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2,2,2-Trifluoroethyl Chlorooxoacetate—Universal Reagent for One-Pot Parallel Synthesis of N^1-Aryl-N^2-alkyl-Substituted Oxamides

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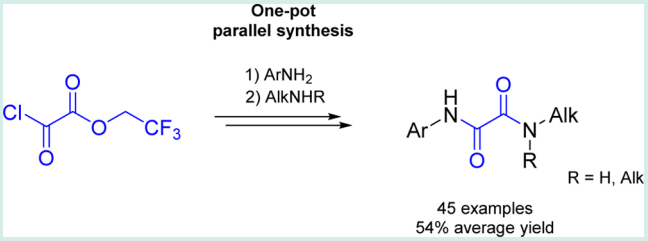
Supporting Information

ABSTRACT: A one-pot parallel synthesis of N^1-aryl-N^2-alkyl-substituted oxamides with 2,2,2-trifluoroethyl chlorooxoacetate was developed. The synthesis of a library of 45 oxamides revealed higher efficiency of this reagent over the known ethyl chlorooxoacetate. The reagent was successfully used to prepare the known oxamide-containing HIV entry inhibitors.



KEYWORDS: *N^1-aryl-N^2-alkyl-substituted oxamides, parallel synthesis, one-pot approach, ethyl chlorooxoacetate, 2,2,2-trifluoroethyl chlorooxoacetate*

INTRODUCTION

The "Escape from Flatland"[1−4] concept has gained considerable attention in designing new scaffolds and compound libraries for drug discovery. Following the concept, we have developed parallel synthesis methods to various drug-like compounds and building blocks with a saturated skeleton including aliphatic sulfonamides,[5] unsymmetrical aliphatic ureas[6] and aliphatic secondary amines.[7,8] One of our recent projects to implement the concept was focused on an N^1-aryl-N^2-alkyl-substituted oxamide motif. This fragment has found its application in medicinal and synthetic organic chemistry: potential human immunodeficiency virus (HIV-1) entry inhibitors[9−12] and antimalarial drugs,[13−15] *N*-heterocyclic carbene (NHC) pre-catalysts including modifications of the Grubbs' second generation catalyst,[16−25] and other bioactive compounds[26−30] are derivatives of the unsymmetrical oxamides (Figure 1). Despite growing interest in sized libraries of these oxamides, suitable methods for their parallel synthesis have remained unknown.

Our typical development procedure involves: experimental design followed by test reactions to optimize conditions, and validation of a method on a series of experiments at the Parallel Synthesis Department. The requirements to the experimental design included (1) use of simple reaction set up (preferably in a one-pot fashion) and work up procedures and (2) use of "universal" starting reagents which could be applicable to various substrates and provide diversity to a library.[6−8] Systematic examination of the available literature revealed that the common synthetic strategy to N^1-aryl-N^2-alkyl-substituted oxamides utilized a stepwise aminolysis of ethyl chlorooxoacetate (**1a**).[22,24,31] The ester chloride reacts with an aryl amine to produce an ester monoamide that undergoes the second aminolysis directly or via activation of an acid

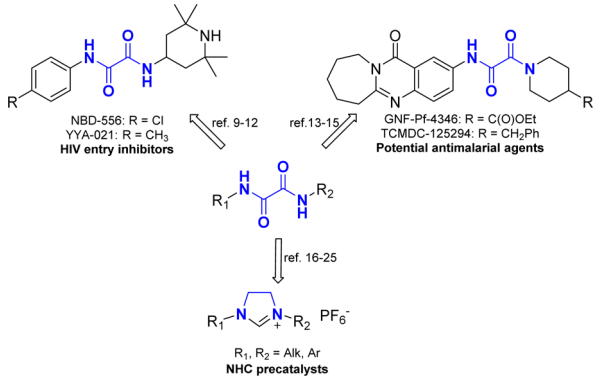


Figure 1. Application of N^1-alkyl-N^2-aryl-substituted oxamides.[9−25]

