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A New Synthesis of 3-Aryl Substituted Oxindoles.

Thi-My Ly,[a] Nieves M. Laso,[a] and Samir Z. Zard [a,b*#]

a) Institut de Chimie des Substances Naturelles, CNRS, F-91198 Gif-sur-Yvette, France.

b) Laboratoire de Synthèse Organique Associé au CNRS, Ecole Polytechnique, F-91128 Palaiseau, France.

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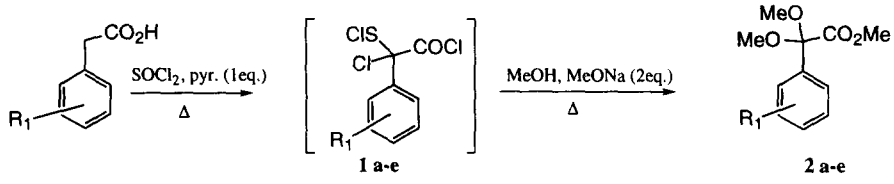
Abstract : *A variety of 3-aryl substituted oxindoles can be rapidly constructed by treatment of a suitable 2,2-dimethoxy arylacetanilide, with titanium tetrachloride or boron trifluoride etherate ; the synthesis of the precursors hinges on a powerful reaction between arylacetic acids and thionyl chloride.* © 1998 Elsevier Science Ltd. All rights reserved.

Of the various existing methods to oxindoles (indolones or indolinones), the most commonly encountered are various Lewis acid-catalysed ($AlCl_3$, $SnCl_4$, TsOH) cyclisations of α-haloacetanilides.[1] Other syntheses were introduced by Frankenfeld,[2] Gassman,[3] and Prabhakar[4] involving a base-catalysed (NaH, LDA) ring closure process starting respectively from α-haloanilides, *N*-acyl-*o*-chloroanilides, and aminobenzoylphenylacetic acid. Other original routes are rhodium(II)-mediated intramolecular aromatic substitution of *N*-aryl diazoamides,[5] and intramolecular Michael addition triggered by lithium-iodine exchange of o-iodoanilide derivatives.[6] As for radical reactions in this area, cyclisations mediated by nickel powder[7a] or zero-valent nickel complexes[7b] as well as the usual methods based on stannane chemistry[8] have been applied to construct the oxindole nucleus; xanthates[9] have also been exploited as an expedient route to oxindoles.

3-Aryl substituted oxindoles constitute an important subclass, some members such as doliracetam[10a] possessing activity on the central nervous system (e. g. cognition enhancing properties, useful in the treatment of Alzheimer's disease and epilepsy), others such as ciclazindol[10b,c] which is an oral hypoglycemic agent are immediate derivatives of oxindoles. One frequently used route to compounds of this family is the addition of an aryl Grignard reagent or an aryllithium to isatin.[11]



1 a-e **2 a-e**

2a : R_1= *p*-F (63%); **2b** : *p*-Br (58%); **2c** : *p*-Ph (61%); **2d** : *m*-OMe (70%); **2e** : *o*-Cl (56%)

Scheme 1

In connection with another project, we have developed a short and flexible route to such oxindoles that complements the existing routes and overcomes some of the drawbacks of the traditional methods (drastic conditions of temperature and limited availability of starting materials). The focal point of our approach is an unusual reaction of phenylacetic acids discovered by Simon and his collaborators[12] in 1967 but which, surprisingly, has almost never been applied in synthesis. It was found that when a phenylacetic acid is exposed to hot

Fax: +33 (0)1 69 07 72 47; E-mail: sam.zard@icsn.cnrs-gif.fr

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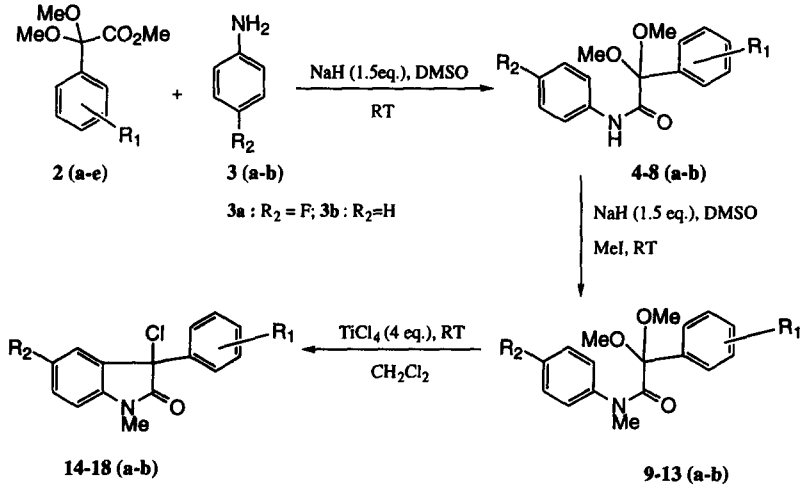
thionyl chloride in the presence of pyridine, a chlorosulfenyl chloride **1** is produced which gives the corresponding methyl α,α–dimethoxyphenylacetate **2** upon heating in refluxing methanol containing two molar equivalents of sodium methoxide (Scheme 1).

If such methyl esters could be converted into anilides, then an intramolecular Friedel-Crafts type reaction would complete the synthesis of the desired oxindoles, as shown in scheme 2. A number of variously substituted α,α-dimethoxyphenylacetates were easily prepared by application of the Simon procedure (Scheme 1) but, not unexpectedly, the sterically hindered ester group could not be easily converted into the desired anilide. After several unsuccessful attempts, we found that the method reported by Singh[13] involving the use of sodium hydride in DMSO allowed the cleavage of the ester group to give the corresponding anilides **4-8 (a-b)** in reasonable yields (Scheme 2, Table 1).



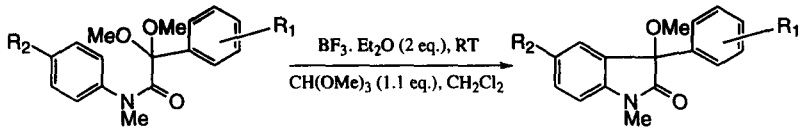
Scheme 2

Table 1 : Reaction of esters **2** with anilines **3** and N-methylation of resulting anilides.

Run	Ester (2) R_1	Aniline (3) R_2	Yields (%) Anilides NH		Yields (%) Anilides N-CH_3	
1	*p*-F	H	**4a**	72	**9a**	72
	p-F	F	**4b**	73	**9b**	73
2	*p*-Br	H	**5a**	54	**10a**	63
	p-Br	F	**5b**	38	**10b**	79
3	*p*-Ph	H	**6a**	70	**11a**	75
	p-Ph	F	**6b**	53	**11b**	84
4	*m*-OMe	H	**7a**	72	**12a**	69
	m-OMe	F	**7b**	55	**12b**	66
5	*o*-Cl	H	**8a**	45	**13a**	71
	o-Cl	F	**8b**	58	**13b**	94

When the cyclisation was conducted in dry dichloromethane using excess titanium tetrachloride, the oxindoles were formed in poor yield. This is not surprising since *N*-unsubstituted anilides exist mostly in an unfavourable conformation[14] for cyclisation. Repeating the reaction with *N*-methylated anilides **9-13 (a-b)** led

to 3-functionalised oxindoles **14-18 (a-b)** much more efficiently: *N*-substitution modifies the rotamer population and improves ring closure (Scheme 2, Table 2). If boron trifluoride etherate is used as the Lewis acid, the cyclisation of the same series of amides **9-13 (a-b)** gives excellent yields of crystalline 3-substituted methoxy-oxindoles **19-23** (Scheme 3, Table 2).



9-13 (a-b) **19-23 (a-b)**

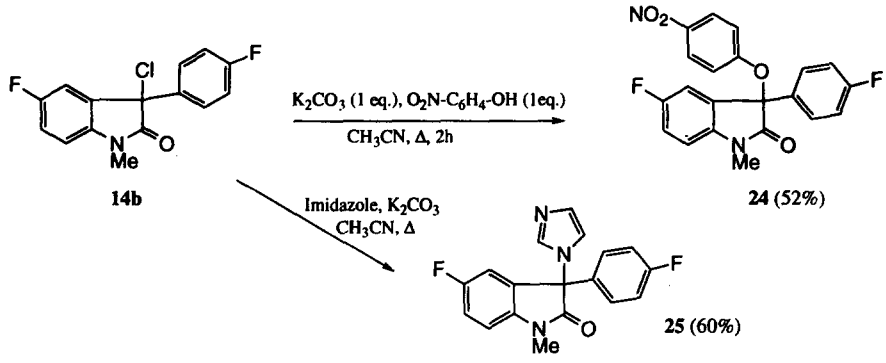
Scheme 3

Table 2 : Chloro- and methoxy- oxindoles formation promoted by $TiCl_4$ and $BF_3.Et_2O$.

Run	R_1	R_2	Chloro oxindoles Yields (%)	Methoxy oxindoles Yields (%)
1	*p*-F	H	**14a** 60	**19a** 81
	p-F	F	**14b** 83	**19b** 91
2	*p*-Br	H	**15a** 60	**20a** 90
	p-Br	F	**15b** 83	**20b** 74
3	*p*-Ph	H	**16a** 62	**21a** 79
	p-Ph	F	**16b** 52	**21b** 69
4	*m*-OMe	H	**17a** 48	**22a** 75
	m-OMe	F	**17b** 53	**22b** 91
5	*o*-Cl	H	**18a** 60	**23a** 80
	o-Cl	F	**18b** 60[a]	**23b** 70[a]

([a] Reaction performed in boiling dichloromethane)

It is thus possible to modify the substitution pattern by modifying the Lewis acid. Moreover, the chlorine atom introduced using titanium tetrachloride can itself be replaced by other nucleophiles.[15] This is illustrated by example **24** pictured in Scheme 4, where a *p*-nitrophenoxy group is incorporated into the system merely by exposure of chloride **14b** to *p*-nitrophenol and potassium carbonate in acetonitrile. Alternatively, the chlorine may be replaced by an imidazole to give for example compound **25** (60%) under similar conditions. Such compounds have been claimed to have antifungal properties.[16]



Scheme 4

In summary, we have described here an efficient, flexible approach to oxindoles which tolerates a large number of desirable functional groups. The extent of literature pertaining to oxindole synthesis demonstrates the interest these compounds generate, not only due to their pharmaceutical properties, but also because of their role as key intermediates in indole synthesis.

Experimental section :

Melting points were determined with a Reichert hot stage apparatus and are uncorrected. IR spectra were recorded as neat films on a Nicolet 205 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were obtained on Brucker AC 200, AC 250 or AM 300 spectrometers as solutions in $CDCl_3$ with tetramethylsilane as internal standard (δ ppm). Mass spectra were recorded on MS 50 (electron impact), MS 9 (chemical ionisation) or MS 80 (high resolution) spectrometers. Matrex 60 (35-70 μm) silica gel was used for column chromatography. Solvents and reagents were purified according to standard laboratory techniques.

General procedure for the preparation of dimethoxyphenylacetic acid methyl ester derivatives.

A solution of phenyl acetic acid derivative (x mmol), pyridine (anhydrous, x mmol) and freshly distilled thionyl chloride (15x mmol) was heated to reflux for 4 hrs under an inert atmosphere. After evaporating to dryness *in vacuo* and after being taken up twice with dry toluene in order to eliminate all traces of thionyl chloride and then concentrated *in vacuo*, the resulting semi-solid product was heated to reflux for 4hrs in dry methanol (1.5x to 2x ml) in the presence of sodium methoxide (2x mmol of a 1N solution). A white precipitate was filtered off and the solvent was removed *in vacuo* . The residual product was passed through a silica gel column, eluting with heptane and ethyl acetate mixtures.

Methyl 4-fluoro-α,α–dimethoxyphenylacetate 2a : Obtained according to the general procedure, column chromatography eluting with heptane/ethyl acetate (8/2) gave rise to a pale yellow oil in 63% yield.
^1H NMR : δ 3.26 (s, 6H, OCH_3); 3.72 (s, 3H, CO_2CH_3); 7.04-7.60 (m, 4H , C_6H_5); ^{13}C NMR : δ 50.2; 52.7; 101.1 ; 115.2 (d, $J_{C\text{-}F}$ = 21.5 Hz, *C*H,Ph-F); 128.7 (d, $J_{C\text{-}F}$ = 8 Hz, *C*H,Ph-F); 132.4; 163.0 (d, $J_{C\text{-}F}$ = 246.0 Hz, C_q-F); 165.5; IR (cm^{-1}) : 2950; 2850 (OMe), 1755 (C=O), 1606 (C=C). Anal. calcd. for $C_{11}H_{13}O_4F$: C : 57.89; H : 5.74. Found : C : 57.55; H : 5.56.

Methyl 4-bromo-α,α–dimethoxyphenylacetate 2b : Obtained as a pale yellow oil in 58% yield. ^1H NMR : δ 3.26 (s, 6H, OCH_3); 3.73 (s, 3H, CO_2CH_3); 7.45-7.60 (m, 4H, C_6H_5). ^{13}C NMR : δ 50.5; 52.9; 101.2; 123.5; 128.6; 131.6; 135.7; 168.9. IR (cm^{-1}) : 2950 (OMe); 1754 (C=O). Anal. calcd. for $C_{11}H_{13}O_4Br$: C : 45.70; H : 4.53. Found : C : 45.51; H : 4.48.

Methyl 4-phenyl-α,α–dimethoxyphenylacetate 2c : Obtained as a white solid in 61% yield; m.p. 93-95°C (from MeOH). ^1H NMR : δ 3.30 (s, 6H, OCH_3); 3.75 (s, 3H, CO_2CH_3); 7.60-7.69 (m, 9H, C_6H_5). ^{13}C NMR : δ 50.6; 53.1; 101.7; 127.3; 127.4; 127.7; 128.9; 135.7; 140.6; 142.1; 169.5. IR (cm^{-1}) : 3050; 2950 (OMe); 1753 (C=O); 1261; 1107; 1076. Anal. calcd. for $C_{17}H_{18}O_4$: C : 71.31; H : 6.34. Found : C :71.32; H : 6.19.

Methyl 3-α,α–trimethoxyphenylacetate 2d : Obtained as a pale yellow oil in 70% yield. ^1H NMR : δ 3.27 (s, 6H, OCH_3); 3.73 (s, 3H, Ar-CH_3); 3.82 (s, 3H, CO_2CH_3); 6.87-7.29 (m, 4H, C_6H_5). ^{13}C NMR : δ 49.7; 52.1; 54.6; 100.9; 111.6; 114.3; 118.4; 128.9;

137.8; 159.3; 168.6. IR (cm^{-1}) : 2950 (OMe); 1754 (C=O). Anal. calcd. for $C_{12}H_{16}O_5$: C : 59.99; H : 6.71. Found : C : 59.44; H : 6.48.

Methyl 2-chloro-α,α–dimethoxyphenylacetate 2e : Obtained as a white solid in 56% yield; m.p. 134-136°C (from MeOH). ^1H NMR : δ 3.58 (s, 6H, OCH_3); 3.77 (s, 3H, CO_2CH_3); 7.29-8.11 (m, 4H, C_6H_5). ^{13}C NMR : δ 50.3; 52.9; 99.3; 126.5 126.7; 130.2 130.5; 132.3; 134.7; 168.1. IR (cm^{-1}) : 1755 (C=O); 1600 (C=C); 1574. m.s. : m/z (CI) : 216 ($M+NH_4^+$).

General procedure for the preparation of N-methyl-N-phenylacetamides

1/ Amidation :

Substituted α,α-dimethoxy-phenylacetic acid methyl ester (x mmol) and sodium hydride (1.5x mmol, oil dispersion) were suspended in a minimum of anhydrous dimethylsulfoxide. Freshly distilled aniline (or *p*-fluoroaniline, x mmol) was added. After stirring at room temperature for 5 hrs, the suspension changed from green to deep red. The reaction was then quenched with iced water and the resulting precipitate was then left for 1 h before being filtered, water-washed and air-dried. The crude product was recrystallised from methanol or diisopropylether to yield a white powder.

N-Phenyl acetamide compounds from aniline and 4-fluoroaniline :

2-(4-Fluorophenyl)-2,2-dimethoxy-N-phenylacetamide (4a) and 2,N-bis-(4-fluorophenyl)-2,2-dimethoxyacetamide (4b) : White solids obtained respectively in 72% and 73% yields after recrystallising from diisopropylether.

4a : m.p. 134-136°C (from iPr_2O). ^1H NMR : δ 3.31 (s, 6H, OCH_3); 7.02-7.11 (m, 3H, C_6H_5); 7.28-7.34 (m, 2H, C_6H_5); 7.55-7.61 (m, 4H, C_6H_5); 8.77 (s, 1H, N*H*). ^{13}C NMR : δ 50.5; 101.7; 116.2 (d, $J_{C\text{-}F}$ = 21.5 Hz, *C*H,Ph-F); 120.5; 125.6; 129.6 (d, $J_{C\text{-}F}$ = 8.2 Hz, *C*H,Ph-F); 130.0; 133.1; 137.1; 163.2 (d, $J_{C\text{-}F}$ = 247.0 Hz, C_q-F); 166.5. IR (cm^{-1}) : 3312 (NH); 1674 (C=O); 1606; 1536.

4b : m.p. 158°C (from iPr_2O). ^1H NMR : δ 3.32 (s, 6H, OCH_3); 7.98-7.09 (m, 4H, C_6H_5); 7.54-7.60 (m, 4H, C_6H_5); 8.74 (s, 1H, N*H*). ^{13}C NMR : δ 50.6; 102.7; 115.5 (d, $J_{C\text{-}F}$ = 20.6 Hz, *C*H,Ph-F); 115.9 (d, $J_{C\text{-}F}$ = 20.2 Hz, *C*H,Ph-F); 121.5 (d, $J_{C\text{-}F}$ = 7.7 Hz, *C*H,Ph-F); 128.8 (d, $J_{C\text{-}F}$ = 8.1 Hz, *C*H,Ph-F); 159.7 (d, $J_{C\text{-}F}$ = 242.3 Hz, C_q-F); 161.0 (d, $J_{C\text{-}F}$ = 250.0 Hz, C_q-F); 166.6. IR (cm^{-1}) : 3302 (NH); 2931, 2831 (OMe); 1678 (C=O).

2-(4-Bromophenyl)-2,2-dimethoxy-N-phenylacetamide (5a) and 2-(4-Bromophenyl)-N-(4-fluorophenyl)-2,2-dimethoxy-acetamide (5b) : White solids obtained respectively in 54% and 50% yields after recrystallising from diisopropylether.

5a : m.p. 151-153°C. ^1H NMR : δ 3.32 (s, 6H, OCH_3); 7.10-7.68 (m, 9H, C_6H_5); 8.75 (s, 1H, N*H*). ^{13}C NMR :δ 50.6; 101.6; 119.7; 123.3; 124.8; 128.6; 129.1; 131.6; 136.3; 137.0; 166.2. IR (cm^{-1}) : 3250 (NH); 2953, 2854 (OMe); 1670 (C=O); 1600 (C=C); 1110; 1067.

5b : m.p. 176°C. ^1H NMR : δ 3.32 (s, 6H, OCH_3); 6.97-7.65 (m, 8H, C_6H_5); 8.73 (s, 1H, N*H*). ^{13}C NMR : δ 50.6; 111.6; 115.8 (d, $J_{C\text{-}F}$ = 22.8, *C*H,Ph-F); 121.4 (d, $J_{C\text{-}F}$ = 7.9 Hz, *C*H,Ph-F); 123.5; 128.6; 131.8; 133.1; 136.2; 159.7 (d, $J_{C\text{-}F}$ = 240.6 Hz, C_q-F); 166.3. IR (cm^{-1}) : 3250 (NH); 3012; 2981, 2943, 2837 (OMe); 1672 (C=O).

2-(*p*-Biphenyl)-2,2-dimethoxy-N-phenylacetamide (6a) and 2-(*p*-biphenyl)-N-(4-fluorophenyl)-2,2-dimethoxy-acetamide (6b): Yellow solids obtained respectively in 70% and 53% yield after recrystallisation from methanol (**6a**) and purification by column chromatography (eluent : dichloromethane/heptane 9/1) (**6b**).

6a : m.p. 178-180°C. ^1H NMR : δ 3.37 (s, 6H, OCH_3); 7.05-7.69 (m, 9H, C_6H_5); 8.80 (s, 1H, N*H*). ^{13}C NMR : δ 50.6; 102.1 119.7; 124.7; 127.2; 127.3; 127.6; 128.9; 129.1; 136.1; 137.3; 140.8; 142.1; 166.8. IR (cm^{-1}) : 3320 (NH); 3056; 2936 (OMe); 1679; 1600 (C=C); 1527.

6b : m.p. 203-204°C. ^1H NMR : δ 3.36 (s, 6H, OCH_3); 7.01 (t, 2H, J = 10.8 Hz, C_6H_5), 7.30-7.50 (m, 3H, C_6H_5); 7.51-7.60 (m, 8H, C_6H_5); 8.78 (s, 1H, N*H*). ^{13}C NMR : δ 50.6; 102.1; 115.8 (d, $J_{C\text{-}F}$ = 22 Hz, *C*H,Ph-F); 121.42 (d, $J_{C\text{-}F}$ = 7.9 Hz, *C*H,Ph-F); 127.2; 127.3; 127.4; 127.6; 128.9; 129.5; 133.3; 140.7; 142.0; 159.6 (d, $J_{C\text{-}F}$ = 241.9 Hz, C_q-F); 167.1. IR (cm^{-1}) : 3303 (NH); 2950; 2850 (OMe); 1677 (C=O); 1530; 1509.

2,2-Dimethoxy-2-(3-methoxyphenyl)-N-phenylacetamide (7a) and N-(4-fluorophenyl)-2,2-Dimethoxy-2-(3-methoxyphenyl)-acetamide (7b) : White solids obtained after purification by column chromatography (eluent : heptane/ethyl acetate 9/1) then recrystallisation respectively from diisopropylether (**7a**, 72%) and from methanol (**7b** , 55%).

7a : m.p.111-112°C. ^1H NMR : δ 3.33 (s, 6H, OCH_3); 3.81 (s, 3H, Ar-OCH_3); 6.82-7.65 (m, 9H, C_6H_5); 8.72 (s, 1H, N*H*). ^{13}C NMR δ 50.6; 55.4; 101.9; 109.9; 112.4; 114.8; 118.9; 119.7; 124.6; 129.1; 129.5; 137.3; 138.7; 159.8. IR (cm^{-1}) : 3300 (NH); 2943 (OMe); 1694 (C=O).

7b : m.p. 110°C. ^1H NMR : δ 3.32 (s, 6H, OCH_3); 3.81 (s, 3H, Ar-OCH_3); 6.82-7.50 (m, 6H, C_6H_5); 7.52-7.60 (m, 2H, C_6H_5); 8.74 (s, 1H, N*H*). ^{13}C NMR : δ 50.5; 50.4; 101.9; 112.5; 114.8; 115.7 (d, $J_{C\text{-}F}$ = 7.6 Hz, *C*H,Ph-F); 118.9; 121.4 (d, $J_{C\text{-}F}$ = 22.4 Hz,

*C*H,Ph-F); 129.5; 133.4; 138.7; 159.9 (d, $J_{C\text{-}F}$ = 268.8 Hz, C_q-F); 159.9; 166.7. IR (cm^{-1}) : 3293 (NH); 2941; 3006; 2837 (OMe); 1683 (C=O); 1600 (C=C).

2-(2-Chlorophenyl)-2,2-dimethoxy-N-phenylacetamide (8a) and 2-(2-chlorophenyl)-N-(4-fluorophenyl)-2,2-dimethoxyacetamide (8b) : White solids obtained respectively in 45% yield (**8a**) after recrystallising from diisopropylether and 58% yield (**8b**) after purification by column chromatography (eluent : dichloromethane/heptane 9/1).

8a : m.p. 79°C. ^{1}H NMR : δ 3.58 (s, 6H, OCH_3); 6.65-8.02 (m, 9H, C_6H_5); 8.89 (s, 1H, N*H*). ^{13}C NMR : δ 50.3; 100.4; 119.8; 123.7; 126.8; 129.2; 130.3; 130.8; 131.1; 134.9; 137.1; 165.9. IR (cm^{-1}) : 3400 (NH); 1700 (C=O); 1600 (C=C); 1400. m/z (CI) : 323 ($M+NH_4^+$).

8b : m.p. 104-105°C. ^{1}H NMR : δ 3.30 (s, 6H, OCH_3); 6.70-8.04 (m, 8H, C_6H_5); 8.85 (s, 1H, N*H*). ^{13}C NMR : δ 50.2; 100.3; 115.7 (d, $J_{C\text{-}F}$ = 22.6 Hz, *C*H,Ph-F); 121.5 (d, $J_{C\text{-}F}$ = 7.7 Hz, *C*H,Ph-F); 126.7; 130.3; 130.7 ; 131.1; 131.6; 133.1; 134.2; 159.8 (d, $J_{C\text{-}F}$ = 225.4, C_q-F); 165.8 . IR (cm^{-1}) : 3325 (NH); 2943; 2837 (OMe); 1692 (C=O).

2/ N- Methylation :

To the pentane-washed sodium hydride (1.3x mmol) were added a solution of amide (x mmol) in dry DMSO (2x ml) and methyl iodide (10x mmol). After stirring for 7 hrs at room temperature, the mixture was poured into saturated ammonium chloride solution, extracted with ethyl acetate, dried over $MgSO_4$ and concentrated *in vacuo* to yield a pale yellow oil which crystallised when treated with diisopropylether.

N-methyl-N-phenylacetamide derivatives:

2-(4-Fluorophenyl)-2,2-dimethoxy-N-methyl-N-phenylacetamide (9a) and 2,N-Bis-(4-fluorophenyl)-2,2-dimethoxy-N-methylacetamide (9b) : White solids obtained respectively in 72% and 73% yields after column chromatography (eluent : dichloromethane/ethyl acetate 7/3).

9a : m.p. 78-79°C. ^{1}H NMR : δ 3.13 (s, 6H, OCH_3); 3.21 (s, 3H, NCH_3); 6.50-6.70 (m, 2H, C_6H_5); 6.74-6.90 (m, 2H, C_6H_5); 6.90-7.16 (m, 5H, C_6H_5). ^{13}C NMR : δ 40.4; 49.7; 100.7; 114.7 (d, $J_{C\text{-}F}$ = 20.8 Hz, *C*H,Ph-F); 127.1; 127.8; 128.3; 128.4; 133.7; 162.6 (d, $J_{C\text{-}F}$ = 245.6 Hz, C_q-F); 167.8. IR (cm^{-1}) : 2950; 2850 (OMe); 1666 (C=O); 1593 (C=C). Anal. calcd. for $C_{17}H_{18}NO_3F$: C : 67.31; H : 5.98. Found : C : 67.06; H : 6.04.

9b : m.p. 76-78°C. ^{1}H NMR : δ 3.12 (s, 6H, OCH_3); 3.20 (s, 3H, NCH_3); 6.58-7.02 (m, 8H, C_6H_5). ^{13}C NMR : δ 40.4; 49.6; 101.0; 114.7 (d, $J_{C\text{-}F}$ = 20.7 Hz, *C*H,Ph-F); 115.1 (d, $J_{C\text{-}F}$ = 18.7 Hz, *C*H,Ph-F); 129.0 (d, $J_{C\text{-}F}$ = 7.3 Hz, *C*H,Ph-F); 130.4 (d, $J_{C\text{-}F}$ = 6.9 Hz, *C*H,Ph-F); 133.6; 139.0; 161.3 (d, $J_{C\text{-}F}$ = 250.3 Hz, C_q-F); 162.6 (d, $J_{C\text{-}F}$ = 246.7 Hz, C_q-F); 167.9. IR (cm^{-1}) : 3068; 2941; 2831 (OMe; NMe); 1660 (C=O); 1604 (C=C); 1509. Anal. calcd. for $C_{17}H_{17}NO_3F_2$: C : 67.55; H : 5.33. Found : C : 67.42; H : 5.44.

2-(4-Bromophenyl)-2,2-dimethoxy-N-methyl-N-phenylacetamide (10a) and 2-(4-bromophenyl)-N-(4-fluorophenyl)-2,2-dimethoxy-N-methylacetamide (10b) : White crystals obtained respectively in 63% and 79% yields after silica gel column chromatography eluting with heptane/ethyl acetate (7/3) then recrystallisation from diisopropylether.

10a : m.p. 72-73°C. ^{1}H NMR : δ 3.13 (s, 6H, OCH_3); 3.21 (s, 3H, NCH_3); 6.50-7.40 (m, 9H, C_6H_5). ^{13}C NMR : δ 40.5; 49.8; 101.3; 122.8; 127.3; 127.9; 128.4; 131.0; 137.0; 167.7. IR (cm^{-1}) : 2943; 2837 (OMe); 1665 (C=O); 1594 (C=C); 1495. Anal. calcd. for $C_{17}H_{18}NO_3Br$: C : 56.06; H : 4.48. Found : C : 55.76; H : 4.94.

10b : m.p. 93-95°C. ^{1}H NMR : δ 3.12 (s, 6H, OCH_3); 3.20 (s, 3H, NCH_3); 6.50-7.31 (m, 8H, C_6H_5). ^{13}C NMR : δ 40.4; 49.7; 100.6; 115.1 (d, $J_{C\text{-}F}$ = 22.1 Hz, *C*H,Ph-F); 122.5; 128.1; 129.6 (d, $J_{C\text{-}F}$ = 5.8 Hz, *C*H,Ph-F) ; 130.9; 136.8; 138.9; 161.3 (d, $J_{C\text{-}F}$ = 260.9 Hz, C_q-F); 167.6. IR (cm-1) : 2950; 2850 (OMe, NMe); 1679 (C=O); 1509. Anal. calcd. for $C_{17}H_{17}NO_3FBr$: C : 53.42; H : 4.48. Found : C : 53.62; H : 4.49.

2-(*p*-Biphenyl)-2,2-dimethoxy-N-methyl-N-phenylacetamide (11a) and 2-(*p*-biphenyl)-N-(4-fluorophenyl)-2,2-dimethoxy-N-methylacetamide (11b) : Colourless oils obtained respectively in 75% and 84% yields.

11a : ^{1}H NMR : δ 3.18 (s, 6H, OCH_3); 3.21 (s, 3H, NCH_3); 6.63-7.60 (m, 14H, C_6H_5).^{13}C NMR : δ 40.3; 49.7; 101.1; 126.5; 127.0; 127.4; 127.8; 128.3; 128.8; 136.6; 140.6; 140.9; 143.0; 167.7. IR (cm^{-1}) : 3063, 3037, 2950, 2831 (OMe, NMe); 1667 (C=O); 1596 (C=C).

11b : ^{1}H NMR : δ 3.17 (s, 6H, OCH_3); 3.20 (s, 3H, NCH_3); 6.50-6.80 (m, 4H, C_6H_5); 7.10 (d, J = 7.5 Hz, C_6H_5); 7.34-7.48 (m, 5H, C_6H_5); 7.57 (d, J = 7.5 Hz, C_6H_5). ^{13}C NMR : δ 40.4; 49.7; 101.0; 114.0 (d, $J_{C\text{-}F}$ = 22.2 Hz, *C*H,Ph-F); 126.5; 127.5; 128.0 (d, $J_{C\text{-}F}$ = 48.7 Hz, *C*H,Ph-F); 128.8; 129.6; 136.7; 139.0; 140.4; 141.0; 161.3 (d, $J_{C\text{-}F}$ = 244.8 Hz, C_q-F); 168.2. IR (cm^{-1}) : 3068; 2950, 2831 (OMe, NMe); 1659 (C=O); 1509.

2,2-Dimethoxy-2-(3-methoxyphenyl)-N-methyl-N-phenylacetamide (12a) and N-(4-fluorophenyl)-2,2-dimethoxy-2-(3-methoxyphenyl)-N-methylacetamide (12b) : Colourless oil (**12a**) obtained in 69 % yield after column chromatography (eluent : heptane/ethyl acetate 7/3) and white solid (**12b**) was isolated in 66 % yield after recrystallisation from diisopropylether.

12a : ^{1}H NMR : δ 3.14 (s, 6H, OC*H*$_3$); 3.20 (s, 3H, NC*H*$_3$); 3.64 (s, 3H, Ar-OC*H*$_3$); 6.40-7.50 (m, 9H, C$_6$*H*$_5$). ^{13}C NMR : δ 40.1; 49.5; 54.9; 100.7; 111.1; 114.4; 118.7; 126.8; 127.8; 128.0; 128.6; 139.1; 142.9; 159.1; 167.7. IR (cm^{-1}) : 3058; 2950, 2837 (OMe, NMe); 1669 (C=O); 1596; 1494. Anal. calcd. for $C_{18}H_{21}NO_4$: C : 68.55; H : 6.71. Found : C : 68.81; H : 6.77.

12b : m.p. 77-79°C. ^{1}H NMR : δ 3.12 (s, 6H, OC*H*$_3$); 3.20 (s, 3H, NC*H*$_3$); 3.70 (s, 3H, Ar-OC*H*$_3$); 6.50-6.56 (m, 3H, C$_6$*H*$_5$); 6.60-6.80 (m, 4H, C$_6$*H*$_5$); 7.00-7.15 (m, 1H, C$_6$*H*$_5$). ^{13}C NMR : δ 40.3; 49.6; 55.0; 100.8; 111.3; 114.6; 114.9 (d, $J_{C\text{-}F}$ = 23.3 Hz, *C*H,Ph-F); 118.7; 129.3 (d, $J_{C\text{-}F}$ = 48.8 Hz, *C*H,Ph-F); 138.9; 139.2; 161.3 (d, $J_{C\text{-}F}$ = 242.5 Hz, C_q-F); 168.1. IR (cm^{-1}) : 2937, 2837 (OMe, NMe); 1668 (C=O); 1596 (C=C); 1506. Anal. calcd. for $C_{18}H_{20}NO_4F$: C : 64.85; H : 6.05. Found : C : 64.89; H : 6.28.

2-(2-Chlorophenyl)-2,2-dimethoxy-N-methyl-N-phenylacetamide (13a) and **2-(2-chlorophenyl)-N-(4-fluorophenyl)-2,2-dimethoxy-N-methylacetamide (13b)** : White solids isolated respectively by column chromatography (**13a**, eluent : heptane/ethyl acetate 5/5, 71%) and by recrystallisation from diisopropylether (**13b**, 94%).

13a : m.p. 76°C. ^{1}H NMR : δ 3.13 (s, 6H, OC*H*$_3$); 3.28 (s, 3H, NC*H*$_3$); 6.62-7.15 (m, 9H, C$_6$*H*$_5$). ^{13}C NMR : δ 40.2; 49.6; 98.5; 125.9; 127.2; 127.8; 128.2; 129.0; 129.7; 129.9; 131.8; 135.4; 142.7; 166.2. IR (cm^{-1}) : 1675 (C=O); 1600 (C=C); 1470. Anal. calcd. for $C_{17}H_{18}NO_3Cl$: C : 63.85; H : 5.67. Found : C : 63.91; H : 5.73.

13b : m.p. 124-126°C. ^{1}H NMR : δ 3.16 (s, 6H, OC*H*$_3$); 3.27 (s, 3H, NC*H*$_3$); 6.50-7.23 (m, 8H, C$_6$*H*$_5$). ^{13}C NMR : δ 40.1; 49.6; 98.4; 114.9 (d, $J_{C\text{-}F}$ = 22.8 Hz, *C*H,Ph-F); 125.8; 129.1; 129.5 (d, $J_{C\text{-}F}$ = 9.0 Hz, *C*H,Ph-F); 129.9; 131.7; 135.3; 138.4; 161.4 (d, $J_{C\text{-}F}$ = 245.7 Hz, C_q-F); 166.1. IR (cm^{-1}) : 2943; 2837 (OMe, NMe); 1673 (C=O); 1510. Anal. calcd. for $C_{17}H_{18}NO_3FCl$: C : 60.45; H : 5.07. Found : C : 60.39; H : 5.12.

Preparation of 3-chloro-3-aryl-oxindole derivatives.

The N-methyl-N-phenylacetamide (x mmol) was dissolved in freshly distilled dichloromethane (10x ml) and titanium tetrachloride (4x mmol) was injected via a syringe. After stirring for 3 hrs at room temperature, the reaction was quenched with iced water, and the mixture was extracted with dichloromethane, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was recrystallised from diisopropylether.

3-Chloro-3-(4-fluorophenyl)-1-methyl-1,3-dihydroindol-2-one (14a) and 3-chloro-3-(4-fluorophenyl)-5-fluoro-1-methyl-1,3-dihydroindol-2-one (14b) : White solids isolated by recrystallisation from diisopropylether with respective yields of 60% and 83%.

14a : m.p. 115-117°C. ^{1}H NMR : δ 3.25 (s, 3H, NC*H*$_3$); 6.85-7.10 (m, 3H, C$_6$*H*$_5$); 7.14-7.25 (m, 1H, C$_6$*H*$_5$); 7.40-7.50 (m, 2H, C$_6$*H*$_5$); 7.50-7.68 (m, 2H, C$_6$*H*$_5$). ^{13}C NMR : δ 27.0; 109.1; 115.5 (d, $J_{C\text{-}F}$ = 21.2 Hz, *C*H,Ph-F); 123.8; 126.1; 127.8 (d, $J_{C\text{-}F}$ = 21.2 Hz, *C*H,Ph-F) 130.7; 132.6; 142.9; 147.0; 163.1 (d, $J_{C\text{-}F}$ = 247.6 Hz, C_q-F); 173.5. IR (cm^{-1}) : 1716 (C=O); 1613 (C=C). Anal. calcd. for $C_{15}H_{11}NOFCl$: C : 65.35; H : 4.02. Found : C : 64.94; H : 4.05.

14b : m.p. 115-116°C. ^{1}H NMR : δ 3.24 (s, 3H, NC*H*$_3$); 6.80-6.90 (dd, 1H, *J* = 8.4, 4.1 Hz, C$_6$*H*$_5$); 7.0-7.22 (m, 4H, C$_6$*H*$_5$); 7.45-7.60 (m, 2H, C$_6$*H*$_5$). ^{13}C NMR : δ 27.1; 65.0; 109.9 (d, $J_{C\text{-}F}$ = 9.8 Hz, *C*H,Ph-F); 114.0 (d, $J_{C\text{-}F}$ = 31.8 Hz, *C*H,Ph-F); 115.7 (d, $J_{C\text{-}F}$ = 28.1 Hz, *C*H,Ph-F); 117.2 (d, $J_{C\text{-}F}$ = 29.1 Hz, *C*H,Ph-F); 129.6 (d, $J_{C\text{-}F}$= 10.2 Hz, *C*H,Ph-F); 132.0 ; 135.0 ; 138.8 ; 158.9 (d, $J_{C\text{-}F}$ = 216.8 Hz, C_q-F); 163.8 (d, $J_{C\text{-}F}$ = 224.4 Hz, C_q-F); 173.0. IR (cm^{-1}) : 1733 (C=O); 1616; 1602 (C=C). Anal. calcd. for $C_{15}H_{11}NOF_2Cl$: C : 61.34; H : 3.43. Found : C : 61.43; H : 3.66.

3-(4-Bromo-phenyl)-3-chloro-1-methyl-1,3-dihydroindol-2-one (15a) and 3-(4-bromophenyl)-3-chloro-5-fluoro-1-methyl-1,3-dihydroindol-2-one (15b) : White solids obtained respectively in 72% and 78% yields after recrystallising from diisopropylether.

15a : m.p. 129-130°C. ^{1}H NMR : δ 3.25 (s, 3H, NC*H*$_3$); 6.95 (d, 1H, *J* = 9.0 Hz, C$_6$*H*$_5$) ; 7.20-7.30 (m, 1H, C$_6$*H*$_5$) ; 7.39-7.50 (m, 6H, C$_6$*H*$_5$). ^{13}C NMR : δ 27.0; 65.9; 109.2; 123.1; 123.5; 123.8; 129.8; 130.8; 131.7; 135.8; 142.9. IR (cm^{-1}) : 1726 (C=O); 1611 (C=C). Anal. calcd. for $C_{15}H_{11}NOBrCl$: C : 53.52; H : 2.84. Found : C : 53.14; H : 3.29.

15b : m.p. 109-110°C. ^{1}H NMR : δ 3.24 (s, 3H, NC*H*$_3$); 6.80-6.92 (m, 1H, C$_6$*H*$_5$); 7.05-7.20 (m, 2H, C$_6$*H*$_5$); 7.40 (d, 2H, *J* = 8.7 Hz); 7.50 (d, 2H, *J* = 8.7 Hz, C$_6$*H*$_5$). ^{13}C NMR : δ 27.2; 65.4; 110.0 (d, $J_{C\text{-}F}$ = 7.5 Hz, *C*H,Ph-F); 114.0 (d, $J_{C\text{-}F}$ = 25.0 Hz, *C*H,Ph-F); 117.4 (d, $J_{C\text{-}F}$ = 23.3 Hz, *C*H,Ph-F); 123.8; 129.3; 131.1; 131.9 ; 135.3; 138.9; 159.7 (d, $J_{C\text{-}F}$ = 241.8 Hz, C_q-F); 172.8. IR (cm^{-1}) : 1732 (C=O); 1618; 1587 (C=C). Anal. calcd. for $C_{15}H_{11}NOFBrCl$: C : 50.81; H : 2.84. Found : C : 50.75; H : 2.81.

3-(*p*-Biphenyl)-3-chloro-1-methyl-1,3-dihydro-indol-2-one (16a) and 3-(*p*-biphenyl)-3-chloro-5-fluoro-1-methyl-1,3-dihydroindol-2-one (16b) : Compound **16a** was obtained as a yellowish oil (60%) and **16b** as a white solid also in 60% yield after recrystallising from diisopropylether.

16a : m.p. 100°C. ^{1}H NMR : δ 3.30 (s, 3H, NC*H*$_3$); 6.91 (d, 1H, *J* = 7.5 Hz, C$_6$*H*$_5$); 7.0-7.20 (m, 1H; C$_6$*H*$_5$); 7.20-7.60 (m, 11H, C$_6$*H*$_5$). ^{13}C NMR : δ 26.9; 62.2; 108.7; 123.0; 126.2; 127.2; 128.5; 128.9; 132.9; 139.8; 140.9; 143.2; 160.0; 173.0. IR (cm^{-1}) : 1733 (C=O); 1615 (C=C). Anal. calcd. for $C_{21}H_{16}NOCl$: C : 75.56; H : 4.83. Found : C : 75.05; H : 4.88.

16b : m.p. 112°C. ^{1}H NMR : δ 3.25 (s, 3H, NCH_3); 6.80-6.90 (dd, 1H, J = 8.5 , 4.0 Hz, C$_6H_5$) ; 7.08-7.25 (m, 2H; C$_6H_5$); 7.30-7.50 (m, 3H, C$_6H_5$); 7.50-7.65 (m, 6H, C$_6H_5$). ^{13}C NMR : δ 27.2; 109.0 (d, $J_{C\text{-}F}$ = 7.7 Hz, *C*H,Ph-F); 114.1 (d, $J_{C\text{-}F}$ = 24.9 Hz, *C*H,Ph-F); 117.1 (d, $J_{C\text{-}F}$ = 23.8 Hz, *C*H,Ph-F); 127.3; 127.5; 127.9; 128.0; 129.0; 135.1; 139.0; 140.3; 142.3; 159.7 (d, $J_{C\text{-}F}$ = 241.0 Hz, C_q-F); 173.5. IR (cm^{-1}) : 1733 (C=O); 1615 (C=C). Anal. calcd. for $C_{21}H_{15}NOFCl$: C : 71.70; H : 4.30. Found : C : 71.42; H : 4.28.

3-Chloro-(3-methoxyphenyl)-1-methyl-1,3-dihydroindol-2-one (17a) and 3-chloro-5-fluoro-3-(3-methoxyphenyl)-1-methyl-1,3-dihydroindol-2-one (17b) : White solids isolated by recrystallisation from diisopropylether respectively in 48% and 53% yields.
17a : m.p. 102-104°C. ^{1}H NMR : δ 3.24 (s, 3H, NCH_3); 3.80 (s, 3H, OCH_3); 6.70-7.50 (m, 8H, C$_6H_5$). ^{13}C NMR : δ 27.0; 55.5 ; 66.0; 109.0; 113.8; 114.4; 119.8; 123.7; 126.0; 129.6; 130.3; 130.5; 138.2; 142.9; 159.7; 173.3. IR (cm^{-1}) : 1731 (C=O); 1511. Anal. calcd. for $C_{16}H_{14}NO_2Cl$: C : 66.79; H : 4.90. Found : C : 66.59; H : 4.92.
17b : m.p. 90-91°C. ^{1}H NMR : δ 3.24 (s, 3H, NCH_3); 3.82 (s, 3H, OCH_3); 6.80-6.92 (m, 2H, C$_6H_5$); 6.98-7.05 (m, 1H, C$_6H_5$); 7.06-7.20 (m, 3H; C$_6H_5$); 7.21-7.31 (m, 1H, C$_6H_5$). ^{13}C NMR : δ 27.1; 55.5; 62.5; 109.7 (d, $J_{C\text{-}F}$ = 7.7 Hz, *C*H,Ph-F); 113.2; 114.0 (d, $J_{C\text{-}F}$ = 25.4 Hz, *C*H,Ph-F); 114.5; 117.0 (d, $J_{C\text{-}F}$ = 23.1 Hz, *C*H,Ph-F); 119.5; 129.7; 137.6; 138.8; 159.7 (d, $J_{C\text{-}F}$ = 270.8 Hz, C_q-F); 159.8 ; 167.0. IR (cm^{-1}) : 1733 (C=O); 1602; 1583 (C=C). Anal. calcd. for $C_{16}H_{13}NO_2FCl$: C : 62.86; H : 4.29. Found : C : 62.46; H : 4.35.

3-Chloro-3-(2-chlorophenyl)-1-methyl-1,3-dihydroindol-2-one (18a) and 3-chloro-3-(2-chlorophenyl)-5-fluoro-1-methyl-1,3-dihydroindol-2-one (18b) : White solids both obtained in 60% yield after recrystallisation from diisopropylether.
18a : m.p. 94°C. ^{1}H NMR : δ 3.32 (s, 3H, NCH_3); 6.81-8.26 (m, 8H, C$_6H_5$). ^{13}C NMR : δ 27.1; 108.9; 123.5; 124.1; 127.1; 130.4; 130.5; 130.6; 131.1; 131.6; 143.5; 173.0. IR (cm^{-1}) : 1735 (C=O); 1615 (C=C); 1492. Anal. calcd. for $C_{15}H_{11}NOCl_2$: C : 61.67; H : 3.79. Found : C : 61.43; H : 4.09.
18b : m.p. 140-142°C. ^{1}H NMR : δ 3.35 (s, 3H, NCH_3); 6.75 (dd, 1H, J = 6.4, 2.5 Hz, C$_6H_5$); 6.86 (dd, 1H, J = 7.0 , 3.3 Hz, C$_6H_5$); 7.06 (td, 1H, J = 8.8, 2.5 Hz, C$_6H_5$); 7.33 (ddd, 2H, J = 15.1, 12.4, 1.6 Hz, C$_6H_5$); 7.34 (dd, 1H, J = 12.4, 1.6 Hz, C$_6H_5$); 7.45 (ddd, 1H, J = 7.8, 7.4, 1.6 Hz, C$_6H_5$); 8.29 (dd, 1H, J = 6.4, 1.6 Hz, C$_6H_5$). ^{13}C NMR : δ 27.3; 109.5 (d, $J_{C\text{-}F}$ = 7.8 Hz, *C*H,Ph-F); 112.2 (d, $J_{C\text{-}F}$ = 25.5 Hz, *C*H,Ph-F); 116.8 (d, $J_{C\text{-}F}$ = 23.7 Hz, *C*H,Ph-F); 127.3; 116.6; 117.0; 125.0; 127.3; 130.7; 131.0; 133.0; 139.0; 159.5 (d, $J_{C\text{-}F}$ = 240.6 Hz, C_q-F); 173. IR (cm^{-1}) : 1735 (C=O); 1615 (C=C); 1492. Anal. calcd. for $C_{15}H_{10}NOFBCl_2$: C : 58.09; H : 3.25. Found : C : 57.71; H : 3.17.

General procedure for the preparation of 3-methoxy-oxindole derivatives

The N-methyl-N-phenylacetamide (x mmol) and trimethyl orthoformate (x mmol) were dissolved in freshly distilled dichloromethane. Freshly distilled boron trifluoride etherate (2x mmol) was injected via a syringe. After stirring for 3 hrs at room temperature, the reaction was quenched with a 5% solution of sodium bicarbonate, and the mixture was extracted with dichloromethane, dried over $MgSO_4$ and concentrated *in vacuo* . The crude product was recrystallised from diisopropylether.

3-(4-Fluorophenyl)-3-methoxy-1-methyl-1,3-dihydroindol-2-one (19a) and 5-fluoro-3-(4-fluorophenyl)-3-methoxy-1-methyl-1,3-dihydroindol-2-one (19b) : White crystals obtained respectively in 81% and 91% yields after column chromatography (eluent : dichloromethane) followed by recrystallisation from diisopropylether.
19a : m.p. 81-82°C. ^{1}H NMR : δ 3.21 (s, 3H, OCH_3); 3.23 (s, 3H, NCH_3); 6.94 (d, 1H, J = 7.8 Hz, C$_6H_5$); 6.99 (t, 2H, J = 8.8 Hz, C$_6H_5$); 7.16 (td, 1H, J = 7.8, 0.8 Hz, C$_6H_5$); 7.36 (dd, 2H, J = 8.8, 5.4 Hz, C$_6H_5$); 7.42 (td, 1H, J = 7.6, 1.3 Hz, C$_6H_5$). ^{13}C NMR : δ 26.6; 53.2; 83.6; 108.7; 115.3 (d, $J_{C\text{-}F}$ = 21.5 Hz; *C*H,Ph-F); 123.5; 125.7; 127.6; 128.4 (d, $J_{C\text{-}F}$ = 8.0 Hz; *C*H,Ph-F); 130.4; 134.5; 144.6; 162.8 (d, $J_{C\text{-}F}$ = 247.5 Hz, C_q-F); 175.1. IR (cm^{-1}) : 3063, 2937, 2831 (NMe, OMe); 1727 (C=O); 1612 (C=C). Anal. calcd. for $C_{16}H_{14}NO_2F$: C : 70.84 ; H : 5.20. Found : C : 70.97; H : 5.25.
19b : m.p. 81-82°C. ^{1}H NMR : δ 3.22 (s, 3H, OCH_3); 3.23 (s, 3H, NCH_3); 6.87 (dd, 1H, J = 8.6, 4.0 Hz, C$_6H_5$); 6.96-7.04 (m, 3H, C$_6H_5$), 7.13 (td, 1H, J = 8.6, 2.6 Hz, C$_6H_5$); 7.31-7.38 (m, 2H, C$_6H_5$). ^{13}C NMR : δ 26.6; 53.4; 83.6; 109.4 (d, $J_{C\text{-}F}$ = 7.7 Hz; *C*H,Ph-F); 113.8 (d, $J_{C\text{-}F}$ = 24.8 Hz; *C*H,Ph-F); 115.5 (d, $J_{C\text{-}F}$ = 21.2 Hz; *C*H,Ph-F); 116.8 (d, $J_{C\text{-}F}$ = 23.1 Hz; *C*H,Ph-F); 128.3 (d, $J_{C\text{-}F}$ = 8 Hz; *C*H,Ph-F); 129.5; 134.1; 140.5; 150.8 (d, $J_{C\text{-}F}$ = 243.8 Hz, C_q-F); 163.0 (d, $J_{C\text{-}F}$ = 247.8 Hz, C_q-F); 174.9. IR (cm^{-1}) : 3075, 2938, 2825 (NMe, OMe); 1728 (C=O); 1619 (C=C). Anal. calcd. for $C_{16}H_{13}NO_2F_2$: C : 66.43; H : 4.53. Found : C : 66.98; H : 4.51.

3-(4-Bromophenyl)-3-methoxy-1-methyl-1,3-dihydro-indol-2-one (20a) and 3-(4-bromophenyl)-5-fluoro-3-methoxy-1-methyl-1,3-dihydroindol-2-one (20b) : White crystals obtained respectively in 90% and 74% yields after column chromatography (eluent : dichloromethane) followed by recrystallisation from diisopropylether (**20a**) and pentane (**20b**).
20a : m.p. 97-98°C. ^{1}H NMR : δ 3.20 (s, 3H, OCH_3); 3.23 (s, 3H, NCH_3); 6.93 (d, 1H, J = 7.8 Hz, C$_6H_5$) 7.10-7.17 (t, 1H, J = 7.5 Hz, C$_6H_5$), 7.22-7.25 (m, 3H, C$_6H_5$); 7.39-7.44 (m, 3H, C$_6H_5$). ^{13}C NMR : δ 26.5; 53.2; 84.0; 108.8; 122.7; 123.6; 125.7; 127.4; 128.2; 130.5; 131.6; 137.9; 140.4; 174.8. IR (cm^{-1}) : 3063, 2931, 2831 (NMe, OMe); 1725 (C=O); 1611 (C=C). Anal. calcd. for $C_{16}H_{14}NO_2Br$: C : 57.85; H : 4.25. Found : C :57.86; H : 4.26.

20b : m.p. 70-71°C. ^{1}H NMR : δ 3.22 (s, 3H, OCH_3); 3.23 (s, 3H, NCH_3); 6.87 (dd, 1H, J= 8.6, 4 Hz, C$_6H_4$-F); 6.99 (dd, 1H, J= 7.4, 2.6 Hz, C$_6H_4$-F), 7.12 (td, 1H, J = 8.6, 2.6 Hz, C$_6H_4$-F); 7.23 (d, 2H, J = 8.7 Hz, C$_6H_5$), 7.44 (d, 2H, J = 8.7 Hz, C$_6H_5$). ^{13}C NMR : δ 26.6; 53.3; 83.7; 109.5 (d, $J_{C\text{-}F}$ = 7.6 Hz; *C*H,Ph-F); 113.6 (d, $J_{C\text{-}F}$ = 24.6 Hz; *C*H,Ph-F); 116.9 (d, $J_{C\text{-}F}$ = 23.1 Hz; *C*H,Ph-F); 122.9; 128.0; 129.2; 131.7; 137.4 ; 140.4; 159.7 (d, $J_{C\text{-}F}$ = 241.0 Hz, *C*$_q$-F); 174.5. IR (cm^{-1}) : 3081, 2931, 2831 (NMe, OMe); 1727 (C=O); 1619 (C=C) ; 1500. Anal. calcd. for $C_{16}H_{13}NO_2FBr$: C : 54.88; H : 3.74. Found : C :54.97; H : 3.84.

3-(*p*-Biphenyl)-3-methoxy-1-methyl-1,3-dihydroindol-2-one (21a) and 3-(*p*-biphenyl)-5-fluoro-3-methoxy-1-methyl-1,3-dihydroindol-2-one (21b) : White crystals obtained respectively in 79% and 69% yields after purification by column chromatography (eluent : dichloromethane) followed by recrystallisation from diisopropylether.

21a : m.p. 78-80°C. ^{1}H NMR : δ 3.24 (s, 3H, OCH_3); 3.25 (s, 3H, NCH_3); 6.94 (d, 1H, J =7.8 Hz, C$_6H_5$) ; 7.16 (td, 1H, J = 7.5, 0.6 Hz, C$_6H_5$), 7.26-7.36 (m, 2H, C$_6H_5$); 7.36-7.47 (m, 5H, C$_6H_5$) ; 7.49-7.56 (m, 4H, C$_6H_5$) . ^{13}C NMR : δ 26.5; 53.2; 83.9; 108.7; 123.5; 125.9; 126.9; 127.2; 127.3; 127.5; 128.0; 128.8; 130.3; 137.7; 140.9; 141.4; 144.7; 174.8. IR (cm^{-1}) : 3063; 3031; 2933; 2825 (NMe, OMe); 1725 (C=O); 1612 (C=C); 1488; 1470. Anal. calcd. for $C_{22}H_{19}NO_2$: C : 80.22; H : 5.81. Found : C : 79.66; H : 5.73.

21b : m.p. 121-123°C. ^{1}H NMR : δ 3.25 (s, 3H, OCH_3); 3.27 (s, 3H, NCH_3); 6.88 (dd, 1H, J = 8.4 , 4 Hz, C$_6H_5$) ; 7.10 (dd, 1H, J = 16.1, 2.5 Hz, C$_6H_5$), 7.13 (dd, 1H, J = 17.3, 2.5 Hz, C$_6H_5$); 7.33-7.50 (m, 5H, C$_6H_5$); 7.50-7.55 (m, 4H, C$_6H_5$) ^{13}C NMR : δ 26.7; 53.4; 84.5; 109.3 (d, $J_{C\text{-}F}$ = 7.9 Hz, *C*H,Ph-F); 113.8 (d, $J_{C\text{-}F}$ = 24.5 Hz, *C*H,Ph-F); 116.7 (d, $J_{C\text{-}F}$ = 24.0 Hz, *C*H,Ph-F); 126.8; 127.3; 127.4; 127.6; 128.9; 129.9; 137.2; 140.6; 140.8; 141.7; 159.7 (d, $J_{C\text{-}F}$ = 237.1 Hz, *C*q-F); 174.8. IR (cm^{-1}) : 3056, 2938, 2825 (NMe, OMe); 1727 (C=O); 1619 (C=C) ; 1494. Anal. calcd. for $C_{22}H_{18}NO_2F$: C : 76.07; H : 5.22. Found : C : 76.04 H : 5.26.

3-Methoxy-3-(3-methoxyphenyl)-1-methyl-1,3-dihydroindol-2-one (22a) and 5-fluoro-3-methoxy-3-(3-methoxyphenyl)-1-methyl-1,3-dihydroindol-2-one (22b) : white crystals isolated in 75% and 91% yields respectively after column chromatography (eluent : dichloromethane) followed by recrystallisation from diisopropylether.

22a : m.p. 45-47°C. ^{1}H NMR : δ 3.230 (s, 3H, OCH_3); 3.234 (s, 3H, NCH_3); 3.80 (s, 3H, Ar-OCH_3); 6.80-6.93 (m, 3H, C$_6H_5$); 7.03-7.04 (m, 1H, C$_6H_5$), 7.10-7.30 (m, 3H, C$_6H_5$); 7.40 (td, 1H, J = 7.7, 1.3 Hz, C$_6H_5$). ^{13}C NMR : δ 26.5; 53.2; 55.4; 84.0; 108.6; 112.3; 118.7; 123.4; 125.8; 128.1; 129.5; 130.3; 140.3; 144.6; 149.5; 159.8; 175.0. IR (cm^{-1}) : 3064, 2997, 2938, 2831 (NMe, OMe); 1722 (C=O); 1609; 1583 (C=C). Anal. calcd. for $C_{17}H_{17}NO_3$: C : 72.07; H : 6.05. Found : C : 72.04; H : 6.04.

22b : m.p. 98-100°C. ^{1}H NMR : δ 3.23 (s, 3H, OCH_3); 3.24 (s, 3H, NCH_3); 3.80 (s, 3H, Ar-OCH_3); 6.80-6.87 (m, 3H, C$_6H_5$); 7.0-7.02 (m, 1H, C$_6H_5$), 7.03 (dd, 1H, J= 18.2, 2.6 Hz, C$_6H_5$); 7.09 (dd, 1H, J = 18.2, 2.6 Hz, C$_6H_5$); 7.22 (dd, 1H, J= 15.6, 7.6 Hz, C$_6H_5$). ^{13}C NMR : δ 26.6; 53.3; 55.4; 84.0; 109.3 (d, $J_{C\text{-}F}$ = 7.7 Hz, *C*H,Ph-F); 112.1; 113.7 (d, $J_{C\text{-}F}$ = 24.6 Hz, *C*H,Ph-F); 113.9; 116.6 (d, $J_{C\text{-}F}$ = 23.7 Hz, *C*H,Ph-F); 118.4; 129.6; 129.9; 139.7; 140.4; 159.6 (d, $J_{C\text{-}F}$ = 242.6 Hz, *C*q-F); 159.8; 174.8. IR (cm^{-1}) : 3075, 2937, 2831 (NMe, OMe); 1727 (C=O). Anal. calcd. for $C_{17}H_{16}NO_3F$: C : 67.76; H : 5.35. Found : C : 67.21; H : 5.35.

3-(2-Chlorophenyl)-3-methoxy-1-methyl-1,3-dihydroindol-2-one (23a) and 3-(2-chlorophenyl)-5-fluoro-3-methoxy-1-methyl-1,3-dihydroindol-2-one (23b) : White crystals isolated after column chromatography (eluent : dichloromethane) and then recrystallised from diisopropylether (**23a**, 80%) and pentane (**23b**, 70%) respectively.

23a : m.p. 87-89°C (*i*Pr$_2$O). ^{1}H NMR : δ 3.19 (s, 3H, OCH_3); 3.30 (s, 3H, NCH_3); 6.86-7.10 (m, 2H, C$_6H_5$); 7.30-7.45 (m, 2H, C$_6H_5$), 8.11-8.15 (d, 1H, J = 7.8 Hz, C$_6H_5$). ^{13}C NMR : δ 26.4; 51.7; 81.5; 108.1; 123.1; 124.8; 126.7; 127.1; 128.3; 128.7; 129.2; 130.3; 130.9; 136.7; 145.5; 173.7. IR (cm^{-1}) : 2825 (OMe); 1725 (C=O). Anal. calcd. for $C_{16}H_{14}NO_2Cl$: C : 66.79; H : 4.90. Found C : 66.82; H : 4.95.

23b : m.p. 91-92°C (pentane). ^{1}H NMR : δ 3.21 (s, 3H, OCH_3); 3.30 (s, 3H, NCH_3); 6.72 (dd, 1H, J = 7.4, 2.6 Hz, C$_6H_5$); 6.82 (dd, 1H, J = 8.7, 4.0 Hz, C$_6H_5$), 7.07 (td, 1H, J = 8.7, 2.6 Hz, C$_6H_5$). ^{13}C NMR : δ 26.7; 52.0; 81.7; 108.8 (d, $J_{C\text{-}F}$ = 7.7 Hz; *C*H,Ph-F); 113.2 (d, $J_{C\text{-}F}$ = 24.6 Hz; *C*H,Ph-F); 116.7 (d, $J_{C\text{-}F}$ = 24.2 Hz; *C*H,Ph-F); 127.0 ; 128.9; 129.6; 130.5; 131.1; 136.3; 141.7; 159.8 (d, $J_{C\text{-}F}$ = 241.1 Hz, *C*$_q$-F); 173.7. IR (cm^{-1}) : 3075; 2938; 2831 (NMe, OMe); 1729 (C=O); 1619 (C=C); 1496. Anal. calcd. for $C_{16}H_{13}NO_2FCl$: C : 62.86; H : 4.29. Found : C : 62.81; H : 4.34.

Nucleophilic substitution of 3-chloro-3-aryl-oxindoles derivatives :

5-Fluoro-3-(4-fluorophenyl)-1-methyl-3-(4-nitrophenoxy)-1,3-dihydroindol-2-one 24 : This compound was obtained via substitution of the 3-chloro-oxindole **14b** (50 mg, 0.17 mmol) by 4-nitrophenol (24 mg, 0.17 mmol) at reflux in acetonitile (2 ml) in the presence of potassium carbonate (23.5 mg, 0.17 mmol) for 2hrs. Silica gel column chromatography eluted with dichloromethane/pentane (9/1) yielded a pale yellow oil in 52% yield.

^{1}H NMR : δ 3.25 (s, 3H, NCH_3); 6.83 (d, 2H, J = 9.2 Hz, C$_6H_5$); 6.94 (dd, 1H, J = 8.7, 4.0 Hz , C$_6H_5$) 7.03-7.13 (m, 3H, C$_6H_5$); 7.18 (td, 1H, J = 8.7, 2.6 Hz, C$_6H_5$); 7.45 (d, 2H, J = 9.2 Hz, C$_6H_5$). ^{13}C NMR : δ 27.0; 85.0; 111.0 (d, $J_{C\text{-}F}$ = 7.7 Hz; *C*H,Ph-F); 114.3 (d, $J_{C\text{-}F}$ = 24.9 Hz; *C*H,Ph-F); 116.7 (d, $J_{C\text{-}F}$ = 21.6 Hz; *C*H,Ph-F); 118.6 (d, $J_{C\text{-}F}$ = 24.1 Hz; *C*H,Ph-F); 125.6 (d, $J_{C\text{-}F}$ = 8.0 Hz; *C*H,Ph-F); 129.3 (d, $J_{C\text{-}F}$ = 8.7 Hz, *C*H,Ph-F); 132.9; 139.6; 143.2; 159.7 (d, $J_{C\text{-}F}$ = 244.8 Hz, *C*$_q$-F); 160.5; 163.4 (d, $J_{C\text{-}F}$ = 249.7 Hz, *C*$_q$-

F); 173.0. IR (cm^{-1}) : 1732 (C=O); 1610, 1591 (C=C) . Anal. calcd. for $C_{21}H_{14}N_2O_4F_2$: C : 63.64; H : 3.56. Found : C : 63.86; H : 3.79.

5-Fluoro-3-(4-fluorophenyl)-3-(imidazol-1-yl)-1-methyl-1,3-dihydroindol-2-one 25 : This compound was obtained via substitution of the 3-chloro-oxindole **14b** (100 mg, 0.34 mmol) by imidazole (excess) at reflux in acetonitrile (4 ml) in the presence of potassium carbonate (47 mg, 0.34 mmol) for 6 hrs. Silica gel column chromatography eluted with dichloromethane/ethyl acetate (7/3) gave a white solid in 60% yield.

m.p. (MeOH) : 130-132°C; ^1H NMR : δ 3.31 (s, 3H, NCH_3); 6.90-7.30 (m, 8H, Im + C_6H_5); 7.57 (s, 2H, Im). ^{13}C NMR : δ 27.13 (NCH_3); 68.2 (*C*q-C=O); 84.9; 110.4 (d, $J_{C\text{-}F}$ = 7.8 Hz; *C*H,Ph-F); 113.9 (d, $J_{C\text{-}F}$ = 25.1 Hz; *C*H,Ph-F); 116.3 (d, $J_{C\text{-}F}$ = 21.6 Hz; *C*H,Ph-F); 117.4 (d, $J_{C\text{-}F}$ = 23.4 Hz; *C*H,Ph-F); 118.4 (*C*H, Im); 128.8 (d, $J_{C\text{-}F}$ = 8.8 Hz; *C*H,Ph-F); 129.4 (*C*q); 130.0 (*C*H, Im); 132.9 (*C*q); 136.5 (*C*q); 143.2; 159.5 (d, $J_{C\text{-}F}$ = 243.7 Hz, C_q-F); 163.2 (d, $J_{C\text{-}F}$ = 250.2 Hz, C_q-F); 172.7. IR (cm^{-1}) : 1728 (C=O); 1604; 1509 (C=C) ; 1497, 1453; 1358; 1274. Anal. calcd. for $C_{18}H_{13}N_3OF_2$. H_2O : C : 62.97; H : 4.40. Found : C : 62.81; H : 4.41.

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