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Synthesis of Ring-Opened Analogues of Oxysterol-Binding Protein-Inhibiting Piperidinyl-thiazole Fungicides

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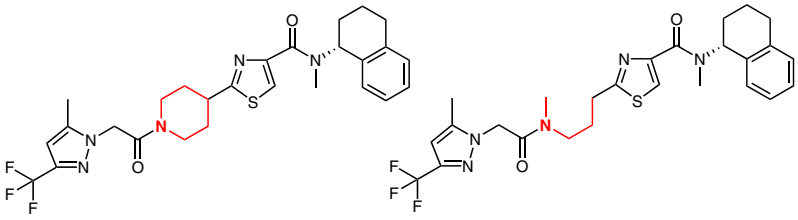

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Abstract Novel aminoethyl-, aminopropyl-, and aminobutyl-substituted thiazole-4-carboxamides have been prepared which are ring-opened analogues of piperidinyl-thiazole fungicides. Depending of the chain length, completely different synthetic approaches had to be chosen which vary from a Sonogashira coupling with a 2-bromothiazole derivative to a thiazole ring construction from different β- and δ-amino acids.

Key words ring opening, piperidine, thiazole, heterocycle, fungicide, crop protection

Oxathiapiprolin (**1**), one of the latest introductions to the fungicide market, controls very efficiently devastating plant diseases, such as potato and tomato late blight caused by *Phytophthora infestans* and grape downy mildew with *Plasmopara viticola* as causal agent, at formerly unimaginably low use rates of 10–20 g/ha.[1,2] Its powerful fungicidal activity is based on a completely novel mode of action, which is the inhibition of the fungal oxysterol-binding protein. One of the final manipulations within the fascinating invention pathway of oxathiapiprolin (**1**) was the introduction of the isoxazoline ring as cyclic peptide mimic of the amide function in the precursor **2**, which itself is highly active.[1,2] Recently, we have reported the synthesis and fungicidal activity of analogues of **2**, in which the amide function linked to the thiazole has been reversed.[3] Another modification of **2**, which we had planned, was to cut its piperidine ring along its axis of symmetry, leading to compounds such as **3**, in which a flexible 3-aminopropyl chain is linking the unchanged pyrazole acetic acid and thiazole carboxamide moieties.

2-(3-Aminopropyl)thiazole-4-carboxylic acid derivatives can be found as a structural motif in tubulin polymerization inhibiting anticancer agents,[4–9] dual agonists of prostaglandin receptors EP2/EP4,[10,11] histamine H_2 receptor agonists,[12] and antitrypanosomal compounds.[13] This qualification for biological activity gave us confidence that we can also reach the desired fungicidal efficacy if we combine the 2-(3-aminopropyl)thiazole-4-carboxylic acid scaffold via consecutive amidations with the 5-methyl-3-trifluoromethylpyrazole acetic acid and 1-aminotetraline end groups of **2**. In this paper we describe the preparation of novel ring-opened analogues of piperdinyl-thiazole fungicides (Figure 1).

