Polyhalonitrobutadienes as Versatile Building Blocks for the Biotargeted Synthesis of Substituted N-Heterocyclic Compounds †

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Abstract: Substituted nitrogen heterocycles are structural key units in many important pharmaceuticals. A new synthetic approach towards heterocyclic compounds displaying antibacterial activity against Staphylococcus aureus or cytotoxic activity has been developed. The selective synthesis of a series of 64 new N-heterocycles from the three nitrobutadienes 2-nitroperchloro-1,3-butadiene, 4-bromotetrachloro-2-nitro-1,3-butadiene and (Z)-1,1,4-trichloro-2,4-dinitrobuta-1,3-diene proved feasible. Their reactions with N-, O- and S-nucleophiles provide rapid access to push-pull substituted benzoxazolines, benzimidazolines, imidazolidines, thiazolidinones, pyrazoles, pyrimidines, pyridopyrimidines, benzoquinolines, isothiazoles, dihydroisoxazoles, and thiophenes with unique substitution patterns. Antibacterial activities of 64 synthesized compounds were examined. Additionally, seven compounds (thiazolidinone, nitropyrimidine, indole, pyridopyrimidine, and thiophene derivatives) exhibited a significant cytotoxicity with IC50-values from 1.05 to 20.1 µM.

In conclusion, it was demonstrated that polyhalonitrobutadienes have an interesting potential as structural backbones for a variety of highly functionalized, pharmaceutically active heterocycles.

Keywords: polyhalonitrobutadienes; nucleophilic substitution; heterocyclization; nitrogen heterocycles; medicinal chemistry

1. Introduction

Halogenated nitrobutadienes are part of a relatively small group of selectively reactive aliphatic nitro compounds [1]. Representatives with one or two nitro and three to five halogen groups are easily accessible by introduction of an activating and directing nitro group into polyhalo-1,3-butadienes [2]. These can be easily obtained in high purity and multigram scale by radical dimerization of industrial solvents such as trichloroethene and 1,2-dichloroethene with subsequent dehydrohalogenation-halogenation, followed by nitration reactions. 2-Nitroperchlorobutadiene (1) has been synthesized in three steps from trichloroethene [3,4] (Scheme 1). 4-Bromotetrachloro-2-nitrobutadiene (2) could be obtained from trichloroethene in five steps [5].
(Z)-1,1,4-Trichloro-2,4-dinitrobutadiene (3) was made accessible in four steps from a Z,E-mixture of 1,2-dichloroethene [6].

![Scheme 1. Synthesis of the polyhalonitrobutadienes 1-3.](image)

Due to their graded reactivity in S_N reactions, nitro-substituted polyhalo-1,3-butadienes have proven to be valuable synthetic precursors for a variety of four- to six-membered, often pharmaceutically active heterocycles. They bear a unique substitution pattern that cannot be accessed easily on an alternative pathway. This structural overview for medicinal chemists demonstrates the broad synthetic potential of the nitrodienes 1, 2, and 3 as a backbone for specifically substituted heterocycles, owing to the additional potential for predictable successive molecular fine tuning.

2. Results and Discussion

2.1. Chemistry

2.1.1. Benzoxazolines and Benzimidazolines

Due to the high electrophilicity of its nitrodichlorovinyl group, 1 reacts readily with various amines which, according to Pearson’s scale, are hard nucleophiles [7]. Thus, reactions of 2-aminophenol derivatives with 1 occur under mild conditions and lead to substitution of both Cl groups of the nitrodichlorovinyl unit with formation of the corresponding (E)-2,3-di-hydrobenzoxazoles 4a,b in reasonable yields [8]. The substructure of a β-nitro-substituted enamine within compounds 4a,b should enable a stabilization caused by a strong hydrogen bond between an oxygen atom of the nitro group and the proton at the oxazoline nitrogen atom. The downfield-shifted 1H nmr signal for the NH-group of 4b at 11.8 ppm in CDCl₃ and 13.6 ppm in DMSO-d₆ points out that H-bonding (Scheme 2) must be important and azoles 4a,b are obtained hereby exclusively as E-isomers. Under mild reaction conditions, benzoxazoline 4b reacts with activated pyridine derivatives, forming betaines 5a-c in 62–74% yield. Treatment of 4b with nicotine under the same reaction conditions furnishes azinate 5d in 53% yield. Synthesis of the novel and structurally interesting cross-conjugated inner salts 5a-d demonstrates the broad synthetic applicability of 2-nitroperchlorobutadiene [9]. Benzoxazoline 6 was obtained in 73% yield as a 1:1 mixture of two isomers by the action of 2-amino-3-methylphenol on the bromonitrodiene 2 at −40 °C in methanol. The reaction of dinitrodiene 3 with 4-methylbenzene-1,2-diamine at −40 °C results almost quantitatively in the formation of benzimidazolide 7a. By treatment of 3 with 2-aminophenol derivatives, the corresponding benzoxazolines 7b,c were obtained in acceptable yields (Scheme 2). Similar benzoxazolines and benzimidazolines exhibit herbicidal activity and act as a model compound when exploring caseinolytic protease as target for herbicides or growth regulators [10].
2.1.2. Imidazolidines

Imidazolidines 8 have been prepared by reaction of nitrodienes 1–3 with N1, N2-diphenylethane-1,2-diamine in methanol. Under optimized conditions, yields of the products 8 reached 86–93% (Scheme 3). Only compound 8a was previously prepared [11] and isolated in 25% yield by reaction of (1,3,4,4-tetrachloro-2-nitrobuta-1,3-dien-1-yl)(p-tolyl)sulfane with N1, N2-diphenylethane-1,2-diamine. Treatment of imidazolidine 8a with a fivefold excess of pyrrolidine in refluxing methanol led to the formation of a S NVin product, the 2-(3,3-dichloro-1-nitro-2-(pyrrolidin-1-yl)allylidene)-1,3-diphenylimidazolidine (9) in 50% yield.

2.1.3. Imidacloprid Analogues

The imidazolidine Imidacloprid (N-{1-[(6-chloro-3-pyridyl)methyl]-4,5-dihydroimidazol-2-yl}-nitramide) has been the most widely used systemic insecticide worldwide. A first synthesis of analogues from nitropolychloroalkenes has been reported [12,13], new types of derivatives are presented here. For instance, 11a and 11b were obtained from nitrodiene 1 and chloropyridines 10a and 10b, respectively [13]. Reaction of imidazolidine 11a with a 2.5-fold excess of N-nucleophiles such as ethyl piperidine-4-carboxylate and 1,2,3,4-tetrahydroisoquinoline in methanol at 35–50 °C leads to compounds 12a and 12b in 60–85% yield, respectively. By using 2-mercaptoethanol-1-ol as S-nucleophile for the reaction with 11a in the presence of sodium ethanolate, the corresponding sulfane
12c was obtained in 63% yield. Treatment of 11b with a fivefold excess of dimethylamine at rt led to the formation of oxazolidine 12d (70%). By the reaction of bromonitrodiene 2 with an equimolar amount of 4-fluorobenzenethiol in DCM at rt, sulfane 13 was obtained as mixture of two isomers in a total yield of 74%. The subsequent vinylic substitution of the monothio compound 13 by means of 10a gave imidazolidine 14 (44%) as well as ketene dithioacetal 15 (30% yield). Arylthiols are known to be both, good nucleophiles as well as good leaving groups. Compound 14 was previously synthesized in 40% yield directly from nitrodiene 2 and diamine 10a [12]. 1,1-Dithio compound 15 could be obtained in 83% yield from diene 2 and two equivalents of 4-fluorobenzenethiol using sodium methanolate as a base. The reaction of diene 2 with diamine 16 [13] at optimized conditions furnished the imidazolidine 17 as a mixture of two isomers in a total yield of 89% (Scheme 4).

![Scheme 3. Synthesis of imidazolidines 8, 9.](image)

### 2.1.4. Thiazolidinones

Thiazolidin-4-ones represent a class of compounds that has proven to exhibit distinctive bio-activity, e.g. antifungal, antibacterial, antitubercular, and anticonvulsant properties [14–17]. Our research in this area is presented through an efficient synthesis of functionalized (Z)-2-allylidene-thiazolidin-4-ones [18]. Nitrodiene 1 reacts with ethyl 2-mercaptoacetate to give the sulfane 18 as single E-isomer [19]. For the subsequent reactions of sulfane 18, we used two aniline derivatives, an activated (ERG) and an antialgae properties [22], show anticancer activity [23,24], and are inhibitors of bacterial enzyme synthetase MurD with E. coli [25].
Scheme 4. Synthesis of Imidacloprid analogues 11, 12, 14, 17.

Other thiazolidinone derivatives can be obtained by treatment of 19a and 19b with 5-formyl-pyrazole 22, previously obtained from 1 in 48% yield, as already reported [26]. Under standard reaction conditions, the corresponding pyrazolyl-thiazolidinones 23a,b were obtained as a mixture of two isomers in relation of 86:14. Formation of a mixture of isomers can be explained in this case by the bulky structure of pyrazole 22 compared with 2-formyl derivatives of furan, thiophene or 1-methylpyrrole (Scheme 5).

2.1.5. Benzazetines

Functionally substituted benzazetines have also been made accessible starting from 1 [27]. The derived bis(benzotriazole) 24 was obtained in 76% yield according to the literature [28]. Single amine exchange of azole 24 is feasible with aromatic, aliphatic, and heteroaromatic amines in methanol at mild reactions conditions and led to 1-benzotriazolyl-1-(organylamino)-2-nitro-3,4,4-trichloro-1,3-butadienes 25a–f in good yields (75–91%). Dienes 25d and 25e have been described, already [26,29]. Heating of nitrodienes 25a–c in different solvents (MeOH for 26a, EtOH for 26b, and THF for 26c) gave the corresponding benzazetines 26a–c in 25–37% yield (Scheme 6). No reaction occurred in diethyl ether, while in benzene, strong tarring was observed [30]. Some details on the synthesis and chemical transformations of benzazetines have been published, already [30]. N-Unsubstituted derivatives are unstable. Stable substituted representatives have become accessible for the first time in recent years. The substructure of a ß-nitro-substituted enamine within compounds 26a–c should enable a stabilization caused by a strong hydrogen bond between an oxygen atom of the nitro group and the single proton at the azetine nitrogen atom. The wide-ranging synthetic possibilities of benzazetines and benzazetes have also been discussed.
2.1.6. Pyrimidines

In the course of the studies concerning polyhalogenated nitrobutadienes, a new ring closure approach to perfunctionalized 5-nitropyrimidines was also developed [33]. Using this protocol starting from 25c-f, four new nitropyrimidines 27c-f were obtained. Even under optimum conditions, yields of the products 27c-f remained moderate, reaching 49–65%. The assumed mechanism for the formation of pyrimidines 27 has been presented in the literature [33]. 5-Nitro-substituted pyrimidines are interesting precursors for the synthesis of a wide range of poly-substituted pyrimidines and other heterocyclic systems with potential biological activity [34]. Among numerous applications, some examples are noteworthy: cytotoxic activity is documented [35,36] as well as the potential to inactivate the human DNA repair process [37]. The broad variety of medicinal applications is further illustrated, e.g. with the

Scheme 5. Synthesis of thiazolidinones 21, 22 and pyrazoles 20 and 23.

4-Ethoxy-2-(2,3,3-trichloro-1-nitro-2-propenylidene)-benzazetine (a regioisomer of compound 26b) can modulate RNA binding proteins [31]. A new prenylated indole alkaloid taichunamide A contains a benzazetidine unit, too [32]. It was isolated from the fungus Aspergillus taichungensis.

Scheme 6. Synthesis of benzazetines 26 and benzotriazoles 25.

2.1.6. Pyrimidines

In the course of the studies concerning polyhalogenated nitrobutadienes, a new ring closure approach to perfunctionalized 5-nitropyrimidines was also developed [33]. Using this protocol starting from 25c-f, four new nitropyrimidines 27c-f were obtained. Even under optimum conditions, yields of the products 27c-f remained moderate, reaching 49–65%. The assumed mechanism for the formation of pyrimidines 27 has been presented in the literature [33]. 5-Nitro-substituted pyrimidines are interesting precursors for the synthesis of a wide range of poly-substituted pyrimidines and other heterocyclic systems with potential biological activity [34]. Among numerous applications, some examples are noteworthy: cytotoxic activity is documented [35,36] as well as the potential to inactivate the human DNA repair process [37]. The broad variety of medicinal applications is further illustrated, e.g. with the
activity against chronic obstructive pulmonary disease [38], applicability against herpes simplex [39], and other viral diseases [40]. Furthermore, one field of application of 5-nitropyrimidines uses their positive modulating effect of the GABAB receptor [41,42]. Pyrimidin-4-yl-1H-indoles are a very rare class of organic compounds; to the best of our knowledge, only 4 representatives are known till today [43–45]. With the aim to synthesize a new pyrimidin-4-yl-1H-indole with potent biological activity, we made an attempt to oxidize the 2,3-dihydroindole 27f. Indeed, by using DDQ as oxidizing agent (ratio 27f: DDQ 1: 2.25, toluene, reflux 5 h), the expected indole 28 was obtained in 66% yield (Scheme 7).

![Scheme 7. Synthesis of pyrimidines 27, 28.](image)

### 2.1.7. Pyrazoles

In the past ten years, different ways to synthesize persubstituted 4-nitropyrazoles have been developed [9,18,26,28,46]. Some of these compounds show high biological activities: they can modulate the biological activity of IFNs-I [47], are active against mycobacterial infections including tuberculosis [48], and are able to reduce prime virulence factors of Vibrio cholerae [49,50]. In the course of our recent studies, the three 1-amino-1-benzotriazolyldienes 25g–i were synthesized in good yields (85–91%) from bis(benzotriazole) 24 using 4-(4-chlorophenyl)piperidin-4-ol, piperazin-1-yl-(tetrahydrofuran-2-yl)methanone and 1-(3-chlorophenyl)piperazine, respectively. The treatment of dienes 25g–i with a twofold excess of methylhydrazine in methanol at −10 °C to rt led to the formation of new nitropyrazoles 29a–c in good yields (74–79%). By saponification of the dichloromethyl group in compound 29c by means of 25% aqueous sulfuric acid at 95–100 °C, the aldehyde 30 was obtained (57%) (Scheme 8) [26]. Other 4-nitropyrazoles are known as hypoxia-selective cytotoxins and radiosensitizers [51]; they can be useful as herbicides [52,53] or show psychosedative actions [54].

### 2.1.8. 4H-Pyrido [1,2-α]Pyrimidines

Recently, a new pathway for the synthesis of 4-(dichloromethylene)-3-nitro-4H-pyrido[1,2-α]pyrimidines with a unique substitution pattern at the pyrimidine ring was developed [28]. Starting with bis(benzotriazole) 24, using a threefold excess of 2-aminopyridines two enamines 31a,b were formed in THF in 81–86% yield. The benzotriazole unit in pyridopyrimidines 31, activated through the neighboring nitro group, acts as a very good leaving group and can be replaced with different nucleophiles at mild reaction conditions. Thus, treatment of compounds 31 with 1-(4-fluoro-phenyl)piperazine in methanol at 40 °C led to the piperazino-substituted pyridopyrimidines 32 in excellent yields. A S_N Vin process in pyridopyrimidines 31 under action of S-nucleophiles such as ethyl 2-mercaptoacetate using sodium ethanolate as base furnished sulfane 33a,b in 93–97% yield. Another possibility to form compounds 33a,b is reaction of sulfane 18 with 2-aminopyridines. At optimum conditions (MeOH, threefold
excess of amino-pyridines, rt), the yields of pyridopyrimidines 33 reached 47–55% (Scheme 9). Similar pyrido[1,2-\(a\)]pyrimidines show antiviral [55], antithrombotic [56], and antibacterial [57–60] activities.

2.1.9. Benzo[\(h\)]quinolines

In the course of our studies on polyhalogenated nitrobutadienes, a new ring closure approach to benzo[\(h\)]quinolines was also developed [61]. Starting from nitrodiene 1 in three steps, the target benzo[\(h\)]quinolines with a unique substitution pattern at the pyridine ring were obtained in good yields. In detail, after mono substitution of one chlorine group in diene 1 sulfanes 34a,b were formed as single isomers each in yields of about 80% according to the literature [62] for the benzyl derivative 34a and literature [9] for the 4-chlorophenyl derivative 34b. In a second step, we synthesized the aminothiobutadienes 35a,b by interaction of sulfane 34a,b with an excess of 1-naphtylamine in methanol at −10 °C to rt. Dienes 35a,b were also formed (76–85% yield) as single E-isomers due to the stable six membered hydrogen bridge between the amino and nitro group. Finally, the ring closure at optimum conditions (twofold excess of triethylamine as a base) proceeded under formation of the expected benzo[\(h\)]quinolines 36a,b in good yields (76–85%). The assumed mechanism for the formation
of benzo[h]quinolines is depicted in the literature [61]. Benzo[h]quinolines are a precious class of organic compounds and show interesting biological properties [63–67]. Oxidation of quinolines 36a,b with excess of hydrogen peroxide in a mixture of acetic acid and chloroform lead to the formation of sulfoxides 37a,b in 89–91% yield. The sulfinyl group is known to be a good leaving group [68–70]. Indeed, treatment of sulfoxide 37a with an excess of pyrrolidine in toluene at 100 °C furnished amino derivative 38 in 77% yield (Scheme 10).

![Scheme 10. Synthesis of benzo[h]quinolines 36–38 and nitrodienes 34, 35.](image_url)

2.1.10. Isothiazoles

The isothiazole 39 was obtained from nitrodiene 1 upon treatment with elemental sulfur at 200 °C [71]. Subsequent reaction with fuming nitric acid provided the 4,5-dichloroisothiazole-3-carboxylic acid (40) [72], which could be easily converted into the corresponding acid chloride 42 with thionyl chloride (93% yield) [28]. Acid 40 reacts with ethyl 2-bromoacetate in the presence of sodium ethanolate under reflux conditions to ester 41 in 58% yield. The esterification of acid chloride 42 with a fourfold excess of 2,2,2-trifluoroethan-1-ol in refluxing THF resulted in the formation of a 2,2,2-trifluoroethyl 4,5-dichloroisothiazole-3-carboxylate (43) (64% yield). Acid chloride 42 smoothly reacted with aromatic and aliphatic amines to provide the corresponding amides 44a–d in 68–95% yield. The reaction of chloride 42 with 2 equivalents of 1-(6-chloropyridin-3-yl)-N-methyl-methanamine in THF furnished amide 44e as mixture of two rotamers in relation 10: 6 with a total yield of 86%. An alternative way to obtain amide 44e is the interaction of carbohydrazide 44a with 1-(6-chloropyridin-3-yl)-N-methylmethanamine at harder reactions conditions (DMSO, 95–100 °C). In this case, amide 44e is formed as a mixture of two rotamers (relation 10:6), with a total yield of 69%. Reacting hydrazide 44a with a fourfold excess of morpholine (DMSO, 90–95 °C) did not lead to the formation of a product similar to amide 44e. Instead, upon substitution of a chlorine group in 5 position of the heterocyclic ring, an isothiazole 45 was formed (78% yield). These amides 44a–e and 45 are interesting candidates for biological testing, as amides of 4-chloroisothiazol-3-carboxylic acid have been shown to exhibit high antibacterial activity [73–75]. Finally, we investigated the interaction of amides 44a–d and ester 41 with 5-nucleophiles such as 4-chlorobenzeneethiol. In all cases, reaction products at 5 position of the heterocyclic ring were formed. Under optimized reaction conditions, the yields of the 5-((4-chlorophenyl)thio)isothiazoles 46a–e were in the range of 67–89% (Scheme 11).
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2.1.11. 4,5-Dihydroisoxazoles

Recently, we developed a novel, fairly general method for the synthesis of dihydroisoxazoles with a chlorinated side chain in 3-position, starting from \textit{gem}-dichloronitroalkenes \cite{76}. In particular, reaction of nitrodiene 1 with a base leads to the formation of 2,3,3-trichloroprop-2-enenitrile oxide. Trapping of this nitrile oxide with an alkene resulted in 4,5-dihydroisoxazole derivatives 47–50, due to a 1,3-dipolar cycloaddition. In detail, reaction of nitrodiene 1 with prop-1-en-2-ylbenzene at optimized conditions furnished 4,5-dihydroisoxazole 47 in 76\% yield. The interaction of the acrylonitrile oxide 1 with tert-butyl acrylate and 2-ethylhexyl acrylate at similar reactions conditions provided alkyl 3-(1,2,2-trichlorovinyl)-4,5-dihydroisoxazole-5-carboxylates 48 and 49 (65 and 60\% yield). Upon treatment of diene 1 with cyclohexene, the hexahydrobenzo-\textit{d}-isoxazole 50 was isolated in 41\% yield (Scheme 12). The yields of 47–49 are quite similar to certain compounds in \cite{76}, whereas for 50 (in...
analogy to the reaction with cyclopentene [76]), the yield is lower as expected. 4,5-Dihydroisoxazoles were found to exhibit potent cytotoxic, antineoplastic [77], and antimalarial activity [78]. Additionally, they can be used as androgenic or antiandrogenic agents or androgen receptor modulators [79] and show antibacterial and antifungal activities [80].

\[
\begin{align*}
\text{from 1} & \quad \begin{array}{c}
\text{Cl} \\
\text{N} \\
\text{Cl}
\end{array} & \quad \begin{array}{c}
\text{Cl} \\
\text{N} \\
\text{Cl}
\end{array} & \quad \begin{array}{c}
\text{Cl} \\
\text{N} \\
\text{Cl}
\end{array} & \quad \begin{array}{c}
\text{Cl} \\
\text{N} \\
\text{Cl}
\end{array} & \quad \begin{array}{c}
\text{Cl} \\
\text{N} \\
\text{Cl}
\end{array} & \quad \begin{array}{c}
\text{Cl} \\
\text{N} \\
\text{Cl}
\end{array}
\end{align*}
\]

from 1

\[
\text{abs. toluene} \quad 80 \, ^\circ\text{C}, \text{20-30 h}
\]

\[
\begin{align*}
\text{10 equiv} & \quad \begin{array}{c}
\text{R}
\end{array} & \quad \begin{array}{c}
\text{Cl}
\end{array} & \quad \begin{array}{c}
\text{N}
\end{array} & \quad \begin{array}{c}
\text{R}^1
\end{array} & \quad \begin{array}{c}
\text{R}^2
\end{array} & \quad \begin{array}{c}
\text{O}
\end{array}
\end{align*}
\]

47-50

\[
\begin{align*}
\text{47, } R = H, R^1 = \text{Me}, R^2 = \text{Ph}, 76\% & \\
\text{48, } R = R^1 = H, R^2 = \text{CO}_2\text{Bu}, 65\% & \\
\text{49, } R = R^1 = H, R^2 = \text{CO}_2\text{CH}_2\text{CH(ET)Bu}, 60\% & \\
\text{50, } R - R^2 = (\text{CH}_2)_n, 41\%
\end{align*}
\]

**Scheme 12.** Synthesis of 4,5-dihydroisoxazoles 47–50.

2.1.12. Thiophenes

In the course of studying nitroperchlorobutadiene 1 as a versatile building block for the directed synthesis of a range of persubstituted heterocycles, we also developed a three-step synthesis to persubstituted 3-amino-4-nitrothiophenes [81]. Incorporating both, an enamine and a thioketene unit, these thiophenes are very electron-rich heterocycles with a unique substitution pattern. Starting from 1, the piperazine derivative 52 was obtained in 90% yield via the dithiolane 51. The push-pull substituted thiophene 53 was efficiently accessible in 85% yield upon treatment of dithiolane 52 with sodium hydride using DMSO as solvent. The regioselective ipso-formylation of the 2-chloro-thiophene 53 under Vilsmeier-Haack conditions led to the carbaldehyde 54 (64% yield), according to [82].

