Reinvestigation of the Nitration of Trichloroethene, Subsequent Reactions of its Nitration Products, and Biological Evaluation of the Synthesized rare Nitroethoxyguanidines, Trichloro-nitroethyloxime Ethers, and Carbimidoyl Halides^[‡]

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The nitration reaction of trichloroethene (**1**) to the main products trichloronitroethene (TCNiE **2**, up to 60.8%, GC), 1,1,2,2-tetrachloro-1-nitroethane (**8**, up to 25.1%, GC), and 1,2,2-trichloro-2-nitroethyl (chloro(nitro)methylene)azinate (**9**, up to 8.0%, GC) was comprehensively investigated and optimized. Different 1,1-diamino-2-chloro-2-nitroethenes, 2-nitroethoxyguanidines, as well as the 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 the (*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 (**20**) inhibited the growth of methicillin-resistant and sensitive *Staphylococcus aureus* (MRSA, MSSA) with minimum inhibitory concentrations (MIC) of $1.3 \mu\text{g}\cdot\text{mL}^{-1}$ and reduced the viability of the MCF-7 cancer cell line with an IC_{50} of $0.2 \mu\text{g}/\text{mL}$.

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 variously functionalized compounds. Particularly, 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 hitherto 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 H₂-receptor antagonist that inhibits stomach acid production. Additionally, it is applied as 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 contrast to this medical application, imidacloprid (Figure 1) is a systemic insecticide which 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 drug and plant protectors.^[2-4]

In contrast to haloalkenes, the introduction of an additional nitro substituent, providing 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 cycloadditions.^[5] Furthermore, such nitroalkenes may be selectively reduced to 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-nitroethene (TCNiE, **2**), a perchlorovinyllogue of nitril chloride. The first attempt to synthesize this useful C₂-building block was carried out already

in the year 1873 upon treatment of tetrachloroethene with a mixture of concentrated sulfuric and red fuming nitric acid.^[6a] Recurrence to this experimental protocol in 1902 exclusively led to isolation of trichloroacetic acid.^[6b] However in 1960 a successful synthesis of **2** with 77.5% chemical 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] The starting material **3** itself was accessible via halonitration of **1** with chlorine gas and N₂O₄ in chloroform for 29 h, but with only 5% chemical yield. An alternative formation of **2** was possible upon reaction of **1** with N₂O₄ in CCl₄ at 0 °C, but also with only 5% yield.^[7] TCNiE (**2**) was also formed via addition of nitryl chloride to dichloroacetylene (**4**) in diethyl ether at 0 °C (no yield given).^[9] The acetylenic precursor **4** itself was obtained upon dehydrochlorination of **1** with KOH in the presence of CaO. Furthermore, heating of **1** with 3 equivalents of nitrogen dioxide in an autoclave at 80 °C for 6 h resulted in **2** with 32% yield.^[10]

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

The current synthesis of **2** is based upon an electrophilic nitration of the inexpensive industrial solvent **1** with nitric acid.^[11,12] Recently, we developed the synthesis of **2** in laboratory scale (100 g and above) via 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 lead to pure **2** in 32% yield. In contrast to previous attempts, careful temperature control of the reaction and of subsequent distillation conditions

allowed the synthesis of 1,1,2-trichloro-2-nitroethene (**2**) with high purity.^[11] 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]

Aside from these synthetic aspects, TCNiE (**2**) shows fungicidal activity against different aquatic weeds^[11] and against *Fusarium oxysporum*.^[14] In addition, **2** is applied for controlling 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 in order to increase the chemical yield of pure nitroethene **2**. In addition, we explored the byproducts of this reaction which result from unfavored reaction pathways, e.g. oxidation or chlorination. In the first 3 entries of Table 1 we applied different amounts of nitric acid, in entries 4 – 9 in combination with sulfuric or phosphoric acid, and in 10 with oleum. In entries 11/12 nitronium tetrafluoroborate was used. Finally, entries 13/14 correspond to mixtures of nitric acid and acetic acid, and 15/16 with trifluoroacetic acid, respectively. At first, we applied a 5% w/w solution of 1,2,4,5-tetrachlorobenzene (**6**) (internal standard) in trichloroethene (**1**). Determined via 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). As the relative amount of **6** remained unchanged during this reaction, additionally 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 conc. HNO₃ and conc. H₂SO₄ (61.3% yield according to GC, entry 4, table 1), whereas the highest ratio of **2** to **6** with a value of 6.7:1 was observed in entry 8 with a 60.8% content of **2**. As byproducts, trichloronitromethane (chloropicrin) (**7**, ranging from 0.4 to 3.4%), 1,1,2,2-tetrachloro-1-nitroethane (**8**, 9.0 to 25.1%), and 1,2,2-trichloro-2-nitroethyl (chloro(nitro)-methylene)azinate (**9**, 0 to 8.0%) were isolated and characterized (Scheme 2, Table 1).

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

The 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%, GC), but could not be isolated even upon purification of the reaction mixture by means of a Fischer Spaltrohr® column HMC 500 C. Nitroethane **8** is known as sterilizer, insecticide, herbicide, and nematocide^[17] It is accessible by condensation of nitrosyl chloride with ethane **1** within 14 days at r.t. in a yield of 88%^[18], or by nitration of **1** with a mixture of 98% H₂SO₄ and 98% HNO₃ (15:11 ratio) at 50-55 °C within 6 h^[17], or by nitration of **1** with 98% HNO₃ and P₂O₅ at 90 °C within 2 h.^[17]

Table 1. Nitration of trichloroethene (**1**) (For exper. details see Supp. Inf.).

