RESEARCH ARTICLE

Synthesis, Enzyme Assays and Molecular Docking Studies of Fluorinated Bioisosteres of Santacruzamate A as Potential HDAC Tracers

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Abstract: Histone deacetylases (HDACs) emerged as important epigenetic regulators of gene expression. In order to identify potential positron emission tomography (PET) tracers for imaging HDACs, we evaluated *in vitro* and *in cellulo* activities of some compounds that were reported as potent HDAC2-selective inhibitors. We observed marked differences between reported activity values and the values obtained in our assays for some of the compounds. To understand the structural basis of the activity of some of these inhibitors, we also performed molecular docking studies to understand their interaction patterns and binding modes with HDAC2. We observed the low affinity compounds **4**, **6** and **7** did not showed equal number of key π - π interactions and hydrogen bonding when compared to high affinity compounds, and could be the possible reason for poor inhibition as reflected in *in vitro* assays. These preliminary experimental and computational results will help to interpret the HDAC affinity values of these key compounds with caution.

Keywords: HDAC inhibitors, enzyme assays, molecular docking, PET tracers.

1. INTRODUCTION

Histone deacetylases (HDACs) are essential post-translational regulators responsible for deacetylation of acetylated lysine residues in histone and non-histone substrates [1, 2]. HDACs are divided into four major classes: class I (HDAC1, 2, 3 and 8), class II (HDAC4, 5, 6, 7, 9 and 10), class III also called sirtuins (SIRT1 to 7) and class IV (HDAC11). All of them are Zn^{2+} -dependent metalloproteins except class III which use nicotinamide adenine dinucleotide (NAD^+) as a cofactor in the deacetylation process [3, 4]. The development of new drugs acting as inhibitors of the HDAC enzymatic activities (HDAC inhibitor, HDACi) is a proven

strategy for many diseases, such as central nervous system disorders, cardiac diseases and different forms of cancer [5-8].

Prototypical Zn^{2+} -dependent HDACi consist of 1) a capping group, also called surface recognition domain, usually a hydrophobic and aromatic group allowing the interaction with the rim of the binding pocket which occludes the entrance of the active site pocket, 2) a linker region with linear or cyclic structure, in which the π - π stacking with aromatic amino acids from HDAC is important for increased affinity, 3) a Zn^{2+} -chelating group and optionally 4) an internal cavity binding domain. Numerous natural and synthetic HDACi have been identified in recent decades [9]. These inhibitors are classified according to their structure into five categories: short-chain fatty acids, hydroxamic acids, cyclic peptides, benzamides and macrocycles. Other compounds, such as polyketides, ortho-anilides, chalcones, tropolones and sulfur containing compounds also display HDAC inhibitory activity [10, 11].

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So far there are four US Food and Drug Administration (FDA)-approved HDACi in clinics for cancer therapy. In 2006, suberoylanilide hydroxamic acid (SAHA, Vorinostat, Zolinza[®]; compound **5**, Fig. 1) was approved as a first in class hydroxamic acid-based HDACi for the treatment of cutaneous T-cell lymphoma (CTCL). In 2009, the class I-specific HDACi romidepsin (FK228, Istodax[®]), a thiol-based depsipeptide, also gained approval for the treatment of CTCL. In 2011, romidepsin was also approved for the treatment of patients suffering from peripheral T-cell lymphoma (PTCL) who have received at least one prior therapy. Two additional hydroxamic acid-based pan-HDACi, PXD101 (Belinostat, Beleodaq[®]) and LBH-589 (Panobinostat, Farydak) were approved in 2014 and 2015, respectively. PXD101 received approval for refractory or relapsed PTCL and LBH-589 was approved for patients with multiple myeloma who received at least two prior regimens including an immunomodulatory agent and the proteasome inhibitor bortezomib [12].

Noteworthy, many of these inhibitors are pan-HDACi thus can cause toxic side effects [6]. Increasing evidence suggest that these side effects could be limited by targeting only a limited number or ideally only one HDAC-isoform, involved in a specific disease or disease subtype, providing ultimately therapeutic tools for personalized treatments [13-16].

In this context, the search for selective HDACi is an ongoing hot topic. A major HDAC-isoform that is involved in various diseases is HDAC2, which is an important factor in cell development, cytokine signaling involved in immune responses and is often significantly overexpressed in cancer like acute myeloid leukemia [6] and gastric [17] and colon cancer [18-20]. In addition, HDAC2 is part of various co-repressor complexes with HDAC1 and 3 often aberrantly recruited by oncogenic fusion proteins [21]. It also controls pro-apoptotic factor p53, [22] regulates memory formation

and synaptic plasticity, [23] and is involved in maintenance of cardiac hypertrophic response [24], thus making HDAC2 a valuable target in the search of cures for these pathologies.

1.1. HDAC Enzyme Activity Inhibition Values from the Literature

Compound **2** (Fig. 1) was first reported by Rajagopal and coworkers, [25] who showed that it had a pan-HDAC IC₅₀ value of 1.1 nM. Subsequently Hooker and coworkers modified compound **1** by adding an additional *N*-methyl group to form compound **1** (martinostat, Fig. 1), as a positron emission tomography (PET) tracer for imaging HDACs [26, 27]. Compound **1** was found to inhibit HDAC2 (IC₅₀ of 2.0 nM) but lacks isoform-selectivity but may be a good lead for the development of a HDAC2-selective inhibitor.

Pavlik *et al.* recently reported the selective and potent HDAC2 inhibitor santacruzamate A, (compound **6**, Fig. 1), with an IC₅₀ value of 119 pM for HDAC2 [28]. Moreover in the same article santacruzamate A-SAHA hybrid **7** (Fig. 1) was described to have good inhibitory activity towards HDAC2 with an IC₅₀ of 3.5 nM.

The synthetic products (santacruzamate A (**6**) and the hybrid **7**) as well as the natural product (isolated from a cyanobacterium) santacruzamate A (**6**) were evaluated for isozyme-selective inhibition of HDAC2 and HDAC4, which are class I and class IIa HDAC, respectively. It was reported that all the three compounds selectively inhibited HDAC2 with relatively little inhibition of HDAC4. In contrast at 1 μ M, SAHA completely inhibited both class I and II HDACs. On this basis, IC₅₀ values were determined using HDAC2, HDAC4 and HDAC6. Against HDAC2, SAHA showed an IC₅₀ of 86 nM, whereas it was reported that the natural and synthetic santacruzamate A compounds have picomolar IC₅₀ values (Table 1). However, all three compounds showed IC₅₀ values >1 μ M against HDAC4. IC₅₀ values obtained with the natural and synthetic santacruzamate A (were identical) and

Fig. (1). Structures of potent HDAC inhibitors investigated in this study.

