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Replacement of an Indole Scaffold Targeting Human 15-Lipoxygenase-1 Using Combinatorial Chemistry

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Dedicated to *François Diederich* on the occasion of his retirement

Human 15-lipoxygenase-1 (15-LOX-1) belongs to the class of lipoxygenases, which catalyze oxygenation of polyunsaturated fatty acids, such as arachidonic and linoleic acid. Recent studies have shown that 15-LOX-1 plays an important role in physiological processes linked to several diseases such as airway inflammation disease, coronary artery disease, and several types of cancer such as rectal, colon, breast and prostate cancer. In this study, we aimed to extend the structural diversity of 15-LOX-1 inhibitors, starting from the recently identified indolyl core. In order to find new scaffolds, we employed a combinatorial approach using various aromatic aldehydes and an aliphatic hydrazide tail. This scaffold-hopping study resulted in the identification of the 3-pyridylring as a suitable replacement of the indolyl core with an inhibitory activity in the micromolar range ($IC_{50} = 16 \pm 6$ μM) and a rapid and efficient structure–activity relationship investigation.

Keywords: 15-lipoxygenase-1, enzyme inhibitors, combinatorial chemistry, acylhydrazone, structure–activity relationships.

Introduction

Several diseases on the World Health Organization's list of top-ten leading causes of death worldwide in 2016, such as ischemic heart disease, stroke, airway inflammation disease, and cancer have been associated with the catalytic action of human 15-lipoxygenase-1 (15-LOX-1).[1–4] This enzyme catalyzes oxygenation of polyunsaturated fatty acids, such as arachidonic and linoleic acid forming several pro-inflammatory mediators.[4]

In the arachidonic acid metabolism pathway, 15-LOX-1 catalyzes the production of hydroperoxy fatty acid (15S)-hydroperoxyeicosatetraenoic acid ((15S)-HpETE), which can then be reduced by 5-LOX to lipoxins, by 15-LOX-1 to eoxins, or by glutathione peroxidase to (15S)-hydroxyeicosatetraenoic acid ((15S)-HETE).[5] In the linoleic acid metabolism pathway, 15-LOX-1 transforms the polyunsaturated fatty acid into (9Z,11E,13S)-13-hydroperoxy-9,11-octadecadienoic acid ((13S)-HpODE), which can then be further
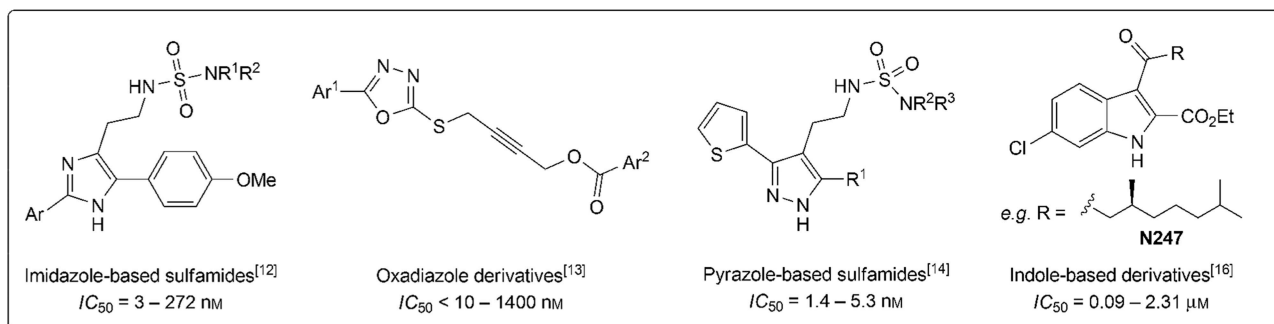

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Figure 1. Structures of representative inhibitors of 15-LOX-1 and initial hit (**N247**) used as starting point in this study.

reduced to (9*Z*,11*E*,13*S*)-13-hydroxy-9,11-octadecadie-noic acid ((13*S*)-HODE).[6,7]

(15*S*)-HETE is reported to be present in the heart tissue of patients with ischemic heart disease and it contributes to accelerated clot formation.[8] Also an increase of 12/15-LOX levels in the peri-infarct cortex of two stroke patients has been reported, suggesting their important role in human stroke.[9] Another metabolite from the linoleic acid metabolism pathway is (13*S*)-HODE, which has been shown to induce airway epithelial injury leading to severe asthma.[10] Furthermore, 15-LOX-1 triggers the formation of several metabolites, resulting in higher secretion of mucins in asthmatic patients.[11] These studies suggest the versatile role of 15-LOX-1 in pathophysiological processes, which have been linked to various diseases. Therefore, the discovery of a potent inhibitor of 15-LOX-1 with physicochemical properties that enable further drug development is essential to unravel the biological roles of the enzyme.

Several 15-LOX-1 inhibitors have been reported featuring moderate to good inhibitory activity, such as imidazole-based sulfamides,[12] oxadiazole derivatives,[13] and pyrazole-based sulfamides (*Figure 1*).[14] Although these inhibitors exhibit potent activity against 15-LOX-1, up to now no inhibitor has reached the market as drug for therapeutic use. This could be attributed to their unfavorable physicochemical and pharmacokinetic properties, which hampered their hit-to-lead optimization and call for the discovery of novel chemical classes.[12,14,15]

In 2015, our group reported a substituted indolyl moiety with various possible extensions at the 3-position as a promising core structure for inhibition of 15-LOX-1. The most potent compound, **N247**, showed a half maximal inhibitory concentration (IC_{50}) of 0.09 ± 0.03 μM (*Figure 1*).[16]

Although the indoles are very potent, their utility is hindered by their low aqueous solubility. Thus, we investigated the possibility of scaffold hopping by starting from the previously reported aliphatic branched tail as fatty acid mimic.[16] In our search for new scaffolds, we applied a combinatorial approach based on acylhydrazone chemistry, in which we let hydrazide **1d** react with various aldehydes. To establish whether the new scaffold could act as 15-LOX-1 inhibitor, we synthesized a series of acylhydrazones, **2–7**. Next, we screened various aromatic aldehydes in combination with the aliphatic tail as hydrazide (**1d**), which resulted in the 3-pyridyl moiety as clear hit. Encouraged by this discovery, we performed a combinatorial screening focusing on the 3-pyridyl moiety that helped us to further explore the chemical space around the initial hit.

Results and Discussion

Acylhydrazones as Inhibitors of 15-LOX-1

In order to enhance the structural diversity of 15-LOX-1 inhibitors, we started our study from the recently identified **N247** bearing an indolyl core.[16] Several studies have shown that even small changes to the indolyl core, such as methylation of the amine or modification of the ethyl ester led to a loss of inhibitory activity.[16,17] In order to investigate whether the indole replacement would be tolerated in terms of activity, we used the aliphatic tail of the most potent indolyl-based inhibitor reported so far as starting point and performed a preliminary screening assay with six acylhydrazones **2–7**, obtained from reacting the aliphatic branched tail as hydrazide with various aldehydes as indole replacement (*Scheme 1*). Although the stereochemistry in the aliphatic branched tail can have an effect on the potency,[16,18] for this preliminary
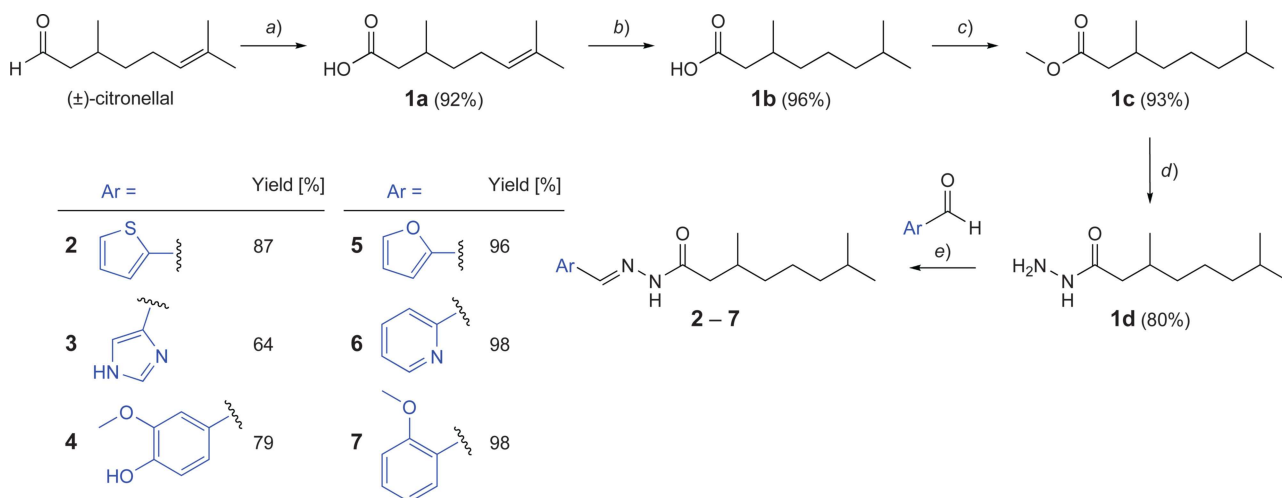
Scheme 1. Synthetic route for the preparation of the aliphatic hydrazide **1d** and synthesis of initial acylhydrazones **2–7**. Reagents and conditions: *a*) Ag$_2$O, H$_2$O, r.t., 16 h; *b*) H$_2$, 10 mol-% Pd/C, EtOH, r.t., 16 h; *c*) cat. H$_2$SO$_4$, MeOH, reflux, 16 h; *d*) hydrazine hydrate, MeOH, reflux, 16 h; *e*) corresponding aldehyde, MeOH, reflux, 16 h.