	1	2	7	8	9	6
Entry	yield (GC) [%]					ratio 2:6
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

The assumed mechanism for the formation of the nitration products **2** and **7-9** is given in Scheme 3. In detail, starting material **1** reacts with a nitronium cation to form the highly substituted ethyl cations **A** and **B**. Subsequent elimination of a proton from **A** leads to the nitroethene **2**, which is then hydrated to the aliphatic alcohol **C**. Afterwards,

dehydrochlorination of **C** provides the acetyl chloride derivative **D** which readily reacts with water to form the 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 the *aci*-form **H** of the abovementioned chlorodinitromethane **G** to form azinate **9**. In addition, formation of nitroethane **8** is conceivable by treatment of ethane derivative **B** with *in situ* formed molecular chlorine (derived from thermal decomposition of chlorinated starting material as previously observed^[19]). It represents an additional source for the main product **2** via dehydrochlorination reaction. The byproduct chloropicrin **7** is formed via chlorination of intermediate **F** through derivative **J**.

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

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

azepane, azocane, and 1-(3-chlorophenyl)piperazine already at mild temperature conditions (MeOH, -20 °C to r.t., 4-fold excess of amine). Thus, the 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 the enamines **10-14** are chemically equivalent due to the possibility to form intramolecular salts of the *aci*-nitro group with free rotation properties along the C-C single bond. Starting from nitroethane **8**, treatment with one equivalent of a secondary aliphatic amine led to elimination of HCl and formation of trichloronitroethene (**2**). Otherwise, on application of a 5-fold excess of an amine, again the first equivalent enabled the dehydrochlorination to give **2**, but two further equivalents formed the diamino-substituted ethene derivatives **10-14** which subsequently were converted into their hydrochlorides by means of the last two equivalents (52-67%), (Scheme 4).

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

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

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

The reaction of azinate **9** with secondary aliphatic amines such as morpholine, 1,2,3,4-tetrahydroisoquinoline, 1-(3-chlorophenyl)piperazine, and piperazine lead to the 2-nitroethyl oximes **19-22** in good yields (71-88%). Best results were achieved with methanol as solvent and with two equivalents of the amine (in case of bisoxime **22** only one equivalent of piperazine is needed). The S_NVin-process on the sp²-carbon atom in **9** is accompanied by the reduction of the *N*-oxide group in the presence of the amine. Thus, the oximes **19-22** are formed as a mixture of isomers (*E*:*Z* = 95:5 as evidenced by ¹H-NMR). The chemistry of this extraordinary structural unit that is represented by the formula R-O-N=C(NO₂)NRR₁ is virtually unknown in the literature. To the best of our knowledge, only two papers dealing with this class of organic compounds have been published yet.^[23] In our present case, the structure of the (*E*)-morpholino(nitro)methanone *O*-(1,2,2-trichloro-2-nitroethyl) oxime (**19**) was evidenced by single-crystal X-ray diffraction analysis (Figure 3).

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

In contrast to the 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. In detail, replacement of the chlorine substituent and also the nitro group resulted in the unexpected formation of the corresponding guanidines **23-25** in moderate to good yields (43-70%), (see Scheme 5). Interestingly, several 1,3-bisaryl-2-organyloxyguanidines are known as potent inhibitors of inosine monophosphate dehydrogenase (IMPDH)^[24a,b] or as immunosuppressants, as anti-cancer, anti-inflammatory, anti-psoriatic, and anti-viral agents.^[24b]

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

Subsequent treatment of oximes **19-21** with aqueous hydrogen chloride (37% HCl) or acetic acid solution of hydrogen bromide (33% HBr) in case of **19** and **20** led to substitution of the methanone nitro-group and formation of the corresponding carbimidoyl halide **26-30** in moderate to very good yields of 44–91%. The nitro-group of the dichloronitromethyl moiety did not react at the selected reaction conditions. In case of the reactions with HCl a 8- to 10-fold excess of hydrogen chloride was necessary (MeOH, 0 °C to r. t.). The processes applying

HBr required only a 1.5-fold excess of this acid (0 °C, then r. t. or then 30-35 °C in case of bromide **28**). The reaction of oxime **21** with HBr ran very slowly at r.t., but at increased temperature upon application of a 3-fold 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 due to the previous oxidation of the bromide anion to bromine by nitrogen dioxide.

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

The reaction of bisoxime ether **22** with hydrogen halides was found to give the corresponding carbimidoyl halides **32** (87%) and **33** (68%), respectively. In both cases, reflux conditions were essential. The accordant products of a single substitution were not observed (Scheme 7). Also the structurally unique products **26-33** belong to a very rare class of compounds, in this case comprising a 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]

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

Biological Assays

A selection of twelve compounds was tested in growth inhibitory assays with the so-called ESKAPE panel that comprises the clinically relevant Gram-negative and Gram-positive bacterial pathogens *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter Sp.* (Table 2). All compounds displayed activity against Methicillin-sensitive and Methicillin-resistant *S. aureus* (MSSA and MRSA), *M. luteus* and *E. faecium* at concentrations between 1.3 and 20 µg/mL. The best profile was obtained for compound **27**, displaying 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 Enterococci or other Gram-negative strains could not be observed at concentrations up to 20 µg/mL.

In order to probe whether the compounds also affected eukaryotic cells, they were tested in a growth assay with the fungus *C. albicans* and in viability assays with four mammalian cell lines (Tables 2 and 3). While 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, L-929, 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 some coherence in the level of activity towards prokaryotic vs. eukaryotic cells. The molecular mechanisms behind these activities remain to be elucidated in future studies.

