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Quinazolin-4-ones, Thienopyrimidin-4-ones and Related Compounds: New Highly Active Powdery Mildewicides [1]

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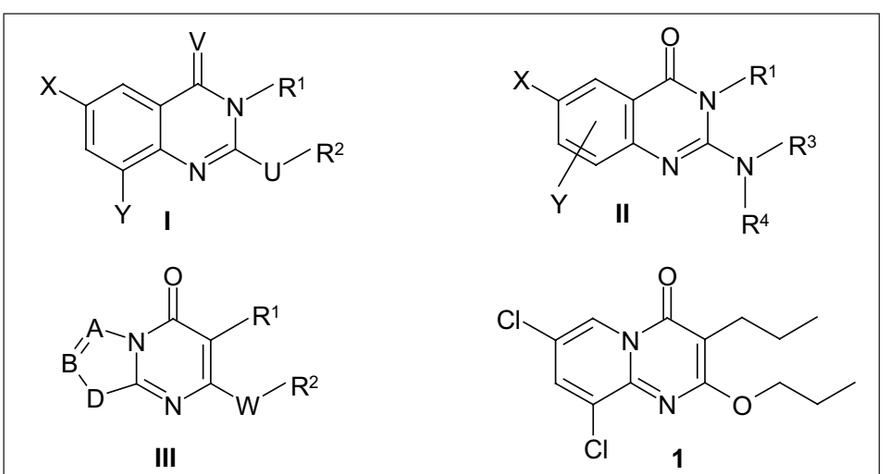
Abstract: In this short review, new quinazolinones and thieno-pyrimidinones with outstanding powdery mildew activity are introduced. The most important inventions of two major players in this field, DuPont and Syngenta, are presented and interesting strategies for the synthesis of 2-alkoxy-3-alkylthieno[2,3-d]pyrimidin-4-ones and related compounds are discussed in detail. The biological activities of selected compounds including the highlights, 6-bromo-2-propoxy-3-propylquinazolin-4-one and 6-chloro-2-propoxy-3-propylthieno[2,3-d]-pyrimidin-4-one are compared and discussed.

Keywords: Powdery mildewicides · Quinazolin-4-one · Tetraalkylorthocarbonate · Thieno[2,3-d]pyrimidin-4-one

Introduction

In the last 30 years, quinazolin-4-ones have often been a topic of interest in fungicidal agrochemical research and many related patents and publications can be found in the literature. The oldest patent application in the quinazolin-4-one area covering compounds with interesting fungicidal activity was published by DuPont in 1973 [2]. However, the fungicidal potential of the 2-alkoxy-3-alkyl-substituted quinazolin-4-ones- and quinazolin-4-thiones (compounds of general structure **I** in Fig. 1) described in this first patent application was not fully recognized at that time. A second patent from DuPont was published in 1975, wherein quinazolin-4-ones with dialkylamino-substituents in the 2-position (compounds of general structure **II** in Fig. 1) were claimed as agrochemical fungicides [3]. Then a period of inactivity followed, until 1993, where again scientists from DuPont re-entered this area and filed a patent application covering pyrido[1,2-a]-pyrimidin-ones with alkoxy- and alkyl-substituents in the pyrimidinone part (compounds of general formula **III** in Fig. 1) [4]. In this application, for the first time the preparation of compounds with longer alkoxy- and alkyl side chains was described.

Some of these compounds showed interesting protective activities against powdery mildew diseases. One of the best compounds of this series, 6,8-dichloro-2-propoxy-3-propyl-pyrido[1,2-a]pyrimidin-4-one (**1**), was prepared and tested at Syngenta [5] and showed good control of pow-



A = CR^5 or N; B = CR^b or N; D = $CR^7 = CR^8$, CR^7 = N, N = CR^8, O, S, or NR^9; X, Y = H, halogen, C_1–C_4-alkyl, C_1–C_4-alkoxy; U, V = O, S; R^1, R^2 = C_1–C_{12}-alkyl, C_3–C_8-alkenyl(alkinyl), C_3–C_8-cycloalkyl; R^3 = C_1–C_8-alkyl, C_3–C_4-alkenyl(alkinyl), methoxy; R^4 = H, C_1–C_4-alkyl; R^5–R^8 = H, halogen, C_1–C_8-alkyl, *etc*.; R^9 = C_1–C_4-alkyl(haloalkyl).

Fig. 1. General formulae of compounds covered by early DuPont patent applications [2–4] and structure of compound **1**.

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dery mildew on barley (EC_{80} = 6 ppm). However, the activity against powdery mildew on apples and grapes was insufficient.

The first breakthrough in the biological activity was achieved with representatives of the 2-alkoxy-3-alkylsubstituted quinazolin-4-one class, possessing alkoxy respectively alkyl side chains with 3 to 5 carbon atoms [6]. This new patent application (WO 94/26722) [6], published in 1994 represents a so-called selection from US 3755582 and US 3867384. The synthesis and biological screening of some compounds covered in WO 94/26722 was repeated by us in 1995. The greenhouse tests revealed that especially 6-bromo-2-propoxy-3-propylquinazolin-4-one (**2**) (see Fig. 3) showed excellent protective activity against powdery mildew diseases on apples, grapes and barley. No further fungicidal activities were detected in our biological screening.

The excellent biological activity of some new representatives of the quinazolinone class convinced chemists of Syngenta Crop Protection AG [5] to enter this promising field.

The Major Syngenta Contributions

Our approach in the quinazolinone field was the replacement of halophenyl by halothienyl, which leads to three isomeric thienopyrimidin-4-ones: thieno[2,3-d]pyrimidin-4-ones **IV**, thieno[3,2-d]-pyrimidin-4-ones **V** and thieno[3,4-d]pyrimidin-4-ones **VI** (see Fig. 2).

For the synthesis of the thieno[3,4-d] pyrimidin-4-ones, we first used a 'quinazoline strategy' (Scheme 1).

Using an aminocarboalkoxy-substituted thiophene as starting material, the first step in the classical synthesis approach was a thiophosgene reaction. Looking more thoroughly into this thiophosgenation reaction in the thiophene series, we recognized that the reaction of 4-amino-3-carbomethoxythiophene (**6**) and 3-amino-2-carbomethoxythiophene (**10**) with thiophosgene works well (yields > 80%, see Scheme 1), but the reaction of thiophosgene with 2-amino-3-carbomethoxythiophene (**12**) only gave unsatisfactory yields of pure 2-isothiocyanato-3-carbomethoxythiophene (**13**) (≤ 40%). This meant that the thieno[3,2-d]- and thieno[3,4-d]-pyrimidin-4-ones could be prepared in good overall yield by simply using the classical quinazolinone-route, outlined in Scheme 1 (only difference in strategy: halogenation must be performed in the last step!). For the synthesis of the thieno[2,3-d]-pyrimidin-4-ones alternative routes, giving better overall yields, were still of interest. Finally, we discovered two favorable routes for the synthesis of the thieno[2,3-d]-pyrimidin-4-ones (Scheme 2). In the first route (Scheme 2a) the crucial step was the reaction of 2-amino-3-carbomethoxythiophene (**12**) with an alkylisothiocyanate, which gave high yields of the corresponding thiourea-thiophene intermediates which could be easily transformed into the halogen-substituted thieno[2,3-d]pyrimidin-4-ones using the

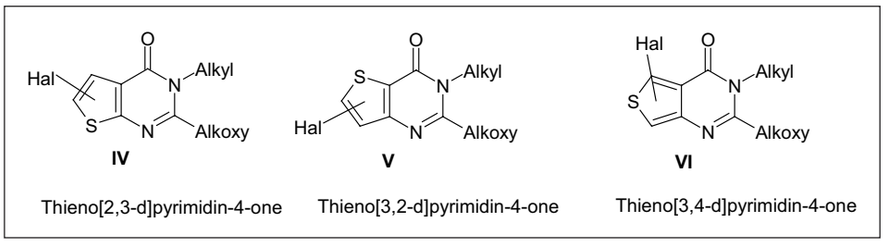
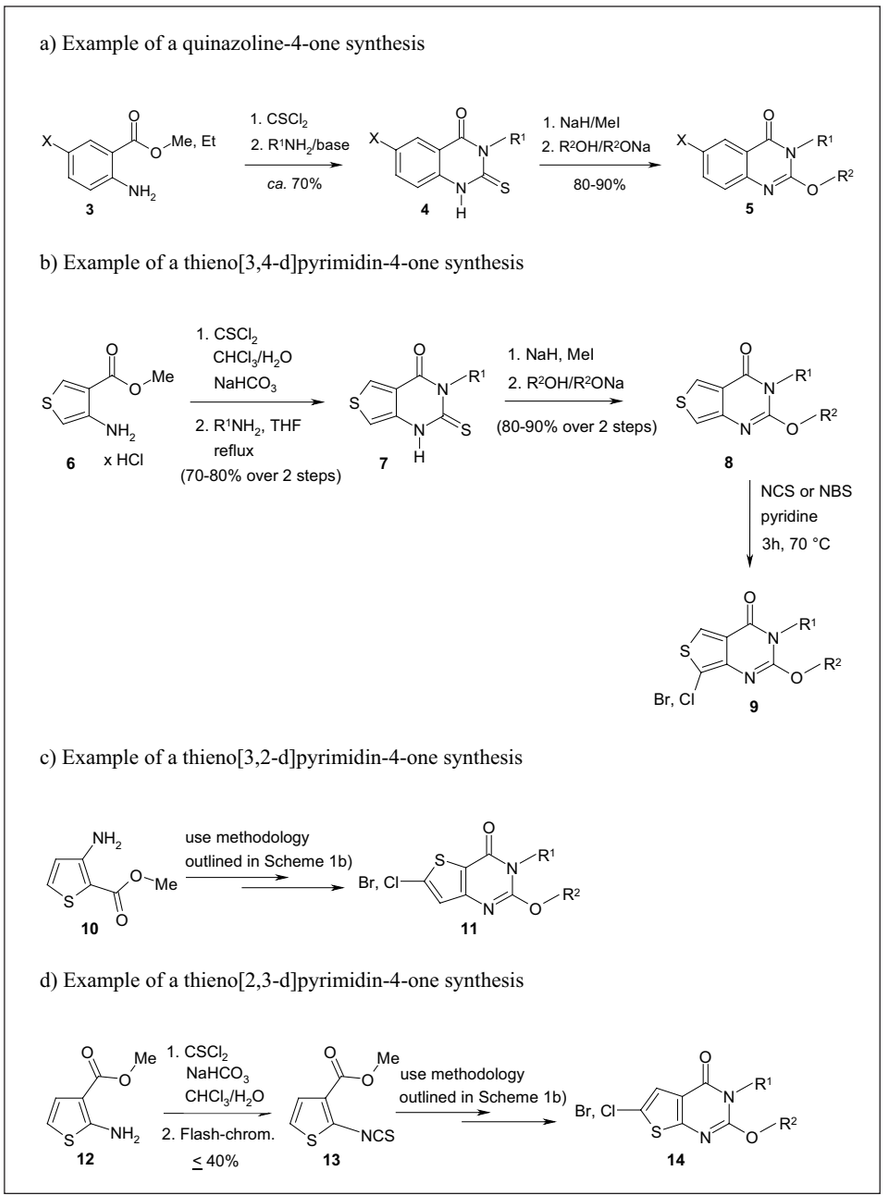


Fig. 2. The three isomeric thienopyrimidin-4-ones [7]



Scheme 1. Examples of classical approaches to halogenated alkoxysubstituted quinazolin-4-ones [6][8] and isomeric alkoxysubstituted thienopyrimidin-4-ones [7]

technology outlined in Scheme 1. In the second route (Scheme 2b), intermediates such as isothiocyanates, which are derived from thiophosgenation reactions, could be totally avoided. The starting materials in this sequence (Scheme 2b), were 2-amino-3-carboxamidothiophenes **16**, which could be easily prepared, even on larger scale, by application of Gewald-type chemistry [9].

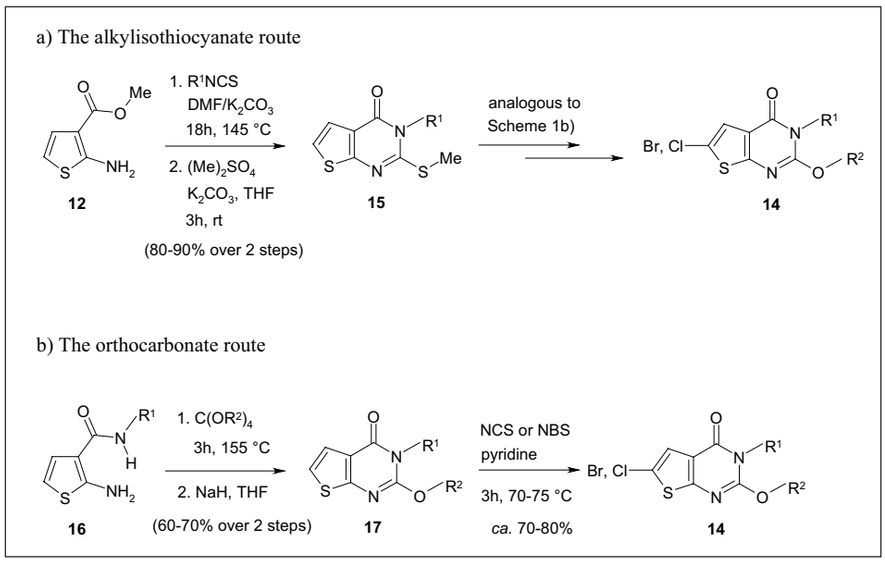
The crucial step of the new sequence was the reaction of 2-amino-3-carboxamidothiophenes **16** with tetraalkylorthocarbonates. We were able to optimize this reaction and in most cases the yields turned out to be satisfactory (60–70%) [10]. Subsequent cyclization in the presence of sodium hydride as the base and halogenation with N-halosuccinimide in pyridine as the solvent gave 6-halosubstituted thieno[2,3-d]pyrimidin-4-ones **14** in good overall yields. From the biological point of view, the best halosubstituted thieno[3,2-d]- and thieno[3,4-d]-pyrimidin-4-ones only showed moderate powdery mildew activity, whereas the best halosubstituted thieno-[2,3-d]-thienopyrimidin-4-ones exhibited excellent activity against all major powdery mildew diseases (see Fig. 3)

With 6-chloro-2-propoxy-3-propylthieno[2,3-d]pyrimidin-4-one (**21**), we discovered an excellent compound for use against powdery mildew diseases, which was at least as active as the quinazolinone **2** (see Fig. 3). Parallel to our work, DuPont carried on with their quinazolinone project and extended it to the thiophene analogues, too. Their respective patent application WO 97/02262 covering thienopyrimidinones [11] was filed nine months earlier than our patent application. As a consequence Syngenta could not independently develop the 2-alkoxysubstituted thieno[2,3-d]pyrimidin-4-ones. However, the excellent powdery mildew activity of **21** (EC_{80} (barley) ≤ 0.002 ppm!!) motivated us to continue our research aiming at even more active members of this chemistry class. Two independent modifications in the chemical structure of thieno[2,3-d]-pyrimidin-4-ones were investigated. The first was the introduction of a cyclopropyl-group in the alkoxy side chain [12] and the second was the replacement of the alkoxy-substituent in 2-position by an alkyl group of suitable chainlength [13]. In this short review, we can only concentrate here on the chemistry and biological properties of the 2,3-dialkylsubstituted thieno[2,3-d]pyrimidin-4-ones. The synthesis of this class of compounds turned out to be straightforward and is shown in Scheme 3.

In this sequence the starting material was again 2-amino-3-carbomethoxythiophene (**12**), which could be simply prepared, even on larger scale, by a known route [9]. The reaction of the aminothiophene **12** with $POCl_3$ in the presence of molar amounts of an appropriate alkylamide gave thieno-amidine intermediates, which were not isolated but directly cyclized in the presence of a base such as sodium hydride to give 2,3-dialkylsubstituted thieno-[2,3-d]pyrimidin-4-ones **23** in excellent overall yield (80–90% with respect to aminothiophene **12**). The final chlorination was favorably performed by the use of the chlorine/pyridine method (see Scheme 3).

From the biological point of view, some of the halogenated 2,3-dialkylsubstiuted thieno-[2,3-d]-pyrimidin-4-ones **24** showed also interesting activities against all the major powdery mildew diseases, but no further extension of the biological spectrum could be achieved with this class of compounds.

Other companies also had the idea to replace alkoxy by alkyl. For example DuPont scientists published the first patent application covering 2-alkylsubstituted quinazolin-4-ones in 1998 [14] but this patent application missed out thienopyrimidin-4-ones with alkylsubstituents in the 2-position. In 1998, AgrEvo (now Bayer CropScience) also entered the quinazolin-4-one/thieno-pyrimidin-4-one field. In their patent application WO 98/49899, thienopyrimidin-4-ones were generically



Scheme 2. Two useful alternative approaches for the synthesis of thieno[2,3-d]pyrimidin-4-ones [7][10]

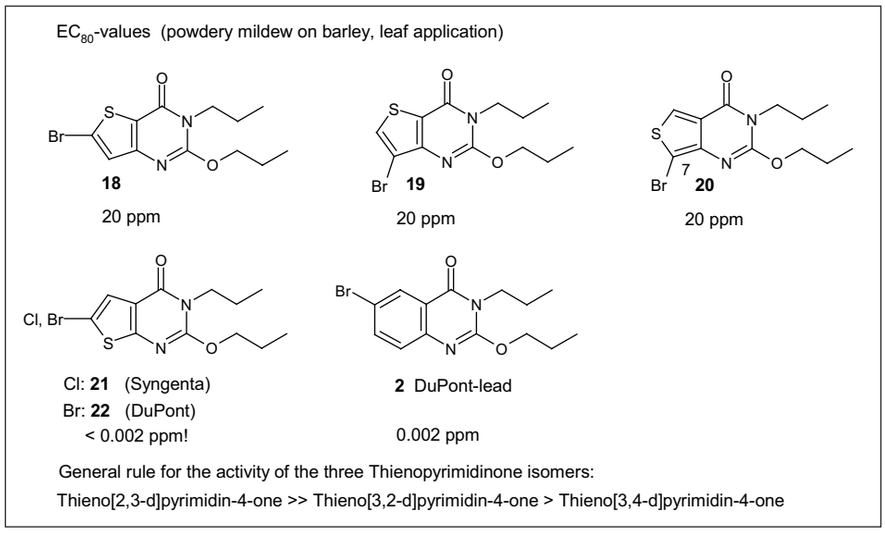


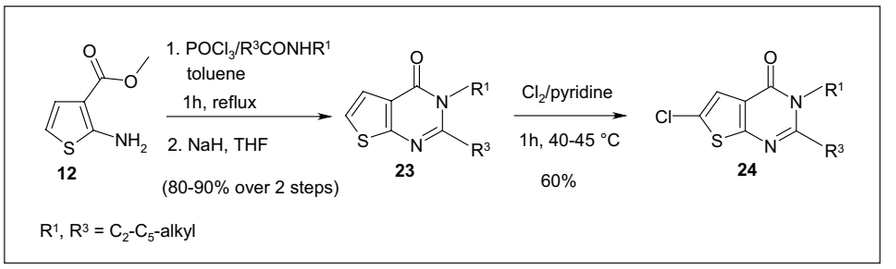
Fig. 3. Comparison of the biological activities of some isomeric thienopyrimidin-4-ones and quinazolin-4-one (**2**)

covered, but examples of 2,3-dialkylsubstituted thienopyrimidin-4-ones were not described [15]. A thorough check of the priority data of the individual 2,3-dialkylated thieno[2,3-d]pyrimidin-4-ones revealed that Syngenta this time had obtained the earliest date for this class of compounds, providing an independent proprietary situation. With the aim to broaden the biological spectrum of the quinazolin-4-ones and thienopyrimidin-4-ones, Syngenta still continued the research in this field. The next change in the basic molecular structure was the replacement of C=O by C=N-R, leading to compounds of the general formula **VII** (Fig. 4). The synthesis of this type of compound (2-alkoxy as well as 2-alkyl-substituted compounds) was described in one of our patent applications [16] and will not be discussed further in this review. Again the biological spectrum could not be broadened and this class of compounds turned out to be only active against powdery mildew diseases.

In our laboratories many other structures were prepared (mainly modifications of the pyrimidinone ring) including novel tricyclic structures (Fig. 4).

One of our promising approaches for a tricyclic molecular design was a 'bridging-approach' for the 2-alkoxy-3-alkyl-thieno[2,3-d]pyrimidin-4-ones, which leads to the 3,4-dihydro-2H-[1,3]oxazino[3,2-a] thieno[2,3-d]pyrimidinone class **XII**. The synthesis of two representatives (**29a** and **29b**) of the compound class **XII** is outlined in Scheme 4.

The starting material in our approach was the commercially available isopropenyl-methylketone, which could be transformed into the β-aminoketone **26** using a published procedure [19][20]. Reduction with $LiAlH_4$ in THF and reaction of the resulting β-amino-alcohol with the thienylisothiocyanate **13** gave a diasterisomeric mixture of the thiourea intermediate **27** in reasonable yields (50–55% over two steps). The following cyclization step could be performed by the use of one of our standard methods (NaH, THF) and subsequent methylation with MeI gave a diasteroisomeric mixture of thieno[2,3-d]pyrimidin-4-ones, which could be separated by flash-chromatography. The major diastereoisomer **28a** obtained in this way was treated with NaH in THF and the resulting 3,4-dihydro-2H-[1,3]oxazino[3,2-a] thieno[2,3-d]pyrimidinone was halogenated using the standard NCS or NBS procedure to give the final *cis*-isomers **29a** and **29b** in moderate to good yields. The corresponding *trans*-isomers of compounds **29a** and **29b** were also prepared using diastereoisomer **28b** instead of **28a** in the synthesis strategy out-



Scheme 3. Synthesis of chlorinated 2,3-dialkylsubstituted thieno[2,3-d]pyrimidin-4-ones [13]

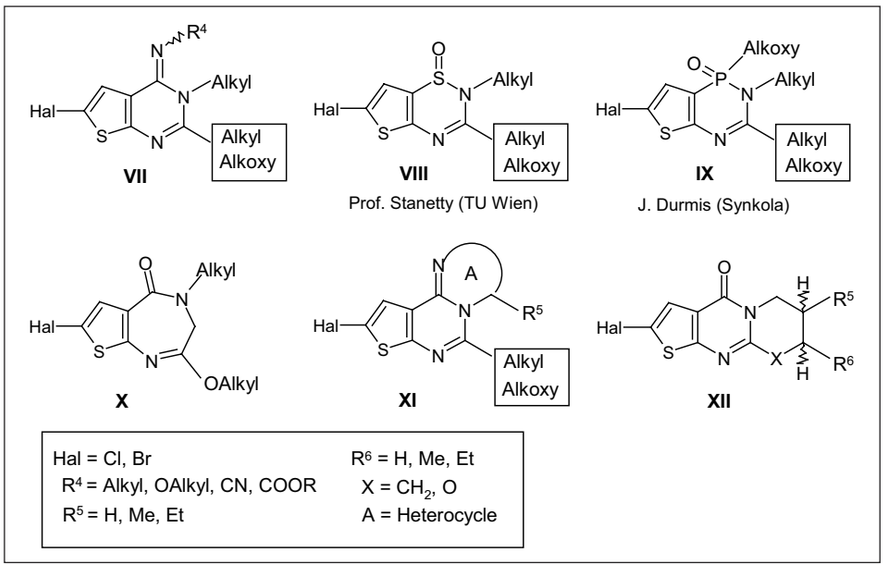
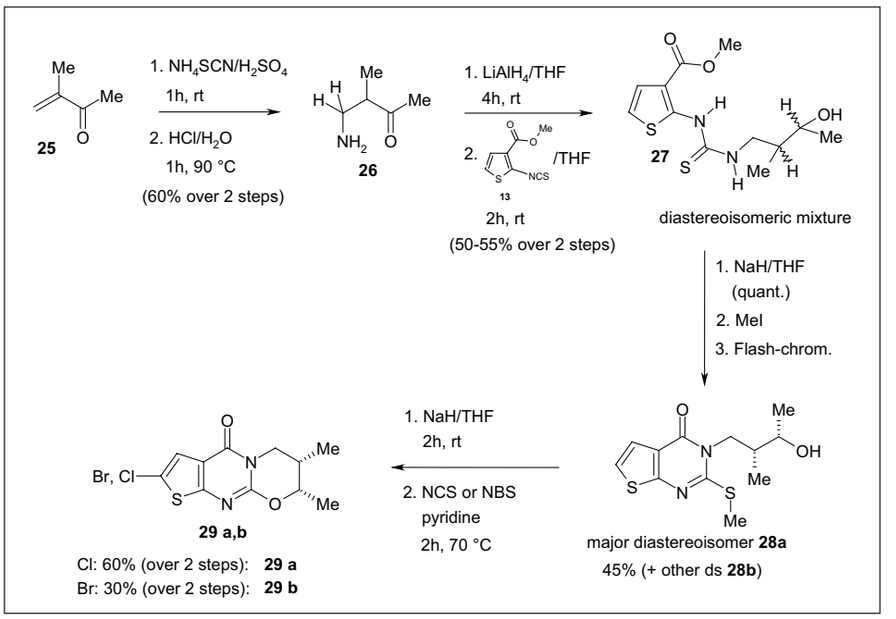


Fig. 4. Variations of the pyrimidinone ring performed by Syngenta (1997–1999) [17]

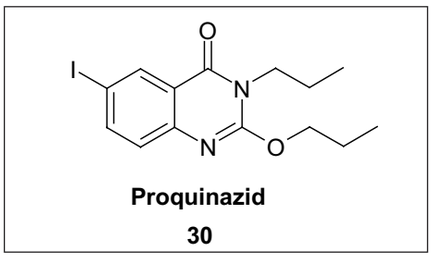


Scheme 4. Synthesis of some representatives of the tricyclic thieno[2,3-d]thienopyrimidinone class **XII** [18–20]

lined in Scheme 4. The *cis* as well as the *trans* isomers turned out to be biologically inactive. Unfortunately, all the approaches shown in Fig. 4, failed to lead to compounds possessing an increased level of biological activity or broader spectrum compared to the halosubstituted 2-alkoxy-3-alkylthieno[2,3-d]pyrimidin-4-one class.

Conclusions

Halosubstituted 2-alkoxy-3-alkylthieno[2,3-d]pyrimidine-4-ones turned out to be a useful source of highly active powdery mildewicides. Some promising approaches (alkyliso-thiocyanate- and an orthocarbonate route; see Scheme 2) for the synthesis of this class of compounds were presented. The best compounds of this class show biological performances comparable to DuPont's best quinazolinones, 6-bromo-2-propoxy-3-propylquinazolin-4-one (**2**) and 6-iodo-2-propoxy-3-propylquinazolin-4-one (**30**) (Fig. 5).



Proquinazid

30

Fig. 5. Structure of Proquinazid

The importance of the quinazolinone/thienopyrimidinone class was strongly corroborated by the publication of the common name **Proquinazid** for compound **30** in 2001, indicating that DuPont recognizes **Proquinazid** as a first development candidate in the quinazolinone field. However, the narrow biological spectrum of this compound (only powdery mildew activity) suggests that **Proquinazid** will most likely not be a stand-alone product, but may be more useful as a mixing partner for *e.g.* strobilurines and triazoles (anti-resistance strategy!).

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[1] Presented in part at the Fifth Conference on Iminium Salts, Stimpfach-Rechenberg (Germany), September 11–13, **2001.**
[2] G.A. Bullock (DuPont), US 3755582, **1973.**
[3] G.A. Bullock, P.J. Sheeran (DuPont), US 3867384, **1975.**
[4] P.T. Selby (DuPont), WO 93/23398, **1993.**
[5] Former Ciba AG, since 1997 Novartis and now Syngenta Crop Protection AG.
[6] J.F. Bereznak, T.P. Selby, C.G. Sternberg (DuPont),WO 94/26722, **1994.**
[7] H. Walter (Novartis AG), WO 97/33890, **1997.**
[8] J.F. Bereznak, E.A. Marshall, C.G. Sternberg, J.A. Sternberg, King-Mo Sun (DuPont), WO 97/48684, **1997.**
[9] S. Gronowitz, J. Fortea-Laguna, S. Ross, B. Sjoberg, N.E. Srjernstrom, *Acta Pharm. Suecica,* **1968,** *5,* 563.
[10] H. Walter (Novartis AG), WO 99/67202, **1999.**
[11] J.F. Bereznak, Z.-Y. Chang, C.G. Gross (DuPont), WO 97/02262, **1997.**
[12] H. Walter (Novartis AG), WO 99/11631, **1999.**
[13] H. Walter (Novartis AG), WO 99/14202, **1999.**
[14] R.F. Bellina, J.F. Bereznak, J.R. Christensen, Z.-Y. Chang, M.M. Fawzi, E.A. Marshall, W.K. Moberg, C.G. Sternberg, M.P. Walker, W.T. Zimmermann (DuPont), WO 98/26664, **1998.**
[15] J.F. Atherall, T.L. Hough, S.D. Lindell, M.J. O'Mahony, E.A. Saville-Stones (AgrEvo), WO 98/49899, **1998.**
[16] H. Walter (Novartis AG), WO 00/31082, **2000.**
[17] J. Durmis, H. Walter, P. Stanetty, unpublished results **1997–1999.**
[18] H. Walter, unpublished results.
[19] R.A. Mathes, F.D. Stewart, F.R. Swedish, *J. Amer. Chem. Soc.* **1948,** *70,* 1452.
[20] I.P. Boiko, Y.F. Malina, O.I. Zhuk, Y.Y. Samitov, B.V. Unkovskii, *Zh. Org. Khim.* **1976,** *12,* 80.