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Synthesis of conformationally locked analogs of quinolin-6-yloxyacetamide fungicides

Fiona Murphy Kessabi, Renaud Beaudegnies, Laura Quaranta and Clemens Lamberth*

Syngenta Crop Protection AG, Chemical Research, Schaffhauserstr. 101, CH-4332 Stein, Switzerland

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ABSTRACT

Three different synthesis pathways delivered novel tricyclic compounds which are conformationally locked analogs of quinolin-6-yloxyacetamide fungicides by cyclization of their acetal or O,S-acetal function to quinoline positions 5 or 7. Examples of the fused ring systems of [1,3]oxathiano[6,5-g]quinoline and [1,3]oxathiocino[6,7-f]quinoline, which have been unknown to the chemical literature before, are herein reported for the first time.

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Recently we have reported on quinolin-6-yloxyacetamides as a new class of experimental fungicides with excellent activity against a broad range of phytopathogens from the group of Ascomycetes and Oomycetes, such as *Phytophthora infestans*, the causal agent of potato late blight, *Mycosphaerella graminicola*, the causal agent of wheat leaf blotch and *Uncinula necator*, the causal agent of grape powdery mildew.[1] Their fungicidal activity is due to their ability to inhibit the fungal tubulin polymerization, leading to microtubule destabilization. Typical examples of this compound class are compounds, in which either a O,S-acetal as in **1** or an acetal as in **2** serves as two-atom spacer between the position 6 of a quinoline ring system and a carboxamide function. The recent finding, that the O,S-acetal of **1** could be reverted (oxygen and sulfur atoms changing place) or replaced by a dithioacetal via a Newman-Kwart-type synthesis approach under preservation of the fungicidal activity demonstrated potential scope in this linker area of the molecule.[2] Therefore we planned to introduce some new structural elements into this part of the scaffold. An idea which immediately came to our mind was to freeze the flexible conformation of the acetal linker by annulation to the quinoline ring system. As demonstrated by target compounds **3** and **4**, both quinoline positions 7 (→ **3**) and 5 (→ **4**) offer the possibility to tight the O,S-acetal or the acetal back to the benzene ring of the quinoline bicycle. The concept of reducing the conformational flexibility of a biologically active compound by freezing a certain conformation through a ring closure reaction, leading to so-called conformationally locked analogs with often increased binding affinity to the target, is well-known in the pharmaceutical and agrochemical lead optimization.[3-6] In this paper we report the synthesis of conformationally locked analogs of quinolin-6-yloxyacetamide fungicides and describe the very first examples of the so far unknown tricyclic ring systems of [1,3]oxathiano[6,5-g]quinoline and [1,3]oxathiocino[6,7-f]quinoline.

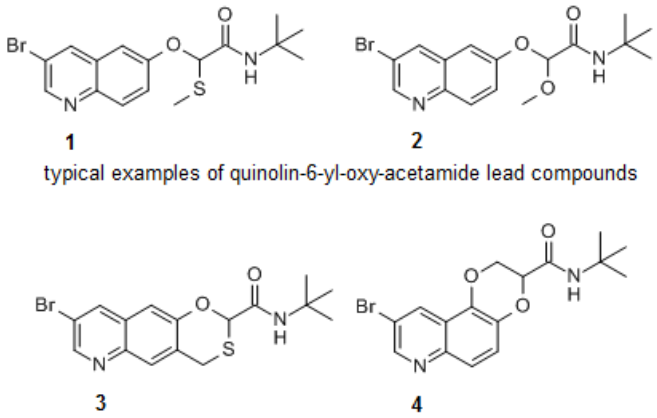

Figure 1. Conformationally locked analogs **3** and **4** of quinolin-6-yloxyacetamide fungicides **1** and **2**.

