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Synthesis of tetra-substituted pyrazoles

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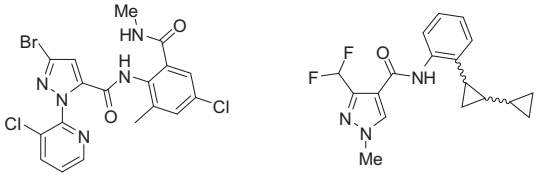
ABSTRACT

A set of highly substituted pyrazoles bearing different functional groups on the pyrazole core was developed. Employing a suitable protecting group strategy we could regioselectively introduce various substituents in position 1, 3 and 4 of the pyrazole. This enabled the synthesis of various derivatives of a pyrazole–biscarboxamide with insecticidal activity. During the optimization process we focused on the precise exchange of carboxamide as well as other functional groups based on the concept of bioisosterism.

1. Introduction

Since insects, fungi and other threats for agriculture become resistant against common pesticides there is an urgent need for novel agrochemicals ensuring the maintenance of world's population with food. Using the concept of bioisosterism—that derivatives with close geometric and electronic properties should show similar effects in biological systems—the optimization of lead structures towards pesticidal agents focuses on physico–chemical properties and metabolic stability.[1–3] Amide bonds are a prevalent motif in natural products as well as other biologically active compounds. Accordingly it's not surprising that several agrochemicals include amides, e.g., the pyrazoles Rynaxypyr (**1**, insecticide) or Sedaxane (**2**, fungicide) Fig. 1.[4] Although amides are easily accessible via simple chemical reactions they can be unstable towards hydrolysis in vivo. For this reason numerous possibilities for the bioisosteric replacement of amides with amide bond mimics have been investigated.[5,6] Due to the requirement for absorption of pesticides into plants, water solubility of the derivatives plays an important role in the optimization process.[7]

Herein we present synthetic studies towards different bioisosters based on the insecticidal pyrazolebiscarboxamide **3** (Fig. 2).[8] This lead structure already has a moderately strong insecticidal effect on chewing insects (e.g., *spodoptera*), but a low solubility in water (1.2 mg/L), which might be the reason for the limited biological activity.



Rynaxypyr (**1**)
insecticide, *DuPont*

Sedaxane (**2**)
fungicide, *Syngenta*

Fig. 1. Modern pesticides with pyrazole core.

When optimizing this insecticide we focused on bioisosteric replacement of the amide-bonds because this might enhance metabolic stability or activity. Amide bond mimics, as well as the introduction of heterocyclic substituents, affect intra- and intermolecular H-bonds the derivatives can form, which might have a positive effect on water solubility.

2. Results and discussion

For mimicking the amide-bonds we targeted the retro-amide-**4**, urea- **5** and ester-moiety **6**, as well as amine **7** and oxomethylene **8**, which are shown exemplarily at position four of the pyrazole (Fig. 3, top row). Beside those modifications we regarded pyridine **9** and the 1,3-dioxanes **10** and **11** as suitable bioisosteres bearing a heterocyclic moiety (Fig. 3, bottom row).

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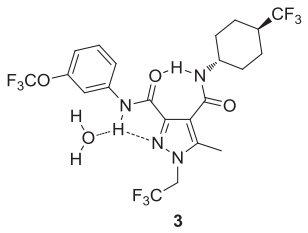


Fig. 2. Insecticidal lead structure **3** (H-bonding network derived from the X-ray crystal structure).

corresponding esters **20** and **23** can act as precursors for the synthesis of several bioisosteres of the lead structure.

2.2. Amide-mimics–esters

We were able to convert carboxylic acid **24** in moderate yield to the first target structure, ester **26**, using the same protocol as per amide synthesis (Scheme 3). Aromatic esters are generally not that stable towards hydrolysis, which may be one reason for the moderate yield. Furthermore phenols show a rather low nucleophilicity.

Employing the same pathway to the alternate ester **6** was less successful and did not lead to the desired product in reasonable

