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Article

Development of Noncovalent Small-Molecule Keap1-Nrf2 Inhibitors by Fragment-Based Drug Discovery

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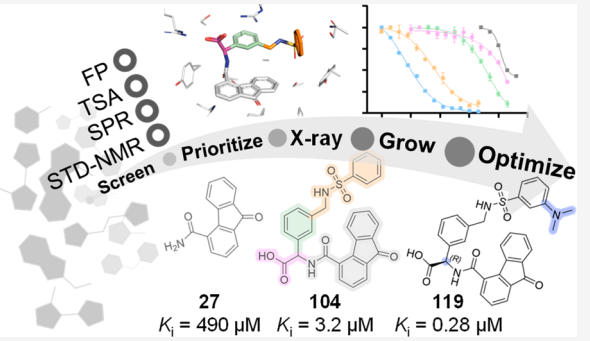
ABSTRACT: Targeting the protein−protein interaction (PPI) between the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) and its repressor, Kelch-like ECH-associated protein 1 (Keap1), constitutes a promising strategy for treating diseases involving oxidative stress and inflammation. Here, a fragment-based drug discovery (FBDD) campaign resulted in novel, high-affinity (K_i = 280 nM), and cell-active noncovalent small-molecule Keap1-Nrf2 PPI inhibitors. We screened 2500 fragments using orthogonal assays—fluorescence polarization (FP), thermal shift assay (TSA), and surface plasmon resonance (SPR)—and validated the hits by saturation transfer difference (STD) NMR, leading to 28 high-priority hits. Thirteen co-structures showed fragments binding mainly in the P4 and P5 subpockets of Keap1's Kelch domain, and three fluorenone-based fragments featuring a novel binding mode were optimized by structure-based drug discovery. We thereby disclose several fragment hits, including their binding modes, and show how FBDD can be performed to find new small-molecule Keap1-Nrf2 PPI inhibitors.



INTRODUCTION

Reactive oxygen species (ROS) generated in low levels during cellular homeostasis are neutralized by endogenous antioxidants and neutralizing enzymes. Several disease conditions, however, lead to ROS amounts exceeding the capacity of these endogenous defense molecules, which result in oxidative stress.[1−3]

The protein−protein interaction (PPI) between the transcription factor nuclear erythroid-related factor 2 (Nrf2) and the Kelch domain of Kelch-like ECH-associated protein 1 (Keap1) is central in the cellular adaptive response to fluctuating levels of ROS and exogenous electrophiles. Keap1 is a substrate adaptor protein and component of the cullin 3 E3 ubiquitin ligase complex that recognizes and ubiquitinates Nrf2, marking it for proteasomal degradation.[4,5] However, when ROS levels increase, key sensor cysteine residues on the broad complex, tramtrack, and bric-à-brac (BTB) domain and intervening region (IVR) of Keap1 are modified, which leads to a conformational change in Keap1 that prevents cullin 3-mediated ubiquitination.[6−8] This results in cytosolic accumulation of Nrf2 followed by translocation into the nucleus, where Nrf2 forms a transcription factor complex that induces expression of detoxifying antioxidant enzymes, such as NAD(P)H:quinone oxidoreductase 1 (NQO1), heme oxygenase 1 (HO-1), and glutathione reductase, and suppresses pro-inflammatory genes.[9−11]

Pharmacological inhibition of the Keap1-Nrf2 PPI has emerged as a promising therapeutic strategy to alleviate oxidative stress and reduce inflammation in pathologies as diverse as CNS injuries and neurodegenerative disorders,[12−16] chronic obstructive pulmonary disease (COPD),[17] metabolic kidney and liver conditions,[11,18,19] and some cancer types.[11] Electrophilic Keap1-Nrf2 inhibitors, which covalently bind the sensor cysteines of Keap1, have been thoroughly explored and are often effective in enhancing the antioxidant defense response.[11,19] A prominent example is dimethyl fumarate (Tecfidera),[20] which is clinically used against multiple sclerosis and psoriasis. However, unspecific reactivity of covalent binders can lead to toxicity and uncertainties about the mode of action.[21,22] An alternative and perhaps more attractive strategy employs noncovalent reversible Keap1-Nrf2 PPI

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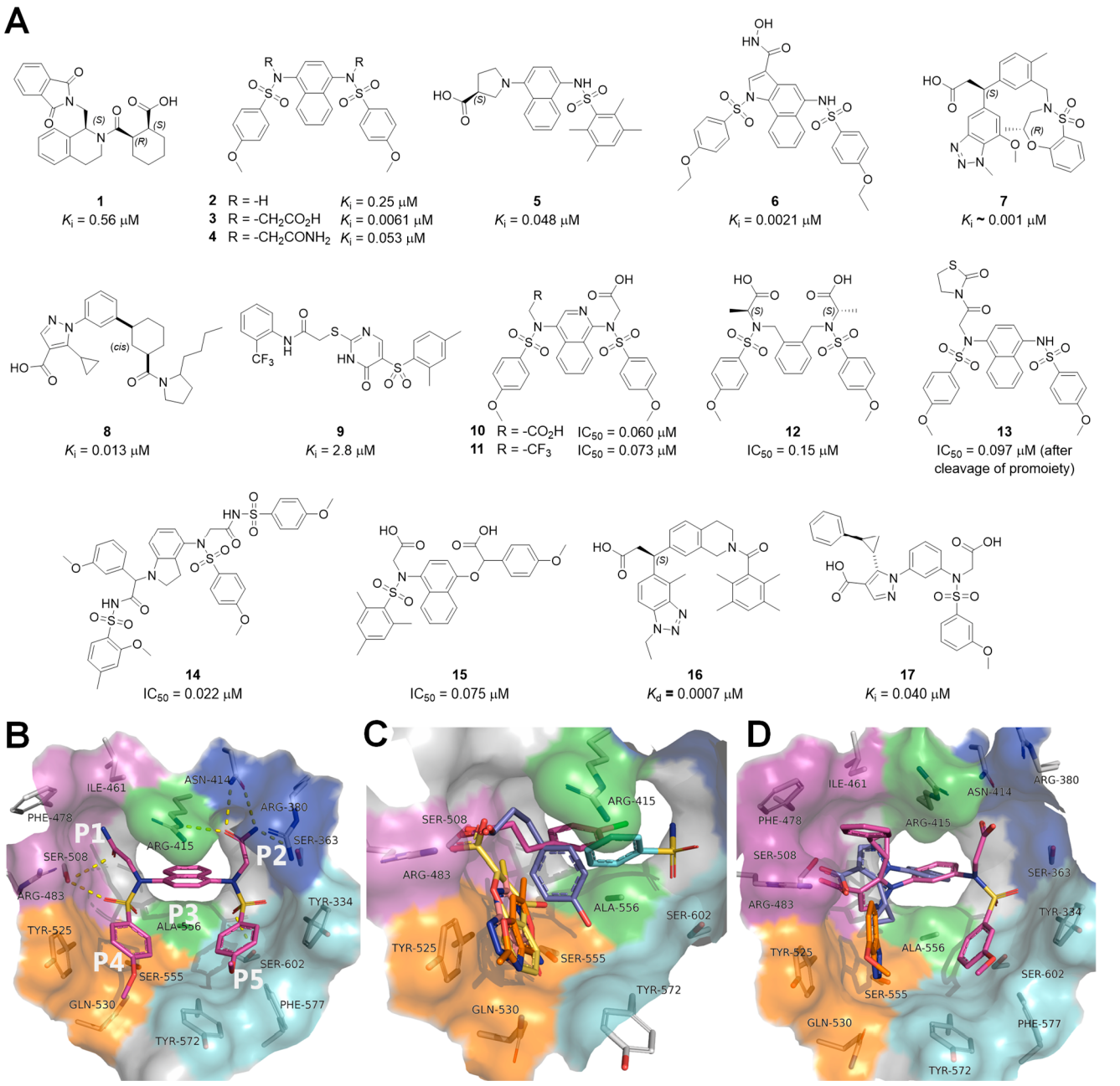

Figure 1. (A) Structures and activities of known noncovalent small-molecule Keap1-Nrf2 PPI inhibitors. For **1**–**9**, FP K_i values are from a previous comparative assessment study of known Keap1 inhibitors.[24] (B) Structure of the Keap1 Kelch domain in complex with compound **4** (PDB ID 4XMB)[29] including indication of the P1–P5 subpockets. (C) Keap1 Kelch domain in complex with three fragments found by X-ray crystallographic screening (PDB IDs 5FNQ, 5FZJ, and 5FZN)[17] and three fragments identified by FP and TSA screening (PDB IDs 5WHO, 5WHL, and 5WIY).[49] (D) Keap1 Kelch domain in complex with two fragments identified by FBDR and compound **17** derived from one of the fragments (PDB IDs 6ZEW, 6ZEX, and 6ZF8).[35]

inhibitors. These bind the Keap1 Kelch domain and displace Nrf2 either partly or fully from Keap1, hence allowing Nrf2 to escape proteasomal degradation.[8] Such inhibitors could provide specific, less toxic, and potent chemical probes and drug leads.[6,11,23] Recently, we assessed and compared the activity of representatives of all small-molecule noncovalent reversible Keap1-Nrf2 inhibitors known from literature and patents.[24] Nine compounds (**1**,[25,26] **2**,[27] **3**,[28] **4**,[29] **5**,[30,31] **6**,[32] **7**,[17] **8**,[33,34] and **9**;[27] Figure 1A) showed robust activities in three orthogonal biochemical and biophysical assays—fluorescence polarization (FP), thermal shift assay (TSA), and surface plasmon resonance (SPR). Further, **1**–**3** and **5**–**8** were able to induce NQO1 enzyme activity in a cell assay,[24] and several of them (**1**, **2**, **4**, **5**, **7**–**9**) have previously been confirmed by X-ray crystallography to bind the Kelch domain.[6,35] However, many of the mentioned compounds have suboptimal properties, such as low affinity (**1**, **2**, and **9**), low solubility (**2**,[36] **4**,[36] and **6**[32]), mutagenic activity (**3**[36]), low metabolic stability (**2**,[36] **3**,[37] **4**,[36] **5**,[30] and **8**[35]), or low bioavailability and high clearance (**7**[17]). Also, their size (molecular weight and total polar surface area), number of hydrogen bond donors, and inclusion of carboxylic acids prevent brain permeability and thus limit their use as chemical probes for investigating CNS diseases.[6] These properties are

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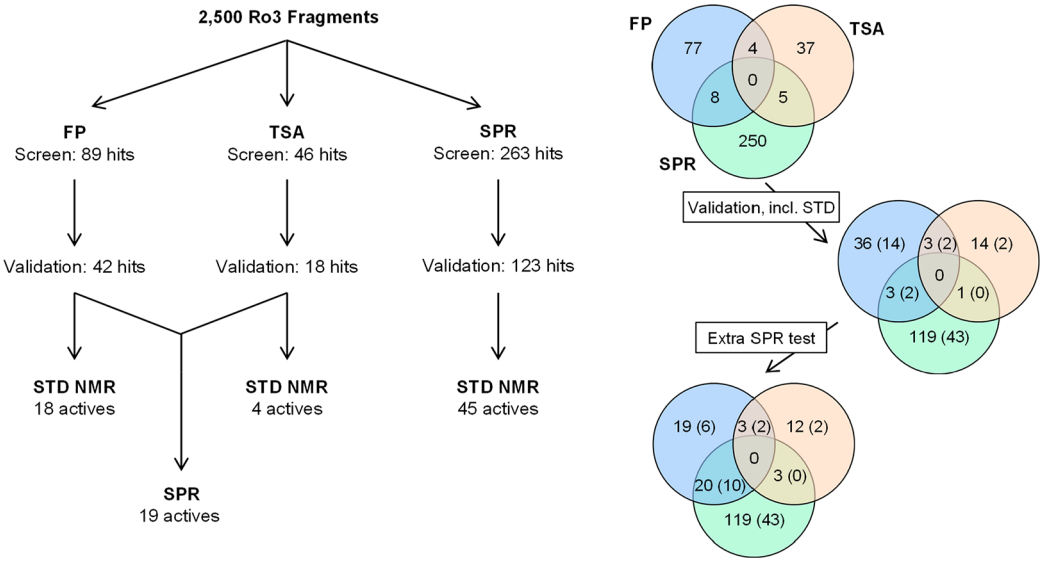

Figure 2. Screening cascade (left) and Venn diagrams (right) of our fragment-screening campaign against the Keap1 Kelch domain. Top Venn diagram shows primary hits, middle one shows hits after validation with number of STD actives in parentheses, and lowest Venn diagram shows final distribution of hits across the assays.

likely a result of the nature of the Keap1 Kelch binding pocket, as, to obtain high affinity, it appears that both the polar arginine-containing subpockets (P1 and/or P2) and the hydrophobic subpockets (P4 and/or P5) need to be occupied (Figure 1B), generally leading to large and charged compounds.[6,11,28,38] Still, optimization and new discoveries have led to Keap1-Nrf2 inhibitors with reduced mutagenicity (**10**),[36] good metabolic stability (**10**–**15**),[36,37,39−42] and even improved oral bioavailability (**13** and **16**;[40,43] Figure 1A). The Keap1 pharmacology toolbox now also includes macrocycles derived from natural products[44] and peptides,[45] and recently, proteolysis targeting chimeras (PROTACs) that use Keap1 as the E3 ligase were developed based on compound **7**.[46]

Fragment-based drug discovery (FBDD) has in recent years become a state-of-the-art strategy for the development of high-quality chemical probes and clinical candidates.[47,48] Previously, FBDD has been used to make **7** after screening 330 fragments by X-ray crystallography that identified three hits binding in the Keap1 Kelch pocket.[17] Another study identified three fragments in the Kelch domain after soaking 11 fragment hits found by FP and TSA screening of 458 fragments.[49] These six fragments bind to hot spots corresponding to the P1, P4, and P5 subpockets (Figure 1C). Recently, we conducted a fragment-based deconstruction reconstruction (FBDR) study and identified six fragments among a 77-membered target-biased fragment library, which bound in P1, P4, and P3/P5. This led to the development of compound **17** (Figure 1A,D) showing nanomolar inhibition of the Keap1-Nrf2 PPI and good microsomal stability, but low permeability over an artificial membrane.[35]

In this work, we investigated first if a larger and commercial library of 2500 fragments screened by biochemical and biophysical assays could provide hits against Keap1, and second if these hits could be optimized by structure-based drug design into new Keap1-Nrf2 inhibitors. This led to several well-characterized fragment hits, some of which featured novel binding modes in the Keap1 Kelch domain, as elucidated by X-ray crystallography. Our fragment-to-lead (F2L) efforts led to a 1700-fold improvement in affinity, producing potent lead compounds that exploit new parts of the Keap1 binding pocket and can be used for further development of drug-like Keap1-Nrf2 PPI inhibitors.

RESULTS

Fragment Screening and Validation. A library of 2500 rule of 3 (Ro3)-compliant fragments[50] was screened for binding to the Keap1 Kelch domain in three assays—FP, TSA, and SPR—each followed by a validation step. These orthogonal assays measure the ability of the fragments to inhibit the Keap1-Nrf2 PPI (FP), stabilize the Kelch domain as a proxy for protein binding (TSA), and directly bind to the Keap1 Kelch domain (SPR). The assays have previously been established and validated during our comparative assessment of known Keap1-Nrf2 inhibitors and in our FBDR study.[24,35]

In the FP competition assay, fragments were screened at 2 mM (2% DMSO) using the Cy5-labeled 9-mer Nrf2 peptide (Cy5-LDEETGEFL-NH_2)[51] as a probe. A short 7-mer Nrf2 peptide (Ac-LDEETGE-OH) was used as a control to assess the stability of the assay throughout the screening. Hits were defined as fragments giving FP values below the average value of negative control wells (2% DMSO) minus three standard deviations (SD) of the same wells within the given 384-well plate and which simultaneously did not change total fluorescence intensity (FLINT) values by 30% of control wells. This hit-threshold corresponded to a reduction of 5−10 mP out of an assay window of 80−90 mP and resulted in 89 primary hits. These hits were next validated in a series of counter-tests including dose−response experiments (0.25−8 mM, 8% DMSO, Cy5-labeled probe) in the absence and presence of 0.01% Triton-X to exclude aggregation-based promiscuous inhibitors.[52] Also, the FLINT were assessed, and the fragments were tested in the absence of Keap1 and by using a FAM-labeled probe (FAM-LDEETGEFL-NH_2) to remove false-positives due to fluorescence inner-filter effects.[53−55] This resulted in 42 validated hits and thus a hit-rate of 1.7% (Figure 2). Out of the 42 hits, 18 did not show any problematic properties in the counter-tests, while 24 had some issues on one or two parameters, e.g., low reduction in

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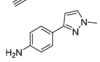
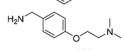
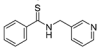
Table 1. Validation Data of High-Priority Fragment Hits[a]

Cmpd	Structure	FP[b] K_i/mM (LE)	TSA[c] ΔT_m @ mM/°C	SPR[d] K_d/mM (LE)	STD NMR[e] STD% @ 1 mM	X-ray[f] Cat. 1/2 PDB ID Subpocket
18		2.6 (0.27)	-	1.8 (0.29)	1.8	1 7OFD P5
19		-	-	3.3 (0.26)	8.3	-
20		-	-	0.85 (0.47)	2.5	2 P2/5
21		-	-	0.90 (0.35)	1.3	-
22		3.4 (0.24)	-	0.84 (0.30)	5.9	-
23		-	-	1.0 (0.27)	1.6	2 P5
24		-	-	0.084 (0.51)	-	2 outside
25		-	-	1.6 (0.27)	1.8	2 P5
26		-	-	1.8 (0.31)	1.7	2 outside
27		0.49 (0.27)	-	0.79 (0.25)	6.1	-
28		-	-	1.1 (0.31)	-	-
29		-	-	1.0 (0.32)	1.2	-
30		-	-	1.7 (0.27)	1.7	-
31		3.3 (0.24)	-	1.2 (0.29)	2.8	-
32		-	-	1.2 (0.29)	1.6	-
33		-	-	1.8 (0.23)	7.7	-
34		2.3 (0.30)	-	0.48 (0.38)	1.8	-
35		-	-	0.56 (0.40)	-	-
36		3.2 (0.21)	0.8 °C @ 4 mM 0.5 °C @ 2 mM 0.2 °C @ 1 mM	-	1.3	1 7OF8 P5
37		2.5 (0.30)	0.9 °C @ 4 mM 0.4 °C @ 2mM 0.4 °C @ 1mM	-	2.4	1 7OFA P1
38		-	-	0.30 (0.48)	3.3	-
39		-	-	0.90 (0.26)	-	2 P4/5
40		-	-	1.0 (0.27)	1.3	-
41		-	-	1.0 (0.37)	2.2	2 P4/5
42		-	-	0.60 (0.40)	-	-
43		-	-	0.82 (0.22)	1.6	1 7OFC P4/5
44		-	-	0.54 (0.21)	ND	1 7OFB P4/5
45		-	-	0.30 (0.44)	1.7	1 7OF9 P5

[a]Data from the validation step (n = 1) is shown for the 28 high-priority fragment hits. [b]K_i values using the Cy5-probe are shown. [c]TSA ΔT_m values are shown at effective concentrations. [d]SPR K_d values are based on steady-state affinity analysis of SPR sensorgrams (R_{max} was fixed to the value of a control peptide H-LDEETGEFL-OH when fitting). [e]STD NMR effects are shown as the highest obtained STD% value for a given signal ("ND": Not determined due to direct saturation of ligand signal in STD NMR). [f]X-ray crystallography data were divided into categories 1 and 2, according to the certainty of which the fragment could be modeled to its respective electron density. "−": Not a screening hit and thus not tested in the validation step. NB: **18**, **22**, **31**, and **34** were not primary SPR hits, but were characterized during the final SPR assessment step.

FP values (questionable activity) or FLINT levels at the border of defined criteria. However, these were still counted as hits in order not to miss potential genuine binders.

In TSA, 46 fragments induced a ΔT_m of at least 0.1 °C relative to the negative control when screened at 2 mM (2% DMSO) and were considered primary hits. This very low hit-threshold was chosen to limit the number of false-negatives, as it was observed that the exact ΔT_m value was sensitive to variations in DMSO/blank wells across the plate. Destabilizing fragments, giving negative ΔT_m values, were not considered. The primary hits were evaluated in a dose−response test (0.5−8 mM, 0.5−8% DMSO), which resulted in 18 validated hits (hit-rate of 0.7%) (Figure 2), where ΔT_m were above 2 × SD of the melting temperature (T_m) of the nearest DMSO wells for at least one test concentration. Ten of these 18 hits showed dose-dependent increments in ΔT_m in the range of 0.2−1.5 °C across 3−4 of the tested concentrations, while the remaining ones only showed effect at 1 or 2 concentrations.

In SPR, the fragments were injected in a OneStep concentration gradient[56,57] at 0.5 mM (2% DMSO) over immobilized Keap1 Kelch domain in a 384-well plate format. To discriminate true Keap1 binding events from nonspecific binding and bulk effects, the primary screen was followed by a counter-screen, where the running and ligand buffers contained 50 μM of the 9-mer Nrf2 peptide (Ac-LDEETGEFL-OH; K_d = 0.7 μM[24]). Thereby, the Keap1 Kelch domain binding pocket is blocked by the peptide, and fragment binding should be hindered leading to reduced response for true binders.[58,59] Hence, hits were defined as fragments inducing response levels ≥4 RU in the primary screen and having an S value ≥0.25, where S is a calculated metric based on the responses from the primary screen and the counter-screen;[58] S = 0.25 corresponds to a reduction in response level by 40%. This led to 263 primary hits. The large number of hits is likely a result of the high sensitivity of SPR, but artifacts such as aggregations or nonspecific events, which for some reason occurred only in the primary assay and not in the counter-screen where the peptide was present, could also contribute. Thus, to further validate the 263 primary hits they were tested in 2-fold serial dilutions (0.0625−1 mM, 4% DMSO) resulting in 123 fragments (hit-rate of 4.9%) showing a concentration dependent response for two or more injections (Figure 2). The remaining primary hits were discarded either due to weak binding, lack of concentration dependent binding, or odd sensorgrams indicating non-fragment-like binding.[58,60,61]

Considering the high number of hits collected from FP, TSA, and SPR at this point (Figure 2), we included two more hit assessment steps to further guide our hit prioritization. First, we tested all 176 validated hits by saturation transfer difference (STD) NMR (1 mM, 4% DMSO-d_6). Sixty-three fragments gave an STD% >1% (4 fragments giving >5%, and 12 fragments giving 2−5%), while 113 fragments showed negligible or no STD effects (Figure 2). Second, we characterized the 53 validated hits from FP and TSA that

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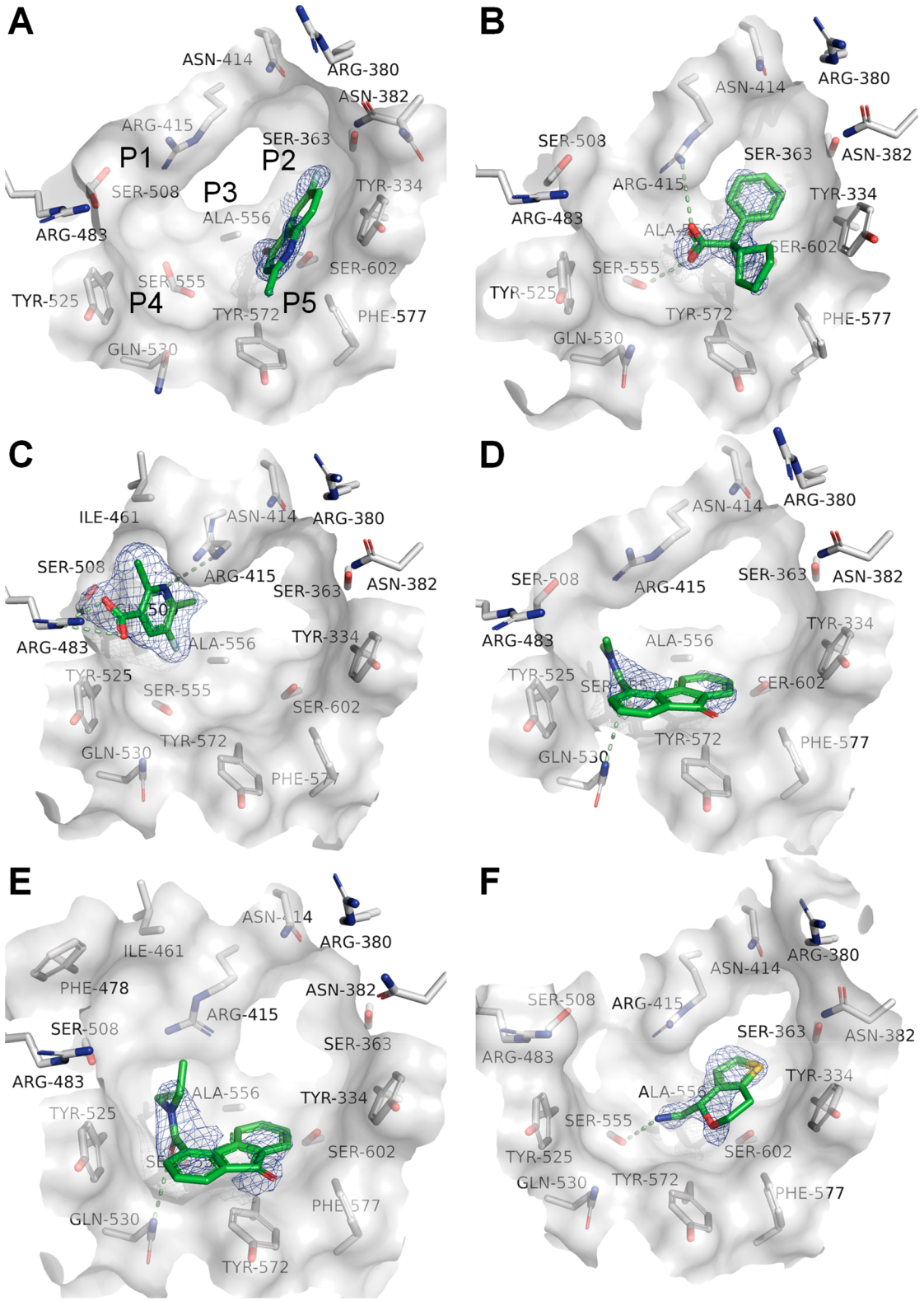

Figure 3. (A–F) X-ray crystal structures of **18** (PDB ID: 7OFD), **36** (PDB ID: 7OF8), **37** (PDB ID: 7OFA), **43** (PDB ID: 7OFC), **44** (PDB ID: 7OFB), and **45** (PDB ID: 7OF9) (green), respectively, in complex with the Keap1 Kelch domain (gray) with indication of the P1–P5 subpockets (A). Standard $2F_o - F_c$ electron density map carved around the fragments at 1.6 Å (blue) contoured at 1σ are shown.

were not picked up by the primary SPR screen, by SPR dose–response (0.125–2 mM, 4% DMSO) resulting in further 19 fragments (17 FP hits, 2 TSA hits) showing a concentration dependent response (Figure 2).

Overall, these efforts resulted in 176 well-characterized hits. In general, there was little overlap between the screening assays, as 99 hits (56%) were active in only one assay, 65 hits (37%) in two assays, 12 hits (7%) in three assays, and none were active in all four assays. This is often seen in fragment-

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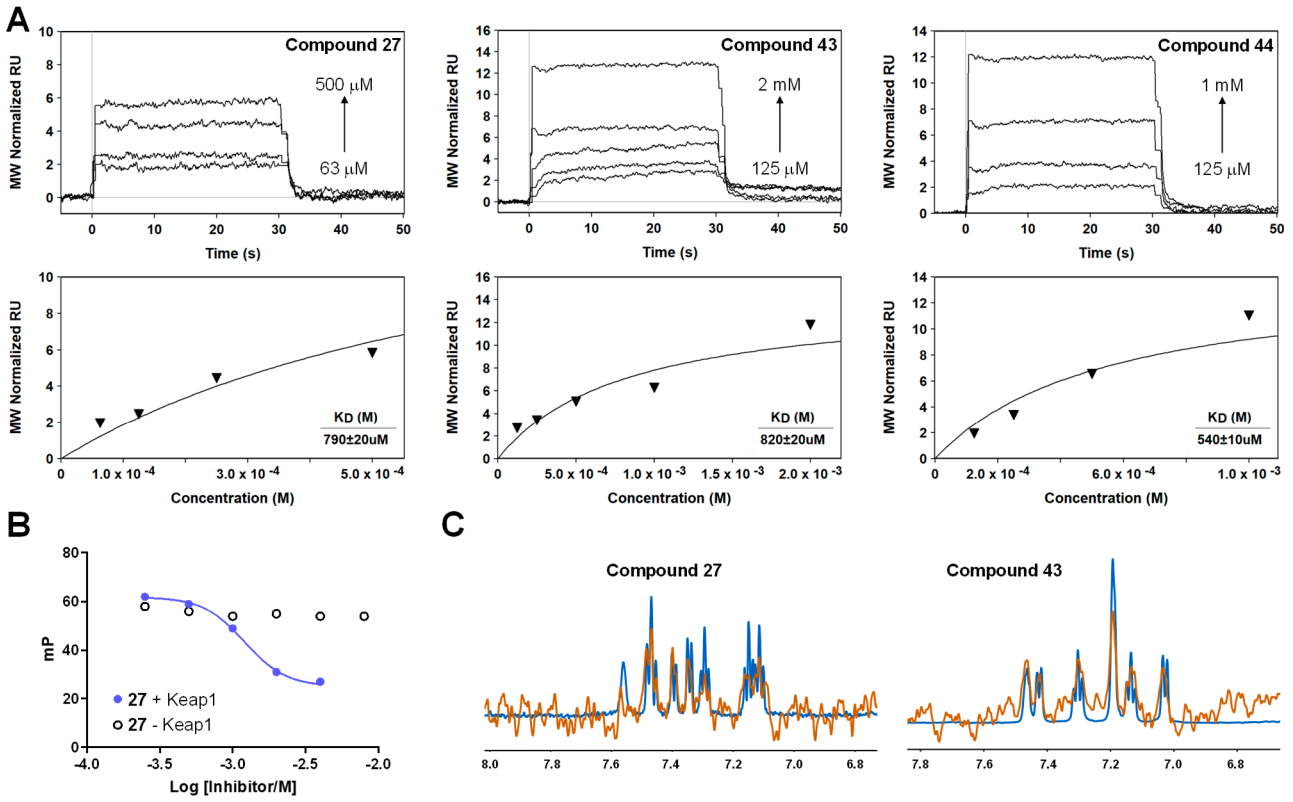

Figure 4. SPR, FP, and STD NMR assay data of fragment hits **27**, **43**, and **44** from the validation step demonstrating binding to the Keap1 Kelch domain. (A) SPR sensorgrams of **27**, **43**, and **44** injected in 2-fold serial dilutions over immobilized Keap1 Kelch, and plots of equilibrium binding responses against the injected concentrations (below). (B) FP concentration−response curve of **27** measured by using the Cy5-Nrf2 peptide probe; either in presence (test) or absence (counter-test) of Keap1. (C) STD NMR of **27** and **43**. ^{1}H 1D and STD NMR spectra (aromatic region of 6.8−8.0 ppm) are shown in blue and brown, respectively. The STD NMR spectra are scaled 16.4-fold for **27** and 64-fold for **43** for better comparison with the ^{1}H 1D NMR spectra and show clear STD signals for the compound peaks at 7.0−7.5 ppm. The scaling factors indicate STD effects of 6.1% and 1.6%, respectively, which was interpreted as evidence for binding. The regions outside 7.0−7.5 ppm illustrate the noise level and show no visible STD signal.

based screening and is likely due to the different sensitivities of the techniques, small variations in experimental conditions, and different read-out principles.[35,62−64] Most hits were found by SPR and fewest by TSA. STD NMR validated more SPR and FP hits (37% and 43%, respectively) than TSA hits (22%) (Figure 2). FP and TSA screening and validation identified 17 and two fragments, respectively, that were not identified as hits in the primary SPR assay, but still gave a concentration dependent response in the follow-up SPR step. This illustrates the value of applying orthogonal assays in order not to miss hits, particularly the FP assay in this case. Among these 19 hits, eight FP hits were also active by STD NMR.

Hit Prioritization. Due to the high number of validated hits, prioritization for subsequent X-ray crystallization was necessary. Fragments with activity in more than one assay and with SPR and STD NMR activity were preferred. Also, the quality of data was re-evaluated, particularly by inspecting if SPR sensorgrams indicated fragment-like behavior (e.g., fast on/off-rates and response level correlating with MW), dose-dependent activity (FP, TSA, SPR), and further taking into account results from the counter-assays (FP and SPR). Affinity and ligand efficiency (LE)[65] were considered when data were robust, and the chemical structures were evaluated for their synthetic feasibility and novelty in relation to the target. The exact STD NMR amplification factor was not emphasized in the prioritization, as a poor correlation with affinity has been reported.[66] This resulted in 28 "high-priority" fragments with measured affinities of 0.084 mM to 3.3 mM and LE values ranging from 0.21 to 0.51 (Table 1). Of these hits, only two were not validated by SPR, and six were not active by STD; instead, these showed good TSA activities (**36** and **37**) or SPR affinities (**24**, **28**, **35**, **39**, **42**, and **44**), respectively.

X-ray Crystallography of Prioritized Fragment Hits. The binding modes of the 28 high-priority hits were assessed using X-ray crystallography by soaking the fragments at 5−20 mM into crystals of the mouse Keap1 Kelch domain in 5−20% DMSO.[17,35] Co-crystal structures of 13 out of the 28 high-priority hits were obtained with good resolutions (Table 1 and Table S1). Six of these showed well-defined electron densities allowing an unambiguous placement of the fragments within the Kelch domain (Figure 3 and Figure S1) (category 1 fragments in Table 1). The electron densities of the remaining seven fragments did not completely cover the modeled fragment structures at standard sigma levels (1σ); thus, although binding to the Kelch domain of these fragments were confirmed by X-ray crystallography, their binding modes are determined with some uncertainty (Figure S1) (category 2 fragments in Table 1).

Six fragments were found in the P5 subpocket, i.e., **18**, **36**, **45**, **23**, and **25**, and they are observed to form close hydrophobic and/or $\pi-\pi$ interactions with the aromatic triad of Tyr334, Tyr572, and Phe577 (Figure 3 and Figure S1). Additionally, **18**, **36**, and **45** form hydrogen bond interactions with Ser602 and Ser555. Fragment **20** is located in proximity

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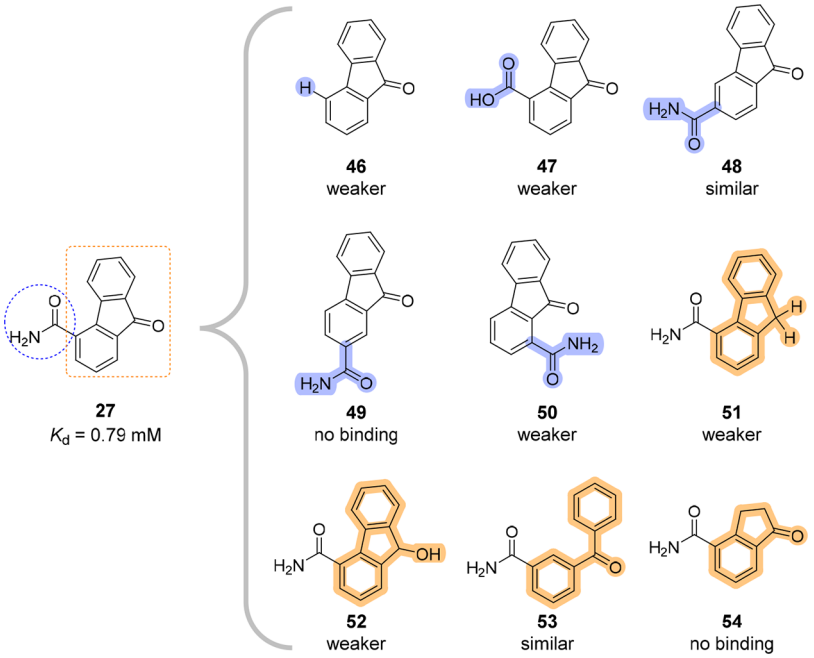

Figure 5. Initial SAR study of the fluorenone carboxamide fragments. This included replacement of the carboxamide substituent, a substituent walk and scaffold hopping of the fluorenone core. The analogues were assessed for affinity to the Keap1 Kelch domain by dose−response SPR tests. Due to the weak affinities, their activities were determined in a semi-quantitative manner and categorized as "similar" to or "weaker" than that of **27** based on response levels and concentration-dependent binding. Sensorgrams are shown in Figure S2.

of the P5 Tyr334, but at the border to P2 and with its methoxy group approaching Arg415 located between P1 and P2; this results in a small conformational change of the Arg415 side chain, which is known for its ligand-induced flexibility (Figure S1).[49] The acid-containing fragment **37** forms a salt-bridge with P1's Arg483, which often accommodates carboxylate groups from small-molecule as well as peptide ligands and is known to be energetically important.[6,29,49] The remaining part of **37** points toward the central cavity of the Keap1 Kelch domain forcing Arg415 to adopt an upward conformation (Figure 3). Fragments **24** and **26** were found to bind in an area close to the P1 Arg483, but outside the canonical binding site (Figure S1). This part of the Keap1 Kelch domain has not been exploited by any known designed or endogenous Keap1 ligands, but based on the high solvent exposure and distance to other important residues, the binding site of fragment **24** and **26** are likely not useful for further ligand optimization.

Finally, four fragments—**43**, **44**, **39**, and **41**—were seen in the area of P4/P5 (Figure 3 and Figure S1). Especially **43** and **44** displayed an interesting and novel binding pose centered around Tyr572 between P4 and P5. These fragments form close $\pi-\pi$ contacts to Tyr572 in a face-to-face orientation, while an edge-to-face interaction to Tyr525 in P4 was seen (Figure 3). This binding mode is in contrast to the published P4 binding fragments as these interact face-to-face with Tyr525 and point toward P1 (PDB IDs 5FZJ, 5WHO, 5WIY, and 6ZEW; Figure 1C,D), rather than edge-to-face with Tyr525 and pointing toward P5. Noticeably, both **43** and **44** form hydrogen bonds via their carbonyl groups to Gln530 and Ser555 (Figure 3).

Overall, among the 13 fragment−Keap1 co-structures obtained here, six fragments were revealed to bind in P5, one in P1, two outside the canonical binding pocket, and four in P4/P5. In contrast to previous fragment screening studies,[17,35,49] we here see a high number of fragments in the P5 subpocket thereby emphasizing this area as an important hot spot. Further, we elucidate a novel fragment binding mode, where two fragments were located along the P4/P5 subpocket and with face-to-face and edge-to-face stacking interactions to Tyr572 and Tyr525, respectively.

Structure−Activity Relationship (SAR) Study of Fluorenone Carboxamide Fragments. Three of the 28 high-priority hits shared the fluorenone carboxamide scaffold, i.e., **27**, **43**, and **44**. These showed about the same SPR affinities during validation (K_d = 0.5−0.8 mM; Table 1 and Figure 4), and the binding poses of **43** and **44** were very similar as determined by X-ray crystallography (Figure 3). Additionally, the fluorenone moiety is a hitherto unexplored chemotype in Keap1 literature, and **43** and **44** displayed a novel pose not adopted by any lead molecules or fragments reported thus far as described above. Based on these results and reflections, we considered this series of fragment hits to be a promising starting point for further optimization into novel inhibitors.

We commenced the SAR investigation on the fluorenone carboxamide fragments by performing small modifications on **27** to assess the importance of the functional groups and their spatial relationship (Figure 5 and Figure S2). The modified compounds (**46**−**54**) showed no apparent improvement in affinity by SPR dose−response tests and confirmed **27** to be the most optimal starting point within proximal chemical space.

We next turned to fragment growing. Based on the binding modes of **43** and **44**, the carboxamide constituted a potential vector for elaborating into the P1 subpocket and was thus chosen as the site of growing. Synthetically, this also meant analogues could easily be accessed via standard amide coupling protocols. We explored an extensive number of amide chains with various functional groups and lengths. We especially sampled acidic chains, since it is known from literature that a

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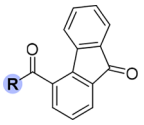
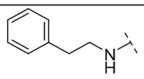
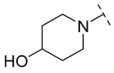
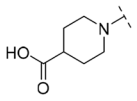
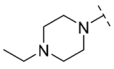
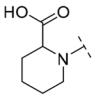
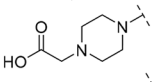
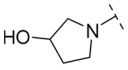
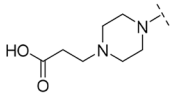
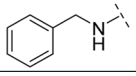
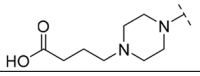
Table 2. SAR Study on the Fluorenone Carboxamide Fragments by Growing[a]



Cmpd	R	SPR (Relative activity)	Cmpd	R	SPR (Relative activity)
55	-NHCH$_3$	weaker	66		no binding
56	-NHCH$_2$CH$_3$	weaker	67[b]	-NHCH$_2$COOH	similar K_d = 220 ± 80 μM
57	-NHCH$_2$CH$_2$CH$_2$CH$_3$	no binding	68	-NHCH$_2$CH$_2$COOH	weaker
58	-NHCH(CH$_3$)$_2$	no binding	69	-NHCH$_2$CH$_2$CH$_2$COOH	no binding
59		similar K_d = 190 ± 40 μM	70	-NH(CH$_3$)CH$_2$COOH	weaker
60		weaker	71	-NH(CH$_3$)CH$_2$CH$_2$COOH	weaker
61		similar K_d = 310 ± 30 μM	72		weaker
62		similar K_d = 350 ± 20 μM	73		weaker
63		similar K_d = 350 ± 200 μM	74		similar K_d = 360 ± 10 μM
64		weaker	75		weaker
65		no binding	76		weaker

[a]The analogues were tested by SPR for affinity to the Keap1 Kelch domain by OneStep (0.5 mM, duplicates) or dose−response multicycle injections (2-fold serial dilutions at 7.8−250 μM; compounds **57**, **58**, **65**, and **69**). Due to the weak affinities of the analogues, their activities were first determined in a semi-quantitative manner and categorized as "similar" to or "weaker" than that of **27** based on response levels. K_d values were estimated for compounds with activities similar to **27** by fixing R_{max} to the value of the control peptide (H-LDEETGEFL-OH) and here reported based on the duplicate OneStep SPR data (mean ± SEM), in an experiment where **27** gave a K_d of 360 ± 30 μM in comparison. [b]X-ray structure available (Figure 6).

carboxylic acid is favorably sited in P1 forming multiple H-bonds and salt bridges with the donor duo of Arg483 and Ser508. Most of these growing analogues (compounds **55**−**76**) displayed weaker binding than **27**; however, **67** featuring a short carboxylic acid chain retained affinity according to SPR (Table 2). We obtained an X-ray crystal structure of **67** in complex with the Kelch domain, which revealed a conserved binding mode for the fragment core, while the carboxylic acid chain probed Ser508 and Arg415 but failed to reach Arg483 (Figure 6A and Figure S3A).

Most high-affinity Keap1 inhibitors (Figure 1) protrude an aromatic core into the central P3 subpocket, forcing Arg415 to adopt an upward conformation. Guided by the obtained X-ray structure, we decided to substitute the α position of the acidic chain of **67** with a phenyl ring to gain access to P3. The resulting compound **77** gratifyingly gave a significant 3.5-fold boost in affinity by FP compared to **67** (Table 3). We further obtained an X-ray crystal structure of **77** in complex with the Keap1 Kelch domain (Figure 6B and Figure S3B). This showed a conserved binding mode of the fragment core, further confirming the firmness of the fragment pose. Importantly, a conformational twist of the acidic chain was seen allowing the carboxylic acid to adopt the canonical interaction motif with Arg483 and Ser508 and the phenyl ring to protrude into P3, inducing the upward conformation of Arg415.

