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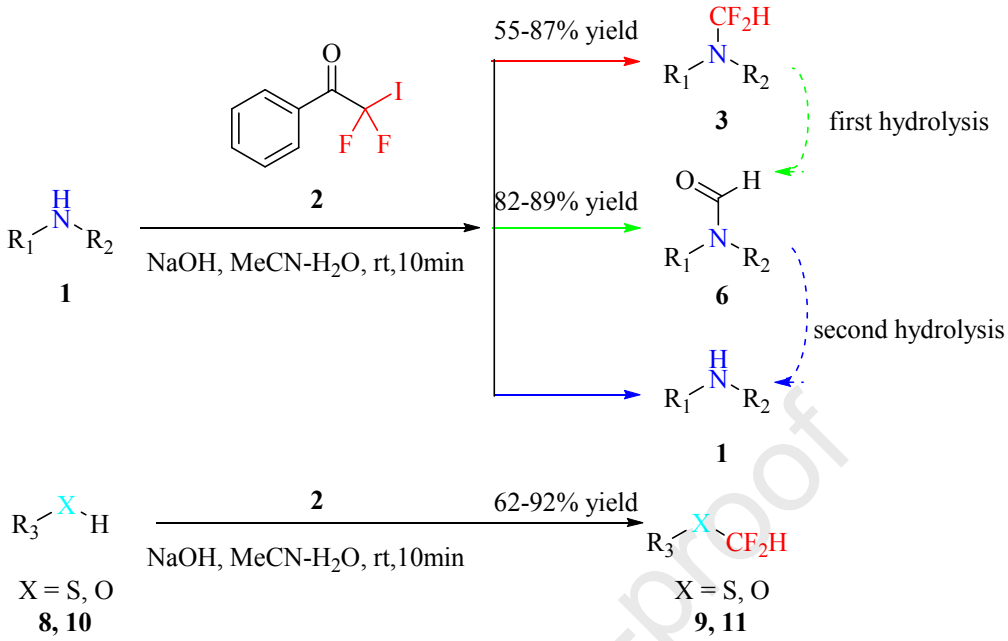
Graphical Abstract



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Study on the mild, rapid and selective difluorocarbene-mediated triclassification of iododifluoroacetophenone with secondary amines and tree model for product classification

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ABSTRACT

Difluorocarbene is a very active and widely used intermediate in organic synthesis. In this work, a room temperature difluorocarbene-mediated triclassification reaction of iododifluoroacetophenone (**2**) and secondary amines with mild condition, short reaction time (only 10 min) and high selectivity had been studied, which produced one of the following three substances: N-CF_2H derivatives (up to 87% yield), formamides (82-89% yield) or the recycled starting secondary amines. This phenomenon was related to the structural stability of the corresponding products. If unstable, it would be hydrolyzed to formamides first, and then further hydrolyzed to starting amines. Based on the geometric structure of the raw materials, the corresponding prediction tree model was established, which provided guidance for the further application of difluoromethylation of Vemurafenib (**1ee**) and AZD9291 (**1ff**).

1. Introduction

Difluorocarbene (:CF_2), an electrophilic ground-state singlet carbine[1], has been extensively used for the synthesis of various structures, such as: tetrafluoroethene[2], -CF_2H[3], gem-difluorocyclopropanes[4], gem-difluoroalkenes[5], trifluoromethylthio group[6], -SCF_2-group[7], difluoro-substituted bicyclo[1.1.1]pentanes[8], difluoromethylene zwitterionic[9], trifluoromethylseleno group[10], trifluoromethoxyl group[11], cyanide anion[12]. Particularly, -CF_2H derivatives are attracting more and more research and application interests in many fields such as medicinal, pharmaceutical and agrochemical research, as well as material science[13], due to its distinctive physics, chemistry and biochemical characterization. The -CF_2H group is the lipophilic bioisostere of the carbonol, carbinol, alcohol, thiol, hydroxamic acid, or amide group [14]. Additionally, the -CF_2H group is weakly acidic [15] and can modulate the basicity of proximal amines [16]. Furthermore, the introduction of -CF_2H group into the molecules could improve their metabolic stability, membrane permeability and hydrogen interactions with proteins [15-16]. So, there are several bioactive molecules with -CF_2H group have been discovered, for examples: proton pump inhibitor (pantoprazole[17]), phophodiesterase-4 inhibitor (roflumilast[18]), COXs/5-LOX inhibitors (celecoxib's analogues[19]), GPR109a agonist (thiobarbituric acid derivative[20]), PI3K Inhibitors (ZSTK474 and its analogues [21]), fungicide (pyrimidinamine derivatives [22]), PI3K inhibitors (PQR530[23], PQR514[24], GDC-0077[25], O-GlcNAcase inhibitor (MK-8719[26]), calcium blocker (riodipine[27]), antibiotic (flomoxef [28]). The published difluoromethylation reactions could be classified into these strategies: Cl/F-exchange [29], deoxofluorination[30], difluorocarbene route[31] and radical-participated singleelectron-transfer (SET) pathway[32].

Among the important organic compounds, formamides have become an important class of compounds because of their wide application in the synthesis of pesticides, herbicides and drugs [33]. Additionally formamides are significant intermediates towards the synthesis of isocyanate[34], formamidine[35], nitrile[34], quinolone antibiotics[36], and 1,2-dihydroquinolines[37].

In this work, Iododifluoroacetophenone (**2**), recently reported as a building block in a series of radical reactions by our group [38], was employed as a difluorocarbene source and, considering the reaction temperature and reaction rate together, had better performance than the reported conditions [39]. The reaction of compound **2** and secondary amines was a difluorocarbene-

mec 52

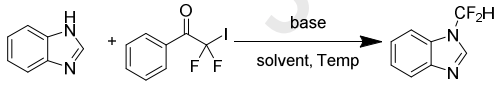
following three substances: N-CF_2H derivatives, formamides or the starting secondary amines. The corresponding classification tree model and its application in pharmaceutical chemistry research had been investigated in this work.

2. Results and discussion

Our initial study was the optimization of the reaction condition of benzimidazole **1a** with iododifluoroacetophenone **2** (Table 1). Firstly, a variety of reaction systems were screened (Table 1, entries 1-6), and only entry 6 furnished the corresponding product **3a** in 50% yield (entry 6). While increasing the reaction temperature, the yield of **3a** was not improved obviously (Table 1, entry 7). Gratifyingly, increasing the amount of **2** led to the improvement of the yield (Table 1, entries 8-10). Using 2.0 equiv. of compound **2** gave a good yield (77%)(entry 9), but when the amount of compound **2** was increased to 2.5 equiv.(entry 10), the yield of **3a** (76%) was not promoted. When anhydrous acetonitrile was used as solvent, the yield decreased to 48% (Table 1, entry 11). In addition, only 52% yield was achieved when the amount of NaOH was reduced to 5.5 equiv. (Table 1, entry 12). Further optimization studies revealed that the yield of **3a** decreased slightly when the KOH or LiOH was used as alkali source. It is worth noting that this reaction takes only 10 minutes according to the monitoring of TLC. The reaction condition of different ratio of the solvent mixture ($MeCN/H_2O$ = 5/1, 10/1 and 20/1, v/v)(entries 15, 9 and 16) was validated here with same product and the similar yield. Therefore, the ratio of the solvent mixture had no great influence. Here, the option $MeCN/H_2O$(10/1, v/v)was selected to form a certain concentration of aqueous NaOH (65 wt%).

Thereafter, the reactivity of reagent **2** and the similar potential difluorocarbene reagents, including $PhCOCF_2Cl$ (**4**), $PhCOCF_2Br$ (**5**), were compared (Table 2). It was found that compounds **4** and **5** were also able to act as difluorocarbene reagents, but slightly worse yields of **3a** were received. So, as shown in Table 2, compound **2** showed the best reaction effect among these three difluoroacetophenones.