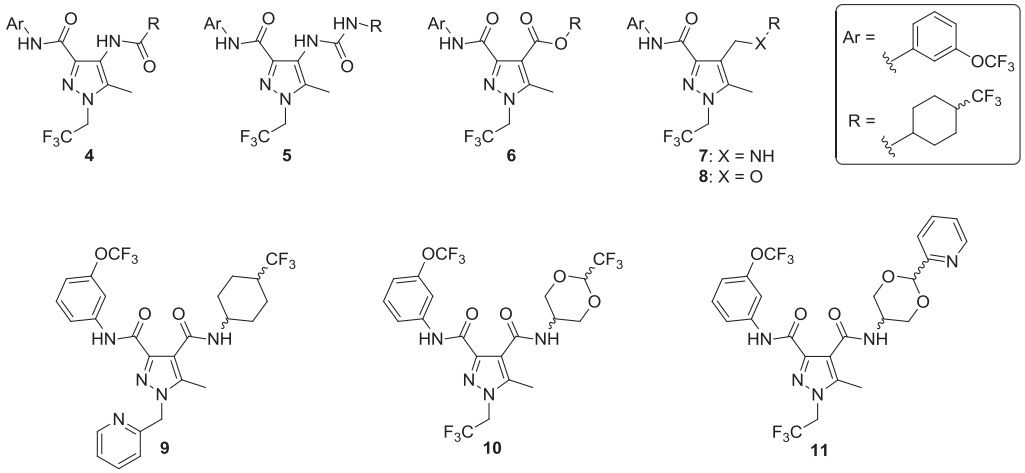


Fig. 3. Target structures, modified at position four of the pyrazole.

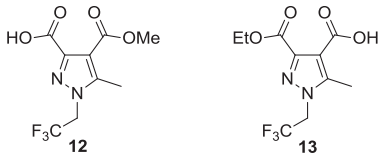


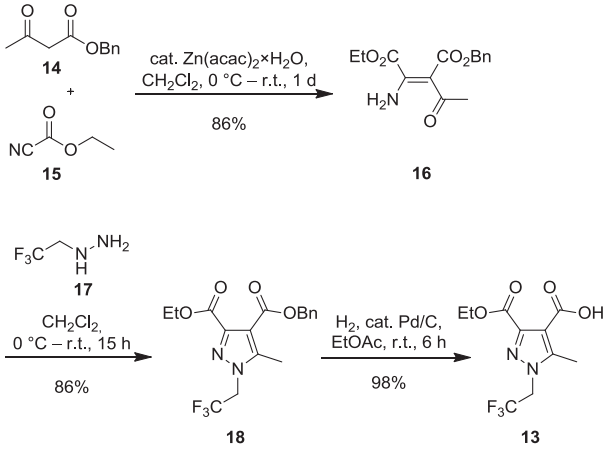
Fig. 4. Orthogonally protected pyrazolebiscarboxylic acids **12** and **13**.

2.1. Synthesis of precursors

Regioselective syntheses of tetra-substituted pyrazoles are subject of ongoing research, but mainly deal with cores bearing alkyl and/or aryl substituents next to at most one functional group.[9–11] Thus synthetic routes for all amide-mimics and 1,3-dioxanes have been designed, which use functional group transfer as a main tool and are based on common precursors—the contrarily protected pyrazolebiscarboxylic acids **12** and **13** (Fig. 4).

While methyl carboxylate **12** was provided by *Bayer CropScience* (BCS), ethyl carboxylate **13** was synthesized in very good yields using a method developed by Veronese et al. for the synthesis of pyrazolebiscarboxylates (Scheme 1).[12] This synthesis proceeded regioselectively as only one isomer, pyrazole-3,4-dicarboxylate **18**, occurred. Its structure was confirmed by X-ray crystallography of the free carboxylic acid **13** (Fig. 5).

The pyrazolecarboxylates, **12** and **13**, were reacted with 3-(trifluoromethoxy)aniline **19** and 4-(trifluoromethyl)cyclohexanamine **22**, respectively, using *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC) as coupling reagent. After saponification free carboxylic acids **21** and **24** were obtained in excellent yields over two steps (Scheme 2, for an X-ray structure of acid **21** see Supplementary data). These acids and the time (Scheme 4), suggesting that alcohol **27** is only poorly nucleophilic. Using EDC with 4-(*N*,*N*-dimethylamino)pyridine (DMAP) as additive in dichloromethane lead primarily to a bicyclic imide **28** through intramolecular ring closure.[13] Presumably deprotonation of the amide–nitrogen occurs, which is then nucleophilic enough to attack the activated carboxylic acid. Due to the formation of the by-product **28** we decided to use the *Mitsunobu*-reaction for the formation of ester **6**.[14] It does not matter that inversion of the alcohol occurs because alcohol **27** was used as a mixture of isomers and we are interested in both diastereomers, i.e., *cis* and *trans* **6**. Unfortunately the yield was also low for this reaction and neither elongated reaction time nor higher temperature (40 °C) improved the efficiency of this reaction.



Scheme 1. Synthesis of ethyl pyrazolecarboxylate **13**.

