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Synthesis and fungicidal activity of tubulin polymerisation promoters. Part 3: Imidazoles

Clemens Lamberth [a,*], Raphael Dumeunier [a], Stephan Trah [a], Sebastian Wendeborn [a], Jeremy Godwin [a], Peter Schneiter [a], Andy Corran [b]

[a] Syngenta Crop Protection AG, Crop Protection Research, Schaffhauserstr. 101, CH-4332 Stein, Switzerland
[b] Syngenta Ltd, Jealott's Hill International Research Centre, Bracknell, Berkshire RG42 6EY, United Kingdom

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ABSTRACT

A novel class of experimental fungicides has been discovered, which consists of special tetrasubstituted imidazoles. They are highly active against important phytopathogens, such as *Botrytis cinerea* (grey mould), *Uncinula necator* (grape powdery mildew), *Mycosphaerella graminicola* (wheat leaf blotch) and *Alternaria solani* (potato and tomato early blight). Their fungicidal efficacy is due to their ability to promote fungal tubulin polymerization, which leads to a disruption of microtubule dynamics. These imidazoles are five-membered ring analogs of similar substituted triazolopyrimidines and pyridazines with the same mode of action. A concise four-step synthesis route has been used to prepare them from commercially available starting materials.

1. Introduction

The tubulin polymerization promoters undoubtedly belong, together with the *Succinate dehydrogenase* inhibitors (SDHI's),[2,3] to those two fungicide classes, which attracted the most attention in the research departments of the agrochemical industry during the first decade of this century. The interest in a certain class of active ingredients is easily measurable by the number of published patents. Regarding the tubulin polymerization promoters, 303 patents have been published since 2000 by nine different companies. In contrast to the SDHI's, of which several examples, such as bixafen,[4] boscalid,[5] fluopyram,[6] fluxapyroxad,[7] furametpyr,[8] isopyrazam,[9] penflufen,[3] penthiopyrad[10] and sedaxane[2] have reached the fungicide market recently, no tubulin polymerization promoter has been commercialized so far. Although the members of this class of experimental fungicides bear one of several different mono- and biheterocyclic scaffolds, they all possess a similar substitution pattern and the same mode of action, which leads to the disruption of the microtubule dynamics. [1,2,4]Triazolo[1,5-*a*]pyrimidines, such as BAS600F (**1**) have been the lead structures for the tubulin polymerization promoters (Fig. 1).[11] The pyrazolopyrimidine **2**,[12] the pyrido[2,3-*b*]pyrazine **3**[13] and the pyrido[3,2-*e*][1,2,4]triazine **4**[14] are further examples, in which the triazole ring of the triazolopyrimidines has been replaced either by another five-membered ring (as in **2**) or by a six-membered heterocycle (as in **3** and **4**). More recently monocyclic scaffolds, such as the pyridine **5**,[15] the pyridazine **6**,[1] the pyrimidine **7**[16] and the pyrazinone **8**,[17] have been in the focus of the research activities. Obviously a closely related substitution pattern is common to those monocyclic, 5,6-bicyclic and 6,6-bicyclic promoters of tubulin polymerization. Adjacent to a ring nitrogen atom they all carry a halogen substituent, next to it there is a 2,4,6-trifluorophenyl ring, which is followed by either an amine or an aryl/heteroaryl group. In the case of the heterobicyclic tubulin promoting fungicides, the second ring, which is annelated between the amino substituent and a ring nitrogen of the fully substituted ring, is generally unsubstituted, whereas all monocyclic compounds, with the exception of the pyridine **5**, are usually fully substituted.

2. Results and discussion

2.1. Chemistry

Inspired by the structural simplicity of the monocyclic tubulin polymerization promoters and impressed by the high fungicidal efficacy of the pyridazine **6**, we decided to design five-membered analogs of it. We planned to remove one of the two adjacent pyridazine ring nitrogen atoms and to replace one of those two ring carbon atoms of **6**, which bear the aryl or heteroaryl substituents, by a nitrogen atom, thus arriving by the imidazole **9** (Scheme 1). Similar tetrasubstituted imidazoles with two different aryl

* Corresponding author. Tel.: +41 62 8660224; fax: +41 62 8660860.
E-mail address: clemens.lamberth@syngenta.com (C. Lamberth).

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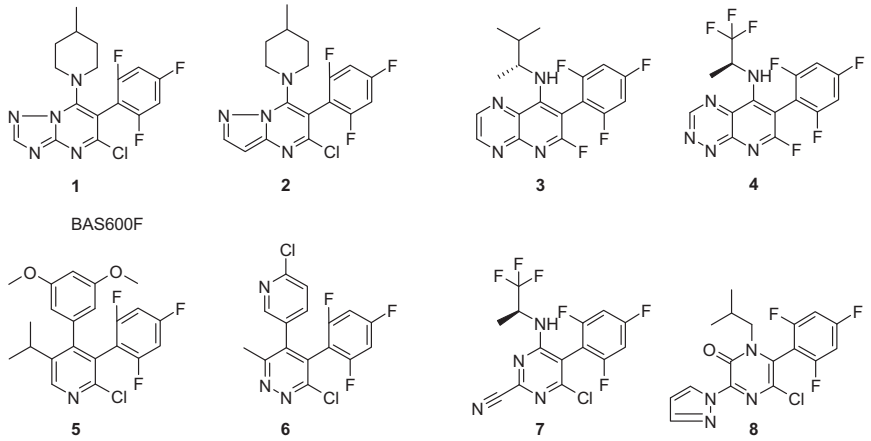
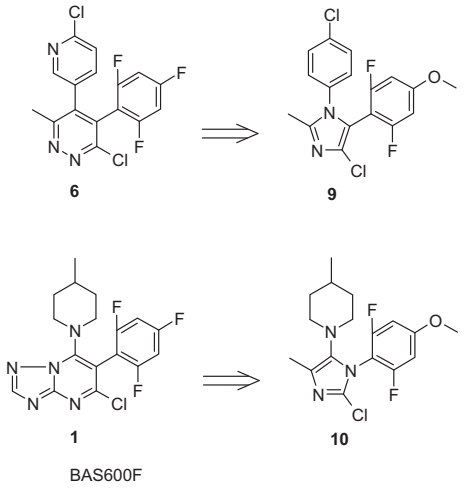


Figure 1. Different mono- and biheterocyclic tubulin polymerization promoters.