Table 1. Optimization of reaction conditions for the difluoromethylation of **1a**

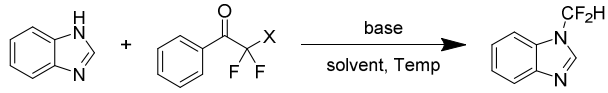


1a **2** **3a**

Entry	**2** (equiv.)	Base (equiv.)	Solvent	Temp (°C)	Time	Yield (%)[a]
1	1.0	Et_3N(2.0)	THF	rt	12h	0[b]
2	1.0	NaH(1.25)	DMSO	rt	12h	0[b]
3	1.0	NaH(1.0)	THF	rt	10min	39
4	1.0	NaH(1.25)	THF	rt	10min	38
5	1.0	NaH(2.0)	THF	rt	10min	32
6	1.0	NaOH(1.0)	$MeCN/H_2O$ (10/1)	rt	10min	50
7	1.0	NaOH(1.0)	$MeCN/H_2O$ (10/1)	50	10min	52
8	1.5	NaOH(1.0)	$MeCN/H_2O$ (10/1)	rt	10min	65
9	2.0	NaOH(1.0)	$MeCN/H_2O$ (10/1)	rt	10min	77
10	2.5	NaOH(1.0)	$MeCN/H_2O$ (10/1)	rt	10min	76
11	2.0	NaOH(1.0)	MeCN	rt	10min	48
12	2.0	KOH(11.0)	$MeCN/H_2O$ (10/1)	rt	10min	52
13	2.0	KOH(11.0)	$MeCN/H_2O$ (10/1)	rt	10min	75
14	2.0	LiOH(11.0)	$MeCN/H_2O$ (10/1)	rt	10min	62
15	2.0	NaOH(1 1.0)	$MeCN/H_2O$ (5/1)	rt	10min	77
16	2.0	NaOH(1 1.0)	$MeCN/H_2O$ (20/1)	rt	10min	77

[a] Isolated yields.
[b] No reaction, and after 12h, compound **2** and it's decomposition product ($PhCO_2CF_2H$) were monitored by TLC.

Table 2. Difluoromethylation of **1a** with different difluoroacetophenones



1a **3a**

Entry[a]	X	Base (equiv.)	Solvent	Temp (°C)	Time	Yield (%)[b]
1	Cl(**4**)	NaOH(11.0)	$MeCN/H_2O$ (10/1)	rt	10min	72
2	Br(**5**)	NaOH(11.0)	$MeCN/H_2O$ (10/1)O	rt	10min	70
3	I(**2**)	NaOH(11.0)	$MeCN/H_2O$ (10/1)	rt	10min	77

[a] For all cases, the reactant conditions were similar to those of entry 9 in Table 1.
[b] Isolated yields.

With the optimum conditions in hand (Table 1, entry 9), the scope of the secondary amines was examined and the results were summarized in Table 3. Multifarious secondary amines, such as benzimidazoles, indoles, indazoles, benzotriazoles, imides, aliphatic secondary amines, imidazoles and N-methylanilines, were investigated. The results showed that the reaction of secondary amines with **2** under this optimized conditions, furnished different products, falling into three main categories: N-CF_2H products, formamides and recovered starting materials.

(i) First of all, stable N-CF_2H products were generated (Table 3, entries 1-12). All benzimidazoles derivatives were successfully N-difluoromethylated under the optimized reaction condition. So, the corresponding N-difluoromethyl tertiary amines were obtained good yield (up to 87%) by difluoromethylation of the substrates with electron donating groups such as methyl, benzyl, mercapto and pyridine (Table 3, entries 2-4), while the yield of the substrates with strong electron withdraw group, such as nitro group, decreased obviously (Table 3, entry 6). For indoles derivatives, the N-difluoromethylation could smoothly implement with good yields for the substrates substituted at their -3 or -6 site with meta-positioning group of aromatic electrophilic substitution reaction (Table 3, entries 7, 9-10). Besides, the optimum condition of the reaction was applied in the N-difluoromethylation of 5-bromo substituted indazole **1k**, and product **3k** was achieved in moderate yield (Table 3, entry 11). To examine the reactivity further, the unsubstituted benzotriazole **1l** was subjected to the reaction conditions furnishing the corresponding product **3l** in 87% isolated yield (Table 3, entry 12).

(ii) In addition, it was found that the N-methylanilines were converted into N-formamides in good yields (82-89%) without any N-CF_2H derivatives (Table 3, entries 13-16), similar to the work of song and other groups [40]. As shown in Table 3, the phenyl substituted N-methylaniline (**1o**) formed formamide **6o** with 89% yield (Table 3, entry 15). When the substituent was naphthyl, the yield of **6m** was 88%, which was similar to that of

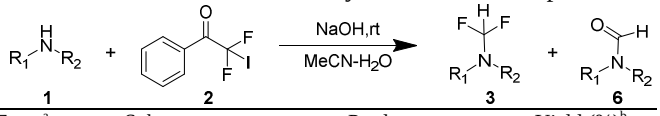
6o (

decreased slightly to 82%, while the substituent of **1n** was ethyl (Table 3, entry 14). This might be because the ethyl group was larger than the methyl group. Moreover, it was found that the para-position was an electron-donating methoxy group, and the yield of **6p** (85%) was decreased slightly (Table 3, entry 16).

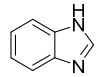
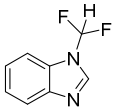
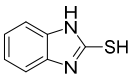
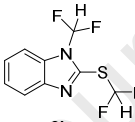
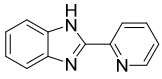
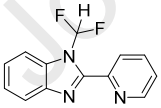
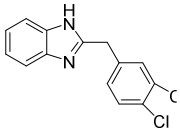
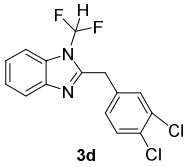
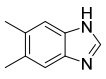
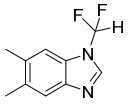
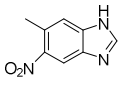
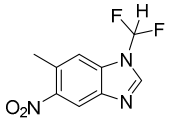
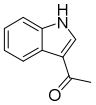
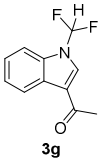
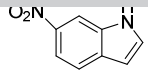
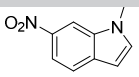
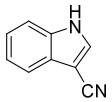
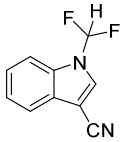
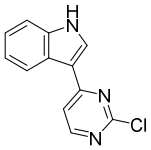
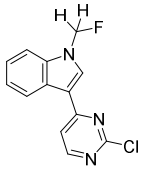
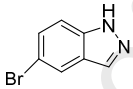
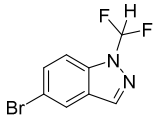
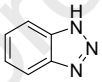
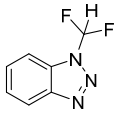
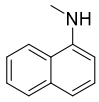
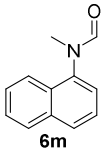
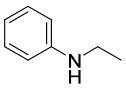
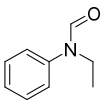
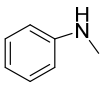
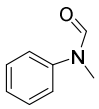
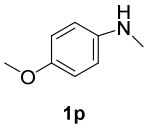
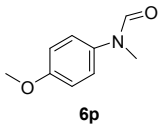
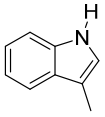
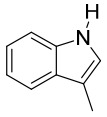
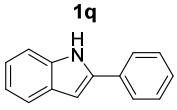
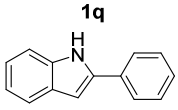
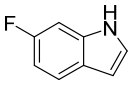
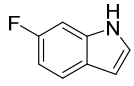
(iii) Finally, after a complex reaction, the starting materials were obtained (Table 3, entries 17-30). For indoles derivatives, the desired difluoromethylated derivatives could not be obtained when the ortho- or para-positioning group was taken, and with the disappearance of compound **2**, only the raw materials were recovered (Table 3, entries 17-21). Similarly, 3-formyl-substituted and 5-amino-substituted indazoles and unsubstituted indazoles were not converted into corresponding products under these conditions, and just raw materials were obtained (Table 3, entries 22-24). Therefore, 5-substituted benzotriazole could not get the desired N-CF_2H derivatives under this optimal condition (Table 3, entries 25-26). In addition, imides (**1aa**), aliphatic secondary amines (**1bb**, **1cc**) and imidazoles (**1dd**) failed to achieve the N-difluoromethylation, too (Table 3, entries 27-30).

In a word, these products could be divided into three categories: stable difluoromethylation products, formamides and starting materials.