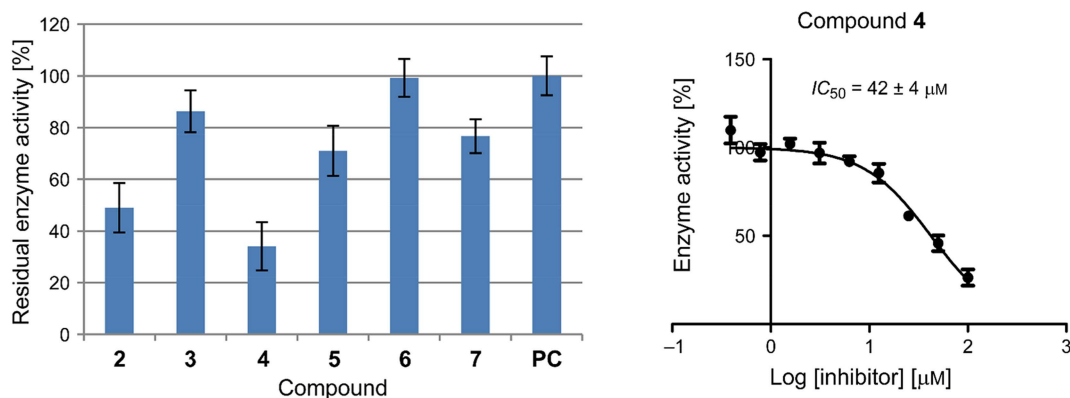**Figure 2.** Left, residual enzyme activity of 15-LOX-1 after incubation with acylhydrazones **2–7** at 100 μM. Right, IC_{50} curve of compound **4**. Positive control (PC) shows the enzyme activity in absence of inhibitor. The experiments were performed in triplicate, and the standard errors are shown.

work, we used the racemic mixture. A four-step synthetic route from commercially available (±)-citronellal afforded hydrazide **1d**. Oxidation of citronellal using *Tollens'* reagent, followed by Pd/C-catalyzed hydrogenation afforded **1b** in 96% yield. Next, *Fischer* esterification to the methyl ester **1c**, followed by hydrazinolysis provided hydrazide **1d** in an overall yield of 66% over four steps. Subsequently, we obtained the six acylhydrazones by letting the hydrazide react with the corresponding aldehydes (*Scheme 1*).

In order to mimic the indole, aromatic aldehydes with 5- and 6-membered rings, displaying various substitution patterns, were used. We screened the compounds against 15-LOX-1 by measuring the for-mation of (13*S*)-HpODE (λ_{max} of 234 nm) from linoleic acid using the UV absorption assay as reported before.[16,18] At 100 μM, compounds **2** and **4** emerged as the two best compounds with 51% and 66% inhibition of the enzymatic activity (*Figure 2*), corresponding to half maximal inhibitory concentrations (IC_{50}) of 59 ± 7 μM and 42 ± 4 μM, respectively. Although the IC_{50} values are much higher than for the indolyl compounds, scaffold hopping from the indolyl core to other aromatic moieties is possible.

Screening of Library of Reaction Mixtures

Compounds **2** and **4** show that the indolyl moiety can be successfully replaced by another aromatic moiety.

Scheme 2. Mixtures prepared for the screening assay against 15-LOX-1.

To improve the potency of the compounds and find new scaffolds, we expanded our library with more aromatic aldehydes. In order to save time and costs, we employed a combinatorial approach in which we let hydrazide **1d** (1.1 equivalents) react with each of the 25 aldehydes. We selected various aromatic aldehydes with diverse substitution patterns and also included **2–7** (*Scheme 2*). Under the applied reaction conditions, the acylhydrazone compounds were formed with full conversion of the aldehyde starting material and without the formation of any side products. Given that **2** and **4** display IC_{50} values of around 50 μM we screened each mixture, except for that with furan aldehyde **5**, which was black and contained insoluble particles, at this concentration. To account for the 0.1 equivalents of unreacted hydrazide **1d** that is expected to be present in the mixtures, we tested it at 5 μM (*Figure 3*).

In the screening assay, the previously identified hits **2** and **4** (IC_{50} 59±7 and 42±4 μM, respectively), resulted in a high residual enzyme activity of around 90%. From the screening of mixtures **17**, **21**, and **22** emerged as new hits. These compounds lower the residual enzyme activity to 74%, 47%, and 70%, respectively. The *ortho*-hydroxy substituent and the acylhydrazone motif on **21** and **22** might be able to coordinate with metals, leading to non-specific interference with the enzyme inhibition.[19] Since compound **21** showed the highest inhibitory potency of the screening, we only discarded **22**. In order to confirm the activity of the novel chemical scaffolds, we synthesized **17** and **21** for determination of their IC_{50} values. Compound **17**, having an IC_{50} value of 16 ± 6 μM (*Figure 4*) can be considered as a novel hit compound which has a promising activity considering its structural simplicity. Compound **21** turned out to be inactive ($IC_{50} > 100$ μM). We suspect that the activity of compound **21** in the mixture screening might be a false positive caused by degradation and/or oxidation of the aldehyde.

Structure–Activity Relationships (SARs) *around the 3-Pyridyl Class*

Having identified **17** as a hit compound, we focused the optimization around the aromatic structure of the 3-pyridyl moiety. To do so, we chose a set of eight 3-pyridyl acylhydrazones bearing various substituents on the ring, while avoiding *ortho*-substituents to circumvent the possibility of metal chelation. The selection was based on commercial availability and structural diversity, including electron-donating substituents, such as *para*-hydroxyl (**27**), *para*-methyl (**34**), or *meta/para*-methoxy groups (**32**, **33**) and electron-withdrawing groups, such as *meta*-fluoro (**29**), *meta/para*-bromo (**30**, **31**), and *para*-trifluoromethyl (**28**) groups (*Scheme 3*).
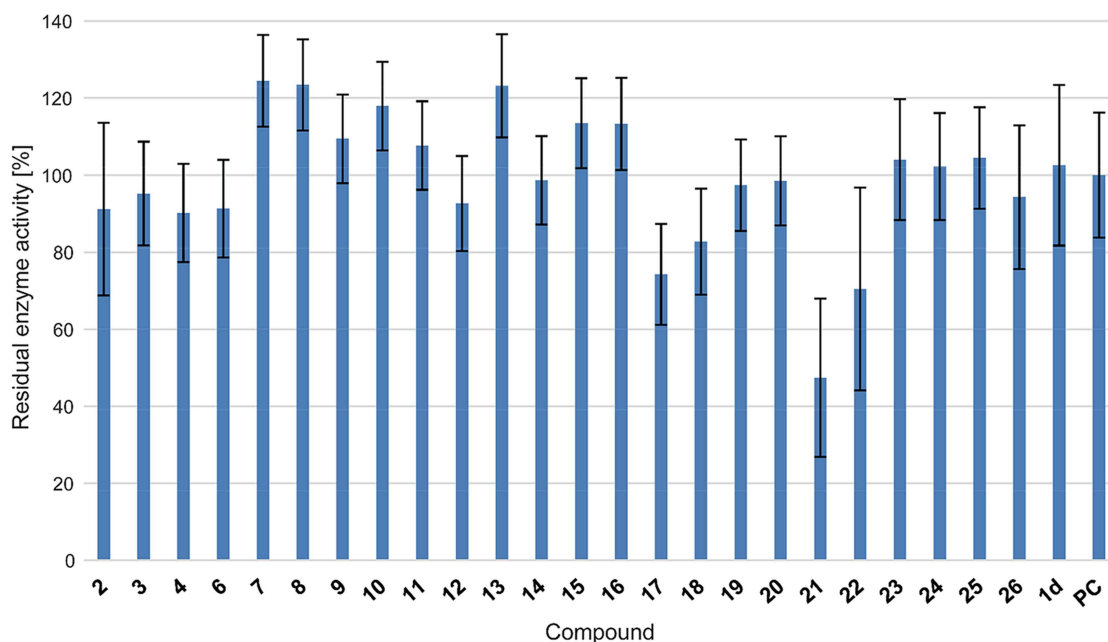
Figure 3. Residual enzyme activity of 15-LOX-1 after incubation with the mixtures of acylhydrazones **2–26** at 50 μM. Hydrazide **1d** was tested at 5 μM. The positive control (PC) shows the enzyme activity in absence of inhibitor. The experiment was performed in triplicate, and the standard error is shown.
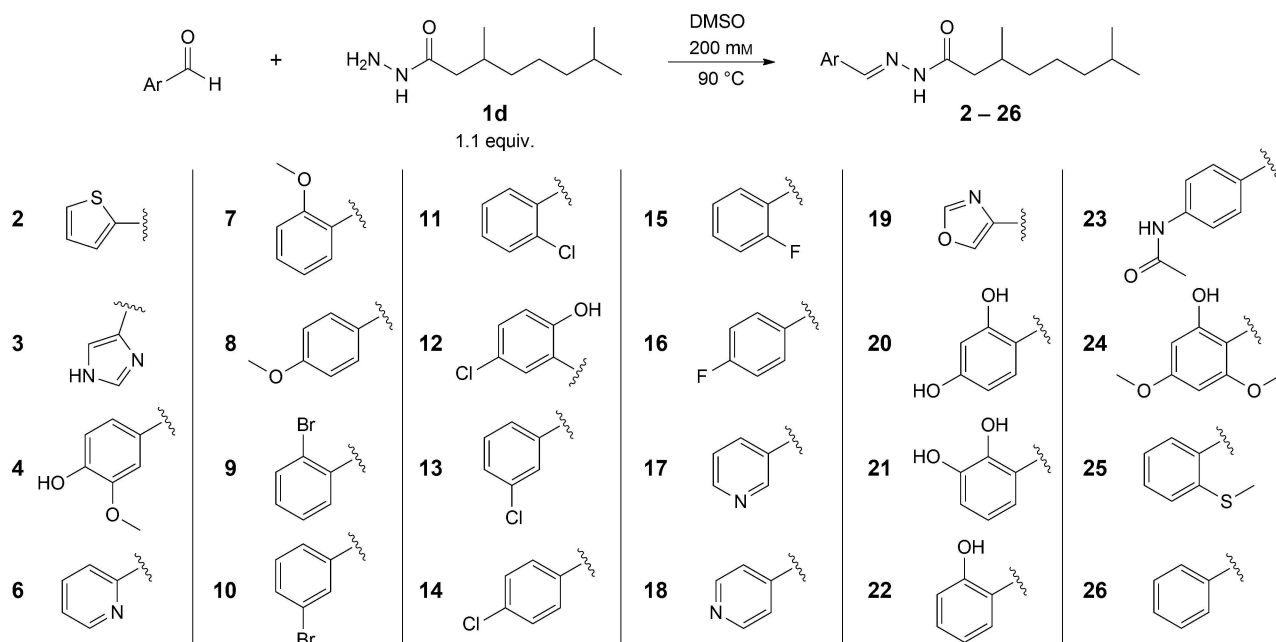

Compound **17**

IC_{50} = 16 ± 6 μM
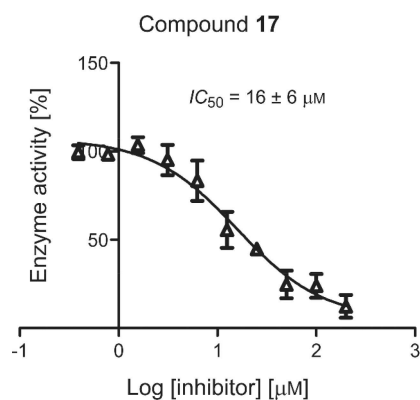
Figure 4. The IC_{50} curve of compound **17**. Measurement was performed two times in triplicate.