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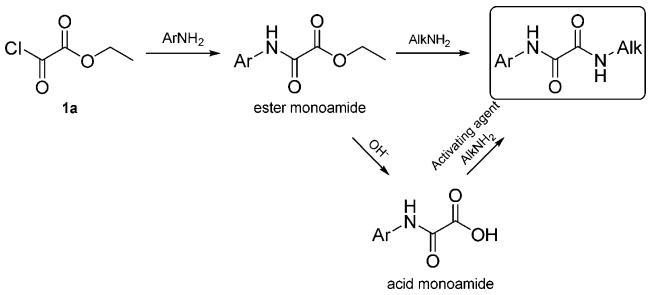
monoamide formed upon saponification of the ester monoamide (Scheme 1). The above strategy was initially selected for

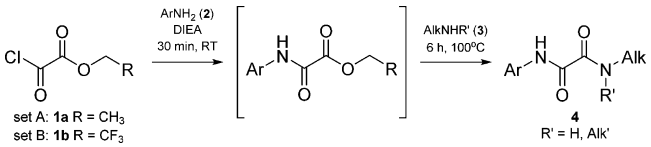
Scheme 1. General Approach to N^1-Aryl-N^2-alkyl-Substituted Oxamides



the method development: it would support simple set up without special reaction conditions (inert atmosphere, cooling upon addition of reagents, etc.); it would allow creation of diverse sets by varying amines; performing the direct aminolysis of the ester monoamide would enable the one-pot procedure. But use of reagent **1a** limited the one-pot method to primary alkyl amines because ethyl ester monoamides reacted poorly with hindered amines. Therefore, the strategy needed modification to satisfy all the requirements to the parallel synthesis design.

The aminolysis of esters depends on the pK_a value of the leaving alcohol group:[32] the lower pK_a value results in higher efficiency of the reaction. In this context, 2,2,2-trifluoroethyl chlorooxoacetate (**1b**) (Scheme 2) could be a more reactive

Scheme 2. One-Pot Synthesis of N^1-Aryl-N^2-alkyl-Substituted Oxamides



alternative to **1a** (the pK_a values of 2,2,2-trifluoroethanol and ethanol are 12.5 and 16, respectively)[33,34] which would enable the one-pot strategy under the parallel synthesis conditions. Our previous experience with the 2,2,2-trifluoroethyl derivatives, bis(2,2,2-trifluoroethyl) carbonate and 2,2,2-trifluoroethyl chloroformate, revealed that moderate reactivity of these reagents compared with the ethyl and the phenyl or the *p*-nitrophenyl analogs supported efficient stepwise aminolysis in the one-pot syntheses of unsymmetrical ureas and 4-substituted semicarbazides.[6,35,36]

To confirm our hypothesis and to evaluate the one-pot strategy in the parallel synthesis of N^1-aryl-N^2-alkyl-substituted oxamides, we performed the experiments with reagents **1a** and **1b** utilizing various amines. The current report describes our results on the method evaluation and presents the comparative study of the efficacy of the above ester chlorides under the parallel synthesis conditions.

RESULTS AND DISCUSSION

Method Development. We arbitrary selected 14 aryl (reagent chemset 2) and 45 alkyl (reagent chemset 3) amines from our internal database for the test experiments. Amines **2** contained the common fragments in the N^1-aryl-N^2-alkyl-substituted oxamide motif - derivatives of aniline, quinoline, pyrazole, and pyridine (Figure 2). Since the aminolysis of ester monoamides was a critical step, diversity reagents **3** comprised structurally different substrates: 10 primary, 15 secondary cyclic and 20 secondary acyclic alkyl amines (Tables 1−3). Then, we created a random 45 member library of the oxamides (Tables 1−3) and performed 90 parallel reactions utilizing ester chlorides **1a** (set A) and **1b** (set B). The library would allow to evaluate all selected alkyl fragments which completely satisfied the purpose of the work and the synthesis of all possible variants (630!) was unnecessary. We conducted the experiments on a millimolar scale because most biochemical assays require milligram quantities of test compounds.