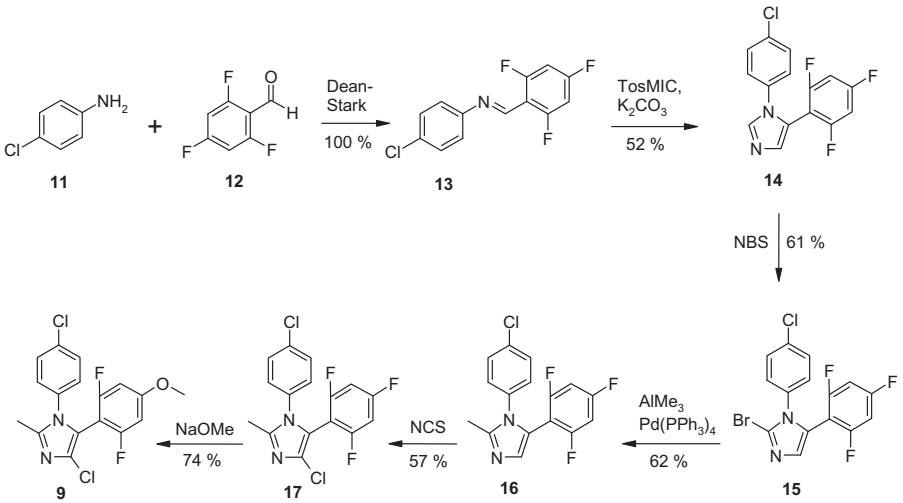


Scheme 1. Imidazoles as five-membered ring mimics of fungicidally active triazolopyrimidines and pyridazines.

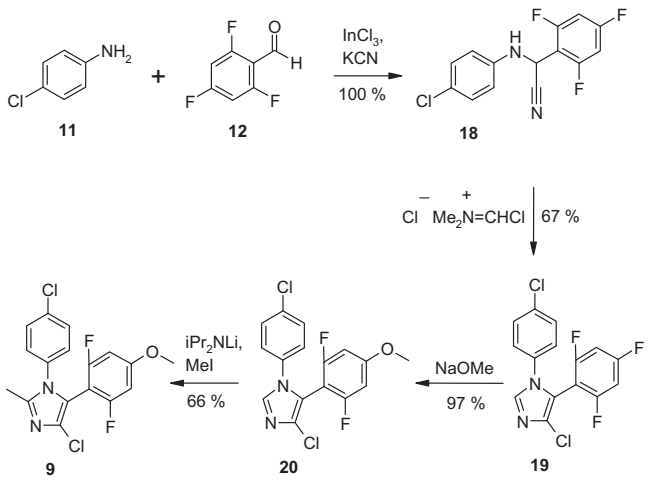
substituents, a chloro and a methyl group have been evaluated as cyclooxygenase-2 (COX-2) inhibitors.[18,19] Another attractive target compound was the imidazole **10**, which is rather mimicking the amino-substituted triazolopyrimidine BAS600F (**1**). Such fully substituted imidazoles bearing alkyl, amino, aryl and halogen substituents have been completely unknown, therefore we had to develop a novel synthesis route.

We chose to construct the heterocyclic scaffold of the first target compound **9** via a van Leusen imidazole synthesis.[20–22] Therefore we converted 4-chloroaniline (**11**) and 2,4,6-trifluorobenzaldehyde (**12**) to the Schiff base **13**. Its cyclisation with the aid of TosMIC resulted in the diarylated imidazole **14**, which could be regioselectively brominated at the carbon atom between the two ring nitrogens. The exchange of the bromo substituent in **15** by a methyl group and the subsequent chlorination of position 5 led to the fully substituted imidazole **17**. Finally the replacement of the fluoro atom in the *para*-phenyl position by a methoxy function delivered the desired target compound **9** (Scheme 2).[23]

Because of the length of this six-step synthesis, we tried to facilitate the preparation of **9** in a much more elegant and efficient fashion, in analogy to a method which had been recently described by De Borggraeve et al.[25] In this regard, we started from the same starting materials **11** and **12**, but this time converted them together with potassium cyanide in an indium(III) chloride catalyzed one-pot three-component Strecker reaction into **18** (Scheme 3).[24]



Scheme 2. TosMIC-based (van Leusen-type) synthesis of the imidazole **9**.



Scheme 3. Vilsmeier reagent-based synthesis of the imidazole **9**.

This α-aminonitrile is then ring-closed with Vilsmeier reagent and hydrochloric acid to the trisubstituted imidazole **19**, which has besides two aryl groups already the required chlorine atom in place. The replacement of the 4-fluoro phenyl substituent in **19** by methoxy and the introduction of the methyl function by direct lithiation of the imidazole and methylation deliver the fungicidally active **9** in only four steps, compared to the six steps required by the TosMIC approach.

A completely different synthesis pathway had to be designed for the preparation of the target compound **10**, intended to be a five-membered monocyclic mimic of the triazolopyrimidine BAS600F (**1**). The route starts from the commercially available glycine amide **21**, which is converted with 2,4,6-trifluorophenylisothiocyanate into the thiourea **22** (Scheme 4). Its alkylation to the *S*-methylisothiourea **23** and subsequent ring-closure reaction with Lawesson's reagent delivers **24**. This trisubstituted imidazole is transformed by bromination of the remaining free imidazole ring position and subsequent palladium-catalyzed bromine-methyl exchange to the fully substituted imidazole **26**. The next two steps are the introduction of a methoxy function into the *para*-position of the phenyl ring and the removal of the methylsulfanyl function in ring position 2 with the aid of Raney-nickel, delivering **28**. Finally, the chlorination of the ring carbon atom between the two heteroatoms yields the tetrasubstituted imidazole **10**, which bears four completely different substituents, an alkyl group, an aryl ring, an amine and a halogen atom.[26]

