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Bicyclic heterocyclic anthranilic diamides as ryanodine receptor modulators with insecticidal activity

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ABSTRACT

The diamide insecticides act on the ryanodine receptor (RyR). The synthesis of various bicyclic anthranilic derivatives is reported. Their activity against the insect ryanodine receptor (RyR) and their insecticidal activity in the greenhouse is presented, as well as structure activity relationship considerations.

1. Introduction

The insect ryanodine receptor (RyR) modulators belong to the most successful class of commercial insecticides introduced recently. Flubendiamide **1**, chlorantraniliprole **2** and cyantraniliprole **3** (Scheme 1) have captured a significant market share only a few years after introduction.[1] Even though the insecticidal properties of the natural product ryanodine have been known and exploited for a long time,[2] the potential of this mode of action has been realized only in the late 1990s, when the diamide insecticides were discovered, originating from a herbicide program at Nihon Nohyaku. Beside their unusual high activity (in some crops, rates as low as 5 g/ha are used), the toxicological profile of the diamides is remarkable, due in part to the high selectivity which these compounds exhibits, between insect and mammalian RyR.

The RyR are ion channels which regulate the release of calcium from intracellular stores located in the sarcoplasmic reticulum. The regulation of intracellular calcium concentration is fundamental for a series of biological processes such as muscle contraction, neurotransmission, hormonal release, gene expression, cell growth and cell differentiation.[3] Calcium mobilization through the RyR in muscle cells governs excitation/contraction coupling, and impairment of the RyR channels leads to serious muscle and neuronal disorders such as paralysis. The molecular details of the interaction of the diamides with the RyR are not understood and probably vary from species to species.[4] Recently, the crystal structure of this giant homotetrameric protein (2.2 MDa), obtained from mouse and rabbit by cryo-electron microscopy[5] is a breakthrough in the area; however due to the poor homology between insect and mammalian RyR, these structures cannot be used to build homology models for the design of new insecticides.

2. Results and discussion

Attracted by the high insecticidal activity of the diamides **1** to **3**, and particularly of the anthranilamides **2** and **3**, we wanted to investigate the potential of bicyclic anthranilamides. First results of compounds having a naphthalene core such as **4** were encouraging: the activity in vitro, measured in a displacement assay of a tritiated chlorantraniliprole analog (see Supplementary part of Ref. 6) as well as the insecticidal activity against leaf feeding insects such as Lepidoptera were outstanding and reached the level of the standards. Naphthalene derivatives have, however relatively high log*P*

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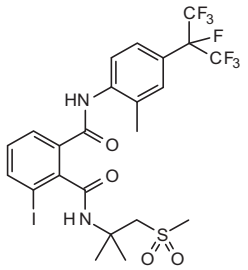
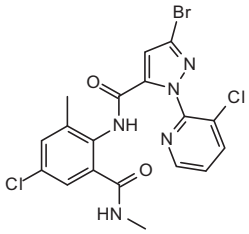
0968-0896/



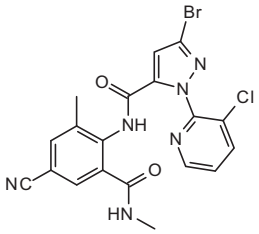
1

Flubendiamide



2

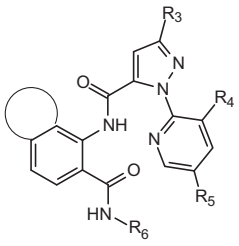
Chlorantraniliprole



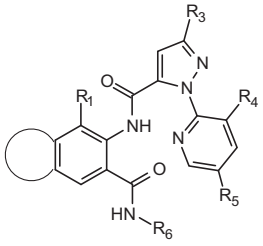
3

Cyantraniliprole

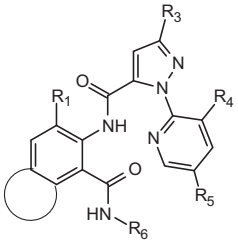
Scheme 1.



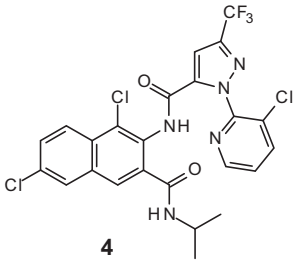
bicyclic anthranilamide type I



bicyclic anthranilamide type II



bicyclic anthranilamide type III



4

Spodoptera activity:
in vitro: IC_{50}: 5nM
in vivo: EC_{80}: 0.2 ppm

Scheme 2.

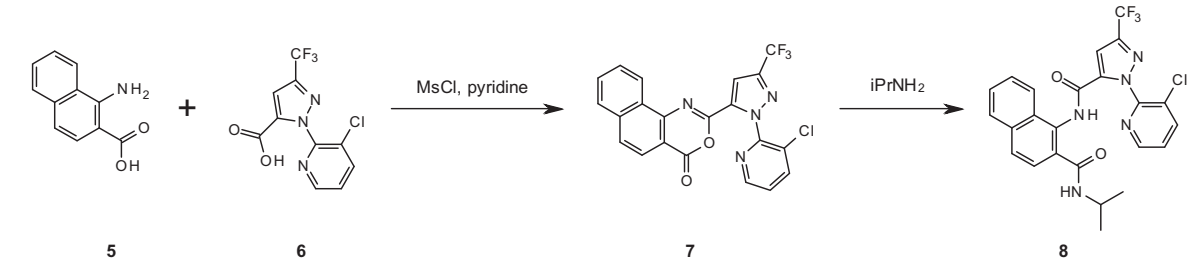
(>4) and our objective was to reduce this lipophilicity by introducing heteroatoms in the bicyclic system, to hopefully expand the biological spectrum of the lead **4**; more hydrophilic compounds have the potential to be systemic in the plant and thus be ingested by sap feeding insects.[7] Three types of bicyclic anthranilamides can be envisaged (types I, II and III as depicted in Scheme 2): For the types II and III, a substituent R^1 (methyl or halogen) ortho to the amino group is required for optimal biological activity: this substituent R^1 deconjugates the adjacent amide from the aromatic ring to which it is attached, and forces a conformation which is believed to be required for biological activity.

2.1. Bicyclic anthranilamides of type I

The synthesis of a naphthalene derivative of type I is depicted in Scheme 3. A benzoxazinone intermediate **7** was prepared in one step from commercially available anthranilic derivative **5** and an acid **6**, in the presence of an excess of mesyl chloride and pyridine.[8] The benzoxazinone reacted with an amine to yield the anthranilic diamide **8**. Compounds of type I were generally poorly active in the insecticidal screen.

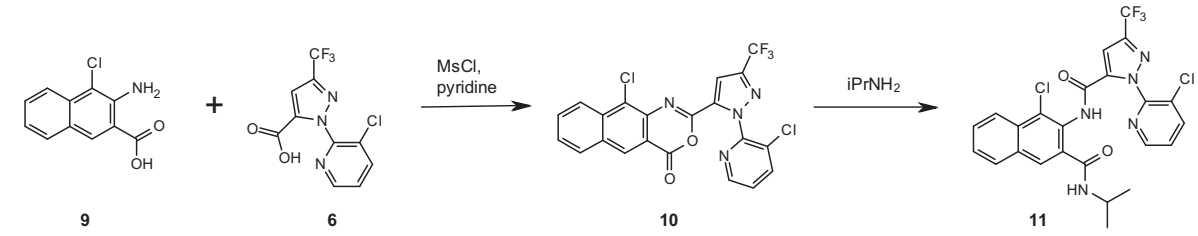
2.2. Bicyclic anthranilamides of type II

Naphthalene derivatives of type II such as **11** was easily prepared from the corresponding commercially available anthranilic acid (Scheme 4). Analogous quinolines and quinoxalines were prepared according to Schemes 5 and 6. The synthetic route is somewhat lengthy but efficient and appropriate to deliver gram quantities of the desired targets. The key step is the cycloaddition of a quinodimethane intermediate[9] such as **14** with maleic diester. The mono acid mono ester **17** was prepared through opening of the corresponding phthalanhydride with methanol. In the case of the pyridine derivatives **17**, this reaction was not regioselective and yielded a 1:1 mixture of **17a** and **17b**. Curtius rearrangement of the mono-acid mixture yielded a BOC protected anthranilic ester mixture which after deprotection gave a mixture of the amino esters **18** and **19** which could be separated with



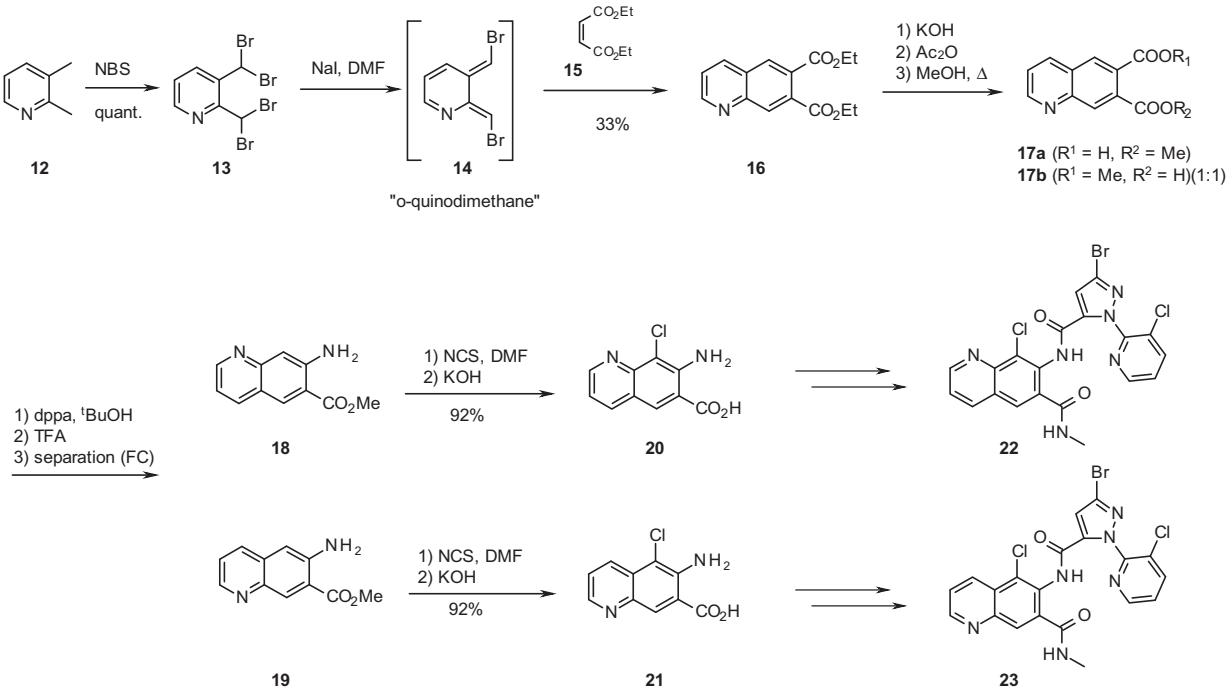
5 6 7 8

Scheme 3.



9 6 10 11

Scheme 4.



12 13 14 16 18 19 20 21 22 23

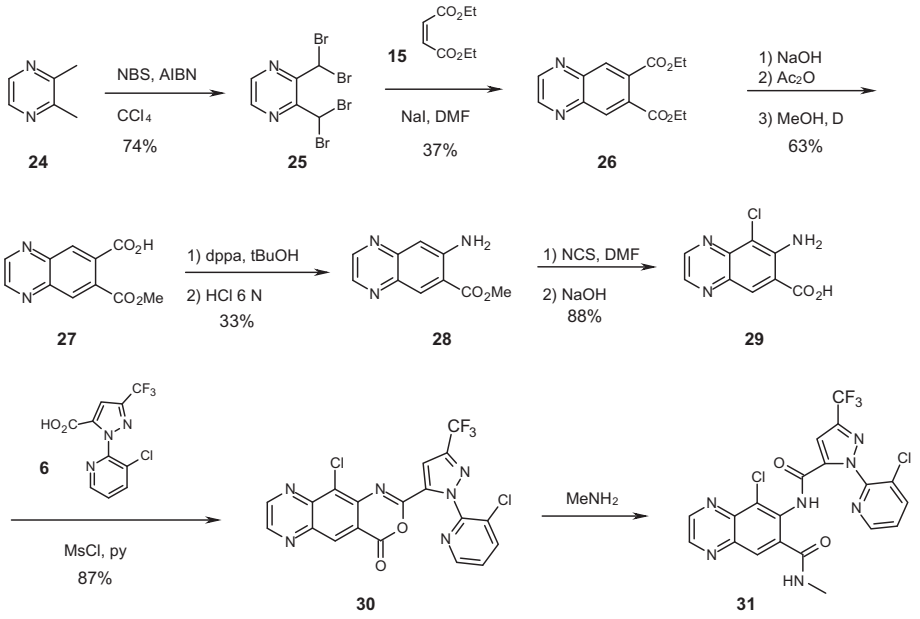
Scheme 5.

flash-chromatography. Each of the anthranilic esters were elaborated separately to the diamides **22** and **23**. Starting from dimethylpyrazine **24**, the same approach delivered the quinoxaline analog **31**, without a regioselectivity issue (Scheme 6).

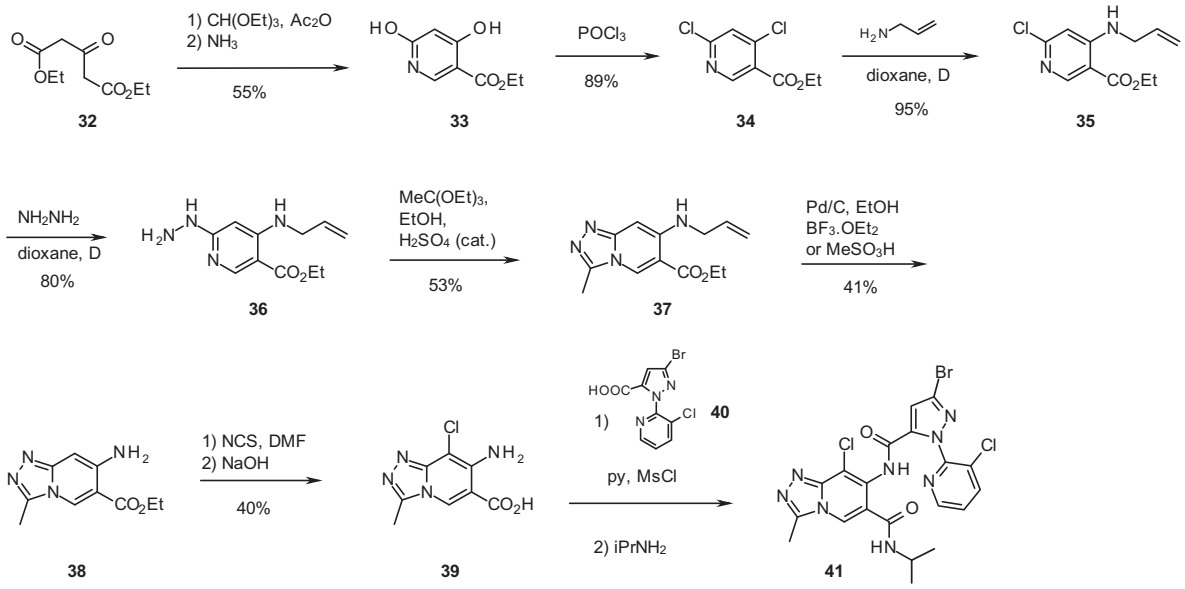
The triazolopyridine **41** was made from the de novo prepared ethyl 4,6-dichloropyridine-3-carboxylate **34**[10] as depicted in Scheme 7. Noteworthy is the preferred reactivity of amines or hydrazines on the position 4 rather than 2 of the pyridine **34**. Triazolopyridines are relatively basic and polar, making their isolation and purification tedious.

An anthranilic derivative with an indoline core **48** was easily made from methyl indoline-6-carboxylate **42** via regioselective nitration and halogenation (Scheme 8).

The dihydrobenzothiophene derivative **58** was made de novo from 2-chloro, 5-nitro benzaldehyde **49** as depicted in Scheme 9. Introduction of the carboxylic functionality ortho to the amine of **53** was performed through the isatin intermediate **55**. This versatile method[11] was used for various other heterocycles as described below. The isatin intermediate is prepared in two steps, first acylating with chloral to give **54**, followed by Friedel–Crafts acylation



Scheme 6.



Scheme 7.

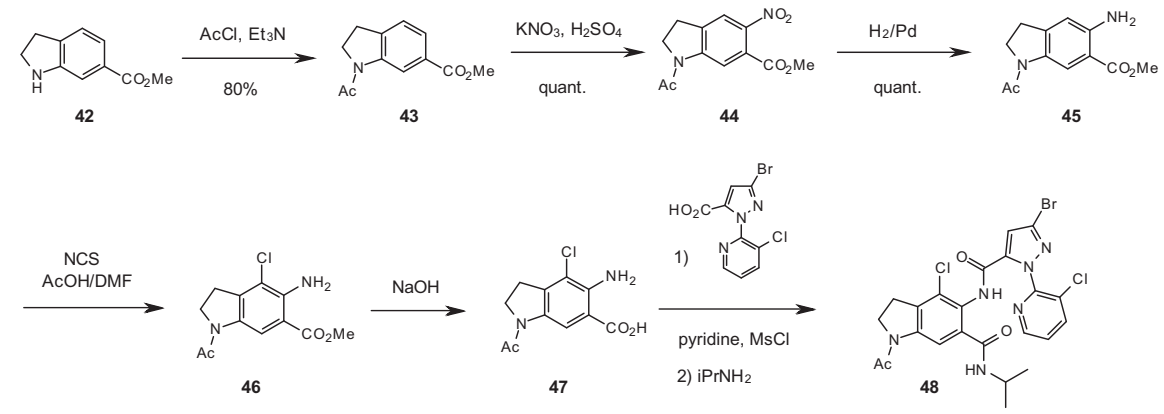
to **55**. After hydrogenation of the thiophene ring, **56** was oxidized under Baeyer–Villiger conditions to give the anthranilic acid which was directly chlorinated with NCS to give **57**. This method turned out to be robust and amenable to upscale (100 g batches).

2.3. Bicyclic anthranilamides of type III

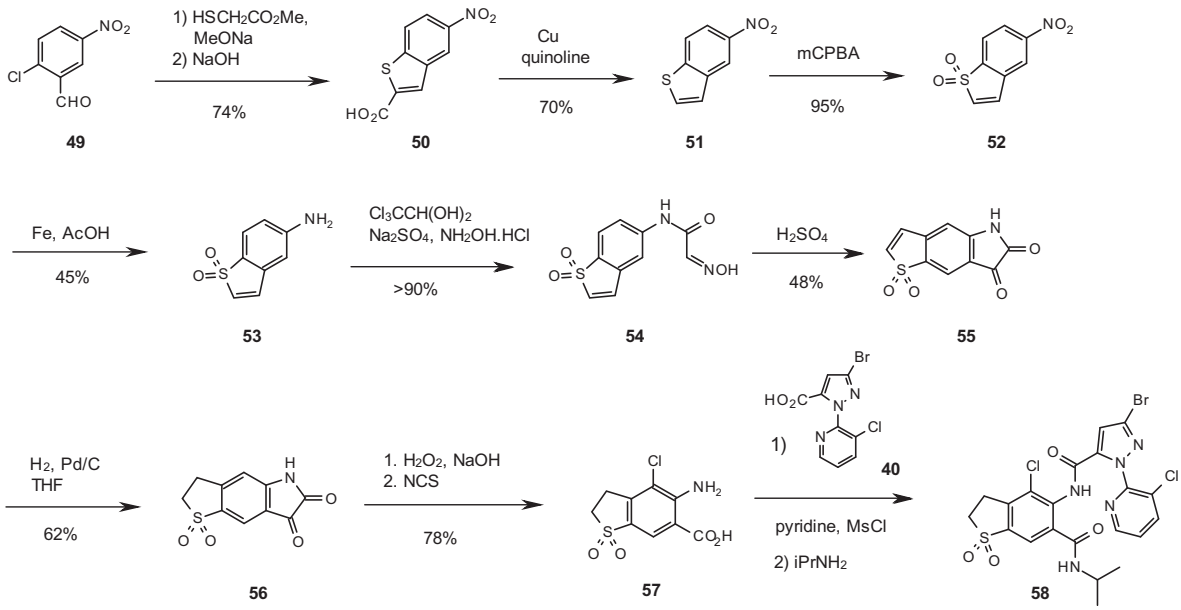
Benzimidazole **68**, benzotriazole **71** and benzothiadiazole **76** were all prepared from the same intermediate, 4-methyl-5-nitrobenzene-1,2-diamine **61**,[12] which was obtained by the selective Zinin reduction[13] of a dinitroaniline **60**. Benzimidazole **68** was made by cyclization of the diamine **61** with formic acid (Scheme 10). The introduction of the carboxylic functionality ortho to the amine was made according to the isatin methodology (**63**–**66**).

Benzotriazole **70** was obtained by diazotization of one amino group of **61** followed by cyclization under elimination of N_2 (Scheme 11). Benzothiadiazole **74** was made from the condensation of the diamine **61** with thionyl chloride[14] (Scheme 11). The anthranilic intermediate **75** was prepared by a Pd-catalyzed carboxylation, since the isatin methodology was not successful (Scheme 11).