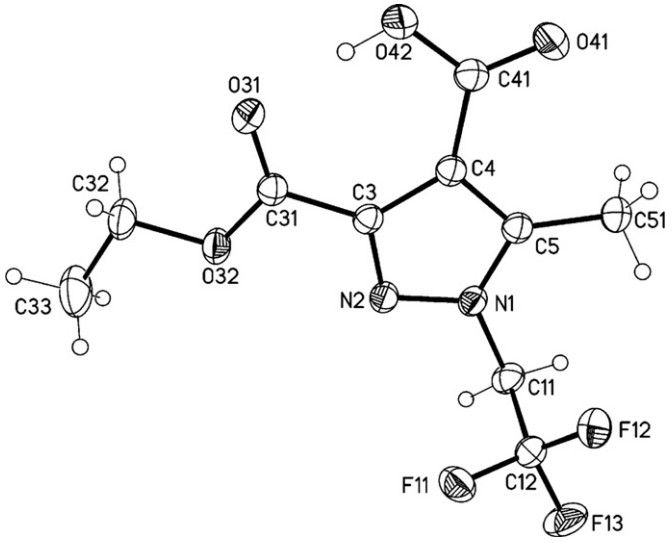
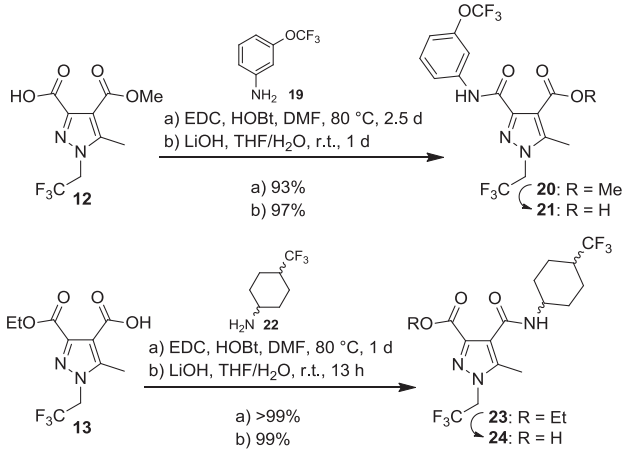
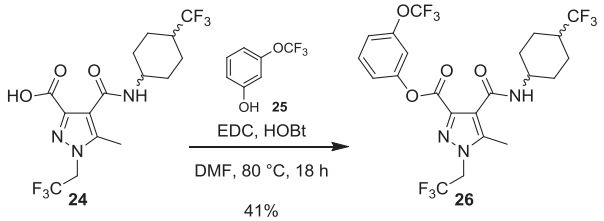


Fig. 5. X-ray crystal structure of carboxylic acid **13**. Displacement parameters are drawn at 50% probability level.



Scheme 2. Synthesis of precursors **20**, **21**, **23** and **24**.

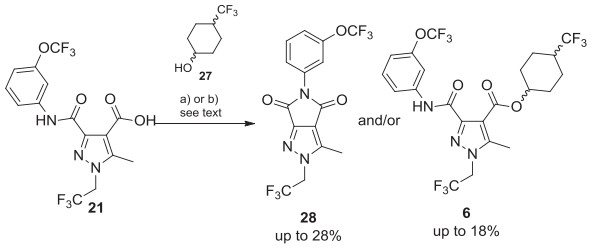


Scheme 3. Synthesis of ester **26**.

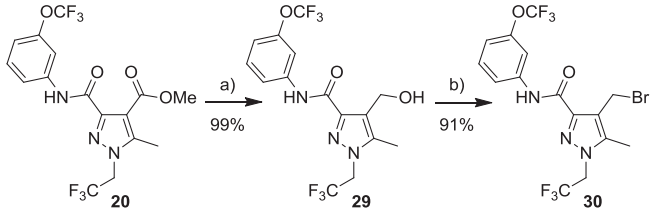
2.3. Amide-mimics–amines and ethers

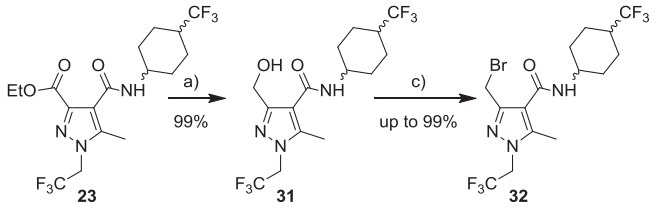
To access more bioisosters of the lead structure we performed a functional group conversion on precursors **20** and **23** with the goal of introducing a leaving group into the pyrazolic system (Scheme 5). To this end we reduced both carboxylates **20** and **23** to alcohols **29** and **31** in quantitative yield, followed by bromination.[15]

These bromides **30** and **32** should serve as starting material for the synthesis of both amines and ethers in one-step. As the synthesis of amine **7** proceeded in a reasonable yield we applied similar conditions to the synthesis of ether **8**, as shown in Scheme 6.

