A general strategy for construction of a difluoromethyl compound library and its application in synthesis of pseudopeptides bearing a terminal difluoromethyl group†

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We describe the development of a novel synthesis strategy that uses common reaction conditions to transform a collection of simple building blocks into complex molecules bearing a terminal difluoromethyl group. The core of this approach is the conscious design and synthesis of new difluorinated building blocks which contain inactive and reactive groups on each side of the CF_2 group. The strategy is illustrated by application to the synthesis of CF_2H-bearing pseudopeptides *via* Ugi reaction.

Introduction

Much attention has been drawn in recent years towards the difluoromethyl group (CF_2H) due to its special physical and chemical properties.[1] Some CF_2H-containing derivatives have been reported to exhibit herbicidal,[2] potential antitumor[3] and antileishmanial activity.[4] Although difluoromethylated compounds have significant applications in drug and pesticide discovery, only a limited number of them are available for evaluation of bioactivity compared to their CF_3 analogues.

As a result of the relative novelty of these difluoromethyl compounds, the synthesis of them has been of interest to synthetic chemists. Different methods for the preparation of CF_2H-containing compounds have been developed in recent years.[5] For example, the commercialization of several straightforward fluorinating agents, such as DAST, SF_4,[6] SeF_4,[7] TBAF[8] and BrF_3,[9] has paved the way for the synthesis of various difluorinated compounds. The nucleophilic, radical, and electrophilic (phenylsulfonyl)difluoromethylations stand out as other novel and promising synthetic methods to access CF_2H-containing molecules.[10] However, the purpose of the present methods is only to difluorinate the specific positions or groups of the target compounds. These methods are limited to the preparation of relatively simple CF_2H-containing compounds and just allow the generation of a single specimen. The procedures tend to be lengthy and tedious and require multistep reactions to prepare CF_2H-containing compounds individually if the target fluorinated compounds contain other reactive groups. In addition, the CF_2H groups are not stable to strong organic bases and can undergo dehydrofluorination.[11] Therefore, there is a clear demand for the development of a novel and general strategy to introduce CF_2H groups and appropriate functional groups into the final molecules in a controlled fashion.

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In this paper, we report a new and efficient strategy for the construction of functionalized small molecules bearing CF_2H in one process. Our overall strategy is outlined in Fig. 1. Ethyl bromodifluoroacetate was used as a starting material. Due to its relatively higher reactivity, which can lead to undesirable side reactions,[12] the bromine atom attached to the right side of difluoromethyl group was replaced by an inactive group such as PhS–, $PhSO_2$– (or referred to as "protected group"). These protected CF_2 derivatives are stable to a wide variety of conditions including strong base. Subsequently, the ester group on the left side of the difluoromethyl unit is converted into the desired reactive functional group such as isocyano, azide or carboxylic group by conventional synthetic methods. These protected functionalized CF_2 building blocks can further undergo many useful reactions such as multicomponent reaction and click reaction. After the construction of the initial scaffolds of target compounds and removal of the inactive groups by the different suitable reducing reagents such as Bu_3SnH/AIBN,[13] $Na/Hg/Na_2HPO_4$[14] or Mg^0/HOAc/NaOAc,[15] structurally complex and diverse molecules with $–CF_2H$ terminal groups can be obtained efficiently and simultaneously in one process (Fig. 1, left).

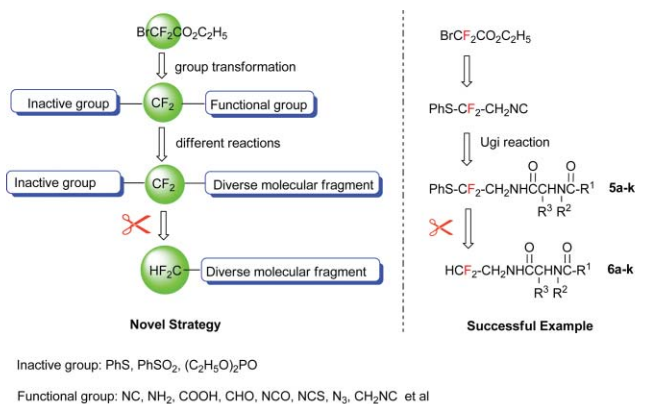


Fig. 1 General strategy for the construction of diverse molecules containing the terminal CF_2H functionality.

Isocyanide-based multicomponent reactions (IMCRs) have attracted considerable interest.[16] The most famous IMCR is the

Ugi four component reaction which involves the reaction of amines, aldehydes, carboxylic acids and isocyanides to form peptidomimetic derivatives. It was reported that some pseudopeptides bearing a CF_2H unit have good bioactivity[17] (Fig. 2). However, the number of examples reported in the literature dealing with flexible and practical syntheses of pseudopeptides bearing a CF_2H unit is scarce.[18]

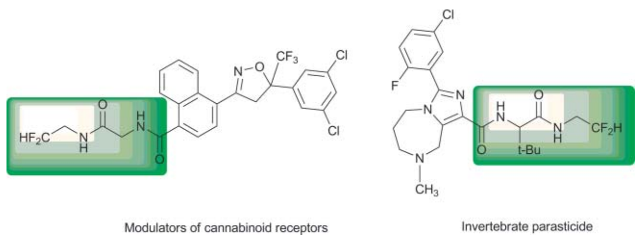


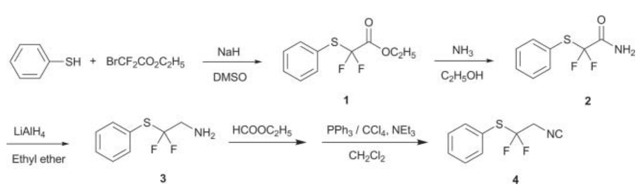
Fig. 2 Two examples of bioactive pseudopeptides bearing the CF_2H group.