For the screening of the analogues **27–34**, we included 3-pyridyl **17** as control. Furthermore, to explore the SAR around the pyridine, we included compounds **6** (2-pyridyl) and **18** (4-pyridyl) that differ in the position of the pyridyl ring nitrogen atom. Interestingly, the SAR was extremely steep and compounds **6**, **18**, and **27–34** were all inactive. Even compound **29**, which differs from **17** only in the small fluorine substituent, does not give a significant inhibitory activity (*Figure 5*).

Replication of the screening result demonstrated that the indolyl moiety can be replaced by other aromatic functionalities (*Figure 3*) and that the unsubstituted 3-pyridyl moiety is the most potent inhibitor (*Figure 5*). Our successful scaffold hopping afforded the unsubstituted 3-pyridyl as an inhibitor of 15-LOX-1

Scheme 3. Synthesis of acylhydrazones **27–34** for optimization based on the 3-pyridyl moiety.
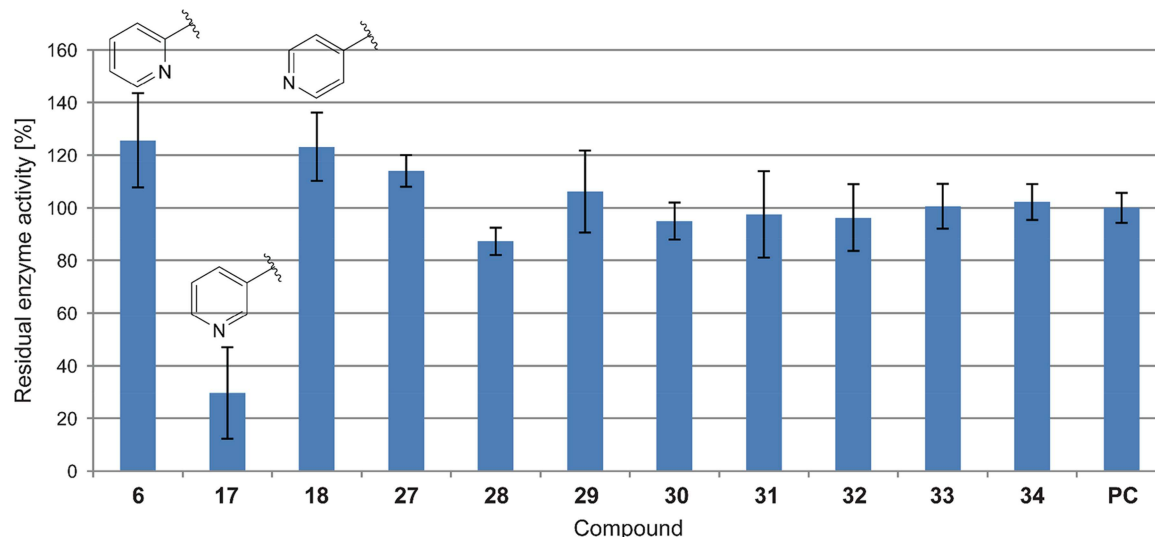
Figure 5. Residual enzyme activity of 15-LOX-1 after incubation with purified 2-, 3-, and 4-pyridyl acylhydrazones (**6**, **17**, and **18**) and substituted 3-pyridyl derivatives (**27–34**) at 50 μM. Positive control (PC) shows the enzyme activity in absence of inhibitor. The experiment was performed in triplicate and the standard error is shown.
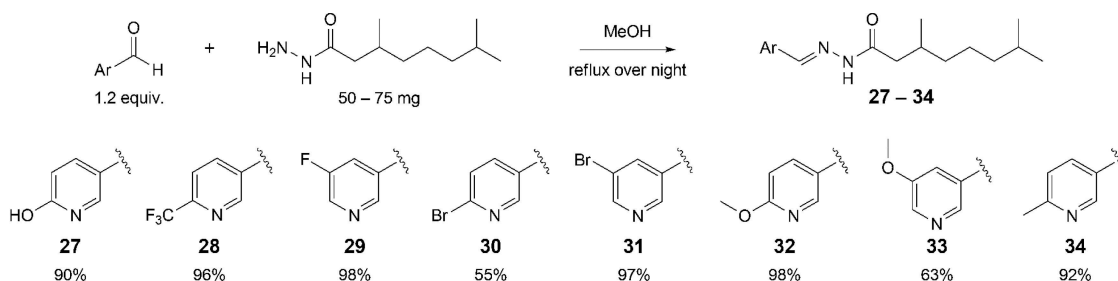
with an IC_{50} value of 16 ± 6 μM. The addition of strongly or weakly electron-donating or -withdrawing groups does not influence the activity. Presumably, this compound occupies a very narrow and specific binding pocket, which does not tolerate the presence of additional substituents, not even a small fluorine atom.

Scheme 4. Synthesis of acylhydrazones **35–38** with selected hydrazides using 3-pyridine carboxaldehyde.

Replacement of the Aliphatic Branched Tail

Having identified the 3-pyridyl moiety as the best replacement of the indolyl moiety, we turned our attention to the aliphatic tail. We recently discovered that the aliphatic tail in 3-position of the substituted indole could be replaced by different moieties, without a large loss in activity.[20] Therefore, we investigated the possibility of combining the 3-pyridyl moiety with hydrazides bearing the four most potent side-groups from our previous study. The four different aromatic hydrazides consisted of an *ortho*-chloro phenoxy (**35**), an *ortho,para*-dichloro phenoxy (**36**), a benzimidazolyl (**37**), and a *meta,para*-dimethoxy benzyl (**38**) moiety (*Scheme 4*). Compared to the aliphatic branched tail, the calculated *logP* (*cLogP*) of the different structures and substituents is lowered significantly (*Table S1*). For future applications and optimizations, these could be interesting starting points compared to the highly lipophilic tail. Unfortunately, biochemical evaluation of the four synthesized acylhydrazones at 50 μM showed no improvement in inhibitory activity compared to compound **17** (*Figure 6*).

Conclusions

In this study, we report on a successful example of scaffold hopping, in which we replaced the established indolyl moiety by other aromatic moieties. Screening

Figure 6. Residual enzyme activity of 15-LOX-1 after incubation with 50 µM of 3-pyridyl derivatives **35–38**. Positive control (PC) shows the enzyme activity in absence of inhibitor. The experiment was performed in triplicate and the standard error is shown.

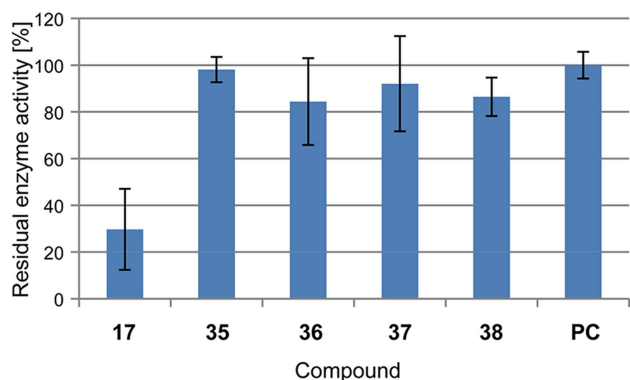of mixtures with a library containing 24 various commercially available aldehydes and an aliphatic hydrazide resulted in 3-pyridine **17** as the most potent inhibitor ($IC_{50} = 16 \pm 6$ µM) despite its structural simplicity. Attempts in further optimizing the 3-pyridyl scaffold using several electron-donating and -withdrawing substituents surprisingly resulted in loss of potency. Of the compounds used in this study, the unsubstituted 3-pyridyl acylhydrazone is the optimal replacement for the indolyl moiety, which constitutes a starting point for future optimization.

Experimental Section

Enzyme Inhibition Studies

The human 15-LOX-1 enzyme was expressed and purified as described before.[18] The activity of 15-LOX-1 was measured by the conversion of linoleic acid into (9Z,11E,13S)-13-hydroperoxy-9,11-octadecadienoic acid ((13S)-HpODE) (λ_{max} 234 nm) using a Synergy H1 hybrid plate reader.[16,18] The conversion rate was followed by measuring the increase in UV absorption over time. The linear part of the plot of the conversion rate was assessed, typically between one and ten minutes.

Screening Assay

The assay was performed using a 96-well plate and HEPES buffer (25 mM, pH 7.5). The substrate, linoleic acid (LA) (*Sigma-Aldrich*, L1376), was diluted in ethanol to 500 µM. The inhibitor (10 mM in DMSO) was diluted

in assay buffer to a concentration of 71.4 µM. The inhibitor solution of 140 µL was mixed with 50 µL of enzyme solution and incubated for 8 min at room temperature. After which, 10 µL of linoleic acid solution was added, which resulted in a mixture with a final dilution of the enzyme of 1:640, 25 µM of the substrate, and 50 µM of the inhibitors (100 µM in preliminary screening). The linear increase of absorbance in the absence of the inhibitor was set to 100%, whereas the increase of absorbance in the absence of the enzyme was set to 0%. All experiments were performed in triplicate, the averages and standard errors were calculated.

IC_{50} Determination

The half-maximal inhibitory concentration (IC_{50}) of the h-15-LOX-1 inhibitors was determined using the procedures as shown above. Using a serial dilution, the desired final concentrations of the inhibitors were achieved ranging from 200 to 0.39 µM. Data analysis was performed using Microsoft Excel professional plus 2016 and GraphPad Prism 5.00.

Chemistry

General Methods. All reagents were purchased from *Sigma–Aldrich*, *TCI Europe*, *Fluorochem*, or *Acros Organics* without purification, unless otherwise stated. All solvents were reagent-grade. Reactions were monitored with thin layer chromatography (TLC) on silica gel-coated aluminum (silica gel *60/Kieselguhr 254*, *Merck*). Purification was performed using flash column chromatography on silica gel (*SiliCycle* 40–63 µm, 230–400 mesh) or using automated column chromatography (*Reveleris*® flash purification system from *Grace Discovery Sciences*). Melting points were measured on a *Stuart*® SMP11 50 W melting point apparatus. NMR spectra were recorded on a *Varian AMX400* or *Bruker Ascend™* 600 MHz spectrometer at 25 °C. Chemical shifts (δ) are reported in ppm relative to the residual solvent peak for ^{1}H-NMR and ^{13}C-NMR or relative to trifluoroacetic acid (TFA, in insert) for ^{19}F-NMR. Splitting patterns are indicated as (*s*) *singlet*, (*d*) *doublet*, (*t*) *triplet*, (*q*) *quartet*, (*quint.*) *quintet*, (*m*) *multiplet*, and (*br.*) broad. Coupling constants (*J*) are reported in Hertz (Hz). High-resolution mass spectra were recorded using a *Thermo Scientific LTQ Orbitrap-XL* mass spectrometer (mass accuracy < 4 ppm). Compounds **1a** and **1b** were synthesized according to literature procedures and all data were in agreement with those previously reported.[16] All final compounds

were analyzed by UPLC-MS (*Thermo Fischer Scientific Vanquish* with *LCQ Fleet* detector, 254 nm) confirming purity ≥ 95% (see *Supporting Information*).