Table 1. Comparison of HDAC activities of compounds 1-10.

Compound	Literature		In Silico Docking Studies		In Vitro Present Study	
	HDAC2 IC ₅₀ (nM)	Pan-HDAC IC ₅₀ (nM)	Binding Energy kcal/mol	Binding Affinity HDAC2 (nM)	HDAC2 IC ₅₀ (nM)	Pan-HDAC IC ₅₀ (nM)
1	2.0 ²⁶	ND	-10.59	17.27	19.41	0.87
2	N.D.	1.1 ²⁵	-11.77	2.36	4.78	1.08
3	651 ²⁷	-	-8.95	275.30	161	45.1
4	0.81* ³⁰	ND	-7.35	3990	87085	9650
5	85.8 ²⁸	ND	-7.92	1570	84.1 (290) [‡]	59.1
6	0.119 ²⁸	ND	-6.83	9810	8% inhibition at 100 μ M (20 % inhibition at 50 μ M) [‡]	11% inhibition at 100 μ M
7	3.5 ²⁸	ND	-7.34	4180	7280	1420
8	1.3 ³⁴	1.8 ³⁵	-8.23	929.77	11 [‡]	ND
9	-	-	-7.10	6270	>10,000 [‡]	ND
10	-	-	-6.25	26240	>10,000 [‡]	ND

*Reported in K_i, inhibition constant. [‡]Result from Oslo. ND-Not determined/Not available.

compound **7** for HDAC6 were found to be 434, 433 and 386 nM respectively, while SAHA showed limited selectivity with an IC₅₀ of 39 nM [28].

Ononye and coworkers reported α -aryl substituted tropolone scaffolds as potent HDAC-selective inhibitors; in particular compound **4** was reported to have a K_i of 0.81 nM [29, 30]. These tropolone derivatives are believed to form a strong bond with the catalytic Zn²⁺ ion *via* the α -hydroxy ketone group of the tropolone and besides high affinities for HDAC2 they were also reported to exhibit cytotoxicity in cancer cells.

During the course of our investigation, Liu Wen and coworkers reported a biological study performed on santacruzamate A **6** as well as its analogues and they observed that santacruzamate A **6** did not show any inhibition of HDAC2 even at a concentration of 2 μ M [31]. We recently started an investigation in search of isozyme-specific HDAC2 inhibitors for potential use as cancer drugs and also for the use of these compounds as possible PET tracers for the *in vivo* imaging of HDAC2. In this context, we report some preliminary results of compounds **1-10** on their pan-HDAC, HDAC2 inhibition assays and *in silico* studies.

2. RESULTS AND DISCUSSION

2.1. Chemistry

We selected some of the literature reported compounds (Fig. 1) and synthesized compounds **1**, **2**, **3**, **4**, **6** and **7** according to reported literature procedures [25-30], whereas compounds **5** and **8** were obtained commercially. Two new fluorinated bioisosteres of santacruzamate A, (compounds **9** and **10**) were synthesized. The martinostat analogue compound **3** was obtained by introduction of a 2-fluoroethyl group

(Fet) in **2** using FetBr in DMF and with K₂CO₃ as base (See Experimental section and Supporting Information for complete characterization of all the final compounds).

For the preparation of santacruzamate A analog **10**, γ -aminobutyric acid **11** (GABA) was first selectively converted to the *N*-ethoxycarbonyl derivative **12a** with ethyl chloroformate in aqueous potassium carbonate solution (Scheme 1) [28]. Then carbamate **12a** was reacted with 3-fluoro-phenethylamine using EDC-HCl/TEA system in the presence of catalytic amount of DMAP in dichloromethane.

Similarly, Fet-santacruzamate A **9** was synthesized from GABA **11** in a four-step synthesis (Scheme 1). Boc protection of the 4-amino group was performed by reaction of di-*tert*-butyl dicarbonate (Boc₂O) in 1M NaOH-THF mixture to form **12b**, which was further reacted with phenethylamine using EDC-HCl in the presence of catalytic amounts of DMAP in dichloromethane and followed by boc-deprotection with TFA yielding 4-amino-*N*-phenethyl-butylamid **13**. Fet-santacruzamate A **9** was prepared from **13** by transcarboxylation, using DBU-CO₂ zwitterionic complex [32], and subsequent *O*-alkylation with 2-bromofluoroethane. The synthesized compounds were characterized by ¹H-, ¹³C- and ¹⁹F-NMR spectra and by ESI-MS. The incorporation of the carboxylate group and the exact position of the 2-fluoroethyl-group were demonstrated using 2D-NMR (¹H-¹H- COSY and ¹H-¹³C HMBC) experiments. ¹H-¹H-COSY and ¹H-¹³C HMBC correlations for Fet-santacruzamate A **9** are listed in Table S1-A and Table S1-B (Supplementary Information, pp. 4-5).

Further in an attempt to radiosynthesis of the ¹⁸F-labeled analogue of santacruzamate-A ([¹⁸F]**10**), new nickel complexes **15** and **16** were prepared from 3-bromophenethyl-santacruzamate A (**14**) by adaptation of a recently described

Scheme 1. Synthesis of fluorinated analogues of Santacruzamate-A. Reagents and conditions: (i) ethyl chloroformate, K_2CO_3 , H_2O , $0^\circ C$ for 2h then 16 h, RT; (ii) Boc_2O , 1M NaOH, THF, 24h, RT; (iii) 3-fluorophenethylamine, Et_3N , CH_2Cl_2 , DMAP, EDC HCl, $0^\circ C$ for 1h then overnight RT; (iv) TFA; (v) phenethylamine, Et_3N , CH_2Cl_2 , DMAP, EDC HCl, $0^\circ C$ for 1h then 16 h, RT; (vi): (1) DBU- CO_2 complex, acetonitrile, 1.5 h, $0-5^\circ C$, (2) $BrCH_2CH_2F$, overnight RT. [B] Synthesis of the nickel aryl complex precursor for the radiosynthesis of ^{18}F -labeled analogue of santacruzamate-A. Reagents and conditions: (i) 3-bromophenethylamine, Et_3N , CH_2Cl_2 , DMAP, EDC HCl, $0^\circ C$ for 1h then overnight RT; (ii) tetramethylenediamine, $Ni(COD)_2$, toluene, RT, 6h; (iii): [2-(2-pyridinyl)phenyl-2-nitrobenzenesulfonamid]silver(I) (17), pyridine, toluene, acetonitrile, RT, 1 min; (iv): $^{18}F^-$, hypervalent iodine oxidant 18, acetonitrile.

