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The syntheses of nonnucleoside, HIV-1 reverse transcriptase inhibitors containing a CF_2 group The $S_{RN}1$ reactions of 2-(bromodifluoromethyl)benzoxazole with the anions derived from heterocyclic thiols and phenolic compounds

Conrad R. Burkholder[a], William R. Dolbier Jr.[a,*], Maurice Médebielle[b,1]

[a]*Department of Chemistry, University of Florida, P.O. Box 117200, Gainesville, FL 32611-7200, USA*
[b]*Université Denis Diderot (Paris 7), Laboratoire d'Electrochimie Moléculaire, UMR CNRS 7591, 2 Place Jussieu, 75251 Paris Cédex 05, France*

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Dedicated to Professor Paul Tarrant on the occasion of his 85th birthday

Abstract

In an effort to prepare new fluorine-containing compounds which are active against HIV, the $S_{RN}1$ reactions of 2-(bromodifluoromethyl)benzoxazole (**5**) with the anions of heterocyclic thiols and phenolic compounds were carried out. The products (**6a–j** and **7a–f**), which all have a CF_2 group, were tested for activity against HIV, and several were found to be active, including **6f** which was very active. By comparing the activity of **6e**, which contains a CF_2 group, to that of **10**, where the CF_2 is replaced by a CH_2 group, it was demonstrated that fluorine atom substitution produces a 10-fold increase in activity against HIV-1.

Keywords: $S_{RN}1$ reactions; Heterocyclic thiols; Phenolic compounds

1. Introduction

The AIDS disease (acquired immunodeficiency syndrome) has been shown to be caused by a virus designated as HIV-1 (human immunodeficiency virus type 1). There is a current worldwide AIDS epidemic of major proportions, especially on the African continent where the rate of infection by HIV in the population has been estimated to be 25% or higher in some African nations.

Recent results in the treatment of AIDS with drugs which work by inhibiting the HIV protease enzyme [1], have lead to a decrease in the number of AIDS-related deaths in the United States; however, it has been found that, in order to prevent the HIV from developing resistance to the drugs, a strict regimen of frequent doses must be followed, as well as using a combination therapy popularly referred to in the press as a drug cocktail. These drugs are exceedingly expensive, have some adverse side effects, and the patient must adhere to a strict drug regimen for the remainder of his life. Thus, the HIV protease inhibitors are an effective treatment, but not the ideal cure that is so highly sought after.

The problem then remains to find new drugs which are effective against AIDS, and especially effective against the resistant mutant strains of HIV which rapidly arise upon treatment with active chemical compounds.

Certain simple chemical compounds known as nonnucleoside reverse transcriptase inhibitors (NNRTIs) [2–4] have been found to be very active against the HIV virus in vitro and in clinical trials; however, they suffer from the drawback of the rapid onset of viral resistance from mutant strains of HIV. If a way could be found to induce activity against mutant strains of HIV, then such compounds would be useful in the treatment of AIDS.

Compound **1** is a potent NNRTI [5–8] agent, although to our knowledge it has not been approved by the FDA for use in AIDS treatment. The aim of the research reported in this paper was to selectively incorporate fluorine substituents into structural analogues of compound **1**, in order to determine the impact of such substitution on biological activity.

* Corresponding author. Tel.: +1-352-392-0591; fax: +1-352-846-1962.
E-mail addresses: wrd@chem.ufl.edu (W.R. Dolbier Jr.), mauricem@paris7.jussieu.fr (M. Médebielle).
[1] Fax: +33-1-44-27-76-25.

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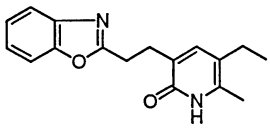
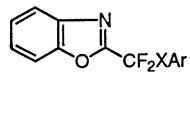
Dramatic enhancements of potency have been reported in many cases for partially fluorinated analogs of biologically active compounds [9]. As part of an ongoing project investigating the synthesis of fluorine-containing heterocycles, synthetic methods were developed whereby various analogs of **1** could be prepared wherein one CH_2 was replaced with a CF_2 and where the other CH_2 was replaced with a heteroatom (X). Thus, the plan was to keep the benzoxazole ring of **1** and modify not only the two-atom tether, but the pyridone ring as well, so that the target compounds would have the general appearance of **2**.



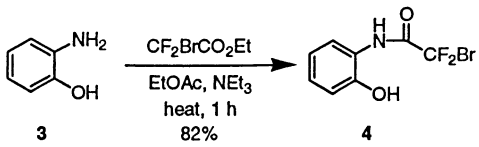
1



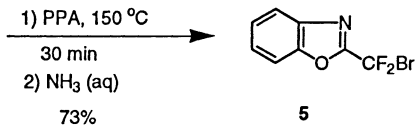
2

2. Chemical results and discussion

Analogues of **1** were, in part, chosen as synthetic targets because of the ready availability of fluorinated precursor, **5**. A convenient two-step synthesis of **5** from 2-aminophenol (**3**) was recently reported, via bromodifluoroacetylation with CF_2BrCO_2Et to give amide **4**, followed by cyclization with polyphosphoric acid (PPA) to give **5** [10].



