and 39.7 ppm (^{13}C). ^{14}N and ^{15}N NMR spectra were reported relative to nitromethane at δ = 0.0 ppm. Mass spectra were obtained with a Hewlett–Packard MS 5989B spectrometer, usually in direct mode with electron impact (70 eV). For chlorinated and brominated compounds, all peak values of molecular ions and fragments refer to the isotope ^{35}Cl and ^{79}Br. High resolution mass spectra were recorded with a Waters mass spectrometer "VG Autospec" (EI), with a WATERS mass spectrometer "Q-Tof Premier" coupled with a Waters "Acquity UPLC" (ESI), or with a Micromass mass spectrometer "LCT" coupled with a Waters "Alliance 2965 HPLC" (ESI) at the Institute of Organic Chemistry, Leibniz University of Hannover.

Nitration of Trichloroethene: Based upon Table 1, Entry 8, a mixture of concd. nitric acid (390 mL, 65% HNO_3) and phosphoric acid (60 mL, 98% H_3PO_4) was heated to 100–105 °C. An initial amount of trichloroethene (**1**; 10–12 mL from a total amount of

120 mL, 1.34 mol) was added to the vigorously stirred nitration mixture. After this initiation (the reaction normally starts within the first 10 to 15 min as indicated by the appearance of reddish-brown nitrous gases), remaining starting material **1** was added dropwise over 1.5 h. Subsequently, the reaction mixture was stirred for additional 5–6 h at 100–105 °C. After complete consumption of the starting material (monitored by GC), the reaction mixture was cooled to room temperature and the organic phase was separated. The inorganic phase was extracted twice with chloroform (2 × 200 mL). The combined organic layers were washed with water (2 × 100 mL) and dried with anhydrous calcium chloride. After evaporation of the solvent on a rotary evaporator the residue was distilled in vacuo at 1 mbar. The first fraction (107.2 g with a content of nitroethene **2** of 72.4%) was obtained at 25–60 °C. A second fraction distilled at an oil-bath temperature of 115–120 °C, with a Liebig-type condenser without cooling water to prevent solidification of partial amounts of resulting azinate **9** (19.1 g, 4.5%, b.p. 82–84 °C/1 mbar, mixture of isomers 95:5). The first fraction was redistilled in a Fischer Spaltrohr® column HMC 500 C to give pure nitroethene **2** (78.0 g, 33%, b.p. 56–57 °C/25 mbar), chloropicrin (**7**; 2.9 g, 1.3%, b.p. 39–40 °C/25 mbar, b.p. 110–111 °C/988 mbar[26]) and nitroethane **8** (23.9 g, 8.4%, b.p. 65–66 °C/25 mbar, b.p. 63 °C/11 mbar[18]).

1,1,2-Trichloro-2-nitroethene (2): Yellow liquid. IR (NaCl): $\tilde{\nu}$ = 2868, 2623, 2361, 2342, 1548, 1324, 1052, 933, 871, 777, 750, 707 cm^{-1}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 128.1 (o, *C*Cl_2); 136.5 (o, *C*ClNO_2) ppm. ^{14}N (28.9 MHz, $CDCl_3$): δ = –17.8 (s) ppm. EIMS: *m*/*z* (%) = 175 (44) [M^+], 129 (100), 94 (53). HRMS (EI): *m*/*z* calcd. for $C_2Cl_3NO_2$ [M^+] 174.8995; found 174.8996.

Trichloronitromethane (7): Colorless liquid. IR (NaCl): $\tilde{\nu}$ = 2900, 2613, 1607, 1331, 1293, 977, 910, 863, 819, 759, 865, 620 cm^{-1}. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 123.4 ppm. ^{14}N (28.9 MHz, $CDCl_3$): δ = –18.0 ppm. EIMS: *m*/*z* (%) = 163 (7) [M^+], 117 (6), 82 (25), 63 (100).

1,1,2,2-Tetrachloro-1-nitroethane (8): Colorless liquid. IR (ATR): $\tilde{\nu}$ = 3004, 1589, 1332, 1311, 1216, 1065, 894, 928, 867, 827, 761, 723, 660, 596 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 6.55 [s, ^1J(*C*,H) = 186.0 Hz, 1 H] ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 114.2 (C1), 74.6 (C2) ppm. ^{14}N (28.9 MHz, $CDCl_3$): δ = –8.9 ppm. EIMS: *m*/*z* (%) = 210 (3) [M – H]$^+$, 165 (48), 129 (14), 101 (100).

(*Z*)-1,2,2-Trichloro-2-nitroethyl [Chloro(nitro)methylene]azinate (9): Yellow oil. IR (NaCl): $\tilde{\nu}$ = 3005, 2891, 2636, 1728, 1597, 1326, 1252, 1106, 1008, 899, 871, 815, 765, 726, 673, 642 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): major isomer δ = 6.95 (s, $^1J_{C,H}$ = 188.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.8 [=C(Cl)NO_2], 109.9 (CCl_2NO_2), 96.8 (CHCl) ppm. Minor isomer δ = 6.51 (s, $^1J_{C,H}$ = 185.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.9 [=C(Cl)NO_2], 109.8 (CCl_2NO_2), 101.0 (CHCl) ppm. ^{14}N (43.4 MHz, $CDCl_3$): δ = –9.8 (CCl_2NO_2), –28.5 (=CNO_2), –66.0 [C=N(O)O] ppm. EIMS: *m*/*z* (%) = 315 (1) [M^+], 299 (1), 279 (1), 252 (17), 130 (100).