method of Lee *et al.* [33]. The oxidative ^{18}F fluorination was performed using 40 μL of ^{18}F -fluoride in water (170 MBq), and was added to 4 ml MeCN containing 20 mg 18-crown-6, the reagents were mixed well to form ^{18}F stock solution. Three experiments were attempted using 1, 2 and 3 mg precursor (16) and 1 equivalent of PIBMP (18). To each reaction vial containing precursor (16), was added 400 μL of ^{18}F stock solution under a rubber septum. Reactions were run for 1 min at room temperature and a color change was observed (to yellow and reddish brown for higher amounts of precursors). However, this initial radiosynthetic attempt for oxidative ^{18}F fluorination was unsuccessful as no product was observed either with HPLC or with iTLC. However, radiosynthesis of $[^{11}C]1$ had successfully started from precursor 2, we used a procedure as previously reported by Hooker and coworkers. And a detailed study on $[^{11}C]1$ will be published in a due course.

2.2. Pan-HDAC and HDAC2 Inhibition Assays

Assays were carried out in two different labs in Luxembourg and Oslo, Norway in order to strengthen the confidence of the results. Different assays conditions were used to verify the results. HDAC enzymes were isolated from K562 cell extracts to measure total HDAC activity as previously described [36, 37]. HDAC fluorogenic assay kits from BPS Bioscience or Active Motif were used to measure HDAC2 activity (See Materials and Methods, Sections 6.1 and 6.2 for details).

Compounds 1 and 2 showed HDAC2 IC_{50} values of 19.4 and 4.8 nM, respectively (Table 1). Both showed a significantly lower pan-HDAC IC_{50} of 0.87 and 1.08 nM, respectively. The fluoroethyl analogue of martinostat 3 was found to be less effective than compound 1 and 2 with a HDAC2 IC_{50} value of 161 nM, and also showed a lower pan-

HDAC IC₅₀ 45.1 nM. Compound **4** which carries a tropolone moiety showed an HDAC2 IC₅₀ value of 87 μ M, although it was reported to have a K_i value of 0.81 nM against HDAC2 [31]. Compound **5** (SAHA) showed an IC₅₀ value of 84 and 59 nM for HDAC2 and pan-HDAC respectively.

The inhibitory activity of compounds **6** and **7** was also found to be far less than reported in the literature (IC₅₀ of 0.119 and 3.5 nM, respectively) [28] for HDAC2. Even at a concentration of 100 μ M **6** was not able to completely block neither total HDAC nor HDAC2 activity. Compound **7** showed an IC₅₀ value of 7.28 μ M and 1.42 μ M for HDAC2 and pan-HDAC respectively (Table 1).

Further, we choose compound **6** to study concentration-response in detail, with compounds **5** and **8** as standards (Fig. 2). We did not observe any effect of **6** under normal assay conditions (manufacturer's protocol), whereas **5** and **8** showed HDAC2 inhibition in agreement with literature values (Fig. 2). Since the observed absence of inhibitory activity for **6** was unexpected, we ran several control experiments. Assays were run against HDAC2 where **6** was used in combination with either **5** or **8** (data not shown), in order to verify if some of **6** or its impurities (if present) would interfere with the assay. We found that the decrease in activity was solely caused by either **5** or **8** and the contribution of **6** was negligible.

Since santacruzamate A **6** was reported as a potent HDAC2 inhibitor, [28] sparked our interest on this molecule for use as a potential radiolabeled probe. Subsequently we could achieve the synthesis of two bioisosteres of santacruzamate A **9** and **10**, and these compounds were tested in HDAC assays. An assay against HDAC2 for two fluorine derivatives **9** and **10** produced no decrease in activity even at a concentration of 10 μ M (Table 1). Equally no inhibitory effect was observed for other class I HDACs (HDAC1 and 3) (data not shown).

We further investigated whether assay conditions could explain the lack of activity of santacruzamate A **6**. As shown in Fig. 3, compound **6** was tested against recombinant HDAC2 enzymes under different assay conditions (HDAC fluorogenic assay from Active Motif vs BPS Bioscience).

Fig. (2). Activity-concentration curves of compound **5**, **6** and **8** using fluorogenic HDAC2 assay (BPS Bioscience, manufacturer's conditions).

Fig. (3). HDAC2 activity of **5**, **6** and **8** under different assay conditions. (a) BPS Bioscience following the manufacturer's protocol. (b) Active Motif assay following the manufacturer's protocol in the presence of HDAC2 enzyme from BPS Bioscience. (c) Active Motif assay with the enzyme and substrate (20 μ M) from BPS Bioscience. (d) Results from (a)-(c) merged.

However, none of these assay conditions could reproduce the subnanomolar affinity reported by Pavlik *et al.*, [28] thus different assay conditions could not explain the lack of effect of **6** on HDAC2 activity that we observed.

Our results for the compounds, **4**, **6** and **7** indicate marked inconsistencies with the results published by Ononye *et al.* and Pavlik *et al.*, and those results should be reconsidered and looked at with caution [28-30].

3. MOLECULAR DOCKING STUDY

To further investigate the interactions of these compounds with the HDAC2 enzyme binding pocket and to predict the *in silico* binding energy and binding affinity predictions we used molecular docking studies. Rational drug design involves investigating new molecules that complement their biological target in shape and charge, and bind to the active site effectively [38]. Molecular docking is an *in silico* modeling method which attempts to predict non-covalent interactions usually between a macromolecule and a small molecule, and is a widely used computational tool both in academia and industry for rapid identification of potential drugs with minimal expense and effort [39].