Procedure for the Preparation of Mixtures. The aldehydes (0.2 mmol) were weighed into 4 mL vials. DMSO (500 μL) was added to reach a concentration of 0.4 mм. The hydrazide (3.3 mmol) was weighed in a 20 mL vial, after which it was dissolved in DMSO (7.5 mL), resulting in a concentration of 0.44 mм. Then, to 1 mL *Eppendorf* tubes, was added the corresponding aldehyde (250 μL) and hydrazide **1d** (250 μL), resulting in a final concentration of 0.2 mм aldehyde and 1.1 equiv. of hydrazide. All reaction mixtures were mixed, shortly centrifuged, and then placed in an aluminum heating block pre-heated to 90 °C overnight.

General procedure for the synthesis of acylhydrazones (*GP-A*). To a solution of hydrazide **1d** (1.0 equiv.) in MeOH (*ca.* 0.07 м), the corresponding aldehyde (1.2 – 1.3 equiv.) was added, and the mixture was stirred at reflux overnight (16 – 18 h). Then, the mixture was concentrated under reduced pressure, and the crude was purified by flash column chromatography. The corresponding acylhydrazones were obtained as mixtures of E_{syn} and E_{anti} isomers (approximately 1:1 ratio)[21] in 55 – 98% yield, and the peaks of both isomers are reported in the ^{1}H- and ^{13}C-NMR spectra.

methyl (±)-3,7-Dimethyloctanoate (**1c**). Acid **1b** (893 mg, 5.18 mmol) was dissolved in MeOH (50 mL, 0.10 м), after which a few drops of sulfuric acid were added, and the mixture was heated to reflux overnight. Then, the mixture was allowed to cool down to room temperature, and the solvent was evaporated under reduced pressure. The resulting crude was dissolved in diethyl ether. The organic layer was washed with a saturated aq. solution of NaHCO$_3$ and a saturated aq. solution of NaCl. The organic layer was dried over MgSO$_4$, filtered, and evaporated to dryness under reduced pressure to afford the product as colorless oil (898 mg, 4.82 mmol, 93% yield). ^{1}H-NMR (400 MHz, CDCl$_3$): 3.66 (*s*, 3 H); 2.30 (*dd, J* = 14.7, 6.0, 1 H); 2.11 (*dd, J* = 14.7, 8.1, 1 H); 2.02 – 1.84 (*m*, 1 H); 1.58 – 1.44 (*m*, 1 H); 1.37 – 1.08 (*m*, 6 H); 0.92 (*d, J* = 6.6, 3 H); 0.85 (*d, J* = 6.6, 6 H). ^{13}C-NMR (101 MHz, CDCl$_3$): 174.0 (C); 51.5 (CH$_3$); 41.8 (CH$_2$); 39.2 (CH$_2$); 37.1 (CH$_2$); 30.5 (CH); 28.1 (CH); 24.8 (CH$_2$); 22.8 (CH$_3$); 22.7 (CH$_3$); 19.9 (CH$_3$). HR-MS: **1c** could not be ionized in ESI+ and APCI experiments.

(±)-3,7-Dimethyloctanehydrazide (**1d**). To a solution of the methyl ester **1c** (1.34 g, 7.19 mmol) in MeOH (71 mL, 0.10 м), hydrazine hydrate (55%, 4.5 mL, 51 mmol, 7 equiv.) was added. The mixture was heated to reflux overnight and then allowed to cool down to room temperature, and the solvent was evaporated under reduced pressure. The crude was purified by flash column chromatography, eluting with CH$_2$Cl$_2$/ MeOH (97:3). Hydrazide **1d** was obtained as white solid (1.07 g, 5.74 mmol, 80% yield). M.p. 68 – 70 °C. ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 8.89 (*s*, 1 H); 4.13 (*s*, 2 H); 2.05 – 1.91 (*m*, 1 H); 1.86 – 1.74 (*m*, 2 H); 1.58 – 1.43 (*m*, 1 H); 1.32 – 0.98 (*m*, 6 H); 0.90 – 0.75 (*m*, 9 H). ^{13}C-NMR (101 MHz, (D$_6$)DMSO): 171.0 (C); 41.1 (CH$_2$); 38.6 (CH$_2$); 36.4 (CH$_2$); 29.9 (CH); 27.3 (CH); 24.1 (CH$_2$); 22.6 (CH$_3$); 22.4 (CH$_3$); 19.4 (CH$_3$). HR-ESI-MS (pos.): 187.1813 (C$_{10}$H$_{23}$N$_2$O$^+$, [*M* + H]$^+$; calc. 187.1805).

3,7-Dimethyl-*N′*-(thiophen-2-ylmethylene) octanehydrazide (**2**). This compound was synthesized according to *GP-A*, starting with thiophene-2-carbaldehyde (42 mg, 0.37 mmol, 1.3 equiv.). The crude was purified by flash column chromatography (CH$_2$Cl$_2$/ MeOH 99:1) to afford the product as yellow oil (67 mg, 0.24 mmol, 87%). ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 11.25 (*s*, 1 H); 11.17 (*s*, 1 H); 8.39 (*s*, 1 H); 8.13 (*s*, 1 H); 7.62 (*d, J* = 5.0, 1 H); 7.58 (*d, J* = 5.0, 1 H); 7.42 – 7.39 (*m*, 1 H); 7.38 – 7.33 (*m*, 1 H); 7.18 – 7.04 (*m*, 2 H); 2.57 (*dd, J* = 13.9, 5.7, 1 H); 2.31 (*dd, J* = 13.8, 8.2, 1 H); 2.15 (*dd, J* = 13.6, 5.8, 1 H); 2.03 – 1.83 (*m*, 3 H); 1.58 – 1.44 (*m*, 2 H); 1.36 – 1.05 (*m*, 12 H); 0.94 – 0.86 (*m*, 6 H); 0.86 – 0.82 (*m*, 12 H). ^{13}C-NMR (101 MHz, (D$_6$)DMSO): 173.6 (C); 168.0 (C); 141.0 (CH); 139.21 (C); 139.19 (C); 137.4 (CH); 130.5 (CH); 129.8 (CH); 128.6 (CH); 127.9 (CH); 127.8 (CH); 127.7 (CH); 41.9 (CH$_2$); 39.2 (CH$_2$); 38.6 (2 CH$_2$), 36.7 (CH$_2$); 36.4 (CH$_2$); 30.0 (CH); 29.6 (CH); 27.3 (2 CH); 24.11 (CH$_2$); 24.07 (CH$_2$); 22.6 (CH$_3$); 22.5 (CH$_3$); 22.45 (CH$_3$); 22.43 (CH$_3$); 19.8 (CH$_3$); 19.5 (CH$_3$). HR-ESI-MS (pos.): 281.168 (C$_{15}$H$_{25}$N$_2$OS$^+$, [*M* + H]$^+$; calc. 281.168).

***N′*-[(1*H*-Imidazol-4-yl)methylene]-3,7-dimethyl- octanehydrazide** (**3**). This compound was synthesized according to *GP-A*, starting with 1*H*-imidazole-4-carbaldehyde (35 mg, 0.37 mmol, 1.3 equiv.). The crude was purified by flash column chromatography (CH$_2$Cl$_2$/ MeOH 95:5) to afford the product as white solid (47 mg, 0.18 mmol, 64%). M.p. 151 – 154 °C. ^{1}H-NMR (600 MHz, (D$_6$)DMSO): 12.76 – 12.26 (*m*, 2 H); 11.22 – 10.88 (*m*, 2 H); 8.19 – 8.05 (*m*, 1 H); 7.90 (*s*, 1 H); 7.78 – 7.67 (*m*, 2 H); 7.56 – 7.44 (*m*, 1 H); 7.32 – 7.21 (*m*, 1 H); 2.57 – 2.34 (*m*, 2 H, overlap with DMSO), 2.24 – 2.08 (*m*, 1 H); 2.01 – 1.85 (*m*, 3 H); 1.57 – 1.44 (*m*, 2 H); 1.35 – 1.19

(m, 6 H); 1.18 – 1.06 (*m*, 6 H); 0.90 – 0.88 (*m*, 6 H); 0.86 – 0.83 (*m*, 12 H). ^{13}C-NMR (151 MHz, (D$_6$)DMSO): 173.3 (C); 167.5 (C); 142.0 (CH); 138.7 (2 CH); 136.58 (C); 136.56 (C); 136.4 (2 CH); 132.8 (CH); 132.3 (CH); 131.2 (CH); 116.5 (CH); 113.3 (CH); 41.9 (CH$_2$); 38.6 (2 CH$_2$), 36.6 (CH$_2$); 36.4 (CH$_2$); 30.0 (CH); 29.3 (CH); 27.36 (CH); 27.34 (CH); 24.2 (CH$_2$); 24.1 (CH$_2$); 22.6 (CH$_3$); 22.5 (CH$_3$); 22.4 (2 CH$_3$), 19.8 (CH$_3$); 19.5 (CH$_3$). Note: one of the CH$_2$ signals, α to the carbonyl, is overlapping with the DMSO signal. Multiple isomers of the imidazole moiety are observed in the carbon NMR spectrum (see gHSQC in *Supporting Information*). HR-ESI-MS (pos.): 265.203 (C$_{14}$H$_{25}$N$_4$O$^+$, [*M* + H]$^+$; calc. 265.202).

N′-[(4-Hydroxy-3-methoxyphenyl)methylidene]-3,7-dimethyloctanehydrazide (**4**).