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

comp.	<i>A. baumannii</i>	<i>E. cloacae</i>	<i>E. faecium</i>	<i>K. pneumoniae</i>	<i>P. aeruginosa</i> PA7	<i>E. coli</i>	<i>M. luteus</i>	<i>S. aureus</i> MRSA	<i>S. aureus</i> MSSA	<i>C. albicans</i>
19	20.0	n.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.

n.a. - not active until max. tested concentration of 20 µg/mL

Table 3: Effect of compounds on cell viability in the WST-1 test. IC₅₀ and IC₉₀ values are given in µg/mL.

comp.	L929		KB-31		MCF-7		FS4-LTM	
	IC50	IC90	IC50	IC90	IC50	IC90	IC50	IC90
19	1.1	2.2	4.0	6.7	0.3	0.5	5.0	>6.7
20	1.5	6.7	n.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

n.a. - not active until max. 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 conc. HNO₃ and conc. H₃PO₄ (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%, GC). As side products, trichloronitromethane (**7**) with up to 3.4%, 1,1,2,2-tetrachloro-1-nitroethane (**8**) with up to 25.1%, and 1,2,2-trichloro-2-nitroethyl (chloro(nitro)methylene)azinate (**9**) with up to 8.0% 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. In detail, 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 the 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 evidenced by single-crystal X-ray diffraction analysis. The products with unique formulas R-O-N=C(NO₂)NRR₁ and R-O-N=C(Hal)NRR₁, respectively, belong to very rare classes of organic compounds. The antimicrobial activity of

the synthesized compounds against Gram-positive bacteria was examined. Particularly, compound *N*-(1,2,2-trichloro-2-nitroethoxy)-3,4-dihydroisoquinoline-2(1*H*)-carbamidoyl chloride (**27**) displayed potent biological activity with MICs of 1.3 and 5 µg/mL against MRSA and *E. faecium* and an IC₅₀ 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 on MERCK aluminum backed TLC plates with silica gel 60, F254. Flash column chromatography was performed over 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 (EA) 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 and are uncorrected. FT-IR spectra were taken on a BRUKER "Alpha-T" spectrometer with solids being measured as KBr pellets. ATR-IR spectra were measured on the same instrument with a BRUKER "Alpha Platinum ATR" single reflection diamond ATR module. ¹H NMR (600 MHz) and ¹³C NMR (150 MHz) were recorded on an "Avance III" 600 MHz FT-NMR spectrometer (Bruker, Rheinstetten, Germany). ¹H NMR (400 MHz) and ¹³C NMR (100 MHz) were measured on an "Avance" 400 MHz FT-NMR spectrometer (also Bruker). ¹⁴N and ¹⁵N NMR were measured at their appropriate resonance frequency on the aforementioned spectrometers; ¹⁵N measurements were performed as gs-¹H, ¹⁵N-HSQC or -HMBC experiments with inverse detection. ¹H and ¹³C NMR spectra were referenced to the residual solvent peak: CDCl₃, δ = 7.26 (¹H), δ = 77.0 (¹³C); DMSO-*d*₆, δ = 2.50 (¹H), 39.7 (¹³C). ¹⁴N and ¹⁵N NMR spectra were reported relative to nitromethane at 0.0 ppm. Mass spectra were obtained on a Hewlett Packard MS 5989B spectrometer, usually in direct mode with electron impact (70 eV). In the case of chlorinated and brominated compounds, all peak values of molecular ions as well as fragments refer to the isotope ³⁵Cl and ⁷⁹Br. 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 entry 8, table 1, a mixture of conc. nitric acid (390 mL, 65% HNO₃) and phosphoric acid (60 mL, 98% H₃PO₄) was heated to 100-105 °C. An initial amount of 10-12 mL of trichloroethene (**1**) (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 appearance of reddish-brown nitrous gases), remaining starting material **1** was added dropwise within 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 (r. t.), and the organic phase was separated. The inorganic phase was extracted twice with chloroform (2 x 200 mL). The combined organic layers were washed with water (2 x 100 mL) and dried with anh. 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 oil bath temperature of 115-120 °C, employing a Liebig-type condenser without any cooling water in order to prevent solidification of partial amounts of the resulting azinate **9** (19.1 g, 4.5%, bp 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%, bp 56-57 °C/25 mbar), chloropicrin (**7**) (2.9 g, 1.3%, bp 39-40 °C/25 mbar, bp 110-111 °C/988 mbar^[26]) and nitroethane **8** (23.9 g, 8.4%, bp 65-66 °C/25 mbar, bp 63 °C/11 mbar^[18]).

1,1,2-Trichloro-2-nitroethene (2). Yellow liquid. IR (NaCl): 2868, 2623, 2361, 2342, 1548, 1324, 1052, 933, 871, 777, 750, 707 cm⁻¹. ¹³C-NMR (100 MHz, CDCl₃): δ = 128.1 (o, CCl₂); 136.5 (o, CCINO₂) ppm. ¹⁴N (28.9 MHz, CDCl₃): δ = -17.8 (s) ppm. EIMS: *m/z* (%) = 175 [M⁺] (44), 129 (100), 94 (53). HRMS (EI): *m/z* calcd for C₂Cl₃NO₂ [M⁺]: 174.8995; found: 174.8996.

Trichloro(nitro)methane (7). Colorless liquid. IR (NaCl): 2900, 2613, 1607, 1331, 1293, 977, 910, 863, 819, 759, 865, 620 cm⁻¹. ¹³C-NMR (100 MHz, CDCl₃): δ = 123.4 ppm. ¹⁴N (28.9 MHz, CDCl₃): δ = -18.0 ppm. EIMS: *m/z* (%) = 163 [M⁺] (7), 117 (6), 82 (25), 63 (100).