In recent years, we have focused on the multicomponent reactions including fluoro-containing building blocks.[19] To demonstrate the potential of the above-mentioned new strategy, in this paper, we described the synthesis of difluoromethyl-containing pseudopeptides *via* Ugi reaction using new difluorinated building block which comprise inactive and active group (phenylthio and isocyano, respectively) on each side of the CF_2 group. The terminal CF_2H functionality has been swiftly incorporated into pseudopeptides by using this new strategy.

Results and discussion

Hu has reported that the reductive cleavage of the weak C–S bond of $PhSCF_2R$ to the corresponding CF_2H-bearing compounds could be achieved easily in the presence of Bu_3SnH/AIBN.[20] Thus, we first explored the possibility of using a phenylthio group to block the left of CF_2 group before it was transformed to highly reactive functionality, isocyano group (Fig. 1, right).

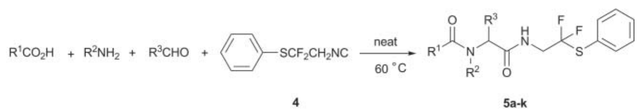
The synthesis of 2,2-difluoro-2-phenylsulfanyl-ethyl-isocyanide **4**, the key building block to realize this strategy, is illustrated in Scheme 1. Ethyl 2,2-difluoro-2-(phenylthio)acetate **1** was readily prepared by the reaction of ethyl 2-bromo-2,2-difluoroacetate with benzenethiol according to the method described in the literature.[12b] The quasi-quantitative amidation then occurred to give the corresponding 2,2-difluoro-2-(phenylthio)acetamide **2** by treatment of **1** with ammonia in methanol. Although amides can very easily be reduced with various reductants to give corresponding amines,[21] in case of compound **2**, the reduction reaction was found to hardly proceed due to the presence of two fluorine atoms. Among several reductants tested, no reaction was observed when $NaBH_4$ and BH_3 were used as reducing agents in refluxing anhydrous THF under argon atmosphere, whereas



Scheme 1 Synthesis of 2,2-difluoro-2-phenylsulfanyl-ethyl-isocyanide **4**.

$LiAlH_4$ gave a very low yield of the expected product; the major unexpected product was 2-phenylsulfanyl-ethylamine. To improve the yields, the reduction of amide **2** was carried out with $LiAlH_4$ at room temperature or 0 °C, the yield of amine **3** increased to 20% and 30%, respectively. Finally, moderate isolated yield (up to 45%) was achieved through the replacement of anhydrous THF with anhydrous diethyl ether at 0 °C. The reaction of amine **3** with ethyl formate yielded formamide, which then reacted with PPh_3/CCl_4 and NEt_3 at 60 °C in anhydrous CH_2Cl_2 successfully afforded the desired novel isocyanide **4** in good yield.[22]

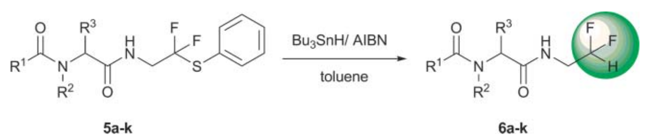
With the PhS-protected difluorinated isocyanide building block in hand, we turned our attention to demonstrate its capability to synthesize the structural diversity of fluorine-containing pseudopeptides *via* Ugi reaction. Thus, several different aldehydes, amines, acids and this novel isocyanide were reacted under solvent-free conditions at 60 °C which we reported previously.[23] In all cases, the reaction proceeded smoothly to give the difluoromethylene compounds in moderate to high yields. Aromatic aldehydes and acids afforded the higher yields of the desired compounds than aliphatic aldehydes and acids (Scheme 2).



5a: R^1 = Ph, R^2 = Ph, R^3 = Ph; **5b**: R^1 = Ph, R^2 = Ph, R^3 = Benzo[d][1,3]dioxol;
5c: R^1 = Ph, R^2 = Ph, R^3 = 4-MeOPh; **5d**: R^1 = Ph, R^2 = Ph, R^3 = 4-MePh;
5e: R^1 = Ph, R^2 = Bu, R^3 = Ph; **5f**: R^1 = Ph, R^2 = Bz, R^3 = Ph;
5g: R^1 = Bu, R^2 = Ph, R^3 = Ph; **5h**: R^1 = Bu, R^2 = Bz, R^3 = 4-MePh;
5i: R^1 = Ph, R^2 = Ph, R^3 = i-Pr; **5j**: R^1 = Bu, R^2 = 4-MeOPh, R^3 = Ph;
5k: R^1 = Ph, R^2 = Bz, R^3 = 4-MePh;

Scheme 2 Synthesis of pseudopeptides bearing the CF_2 unit *via* Ugi reaction.

At the final stage of the strategy, we tried to remove the inactive protection group (PhS) using Bu_3SnH/AIBN according to the literature method.[20] The deprotection of **5a** was studied as a model reaction. After stirring at 90 °C for 24 h in toluene, the desired product **6a** was isolated in only about 20% yield. Several attempts have been put forth to improve yields including prolonging the reaction time and elevating the reaction temperature, but failed to enhance the yield of **6a** above 40%. In the end, the good result (75% isolated yield) for this reaction was achieved by adding two equivalent of Bu_3SnH to the solution in approximately two equal portions over a period of 16 h. Thus, the PhS group on Ugi products **5b–k** could be cleaved smoothly using the reaction conditions optimized for **5a** and the final target compounds **6b–k** were obtained in good yields (Scheme 3).



Scheme 3 Synthesis of pseudopeptides containing CF_2H group.

Conclusion

In summary, we have presented a general and efficient synthesis strategy that uses common reaction conditions to transform relatively simple and similar substrates into more and complex molecules having terminal CF_2H functionality. The core of this approach is the conscious design and synthesis of new difluorinated building blocks which contain an inactive group (easily introduced and removed) and a reactive group on each side of the CF_2 group. To explore the validity and feasibility of this protocol, we reported the realization of this strategy by detailing the first example of Ugi four component reaction for the synthesis of CF_2H-bearing pseudopeptides using phenylthio as protecting group and Bu_3SnH/AIBN for PhS removal at the beginning and end of the route, respectively. The synthesis of more complex CF_2-bearing molecules and the evaluation and optimization of this strategy with new difluorinated building blocks are in progress and will be reported in due course.