Table 3 . The reaction of secondary amines with compound **2**



1 **2** **3** **6**

Entry[a]	Substrate	Product	Yield (%)[b]	
			3	**6**
1	 **1a**	 **3a**	77	ND
2	 **1b**	 **3b**	87[c]	ND
3	 **1c**	 **3c**	82	ND
4	 **1d**	 **3d**	65	ND
5	 **1e**	 **3e**	83	ND
6	 **1f**	 **3f**	55	ND
7	 **1g**	 **3g**	81	ND
8	 **1h**	 **3h**	85	ND
9	 **1i**	 **3i**	82	ND
10	 **1j**	 **3j**	70	ND
11	 **1k**	 **3k**	69	ND
12	 **1l**	 **3l**	87	ND
13	 **1m**	 **6m**	ND	88
14	 **1n**	 **6n**	ND	82
15	 **1o**	 **6o**	ND	89
16	 **1p**	 **6p**	ND	85
17	 **1q**	 **1q**	ND	ND
18	 **1r**	 **1r**	ND	ND
19	 **1s**	 **1s**	ND	ND
20	 **1t**	**1t**	ND	ND

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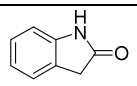
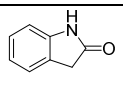
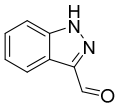
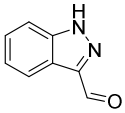
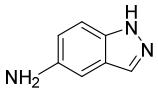
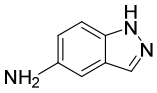
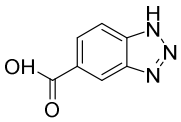
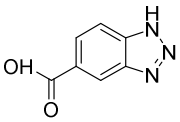
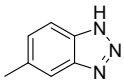
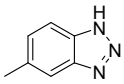
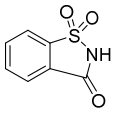
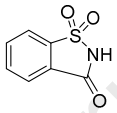
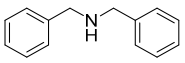
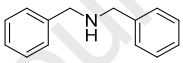
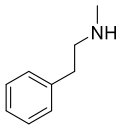
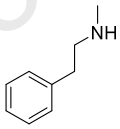
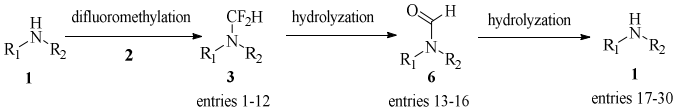
Entry[a]	Substrate	Product	Yield (%)[b] 3	6
21	 1u	 1u	ND	ND
22	 1v	 1v	ND	ND
23	 1w	 1w	ND	ND
24	 1x	 1x	ND	ND
25	 1y	 1y	ND	ND
26	 1z	 1z	ND	ND
27	 1aa	 1aa	ND	ND
28	 1bb	 1bb	ND	ND
29	 1cc	 1cc	ND	ND
30	 1dd	 1dd	ND	ND

[a] For all cases, the reactant conditions were similar to those of entry 9 in Table 1.

[b] Isolated yields.

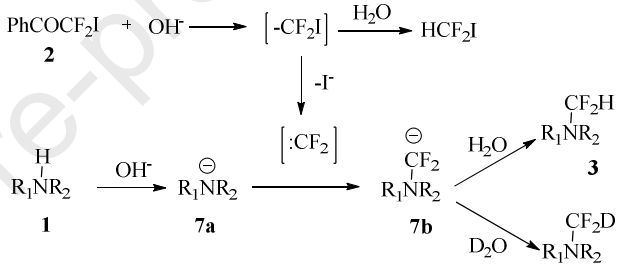
[c] Reagent **2** was used in 4.0 equiv.

In view of the above categories, the speculative mechanism was as follows. Firstly, N-CF_2H derivatives **3** were provided by secondary amines **1** via difluorocarbene-mediated N-difluoromethylation, some of which were stable (Table 3, entries 1-12), while others were completely hydrolyzed to the corresponding formamides **6**. Immediately, some formamides **6** from the first hydrolyzation were stable enough (Table 3, entries 13-16), and the others undergo the second hydrolyzation to the starting raw materials **1** (Table 3, entries 17-30) (scheme. 1). The fluoride ions produced after hydrolysis could be detected by (for details, see support information).



Scheme 1. Plausible mechanism

The mechanism for difluorocarbene-mediated N-difluoromethylation using **2** was proposed in Scheme 2. Iododifluoromethyl anion (CF_2I^-) was generated from reagent **2** under the nucleophilic attack by hydroxide ion, and the CF_2I^- species readily undergoes α-elimination of an iodine ion to release difluorocarbene (:CF_2)[41]. The difluorocarbene was captured by **7a** to give the N-difluoromethylated tertiary amines **3** via anionic intermediates **7b**. Evidence for the proposed mechanism was provided by carrying out the reaction in D_2O instead of H_2O. Comparison of the ^{1}H NMR of **3a** and its deuterium product **3a'** shown that **3a** had a characteristic triple peak of -CF_2H (7.33 ppm (t, J = 60.30 Hz, 1H)) (Fig. 1), while the corresponding peak area of **3a'** was small (D/H = 9/1) (Fig. 2). No H/D exchange was found even to prolong the reaction and add H_2O.



Scheme 2.

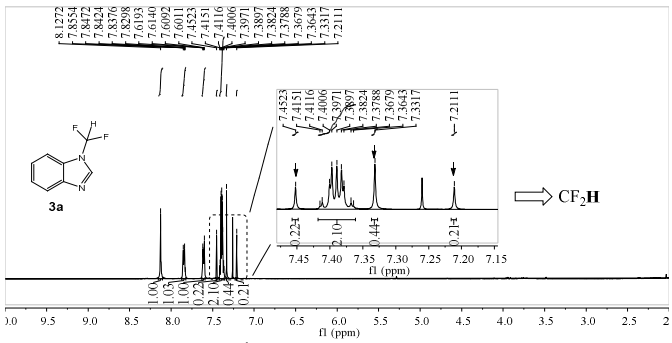


Fig. 1. ^{1}H NMR spectroscopy of **3a.**

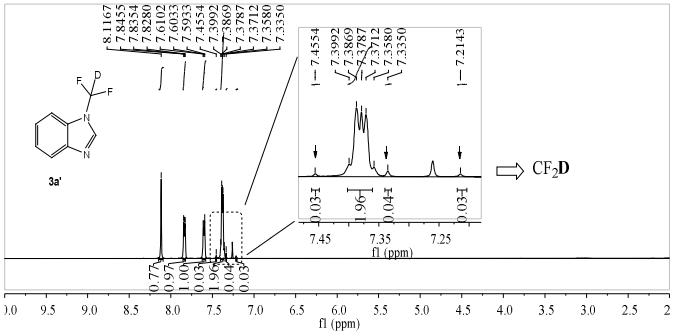


Fig . 2 . ^{1}H NMR spectroscopy of **3a'**.

In order to further explore the relationship between the geometric parameters of the starting moleculars and the categories of products, Gausian 03W was employed to calculate bond lengths (BL1, BL2, BL3) and bond angles (∠a, ∠b, ∠c) of the raw materials. As shown in Table 4, R_1 was the atom of the

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away from the aromatic ring. Based on the datum in Table 4, a tree model (Fig. 3) was proposed, as shown below:

A) if ∠c > 120°, formamides **6m-6p** were formed;

B) On the contrary, if ∠c < 120°, there were three cases:

i) if 1.00700 ≤ BL2 < 1.00800, the corresponding stable difluoromethyl products were obtained;

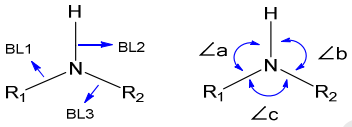
ii) when BL2 < 1.00700 or BL2 > 1.00900, it was certain that N-CF_2H derivatives were failed to be achieved by this method, such as **1q-1u**, **1w-1x** and **1aa-1cc**;

iii) while 1.00800 < BL2 < 1.00900, it was uncertain that the stable difluoromethyl products were obtained under these conditions, such as **1l**, and also might be to recover raw materials, for example, **1v**, **1y-1z** and **1dd**.

Based on the geometric information of secondary amines and tree model, the product of secondary amine was predicted under the optimal conditions, which provided guidance for difluoromethylation or formamide modification of the required molecules.

Vemurafenib (**1ee**), with a 3, 5-substituted pyrrolopyridine skeleton, was the ATP competitive $BRAF^{V600E}$ selective inhibitor [42]. In addition, AZD9291 was a potent EGFR inhibitor of 3rd generation with a pyrimidoindole group [43], and one of its intermediates, compound **1ff**, was selected to verify this difluorocarbene-mediated triclassification and the corresponding prediction tree model.