The next successive steps were performed with the most stable derivative 3-morpholino-4-nitro-5-(vinylsulfanyl)thiophene-2-carbaldehyde (55) [82]. Knoevenagel condensation of thiophene 55 with malononitrile in ethanol in the presence of a catalytic amount of sodium ethanolate gave the gem-dicyanovinylthiophene 56 in 68% yield [83]. Oxidation of the vinylsulfanylthiophene 56 with threefold excess of hydrogen peroxide in acetic acid at 50–55 °C furnished sulfone 57 in 82% yield. Interaction of carbaldehyde 55 with an excess of dimedone, (2,4,6-trichlorophenyl)hydrazine and Meldrum’s acid in methanol led to the formation of bis(5,5-dimethylcyclohexane-1,3-dione) 58, vinylsulfanyl-thiophene 59 and 1,3-dioxane-4,6-dione 60, respectively (Scheme 13).

2-Chloro-3-amino-4-nitro-5-(vinylsulfanyl)thiophenes similarly to compound 53 were identified as anti-HIV compounds to treat drug-resistant retroviral infections [84] and show antiviral activity [85]. Other 3(4)-nitrothiophenes can be used in fungicidal and/or bactericidal compositions [86], and show insecticidal and acaricidal activity [87].

2.2. Biological Activity of the Polyhalonitrobutadiene Derivatives

Evaluation of the biological activity of the chosen polyhalonitrobutadiene derivatives showed that most of them did not display antibacterial or cytotoxic effects, i.e., residual growth or viability after incubation for 1 and 3 days, respectively, were higher than 50%. Tables with all primary screening data are shown in Supplementary Figures S204–S205. None of the derivatives showed an antibacterial activity against the uropathogenic *Escherichia coli* strain UPEC 796, whereas some had antibacterial activity against *Staphylococcus aureus*. The cytotoxic activity of nine compounds could be proven, as these compounds had IC₅₀-values < 50 μM in the viability assay. Among those compounds was the “conjugate” 23b of the pyrazole 22 and the thiazolidinone 19b. Whereas the compound series 21 was more or less completely inactive, introduction of the pyrazole group proved successful. In particular, the introduction of a CF₃ substituent resulted in a compound with significant cytotoxicity (IC₅₀ = 6.2 ± 1.8 μM). Similarly, among the pyrimidines 27, 28, the most potent derivatives were those with the aromatic residues at the nitropyrimidine—core, namely 27c and 28 with IC₅₀-values of 1.5 ± 0.4 μM and 1.05 ± 0.2 μM, respectively. The non-aromatic nature of the ring next to the pyrimidine core in 27f prevented the cytotoxic activity. Following the synthesis route of the pyridopyrimidines

\[
\begin{align*}
\text{interaction of carbaldehyde } 55 \text{ with an excess of dimedone, (2,4,6-trichlorophenyl)hydrazine and Meldrum’s acid in methanol led to the formation of bis(5,5-dimethylcyclohexane-1,3-dione) } 58, \text{ vinylsulfanyl-thiophene } 59 \text{ and 1,3-dioxane-4,6-dione } 60, \text{ respectively (Scheme 13)}.
\end{align*}
\]
32 and 33 revealed that the precursor with the leaving group benzotriazole was the only cytotoxic compound \((IC_{50} = 6.0 \text{ and } 5.7 \pm 1.0 \, \mu\text{M})\), and that cytotoxicity was lost, when the benzotriazole group was replaced. In addition, the benzo[h]quinolines 36, 38 lost the cytotoxic activity, which was still observed for the intermediate naphthalene-aminothiobutadiene 35. All tested derivatives of both the groups of isothiazoles and dihydroisoxazoles were inactive, whereas among the thiophenes, the derivatives with a cyclic dione residue 58 and 60 represented cytotoxic compounds \((IC_{50} = 3.1 \pm 0.4 \, \mu\text{M} \text{ and } 20.1 \pm 3.9 \, \mu\text{M})\). Obviously, the morpholino-nitrothiophene structure was not sufficient for biological activity as compound 59 was completely inactive.

![Scheme 13. Synthesis of thiophenes 53–60 and dithiolanes 51, 52.](image)

3. Experimental

3.1. General Information

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. Melting points (m.p.) were determined in capillary tubes with a Büchi B-520 instrument and
were not corrected. FTIR spectra were recorded with a Bruker “Alpha-T” spectro-meter 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. 1H NMR and 13C NMR spectra at 600 and 150 MHz, respectively, were recorded with an “Avance III” 600 MHz FT-NMR spectrometer (Bruker, Rheinstetten, Germany). 1H NMR and 13C NMR spectra at 400 and 100 MHz, respectively, were recorded with an “Avance” 400 MHz FT-NMR spectrometer (also Bruker). 1H NMR and 13C NMR spectra at 200 and 50 MHz, respectively, were recorded with an DPX 200 spectrometer (also Bruker). 14N and 15N NMR spectra were measured at their appropriate resonance frequency on the aforementioned spectrometers; 15N measurements were taken 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) and 77.0 ppm (13C); DMSO-d6, δ = 2.50 (1H), and 39.7 ppm (13C). 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 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” with a Waters “Alliance 2965 HPLC” (ESI) at the Institute of Organic Chemistry, Leibniz University of Hannover and at the Georg-August University of Göttingen.

3.2. Synthesis

Pentachloro-2-nitro-1,3-butadiene (1) was prepared from 2H-pentachloro-1,3-butadiene in 53% yield (b.p. 69–71 °C/1 mbar) according to the literature [3,4]. (Z)- and (E)-4-Bromotetrachloro-2-nitrobuta-1,3-diene (2) was obtained from (Z)- and (E)-1-bromotetrachlorobuta-1,3-diene in 56% yield (b.p. 84–86 °C/1.3 mbar) [5]. (Z)-1,1,4-Trichloro-2,4-dinitrobuta-1,3-diene (3) was synthetized from the (Z)- and (E)-1-bromo-1,4,4-trichlorobuta-1,3-diene in 18% yield, m.p. 70–71 °C [6].

Synthesis of 4-methyl-2-(2,3,3-trichloro-1-nitroprop-2-en-1-ylidene)-2,3-dihydro-1,3-benzoxazole (4a) (General method). At –40 °C, a solution of nitrodiene 1 (2.71 g, 10.0 mmol) in 5 mL methanol (MeOH) was added dropwise to a suspension of 2-amino-3-methylphenol (3.94 g, 32.0 mmol) in 30 mL MeOH within 5 min. The resulting mixture was kept for 1 h at this temperature, and was then allowed to reach room temperature (r.t.). After 5 h stirring, the mixture was poured into a cold solution (0 °C) of HCl in 250 mL of water. After 20 min, the precipitate was filtered off, washed with cold water (3 × 40 mL) and diethyl ether (2 × 10 mL). Drying in vacuo gave 2.57 g of oxazole 4a, yield 80%, yellowish solid m.p. 149–151 °C; IR (KBr) vmax = 3089, 1612, 1382, 1079, 968, 520 cm⁻¹; 1H NMR (200 MHz, CDCl3), δ = 2.61 (3H, s, CH3 Ph), 7.21–7.33 (2H, m, H Ph), 7.36–7.41 (1H, m, H Ph), 11.78 (1H, s, NH) ppm; 13C NMR (50 MHz, CDCl3) δ = 16.6 (CH3), 107.0 (C NO2), 108.7 (CH), 120.2 (CCl2), 123.4 (C Me), 125.4 (CH), 127.4, 127.6 (CH), 128.2, 146.6, 159.0 ppm; MS m/z (Irel, %): 320 [M⁺] (4), 285 [M − Cl]⁺ (10), 274 [M-NO2]⁺ (65), 239 [M-Cl-NO2]⁺ (100); HRMS (ESI⁻) m/z calc'd for C11H8N2O2Cl3 [M − H]⁻: 318.9444; found: 318.9446.

5-Methyl-2-(2,3,3-trichloro-1-nitroprop-2-en-1-ylidene)-2,3-dihydro-1,3-benzoxazole (4b). Same procedure as for 4a, but using 2-amino-4-methylphenol (3.94 g, 32.0 mmol). Yield 2.18 g (68%), yellowish solid, m.p. 168–170 °C. IR (KBr) vmax = 3380, 1612, 1434, 1375, 1056, 922 cm⁻¹. 1H NMR (400 MHz, DMSO-d6) δ = 2.42 (3H, s, CH3 Ph), 7.20 (1H, d, J = 8.3 Hz, H Ph), 7.36 (1H, s, H Ph), 7.69 (1H, d, J = 8.3 Hz, H Ph), 13.64 (1H, s, NH) ppm; 13C NMR (100 MHz, DMSO-d6) δ = 21.2 (CH3), 105.4 (C NO2), 111.0 (CH), 113.6 (CH), 122.1 (CCl2), 126.0 (CH), 126.6, 129.8, 136.4, 144.8, 158.0 (NCO) ppm. MS m/z (Irel, %): 320 [M⁺] (2), 285 [M-Cl]⁺ (4), 274 [M-NO2]⁺ (55), 239 [M-Cl-NO2]⁺ (100), 204 [M-2Cl-NO2]⁺ (14); HRMS (ESI⁺) m/z calc'd for C11H6N2O2Cl3 [M + H]⁺: 318.9453; found: 318.9444.

Synthesis of [1-(1,3-benzoxazol-2-yl)-3,3-dichloro-2-[4-(dimethylamino)pyridinium-1-yl]prop-2-en-1-ylidene][oxido]-l5-azanyloxiadamide (5a) (General method). To a suspension of benzoxazole 4b (0.322 g,
1.00 mmol) in 15 mL MeOH at 0 °C, a solution of 4-dimethylaminopyridine (DMAP) (0.257 g, 2.1 mmol) in 3 mL MeOH was added dropwise. The mixture was stirred for 1 h at 0 °C and at rt. for 12 h. Subsequently, the precipitate was filtered off at 0 °C and washed with water (2 × 10 mL) and cold MeOH (5 mL). Finally, the product 5a was dried in vacuo. Yield 0.301 g (74%), yellowish solid, m.p. 189–190 °C. IR (ATR) νmax = 1641, 1531, 1355, 1139, 1055, 790 cm⁻¹; ¹H NMR (400 MHz, DMSO-d₆) δ = 2.38 (3H, s, CH₃ Ph), 3.23 (6H, s, Ni(CH₂)₂), 6.99 (1H, d, J = 7.8 Hz, H Ph), 7.06 (2H, d, J = 6.7 Hz, H pyr), 7.33 (1H, s, H Ph), 7.43 (1H, d, J = 7.9 Hz, H Ph), 8.29 (2H, d, J = 6.7 Hz, H pyr) ppm; ¹³C NMR (100 MHz, DMSO-d₆) δ = 39.7 (CH₃), 40.2 (NCH₂), 103.7, 107.3 (CH), 109.3 (CH), 117.8 (CH), 122.7, 123.6 (CH), 133.2, 135.8, 142.3 (CH), 142.5, 147.8, 154.4, 160.9 ppm; MS m/z (rel. %): 406 [M⁺] (1), 273 [M-benzoxazole-H]⁺ (45), 238 [M-benzoxazole-HCl]⁺ (3), 122 [DMAP]⁺ (73), 100 (100); HRMS (ESI⁺) m/z calcld for C₁₅H₁₇N₃O₃Cl₂ [M + H]⁺: 407.0672; found: 407.0675.

[(1-(1,3-Benzoxazol-2-yl)-3,3-dichloro-2-[4-(morpholin-4-yl)pyridinium-1-yl]prop-2-en-1-ylidene](oxido)-l₅-azanyl)oxidanide (5b). Following the typical procedure for 5a, using 4b (0.322 g, 1.00 mmol) and 4-(4-morpholino)pyridine (0.345 g, 2.1 mmol) at −18 °C and holding at this temperature for 3 h. Yield 0.270 g (62%), yellowish solid, m.p. 180–181 °C. IR (ATR) νmax = 1640, 1548, 1348, 1253, 1156, 792 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆) δ = 2.38 (3H, s, CH₃ Ph), 3.73 (8H, s, H morph), 7.00 (1H, dd, J = 8.1 Hz, J = 1.3 Hz, H Ph), 7.25 (2H, d, J = 7.8, H pyr), 7.34 (1H, s, H Ph), 7.43 (1H, d, J = 8.2, H Py), 8.34 (2H, d, J = 7.6, H pyr) ppm; ¹³C NMR (100 MHz, DMSO-d₆) δ = 21.3 (CH₃), 46.6 (N(CH₂)₂), 65.6 (O(CH₂)₂), 103.8, 107.5 (CH), 109.3 (CH), 117.8 (CH), 122.9, 123.9 (CH), 133.2, 135.7, 142.5, 143.0 (CH), 147.8, 151.6, 160.8 ppm; MS m/z (rel. %): 448 [M⁺] (1), 325 [M-HCl-morpholine]⁺ (1), 316 [M-methylbenzoxazole]⁺ (1), 269 [M-pyridine+H]⁺ (4), 165 (100), 132 [methylbenzoxazole]⁺ (12); HRMS (ESI⁺) m/z calcld for C₂₀H₁₉N₄O₄Cl₂ [M + H]⁺: 449.0778; found: 449.0780.

1-(Pyridin-4-yl)pyrroolidin-2-one as starting material for the synthesis of azinate 5c was obtained from 4-aminoypyridine and 4-chlorobutanol chloride according to the literature [88]. Yield 65%, colorless liquid. ¹H NMR (600 MHz, CDCl₃) δ = 2.17 (2H, t, J = 7.7 Hz, CH₂ pyrro), 2.61 (2H, t, J = 8.2 Hz, CH₂ pyrro), 3.82 (2H, t, J = 7.1 Hz, CH₂ pyrro), 7.57 (2H, d, J = 4.9 Hz, H pyr), 8.00 (2H, d, J = 4.9 Hz, H pyr) ppm; ¹³C NMR (600 MHz, CDCl₃) δ = 17.6 (CH₃), 32.8 (CH₂), 47.4 (CH₂), 112.8 (CH), 145.8, 150.4 (CH), 175.2 (CO) ppm; MS m/z (rel. %): 162 [M⁺] (31), 147 [M-OH]⁺ (25), 119 [M-CH₂CHO]⁺ (10), 107 [M-CH₂CH₂CO+H]⁺ (100).

[(1-(1,3-Benzoxazol-2-yl)-3,3-dichloro-2-[4-(2-oxopyrroloidin-1-yl)pyridinium-1-yl]prop-2-en-1-ylidene](oxido)-l₅-azanyl)oxidanide (5e). Same procedure as for 5a, using 1-(pyridin-4-yl)pyrroolidin-2-one (0.341 g, 2.1 mmol) and holding this temperature for 2 h. Stirring was continued for 24 h at rt. Yield 67%, yellow solid, m.p. 157–158 °C. IR (ATR) νmax = 1733, 1627, 1550, 1349, 1257, 1157 cm⁻¹. ¹H NMR (600 MHz, DMSO-d₆) δ = 2.13 (2H, t, J = 7.6 Hz, CH₂ pyrro), 2.39 (3H, s, CH₃ Ph), 2.67 (2H, t, J = 8.0 Hz, CH₂ pyrro), 3.99 (2H, t, J = 7.2 Hz, CH₂ pyrro), 7.01 (1H, dd, J = 8.2 Hz, J = 0.8 Hz, H Ph), 7.35 (1H, s, H Ph), 7.45 (1H, d, J = 8.2 Hz, H Ph), 8.25 (2H, d, J = 7.0, H pyr), 8.99 (2H, d, J = 7.5 Hz, H pyr) ppm; ¹³C NMR (150 MHz, DMSO-d₆) δ = 17.1 (CH₂), 21.2 (CH₃), 32.7 (CH₂), 48.1 (CH₂), 104.0, 109.4 (CH), 113.9 (CH), 117.9, 123.8 (CH), 124.0, 133.3, 136.2, 142.5, 145.7 (CH), 147.8, 152.6, 160.5, 177.5 ppm; ¹⁵N NMR (43.4 MHz, DMSO-d₆, doped with nitrromethane (0.0 ppm)) δ = −187.0 (N-pyridine), −235.2 (N-pyrroloidine) ppm, other N-atoms could not be detected; MS m/z (rel. %): 446 [M⁺] (1), 411 [M-CI]⁺ (1), 162 [pyridinyl-pyrroloidinedione]⁺ (45), 133 [methylbenzoxazole+H]⁺ (6), 107 (100); HRMS (ESI⁺) m/z calcld for C₂₀H₁₉N₄O₄Cl₂ [M + H]⁺: 447.0621; found: 447.0623.
calcium chloride and purified by column chromatography using DCM–petroleum ether (1:1). The product 5d was dried and vacuo. Yield 0.237 g (53%), yellow solid, m.p. 96–98 °C. IR (ATR) ν_max = 1622, 1516, 1534, 1411, 1062 cm⁻¹. ¹H NMR (200 MHz, CDCl₃) δ = 2.61 (3H, s), 2.77 (1H, CH₂O), 2.78–2.90 (1H, CH₂Ph), 2.99–3.18 (1H, CH₃), 3.63–3.89 (1H, CH₂Ph), 7.00 (1H, dd, J = 1.0 Hz, J = 8.2 Hz, CH₂C–H), 7.49 (1H, s, H Ph), 7.49 (1H, d, J = 5.6 Hz, H Ph), 8.49 (1H, d, J = 7.8 Hz, H pyr), 9.03 (1H, d, J = 5.6 Hz, H pyr), 9.15 (1H, s, H pyr) ppm; ¹³C NMR (100 MHz, CDCl₃) δ = 21.5 (CH₂Ph), 23.1 (CH₂), 35.8 (CH₂), 40.3 (CH₃ pyrro), 56.6 (CH₂) 72.1 (CH pyr), 104.3 (CNOO), 109.8 (CH Ph), 118.0 (CH Ph), 124.0 (CH Py), 127.0 (CH Py), 128.5 (CCL₂), 133.7 (CCH₃), 136.3, 142.2, 143.6 (CH pyr), 145.2 (CH pyr), 145.5 (CH pyr), 145.7, 148.3 (C-pyrr), 160.1 (NCOO) ppm; MS (ESI⁺) m/z calc for C₂₁H₂₁N₂O₂Cl₂ [M + H⁺]: 447.1; found 447.1.

2-[3-Bromo-2,3-dichloro-1-nitroprop-2-en-1-ylidene]-4-methyl-2,3-dihydro-1,3-benzoxazole (6). Same procedure as for 4a, but starting from 2 (316 mg, 1.00 mmol, a 47: 53 mixture of isomers) using 2-amino-3-methylphenol (394 mg, 3.20 mmol). A 1:1 mixture of isomers was obtained. Yield 73%, yellowish solid, m.p. 145–146 °C. IR (KBr) ν_max = 3329, 1620, 1571 (NO₂), 1376, 1320, 1047 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ = 2.61 (3H, s), 3.70 (1H, CH₂O), 7.22–7.41 (3H, m, H Ph), 11.77 (1H, s, NH) ppm; ¹³C NMR (50 MHz,CDCl₃) δ = 16.6 (CH₂), 106.9 (CNOO), 108.7 (CH), 114.9, 115.8 (CClBr); 121.8, 123.7 (CCl); 123.4 (C Me), 125.4 (CH), 127.4, 127.6 (CH), 146.7, 158.7, 158.9 (NCOO) ppm; MS m/z (rel. %): 364 [M⁺] (2), 329 [M – Cl⁺] (4), 318 [M–NO₂]⁺ (19), 285 [M – Br⁺] (25), 283 [M–Cl–NO₂]⁺ (50), 239 [M–Br–NO₂]⁺ (100); HRMS (ESI⁻) m/z calc for C₁₁H₈N₂O₃ClBr [M – H⁻]: 362.8944; found: 362.8948.

2-((Z)-3-chloro-1,3-dinitroallylidene)-5-methyl-2,3-dihydro-1H-benzo[d]imidazole (7a). Same procedure as for 4a, but starting from 3 (247 mg, 1.00 mmol, only Z-isomer) using 4-methylbenzene-1,2-diamine (257 mg, 2.10 mmol). Yield 93%, red solid, m.p. 165–167 °C. IR (KBr) ν_max = 3329, 1620, 1577 (NO₂), 1410, 1268, 897 cm⁻¹. ¹H NMR spectrum (200 MHz, DMSO-d₆) δ = 2.49 (3H, s, CH₃ Ph), 7.36 (1H, d, J = 8.5 Hz, H Ph), 7.58 (1H, s, H Ph), 7.67 (1H, d, J = 8.5 Hz, H Ph), 9.14 (1H, s, CH), 14.45 (2H, s, NH) ppm; ¹³C NMR (50 MHz, DMSO-d₆) δ = 21.4 (CH₃), 106.9 (CNOO), 113.4 (CH), 113.6 (CH), 120.1 (CCNNO₂), 127.5 (CH), 129.1 (C Me), 129.2 (CH), 131.2, 136.1, 142.3 (NCOO) ppm; MS m/z (rel. %): 296 [M⁺] (5), 250 [M–NO₂]⁺ (55), 233 [M–NO₂–OH]⁺ (12), 204 [M–2NO₂]⁺ (60), 169 [M–Cl–NO₂]⁺ (48), 157 (100); HRMS (ESI⁺) m/z calc for C₁₁H₈N₂O₃ClBr [M – H⁺]: 395.0240; found: 395.0248.

2-(3-Chloro-1,3-dinitroprop-2-en-1-ylidene)-5-methyl-2,3-dihydro-1,3-benzoxazole (7b). Same procedure as for 4a, but using 3 (247 mg, 1.00 mmol, only Z-isomer) and 2-amino-4-methylphenol (394 mg, 3.20 mmol). Yield 67%, yellow solid, m.p. 110–112 °C. IR (KBr) ν_max = 3250, 1602, 1545 (NO₂), 1289, 1065, 871 cm⁻¹. ¹H NMR (200 MHz, DMSO-d₆) δ = 2.49 (3H, s, CH₃ Ph), 7.25 (1H, d, J = 8.3 Hz, H Ph), 7.55 (1H, s, H Ph), 7.63 (1H, d, J = 8.5 Hz, H Ph), 9.09 (1H, s, CH), 10.66 (1H, s, NH); ¹³C NMR (50 MHz, DMSO-d₆) δ = 21.2 (CH₃), 110.8 (CH), 112.5 (CNOO₂), 118.5 (CCNNO₂), 119.1 (CH), 126.8 (CH), 129.5 (CH), 134.5 (C Me), 139.4, 148.2, 157.2 (NCOO) ppm; MS m/z (rel. %): 297 [M⁺] (3), 251 [M – NO₂]⁺ (45), 234 [M–NO₂–OH]⁺ (13), 158 (100); HRMS (ESI⁻) m/z calc for C₁₁H₇N₃O₃Cl [M – H⁻]: 296.0072; found: 296.0070.