We performed docking studies using Autodock 4.2.6 in a Cygwin Linux environment. Following ligand and target preparation in Autodock Tools 1.5.6, the energy minimized compounds were docked into the binding pocket in HDAC2 crystal structure [40]. The HDAC2 crystal structure used in the docking studies was obtained from the RCSB Protein Data Bank (PDB ID: 4lxz). For the receptor preparation, water molecules were removed, polar hydrogen atoms were

Scheme 2. 3D representation of predicted binding models of **2**, **1**, **4** (top row, left to right) and **5**, **6**, **7** (bottom row, left to right) respectively in the binding pocket of HDAC2. Key Interactions between the protein residues (blue) and the ligand (grey) are shown and the zinc ion is shown as a yellow sphere (rest of the protein residues omitted for clarity). Residues shown in orange are involved in π - π stacking.

added, and Kollman united atom partial charges were assigned to HDAC2 using Autodock Tools at a pH of 7.4. For the ligand preparation, the 3D structure was generated with the use of ChemBioOffice Version 11.0 and the mm2 energy of the molecule was minimized to minimum RMS Gradient of 0.050 for each ligand. To understand the importance of Zn^{2+} binding site in HDAC2, docking was performed by setting the grid box size at 60x60x60 units of 0.375Å spacing along the x , y , and z axes, and centered on atom ZN401. Cygwin Terminal was used to run AutoGrid to generate the grid map of the various ligand and receptor atoms. After the grid map was generated, the Lamarckian genetic algorithm (LGA) implemented in AutoDock was applied to estimate the possible conformations of the ligand-protein complex. AutoDock simulations were performed 50 times to be sure to cover all possible binding possibilities. The result with the lowest docking energy analysis in cluster rank 1 was used for further analysis. For visualization of the docked conformations, Chimera 1.10.1 software package was used.

Our docking study indicated martinostat derivatives **1-3** fit well in the binding pocket and showed calculated HDAC2 binding affinity values of 17.3, 2.4, and 275 nM, respectively. Also these three compounds can chelate Zn^{2+} , with measured distance of **1** (O-H), (C=O), **2** and **3** (C=O) from Zn^{2+} being 1.72, 1.78 and 1.75 Å, respectively. Additionally, all three compounds showed two π - π interactions with Phe155A and Phe210A, which attributes to the favorable interaction with HDAC2. A similar π - π stacking interaction was also observed for chidamide with Phe155A and Phe210A in the binding pocket of HDAC2 [41] Besides key hydrogen bonding contacts, compound **2**

also exhibited an additional hydrogen bond contact with Asp104. The key interactions in the catalytic pocket are with His183, Asp181, Asp269 and Tyr308, as well as compound **2** additionally forming a key hydrogen bond with Asp104. (See Table S2, Supporting Information for more details)

Further for compound **4**, an *in silico* binding affinity value of 3.99 μM was obtained, and the methoxy group was observed to interact with Zn^{2+} ion (1.90 Å) instead of the anticipated hydroxyl ketone moiety. Compound **4** makes one π - π interaction with Phe155A and only one hydrogen bonding contact with His145A in the binding pocket, explaining its low binding affinity. For compounds **6** and **7**, an *in silico* binding affinity value of 9.8 and 4.2 μM was obtained and no π - π contacts were observed as anticipated. The lower binding energy for **6** and **7** in these simulation studies could be because of lack of any π - π interactions. Similarly compounds **9** and **10** showed an *in silico* binding affinity value of 6.3 and 26.2 μM , respectively. Although *in silico* results have to be read with caution due to their inconsistencies, our *in vitro* assays for compounds **1-4**, **6**, **7**, **9** and **10** generally agree with our *in silico* simulation studies.

4. CONCLUSION

In summary we have studied selected potent HDAC inhibitors for their HDAC2 and pan HDAC inhibitory activity in order to identify potential HDAC2 PET tracers. We observed that the IC_{50} values of compounds **1**, **3**, **5** and **8** are in agreement with literature values. However, we have found major differences in the IC_{50} values for the α -aryl tropolone **4**, santacruzamate A **6** and santacruzamate A-

SAHA hybrid **7** against the literature reports. We further carefully, i) studied the inhibitory effect of santacruzamate A **6** by using different assay conditions and different concentrations against control compounds **5** and **8**, but we could not reproduce the literature affinity values and ii) performed molecular docking studies, which were also in agreement with our *in vitro* assay results, additionally the docking studies showed the key interactions of the potent compounds (example, **1** and **2**) in HDAC2 binding pocket, while compounds **4**, **6** and **7** did not show key π - π interactions and additional hydrogen bonding to contribute to higher affinity. Our results suggest that the presence of an aryl group for a π - π interaction, a hydrogen bond donor and an appropriate bulky cap group can be helpful for achieving selectivity when designing new HDAC2 inhibitors. In line with santacruzamate A **6** results, fluorinated bioisosteres of santacruzamate A, **9** and **10** did not show any HDAC2 inhibition even at 10 μ M concentration. Further, literature inhibitory activity for compounds **4**, **6** and **7** has to be read with caution and hope these results will be useful for other researchers working with these compounds in the area of epigenetics.

5. MATERIAL AND METHODS

5.1. Cell Culture, Total Protein Extraction and *in vitro* HDAC Activity Assays (Luxembourg)

Chronic myeloid leukemia K-562 cells (American Type Culture Collection, Manassas, USA) were cultured in RPMI 1640 (BioWhittaker®, Lonza, Verviers, Belgium) supplemented with 10% heat-inactivated fetal calf serum (BioWhittaker®) and 1% antibiotic-antimycotic (Bio Whittaker®) at 37°C in humid atmosphere and 5% CO₂. Cells were harvested, washed in cold PBS 1x, and lysed in MPER® (Thermo-scientific, Erembodegem-Aalst, Belgium) supplemented by 1x protease inhibitor cocktail (Complete EDTA-free, Roche, Prophac, Luxembourg, Luxembourg) according to manufacturer's instructions. HDAC activity assays were carried out as previously described [36]. For total HDAC activity assay, we used 10 μ g of K-562 total protein extracts. The quantity of enzymes per well, concentration of substrates and cofactor, and incubation times were used as previously reported [37]. IC₅₀ values were determined using the GraphPad Prism 6.0 software.

5.2. Fluorogenic HDAC2 Assay (Oslo)

HDAC2 activity in the presence of the different inhibitors was measured by using HDAC fluorogenic assay kits from BPS Bioscience, (CA, USA) or Active Motif (CA, USA). The HDAC2 enzyme was obtained from BPS Bioscience (concentration as recommended by producer (BPS Bioscience) or 56 ng/reaction (using assay from Active Motif)).