1,1,2,2-Tetrachloro-1-nitroethane (8). Colorless liquid. IR (ATR): 3004, 1589, 1332, 1311, 1216, 1065, 894, 928, 867, 827, 761, 723, 660, 596 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃): δ =

6.55 (s, 1 H, $^1J_{\text{C,H}} = 186.0$ Hz) ppm. ^{13}C -NMR (100 MHz, CDCl_3): $\delta = 114.2$ (C1), 74.6 (C2) ppm. ^{14}N (28.9 MHz, CDCl_3): $\delta = -8.9$ ppm. EIMS: m/z (%) = 210 $[\text{M} - \text{H}]^+$ (3), 165 (48), 129 (14), 101 (100).

(Z)-1,2,2-Trichloro-2-nitroethyl (chloro(nitro)methylene)azinate (9). Yellow oil. IR (NaCl): 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 $\delta = 6.95$ (s, 1 H, $^1J_{\text{C,H}} = 188.0$ Hz) ppm. ^{13}C -NMR (100 MHz, CDCl_3): $\delta = 145.8$ ($=\text{C}(\text{Cl})\text{NO}_2$), 109.9 (CCl_2NO_2), 96.8 (CHCl) ppm. Minor isomer $\delta = 6.51$ (s, 1 H, $^1J_{\text{C,H}} = 185.0$ Hz) ppm. ^{13}C -NMR (100 MHz, CDCl_3): $\delta = 144.9$ ($=\text{C}(\text{Cl})\text{NO}_2$), 109.8 (CCl_2NO_2), 101.0 (CHCl) ppm. ^{14}N (43.4 MHz, CDCl_3): $\delta = -9.8$ (CCl_2NO_2), -28.5 ($=\text{CNO}_2$), -66.0 ($\text{C}=\text{N}(\text{O})\text{O}$) ppm. EIMS: m/z (%) = 315 $[\text{M}^+]$ (1), 299 (1), 279 (1), 252 (17), 130 (100).

General Procedure I

1,1-Bis(morpholin-4-yl)-2-chloro-2-nitroethene (10). A solution of morpholine (3.66 g, 42.00 mmol) in 10 mL of MeOH was added dropwise to a solution of nitroethene **2** (1.76 g, 10.00 mmol) in 50 mL of MeOH at -20°C within 10 min. The resulting mixture was kept at the same temperature for additional 60 min with stirring. After 3 h at r. t. and subsequent cooling to 0°C the resulting precipitate was filtered off, washed with cold MeOH (5 mL), and then dried in vacuo to give **10** as a yellow solid in 76% yield (2.11 g); m.p. $217\text{--}218^\circ\text{C}$. IR (KBr): $\nu = 2919, 2858, 1537, 1497, 1384, 1280, 1233, 1162, 1108, 1068, 1028, 1000, 877, 631$ cm^{-1} . ^1H -NMR (400 MHz, CDCl_3): $\delta = 4.00\text{--}3.68$ (m, 8 H, 4 OCH_2), 3.59–3.23 (m, 8 H, 4 NCH_2) ppm. ^{13}C -NMR (100 MHz, CDCl_3): $\delta = 162.0$ (C1), 102.5 (C2), 65.9 (4 OCH_2), 50.7 (2 NCH_2) 50.3 (2 NCH_2) ppm. EIMS: m/z (%) = 277 $[\text{M}^+]$ (8), 231 (18), 169 (27), 146 (100). HRMS (EI): m/z calcd for $\text{C}_{10}\text{H}_{16}\text{ClN}_3\text{O}_4$ (M^+): 277.0829; found: 277.0818.

Nitroethene 10 was synthesized from ethane **8** (0.21 g, 1.00 mmol) and morpholine (0.45 g, 5.20 mmol) according to **General Procedure I** at -20°C for 1 h, then 5 h at r. t. in 63% yield.

1,1-Bis(piperidin-1-yl)-2-chloro-2-nitroethene (11) was obtained from nitroethene **2** (1.76 g, 10.00 mmol) and piperidine (3.57 g, 42 mmol) applying **General Procedure I**. Yellow solid,

78% yield (2.14 g). M. p. 158–159 °C. IR (KBr): ν = 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 [M^+] (7), 227 (20), 144 (100). HRMS (ESI): m/z calcd for $\text{C}_{12}\text{H}_{20}\text{ClN}_3\text{O}_2$ [$\text{M}+\text{H}$] $^+$: 274.1322; found: 274.1324.

Nitroethene 11 was synthesized from **8** (0.21 g, 1.00 mmol) and piperidine (0.44 g, 5.20 mmol) following **General Procedure 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 also synthesized following **General Procedure I** from nitroethene **2** (1.76 g, 10.00 mmol) and azepane (4.16 g, 42 mmol) and was obtained as a yellow solid in 75% yield (2.14 g). M.p. 156–158 °C. IR (KBr): ν = 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 [M^+] (5), 265 (3), 255 (11), 158 (30), 105 (100). HRMS (ESI): m/z calcd for $\text{C}_{14}\text{H}_{25}\text{ClN}_3\text{O}_2$ [$\text{M}+\text{H}$] $^+$: 302.1635; found: 302.1634.

Nitroethene 12 was obtained following **General Procedure I** from ethane **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 following **General Procedure I** from nitroethene **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): ν = 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 [M^+] (1), 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.

Nitroethene 13 was obtained 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.

1,1-Bis(1-(3-chlorophenyl)piperazine-4-yl)-2-chloro-2-nitroethene (14) was synthesized following **General Procedure I** from nitroethene **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): ν = 3115, 2912, 2850, 1594, 1567, 1534, 1486, 1387, 1342, 1288, 1228, 1163, 1071, 1028, 941, 855, 769, 689 cm^{-1} . 1H -NMR (400 MHz, DMSO- d_6): δ = 7.70-6.51 (m, 8 H, Ar), 3.75-3.12 (m, 16 H, piperazinyl-H) ppm. ^{13}C -NMR (100 MHz, DMSO- d_6): 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 NCH₂), 49.2 (2 NCH₂), 47.4 (2 NCH₂), 47.1 (2 NCH₂) ppm. EIMS: m/z (%) = 495 $[M^+]$ (1), 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.