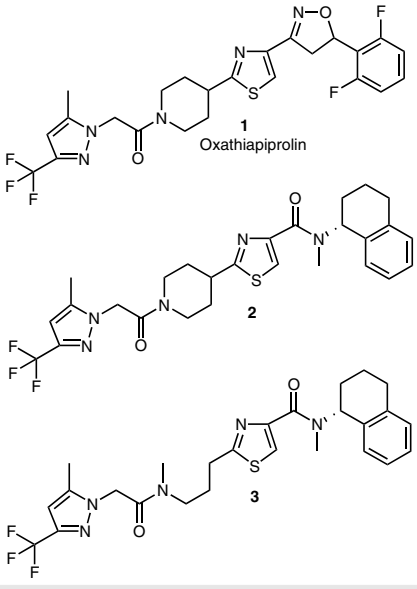


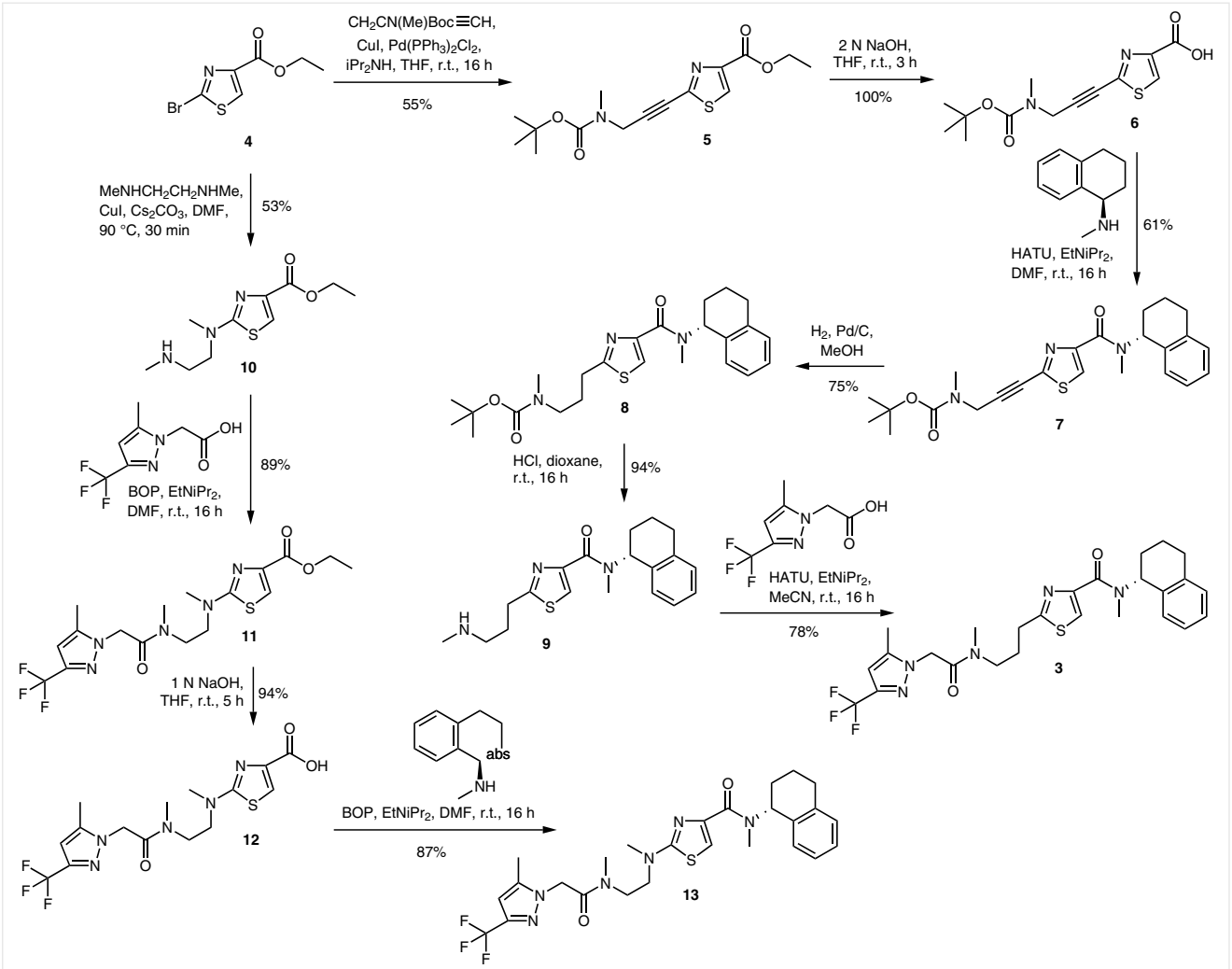
Figure 1 Oxathiapiprolin (**1**), its amide bioisostere **2** and **3**, the ring-opened version of it