2.2. Structure–activity relationships

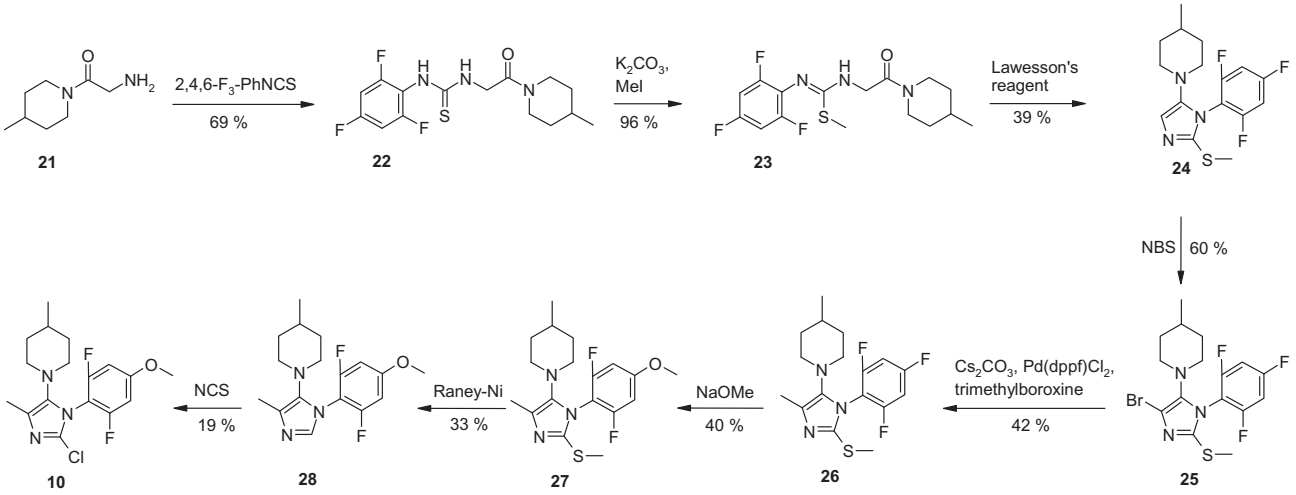
Quite soon we found out, that the diarylated imidazole **9** possesses a much higher fungicidal activity than the amino-substituted imidazole **10**. Therefore we will focus on **9** and its derivatives in the forthcoming analysis of the structure–activity relationship of the novel imidazole fungicides. Each of the four different ring positions of such imidazoles bear a specific substituent, which exerts a distinct influence on the fungicidal efficacy. As it was clear from the beginning, that the chlorine atom in position 4 is very important, we concentrated our efforts regarding the optimization of the biological efficacy on the variation of the substituents in ring positions 1, 2 and 5.

2.2.1. Influence of the substituent in imidazole position 1 on the fungicidal activity

In analogy to the structurally related pyridazine fungicides,[1] a 4-chlorophenyl group between the 2,6-dihalophenyl and methyl substituents seems to deliver the best broad-spectrum fungicidal activity (Table 1, entry 1, **9**). Moving this halogen substituent from the *para* position to the *meta* position of the phenyl ring (entry 2) or replacing it by an electron-donating methoxy group (entry 3) reduces the potency, especially against *Mycosphaerella graminicola* and *Alternaria solani*. Only the exchange of the phenyl ring in imidazole position 1 by a pyridine under preservation of the position of the chloro substituent (entry 4) leads to a equipotent efficacy, at least in the control of *Botrytis cinerea* and *A. solani*. The replacement of the *N*-phenyl to a N-benzylimidazole (entry 5) results in considerably weaker fungicidal activity against all three important phytopathogens.

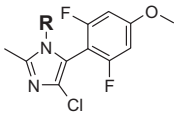
2.2.2. Influence of the substituent in imidazole position 2 on the fungicidal activity

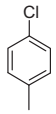
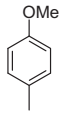
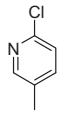
As it is obvious from the synthesis routes described in Schemes 1 and 2, it is easily possible to vary the substituent at the ring carbon between the two imidazole nitrogen atoms broadly. A hydrogen atom (Table 2, entry 1) in this position leads to only weak fungicidal activity, pointing out to the need of a substituted carbon atom in imidazole position 2. It was possible to introduce three different halogen atoms into this position, a fluorine (entry 2), a chlorine (entry 3) and a bromine atom (entry 4). From these halogens,



Scheme 4. Synthesis of the imidazole **10**.

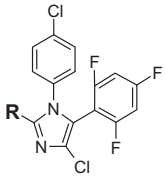
Table 1
Influence of the substituent R in imidazole position 1 on the fungicidal activity[a]



Entry	R	*Botrytis cinerea* (tomato grey mould)	*Uncinula necator* (grape powdery mildew)	*Mycosphaerella graminicola* (wheat leaf blotch)	*Alternaria solani* (tomato early blight)
1 (**9**)		2	1	2	1
2		1	1	20	4
3		17	2	63	12
4		2	3	6	1
5		41	16	76	59

[a] Results are given as the EC_{80} (mg L^{-1}).

Table 2
Influence of the substituent R in imidazole position 2 on the fungicidal activity[a]

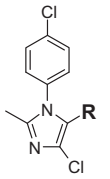


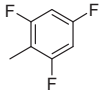
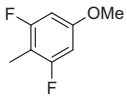
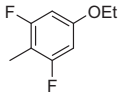
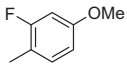
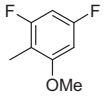
entry	R	*Botrytis cinerea* (tomato grey mould)	*Uncinula necator* (grape powdery mildew)	Mycosphaerella graminicola (wheat leaf blotch)	*Alternaria solani* (tomato early blight)
1	H	33	59	67	>200
2	F	180	78	65	98
3	Cl	54	1	44	57
4	Br	45	43	83	144
5		(**17**)	CH_3	8	
					2
	15				
6					
6	OCH_3	173	65	42	71

[a] Results are given as the EC_{80} (mg L^{-1}).

the chloro function seems to have the highest fungicidal activity, especially against *Uncinula necator*. Finally, we also checked the potential of a methyl (entry 5, **17**) and a methoxy group (entry 6). The methyl substituent shows by far the best broad-spectrum activity of all substituents tested in this position, as it is also the case in the structurally related pyridazine fungicides, whereas the methoxy function gave rather poor results.

Table 3
Influence of the substituent R in imidazole position 5 on the fungicidal activity[a]



Entry	R	*Botrytis cinerea* (tomato grey mould)	*Uncinula necator* (grape powdery mildew)	*Mycosphaerella graminicola* (wheat leaf blotch)	*Alternaria solani* (tomato early blight)
1 (**9**)		8	2	6	15
2		2	1	2	1
3		32	1	67	4
4		72	16	61	35
5		82	11	65	37

[a] Results are given as the EC_{80} (mg L^{-1}).

2.2.3. Influence of the substituent in imidazole position 5 on the fungicidal activity

The 2,4,6-trifluorophenyl ring, which is present in the lead structures 1 to 8 (Fig. 1), delivers also in combination with the imidazole scaffold strong fungicidal activity (Table 3, entry 1). However, this substituent in imidazole position 5 is clearly outperformed by a 2,6-difluoro4-methoxy group, which gives the best results against the tested plant pathogens (entry 2). We tried to further improve the fungicidal activity of this substituent, but several different manipulations in the phenyl ring, for example, the replacement of the *para*-methoxy function by an ethoxy group (entry 3), the exchange of one of the *ortho*-fluoro atoms by hydrogen (entry 4) and the methoxy function changing places with one of the fluorine atoms (entry 5) did not lead to any improvement.