General Procedure I

2-Chloro-1,1-bis(morpholin-4-yl)-2-nitroethene (10): A solution of morpholine (3.66 g, 42.00 mmol) in MeOH (10 mL) was added dropwise to a solution of nitroethene **2** (1.76 g, 10.00 mmol) in MeOH (50 mL) at –20 °C over 10 min. The resulting mixture was kept at the same temperature for an additional 60 min with stirring. After 3 h at r.t. and subsequent cooling to 0 °C the resulting precipitate was filtered, washed with cold MeOH (5 mL), and dried in vacuo to give **10** as a yellow solid in 76% yield (2.11 g), m.p. 217–218 °C. IR (KBr): $\tilde{\nu}$ = 2919, 2858, 1537, 1497, 1384, 1280, 1233, 1162, 1108, 1068, 1028, 1000, 877, 631 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.00–3.68 (m, 8 H, 4 OCH_2), 3.59–3.23 (m, 8 H, 4 NCH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.0 (C1), 102.5 (C2), 65.9 (4 OCH_2), 50.7 (2 NCH_2) 50.3 (2 NCH_2) ppm. EIMS: *m*/*z* (%) = 277 (8) [M^+], 231 (18), 169 (27), 146 (100). HRMS (EI): *m*/*z* calcd. for $C_{10}H_{16}ClN_3O_4$ [M^+] 277.0829; found 277.0818.

10 was also synthesized from nitroethane **8** (0.21 g, 1.00 mmol) and morpholine (0.45 g, 5.20 mmol) according to a similar procedure to **GP I** at –20 °C for 1 h, then 5 h at r.t. in 63% yield.

2-Chloro-2-nitro-1,1-bis(piperidin-1-yl)ethene (11): Was obtained from **2** (1.76 g, 10.00 mmol) and piperidine (3.57 g, 42 mmol) by applying **General Procedure I**. Yellow solid, 78% yield (2.14 g). M. p. 158–159 °C. IR (KBr): $\tilde{\nu}$ = 2948, 2856, 1539, 1485, 1445, 1364, 1281, 1266, 1184, 1158, 1106, 1067, 995, 871, 739 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.46–3.31 (m, 4 H, 2 NCH_2), 3.30–3.17 (m, 4 H, 2 NCH_2), 1.89–1.53 (m, 12 H, 6 CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.9 (C1), 102.0 (C2), 51.8 (2 NCH_2), 51.0 (2 NCH_2), 25.4 (2 CH_2), 25.1 (2 CH_2), 23.9 (2 CH_2) ppm. EIMS: *m*/*z* (%) = 273 (7) [M^+], 227 (20), 144 (100). HRMS (ESI): *m*/*z* calcd. for $C_{12}H_{20}ClN_3O_2$ [M + H]$^+$ 274.1322; found 274.1324.

11 was also synthetized from **8** (0.21 g, 1.00 mmol) and piperidine (0.44 g, 5.20 mmol) following a similar procedure to **GP I** at –20 °C for 1 h, then 5 h at r.t. in 55% yield.

1,1-Bis(azepan-1-yl)-2-chloro-2-nitroethene (12): Was obtained by following **General Procedure I** from **2** (1.76 g, 10.00 mmol) and azepane (4.16 g, 42 mmol) as a yellow solid in 75% yield (2.14 g), m.p. 156–158 °C. IR (KBr): $\tilde{\nu}$ = 2920, 2856, 1527, 1469, 1365, 1353, 1303, 1261, 1167, 1066, 991, 962, 949, 860, 741, 683 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.65–3.32 (m, 8 H, 4 NCH_2), 1.90–1.52 (m, 16 H, 8 CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3 (C1), 102.5 (C2), 55.0 (2 NCH_2), 51.9 (2 NCH_2), 29.6 (2 CH_2), 29.3 (2 CH_2), 26.6 (2 CH_2), 25.9 (2 CH_2) ppm. EIMS: *m*/*z* (%) = 301 (5) [M^+], 265 (3), 255 (11), 158 (30), 105 (100). HRMS (ESI): *m*/*z* calcd. for $C_{14}H_{25}ClN_3O_2$ [M + H]$^+$ 302.1635; found 302.1634.

12 was also obtained by following a similar procedure to **GP I** from **8** (0.21 g, 1.00 mmol) and piperidine (0.52 g, 5.20 mmol) at –20 °C for 1 h, then 3 h at r.t. in 67% yield.

1,1-Bis(azocan-1-yl)-2-chloro-2-nitroethene (13): Was prepared by following **General Procedure I** from **2** (1.76 g, 10.00 mmol) and azocane (4.47 g, 42 mmol) as a yellow solid in 73% yield (2.41 g), m.p. 138–139 °C. IR (KBr): $\tilde{\nu}$ = 2916, 2848, 1504, 1476, 1397, 1298, 1253, 1216, 1176, 1050, 992, 946, 854, 754, 686, 610 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.70–3.30 (m, 8 H, 4 NCH_2), 1.91–1.43 (m, 20 H, 10 CH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.1 (C1), 101.0 (C2), 53.6 (2 NCH_2), 49.8 (2 NCH_2), 28.4 (2 CH_2), 26.9 (2 CH_2), 26.2 (2 CH_2), 25.4 (2 CH_2), 25.1 (2 CH_2) ppm. EIMS: *m*/*z* (%) = 329 (1) [M^+], 283 (34), 172 (47), 112 (100). HRMS (ESI): *m*/*z* calcd. for $C_{16}H_{29}ClN_3O_2$ [M + H]$^+$ 330.1948; found 329.1945.