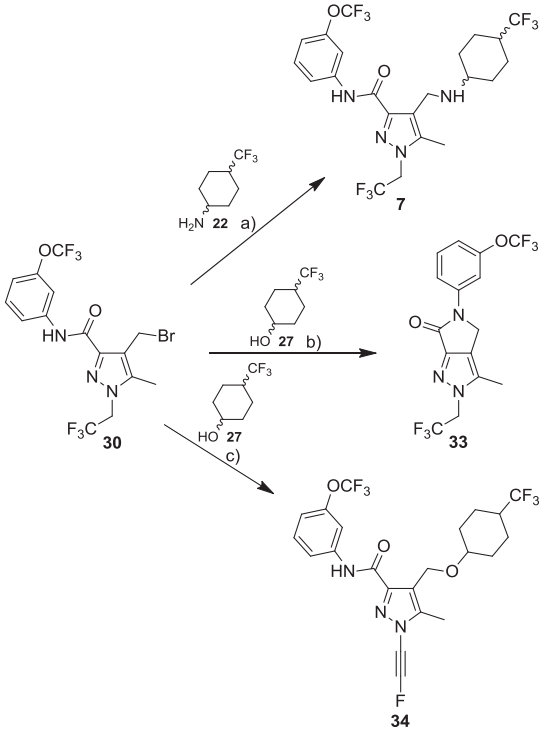


Scheme 4. Synthesis of ester **6** and cyclic by-product **28**. Reagents and conditions: (a) EDC, cat. DMAP, CH_2Cl_2, rt, 3d; (b) PPh_3, DIAD, THF, rt, 20 h to 3 days.





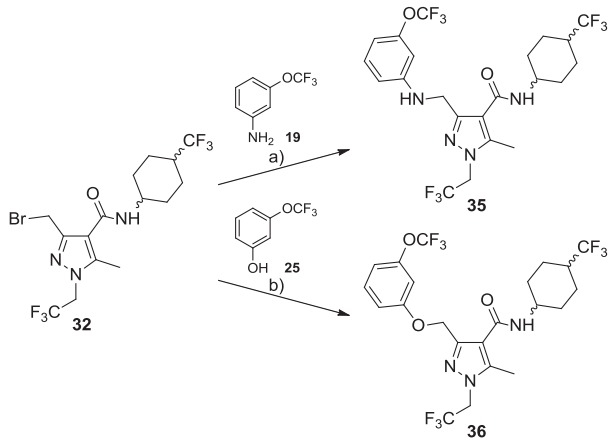
Scheme 5. Synthesis of bromides **30** and **32**. Reagents and conditions: (a) $NaBH_4$, MeOH, rt, 1d; (b) CBr_4, PPh_3, MeCN, 65 °C, 14 h; (c) PBr_3, pyridine, Et_2O, 0 °C rt, 5–15 h.



Scheme 6. Conversion of bromide **30** with different nucleophiles. Reagents and conditions: (a) K_2CO_3, DMF, 90 °C, 1.5 h, 65%; (b) Cs_2CO_3, DMF, 90 °C, 1.5 h, 70%; (c) NaH, DMF, rt −80 °C, 30 min, 5%.

Again the amide functionality showed a high nucleophilicity, because intramolecular cyclization was faster than addition of moderately nucleophilic alcohol **27** and yielded the bicyclic system **33** in good yield. Changing the base to potassium carbonate also led to the intramolecular addition albeit in lower yield (33%). The use of the stronger base sodium hydride led to a coupled product **34** in a small amount and in addition caused defluorination at the trifluoroethyl-unit. Due to low yield only one isomer (*cis* or *trans*) of compound **34** could be isolated and identified, though a mixture of isomers was employed for alcohol **27**.

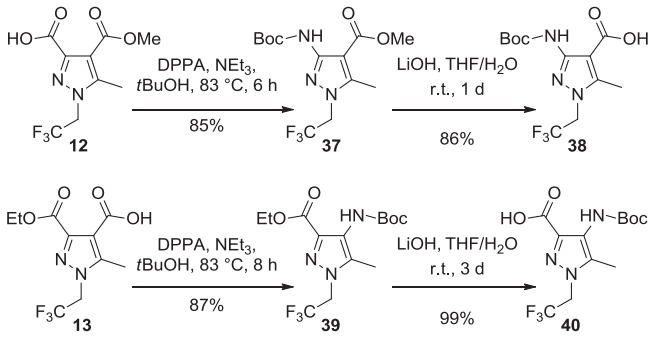
The second bromide **32** could easily be employed for the synthesis of amine **35** and ether **36** without degradation or other side reactions (Scheme 7). To facilitate substitution with phenol **25** we added tetrabutylammonium iodide to the reaction mixture.



Scheme 7. Synthesis of amine **35** and ether **36**. Reagents and conditions: (a) K_2CO_3, DMF, 90 °C, 5 h–17 h, up to 46%; (b) K_2CO_3, Bu_4NI, DMF, 90 °C, 17 h to days, up to 77%.