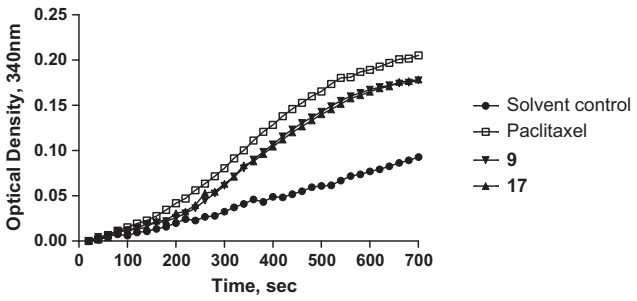


Figure 2. Degree of polymerization of pure porcine tubulin in the presence of paclitaxel and imidazoles **9** and **17** at 1.25 μg ml^{-1} in function of time (values presented are a mean of two replicates).

2.3. Mode of action

The highly active imidazole fungicides **9** and **17** (see Tables 1 and 2) were submitted to a polymerisation assay on pure porcine tubulin to check if also these five-membered monocyclic compounds, as already confirmed for the mentioned bicyclic pyridopyrazine **3**[13] and six-membered monocyclic pyridazine **6**,[1] are disrupters of the microtubule dynamics. They were compared against paclitaxel, which is a known tubulin polymerisation promoter and for which a clear increase in the OD_{340} value could be detected at 1.25 μg ml^{-1}. A very similar pattern was observed in two different replicates for **9** and **17**, indicating a similar effect on tubulin polymerization (Fig. 2).

3. Conclusions

Novel tetrasubstituted imidazoles have been discovered as a new class of fungicidally active compounds, which are able to control economically important plant diseases from the family of Ascomycetes, such as *B. cinerea*, *U. necator*, *M. graminicola* and *A. solani*. The most active compounds possess a similar substitution pattern as related six-membered pyridazine fungicides. Their mode of action is the promotion of tubulin polymerization, leading to the disruption of microtubule dynamics. These fully substituted imidazoles can be prepared in only four steps, the key step is the condensation of an α-aminonitrile with Vilsmeier reagent to a 1,5-disubstituted-4-haloimidazole.

A structure–activity relationship study revealed the molecular requirements for the best fungicidal activity. As it turned out, each ring carbon of the imidazole scaffold as well as the substituted nitrogen atom have to be specifically substituted to reach the optimum efficacy. The most active imidazole fungicides bear a methyl substituent in position 2, which means at the ring carbon between the two heteroatoms. In addition, it is also important, that there is a chlorine atom linked to the other carbon atom, which is adjacent to the unsubstituted ring nitrogen. Furthermore, the third ring carbon typically bears a bis-*ortho* halogen-substituted phenyl ring with an additional *para*-substituent. Finally, we obtained the best fungicidal results with a *para*-substituted phenyl or pyridyl moiety linked to the imidazole ring nitrogen.

4. Experimental section

4.1. Chemistry

All new compounds were characterized by standard spectroscopical methods. ^{1}H NMR spectra were recorded on a Varian Unity 400 spectrometer at 400 MHz using $CDCl_3$ as solvent and tetramethylsilane as internal standard. Chemical shifts are reported in ppm downfield from the standard (δ = 0.00), coupling constants in Hz. Mass spectra were recorded on a Micromass LCT mass spectrometer. Melting points were determined on a Büchi 535 melting point apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F524 precoated plates. Preparative flash chromatography was performed using silica gel 60 (40–63 μm, E. Merck). All reactions were carried out under anhydrous conditions in an inert atmosphere (nitrogen or argon) with dry solvents.

4.1.1. (4-Chloro-phenyl)-[1-(2,4,6-trifluoro-phenyl)-meth-(*E*)-ylidene]amine (13)

A mixture of 4-chloro-aniline (**11**, 20.4 g, 0.16 mol) and 2,4,6-trifluoro-benzaldehyde (**12**, 25.5 g, 0.16 mol) in 780 ml of toluene is heated to reflux in a Dean-Stark apparatus for 4 d. Subsequently the mixture is cooled, evaporated under reduced pressure to obtain (4-chloro-phenyl)-[1-(2,4,6-trifluoro-phenyl)-meth-(*E*)-ylidene]amine (**13**, 43.8 g, 0.16 mol, 100%). ^{1}H NMR ($CDCl_3$): δ = 6.77 (t, 2H, *J* = 8.7), 7.08 (d, 2H, *J* = 8.6), 7.28 (d, 2H, *J* = 8.65), 8.49 (s, 1H). LC–MS: t_R = 5.99 min, *m/z* = 270 [M+1].

4.1.2. 1-(4-Chloro-phenyl)-5-(2,4,6-trifluoro-phenyl)-1*H*-imidazole (14)

Toluenesulfonylmethyl isocyanide (TosMIC, 36.5 g, 0.18 mol) and anhydrous potassium carbonate (34.4 g, 0.25 mol) are added to a solution of (4-chloro-phenyl)-[1-(2,4,6-trifluoro-phenyl)-meth-(*E*)-ylidene]amine (**13**, 33.6 g, 0.12 mol) in a mixture of 460 ml of *N*,*N*-dimethylformamide and 375 ml of 1,2-dimethoxyethane. The reaction mixture is heated for 2 h at 100 °C, then cooled to room temperature and filtered. The filtrate is evaporated, the residue is absorbed on Isolute® HM-N and purified by chromatography on silica gel, using a mixture of heptane/*t*-butyl methyl ether 3:1 as eluent, to obtain 1-(4-chloro-phenyl)-5-(2,4,6-trifluoro-phenyl)-1*H*-imidazole (**14**, 19.9 g, 65 mmol, 52%). ^{1}H NMR ($CDCl_3$): δ = 6.59 (t, 2H, *J* = 7.3), 7.02 (d, 2H, *J* = 8.7), 7.22 (s, 1H), 7.28 (d, 2H, *J* = 8.6), 7.72 (s, 1H). LC–MS: t_R = 1.80 min, *m/z* = 309 [M+1].

4.1.3. 2-Bromo-1-(4-chloro-phenyl)-5-(2,4,6-trifluoro-phenyl)-1*H*-imidazole (15)

A mixture of 1-(4-chloro-phenyl)-5-(2,4,6-trifluoro-phenyl)-1*H*-imidazole (**14**, 4.0 g, 13 mmol) and N-bromosuccinimide (3.5 g, 20 mmol) in 40 ml of chloroform is heated for 1 h to 80 °C. Subsequently the mixture is cooled to room temperature, then Isolute® HM-N is added and the solvent is removed under reduced pressure. The residue is purified by column chromatography on silica gel, using a mixture of heptane/ethyl acetate 4:1 as eluent, to obtain 2-bromo-1-(4-chloro-phenyl)-5-(2,4,6-trifluoro-phenyl)-1*H*-imidazole (**15**, 3.1 g, 8.0 mmol, 61%) as a pale yellow-orange solid. ^{1}H NMR ($CDCl_3$): δ = 6.55 (t, 2H, *J* = 7.2), 7.05 (d, 2H, *J* = 8.5), 7.14 (s, 1H), 7.29 (d, 2H, *J* = 8.6). LC–MS: t_R = 2.02 min, *m/z* = 389 [M+1], 391 [M+3].