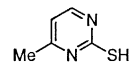
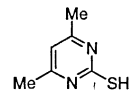
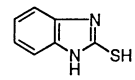
3 **4**



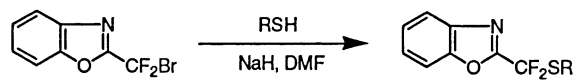
5

It was expected that the CF_2Br group of **5** would be reactive with sulfur nucleophiles [11]. Initial experimentation with **5** and sodium thiolate lead to the observation that the reaction giving **6a** was rapid and exothermic, being complete in only 15 min. It was soon discovered that a wide range of anions from mercapto-substituted heterocycles, RSH, were able to be successfully reacted with **5** to give **6a–j**, as can be seen by looking at Table 1. The anions were conveniently generated using dry NaH, which was weighed out rapidly in the air and transferred to the reaction apparatus as quickly as possible. The isolated yields of these reactions vary from 51 to 86%, and no significant optimization of the yields was performed other than using a two-fold excess of the anion and following the reaction by TLC until the starting material (**5**) was gone. By looking at Table 1, it can be seen that substitution of an aromatic CH with a nitrogen leads to lowered reactivity with **5**. Thus, the anion

Table 1
Conditions and isolated yields for the reactions of **5** with the anions of benzenethiol and mercapto-substituted heterocycles (RSH) to give **6a–j**

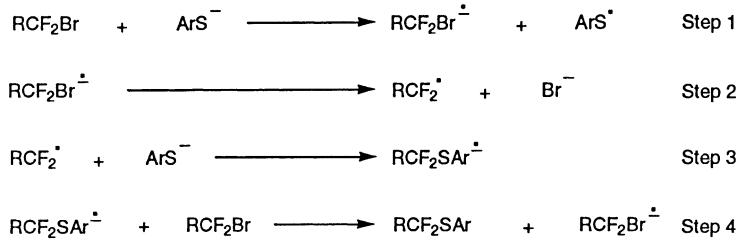
Entry	RSH	Conditions	Product	% Yield
1		RT, 15 min	**6a**	86
2		RT, 23 h	**6b**	82
3		RT, 23 h	**6c**	51
4		RT, 23 h	**6d**	76
5		60°C, 24 h	**6e**	65
6		60°C, 24 h	**6f**	62
7		60°C, 24 h	**6g**	74
8		60°C, 24 h	**6h**	72
9		60°C, 24 h	**6i**	59
10		100°C, 23 h	**6j**	84

of 2-mercaptopyridine (entry 2) is much less reactive than benzenethiolate (Entry 1). Multiple nitrogen substitution in the heterocyclic ring of the anion results in greatly reduced reactivity as can be seen for the anion of 5-mercapto-1-methyltetrazole, which only reacted at 100°C after 24 h (Entry 10). This is consistent with an electronic effect where electron-withdrawing substitution of the anion slows down the reaction.



5 **6a-j**

Several sulfur-based nucleophiles that did not work in this reaction were discovered: for example, the anions of 5-methyl-1,3,4-thiadiazole-2-thiol, 2-imidazolidinethione, 2-mercaptobenzoxazole, 6-mercaptopurine, pentafluorobenzenethiol, 2-thiouracil and 4-(trifluoromethyl)-2-pyrimidinethiol gave decomposition from which none of the desired product could be isolated. Also, the attempted reaction of sodium thiocyanate lead to decomposition.



Scheme 1. Steps of the $S_{RN}1$ reaction.sc1

The displacement of bromide from the CF_2Br group does not occur by a simple S_N2 mechanism due to the presence of the alpha fluorines. Instead, it proceeds by an $S_{RN}1$ mechanism [12] involving a single electron transfer chain process as represented in Scheme 1. The observation that the presence of 1,4-dinitrobenzene strongly inhibits the reaction of **5** with sodium benzenethiolate is evidence for the $S_{RN}1$ mechanism. Thus, the reaction of the CF_2Br group is limited to nucleophiles that can react by such an $S_{RN}1$ mechanism.

It was found that sodium phenolate reacts with the CF_2Br of **5** much more slowly than sodium benzenethiolate; however, after 24 h at room temperature, the reaction was complete, and the desired product **7b** was isolated in 70% yield. In fact, other substituted phenolates, as well as related benzenoid derivatives reacted with **5** to give the expected displacement products **7a–f** (Table 2). The only heterocyclic oxyanion that was tried for this reaction was the anion of 2-hydroxypyridine, and it gave only decomposition when heated with **5**.

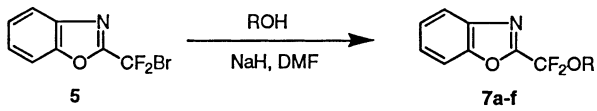
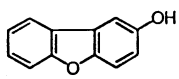
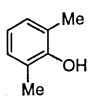
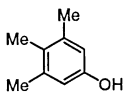
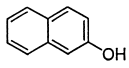
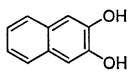
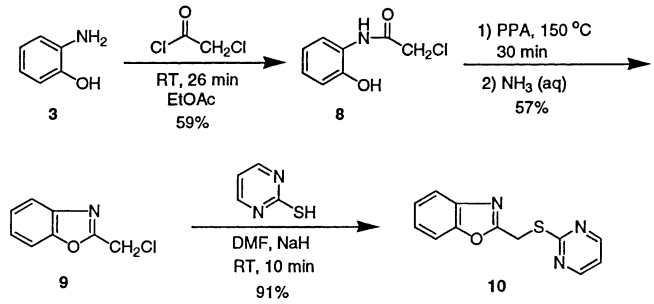


Table 2
Conditions and isolated yields for the reactions of **5** with the anions of phenol and hydroxybenzenoid compounds to give products **7a–f**

Entry	ROH	Conditions	Product	% Yield
1		RT, 6 h	**7a**	44
2		RT, 24 h	**7b**	70
3		RT, 24 h	**7c**	32
4		RT, 24 h	**7d**	47
5		RT, 24 h	**7d**	42
6		100°C, 2 h	**7f**	28

In order to be able to determine whether the fluorine substitution enhances the activity against HIV, it was necessary to prepare at least one analog of an active compound where the only difference in the chemical structure is the replacement of the two fluorine atoms with two hydrogen atoms. The active compound that was chosen for this study was **6e**, and the hydrogen-substituted analog **10** was easily synthesized in three steps. Firstly, 2-aminophenol was chloroacetylated with chloroacetyl chloride to give amide **8** in moderate yield; secondly, amide **8** was cyclodehydrated by heating with polyphosphoric acid to give 2-(chlorodifluoromethyl)benzoxazole **9** in moderate yield; and lastly, **9** was allowed to react with the anion of 2-mercaptopyrimidine to give **10** in excellent yield.