2-(3-Chloro-1,3-dinitroprop-2-en-1-ylidene)-4-methyl-2,3-dihydro-1,3-benzoxazole (7e). Same procedure as for 4a, using 3 (247 mg, 1.00 mmol, only Z-isomer) and 2-amino-3-methylphenol (394 mg, 3.20 mmol). Yield 85%, yellow solid, m.p. 102–103 °C. IR (KBr) ν_max = 3254, 1625, 1579 (NO₂), 1520, 1077, 646 cm⁻¹. ¹H NMR (200 MHz, DMSO-d₆) δ = 2.53 (3H, s, CH₃ Ph), 7.19 (1H, d, J = 7.5 Hz, H Ph), 7.30 (1H, t, J = 7.5 Hz, H Ph), 7.52 (1H, d, J = 8.0 Hz, H Ph), 9.20 (1H, s, CH), 10.19 (1H, s, NH) ppm; ¹³C NMR (50 MHz, DMSO-d₆) δ = 16.5 (CH₃), 108.5 (CH), 113.6 (CNOO₂), 115.9 (CCNNO₂), 125.0 (CH), 125.5 (CH), 130.3 (CH), 140.3, 150.3, 156.3 (NCOO) ppm; MS m/z (rel. %): 297 [M⁺] (3), 251 [M–NO₂]⁺ (40), 234 [M–NO₂–OH]⁺ (12), 158 (100); MS (ESI⁻) m/z calc for C₁₁H₇N₃O₃Cl [M – H⁻]: 296.0; found: 296.0.

Synthesis of 2-(3-bromo-2,3-dichloro-1-nitroprop-2-en-1-ylidene)-1,3-diphenylimidazolidine (8b) (General method). To a solution of N,N'-diphenylethylene-1,2-diamine (0.446 g, 2.1 mmol) in 10 mL MeOH at
−40 °C a solution of nitrodiene 2 (0.316 g, 1.0 mmol) in 5 mL MeOH was added dropwise. After 1 h of stirring at −40 °C, the solution was allowed to reach r.t. and stirred for another 5 h. The precipitate was filtered off, washed with water (3 × 20 mL), MeOH (1 × 10 mL), diethyl ether (2 × 10 mL) and dried in vacuo. A 1:1 mixture of isoamyls was obtained. Yield 0.410 g (90%), yellow solid, m.p. 222–223 °C. IR (KBr) ν_max = 3455, 3059, 1594, 1523, 1295, 761 cm⁻¹. 1H NMR (200 MHz, DMSO-d₆) δ = 4.37 (4H, s, CH₂), 7.25–7.47 (10H, m, H Ph) ppm; 13C NMR (50 MHz, DMSO-d₆) δ = 51.0, 50.9 (CH₂), 104.4, 105.9 (CNO₂), 107.2, 107.7 (CBrCl), 122.4, 122.5 (CH), 127.0 (CH), 127.8, 129.5, 129.6 (CH), 139.9, 140.0 (NC Ph), 155.0, 155.7 (NCN) ppm; MS m/z (I rel, %): 453 [M⁺] (3), 418 [M – Cl⁺] (3), 374 [M-Br⁺] (45), 339 [M-Cl-Br⁺] (8), 279 [M-C₂Cl₂Br⁺] (100); HRMS (ESI⁺) m/z calcd for C₁₈H₁₅N₃O₂ClBr [M + H⁺]: 453.9719; found: 453.9728.

2-(3-Chloro-1,3-dinitroprop-2-en-1-ylidene)-1,3-diphenylimidazolidine (8c). Same procedure as for 8b, using nitrodiene 3 (0.247 g, 1.0 mmol). Yield 86%, yellow solid, m.p. 236–237 °C. IR (KBr) ν_max = 3054, 1570, 1491, 1349, 1193, 999 cm⁻¹. 1H NMR (200 MHz, CDCl₃) δ = 4.58 (4H, s, CH₂), 7.29–7.33 (3H, m, H Ph), 7.39–7.54 (6H, m, H Ph), 8.69 (1H, s, CH) ppm; 13C NMR (50 MHz, DMSO-d₆) δ = 50.6 (CH₂), 105.1, 117.8 (CNO₂), 123.2 (CH), 128.4 (CH), 129.0 (CH), 130.0 (CH), 136.7 (NC Ph), 158.7 (NCN) ppm; MS m/z (I rel, %): 386 [M⁺] (20), 340 [M – NO₂⁺] (60), 305 [M-NO₂-Cl⁺] (3), 281 [M-(CH=CCNO₂)+H⁺] (20), 247 [M-(CH=CCNO₂)+OH⁺] (100); HRMS (ESI⁺) m/z calcd for C₁₈H₁₅N₃O₄Cl [M + H⁺]: 387.0855; found: 387.0865.

Synthesis of 2-[3,3-dichloro-2-nitro-1-(pyrrolidin-1-yl)prop-2-en-1-ylidene]-1,3-diphenylimidazolidine (9). To a suspension of imidazolidine 8a (0.387 g, 1.0 mmol) in 10 mL MeOH at r.t. a solution of pyrrolidine (0.356 g, 5.0 mmol) in 5 mL MeOH was added. Subsequently, the mixture was stirred for 3 h at r.t. and 4 h at reflux. After cooling to 10 °C, the pH was adjusted to 6–7 with HCl (5%). The resulting precipitate was filtered off and washed with water (3 × 20 mL), MeOH (2 × 10 mL) and dried in vacuo. Yield 0.223 g (50%), yellow solid, m.p. 156–159 °C. IR (KBr) ν_max = 2968, 2868, 2868, 1597, 1497, 1347, 908 cm⁻¹. 1H NMR (200 MHz, DMSO-d₆) δ = 1.52–1.56 (4H, m, CH₂ ppyr), 2.68–2.73 (4H, m, CH₂ ppyr), 4.29 (4H, s, CH₂ im), 7.21–7.44 (10H, m, H Ph) ppm; 13C NMR (50 MHz, DMSO-d₆) δ = 25.0 (CH₂), 50.1 (CH₂), 51.0 (CH₂), 98.6 (CCL₂), 104.7 (CNO₂), 122.8 (CH), 126.7 (CH), 129.2 (CH), 140.2, 140.6, 157.1 (NCN) ppm; MS m/z (I rel, %): 444 [M⁺] (2), 427 [M-OH⁺] (2), 408 [M-HCl⁺] (3), 373 [M-pyrrolidine]+ (22), 281 [M-(CCL₂=C)-pyrrolidine+H⁺] (20), 264 [M-(CCL₂=C)-pyrrolidine-O⁺] (85), 248 [M-(CCL₂=C)-pyrrolidine-2O⁺] (100); HRMS (ESI⁺) m/z calcd for C₂₂H₂₃N₄O₂Cl [M + H⁺]: 445.1193; found: 445.1190.

Synthesis of ethyl 1-(1,1-dichloro-3-[1-(6-chloropyridin-3-yl)methyl]imidazolidin-2-ylidene)-3-nitroprop-1-en-2-yl)piperidine-4-carboxylate (12a) (General method). To a suspension of compound 11a (0.384 g, 1.0 mmol) and piperidine-4-carboxylic acid ethyl ester (0.393 g, 2.5 mmol) in 15 mL MeOH at r.t., a solution of sodium ethanolate (0.177 g, 2.6 mmol) in 5 mL MeOH was added, and stirred for 24 h at 35 °C. At r.t. 3 drops of conc. HCl were added before adding 50 mL cold water. The resulting precipitate was filtered off and washed with cold MeOH (2 × 7 mL) and water (3 × 10 mL). The product was dried in vacuo. Yield 0.303 g (60%), yellow solid, m.p. 60–62 °C. IR (KBr) ν_max = 3319, 1726, 1561, 1319, 1177, 1043 cm⁻¹. 1H NMR (200 MHz, DMSO-d₆) δ = 1.16 (3H, t, J = 6.9 Hz, CH₃ Et), 1.53–1.76 (4H, m, CH₂ ppyr), 2.28–2.42 (1H, m, CH ppyr), 2.73 (4H, s, CH₂ ppyr), 3.35 (2H, s, CH₂ imi), 3.67 (2H, s, CH₂ imi), 4.06 (2H, q, J = 6.9 Hz, CH₂ Et), 4.37–4.47 (2H, m, ppyr-CH₂-imi), 7.56 (1H, d, J = 8.1 Hz, H ppyr), 7.81 (1H, d, J = 8.2 Hz, H ppyr), 8.36 (1H, s, H ppyr), 9.43 (1H, s, NH) ppm; 13C NMR (50 MHz, DMSO-d₆) δ = 14.3 (CH₃), 28.4 (CH₂), 40.5 (CH), 42.2 (CH₂), 48.0 (CH₂ ppyr), 48.4 (CH₂), 49.8 (CH₂), 60.1 (CH₂), 102.8 (CNO₂), 103.6 (CCL₂), 124.4 (CH), 131.4, 138.8 (CH), 141.3, 148.9 (CH), 149.7, 160.1, 174.4 ppm; MS m/z (I rel, %): 503 [M⁺] (3), 467 [M – HCl⁺] (3), 377 [M-CH₂piperidinyl⁺] (2), 254 [M-C₂Cl₂-piperidinyl⁺] (18), 126 [CH₂piperidinyl⁺] (100); HRMS (ESI⁺) m/z calcd for C₂₆H₂₃N₃O₄Cl [M + H⁺]: 502.0821; found: 502.0818.
2-(1,1-Dichloro-3-[[6-chloropyridin-3-yl)methyl]imidazolidin-2-ylidene]-3-nitroprop-1-en-2-yl)-1,2,3,4-tetrahydroisoquinoline (12b). Same procedure as for 12a, using 11a (0.384 g, 1.00 mmol) and 1,2,3,4-tetrahydroisoquinoline (0.368 g, 2.50 mmol) and stirring for 4 h at 50 °C. Yield 85%, orange solid, m.p. 146–148 °C. IR (KBr) νmax = 3318, 2895, 1559, 1460, 1320, 749 cm⁻¹. ¹H NMR spectrum (200 MHz, CDCl₃) δ = 2.70–3.16 (2H, m, CH₂ pip), 3.30–3.55 (2H, m, CH₂ pip), 3.59–3.90 (4H, m, CH₂ imi), 4.08 (1H, d, J = 15.2 Hz, NCH₂), 4.26–4.38 (2H, m, CH₂ pip), 4.67 (1H, d, J = 15.2 Hz, NCH₂), 6.91–6.97 (1H, m, H Ph), 7.07–7.15 (3H, m, H Ph), 7.32 (1H, d, J = 8.2 Hz, H pyr), 7.60 (1H, dd, J = 8.3 Hz, J = 2.5 Hz, H pyr), 8.30 (1H, d, J = 2.4 Hz, H pyr), 9.56 (1H, s, NH) ppm; ¹³C NMR (50 MHz, CDCl₃) δ = 29.7 (CH₂), 41.7 (CH₂), 48.7 (CH₂), 49.6 (CH₂), 51.3 (CH₂), 105.1, 105.7, 124.7 (CH), 125.7 (CH), 126.7 (CH), 126.3 (CH), 128.8 (CH), 129.6, 133.9, 134.9, 138.2 (CH), 139.7, 148.9 (CH), 151.6, 160.2 ppm; MS m/z (rel. %): 479 [M⁺] (2), 443 [M – HCl⁺] (3), 407 [M-2(HCl)⁺] (5), 276 [M-C₂Cl₂-isooquinolinoine + H⁺] (7), 126 [Cl-pyr-CH₂⁺] (100); HRMS (ESI⁺) m/z calc'd for C₂₂H₁₉N₅O₂Cl₃ [M + H⁺]: 478.0610; found: 478.0606.

2-(1,1-Dichloro-3-[[6-chloropyridin-3-yl)methyl]imidazolidin-2-ylidene]-3-nitroprop-1-en-2-yl)sulfonyl]-ethanol (12c). Same procedure as for 12a, using 11a (0.384 g, 1.00 mmol), 2-mercaptoethanol (0.086 g, 1.1 mmol) and sodium ethanolate (0.082 g, 1.2 mmol) in EtOH. The mixture was stirred for 12 h at 40 °C. Yield 0.268 g (63%), orange solid, m.p. 185–187 °C. IR (KBr) νmax = 3220, 2974, 1575, 1299, 1125, 844 cm⁻¹. ¹H NMR spectrum (200 MHz, DMSO-d₆) δ = 2.77 (2H, t, J = 6.4 Hz, SCH₂), 3.53 (2H, t, J = 6.4 Hz, CH₂OH), 3.73 (4H, s, CH₂), 4.30 (2H, s, NCH₂), 4.70 (1H, s, OH), 7.53 (1H, d, J = 8.3 Hz), 7.75 (1H, dd, J = 8.5 Hz, J = 2.5 Hz), 8.33 (1H, d, J = 2.3 Hz), 9.55 (1H, s, NH) ppm; ¹³C NMR (50 MHz, DMSO-d₆) δ = 34.9 (CH₂), 42.4 (CH₂), 48.9 (CH₂), 50.8 (CH₂), 60.1 (CH₂), 102.8 (CNO₂), 115.1 (CCl₂), 124.3 (CH), 131.6, 131.9, 138.1 (CH), 148.0 (CH), 149.5, 159.7 ppm; MS m/z (rel. %): 424 [M⁺] (1), 254 [M-C₂Cl₂-mercaptoethanol + H⁺] (27), 235 [M – C₂Cl₂-S-H₂O]⁺ (12), 126 [Cl-pyr-CH₂⁺] (100); HRMS (ESI⁺) m/z calc'd for C₁₄H₁₄N₄O₂SCl₂ [M + H⁺]: 422.9858; found: 422.9854.

1,1-Dichloro-3-[[6-chloropyridin-3-yl)methyl]-1,3-oxazolidin-2-ylidene]-N,N-dimethyl-3-nitroprop-1-en-2-amine (12d). Same procedure as for 12a, using pyridine 11b (0.385 g, 1.00 mmol) and dimethy lamine (0.366 g, 5.00 mmol) and stirring at r.t. for 5 h. Yield 70%, yellow solid, m.p. 127–129 °C. IR (KBr) νmax = 2868, 1597, 1561, 1298, 1118, 903 cm⁻¹. ¹H NMR spectrum (400 MHz, DMSO-d₆) δ = 2.59 (6H, s, NCH₃), 3.96–4.10 (2H, m, CH₂ oxo), 4.52–4.81 (4H, m, CH₂ oxo, NCH₂), 5.79 (1H, d, J = 7.7 Hz, H pyr), 7.91 (1H, d, J = 7.5 Hz, H pyr), 8.41 (1H, s, H pyr) ppm; ¹³C NMR (100 MHz, DMSO-d₆) δ = 42.0 (CH₂), 49.3 (CH₂), 50.8 (CH₂), 68.2 (CH₂), 104.0, 105.1, 124.4 (CH), 130.0, 139.8 (CH), 142.1, 149.8 (CH), 150.1, 165.4 ppm; MS m/z (rel. %): 392 [M⁺] (1), 311 [M – Cl-N₂O₂⁺] (1), 254 [M – C₂Cl₂-N(CH₃)₂⁺] (2), 126 [Cl-pyr-CH₂⁺] (100); HRMS (ESI⁺) m/z calc'd for C₁₉H₁₆N₄O₂Cl₂ [M + H⁺]: 393.0283; found: 393.0280.

Synthesis of 1-[[4-bromo-1,3,4-trichloro-2-nitrobuta-1,3-dien-1-yl)sulfonyl]-4-fluorobenzene (13). To a solution of nitrodime 2 (0.316 g, 1.00 mmol) in dry DCM (15 mL) at 0 °C, a solution of 4-fluorothiophenone (0.128 g, 1.00 mmol) in 5 mL of dry DCM was added and stirred for 3 h. After reaching r.t. and further stirring for 24 h the mixture was concentrated and water (20 mL) was added before extraction with chloroform (3 x 10 mL). The product was purified by column chromatography using petroleum ether-ethyl acetate (10:1) and dried in vacuo. 1 A 1:1 mixture of isomers was obtained. Yield 0.301 g (74%), yellow solid, m.p. 98–99 °C. IR (ATR) νmax = 1587, 1292, 1223, 815, 526 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 7.11–7.25 (2H, m, H Ph), 7.48–7.64 (2H, m, H Ph) ppm; ¹³C NMR (101 MHz, CDCl₃) δ = 115.2, 116.4 (CClBr), 117.0, 117.2 (CH), 124.0, 124.1, 124.2, 124.5, 138.3, 138.4 (CH), 157.3, 157.8 (CCl₅), 163.4, 165.9 (CF) ppm, CNO₂ could not be detected; MS m/z (rel. %): 405 [M⁺] (1), 370 [M – Cl⁺] (1), 326 [M – Br⁺] (6), 291 [M – Br-Cl⁺] (3), 127 [S-Ph-F⁺] (100); HRMS (ESI⁺) m/z calc'd for C₁₀H₅NO₂Cl₂SBr [M + H⁺]: 405.8269; found: 405.8286.

Synthesis of 5-(((2E)-2-(3-bromo-2,3-dichloro-1-nitroallylidene)imidazolidin-1-yl)methyl)-2-chloropyridine (14) and 1,1′-[[4-bromo-3,4-dichloro-2-nitrobuta-1,3-diene-1,1-diyldisulfanediyl]bis(4-fluorobenzene) (15). A solution of N-[[6-chloropyridin-3-yl)methyl]ethane-1,2-diamine 10a (0.515 g, 3.0 mmol) in MeOH
(5 mL) was added to a suspension of diene 13 (0.407 g, 1.0 mmol, a 1: 1 mixture of isomers) in MeOH (10 mL) at -10 °C and stirred for 1 h at the same temperature. The precipitated bisthiodiene 15 was filtered off, washed with water and cold MeOH (2 × 3 mL), and dried under reduced pressure to yield diene 15. The collected filtrates were carefully neutralized by means of hydrochloric acid and stirred with additional 50 mL of water. Again, the solid was filtered off, and then washed with water and diethyl ether (3 × 5 mL). Recrystallization from methanol gave imidazolidine 14.

**Imidazolidine 14.** A 1: 1 mixture of isomers was obtained. Yield 0.189 g (44%), white solid, m.p. 172–173 °C. IR (KBr) ν max = 3312, 3055, 2917, 1588, 1413, 1317, 1257, 1177, 1106, 1049, 770 cm-1. 1H NMR (200 MHz, DMSO-d6) δ = 3.67–3.90 (4H, m, CH2 imi), 4.46–4.60 (2H, m, NCH2-pyr), 7.48–7.60 (1H, m, H pyr), 8.24–8.39 (1H, m, H pyr), 9.41 (1H, s, NH) ppm; 13C NMR (50 MHz, DMSO-d6) δ = 42.7 (CH2 imi), 49.4 (NCH2-pyr), 50.8 (CH imi), 103.4, 105.2 (CNO2), 113.0, 113.8 (CClBr), 124.3, 124.4 (CH), 26.6, 128.7, 131.4, 131.5, 137.9, 138.0 (CN) ppm; MS m/z (I rel, %): 426 [M+]+ (1), 380 [M-NO2]+ (1), 347 [M-Br]+ (20), 314 [M-pyr]+ (3), 312 [M-Br-Cl]+ (3), 254 [M-Cl2Br]+ (35), 126 [Cl-pyr-CH2]2+ (100); HRMS (ESI+) m/z calcld for C12H9N4O2ClBr [M+H]+: 424.8980; found: 424.8967.

**Bisthiodiene 15.** A 1: 1 mixture of isomers was obtained. Yield 0.150 g (30%), yellow solid, m.p. 141–142 °C. IR (ATR) ν max = 1589, 1489, 1293, 1230, 823, 505 cm-1. 1H NMR (400 MHz, CDCl3) δ = 6.84–7.01 (6H, m, H Ph), 7.05–7.17 (2H, m, H Ph) ppm; 13C NMR (101 MHz, CDCl3) δ = 115.1, 117.2 (CClBr), 116.3–116.7 (CH Ph), 123.4, 125.5, 126.1 (Cp-Ch-S), 133.4, 133.5, 136.5, 136.6, 136.7 (C Ph), 138.3, 138.4 (CNO2), 151.9, 151.95 (COS), 163.1 (CF, JCF = 251.5 Hz), 163.1 (CF, JCF = 252.3 Hz) ppm; MS m/z (I rel, %): 497 [M+]2 (2), 462 [M – Cl]+ (2), 418 [M – Br]+ (30), 383 [M – Br-Cl]+ (3), 372 [M – Br-NO2]+ (4), 127 [S-Ph-F]+ (100); HRMS (ESI+) m/z calcld for C16H9Br2Cl2F2S2 [M+H]+: 497.8979; found: 497.8988.

**Alternative synthesis of diene 15.** To a solution of bromonitrodiene 2 (0.316 g, 1.0 mmol, a 47: 53 mixture of isomers) and 4-fluorobenzenethiol (0.256 g, 2.0 mmol) in MeOH (10 mL) at 0 °C, a solution of sodium methanolate (0.108 g, 2.0 mmol) was added to a suspension of diene 15 (0.407 g, 1.0 mmol, a 1: 1 mixture of isomers) in MeOH (10 mL). A 1: 1 mixture of isomers was obtained. Yield of bisthiodiene 15 is 0.414 g (83%, a 1:1 mixture of isomers).

**N,N’-Bis(2-chloro-1,3-thiazol-5-yl)methylthiethane-1,2-diamine (16)** was prepared according to the literature [13] in 70% yield.

**Synthesis of 5,5’-[(2-(3-bromo-2,3-dichloro-1-nitroprop-2-en-1-ylidene)imidazolidine-1,3-diyl)dimethanediyl]-bis[2-chloro-1,3-thiazole] (17).** To a solution of diene 2 (0.166 g, 0.5 mmol) in a mixture of MeOH and water (10 mL, 10: 1) at 0 °C, N,N’-bis[2-chloro-1,3-thiazol-5-yl]methylthiethane-1,2-diamine (16) (0.170 g, 0.5 mmol) and Na2CO3 (0.112 g, 2.0 mmol) were added carefully. After 1 h at 0 °C, the mixture was allowed to reach r.t. and stirred for another 5 h. Subsequently, the mixture was concentrated in vacuo and the resulting precipitate was filtered off and washed with cold MeOH (2 × 5 mL) and then again with MeOH (1 × 5 mL). A 1: 1 mixture of isomers was obtained. Yield 0.252 g (89%), white solid, mp 162–163 °C. IR (ATR) ν max = 1569, 1533, 1325, 1143, 1046, 770 cm-1. 1H NMR (400 MHz, DMSO-d6) δ = 3.73–3.96 (4H, m, CH2), 4.58–4.80 (4H, m, CH2), 7.69 (2H, s, CH) ppm; 13C NMR (100 MHz, DMSO-d6) δ = 45.2, 45.4 (CH2 imi), 45.2, 45.4 (CH2 imi), 47.2, 47.3 (imi-CH2), 98.1, 99.7 (CNO2), 109.7, 110.6 (CClBr), 127.0, 128.8 (CCl), 133.6, 133.7 (NC thiaz), 141.8, 141.9 (NC thiaz), 151.7, 151.8 (NCS), 161.6, 161.8 (NCN) ppm; MS m/z (I rel, %): 563 [M+H]+ (1), 527 [M – Cl]+ (1), 484 [M – Br]+ (1), 132 [thiazole-Cl-CH2]+ (100); HRMS (ESI+) m/z calcld for C14H11N3O2ClBr2 [M+H]+: 563.8286; found: 563.8284.