Experimental

General methods

All reagents were of analytical grade, and obtained from commercial suppliers and used with further purification. Melting points were measured in an open capillary using Büchi melting point B-540 apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer (400 MHz and 100 MHz, respectively) using TMS as internal standard. The ^{19}F NMR were obtained using a Bruker AM-400 spectrometer (376 MHz) and measured with external CF_3CO_2H as the standard. $CDCl_3$ was used as the NMR solvent in all cases. Gas chromatography-mass spectra (GC-MS) were recorded on HP 5973 MSD with 6890 GC. High resolution mass spectra (HRMS) were recorded under electron impact conditions using a MicroMass GCT CA 055 instrument and recorded on a MicroMass LCTTM spectrometer. Column chromatography was carried out with Merck 60 (230-400 mesh) silica gel.

Ethyl 2,2-difluoro-2-(phenylthio)acetate (1). NaH (0.26 g, 11 mmol) was added to a solution of thiophenol (1.10 g, 10 mmol) in DMSO (10 mL) at room temperature. After the mixture was stirred for 1 h, ethyl bromodifluoroacetate (2.23 g, 11 mmol) was added to the solution. The mixture was stirred at the same temperature for 15 h (TLC), quenched with aqueous NH_4Cl solution and extracted with Et_2O. The organic layer was washed successively with water and brine, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was chromatographed on a silica gel column to give **1**. Yield: 87%. GC-MS: m/z = 232, 159, 109, 77.

2,2-Difluoro-2-(phenylthio)acetamide (2). Ammonia was bubbled through a solution of acetate **1** (1.16 g, 5 mmol) in methanol (10 mL) for 1 h (TLC) and then the mixture was concentrated *in vacuo*, a white solid product **2** was obtained. The resultant solid was directly used for the next step without further purification. Yield: 98%. Mp = 114.4–115.0 °C. GC-MS: m/z = 203, 159, 110, 77.

2,2-Difluoro-2-(phenylthio)ethanamine (3). A solution of the amide **2** (1.12 g, 5 mmol) in dry diethyl ether (10 mL) was added dropwise to a suspension of lithium aluminium hydride (0.38 g, 10 mmol) in dry diethyl ether (10 mL) at 0 °C under argon atmosphere. The reaction mixture was then stirred at 0 °C for 1 h, and quenched with H_2O (1 mL) in order to destroy the excess of lithium aluminium hydride. The resulting suspension was stirred for 30 more minutes and filtered. The filtrate was diluted with ethyl acetate, washed successively with H_2O and brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to leave the crude product. The resultant crude residue was purified by chromatography to obtain the product **3**. Yield: 45%, light-yellow liquid, ^{1}H NMR: δ = 7.63 (d, J = 7.3 Hz, 2H), 7.47-7.38 (m, 3H), 3.13 (t, J = 12.6 Hz, 2H), 1.49 (s, 2H); ^{13}C NMR: δ = 136.2, 129.9, 129.4 (t, $^1J_{CF}$ = 279.4 Hz), 129.2, 126.7, 48.6 (t, $^2J_{CF}$ = 27.5 Hz); ^{19}F NMR: δ = −82.2 (t, J = 12.5 Hz); GC-MS: m/z = 189, 160, 109, 77.

(1,1-Difluoro-2-isocyanoethyl)(phenyl)sulfane (4). The amine **3** (0.95 g, 5.00 mmol) and 20 mL ethyl formate were added into a flask and the mixture was stirred 12 h (GC-MS) at room temperature and then concentrated *in vacuo*, a light-yellow liquid product *N*-(2,2-difluoro-2-(phenylthio)ethyl) formamide was obtained quantitatively. The resultant liquid was directly used for the next step without further purification. *N*-(2,2-difluoro-2-(phenylthio)ethyl)formamide (1.08 g, 5 mmol), PPh_3 (2.60 g, 10 mmol), CCl_4 (1.0 mL, 10 mmol), triethylamine (1.4 mL, 10 mmol) and dry CH_2Cl_2 (20 mL) were added into a flask and the mixture was stirred at 40 °C for about 1.5 h (GC-MS). Then, the dark brown reaction mixture was cooled to room temperature. Subsequently, the mixture was poured into cool water and extracted with CH_2Cl_2 (50 mL × 3). The organic layer was washed successively with H_2O (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to get the crude product. The resultant crude residue was purified by chromatography, and isocyanide **4** was obtained. Yield: 70%, light-yellow liquid, ^{1}H NMR: δ = 7.67 (d, J = 7.5 Hz, 2H), 7.52 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 3.87 (t, J = 11.0 Hz, 2H); ^{13}C NMR: δ = 162.7, 136.5, 130.9, 129.7, 125.1, 124.7 (t, $^1J_{CF}$ = 281.7 Hz), 47.3 (t, $^2J_{CF}$ = 33.3 Hz); ^{19}F NMR: δ = −80.6 (t, J = 11.0 Hz); GC-MS: m/z = 199, 159, 135, 117, 109, 77. HRMS (EI): calcd for $C_9H_7F_2NS$ (M^+): 199.0267, found: 199.0263.

General procedure for compounds 5a–k

To a stirred amine (1 mmol), aldehyde (1 mmol) was added in portions for about 5 min. The mixture was stirred for 30 min again at room temperature. Then, the reaction mixture was heated to 60 °C and the isocyanide **4** (1 mmol) and carboxylic acid (1 mmol) were added. Stirring was continued at 60 °C for 1 h (TLC). The crude residue was purified by chromatography to give the desired products **5**.