3. Biological activity

Compounds **6a–j**, **7a–f** and **10** were evaluated in the preliminary screen of the In Vitro Anti-AIDS Drug Discovery Program at the National Cancer Institute.[2] The activity data are reported as effective concentration (EC_{50}), the concentration of compound for which there is 50% protection in cells infected by HIV-1. The data for the active compounds are presented in Table 3; those compounds not included in the table were found to be inactive. The compounds are listed in order of decreasing potency, and it should be noted that smaller values for the EC_{50} are an indication of higher activity.

There are several points that are worth mentioning concerning the structure activity relationships in this series of compounds. Firstly, all of the active compounds were derivatives of benzoxazole, this system having been chosen to test the impact of fluorine substitution on activity (a) on the basis of the activity of prototype molecule **1**, and (b)

[2] For a description of the Anti-AIDS testing protocol see [3].

Table 3
Effective concentrations (EC_{50}) of active compounds against HIV-1

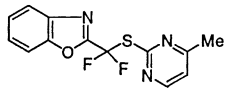
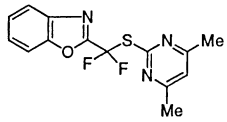
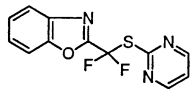
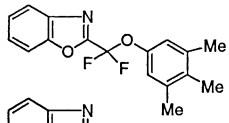
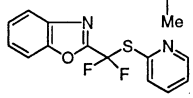
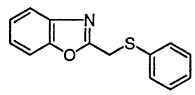
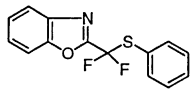
Entry	Number	Structure	$EC_{50}\times10^{-6}$ M
1	**6f**		0.0646
2	**6g**		2.16
3	**6e**		3.14
4	**7d**		13.0
5	**6b**		29.2
6	**10**		35.3
7	**6a**		36.0

Table 4
Effective concentrations (EC_{50}) for **6e** and **6f** against drug-resistant mutant strains of HIV

Entry	HIV variant strains	$EC_{50}\times10^{-6}$ M **6e**	$EC_{50}\times10^{-6}$ M **6f**
1	HIV-1 (IIIB)	3.36	0.067
2	DdI resistant[a]	Inactive	0.159
3	4×AZT (AZT-R)[b]	0.373	Inactive
4	OC/100[c]	4.08	0.38
5	HEPT/236[d]	8.64	0.11
6	Calo resistant[e]	3.2	0.43
7	DPS[f]	Inactive	Inactive
8	HIV-2 (ROD)	Inactive	Inactive
9	SIV (B670)[g]	Inactive	Inactive

[a] A ddI-resistant mutant bearing a mutation at amino acid codon 74.
[b] AZT-resistant mutant bearing four mutations.
[c] An oxathiin carboxanilide-resistant mutant bearing a mutation at amino acid codon 100, changing from leucine to isoleucine.
[d] A HEPT-resistant mutant bearing a mutation at amino acid codon 236.
[e] A Calanolide-resistant mutant bearing a mutation at amino acid codon 139, changing from threonine to isoleucine.
[f] A diphenyl sulfone-resistant mutant bearing a mutation at amino acid codon 181, changing from tyrosine to cysteine.
[g] Simian immunodeficiency virus.

because of synthetic convenience (based on availability of precursor **5**). Secondly, only compounds with six-membered rings such as benzene, pyridine or pyrimidine rings attached to the sulfur were active, while compounds with five-membered rings such as **6c**, **6d**, **6h**, **6i**, and **6j** were inactive. Of the compounds with six-membered rings, it was found that those with a pyrimidine ring was most potent, followed by those with a pyridine ring, and then those with a benzene ring. This conclusion follows by comparing the activities of compounds **6e** (Entry 3), **6b** (Entry 5) and **6a** (Entry 7). Furthermore, the activity of the pyrimidine-substituted compound is greatly enhanced by the addition of a methyl group in the 4-positon of the pyrimidine ring as in **6f** (Entry 1), which was the most potent compound in this study; however, having two methyls, as in **6g** (Entry 2), did not further enhance the activity, and, in fact, the addition of a second methyl produced a decrease in potency. Nearly all of the active compounds had a sulfur atom in the tether connecting the two heterocyclic rings, while compounds with an oxygen in place of the sulfur were all inactive except for **7d** (Entry 4). From comparing the activity of **6a** (Entry 7) to **7b** which was inactive, it can be concluded that having a sulfur in the tether rather than an oxygen, enhances the activity. Lastly, but most importantly, a comparison of the activity of the fluorine-containing compound **6e** (Entry 3), to the hydrogen-substituted analog **10** (Entry 6), leads to the conclusion that fluorine substitution is responsible for a 10-fold increase in potency. One can speculate why this is so. The fluorine substituents may enhance the lipophilicity of the adjacent benzoxazole ring, thus increasing it's binding to the lipophilic pocket of the binding site of the reverse transcriptase enzyme. If this is the case, then it may well be that this enhancement of activity by fluorine substitution, could be applicable to many other biologically active compounds where it is possible to replace a CH_2 group which is adjacent to an aromatic ring with a CF_2 group.

Compounds **6e** and **6f** were referred for testing in the advanced screens, and the results can be seen by looking at Table 4. Although the activity of **6f** against the wild type HIV-1 (III B) was very good (Entry 1), it was inactive against a number of mutant strains of HIV (Entries 3, 7, 8 and 9). Compound **6e** was similarly inactive in a number of cases (Entries 2, 7, 8 and 9).

Although the results of these studies have demonstrated that fluorine atom substitution can enhance the activity against HIV substantially, it must be concluded from the advanced screening that there is no unusual activity against drug resistant mutant strains of HIV induced by fluorine atom substitution. Consequently, even the most potent compound (**6f**) resulting from this work is unlikely to be clinically useful in the treatment of AIDS. The discovery that fluorine atom substitution enhances biological activity is an intriguing result which may well be widely applicable to other biologically active systems.