This compound was synthesized according to *GP-A*, starting with 4-hydroxy-3-methoxybenzaldehyde (53 mg, 0.35 mmol, 1.2 equiv.). The crude was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 99:1) to afford the product as white solid (71 mg, 0.22 mmol, 79%). M.p. 126 – 129 °C. ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 11.11 (*s*, 1 H); 11.02 (*s*, 1 H); 9.45 (br. *s*, 2 H); 8.03 (*s*, 1 H); 7.84 (*s*, 1 H); 7.25 (*s*, 1 H); 7.19 (*s*, 1 H); 7.07 – 6.97 (*m*, 2 H); 6.80 (2*dd* overlap, *J* = 8.1, 1.5, 2 H); 3.81 (*d*, *J* = 1.6, 3 H); 3.79 (*d*, *J* = 1.6, 3 H); 2.66 – 2.75 (*m*, 1 H); 2.40 – 2.31 (*m*, 1 H); 2.18 – 2.10 (*m*, 1 H); 2.03 – 1.86 (*m*, 3 H); 1.60 – 1.41 (*m*, 2 H); 1.36 – 1.21 (*m*, 6 H); 1.20 – 1.07 (*m*, 6 H); 0.92 – 0.86 (*m*, 6 H); 0.87 – 0.81 (*m*, 12 H). ^{13}C-NMR (101 MHz, (D$_6$)DMSO): 173.6 (C); 167.7 (C); 148.8 (C); 148.5 (C); 148.0 (C); 147.9 (C); 146.3 (CH); 142.6 (CH); 125.83 (C); 125.75 (C); 121.9 (CH); 120.7 (CH); 115.6 (CH); 115.4 (CH); 109.5 (CH); 108.9 (CH); 55.52 (CH$_3$); 55.45 (CH$_3$); 41.9 (CH$_2$); 39.47 (CH$_2$); 38.6 (2 CH$_2$), 36.7 (CH$_2$); 36.4 (CH$_2$); 30.1 (CH); 29.6 (CH); 27.34 (CH); 27.32 (CH); 24.13 (CH$_2$); 24.08 (CH$_2$); 22.6 (CH$_3$); 22.5 (CH$_3$); 22.4 (2 CH$_3$), 19.8 (CH$_3$); 19.5 (CH$_3$). HR-ESI-MS (pos.): 321.218 (C$_{18}$H$_{29}$N$_2$O$_3$$^+$, [*M* + H]$^+$; calc. 321.217).

N′-[(Furan-2-yl)methylidene]-3,7-dimethyloctanehydrazide (**5**).

This compound was synthesized according to *GP-A*, starting with furan-2-carbaldehyde (32 mg, 0.33 mmol, 1.2 equiv.). The crude was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 99:1) to afford the product as brown oil (70 mg, 0.26 mmol, 95%). ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 11.24 (*s*, 1 H); 11.14 (*s*, 1 H); 8.06 (*s*, 1 H); 7.85 (*s*, 1 H); 7.82 – 7.74 (*m*, 2 H); 6.90 – 6.76 (*m*, 2 H); 6.61 – 6.58 (*m*, 2 H); 2.57 (*dd*, *J* = 13.9, 5.7, 1 H); 2.37 (*dd*, *J* = 14.9, 8.2, 1 H); 2.16 (*dd*, *J* = 13.6, 5.8, 1 H); 2.05 – 1.79 (*m*, 3 H); 1.58 – 1.44 (*m*, 2 H); 1.36 – 1.05 (*m*, 12 H); 0.91 – 0.86 (*m*, 6 H); 0.86 – 0.82 (*m*, 12 H). ^{13}C-NMR (101 MHz, (D$_6$)DMSO): 173.7 (C); 168.0

(C); 149.5 (C); 149.4 (C); 144.9 (CH); 144.7 (CH); 135.7 (CH); 132.5 (CH); 113.0 (CH); 112.7 (CH); 112.1 (CH); 112.0 (CH); 41.9 (CH$_2$); 38.9 (CH$_2$); 38.60 (CH$_2$); 38.58 (CH$_2$); 36.6 (CH$_2$); 36.4 (CH$_2$); 30.0 (CH); 29.2 (CH); 27.4 (2 CH); 24.10 (CH$_2$); 24.06 (CH$_2$); 22.6 (CH$_3$); 22.5 (CH$_3$); 22.4 (2 CH$_3$), 19.8 (CH$_3$); 19.5 (CH$_3$). HR-ESI-MS (pos.): 265.191 (C$_{15}$H$_{25}$N$_2$O$_2$$^+$, [*M* + H]$^+$; calc. 265.191).

3,7-Dimethyl-*N′*-[(pyridin-2-yl)methylidene]octanehydrazide (**6**).

This compound was synthesized according to *GP-A*, starting with picolinaldehyde (41 mg, 0.38 mmol, 1.4 equiv.). The crude was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 99:1) to afford the product as yellow oil (75 mg, 0.27 mmol, 98%). ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 11.53 (*s*, 1 H); 11.42 (*s*, 1 H); 8.61 – 8.48 (*m*, 2 H); 8.18 (*s*, 1 H); 8.01 (*s*, 1 H); 8.61 – 7.48 (*m*, 4 H); 7.44 – 7.25 (*m*, 2 H); 2.65 (*dd*, *J* = 14.4, 5.7, 1 H); 2.43 (*dd*, *J* = 14.3, 8.1, 1 H); 2.21 (*dd*, *J* = 13.9, 6.0, 1 H); 2.09 – 1.86 (*m*, 3 H); 1.57 – 1.43 (*m*, 2 H); 1.36 – 1.04 (*m*, 12 H); 0.95 – 0.87 (*m*, 6 H); 0.87 – 0.78 (*m*, 12 H). ^{13}C-NMR (101 MHz, (D$_6$)DMSO): 174.1 (C); 168.4 (C); 153.3 (C); 153.2 (C); 149.5 (2 CH); 146.0 (CH); 142.8 (CH); 136.8 (CH); 136.7 (CH); 124.2 (CH); 124.0 (CH); 119.7 (CH); 119.2 (CH); 41.9 (CH$_2$); 39.13 (CH$_2$); 38.60 (CH$_2$); 38.58 (CH$_2$); 36.6 (CH$_2$); 36.4 (CH$_2$); 30.0 (CH); 29.5 (CH); 27.4 (2 CH); 24.2 (CH$_2$); 24.1 (CH$_2$); 22.6 (CH$_3$); 22.5 (CH$_3$); 22.4 (2 CH$_3$), 19.8 (CH$_3$); 19.5 (CH$_3$). HR-ESI-MS (pos.): 276.207 (C$_{16}$H$_{26}$N$_3$O$^+$, [*M* + H]$^+$; calc. 276.207).

N′-[(2-Methoxyphenyl)methylidene]-3,7-dimethyloctanehydrazide (**7**).

This compound was synthesized according to *GP-A*, starting with 2-methoxybenzaldehyde (48 mg, 0.35 mmol, 1.3 equiv.). The crude was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 99.5:0.5) to afford the product as white solid (79 mg, 0.26 mmol, 94%). M.p. 88 – 90 °C. ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 11.30 (*s*, 1 H); 11.17 (*s*, 1 H); 8.51 (*s*, 1 H); 8.30 (*s*, 1 H); 7.77 (*t*, *J* = 8.4, 2 H); 7.42 – 7.30 (*m*, 2 H); 7.12 – 7.04 (*m*, 2 H); 6.98 (*q*, *J* = 7.5, 2 H); 3.85 – 3.81 (*m*, 6 H); 2.64 (*dd*, *J* = 14.2, 5.8, 1 H); 2.37 (*dd*, *J* = 14.1, 8.1, 1 H); 2.16 (*dd*, *J* = 13.5, 5.7, 1 H); 2.05 – 1.82 (*m*, 3 H); 1.57 – 1.42 (*m*, 2 H); 1.34 – 1.05 (*m*, 12 H); 0.92 – 0.86 (*m*, 6 H); 0.86 – 0.81 (*m*, 12 H). ^{13}C-NMR (101 MHz, (D$_6$)DMSO): 173.8 (C); 167.9 (C); 157.6 (C); 157.5 (C); 141.1 (CH); 137.9 (CH); 131.3 (CH); 131.0 (CH); 125.4 (CH); 125.0 (CH); 122.4 (C); 122.3 (C); 120.7 (CH); 120.6 (CH); 111.78 (CH); 111.76 (CH); 55.7 (CH$_3$); 55.63 (CH$_3$); 41.9 (CH$_2$); 39.33 (CH$_2$); 38.61 (CH$_2$); 38.59 (CH$_2$); 36.7 (CH$_2$); 36.5 (CH$_2$); 30.1 (CH); 29.5 (CH); 27.36 (CH); 27.35 (CH); 24.2 (CH$_2$); 24.1 (CH$_2$); 22.6 (CH$_3$); 22.5 (CH$_3$); 22.4 (2 CH$_3$), 19.9 (CH$_3$); 19.5 (CH$_3$). HR-ESI-MS (pos.): 305.222 (C$_{18}$H$_{29}$N$_2$O$_2$$^+$, [*M* + H]$^+$; calc. 305.222).

3,7-Dimethyl-*N*′-[(pyridin-3-yl)methylidene]octa-nehydrazide (**17**). This compound was synthesized according to *GP-A*, starting with nicotinaldehyde (35 mg, 0.32 mmol, 1.2 equiv.). The crude was purified by flash column chromatography (CH₂Cl₂/MeOH 97:3) to afford the product as pale yellow solid (72 mg, 0.26 mmol, 97%). M.p. 76–77 °C. ¹H-NMR (400 MHz, (D₆)DMSO): 11.47 (*s*, 1 H); 11.37 (*s*, 1 H); 8.80 (*s*, 2 H); 8.57 (*s*, 2 H); 8.21 (*s*, 1 H); 8.10–8.01 (*m*, 2 H); 8.00 (*s*, 1 H); 7.49–7.40 (*m*, 2 H); 2.64 (*dd*, *J* = 14.3, 5.7, 1 H); 2.42 (*dd*, *J* = 14.3, 8.1, 1 H); 2.20 (*dd*, *J* = 13.9, 6.0, 1 H); 2.07–1.87 (*m*, 3 H); 1.58–1.43 (*m*, 2 H); 1.39–1.05 (*m*, 12 H); 0.93–0.88 (*m*, 6 H); 0.84 (*t*, *J* = 7.0, 12 H). ¹³C-NMR (101 MHz, (D₆)DMSO): 174.1 (C); 168.3 (C); 150.5 (CH); 150.2 (CH); 148.6 (CH); 148.2 (CH); 143.0 (CH); 139.5 (CH); 133.3 (CH); 133.1 (CH); 130.29 (C); 130.25 (C); 123.9 (2 CH); 41.9 (CH₂); 39.2 (CH₂); 38.59 (CH₂); 38.58 (CH₂); 36.6 (CH₂); 36.4 (CH₂); 30.0 (CH); 29.5 (CH); 27.3 (2 CH); 24.12 (CH₂); 24.07 (CH₂); 22.6 (CH₃); 22.5 (CH₃); 22.4 (2 CH₃); 19.8 (CH₃); 19.5 (CH₃). HR-ESI-MS (pos.): 276.207 (C₁₆H₂₆N₃O⁺, [*M* + H]⁺; calc. 276.207).

