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Article

N-Acyl-3,3-difluoro-2-oxoindoles as Versatile Intermediates for the Preparation of Different 2,2-Difluorophenylacetic Derivatives

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Este trabalho descreve a versatilidade sintética dos derivados *N*-Acil-3,3-diflúor-2-oxoindóis, obtidos a partir da reação de *N*-acilisatinas com dietilaminotrifluoreto de enxofre (DAST) que, através da reação com diferentes nucleófilos, promovem a abertura do anel heterocíclico, levando à formação de vários produtos. A reação de *N*-Acil-3,3-diflúor-2-oxoindóis com água fornece os ácidos 2-(2-*N*-acilfenil)-2,2-difluoracéticos e com álcoóis fornece os ésteres correspondentes. Reações com aminas e glicina levam à formação das correspondentes amidas 2-(2-*N*-acilfenil)-2,2-difluoracetamidas. Na reação com tiossemicarbazidas os derivados difluortiossemicarbazidas são obtidos. Estes últimos sofrem uma ciclização catalisada por ácido para fornecer *N*-(2-((5-aminoaril-1,3,4-tiadiazol-2-il)difluormetil)-4-(*R*)-fenil)acetamida. A estrutura de *N*-(2-((5-amino-1,3,4-tiadiazol-2-il)difluormetil)-4-metilfenil)acetamida foi determinada por raio-X.

This paper describes the versatility of *N*-Acyl-3,3-difluoro-2-oxoindoles, obtained from the the reaction of *N*-acylisatins with (diethylamino)sulphur trifluoride (DAST) which, on opening of the heterocyclic ring by reactions with nucleophiles, lead to the formation of a variety of products: reaction with water yields 2-(2-amidoacyl)-2,2-difluoroacetic acids, with alcohols yields alkyl 2-(2-amidoacyl)-2,2-difluoroacetates, with amines and glycine yields 2-(2-amidoacyl)-2,2-difluoroacetamides and with thiosemicarbazides yields difluorothiosemicarbazide derivatives. The latter undergo acid-catalysed cyclizations to yield *N*-(2-((5-aminoaryl-1,3,4-thiadiazol-2-yl) difluoromethyl)-4-(*R*)-phenyl)acetamide. The X-ray structure of *N*-(2-((5-amino-1,3,4-thiadiazol-2-yl)difluoromethyl)-4-methylphenyl)acetamide has been determined.

Keywords: isatins, DAST, deoxo-fluor, 1,3,4-thiadiazoles, 3,3-difluoro-2-oxoindoles, N-acyl-3,3-difluoro-2-oxoindoles

Introduction

Substitution of fluorine into an organic molecule introduces minimal steric alterations, a fact that can facilitate interactions of a fluorinated biomolecule with enzyme active sites, receptor recognition sites and other biological systems.[1] Additionally, the highly electronegative centre can alter significantly the physical-chemical properties, including pK_a values, dipole moments, chemical reactivity and lipophilicity. [2] Moreover, pharmacological interest in *gem*-difluoro compounds is in part associated with the fact that the CF_2 and CO groups have isopolar and isosteric characteristics. Fluorinated drugs are used for the treatment of many diseases including depression, inflammation, malaria, psychosis, viral diseases, and as well as general anaesthetics .[3]

Isatins (1H-indole-2,3-diones) are synthetically versatile substrates, since they can be used for the synthesis of a large variety of heterocyclic compounds, such as indoles and quinolines and also as raw material for drug synthesis .[4]

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We have previously reported the reduction of 3,3-difluoro-2-oxoindoles with a borane complex to obtain 3-fluoroindoles.[5] In this paper we have used *N*-acylisatins (**1**-**6**) as precursors of *N*-acyl-3,3-difluoro-2-oxoindoles (**7**-**12**) *via* fluorination reactions with diethylaminosulphur trifluoride (DAST). *N*-acyl-3,3-difluoro-2-oxoindoles (**7**-**12**) have been shown to be versatile intermediates which, on reaction with nucleophiles, lead to the formation of a variety of heterocyclic ring opened products.

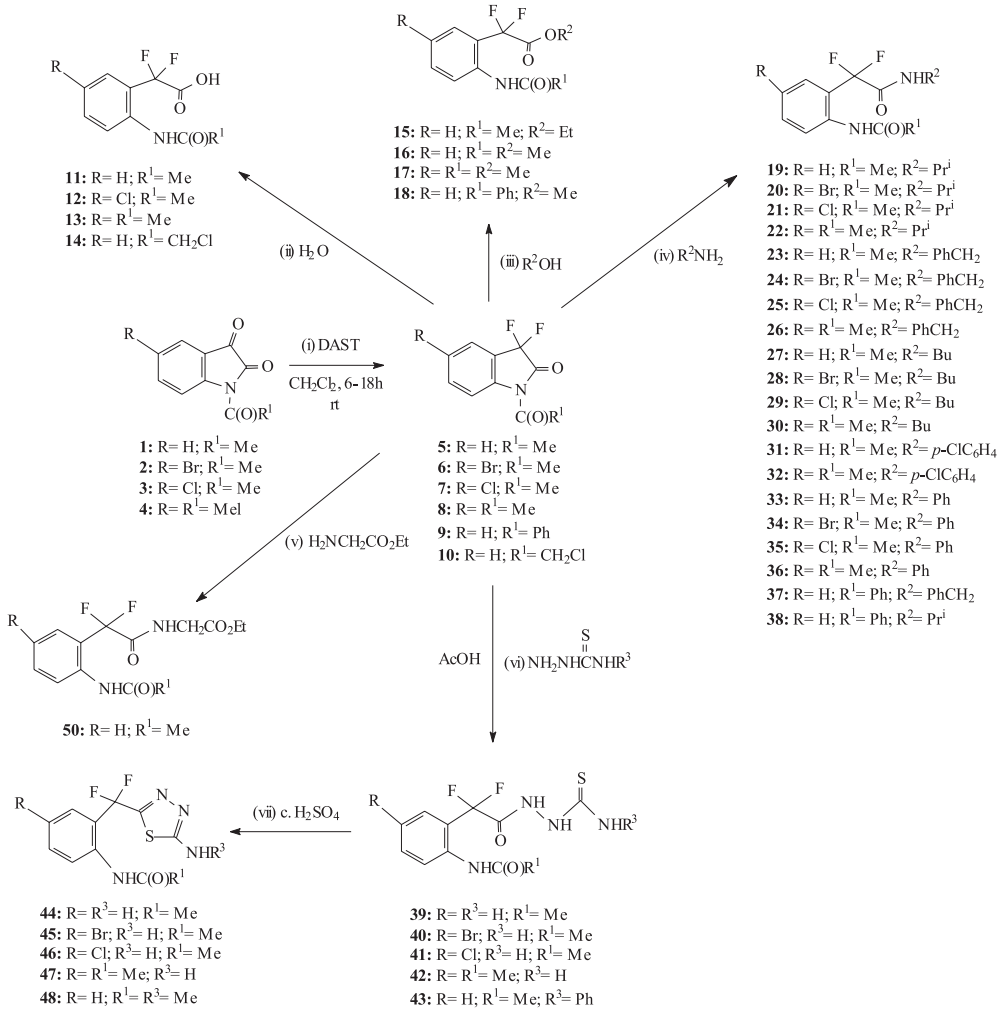
Results and Discussion

Isatins and derivatives can undergo nucleophilic attack at positions C-2 and/or C-3. The chemoselectivity of these reactions depends on the nature of the nucleophiles, on the nature of the substituents attached to the isatin nucleus, especially those bonded to the nitrogen atom.[4] The literature describes that *N*-acylisatins undergo reactions with primary amines and alcohols giving heterocycle ring-opened products.[6,7] The 2- and 3-sited carbonyl groups in isatins have different characteristics, in which the carbonyl at C_3 has a strong ketonic nature, while that at C_2 is typically an amide.

In this work we have reacted compounds 1-6 towards DAST, a specific reagent for conversion of aldehyde and ketone to *gem*-difluoro compounds (**7**-**12**).[8] We have also investigated the enhanced electrophilicity of the C_2 carbonyl group resulting from the introduction of the two fluorine atoms at C-3 and from acylation of N-1, which facilitate the attack of a second nucleophile at the C_2 carbonyl, leading to the formation of (**13**-**46**) on opening of the heterocyclic ring.

*Fluorination of the **N**-acylisatins (**1**-**6**) to give **N**-acyl-3,3-difluoro-2-oxoindoles (**7**-**12**)*

N-acylisatins were obtained by *N*-acetylation (**1**-**4**), *N*-chloroacetylation (**5**) and *N*-benzoylation (**6**) of the appropriate isatins by methods described in the literature.[9-11] The isatins were either commercially available or were synthesized.[12]



Scheme 1. Reactions using *N*-Acyl-3,3-difluoro-2-oxoindoles as starting materials.

One of the most common and successful means of obtaining *gem*-difluoro compounds is the transformation of either aldehydic or ketonic carbonyl groups into the CF_2 group.[13] Many methods for this conversion have been described, but the use of diethylaminosulphur trifluoride (DAST) offers certain advantages: it is commercially available, highly selective, easy handled and generally produces high yields of fluorinated products. Middleton and Bingham were the first to utilize DAST with non-acetylated isatins.[8]

We have explored the difference in reactivities of the C_2 and C_3 carbonyl groups. Reactions of *N*-acylisatins with DAST were carried out under mild conditions, such as in CH_2Cl_2 solution at room temperature. The *N*-acyl-3,3-difluoro-2-oxoindoles (**7**-**12**) were produced in high yields as shown in Scheme 1.[7] The loss of the C-3 carbonyl peak and the presence of the triplet signal for C-3 due to $J_{(C,F)}$ in the proton decoupled ^{13}C NMR spectra were clear indications of the transformation of CO to CF_2 at C-3. The δ ^{19}F NMR values for the *N*-acyl-3,3-difluoro-2-oxoindole derivatives fall in the narrow region of –105.9 to –106.7 ppm, compared to the δ ^{19}F value of –112.4 ppm for the non-acylated compound, 3,3-difluoro-2-oxoindole.[4-7] DAST is known to be a suitable reagent for small-scale reactions; its propensity to undergo dangerous decomposition with gas evolution on heating above 90 °C limits its use in large scale reactions. For scaling-up reactions, we have used dimethoxydiethylaminosulphur trifluoride (Deoxo-Fluor) as a thermally more stable alternative but equally effective reagent.[14] *N*-Chloroacetyl-3,3-difluoro-2-oxoindole (**11**) and *N*-benzoyl-3,3-difluoro-2-oxoindole (**12**) were produced in order to confirm the generality of the methodology.

*Reactions of **7**-**12** with nucleophiles*

Additionally, we have investigated the enhanced electrophilicity of the C_2 carbonyl after the introduction of the two fluorine atoms at position 3 and also by acylation at N-1. These substitutions facilitate the attack of a second nucleophile at the C_2 carbonyl, leading to the formation of (**13**-**46**) on opening of the heterocyclic ring.