4. Experimental section

4.1. General comments

Melting points are uncorrected. The ^{1}H NMR spectra were measured at 300 MHz and chemical shifts are reported

in ppm downfield of internal $SiMe_4$. The ^{19}F NMR spectra were measured at 282 MHz, and chemical shifts are reported in ppm upfield of internal $CFCl_3$. The ^{13}C NMR spectra were measured at 75 MHz with all protons decoupled, and the chemical shifts are reported in ppm downfield of $SiMe_4$. The mass spectra were recorded at 70 eV. All of the solvents and reagents were used as received from the supplier without purification.

4.1.1. 2-(Bromodifluoromethyl)benzoxazole (**5**)

Compound **5** was prepared according to a previously reported procedure [10].

4.2. General procedure for $S_{RN}1$ reactions of compound **5**

A 25 ml, three-necked, round-bottom flask was equipped with a magnetic stirrer, two rubber septa and a glass stopper. After flushing with nitrogen, 15 ml of dry DMF (commercial anhydrous) was added by syringe followed by 204 mg (8.08 mmol) of NaH (dry, 95%).

To the stirred suspension was added 8.08 mmol of the indicated mercaptoheterocycle or phenolic compound, a little bit at a time, over a period of 5 min. Hydrogen gas was evolved and the flask became warm. After stirring for 20 min, a clear solution was obtained.

Then 1.00 g (4.03 mmol) of 2-(bromodifluoromethyl)-benzoxazole (**5**) was added all at once, and the solution was allowed to stir at the indicated temperature for the indicated amount of time. The product was isolated by one of the three following procedures.

Procedure A: The reaction mixture was poured into a solution of 0.43 g (8.04 mmol) of NH_4Cl in 45 ml of water, and the mixture was extracted five times with 10 ml portions of $CHCl_3$. The combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation at reduced pressure (water aspirator, 70°C). The resulting liquid was subjected to full vacuum (0.15 mm) for 6 h to remove the DMF. The resulting oil was purified by flash column chromatography [13] on silica gel and eluting with ethyl acetate/hexane.

Procedure B: The reaction mixture was poured into 45 ml of water, and the mixture was extracted five times with 10 ml portions of $CHCl_3$. The combined organic layers were washed five times with 50 ml portions of water to remove the DMF, then dried over Na_2SO_4 and concentrated by rotary evaporation at reduced pressure (water aspirator, 70°C). The resulting oil was purified by flash column chromatography [13] on silica gel and eluting with ethyl acetate/hexane.

Procedure C: The reaction mixture was poured into 45 ml of water, and the resulting precipitate was collected by suction filtration and purified by recrystallization.

4.2.1. 2-[Difluoro(phenylthio)methyl]benzoxazole (**6a**)

Following the *General Procedure*, the reaction of **5** with thiophenol was carried out at room temperature for 15 min. After workup by *Procedure A*, 0.9596 g (86%) of **6a** was obtained as a white solid, mp 59.5–61.8°C: ^1H NMR ($CDCl_3$) δ 7.82 (dm, 1H, J=7.6 Hz), 7.64 (m, 3H), 7.5–7.35 (m, 5H); ^{19}F NMR ($CDCl_3$) ϕ −74.9 (s); ^{13}C NMR ($CDCl_3$) δ 156.5 (t, J_{CF}=33.5 Hz), 150.6 (s), 139.8 (s), 136.9 (s), 130.7 (s), 129.3 (s), 127.1 (s), 125.5 (s), 124.6 (t, J_{CF}=2.0 Hz), 121.4 (s), 121.0 (t, J_{CF}=277.5 Hz), 111.4 (s); HRMS (70 eV) calcd for $C_{14}H_9F_2NOS$ 277.0373, found 277.0328. Anal. Calcd for $C_{14}H_9F_2NOS$: C, 60.64; H, 3.27; N, 5.05. Found C, 60.57; H, 3.02; N, 4.90.

4.2.2. 2-[Difluoro-(2-pyridylthio)methyl]benzoxazole (**6b**)

Following the *General Procedure*, the reaction of **5** with 2-mercaptopyridine was carried out at room temperature for 23 h. After workup by *Procedure A*, 0.9172 g (82%) of **6b** was obtained as a yellow solid, mp 50–54°C: ^1H NMR ($CDCl_3$) δ 8.45 (ddd, 1H, J=1.0, 2.0, and 4.8 Hz), 7.81 (dm, 1H, J=7.8 Hz), 7.7–7.6 (m, 3H), 7.48 (dt, 1H, J_d=1.5 and J_t=7.3 Hz), 7.42 (dt, 1H, J_d=1.3 and J_t=7.4 Hz), 7.2 (ddd, 1H, J=1.6, 4.9, and 7.2 Hz); ^{19}F NMR ($CDCl_3$) ϕ −74.3 (s); ^{13}C NMR ($CDCl_3$) δ 156.6 (t, J_{CF}=33.0 Hz), 150.6 (s), 150.4 (s), 150.2 (t, J_{CF}=2.5 Hz), 139.9 (s), 137.4 (s), 128.4 (t, J_{CF}=1.8 Hz), 127.2 (s), 125.5 (s), 123.4 (s), 121.4 (s), 121.2 (t, J_{CF}=277.2 Hz), 111.5 (s); HRMS (70 eV) calcd for $C_{13}H_8F_2N_2OS$ 278.0325, found 278.0325. Anal. Calcd for $C_{13}H_8F_2N_2OS$: C, 56.11; H, 2.90; N, 10.07. Found C, 55.95; H, 2.76; N, 9.96.