4.1.4. 1-(4-chloro-phenyl)-2-methyl-5-(2,4,6-trifluoro-phenyl)-1*H*-imidazole (16)

Tetrakis(triphenylphosphine)palladium (0.13 g, 0.11 mmol) is added to as solution of 2-bromo-1-(4-chloro-phenyl)-5-(2,4,6-trifluoro-phenyl)-1*H*-imidazole (**15**, 3.1 g, 8.0 mmol) in 162 ml of tetrahydrofuran. This mixture is heated to reflux for 10 min, then the oil bath is removed and 12 ml of a 2 M solution of trimethylaluminum in toluene are added slowly. The reaction mixture is heated to reflux for 7 h, then cooled to 0 °C. First 5 ml of methanol and then Isolute® HM-N is added and the solvents are removed under reduced pressure. The residue is purified by chromatography on silica gel, using a mixture of heptane/ethyl acetate 1:1 as eluent, to obtain 1-(4-chloro-phenyl)-2-methyl-5-(2,4,6-trifluoro-phenyl)-1*H*-imidazole (**16**, 1.6 g, 5.0 mmol, 62%) as a yellowish solid. ^{1}H NMR ($CDCl_3$): δ = 2.31 (s, 3H), 6.56 (t, 2H, *J* = 7.4), 7.07 (d, 2H, *J* = 8.5), 7.13 (s, 1H), 7.28 (d, 2H, *J* = 8.6). LC–MS: t_R = 1.36 min, *m/z* = 323 [M+1].

4.1.5. 4-Chloro-1-(4-chloro-phenyl)-2-methyl-5-(2,4,6-trifluoro-phenyl)-1*H*-imidazole (17)

A mixture of 1-(4-chloro-phenyl)-2-methyl-5-(2,4,6-trifluoro-phenyl)-1*H*-imidazole (**16**, 1.6 g, 5.0 mol) and N-chlorosuccinimide (0.8 g, 6.2 mmol) in 32 ml of chloroform is heated for 16 h to 80 °C. Subsequently the mixture is cooled to room temperature, then Isolute® HM-N is added and the solvent is removed under reduced pressure. The residue is purified by column chromatography on silica gel, using a mixture of heptane/ethyl acetate 4: 1 as eluent, to obtain 4-chloro-1-(4-chloro-phenyl)-2-methyl-5-(2,4,6-trifluoro-phenyl)-1*H*-imidazole (**17**, 1.0 g, 2.8 mmol, 57%) as a white solid.

^{1}H NMR ($CDCl_3$): δ = 2.30 (s, 3H), 6.63 (t, 2H, J = 7.3), 7.07 (d, 2H, J = 8.5), 7.36 (d, 2H, J = 8.6). LC–MS: t_R = 1.96 min, m/z = 357 [M+1].

4.1.6. 4-Chloro-1-(4-chloro-phenyl)-5-(2,6-difluoro-4-methoxy-phenyl)-2-methyl-1*H*-imidazole (9)

A mixture of 4-chloro-1-(4-chloro-phenyl)-2-methyl-5-(2,4,6-trifluoro-phenyl)-1*H*-imidazole (**17**, 0.4 g, 1.1 mmol), 0.48 ml of a 0.18 M solution of sodium methoxide in methanol and 5 ml of methanol is stirred for 16 h at room temperature. Subsequently the reaction mixture is poured on ice-water and extracted twice with ethyl acetate. The combined organic layer is washed with brine, dried over sodium sulfate and concentrated under reduced pressure to deliver directly 4-chloro-1-(4-chloro-phenyl)-5-(2,6-difluoro-4-methoxy-phenyl)-2-methyl-1*H*-imidazole (**9**, 0.3 g, 0.8 mol 74%). ^{1}H NMR ($CDCl_3$): δ = 2.29 (s, 3H), 3.76 (s, 3H), 6.38 (d, 2H, J = 9.1), 7.07 (d, 2H, J = 8.6), 7.34 (d, 2H, J = 8.7). LC–MS: t_R = 1.95 min, m/z = 369 [M], 371 [M+2].

4.1.7. (4-Chloro-phenylamino)-(2,4,6-trifluoro-phenyl)-acetonitrile (18)

To a solution of 4-chloroaniline (**11**, 5.0 g, 39 mmol) in 64 ml of tetrahydrofuran are added consecutively 2,4,6-trifluoro-benzaldehyde (**12**, 6.6 g, 41 mmol), indium(III) chloride (9.5 g, 43 mmol) and potassium cyanide (10.2 g, 0.16 mol). The reaction mixture is stirred for 16 h at room temperature, then diluted with water and extracted with ethyl acetate. The combined organic layer is dried over sodium sulfate and evaporated to deliver (4-chloro-phenylamino)-(2,4,6-trifluorophenyl)-acetonitrile (**18**, 11.7 g, 39 mmol, 100%). ^{1}H NMR ($CDCl_3$): δ = 4.23 (d, 1H, J = 10.5), 5.56 (d, 1H, J = 9.0), 6.64 (d, 2H, J = 8.2), 6.72 (t, 2H, J = 8.3), 7.15–7.23 (m, 2H). LC–MS: t_R = 1.91 min, m/z = 297 [M+1].

4.1.8. 4-Chloro-1-(4-chloro-phenyl)-5-(2,4,6-trifluoro-phenyl)-1H-imidazole (19)

Chloromethylenedimethyliminium chloride (Vilsmeier reagent, 2.6 g, 20 mmol) and 1.7 ml of a 4 N solution of hydrochloric acid in dioxane are added consecutively to a solution of (4-chloro-phenylamino)-(2,4,6-trifluorophenyl)-acetonitrile (**18**, 2.0 g, 6.7 mmol) in 28 ml of dioxane. The reaction mixture is stirred for 2 h at 100 °C and then cooled to room temperature. Isolute® HM-N is added and the solvent is removed under reduced pressure. The residue is purified by chromatography on silica gel, using a mixture of heptane/ethyl acetate 3:2 as eluent, to deliver 4-chloro-1-(4-chloro-phenyl-5-(2,4,6-trifluoro-phenyl)-1*H*-imidazole (**19**, 1.6 g, 4.5 mmol, 67%). ^{1}H NMR ($CDCl_3$): δ = 6.69 (t, 2H, J = 7.4), 7.08 (d, 2H, J = 8.6), 7.37 (d, 2H, J = 8.5), 7.70 (s, 1H). LC-MS: t_R = 1.93 min, m/z = 343 [M+1], 345 [M+3].