Indazole **87** was prepared from the commodity 2,4-dimethylaniline **77** (Scheme 12). The key step was the diazotization of the nitration product **78**, which spontaneously cyclized under the elimination of N_2. We believe that the nitro group enhances the



Scheme 8.



Scheme 9.

acidity of the proton on the methyl substituent, which favors the cyclization. The final diamide was made from the aminolysis of the isatoic anhydride intermediate **84**. Upscale of these last steps proved to be difficult.

The key step in the synthesis of benzoxazole **97** was the cyclization of oxime **90** under aromatic nucleophilic displacement of a nitro group at 150 °C (Scheme 13). Once again the second nitro group is activating the desired cyclization reaction. Initial transformation of a benzoic acid **88** to an acetophenone **89** was made on a larger scale (10 g) by condensation with a malonate followed by bis-decarboxylation.

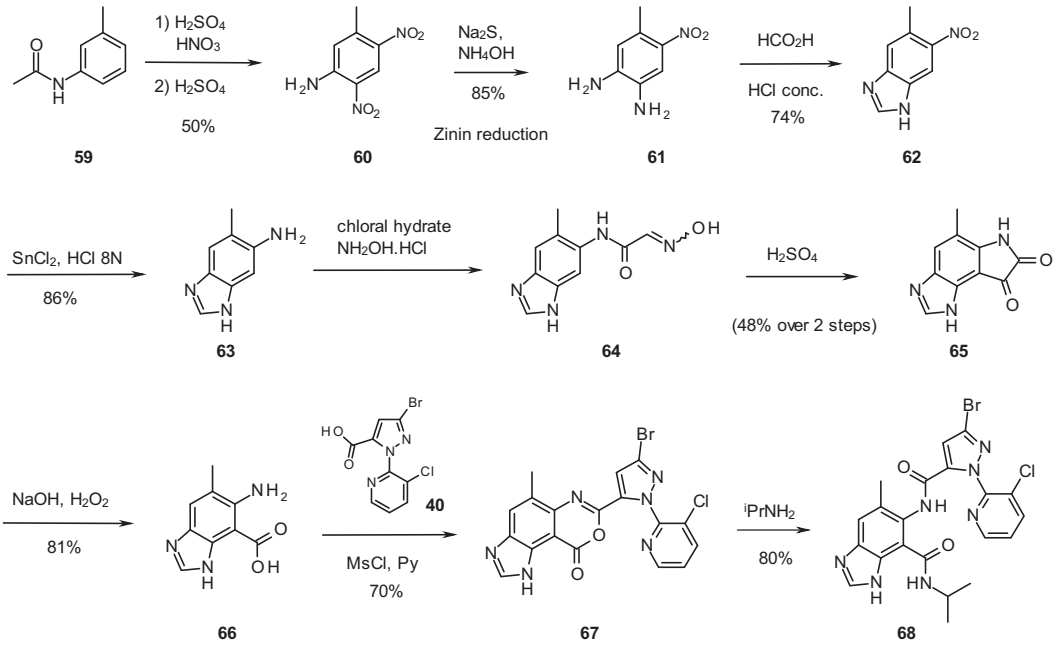
The preparation of the corresponding 3-amino-benzisoxazole **108** was less straightforward (Scheme 14). The key intermediate **103**, an ortho fluoro benzonitrile derivative, was prepared in six steps from the fluoro aniline **98**. Cyclization of **103** with *N*-acetyl hydroxylamine[15] to the benzisoxazole **104** was quantitative. Bis-protection of the more reactive amino group with BOC was required to elaborate the intermediate **107** to the final diamide **108**.

Finally, the preparation of triazolo-pyridine **116** is depicted in Scheme 15. The monocyclic anthranilic derivative **111** was made by a Snieckus–Fries rearrangement, as described by Novartis researchers.[16]

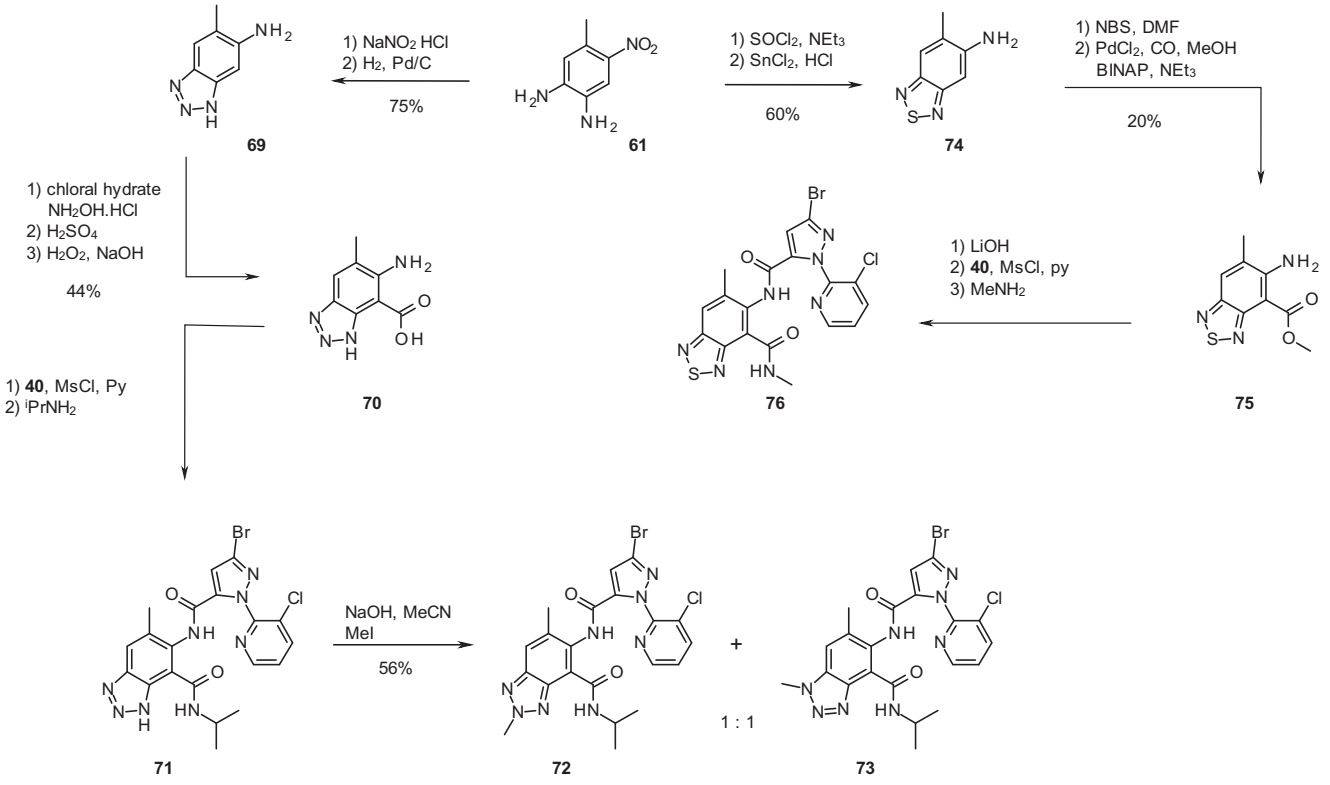
2.4. Biological results

Results of the biological testing against plant herbivorous insects as well as results from a binding assay (in vitro activity) are presented in Table 1. Bicyclic anthranilamides of type I were generally poorly active in vivo (see **8**). This is believed to be due to steric clash at the receptor level. In contrast, the best compounds of type II and III showed activity comparable the standards **2** and **3** in vitro as well as in vivo (see **4**, **23**, **68** and **87**).

There are clear differences at the receptor level across the target insects.[4] This is clearly seen for some compounds in the binding assay (**23** and **68**). Compounds with low log*P* are prone to be systemic in the plant, and activity in vivo is seen against the green peach aphids *Myzus persicae*. The naphthalene derivative **4** is active at the nM range in vitro against *Spodoptera* (chewing) and *Myzus* (sucking). However it is active in vivo only against *Spodoptera* since it is not plant systemic due to its high log*P* (4.86). By contrast, the indazole derivative **87** is active in vivo against both insect species:



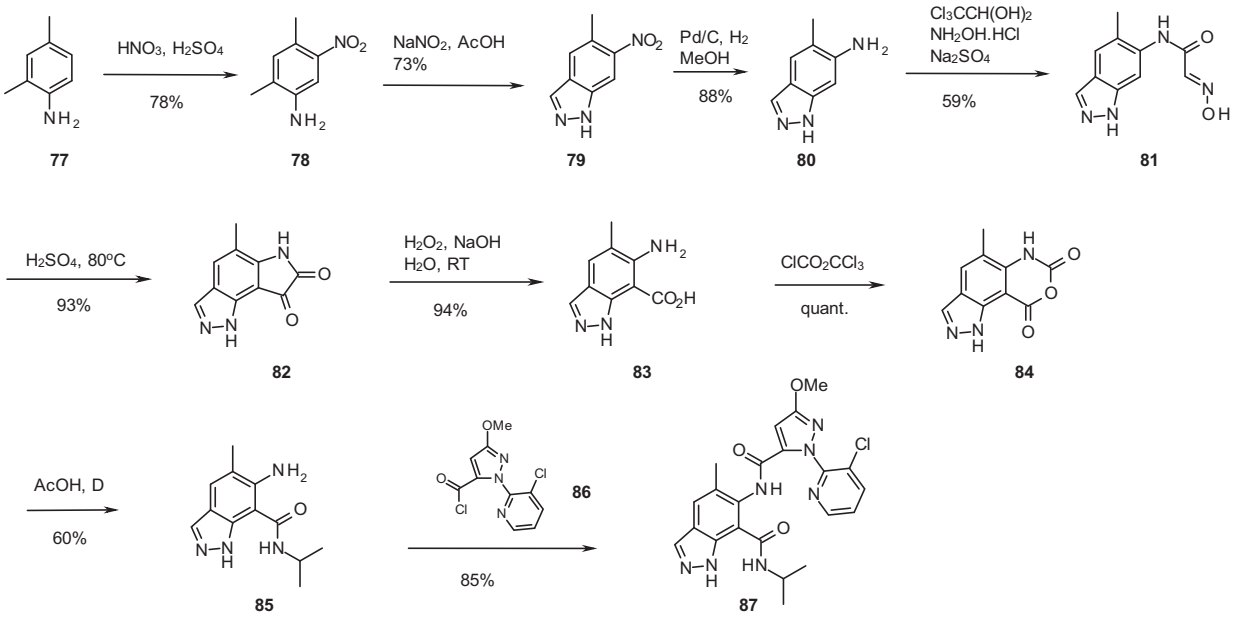
Scheme 10.



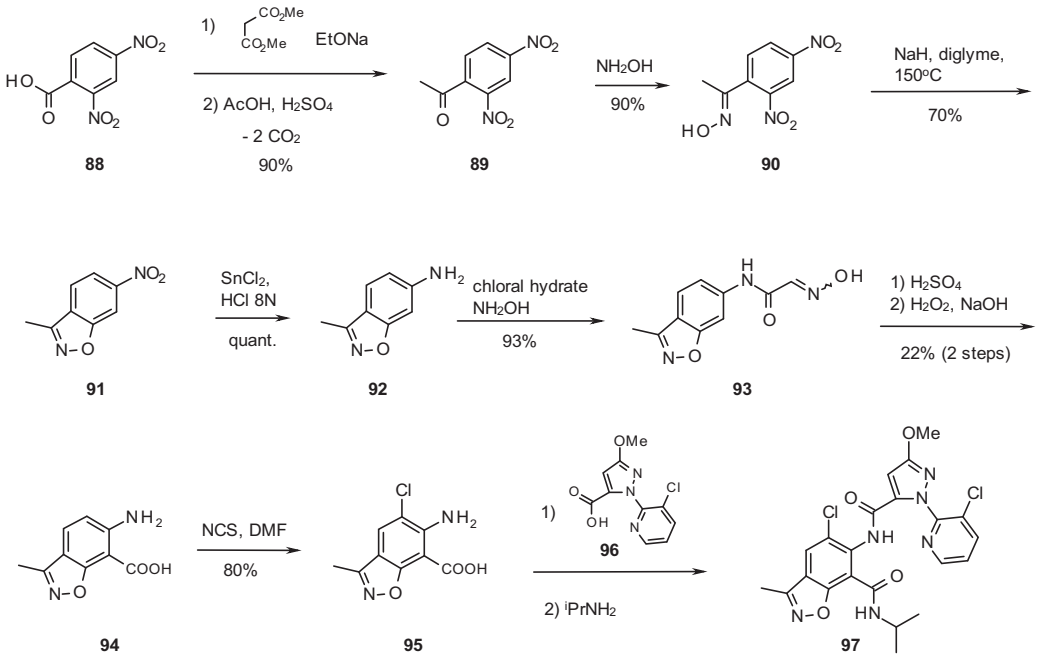
Scheme 11.

with a log*P* of 1.71, it is expected to be present in the sap from which the sucking pests feed.

In the absence of any structural information at the receptor level, one can develop a pharmacophore model rationalizing the experimental data. For example, the high activity of the naphthalene derivative **4** of type II or of the indazole **87** of type III shows that the active site is large enough to accommodate a bicyclic system of type II or III. Introducing heteroatoms in the bicycle was indifferent in the case of the quinoline derivative **23**. However introducing a nitrogen atom such as in the regioisomeric quinoline **22** or in the quinoxaline **31** was detrimental for activity. Similarly for the bicyclic systems of type III, varying the position of the heteroatoms in the five-membered ring shows that the benzimidazole **68** and the indazole **87** are by far the



Scheme 12.



Scheme 13.

most active derivatives. Intermediate activity was observed for the benzotriazoles **71** and **72** or benzisoxazole **97** while benzothiadiazole **76** was completely inactive.

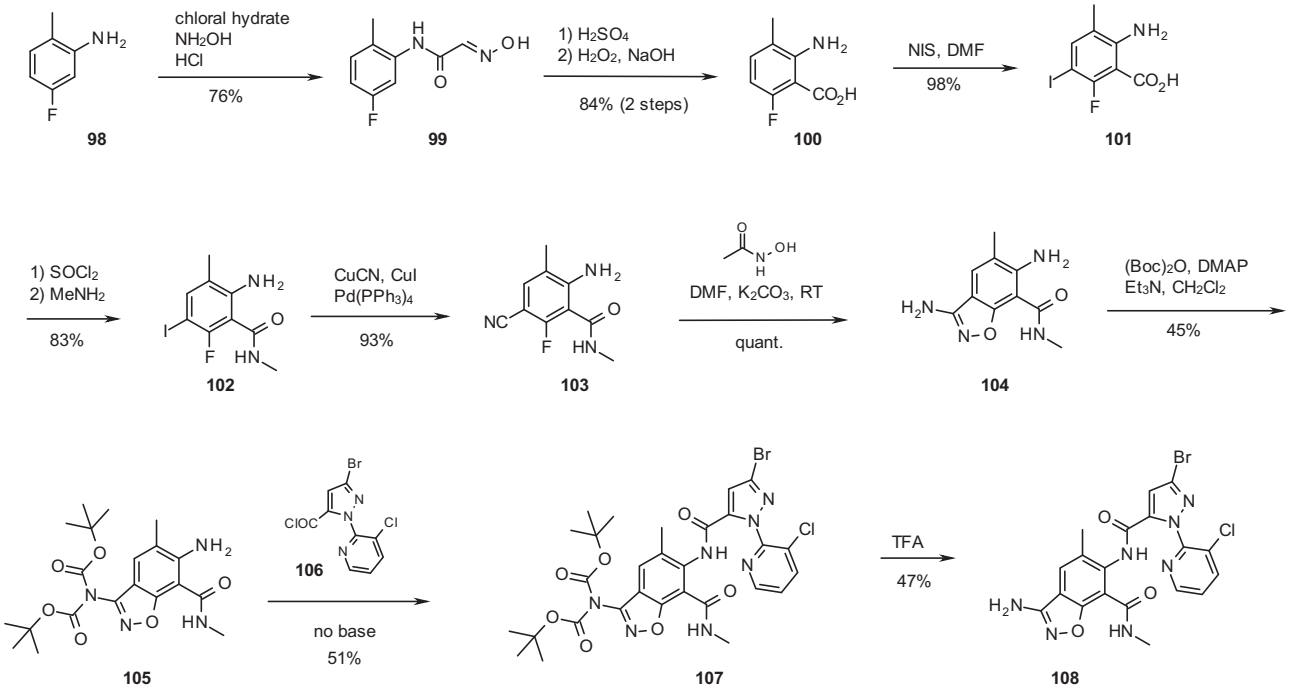
Only a few analogs were active against both insect types in vivo. A good combination of intrinsic activity against both species and good bioavailability properties (low log*P* and aqueous solubility) are clearly required. Compounds **3** and the indazole **87** are the most interesting in this respect, and one can see the indazole moiety in **87** as a bioisosteric replacement of the cyano phenyl moiety in **3**.

3. Conclusions

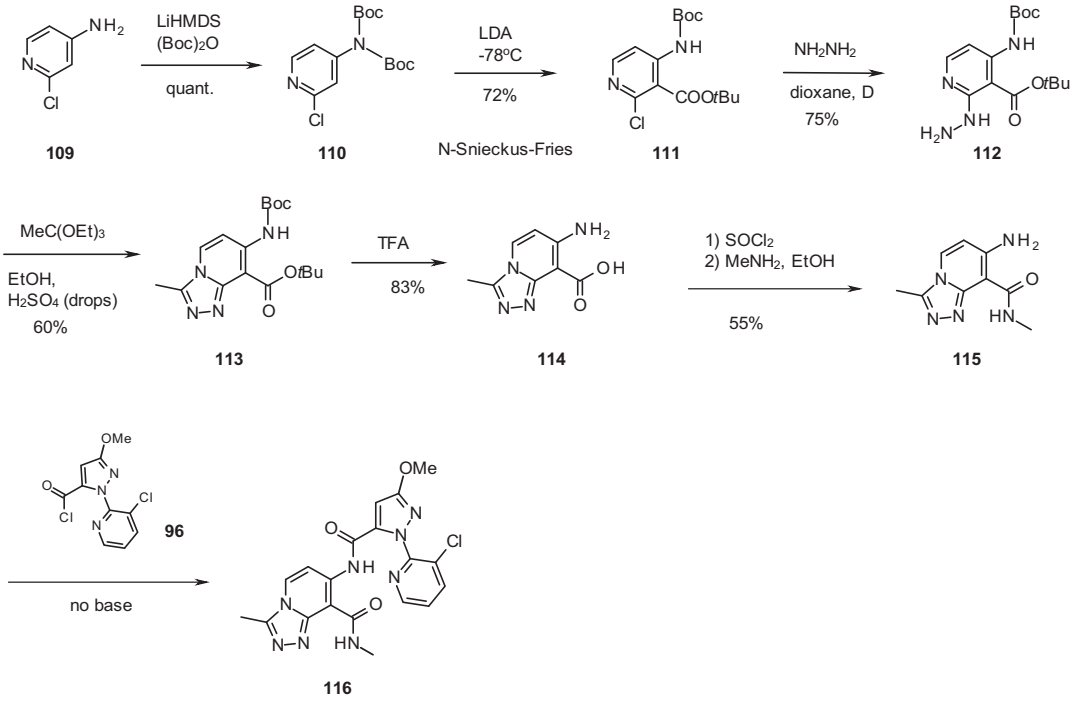
New bicyclic anthranilic diamides have been prepared and were shown to reach the level of activity of the best anthranilamide insecticides chlorantraniliprole **2** or cyantraniliprole **3**. High levels of insecticidal activity in the greenhouse was observed against chewing pests and in some cases even against sucking pests. Log*P* is a good bioavailability model to understand the translation of in vitro activity to potent insecticidal activity against sucking pests in the greenhouse.

4. Experimental section

All new compounds were characterized by standard spectroscopical methods. ^{1}H NMR spectra were recorded on a Varian Unity 400 spectrometer at 400 MHz using $CDCl_3$ or DMSO-d_6 as solvent. Chemical shifts are reported in ppm downfield from the standard (d = 0.00). Mass spectra were recorded on a Micromass LCT mass spectrometer. Melting points were determined on a Büchi 535



Scheme 14.



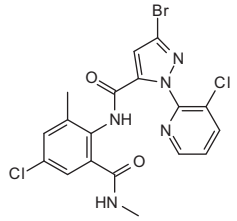
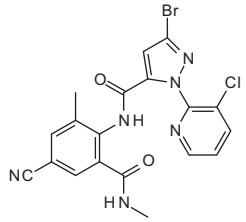
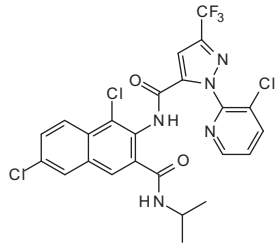
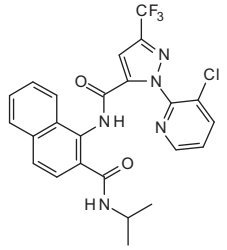
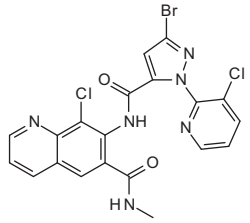
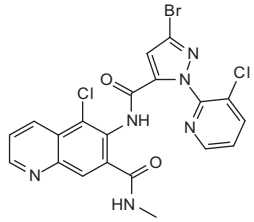
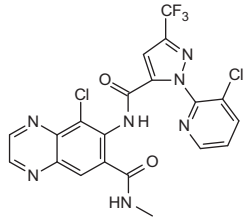
Scheme 15.

melting point apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F524 precoated plates. Preparative flash chromatography was performed using silica gel 60 (40–63 ml, E. Merck). Reactions were generally carried out under anhydrous conditions in an inert atmosphere (nitrogen or argon) with dry solvents.