4.2.3. 2-[Difluoro-[(1H-imidazol-2-yl)thio]methyl]-benzoxazole (**6c**)

Following the *General Procedure*, the reaction of **5** with 2-mercaptoimidazole was carried out at room temperature for 23 h. After workup by *Procedure A*, 0.5445 g (51%) of **6c** was obtained as an off-white solid, mp 162.5–163.8°C: ^1H NMR ($CDCl_3$) δ 7.79 (m, 1H), 7.57 (m, 1H), 7.44 (m, 2H), 7.28 (s, 2H); ^{19}F NMR ($CDCl_3$) ϕ −74.1 (s); ^{13}C NMR (DMSO-d_6) δ 155.3 (t, J_{CF}=33.0 Hz), 150.4 (s), 139.4 (s), 127.9 (s), 126.9 (t, J_{CF}=3.5 Hz), 126.0 (s), 121.4 (s), 120.4 (t, J_{CF}=278.2 Hz), 112.0 (s); HRMS (70 eV) calcd for $C_{11}H_7F_2N_3OS$ 267.0278, found 267.0265. Anal. Calcd for $C_{11}H_7F_2N_3OS$: C, 49.44; H, 2.64; N, 15.72. Found C, 49.90; H, 2.55; N, 15.72.

4.2.4. 2-[Difluoro-[(1-methyl-1H-imidazol-2-yl)thio]-methyl]benzoxazole (**6d**)

Following the *General Procedure*, the reaction of **5** with 2-mercapto-1-methylimidazole was carried out at room temperature for 23 h. After workup by *Procedure A*, 0.8575 g (76%) of **6d** was obtained as a pale amber solid, mp 84.0–86.6°C: ^1H NMR ($CDCl_3$) δ 7.82 (m, 1H), 7.63 (m, 1H), 7.49 (dt, 1H, J_d=1.5 and J_t=7.6 Hz), 7.43 (dt, 1H, J_d=1.3 and J_t=7.4 Hz), 7.16 (br s, 2H), 3.84 (s, 3H); ^{19}F NMR ($CDCl_3$) ϕ −74.1 (s); ^{13}C NMR ($CDCl_3$) δ 155.3 (t, J_{CF}=32.7 Hz), 150.4 (s), 139.4 (s), 131.3 (s), 129.9 (t, J_{CF}=2.8 Hz), 127.1 (s), 125.6 (s), 125.3 (s), 121.1 (s),

120.4 (t, J_{CF}=280.0 Hz), 111.2 (s), 34.1 (s); HRMS (70 eV) calcd for $C_{12}H_9F_2N_3OS$ 281.0434, found 281.0433. Anal. Calcd for $C_{12}H_9F_2N_3OS$: C, 51.24; H, 3.22; N, 14.94. Found C, 51.27; H, 3.08; N, 14.75.

4.2.5. 2-[Difluoro-(2-pyrimidinylthio)methyl]benzoxazole (**6e**)

Following the *General Procedure*, the reaction of **5** with 2-mercaptopyrimidine was carried out at 60°C for 24 h. After workup by *Procedure A*, 0.7311 g (65%) of **6e** was obtained as an amber solid, mp 64.0–68.5°C: ^{1}H NMR ($CDCl_3$) δ 8.41 (d, 2H, J=4.9 Hz), 7.82 (dm, 1H, J=7.3 Hz), 7.64 (dm, 1H, J=7.3 Hz), 7.5–7.4 (m, 2H), 7.0 (t, 1H, J=4.9 Hz); ^{19}F NMR ($CDCl_3$) ϕ −77.3 (s); ^{13}C NMR ($CDCl_3$) δ 166.7 (t, J_{CF}=5.6 Hz), 157.4 (s), 157.1 (t, J_{CF}=32.2 Hz), 150.4 (s), 140.1 (s), 126.8 (s), 125.2 (s), 121.2 (s), 120.4 (t, J_{CF}=273.7 Hz), 111.3 (s); HRMS (FAB) calcd for $C_{12}H_8F_2N_3OS$ 280.0356, found 280.0352. Anal. Calcd for $C_{12}H_7F_2N_3OS$: C,51.61; H, 2.53; N, 15.05. Found C, 51.93; H, 2.46; N, 14.86.

4.2.6. 2-[Difluoro[(4-methyl-2-pyrimidinyl)thio]methyl]-benzoxazole (**6f**)

Following the *General Procedure*, the reaction of **5** with 2-mercapto-4-methylpyrimidine hydrochloride was carried out at 60°C for 24 h with the exception that 408 mg (16.16 mmol) of NaH was used.. After workup by *Procedure B*, 0.7294 g (62%) of **6f** was obtained as a yellow solid, mp 69.5–72.6°C: ^{1}H NMR ($CDCl_3$) δ 8.22 (d, 1H, J=5.1 Hz), 7.82 (dm, 1H, J=7.3 Hz), 7.64 (dm, 1H, J=7.6 Hz), 7.49–7.38 (m, 2H), 6.82 (d, 1H, J=4.9 Hz), 2.18 (s, 3H); ^{19}F NMR ($CDCl_3$) ϕ −77.4 (s); ^{13}C NMR ($CDCl_3$) δ 168.1 (s), 166.0 (t, J_{CF}=6.0 Hz), 157.6 (t, J_{CF}=32.0 Hz), 156.9 (s), 150.3 (s), 140.2 (s), 126.7 (s), 125.2 (s), 121.1 (s), 120.6 (t, J_{CF}=273.0 Hz), 117.9 (s), 111.2 (s), 23.5 (s); HRMS (70 eV) calcd for $C_{13}H_9F_2N_3OS$ 293.0434, found 293.0435. Anal. Calcd for $C_{13}H_9F_2N_3OS$: C, 53.24; H, 3.09; N, 14.33. Found C, 53.24; H, 3.03; N, 14.00.