Nitroethene 14 was obtained 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 5 mL of MeOH was added dropwise to a solution of azinate **9** (1.58 g, 5.00 mmol) in 10 mL of MeOH at -10 °C within 20 min. The resulting mixture was kept at the same temperature for additional 60 min with stirring. After 4 h at r. t. and subsequent cooling to 0 °C the resulting precipitate was filtered off, washed with cold MeOH (5 mL), and then dried in vacuo to give **19** as a mixture of *E*- and *Z*-isomeres (94.4: 5.6). Yellow solid, 78% yield (1.37 g); m.p. 108–109 °C. IR (KBr): ν = 2986, 2866, 1693, 1593, 1556, 1338, 1269, 1113, 1090, 968, 890, 800, 714, 588 cm^{-1} . 1H -NMR (400 MHz, CDCl₃): Major isomer, δ = 6.67 (s, 1 H, $^1J_{C,H}$ = 188.2 Hz), 3.79-3.55 (m, 4 H, 2 OCH₂), 3.37-3.30 (m, 4 H, 2 NCH₂) ppm. ^{13}C -NMR (100 MHz, CDCl₃): δ = 156.8 (=C(NR₂)NO₂), 110.8

(CCl₂NO₂), 96.9 (CHCl), 66.2 (2 OCH₂), 48.4 (2 NCH₂) ppm. ¹⁴N (28.9 MHz, CDCl₃): δ = -8.8 (NO₂), -14.0 (NO₂), -75.0 (C=N-O), -313.3 (NCH₂) ppm. Minor isomer, δ = 6.27 (s, 1 H, ¹J_{C,H} = 184.8 Hz), 3.79-3.55 (m, 4 H, 2 OCH₂), 3.41-3.36 (m, 4 H, 2 NCH₂) ppm. ¹³C-NMR (100 MHz, CDCl₃): δ = 153.5 (=C(NR₂)NO₂), 110.7 (CCl₂NO₂), 100.9 (CHCl), 66.3 (2 OCH₂), 48.3 (2 NCH₂) ppm. EIMS: *m/z* (%) = 350 [M⁺] (2), 304 (8), 269 (2), 128 (20), 112 (100). HRMS (EI): *m/z* calcd for C₇H₉Cl₃N₄O₆ (M⁺): 349.9588; found: 349.9580. The structure of the *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) was prepared following **General Procedure II** from azinate **9** (1.58 g, 5.00 mmol) and 1,2,3,4-tetrahydroisoquinoline (1.47 g, 11 mmol) as a pale yellow solid in 71% yield (1.41 g), m.p. 85–87 °C. IR (KBr): ν = 2998, 1686, 1583, 1562, 1497, 1443, 1394, 1329, 1251, 1101, 1048, 998, 953, 800, 756, 692 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃): δ = 7.27-7.22 (m, 2H), 7.20-7.16 (m, 1H), 7.07-7.02 (m, 1H), 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. ¹³C-NMR (100 MHz, CDCl₃): δ = 157.2 (=C(NR₂)NO₂), 133.0 (Cq), 130.8 (Cq), 129.1 (CH), 127.3 (CH), 126.8 (CH), 126.1 (CH), 110.9 (CCl₂NO₂), 97.1 (CHCl), 49.7 (CH₂), 46.4 (CH₂), 28.6 (CH₂) ppm. EIMS: *m/z* (%) = 396 [M⁺] (1), 350 (1), 304 (1), 193 (5), 158 (48), 104 (100). HRMS (ESI) [M+H]⁺: *m/z* calcd for C₁₂H₁₂Cl₃N₄O₅ [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) was obtained following **General Procedure II** from azinate **9** (1.58 g, 5.00 mmol) and 1-(3-chlorophenyl)piperazine (2.16 g, 11 mmol) as a pale yellow solid in 79% yield (1.82 g). M.p. 131–132 °C. IR (KBr): ν = 2948, 2834, 1690, 1592, 1556, 1453, 1400, 1334, 1315, 1219, 1148, 1118, 1015, 956, 869, 807, 731, 692, 632 cm⁻¹. ¹H-NMR (400 MHz, CDCl₃): δ = 7.25-7.18 (m, 1H), 6.94-6.88 (m, 2H), 6.82-6.78 (m, 1H), 6.69 (s, 1 H, CHCl), 3.52-3.46 (m, 4 H), 3.33-3.25 (m, 4 H) ppm. ¹³C-NMR (100 MHz, CDCl₃): δ = 156.9 (=C(NR₂)NO₂), 151.6 (Cq), 135.2 (Cq), 130.4 (CH), 121.0 (CH), 116.9 (CH), 114.9 (CH), 110.9 (CCl₂NO₂), 97.1 (CHCl), 49.1 (2 CH₂), 48.2 (2 CH₂) ppm. EIMS: *m/z* (%) = 459 [M⁺] (16), 331 (2), 221 (100), 139 (85). HRMS (ESI): *m/z* calcd for C₁₃H₁₄Cl₄N₅O₅ [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) was synthesized following

General Procedure II from azinate **9** (1.58 g, 5.00 mmol) and piperazine (0.47 g, 5.50 mmol) as a pale yellow solid in 88% yield (1.35 g). M.p. 184–186 °C. IR (ATR): ν = 3001, 2936, 1675, 1591, 1558, 1447, 1401, 1357, 1332, 1285, 1204, 1092, 1007, 969, 892, 809, 758, 683, 621 cm^{-1} . ^1H -NMR (600 MHz, DMSO-d_6): δ = 7.47 (s, 2 H, CHCl, $^1J_{\text{C,H}}$ = 187.7 Hz), 3.44 (s, 8 H) ppm. ^{13}C -NMR (150 MHz, DMSO-d_6): δ = 156.7 ($=\text{C}(\text{NR}_2)\text{NO}_2$), 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 ($\text{C}=\text{N}-\text{O}$), -314.4 (NCH_2) ppm. EIMS: m/z (%) = 612 [M^+] (1), 566 (1), 531 (2), 328 (4), 282 (7), 138 (100). HRMS (ESI): m/z calcd for $\text{C}_{10}\text{H}_{11}\text{Cl}_6\text{N}_8\text{O}_{10}$ [$\text{M}+\text{H}$] $^+$: 612.8729; found: 612.8732.

