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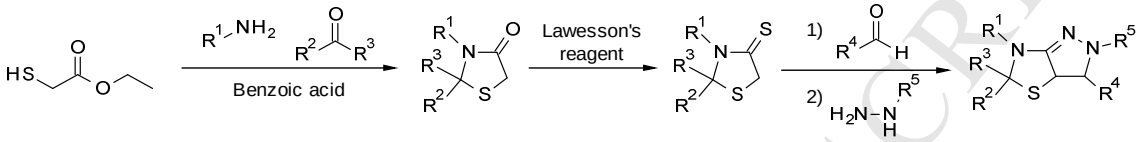

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1. Introduction

Approximately 70% of all commercially available agrochemicals and pharmaceuticals belong to the group of heterocycles.[1] Most of these active ingredients bear either one or more heteromonocyclic scaffolds or a benzannulated bicyclic core. There are only a few highly active compound classes known, which contain a bicyclic scaffold made up of two different heterocycles. Examples for such rare heterobicyclic active ingredients are the cephalosporin antibiotics,[2] such as cefalexin (**1**), the imidazothiazole anthelminthics,[3] such as levamisole (**2**), and the triazolopyrimidine herbicides,[4] such as florasulam (**3**) (Figure 1).

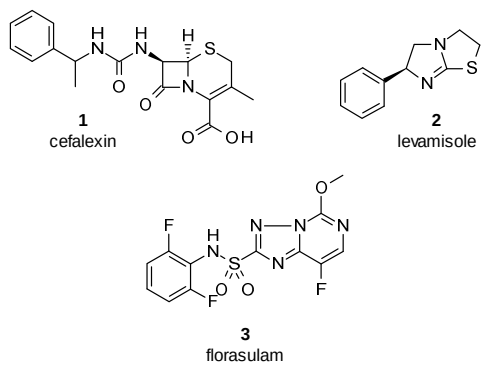


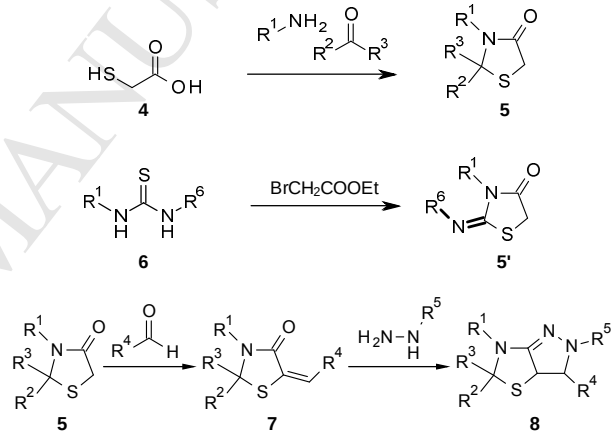
Figure 1. Different heterobicyclic active ingredients.

Possible reasons for this obvious underrepresentation of heterobicyclic compounds amongst the group of biologically active compound classes are the lack of general reaction methods, lengthy synthesis pathways, inavailability of complex intermediates etc. On the other hand, a heterobicyclic scaffold should be the ideal core of an active ingredient, because its physico-chemical properties, influencing the uptake and translocation of the pharmaceutical or agrochemical, can be fine-tuned by the choice of the right heterocyclic rings and the number of heteroatoms. And, in addition, a heterobicyclic scaffold should be an appropriate core to link several pharmacophoric substituents with the right exit-bond vectors into the three-dimensional space for perfect binding at the target-site of the enzyme. We decided to design a general synthesis of a so far scarcely described heterobicyclic ring system, which should fulfill two important criteria: 1. the completion in only few steps from versatile starting materials; and 2. the possibility to introduce a broad range of diverse substituents. To keep the synthesis sequence as concise as possible, we planned from the beginning the involvement of special types of one-pot reactions. In the meantime, multicomponent reactions[5] and cascade reactions[6] are well-established as powerful tools for the rapid construction of complex and structurally diverse compounds from relatively simple building blocks. High atom-economy and chemical efficiency are typical features of such one-pot reactions. Because of the mentioned ubiquitous availability of heterocyclic scaffolds in pharmaceuticals and agrochemicals, the assembly of heterocycles *via* multicomponent[7] or cascade[8] reactions has been an especially emerging field of interest recently. Therefore there is an existing arsenal of suitable reactions to choose from, but also the possibility to add completely novel reactions to this collection of known one-pot transformations.

2. Results and discussion

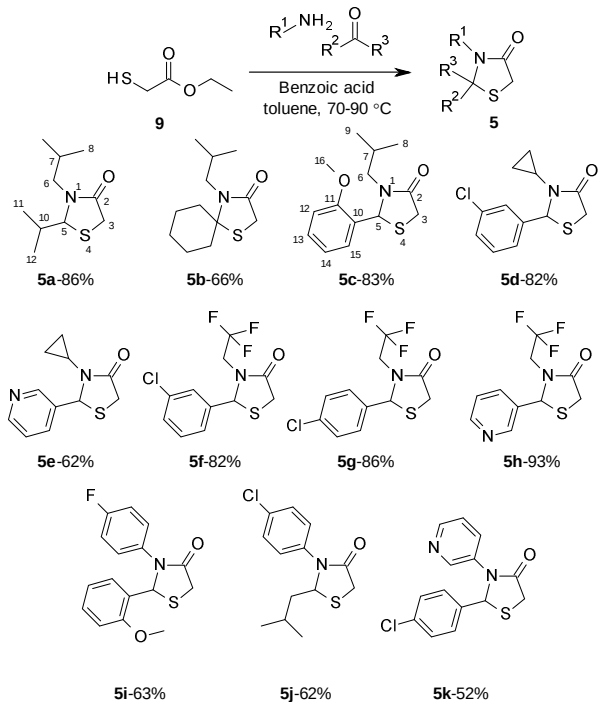
We chose 3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazole as the heterobicyclic scaffold of our model study for several different reasons. First, only a few single examples of this ring system have been described in the literature so far, always without focusing on an optimized synthesis.[9,10] Second, two ring nitrogen and two ring carbon atoms are perfectly suited to carry up to five different substituents, which could act as potential pharmacophores. Third, according to the very limited existing literature, it should be possible to assemble a tetrasubstituted tetrahydropyrazolo[3,4-d]thiazole from mercapoacetic acid, an amine, a hydrazine and two carbonyl compounds. The abundant commercial availability of such reagents should ensure the broad variability of the desired substituents.

The synthesis of such tetrahydropyrazolo[3,4-d]thiazoles **8** has been described in two steps from thiazolidin-4-ones **5** *via* Claisen condensation with an aldehyde to the arylidene derivative **7** and subsequent ring condensation with a hydrazine derivative to the target compound **8** (Scheme 1). The required key intermediate **5** could usually be prepared by ring closure either from an imine and mercaptoacetic acid **4**[9] or from a thiourea **6** and bromoacetic ester (towards **5'**).[10]



Scheme 1. Known synthesis pathways to 3,3a,5,6-tetrahydro-2H-pyrazolo[3,4-d]thiazoles **8**.

We decided to start our general synthesis of pyrazolothiazolidines *via* the mercaptoacetic acid route to a 4-thiazolidinone **5**. This would allow the introduction of a broader varity of substituents between the two thiazolidinone heteroatoms compared to the bromoacetic acid alternative. Furthermore the synthesis of thiazolidinones **5** by one-pot three-component condensation of an amine, a carbonyl compound and mercaptoactic acid **4** has been well described; usually this multicomponent reaction is performed in the presence of an acidic or desiccant reagent, such as zinc(II) chloride,[11] *p*-toluenesulfonic acid,[12] lanthanum (III) triflate,[13] sodium sulfate,[14] dicyclohexylcarbodiimide,[15] polyethylene glycol,[16] ionic liquid,[17] ferrite,[18] zeolite[19] and baker's yeast.[20] We found out, that most of these conditions were not suitable for a broadly applicable three-component condensation. In our detailed optimization screening for this reaction we found, that a diverse variety of carbonyl compounds and amines can be transformed into 4-thiazolidinones **5** in the presence of benzoic acid, a reagent, which had never been used in this reaction before. Moreover, we replaced the mercaptoactic acid by its ethyl ester **9**. These two improvements allowed the synthesis of thiazolidin-4-ones **5a-k** with several different substituents in positions 2 and 3 in 74% average yield (Scheme 2).



Scheme 2. Benzoic acid mediated synthesis of thiazolidin-4-ones **5a-k**.

The reaction tolerates a wide variety of aldehydes: aliphatic (both branched and linear, also the latter are lower yielding due to the occurrence of aldol side reaction), aromatic (with electron donating or electron withdrawing group around the ring) and heteroaromatic. Similarly, the reaction performed very well with a broad selection of amines: aliphatic (linear and sterically hindered), aromatic and heteroaromatic. However, it is worth mentioning that the reaction with poorly nucleophilic amines such as anilines or amino-pyridines were found to require longer reaction time and higher temperature to progress. This observation indicated that the lactamization was the rate determining step in the thiazolidin-4-one synthesis which was confirmed by the isolation of intermediate **10** towards **5k** (Figure 2).

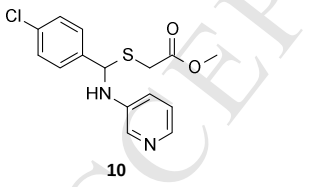
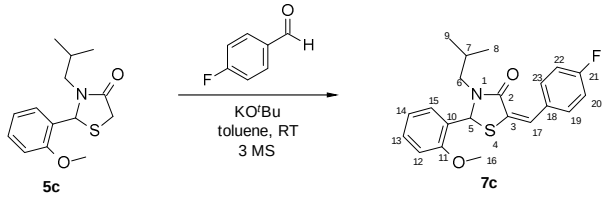


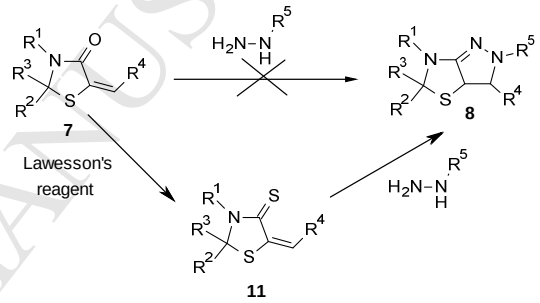
Figure 2.Intermediate **10**

The next step in our planned synthesis pathway to tetrahydropyrazolo[3,4-d]thiazoles was the aldol condensation of an aldehyde to the methylene function in position 5 of the thiazolidin-4-one. Such arylidenations have been achieved with the aid of sodium acetate in acetic acid,[21] sodium ethoxide,[22] potassium ethoxide,[23] potassium *tert*-butoxide[24] and montmorillonite.[25] We found, that only potassium *tert*-butoxide was effective enough to facilitate the aldol condensation at the relatively unreactive methylene function of the thiazolidin-4-one ring (Scheme 3). The newly formed Michael acceptor **7** was usually obtained as a 9:1 mixture of diastereoisomer.[26]



Scheme 3. *Tert*-butoxide mediated synthesis of 5-arylidene-thiazolidin-4-one **7g**.

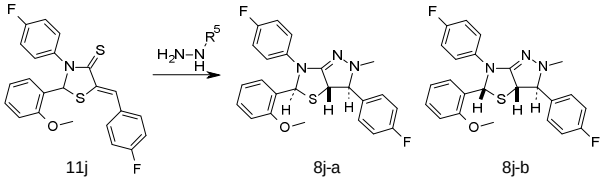
As last step in our reaction sequence, we had foreseen the condensation of the 5-arylidene-thiazolidin-4-ones **7** with different hydrazine derivatives to the desired tetrahydropyrazolo[3,4-d]thiazoles **8**. Unfortunately several attempts with different basic reagents, such as piperidine, pyridine, potassium *tert*-butoxide and sodium acetate did not accomplish this ring closure reaction (Scheme 4). Therefore we tried to enhance the activity of the thiazolidinone lactame function. One obvious possibility was the conversion of the 4-thiazolidinone **7** into a 4-thiazolidine-thione **11**. Such a transformation is easily possible with Lawesson's reagent.[27]



Scheme 4. Synthesis of tetrahydropyrazolo[3,4-d]thiazoles *via* 5-arylidenethiazolidin-4-thiones.

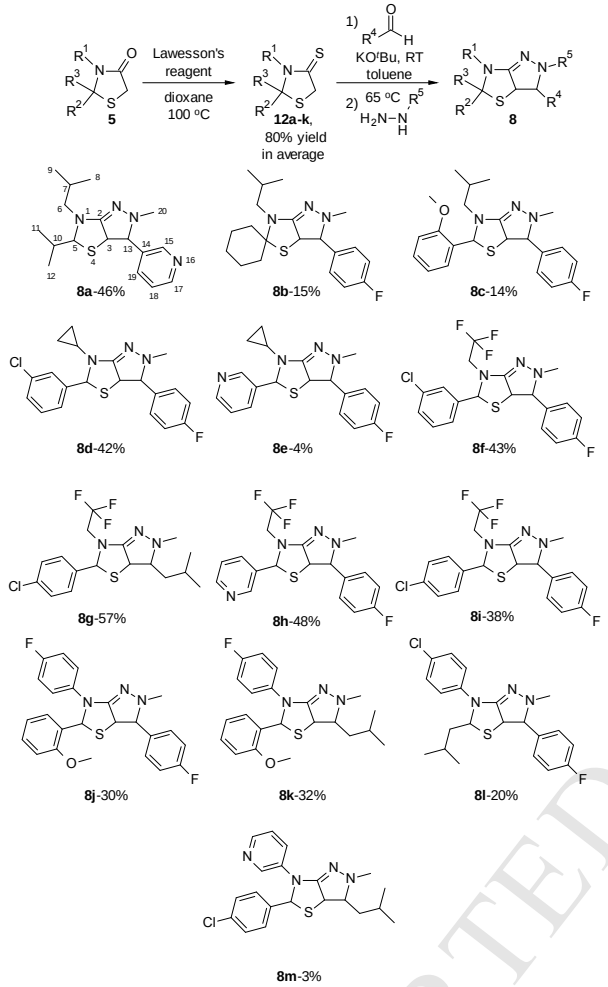
A solvent screen was undertaken to probe the reactivity of the resulting 5-arylidene-thiazolidin-4-thiones **11** with methylhydrazine. Pleasingly the desired pyrazolothiazolidines **8** were obtained in all solvents, ranging from polar protic (entry 1) to apolar aprotic (entries 5, 6). as a mixture of two diastereoiomers out of the four possible ones (Table 1). Interestingly, the diastereomeric ratio was strongly influenced by the nature of the solvent, and by using either methanol (entry 1) or heptane (entry 6), one could obtain one diastereoisomer or the other preferentially.