4.2.7. 2-[Difluoro-[(4,6-dimethyl-2-pyrimidinyl)-thio]methyl]benzoxazole (**6g**)

Following the *General Procedure*, the reaction of **5** with 4,6-dimethyl-2-mercaptopyrimidine was carried out at 60°C for 24 h. After workup by *Procedure B*, 0.9172 g (74%) of **6g** was obtained as an off-white solid, mp 57.3–62.0°C: ^{1}H NMR ($CDCl_3$) δ 7.82 (dm, 1H, J=7.3 Hz), 7.63 (dm, 1H, J=7.3 Hz), 7.43 (m, 2H), 6.65 (s, 1H), 2.12 (s, 6H); ^{19}F NMR ($CDCl_3$) ϕ −77.5 (s); ^{13}C NMR ($CDCl_3$) δ 167.4 (s), 165.3 (t, J_{CF}=6.0 Hz), 157.9 (t, J_{CF}=32.2 Hz), 150.2 (s), 140.3 (s), 126.6 (s), 125.1 (s), 121.1 (s), 120.8 (t, J_{CF}=272.5 Hz), 117.3 (s), 111.1 (s), 23.2 (s); HRMS (70 eV) calcd for $C_{14}H_{11}F_2N_3OS$ 307.0591, found 307.0591. Anal. Calcd for $C_{14}H_{11}F_2N_3OS$: C, 54.72; H, 3.61; N, 13.67. Found C, 54.91; H, 3.56; N, 13.49.

4.2.8. 2-[Difluoro-[(1-methyl-1H-1,3,4-triazol-2-yl)thio]methyl]benzoxazole (**6h**)

Following the *General Procedure*, the reaction of **5** with 4-methyl-4*H*-1,2,4-triazole-3-thiol was carried out at 60°C for 24 h. After workup by *Procedure A*, 0.814 g (72%) of **6h** was obtained as a pale yellowish solid, mp 143.6–145.5°C: ^{1}H NMR ($CDCl_3$) δ 8.40 (s, 1H), 7.82 (dm, 1H, J=7.3 Hz), 7.65 (dm, 1H, J=8.0 Hz), 7.52 (dt, 1H, J_d=1.5 and J_t=7.4 Hz), 7.45 (dt, 1H, J_d=1.3 and J_t=7.3 Hz), 3.87 (s, 3H); ^{19}F NMR ($CDCl_3$) ϕ −72.1 (s); ^{13}C NMR ($CDCl_3$) δ 154.6 (t, J_{CF}=32.2 Hz), 150.5 (s), 147.4 (s), 140.7 (s), 139.3 (s), 127.5 (s), 125.6 (s), 121.3 (s), 120.0 (t, J_{CF}=281.5 Hz), 111.4 (s), 32.0 (s); HRMS (70 eV) calcd for $C_{11}H_8F_2N_4OS$ 282.0387, found 282.0382. Anal. Calcd for $C_{11}H_8F_2N_4OS$: C, 46.81; H, 2.86; N, 19.85. Found C, 46.70; H, 2.66; N, 19.84.

4.2.9. 2-[Difluoro-[(1H-benzimidazol-2-yl)thio]methyl]-benzoxazole (**6i**)

Following the *General Procedure*, the reaction of **5** with 2-mercaptobenzimidazole was carried out at 60°C for 24 h. After workup by *Procedure C* with recrystallization from THF (2 crops), 0.7599 g (59%) of **6i** was obtained as a white solid, mp 267°C (dec): ^{1}H NMR (DMSO-d_6) δ 13.5 (br s, 1H), 7.91 (m, 2H), 7.66–7.52 (m, 4H), 7.36–7.22 (m, 2H); ^{19}F NMR (DMSO-d_6) ϕ −71.2 (s); ^{13}C NMR (125.7 MHz, DMSO-d_6) δ 154.9 (t, J_{CF}=32.6 Hz), 150.2 (s), 139.1 (s), 136.2 (s), 127.9 (s), 126.0 (s), 123.2 (br s), 121.3 (s), 120.3 (t, J_{CF}=279.2 Hz), 111.9 (s); HRMS (70 eV) calcd for $C_{15}H_9F_2N_3OS$ 317.0434, found 317.0428. Anal. Calcd for $C_{15}H_9F_2N_3OS$: C, 56.78; H, 2.86; N, 13.24. Found C, 56.68; H, 2.74; N, 13.09.

4.2.10. 2-[Difluoro-[(1-methyl-1H-tetrazol-5-yl)-thio]methyl]benzoxazole (**6j**)

Following the *General Procedure*, the reaction of **5** with 5-mercapto-1-methyltetrazole was carried out at 100°C for 23 h. After workup by *Procedure B*, 0.9642 g (84%) of **6j** was obtained as a yellow solid, mp 79.0–82.0°C: ^{1}H NMR ($CDCl_3$) δ 7.83 (dm, 1H, J=7.6 Hz), 7.66 (dm, 1H, J=7.8 Hz), 7.54 (dt, 1H, J_d=1.5 and J_t=7.4 Hz), 7.48 (dt, 1H, J_d=1.3 and J_t=7.5 Hz), 4.25 (s, 3H); ^{19}F NMR ($CDCl_3$) ϕ −70.4 (s); ^{13}C NMR ($CDCl_3$) δ 153.9 (t, J_{CF}=31.5 Hz), 150.4 (s), 144.0 (t, J_{CF}=2.5 Hz), 139.1 (s), 127.76 (s), 125.7 (s), 121.3 (s), 119.6 (t, J_{CF}=282.8 Hz), 111.4 (s), 34.8 (s); HRMS (70 eV) calcd for $C_{10}H_7F_2N_5OS$ 283.0339, found 283.0347. Anal. Calcd for $C_{10}H_7F_2N_5OS$: C, 42.40; H, 2.49; N, 24.72. Found C, 42.55; H, 2.49; N, 24.44.