The literature describes that N-acylisatins can be solvolized only on heating and there is no precedent for hydrolysis.[15-17] We, however, have found that our fluorinated derivatives (**7**-**12**) were readily hydrolyzed and solvolyzed at room temperature confirming the enhanced eletrophilicity of C_2 and thereby allowing an easy opening of the heterocyclic ring. Difluoroacids (**13**-**16**) were produced in water, difluoroesters (**17**-**20**), in alcohols and difluoroamides (**21**-**40**) in amines. Esterified aminoacids (**41**) and thiosemicarbazides derivatives (**42**-**46**) were obtained on reaction with thiosemicarbazides.[15-19] The phenylacetic derivatives (**13**-**40**) are similar in structure to diclofenac and also have anti-inflammatory activities. A patent covering the pharmaceutical potential and syntheses of such compounds has been issued.[7]

*Formation of **13**-**16** and **17**-**20***

Solvolysis with anhydrous MeOH and EtOH, at room temperature during 2 to 24h produced the 2,2-difluoro-2-(2-acetamidophenyl)-2,2-difluoracetates (**17**-**20**) in yields above 75% [reaction *(ii)* in Scheme 1]. In the case of *N*-chloroacetyl-3,3-difluoro-2-oxoindole (11), the use of wet EtOH led to the formation of both the ester and acid. The 2-(2-acetamidophenyl)-2,2-difluoroacetic acids (**13**-**16**) were best obtained using aqueous acetone as the reaction medium [reaction *(iii)* in Scheme 1]. The δ ^{19}F values were in the ranges -102.1 to –103.3 ppm for (**13**-**16**) and -103.1 to –103.8 ppm for (**17**-**20**).

*Formation of **21**-**41***

Reactions of (**7**-**12**) with amines also proceeded readily with the formation of (**21**-**40**) in yields ranging from 40 to 80% [reaction *(iv)* in Scheme 1]. The protected amino acid, ethyl glycinate, reacted as its hydrochloride salt with *N*-acetyl-3,3-difluoro-2-oxoindole (**7**) to give 2-(acetamidophenyl)-*N*-(2-carboxy-2-ethoxyethyl)-2,2-difluoroacetamide (**41**), in a 59% yield after chromatographic separation [reaction *(v)* in Scheme 1]. The δ ^{19}F values were in the range of -100.3 to -105.0 ppm for (**21**-**40**).

*Reactions of **7**-**12** with thiosemicarbazides and subsequent cyclization reactions*

The reactions of (**7**-**12**) with thiosemicarbazides in acetic acid led to the opening of the heterocyclic ring to give compounds (**42**-**46**) [reaction *(vi)* in Scheme 1]. Compounds (**42**-**46**) were not recrystallized due to their instability when heated in solution and hence purifications were only attempted by washing with ethyl ether. The presence of the NH protons signals in the ^1H NMR spectra confirmed the formation of (**42**-**46**).

Such compounds were further treated with concentrated sulphuric acid resulting in the formation of 1,3,4-thiadiazole derivatives (**47**-**51**) as products of a five-membered ring closure reaction with subsequent elimination of water as shown in reaction *(vii)* in Scheme 1. The absences of the carbonyl group peaks in the IR spectra of (**47**-**51**) were useful indicators of the cyclization reactions. Significant

differences shifts in the δ ^{19}F values for compounds (**7**-**12**) (*ca*. –106 ppm), (**42**-**46**) (*ca*. –99 ppm) and for (**47**-**51**) generally *ca*. –81 ppm were observed. The acid-catalyzed cyclized product 50 was further characterized by its crystal structure determination (Figure 1).

Compound 50 crystallizes in the space group $P2_1/a$. Atom numbering scheme and atom arrangements are shown in Figure 1a. Selected bond lengths and angles are listed in Table 1. The 1,3,4-thiadiazole and the aryl rings are essentially planar. The methyl and the acetamide groups are nearly coplanar with the attached phenyl ring. The thiadiazole and aryl rings are nearly orthogonal as shown by the angle of 82.22 (6)^o between the best planes. This *V-shaped* arrangement of 50, see Figure 1b and Table 2, allows the formation of a weak intramolecular C6-H6----F2 H-bond, see Figure 1c and Table 2. Strong intermolecular H-bonds also arise, to give *(a)* dimers formed from N3-H3A---N2 interactions [symmetry operation: 1-x, -y, -z], *(b)* dimers formed from N3-H3B---O1 interactions [symmetry operation: ½+x, ½-y, z] and *(c)* chains formed from N4-H4---N1 interactions [symmetry operation: - ½+x, - ½-y, z.], see Figure 1d.

Pharmacological investigations of the compounds in this series and related derivatives and their respectives biological activities are currently being carried out.

Table 1. Selected bond lengths [Å] and angles [^{o}] for (50)

S(1)-C(8)	1.734(2)	S(1)-C(9)	1.752(2)
F(1)-C(7)	1.371(2)	F(2)-C(7)	1.382(2)
N(1)-C(8)	1.291(3)	N(1)-N(2)	1.383(2)
N(2)-C(9)	1.326(3)	N(3)-C(9)	1.328(3)
N(4)-C(10)	1.354(3)	N(4)-C(2)	1.427(2)
C(10)-C(11)	1.507(3)	O(1)-C(10)	1.225(3)
C(1)-C(7)	1.509(3)	C(5)-C(12)	1.504(3)
C(7)-C(8)	1.509(3)		
C(8)-S(1)-C(9)	86.09(9)	C(8)-N(1)-N(2)	112.76(16)
C(9)-N(2)-N(1)	111.99(16)	C(10)-N(4)-C(2)	122.12(17)
C(2)-C(1)-C(7)	119.61(17)	C(6)-C(1)-C(7)	120.86(17)
C(1)-C(2)-N(4)	121.16(18)	C(3)-C(2)-N(4)	119.58(17)
C(2)-C(3)-C(4)	120.71(18)	C(4)-C(5)-C(12)	121.17(18)
C(6)-C(5)-C(12)	121.04(18)	F(1)-C(7)-F(2)	104.98(15)
F(1)-C(7)-C(1)	110.36(16)	F(2)-C(7)-C(1)	109.67(16)
F(1)-C(7)-C(8)	108.31(16)	F(2)-C(7)-C(8)	107.61(16)
C(1)-C(7)-C(8)	115.37(16)	N(1)-C(8)-C(7)	122.94(18)
N(1)-C(8)-S(1)	115.46(16)	C(7)-C(8)-S(1)	121.57(15)
N(2)-C(9)-N(3)	124.20(19)	N(2)-C(9)-S(1)	113.71(15)
N(3)-C(9)-S(1)	122.08(16)	O(1)-C(10)-N(4)	122.57(18)
O(1)-C(10)-C(11)	122.72(18)	N(4)-C(10)-C(11)	114.67(18)

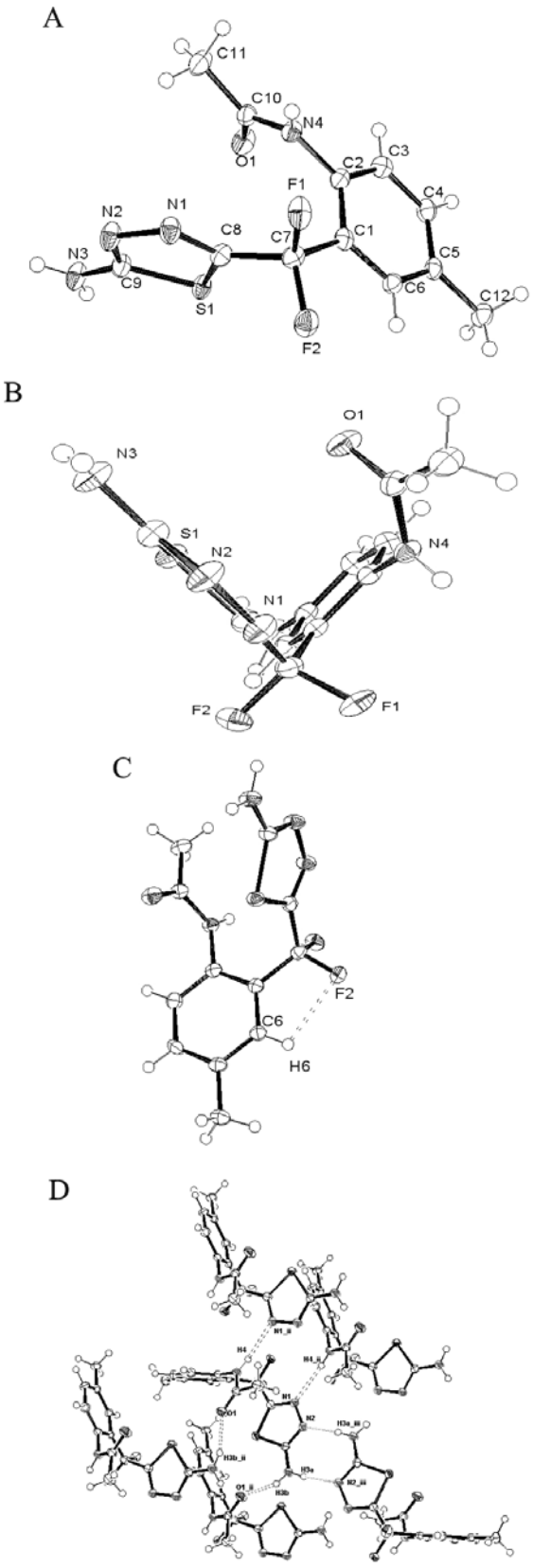


Figure 1. Crystal structure of 50: (A) Atom arrangements; (B) the *V-shape* conformation; (C) Intramolecular H-bonds; (D) Intermolecular H-bonds.

Table 2. Hydrogen bonding parameters

D-H---A	D-H (Å)	H---A (Å)	D---A (Å)	D-H---A (°)
N3-H3a---N2[a]	0.86	2.32	3.154(2)	164
N3-H3b---O1[b]	0.86	2.00	2.805(2)	155
N4-H4---N1[c]	0.86	2.35	3.159(2)	158
C6-H6 ---F2 [d]	0.93	2.33	2.692(3)	102

Symmetry operations: *a*: 1-x, -y, -z; *b*: ½+x, ½-y, z; *c*:- ½+x,- ½-y, z; *d*: intramolecular.

Conclusions

This paper confirms the versatility of 3,3-difluoro-2-oxoindoles in synthetic reactions. Efficient and practical synthesis of novel 2-(2-acetamidophenyl)-2,2-difluoroacetic acids (**13**-**16**), esters (**17**-**20**), 2-(2-acetamidophenyl)-2,2-difluoro-N-aryl or acyl derivatives (**21**-**41**), thiosemicarbazide derivatives (**42**-**46**) and 1,3,4-thiadiazolyl difluoromethyl derivatives (**47**-**51**) have been carried out.

DAST and Deoxo-fluor have been shown to be excellent selective fluorinated agents for the fluorination of C_3 carbonyls in isatins.[8] The eletrophilicity of the carbonyl at C_2 is enhanced both by the introduction of the CF_2 group at C_3 and by acylation at N-1.

Experimental

General

All melting points were determined using a Mettler FP90 instrument attached to a FP81HF oven. Infrared spectra were recorded in KBr disks using a Nicolet 205 IR spectrometer. Gas chromatography was carried out on a Varian 3300 attached to a Varian 4400 integrator. The carrier gas used was nitrogen and detection was by FID. The column used was DB-1. GC/MS were recorded on a Hewlett Packard 5960 interfaced to a chromatograph Hewlett Packard 5890. NMR spectra were recorded on a Bruker HC200 instrument: internal standards used were TMS for ^{1}H and ^{13}C and $CFCl_3$ for ^{19}F NMR. Isatin (Vetec) and DAST (Aldrich) were commercial products.