The synthesis was performed as a two-step procedure (Scheme 2). Briefly, to an acetonitrile solution of amine **2** (1 equiv) and a base, *N*,*N*-diisopropylethylamine, (1.5 equiv or 2.7 equiv for free aryl amines or aryl amine hydrochlorides) in a sealed 8 mL vial was added chlorooxoacetate ester **1a** or **1b** (1 equiv). The obtained mixture was left shaking at room temperature for 30 min (Figure S1). Then, amine **3** (1 equiv) was added to the vial and the mixture was heated in an oven at 100 °C for 6 h (Figure S2). The aforementioned conditions were sufficient for both aminolysis steps. A simple work up, treatment with a $CHCl_3$-water (3/4, v/v) mixture with subsequent separation and evaporation of the organic phase, resulted in crude product **4**. We analyzed the crude samples with LC-MS (Figures S3−S56) and subjected to purification those having less than 90% product content. Identities and purities of the synthesized compounds were further confirmed by means of ^{1}H and ^{13}C NMR spectroscopy and LC-MS.

To compare reagents **1a** and **1b** in the synthesis, we arranged the experimental results based on the type of the alkyl amines

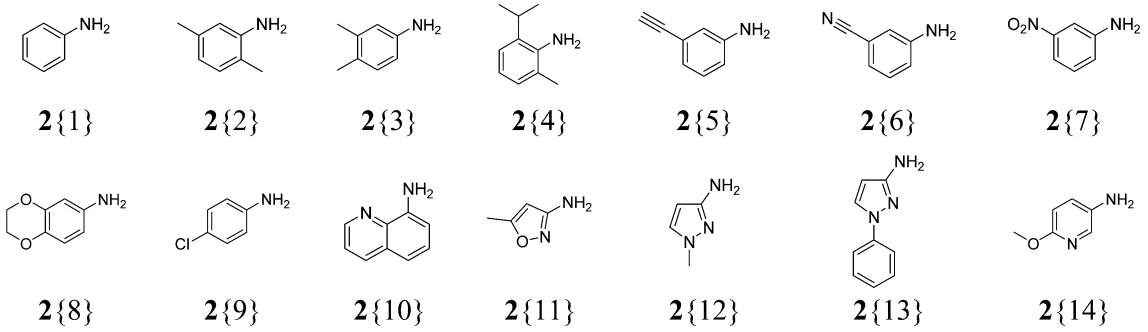


Figure 2. Diversity reagents **2**.

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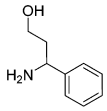
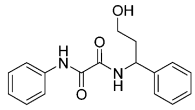
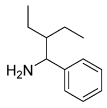
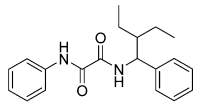
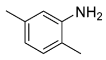
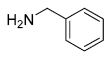
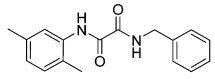
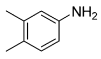
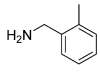
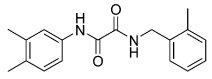
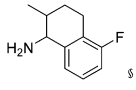
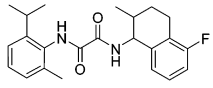
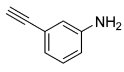
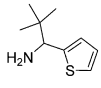
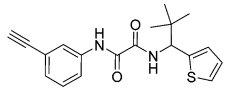
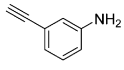
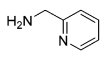
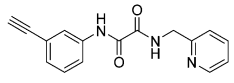
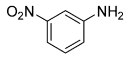
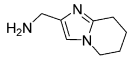
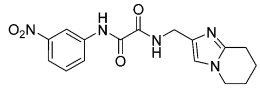
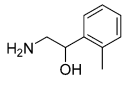
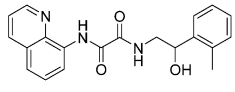
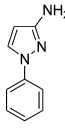
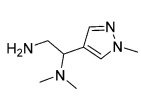
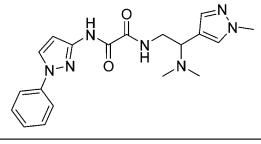
Table 1. Results of the Parallel Synthesis of N^1-Aryl-N^2-alkyl-Substituted Oxamides Derived from Primary Alkyl Amines

Compound	Amine **2**	Amine **3**	Oxamide **4**	Product[#] (%) in crude sample, set A/ set B	Yield[*] (%), set A/ set B
4{1,1}				99/98	70/72
4{1,2}				44/97	39/75
4{2,3}				90/91	73/69
4{3,4}				71/81	12/35
4{4,5}				< 5/88	< 5/36
4{5,6}				38/90	5/23
4{5,7}				67/60	37/30
4{7,8}				99/97	78/66
4{10,9}				97/99	82/82
4{13,10}				98/91	78/66

[#]Product content was determined by LC-MS. [*]Isolated yield. [§]Mixture of isomers, 54/46, trans/cis.

and examined two parameters: amount of the product in the crude samples and the isolated yields.

Primary Alkyl Amines. Both reagents showed similar efficiencies in the experiments with the hindered primary alkyl amines, for example, **4**{*1,1*}, **4**{*2,3*}, and **4**{*10,9*}, in Table 1, resulting in the high purity products without a need for chromatography step. The yields for these samples ranged from 30% to 82%. But reagent **1a** was less efficient than **1b** in the experiments with the hindered primary alkyl amines, for example, **4**{*1,2*}, **4**{*4,5*}, and **4**{*5,6*}: the LC-MS analysis of set A revealed complex mixtures with lower product contents (<50%) compared with those for set B (>85%) and identified the ester monoamides as main impurities (Figures S5 and S7). Consequently, the isolated yields in these reactions were substantially higher in set B than those in set A.

Cyclic Secondary Alkyl Amines. The LC-MS of the crude mixtures of set A showed more than 50% product content only in the experiments with the less hindered and more reactive alkyl amines, for example, **4**{*1,12*}, **4**{*6,15*}, and **4**{*13,25*} (Table 2). For most cases with these amines, the product content in set A was below 30% with an average value close to 13%. We identified the impurities to be the starting alkyl amines, and the acid monoamides (Figures S15, S17, and S21). The low product content complicated the purification or made it impossible for compounds **4**{*3,13*}, **4**{*3,14*}, **4**{*3,16*}, **4**{*3,18*}, **4**{*3,19*}, **4**{*3,22*}, and **4**{*3,24*} from this set. The isolated yields in set A were below 55%. For set B, all the experiments succeeded in the products with more than 65% product content. The isolated yields in set B ranged from low to high. Overall, the values of the yields were substantially higher for the experiments in set B than those in set A.

Acyclic Secondary Alkyl Amines. Similarly to the experiments with the cyclic alkyl amines, reagent **1a** was inefficient in the parallel synthesis of the oxamides derived from the acyclic secondary amino substrates. The LC-MS analysis of the crude samples in set A showed complex mixtures with the average product content close to 21% (Table 3 and Figures S33−S56). The identified impurities were amines **3**, the acid monoamides (for example, **4**{*2,29*} and **4**{*14,44*}), the ester monoamides (for example, **4**{*6,33*} and **4**{*11,42*}), or mixtures of both monoamides (for example, **4**{*2,28*} and **4**{*9,37*}). The product content was above 35% only in 5 experiments with less hindered amines **3**. The isolated yields in set A were below 20%, most reactions resulted in no product because the low

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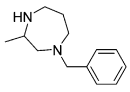
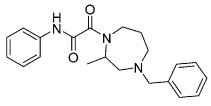
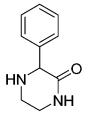
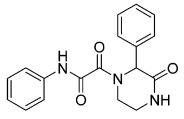
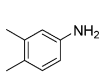
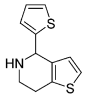
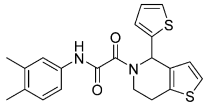
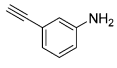
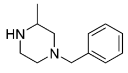
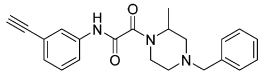
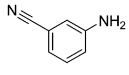
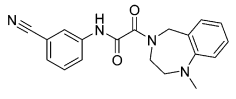
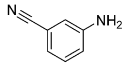
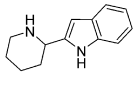
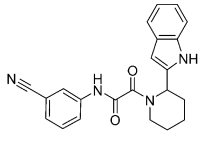
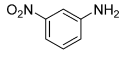
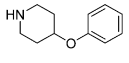
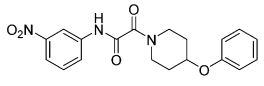
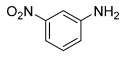
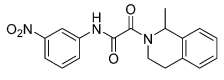
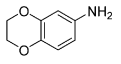
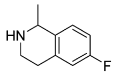
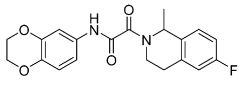
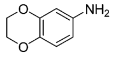
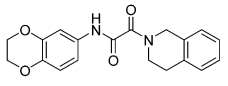
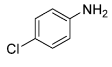
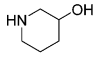
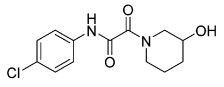
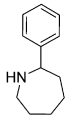
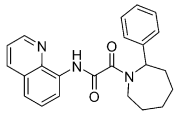
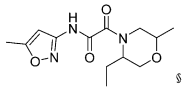
Table 2. Results of the Parallel Synthesis of N^1-Aryl-N^2-alkyl-Substituted Oxamides Derived from Cyclic Secondary Alkyl Amines

Compound	Amine **2**	Amine **3**	Oxamide **4**	Product[#] (%) in crude sample, set A/ set B	Yield[*] (%), set A/ set B
4{1,11}				16/66	< 5/24
4{1,12}				71/86	20/55
4{3,13}				5/88	< 5/69
4{5,14}				8/82	< 5/37
4{6,15}				81/83	31/58
4{6,16}				12/65	< 5/30
4{7,17}				64/79	19/42
4{7,18}				14/87	< 5/58
4{8,19}				26/84	< 5/60
4{8,20}				83/95	54/90
4{9,21}				67/85	13/24
4{10,22}				< 5/75	< 5/43
4{11,23}		 [§]	 [§]	47/99	18/56
4{11,24}				17/74	< 5/23
4{13,25}		[†]	[†]	62/84	38/83

[#]Product content was determined by LC-MS. [*]Isolated yield. [§]Mixture of isomers, 70/30, trans/cis. [†]Mixture of isomers, 96/4, trans/cis.

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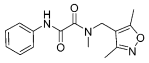
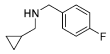
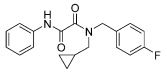
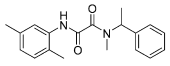
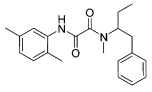
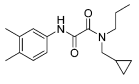
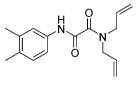
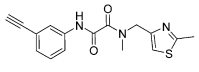
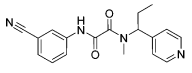
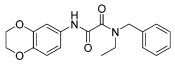
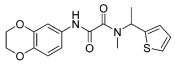
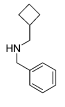
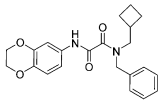
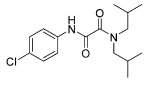
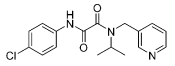
Table 3. Results of the Parallel Synthesis of N^1-Aryl-N^2-alkyl-Substituted Oxamides Derived from Acyclic Secondary Alkyl Amines

Compound	Amine **2**	Amine **3**	Oxamide **4**	Product[#] (%) in crude sample, set A/ set B	Yield[*] (%), set A/ set B
4{1,26}				70/90	20/61
4{1,27}				17/91	< 5/85
4{2,28}				< 5/85	< 5/45
4{2,29}				9/71	< 5/24
4{3,30}				10/92	< 5/48
4{3,31}				7/82	< 5/25
4{5,32}				42/94	10/90
4{6,33}				< 5/85	< 5/45
4{8,34}				19/93	< 5/83
4{8,35}				< 5/97	< 5/83
4{8,36}				14/93	< 5/74
4{9,37}				< 5/91	< 5/77
4{9,38}				< 5/72	< 5/21
4{10,39}				63/93	17/88
4{10,40}				74/87	19/48
4{11,41}				20/96	< 5/64
4{11,42}				10/88	< 5/33
4{12,43}				16/85	< 5/35
4{14,44}				36/86	6/35
4{14,45}				28/93	9/74

[#]Product content was determined by LC-MS. [*]Isolated yield.

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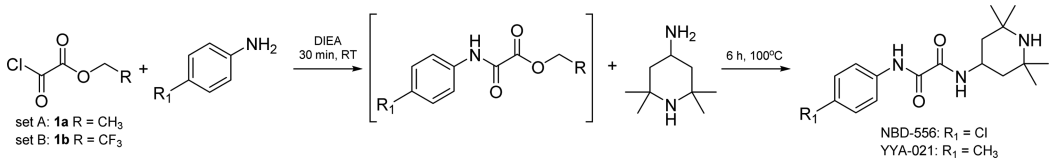

Figure 3. One-pot parallel synthesis of the known HIV entry inhibitors.

product content made the purification step impossible. The employment of **1b** was successful: the LC-MS analysis revealed that 11 experiments resulted in more than 90% product content; in other experiments, it ranged between 70% and 88%. The isolated yields in set B were at least 3 times higher than those for the same experiments in set A.

The experimental data clearly confirmed the influence of the leaving alcohol group on the activity of the ester monoamides. The ethyl monoamides reacted with the strongly nucleophilic primary alkyl amines and failed with the amines with hindered amino group affording the complex mixtures which contained the product and the intermediate, the ester monoamide, or the side product, the acid monoamide. The inefficient aminolysis resulted in the substantially lower isolated yields in set A than those in set B. On the other hand, reagent **1b** was effective in all conducted experiments: its moderate reactivity allowed to perform the first aminolysis with the aryl amines without formation of symmetrical bisamides and was substantial to complete the second aminolysis. Many experiments in set B provided the products in high purity without the chromatography purification. The above observations made **1b** a "universal" reagent for the parallel synthesis of N^1-aryl-N^2-alkyl-substituted oxamides.

Practical Application. We additionally verified the method on the known bioactive compounds: N^1-(4-chlorophenyl)-N^2-(2,2,6,6-tetramethylpiperidin-4-yl)oxamide (NBD-556) and N^1-(2,2,6,6-tetramethylpiperidin-4-yl)-N^2-(*p*-tolyl)oxamide (YYA-021). The parallel synthesis of NBD-556 and YYA-021 was accomplished in two sets (4 reactions) on a millimolar scale under similar conditions to those applied to the synthesis of the 45-member library (Figure 3). For the crude samples of set A, the LC-MS analysis showed 68 and 78% product content for NBD-556 and YYA-021, respectively, identifying the unreacted ester monoamide and *bis*-tolyl oxamide as main impurities (Figures S57, S58, S61, and S62). For the samples of set B, the product content was close to 100% (Figures S59, S60, S63, and S64) which resulted in 67% and 62% isolated yields for NBD-556 and YYA-021, respectively. These values were higher than the reported in the literature (30−40%).[12,37,38]

CONCLUSIONS

We have developed the one-pot parallel synthesis approach to N^1-aryl-N^2-alkyl-substituted oxamides from the chlorooxoacetate esters. The reaction proceeded through the direct aminolysis of the ester monoamide intermediate which required good leaving alcohol group to interact with hindered amines. The commonly utilized ethyl chlorooxoacetate limited the approach because of the low reactivity and was substituted with the alternative reagent, 2,2,2-trifluoroethyl chlorooxoacetate. We validated the method on the 45 member library of N^1-aryl-N^2-alkyl-substituted oxamides synthesized on a millimolar scale utilizing both chlorooxoacetates. The obtained results confirmed higher efficiency of the 2,2,2-trifluoroethyl derivative compared with the ethyl analog. The experiments with the latter reagent failed in most cases. We additionally tested the approach in the parallel synthesis of the known bioactive oxamides, N^1-(4-chlorophenyl)-N^2-(2,2,6,6-tetramethylpiperidin-4-yl)oxamide and N^1-(2,2,6,6-tetramethylpiperidin-4-yl)-N^2-(*p*-tolyl)oxamide, and obtained the products in higher yields than those reported in the previously published procedures.

The successful employment of 2,2,2-trifluoroethyl chlorooxoacetate with different alkyl amino substrates allowed to suggest it as the "universal" reagent for the parallel synthesis of N^1-aryl-N^2-alkyl-substituted oxamides. We believe that the developed approach would help synthetic and medicinal chemists in expanding variety of the compounds with this structural motif.

EXPERIMENTAL PROCEDURES

All chemicals and solvents were obtained from commercially available sources (Enamine, Sigma-Aldrich) and used without further purification. ^{1}H and ^{13}C NMR spectra were acquired on Bruker Avance DRX 500 spectrometer using DMSO-d_6 as a solvent and tetramethylsilane (TMS) as an internal standard. IR spectra were recorded on PerkinElmer Spectrum BX II. Melting points were determined on Buchi melting point apparatus and are uncorrected. LC-MS data were recorded on Agilent 1100 HPLC equipped with diode-matrix and mass-selective detector, column: Zorbax SB-C18, 4.6 mm × 15 mm. Eluent, A, acetonitrile−water with 0.1% of TFA (95:5); B, water with 0.1% of TFA. The flash chromatography purification was performed using Companion Combi-Flash instrument with UV-detector and reusable LukNova column [gradient elution; eluent, A, $CHCl_3$; B, $CHCl_3$/methanol (7:3, v:v)].

General Procedure for the Synthesis of N^1-Aryl-N^2-alkyl-Substituted Oxamides. A mixture of ethyl chlorooxoacetate (**1a**), set A, or 2,2,2-trifluoroethyl chlorooxoacetate (**1b**), set B, (1 mmol), aniline **2**{*1*} (1 mmol), and DIEA (1.5 or 2.7 mmol if the amine was in form of hydrochloride) in 2 mL of acetonoitrile was shaken in an 8 mL sealed vial at room temperature for 30 min. Then, 3-amino-3-phenylpropan-1-ol **3**{*1*} (1.1 mmol) was added and the reaction mixture was heated at 100 °C for 6 h. After it was cooled to room temperature, chloroform (3 mL) and water (4 mL) were added sequentially, and the organic phase was washed with water (4 mL) twice, separated, and evaporated to yield oxamide **4**{*1,1*} in >98% purity according to the LC-MS analysis. Yield: 209 mg, 70% (set A)/215 mg, 72% (set B), white solid, mp 197−199 °C. IR (KBr): ν (cm^{-1}) 3302, 1659, 1510, 1440,1053. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.95 (m, 1H, CH_2), 2.10 (m, 1H, CH_2), 3.41 (m, 2H, CH_2), 4.63 (br.s, 1H, OH), 5.05 (q, J = 8.1 Hz, 1H, CH), 7.12 (t, J = 7.2 Hz, 1H, Ar), 7.23 (t, J = 7.2 Hz, 1H, Ar), 7.33 (m, 4H, Ar), 7.39 (d, J = 7.6 Hz, 2H, Ar), 7.80 (d, J = 7.1 Hz, 2H, Ar), 9.46 (d, J = 8.6 Hz, 1H, NH), 10.59 (s, 1H, NH). ^{13}C NMR (125.75 MHz, DMSO-d_6): δ = 38.0, 50.9, 57.7, 120.4, 124.6, 126.8, 127.0, 128.4, 128.8, 137.7, 142.9, 158.8, 159.7. MS (APSI) m/z $[M + H]^+$ calculated for $C_{17}H_{19}N_2O_3$: 299.1; found 299.2.

The remaining compounds in the library were synthesized under the essentially identical conditions. If the product

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content in the crude material was below 90%, the samples were subjected to flash chromatography.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscombsci.5b00091.

Details of experimental set up; LC-MS data, ^{1}H and ^{13}C NMR spectra, and analytical data for selected synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS

HIV-1, human immunodeficiency virus; NHC, *N*-heterocyclic carbene; DIEA, *N*,*N*-diisopropylethylamine

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