Hypothesizing that a variety of such acidic chains substituted with aromatic rings could be beneficial for binding, we systematically sampled these analogues by varying (1) the length of the acidic chain (1−3 spacing carbons between N and the carboxy group), (2) the regioisomery of the aryl substituent on the chain, and (3) the spacing of the aryl from the acidic chain (none or one methylene corresponding to a phenyl and benzyl chain substituent, respectively). Including **77**, this resulted in a series of 18 compounds (**77**−**94**), which we assessed by FP (Table 3). This revealed other analogues, which were equipotent with **77**, e.g., **83** and **89**. Interestingly, these three compounds had all different acidic linker lengths (from 1−3 carbons). Unfortunately, we were not able to obtain X-ray crystal structures of **83** and **89** in complex with the Keap1 Kelch domain. However, molecular docking of **89** and **83** gave very attractive-looking binding modes (Figure 6C), which could guide future optimizations. Here, however, we

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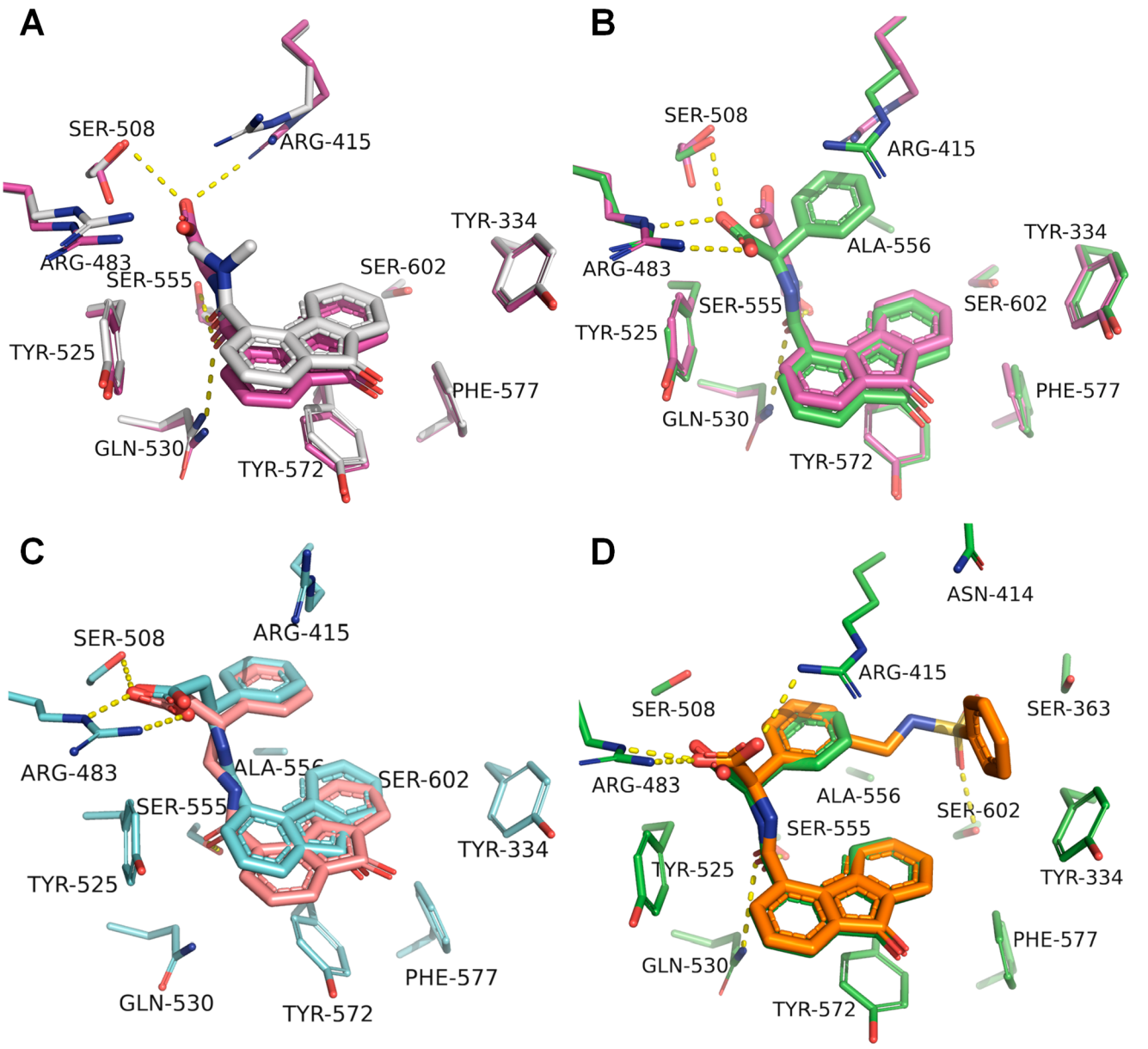

Figure 6. X-ray structures and docking poses of key analogues in the optimization process. (A) X-ray crystal structure of **67** (magenta) (PDB ID: 7OFE) and **43** (gray) in complex with the Keap1 Kelch domain. (B) X-ray structure of 77 (green) (PDB ID: 7OFF) and **67** (magenta) in complex with the Keap1 Kelch domain. (C) Docking pose of **83** (cyan) and **89** (salmon). (D) Docking pose of **104** (orange) and X-ray of 77 (green).

decided to prioritize 77 given its smaller size and the available co-structure.

Next, we installed substituents on the fluorenone core of 77 to probe residues in the P4 and P5 subpockets. Unfortunately, this resulted in significant losses in affinity, as seen for compounds **95**−**98** (Table 4), and we therefore decided not to pursue fluorenone substitution further. Instead, we pursued growing into the unoccupied right-hand side (P2/P5) of the Kelch binding pocket using the installed phenyl ring as a linker. Standard small modifications were performed to assess the steric and electronic demands in the *meta*- and *para*-positions, which X-ray crystallography and docking suggested to be the most feasible growth vectors. This gave modest improvements in affinity, and both the *meta*- and *para*-positions permitted bulky and lipophilic substituents (compounds **99**−**103**) (Table 4).

Inspired by literature compound motifs (Figure 1) and guided by molecular docking, we decided to substitute the phenyl ring of 77 with a phenylsulfonamidomethyl group in the *meta*-position. Gratifyingly, this resulted in a ∼70-fold improvement for **104** (compared to 77) displaying low micromolar affinity (K_i = 3.2 μM) in our FP assay (Table 4). LE is 0.19 and 0.20 for 77 and **104**, respectively, and was thus retained, indicating that the phenylsulfonamidomethyl group was indeed an efficient growth moiety. We were unable to obtain X-ray crystal structures of **104**, but docking showed a good fit at the right-hand side of the pocket (P5), with the sulfonamide forming H-bonds with Ser602 and Ser363, and the benzene engaging in aromatic interactions with Tyr334 (Figure 6D).

Incited by this result, we introduced various substituents on the aromatic ring placed in P5 focusing on electron-donating groups, as in compounds **105**−**111**, since such modifications

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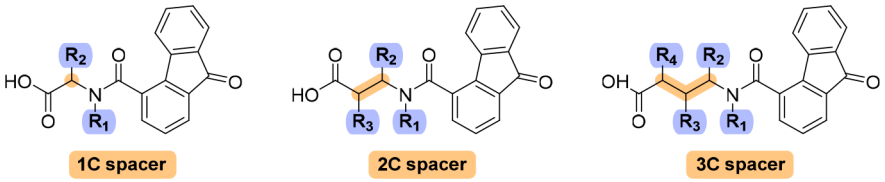
Table 3. Systematic Linker SAR of Fragment Analogue 77[a]



Cmpd	spacer	R_1	R_2	R_3	R_4	FP (K_i/μM)	Cmpd	spacer	R_1	R_2	R_3	R_4	FP (K_i/μM)
77[b]	1C	H	Ph	-	-	217 ± 43	**86**	2C	Bn	H	H	-	880 ± 130
78	1C	H	Bn	-	-	568 ± 14	**87**	3C	H	H	H	Ph	466 ± 45
79	1C	Ph	H	-	-	449 ± 120	**88**	3C	H	H	H	Bn	387 ± 60
80	1C	Bn	H	-	-	513 ± 71	**89**	3C	H	H	Ph	H	303 ± 55
81	2C	H	H	Ph	-	1960 ± 670	**90**	3C	H	H	Bn	H	333 ± 72
82	2C	H	H	Bn	-	296 ± 35	**91**	3C	H	Ph	H	H	1890 ± 250
83	2C	H	Ph	H	-	174 ± 19	**92**	3C	H	Bn	H	H	1040 ± 58
84	2C	H	Bn	H	-	1590 ± 14	**93**	3C	Ph	H	H	H	1930 ± 320
85	2C	Ph	H	H	-	1450 ± 360	**94**	3C	Bn	H	H	H	988 ± 63

[a]FP K_i values are shown as mean ± SEM based on ≥3 individual measurements using the Cy5-probe. [b]X-ray structure available (Figure 6). Compound **67** was tested for comparison and showed a K_i value of 754 ± 68 μM (see also Figure 8).

have previously led to enhanced affinities of Keap1 inhibitors.[29,35] The *para*- and *meta*-methoxy substituted compounds **106** and **107** were the best compounds in this series with a 3-fold improvement relative to **104** (K_i = 1.1 μM; Table 4). Compounds **112**−**114** were then made in an attempt to combine the favorable *para*-methoxy group on the aromatic ring placed in P5 with small lipophilic substituents at the aromatic core; however, this only led to impaired affinities (Table 4). Further exploration of the electron-donating effects around the P5-binding aromatic ring was done with compounds **115**−**118**, and both *ortho*- and *para*-dimethylamine substituents resulted in a further 2-fold affinity enhancement, as compounds **117** and **118** showed a K_i value of about 600 nM. Chiral HPLC provided the pure enantiomers of **118** (>99% ee; Figure S4). The K_i value of the first enantiomer (**119**) was determined to 281 nM, demonstrating a much higher affinity compared to the other enantiomer (**120**; K_i = 6.3 μM) and a 2-fold higher affinity relative to the racemate (**118**) (Table 4). We were not able to obtain a co-structure of **119** in complex with the Keap1 Kelch domain. Instead, molecular docking suggested that **119** and **120** were the *R*- and *S*-enantiomers of **118**, respectively (Figure S4). This correlates with the fact that it was the *R*-enantiomer of **77** that was observed in the co-structure with the Keap1 kelch domain after soaking **77** as a racemate (Figure 6B).

SPR binding curves for compounds **107** and **119** showed concentration-dependent responses and saturation at the highest concentrations at levels correlating with the MW of the compounds (Figure S5). The SPR measured K_d values were in range with the K_i values from FP. Thereby, SPR provided evidence for direct binding of **107** and **119** to the Keap1 Kelch domain.

Cellular Activity. We next evaluated our compounds for their ability to upregulate Nrf2-controlled genes in HaCaT human keratinocytes. 4-Octyl-itaconate (4-OI), which covalently binds Keap1 and activates Nrf2,[67,68] and the noncovalent high-affinity and membrane-permeable Keap1-Nrf2 inhibitor **8**[24,34,35] were included as positive controls. Quantitative real-time PCR (qPCR) revealed an increased transcription of HO-1 and NQO1 when cells were stimulated with **107**, **119**, and **8**. Compounds **107** and **8** also upregulated aldo-keto reductase family 1 member b10 (AKR1B10), and **8** stimulated transcription of thioredoxin reductase 1 (TXRT1) (Figure 7A). NQO1 and TXTR1 protein levels were increased for compounds **107** and **119**, while 4-OI and **8** also induced higher HO-1 expression as seen by Western Blot analysis (Figure 7B). The effects of **107** and **119** were smaller than for **8**, likely reflecting the high affinity and membrane permeability of **8**,[24,34,35] and a high concentration was used (200 μM). Importantly, none of the compounds showed any sign of cytotoxicity as evaluated visually (cf. morphology and cell attachment) and by measuring cleaved caspase 3 and PARP as markers for apoptosis (data not shown). Lastly, by comparing wild-type (WT) and Nrf2 knockout (KO) cells, it was observed that the compound-induced upregulation of Nrf2-controlled genes and corresponding proteins indeed depended on Nrf2 (Figure 7C−**D**).

Chemistry. The fragment hit **27** was obtained from commercial vendors via the screening library but was also synthesized and retested to verify its activity and provide sufficient quantities of material for further characterization. The fragment alongside many of the initial regioisomery and scaffold hopping analogues (i.e., **49**−**51** and **53**) were synthesized by amidating the corresponding acid chlorides, which were either commercially available or obtained from the carboxylic acids by treatment with thionyl chloride (Scheme 1). Other initial analogues were obtained through conventional chemical transformations: the alcohol analogue **52** was obtained through reduction of the ketone functionality of **27** with $NaBH_4$, and the truncated analogue **54** was obtained through base-catalyzed hydration of the corresponding nitrile (Scheme 1). The 3-carboxamide regioisomer **48** required *de novo* fluorenone synthesis. This was carried out through a Suzuki−Miyaura cross-coupling to obtain the biphenyl dicarboxylic acid **48a**, which was subsequently subjected to a Friedel−Crafts-type ring closure to obtain the fluorenone carboxylic acid **48b** and amidated using the previous $SOCl_2$/NH_4OH amidation protocol to arrive at the target molecule **48** (Scheme 1).

The initial growing analogues **55**−**76** were readily synthesized, mostly by treating fluorenone-4-carbonyl chloride with various functionalized (optionally protected) amine building blocks, which were generally commercially available or obtained in a few synthetic steps (Scheme 1). In contrast,

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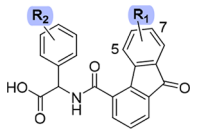
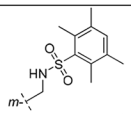
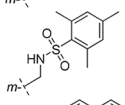
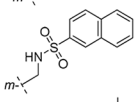
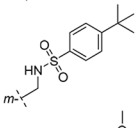
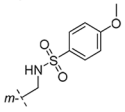
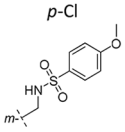
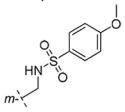
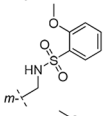
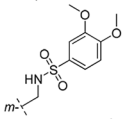
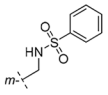
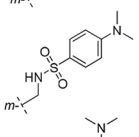
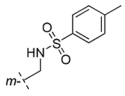
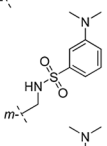
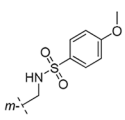
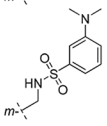
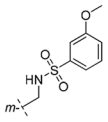
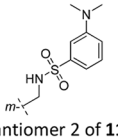
Table 4. SAR of Lead Compound 77[a]



Cmpd	R_1	R_2	FP (K_i/μM)	Cmpd	R_1	R_2	FP (K_i/μM)
95	7-F	H	669 ± 170	**108**	H		58.2 ± 3.2
96	5-F	H	369 ± 72	**109**	H		28.0 ± 3.8
97	7-Cl	H	528 ± 76	**110**	H		1.69 ± 0.55
98	7-OH	H	2410 ± 550	**111**	H		6.31 ± 0.67
99	H	*p*-Cl	163 ± 47	**112**	H	 *p*-Cl	11.0 ± 3.1
100	H	*m*-Cl	91.4 ± 28	**113**	H	 *p*-Me	4.57 ± 0.58
101	H	*m,p*-Cl	88.6 ± 24	**114**	H	 *p*-OMe	10.5 ± 1.8
102	H	*m*-Me	122 ± 5.0	**115**	H		20.0 ± 0.73
103	H	*m*-OMe	145 ± 35	**116**	H		3.34 ± 0.88
104	H		3.19 ± 0.47	**117**	H		0.584 ± 0.074
105	H		1.69 ± 0.28	**118**	H		0.630 ± 0.093
106	H		1.12 ± 0.15	**119**	H	 enantiomer 1 of **118**	0.281 ± 0.070
107	H		1.08 ± 0.064	**120**	H	 enantiomer 2 of **118**	6.33 ± 1.2

[a]FP K_i values are shown as mean ± SEM based on ≥3 individual measurements using the Cy5-probe.

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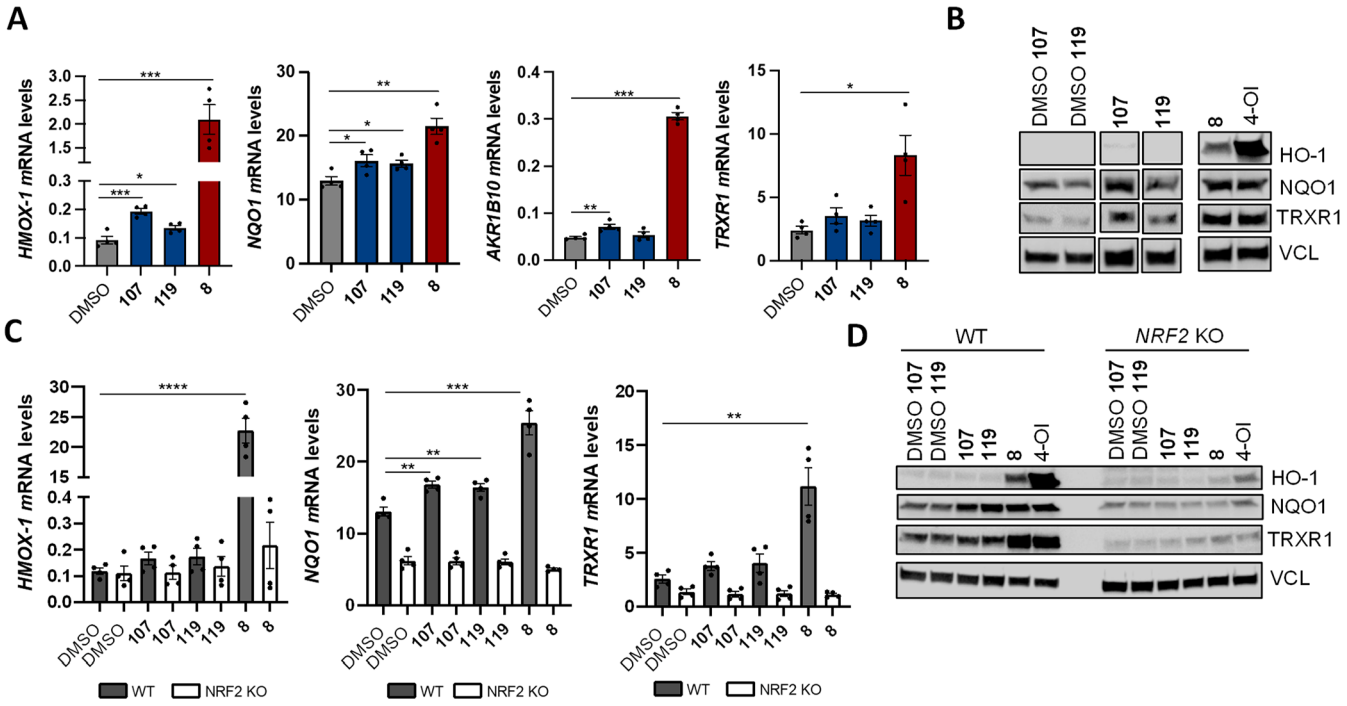

Figure 7. (A, B) WT HaCaT cells were stimulated with the following compounds (**107**, **119**, **8** or 4-OI) at 200 μM for 5 h (A) or 24 h (B). The mRNA levels of different Nrf2-regulated genes were assessed by qPCR (A), while protein levels were determined by immunoblotting from whole-cell extracts following compound stimulation (B). HMOX-1 is the gene encoding HO-1. Vinculin (VCL) is the loading control. (C, D) WT and *NRF2* KO HaCaT cells were stimulated as in (A) and (B). mRNA levels (C) and protein levels (D) were determined by qPCR and immunoblotting, respectively. In (A) and (C), data are the means of two independent experiments performed in biological duplicates, where bars represent the SEM. Statistical analyses was calculated using a Student's *t* test (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and ****$p < 0.0001$).

the growing analogue **77** and its systematic linker variations **78**–**94** required much more bespoke synthesis of the amine building blocks (Scheme 2 and 3). Generally, this involved installation of the amino functionality masked as a nitro group via 1,2-addition/Henry reaction (**81** and **82**) or 1,4-addition/Michael reaction (**87**–**92**). Reduction of the nitro group was generally performed with Raney nickel in the presence of Boc anhydride to trap the amine *in situ* and prevent undesired cyclization, which was then followed by a subsequent deprotection step.[69] In other cases, the amine building blocks were obtained through aza-Michael addition (**85** and **86**), direct *N*-alkylation (**93**) or reductive amination (**94**). Some 1C and 2C amine chains derived from α- and β-amino acids were commercially available and simply required a carboxylic acid protection step (**77**–**79**, **83**, **84**). The amines were coupled with fluorenone-4-carboxylic acid mostly via a standard EDC/HOBt protocol, and the carboxylic acid functionalities were finally deprotected to furnish the target molecules.

The fluorenone-substituted analogues of **77** (**95**–**98**) were synthesized through the same Suzuki–Miyaura/Friedel–Crafts sequence applied to **48** (*vide supra*, Scheme 4). Substitutions on the phenyl ring of **77** were installed either through commercially available substituted phenyl glycinate building blocks (**99**–**101**) or through *de novo* synthesis (**102** and **103**) (Scheme 4). The latter involved synthesis of α-ketoesters by Grignard reagent formation followed by electrophilic trapping with diethyl oxalate. Condensation with hydroxylamine furnished oximes, which were subsequently reduced to the amines, ready for coupling with fluorenone-4-carboxylic acid (Scheme 4).

The sulfonamide aromatic bromide building blocks **104a**–**118a** were synthesized from commercially available sulfonyl chlorides and amines (Scheme 5). α-Ketoesters **104b**–**118b** were then formed analogous to compounds **102** and **103** but via halogen–lithium exchange of the corresponding aromatic bromides using *n*-BuLi instead of Grignard reagent formation; this would be followed by a re-protection step of the esters, in cases where hydrolysis had occurred. Oximes (**104c**–**118c**) were formed by condensation with hydroxylamine, and these were then reduced into amines (**104d**–**118d**). Amide coupling with fluorenone-4-carboxylic acid and ester deprotection gave the final compounds **104**–**118** (Scheme 5).

DISCUSSION AND CONCLUSIONS

We here report a complete FBDD study starting with a screening of 2500 fragments against the Keap1 Kelch domain using three orthogonal primary assays (FP, TSA, and SPR) and validation by STD NMR and dose–response SPR. Twenty-eight fragments were prioritized for X-ray crystallography leading to 13 fragment–Keap1-Kelch co-structures. Three of the hits sharing the same fluorenone carboxamide scaffold were progressed into novel high-affinity lead compounds by an extensive optimization process involving fragment growing by structure-based drug design. The best compounds were active in cells without causing toxicity.

In this study, we address several key aspects of FBDD in relation to PPIs and particularly Keap1. First, we demonstrate that screening a general commercially available fragment library with biochemical and biophysical assays can give several useful fragment hits toward Keap1, as many could be advanced to the stage of X-ray crystallography and lead optimization. One challenge of FBDD is to reliably identify fragment hits, without discarding genuine hits or being overwhelmed with false positives. The weak affinities and

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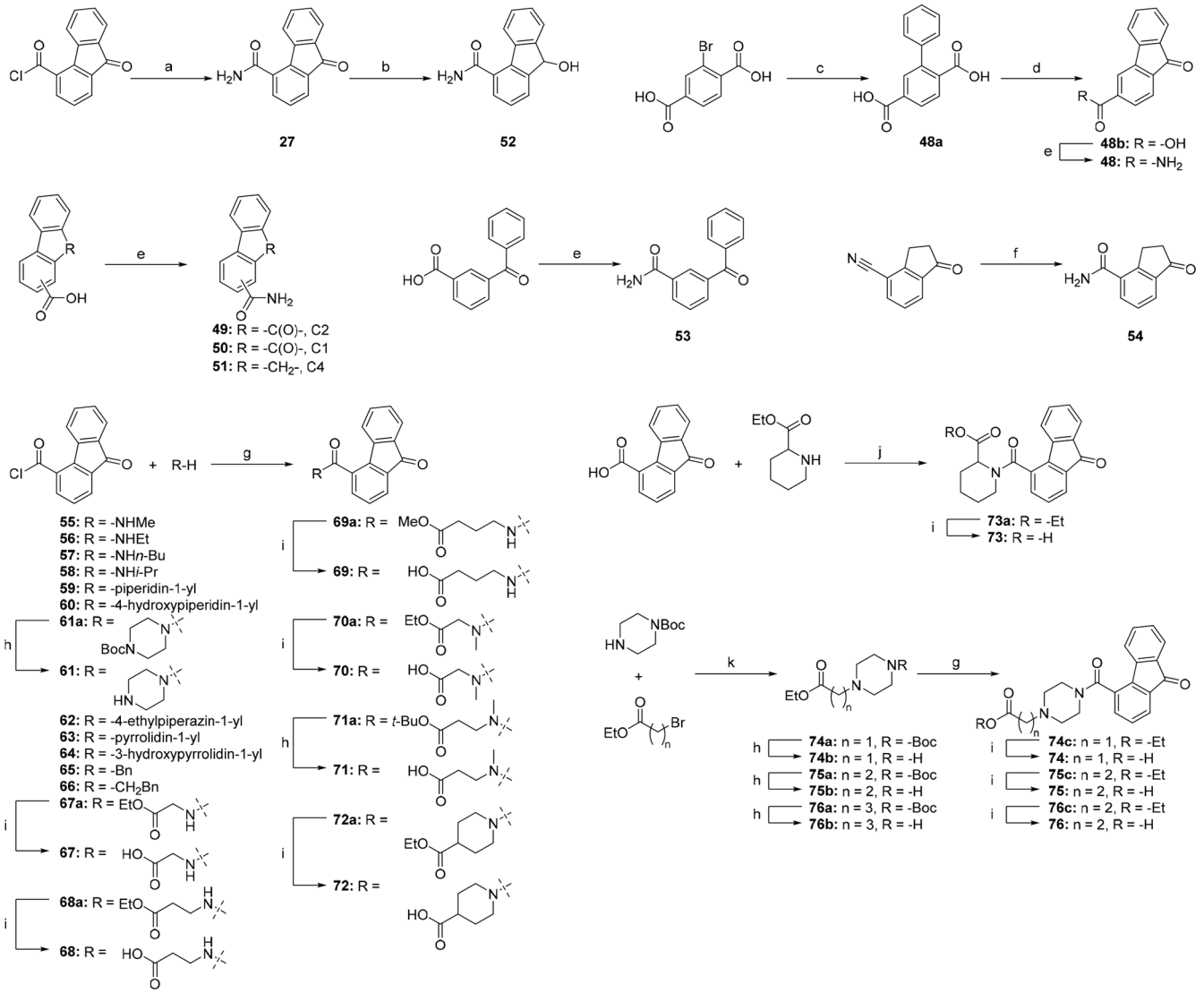
Scheme 1. Synthesis of Initial Modification and Growing Analogues[a]



[a]Reagents and conditions: (a) NH_4OH, THF, H_2O, 0 °C−rt, 1 h, 80%. (b) $NaBH_4$, MeOH, rt, 2 h, 84%. (c) Phenylboronic acid, $Pd(OAc)_2$, K_3PO_4, DMA, H_2O, rt, 26 h; then MW 150 °C, 30 min, 18%. (d) H_2SO_4, 55 °C, 20 min, 74%. (e) $SOCl_2$, DMF, DCM, reflux, 2 h; then NH_4OH, 0 °C−rt, 10 min−overnight, 6−91%. (f) K_2CO_3, *i*-PrOH, H_2O, MW 150 °C, 20 min, 63%. (g) Et_3N, DCM, rt, 14−55 h, 43%−quantitative. (h) TFA, DCM, 0 °C−rt or rt, 14−28 h, 41%−quantitative. (i) aq. NaOH, EtOH, or MeOH, rt, 16−23 h, 13−56%. (j) EDC·HCl, HOBt, DIPEA, DMF, 0 °C, 30 min; then amine, rt, 16 h, yield ND. (k) Et_3N, MeCN, or DCM, rt, 19−39 h, 67%−quantitative.

unspecific nature of fragments and the different assay sensitivities can make this a complicated task. The implementation of the SPR counter-screen, where the binding pocket of Keap1 was blocked with a peptide, was key in tackling this, as was the thorough hit characterization by SPR dose−response and STD NMR in order to measure affinities and evaluate if the fragments were genuine binders or not. The resulting data set also laid a solid foundation for prioritizing which hits should be characterized by X-ray crystallography. In this process we emphasized activity in SPR and STD NMR, SPR data quality, affinity, LE, and chemical structure (novelty and synthetic feasibility).

Second, our work illustrates the importance of X-ray crystallography in FBDD. A well-defined electron density of a fragment in the pocket is a definitive hit validation result. In two cases, we observed binding outside the canonical pocket; knowledge that made us deprioritize these hits. Also, the 13 fragment−Keap1 co-structures revealed new types of ligand interactions across Keap1's P1−P5 subpockets. In contrast to previous FBDD reports, we see a high number of fragments in P5 suggesting this area to be an important hot spot. In addition, X-ray crystallography was invaluable in the initial optimization stage, where fragment analogues bind weakly and molecular docking is unreliable. Our co-structures allowed us to pick two fragments, **43** and **44**, that bind the Keap1 Kelch domain in a unique way along the P4−P5 region; this structural insight facilitated the design of analogues growing into the adjacent P1 and P3 subpockets. Subsequently, it was essential for our confidence in the design strategy to obtain X-ray co-structures of analogues **67** and **77** showing the anticipated interactions to the Keap1 Kelch domain.

Third, our work includes a successful F2L process.[70] The weak fragment hit **27** (K_i = 490 μM) was optimized to the lead-sized compound **119** with a K_i of 281 nM to the Keap1

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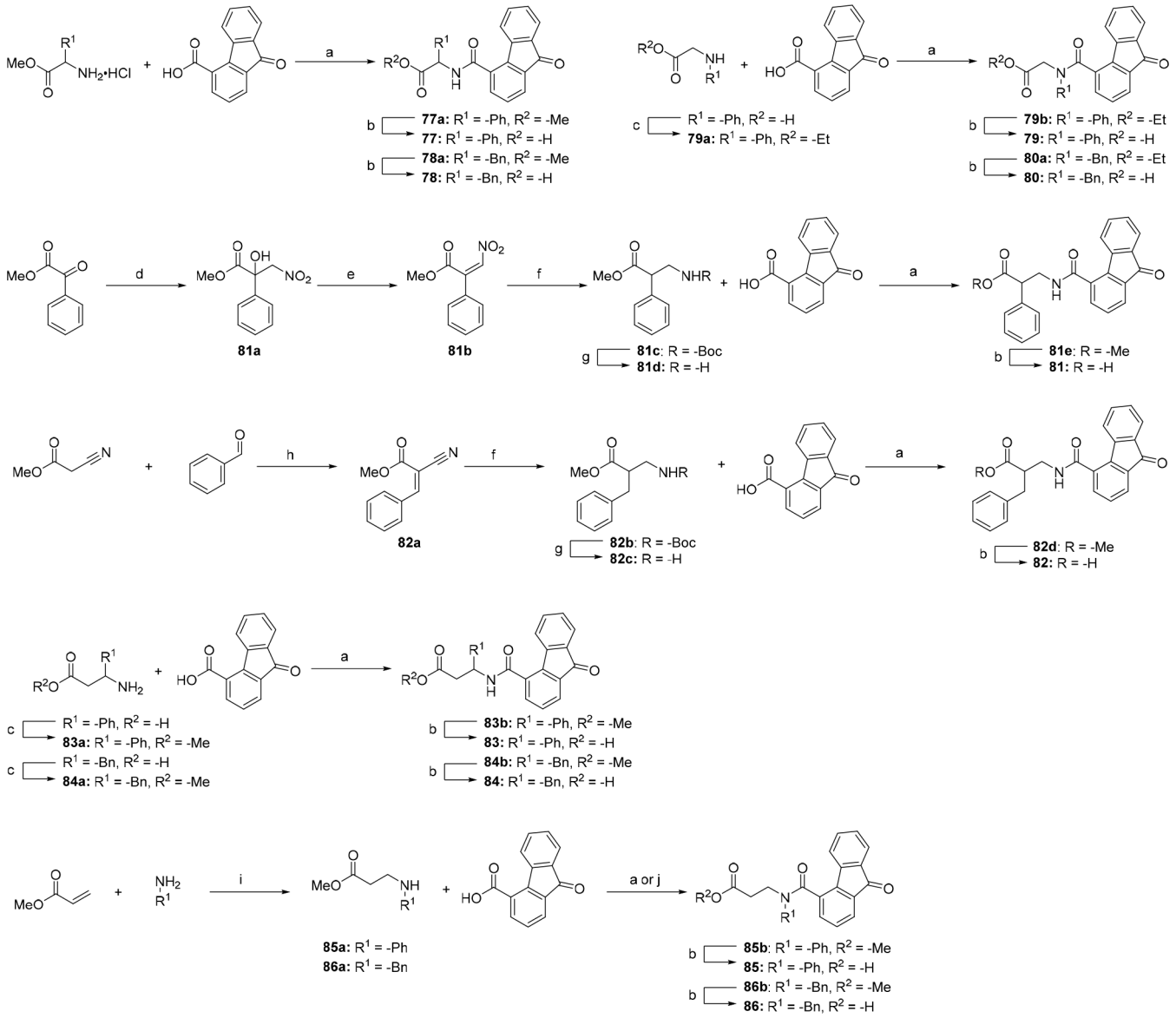
Scheme 2. Synthesis of Systematic Linker Analogues of 77[a]



[a]Reagents and conditions: (a) EDC·HCl, HOBt, DIPEA, DMF, 0 °C, 30 min; then amine, rt, 5−55 h, 21%−quantitative. (b) aq. NaOH, MeOH, or EtOH, rt, 1−26 h, 4−71%. (c) TMSCl, EtOH, or MeOH, rt, 18 h, quantitative. (d) $MeNO_2$, Et_3N, rt, 22 h, 81%. (e) Ac_2O, DMSO, rt, 42 h, 80%. (f) H_2, Raney Ni, Boc_2O, EtOH, rt, 21−28 h, quantitative. (g) TFA, DCM, 0 °C, 3−44 h, quantitative. (h) Et_3N, EtOH, MW @ 65 °C, 35 min, quantitative. (i) H_2O/TFE or MeOH, 80 or 0 °C−rt, 20−23 h, 36−61%. (j) $(COCl)_2$, DMF, DCM, 0 °C, 1.5 h; then amine, Et_3N, DCM, 0 °C−rt, 19 h, 69%.

Kelch domain, thereby demonstrating a 1700-fold increase in affinity. Also, the binding mode of the parent fragment is retained in the lead compounds, as seen when comparing X-ray structures of the fragments (**43** and **44**, hit analogues of **27**; Figure 3D,E) and early leads **67** and **77** (Figure 6A,B) with molecular docking results of more advanced leads such as **104** (Figure 6D) and **119** (Figure S4). LE dropped from the parent fragment **27** (LE = 0.27 kcal/mol/heavy atom) to the initial more potent analogue **77** (LE = 0.19 kcal/mol/heavy atom) bearing a phenylglycine *N*-side chain. However, this was partly regained during subsequent optimization, where the phenylsulfonamidomethyl was attached to the central benzene ring and electron-donating substituents further added to the sulfonamide aryl ring, as seen for compounds **104**, **107**, **118**, and **119** (LE = 0.20−022 kcal/mol/heavy atom; Figure 8A). Lipophilic ligand efficiency (LLE)—a metric considered important in lead optimization as a tool to control lipophilicity relative to potency and thus a predictive marker for drug-like properties[71−73]—was high for our final leads (**107**, **118** and **119**; LLE = 5.3−5.7) and within the recommended range of 5 to 7 (Figure 8A). However, this is partly driven by a high polarity; $cLogD_{7.4}$ and tPSA are 0.8−1.1 and 133−139 Å for compounds **107** and **119** (Figure 8B). Considering various prediction rules and guidelines,[74−76] these cLogD and tPSA values are at the limit of what is generally considered favorable for membrane permeability. This issue is particularly pertinent for compounds targeting the Keap1 Kelch domain, as the three arginines in the pocket most often give rise to inhibitors containing carboxylic acid groups (Figure 1). Such acid-containing compounds require special fine-tuning of phys-

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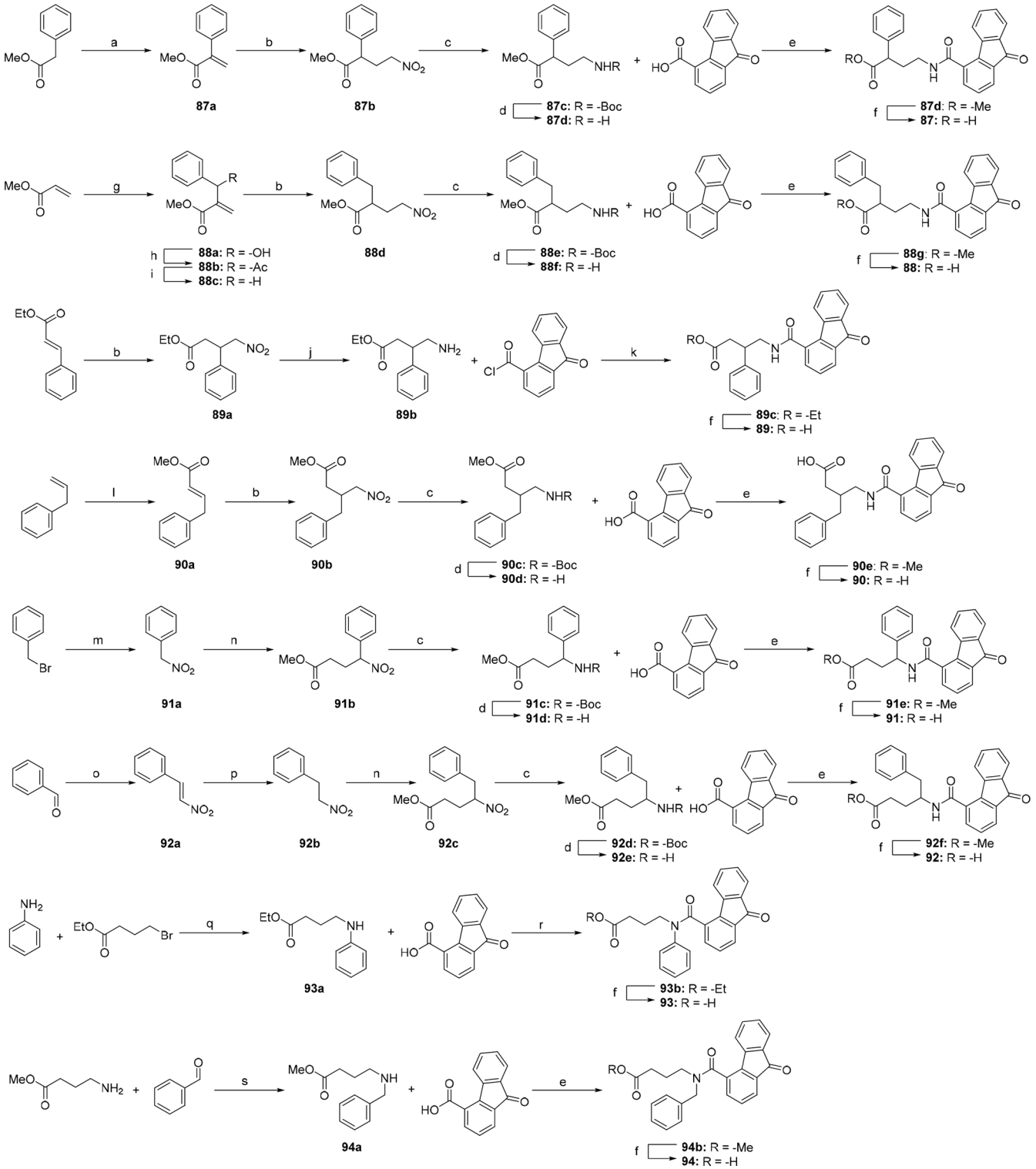
Scheme 3. Synthesis of Systematic Linker Analogues of 77 (Continued)[a]



[a]Reagents and conditions: (a) $(CH_2O)_n$, Bu_4NHSO_4, K_2CO_3, PhMe, 80 °C, 18 h, 43%. (b) $MeNO_2$, DBU, MeCN, 0 °C−rt, 8−21 h, 30%−quantitative. (c) H_2, Raney Ni, Boc_2O, EtOH, rt, 2−72 h, 89%−quantitative. (d) TFA, DCM, 0 °C−rt, 2.5−40 h, yield ND. (e) EDC·HCl, HOBt, DIPEA, DMF, 0 °C, 30 min; then amine, rt, 17−38 h, 23−74%. (f) aq. NaOH, MeOH or EtOH, rt, 2−72 h, 22−94%. (g) DABCO, 0 °C−rt, 29 h, 66%. (h) Ac_2O, DMAP, Et_3N, DCM, 0 °C−rt, 17 h, 74%. (i) DABCO, THF, H_2O, rt, 15 min; then $NaBH_4$, rt, 30 min, 65%. (j) $NaBH_4$, $NiCl_2 \cdot 6H_2O$, EtOH, 0 °C, 2.5 h, yield ND. (k) Et_3N, DCM, 0 °C, 1 h, 18%. (l) Methyl acrylate, Grubbs's cat. M2a, DCM, reflux, 14 h, 88%. (m) $NaNO_2$, $CO(NH_2)_2$, DMF, −10 °C, 4 h, 23%. (n) Methyl acrylate, DBU, MeCN, 0 °C−rt, 17−72 h, quantitative. (o) $MeNO_2$, NH_4OAc, PhMe, 100 °C, 17 h, 90%. (p) $NaBH_4$, silica gel, $CHCl_3$, *i*-PrOH, 0 °C−rt, 21 h, 94%. (q) Et_3N, rt, 72 h, quantitative. (r) $(COCl)_2$, DMF, DCM, 0 °C, 1.5 h; then Et_3N, DCM, 0 °C−rt, 72 h, 64%. (s) Et_3N, $MgSO_4$, THF, rt, 20 h; then $NaBH_4$, MeOH, −20−0 °C, 2 h, 47%.

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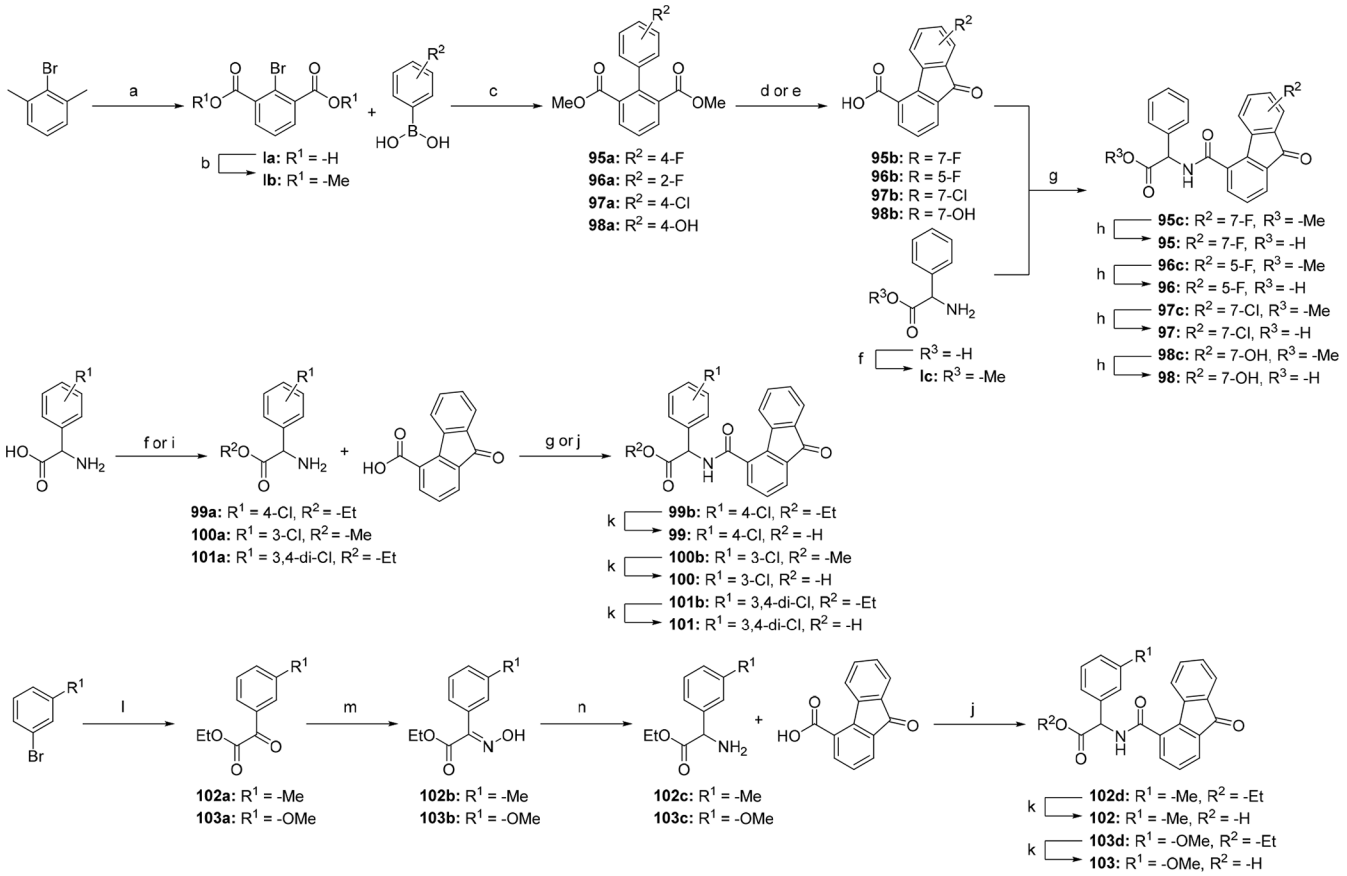
Scheme 4. Synthesis of Growing Analogues of 77[a]



[a]Reagents and conditions: (a) $KMnO_4$, *t*-BuOH, H_2O, 70 °C, 24 h, 76%. (b) $SOCl_2$, rt−100 °C, 9 h; then MeOH, Et_3N, 0 °C−rt, 2 h, 82%. (c) Appropriate phenylboronic acid, Pd(dppf)Cl_2·DCM or $Pd(PPh_3)_4$, K_2CO_3, 1,4-dioxane, H_2O, MW @ 95−110 °C, 1−1.5 h, 50−69%. (d) H_2SO_4, 55 °C, 40 min; then NaOH, MeOH, DCM, rt, 3 h, 61%. (e) PPA, 140 °C, 1 h; then NaOH, MeOH, DCM, rt, 1−24 h, 36−87%. (f) TMS-Cl, MeOH, rt, 23−24 h, yield ND. (g) EDC·HCl, HOBt, DIPEA, DMF, 0 °C, 30 min; then amine, rt, 5−24 h, 19−65%. (h) NaOH, DCM, MeOH, rt, 1 h, 6−42%. (i) $SOCl_2$, EtOH, 0 °C−reflux, 5 h, yield ND. (j) EDC·HCl, DMAP, DMF, rt, 4 h, yield ND. (k) aq. NaOH, EtOH, rt−reflux, 2−24 h, 81% over 3 steps. (l) Mg, Et_2O, reflux, 1 h; then diethyl oxalate, −78 °C, 1 h, 62%. (m) NH_2OH·HCl, NaOAc, MeOH, 60 °C, 3 h, yield ND. (n) H_2, Pd/C, MeOH, THF, rt, 3.5 h, quantitative over 2 steps.

icochemical properties in order to achieve membrane permeability and thus cell activity, as experienced by us and others.[34,35,77] In accordance with this analysis, compounds **107** and **119** did show cellular activity (Figure 7), however, to a lesser extent than the more lipophilic and less polar control compound **8** (cLogD = 2.2; tPSA = 73 Å^2).