4.1. 2-(3-Chloro-2-pyridyl)-*N*-[1,6-dichloro-3-(isopropylcarbamoyl)-2-naphthyl]-5-methyl-pyrazole-3-carboxamide (4)

(a) 0.14 ml (1.86 mmol) methanesulfonyl chloride was stirred in 2 ml acetonitrile under nitrogen and the solution was cooled to 0 °C. A solution of 418 mg (1.43 mmol) 2-(3-chloro-2-pyridyl)-5-(trifluo-

Table 1

	Structure	Type	In vitro IC_{50} (nM)* Spo	In vitro IC_{50} (nM)* Myzus	In vivo EC_{80} (ppm)** Spo	In vivo EC_{80} (ppm)** Myzus	log*P***
2		–	3	2	0.8	200	2.78 (e)
3		–	5	1	0.2	3.1	1.91 (e)
4		II	5	5	0.2	>200	4.86 (c)
8		I	570	nd	>200	>200	3.82 (c)
22		II	102	nd	50	>200	1.86 (e)
23		II	3	50	0.8	50	2.34 (e)
31		II	200	600	12.5	>200	2.41 (c)

(*continued on next page*)

Table 1 (*continued*)

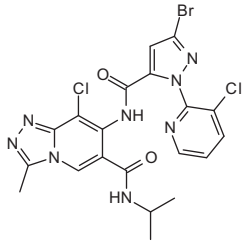
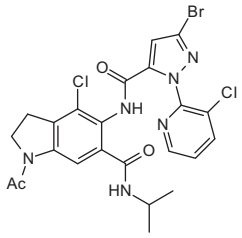
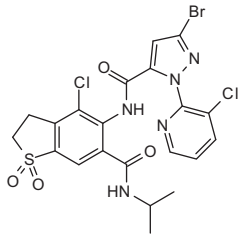
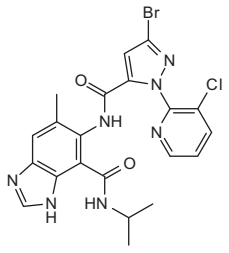
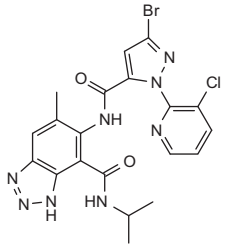
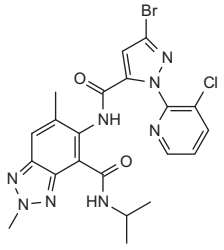
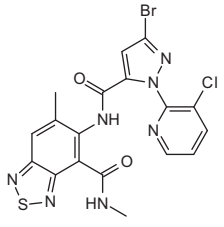
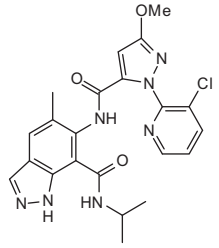
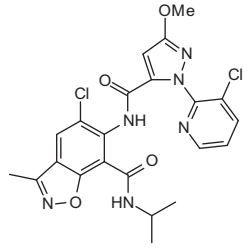
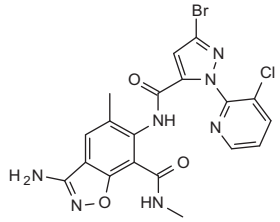
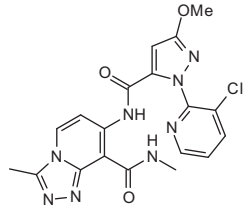
	Structure	Type	In vitro IC_{50} (nM)[*] Spo	In vitro IC_{50} (nM)[*] Myzus	In vivo EC_{80} (ppm)[**] Spo	In vivo EC_{80} (ppm)[**] Myzus	log *P*[***]
41		II	>4000	>4000	>200	>200	1.16 (e)
48		II	nd	nd	3.1	>200	2.85 (c)
58		II	nd	nd	~200	50	2.44 (c)
68		III	8	40	0.8	200	2.37 (c)
71		III	40	65	0.8	>200	2.10 (e)
72		III	258	315	0.8	>200	2.12 (c)
76		III	>4000	>4000	>200	>200	2.09 (c)

Table 1 (*continued*)

	Structure	Type	In vitro IC_{50} (nM)* Spo	In vitro IC_{50} (nM)* Myzus	In vivo EC_{80} (ppm)** Spo	In vivo EC_{80} (ppm)** Myzus	log*P***
87		III	5	16	<0.2	12.5	1.71 (e)
97		III	98	45	12.5	>200	2.14 (e)
108		III	nd	nd	50–12.5	~200	1.52 (e)
116		III	nd	nd	12.5	>200	(c)

nd: not determined.

* Displacement assay as described in Ref. 6, supplementary part.

** In vivo microscreening as described in Ref. 8: example B8 p 196: Spo: *Spodoptera littoralis*, example B6 p 195: Myzus: *Myzus persicae*.

*** log*P* (e): experimental, (c): calculated.

romethyl)pyrazole-3-carboxylic acid and 0.2 ml (2.4 mmol) pyridine in 2 ml acetonitrile were added dropwise to the reaction mixture over 10 minutes. The reaction mixture was stirred for a further 30 min, then 367 mg (1.43 mmol) 3-amino-4,7-dichloro-naphthalene-2-carboxylic acid was added in portion in a suspension with 2 ml acetonitrile and a second portion of 0.41 ml (5.0 mmol) pyridine. After stirring for 40 min a solution of 0.14 ml (1.86 mmol) methanesulfonyl chloride in 1 ml acetonitrile was added dropwise over 5 min. After stirring for a further 45 min a second portion of methanesulfonyl chloride (0.44 ml, 5.7 mmol) was added portionwise, again maintaining the temperature at 0 °C. The reaction mixture was then allowed to warm to RT and stirred for 2 h at RT. The reaction was quenched by the addition of water and was stirred for 10 min. The suspended solid was collected by filtration and washed with water and hexane to afford 606 mg 7,10-dichloro-2-[2-(3-chloro-2-pyridyl)-5-methyl-pyrazol-3-yl]benzo[*g*][3,1]benzoxazin-4-one (83%) as a pale yellow solid.

MS (electrospray): $m/z = 456$ [M+1].

(b) In a nitrogen atmosphere 0.1 ml (1.17 mmol) of isopropylamine in anhydrous THF was added with stirring to a solution of 0.2 g (0.15 mmol) of 7,10-dichloro-2-[2-(3-chloro-2-pyridyl)-5-methyl-pyrazol-3-yl]benzo[*g*][3,1]benzoxazin-4-one in 5 ml of anhydrous THF. The clear solution was stirred for one hour after which time TLC showed no remaining starting material. The reaction mixture was then concentrated in vacuum. The residue was purified by flash-chromatography [silica gel; hexane, followed by hexane/ethyl acetate (2:1)], to give 2-(3-chloro-2-pyridyl)-*N*-[1,6-dichloro-3-(isopropylcarbamoyl)-2-naphthyl]-5-methyl-pyrazole-3-carboxamide (**4**) (152 mg, 68%) as a white powder. ^{1}H NMR (DMSO-d_6): 1.05 (d, 6H), 3.9 (m, 1H), 7.65 (m, 1H), 7.75 (dd, 1H), 7.89 (s, 1H), 8 (s, 1H), 8.2 (d, 1H), 8.25 (d, 1H), 8.3 (d, 1H), 8.35 (b, 1H), 8.5 (d, 1H), 10.8 (s, 1H); MS (electrospray): $m/z = 570$ [M+1].

4.2. 2-[2-(3-Chloro-2-pyridyl)-5-(trifluoromethyl)pyrazol-3-yl] benzo[*h*][3,1]benzoxazin-4-one (7)

To a solution of 93 mg (0.5 mmol) 1-aminonaphthalene-2-carboxylic acid in 3 ml pyridine was added 155 mg (0.5 mmol) of 2-(3-chloro-2-pyridyl)-5-(trifluoromethyl)pyrazole-3-carbonyl chloride whilst stirring. The reaction was stirred at RT for 2 h before further addition of acid chloride (80 mg, 0.25 mmol). After one additional hour of stirring at RT, the reaction mixture was concentrated under vacuum. The residue was triturated in water and the resulting yellowish solid was filtered off, washed with water and dried under vacuum. The resulting solid was treated with chloroform and some

insoluble impurities were removed by filtration. Evaporation of the chlorinated solvent gave 2-[2-(3-chloro-2-pyridyl)-5-(trifluoromethyl)pyrazol-3-yl]benzo[*h*][3,1]benzoxazin-4-one (**7**) (82 mg, 37%) as a yellow solid.

^{1}H NMR ($CDCl_3$, 400 MHz): 7.45 (m, 2H), 7.6 (s, 1H), 7.7 (m, 2H), 7.9 (m, 2H), 8.1 (m, 2H), 8.65 (s, 1H); MS (electrospray): m/z = 443 [M+1].

4.3. 2-(3-Chloro-2-pyridyl)-*N*-[2-(isopropylcarbamoyl)-1-naphthyl]-5-(trifluoromethyl)pyrazole-3-carboxamide (8)

To a solution of 45 mg (0.1 mmol) 2-[2-(3-chloro-2-pyridyl)-5-(trifluoromethyl)pyrazol-3-yl]benzo[*h*][3,1]benzoxazin-4-one in 2 ml THF was added 60 mg (1 mmol) isopropylamine. The reaction was stirred at RT overnight and was concentrated under vacuum to give an orange solid (45 mg). TLC (EtOAc–hexane, 1:1) indicated a mixture, the lowest spot being the desired material. The crude product was purified by TLC preparative (DCM–MeOH, 10:1) to give 2-(3-chloro-2-pyridyl)-*N*-[2-(isopropylcarbamoyl)-1-naphthyl]-5-(trifluoromethyl)pyrazole-3-carboxamide (**8**) (17 mg, 33%) as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): 1.2 (d, 6H), 4.2 (m, 1H), 6.15 (d, 1H), 7.1 (d, 1H), 7.35 (m, 2H), 7.5 (m, 1H), 7.6 (m, 1H), 7.75 (s, 1H), 7.85 (m, 2H), 8.45 (s, 1H), 11 (s, 1H); MS (electrospray): m/z = 502 [M+1].

4.4. 1-Chloro-3-methyl-naphthalen-2-amine (9)

1.9 g (14.7 mmol) of *N*-chlorosuccinimide and 10 mg of 2,2′-azoisobutyric nitrile were added to a suspension of 2.5 g (13.3 mmol) of 2-amino-3-carboxy-naphthalene in 100 ml of tetrachloromethane. The reaction mixture was stirred for 18 h at RT, treated with 250 ml of aqueous sodium chloride solution and extracted with ethyl acetate (3 × 250 ml). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuum to afford 2.78 g 1-chloro-3-methyl-naphthalen-2-amine (**9**) (95%) in the form of a brown solid.

^{1}H NMR ($CDCl_3$): 8.53 (s, 1H), 7.98 (d, 1H), 7.73 (d, 1H), 7.55 (t, 1H), 7.25 (t, 1H). MS (electrospray): m/z = 222 [M+1].

4.5. 10-Chloro-2-[2-(3-chloro-2-pyridyl)-5-(trifluoromethyl)pyrazol-3-yl]benzo[*g*][3,1]benzoxazin-4-one (10)

In a nitrogen atmosphere 0.5 ml (5.75 mmol) oxalyl chloride was added dropwise at RT while stirring to a suspension of 295 mg (1.0 mmol) of 5-carboxy-1-(3-chloropyrid-2-yl)-3-trifluoromethyl-pyrazole in 2 ml dichloromethane. The reaction mixture was stirred for 1 h and then added dropwise to a solution of 0.25 g (1 mmol) 1-chloro-3-methyl-naphthalen-2-amine (**9**) in 20 ml dichloromethane and 0.38 ml (2.81 mmol) triethylamine. The reaction mixture was subsequently stirred for 3 h. Further 0.7 ml triethylamine (5 mmol) was added, followed by the addition in a single portion of 0.22 ml (2.8 mmol) methane sulfonic acid chloride. The reaction mixture was then stirred for 18 h and concentrated in vacuum, and the residue was purified by flash-chromatography [silica gel; hexane/ethyl acetate (3:1)], to afford 96 mg 10-chloro-2-[2-(3-chloro-2-pyridyl)-5-(trifluoromethyl) pyrazol-3-yl]benzo[*g*][3,1]benzoxazin-4-one (**10**) (20%).

^{1}H NMR ($CDCl_3$): 8.78 (s, 1H), 8.61 (m, 1H), 8.30 (m, 2H), 8.03 (dd, 1H), 7.78 (m, 1H), 7.67 (m, 1H), 7.56 (m, 2H); MS (electrospray): m/z = 477 [M+1], 479 [M+3], 481 [M+5].

4.6. *N*-[1-Chloro-3-(isopropylcarbamoyl)-2-naphthyl]-2-(3-chloro-2-pyridyl)-5-(trifluoromethyl)pyrazole-3-carboxamide (11)

To a solution of 70 mg (0.15 mmol) 10-chloro-2-[2-(3-chloro-2-pyridyl)-5-(trifluoromethyl)pyrazol-3-yl]benzo[*g*][3,1]benzoxazin-4-one in 5 ml anhydrous THF under nitrogen was added 0.037 ml (0.45 mmol) isopropyl amine and the reaction was heated at 50 °C for 1 h. The solvent was removed under vacuum and the residue purified by flash-chromatography (SiO_2; hexane then EtOAc–hexane, 1:3) to give 30 mg *N*-[1-chloro-3-(isopropyl-carbamoyl)-2-naphthyl]-2-(3-chloro-2-pyridyl)-5-(trifluoromethyl) pyrazole-3-carboxamide (**11**) (37%).

^{1}H NMR ($CDCl_3$, 400 MHz): 1.2 (d, 6H), 4.2 (m, 1H), 6.2 (d, 1H), 7.2 (m, 1H), 7.35 (m, 2H), 7.6 (m, 2H), 7.65 (s, 1H), 7.8 (d, 1H), 7.9 (s, 1H), 8.4 (d, 1H), 10.7 (s, 1H); MS (electrospray): m/z = 536 [M+1].

4.7. 2,3-Bis(dibromomethyl)pyridine (13)

A solution of 20.0 g (186 mmol) 2,3-dimethylpyridine and 150 g (835 mmol) *N*-bromo-succinimide in 1.2 L CCl_4 was irradiated with a 150 Watt lamp at reflux temperature during 20 h. After cooling, the solution was filtered and the organic phase was washed with a 5% sodium thiosulfate solution and water. Evaporation of the organic phase afforded 62.0 g 2,3-bis(dibromomethyl)pyridine (**13**) (78%).

^{1}H NMR ($CDCl_3$): 6.92 (s, 1H), 7.4 (s, 1H), 7.45 (m, 1H), 8.25 (m, 1H), 8.5 (m, 1H). LC–MS: t_R = 1.91 min, m/z = 419 [M+1], 421 [M+3], 423 [M+5], 425 [M+7], 427 [M+9]. Mp: 157–160 °C.

4.8. Diethyl quinoline-6,7-dicarboxylate (16)

To a solution of 62.0 g (144 mmol) 2,3-bis(dibromomethyl)pyridine (**13**) and 70.0 g (400 mmol) diethyl maleate in 500 ml DMF was added 61.5 g (400.0 mmol) NaI and the mixture was heated at 80 °C during 6 h. After evaporation of the solvent, the residue was dissolved in 2000 ml ethyl acetate and washed with a sodium bicarbonate solution and water (6 times). Evaporation of the solvent and purification of the residue with flash-chromatography afforded 8.0 g diethyl quinoline-6,7-dicarboxylate (**16**) as a dark oil (20%).

^{1}H NMR ($CDCl_3$, 400 MHz): 1.45 (t, 6H), 4.45 (q, 4H), 7.55 (q, 1H), 8.25 (m, 2H), 8.25 (s, 1H), 9.05 (m, 1H). MS (electrospray): m/z = 274 [M+1].

4.9. 7-Methoxycarbonylquinoline-6-carboxylic acid and 6-methoxycarbonylquinoline-7-carboxylic acid (17a) and (17b)

(a) 14 g (51.2 mmol) diethyl quinoline-6,7-dicarboxylate and 5.0 g (86 mmol), 14.6 g (270 mmol) KOH were dissolved in 100 ml dioxane and 50 ml water. The reaction mixture was stirred at RT overnight. After evaporation of the dioxane, the solution was made acidic (pH ~2) with HCl 2 N and was extracted with ethyl acetate and THF. After evaporation of the solvent, the residue was crystallized successively in diethyl ether and acetonitrile to give 3.6 g quinoline-6,7-dicarboxylic acid (64%).

^{1}H NMR (DMSO-d_6, 400 MHz): 7.7 (dd, 1H), 8.25 (s, 1H), 8.4 (s, 1H), 8.55 (d, 1H), 9.05 (m, 1H), 13.3 (br, 2H).

(b) 4.83 g (22.3 mmol) quinoline-6,7-dicarboxylic acid was heated at 140 °C in 30 ml (317.0 mmol) acetic anhydride for one day. After completion, the reaction mixture was cooled and concentrated under vacuum. The crude furo[3,4-*g*]quinoline-6,8-dione (4.45 g, 92%) was used directly in the following step.

(c) 4.45 g (22.3 mmol) furo[3,4-*g*]quinoline-6,8-dione dissolved in 50 ml methanol was heated at 75° overnight. After evaporation of the methanol, the residue was crystallized in hexane to give 4.67 g (90%) of a 1:1 mixture 7-methoxycarbonylquinoline-6-carboxylic acid and 6-methoxycarbonylquinoline-7-carboxylic acid (**17a**) and (**17b**).

^{1}H NMR (DMSO-d_6, 400 MHz): 3.85 (s, 6H), 7.7 (dd, 2H), 8.2 (s, 1H), 8.35 (s, 1H), 8.4 (s, 1H), 8.5 (s, 1H), 8.55 (m, 2H), 9.05 (m, 2H), 13.5 (s, 1H). MS (electrospray): m/z = 230 [M−1]. Mp: 195–198 °C.

4.10. Methyl 7-aminoquinoline-6-carboxylate (18) and methyl 6-aminoquinoline-7-carboxylate (19)

(a) To 4.67 g (20 mmol) of a 1:1 mixture of 7-methoxycarbonylquinoline-6-carboxylic acid and 6-methoxycarbonylquinoline-7-carboxylic acid (**17a**) and (**17b**) in 80 ml *tert*-butanol was added 8 ml (37 mmol) diphenylphosphoryl azide and (7 ml, 51.8 mmol) triethylamine. The reaction mixture was heated at 80 °C overnight. After evaporation of the solvent, the residue was taken up in 500 ml ethyl acetate and 100 ml THF and the resulting organic was washed with water twice. The organic was dried and concentrated under vacuum. The crude compound was purified by flash-chromatography using dichloromethane and ethyl acetate as solvent to afford 8.0 g (55%) of a 1:1 mixture methyl 7-(*tert*-butoxycarbonylamino)quinoline-6-carboxylate and methyl 6-(*tert*-butoxycarbonylamino)quinoline-7-carboxylate.

^{1}H NMR ($CDCl_3$, 400 MHz): 1.5 (s, 18H), 3.9 (d, 6H), 7.2 (m, 1H), 7.35 (m, 1H), 8 (m, 2H), 8.5 (s, 1H), 8.7 (m, 1H), 8.75 (m, 2H), 8.85 (m, 2H), 8.95 (s, 1H), 10.1 (s, 1H), 10.2 (s, 1H). MS (electrospray): m/z = 303 [M+1]. Mp: 169–180 °C.

(b) To 8.0 g (26.4 mmol) of a 1:1 mixture of methyl 7-(*tert*-butoxycarbonylamino)quinoline-6-carboxylate and methyl 6-(*tert*-butoxycarbonylamino)quinoline-7-carboxylate in 80 ml dioxane was added 60 ml HCl 6 M. The reaction mixture was stirred at 50 °C overnight. After evaporation of the solvent, the residue was taken up in THF and washed with alkaline water. The organic phase was dried and concentrated under vacuum. The crude compound was purified by flash-chromatography to yield 0.84 g of methyl 6-aminoquinoline-7-carboxylate (**19**) and (0.71 g, 13.2%) of methyl 7-aminoquinoline-6-carboxylate (**18**) (15.5%).

Methyl 7-aminoquinoline-6-carboxylate (**18**): ^{1}H NMR ($CDCl_3$, 400 MHz): 4 (s, 3H), 5.85 (s, 2H), 7.1 (m, 1H), 7.2 (s, 1H), 8 (d, 1H), 8.45 (s, 1H), 8.8 (m, 1H). MS (electrospray): m/z = 203 [M+1].

Methyl 6-aminoquinoline-7-carboxylate (**19**): ^{1}H NMR ($CDCl_3$, 400 MHz): 4 (s, 3H), 5.7 (s, 2H), 6.9 (s, 1H), 7.3 (m, 1H), 7.85 (d, 1H), 8.65 (m, 1H), 8.75 (s, 1H). MS (electrospray): m/z = 203 [M+1].