Table 4 . Bond lengths and bond angles of secondary amines



Compound	BL1(Å)	BL2(Å)	BL3(Å)	∠a(°)	∠b(°)	∠c(°)
1a	1.38468	1.00774	1.37738	126.8592	126.37298	106.7678
1b	1.3887	1.00786	1.37798	126.95361	126.51765	106.52873
1c	1.38119	1.00754	1.38893	126.07126	125.94739	107.12886
1d	1.38218	1.00714	1.38394	125.90382	126.70491	107.30454
1e	1.38501	1.00759	1.37793	126.96898	126.36797	106.66305
1f	1.36171	1.00735	1.36559	128.55083	118.70842	112.74064
1g	1.38866	1.00743	1.36847	125.28876	125.09469	109.61654
1h	1.37985	1.00700	1.37865	125.44173	125.43791	109.12035
1i	1.38623	1.00734	1.36909	125.32171	124.82842	109.84986
1j	1.4006	1.00747	1.35706	126.29907	126.16111	107.53973
1k	1.36693	1.00701	1.35934	128.45793	118.82933	112.71273
1l	1.36476	1.00838	1.3657	130.04117	118.94554	111.01318
1m	1.39354	1.00956	1.45044	113.66592	113.4033	120.85331
1n	1.39255	1.01143	1.45449	113.66315	113.78608	121.97312
1o	1.3914	1.00949	1.44932	113.95861	114.65404	121.7517
1q	1.37889	1.00612	1.38547	125.57227	125.34609	109.08163
1r	1.44527	1.01800	1.46401	110.18062	110.14128	107.27486
1s	1.37716	1.00646	1.38597	125.39113	125.28773	109.32115
1t	1.38039	1.00642	1.38316	125.41993	125.29001	109.29003
1u	1.40071	1.00914	1.38779	125.578	121.68211	112.74406
1v	1.37334	1.00863	1.34214	127.98057	118.58547	113.43396
1w	1.36761	1.00679	1.36083	128.43484	118.79363	112.77152
1x	1.37137	1.00646	1.35679	128.51589	118.90866	112.57414
1y	1.36317	1.00812	1.36968	130.04939	118.93524	111.01526
1z	1.36494	1.00824	1.36539	130.11038	118.94419	110.94543
1aa	1.80652	1.01292	1.37835	120.76067	119.50505	118.11586
1bb	1.46342	1.01679	1.4637	109.44363	109.01026	113.7287
1cc	1.46129	1.01805	1.45844	108.59049	109.20728	113.18528
1dd	1.38219	1.00831	1.37175	126.02834	126.28243	107.68925

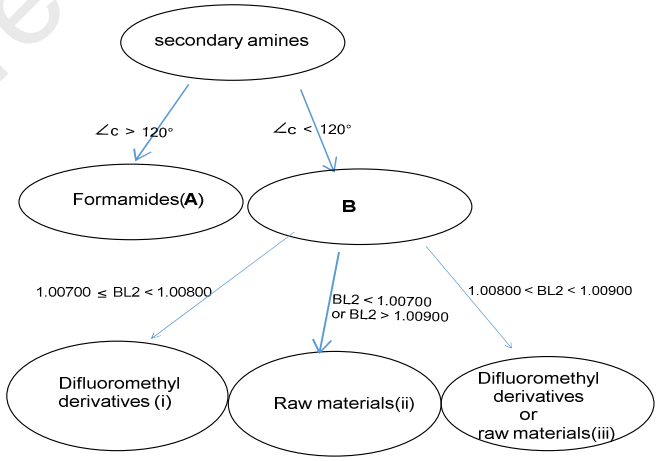
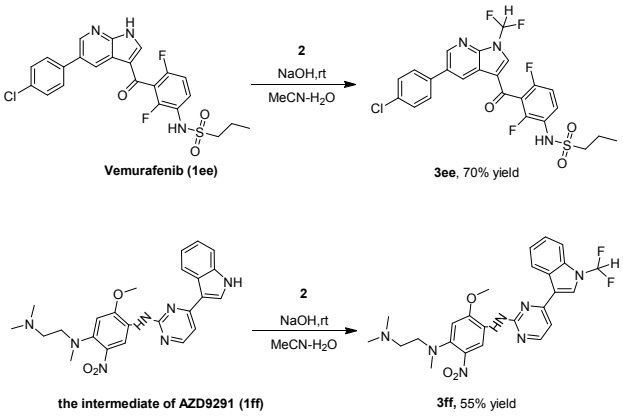


Fig .3 . Tree model for the prediction of the products

Firstly, the bond lengths and bond angles of compounds **1ee** and **1ff** were calculated and the results were shown in Table 5. According to the above mentioned tree model, the compound **1ee** was belong to B-iii leaf node (uncertain to obtain the corresponding stable N-CF_2H derivative **3ee**), and the compound **1ff** was belong to B-i leaf node (definitely to form the stable N-CF_2H derivative **3ff**), respectively. It should be noted that there are two types of secondary amines in **3ee** and **3ff**. Our strategy selectively reacted with pyrrole ring without contacting sulfonamides or aryl-aryl secondary amines. Fortunately, the product **3ee** and **3ff** was successfully obtained in 70% and 55% yield from **1ee** and **1ff** using this difluorocarbene-mediated triclassification reaction (scheme. 3). This result was consistent with the examples shown in Table 3, which further underpins the advantages of our strategy in the prediction and selective formation of N-CF_2H compounds.

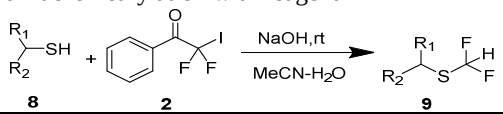
Tab

Compound	BL1(Å)	BL2(Å)	BL3(Å)	∠a(°)	∠b(°)	∠c(°)
1ee	1.38708	1.00883	1.36419	124.14938	126.47237	109.37824
1ff	1.38375	1.00755	1.36563	125.59488	124.60402	109.79080

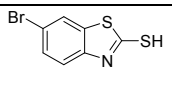
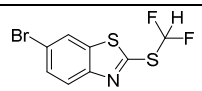
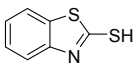
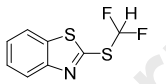
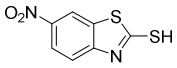
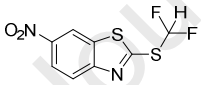
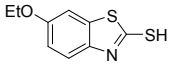
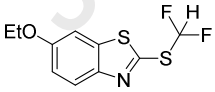
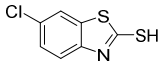
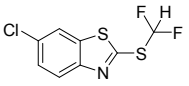
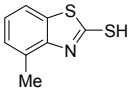
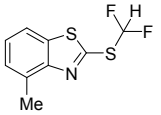
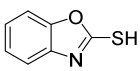
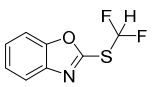
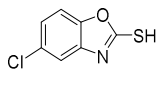
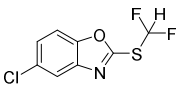


Scheme 3. Synthesis of products **3ee** and **3ff**

Table 6. S-difluoromethylation with reagent **2**

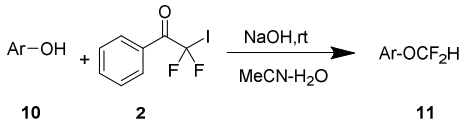


8 2 9

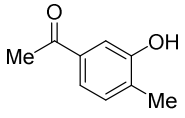
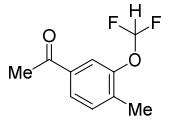
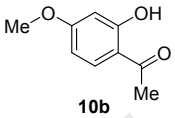
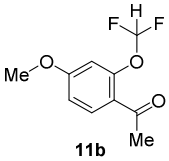
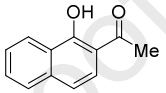
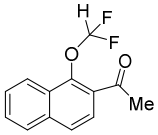
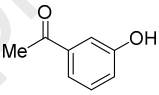
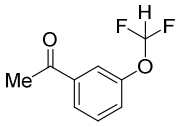
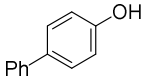
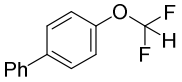
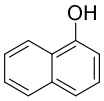
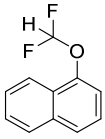
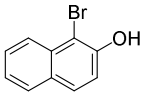
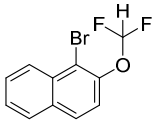
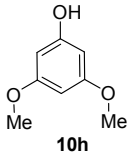
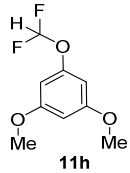
Entry[a]	Substrate	Product	Yield (%)[b]
1	 **8a**	 **9a**	91
2	 **8b**	 **9b**	92
3	 **8c**	 **9c**	75
4	 **8d**	 **9d**	86
5	 **8e**	 **9e**	90
6	 **8f**	 **9f**	89
7	 **8g**	 **9g**	91
8	 **8h**	 **9h**	89

[a] For all cases, the reactant conditions were similar to those of entry 9 in Table 1.