1,3-Bis(4-chlorophenyl)-2-(1,2,2-trichloro-2-nitroethoxy)guanidine (23) was synthesized 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. as a beige solid in 65% yield (1.54 g). M.p. 141–142 °C. IR (ATR): ν = 3417, 1638, 1584, 1532, 1490, 1431, 1299, 1345, 1137, 1088, 1014, 931, 829, 709, 663, 562 cm^{-1} . ^1H -NMR (400 MHz, CDCl_3): δ = 7.34–7.20 (m, 4H), 7.14–7.08 (m, 4H), 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 ($=\text{C}(\text{NAr}_2)_2$), 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 [M^+] (5), 294 (10), 278 (12), 263 (8), 243 (6), 127 ($\text{NH}_2\text{C}_6\text{H}_4\text{Cl}$) (100). HRMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{12}\text{Cl}_5\text{N}_4\text{O}_3$ [$\text{M}+\text{H}$] $^+$: 470.9352; found: 470.9358.

1,3-Bis(4-bromophenyl)-2-(1,2,2-trichloro-2-nitroethoxy)guanidine (24) was prepared 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. as a beige solid in 70% yield (1.97 g). M.p. 154–156 °C. IR (ATR): ν = 3413, 3396, 1640, 1585, 1531, 1487, 1432, 1362, 1298, 1233, 1133, 1119, 1011, 930, 826, 713, 661, 539 cm^{-1} . ^1H -NMR (400 MHz, CDCl_3): δ = 7.48 (d, 2 H, J = 8.7 Hz), 7.36 (d, 2 H, J = 8.6 Hz), 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 ($=\text{C}(\text{NAr}_2)_2$), 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 [M^+] (5), 382 (10), 366 (12), 354 (7), 287 (20), 171 (100). HRMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{12}\text{Br}_2\text{Cl}_3\text{N}_4\text{O}_3$ [$\text{M}+\text{H}$] $^+$: 558.8342; found: 558.8341.

1,3-Bis(4-fluorophenyl)-2-(1,2,2-trichloro-2-nitroethoxy)guanidine (25) was synthesized following **General Procedure II** from azinate **9** (1.58 g, 5.00 mmol) and (2.44 g, 22 mmol) 4-fluoroaniline, reaction time 1 h at -10 °C and 18 h at r. t. as a beige solid in 43% yield (0.95 g). M.p. 81–82 °C. IR (ATR): ν = 3416, 1640, 1586, 1541, 1506, 1395, 1299, 1211, 1140, 1013, 933, 831, 710, 659, 608, 513 cm^{-1} . ^1H -NMR (400 MHz, CDCl_3): δ = 7.21–7.12 (m, 4 H), 7.10–7.01 (m, 2 H), 6.99–6.89 (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, CF, $^1J_{\text{C,F}}$ = 242.8 Hz), 159.2 (d, CF, $^1J_{\text{C,F}}$ = 242.8 Hz), 152.9 ($=\text{C}(\text{NAr}_2)_2$), 134.3 (Cq), 132.1 (Cq), 127.2 (d, 2 CH, $^3J_{\text{C,F}}$ = 8.4 Hz), 121.6 (d, 2 CH, $^3J_{\text{C,F}}$ = 8.4 Hz), 116.7 (d, 2 CH, $^2J_{\text{C,F}}$ = 23.4 Hz), 115.6 (d, 2 CH, $^2J_{\text{C,F}}$ = 23.4 Hz), 111.6 (CCl_2NO_2), 97.3 (CHCl) ppm. EIMS: m/z (%) = 438 [M^+] (5), 262 (20), 246 (19), 231 (12), 111 (100). HRMS (ESI): m/z calcd for $\text{C}_{15}\text{H}_{12}\text{Cl}_3\text{F}_2\text{N}_4\text{O}_3$ [$\text{M}+\text{H}$] $^+$: 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 5 mL of MeOH at 0 °C was added dropwise 1 mL (10 mmol) of conc. aqueous HCl (37%) within 10 min. The resulting 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 30 mL cold water and extracted with chloroform (3 x 20 mL). The organic phase was washed with water (2 x 15 mL) and then dried with calcium chloride. After evaporation of the solvent the obtained oil was purified by column chromatography (petrol ether: ethyl acetate 10:1) and finally dried in vacuo. The resulting pure oil was obtained in 72% yield (246 mg). IR (ATR): ν = 2972, 2859, 1588, 1452, 1372, 1326, 1267, 1233, 1117, 1031, 961, 900, 835, 720 cm^{-1} . ^1H -NMR (400 MHz, CDCl_3): δ = 6.66 (s, 1 H, $^1J_{\text{C,H}}$ = 187.8 Hz), 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 ($=\text{C}(\text{NR}_2)\text{Cl}$), 111.2 (CCl_2NO_2), 96.8 (CHCl), 65.9 (2 OCH_2), 47.9 (2 NCH_2) ppm. EIMS: m/z (%) = 339 [M^+] (12), 258 (5), 163 (50), 163 (17), 133 (100). HRMS (ESI): m/z calcd for $\text{C}_7\text{H}_{10}\text{Cl}_4\text{N}_3\text{O}_4$ [$\text{M}+\text{H}$] $^+$: 339.9425; found: 339.9429.