13 was also obtained by following **General Procedure I** from **8** (0.21 g, 1.00 mmol) and azocane (0.59 g, 5.20 mmol) at –20 °C for 1 h, then 4 h at r.t. in 64% yield.

2-Chloro-1,1-bis[1-(3-chlorophenyl)piperazine-4-yl]-2-nitroethene (14): Was synthesized by following **General Procedure I** from **2** (1.76 g, 10.00 mmol) and 1-(3-chlorophenyl)piperazine (8.26 g, 42 mmol) as a yellow solid in 64% yield (3.18 g), m.p. 180–182 °C. IR (KBr): $\tilde{\nu}$ = 3115, 2912, 2850, 1594, 1567, 1534, 1486, 1387, 1342, 1288, 1228, 1163, 1071, 1028, 941, 855, 769, 689 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 7.70–6.51 (m, 8 H, Ar), 3.75–3.12 (m, 16 H, piperazinyl-H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ =

161.4 (C1), 151.8 (C5), 134.1 (C7), 130.8 (C9), 118.9 (C8), 115.3 (C6), 114.3 (C10), 101.0 (C2), 49.7 (2 NCH_2), 49.2 (2 NCH_2), 47.4 (2 NCH_2), 47.1 (2 NCH_2) ppm. EIMS: *m/z* (%) = 495 (1) [M^+], 478 (25), 449 (2), 300 (7), 166 (100). HRMS (ESI): *m/z* calcd. for $C_{22}H_{24}Cl_3N_5O_2Na$ [M + Na]$^+$ 518.0893; found 518.0890.

14 was also obtained by following **General Procedure I** from **8** (0.21 g, 1.00 mmol) and 1-(3-chlorophenyl)piperazine (1.02 g, 5.20 mmol) at –20 °C for 1 h, then 4 h at r.t. in 52% yield.

General Procedure II

(*E*)-Morpholino(nitro)methanone *O*-(1,2,2-Trichloro-2-nitroethyl) Oxime (19): A solution of morpholine (0.96 g, 11.00 mmol) in MeOH (5 mL) was added dropwise to a solution of azinate **9** (1.58 g, 5.00 mmol) in MeOH (10 mL) at –10 °C over 20 min. The resulting reaction mixture was kept at the same temperature for an additional 60 min with stirring. After 4 h at r.t. and subsequent cooling to 0 °C the resulting precipitate was filtered, washed with cold MeOH (5 mL), and then dried in vacuo to give **19** as a mixture of *E*- and *Z*-isomers (94.4:5.6). Yellow solid, 78% yield (1.37 g), m.p. 108–109 °C. IR (KBr): $\tilde{\nu}$ = 2986, 2866, 1693, 1593, 1556, 1338, 1269, 1113, 1090, 968, 890, 800, 714, 588 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): Major isomer, δ = 6.67 (s, $^1J_{C,H}$ = 188.2 Hz, 1 H), 3.79–3.55 (m, 4 H, 2 OCH_2), 3.37–3.30 (m, 4 H, 2 NCH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.8 [=$C(NR_2)NO_2$], 110.8 (CCl_2NO_2), 96.9 (CHCl), 66.2 (2 OCH_2), 48.4 (2 NCH_2) ppm. ^{14}N (28.9 MHz, $CDCl_3$): δ = –8.8 (NO_2), –14.0 (NO_2), –75.0 (C=N-O), –313.3 (NCH_2) ppm. Minor isomer, δ = 6.27 (s, $^1J_{C,H}$ = 184.8 Hz 1 H), 3.79–3.55 (m, 4 H, 2 OCH_2), 3.41–3.36 (m, 4 H, 2 NCH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.5 [=$C(NR_2)$-NO_2], 110.7 (CCl_2NO_2), 100.9 (CHCl), 66.3 (2 OCH_2), 48.3 (2 NCH_2) ppm. EIMS: *m/z* (%) = 350 (2) [M^+], 304 (8), 269 (2), 128 (20), 112 (100). HRMS (EI): *m/z* calcd. for $C_7H_9Cl_3N_4O_6$ [M^+] 349.9588; found 349.9580. The structure of *E*-oxime **19** was evidenced by single-crystal X-ray diffraction analysis (Figure 3).

(*E*)-[3,4-Dihydroisoquinolin-2(1*H*)-yl](nitro)methanone *O*-(1,2,2-Trichloro-2-nitroethyl) Oxime (20): The product was prepared by following **General Procedure II** from azinate **9** (1.58 g, 5.00 mmol) and 1,2,3,4-tetrahydroisoquinoline (1.47 g, 11 mmol). Pale yellow solid, 71% yield (1.41 g), m.p. 85–87 °C. IR (KBr): $\tilde{\nu}$ = 2998, 1686, 1583, 1562, 1497, 1443, 1394, 1329, 1251, 1101, 1048, 998, 953, 800, 756, 692 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.22 (m, 2 H), 7.20–7.16 (m, 1 H), 7.07–7.02 (m, 1 H), 6.70 (s, 1 H, CHCl), 4.52 (s, 2 H), 3.66–3.54 (m, 2 H), 3.05–3.00 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.2 [=$C(NR_2)NO_2$], 133.0 (Cq), 130.8 (Cq), 129.1 (CH), 127.3 (CH), 126.8 (CH), 126.1 (CH), 110.9 (CCl_2NO_2), 97.1 (CHCl), 49.7 (CH_2), 46.4 (CH_2), 28.6 (CH_2) ppm. EIMS: *m/z* (%) = 396 (1) [M^+], 350 (1), 304 (1), 193 (5), 158 (48), 104 (100). HRMS (ESI): *m/z* calcd. for $C_{12}H_{12}Cl_3N_4O_5$ [M + H]$^+$ 396.9873; found 396.9878.