[b] Isolated yields.



10 2 11

Entry[a]	Substrate	Product	Yield (%)[b]
1	 **10a**	 **11a**	81
2	 **10b**	 **11b**	78
3	 **10c**	 **11c**	62
4	 **10d**	 **11d**	82
5	 **10e**	 **11e**	68
6	 **10f**	 **11f**	70
7	 **10g**	 **11g**	72
8	 **10h**	 **11h**	80

[a] For all cases, the reactant conditions were similar to those of entry 9 in Table 1.

[b] Isolated yields.

Furthermore, iododifluoroacetophenone **2** was applied in the S-difluoromethylation of different heteroarylthiols, and the desired difluoromethylated products were obtained in 75-92% yield (Table 6). Moreover, the O-difluoromethylation of eight phenols was carried out smoothly in 62-82% yield (Table 7). Compared with the reported works [44], this reaction had the advantages of short reaction time, mild conditions and high yield. Therefore, it could be said that the reagent **2** was applied

succ): δ 7.81 (dd, *J* = 5.75 Hz, 1H), 7.71 (d, *J* = 7.85Hz, 1H), 7.50 (t, *J* = 58.20Hz, 1H), 7.45-7.38 (m,2H), 7.35 (t, *J* = 56.25 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.32, 139.20, 132.32, 125.68, 124.76, 122.21, 119.98 (t, J_{C-F} = 278.36 Hz), 112.12, 109.49 (t, J'_{C-F}= 248.95 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ -91.10 (dd, *J* = 70.35 Hz, 2F), -95.82 (dd, *J* = 72.99 Hz, 2F); IR (KBr) ν: 1450, 1348, 1146, 1111, 1069, 935, 767, 743 cm^{-1}.

difluorocarbene-mediated reaction.

3. Conclusions

In summary, a mild, fast, selective difluorocarbene-mediated triclassification reaction had been developed for secondary amines using compound **2** as difluoromethylating agent, which produced one of the following three substances: N-CF_2H derivatives (up to 87% yield), formamides (82-89% yield) or the starting secondary amines. Subsequently, a tree model was proposed to predict the possible product structure, according to the geometric information of the starting molecular. This difluorocarbene-mediated triclassification reaction and the corresponding tree model were used to implement the late stage modifications of medicinal drugs. In addition, this method was successfully applied to the S- and O-difluoromethylations to obtain the corresponding S- and O-CF_2H derivatives with satisfactory yields.

4. Experimental section

4.1. General

All reagents were commercially available and used without further purification unless indicated otherwise. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on GF254 plates (1 mm layer thickness) using UV light as visualizing agent. Flash chromatography was performed with 300-400 mesh silica gels. The NMR spectra for ^{1}H, ^{13}C, and ^{19}F were recorded in $CDCl_3$ or DMSO-d_6 at 500, 125, and 470MHz, respectively. 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. HRMS (m/z) were also measured using ESI techniques (Q-Tof positiveion) (**3ff**).

*4.2. General synthetic method of **3a-3l** and **3ee-ff***

A mixture of **1** (1 mmol), NaOH(11 mmol, 0.44g) was dissolved in CH_3CN(CH_3CN/H_2O= 10/1, V/V, 11mL) in an oven dried 50 mL round bottom flask containing a stir bar. Iododifluoroacetophenone (**2**) (2 mmol, 0.56g), was added to the reaction mixture and stirred at room temperature for about 10 minutes. After the reaction was completed as indicated by TLC the reaction mixture was removed under reduced pressure. And then, the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (25 mL × 3), followed by brine (50 mL). The organic extract was dried over $NaSO_4$, filtered and evaporated under reduced pressure. The crude product was further purified by silica gel column chromatography using (pet ether/EtOAc) to furnish the corresponding difluoromethylation products **3a-3l** and **3ee-3ff** in 65-88% yield.

*4.2.1 1-(difluoromethyl)-1H-benzo[d]imidazole (**3a**)*

Light yellow liquid; Yield = 77%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (s, 1H), 7.86-7.82 (m, 1H), 7.62-7.59 (m, 1H), 7.42-7.36 (m, 2H), 7.33 (t, *J* = 60.30 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.79, 139.25, 130.48, 124.80, 124.17, 120.82, 111,09, 109.05(t, J_{C-F} = 248.13 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ -91.45 (d, *J* = 75.48 Hz, 2F); IR (KBr) ν: 1607, 1458, 1285, 1227, 1204, 1102, 1046, 815, 743 cm^{-1}.

*4.2.2 1-(difluoromethyl)-2-((difluoromethyl)thio)-1H-benzo[d]imidazole (**3b**)*

Colorless liquid; Yield = 82%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.20 (t, *J* =59.45 Hz, 1H), 8.65 (d, *J* = 5.50 Hz, 1H), 8.48 (d, *J* =8.00 Hz, 1H),7.89-7.83 (m,3H), 7.42-7.36 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.18, 148.64, 148.24, 142.62, 137.39, 132.78, 125.14, 124.78, 124.69, 124.30, 120.49, 113.53, 110.63 (t, J_{C-F} = 248.29 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ -97.46 (d, *J* = 75.39 Hz, 2F); IR (KBr) ν: 1452, 1438, 1366, 1336, 1172, 1077, 1041, 931, 766, 755, 742 cm^{-1}; HRMS (EI-TOF) calculated for $C_{13}H_9F_2N_3$ $[M]^+$: 245.0764; found: 245.0759.

*4.2.3 1-(difluoromethyl)-2-(pyridin-2-yl)-1H-benzo[d]imidazole (**3c**)*

*4.2.4 2-(3,4-dichlorobenzyl)-1-(difluoromethyl)-1H-benzo[d]imidazole(**3d**)*

White solid; mp. 185-186□; Yield = 65%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80-7.76(m, 1H), 7.57-7.54 (m, 1H), 7.41-7.38 (m, 2H), 7.38-7.34 (m,2H), 7.21 (t, *J* = 58.95 Hz, 1H), 7.11 (d, *J* = 8.35 Hz, 1H), 4.36(s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.91, 142.42, 135.23, 133.11, 132.18, 131.79, 130.93, 130.48, 127.90, 124.57, 124.10, 120.32, 111.02, 108.67 (t, J_{C-F} = 247.68 Hz), 33.87; ^{19}F NMR (470 MHz, $CDCl_3$): δ -93.96 (d, *J* = 70.03 Hz, 2F); IR (KBr) *ν*: 1472, 1458, 1342, 1157, 1087, 1053, 1033, 931, 741cm^{-1}; HRMS (EI-TOF) calculated for $C_{15}H_{10}Cl_2F_2N_2$ $[M]^+$: 326.0189; found: 326.0186.

*4.2.5 1-(difluoromethyl)-5,6-dimethyl-1H-benzo[d]imidazole(**3e**)*

White solid; mp. 131-132□; Yield = 83%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.58 (s, 1H), 7.37 (s, 1H), 7.27 (t, *J* = 60.40 Hz, 1H), 2.39 (s, 3H), 2.37 (s.3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.48, 138.34, 134.19, 133.19, 128.99, 120.84, 111.25, 109.03 (t, J_{C-F} = 247.68 Hz), 20.51, 20.25; ^{19}F NMR (470 MHz, $CDCl_3$): δ -93.78 (d, *J* = 75.62 Hz, 2F); IR (KBr) ν: 1416, 1370, 1211, 1082, 1046, 1026, 866, 851cm^{-1}.

*4.2.6 1-(difluoromethyl)-6-methyl-5-nitro-1H-benzo[d]imidazole (**3f**)*

Yellow liquid; Yield = 55%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37 (s, 1H), 8.35 (s, 1H), 7.64 (s, 1H), 7.49 (t, *J* = 60.3 Hz, 1H), 2.58 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.65, 136.53, 135.15, 135.14, 127.85, 127.49, 112.51 (t, J_{C-F} = 246.25 Hz), 108.13, 20.31; ^{19}F NMR (470 MHz, $CDCl_3$): δ -94.71 (d, *J* = 75.20 Hz, 2F); IR (KBr) ν: 1528, 1323, 1144, 1044, 1893, 865, cm^{-1}; HRMS (EI-TOF) calculated for $C_9H_7F_2N_3O_2$ $[M]^+$: 227.0506; found: 227.0505.