4.1.9. 4-Chloro-1-(4-chloro-phenyl)-5-(2,6-difluoro-4-methoxy-phenyl)-1*H*-imidazole (20)

To a solution of 4-chloro-1-(4-chloro-phenyl)-5-(2,4,6-trifluoro-phenyl)-1*H*-imidazole (**19**, 1.6 g, 4.6 mmol) in 28 ml of tetrahydrofuran is added at 0 °C 1.7 ml of a 30% sodium methoxide solution in methanol. The reaction mixture is stirred for 16 h at room temperature. Subsequently it is diluted with aqueous ammonium chloride solution and extracted with ethyl aceate. The organic layer is dried over sodium sulfate and evaporated to deliver 4-chloro-1-(4-chloro-phenyl)-5-(2,6-difluoro-4-methoxy-phenyl)-1*H*-imidazole (**20**, 1.6 g, 4.6 mmol, 97%). ^{1}H NMR ($CDCl_3$): δ = 3.74 (s, 3H), 6.40 (d, 2H, J = 9.5), 7.03 (d, 2H, J = 8.7), 7.29 (d, 2H, J = 9.0), 7.60 (s, 1H). LC–MS: t_R = 1.93 min, m/z = 355 [M+1], 357 {M+3].

4.1.10. 4-Chloro-1-(4-chloro-phenyl)-5-(2,6-difluoro-4-methoxy-phenyl)-2-methyl-1*H*-imidazole (9)

To a solution of 4-chloro-1-(4-chloro-phenyl)-5-(2,6-difluoro-4-methoxy-phenyl)-1H-imidazole (**20**, 1.6 g, 4.6 mmol) in 37 ml of tetrahydrofuran is added at – 20 °C 3.2 ml of a 1.8 M solution of lithium diisopropylamide in tetrahydrofuran. The mixture is stirred for 30 min at −20 °C, then methyl iodide (1.9 g, 13.4 mmol) is added. The reaction mixture is stirred for further 30 min at −20 °C, then for 30 min at room temperature. Subsequently Isolute® HM-N is added to the reaction mixture and the solvent is evaporated. The residue is purified by chromatography on silica gel, using a mixture of heptane/ethyl acetate 2:1 as eluent, to obtain delivering 4-chloro-1-(4-chloro-phenyl)-5-(2,6-difluoro-4-methoxy-phenyl)-2-methyl-1*H*-imidazole (**9**, 1.1 g, 3.0 mmol, 66%). ^{1}H NMR ($CDCl_3$): δ = 2.29 (s, 3H), 3.76 (s, 3H), 6.38 (d, 2H, J = 9.1), 7.07 (d, 2H, J = 8.6), 7.34 (d, 2H, J = 8.7). LC-MS: t_R = 1.96 min, m/z = 371 [M+2].

4.1.11. 1-[2-(4-methyl-piperidin-1-yl)-2-oxo-ethyl]-3-(2,4,6-trifluoro-phenyl)-thiourea (22)

N,N-diisopropylethylamine (14.8 g, 0.11 mol) and 2,4,6-trifluorophenyl isothiocyanate (11.1 g, 57 mol) are added successively to a solution of 2-amino-1-(4-methyl-piperidin-1-yl)-ethanone hydrochloride salt (**21**, 11 g, 57 mol) in 385 ml of dichloromethane. The reaction mixture is stirred for 1 h at room temperature and then evaporated under reduced pressure. The residue is purified by column chromatography on silica gel, using a mixture of heptane/ethyl acetate 1:1 as eluent, to obtain 1-[2-(4-methyl-piperidin-1-yl)-2-oxo-ethyl]-3-(2,4,6-trifluoro-phenyl)-thiourea (**22**, 13.6 g, 39 mmol, 69%) as an orange solid. ^{1}H NMR ($CDCl_3$): δ = 0.94 (d, 3H, J = 6.4), 0.95–1.14 (m, 2H), 1.52–1.68 (m, 2H), 1.74 (d, 1H, J = 13.1), 2.60 (dt, 1H, J = 2.5, 13.0), 3.00 (dt, 1H, J = 2.5, 13.0), 3.75 (bd, 1H, J = 6.0, 13.0), 4.30 (bd, 1H, J = 13.2), 4.40 (bs, 2H), 6.78 (t, 2H, J = 7.8), 7.80 (br s, 1H), 8.10 (br s, 1H). LC-MS: t_R = 1.72 min, m/z = 346 [M+1].

4.1.12. 2-Methyl-1-[2-(4-methyl-piperidin-1-yl)-2-oxo-ethyl]-3-(2,4,6-trifluoro-phenyl)-isothiourea (23)

Anhydrous potassium carbonate (8.2 g, 59 mmol) and iodomethane (11.2 g, 78 mmol) are successively added to a solution of 1-[2-(4-methyl-piperidin-1-yl)-2-oxo-ethyl]-3-(2,4,6-trifluoro-phenyl)-thiourea (**22**, 13.6 g, 39 mmol) in 136 ml of acetonitrile. The reaction mixture is stirred for 1 h at room temperature and then concentrated under reduced pressure. The residue is taken up in ethyl acetate and washed with water and brine. The organic layer is dried over sodium sulfate and evaporated. The remainder is purified by column chromatography on silica gel, using a mixture of heptane/ethyl acetate 1:1 as eluent, to obtain 2-methyl-1-[2-(4-methyl-piperidin-1-yl)-2-oxo-ethyl]-3-(2,4,6-trifluoro-phenyl)-isothiourea (**23**, 13.6 g, 38 mmol, 96%). ^{1}H NMR ($CDCl_3$): δ = 0.97 (d, 3H, J = 6.4), 1.11 (dq, 2H, J = 2.5, 13.2), 1.54–1.71 (m, 1H), 1.72 (d, 1H, J = 13.4), 2.44 (s, 3H), 2.67 (dt, 1H, J = 2.5, 13.0), 3.00 (dt, 1H, J = 2.5, 13.0), 3.72 (bd, 1H, J = 13.6), 4.22 (s, 2H), 4.55 (d, 1H, J = 13.0), 6.28 (s, 1H), 6.66 (t, 2H, J = 8.2). LC–MS: t_R = 1.88 min, m/z = 360 [M+1].