(*E*)-[4-(3-Chlorophenyl)piperazin-1-yl](nitro)methanone *O*-(1,2,2-Trichloro-2-nitroethyl) Oxime (21): The product was prepared by following **General Procedure II** from azinate **9** (1.58 g, 5.00 mmol) and 1-(3-chlorophenyl)piperazine (2.16 g, 11 mmol). Pale yellow solid, 79% yield (1.82 g), m.p. 131–132 °C. IR (KBr): $\tilde{\nu}$ = 2948, 2834, 1690, 1592, 1556, 1453, 1400, 1334, 1315, 1219, 1148, 1118, 1015, 956, 869, 807, 731, 692, 632 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.18 (m, 1 H), 6.94–6.88 (m, 2 H), 6.82–6.78 (m, 1 H), 6.69 (s, 1 H, CHCl), 3.52–3.46 (m, 4 H), 3.33–3.25 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.9 [=$C(NR_2)NO_2$], 151.6 (Cq), 135.2 (Cq), 130.4 (CH), 121.0 (CH), 116.9 (CH), 114.9 (CH), 110.9 (CCl_2NO_2), 97.1 (CHCl), 49.1 (2 CH_2), 48.2 (2 CH_2) ppm. EIMS: *m/z* (%) = 459 (16) [M^+], 331 (2), 221 (100), 139 (85). HRMS (ESI): *m/z* calcd. for $C_{13}H_{14}Cl_4N_5O_5$ [M + H]$^+$ 459.9749; found 459.9747.

(1*E*,1′*E*)-Nitro(4-{(*E*)-nitro[(1,2,2-trichloro-2-nitroethoxy)imino]-methyl}piperazin-1-yl)methanone *O*-(1,2,2-Trichloro-2-nitroethyl) Oxime (22): The product was synthesized by following **General Procedure II** from azinate 9 (1.58 g, 5.00 mmol) and piperazine (0.47 g, 5.50 mmol). Pale yellow solid, 88% yield (1.35 g), m.p. 184–186 °C. IR (ATR): $\tilde{\nu}$ = 3001, 2936, 1675, 1591, 1558, 1447, 1401, 1357, 1332, 1285, 1204, 1092, 1007, 969, 892, 809, 758, 683, 621 cm^{-1}. ^{1}H NMR (600 MHz, [D_6]DMSO): δ = 7.47 (s, $^1J_{C,H}$ = 187.7 Hz, 2 H, CHCl), 3.44 (s, 8 H) ppm. ^{13}C NMR (150 MHz, [D_6]DMSO): δ = 156.7 [=$C(NR_2)NO_2$], 110.9 (CCl_2NO_2), 96.8 (CHCl), 48.1 (4 CH_2) ppm. ^{14}N (43.4 MHz, $CDCl_3$): δ = –12.1 (NO_2), –19.5 (NO_2), –72.4 (C=N-O), –314.4 (NCH_2) ppm. EIMS: *m/z* (%) = 612 (1) [M^+], 566 (1), 531 (2), 328 (4), 282 (7), 138 (100). HRMS (ESI): *m/z* calcd. for $C_{10}H_{11}Cl_6N_8O_{10}$ [M + H]$^+$ 612.8729; found 612.8732.

1,3-Bis(4-chlorophenyl)-2-(1,2,2-trichloro-2-nitroethoxy)guanidine (23): The product was synthesized by following **General Procedure II** from azinate **9** (1.58 g, 5.00 mmol) and (2.81 g, 22 mmol) 4-chloroaniline, reaction time 1 h at –10 °C and 14 h at r.t. Beige solid, 65% yield (1.54 g), m.p. 141–142 °C. IR (ATR): $\tilde{\nu}$ = 3417, 1638, 1584, 1532, 1490, 1431, 1299, 1345, 1137, 1088, 1014, 931, 829, 709, 663, 562 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.20 (m, 4 H), 7.14–7.08 (m, 4 H), 6.72 (s, 1 H, CHCl), 6.48 (br. s, 1 H, NH), 5.43 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.8 [=$C(NAr_2)_2$], 129.6 (2 CH), 129.4 (2 CH), 128.8 (2 CH), 128.5 (2 CH), 125.4 (Cq), 125. 6 (Cq), 120.5 (Cq), 120.3 (Cq), 111.5 (CCl_2NO_2), 97.1 (CHCl) ppm. EIMS: *m/z* (%) = 470 (5) [M^+], 294 (10), 278 (12), 263 (8), 243 (6), 127 (100) [$NH_2C_6H_4Cl$]. HRMS (ESI): *m/z* calcd. for $C_{15}H_{12}Cl_5N_4O_3$ [M + H]$^+$ 470.9352; found 470.9358.