**Ethyl (1,3,4,4-tetrachloro-2-nitrobuta-1,3-dien-1-yl)sulfonylacetate (18)** was prepared according to the literature [18] in 80% yield.
Synthesis of 3-[4-(propan-2-yl)phenyl]-2-(2,3,3-trichloro-1-nitroprop-2-en-1-ylidene)-1,3-thiazolidin-4-one (19a) (General method). To a suspension of the acetate 18 (0.355 g, 1.0 mmol) in MeOH (3 mL) at −18 °C a solution of 4-(propan-2-yl)aniline (0.297 g, 2.2 mmol) in MeOH (3 mL) was added dropwise within 10 min. The mixture was stirred for 3 h at −18 °C and 12 h at rt. before it was concentrated. The resulting precipitate was filtered off and washed with cold MeOH (1 × 5 mL), water (2 × 5 mL) and again MeOH (2 × 5 mL). The product was dried in vacuo. Yield 0.298 g (73%), beige solid, m.p. 208–209 °C. IR (ATR) ν_max = 2962, 1758, 1520, 1289, 1167, 686 cm⁻¹. 1H NMR (400 MHz, DMSO-d₆) δ = 1.22 (3H, d, J = 6.9 Hz, i-Pr), 1.23 (3H, d, J = 6.9 Hz, i-Pr), 2.95 (1H, sep, J = 6.8 Hz, i-Pr), 4.13 (1H, d, J = 18.7 Hz, SCH₂), 4.17 (1H, d, J = 18.7 Hz, S.CH₂), 7.28–7.33 (2H, m, H Ar), 7.34–7.40 (2H, m, H Ar) ppm. 13C NMR (100 MHz, DMSO-d₆) δ = 23.6, 23.8 (CH₃), 32.5 (CH₂), 33.6 (CH i-Pr), 121.3 (CCl₂), 121.4 (CNO₂), 126.9 (CH), 127.3 (CH), 127.4 (CH), 128.4, 128.8 (CH), 132.1 (CH), 150.6, 165.8 (NCS), 174.1 (C=O) ppm; MS m/z (I_rel, %): 406 [M⁺] (10), 389 [M-OH]⁺ (5), 371 [M-Cl]⁺ (5), 278 [M-C₂Cl₃+H⁺] (15), 261 [M-C₂Cl₃+O⁺] (100); MS (ESI⁻) m/z calcd for C₁₅H₁₂N₂O₃Cl₃S: 405.0; found: 405.0.

2-(2,3,3-Trichloro-1-nitroprop-2-en-1-ylidene)-3-[4-(trifluoromethyl)phenyl]-1,3-thiazolidin-4-one (19b). Same procedure as for 19a, using 4-(trifluoromethyl)aniline (0.355 g, 2.2 mmol) at 0 °C for 3 h and 15 h at rt. Yield 0.330 g (76%), yellow solid, m.p. 228–229 °C. IR (ATR) ν_max = 3058, 1737, 1515, 1285, 1170, 691 cm⁻¹. 1H NMR (400 MHz, DMSO-d₆) δ = 4.13 (1H, d, J = 18.7 Hz, S.CH₂), 4.20 (1H, d, J = 18.7 Hz, S.CH₂), 7.67–7.74 (2H, m, H Ar), 7.91–7.98 (2H, m, H Ar) ppm. 13C NMR (400 MHz, DMSO-d₆) δ = 32.8 (CH₂), 121.2 (CNO₂), 121.3 (CCl₂), 123.9 (ICF = 272.4 Hz, CF₃), 126.2 (ICF = 3.9 Hz, CH), 126.6 (ICF = 4.2 Hz, CH), 128.9 (CH), 129.1, 130.2 (CH), 130.7 (ICF = 32.3 Hz, CF₃-C), 138.1, 165.4 (NCS), 173.9 (C=O) ppm; MS m/z (I_rel, %): 432 [M⁺³] (3), 397 [M – Cl⁺] (12), 304 [M-C₂Cl₃+H⁺] (30), 287 [M-C₂Cl₃-O⁺] (93); 145 (100); HRMS (ESI⁻) m/z calcd for C₁₅H₁₄F₃N₂O₃Cl₂S: 430.9044; found: 430.9062.

Synthesis of 3-(hydrazinylidenemethyl)-4-nitro-N-[4-(propan-2-yl)phenyl]-1H-pyrazol-5-amine (20a). To a stirred suspension of thiazolidinone 19a (0.405 g, 1.0 mmol) in MeOH (10 mL) at −18 °C, a solution of hydrazine hydrate (0.400 g, 8.0 mmol) in MeOH (5 mL) was added dropwise within 5 min. Subsequently, the mixture was allowed to reach 0 °C. After 5 h with stirring at 0 °C, the solution was concentrated and neutralized to pH 7 with HCl (5%), then extracted with ethyl acetate (3 × 10 mL). The combined organic phases were purifed over a short column chromatography using ethyl acetate-petroleum ether (1:1). Subsequently, the obtained solution was concentrated and the resulting precipitate was filtered and washed with diethyl ether (2 × 3 mL). Yield 0.150 g (52%), red solid, m.p. 194–195 °C. IR (ATR) ν_max = 3365, 2956, 1597, 1562, 1461, 1350, 579 cm⁻¹. 1H NMR (400 MHz, DMSO-d₆) δ = 1.18 (6H, d, J = 6.9 Hz, CH₃ i-Pr), 2.85 (1H, sep, J = 6.8 Hz, CH i-Pr), 7.16 (2H, d, J = 8.5 Hz, H Ar), 7.61 (2H, d, J = 8.4 Hz, H Ar), 8.07 (1H, s, NCH), 8.15 (2H, s, N-NH₂), 8.53 (1H, s, NH anil), 13.29 (1H, s, NH pyr) ppm. 13C NMR (100 MHz, DMSO-d₆) δ = 24.2 (CH₃), 32.9 (CH i-Pr), 117.4 (CNO₂), 118.0 (2 × CH Ph), 122.7 (NCH), 126.7 (2 × CH Ph), 138.3, 138.7, 141.4, 147.4 (NNHC) ppm; MS m/z (I_rel, %): 288 [M⁺] (60), 273 [M – CH₃]⁺ (100), 256 [M-CH₂-CH₂OH]⁺ (5), 245 [M-i-Pr]⁺ (8), 169 [M-NNH-Ph-i-Pr]⁺ (5); HRMS (ESI⁻) m/z calcd for C₁₃H₁₂N₂O₂: 287.1261; found: 287.1272.

Synthesis of 3-(hydrazinylidenemethyl)-4-nitro-N-[4-(trifluoromethyl)phenyl]-1H-pyrazol-5-amine (20b). To a stirred suspension of thiazolidinone 19b (0.434 g, 1.0 mmol) in MeOH (10 mL) at −18 °C, a solution of hydrazine hydrate (0.250 g, 5.0 mmol) in MeOH (5 mL) was added dropwise within 5 min. Subsequently, the mixture was allowed to reach 0 °C. After 5 h with stirring at 0 °C and 18 h at rt., the solution was concentrated and the resulting precipitate filtered off. Washing the product with cold MeOH (2 × 5 mL) and drying in vacuo yielded the pyrazole 20b. Yield 0.145 g (46%), yellow solid, m.p. 248–250 °C. IR (ATR) ν_max = 3440, 1602, 1516, 1327, 1160, 832 cm⁻¹. 1H NMR (400 MHz, DMSO-d₆) δ = 7.63 (2H, d, J = 8.7 Hz, H Ph), 7.91 (2H, d, J = 8.6 Hz, H Ph), 8.07 (1H, s, NCH), 8.21 (2H, s, NH₂), 8.97 (1H, s, Ph-NH), 13.45 (1H, s, NH Pyr) ppm. 13C NMR (100 MHz, DMSO-d₆) δ = 117.6 (2 × CH Ph), 117.8 (CNO₂), 121.0 (ICF = 32.1 Hz, CCF₃), 122.2 (ICF = 270.7 Hz, CF₃), 122.5 (NCH), 126.2 (ICF = 3.7 Hz, 2 × CH Ph), 139.0, 144.2, 146.4 (NNHC) ppm; MS m/z (I_rel, %): 314 [M⁺] (2), 270 [M-CH₂=NNH₂]⁺.
(3), 254 [M-CH₂=NH₂-O]+ (14), 161 [CF₃-Ph-NH₂]+ (60), 142 [CF₂-Ph-NH₂]+ (27), 96 (100); HRMS (ESI)+ m/z calc for C₁₁H₈N₆O₂F₃ [M - H]+: 313.0665; found: 313.0666.

Synthesis of 5-(furan-2-ylmethyldiene)-3-[4-(propan-2-yl)phenyl]-2-(2,3,3-trichloro-1-nitroprop-2-en-1-ylidene)-1,3-thiazolidin-4-one (21a) (General method). To a suspension of thiazolidinone 19a (0.408 g, 1.0 mmol) in acetic acid (15 mL) furan-2-carbaldehyde (0.115 g, 1.2 mmol) and triethylamine (0.152 g, 1.5 mmol) were added. The resulting mixture was refluxed for 4 h. After concentration of this mixture in vacuo to a volume of about 3 mL and cooling to r.t., the resulting precipitate was filtered off and washed with water (2 × 10 mL) and cold MeOH (1 × 2 mL). The product was dried in vacuo. Yield 0.466 g (96%), orange solid, m.p. 228–229 °C. IR (ATR) νmax = 2958, 1718, 1598, 1519, 1167, 764 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆) δ = 1.24 (3H, d, J = 6.9 Hz, CH₃-Pr), 1.25 (3H, d, J = 6.9 Hz, CH₃-i-Pr), 2.97 (1H, sep, J = 6.8 Hz, CH-i-Pr), 6.86 (1H, dd, J = 1.8 Hz, J = 3.6 Hz, H fur), 7.34 (1H, d, J = 3.5 Hz, H fur), 7.37–7.45 (4H, m, H Ar), 7.90 (1H, s, =CH), 8.30 (1H, d, J = 1.7 Hz, H fur) ppm; ¹³C NMR (100 MHz, DMSO-d₆) δ = 23.6 (CH₃), 23.9 (CH₃), 33.6 (CH-i-Pr), 114.4 (CH), 116.7, 120.8 (CNO₂), 121.0 (CCl₂), 121.8 (CH), 126.9 (CH), 127.3 (CH), 127.4 (CH), 128.8 (CH), 128.8 (CCl-CCl₂), 132.1, 149.4 (CH), 149.9, 150.8, 158.5 (NCS), 166.5 (C=O) ppm; MS m/z (Irel, %): 484 [M⁺] (6), 449 [M-Cl⁺] (2), 339 [M-C₂Cl₁-O⁺] (75), 325 [M-furan-CH=CS-C⁺] (7), 124 [M-furan-CH=C=S⁺] (100). HRMS (ESI)+ m/z calc for C₁₀H₁₃N₂O₂ClSNa [M + Na]+: 506.9716; found: 506.9712.

3-[4-(Propan-2-yl)phenyl]-5-(thiophen-2-ylmethylidene)-2-(2,3,3-trichloro-1-nitroprop-2-en-1-ylidene)-1,3-thiazolidin-4-one (21b). Same procedure as for 21a, using thiophene-2-carbaldehyde (0.135 g, 1.2 mmol). After filtration of the product, it was further purified by column chromatography using chloroform. Yield 0.462 g (90%), dark yellow solid, m.p. 221–223 °C. IR (ATR) νmax = 2963, 1717, 1586, 1525, 1258, 729 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 1.29 (6H, d, J = 6.7 Hz, CH₃-i-Pr), 2.99 (1H, sep, J = 6.9 Hz, CH-i-Pr), 7.16–7.20 (1H, m, H Ar), 7.24–7.27 (1H, d, J = 5.0 Hz, H thien), 7.27–7.30 (1H, m, H Ar), 7.35–7.39 (2H, m, H Ar), 7.56 (1H, d, J = 3.7 Hz, H thien), 7.78 (1H, m, H Ar), 8.12 (1H, s, =CH) ppm; ¹³C NMR (100 MHz, CDCl₃) δ = 23.5 (CH₂), 23.7 (CH₃), 34.1 (CH-i-Pr), 117.6, 120.6 (CCl₂), 122.6 (CNO₂), 126.8 (CH), 127.4 (CH), 127.8 (CH), 127.9 (CH), 129.1 (CH), 129.6 (CH), 129.7 (CCl₂CCl₂), 131.6, 133.6 (CH), 134.8 (CH), 137.6, 151.4 (i-Pr-C), 155.3 (NCS), 166.7 (C=O) ppm; MS m/z (Irel, %): 500 [M⁺] (3), 465 [M-Cl⁺] (2), 372 [M-C₂Cl₁+H⁺] (4), 355 [M-C₂Cl₁-O⁺] (73), 140 [thieryl-C≡CS⁺] (100). HRMS (ESI)+ m/z calc for C₂₀H₁₅N₂O₂Cl₃SNa [M + Na]+: 522.9487; found: 522.9482.

5-[(1-Methyl-1H-pyrrol-2-yl)methyldiene]-3-[4-(propan-2-yl)phenyl]-2-(2,3,3-trichloro-1-nitroprop-2-en-1-ylidene)-1,3-thiazolidin-4-one (21c). Same procedure as for 21a, using 1-methyl-1H-pyrrole-2-carbaldehyde (0.328 g, 3.0 mmol) and triethylamine (0.304 g, 3.0 mmol). The mixture was refluxed for 6 h. Yield 0.459 g (92%), red solid, m.p. 244–246 °C. IR (ATR) νmax = 2986, 1700, 1584, 1520, 1273, 745 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆) δ = 1.24 (3H, d, J = 6.9 Hz, CH₃-i-Pr), 1.25 (3H, d, J = 6.9 Hz, CH₃-i-Pr), 2.98 (1H, sep, J = 6.9 Hz, CH-i-Pr), 3.83 (3H, s, NCH₃), 6.47 (1H, dd, J = 2.6 Hz, J = 4.2 Hz, H pyrr), 6.88 (1H, d, J = 1.1 Hz, J = 4.2 Hz, H pyrr), 7.36–7.44 (5H, m, 4H Ph, H pyrr), 7.84 (1H, s, =CH) ppm; ¹³C NMR (100 MHz, DMSO-d₆) δ = 23.6 (CH₃), 23.9 (CH₃-i-Pr), 33.6 (NCH₃), 34.3 (CH-i-Pr), 111.5 (CCl₂), 111.9 (CH), 118.0 (CH), 120.2 (CNO₂), 121.2, 124.9 (CH), 126.9 (CH), 127.4 (2 × CH), 128.0, 128.6, 128.7 (CH), 131.8 (CH), 132.2, 150.7 (i-Pr-C), 157.5 (NCS), 166.5 (C=O) ppm; MS m/z (Irel, %): 497 [M⁺] (10), 462 [M-Cl⁺] (1), 361 [M-pyrryl-CH=CS=S⁺] (3), 352 [M-C₂Cl₁-H⁺] (25), 137 [M-pyrryl-CH=CS⁺] (100). HRMS (ESI)+ m/z calc for C₂₁H₁₆N₂O₂Cl₃SNa [M + Na]+: 520.0032; found: 520.0018.

5-(Furan-2-ylmethyldiene)-2-(2,3,3-trichloro-1-nitroprop-2-en-1-ylidene)-3-[4-(trifluoromethyl) phenyl]-1,3-thiazolidin-4-one (21d). Same procedure as for 21a, using thiazolidinone 21b (0.433 g, 1.0 mmol), furan-2-carbaldehyde (0.115 g, 1.2 mmol) and triethylamine (0.152 g, 1.5 mmol). Yield 0.374 g (73%), orange solid, m.p. 227–229 °C. IR (ATR) νmax = 3130, 1720, 1525, 1286, 1162, 622 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 6.67 (1H, dd, J = 1.8 Hz, J = 3.6 Hz, H fur), 6.98 (1H, d, J = 3.6 Hz, H fur), 7.41–7.45 (1H, m, H Ar), 7.50–7.55 (1H, m, H Ar), 7.72 (1H, s, =CH), 7.78–7.84 (2H, m, H Ar), 7.85
5-(Thiophen-2-ylmethylidene)-2-(2,3,3-trichloro-1-nitroprop-2-en-1-ylidene)-3-[4-(trifluoromethyl)phenyl]-1,3-thiazolidin-4-one (21e).

Synthesis of 5-[[3-(Morpholin-4-yl)-4-nitro-1H-pyrazol-5-yl)methylidene]-3-[4-(propan-2-yl)phenyl]-1,3-thiazolidin-4-one (23a) (General method).
(83), 598 [M-2(CH₃)]⁺ (22), 582 [M-NO₂⁺] (20), 499 [M-C₂Cl₃]⁺ (10), 146 (100); HRMS (ESI⁺) m/z calcd for C₂H₃₂N₆O₃Cl₂SNa [M + Na⁺]: 651.0363; found: 651.0360.

5-[(1-(Morpholin-4-yl)-4-nitro-1H-pyrazole-5-yl)methylidene]-2-(2,3,3-trichloro-1-nitropropylidene)-2-[4-( trifluoromethyl)phenyl]-1,3-thiazolidin-4-one (25a). A solution of azole 121.5 (CH), 124.0, 125.3 (CH), 128.3 (CH), 129.5 (CH), 131.9, 145.3, 145.6, 150.6 ppm, three C signals was prepared according to the literature [28] in 76% yield.

Synthesis of N-[(1H-Benzotriazol-1-yl)-3,4,4-trichloro-2-nitrobuta-1,3-diene-1,1-diyl]bis(1H-benzotriazole) (24a). A suspension of azole 129 (1H, s, NH) ppm; [M] (rel., %): 654 [M⁺] (35), 639 [M – CH₃]⁺ (60), 619 [M – Cl]⁺ (8), 145 [Ph-CF₃]⁺ (50), 127 (100); HRMS (ESI⁺) m/z calcd for C₂₂H₁₆N₆O₄Cl₂S₃Na [M + Na⁺]: 676.9767; found: 676.9769.

N-[1-(1H-Benzotriazol-1-yl)-3,4,4-trichloro-2-nitrobuta-1,3-dien-1-yl]-2-ethoxyaniline (25a). The reaction mixture was re-dried and washed with HCl (10%, 5 mL), cold water (5 mL) and cold Et₂O (2 × 5 mL). The product was dried in vacuo. Yield 0.392 g (89%), yellow solid, m.p. 128–129 °C. IR (KBr) v_max = 1621, 1580, 1463, 1252, 1023, 753 cm⁻¹. ¹H NMR (200 MHz, CDCl₃) δ = 3.91 (3H, s, OCH₃), 6.15 (1H, dd, J = 1.3 Hz, J = 8.0 Hz, H Ar), 6.46 (1H, ddd, J = 7.7 Hz, J = 1.2 Hz, J = 7.5 Hz, H Ar), 6.82 (1H, dd, J = 1.5 Hz, J = 8.3 Hz, H Ar), 7.00 (1H, ddd, J = 8.3 Hz, J = 1.4 Hz, J = 7.5 Hz, H Ar), 7.27–7.42 (2H, m, H Bzt), 8.02–8.06 (1H, m, H Bzt), 11.65 (1H, s, NH) ppm; ¹³C NMR (50 MHz, CDCl₃) δ = 55.9 (OCH₃), 109.8 (CH Bzt), 111.3 (CH Ar), 120.6 (CH Ar), 120.9 (CH Bzt), 122.2 (CH Ar), 123.8 (CNH), 125.3 (CH Bzt), 128.6 (CH Ar), 129.5 (CH Bzt), 131.9, 145.3 (NCN), 145.9, 151.4 (OOC₃H₃) ppm, three C signals from butadiene-chain due to their low intensity could not be detected; MS m/z (%): 439 [M⁺] (4), 403 [M-Cl]⁺ (3), 358 [M-Cl-NO₂]⁺ (3), 331 [M-Ph-OCH₃]⁺ (6), 122 [H₂NPhOCH₃]⁺ (100); HRMS (ESI⁺) m/z calcd for C₁₇H₁₄N₅O₃Cl₂ [M + H⁺]: 440.0079; found: 440.0077.

N-[1-(1H-Benzotriazol-1-yl)-3,4,4-trichloro-2-nitrobuta-1,3-dien-1-yl]-2-ethoxyaniline (25b). A solution of azole 128 (0.434 g, 1.0 mmol) in MeOH (10 mL) at 0 °C, 2-methoxyaniline (0.129 g, 1.05 mmol) was added. The mixture was allowed to reach r.t. and stirred for another 3 h. After evaporation of the solvent, HCl (10%, 10 mL) was added and the resulting sludge was stirred for 20 min. The precipitate was then filtered off and washed with HCl (10%, 5 mL), cold water (5 mL) and cold Et₂O (2 × 5 mL). The product was dried in vacuo. Yield 0.355 g (78%), orange solid, m.p. 145–146 °C. IR (ATR) v_max = 1620, 1583, 1471, 1241, 1147, 741 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 1.56 (3H, t, J = 7.0 Hz, OCH₂CH₃), 4.15 (2H, q, J = 6.7 Hz, OCH₂CH₃), 5.99 (1H, dd, J = 1.0 Hz, J = 8.0 Hz, H Ar), 6.41 (1H, ddd, J = 7.6 Hz, J = 1.0 Hz, J = 7.9 Hz, H Ar), 6.82 (1H, dd, J = 8.3 Hz, J = 0.9 Hz, H Ar), 6.97 (1H, ddd, J = 8.0 Hz, J = 1.2 Hz, J = 7.8 Hz, H Ar), 7.31 (1H, d, J = 8.0 Hz, H Bzt), 7.37 (ddd, J = 7.0 Hz, J = 1.1 Hz, J = 8.1 Hz, H Bzt), 7.43 (1H, t, J = 7.36 Hz, H Bzt), 8.06 (1H, d, J = 8.2 Hz, H Bzt) ppm; ¹³C NMR (100 MHz, CDCl₃) δ = 14.7 (CH₃), 64.7 (OCH₂), 109.8 (CH), 112.2 (CH), 120.6 (CH), 120.7 (CH), 121.5 (CH), 124.0, 125.3 (CH), 128.3 (CH), 129.5 (CH), 131.9, 145.3, 145.6, 160.6 ppm, three C signals from butadiene-chain due to their low intensity could not be detected; MS m/z (%): 453 [M⁺] (1), 417 [M – HCl⁺] (1), 390 [M-Cl-N₂]⁺ (1), 135 [NPhOEt₂]⁺ (38), 100 (100); HRMS (ESI⁺) m/z calcd for C₁₈H₁₅N₅O₃Cl₂ [M + H⁺]: 454.0235; found: 454.0234.