Table 1- Solvent screen for synthesis of tetrahydropyrazolo[3,4-d]thiazoles.



Entry	Solvent	Diastereomeric Ratio
1	MeOH	1:2
2	CH_3CN	3:1
3	THF	2:1
4	$CHCl_3$	1:1
5	Toluene	1:1
6	Heptane	5:1

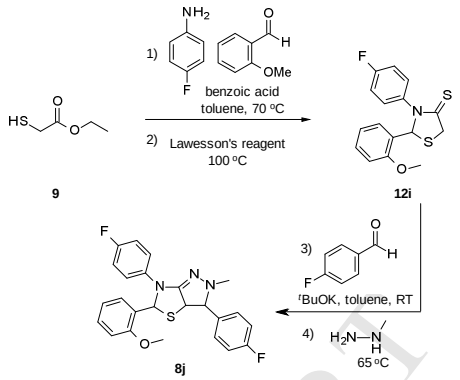
To optimize the synthesis route to only three steps, we went back to the products of the first step, the thiazolidin-4-ones **6** and converted them with Lawesson's reagent into the corresponding thiono derivatives **12** (Scheme 5). These intermediates could then be converted in a one-pot two-step sequence *via* the 5-arylidenethiazolidin-4-thiones **11** into the tetrasubstituted bicyclic tetrahydropyrazolo[3,4-d]thiazoles **8**.



Scheme 5. Concise approach from thiazolidinthi-4-ones to tetrahydropyrazolo[3,4-d]thiazoles.

The whole new reaction sequence to tetrahydropyrazolo[3,4-d]thiazoles contains only three steps, two of which allow the conversion of three different chemicals to a new reaction product. The aldehydes, ketones and amines are broadly variable, which results in diverse range of different substitution pattern in the final products **8**. **8e**, for instance, bears an alkyl, a cycloalkyl, an aryl and a heteroaryl substituent.

Furthermore, it is possible to reduce this synthesis to two consecutive one-pot processes, by adding the Lawesson's reagent upon formation of the thiazolidinone. The reaction is not as clean as the stepwise process but the desired product is obtained in 50 to 60% overall yield (Scheme 6). With this two-step procedure our tetrahydropyrazolo[3,4-d]thiazole synthesis lines up with some recently published great examples, which reported the efficient synthesis of other heterobicyclic compounds in just two steps by multicomponent-cascade reaction sequences.[28]



Scheme 6: Two consecutive one-pot processes

Conclusion

A general synthesis of 3,3a,5,6-tetrahydropyrazolo[3,4-d]thiazoles **8** has been achieved, in which this heterobicyclic scaffold is assembled in only three steps from two carbonyl compounds, an amine, a hydrazine and ethyl thioglycolate **9**. Each of the three steps is optimized for the highest variability of the applied reagents. Several improvements of literature-known procedures have been found, e.g. the application of mercaptoacetic acid esters as starting material and of benzoic acid as acidic reagent in the synthesis of thiazolidin-4-ones as well as the use of thiazolidin-4-thiones instead of thiazolidin-4-ones in the ring condensation to the desired tetrahydropyrazolo[3,4-d]thiazoles. We are confident, that such learnings from our route optimization can be applied to the synthesis of other heterobicyclic systems.

Experimental section

4.1. General experimental

All reactions were performed in degassed but not anhydrous solvent unless otherwise stated and under a nitrogen atmosphere (balloon). For reactions conducted under anhydrous conditions glassware was dried in an oven at 100 °C and purged with nitrogen. Bulk solutions were evaporated under reduced pressure using a Büchi rotary evaporator. Reagents used were obtained from commercial suppliers and used without further purification. Column chromatography was carried out using RediSep 4-12-24-40-80-120-330 g; Si60 (35-70 µm). All reactions were monitored by thin-layer chromatography (TLC) when practical, using Macherey-Nagel SIL G-25 / UV_{254} treated silica which were revealed by UV light (250 nm) or by staining with aqueous basic potassium permanganate solutions. Low resolution mass spectrometry was recorded on Waters UPLC-DAD-SQD/MS (ionization: ElectroSpray +/-, column: Acquity UPLC HSS T3 2.1X30 mm – 1.8 µm, mobile phase A (water + 5% MeOH + 0.05% formic acid) and B (Acetonitrile + 0.05% formic acid) and detection total absorbance 210-400 nm). All ^{1}H and ^{13}C NMR spectra were recorded using a Bruker 400 MHz and are quoted in ppm. Unless otherwise stated all experiments were carried out using $CDCl_3$ as solvent. Chemical shifts (δ) are given in parts per million (ppm), and coupling constants (*J*) are given in Hertz (Hz). The ^{1}H NMR spectra are reported as follows: ppm (multiplicity, number of protons, coupling constants and assignment). Two-dimensional (COSY, HMQC, HMBC) NMR spectroscopy were used to assist the assignment of signals in the ^{1}H and ^{13}C NMR spectra (s = singlet, br s = broad singlet, d = doublet, br d = broad doublet, t = triplet, q = quartet, m = multiplet, quin = quintet, sept = septuplet, dd = doublet of doublet, dt = doublet of triplet, td = triplet of doublet, dq = doublet of quadruplet, ddd = doublet of doublet of doublet).

4.2. Preparation of thiazolidinones 5a-k

General procedure A: a round-bottom flask, equipped with a rubber seal and a magnetic stirrer bar, was charged with ethyl thioglycolate **9** (1.0 eq.), benzoic acid (1.5 eq.) and toluene (0.6mol/L). Then, amine (1.5 eq.) and aldehyde/ketone (1.5 eq.) were added. The reaction was stirred at 70 °C to 90 °C under a N_2 atmosphere. Upon completion (monitored by ^{1}H NMR spectroscopy and TLC) the reaction mixture was concentrated under vacuum and the crude residue was dissolved in DCM and washed twice with 1M aqueous K_2CO_3. The combined aqueous layers were re-extracted once with DCM and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by FCC.

*4.2.1. 3-Isobutyl-2-isopropyl-thiazolidin-4-one (**5a**).* Prepared according to the general procedure **A** with ethyl thioglycolate (5.0 g), isopropylamine and isobutyraldehyde. After stirring at 70 °C for 18h, **5a** (8.4 g, 86%) was isolated by flash column chromatography (heptane / ethyl acetate gradient from pure heptane to Hept/EtOAc 3:1, Rf = 0.47 in Hept/EtOAc 2:1) as a yellow oil. **IR** (cm^{-1}) υ_{max} 1669 (C=O), 1412, 1274. **^{1}H NMR** (400 MHz, CHLOROFORM-*d*) δ ppm 4.67 (dd, 1H, *J* = 3.0 Hz, *J* =2.0 Hz, H-5), 3.62 (dd, 1H, *J* = 14.0 Hz, *J* = 10.0 Hz, H-6), 3.50 (br. s, 2H, H-3), 2.70 (dd, 1H, *J* = 14.0 Hz, *J* = 6.0 Hz, H-6'), 2.19-2.31 (m, 1H, H-7), 1.92-2.03 (m, 1H, H-10), 0.95 (dd, 6H, *J* = 6.5 Hz, *J* = 2.5 Hz, H-8 and H-9), 0.88 (d, 3H, *J* = 6.5 Hz, H-11 or H-12), 0.84 (d, 3H, *J* = 6.5 Hz, H-12 or H-11). **^{13}C NMR** (101 MHz, CHLOROFORM-*d*) δ ppm 171.5 (C-2), 67.7 (C-5), 49.6 (C-6), 32.4 (C-3), 30.3 (C-10), 26.1 (C-7), 20.4 (C-8 or C-9), 19.7 (C-11 or C-12), 18.7 (C-9 or C-8), 13.6 (C-12 or C-11). **m/z** (ES+) 202 ([M+H]+, 100%).

*4.2.2. 1-Isobutyl-4-thia-1-azaspiro[4.5]decan-2-one (**5b**).* Prepared according to the general procedure **A** with ethyl thioglycolate (1.0 g), isopropylamine and cycohexanone. After stirring at 70 °C for 48h, **5b** (1.5 g, 66%) was isolated by flash column chromatography (heptane / ethyl acetate gradient from pure heptane to Hept/EtOAc 1:3, Rf = 0.30 in Hept/EtOAc 2:1) as a light yellow oil. **IR** (cm^{-1}) υ_{max} 1670 (C=O), 1397. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 3.49 (s, 2H, H-3), 3.07 (d, 2H, *J* = 7.5 Hz, H-6), 1.98-2.11 (m, 1H, H-7), 1.57-1.71 (m, 10H, H-10, H-11, H-12, H-13 and H-14), 0.91 (d, 6H, *J* = 7.0 Hz, H-8 and H-9). **^{13}C NMR** (101 MHz, CHLOROFORM-d) δ ppm 171.9 (C-2), 74.3 (C-5), 49.4 (C-6), 38.2 (2C, $\underline{C}H_2$), 31.4 (C-3), 28.4 (C-7), 24.6 ($\underline{C}H_2$), 23.6 (2C, $\underline{C}H_2$), 20.3 (C-8 and C-9). **m/z** (ES+) 228 ([M+H]+, 100%).

*4.2.3. 3-Isobutyl-2-(2-methoxyphenyl)thiazolidin-4-one (**5c**).* Prepared according to the general procedure **A** with ethyl thioglycolate (3.0 g), isopropylamine and o-anisaldehyde. After stirring at 70 °C for 18h, **5c** (6.5 g, 83%) was isolated by flash column chromatography (heptane / ethyl acetate gradient from pure heptane to Hept/EtOAc 4:1, Rf = 0.20 in Hept/EtOAc 4:1) as a light yellow oil. **IR** (cm^{-1}) υ_{max} 1675 (C=O), 1489, 1408, 1242, 754. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 7.34 (td, 1H, *J* = 8.0 Hz, *J* = 1.5 Hz, H-Ar), 7.09 (dd, 1H, *J* = 7.5 Hz, *J* = 1.5 Hz, H-Ar), 6.90-7.03 (m, 2H, H-Ar), 5.99 (d, 1H, *J* = 1.5 Hz, H-5), 3.90 (s, 3H, H-16), 3.76 (dd, 1H, *J* = 15.0 Hz, *J* = 1.5 Hz, H-3), 3.56-3.69 (m, 2H, H-3' and H-6), 2.50 (dd, 1H, *J* = 13.5 Hz, *J* = 6.0 Hz, H-6'), 1.88-2.09 (m, 1H, H-7), 0.90 (d, 3H, *J* = 7.0 Hz, H-8 or H-9), 0.89 (d, 3H, *J* = 7.0 Hz, H-9 or H-8). **^{13}C NMR** (101 MHz, CHLOROFORM-d) δ ppm 172.3 (C-2), 156.8 (C-11), 129.7 (C_{Ar}), 127.9 (C-10), 126.1 (C_{Ar}), 120.9 (C_{Ar}), 111.0 (C_{Ar}), 58.2 (C-5), 55.6 (C-16), 50.3 (C-6), 32.5 (C-3), 26.4 (C-7), 20.3 (C-8 or C-9), 19.8 (C-9 or C-8). **m/z** (ES+) 266 ([M+H]+, 100%).

*4.2.4. 2-(3-Chlorophenyl)-3-cyclopropyl-thiazolidin-4-one (**5d**).* Prepared according to the general procedure **A** with ethyl thioglycolate (3.0 g), cyclopropylamine and m-chlorobenzaldehyde. After stirring at 70 °C for 18h, **5d** (6.1 g, 82%) was isolated by flash column chromatography (heptane / ethyl acetate gradient from pure heptane to Hept/EtOAc 3:2, Rf = 0.53 in Hept/EtOAc 1:1) as an orange oil. **IR** (cm^{-1}) υ_{max} 1675 (C=O), 1391 (C=C), 1359, 683 (C=C_{Ar}). **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 7.30-7.35 (m, 3H, H-Ar), 7.18-7.22 (m, 1H, H-Ar), 5.44 (s, 1H, H-5), 3.83 (d, 1H, *J* = 15.5 Hz, H-3), 3.65 (d, 1H, *J* = 15.5 Hz, H-3'), 2.23-2.32 (m, 1H, H-6), 0.80-1.01 (m, 2H, H-7 or H-8), 0.52-0.64 (m, 2H, H-8 or H-7). **^{13}C NMR** (101 MHz, CHLOROFORM-d) δ ppm 172.1 (C-2), 142.8 (C-9), 135.0 (C-11), 130.3 (C-Ar), 129.1 (C-Ar), 126.6 (C-Ar), 124.6 (C-Ar), 63.9 (C-5), 33.1 (C-3), 26.1 (C-6), 7.7 (C-7 or C-8), 5.1 (C-8 or C-7). **m/z** (ES+) 254 ([M+H]+, 100%).

*4.2.5. 3-Cyclopropyl-2-(3-pyridyl)thiazolidin-4-one (**5e**)* Prepared according to the general procedure **A** with ethyl thioglycolate (5.0 g), cyclopropylamine and 3-pyridincarboxaldehyde. After stirring at 70 °C for 18h, **5e** (6.7 g, 62%) was isolated by flash column chromatography (heptane / ethyl acetate gradient from pure heptane to Hept/EtOAc 1:4, Rf = 0.03 in Hept/EtOAc 1:2) as a light yellow oil. **IR** (cm^{-1}) υ_{max} 1673 (C=O), 1392 (C=C), 1357, 1025, 710 (C=C_{Ar}). **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 8.62 (dd, 1H, *J* = 5.0 Hz, *J* = 2.0 Hz, H-12), 8.59 (d, 1H, *J* = 2.0 Hz, H-10), 7.71 (dt, 1H, *J* = 8.0 Hz, *J* = 2.0 Hz, H-14), 7.36 (dd, 1H, *J* = 8.0 Hz, *J* = 5.0 Hz, H-13), 5.52 (d, 1H, *J* = 1.0 Hz, H-5), 3.84 (app. dd, 1H, *J* = 16.5 Hz, *J* = 1.0 Hz, H-3), 3.69 (d, 1H, *J* = 16.5 Hz, H-3'), 2.21 (m, 1H, H-6), 0.82-1.04 (m, 2H, H-7 or H-8), 0.51-0.71 (m, 2H, H-8 or H-7). **^{13}C NMR** (101 MHz, CHLOROFORM-d) δ ppm 171.9 (C-2), 150.4 (C-12), 148.4 (C-10), 136.2 (C-9), 134.3 (C-14), 124.0 (C-13), 62.2 (C-5), 33.2 (C-3), 26.0 (C-6), 7.8 (C-7 or C-8), 5.1 (C-8 or C-7). **m/z** (ES+) 221 ([M+H]+, 100%).