***N*-(2-(2,2-difluoro-2-(phenylthio)ethylamino)-2-oxo-1-phenylethyl)-*N*-phenylbenzamide (5a).** White solid. Yield: 84%. Mp: 155.2–156.3 °C, ^{1}H NMR: δ = 7.59 (d, J = 7.3 Hz, 2H), 7.46-7.28 (m, 10H), 7.23-7.12 (m, 3H), 7.06-7.01 (m, 5H), 6.58 (t, J = 6.0 Hz, 1H), 6.25 (s, 1H), 4.07-3.85 (m, 2H);^{13}C NMR: δ = 171.4, 169.9, 141.3, 136.4, 135.7, 134.0, 130.1, 130.0, 130.0, 129.7, 129.2, 128.6, 128.5, 128.5, 127.6 (t, $^1J_{CF}$ = 280.3 Hz), 127.3, 125.9, 67.0, 44.8 (t, $^2J_{CF}$ = 28.7 Hz); ^{19}F NMR: δ = −78.9 (dt, J_{F-F} = 212.4 Hz, J_{H-F} = 12.5 Hz, 1F), −79.5 (dt, J_{F-F} = 212.4 Hz, J_{H-F} = 12.5 Hz, 1F).

***N*-(1-(benzo[*d*][1,3]dioxol-5-yl)-2-(2,2-difluoro-2-(phenylthio)-ethylamino)-2-oxoethyl)-*N*-phenylbenzamide (5b).** White solid. Yield: 82%. Mp: 133.2–134.1 °C, ^{1}H NMR: δ = 7.60 (d, J = 7.5 Hz, 2H), 7.46-7.31 (m, 5H), 7.22-7.02 (m, 8H), 6.81 (d, J = 8.7 Hz, 2H), 6.71 (d, J = 7.8 Hz, 1H), 6.51 (t, J = 6.0 Hz, 1H), 6.14 (s, 1H), 5.94 (s, 2H), 4.01-3.90 (m, 2H); ^{13}C NMR: δ = 171.4, 169.8, 147.8, 147.7, 141.2, 136.4, 135.7, 130.1, 129.6, 129.2, 128.6, 127.6 (t, $^1J_{CF}$ = 279.9 Hz), 127.4, 125.9, 124.2, 110.5, 108.2, 101.2, 66.5, 44.9 (t, $^2J_{CF}$ = 28.8 Hz); ^{19}F NMR: δ = −78.9 (dt, J_{F-F} = 212.0 Hz, J_{H-F} = 12.6 Hz, 1F), −79.5 (dt, J_{F-F} = 212.3 Hz, J_{H-F} = 12.7 Hz, 1F).

***N*-(2-(2,2-difluoro-2-(phenylthio)ethylamino)-1-(4-methoxyphenyl)-2-oxoethyl)-*N*-phenylbenzamide (5c).** White solid. Yield: 80%. Mp: 162.1–163.0 °C, ^{1}H NMR: δ = 7.59 (d, J = 7.5 Hz, 2H), 7.46-7.32 (m, 5H), 7.23-6.99 (m, 10H), 6.79 (d, J = 8.6 Hz, 2H), 6.48 (t, J = 5.8 Hz, 1H), 6.25 (s, 1H), 4.06-3.85 (m, 2H), 3.78 (s, 3H); ^{13}C NMR: δ = 171.4, 170.0, 159.8, 141.1, 136.4, 135.8, 131.6, 130.2, 130.1, 129.6, 129.2, 128.6, 128.5, 127.6 (t, $^1J_{CF}$ = 280.2 Hz), 127.3, 125.9, 113.9, 66.0, 55.2, 44.9 (t, $^2J_{CF}$ = 28.7 Hz); ^{19}F NMR: δ = −78.9 (dt, J_{F-F} = 212.5 Hz, J_{H-F} = 12.6 Hz, 1F), −79.5 (dt, J_{F-F} = 212.0 Hz, J_{H-F} = 12.7 Hz, 1F).

***N*-(2-(2,2-difluoro-2-(phenylthio)ethylamino)-2-oxo-1-*p*-tolylethyl)-*N*-phenylbenzamide (5d).** White solid. Yield: 79%. Mp: 125.0–125.8 °C, ^{1}H NMR: δ = 7.59 (d, J = 7.4 Hz, 2H), 7.46-7.33 (m, 5H), 7.22-7.02 (m, 12H), 6.51 (t, J = 6.0 Hz, 1H), 6.20 (s, 1H), 4.02-3.89 (m, 2H), 3.32 (s, 3H); ^{13}C NMR: δ = 171.4, 169.9, 141.5, 138.5, 136.4, 135.8, 131.0, 130.1, 130.0, 129.9, 129.6, 129.3, 129.2, 128.6, 128.5, 127.6 (t, $^1J_{CF}$ = 280.0 Hz), 127.3, 125.9, 66.7, 44.8 (t, $^2J_{CF}$ = 28.9 Hz), 21.1; ^{19}F NMR: δ = −78.9 (dt, J_{F-F} = 212.3 Hz, J_{H-F} = 12.3 Hz, 1F), −79.5 (dt, J_{F-F} = 212.4 Hz, J_{H-F} = 12.0 Hz, 1F).

***N*-butyl-*N*-(2-(2,2-difluoro-2-(phenylthio)ethylamino)-2-oxo-1-phenylethyl)benzamide (5e).** White solid. Yield: 74%. Mp: 119.0–120.0 °C, ^{1}H NMR: δ = 7.62 (d, J = 7.4 Hz, 2H), 7.48-7.37 (m, 13H), 6.98 (s, 1H), 5.77 (s, 1H), 4.02-3.86 (m, 2H), 3.36-3.24 (m, 2H), 1.44 (s, 1H), 1.09-0.97 (m, 3H), 0.63 (s, 3H); ^{13}C NMR: δ = 172.9, 170.1, 136.4, 134.7, 130.1, 129.7, 129.3, 129.0, 128.9, 128.6, 128.5, 127.6 (t, $^1J_{CF}$ = 280.3 Hz), 126.6, 125.9, 66.3, 44.7 (t, $^2J_{CF}$ = 28.8 Hz), 31.3, 31.1, 19.8, 13.3; ^{19}F NMR: δ = −79.2 (s).