4.11. 7-[[5-Bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carbonyl] amino]-8-chloro-*N*-methyl-quinoline-6-carboxamide (22)

(a) 0.71 g (3.5 mmol) methyl 7-aminoquinoline-6-carboxylate and 0.47 g (3.5 mmol) *N*-chloro-succinimide was suspended in 10 ml DMF and heated at 80 °C for 4 h. Further 50 mg (0.4 mmol) NCS was added and the reaction was heated 3 h at 90 °C. After cooling, the mixture was poured into 150 ml ice water. The mixture was stirred 30 min and the resulting solid was filtered and dried to yield 0.77 g methyl 7-amino-8-chloro-quinoline-6-carboxylate as a yellow solid (92%).

^{1}H NMR ($CDCl_3$, 400 MHz): 4 (s, 3H), 6.50 (b, 2H), 7.2 (dd, 1H), 8.05 (d, 1H), 8.45 (s, 1H), 8.95 (d, 1H). MS (electrospray): m/z = 237 [M+1], 239 [M+3].

(b) 0.77 g (3.25 mmol) methyl 7-amino-8-chloro-quinoline-6-carboxylate and 0.5 g (9 mmol) KOH were suspended in 5 ml of water and 15 ml dioxane. The reaction mixture was stirred 4 h at RT and concentrated under vacuum. The resulting crude potassium salt of 7-amino-8-chloro-quinoline-6-carboxylic acid (570 mg, 68%) was directly used in the next step.

(c) 570 mg (2.2 mmol) 7-amino-8-chloro-quinoline-6-carboxylic acid as the potassium salt was suspended in 20 ml acetonitrile. 660 mg (2.2 mmol) 5-bromo-2-(3-chloro-2-pyridyl) pyrazole-3-carboxylic acid (**40**) and 1.3 ml (15 mmol) pyridine were added. A solution of 0.850 ml (10.7 mmol) mesylchloride in 5 ml acetonitrile was slowly added at 0 °C and the mixture was warmed up to RT and further stirred for 1 h. The mixture was then poured on ice water and filtered after 15 min to afford 810 mg 2-[5-bromo-2-(3-chloro-2-pyridyl)pyrazol-3-yl]-10-chloro-pyrido [3,2-*g*][3,1]benzoxazin-4-one (76%).

^{1}H NMR ($CDCl_3$, 400 MHz): 7.35 (s, 1H), 7.5 (dd, 1H), 7.6 (dd, 1H), 8 (d, 1H), 8.35 (d, 1H), 8.6 (d, 1H), 8.7 (s, 1H), 9.15 (s, 1H). Mp >250 °C.

(d) 0.40 g (0.8 mmol) 2-[5-bromo-2-(3-chloro-2-pyridyl)pyrazol-3-yl]-10-chloro-pyrido[3,2-*g*][3,1]benzoxazin-4-one and 1 ml methylamine 2 M in THF were added successively to 20 ml THF and stirred for 8 h. After evaporation, the residue was crystallized in diethyl ether to give 0.42 g 7-[[5-bromo-2-(3-chloro-2-pyridyl) pyrazole-3-carbonyl]amino]-8-chloro-*N*-methyl-quinoline-6-carboxamide (**22**) (97%).

^{1}H NMR (DMSO-d_6, 400 MHz): 2.7 (d, 3H), 7.55 (s, 1H), 7.6 (dd, 1H), 7.7 (dd, 1H), 8.1 (s, 1H), 8.15 (d, 1H), 8.45 (d, 1H), 8.5 (m, 2H), 9.1 (s, 1H), 10.75 (s, 1H). MS (electrospray): m/z = 519 [M+1], 521 [M+3], 523 [M+5]. Mp 221–224 °C.

4.12. 6-[[5-Bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carbonyl] amino]-5-chloro-*N*-methyl-quinoline-7-carboxamide (23)

(a) 0.84 g (4.1 mmol) methyl 6-aminoquinoline-7-carboxylate and 0.56 g (4.1 mmol) *N*-chloro-succinimide were suspended in 10 ml DMF and heated at 80 °C during 4 h. Further 50 mg (0.4 mmol) NCS was added and the reaction was further heated 3 h at 90 °C. After cooling, the mixture was poured into 100 ml ice water. The mixture was stirred 30 min and the resulting solid was filtered and dried to give methyl 6-amino-5-chloro-quinoline-7-carboxylate (0.90 g, 92%) as a yellow solid.

^{1}H NMR ($CDCl_3$, 400 MHz): 4 (s, 3H), 6.3 (b, 2H), 7.45 (dd, 1H), 8.3 (d, 1H), 8.7 (s, 1H). MS (electrospray): m/z = 237 [M+1], 239 [M+3].

(b) 0.9 g (3.8 mmol) methyl 6-amino-5-chloro-quinoline-7-carboxylate and 0.5 g (9 mmol) KOH were suspended in 5 ml water and 15 ml dioxane. The reaction mixture was stirred 4 h at RT and then concentrated under vacuum to yield the crude potassium salt of 6-amino-5-chloro-quinoline-7-carboxylic acid (570 mg, 58%) which was directly used in the next step.

(c) 570 mg (2.2 mmol) 6-amino-5-chloro-quinoline-7-carboxylic acid as the potassium salt obtain in the previous step was suspended in 20 ml acetonitrile. 660 mg (2.2 mmol) 5-bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carboxylic acid and 1.3 ml (15 mmol) pyridine were added. A solution of 0.850 ml (10.7 mmol) mesylchloride in 5 ml acetonitrile was slowly added at 0 °C and the mixture was warmed up to RT and further stirred for 1 h. The mixture was then poured on ice water and filtered after 15 min to afford 880 mg 2-[5-bromo-2-(3-chloro-2-pyridyl)pyrazol-3-yl]-10-chloro-pyrido[2,3-*g*][3,1]benzoxazin-4-one (83%).

^{1}H NMR ($CDCl_3$, 400 MHz): 7.35 (s, 1H), 7.5 (dd, 1H), 7.65 (dd, 1H), 8 (d, 1H), 8.6 (m, 2H), 8.95 (s, 1H), 9.1 (m, 1H). Mp >250 °C.

(d) To a solution of 0.40 g (0.8 mmol) 2-[5-bromo-2-(3-chloro-2-pyridyl)pyrazol-3-yl]-10-chloro-pyrido[2,3-*g*][3,1]benzoxazin-4-one in 20 ml THF was added 1 ml methylamine 2 M in THF and the mixture was stirred for 8 h at RT. After evaporation, the residue was crystallized in diethyl ether to afford 0.42 g 6-[[5-bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carbonyl]amino]-5-chloro-*N*-methyl-quinoline-7-carboxamide (**23**) (97%).

^{1}H NMR ($CDCl_3$, 400 MHz): 3 (d, 3H), 6.65 (b, 1H), 7.3 (m, 2H), 7.8 (d, 1H), 7.85 (s, 1H), 8.15 (d, 1H), 8.45 (d, 1H), 8.75 (d, 1H), 10.25 (s, 1H). MS (electrospray): m/z = 519 [M+1], 521 [M+3], 523 [M+5]. Mp 209–212 °C.

4.13. Quinoxaline-6,7-dicarboxylic acid diethyl ester (26)

(a) A solution of 10.0 g (93.0 mmol) 2,3-dimethylpyrazine and 70.0 g (390 mmol) *N*-bromo-succinimide in 800 ml CCl_4 was irradiated with a 250 Watt lamp at reflux temperature during 20 h. After

cooling the solution was filtered and the organic phase was washed with a 5% sodium thiosulfate solution and water. After evaporation of the organic phase, the residue was crystallized in ethanol to give 29.1 g 2,3-bis-dibromomethyl-pyrazine (**25**) (74%).

^{1}H NMR ($CDCl_3$, 400 MHz): 7.1 (s, 2H), 8.6 (s, 2H). MS (electrospray): m/z = 420 [M+1], 422 [M+3], 424 [M+5], 426 [M+7], 428 [M+9]. Mp: 167–170 °C.

(b) To a solution of 38.0 g (90.0 mmol) 2,3-bis-dibromomethyl-pyrazine (**25**) and 70.0 g (400 mmol) diethyl maleate in 450 ml DMF was added 40.0 g (270.0 mmol) NaI and the mixture was heated at 80 °C during 20 h. After evaporation of the solvent, the residue was dissolved in 1000 ml *t*-butyl-methyl ether and washed with a 5% sodium thiosulfate solution and water (5 times). Evaporation of the solvent and purification of the residue with flash-chromatography gave 9.1 g quinoxaline-6,7-dicarboxylic acid diethyl ester (**26**) (37%) as a dark oil.

^{1}H NMR ($CDCl_3$, 400 MHz): 1.45 (t, 6H), 4.45 (q, 4H), 8.5 (s, 2H), 9.0 (s, 2H). MS (electrospray): m/z = 275 [M+1].

4.14. Quinoxaline-6,7-dicarboxylic acid monomethyl ester (27)

11.8 g (43.0 mmol) quinoxaline-6,7-dicarboxylic acid diethyl ester and 5.0 g (86 mmol) KOH dissolved in 100 ml dioxane and 50 ml water was stirred at RT during 20 h. After evaporation of the solvent, the solution was made slightly acidic (pH ~5) with HCl 2 N and was extracted with methylene chloride. After evaporation of the organic phase, 6.6 g quinoxaline-6,7-dicarboxylic acid was isolated. This product was directly dissolved in 25 ml (265 mmol) acetanhydride and heated at reflux during 8 h. Acetanhydride was evaporated and 6.2 g furo[3,4-*g*]quinoxaline-6,8-dione was isolated. Without purification, this material was dissolved in 50 ml methanol and heated at reflux during 1 h. After evaporation of the solvent, the residue was crystallized in diisopropyl ether to give 6.25 g quinoxaline-6,7-dicarboxylic acid monomethyl ester (**27**) (63%).

^{1}H NMR (DMSO-d_6, 400 MHz): 3.73 (s, 3H), 8.20 (s, 1H), 8.35 (s, 1H), 9.0 (2 s, 2H), 13.6 (s, b, 1H). MS (electrospray): m/z = 231 [M+1].

4.15. 7-Amino-quinoxaline-6-carboxylic acid methyl ester (28)

(a) 7.1 g (30.6 mmol) quinoxaline-6,7-dicarboxylic acid monomethyl ester (**27**) (8 ml, 59.2 mmol) NEt_3, 1 g molecular sieve 4 Å and 10 ml (46.4 mmol) diphenylphosphonic azide were successively added to 100 ml *tert*-butanol. The mixture was heated at 85 °C during 20 h. After cooling, the mixture was filtered and the solid was washed with 1000 ml THF. The filtrate was evaporated and submitted to flash-chromatography to give 7.45 g 7-*tert*-butoxycarbonylamino-quinoxaline-6-carboxylic acid methyl ester (80%).

^{1}H NMR ($CDCl_3$, 400 MHz): 1.6 (s, 9H), 4.05 (s, 3H), 8.75 (d, 1H), 8.8 (s, 1H) 8.85 (dd, 1H) 9.5 (s, 1H). LC–MS: t_R = 2.06 min, m/z = 304 [M+1]. Mp: 196–198 °C.

(b) 7.1 g (24.0 mmol) 7-*tert*-butoxycarbonylamino-quinoxaline-6-carboxylic acid methyl ester was added to 50 ml dioxane and 110 ml HCl 6 N and heated at 50 °C. The organic phase was evaporated and the residue was diluted with 150 ml water. The water phase was neutralized with NaOH 2 N (~pH 8), saturated with NaCl and extracted with ethyl acetate and THF. After evaporation of the solvent, the residue was submitted to flash-chromatography to give 2.2 g 7-amino-quinoxaline-6-carboxylic acid methyl ester (**28**) (41%).

^{1}H NMR ($CDCl_3$, 400 MHz): 4 (s, 3H), 6.00 (br, 2H), 7.15 (s, 1H), 8.55 (d, 1H) 8.65 (d, 1H) 8.7 (s, 1H). LC (electrospray): m/z = 204 [M+1]. Mp: 180–182 °C.

4.16. 7-Amino-8-chloro-quinoxaline-6-carboxylic acid methyl ester (29)

2.07 g (10.2 mmol) 7-amino-quinoxaline-6-carboxylic acid methyl ester (**28**) and 1.36 g (10.2 mmol) *N*-chloro-succinimide were suspended in 5 ml DMF and heated at 95 °C during 30 min. After cooling, the mixture was poured into 150 ml ice water. The mixture was stirred 15 min and filtered. The compound was dried and crystallized in hexane to give 2.15 g 7-amino-8-chloro-quinoxaline-6-carboxylic acid methyl ester (**29**) (88%).

^{1}H NMR ($CDCl_3$, 400 MHz): 4 (s, 3H), 6.6 (br, 2H), 8.55 (d, 1H) 8.65 (s, 1H) 8.7 (s, 1H). LC (electrospray): m/z = 238 [M+1], 240 [M+3]. Mp: 182–184 °C.

4.17. 9-Chloro-2-[2-(3-chloro-pyridin-2-yl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-3-oxa-1,5,8-triaza-anthracen-4-one (30)

A solution of 2.15 g (9.05 mmol) 7-amino-8-chloro-quinoxaline-6-carboxylic acid methyl ester (**29**) in 20 ml methanol, 20 ml dioxane and 12 ml NaOH 1 N was stirred 20 h at RT. The mixture was evaporated and the residue was taken twice in toluene and evaporated. The sodium salt obtained was suspended in 70 ml acetonitrile and 2.65 g (9.1 mmol) 2-(3-chloro-pyridin-2-yl)-5-trifluoromethyl-2*H*-pyrazole-3-carboxylic acid (**6**) followed by 3.5 ml (40.7 mmol) pyridine were added. A solution of 2.5 ml (31.7 mmol) mesylchloride in 10 ml acetonitrile was slowly added at 0 °C and the mixture was warmed up to RT and further stirred for 1 h. The mixture was then poured onto ice water (400 ml) and filtered after 15 min. The resulting solid was crystallized in isopropanol to give 3.77 g 9-chloro-2-[2-(3-chloro-pyridin-2-yl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-3-oxa-1,5,8-triaza-anthracen-4-one (**30**) (87%).

^{1}H NMR (DMSO-d_6, 400 MHz): 7.55 (m, 1H), 7.60 (s, 1H), 8.05 (d, 1H), 8.60 (d, 1H), 9.00 (s, 1H), 9.02 (s, 1H), 9.10 (s, 1H). MS (electrospray): m/z = 478 [M+1], 479 [M+3].

4.18. 8-Chloro-7-[[2-(3-chloro-2-pyridyl)-5-(trifluoromethyl)pyrazole-3-carbonyl]amino]-*N*-methyl-quinoxaline-6-carboxamide (31)

A solution of 55 mg (1.15 mmol) 9-chloro-2-[2-(3-chloro-pyridin-2-yl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-3-oxa-1,5,8-triaza-anthracen-4-one (**30**) in 15 ml (15.0 mmol) methylamine 1 N in THF was stirred for 4 h at RT. The mixture was then concentrated under vacuum. The crude material was triturated in diethyl ether. The resulting solid was isolated by filtration, washed with ether to give 470 mg 8-chloro-7-[[2-(3-chloro-2-pyridyl)-5-(trifluoromethyl)pyrazole-3-carbonyl]amino]-*N*-methyl-quinoxaline-6-carboxamide (**31**) (81%) as a crystalline solid.

^{1}H NMR ($CDCl_3$, 400 MHz): 2.7 (d, 3H), 7.65 (dd, 1H), 7.9 (s, 1H), 8.15 (s, 1H), 8.25 (d, 1H), 8.55 (d,12H), 8.65 (s, 1H), 9.1 (d, 2H), 11.05 (s, 1H); MS (electrospray): m/z = 510 [M+1], 512 [M+3]. Mp: 205–208 °C.

4.19. Ethyl 4-(allylamino)-6-chloro-pyridine-3-carboxylate (35)

To a solution of 43.0 g (195 mmol) ethyl 4,6-dichloropyridine-3-carboxylate (**34**) in 250 ml dioxane was slowly added 43.0 ml (526 mmol) prop-2-en-1-amine. The addition was slightly exothermic and the temperature reached 40 °C. The reaction was stirred overnight at RT. The reaction mixture was concentrated under vacuum, taken up in 500 ml water and stirred 30 min at RT. The resulting solid was collected by filtration, washed with water and dried. The resulting solid was taken up again in 500 ml water and 60 ml ethanol. The mixture was stirred 30 min. The solid was filtered off and dried to give 44.8 g ethyl 4-(allylamino)-6-chloro-pyridine-3-carboxylate (**35**) (95%).

^{1}H NMR ($CDCl_3$, 400 MHz): 1.4 (t, 3H), 3.4 (m, 2H), 4.4 (q, 2H), 5.3 (m, 2H), 5.9 (m, 1H), 6.55 (s, 1H), 8.35 (s, 1H), 8.7 (s, 1H); mp: 67–69 °C]. LC–MS: t_R = 1.52 min, m/z = 241 [M+1].

4.20. Ethyl 4-(allylamino)-6-hydrazino-pyridine-3-carboxylate (36)

To a solution of 38.0 g (158.0 mmol) ethyl 4-(allylamino)-6-chloro-pyridine-3-carboxylate (**35**) in 500 ml 1,4-dioxane was added under stirring 45.0 ml (840.0 mmol) hydrazine hydrate . The mixture was heated at 120 °C during 20 h. After evaporation of the solvent, the residue was dissolved in ethyl acetate and washed with water (2 times) and brine. The organic phase was dried over $MgSO_4$ and concentrated under vacuum. The crude compound was purified by crystallization using petroleum ether and diisopropyl ether to afford 30.3 g ethyl 4-(allylamino)-6-hydrazino-pyridine-3-carboxylate (**36**) was obtained (81%).

^{1}H NMR ($CDCl_3$, 400 MHz): 1.4 (t, 3H), 3.4 (m, 2H), 4.3 (q, 2H), 5.2 (d, 1H), 5.3 (d, 1H), 5.9 (s, 1H), 5.95 (m, 1H), 6.25 (s, 1H), 8.2 (s, 1H), 8.6 (s, 1H).). MS (electrospray): m/z = 237 [M+1]. Mp: 110–112 °C.

4.21. Ethyl 7-(allylamino)-3-methyl-[1,2,4]triazolo[4,3-*a*]pyridine-6-carboxylate (37)

To a solution of 2.7 g (11.4 mmol) ethyl 4-(allylamino)-6-hydrazino-pyridine-3-carboxylate (**36**) in 35 ml methanol was added 2 drops conc. sulfuric acid and 3.5 ml (17.1 mmol) triethylorthoacetate. The mixture was heated at 85 °C for 90 min. After evaporation of the solvent, the residue was dissolved in ethyl acetate and washed with water (2 times) and brine. The solvent was removed under vacuum and the residue purified by flash-chromatography (SiO_2; EtOAc then EtOAc–MeOH, 9:1) to give 1.55 g ethyl 7-(allylamino)-3-methyl-[1,2,4]triazolo[4,3-*a*]pyridine-6-carboxylate (**37**) (53%) as a yellow solid.

^{1}H NMR ($CDCl_3$, 400 MHz): 1.45 (t, 3H), 2.7 (s, 3H), 3.85 (m, 2H), 4.45 (q, 2H), 5.25 (d, 1H), 5.35 (d, 1H), 5.95 (m, 1H), 6.45 (s, 1H), 7.6 (s, 1H), 8.5 (s, 1H). LC–MS: t_R = 0.67 min, m/z = 261 [M+1]. Mp: 121–123 °C.

4.22. Ethyl 7-amino-3-methyl-[1,2,4]triazolo[4,3-*a*]pyridine-6-carboxylate (38)

1.3 g (5 mmol) ethyl 7-(allylamino)-3-methyl-[1,2,4]triazolo [4,3-*a*]pyridine-6-carboxylate (**37**), 1.0 ml (7.96 mmol) boron trifluoride diethyl etherate and 100 mg Pd/C 10% were successively added to 15 ml ethanol. The mixture was heated at 100 °C for 4 days. The mixture was allowed to cool down, filtered on cellite and concentrated under vacuum. The solid residue was taken up in water and ethyl acetate and the organic phase was successively washed with a saturated sodium bicarbonate solution and water. The organic phase was dried over $MgSO_4$ and concentrated under vacuum. The residue was purified by flash-chromatography (SiO_2; EtOAc to EtOAc–MeOH, 9:1) to give 225 mg ethyl 7-amino-3-methyl-[1,2,4]triazolo[4,3-*a*]pyridine-6-carboxylate (**38**) (18%) as a yellow solid.

^{1}H NMR (DMSO-d_6, 400 MHz): 1.35 (t, 3H), 2.6 (s, 3H), 4.35 (q, 2H), 6.5 (s, 1H), 6.6 (s, 2H), 8.7 (s, 1H); MS (electrospray): m/z = 221 [M+1].

4.23. 7-[[5-Bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carbonyl] amino]-8-chloro-*N*-isopropyl-3-methyl-[1,2,4]triazolo[4,3-*a*] pyridine-6-carboxamide (41)

(a) 200 mg (0.91 mmol) ethyl 7-amino-3-methyl-[1,2,4]triazolo [4,3-*a*]pyridine-6-carboxylate (**38**) and 125 mg (0.91 mmol) *N*-chlorosuccinimide were suspended in 5 ml DMF and heated at 90 °C for 90 min. After cooling, the mixture was poured into ice water. The mixture was stirred 15 min and filtered. The collected solid was washed with diisopropyl ether. The compound was dried to give 90 mg ethyl 7-amino-8-chloro-3-methyl-[1,2,4]triazolo [4,3-*a*]pyridine-6-carboxylate (40%) as a yellow solid.