*4.2.6. 2-(3-Chlorophenyl)-3-(2,2,2-trifluoroethyl)thiazolidin-4-one (**5f**).* Prepared according to the general procedure **A** with ethyl thioglycolate (3.0 g), 2,2,2-trifluoroethylamine and m-chlorobenzaldehyde. After stirring at 70 °C for 18h, **5f** (7.1 g, 82%) was isolated by flash column chromatography (heptane / ethyl acetate gradient from pure heptane to Hept/EtOAc 3:2, Rf = 0.82 in Hept/EtOAc 1:1) as a yellow oil. **IR** (cm^{-1}) υ_{max} 1685 (C=O), 1396 (C=C), 1266, 1158, 1138, 707 (CF_3), 683 (C=C_{Ar}). **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 7.37-7.41 (m, 2H, H-12 and H-13), 7.31-7.33 (m, 1H, H-9), 7.21 (dt, 1H, *J* = 7.0 Hz, *J* = 2.0 Hz, H-11), 5.76 (s, 1H, H-5), 4.51 (dq, 1H, *J* = 15.0 Hz, *J* = 9.5 Hz, H-6), 3.83 (s, 2H, H-3), 3.07 (dq, 1H, *J* = 15.0 Hz, *J* = 8.5 Hz, H-6'). **^{13}C NMR** (101 MHz, CHLOROFORM-d) δ ppm 171.6 (C-2), 140.0 (Cquat), 135.4 (Cquat), 130.6 (C-12 or C-13), 123.0 (C-13 or C-12), 127.4 (C-9), 125.5 (C-11), 123.9 (q, *J* = 282.0 Hz, C-7), 62.4 (C-5), 43.2 (q, *J* = 34.5 Hz, C-6), 31.9 (C-3). **m/z** (ES+) 296 ([M+H]+, 100%).

***4.2.7.** 2-(4-Chlorophenyl)-3-(2,2,2-trifluoroethyl)thiazolidin-4-one (**5g**).* Prepared according to the general procedure **A** with ethyl thioglycolate (3.0 g), 2,2,2-trifluoroethylamine and p-chlorobenzaldehyde. After stirring at 70 °C for 18h, **5g** (7.5 g, 86%) was isolated by flash column chromatography (heptane / ethyl acetate gradient from pure heptane to Hept/EtOAc 3:2, Rf = 0.82 in Hept/EtOAc 1:1) as a yellow oil. **IR** (cm^{-1}) υ_{max} 1686 (C=O), 1394 (C=C), 1264, 1154, 1136, 709 (CF_3), 683 (C=C_{Ar}). **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 7.42 (d, 2H, *J* = 8.5 Hz, H-10 and H-12), 7.28 (d, 2H, *J* = 8.5 Hz, H-9 and H-13), 5.78 (s, 1H, H-5), 4.49 (dq, 1H, *J* = 15.5 Hz, *J* = 9.5 Hz, H-6), 3.83 (s, 2H, H-3), 3.05 (dq, 1H, *J* = 15.5 Hz, *J* = 8.5 Hz, H-6'). **^{13}C NMR** (101 MHz, CHLOROFORM-d) δ ppm 171.6 (C-2), 136.1 (C-8 or C-11), 135.8 (C-11 or C-8), 129.7 (C-10 and C-12), 128.9 (C-9 and C-13), 123.8 (q, *J* = 282.0 Hz, C-7), 62.5 (C-5), 43.1 (q, *J* = 34.5 Hz, C-6), 32.1 (C-3). **m/z** (ES+) 296 ([M+H]+, 100%).

*4.2.8. 2-(3-Pyridyl)-3-(2,2,2-trifluoroethyl)thiazolidin-4-one (**5h**).* Prepared according to the general procedure **A** with ethyl thioglycolate (3.0 g), 2,2,2-trifluoroethylamine and 3-pyridinecarboxaldehyde. After stirring at 70 °C for 18h, **5h** (7.2 g, 93%) was isolated by flash column chromatography (heptane / ethyl acetate gradient from pure heptane to Hept/EtOAc 1:4, Rf = 0.19 in Hept/EtOAc 2:1) as a yellow oil. **IR** (cm^{-1}) υ_{max} 1693 (C=O), 1396 (C=C), 1264, 1153, 1135, 711 (CF_3), 639 (C=C_{Ar}). **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 8.69 (dd, 1H, *J* = 5.0 Hz, *J* = 2.0 Hz, H-9), 8.60 (d, 1H, *J* = 2.0 Hz, H-11), 7.70 (dt, 1H, *J* = 8.0 Hz, *J* = 2.0 Hz, H-13), 7.41 (dd, 1H, *J* = 8.0 Hz, *J* = 5.0 Hz, H-12), 5.82 (s, 1H, H-5), 4.50 (dq, 1H, *J* = 15.0 Hz, *J* = 9.5 Hz, H-6), 3.86 (s, 2H, H-3), 3.05 (dq, 1H, *J* = 15.0 Hz, *J* = 8.0 Hz, H-6'). **^{13}C NMR** (101 MHz, CHLOROFORM-d) δ ppm 171.5 (C-2), 151.3 (C-9), 149.1 (C-11), 135.1 (C-13), 133.5 (C-8), 124.1 (C-12), 123.5 (q, *J* = 283.0 Hz, C-7), 60.8 (C-5), 43.2 (q, *J* = 34.5 Hz, C-6), 32.0 (C-3). **m/z** (ES+) 263 ([M+H]+, 100%).

*4.2.9. 3-(4-Fluorophenyl)-2-(2-methoxyphenyl)thiazolidin-4-one (**5i**).* Prepared according to the general procedure **A** with ethyl thioglycolate (15.0 g), p-fluoroaniline and o-anisaldehyde. After stirring at 70 °C for 48h, **5i** (28.2 g, 63%) was isolated by flash column chromatography (heptane / ethyl acetate gradient from pure heptane to Hept/EtOAc 3:1, Rf = 0.10 in Hept/EtOAc 4:1) as a yellow oil. **IR** (cm^{-1}) υ_{max} 1682 (C=O), 1506, 1240, 1218, 1266, 835, 752, 733. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 7.23-7.29 (m, 3H, H-8, H-10 and H-15 or H-17), 7.19 (dd, *J* = 7.5 and 1.5 Hz, 1H, H-17 or H-15), 6.94-7.01 (m, 2H, H-7 and H-11), 6.90 (d, *J* = 2.5 Hz, 1H, H-14), 6.87 (t, *J* = 4.5 Hz, 1H, H-16), 6.38 (br. s, 1H, H-5), 3.95 (dd, *J* = 15.5 Hz, *J* = 1.5 Hz, 1H, H-3), 3.87 (s, 3H, H-18), 3.78 (d, *J* = 15.5 Hz, 1H, H-3'). **^{13}C NMR** (101 MHz, CHLOROFORM-d) δ ppm 171.6 (C-2), 160.8 (d, *J* = 248.5 Hz, C-9), 156.6 (C-13), 133.9 (d, *J* = 4.0 Hz, C-6), 129.9 (C_{Ar}), 127.6 (C-12), 126.9 (C_{Ar}), 126.6 (d, *J* = 8.0 Hz, C-7 and C-11), 120.8 (C_{Ar}), 115.8 (d, *J* = 23.0 Hz, C-8 and C-10), 111.1 (C_{Ar}), 60.5 (C-5), 55.6 (C-18), 33.3 (C-3). **m/z** (ES+) 304 ([M+H]+, 100%).

*4.2.10. 3-(4-Chlorophenyl)-2-isobutyl-thiazolidin-4-one (**5j**).* Prepared according to the general procedure **A** with ethyl thioglycolate (2.0 g), p-chloroaniline and isobutyraldehyde. After stirring at 70 °C for 48h, **5j** (3.3 g, 62%) was isolated by flash column chromatography (heptane / ethyl acetate gradient from pure heptane to Hept/EtOAc 3:1, Rf = 0.43 in Hept/EtOAc 4:1) as a yellow oil. **IR** (cm^{-1}) υ_{max} 1683 (C=O), 1491, 1387, 1349, 1089, 826. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 7.39-7.45 (m, 2H, H-7 and H-11), 7.21-7.26 (m, 2H, H-8 and H-10), 5.14 (ddd, 1H, *J* = 9.5, 4.0 and 1.0 Hz, H-5), 3.77 (dd, 1H, *J* = 15.5 Hz, *J* = 1.0 Hz, H-3), 3.70 (d, 1H, *J* = 15.5 Hz, H-3'), 1.72-1.83 (m, 1H, H-13), 1.52-1.66 (m, 2H, H-12), 0.91 (d, 3H, *J* = 6.5 Hz, H-14 or H-15), 0.85 (d, 3H, *J* = 6.5 Hz, H-15 or H-14). **^{13}C NMR** (101 MHz, CHLOROFORM-d) δ ppm 170.7 (C-2), 136.0 (C-9), 133.2 (C-6), 129.7 (C-7 and C-11), 127.5 (C-8 and C-10), 62.4 (C-5) , 45.2 (C-12), 32.4 (C-3), 24.9 (C-13), 23.7 (C-14 or C-15), 21.1 (C-15 or C-14). **m/z** (ES+) 270 ([M+H]+, 100%).

*4.2.11. 2-(4-Chlorophenyl)-3-(3-pyridyl)thiazolidin-4-one (**5k**).* Prepared according to the general procedure **A** with ethyl thioglycolate (3.0 g), 3-aminopyridine and p-chlorobenzaldehyde. After stirring at 90 °C for 4 days, **6k** (4.4 g, 52%) was isolated by flash column chromatography (heptane / ethyl acetate gradient from pure heptane to pure EtOAc, Rf = 0.15 in Hept/EtOAc 1:1) as a yellow oil. **IR** (cm^{-1}) υ_{max} 1684 (C=O), 1480, 1369, 1088, 1013, 706. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 8.45 (br. d, 1H, *J* = 2.0 Hz, H-7), 8.43 (dd, 1H, *J* = 5.0 Hz, *J* = 1.5 Hz, H-9), 7.59 (ddd, 1H, *J* = 8.0 Hz, *J* = 2.5 Hz, *J* = 1.5 Hz, H-11), 7.23-7.31 (m, 5H, H-13, H-14, H-16, H-17 and H-10), 6.13 (s, 1H, H-5), 3.99 (d, 1H, *J* = 16.0 Hz, H-3), 3.91 (d, 1H, *J* = 16.0 Hz, H-3'). **^{13}C NMR** (101 MHz, CHLOROFORM-d) δ ppm 171.1 (C-2), 148.0 (C-9), 146.2 (C-7), 137.1 (Cquat), 135.2 (Cquat), 134.1 (Cquat), 132.8 (C-11), 129.4 (C-14 and C-16), 128.4 (C-13 and C-17), 123.7 (C-10), 64.4 (C-5), 33.2 (C-3). **m/z** (ES+) 291 ([M+H]+, 100%).

4.3. Preparation of thiazolidinthiones 12a-k

General procedure B: a one-necked flask, equipped with a magnetic stirrer bar was charged with thiazolidinone **5** (1.0 eq.), Lawesson's reagent (0.6 eq.) and 1,4-dioxane (0.5 mol/L). The reaction was stirred at 100 °C overnight. Upon completion (monitored by LCMS), 1,4-dioxane was removed under vacuum and the crude product was purified by FCC.

*4.3.1. 3-Isobutyl-2-isopropyl-thiazolidin-4-thione **(12a)**.* Prepared according to the general procedure **B** with ethyl 3-isobutyl-2-isopropyl-thiazolidin-4-one **5a** (1.0 g). **12a** (1.0 g, 90%) was isolated by flash column chromatography (heptane / ethyl acetate gradient from pure heptane to pure EtOAc, Rf = 0.86 in Hept/EtOAc 1:1) as an orange oil. **IR** (cm^{-1}) υ_{max} 1461, 1386, 1216, 1136 (C=S), 1092. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 5.07 (br. s, 1H, H-5), 4.42 (dd, 1H, *J* = 13.5 Hz, *J* = 8.5 Hz, H-6'), 4.17 (br. s, 2H, H-3), 2.94 (dd, 1H, *J* = 13.5 Hz, *J* = 7.0 Hz, H-6), 2.34-2.43 (m, 1H, H-10), 2.23-2.33 (m, 1H, H-7), 1.1 (t, 6H, *J* = 7.0 Hz, H-9 or H-8 and H-12 or H-11), 0.94 (d, 3H, *J* = 7.0 Hz, H-8 or H-9), 0.84 (d, 3H, *J* = 7.0 Hz, H-11 or H-12). **^{13}C NMR** (101 MHz, CHLOROFORM-d) δ ppm 197.4 (C-2), 78.0 (C-5), 54.9 (C-6), 45.7 (C-3), 31.4 (C-7), 26.0 (C-10), 20.4 (C-8 or C-9), 19.8 (C-11 or C-12), 19.3 (C-11 or C-12), 14.0 (C-8 or C-9). **m/z** (ES+) 217 ([M+H]+, 100%).

*4.3.2. 1-Isobutyl-4-thia-1-azaspiro[4.5]decan-2-thione **(12b)**.* Prepared according to the general procedure **B** with 1-isobutyl-4-thia-1-azaspiro[4.5]decan-2-one **5b** (0.9 g). **12b** (0.9 g, 86%) was isolated by flash column chromatography (heptane / ethyl acetate gradient from pure heptane to Hept/EtOAc 1:1, Rf = 0.65 in Hept/EtOAc 2:1) as a red oil. **IR** (cm^{-1}) υ_{max} 1462, 1385, 1181, 1148, 1130 (C=S), 1107. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 4.08 (s, 2H, H-3), 3.53 (d, 2H, *J* = 8.0 Hz, H-6), 2.30-2.52 (m, 1H, H-7), 1.69-1.91 (m, 6H, H-11, H-12 and H-13), 1.47-1.68 (m, 4H, H-10 and H-14), 0.90 (d, 6H, *J* = 7.0 Hz, H-9 and H-8).**^{13}C** NMR (101 MHz, CHLOROFORM-d) δ ppm 198.4 (C-2), 84.9 (C-5), 54.0 (C-6), 43.4 (C-3), 37.5 (C-11 and C-13), 27.4 (C-7), 24.6 (C-12), 24.3 (C-10 and C-14), 20.5 (C-8 and C-9). **m/z** (ES+) 244 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for [M+H] ($C_{12}H_{22}NS_2$+) requires **m/z** 244.1188, found **m/z** 244.1186.