N’-[1-(1H-Benzotriazol-1-yl)-3,4,4-trichloro-2-nitrobuta-1,3-dien-1-yl]-N,N-dimethylbenzene-1,4-di-amine (25c). The reaction mixture was re-dried and washed with HCl (10%, 5 mL), cold water (5 mL) and cold Et₂O (2 × 5 mL). The product was dried in vacuo. Yield 0.413 g (91%), dark red solid, m.p. 147–148 °C. IR (ATR) v_max = 2891, 1620, 1491, 1358, 1168, 818 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 2.81 (6H, s,
Synthesis of N’-[6-(Dichloromethyl)-2-methyl-5-nitropyrimidin-4-yl]-N, N-dimethylbenzene-1,4-diamine (25f).

Same procedure as for 25a, using 1H-indole (0.125 g, 1.05 mmol). Yield 0.354 g (87%), yellow solid, m.p. 178–179 °C. IR (ATR) νmax = 3065, 1533, 1295, 1023, 905, 655 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 3.34-3.46 (2H, m, CH₂ ind), 3.89-4.25 (2H, m, CH₂ ind), 5.06-6.38 (1H, s, H ind), 6.66-7.00 (1H, m, H Bzt), 7.06 (1H, s, H ind), 7.29-7.36 (1H, m, H ind), 7.40-7.88 (3H, m, 2H Bzt, 1H ind), 8.16 (1H, d, J = 8.1 Hz, H Bzt) ppm; ¹³C NMR (100 MHz, CDCl₃) δ = 29.2 (CH₂), 54.5 (CH₂), 113.9 (CNO₂), 121.1 (2 × CH), 123.2, 125.9 (2 × CH), 126.0 (CH), 127.9 (CH), 128.0 (CH), 130.0 (CH), 131.8 (CCl₃), 141.2 (NCN), 146.1, 146.2 ppm; MS m/z (Irel, %): 435 [M⁺]⁺ (12), 289 [M-indolin-N₂⁺]⁺ (34), 271 [M-Bzt-NO₂⁺]⁺ (79), 118 [benzotriazole]⁺ (100); HRMS (ESI⁺) m/z calc for C₁₈H₁₅N₃O₂Cl₃ [M + H⁺]: 436.0129; found: 436.0127.

Synthesis of 5-Methoxy-8-(2,3,3-trichloro-1-nitroprop-2-en-1-ylidene)-7-azabicyclo[4.2.0]octa-1,3,5-triene (26a) (General method). A suspension of azoee 25a (0.441 g, 1.0 mmol) in MeOH (10 mL) was stirred at reflux for 5 h. Subsequently, the mixture was concentrated and cooled to 0 °C. The precipitate was filtered off and washed with diethyl ether (2 × 5 mL). Yield 0.119 g (37%), yellow solid, m.p. 168–169 °C. IR (KBr) νmax = 3112, 1637, 1536, 1395, 1083, 859 cm⁻¹. ¹H NMR (200 MHz, DMSO-d₆) δ = 3.96 (4H, s, OCH₂), 7.30–7.42 (2H, m, CH), 7.74 (1H, dd, J = 2.3 Hz, J = 7.6 Hz, CH), 12.40 (1H, s, NH) ppm; ¹³C NMR (50 MHz, DMSO-d₆) δ = 57.0 (OCH₃), 110.9 (CH), 114.3 (CH), 119.5, 123.9 (CH), 124.0, 125.9, 130.6, 134.0, 147.3, 153.9 (COCH₃) ppm; MS m/z (Irel, %): 320 [M⁺]⁺ (1), 284 [M – HCl⁺]⁺ (12), 256 [M-NO₂-NH₂H⁺]⁺ (40), 64 (100); HRMS (ESI⁺) m/z calc for C₁₈H₁₅N₃O₂Cl₃ [M + H⁺]: 320.9595; found: 320.9594.

5-Ethoxy-8-(2,3,3-trichloro-1-nitroprop-2-en-1-ylidene)-7-azabicyclo[4.2.0]octa-1,3,5-triene (26b). Same procedure as for 26a, using azoee 25b (0.455, 1.0 mmol) and refluxing in EtOH for 10 h. Yield 0.091 g (27%), yellow solid, m.p. 204–205 °C. IR (KBr) νmax = 2992, 1647, 1533, 1378, 1234, 554 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆) δ = 1.42 (3H, t, J = 7.0 Hz, OCH₂CH₃), 4.16–4.26 (2H, m, OCH₂CH₃), 7.30–7.38 (2H, m, CH), 7.71 (1H, dd, J = 1.5 Hz, J = 8.2 Hz, CH), 12.37 (1H, s, NH) ppm; ¹³C NMR (100 MHz, DMSO-d₆) δ = 14.5 (CH₃), 65.4 (OCH₃), 110.7 (CH), 114.9 (CH), 119.5, 123.9 (CH), 124.0, 125.9, 130.6, 133.9, 146.5, 153.9 ppm; MS m/z (Irel, %): 334 [M⁺]⁺ (3), 299 [M – Cl⁺]⁺ (52), 271 [M-ClEtO⁺H⁺]⁺ (100); HRMS (ESI⁺) m/z calc for C₁₂H₁₀N₂O₃Cl [M + H⁺]: 334.9752; found: 334.9750.

Synthesis of N,N-Dimethyl-8-(2,3,3-trichloro-1-nitroprop-2-en-1-ylidene)-7-azabicyclo[4.2.0]octa-1,3,5-trien-3-amine (26c). A suspension of azoee 25c (0.454 g, 1.0 mmol) in THF (20 mL) was stirred at reflux for 10 h. After evaporation of the solvent, dilute HCl (10 mL) was added and the mixture stirred for 15 min. Subsequently, the mixture was extracted with chloroform and purified by column chromatography using petroleum ether - ethyl acetate (1:1). Yield 0.084 g (25%), red solid, m.p. 171–173 °C. IR (KBr) νmax = 2856, 1567, 1369, 1063, 846, 550 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆) δ = 2.97 (6H, s, N(CH₃)₂), 7.22 (1H, d, J = 2.0 Hz, CH), 7.32 (1H, d, J = 9.0 Hz, CH), 7.36 (1H, dd, J = 2.1 Hz, J = 9.2 Hz, CH), 12.65 (1H, s, NH) ppm; ¹³C NMR (100 MHz, DMSO-d₆) δ = 40.3 (Me), 98.6 (CH), 117.8 (CH), 119.9, 121.1 (CH), 124.0, 125.6, 130.9, 133.5, 147.5 (CNO₂), 153.1 ppm; MS m/z (Irel, %): 333 [M⁺]⁺ (27), 298 [M – Cl⁺]⁺ (40), 270 [M-NO₂-NH₃⁺]⁺ (100); HRMS (ESI⁺) m/z calc for C₁₂H₁₁N₃O₂Cl [M + H⁺]: 333.9917; found: 333.9919.

Synthesis of N’-[6-(Dichloromethyl)-2-methyl-5-nitropyrimidin-4-yl]-N, N-dimethylylbenzene-1,4-diamine (27c).

To a solution of the nitrobutadiene 25c (0.454 g, 1.0 mmol) and acetamide hydrochloride (0.284 g, 3.0 mmol) in 20 mL dry THF, sodium hydride (0.160 g, 4.0 mmol, 60%) was added at 0 °C. The solution was thoroughly stirred for 1 h at 0 °C and then at r.t. for 2 d. After evaporation of the solvent and...
addition of 10% HCl (5 mL) the precipitate was filtered off and washed with 10% HCl (2 × 10 mL), cold water (10 mL), cold MeOH (2 × 5 mL) and dried in vacuo. Yield 0.232 g (65%), yellow solid, m.p. 124–125 °C. IR (KBr) νmax = 3231, 1612, 1573 (NO2), 1517, 1204, 746 cm⁻¹. 1H NMR (400 MHz, CDCl3) δ = 2.64 (3H, s, CCH3), 2.99 (6H, s, NCH3), 6.74 (2H, d, J = 9.0 Hz, H Ar), 7.40 (2H, d, J = 8.9 Hz, H Ar), 7.42 (1H, s, CHCl3), 9.73 (1H, s, NH) ppm; 13C NMR (100 MHz, CDCl3) δ = 26.5 (CH3), 40.5 (NCH3), 66.8 (CHCl3), 112.3 (CH), 122.8, 124.5 (CH), 125.3, 148.9, 153.2, 160.6, 171.0 ppm; MS m/z (rel, %): 355 [M⁺] (39), 136 [phenylendiamine+H⁺] (100); HRMS (ESI⁺) m/z calcld for C14H16N3O2Cl2 [M + H⁺]: 356.0767; found: 356.0764.

6-(Dichloromethyl)-N,N,2-trimethyl-5-nitropyrimidin-4-amine (27d). Same procedure as for 27c, using diene 25d (0.363 g, 1.0 mmol). The precipitate was further purified by column chromatography using petroleu ether - ethyl acetate, 5: 1. Yield 0.148 g (56%), yellowish solid, m.p. 82–83 °C.

1-(6-(Dichloromethyl)-2-methyl-5-nitropyrimidin-4-yl)quinolin-8-amine (27e). Same procedure as for 27c, using azole 25e (0.462 g, 1.0 mmol) as starting material. Yield 0.178 g (49%), yellow solid, m.p. 217–219 °C.

1-(6-(Dichloromethyl)-2-methyl-5-nitropyrimidin-4-yl) 2,3-dihydro-1H-indole (27f). Same procedure as for 27c, using diene 25f (0.437 g, 1.0 mmol), DMSO (25 mL) and NaOH (30%, 4 mmol). Yield 0.216 g (64%), yellow solid, m.p. 132–133 °C. IR (ATR) νmax = 3048, 1589 (NO2), 1340 (NO2), 1209, 768 cm⁻¹. 1H NMR (400 MHz, CDCl3) δ = 2.82 (3H, s, CCH3), 7.37 (1H, s, CHCl3), 7.52 (1H, dd, J = 8.3 Hz, J = 4.2 Hz, H quin), 7.58–7.63 (2H, m, H quin), 8.21 (1H, dd, J = 8.3 Hz, J = 1.6 Hz, H quin), 8.94 (1H, dd, J = 4.2 Hz, J = 1.6 Hz, H quin), 9.04–9.07 (1H, m, H quin), 12.17 (1H, s, NH) ppm; 13C NMR (100 MHz, CDCl3) δ = 26.6 (CH3), 66.4 (CHCl3), 118.4 (CH), 122.0 (CH), 122.93 (CH), 124.6, 127.0 (CH), 128.1, 130.4, 134.6 (CH), 139.3, 149.0 (CH), 152.1, 159.7, 170.9 ppm; MS m/z (rel, %): 363 [M⁺] (15), 317 [M-NO₂⁺] (100), 281 [M - CHCl₂]⁺ (25), 235 [M - quin]+ (12), 128 [quinoline]+ (45); HRMS (ESI⁺) m/z calcld for C15H12N2O2Cl [M + H⁺]: 364.0368; found: 364.0368.

Synthesis of 1-(6-(Dichloromethyl)-2-methyl-5-nitropyrimidin-4-yl)-1H-indole (28). A solution of pyrimidine 27f (0.400 g, 1.2 mmol) and DDQ (0.600 g, 2.7 mmol) in toluene (10 mL) was heated to reflux for 5 h, allowed to cool down to r.t., and the precipitate filtered off. The filtrate was purified by column chromatography using petroleum ether–ethyl acetate, 25: 1. The product was dried in vacuo. Yield 0.267 g (66%), m.p. 103–104 °C. IR (ATR) νmax = 3022, 1589 (NO2), 1342, 1261 (NO2), 1099, 745 cm⁻¹. 1H NMR (600 MHz, CDCl3) δ = 2.92 (3H, s, CCH3), 6.79 (1H, dd, J = 3.7 Hz, J = 0.7 Hz, H ind), 7.01 (1H, s, CHCl3), 7.12 (1H, d, J = 3.7 Hz, H ind), 7.30 (1H, t, J = 8.0 Hz, H ind), 7.36 (1H, d, J = 8.4 Hz, H ind), 7.63 (1H, d, J = 8.2 Hz, H ind), 8.10 (1H, d, J = 9.1 Hz, H ind) ppm; 13C NMR (150 MHz, CDCl3) δ = 26.2 (CH3), 64.8 (CHCl3), 110.9 (CH), 114.1 (CH), 121.6 (CH), 123.8 (CH), 124.5 (CH), 124.9 (CH), 128.3, 130.4, 135.4, 150.5, 157.6, 170.5 ppm; MS m/z (rel, %): 336 [M⁺] (100), 291 [M + H-NO₂⁺] (42), 238 [M-CH₃-CHCl₂]⁺ (48), 116 [indole]+ (62); HRMS (ESI⁺) m/z calcld for C14H11N4O2Cl2 [M + H⁺]: 337.0259; found: 337.0261.
Synthesis of 1-[1-(1H-Benzotriazol-1-yl)-3,4,4-trichloro-2-nitrobuta-1,3-dien-1-yl]-4-(4-chlorophenyl)piperidin-4-ol (25g). Same procedure as for 25a, using 4-(4-chlorophenyl)piperidin-4-ol (0.223 g, 1.05 mmol). Yield 0.482 g (91%), yellowish solid, m.p. 149–150 °C. IR (ATR) νmax = 2931, 1565, 1498, 1290, 1005, 749 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 1.83–2.03 (2H, m, H pip), 2.33–2.61 (2H, m, H pip), 2.95–3.25 (2H, m, NCH₂), 3.76–4.08 (3H, m, OH + NCH₂), 7.35–7.38 (2H, m, H Ar), 7.45–7.47 (2H, m, H Ar), 7.47–7.79 (3H, m, H Bzt), 8.10–8.13 (1H, m, H Bzt) ppm; ¹³C NMR (100 MHz, CDCl₃) δ = 38.3 (CH₂), 47.3 (CH₂), 70.4 (COH), 110.4 (CH), 111.89 (CNO₂), 120.9 (CH), 124.8 (CCl), 125.9 (2 x CH), 126.0 (CH), 126.2 (CCl₂), 128.8 (2 x CH), 130.6 (CH), 132.4, 133.6 (CCl), 144.8, 146.1, 148.0 (CNN) ppm; MS m/z (Irel, %): 527 [M⁺] (1), 499 [M-N₂⁺] (1), 453 [M-N₂-N₂O₂⁺] (1), 416 [M-Ph-Cl]+ (1), 111 [PhCl]+ (20), 91 (100); HRMS (ESI⁺) m/z calcd for C₂₁H₁₈N₅O₃Cl [M + H⁺]*: 538.0158; found: 528.0156.

1-[1-(1H-Benzotriazol-1-yl)-3,4,4-trichloro-2-nitrobuta-1,3-dien-1-yl]piperazin-1-yl(tetrahydrofuran-2-yl)methanone (25h). Same procedure as for 25a, using piperazin-1-yl(tetrahydrofuran-2-yl)methanone (0.193 g, 1.05 mmol). Yield 0.426 g (85%), yellowish solid, m.p. 170–172 °C. IR (KBr) νmax = 2871, 1657, 1560, 1290, 1006, 747 cm⁻¹. ¹H NMR (200 MHz, CDCl₃) δ = 1.80–2.11 (3H, m, CH₂ fur), 2.30–2.49 (1H, m, CH₂ fur), 3.18–3.60 (4H, m, NCH₂), 3.72–4.41 (6H, m, 2NCH₂, OCH₂), 4.52–4.67 (1H, m, OCH), 7.48–7.80 (3H, m, H Bzt), 8.17–8.20 (1H, m, H Bzt) ppm; ¹³C NMR (50 MHz, CDCl₃) δ = 25.7 (CH₂), 27.7 (CH₂), 41.8 (NCH₂), 45.2 (NCH₂), 50.6 (NCH₂), 69.2 (OCH₂), 76.1 (OCH), 110.2 (CH), 116.2 (CCl₂), 120.6 (CNO₂), 121.1 (CH), 125.5, 126.1 (CH), 129.9, 130.7 (CH), 146.6, 147.5 (CNN), 169.7 (CO=O) ppm; MS m/z (Irel, %): 500 [M⁺] (1), 465 [M-Cl⁺] (1), 426 [M-N₂-NO₂⁺] (1), 337 [M-Bzt-NO₂⁺] (4), 119 [Bzt + H⁺] (16), 92 (100); HRMS (ESI⁺) m/z calcd for C₁₂H₁₉N₅O₂Cl [M + H⁺]: 501.0606; found: 501.0605.

Synthesis of 4-(4-Chlorophenyl)-1-[5-(dichloromethyl)-1-methyl-4-nitro-1H-pyrazol-3-yl]piperidin-4-ol (29a) (General method). To a suspension of azole 25g (0.529 g, 1.0 mmol) in MeOH (10 mL) at −10 °C, methylhydrazine (0.921 g, 2.0 mmol) was added dropwise. After 2 h, the solution was allowed reach r.t. and stirred for 1 d. The solution was then concentrated and 10% HCl (5 mL) was added. The resulting precipitate was filtered off, washed with water, and purified by column chromatography using chloroform. Yield 0.311 g (74%), yellowish solid, m.p. 95–96 °C. IR (ATR) νmax = 2951, 1553, 1484, 1348, 1024, 746 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 1.65 (1H, s, OH), 1.78–1.85 (2H, m, CCH₂), 2.28 (2H, ddd, J = 13.1 Hz, J = 4.2 Hz, J = 13.1 Hz, CCH₂), 3.33 (2H, ddd, J = 12.5 Hz, J = 2.5 Hz, J = 12.5 Hz, NCH₂), 3.51–3.59 (2H, m, NCH₂), 4.12 (3H, s, NCH₃), 3.74 (2H, d, J = 8.7 Hz, H Ar), 7.47 (2H, d, J = 8.7 Hz, H Ar), 7.88 (1H, s, CHCl₂) ppm; ¹³C NMR (100 MHz, CDCl₃) δ = 38.0 (2 x CH₂), 39.7 (NCH₂), 46.0 (2 x NCH₂), 57.8 (CH₂), 71.1 (HO-C), 120.4 (CNO₂), 126.1 (CH), 129.2 (CH), 133.0 (CCl), 137.9, 146.5, 152.8 (NC-pyr) ppm; MS m/z (Irel, %): 418 [M⁺] (3), 401 [M-OH⁺] (6), 383 [M-Cl⁻] (5), 367 [M-Cl-O⁺] (4), 347 [M-Cl-HCl]+ (4), 100 (100); HRMS (ESI⁺) m/z calcd for C₁₆H₁₅N₄O₃Cl [M + H⁺]*: 419.0439; found: 419.0437.

1-[1-(1H-Benzotriazol-1-yl)-3,4,4-trichloro-2-nitrobuta-1,3-dien-1-yl]-4-(4-chlorophenyl)piperazin-1-yl(tetrahydrofuran-2-yl)methanone (29b). Same procedure as for 29a, using diene 25h (0.502 g, 1.0 mmol) and DCM as the eluent. Yield 0.310 g (79%), yellowish oil. IR (ATR) νmax = 2954, 1647, 1551, 1341, 1198, 745 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 1.86–2.12 (3H, m, CH₂ Fur), 2.25–2.35 (1H, m, CH₂ Fur), 3.17–3.31 (4H, m, NCH₂), 3.63–3.73 (2H, m, NCH₂), 3.79–3.98 (4H, m, NCH₂, OCH₂), 4.10 (3H, s, NCH₃), 4.64 (1H, dd, J = 5.6
Hz, J = 7.5 Hz, COCHO), 7.84 (1H, s, CHCl₂) ppm; \(^{13}C\) NMR (100 MHz, CDCl₃) δ = 25.7 (CH₂), 28.4 (CH₂), 39.7 (NCH₃), 41.6 (NCH₂), 45.0 (NCH₂), 49.6 (NCH₂), 50.0 (NCH₂), 57.6 (CH), 69.1 (OCH), 75.9 (OCH), 120.5 (CNO₂), 138.1, 152.1, 170.1 (C=O ppm); MS m/z (Irel, %): 391 [M⁺] (100), 374 [M – OH]⁺ (20), 356 [M – Cl]⁺ (65), 320 [M – furan]⁺ (20), 292 [M-CO-furan]⁺ (35); HRMS (ESI⁺) m/z calcd for C₁₄H₁₁N₉O₄Cl₂ [M + H⁺]: 392.0887; found: 392.0889.

1-(3-Chlorophenyl)-4-[5-(dichloromethyl)-1-methyl-4-nitro-1H-pyrazol-3-yl]piperazine (29c). Same procedure as for 29a, using diene 25i (0.514 g, 1.0 mmol) and a mixture of petroleum ether and ethyl acetate (5:1) as the eluent. Yield 0.299 g (74%), yellow solid, m.p. 162–163 °C. IR (ATR) ν\text{max} = 2832, 1552, 1475, 1338, 936, 737 cm⁻¹. \(^1H\) NMR (400 MHz, CDCl₃) δ = 3.31–3.36 (4H, m, NCH₂), 3.38–3.43 (4H, m, NCH₂), 4.13 (3H, s, NCH₃), 6.81–6.86 (2H, m, H Ar), 6.93 (1H, t, J = 2.1 Hz, H Ar), 7.18 (1H, t, J = 8.0 Hz, H Ar), 7.87 (1H, s, CHCl₂) ppm; \(^{13}C\) NMR (100 MHz, CDCl₃) δ = 39.7 (CH₃), 48.5 (NCH₂), 49.5 (NCH₂), 57.7 (CHCl₂), 114.1 (CH), 116.1 (CH), 119.7 (CH), 120.5 (CNO₂), 130.1 (CH), 135.0 (CCI), 138.0, 152.2 (CN), 152.3 (CN) ppm; MS m/z (Irel, %): 403 [M⁺] (45), 357 [M – NO₂]⁺ (6), 322 [M-NO₂-Cl]⁺ (22), 138 [PhCNCH⁺] (100); HRMS (ESI⁺) m/z calcd for C₁₃H₁₇N₅O₂Cl [M + H⁺]: 404.0442; found: 404.0443.

