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Synthesis and relative binding affinity to steroid receptors and antiproliferative activity on MCF-7 cells of 2,3-disubstituted indenes

Serge Kirkiacharian [a,*], Pantelis G. Koutsourakis [a], Daniel Philibert [b], Francoise Bouchoux [b], Patrick Van De Velde [b]

[a] *Laboratoire de Chimie Thérapeutique, Faculté de Pharmacie de Paris-Sud, 5, rue Jean-Baptiste Clément, F-92296 Chatenay-Malabry Cedex, France*

[b] *Laboratoire de Physiologie des hormones, Laboratoires Roussel, Groupe HMR, 101 route de Noisy, F-93230 Romainville Cedex, France*

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Abstract

The study of the relative binding affinity of a set of 2,3-disubstituted indenes to the receptors of steroid hormones indicates a weak effect of some derivatives on estrogen, progesterone and androgen receptors. The antiproliferative effect on human MCF-7 cells also shows a weak activity for three derivatives.

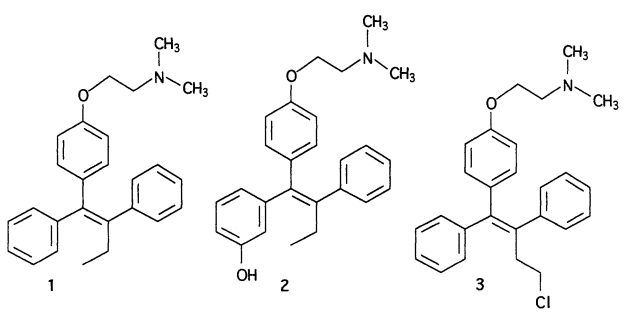
Keywords: Binding affinity; Steroid receptor; Antiproliferative activity

1. Introduction

The 2,3-disubstituted indenes, 1,2-disubstituted dihydronaphthalenes, 3,4-disubstituted 2*H*-chromenes and their dihydro derivatives are structurally related to naturally occuring steroid hormones and present either agonist and/or antagonist activities [1].

Although much work was performed in order to prepare antifertility agents [2], the research in this field was developed further since the introduction of Tamoxifene (**1**) (*Z*)-2-[4-(1,2-(Diphenyl-1-butenyl)phenoxy] *N*,*N*-dimethylethanamine [3] in the treatment of the hormonal dependant breast cancer [4,5]. Droloxifene (**2**) [6] and Toremifene (**3**) [7] are two other triarylethylenes that are devoted to the same therapeutic action. However, the *para*-hydroxylated metabolite to the geminal phenyl ring of the *Z*-triarylethylenes can isomerize to the *E*-derivatives, via a tautomeric quinoid intermediate, presenting more potent agonist activity, which is therefore unfavourable to their antiproliferative action [8–10].

The continuing interest in this area led to the preparation of compounds which could not isomerize. Some



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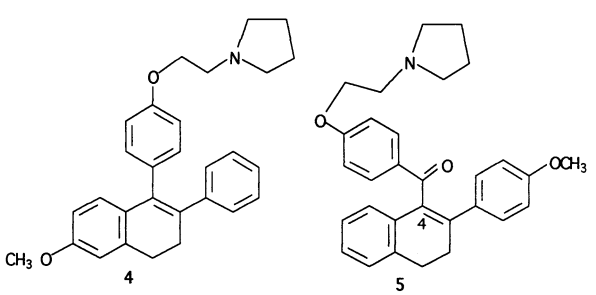
derivatives: Raloxifene (**6**) (benzothiophene) [11], Nafoxidine (**4**), Trioxifene (**5**) [12–14] (dihydronaphthalenes), diaryl-2H-chromene or (2,3-diaryl 2H-1-benzopyrane) (**7**) [15] are described as antiproliferative derivatives and selective estrogen receptor modulators (SERMs) [16].



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* Corresponding author. Tel./fax: +33-14683-5651.