4.1.13. 4-methyl-1-[2-methylsulfanyl-3-(2,4,6-trifluoro-phenyl)-3*H*-imidazol-4-yl]-piperidine (24)

2,4-Bis-(4-methoxyphenyl)-2,4-dithioxo-1,3,2,4-dithiadiphosphetane (Lawesson's reagent, 3.6 g, 8.9 mol) is added to a solution of 2-methyl-1-[2-(4-methyl-piperidin-1-yl)-2-oxo-ethyl]-3-(2,4,6-trifluoro-phenyl)-isothiourea (**23**, 5.7 g, 15.9 mmol) in 57 ml of 1,2-dimethoxyethane. The reaction mixture, which changes its colour from green to red, is stirred for 16 h at room temperature and then evaporated. The residual purple oil is diluted with *tert*-butyl methyl ether, the precipitate is filtered and the filtrate is stirred with 4 N sodium hydroxide solution, hereby the colour changes from purple to blue. The aqueous phase is extracted with ethyl acetate, the combined organic layer is washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The

remainder is purified by column chromatography on silica gel, using a mixture of heptane/ethyl acetate 7:3 as eluent, to obtain 4-methyl-1-[2-methylsulfanyl-3-(2,4,6-trifluoro-phenyl)-3*H*-imidazol-4-yl]-piperidine (**24**, 2.1 g, 6.3 mmol, 39%). ^{1}H NMR ($CDCl_3$): δ = 0.86 (d, 3H, *J* = 6.5), 0.99 (dq, 2H, *J* = 4.0, 12.0), 1.30–1.45 (m, 1H), 1.52 (d, 2H, *J* = 12.8), 2.48 (s, 3H), 2.59 (dt, 2H, *J* = 2.5, 11.9), 2.91 (d, 2H, *J* = 12.0), 6.72 (s, 1H), 6.85 (t, 2H, *J* = 7.9). LC–MS: t_R = 2.01 min, *m/z* = 342 [M+1].

4.1.14. 1-[5-bromo-2-methylsulfanyl-3-(2,4,6-trifluoro-phenyl)-3*H*-imidazol-4-yl]-4-methyl-piperidine (25)

N-bromosuccinimide (1.4 g, 7.9 mmol) is added to a solution of 4-methyl-1-[2-methylsulfanyl-3-(2,4,6-trifluoro-phenyl)-3*H*-imidazol-4-yl]-piperidine (**24**, 2.1 g, 6.1 mmol) in 25 ml of chloroform. The reaction mixture is stirred for 15 min at room temperature, then diluted with dichloromethane and 1 N sodium hydroxide solution. The phases are separated and the aqueous phase is extracted with dichloromethane. The combined organic layer is washed with 1 N sodium hydroxide solution and brine, dried over sodium sulfate and evaporated under reduced pressure. The residue is purified by column chromatography on silica gel, using a mixture of heptane/ethyl acetate 9:1 as eluent, to obtain 1-[5-bromo-2-methylsulfanyl-3-(2,4,6-trifluoro-phenyl)-3*H*-imidazol-4-yl]-4-methyl-piperidine (**25**, 1.53 g, 3.6 mmol, 60%) as a yellowish solid. ^{1}H NMR ($CDCl_3$): δ = 0.85 (d, 3H, *J* = 6.4), 0.79–0.89 (m, 2H), 1.34–1.37 (m, 1H), 1.52 (d, 2H, *J* = 11.8), 2.53 (s, 3H), 2.84 (d, 2H, *J* = 11.6), 3.06 (dt, 2H, *J* = 2.2, 11.7), 6.85 (t, 2H, *J* = 7.8). LC–MS: t_R = 2.18 min, *m/z* = 422 [M+2].

4.1.15. 4-Methyl-1-[5-methyl-2-methylsulfanyl-3-(2,4,6-trifluoro-phenyl)-3*H*-imidazol-4-yl]-piperidine (26)

Cesium carbonate (4.7 g, 14 mmol), trimethylboroxine (0.7 g, 5.3 mmol) and [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium(II) complex with dichloromethane (0.9 g, 1.1 mmol) are added to a solution of 1-[5-bromo-2-methylsulfanyl-3-(2,4,6-trifluoro-phenyl)-3*H*-imidazol-4-yl]-4-methyl-piperidine (**25**, 1.5 g, 3.6 mmol) in 31 ml of dioxane. The reaction mixture is heated to 90 °C for 16 h, then cooled to room temperature and filtered. The filtrate is washed with water and brine, dried over sodium sulfate and evaporated under reduced pressure. The residue is purified by column chromatography on silica gel, using a mixture of heptane/ethyl acetate 4:1 as eluent, to obtain 4-methyl-1-[5-methyl-2-methylsulfanyl-3-(2,4,6-trifluoro-phenyl)-3*H*-imidazol-4-yl]-piperidine (**26**, 0.55 g, 1.5 mmol, 42%) as an orange solid. ^{1}H NMR ($CDCl_3$): δ = 0.85 (d, 3H, *J* = 6.6), 0.81–0.91 (m, 2H), 1.24–1.36 (m, 1H), 1.49 (d, 2H, *J* = 12.0), 2.26 (s, 3H), 2.47 (s, 3H), 2.80–2.87 (m, 4H), 6.83 (t, 2H, *J* = 7.8). LC–MS: t_R = 1.99 min, *m/z* = 356 [M+1], 358 [M+3].

4.1.16. 1-[3-(2,6-Difluoro-4-methoxy-phenyl)-5-methyl-2-methylsulfanyl-3*H*-imidazol-4-yl]-4-methyl-piperidine (27)

To a solution of 4-methyl-1-[5-methyl-2-methylsulfanyl-3-(2,4,6-trifluoro-phenyl)-3*H*-imidazol-4-yl]-piperidine (**26**, 0.62 g, 1.8 mmol) in 6 ml of tetrahydrofuran is added 1.0 ml of a 5.4 M solution of sodium methoxide in methanol. The reaction mixture is heated for 30 min to reflux, then cooled to room temperature and poured into cold 1 N hydrochloric acid. The resulting suspension is extracted twice with ethyl acetate and the combined organic layer is washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The residue is purified by column chromatography on silica gel, using a mixture of heptane/ethyl acetate 3:2 as eluent, to obtain 1-[3-(2,6-difluoro-4-methoxy-phenyl)-5-methyl-2-methylsulfanyl-3*H*-imidazol-4-yl]-4-methyl-piperidine (**27**, 0.26 g, 0.7 mmol, 40%). ^{1}H NMR ($CDCl_3$): δ = 0.84 (d, 3H, *J* = 6.6), 0.87–0.94 (m, 2H), 1.25–1.34 (m, 1H), 1.49 (d, 2H, *J* = 12.1), 2.25 (s, 3H), 2.47 (s, 3H), 2.79–2.91 (m, 4H), 3.86 (s, 3H), 6.57 (d, 2H, *J* = 8.9). LC–MS: t_R = 1.81 min, *m/z* = 368 [M+1].