2.4. Amide-mimics–retroamides

For the synthesis of retroamides **4** and **43** nitrogen substituted pyrazoles were needed. Those could easily be obtained from carboxylic acids **12** and **13** through *Curtius* rearrangement.[16] After saponification both Boc-protected amino carboxylic acids **38** and **40** were synthesized in good yields and readily crystallized (see Scheme 8, X-ray crystal structures shown in Fig. 6).



Scheme 8. Synthesis of amino carboxylic acids **38** and **40**.

Amide formation with carboxylic acid **38** led to amide **41**, which could also be crystallized (Fig. 6). The X-ray crystal structure of amide **41** (pure *trans* isomer crystallized) proofed the configuration of the cyclohexane moiety to be correct, which was determined by comparison of ^{1}H NMR spectra with the data for the lead compound **3** before. Thus we continued to elucidate *cis* or *trans* configurations via NMR analyses.

As it is shown in Scheme 9 further steps for the synthesis of both retroamides proceeded in good to excellent yields. We were able to get an X-ray of the *cis* isomer of target structure **4**, which helped us once more to determine the configuration of the cyclohexyl-substituents. The solid state structure of this bisamide is surprising since both carbonyl groups point in a similar direction (Fig. 7). Importantly, there are no intramolecular hydrogen bonds between the amide groups, thus we assume the structure to be less rigid than is the case for the lead structure **3**, which we hoped would enhance water solubility.

2.5. Amide-mimics–urea derivatives

Besides retroamides urea derivatives were accessible via *Curtius* rearrangement too.[16] Again starting from carboxylic acids **12** and **13** the significant moiety was introduced within one step. Whereas urea formation at position 3 of the pyrazole occurred at room temperature we observed amide synthesis at position 4 using the same reaction conditions. Therefore we heated the reaction mixture to 90 °C before adding the amine to facilitate rearrangement of the azide to the intermediate isocyanate (Scheme 10).

Saponification of ester **46** led directly to the bicyclic pyrimidinedione **49**. The free acid **48** was only obtained as a side product. Deprotection in acidic media or under nucleophilic conditions using lithium iodide did not lead to free acid **48** either (Scheme 11). Therefore we decided to convert ester **46** directly into an amide using a protocol described by *Weinreb*.[17] Trimethylaluminium allows the one step conversion of esters into amides through activation of the corresponding amine in situ. Thus we were able to synthesize urea **50** in low yield, but unreacted ester **46** could be recovered after column chromatography.

A standard protocol using EDC was used for the synthesis of the other urea derivative **5**. Employing saponification of ester **47** followed by amide-synthesis we were able to synthesize urea **5** in medium yield over two steps (Scheme 12).

2.6. Other bioisosteres

In order to improve the water solubility of the lead structure, we introduced a pyridine-moiety as a replacement for the trifluoromethyl group. Since this position is easily accessible we derivatized the functional group on the central pyrazole core. As was the case for the synthesis of trifluoroethyl substituted pyrazole **18** we obtained only one regioisomer **53** in the condensation of β-enaminoketone **16** with hydrazine **52** (Scheme 13).[12] Further deprotection and coupling steps provided pyrazolebiscarboxamide **9** in good to excellent yields (48% overall, 5 steps).

Another approach to enhance water solubility is the introduction of further heteroatoms. Thus we regarded acetals **10** and **11** as interesting targets, whose syntheses are based on diol **58**, which can be obtained in good yield from acid **21** (Scheme 14). There is very little literature available about the synthesis of acetals derived from trifluoroacetaldehyde and we initially followed a route via activation of the diol as described by *Smithers*.[18] With tosylchloride we did not achieve monotosylation of the diol, and instead the bicyclic product **59** was isolated (Scheme 14).

Since the linear route did not succeed, we examined a building block approach with protected serinol **60** (Scheme 15).[18,19] It was possible to cyclize activated diol **61** with in situ generated fluoral **63**, but the products obtained were supposed to be oxazolidines **65**, not acetals **64**, as determined by NMR spectroscopy. It appears that the reaction is not reproducible and not suitable for the synthesis of those oxazolidines or acetals, such as **64**.