*4.3.3. 3-Isobutyl-2-(2-methoxyphenyl)thiazolidin-4-thione **(12c)**.* Prepared according to the general procedure **B** with ethyl 3-isobutyl-2-(2-methoxyphenyl)thiazolidin-4-one **5c** (2.5 g). **12c** (2.6 g, 99%) was isolated by flash column chromatography (heptane / ethyl acetate gradient from pure heptane to Hept/EtOAc 1:4, Rf = 0.55 in Hept/EtOAc 2:1) as an orange oil. **IR** (cm^{-1}) υ_{max} 1459, 1240, 1137 (C=S), 1105. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 7.30-7.38 (m, 1H, H_{Ar}), 6.92-7.00 (m, 3H, H_{Ar}), 6.38 (d, 1H, *J* = 2.0 Hz, H-5), 4.07-4.58 (m, 3H, H-3 and H-6), 3.89 (s, 3H, H-16), 2.71 (dd, 1H, *J* = 13.0 Hz, 7.0 Hz, H-6'), 1.93-2.42 (m, 1H, H-7), 0.97 (d, 3H, *J* = 7.0 Hz, H-8 or H-9), 0.94 (d, 3H, *J* = 7.0 Hz, H-9 or H-8). **^{13}C NMR** (101 MHz, CHLOROFORM-d) δ ppm 198.7 (C-2), 156.5 (C-11), 130.1 (C_{Ar}), 126.8 (C-10), 126.0 (C_{Ar}), 121.0 (C_{Ar}), 111.1 (C_{Ar}), 68.2 (C-5), 55.7 (C-16), 55.6 (C-6), 45.4 (C-3), 26.2 (C-7), 20.3 (C-8 or C-9), 19.9 (C-9 or C-8). **m/z** (ES+) 282 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for [M+H] ($C_{14}H_{20}ONS_2$+) requires **m/z** 282.0980, found **m/z** 282.0982.

*4.3.4. 2-(3-Chlorophenyl)-3-cyclopropyl-thiazolidin-4-thione **(12d)**.* Prepared according to the general procedure **B** with 2-(3-chlorophenyl)-3-cyclopropyl-thiazolidin-4-one **5d** (3.9 g). **12d** (3.8 g, 92%) was isolated by flash column chromatography (heptane / ethyl acetate gradient from pure heptane to Hept/EtOAc 1:4, Rf = 0.89 in Hept/EtOAc 2:1) as a yellow oil. **IR** (cm^{-1}) υ_{max} 1444, 1404, 1277, 1131 (C=S), 1079. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 7.33-7.36 (m, 2H, H-12 and H-13), 7.23-7.66 (m, 1H, H-10), 7.08-7.19 (m, 1H, H-14), 5.83 (d, 1H, *J* = 2.0 Hz, H-5), 4.45 (app. ddd, 1H, *J* = 16.5 Hz, *J* = 2.0 Hz, *J* = 1.0 Hz, H-3), 4.29 (d, 1H, *J* 16.5 Hz, H-3'), 2.65-2.75 (m, 1H, H-6), 1.07-1.18 (m, 1H, H-7 or H-8), 0.87-0.98 (m, 1H, H-7 or H-8), 0.70-0.83 (m, 2H, H-8 or H-7). **^{13}C NMR** (101 MHz, CHLOROFORM-d) δ ppm 199.9 (C-2), 142.0 (C-9), 135.2 (C-11), 130.6 (C-13), 129.3 (C-12), 126.4 (C-10), 124.3 (C-14), 73.0 (C-5), 46.0 (C-3), 31.9 (C-6), 9.4 (C-7 or C-8), 7.3 (C-8 or C-7). **m/z** (ES+) 270 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for [M+H] ($C_{12}H_{13}NClS_2$+) requires **m/z** 270.0172, found **m/z** 270.0171.

*4.3.5. 3-Cyclopropyl-2-(3-pyridyl)thiazolidin-4-thione **(12e)**.* Prepared according to the general procedure **B** with 3-cyclopropyl-2-(3-pyridyl)thiazolidin-4-one **5e** (0.8 g). **12e** (0.3 g, 40%) was isolated by flash column chromatography (heptane / ethyl acetate gradient from pure heptane to Hept/EtOAc 1:4, Rf = 0.27 in Hept/EtOAc 1:1) as an orange oil. **IR** (cm^{-1}) υ_{max} 1442, 1403, 1271, 1132 (C=S), 1027. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 8.62 (br. d, 1H, *J* = 2.5 Hz, H-12), 8.58 (br. s, 1H, H-10), 7.63 (dt, 1H, *J* = 8.0 Hz, *J* = 1.5 Hz, H-14), 7.38 (dd, 1H, *J* = 8.0 Hz, *J* = 5.5 Hz, H-13), 5.91 (d, 1H, *J* = 2.0 Hz, H-5), 4.46 (app. ddd, 1H, *J* = 17.0 Hz, *J* = 2.0 Hz, *J* = 1.0 Hz, H-3'), 4.31 (d, 1H, *J* = 17.0 Hz, H-3), 2.62 (app. dt, 1H, *J* = 11.5 Hz, *J* = 5.5 Hz, H-6), 1.09-1.19 (m, 1H, H-8 or H-7), 0.90-0.99 (m, 1H, H-8 or H-7), 0.74-0.82 (m, 2H, H-7 or H-8). **^{13}C NMR** (101 MHz, CHLOROFORM-d) δ ppm 199.8 (C-2), 150.5 (C-12), 147.9 (C-10), 135.7 (C-9), 133.9 (C-14), 124.2 (C-13), 71.2 (C-5), 40.1 (C-3), 31.8 (C-6), 9.6 (C-7 or C-8), 7.4 (C-8 or C-7). **m/z** (ES+) 237 ($[M+H]^+$, 100%).

*4.3.6. 2-(3-Chlorophenyl)-3-(2,2,2-trifluoroethyl)thiazolidin-4-thione **(12f)**.* Prepared according to the general procedure **B** with 2-(3-chlorophenyl)-3-(2,2,2-trifluoroethyl)thiazolidin-4-one **5f** (2.4 g). **12f** (1.9 g, 77%) was isolated by flash column chromatography (heptane / ethyl acetate gradient from pure heptane to Hept/EtOAc 3:1, Rf = 0.88 in Hept/EtOAc 1:1) as an orange oil. **IR** (cm^{-1}) υ_{max} 1450, 1402, 1260, 1134 (C=S), 1109, 1079. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 7.29-7.37 (m, 2H, H-11 and H-12), 7.18-7.23 (m, 1H, H-9), 7.09 (dt, 1H, *J* = 17.0 Hz, *J* = 2.0 Hz, H-13), 6.02 (s, 1H, H-5), 5.30 (dq, 1H, *J* = 15.0 Hz, *J* = 9.5 Hz, H-6), 4.38 (app. ddd, 1H, *J* = 17.0 Hz, *J* = 2.0 Hz, *J* = 1.0 Hz, H-3), 4.32 (dd, 1H, *J* = 17.0 Hz, *J* = 1.0 Hz Hz, *J* = H-3'), 3.20-3.33 (m, 1H, H-6'). **^{13}C NMR** (101 MHz, CHLOROFORM-d) δ ppm 201.3 (C-2), 139.2 (C-8), 135.6 (C-10), 130.9 (C-11 or C-12), 130.3 (C-12 or C-11), 127.5 (C-9), 125.5 (C-13), 124.5 (q, *J* = 280.0 Hz, C-7), 72.0 (C-5), 47.3 (q, *J* = 34.0 Hz, C-6), 45.0 (C-3). **m/z** (ES+) 312 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for [M+H] ($C_{11}H_{10}NClF_3S_2$+) requires **m/z** 311.9890, found **m/z** 311.9890.

*4.3.7. 2-(4-Chlorophenyl)-3-(2,2,2-trifluoroethyl)thiazolidin-4-thione **(12g)**.* Prepared according to the general procedure **B** with 2-(4-chlorophenyl)-3-(2,2,2-trifluoroethyl)thiazolidin-4-one **5g** (2.8 g). **12g** (2.6 g, 89%) was isolated by flash column chromatography (heptane / ethyl acetate gradient from pure heptane to Hept/EtOAc 1:1, Rf = 0.91 in Hept/EtOAc 1:1) as an orange oil. **IR** (cm^{-1}) υ_{max} 1446, 1401, 1258, 1134 (C=S), 1108, 1089. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 7.31-7.39 (m, 2H, H-10 and H-12), 7.15-7.21 (m, 2H, H-9 and H-13), 6.04 (s, 1H, H-5), 5.28 (dq, 1H, *J* = 15.0 Hz, *J* = 9.5 Hz, H-6), 4.37 (app. ddd, 1H, *J* =17.0 Hz, *J* = 2.0 Hz, *J* = 0.5 Hz, H-3), 4.31 (dd, 1H, *J* = 17.0 Hz, *J* = 1.0 Hz, H-3'), 3.24 (dq, 1H, *J* = 15.0 Hz, *J* = 8.0 Hz, H-6'). **^{13}C NMR** (101 MHz, CHLOROFORM-d) δ ppm 201.3 (C-2), 136.2 (C-11), 135.5 (C-8), 129.8 (C-10 and C-12), 128.9 (C-9 and C-13), 123.5 (q, *J* 280.0 Hz, C-7), 72.0 (C-5), 47.2 (q, *J* 34.0 Hz, C-6), 45.0 (C-3). **m/z** (ES+) 312 ($[M+H]^+$, 100%), HRMS (ES+) exact mass

calculated for [M+H] ($C_{11}H_{10}NClF_3S_2$+) requires **m/z** 311.9890, found **m/z** 311.9887.

*4.3.8. 2-(3-Pyridyl)-3-(2,2,2-trifluoroethyl)thiazolidin-4-thione (**12h**).* Prepared according to the general procedure **B** with 2-(3-pyridyl)-3-(2,2,2-trifluoroethyl)thiazolidin-4-one **5h** (5.5 g). **12h** (2.1 g, 36%) was isolated by flash column chromatography (heptane / ethyl acetate gradient from pure heptane to Hept/EtOAc 1:3, Rf = 0.53 in Hept/EtOAc 2:1) as an orange oil. **IR** (cm^{-1}) υ_{max} 1449, 1402, 1259, 1136 (C=S), 1108. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 8.62 (dd, 1H, *J* = 5.0 Hz, *J* = 2.0 Hz, H-11), 8.51 (d, 1H, *J* = 2.0 Hz, H-9), 7.59 (dt, 1H, *J* = 8.0 Hz, *J* = 2.0 Hz, H-13), 7.34 (dd, 1H, *J* = 8.0 Hz, *J* = 5.0 Hz, H-12), 6.10 (s, 1H, H-5), 4.37-4.43 (m, 1H, H-6), 4.40 (app. ddd, 1H, *J* = 17.0 Hz, *J* = 1.5 Hz, *J* = 1.0 Hz, H-3), 4.34 (dd, 1H, *J* = 17.0 Hz, *J* = 1.0 Hz, H-3'), 3.15-3.36 (m, 1H, H-6'). **^{13}C NMR** (101 MHz, CHLOROFORM-d) δ ppm 201.3 (C-2), 151.5 (C-11), 149.0 (C-9), 135.1 (C-13), 133.0 (C-8), 124.4 (C-12), 123.5 (q, *J* = 281 Hz, C-7), 70.2 (C-5), 47.3 (q, *J* = 34 Hz, C-6), 45.0 (C-3). **m/z** (ES+) 279 ([M+H]$^+$, 100%), HRMS (ES+) exact mass calculated for [M+H] ($C_{10}H_{10}N_2F_3S_2$+) requires **m/z** 279.0232, found **m/z** 279.0227.

*4.3.9. 3-(4-Fluorophenyl)-2-(2-methoxyphenyl)thiazolidin-4-thione (**12i**).* Prepared according to the general procedure **B** with 3-(4-fluorophenyl)-2-(2-methoxyphenyl)thiazolidin-4-one **5i** (1.2 g). **12i** (1.2 g, 96%) was isolated by flash column chromatography (heptane / ethyl acetate gradient from pure heptane to Hept/EtOAc 3:1, Rf = 0.69 in Hept/EtOAc 1:1) as an orange oil. **IR** (cm^{-1}) υ_{max} 1505, 1434, 1243, 1136 (C=S), 1048. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 7.17-7.24 (m, 2H, H-15 and H-17), 7.02-7.08 (m, 2H, H-7 and H-11), 6.89-6.96 (m, 2H, H-8 and H-10), 6.86 (t, 1H, *J* = 7.5 Hz, H-16), 6.76 (d, 1H, *J* = 8.5 Hz, H-14), 6.54 (br. s, 1H, H-5), 4.51 (dd, 1H, *J* =16.5 Hz, *J* = 2.0 Hz, H-3), 4.38 (d, 1H, *J* = 16.5 Hz, H-3'), 3.70 (s, 3H, H-18). **^{13}C NMR** (101 MHz, CHLOROFORM-d) δ ppm 200.4 (C-2), 161.9 (d, *J* = 247.0 Hz, C-9), 156.7 (C-13), 136.0 (d, *J* = 4.0 Hz, C-6), 130.6 (C-15), 129.1 (C-7 or C-11), 129.0 (C-11 or C-7), 128.1 (C-17), 126.1 (C-12), 120.9 (C-16), 116.4 (C-8 or C-10), 116.2 (C-10 or C-8), 111.2 (C-14), 71.2 (C-5), 55.6 (C-18), 46.5 (C-3). **m/z** (ES+) 320 ([M+H]$^+$, 100%), HRMS (ES+) exact mass calculated for [M+H] ($C_{16}H_{15}ONClFS_2$+) requires **m/z** 320.0574, found **m/z** 320.0571.

*4.3.10. 3-(4-Chlorophenyl)-2-isobutyl-thiazolidin-4-thione (**12j**).* Prepared according to the general procedure **B** with 3-(4-chlorophenyl)-2-isobutylthiazolidin-4-one **5j** (0.8 g). **12j** (0.7 g, 83%) was isolated by flash column chromatography (heptane / ethyl acetate gradient from pure heptane to Hept/EtOAc 1:1, Rf = 0.60 in Hept/EtOAc 2:1) as a yellow oil. **IR** (cm^{-1}) υ_{max} 1488, 1435, 1140 (C=S), 1089. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 7.38-7.44 (m, 2H, H_{Ar}), 7.11-7.16 (m, 2H, H_{Ar}), 5.24 (app. ddt, 1H, *J* = 11.0 Hz, *J* = 2.0 Hz, *J* = 1.0 Hz, H-5), 4.29 (dd, 1H, *J* = 16.0 Hz, *J* = 2.0 Hz, H-3), 4.24 (dd, 1H, *J* = 16.0 Hz, *J* = 1.0 Hz, H-3'), 1.65-1.74 (m, 1H, H-13), 1.57-1.65 (m, 1H, H-12), 1.45-1.54 (m, 1H, H-12'), 0.84 (d, 3H, *J* = 7.0 Hz, H-14 or H-15), 0.73 (d, 3H, *J* = 7.0 Hz, H-15 or H-14). **^{13}C NMR** (101 MHz, CHLOROFORM-d) δ ppm 199.6 (C-2), 138.3 (C_{quat}), 134.8 (C_{quat}), 130.1 (2xC_{Ar}), 128.9 (2xC_{Ar}), 73.2 (C-5), 45.1 (C-3), 44.7 (C-12), 25.6 (C-13), 23.6 (C-14), 20.8 (C-15). **m/z** (ES+) 286 ([M+H]$^+$, 100%), HRMS (ES+) exact mass calculated for [M+H] ($C_{13}H_{17}NClS_2$+) requires **m/z** 286.0485, found **m/z** 286.0487.

*4.3.11. 2-(4-Chlorophenyl)-3-(3-pyridyl)thiazolidin-4-thione (**12k**).* Prepared according to the general procedure **B** with 3-(4-chlorophenyl)-3-(3-pyridyl)thiazolidin-4-one **5k** (1.0 g). **12k** (0.9 g, 86%) was isolated by flash column chromatography (heptane / ethyl acetate gradient from pure heptane to Hept/EtOAc 1:1, Rf = 0.51 in Hept/EtOAc 1:1) as a yellow oil. **IR** (cm^{-1}) υ_{max} 1435, 1396, 1190, 1148, 1140 (C=S), 1104. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 8.45 (br. d, 1H, *J* = 4.0 Hz, H-9), 8.36 (br. s, 1H, H-7), 7.40 (d, 1H, *J* = 8.0 Hz, H-11), 7.23-7.32 (m, 5H, H-10, H-13, H-14, H-16 and H-17), 6.27 (s, 1H, H-5), 4.63 (dd, 1H, *J* = 17.5 Hz, *J* = 2.0 Hz, H-3), 4.54 (d, 1H, *J* = 17.5 Hz, H-3'). **^{13}C NMR** (101 MHz, CHLOROFORM-d) δ ppm 200.6 (C-2), 149.5 (C-9), 148.5 (C-7), 136.6 (Cquat), 135.9 (Cquat), 135.8 (Cquat), 135.5 (C-11), 129.4 (C-13 and C-17 or C-14 and C-16), 129.2 (C-13 and C-17 or C-14 and C-16), 123.9 (C-10), 75.4 (C-5), 46.2 (C-3). **m/z** (ES+) 307 ([M+H]+, 100%).

4.4. Preparation of pyrazolothiazoles 8a-k

General procedure C: a dried one-necked flask, equipped with a magnetic stirrer bar, was charged with thiazolidinethione **12** (1.0 eq.), an aldehyde (1.1 eq.) and dry toluene (0.1 mol/L). Then, potassium ^{t}butoxide (1.1 eq.) was added dropwise. After stirring for 5 min under nitrogen, 3Å molecular sieves were added to the reaction. The mixture was left under a nitrogen atmosphere and stirred at RT until completion (monitored by LCMS, usually 30 min). Then, methylhydrazine (10.0 eq) was added and the reaction was stirred at 65 °C overnight. The toluene was removed under vacuum and the crude product was purified by FCC.

*4.4.1. 6-Isobutyl-5-isopropyl-2-methyl-3-(3-pyridyl)-3,3a,5,6a-tetrahydro-1H-pyrazolo[3,4-d]thiazole (**8a**).* Prepared according to the general procedure **C** with 3-isobutyl-2-isopropyl-thiazolidin-4-thione **12a** (335 mg) and 3-pyridinecarboxaldehyde. **8a** (225 mg, 46 %) was isolated by flash column chromatography (cyclohexane / EtOAc gradient from pure cyclohexane to pure EtOAc, Rf = 0.1 in EtOAc) as a yellow oil. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 8.64 (d, 1H, *J* = 2.0 Hz, H-15), 8.58 (dd, 1H, *J* = 8.0 Hz, *J* = 2.0 Hz, H-17), 7.84 (dt, 1H, *J* = 8.0 Hz, *J* = 2.0 Hz, H-19), 7.30 (dd, 1H, *J* = 8.0 Hz, *J* = 6.0 Hz, H-18), 4.77 (br. d, 1H, *J* = 3.5 Hz, H-5), 4.65 (d, 1H, *J* = 11.5 Hz, H-3), 3.77 (d, 1H, *J* = 11.5 Hz, H-13), 3.18 (dd, 1H, *J* = 13.5 Hz, *J* = 7.0 Hz, H-6'), 2.96 (dd, 1H, *J* = 13.5 Hz, *J* = 8.0 Hz, H-6), 2.58 (s, 3H, H-20), 2.14-2.24 (m, 1H, H-7), 2.05-2.13 (m, 1H, H-10), 0.93-0.99 (m, 9H, H-8 and H-9, H-12 or H-11), 0.88 (d, 3H, *J* = 7.0 Hz, H-11 or H-12). **^{13}C** NMR (101 MHz, CHLOROFORM-d) δ ppm 163.3 (C-2), 149.8 (C-17), 149.3 (C-15), 134.8 (C-19), 133.3 (C-14), 123.6 (C-18), 81.7 (C-5), 81.43 (C-13), 58.6 (C-3), 55.8 (C-6), 44.0 (C-20), 33.57 (C-10), 27.0 (C-7), 20.3 (C-8 or C-9), 20.2 (C-9 or C-8), 19.5 (C-11 or C-12), 15.0 (C-12 or C-11). **m/z** (ES+) 319 ([M+H]+, 100%).

*4.4.2. 3-(4-Fluorophenyl)-6-isobutyl-2-methyl-spiro[3,3a-dihydropyrazolo[3,4-d]thiazole-5,1'-cyclohexane] (**8b**).* Prepared according to the general procedure **C** with 1-isobutyl-4-thia-1-azaspiro[4.5]decan-2-thione **12b** (170 mg) and p-fluorobenzaldehyde. **8b** (38 mg, 15 %) was isolated by flash column chromatography (heptane / EtOAc gradient from pure heptane to hept/EtOAc 2:1, Rf = 0.1 in EtOAc) as a light yellow oil. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 7.19-7.29 (m, 2H, H-17 and H-21), 6.77-6.88 (m, 2H, H-18 and H-20), 4.36 (d, 1H, *J* = 11.5 Hz, H-3), 3.43 (d, 1H, *J* = 11.5 Hz, H-15), 2.96 (dd, 1H, *J* = 13.5, 6.5 Hz, H-6), 2.56 (dd, 1H, *J* = 13.5 Hz, *J* = 8.5 Hz, H-6'), 2.36 (s, 3H, H-22), 1.97-2.05 (m, 1H, H-7), 1.13-1.81 (m, 10H, H-10, H-11, H12, H-13 and H-14), 0.74 (d, 3H, *J* = 6.5 Hz, H-8 or H-9), 0.69 (d, 3H, *J* = 6.5 Hz, H-9 or H-8).**^{13}C** NMR (101 MHz, CHLOROFORM-d) δ ppm 162.5 (d, *J* = 245.0 Hz, C-19), 161.8 (C-2), 133.2 (d, *J* = 3.0 Hz, C-16), 129.0 (d, *J* = 8.0 Hz, C-17 and C-21), 115.5 (d, *J*

= 22.0 Hz, C-18 and C-20), 85.6 (C-5), 82.7 (C-15), 55.9 (C-3), 51.1 (C-6), 43.8 (C-22), 39.5 ($\underline{C}H_2$), 37.7 ($\underline{C}H_2$), 26.6 (C-7), 24.9 ($\underline{C}H_2$), 24.7 ($\underline{C}H_2$), 23.7 ($\underline{C}H_2$), 20.3 (C-8 or C-9), 20.2 (C-9 or C-8). **m/z** (ES+) 362 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for [M+H] ($C_{20}H_{29}FN_3S$+) requires **m/z** 362.2061, found **m/z** 362.2057.

*4.3.3. 3-(4-Fluorophenyl)-6-isobutyl-5-(2-methoxyphenyl)-2-methyl-3a,5-dihydro-3H-pyrazolo[3,4-d]thiazole (**8c**).* Prepared according to the general procedure **C** with 3-isobutyl-2-(2-methoxyphenyl)thiazolidin-4-thione **12c** (150 mg) and p-fluorobenzaldehyde. **8c** (30 mg, 14 %) was isolated by flash column chromatography (heptane / EtOAc gradient from pure heptane to hept/EtOAc 2:1) as a light yellow oil as a 1: 0.7 mixture of diastereoisomers.

Major diastereoisomer: **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 7.20-7.43 (m, 4H, H_{Ar}), 6.73-7.03 (m, 4H, H_{Ar}), 6.04 (s, 1H, H-5), 4.66 (d, 1H, *J* = 11.5 Hz, H-3), 3.67-3.87 (m, 4H, H-16 and H-17), 3.14 (dd, 1H, *J* = 14.0 Hz, *J* = 8.0 Hz, H-6), 2.92 (dd, 1H, *J* = 14.0 Hz, *J* = 7.5 Hz, H-6'), 2.55 (s, 3H, H-24), 1.93-2.05 (m, 1H, H-7), 0.86 (d, 3H, *J* = 6.5 Hz, H-8 or H-9), 0.85 (d, 3H, *J* = 6.5 Hz, H-9 or H-8).**^{13}C** NMR (101 MHz, CHLOROFORM-d) δ ppm 163.7 (C-2), 162.6 (d, *J* = 245.0 Hz, C-21), 160.8 (C-15), 133.1 (d, *J* = 3.0 Hz, C-18), 130.6 (C-10), 129.3 (C_{Ar}), 129.0 (d, *J* = 8.0 Hz, C-19 and C-23), 125.5 (C_{Ar}), 120.5 (C_{Ar}), 115.6 (d, *J* = 22.0 Hz, C-20 and C-22), 110.6 (C_{Ar}), 82.3 (C-17), 69.2 (C-5), 57.9 (C-3), 55.4 (C-16), 54.7 (C-6), 44.0 (C-24), 26.7 (C-7), 20.3 (C-8 or C-9), 20.2 (C-9 or C-8). **m/z** (ES+) 400 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for [M+H] ($C_{22}H_{27}FN_3S$+) requires **m/z** 400.1853, found **m/z** 400.1849.

Minor diastereoisomer: **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 7.20-7.43 (m, 4H, H_{Ar}), 6.73-7.03 (m, 4H, H_{Ar}), 6.04 (s, 1H, H-5), 4.72 (d, 1H, *J* = 12.0 Hz, H-3), 3.67-3.87 (m, 4H, H-16 and H-17), 3.15 (dd, 1H, *J* = 14.0, 8.5 Hz, H-6), 2.42 (dd, 1H, *J* = 14.0 Hz, *J* = 7.0 Hz, H-6'), 2.56 (s, 3H, H-24), 1.77-1.89 (m, 1H, H-7), 0.79 (d, 3H, *J* = 6.5 Hz, H-8 or H-9), 0.70 (d, 3H, *J* = 6.5 Hz, H-9 or H-8).**^{13}C** NMR (101 MHz, CHLOROFORM-d) δ ppm 163.7 (C-2), 162.6 (d, *J* = 245.0 Hz, C-21), 160.8 (C-15), 133.0 (d, *J* = 3.0 Hz, C-18), 130.7 (C-10), 129.4 (C_{Ar}), 129.2 (d, *J* = 8.0 Hz, C-19 and C-23), 126.0 (C_{Ar}), 121.0 (C_{Ar}), 115.7 (d, *J* = 22.0 Hz, C-20 and C-22), 111.6 (C_{Ar}), 82.0 (C-17), 69.2 (C-5), 58.0 (C-3), 55.6 (C-16), 51.8 (C-6), 43.9 (C-24), 26.4 (C-7), 20.1 (C-8 or C-9), 19.8 (C-9 or C-8). **m/z** (ES+) 400 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for [M+H] ($C_{22}H_{27}FN_3S$+) requires **m/z** 400.1853, found **m/z** 400.1848.

*4.3.4. 5-(3-Chlorophenyl)-6-cyclopropyl-3-(4-fluorophenyl)-2-methyl-3a,5-dihydro-3H-pyrazolo[3,4-d]thiazole (**8d**).* Prepared according to the general procedure **C** with 2-(3-chlorophenyl)-3-cyclopropyl-thiazolidin-4-thione **12d** (209 mg) and p-fluorobenzaldehyde. **8d** (126 mg, 42 %) was isolated by flash column chromatography (heptane / EtOAc gradient from pure heptane to pure EtOAc) as a light yellow oil.

Major diastereoisomer: **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 7.47-7.50 (m, 1H, H_{Ar}), 7.41-7.46 (m, 2H, H-17 and H-21), 7.36-7.40 (m, 1H, H_{Ar}), 7.32-7.36 (m, 2H, H_{Ar}), 7.07-7.08 (m, 2H, H-18 and H-20), 5.78 (s, 1H, H-5), 4.68 (d, 1H, *J* = 12.0 Hz, H-3), 3.93 (d, 1H, *J* = 12.0 Hz, H-15), 2.69 (s, 3H, H-22), 2.11-2.20 (m, 1H, H-6), 0.81-0.97 (m, 2H, H-7 or H-8), 0.46-0.64 (m, 1H, H-8 or H-7), 0.36-0.46 (m, 1H, H-8 or H-7). **^{13}C** NMR (101 MHz, CHLOROFORM-d) δ ppm 162.7 (d, *J* = 245.0 Hz, C-21), 161.4 (C-2), 141.6 (C-13), 134.6 (C-10), 132.7 (d, *J* = 3.0 Hz, C-16), 130.0 (C_{Ar}), 129.2 (d, *J* = 16.0 Hz, C-17 and C-21), 129.1 (C_{Ar}), 128.3 (C_{Ar}), 126.4 (C_{Ar}), 115.7 (d, *J* = 20.0 Hz, C-18 and C-20), 82.9 (C-15), 73.0 (C-5), 58.8 (C-3), 43.8 (C-22), 25.6 (C-6), 8.1 (C-7 or C-8), 6.3 (C-8 or C-7). **m/z** (ES+) 388 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for [M+H] ($C_{20}H_{20}ClFN_3S$+) requires **m/z** 388.1045, found **m/z** 388.1046.

Minor Diastereoisomer: (selected data) **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 7.40-7.44 (m, 2H, H-17 and H-21), 7.24-7.29 (m, 3H, H_{Ar}), 7.13-7.18 (m, 1H, H_{Ar}), 7.00-7.06 (m, 2H, H-18 and H-20), 5.73 (s, 1H, H-5), 4.84 (d, 1H, *J* = 12.0 Hz, H-3), 3.89 (d, 1H, *J* = 12.0 Hz, H-15), 2.67 (s, 3H, H-22), 2.52-2.58 (m, 1H, H-6), 0.71-0.92 (m, 2H, H-7 or H-8), 0.37-0.47 (m, 1H, H-8 or H-7), 0.20-0.30 (m, 1H, H-8 or H-7). **m/z** (ES+) 388 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for [M+H] ($C_{20}H_{20}ClFN_3S$+) requires **m/z** 388.1045, found **m/z** 388.1050.

*4.3.5. 6-Cyclopropyl-3-(4-fluorophenyl)-2-methyl-5-(3-pyridyl)-3a,5-dihydro-3H-pyrazolo[3,4-d]thiazole (**8e**).* Prepared according to the general procedure **C** with 3-cyclopropyl-2-(3-pyridyl)thiazolidin-4-thione **12e** (343 mg) and p-fluorobenzaldehyde. **8e** (20 mg, 4 %) was isolated by flash column chromatography (Heptane/EtOAc gradient from pure heptane to pure EtOAc, Rf = 0.1 in EtOAc) as a light yellow oil. **Major diastereoisomer:** **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 8.66 (d, 1H, *J* = 2.0 Hz, H-10), 8.61 (dd, 1H, *J* = 5.0 Hz Hz, *J* = 2.0 Hz, H-12), 7.91 (dt, 1H, *J* = 8.0 Hz, *J* = 2.0 Hz, H-14), 7.42-7.48 (m, 2H, H-17 and H-21), 7.28-7.31 (m, 1H, H-13), 7.03-7.10 (m, 2H, H-18 and H-20), 5.83 (s, 1H, H-5), 4.69 (d, 1H, *J* = 11.5 Hz, H-3), 3.92 (d, 1H, *J* = 11.5 Hz, H-15), 2.66 (s, 3H, H-22), 2.05-2.11 (m, 1H, H-6), 0.82-0.91 (m, 2H, H-7 or H-8), 0.50-0.58 (m, 1H, H-8 or H-7), 0.37-0.47 (m, 1H, H-8 or H-7). **^{13}C** NMR (101 MHz, CHLOROFORM-d) δ ppm 162.9 (d, *J* = 247.0 Hz, C-19), 161.4 (C-2), 150.8 (C-12), 149.7 (C-10), 136.2 (C-9), 136.1 (C-14), 132.7 (C-16), 129.3 (d, *J* = 16.0 Hz, C-17 and C-21), 123.9 (C-13), 115.9 (d, *J* = 20.0 Hz, C-18 and C-20), 83.1 (C-15), 71.2 (C-5), 59.0 (C-3), 44.0 (C-22), 25.8 (C-6), 8.5 (C-7 or C-8), 6.5 (C-8 or C-7). **m/z** (ES+) 355 ($[M+H]^+$, 100%).

Minor diastereoisomer: **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 8.52-8.54 (m, 2H, H-10 and H-12), 7.63 (dt, 1H, *J* = 8.0 Hz, *J* = 2.0 Hz, H-14), 7.37-7.42 (m, 2H, H-17 and H-21), 7.21-7.25 (m, 1H, H-13), 7.01-7.05 (m, 2H, H-18 and H-20), 5.74 (s, 1H, H-5), 4.83 (d, 1H, *J* = 11.0 Hz, H-3), 3.88 (d, 1H, *J* = 11.0 Hz, H-15), 2.66 (s, 3H, H-22), 2.50-2.57 (m, 1H, H-6), 0.80-0.89 (m, 1H, H-7 or H-8), 0.70-0.78 (m, 1H, H-7 or H-8), 0.35-0.42 (m, 1H, H-8 or H-7), 0.07-0.15 (m, 1H, H-8 or H-7). **^{13}C** NMR (101 MHz, CHLOROFORM-d) δ ppm 163.7 (C-2), 162.9 (d, *J* = 247.0 Hz, C-19), 150.1 (C-12), 148.2 (C-10), 134.5 (C-9), 134.5 (C-14), 132.8 (C-16), 129.2 (d, *J* = 16.0 Hz, C-17 and C-21), 123.8 (C-13), 115.8 (d, *J* = 20.0 Hz, C-18 and C-20), 83.6 (C-15), 72.2 (C-5), 58.0 (C-3), 44.1 (C-22), 28.7 (C-6), 6.3 (C-7 or C-8), 5.5 (C-8 or C-7).

*4.3.6. 5-(3-Chlorophenyl)-3-(4-fluorophenyl)-2-methyl-6-(2,2,2-trifluoroethyl)-3a,5-dihydro-3H-pyrazolo[3,4-d]thiazole (**8f**).* Prepared according to the general procedure **C** with 2-(3-chlorophenyl)-3-(2,2,2trifluoroethyl)thiazolidin-4-thione **12f** (226 mg) and p-fluorobenzaldehyde. **8f** (134 mg, 43 %) was isolated by flash column chromatography (heptane / EtOAc gradient from pure heptane to pure EtOAc, Rf = 0.1 in EtOAc) as a light yellow oil.

Major diastereoisomer: **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 7.22-7.29 (m, 3H, H-16, H-20 and H_{Ar}), 7.10-7.20 (m, 3H, H_{Ar}), 6.82-6.89 (m, 2H, H-17 and H-19), 5.87 (s, 1H, H-5), 4.63 (d, 1H, *J* = 12.0 Hz, H-3), 3.93 (dq, 1H, *J* = 16.0 Hz, *J* = 9.0 Hz, H-6), 3.76 (d, 1H, *J* = 12.0 Hz, H-14), 2.86-3.01 (m, 1H, H-6'), 2.43 (s, 3H, H-21). **^{13}C** NMR (101 MHz, CHLOROFORM-d) δ ppm 162.8 (d, *J* = 250.0 Hz, C-18), 160.8 (C-2), 138.1 (C-8 or C-12), 135.3 (C-12 or C-8), 132.3 (d, *J* = 3.0 Hz, C-15), 130.5 (C_{Ar}), 130.4 (C_{Ar}), 129.2 (d, *J* = 8.0 Hz, C-16 and C-20), 128.8 (C_{Ar}), 127.1 (C_{Ar}), 124.1 (q, *J*

= 279.0 Hz, C-7), 115.7 (d, *J* = 21.0 Hz, C-17 and C-19), 82.4 (C-14), 73.4 (C-5), 57.8 (C-3), 44.4 (q, *J* = 35.0 Hz, C-6), 43.5 (C-21). **m/z** (ES+) 430 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for [M+H] ($C_{19}H_{17}ClF_4N_3S$+) requires **m/z** 430.0762, found **m/z** 430.0763.

Minor diastereoisomer: ^{1}**H NMR** (400 MHz, CHLOROFORM-d) δ ppm 7.32-7.39 (m, 2H, H-16 and H-20), 7.18-7.23 (m, 3H, H_{Ar}), 7.02-7.12 (m, 1H, H_{Ar}), 6.92-7.00 (m, 2H, H-17 and H-19), 5.72 (s, 1H, H-5), 4.79 (d, 1H, *J* = 11.5 Hz, H-3), 3.89 (d, 1H, *J* = 11.5 Hz, H-14), 3.74-3.84 (m, 2H, H-6), 2.57 (s, 3H, H-21). ^{13}**C** NMR (101 MHz, CHLOROFORM-d) δ ppm 162.8 (d, *J* = 250.0 Hz, C-18), 161.2 (C-2), 142.2 (C-8 or C-12), 135.0 (C-12 or C-8), 132.3 (d, *J* = 3.0 Hz, C-15), 130.3 (C_{Ar}), 129.1 (d, *J* = 6.0 Hz, C-16 and C-20), 129.0 (C_{Ar}), 126.2 (C_{Ar}), 124.2 (C_{Ar}), 124.0 (q, *J* = 279.0 Hz, C-7), 115.8 (d, *J* = 22.0 Hz, C-17 and C-19), 83.4 (C-14), 74.0 (C-5), 56.9 (C-3), 48.2 (q, *J* = 35.0 Hz, C-6), 43.7 (C-21). **m/z** (ES+) 430 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for [M+H] ($C_{19}H_{17}ClF_4N_3S$+) requires **m/z** 430.0762, found **m/z** 430.0762.

*4.3.7. 5-(4-Chlorophenyl)-3-isobutyl-2-methyl-6-(2,2,2-trifluoroethyl)-3a,5-dihydro-3H-pyrazolo[3,4-d]thiazole (**8g**).* Prepared according to the general procedure **C** with 3-(3-chlorophenyl)-3-(2,2,2trifluoroethyl)thiazolidin-4-thione **12g** (209 mg) and isobutyraldehyde. **8g** (150 mg, 57%) was isolated by flash column chromatography (heptane / EtOAc gradient from pure heptane to pure EtOAc, Rf = 0.1 in EtOAc) as a light yellow oil.

Major diastereoisomer: ^{1}**H NMR** (400 MHz, CHLOROFORM-d) δ ppm 7.30-7.56 (m, 4H, H-9, H-10, H-12 and H-13), 6.11 (s, 1H, H-5), 4.45 (d, 1H, *J* = 12.0 Hz, H-3), 4.08 (dq, 1H, *J* = 15.5 Hz, *J* = 9.5 Hz, H-6), 2.97-3.16 (m, 2H, H-6' and H-14), 2.72 (s, 3H, H-19), 1.49-1.74 (m, 3H, H-15 and H-16), 0.98 (d, 3H, *J* = 6.0 Hz, H-17 or H-18), 0.89 (d, 3H, *J* = 6.0 Hz, H-18 or H-17). ^{13}**C** NMR (101 MHz, CHLOROFORM-d) δ ppm 161.5 (C-2), 136.0 (C-11), 134.8 (C-8), 130.3 (C-10 and C-12), 129.5 (C-9 and C-13), 124.0 (q, *J* = 270.0 Hz, C-7), 77.9 (C-14), 73.4 (C-5), 54.8 (C-3), 44.1 (q, *J* = 35.0 Hz, C-6), 43.8 (C-19), 40.2 (C-15), 27.2 (C-16), 24.2 (C-17 or C-18), 21.8 (C-18 or C-17). **m/z** (ES+) 392 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for [M+H] ($C_{17}H_{22}ClF_3N_3S$+) requires **m/z** 392.1170, found **m/z** 392.1167.

Minor diastereoisomer: ^{1}**H NMR** (400 MHz, CHLOROFORM-d) δ ppm 7.33-7.44 (m, 2H, H_{Ar}), 7.20-7.25 (m, 2H, H_{Ar}), 5.76 (s, 1H, H-5), 4.48 (d, 1H, *J* = 12.0 Hz, H-3), 3.73-3.92 (m, 2H, H-6), 2.97-3.10 (m, 1H, H-14), 2.72 (s, 3H, H-19), 1.49-1.73 (m, 3H, H-15 and H-16), 0.93 (d, 3H, *J* = 6.0 Hz, H-17 or H-18), 0.87 (d, 3H, *J* = 6.0 Hz, H-18 or H-17). ^{13}**C** NMR (101 MHz, CHLOROFORM-d) δ ppm 161.5 (C-2), 138.8 (C-11), 134.5 (C-8), 129.1 (C-10 and C-12), 127.2 (C-9 and C-13), 124.0 (q, *J* = 270.0 Hz, C-7), 79.0 (C-14), 74.1 (C-5), 53.6 (C-3), 44.5 (q, *J* = 35.0 Hz, C-6), 43.9 (C-19), 40.3 (C-15), 27.2 (C-16), 24.1 (C-17 or C-18), 21.6 (C-18 or C-17). **m/z** (ES+) 392 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for [M+H] ($C_{17}H_{22}ClF_3N_3S$+) requires **m/z** 392.1170, found **m/z** 392.1170.

*4.3.8. 3-(4-Fluorophenyl)-2-methyl-5-(3-pyridyl)-6-(2,2,2-trifluoroethyl)-3a,5-dihydro-3H-pyrazolo[3,4-d]thiazole (**8h**).* Prepared according to the general procedure **C** with 2-(3-pyridyl)-3-(2,2,2trifluoroethyl)thiazolidin-4-thione **12h** (210 mg) and p-fluorobenzaldehyde. **8h** (138 mg, 48 %) was isolated by flash column chromatography (heptane / EtOAc gradient from pure heptane to pure EtOAc, Rf = 0.1 in EtOAc) as a light yellow oil.

Major diastereoisomer: ^{1}**H NMR** (400 MHz, CHLOROFORM-d) δ ppm 8.72 (dd, 1H, *J* = 5.0 Hz, *J* = 2.0 Hz, H-11), 8.69 (d, 1H, *J* = 2.0 Hz, H-9), 7.87 (dt, 1H, *J* = 8.0 Hz, *J* 2.0 Hz, H-13), 7.41-7.52 (m, 3H, H-12, H-16 and H-20), 7.03-7.13 (m, 2H, H-17 and H-19), 6.17 (s, 1H, H-5), 4.88 (d, 1H, *J* = 12.0 Hz, H-3), 4.10-4.26 (m, 1H, H-6), 3.94-4.06 (m, 1H, H-14), 3.04-3.19 (m, 1H, H-6'), 2.66 (s, 3H, H-21). ^{13}**C** NMR (101 MHz, CHLOROFORM-d) δ ppm 162.7 (d, *J* = 250.0 Hz, C-18), 160.7 (C-2), 151.6 (C-11), 150.3 (C-9), 136.5 (C-13), 135.9 (C-8), 132.1 (d, *J* = 3.0 Hz, C-15), 129.2 (d, *J* = 8.0 Hz, C-16 and C-20), 124.1 (C-12), 124.1 (q, = *J* 279.0 Hz, C-7), 115.8 (d, *J* = 22.0 Hz, C-17 and C-19), 82.5 (C-14), 71.5 (C-5), 57.9 (C-3), 44.2 (q, *J* = 35.0 Hz, C-6), 43.5 (C-21). **m/z** (ES+) 383 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for [M+H] ($C_{18}H_{17}F_4N_4S$+) requires **m/z** 397.1104, found **m/z** 397.1103.

Minor diastereoisomer: ^{1}**H NMR** (400 MHz, CHLOROFORM-d) δ ppm 8.59 (dd, 1H, *J* = 5.0 Hz, *J* = 2.0 Hz, H-11), 8.55 (d, 1H, *J* = 2.0 Hz, H-9), 7.70 (dt, 1H, *J* = 8.0 Hz, *J* = 2.0 Hz, H-13), 7.41-7.52 (m, 2H, H-16 and H-20), 7.34 (dd, 1H, *J* = 8.0 Hz, *J* 5.0 Hz, H-12), 7.03-7.13 (m, 2H, H-17 and H-19), 5.84 (s, 1H, H-5), 4.90 (d, 1H, *J* = 11.5 Hz, H-3), 3.94-4.06 (m, 2H, H-6 and H-14), 3.72-3.85 (m, 1H, H-6'), 2.66 (s, 3H, H-21). ^{13}**C** NMR (101 MHz, CHLOROFORM-d) δ ppm 162.7 (d, *J* = 250.0 Hz, C-18), 160.7 (C-2), 150.3 (C-11), 147.7 (C-9), 134.0 (C-13), 135.9 (C-8), 132.1 (d, *J* = 3.0 Hz, C-15), 129.1 (d, *J* 8.0 = Hz, C-16 and C-20), 123.8 (C-12), 124.1 (q, *J* = 279.0 Hz, C-7), 115.7 (d, *J* = 22.0 Hz, C-17 and C-19), 83.6 (C-14), 72.7 (C-5), 57.0 (C-3), 48.5 (q, *J* =35.0 Hz, C-6), 43.5 (C-21). **m/z** (ES+) 383 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for [M+H] ($C_{18}H_{17}F_4N_4S$+) requires **m/z** 397.1104, found **m/z** 397.1101.

*4.3.9. 5-(4-chlorophenyl)-3-(4-fluorophenyl)-2-methyl-6-(2,2,2-trifluoroethyl)-3a,5-dihydro-3H-pyrazolo[3,4-d]thiazole (^{1}**H**).* Prepared according to the general procedure **C** with 3-(3-chlorophenyl)-3-(2,2,2trifluoroethyl)thiazolidin-4-thione **12g** (220 mg) and p-fluorobenzaldehyde. **8i** (115 mg, 38 %) was isolated by flash column chromatography (heptane / EtOAc gradient from pure heptane to pure EtOAc, Rf = 0.1 in EtOAc) as a light yellow oil.

Major diastereoisomer: ^{1}**H NMR** (400 MHz, CHLOROFORM-d) δ ppm 7.22-7.28 (m, 2H, H-16 and H-20), 7.20 (app. d, 4H, *J* = 2.5 Hz, H-9, H-10, H-12 and H-13), 6.81-6.88 (m, 2H, H-17 and H-19), 5.90 (s, 1H, H-5), 4.63 (d, 1H, *J* = 12.0 Hz, H-3), 3.91 (dq, 1H, *J* = 15.5 Hz, *J* = 9.5 Hz, H-6), 3.74 (d, 1H, *J* = 12.0 Hz, H-14), 2.82-3.00 (m, 1H, H-6'), 2.43 (s, 3H, H-21). ^{13}**C** NMR (101 MHz, CHLOROFORM-d) δ ppm 162.8 (d, *J* = 245.0 Hz, C-18), 161.0 (C-2), 136.2 (C-8 or C-11), 134.3 (C-11 or C-8), 132.2 (d, *J* = 4.0 Hz, C-15), 130.3 (C-9 and C-13), 129.5 (C-10 and C-12), 129.2 (d, *J* = 8.0 Hz, C-16 and C-20), 124.0 (q, *J* = 279.0 Hz, C-7), 115.8 (d, *J* = 21.0 Hz, C-17 and C-19), 82.4 (C-14), 73.5 (C-5), 57.8 (C-3), 44.3 (q, *J* = 34.0 Hz, C-6), 43.5 (C-21). **m/z** (ES+) 430 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for [M+H] ($C_{19}H_{17}ClF_4N_3S$+) requires **m/z** 430.0762, found **m/z** 430.0766.

Minor diastereoisomer: ^{1}**H NMR** (400 MHz, CHLOROFORM-d) δ ppm 7.40-7.47 (m, 2H, H-16 and H-20), 7.32-7.38 (m, 2H, H-10 and H-12), 7.22-7.26 (m, 2H, H-9 and H-13), 7.01-7.09 (m, 2H, H-17 and H-19), 5.80 (s, 1H, H-5), 4.87 (d, 1H, *J* = 12.0 Hz, H-3), 3.96 (d, 1H, *J* = 12.0 Hz, H-14), 3.77-3.94 (m, 2H, H-6), 2.65 (s, 3H, H-21). ^{13}**C** NMR (101 MHz, CHLOROFORM-d) δ ppm 162.8 (d, *J* = 245.0 Hz, C-18), 161.3 (C-2), 138.2 (C-8 or C-11), 134.8 (C-11 or C-8), 132.3 (d, *J* = 3.0 = Hz, C-15), 129.2 (C-10 and C-12), 129.1 (d, *J* = 8.0 = Hz, C-16 and C-20), 127.5 (C-9 and C-13), 123.9 (q, *J* = 280.0 Hz, C-7), 115.8 (d, *J* = 21.0 Hz, C-17 and C-19), 83.5 (C-14), 74.1 (C-5), 56.9 (C-3), 48.5 (q, *J* = 35.0 Hz, C-6), 43.7 (C-21). **m/z** (ES+) 430 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for [M+H] ($C_{19}H_{17}ClF_4N_3S$+) requires **m/z** 430.0762, found **m/z** 430.0764.

*4.3.10. 3,6-Bis(4-fluorophenyl)-5-(2-methoxyphenyl)-2-methyl-3a,5-dihydro-3H-pyrazolo[3,4-d]thiazole **(8j)**.* Prepared according to the general procedure **C** with 3-(4-fluorophenyl)-2-(2-methoxyphenyl)thiazolidin-4-thione **12i** (200 mg) and p-fluorobenzaldehyde. **8j** (82 mg, 30 %) was isolated by flash column chromatography (heptane / EtOAc gradient from pure heptane to pure EtOAc, Rf = 0.1 in EtOAc) as a light yellow oil (unseparable mixture of diastereoisomers).**^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 7.15-7.45 (m, 12H, H_{Ar}), 6.72-7.05 (m, 13H, H-5a and H_{Ar}), 6.60 (s, 1H, H-5b), 4.75 (d, 1H, *J* = 12.0 Hz, H-3a), 4.72 (d, 1H, *J* = 12.0 Hz, H-3b), 3.92 (d, 1H, *J* = 12.0 Hz, H-14a), 3.91 (d, 1H, *J* = 12.0 Hz, H-14b), 3.83 (s, 6H, H-18), 3.91 (s, 6H, H-26). **^{13}C** NMR (101 MHz, CHLOROFORM-d) δ ppm 162.7 (d, *J* = 245.0 Hz, C_{quat}-F), 162.6 (d, *J* = 245.0 Hz, C_{quat}-F), 159.3 (C-2a), 158.3 (C-2b), 156.2 (C-17b), 155.5 (C-17a), 136.1 (d, *J* = 2.0 Hz, C-6a), 136.0 (d, *J* = 2.0 Hz, C-6b), 132.7 (d, *J* = 3.0 Hz, C-20b), 132.5 (d, *J* = 3.0 Hz, C-20a), 129.8 (C_{Ar}), 129.6 (C_{Ar}), 129.1 (d, *J* = 8.0 Hz, C-21a and C-25a), 129.0 (d, *J* = 8.0 Hz, C-21b and C-25b), 127.8 (C-12a), 127.4 (C-12b), 127.3 (C_{Ar}), 124.7 (C_{Ar}), 121.4 (C_{Ar}), 120.7 (C_{Ar}), 119.5 (d, *J* = 8.0 Hz, C-11a and C-7a), 119.4 (d, *J* = 8.0 Hz, C-11b and C-7b), 115.7 (d, *J* = 21.0 Hz, C_{Ar}-CF), 115.6 (d, *J* = 21.0 Hz, C_{Ar}-CF), 115.3 (d, *J* = 21.0 Hz, C_{Ar}-CF), 110.8 (C_{Ar}), 110.7 (C_{Ar}), 82.1 (C-14b), 80.8 (C-14a), 68.7 (C-5b), 66.9 (C-5a), 59.1 (C-3b), 58.4 (C-3a), 55.7 (C-18b), 55.5 (C-18a), 43.9 (C-26a), 43.6 (C-26b). **m/z** (ES+) 438 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for [M+H] ($C_{24}H_{22}F_2N_3OS$+) requires **m/z** 438.1446, found **m/z** 438.1442.

*4.3.11. 6-(4-Fluorophenyl)-3-isobutyl-5-(2-methoxyphenyl)-2-methyl-3a,5-dihydro-3H-pyrazolo[3,4-d]thiazole **(8k)**.* Prepared according to the general procedure **C** with 3-(4-fluorophenyl)-2-(2-methoxyphenyl)thiazolidin-4-thione **12i** (185 mg) and isobutyraldehyde. **8k** (74 mg, 32 %) was isolated by flash column chromatography (heptane / EtOAc gradient from pure heptane to Heptane/EtOAc 3:2, Rf = 0.49 in Hept/EtOAc 1:2) as a light yellow oil.

Major diastereoisomer: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.17-7.49 (m, 4H, H_{Ar}), 6.77-7.13 (m, 5H, H-5 and H_{Ar}), 4.43 (d, 1H, *J* = 12.0 Hz, H-3), 3.91 (s, 3H, H-18), 3.01-3.15 (m, 1H, H-19), 2.82 (s, 3H, H-24), 1.48-1.72 (m, 3H, H-20 and H-21), 0.80-1.02 (m, 6H, H-22 and H-23). **^{13}C** NMR (101 MHz, CHLOROFORM-d) δ ppm 159.1 (C-2), 157.9 (d, *J* = 240.0 Hz, C-9), 156.2 (C-13), 136.1 (d, *J* = 3.0 Hz, C-6), 129.7 (C_{Ar}), 128.6 (C-12), 127.4 (C_{Ar}), 121.4 (C_{Ar}), 119.4 (d, *J* = 8.0 Hz, C-11 and C-7), 115.2 (d, *J* = 22.0 Hz, C-8 and C-10), 110.7 (C_{Ar}), 77.6 (C-14), 66.9 (C-5), 56.0 (C-3), 55.8 (C-18), 43.8 (C-24), 40.4 (C-20), 27.2 (C-21), 24.2 (C-22 or C-23), 21.9 (C-23 or C-22). **m/z** (ES+) 400 ($[M+H]^+$, 100%)

Minor diastereoisomer: ^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.17-7.49 (m, 4H, H_{Ar}), 6.77-7.13 (m, 4H, H_{Ar}), 6.63 (s, 1H, H-5), 4.48 (d, 1H, *J* = 12.0 Hz, H-3), 3.93 (s, 3H, H-18), 3.01-3.15 (m, 1H, H-19), 2.80 (s, 3H, H-24), 1.48-1.72 (m, 3H, H-20 and H-21), 0.80-1.02 (m, 6H, H-22 and H-23). **^{13}C** NMR (101 MHz, CHLOROFORM-d) δ ppm 162.0 (C-13), 159.1 (C-2), 157.9 (d, *J* = 240.0 Hz, C-9), 136.1 (d, *J* = 3.0 Hz, C-6), 129.4 (C_{Ar}), 128.1 (C-12), 127.3 (C_{Ar}), 120.7 (C_{Ar}), 119.5 (d, *J* = 8.0 Hz, C-11 and C-7), 115.5 (d, *J* = 22.0 Hz, C-8 and C-10), 110.8 (C_{Ar}), 77.6 (C-14), 66.8 (C-5), 56.0 (C-3), 55.6 (C-18), 44.0 (C-24), 40.2 (C-20), 27.1 (C-21), 24.2 (C-22 or C-23), 21.6 (C-23 or C-22).

*4.3.12. 6-(4-Chlorophenyl)-3-(4-fluorophenyl)-5-isobutyl-2-methyl-3a,5-dihydro-3H-pyrazolo[3,4-d]thiazole **(8l)*** Prepared according to the general procedure **C** with 3-(4-chlorophenyl)-2-isobutyl-thiazolidin-4-thione **12j** (200 mg) and p-fluorobenzaldehyde. **8l** (56 mg, 20 %) was isolated by flash column chromatography (heptane / EtOAc gradient from pure heptane to pure EtOAc, Rf = 0.1 in EtOAc) as a light yellow oil.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.39-7.49 (m, 4H, H-18, H-22 and H_{Ar}), 7.30-7.36 (m, 2H, H_{Ar}), 7.03-7.12 (m, 2H, H-19 and H-21), 5.68 (dd, 1H, *J* = 10.5 Hz, *J* = 3.0 Hz, H-5), 4.67 (d, 1H, *J* = 12.0 Hz, H-3), 3.90 (d, 1H, *J* = 12.0 Hz, H-16), 2.67 (s, 3H, H-23), 1.92-2.07 (m, 1H, H-12), 1.62-1.80 (m, 2H, H-12' and H-13), 0.97 (d, 3H, *J* = 7.0 Hz, H-14 or H-15), 0.94 (d, 3H, *J* = 7.0 Hz, H-15 or H-14). **^{13}C** NMR (101 MHz, CHLOROFORM-d) δ ppm 162.7 (d, *J* = 245.0 Hz, C-20), 157.4 (C-2), 138.2 (C-6), 132.6 (d, *J* = 3.0 Hz, C-17), 129.2 (d, *J* = 11.0 Hz, C-18 and C-22), 129.1 (2xC_{Ar}), 128.2 (C-9), 121.0 (C_{Ar}), 115.7 (d, *J* = 20.0 Hz, C-19 and C-21), 82.3 (C-16), 7.06 (C-5), 58.3 (C-3), 44.1 (C-12), 43.6 (C-23), 25.2 (C-13), 23.8 (C-14 or C-15), 21.2 (C-15 or C-14). **m/z** (ES+) 404 ($[M+H]^+$, 100%), HRMS (ES+) exact mass calculated for [M+H] ($C_{21}H_{24}ClFN_3S$+) requires **m/z** 404.1358, found **m/z** 404.1357.

*4.3.13. 5-(4-Chlorophenyl)-3-isobutyl-2-methyl-6-(3-pyridyl)-3a,5-dihydro-3H-pyrazolo[3,4-d]thiazole **(8m)**.*

Prepared according to the general procedure **C** with 2-(4-chlorophenyl)-3-(3-pyridyl)thiazolidin-4-thione **13k** (250 mg) and isobutyraldehyde. **8m** (10 mg, 3 %) was isolated by flash column chromatography (heptane / EtOAc gradient from pure heptane to pure EtOAc, Rf = 0.26 in Hept/EtOAc 1:1) as a light yellow oil. **^{1}H NMR** (400 MHz, CHLOROFORM-d) δ ppm 8.50 (br. s, 1H, H-7), 8.22 (d, 1H, *J* = 1.5 Hz, H-9), 8.16 (dt, 1H, *J* = 8.5 and 1.5 Hz, H-11), 7.33 (d, 2H, *J* = 8.5 Hz, H-14 and H-16), 7.21-7.25 (m, 1H, H-10), 7.18 (d, 2H, *J* = 8.5 Hz, H-13 and H-17), 6.42 (s, 1H, H-5), 4.53 (d, 1H, *J* = 11.0 Hz, H-3), 3.09 (td, 1H, *J* = 11.0 and 4.0 Hz, H-18), 2.81 (s, 3H, H-23), 1.57-1.69 (m, 2H, H-19), 1.44-1.52 (m, 1H, H-20), 0.93 (d, 3H, *J* = 6.5 Hz, H-22 or H-21), 0.87 (d, 3H, *J* = 6.5 Hz, H-21 or H-22). **^{13}C** NMR (101 MHz, CHLOROFORM-d) δ ppm 158.5 (C-2), 149.0 (C-6), 143.4 (C-9), 138.8 (C-7), 138.5 (C-12), 134.4 (C-15), 129.5 (C-14 and C-16), 126.4 (C-13 and C-17), 124.9 (C-11), 123.8 (C-10), 76.7 (C-18), 72.1 (C-5), 54.7 (C-3), 43.9 (C-23), 40.1 (C-19), 27.2 (C-20), 22.4 (C-21 or C-22), 21.6 (C-22 or C-21). **m/z** (ES+) 387 ($[M+H]^+$, 100%).