3,7-Dimethyl-*N*′-[(pyridin-4-yl)methylidene]octa-nehydrazide (**18**). This compound was synthesized according to *GP-A*, starting with isonicotinaldehyde (78 mg, 0.73 mmol, 1.7 equiv.). The crude was purified by flash column chromatography (CH₂Cl₂/MeOH 97.5:2.5) to afford the product as yellow oil (90 mg, 0.33 mmol, 78%). ¹H-NMR (400 MHz, (D₆)DMSO): 11.58 (*s*, 1 H); 11.49 (*s*, 1 H); 8.69–8.55 (*m*, 4 H); 8.17 (*s*, 1 H); 7.95 (*s*, 1 H); 7.66–7.56 (*m*, 4 H); 2.66 (*dd*, *J* = 14.3, 5.9, 1 H); 2.44 (*dd*, *J* = 14.3, 8.1, 1 H); 2.22 (*dd*, *J* = 14.1, 6.1, 1 H); 2.14–1.86 (*m*, 3 H); 1.58–1.43 (*m*, 2 H); 1.37–1.05 (*m*, 12 H); 0.94–0.88 (*m*, 6 H); 0.87–0.81 (*m*, 12 H). ¹³C-NMR (101 MHz, (D₆)DMSO) 174.3 (C); 168.5 (C); 150.2 (4 CH); 143.3 (CH); 141.6 (C); 141.5 (C); 139.8 (CH); 130.6 (CH); 121.2 (CH); 120.9 (CH); 120.6 (CH); 41.9 (CH₂); 39.16 (CH₂); 38.58 (2 CH₂); 36.6 (CH₂); 36.4 (CH₂); 30.0 (CH); 29.5 (CH); 27.3 (2 CH); 24.13 (CH₂); 24.05 (CH₂); 22.54 (CH₃); 22.51 (CH₃); 22.4 (2 CH₃); 19.8 (CH₃); 19.5 (CH₃). HR-ESI-MS (pos.): 276.207 (C₁₆H₂₆N₃O⁺, [*M* + H]⁺; calc. 276.207).

N*′-[(2,3-Dihydroxyphenyl)methylidene]-3,7-dimethyloctanehydrazide (**21**). This compound was synthesized according to *GP-A*, starting with 2,3-dihydroxybenzaldehyde (45 mg, 0.32 mmol, 1.2 equiv.). The crude was purified by flash column chromatography (CH₂Cl₂/MeOH 99:1) to afford the product as brown solid (71 mg, 0.23 mmol, 86%). M.p. 148–151 °C. ¹H-NMR (400 MHz, (D₆)DMSO): 8.30 (*s*, 1 H); 8.24 (*s*, 1 H); 7.04 (*d*, *J* = 7.8, 1 H); 6.91 (*d*, *J* = 7.7, 1

H); 6.86–6.77 (*m*, 2 H); 6.75–6.63 (*m*, 2 H); 2.57 (*dd*, *J* = 14.2, 6.0, 1 H); 2.35 (*dd*, *J* = 14.4, 7.8, 1 H); 2.21 (*dd*, *J* = 13.7, 5.9, 1 H); 2.10–1.85 (*m*, 3 H); 1.62–1.43 (*m*, 2 H); 1.37–1.07 (*m*, 12 H); 0.93–0.88 (*m*, 6 H); 0.86–0.82 (*m*, 12 H). Note: none of the exchangeable protons were observed. ¹³C-NMR (101 MHz, (D₆)DMSO): 173.3 (C); 167.8 (C); 147.1 (CH); 145.9 (C); 145.6 (C); 145.5 (C); 145.1 (C); 141.5 (CH); 120.4 (C); 119.9 (CH); 119.2 (CH); 119.0 (CH); 118.7 (C); 117.22 (CH); 117.16 (CH); 116.5 (CH); 41.6 (CH₂); 39.39 (CH₂); 38.58 (2 CH₂); 36.6 (CH₂); 36.4 (CH₂); 30.0 (CH); 29.4 (CH); 27.3 (2 CH); 24.12 (CH₂); 24.06 (CH₂); 22.55 (CH₃); 22.53 (CH₃); 22.4 (2 CH₃); 19.8 (CH₃); 19.5 (CH₃). HR-ESI-MS (pos.): 307.202 (C₁₇H₂₇N₂O₃⁺, [*M* + H]⁺; calc. 307.202).

N*′-[(6-Hydroxypyridin-3-yl)methylidene]-3,7-dimethyloctanehydrazide (**27**). This compound was synthesized according to *GP-A*, starting with 6-hydroxynicotinaldehyde (63 mg, 0.51 mmol, 1.2 equiv.). The crude was purified by flash column chromatography (CH₂Cl₂/MeOH 92:8) to afford the product as white solid (110 mg, 0.38 mmol, 90%). M.p. 148–151 °C. ¹H-NMR (400 MHz, (D₆)DMSO): 11.85 (*s*, 2 H); 11.15 (*s*, 1 H); 11.06 (*s*, 1 H); 7.96 (*s*, 1 H); 7.82 (*t*, *J* = 2.8, 1 H); 7.80 (*t*, *J* = 2.8, 1 H); 7.75 (*s*, 1 H); 7.69 (*d*, *J* = 2.5, 1 H); 7.64 (*d*, *J* = 2.5, 1 H); 6.41 (*d*, *J* = 2.5, 1 H); 6.38 (*d*, *J* = 2.5, 1 H); 2.57 (*dd*, *J* = 14.3, 6.0, 1 H); 2.35 (*dd*, *J* = 14.2, 8.0, 1 H); 2.13 (*dd*, *J* = 13.5, 5.8, 1 H); 2.01–1.82 (*m*, 3 H); 1.59–1.41 (*m*, 2 H); 1.34–1.04 (*m*, 12 H); 0.95–0.78 (*m*, 18 H). ¹³C-NMR (101 MHz, (D₆)DMSO): 173.5 (C); 167.7 (C); 162.3 (C); 162.2 (C); 142.7 (CH); 139.1 (CH); 137.3 (CH); 136.8 (CH); 136.6 (CH); 136.4 (CH); 120.8 (CH); 120.7 (CH); 113.5 (2 C), 41.8 (CH₂); 39.19 (CH₂); 38.62 (CH₂); 38.60 (CH₂); 36.6 (CH₂); 36.4 (CH₂); 30.1 (CH); 29.4 (CH); 27.4 (2 CH); 24.2 (CH₂); 24.1 (CH₂); 22.6 (CH₃); 22.5 (CH₃); 22.4 (2 CH₃), 19.9 (CH₃); 19.5 (CH₃). HR-ESI-MS (pos.): 292.202 (C₁₆H₂₆N₃O₂⁺, [*M* + H]⁺; calc. 292.202).

3,7-Dimethyl-*N*′-{[6-(trifluoromethyl)pyridin-3-yl]methylidene}octanehydrazide (**28**). This compound was synthesized according to *GP-A*, staring with 6-(trifluoromethyl)nicotinaldehyde (88 mg, 0.50 mmol, 1.2 equiv.). The crude was purified by flash column chromatography (CH₂Cl₂/MeOH 94:6) to afford the product as pale yellow solid (137 mg, 0.398 mmol, 96%). M.p. 109–111 °C. ¹H-NMR (600 MHz, (D₆)DMSO): 11.66 (*s*, 1 H); 11.58 (*s*, 1 H); 8.99 (*s*, 2 H); 8.34 (*d*, *J* = 8.2, 1 H); 8.32–8.28 (*m*, 2 H); 8.08 (*s*, 1 H); 7.96 (*d*, *J* = 8.2, 1 H); 7.94 (*d*, *J* = 8.2, 1 H); 2.66 (*dd*, *J* = 14.4, 6.0, 1 H); 2.46 (*dd*, *J* = 14.5, 8.0, 1 H); 2.23 (*dd*, *J* = 14.1, 6.1, 1 H); 2.05 (*dd*, *J* = 14.0, 8.1, 1 H); 2.00–1.87 (*m*, 2 H); 1.55–1.44 (*m*, 2 H); 1.37–1.07 (*m*, 12 H); 0.92

(*d*, *J* = 6.6, 3 H); 0.90 (*d*, *J* = 6.6, 3 H); 0.86 – 0.80 (*m*, 12 H). ^{13}C-NMR (151 MHz, (D$_6$)DMSO): 174.3 (C); 168.5 (C); 148.7 (CH); 148.4 (CH); 146.3 (dq overlap, *J* = 34.2, 2 CCF$_3$), 141.5 (CH); 138.0 (CH); 135.5 (CH); 135.1 (CH); 133.7 (C); 133.6 (C); 121.58 (q overlap, *J* = 273.8, 2 CF$_3$), 120.90 (2 CH); 41.9 (CH$_2$); 39.15 (CH$_2$); 38.60 (CH$_2$); 38.57 (CH$_2$); 36.6 (CH$_2$); 36.4 (CH$_2$); 30.0 (CH); 29.5 (CH); 27.3 (2 CH); 24.11 (CH$_2$); 24.07 (CH$_2$); 22.6 (CH$_3$); 22.5 (CH$_3$); 22.4 (2 CH$_3$), 19.8 (CH$_3$); 19.5 (CH$_3$). ^{19}F-NMR (376 MHz, (D$_6$)DMSO): −67.96 (*d*, *J* = 8.1). HR-ESI-MS (pos.): 344.195 (C$_{17}$H$_{25}$F$_3$N$_3$O$^+$, [*M* + H]$^+$; calc. 344.194).

N′-[(5-Fluoropyridin-3-yl)methylidene]-3,7-di-methyloctanehydrazide (**29**). This compound was synthesized according to *GP-A*, starting with 5-fluoro-nicotinaldehyde (67 mg, 0.53 mmol, 1.2 equiv.). The crude was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 98:2) to afford the product as white solid (125 mg, 0.426 mmol, 98%). M.p. 60 – 62 °C. ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 11.53 (2*s* overlap, 2 H); 8.71 (*s*, 1 H); 8.69 (*s*, 1 H); 8.62 – 8.53 (*m*, 2 H); 8.26 (*s*, 1 H); 8.02 (*s*, 1 H); 7.93 (*dd*, *J* = 9.9, 2.6, 2 H); 2.68 (*dd*, *J* = 14.3, 5.8, 1 H); 2.41 (*dd*, *J* = 14.3, 8.2, 1 H); 2.21 (*dd*, *J* = 14.0, 6.1, 1 H); 2.10 – 1.84 (*m*, 3 H); 1.62 – 1.42 (*m*, 2 H); 1.36 – 1.04 (*m*, 12 H); 0.90 (*t*, *J* = 7.2, 6 H); 0.86 – 0.80 (*m*, 12 H). ^{13}C-NMR (101 MHz, (D$_6$)DMSO): 174.2 (C); 168.4 (C); 159.19 (*d*, *J* = 254.5, C), 159.14 (*d*, *J* = 254.5, C), 144.7 (*d*, *J* = 3.6, CH); 144.5 (*d*, *J* = 3.6, CH); 141.70 (CH); 141.67 (CH); 138.82 – 137.95 (*m*, 2 CH); 132.3 (C); 132.2 (C); 119.6 (*d*, *J* = 19.2, CH); 119.3 (*d*, *J* = 19.2, CH); 41.9 (CH$_2$); 39.16 (CH$_2$); 38.59 (2 CH$_2$), 36.6 (CH$_2$); 36.4 (CH$_2$); 30.0 (CH); 29.6 (CH); 27.3 (2 CH); 24.2 (CH$_2$); 24.1 (CH$_2$); 22.6 (CH$_3$); 22.5 (CH$_3$); 22.4 (2 CH$_3$), 19.8 (CH$_3$); 19.5 (CH$_3$). ^{19}F-NMR (376 MHz, (D$_6$)DMSO): −128.51 (*d*, *J* = 9.7), −128.56 (*d*, *J* = 9.8). HR-ESI-MS (pos.): 294.198 (C$_{16}$H$_{25}$FN$_3$O$^+$, [*M* + H]$^+$; calc. 294.198).