(E)-N-(1,2,2-trichloro-2-nitroethoxy)-3,4-dihydroisoquinoline-2(1H)-carbimidoyl chloride (27) was prepared following **General Procedure III** from oxime **20** (398 mg, 1.00 mmol) and 1 mL (10 mmol) of aqueous 37% HCl as a white solid in 91% yield (352 mg). M.

p. 109–110 °C. IR (KBr): ν = 2996, 2859, 1569, 1498, 1445, 1390, 1347, 1243, 1114, 1004, 955, 871, 753, 628 cm^{-1} . ^1H -NMR (400 MHz, CDCl_3): δ = 7.24–7.19 (m, 2H), 7.18–7.10 (m, 2H), 6.72 (s, 1 H, CHCl), 4.60 (s, 2 H), 3.74 (t, 2 H, J = 5.9 Hz), 2.94 (t, 2 H, J = 5.9 Hz) ppm. ^{13}C -NMR (100 MHz, CDCl_3): δ = 147.1 ($=\text{C}(\text{NR}_2)\text{Cl}$), 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 [M^+] (5), 304 (4), 209 (28), 193 (100). HRMS (ESI): m/z calcd for $\text{C}_{12}\text{H}_{12}\text{Cl}_4\text{N}_3\text{O}_3$ [$\text{M}+\text{H}$] $^+$: 385.9633; found: 384.9631.

(*E*)-*N*-(1,2,2-trichloro-2-nitroethoxy)morpholine-4-carbimidoyl bromide (28) was obtained following **General Procedure III** from oxime **19** (352 mg, 1.00 mmol) and 365 mg (1.50 mmol) of 33% HBr in acetic acid. Reaction time 1 h at 0 °C, 24 h at r. t., and further 5 h at 30–35 °C. Yellow oil, 44% yield (170 mg). IR (ATR): ν = 2973, 2858, 1588, 1451, 1369, 1266, 1226, 1114, 1026, 955, 717 cm^{-1} . ^1H -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 ($=\text{C}(\text{NR}_2)\text{Br}$), 111.1 (CCl_2NO_2), 96.5 (CHCl), 65.8 (2 OCH_2), 49.3 (2 NCH_2) ppm. EIMS: m/z (%) = 383 [M^+] (5), 337 (5), 304 (5), 207 (55), 177 (55), 112 (100). HRMS (ESI): m/z calcd for $\text{C}_7\text{H}_{10}\text{BrCl}_3\text{N}_3\text{O}_4$ [$\text{M}+\text{H}$] $^+$: 383.8920; found: 383.8914.

(*E*)-*N*-(1,2,2-trichloro-2-nitroethoxy)-3,4-dihydroisoquinoline-2(1*H*)-carbimidoyl bromide (29) was synthesized following **General Procedure III** from oxime **20** (398 mg, 1.00 mmol) and 365 mg (1.50 mmol) of 33% HBr 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): ν = 2995, 2857, 1562, 1497, 1383, 1346, 1240, 1114, 1088, 950, 859, 752, 641 cm^{-1} . ^1H -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, 2 H, J = 5.9 Hz), 2.93 (t, 2 H, J = 5.9 Hz) ppm. ^{13}C -NMR (100 MHz, CDCl_3): δ = 140.1 ($=\text{C}(\text{NR}_2)\text{Br}$), 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 [M^+] (3), 350 (3), 253 (4), 237 (14), 104 (100). HRMS (ESI): m/z calcd for $\text{C}_{12}\text{H}_{12}\text{BrCl}_3\text{N}_3\text{O}_3$ [$\text{M}+\text{H}$] $^+$: 429.9128; found: 429.9127.

(*E*)-4-(3-chlorophenyl)-*N*-(1,2,2-trichloro-2-nitroethoxy)piperazine-1-carbimidoyl chloride (30) was synthesized following **General Procedure III** from oxime **21** (461 mg,

1.00 mmol) and 1 mL (10 mmol) of aqueous 37% HCl. 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): ν = 2996, 2856, 1587, 1564, 1484, 1448, 1377, 1229, 1119, 1023, 948, 905, 836, 723, 684 cm^{-1} . ^1H -NMR (400 MHz, CDCl_3): δ = 7.20 (t, 1 H, J = 8.2 Hz), 6.91–6.87 (m, 2 H), 6.81 (ddd, 1 H, J = 8.2, 2.3, 0.9 Hz), 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 ($=\text{C}(\text{NR}_2)\text{Cl}$), 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 [M^+] (10), 337 (5), 256 (25), 221 (45), 193 (27), 139 (100). HRMS (ESI): m/z calcd for $\text{C}_{13}\text{H}_{14}\text{Cl}_5\text{N}_4\text{O}_3$ [$\text{M}+\text{H}$] $^+$: 448.9509; found: 448.9514.