Overall, we disclose a range of well-characterized fragment hits and new lead molecules that bind with high affinity to the Keap1 Kelch domain. Compound **119** and analogues share some structural features with known Keap1 inhibitors (Figure 1), e.g. a carboxylic acid group in P1, a central aromatic ring in P3, and a phenylsulfonamide in P5. However, the fluorenone moiety is not seen in any Keap1 inhibitors and binds in the P4−P5 subpockets of the Keap1 Kelch domain in a unique way (Figure S6). Future optimization should focus on balancing lipophilicity and polarity to enhance cellular activity, keeping in mind that the optimal ranges are likely narrower than usual due to the carboxylic acid group that seems obligatory for affinity. The structural insight of the ligand−Keap1 interactions provided herein can support this process and give rise to a variety of future design pathways perhaps leading to biological active and drug-like noncovalent Keap1-Nrf2 PPI inhibitors.

EXPERIMENTAL SECTION

General Procedures. All chemicals used for synthesis were obtained from commercial suppliers and used without prior purification. ^{1}H NMR, ^{13}C NMR, and 2D NMR (^{1}H−^{1}H COSY, ^{1}H−^{13}C HSQC) spectra were recorded using either a 600 MHz Bruker Avance III HD instrument equipped with a cryogenically cooled 5 mm dual probe or a 400 MHz Bruker Avance III instrument equipped with a 5 mm broad band probe. Samples were dissolved in either DMSO-d_6 (VWR Chemicals, 99.80% D) or $CDCl_3$ (Cambridge Isotope Laboratories, Inc., 99.8% D) and analyzed at 300 K. Thin layer chromatography (TLC) analyses were performed using TLC silica gel 60 F_{254} aluminum plates (Merck). Liquid chromatography−mass spectra (LC-MS) were obtained with an Agilent 6410 Triple Quadrupole Mass Spectrometer instrument using electron spray ionization (ESI) coupled to an Agilent 1200 high-performance liquid chromatography system (ESI−LC-MS) with a C18 reversed-phase column (Zorbax Eclipse XBD-C18, 4.6 mm × 50 mm), an autosampler, and a diode array detector, using a linear gradient of the binary solvent system of buffer A (Milli-Q H_2O/MeCN/formic acid, 95:5:0.1 v/v%) to buffer B (Milli-Q H_2O/MeCN/formic acid, 5:95:0.043 v/v%) with a flow rate of 1 mL/min. During ESI−LC-MS analysis, evaporative light scattering traces were obtained with a Sedere Sedex 85 Light Scattering Detector. Flash column chromatography was carried out using either prepacked RediSep Rf silica flash cartridges or a RediSep Rf reversed-phase C18 cartridge on a CombiFlash Rf+ apparatus. Preparative reverse phase HPLC was

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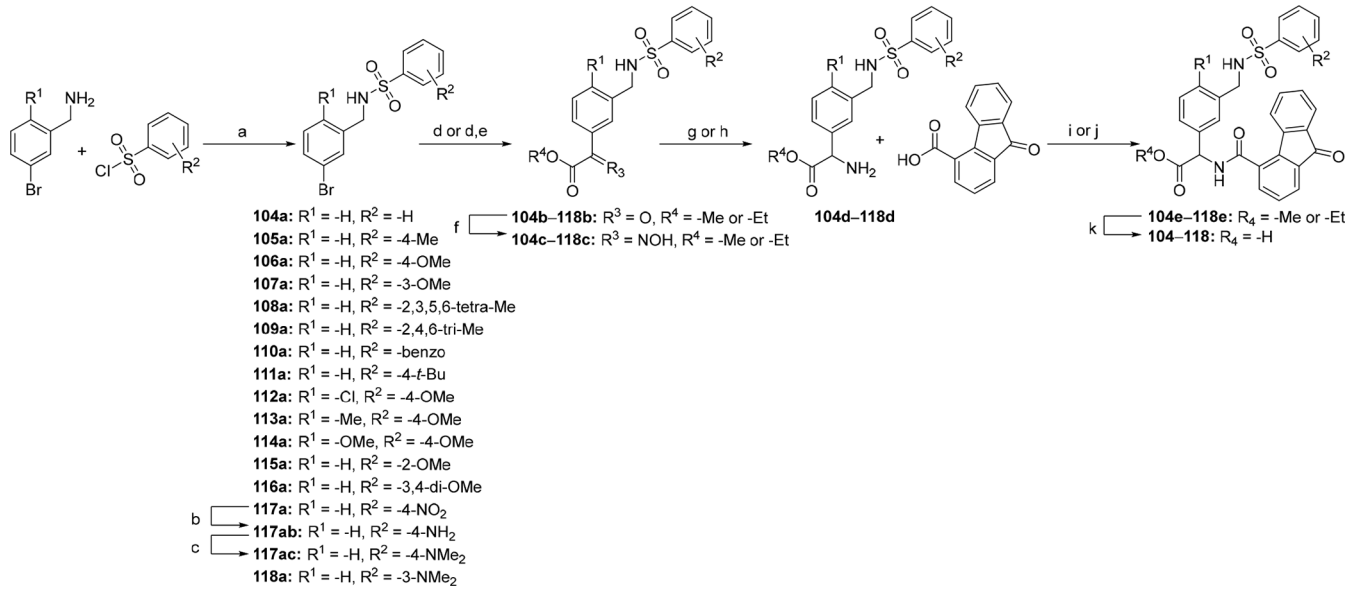
Scheme 5. Synthesis of Sulfonamide Analogues of 77[a]



[a]Reagents and conditions: (a) Et_3N, DCM, 50 °C, 3 h, quantitative. (b) $SnCl_2$, HCl, 0 °C−rt, 2.5 h, yield ND. (c) MeI, Et_3N, DCM, MeCN, rt, 3 days, 32% over 2 steps. (d) *n*-BuLi, THF, −78 °C, 15 min; then diethyl oxalate, −78 °C, 30 min, 12%; (e) TMS-Cl, MeOH or EtOH, rt, 23−24 h, 12−54% over 2 steps. (f) NH_2OH·HCl, NaOAc, MeOH, 60 °C, 3 h, quantitative. (g) H_2, Pd/C, MeOH, THF, rt, overnight, 30−67%. (h) Zn, HCO_2H, MeOH, H_2O, 0 °C−rt, overnight, 41−81%. (i) EDC·HCl, DMAP, DMF, rt, 4 h, 28%. (j) EDC·HCl, HOBt, DMF, 0 °C, 30 min; then DIPEA, rt, 6−24 h, 41−81%. (k) aq. NaOH, EtOH, rt, 6−24 h, 15−94%.

Figure 8. (A) Representative FP data for key fragment and lead compounds illustrating the F2L progress. (B) Structure and key physicochemical properties for two lead compounds **107** and **119**. K_i values are from Tables 1, 3, and 4. LLE values are calculated based on K_i values from FP and cLogD values at pH 7.4 using ChemAxon's MarvinSketch v 20.3. ChemDraw 16.0 was used for determining tPSA.

performed using an Agilent 1200 series HPLC preparative system with an Agilent Zorbax 300-SB-C18 column (21.2 × 250 mm) and with a linear gradient of buffer A (Milli-Q H_2O:MeCN:TFA 95:5:0.1 v/v%) to buffer B (Milli-Q H_2O:MeCN:TFA 5:95:0.1 v/v%). Microwave-assisted synthesis was carried out using a Biotage Initiator+ apparatus. All final compounds showed ≥95% purity according to the NMR and LC-MS results.

General Procedure A: Primary Amidation of Carboxylic Acids. A round-bottomed flask was charged with the appropriate carboxylic acid (2.00−5.00 mmol, 1.00 equiv), $SOCl_2$ (2.00 equiv), DMF (0.10 equiv) and DCM (0.3−2.0 M) and the solution heated at reflux for 2 h. After cooling to rt, the mixture was slowly dripped into vigorously stirring 25% NH_4OH (50.0 equiv) cooled at 0 °C over 5−10 min. The mixture was stirred at rt for 1−24 h. If (a) precipitate formation, the solid was collected by filtration and thoroughly washed with water; (b) solution formation, the mixture was extracted with EtOAc (3 × 10 mL/mmol), and the combined organic phases were concentrated to dryness *in vacuo*. Optional purification was carried out as specified in individual cases.

General Procedure B: Amination of 9-Oxo-9*H*-fluorene-4-carbonyl Chloride. A vial was charged with the appropriate amine, amine hydrochloride or amine trifluoroacetate (2.00−5.00 equiv), Et_3N (1.50−10.0 equiv) and then a solution of commercially available 9-oxo-9*H*-fluorene-4-carbonyl chloride (1.0 equiv, 0.4−2.0 mmol) in DCM (0.1 M). The mixture was stirred at rt for 1−72 h. Upon reaction completion, workup and optional purification were carried out as specified in individual cases.

General Procedure C: Boc or *t*-Bu Ester Deprotection. A solution of the Boc protected amine or *tert*-butyl ester (0.50−5.00 mmol, 1.00 equiv) in DCM (0.1−0.2 M) was cooled to 0 °C and dropwise added TFA (15.0−130 equiv). The mixture was stirred and slowly allowed to reach rt over 2.5−44 h. Upon reaction completion, solvent and excess TFA was removed under a stream of N_2. Optional workup was performed by redissolving the residue in water (2 mL/mmol) and basifying the solution with sat. Na_2CO_3. The mixture was extracted with EtOAc (3 × 3 mL/mmol), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. Optional purification was carried out as specified in individual cases.

General Procedure D: Base-Catalyzed Ester Hydrolysis. A solution of the ester (0.12−1.68 mmol, 1.00 equiv), in either MeOH (if methyl ester, 0.1−0.2 M) or EtOH (if ethyl ester, 0.1−0.2 M) was added aq. 1 M NaOH (3.00−10.0 equiv). The mixture was stirred at rt for 1−72 h. Upon reaction completion, the mixture was added

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water (10 mL/mmol), pH adjusted appropriately with 1 M HCl, extracted with EtOAc (3 × 20 mL/mmol), and the combined organic phases were dried over Na_2SO_4 and concentrated to dryness *in vacuo*. Optional purification was carried out as specified in individual cases.

General Procedure E: EDC/HOBt-Based Amide Coupling. A solution of the carboxylic acid (0.13−1.3 mmol, 1.00 equiv) in anhydrous DMF (0.1−0.3 M) was cooled to 0 °C and then added EDC·HCl (1.50 equiv), HOBt (1.50 equiv) and DIPEA (2.00−5.00 equiv). The mixture was stirred at 0 °C for 0.5−1 h. Upon complete pre-activation, the appropriate amine, amine hydrochloride or amine trifluoroacetate (1.00−2.32 equiv) was added. The mixture was stirred at rt for 5−55 h. Upon reaction completion, the mixture was added water and extracted with EtOAc (4 × 10 mL/mmol). The combined organic phases were washed with 1 M HCl (1 × 10 mL/mmol) and sat. Na_2CO_3 (1 × 10 mL/mmol), dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. Optional purification was carried out as specified in individual cases.

General Procedure F: Amine *N*-Alkylation with Alkyl Halides. A solution of the amine (5.00 mmol, 1.00 equiv) and Et_3N (1.10 equiv) in MeCN (0.2 M) was added the alkyl halide (1.00−1.10 equiv). The mixture was stirred at rt for 19−39 h. Upon reaction completion, the mixture was concentrated to dryness *in vacuo*. The residue was redissolved in EtOAc (2 mL/mmol), washed with sat. $NaHCO_3$ (1 mL/mmol), dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*.

General Procedure G: Amino Acid TMS-Cl-Mediated Esterification. To the amino acid (0.50−33.0 mmol, 1.00 equiv) was slowly added TMS-Cl (2.00 equiv) and then MeOH or EtOH (1.0−5.0 mL/mmol). The mixture was stirred at rt for 18−70 h. Upon reaction completion, the mixture was concentrated to dryness *in vacuo*.

General Procedure H: Aliphatic Nitro or Nitrile Group Reduction and *In Situ* Boc-Protection. A solution of the aliphatic nitro or nitrile compound (1.00−2.32 mmol, 1.00 equiv) and Boc_2O (1.10 equiv) in abs. EtOH (0.2 M) was degassed with N_2 for 10 min. 50% RaNi in H_2O (100 w/w%) was triturated with abs. EtOH (3 × 2 mL/mmol) and then added to the degassed solution as a suspension in abs. EtOH (2 mL/mmol). The mixture was subjected to three vacuum-nitrogen cycles and then put under H_2. The mixture was stirred at rt for 2−72 h. Upon reaction completion, the mixture was subjected to three vacuum-nitrogen cycles and then filtered through a short pad of Celite, washing the filter cake several times with EtOAc (without having the filter cake become dry at any stage). The combined filtrates were concentrated to dryness *in vacuo*.

General Procedure I: Acid Chloride Formation and Amide Coupling. A solution of the carboxylic acid (1.00 mmol, 1.00 equiv) in DCM (0.1 M) was cooled to 0 °C and then dropwise added oxalyl chloride (6.00 equiv) and DMF (3 drops). The mixture was stirred at 0 °C for 1.5 h. Upon reaction completion, the mixture concentrated to dryness *in vacuo*. The prepared acid chloride was redissolved in DCM (0.1 M), cooled to 0 °C and then added the appropriate amine (2.00 equiv) and Et_3N (2.00 equiv). The mixture was stirred and allowed to slowly warm to rt over 19−72 h. Upon reaction completion, the mixture was diluted with DCM (10 mL/mmol) and washed with water (15 mL/mmol). The aq. phase was re-extracted with DCM (2 × 10 mL), and the combined organic phases were washed with 1 M HCl (2 × 10 mL/mmol) and sat. brine (10 mL/mmol), dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. Optional purification was carried out as specified in individual cases.

General Procedure J: Nitroalkane Michael Addition. A mixture of DBU (2.00−4.00 equiv) and nitroalkane (1.00−20.0 equiv) was stirred at rt for 20 min. The mixture was then cooled to 0 °C and a solution of the Michael acceptor (1.00−8.80 mmol, 1.00 equiv) in MeCN (1.0 M) was added dropwise. The mixture was stirred and allowed to slowly reach rt over 14−72 h. Upon reaction completion, the mixture was partitioned between EtOAc (5 mL/mmol) and 1 M HCl (5 mL/mmol), and the aq. layer further extracted with EtOAc (3 × 5 mL/mmol). The combined organic phases were washed with sat. brine (10 mL/mmol), dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*.

General Procedure K: Microwave-Assisted Suzuki−Miyaura Cross-Coupling. A MW vial was charged with the aryl bromide (0.50−1.00 mmol, 1.00 equiv), the boronic acid (1.50 equiv), K_2CO_3 (3.00 equiv), and 4:1 1,4-dioxane:H_2O (0.1 M). The solution was degassed with N_2 for 10 min. Then Pd(dppf)Cl_2·DCM or Pd(PPh_3)$_4$ (0.05 equiv) was added. The vial was capped, subjected to three vacuum-N_2 cycles, and the mixture stirred under MW irradiation at 95−110 °C for 1−1.5 h. Upon reaction completion, the mixture was added water (20 mL/mmol) and extracted with EtOAc (3 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. Purification was carried out as specified in individual cases.

General Procedure L: *De Novo* Fluorenone Synthesis and Ester Hydrolysis. Polyphosphoric acid (PPA, 6.2 g/mmol) was heated to 140 °C and then portion wise added the biphenyl-2,6-diester (0.15−0.50 mmol, 1.00 equiv). The mixture was stirred at 140 °C for 1 h. Upon reaction completion, the mixture was poured into crushed ice. The resulting precipitate was collected by filtration, washed with water and dried *in vacuo*. The crude ester was then redissolved in DCM (0.017 M) and added 3 M NaOH in MeOH (20.0 equiv). The mixture was stirred at rt or reflux for 1−24 h. Upon reaction completion, the mixture was concentrated to dryness *in vacuo*. The residue was redissolved in water (67 mL/mmol), the pH adjusted with conc. HCl to <2, and the mixture extracted with EtOAc (3 × 67 mL/mmol). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*.

General Procedure M: Alternative Base-Catalyzed Ester Hydrolysis. To a solution of the methyl ester (0.025−0.19 mmol, 1.00 equiv) in DCM (0.01−0.1 M) was added 3 M NaOH in MeOH (6.00−60.0 equiv). The mixture was stirred at rt for 1−24 h. Upon reaction completion, the mixture was concentrated to dryness *in vacuo*. The residue was redissolved in water (100 mL/mmol), the pH adjusted with conc. HCl to <2, and the mixture extracted with EtOAc (3 × 100 mL/mmol).). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. Purification was carried out as specified in individual cases.

General Procedure N: EDC/DMAP-Based Amide Coupling. A solution of 9-oxo-9*H*-fluorene-4-carboxylic acid (0.13−0.54 mmol, 1.00 equiv), the appropriate amine hydrochloride (1.00 equiv), EDC·HCl (1.30 equiv) and DMAP (1.50−4.00 equiv) in anhydrous DMF (0.25 M) was stirred at rt for 4 h to overnight. Upon reaction completion, the mixture was added water (60 mL/mmol) and the aq. phase extracted with DCM (3 × 40 mL/mmol). The combined organic phases were washed sat. brine (40 mL/mmol), dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*.

General Procedure O: Grignard Reaction. To activated magnesium turnings (1.05 equiv) under argon was slowly added a solution of the appropriate aryl bromide (1.05 equiv) in THF (1.2 M) to achieve a gentle reflux. The mixture was then stirred at reflux for 1−13 h. The prepared Grignard reagent was then cooled to −70 °C and added dropwise to a solution of diethyl oxalate (2.85 mmol, 1.00 equiv) in THF (0.4 M) at −70 °C. The mixture was stirred at −70 °C for 1 h. Upon reaction completion, sat. NH_4Cl (0.3 mL) and water (1 mL) were added, and the mixture extracted with EtOAc (3 × 2 mL). The combined organic phases were washed with sat. brine, dried over $MgSO_4$, filtered, and concentrated to dryness *in vacuo*.

General Procedure P: Oxime Formation. A mixture of the appropriate aryl glyoxylate (3.93 mmol, 1.00 equiv), anhydrous NaOAc (1.20 equiv) and NH_2OH·HCl (1.60 equiv) in MeOH (70 mL) was stirred at 60 °C for 3 h. Upon reaction completion, the mixture was concentrated *in vacuo*. The residue was redissolved in EtOAc and washed with water and sat. brine, dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. Optional purification was carried out as specified in individual cases.

General Procedure Q: Oxime Reduction. A mixture of oxime (1.76 mmol, 1.00 equiv) and 5 wt% Pd/C (50% wet; 1.00 equiv) in MeOH:THF (3:1, 0.12 M) was subjected to three vacuum-N_2 cycles followed by three vacuum-H_2 cycles. The reaction mixture was then

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stirred under 1 atm of H_2 at rt for 3.5 h. Upon reaction completion, the reaction mixture was filtrated through a pad of Celite, which was further washed several times with EtOAc. The combined filtrates were concentrated to dryness *in vacuo*. Optional purification was carried out as specified in individual cases.

General Procedure R: Sulfonamide Coupling. To a solution of the appropriate (3-bromophenyl)methanamine (1.00 equiv) and Et_3N (3.00 equiv) in dry DCM under N_2 was added the appropriate benzenesulfonyl chloride (1.00 equiv). The mixture was stirred at reflux for 3 h. Upon reaction completion, the mixture was quenched with water and concentrated *in vacuo*. The residue was then extracted with EtOAc. The combined organic phases were washed with 1 M HCl and sat. brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*.

General Procedure S: Oxalate Acid Synthesis and TMS-Cl-Mediated Esterification. A solution of aryl bromide (1.00 equiv) in dry THF was cooled to −78 °C and then added 1.60 M *n*-BuLi in hexane (3.30 equiv) under N_2. The mixture was stirred at −78 °C for 15−30 min. Then, a solution of diethyl oxalate (1.20 equiv) in dry THF was added dropwise. The mixture was stirred at −78 °C for a further 30 min. Upon reaction completion, the mixture was quenched by addition of sat. aq. NH_4Cl at −78 °C. The solution was basified with $NaHCO_3$ and extracted with diethyl ether. The aq. phase was acidified to pH 2 with 6 N HCl and extracted with EtOAc. The combined organic phases were collected and evaporated to get the product. In the cases where the ester had converted to the corresponding acid, a re-protection step was conducted. Here, TMS-Cl (2.00 equiv) was slowly added to the acid (1.00 equiv) followed by MeOH/EtOH (1.0−5.0 mL/mmol). The mixture was stirred at rt for 24 h. Upon reaction completion, the mixture was concentrated to dryness *in vacuo* and used in the next step without further purification.

General Procedure T: Oxime Reduction. To a solution of oxime (1.00 equiv) and 88% formic acid in methanol and water at 0 °C was added zinc dust (3.00 equiv) portion-wise over 1 h. The suspension was stirred for 9−24 h at room temperature. Upon reaction completion, the mixture was filtered through Celite and washed several times with EtOAc or methanol. The filtrate was concentrated, and the compound was used as starting material in the next steps without further purification.

General Procedure U: EDC-Based Amide Coupling. A solution of EDC·HCl (1.50 equiv) and HOBt (1.50 equiv) in DMF was added dropwise to a stirred suspension of acid (1.00 equiv) and amine (1.00 equiv) in DMF at 0 °C under argon atmosphere for 30 min. DIPEA (2.20 equiv) was added dropwise to the mixture, which was then stirred at 25 °C for 24 h. Water (3 mL/mmol) was added and the mixture extracted with EtOAc (3 × 3 mL/mmol). The combined organic layers were washed with 1 M HCl (3 mL/mmol), sat. Na_2CO_3 (3 mL/mmol), and sat. brine (3 mL/mmol), dried over Na_2SO_4, filtered, and evaporated to dryness *in vacuo*.

*9-Oxo-9H-fluorene-4-carboxamide (**27**).* This previously reported compound was synthesized according to a literature protocol with minor deviations.[78] A solution of commercially available 9-oxo-9*H*-fluorene-4-carbonyl chloride (1.00 g, 4.12 mmol, 1.00 equiv) in THF (40.0 mL) was cooled to 0 °C and dropwise added 25% NH_4OH (6.4 mL, 41.2 mmol, 10.0 equiv) over 10 min. The mixture was then stirred at rt for additional 50 min. Upon reaction completion as detected by TLC (R_f = 0.14, hep:EtOAc 1:1), THF was removed by evaporation *in vacuo*. The resulting suspension was filtered, and the solid washed with water (20 mL) and dried *in vacuo* to afford the title compound **27** as a light-yellow solid (0.74 g, 3.30 mmol, 80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.19 (s, 1H), 7.89 (dt, J = 7.6, 0.9 Hz, 1H), 7.77 (s, 1H), 7.68 (dd, J = 7.3, 1.2 Hz, 1H), 7.65 (dt, J = 7.2, 1.0 Hz, 1H), 7.64−7.57 (m, 2H), 7.47−7.43 (m, 1H), 7.40 (dd, J = 7.6, 1.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.43, 169.45, 142.83, 139.86, 135.35, 133.84, 133.75, 133.37, 133.07, 129.63, 129.25, 124.53, 124.03, 123.85. LC-MS (ESI): m/z 224.2 $[M+1]^+$, t_R = 2.33 min.

*[1,1′-Biphenyl]-2,5-dicarboxylic acid (**48a**).* This previously reported compound was synthesized according to a literature protocol with major deviations.[79] A MW vial was charged with commercially available 2-bromoterephthalic acid (0.25 g, 1.00 mmol, 1.0 equiv), phenylboronic acid (0.18 g, 1.50 mmol, 1.50 equiv), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 0.010 equiv), K_3PO_4 (0.42 g, 2.00 mmol, 2.00 equiv), DMA (2.0 mL), and H_2O (2.0 mL). The vial was capped, and the mixture stirred at rt for 26 h and subjected to MW irradiation at 150 °C for 2 × 15 min. Upon reaction completion as detected by LC-MS, the mixture was added 1 M NaOH (10 mL) and washed with EtOAc (2 × 20 mL). The aqueous phase was acidified with 2 M HCl and extracted with EtOAc (4 × 20 mL), and the combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by preparative HPLC (buffer A:B 0−100%) afforded the title compound **48a** as a white solid (0.044 g, 0.18 mmol, 18%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.18 (s, 2H), 7.99 (dd, J = 8.0, 1.7 Hz, 1H), 7.88 (d, J = 1.7 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.50−7.33 (m, 5H). LC-MS (ESI): m/z 241.0 $[M-1]^-$, t_R = 2.34 min.

*9-Oxo-9H-fluorene-3-carboxylic acid (**48b**).* This previously reported compound was synthesized according to a literature protocol with minor deviations.[80] A vial was charged with **48a** (0.040 g, 0.17 mmol, 1.00 equiv) and conc. H_2SO_4 (5.0 mL). The vial was capped and stirred at 55 °C for 20 min. Upon reaction completion as detected by TLC (R_f = 0.51, hep:EtOAc 1:1), the mixture was poured into 100 mL crushed ice. The mixture was extracted with EtOAc (2 × 50 mL), and the combined organic phases were washed with sat. brine (50 mL), dried over Na_2SO_4, and concentrated *in vacuo* to afford the title compound **48b** as a yellow solid (0.028 g, 0.12 mmol, 74%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.42 (s, 1H), 8.31 (d, J = 1.3 Hz, 1H), 8.02−7.91 (m, 2H), 7.71 (d, J = 7.6 Hz, 1H), 7.66 (ddt, J = 7.7, 4.0, 1.9 Hz, 2H), 7.43 (td, J = 7.5, 0.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.44, 166.48, 144.07, 143.29, 136.78, 136.39, 135.77, 133.31, 130.77, 129.87, 124.13, 123.87, 121.77, 121.57. LC-MS (ESI): m/z 223.0 $[M-1]^-$, t_R = 2.80−3.05 min.

*9-Oxo-9H-fluorene-3-carboxamide (**48**).* This previously reported compound was synthesized according to general procedure A. Starting from **48b** (1.12 g, 5.00 mmol, 1.00 equiv) and following purification by normal-phase flash chromatography (hep:EtOAc 0−100%), the title compound **48** was obtained as a yellow solid (0.063 g, 0.28 mmol, 6%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.24 (d, J = 1.3 Hz, 1H), 8.14 (s, 1H), 7.84 (dq, J = 7.3, 1.2 Hz, 2H), 7.74−7.57 (m, 4H), 7.42 (td, J = 7.4, 0.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.52, 167.01, 143.90, 143.42, 140.54, 135.67, 135.12, 133.42, 129.75, 128.73, 124.08, 123.70, 121.31, 120.10. LC-MS (ESI): m/z 224.4 $[M+1]^+$, t_R = 1.84 min.

*9-Oxo-9H-fluorene-2-carboxamide (**49**).* This previously reported compound was synthesized according to general procedure A. Starting from commercially available 9-oxo-9*H*-fluorene-2-carboxylic acid (1.00 g, 4.50 mmol, 1.00 equiv), the title compound **49** was obtained as a yellow solid (0.59 g, 2.60 mmol, 59%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.14 (dd, J = 7.7, 1.7 Hz, 2H), 8.11 (d, J = 1.5 Hz, 1H), 7.89 (d, J = 7.7 Hz, 1H), 7.88−7.85 (m, 1H), 7.65 (dtd, J = 7.7, 3.8, 1.2 Hz, 2H), 7.50 (s, 1H), 7.44 (td, J = 7.5, 1.0 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.49, 166.56, 146.29, 143.12, 135.51, 135.18, 134.77, 133.83, 133.27, 130.08, 124.07, 122.71, 121.83, 121.02. LC-MS (ESI): m/z 224.1 $[M+1]^+$, t_R = 2.50 min.

*9-Oxo-9H-fluorene-1-carboxamide (**50**).* This previously reported compound was synthesized according to general procedure A. Starting from commercially available 9-oxo-9*H*-fluorene-1-carboxylic acid (1.00 g, 4.50 mmol, 1.00 equiv) and following purification by normal-phase flash chromatography (hep:EtOAc 0−100%), the title compound **50** was obtained as a yellow solid (0.26 g, 1.20 mmol, 26%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (s, 1H), 7.88 (dd, J = 7.4, 1.0 Hz, 1H), 7.83 (dd, J = 7.3, 1.0 Hz, 1H), 7.70−7.64 (m, 2H), 7.64−7.59 (m, 2H), 7.51 (dd, J = 7.8, 1.0 Hz, 1H), 7.40 (td, J = 7.4, 0.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.55, 167.08, 144.23, 143.03, 135.52, 135.46, 135.03, 132.89, 129.72, 129.23, 129.15, 124.12, 122.17, 121.05. LC-MS (ESI): m/z 224.1 $[M+1]^+$, t_R = 2.67 min.

*9H-Fluorene-4-carboxamide (**51**).* This previously reported compound was synthesized according to general procedure A. Starting from commercially available 9*H*-fluorene-4-carboxylic acid

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(0.89 g, 4.20 mmol, 1.00 equiv), the title compound **51** was obtained as an off-white solid (0.80 g, 3.80 mmol, 91%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.09−8.02 (m, 1H), 7.99 (s, 1H), 7.64 (dd, J = 6.7, 1.9 Hz, 1H), 7.62−7.58 (m, 2H), 7.39−7.29 (m, 4H), 3.94 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.98, 143.91, 143.43, 139.79, 136.95, 132.49, 126.88, 126.44, 126.17, 125.80, 125.41, 124.86, 123.11, 36.25. LC-MS (ESI): m/z 210.1 $[M+1]^+$, t_R = 2.63 min.

*9-Hydroxy-9H-fluorene-4-carboxamide (**52**).* This previously unreported compound was synthesized according to a literature protocol with minor deviations.[81] A solution of **27** (0.10 g, 0.44 mmol, 1.00 equiv) in MeOH (5.0 mL) was slowly treated with $NaBH_4$ (0.025 g, 0.66 mmol, 1.50 equiv). The mixture was stirred at rt for 2 h. Upon reaction completion as detected by TLC (R_f = 0.12, hep:EtOAc 1:1), the mixture was cooled to 0 °C and quenched with sat. aq. NH_4Cl (3 mL) and H_2O (3 mL). The mixture was then partitioned between EtOAc (20 mL) and H_2O (20 mL), the aq. phase was extracted with EtOAc (2 × 15 mL), and the combined organic phases were washed with sat. brine (20 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude was purified by normal-phase flash chromatography (hep:EtOAc 0−100%) to afford the title compound **52** as a white solid (0.076 g, 0.34 mmol, 84%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (s, 1H), 7.94−7.87 (m, 1H), 7.67−7.61 (m, 1H), 7.62−7.55 (m, 2H), 7.41−7.27 (m, 4H), 5.87 (d, J = 7.3 Hz, 1H), 5.45 (d, J = 7.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.68, 147.97, 147.34, 138.16, 135.44, 132.32, 128.07, 127.53, 126.99, 126.87, 125.70, 124.75, 123.04, 72.97. LC-MS (ESI): m/z 226.1 $[M+1]^+$, t_R = 1.83 min.

*3-Benzoylbenzamide (**53**).* This previously reported compound was synthesized according to general procedure A. Starting from commercially available 3-benzoylbenzoic acid (1.0 g, 4.40 mmol, 1.00 equiv) and following purification by normal-phase flash chromatography (hep:EtOAc 0−80%), the title compound **53** was obtained as a white solid (0.62 g, 2.80 mmol, 63%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (t, J = 1.8 Hz, 1H), 8.16 (dt, J = 7.8, 1.4 Hz, 2H), 7.87 (dt, J = 7.6, 1.4 Hz, 1H), 7.79−7.73 (m, 2H), 7.73−7.68 (m, 1H), 7.65 (t, J = 7.7 Hz, 1H), 7.58 (dd, J = 8.3, 7.0 Hz, 2H), 7.52 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 195.44, 167.00, 137.14, 136.75, 134.51, 132.88, 132.12, 131.32, 129.65, 128.65, 128.54. LC-MS (ESI): m/z 226.1 $[M+1]^+$, t_R = 2.51 min.

*1-Oxo-2,3-dihydro-1H-indene-4-carboxamide (**54**).* This previously reported compound was synthesized according to a literature protocol with minor deviations.[82] A MW vial was charged with commercially available 1-oxo-2,3-dihydro-1*H*-indene-4-carbonitrile (0.16 g, 1.00 mmol, 1.00 equiv), K_2CO_3 (0.007 g, 0.050 mmol, 0.05 equiv), *i*-PrOH (2.8 mL) and H_2O (5.7 mL). The vial was capped and the mixture subjected to MW irradiation at 150 °C for 15 min. Upon reaction completion as detected by TLC (R_f = 0.22, DCM:MeOH 95:5), the mixture was filtered and the filtrate concentrated *in vacuo*. The crude was purified by preparative HPLC (buffer A:B 0−50%) to afford the title compound **54** as a white solid (0.11 g, 0.63 mmol, 63%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (dd, J = 7.5, 1.2 Hz, 2H), 7.74 (dd, J = 7.6, 1.1 Hz, 1H), 7.50 (t, J = 7.5 Hz, 2H), 3.38−3.25 (m, 2H), 2.74−2.55 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 206.13, 168.26, 154.25, 137.52, 133.58, 133.21, 127.37, 124.95, 35.79, 25.90. LC-MS (ESI): m/z 176.1 $[M+1]^+$, t_R = 1.71 min.

*N-Methyl-9-oxo-9H-fluorene-4-carboxamide (**55**).* This previously reported compound was synthesized according to general procedure B starting from 9-oxo-9*H*-fluorene-4-carbonyl chloride (0.121 g, 0.50 mmol, 1.00 equiv), methylamine hydrochloride (0.068 g, 1.00 mmol, 2.00 equiv) and Et_3N (0.278 mL, 2.00 mmol, 4.00 equiv). Upon reaction completion, the mixture was washed with 1 M HCl (3 mL) and sat. $NaHCO_3$ (3 mL), and the organic phase was dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. Following purification by normal-phase flash chromatography (DCM:MeOH 0−10%), the title compound **55** was obtained as a light yellow solid (0.091 g, 0.39 mmol, 76%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75−8.45 (m, 1H), 7.73−7.67 (m, 2H), 7.65 (ddd, J = 7.3, 1.2, 0.7 Hz, 1H), 7.60 (td, J = 7.6, 1.3 Hz, 1H), 7.56 (dd, J = 7.7, 1.2 Hz, 1H), 7.47−7.38 (m, 2H), 2.86 (d, J = 4.6 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.38, 167.80, 142.73, 140.05, 135.42, 133.79, 133.75, 133.35, 132.93, 129.64, 129.31, 124.54, 123.88, 123.78, 26.07. LC-MS (ESI): m/z 238.1 $[M+1]^+$, t_R = 2.50 min.

*N-Ethyl-9-oxo-9H-fluorene-4-carboxamide (**56**).* This previously reported compound was synthesized according to general procedure B starting from 9-oxo-9*H*-fluorene-4-carbonyl chloride (0.121 g, 0.50 mmol, 1.00 equiv), ethylamine hydrochloride (0.082 g, 1.00 mmol, 2.00 equiv) and Et_3N (0.278 mL, 2.00 mmol, 4.00 equiv). Upon reaction completion, the mixture was washed with 1 M HCl (3 mL) and sat. $NaHCO_3$ (3 mL), and the organic phase was dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. Following purification by normal-phase flash chromatography (DCM:MeOH 0−10%), the title compound **56** was obtained as a yellow solid (0.095 g, 0.38 mmol, 74%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.71 (t, J = 5.6 Hz, 1H), 7.73 (dt, J = 7.6, 0.9 Hz, 1H), 7.69 (dd, J = 7.3, 1.2 Hz, 1H), 7.65 (dt, J = 7.3, 0.9 Hz, 1H), 7.61 (td, J = 7.6, 1.3 Hz, 1H), 7.55 (dd, J = 7.7, 1.2 Hz, 1H), 7.47−7.37 (m, 2H), 3.36 (qd, J = 7.2, 5.5 Hz, 2H), 1.18 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.40, 167.13, 142.78, 139.99, 135.38, 133.77, 133.36, 133.11, 129.63, 129.29, 124.49, 123.88, 123.77, 33.97, 14.46. LC-MS (ESI): m/z 252.2 $[M+1]^+$, t_R = 2.73 min.

*N-Butyl-9-oxo-9H-fluorene-4-carboxamide (**57**).* This previously reported compound was synthesized according to general procedure B starting from 9-oxo-9*H*-fluorene-4-carbonyl chloride (0.24 g, 1.00 mmol, 1.00 equiv), *n*-butylamine (0.30 mL, 3.00 mmol, 3.00 equiv) and Et_3N (0.21 mL, 1.50 mmol, 1.50 equiv). Upon reaction completion, the mixture was diluted with DCM (10 mL), washed with 2 M HCl (2 × 15 mL), sat. brine (15 mL), and the organic phase was dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. Following purification by normal-phase flash chromatography (hep:EtOAc 0−100%), the title compound **57** was obtained as a yellow solid (0.17 g, 0.62 mmol, 62%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.70 (d, J = 5.7 Hz, 1H), 7.75−7.67 (m, 2H), 7.65 (dt, J = 7.3, 0.9 Hz, 1H), 7.60 (td, J = 7.6, 1.3 Hz, 1H), 7.54 (dd, J = 7.7, 1.2 Hz, 1H), 7.48−7.34 (m, 2H), 3.34 (td, J = 7.1, 5.7 Hz, 2H), 1.65−1.48 (m, 2H), 1.46−1.29 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.40, 167.30, 142.78, 140.00, 135.33, 133.79, 133.78, 133.36, 133.12, 129.65, 129.29, 124.47, 123.89, 123.73, 38.75, 30.88, 19.60, 13.64. LC-MS (ESI): m/z 280.2 $[M+1]^+$, t_R = 3.27 min.

*N-Isopropyl-9-oxo-9H-fluorene-4-carboxamide (**58**).* This previously reported compound was synthesized according to general procedure B starting from 9-oxo-9*H*-fluorene-4-carbonyl chloride (0.24 g, 1.00 mmol, 1.00 equiv), isopropylamine (0.26 mL, 3.00 mmol, 3.00 equiv) and Et_3N (0.21 mL, 1.50 mmol, 1.50 equiv). Upon reaction completion, the mixture was diluted with DCM (20 mL) and washed with 1 M HCl (20 mL), 1 M NaOH (20 mL), sat. brine (20 mL), and the organic phase was dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. The title compound **58** was obtained as a yellow solid (0.27 g, 1.00 mmol, quantitative). ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.80 (dt, J = 7.7, 0.9 Hz, 1H), 7.66−7.65 (m, 1H), 7.65−7.63 (m, 1H), 7.48−7.41 (m, 2H), 7.30 (td, J = 7.4, 0.9 Hz, 1H), 7.29−7.23 (m, 1H), 5.92 (d, J = 7.9 Hz, 1H), 4.37 (dp, J = 7.9, 6.5 Hz, 1H), 1.33 (dd, J = 6.6, 0.8 Hz, 6H). ^{13}C NMR (151 MHz, chloroform-*d*) δ 193.18, 167.76, 143.17, 141.20, 135.18, 135.11, 134.26, 132.94, 132.43, 129.59, 129.09, 125.39, 124.40, 124.13, 42.35, 22.87. LC-MS (ESI): m/z 266.2 $[M+1]^+$, t_R = 2.94 min.

*4-(Piperidine-1-carbonyl)-9H-fluoren-9-one (**59**).* This previously reported compound was synthesized according to general procedure B starting from 9-oxo-9*H*-fluorene-4-carbonyl chloride (0.121 g, 0.50 mmol, 1.00 equiv), piperidine (0.085 g, 1.00 mmol, 2.00 equiv) and Et_3N (0.139 mL, 1.00 mmol, 2.00 equiv). Upon reaction completion, the mixture was diluted with DCM (5 mL), washed with sat. $NaHCO_3$ (3 mL) and 1 M HCl (3 mL), and the organic phase was dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. Following purification by normal-phase flash chromatography (DCM:MeOH 0−10%), the title compound **59** was obtained as a yellow solid (0.063 g, 0.22 mmol, 43%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.71−7.59 (m, 3H), 7.49−7.37 (m, 4H), 3.75 (t, J = 5.2

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Hz, 2H), 3.33−3.10 (m, 2H), 1.73−1.53 (m, 4H), 1.51−1.34 (m, 1H), 1.35−1.18 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.19, 166.33, 142.35, 139.10, 135.60, 133.80, 133.36, 132.47, 131.56, 129.76, 124.13, 124.01, 122.46, 47.38, 41.76, 26.03, 25.10, 23.86. LC-MS (ESI): m/z 292.2 $[M+1]^+$, t_R = 3.28 min.

*4-(4-Hydroxypiperidine-1-carbonyl)-9H-fluoren-9-one (**60**).* This previously unreported compound was synthesized according to general procedure B starting from 9-oxo-9*H*-fluorene-4-carbonyl chloride (0.121 g, 0.50 mmol, 1.00 equiv), 4-hydroxypiperidine (0.101 g, 1.00 mmol, 2.00 equiv) and Et_3N (0.139 mL, 1.00 mmol, 2.00 equiv). Upon reaction completion, the mixture was concentrated to dryness *in vacuo*. Following purification by normal-phase flash chromatography (DCM:MeOH 0−10%), the title compound **60** was obtained as a yellow solid (0.15 g, 0.50 mmol, quantitative). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79−7.55 (m, 3H), 7.56−7.26 (m, 4H), 5.02 (s, 1H), 4.16 (dt, J = 11.8, 5.0 Hz, 1H), 3.75 (tt, J = 8.2, 3.8 Hz, 1H), 3.48−3.30 (m, 2H), 3.08 (dddd, J = 26.8, 13.1, 9.2, 3.4 Hz, 1H), 1.98−1.80 (m, 1H), 1.71−1.40 (m, 2H), 1.38−1.00 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.19, 166.39, 142.34, 139.13, 135.66, 133.86, 133.37, 132.50, 131.46, 129.77, 124.14, 124.06, 122.51, 122.33, 65.17, 44.05, 38.47, 34.50, 33.49. LC-MS (ESI): m/z 308.2 $[M+1]^+$, t_R = 2.37 min.

*tert-Butyl 4-(9-oxo-9H-fluorene-4-carbonyl)piperazine-1-carboxylate (**61a**).* This previously unreported compound was synthesized according to general procedure B starting from 9-oxo-9*H*-fluorene-4-carbonyl chloride (0.121 g, 0.50 mmol, 1.00 equiv), *tert*-butyl piperazine-1-carboxylate (0.19 g, 1.00 mmol, 2.00 equiv) and Et_3N (0.139 mL, 1.00 mmol, 2.00 equiv). Upon reaction completion, the mixture was diluted with DCM (5 mL), washed with sat. $NaHCO_3$ (3 mL) and 1 M HCl (3 mL), and the organic phase was dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. The title compound **61a** was obtained as a yellow oil (0.27 g, ∼0.50 mmol, quantitative). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.89−7.11 (m, 7H), 3.77 (t, J = 5.3 Hz, 2H), 3.51 (dt, J = 15.5, 5.5 Hz, 1H), 3.30 (s, 4H), 2.80 (t, J = 5.2 Hz, 1H), 1.39 (s, 9H).