Other approaches for the synthesis of acetal **64** employing the ethyl hemiacetal of trifluoroacetaldehyde, which is easier to handle,

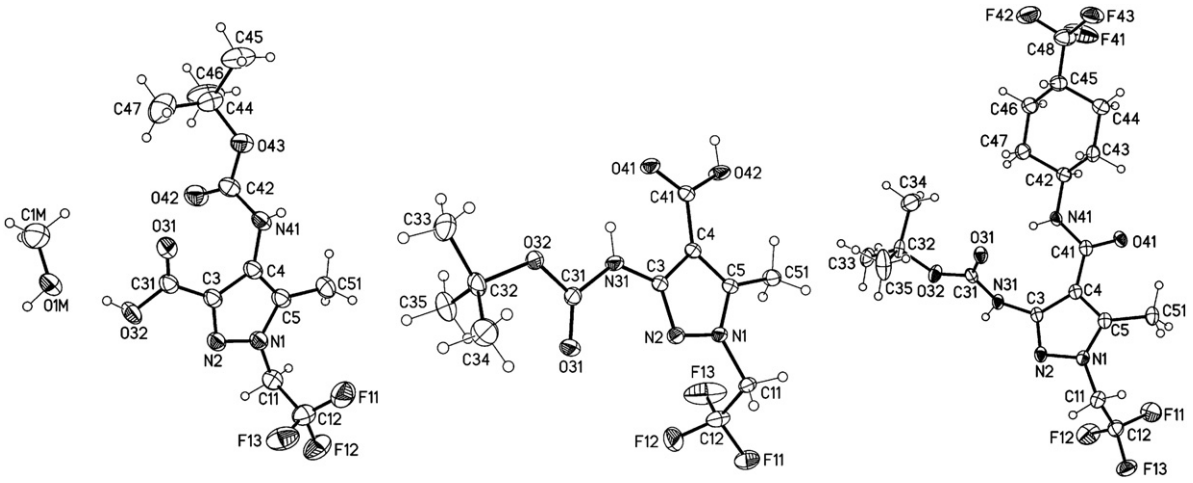
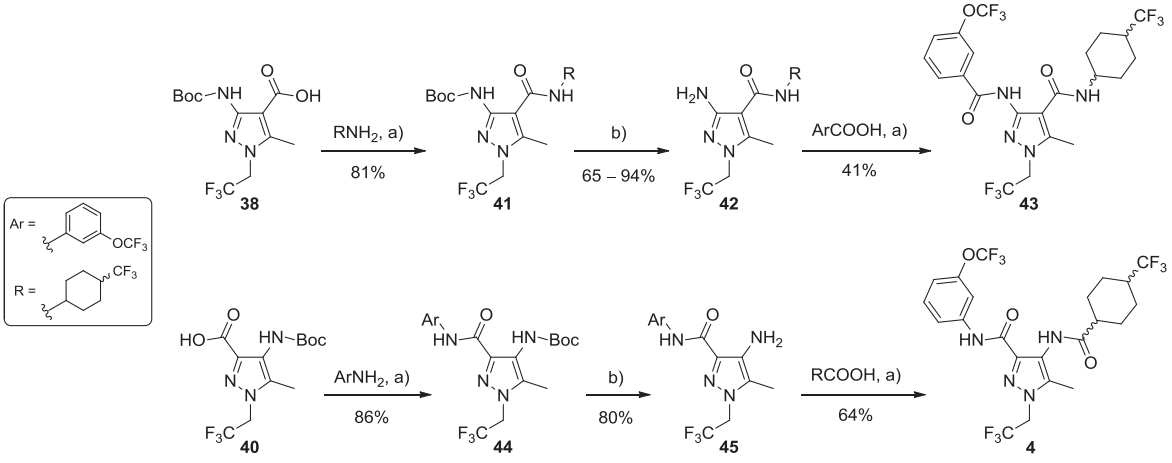


Fig. 6. X-ray structure of carboxylic acids **40** (left) and **38** (middle) as well as amide **41** (right). Displacement parameters are drawn at 50% probability level.



Scheme 9. Synthesis of retroamides **4** and **43**. Reagents and conditions: (a) EDC, HOBt, DMF, 80 °C, 7 h to 3 days; (b) TFA, H_2O, CH_2Cl_2, rt, 20–50 min.

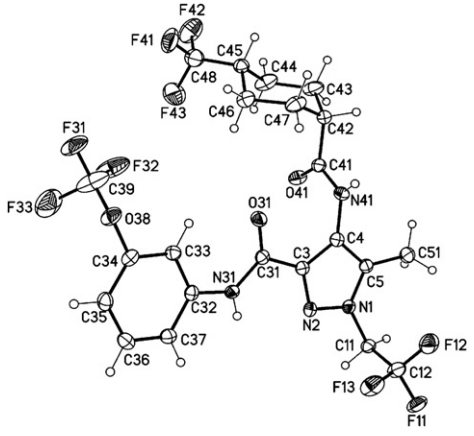
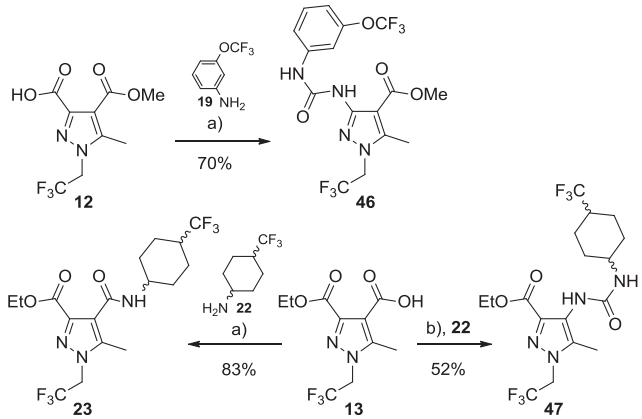
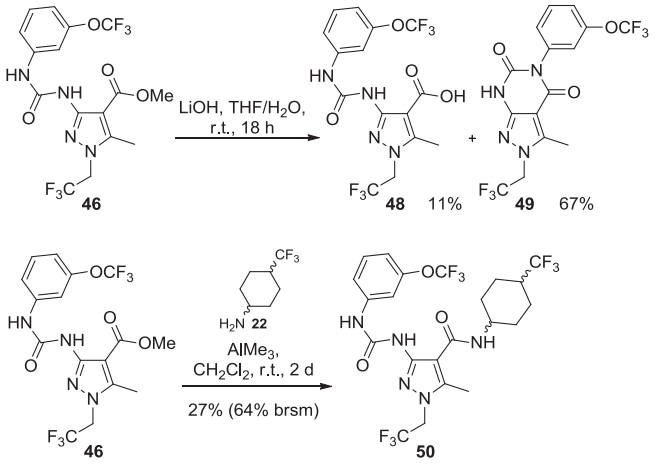


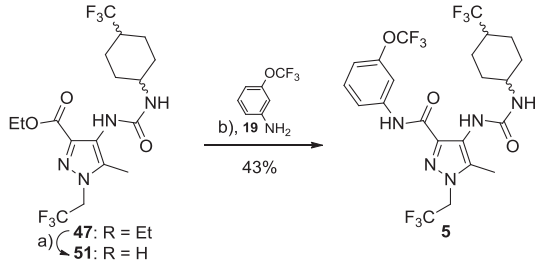
Fig. 7. Solid state structure of retroamide **4**. Displacement parameters are drawn at 50% probability level, only the major part of the disordered trifluoroethyl group is shown.



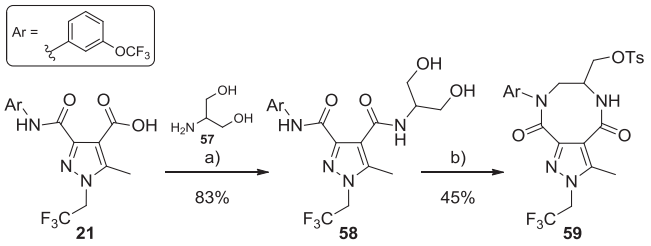
Scheme 10. *Curtius* rearrangement towards ureas **46** and **47**. Reagents and conditions: (a) NEt_3, DPPA, DMF, 0 °C to rt, 3–18 h; (b) NEt_3, DPPA, DMF, 90 °C, 3 h, then **22**, 0 °C to rt, 2.5 h.



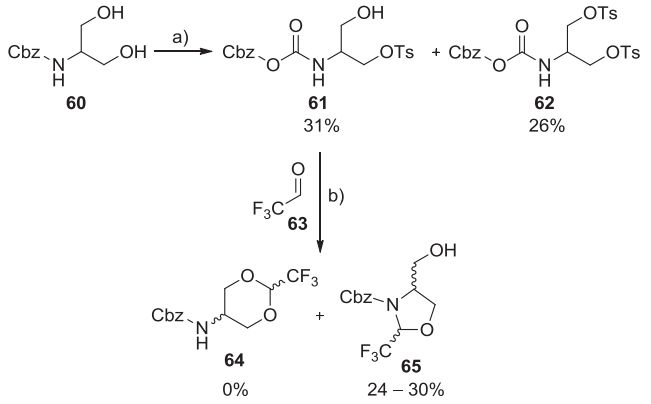
Scheme 11. Synthesis of urea **50**.



Scheme 12. Synthesis of urea **5**. Reagents and conditions: (a) LiOH, THF/H_2O, rt, 21 h, 99%; (b) EDC, HOBt, DMF, 80 °C, 1d.



Scheme 14. Isolation of a bicyclic product on the route to acetal **10**. Reagents and conditions: (a) EDC, HOBt, DMF, 80 °C, 2.5d; (b) *p*TsCl, NEt_3, CH_2Cl_2, 0 °C rt, 3d.



Scheme 15. Synthesis of trifluoromethyl substituted oxazolidine **65**. Reagents and conditions: (a) *p*TsCl, NEt_3, CH_2Cl_2, 0 °C to rt, 1d; (b) in situ generated **63**, THF, −78 °C to rt, 4 h, then K_2CO_3, 55 °C, 15 h.

under various conditions did not succeed. Nor did the conversion of this hemiacetal into its tosylate give any advantage.[20,21]

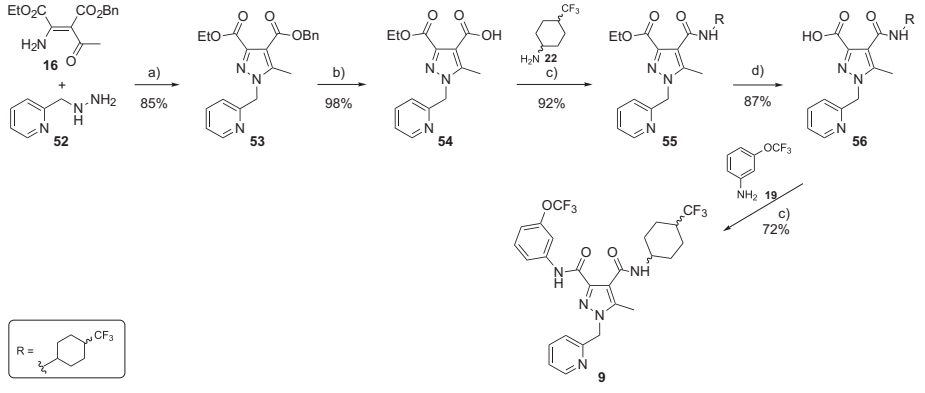
Since the synthesis of acetal **10** had failed, we decided to introduce a dioxane and pyridine moiety simultaneously to give acetal **11**. We recently reported the synthesis for 5-amino-1,3-dioxane **66** and for this reason we decided to compare the linear approach with a building block strategy for the synthesis of acetal **11** (Scheme 16).[22]

The building block strategy using **66** is feasible, but the overall yield starting from acid **21** and serinol **57** is higher for the linear route (32% vs 27%). Furthermore only two steps instead of four are necessary in this pathway, since no building block has to be synthesized beforehand.

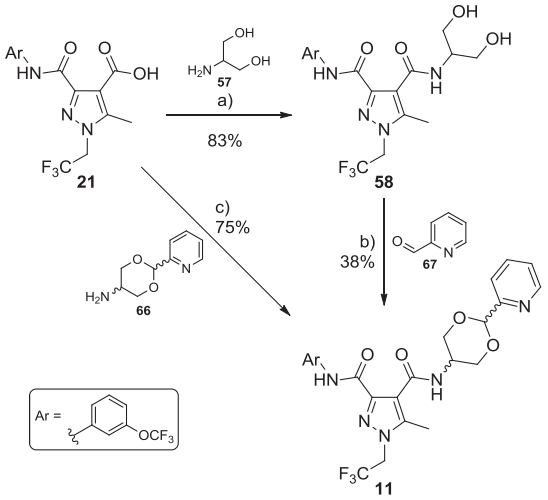
Overall we were able to synthesize nine amide bond-mimics of the lead structure as well as two isosteres with a pyridine moiety. These and all precursors and side products are currently under investigation for their biological activity.

3. Conclusions

In the present study the design and synthesis of highly substituted pyrazoles is reported. Central amide bonds of an insecticidal lead structure were converted into a retroamide-, urea- and ester-moiety, as well as an amine- and oxomethylene-group, based on the concept of bioisosterism. Furthermore pyridine substituents were introduced. Due to the high nucleophilicity of the



Scheme 13. Synthesis of pyridinomethylpyrazole **9**. Reagents and conditions: (a) $ClCH_2CH_2Cl$, 0 °C to rt, 15 h; (b) H_2, Pd/C, EtOAc, rt, 21 h; (c) EDC, HOBt, DMF, 70 °C, 3–4 d; (d) LiOH, THF/H_2O, rt, 1d.



Scheme 16. Synthesis of pyridine acetal **11**. Reagents and conditions: (a) EDC, HOBt, DMF, 80 °C, 2.5d; (b) NBS, $MgSO_4$, toluene, 130 °C, 2d; (c) EDC, HOBt, DMF, 80 °C 15 h.

aromatic amide, interesting bicyclic products with 5-, 6- and 8-membered rings were also obtained and are currently being examined for their biological activity.

4. Experimental section

Supplementary data: Experimental details and spectroscopic data of all new compounds and X-ray crystal structure data of compounds **4** (CCDC-813080), **13** (CCDC-813081), **21** (CCDC-813082), **38** (CCDC-813083), **40** (CCDC-813084) and **41** (CCDC-813085).

Acknowledgements

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