The synthesis of the [1,3]oxathiano[6,5-g]quinoline derivative **3** started from commercially available 2-hydroxy-5-nitrobenzyl bromide (**5**), which was converted with thiourea into the benzyl imidothiocarbamate **6**.[7] Under basic conditions the thiopseudourea function of **6** could be cleaved to obtain the benzylmercaptan **7**.[8] Both phenol and thiol functions of **7** were then cylized with ethyl glyoxylate to the 1,3-benzoxathian

* Corresponding author. Tel.: +41-62-866-0224; fax: +41-62-866-0860; e-mail: clemens.lamberth@syngenta.com

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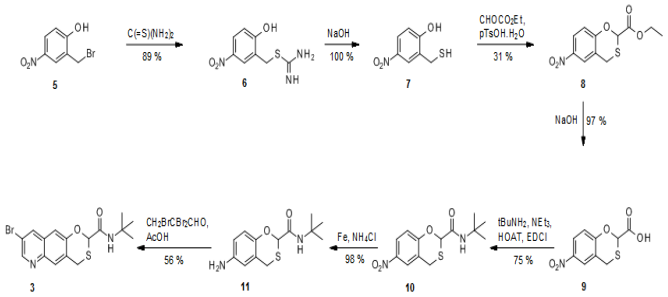
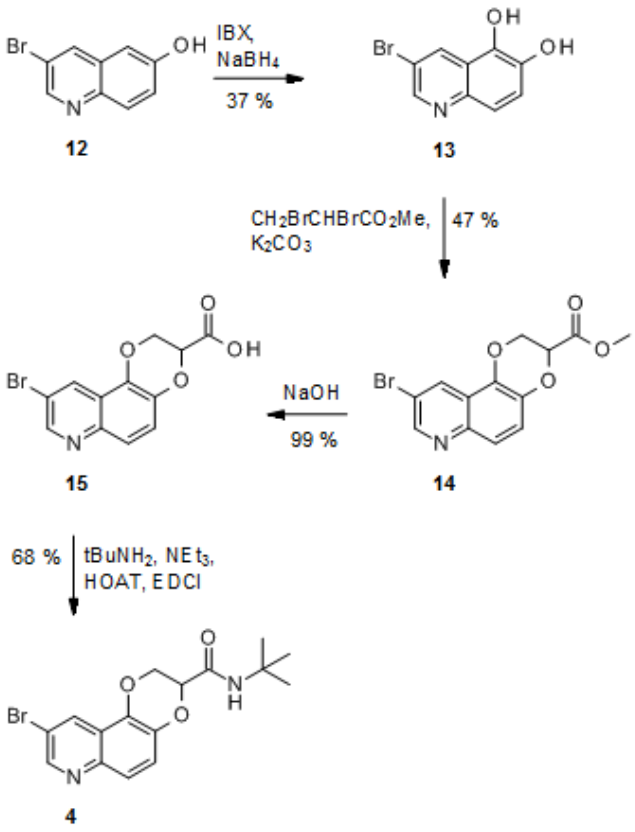
derivative **8**. 2-Substituted 1,3-benzoxathians have found application as isovanillyl sweeteners,[9-11] but also as antioxidants[12] and insecticides.[13] However, so far a 1,3-benzoxathian derivative with a carboxyl function in position 2, such as **8**, has never been described. Ester saponification of **8** and subsequent amidation with tert-butylamine delivered amide **10**. The reduction of the nitro function under Bechamp conditions afforded the 6-amino-1,3-benzoxathian **11**. This intermediate could be directly converted by a special Skraup-type cyclization with 2,2,3-tribromopropanal, which we have worked out recently,[14] into the desired [1,3]oxathiano[6,5-g]quinoline **3**, a conformationally locked analog of lead structure **1**, in which the methylsulfanyl function has been cyclized to position 7 of the quinoline.



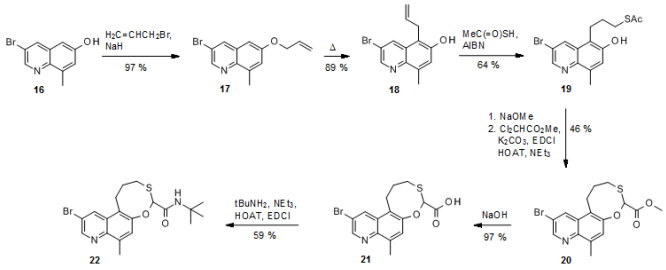
Scheme 1. Synthesis of the [1,3]oxathiano[6,5-g]quinoline derivative **3**.