4.1.17. 1-[3-(2,6-difluoro-4-methoxy-phenyl)-5-methyl-3*H*-imidazol-4-yl]-4-methyl-piperidine (28)

To a solution of 1-[3-(2,6-difluoro-4-methoxy-phenyl)-5-methyl-2-methylsulfanyl-3H-imidazol-4-yl]-4-methyl-piperidine (**27**, 0.23 g, 0.6 mmol) in 5 ml of ethanol are added 22 ml of an aqueous Raney-Nickel suspension (100 g/l). The resulting black suspension is heated to reflux for 90 min and then cooled to room temperature. Celite is added to the mixture and the suspension is filtered through a Celite pad. The Celite is rinsed with ethanol and water, taking care that the pad always stays wet. The filtrate is concentrated under reduced pressure, the residue taken up in ethyl acetate and washed with water. The aqueous phase is extracted with ethyl acetate, the combined organic layer is washed with brine, dried over sodium sulfate and evaporated under reduced pressure. The residue is purified by column chromatography on silica gel, using a mixture of heptane/ethyl acetate 1:4 as eluent, to obtain 1-[3-(2,6-difluoro-4-methoxy-phenyl)-5-methyl-3*H*-imidazol-4-yl]-4-methyl-piperidine (**28**, 67 mg, 0.2 mmol, 33%) as a white solid. ^{1}H NMR ($CDCl_3$): δ = 0.86 (d, 3H, *J* = 6.5), 0.88–0.98 (m, 2H), 1.30–1.37 (m, 1H), 1.49 (d, 2H, *J* = 12.1), 2.26 (s, 3H), 2.83–2.91 (m, 4H), 3.85 (s, 3H), 6.56 (d, 2H, *J* = 8.9), 7.22 (s, 1H). LC–MS: t_R = 1.34 min, *m/z* = 322 [M+1].

4.1.18. 1-[2-Chloro-3-(2,6-difluoro-4-methoxy-phenyl)-5-methyl-3*H*-imidazol-4-yl]-4-methyl-piperidine (10)

N-chlorosuccinimide (35 mg, 0.3 mmol) is added to a solution of 1-[3-(2,6-difluoro-4-methoxy-phenyl)-5-methyl-3*H*-imidazol-4-yl]-4-methyl-piperidine (**28**, 67 mg, 0.2 mmol) in 2 ml of chloroform. The reaction mixture is stirred for 1.5 h at 0 °C, then concentrated under reduced pressure and diluted with methanol. Isolute® HM-N is added and the solvent is removed under reduced pressure. The residue is purified by column chromatography on silica gel, using a mixture of heptane/ethyl acetate 4:1 as eluent, to obtain 1-[2-chloro-3-(2,6-difluoro-4-methoxy-phenyl)-5-methyl-3*H*-imidazol-4-yl]-4-methyl-piperidine (**10**, 14 mg, 0.04 mmol, 19%) as a yellow oil. ^{1}H NMR ($CDCl_3$): δ = 0.85 (d, 3H, *J* = 6.6), 0.88–0.95 (m, 2H), 1.25–1.35 (m, 1H), 1.49 (d, 2H, *J* = 12.2), 2.21 (s, 3H), 2.82 (dt, 2H, *J* = 2.3, 11.5), 2.90 (d, 2H, *J* = 11.2), 3.87 (s, 3H), 6.59 (d, 2H, *J* = 8.9). LC–MS: t_R = 2.16 min, *m/z* = 356 [M+1].

4.2. Biology

All tested compounds have been at least 95% pure, the purification has been either performed via chromatography (see chapters 4.15, 4.19 and 4.10) or by crystalisation.

4.2.1. Botrytis cinerea (Botryotinia fuckeliana)/tomato (action against grey mould on tomato)

Four-week old tomato plants cv. Roter Gnom were treated in a spray chamber with the formulated test compound diluted in water. The test plants were inoculated by spraying them with a spore suspension two days after application. The inoculated test plants were incubated at 20 °C and 95% rh in a greenhouse and the percentage leaf area covered by disease was assessed when an appropriate level of disease appeared on untreated check plants (5–6 days after application).

4.2.2. Uncinula necator (Erysiphe necator)/grape (action against powdery mildew on grape)

5-week old grape seedlings cv. Gutedel are sprayed in a spray chamber with the formulated test compound diluted in water. The test plants are inoculated by shaking plants infected with grape powdery mildew above them 1 day after application. The inoculated test plants are incubated at 24/22 °C (day/night) and 70% rh under a light regime of 14/10 h (light/dark) and the percentage leaf area covered by disease is assessed when an appropriate

level of disease appears on untreated check plants (7–9 days after application).

4.2.3. Mycosphaerella graminicola (Septoria tritici)/wheat (action against leaf blotch on wheat)

Two-week old wheat plants cv. Riband were treated in a spray chamber with the formulated test compound diluted in water. The test plants were inoculated by spraying a spore suspension on them one day after application. After an incubation period of 1 day at 22 °C/21 °C (day/night) and 95% rh, the inoculated test plants were kept at 22 °C/21 °C (day/night) and 70% rh in a greenhouse. Efficacy was assessed directly when an appropriate level of disease appeared on untreated check plants (16–19 days after application).

4.2.4. Alternaria solani/tomato (action against early blight on tomato)

Four-week old tomato plants cv. Roter Gnom were treated in a spray chamber with the formulated test compound diluted in water. The test plants were inoculated by spraying them with a spore suspension two days after application. The inoculated test plants were incubated at 22/18 °C (day/night) and 95% rh in a greenhouse and the percentage leaf area covered by disease was assessed when an appropriate level of disease appeared on untreated check plants (5–7 days after application).

4.3. Biochemistry

4.3.1. Compounds testing on pure porcine tubulin

The HTS-tubulin polymerisation assay kit (Cytoskeleton Inc., Denver, USA) has been used following the manufacturer instruction. The standard polymerisation reaction contains 100 μl volume of 4 mg/ml tubulin in 80 mM PIPES ph 6.9, 0.5 mM EGTA, 2 mM $MgCl_2$ and 1 mM GTP. The polymerisation was started by incubation at 37 °C and followed by absorption readings at 340 nm (Spectramax). Paclitaxel and DMSO were used as positive and negative controls, respectively. 4-Chloro-1-(4-chloro-phenyl)-5-(2,6-difluoro-4-methoxy-phenyl)-2-methyl-1*H*-imidazole (**9**) and 4-chloro-1-(4-chloro-phenyl)-2-methyl-5-(2,4,6-trifluoro-phenyl)-1*H*-imidazole (**17**) were added in different wells of a 96-well plate at the beginning of the reaction at 1.25 $\mu g.ml^{-1}$ in a DMSO solution (0.2 mM).

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