Synthesis of 3-[4-(3-Chlorophenyl)piperazin-1-yl]-1-methyl-4-nitro-1H-pyrazole-5-carbaldehyde (30). Pyrazole 29c (0.405 g, 1.0 mmol) was suspended in 10 mL sulfuric acid (25%) and heated to 95–100 °C for 1 h. After cooling to rt., the solution was extracted with chloroform (3 × 10 mL) and purified by column chromatography using petroleum ether - ethyl acetate (5:1). The product was dried in vacuo. Yield 0.199 g (57%), yellow solid, m.p. 159–160 °C. IR (ATR) ν\text{max} = 2827, 1683, 1546, 1474, 1236, 775 cm⁻¹. \(^1H\) NMR (400 MHz, CDCl₃) δ = 3.32–3.38 (4H, m, NCH₂), 3.45–3.5 (4H, m, NCH₂), 6.81–6.87 (2H, m, H Ph), 6.93 (1H, t, J = 2.0 Hz, H Ph), 7.19 (1H, t, J = 8.1 Hz, H Ph), 10.43 (1H, s, CHO) ppm; \(^{13}C\) NMR (100 MHz, CDCl₃) δ = 40.9 (NCH₂), 48.5 (2 × NCH₂), 49.4 (2 × NCH₂), 114.2 (CH), 116.1 (CH), 119.8 (CH), 125.7 (CNO₂), 130.1 (CH), 135.0 (CCI), 135.2 (CCHO), 151.9, 152.1, 181.8 (CHO) ppm; MS m/z (Irel, %): 349 [M⁺] (103), 332 [M – OH]⁺ (5), 314 [M – Cl]⁺ (4), 304 [M-NO₂+H]+ (20), 138 [PhCNCH⁺] (75); HRMS (ESI⁺) m/z calcd for C₁₃H₁₇N₅O₂Cl [M + H⁺]: 350.1014; found: 350.1016.

Synthesis of 2-(1H-Benzotriazol-1-yl)-4-(dichloromethylidene)-3-nitro-4H-pyridol[1,2-alpyrimidine (31a) (General method). To a solution of azole 24 (0.437 g, 1.0 mmol) in THF (10 mL), 2-aminopyridine (0.282 g, 3.0 mmol) was added at rt. The solution was stirred for 8 h, then concentrated, and the residue treated with dilute HCl for 1 h, filtered off and washed with water (2 × 10 mL) and cold MeOH (5 mL). The product was dried in vacuo. Yield 0.304 g (81%), red solid, m.p. 158–160 °C. IR (KBr) ν\text{max} = 3082, 1628, 1552, 1434, 1307, 1215 cm⁻¹. \(^1H\) NMR (200 MHz, DMSO-d₆) δ = 7.50–7.64 (2H, m, H Ar), 7.64–7.75 (1H, m, H Bzt), 7.87 (1H, d, J = 8.3 Hz, H Ar), 7.90–7.95 (1H, m, H Bzt), 8.21 (1H, d, J = 7.8 Hz, H Bzt), 8.22–8.32 (1H, m, H Bzt), 8.99 (1H, dd, J = 6.8 Hz, 0.9 Hz, H Ar) ppm; \(^{13}C\) NMR (50 MHz, DMSO-d₆) δ = 102.3 (CCL₂), 113.0 (CH), 119.2 (CH), 120.0 (CH), 121.3 (CNO₂), 123.7 (CH), 125.5 (CH), 126.3, 129.6 (CH), 132.3, 138.8 (CH), 143.6 (CH), 145.6, 148.0, 151.3 ppm; MS m/z (Irel, %): m/z (%) = 374 [M⁺] (1), 256 [M-benzotriazole]⁺ (14), 219 (18), 119 [benzotriazole] (14), 92 (100); HRMS (ESI⁺) m/z calcd for C₁₃H₁₈N₅O₂Cl₂ [M + H⁺]: 375.0164; found: 375.0164.

2-(1H-Benzotriazol-1-yl)-7-chloro-(dichloromethylidene)-3-nitro-4H-pyridol[1,2-alpyrimidine (31b). Same procedure as for 31a, using 2-amino-5-chloropyridine (0.386 g, 3.0 mmol) and heating the reaction mixture to 45 °C. Yield 0.352 g (86%), orange solid, m.p. 182–184 °C. IR (KBr) ν\text{max} = 3066, 1505, 1437, 1318, 1238, 1222 cm⁻¹. \(^1H\) NMR (200 MHz, DMSO-d₆) δ = 7.55 (1H, t, J = 7.9 Hz, H Bzt), 7.71 (1H, t, J = 8.1 Hz, H Bzt), 7.86 (1H, d, J = 9.3 Hz, H pyr), 7.92 (1H, d, J = 8.2 Hz, H Bzt), 8.23 (1H, d, J = 8.2 Hz, H Bzt), 8.35 (1H, dd, J = 9.4 Hz, J = 2.3 Hz, H pyr), 9.35 (1H, d, J = 2.3 Hz, H pyr) ppm; \(^{13}C\) NMR (50 MHz, DMSO-d₆) δ = 102.8 (CCL₂), 112.9 (CH), 119.9 (CH), 122.2 (CNO₂), 124.7 (CCI), 124.8 (CH), 125.6 (CH), 129.6 (CH), 132.3, 136.6 (CH), 143.1 (CH), 145.6, 147.7 (NC), 150.6 ppm; MS m/z (Irel, %): 408 [M⁺] (1), 380 [M – N₂]⁺ (1), 373 [M – Cl]⁺ (2), 334 [M-NO₂-NO₂]⁺ (7), 112 (100); HRMS (ESI⁺) m/z calcd for C₁₅H₁₆N₉O₄Cl₂ [M + H⁺]: 408.9769; found: 408.9768.
Synthesis of 4-(dichloromethylidene)-2-{[4-(4-fluorophenyl)piperazin-1-yl]-3-nitro-4H-pyrido[1,2-alpyrimidine (32a) (General method). To a solution of pyrimidine 31a (0.375 g, 1 mmol) in MeOH (10 mL) 1-(4-fluorophenyl)piperazine (0.216 g, 1.2 mmol) was added and the mixture stirred at 40 °C for 5 h. Subsequently, the mixture was cooled to 0 °C and treated with dilute HCl for 1 h. The precipitate was filtered off and washed with water (2 × 5 mL) and cold MeOH (5 mL). The product was dried in vacuo. Yield 0.423 g (97%), yellow solid, m.p. 126–127 °C. IR (KBr) νmax = 1639, 1551, 1504, 1253, 1145, 933 cm⁻¹. 1H NMR (200 MHz, DMSO-d₆) δ = 3.15–3.50 (4H, m, NCH₂), 3.78–4.31 (4H, m, NCH₂), 6.78–7.18 (5H, m, H Pyr, 4H Ph-F), 7.31 (1H, d, J = 8.6 Hz, H pyr), 7.94 (1H, ddd, J = 8.6 Hz, J = 1.3 Hz, J = 7.3 Hz, H pyr), 8.60 (1H, dd, J = 7.2 Hz, J = 1.3 Hz, H pyr) ppm; 13C NMR (50 MHz, DMSO-d₆) δ = 49.5 (4 × NCH₂), 94.9 (CCl₂), 114.7 (CH), 115.6 (JCF = 21.6 Hz, 2 × CH Ph), 118.1 (JCF = 7.9 Hz, 2 × CH Ph), 120.5 (CNO₂), 122.7 (CH), 128.2 (CCl₂), 137.1 (CH), 142.0 (CH), 147.3 (NC Ph), 151.5, 156.6 (JCF = 235.9 Hz, CF), 156.1 (NCN) ppm; MS m/z (rel %): 435 [M⁺] (7), 256 [M-morph-Ph-F]⁺ (10), 179 [Morph-Ph-F]⁺ (15), 95 (100); HRMS (ESI⁺) m/z calcd for C₁₀H₁₀N₅O₂Cl₂F [M + H⁺]: 436.0738; found: 436.0736.

7-Chloro-4-(dichloromethylidene)-2-{[4-(4-fluorophenyl)piperazin-1-yl]-3-nitro-4H-pyrido[1,2-alpyrimidine (32b). Same procedure as for 32a, using compound 31b (0.410 g, 1.0 mmol) but without adding HCl. Yield 0.447 g (95%), yellow solid, m.p. 141–142 °C. IR (KBr) νmax = 1635, 1563, 1493, 1373, 1237, 827 cm⁻¹. 1H NMR (200 MHz, DMSO-d₆) δ = 3.14–3.29 (4H, m, NCH₂), 3.50–3.43 (4H, m, NCH₂), 6.95–7.14 (4H, m, H Ph), 7.31 (1H, d, J = 9.4 Hz, H pyr), 7.99 (1H, d, J = 9.5 Hz, J = 2.3 Hz, H pyr); 8.92 (1H, d, J = 8.9 Hz, H pyr) ppm; 13C NMR (50 MHz, DMSO-d₆) δ = 49.4 (4 × NCH₂), 94.7 (CCl₂), 115.3 (JCF = 21.9 Hz, 2 × FCCH), 117.6 (JCF = 7.7 Hz, 2 × CH Ph), 120.1 (CCl₁), 121.1 (CNO₂), 123.9 (CH), 127.6, 134.7 (NCH), 141.8 (JCF = 1.8 Hz, NC Ph), 150.4, 156.2 (JCF = 236.4 Hz, CF), 156.0 ppm; MS m/z (rel %): 469 [M⁺] (8), 290 [M-piperazine-Ph-F]⁺ (3), 179 [piperazine-Ph-F]⁺ (20), 112 (100); HRMS (ESI⁺) m/z calcd for C₁₀H₁₀N₅O₂Cl₂F [M + H⁺]: 470.0348; found: 470.0350.

Synthesis of Ethyl 4-(dichloromethylidene)-3-nitro-4H-pyrido[1,2-alpyrimidin-2-yl]sulfanylacetate (33a) (General method). To a solution of pyrimidine 31a (0.375 g, 1.0 mmol) in EtOH (10 mL), ethyl 2-mercaptocetate (0.240 g, 2.0 mmol) and sodium ethanolate (0.204 g, 3.0 mmol) were added. The solution was stirred at r.t. for 3 d. Subsequently, dilute HCl (5 mL) was added under stirring for 30 min. The resulting precipitate was filtered off, washed with water (2 × 5 mL) and cold MeOH (3 mL), and dried in vacuo. Yield 0.365 g (97%).

Alternative synthesis of pyrimidine 33a from nitrodiene 18. To a solution of nitrobutadiene 18 (0.355 g, 1.0 mmol) in MeOH (10 mL) 2-aminopyridine (0.282 g, 3.0 mmol) was added. After stirring at r.t. for 1 d, the solution was concentrated and the resulting precipitate filtered off, washed with water (2 × 3 mL), cold MeOH (3 mL) and dried in vacuo. Yield 0.177 g (47%) of 33a, orange solid, m.p. 147–148 °C. IR (ATR) νmax = 1731, 1597, 1451, 1202, 1141, 764 cm⁻¹. 1H NMR (400 MHz, CDCl₃) δ = 1.27 (3H, t, J = 7.1 Hz, OCH₂CH₂), 3.85 (2H, s, SCH₂), 4.20 (2H, q, J = 7.1 Hz, OCH₂), 7.00 (1H, ddd, J = 1.3 Hz, J = 6.9 Hz, J = 6.9 Hz, CH), 7.23 (1H, ddd, J = 1.2 Hz, J = 0.6 Hz, J = 9.0 Hz, CH), 7.72 (1H, ddd, J = 1.7 Hz, J = 7.1 Hz, J = 8.8 Hz, CH), 8.04 (1H, ddd, J = 1.6 Hz, J = 0.7 Hz, J = 6.9 Hz, NCH) ppm; 13C NMR (100 MHz, CDCl₃) δ = 142.3 (CH₂), 33.7 (SCH₂), 61.5 (OCH₂), 114.5 (CH), 117.1 (CCl₂), 123.0 (CH), 125.1 (CNO₂), 135.6 (NCH), 140.0 (CH), 149.7 (NCN), 161.4 (SCN), 169.3 (C=O) ppm, NCCCH₂ could not be detected; MS m/z (rel %): 375 [M⁺] (10), 340 [M-Cl⁺] (9), 288 [M-CH₂CO₂Et⁺] (25), 209 [M-HNO₂-SCH₂CO₂Et⁺] (95), 149 (100); HRMS (ESI⁺) m/z calcd for C₁₃H₁₃N₃O₂Cl₂SNa [M + Na⁺]: 397.9745; found: 397.9746.

Ethyl [7-chloro-4-(dichloromethylidene)-3-nitro-4H-pyrido[1,2-alpyrimidin-2-yl]sulfanylacetate (33b). Same procedure as for 33a but starting from compounds 31b (Yield 0.382 g, 93%), or 18 (Yield 0.226 g, 55%), orange solid, m.p. 171–172 °C. IR (ATR) νmax = 3074, 1727, 1626, 1489, 1235, 741 cm⁻¹. 1H NMR (200 MHz, CDCl₃) δ = 1.27 (3H, t, J = 7.1 Hz, CH₂), 3.83 (2H, s, SCH₂), 4.19 (2H, q, J = 7.2 Hz, OCH₂), 7.17 (1H, dd, J = 9.4 Hz, J = 0.5 Hz, CH), 7.63 (1H, dd, J = 9.5 Hz, J = 2.3 Hz, CH), 8.05 (1H, dd, J = 2.3 Hz, J = 0.6 Hz, NCH) ppm; 13C NMR (50 MHz, CDCl₃) δ = 14.3 (CH₃), 33.6 (SCH₂), 61.6 (OCH₂), 117.5 (CCl₂),
121.4 (CNO), 122.2 (CCI), 123.2 (CH), 124.4 (NC), 133.0 (CH), 140.5 (CH), 148.2, 163.7 (SC), 169.2 (C=O) ppm; MS m/z (Irel %): 409 [M]+ (10), 373 [M-Cl]+, 363 [M-NO2]+ (15), 321 [M-C6H5CO2Et]+ (45), 242 (100); HRMS (ESI+) m/z calcd for C13H10N2O3Cl3SNa [M + Na]+: 431.9355; found: 431.9357.

**Synthesis of N-[4-(benzylsulfanyl)-3,4,4-trichloro-2-nitrobuta-1,3-dien-1-yl]naphthalen-1-amine** (35a) **(General method).** To a solution of diene 34a (0.359 g, 1.0 mmol) in MeOH (10 mL) at −10 °C, naphthalen-1-amine (0.315 g, 2.2 mmol) was added. The solution was kept at −10 °C for 2 h and then allowed to warm up to r.t. for 8 h. Subsequently, the solution was concentrated and the resulting precipitate was filtered off, washed with water (2 × 5 mL) and cold MeOH (5 mL), and dried in vacuo. Yield 0.428 g (92%), green-yellow solid, m.p. 132–133 °C. IR (ATR) νmax = 1536, 1332, 1149, 939, 768, 702 cm−1. 1H NMR (400 MHz, CDCl3) δ = 3.47 (2H, q, J = 12.4 Hz, SCH2), 6.86 (2H, dd, J = 7.7 Hz, J = 1.7 Hz, H Ph), 7.14–7.25 (3H, m, H Ar), 7.57 (1H, dd, J = 7.8 Hz, J = 7.8 Hz, H Ph), 7.59–7.65 (2H, m, H Ph), 7.73 (1H, d, J = 7.4 Hz, H Ar), 7.93 (1H, d, J = 8.2 Hz, H Ar), 7.94–7.99 (2H, m, H Ar), 13.32 (1H, s, NH) ppm; 13C NMR (100 MHz, CDCl3) δ = 38.5 (C2H), 121.5 (CH), 122.0 (CNO), 122.9 (CH), 123.9 (C(Cl)2), 125.4 (CH), 127.2 (CH), 127.8 (CH), 128.0 (CCI), 128.2 (CH), 128.5, 128.6 (CH), 128.7 (2 × CH), 128.7 (CH), 128.9 (2 × CH), 133.4, 134.1, 134.2, 159.7 (NCS) ppm; MS m/z (Irel %): 464 [M]+ (11), 447 [M – NO]+ (1), 418 [M – NO2]+ (1), 127 [naphthalene]+ (11), 91 [PhCH2]+ (100); HRMS (ESI+) m/z calcd for C21H16N2O2Cl3S [M + H]+: 464.9993; found: 464.9991.

**N-[3,4,4-Trichloro-1-[4-chlorophenyl]sulfanyl]-2-nitrobuta-1,3-dien-1-yl]naphthalen-1-amine** (35b). Same procedure as for 33a, but starting from 34b. Yield 0.423 g (87%), yellow-green solid, m.p. 185–186 °C. IR (ATR) νmax = 1538, 1472, 1345, 1161, 824, 767 cm−1. 1H NMR (400 MHz, CDCl3) δ = 6.68 (2H, d, J = 8.8 Hz, H Ar), 6.71 (2H, d, J = 8.8 Hz, H Ar), 7.33–7.43 (3H, m, H Ar), 7.48 (1H, ddd, J = 6.8 Hz, J = 1.2 Hz, J = 8.1 Hz, H Ar), 7.55 (1H, d, J = 8.5 Hz, H Ar), 7.71–7.80 (2H, m, H Ar), 11.96 (1H, s, NH) ppm; 13C NMR (100 MHz, CDCl3) δ = 121.4, 121.3 (CH), 123.8 (CNO), 124.6 (CH), 124.9 (CH), 125.6, 126.8 (CH), 126.9 (CH), 128.4 (CH), 128.5, 128.7 (CH), 129.1 (2 × CH), 133.2, 133.6, 134.3 (2 × CH), 135.4, 160.8 (NCS) ppm; MS m/z (Irel %): 484 [M]+ (5), 449 [M+Cl]+ (5), 438 [M-NO2]+ (3), 356 [M – naphthalene]+ (2), 143 [naphthylamine]+ (60), 127 [naphthalene]+ (100); HRMS (ESI+) m/z calcd for C20H13N2O2Cl2S [M + Na]+: 484.9446; found: 484.9443.

**Synthesis of 2-(Benzylsulfanyl)-4-(dichloromethyl)-3-nitrobenzo[h]quinoline** (36a) **(General method).** To a solution of diene 35a (0.466 g, 1.0 mmol) in chloroform (10 mL) at 0 °C, triethylamine (0.202 g, 2.0 mmol) was added. The solution was kept at 0 °C for 2 h and then allowed to warm up to r.t. for 3 h. Subsequently, the solution was concentrated and diluted with 5 mL MeOH. The resulting precipitate was filtered off, washed with 10%aq. HCl (2 × 5 mL), water (2 × 5 mL) and cold MeOH (5 mL), and dried in vacuo to give benzoquinoline 36a. Yield 0.326 g (76%), yellow solid, m.p. 173–174 °C. IR (ATR) νmax = 3033, 1541, 1336, 1198, 828, 711 cm−1. 1H NMR (400 MHz, CDCl3) δ = 4.78 (2H, s, SCH2), 7.12 (1H, s, CHC2), 7.27–7.36 (3H, m, H Ph), 7.48–7.52 (2H, m, H Ph), 7.57 (1H, ddd, J = 7.2 Hz, J = 1.1 Hz, J = 7.9 Hz, H Ar), 7.79 (1H, ddd, J = 7.3 Hz, J = 1.4 Hz, J = 7.3 Hz, H Ar), 7.95 (2H, d, J = 9.0 Hz, H Ar), 8.64 (1H, d, J = 9.4 Hz, H Ar), 9.18 (1H, d, dd, J = 7.6 Hz, J = 0.8 Hz, H Ar) ppm; 13C NMR (100 MHz, CDCl3) δ = 35.8 (SCH2), 63.4 (CHC2), 119.2, 122.3 (CH), 125.4 (CH), 127.7 (CH), 128.0 (CH), 128.5 (CH), 128.7 (2 × CH), 129.0 (2 × CH), 130.1 (CH), 130.4, 134.2, 134.8, 136.1, 139.4, 147.7, 149.8 ppm; MS m/z (Irel %): 428 [M]+ (2), 344 [M-C6H5CO2]+ (2), 91 [PhCH2]+ (100); HRMS (ESI+) m/z calcd for C21H13O2Cl2S [M + Na]+: 451.0051; found: 451.0050.

2-[4-Chlorophenyl)sulfanyl]-4-(dichloromethyl)-3-nitrobenzo[h]quinoline (36b). Same procedure as for 36a, but starting from 35b. Yield 0.382 g (85%), yellow solid, m.p. 162–163 °C. IR (ATR) νmax = 3073, 1572, 1541, 1388, 1028, 739 cm−1. 1H NMR (400 MHz, CDCl3) δ = 7.19 (1H, s, CHC2), 7.53 (2H, d, J = 8.6 Hz, H Ph), 7.58 (1H, ddd, J = 7.1 Hz, J = 1.3 Hz, J = 8.3 Hz, H Ph), 7.63 (2H, d, J = 8.6 Hz, H Ph), 7.72 (1H, ddd, J = 7.0 Hz, J = 1.1 Hz, J = 8.1 Hz, H Ph), 7.88 (1H, d, J = 7.9 Hz, H Ph), 7.92 (1H, d, J = 9.3 Hz, H Ph), 8.32 (1H, d, J = 8.3 Hz, H Ph), 8.61 (1H, d, J = 9.3 Hz, H Ph) ppm; 13C NMR (100 MHz, CDCl3) δ = 63.4 (CHC2), 119.8, 122.0 (CH), 125.3 (CH), 127.2, 127.8 (CH), 128.0 (CH), 129.1 (CH), 129.6 (2 × CH), 130.1...
Synthesis of 2-[(4-Chlorophenyl)sulfinyl]-4-(dichloromethyl)-3-nitrobenzo[h]quinoline (37b). Same procedure as for 37a, but starting from 36b (0.450 g, 1.0 mmol). Yield 0.424 g (91%), yellow solid, m.p. 166–168 °C. IR (ATR) νmax = 3082, 1546, 1342, 1092, 828, 750 cm⁻¹. 1H NMR (400 MHz, CDCl3) δ = 7.20 (1H, s, CHCl2), 7.50 (2H, d, J = 8.6 Hz, H Ar), 7.84–7.91 (2H, m, H Ar), 7.95–8.03 (3H, m, H Ar), 8.12 (1H, d, J = 9.4 Hz, H Ar), 8.71 (1H, d, J = 9.4 Hz, H Ar), 9.28–9.33 (1H, m, H Ar) ppm; 13C NMR (100 MHz, CDCl3) δ = 62.4 (CH2Cl), 122.0 (CH), 123.3, 125.8 (CH), 127.0 (2 × CH), 128.2 (CH), 128.8 (CH), 129.7 (2 × CH), 130.5, 131.0 (CH), 131.0, 132.0 (CH), 134.0, 136.0, 138.0 (CNO2), 138.3, 141.1, 148.2, 153.4 (NCS) ppm; MS m/z (rel. %): 464 [M⁺]² (2), 418 [M-NO2]⁺ (2), 365 [M-O-CHCl2]⁺ (38), 335 [M-CHCl2-NO2]⁺ (12), 111 [PhCl⁺] (50), 100 (100); HRMS (ESI⁺) m/z calcd for C21H14N2O3Cl2Na [M + Na⁺]: 486.9454; found: 486.9454.