^{1}H NMR (DMSO-d_6, 400 MHz): 1.35 (t, 3H), 2.65 (s, 3H), 4.4 (q, 2H), 6.8 (s, 2H), 8.7 (s, 1H). MS (electrospray): m/z = 255 [M+1]. Mp: 212–214 °C.

(b) 90 mg (0.35 mmol) ethyl 7-amino-8-chloro-3-methyl-[1,2,4]triazolo[4,3-*a*]pyridine-6-carboxylate and 54 mg (1 mmol) KOH were suspended in 1 ml water and 3 ml 1,4-dioxane. The reaction mixture was stirred 4 h at RT. The reaction mixture was then concentrated under vacuum and the resulting crude containing the product as a potassium salt of 7-amino-8-chloro-3-methyl-[1,2,4]triazolo[4,3-*a*]pyridine-6-carboxylic acid (**39**) was used as such in the next step.

(c) 700 mg (3.1 mmol) 7-amino-8-chloro-3-methyl-[1,2,4]triazolo[4,3-*a*]pyridine-6-carboxylic acid as the potassium salt (**39**) was suspended in 20 ml acetonitrile. 930 mg (2.2 mmol) 5-bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carboxylic acid (**40**) and 1.3 ml (15 mmol) pyridine were added. 0.850 ml (10.7 mmol) mesylchloride in 5 ml acetonitrile were slowly added at 0 °C and the mixture was warmed up to RT and stirred for 1 h. The mixture was then poured into ice water and filtered after 15 min. The resulting solid, 9-chloro-2-[2-(3-chloro-pyridin-2-yl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-3-oxa-1,5,8-triaza-anthracen-4-one (**30**) was poorly soluble in any solvent and was used directly in the next step.

(d) Crude 9-chloro-2-[2-(3-chloro-pyridin-2-yl)-5-trifluoromethyl-2*H*-pyrazol-3-yl]-3-oxa-1,5,8-triaza-anthracen-4-one as described above was dissolved in 5 ml (58 mmol) isopropylamine and stirred at RT overnight. The reaction was then concentrated under vacuum. The residue was purified by successive crystallization and trituration in acetonitrile, isopropanol and diethyl ether to give 240 mg (14% over two steps) 7-[[5-bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carbonyl]amino]-8-chloro-*N*-isopropyl-3-methyl-[1,2,4]triazolo[4,3-*a*]pyridine-6-carboxamide (**41**).

^{1}H NMR (DMSO-d_6, 400 MHz): 1.05 (d, 3H), 2.7 (s, 3H), 3.85 (m, 1H), 7.5 (s, 1H), 7.6 (dd, 1H), 8.15 (d, 1H), 8.25 (s, 1H), 8.45 (s, 1H), 8.5 (d, 1H), 10.75 (s, 1H). MS (electrospray): m/z = 553 [M+1]. Mp: 245–248 °C.

4.24. Methyl 1-acetylindoline-6-carboxylate (43)

A solution of methyl indoline-6-carboxylate (**42**) (50 mg, 0.28 mmol) in dichloromethane (10 mL) was cooled to −30 °C, treated with triethylamine (0.04 mL, 0.3 mmol) followed by dropwise addition of acetyl chloride (0.02 mL, 0.3 mmol), and warmed to RT. The reaction mixture was quenched with water and extracted with dichloromethane. The combined organic layers were washed with water, brine solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash-chromatography using ethyl acetate/hexane (3:7) to afford 49 mg 1-acetylindoline-6-carboxylate (**43**) as a white solid (80%).

^{1}H NMR ($CDCl_3$, 400 MHz): 8.73 (s, 1H), 7.67 (d, 1H), 7.16 (d, 1H), 4.04 (t, 2H), 3.82 (s, 3H), 3.17 (t, 2H), 2.18 (s, 3H).); MS (electrospray): m/z = 220 [M+1].

4.25. Methyl 1-acetyl-5-nitro-indoline-6-carboxylate (44)

A solution of methyl 1-acetylindoline-6-carboxylate (**43**) (40 mg, 0.18 mmol) stirred in cold sulfuric acid (20 mL) was cooled to 0 °C, treated with potassium nitrate (15 mg, 0.15 mmol) and stirred for 30 min. The reaction mixture was quenched with ice

and extracted with ethyl acetate (20 mL × 2). The combined organic layers were washed with brine solution, dried with anhydrous sodium sulfate and concentrated under reduced pressure to get 50 mg 1-acetyl-5-nitro-indoline-6-carboxylate (**44**) (quant.).

^{1}H NMR (DMSO, 400 MHz): 8.23 (s, 1H), 8.00 (s, 1H), 4.22 (t, 2H), 3.83 (S, 3H), 3.25 (t, 2H), 2.22 (s, 3H). MS (electrospray): m/z = 265 [M+1].

4.26. Methyl 1-acetyl-5-amino-indoline-6-carboxylate (45)

A solution of 1-acetyl-5-nitro-indoline-6-carboxylate (**44**) (3 g, 11.36 mmol) in methanol (200 mL) and THF (200 mL) was treated with 5% Pd/C (300 mg, 10 mol %) and stirred for 4 h under H_2 (1 bar). A white turbid precipitate was formed after 15 min. The reaction mixture was filtered through *Celite* and the residue was repeatedly washed with hot dichloromethane, hot methanol, and hot ethanol. The filtrate was then concentrated, and the residue obtained was washed with hexane, diethyl ether and finally dried under high vacuum to obtain 2.6 g 1-acetyl-5-amino-indoline-6-carboxylate (**45**) (quant.).

^{1}H NMR (DMSO, 400 MHz): 8.38 (s, 1H), 6.65 (s, 1H), 6.54 (s, 2H), 3.99 (t, 2H), 3.76 (s, 3H), 3.05 (t, 2H), 2.09 (s, 3H). MS (electrospray): m/z = 235 [M+1].

4.27. 1-Acetyl-5-[[5-bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carbonyl]amino]-4-chloro-*N*-isopropyl-indoline-6-carboxamide (48)

(a) To a solution of methyl 1-acetyl-5-amino-indoline-6-carboxylate (**45**) (982 mg, 4.19 mmol) in acetic acid (100 mL) and *N*, *N*-dimethyl formamide (100 mL) was added *N*-chlorosuccinimide (586 mg, 4.4 mmol) and stirred for 12 h. A further 30 mL of acetic acid was added and stirred for 4 h, and the reaction mixture was quenched with water (10 mL). *N*,*N*-Dimethyl formamide and acetic acid were distilled of under reduced pressure. The black residue obtained was stirred in 1:1 mixture of dichloromethane–water, and the organic layer was then separated. The aqueous layer was washed with dichloromethane (3×). The combined organic layers were washed with saturated sodium bicarbonate solution followed by brine, and dried with anhydrous sodium sulfate and concentrated under reduced pressure to obtain 140 mg 1-acetyl-5-amino-4-chloro-indoline-6-carboxylate (**46**) (10%), which was used directly in the next step.

MS (electrospray): m/z = 269 [M+1], 271 [M+3].

(b) To a solution of methyl 1-acetyl-5-amino-4-chloro-indoline-6-carboxylate (**46**) (300 mg, 1.1 mmol) in methanol (40 mL) and THF (10 mL) was added 1 N sodium hydroxide (1.1 mL, 1.1 mmol) solution. The reaction mixture was stirred at 55 °C for 1 h (LCMS showed only 5% conversion), treated with a few drops of water and 2 equiv sodium hydroxide solution, and stirred for 4 h. The reaction mixture was cooled to RT and passed through Dowex (H^+) ion exchange column. The column was washed with methanol and the eluent was concentrated reduced pressure to obtain 300 mg 1-acetyl-5-amino-4-chloro-indoline-6-carboxylic acid (**47**) (quant.). MS (electrospray): m/z = 255 [M+1].

(c) A solution of 1-acetyl-5-amino-4-chloro-indoline-6-carboxylic acid (**47**) (150 mg, 0.5 mmol) in THF and acetonitrile (1:1, 40 mL) was cooled to 10 °C, treated with pyridine (0.3 mL, 4.3 mmol), *N*-(3-chloropyridin-2-yl)-3-bromopyrazole-5-carboxylic acid (**40**) (170 mg, 0.5 mmol) and methanesulfonyl chloride (0.4 mL, 3.7 mmol) and stirred for 6 h. Another 7.4 equiv of pyridine and 6.4 equiv methanesulfonyl chloride was added at 10 °C and stirred for 3 h. Acetonitrile and THF were distilled off and the residue was dissolved in dichloromethane and water (1:1). The organic layer was separated and washed with saturated sodium bicarbonate solution. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine, dried with anhydrous sodium sulfate, and concentrated to afford 600 mg crude 6-acetyl-2-[5-bromo-2-(3-chloro-2-pyridyl)pyrazol-3-yl]-9-chloro-7,8-dihydropyrrolo[2,3*g*][3,1]benzoxazin-4-one which was directly used in the next step.

The above crude product (600 mg) was dissolved in THF (40 mL), treated with isopropyl amine (2 mL, 23 mmol), and stirred at RT for 8 h. After completion of the reaction, THF was distilled out and the residue was then purified by flash-chromatography using ethyl acetate/hexane (8:2) to get 100 mg 1-acetyl-5-[[5-bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carbonyl]amino]-4-chloro-*N*-isopropyl-indoline-6-carboxamide (**48**) (15%).

^{1}H NMR ($CDCl_3$, 400 MHz): 9.91 (s, 1H), 8.40 (d, 1H), 8.38 (s, 1H), 7.74 (d, 1H), 7.45 (s, 1H), 6.92 (s, 1H), 5.98 (d, 1H), 4.05 (m, 3H), 3.16 (t, 2H), 2.17 (s, 3H), 1.22 (d, 6H). MS (electrospray): m/z = 580 [M+1]. Mp 155–165 °C.

4.28. 5-Nitrobenzothiophene-2-carboxylic acid (50)

To a solution of methyl thioglycolate (530 mg, 5 mmol) in absolute methanol (20 mL) at 40 °C was added a solution of sodium methoxide (320 mg, 6 mmol) in methanol (5 mL). The reaction mixture was heated to 50 °C and treated drop wise a solution of 2-chloro-5-nitro benzaldehyde (**49**) (1 g, 5 mmol) in methanol (10 mL) was added drop wise. A precipitate was formed during the addition. The resulting suspension was heated at 60 °C for 1.5 h and cooled to RT. A solution of sodium hydroxide (2 mL, 2.5 N solution) was added and the reaction mixture was refluxed for 2 h, cooled to 0 °C and acidified with conc. hydrochloric acid (pH 4). The resulting solid was isolated by filtration, redissolved in hot sodium hydroxide solution, and acidified with drop wise addition of conc. hydrochloric acid. The solid obtained was isolated by filtration, washed with water, co-evaporated with toluene, and dried to get 880 mg 5-nitrobenzothiophene-2-carboxylic acid (**50**) (74%).

^{1}H NMR (DMSO, 400 MHz): 8.90 (d, 1H), 8.75 (d, 1H), 8.32 (t, 1H), 8.05 (d, 1H), 3.33 (s, 3H). MS (electrospray): m/z = 222 [M−1].

4.29. 5-Nitrobenzothiophene (51)

To a solution of 5-nitrobenzothiophene-2-carboxylic acid (**50**) (40 g, 179 mmol) in quinoline (350 mL) was added copper powder (11.3 g, 179 mmol) with good mechanical stirring. The reaction mixture was heated to 190 °C until gas evolution was complete, then cooled to RT, poured into crushed ice and acidified with conc. hydrochloric acid. The resulting suspension was warmed with ethyl acetate, layers separated, and the organic layer washed with 2 N hydrochloric acid, water, brine solution, dried with anhydrous sodium sulfate, and concentrated to obtain 30.5 g 5-nitrobenzothiophene (**51**) (95%).

^{1}H NMR (DMSO, 400 MHz): 8.85 (d, 1H), 8.31 (d, 1H), 8.18 (dd, 1H), 8.06 (d, 1H), 7.73 (d, 1H). LC–MS: (electrospray): m/z = 180 [M+1].

4.30. 5-Nitrobenzothiophene 1,1-dioxide (52)

To a solution of 5-nitrobenzothiophene (**51**) (23.8 g, 132 mmol) in dichloromethane (400 mL) was added *meta*-chloroperbenzoic acid (45.8 g, 265 mmol) portion wise at 0 °C under N_2. The reaction mixture was stirred overnight at RT and was poured into water. The organic layer was separated, washed with 1 N sodium hydroxide solution, brine solution, dried with anhydrous sodium sulfate, and concentrated to afford 20.2 g 5-nitrobenzothiophene-1,1-dioxide (**52**) (72%) was obtained after recrystallization with acetone/hexane.

^{1}H NMR, (DMSO, 400 MHz): 8.44 (m, 2H), 8.16 (d, 1H), 7.78 (d, 1H), 7.63 (d, 1H). LC–MS: (electrospray): m/z = 211 [M+1].

4.31. 1,1-Dioxobenzothiophen-5-amine (53)

To a solution of 5-nitrobenzothiophene-1,1-dioxide (**52**) (1.6 g, 7.5 mmol) in acetic acid (30 mL) was added iron powder (1.3 g, 22 mmol) under N_2. The reaction mixture was refluxed for 3 h and filtered through *Celite*. The filtrate was evaporated under reduced pressure. The residue was co-evaporated with toluene and was then purified by flash-chromatography using ethyl acetate/hexane (1:1) to get 610 mg 1,1-dioxobenzothiophen-5-amine (**53**) (45%).

^{1}H NMR (DMSO, 400 MHz): 7.41 (m, 2H), 7.15 (d, 1H), 6.61 (d, 1H), 6.58 (dd, 1H), 6.17 (s, 2H). MS (electrospray): m/z = 182 [M+1].

4.32. (2*Z*)-*N*-(1,1-Dioxobenzothiophen-5-yl)-2-hydroxyimino-acetamide (54)

A suspension of chloral hydrate (410 mg, 2.48 mmol), sodium sulfate (2.3 g, 16.57 mmol) and hydroxyl amine hydrochloride (370 mg, 5.41 mmol) in water (10 mL) was heated at 40 °C into a colorless solution. To this solution was added a solution of 1, 1-dioxobenzothiophen-5-amine (**53**) (300 mg, 1.65 mmol) in ethanol (2 mL) and 1 N hydrochloric acid (1.6 mL, 1.65 mmol). The resulting brown solution was stirred at 60 °C for 4.5 h (turned into a yellow solution). The reaction mixture was poured into crushed ice and extracted with ethyl acetate. The combined organic layers were washed with water, brine solution, dried with anhydrous sodium sulfate, and concentrated to get 320 mg crude (2*Z*)-*N*-(1,1-dioxobenzothiophen-5-yl)-2-hydroxyimino-acetamide (**54**) (78%).

^{1}H NMR (DMSO, 400 MHz): 12.34 (s, 1H), 10.63 (s, 1H), 8.00 (s, 1H), 7.80 (s, 2H), 7.67 (s, 1H), 7.65 (d, 1H), 7.36 (d, 1H). MS (electrospray): m/z = 251 [M−1].

4.33. 1,1-Dioxo-5*H*-thieno[2,3-*f*]indole-6,7-dione (55)

Concentrated sulfuric acid (3 mL) was warmed up to 70 °C and treated portionwise (2*Z*)-*N*-(1,1-dioxobenzothiophen-5-yl)-2-hydroxyimino-acetamide (**54**) (140 mg, 0.55 mmol), and stirred at 90 °C for 30 min under N_2. The reaction mixture was poured into crushed ice and extracted with ethyl acetate. The combined organic layers were washed with sodium bicarbonate solution, brine solution, dried with anhydrous sodium sulfate, and concentrated to get 80 mg crude compound 1,1-dioxo-5*H*-thieno[2,3-*f*]indole-6,7-dione (**55**) (58%).

^{1}H NMR (DMSO, 400 MHz): 7.71 (s, 1H), 7.60 (d, 1H), 7.49 (d, 1H), 6.94 (s, 1H). MS (electrospray): m/z = 236 [M+1].

4.34. 1,1-Dioxo-3,5-dihydro-2*H*-thieno[2,3-*f*]indole-6,7-dione (56)

To a solution of 1,1-dioxo-5*H*-thieno[2,3-*f*]indole-6,7-dione (**55**) (50 mg, 0.2 mmol) in THF (20 mL) was added 5% Pd/C (10 mg, 20% wt) and stirred at RT under H_2 (1 bar) for 30 min, and filtered through *Celite*. The filtrate was evaporated under reduced pressure. The residue was then purified by flash-chromatography using ethyl acetate/hexane (1:1) to get 10 mg 1,1-dioxo-3,5-dihydro-2*H*-thieno[2,3-*f*]indole-6,7-dione (**56**) (20%).

^{1}H NMR (DMSO, 400 MHz): 11.46 (s, 1H), 7.81 (s, 1H), 6.96 (s, 1H), 3.61 (t, 2H), 3.40 (t, 2H). MS (electrospray): m/z = 235 (M−1).

4.35. 5-Amino-4-chloro-1,1-dioxo-2,3-dihydrobenzothiophene-6-carboxylic acid (57)

(a) A solution of 1,1-dioxo-3,5-dihydro-2*H*-thieno[2,3-*f*]indole-6,7-dione (**56**) (1.0 g, 4.2 mmol) in 1 M sodium hydroxide (40 mL) was warmed to 40 °C, treated drop wise with 30% hydrogen peroxide (1 mL, 0.8 mmol) and stirred for 1 h. The reaction mixture was cooled to RT, added with water (10 mL), and acidified with 10% hydrochloric acid to pH 1. The solid precipitated was filtered, washed with water and diethyl ether, and dried to get 900 mg (1*Z*,3*E*)-1-(1,1-dioxo-2,3-dihydrothiophen-5-yl)-2-methyl-penta-1,3-dien-3-amine (94%).

^{1}H NMR (DMSO, 400 MHz): 7.91 (s, 1H), 6.73 (s, 1H), 3.48 (t, 2H), 3.22 (t, 2H). MS (electrospray): m/z = 228 [M+1].

(b) To a solution of above compound (900 mg, 3.96 mmol) in *N*, *N*-dimethylformamide (30 mL) was added *N*-chlorosuccinimide (630 mg, 4.75 mmol) under N_2 atm, and stirred at RT for 12 h. The solvent was evaporated under vacuum. The residue poured into crushed ice, extracted with ethyl acetate, layers separated, organic layer washed with water (3×), brine solution, and dried with anhydrous sodium sulfate concentrated. The residue was washed with diethyl ether and dried to get crude 800 mg 5-amino-4-chloro-1,1-dioxo-2,3-dihydrobenzothiophene-6-carboxylic acid (**57**) (80%).

^{1}H NMR (DMSO, 400 MHz): 13.63 (s, 1H, br), 7.97 (s, 1H), 7.52 (s, 2H, br), 3.61 (t, 2H), 3.30 (t, 2H). MS (electrospray): m/z = 260 [M−1].

4.36. 5-Bromo-*N*-[4-chloro-6-(isopropylcarbamoyl)-1,1-dioxo-2,3-dihydrobenzothiophen-5-yl]-2-(3-chloro-2-pyridyl)pyrazole-3-carboxamide (58)

N-(3-Chloropyridin-2-yl)-3-bromopyrazole-5-carboxylic acid (**40**) (460 mg, 1.53 mmol) was dissolved in dichloromethane (15 mL) and added with 1 drop of *N*,*N*-dimethylformamide followed by addition of oxalyl chloride (0.14 mL, 1.68 mmol) and stirred at RT 15 min. The solvent was evaporated under N_2, and the residue was dissolved in acetonitrile (7 mL) and added drop wise to a mixture of 5-amino-4-chloro-1,1-dioxo-2,3-dihydrobenzothiophene-6-carboxylic acid (**57**) (400 mg, 1.53 mmol) in pyridine (5 mL) at 0 °C. The reaction mixture was stirred for 1 h at RT. Methanesulfonyl chloride (0.4 mL, 5.2 mmol) was added to the reaction mixture, stirred for 2 h, treated with isopropyl amine (2.6 mL) and stirred for 12 h. The solvent was evaporated under vacuum and dissolved in dichloromethane (30 mL), washed with water, satd sodium bicarbonate solution, brine solution, dried with anhydrous sodium sulfate, and concentrated to afford 210 mg 5-bromo-*N*-[4-chloro-6-(isopropylcarbamoyl)-1,1-dioxo-2,3-dihydrobenzothiophen-5-yl]-2-(3-chloro-2-pyridyl)pyrazole-3-carboxamide (**58**) (24%) was obtained by prep HPLC.

^{1}H NMR (DMSO, 400 MHz): 10.73 (s, 1H), 8.48 (dd, 1H), 8.40 (d, 1H), 8.16 (dd, 1H), 7.73 (s, 1H), 7.61 (m, 1H)), 7.50 (s, 1H), 3.92 (m, 1H), 3.74 (t, 2H), 3.38 (t, 2H), 1.05 (d, 6H). MS (electrospray): m/z = 587 [M+1].