***N*-benzyl-*N*-(2-(2,2-difluoro-2-(phenylthio)ethylamino)-2-oxo-1-phenylethyl)benzamide (5f).** White solid. Yield: 78%. Mp: 120.2–121.1 °C, ^{1}H NMR: δ = 7.57 (d, J = 7.5 Hz, 2H), 7.52 (d, J = 7.2 Hz, 2H), 7.46-7.33 (m, 11H), 7.21-7.16 (m, 3H), 7.09 (d, J = 7.1 Hz, 2H), 6.35 (s, 1H), 5.57 (s, 1H), 4.79 (d, J = 16.5 Hz, 1H), 4.51 (d, J = 16.5 Hz, 1H), 3.91-3.83 (m, 2H); ^{13}C NMR: δ = 173.3, 169.5, 136.4, 135.9, 134.2, 130.1, 130.0, 129.5, 129.2, 128.9, 128.8, 128.5, 128.4, 127.5 (t, $^1J_{CF}$ = 280.4 Hz), 127.1, 127.0, 126.8, 125.9, 65.1, 60.4, 44.8 (t, $^2J_{CF}$ = 28.9 Hz); ^{19}F NMR: δ = −78.9 (dt, J_{F-F} = 212.6 Hz, J_{H-F} = 12.5 Hz, 1F), −79.5 (dt, J_{F-F} = 212.7 Hz, J_{H-F} = 12.4 Hz, 1F).

***N*-(2-(2,2-difluoro-2-(phenylthio)ethylamino)-2-oxo-1-phenylethyl)-*N*-phenylpentanamide (5g).** White solid. Yield: 65%. Mp: 107.0–108.0 °C, ^{1}H NMR: δ = 7.57 (d, J = 7.4 Hz, 2H), 7.45-7.35 (m, 4H), 7.23-7.15 (m, 9H), 6.34 (s, 1H), 6.11 (s, 1H), 3.98-3.84 (m, 2H), 2.10-2.05 (m, 2H), 1.60-1.56 (m, 2H), 1.27-1.17 (m, 2H), 0.80 (t, J = 7.3 Hz, 3H); ^{13}C NMR: δ = 174.1, 170.0, 140.2, 136.4, 133.9, 130.2, 130.1, 129.2, 129.0, 128.5, 128.3, 128.2, 127.6 (t, $^1J_{CF}$ = 284.1 Hz), 125.9, 65.3, 44.8 (t, $^2J_{CF}$ = 28.9 Hz), 34.5, 27.4, 22.3, 13.8; ^{19}F NMR: δ = −78.9 (dt, J_{F-F} = 212.2 Hz, J_{H-F} = 12.3 Hz, 1F), −79.5 (dt, J_{F-F} = 212.0 Hz, J_{H-F} = 12.6 Hz, 1F).

***N*-benzyl-*N*-(2-(2,2-difluoro-2-(phenylthio)ethylamino)-2-oxo-1-*p*-tolylethyl)pentanamide (5h).** White solid. Yield: 63%. Mp: 94.1–95.2 °C, ^{1}H NMR: δ = 7.56 (d, J = 7.3 Hz, 2H), 7.45-7.34 (m, 3H), 7.24-7.14 (m, 5H), 7.08 (d, J = 7.7 Hz, 2H), 7.03 (d, J = 7.0 Hz, 2H), 6.17 (t, J = 5.8 Hz, 1H), 5.87 (s, 1H), 4.72 (d, J = 17.3 Hz, 1H), 4.50 (d, J = 17.5 Hz, 1H), 3.97-3.76 (m, 2H), 2.33-2.21 (m, 4H), 1.69-1.54 (m, 3H), 1.27 (dd, J = 14.4, 7.3 Hz, 2H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR: δ = 175.2, 170.1, 138.6, 137.5, 136.4, 130.1, 129.7, 129.5, 129.2, 128.6 (t, $^1J_{CF}$ = 279.9 Hz), 128.4, 127.0, 126.2, 120.2, 63.3, 50.3, 44.9 (t, $^2J_{CF}$ = 28.6 Hz), 33.7, 27.3, 22.4, 21.1, 13.8; ^{19}F NMR: δ = −78.9 (dt, J_{F-F} = 212.1 Hz, J_{H-F} = 12.5 Hz, 1F), −79.5 (dt, J_{F-F} = 212.1 Hz, J_{H-F} = 12.8 Hz, 1F).

***N*-(1-(2,2-difluoro-2-(phenylthio)ethylamino)-3-methyl-1-oxobutan-2-yl)-*N*-phenylbenzamide (5i).** White solid. Yield: 55%. Mp: 98.3–99.5 °C, ^{1}H NMR: δ = 8.06 (s, 1H), 7.66-7.64 (m, 2H), 7.48-7.37 (m, 3H), 7.31-7.29 (m, 2H), 7.26-7.13 (m, 8H), 4.40 (d, J = 11.1 Hz, 1H), 4.04-3.82 (m, 2H), 2.84-2.73 (m, 1H), 1.16 (d, J = 6.5 Hz, 3H), 1.08 (d, J = 6.6 Hz, 3H); ^{13}C NMR: δ = 172.7, 171.1, 136.4, 136.0, 130.1, 129.9, 129.2, 129.1, 128.6, 128.5, 127.8 (t, $^1J_{CF}$ = 280.5 Hz), 127.4, 126.1, 44.3 (t, $^2J_{CF}$ = 28.9 Hz), 26.8, 20.2, 19.9; ^{19}F NMR: δ = −79.1 (t, J = 12.1 Hz).