5.3. Experimental Section

(E)-3-(4((((3R,5R,7R)-Adamantan-1-ylmethyl)(methyl)amino)methyl)-phenyl)-N-hydroxy acrylamide [1, Martino-stat]

Colorless Powder, ¹H NMR (CD₃OD): δ 1.46 (brs, 6H, CH₂), 1.56-1.68 (m, 6H, CH₂), 1.85 (brs, 3H), 2.03 (brs, 2H),

2.13 (s, 3H, Me), 3.46 (s, 2H, CH₂), 6.38 (d, J = 15.8 Hz, 1H, CH), 7.24-7.48 (m, 5H, Ar). ¹³C NMR (CD₃OD): δ 30.1 (3C), 36.3, 38.4 (3C), 42.4 (3C), 46.4, 66.0, 72.1, 118.3, 128.7 (2C), 130.6 (2C), 135.1, 141.1, 143.61, 166.5. HRMS (ESI) Calcd. for C₂₂H₃₁N₂O₂ [M+H]⁺: 355.2380. Found: 355.2390.

(E)-3-(4((((3R,5R,7R)-Adamantan-1-ylmethyl)amino)methyl)-phenyl)-N-hydroxy Acrylamide [2], N-Desmethyl-Martinostat]

Colourless Powder, ¹H NMR (CD₃OD): δ 1.58-1.77 (m, 13H), 1.98-2.02 (m, 3H), 2.67 (s, 2H, CH₂), 4.25 (s, 2H, CH₂), 6.54 (d, J 15.7 Hz, 1H, CH), 7.54-7.65 (m, 5H, Ar). ¹³C NMR (CD₃OD): δ 29.5 (3C), 33.4, 37.5 (3C), 40.7 (3C), 52.9, 59.9, 120.1, 129.5, 132.0, 133.6, 137.7, 140.5, 166.0. HRMS (ESI) Calcd. for C₂₁H₂₉N₂O₂ [M+H]⁺: 341.2224. Found: 341.2244.

(E)-3-(4((((3R,5R,7R)-Adamantan-1-ylmethyl)(2-fluoroethyl)amino)methyl)-phenyl)-N-hydroxyacrylamide [3, Fluoroethyl-Martinostat]

Colourless Powder, ¹H NMR (CD₃OD): δ 1.55-1.68 (m, 12H, CH&CH₂), 1.80-1.88 (m, 3H, CH&CH₂), 2.87-2.95 (m, 2H, CH₂), 4.14-4.32 (m, 2H, CH₂), 4.52-4.60 (m, 4H, 2CH₂), 6.37 (d, 1H, J 15.2, CH), 7.22-7.29 (m, 2H, Ar), 7.42-7.49 (m, 3H, Ar). ¹³C NMR (CD₃OD): δ 30.0, 37.0, 38.1, 42.3, 54.2, 60.0, 60.9, 66.3, 82.1, 83.8, 118.7, 128.8, 129.0, 129.1, 135.5, 141.6, 166.6. HRMS (ESI) Calcd. for C₂₃H₃₂FN₂O₂ [M+H]⁺: 387.2442. Found: 387.2406.

α -(4-Methoxyphenyl) Tropolone [4]

Yellow Powder, ¹H NMR (CDCl₃): δ 3.86 (s, 3H, OMe), 6.95-7.00 (m, 2H, Ar), 7.03-7.09 (m, 1H, Ar), 7.31-7.43 (m, 2H, Ar), 7.46-7.51 (m, 2H, Ar), 7.56-7.61 (m, 1H, Ar). ¹³C NMR (CDCl₃): δ 55.5, 113.9 (2C), 122.1, 127.5, 130.9 (2C), 132.3, 136.5, 138.8, 140.6, 159.9, 170.5, 171.4. HRMS (ESI) Calcd. For C₁₄H₁₃O₃ [M+H]⁺: 229.0859. Found: 229.0848.

[3-[2-(phenyl)-ethylcarbamoyl]-propyl]-carbamic Acid ethyl ester [6, Santacruzamate A]

Colourless Powder, mp. 114-115 °C, Lit. [28] mp. 112-113 °C. R_f [A] = 0.64, R_f [B] = 0.76. ¹H-NMR (CDCl₃) δ 1.22 (t, J = 7.1 Hz, 3H, CH₃CH₂O), 1.79 (pent, J = 6.8 Hz, 2H, 3-CH₂), 2.16 (t, J = 7.0 Hz, 2H, 2-CH₂), 2.82 (t, J = 7.1 Hz, 2H, PhCH₂CH₂), 3.16 (dd, J = 6.1, 12.3 Hz, 2H, 4-CH₂), 3.51 (dd, J = 7.0, 13.0 Hz, 2H, PhCH₂CH₂), 4.08 (q, J = 7.1 Hz, 2H, CH₃CH₂O), 4.93 (br s, 1H, NH), 5.93 (br s, 1H, NH), 7.18-7.31 (m, 5H, PhCH₂CH₂). ¹³C-NMR (CDCl₃) δ 14.6 (CH₃CH₂O), 26.1 (C-3), 33.6 (C-2), 35.6 (PhCH₂CH₂), 40.1 (C-4), 40.6 (PhCH₂CH₂), 60.8 (CH₃CH₂O), 126.4 (Ph-C4), 128.6 (Ph-C2,6), 128.7 (Ph-C3,5), 138.8 (Ph-C1), 157.1 (NHCOOEt), 172.5 (CH₂CONH). HRMS (ESI) Calcd. For C₁₅H₂₃N₂O₃ [M+H]⁺: 279.1703. Found: 279.1709.

N¹-Hydroxy-N⁵-(2-phenethyl)-pentanediamide [7, Santacruzamate-SAHA Hybrid]

Yellow Powder, ¹H NMR (CDCl₃ and a drop of CD₃OD): δ 1.82-1.86 (m, 2H, CH₂), 2.03-2.06 (m, 2H, CH₂), 2.13-2.18 (m, 2H, CH₂), 2.79-2.84 (m, 2H, CH₂), 3.37-3.48 (m, 2H,

CH₂), 7.19-7.32 (m, 5H, Ar). ¹³C-NMR (CDCl₃ and a drop of CD₃OD): δ 22.0, 32.1, 35.1, 35.5, 40.8, 126.4, 128.6, 128.7, 139.0, 169.2, 173.9. HRMS (ESI) Calcd. For C₁₃H₁₉N₂O₃ [M+H]⁺: 251.1390. Found: 251.1385.