N′-[(6-Bromopyridin-3-yl)methylidene]-3,7-di-methyloctanehydrazide (**30**). This compound was synthesized according to *GP-A*, starting with 6-bromo-nicotinaldehyde (68 mg, 0.37 mmol, 1.3 equiv.). The crude was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 97.5:2.5) to afford the product as white solid (54 mg, 0.15 mmol, 55%). M.p. 113 – 115 °C. ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 11.54 (*s*, 1 H); 11.45 (*s*, 1 H); 8.60 (*dt*, *J* = 7.9, 2.1, 2 H); 8.19 (*s*, 1 H); 8.07 – 7.98 (*m*, 2 H); 7.97 (*s*, 1 H); 7.74 – 7.60 (*m*, 2 H); 2.63 (*dd*, *J* = 14.3, 5.8, 1 H); 2.43 (*dd*, *J* = 14.3, 8.2, 1 H); 2.20 (*dd*, *J* = 14.0, 6.1, 1 H); 2.05 – 1.81 (*m*, 3 H); 1.63 – 1.41 (*m*, 2 H); 1.38 – 1.06 (*m*, 12 H); 0.93 – 0.87 (*m*, 6 H); 0.86 – 0.81 (*m*, 12 H). ^{13}C-NMR (101 MHz, (D$_6$)DMSO): 174.1 (C); 168.4 (C); 149.2 (CH); 149.0 (CH); 142.0 (C); 141.8 (CH); 141.7 (C);

138.3 (CH); 136.3 (CH); 136.0 (CH); 130.21 (C); 130.15 (C); 128.33 (CH); 128.29 (CH); 41.9 (CH$_2$); 38.62 (CH$_2$); 38.60 (CH$_2$); 36.6 (CH$_2$); 36.4 (CH$_2$); 30.0 (CH); 29.5 (CH); 27.3 (2 CH); 24.13 (CH$_2$); 24.07 (CH$_2$); 22.6 (CH$_3$); 22.5 (CH$_3$); 22.4 (2 CH$_3$), 19.8 (CH$_3$); 19.5 (CH$_3$). Note: one of the CH$_2$ signals, α to the carbonyl, is overlapping with the DMSO signal. HR-ESI-MS (pos.): 354.118 (C$_{16}$H$_{25}$BrN$_3$O$^+$, [*M* + H]$^+$; calc. 354.118).

N′-[(5-Bromopyridin-3-yl)methylidene]-3,7-di-methyloctanehydrazide (**31**). This compound was synthesized according to *GP-A*, starting with 5-bromo-nicotinaldehyde (68 mg, 0.37 mmol, 1.3 equiv.). The crude was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 98:2) to afford the product as pale yellow solid (97 mg, 0.27 mmol, 97%). M.p. 81 – 83 °C. ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 11.60 (*s*, 1 H); 11.48 (*s*, 1 H); 8.81 (*d*, *J* = 1.8, 1 H); 8.79 (*d*, *J* = 1.8, 1 H); 8.70 (*d*, *J* = 2.3, 1 H); 8.69 (*d*, *J* = 2.3, 1 H); 8.27 (app. t, *J* = 2.0, 1 H); 8.25 (app. t, *J* = 2.0, 1 H); 8.19 (*s*, 1 H); 7.97 (*s*, 1 H); 2.68 (*dd*, *J* = 14.3, 5.8, 1 H); 2.39 (*dd*, *J* = 14.3, 8.2, 1 H); 2.21 (*dd*, *J* = 13.9, 6.1, 1 H); 2.09 – 1.86 (*m*, 3 H); 1.55 – 1.43 (*m*, 2 H); 1.38 – 1.06 (*m*, 12 H); 0.92 – 0.87 (*m*, 6 H); 0.86 – 0.80 (*m*, 12 H). ^{13}C-NMR (101 MHz, (D$_6$)DMSO): 174.2 (C); 168.4 (C); 150.8 (CH); 150.6 (CH); 146.8 (CH); 146.6 (CH); 141.3 (CH); 137.9 (CH); 135.5 (CH); 135.2 (CH); 132.32 (C); 132.27 (C); 120.53 (C); 120.47 (C); 41.8 (CH$_2$); 39.20 (CH$_2$); 38.60 (CH$_2$); 38.58 (CH$_2$); 36.6 (CH$_2$); 36.4 (CH$_2$); 30.0 (CH); 29.5 (CH); 27.3 (2 CH); 24.15 (CH$_2$); 24.07 (CH$_2$); 22.5 (2 CH$_3$); 22.4 (2 CH$_3$); 19.8 (CH$_3$); 19.5 (CH$_3$). HR-ESI-MS (pos.): 354.118 (C$_{16}$H$_{25}$BrN$_3$O$^+$, [*M* + H]$^+$; calc. 354.118).

N′-[(6-Methoxypyridin-3-yl)methylidene]-3,7-dimethyloctanehydrazide (**32**). This compound was synthesized according to *GP-A*, starting with 6-methox-ynicotinaldehyde (49 mg, 0.36 mmol, 1.3 equiv.). The crude was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 98.5:1.5) to afford the product as white solid (82 mg, 0.27 mmol, 98%). M.p. 75 – 76 °C. ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 11.30 (*s*, 1 H); 11.22 (*s*, 1 H); 8.39 – 8.31 (*m*, 2 H); 8.17 (*s*, 1 H); 8.07 – 7.98 (*m*, 2 H); 7.95 (*s*, 1 H); 6.88 (*t*, *J* = 8.0, 2 H); 3.88 (2*s* overlap, 6 H); 2.61 (*dd*, *J* = 14.3, 5.8, 1 H); 2.39 (*dd*, *J* = 14.3, 8.2, 1 H); 2.17 (*dd*, *J* = 13.9, 6.1, 1 H); 2.04 – 1.83 (*m*, 3 H); 1.59 – 1.42 (*m*, 2 H); 1.36 – 0.99 (*m*, 12 H); 0.93 – 0.87 (*m*, 6 H); 0.86 – 0.81 (*m*, 12 H). ^{13}C-NMR (101 MHz, (D$_6$)DMSO): 173.8 (C); 168.0 (C); 164.4 (C); 164.2 (C); 147.1 (CH); 146.7 (CH); 143.1 (CH); 139.4 (CH) 136.0 (CH); 135.6 (CH); 124.29 (C); 124.28 (C); 111.2 (2 CH); 53.5 (CH$_3$); 53.4 (CH$_3$); 41.9 (CH$_2$); 39.22 (CH$_2$); 38.61 (CH$_2$); 38.59 (CH$_2$); 36.6 (CH$_2$); 36.4 (CH$_2$); 30.0 (CH); 29.5 (CH); 27.3

(2 CH); 24.13 (CH$_2$); 24.07 (CH$_2$); 22.54 (CH$_3$); 22.51 (CH$_3$); 22.4 (2 CH$_3$); 19.8 (CH$_3$); 19.5 (CH$_3$). HR-ESI-MS (pos.): 306.218 (C$_{17}$H$_{28}$N$_3$O$_2^+$, [M + H]$^+$; calc. 306.218).

***N*′-[(5-Methoxypyridin-3-yl)methylidene]-3,7-dimethyloctanehydrazide** (**33**). This compound was synthesized according to *GP-A*, starting with 5-methoxynicotinaldehyde (46 mg, 0.33 mmol, 1.2 equiv.). The crude was purified by automated column chromatography (CH$_2$Cl$_2$/MeOH 97:3 to 92:8) to afford the product as yellow oil (53 mg, 0.17 mmol, 63%). ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 11.48 (*s*, 1 H); 11.38 (*s*, 1 H); 8.41 (*s*, 1 H); 8.39 (*s*, 1 H); 8.32–8.28 (*m*, 2 H); 8.21 (*s*, 1 H); 7.99 (*s*, 1 H); 7.64–7.53 (*m*, 2 H); 3.87 (2*s* overlap, 6 H); 2.66 (*dd, J* = 14.3, 5.8, 1 H); 2.40 (*dd, J* = 14.3, 8.2, 1 H); 2.20 (*dd, J* = 13.9, 6.1, 1 H); 2.06–1.83 (*m*, 3 H); 1.59–1.43 (*m*, 2 H); 1.37–1.05 (*m*, 12 H); 0.95–0.87 (*m*, 6 H); 0.86–0.79 (*m*, 12 H). ^{13}C-NMR (101 MHz, (D$_6$)DMSO): 174.1 (C); 168.3 (C); 155.5 (2 C, 142.9 (CH); 141.1 (CH); 140.4 (CH); 139.34 (CH); 139.26 (CH); 138.5 (CH); 131.01 (C); 130.98 (C); 116.6 (CH); 115.8 (CH); 55.6 (CH$_3$); 55.5 (CH$_3$); 41.8 (CH$_2$); 38.61 (2 CH$_2$), 36.7 (CH$_2$); 36.4 (CH$_2$); 30.0 (CH); 29.6 (CH); 27.34 (CH); 27.31 (CH); 24.11 (CH$_2$); 24.07 (CH$_2$); 22.56 (CH$_3$); 22.51 (CH$_3$); 22.4 (2 CH$_3$); 19.8 (CH$_3$); 19.5 (CH$_3$). Note: one of the CH$_2$ signals, α to the carbonyl, is overlapping with the DMSO signal. HR-ESI-MS (pos.): 306.218 (C$_{17}$H$_{28}$N$_3$O$_2^+$, [M + H]$^+$; calc. 306.218).