*4-(Piperazine-1-carbonyl)-9H-fluoren-9-one (**61**).* This previously unreported compound was synthesized according to general procedure C. Starting from **61a** (0.27 g, 0.50 mmol, 1.00 equiv) and TFA (0.574 mL, 7.50 mmol, 15.0 equiv) and following purification by normal-phase flash chromatography (DCM:MeOH 0−10%), the title compound **61** was obtained as a yellow solid (0.087 g, 0.30 mmol, 58%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.69−7.61 (m, 3H), 7.48−7.39 (m, 4H), 3.82−3.72 (m, 1H), 3.72−3.61 (m, 1H), 3.29−3.18 (m, 1H), 3.18−3.07 (m, 1H), 2.92−2.81 (m, 2H), 2.70−2.58 (m, 1H), 2.55−2.44 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.18, 166.52, 142.28, 139.23, 135.62, 133.82, 133.37, 132.65, 131.19, 129.81, 129.77, 124.15, 124.11, 122.49, 47.53, 45.70, 45.03, 42.00. LC-MS (ESI): m/z 293.2 $[M+1]^+$, t_R = 1.69 min.

*4-(4-Ethylpiperazine-1-carbonyl)-9H-fluoren-9-one (**62**).* This previously unreported compound was synthesized according to general procedure B starting from 9-oxo-9*H*-fluorene-4-carbonyl chloride (0.121 g, 0.50 mmol, 1.00 equiv), 1-ethylpiperazine (0.114 g, 1.00 mmol, 2.00 equiv), and Et_3N (0.139 mL, 1.00 mmol, 2.00 equiv). Upon reaction completion, the mixture was concentrated to dryness *in vacuo*. Following purification by normal-phase flash chromatography (DCM:MeOH 0−10%), the title compound **62** was obtained as a yellow solid (0.14 g, 0.44 mmol, 88%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.73−7.59 (m, 3H), 7.52−7.38 (m, 4H), 3.84 (dt, J = 10.6, 5.0 Hz, 1H), 3.78−3.64 (m, 1H), 3.40−3.22 (m, 1H), 3.24−3.11 (m, 1H), 2.58−2.44 (m, 2H), 2.40−2.24 (m, 3H), 2.18−2.07 (m, 1H), 0.97 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.15, 166.47, 142.22, 139.24, 135.58, 133.82, 133.37, 132.63, 131.08, 129.83, 129.76, 124.17, 124.14, 122.56, 52.48, 51.75, 51.39, 46.49, 41.12, 11.77. LC-MS (ESI): m/z 321.1 $[M+1]^+$, t_R = 1.42 min.

*4-(Pyrrolidine-1-carbonyl)-9H-fluoren-9-one (**63**).* This previously unreported compound was synthesized according to general procedure B starting from 9-oxo-9*H*-fluorene-4-carbonyl chloride (0.121 g, 0.50 mmol, 1.00 equiv), pyrrolidine (0.071 g, 1.00 mmol, 2.00 equiv), and Et_3N (0.139 mL, 1.00 mmol, 2.00 equiv). Upon reaction completion, the mixture was concentrated to dryness *in vacuo*. Following purification by normal-phase flash chromatography (DCM:MeOH 0−10%), the title compound **63** was obtained as a yellow-brown solid (0.12 g, 0.43 mmol, 86%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70−7.64 (m, 2H), 7.62 (td, J = 7.6, 1.2 Hz, 1H), 7.52 (dd, J = 7.7, 1.3 Hz, 1H), 7.46 (d, J = 7.3 Hz, 1H), 7.45−7.39 (m, 2H), 3.62 (t, J = 7.0 Hz, 2H), 3.15 (t, J = 6.7 Hz, 2H), 1.91 (qd, J = 6.7, 0.9 Hz, 2H), 1.85−1.73 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.22, 166.14, 142.44, 138.85, 135.74, 133.75, 133.33, 132.56, 129.79, 124.12, 124.09, 122.15, 47.80, 45.36, 25.54, 23.99. LC-MS (ESI): m/z 278.2 $[M+1]^+$, t_R = 2.94 min.

*4-(3-Hydroxypyrrolidine-1-carbonyl)-9H-fluoren-9-one (**64**).* This previously unreported compound was synthesized according to general procedure B starting from 9-oxo-9*H*-fluorene-4-carbonyl chloride (0.121 g, 0.50 mmol, 1.00 equiv), 3-hydroxypyrrolidine (0.087 g, 1.00 mmol, 2.00 equiv) and Et_3N (0.139 mL, 1.00 mmol, 2.00 equiv). Upon reaction completion, the mixture was concentrated to dryness *in vacuo*. Following purification by normal-phase flash chromatography (DCM:MeOH 0−10%), the title compound **64** was obtained as a yellow solid (0.095 g, 0.32 mmol, 63%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.70−7.64 (m, 4H), 7.59 (dtd, J = 16.0, 7.6, 1.2 Hz, 2H), 7.51 (td, J = 7.4, 1.2 Hz, 2H), 7.46 (td, J = 7.5, 1.7 Hz, 4H), 7.44−7.40 (m, 2H), 5.05 (d, J = 3.1 Hz, 1H), 4.93 (d, J = 3.4 Hz, 1H), 4.38 (td, J = 4.1, 1.7 Hz, 1H), 4.21 (td, J = 4.5, 1.9 Hz, 1H), 3.79−3.52 (m, 4H), 3.38−3.16 (m, 3H), 3.00 (d, J = 11.1 Hz, 1H), 1.99 (dtd, J = 13.5, 9.1, 4.5 Hz, 1H), 1.94−1.82 (m, 2H), 1.81−1.67 (m, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.23, 166.54, 166.52, 142.38, 142.36, 138.96, 138.87, 135.70, 135.66, 133.78, 133.75, 133.31, 132.62, 132.49, 132.40, 129.84, 129.82, 129.79, 124.17, 124.05, 124.02, 122.46, 122.30, 69.04, 68.16, 56.02, 53.82, 45.81, 43.56, 40.06, 39.92, 39.29, 39.15, 33.88, 32.32. Rotamers seen. LC-MS (ESI): m/z 294.1 $[M+1]^+$, t_R = 1.67 min.

*N-Benzyl-9-oxo-9H-fluorene-4-carboxamide (**65**).* This previously reported compound was synthesized according to general procedure B starting from 9-oxo-9*H*-fluorene-4-carbonyl chloride (0.24 g, 1.00 mmol, 1.00 equiv), benzylamine (0.328 mL, 3.00 mmol, 3.00 equiv) and Et_3N (0.21 mL, 1.50 mmol, 1.50 equiv). Upon reaction completion, the mixture was diluted with DCM (20 mL), washed with 0.5 M HCl (20 mL), 1 M NaOH (20 mL) and sat. brine (20 mL), and the organic phase was dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. The title compound **65** was obtained as a light yellow solid (0.20 g, 0.65 mmol, 65%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.27 (t, J = 6.0 Hz, 1H), 7.70 (dd, J = 7.3, 1.1 Hz, 1H), 7.66−7.62 (m, 1H), 7.61 (dd, J = 7.7, 1.1 Hz, 1H), 7.53 (dt, J = 7.6, 0.9 Hz, 1H), 7.49−7.35 (m, 7H), 7.33−7.26 (m, 1H), 4.54 (d, J = 6.0 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.36, 167.35, 142.63, 140.09, 138.81, 135.19, 133.81, 133.74, 133.33, 132.77, 129.64, 129.35, 128.37, 127.65, 127.00, 124.63, 123.87, 123.82, 42.71. LC-MS (ESI): m/z 314.1 $[M+1]^+$, t_R = 3.25 min.

*9-Oxo-N-phenethyl-9H-fluorene-4-carboxamide (**66**).* This previously reported compound was synthesized according to general procedure B starting from 9-oxo-9*H*-fluorene-4-carbonyl chloride (0.24 g, 1.00 mmol, 1.00 equiv), 2-phenylethan-1-amine (0.378 mL, 3.00 mmol, 3.00 equiv) and Et_3N (0.21 mL, 1.50 mmol, 1.50 equiv). Upon reaction completion, the mixture was washed with 1 M HCl (15 mL) and sat. brine (15 mL), and the organic phase was dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. Following purification by normal-phase flash chromatography (hep:EtOAc 0−100%), the title compound **66** was obtained as a light yellow solid (0.19 g, 0.65 mmol, 65%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.80 (t, J = 5.6 Hz, 1H), 7.68 (dd, J = 7.2, 1.3 Hz, 1H), 7.66−7.60 (m, 1H), 7.60−7.55 (m, 1H), 7.53 (td, J = 7.5, 1.2 Hz, 1H), 7.49 (dd, J = 7.7, 1.3 Hz, 1H), 7.43 (d, J = 7.4 Hz, 1H), 7.39 (td, J = 7.3, 1.4 Hz, 1H), 7.31 (d, J = 5.6 Hz, 4H), 7.27−7.19 (m, 1H), 3.61 (td, J = 7.2, 5.6 Hz, 2H), 2.91 (t, J = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.37, 167.32, 142.63, 140.09, 139.23, 135.39, 133.81, 133.75, 133.28, 132.92, 129.57, 129.23, 128.71, 128.29, 126.16, 124.53, 123.94, 123.79, 40.42, 34.81. LC-MS (ESI): m/z 328.2 $[M+1]^+$, t_R = 3.36 min.

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*Ethyl (9-oxo-9H-fluorene-4-carbonyl)glycinate (**67a**).* This previously unreported compound was synthesized according to general procedure B starting from 9-oxo-9*H*-fluorene-4-carbonyl chloride (0.121 g, 0.50 mmol, 1.00 equiv), ethyl glycinate hydrochloride (0.140 g, 1.00 mmol, 2.00 equiv) and Et_3N (0.278 mL, 2.00 mmol, 4.00 equiv). Upon reaction completion, the mixture was washed with 1 M HCl (3 mL) and sat. $NaHCO_3$ (3 mL), and the organic phase was dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. The title compound **67a** was obtained as a yellow solid (0.55 g, ∼0.50 mmol, quantitative). The crude was used without further characterization.

*(9-Oxo-9H-fluorene-4-carbonyl)glycine (**67**).* This previously reported compound was synthesized according to general procedure D. Starting from **67a** (0.55 g, ∼0.50 mmol, 1.00 equiv) and following purification by preparative HPLC (buffer A:B 0−70%), the title compound **67** was obtained as a light yellow solid (0.044 g, 0.15 mmol, 36%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.76 (s, 1H), 9.10 (t, J = 5.9 Hz, 1H), 7.95 (dt, J = 7.7, 0.8 Hz, 1H), 7.71 (dd, J = 7.3, 1.2 Hz, 1H), 7.65 (ddd, J = 7.3, 1.2, 0.7 Hz, 1H), 7.61−7.52 (m, 2H), 7.46 (t, J = 7.5 Hz, 1H), 7.41 (td, J = 7.4, 0.9 Hz, 1H), 4.01 (d, J = 5.9 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.41, 171.03, 167.99, 142.63, 140.37, 135.24, 133.91, 133.90, 133.32, 132.27, 129.68, 129.29, 124.81, 124.52, 123.76, 41.19. LC-MS (ESI): m/z 282.1 $[M+1]^+$, t_R = 2.30 min.

*Ethyl 3-(9-oxo-9H-fluorene-4-carboxamido)propanoate (**68a**).* This previously unreported compound was synthesized according to general procedure B starting from 9-oxo-9*H*-fluorene-4-carbonyl chloride (0.121 g, 0.50 mmol, 1.00 equiv), ethyl 3-aminopropanoate hydrochloride (0.154 g, 1.00 mmol, 2.00 equiv) and Et_3N (0.278 mL, 2.00 mmol, 4.00 equiv). Upon reaction completion, the mixture was washed with 1 M HCl (3 mL) and sat. $NaHCO_3$ (3 mL), and the organic phase was dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. The title compound **68a** was obtained as a yellow solid (yield ND). The crude was used without further characterization.

*3-(9-Oxo-9H-fluorene-4-carboxamido)propanoic acid (**68**).* This previously reported compound was synthesized according to general procedure D. Starting from **68a** (crude weight, 0.50 mmol assumed, 1.00 equiv) and following purification by preparative HPLC (buffer A:B 0−70%), the title compound as a light yellow solid (0.082 g, 0.28 mmol, 55% over two steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.28 (s, 1H), 8.79 (t, J = 5.5 Hz, 1H), 7.77−7.71 (m, 1H), 7.69 (dd, J = 7.3, 1.2 Hz, 1H), 7.65 (dt, J = 7.4, 0.9 Hz, 1H), 7.59 (td, J = 7.6, 1.3 Hz, 1H), 7.54 (dd, J = 7.7, 1.2 Hz, 1H), 7.47−7.37 (m, 2H), 3.54 (td, J = 6.9, 5.4 Hz, 2H), 2.58 (t, J = 6.9 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.39, 172.72, 167.44, 142.69, 140.08, 135.42, 133.85, 133.79, 133.32, 132.80, 129.63, 129.24, 124.58, 123.97, 123.84, 35.43, 33.50. LC-MS (ESI): m/z 296.1 $[M+1]^+$, t_R = 2.31 min.

*Methyl 3-(9-oxo-9H-fluorene-4-carboxamido)butanoate (**69a**).* This previously unreported compound was synthesized according to general procedure B starting from 9-oxo-9*H*-fluorene-4-carbonyl chloride (0.24 g, 1.00 mmol, 1.00 equiv), methyl 4-aminobutanoate hydrochloride (0.46 g, 3.00 mmol, 3.00 equiv) and Et_3N (0.21 mL, 1.50 mmol, 1.50 equiv). Upon reaction completion, the mixture was diluted with DCM (20 mL), washed with 1 M HCl (20 mL), 1 M NaOH (20 mL) and sat. brine (20 mL), and the organic phase was dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. The title compound **69a** was obtained as a yellow-orange solid (0.31 g, 0.97 mmol, 97%). The crude was used without further characterization.

*3-(9-Oxo-9H-fluorene-4-carboxamido)butanoic acid (**69**).* This previously unreported compound was synthesized according to general procedure D. Starting from **69a** (0.16 g, 0.50 mmol, 1.00 equiv) and following purification by preparative HPLC (buffer A:B 0−100%), the title compound **69** was obtained as a light yellow solid (0.15 g, 0.25 mmol, 52%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.10 (s, 1H), 8.74 (t, J = 5.6 Hz, 1H), 7.72 (dt, J = 7.7, 0.8 Hz, 1H), 7.69 (dd, J = 7.3, 1.1 Hz, 1H), 7.68−7.63 (m, 1H), 7.61−7.54 (m, 2H), 7.44 (t, J = 7.5 Hz, 1H), 7.41 (td, J = 7.4, 0.9 Hz, 1H), 3.36 (td, J = 6.9, 5.5 Hz, 2H), 2.33 (t, J = 7.3 Hz, 2H), 1.81 (p, J = 7.2 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.40, 174.15, 167.45, 142.76, 140.06, 135.38, 133.86, 133.80, 133.37, 132.98, 129.68, 129.31, 124.56, 123.91, 123.81, 38.53, 31.05, 24.23. LC-MS (ESI): m/z 310.2 $[M+1]^+$, t_R = 2.41 min.

*Ethyl N-methyl-N-(9-oxo-9H-fluorene-4-carbonyl)glycinate (**70a**).* This previously unreported compound was synthesized according to general procedure B starting from 9-oxo-9*H*-fluorene-4-carbonyl chloride (0.121 g, 0.50 mmol, 1.00 equiv), ethyl methylglycinate hydrochloride (0.154 g, 1.00 mmol, 2.00 equiv) and Et_3N (0.278 mL, 2.00 mmol, 4.00 equiv). Upon reaction completion, the mixture was washed with 1 M HCl (3 mL) and sat. $NaHCO_3$ (3 mL), and the organic phase was dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. The title compound **70a** was obtained as a yellow solid (yield ND). The crude was used without further characterization.

*N-methyl-N-(9-oxo-9H-fluorene-4-carbonyl)glycine (**70**).* This previously unreported compound was synthesized according to general procedure D. Starting from **70a** (crude weight, 0.50 mmol assumed, 1.00 equiv) and following purification by preparative HPLC (buffer A:B 0−70%), the title compound **70** was obtained as a yellow solid (0.019 g, 0.063 mmol, 13% over two steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.96 (s, 1H), 7.83−7.32 (m, 7H), 4.54−3.73 (m, 2H), 3.21−2.85 (m, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.25, 170.41, 170.23, 168.91, 168.75, 142.27, 139.51, 135.41, 133.91, 133.28, 132.79, 132.29, 130.87, 129.83, 129.74, 129.60, 124.33, 123.96, 123.27, 122.98, 48.52, 37.37, 33.76. Amide rotamers seen. LC-MS (ESI): m/z 296.1 $[M+1]^+$, t_R = 2.43 min.

*tert-Butyl 3-(N-methyl-9-oxo-9H-fluorene-4-carboxamido)-propanoate (**71a**).* This previously unreported compound was synthesized according to general procedure B starting from 9-oxo-9*H*-fluorene-4-carbonyl chloride (0.121 g, 0.50 mmol, 1.00 equiv), *tert*-butyl 3-(methylamino)propanoate (0.159 g, 1.00 mmol, 2.00 equiv) and Et_3N (0.278 mL, 2.00 mmol, 4.00 equiv). Upon reaction completion, the mixture was washed with 1 M HCl (3 mL) and sat. $NaHCO_3$ (3 mL), and the organic phase was dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. The title compound **71a** was obtained as a yellow solid (yield ND). The crude was used without further characterization.

*3-(N-Methyl-9-oxo-9H-fluorene-4-carboxamido)propanoic acid (**71**).* This previously unreported compound was synthesized according to general procedure C. Starting from **71a** (crude weight, 0.50 mmol assumed, 1.00 equiv) and TFA (5.0 mL, 65.3 mmol, 130.0 equiv) and following purification by preparative HPLC (buffer A:B 0−70%), the title compound **71** was obtained as a yellow solid (0.13 g, 0.41 mmol, 79% over two steps). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.39 (s, 1H), 7.71−7.29 (m, 7H), 3.88−3.29 (m, 2H), 2.98 (d, J = 158.8 Hz, 3H), 2.71 (t, J = 7.2 Hz, 1H), 2.56−2.39 (m, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.20, 172.92, 172.11, 168.08, 142.35, 142.29, 139.24, 139.03, 135.71, 135.61, 133.81, 133.73, 133.36, 133.32, 132.81, 132.67, 131.58, 131.35, 129.85, 129.75, 129.72, 129.57, 124.18, 124.08, 122.43, 122.29, 45.94, 43.18, 43.01, 39.29, 39.15, 36.60, 36.46, 32.52, 31.64. Amide rotamers seen. LC-MS (ESI): m/z 310.2 $[M+1]^+$, t_R = 2.40 min.

*Ethyl 1-(9-oxo-9H-fluorene-4-carbonyl)piperidine-4-carboxylate (**72a**).* This previously unreported compound was synthesized according to general procedure B starting from 9-oxo-9*H*-fluorene-4-carbonyl chloride (0.121 g, 0.50 mmol, 1.00 equiv), ethylpiperidine-4-carboxylate (0.157 g, 1.00 mmol, 2.00 equiv) and Et_3N (0.278 mL, 2.00 mmol, 4.00 equiv). Upon reaction completion, the mixture was washed with 1 M HCl (3 mL) and sat. $NaHCO_3$ (3 mL), and the organic phase was dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. The title compound **72a** was obtained as a yellow solid (yield ND). The crude was used without further characterization.

*1-(9-Oxo-9H-fluorene-4-carbonyl)piperidine-4-carboxylic acid (**72**).* This previously unreported compound was synthesized according to general procedure D. Starting from **72a** (crude weight, 0.50 mmol assumed, 1.00 equiv) and following purification by preparative HPLC (buffer A:B 0−80%), the title compound **72** was obtained as a light yellow solid (0.067 g, 0.20 mmol, 42% over two

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steps). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.70−7.65 (m, 2H), 7.62 (td, J = 7.6, 1.1 Hz, 1H), 7.56−7.32 (m, 4H), 4.58−4.41 (m, 1H), 3.43 (dt, J = 13.8, 4.5 Hz, 1H), 3.23−2.94 (m, 2H), 2.61−2.51 (m, 1H), 2.09−1.92 (m, 1H), 1.80−1.55 (m, 2H), 1.55−1.05 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.18, 175.32, 175.27, 166.50, 166.44, 142.31, 139.06, 135.72, 135.47, 133.73, 133.36, 132.58, 132.48, 131.33, 129.81, 129.71, 124.15, 122.60, 122.28, 46.05, 45.56, 28.56, 28.07, 27.55, 27.42. Amide rotamers seen. LC-MS (ESI): m/z 336.1 $[M+1]^+$, t_R = 2.51 min.

*Ethyl 1-(9-oxo-9H-fluorene-4-carbonyl)piperidine-2-carboxylate (**73a**).* This previously unreported compound was synthesized according to general procedure E. Starting from 9-oxo-9*H*-fluorene-4-carbonyl chloride (0.285 g, 1.27 mmol, 1.00 equiv) and ethyl piperidine-2-carboxylate (0.200 g, 1.27 mmol, 1.00 equiv), the title compound **73a** was obtained as a yellow solid (0.68 g, ∼1.27 mmol, quantitative). The crude was used without further characterization.

*1-(9-Oxo-9H-fluorene-4-carbonyl)piperidine-2-carboxylic acid (**73**).* This previously unreported compound was synthesized according to general procedure D. Starting from **73a** (0.68 g, 1.27 mmol assumed, 1.00 equiv) and following purification by preparative HPLC (buffer A:B 0−100%), the title compound **73** was obtained as a yellow solid (0.089 g, 0.26 mmol, 21%). LC-MS (ESI): m/z 336.1 $[M+1]^+$, t_R = 2.07 min.

*tert-Butyl 4-(2-ethoxy-2-oxoethyl)piperazine-1-carboxylate (**74a**).* This previously reported compound was synthesized according to general procedure F. Starting from *tert*-butyl piperazine-1-carboxylate (0.931 g, 5.00 mmol, 1.00 equiv) and ethyl 2-bromoacetate (0.610 mL, 5.50 mmol, 1.10 equiv), the title compound **74a** was obtained as a white solid (1.36 g, ∼5.00 mmol, quantitative). LC-MS (ESI): m/z 273.2 $[M+1]^+$, t_R = 1.86−2.20 min.

*Ethyl 2-(piperazin-1-yl)acetate (**74b**).* This previously reported compound was synthesized according to general procedure C. Starting from **74a** (1.36 g, 5.00 mmol, 1.00 equiv) and TFA (5.74 mL, 75.0 mmol, 15.0 equiv), the title compound **74b** was obtained as an oil (0.35 g, 2.04 mmol, 41%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 4.18 (q, J = 7.1 Hz, 2H), 3.26 (s, 2H), 3.25−3.20 (m, 4H), 2.90−2.83 (m, 4H), 1.29−1.25 (m, 3H). LC-MS (ESI): m/z 173.1 $[M+1]^+$, t_R = 0.80 min.

*Ethyl 2-(4-(9-oxo-9H-fluorene-4-carbonyl)piperazin-1-yl)acetate (**74c**).* This previously unreported compound was synthesized according to general procedure B starting from **74b** (0.35 g, 2.04 mmol, 1.00 equiv), 9-oxo-9*H*-fluorene-4-carbonyl chloride (0.099 g, 0.41 mmol, 1.00 equiv) and Et_3N (0.085 mL, 0.61 mmol, 1.50 equiv). Upon reaction completion, the mixture was diluted with DCM (10 mL), washed with 1 M NaOH (10 mL), and the organic phase was dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. The title compound **74c** was obtained as golden-brown oil (0.15 g, ∼0.41 mmol, quantitative). LC-MS (ESI): m/z 379.2 $[M+1]^+$, t_R = 2.48 min.

*1-(Carboxymethyl)-4-(9-oxo-9H-fluorene-4-carbonyl)piperazin-1-ium trifluoroacetate (**74**).* This previously unreported compound was synthesized according to general procedure D. Starting from **74c** (0.15 g, 0.41 mmol assumed, 1.00 equiv) and following purification by preparative HPLC (buffer A:B 0−50%), the title compound **74** was obtained as a yellow solid (0.098 g, 0.21 mmol, 51%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76−7.67 (m, 2H), 7.64 (td, J = 7.6, 1.2 Hz, 1H), 7.58−7.40 (m, 4H), 3.93 (m, 4H), 3.40 (d, J = 87.2 Hz, 4H), 3.01 (d, J = 58.0 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.17, 171.17, 166.56, 142.22, 139.29, 135.64, 133.84, 133.36, 132.63, 131.01, 129.81, 129.77, 124.20, 124.13, 122.61, 58.07, 51.98, 51.29, 46.40, 41.05. LC-MS (ESI): m/z 351.2 $[M+1]^+$, t_R = 1.90 min.

*tert-Butyl 4-(3-ethoxy-3-oxopropyl)piperazine-1-carboxylate (**75a**).* This previously reported compound was synthesized according to general procedure F. Starting from *tert*-butyl piperazine-1-carboxylate (0.931 g, 5.00 mmol, 1.00 equiv) and ethyl 3-bromopropanoate (0.641 mL, 5.00 mmol, 1.00 equiv), the title compound **75a** was obtained as a slightly yellow oil (0.96 g, 3.35 mmol, 67%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 4.14 (q, J = 7.1 Hz, 2H), 3.42 (t, J = 5.1 Hz, 4H), 2.71 (t, J = 7.3 Hz, 2H), 2.49 (t, J = 7.3 Hz, 2H), 2.41 (t, J = 5.1 Hz, 4H), 1.45 (s, 9H), 1.25 (t, J = 7.1 Hz, 3H).

*4-(3-Ethoxy-3-oxopropyl)piperazin-1-ium trifluoroacetate (**75b**).* This previously reported compound was synthesized according to general procedure C. Starting from **75a** (0.962 g, 3.36 mmol, 1.00 equiv) and TFA (3.86 mL, 50.39 mmol, 15.0 equiv), the title compound **75b** was obtained as a yellowish solid (2.55 g, ∼3.36 mmol, quantitative). ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.11 (q, J = 7.1 Hz, 2H), 3.51−3.30 (m, 9H), 2.82 (t, J = 7.4 Hz, 2H), 1.21 (t, J = 7.1 Hz, 3H).

*Ethyl 3-(4-(9-oxo-9H-fluorene-4-carbonyl)piperazin-1-yl)-propanoate (**75c**).* This previously unreported compound was synthesized according to general procedure B starting from **75b** (2.55 g, 3.36 mmol assumed, 1.00 equiv), 9-oxo-9*H*-fluorene-4-carbonyl chloride (0.408 g, 1.68 mmol, 1.00 equiv) and Et_3N (2.34 mL, 16.8 mmol, 10.0 equiv). Upon reaction completion, the mixture was concentrated *in vacuo*, redissolved in EtOAc, washed with sat. $NaHCO_3$, and the organic phase was dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. The title compound **75c** was obtained as golden-brown oil (1.54 g, ∼1.68 mmol, quantitative). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.72−7.66 (m, 2H), 7.47−7.44 (m, 2H), 7.37−7.29 (m, 3H), 4.13 (q, J = 7.1 Hz, 2H), 3.91 (dtd, J = 15.9, 9.3, 2.8 Hz, 2H), 3.32 (tdd, J = 12.9, 10.2, 5.5 Hz, 2H), 2.71 (dd, J = 7.2, 6.4 Hz, 2H), 2.61 (qt, J = 10.7, 5.6 Hz, 2H), 2.50−2.44 (m, 2H), 2.41−2.25 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H).

*1-(2-Carboxyethyl)-4-(9-oxo-9H-fluorene-4-carbonyl)piperazin-1-ium trifluoroacetate (**75**).* This previously unreported compound was synthesized according to general procedure D. Starting from **75c** (1.54 g, 1.68 mmol assumed, 1.00 equiv) and following purification by preparative HPLC (buffer A:B 0−70%), the title compound **75** was obtained as a yellow solid (0.18 g, 0.37 mmol, 22%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (dd, J = 7.3, 1.2 Hz, 1H), 7.70−7.66 (m, 1H), 7.63 (td, J = 7.6, 1.2 Hz, 1H), 7.59 (dd, J = 7.7, 1.2 Hz, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.49−7.40 (m, 2H), 4.79−2.83 (m, 10H), 2.74 (t, J = 7.3 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.10, 171.54, 166.70, 142.11, 139.68, 135.76, 133.98, 133.37, 132.82, 129.92, 129.76, 124.63, 124.18, 122.67, 51.48, 51.08, 50.77, 43.36, 38.30, 28.68. LC-MS (ESI): m/z 365.3 $[M+1]^+$, t_R = 1.85 min.

*tert-Butyl 4-(4-ethoxy-4-oxobutyl)piperazine-1-carboxylate (**76a**).* This previously reported compound was synthesized according to general procedure F. Starting from *tert*-butyl piperazine-1-carboxylate (0.931 g, 5.00 mmol, 1.00 equiv) and ethyl 4-bromobutanoate (0.715 mL, 5.00 mmol, 1.00 equiv), the title compound **76a** was obtained as an oil (yield ND). The crude was used without further characterization.

*Ethyl 4-(piperazin-1-yl)butanoate (**76b**).* This previously reported compound was synthesized according to general procedure C. Starting from **76a** (crude weight, 5.00 mmol assumed, 1.00 equiv) and TFA (5.0 mL, 65.30 mmol, 13.1 equiv), the title compound **76b** was obtained (0.46 g, 2.31 mmol, 46%). LC-MS (ESI): m/z 201.2 $[M+1]^+$, t_R = 0.63 min.

*Ethyl 4-(4-(9-oxo-9H-fluorene-4-carbonyl)piperazin-1-yl)-butanoate (**76c**).* This previously unreported compound was synthesized according to general procedure B starting from **76b** (0.46 g, 2.31 mmol, 2.00 equiv), 9-oxo-9*H*-fluorene-4-carbonyl chloride (0.279 g, 1.15 mmol, 1.00 equiv) and Et_3N (0.85 mL, 6.10 mmol, 5.30 equiv). Upon reaction completion, the mixture was concentrated *in vacuo*, redissolved in EtOAc, washed with sat. $NaHCO_3$, and the organic phase was dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. The title compound **76c** was obtained as yellow-brown oil (0.59 g, ∼1.15 mmol, quantitative). LC-MS (ESI): m/z 407.2 $[M+1]^+$, t_R = 1.67 min.

*1-(3-Carboxypropyl)-4-(9-oxo-9H-fluorene-4-carbonyl)-piperazin-1-ium trifluoroacetate (**76**).* This previously unreported compound was synthesized according to general procedure D. Starting from **76c** (0.59 g, 1.15 mmol assumed, 1.00 equiv) and following purification by preparative HPLC (buffer A:B 0−50%), the title compound **76** was obtained as a yellow solid (0.26 g, 0.53 mmol, 46%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (dd, J = 7.3, 1.1 Hz, 1H), 7.70−7.66 (m, 1H), 7.66−7.56 (m, 2H), 7.47 (dt, J = 20.4, 7.3 Hz, 3H), 5.10−2.81 (m, 10H), 2.33 (t, J = 7.1 Hz, 2H), 1.86 (p, J = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-*d6*) δ 192.10, 173.41,

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166.70, 142.11, 135.77, 133.98, 133.37, 132.85, 129.93, 129.74, 124.64, 124.19, 122.66, 55.05, 50.52, 43.31, 30.42, 18.91. LC-MS (ESI): m/z 379.2 $[M+1]^+$, t_R = 1.86 min.

*Methyl 2-(9-oxo-9H-fluorene-4-carboxamido)-2-phenylacetate (**77a**).* This previously unreported compound was synthesized according to general procedure E. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.222 g, 0.99 mmol, 1.00 equiv) and methyl 2-amino-2-phenylacetate hydrochloride (0.200 g, 0.99 mmol, 1.00 equiv), the title compound **77a** was obtained as a yellow solid (1.40 g, ~0.99 mmol, quantitative). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.66 (d, J = 6.9 Hz, 1H), 7.74−7.35 (m, 12H), 5.74 (d, J = 6.1 Hz, 1H), 3.72 (s, 3H). LC-MS (ESI): m/z 372.1 $[M+1]^+$, t_R = 2.21 min.

*2-(9-oxo-9H-fluorene-4-carboxamido)-2-phenylacetic acid (**77**).* This previously Unreported compound was synthesized according to general procedure D. Starting from **77a** (1.40 g, 0.99 mmol assumed, 1.00 equiv) and following purification by preparative HPLC (buffer A:B 0−100%), the title compound **77** was obtained as a yellow solid (0.16 g, 0.44 mmol, 44%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.72 (dd, J = 7.3, 1.2 Hz, 1H), 7.70−7.66 (m, 1H), 7.63 (td, J = 7.6, 1.2 Hz, 1H), 7.59 (dd, J = 7.7, 1.2 Hz, 1H), 7.50 (d, J = 7.5 Hz, 1H), 7.49−7.40 (m, 2H), 4.79−2.83 (m, 10H), 2.74 (t, J = 7.3 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.93, 172.15, 167.92, 143.18, 140.86, 136.90, 135.61, 134.69, 134.20, 133.81, 132.63, 130.13, 129.61, 128.99, 128.67, 128.60, 125.19, 124.61, 124.27, 57.53. LC-MS (ESI): m/z 358.2 $[M+1]^+$, t_R = 2.98 min.

*Methyl (9-oxo-9H-fluorene-4-carbonyl)phenylalaninate (**78a**).* This previously reported compound was synthesized according to general procedure E. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.208 g, 0.927 mmol, 1.00 equiv) and methyl phenylalaninate hydrochloride (0.200 g, 0.927 mmol, 1.00 equiv), the title compound **78a** was obtained as a yellow solid (0.283 g, 0.735 mmol, 80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.24 (d, J = 7.8 Hz, 1H), 7.73−7.17 (m, 12H), 4.90−4.79 (m, 1H), 3.74 (s, 3H), 3.24 (dd, J = 13.9, 4.9 Hz, 1H), 3.00 (dd, J = 13.9, 10.7 Hz, 1H). LC-MS (ESI): m/z 386.2 $[M+1]^+$, t_R = 2.44 min.

*(9-Oxo-9H-fluorene-4-carbonyl)phenylalanine (**78**).* This previously unreported compound was synthesized according to general procedure D. Starting from **78a** (0.283 g, 0.735 mmol assumed, 1.00 equiv) and following purification by normal-phase flash chromatography (1% AcOH in DCM:1% AcOH in MeOH 0−5%), the title compound **78** was obtained as a yellow solid (0.124 g, 0.335 mmol, 46%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.00−12.93 (m, 1H), 9.11 (d, J = 8.3 Hz, 1H), 7.70−7.58 (m, 2H), 7.47−7.16 (m, 10H), 4.81−4.73 (m, 1H), 3.26 (dd, J = 14.0, 4.3 Hz, 1H), 2.96 (dd, J = 14.0, 11.1 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.36, 172.82, 167.46, 142.41, 140.25, 137.84, 135.21, 133.82, 133.71, 133.21, 132.26, 129.58, 129.21, 129.09, 128.22, 126.50, 124.71, 124.15, 123.69, 53.75, 36.26. LC-MS (ESI): m/z 372.2 $[M+1]^+$, t_R = 2.19 min.

*Ethyl phenylglycinate hydrochloride (**79a**).* This previously reported compound was synthesized according to general procedure G. Starting from *N*-phenylglycine (0.300 g, 1.98 mmol, 1.00 equiv), the title compound **79a** was obtained as a dark solid (yield ND). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.14−7.07 (m, 3H), 6.68−6.56 (m, 4H), 4.11 (q, J = 7.1 Hz, 2H), 3.89 (s, 2H), 1.19 (t, J = 7.1 Hz, 3H). LC-MS (ESI): m/z 180.0 $[M+1]^+$, t_R = 2.04 min.

*Ethyl N-(9-oxo-9H-fluorene-4-carbonyl)-N-phenylglycinate (**79b**).* This previously reported compound was synthesized according to general procedure E. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.475 g, 2.12 mmol, 1.00 equiv) and **79a** (0.380 g, 2.12 mmol, 1.00 equiv), the title compound **79b** was obtained as a red solid (0.627 g, 1.626 mmol, 77%). The crude was used without further characterization.

*N-(9-Oxo-9H-fluorene-4-carbonyl)-N-phenylglycine (**79**).* This previously unreported compound was synthesized according to general procedure D. Starting from **79b** (0.627 g, 1.63 mmol, 1.00 equiv) and following purification by preparative HPLC (buffer A:B 0−70%), the title compound **79** was obtained as a yellow solid (0.020 g, 0.056 mmol, 4%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 (s, 1H), 8.05−7.09 (m, 12H), 4.62 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.21, 170.25, 168.22, 142.32, 142.22, 140.63, 135.41, 133.53, 133.27, 131.24, 129.91, 129.12, 128.82, 127.53, 127.45, 124.05, 123.98, 123.72, 51.29. LC-MS (ESI): m/z 358.1 $[M+1]^+$, t_R = 2.16 min.

*Ethyl N-benzyl-N-(9-oxo-9H-fluorene-4-carbonyl)glycinate (**80a**).* This previously unreported compound was synthesized according to general procedure E. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.232 g, 1.035 mmol, 1.00 equiv) and ethyl benzylglycinate (0.200 g, 1.035 mmol, 1.00 equiv), the title compound **80a** was obtained as a dark solid (0.264 g, 0.740 mmol, 71%). The crude was used without further characterization.

*N-Benzyl-N-(9-oxo-9H-fluorene-4-carbonyl)glycine (**80**).* This previously unreported compound was synthesized according to general procedure D. Starting from **80a** (0.264 g, 0.662 mmol, 1.00 equiv) and following purification by preparative HPLC (buffer A:B 0−100%), the title compound **80** was obtained as a yellow solid (0.011 g, 0.030 mmol, 4%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.93 (s, 1H), 8.00−7.13 (m, 12H), 5.01−3.71 (m, 4H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.22 (d, J = 7.4 Hz), 170.18 (d, J = 2.6 Hz), 169.33, 169.01, 142.22 (d, J = 10.0 Hz), 139.91, 139.66, 136.49, 135.97, 135.28, 134.98, 134.05, 133.94, 133.30, 133.28, 132.54, 132.32, 130.59, 130.51, 129.86, 129.76, 129.60, 129.55, 128.73, 128.59, 128.47, 127.65, 127.48, 127.25, 124.43, 124.41, 123.90, 123.65, 123.11, 52.72, 49.99, 49.24, 46.79. LC-MS (ESI): m/z 372.1 $[M+1]^+$, t_R = 2.26 min.

*Methyl 2-hydroxy-3-nitro-2-phenylpropanoate (**81a**).* This previously reported compound was synthesized according to a literature protocol with minor deviations.[83] To a solution of commercially available methyl 2-oxo-2-phenylacetate (1.481 mL, 10.5 mmol, 1.00 equiv) in $MeNO_2$ (41.6 mL) was added Et_3N (0.290 mL, 2.08 mmol, 0.20 equiv). The mixture was stirred at rt for 22 h. Upon reaction completion as detected by TLC, the mixture was concentrated to dryness *in vacuo*. Purification by normal-phase flash chromatography (hep:EtOAc 0−70%) afforded the title compound **81a** as a white solid (2.36 g, 10.5 mmol, 81%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.57−7.50 (m, 2H), 7.44−7.31 (m, 3H), 6.86 (d, J = 1.2 Hz, 1H), 5.59 (dd, J = 13.5, 1.3 Hz, 1H), 4.83 (d, J = 13.5 Hz, 1H), 3.72 (s, 3H).

*Methyl 3-nitro-2-phenylacrylate (**81b**).* This previously reported compound was synthesized according to a literature protocol with minor deviations.[83] To a solution of **81a** (1.90 g, 8.46 mmol, 1.00 equiv) in DMSO (20 mL) was added Ac_2O (2.4 mL, 25.4 mmol, 3.00 equiv). The mixture was stirred at rt for 42 h. Upon reaction completion as detected by LC-MS, the mixture was added water, extracted with DCM (3 × 50 mL), and the combined organic phases were washed with sat. $NaHCO_3$ (50 mL) and sat. brine (50 mL), dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. Purification by normal-phase flash chromatography (hep:EtOAc 0−45%) afforded the title compound **81b** as a yellow oil (1.58 g, 7.64 mmol, 80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (s, 1H), 7.67−7.63 (m, 2H), 7.62−7.48 (m, 3H), 3.93 (s, 3H). LC-MS (ESI): m/z 208.1 $[M+1]^+$, t_R = 4.10 min.

*Methyl 3-((tert-butoxycarbonyl)amino)-2-phenylpropanoate (**81c**).* This previously reported compound was synthesized according to general procedure H. Starting from **81b** (0.414 g, 2.00 mmol, 1.00 equiv), the title compound **81c** was obtained as a yellow oil (0.670 g, ~2.00 mmol, quantitative). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33 (d, J = 7.3 Hz, 2H), 7.30−7.22 (m, 3H), 4.03 (q, J = 7.1 Hz, 2H), 3.85 (t, J = 7.6 Hz, 1H), 3.59 (d, J = 2.1 Hz, 4H), 3.56−3.45 (m, 1H), 1.99 (s, 3H), 1.47 (s, 4H), 1.21−1.14 (m, 3H).

*Methyl 3-amino-2-phenylpropanoate trifluoroacetate (**81d**).* This previously reported compound was synthesized according to general procedure C. Starting from **81c** (0.670 g, 2.00 mmol assumed, 1.00 equiv) and TFA (35.6 mL, 311.9 mmol, 130 equiv), the title compound **81d** was obtained as an orange oil (0.663 g, ~2.00 mmol, quantitative). LC-MS (ESI): m/z 180.1 $[M+1]^+$, t_R = 2.42 min.

*Methyl 3-(9-oxo-9H-fluorene-4-carboxamido)-2-phenylpropanoate (**81e**).* This previously unreported compound was synthesized according to general procedure E. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.224 g, 1.00 mmol, 1.00 equiv) and **81d** (0.663 g, 2.00 mmol assumed, 2.00 equiv), the title compound **81e** was obtained as a yellow solid (0.079 g, 0.205 mmol, 21%). ^{1}H NMR (600

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MHz, DMSO-d_6) δ 8.89 (t, J = 5.6 Hz, 2H), 7.67 (dd, J = 7.1, 1.4 Hz, 2H), 7.63 (dt, J = 7.3, 1.0 Hz, 2H), 7.56−7.51 (m, 3H), 7.43−7.28 (m, 3H), 4.09 (t, J = 7.7 Hz, 2H), 3.91−3.74 (m, 2H), 3.62 (s, 5H). LC-MS (ESI): m/z 386.2 $[M+1]^+$, t_R = 4.35 min.

*3-(9-Oxo-9H-fluorene-4-carboxamido)-2-phenylpropanoic acid (**81**).* This previously unreported compound was synthesized according to general procedure D. Starting from **81e** (0.079 g, 0.205 mmol, 1.00 equiv), the title compound **81** was obtained as a yellow solid (0.041 g, 0.110 mmol, 54%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.61 (s, 1H), 8.86 (t, J = 5.6 Hz, 1H), 7.69−7.57 (m, 2H), 7.57−7.44 (m, 2H), 7.42−7.38 (m, 2H), 7.38−7.35 (m, 5H), 7.31 (h, J = 4.1 Hz, 1H), 4.00 (t, J = 7.7 Hz, 1H), 3.79 (dddd, J = 54.5, 13.5, 7.7, 5.6 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.85, 173.82, 168.06, 143.04, 140.62, 137.73, 135.91, 134.28 (two signals), 133.74, 133.09, 130.08, 129.66, 129.06, 128.62, 127.89, 125.11, 124.52, 124.26, 50.78, 42.40. LC-MS (ESI): m/z 372.1 $[M+1]^+$, t_R = 3.93 min.

*Methyl 2-cyano-3-phenylacrylate (**82a**).* This previously reported compound was synthesized according to a literature protocol with no deviations.[84] Starting from methyl 2-cyanoacetate (0.088 mL, 1.00 mmol, 1.00 equiv), benzaldehyde (0.101 mL, 1.00 mmol, 1.00 equiv), Et_3N (0.014 mL, 0.10 mmol, 0.10 equiv) and abs. EtOH (3.00 mL), the title compound **82a** was obtained as a white solid (0.193 g, ∼1.00 mmol, quantitative). ^{1}H NMR (600 MHz, chloroform-d) δ 8.27 (s, 1H), 8.02−7.97 (m, 2H), 7.60−7.54 (m, 2H), 7.54−7.47 (m, 2H), 3.94 (s, 3H). LC-MS (ESI): m/z 188.1 $[M+1]^+$, t_R = 4.25 min.

*Methyl 2-benzyl-3-((tert-butoxycarbonyl)amino)propanoate (**82b**).* This previously reported compound was synthesized according to general procedure H. Starting from **82a** (0.193 g, 1.00 mmol, 1.00 equiv), the title compound **82b** was obtained as an orange oil (0.349 g, ∼1.00 mmol, quantitative). ^{1}H NMR (400 MHz, chloroform-d) δ 7.23 (dd, J = 6.2, 1.7 Hz, 2H), 7.20−7.04 (m, 3H), 4.81 (s, 1H), 3.61 (s, 2H), 3.39−3.15 (m, 2H), 2.90 (s, 1H), 1.49 (s, 3H), 1.43 (d, J = 6.2 Hz, 1H), 1.37 (d, J = 1.6 Hz, 1H), 1.22 (t, J = 7.1 Hz, 1H). LC-MS (ESI): m/z 294.2 $[M+1]^+$, t_R = 4.60 min.