(*E*)-4-(4-bromo-3-chlorophenyl)-*N*-(1,2,2-trichloro-2-nitroethoxy)piperazine-1-carbimidoyl bromide (31) was prepared following **General Procedure III** from oxime **21** (461 mg, 1.00 mmol) and 730 mg (3.00 mmol) of 33% HBr in acetic acid. Reaction time 1 h at r. t., then reflux 10 h. Brown oil, 52% yield (298 mg). IR (ATR): ν = 2988, 2832, 1584, 1476, 1449, 1379, 1328, 1224, 1115, 1022, 942, 842, 802, 758, 719 cm^{-1} . ^1H -NMR (400 MHz, CDCl_3): δ = 7.45 (d, 1 H, J = 8.9 Hz), 6.98 (d, 1 H, J = 2.9 Hz), 6.70 (s, 1 H, CHCl), 6.69 (dd, 1 H, J = 8.9, 2.9 Hz), 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 ($=\text{C}(\text{NR}_2)\text{Br}$), 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 [M^+] (7), 524 (2), 381 (20), 297 (80), 273 (15), 219 (100). HRMS (ESI): m/z calcd for $\text{C}_{13}\text{H}_{13}\text{Br}_2\text{Cl}_4\text{N}_4\text{O}_3$ [$\text{M}+\text{H}$] $^+$: 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) was obtained following **General Procedure III** from dioxime **22** (615 mg, 1.00 mmol) and 1 mL (10 mmol) of aqueous 37% HCl. Reaction time 1 h at r. t, then reflux for 1 h, after cooling to r. t. the resulting precipitate was filtered off, washed with methanol (2 x 5 mL) and dried *in vacuo*, further purification by column chromatography is not needed. White solid, 87% yield (517 mg). M.p. 137–139 °C. IR (ATR): ν = 2993, 2865, 1580, 1451, 1389, 1281, 1230, 1165, 1125, 1015, 936, 862, 752, 718, 632, 495 cm^{-1} . ^1H -NMR (600 MHz, CDCl_3): δ = 6.66 (s, 2 H, CHCl, $^1J_{\text{C,H}}$ = 187.6 Hz), 3.50 (s, 8 H) ppm. ^{13}C -NMR (150 MHz, CDCl_3): δ = 147.0 ($=\text{C}(\text{NR}_2)\text{Cl}$), 111.2 (CCl_2NO_2), 96.8 (CHCl), 46.6 (4 CH_2) ppm. ^1H -NMR (600 MHz, $\text{DMSO}-d_6$): δ = 7.173 (s, 1 H, CHCl), 7.172 (s, 1 H, CHCl), 4.42 (s, 8 H) ppm.

^{13}C -NMR (150 MHz, DMSO- d_6): δ = 147.0 (=C(NR₂)Cl), 111.2 (CCl₂NO₂), 96.9 (CHCl), 46.3 (4 CH₂) ppm. ^{14}N (43.4 MHz, DMSO- d_6): δ = -10.9 (s, NO₂, CCl₂NO₂), -78.7 (s, C=N-O), -300.8 (s, NCH₂) ppm. EIMS: m/z (%) = 594 [M⁺] (6), 509 (7), 398 (7), 222 (73), 206 (25), 192 (83), 171 (100). HRMS (ESI): m/z calcd for C₁₀H₁₁Cl₈N₆O₆ [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) was synthesized following **General Procedure III** from dioxime **22** (615 mg, 1.00 mmol) and 730 mg (3.00 mmol) of 33% HBr in acetic acid. Reaction time 1 h at r. t., then reflux for 10 h. White solid, 68% yield (464 mg). M.p. 160–162 °C. IR (ATR): ν = 2993, 2864, 1584, 1575, 1450, 1383, 1279, 1224, 1162, 1121, 1009, 933, 860, 741, 717, 642, 600, 493 cm⁻¹. ^1H -NMR (400 MHz, CDCl₃): δ = 6.68 (s, 2 H, CHCl, $^1J_{\text{C,H}}$ = 187.6 Hz), 3.54 (s, 8 H) ppm. ^{13}C -NMR (100 MHz, CDCl₃): δ = 140.0 (=C(NR₂)Br), 111.1 (CCl₂NO₂), 96.6 (CHCl), 48.1 (4 CH₂) ppm. EIMS: m/z (%) = 678 [M⁺] (7), 599 (4), 504 (10), 407 (22), 312 (39), 282 (40), 110 (100). HRMS (ESI): m/z calcd for C₁₀H₁₀Br₂Cl₆N₆O₆ [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 (MH) 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 an 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 x 10⁶ cfu/mL (resulting in 5 x 10⁵ 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 according to 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 $\mu\text{g/mL}$. 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 according to 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 in order to induce a primary cell-like behaviour (Pub.No.: US2011/0189142 A2).

Briefly, the subconfluent cells were washed with EBSS (Earle's Balanced Salt Solution, Gibco) without Ca and Mg, trypsinized and resuspended in DMEM containing 5% FBS (L929, KB-31, FS4-LTM) or RPMI containing 5% FBS, 0.5% MEM NEAA (Minimum Essential Medium Non-Essential Amino Acids, Gibco), 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 the cell lines L929, KB-3-1 and MCF-7, respectively, and for 24 h with the cell line FS4-LTM. After the incubation period 5 µL WST-1 (ready to use solution by Roche) was added. The MTPs 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, Männedorf, Switzerland). The percentage of viable cells was calculated as the mean with respect to the controls set to 100%.

Crystal Data

19: $\text{C}_7\text{H}_9\text{Cl}_3\text{N}_4\text{O}_6$, (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 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 using SHELXS-97^[30] and refined using alternating cycles of least squares refinements against F^2 (SHELXL-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.

$\text{C}_7\text{H}_9\text{Cl}_3\text{N}_4\text{O}_6$ crystallized in the triclinic space group $\bar{P}1$ (no. 2), lattice parameters $a = 7.700(2)$ Å, $b = 9.002(2)$ Å, $c = 10.018(2)$ Å, $\alpha = 89.55(2)^\circ$, $\beta = 79.67(2)^\circ$, $\gamma = 84.60(2)^\circ$, $V = 680.1(3)$ Å³, $Z = 2$, $d_{\text{calc.}} = 1.717$ g cm⁻³, $F(000) = 356$ 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.

Further details of the crystal structure investigations have been deposited with the Cambridge Crystallographic Data Center, CCDC 1034618. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44(1223)-336 033; e-mail: fileserv@ccdc.ac.uk or <http://www.ccdc.cam.ac.uk>).

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

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