4.37. 5-Methyl-2,4-dinitro-aniline (60)

Nitric acid (29.5 ml) was added in several portions in sulfuric acid (178 ml) at 2–5 °C. Then *N*-(*meta*-tolyl)acetamide (50 g, 0.335 mol) was added and the reaction mixture was warmed to RT. After 4 h, the reaction mixture was poured into ice water (2 L) and an orange precipitate was formed. The resulting suspension was stirred overnight at RT, filtered and the precipitate obtained was washed with water and dried. The collected solid was solved in sulfuric acid 50% (350 ml) and stirred 4 h at 80 °C. The reaction mixture was cooled down to RT, water (1 L) was added and the suspension obtained was stirred overnight at RT. The precipitate obtained was filtered, and dried. The solid obtained was crystallized in ethyl acetate and cyclohexane to give 23.4 g 5-methyl-2,4-dinitro-aniline (**60**) as a yellow solid (37%).

^{1}H NMR (DMSO-d_6, 400 MHz): 8.78 (s, 1H); 8.15 (br s, 2H); 6.9 (s, 1H); 2.5 (s, 3H). MS (electrospray): m/z = 198 [M+1].

4.38. 4-Methyl-5-nitro-benzene-1,2-diamine (61)

5-Methyl-2,4-dinitro-aniline (**60**) (5 g, 25.36 mmol) was dissolved in ethanol (150 ml) and the resulting solution was heated at 100 °C. Sodium sulfide (9 g, 115 mmol) dissolved in 150 ml water was added to the reaction mixture. The resulting mixture was cooled down to RT and further stirred for 2 h. The reaction mixture was then poured into water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated. The crude product was purified by flash-chromatography over silica gel to give 2.9 g 4-methyl-5-nitro-benzene-1,2-diamine (**61**) as a yellow solid (68%).

^{1}H NMR (400 MHz, $CDCl_3$): 7.5 (s, 1H), 6.4 (s, 1H), 4.35 (br s, 2H), 3.6 (br s, 2H), 2.45 (s, 3H). LC–MS: t_R = 0.92 min, m/z = 168 [M+1].

4.39. 6-Methyl-3*H*-benzimidazol-5-amine (63)

(a) 4-Methyl-5-nitro-benzene-1,2-diamine (**61**) (3.0 g, 17.9 mmol) was dissolved in formic acid (2.5 ml) and water (5 ml) and HCl concentrated (5 ml) were added. The resulting mixture was stirred 2 h at 100 °C. The reaction mixture was basified with a 2 M solution of NaOH and the aqueous layer was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$, filtered and evaporated. The crude product was crystallized in ethyl acetate and THF to give 2.34 g 5-methyl-6-nitro-1*H*-benzimidazole (**62**) as a beige solid (74%).

LC–MS: t_R = 0.84 min, m/z = 178 [M+1].

(b) 5-Methyl-6-nitro-1*H*-benzimidazole (**62**) (2.3 g, 13.0 mmol) was dissolved in HCl 8 N (40 ml). Tin(II) chloride anhydrous (10.0 g, 52.7 mmol) was added and the resulting mixture was stirred 2 h at RT. The reaction was then quenched at 0 °C with NaOH. The aqueous layer was extracted with ethyl acetate (3 times) and the combined organic layers were dried over $MgSO_4$, filtered and evaporated under vacuum to give 1.64 g 6-methyl-3*H*-benzimidazol-5-amine (**63**) (86%).

^{1}H NMR (DMSO-d_6, 400 MHz): 11.00–1 2.00 (br s, 1H); 7.8 (s, 1H); 7.15 (s, 1H); 6.75 (s, 1H); 4–5 (br s, 2H); 2.15 (s, 3H). LC–MS: t_R = 0.19 min, m/z = 148 [M+1].

4.40. (2*E*)-2-Hydroxyimino-*N*-(6-methyl-3*H*-benzimidazol-5-yl) acetamide (64)

Sodium sulfate (27.8 g, 0.195 mol) was dissolved in water (65 ml) and 2,2,2-trichloroethane-1,1-diol (1.98, 11.9 mmol) was added. Then 6-methyl-3*H*-benzimidazol-5-amine (**63**) (1.6 g, 10.8 mmol) dissolved in 12 ml HCl 1 N (11.9 mmol) was added to the reaction mixture, followed by 2.42 g (34.8 mmol) hydroxylamine hydrochloride. The resulting mixture was slowly heated over 3 h until 80 °C. The reaction mixture was then cooled down to 0 °C and filtered. The precipitate obtained was washed with water and dried under vacuum to give 1.9 g (2*E*)-2-hydroxyimino-*N*-(6-methyl-3*H*-benzimidazol-5-yl)acetamide (**64**) (80%).

^{1}H NMR (DMSO-d_6, 400 MHz): 12.25 (s, 1H); 9.6 (s, 1H); 8.8 (s, 1H); 7.9 (s, 1H); 7.75 (s, 1H); 7.55 (s, 1H); 2.25 (s, 3H). LC–MS: t_R = 0.20 min, m/z = 219 [M+1].

4.41. 5-Methyl-1,6-dihydropyrrolo[3,2-*e*]benzimidazole-7,8-dione (65)

(2*E*)-2-Hydroxyimino-*N*-(6-methyl-3*H*-benzimidazol-5-yl)acetamide (**64**) (1.9 g, 8.7 mmol) was dissolved in concentrated sulfuric acid (30 mL) and the reaction mixture was stirred 3 h at 80 °C. Then reaction mixture was cooled down at RT, NaOH 30% was added up to pH 3–4. The resulting mixture was poured into water; the precipitate formed was filtered and dried to give 1.05 g 5-methyl-1,6-dihydropyrrolo[3,2-*e*]benzimidazole-7,8-dione (**65**) (60%).

^{1}H NMR (DMSO-d_6, 400 MHz): 13.1 (br s, 1H); 10.9 (s, 1H); 8.15 (s, 1H); 7.7 (s, 1H); 2.25 (s, 3H). LC–MS: t_R = 0.23 min, m/z = 202 [M+1].

4.42. 5-Amino-6-methyl-3*H*-benzimidazole-4-carboxylic acid (66)

5-Methyl-1,6-dihydropyrrolo[3,2-*e*]benzimidazole-7,8-dione (**65**) (1 g, 4.97 mmol) was dissolved in 5.7 ml NaOH 3 N. The solution was heated at 80 °C, and 0.7 ml H_2O_2 30% was added. The resulting mixture was stirred 2 h at 80 °C. The reaction mixture was cooled down at 0 °C and quenched with HCl concentrated to pH 4–5. The resulting mixture was diluted with water and filtered. The precipitate obtained was washed with diethyl ether to give 773 mg 5-amino-6-methyl-3*H*-benzimidazole-4-carboxylic acid (**66**) as a beige solid (81%).

^{1}H NMR (DMSO-d_6, 400 MHz): 12.5–11.5 (br s, 1H); 8 (br s, 1H); 7.55 (s, 1H); 2.25 (s, 3H). LC–MS: t_R = 0.25 min, m/z = 190 [M−1].

4.43. 5-[[5-Bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carbonyl] amino]-*N*-isopropyl-6-methyl-3*H*-benzimidazole-4-carboxamide (68)

(a) Under inert and dry atmosphere, 5-amino-6-methyl-3*H*-benzimidazole-4-carboxylic acid (**65**) (380 mg, 1.98 mmol) and 5-bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carboxylic acid (**40**) (631 mg, 2.08 mmol) were dissolved in acetonitrile (20 ml) and pyridine (0.72 ml, 8.94 mmol) was added. The resulting mixture was cooled down at 0–5 °C and methanesulfonyl chloride (0.540 ml, 6.95 mmol) was added slowly. The reaction was stirred overnight at RT. The reaction mixture was then filtered and the precipitate was washed with ice water, diethyl ether and dried under vacuum to give 655 mg crude 7-[5-bromo-2-(3-chloro-2-pyridyl)pyrazol-3-yl]-5-methyl-1*H*-imidazo[4,5-*f*][3,1]benzoxazin-9-one (**67**) as a beige solid.

LC–MS: t_R = 0.66 min, m/z = 459 [M−1].

(b) 7-[5-Bromo-2-(3-chloro-2-pyridyl)pyrazol-3-yl]-5-methyl-1*H*-imidazo[4,5-*f*][3,1]benzoxazin-9-one (**67**) (250 mg, 0.54 mmol) was dissolved in THF (10 ml) then isopropylamine (2.5 ml, 29 mmol) and dimethylformamide (1 ml) were added. The reaction mixture was heated at 80 °C and stirred one night at 80 °C. The resulting mixture was evaporated and the crude residue was purified by flash-chromatography over silica gel to give 132 mg 5-[[5-bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carbonyl]amino]-*N*-isopropyl-6-methyl-3*H*-benzimidazole-4-carboxamide (**68**) (47%).

^{1}H NMR (400 MHz, $CDCl_3$): 12.35 (s, 1H), 11.9 (s, 1H), 10.4 (d, 1H), 8.45 (dd, 2H), 7.95 (s, 1H), 7.8 (dd, 1H), 7.4 (s, 1H), 7.35 (m, 1H), 7.15 (s, 1H), 4,4 (m, 1H), 2.3 (s, 3H), 1.35 (d, 6H). LC–MS: t_R = 1.41 min, m/z = 518 [M+1].

4.44. 6-Methyl-3a,7a-dihydro-3*H*-benzotriazol-5-amine (69)

(a) 4-Methyl-5-nitro-benzene-1,2-diamine (**61**) (1.4 g, 8.37 mmol) was dissolved in hydrochloric acid (20 ml, 1 N), the solution was cooled to 0 °C and sodium nitrite (635 mg, 9.212 mmol) was added. The beige suspension was stirred for 2 h at RT. The mixture was filtered to give 5-methyl-6-nitro-3a,7a-dihydro-1*H*-benzotriazole as a beige crystal (1.12 g, 75%).

^{1}H NMR (DMSO-d_6, 400 MHz): 2.65 (s, 3H), 7.90 (br, 1H), 7.75 (br, 1H), 16.4 (br, 1H). LC–MS: t_R = 1.22 min, m/z = 179 [M+1].

(b) To 5-methyl-6-nitro-3a,7a-dihydro-1*H*-benzotriazole (1.1 g, 6.17 mmol) in ethanol (20 ml) was added Pd/C (10%, 0.5 g) and the flask was filled with hydrogen. Reaction mixture was stirred at RT for 3 h. As the reaction was not complete, 100 mg Pd/C (10%) were

added and the reaction mixture was further heated at 50 °C for 2 h. The reaction mixture was filtered on cellite and washed with ethanol. The filtrate was concentrated on vacuum to give 6-methyl-3a,7a-dihydro-3*H*-benzotriazol-5-amine (**69**) (922 mg, 100%).

^{1}H NMR (DMSO-d_6, 400 MHz): 2.18 (s, 3H), 5.35 (br, 2H), 6.7 (s, 1H), 7.55 (s, 1H), 14.7 (br, 1H). LC–MS: t_R = 0.24 min, m/z = 149 [M+1].

4.45. 5-Amino-6-methyl-3a,7a-dihydro-3*H*-benzotriazole-4-carboxylic acid (70)

(a) To a solution of sodium sulfate (1.91 g, 13.44 mmol) in water (60 ml) was added chloral hydrate (1.31 g, 7.92 mmol) at RT. To the resulting clear solution was added a solution of 6-methyl-3a,7a-dihydro-3*H*-benzotriazol-5-amine (**69**) (910 mg, 6.14 mmol) in 1 N aqueous hydrochloric acid (1 ml). The resulting mixture turned cloudy and hydroxylamine hydrochloride (1.6 g, 23.09 mmol) was then added. The resulting reaction mixture was heated gradually from RT to 80 °C. It was then stirred for an additional 30 min at 80 °C. The reaction mixture was then cooled down to RT with an ice bath and the solid formed was filtrated. The compound was washed thoroughly with water and dried at 50 °C overnight to afford (2*E*)-2-hydroxyimino-*N*-(6-methyl-3*H*-benzotriazol-5-yl) acetamide (520 mg, 38.6%).

^{1}H NMR (DMSO-d_6, 400 MHz): 2.4 (s, 3H), 7.75 (s, 1H), 7.8 (br, 1H), 8.1 (s, 1H), 12.3 (s, 1H). LC–MS: t_R = 0.83 min, m/z = 220 [M+1].

(b) (2*E*)-2-Hydroxyimino-*N*-(6-methyl-3*H*-benzotriazol-5-yl) acetamide (509 mg, 2.32 mmol) was dissolved in concentrated sulfuric acid (10 mL) and the reaction mixture was stirred 3 h at 80 °C. Then reaction mixture was cooled down at RT, sodium hydroxide 30% was added to get a pH value of 3–4. The resulting mixture was poured into water, the precipitate formed was filtered and dried to give 5-methyl-1,6-dihydropyrrolo[3,2-*e*]benzotriazole-7,8-dione (312 mg, 68%).

^{1}H NMR (DMSO-d_6, 400 MHz): 11.2 (br s, 1H); 8.2 (s, 1H); 2.30 (s, 3H). LC–MS: t_R = 0.90 min, m/z = 203 [M+1].

(c) 5-Methyl-1,6-dihydropyrrolo[3,2-*e*]benzotriazole-7,8-dione (3.21 g, 15.89 mmol) was dissolved in sodium hydroxide 3 N (18.5 ml) and heated at 80 °C. At that temperature, 2.3 ml H_2O_2 30% were added. The resulting mixture was stirred 2 h at 80 °C. The reaction mixture was cooled down to 0 °C and neutralized with concentrated HCl to pH 4–5. The resulting mixture was diluted with water and filtered. The precipitate obtained was washed with diethyl ether to give 5-amino-6-methyl-3a,7a-dihydro-3*H*-benzotriazole-4-carboxylic acid (**70**) as a beige solid (1.75 g, 60%).

^{1}H NMR (DMSO-d_6, 400 MHz): 14.6 (br s, 1H); 7.80 (s, 1H); 2.20 (s, 3H). LC–MS: t_R = 0.95 min, m/z = 191 [M−1].

4.46. 5-[[5-Bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carbonyl] amino]-*N*-isopropyl-6-methyl-3a,7a-dihydro-3*H*-benzotriazole-4-carboxamide (71)

(a) Under inert and dry atmosphere, 5-amino-6-methyl-3a,7a-dihydro-3*H*-benzotriazole-4-carboxylic acid (**70**) (1.3 g, 6.76 mmol) and 5-bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carboxylic acid (**40**) (2.15 g, 7.10 mmol) were dissolved in acetonitrile (30 ml) and pyridine (2.5 ml, 30.43 mmol) was added. The resulting mixture was cooled to 0–5 °C and methanesulfonyl chloride (1.84 ml, 23.67 mmol) was added slowly. The reaction was stirred overnight at RT. The reaction mixture was filtered and the precipitate formed was washed with ice water, diethyl ether and dried under vacuum to give crude 7-[5-bromo-2-(3-chloro-2-pyridyl) pyrazol-3-yl]-5-methyl-3a,9b-dihydro-1*H*-triazolo[4,5-*f*][3,1]benzoxazin-9-one as a beige solid (2.2 g, 66%).

LC–MS: t_R = 1.73 min, m/z = 460 [M+1].

(b) 7-[5-Bromo-2-(3-chloro-2-pyridyl)pyrazol-3-yl]-5-methyl-3a,9b-dihydro-1*H*-triazolo[4,5-*f*][3,1]benzoxazin-9-one (500 mg, 1.09 mmol) was dissolved in THF (30 ml) and 2 ml (48.4 mmol) isopropylamine were added. The reaction mixture was heated at 80 °C and stirred overnight at 80 °C. The resulting mixture was evaporated and the residue was purified by flash-chromatography over silica gel to give 5-[[5-bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carbonyl]amino]-*N*-isopropyl-6-methyl-3a,7a-dihydro-3*H*-benzotriazole-4-carboxamide (**71**) (190 mg, 33.7%).

^{1}H NMR (400 MHz, $CDCl_3$): 12.7 (br, 1H), 12.3 (br, 1H), 9.5 (br, 1H), 8.45 (dd, 1H), 7.85 (q, 1H), 7.40 (m, 2H), 7.20 (s, 1H), 4.35 (m, 1H), 2.30 (s, 3H), 1.4 (d, 6H). LC–MS: t_R = 1.65 min, m/z = 519 [M+1].

4.47. 5-[[5-Bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carbonyl] amino]-*N*-isopropyl-2,6-dimethyl-benzotriazole-4-carboxamide (72) and 5-[[5-bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carbonyl]amino]-*N*-isopropyl-1,6-dimethyl-3a,7a-dihydrobenzotriazole-4-carboxamide (73)

To a solution of 5-[[5-bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carbonyl]amino]-*N*-isopropyl-6-methyl-3a,7a-dihydro-3*H*-benzotriazole-4-carboxamide (**71**) (350 mg, 0.675 mmol) in acetonitrile (10 ml) was added sodium hydroxide (27 mg, 675 mmol) with one drop of water, the solution was stirred at RT for 1 h. Then methyl iodide (96 mg, 675 mmol) was added, and the reaction mixture was stirred overnight at RT. To have a complete conversion, more sodium hydroxide (10 mg, 250 mmol) and methyl iodide (30 mg, 212 mmol) were added, and the mixture was further stirred at 40 °C for 2 h. Ammonium chloride was then added and the mixture was extracted with ethyl acetate. The organic phase was dried over $MgSO_4$ and concentrated on vacuum. The residue was purified on silica gel to give the two isomers.

5-[[5-Bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carbonyl]amino]-*N*-isopropyl-2,6-dimethyl-benzotriazole-4-carboxamide (**72**) (93 mg, 26%) and 5-[[5-bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carbonyl] amino]-*N*-isopropyl-1,6-dimethyl-3a,7a-dihydrobenzotriazole-4-carboxamide (**73**) (106 mg, 29%).

5-[[5-bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carbonyl] amino]-*N*-isopropyl-2,6-dimethyl-benzotriazole-4-carboxamide (**72**): ^{1}H NMR (DMSO-d_6): 10.5 (br, 1H), 8.5 (m, 1H), 8.18 (q, 1H), 8.00 (d, 1H), 7.85 (s, 1H), 7.6 (m, 1H), 7.4 (s, 1H), 4.50 (s, 1H), 2.25 (s, 3H), 1.10 (d, 6H). LC–MS: t_R = 1.76 min, m/z = 533 [M+1].

5-[[5-bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carbonyl] amino]-*N*-isopropyl-1,6-dimethyl-3a,7a-dihydrobenzotriazole-4-carboxamide (**73**): ^{1}H NMR (DMSO-d_6): 10.5 (br, 1H), 8.5 (m, 1H), 8.3 (d, 1H), 8.15 (dd, 1H), 7.80 (s, 1H), 7.60 (m, 1H), 7.45 (s, 1H), 4.30 (s, 3H), 2.3 (s, 3H), 1.10 (d, 6H). LC–MS: t_R = 1.76 min, m/z = 533 [M+1].

4.48. 6-Methyl-2,1,3-benzothiadiazol-5-amine (74)

Under dry atmosphere, 4-methyl-5-nitro-benzene-1,2-diamine (**61**) (10 g, 59.8 mmol) was dissolved in dichloromethane (500 ml) and triethylamine (24.21 g, 239.3 mmol) was added followed by the slow addition of thionylchloride (14.23 g, 119.63 mmol). The suspension was stirred 5 h at RT. The reaction mixture was evaporated under vacuum, the residue was taken up in water (700 ml) and HCl was added to pH 1. The resulting mixture was stirred 1 h and the precipitate formed was filtered to get brown solid. This solid (1 g, 5.122 mmol) was dissolved in HCl 8 N (60 ml), Tin(II) chloride anhydrous (5 g, 26.3 mmol) was added and the resulting mixture was stirred 2 h at RT. The reaction was then quenched at 0 °C with NaOH. The aqueous layer was extracted with ethyl acetate 3 times and the combined organic layer was dried over $MgSO_4$, filtered and evaporated under vacuum

to give 600 mg 6-methyl-2,1,3-benzothiadiazol-5-amine (**74**) (71%).

^{1}H NMR (400 MHz, $CDCl_3$,): 7.69 (s, 1H), 7.02 (s, 1H), 2.4 (s, 3H). LC–MS: t_R = 1.18 min, m/z = 166 [M+1].

4.49. Methyl 5-amino-6-methyl-2,1,3-benzothiadiazole-4-carboxylate (75)

(a) 6-Methyl-2,1,3-benzothiadiazol-5-amine (**74**) (4.4 g, 26.6 mmol) was dissolved in 300 ml DMF and NBS (4.5 g, 25.3 mmol) was added. The reaction mixture was stirred 6 h at 80 °C. The solvent was removed under vacuum and the residue was dissolved in ethyl acetate and washed with water and brine. The combined organic layer was dried over $MgSO_4$, filtered and evaporated under vacuum to give 5.8 g crude 4-bromo-6-methyl-2,1,3-benzothiadiazol-5-amine as a solid (89%), which was further used without purification.