Synthesis of 4-(Dichloromethyl)-3-nitro-2-(pyrroldin-1-yl)benzo[h]quinoline (38). A solution of quinoline 37a (0.445 g, 1.0 mmol) in toluene (10 mL), pyrrolidine (0.107 g, 1.5 mmol) was added and the mixture was heated to 100 °C for 3 h. After cooling, the crude product was purified by column chromatography using petroleum ether - ethyl acetate (10: 1). Yield 0.290 g (77%), red solid, m.p. 169–170 °C. IR (ATR) νmax = 2884, 1584, 1506, 1359, 821, 734 cm⁻¹. 1H NMR (400 MHz, CDCl3) δ = 1.99–2.09 (4H, m, NCC2H), 3.61–3.71 (4H, m, NCC2H), 7.07 (1H, s, CHCl2), 7.61–7.71 (3H, m, H Ar), 7.85 (1H, dd, J = 7.6 Hz, J = 1.3 Hz, H Ar), 8.50 (1H, d, J = 9.3 Hz, H Ar), 9.03 (1H, d, J = 7.9 Hz, H Ar) ppm; 15C NMR (100 MHz, CDCl3) δ = 25.5 (2 × NCC2H), 48.1 (2 × NCC2H), 64.0 (CH2Cl), 113.9, 122.6 (CH), 124.1 (CH), 125.5 (CH), 126.6 (CH), 127.6 (CH), 129.2 (CH), 130.2, 130.4 (CNO2), 134.3, 135.6, 145.5, 147.5 ppm; MS m/z (rel. %): 375 [M⁺] (100), 358 [M – OH⁺] (15), 340 [M – Cl⁺] (5), 329 [M – NO2⁺] (12), 259 [M-NO2-Pyr⁺] (30); HRMS (ESI⁺) m/z calcd for C19H15N3O2Cl2Na [M + Na⁺]: 398.0439; found: 398.0440.

Synthesis of 2-ethoxy-2-oxoethyl 4,5-dichloro-1,2-thiazole-3-carboxylate (41). To a solution of isothiazole 40 (0.198 g, 1.0 mmol) and ethyl bromoacetate (0.501 g, 3.0 mmol) in EtOH (10 mL), sodium ethanolate (0.204 g, 3.0 mmol) was added at r.t. The mixture was heated to reflux for 3 d. The product was extracted with chloroform (3 × 10 mL) and purified through a short column chromatography using petroleum ether – ethyl acetate (10:1). Yield 0.165 g (58%), yellowish solid, m.p. 31–33 °C. IR (KBr) νmax = 2983, 1743, 1427, 1193, 1038, 947 cm⁻¹. 1H NMR (200 MHz, CDCl3) δ = 1.31 (3H, t, J = 7.1 Hz, OCH2CH3), 4.28 (2H, q, J = 7.1 Hz, OCH2CH3), 4.91 (2H, s, OCH2C=O) ppm; 13C NMR (50 MHz, CDCl3) δ = 14.0 (CH3), 61.7 (OCH2CH3, OCH2C=O), 126.1 (CCl), 150.8 (SCCl), 153.1 (C=N), 158.2, 166.7; MS m/z (rel. %): 283 [M⁺] (18), 238 [M – OEt⁺] (15), 210 [M – CO2Et⁺] (12), 180 [M – OCH2CO2Et⁺] (100); HRMS (ESI⁺) m/z calcd for C8H7NO4Cl2SnA [M + Na⁺]: 305.9371; found: 305.9370.
Synthesis of 2,2,2-Trifluoroethyl 4,5-dichloro-1,2-thiazole-3-carboxylate (43). A solution of isothiazole 42 (0.217 g, 1.0 mmol) and 2,2,2-trifluoroethanol (0.300 g, 4.0 mmol) in 20 mL dry THF was refluxed for 4 d. After cooling to r.t., the solution was concentrated, diluted with water (20 mL), extracted with hexane (3 × 20 mL), and washed with water (2 × 20 mL). Subsequently, the product was purified by column chromatography (hexane). Yield 0.179 g (64%), white solid, m.p. 51–52 °C. IR (KBr) νmax cm⁻¹: 1741, 1430, 1358, 1167, 1091, 745. 1H NMR (200 MHz, CDCl₃) δ = 4.61 (2H, q, J = 8.2 Hz, OCH₂); 13C NMR (50 MHz, CDCl₃) δ = 61.3 (JCF = 37.1 Hz, CH₂), 122.6 (JCF = 276.0 Hz, CF₃), 126.3 (CCl), 151.3 (C≡N), 152.3 (SCl), 157.3 (C=O) ppm; MS m/z (rel. %): 279 [M⁺] (15), 244 [M – Cl]⁺ (2), 197 [M-CH₂CF₃+H]⁺ (12), 180 [M-OCH₂CF₃]+ (100), 153 [M-CO₂CH₂CF₃+H]⁺ (40); HRMS (ESI⁺) m/z calcd for C₉H₁₀NO₂Cl₂SF₃Na [M + Na⁺]: 301.9033; found: 301.9035.

Synthesis of 4,5-Dichloro-N′-phenyl-1,2-thiazole-3-carbonylhydrazide (44a) (General method). To a suspension of phenylazidobenzene (0.324 g, 3.0 mmol) in dry THF (10 mL), the isothiazole 42 (0.216 g, 1.0 mmol) was added at r.t. The mixture was stirred for 1 d. After removal of the solvent, the residue was treated with cold HCl (10%) and the resulting precipitate filtered off. Subsequently, it was washed with cold water (3 × 5 mL) and Et₂O (2 × 3 mL). The product was dried in vacuo. Yield 0.216 g (75%), light brown solid, m.p. 145–147 °C. IR (KBr) νmax cm⁻¹: 3254, 1678, 1605, 1351, 884, 746 cm⁻¹. 1H NMR (200 MHz, CDCl₃) δ = 6.88–6.96 (3H, m, H Ph), 7.20–7.26 (3H, m, NH, 2H Ph), 8.81 (1H, s, NH) ppm; 13C NMR (50 MHz, CDCl₃) δ = 113.8 (2 × CH), 121.6 (CH), 125.3 (CCl), 129.2 (2 × CH), 147.3, 150.9 (CCl), 155.3, 158.9 ppm; MS m/z (rel. %): 287 [M⁺] (14), 180 [M-CONHNHPh]⁺ (5), 107 [PhNHNH]⁺ (100); HRMS (ESI⁺) m/z calcd for C₁₀H₇N₂OCl₂SF₃Na [M + Na⁺]: 309.9585; found: 309.9585.

4,5-Dichloro-N′-[3-(trifluoromethyl)phenyl]-1,2-thiazole-3-carbonylhydrazide (44b). Same procedure as for 44a, but using 3-trifluoromethylphenylhydrazine (0.370 g, 2.1 mmol) and stirring the mixture at reflux for 6 h. Yield 0.338 g (95%), yellowish solid, m.p. 152–153 °C. IR (KBr) νmax cm⁻¹: 3300, 1691, 1497, 1340, 1161, 798 cm⁻¹. 1H NMR (200 MHz, DMSO-d₆) δ = 7.03–7.09 (3H, m, H Ar), 7.34–7.49 (1H, m, H Ar), 8.57 (1H, s, NH), 10.79 (1H, s, NH) ppm; 13C NMR (50 MHz, DMSO-d₆) δ = 108.2 (JCF = 3.9 Hz, CH), 115.2 (JCF = 4.0 Hz, CH), 116.1 (CH), 124.6 (JCF = 271.5 Hz, CF₃), 123.0 (CCl), 129.7 (JCF = 31.3 Hz, CF₃CF), 130.2 (CH), 149.5 (CCl), 149.9, 157.8, 160.1 (C=O) ppm; MS m/z (rel. %): 355 [M⁺] (25), 336 [M-F⁺] (2), 180 [M-CF₃-Ph-NHNH⁺]⁺ (60), 175 [CF₃-Ph-NHNH⁺]⁺ (100), 152 [M-CONHNHPh-CF₃]+ (10); HRMS (ESI⁺) m/z calcd for C₁₁H₈N₂OCl₂SF₃Na [M + Na⁺]: 377.9458; found: 377.9459.

4,5-Dichloro-N-(4-cyano-2,5-difluorophenyl)-1,2-thiazole-3-carboxamide (44c). Same procedure as for 44a, but using 4-cyano-2,5-difluoroaniline (0.354 g, 2.3 mmol) and stirring the mixture at reflux for 6 h. Yield 0.227 g (68%), white solid, m.p. 164–166 °C. IR (KBr) νmax cm⁻¹: 3361, 2237 (CN), 1715, 1528, 1190, 673 cm⁻¹. 1H NMR (200 MHz, CDCl₃) δ = 4.41 (1H, dd, J = 9.8 Hz, J = 5.4 Hz, H Ar), 8.57 (1H, dd, J = 10.6 Hz, J = 6.2 Hz, H Ar), 9.49 (1H, s, NH) ppm; 13C NMR (50 MHz, CDCl₃) δ = 95.6 (JCF = 18.8 Hz, 9.6 Hz, C(NCN)), 108.6 (JCF = 28.7 Hz, 1.5 Hz, CH), 112.9 (JCF = 2.3 Hz, C(NCN)), 118.3 (JCF = 24.5 Hz, 2.3 Hz, CH), 125.7 (CCl), 131.7 (JCF = 11.9 Hz, NC Ph), 147.5 (JCF = 244.0 Hz, 2.8 Hz, CF), 152.1 (CCl), 154.6, 156.3 (C=O), 160.1 (JCF = 255.3 Hz, 2.3 Hz, CF) ppm; MS m/z (rel. %): 333 [M⁺] (22), 180 [M-NH-Ph-F₂(CN)]⁺ (100), 152 [M-CONHNH-Ph-F₂(CN)]⁺ (15); HRMS (ESI⁺) m/z calcd for C₁₁H₃N₃OCl₂SF₂Na [M + Na⁺]: 355.9240; found: 355.9241.

4,5-Dichloro-N-[2-(1H-indol-3-yl)ethyl]-1,2-thiazole-3-carboxamide (44d). Same procedure as for 44a, but using tryptamine (0.352 g, 2.2 mmol) and triethylamine (0.223 g, 2.1 mmol). Yield 0.265 g (78%), white solid, m.p. 183–185 °C. IR (KBr) νmax cm⁻¹: 3302, 1650, 1537, 1349, 946, 738 cm⁻¹. 1H NMR (200 MHz, CDCl₃) δ = 3.08 (2H, t, J = 8.1 Hz, Ind-CH₂), 3.72–3.82 (2H, m, NCH₂), 7.07 (1H, s, NH-C=O), 7.11–7.25 (3H, m, 2H Ar, NCH), 7.37 (1H, d, J = 7.7 Hz, H Ar), 7.63 (1H, d, J = 7.7 Hz, H Ar), 8.15 (1H, s, NH) ppm; 13C NMR (50 MHz, CDCl₃) δ = 25.3 (CH₃), 39.6 (CH₂), 111.2 (CH₂), 111.2, 118.7 (CH), 119.5 (CH), 122.1 (CH, CCl), 122.2 (CH), 127.2, 136.4, 150.4 (CCl), 156.7, 159.0 (C=O) ppm; MS m/z (rel. %): 339 [M⁺] (4), 180 [M-NHCH₂-Ind]+ (5), 143 [Ind-CH₃CH₂]+ (100), 130 [Ind-CH₂]+ (91); HRMS (ESI⁺) m/z calcd for C₁₄H₁₁N₃OCl₂Na [M + Na⁺]: 361.9900; found: 361.9898.
4,5-Dichloro-N-[(6-chloropyridin-3-yl)methyl]-N-methyl-1,2-thiazole-3-carboxamide (44e). Same procedure as for 44a, but using isothiazole 42 and 1-(6-chloropyridin-3-yl)-N-methylmethanamine (0.313 g, 2.0 mmol) at 0 °C and then stirring at r.t. for 5 h. Yield 0.290 g (86%).

Alternative synthesis of thiazole 44e: To a suspension of 4,5-dichloro-N’-phenyl-1,2-thiazole-3-carbohydrazide (44a) (0.288 g, 1.0 mmol) in DMSO (10 mL), 1-(6-chloropyridin-3-yl)-N-methylmethanamine (0.313 g, 2.0 mmol) was added. The mixture was heated to 100 °C for 8 h. After cooling to r.t., water (50 mL) was added and the mixture extracted with chloroform (3 × 15 mL). Subsequently, the product was purified by column chromatography using petroleum ether-ethyl acetate (3: 1). The product was dried in vacuo. Yield 0.232 g (69%), a mixture of two rotamers in relation 10: 6, yellowish solid, m.p. 43–45 °C. IR (KBr) νmax = 2934, 1651, 1460, 1349, 1106, 834 cm⁻¹. 1H NMR (600 MHz, CDCl₃) for major isomer δ = 2.90 (3H, s, NCH₃), 4.73 (2H, s, NCH₂), 7.34 (1H, d, J = 8.2 Hz, H pyr), 7.71 (1H, dd, J = 2.5 Hz, J = 8.3 Hz, H pyr), 8.37 (1H, d, J = 2.3 Hz, H pyr) ppm; minor isomer δ = 3.02 (1.8H, s, NCH₃), 4.48 (1.2H, s, NCH₂), 7.34 (0.6H, d, J = 8.2 Hz, H pyr), 7.72 (0.6H, dd, J = 2.5 Hz, J = 8.3 Hz, H pyr), 8.28 (0.6H, d, J = 2.3 Hz, H pyr) ppm; 13C NMR (100 MHz, CDCl₃) for major isomer δ = 35.7 (NCH₃), 47.8 (2H, CH₂), 122.5 (CCI), 124.6 (CH), 130.7 (CH₂(C)), 138.8 (1H), 149.6 (CCI), 151.2 (NCCI), 159.6, 162.8 (C=O) ppm; minor isomer δ = 32.8 (NCH₃), 51.2 (NCH₂), 123.2 (CCI), 124.5 (CH), 150.3 (CH₂(C)), 138.1 (CH), 148.9 (CH), 151.5 (NCCI), 159.5, 162.4 (C=O) ppm; 15N NMR (43.4 MHz, CDCl₃, doped with nitrromethane (0.0 ppm)) δ = -267.5 (NMe, minor isomer), -266.3 (NMe, major isomer), -75.7 (NCCI, major isomer), -75.5 (NCCI, minor isomer) ppm, N5 not detected; MS m/z (Irel, %): 337 [M⁺] (3), 319 [M-CH₃]⁺ (2), 300 [M-CI]⁺ (6), 180 [M-CH₂-N-C₂H₃-isothiazole]⁺ (14), 155 [isothiazole-N-C₂H₂-C₃H₃]⁺ (100); HRMS (EI⁺) m/z calcd for C₁₁H₈N₃OCl₃SnA [M + Na]⁺: 357.9351; found: 357.9352.

4-Chloro-5-(morpholin-4-yl)-N’-phenyl-1,2-thiazole-3-carbohydrazide (45). Following the alternative procedure for azole 44e using morpholine (0.348 g, 4.0 mmol). The mixture was stirred at 90–95 °C for 4 h. Yield 0.264 g (78%), yellowish solid, m.p. 163–164 °C. IR (ATR) νmax = 3294, 1695, 1494, 1403, 1115, 688 cm⁻¹. 1H NMR (400 MHz, CDCl₃) δ = 3.32–3.41 (4H, m, NCH₂), 3.82–3.91 (4H, m, OCH₂), 6.24 (1H, s, Ph-NH), 6.88–6.95 (3H, m, H Ph), 7.21–7.26 (2H, m, H Ph), 8.78 (1H, s, CONH) ppm; 13C NMR (100 MHz, CDCl₃) δ = 50.8 (2 × NCH₂), 66.0 (2 × OCH₂), 108.9, 113.8 (2 × CH), 121.4 (CH), 129.2 (2 × CH), 147.7, 156.0 (NCC=O), 160.1 (C=O), 173.1 (morph-C) ppm; MS m/z (Irel, %): 338 [M⁺] (75), 303 [M-CI]⁺ (8), 231 [M-PhNHH⁺] (35), 197 [M-PhNHH=Cl+H⁺] (100), 107 [PhNHH⁺] (60); HRMS (EI⁺) m/z calcd for C₁₁H₁₄N₄OCl₃SnA [M + Na]⁺: 361.0502; found: 361.0502.

Synthesis of 4-chloro-5-[4-chlorophenyl]sulfonyl]-N’-phenyl-1,2-thiazole-3-carbohydrazide (46a) (General method). To a solution of isothiazole 44a (0.288 g, 1.0 mmol) in DMSO (10 mL), 4-chlorothiophenol (0.173 g, 1.2 mmol) and sodium ethanolate (0.082 g, 1.2 mmol) were added. The mixture was stirred at 110 °C for 8 h. After concentration at 100 °C, it was poured into 50 mL diluted HCl (5%) and then stirring at r.t. for 8 h. The product was dried in vacuo. Yield 0.266 g (67%), white solid, m.p. 169–170 °C. IR (ATR) νmax = 3250, 1655, 1493, 1094, 896, 695 cm⁻¹. 1H NMR (400 MHz, CDCl₃) δ = 6.68–6.95 (3H, m, H Ph), 7.20–7.26 (2H, m, H Ph), 7.43 (2H, d, J = 8.5 Hz, H Ar), 7.53 (2H, d, J = 8.5 Hz, H Ar), 8.7 (1H, s, CONH) ppm; 13C NMR (100 MHz, CDCl₃) δ = 131.8 (2 × CH), 121.6 (CH), 123.3, 128.2 (CCI), 129.2 (2 × CH), 130.5 (2 × CH), 134.7 (2 × CH), 136.7 (CS-Thiaz), 147.5, 155.5 (CCI=O), 159.3, 160.9 (C=O) ppm; MS m/z (Irel, %): 395 [M⁺] (20), 288 [M-PhNHH⁺] (10), 261 [M-PhNHNHCO+H⁺] (4), 225 [M-PhNHNHCO-Cl⁺] (15), 107 [HNHPh⁺] (100); HRMS (EI⁺) m/z calcd for C₁₆H₁₁N₃OCl₂S₂Na [M + Na⁺]: 417.9618; found: 417.9617.

4-Chloro-5-[4-chlorophenyl]sulfanyl]-N’-[3-(trifluoromethyl)phenyl]-1,2-thiazole-3-carbohydrazide (46b). Same procedure as for 46a, but using 44b (0.356 g, 1.0 mmol). The product was purified using petroleum ether-ethyl acetate (10: 1). Yield 0.325 g (70%), white solid, m.p. 144–145 °C. IR (ATR) νmax
= 3246, 1662, 1476, 1338, 1123, 694 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 6.39 (1H, s br, NH), 7.05 (1H, dd, J = 8.0 Hz, J = 2.1 Hz, H Ar), 7.11 (1H, s, H Ar), 7.15 (1H, d, J = 7.9 Hz, H Ar), 7.32 (1H, t, J = 8.0 Hz, H Ar), 7.44 (2H, d, J = 8.6 Hz, H Ar), 7.54 (2H, d, J = 8.6 Hz, H Ar), 8.77 (1H, s, NH). ¹³C (100 MHz, CDCl₃) δ = 110.2 (JCF = 4.1 Hz, CH), 116.8 (CH), 118.1 (JCF = 3.9 Hz, CH), 123.9 (JCF = 272.5 Hz, CF₃), 123.1 (CCl₂), 128.0 (CCl₂), 129.7 (CH), 130.9 (2 × CH), 131.6 (JCF = 32.2 Hz, CCF₃), 134.8 (2 × CH), 136.9 (CS), 148.1 (N₂H₂), 151.5 (SCN), 159.5 (CCO), 161.5 (C=O) ppm; MS m/z (Irel, %): 463 [M⁺] (35), 288 [M-N₂H₂SCI]⁺ (93), 225 [M-CON₂H₂SCI]⁺ (80), 145 [PhCF₃]⁺ (100); HRMS (ESI⁺) m/z calcd for C₁₇H₁₀N₃OCl₂S₂F₂Na [M + Na⁺]: 485.9492; found: 485.9494.

4-Chloro-5-[(4-chlorophenyl)sulfanyl]-N-(4-cyano-2,5-difluorophenyl)-1,2-thiazole-3-carboxamide (46c). Same procedure as for 46a, but using 44c (0.334 g, 1.0 mmol). The product was purified by using petroleum ether-ethyl acetate (10: 1). Yield 0.367 g (83%), white solid, m.p. 152–153 °C. IR (ATR) νmax = 3384, 2241 (CN), 1703, 1473, 1196, 617 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 7.24–7.66 (5H, m, H Ar), 8.57 (1H, s, H Ar), 9.47 (1H, s, NH) ppm; ¹³C NMR (101 MHz, CDCl₃) δ = 95.4 (JCF = 19.8 Hz, 11.0 Hz, Ar CCN), 108.6 (JCF = 28.6 Hz, CH), 112.9 (Ph-CN), 118.3 (JCF = 24.2 Hz, CH), 123.0 (CCl₂), 127.6 (CCl₂), 130.7 (2 × CH), 131.9 (JCF = 11.7 Hz, CHN), 135.0 (2 × CH), 137.1 (SC), 147.5 (JCF = 244.3 Hz, CF), 154.9 (SCS), 156.9 (SNC), 160.2 (JCF = 253.8 Hz, CF), 163.0 (C=O) ppm; MS m/z (Irel, %): 441 [M⁺] (40), 288 [M-NHPh₂CN⁺] (100), 225 [M-CICOPh₂CN⁺] (80), 143 [PhSCI⁺] (53); HRMS (ESI⁺) m/z calcd for C₁₇H₂₁N₂OCl₂S₂F₂Na [M + Na⁺]: 463.9273; found: 463.9271.

4-Chloro-5-[(4-chlorophenyl)sulfanyl]-N-[2-(1H-indol-3-yl)ethyl]-1,2-thiazole-3-carboxamide (46d). Same procedure as for 46a, but using 44d (0.340 g, 1.0 mmol). After addition of HCl the crude product precipitated and was filtered off, washed with diluted HCl (3 mL), water (2 × 5 mL), cold MeOH (3 mL) and dried in vacuo. Yield 0.399 g (89%), white solid, m.p. 176–177 °C. IR (ATR) νmax = 3280, 1667, 1525, 1338, 821, 740 cm⁻¹. ¹H NMR (400 MHz, DMSO-d₆) δ = 2.88–2.99 (2H, m, Ind-CH₂), 3.47–3.58 (2H, m, NCH₂), 6.98 (1H, t, J = 7.0 Hz, H ind), 7.06 (1H, t, J = 7.0 Hz, H ind), 7.19 (1H, s, H ind), 7.34 (1H, d, J = 7.7 Hz, H ind), 7.51–7.73 (5H, m, H ind, 4H Ar), 8.84 (1H, s, CONH), 10.82 (1H, s, NH ind); ¹³C NMR (101 MHz, DMSO-d₆) δ = 25.1 (ind-CH₂), 39.7 (NCH₂), 111.5, 111.6 (CH), 118.4 (CH), 118.5 (CH), 121.1 (CH), 121.5, 122.8 (NCH), 127.4, 128.8, 130.6 (2 × CH), 134.5 (2 × CH), 153.5 (SC), 136.4, 158.6 (CCO), 159.4 (SCS), 159.8 (C=O) ppm; MS m/z (Irel, %): 447 [M⁺] (3), 288 [M-NHCH₂(eq)⁺] (1), 143 [PhSCI⁺] (100), 130 [IndCH₂⁺] (53); HRMS (ESI⁺) m/z calcd for C₂₀H₁₅N₃OCl₂S₂Na [M + Na⁺]: 469.9931; found: 469.9931.