1,3-Bis(4-bromophenyl)-2-(1,2,2-trichloro-2-nitroethoxy)guanidine (24): The product was prepared by following **General Procedure II** from azinate **9** (1.58 g, 5.00 mmol) and (3.78 g, 22 mmol) 4-bromoaniline, reaction time 1 h at –10 °C and 18 h at r.t. Beige solid, 70% yield (1.97 g), m.p. 154–156 °C. IR (ATR): $\tilde{\nu}$ = 3413, 3396, 1640, 1585, 1531, 1487, 1432, 1362, 1298, 1233, 1133, 1119, 1011, 930, 826, 713, 661, 539 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 8.7 Hz, 2 H), 7.36 (d, *J* = 8.6 Hz, 2 H), 7.10–7.02 (m, 4 H), 6.72 (s, 1 H, CHCl), 6.48 (br. s, 1 H, NH), 5.41 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.6 [=$C(NAr_2)_2$], 137.5 (Cq), 135.4 (Cq), 132.9 (2 CH), 132.0 (2 CH), 125.7 (2 CH), 120.8 (2 CH), 119.4 (Cq), 115.7 (Cq), 111.5 (CCl_2NO_2), 97.1 (CHCl) ppm. EIMS: *m/z* (%) = 558 (5) [M^+], 382 (10), 366 (12), 354 (7), 287 (20), 171 (100). HRMS (ESI): *m/z* calcd. for $C_{15}H_{12}Br_2Cl_3N_4O_3$ [M + H]$^+$ 558.8342; found 558.8341.

1,3-Bis(4-fluorophenyl)-2-(1,2,2-trichloro-2-nitroethoxy)guanidine (25): The product was synthesized by following **General Procedure II** from azinate **9** (1.58 g, 5.00 mmol) and 4-fluoroaniline (2.44 g, 22 mmol), reaction time 1 h at –10 °C and 18 h at r.t. Beige solid, 43% yield (0.95 g), m.p. 81–82 °C. IR (ATR): $\tilde{\nu}$ = 3416, 1640, 1586, 1541, 1506, 1395, 1299, 1211, 1140, 1013, 933, 831, 710, 659, 608, 513 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.12 (br. m, 4 H), 7.10–7.01 (br. m, 2 H), 6.99–6.89 (br. m, 2 H), 6.71 (s, 1 H, CHCl), 6.46 (br. s, 1 H, NH), 5.29 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1 (d, $^1J_{C,F}$ = 242.8 Hz, CF), 159.2 (d, $^1J_{C,F}$ = 242.8 Hz, CF), 152.9 [=$C(NAr_2)_2$], 134.3 (Cq), 132.1 (Cq), 127.2 (d, $^3J_{C,F}$ = 8.4 Hz, 2 CH), 121.6 (d, $^3J_{C,F}$ = 8.4 Hz, 2 CH), 116.7 (d, $^2J_{C,F}$ = 23.4 Hz, 2 CH), 115.6 (d, $^2J_{C,F}$ = 23.4 Hz, 2 CH), 111.6 (CCl_2NO_2), 97.3 (CHCl) ppm. EIMS: *m/z* (%) = 438 (5) [M^+], 262 (20), 246 (19), 231 (12), 111 (100). HRMS (ESI): *m/z* calcd. for $C_{15}H_{11}Cl_3F_2N_4O_3$ [M + H]$^+$ 438.9943; found 438.9946.

General Procedure III

(*E*)-*N*-(1,2,2-Trichloro-2-nitroethoxy)morpholine-4-carbimidoyl Chloride (26): To a suspension of oxime **19** (352 mg, 1.00 mmol) in MeOH (5 mL) at 0 °C was added dropwise concd. aqueous HCl (37%, 1 mL, 10 mmol) over 10 min. The resulting reaction mixture was kept at the same temperature for an additional 60 min and then for 18 h at r.t. with stirring. Upon completion of the reaction, the cooled reaction mixture was diluted with cold water (30 mL) and extracted with chloroform (3 × 20 mL). The organic phase was washed with water (2 × 15 mL) and then dried with calcium chloride. After evaporation of the solvent the obtained oil was purified by column chromatography (petroleum ether/ethyl acetate, 10:1) and finally dried in vacuo. Pure oil, 72% yield (246 mg). IR (ATR): $\tilde{\nu}$ = 2972, 2859, 1588, 1452, 1372, 1326, 1267, 1233, 1117, 1031, 961, 900, 835, 720 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.66 (s, $^1J_{C,H}$ = 187.8 Hz, 1 H), 3.76–3.71 (m, 4 H, 2 OCH_2), 3.43–3.39 (m, 4 H, 2 NCH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.6 [=C(NR_2)Cl], 111.2 (CCl_2NO_2), 96.8 (CHCl), 65.9 (2 OCH_2), 47.9 (2 NCH_2) ppm. EIMS: *m*/*z* (%) = 339 (12) [M$^+$], 258 (5), 163 (50), 163 (17), 133 (100). HRMS (ESI): *m*/*z* calcd. for $C_7H_{10}Cl_4N_3O_4$ [M + H]$^+$ 339.9425; found 339.9429.