(3-Phenethylcarbamoyl-propyl)-carbamic acid 2-fluoroethyl ester (9, Fluoroethyl-Santacruzamate A)

Method A

All operations were carried out in a dry reaction vessel under argon atmosphere. DBU-CO₂ complex (470 mg, 2.4 mmol) was suspended in anhydrous acetonitrile (10 mL) and cooled to 0 °C in an ice-water bath. A solution of 4-amino-*N*-phenethyl-butylamide (**13** free base, 412 mg, 2 mmol) in anhydrous acetonitrile (15 mL) was added dropwise (60-70 min) with stirring. 2-fluoroethyl bromide (380 mg, 240 μL, 3 mmol) was added and the reaction mixture was stirred for further 24 h at room temperature. The clear solution was poured on to water (30 mL) and the resulting suspension was extracted with chloroform (4 x 50 mL). The combined organic phase was washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (80 g Kieselgel, eluent: ethylacetate-chloroform 7:3 (v/v), 50 mL fractions). Yield: 172 mg (30 %).

Method B

To a solution of 4-amino-*N*-phenethyl-butylamide (**13**) free base (412 mg, 2 mmol, 1 eq.) in anhydrous *N,N*-dimethylformamide (40 mL) was added Cs₂CO₃ (1.95 g, 6 mmol, 3 eq.) and tetrabutylammonium trifluoromethanesulfonate (2.35 g, 6 mmol, 3 eq.). Carbon dioxide gas (20 mL/min) was bubbled through the suspension for 60 min at room temperature. Thereafter, 2-fluoroethyl-bromide (760 mg, 480 μL, 6 mmol) was added and the reaction mixture was stirred for further 24 h at room temperature. The solvent was removed under reduced pressure. Water (30 mL) was added to the residue and the suspension was extracted with chloroform (4 x 50 mL). The combined organic layer was washed with brine (20 mL) and dried (Na₂SO₄). The solvent was removed in vacuum and the residue was purified by column chromatography on silica gel as described above. Yield: 390 mg (65%). mp. 98-99 °C. *R*_f [C] = 0.27, *R*_f [D] = 0.47, *R*_f [E] = 0.24. ¹H-NMR (CDCl₃) δ 1.80 (pent, *J* = 6.9 Hz, 2H, 3-CH₂), 2.17 (t, *J* = 7.0 Hz, 2-CH₂), 2.81 (t, *J* = 7.0 Hz, 2H, PhCH₂CH₂), 3.18 (q, *J* = 6.4 Hz, 2H, 4-CH₂), 3.51 (dd, *J* = 7.0 Hz, 13.0 Hz, 2H, PhCH₂CH₂), 4.21-4.31 (m, 2H, CH₂CH₂F), 4.50-4.61 (m, 2H, CH₂CH₂F), 5.21 (br s, 1H, FCH₂CH₂OCONHCH₂), 5.89 (br s, 1H, CONHCH₂), 7.17-7.31 (m, 5H, PhCH₂CH₂). ¹³C-NMR (CDCl₃) δ 25.8 (C-3), 33.6 (C-2), 35.6 (PhCH₂CH₂), 40.3 (C-4), 40.5 (PhCH₂CH₂), 63.7 (d, ²*J*_{C,F} = 20.1 Hz, CH₂CH₂F), 81.8 (d, ¹*J*_{C,F} = 169.5 Hz, CH₂CH₂F), 126.4 (Ph-C4), 128.6 and 128.7 (Ph-C2,6 or Ph-C3,5), 138.8 (Ph-C1), 156.4 (COONHCH₂), 172.4 (NHCOCH₂). ¹⁹F-NMR (CDCl₃): δ 224.6 (tt, *J* = 29.4 and 47.8 Hz). ESI-MS *m/z*: 297 [M+H]⁺. C₁₅H₂₁N₂O₃ (296.34).

3-[2-(3-Fluorophenyl)-ethylcarbamoyl]-propyl]-carbamic acid ethyl ester [10, 3-Fluoro phenethyl-Santacruzamate A]

4-[(Ethoxycarbonyl)amino]butanoic acid (**12a**, 700 mg, 4 mmol) was dissolved in anhydrous dichloromethane (14 mL)

under argon atmosphere. The solution was cooled to 0 °C. Triethylamine (1.2 mL, 870 mg, 8.6 mmol) and 3-fluorophenethylamine (0.6 mL, 4.6 mmol) were added consecutively. Afterwards EDC-HCl (900 mg, 4.7 mmol) was added in one portion. Catalytic amount DMAP (30 mg) was added, the resulting mixture was stirred for 1 h at 0 °C and then for 16 h at room temperature. The reaction mixture was diluted with dichloromethane (30 mL) and consecutively washed with 1M HCl, saturated NaHCO₃ solution and water (20 mL of each). The combined extracts were dried (Na₂SO₄) and evaporated to give an oily residue. The crude product was crystallized from hexane. — Yield: 723 mg (61%). mp. 107-109 °C. *R*_f [A] = 0.58, *R*_f [B] = 0.75. ¹H-NMR (CDCl₃) δ 1.22 (t, *J* = 7.1 Hz, 3H, CH₃CH₂O), 1.79 (pent, *J* = 6.8 Hz, 2H, 3-CH₂), 2.17 (t, *J* = 6.9 Hz, 2H, 2-CH₂), 2.82 (t, *J* = 7.1 Hz, 2H, PhCH₂CH₂), 3.17 (dd, *J* = 5.8, 11.8 Hz, 2H, 4-CH₂), 3.51 (dd, *J* = 7.0, 13.0 Hz, 2H, PhCH₂CH₂), 4.09 (q, *J* = 7.1 Hz, 2H, CH₃CH₂O), 4.92 (br s, 1H, NH), 6.08 (br s, 1H, NH), 6.89-7.27 (m, 5H, PhCH₂CH₂). ¹³C-NMR (CDCl₃) δ = 14.6 (CH₃CH₂O), 26.2 (C-3), 33.5 (C-2), 35.3 (PhCH₂CH₂), 40.0 (C-4), 40.4 (PhCH₂CH₂), 60.8 (CH₃CH₂O), 113.3 (d, ²*J*_{C,F} = 21 Hz, Ph-C4), 115.5 (d, ²*J*_{C,F} = 20.9 Hz, Ph-C2), 124.3 (d, ⁴*J*_{C,F} = 2.7 Hz, Ph-C6), 129.9 (d, ³*J*_{C,F} = 8.3 Hz, Ph-C5), 141.4 (d, ³*J*_{C,F} = 7.2 Hz, Ph-C1), 157.2 (NHCOOEt), 162.9 (d, ¹*J*_{C,F} = 245.7 Hz, Ph-C3), 172.6 (CH₂CONH). — ¹⁹F-NMR (CDCl₃): δ = -113.3 — C₁₅H₂₁FN₂O₃ (296.34).