***N*-(2-(2,2-difluoro-2-(phenylthio)ethylamino)-2-oxo-1-phenylethyl)-*N*-(4-methoxyphenyl)pentanamide (5j).** White solid. Yield: 62%. Mp: 128.0–128.9 °C, ^{1}H NMR: δ = 7.56 (d, J = 7.5 Hz, 2H), 7.44-7.13 (m, 10H), 6.70 (s, 2H), 6.32 (s, 1H), 6.14 (s, 1H), 4.00-3.79 (m, 2H), 3.75 (s, 3H), 2.20-1.99 (m, 2H), 1.60-1.52 (m, 2H), 1.26-1.17 (m, 2H), 0.80 (t, J = 7.31 Hz, 3H); ^{13}C NMR: δ = 174.6, 170.1, 159.1, 136.4, 134.0, 132.7, 131.3, 130.5, 130.1, 129.2, 128.4, 128.3, 127.6 (t, $^1J_{CF}$ = 280.3 Hz), 125.9, 114.0, 64.9, 55.3, 44.8 (t, $^2J_{CF}$ = 29.1 Hz), 34.4, 27.4, 22.3, 13.8; ^{19}F NMR: δ = −78.8 (dt, J_{F-F} = 211.9 Hz, J_{H-F} = 12.4 Hz, 1F), −79.5 (dt, J_{F-F} = 211.7 Hz, J_{H-F} = 12.6 Hz, 1F).

***N*-benzyl-*N*-(2-(2,2-difluoro-2-(phenylthio)ethylamino)-1-(4-methoxyphenyl)-2-oxoethyl)benzamide (5k).** White solid. Yield: 77%. Mp: 53.5–54.2 °C, ^{1}H NMR: δ = 7.59 (d, J = 7.3 Hz, 2H), 7.53-7.37 (m, 10H), 7.24-7.19 (m, 3H), 7.11 (d, J = 6.7 Hz, 2H), 6.86 (d, J = 6.7 Hz, 2H), 6.22 (s, 1H), 5.50 (s, 1H), 4.78 (d, J = 16.6 Hz, 1H), 4.47 (d, J = 16.4 Hz, 1H), 3.95-3.85 (m, 2H), 3.82 (s, 3H); ^{13}C NMR: δ = 173.2, 169.8, 159.9, 136.4, 135.9, 131.1, 130.2, 130.0, 129.3, 128.5, 128.4, 127.5 (t, $^1J_{CF}$ = 280.0 Hz), 127.1, 127.1, 126.8, 126.0, 125.9, 114.3, 64.1, 60.4, 55.3, 44.8 (t, $^2J_{CF}$ = 28.7 Hz); ^{19}F NMR: δ = −79.2 (d, J = 11.9 Hz, 1F), −79.3 (d, J = 11.6 Hz, 1F).

General procedure for compounds 6a–k

To a solution of **5** (0.5 mmol) in dry toluene (1 mL) was added Bu_3SnH (150 mg, 0.5 mmol) under argon atmosphere. Deoxygenation was continued for 5 min. Azo-bis-isobutryonitrile (AIBN) (13 mg, 0.08 mmol) was added and the solution was heated at 90 °C for 8 h. Another portion of Bu_3SnH (150 mg, 0.5 mmol) was added and stirring was continued for 8 h (TLC). The mixture was concentrated under reduced pressure and the residue was dissolved in EtOAc (5 mL). The solution was stirred overnight with KF/H_2O (15 mg/0.15 mL) and extracted with EtOAc (20 mL × 3). The organic phase was washed successively with water (20 mL) and brine (20 mL), and dried over anhydrous Na_2SO_4. After solvent removal, the crude product was purified by chromatography to give desired products **6**.

***N*-(2-(2,2-difluoroethylamino)-2-oxo-1-phenylethyl)-*N*-phenylbenzamide (6a).** White solid. Yield: 65%. Mp: 122.2–123.0 °C, ^{1}H-NMR: δ = 7.31-7.28 (m, 7H), 7.19-6.97 (m, 8H), 6.27 (s, 1H), 6.08 (s, 1H), 5.90 (tt, J = 56.0, 3.9 Hz, 1H), 3.80-3.60 (m, 2H); ^{13}C NMR: δ = 171.3, 170.3, 141.5, 135.6, 134.1, 129.9, 129.8, 129.7, 128.8, 128.7, 128.6, 128.5, 127.6, 127.3, 113.5 (t, $^1J_{CF}$ = 241.6 Hz), 67.4, 42.1 (t, $^2J_{CF}$ = 26.8 Hz); ^{19}F NMR: δ = −122.8 (dt, J = 56.7, 14.8 Hz); HRMS (ESI): calcd for $C_{23}H_{20}F_2N_2O_2$ ([M+H]$^+$): 395.1571, found: 395.1555.

***N*-(1-(benzo[*d*][1,3]dioxol-5-yl)-2-(2,2-difluoroethylamino)-2-oxoethyl)-*N*-phenylbenzamide (6b).** White solid. Yield: 67%. Mp: 62.3–63.0 °C, ^{1}H NMR: δ = 7.31 (d, J = 7.1 Hz, 2H), 7.22-6.98 (m, 8H), 6.82-6.70 (m, 3H), 6.25 (s, 1H), 5.96 (s, 1H), 5.95 (s, 2H), 5.91 (tt, J = 56.0, 4.2 Hz, 1H), 3.78-3.65 (m, 2H); ^{13}C NMR: δ = 171.3, 170.3, 148.0, 147.9, 141.5, 135.6, 129.9, 129.7, 128.6, 128.5, 127.8, 127.6, 127.4, 124.0, 113.5 (t, $^1J_{CF}$ = 241.6 Hz), 110.2, 108.3, 101.3, 67.0, 42.1 (t, $^2J_{CF}$ = 26.7 Hz); ^{19}F NMR: δ = −122.8 (dt, J = 56.2, 14.7 Hz); HRMS (ESI): calcd for $C_{24}H_{20}F_2N_2O_4$ ([M+H]$^+$): 439.1469, found: 439.1455.