4.2.11. 2-(Difluoro-2-benzoxazolylmethoxy)dibenzofuran (**7a**)

Following the *General Procedure*, the reaction of **5** with 2-hydroxydibenzofuran was carried out at room temperature for 6 h. After workup by *Procedure B*, 0.620 g (44%) of **7a** was obtained as a white solid, mp 106.0–108.0°C: ^{1}H NMR ($CDCl_3$) δ 7.96–7.87 (m, 3H), 7.67 (m, 1H), 7.59–

7.33 (m, 7H); ^{19}F NMR ($CDCl_3$) ϕ −68.4 (s); ^{13}C NMR ($CDCl_3$) δ 156.9 (s), 154.5 (t, J_{CF}=42.8 Hz), 153.9 (s), 150.5 (s), 144.7 (t, J_{CF}=2.0 Hz), 139.7 (s), 127.7 (s), 127.1 (s), 125.4 (s), 125.0 (s), 123.6 (s), 122.8 (s), 121.5 (s), 121.3 (s), 120.8 (s), 115.7 (t, J_{CF}=260.9 Hz), 114.3 (t, J_{CF}=1.0 Hz), 112.1 (s), 111.7 (s), 111.4 (s); HRMS (70 eV) calcd for $C_{20}H_{11}F_2NO_3$ 351.0707, found 351.0703. Anal. Calcd for $C_{20}H_{11}F_2NO_3$: C, 68.38; H, 3.16; N, 3.99. Found C, 68.48; H, 3.12; N, 3.97.

4.2.12. 2-[Difluoro(phenoxy)methyl]benzoxazole (**7b**)

Following the *General Procedure*, the reaction of **5** with phenol was carried out at room temperature for 24 h. After workup by *Procedure B*, 0.7347 g (70%) of **7b** was obtained as a pale amber liquid: ^{1}H NMR ($CDCl_3$) δ 7.88 (dm, 1H, J=7.3 Hz), 7.66 (dm, 1H, J=7.3 Hz), 7.54–7.26 (m, 7H); ^{19}F NMR ($CDCl_3$) ϕ −68.3 (s); ^{13}C NMR ($CDCl_3$) δ 154.5 (t, J_{CF}=42.6 Hz), 150.5 (s), 149.4 (s), 139.6 (s), 129.5 (s), 127.1 (s), 126.4 (s), 125.4 (s), 121.8 (s), 121.5 (s), 115.5 (t, J_{CF}=261.1 Hz), 111.3 (s); HRMS (70 eV) calcd for $C_{14}H_9F_2NO_2$ 261.0601, found 261.0590. Anal. Calcd for $C_{14}H_9F_2NO_2$: C, 64.37; H, 3.47; N, 5.36. Found C, 64.29; H, 3.42; N, 5.29.

4.2.13. 2-[Difluoro-(2,6-dimethylphenoxy)methyl]-benzoxazole (**7c**)

Following the *General Procedure*, the reaction of **5** with 2,6-dimethylphenol was carried out at room temperature for 24 h. After workup by *Procedure B*, 0.379 g (32%) of **7c** was obtained as a clear, pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.90 (dm, 1H, J=7.1 Hz), 7.68 (dm, 1H, J=7.3 Hz), 7.54–7.44 (m, 2H), 7.10 (m, 3H), 2.41 (s, 6H); ^{19}F NMR ($CDCl_3$) ϕ −66.7 (s); ^{13}C NMR ($CDCl_3$) δ 155.0 (t, J_{CF}=43.1 Hz), 150.6 (s), 146.6 (t, J_{CF}=2.0 Hz), 139.7 (s), 132.7 (s), 129.0 (s), 127.1 (s), 126.5 (s), 125.4 (s), 121.5 (s), 116.3 (t, J_{CF}=262.6 Hz), 111.4 (s), 17.1 (t, J_{CF}=3.3 Hz); HRMS (70 eV) calcd for $C_{16}H_{13}F_2NO_2$ 289.0914, found 289.0895. Anal. Calcd for $C_{16}H_{13}F_2NO_2$: C, 66.43; H, 4.53; N, 4.84. Found C, 66.34; H, 4.57; N, 4.84.

4.2.14. 2-[Difluoro-(3,4,5-trimethylphenoxy)methyl]-benzoxazole (**7d**)

Following the *General Procedure*, the reaction of **5** with 3,4,5-trimethylphenol was carried out at room temperature for 24 h. After workup by *Procedure B*, 0.5699 g (47%) of **7d** was obtained as a white solid, mp 40.0–42.6°C: ^{1}H NMR ($CDCl_3$) δ 7.87 (dm, 1H, J=7.3 Hz); 7.66 (dm, 1H, J=7.6 Hz), 7.52–7.42 (m, 2H), 6.98 (s, 2H), 2.29 (s, 6H), 2.14 (s, 3H); ^{19}F NMR ($CDCl_3$) ϕ −68.0 (s); ^{13}C NMR ($CDCl_3$) δ 154.8 (t, J_{CF}=43.1 Hz), 150.5 (s), 146.5 (t, J_{CF}=1.8 Hz), 139.7 (s), 137.8 (s), 133.3 (s), 127.0 (s), 125.3 (s), 121.5 (s), 120.6 (s), 115.5 (t, J_{CF}=260.1 Hz), 111.3 (s), 20.5 (s), 14.8 (s); HRMS (70 eV) calcd for $C_{17}H_{15}F_2NO_2$ 303.1071, found 303.1074. Anal. Calcd for $C_{17}H_{15}F_2NO_2$: C, 67.32; H, 4.98; N, 4.62. Found C, 67.19; H, 5.07; N, 4.64.