General procedure for N-acylation of 5-substituted isatin derivatives

A reaction mixture of 5-substituted isatins (1 mol) and acyl anhydride or acyl chloride (10 mol) was refluxed for 4 h and cooled to 0°C. The precipitate was collected, washed with hexane (200 ml) and air-dried. Recrystallisation was from EtOAc/hexane.[9]

General procedure for difluorination of the N-acylisatin

The *N*-acylisatin derivative (1 mmol) was suspended or dissolved in dichloromethane (10 mL). DAST (2 mmol) was added. The reaction mixture was stirred at room temperature. When the reaction was complete, the reaction mixture was extracted with cold water (20 mL), the aqueous phase was subsequently re-extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over anhydrous sodium sulfate, filtered and then evaporated at reduced pressure. Purifications of the products were either by recrystallisation or by sublimation.

*N-Acetyl-3,3-difluoro-2-oxoindole (**7**)*

Yield 94% by sublimation. mp 109-111°C. IR (KBr) ν_{max}/cm^{-1}: 1792 (CO at C_2); 1724 (NAc); 1082 (CF_2); *m/z* (%): 211 (20), 169 (100), 141 (70), 114 (7), 95 (5). ^{1}H NMR ($CDCl_3$, δ): 2.68 (s, CH_3), 7.33 (t, *J* 8 Hz, H_5), 7.50-7.65 (m, H_4 and H_6), 8,29 (d, *J* 8 Hz, H_7). ^{13}C NMR ($CDCl_3$, δ): 26.1 (CH_3), 109.8 (t, $J_{C,F}$ 247 Hz, C_3), 117.5 (C_7), 119.4 (t, $J_{C,F}$ 23 Hz, C_{3a}), 124.3 (C_5), 126.2 (C_4), 134.0 (C_6), 140.8 (t, $J_{C,F}$ 6 Hz, C_{7a}), 165.6 (t, $J_{C,F}$ 31 Hz, C_2), 169.6 (NAc). ^{19}F NMR ($CDCl_3$, δ): - 106.5.

*N-Acetyl-5-bromo-3,3-difluoro-2-oxoindole (**8**)*

Yield 65 % (n-hexane/AcOEt, 1:1). mp 144-145 °C. IR (KBr) ν_{max}/cm^{-1}: 1799 (CO at C_2), 1754 (NAc), 1095 (CF_2). *m/z* (%): 289 (11), 247 (100), 228 (5), 219 (49), 201 (3), 182 (13), 168 (5), 139 (30), 112 (8), 88 (11), 75 (15), 51 (3). ^{1}H NMR ($CDCl_3$, δ): 2.70 (s, Me), 7.69 (dd, *J* 8 and 2 Hz, H_6), 7.76 (d, *J* 8 Hz, H_4), 8.21 (d, *J* 8 Hz, H_7). ^{13}C NMR ($CDCl_3$, δ): 26.2 (Me), 109.1 (t, $J_{C,F}$ 249 Hz, C_3), 119.2 (C_7), 121.3 (t, $J_{C,F}$ 17 Hz, C_{3a}), 129.3 (C_5), 127.5 (C_6), 137.0 (C_4), 139.8 (C_{7a}), 164.8 (t, $J_{C,F}$ 31 Hz, C_2), 169.4 (NAc). ^{19}F NMR ($CDCl_3$, δ): - 106.6.

*N-Acetyl-5-chloro-3,3-difluoro-2-oxoindole (**9**)*

Yield 88% (n-hexane/AcOEt, 1:1). mp 134-136 °C. IR (KBr) ν_{max}/cm^{-1}: 1800 (CO at C_2), 1753 (NAc), 1095 (CF_2) cm^{-1}. *m/z* (%): 245 (12), 203 (100), 183 (5), 175 (48), 164 (2), 148 (123), 138 (7), 129 (13), 109 (3), 88 (8), 75 (12), 51 (2). ^{1}H NMR ($(CD_3)_2CO$, δ): 2.67 (s, Me), 7.90 (dd, *J* 9 and 2 Hz, H_6), 7.80 (d, *J* 2 Hz, H_4), 8.30 (d, *J* 9 Hz, H_7). ^{13}C NMR (C_2D_6CO, δ): 26.7 (Me), 110.78 (C_3), 120.3 (C_7), 121.9 (C_{3a}), 122.4 (C_6), 132.4(C_5), 135.3 (C_4), 141.5 (C_{7a}), 170.8 (NAc). ^{19}F NMR ($CDCl_3$, δ): - 106.4.

*N-Acetyl-3,3-difluoro-5-methyl-2-oxoindole (**10**)*

Yied 93% (n-hexane/AcOEt, 1:1). mp 72-74°C. IR (KBr) ν_{max}/cm^{-1}: 1792 (CO at C_2), 1723 (NAc), 1090 (CF_2), *m/z* (%): 225 (19), 183 (100), 155 (76), 135 (7), 127 (9),

107 (5). ^{1}H NMR ($CDCl_3$, δ): 2.39 (s, ArMe), 2.66 (s, Me), 7.32-7.41 (m, H_4 and H_6), 8.15 (d, *J* 8 Hz, H_7). ^{13}C NMR ($CDCl_3$, δ): 21.0 (ArMe), 26.4 (CH_3), 110.0 (t, $J_{C,F}$ 296 Hz, C_3), 117.4 (C_7), 119.32 (t, $J_{C,F}$ 22 Hz, C_{3a}), 124.7 (C_4), 134.6 (C_6), 136.5 (C_5), 138.5 (C_{7a}), 165.8 (t, $J_{C,F}$ 31 Hz, C_2), 169.6 (NAc). ^{19}F NMR ($CDCl_3$, δ): - 106.2.

*N-Chloroacetyl-3,3-difluoro-2-oxoindole (**11**)*

Yield 86 %. mp 113-115 °C. IR (KBr) ν_{max}/cm^{-1}: 1787 (C_2) 1739 (NCOCH$_2$Cl), 1080 (CF_2). *m/z* (%): 245 (40), 169 (100), 141 (97), 114 (16), 77 (34). ^{1}H NMR ((CD_3)$_2$CO, δ): 4.99 (s, 2H), 7.45 (t, *J* 7 Hz, H_5), 7.75 (H_4), 7.70 (H_6), 8.30 (d, *J* 7 Hz, H_7). ^{13}C NMR (CD_3)$_2$CO, δ): 46.9 (CH_2Cl), 111.1 (t, $J_{C,F}$ 245 Hz, C_3), 120.2 (t, $J_{C,F}$ 23 Hz, C_{3a}), 125.8 (C_4), 127.9 (C_5), 135.7 (C_6), 118.4 (C_7), 142.1 (t, $J_{C,F}$ 7Hz, C_{7a}), 166.4 (t, $J_{C,F}$ 31 Hz, C_2), 167.3 (NCOCH$_2$Cl). ^{19}F NMR ($CFCl_3$, δ): -105.8.

*N-Benzoyl-3,3-difluoro-2-oxoindole (**12**)*

Yield 95 % yield. mp 138-139 °C. IR (KBr) ν_{max}/cm^{-1}: 1783 (CO at C_2), 1702 (NCOPh), 1082 (CF_2). *m/z* (%): 273 (11), 168 (3), 105 (100), 77 (83). ^{1}H NMR ($CDCl_3$, δ): 7.37 (t, *J* 8 Hz, H_5), 7.44-7.88 (m, H_4 and H_6), 7.90 (d, *J* 8 Hz, H_7). ^{13}C NMR ($CDCl_3$, δ): 110.3 (t, $J_{C,F}$ 247 Hz, C_3), 116.3 (C_7), 120.0 (t, $J_{C,F}$ 22 Hz, C_{3a}), 124.7 (C_4), 126.1 (C_5), 128.5 (C_{11} and C_{13}), 129.6 (C_{10} and C_{14}), 133.1 (C_9), 133.7 (C_{12}), 134.0 (C_6), 141.2 (t, $J_{C,F}$ 6 Hz, C_{7a}), 164.5 (t, $J_{C,F}$ 31 Hz, C_2), 167.9 (COC$_6$H$_5$). ^{19}F NMR ($CFCl_3$, δ): -106.7.

*General procedure for the heterocyclic ring opening of N-Acyl -3,3-difluoro-2-oxoindoles, **7-12**, giving **13-16** and **17-20***

N-Acyl-3,3-difluoro-2-oxoindole compounds, **7**-**12**, (0.1 mol) were dissolved in methanol or ethanol anhydrous (5 mL) and the mixture was stirred, at room temperature, during 2-24 h, to form the methyl or ethyl ester compounds. To obtain the 2,2-difluoro-2-(2-amidophenyl) acetic acids, the indoles were refluxed in a mixture of acetone/water (2:1) for 2-6 h.

*2-(2-Acetamidophenyl)-2,2-difluoroacetic acid (**13**)*

Yield 98 % (n-hexane/AcOEt, 1:1). mp 170-172 °C. IR (KBr) ν_{max}/cm^{-1}: 3277 (NH), 1720(CO), 1078 (CF_2). *m/z* (%): 229 (20), 211 (8), 187 (48), 169 (50), 142 (100), 114 (10), ^{1}H NMR ($CDCl_3$+DMSO-d$_6$, δ): 2.10 (s, NAc), 6.29 (bs, COOH), 7.26 (t, *J* 8 Hz, H_5), 7.47 (t, *J* 8 Hz, H_6), 7.60 (d, *J* 8 Hz, H_4), 7.80 (d, *J* 8 Hz, H_7), 8.80 (bs, NH). ^{13}C NMR ($CDCl_3$+DMSO-d$_6$, δ): 23.5 (COCH$_3$), 112.9 (t, $J_{C,F}$ 249 Hz, C_3), 125.1 (C_5), 125.8 (t, $J_{C,F}$ 8 Hz, C_4), 126.3 (bs, C_{3a}), 126.8 (C_7), 131.1 (C_6), 135.5 (C_{7a}), 165.2 (t, $J_{C,F}$ 33 Hz, C_2), 168.8 (NAc). ^{19}F NMR ($CDCl_3$+DMSO-d$_6$, δ): -102.5.

*2-(2-Acetamido-5-chlorophenyl)-2,2-difluoroacetic acid (**14**)*

Yield 100 % (aqueous acetone). mp 165-167 °C. IR (KBr) ν_{max}/cm^{-1}: 3309, 1759 (CO), 1084 (CF_2). ^{1}H NMR ((CD_3)$_2$CO, δ): 2.15 (s, NAc), 7.30 (d, *J* 2 Hz, H_4), 7.67 (dd, *J* 8 and 2 Hz, H_6), 7.88 (d, *J* 9 Hz, H_7), 8.73 (bs, NH), 10.09 (bs, COOH), ^{13}C NMR ((CD_3)$_2$CO, δ): 24.0 (COCH$_3$), 116.2 (C_3), 127.0 (C_{3a}), 127.2 (C_6), 129.8 (C_7), 131.5 (C_5), 132.8 (C_4), 136.0 (C_{7a}), 165.1 (t, $J_{C,F}$ 33 Hz, C_2), 170.3 (NAc). ^{19}F NMR ((CD_3)$_2$CO, δ): -102.4.

*2-(2-Acetamido-5-methylphenyl)-2,2-difluoroacetic acid (**15**)*

Yield 95 %. mp 164-167 °C. IR (KBr) ν_{max}/cm^{-1}: 3280, 1720 (CO), 1091 (CF_2). ^{1}H NMR ($CDCl_3$ + DMSO-d$_6$, δ): 2.10 (s, COCH$_3$), 2.35 (s, Me), 7.23 (d, *J* 8 Hz, H_6), 7.38 (s, H_4), 7.76 (d, *J* 8 Hz, H_7), 8.39 (bs, NH). ^{13}C NMR ((CD_3)$_2$CO, δ): 20.8 (Me), 23.7 (COCH$_3$), 114.4 (t, $J_{C,F}$ 248 Hz, C_3), 126.8 (C_{3a}), 126.9 (t, $J_{C,F}$ 8 Hz, C_4), 127.1 (C_7), 132,89 (C_6), 134.3 (C_5), 135.9 (C_{7a}), 165.5 (t, $J_{C,F}$ 34 Hz, C_2), 169.4 (NAc). ^{19}F NMR ((CD_3)$_2$CO, δ): -103.3.

*2-(2-Chloroacetamidophenyl)-2,2-difluoroacetic acid (**16**)*

Yield 94 %. mp 123-125 °C. IR (KBr) ν_{max}/cm^{-1}: 3393 (NH), 1760 (CO$_2$H), 1094 (CF_2), 1677 (COCH$_2$Cl). ^{1}H NMR (C_2D_6CO, δ): 4.29 (s, CH$_2$Cl), 7.35 (t, *J* 8 Hz, H_5), 7.53 (t, *J* 8 Hz, H_6), 7.64 (d, *J* 8 Hz, H_4), 7.99 (d, *J* 8 Hz, H_7), 9.18 (bs, NH). ^{13}C NMR (C_2D_6CO, δ): 44.1 (CH_2Cl), 114.9 (t, $J_{C,F}$ 250 Hz, C_2), 125.9 (t, $J_{C,F}$ 24 Hz, C_{3a}), 126.9 (C_7), 127.0 (C_5), 127.6 (t, $J_{C,F}$ 8 Hz, C_4), 133.1 (C_6), 136.5 (C_{7a}), 165.7 (C_2), 166.0 (COCH$_2$Cl). ^{19}F NMR (C_2D_6CO, δ): -102.1.

*Ethyl 2-(2-acetamidophenyl)-2,2-difluoroacetate (**17**)*

Yield 75%. (n-hexane/AcOEt, 1:1). mp 64-66 °C. IR (KBr) ν_{max}/cm^{-1}: 3313 (NH), 1769 (CO$_2$CH$_3$), 1665 (NAc), 1095 (CF_2). m/z (%): 257 (13), 215 (35), 197 (7), 184 (9), 169 (7), 142 (100), 134 (2), 122 (4), 102 (9), 95 (7), 88 (4), 75 (4), 63 (4), 51(1). ^{1}H NMR ((CD_3)$_2$CO, δ): 1.29 (t, *J* 7 Hz, CH$_2$CH$_3$), 2.20 (s, COCH$_3$), 4.30 (m, *J* 7 Hz, CH$_2$CH$_3$), 7.56 (d, *J* 8 Hz, H_4), 7.22 (t, *J* 8 Hz, H_5), 7.48 (d, *J* 8 Hz, H_6), 8.12 (d, *J* 8 Hz, H_7 and NH). ^{19}F NMR ((CD_3)$_2$CO, δ): -103.7.

*Methyl 2-(2-acetamidophenyl) 2,2-difluoroacetate (**18**)*

Yield 75% (n-hexane/AcOEt, 1:1). mp 119-121 °C. IR (KBr) ν_{max}/cm^{-1}: 3381 (NH), 1762 (CO$_2$CH$_3$), 1699

(COCH$_3$), 1090 (CF$_2$). *m/z* (%): 243 (6), 201 (15) 183 (3), 142 (100), ^{1}H NMR (CDCl$_3$, δ): 2.11 (s, COCH$_3$), 3.77 (s, CO$_2$CH$_3$), 7.14 (t, *J* 8 Hz, H$_5$), 7.42 (t, *J* 8 Hz, H$_6$), 7.49 (d, *J* 8 Hz, H$_4$), 7.89 (bs, NH), 8.00 (d, *J* 8 Hz, H$_7$), 8.40 (bs, NH). ^{13}C NMR (CDCl$_3$, δ): 23.4 (COMe), 53.0 (CO$_2$CH$_3$), 112.4 (t, $J_{C,F}$ 251 Hz, C$_3$), 121.5 (C$_{3a}$), 123.7 (C$_7$ and C$_5$), 125.0 (t, $J_{C,F}$ 8 Hz, C$_4$), 131.1 (C$_6$), 134.8 (C$_{7a}$), 163.9 (t, $J_{C,F}$ 35 Hz, C$_2$), 167.6 (NAc). ^{19}F NMR (CDCl$_3$, δ): -103.8.

*Methyl 2-(2-acetamido-5-methylphenyl)-2,2-difluoro-acetate (**19**)*

Yield 90%. mp 101-103 °C. IR (KBr) ν_{max}/cm^{-1}: 3279 (NH), 1770 (CO at C$_2$), 1666 (COCH$_3$), 1088 (CF$_2$). *m/z* (%): 257 (47), 215 (98), 198 (9), 156 (100), 127 (22). ^{1}H NMR (CDCl$_3$, δ): 2.14 (s, COCH$_3$), 2.35 (s, ArCH$_3$), 3.83 (s, CO$_2$CH$_3$), 7.25 (bs, H$_6$), 7.37 (bs, H$_4$), 7.85 (bs, NH and H$_7$). ^{13}C NMR (CDCl$_3$, δ): 20.8 (ArCH$_3$), 24.1 (COCH$_3$), 53.9 (CO$_2$Me), 113.3 (t, $J_{C,F}$ 251 Hz, C$_3$), 122.9 (C$_{3a}$), 125.2 (C$_7$), 126.3 (t, $J_{C,F}$ 8 Hz, C$_4$), 132.3 (C$_6$), 132.9 (C$_5$), 134..9 (C$_{7a}$), 164.8 (t, $J_{C,F}$ 35 Hz, C$_2$), 168.8 (NAc). ^{19}F NMR (CDCl$_3$, δ): -103.2.

*Methyl 2-(2-benzamidophenyl)-2,2-difluoroacetate (**20**)*

Yield 83% (n-hexane/AcOEt, 1:1). mp 118-120°C. IR (KBr) ν_{max}/cm^{-1}: 3246 (NH), 1777 (CO$_2$CH$_3$), 1660 (COC$_6$H$_5$), 1072 (CF$_2$). *m/z* (%): 305 (85), 246 (9), 226 (6), 183 (78), 105 (99), 78 (12), 77 (100), 51 (47), ^{1}H NMR (CDCl$_3$, δ): 3.83 (s, CO$_2$CH$_3$), 7.21-7.3 (m, H$_5$), 7.48- 7.65 (m, H$_4$, H$_6$, H$_{12}$, H$_{11}$ and H$_{11'}$), 7.98-8.02 (m, H$_{10}$ and H$_{10'}$), 8.41(d, *J* 8 Hz, H$_7$), 8.93 (bs, NH). ^{13}C NMR (CDCl$_3$, δ): 54.0 (CO$_2$CH$_3$), 113.6 (t, $J_{C,F}$ 251 Hz, C$_3$), 122.3 (t, $J_{C,F}$ 23 Hz, C$_{3a}$), 124.4 (C$_7$), 124.6 (C$_5$), 126.2 (t, $J_{C,F}$ 8 Hz, C$_4$), 127.3 (C$_{11}$ and C$_{13}$), 128.8(C$_{10}$ and C$_{14}$), 132.0 (C$_6$), 132.2 (C$_{12}$), 134.5 (C$_9$), 136.2 (C$_{7a}$), 165.2 (t, $J_{C,F}$ 35 Hz, C$_2$), 165.4 (COC$_6$H$_5$). ^{19}F NMR (CDCl$_3$, δ): -103.6.

*General procedure for the reaction of **7-12** with amines*

To a stirred solution of the *N*-Acyl-3,3-difluoro-2-oxoindole derivative, **7-12**, (1 mmol) in dichloromethane (20 mL) was added the amine (5 mmol) at room temperature. After 2 h, the mixture was successively washed with water (3 x 10 mL), a solution of 0.6 N HCl (2 x 10 mL) and again with water (3 x 10 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, rotary evaporated and the solid residue recrystallized from a suitable solvent.

*2-(2-Acetamidophenyl)-2,2-difluoro-N-isopropylacetamide (**21**)*

Yield 80 % (water). mp 115-118 ºC. IR (KBr) ν_{max}/cm^{-1}: 3297 (NH), 1699 (CO at C$_2$), 1680 (COMe), 1071 (CF$_2$). *m/z* (%): 270 (18), 228 (6), 185 (17), 143 (100). ^{1}H NMR (CDCl$_3$, δ): 1.18 (d, *J* 6 Hz, CHMe$_2$), 2.19 (s, COCH$_3$), 4.04 (m, CHMe$_2$), 6.33 (bs, NH), 7.12 (t, *J* 8 Hz, H$_5$), 7.41-7.48 (m, H$_4$ and H$_6$), 8.19 (d, *J* 8 Hz, H$_7$), 9.68 (bs, NH). ^{13}C NMR (CDCl$_3$, δ): 22.2 (CHMe$_2$), 24.6 (COMe), 42.7 (CHMe$_2$), 114.7 (t, $J_{C,F}$ 253 Hz, C$_3$), 123.0 (C$_{3a}$), 123.9 (C$_5$), 124.7 (C$_7$), 125.3 (t, $J_{C,F}$ 9 Hz, C$_4$), 131.9 (C$_6$), 137.1 (C$_{7a}$), 164.8 (t, $J_{C,F}$ 31 Hz, C$_2$), 168.9 (COMe). ^{19}F NMR (CDCl$_3$, δ): -104.2.

*2-(2-Acetamido-5-bromophenyl)-2,2-difluoro-N-isopropyl-acetamide (**22**)*

Yield 60 %. (methanol/water, 1:1). mp 166 ºC. IR (KBr) ν_{max}/cm^{-1}: 3325 (NH), 1677 (COCH$_3$), 1075 (CF$_2$). *m/z* (%): 350 (18), 348 (20), 288 (27), 265 (12), 248 (8), 232 (2), 221 (100), 201 (17), 182 (5), 165 (7), 114 (12), 86 (15), 75 (10). ^{1}H NMR (CDCl$_3$, δ): 1.25 (t, *J* 6 Hz, CHMe$_2$), 2.20 (s, NCOMe), 4.07 (m, *J* 7 Hz, CH(CH$_3$)$_2$), 6.49 (bs, NH), 7.54 (H$_4$), 7.59 (H$_6$), 8.16 (d, *J* 9 Hz, H$_7$), 9.90 (bs, NH). ^{13}C NMR (CDCl$_3$, δ): 22.1 (CHMe$_2$), 24.5 (COMe), 42.8 (CHMe$_2$), 116.2 (t, $J_{C,F}$ 127,35 Hz, C$_3$), 124.3 (t, $J_{C,F}$ 24 Hz, C$_{3a}$), 128.1 (C$_5$), 127.9 (C$_7$), 134.7 (C$_4$), 128.3 (C$_6$), 136.1 (C$_{7a}$), 164.2 (t, $J_{C,F}$ 31 Hz, C$_2$), 168.7 (COMe). ^{19}F NMR (CDCl$_3$, δ): -104.8.

*2-(2-Acetamido-5-chlorophenyl)-2,2-difluoro-N-isopropyl-acetamide (**23**)*

Yield 60 %(from methanol/water, 1:1). mp 98 ºC. IR (KBr) ν_{max}/cm^{-1}: 3300 (NH), 1766.3 (CO at C$_2$), 1675 (COMe), 1078 (CF$_2$). *m/z* (%): 304 (25), 262 (20), 244 (26), 219 (16), 203 (12), 177 (100), 157 (18), 148 (8), 113 (5), 95 (4), 86 (14), 75 (4). ^{1}H NMR ((CD$_3$)$_2$CO, δ): 1.18 (t, CH$_3$), 1.29 (t, CH$_3$), 2.13 (s, COMe), 4.04 (m, CHMe$_2$), 7.55 (H$_4$), 7.51 (d, *J* 8 Hz, H$_6$), 8.22 (d, *J* 8 Hz, H$_7$), 9.79 (bs, NH). ^{13}C NMR ((CD$_3$)$_2$CO, δ): 22.4 (CHMe$_2$), 24.8 (COMe), 43.8 (CHMe$_2$), 115.1 (C$_3$), 120.2 (C$_{3a}$), 126.3 (C$_5$), 126.6 (C$_7$), 126.8 (C$_4$), 132.6 (C$_6$), 137.4 (C$_{7a}$), 164.9 (C$_2$), 169.2 (COMe). ^{19}F NMR ((CD$_3$)$_2$CO, δ): -103.3.

*2-(2-Acetamido-5-methylphenyl)-2,2-difluoro-N-iso-propylacetamide (**24**)*

Yied 70 % (methanol/water,1:1). mp 284 ºC. IR (KBr) ν_{max}/cm^{-1}: 3340 (NH), 1696 (CO at C$_2$), 1668 (COMe), 1079 (CF$_2$). *m/z* (%): 284 (30), 242 (10), 224 (15), 209 (1), 199 (22), 183 (19), 157 (100), 137 (21), 127 (7), 89 (6), 77 (4). ^{1}H NMR ((CD$_3$)$_2$CO, δ): 1.18 (t, CH$_3$), 2.03 (t, CH$_3$), 2.09 (s, COCH$_3$), 2.32 (CH$_3$), 4.07 (m, CHMe$_2$), 7.33 (H$_4$), 7.27 (d, *J* 8 Hz, H$_6$), 8.02 (d, *J* 8 Hz, H$_7$), 9.65 (bs, NH). ^{13}C NMR ((CD$_3$)$_2$CO, δ): 22.0 (CHMe$_2$), 24.3 (COMe), 28.6 (Me), 43.2 (CHMe$_2$), 112.7 (C$_3$), 124.5 (C$_{3a}$), 134.3 (C$_5$), 125.9 (C$_7$), 126.6 (C$_4$), 132.7 (C$_6$), 135.5 (C$_{7a}$), 165.3 (C$_2$), 168.5 (COMe). ^{19}F NMR ((CD$_3$)$_2$CO, δ): -102.9.

*2-(2-Acetamidophenyl)-N-benzyl-2,2-difluoroacetamide (**25**)*

Yield 69 % (aqueous acetone). mp 151-153 ^{o}C. IR (KBr) ν_{max}/cm^{-1}: 3326 (NH), 1690 (CO at C_2),1658 (COMe), 1080 (CF_2). *m/z* (%): 318(23), 276(7), 258(17), 185(14), 142(93), 106(30), 91(100). ^{1}H NMR (DMSO-d$_6$, δ): 2.01 (s, COCH$_3$), 4.34 (d, *J*= 6 Hz, CH$_2$Ph), 7.19- 7.35 (m, 6H), 7.49-7.60 (m, 2H), 7.76 (d, *J* 8 Hz, H_7), 9.40 (bs, NH), 9.55 (bs, NH). ^{13}C NMR (DMSO-d$_6$, δ): 23.6 (COCH$_3$), 48.6 (CH$_2$), 114.5 (t, $J_{C,F}$ 251 Hz, C_3), 124.8 (C_5), 125.2 (C_{3a}), 126.0 (t, $J_{C,F}$ 8 Hz, C_4), 127.1 (C_7), 127.2 (C_{11}, C_{12} and C_{13}), 128.3 (C_{10} and C_{14}), 131.4 (C_6), 136.0 ($C_{Ar}CH_2$), 137.9 (C_{7a}), 164.0 (t, *J* 31 Hz, C_2), 168.3 (COMe). ^{19}F NMR (DMSO-d$_6$, δ): -100.3.

*2-(2-Acetamido-5-bromophenyl)-N-benzyl-2,2-difluoro-acetamide (**26**)*

Yield 60 % (aqueous methanol). IR (KBr) ν_{max}/cm^{-1}: 3313 (NH), 1686 (CO at C_2),1665 (COMe), 1091 (CF_2). *m/z* (%): 396(6), 356(5), 336(9), 289(2), 263(2), 247(2), 222(35), 140(6), 106(41), 91(100), 77(5), 65(17), 51(4). ^{1}H NMR(DMSO-d$_6$, δ): 1.94 (s, CH_3), 4.37 (d, *J* 6 Hz), 7.23-7.36(m, H_4, H_6 and 3H_{Ar}), 7.74 (H_7), 9.47 (bs, NH), 9.65 (bs, NH). ^{13}C NMR(DMSO-d$_6$, δ): 23.5 (CH_3), 42.6 (CH_2), 116.3 (t, $J_{C,F}$ 127 Hz, C_3), 126.9 (C_{3a}), 127.1 (t, *J* 8 Hz, C_4), 127.8 (o-C_{Ar}), 128.4 (C_7), 128.6 (C_5), 128.8 (m-C_{Ar}), 134.4 (C_6), 135.3 ($C_{Ar}CH_2$), 137.8 (C_{7a}), 163.3 (t, *J* 30 Hz, C_2), 168.5 (COMe). ^{19}F NMR ($CDCl_3$+DMSO-d$_6$, δ): -102.8.

*2-(2-Acetamido-5-chlorophenyl)-N-benzyl-2,2-difluoro-acetamide (**27**)*

Yield 65 % (aqueous methanol). mp 140-142 ^{o}C. IR (KBr) ν_{max}/cm^{-1}: 3330 (NH), 1686 (CO at C_2),1665 (COMe), 1098 (CF_2). *m/z* (%): 352(20), 310(14), 292(22), 272(1), 219(7), 185(3), 176(60), 157(6), 148(4), 106(39), 91(100), 77(6), 65(15), 51(5). ^{1}H NMR((CD$_3$)$_2$O δ): 2.11 (s, Me), 4.52 (d, *J* 6 Hz), 7.21-7.34 (m, 5 H_{Ar}), 7.53 (d, *J* 9 Hz, H_6), 7.57 (d, *J* 2 Hz, H_4), 8.22 (d, *J* 9 Hz, H_7), 8.92 (bs, NH), 9.67 (bs, NH). ^{13}C NMR ((CD$_3$)$_2$O, δ): 24.4 (Me), 44.1 (CH_2), 168.8 (COMe), 165.6 (t, *J* 31 Hz, C_2), 114.9 (t, $J_{C,F}$ 253 Hz, C_3), 125.6 (C_{3a}), 126.3 (t, $J_{C,F}$ 8 Hz, C_4), 128.3 (C_{Ar}), 128.5 (C_7), 129.4 (C_5), 129.4 (C_{Ar}), 136.9 (C_6), 138.4 (C_{7a}), 138.4 ($C_{Ar}CH_2$). ^{19}F NMR ($CDCl_3$, δ): -103.4.

*2-(2-Acetamido-5-methylphenyl)-N-benzyl-2,2-difluoro-acetamide (**28**)*

Yield 59 % (aqueous methanol). mp 147-149 ^{o}C. IR (KBr) ν_{max}/cm^{-1}: 3322 (NH), 1684 (CO at C_2), 1663 (COMe), 1093 (CF_2). *m/z* (%): 332(31), 290(10), 272(26), 252(5), 199(13), 183(19), 156(100), 137(12), 127(6), 106(32), 91(92), 77(8), 65(16). ^{1}H NMR ((CD$_3$)$_2$CO, δ): 2.07 (s, COMe), 4.50 (d, *J* 6 Hz, PhCH$_2$), 7.39 (s, H_6), 7.23-7.38 (m, H_4), 8.02 (d, *J* 8 Hz, H_7), 8.73 (bs, NH), 9.45 (bs, NH). ^{13}C NMR ((CD$_3$)$_2$CO, δ): 24.3 (COMe), 28.6 (Me), 44.1 (CH$_2$), 115.8 (t, $J_{C,F}$ 252 Hz, C_3), 125.4 (C_7), 166.1 (t, $J_{C,F}$ 31 Hz, C_2), 168.7 (COMe). ^{19}F NMR ((CD$_3$)$_2$CO, δ): -103.0.

*2-(2-Acetamidophenyl)-N-butyl-2,2-difluoroacetamide (**29**)*

Yied 50 % (aqueous methanol). mp 114-115 ºC. IR (KBr) ν_{max}/cm^{-1}: 3312 (NH), 1677 (COMe), 1081 (CF_2). *m/z* (%): 284(10), 269(1), 255(1), 242(6), 224(14), 212(1), 185(12), 142(100), 123(18), 102(16), 93(4), 74(6), 65(4), 57(14). ^{1}H NMR ($CDCl_3$, δ): 0.90 (t, *J* 7 Hz, CH$_3$CH$_2$), 1.23-1.28 (m, CH$_2$CH$_2$CH$_3$), 2.20 (s, COMe), 3.29 (q, *J* 7 Hz, NHCH$_2$CH$_2$), 7.41-7.49 (H_4 and H_6), 7.13 (t, *J* 7 Hz, H_5), 8.20 (d, *J* 8 Hz, H_7), 6.76 (bs, NH), 9.82 (bs, NH). ^{13}C NMR ($CDCl_3$, δ): 13.5 (CH$_3$CH$_2$), 19.8 (CH$_3$CH$_2$), 24.5 (COMe), 31.0 (CH$_3$CH$_2$CH$_2$), 39.7 (CH$_2$NH), 114.5 (C_3), 123.8 (C_5), 124.5 (C_7), 125.2 (t, $J_{C,F}$ 8 Hz, C_4), 131.8 (C_6), 136.8 (C_{7a}), 165.6 (t, $J_{C,F}$ 31 Hz, C_2), 168.9 (COCH$_3$). ^{19}F NMR ($CDCl_3$, δ): -104.7.

*2-(2-Acetamido-5-bromophenyl)-N-butyl-2,2-difluoro-acetamide (**30**)*

Yield 60% (aqueous methanol). mp 154-156 ºC. IR (KBr) ν_{max}/cm^{-1}: 3320 (NH), 1675 (COCH$_3$), 1075 (CF_2). *m/z* (%): 362 (22), 320 (17), 304 (27), 262 (12), 247 (17), 222 (100), 220 (95), 201 (20), 182 (20), 140 (7), 114 (55), 74 (67), 57(15). ^{1}H NMR ($CDCl_3$, δ): 0.92 (t, *J* 7 Hz, CH$_3$CH$_2$), 1.25-1.70 (m, CH$_2$CH$_2$CH$_3$), 2.20 (s, COMe), 3.31 (q, *J* 7 Hz, NHCH$_2$CH$_2$), 6.70 (bs, NH), 7.56 (d, *J* 10 Hz, H_6), 7.60 (d, *J* 2 Hz, H_4), 8.16 (d, *J* 9 Hz, H_7) 9.86 (bs, NH). ^{13}C NMR ($CDCl_3$, δ): 13.5 (CH$_3$CH$_2$), 19.9 (CH$_3$CH$_2$), 24.6 (COMe), 31.0 (CH$_3$CH$_2$CH$_2$), 39.9 (CH$_2$NH), 116.4 (C_3), 125.9 (C_{3a}), 128.0 (C_7), 128.2 (C_{7a}), 128.2 (C_4), 134.7 (C_5), 136.1 (C_6), 168.8 (COMe). ^{19}F NMR ($CDCl_3$, δ): -105.0.

*2-(2-Acetamido-5-chlorophenyl)-N-butyl-2,2-difluoro-acetamide (**31**)*

Yield 62% (aqueous methanol). mp 155-156 ºC. IR (KBr) ν_{max}/cm^{-1}: 3311 (NH), 1676 (COCH$_3$), 1085 (CF_2). *m/z* (%): 318 (18), 303 (1), 276 (16), 258 (26), 248 (2), 218 (8), 203 (24), 176 (100), 157 (24), 148 (11), 113 (8), 88 (3), 74 (32), 57 (39). ^{1}H NMR ($CDCl_3$, δ): 0.92 (t, *J* 8 Hz, CH$_3$CH$_2$), 1.25-1.72 (m, CH$_2$CH$_2$CH$_3$), 2.20 (s, COCH$_3$), 3.31 (q, *J* 7 Hz, NHCH$_2$CH$_2$), 6.73 (bs, NH), 7.39 (d, *J* 2 Hz, H_6), 7.75 (d, *J* 2 Hz, H_4), 8.20 (d, *J* 8 Hz, H_7), 9.85 (bs, NH). ^{13}C NMR ($CDCl_3$, δ): 13.5 (CH$_3$CH$_2$), 19.6 (CH$_3$CH$_2$), 24.5 (COMe), 31.0 (CH$_3$CH$_2$CH$_2$), 39.9 (CH$_2$NH), 113.7

(C_3), 124.2 (t, $J_{C,F}$ 24 Hz, C_{3a}), 125.3 (C_7), 125.5 (C_4), 129.1 (C_5), 131.7 (C_6), 135.6 (C_{7a}), 165.1 (t, $J_{C,F}$ 30 Hz, C_2), 168.8 (COMe). ^{19}F NMR ($CDCl_3$, δ): -105.0.

*2-(2-Acetamido-5-methylphenyl)-N-butyl-2,2-difluoro-acetamide (**32**)*

Yield 60% (aqueous methanol). mp 145-147 ºC. IR (KBr) ν_{max}/cm^{-1}: 3321 (NH), 1673 (COMe), 1079 (CF_2). *m/z* (%): 298 (17), 256 (7), 238 (12), 198 (8), 183 (26), 164 (3), 156 (100), 137 (19), 109 (7), 74 (14). ^{1}H NMR ($CDCl_3$, δ): 0.92 (t, *J* 7 Hz, CH_3CH_2), 1.24-1.54 (m, $CH_2CH_2CH_3$), 2.18 (s, $COCH_3$), 2.32 (s, CH_3), 3.29 (q, *J* 14 Hz, $NHCH_2CH_2$), 7.26-7.27 (H_4 and H_6), 8.04 (d, *J* 8 Hz, H_7), 9.62 (bs, NH). ^{13}C NMR ($CDCl_3$, δ): 13.5 (CH_3CH_2), 19.9 (CH_3CH_2), 20.8 (Me), 24.5 (COMe), 31.0 ($CH_3CH_2CH_2$), 39.7 (CH_2NH), 114.6 (t, $J_{C,F}$ 253 Hz, C_3), 122.9 (t, $J_{C,F}$ 24 Hz, C_{3a}), 125.3 (C_4), 127.3 (C_7), 132.4 (C_6), 133.7 (C_{7a}), 134.2 (C_5), 165.6 (t, $J_{C,F}$ 31 Hz, C_2), 168.8 ($COCH_3$). ^{19}F NMR ($CDCl_3$, δ): -104.6.

*2-(2-Acetamidophenyl)-N-(4-chlorophenyl)-2,2-difluoro-acetamide (**33**)*

Yield 55 % (aqueous acetone). mp 172-173 ºC. IR (KBr) ν_{max}/cm^{-1}: 3312 (NH), 1691 (C_2), 1666 (COMe), 1091 (CF_2). *m/z* (%): 338 (7), 340 (2), 212 (2), 184 (7), 170 (16), 142 (79), 127 (100). ^{1}H NMR (($CD_3)_2CO$, δ): 2.12 (s, MeCO), 7.29 (t, *J* 8 Hz, H_5), 7.38 (m, $2H_{Ar}$), 7.51 (t, *J* 8 Hz, H_6), 7.69 (d, *J* 8 Hz, H_4), 7.74 (m, $2H_{Ar}$) and 8.04 (d, *J* 8 Hz, H_7). ^{13}C NMR (($CD_3)_2CO$, δ): 24.2 (COMe), 115.6 (t, $J_{C,F}$ 252 Hz, C_3), 121.5 (C_{3a}), 123.4 ($2C_{Ar}$), 125.3 (C_5), 126.0 (C_7), 126.9 (t, $J_{C,F}$ 8 Hz, C_4), 129.7 ($2C_{Ar}$), 131.0 (C_{Cl}), 132.6 (C_6), 136.6 (NC_{Ph}), 137.5 (C_{7a}), 164.0 (t, $J_{C,F}$ 31 Hz, C_2), 169.0 (COMe). ^{19}F NMR (($CD_3)_2CO$, δ): -102.1. Anal. Calcd for $C_{16}H_{13}ClF_2N_2O_2$: C 56.80, H 3.84, N 8.28. Found C 56.55, H 3.65, N 8.18%.

*2-(2-Acetamido-5-methylphenyl)-N-(4-chlorophenyl)-2,2-difluoroacetamide (**34**)*

Yield 60% (aqueous acetone). mp 219-221ºC. IR (KBr) ν_{max}/cm^{-1}: 3314 (NH), 1693 (CO at C_2), 1669 (COMe), 1086 (CF_2). *m/z* (%): 352 (7), 312 (3), 292 (6), 269 (2), 242 (2), 226 (3), 198 (5), 184 (15), 169 (2), 156 (60), 137 (10), 127 (100), 109 (9), 89 (9), 75 (7), 63 (5), 51 (3). ^{1}H NMR ($CDCl_3$ + DMSO-d_6, δ): 2.15 (s, COMe), 2.37 (s, CH_3), 7.28 (d, *J* 8 Hz, H_6), 7.44 (m, $2H_{Ar}$), 7.58 (m, $2H_{Ar}$), 7.69 (H_4), 7.85 (d, *J* 8 Hz, H_7), 10.52 (bs, NH). ^{13}C NMR ($CDCl_3$ + DMSO-d_6, δ): 20.9 (COMe), 24.2 (Me), 114.4 (t, $J_{C,F}$ 254 Hz, C_3), 124.2 (t, $J_{c,F}$ 24 Hz, C_{3a}), 125.2 ($2C_{Ar}$), 125.5 (C_7), 126.4 ($2C_{Ar}$), 128.7 (C_4), 132.2 (C_6), 133.5 (C_5), 135.6 (C_{7a}), 163.3 (t, $J_{C,F}$ 31 Hz, C_2), 169.0 (COMe). ^{19}F NMR ($CDCl_3$, δ): -104.0.

*2-(2-Acetamidophenyl)-2,2-difluoro-N-phenylacetamide (**35**)*

Yield 81% (aqueous methanol). mp 168-170 ºC. IR (KBr) ν_{max}/cm^{-1}: 3303 (NH), 1692 (CO at C_2), 1664 (COMe), 1078 (CF_2). *m/z* (%): 304 (10), 244 (7), 170 (7), 142 (60), 93 (100). ^{1}H NMR (($CD_3)_2CO$, δ): 2.12 (s, CH_3CO), 7.17-7.32 (m, H_5 and $1H_{Ar}$), 7.34-7.39 (m, $2H_{Ar}$), 7.50 (t, *J* 8 Hz, H_6), 7.61-7.72 (m, H_4 and $2H_{Ar}$), 8.12 (d, *J* 8 Hz, H_7), 9.34 (bs, NH), 10.02 (bs, NH). ^{13}C NMR (($CD_3)_2CO$, δ): 24.3 (MeCO), 115.6 (t, *J* 253 Hz, C_3), 121.5 (C_{3a}), 121.9 ($2C_{Ar}$), 125.1 (C_5), 125.8 (C_7), 126.3 ($1C_{Ar}$), 126.8 (t, $J_{C,F}$ 8 Hz, C_4), 129.7 ($2C_{Ar}$), 132.5 (C_6), 137.8 (C_{7a}), 164.1 (t, $J_{C,F}$ 31 Hz, C_2), 168.9 (COMe). ^{19}F NMR (($CD_3)_2CO$, δ): -102.26. Anal. Calcd for $C_{16}H_{14}F_2N_2O_2$: C 63.15, H 4.60, N 9.24. Found C 63.10, H 4.47, N 9.14 %

*2-(2-Acetamidophenyl)-2,2-difluoro-N-phenylacetamide (**36**)*

Yield 70% (methanol). mp 181-183 ºC. IR (KBr) ν_{max}/cm^{-1}: 3297 (NH), 1692 (CO at C_2), 1672 (COMe), 1098 (CF_2). *m/z* (%): 382 (10), 342 (1), 324 (10), 289 (1), 248 (5), 222 (30), 201 (7), 182 (2), 140 (7), 93 (100), 77 (16), 65 (7), 51 (5). ^{1}H NMR($CDCl_3$, δ): 2.22 (s, MeCO), 7.25 (t, *J* 7 Hz, H_{Ar}), 7.37 (t, *J* 8 Hz, H_{Ar}), 7.53 (d, *J* 8 Hz, H_6), 7.58 (d, *J* 2 Hz, H_{Ar}), 7.68 (d, *J* 2 Hz, H_4), 8.14 (d, *J* 9 Hz, H_7), 8.33 (bs, NH), 9.57 (bs, NH). ^{13}C NMR ($CDCl_3$, δ): 24.6 (MeCO), 116.6 (C_3), 120.9 (C_4), 124.2 (t, $J_{C,F}$ 24 Hz, C_{3a}), 126.3 (C_7), 126.5 ($1C_{Ar}$), 128.7 ($2C_{Ar}$), 129.3 (C_5), 129.3 ($2C_{Ar}$), 135.0 (C_6), 135.3 (C_{7a}), 162.7 (t, $J_{C,F}$ 20 Hz, C_2), 169.0 (COMe). ^{19}F NMR ($CDCl_3$, δ): -104.6.

*2-(2-Acetamido-5-chlorophenyl)-2,2-difluoro-N-phenyl-acetamide (**37**)*

Yied 75 % (aqueous methanol). mp 175-178ºC. IR (KBr) ν_{max}/cm^{-1}: 3303 (NH), 1691 (CO at C_2), 1672 ($COCH_3$), 1077 (CF_2). *m/z* (%): 338 (8), 296 (2), 278 (9), 245 (1), 219 (2), 204 (4), 176 (3), 157 (30), 148 (6), 120 (4), 111 (3), 93 (100), 77 (18), 65 (8), 51 (6). ^{1}H NMR($CDCl_3$ + DMSO-d_6, δ): 2.19 (s, CH_3CO), 7.29 (2 H_{Ar}), 7.38 (2 H_{Ar}), 7.41 (d, *J* 2 Hz, H_4), 7.63 (d, *J* 7 Hz, H_6), 8.10 (d, *J* 9 Hz, H_7), 8.12 (bs, NH), 9.59 (bs, NH). ^{13}C NMR ($CDCl_3$, δ): 24.4 (CH_3CO), 113.6 (C_3), 121.4 ($1C_{Ar}$), 125.0 (C_{3a}), 125.8 (C_7), 126.0 (C_4), 128.9 ($2C_{Ar}$), 129.3 (C_5), 131.5 (C_6), 135.2 ($1C_{Ar}$), 136.4 (C_{7a}), 163.1 (t, $J_{C,F}$ 31 Hz, C_2), 169.1 ($COCH_3$). ^{19}F NMR (($CD_3)_2CO$, δ): -104.6.

*2-(2-Acetamide-5-methylphenyl)-2,2-difluoro-N-phenyl-acetamide (**38**)*

Yield 70% (methanol). mp 183-185 ºC. IR (KBr) ν_{max}/cm^{-1}: 3301 (NH), 1692 (CO at C_2), 1669 (COMe), 1082 (CF_2). *m/z* (%): 318 (46), 276 (3), 258 (23), 235 (11), 221 (4), 208

(2), 198 (9), 184 (12), 168 (2), 109 (9), 93 (100), 77 (19), 65 (9), 51 (7). ^{1}H NMR($CDCl_3$ + DMSO-d_6, δ): 2.14 (s, MeCO), 2.33 (s, Me), 7.15 (d, *J* 7 Hz, H_6), 7.17-7.33 (m, 2 H_{Ar}), 7.34-7.45 (m, 2 H_{Ar}), 7.62 (1H_{Ar}), 7.66 (s, H_4), 7.87 (d, *J* 8 Hz, H_7), 9.40 (bs, NH), 10.06 (bs, NH). ^{13}C NMR ($CDCl_3$ + DMSO-d_6, δ): 20.3 (MeCO), 23.8 (CH_3) 114.0 (t, $J_{C,F}$ 254 Hz, C_3), 120.8 (C_4), 123.6 (t, $J_{C,F}$ 24 Hz, C_{3a}), 125.0 (C_6), 125.7 (C_7), 126.0 (1C_{Ar}), 128.3 (2C_{Ar}), 131.7 (C_5), 136.1 (1C_{Ar}), 133.8 (C_{7a}), 162.9 (t, $J_{C,F}$ 31 Hz, C_2), 168.6 (COMe). ^{19}F NMR ($CDCl_3$, δ): -104.1.

*2-(2-Benzamidophenyl)-N-benzyl-2,2-difluoroacetamide (**39**)*

Yield 75 % (ethanol). mp 149-151 ^{o}C. IR (KBr) ν_{max}/cm^{-1}: 3263 (NH), 1690 CO at C_2), 1657 (COPh), 1081 (CF_2). *m/z* (%): 380(13), 258(10), 247(5), 142(12), 105(100), 91(29), 77(49). ^{1}H NMR (DMSO-d_6, δ): 4.36 (d, *J* 6 Hz, CH_2), 7.18-7.36 (m, H_5 and 5H_{Ar}), 7.55-7.67 (m, H_4, H_6 and 3H_{Ar}), 7.97-8.02 (dd, *J* 2 and 8 Hz, 2H_{Ar}), 8.10 (d, *J* 8 Hz, H_7), 9.78 (bs, NH), 10.45 (s, NH). ^{13}C NMR (DMSO-d_6, δ): 42.6 (CH_2), 114.6 (t, $J_{C,F}$ 252 Hz, C_3), 124.6 (C_{3a}), 125.0 (C_5), 125.4 (C_7), 125.9 (t, $J_{C,F}$ 8 Hz, C_4), 127.1 (C_{Ar}), 128.3 (C_{Ar}), 128.7 (C_{Ar}), 131.6 (C_{Ar}), 131.9 (C6), 134.1 (CH_2Ph), 136.1 (C_{ArCO}), 137.6 (C_{7a}), 164.7 (t, $J_{C,F}$ 31 Hz, C_2), 164.7 (COPh). ^{19}F NMR (DMSO-d_6, δ): -101.8.

*2-(2-Benzamidophenyl)-2,2-difluoro-N-isopropylacetamide (**40**)*

Yied 43 % (aqueous methanol). mp 163-165 ºC. IR (KBr) ν_{max}/cm^{-1}: 3280 (NH), 1683 (COPh), 1662 (C_2), 1117 (CF_2). ^{1}H NMR ($CDCl_3$, δ): 1119 (d, *J* 6 Hz, (Me_2CH), 4.12 (m, CHMe_2), 6.43 (bs, NH), 7.18 (t, *J* 8 Hz, H_5), 7.48-7.55 (m, H_4, H_6 and H_{12}), 8.07-8.12 (m, H_{10} and H_{14}), 8.38 (d, *J* 8 Hz, H_7), 10.69 (bs, NH). ^{13}C NMR ($CDCl_3$, δ): 22.2 (Me_2CH), 42.6 (Me_2CH), 114,.5 (t, $J_{C,F}$ 253 Hz, C_3), 123.3 (t, $J_{C,F}$ 24 Hz, C_{3a}), 124.0 (C_5), 125.0 (C_7), 125.3 (t, $J_{C,F}$ 8 Hz, C_4), 127.7 ($C_{Ar\text{-}10}$ and $C_{Ar\text{-}14}$), 128.7 ($C_{Ar\text{-}11}$ and $C_{Ar\text{-}13}$), 131.8 ($C_{Ar\text{-}12}$), 131.8 (C_6), 134.7 ($C_{Ar\text{-}9}$), 137.0 (C_{7a}), 164.9 (t, $J_{C,F}$ 31 Hz, C_2), 165.7 (COPh).^{19}F NMR ($CDCl_3$, δ): -104.8.

*Reaction of N-acetyl-3,3-difluoro-2-oxoindole (**7**) with ethyl glycinate hydrochloride: formation of ethyl N-(2-acetamidophenyl-2,2-difluoro-acetyl-glycinate (**41**)*

A mixture of *N*-acetyl-3,3-difluoro-2-oxoindole (**7**) (1 mol), glycine ethyl ester hydrochloride (1 mol), triethylamine (7 ml) and 1,4-dioxane (70 ml) was refluxed for 5 hours, cooled and extracted with dichloromethane/water (pH= 6). The combined organic phases were dried over anhydrous sodium sulphate, filtered and the filtrate evaporated. The residue was chromatographed on silica gel using hexane/ethyl acetate (1:1) as eluent; yield: 59%. *m/z* (%): 314 (3), 254 (6), 184 (6), 169 (11), 142 (100), 123 (11), 114 (24), 102 (28), 74 (12), 56 (14). ^{1}H NMR ($CHCl_3$, δ): 1.25 (CH_3), 2.20 (CH_3), 4.04 (CH_2), 4.21 (CH_2), 7.17 (CH), 7.45 (CH), 7.53 (CH), 8.13 (CH), 9.52 (NH). ^{13}C NMR ($CHCl_3$, δ):13.3 (CH_3), 23.8 (CH_3), 40.7 (CH), 61.4 (CH_2), 113.6 (t, $J_{C,F}$ 253 Hz, C_3), 122.2 (C_{3a}), 123.5 (C_5), 124.2 (C_7), 124.8 (C_4), 131.3 (C_6), 135.8 (C_{7a}), 164.9 (t, $J_{C,F}$ 31.5 Hz, C_2), 167.8 (C=O), 168.4 (C=O). ^{19}F NMR ($CHCl_3$, δ): - 104.8.

*General procedure for the reaction of **7**-**12** with thiosemicarbazides*

The thiosemicarbazide (0.03mole) was added to a suspension of the *N*-acetyl-3,3-difluoro-2-oxoindole derivative 7-12 (1.0 g) in 5 mL of glacial acetic acid. The reaction mixture was stirred for 1.5 h, filtered and the precipitate of 42-46 was collected and washed with ether (5 x 5 mL) and dried in air.

*1-(2-(2-acetamidophenyl)-2,2-difluoroacetyl)thiosemicarbazide (**42**)*

Yield 72%. mp 185-188 ^{o}C. IR (KBr) ν_{max}/cm^{-1}: 1715 (C=O), 1629 (C=O), 1057 (CF_2). *m/z* (%): 302 (7), 284 (10), 242 (13), 226 (22), 209 (18), 185 (82), 169 (55), 150 (17), 142 (100), 118 (27), 102 (17), 91 (33), 60 (22). ^{1}H NMR (DMSO-d_6, δ): 2.05 (CH_3), 10.92 (NH), 9.75 (NH), 9.44 (NH), 7.32-8.03 ($H_{arom.}$ and NH_2). ^{13}C NMR (DMSO-d_6, δ): 23.1 (CH_3), 114,.6 (t, $J_{C,F}$ 252 Hz, C_3), 124.4 (C_{3a}), 125.4 (C_5), 126.9 (C_7), 127.7 (C_4), 131.5 (C_6), 135.1 (C_{7a}), 162.8 (t, $J_{C,F}$ 18,5 Hz, C_2), 169.2 (C=O), 181.9 (C=S). ^{19}F NMR (DMSO-d_6, δ): -99.4.

*1-(2-(2-acetamido-5-bromophenyl)-2,2-difluoroacetyl) thiosemicarbazide (**43**)*

Yield 83%. mp 221-224 ^{o}C . IR (KBr) ν_{max}/cm^{-1}: 1714 (C=O), 1628 (C=O), 1064m (CF_2). ^{1}H NMR (DMSO-d_6, δ): 2.06 (CH_3), 7.49 (H_6), 7.45 (H_4), 7.76 (H_7), 8.05 (NH_2), 9.46 (NH), 9.78 (NH), 10.97 (NH). ^{13}C NMR (DMSO-d_6, δ): 23.6 (CH_3), 113.7 (t, $J_{C,F}$ 222 Hz, C_3), 123.6 (C_{3a}), 128.7 (C_5), 129.3 (C_7), 130.6 (C_4), 134.8 (C_6), 135.1 (C_{7a}), 162.8 (t, $J_{C,F}$ 30 Hz, C_2), 169.7 (C=O), 182.5 (C=S). ^{19}F NMR (DMSO-d_6, δ): -99.8.

*1-(2-(2-acetamido-5-chlorophenyl)-2,2-difluoroacetyl) thiosemicarbazide (**44**)*

Yied 66%. mp 221-226 ^{o}C. IR (KBr) ν_{max}/cm^{-1}: 1709 (C=O), 1657 (C=O), 1091 (CF_2). *m/z* (%): 336 (4), 256 (53), 219 (97), 203 (23), 192 (32), 184 (13), 176 (95), 160 (39), 133 (46), 118 (90), 100 (17), 91 (69), 74 (38), 60 (100).

^{1}H NMR (DMSO-d_{63}, δ): 2.06 (CH_3), 7.54 (H_6), 7.62 (H_4), 7.78 (H_7), 8.08 (NH), 9.48 (NH), 9.81 (NH), 10.98 (NH). ^{13}C NMR (DMSO-d_6, δ): 23.1 (CH_3), 113.9 (t, $J_{C,F}$ 244 Hz, C_3), 125.6 (C_{3a}), 128.1 (C_7), 128.7 (C_5), 129.5 (C_4), 131.4 (C_6), 134.2 (C_{7a}), 162.3 (t, $J_{C,F}$ 31 Hz, C_2), 169.3 (C=O), 181.9 (C=S). ^{19}F NMR (DMSO-d_6, δ): -100.0.

*1-(2-(2-acetamido-5-methylphenyl)-2,2-difluoroacetyl) thiosemicarbazide (**45**)*

Yield 58%. mp 209-212 °C. IR (KBr) ν_{max}/cm^{-1}: 1710 (C=O), 1657 (C=O), 1069 (CF_2). *m/z* (%): 316 (4), 257 (13), 199 (36), 183 (75), 164 (37), 156 (100), 134 (23), 127 (41), 118 (34), 109 (25), 91 (57), 76 (43), 60 (23). ^{1}H NMR (DMSO-d_6, δ): 2.03 (CH_3), 2.35 (CH_3), 7.26(H_6), 7.41 (H_4), 7.78 (H_7), 8.05(NH_2), 9.44 (NH), 9.67 (NH), 10.86 (NH). ^{13}C NMR (DMSO-d_6, δ): 19.8 (CH_3), 22.4 (CH_3), 114.0 (t, $J_{C,J}$ 252.5 Hz, C_3), 125.6 (C_{3a}), 126.6 (C_7), 127.3 (C_4), 131.3 (C_6), 132.0 (C_5), 134.4 (C_{7a}), 162.1 (t, $J_{C,F}$ 21 Hz, C_2), 168.7 (C=O), 181.4 (C=S). ^{19}F NMR (DMSO-d_6, δ): -99.8.

*1-(2-(2-acetamidophenyl)-2,2-difluoroacetyl)-4-phenyl-thiosemicarbazide (**46**)*

Yield 77%. IR (KBr) ν_{max}/cm^{-1}: 1713 (C=O), 1685 (C=O), 1084 (CF_2). ^{1}H NMR (DMSO-d_6, δ): 2.04 (CH_3), 7.09-7.66 (H_{arom}.), 9.80 (NH), 10.09 (NH), 11.05 (NH). ^{13}C NMR (DMSO-d_6, δ): 23.9 (CH_3), 115.8 (t, $J_{C,F}$ 253 Hz), 125.4, 125.8, 126.4, 127.5, 129.0 (C_5), 132.4 (C_4), 135.6 (C_{7a}), 139.8 (C_6), 163.7 (t, $J_{C,F}$ 33.5 Hz, C_2), 170.5 (C=O), 181.6 (C=S). ^{19}F NMR (DMSO-d_6, δ): -99.6.

*General procedure for the cyclization of 42-46 in acidic medium to give **47-51***

Finely ground thiosemicarbazide, **42**-**46**, (12g) was added over 15-20 min with vigorous stirring to cooled (5°C) concentrated sulfuric acid (96 mL). The reaction mixture was stirred until complete dissolution, poured onto a mixture of 1440 g of ice and 360 mL of water, and concentrated aqueous ammonia was added with stirring to pH 6. The precipitate of **47**-**51** was filtered off, washed with water (3 x 20 mL), and dried. The products were purified by crystallization from aqueous methanol.

*N-(2-((5-amino-1,3,4-thiadiazol-2-yl)difluoromethyl) phenyl)acetamide (**47**)*

Yield 87%. mp 198-200 °C. IR (KBr) ν_{max}/cm^{-1}: 1680 (C=O), 1035 (CF_2), 3356 and 3178 (NH). *m/z* (%): 284 (78), 242 (100), 225 (99), 209 (41), 180 (49), 167 (41), 150 (22), 142 (23), 134 (20), 127 (13), 102 (16), 60 (17). ^{1}H NMR (DMSO-d_6, δ): 1.91 (CH_3), 7.36-7.70 (H arom. and NH_2), 9.12 (NH). ^{13}C NMR (DMSO-d_6, δ): 23.9 (CH_3), 117.6 (t, $J_{C,F}$ 239 Hz. C_3), 126.9 (C_4 and C_5), 129.7 (C_{3a}), 130.2 (C_7), 132.4 (C_6), 136.7 (C_{7a}), 153.7 (t, $J_{C,F}$ 337.5 Hz. C_2), 169.6 (C=O), 171.6 (C-S). ^{19}F NMR (DMSO-d_6, δ): -81.6.

*N-(2-((5-amino-1,3,4-thiadiazol-2-yl)difluoromethyl)-4-bromophenyl)acetamide (**48**)*

Yield 92%. mp 212-214 °C. IR (KBr) ν_{max}/cm^{-1}: 1675 (C=O), 1045 (CF_2), 3345,3 (NH). ^{1}H NMR (DMSO-d_6, δ): 1.91 (CH_3), 7.45 (H_4), 7.74 (H_6), 7.77 (H_7),), 7.81 (NH_2), 9.18 (NH). ^{13}C NMR (DMSO-d_6, δ): 22.2 (CH_3), 117.5 (t, $J_{C,F}$ = 120 Hz, C_3), 127.9 (C_{3a}), 128.0 (C_7), 130.4 (C_5), 130.7 (C_4), 133.6 (C_6), 134.5 (C_{7a}), 151.4 (t, $J_{C,F}$ = 33 Hz, C_2), 168.0 (C=O), 170.1 (C-S). ^{19}F NMR (DMSO-d_6, δ): -81.6.

*N-(2-((5-amino-1,3,4-thiadiazol-2-yl)difluoromethyl)-4-chlorophenyl)acetamide (**49**)*

Yield 90 %. mp 212-216 °C. IR (KBr) ν_{max}/cm^{-1}: 1674 (C=O), 1047 (CF_2), 3357 (NH). *m/z* (%): 318 (49), 276 (100), 259 (79), 243 (27), 214 (52), 201(29), 176 (23), 60 (38). ^{1}H NMR (DMSO-d_6, δ): 1.92 (CH_3), 7.51 (H_6), 7.63 (H_4), 7.72 (H_7), 7.74 (NH_2), 9.19 (NH). ^{13}C NMR (DMSO-d_6, δ): 22.8 (CH_3), 115.8 (t, $J_{C,F}$ 240 Hz, C_3), 125.7 (C_5 & C_{3a}), 125.8 (C_7), 130.1 (C_4), 131.3 (C_6), 134.6 (C_{7a}), 152.0 (t, $J_{C,F}$ 33.5 Hz, C_2), 168.7 (C=O), 170.8 (C-S). ^{19}F NMR (DMSO-d_6, δ): -81.6. Anal. Calcd for $C_{11}H_9ClF_2N_4OS$: C 41.50, H 2.83, N 17.61. Found C 41.52, H 2.77, N 17.21%.

*N-(2-((5-amino-1,3,4-thiadiazol-2-yl)difluoromethyl)-4-methylphenyl)acetamide (**50**)*

Yield 92%. mp 211-215 °C. IR (KBr) ν_{max}/cm^{-1}: 3367 (NH), 3305 (NH), 1681 (C=O), 1036 (CF_2). *m/z* (%): 298 (86), 256 (100), 239 (93), 223 (52), 194 (99), 181 (66), 156 (44), 148 (50), 127 (28), 101 (47), 77 (18), 60 (14). ^{1}H NMR (DMSO-d_6, δ): 1.89 (CH_3), 2.37 (CH_3), 7.29 (H_6), 7.33 (H_4), 7.49 (H_7), 7.69 (NH_2), 9.06 (NH). ^{13}C NMR (DMSO-d_6, δ): 20,42 (CH_3), 22.8 (CH_3), 116.5 (t, $J_{C,F}$ 238 Hz, C_3), 126.1 (C_7), 129.3 (C_4), 129.3 (C_{3a}), 131.8 (C_6), 133.0 (C_5), 135.4 (C_{7a}), 152.7 (t, $J_{C,F}$ 338 Hz, C_2), 168.5 (C=O), 170.5 (C-S). ^{19}F NMR (DMSO-d_6, δ): - 81.6. Anal. Calcd for $C_{12}H_{12}F_2N_4OS$: C 48.32, H 4.02, N 18.79. Found C 48.22, H 3.73, N 18.41%.

*N-(2-(difluoro(5-(methylamino)-1,3,4-thiadiazol-2-yl) methyl)phenyl)acetamide (**51**)*

Yield 96 %. mp 149-150 °C. IR (KBr) ν_{max}/cm^{-1}: 1671 (C=O), 1061 (CF_2). ^{1}H NMR (DMSO-d_6, δ): 1.90 (CH_3), 2.88 (CH_3), 7.34-7.69 (H_{arom}.), 8.09 (NH), 9.10 (NH). ^{13}C NMR (DMSO-d_6, δ): 22.5 (CH_3), 31.0 (CH_3), 116.1 (t, $J_{C,F}$ 239 Hz, C_3), 125.5, 128.8, 131.0, 135.2, 151.7 (t, $J_{C,F}$ 33.5 Hz, C_2), 168.1 (C=O), 170.7 (C=S). ^{19}F NMR (DMSO-d_6, δ):

- 81.3. Anal. Calcd for $C_{12}H_{12}F_2N_4OS$: C 48.32, H 4.02, N 18.79. Found C 48.54, H 4.12, N 18.25%.

X-ray crystallography

The crystals of **50** were grown from methanol/water. The intensity data in each case were collected at 120K on a Nonius Kappa CCD area detector system by the EPSRC X-ray crystallographic service at the University of Southampton, UK. The entire process of data collection, cell refinement and data reduction was accomplished by means of the programs DENZO and COLLECT.[20, 21] Correction for absorption was achieved in each case by a semi-empirical method based upon the variation of equivalent reflections with the program SORTAV.[22] The structures were solved by direct methods in SHELXS-97 [23] within the OSCAIL suite of programs and refined in SHELXL-97.[24,25] Approximate positions for H atoms were obtained from difference maps and were refined with a riding model. PLATON was used for the data analysis.[26] The program ORTEP-3 for Windows was used to obtain the Figures.[27] Conformational and H-bonding analysis was performed using PLATON.[26] Crystal data and structure refinement details are listed in Table 3. "CCDC 616842 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif."

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Table 3. Crystal data and structure refinement for **50**

Empirical formula	$C_{12}H_{12}F_2N_4OS$
Formula weight	298.32
Temperature	393(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/a$
Unit cell dimensions	a = 7.5649(7) Å α = 90 ^{o}
	b = 10.2480(6) Å β = 100.644(3) ^{o}
	c = 16.8212(14) Å δ = 90 ^{o}
Volume	1281.63(18 Å ^{3}
Z	4
Density (calculated)	1.546 Mg/m^3
Absorption coefficient	0.278 mm^{-1}
F(000)	616
Crystal size	0.42 x 0.34 x 0.30 mm
Theta range for data collection	3.39 to 27.52 ^{o}
Index ranges	-9<=h<=9; -11<=k<=13; -18<=l<=21
Reflections collected	14720
Independent reflections	2923 [R(int) = 0.0429]
Reflections observed (>2σ)	2322
Data Completeness	0.992
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2923 / 0 / 184
Goodness-of-fit on F^2	1.032
Final R indices [I>2s σ (I)]	R1 = 0.0478 wR2 = 0.1277
R índices (all data)	R1 = 0.0645 wR2 = 0.1410
Largest diff. peak and hole	0.452 and -0.505 e Å $^{-3}$

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