***N*-(2-(2,2-difluoroethylamino)-1-(4-methoxyphenyl)-2-oxoethyl)-*N*-phenylbenzamide (6c).** White solid. Yield: 69%. Mp: 136.5–137.2 °C, ^{1}H NMR: δ = 7.31 (d, J = 7.3 Hz, 2H), 7.21-6.97 (m, 10H), 6.80 (d, J = 8.6 Hz, 2H), 6.25 (s, 1H), 6.08 (s, 1H), 5.91 (tt, J = 56.1, 4.1 Hz, 1H), 3.78 (s, 3H), 3.76-3.60 (m, 2H); ^{13}C NMR: δ = 171.3, 170.6, 159.8, 141.3, 135.8, 131.5, 130.1, 129.6, 128.5, 127.6, 127.3, 126.1, 114.0, 113.6 (t, $^1J_{CF}$ = 241.5 Hz), 66.3, 55.2, 42.1 (t, $^2J_{CF}$ = 26.7 Hz); ^{19}F NMR: δ = −122.8 (dt, J = 56.0, 14.8 Hz); HRMS (ESI): calcd for $C_{24}H_{22}F_2N_2O_3$ ([M+H]$^+$): 425.1677, found: 425.1673.

***N*-(2-(2,2-difluoroethylamino)-2-oxo-1-*p*-tolylethyl)-*N*-phenylbenzamide (6d).** White solid. Yield: 70%. Mp: 111.5–112.3 °C, ^{1}H NMR: δ = 7.32 (d, J = 7.1 Hz, 2H), 7.22-7.05 (m, 10H), 6.99-6.98 (m, 2H), 6.25 (s, 1H), 6.04 (s, 1H), 5.91 (tt, J = 56.1, 4.1 Hz, 1H), 3.75-3.64 (m, 2H), 2.32 (s, 3H); ^{13}C NMR: δ = 171.3, 170.6, 141.5, 138.7, 135.8, 131.1, 129.9, 129.8, 129.6, 129.4, 128.6, 127.6, 127.3, 113.6 (t, $^1J_{CF}$ = 241.5 Hz), 110.6, 67.1, 42.1 (t, $^2J_{CF}$ = 26.8 Hz), 21.1; ^{19}F NMR: δ = −122.8 (dt, J = 56.3, 14.3 Hz); HRMS (ESI): calcd for $C_{24}H_{22}F_2N_2O_2$ ([M+H]$^+$): 409.1728, found: 409.1719.

***N*-butyl-*N*-(2-(2,2-difluoroethylamino)-2-oxo-1-phenylethyl)-benzamide (6e).** White solid. Yield: 70%. Mp: 104.0–105.2 °C, ^{1}H NMR: δ = 7.42-7.38 (m, 10H), 6.70 (s, 1H), 5.88 (tt, J = 56.1, 3.6 Hz, 1H), 5.66 (s, 1H), 3.69-3.58 (m, 2H), 3.31-3.21 (m, 2H), 1.37-1.31 (m, 1H), 1.06-1.02 (m, 3H), 0.60 (s, 3H); ^{13}C NMR: δ = 172.9, 170.6, 136.3, 134.8, 129.7, 129.0, 128.9, 128.7, 128.5, 126.5, 113.5 (t, $^1J_{CF}$ = 241.6 Hz), 64.2, 49.1, 41.9 (t, $^2J_{CF}$ = 26.6 Hz), 31.1, 19.7, 13.3; ^{19}F NMR: δ = −122.8 (d, J = 53.2 Hz); HRMS (ESI): calcd for $C_{21}H_{24}F_2N_2O_2$ ([M+H]$^+$): 375.1884, found: 375.1877.

***N*-benzyl-*N*-(2-(2,2-difluoroethylamino)-2-oxo-1-phenylethyl)-benzamide (6f).** White solid. Yield: 76%. Mp: 112.0–113.0 °C, ^{1}H NMR: δ = 7.52 (d, J = 7.6 Hz, 2H), 7.41-7.35 (m, 8H), 7.25-7.18 (m, 5H), 6.12 (s, 1H), 5.86 (t, J = 56.1 Hz, 1H), 5.32 (s, 1H), 4.78 (d, J = 16.6 Hz, 1H), 4.41 (d, J = 16.1 Hz, 1H), 3.68-3.53 (m, 2H); ^{13}C NMR: δ = 173.1, 170.0, 135.7, 134.3, 130.1, 129.4, 129.1, 129.0, 128.6, 127.4, 127.0, 126.8, 113.5 (t, $^1J_{CF}$ = 241.6 Hz), 67.7, 65.0, 42.0 (t, $^2J_{CF}$ = 26.9 Hz); ^{19}F NMR: δ = −122.8 (d, J = 55.4 Hz); HRMS (ESI): calcd for $C_{24}H_{22}F_2N_2O_2$ ([M+H]$^+$): 409.1728, found: 409.1715.

***N*-(2-(2,2-difluoroethylamino)-2-oxo-1-phenylethyl)-*N*-phenylpentanamide (6g).** White solid. Yield: 51%. Mp: 88.0–89.1 °C, ^{1}H NMR: δ = 7.25-7.13 (m, 10H), 6.09 (s, 1H), 5.98 (s, 1H), 5.87 (tt, J = 56.0, 4.1 Hz, 1H), 3.73-3.62 (m, 2H), 2.09-2.04 (m, 2H), 1.59-1.55 (m, 2H), 1.27-1.19 (m, 2H), 0.81 (t, J = 7.4 Hz, 3H); ^{13}C NMR: δ = 174.1, 170.6, 140.3, 134.0, 130.2, 130.1, 129.0, 128.6, 128.5, 128.2, 113.5 (t, $^1J_{CF}$ = 241.6 Hz), 65.6, 42.0 (t, $^2J_{CF}$ = 26.7 Hz), 34.5, 27.4, 22.3, 13.8; ^{19}F NMR: δ = −122.8 (dt, J = 56.0, 14.8 Hz); HRMS (ESI): calcd for $C_{21}H_{24}F_2N_2O_2$ ([M+H]$^+$): 375.1884, found: 375.1873.