(b) To a solution of 4-bromo-6-methyl-2,1,3-benzothiadiazol-5-amine (5.8 g, 23.77 mmol) in methanol (80 mL) in an autoclave was added palladium[II] chloride (90 mg, 0.51 mmol), (2,2'-bis (diphenylphosphino)-1,1′-binaphthyl, BINAP, 504 mg, 0.81 mmol) and triethylamine (6.6 mL). The autoclave was flushed with carbon monoxide, and then pressurized at 8 bar with carbon monoxide and heated at 100 °C for 16 h. After this time, TLC analysis showed the reaction was incomplete and thus palladium[II] chloride (90 mg, 0.51 mmol), and BINAP (504 mg, 0.81 mmol) were added and heating continued for a further 5 h at 100 °C under 8 bar of carbon monoxide. TLC analysis indicated that the reaction was incomplete and thus a further portion of palladium[II] chloride (90 mg, 0.51 mmol), and BINAP (504 mg, 0.81 mmol) were added and the reaction heated at 100 °C for 16 h under 8 bar of carbon monoxide. TLC analysis after this time showed complete consumption of the starting material. The reaction mixture was concentrated in vacuum, adsorbed onto silica gel and purified by flash-chromatography eluting with hexane/ethyl acetate (5:1) to give 1.97 g methyl 5-amino-6-methyl-2,1,3-benzothiadiazole-4-carboxylate (**75**) (22%) as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): 7.8 (s, 1H), 7.15 (br, 2H), 4.15 (s, 3H), 2.4 (s, 3H). LC–MS: t_R = 1.34 min, m/z = 224 [M+1].

4.50. 5-[[5-Bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carbonyl]amino]-*N*,6-dimethyl-2,1,3-benzothiadiazole-4-carboxamide (76)

5-Amino-6-methyl-2,1,3-benzothiadiazole-4-carboxylate (**75**) (470 mg, 2.10 mmol) was dissolved in a mixture of dioxane/water 1:1 (20 ml) and lithium hydroxide monohydrate (97 mg, 2.315 mmol) was added. The reaction was stirred 2 days at RT and then evaporated under vacuum. Under inert and dry atmosphere, the crude obtained and 5-bromo-2-(3-chloro-2-pyridyl) pyrazole-3-carboxylic acid (**40**) (583 mg, 1.92 mmol) were dissolved in acetonitrile (20 ml) and pyridine (0.72 ml, 8.94 mmol) was added. The resulting mixture was cooled down to 0–5 °C and methanesulfonyl chloride (0.540 ml, 6.95 mmol) was slowly added. The reaction was stirred 2 days at RT. After 2 days, the reaction mixture was evaporated under vacuum and the residue was dissolved in ethylacetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated under vacuum. The crude obtained was purified by flash-chromatography to give 7-[5-bromo-2-(3-chloro-2-pyridyl)pyrazol-3-yl]-5-methyl-[1,2,5] thiadiazolo[3,4-*f*][3,1]benzoxazin-9-one as an intermediate. This intermediate (125 mg) was dissolved in a 1 M methylamine ethanol solution (10 ml) and the resulting mixture was stirred overnight at RT. A few drops DMF were added to get a clear solution and the resulting mixture was stirred 16 more hours at RT. The suspension obtained was filtered. The mother liquid was evaporated under vacuum and the residue was dissolved in ethylacetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated under vacuum. The crude was purified by flash-chromatography to give 5-[[5-bromo-2-(3-chloro-2-pyridyl) pyrazole-3-carbonyl]amino]-*N*,6-dimethyl-2,1,3-benzothiadiazole-4-carboxamide (**76**) (100 mg, 9.5%).

^{1}H NMR (400 MHz, $CDCl_3$): 12 (s, 1H), 9.65 (br s, 1H), 8.2 (d, 1H), 8.45 (dd, 2H), 7.9 (s, 1H), 7.6 (t, 1H), 7 (d, 1H), 6.9 (t, 1H), 3.1 (d, 3H), 2.25 (s, 3H). MS (electrospray): m/z = 504 [M+1], 506 [M+3], 508 [M+5].

4.51. 2-[(*E*)-Hydroxyimino]-*N*-(5-methyl-1*H*-indazol-6-yl)-acetamide (81)

To a solution of sodium sulfate (8.69 g, 61.15 mmol) in 20 ml water was added chloral hydrate (0.62 g, 3.74 mmol) at RT. To the resulting clear solution was added a solution of 5-methyl-6-aminoindazol (**80**) (0.5 g, 3.4 mmol, prepared as described in Ref. 17) solved in 3.7 ml 1 N hydrochloric acid. The resulting mixture turned cloudy and hydroxylamine hydrochloride (0.75 g, 10.9 mmol) was added. The resulting reaction mixture was heated gradually to 80 °C and further stirred for an additional 30 min at that temperature. The reaction mixture was then cooled down to RT with an ice bath. The solid formed was filtrated, washed thoroughly with water and dried at 50 °C overnight to afford 2-[(*E*)-hydroxyimino]-*N*-(5-methyl-1*H*-indazol-6-yl)-acetamide as a brown powder of >95% purity according to HPLC.

^{1}H NMR (DMSO, 400 MHz): 2.40 (s, 3H), 3.75 (br, 1H).7.65 (s, 1H), 7.85 (s, 1H), 7.80 (s, 1H), 9.45 (s, 1H), 12.3 (br, 1H) 12.9 (br, 1H). LC–MS: t_R = 1.02 min, m/z = 219 [M+1].

4.52. 5-Methyl-1,6-dihydro-pyrrolo[2,3-*g*]indazole-7,8-dione (82)

To concentrated sulfuric acid (119 ml) was added portion-wise 2-[(*E*)-hydroxyimino]-*N*-(5-methyl-1*H*-indazol-6-yl)-acetamide (**81**) (34.7 g, 146.3 mmol). The addition was strongly exothermic and the internal temperature was maintained to 70 °C with an ice bath. At the end of the addition, the resulting reaction mixture was heated at 80 °C and stirred for 45 min at that temperature. According to LC–MS analysis, the reaction had then reached completion. The reaction mixture was cooled down to RT. The reaction mixture was poured onto 3.00 kg of ice. The resulting dark-brown suspension was stirred for 30 min and then filtrated. The compound isolated was washed extensively with water and dried in vacuum at 55 °C. 5-Methyl-1,6-dihydro-pyrrolo[2,3-*g*]indazole-7,8-dione (**82**) was obtained as a red-brown powder (27.6 g, 94%).

^{1}H NMR (DMSO, 400 MHz): 2.25 (s, 3H), 7.90 (s, 1H), 8.00 (s, 1H), 11.1 (br, 1H). LC–MS: t_R = 1.01 min, m/z = 202 [M+1].

4.53. 6-Amino-5-methyl-1*H*-indazole-7-carboxylic acid (83)

To a solution of 5-methyl-1,6-dihydro-pyrrolo[2,3-*g*] indazole-7,8-dione (**82**) (23 g, 114.3 mmol) in a 4 N aqueous sodium hydroxide solution (160 ml) at RT, was added dropwise 30% aqueous hydrogen peroxide solution (27 ml) maintaining the temperature below 30 °C with external cooling. The resulting reaction mixture was stirred at RT for 2 h. According to TLC, the reaction was complete after 2 h. The pH was adjusted to pH 3.5 by addition of concentrated hydrochloric acid. The resulting brown suspension was filtered and the compound isolated was washed with cold water and dried in vacuum at 50 °C to afford 6-amino-5-methyl-1*H*-indazole-7-carboxylic acid (**83**) as brown solid (21 g, 94%).

^{1}H NMR (DMSO, 400 MHz): 2.20 (s, 3H), 7.55 (s, 1H), 7.75 (s, 1H), 12.1 (br, 1H). LC–MS: t_R = 1.01 min, m/z = 192 [M+1].

4.54. 5-Methyl-1,6-dihydro-8-oxa-1,2,6-triaza-cyclopenta[*a*]-naphthalene-7,9-dione (84)

In a solution of 180 ml 1,4-dioxane and 100 ml THF, 10 g (52.2 mmol) 6-amino-5-methyl-1*H*-indazole-7-carboxylic acid (**83**) was suspended. Triphosgen (31 g, 104.6 mmol) was added and the suspension was heated at 50 °C for 18 h. The suspension was filtered and washed with diethyl ether. The mother liquor was diluted with 200 ml diethyl ether and the precipitated crystals were filtered. 5-Methyl-1,6-dihydro-8-oxa-1,2,6-triaza-cyclopenta [*a*]naphthalene-7,9-dione (**84**) (9.97 g, quant.) was directly submitted to the next step.

^{1}H NMR (DMSO, 400 MHz): 2.40 (s, 3H), 4.50 (br, 1H), 8.00 (s, 1H), 8.10 (s, 1H). LC–MS: t_R = 1.05 min, m/z = 218 [M+1].

4.55. 6-Amino-5-methyl-1*H*-indazole-7-carboxylic acid isopropylamide (85)

5-Methyl-1,6-dihydro-8-oxa-1,2,6-triaza-cyclopenta[*a*]naphthalene-7,9-dione (**84**) (1.1 g, 5.1 mmol) was suspended in 30 ml acetic acid and 1.5 ml isopropylamine (36.9 mmol) was added. The suspension was heated at reflux at reflux for 18 h. Another 1.5 ml (36.9 mmol) isopropyl amine was added and the mixture was further heated 8 h at reflux. The mixture was cooled down and poured onto 200 ml water. After 30 min stirring, the solid formed was filtered and washed with water. It was dissolved in ethyl acetate and filtered over a short pad of silica gel and crystallized from petrol ether and diisopropylether to give 6-amino-5-methyl-1*H*-indazole-7-carboxylic acid isopropylamide (**85**) (0.71 g, 60%).

^{1}H NMR ($CDCl_3$, 400 MHz): 1.30 (d, 6H), 2.25 (s, 3H), 4.35 (m, 1H), 6.45 (br, 2H), 7.48 (s, 1H), 7.85 (s, 1H), 8.40 (br, 1H). LC–MS: t_R = 1.37 min, m/z = 233 [M+1].

Melting point: 173.5 °C.

4.56. 6-{[2-(3-Chloro-pyridin-2-yl)-5-methoxy-2*H*-pyrazole-3-carbonyl]-amino}-5-methyl-1*H*-indazole-7-carboxylic acid isopropylamide (87)

(a) 2-(3-Chloro-pyridin-2-yl)-5-methoxy-2*H*-pyrazole-3-carboxylic acid (110 g, 434 mmol) was solved in 1200 ml methylene chloride. Oxalyl chloride (74.5 ml, 867 mmol) was slowly added at RT. After addition of 2 ml dimethylformamide, the mixture was stirred for 18 h at RT. Oxalyl chloride (10 ml, 116 mmol) was added and the mixture was heated at 40 °C for 30 min. The mixture was concentrated, evaporated and dried to give 2-(3-chloro-pyridin-2-yl)-5-methoxy-2*H*-pyrazole-3-carbonyl chloride (**86**) which was directly used in the next step.

(b) 6-Amino-5-methyl-1*H*-indazole-7-carboxylic acid isopropylamide (**85**) (1.0 g, 4.3 mmol) was suspended in 20 ml CH_3CN. 2-(3-Chloro-pyridin-2-yl)-5-methoxy-2*H*-pyrazole-3-carbonyl chloride (**86**) (1.23 g, 4.51 mmol) was added in several portions. The mixture was stirred at RT for 39 h. A saturated solution of $NaHCO_3$ in water (15 ml) was added and the mixture was stirred for a few minutes. After filtration and trituration in diisopropylether, 6-{[2-(3-chloro-pyridin-2-yl)-5-methoxy-2*H*-pyrazole-3-carbonyl]-amino}-5-methyl-1*H*-indazole-7-carboxylic acid isopropylamide (**87**) was isolated as a solid material (1.94 g, 85%).

^{1}H NMR (400 MHz, $CDCl_3$): 10.8 (br s, 1H), 9.6 (br s, 1H), 8.40 (d, 1H), 7.86 (s, 1H), 7.81 (d, 1H), 7.30 (dd, 1H), 7.20 (s, 1H), 6.95–6.70 (br s, 1H), 6.82 (s, 1H), 4.27–4.18 (m, 1H), 4.03 (s, 3H), 2.03 (s, 3H), 1.13 (d, 6H). MS (electrospray): m/z = 452 [M+1].

4.57. 1-(2,4-Dinitrophenyl)ethanone oxime (90)

To a stirred solution of 44.5 g (210 mmol) 1-(2,4-dinitrophenyl) ethanone (**89**) and 17 ml pyridine in 200 ml ethanol was added 16 g (210 mmol) hydroxylamine hydrochloride and the reaction was heated and stirred at 80 °C for 3 h. The solvent was removed under vacuum and the residue was taken up in ethyl acetate. The organic phase was washed with water (2 times) and brine, dried and concentrated under vacuum. The crude compound was then purified by crystallization in petroleum ether to yield 42.5 g (90%) 1-(2,4-dinitrophenyl)ethanone oxime (**90**) (42.5 g, 90%) as a mixture of *E* and *Z* isomers.

^{1}H NMR ($CDCl_3$, 400 MHz): 8.94 and 8.80 (2s, 1H), 8.55 and 8.48 (2d, 1H), 8.18 (2b, 1H), 7.20 and 7.50 (2d, 1H), 2.32 and 2.24 (2s, 3H). MS (electrospray): m/z = 224 [M−1]. Mp: 115–125 °C.

4.58. 3-Methyl-6-nitro-1,2-benzoxazole (91)

To a suspension of 1.2 g sodium hydride (65%, 32.5 mmol) in 25 ml diglyme was added dropwise a solution of 5 g (22 mmol) 1-(2,4-dinitrophenyl)ethanone oxime in 15 ml diglyme. The resulting reaction mixture was heated at 150 °C and stirred for 4 h at that temperature. The reaction mixture was then cooled down to RT and slowly poured into 250 ml water. The aqueous phase was extracted with ethyl acetate dried with magnesium sulfate and concentrated under vacuum. The resulting residue was purified by flash-chromatography using a mixture of heptane/dichloromethane/ethyl acetate 10:10:1 as eluent to yield 2 g (51%) 3-methyl-6-nitro-1,2-benzoxazole (**91**) as a yellow solid.

^{1}H NMR (DMSO-d_6, 400 MHz): 2.65 (s, 3H), 8.15 (d, 1H), 8.25 (d, 1H), 8.65 (s, 1H). MS (electrospray): m/z = 178 [M+1]. Mp: 110–111 °C.

4.59. 3-Methyl-1,2-benzoxazol-6-amine (92)

To a solution of 1 g (5.6 mmol) 3-methyl-6-nitro-1,2-benzoxazole (**91**) in 60 ml 6 N HCl solution at RT was added portion-wise 5 g (22 mmol) Tin(II) chloride dihydrate . The resulting reaction mixture was stirred at RT for 6 h. The pH was adjusted to pH 12–13 by the addition of concentrated sodium hydroxide. The aqueous phase was extracted with ethyl acetate, dried over magnesium sulfate and concentrated under vacuum. This yielded 0.72 g (86%) 3-methyl-1,2-benzoxazol-6-amine (**92**) as an off-white solid.

^{1}H NMR (DMSO-d_6, 400 MHz): 2.35 (s, 3H), 5.8 (s, 2H), 6.55 (s, 1H), 6.6 (d, 1H), 7.4 (s, 1H). LC–MS: t_R = 1.22 min, m/z = 190 [M +42 (CH_3CN)]. Mp: 111–113 °C.

4.60. (2*E*)-2-Hydroxyimino-*N*-(3-methyl-1,2-benzoxazol-6-yl) acetamide (93)

To a solution of 0.7 g (4.7 mmol) of 3-methyl-1,2-benzoxazol-6-amine (**92**) and 1.6 g (11.2 mmol) sodium sulfate in 30 ml water was added 1.1 g (7.4 mmol) chloral hydrate, 0.5 ml concd HCl and 1.3 g (18.8 mmol) hydroxylamine hydrochloride at RT. The resulting reaction mixture was heated gradually to 80 °C and stirred for 4 h at that temperature. The reaction mixture was then cooled down to RT with an ice bath. The solid formed was filtrated, washed thoroughly with water and diisopropylether and dried at 50 °C overnight to afford 0.89 g (81%) (2*E*)-2-hydroxyimino-*N*-(3-methyl-1,2-benzoxazol-6-yl)acetamide (**93**) as an off-white powder.

^{1}H NMR (DMSO-d_6, 400 MHz): 2.5 (s, 3H), 7.55 (d, 1H), 7.7 (s, 1H), 7.75 (d, 1H), 8.2 (s, 1H), 10.55 (s, 1H), 12.3 (s, 1H). LC–MS: t_R = 1.39 min, m/z = 220 [M+1]. Mp: 225–227 °C.

4.61. 6-Amino-3-methyl-1,2-benzoxazole-7-carboxylic acid (94)

A solution of (2*E*)-2-hydroxyimino-*N*-(3-methyl-1,2-benzoxazol-6-yl)acetamide (**93**) (0.89 g, 4 mmol) in concentrated sulfuric acid (10 mL) was stirred 8 h at 85 °C. The reaction mixture was

poured into a mixture of ice and water, stirred and filtered. The precipitate obtained was washed with diisopropyl ether to give 0.46 g (57.5%) 3-methyl-6*H*-pyrrolo[2,3-g][1,2]benzoxazole-7,8-dione. This material was solved in 10 mL water and sodium hydroxide (0.4 g, 10 mmol) followed by 0.8 ml hydrogen peroxide 30% (8.4 mmol) were added slowly. The resulting mixture was stirred 6 h at 70 °C and then overnight at RT. The reaction mixture was neutralized with concd HCl to pH 4–5. The aqueous layer was extracted with ethyl acetate, dried over $MgSO_4$, filtered and evaporated. The residue was purified by chromatography with the Sandoz eluent. The product obtained was solved in water, acidified to pH 4–5 with 2 N HCl and extracted again with ethyl acetate, dried over $MgSO_4$, filtered and evaporated to give 6-amino-3-methyl-1,2-benzoxazole-7-carboxylic acid (**94**) as an orange solid.

^{1}H NMR (DMSO-d_6, 400 MHz): 2.4 (s, 3H), 6.75 (d, 1H), 7.55 (d, 1H). LC–MS: t_R = 1.12 min, m/z = 191 [M−1].

4.62. 6-Amino-5-chloro-3-methyl-1,2-benzoxazole-7-carboxylic acid (95)

6-Amino-3-methyl-1,2-benzoxazole-7-carboxylic acid (**94**) (9.6 g, 50.0 mmol) was dissolved in dimethylformamide (70 ml) and 6.7 g *N*-chlorosuccinimide (50.0 mmol) were added. The resulting mixture was stirred at 90 °C for 90 min, cooled down and poured into water. The precipitate formed was filtered, dried and washed with diisopropylether to give 6-amino-5-chloro-3-methyl-1,2-benzoxazole-7-carboxylic acid (**95**) as a powder (9.0 g, 80%).

^{1}H NMR (DMSO-d_6, 400 MHz): 13.35 (s, 1H), 8 (s, 1H), 7.55 (s, 2H), 2.45 (s, 3H).MS (electrospray): m/z = 227 [M+1], 229 [M+3].

4.63. 5-Chloro-6-[[2-(3-chloro-2-pyridyl)-5-methoxy-pyrazole-3-carbonyl]amino]-*N*-isopropyl-3-methyl-1,2-benzoxazole-7-carboxamide (97)

(a) 2-(3-Chloro-2-pyridyl)-5-methoxy-pyrazole-3-carboxylic acid (**96**) (10 g, 39.45 mmol) was dissolved in dichloromethane (150 ml) and 3 drops of DMF was added followed by the dropwise addition of 15.0 mL oxalyl chloride (78.9 mmol). The brown suspension turned to a red solution. The reaction mixture was stirred for 3 h at 40 °C and evaporated to give crude 2-(3-chloro-2-pyridyl)-5-methoxy-pyrazole-3-carbonyl chloride (10.2 g, 95%) which was directly used in the next step.

(b) In a solution of 20 ml THF and 50 ml acetonitrile, 2.3 ml methanesulfonyl chloride (29.85 mmol) and 4 ml pyridine were added followed by 2.25 g 6-amino-5-chloro-3-methyl-1,2-benzoxazole-7-carboxylic acid (**95**) (9.95 mmol) and 2.53 g 2-(3-chloro-2-pyridyl)-5-methoxy-pyrazole-3-carbonyl chloride (step a, 9.3 mmol) was added in several portions. The mixture was stirred at RT for 39 h. A saturated solution of $NaHCO_3$ in water (15 ml) was added and the mixture was stirred for a few minutes. After filtration, 5-chloro-7-[2-(3-chloro-2-pyridyl)-5-methoxy-pyrazol-3-yl]-3-methyl-3a,6,7,9b-tetrahydroisoxazolo[5,4-*f*][3,1]benzoxazin-9-one (4.2 g, 93%) was isolated as a solid which was directly used in the next step.

(c) 5-Chloro-7-[2-(3-chloro-2-pyridyl)-5-methoxy-pyrazol-3-yl]-3-methyl-3a,6,7,9b-tetrahydroisoxazolo[5,4-*f*][3,1]benzoxazin-9-one (1.05 g, 2.28 mmol) obtained from the previous step was suspended in 15 ml acetonitrile and 0.38 ml isopropylamine (9.2 mmol) was added. The suspension was heated at reflux for 18 h. The mixture was cooled down and poured on 100 ml water. After 30 min stirring, the crystalline material was filtered and washed with water. The solid was dissolved in ethyl acetate and filtered over a short pad of silica gel to afford (0.92 g, 80%). 5-Chloro-6-[[2-(3-chloro-2-pyridyl)-5-methoxy-pyrazole-3-carbonyl]amino]-*N*-isopropyl-3-methyl-1,2-benzoxazole-7-carboxamide (**97**) after crystallization in petrol ether and diisopropylether.