(*E*)-*N*-(1,2,2-Trichloro-2-nitroethoxy)-3,4-dihydroisoquinoline-2(1*H*)-carbimidoyl Chloride (27): The product was prepared by following **General Procedure III** from oxime **20** (398 mg, 1.00 mmol) and aqueous HCl (37%, 1 mL, 10 mmol). White solid, 91% yield (352 mg), m.p. 109–110 °C. IR (KBr): $\tilde{\nu}$ = 2996, 2859, 1569, 1498, 1445, 1390, 1347, 1243, 1114, 1004, 955, 871, 753, 628 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24–7.19 (m, 2 H), 7.18–7.10 (m, 2 H), 6.72 (s, 1 H, CHCl), 4.60 (s, 2 H), 3.74 (t, *J* = 5.9 Hz, 2 H), 2.94 (t, *J* = 5.9 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.1 [=C(NR_2)Cl], 133.8 (Cq), 132.1 (Cq), 128.7 (CH), 126.9 (CH), 126.5 (CH), 126.2 (CH), 111.3 (CCl_2NO_2), 97.0 (CHCl), 49.4 (CH_2), 45.2 (CH_2), 28.4 (CH_2) ppm. EIMS: *m*/*z* (%) = 385 (5) [M$^+$], 304 (4), 209 (28), 193 (100). HRMS (ESI): *m*/*z* calcd. for $C_{12}H_{12}Cl_4N_3O_3$ [M + H]$^+$ 385.9633; found 384.9631.

(*E*)-*N*-(1,2,2-Trichloro-2-nitroethoxy)morpholine-4-carbimidoyl Bromide (28): The product was obtained by following **General Procedure III** from oxime **19** (352 mg, 1.00 mmol) and HBr (33%, 365 mg, 1.50 mmol) in acetic acid. Reaction time 1 h at 0 °C, 1 d at r. t., and a further 5 h at 30–35 °C. Yellow oil, 44% yield (170 mg). IR (ATR): $\tilde{\nu}$ = 2973, 2858, 1588, 1451, 1369, 1266, 1226, 1114, 1026, 955, 717 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.66 (s, 1 H, CHCl), 3.70–3.65 (m, 4 H, 2 OCH_2), 3.45–3.40 (m, 4 H, 2 NCH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.7 [=C(NR_2)-Br], 111.1 (CCl_2NO_2), 96.5 (CHCl), 65.8 (2 OCH_2), 49.3 (2 NCH_2) ppm. EIMS: *m*/*z* (%) = 383 (5) [M$^+$], 337 (5), 304 (5), 207 (55), 177 (55), 112 (100). HRMS (ESI): *m*/*z* calcd. for $C_7H_{10}BrCl_3N_3O_4$ [M + H]$^+$ 383.8920; found 383.8914.

(*E*)-*N*-(1,2,2-Trichloro-2-nitroethoxy)-3,4-dihydroisoquinoline-2(1*H*)-carbimidoyl Bromide (29): The product was synthesized by following **General Procedure III** from oxime **20** (398 mg, 1.00 mmol) and HBr (33%, 365 mg, 1.50 mmol) in acetic acid. Reaction time 1 h at 0 °C, and 18 h at r.t. White solid, 68% yield (293 mg), m.p. 240–241 °C. IR (ATR): $\tilde{\nu}$ = 2995, 2857, 1562, 1497, 1383, 1346, 1240, 1114, 1088, 950, 859, 752, 641 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.20 (m, 2 H), 7.19–7.12 (m, 2 H), 6.73 (s, 1 H, CHCl), 4.64 (s, 2 H), 3.77 (t, *J* = 5.9 Hz, 2 H), 2.93 (t, *J* = 5.9 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.1 [=C(NR_2)Br], 133.9 (Cq), 132.2 (Cq), 128.7 (CH), 126.9 (CH), 126.5 (CH), 126.2 (CH), 111.3 (CCl_2NO_2), 96.8 (CHCl), 50.8 (CH_2), 46.9 (CH_2), 28.4 (CH_2) ppm. EIMS: *m*/*z* (%) = 429 (3) [M$^+$], 350 (3), 253 (4), 237 (14), 104 (100). HRMS (ESI): *m*/*z* calcd. for $C_{12}H_{12}BrCl_3N_3O_3$ [M + H]$^+$ 429.9128; found 429.9127.

(*E*)-4-(3-Chlorophenyl)-*N*-(1,2,2-trichloro-2-nitroethoxy)piperazine-1-carbimidoyl Chloride (30): The product was synthesized by following **General Procedure III** from oxime **21** (461 mg, 1.00 mmol) and aqueous HCl (37%, 1 mL, 10 mmol). Reaction time 1 h at 0 °C, 15 h at r.t. Orange solid, 46% yield (207 mg), m.p. 214–215 °C. IR (ATR): $\tilde{\nu}$ = 2996, 2856, 1587, 1564, 1484, 1448, 1377, 1229, 1119, 1023, 948, 905, 836, 723, 684 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20 (t, *J* = 8.2 Hz, 1 H), 6.91–6.87 (m, 2 H), 6.81 (ddd, *J* = 8.2, 2.3, 0.9 Hz, 1 H), 6.68 (s, 1 H, CHCl), 3.61–3.56 (m, 4 H), 3.25–3.21 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.7 (Cq), 147.4 [=C(NR_2)Cl], 135.1 (Cq), 130.2 (CH), 120.5 (CH), 116.6 (CH), 114.6 (CH), 111.2 (CCl_2NO_2), 96.9 (CHCl), 48.3 (2 CH_2), 47.4 (2 CH_2) ppm. EIMS: *m*/*z* (%) = 448 (10) [M$^+$], 337 (5), 256 (25), 221 (45), 193 (27), 139 (100). HRMS (ESI): *m*/*z* calcd. for $C_{13}H_{14}Cl_5N_4O_3$ [M + H]$^+$ 448.9509; found 448.9514.