[3-[2-(3-Bromophenyl)-ethylcarbamoyl]-propyl]-carbamic acid ethyl ester (14, 3-bromophenethyl-Santacruzamate A)

14 was prepared from **12a** (1.9 g, 10.8 mmol) and 3-bromophenethylamine according to the procedure described for compound **10**. — Yield: 2.89 g (75 %) — mp. 107-109 °C — *R*_f [A] = 0.58, *R*_f [B] = 0.07, *R*_f [C] = 0.75 — ¹H-NMR (CDCl₃) δ = 1.23 (t, *J* = 7.1 Hz, 3H, CH₃CH₂O), 1.79 (pent, *J* = 7.0 Hz, 2H, 3-CH₂), 2.18 (t, *J* = 6.9 Hz, 2H, 2-CH₂), 2.80 (t, *J* = 7.1 Hz, 2H, PhCH₂CH₂), 3.17 (br m, 2H, 4-CH₂), 3.50 (dd, *J* = 7.0, 13.0 Hz, 2H, PhCH₂CH₂), 4.09 (q, *J* = 7.1 Hz, 2H, CH₃CH₂O), 4.90 (br s, 1H, NH), 6.12 (br s, 1H, NH), 7.12-7.36 (m, 5H, PhCH₂CH₂). — ¹³C-NMR (CDCl₃) δ = 14.6 (CH₃CH₂O), 26.3 (C-3), 33.5 (C-2), 35.2 (PhCH₂CH₂), 40.0 (C-4), 40.4 (PhCH₂CH₂), 60.8 (CH₃CH₂O), 122.5 (Ph-C3), 127.4 (Ph-C6), 129.6 (Ph-C4), 130.1 (Ph-C5), 131.8 (Ph-C2), 141.3 (Ph-C1), 157.2 (NHCOOEt), 172.6 (CH₂CONH). — C₁₅H₂₁BrN₂O₃ (357.24).

2-(2-Pyridinyl)-2-nitrobenzenesulfonanilide [33]

The free base of 2-(2-pyridinyl)aniline (CAS RN: [29528-30-1]) was liberated from its dihydrochloride salt (1.5 g, 6.17 mmol, CAS RN: 18471-73-3). Yield: 1.05 g (quant). 2-(2-pyridinyl)aniline (1.05 g, 6.17 mmol) was dissolved in anhydrous dichloromethane (10 mL) under argon. The solution was cooled down to 0 °C and pyridine (2 mL) was added. 2-Nitrobenzenesulfonylchloride (2.7 g, 12.1 mmol) was given and the mixture was stirred for 2 h at room temperature. The reaction mixture was poured on to water (40 mL) and the resulting suspension was extracted with dichloromethane (3 x 50 mL). The combined organic layer was washed with brine (50 mL) and dried (Na₂SO₄). The solvent was removed under diminished pressure to yield a yellowish oily residue (ca. 3.39 g). The crude product was

purified by column chromatography on silica gel (Kieselgel: 100 g, eluent: hexane-ethyl acetate 7:3 (v/v), fractions: 50 mL). The purified product (1.89 g) was crystallized from diethyl-ether (25 mL). Yield: 1.35 g (61 %). — R_f [B] = 0.47, R_f [D] = 0.23. — $^1\text{H-NMR}$ (CDCl_3) δ = 7.18 (dt, J = 7.7 Hz, 1.1 Hz, 1H), 7.24 (ddd, J = 7.5 Hz, 7.5 Hz, 1.0 Hz, 1H), 7.37 (dt, J = 7.7 Hz, 1.4 Hz, 1H), 7.51-7.62 (m, 5H), 7.73 (dt, J = 7.8 Hz, 1.8 Hz, 1H), 7.81 (dd, J = 8.3 Hz, 0.9 Hz, 1H), 7.92 (dd, J = 7.6 Hz, 1.5 Hz, 1H), 8.72 (dd, J = 4.9 Hz, 0.9 Hz, 1H), 13.0 (br s, 1H). — $^{13}\text{C-NMR}$ (CDCl_3) δ = 121.6, 121.7, 122.1, 124.5, 124.7, 126.8, 128.8, 130.1, 130.7, 131.9, 133.2, 133.3, 136.1, 137.6, 147.7, 156.6. — $\text{C}_{17}\text{H}_{13}\text{N}_3\text{O}_4\text{S}$ (355.37).

**[2-(2-Pyridinyl)phenyl-2-nitrobenzenesulfonamide]
silver(I) (17, CAS RN: [1403599-78-9]) [33]**

Silver(I) oxide (410 mg, 1.75 mmol) was suspended in dry acetonitrile (7 mL) under argon atmosphere. A solution of 2-(2-pyridinyl)phenyl-2-nitrobenzenesulfonamide (1.25 g, 3.5 mmol) in dry acetonitrile (10 mL) was added dropwise at room temperature. The reaction mixture was stirred at 65 °C for 16 h. The mixture was filtered and the filtrate was evaporated to dryness. Dry hexane (60 mL) was added to the residue and the precipitated product was filtered off. The product was dried *in vacuo*. Yield: 1.45 g (89 %). — $^1\text{H-NMR}$ (CDCl_3) δ = 6.73 (d, J = 7.0 Hz, 1H), 6.86 (d, J = 6.8 Hz, 1H), 7.08 (d, J = 7.0 Hz, 1H), 7.2 (t, J = 7.3 Hz, 1H), 7.25-7.31 (m, 3H), 7.35-7.38 (m, 1H), 7.43-7.48 (m, 3H), 8.61 (br s, 1H). — $\text{C}_{17}\text{H}_{12}\text{AgN}_3\text{O}_4\text{S}$ (462.23).

**Nickel [3-[2-(3-substituted-phenyl)-ethylcarbamoyl]-propyl]-
carbamic acid ethyl ester] bromide complex (15)**

[3-[2-(3-Bromophenyl)-ethylcarbamoyl]-propyl]-carbamic acid ethyl ester (**14**, 512 mg, 1.43 mmol) was dissolved in dry toluene (16 mL) under argon. TMEDA (0.22 mL, 1.43 mmol) and $\text{Ni}(\text{COD})_2$ were added consecutively and the reaction mixture was stirred at room temperature for 16 h. Pentane (64 mL) was added and the mixture was stirred for 15 min at RT. The precipitated solid was filtered and dried *in vacuo*. Yield: 619 mg (81 %) as beige solid — $^1\text{H-NMR}$ and $^{13}\text{C-NMR}$ spectra were not obtained due to the low solubility of the product.