We started the synthesis of **3** with the Sonogashira coupling of commercially available ethyl 2-bromothiazole-4-carboxylate (**4**) with *N*-Boc-*N*-methylpropargylamine to de-

liver the alkyne **5**. Other 2-alkynylthiazole derivatives have been used as building blocks in the synthesis of nosiheptide[14,15] and of analogues of epothilone E,[16,17] complanadine A,[18] setileuton,[19] and the glutamate receptor agonists MPEP and MTEP.[20] The ester saponification of **5** delivered the carboxylic acid **6**, which was converted into the amide **7** under standard peptide coupling conditions. Originally, we had planned the removal of the Boc protecting group as next step, but our reagent of choice, hydrochloric acid in dioxane, did not only cleave the carbamate but also added one equivalent of HCl to the C–C triple bond, resulting in chlorovinyl formation. Therefore we decided to hydrogenate first the alkyne function of **7** to the saturated aminopropyl scaffold of **8**. Now the Boc group could be removed without any undesired side reaction to deliver the secondary amine **9**, which was transformed by amidation with 5-methyl-3-trifluoromethylpyrazole acetic acid into the target compound **3** (Scheme 1).

The same bromothiazole starting material **4** enabled also the preparation of **13**, a ring-opened derivative of the corresponding piperazine-thiazole analogue of the piperidine-thiazole **2** which also possesses excellent fungicidal activity. In this regard, **4** was transformed with *N*,*N*′-dimethylethylenediamine under the conditions of a copper-catalyzed Buchwald–Hartwig amination to the thiazole derivative **10**. Two different amidation reactions, interrupted by an ester saponification, delivered smoothly the desired product **13**, which carries, as also **3**, a three-atom linker between the amide function and the thiazole ring (Scheme 1).

The aminopropylthiazole derivative **3** as well as some of its analogues with different amines in place of the aminotetraline showed excellent activity against the important pathogens *P. infestans* and *P. viticola* down to the low dose of 6 ppm. This convinced us that the piperidine ring of lead compound **2** is not part of the pharmacophore, but rather a spacer in the center core of the molecule which does not

