SYNTHESIS OF INDANYL ANALOGS OF 3-[3-(4-ARYLPIPERAZIN-1-YL) PROPYL]-2-OXO-2,3-DIHYDRO[1,3]BENZOXAZOLES

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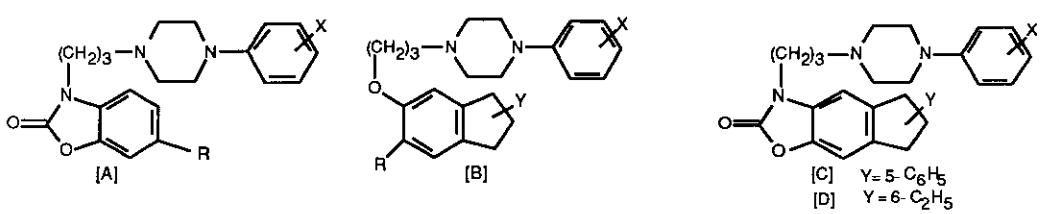
Abstract - Original indanyl analogs of 3-[3-(4-arylpiperazin-1-yl)propyl]-dihydro-2-oxo[1,3]benzoxazoles were synthesized from 6-acyl-2-oxo-2,3-dihydro[1,3]benzoxazoles.

Benzoxazolinone, 2-oxo-2,3-dihydro[1,3]benzoxazole, is a powerful pharmacophore associated with some activities, particularly sedative and analgesic one .[1-3] Previous studies have shown that 6-acylation [4]or 6- alkylation [5] of the aromatic nucleus enhances the original analgesic activity.This activity is greatly increased by alkylation of the NH group of the oxazole moiety by various chloropropylarylpiperazines[6] such as in the 3-[3-(4-arylpiperazin-1-yl)propyl]-2,3-dihydro-2-oxo[1,3]benzoxazoles (Structure **[A]**, Scheme 1). Moreover, through efforts to find a new type of psychotropic compounds, 3-arylpiperazinylpropyloxyindan derivatives[7] (Structure **[B]**, Scheme 1) were shown to have antianxiety activities.For these latter structures, the indan nucleus could be considered as a molecular framework[8] to which the functional group is attached and which can serve to hold the biological activity. Indanes and their more used chemically precursors indanones are important intermediates[8] in medicinal chemistry due to their incorporation into many natural products and pharmacologically active molecules. Recent examples of their pharmaceutical value include use as reagents to make conformationally restrained analogs of trimethoprim,[9] normolipemic benzoxazinyl derivatives[10] and as versatile intermediates for synthesis of adenosine receptors agonists,[11] antipsychotic analogs[12]or phosphodiesterase inhibitors.[13] In the aim to associate the analgesic activity of structure [A] with a sedative factor, our interest was directed towards the synthesis of structures **[C]** and **[D]** in which the two pharmacophores indanyl and arylpiperazinylalkyl moiety were incorporated in the benzoxazolinonyl heterocyclic nucleus (Scheme 1).

Scheme 1

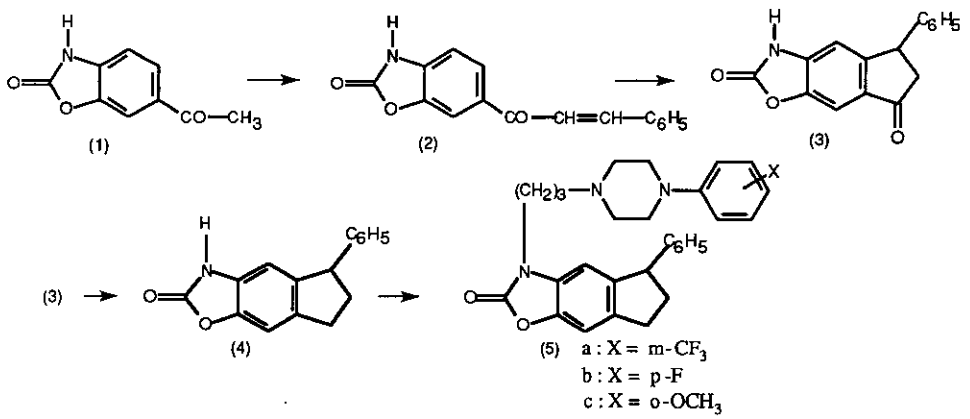


We have therefore investigated several methods to provide access to such compounds. These methods use as starting materials various earlier described 6- acyl -2-oxo-2,3-dihydro[1,3]benzoxazoles.[4]

3-[3-(4-arylpiperazin-1-yl)propyl]-2-oxo-5-phenylcyclopenta[f]-2,3-dihydro[1,3]benzoxazoles (Structure C)

The synthesis (Scheme 2) involved reaction of 6-acetyl-2-oxo-2,3-dihydro[1,3]benzoxazole with benzaldehyde in basic medium.[5] The chalcone (**2**) led to the indanone (**3**) by heating in polyphosphoric acid.[14] Reduction of **3** with triethylsilane in trifluoroacetic acid medium[15] gave the indanyl derivative (**4**), sodium derivative of which was then alkylated by an appropriate chloropropylarylpiperazine[16] to give the tittle compounds (**5**).

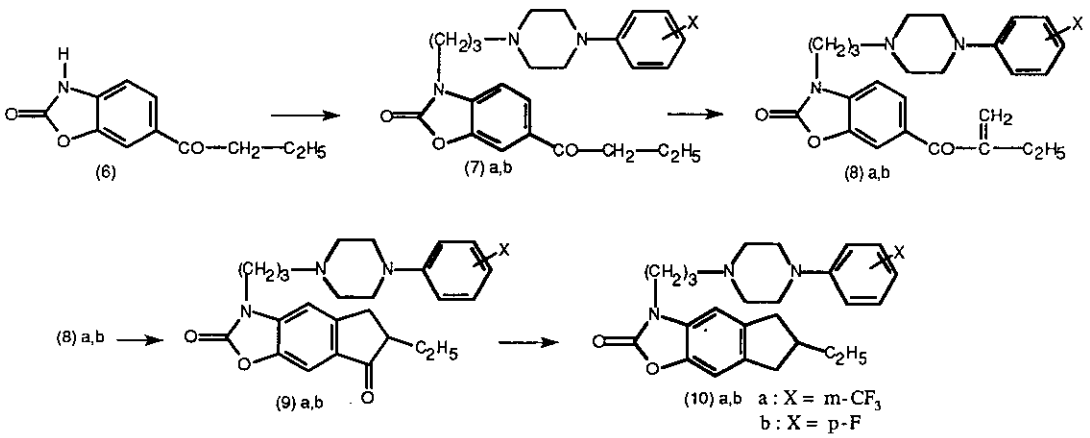
Scheme 2



3-[3-(4-arylpiperazin-1-yl)propyl]-2-oxo-6-ethylcyclopenta[f]-2,3-dihydro[1,3]benzoxazoles (Structure D)

In a first approach we have tried a method previously developed [10] i.e. α-methylenation of 6-butyryl-2-oxo-2,3-dihydro[1,3]benzoxazole (**6**) by using 1,3,5-trioxane, morpholine hydrochloride and sodium acetate in acetic acid. However, due to the NH acidic group, this approach was unsuccessfull. In an alternative procedure (Scheme 3) , we have first tried the alkylation of the NH group of **6** . Treatment of the resulting **7** with 1,3,5-trioxane, morpholine hydrochloride and sodium acetate in acetic acid gave the α, β-ethylenic ketones (**8**). Stirring **8** at room temperature with concentrated sulfuric acid [10] resulted in an intramolecular cycloalkylation of the aromatic ring producing the desired tricyclic derivatives (**9**). Reduction of **9** with triethylsilane in trifluoroacetic acid afforded the tittled compounds (**10**).

Scheme 3



EXPERIMENTAL

Melting points were determined on a Büchi 510 apparatus and are uncorrected. Ir spectra were recorded on a Perkin Elmer 297 spectrophotometer and ^{1}H nmr spectra on a Brücker 80 MHz apparatus with TMS as internal standard. Elemental analyses were performed by the CNRS Center, Vernaison, France. Starting materials and intermediates(1), (2), (6) were prepared by published procedures.[4, 5]

2,7-Dioxo-5-phenylcyclopenta[f]-2,3-dihydro[1,3]benzoxazole (3)

Compound (**2**) (15 g, 0.056 mol) was added dropwise to hot (120°C) polyphosphoric acid (120 g).The reaction medium was stirred at this temperature for 55 min then quenched with ice water. The solid obtained was filtered under vacuum, washed with water and stirred in refluxing chloroform (125 ml) for 2 h. After filtration and evaporation of the organic phase , the residue was purified by recrystallization from ethanol to give pure **3** (10.5 g , 70%). mp 229-231°C ; ir(KBr) : 1795-1775, 1665 cm^{-1}; ^{1}H nmr (DMSO-d_6) δ : 7.55 (s, 1H) ; 7.50-7.12 (m, 5H) ; 6.82 (s, 1H) ; 4.67 (dd, J = 3.75 and 7.5 Hz, 1H) ; 3.25 (dd, J = 7.5 and 17.5 Hz, 1H) ; 2.64 (dd, J = 3.75 and 17.5 Hz, 1H). Anal. Calcd for $C_{16}H_{11}NO_3$: C, 72.45 ; H, 4.18 ; N, 5.28 . Found : C, 72.16 ; H, 4.18 ; N, 5.23.

2-Oxo-5-phenylcyclopenta[f]-2,3-dihydro[1,3]benzoxazole (4)

To a solution of the indanone (**3**) (5.31 g, 0.02 mol) in trifluoroacetic acid (22.8 g, 0.2 mol) was added dropwise 5.25 g (0.045 mol) of triethylsilane.The reaction medium was stirred at room temperature for 72 h then quenched with ice water (300 ml) and the resulting solid was filtered under vacuum. The solid obtained was washed with water and purified by recrystallization from toluene to give **4** (2.8 g , 55%).mp 154-156°C ; ir(KBr) : 3300-2850, 1780, 1750, 1620, 1600,

1475, 725, 675 cm^{-1}; ^1H nmr (DMSO-d_6) δ : 9.78 (s, 1H, signal dissapeared after adding D_2O) ; 7.50-7.00 (m, 6H) ; 6.58 (s, 1H) ; 4.28 (t, J = 6 Hz, 1H) ; 3.20-1.90 (m, 4H). Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.46 ; H, 5.22 ; N, 5.58 . Found : C, 76.38 ; H, 5.27 ; N, 5.38 .

General Procedure for the Synthesis of 3-[3-(4-arylpiperazin-1-yl)propyl]-2-oxo-5-phenyl cyclopenta[f]-2,3-dihydro[1,3]benzoxazoles (5a-c)

Compound (4) (6 g, 0.024 mol) was dissolved in an ethanolic solution of sodium ethoxide (0.024 atg of Na in 100 ml of absolute ethanol). After evaporation of the solvent, the solid residue was dissoved in dimethylformamide (50 ml) and then an equimolar quantity (0.024 mol) of the appropriate1-(3-chloropropyl)-4-arylpiperazine was slowly added. The mixture was heated at reflux for 75 min. After cooling, the precipitate was filtered, treated with dimethylformamide and the filtrate was evaporated under vacuum. The residue was taken up with water and was stirred for 2 h. The solid residue was collected by filtration and crystallized from an appropriate solvent (Table I)

General Procedure for the Synthesis of 3-[3-(4-Arylpiperazin-1-yl)propyl]-2-oxo-6-butyryl-2,3-dihydro[1,3]benzoxazoles (7a-b)

These compounds (Table II) were prepared from **6** (4.9 g, 0.024 mol) in dimethylformamide (50 ml) by treatment with the appropriate1-(3-chloropropyl)-4-arylpiperazine (0.024 mol) as described for the preparation of **5** .

General Procedure for the Synthesis of 3-[3-(4-Arylpiperazin-1-yl)propyl]-2-oxo-6-(2-methylenebutyryl)-2,3-dihydro[1,3]benzoxazoles (8)

A mixture of **7** (0.04 mol), 1,3,5-trioxane (5.40 g, 0.06 mol), morpholine hydrochloride (7.32 g, 0.06 mol) and sodium acetate (20 g, 0.24 mol) in acetic acid (300 ml) was heated at reflux for 5 h. After filtration and evaporation of the filtrate, the residue was taken up with water (500 ml). The aqueous mixture was made basic with 10 % aqueous solution of sodium hydroxyde and extracted with ethyl acetate. The organic layer was evaporated and the residue was crystallized from an appropriate solvent (Table III).

General Procedure for the Synthesis of 3-[3-(4-Arylpiperazin-1-yl)propyl]-2,7-dioxo-6-ethyl-cyclopenta[f]-2,3-dihydro[1,3]benzoxazoles (9a-b)

A solution of the appropriate enone (**8**) (0.025 mol) in concentrated sulfuric acid (25 ml) was stirred at room temperature for 18 h. The mixture was then poured into cold water and made basic with a 10% aqueous solution of sodium hydroxyde. The separated solid was filtered, washed with water, dried and crystallized from an appropriate solvent (Table IV).

Table I. Physical and spectral data of compounds (5)

Compd	yield % (Solvent)	mp (°C)	ir (KBr) νC=O	^{1}Hnmr ($CDCl_3$) δ	Molecular formula	Analysis (%) calcd / found C	H	N
5 a	68 (cyclohexane-ethanol(4/2))	140	1755	6.94-7.40 (m, 10 H) ; 6.59 (s, 1H) ; 4.28 (t, J=6 Hz, 1H) ; 3.78 (t, J = 7 Hz, 2H) ; 3.10-1.82(m, 16H).	$C_{29}H_{30}N_3O_2F_3$	69.08 69.10	5.79 5.76	8.05 8.07
5 b	65 (cyclohexane-ethanol(4/1))	121	1755	7.23 (m, 5H) ; 7.09 (s, 1H) ; 6.88 (m, 4H) ; 6.59 (s,1H) ; 4.30 (t,J= 6 Hz, 1H) ; 3.85 (t, J = 7 Hz, 2H) ; 3.12-1.83 (m, 16H).	$C_{29}H_{30}N_3O_2F$	73.80 73.83	6.44 6.32	8.91 9.03
5 c	62 (ethanol)	115	1755	7.22 (m, 5H) ; 7.13 (s,1H) ; 6.92 (m, 4H) ; 6.61 (s,1H) ; 4.42 (t,J = 6 Hz, 1H) ; 3.83 (s, 3H) ; 3.81 (t, J = 7 Hz, 2H) ; 3.12- 1.83 (m, 16H).	$C_{30}H_{33}N_3O_2$	74.50 74.43	6.87 6.72	8.68 8.58

General Procedure for the Synthesis of 3-[3-(4-Arylpiperazin-1-yl)propyl]-2-oxo-6-ethyl-cyclopenta[f]-2,3-dihydro[1,3]benzoxazoles (10a-b)

To a solution of the indanone **9** (0.018 mol) in trifluoroacetic acid (58 g, 0.4 mol) was added dropwise (5.14 g , 0.044 mol) of triethylsilane.The reaction mixture was stirred at room temperature for 72 h then quenched with ice water (300 ml) . The mixture was made basic by addition of a 10% aqueous solution of sodium hydroxyde and filtered under vacuum. The solid obtained was washed with water and purified by recrystallization from an appropriate solvent (Table V).

Table II. Physical and spectral data of compounds (7)

Compd	yield % (Solvent)	mp (°C)	ir (KBr) ν C=O	^{1}Hnmr ($CDCl_3$) δ	Molecular formula	Analysis (%) calcd / found C	H	N
7a	70 (ethanol))	189-190	1755 1665	7.88 (dd, J = 1.8 and 8.4Hz, 1H) ; 7.24 (s, 1H) ; 7.42-7.15 (m, 5H)) ; 4.40 (t, J = 7 Hz, 2H) ; 3.16 (m, 2H) ; 2.92 (t, J = 6 Hz, 2H) ; 2.53 (m, 2H) ; 2.53 (*m*, 6H) ; 2.20-1.70 (*m*, 4H) ; 1.00 (t, J = 7 Hz, 3H).	$C_{25}H_{28}N_3O_3F_3$	63.15 63.25	5.93 5.88	8.84 8.71
7b	67 (ethanol)	190	1755 1665	7.86 (dd, J = 1.8 and 8.4 Hz, 1H) ; 7.27 (s, 1H) ; 7.10 (d, J = 8.4 Hz, 1H) ; 6.86 (m, 4H) ; 4.00 (t, J = 7 Hz, 2H) ; 3.18 (m , 2H) ; 3.00 (t, J = 6 Hz, 2H) ; 2.53 (m, 4H) 2.18-1.70 (m, 4H) ; 1.00 (t, J = 7 Hz, 3H).	$C_{24}H_{28}N_3O_3F$	67.75 67.81	6.63 6.52	9.87 9.77

Table III. Physical and spectral data of compounds (8)

Compd	yield % (Solvent)	mp (°C)	ir (KBr) ν C=O	^{1}Hnmr ($CDCl_3$) δ	Molecular formula	Analysis (%) calcd / found C	H	N
8a	55 (cyclohexane)	89-90	1765 1645	7.71 (dd, J = 1.6 and 8.8 Hz, 1H) ; 7.63 (s, 1H) ; 7.32-6.85 (m, 5H) ; 5.74 (s, 1H) ; 5.46 (s, 1H) ; 3.98 (t, J = 7 Hz, 2H) ; 3.08 (m, 4H) ; 2.48 (m, 8H) ; 2.05 (q, J = 7.4 Hz, 2H) ; 1.11 (t, J = 7.4 Hz, 3H).	$C_{26}H_{28}N_3O_3F_3$	64.05 64.15	5.79 5.58	8.62 8.68
8b	55 (cyclohexane)	85-86	1765 1645	7.75 (dd, J = 1.6 and 8.8 Hz, 1H) ; 7.65 (s, 1H) ; 7.13 (d, J = 8.8 Hz, 1H) ;6.90 (m, 4H) ; 5.74 (s, 1H) ; 5.46 (s, 1H) ; 3.98 (t, J = 7 Hz, 2H) ; 3.08 (m, 4H) ; 2.48 (m, 8H) ; 2.05 (q, J = 7.4 Hz, 2H) ; 1.11 (t, J = 7.4 Hz, 3H).	$C_{25}H_{28}N_3O_3F$	68.63 68.89	6.45 6.40	9.60 9.45

Table IV. Physical and spectral data of compounds (9)

Compd	yield % (Solvent)	mp (°C)	ir (KBr) ν C=O	^{1}Hnmr ($CDCl_3$) δ	Molecular formula	Analysis (%) calcd / found C	H	N
9a	58 (ethanol)	140 1680	1765	7.50 (s, 1H) ; 7.00-7.11 (m, 5H) ; 4.00 (t, J = 7 Hz, 2H) ; 3.50-2.45 (m, 15H) ; 2.08 (q, J = 7 Hz, 2H) ; 1.00 (t, J = 7 Hz, 3H)	$C_{26}H_{28}N_3O_3F_3$	64.05 64.10	5.79 5.85	8.62 8.55
9b	59 (ethanol)	115-116	1765 1680	7.50 (s, 1H) ; 7.08 (s, 1H) ; 6.84 (m,4H) ; 4.00 (t, J = 7 Hz, 2H) ; 3.50-2.45 (m, 15H) ; 1.00 (t, J = 7 Hz, 3H)	$C_{25}H_{28}N_3O_3F$	70.89 70.67	7.14 7.24	9.92 9.82

Table V. Physical and spectral data of compounds (10)

Compd	yield % (Solvent)	mp (°C)	ir (KBr) ν C=O	^{1}Hnmr ($CDCl_3$) δ	Molecular formula	Analysis (%) calcd / found C	H	N
10a	52 (cyclohexane-ethanol (4:1))	113-114	1755	7.50-6.96(m, 5H) ; 6.84 (s, 1H) ; 3.89 (t, J= 7 Hz, 2H) ; 3.27-1.80 (m, 17H) ; 1.50 (m, 2H) ; 0.93 (t, J = 7.7 Hz, 3H)	$C_{26}H_{30}N_3O_2F_3$	66.08 65.83	6.18 6.24	8.09 8.08
10b	57 (cyclohexane-ethanol (4:1))	119-120	1755	7.20 (s, 1H) ; 7.00-6.81(m, 5H) ; 3.89 (t, J= 7 Hz, 2H) ; 3.27-1.80 (m, 17H) ; 1.50 (m, 2H) ; 0.93 (t, J = 7.7 Hz, 3H)	$C_{25}H_{30}N_3O_2F$	70.89 70.63	7.14 7.09	9.92 9.96

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