4.2.15. 2-[Difluoro-(2-naphthalenyloxy)methyl]-benzoxazole (**7e**)

Following the *General Procedure*, the reaction of **5** with 2-naphthol was carried out at room temperature for 24 h. After workup by *Procedure B*, 0.5322 g (42%) of **7e** was obtained as a white solid, mp 51.5–53.6°C: ^{1}H NMR ($CDCl_3$) δ 7.9–7.78 (m, 5H), 7.66 (dm, 1H, J=7.3 Hz), 7.54–7.42 (m, 5H); ^{19}F NMR ($CDCl_3$) ϕ −68.0 (s); ^{13}C NMR ($CDCl_3$) δ 154.6 (t, J_{CF}=42.8 Hz), 150.6 (s), 147.0 (s), 139.7 (s), 133.6 (s), 131.6 (s), 129.7 (s), 127.71 (s), 127.67 (s), 127.2 (s), 126.8 (s), 126.0 (s), 125.5 (s), 121.6 (s), 121.0 (s), 118.9 (s), 115.8 (t, J_{CF}=261.1 Hz), 111.4 (s); HRMS (70 eV) calcd for $C_{18}H_{11}F_2NO_2$ 311.0758, found 311.0783. Anal. Calcd for $C_{18}H_{11}F_2NO_2$: C, 69.45; H, 3.56; N, 4.50. Found C, 69.41; H, 3.49; N, 4.40.

4.2.16. 2-[Difluoro-(3-hydroxy-2-naphthalenyloxy)-methyl]benzoxazole (**7f**)

Following the *General Procedure*, the reaction of **5** with 2,3-dihydroxynaphthalene was carried out at 100°C for 2 h. After workup by *Procedure B*, 0.3684 g (28%) of **7f** was obtained as a white solid, mp 114–201°C: ^{1}H NMR ($CDCl_3$) δ 7.86 (dm, 1H, J=7.6 Hz), 7.81 (br s, 1H), 7.75 (dm, 1H, J=8.1 Hz), 7.69 (dm, 1H, J=8.1 Hz), 7.62 (dm, 1H, J=8.1 Hz), 7.52–7.32 (m, 5H); ^{19}F NMR ($CDCl_3$) ϕ −67.2 (s); ^{13}C NMR ($CDCl_3$) δ 154.6 (t, J_{CF}=43.6 Hz), 150.5 (s), 147.0 (s), 138.8 (s), 137.9 (s), 132.9 (s), 128.1 (s), 127.6 (s), 127.5 (s), 126.5 (s), 126.4 (s), 125.8 (s), 124.3 (s), 121.4 (s), 120.5 (s), 115.7 (t, J_{CF}=261.9 Hz), 112.9 (s), 111.5 (s); HRMS (70 eV) calcd for $C_{18}H_{11}F_2NO_3$ 327.0707, found 327.0681. Anal. Calcd for $C_{18}H_{11}F_2NO_3$: C, 66.06; H, 3.39; N, 4.28. Found C, 65.81; H, 3.01; N, 4.21.

4.2.17. 2-Chloro-N-(2-hydroxyphenyl)acetamide (**8**)

To a rapidly stirred solution of 5.00 g (0.0458 mol) of 2-aminophenol in 50 ml of ethyl acetate was added 5.18 g (0.0459 mol) of chloroacetyl chloride over a period of two min. Some gas was evolved, and the flask became warm. After stirring for 26 min, the mixture was washed with 20 ml of dilute HCL (9 parts water to 1 part conc. HCl), and the aqueous layer was extracted three times with 10 ml portions of ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated by rotary evaporation at reduced pressure (water aspirator, 70°C) to give 7.87 g of a crude, off-white solid. Recrystallization fom 19 ml of ethylene chloride (one crop) gave 5.00 g (59%) of **8** as a white solid, mp 132–135.2°C ([14] mp 139–140.5°C): ^{1}H NMR (DMSO-d_6) δ 10.0 (br s, 1H), 9.45 (br s, 1H), 7.90 (dd, 1H, J=8.0 and 1.5 Hz), 6.93 (m, 2H), 6.78 (dt, 1H, J_d=1.7 and J_t=7.6 Hz).

4.2.18. 2-(Chloromethyl)benzoxazole (**9**)

A 250 ml, single-necked, round-bottom flask was equipped with an egg-shaped stir bar and a $CaSO_4$ drying tube. To the flask 19 g of polyphosphoric acid and 4.50 g (24.2 mmol) of amide **8** was added. The flask was heated in

an oil bath at 150°C for 30 min. The solid amide slowly dissolved as it reacted.

After cooling to room temperature, 239 ml of crushed ice and 44 ml of concentrated aqueous ammonia were added and the mixture was triturated with a spatula until all of the PPA had dissolved. The mixture was extracted five times with 40 ml portions of $CHCl_3$, and the combined organic layers were dried over Na_2SO_4, then concentrated by rotary evaporation at reduced pressure (water aspirator, 70°C) to give a liquid. Purification by simple vacuum distillation gave 2.31 g (57%) of a clear, colorless distillate, bp 99°C at 4.0 mm ([15] bp 65–68°C at 0.05 mm), which was pure 9: ^{1}H NMR ($CDCl_3$) δ 7.75 (m, 1H), 7.55 (m, 1H), 7.37 (m, 2H), 4.76 (s, 2H).

*4.2.19. 2-[(2-pyrimidinylthio)methyl]benzoxazole (**10**)*

Following the *General Procedure*, the reaction of **9** with 2-mercaptopyrimidine was carried out at room temperature for 10 min. After workup by *Procedure B*, 0.890 g (91%) of **10** was obtained as a white solid, mp 56.0–57.9°C: ^{1}H NMR ($CDCl_3$) δ 8.55 (d, 1H, J=4.9 Hz), 7.70 (m, 1H), 7.50 (m, 1H), 7.30 (m, 2H), 7.01 (t, 1H, J=4.8 Hz), 4.71 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 169.9, 162.7, 157.1, 150.7, 140.9, 124.7, 124.0, 119.7, 116.8, 110.3, 27.4; HRMS (70 eV) calcd for $C_{12}H_9N_3OS$ 243.0466, found 243.0464. Anal. Calcd for $C_{12}H_9N_3OS$: C, 59.24; H, 3.73; N, 17.27. Found C, 59.20; H, 3.71; N, 17.31.

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