(*E*)-4-(4-Bromo-3-chlorophenyl)-*N*-(1,2,2-trichloro-2-nitroethoxy)-piperazine-1-carbimidoyl Bromide (31): The product was prepared by following **General Procedure III** from oxime **21** (461 mg, 1.00 mmol) and HBr (33%, 730 mg, 3.00 mmol) in acetic acid. Reaction time 1 h at r.t., then at reflux temperatures for 10 h. Brown oil, 52% yield (298 mg). IR (ATR): $\tilde{\nu}$ = 2988, 2832, 1584, 1476, 1449, 1379, 1328, 1224, 1115, 1022, 942, 842, 802, 758, 719 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 8.9 Hz, 1 H), 6.98 (d, *J* = 2.9 Hz, 1 H), 6.70 (s, 1 H, CHCl), 6.69 (dd, *J* = 8.9, 2.9 Hz, 1 H), 3.64–3.60 (m, 4 H), 3.22–3.17 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.6 (Cq), 140.3 [=C(NR_2)Br], 135.0 (Cq-Cl), 133.8 (CH), 117.9 (CH), 116.2 (CH), 112.4 (Cq-Br), 111.2 (CCl_2NO_2), 96.9 (CHCl), 48.6 (2 CH_2), 48.2 (2 CH_2) ppm. EIMS: *m*/*z* (%) = 570 (7) [M$^+$], 524 (2), 381 (20), 297 (80), 273 (15), 219 (100). HRMS (ESI): *m*/*z* calcd. for $C_{13}H_{13}Br_2Cl_4N_4O_3$ [M + H]$^+$ 570.8109; found 570.8106.

(1*E*,4*E*)-*N*′^{1},*N*′^{4}-Bis(1,2,2-trichloro-2-nitroethoxy)piperazine-1,4-bis(carbimidoyl Dichloride) (32): The product was obtained by following **General Procedure III** from dioxime **22** (615 mg, 1.00 mmol) and HCl (37%, 1 mL, 10 mmol). Reaction time 1 h at r.t., then at reflux temperatures for 1 h. After cooling to r.t. the resulting precipitate was filtered, washed with methanol (2 × 5 mL), and dried in vacuo. White solid, 87% yield (517 mg), m.p. 137–139 °C. IR (ATR): $\tilde{\nu}$ = 2993, 2865, 1580, 1451, 1389, 1281, 1230, 1165, 1125, 1015, 936, 862, 752, 718, 632, 495 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 6.66 (s, $^1J_{C,H}$ = 187.6 Hz, 2 H, CHCl), 3.50 (s, 8 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 147.0 [=C(NR_2)Cl], 111.2 (CCl_2NO_2), 96.8 (CHCl), 46.6 (4 CH_2) ppm. ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 7.173 (s, 1 H, CHCl), 7.172 (s, 1 H, CHCl), 4.42 (s, 8 H) ppm. ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 147.0 [=C(NR_2)Cl], 111.2 (CCl_2NO_2), 96.9 (CHCl), 46.3 (4 CH_2) ppm. ^{14}N (43.4 MHz, [D$_6$]DMSO): δ = –10.9 (s, NO_2, CCl_2NO_2), –78.7 (s, C=N-O), –300.8 (s, NCH_2) ppm. EIMS: *m*/*z* (%) = 594 (6) [M$^+$], 509 (7), 398 (7), 222 (73), 206 (25), 192 (83), 171 (100). HRMS (ESI): *m*/*z* calcd. for $C_{10}H_{11}Cl_8N_6O_6$ [M + H]$^+$ 590.8248; found 590.8254.

(1*E*,4*E*)-*N*′^{1},*N*′^{4}-Bis(1,2,2-trichloro-2-nitroethoxy)piperazine-1,4-bis(carbimidoyl Dibromide) (33): The product was synthesized by following **General Procedure III** from dioxime **22** (615 mg, 1.00 mmol) and HBr (33%, 730 mg, 3.00 mmol) in acetic acid. Reaction time 1 h at r.t., then at reflux temperatures for 10 h. White solid, 68% yield (464 mg), m.p. 160–162 °C. IR (ATR): $\tilde{\nu}$ = 2993, 2864, 1584, 1575, 1450, 1383, 1279, 1224, 1162, 1121, 1009, 933, 860, 741, 717, 642, 600, 493 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ

= 6.68 (s, $^1J_{C,H}$ = 187.6 Hz, 2 H, CHCl), 3.54 (s, 8 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.0 [=C(NR_2)Br], 111.1 (CCl_2NO_2), 96.6 (CHCl), 48.1 (4 CH_2) ppm. EIMS: *m*/*z* (%) = 678 (7) [M^+], 599 (4), 504 (10), 407 (22), 312 (39), 282 (40), 110 (100). HRMS (ESI): *m*/*z* calcd. for $C_{10}H_{10}Br_2Cl_6N_6O_6$ [M + H]$^+$ 678.7238; found 678.7232.