E-mail address: serge.kirkiacharian@cep.u-psud.fr (S. Kirkiacharian)

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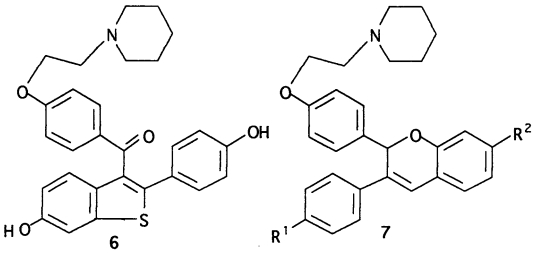

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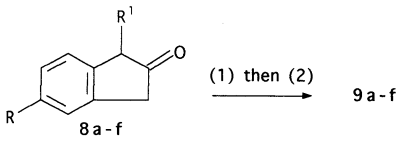


Scheme 1. (1): $BrMg–C_6H_4–O–CH_2–CH_2–N(C_2H_5)_2$ (p). (2): H_3O^+. R = H, OCH_3. $R^1 = C_2H_5$, C_6H_5, $C_6H_4–OCH_3$ (p), $C_6H_3–(OCH_3)_2$ (m,p), $C_6H_4–OCH_2CH_2N(C_2H_5)$ (p).

During the course of an ongoing program related to the preparation of various antiestrogens, our attention was focused on the fact that although many disubstituted indenes or indenones were already prepared as tumor inhibiting antiestrogens or as photofluorogenic estrogen ligands [17–20], none of them present a dialkylaminoalkoxy basic side chain on the 2-phenyl group. Therefore we decided the investigation of the structure–receptor binding affinity relationships of the indenes **9a–g** in order to study the influence of a *para*-substituted basic side chain on the phenyl group at position 2 of a rigid coplanar indene system (see Table 1).

2. Synthesis

There are at present some routes available for the preparation of 2,3-disubstituted indenes. They involve an acid cyclization step [2,18]. The intermediates are conveniently substituted acids which are cyclized by hydrofluoric acid [2], or ketones which are converted to indenes by polyphosphoric acid [18]. Since our derivatives present a basic aminoalkoxy group, the application of these methods would lead to degradation during the cyclization step. In order to circumvent this difficulty, we performed a new route in which the 2-phenyl bearing the dialkylaminoalkoxy ether group is introduced at the final step via a Grignard reaction (Scheme 1). The key intermediates are conveniently substituted 1-alkyl or 1-aryl indan-2-ones **8a–g** obtained by hydroboration followed by chromic acid oxidation [21] of 1-susbtituted indenes [22].

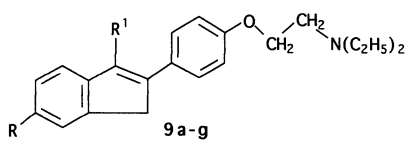
For all derivatives, the carbinols obtained from the Grignard reaction were not separated and were converted by dehydration to the corresponding ethylenic compounds. These were purified by column chromatography over silica gel. Their structure was determined by elemental analysis, infrared and ^1H NMR spectroscopy.

Compound **9g** was prepared by a different route involving the synthesis of the indene **8h** substituted at 2 and 3 positions by a 4-methoxyphenyl group followed by demethylation with aluminium chloride to the corresponding bis-hydroxy derivative **8i** and alkylation with diethylaminoethylchloride to the expected derivative **9g** bearing two basic diethylaminoethoxyphenyl groups (Scheme 2).

The basic derivatives were converted further into hydrochlorides or methanesulfonates and studied for both their relative binding affinity to the recombinant human steroid receptors and their antiproliferative activity on MCF-7 cells.

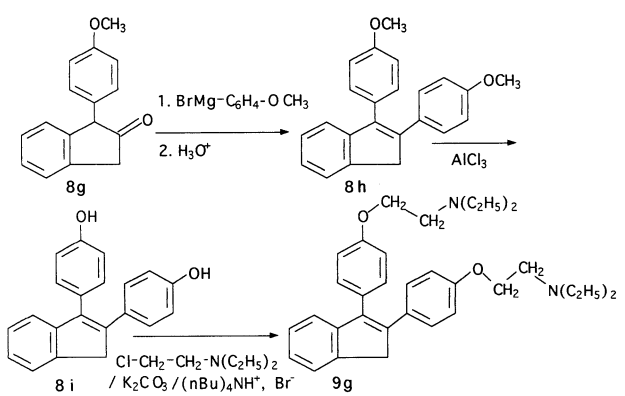
All the prepared indenes must be stored under vacuum and protected from humidity and light to avoid oxidation leading to a brown colouring.