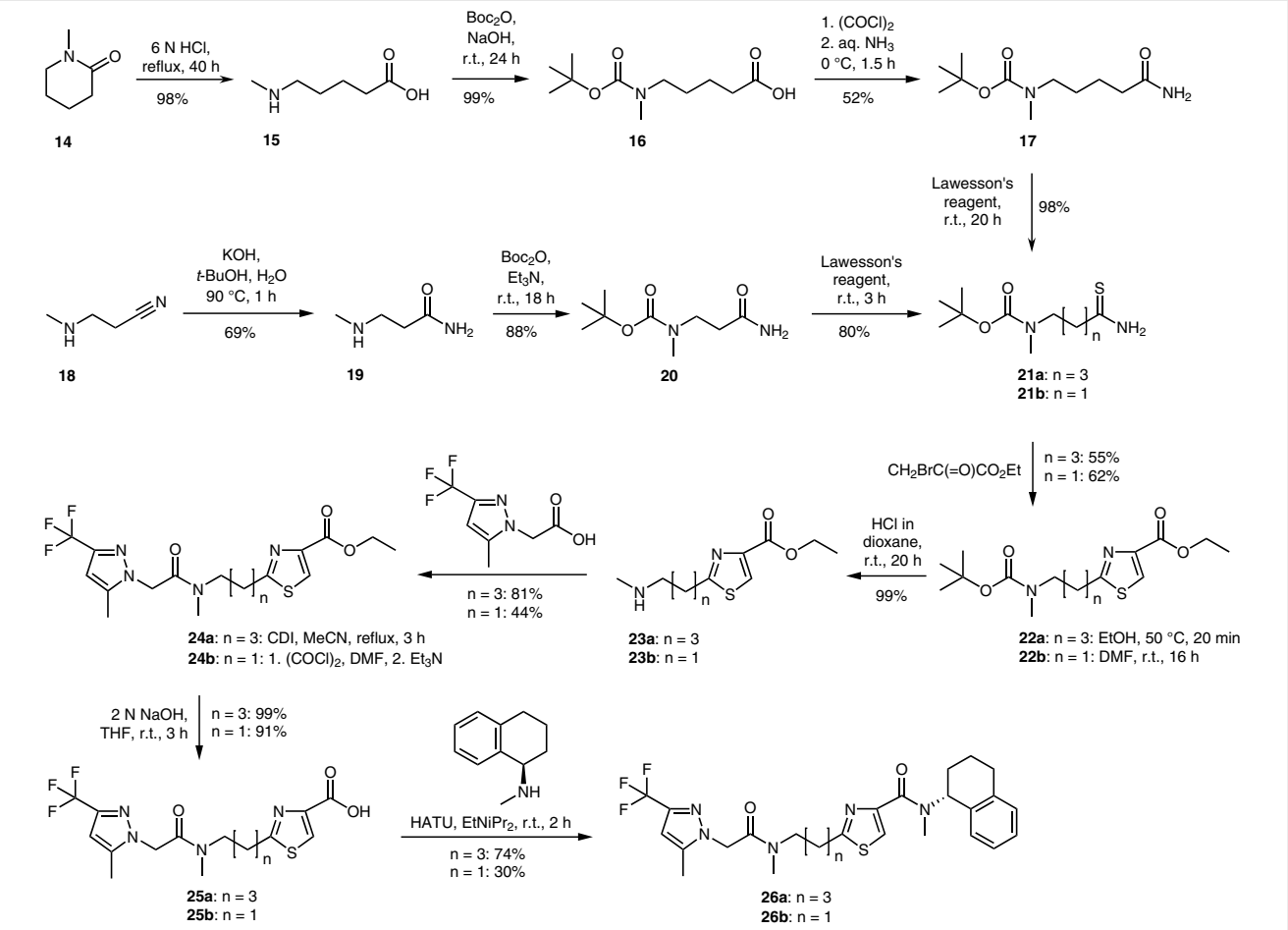


Scheme 1 Synthesis of the fungicidally active compounds **3** and **13**

seem to be involved in target binding. Therefore we decided to prepare further analogues of **3** with varied chain length. In particular we were interested to check if the addition or the removal of one methylene group would eventually increase the fungicidal activity.

The synthesis of **26a**, the derivative of **3** which is elongated by one additional methylene group, started with the ring-opening of *N*-methylpiperidone (**14**) to the δ-amino acid **15** (Scheme 2). After Boc protection of the secondary amine, the acid function of the resulting **16** was converted via the primary amide **17** into the thioamide **21a**. Compound **21b**, its corresponding equivalent with one methylene group less in the alkyl chain compared to **3**, could be prepared in only two steps from *N*-cyanoethyl-*N*-methylamine (**18**) by conversion of the amine into the *tert*-butoxycarbonyl (Boc) carbamate and subsequent reaction of the nitrile to a thioamide. Also **21b** has not been described in the literature before, but its *N*-desmethyl analogue has been used for the synthesis of DNA-cleaving agents.[21,22] Compounds **21a** and **21b** were then transformed by the same sequence of five final steps. First the thioamide function upon treatment with ethyl bromopyruvate underwent ring condensation to the thiazole esters **22a**,**b**. Then removal of the Boc protecting group and subsequent amidation with 5-methyl-3-trifluoromethylpyrazole acetic acid delivered **24a**,**b**. Finally another deprotection–amidation sequence, the ester saponification to the carboxylic acid **25a**,**b** and its conversion with aminotetraline afforded **26a** with one methylene group more and **26b** with one methylene group less than the aminopropylthiazole derivative **3**. In contrast to their very active role model **3**, both stretched and shortened analogues **26a**,**b** displayed only weak fungicidal efficacy.

In conclusion, we have explored the scope around analogues of piperidinyl-thiazole fungicides, in which the piperidine ring has been replaced by a flexible alkyl chain of different length. As it turned out, only compounds as **3**, which retain the three-carbon linker between the amide nitrogen atom and the thiazole ring of lead compound **2**, showed a sufficient level of fungicidal activity.



Scheme 2 Synthesis of compounds **26a** and **26b**, analogues of experimental fungicide **3** with shortened or extended chain length

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588473.

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