Biological Assays

Investigation of the Antimicrobial Activities: Overnight cultures of the bacteria were grown aerobically at 37 °C in either Müller Hinton broth with added 1% glucose and pH 7.2 for Gram-negative strains, Trypticase soy yeast extract medium (TSY – 30 g/l trypticase soy broth, 3 g/L yeast extract, pH 7.2) for Gram-positive strains and *Escherichia coli*, and a universal medium for *Candida albicans* (Y – 3 g/L yeast extract, 3 g/L malt extract, 5 g/L peptone from soybeans, 10 g/L glucose, pH 7.2). The cultures were adjusted to 1×10^6 cfu/mL (which resulted in 5×10^5 cfu/mL in the test). 50 μL of test culture was added to 50 μL of a serial dilution of the test compounds in the appropriate medium for the different strains in accordance with standardized procedures.[27] Test compounds from stock solutions in DMSO were used at final concentrations of 20, 10, 5, 2.5, 1.3 and 0.6 μg/mL. The highest DMSO concentration in the assay was 1%, which had no apparent effect to the growth of the bacteria. After an incubation time of 18 h at 37 °C under moist conditions, the optical density at 600 nm was measured with a Fusion Universal Microplate Analyser (Perkin–Elmer, Waltham, USA). The lowest concentration that completely suppressed growth defined the MIC values.

The following bacterial strains were used: Gram-negative: *Acinetobacter baumannii* (DSM 30007), *Enterobacter cloacae* (DSM 26481), *Escherichia coli* (DSM 1116), *Klebsiella pneumoniae* (DSM 11678) and *Pseudomonas aeruginosa* PA7 (DSM 24068). Gram-positive: *Enterococcus faecium* (DSM 20477), *Staphylococcus aureus* MRSA (DSM 11822), *Staphylococcus aureus* MSSA (DSM 346). Yeast: *Candida albicans* (DSM 11225).

Cell Viability Tests: The effect of compound on cell viability was probed with a WST-1 tests by a procedure in accordance with Ishiyama et al.[28] modified by Sasse et al.[29] The following immortalized cell lines were used: The mouse fibroblast cell line L929 (DSM ACC 2), the human cervix carcinoma cell line KB-3-1 (DSM ACC 158) and the human breast cancer cell line MCF-7 (DSM ACC 115). In addition, the conditional immortalized human fibroblast cell line FS4-LTM was used without doxycyclin to induce primary cell-like behavior (Pub. No.: US2011/0189142 A2).

Briefly, the subconfluent cells were washed with Earle's Balanced Salt Solution, Gibco, without Ca and Mg, trypsinized and re-suspended in Dulbecco's modified eagle's medium that contained 5% fetal bovine serum (FBS; L929, KB-31, FS4-LTM) or Roswell Park Memorial Institute medium that contained 5% FBS, 0.5% Minimum Essential Medium Non-Essential Amino Acids, Gibco (MEM NEAA), 0.5% GlutaMAX (Gibco) and insulin at 5 μg/mL (MCF-7). 60 μL of serial dilutions of the test compounds were added to 120 μL aliquots of a cell suspension (5000 cells) in 96-well microtiter plates. Blank and solvent controls were incubated under identical conditions. The compounds were incubated for 5 d with cell lines L929, KB-3-1, and MCF-7, respectively, and for 24 h with cell line FS4-LTM. After the incubation period 5 μL WST-1 (ready to use solution by Roche) was added. The microsomal triglyceride transfer proteins were briefly shaken and then centrifuged at 1800 g for 3 min. The incubation time of the plates at 37 °C varied between the cell lines from 20 min for KB-3-1 to 2 h for MCF-7 before measuring at 450 nm (reference 600 nm) at the Infinite 200 PRO plate reader (Tecan, Männedrof, Switzerland). The percentage of viable cells was calculated as the mean with respect to the controls set to 100%.

Crystal Data

19: $C_7H_9Cl_3N_4O_6$, (351.53 g mol^{-1}): A suitable single crystal of the title compound was selected under a polarization microscope and mounted in a glass capillary (d = 0.3 mm). The crystal structure was determined by X-ray diffraction analysis by using graphite monochromated Mo-K_α radiation (0.71073 Å) [T = 223(2) K], whereas the scattering intensities were collected with a single crystal diffractometer (STOE IPDS II). The crystal structure was solved by direct methods by using SHelfls-97[30] and refined by using alternating cycles of least-squares refinements against F^2 (shelfll-97).[30] All non-H atoms were located in difference Fourier maps and were refined with anisotropic displacement parameters. The H positions were determined by a final difference Fourier synthesis.

$C_7H_9Cl_3N_4O_6$ crystallized in the triclinic space group $P\bar{1}$ (no. 2), lattice parameters a = 7.700(2) Å, b = 9.002(2) Å, c = 10.018(2) Å, α = 89.55(2)°, β = 79.67(2)°, γ = 84.60(2)°, V = 680.1(3) Å^3, Z = 2, $d_{calcd.}$ = 1.717 g cm^{-3}, F(000) = 356 by using 2458 independent reflections and 218 parameters. $R1$ = 0.0408, $wR2$ = 0.0978 [$I > 2\sigma(I)$], goodness of fit on F^2: 1.028, residual electron density: 0.332 and –0.292 e Å^{-3}.

CCDC-1034618 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Further experimental details and copies of the ^{1}H and ^{13}C NMR spectra.

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