Table 1



9a-g

9	R	R^1
a	OCH_3	C_2H_5
b	H	C_6H_5
c	H	$C_6H_4–OCH_3$ (p)
d	H	$C_6H_4–(OCH_3)_2$ (m,p)
e	OCH_3	C_6H_5
f	OCH_3	$C_6H_4–O–CH_3$ (p)
g	H	$C_6H_4–O–CH_2–CH_2–N(C_2H_5)_2$ (p)



Scheme 2.

3. Experimental

3.1. Chemistry

Analyses (C, H, N) were within $\pm 0.5\%$ of the theoretical value. Melting points are not corrected. The ^{1}H NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with TMS as internal reference on a Varian T60 spectrometer. Chemical shifts are in (δ) ppm and coupling constants (J) in Hz. The IR spectra of the disubstituted indenes present bands at 2900–2990 and 1600 cm^{-1}.

3.1.1. Preparation of indenes **9a–g**

3.1.1.1. ***Typical procedure:*** *3-ethyl-6-methoxy-2-(4-diethylaminoethoxyphenyl)indene* ***(9a)***. In a nitrogen flushed three necked 500 ml dry round bottom flask, fitted with a magnetic stirring bar and a reflux condenser topped with a calcium chloride drying tube, were added magnesium turnings (250 mg, 10.5 mmol), a trace crystal of iodine and 50 ml anhydrous THF (distilled over benzophenone ketyl) followed by a solution of 4-(2-diethylaminoethyoxy)bromobenzene (1.9 g, 7 mmol) in THF (20 ml). The mixture was refluxed (1 h). After cooling, 1-ethyl-5-methoxyindan-2-one [22] (1.10 g, 6 mmol) dissolved in dry THF (30 ml) was added dropwise and the mixture refluxed (4 h). After cooling the reaction mixture was hydrolyzed by a saturated ammonium chloride solution. The two phases were separated and the aqueous phase extracted with THF (3×30 ml portions). The mixed organic phases were washed with a saturated NaCl aqueous solution, dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The residue was heated at 120°C (2 h) with $KHSO_4$ (1 g, 13 mmol). After cooling, water (50 ml) was added and the mixture extracted with dichloromethane (DCM) (3×30 ml portions). The organic phase was washed with water until neutrality, dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The residue was recrystallized in methanol. All derivatives were prepared according to the same procedure.

Molecular formula; m.p. °C (solvent); yield (%) and ^{1}H NMR spectra are given for all derivatives.

9a: $C_{24}H_{31}NO_2$; 82°C (methanol); yield: 50%; ^{1}H NMR: 1.1, t, 9H, $J = 7$ Hz: CH_2CH_3; 2.8, q, 6H, CH_2–N–CH_2CH_3; 3.6, s, 2H, CH_2 (indene); 3.8, s, 3H, OCH_3; 4.2, t, 2H, OCH_2; 6.6–7.8, m, 7H, arom. The hydrochloride was prepared by the action of HCl gas on a solution of the basic derivative in a mixture of DCM–diethyl ether (90/10). Hydrochloride: $C_{24}H_{32}ClNO_2$; m.p. 141°C (diethyl ether) (yield: 91%).

9b: $C_{27}H_{29}NO$; 184°C (methanol); yield: 45%; ^{1}H NMR: 1.1, t, 6H, $J = 7$ Hz: CH_2CH_3; 2.7, q, 6H, CH_2–N–CH_2CH_3; 3.6, s, 2H, CH_2 (indene); 4.2, t, 2H, OC*H*2; 6.6–7.4, m, 13H, arom. Methanesulfonate: $C_{28}H_{33}NO_4$ S; m.p. 288°C (diethyl ether) (yield: 91%).

9c: $C_{28}H_{31}NO_2$; 228°C (methanol); yield: 43%; ^{1}H NMR: 1.1, t, 6H, $J = 7$ Hz: CH_2CH_3; 2.8, q, 6H, CH_2–N–CH_2CH_3; 3.6, s, 2H, CH_2 (indene); 3.8, s, 3H, OCH_3; 4.1, t, 2H, $J = 8$ Hz: OCH_2; 6.6–7.7, m, 12H, arom. Methanesulfonate: $C_{29}H_{35}NO_5S$; m.p. 313°C (diethyl ether) (yield: 92%).

9d: $C_{24}H_{33}NO_3$; 266°C (methanol); yield: 42%; ^{1}H NMR: 1.1, t, 6H, $J = 7$ Hz: CH_2CH_3; 2.8, q, 6H, CH_2–N–CH_2CH_3; 3.6, s, 2H, CH_2 (indene); 3.8, s, 6H, OCH_3; 4.1, t, 2H, $J = 8$ Hz: OCH_2; 6.7–7.5, m, 11H, arom. Methanesulfonate: $C_{30}H_{37}NO_6S$; m.p. 338°C (diethyl ether) (yield: 89%).

9e: $C_{28}H_{31}NO_2$; 183°C (methanol); yield: 10%; ^{1}H NMR: 1.1, t, 6H, $J = 7$ Hz: CH_2CH_3; 2.8, q, 6H, CH_2–N–CH_2CH_3; 3.65, s, 2H, CH_2 (indene); 3.8, s, 3H, OCH_3; 4.1, t, 2H, $J = 8$ Hz: OCH_2; 6.7–7.9, m, 12H, arom. Methanesulfonate: $C_{29}H_{35}NO_5S$; m.p. 267°C (methanol) (yield: 90%).

9f: $C_{29}H_{33}NO_3$; 138°C (ethanol); yield: 12%; ^{1}H NMR: 1.1, t, 12H, $J = 7$ Hz: CH_2CH_3; 2.8, q, 12H, CH_2–N–CH_2CH_3; 3.65, s, 2H, CH_2 (indene); 3.8, s, 3H, OCH_3; 4.1, t, 2H, $J = 8$ Hz: OCH_2; 6.4–7.8, m, 11H, arom. Methanesulfonate: $C_{30}H_{37}NO_6S$; m.p. 228°C (ethanol) (yield: 84%).

3.1.2. Preparation of indene (9g)

This compound was obtained by alkylation of the indene **8i** which in turn was prepared by demethylation with aluminium chloride from derivative **8h**.

3.1.3. Preparation of bis-2,3-(4-methoxyphenyl)indene (8h)

This derivative was prepared by a Grignard condensation of 4-methoxyphenylmagnesium bromide and 1-(4-methoxyphenyl)indan-2-one [22] according to a described procedure [2,23].

3.1.4. Preparation of bis-2,3-(4-hydroxyphenyl)indene (8i)

In a 100 ml dry round bottom flask, fitted with a magnetic stirring bar and a reflux condenser topped with a calcium chloride drying tube, a mixture of 2,3-(4-methoxyphenyl)indene) (**8h**) (1 g, 300 mmol) and aluminium chloride (120 mg, 900 mmol) was heated at 110°C (1 h). After cooling, diethyl ether (20 ml) was added and hydrolysis performed by addition of a 1 M hydrochloric acid aqueous solution (50 ml). The two phases are separated and the aqueous phase extracted with diethyl ether (3×30 ml portions). The mixed organic phases were washed to neutrality with a NaCl saturated aqueous solution, dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The residue was purified by column chromatography over silica gel (eluent DCM–ethanol, 98/2). Yield 750 mg (83%). This fraction was used directly for the preparation of indene **9g** by alkylation.

*3.1.5. Preparation of bis-2,3-(4-diethylamino-ethoxyphenyl)indene (**9g**)*

In a 500 ml dry round bottom flask fitted with a magnetic stirring bar and a reflux condenser topped with a calcium chloride drying tube, a mixture of the bis-hydroxylated indene **8i** (500 mg, 1.7 mmol), diethylaminoethylchloride hydrochloride (1.15 g, 6.7 mmol), sodium hydroxide (2.1 g, 25 mmol), tetrabutylammonium bromide (60 mg, 0.17 mmol), DCM (50 ml) and water (50 ml) was stirred (0°C, 1 h), then (r.t., 1 h) and overnight (40°C). After cooling, the organic phase was separated and the aqueous phase extracted with DCM (3×30 ml portions). The mixed organic solution was washed with water to neutrality, dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure. The residue was recrystallized.

9g: $C_{35}H_{42}N_2O_2$ m.p.: 209°C (methanol); yield: 640 mg (77%), ^{1}H NMR (DMSO): 1.1, t, 12H, $J = 7$ Hz: CH_2CH_3; 2.7, q, 8H, CH_2–N–CH_2CH_3; 3.6, s, 2H, CH_2 (indene); 4.1, t, 4H, $J = 8$ Hz: OCH_2; 6.6–7.5, 12H, arom.

3.1.6. Preparation of methanesulfonates

*3.1.6.1. **Typical procedure:** Bis-methanesulfonate of **9g**.* In a 100 ml dry round bottom flask fitted with a magnetic stirring bar and a reflux condenser topped with a calcium chloride drying tube were added, the indene **9g** (100 mg, 0.2 mmol) and methanesulfonic acid (50 mg, 0.52 mmol) and the mixture was refluxed (20 min). After cooling, the precipitate was collected by filtration and recrystallized in methanol. Bis-methanesulfonate: $C_{37}H_{50}N_2O_8S_2$ m.p.: 306°C (dec.) (methanol); yield: 134 mg (94%). IR: 2940, 2650, 2480 cm^{-1}.

3.2. Pharmacology

The evaluation of the antiproliferative activity was achieved by determination of the DNA concentration in estradiol-stimulated human MCF-7 breast cancer cells, according to a previously described procedure [24,26]. The results are expressed as a percentage of DNA decrease, relative to estradiol stimulated controls.

The study of the relative binding affinities to the steroid hormone receptors was performed according to the following procedures.

3.2.1. Binding assay

3.2.1.1. Compounds. The tritiated markers, estradiol (sp.act.: 1.48 TBq/mmol), R 5020 [(17β)-17-(1-oxopropyl)-17-methyl-estra-4,9-dien-3-one], (sp.act.: 2.07 TBq/mmol), testosterone (sp.act.: 2 TBq/mmol), RU 28362 [11β,17β-dihydroxy-6-methyl-17α-(propyl-1-ynyl) androst-1,4,6-trien-3-one] (sp.act.: 2.75 TBq/mmol) and aldosterone (sp.act.: 1.85 TBq/mmol) of estrogen (ER), progestin (PR), androgen (AR), glucocorticoid (GR) and mineralocorticoid (MR) receptors, respectively, were prepared by the Radiomolecules Department of Hoechst Marion Roussel (HMR), Romainville. Cold estradiol (HMR), progesterone (HMR), testosterone (HMR), dexamethasone (HMR) and aldosterone (Fluka) were used as reference hormones for ER, PR, AR, GR and MR, respectively.

3.2.1.2. Receptor preparation. Extracts of SF9 insect cells, in which the different human steroid receptor genes were transfected and expressed using recombinant baculovirus processing [25], were provided by Professor Chambon (Laboratoire de Génétique Moléculaire des Eucaryotes, Strasbourg). Briefly, cell extracts were prepared as follows:

SF9 cells were harvested, resuspended in a specific buffer (see below) and broken using two freeze–thaw (-80°C at 0°C) cycles. Protein extracts were ultracentrifuged between 0 and 4°C at 209 000*g* for 30 min, the supernatants or cytosols were aliquoted and kept in liquid nitrogen until use.

Specific buffers:

Estrogen receptor: 20 mM Tris–HCl pH 8, EDTA 0.5 mM, DTT 2 mM, glycerol 20%, KCl 400 mM, PIS 1‰ (protease inhibitor solution containing the following peptides Sigma at a concentration of 2.5 μg/ml: aprotinine, leupeptine, antipain, chymostatine and pepstatine).

Progestin receptor: 20 mM Tris–HCl pH 8, EDTA 0.5 mM, DTT 2 mM, glycerol 20%, KCl 400 mM, PIS 1‰.

Androgen receptor: 20 mM Tris–HCl pH 7.5, EDTA 1 mM, PMSF 0.1 mM, sodium molybdate 20 mM, glycerol 10%, PIS 1‰.

Glucocorticoid receptor: mono potassium phosphate 50 mM–NaOH pH 7, glycerol 20%, DTT 5 mM, sodium molybdate 20 mM, PIS 1‰.

Mineralocorticoid receptor: 20 mM Tris–HCl pH 7.4, glycerol 10%, sodium tungstate 20 mM, EDTA 1 mM, PIS 1‰.

3.2.1.3. Relative binding affinities (RBA). The cytosols of insect cell extracts were diluted (in TSG buffer: 10 mM Tris–HCl pH 7.4, sucrose 0.25 M, gelatine 1‰, for ER, PR and MR; in TSG buffer containing DTT 2 mM, sodium molybdate 20 mM, PMSF 0.1 mM for AR; in TSG buffer containing DTT 2 mM, sodium molybdate 20 mM for GR) to a final receptor concentration of 0.5–0.7 nM. Aliquots of 125 μl were incubated for 24 h at 0°C with 2.5 or 5.0 nM of the relevant ^{3}H-ligand (^{3}H-estradiol for ER, ^{3}H-R 5020 for PR, ^{3}H-testosterone fo AR, ^{3}H-RU 28362 for GR and ^{3}H-aldosterone for MR) in the presence of increasing concentrations (1–25000 nM) of cold reference or test compounds. After incubation, the bound tritiated lig-

Table 2
Relative binding affinities to steroid receptors and antiproliferative activity

Compounds	Glucocorticoid and mineralocorticoid receptors 4H/0°C 24H/0°C[a]	Progesterone receptor 2H/0°C 24H/0°C[a]	Androgen receptor 4H/0°C 24H/0°C[a]	Estrogen receptor 2H/0°C 5H/0°C[a]	Antiproliferative action on MCF-7 cells at 10^{-6} M[b]
9a	0	0	0	0	0
	0	0	0.02	0.01	−15%
9b	0	0	0	0	0
	0	0	0	0	0
9c	0	0.04	0	0	0
	0	0.2	0	0	0
9d	0	0	0	0	0
	0	0	0	0	0
9e	0	0	0	0.1	−6%
9f	0	0	0	0.1	−6%
9g	0	0.03	0	0	0
	0	0	0	0	0

[a] At 0°C: Dexamethasone = 100; Aldosterone = 100; Progesterone = 100; Testosterone = 100; Estradiol = 100.
[b] The negative sign indicates an antiproliferative activity (Estradiol = 100% enhancement of proliferative effect).

and was measured by the dextran-coated charcoal (DCC) adsorption technique (26): a 0.1 ml aliquot of incubated cytosol was stirred for 10 min with 0.1 ml DCC solution (1.25% NoritA charcoal and 0.625% dextran T70 in TSG buffer) in a 96 well microtitration plate and centrifuged for 10 min at 800*g*. The radioactivity of a 0.1 ml supernatant sample was counted.

RBA calculation: the RBA was defined as the ratio of the concentration of the reference compound over the concentration of the competitor required to inhibit ^{3}H-ligand binding by 50% and multiplied by 100. The RBAs of estradiol, progesterone, testosterone, dexamethasone and aldosterone were taken as equal to 100.

4. Results and discussion

The study of the relative binding affinity to steroid receptors of the prepared hydrochlorides and methanesulfonates of compounds **9a–g** led to the results presented in Table 2.

The examination of the data reported in Table 2, indicates the absence of any binding affinity to the glucocorticoid and mineralocorticoid receptors and a weak binding affinity to progesterone, androgen and estrogen receptors for compounds **9a**, **9c**, **9e**, **9f** and **9g**. Furthermore, only compounds **9a**, **9e**, **9f** present a binding affinity to the estrogen receptor and an antiproliferative activity on MCF-7 cells ranging from 6% for compounds **9e** and **9f** presenting both a 6-methoxy group and a 3-phenyl group for **9e** and a 3-(4-methoxyphenyl) group for **9f** to 15% for compound **9a** substituted by a 6-methoxy group and a 3-ethyl group. The presence of a 6-methoxy group on the indene ring is therefore an interesting substitution which increases the receptor binding affinity to the estrogen receptor. This result is not surprising as it is the surrogate for the A ring of estradiol in binding to the estrogen receptor.

In conclusion, this study indicates that the substitution by a basic 4-(dialkylaminoethoxy)phenyl group at the 2-position of indenes leads to a weak estrogen receptor binding affinity and to a weak antiproliferative activity on human mammary MCF-7 tumor cells. These results could be the consequence of the more planar structure of these indene derivatives than the known triarylethylenes and their antiestrogen analogues and to the non ionic character of the corresponding binding site of the estrogen receptor.

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