*Methyl 3-amino-2-benzylpropanoate trifluoroacetate (**82c**).* This previously reported compound was synthesized according to general procedure C. Starting from **82b** (0.349 g, 1.00 mmol assumed, 1.00 equiv) and TFA (17.6 mL, 154.7 mmol, 130 equiv), the title compound **82c** was obtained as an orange-brown oil (1.28 g, ∼1.00 mmol, quantitative). LC-MS (ESI): m/z 194.2 $[M+1]^+$, t_R = 2.70 min.

*Methyl 2-benzyl-3-(9-oxo-9H-fluorene-4-carboxamido)-propanoate (**82d**).* This previously unreported compound was synthesized according to general procedure E. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.224 g, 1.00 mmol, 1.00 equiv) and **81d** (1.277 g, 1.00 mmol assumed, 1.00 equiv), the title compound **82d** was obtained as a yellow oil (0.124 g, 0.310 mmol, 31%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.91 (t, J = 5.8 Hz, 1H), 7.75−7.66 (m, 2H), 7.61−7.36 (m, 4H), 7.34−7.26 (m, 2H), 7.22 (dt, J = 6.2, 1.4 Hz, 3H), 3.62−3.46 (m, 5H), 3.12−3.01 (m, 1H), 2.97−2.83 (m, 2H). LC-MS (ESI): m/z 400.2 $[M+1]^+$, t_R = 4.55 min.

*2-Benzyl-3-(9-oxo-9H-fluorene-4-carboxamido)propanoic acid (**82**).* This previously unreported compound was synthesized according to general procedure D. Starting from **82d** (0.124 g, 0.310 mmol, 1.00 equiv), the title compound **82d** was obtained as a yellow solid (0.068 g, 0.219 mmol, 71%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.37 (s, 1H), 8.89 (t, J = 5.6 Hz, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.70 (dd, J = 7.3, 1.2 Hz, 1H), 7.65 (d, J = 7.3 Hz, 1H), 7.58 (td, J = 7.6, 1.3 Hz, 1H), 7.52 (dd, J = 7.7, 1.2 Hz, 1H), 7.42 (dt, J = 21.5, 7.5 Hz, 2H), 7.30 (t, J = 7.5 Hz, 2H), 7.27−7.19 (m, 3H), 3.62−3.42 (m, 2H), 3.04−2.96 (m, 1H), 2.94−2.84 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.89, 175.07, 168.14, 143.15, 140.65, 139.47, 135.90, 134.42, 134.31, 133.81, 133.20, 130.15, 129.72, 129.31, 128.78, 126.74, 125.13, 124.52, 124.33, 46.94, 41.34, 35.91. LC-MS (ESI): m/z 386.2 $[M+1]^+$, t_R = 4.07 min.

*3-Amino-3-phenylpropanoic acid hydrochloride (**83a**).* This previously reported compound was synthesized according to general procedure G. Starting from 3-amino-3-phenylpropanoic acid (0.826 g, 5.00 mmol, 1.00 equiv), the title compound **83a** was obtained as a light-yellow solid (1.13 g, ∼5.00 mmol, quantitative). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.77 (s, 3H), 7.60−7.48 (m, 2H), 7.44−7.40 (m, 2H), 7.40−7.36 (m, 1H), 4.63−4.51 (m, 1H), 3.54 (s, 3H), 3.22 (dd, J = 16.2, 5.9 Hz, 1H), 3.01 (dd, J = 16.2, 8.7 Hz, 1H).

*Methyl 3-(9-oxo-9H-fluorene-4-carboxamido)-3-phenylpropanoate (**83b**).* This previously unreported compound was synthesized according to general procedure E. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.100 g, 0.446 mmol, 1.00 equiv) and **83a** (0.096 g, 0.446 mmol, 1.00 equiv), the title compound **83b** was obtained as a yellow solid (0.280 g, ∼0.446 mmol, quantitative). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.33 (d, J = 8.3 Hz, 1H), 7.95 (s, 3H), 7.70 (dd, J = 6.7, 1.7 Hz, 1H), 7.62 (dq, J = 5.8, 1.9 Hz, 1H), 7.52−7.28 (m, 10H), 5.53 (td, J = 8.8, 6.1 Hz, 1H), 3.60 (s, 3H), 2.96−2.90 (m, 2H). LC-MS (ESI): m/z 386.2 $[M+1]^+$, t_R = 4.32 min.

*3-(9-Oxo-9H-fluorene-4-carboxamido)-3-phenylpropanoic acid (**83**).* This previously unreported compound was synthesized according to general procedure D. Starting from **83b** (0.280 g, 0.446 mmol assumed, 1.00 equiv), the title compound **83** was obtained as a yellow solid (0.070 g, 0.189 mmol, 42%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.45−12.25 (m, 1H), 9.29 (d, J = 8.3 Hz, 1H), 7.69 (dd, J = 7.1, 1.4 Hz, 1H), 7.64−7.60 (m, 1H), 7.49 (dd, J = 7.7, 1.4 Hz, 1H), 7.47−7.43 (m, 3H), 7.42−7.34 (m, 5H), 7.33−7.29 (m, 1H), 5.50 (td, J = 8.8, 6.0 Hz, 1H), 2.86 (dd, J = 16.0, 9.2 Hz, 1H), 2.79 (dd, J = 16.0, 6.0 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.37, 171.69, 166.55, 142.49, 142.08, 140.03, 135.18, 133.78, 133.62, 133.26, 132.77, 129.60, 129.31, 128.43, 127.22, 126.70, 124.58, 123.90, 123.80, 50.00, 40.42. LC-MS (ESI): m/z 372.1 $[M+1]^+$, t_R = 3.90 min.

*Methyl 3-amino-4-phenylbutanoate hydrochloride (**84a**).* This previously reported compound was synthesized according to general procedure G. Starting from 3-amino-4-phenylbutanoic acid (0.358 g, 2.00 mmol, 1.00 equiv), the title compound **84a** was obtained as a yellow solid (0.689 g, ∼2.00 mmol, quantitative). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.31 (s, 2H), 7.34 (t, J = 7.4 Hz, 1H), 7.30−7.24 (m, 2H), 3.68 (q, J = 6.5 Hz, 1H), 3.56 (d, J = 14.4 Hz, 6H), 3.16 (s, 2H), 3.08 (dd, J = 13.6, 5.6 Hz, 1H), 2.82 (dd, J = 13.6, 8.5 Hz, 1H), 2.68 (dd, J = 16.8, 7.0 Hz, 1H), 2.56 (dd, J = 16.7, 5.7 Hz, 1H). LC-MS (ESI): m/z 194.1 $[M+1]^+$, t_R = 2.46 min.

*Methyl 3-(9-oxo-9H-fluorene-4-carboxamido)-4-phenylbutanoate (**84b**).* This previously unreported compound was synthesized according to general procedure E. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.224 g, 1.00 mmol, 1.00 equiv) and **84a** (0.230 g, 1.00 mmol, 1.00 equiv), the title compound **84b** was obtained as a yellow solid (0.334 g, 0.836 mmol, 84%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.72 (d, J = 8.7 Hz, 1H), 7.69−7.57 (m, 2H), 7.46−7.39 (m, 2H), 7.34 (s, 1H), 7.30 (d, J = 5.9 Hz, 4H), 4.67 (ddt, J = 10.8, 8.6, 4.4 Hz, 1H), 3.60 (s, 3H), 2.98−2.75 (m, 2H), 2.73−2.57 (m, 2H), 0.84 (d, J = 7.1 Hz, 5H). LC-MS (ESI): m/z 400.1 $[M+1]^+$, t_R = 4.46 min.

*3-(9-Oxo-9H-fluorene-4-carboxamido)-4-phenylbutanoic acid (**84**).* This previously unreported compound was synthesized according to general procedure D. Starting from **84b** (0.334 g, 0.836 mmol assumed, 1.00 equiv), the title compound **84** was obtained as a yellow solid (0.106 g, 0.275 mmol, 33%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.31 (s, 1H), 8.69 (d, J = 8.7 Hz, 1H), 7.69−7.58 (m, 2H), 7.47−7.39 (m, 2H), 7.39−7.33 (m, 2H), 7.32−7.27 (m, 4H), 7.24 (d, J = 6.9 Hz, 1H), 4.71−4.62 (m, 1H), 3.00−2.75 (m, 2H), 2.57 (d, J = 7.0 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.89, 172.85, 167.14, 142.93, 140.60, 138.96, 135.87, 134.28, 134.22, 133.66, 133.37, 129.97, 129.73, 129.58, 128.68, 126.79, 124.99, 124.66, 124.13, 48.24. LC-MS (ESI): m/z 386.1 $[M+1]^+$, t_R = 4.02 min.

*Methyl 3-(phenylamino)propanoate (**85a**).* This previously reported compound was synthesized according to a literature protocol with minor deviations.[85] A solution of aniline (0.452 mL, 5.00 mmol, 1.00 equiv) and methyl acrylate (0.916 mL, 10.0 mmol, 2.00 equiv) in water (4.4 mL) and TFE (0.6 mL) was stirred at 80 °C for 23 h. Upon reaction completion as detected by TLC (R_f = = 0.7, hep:EtOAc 1:1), the mixture was diluted with water and extracted with DCM (3 × 30 mL). The combined organic phases were dried over Na_2SO_4, and concentrated *in vacuo*. Following purification by

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normal-phase flash chromatography (hep:EtOAc 0−50%), the title compound **85a** was obtained as a yellow/orange oil (0.324 g, 1.808 mmol, 36%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.23−7.15 (m, 2H), 6.82−6.38 (m, 3H), 3.70 (s, 3H), 3.47 (t, J = 6.4 Hz, 2H), 2.64 (t, J = 6.4 Hz, 2H).

*Methyl 3-(9-oxo-N-phenyl-9H-fluorene-4-carboxamido)-propanoate (**85b**).* This previously unreported compound was synthesized according to general procedure I. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.224 g, 1.00 mmol, 1.00 equiv) and **85a** (0.324 g, 1.81 mmol, 1.81 equiv), the title compound **85b** was obtained as an orange oil (0.265 g, 0.688 mmol, 69%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.79−7.68 (m, 2H), 7.65 (d, J = 7.2 Hz, 1H), 7.52−7.41 (m, 2H), 7.27 (dd, J = 7.8, 1.2 Hz, 1H), 7.23−7.15 (m, 2H), 7.13 (t, J = 7.5 Hz, 3H), 4.25 (t, J = 7.0 Hz, 2H), 3.57 (s, 3H), 2.76−2.67 (m, 2H). LC-MS (ESI): m/z 386.1 $[M+1]^+$, t_R = 4.00 min.

*3-(9-Oxo-N-phenyl-9H-fluorene-4-carboxamido)propanoic acid (**85**).* This previously unreported compound was synthesized according to general procedure D. Starting from **85b** (0.265 g, 0.688 mmol, 1.00 equiv) and following purification by reversed-phase flash chromatography (buffer A:B 0−50%), the title compound **85** was obtained as a yellow solid (0.122 g, 0.328 mmol, 48%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.37 (s, 1H), 7.78−7.60 (m, 3H), 7.44 (ddd, J = 15.8, 7.4, 1.1 Hz, 2H), 7.28−7.17 (m, 3H), 7.22−7.09 (m, 4H), 4.21 (s, 2H), 2.61 (t, J = 7.2 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.66, 172.91, 168.22, 142.85, 141.52, 140.39, 136.22, 134.16, 133.83, 133.70, 132.41, 130.31, 129.68, 129.22, 128.27, 128.17, 124.53, 124.28, 123.64, 45.20, 32.56. LC-MS (ESI): m/z 372.2 $[M+1]^+$, t_R = 3.97 min.

*Methyl 3-(benzylamino)propanoate (**86a**).* This previously reported compound was synthesized according to a literature protocol with minor deviations.[86] A solution benzylamine (2.93 mL, 20.0 mmol, 1.00 equiv) in anhydrous MeOH (4.0 mL) was cooled to 0 °C and then added a solution of methyl acrylate (2.84 mL, 22.0 mmol, 1.10 equiv) in anhydrous MeOH. The mixture was stirred and allowed to slowly warm to rt over 20 h. Upon reaction completion, the mixture was concentrated to dryness *in vacuo*. Following purification by normal-phase flash chromatography (DCM:MeOH 0−10%), the title compound **86a** was obtained as a colorless oil (2.36 g, 12.2 mmol, 61%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.24 (d, J = 4.4 Hz, 4H), 7.19−7.13 (m, 1H), 3.73 (s, 3H), 3.60 (s, 3H), 2.83 (t, J = 6.5 Hz, 2H), 2.47 (t, J = 6.5 Hz, 2H), 1.93 (s, 2H). LC-MS (ESI): m/z 194.1 $[M+1]^+$, t_R = 2.30 min.

*Methyl 3-(N-benzyl-9-oxo-9H-fluorene-4-carboxamido)-propanoate (**86b**).* This previously unreported compound was synthesized according to general procedure E. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.224 g, 1.00 mmol, 1.00 equiv) and **86a** (0.193 g, 1.00 mmol, 1.00 equiv) and following purification by normal-phase flash chromatography (hep:EtOAc 0−80%), the title compound **86b** was obtained as a yellow solid (0.236 g, 0.591 mmol, 59%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.71−7.56 (m, 2H), 7.54−7.33 (m, 4H), 7.21 (ddd, J = 13.2, 7.8, 6.1 Hz, 1H), 7.13−7.08 (m, 1H), 4.82 (t, J = 12.5 Hz, 1H), 4.47 (s, 1H), 3.64 (s, 1H), 3.40 (s, 1H), 3.32 (s, 3H), 2.50 (h, J = 2.4, 1.9 Hz, 6H). LC-MS (ESI): m/z 400.2 $[M+1]^+$, t_R = 4.60 min.

*3-(N-Benzyl-9-oxo-9H-fluorene-4-carboxamido)propanoic acid (**86**).* This previously unreported compound was synthesized according to general procedure D. Starting from **86b** (0.236 g, 0.591 mmol, 1.00 equiv) and following purification by reversed-phase flash chromatography (buffer A:B 0−35%), the title compound **86** was obtained as a yellow solid (0.086 g, 0.223 mmol, 38%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.37 (s, 1H), 7.73−7.54 (m, 3H), 7.55−7.31 (m, 7H), 7.23 (qd, J = 7.6, 6.5, 3.6 Hz, 2H), 7.12 (td, J = 6.0, 5.6, 3.0 Hz, 2H), 4.82 (d, J = 8.5 Hz, 1H), 4.49 (s, 1H), 2.77−2.63 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.65, 173.36, 172.49, 169.28, 137.39, 136.87, 135.92, 135.70, 134.35, 133.84, 133.16, 131.66, 130.31, 130.11, 129.13, 129.03 (two signals), 128.02 (two signals), 127.63, 124.69 (two signals), 123.06, 52.58, 47.65, 44.21, 41.74, 33.12, 32.15. LC-MS (ESI): m/z 386.2 $[M+1]^+$, t_R = 4.13 min.

*Methyl 2-phenylacrylate (**87a**).* This previously reported compound was synthesized according to a literature protocol with minor deviations.[87] To a solution of methyl 2-phenylacetate (1.41 mL, 10.0 mmol, 1.00 equiv) in toluene (20.0 mL) was added K_2CO_3 (2.07 g, 15.0 mmol), tetrabutylammonium bisulfate (0.34 g, 1.00 mmol, 0.10 equiv) and paraformaldehyde (0.45 g, 15.0 mmol, 1.50 equiv). The mixture was stirred at 80 °C for 18 h. Upon reaction completion as detected by TLC (R_f = 0.75, hep:EtOAc 1:1), the mixture was added water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. Purification by normal phase flash chromatography (hep:EtOAc 0−20%) afforded the title compound as a colorless oil (0.699 g, 4.31 mmol, 43%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.51−7.33 (m, 5H), 6.37 (d, J = 1.2 Hz, 1H), 5.90 (d, J = 1.2 Hz, 1H), 3.83 (s, 3H).

*Methyl 4-nitro-2-phenylbutanoate (**87b**).* This previously reported compound was synthesized according to general procedure J. Starting from **87a** (0.324 g, 2.00 mmol, 1.00 equiv) and nitromethane (2.17 mL, 40.0 mmol, 20.0 equiv), the title compound **87b** was obtained (0.50 g, ∼2.00 mmol, quantitative). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.41−7.17 (m, 7H), 4.41−4.26 (m, 4H), 3.69 (s, 3H), 2.74 (dq, J = 14.3, 7.2 Hz, 1H), 2.46 (ddt, J = 14.7, 8.0, 6.6 Hz, 1H).

*Methyl 4-((tert-butoxycarbonyl)amino)-2-phenylbutanoate (**87c**).* This previously reported compound was synthesized according to general procedure H. Starting from **87b** (0.50 g, 2.00 mmol assumed, 1.00 equiv), the title compound **87c** was obtained (0.522 g, 1.78 mmol, 89%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.30−7.23 (m, 5H), 3.66 (s, 3H), 3.61 (s, 1H), 3.09 (d, J = 7.4 Hz, 2H), 2.27 (dt, J = 14.7, 7.2 Hz, 1H), 1.96 (dq, J = 13.7, 7.1 Hz, 1H), 1.43 (s, 9H). LC-MS (ESI): m/z 194.3 $[M+1]^+$ (Boc-deprotected), t_R = 2.46 min.

*Methyl 4-amino-2-phenylbutanoate trifluoroacetate (**87d**).* This previously reported compound was synthesized according to general procedure E. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.224 g, 1.00 mmol, 1.00 equiv) and **87c** (0.522 g, 1.78 mmol, 1.00 equiv), and following purification by normal-phase flash chromatography (hep:EtOAc 0−50%), the title compound **87d** was obtained as a yellow solid (0.195 g, 0.49 mmol, 49%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (t, J = 5.5 Hz, 1H), 7.70 (dd, J = 7.4, 1.4 Hz, 2H), 7.66 (d, J = 7.3 Hz, 1H), 7.57 (td, J = 7.5, 1.2 Hz, 2H), 7.45 (d, J = 7.5 Hz, 1H), 7.42 (dd, J = 7.1, 1.1 Hz, 1H), 7.40−7.33 (m, 2H), 7.33−7.27 (m, 3H), 3.81 (t, J = 7.5 Hz, 1H), 3.61 (s, 3H), 3.35−3.18 (m, 2H), 2.32 (dq, J = 14.1, 7.2 Hz, 1H), 2.05−1.92 (m, 1H). LC-MS (ESI): m/z 400.4 $[M+1]^+$, t_R = 2.46 min.

*4-(9-Oxo-9H-fluorene-4-carboxamido)-2-phenylbutanoic acid (**87**).* This previously unreported compound was synthesized according to general procedure D. Starting from **87d** (0.19 g, 0.49 mmol, 1.00 equiv) and following purification by reversed-phase flash chromatography (buffer A:B 0−50%), the title compound **87** was obtained as a yellow solid (0.144 g, 0.37 mmol, 76%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.40 (s, 1H), 8.77 (t, J = 5.4 Hz, 1H), 7.70 (ddd, J = 7.2, 5.9, 1.0 Hz, 2H), 7.65 (dt, J = 7.3, 0.9 Hz, 1H), 7.56 (td, J = 7.4, 1.2 Hz, 2H), 7.44 (t, J = 7.5 Hz, 1H), 7.41 (td, J = 7.4, 0.9 Hz, 1H), 7.38−7.34 (m, 2H), 7.34−7.30 (m, 2H), 7.30−7.26 (m, 1H), 3.68 (t, J = 7.5 Hz, 1H), 3.35−3.21 (m, 2H), 2.34−2.25 (m, 1H), 1.95 (dq, J = 14.1, 7.2 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.39, 174.44, 167.43, 142.73, 140.08, 139.37, 135.34, 133.88, 133.81, 133.36, 132.90, 129.69, 129.30, 128.56, 127.82, 127.04, 124.58, 123.90, 123.82, 48.26, 37.36, 32.34. LC-MS (ESI): m/z 386.2 $[M+1]^+$, t_R = 4.00 min.

*Methyl 2-(hydroxy(phenyl)methyl)acrylate (**88a**).* This previously reported compound was synthesized according to a literature protocol with minor deviations.[88] A mixture of benzaldehyde (1.02 mL, 10.0 mmol, 1.00 equiv) and methyl acrylate (0.95 mL, 10.5 mmol, 1.05 equiv) was cooled to 0 °C and then added DABCO (1.02 g, 10.0 mmol). The mixture was stirred and slowly allowed to reach rt over 26 h. Then, additional methyl acrylate (0.95 mL, 10.5 mmol, 1.05 equiv) was added and the mixture stirred at rt for additional 3 h. Upon reaction completion as detected by TLC (R_f = 0.52, hep:EtOAc 1:1), the mixture was diluted with diethyl ether (25 mL) and washed with 0.5 M HCl (2 × 30 mL). The combined aq. phases were re-

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extracted with diethyl ether (25 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. Following purification by normal-phase flash chromatography (hep:EtOAc 0−35%), the title compound **88a** was obtained as a colorless oil (1.27 g, 6.59 mmol, 66%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.41−7.33 (m, 4H), 7.32−7.24 (m, 1H), 6.34 (t, J = 0.9 Hz, 1H), 5.83 (t, J = 1.2 Hz, 1H), 5.57 (s, 1H), 3.73 (s, 3H).

*Methyl 2-(acetoxy(phenyl)methyl)acrylate (**88b**).* This previously reported compound was synthesized according to a literature protocol with minor deviations.[88] A solution of acetic anhydride (0.62 mL, 6.59 mmol, 1.00 equiv), Et_3N (0.92 mL, 6.59 mmol, 1.00 equiv) and 4-DMAP (0.081 g, 0.66 mmol, 0.10 equiv) in DCM (33 mL) was cooled to 0 °C and then added **88a** (1.27 g, 6.59 mmol, 1.00 equiv). The mixture was stirred and slowly allowed to reach rt over 17 h. Upon reaction completion as detected by TLC (R_f = 0.69, hep:EtOAc 1:1), the mixture was washed with sat. $NaHCO_3$ (20 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. Following purification by normal-phase flash chromatography (hep:EtOAc 0−40%), the title compound **88b** was obtained as a colorless oil (0.941 g, 4.89 mmol, 74%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.41−7.27 (m, 5H), 6.69 (t, J = 1.1 Hz, 1H), 6.40 (t, J = 0.9 Hz, 1H), 5.86 (t, J = 1.2 Hz, 1H), 3.71 (s, 3H), 2.11 (s, 3H).

*Methyl 2-benzylacrylate (**88c**).* This previously reported compound was synthesized according to a literature protocol with minor deviations.[89] To a solution of **88b** (0.941 g, 4.89 mmol, 1.00 equiv) in THF (7.0 mL) and water (2.0 mL) was added DABCO (0.549 g, 4.89 mmol, 1.00 equiv). The mixture was stirred at rt for 15 min. Then, $NaBH_4$ (0.185 g, 4.89 mmol, 1.00 equiv) was added, and the mixture stirred at rt for 30 min. Upon reaction completion as detected by TLC (R_f = 0.77, hep:EtOAc 1:1), the mixture was concentrated to dryness *in vacuo*. Following purification by normal-phase flash chromatography (hep:EtOAc 0−20%), the title compound **88c** was obtained as a colorless oil (0.562 g, 3.19 mmol, 65%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.33−7.27 (m, 2H), 7.21 (td, J = 7.4, 6.8, 1.6 Hz, 3H), 6.24 (q, J = 1.0 Hz, 1H), 5.46 (q, J = 1.5 Hz, 1H), 3.74 (s, 3H), 3.64 (d, J = 1.4 Hz, 2H).

*Methyl 2-benzyl-4-nitrobutanoate (**88d**).* This previously reported compound was synthesized according to general procedure J. Starting from **88c** (0.352 g, 2.00 mmol, 1.00 equiv) and nitromethane (2.17 mL, 40.0 mmol, 20.0 equiv), the title compound **88d** was obtained as a golden-brown oil (0.53 g, ∼2.00 mmol, quantitative). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.35−7.17 (m, 3H), 7.16−7.12 (m, 2H), 4.32 (s, 2H), 3.66 (s, 3H), 3.08−3.00 (m, 1H), 2.84−2.76 (m, 2H), 2.31−2.14 (m, 2H).

*Methyl 2-benzyl-4-((tert-butoxycarbonyl)amino)butanoate (**88e**).* This previously unreported compound was synthesized according to general procedure H. Starting from **88d** (0.53 g, 2.00 mmol, 1.00 equiv), the title compound **88e** was obtained as a golden-brown oil (0.675 g, ∼2.00 mmol, quantitative). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.32−7.00 (m, 8H), 3.72 (d, J = 7.0 Hz, 2H), 3.61 (s, 3H), 3.01−2.88 (m, 1H), 2.73 (d, J = 4.8 Hz, 2H), 1.87−1.76 (m, 1H), 1.71 (dd, J = 13.2, 6.2 Hz, 1H), 1.42 (s, 9H). LC-MS (ESI): m/z 208.3 $[M+1]^+$ (Boc-deprotected), t_R = 2.56 min.

*Methyl 4-amino-2-benzylbutanoate trifluoroacetate (**88f**).* This previously reported compound was synthesized according to general procedure C. Starting from **88e** (0.67 g, 2.00 mmol assumed, 1.00 equiv) and TFA (20 mL, 260 mmol, 130 equiv), the title compound **88f** was obtained as an orange-brown oil (yield ND). LC-MS (ESI): m/z 208.3 $[M+1]^+$, t_R = 1.46 min.

*Methyl 2-benzyl-4-(9-oxo-9H-fluorene-4-carboxamido)-butanoate (**88g**).* This previously unreported compound was synthesized according to general procedure E. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.224 g, 1.00 mmol, 1.00 equiv) and **88f** (crude weight, 2.00 mmol assumed, 1.00 equiv), and following purification by normal-phase flash chromatography (hep:EtOAc 0−50%), the title compound **88g** was obtained as a yellow solid (0.199 g, 0.48 mmol, 48%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.75 (t, J = 5.5 Hz, 1H), 7.72−7.68 (m, 2H), 7.65 (d, J = 7.3 Hz, 1H), 7.54 (ddd, J = 14.5, 7.6, 1.2 Hz, 2H), 7.47−7.38 (m, 2H), 7.27 (dd, J = 7.9, 6.6 Hz, 2H), 7.23−7.15 (m, 3H), 3.56 (s, 3H), 3.35 (dt, J = 12.9, 6.5 Hz, 2H), 2.92−2.76 (m, 3H), 1.87 (dq, J = 14.1, 7.3 Hz, 1H), 1.76 (dt, J = 13.0, 6.5 Hz, 1H). LC-MS (ESI): m/z 414.1 $[M+1]^+$, t_R = 4.40 min.

*2-Benzyl-4-(9-oxo-9H-fluorene-4-carboxamido)butanoic acid (**88**).* This previously unreported compound was synthesized according to general procedure D. Starting from **88g** (0.20 g, 0.48 mmol, 1.00 equiv) and following purification by reversed-phase flash chromatography (buffer A:B 0−60%), the title compound **88** was obtained as a yellow solid (0.141 g, 0.35 mmol, 74%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.25 (s, 1H), 8.75 (t, J = 5.5 Hz, 1H), 7.69 (td, J = 7.2, 1.0 Hz, 2H), 7.65 (dt, J = 7.3, 0.9 Hz, 1H), 7.54 (ddd, J = 14.8, 7.5, 1.2 Hz, 2H), 7.45−7.38 (m, 2H), 7.29−7.25 (m, 2H), 7.24−7.17 (m, 3H), 3.46−3.30 (m, 2H), 2.92−2.77 (m, 2H), 2.75−2.66 (m, 1H), 1.90−1.66 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.39, 175.88, 167.35, 142.72, 140.06, 139.30, 135.36, 133.82, 133.80, 133.35, 132.91, 129.65, 129.29, 128.86, 128.18, 126.14, 124.56, 123.88, 123.85, 44.27, 37.42, 37.20, 30.95. LC-MS (ESI): m/z 400.2 $[M+1]^+$, t_R = 4.15 min.

*Ethyl 4-nitro-3-phenylbutanoate (**89a**).* This previously reported compound was synthesized according to a literature protocol with minor deviations.[90] A mixture of DBU (1.5 mL, 10.0 mmol, 1.00 equiv), nitromethane (1.1 mL, 20.0 mmol, 2.00 equiv) and MeCN (5.0 mL) was stirred at rt for 20 min. The mixture was cooled to 0 °C and then dropwise added ethyl cinnamate (1.7 mL, 10.0 mmol, 1.00 equiv). The mixture was stirred at 0 °C for 8 h. Upon reaction completion as detected by LC-MS, the mixture was poured into water. The pH was adjusted to 2 with 10% HCl and the mixture extracted with diethyl ether. The combined organic phases were washed with water, dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. Following purification by normal-phase flash chromatography (hep:EtOAc 0−35%), the title compound **89a** was obtained as a yellow oil (0.668 g, 2.82 mmol, 28%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.31−7.12 (m, 6H), 4.66 (dd, J = 12.6, 7.1 Hz, 1H), 4.57 (dd, J = 12.5, 7.8 Hz, 1H), 4.01 (qd, J = 7.2, 1.0 Hz, 2H), 3.96−3.86 (m, 1H), 2.70 (d, J = 1.5 Hz, 1H), 2.68 (d, J = 1.7 Hz, 1H), 1.10 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 170.72, 138.47, 129.20, 128.17, 127.49, 79.61, 61.06, 40.38, 37.95, 14.20.

*Ethyl 4-amino-3-phenylbutanoate (**89b**).* This previously reported compound was synthesized according to a literature protocol with minor deviations.[91] A solution of **89a** (0.190 g, 0.801 mmol, 1.00 equiv) and $NiCl_2{\cdot}6H_2O$ (0.104 g, 0.801 mmol, 1.00 equiv) in EtOH (5 mL) was cooled to 0 °C and then portion wise added $NaBH_4$ (0.364 g, 9.610 mmol, 12.0 equiv). The mixture was stirred at 0 °C for 2.5 h. Upon reaction completion as detected by LC-MS, the mixture was quenched with sat. NH_4Cl (6 mL) and extracted with DCM (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo* to afford the title compound **89b** as a white solid (0.137 g, 0.661 mmol, 83%). ^{1}H NMR (600 MHz, DMSO-d6) δ 7.92 (s, 3H), 7.36−7.25 (m, 5H), 3.98−3.88 (m, 2H), 3.47−3.41 (m, 1H), 3.16−3.09 (m, 1H), 3.06−2.98 (m, 1H), 2.91 (dd, J = 16.0, 5.4 Hz, 1H), 2.64 (dd, J = 16.0, 9.7 Hz, 1H), 1.03 (t, J = 7.1 Hz, 3H). LC-MS (ESI): m/z 208.1 $[M+1]^+$, t_R = 1.34 min.

*Ethyl 4-(9-oxo-9H-fluorene-4-carboxamido)-3-phenylbutanoate (**89c**).* This previously unreported compound was synthesized according to general procedure B starting from 9-oxo-9*H*-fluorene-4-carbonyl chloride (0.161 g, 0.66 mmol, 1.00 equiv), **89b** (0.137 g, 0.66 mmol, 1.00 equiv) and Et_3N (0.14 mL, 0.99 mmol, 1.50 equiv). Upon reaction completion, the mixture was diluted with DCM (20 mL), washed with 1 M HCl (20 mL) and sat. $NaHCO_3$ (3 mL), and the organic phase was dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. Following purification by normal-phase flash chromatography (hep:EtOAc 0−100%), the title compound **89c** was obtained as a yellow solid (0.051 g, 0.12 mmol, 19%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.78 (t, 1H), 7.70−7.05 (m, 12H), 3.99−3.90 (m, 2H), 3.72−3.66 (m, 1H), 3.54−3.42 (m, 2H), 2.84 (dd, J = 15.7, 5.4 Hz, 1H), 2.66 (dd, J = 15.7, 9.4 Hz, 1H), 1.04 (t, J = 7.1 Hz, 3H). LC-MS (ESI): m/z 414.2 $[M+1]^+$, t_R = 2.54 min.

*4-(9-Oxo-9H-fluorene-4-carboxamido)-3-phenylbutanoic acid (**89**).* This previously unreported compound was synthesized

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according to general procedure D. Starting from **89c** (0.051 g, 0.12 mmol, 1.00 equiv) and following purification by preparative HPLC (buffer A:B 0−100%), the title compound **89** was obtained as a yellow solid (0.030 g, 0.078 mmol, 65%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.08 (s, 1H), 8.77 (t, J = 5.6 Hz, 1H), 7.67−7.20 (m, 12H), 3.70−3.64 (m, 1H), 3.51−3.39 (m, 2H), 2.76 (dd, J = 15.9, 5.5 Hz, 1H), 2.63−2.55 (m, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.39, 172.98, 167.40, 142.59, 142.08, 140.11, 135.37, 133.80 (d, J = 1.8 Hz), 133.26, 132.79, 129.58, 129.20, 128.24, 127.84, 124.56, 123.94, 123.79, 44.34, 41.29, 38.26. LC-MS (ESI): m/z 769.3 $[2M-1]^-$, t_R = 2.93 min.

*Methyl (E)-4-phenylbut-2-enoate (**90a**).* This previously reported compound was synthesized according to a literature protocol with minor deviations.[92] A solution of methyl acrylate (2.25 mL, 25.0 mmol, 2.50 equiv) and allylbenzene (1.32 mL, 10.0 mmol, 1.00 equiv) in DCM (50.0 mL) was degassed with nitrogen for 10 min. Then, Grubbs's catalyst M2a (0.126 g, 0.15 mmol, 0.015 equiv) was added, and the system subjected to further three vacuum-nitrogen cycles. The mixture was stirred under nitrogen at reflux for 14 h. Upon reaction completion as detected by TLC (R_f = 0.77, hep:EtOAc 1:1), the mixture was concentrated to dryness *in vacuo*. Following purification by normal-phase flash chromatography (hep:EtOAc 0−15%), the title compound **90a** was obtained as a pinkish oil (1.55 g, 8.80 mmol, 88%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.31 (dd, J = 8.1, 6.7 Hz, 2H), 7.28−7.19 (m, 1H), 7.17 (dd, J = 7.0, 1.8 Hz, 2H), 7.11 (dt, J = 15.5, 6.8 Hz, 1H), 5.82 (dt, J = 15.6, 1.7 Hz, 1H), 3.72 (s, 3H), 3.53 (dd, J = 6.8, 1.6 Hz, 2H).

*Methyl 3-benzyl-4-nitrobutanoate (**90b**).* This previously reported compound was synthesized according to general procedure J. Starting from **90a** (1.55 g, 8.80 mmol, 1.00 equiv) and nitromethane (9.53 mL, 175.9 mmol, 20.0 equiv), the title compound **90b** was obtained (2.57 g, ∼8.80 mmol, quantitative). LC-MS (ESI): m/z 238.1 $[M+1]^+$, t_R = 4.44 min.

*Methyl 3-benzyl-4-((tert-butoxycarbonyl)amino)butanoate (**90c**).* This previously unreported compound was synthesized according to general procedure H. Starting from **90b** (0.24 g, 1.00 mmol, 1.00 equiv), the title compound **90c** was obtained (0.32 g, ∼1.00 mmol, quantitative). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.35−7.09 (m, 6H), 3.52 (s, 3H), 3.51−3.40 (m, 1H), 2.96 (dt, J = 13.4, 5.8 Hz, 1H), 2.84 (dt, J = 13.1, 6.2 Hz, 1H), 2.61 (dd, J = 13.7, 6.3 Hz, 1H), 2.48−2.40 (m, 1H), 2.31−2.06 (m, 3H), 1.37 (s, 9H). LC-MS (ESI): m/z 308.3 $[M+1]^+$ (Boc-deprotected), t_R = 4.68 min.

*Methyl 4-amino-3-benzylbutanoate trifluoroacetate (**90d**).* This previously reported compound was synthesized according to general procedure C. Starting from **90c** (0.32 g, 1.00 mmol assumed, 1.00 equiv) and TFA (10 mL, 130 mmol, 130 equiv), the title compound **90d** was obtained as a slight brown oil (yield ND). LC-MS (ESI): m/z 208.1 $[M+1]^+$, t_R = 2.78 min.

*Methyl 3-benzyl-4-(9-oxo-9H-fluorene-4-carboxamido)-butanoate (**90e**).* This previously unreported compound was synthesized according to general procedure E. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.224 g, 1.00 mmol, 1.00 equiv) and **90d** (crude weight, 1.00 mmol assumed, 1.00 equiv), and following purification by normal-phase flash chromatography (DCM:MeOH 0−3%), the title compound **90e** was obtained as a yellow oil (0.30 g, 0.74 mmol, 74%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.79 (t, J = 5.7 Hz, 1H), 7.74−7.68 (m, 2H), 7.65 (d, J = 7.3 Hz, 1H), 7.57 (dtd, J = 7.6, 3.7, 1.3 Hz, 2H), 7.49−7.36 (m, 2H), 7.31 (t, J = 7.5 Hz, 2H), 7.26−7.19 (m, 3H), 3.55 (s, 3H), 3.40 (dt, J = 13.4, 5.7 Hz, 1H), 3.31−3.23 (m, 1H), 2.86 (d, J = 4.6 Hz, 1H), 2.75 (s, 1H), 2.60 (dd, J = 13.6, 6.9 Hz, 1H), 2.46−2.38 (m, 2H), 2.30−2.21 (m, 1H). LC-MS (ESI): m/z 414.1 $[M+1]^+$, t_R = 4.02 min.

*3-Benzyl-4-(9-oxo-9H-fluorene-4-carboxamido)butanoic acid (**90**).* This previously unreported compound was synthesized according to general procedure D. Starting from **90e** (0.30 g, 0.74 mmol, 1.00 equiv) and following purification by reversed-phase flash chromatography (buffer A:B 0−50%), the title compound **90** was obtained as a yellow solid (0.190 g, 0.48 mmol, 64%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.16 (s, 1H), 8.77 (t, J = 5.6 Hz, 1H), 7.74−7.68 (m, 2H), 7.65 (d, J = 7.3 Hz, 1H), 7.59−7.53 (m, 2H), 7.47−7.38 (m, 2H), 7.32 (t, J = 7.5 Hz, 2H), 7.27−7.19 (m, 3H), 3.39 (dt, J = 13.4, 5.9 Hz, 1H), 3.29 (dt, J = 13.0, 6.1 Hz, 1H), 2.74 (dd, J = 13.6, 6.8 Hz, 1H), 2.63 (dd, J = 13.7, 6.9 Hz, 1H), 2.41 (p, J = 6.6 Hz, 1H), 2.33 (dd, J = 16.1, 6.5 Hz, 1H), 2.18 (dd, J = 16.1, 6.6 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.39, 173.63, 167.72, 142.73, 140.09, 139.68, 135.32, 133.94, 133.78, 133.35, 132.91, 129.66, 129.27, 129.11, 128.28, 126.03, 124.56, 123.89, 123.79, 42.19, 37.49, 36.52, 35.82. LC-MS (ESI): m/z 400.4 $[M+1]^+$, t_R = 2.29 min.

*(Nitromethyl)benzene (**91a**).* This previously reported compound was synthesized according to a literature protocol with minor deviations.[93] To a stirring solution of $NaNO_2$ (1.04 g, 15.0 mmol, 1.50 equiv) in DMF (10.0 mL) was added urea (1.20 g, 20.0 mmol, 2.00 equiv). The mixture was stirred until complete dissolution, upon which it was cooled to −10 °C and dropwise added a solution of benzyl bromide (1.19 mL, 10.0 mmol, 1.00 equiv) in DMF (10.0 mL) over 10 min. The mixture was then stirred at −10 °C for 4 h. Upon reaction completion as detected by TLC (R_f = 0.66, hep:EtOAc 1:1), the mixture was poured into ice-cooled water (50 mL) and extracted with diethyl ether (3 × 20 mL). The combined organic phases were washed with ice-cooled sat. brine (50 mL), dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. Following purification by normal-phase flash chromatography (hep:EtOAc 0−20%), the title compound **91a** was obtained as a colorless oil (0.318 g, 2.32 mmol, 23%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.54−7.32 (m, 5H), 5.45 (s, 2H).

*Methyl 4-nitro-4-phenylbutanoate (**91b**).* This previously reported compound was synthesized according to general procedure J. Starting from **91a** (0.318 g, 2.32 mmol, 1.00 equiv) and methyl acrylate (0.209 mL, 2.32 mmol, 1.00 equiv), the title compound **91b** was obtained as a yellowish oil (0.552 g, ∼2.32 mmol, quantitative). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.62−7.20 (m, 6H), 3.65 (s, 3H), 3.33 (t, J = 6.7 Hz, 1H), 2.71 (dt, J = 9.6, 5.9 Hz, 2H), 2.33−2.19 (m, 2H).

*Methyl 4-((tert-butoxycarbonyl)amino)-4-phenylbutanoate (**91c**).* This previously reported compound was synthesized according to general procedure H. Starting from **91b** (0.55 g, 2.32 mmol assumed, 1.00 equiv), the title compound **91c** was obtained (0.817 g, ∼2.32 mmol, quantitative). LC-MS (ESI): m/z 194.1 $[M+1]^+$ (Boc-deprotected), t_R = 4.24 min.

*Methyl 4-amino-4-phenylbutanoate trifluoroacetate (**91d**).* This previously reported compound was synthesized according to general procedure C. Starting from **91c** (0.82 g, 2.32 mmol assumed, 1.00 equiv) and TFA (23 mL, 302 mmol, 130 equiv), the title compound **91d** was obtained (yield ND). LC-MS (ESI): m/z 194.1 $[M+1]^+$, t_R = 1.00 min.

*Methyl 4-(9-oxo-9H-fluorene-4-carboxamido)-4-phenylbutanoate (**91e**).* This previously unreported compound was synthesized according to general procedure E. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.224 g, 1.00 mmol, 1.00 equiv) and **91d** (crude weight, 2.32 mmol assumed, 2.32 equiv), and following purification by normal-phase flash chromatography (hep:EtOAc 0−80%), the title compound **91e** was obtained as a yellow solid (0.257 g, 0.64 mmol, 64%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.22 (d, J = 8.4 Hz, 1H), 7.70 (dd, J = 7.3, 1.2 Hz, 1H), 7.64−7.60 (m, 1H), 7.57 (dd, J = 7.7, 1.2 Hz, 1H), 7.50−7.24 (m, 9H), 5.10 (td, J = 8.6, 6.3 Hz, 1H), 3.60 (s, 3H), 2.45−2.36 (m, 2H), 2.15−1.98 (m, 2H). LC-MS (ESI): m/z 400.4 $[M+1]^+$, t_R = 2.41 min.

*4-(9-Oxo-9H-fluorene-4-carboxamido)-4-phenylbutanoic acid (**91**).* This previously unreported compound was synthesized according to general procedure D. Starting from **91e** (0.26 g, 0.64 mmol, 1.00 equiv) and following purification by reversed-phase flash chromatography (buffer A:B 0−50%), the title compound **91** was obtained as a light yellow solid (0.054 g, 0.14 mmol, 22%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.16 (s, 1H), 9.22 (d, J = 8.4 Hz, 1H), 7.70 (dd, J = 7.3, 1.1 Hz, 1H), 7.62 (dt, J = 7.3, 1.0 Hz, 1H), 7.57 (dd, J = 7.6, 1.2 Hz, 1H), 7.46 (t, J = 7.5 Hz, 1H), 7.44−7.37 (m, 4H), 7.37−7.33 (m, 1H), 7.33−7.27 (m, 3H), 5.11 (td, J = 8.7, 6.2 Hz, 1H), 2.38−2.27 (m, 2H), 2.10−1.94 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.34, 173.91, 166.96, 142.82, 142.49, 139.96, 135.04, 133.74, 133.65, 133.29, 132.86, 129.63, 129.35, 128.41, 127.07,

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126.63, 124.52, 123.85, 123.61, 52.54, 30.91, 30.82. LC-MS (ESI): m/z 386.2 $[M+1]^+$, t_R = 3.98 min.

*(E)-(2-Nitrovinyl)benzene (**92a**).* This previously reported compound was synthesized according to a literature protocol with minor deviations.[94] To a solution of benzaldehyde (1.02 mL, 10.0 mmol, 1.00 equiv) and NH_4OAc (0.46 g, 6.00 mmol, 0.60 equiv) in toluene (50.0 mL) was added nitromethane (21.7 mL, 400.0 mmol, 40.00 equiv). The mixture was stirred at 100 °C for 17 h. Upon reaction completion as detected by TLC (R_f = 0.68, hep:EtOAc 1:1), the mixture was cooled to rt, diluted with water (100 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with sat. brine (50 mL), dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. Following purification by normal-phase flash chromatography (hep:EtOAc 0−10%), the title compound **92a** was obtained as a yellow solid (1.34 g, 9.01 mmol, 90%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.01 (d, J = 13.7 Hz, 1H), 7.59 (d, J = 13.7 Hz, 1H), 7.57−7.42 (m, 5H).