^{1}H NMR (400 MHz, $CDCl_3$): 11.37 (br s, 1H), 8.46 (m, 1H), 7.79 (m, 1H), 7.75 (s, 1H), 7.30 (m, 1H), 7.06 (br, 1H), 6.55 (s, 1H), 4.33 (m, 1H), 4.02 (s, 1H), 2.56 (s, 1H), 1.33 (d, 6H). MS (electrospray): m/z = 503 [M+1], 505 [M+3], 507 [M+5].

4.64. (2*E*)-*N*-(5-Fluoro-2-methyl-phenyl)-2-hydroxyimino-acetamide (99)

To a solution of sodium sulfate (600 g, 4.22 mol) in 1500 ml water was added chloral hydrate (42.75 g, 258 mmol) at RT. To the resulting clear solution was added a solution of 5-fluoro-2-methyl-aniline (30 g, 239 mmol) in 1 N aqueous hydrochloric acid (261 ml). The resulting mixture turned cloudy and hydroxylamine hydrochloride (52.23 g, 751 mmol) was then added. The resulting reaction mixture was heated to 80 °C and stirred for an additional 3 h at that temperature. The reaction mixture was then cooled down to RT with an ice bath and the solid formed was filtrated. The filter cake was washed thoroughly with water and dried at 50 °C overnight to afford (2*E*)-*N*-(5-fluoro-2-methyl-phenyl)-2-hydroxyimino-acetamide (**99**) (35.86 g, 76%).

^{1}H NMR (DMSO-d_6, 400 MHz): 2.20 (s, 3H), 6.95 (m, 1H), 7.25 (t, 1H), 7.5 (q, 1H), 7.7 (s, 1H), 9.5 (s, 1H) 12.25 (s, 1H). LC–MS: t_R = 1.29 min, m/z = 196 [M+1].

4.65. 2-Amino-6-fluoro-3-methyl-benzoic acid (100)

A solution of (2*E*)-*N*-(5-fluoro-2-methyl-phenyl)-2-hydroxyimino-acetamide (**99**) (35.8 g, 182 mmol) in 200 mL concentrated sulfuric acid was stirred 8 h at 85 °C. The reaction mixture was then poured into a mixture of ice and water (3 L), stirred and filtered. The precipitate obtained was washed with diisopropyl ether to give 4-fluoro-7-methyl-indoline-2,3-dione (26.8 g, 149 mmol). This intermediate was dissolved in a 2 N solution of sodium hydroxide (175 ml) and 37.0 ml hydrogen peroxide 30% (388 mmol) was added slowly. The resulting mixture was heated 3 h at 80 °C. The reaction mixture was cooled down and acidified to pH 4–5 with 2 M HCl. The aqueous layer was extracted with ethyl acetate, dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash-chromatography. The product obtained was solved again in water, acidified to pH 4–5 with 2 M HCl, extracted with ethyl acetate, dried over $MgSO_4$ and evaporated to give 22.24 g 2-amino-6-fluoro-3-methyl-benzoic acid (**100**) (88%).

^{1}H NMR (DMSO-d_6, 400 MHz): 2.2 (s, 3H), 6.25 (t, 1H), 7.1 (t, 1H). LC–MS: t_R = 1.25 min, m/z = 170 [M+1].

4.66. 2-Amino-6-fluoro-5-iodo-3-methyl-benzoic acid (101)

To a solution of 2-amino-6-fluoro-3-methyl-benzoic acid (**100**) (22.24 g, 0.131 mol) in *N*,*N*-dimethylformamide (500 ml) was added *N*-iodosuccinimide (28.1 g, 0.124 mol).The reaction mixture was heated at 80 °C for 2 h. After cooling, the reaction mixture was concentrated in vacuum. The residue was diluted with ethyl acetate and washed with water. The aqueous phase was extracted 3 times with ethyl acetate. The combined organic phases were dried on $MgSO_4$ and concentrated to afford 37.97 g 2-amino-6-fluoro-5-iodo-3-methyl-benzoic acid (**101**) (98%).

^{1}H NMR (DMSO-d_6, 400 MHz): 2.00 (s, 3H), 7.45 (t, 1H). LC–MS: t_R = 1.60 min, m/z = 296 [M+1].

4.67. 2-Amino-6-fluoro-5-iodo-*N*,3-dimethyl-benzamide (102)

(a) 2-Amino-6-fluoro-5-iodo-3-methyl-benzoic acid (**101**) (37.9 g, 0.128 mol) was solved in 600 ml toluene. Thionyl chloride (46.6 ml, 0.642 mol) was slowly added at RT. The mixture was stir-

red for 18 h at RT. The mixture was concentrated in vacuum, and the residual acid chloride was directly used in the next step.

(b) To a cooled solution of the acid chloride obtained in the previous step in 600 ml THF was slowly added 21.6 ml triethylamine (0.154 mol) and 36.7 ml of solution of methylamine 33% in methanol (0.390 mol) at 0–5 °C. The reaction mixture was stirred at RT overnight. The solution was concentrated in vacuum and water and ethyl acetate were added. The organic phase was separated, dried over $MgSO_4$, and concentrated in vacuum to give 25.53 g 2-amino-6-fluoro-5-iodo-*N*,3-dimethyl-benzamide (**102**) (65%).

^{1}H NMR ($CDCl_3$, 400 MHz): 2.10 (s, 3H), 3.00 (d, 3H), 6.00 (br, 2H), 6.60 (br, 1H), 7.40 (d, 1H). LC–MS: t_R = 1.52 min, m/z = 309 [M+1].

4.68. 2-Amino-5-cyano-6-fluoro-*N*,3-dimethyl-benzamide (103)

To a degassed solution of 2-amino-6-fluoro-5-iodo-*N*,3-dimethyl-benzamide (**102**) (13.7 g, 44.5 mmol), in 250 ml DMF was added copper iodide (847.1 mg, 44.4 mmol), $Pd(PPh_3)_4$ (2.56 g, 2.2 mmol) and copper cyanide (19.91 g, 222.3 mmol). The mixture was heated at 90 °C for 48 h. After cooling, the mixture was filtered on cellite. After concentration in vacuum, the residue was solved in ethyl acetate and washed with water. The aqueous phase was extracted with ethyl acetate (3 times), the combined organic phases were dried on $MgSO_4$ and concentrated in vacuum to give 8.63 g 2-amino-5-cyano-6-fluoro-*N*,3-dimethyl-benzamide (**103**) (77%).

^{1}H NMR ($CDCl_3$, 400 MHz): 2.10 (s, 3H), 2.75 (d, 3H), 6.50 (br, 2H), 7.40 (d, 1H), 8.45 (br, 1H). LC–MS: t_R = 1.17 min, m/z = 208 [M+1].

4.69. 3,6-Diamino-*N*,5-dimethyl-1,2-benzoxazole-7-carboxamide (104)

To a solution of acetohydroxamic acid (3.26 g, 43.43 mmol) in 150 ml DMF was added potassium carbonate (10.67 g, 77.21 mmol) followed by 2 ml water. The mixture was stirred at RT for 30 min and 2-amino-5-cyano-6-fluoro-*N*,3-dimethyl-benzamide (**103**) (4 g, 19.30 mmol) was added. The reaction mixture was stirred at RT overnight. The reaction was quenched with water and the product was extracted with ethyl acetate (5 times). The organic phases were dried on $MgSO_4$ and concentrated. The residue was dissolved in a minimum of ethyl acetate/dichloromethane and cyclohexane was added to get 2.49 g 3,6-diamino-*N*,5-dimethyl-1,2-benzoxazole-7-carboxamide (**104**) as brown crystals (59%).

^{1}H NMR ($CDCl_3$, 400 MHz): 2.13 (s, 3H), 2.85 (d, 3H), 6.15 (br, 2H), 7.30 (br, 2H), 7.50 (s, 1H), 7.75 (br, 1H). LC–MS: t_R = 1.07 min, m/z = 221 [M+1].

4.70. *tert*-Butyl *N*-[6-amino-5-methyl-7-(methylcarbamoyl)-1,2-benzoxazol-3-yl]-*N*-*tert*-butoxycarbonyl-carbamate (105)

To a solution of 3,6-diamino-*N*,5-dimethyl-1,2-benzoxazole-7-carboxamide (**104**) (2.3 g, 10.44 mmol) in 100 ml dichloromethane was added triethylamine (14.6 ml) followed by di-*tert*-butyl dicarbonate (2.28 g, 10.44 mmol), and a catalytic amount of 4-dimethylaminopyridine. The reaction mixture was stirred at RT overnight. A second portion of di-*tert*-butyl dicarbonate (22.8 g, 104.4 mmol) dissolved in 50 ml dichloromethane was added. After 3 h at RT, the conversion was complete. After evaporation of the solvent, the residue was taken in ethyl acetate and washed with water. The organic phase was dried on $MgSO_4$ and concentrated in vacuum. The crude product was purified by flash-chromatography to give 1.84 g *tert*-butyl *N*-[6-amino-5-methyl-7-(methylcarbamoyl)-1,2-benzoxazol-3-yl]-*N*-*tert*-butoxycarbonyl-carbamate (**105**) as beige crystals (42%).

^{1}H NMR ($CDCl_3$, 400 MHz): 1.30 (s, 18H) 2.13 (s, 3H), 3.00 (d, 3H), 6.80 (br, 1H), 7.40 (br, 2H). LC–MS: t_R = 1.90 min, m/z = 421 [M+1].

4.71. *tert*-Butyl *N*-[6-[[5-bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carbonyl]amino]-5-methyl-7-(methylcarbamoyl)-1,2-benzoxazol-3-yl]-*N*-*tert*-butoxycarbonyl-carbamate (107)

To a solution of *tert*-butyl *N*-[6-amino-5-methyl-7-(methylcarbamoyl)-1,2-benzoxazol-3-yl]-*N*-*tert*-butoxycarbonyl-carbamate (**105**) (0.4 g, 0.949 mmol) in 20 ml THF was slowly added 5-bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carbonyl chloride (0.416 g, 1.30 mmol). The reaction mixture was stirred at RT overnight. Water was added and product was extracted with ethyl acetate. The organic phase was dried on $MgSO_4$ and concentrated in vacuum. The crude product was purified by flash-chromatography to give 370 mg *tert*-butyl *N*-[6-[[5-bromo-2-(3-chloro-2-pyridyl) pyrazole-3-carbonyl]amino]-5-methyl-7-(methylcarbamoyl)-1,2-benzoxazol-3-yl]-*N*-*tert*-butoxycarbonyl-carbamate (**107**) as beige crystals (55.3%).

^{1}H NMR ($CDCl_3$, 400 MHz): 1.25 (s, 18H) 2.13 (s, 3H), 3.00 (d, 3H), 7.00 (s, 1H), 7.15 (m, 1H) 7.15 (m, 1H) 7.20 (m, 1H) 7.30 (s, 1H), 7.7 (m, 1H), 8.3 (m, 1H), 11.8 (s, H). LC–MS: t_R = 2.02 min, m/z = 706 [M+1].

4.72. 3-Amino-6-[[5-bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carbonyl]amino]-*N*,5-dimethyl-1,2-benzoxazole-7-carboxamide (108)

tert-Butyl *N*-[6-[[5-bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carbonyl]amino]-5-methyl-7-(methylcarbamoyl)-1,2-benzoxazol-3-yl]-*N*-*tert*-butoxycarbonyl-carbamate (**107**) (100 mg, 110 mmol) was dissolved in 5 ml CH_2Cl_2 and 5 ml trifluoroacetic acid were added. The reaction mixture was stirred at RT for 3 h. Water was added and the product was extracted with ethyl acetate. The organic phase was dried on $MgSO_4$ and concentrated in vacuum. The crude residue was purified by flash-chromatography to give 33 mg 3-amino-6-[[5-bromo-2-(3-chloro-2-pyridyl)pyrazole-3-carbonyl]amino]-*N*,5-dimethyl-1,2-benzoxazole-7-carboxamide (**108**) as beige crystals (60%).

^{1}H NMR (DMSO, 500 MHz): 2.21 (s, 3H), 2.72 (d, 3H), 6.44 (s, 2H), 7.41 (s, 1H) 7.60 (m, 1H) 7.73 (s, 1H) 8.16 (m, 1H), 8.22 (q, 1H), 8.50 (m, 1H), 10.44 (s, 1H). LC–MS: t_R = 1.50 min, m/z = 504 [M+1], 506 [M+3].

4.73. *tert*-Butyl *N*-*tert*-butoxycarbonyl-*N*-(2-chloro-4-pyridyl)-carbamate (110)

A solution of 5.9 g 2-chloropyridin-4-amine (46.0 mmol) in 400 ml THF under nitrogen atmosphere was cooled down to 0 °C. Lithium bis(trimethylsilyl)amide 1 M in THF (100 ml, 100 mmol) was added dropwise. After the addition, the reaction mixture was stirred 30 min at 0 °C. A solution of di-*tert*-butyl dicarbonate (22 g, 101 mmol) in 100 ml THF was added slowly at 0–5 °C. The reaction mixture was stirred one night at RT and then quenched with ammonium chloride and brine. The organic layer was washed with brine, dried over $MgSO_4$, filtered and evaporated under vacuum to give *tert*-butyl *N*-*tert*-butoxycarbonyl-*N*-(2-chloro-4-pyridyl)carbamate (**110**) as an orange solid (15.8 g, quant.).

^{1}H NMR (400 MHz, $CDCl_3$): 8.37 (d, 1H), 7.19 (d, 1H), 7.05 (dd, 1H), 1.45 (s, 18H). MS (electrospray): m/z = 329 [M+1].

4.74. *tert*-Butyl 4-(*tert*-butoxycarbonylamino)-2-chloro-pyridine-3-carboxylate (111)

According to Ref. 16: under inert atmosphere, a solution of diisopropylamine (23 ml, 160 mmol) in 350 ml THF was cooled to

−75 °C. A solution of 100 ml *n*BuLi (1.6 M in hexane, 160 mmol) was added and the resulting mixture was stirred 30 min at −75 °C. *tert*-Butyl *N*-*tert*-butoxycarbonyl-*N*-(2-chloro-4-pyridyl)-carbamate (**110**) (15.6 g, 46 mmol) in 50 ml THF was added to the reaction mixture at −75 °C. After the addition, the reaction was stirred 1 h at −75 °C and then carefully quenched with ammonium chloride and brine. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, evaporated under vacuum and washed with heptane to give 11.2 g *tert*-butyl 4-(*tert*-butoxycarbonylamino)-2-chloro-pyridine-3-carboxylate (**111**) as a yellow solid (72%).

^{1}H NMR (400 MHz, CDCl3): 8.7 (br s, 1H), 8.2 (dd, 1H), 1.65 (s, 9H), 1.52 (s, 9H). LC–MS: t_R = 2.07 min, m/z = 329 [M+1], 331 [M +3]. Mp: 135–137 °C.

4.75. *tert*-Butyl *N*-(3-acetyl-2-hydrazino-4-pyridyl)carbamate (112)

To a solution of *tert*-butyl 4-(*tert*-butoxycarbonylamino)-2-chloro-pyridine-3-carboxylate (**111**) (1.1 g, 3.3 mmol) in 15 ml dioxane was added hydrazine hydrate (0.23 g, 3.63 mmol) followed by ethyl diisopropylamine (0.48 g, 3.63 mmol). The resulting mixture was stirred one night at 60 °C. Hydrazine hydrate (0.2 g, 3.3 mmol) was added and the mixture was stirred overnight at 60 °C. The reaction mixture was evaporated under vacuum and the residue was solved in ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, filtered, evaporated under vacuum. The solid obtained was washed in diisopropylether to give 0.89 g *tert*-butyl *N*-(3-acetyl-2-hydrazino-4-pyridyl)carbamate (**112**) as a yellow solid (40%).

^{1}H NMR (DMSO-d_6, 400 MHz): 10.12 (s, 1H), 8.4 (br s, 1H), 8.1 (d, 1H), 7.4 (d, 1H), 4.42 (br s, 2H), 1.6 (s, 9H), 1.45 (s, 9H). LC–MS: t_R = 1.25 min, m/z = 325 [M+1]. Mp: 152–154 °C.

4.76. *tert*-Butyl *N*-(8-acetyl-3-methyl-[1,2,4]triazolo[4,3-*a*]pyridin-7-yl)carbamate (113)

To a solution of *tert*-butyl *N*-(3-acetyl-2-hydrazino-4-pyridyl)-carbamate (**112**) (1.1 g, 4.1 mmol) in 30 ml ethanol was added 3 drops concentrated sulfuric acid, followed by triethylorthoacetate (1 ml, 5.4 mmol). The resulting mixture was stirred 30 min at 70 °C. The reaction mixture was evaporated and the residue was solved in ethyl acetate, washed with water and a saturated bicarbonate solution. The aqueous layer was extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$, filtered and evaporated under vacuum to give 0.49 g *tert*-butyl *N*-(8-acetyl-3-methyl-[1,2,4]triazolo[4,3-*a*]pyridin-7-yl)carbamate (**113**) as a solid (45%).

^{1}H NMR (400 MHz, $CDCl_3$): 11.0 (br s, 1H), 8.3 (d, 1H), 7.8 (d, 1H), 2.69 (s, 3H) 1.71 (s, 9H), 1.55 (s, 9H). LC–MS: t_R = 1.42 min, m/z = 349 [M+1]. Mp: 220–222 °C.

4.77. 7-Amino-3-methyl-[1,2,4]triazolo[4,3-*a*]pyridine-8-carboxylic acid (114)

A solution of *tert*-butyl *N*-(8-acetyl-3-methyl-[1,2,4]triazolo [4,3-*a*]pyridin-7-yl)carbamate (**113**) (0.48 mg, 1.38 mmol) in 2 ml trifluoroacetic acid was stirred 45 min at 70 °C. The reaction mixture was cooled, evaporated under vacuum and taken in water, followed by a saturated bicarbonate solution and 3–4 drops of potassium carbonate solution. The aqueous layer was acidified until pH 3 with HCl 2 M, brine was added and a precipitate was formed. The solid was filtered, washed with acetonitrile and dried to afford 0.18 g 7-amino-3-methyl-[1,2,4]triazolo[4,3-*a*]pyridine-8-carboxylic acid (**114**) as a trifluoroacetate salt (42%).

^{1}H NMR (DMSO-d_6, 400 MHz): 14.05 (s, 2H), 8.75 (br s, 1H), 8.7 (br s, 1H), 8.4 (d, 1H), 6.95 (d, 1H), 2.6 (s, 3H). LC–MS: t_R = 0.16 min, m/z = 193 [M+1]. Mp: 233–235.

4.78. 7-Amino-*N*,3-dimethyl-[1,2,4]triazolo[4,3-*a*]pyridine-8-carboxamide (115)

To a solution of 7-amino-3-methyl-[1,2,4]triazolo[4,3-*a*]pyridine-8-carboxylic acid trifluoroacetate salt (**114**) (1.1 g, 3.6 mmol) in 20 ml water was added sodium hydroxide (144 mg, 7.2 mmol). The resulting mixture was stirred 1 h at RT and evaporated under vacuum to give 7-amino-3-methyl-[1,2,4]triazolo[4,3-*a*]pyridine-8-carboxylic acid as a sodium salt. This salt was taken in 20 ml thionyl chloride and the resulting suspension was stirred 20 h at 90 °C. The reaction mixture was evaporated and the residue was taken in 20 ml THF. The resulting suspension was slowly added to a 10 ml ethanol solution of methylamine (10 mmol) in 100 ml THF. After 5 min, the reaction mixture was quenched with water and brine. The organic layer was separated, dried over $MgSO_4$, filtered and evaporated under vacuum to give 0.58 g 7-amino-*N*,3-dimethyl-[1,2,4]triazolo[4,3-*a*]pyridine-8-carboxamide (**115**) as solid (55%).

^{1}H NMR (DMSO-d_6, 400 MHz): 9.62 (d, 1H), 9.05 (br s, 1H), 8.1 (d, 1H), 7.4 (br s, 1H), 6.55 (d, 1H), 2.85 (d, 3H), 2.55 (s, 3H). LC–MS: t_R = 0.24 min, m/z = 193 [M+1].

4.79. 7-[[2-(3-Chloro-2-pyridyl)-5-methoxy-pyrazole-3-carbonyl]amino]-*N*,3-dimethyl-[1,2,4]triazolo[4,3-*a*]pyridine-8-carboxamide (116)

To a solution of 7-amino-*N*,3-dimethyl-[1,2,4]triazolo[4,3-*a*] pyridine-8-carboxamide (**115**) (250 mg, 1.2 mmol) in 10 ml THF was added 2-(3-chloro-2-pyridyl)-5-methoxy-pyrazole-3-carbonyl chloride (326 mg, 1.2 mmol) was added. The reaction was stirred 1 week at RT. The reaction mixture was poured into water and the mixture obtained was basified (pH 7–8) with potassium carbonate. The aqueous layer was extracted with a mixture of ethyl acetate/THF 2:1. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash-chromatography to give 7 mg 7-[[2-(3-chloro-2-pyridyl)-5-methoxy-pyrazole-3-carbonyl]amino]-*N*,3-dimethyl-[1,2,4]triazolo[4,3-*a*]pyridine-8-carboxamide (**116**) (1%).

^{1}H NMR (400 MHz, $CDCl_3$): 8.52 (d, 1H), 8.48 (d, 1H), 7.9 (d, 1H), 7.75 (d, 1H), 7.4 (m, 1H), 6.7 (s, 1H), 4 (s, 3H), 3.1 (d, 3H), 2.75 (s, 3H). LC–MS: t_R = 1.58 min, m/z = 441 [M+1].

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