***N*-benzyl-*N*-(2-(2,2-difluoroethylamino)-2-oxo-1-*p*-tolylethyl)-pentanamide (6h).** White solid. Yield: 54%. Mp: 63.0-63.9 °C, ^{1}H NMR: δ = 7.27-7.18 (m, 4H), 7.11-7.08 (m, 4H), 6.30 (s, 1H), 5.84 (tt, J = 56.1, 4.0 Hz, 1H), 5.74 (s, 1H), 3.73-3.62 (m, 2H), 4.73 (d, J = 17.6 Hz, 1H), 4.47 (d, J = 18.6 Hz, 1H), 3.69-3.53 (m, 2H), 2.38-2.26 (m, 4H), 1.83-1.58 (m, 3H), 1.29 (dd, J = 14.2, 7.8 Hz, 2H), 0.86 (t, J = 7.3 Hz, 2H); ^{13}C NMR: δ = 175.1, 170.7, 138.7, 137.4, 131.5, 129.6, 129.5, 128.5, 127.1, 126.2, 113.6 (t, $^1J_{CF}$ = 241.5 Hz), 63.3, 50.3, 41.9 (t, $^2J_{CF}$ = 26.9 Hz), 33.7, 27.3, 22.4, 21.1, 13.8; ^{19}F NMR: δ = −122.7 (dt, J = 56.1, 14.6 Hz); HRMS (ESI): calcd for $C_{23}H_{28}F_2N_2O_2$ ([M+H]$^+$): 403.2197, found: 403.2189.

***N*-(1-(2,2-difluoroethylamino)-3-methyl-1-oxobutan-2-yl)-*N*-phenylbenzamide (6i).** White solid. Yield: 64%. Mp: 94.0–94.9 °C, ^{1}H NMR: δ = 7.85 (s, 1H), 7.35-7.29 (m, 2H), 7.28-7.08 (m, 8H), 5.90 (tt, J = 56.1, 4.0 Hz, 1H), 4.41 (d, J = 11.3 Hz, 1H), 3.76-3.66 (m, 2H), 2.80-2.74 (m, 1H), 1.17 (d, J = 6.50 Hz, 3H), 1.07 (d, J = 6.60 Hz, 3H); ^{13}C NMR: δ = 172.7, 171.5, 142.6, 135.9, 130.0, 129.1, 128.6, 128.3, 127.9, 127.4, 113.5 (t, $^1J_{CF}$ = 241.7 Hz), 41.6 (t, $^2J_{CF}$ = 26.1 Hz), 26.9, 20.1, 19.9; ^{19}F NMR: δ = −122.9 (dt, J = 25.6, 15.4 Hz, 1F), −123.1 (dt, J = 24.7, 15.2 Hz, 1F); HRMS (ESI): calcd for $C_{20}H_{22}F_2N_2O_2$ ([M+H]$^+$): 361.1728, found: 361.1726.

***N*-(2-(2,2-difluoroethylamino)-2-oxo-1-phenylethyl)-*N*-(4-methoxyphenyl)pentanamide (6j).** Light-yellow viscous liquid. Yield: 52%. ^{1}H NMR: δ = 7.28-7.12 (m, 7H), 6.83-6.71 (m, 2H), 6.34 (d, J = 6.0 Hz, 1H), 6.08 (s, 1H), 5.86 (tt, J = 56.1, 4.2 Hz, 1H), 3.76(s, 3H), 3.70-3.60 (m, 2H), 2.08-2.03 (m, 2H), 1.57-1.52 (m, 2H), 1.29-1.19 (m, 2H), 0.81 (t, J = 7.3 Hz, 3H); ^{13}C NMR: δ = 174.6, 170.8, 159.0, 134.2, 132.7, 131.3, 130.3, 128.5, 128.4, 114.0, 113.6 (t, $^1J_{CF}$ = 241.6 Hz), 65.1, 55.3, 42.0 (t, $^2J_{CF}$ = 26.7 Hz), 34.4, 27.4, 22.3, 13.8; ^{19}F NMR: δ = −122.7 (dt, J = 56.0, 14.8 Hz); HRMS (ESI): calcd for $C_{22}H_{26}F_2N_2O_3$ ([M+H]$^+$): 405.1990, found: 405.1980.

***N*-benzyl-*N*-(2-(2,2-difluoroethylamino)-1-(4-methoxyphenyl)-2-oxoethyl)benzamide (6k).** White solid. Yield: 72%. Mp: 137.5-138.4 °C, ^{1}H NMR: δ = 7.53 (d, J = 6.7 Hz, 2H), 7.44-7.35 (m, 5H), 7.27-7.20 (m, 5H), 6.88 (d, J = 8.4 Hz, 2H), 6.05 (s, 1H), 5.89 (t, J = 62.3 Hz, 1H), 5.23 (s, 1H), 4.77 (d, J = 16.6 Hz, 1H), 4.39 (d, J = 15.9 Hz, 1H), 3.83 (s, 3H), 3.71-3.53 (m, 2H); ^{13}C

NMR: $\delta = 173.1$, 170.3, 160.0, 136.8, 136.7, 135.7, 131.0, 130.1, 128.6, 127.3, 127.0, 126.8, 126.2, 114.5, 113.5 (t, $^1J_{CF} = 241.8$ Hz), 64.3, 60.4, 53.4, 42.0 (t, $^2J_{CF} = 26.9$ Hz); ^{19}F NMR: $\delta = -122.8$ (d, $J = 56.0$ Hz); HRMS (ESI): calcd for $C_{25}H_{24}F_2N_2O_3$ ($[M+H]^+$): 439.1833, found: 439.1828.

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