*4.2.7 1-(1-(difluoromethyl)-1H-indol-3-yl)ethan-1-one (**3g**)*

Yellow liquid; Yield = 81%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.42-8.36 (m, 1H), 7.92 (s, 1H), 7.56-7.52 (m, 1H), 7.39-7.34 (m, 2H), 7.33 (t, *J* = 60.68 Hz, 1H), 2.53(s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.54, 134.41, 129.68, 126.61, 124.97, 124.17, 123.12, 120.14, 111.70, 109.72(t, J_{C-F} = 247.88 Hz) , 27.67; ^{19}F NMR (470 MHz, $CDCl_3$): δ -93.11 (d, *J* = 75.95 Hz, 2F); IR (KBr) ν: 1647, 1544, 1463, 1436, 1212, 1201, 1057, 1013, 802, 748 cm^{-1}.

*4.2.8 1-(difluoromethyl)-6-nitro-1H-indole (**3h**)*

C 160, 8.52 (s, 1H), 8.13 (dd, *J* = 4.35 Hz, 1H), 7.71 (d, *J* =8.75 Hz, 1H), 7.56 (d, *J* =3.50 Hz, 1H), 7.34 (t, *J* = 60.40 Hz, 1H), 6.75(d, *J* = 3.45 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.31, 134.48, 132.64, 128.51, 121.55, 117.42, 109.76 (t, J_{C-F} = 247.06 Hz), 107.70, 106.26; ^{19}F NMR (470 MHz, $CDCl_3$): δ -91.46 (d, *J* = 75.53 Hz, 2F); IR (KBr) ν: 1508, 1456, 1335, 1206, 1041, 798 cm^{-1}; HRMS (EI-TOF) calculated for $C_9H_6F_2N_2O_2$ $[M]^+$: 212.0397; found: 212.0398.

*4.2.9 1-(difluoromethyl)-1H-indole-3-carbonitrile (**3i**)*

Yellow liquid; Yield = 82%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (s, 1H), 7.78 (d, *J* = 7.85 Hz, 1H), 7.62 (d, *J* = 8.15 Hz, 1H), 7.47-7.40 (m, 2H), 7.31 (t, *J* = 60.35 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 133.04, 130.37, 127.77, 125.78, 124.15, 120.38, 114.16, 111.63, 109.40 (t, J_{C-F} = 249.15 Hz), 91.14; ^{19}F NMR (470 MHz, $CDCl_3$): δ -91.46 (d, *J* = 75.48 Hz, 2F); IR (KBr) ν: 2229, 1462, 1421, 1369, 1182, 1140, 1052, 1032, 800, 742 cm^{-1}; HRMS (EI-TOF) calculated for $C_{10}H_6F_2N_2$ $[M]^+$: 192.0499; found: 192.0500.

*4.2.10 3-(2-chloropyrimidin-4-yl)-1-(fluoromethyl)-1H-indole (**3j**)*

Yellow solid; mp. 149-151□; Yield = 70%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.50 (d, *J* = 2.65 Hz, 1H), 8.33 (t, *J* = 5.00 Hz, 1H), 7.56 (t, *J* = 4.38 Hz, 1H), 7.47 (d, *J* = 5.25 Hz, 2H), 7.40-7.35 (m, 2H), 7.30 (t, *J* = 60.65 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.31, 161.47, 159.02, 134.88, 126.23, 124.83, 123.74, 122.19, 116.39, 114.95, 111.81,109.83(t, J_{C-F} = 247.48 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ -92.78 (dd, *J* = 75.20 Hz, 2F); IR (KBr) ν: 1574, 1364, 1320, 1219, 1160, 1042, 752 cm-1; HRMS (EI-TOF) calculated for $C_{13}H_9ClFN_3$ [M]+: 261.0469; found: 261.0435.

*4.2.11 5-bromo-1-(difluoromethyl)-1H-indazole (**3k**)*

Light yellow liquid; Yield = 69%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.85 (d, *J* = 1.00 Hz, 1H), 7.60 (d, *J* = 9.25 Hz, 1H), 7.44 (t, *J* = 60.45 Hz, 1H), 7.39 (dd, *J* = 9.25 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.76, 131.99, 123.12, 123.00, 120.10, 119.32, 117.36, 111.57 (t, J_{C-F} = 252.90 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ -93.91 (s, 2F); IR (KBr) ν: 1508, 1364, 1147, 1138, 1113, 1081, 857, 804, 777 cm^{-1}.

*4.2.12 1-(difluoromethyl)-1H-benzo[d][1,2,3]triazole(**3l**)*

Light yellow liquid; Yield = 87%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (dt, *J* = 4.20 Hz, 1H), 7.86 (t, *J* = 58.50 Hz, 1H), 7.62-7.59 (d, *J* = 8.30 Hz, 1H), 7.59-7.63 (m, 1H), 7.46-7.50 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.48, 129.47, 125,57 120.48, 111.30 (t, J_{C-F} = 250.00 Hz), 109.31; ^{19}F NMR (470 MHz, $CDCl_3$): δ -97.17 (d, *J* = 73.18 Hz, 2F); IR (KBr) ν: 1456, 1388, 1296, 1137, 1108, 1074, 936, 823, 746 cm^{-1}.

*4.2.13 O-(3-(5-(4-chlorophenyl)-1-(difluoromethyl)-1H-pyrrolo [2,3-b]pyridine-3-carbonyl)-2,4-difluorophenyl)propane-1-sulfonamide (**3ee**)*

White solid; mp. 241-243□; Yield = 70%; ^{1}H NMR (500MHz, DMSO): δ 8.84 (d, *J* = 2.10 Hz, 1H), 8.72 (s, 1H), 8.69 (d, *J* = 1.90 Hz, 1H), 8.20 (t, *J* = 58.70 Hz, 1H), 7.84 (dd, *J* = 19.0, 8.60 Hz, 4H), 7.58 (d, *J* = 8.50 Hz, 2H), 7.50 (t, *J* = 8.70 Hz, 1H), 3.51 (t, *J* = 7.65 Hz, 2H), 1.84 -1.73 (m, 2H), 0.99 (t, *J* = 7.40 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 180.65, 146.90, 145.29, 137.12 (d, J_{C-F} = 10.4 Hz), 136.40, 134.35, 133.60, 131.75, 130.36, 129.78, 129.37, 128.86, 128.59, 118.97, 118.41, 114.02, 113.28 (d, J'_{C-F} = 23.2 Hz), 110.76, 108.77, 107.08 (t, $^1J_{C-F}$ = 249.38 Hz), 55.92, 16.84, 12.75 ; ^{19}F NMR (470 MHz, $CDCl_3$): δ -96.17 (d, *J* = 75.20 Hz, 2F), -106.60 (dd, *J* = 18.8 Hz, 1F), -1149, 1123, 1065, 1046, 1012 cm^{-1}; HRMS (EI-TOF) calculated for $C_{24}H_{18}ClF_4N_3O_3S$ $[M]^+$: 539.0694; found: 539.0696.

*4.2.14 N^1-(4-(1-(difluoromethyl)-1H-indol-3-yl)pyrimidin-2-yl)-N^4-(2-(dimethylamino)ethyl)-2-methoxy-N^4-methyl-5-nitrobenzene-1,4-diamine (**3ff**)*

Yellow solid; mp. 184-186□; Yield = 55%; ^{1}H NMR(500 MHz, DMSO-d_6): δ12.12 (s, 1H), 8.88 (s, 1H), 8.34 (t, *J* = 2.40Hz, 2H), 8.16 (s, 1H), 7.69 (t, *J* = 58.45Hz, 1H), 7.48 (d, *J* = 8.10Hz, 1H), 7.34 (d, *J* = 5.35Hz, 1H), 7.18 (t, *J* = 7.45Hz, 1H), 7.08 (t, *J* = 7.55Hz, 1H), 7.05 (s, 1H), 4.04 (s, 3H), 3.91 (t, *J* = 6.10Hz, 2H), 3.75 (t, *J* = 6.20Hz, 2H), 3.36 (s, 6H), 2.84 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ163.11, 160.12, 157.56, 154.43, 142.74, 137.64, 135.63, 129.75, 129.44, 128.87, 125.41, 122.61 (t, J_{C-F} = 270.00Hz), 122.14, 121.10, 118.14, 113.67, 112.62, 108.59, 104.95, 58.01, 57.33, 48.43, 45.85, 43.15; ^{19}F NMR (470 MHz, DMSO-d_6): δ -75.31 (s, 2F); IR (KBr) ν: 1716, 1698, 1651, 1647, 1575, 1563, 1556, 1541, 1457, 1196, 1132, 1076 cm^{-1}; ESI-HRMS(m/z): calculated for $C_{25}H_{27}F_2N_7O_3(M+H)^+$: 512.2216, found: 512.2212.