*(2-Nitroethyl)benzene (**92b**).* This previously reported compound was synthesized according to a literature protocol with minor deviations.[95] A mixture of **92a** (1.34 g, 8.98 mmol, 1.00 equiv) and 60 Å 230−400 mesh silica gel (17.0 g) in $CHCl_3$ (70.0 mL) and *i*-PrOH (20.0 mL) was cooled to 0 °C and added $NaBH_4$ (0.75 g, 19.76 mmol, 2.20 equiv) in four portions over 20 min. The mixture was stirred and slowly allowed to reach rt over 21 h. Upon reaction completion, the mixture was cooled back to 0 °C and carefully added 0.2 M HCl (100 mL). The mixture was filtered through a sintered funnel and the filter cake washed with DCM (50 mL). The filtrate was washed with water (70 mL), and the aq. phase re-extracted with DCM (3 × 30 mL). The combined organic phases were washed with sat. brine (2 × 30 mL), dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo* to afford the title compound as a golden-brown oil (1.27 g, 8.42 mmol, 94%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.36−7.30 (m, 2H), 7.30−7.26 (m, 1H), 7.24−7.19 (m, 2H), 4.61 (t, J = 7.4 Hz, 2H), 3.33 (t, J = 7.4 Hz, 2H).

*Methyl 4-nitro-5-phenylpentanoate (**92c**).* This previously reported compound was synthesized according to general procedure J. Starting from **92b** (0.151 g, 1.00 mmol, 1.00 equiv) and methyl acrylate (0.090 mL, 1.00 mmol, 1.00 equiv), the title compound **92c** was obtained (0.26 g, ∼1.00 mmol, quantitative). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.37−7.01 (m, 5H), 4.80 (tdd, J = 8.4, 7.1, 4.7 Hz, 1H), 3.68 (s, 3H), 3.29 (dd, J = 14.2, 8.4 Hz, 1H), 3.07 (dd, J = 14.2, 5.9 Hz, 1H), 2.44−2.13 (m, 6H). LC-MS (ESI): m/z 238.0 $[M+1]^+$, t_R = 3.52 min.

*Methyl 4-((tert-butoxycarbonyl)amino)-5-phenylpentanoate (**92d**).* This previously reported compound was synthesized according to general procedure H. Starting from **92c** (0.26 g, 1.00 mmol assumed, 1.00 equiv), the title compound **92d** was obtained as a yellow oil (0.36 g, ∼1.00 mmol, quantitative). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.48−7.02 (m, 5H), 3.65 (s, 3H), 2.84−2.68 (m, 2H), 2.41−2.33 (m, 4H), 2.08−1.91 (m, 2H), 1.92−1.78 (m, 1H), 1.39 (s, 9H). LC-MS (ESI): m/z 308.2 $[M+1]^+$, t_R = 4.60 min.

*Methyl 4-amino-5-phenylpentanoate trifluoroacetate (**92e**).* This previously reported compound was synthesized according to general procedure C. Starting from **92d** (0.36 g, 1.00 mmol assumed, 1.00 equiv) and TFA (10 mL, 130 mmol, 130 equiv), the title compound **92e** was obtained as a brown oil (0.49 g, ∼1.00 mmol, quantitative). LC-MS (ESI): m/z 208.1 $[M+1]^+$, t_R = 2.79 min.

*Methyl 4-(9-oxo-9H-fluorene-4-carboxamido)-5-phenylpentanoate (**92f**).* This previously unreported compound was synthesized according to general procedure E. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.224 g, 1.00 mmol, 1.00 equiv) and **92e** (0.49 g, 1.00 mmol assumed, 1.00 equiv), and following purification by normal-phase flash chromatography (hep:EtOAc 0−50%), the title compound **92f** was obtained as a yellow solid (0.21 g, 0.51 mmol, 51%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59 (d, J = 8.8 Hz, 1H), 7.67 (dd, J = 6.7, 1.9 Hz, 1H), 7.61 (dd, J = 7.3, 1.2 Hz, 1H), 7.47−7.15 (m, 10H), 4.33 (dq, J = 9.1, 4.6 Hz, 1H), 3.60 (s, 3H), 2.89 (dd, J = 13.7, 5.4 Hz, 1H), 2.79 (dd, J = 13.6, 8.9 Hz, 1H), 2.49−2.33 (m, 1H), 2.00−1.88 (m, 1H), 1.76 (dtd, J = 14.4, 8.5, 6.1 Hz, 1H). LC-MS (ESI): m/z 414.2 $[M+1]^+$, t_R = 4.50 min.

*4-(9-Oxo-9H-fluorene-4-carboxamido)-5-phenylpentanoic acid (**92**).* This previously unreported compound was synthesized according to general procedure D. Starting from **92f** (0.21 g, 0.51 mmol, 1.00 equiv) and following purification by reversed-phase flash chromatography (buffer A:B 0−50%), the title compound **92** was obtained as a light yellow solid (0.085 g, 0.21 mmol, 41%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.09 (s, 1H), 8.58 (d, J = 8.8 Hz, 1H), 7.66 (dd, J = 6.5, 2.0 Hz, 1H), 7.64−7.56 (m, 1H), 7.45−7.31 (m, 5H), 7.28 (d, J = 4.4 Hz, 4H), 7.20 (dt, J = 8.7, 4.1 Hz, 1H), 4.34 (tp, J = 9.3, 4.8 Hz, 1H), 2.89 (dd, J = 13.6, 5.4 Hz, 1H), 2.79 (dd, J = 13.7, 8.9 Hz, 1H), 2.46−2.29 (m, 2H), 1.96−1.84 (m, 1H), 1.74 (dtd, J = 14.0, 8.5, 6.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.37, 174.16, 167.03, 142.47, 140.15, 138.80, 135.28, 133.82, 133.71, 133.20, 132.88, 129.49, 129.17, 129.15, 128.10, 126.15, 124.50, 124.00, 123.68, 49.93, 40.38, 30.51, 29.59. LC-MS (ESI): m/z 400.4 $[M+1]^+$, t_R = 2.22 min.

*Ethyl 4-(phenylamino)butanoate (**93a**).* This previously reported compound was synthesized according to a literature protocol with minor deviations.[96] A mixture of aniline (0.91 mL, 10.0 mmol, 1.00 equiv), ethyl 4-bromobutyrate (1.72 mL, 12.0 mmol, 1.20 equiv) and Et_3N (1.67, 12.0 mmol, 1.20 equiv) was stirred at rt for 72 h. Upon reaction completion, the mixture was added water (50 mL) and extracted with DCM (3 × 30 mL). The combined organic phases were washed with sat. brine (30 mL), dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo* to afford the title compound **93a** (2.13 g, ∼10.0 mmol, quantitative). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.21−7.15 (m, 2H), 6.76−6.71 (m, 1H), 6.67−6.62 (m, 2H), 4.14 (q, J = 7.2 Hz, 2H), 3.19 (t, J = 6.9 Hz, 2H), 2.43 (t, J = 7.2 Hz, 2H), 1.95 (q, J = 7.1 Hz, 2H), 1.26 (t, J = 7.1 Hz, 4H).

*Ethyl 4-(9-oxo-N-phenyl-9H-fluorene-4-carboxamido)butanoate (**93b**).* This previously unreported compound was synthesized according to general procedure I. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.224 g, 1.00 mmol, 1.00 equiv) and **93a** (0.48 g, 2.00 mmol assumed, 2.00 equiv) and following purification by normal-phase flash chromatography (hep:EtOAc 0−50%), the title compound **93b** was obtained (0.27 g, 0.64 mmol, 64%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.76−7.62 (m, 3H), 7.45 (ddt, J = 8.6, 5.1, 1.7 Hz, 2H), 7.32 (dd, J = 7.7, 1.1 Hz, 1H), 7.24−7.06 (m, 6H), 4.11−3.97 (m, 4H), 2.45 (t, J = 7.3 Hz, 2H), 1.86 (p, J = 7.4 Hz, 2H), 1.18 (t, J = 7.1 Hz, 3H). LC-MS (ESI): m/z 414.2 $[M+1]^+$, t_R = 4.72 min.

*4-(9-Oxo-N-phenyl-9H-fluorene-4-carboxamido)butanoic acid (**93**).* This previously unreported compound was synthesized according to general procedure D. Starting from **93b** (0.27 g, 0.64 mmol, 1.00 equiv) and following purification by reversed-phase flash chromatography (buffer A:B 0−50%), the title compound **93** was obtained as a yellow solid (0.23 g, 0.60 mmol, 94%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.99 (s, 1H), 7.74−7.67 (m, 2H), 7.67−7.62 (m, 1H), 7.45 (ddd, J = 8.9, 7.1, 1.9 Hz, 2H), 7.31 (dd, J = 7.8, 1.1 Hz, 1H), 7.23−7.11 (m, 6H), 4.02 (t, J = 7.4 Hz, 2H), 2.36 (t, J = 7.3 Hz, 2H), 1.83 (p, J = 7.4 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 192.13, 173.84, 167.72, 142.43, 141.23, 139.80, 135.62, 133.77, 133.31, 133.26, 132.03, 129.84, 129.18, 128.73, 127.74, 127.52, 124.10, 123.76, 122.84, 47.79, 30.88, 22.53. LC-MS (ESI): m/z 386.4 $[M+1]^+$, t_R = 2.19 min.

*Methyl 4-(benzylamino)butanoate (**94a**).* This previously reported compound was synthesized according to a literature protocol with minor deviations.[97] To a solution of methyl 4-aminobutanoate hydrochloride (0.77 g, 2.50 mmol, 1.00 equiv) in anhydrous THF (5.0 mL) was added Et_3N (0.94 mL, 6.75 mmol, 2.50 equiv), benzaldehyde (0.23 mL, 2.25 mmol, 0.90 equiv) and $MgSO_4$ (0.45 g, 3.75 mmol, 1.50 equiv). The mixture was stirred at rt for 20 h. Upon reaction completion, the mixture was added MeOH (5.0 mL), cooled to −20 °C and added $NaBH_4$ in portions over 20 min. The mixture was stirred at 0 °C for 2 h. Upon reaction completion as detected by TLC (R_f = 0.56, hep:EtOAc 1:1), the mixture was carefully added 0.2 M HCl (10 mL) at 0 °C. The aq. phase was basified with 1 M NaOH to pH > 12, and the resulting precipitate isolated by suction filtration. The filtrate was further extracted with DCM (2 × 10 mL), filtered, and concentrated to dryness *in vacuo* to afford the title compound **94a**

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as a colorless oil (0.246 g, 1.19 mmol, 47%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.35−7.13 (m, 14H), 5.89 (s, 3H), 4.38 (s, 3H), 3.33 (t, J = 7.1 Hz, 5H), 3.23−3.14 (m, 3H).

*Methyl 4-(N-benzyl-9-oxo-9H-fluorene-4-carboxamido)-butanoate (**94b**).* This previously unreported compound was synthesized according to general procedure E. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.224 g, 1.00 mmol, 1.00 equiv) and **94a** (0.25 g, 1.00 mmol assumed, 1.00 equiv), and following purification by normal-phase flash chromatography (hep:EtOAc 0−50%), the title compound **94b** was obtained as a yellow oil (0.093 g, 0.23 mmol, 23%). LC-MS (ESI): m/z 414.4 $[M+1]^+$, t_R = 2.54 min.

*4-(N-Benzyl-9-oxo-9H-fluorene-4-carboxamido)butanoic acid (**94**).* This previously unreported compound was synthesized according to general procedure D. Starting from **94b** (0.093 g, 0.23 mmol, 1.00 equiv) and following purification by reversed-phase flash chromatography (buffer A:B 0−50%), the title compound **94** was obtained as a yellow solid (0.058 g, 0.15 mmol, 63%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.01 (s, 1H), 7.74−7.01 (m, 15H), 4.62 (d, J = 139.2 Hz, 2H), 3.72−2.96 (m, 2H), 2.38−1.53 (m, 4H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 174.45, 174.03, 168.82, 142.86, 139.98, 139.66, 137.50, 136.96, 135.78, 135.62, 134.28, 133.82, 133.11, 131.77, 130.30, 130.20, 130.04, 129.09, 129.07, 128.89, 128.01, 127.88, 127.62, 124.62, 124.56, 122.99, 122.80, 52.31, 47.73, 44.85, 31.73, 30.75, 23.54, 22.65. LC-MS (ESI): m/z 400.4 $[M+1]^+$, t_R = 2.26 min.

*2-Bromoisophthalic acid (**Ia**).* This previously reported compound was synthesized according to a literature protocol with minor deviations.[98] To a solution of 2-bromo-*m*-xylene (5.00 mL, 38.0 mmol, 1.00 equiv) in *t*-BuOH (30 mL) and H_2O (30 mL) was portion wise added $KMnO_4$ (15.0 g, 95.0 mmol, 2.50 equiv). The mixture was stirred at 70 °C for 2 h, before it was cooled to rt and portion wise added additional $KMnO_4$ (15.0 g, 95.0 mmol, 2.50 equiv). The mixture was stirred at 70 °C overnight. Upon reaction completion as detected by LC-MS, the hot mixture was filtered and the filter cake washed with H_2O (3 × 40 mL). The combined filtrates were acidified to pH 2 with conc. HCl and extracted with EtOAc (4 × 60 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo* to afford the title compound **Ia** as an off-white solid (7.20 g, 29.4 mmol, 77%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.57 (s, 2H), 7.70 (d, J = 7.6 Hz, 2H), 7.55−7.49 (m, 1H). LC-MS (ESI): m/z 244.8, 247.0 $[M+1]^+$, t_R = 1.95 min.

*Dimethyl 2-bromoisophthalate (**Ib**).* This previously reported compound was synthesized according to a literature protocol with minor deviations.[98] A solution of **Ia** (4.20 g, 17.0 mmol, 1.00 equiv) in $SOCl_2$ (29.5 mL, 404 mmol, 23.8 equiv) was gradually heated to 100 °C from rt over a period of 5 h and then stirred at this temperature for additional 15 h. Upon reaction completion as detected by TLC (derivatization with MeOH), the mixture concentrated to dryness *in vacuo*. The residue was cooled to 0 °C and slowly added MeOH (21 mL) and Et_3N (10.5 mL, 75.3 mmol, 4.43 equiv). The mixture was stirred at rt for 4 h. Upon reaction completion as detected by LC-MS, the mixture was concentrated *in vacuo*. The residue was added H_2O, extracted with EtOAc (1 × 40 mL and 2 × 25 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo* to afford the title compound **Ib** as an orange-brown oil (3.77 g, 13.8 mmol, 82%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.80 (d, J = 7.7 Hz, 2H), 7.60 (t, J = 7.7 Hz, 1H), 3.88 (s, 6H). LC-MS (ESI): m/z 273.0, 275.0 $[M+1]^+$, t_R = 4.07 min.

*Methyl 2-amino-2-phenylacetate hydrochloride (**Ic**).* This previously reported compound was synthesized according to general procedure G. Starting from 2-phenylglycine (5.00 g, 33.0 mmol, 1.00 equiv), the title compound **Ic** was obtained as a light orange solid (yield ND). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.40−7.27 (m, 5H), 5.76 (s, 1H), 4.56 (s, 1H), 3.60 (s, 3H). LC-MS (ESI): m/z 166.1 $[M+1]^+$, t_R = 0.65 min.

*Dimethyl 4′-fluoro-[1,1′-biphenyl]-2,6-dicarboxylate (**95a**).* This previously unreported compound was synthesized according to general procedure K. Starting from **Ib** (0.137 g, 0.50 mmol, 1.00 equiv) and (4-fluorophenyl)boronic acid (0.105 g, 0.75 mmol, 1.50 equiv) and following purification by normal-phase flash chromatography (hep:EtOAc 0−25%), the title compound **95a** was obtained (0.100 g, 0.34 mmol, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 7.8 Hz, 2H), 7.41 (t, J = 7.8 Hz, 1H), 7.13−7.04 (m, 2H), 7.03−6.93 (m, 2H), 3.51 (s, 6H). LC-MS (ESI): m/z 289.1 $[M+1]^+$, t_R = 4.48 min.

*7-Fluoro-9-oxo-9H-fluorene-4-carboxylic acid (**95b**).* This previously reported compound was synthesized according to a literature protocol with minor deviations.[80] To **95a** (0.163 g, 0.57 mmol, 1.00 equiv) was added H_2SO_4 (10 mL). The mixture was stirred at 55 °C for 40 min. Upon reaction completion, the mixture was poured into 100 mL crushed ice and extracted with EtOAc (3 × 40 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The solid was triturated with water and dried *in vacuo*. The crude ester was then redissolved in DCM (9.0 mL) and added 3 M NaOH in MeOH (1.0 mL, 3.00 mmol, 5.26 equiv). The mixture was stirred at rt for 3 h. Upon reaction completion, the mixture was concentrated to dryness *in vacuo*. The residue was redissolved in water (15 mL), the pH adjusted with conc. HCl to <2, and the mixture extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo* to afford the title compound **95b** as a yellow solid (0.088 g, 0.35 mmol, 61%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.71 (s, 1H), 8.36−8.32 (m, 1H), 8.00 (dd, J = 7.9, 1.3 Hz, 1H), 7.84−7.81 (m, 1H), 7.52−7.46 (m, 3H). LC-MS (ESI): m/z 243.1 $[M+1]^+$, t_R = 4.03 min.

*Methyl 2-(7-fluoro-9-oxo-9H-fluorene-4-carboxamido)-2-phenylacetate (**95c**).* This previously unreported compound was synthesized according to general procedure E. Starting from **95b** (0.088 g, 0.35 mmol, 1.00 equiv) and **Ic** (0.069 g, 0.42 mmol assumed, 1.20 equiv), and following purification by normal-phase flash chromatography (hep:EtOAc 0−35%), the title compound **95c** was obtained as a yellow solid (0.073 g, 0.19 mmol, 54%). ^{1}H NMR (600 MHz, DMSO) δ 9.66 (d, J = 6.8 Hz, 1H), 7.76 (dd, J = 8.4, 4.6 Hz, 1H), 7.73 (d, J = 1.1 Hz, 0H), 7.59 (dd, J = 7.7, 1.2 Hz, 1H), 7.51−7.49 (m, 2H), 7.48 (dd, J = 7.4, 2.6 Hz, 1H), 7.44−7.34 (m, 5H), 5.72 (d, J = 6.8 Hz, 1H), 3.72 (s, 3H). LC-MS (ESI): m/z 390.1 $[M+1]^+$, t_R = 4.55 min.

*2-(7-Fluoro-9-oxo-9H-fluorene-4-carboxamido)-2-phenylacetic acid (**95**).* This previously unreported compound was synthesized according to general procedure M. Starting from **95c** (0.073 g, 0.19 mmol, 1.00 equiv), and following purification by reversed-phase flash chromatography (buffer A:buffer B 0−100%), the title compound **95** was obtained as a yellow solid (0.032 g, 0.080 mmol, 42%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.05 (s, 1H), 9.52 (d, J = 7.1 Hz, 1H), 7.77 (dd, J = 8.4, 4.6 Hz, 1H), 7.71 (dd, J = 7.3, 1.2 Hz, 1H), 7.59 (dd, J = 7.7, 1.2 Hz, 1H), 7.51 (d, J = 6.9 Hz, 1H), 7.47 (dd, J = 7.4, 2.6 Hz, 1H), 7.44−7.40 (m, 3H), 7.39−7.35 (m, 1H), 7.29 (td, J = 8.8, 2.6 Hz, 1H), 5.61 (d, J = 7.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.17, 167.84, 140.48, 139.33, 136.78, 136.39, 135.11, 134.50, 132.28, 129.35, 129.03, 128.68, 128.65, 126.57, 126.49, 125.57, 121.69, 121.46, 111.89, 57.57. LC-MS (ESI): m/z 376.1 $[M+1]^+$, t_R = 4.10 min.

*Dimethyl 2′-fluoro-[1,1′-biphenyl]-2,6-dicarboxylate (**96a**).* This previously unreported compound was synthesized according to general procedure K. Starting from **Ib** (0.137 g, 0.50 mmol, 1.00 equiv) and (2-fluorophenyl)boronic acid (0.105 g, 0.75 mmol, 1.50 equiv) and following purification by normal-phase flash chromatography (hep:EtOAc 0−35%), the title compound **96a** was obtained (yield ND). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (dd, J = 7.5, 2.0 Hz, 2H), 7.45 (dd, J = 8.7, 6.9 Hz, 1H), 7.33−7.21 (m, 2H), 7.10−7.01 (m, 2H), 3.53 (d, J = 2.9 Hz, 6H). LC-MS (ESI): m/z 289.1 $[M+1]^+$, t_R = 4.44 min.

*5-Fluoro-9-oxo-9H-fluorene-4-carboxylic acid (**96b**).* This previously unreported compound was synthesized according to general procedure L. Starting from **96a** (0.044 g, 0.15 mmol, 1.00 equiv), the title compound **96b** was obtained as a yellow-orange solid (0.032 g, 0.13 mmol, 87%). LC-MS (ESI): m/z 243.0 $[M+1]^+$, t_R = 3.64 min.

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*Methyl 2-(5-fluoro-9-oxo-9H-fluorene-4-carboxamido)-2-phenylacetate (**96c**).* This previously unreported compound was synthesized according to general procedure E. Starting from **96b** (0.032 g, 0.13 mmol, 1.00 equiv) and **Ic** (0.026 g, 0.13 mmol assumed, 1.00 equiv), the title compound **96c** was obtained (0.0098 g, 0.025 mmol, 19%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.46 (d, J = 7.5 Hz, 1H), 7.77 (dd, J = 6.6, 2.0 Hz, 1H), 7.61−7.30 (m, 10H), 5.69 (d, J = 7.5 Hz, 1H), 3.72 (d, J = 14.8 Hz, 3H). LC-MS (ESI): m/z 373.3 $[M+1]^+$, t_R = 4.27 min.

*2-(5-Fluoro-9-oxo-9H-fluorene-4-carboxamido)-2-phenylacetic acid (**96**).* This previously unreported compound was synthesized according to general procedure M. Starting from **96c** (0.0098 g, 0.025 mmol, 1.00 equiv), and following purification by reversed-phase flash chromatography (buffer A:buffer B 0−55%), the title compound **96** was obtained as a yellow solid (0.0004 g, 0.0011 mmol, 4.2%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.94 (s, 1H), 9.31 (d, J = 7.2 Hz, 1H), 7.87−7.23 (m, 11H), 5.65−5.53 (m, 1H). LC-MS (ESI): m/z 376.1 $[M+1]^+$, t_R = 3.83 min.

*Dimethyl 4′-chloro-[1,1′-biphenyl]-2,6-dicarboxylate (**97a**).* This previously unreported compound was synthesized according to general procedure K. Starting from **Ib** (0.137 g, 0.50 mmol, 1.00 equiv) and (4-chlorophenyl)boronic acid (0.118 g, 0.75 mmol, 1.50 equiv) and following purification by normal-phase flash chromatography (hep:EtOAc 0−20%), the title compound **97a** was obtained as a slight brown solid (0.105 g, 0.345 mmol, 69%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 7.8 Hz, 2H), 7.38 (t, J = 7.8 Hz, 1H), 7.26−7.20 (m, 2H), 7.06−7.02 (m, 2H), 3.48 (s, 6H). LC-MS (ESI): m/z 305.0 $[M+1]^+$, t_R = 4.70 min.

*7-Chloro-9-oxo-9H-fluorene-4-carboxylic acid (**97b**).* This previously reported compound was synthesized according to general procedure L. Starting from **97a** (0.105 g, 0.34 mmol, 1.00 equiv), the title compound **97b** was obtained as a yellow solid (0.071 g, 0.28 mmol, 80%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.73 (s, 1H), 8.32 (d, J = 8.3 Hz, 1H), 8.02 (dd, J = 7.9, 1.3 Hz, 1H), 7.85 (dd, J = 7.4, 1.3 Hz, 1H), 7.74 (dd, J = 8.3, 2.2 Hz, 1H), 7.69 (d, J = 2.2 Hz, 1H), 7.53 (t, J = 7.6 Hz, 1H). LC-MS (ESI): m/z 259.0 $[M+1]^+$, t_R = 4.33 min.

*Methyl 2-(7-chloro-9-oxo-9H-fluorene-4-carboxamido)-2-phenylacetate (**97c**).* This previously unreported compound was synthesized according to general procedure E. Starting from **97b** (0.071 g, 0.276 mmol, 1.00 equiv) and **Ic** (0.055 g, 0.331 mmol, 1.00 equiv) and following purification by normal-phase flash chromatography (hep:EtOAc 0−70%)„ the title compound **97c** was obtained as a yellow solid (0.073 g, 0.18 mmol, 65%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.68 (d, J = 6.8 Hz, 1H), 7.77−7.71 (m, 2H), 7.66 (d, J = 2.1 Hz, 1H), 7.61 (s, 1H), 7.60 (d, J = 2.1 Hz, 1H), 7.53−7.37 (m, 6H), 5.73 (d, J = 6.8 Hz, 1H), 3.73 (s, 3H). LC-MS (ESI): m/z 406.1 $[M+1]^+$, t_R = 4.77 min.

*2-(7-Chloro-9-oxo-9H-fluorene-4-carboxamido)-2-phenylacetic acid (**97**).* This previously unreported compound was synthesized according to general procedure M. Starting from **97c** (0.073 g, 0.18 mmol, 1.00 equiv), and following purification by reversed-phase flash chromatography (buffer A:buffer B 0−65%), the title compound **97** was obtained as a yellow solid (0.0074 g, 0.018 mmol, 10%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.06 (s, 1H), 9.55 (d, J = 7.1 Hz, 1H), 7.75 (dd, J = 7.7, 6.3 Hz, 2H), 7.66 (d, J = 2.1 Hz, 1H), 7.62 (dd, J = 7.7, 1.2 Hz, 1H), 7.53−7.50 (m, 3H), 7.47 (t, J = 7.5 Hz, 1H), 7.45−7.34 (m, 3H), 5.63 (d, J = 7.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 191.56, 172.13, 167.73, 141.76, 136.78, 135.14, 134.79, 134.75, 129.94, 129.04, 128.67, 126.18, 125.63, 124.20, 57.55. LC-MS (ESI): m/z 392.0 $[M+1]^+$, t_R = 4.30 min.

*Dimethyl 4′-hydroxy-[1,1′-biphenyl]-2,6-dicarboxylate (**98a**).* This previously unreported compound was synthesized according to general procedure K. Starting from **Ib** (0.273 g, 1.00 mmol, 1.00 equiv) and (4-hydroxyphenyl)boronic acid (0.204 g, 1.50 mmol, 1.50 equiv) and following purification by normal-phase flash chromatography (hep:EtOAc 0−30%), the title compound **98a** was obtained as a slight brown oil (0.143 g, 0.50 mmol, 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 7.7 Hz, 2H), 7.37 (t, J = 7.7 Hz, 1H), 7.00−6.93 (m, 2H), 6.68−6.61 (m, 2H), 3.55 (s, 6H). LC-MS (ESI): m/z 285.1 $[M+1]^+$, t_R = 3.87 min.

*7-Hydroxy-9-oxo-9H-fluorene-4-carboxylic acid (**98b**).* This previously unreported compound was synthesized according to general procedure L. Starting from **98a** (0.143 g, 0.50 mmol, 1.00 equiv), the title compound **98b** was obtained as a red-orange solid (0.043 g, 0.18 mmol, 36%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.89 (dd, J = 8.0, 1.3 Hz, 1H), 7.72−7.66 (m, 1H), 7.34 (t, J = 7.6 Hz, 1H), 7.01 (d, J = 2.5 Hz, 1H), 6.96 (dd, J = 8.4, 2.5 Hz, 1H). LC-MS (ESI): m/z 239.0 $[M-1]^-$, t_R = 3.44 min.

*Methyl 2-(7-hydroxy-9-oxo-9H-fluorene-4-carboxamido)-2-phenylacetate (**98c**).* This previously unreported compound was synthesized according to general procedure E. Starting from **98b** (0.043 g, 0.19 mmol, 1.00 equiv) and **Ic** (0.038 g, 0.23 mmol, 1.20 equiv) and following purification by normal-phase flash chromatography (DCM:MeOH 0−10%)„ the title compound **98c** was obtained as a yellow-orange solid (0.018 g, 0.046 mmol, 24%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.61 (s, 1H), 7.96 (s, 1H), 5.12 (s, 1H) (missing protons due to dilute sample). LC-MS (ESI): m/z 386.1 $[M+1]^+$, t_R = 3.99 min.

*2-(7-Hydroxy-9-oxo-9H-fluorene-4-carboxamido)-2-phenylacetic acid (**98**).* This previously unreported compound was synthesized according to general procedure M. Starting from **98c** (0.012 g, 0.046 mmol, 1.00 equiv), and following purification by reversed-phase flash chromatography (buffer A:buffer B 0−50%), the title compound **98** was obtained as a yellow solid (0.0010 g, 0.0027 mmol, 6%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.16 (s, 1H), 9.39−9.35 (m, 1H), 7.59 (dd, J = 7.3, 1.1 Hz, 1H), 7.51 (d, J = 1.7 Hz, 1H), 7.49−7.47 (m, 2H), 7.40 (dd, J = 8.2, 6.5 Hz, 2H), 7.37−7.34 (m, 1H), 7.28 (t, J = 7.5 Hz, 1H), 6.97 (d, J = 2.4 Hz, 1H), 6.77 (dd, J = 8.3, 2.5 Hz, 1H), 5.58 (d, J = 7.2 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 193.06, 172.15, 159.39, 141.88, 135.90, 134.38, 133.95, 128.92, 128.61, 126.08, 125.07, 120.70, 111.85, 57.59. LC-MS (ESI): m/z 374.1 $[M+1]^+$, t_R = 3.60 min.

*Ethyl 2-amino-2-(4-chlorophenyl)acetate (**99a**).* This previously reported compound was synthesized according to a literature protocol with minor deviations.[99] To a suspension of 2-amino-2-(4-chlorophenyl)acetic acid (0.100 g, 0.54 mmol, 1.00 equiv) in abs. EtOH (1.1 mL) was dropwise added $SOCl_2$ (0.755 mL, 0.65 mmol, 1.20 equiv) under cooling at 0 °C. The mixture was then heated at reflux for 5 h. Upon reaction completion, the mixture was cooled to rt and concentrated *in vacuo*. The crude residue was redissolved in DCM (4.0 mL) and carefully treated with 30 w/w% NH_4OH (0.4 mL). The mixture was stirred at rt for 2 h. Upon reaction completion, the layers were separated, and the aq. layer extracted with DCM. The combined organic layers were washed with sat. aq. $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo* to afford the title compound as a white solid (0.115 g, 0.54 mmol, quantitative). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.08 (s, 3H), 7.60−7.48 (m, 4H), 5.31 (s, 1H), 4.28−4.10 (m, 2H), 1.14 (t, J = 7.1 Hz, 3H). LC-MS (ESI): m/z 214.0 $[M+1]^+$, t_R = 2.77 min.

*Ethyl 2-(4-chlorophenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)-acetate (**99b**).* This previously unreported compound was synthesized according to general procedure N. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.121 g, 0.54 mmol, 1.00 equiv) and **99a** (0.115 g, 0.54 mmol, 1.00 equiv), the title compound **99b** was obtained as an orange-brown oil (yield ND).

*2-(4-Chlorophenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetic acid (**99**).* This previously unreported compound was synthesized according to general procedure D. Starting from **99b** (crude weight, 0.54 mmol assumed, 1.00 equiv) and following purification by reversed-phase flash chromatography, the title compound **99** was obtained as a yellow solid (0.021 g, 0.054 mmol, 10%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.15 (s, 1H), 9.55 (d, J = 7.2 Hz, 1H), 7.73−7.67 (m, 2H), 7.64 (d, J = 6.6 Hz, 1H), 7.57 (dd, J = 7.7, 1.1 Hz, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.50−7.44 (m, 3H), 7.44 (s, 1H), 7.43−7.36 (m, 1H), 5.67 (d, J = 7.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.84, 135.58, 134.24, 132.49, 130.59, 130.19, 129.66, 128.97,

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124.58, 124.31, 56.76. LC-MS (ESI): m/z 392.1 $[M+1]^+$, t_R = 4.16 min.

*Methyl 2-amino-2-(3-chlorophenyl)acetate hydrochloride (**100a**).* This previously reported compound was synthesized according to general procedure G. Starting from 2-amino-2-(3-chlorophenyl)acetic acid (0.092 g, 0.50 mmol, 1.00 equiv), the title compound **100a** was obtained as a white solid (0.118 g, 0.50 mmol, quantitative). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (s, 3H), 7.69 (d, J = 2.0 Hz, 1H), 7.64−7.48 (m, 3H), 5.44 (s, 1H), 3.80 (s, 3H), 1.33 (s, 2H). LC-MS (ESI): m/z 200.0 $[M+1]^+$, t_R = 3.58 min.

*Methyl 2-(3-chlorophenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetate (**100b**).* This previously unreported compound was synthesized according to general procedure N. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.121 g, 0.54 mmol, 1.00 equiv) and **100a** (0.118 g, ∼0.54 mmol, 1.00 equiv), the title compound **100b** was obtained as a yellow oil (yield ND). LC-MS (ESI): m/z 406.0 $[M+1]^+$, t_R = 4.50 min.

*2-(3-Chlorophenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetic acid (**100**).* This previously unreported compound was synthesized according to general procedure D. Starting from **100b** (crude weight, 0.54 mmol assumed, 1.00 equiv) and following purification by reversed-phase flash chromatography, the title compound **100** was obtained as a yellow solid (0.024 g, 0.061 mmol, 11%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.33−13.28 (m, 1H), 9.58 (d, J = 7.3 Hz, 1H), 7.81 (d, J = 2.1 Hz, 1H), 7.76−7.63 (m, 4H), 7.60 (dd, J = 7.7, 1.2 Hz, 1H), 7.54 (dd, J = 8.4, 2.1 Hz, 1H), 7.46 (t, J = 7.4 Hz, 2H), 7.45−7.37 (m, 1H), 5.74 (d, J = 7.3 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.85, 171.41, 167.92, 143.07, 140.87, 138.15, 135.57, 134.60, 134.29, 133.84, 132.36, 131.52, 131.30, 131.17, 130.67, 130.25, 129.75, 129.15, 125.38, 124.54, 124.35, 56.31. LC-MS (ESI): m/z 392.1 $[M+1]^+$, t_R = 4.16 min.

*Ethyl 2-amino-2-(3,4-dichlorophenyl)acetate (**101a**).* This previously reported compound was synthesized according to general procedure G. Starting from 2-amino-2-(3,4-dichlorophenyl)acetic acid (0.051 g, 0.25 mmol, 1.00 equiv), the title compound **101a** was obtained as a white solid (0.071 g, 0.25 mmol, quantitative). LC-MS (ESI): m/z 250.0 $[M+1]^+$, t_R = 3.05 min.

*Ethyl 2-(3,4-dichlorophenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetate (**101b**).* This previously unreported compound was synthesized according to general procedure N. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.056 g, 0.25 mmol, 1.00 equiv) and **101a** (0.071 g, 0.25 mmol, 1.00 equiv), the title compound **101b** was obtained as an orange oil (yield ND). LC-MS (ESI): m/z 454.0 $[M+1]^+$, t_R = 4.95 min.

*2-(3,4-Dichlorophenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)-acetic acid (**101**).* This previously unreported compound was synthesized according to general procedure D. Starting from **101b** (crude weight, 0.25 mmol assumed, 1.00 equiv) and following purification by reversed-phase flash chromatography, the title compound **101** was obtained as a yellow solid (32 mg, 0.075 mmol, 30%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.56 (d, J = 7.3 Hz, 1H), 7.80 (d, J = 2.1 Hz, 1H), 7.72 (dd, J = 7.3, 1.1 Hz, 1H), 7.69 (d, J = 8.3 Hz, 1H), 7.68 (dd, J = 6.8, 4.5 Hz, 1H), 7.65 (d, J = 7.3 Hz, 1H), 7.59 (dd, J = 7.7, 1.1 Hz, 1H), 7.53 (dd, J = 8.4, 2.1 Hz, 1H), 7.46 (td, J = 7.5, 1.5 Hz, 2H), 7.40 (td, J = 7.4, 1.0 Hz, 1H), 5.72 (d, J = 7.2 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.85, 171.38, 167.91, 143.06, 140.86, 138.21, 135.57, 134.59, 134.28, 133.84, 132.37, 131.51, 131.27, 131.15, 130.65, 130.25, 129.75, 129.13, 125.37, 124.53, 124.35, 56.34, 40.53, 40.40, 40.26. LC-MS (ESI): m/z 426.1 $[M+1]^+$, t_R = 4.37 min.

*Ethyl 2-oxo-2-(m-tolyl)acetate (**102a**).* This previously reported compound was synthesized according to general procedure O. Starting from 1-bromo-3-methylbenzene (2.99 mmol, 1.05 equiv), the title compound **102a** was obtained as a pale yellow solid (0.356 g, 1.85 mmol, 62%). The crude was used without further characterization.

*Ethyl 2-(hydroxyimino)-2-(m-tolyl)acetate (**102b**).* This previously reported compound was synthesized according to general procedure P. Starting from **102a** (3.93 mmol, 1.00 equiv), the title compound **102b** was obtained (yield ND). The crude was used without further characterization.

*Ethyl 2-amino-2-(m-tolyl)acetate (**102c**).* This previously reported compound was synthesized according to general procedure Q. Starting from **102b** (1.76 mmol, 1.00 equiv), the title compound **102c** was obtained (0.340 g, 1.76 mmol, quantitative). LC-MS (ESI): m/z 194.2 $[M+1]^+$, t_R = 2.75 min.

*Ethyl 2-(9-oxo-9H-fluorene-4-carboxamido)-2-(m-tolyl)acetate (**102d**).* This previously unreported compound was synthesized according to general procedure N. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.081 g, 0.362 mmol, 1.00 equiv) and **102c** (0.070 g, 0.362 mmol, 1.00 equiv), the title compound **102d** was obtained (yield ND). LC-MS (ESI): m/z 400.2 $[M+1]^+$, t_R = 4.61 min.

*2-(9-Oxo-9H-fluorene-4-carboxamido)-2-(m-tolyl)acetic acid (**102**).* This previously unreported compound was synthesized according to general procedure D. Starting from **102d** (crude weight, 0.362 mmol assumed, 1.00 equiv) and following purification by reversed-phase flash chromatography, the title compound **102** was obtained as a yellow solid (0.037 g, 0.100 mmol, 28% over 2 steps). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.99 (s, 1H), 9.46 (d, J = 7.2 Hz, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.69 (dd, J = 7.3, 1.2 Hz, 1H), 7.64 (d, J = 7.3 Hz, 1H), 7.56 (dd, J = 7.7, 1.2 Hz, 1H), 7.47−7.41 (m, 2H), 7.39 (td, J = 7.4, 1.0 Hz, 1H), 7.32 (s, 1H), 7.31−7.26 (m, 2H), 7.18 (d, J = 6.6 Hz, 1H), 5.57 (d, J = 7.1 Hz, 1H), 2.32 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.9−192.90 (m), 172.19, 167.93, 143.19, 140.86, 138.15, 134.71, 134.19, 130.13, 129.60, 129.21 (d, J = 6.8 Hz), 125.79, 125.17, 124.63, 124.26, 57.54, 21.47. LC-MS (ESI): m/z 372.2 $[M+1]^+$, t_R = 3.89 min.

*Ethyl 2-(3-methoxyphenyl)-2-oxoacetate (**103a**).* This previously reported compound was synthesized according to general procedure O. Starting from 1-bromo-3-methoxybenzene (5.00 mmol, 1.05 equiv), the title compound **103a** was obtained (1.04 g, 5.00 mmol, quantitative). LC-MS (ESI): m/z 209.1 $[M+1]^+$, t_R = 4.37 min.

*Ethyl 2-(hydroxyimino)-2-(3-methoxyphenyl)acetate (**103b**).* This previously unreported compound was synthesized according to general procedure P. Starting from **103a** (3.92 mmol, 1.00 equiv), the title compound **103b** was obtained after purification by normal-phase flash chromatography (hep:EtOAc 0−100%) (0.374 g, 1.68 mmol, 43%). LC-MS (ESI): m/z 224.1 $[M+1]^+$, t_R = 3.73 min.

*Ethyl 2-amino-2-(3-methoxyphenyl)acetate (**103c**).* This previously reported compound was synthesized according to general procedure Q. Starting from **103b** (1.76 mmol, 1.00 equiv), the title compound **103c** was obtained (0.368 g, 1.76 mmol, quantitative). LC-MS (ESI): m/z 210.2 $[M+1]^+$, t_R = 2.60 min.

*Ethyl 2-(3-methoxyphenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetate (**103d**).* This previously unreported compound was synthesized according to general procedure N. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.030 g, 0.132 mmol, 1.00 equiv) and **103c** (0.046 g, 0.132 mmol, 1.00 equiv), the title compound **103d** was obtained (yield ND). LC-MS (ESI): m/z 416.2 $[M+1]^+$, t_R = 4.63 min.

*2-(3-Methoxyphenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)-acetic acid (**103**).* This previously unreported compound was synthesized according to general procedure D. Starting from **103d** (crude weight, 0.112 mmol assumed, 1.00 equiv) and following purification by reversed-phase flash chromatography, the title compound **103** was obtained as a yellow solid (0.032 g, 0.083 mmol, 74% over 2 steps). ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.93 (s, 1H), 7.69 (dd, J = 7.3, 3.1 Hz, 1H), 7.65−7.56 (m, 3H), 7.45−7.39 (m, 2H), 7.38−7.32 (m, 1H), 7.26 (t, J = 8.0 Hz, 1H), 7.06 (dd, J = 7.2, 1.6 Hz, 2H), 6.86 (d, J = 8.2 Hz, 1H), 5.35 (d, J = 7.0 Hz, 1H), 3.73 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.06, 159.55, 143.17, 135.59, 134.31, 133.82, 133.20, 131.86, 131.33, 131.10, 130.06, 129.73, 129.48, 125.06, 124.22, 120.52, 113.81, 112.99. LC-MS (ESI): m/z 388.1 $[M+1]^+$, t_R = 3.95 min.

*N-(3-Bromobenzyl)benzenesulfonamide (**104a**).* This previously reported compound was synthesized according to general procedure R. To a solution of (3-bromophenyl)methanamine (2.22 g, 10.0 mmol, 1.00 equiv) and Et_3N (4.18 mL, 30.0 mmol, 3.00 equiv) in dry DCM (20.0 mL) under N_2 was added benzenesulfonyl chloride

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(1.276 mL, 10.0 mmol, 1.00 equiv). The mixture was stirred at reflux for 3 h. Upon reaction completion, the mixture was quenched with water (30 mL) and concentrated *in vacuo*. The residue was then extracted with EtOAc (3 × 20 mL), and the combined organic phases were washed with 1 M HCl (2 × 20 mL) and sat. brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the title compound **104a** (3.26 g, 10.0 mmol, quantitative). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.22 (t, J = 6.4 Hz, 1H), 7.82−7.75 (m, 2H), 7.65−7.54 (m, 3H), 7.44−7.37 (m, 2H), 7.28−7.20 (m, 2H), 4.02 (d, J = 6.3 Hz, 2H). LC-MS (ESI): m/z 327.0 + 329.0 $[M+1]^+$, t_R = 4.50 min.

*Ethyl 2-oxo-2-(3-(phenylsulfonamidomethyl)phenyl)acetate (**104b**).* This previously reported compound was synthesized according to a literature protocol with minor deviations (general procedure S).[100] A solution of **104a** (0.326 g, 1.00 mmol, 1.00 equiv) in dry THF (2.2 mL) was cooled to −78 °C and then added 2.5 M *n*-BuLi in hexane (0.932 mL, 2.33 mmol, 2.33 equiv) under N_2. The mixture was stirred at −78 °C for 15 min. Then, a solution of diethyl oxalate (0.137 mL, 1.00 mmol, 1.00 equiv) in dry THF (0.5 mL) was added dropwise, and the mixture was stirred at −78 °C for a further 20 min. Upon reaction completion, the mixture was quenched by addition of sat. aq. NH_4Cl at −78 °C. The crude mixture was here extracted with EtOAc (3 × 3 mL), and the combined organic layers were washed with sat. brine, dried over Na_2SO_4, filtered, and concentrated to dryness *in vacuo*. Purification by normal-phase flash chromatography (hep:EtOAc 0−100%) afforded the title compound **104b** (0.043 g, 0.121 mmol, 12%). LC-MS (ESI): m/z 348.0 $[M+1]^+$, t_R = 4.32 min.

*Ethyl 2-(hydroxyimino)-2-(3-(phenylsulfonamidomethyl)-phenyl)acetate (**104c**).* This previously unreported compound was synthesized according to general procedure P. Starting from **104b** (0.727 mmol, 1.00 equiv), the title compound **104c** was obtained (0.263 g, 0.727 mmol, quantitative). LC-MS (ESI): m/z 363.1 $[M+1]^+$, t_R = 3.93 min.

*Ethyl 2-amino-2-(3-(phenylsulfonamidomethyl)phenyl)acetate (**104d**).* This previously unreported compound was synthesized according to general procedure Q. Starting from **104c** (0.52 mmol, 1.00 equiv) and following purification by reversed-phase flash chromatography, the title compound **104d** was obtained as an off-white solid (0.038 g, 0.153 mmol, 30%). LC-MS (ESI): m/z 349.1 $[M+1]^+$, t_R = 2.12 min.