3,7-Dimethyl-*N*′-[(6-methylpyridin-3-yl)methylidene]octanehydrazide (**34**). This compound was synthesized according to *GP-A*, starting with 6-methylnicotinaldehyde (67 mg, 0.55 mmol, 1.3 equiv.). The crude was purified by automated column chromatography (CH$_2$Cl$_2$/MeOH 97:3 to 92:8) to afford the product as white solid (110 mg, 0.379 mmol, 92%). M.p. 135–136 °C. ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 11.39 (*s*, 1 H); 11.29 (*s*, 1 H); 8.66 (*d, J* = 2.2, 1 H); 8.63 (*d, J* = 2.2, 1 H); 8.18 (*s*, 1 H); 7.97 (*s*, 1 H); 7.96–7.91 (*m*, 2 H); 7.30 (app. *t, J* = 7.6, 2 H); 2.63 (*dd, J* = 14.3, 6.0, 1 H); 2.49 (2*s* overlap, 6 H); 2.40 (*dd, J* = 14.3, 8.0, 1 H); 2.18 (*dd, J* = 13.7, 6.0, 1 H); 2.05–1.83 (*m*, 3 H); 1.56–1.43 (*m*, 2 H); 1.34–0.98 (*m*, 12 H); 0.93–0.87 (*m*, 6 H); 0.85–0.80 (*m*, 12 H). ^{13}C-NMR (101 MHz, (D$_6$)DMSO): 174.0 (C); 168.2 (C); 159.4 (C); 159.1 (C); 148.1 (CH); 147.8 (CH); 143.2 (CH); 139.7 (CH); 133.5 (CH); 133.2 (CH); 127.56 (C); 127.55 (C); 123.30 (CH); 123.26 (CH); 41.9 (CH$_2$); 39.22 (CH$_2$); 38.62 (CH$_2$); 38.60 (CH$_2$); 36.6 (CH$_2$); 36.5 (CH$_2$); 30.0 (CH); 29.5 (CH); 27.5 (2 CH); 24.14 (CH$_2$); 24.09 (CH$_2$); 24.0 (2 CH$_3$); 22.57 (CH$_3$); 22.54 (CH$_3$); 22.4 (2 CH$_3$); 19.8 (CH$_3$); 19.5 (CH$_3$). HR-ESI-MS (pos.): 290.223 (C$_{17}$H$_{28}$N$_3$O$^+$, [M + H]$^+$; calc. 290.223).

2-(2-Chlorophenoxy)-*N*′-[(pyridin-3-yl)methylidene]acetohydrazide (**35**). This compound was synthesized using similar conditions to *GP-A*, starting with nicotinaldehyde (32 mg, 0.30 mmol, 1.2 equiv.) and 2-(2-chlorophenoxy)acetohydrazide (50 mg, 0.25 mmol). The crude was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 96.5:3.5) to afford the product as white solid (65 mg, 0.22 mmol, 89%). NMR Analysis showed that the product is a mixture of E_{syn} and E_{anti} conformers (ratio 71:29). M.p. 152–154 °C. ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 11.79 (br. *s*, 2 H); 8.88 (*s*, 1 H); 8.84 (*s*, 1 H); 8.64–8.54 (*m*, 2 H); 8.33 (*s*, 1 H); 8.17–8.09 (*m*, 2 H); 8.05 (*s*, 1 H); 7.52–7.38 (*m*, 4 H); 7.34–7.21 (*m*, 2 H); 7.14–6.91 (*m*, 4 H); 5.30 (*s*, 2 H); 4.79 (*s*, 2 H). ^{13}C-NMR (101 MHz, (D$_6$)DMSO): 168.7 (C); 164.0 (C); 153.6 (C); 153.4 (C); 150.8 (CH); 150.6 (CH); 148.8 (CH); 148.6 (CH); 145.1 (CH); 141.1 (CH); 133.6 (CH); 133.5 (CH); 130.1 (CH); 130.0 (CH); 129.9 (2 C), 128.3 (CH); 128.1 (CH); 124.0 (CH); 123.9 (CH); 122.2 (CH); 121.6 (CH); 121.2 (2 C), 114.1 (CH); 113.8 (CH); 67.0 (CH$_2$); 65.4 (CH$_2$). HR-ESI-MS (pos.): 290.070 (C$_{14}$H$_{13}$ClN$_3$O$_2^+$, [M + H]$^+$; calc. 290.069).

2-(2,4-Dichlorophenoxy)-*N*′-[(pyridin-3-yl)methylidene]acetohydrazide (**36**). This compound was synthesized using similar conditions to *GP-A*, starting with nicotinaldehyde (31 mg, 0.29 mmol, 1.3 equiv.) and 2-(2,4-dichlorophenoxy)acetohydrazide (51 mg, 0.22 mmol). The crude was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 98:2) to afford the product as white solid (61 mg, 0.19 mmol, 87%). NMR Analysis showed that the product is a mixture of E_{syn} and E_{anti} conformers (ratio 75:25). M.p. 182–184 °C. ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 11.80 (br. *s*, 2 H); 8.88 (*s*, 1 H); 8.83 (*s*, 1 H); 8.63–8.57 (*m*, 2 H); 8.32 (*s*, 1 H); 8.15–8.08 (*m*, 2 H); 8.04 (*s*, 1 H); 7.66–7.55 (*m*, 2 H); 7.51–7.43 (*m*, 2 H); 7.41–7.29 (*m*, 2 H); 7.14–7.07 (*m*, 2 H); 5.32 (*s*, 2 H); 4.82 (*s*, 2 H). ^{13}C-NMR (101 MHz, (D$_6$)DMSO): 168.5 (C); 163.7 (C); 152.8 (C); 152.6 (C); 150.8 (CH); 150.6 (CH); 148.8 (CH); 148.5 (CH); 145.2 (CH); 141.2 (CH); 133.58 (CH); 133.52 (CH); 129.93 (C); 129.85 (C); 129.4 (CH); 129.2 (CH); 128.1 (CH); 127.8 (CH); 125.2 (C); 124.5 (C); 124.0 (CH); 123.8 (CH); 122.5 (C); 122.2 (C); 115.4 (CH); 115.2 (CH); 67.1 (CH$_2$); 65.7 (CH$_2$). HR-ESI-MS (pos.): 324.031 (C$_{14}$H$_{12}$Cl$_2$N$_3$O$_2^+$, [M + H]$^+$; calc. 324.030).

2-[(1*H*-Benzimidazol-2-yl)sulfanyl]-*N*′-[(pyridin-3-yl)methylidene]acetohydrazide (**37**). This compound was synthesized using similar conditions to *GP-A*, starting with nicotinaldehyde (33 mg, 0.31 mmol, 1.3 equiv.) and 2-[(1*H*-benzimidazol-2-yl)sulfanyl]aceto-

hydrazide (51 mg, 0.23 mmol). The crude was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 94:6) to afford the product as yellow solid (52 mg, 0.17 mmol, 72%). NMR Analysis showed that the product is a mixture of E_{syn} and E_{anti} conformers (ratio 64:36). M.p. 148–152 °C. ^{1}H-NMR (600 MHz, (D$_6$)DMSO): 12.59 (br. *s*, 2 H); 12.01 (br. *s*, 1 H); 11.80 (br. *s*, 1 H); 8.87 (*d, J* = 1.7, 1 H); 8.83 (*d, J* = 1.7, 1 H); 8.61–8.58 (*m*, 2 H); 8.27 (*s*, 1 H); 8.09 (*dt, J* = 8.0, 2.0, 2 H); 8.06 (*s*, 1 H); 7.58–7.32 (*m*, 6 H); 7.16–7.08 (*m*, 4 H); 4.61 (*s*, 2 H); 4.19 (*s*, 2 H). ^{13}C-NMR (151 MHz, (D$_6$)DMSO): 169.3 (C); 164.1 (C); 150.7 (CH); 150.5 (CH); 149.7 (C); 149.5 (C); 148.8 (CH); 148.6 (CH); 144.3 (CH); 143.5 (2 C) 140.8 (CH); 135.5 (2 C), 133.5 (CH); 133.4 (CH); 130.02 (C); 129.95 (C); 124.0 (CH); 123.9 (CH); 121.6 (2 CH); 121.1 (2 CH); 117.3 (2 CH); 110.3 (2 CH); 34.2 (CH$_2$); 33.5 (CH$_2$). HR-ESI-MS (pos.): 312.092 (C$_{15}$H$_{14}$N$_5$OS$^+$, [*M*+H]$^+$; calc. 312.091).

2-(3,4-Dimethoxyphenyl)-*N*′-[(pyridin-3-yl)methylidene]acetohydrazide (**38**). This compound was synthesized using similar conditions to *GP-A*, starting with nicotinaldehyde (43 mg, 0.41 mmol, 2.7 equiv.) and 2-(3,4-dimethoxyphenyl)acetohydrazide (31 mg, 0.15 mmol). The crude was purified by flash column chromatography (CH$_2$Cl$_2$/MeOH 97:3) to afford the product as yellow solid (33 mg, 0.11 mmol, 74%). NMR analysis showed that the product is a mixture of E_{syn} and E_{anti} conformers (ratio 60:40). M.p. 145–148 °C. ^{1}H-NMR (400 MHz, (D$_6$)DMSO): 11.67 (*s*, 1 H); 11.46 (*s*, 1 H); 8.86 (*d, J* = 1.7, 1 H); 8.81 (*d, J* = 1.7, 1 H); 8.58 (*dd, J* = 4.8, 1.6, 2 H); 8.27 (*s*, 1 H); 8.13 (app. *dt, J* = 8.0, 2.0, 1 H); 8.07 (app. *dt, J* = 8.0, 2.0, 1 H); 8.02 (*s*, 1 H); 7.60–7.40 (*m*, 2 H); 6.95–6.78 (*m*, 6 H); 3.91 (*s*, 2 H); 3.75 (*s*, 3 H); 3.72 (*s*, 3 H); 3.70 (*s*, 3 H); 3.68 (*s*, 3 H); 3.47 (*s*, 2 H). ^{13}C-NMR (101 MHz, (D$_6$)DMSO): 172.7 (C); 167.0 (C); 150.6 (CH); 150.3 (CH); 148.7 (CH); 148.6 (C); 148.4 (C); 148.3 (CH); 147.7 (C); 147.5 (C); 143.7 (CH); 139.9 (CH); 133.34 (CH); 133.27 (CH); 130.2 (2 C), 127.9 (C); 127.8 (C); 123.9 (2 CH); 121.3 (CH); 121.1 (CH); 113.3 (CH); 113.0 (CH); 111.9 (CH); 111.8 (CH); 55.6 (CH$_3$); 55.50 (CH$_3$); 55.46 (CH$_3$); 55.3 (CH$_3$); 40.8 (CH$_2$); 38.6 (CH$_2$). HR-ESI-MS (pos.): 300.135 (C$_{16}$H$_{18}$N$_3$O$_3$$^+$, [*M*+H]$^+$; calc. 300.134).

Author Contribution Statement

R. V. D. V., *F. J. D.*, and *A. K. H. H.* conceived the project, *D. P.* performed the synthesis, *D. P.*, *H. G.*, and *R. V. D. V.* performed enzyme-inhibition studies, *F. J. D.* and *A. K. H. H.* supervised the project, *D. P.*, *R. V. D. V.*, and *A. K. H. H.* wrote the manuscript.

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