*4.3. General synthetic method of **6m-6p***

A mixture of **1** (1 mmol), NaOH(11 mmol, 0.44g) was dissolved in CH_3CN(CH_3CN/H_2O= 10/1, V/V, 11mL) in an oven dried 50 mL round bottom flask containing a stir bar. Iododifluoroacetophenone (**2**) (2 mmol, 0.56g), was added to the reaction mixture and stirred at room temperature for about 10 minutes. After the reaction was completed as indicated by TLC the reaction mixture was removed under reduced pressure. And then, the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (25 mL × 3), followed by brine (50 mL). The organic extract was dried over NaSO4, filtered and evaporated under reduced pressure. The crude product was further purified by silica gel column chromatography using (pet ether/EtOAc) to furnish the formamides **6m-6p**.

*4.3.1 N-methyl-N-(naphthalen-1-yl)formamide(**6m**)*

Brown liquid; Yield = 88%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.29 (s, 1H), 7.92 (dd, *J* = 9.00 Hz, 1H), 7.89 (d, *J* = 8.30 Hz, 1H), 7.82 (d, *J* = 7.60 Hz, 1H), 7.61 – 7.54 (m, 2H), 7.50 (t, *J* = 10.00 Hz, 1H), 7.34 (d, *J* = 7.20 Hz, 1H), 3.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.50, 138.31, 134.63, 130.50, 128.98, 128.64, 127.42, 126.81, 125.59, 125.22, 122.40, 34.31.

*4.3.2 N-ethyl-N-phenylformamide (**6n**)*

Yellow liquidl; Yield = 82%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.35 (s, 1H), 7.41 (t, *J* = 7.80 Hz, 2H), 7.29 (t, *J* = 7.50 Hz, 1H), 7.16 (d, *J* = 7.50 Hz, 2H), 3.86 (q, *J* = 7.20 Hz, 2H), 1.16 (t, *J* = 7.20 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.05, 140.84, 129.64, 126.87, 124.28, 40.09, 13.05.

*4.3.3 N-methyl-N-phenylformamide (**6o**)*

Yellow liquid; Yield = 89%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.47(s, 1H), 7.43-7.38(m, 2H), 7.29-7.25 (m, 1H), 7.18-7.15 (m, 2H), 3.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.36, 142.22, 129.64, 126.42, 122.40, 32.07.

*4.3.4 N-(4-methoxyphenyl)-N-methylformamide (**6p**)*

Yellow liquid; Yield = 85%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.34 (s, 1H), 7.09 (d, *J* = 8.90 Hz, 2H), 6.92 (d, *J* = 8.80 Hz, 2H), 3.81 (s, 3H), 3.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.48, 158.32, 135.28, 124.68, 114.78, 55.57, 32.71; IR (KBr) ν: 1674,

151- IHz, $C_9H_{11}NO_2$ [M]$^+$: 165.0789; found: 165.0791.

4.4. General synthetic method of S- and O- CF_2H derivatives

A mixture of **8** or **10** (1 mmol), NaOH(11 mmol, 0.44g) was dissolved in CH_3CN(CH_3CN/H_2O= 10/1, V/V, 11mL) in an oven dried 50 mL round bottom flask containing a stir bar. Iododifluoroacetophenone (**2**) (2 mmol, 0.56g), was added to the reaction mixture and stirred at room temperature for about 10 minutes. After the reaction was completed as indicated by TLC the reaction mixture was removed under reduced pressure. And then, the reaction mixture was diluted with water (50 mL) and extracted with EtOAc (25 mL × 3), followed by brine (50 mL). The organic extract was dried over $NaSO_4$, filtered and evaporated under reduced pressure. The crude product was further purified by silica gel column chromatography using (pet ether/EtOAc) to furnish the S- and O-CF_2H derivatives **9a-9h** and **11a-11h**.

*4.4.1 6-bromo-2-((difluoromethyl)thio)benzo[d]thiazole (**9a**)*

Yellow liquid; Yield = 91%; ^{1}H NMR (500MHz, $CDCl_3$): δ 7.96 (d, *J* = 1.90 Hz, 1H), 7.83 (d, *J* = 8.70 Hz, 1H), 7.63 (t, *J* = 55.80 Hz, 1H), 7.59 (dd, *J* = 8.70 Hz, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.23, 152.01, 137.70, 130.48, 124.10, 124.03, 120.29(t, J_{C-F} = 275.58 Hz), 118.09; ^{19}F NMR (470 MHz, $CDCl_3$): δ -94.37 (dt, *J* = 70.22 Hz, 2F); IR (KBr) ν: 1469, 1432, 1279, 1081, 998, 808, 775 cm^{-1}.

*4.4.2 2-((difluoromethyl)thio)benzo[d]thiazole (**9b**)*

Light yellow liquid; Yield = 92%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, *J* = 8.10 Hz, 1H), 7.83 (d, *J* = 8.05 Hz, 1H), 7.64 (t, *J* = 55.90 Hz, 1H), 7.51-7.47 (m, 1H), 7.42-7.38 (m, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.32, 153.19, 136.26, 126.94, 125.92, 123.14, 122.75, 120.55 (t, J_{C-F} = 275.35 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ -93.26 (dd, *J* = 69.98 Hz, 2F); IR (KBr) ν: 1465, 1427, 1311, 1287, 1071, 994, 782, 756, 726 cm^{-1}.

*4.4.3 2-((difluoromethyl)thio)-6-nitrobenzo[d]thiazole (**9c**)*

Light yellow solid; mp. 94-95□; Yield = 75%; ^{1}H NMR (500 MHz，$CDCl_3$): δ 8.75 (d, *J* = 2.15 Hz, 1H), 8.35 (dd, *J* = 9.00 Hz, 1H), 8.04 (d, *J* = 8.95 Hz, 1H), 7.79 (t, *J* = 55.45 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 164.83, 156.19, 145.02, 135.80, 122.74, 122.22, 119.72(t, J_{C-F} = 275.94 Hz), 117.71; ^{19}F NMR (470MHz, $CDCl_3$): δ -93.92(d, *J* = 69.28 Hz, 2F); IR (KBr) ν: 1510, 1325, 1286, 1043, 1003, 742 cm^{-1}.

*4.4.4 2-((difluoromethyl)thio)-6-ethoxybenzo[d]thiazole (**9d**)*

Light yellow soild; mp. 44-46℃; Yield = 86%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (t, *J*= 56.00 Hz, 1H), 7.66-7.64 (m, 1H), 7.32-7.27 (m, *2*H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.51, 152.55, 147.54, 138.00, 123.58, 120.32 (t, J_{C-F} = 275.61Hz), 116.55, 104.21, 64.18, 14.76; ^{19}F NMR (470 MHz, $CDCl_3$): δ -93.79 (d, *J* = 70.22 Hz, 2F); IR (KBr) ν: 2982, 1601, 1483, 1470, 1449, 1394, 1258, 1225, 1085, 998, 940, 823, 782 cm^{-1}.

*4.4.5 6-chloro-2-((difluoromethyl)thio)benzo[d]thiazole (**9e**)*

Light yellow liquid; Yield = 90%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.70 Hz, 1H), 7.80 (d, *J* = 2.00 Hz, 1H), 7.63 (t, *J* = 55.80 Hz, 1H), 7.45 (dd, *J* = 8.70 Hz, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.79, 151.41, 137.02, 131.74, 127.50, 123.49, 122.24, 120.04 (t, J_{C-F} = 275.68 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ -94.34 (d, *J* = 70.78 Hz, 2F); IR (KBr) ν: 1434, 1085, 999, 817, 780 cm^{-1}.