4.5. Preparation of 5-[(4-fluorophenyl)methylene]-3-isobutyl-2-(2-methoxyphenyl)thiazolidin-4-one 7c : a dried one-necked flask, equipped with a magnetic stirrer bar, was charged with thiazolidinone **5c** (1.0 g, 1.0 eq.), *p*-fluorobenzaldehyde (0.4 mL, 1.1 eq.) and dry toluene (30 mL, 0.1 mol/L). Then, potassium ^{t}butoxide (4.1 mL, 1.1 eq.) was added dropwise. After stirring for 5 min under nitrogen, 3Å molecular sieves were added to the reaction. The mixture was left under a nitrogen atmosphere and stirred at RT until completion (monitored by LCMS, usually 30 min). Then, the solvent was removed under vacuum and the crude material was purified by FCC (heptane / EtOAc gradient from pure heptane to Heptane/EtOAc 2:1, Rf = 0.74 in Hept/EtOAc 1:1) giving 0.51g (37% yield) of desired product as a yellow oil.

^{1}H NMR (400 MHz, CHLOROFORM-d) δ ppm 7.51 (s, 1H, H-17), 7.43-7.50 (m, 2H, H-19 and H-23), 7.31 (td, 1H, *J* = 8.0 Hz, *J* = 2.0 Hz, H-13), 7.01-7.12 (m, 3H, H-15, H-20 and H-22), 6.88-6.99 (m, 2H, H-12 and H-14), 6.28 (s, 1H, H-5), 3.89 (s, 3H, H-16), 3.82 (dd, 1H, *J* = 14.0 Hz, *J* = 9.0 Hz, H-6), 2.67 (dd, 1H, *J* = 14.0 Hz, *J* = 6.0 Hz, H-6'), 1.95-2.08 (m, 1H, H-7), 0.92 (d, 3H, *J* = 6.5 Hz, H-8 or H-9), 0.91 (d, 3H, *J* = 6.5 Hz, H-9 or H-8).**^{13}C** NMR (101 MHz, CHLOROFORM-d) δ ppm 167.2 (C-2), 161.9 (d, *J* = 248.0 Hz, C-21), 157.1 (C-11), 131.7 (d, C-18), 131.1 (d, *J* = 8.0 Hz, C-19 and C-23), 130.1 (C-13), 126.5 (C-15), 126.3 (C-3), 125.9 (C-10), 124.0 (C-17), 121.2 (C-14), 115.6 (d, *J* = 21.0 Hz, C-20 and C-22), 111.0 (C-12), 56.8 (C-5), 55.7 (C-16), 50.7 (C-6), 26.6 (C-7), 20.3 (C-8 or C-9), 19.8 (C-9 or C-8). **m/z** (ES+) 372 ($[M+H]^+$, 100%).

References and notes

1. Lamberth, C., Dinges, J. in Bioactive Heterocyclic Compound Classes, Lamberth, C., Dinges, J. (Eds.), Wiley-VCH, Weinheim, 2012, p. 3-20.
2. a) Zwanenburg, B.; Kemperman, G. J.; Zhu, J.; De Gelder, R.; Dommerholt, F. J.; Titulaer, G. T. M.; Keltjens, R.; Klunder, A. J. H. in Synthesis of β-Lactam Antibiotics, Bruggink, A. (Ed.), Kluwer Academic Publishers, Dordrecht, 2001, pp. 56-101; b) Pitlik, J. *Bioorg. Med. Chem.* **1995**, *3*, 1157-1181.
3. a) Amery, W. K. P.; Bruynseels, J. P. J. M. *Int. J. Immunopharmcol.* **1992**, *14*, 481-486; b) Janssen, P. A. J. *Prog. Drug Res.* **1976**, *20*, 347-383.
4. a) Johnson, T. C. in Bioactive Heterocyclic Compound Classes, Lamberth, C., Dinges, J. (Eds.), Wiley-VCH, Weinheim, 2012, p. 51-60; b) Johnson, T. C.; Mann, R. K.; Schmitzer, P. R.; Gast, R. E.; deBoer, G. J. in Modern Crop Protection Compounds, Krämer, W., Schirmer, U., Jeschke, P., Witschel, M. (Eds.), Wiley-VCH, Weinheim, 2012, p. 99-117.
5. a) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083-3135; b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17; c) Multicomponent Reactions, Zhu, J.; Bienayme, H. (Eds.), Wiley-VCH, Weinheim, 2005; d) Hulme, C.; Gore, V. *Curr. Med. Chem*. **2003**, *10*, 51.
6. a) Tietze, L. F.; Brasche, G.; Gericke, K. M. Domino Reactions in Organic Synthesis, Wiley-VCH, Weinheim, 2006; b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134-7186; c) Pellisier, H. *Tetrahedron* **2006**, *62*, 2143-2173; d) Pellissier, H. *Tetrahedron* **2006**, *62*, 1619-1665; e) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115-136.
7. a) Synthesis of Heterocycles *via* Multicomponent Reactions; *Top. Heterocycl. Chem.* **2010**, *23*, Orru, R. V. A., Ruijter, E. (Eds.), Springer, Berlin, 2010; b) Jiang, B.; Shi, F.; Tu, S.-J. *Curr. Org. Chem.* **2010**, *14*, 357; c) Jiang, B.; Rajale, T.; Wever, W.; Tu, S.-J.; Li, G. *Chem. Asian J.* **2010**, *5*, 2318; d) Ivachtchenko, A. V.; Ivanenkov, Y. A.; Kysil, V. M:; Krasavin, M. Y.; Ilyin, A. P. *Russ. Chem. Rev.* **2010**, *79*, 787, e) Sunderhaus, J. D.; Martin, S. F. *Chem. Eur. J.* **2009**, *15*, 1300; f) D'Souza, D. M.; Müller, T. J. *J. Chem. Soc. Rev.* **2007**, *36*, 1095; g) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471; h) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133.
8. a) Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Acc. Chem. Res.* **2012**, *45*, 1278-1293; b) Padwa, A.; Bur, S. K. *Tetrahedron* **2007**, *63*, 5341-5378; c), Tietze, L. F.; Rackelmann, N. *Pure Appl. Chem.* **2004**, *76*, 1967-1983.
9. A) Sayed, H. H.; Morsy, E. M. H.; Kotb, E. R. *Synth. Commun.* **2010**, *40*, 2712-2722; b) Cherkupally, S. R.; Dasari, C. R.; Vookanti, Y.; Adki, N. *Org. Commun.* **2010**, *3*, 57-69; c) Reddy, C. S.; Srinivas, A.; Nagaraj, A. *Chem. Pharm. Bull.* **2009**, *57*, 685-693; d) Turgut, Z.; Yolacan, C.; Aydogan, F.; Bagdatli, E.; Ocal, N. *Molecules* **2007**, *12*, 2151-2159; e) Abdel-Megid, M.; Awas, M. A. A. *Heterocycl. Commun.* **2002**, *8*, 161-168; f) El-Zohry, M. F.; Awad, I. M. A.; Abdel-Hafez, A. A. *Arch. Pharm.* **1993**, *326*, 115-118.
10. a) Faidallah, H. M.; Khan, K. A.; Asiri, A. M. *J. Fluorine Chem.* **2011**, *132*, 131-137; b) Al-Saadi, M. S.; Rostom, S. A. F.; Faidallah, H. M. *Arch. Pharm. Chem. Life Sci*. **2008**, *341*, 181-190.
11. a) Shah, P. M.; Patel, M. P. *Ind. J. Chem.* **2011**, *50B*, 310-314; b) Srinivas, A.; Nagaraj, A.; Reddy, C. S. *J. Heterocycl. Chem.* **2008**, *45*, 999-1003; c) Gurav, V. M.; Huge, K. G.; Kondaya, G. C. *J. Indian Chem. Soc.* **2007**, *84*, 1174-1175; d) Desai, K. G.; Desai, K. R. J. *Sulfur Chem.* **2006**, *27*, 315-328; e) Srivastava, S. K.; Srivastava, S. L.; Srivastava, S. D. *J. Ind. Chem. Soc.* **2002**, *77*, 104-105.
12. Zhou, Z. Z.; Huang, W.; Ji, F. Q.; Ding. M. W.; Yang, G. F. *Heteroatom Chem.* **2007**, *18*, 381-3989.
13. Bhatt, R. K.; Sharma, S.; Nath, M. *Monatsh. Chem.* **2012**, *143*, 309-316.
14. Sharma, R. C.; Kumar. D. *J. Ind. Chem. Soc* **2000**, *77*, 492-493.
15. a) Rawal, R. K.; Prabhakar, Y. S.; Katti, S. B.; De Clercq, E. Biorog. Med. Chem. 2005, 13, 6771-6776; b) Srivastava, T.; Haq, W.; Katti, S. B. *Tetrahedron* **2002**, *58*, 7619-7624.
16. Bhosle, M. R.; Mali, J. R.; Mulay, A. A.; Mane, R. A. *Heteroat. Chem.* **2012**, *23*, 166-170.
17. a) Arya, K.; Rawat, D. S.; Dandia, A.; Sasai, H. *J. Fluorine Chem.* **2012**, *137*, 117-122; b) Lingampalle, D.; Jawale, D.; Waghmare, R.; Mane, R. *Synth. Commun.* **2010**, *40*, 2397-2401; c) Yadav, A. K.; Kumar, M.; Yadav, T.; Jain, R. *Tetrahedron Lett.* **2009**, *50*, 5031-5034; d) Zhang, X.; Li, X.; Li, D.; Qu, G.; Wang, J.; Loiseau, P. M.; Fan, X. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6280-6283; e) Fraga-Dubreuil, J.; Bazureau, J. P. *Tetrahedron* **2003**, *59*, 6121-6130.
18. Sadashivaa, C. T.; Narendra, J. N.; Chandraa, S.; Kavithaa, C. V.; Thimmegowdab, A.; Subhashc, M. N.; Rangapaa, K. S. *Eur. J. Med. Chem.* **2009**, *44*, 4848-4854.
19. Meshram, J.; Ali, P.; Tiwari, V. *Green Chem. Lett. Rev.* **2010**, *3*, 195-200.
20. Pratap, U. R.; Jawale, D. V.; Bhosle, M. R.; Mane, R. A. *Tetrahedron Lett.* **2011**, *52*, 1689-1691.
21. a) Srinivas, A.; Nagaraj, A.; Reddy, C. S. *Eur. J. Med. Chem.* **2010**, *45*, 2353-2358; b) Thadhaney, B.; Sharma, S.; Sharma, C.; Talesara, G. L. *J. Ind. Chem. Soc.* **2009**, *86*, 1204-1213; c) Reddy, C. S.; Srinivas, A.; Nagaraj, A. *Chem. Pharm. Bull.* **2009**, *57*, 685-693; d) Zhou, J.-F.; Sun, X.-J.; Zhu, F.-X.; Li, Y.-L-; Gong, G.-X. *Synth. Commun.* **2008**, *38*, 4182-4187; e) Merja, B. C.; Joshi, A. M.; Parikh, K. A.; Parikh, A. R. *Ind. J. Chem.* **2004**, *43B*, 909-912.
22. a) Dua, R.; Sonwane, S. K.; Srivastava, S. K.; Srivastava, S. D. *J. Chem. Pharm. Res.* **2010**, *2*, 415-423; b) Shashank, D.; Vishawanth, T.; Arif, P. M:; Balasubramaniam, V.; Nagendra, A.; Perumal, P.; Suthakaran, R. *Int. J. ChemTech Res.* **2009**, *1*, 1224-1231; c) Öcal, N.; Aydogan, F.; Yolacan, C.; Turgut, Z. *J. Heterocycl. Chem.* **2003**, *40*, 721-724;
23. Panda, S.; Dash, S. K. *J. Chem. Pharm. Res*. 2010, 2, 449-457.
24. Kaminskyy, D.; Khyluk, D.; Vasylenko, O.; Lesyk, R. *Tetrahedron Lett.* **2012**, *53*, 557-559.
25. Arya, K.; Dandia, A. *J. Fluorine Chem.* **2007**, *128*, 224-231.
26. Russel, A. J.; Westwood, I. M.; Crawford, M. H. J.; Robinson, J.; Kawamura, A.; Redfield, C.; Laurieri, N.; Lowe, E. D.; Davies, S. G.; Sim, E. *Bioorg. Med. Chem.* **2009** *17*, 905-918; b) Ohishi, Y.; Mukai, T.; Naghara, M.; Yajima, M.; Kajikawa, N.; Miyahara, K.; Takeno, T. *Chem. Pharm. Bull.* **1990**, *38*, 1911-1919; c) Li, Q.; Wu, J.; Zheng, H.; Liu, K.; Guo, T. L.; Eblen, S. T.; Grant, S.; Zhang, S. *Bioorg. Med. Chem.* **2010**, *20*, 4526-4530; d) Panda, S.; Dash, S. K. J. *Chem. Pharm. Res.* **2010**, *2*, 449-457; e) Eggers, K.; Fyles, T. M.; Montoya-Pelaez, P. J. *J. Org. Chem.* **2001**, *66*, 2966-2977; f) Kaminskyy, D.; Khyluk, D.; Vasylenko, O.; Lesyk, R. *Tetrahedron Lett.* **2012**, *53*, 557-559
27. a) Pawelczyk, A.; Zaprutko, L. *Flavour Fragr. J.* **2011**, *26*, 101-106; b) Vintonyak, V. V.; Warburg, K.; Kruse, H.; Grimme, S.; Hübel, K.; Rauh, D.; Waldmann, H. *Angew. Chem. Int. Ed.* **2010**, *49*, 5902-5905; c) Metwally, N. H. *Phosphorus Sulfur Silicon* **2008**, *183*, 34-43; d) Rao, A.; Carbone, A.; Chimirri, A.; De Clercq, E.; Monforte, A. M.; Montforte, P.; Pannecouque, C.; Zappala, M. *Farmaco* **2002**, *57*, 747-751.
28. a) Xu, Z.; De Moliner, F.; Cappelli, A. P. ; Hulme, C. *Angew. Chem. Int. Ed.* **2012**, *51*, 8037-8040 ; b) Ausmees, K. ; Kriis, K.; Pehk, T.; Werner, F.; Järving, I.; Lopp, M.; Kanger, T. *J. Org. Chem.* **2012**, *77*, 10680-10687.