*Ethyl 2-(9-oxo-9H-fluorene-4-carboxamido)-2-(3-(phenylsulfonamidomethyl)phenyl)acetate (**104e**).* This previously unreported compound was synthesized according to general procedure N. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.030 g, 0.132 mmol, 1.00 equiv) and **104d** (0.046 g, 0.132 mmol, 1.00 equiv), the title compound **104e** was obtained (yield ND). LC-MS (ESI): m/z 555.2 $[M+1]^+$, t_R = 4.31 min.

*2-(9-Oxo-9H-fluorene-4-carboxamido)-2-(3-(phenylsulfonamidomethyl)phenyl)acetic acid (**104**).* This previously unreported compound was synthesized according to general procedure D. Starting from **104e** (crude weight, 0.132 mmol assumed, 1.00 equiv) and following purification by reversed-phase flash chromatography, the title compound **104** was obtained as a yellow solid (0.024 g, 0.046 mmol, 35% over 2 steps). ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.06 (s, 1H), 9.49 (d, J = 7.2 Hz, 1H), 8.24−7.16 (m, 16H), 5.59 (d, J = 7.2 Hz, 1H), 3.98 (d, J = 6.4 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.43, 171.54, 167.43, 142.66, 140.54, 140.39, 137.96, 136.37, 135.16, 134.22, 133.72, 133.32, 132.35, 132.08, 129.64, 129.16, 129.12, 128.48, 127.41, 127.31, 126.94, 126.44, 126.43, 124.73, 124.14, 123.78, 56.92, 46.02. LC-MS (ESI): m/z 527.1 $[M+1]^+$, t_R = 4.07 min.

*N-(3-Bromobenzyl)-4-methylbenzenesulfonamide (**105a**).* This previously reported compound was synthesized according to general procedure R. Starting from (3-bromophenyl)methanamine hydrochloride (0.220 g, 1.00 mmol, 1.00 equiv) and 4-methylbenzenesulfonyl chloride (0.190 g, 1.00 mmol, 1.00 equiv), the title compound **105a** was obtained (0.34 g, 1.00 mmol, quantitative). LC-MS (ESI): m/z 340.0 $[M+1]^+$, t_R = 4.64 min.

*Ethyl 2-(3-(((4-methylphenyl)sulfonamido)methyl)phenyl)-2-oxoacetate (**105b**).* This previously unreported compound was synthesized according to general procedure S. Starting from **105a** (0.180 g, 0.500 mmol, 1.00 equiv) and following purification by normal-phase flash chromatography (hep:EtOAc 0−20%), the title compound **105b** was obtained as a colorless oil (0.053 g, 0.140 mmol, 28%). ^{1}H NMR (600 MHz, chloroform-d) δ 7.83 (d, J = 7.8 Hz, 1H), 7.73 (d, J = 1.9 Hz, 1H), 7.68−7.65 (m, 2H), 7.51 (dt, J = 7.6, 1.5 Hz, 1H), 7.39 (d, J = 7.7 Hz, 1H), 7.23 (d, J = 7.8 Hz, 3H), 4.38 (q, J = 7.2 Hz, 2H), 4.14 (d, J = 6.4 Hz, 2H), 2.36 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H). LC-MS (ESI): m/z 362.2 $[M+1]^+$, t_R = 4.46 min.

*Ethyl 2-(hydroxyimino)-2-(3-(((4-methylphenyl)sulfonamido)-methyl)phenyl)acetate (**105c**).* This previously unreported compound was synthesized according to general procedure P. Starting from **105b** (0.020 g, 0.055 mmol, 1.00 equiv), the title compound **105c** was obtained as an off-white solid (0.02 g, 0.06 mmol, quantitative). LC-MS (ESI): m/z 377.0 $[M+1]^+$, t_R = 4.02 and 4.16 min.

*Ethyl 2-amino-2-(3-(((4-methylphenyl)sulfonamido)methyl)-phenyl)acetate (**105d**).* This previously unreported compound was synthesized according to general procedure Q. Starting from **105c** (0.022 g, 0.057 mmol, 1.00 equiv), the title compound **105d** was obtained as a colorless oil (0.014 g, 0.037 mmol, 67%). LC-MS (ESI): m/z 363.2 $[M+1]^+$, t_R = 3.20 min.

*Ethyl 2-(3-(((4-methylphenyl)sulfonamido)methyl)phenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetate (**105e**).* This previously unreported compound was synthesized according to general procedure N. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.051 g, 0.228 mmol, 1.00 equiv) and **105d** (0.083 g, 0.228 mmol, 1.00 equiv), the title compound **105e** was obtained (0.036 g, 0.063 mmol, 28%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.70−7.63 (m, 3H), 7.62−7.57 (m, 1H), 7.48 (dd, J = 7.7, 1.3 Hz, 1H), 7.46−7.42 (m, 1H), 7.31−7.20 (m, 10H), 6.93 (d, J = 7.0 Hz, 1H), 5.69 (d, J = 7.0 Hz, 1H), 4.18 (dd, J = 33.0, 7.1 Hz, 2H), 4.06 (s, 2H), 2.35 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H). LC-MS (ESI): m/z 569.1 $[M+1]^+$, t_R = 4.66 min.

*2-(9-Oxo-9H-fluorene-4-carboxamido)-2-(3-(phenylsulfonamidomethyl)phenyl)acetic acid (**105**).* This previously unreported compound was synthesized according to general procedure D. Starting from **105e** (0.023 g, 0.041 mmol, 1.00 equiv) and following purification by reversed-phase flash chromatography, the title compound **105** was obtained as a yellow solid (0.016 g, 0.029 mmol, 70%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.07 (s, 1H), 9.50 (d, J = 7.2 Hz, 1H), 8.09 (t, J = 6.4 Hz, 1H), 7.71 (dd, J = 7.9, 6.4 Hz, 4H), 7.64 (d, J = 7.3 Hz, 1H), 7.57 (dd, J = 7.7, 1.2 Hz, 1H), 7.48−7.45 (m, 1H), 7.45−7.42 (m, 1H), 7.42−7.37 (m, 5H), 7.32 (t, J = 7.6 Hz, 1H), 7.24 (d, J = 7.6 Hz, 1H), 5.60 (d, J = 7.2 Hz, 1H), 3.96 (d, J = 6.3 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.93, 172.05, 167.93, 143.16, 143.10, 140.89, 138.53, 138.13, 136.85, 135.66, 134.72, 134.22, 133.81, 132.58, 130.14, 130.10, 129.62, 128.98, 127.91, 127.83, 127.41, 127.04, 125.23, 124.64, 124.28, 57.41, 46.50, 21.44. LC-MS (ESI): m/z 541.1 $[M+1]^+$, t_R = 4.15 min.

*N-(3-Bromobenzyl)-4-methoxybenzenesulfonamide (**106a**).* This previously reported compound was synthesized according to an general procedure R. Starting from (3-bromophenyl)methanamine hydrochloride (0.220 g, 1.00 mmol, 1.00 equiv) and 4-methoxybenzenesulfonyl chloride (0.210 g, 1.00 mmol, 1.00 equiv), the title compound **106a** was obtained (0.31 g, 0.86 mmol, 86%). LC-MS (ESI): m/z 356.0 $[M+1]^+$, t_R = 4.46 min.

*Ethyl 2-(3-(((4-methoxyphenyl)sulfonamido)methyl)phenyl)-2-oxoacetate (**106b**).* This previously unreported compound was synthesized according to general procedure S. Starting from **106a** (0.210 g, 0.500 mmol, 1.00 equiv) and following purification by normal-phase flash chromatography (hep:EtOAc 0−20%), the title compound **106b** was obtained as a colorless oil (0.052 g, 0.14 mmol, 23%). ^{1}H NMR (600 MHz, chloroform-d) δ 7.81 (dt, J = 7.8, 1.5 Hz, 1H), 7.73 (d, J = 1.9 Hz, 1H), 7.71−7.68 (m, 2H), 7.51−7.48 (m, 1H), 7.37 (t, J = 7.8 Hz, 1H), 6.89−6.86 (m, 2H), 4.82 (t, J = 6.5 Hz, 1H), 4.39−4.35 (m, 2H), 4.13 (d, J = 5.9 Hz, 2H), 3.80 (s, 3H), 1.35

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(td, J = 7.2, 0.7 Hz, 3H). LC-MS (ESI): m/z 378.1 $[M+1]^+$, t_R = 4.38 min.

*Ethyl 2-(3-(((4-methoxyphenyl)sulfonamido)methyl)phenyl)-2-oxoacetateacetate (**106c**).* This previously unreported compound was synthesized according to general procedure P. Starting from **106b** (0.041 g, 0.110 mmol, 1.00 equiv), the title compound **106c** was obtained as an off-white solid (0.040 g, 0.100 mmol, quantitative). LC-MS (ESI): m/z 393.2 $[M+1]^+$, t_R = 3.89 and 4.04 min.

*Ethyl 2-amino-2-(3-(((4-methylphenyl)sulfonamido)methyl)-phenyl)acetate (**106d**).* This previously unreported compound was synthesized according to general procedure Q. Starting from **106c** (0.040 g, 0.100 mmol, 1.00 equiv), the title compound **106d** was obtained as a colorless oil (0.024 g, 0.062 mmol, 63%). LC-MS (ESI): m/z 379.3 $[M+1]^+$, t_R = 3.13 min.

*Ethyl 2-(3-(((4-methoxyphenyl)sulfonamido)methyl)phenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetate (**106e**).* This previously unreported compound was synthesized according to general procedure U. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.016 g, 0.068 mmol, 1.00 equiv) and **106d** (0.026 g, 0.068 mmol, 1.00 equiv), the title compound **106e** was obtained (0.020 g, 0.034 mmol, 51%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.73−7.69 (m, 2H), 7.67 (dd, J = 7.4, 1.1 Hz, 1H), 7.60−7.58 (m, 1H), 7.48 (dd, J = 7.7, 1.2 Hz, 1H), 7.46−7.43 (m, 1H), 7.32−7.29 (m, 2H), 7.29−7.26 (m, 3H), 7.22−7.20 (m, 4H), 6.89−6.87 (m, 2H), 5.69 (d, J = 7.0 Hz, 1H), 4.16−4.10 (m, 1H), 4.06 (dd, J = 6.2, 3.3 Hz, 2H), 3.78 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H). LC-MS (ESI): m/z 585.2 $[M+1]^+$, t_R = 4.52 min.

*2-(3-(((4-Methoxyphenyl)sulfonamido)methyl)phenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetic acid (**106**).* This previously unreported compound was synthesized according to general procedure D. Starting from **106e** (0.020 g, 0.034 mmol, 1.00 equiv) and following purification by reversed-phase flash chromatography, the title compound **106** was obtained as a yellow solid (0.018 g, 0.031 mmol, 94%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.07 (s, 1H), 9.50 (d, J = 7.2 Hz, 1H), 8.02 (t, J = 6.4 Hz, 1H), 7.76−7.73 (m, 2H), 7.71 (ddd, J = 7.3, 5.4, 1.0 Hz, 2H), 7.64 (dt, J = 7.3, 1.0 Hz, 1H), 7.57 (dd, J = 7.7, 1.2 Hz, 1H), 7.48−7.45 (m, 1H), 7.45−7.43 (m, 1H), 7.42 (d, J = 1.6 Hz, 1H), 7.40−7.37 (m, 2H), 7.32 (t, J = 7.6 Hz, 1H), 7.24 (dt, J = 7.7, 1.4 Hz, 1H), 7.11−7.08 (m, 2H), 5.61 (d, J = 7.2 Hz, 1H), 3.94 (d, J = 6.4 Hz, 2H), 3.83 (s, 3H). ^{13}C NMR (600 MHz, DMSO-d_6) δ 192.93, 172.06, 167.93, 162.57, 143.16, 140.89, 138.53, 136.84, 135.66, 134.72, 134.22, 133.81, 132.66, 132.58, 130.14, 129.61, 129.16, 128.97, 127.92, 127.83, 127.39, 125.22, 124.64, 124.27, 114.78, 57.42, 56.09, 46.51. LC-MS (ESI): m/z 557.10 $[M+1]^+$, t_R = 4.01 min.

*N-(3-Bromobenzyl)-4-methoxybenzenesulfonamide (**107a**).* This previously reported compound was synthesized according to general procedure R. Starting from (3-bromophenyl)methanamine hydrochloride (2.22 g, 10.0 mmol, 1.00 equiv) and 3-methoxybenzenesulfonyl chloride (2.07 g, 10.0 mmol, 1.00 equiv), the title compound **107a** was obtained as a brown oil (1.66 g, 4.66 mmol, 39%). LC-MS (ESI): m/z 357.1 $[M+1]^+$, t_R = 4.58 min.

*Ethyl 2-(3-(((4-methoxyphenyl)sulfonamido)methyl)phenyl)-2-oxoacetate (**107b**).* This previously unreported compound was synthesized according to general procedure S. Starting from **107a** (0.180 g, 0.500 mmol, 1.00 equiv) and following purification by normal-phase flash chromatography (hep:EtOAc 0−20%), the title compound **107b** was obtained as a colorless oil (0.023 g, 0.07 mmol, 14%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.81 (ddd, J = 8.3, 3.9, 1.8 Hz, 1H), 7.74 (d, J = 2.1 Hz, 1H), 7.51−7.48 (m, 1H), 7.39−7.30 (m, 3H), 7.27−7.25 (m, 1H), 7.01 (ddt, J = 6.7, 2.6, 1.5 Hz, 1H), 4.40−4.35 (m, 2H), 4.18−4.14 (m, 2H), 3.76 (dt, J = 2.7, 1.1 Hz, 3H), 1.37−1.33 (m, 3H). LC-MS (ESI): m/z 378.2 $[M+1]^+$, t_R = 4.36 min.

*Ethyl 2-(3-(((3-methoxyphenyl)sulfonamide)methyl)phenyl)-2-oxoacetateacetate (**107c**).* This previously unreported compound was synthesized according to general procedure P. Starting from **107b** (0.040 g, 0.100 mmol, 1.00 equiv), the title compound **107c** was obtained as an off-white solid (0.037 g, 0.08 mmol, 76%). LC-MS (ESI): m/z 393.1 $[M+1]^+$, t_R = 4.05 and 4.12 min.

*Ethyl 2-amino-2-(3-(((3-methylphenyl)sulfonamido)methyl)-phenyl)acetate (**107d**).* This previously unreported compound was synthesized according to general procedure T. Starting from **107c** (0.032 g, 0.080 mmol, 1.00 equiv), the title compound **107d** was obtained as a colorless oil (0.026 g, 0.053 mmol, 41%). LC-MS (ESI): m/z 379.2 $[M+1]^+$, t_R = 3.00 min.

*Ethyl 2-(3-(((3-methoxyphenyl)sulfonamido)methyl)phenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetate (**107e**).* This previously unreported compound was synthesized according to general procedure U. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.016 g, 0.068 mmol, 1.00 equiv) and **107d** (0.027 g, 0.072 mmol, 1.00 equiv), the title compound **107e** was obtained (0.018 g, 0.030 mmol, 42%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.67−7.63 (m, 1H), 7.59−7.56 (m, 1H), 7.46 (ddd, J = 15.7, 7.3, 1.5 Hz, 2H), 7.38−7.31 (m, 2H), 7.32−7.28 (m, 3H), 7.27 (d, J = 3.5 Hz, 2H), 7.26−7.23 (m, 1H), 7.21 (d, J = 1.9 Hz, 1H), 7.01−6.98 (m, 2H), 5.68 (d, J = 7.0 Hz, 1H), 4.84 (t, J = 6.3 Hz, 1H), 4.27−4.10 (m, 2H), 4.09 (dd, J = 6.4, 3.3 Hz, 2H), 3.74 (s, 3H), 1.19 (t, J = 7.1 Hz, 3H). LC-MS (ESI): m/z 585.2 $[M+1]^+$, t_R = 4.54 min.

*2-(3-(((3-Methoxyphenyl)sulfonamido)methyl)phenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetic acid (**107**).* This previously unreported compound was synthesized according to general procedure D. Starting from **107e** (0.126 g, 0.221 mmol, 1.00 equiv) and following purification by reversed-phase flash chromatography, the title compound **107** was obtained as a yellow solid (0.020 g, 0.035 mmol, 16%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.06 (s, 1H), 9.49 (d, J = 7.2 Hz, 1H), 8.18 (t, J = 6.4 Hz, 1H), 7.71 (td, J = 1.0 Hz, 2H), 7.64 (dt, J = 7.3, 1.0 Hz, 1H), 7.57 (dd, J = 7.7, 1.2 Hz, 1H),) δ 7.52−7.49 (m, 1H), 7.47 (td, J = 7.6, 1.3 Hz, 1H), 7.45−7.42 (m, 1H), 7.43 (d, J = 1.8 Hz, 1H), 7.41−7.38 (m, 3H), 7.36−7.31 (m, 2H), 7.25 (dt, J = 7.8, 1.4 Hz, 1H), 7.20 (ddd, J = 8.3, 2.6, 0.9 Hz, 1H), 5.60 (d, J = 7.3 Hz, 1H), 3.98 (d, J = 6.3 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.93, 172.04, 167.93, 159.93, 143.16, 142.21, 140.89, 138.48, 136.87, 135.66, 134.71, 132.58, 130.88, 130.14, 129.62, 128.98, 127.89, 127.82, 127.44, 125.23, 124.64, 124.27, 119.09, 118.81, 111.92, 57.41, 56.04, 46.53, 40.55, 40.41. LC-MS (ESI): m/z 557.1 $[M+1]^+$, t_R = 4.06 min.

*N-(3-Bromobenzyl)-2,3,5,6-tetramethylbenzenesulfonamide (**108a**).* This previously reported compound was synthesized according to general procedure R. Starting from (3-bromophenyl)-methanamine hydrochloride (2.22 g, 10.00 mmol, 1.00 equiv) and 2,3,5,6-tetramethylbenzenesulfonyl chloride (2.32 g, 10.00 mmol, 1.00 equiv), the title compound **108a** was obtained as a white solid (3 g, 7.87 mmol, 79%). LC-MS (ESI): m/z 382.1 $[M+1]^+$, t_R = 5.11 min.

*Ethyl 2-oxo-2-(3-(((2,3,5,6-tetramethylphenyl)sulfonamido)-methyl)phenyl)acetate (**108b**).* This previously unreported compound was synthesized according to general procedure S. Starting from **108a** (0.380 g, 1.00 mmol, 1.00 equiv) and following purification by normal-phase flash chromatography (hep:EtOAc 0−20%), the title compound **108b** was obtained as a colorless oil (0.023 g, 0.07 mmol, 14%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.76 (dt, J = 7.7, 1.5 Hz, 1H), 7.66 (t, J = 1.8 Hz, 1H), 7.42 (dt, J = 7.7, 1.5 Hz, 1H), 7.31 (t, J = 7.7 Hz, 1H), 7.02 (s, 1H), 4.38 (q, J = 7.1 Hz, 2H), 4.12 (d, J = 6.3 Hz, 2H), 2.45 (s, 6H), 2.15 (s, 7H), 1.36 (t, J = 7.2 Hz, 3H). LC-MS (ESI): m/z 421.1 $[M+1]^+$, t_R = 4.81 min.

*Ethyl 2-(hydroxyimino)-2-(3-(((2,3,5,6-tetramethylphenyl)-sulfonamido)methyl)phenyl (**108c**).* This previously unreported compound was synthesized according to general procedure P. Starting from **108b** (0.065 g, 0.160 mmol, 1.00 equiv), the title compound **108c** was obtained as an off-white solid (0.070 g, 0.170 mmol, quantitative). LC-MS (ESI): m/z 419.2 $[M+1]^+$, t_R = 4.41 and 4.51 min.

*Ethyl 2-amino-2-(3-(((2,3,5,6-tetramethylphenyl)sulfonamido)-methyl)phenyl)acetate (**108d**).* This previously unreported compound was synthesized according to general procedure T. Starting from **108c** (0.070 g, 0.170 mmol, 1.00 equiv), the title compound **108d** was obtained as a colorless oil (0.050 g, 0.130 mmol, 77%). LC-MS (ESI): m/z 405.4 $[M+1]^+$, t_R = 3.37 min.

*Ethyl 2-(9-oxo-9H-fluorene-4-carboxamido)-2-(3-(((2,3,5,6-tetramethylphenyl)sulfonamido)methyl)phenyl)acetate (**108e**).* This previously unreported compound was synthesized according to

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general procedure U. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.030 g, 0.133 mmol, 1.00 equiv) and **108d** (0.054 g, 0.133 mmol, 1.00 equiv), the title compound **108e** was obtained (0.032 g, 0.052 mmol, 39%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.65 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.59−7.56 (m, 1H), 7.46 (ddd, *J* = 13.4, 7.3, 1.3 Hz, 2H), 7.31 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.27 (s, 2H), 7.26−7.24 (m, 2H), 7.24−7.21 (m, 1H), 7.21 (t, *J* = 1.6 Hz, 1H), 7.19 (d, *J* = 1.9 Hz, 2H), 7.16 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.05 (s, 1H), 6.95 (d, *J* = 7.1 Hz, 1H), 5.69 (d, *J* = 7.1 Hz, 1H), 4.18 (ddd, *J* = 66.0, 10.8, 7.1 Hz, 1H), 4.02 (dt, *J* = 5.7, 2.2 Hz, 2H), 2.45 (s, 6H), 2.18 (s, 6H), 1.19 (t, *J* = 7.1 Hz, 3H). LC-MS (ESI): *m*/*z* 611.2 $[M+1]^+$, t_R = 4.99 min.

*2-(9-Oxo-9H-fluorene-4-carboxamido)-2-(3-(((2,3,5,6-tetramethylphenyl)sulfonamido)methyl)phenyl)acetic acid (**108**).* This previously unreported compound was synthesized according to general procedure D. Starting from **108e** (0.022 g, 0.035 mmol, 1.00 equiv) and following purification by reversed-phase flash chromatography, the title compound **108** was obtained as a yellow solid (0.018 g, 0.032 mmol, 89%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.10 (s, 1H), 9.29 (s, 1H), 8.04 (t, *J* = 6.3 Hz, 1H), 7.73−7.62 (m, 3H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.41−7.34 (m, 3H), 7.27 (t, *J* = 7.9 Hz, 1H), 7.21−7.15 (m, 2H), 5.50 (d, *J* = 7.0 Hz, 1H), 3.99 (d, *J* = 6.3 Hz, 2H), 2.46 (s, 6H), 2.21 (s, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.93, 172.17, 167.64, 143.15, 140.87, 139.17, 138.62, 135.89, 135.65, 135.41, 134.77, 134.60, 134.26, 133.81, 132.74, 130.11, 129.65, 128.61, 127.71, 127.02, 125.21, 124.65, 124.27, 45.71, 40.55, 40.41, 20.98, 18.13. LC-MS (ESI): *m*/*z* 583.1 $[M+1]^+$, t_R = 4.52 min.

*N-(3-Bromobenzyl)-2,4,6-trimethylbenzenesulfonamide (**109a**).* This previously reported compound was synthesized according to an general procedure R. Starting from (3-bromophenyl)methanamine hydrochloride (0.55 g, 2.50 mmol, 1.00 equiv) and 2,4,6-trimethylbenzenesulfonyl chloride (0.55 g, 2.50 mmol, 1.00 equiv), the title compound **109a** was obtained as a white solid (0.77 g, 2.09 mmol, 84%). LC-MS (ESI): *m*/*z* 368.0 $[M+H]^+$, t_R = 5.0 min.

*Ethyl 2-oxo-2-(3-(((2,4,6-trimethylphenyl)sulfonamido)methyl)-phenyl)acetate (**109b**).* This previously unreported compound was synthesized according to general procedure S. Starting from **109a** (0.370 g, 1.00 mmol, 1.00 equiv) and following purification by normal-phase flash chromatography (hep:EtOAc 0−20%), the title compound **109b** was obtained as a colorless oil (0.032 g, 0.08 mmol, 12%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.79 (dt, *J* = 7.8, 1.5 Hz, 1H), 7.70 (t, *J* = 1.9 Hz, 1H), 7.48−7.43 (m, 1H), 7.34 (t, *J* = 7.7 Hz, 1H), 6.84 (d, *J* = 1.2 Hz, 2H), 4.38 (q, *J* = 7.2 Hz, 2H), 4.11 (d, *J* = 6.1 Hz, 2H), 2.54 (s, 6H), 2.21 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H). LC-MS (ESI): *m*/*z* 390.1 $[M+1]^+$, t_R = 4.75 min.

*Ethyl 2-(hydroxyimino)-2-(3-(((2,4,6-trimethylphenyl)-sulfonamido)methyl)phenyl)acetate (**109c**).* This previously unreported compound was synthesized according to general procedure P. Starting from **109b** (0.024 g, 0.06 mmol, 1.00 equiv), the title compound **109c** was obtained as an off-white solid (0.023 g, 0.06 mmol, quantitative). LC-MS (ESI): *m*/*z* 405.3 $[M+1]^+$, t_R = 4.33 and 4.46 min.

*Ethyl 2-amino-2-(3-(((2,4,6-trimethylphenyl)sulfonamido)-methyl)phenyl)acetate (**109d**).* This previously unreported compound was synthesized according to general procedure T. Starting from **109c** (0.023 g, 0.06 mmol, 1.00 equiv), the title compound **109d** was obtained as a colorless oil (0.013 g, 0.032 mmol, 53%). LC-MS (ESI): *m*/*z* 391.3 $[M+1]^+$, t_R = 3.46 min.

*Ethyl 2-(9-oxo-9H-fluorene-4-carboxamido)-2-(3-(((2,4,6-trimethylphenyl)sulfonamido)methyl)phenyl)acetate (**109e**).* This previously unreported compound was synthesized according to general procedure U. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.014 g, 0.041 mmol, 1.00 equiv) and **109d** (0.016 g, 0.041 mmol, 1.00 equiv), the title compound **109e** was obtained (0.005 g, 0.008 mmol, 20%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.66 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.58 (dd, *J* = 6.6, 2.0 Hz, 1H), 7.48 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.43 (dd, *J* = 6.8, 1.8 Hz, 1H), 7.32−7.30 (m, 1H), 7.27 (d, *J* = 3.0 Hz, 1H), 7.26 (d, *J* = 2.9 Hz, 1H), 7.25 (d, *J* = 2.7 Hz, 1H), 7.24 (d, *J* = 2.0 Hz, 1H), 7.22−7.20 (m, 2H), 6.95 (d, *J* = 7.1 Hz, 1H), 6.89 (d, *J* = 9.2 Hz, 1H), 5.69 (d, *J* = 7.1 Hz, 1H), 4.23 (d, *J* = 7.2 Hz, 1H), 4.13 (dd, *J* = 10.8, 7.1 Hz, 1H), 4.01 (d, *J* = 2.8 Hz, 2H), 2.53 (s, 6H), 2.21 (s, 3H), 1.19 (t, *J* = 4.5 Hz, 3H). LC-MS (ESI): *m*/*z* 597.2 $[M+1]^+$, t_R = 4.91 min.

*2-(9-Oxo-9H-fluorene-4-carboxamido)-2-(3-(((2,4,6-trimethylphenyl)sulfonamido)methyl)phenyl)acetic acid (**109**).* This previously unreported compound was synthesized according to general procedure D. Starting from **109e** (0.005 g, 0.008 mmol, 1.00 equiv) and following purification by reversed-phase flash chromatography, the title compound **109** was obtained as a yellow solid (0.020 g, 0.035 mmol, 16%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.05 (s, 1H), 9.45 (d, *J* = 7.3 Hz, 1H), 8.02 (t, *J* = 6.3 Hz, 1H), 7.71 (dd, *J* = 7.5, 2.5 Hz, 2H), 7.65 (d, *J* = 7.3 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 1H), 7.45 (dt, *J* = 14.7, 7.5 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.35 (d, *J* = 8.8 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 7.7 Hz, 1H), 7.00 (s, 2H), 5.56 (d, *J* = 7.2 Hz, 1H), 3.97 (d, *J* = 6.3 Hz, 2H), 2.55 (s, 6H), 2.24 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.93, 172.02, 167.91, 138.80, 138.71, 136.70, 135.65, 135.12, 134.71, 134.23, 133.82, 132.57, 132.10, 130.14, 129.61, 128.82, 127.83, 127.69, 127.17, 125.24, 124.64, 124.28, 57.39, 45.67, 40.55, 40.41, 23.03, 20.84. LC-MS (ESI): *m*/*z* 569.3 $[M+1]^+$, t_R = 4.43 min.

*N-(3-Bromobenzyl)naphthalene-2-sulfonamide (**110a**).* This previously reported compound was synthesized according to general procedure R. Starting from (3-bromophenyl)methanamine hydrochloride (1.11 g, 5.00 mmol, 1.00 equiv) and naphthalene-2-sulfonyl chloride (1.13 g, 5.00 mmol, 1.00 equiv), the title compound **110a** was obtained as a white solid (1.67 g, 4.45 mmol, 89%). LC-MS (ESI): *m*/*z* 378.0 $[M+H]^+$, t_R = 4.76 min.

*Ethyl 2-(3-((naphthalene-2-sulfonamido)methyl)phenyl)-2-oxoacetate (**110b**).* This previously unreported compound was synthesized according to general procedure S. Starting from **110a** (0.19 g, 0.50 mmol, 1.00 equiv) and following purification by normal-phase flash chromatography (hep:EtOAc 0−20%), the title compound **110b** was obtained as a colorless oil (0.071 g, 0.18 mmol, 36%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 8.33 (d, *J* = 1.9 Hz, 1H), 7.89−7.81 (m, 3H), 7.75 (d, *J* = 2.0 Hz, 2H), 7.73 (d, *J* = 1.8 Hz, 1H), 7.60−7.51 (m, 2H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.29 (s, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 4.17 (d, *J* = 6.3 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H). LC-MS (ESI): *m*/*z* 415.2 $[M+18]^+$, t_R = 4.57 min.

*Ethyl 2-(hydroxyimino)-2-(3-((naphthalene-2-sulfonamido)-methyl)phenyl)acetate (**110c**).* This previously unreported compound was synthesized according to general procedure P. Starting from **110b** (0.014 g, 0.04 mmol, 1.00 equiv), the title compound **110c** was obtained as an off-white solid (0.021 g, 0.05 mmol, quantitative). LC-MS (ESI): *m*/*z* 413.1 $[M+1]^+$, t_R = 4.25 and 4.37 min.

*Ethyl 2-amino-2-(3-((naphthalene-2-sulfonamido)methyl)-phenyl)acetate (**110d**).* This previously unreported compound was synthesized according to general procedure T. Starting from **110c** (0.020 g, 0.05 mmol, 1.00 equiv), the title compound **110d** was obtained as a colorless oil (0.015 g, 0.039 mmol, 81%). LC-MS (ESI): *m*/*z* 399.2 $[M+1]^+$, t_R = 3.21 min.

*Ethyl 2-(3-((naphthalene-2-sulfonamido)methyl)phenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetate (**110e**).* This previously unreported compound was synthesized according to general procedure U. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.016 g, 0.070 mmol, 1.00 equiv) and **110d** (0.026 g, 0.064 mmol, 1.00 equiv), the title compound **110e** was obtained (0.008 g, 0.013 mmol, 19%). ^{1}H NMR (600 MHz, chloroform-*d*) δ δ 8.36−8.33 (m, 1H), 7.87 (d, *J* = 8.5 Hz, 2H), 7.84−7.79 (m, 1H), 7.73 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.65 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.61−7.50 (m, 3H), 7.48−7.38 (m, 2H), 7.32−7.15 (m, 6H), 6.89 (d, *J* = 7.0 Hz, 1H), 5.67 (d, *J* = 7.0 Hz, 1H), 4.76 (t, *J* = 6.2 Hz, 1H), 4.22 (dq, *J* = 10.8, 7.1 Hz, 1H), 4.16−4.02 (m, 3H), 1.19 (s, 3H). LC-MS (ESI): *m*/*z* 605.2 $[M+1]^+$, t_R = 4.75 min.

*2-(3-((Naphthalene-2-sulfonamido)methyl)phenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetic acid (**110**).* This previously unreported compound was synthesized according to general procedure D. Starting from **110e** (0.012 g, 0.02 mmol, 1.00 equiv) and following purification by reversed-phase flash chromatography, the title compound **110** was obtained as a yellow solid (0.007 g, 0.013 mmol, 66%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.07 (s, 1H), 9.49

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(d, J = 7.3 Hz, 1H), 8.46 (d, J = 1.9 Hz, 1H), 8.28 (t, J = 6.4 Hz, 1H), 8.16 (d, J = 8.0 Hz, 1H), 8.13 (d, J = 8.7 Hz, 1H), 8.04 (d, J = 8.1 Hz, 1H), 7.86 (dd, J = 8.6, 1.9 Hz, 1H), 7.73−7.69 (m, 3H), 7.67 (d, J = 1.3 Hz, 1H), 7.63 (d, J = 7.3 Hz, 1H), 7.56 (dd, J = 7.7, 1.2 Hz, 1H), 7.47−7.45 (m, 2H), 7.44 (d, J = 1.6 Hz, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.37 (dt, J = 7.4, 3.4 Hz, 2H), 7.30 (t, J = 7.6 Hz, 1H), 7.25 (dt, J = 7.6, 1.5 Hz, 1H), 5.60 (d, J = 7.2 Hz, 1H), 4.02 (d, J = 6.3 Hz, 2H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.93, 172.04, 167.92, 143.16, 138.53, 137.98, 136.89, 135.66, 134.72, 134.62, 134.22, 133.81, 132.57, 132.22, 130.12, 129.86, 129.67, 129.61, 129.16, 128.96, 128.29, 128.01, 127.90, 127.88, 127.81, 127.44, 125.22, 124.63, 124.26, 122.75, 57.41, 46.53. LC-MS (ESI): m/z 557.1 $[M+1]^+$, t_R = 4.31 min.

*N-(3-Bromobenzyl)-4-(tert-butyl)benzenesulfonamide (**111a**).* This previously reported compound was synthesized according to general procedure R. Starting from (3-bromophenyl)methanamine hydrochloride (0.550 g, 2.500 mmol, 1.00 equiv) and 4-(*tert*-butyl)benzenesulfonyl chloride (0.550 g, 2.500 mmol, 1.00 equiv), the title compound **111a** was obtained as a white solid (0.930 g, 2.422 mmol, 98%). LC-MS (ESI): m/z 382.0 $[M+H]^+$, t_R = 5.02 min.

*Ethyl 2-(3-(((4-(tert-butyl)phenyl)sulfonamido)methyl)phenyl)-2-oxoacetate (**111b**).* This previously unreported compound was synthesized according to general procedure S. Starting from **111a** (0.510 g, 1.330 mmol, 1.00 equiv) and following purification by normal-phase flash chromatography (hep:EtOAc 0−20%), the title compound **111b** was obtained as a colorless oil (0.141 g, 0.350 mmol, 26%). ^{1}H NMR (600 MHz, chloroform-d) δ 7.79 (ddq, J = 7.9, 4.2, 2.0 Hz, 1H), 7.75 (d, J = 2.1 Hz, 1H), 7.68 (dp, J = 8.3, 2.2 Hz, 2H), 7.50−7.45 (m, 1H), 7.41 (dp, J = 7.8, 2.5 Hz, 2H), 7.34 (ddt, J = 11.0, 7.7, 3.1 Hz, 1H), 4.39−4.34 (m, 2H), 4.17−4.13 (m, 2H), 1.37−1.32 (m, 3H), 1.27−1.24 (m, 9H). LC-MS (ESI): m/z 421.3 $[M+18]^+$, t_R = 4.84 min.

*Ethyl 2-(3-(((4-(tert-butyl)phenyl)sulfonamido)methyl)phenyl)-2-(hydroxyimino)acetate (**111c**).* This previously unreported compound was synthesized according to general procedure P. Starting from **111b** (0.040 g, 0.100 mmol, 1.00 equiv), the title compound **111c** was obtained as an off-white solid (0.051 g, 0.12 mmol, quantitative). LC-MS (ESI): m/z 436.1 $[M+18]^+$, t_R = 4.45 and 4.60 min.

*Ethyl 2-amino-2-(3-((naphthalene-2-sulfonamido)methyl)-phenyl)acetate (**111d**).* This previously unreported compound was synthesized according to general procedure Q. Starting from **111c** (0.051 g, 0.12 mmol, 1.00 equiv), the title compound **111d** was obtained as a colorless oil (0.028 g, 0.069 mmol, 58%). LC-MS (ESI): m/z 405.2 $[M+1]^+$, t_R = 3.45 min.

*Ethyl 2-(3-(((4-(tert-butyl)phenyl)sulfonamido)methyl)phenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetate (**111e**).* This previously unreported compound was synthesized according to general procedure U. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.016 g, 0.070 mmol, 1.00 equiv) and **111d** (0.028 g, 0.070 mmol, 1.00 equiv), the title compound **111e** was obtained (0.036 g, 0.050 mmol, 71%). ^{1}H NMR (600 MHz, chloroform-d) δ 7.72−7.69 (m, 2H), 7.67 (dd, J = 7.3, 1.2 Hz, 1H), 7.61−7.58 (m, 1H), 7.49 (dd, J = 7.7, 1.2 Hz, 1H), 7.47−7.44 (m, 3H), 7.31 (dt, J = 6.3, 1.7 Hz, 2H), 7.27 (td, J = 7.6, 2.5 Hz, 2H), 7.24−7.20 (m, 3H), 6.93 (d, J = 7.1 Hz, 1H), 5.70 (d, J = 7.0 Hz, 1H), 4.27−4.11 (m, 2H), 4.09 (s, 2H), 1.28 (s, 9H), 1.20 (d, J = 7.1 Hz, 3H). LC-MS (ESI): m/z 628.4 $[M+18]^+$, t_R = 5.08 min.

*2-(3-(((4-(tert-Butyl)phenyl)sulfonamido)methyl)phenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetic acid (**111**).* This previously unreported compound was synthesized according to general procedure D. Starting from **111d** (0.036 g, 0.05 mmol, 1.00 equiv) and following purification by reversed-phase flash chromatography, the title compound **111** was obtained as a yellow solid (0.0058 g, 0.010 mmol, 20%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.07 (s, 1H), 9.49 (d, J = 7.2 Hz, 1H), 8.12 (t, J = 6.4 Hz, 1H), 7.75−7.68 (m, 4H), 7.64 (d, J = 7.3 Hz, 1H), 7.60−7.55 (m, 3H), 7.48 (dd, J = 7.5, 1.3 Hz, 1H), 7.46−7.41 (m, 2H), 7.41−7.35 (m, 2H), 7.29 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 7.7 Hz, 1H), 5.61 (d, J = 7.2 Hz, 1H), 3.99 (d, J = 6.4 Hz, 2H), 1.31 (s, 9H), 1.26−1.23 (m, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.93, 172.05, 167.93, 155.74, 140.89, 138.52, 138.49, 138.23, 135.66, 134.71, 134.22, 132.58, 130.14, 129.61, 128.93, 127.92, 127.78, 127.36, 126.85, 126.46, 125.22, 124.64, 124.27, 57.44, 46.52, 40.54, 40.41, 35.28, 31.28. LC-MS (ESI): m/z 583.2 $[M+1]^+$, t_R = 4.54 min.

*N-(5-Bromo-2-chlorobenzyl)-4-methoxybenzenesulfonamide (**112a**).* This previously reported compound was synthesized according to general procedure R. Starting from (5-bromo-2-chlorophenyl)methanamine hydrochloride (0.110 g, 0.50 mmol, 1.00 equiv) and 4-methoxybenzenesulfonyl chloride (0.100 g, 0.50 mmol, 1.00 equiv), the title compound **112a** was obtained as a white solid (0.190 g, 0.470 mmol, 96%). LC-MS (ESI): m/z 390.0 $[M+H]^+$, t_R = 4.76 min.

*Methyl 2-(4-chloro-3-(((4-methoxyphenyl)sulfonamido)methyl)-phenyl)-2-oxoacetate (**112b**).* This previously unreported compound was synthesized according to general procedure S. Starting from **112a** (0.150 g, 0.370 mmol, 1.00 equiv) and following purification by normal-phase flash chromatography (hep:EtOAc 0−20%), the title compound **112b** was obtained as a colorless oil (0.079 g, 0.18 mmol, 49%). LC-MS (ESI): m/z 413.2 $[M+1]^+$, t_R = 4.63 min.

*Methyl 2-(4-chloro-3-(((4-methoxyphenyl)sulfonamido)methyl)-phenyl)-2-(hydroxyimino)acetate (**112c**).* This previously unreported compound was synthesized according to general procedure P. Starting from **112b** (0.060 g, 0.140 mmol, 1.00 equiv), the title compound **112c** was obtained as an off-white solid (0.046 g, 0.110 mmol, 78%). LC-MS (ESI): m/z 413.1 $[M+1]^+$, t_R = 4.12 and 4.27 min.

*Methyl 2-amino-2-(4-chloro-3-(((4-methoxyphenyl)-sulfonamido)methyl)phenyl)acetate (**112d**).* This previously unreported compound was synthesized according to general procedure Q. Starting from **112c** (0.046 g, 0.110 mmol, 1.00 equiv), the title compound **112d** was obtained as a colorless oil (0.025 g, 0.07 mmol, 64%). LC-MS (ESI): m/z 398.1 $[M+1]^+$, t_R = 3.29 min.

*Methyl 2-(4-chloro-3-(((4-methoxyphenyl)sulfonamido)methyl)-phenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetate (**112e**).* This previously unreported compound was synthesized according to general procedure U. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.015 g, 0.007 mmol, 1.00 equiv) and **112d** (0.025 g, 0.007 mmol, 1.00 equiv), the title compound **112e** was obtained (0.025 g, 0.004 mmol, 57%). LC-MS (ESI): m/z 601.2 $[M+1]^+$, t_R = 5.14 min.

*2-(4-Chloro-3-(((4-methoxyphenyl)sulfonamido)methyl)phenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetic acid (**112**).* This previously unreported compound was synthesized according to general procedure D. Starting from **112e** (assumed to be 0.004 mmol, 1.00 equiv) and following purification by reversed-phase flash chromatography, the title compound **112** was obtained as a yellow solid (0.0052 g, 0.009 mmol, 23%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.20 (s, 1H), 9.55 (d, J = 7.3 Hz, 1H), 8.09 (t, J = 6.3 Hz, 1H), 7.78−7.69 (m, 4H), 7.67−7.62 (m, 2H), 7.59 (dd, J = 7.7, 1.2 Hz, 1H), 7.51−7.42 (m, 2H), 7.44−7.37 (m, 3H), 7.12−7.06 (m, 2H), 5.65 (d, J = 7.3 Hz, 1H), 4.07−3.96 (m, 2H), 3.83 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.90, 171.72, 167.91, 162.65, 143.12, 140.92, 136.17, 135.67, 135.44, 134.71, 134.26, 133.82, 132.47, 132.36, 132.33, 130.21, 130.18, 129.71, 129.65, 129.22, 129.11, 125.31, 124.65, 124.30, 114.80, 56.86, 56.09, 44.10. LC-MS (ESI): m/z 591.1 $[M+1]^+$, t_R = 4.70 min.

*N-(5-Bromo-2-methylbenzyl)-4-methoxybenzenesulfonamide (**113a**).* This previously unreported compound was synthesized according to general procedure R. Starting from (5-bromo-2-methylphenyl)methanamine hydrochloride (0.089 g, 0.38 mmol, 1.00 equiv) and 4-methoxybenzenesulfonyl chloride (0.92 g, 0.44 mmol, 1.10 equiv), the title compound **113a** was obtained as a white solid (0.10 g, 0.27 mmol, 71%). LC-MS (ESI): m/z 370.0 $[M+H]^+$, t_R = 4.73 min.

*Methyl 2-(3-(((4-methoxyphenyl)sulfonamide)methyl)-4-methyl-phenyl)-2-oxoacetate (**113b**).* This previously unreported compound was synthesized according to general procedure S. Starting from **113a** (0.100 g, 0.26 mmol, 1.00 equiv) and following purification by normal-phase flash chromatography (hep:EtOAc 0−20%), the title compound **113b** was obtained as a colorless oil (assumed to be 0.26 mmol, quantitative). LC-MS (ESI): m/z 378.1 $[M+1]^+$, t_R = 4.41 min.

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*Methyl 2-(hydroxyimino)-2-(3-(((4-methoxyphenyl)-sulfonamido)methyl)-4-methylphenyl)acetate (**113c**).* This previously unreported compound was synthesized according to general procedure P. Starting from **113b** (assumed 0.270 mmol, 1.00 equiv), the title compound **113c** was obtained as a white solid (0.064 g, 0.160 mmol, 59%). LC-MS (ESI): m/z 393.1 $[M+1]^+$, t_R = 4.04 and 4.20 min.

*Methyl 2-amino-2-(3-(((4-methoxyphenyl)sulfonamido)methyl)-4-methylphenyl)acetate (**113d**).* This previously unreported compound was synthesized according to general procedure T. Starting from **113c** (0.064 g, 0.160 mmol, 1.00 equiv), the title compound **113d** was obtained as a colorless oil (0.035 g, 0.090 mmol, 56%). LC-MS (ESI): m/z 393.2 $[M+1]^+$, t_R = 3.16 min.