2-Ethoxy-2-oxoethyl 4-chloro-5-[(4-chlorophenyl)sulfanyl]-1,2-thiazole-3-carboxylate (46e). Same procedure as for 46a, but using 41 (0.284 g, 1.0 mmol). The product was purified by using petroleum ether-ethyl acetate (10: 1). Yield 0.267 g (68%), yellowish solid, m.p. 72–73 °C. IR (ATR) νmax = 1755, 1722, 1344, 1198, 1084, 505 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 1.28 (3H, t, J = 7.0 Hz, OCH₂CH₃), 4.25 (2H, q, J = 7.0 Hz, OCH₂), 4.87 (2H, s, OCH₂), 7.42 (2H, d, J = 8.7 Hz, H Ar), 7.51 (2H, d, J = 8.6 Hz, H Ar) ppm; ¹³C NMR (101 MHz, CDCl₃) δ = 141.1 (CH₃), 61.6 (OCH₂CH₃), 61.7 (COOC₂H₅), 124.0 (CCI), 128.1 (CCI), 130.5 (2 × CH), 134.6 (2 × CH), 136.7 (SC Ar), 153.5 (NC), 158.6, 160.9 (C=O), 166.8 (COOEt); MS m/z (Irel, %): 391 [M⁺] (48), 288 [M-OCH₂CO₂Et⁺] (50), 225 [M-CO₂H₂CO₂Et⁺Cl⁺] (70), 144 [ClPCH⁺] (100); HRMS (ESI⁺) m/z calcd for C₁₄H₁₁NOCl₂S₂Na [M + Na⁺]: 413.9405; found: 413.9405.

Synthesis of 5-methyl-5-phenyl-3-(trichloroethenyl)-4,5-dihydro-1,2-oxazole (47) (General method). To a solution of nitrodiene 1 (0.271 g, 1.0 mmol) in dry toluene (10 mL) prop-1-en-2-ylbenzene (1.182 g, 10.0 mmol), 18-crown-6 (0.066 g, 0.25 mmol), activated molar sieves 4 Å (0.250 g), and powdered NaOH (0.120 g, 3.0 mmol) were added under nitrogen atmosphere. The mixture was then stirred at 60 °C for 16 h, and at 80 °C for another 16 h. After completion of the reaction, the solvent was evaporated, 10% aq. HCl (10 mL) was added, and the mixture was extracted with DCM (3 × 10 mL). The crude product was purified by column chromatography using petroleum ether-ethyl acetate (10: 1). Yield 0.221 g (76%), yellow viscous oil. IR (ATR) νmax = 2977, 1684, 1446, 1265, 859, 697 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 1.77 (3H, s, CH₃), 3.43 (1H, d, J = 16.9 Hz, ONCCH₂), 3.50 (1H, d, J = 16.9 Hz,
ONCH₃), 7.37–7.48 (5H, m, H Ph) ppm; ¹³C NMR (100 MHz, CDCl₃) δ = 27.8 (CH₃), 50.1 (CH₂), 90.3 (OCCCH₂), 121.7, 124.5 (2 × CH), 127.7 (CH), 128.6 (2 × CH), 137.1 (CCL₂), 144.2, 152.5 (NCCCl) ppm; MS m/z (Irel, %): 289 [M⁺] (4), 274 [M-CH₃]⁺ (4), 117 [PhC₂H₃]⁺ (60), 105 (100); HRMS (ESI⁺) m/z calcd for C₁₂H₁₀NO₃Cl₃Na [M + Na⁺]: 311.9726; found: 311.9725.

** tert-Butyl 3-(trichloroethenyl)-4,5-dihydro-1,2-oxazole-5-carboxylate (48).** Same procedure as for 47, but using tert-butyl prop-2-enoate (1.282 g, 10.0 mmol). Yield 0.195 g (65%), yellowish oil. IR (ATR) νmax = 2981, 1732, 1368, 1232, 1150, 838 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 1.47 (9H, s, CCH₃), 3.53 (2H, d, J = 9.4 Hz, ONCCCH₂), 5.03 (1H, t, J = 9.4 Hz, OCH) ppm; ¹³C NMR (100 MHz, CDCl₃) δ = 27.8 (3 × CH₃), 40.0 (CH₂), 80.2 (OCH), 83.1 (OCMe₂), 120.5 (CCL), 125.2 (CCL₂), 152.3 (ONC), 168.0 (C=O) ppm; ¹⁵N NMR (43.4 MHz, CDCl₃, doped with nitromethane (0.0 ppm)) δ = 7.8 ppm; MS m/z (Irel, %): 299 [M⁺] (12), 200 [M-CO₂CMe₃]⁺ (100), 170 [M-C₂Cl₃]⁺ (12), 129 [C₂Cl₃]⁺ (52), 100 [CO₂CMe₃H⁺] (95); HRMS (ESI⁺) m/z calcd for C₁₀H₁₂NO₃Na [M + Na⁺]: 321.9781; found: 321.9781.

** 2-Ethylhexyl 3-(trichloroethenyl)-4,5-dihydro-1,2-oxazole-5-carboxylate (49).** Same procedure as for 47, but using 2-ethylhexyl ethyl prop-2-enoate (1.843 g, 10.0 mmol). Yield 0.216 g (60%), yellowish oil. IR (ATR) νmax = 2958, 2860, 1732, 1461, 1162, 851 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 0.86–0.88 (6H, m, 2 × CH₃), 1.19–1.42 (8H, m, 4 × CH₂), 1.60–1.64 (1H, m, CH), 3.60 (1H, d, J = 10.7 Hz, ONCCCH₂), 3.61 (1H, d, J = 7.8 Hz, ONCCCH₂), 4.06–4.18 (2H, m, OCH₂), 5.17 (1H, dd, J = 10.7 Hz, J = 7.7 Hz, OCH) ppm; ¹³C NMR (100 MHz, CDCl₃) δ = 10.9 (CH₃), 14.0 (CH₃), 22.9 (CH₂), 23.6 (CH₂), 28.8 (CH₂), 30.2 (CH₂), 28.6 (CH₂), 40.2 (ONCCCH₂), 68.5 (OCH₂), 79.6 (OCH), 120.4 (CCL), 125.5 (CCL₂), 152.4 (ONC), 169.2 (C=O) ppm; MS m/z (Irel, %): 355 [M⁺] (10), 320 [M-Cl⁺] (22), 198 [M-CO₂C₈H₁₇⁺] (100); HRMS (ESI⁺) m/z calcd for C₁₄H₂₃NO₃Na [M + Na⁺]: 378.0407; found: 378.0406.

** 3-(Trichloroethenyl)-3a,4,5,6,7,7a-hexahydro-1,2-benzoxazole (50).** Same procedure as for 47, but using cyclohexene (0.821 g, 10.0 mmol). Yield 0.104 g (41%), yellowish oil. IR (ATR) νmax = 2935, 2863, 1448, 912, 838, 739 cm⁻¹. ¹H NMR (400 MHz, CDCl₃) δ = 1.23–1.43 (2H, m, CH₂), 1.48–1.64 (3H, m, CH₂), 1.72–1.82 (1H, m, CH₂), 1.83–1.93 (1H, m, CH₂), 2.00–2.09 (1H, m, CH₂), 2.32–2.31 (4H, CH₂), 4.58 (1H, dd, J = 8.2 Hz, J = 4.2 Hz, CH) ppm; ¹³C NMR (100 MHz, CDCl₃) δ = 19.9 (CH₂), 21.7 (CH₂), 24.8 (CH₂), 25.3 (CH₂), 46.1 (CH), 81.4 (CH), 121.0 (CCL), 124.4 (CCL₂), 159.1 (ONC) ppm; MS m/z (Irel, %): 253 [M⁺] (75), 218 [M-CH₃⁺] (5), 182 [M-Cl-HCl⁺] (16), 91 (100); HRMS (ESI⁺) m/z calcd for C₁₄H₂₃NO₂Cl₂Na [M + Na⁺]: 275.9726; found: 275.9725.

**Synthesis of 1-[11,1-dichloro-3-(1,3-dithiolan-2-ylidene)-3-nitroprop-1-en-2-yl]-4-(4-fluorophenyl)piperazine (52).** A solution of dithiolane 51 (0.292 g, 1.0 mmol) in MeOH (10 mL) and 1-((4-fluorophenyl)piperazine (0.433 g, 2.4 mmol) was stirred at reflux for 7 d. After cooling, the solution was concentrated with water for 30 min. The resulting precipitate was filtered off and washed with water (2 × 5 mL). Yield 0.393 g (90%), orange solid, m.p. 47–50 °C. IR (KBr) νmax = 2825, 1509, 1272, 1226, 954, 816 cm⁻¹. ¹H NMR (200 MHz, CDCl₃) δ = 3.08–3.39 (8H, m, NCH₂), 3.48–3.61 (4H, m, SCH₂), 6.80–7.11 (4H, m, H Ar) ppm; ¹³C NMR (50 MHz, CDCl₃) δ = 37.6 (SCH₂), 40.1 (SCH₂), 49.2 (2 × NCH₂), 50.6 (2 × NCH₂), 113.3 (CCL₂), 115.5 (JCF = 21.9 Hz, 2 × CH₂), 118.2 (JCF = 7.7 Hz, 2 × CH₂), 130.9 (CNO₂), 139.0 (CN), 147.9 (JCF = 2.2 Hz, NC Ar), 157.3 (JCF = 238.9 Hz, CF), 170.4 (SCS) ppm; MS m/z (Irel, %): 439 [M⁺] (25), 418 [M − OH⁺] (4), 389 [M − NO₂⁺] (7), 179 [F-PH-piperazine⁺] (15), 122 (100); HRMS (ESI⁺) m/z calcd for C₂₉H₁₆N₃O₂F₂C₁₂S₂ [M⁺]: 435.0045; found: 435.0047.

**Synthesis of 1-[2-Chloro-5-(ethenylsulfanyl)-4-nitrothiophen-3-yl]-4-(4-fluorophenyl)piperazine (53).** An aqueous solution of NaOH (3.0 mmol, 40%) was added dropwise to a solution of dithiolane 52 (0.436 g, 1.0 mmol) in DMSO (10 mL) at 0 °C. After 1 h at 0 °C, the mixture was stirred at rt. for an additional 3 h. Subsequently, cold water was added and the mixture was treated dropwise with diluted HCl until a precipitate formed. The precipitate was filtered off and washed with water (2 × 5 mL) and cold MeOH (3 mL). Yield 0.340 g (85%), yellowish solid, m.p. 83–86 °C. IR (KBr) νmax = 2829, 1543, 1511, 1322, 1233, 831 cm⁻¹. ¹H NMR (200 MHz, CDCl₃) δ = 3.16–3.26 (4H, m, NCH₂), 3.31–3.47 (4H, m, NCH₂), 5.83 (1H, d, J = 9.1 Hz, SCH₂), 8.55 (1H, d, J = 5.9 Hz, SCH₂), 6.55 (1H, dd, J = 16.4 Hz, J = 9.2 Hz).
After cooling to r.t., the mixture was treated with diluted HCl and the resulting precipitate was filtered off. A solution of thiophene 53 (0.300 g, 1.0 mmol) and POC13 (0.307 g, 2.0 mmol) in dry DMF was stirred at r.t. for 1 d and then at 55 °C for 2 d. After cooling down to 0 °C, cold water (15 mL) was added and the mixture extracted with chloroform (3 × 10 mL). After drying over CaCl2, the crude product was purified by column chromatography using petroleum ether-ethyl acetate (2: 1). Yield 0.252 g (64%), orange solid, m.p. 104–105 °C. IR (ATR) νmax = 2833, 1621, 1531, 1505, 1223, 997 cm−1. 1H NMR (400 MHz, CDCl3) δ = 3.25–3.33 (4H, m, NCH2), 3.50–3.59 (4H, m, OCH2), 5.99 (2H, dd, J = 16.7 Hz, J = 9.4 Hz, CH2vin) ppm. Yield 0.312 g (82%), red solid, m.p. 121–123 °C. IR (KBr) νmax = 2857, 2223 (CN), 1541, 1340, 1111, 857 cm−1. 13C NMR (100 MHz, CDCl3) δ = 3.23–3.30 (4H, m, NCH2), 3.84–3.90 (4H, m, OCH2), 6.15 (1H, dd, J = 9.3, J = 1.4, CH2cisvin), 6.45 (1H, dd, J = 16.2, J = 1.3, CH2transvin), 7.09 (1H, dd, J = 16.3, J = 9.3, CHvin) ppm, 8.02 (1H, s, SCCH). 13C NMR (50 MHz, CDCl3) δ = 52.0 (2 × NCH2), 67.0 (2 × OCH2), 80.3 (C(CN2)), 112.2 (2 × CN), 113.3, 124.1 (CH2vin), 127.4 (SC), 138.5 (CHvin), 146.8 (SCCH), 151.4 (C-morph), 166.1 (SO2C), CNO2 could not be detected. Mass spectrum, m/z (Irel, %): 380 [M+H]+ (3), 363 [M-OH]+ (5), 346 [M-HNO2]+ (3), 179 [piperazine-Ph-F]+ (7), 122 (100); HRMS (ESI+) m/z calcd for C17H15N3O2S2Na [M + Na]+: 416.0515 ; found: 416.0514.

Synthesis of [5-(Ethenylsulfanyl)-3-(morpholin-4-yl)-4-nitrothiophene-2-yl]methylenedipropanedinitrile (57). A solution of thiophene 56 (0.348 g, 1.0 mmol) and hydrogen peroxide (3.0 mmol, 35%) in acetic acid was stirred at 50–55 °C for 3 h. After cooling, ice was poured into the mixture and the resulting precipitate was filtered off and washed with water (3 × 5 mL). Yield 0.312 g (82%), red solid, m.p. 121–123 °C. IR (KBr) νmax = 2857, 2223 (CN), 1541, 1340, 1111, 857 cm−1. 1H NMR (200 MHz, CDCl3) δ = 3.23–3.30 (4H, m, NCH2), 3.84–3.90 (4H, m, OCH2), 6.15 (1H, dd, J = 9.3, J = 1.4, CH2cisvin), 6.45 (1H, dd, J = 16.2, J = 1.3, CH2transvin), 7.09 (1H, dd, J = 16.3, J = 9.3, CHvin) ppm, 8.02 (1H, s, SCCH). 13C NMR (50 MHz, CDCl3) δ = 52.0 (2 × NCH2), 67.0 (2 × OCH2), 80.3 (C(CN2)), 112.2 (2 × CN), 113.3, 124.1 (CH2vin), 127.4 (SC), 138.5 (CHvin), 146.8 (SCCH), 151.4 (C-morph), 166.1 (SO2C), CNO2 could not be detected. Mass spectrum, m/z (Irel, %): 380 [M+H]+ (3), 363 [M-OH]+ (5), 346 [M-HNO2]+ (3), 179 [piperazine-Ph-F]+ (7), 122 (100); HRMS (ESI+) m/z calcd for C17H15N3O2S2Na [M + Na]+: 416.0515 ; found: 416.0514.

Synthesis of 4-[5-(Ethenylsulfanyl)-4-nitro-2-(2,4,6-trichlorophenyl)hydrazinylidene)methylthiophen-3-yl]morpholine (59). A solution of thiophene 55 (0.300 g, 1.0 mmol) and (2,4,6-trichlorophenyl)-hydrazine (0.634 g, 3.0 mmol) in MeOH (15 mL) was refluxed for 3 h. After cooling to r.t., the mixture was treated with diluted HCl and the resulting precipitate was filtered off and washed with water (2 × 5 mL) and cold MeOH (3 mL). Yield 0.425 g (86%), orange solid, m.p. 192–194 °C. IR (KBr) νmax = 3228, 1520, 1445, 1332, 1107, 851 cm−1. 1H NMR (200 MHz, CDCl3) δ =...
3.05–3.19 (4H, m, NCH₂), 3.75–3.82 (4H, m, OCH₂), 5.87 (2H, dd, J = 16.7 Hz, J = 9.4 Hz, CH₂vin), 6.65 (1H, dd, J = 16.7 Hz, J = 9.4 Hz, SCHvin), 7.36 (2H, s, H Ar), 7.64 (1H, br s, NH), 8.01 (1H, s, NCH) ppm; ¹³C (50 MHz, CDCl₃) δ = 51.0 (2 × NCH₂), 67.5 (2 × OCH₂), 126.4 (CH₂vin), 126.8 (SCHvin), 127.6 (2 × CCI), 129.0 (2 × CH), 129.1 (CCI), 130.1 (SC), 133.3 (NCH), 135.8 (NHCl), 139.5 (CNO₂), 142.3 (SCS), 148.5 (C-morph) ppm; MS m/z (Irel, %): 492 [M⁺] (12), 433 [M-SC₂H₃⁺] (2), 298 [M-NHPhCl₃⁺] (55), 195 [H₂NPhCl₃⁺] (100); HRMS (ESI⁺) m/z calc for C₁₇H₁₅N₂O₃Cl₃S₂Na [M + Na⁺]: 514.9549; found: 514.9547.

Synthesis of 5-[[5-(Ethenylsulfanyl)-3-(morpholin-4-yl)-4-nitrothiophen-2-yl]methylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (60). A solution of thiophene 55 (0.300 g, 1.0 mmol), 2,2-dimethyl-1,3-dioxane-4,6-dione (0.288 g, 2.0 mmol) and piperidine (8.5 mg, 0.1 mmol) in MeOH (15 mL) was stirred at r.t. for 1 d. Then another 0.288 g of 2,2-dimethyl-1,3-dioxane-4,6-dione were added and the mixture was stirred for an additional 2 d. Subsequently, the mixture was treated with diluted HCl and the resulting precipitate was filtered off and washed with water (2 × 5 mL) and cold MeOH (3 mL). Yield 0.333 g (73%), red solid, m.p. 173–174 °C. IR (ATR) νmax = 1683, 1516, 1332, 1197, 1113, 787 cm⁻¹. ¹H NMR (200 MHz, CDCl₃) δ = 1.76 (6H, s, CH₃), 3.33–3.39 (4H, m, NCH₂), 3.93–3.96 (4H, m, OCH₂), 6.00 (2H, dd, J = 16.8 Hz, J = 9.5 Hz, CH₂vin), 6.75 (1H, dd, J = 16.8 Hz, J = 9.5 Hz, SCHvin), 6.86 (1H, s, SCCH) ppm; ¹³C (200 MHz, CDCl₃) δ = 27.5 (2 × CH₂), 53.2 (2 × NCH₂), 67.1 (2 × OCH₂), 103.6 (CMe₂), 104.7 (CC=O), 119.5 (SC), 124.9 (SCHvin), 128.7 (CH₂vin), 137.2 (CNO₂), 144.1 (SCCH), 156.9 (SCS), 161.4 (C-morph), 162.3 (C=O), 163.4 (C=O) ppm; MS m/z (Irel, %): 426 [M⁺] (100), 409 [M-OH⁺] (10), 351 [M-2Me₂CO₂H⁺] (24), 295 [M-NO₂-morph+H⁺] (27); HRMS (ESI⁺) m/z calc for C₁₇H₁₈N₂O₇S₂Na [M + Na⁺]: 449.0453; found: 449.0453.

3.3. Evaluation of Biological Activity

For a first evaluation of the biological activity of heterocycles, the influence of the compounds on the growth of bacteria, namely of the Gram-positive strain Staphylococcus aureus SH—1000 and of the Gram-negative uropathogenic strain Escherichia coli UPEC796, and on the viability of mammalian cells, namely the murine fibroblast cell line L929, was evaluated.

Bacteria were cultivated in the complex Lysogeny broth. An aliquot of an overnight culture was diluted with fresh medium to an OD₆₀₀ (optical density at 600 nm) of 0.1–0.2. This intermediate culture was incubated at 37 °C with shaking until an OD₆₀₀ = 0.5 was reached to generate a culture of exponentially growing cells. The cells were again diluted with fresh medium to an OD₆₀₀ = 0.2 to generate the working culture.

In each well of a 96-well plate, 90 µl Lysogeny broth were placed, to which 1.8 µl of a cell suspension with 3 × 10⁶ cells/mL were seeded. The incubation was started after the addition of 90 µl of the working culture, resulting in a total volume of 180 µl. The microtiter plates were incubated at 37 °C. Bacterial growth was followed by determination of the OD₆₀₀ with the microplate spectrophotometer PowerWave™ (BioTek; Bad Friedrichshall, Germany) in regular time intervals, starting 2 h after the inoculation. The final value was obtained after a growth period of 24 h.

L929 cells were cultivated in RPMI cell culture medium, supplemented with 10% FBS (serum) in a cell culture incubator at 37 °C and 10% CO₂. 60 µl of a cell suspension with 3 × 10⁴ cells/mL were seeded in each well of an assay-ready 96 well microtiter plate. The assay-ready microtiter plates were prepared from the 10 mM DMSO stock solutions of the compounds with the Echo® 525 acoustic liquid handler (Labcyte Inc., USA). The microtiter plates with compounds and cells were incubated at 37 °C, 10% CO₂ in a cell culture incubator for three days. The remaining viability of cells was assessed with the alamarBlue® assay [88] (Thermo Fisher Scientific (Waltham, MA, USA) according to the instructions given by the manufacturer, i.e., 5 µl of the resazurin-solution were given in each well of the 96-well plate and incubated for up to 4 h. The turnover was determined via the fluorescence of resorufin (λex = 540 nm; λem = 600 nm) with the multi-mode microplate reader Synergy™ 4 (BioTek).

The primary evaluation of the biological activity was done with a single concentration of the compounds, which was 100 µM in the bacterial assays and 10 µM in the cell culture assay. Compounds
were considered to show activity in these assays, when the residual growth or viability, respectively, was reduced to 50% or less of the growth or viability of an untreated bacterial or cell culture. The activities of these compounds were validated by investigating the influences of compound concentrations and determinations of the EC\textsubscript{50} values (concentration resulting in 50% of the observed effect). Diluted compound solutions were prepared either by manual serial dilutions using eight channel pipettes or again with the Echo\textsuperscript{®} 525 transferring varying volumes from the compound plate to the assay plate.

The EC\textsubscript{50} values were determined by nonlinear regression with a 4-parameter equation using the respective module from GraphPad Prism.

4. Conclusions

Starting from three polyhalogenated nitro-1,3-butadienes, we developed an efficient and practical strategy for the multigram synthesis of the following heterocycles with unique substitution patterns: benzoxazolines, benzimidazolines, imidazolidines, Imidacloprid analogues, thia-zolidinones, pyrimidines, pyrazoles, 4H-pyrido[1,2-α]pyrimidines, benzo[h]quinolines, isothiazoles, dihydroisoxazoles, and thiophenes. Quite some of these heterocycles deserve interest as key units in synthesis, chemical biology, and medicinal chemistry. Successive synthetic modifications of the heterocycles are predictable and feasible.

Supplementary Materials: The following are available online, Figures S1–S203: \textsuperscript{1}H–NMR, \textsuperscript{13}C–NMR, \textsuperscript{15}N, \textsuperscript{1}H–HMBC–NMR, and mass spectra. Figures S204 and S205: Biological profiling of compounds 4a–58.

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