The synthesis of target compound **4**, in which the acetal bridge has been tied back to position 5 of the quinoline, followed a completely different strategy. Here, we started from 3-bromo-quinolin-6-ol (**12**), which can be prepared in only two steps by Skraup cyclization from 4-nitroaniline and 2,2,3-tribromopropanal.[14] The introduction of a second phenol function was achieved by oxidation with 2-iodoxybenzoic acid (IBX).[14] Both hydroxyl groups of the resulting **13** were then ring-closed with methyl 2,3-dibromopropanoate to the [1,4]dioxano[2,3-f]quinoline **14**. Compounds with this tricyclic ring system are found in experimental compounds of several different medicinal chemistry indications. The most prominent examples of a drug candidate with such a scaffold are the dual SSRI/5-HT_{1A} antagonists WAY-253752[15] and WAY-262398.[16] Ester saponification of delivered the carboxylic acid **15**, which was transformed into the tert-butyl amide **4**, a conformationally locked analog of the quinolin-6-yloxyacetamide **2**.



Scheme 2. Synthesis of the [1,4]dioxano[2,3-f]quinoline derivative **4**.

Another 5,6-annulated O,S-acetal mimic, the dihydro[1,3]oxathiocino[6,7-f]quinoline derivative **22**, was prepared in a completely different manner. O-allylation of 3-bromo-8-methylquinolin-6-ol **16**[14] and subsequent regioselective thermal Claisen rearrangement of the allyl ether delivered the tetrasubstituted quinoline **18**. Radical addition of thioacetic acid to the alkene function[17,18] transformed the allyl group of **18** into the S-3-(5-quinolinyl)propyl thioacetate **19**. After cleavage of the thioester under basic conditions, the aromatic hydroxyl group and the aliphatic mercaptan function can be cyclized with methyl dichloroacetate to the desired dihydro[1,3]oxathiocino[6,7-f]quinoline **20**. So far compounds with this unique tricyclic scaffold have not been described in the literature. Saponification of the methyl ester in **20** to the free acid **21** and subsequent amidation delivered the conformationally locked analog **22** of the O,S-acetal derivative **3**.



Scheme 3. Synthesis of the dihydro[1,3]oxathiocino[6,7-f]quinoline derivative **22**.

In conclusion, we have developed three different methods for the synthesis of conformationally locked analogs of quinolin-6-yloxyacetamide fungicides, which have their acetal or O,S-acetal function tied back to the neighboring positions of quinoline ring.

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Supplementary data

Supplementary data (experimental details and spectroscopic data for compounds **3** - **22**) associated with this article can be found in the online version.

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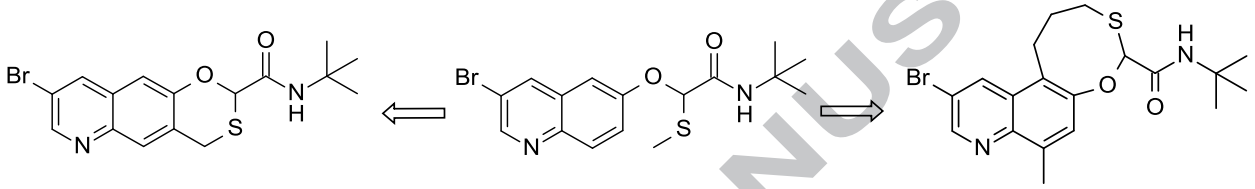

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Highlights

- Three different methods for the synthesis of conformationally locked quinoil-6-yloxyacetamide fungicides are described
- The O,S-acetal of the lead compounds has been tied back to the adjacent quinoline positions 5 or 7
- First examples with a [1,3]oxathiano[6,5-g]quinoline scaffold are described
- First examples with a [1,3]oxathiocino[6,7-f]quinoline scaffold are described

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