*4.4.6 2-((difluoromethyl)thio)-4-methylbenzo[d]thiazole (**9f**)*

$CDCl_3$): δ 7.65 (t, *J* = 56.00 Hz, 1H), 7.66-7.64 (m, 1H), 7.32-7.27 (m, *2*H), 2.73(s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.42, 152.31, 135.95, 133.06, 127.18, 125.62, 120.48(t, J_{C-F} = 274.86Hz), 118.58, 18.32; ^{19}F NMR (470 MHz, $CDCl_3$): δ -93.40 (d, *J* = 70.22 Hz, 2F); IR (KBr) ν: 1466, 1083, 1019, 880, 782, 766, 745 cm^{-1}; HRMS (EI-TOF) calculated for $C_9H_7F_2NS_2$ [M]$^+$: 230.9988; found: 230.9989.

*4.4.7 2-((difluoromethyl)thio)benzo[d]oxazole (**9g**)*

Yellow liquid; Yield = 91%; ^{1}H NMR (500MHz, $CDCl_3$): δ 7.71 (t, *J* = 55.65 Hz, 1H), 7.68-7.60 (m, 1H), 7.51-7.48 (m, 1H), 7.37-7.31 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.51, 151.99, 141.50, 125.46, 125.23, 120.05(t, J_{C-F} = 274.79 Hz), 117.85, 110.64; ^{19}F NMR(470 MHz, $CDCl_3$) : δ -94.34 (d, *J* = 69.65 Hz, 2F); IR (KBr) ν: 1511, 1453, 1371, 1138, 1073, 782, 744 cm^{-1}.

*4.4.8 5-chloro-2-((difluoromethyl)thio)benzo[d]oxazole (**9h**)*

Yellow liquid; Yield = 89%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (t, *J* = 55.55 Hz, 1H), 7.65 (d, *J* = 1.85 Hz, 1H), 7.43 (m, *J* = 8.70 Hz, 1H), 7.31 (dd, *J* = 8.65 Hz, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.25, 142.24, 130.63, 125.50, 119.58 (t, J_{C-F} = 275.30 Hz), 117.38, 111.06; ^{19}F NMR (470 MHz, $CDCl_3$): δ -93.33 (d, *J* = 69.84 Hz, 2F); IR (KBr) ν: 1507, 1449, 1146, 1073, 919, 806, 781 cm^{-1}.

*4.4.9 1-(3-(difluoromethoxy)-4-methylphenyl)ethan-1-one (**11a**)*

Light yellow liquid; Yield = 81%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (dd, *J* = 7.70 Hz, 1H), 7.65 (s, 1H), 7.31 (d, *J* = 7.85 Hz, 1H), 6.57 (t, *J* = 73.50 Hz, 1H), 2.57 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.87, 149.80 (t, J'_{C-F} = 2.59 Hz), 136.48, 135.95, 131.59, 125.55, 118.15, 116.00 (t, J_{C-F} = 258.14 Hz), 26.53, 16.52; ^{19}F NMR (470 MHz, $CDCl_3$): δ -80.77 (dd, *J* = 91.98 Hz, 2F).

*4.4.10 1-(2-(difluoromethoxy)-4-methoxyphenyl)ethan-1-one(**11b**)*

Light yellow liquid; Yield = 78%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (d, *J* = 8.80 Hz, 1H), 6.77 (dd, *J* = 8.80 Hz, 1H), 6.63 (d, *J* = 2.15 Hz, 1H), 6.59 (t, *J* = 73.30 Hz, 1H), 3.84 (s, 3H), 2.57(s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.66, 163.86, 151.73, 132.66, 123.47, 116.15 (t, J_{C-F} = 258.21 Hz), 110.61, 105.60, 55.80, 31.13; ^{19}F NMR (470 MHz, $CDCl_3$): δ -80.82 (dd, *J* = 91.89 Hz, 2F).

*4.4.11 1-(1-(difluoromethoxy)naphthalen-2-yl)ethan-1-one (**11c**)*

Light yellow liquid; Yield = 62%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (t, *J* = 4.33 Hz, 1H), 7.89 (t, *J* = 4.48 Hz, 1H), 7.81(d, *J* = 8.50 Hz, 1H), 7.70 (d, *J* = 8.55 Hz, 1H), 7.64 (q, *J* = 3.13 Hz, 2H), 6.62 (t, *J* = 74.30 Hz, 1H), 2.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.89, 145.41, 136.28, 130.05, 128.67, 128.05, 127.91, 127.74, 126.91, 124.92, 123.26, 117.71 (t, J_{C-F} = 260.81 Hz), 30.67; ^{19}F NMR (470 MHz，$CDCl_3$): δ -80.27 (d, *J* = 93.11 Hz, 2F).

*4.4.12 1-(3-(difluoromethoxy)phenyl)ethan-1-one (**11d**)*

Light yellow liquid; Yield = 82%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.70 Hz, 1H), 7.68 (s,1H), 7.46 (t, *J* = 7.90 Hz, 1H), 7.32 (d, *J* = 8.10 Hz, 1H), 6.56 (t, *J* = 73.25 Hz, 1H), 2.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.89, 151.31, 138.82, 130.12, 125.37, 124.31, 118.96, 115.65 (t, J_{C-F} = 259.20 Hz), 26.64.; ^{19}F NMR (470 MHz, $CDCl_3$): δ -82.31 (d, *J* = 92.31 Hz, 2F).

*4.4.13 4-(difluoromethoxy)-1,1'-biphenyl (**11e**)*

$CDCl_3$): δ 7.60 (t, *J* = 8.75 Hz, 4H), 7.48 (t, *J* = 7.53 Hz, 2H), 7.39 (t, *J* = 7.30 Hz, 1H), 7.22 (d, *J* = 8.35 Hz, 2H), 6.57 (t, *J* = 73.85 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.67, 140.10, 138.63, 128.92, 128.54, 127.51, 127.07, 119.86, 116.03 (t, J_{C-F} = 258.01 Hz); ^{19}F NMR (470 MHz, $CDCl_3$): δ -80.69 (d, *J* = 92.45 Hz, 2F).

*4.4.14 1-(difluoromethoxy)naphthalene (**11f**)*

Colorless liquid; Yield = 70%; ^{1}H NMR (500 MHz，$CDCl_3$): δ 8.23-8.18 (m, 1H), 7.90-7.85 (m, 1H), 7.72 (d, *J* = 8.30 Hz, 1H), 7.60-7.54 (m, 2H), 7.43 (t, *J* = 7.95 Hz, 1H), 7.21 (d, *J* = 7.55 Hz, 1H), 6.68 (t, *J* = 74.05 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.48, 134.75, 127.79, 126.99, 126.65, 126.49, 125.41, 125.36, 121.64, 116.63 (t, J_{C-F} = 256.73 Hz), 113.70; ^{19}F NMR(470 MHz, $CDCl_3$): δ -80.90 (d, *J* = 94.28 Hz, 2F).

*4.4.15 1-bromo-2-(difluoromethoxy)naphthalene (**11g**)*

White solid; mp. 55-56℃; Yield = 70%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.29 (d, *J* = 8.55 Hz, 1H), 7.84 (t, *J* = 7.05 Hz, 2H), 7.64 (t, *J* = 7.30 Hz, 1H), 7.54 (t, *J* = 7.50 Hz, 1H), 7.40 (d, *J* = 8.85 Hz, 1H), 6.63 (t, *J* = 73.60 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.04, 132.80, 132.22, 129.23, 128.21, 128.19, 127.19, 126.57, 120.57, 116.30 (t, J_{C-F} = 260.95 Hz), 114.69; ^{19}F NMR (470 MHz, $CDCl_3$): δ -80.75 (d, *J* = 92.21 Hz, 2F).

*4.4.16 1-(difluoromethoxy)-3,5-dimethoxybenzene(**11h**)*

Light yellow liquid; Yield = 80%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.49 (t, *J* = 74.05 Hz, 1H), 6.30 (m, 1H), 6.27 (m, 2H), 3.78 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.50, 153.06, 116.01 (t, J_{C-F} = 257.00 Hz), 97.80, 97.32, 55.51; ^{19}F NMR(470 MHz, $CDCl_3$): δ -80.67 (dd, *J* = 92.64 Hz, 2F).

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Supplementary Material

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Highlights:

- A mild, rapid and selective difluorocarbene-mediated triclassification of iododifluoroacetophenone with secondary amines was developed to achieve the N-CF_2H derivatives, formamides from appropriate secondary amines.
- The corresponding prediction tree model was based on the geometry structure of raw materials.
- This difluorocarbene-mediated triclassification reaction and the corresponding tree model were used to implement the late stage modifications of medicinal drugs.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: