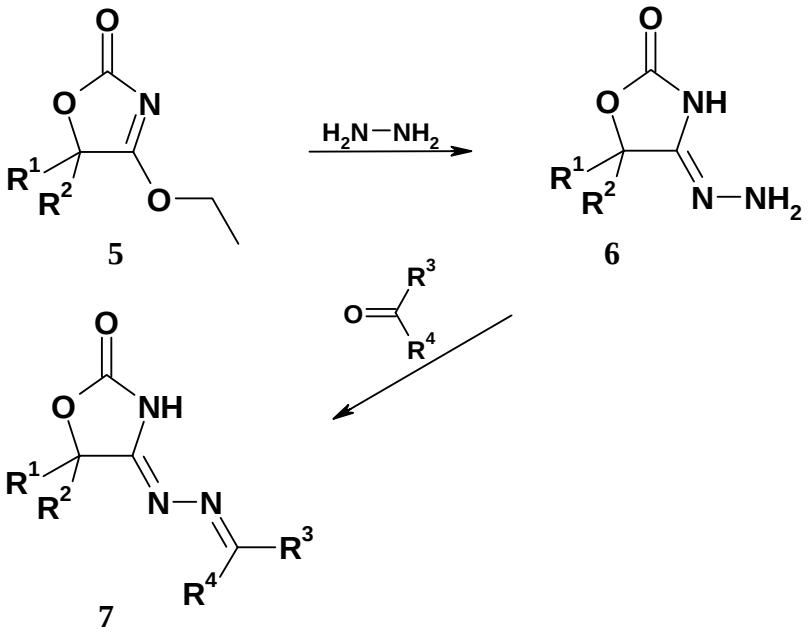
9 Summary

The objective of this work was the synthesis, analysis and biological evaluations of 4-hydrazono-1,3-oxazolidin-2-ones, 5-ethoxy-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-ones and 1*H*,7*H*-furo[3,4-d]-pyrimidin-2,4,5-triones.

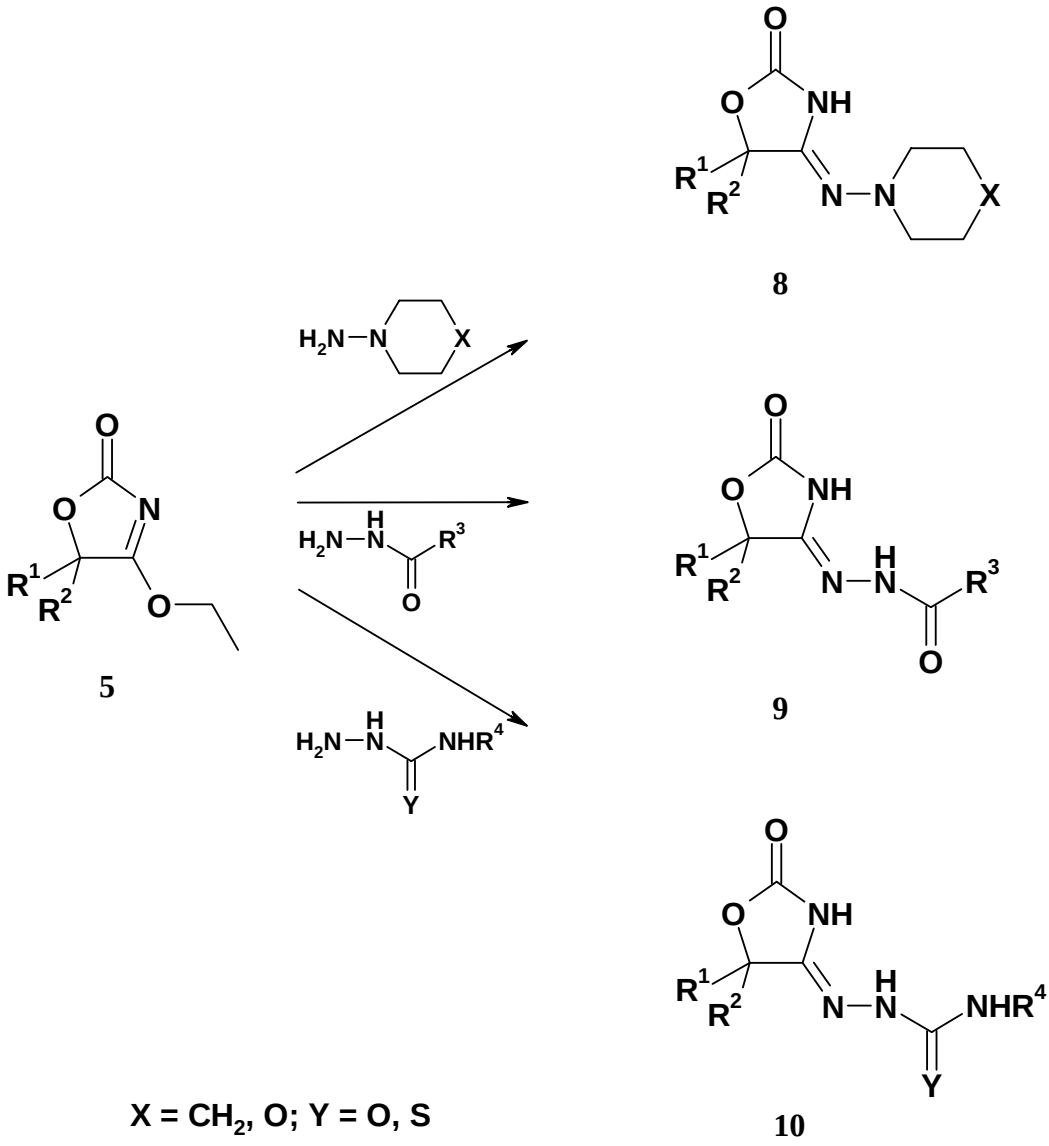
In the context of structure variations a series of 4-hydrazono-1,3-oxazolidin-2-ones were prepared and tested for antimalarial activity. Hereby a new synthetic pathway, using the 4-ethoxy-1,3-oxazol-2(5*H*)-ones **5** as intermediates, was established:
α-hydroxy-carbonitriles and ethanol / $HCl_{(g)}$ gave in a *Pinner*-reaction the α-hydroxy-ethylimidate-hydrochlorides. Cyclisation of the correspondent bases with 1,1´-carbonyldiimidazole (CDI) lead to the 4-ethoxy-1,3-oxazol-2(5*H*)-ones **5**.
Hydrazinolysis of **5** followed by condensation with various ketones gave the final compounds, differing in the alkylidene-substituents (**scheme 1**). Derivatives with methyl-, aryl- as well as cyclohexyl- as an alkyl-, alkyl-substitution pattern were synthesized. Crystallographic investigations prove the (*Z*)-configuration of **7**.

scheme 1:



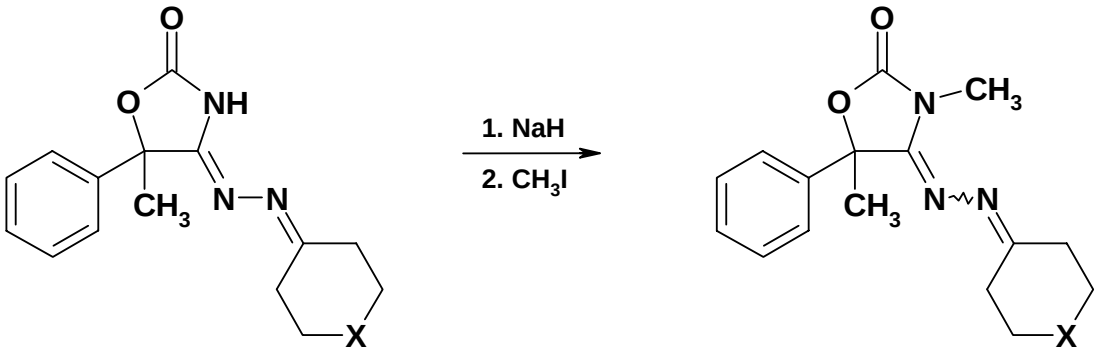
Different hydrazine-derivatives were successfully used to convert **5** into the 4-morpholine-4-ylimino-**8**, 4-acylhydrazono-**9** and 4-(thio)semicarbazono-derivatives **10** as a modification of the 4-positioned azine-structure.

scheme 2:



N-3 of the pharmaceutical lead **7** was methylated with iodomethane. The compound **11** was obtained as a mixture of the (*E*)- and (*Z*)-isomer. Dissolved in DMSO, complete transformation to the (*Z*)-isomer was discovered.

scheme 3:



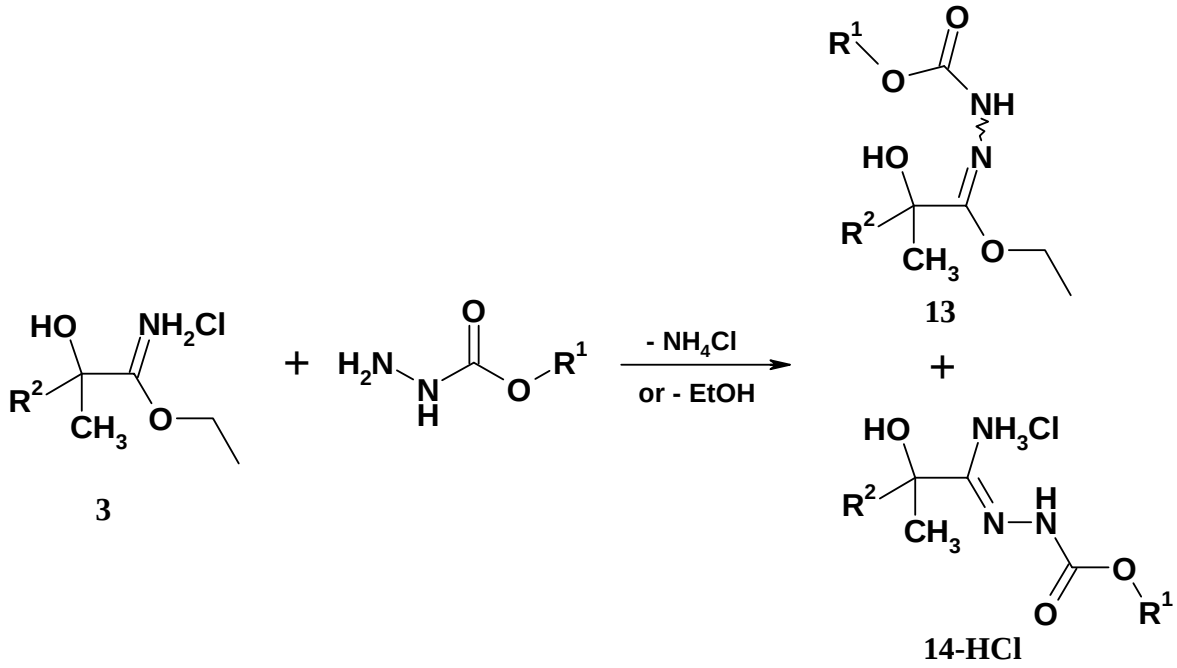
7 **11**

X = CH_2, O

Variations of the antifungal active 5-alkoxy-3-phenyl-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-one resulted in the 5-ethoxy-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-ones **15** that were also accessable from the α-hydroxy-ethylimidate-hydrochlorides.

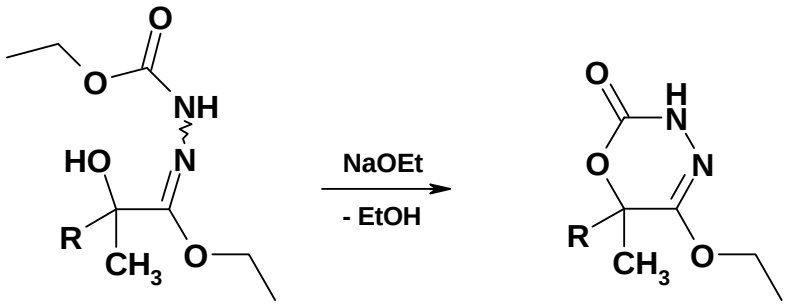
Reaction of the α-hydroxy-ethylimidate-hydrochlorides **3** with carbazates yielded the (*E/Z*) α-hydroxycarbazon-ester **13**, whereas the formation of the *E*-isomer was preferred. As a side reaction α-hydroxy-*N′*-ethoxycarbonylamidrazone **14** was formed by loss of ethanol instead of ammoniumchloride.

scheme 4:



Heating of the (*E*/*Z*) mixture of **13** in ethanol with sodium ethoxide afforded cyclisation in a very high yield. Thus isomerisation at high temperatures as described in literature could be confirmed.

scheme 5:



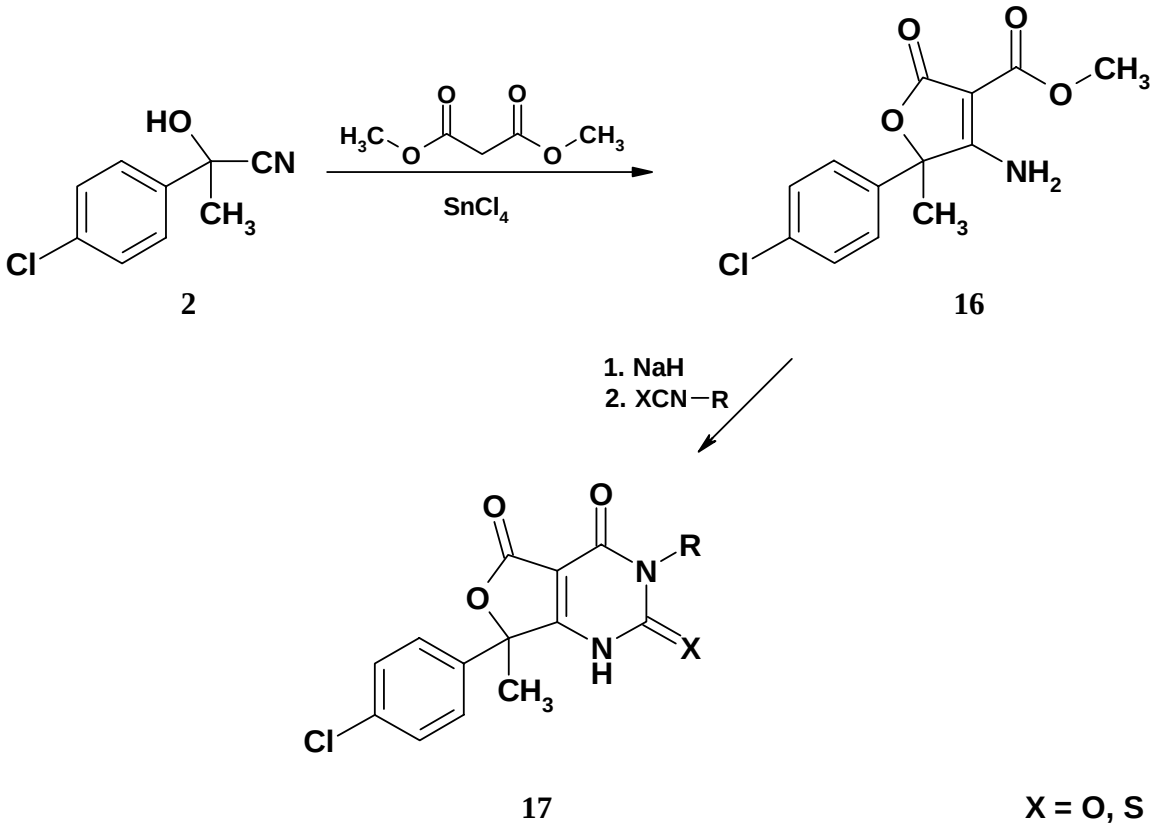
13 **15**

On addition of the hydrazine-carbonyl-component and subsequent intramolecular ring closure, an elegant pathway for synthesizing 5-ethoxy-3,6-dihydro-2*H*-1,3,4-oxadiazin-2-ones unsubstituted on the *N*-3 was developed.

Starting from α-hydroxy-carbonitriles the bicyclic system 1*H*,7*H*-furo[3,4-d]-pyrimidin-2,4,5-trione **17** was built up in a two-step reaction.

Adding dimethylmalonate to α-hydroxy-carbonitrile and spontaneous ring closure by means of tin(IV)-chloride as a Lewis acid leads to the methyl-4-amino-2-oxo-2,5-dihydrofuran-3-carboxylate **16**. Deprotonating of **16** and the addition of iso(thio)cyanates is followed again by spontaneous intramolecular cyclisation.

scheme 6:



2 **16**

17 **X = O, S**

The synthetic and analytical chapters are followed by the methods of the biological evaluations and the discussion of their results.

Evaluation of the antimalarial activity of 4-hydrazono-1,3-oxazolidin-2-ones **7-11** resulted in the following structure-activity-relationships:

- The 4-positioned azine structure is essential for the antimalarial effect.
- Variation of the alkylidene part did not essentially effect the activity.
- Methylation of *N*-3 goes along with an enormous diminution of the effect.

- Elimination of the carbonyl-group in 2-position is also associated with an effect diminishment.
- Aryl- alkyl-substitution in 5-position is predominant to alkyl- alkyl-substitution.

Selected substances were evaluated for antibacterial properties. Herein, compound **7m** revealed inhibition of the growth of *S. aureus* and *E. faecalis*, each with a MIC of 64 μg/ml.

Tests for fungicide, insecticide, acaricide and herbicide activity showed little or no effects.

None of the substances screened for antituberculosis activity showed any effect on *Mycobacterium tuberculosis*.