**Nickel [3-[2-(3-substituted-phenyl)-ethylcarbamoyl]-propyl]-
carbamic acid ethyl ester] complex (16, 3-(Phenethyl-
Santacruzamate A)-nickel aryl complex)**

To a mixture of [2-(2-Pyridinyl)phenyl-2-nitrobenzenesulfonamide]silver(I) (**17**, 227 mg, 0.49 mmol, 1 equiv) and the nickel aryl bromide complex **15** (260 mg, 0.49 mmol, 1 equiv) a solution of dry pyridine was added (79 μL , 0.98 mmol, 2 equiv) in dry toluene (4 mL) under argon atmosphere. Dry acetonitrile (1 mL) was added and the mixture stirred at ambient temperature for 3 min. Thereafter, the solution was filtered and the cake was washed with dry dichloromethane (3 x 5 mL). The solvent was evaporated *in vacuo* and the residue was redissolved in dry dichloromethane (8 mL). The solution was filtered through Celite (ca. 2 g) and the filtrate was concentrated *in vacuo*. The residue was dissolved in dry dichloromethane (3 mL) under argon and *n*-pentane (17 mL) was given. The mixture was stirred at room temperature and the precipitate was filtered off (under argon

atmosphere). The product was washed with pentane (3 x 5 mL) and dried *in vacuo*. Yield: 328 mg (87 %) as yellow solid —

$^1\text{H-NMR}$ (CDCl_3) δ = 1.23 (t, J = 7.0 Hz, 3H, $\text{CH}_3\text{CH}_2\text{O}$), 1.79 (pent, J = 7.0 Hz, 2H, 3- CH_2), 2.17 (t, J = 7.0 Hz, 2H, 2- CH_2), 2.80 (t, J = 7.0 Hz, 2H, PhCH_2CH_2), 3.18 (dd, J = 12.6 Hz, 6.2 Hz, 2H, 4- CH_2), 3.50 (dd, J = 13.0 Hz, 7.0 Hz, 2H, PhCH_2CH_2), 4.09 (q, J = 7.0 Hz, 2H, $\text{CH}_3\text{CH}_2\text{O}$), 4.90 (br s, 1H, NH), 6.08 (br s, 1H, NH), 6.77 (d, J = 7.3 Hz, 1H), 6.97 (d, J = 7.5 Hz, 1H), 7.09 (d, J = 7.3 Hz, 1H), 7.12-7.18 (m, 3H, PhCH_2CH_2), 7.24-7.32 (m, 5H), 7.34-7.36 (m, 2H, PhCH_2CH_2), 7.37-7.39 (m, 1H), 7.42-7.50 (m, 4H), 7.69 (br t, 1H), 8.57-8.60 (m, 2H). — $^{13}\text{C-NMR}$ (CDCl_3) δ = 14.6 ($\text{CH}_3\text{CH}_2\text{O}$), 26.3 (C-3), 33.6 (C-2), 35.3 (PhCH_2CH_2), 40.0 (C-4), 40.4 (PhCH_2CH_2), 60.8 ($\text{CH}_3\text{CH}_2\text{O}$), 122.4, 122.5 (Ph-C-3), 123.1, 123.8, 124.6, 126.0, 127.4 (Ph-C-6), 129.6 (Ph-C-4), 129.7, 130.1 (Ph-C-5), 130.3, 130.4, 130.5, 130.6, 130.7, 131.8 (Ph-C-2), 136.1, 137.0, 137.6, 138.1, 141.3 (Ph-C1), 143.1, 147.6, 150.0, 150.4, 157.2 (NHCOOEt), 161.1, 172.5 (CH_2CONH). — $\text{C}_{37}\text{H}_{38}\text{N}_6\text{NiO}_7\text{S}$ (769.49).

Synthesis of the Hypervalent Iodine Oxidant [33, 42]

**1,1'-(Phenyl- λ^3 -iodanediyl)-bis(4-methoxypyridinium)-
bis(trifluoromethanesulfonate) (18)**

18 was synthesized according to the procedure of Weiß and Seubert [42]. All operations were carried out in a dry reaction vessel in anhydrous solvent under argon atmosphere. (Diacetoxyiodo)benzene (3.0 g, 9.3 mmol) was dissolved in dichloromethane (100 mL) under argon atmosphere. Trimethylsilyl trifluoromethanesulfonate (3.4 mL, 18.6 mmol) was added dropwise to this solution at ambient temperature. A solution of 4-methoxypyridine (1.9 mL, 2.03 g, 18.6 mmol) in dichloromethane (15 mL) was dropped in and the reaction mixture was stirred for 15 min at room temperature. The solvent was removed under diminished pressure and anhydrous diethyl ether (100 mL) was given to the residue. The mixture was stirred for 1 h under argon, the precipitated solid was filtered off and washed with dry diethyl ether (40 mL). The product was dried *in vacuo* (3×10^{-1} mbar, 16 h). Yield: 6.06 g (90 %) off white solid. — $^1\text{H-NMR}$ (CD_3CN) δ = 4.04 (s, 6H, 2 x OCH_3), 7.30 (d, J = 6.5 Hz, 4H, H-3,5 pyridine), 7.36 (t, J = Hz, 7.5 H, H-2,6 Ph), 7.56 (t, J = 7.5 Hz, 1H, H-4 Ph), 7.85 (d, J = Hz, 2H, H-3,5 Ph), 8.43 (d, J = 7.5 Hz, 4H, H-2,6 pyridine). — $^{13}\text{C-NMR}$ (CDCl_3) δ = 58.9 (OCH_3), 94.8 (C-1 Ph), 114.0 (C-3,5 pyridine), 122.1 (q, $J_{\text{C,F}}$ = 320.7 Hz, CF_3SO_3), 128.8 (C-4 Ph), 131.6 (C-3,5 Ph), 138.5 (C-2,6 Ph), 144.0 (C-2,6 pyridine), 173.8 (C-4 pyridine). — $^{19}\text{F-NMR}$ (CDCl_3): δ = - 79.3 — $\text{C}_{20}\text{H}_{19}\text{F}_6\text{IN}_2\text{O}_8\text{S}_2$ (720.40).

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's web site along with the published article.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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