*Methyl 2-(4-methoxy-3-(((4-methoxyphenyl)sulfonamido)-methyl)phenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetate (**113e**).* This previously unreported compound was synthesized according to general procedure U. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.021 g, 0.09 mmol, 1.00 equiv) and **113d** (0.035 g, 0.009 mmol, 1.00 equiv), the title compound **113e** was obtained (0.020 g, 0.034 mmol, 38%). LC-MS (ESI): m/z 585.2 $[M+1]^+$, t_R = 4.66 min.

*2-(3-(((4-Methoxyphenyl)sulfonamido)methyl)-4-methylphenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetic acid (**113**).* This previously unreported compound was synthesized according to general procedure D. Starting from **113d** (0.020 g, 0.03 mmol, 1.00 equiv) and following purification by reversed-phase flash chromatography, the title compound **113** was obtained as a yellow solid (0.0036 g, 0.006 mmol, 21%). ^{1}H NMR (600 MHz, DMSO-d_6)) δ 13.01 (s, 1H), 9.44 (d, J = 7.3 Hz, 1H), 7.85 (t, J = 6.2 Hz, 1H), 7.78−7.74 (m, 2H), 7.76−7.71 (m, 1H), 7.70 (dd, J = 7.3, 1.2 Hz, 1H), 7.64 (dt, J = 7.3, 1.0 Hz, 1H), 7.56 (dd, J = 7.7, 1.2 Hz, 1H), 7.47 (td, J = 7.6, 1.3 Hz, 1H), 7.43 (t, J = 7.5 Hz, 1H), 7.42−7.36 (m, 2H), 7.30 (dd, J = 7.8, 2.0 Hz, 1H), 7.15 (d, J = 7.9 Hz, 1H), 7.13−7.06 (m, 2H), 5.56 (d, J = 7.2 Hz, 1H), 3.89 (dd, J = 21.5, 6.2 Hz, 2H), 3.83 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.94, 172.18, 167.90, 162.56, 143.18, 140.90, 136.67, 135.84, 135.66, 134.73, 134.25, 134.22, 133.81, 132.61, 132.45, 130.64, 130.13, 129.60, 129.20, 129.13, 127.52, 125.21, 124.68, 124.26, 114.75, 57.20, 56.08, 44.81, 18.69. LC-MS (ESI): m/z 587.2 $[M+1]^+$, t_R = 4.21 min.

*N-(5-Bromo-2-methoxybenzyl)-4-methoxybenzenesulfonamide (**114a**).* This previously reported compound was synthesized according to general procedure R. Starting from (5-bromo-2-methoxyphenyl)methanamine hydrochloride (0.110 g, 0.500 mmol, 1.00 equiv) and 4-methoxybenzenesulfonyl chloride (0.100 g, 0.500 mmol, 1.00 equiv), the title compound **114a** was obtained as a white solid (0.160 g, 0.410 mmol, 82%). LC-MS (ESI): m/z 386.0 $[M+H]^+$, t_R = 4.64 min.

*Methyl 2-(3-(((4-methoxyphenyl)sulfonamido)methyl)-4-methyl-phenyl)-2-oxoacetate (**114b**).* This previously unreported compound was synthesized according to general procedure S. Starting from **114a** (0.160 g, 0.430 mmol, 1.00 equiv) and following purification by normal-phase flash chromatography (hep:EtOAc 0−20%), the title compound **114b** was obtained as a colorless oil (0.120 g, 0.290 mmol, 41%). LC-MS (ESI): m/z 394.1 $[M+1]^+$, t_R = 4.32 min.

*Methyl 2-(hydroxyimino)-2-(4-methoxy-3-(((4-methoxyphenyl)-sulfonamido)methyl)phenyl)acetate (**114c**).* This previously unreported compound was synthesized according to general procedure P. Starting from **114b** (0.109 g, 0.290 mmol, 1.00 equiv), the title compound **114c** was obtained as a white solid (0.104 g, 0.250 mmol, 88%). LC-MS (ESI): m/z 409.1 $[M+1]^+$, t_R = 4.27 and 4.32 min.

*Methyl 2-amino-2-(3-(((3,4-dimethoxyphenyl)sulfonamido)-methyl)phenyl)acetate (**114d**).* This previously unreported compound was synthesized according to general procedure T. Starting from **114c** (0.104 g, 0.25 mmol, 1.00 equiv), the title compound **114d** was obtained as a colorless oil (0.055 g, 0.140 mmol, 56%). LC-MS (ESI): m/z 395.2 $[M+1]^+$, t_R = 3.12 min.

*Methyl 2-(4-methoxy-3-(((4-methoxyphenyl)sulfonamido)-methyl)phenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetate (**114e**).* This previously unreported compound was synthesized according to general procedure U. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.031 g, 0.140 mmol, 1.00 equiv) and **114d** (0.055 g, 0.014 mmol, 1.00 equiv), the title compound **114e** was obtained (0.040 g, 0.070 mmol, 50%). LC-MS (ESI): m/z 601.2 $[M+1]^+$, t_R = 4.59 min.

*2-(4-Methoxy-3-(((4-methoxyphenyl)sulfonamido)methyl)-phenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetic acid (**114**).* This previously unreported compound was synthesized according to general procedure D. Starting from **114d** (0.040 g, 0.060 mmol, 1.00 equiv) and following purification by reversed-phase flash chromatography, the title compound **114** was obtained as a yellow solid (0.012 g, 0.030 mmol, 19%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.99 (s, 1H), 9.43 (d, J = 7.1 Hz, 1H), 7.81 (t, J = 6.3 Hz, 1H), 7.77−7.75 (m, 1H), 7.73−7.69 (m, 4H), 7.64 (dt, J = 7.3, 0.9 Hz, 1H), 7.57 (dd, J = 7.7, 1.2 Hz, 1H), 7.49 (td, J = 7.6, 1.3 Hz, 1H), 7.45−7.42 (m, 3H), 7.39 (td, J = 7.4, 1.0 Hz, 1H), 7.36 (dd, J = 8.5, 2.4 Hz, 1H), 6.92 (d, J = 8.6 Hz, 1H), 5.53 (d, J = 7.1 Hz, 1H), 3.89 (qd, J = 15.0, 6.3 Hz, 2H), 3.83 (s, 3H), 3.71 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.96, 172.36, 167.87, 162.49, 156.83, 143.20, 140.91, 135.68, 134.74, 134.22, 133.82, 132.65, 132.59, 130.13, 129.59, 129.16, 129.08, 128.76, 128.35, 125.60, 125.20, 124.71, 124.25, 114.65, 110.98, 57.02, 56.06, 55.91, 41.52. LC-MS (ESI): m/z 587.2 $[M+1]^+$, t_R = 4.21 min.

*N-(3-Bromobenzyl)-2-methoxybenzenesulfonamide (**115a**).* This previously reported compound was synthesized according to general procedure R. Starting from (3-bromophenyl)methanamine hydrochloride (0.200 g, 1.00 mmol, 1.00 equiv) and 2-methoxybenzenesulfonyl chloride (0.220 g, 1.00 mmol, 1.00 equiv), the title compound **115a** was obtained as a white solid (0.370 g, 1.050 mmol, quantitative). LC-MS (ESI): m/z 356.0 $[M+H]^+$, t_R = 4.40 min.

*Ethyl 2-(3-(((2-methoxyphenyl)sulfonamido)methyl)phenyl)-2-oxoacetate (**115b**).* This previously unreported compound was synthesized according to general procedure S. Starting from **115a** (0.037 g, 1.330 mmol, 1.00 equiv) and following purification by normal-phase flash chromatography (hep:EtOAc 0−20%), the title compound **115b** was obtained as a colorless oil (0.061 g, 0.160 mmol, 15%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.80−7.72 (m, 2H), 7.68 (d, J = 1.9 Hz, 1H), 7.46−7.41 (m, 1H), 7.44−7.38 (m, 1H), 7.30 (t, J = 7.7 Hz, 1H), 7.01−6.92 (m, 1H), 6.83 (dd, J = 8.4, 1.0 Hz, 1H), 4.37 (q, J = 7.1 Hz, 2H), 4.11 (d, J = 6.5 Hz, 2H), 3.81 (s, 3H), 1.35 (t, J = 7.2 Hz, 3H). LC-MS (ESI): m/z 378.1 $[M+18]^+$, t_R = 4.23 min.

*Ethyl 2-(hydroxyimino)-2-(3-(((2-methoxyphenyl)sulfonamido)-methyl)phenyl)acetate (**115c**).* This previously unreported compound was synthesized according to general procedure P. Starting from **115b** (0.061 g, 0.16 mmol, 1.00 equiv), the title compound **115c** was obtained as an off-white solid (0.058 g, 0.150 mmol, 92%). LC-MS (ESI): m/z 393.1 $[M+1]^+$, t_R = 3.81 and 3.96 min.

*Ethyl 2-amino-2-(3-(((2-methoxyphenyl)sulfonamido)methyl)-phenyl)acetate (**115d**).* This previously unreported compound was synthesized according to general procedure T. Starting from **115c** (0.058 g, 0.150 mmol, 1.00 equiv), the title compound **115d** was obtained as a colorless oil (0.047 g, 0.096 mmol, 64%). LC-MS (ESI): m/z 379.1 $[M+1]^+$, t_R = 2.71 min.

*Ethyl 2-(3-(((2-methoxyphenyl)sulfonamido)methyl)phenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetate (**115e**).* This previously unreported compound was synthesized according to general procedure U. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.028 g, 0.125 mmol, 1.00 equiv) and **115d** (0.047 g, 0.125 mmol, 1.00 equiv), the title compound **115e** was obtained (0.037 g, 0.060 mmol, 48%). LC-MS (ESI): m/z 585.2 $[M+1]^+$, t_R = 4.43 min.

*2-(3-(((2-Methoxyphenyl)sulfonamido)methyl)phenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetic acid (**115**).* This previously unreported compound was synthesized according to general procedure D. Starting from **115d** (0.036 g, 0.05 mmol, 1.00 equiv) and following purification by reversed-phase flash chromatography, the title compound **115** was obtained as a yellow solid (0.031 g, 0.056 mmol, quantitative). ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.05 (s, 1H), 9.45 (d, J = 7.3 Hz, 1H), 7.80 (t, J = 6.4 Hz, 1H), 7.72 (ddd, J = 10.3, 7.5, 1.5 Hz, 3H), 7.67−7.62 (m, 1H), 7.59−7.53 (m, 2H), 7.50−7.42 (m, 2H), 7.42−7.33 (m, 3H), 7.28 (t, J = 7.6 Hz, 1H), 7.22 (dt, J = 7.7, 1.5 Hz, 1H), 7.14 (dd, J = 8.4, 1.0 Hz, 1H), 7.04 (td,

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J = 7.6, 1.0 Hz, 1H), 5.56 (d, J = 7.2 Hz, 1H), 4.04 (d, J = 6.4 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.93, δ 172.04, 167.93, 156.66, 143.16, 140.88, 138.9, 136.60, 135.66, 134.81, 134.71, 134.23, 133.81, 132.57, 130.15, 129.71, 129.63, 128.78, 128.65, 127.85, 127.72, 127.13, 125.23, 124.64, 124.28, 120.43, 113.13, 57.44, 56.40, 46.53. LC-MS (ESI): m/z 557.1 $[M+1]^+$, t_R = 3.93 min.

*N-(3-Bromobenzyl)-3,4-dimethoxybenzenesulfonamide (**116a**).* This previously reported compound was synthesized according to general procedure R. Starting from (3-bromophenyl)methanamine hydrochloride (0.220 g, 1.000 mmol, 1.00 equiv) and 3,4-dimethoxybenzenesulfonyl chloride (0.230 g, 1.000 mmol, 1.00 equiv), the title compound **116a** was obtained as a white solid (0.530 g, 1.050 mmol, quantitative). LC-MS (ESI): m/z 386.0 $[M+H]^+$, t_R = 4.20 min.

*Ethyl 2-(3-(((3,4-dimethoxyphenyl)sulfonamido)methyl)phenyl)-2-oxoacetate (**116b**).* This previously unreported compound was synthesized according to general procedure S. Starting from **116a** (0.530 g, 1.050 mmol, 1.00 equiv) and following purification by normal-phase flash chromatography (hep:EtOAc 0−20%), the title compound **116b** was obtained as a colorless oil (0.022 g, 0.050 mmol, 5%). ^{1}H NMR (600 MHz, chloroform-d) δ 7.81 (dt, J = 7.8, 1.5 Hz, 1H), 7.76 (d, J = 1.9 Hz, 1H), 7.51−7.48 (m, 1H), 7.40 (dd, J = 8.4, 2.1 Hz, 1H), 7.37 (t, J = 7.7 Hz, 1H), 7.22 (d, J = 2.2 Hz, 1H), 6.84 (d, J = 8.5 Hz, 1H), 4.37 (q, J = 7.2 Hz, 2H), 4.14 (d, J = 5.9 Hz, 2H), 3.87 (s, 3H), 3.82 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H). LC-MS (ESI): m/z 408.3 $[M+1]^+$, t_R = 4.87 min.

*Ethyl 2-(3-(((3,4-dimethoxyphenyl)sulfonamido)methyl)phenyl)-2-(hydroxyimino)acetate (**116c**).* This previously unreported compound was synthesized according to general procedure P. Starting from **116b** (0.022 g, 0.540 mmol, 1.00 equiv), the title compound **116c** was obtained as an off-white solid (0.014 g, 0.030 mmol, 6%). LC-MS (ESI): m/z 393.1 $[M+1]^+$, t_R = 3.72 and 3.85 min.

*Ethyl 2-amino-2-(3-(((3,4-dimethoxyphenyl)sulfonamido)-methyl)phenyl)acetate (**116d**).* This previously unreported compound was synthesized according to general procedure T. Starting from **116c** (0.014 g, 0.030 mmol, 1.00 equiv), the title compound **116d** was obtained as a colorless oil (0.002 g, 0.009 mmol, 64%). LC-MS (ESI): m/z 423.2 $[M+1]^+$, t_R = 2.82 min.

*Ethyl 2-(3-(((3,4-dimethoxyphenyl)sulfonamido)methyl)phenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetate (**116e**).* This previously unreported compound was synthesized according to general procedure U. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.0011 g, 0.005 mmol, 1.00 equiv) and **116d** (0.002 g, 0.005 mmol, 1.00 equiv) the title compound **116e** was obtained (yield ND). LC-MS (ESI): m/z 615.2 $[M+1]^+$, t_R = 4.41 min.

*2-(3-(((3,4-Dimethoxyphenyl)sulfonamido)methyl)phenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetic acid (**116**).* This previously unreported compound was synthesized according to general procedure D. Starting from **116e** (assumed to be 0.005 mmol, 1.00 equiv) and following purification by reversed-phase flash chromatography, the title compound **111** was obtained as a yellow solid (0.0015 g, 0.003 mmol, 51%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.49 (d, J = 7.3 Hz, 1H), 8.00 (t, J = 6.4 Hz, 1H), 7.71 (dd, J = 7.5, 4.0 Hz, 2H), 7.64 (d, J = 7.3 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.46 (dd, J = 16.2, 7.7 Hz, 2H), 7.43 (d, J = 5.1 Hz, 1H), 7.41−7.36 (m, 3H), 7.35−7.30 (m, 2H), 7.25 (d, J = 7.6 Hz, 1H), 7.11 (d, J = 8.5 Hz, 1H), 5.60 (d, J = 7.2 Hz, 1H), 3.94 (d, J = 6.4 Hz, 2H), 3.83 (s, 3H), 3.80 (s, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.95, 172.05, 167.95, 149.15, 143.15, 140.88, 138.55, 134.70, 134.21, 133.80, 132.56, 132.42, 129.62, 127.39, 124.28, 152.35, 136.85, 135.67, 130.14, 127.89, 127.84, 125.23, 124.62, 120.75, 111.62, 57.44, 56.28, 56.21, 46.54. LC-MS (ESI): m/z 587.0 $[M+1]^+$, t_R = 3.92 min.

*N-(3-Bromobenzyl)-4-nitrobenzenesulfonamide (**117a**).* This previously reported compound was synthesized according to general procedure R. Starting from (3-bromophenyl)methanamine hydrochloride (0.300 g, 1.340 mmol, 1.00 equiv) and 4-nitrobenzenesulfonyl chloride (0.300 g, 1.340 mmol, 1.00 equiv) and following purification by normal-phase flash chromatography (DCM:MeOH), the title compound **117a** was obtained as an orange solid (0.180 g, 0.480 mmol, 36%). ^{1}H NMR (400 MHz, chloroform-d) δ 8.28−8.20 (m, 2H), 7.94−7.86 (m, 2H), 7.30 (dt, J = 6.9, 2.2 Hz, 1H), 7.18 (d, J = 1.9 Hz, 1H), 7.12−7.02 (m, 2H), 4.99 (t, J = 6.1 Hz, 1H), 4.15 (d, J = 6.2 Hz, 2H). LC-MS (ESI): m/z 388.0 $[M+18]^+$, t_R = 4.62 min.

*4-Amino-N-(3-bromobenzyl)benzenesulfonamide (**117ab**).* A solution of **117a** (0.370 g, 1.00 mmol, 1.00 equiv) in EtOH (3 mL) was slowly added to a solution of $SnCl_2$ (0.660 g, 3.500 mmol, 3.50 equiv) in 13% aq. HCl (1 mL) under cooling with an ice bath. After 30 min, the reaction mixture was allowed to warm to rt and then stirred for an addition 2 h. Upon reaction completion, the solvent was evaporated under reduced pressure and the residue treated with 2 N KOH and EtOAc. The organic phase was dried and concentrated *in vacuo* to afford the title compound **117ab** (0.420 g crude, 1.20 mmol, quantitative). LC-MS (ESI): m/z 341.0 $[M+1]^+$, t_R = 4.22 min.

*N-(3-Bromobenzyl)-4-(dimethylamino)benzenesulfonamide (**117ac**).* To a solution of **117ab** (0.354 g, 1.00 mmol, 1.00 equiv) in DCM/MeCN (1:1, 8 mL) was added Et_3N (0.437 g, 3.00 mmol, 3.00 equiv) and then CH_3I (0.142 g, 10.0 mmol, 10.0 equiv). The reaction mixture was stirred at rt for 72 h. Upon reaction completion as detected by HPLC, the reaction mixture was quenched with water and extracted with DCM. The combined organic layers were washed with sat. brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude was purified by normal-phase flash chromatography (DCM:MeOH 0−10%) to afford the title compound **117ac** (0.118 g, 0.320 mmol, 32%). ^{1}H NMR (400 MHz, chloroform-d) δ 7.65−7.57 (m, 2H), 7.29 (dt, J = 6.4, 2.2 Hz, 1H), 7.21 (s, 1H), 7.13−7.03 (m, 2H), 6.67−6.59 (m, 2H), 4.53 (s, 1H), 4.00 (s, 2H), 2.99 (s, 6H). LC-MS (ESI): m/z 369.0 $[M+1]^+$, t_R = 4.78 min.

*Ethyl 2-(3-(((4-(dimethylamino)phenyl)sulfonamido)methyl)-phenyl)-2-oxoacetate (**117b**).* This previously unreported compound was synthesized according to general procedure S. Starting from **117ac** (0.118 g, 0.320 mmol, 1.00 equiv) and following purification by normal-phase flash chromatography (hep:EtOAc 0−20%), the title compound **117b** was obtained as a colorless oil (0.140 g, 0.360 mmol, quantitative). LC-MS (ESI): m/z 391.1 $[M+1]^+$, t_R = 4.77 min.

*Ethyl 2-(3-(((3-(dimethylamino)phenyl)sulfonamido)methyl)-phenyl)-2-(hydroxyimino)acetate (**117c**).* This previously unreported compound was synthesized according to general procedure P. Starting from **117b** (assumed to be 0.320 mmol, 1.00 equiv), the title compound **117c** was obtained as a white solid (0.130 g, 0.320 mmol, quantitative). LC-MS (ESI): m/z 406.1 $[M+1]^+$, t_R = 4.43 and 4.58 min.

*Ethyl 2-amino-2-(3-(((3-(dimethylamino)phenyl)sulfonamido)-methyl)phenyl)acetate (**117d**).* This previously unreported compound was synthesized according to general procedure T. Starting from **117c** (assumed 0.320 mmol, 1.00 equiv), the title compound **117d** was obtained as an oil (yield ND). LC-MS (ESI): m/z 392.2 $[M+1]^+$, t_R = 3.63 min.

*Ethyl 2-(3-(((4-(dimethylamino)phenyl)sulfonamido)methyl)-phenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetate (**117e**).* This previously unreported compound was synthesized according to general procedure U. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.022 g, 0.100 mmol, 1.00 equiv) and **117d** (assumed to be 0.100 mmol, 1.00 equiv), the title compound **117e** was obtained (yield ND). LC-MS (ESI): m/z 598.2 $[M+1]^+$, t_R = 5.02 min.

*2-(3-(((4-(Dimethylamino)phenyl)sulfonamido)methyl)phenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetic acid (**117**).* This previously unreported compound was synthesized according to general procedure D. Starting from **117e** (assumed to be 0.100 mmol, 1.00 equiv) and following purification by reversed-phase flash chromatography, the title compound **117** was obtained as a yellow solid (0.018 g, 0.030 mmol, 30%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.08 (s, 1H), 9.49 (d, J = 7.3 Hz, 1H), 7.76 (t, J = 6.5 Hz, 1H), 7.71 (ddd, J = 7.3, 4.2, 1.0 Hz, 2H), 7.64 (dt, J = 7.3, 0.9 Hz, 1H), 7.62−7.49 (m, 3H), 7.46 (td, J = 7.5, 1.3 Hz, 1H), 7.46−7.40 (m, 2H), 7.42−7.36 (m, 2H), 7.36−7.21 (m, 2H), 6.80−6.74 (m, 2H), 5.60 (d, J = 7.3 Hz, 1H), 3.88 (d, J = 6.3 Hz, 2H), 2.99 (s, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.94, 172.06, 167.93, 158.77, 143.16, 140.88, 138.79, 136.80, 135.67, 134.71, 134.21, 133.81, 132.58, 130.13, 129.61, 128.95, 128.68, 127.89, 127.83, 127.32, 126.03, 125.22, 124.63,

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124.27, 111.46, 57.43, 46.51, 40.53. LC-MS (ESI): m/z 570.2 $[M+1]^+$, t_R = 4.68 min.

*N-(3-Bromobenzyl)-3-(dimethylamino)benzenesulfonamide (**118a**).* This previously unreported compound was synthesized according to general procedure R. Starting from (3-bromophenyl)-methanamine hydrochloride (0.360 g, 1.650 mmol, 1.00 equiv) and 3-(dimethylamino)benzenesulfonyl chloride (0.36 g, 1.65 mmol, 1.00 equiv) and following purification by normal-phase flash chromatography (DCM:MeOH), the title compound **118a** (0.250 g, 0.670 mmol, 41%) was obtained as a white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.10 (t, J = 6.4 Hz, 1H), 7.40 (dp, J = 3.7, 2.0 Hz, 2H), 7.34 (t, J = 8.0 Hz, 1H), 7.27−7.20 (m, 2H), 7.04 (dt, J = 7.5, 1.1 Hz, 1H), 7.01 (t, J = 2.1 Hz, 1H), 6.91 (dd, J = 8.4, 2.6 Hz, 1H), 4.00 (d, J = 6.4 Hz, 2H), 2.94 (s, 6H). LC-MS (ESI): m/z 369.0 $[M+H]^+$, t_R = 4.66 min.

*Ethyl 2-(3-(((3-(dimethylamino)phenyl)sulfonamido)methyl)-phenyl)-2-oxoacetate (**118b**).* This previously unreported compound was synthesized according to general procedure S. Starting from **118a** (0.250 g, 0.670 mmol, 1.00 equiv) and following purification by normal-phase flash chromatography (hep:EtOAc 0−20%), the title compound **118b** was obtained as a colorless oil (0.14 g, 0.36 mmol, 54%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.18 (t, J = 6.4 Hz, 1H), 7.89 (t, J = 6.5 Hz, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.57−7.52 (m, 3H), 6.77−6.68 (m, 2H), 4.44 (q, J = 7.1 Hz, 2H), 4.02 (d, J = 6.4 Hz, 2H), 2.99 (s, 6H), 1.35 (t, J = 7.1 Hz, 3H). LC-MS (ESI): m/z 408.2 $[M+18]^+$, t_R = 3.46 min.

*Ethyl (E)-2-(3-(((3-(dimethylamino)phenyl)sulfonamido)methyl)-phenyl)-2-(hydroxyimino)acetate (**118c**).* This previously unreported compound was synthesized according to general procedure P. Starting from **118b** (0.140 g, 0.360 mmol, 1.00 equiv), the title compound **118c** was obtained as a white solid (0.168 g, 0.410 mmol, quantitative). LC-MS (ESI): m/z 406.2 $[M+1]^+$, t_R = 4.11 and 4.25 min.

*Ethyl 2-amino-2-(3-(((3-(dimethylamino)phenyl)sulfonamido)-methyl)phenyl)acetate (**118d**).* This previously unreported compound was synthesized according to general procedure T. Starting from **118c** (0.170 g, 0.410 mmol, 1.00 equiv), the title compound **118d** was obtained as an oil (0.123 g, 0.096 mmol, 64%). LC-MS (ESI): m/z 392.3 $[M+1]^+$, t_R = 2.91 min.

*Ethyl 2-(3-(((3-(dimethylamino)phenyl)sulfonamido)methyl)-phenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetate (**118e**).* This previously unreported compound was synthesized according to general procedure U. Starting from 9-oxo-9*H*-fluorene-4-carboxylic acid (0.070 g, 0.313 mmol, 1.00 equiv) and **118d** (0.123 g, 0.313 mmol, 1.00 equiv), the title compound **118e** was obtained (0.085 g, 0.142 mmol, 45%). LC-MS (ESI): m/z 598.2 $[M+1]^+$, t_R = 4.80 min.

*2-(3-(((3,4-Dimethoxyphenyl)sulfonamido)methyl)phenyl)-2-(9-oxo-9H-fluorene-4-carboxamido)acetic acid (**118**).* This previously unreported compound was synthesized according to general procedure D. Starting from **118d** (0.085 g, 0.142 mmol, 1.00 equiv) and following purification by reversed-phase flash chromatography, the title compound **118** was obtained as a yellow solid (0.012 g, 0.020 mmol, 15%). ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.06 (s, 1H), 9.49 (d, J = 7.3 Hz, 1H), 7.76 (t, J = 6.5 Hz, 1H), 7.71 (ddd, J = 7.3, 5.0, 1.0 Hz, 2H), 7.64 (dt, J = 7.3, 0.9 Hz, 1H), 7.62−7.55 (m, 3H), 7.46 (td, J = 7.6, 1.3 Hz, 1H), 7.46−7.41 (m, 2H), 7.41−7.36 (m, 2H), 7.33 (t, J = 7.6 Hz, 1H), 7.25 (dt, J = 7.6, 1.5 Hz, 1H), 6.80−6.74 (m, 2H), 5.60 (d, J = 7.2 Hz, 1H), 3.88 (d, J = 6.3 Hz, 2H), 2.99 (s, 6H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 192.93, 172.07, 167.93, 152.90, 143.16, 140.88, 138.79, 136.80, 135.67, 134.72, 134.22, 133.81, 132.59, 130.13, 129.61, 128.94, 128.68, 127.89, 127.82, 127.32, 126.04, 125.21, 124.64, 124.27, 111.46, 57.43, 46.51, 40.55, 40.41. LC-MS (ESI): m/z 570.2 $[M+1]^+$, t_R = 4.28 min.

Fragment Library. The Maybridge Ro3 Diversity Fragment Library was purchased in 2015 from Thermo Fisher Scientific (US). The 2500 fragments came in two sets—a core set of 1000 fragments and a supplement set of 1500 fragments with structural similarities to the core set—as 100 mM DMSO-d_6 stocks with >95% purity (NMR, LC-MS). A PAINS filter was applied to the library,[101] and hits were checked by the FAF-Drugs4 filtering tool[102] for potential problematic structural features.

Expression and Purification of the Human and Mouse Keap1 Kelch Domains. The recombinant His-tagged human Kelch domain (residues 321−609, UniProt Q14145) was cloned into a pRSET A vector and expressed in *Escherichia coli* BL21 (DE3) pLysS followed by purification by column chromatography, as previously described.[24] The recombinant His-tagged mouse Kelch domain (residue 322−624, UniProt Q9Z2X8) was also cloned into a pRSET A vector and expressed in *Escherichia coli* BL21 (DE3) pLysS followed by purification by column chromatography, as previously described.[35]

Fluorescence Polarization Assay. The 2500 fragments and lead compounds were tested for their ability to inhibit the interaction between the human Keap1 Kelch domain and the peptide probes—Cy5-Nrf2 (Cy5-LDEETGEFL-NH_2) and FAM-Nrf2 (5(6)-FAM-LDEETGEFL-NH_2)—as described previously.[24,35] The 9mer Nrf2 peptide H-Nrf2-OH (H-LDEETGEFL-OH) and the short 7mer Nrf2 peptide (Ac-LDEETGE-OH) were used as controls. The assay was performed in a 1× HBSTET assay buffer (10 mM HEPES, 150 mM NaCl, 0.005% Tween20, 3 mM EDTA, 1 mM TCEP, pH = 7.4) using black flat-bottom 384-well plates (Corning Life Sciences, NY) and a volume of 30 μL/well. Fragments were screened at 2 mM (2% DMSO) using Cy5-Nrf2 as a probe (3 nM) and Keap1 Kelch at 14 nM. Each assay plate contained 320 fragments, 40 control wells (assay buffer with 2% DMSO), and 16 wells with the 7mer Nrf2 control peptide in two concentrations (6 and 100 μM, respectively). Assay plates were spun-down to ascertain proper mixing and removal of potential air bubbles and incubated for 10−15 min at room temperature before measuring the FP levels on a Safire2 plate-reader (Tecan, Männedorf, Switzerland). Hits were validated by dose−response tests (6-points, 0.25−8 mM fragment concentration, 8% DMSO) using Cy5-Nrf2 as probe and counter tested by first performing the dose−response experiments with the FAM-Nrf2 probe; second, by replacing Tween20 with 0.01% Triton-X in the assay buffer (using Cy5-Nrf2 as probe); and third, by omitting the Keap1 Kelch domain (using Cy5-Nrf2 as probe). Standard assay buffer (incl. 2, 4, or 8% DMSO) and Cy5-Nrf2 were used to determine K_i values of analogues and lead compounds. FP values were fitted to the equation Y = Bottom + (Top − Bottom)/[1 + ($10^{\text{HillSlope}*(\text{LogIC}_{50}-X)}$)], where X is the logarithmic value of compound concentration. Hereby, the IC_{50} value was obtained, which together with the K_d value, probe, and Keap1 Kelch concentrations was used to calculate the theoretical competitive inhibition constant, the K_i value.[103]

Thermal Shift Assay. Melting curves of Keap1 with and without the presence of compounds were determined by TSA using the Sypro Orange dye (Life Technologies), a Stratagene Mx3005P RT-PCR apparatus (Agilent Technologies, Waldbronn, Germany), and clear nonskirted 96-well PCR-plates, as described previously.[24,35] The 2500 fragments were screened at 2 mM (2% DMSO) in the presence of human Keap1 Kelch domain (final concentration: 0.1 mg/mL; 3 μM) and Sypro Orange (final concentration: 8×) using the 1× HBSTET assay buffer and final sample volume of 25 μL/well. On each plate, 8 wells of blanks (2% DMSO) and 8 wells of positive control (20 μM of *N*,*N*′-(naphthalene-1,4-diyl)bis(4-methoxybenzenesulfonamide)[27] in 4% DMSO) were included for reference. Hits were validated by dose−response tests (5-points, 0.5−8 mM fragment concentration, 0.5−8% DMSO). The plates were sealed and spun-down for 2 min at 500*g*, and measured from 25−95 °C in 70 cycles with a 1 °C temperature increase per minute and fluorescence intensities measured at each cycle. The sigmoidal plot of the normalized fluorescence intensity values versus temperature were fitted to the Boltzmann equation Y = Bottom + (Top − Bottom)/(1 + exp((T_m − X)/Slope)), where X is temperature in °C, whereby the melting temperature (T_m), where 50% of protein is denatured, was determined. The difference in T_m (ΔT_m) of each compound concentration compared to DMSO blanks were plotted as dose−response curves and fitted to the equation $\Delta T_m = \Delta T_m$-max × X/

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(EC_{50} + X), with ΔT_m-max being the maximal obtained T_m and X the compound concentration.

Surface Plasmon Resonance. SPR measurements were performed at 25 °C using a Pioneer FE SPR system (Sartorius), as described previously.[24,35] The Keap1 Kelch domain was covalently immobilized to the biosensor chip by amine coupling up to a level between 3900−4800 RU during screening, 3000−4100 RU during hit validation, and 10 000 RU for lead compound characterization using a 10 mM NaOAc pH 5 immobilization buffer. The 2500 fragments were screened at 0.5 mM in a 384-well plate format and with the 1× HBSTET buffer supplemented with 2% DMSO as running buffer. The fragments were injected over immobilized Keap1 in a gradient using the OneStep injection at 150 μL/min flow rate and 30 s dissociation. Microcalibration (low limit 1% and high limit 3%) was performed to adjust for DMSO bulk effects. Two Nrf2-derived peptides (H-LDEETGEFL-OH and Ac-LDEETGEFL-OH)[24] were used as controls before, during and after each 384-well plate test to evaluate the activity of the immobilized Keap1 on the sensor chip. A counter-screen where the Nrf2 binding site at Keap1 was blocked with the Ac-LDEETGEFL-OH peptide was run as described above, but where the ligand and running buffer was supplemented with 50 μM peptide. Fragments were defined as hits if normalized binding response at 57 s injection time (2 s window) was ≥4 RU and $S \geq 0.25$ ($S = (R_{noncompetitive} - R_{competitive})/(R_{noncompetitive} + R_{competitive})$. To validate the primary hits, they were tested by 2-fold serial dilutions (0.0625−1 mM, 4% DMSO) using standard injections at a 30 μL/min flow rate. Here, microcalibration was performed with low and high limits of 3.5% and 4.5% DMSO, respectively. Data were analyzed using Qdat Data Analysis Tool version 2.6.3.0 (Sartorius). The sensorgrams were corrected for buffer bulk effects and unspecific binding to the chip matrix by subtraction of blank and reference surface (a blank flow cell channel activated by injection of EDC/NHS and inactivated by injection of ethanolamine). Hits were considered validated when showing a well-behaved concentration-dependent binding response. The dissociation constants (K_d) were estimated by plotting MW normalized response levels (RU_{norm}) at equilibrium (R_{eq}) against the injected concentration and curve-fitted to a Langmuir (1:1) binding isotherm, while $R_{norm,max}$ of the fragments were fixed to the normalized R_{max} level of the control peptide H-LDEETGEFL-OH. Response levels (RU) are converted to RU_{norm} in Qdat by multiplying the responses with the ratio of the median MW (of all tested compounds in the given experiment) and MW of the specific test compound; hence, $RU_{norm} = RU \times MW_{Median}/MW_{test\ compound}$. The lead compounds were injected in concentration series (2-fold serial dilution) or as OneStep gradient injections and K_d values were determined by kinetic fitting of the SPR sensorgrams to a simple 1:1 interaction model.

Saturation-Transfer Difference NMR. Fragments were tested at 1 mM concentration by STD-NMR in 4% DMSO-d_6 and using an irradiation frequency of 0.45 ppm, as described previously.[35] A standard PBS buffer (0.01 M phosphate buffer, 0.0027 M KCl and 0.137 M NaCl, 1 mM TCEP, pH 7.4) was used to prepare a stock solution of Keap1 Kelch (6 μM) in PBS buffer (10 v/v% D_2O, 3% DMSO-d_6), which was used to dilute each of the 100 mM DMSO-d_6 fragment stock solutions to 1 mM and a final volume of 160 μL per sample in 4% DMSO-d_6. A fully automated Gilson 215 liquid handling system was used to transfer the sample solutions to 3 mm NMR tubes. Standard 1D and STD NMR spectra were acquired at 280 K with a Bruker 600 MHz NMR spectrometer equipped with a cryoprobe. A Bruker SampleJet sample changer was used, allowing sequential measurement of all samples without user intervention. Receiver gain was kept constant for all measurements to ensure results comparability. Fragments were considered validated by STD NMR, if at least one signal in the ^1H NMR spectrum demonstrated an STD% > 1%, as measured by the ratio between the intensities of the STD signal and the 1D signal (ISTD/I1D).

Crystallization, X-ray Data Collection, and Structure Determination. Mouse Keap1 Kelch domain protein crystals were obtained as described previously.[35] For obtaining co-structures of protein−ligand complexes, crystals were soaked for 1−17 h with 5−20 mM ligand (5−20% DMSO) from 100 mM DMSO stocks in a solution containing 100 mM Bis-Tris pH 7.0, 25% PEG 4K. The crystals were then harvested in liquid nitrogen for X-ray diffraction. Data for the mouse Keap1 Kelch domain in complex with **36**, **37**, **44**, and **45** were collected from the ID29 beamline;[104] and in complex with **43** from the ID23-1 beamline at the European Synchrotron Radiation Facility (ESRF; Grenoble, France).[105] X-ray diffraction data for the mouse Keap1 Kelch domain in complex with **18** was collected from the P13 beamline; and in complex with **67** from the P14 beamline at DESY (Hamburg, Germany).[106] Data for compound **77** in complex with mouse Keap1 Kelch domain were collected from the BioMAX beamline (MAX IV, Lund, Sweden).[107] Diffraction images were integrated, scaled, and merged using autoprocessed beamline tools,[108−112] while in some cases it proved necessary to reprocess the data and scaling using XDS.[113] The structures were solved using PHASER[114] with PDB ID 6ZF4[35] as the search model for molecular replacement. Restraints for the fragments/compounds were prepared using the AceDRG[115] followed by Model building and refinement using COOT[116] and Phenix.refine.[117] Figures were prepared using PyMOL (The PyMOL Molecular Graphics System, Version 2.3.4 Schrödinger, LLC).[118]

Molecular Docking. *In silico* experiments were performed using Schrödinger's Maestro software (version 12.7).[119] For Figure 6C, the protein from the PDB ID 5FNU X-ray structure was used as receptor grid while retaining the five conserved waters at the opening of the central Kelch domain channel, as previously described.[35] The structure of the Keap1 Kelch domain in complex with compound **77** (PDB ID: 7OFF) was used as grid when docking **77** analogues. Ligands were prepared by LigPrep with default settings. Ligand docking and scoring were performed using Glide with default settings and with the SP (standard precision) or XP (extra precision) scoring function. PyMOL was applied for analyses and visualization of docking poses.[118]

qPCR. RNA was extracted from the samples using the High Pure RNA Isolation Kit (Roche, 11828665001) according to the manufacturer's instructions. RNA was eluted in 60 μL of sterile RNase-free water. The quality and purity of the RNAs were assessed by Nanodrop spectrometry (DeNovix DS-11). Using the TaqMan detection systems, the gene expression of HO-1, NQO1, AKR1B10, and TRXR1 was determined by real-time PCR. In accordance with the manufacturer's recommendations (Applied Biosciences) the premade TaqMan assays and RNA-to-Ct-1-Step kit was used to analyze the RNA levels. The commercially available TaqMan assay (Thermo Fischer Scientific, cat. no. 4392938) was used, and samples were analyzed in a final volume of 10 μL reaction mix containing 5 μL of master mix, 0.2 μL of RT enzyme, 2.3 μL of nuclease-free water, 0.2 μL of primers (TATA-Box Binding Protein/TBP; Hs00427620_m1, AKR1B10; Hs00252524_m1, HO-1; Hs01110250, NqO1; Hs01045993_g1, and TRXR1; Hs00917067_m1, Thermo Fisher), and 2 μL of pure RNA. The samples were analyzed using a QuantStudioTM 3 Real-Time PCR instrument with the following program: 1 × (10 min, 48.0 °C; 10 min, 95.0 °C); 40 × (30 s, 95.0 °C; 1 min, 60.0 °C). The C_t values were extracted by use of the ThermoFisher Cloud Software.

Western Blotting. After compound stimulation, the cells were lysed in 70 μL of ice-cold Pierce RIPA lysis buffer (Thermo Scientific) supplemented with 10 mM NaF, 1× complete protease cocktail inhibitor (Roche), and 5 IU mL-1 benzonase (Sigma), respectively. By using a BCA protein assay kit (Thermo Scientific) the protein concentration was determined. 1×XT sample buffer (Bio-Rad) and 1×XT reducing agent (Bio-Rad) were added to samples, and lysates were denatured by boiling for 3 min at 95 °C. A total volume of 25 μL of reduced samples was separated by SDS-PAGE on a 4−20% Criterion TGX precast gradient gel (Bio-Rad). The gel ran initially for 20 min at 70 V and 45 min at 120 V and was then transferred onto a PVDF membrane (Bio-Rad) by using a Trans-Blot Turbo transfer system. Membranes were then blocked in 5% skim milk (Sigma-Aldrich) in PBS supplemented with 0.05% Tween-20 (PBST) for 1 h at room temperature on a shaker. Membranes were fractionated accordingly to the sizes of investigated proteins and probed with

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antibodies overnight at 4 °C on a shaker. Following primary antibodies were used in PBS Tween 0.05%: anti-HO-1 (Cell Signaling 1/1000), anti-NqO1 (Cell Signaling, 1/1000), anti-TRXR1 (Cell Signaling, 1/1000), anti-Cl-Caspase-3 (Cell Signaling, 1/1000), anti-Cl-PARP (Cell Signaling, 1/1000) and anti-Vinculin (VCL; Sigma-Aldrich 1/10 000) used as loading control. The membranes were washed three times in PBST and then incubated for 1 h at room temperature in secondary antibodies, peroxidase-conjugated F(ab)2 donkey anti-mouse IgG (H + L) (1:10 000) or peroxidase-conjugated F(ab)2 donkey anti-rabbit IgG (H + L) (1:10 000) (Jackson ImmunoResearch), in PBST 1% milk. Membranes were washed three times and exposed using the SuperSignal West PicoPLUS chemiluminescent substrate and the iBrightTM Imaging System Model No. CL1500.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jmedchem.2c00830.

X-ray data collection and refinement statistics of the eight deposited PDB structures (Table S1), X-ray co-structures of category 1 and 2 fragment hits (at 0.5σ) (Figure S1), SPR sensorgrams of initial analogues (Figure S2), X-ray co-structures (including electron densities) of **67** and **77** in complex with the Keap1 Kelch domain (Figure S3), chiral HPLC data and molecular docking of **119** and **120** (Figure S4), SPR data of **107** and **119** (Figure S5), binding mode of **119** and known Keap1 inhibitors (Figure S6), and HPLC traces of key final compounds (Figure S7) (PDF)

Molecular formula strings (CSV)

PDB structure file for 7OFD (**18**) (PDB)

PDB structure file for 7OF8 (**36**) (PDB)

PDB structure file for 7OFA (**37**) (PDB)

PDB structure file for 7OFC (**43**) (PDB)

PDB structure file for 7OFB (**44**) (PDB)

PDB structure file for 7OF9 (**45**) (PDB)

PDB structure file for 7OFE (**67**) (PDB)

PDB structure file for 7OFF (**77**) (PDB)

Accession Codes

Structure factors and coordinate files of mouse Keap1 Kelch domain in complex with the eight compounds are deposited in the Protein Data Bank as follows: 7OFD (**18**), 7OF8 (**36**), 7OFA (**37**), 7OFC (**43**), 7OFB (**44**), 7OF9 (**45**), 7OFE (**67**), and 7OFF (**77**). The authors will release the atomic coordinates upon article publication.

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D.N. and K.T.T contributed equally to this work. J.S.P., S.M.Ø.S., and Y.Q. contributed equally to this work. The manuscript was written by A.B., K.T.T., and D.N. with contributions from all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

AKR1B10, aldo-keto reductase family 1 member b10; BTB, broad complex, tramtrack, and bric-à-brac; COPD, chronic obstructive pulmonary disease; F2L, fragment-to-lead; FAM, 5(6)-carboxyfluorescein; FBDD, fragment-based drug discovery; FBDR, fragment-based deconstruction reconstruction; FLINT, total fluorescence intensity; FP, fluorescence polarization; HO-1, heme oxygenase 1; IVR, intervening region; Keap1, Kelch-like ECH-associated protein 1; KO, knockout; LE, ligand efficiency; LLE, lipophilic ligand efficiency; NQO1, NAD(P)H dehydrogenase (quinone) 1; Nrf2, nuclear factor erythroid 2-related factor 2; 4-OI, 4-octyl-itaconate; PPI, protein−protein interaction; qPCR, quantitative real-time PCR; Ro3, rule of 3; ROS, reactive oxygen species; SD, standard deviation; SPR, surface plasmon resonance; STD NMR, saturation-transfer difference NMR; TSA, thermal shift assay; TXRT1, thioredoxin reductase 1; VCL, vinculin; WT, wild-type

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