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# DESIGN AND SYNTHESIS OF TWO 3-AZA-BICYCLO[3.3.1]NONENE-ESTRONE DERIVATIVES

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**Abstract**
Several 3-Aza-bicyclo[3.3.1]nonene derivatives have been prepared; however, some methods use expensive reagents and require special conditions. The aim of this study is to synthesize two new 3-Aza-bicyclo[3.3.1]nonene-estrone derivatives using a series of reactions which involve; *i*) imination; *ii*)cyclization; *ii*) addition. Chemical structure of the compounds was confirmed using elemental analysis and NMR spectrum. In conclusion, in this study, is reported a facile synthesis of two 3-Aza-bicyclo[3.3.1]nonene-steroid derivatives.

**Keywords:** Steroid, bicycle, estrone, cyclization.

## Introduction

For several years, some bicycle-derivatives with biological activity have been prepared to different clinical pathologies such as pain[i], infections[ii], cancer[iii], hypertension[iv] and others. It is noteworthy, that several 3-Aza-bicyclo[3.3.1]nonene analogs have been developed[v,vi]; for example, the synthesis of (1*S*,5*R*,6*S*)-2,2,6-trimethyl-3-aza-bicyclo[3.3.1]non-3-en-6-yl acetate by the reaction of (-)-β-pinene in presence of KCN[vii]. Other study shown the condensation of 5-acetonyl-4,6-bis(aci-nitro)-2-cyclohexenone with formaldehyde and a primary amine to form the 9-acetonyl-3-methyl-1,5-dinitro-3-azabicyclo[3.3.1]non-6-en-8-one[viii]. In addition, other report showed the preparation of 7-benzyl-3-thia-7-azabicyclo [3.3. 1] nonan-9-one from 4-thianone and benzylamine[ix]. Another report indicate theCu(bpy)Cl-catalysed*N*-acyliminium ion cyclisation to form a 3-azabicyclo[3.3.1]non-6-ene[x]. Additionally, a N-Arylmethyl-3-azabicyclo[3.3.1]nonan-9-one was prepared using a multicomponent system (cycohexanone, benzylamine and formaldehyde)[xi]. Recently was

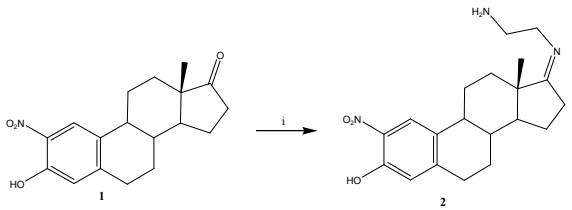
synthetized the 3-(2-amino-ethyl)-1,5-dinitro-9-(3-oxobutyl)-3-aza-bicyclo[3.3.1]non-6-ene-7-carboxylic acid from 3,5-dinitrobenzoic acid, ethylenediamine and formaldehyde[xii]. All these data indicate the preparation of several 3-azabicyclo[3.3.1]nonane derivatives; however, there is scarce information on the synthesis of steroids bound to 3-Azabicyclo [3.3.1]nonane system. Therefore, the aim of this study was synthesize two 3-azabicyclo[3.3.1]non-6-ene-7-carboxamide-steroid derivatives using some chemical tools.

## Results and Discussion

In this study, two azabicyclo[3.3.1]nonane-estrone derivatives were prepared using the following chemical strategies:

### *Preparation of an imino-steroid derivative*

There are methods for synthesis of imino groups which use several reagents such as chloroacetyl chloride/triethylamine[xii], iodine[xiv], salicylaldehyde[xv], acetic acid[xvi], boric acid[xvii] and others. In this study, 2-nitroestrone reacted with ethylenediamine to form an amino-steroid derivative (compound 2) using boric acid as catalyst.




1 2

**Figure 1**. Reaction of 2-nitroestrone (**1**) with ethylenediamine (i) to form the (13S,Z)-17-((2-aminoethyl)-imino)-13-methyl-2-nitro-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-ol (**2**)

The $^{1}$H NMR spectrum of **2** shows signals at 1.00 ppm for methyl group bound to steroid nucleus; at 1.22-3.00, 6.66-8.10 ppm for steroid moiety; at 3.10-3.50 ppm for methylene groups bound to both amino groups; 6.10 ppm for both amino and hydroxyl groups. $^{13}$C NMR spectra showed chemical shifts at 15.72 ppm for methyl group bound to steroid nucleus; at 21.94-37.62, 41.05-44.10 and 54.26-148.50 ppm for steroid moiety; at 41.00-54.14 ppm for methylene groups bound to both amino groups; at 176.82 ppm for imino group. In addition, the mass spectrum from **2** showed a molecular ion (m/z) 357.20.

### *Synthesis of a fluoro-3-Aza-bicyclo[3.3.1]non-6-ene derivative*

Several 3-Aza-bicyclo[3.3.1]none analogs have been synthesized using some reagents such as methyl iodide[xviii] $H_2SO_4$[xix], Pd/C[xx], monocyclic urethane[xxi] and others. Analyzing these data and other report which indicate the preparation of a 3-Aza-bicyclo[3.3.1]none using some multicomponent systems[xii]; therefore, in this study the fluoro-3-Aza-bicyclo[3.3.1]non-6-ene derivative (compound **4**) was prepared using the multicomponent system (3,5-dinitrobenzoic acid, sodium ethoxide, ethylenediamine and formaldehyde). The $^{1}$H NMR spectrum of **4** shows signals at 1.04 ppm for amino group; at 2.10 ppm for methyl group bound to ketone; at 2.74-2.82 ppm for methylene group bound to both 3-Aza-bicyclo[3.3.1]non-6-ene and ketone group; at 2.50, 2.73, 2.88 and 3.60-6.40 for 3-Aza-bicyclo[3.3.1]non-6-ene; at 2.66 and 3.06 for methylene groups bound to both amino groups. $^{13}$C NMR spectra showed chemical shifts at 29.72 ppm for methyl group; at 32.44, 50.72-57.94 and 89.77-155.02 ppm for 3-Aza-bicyclo[3.3.1]non-6-ene; at 37.94 ppm for methylene group bound to both 3-Aza-bicyclo[3.3.1]non-6-ene and ketone group; at 39.40 and 58.25 ppm for methylene groups bound to bot amino groups; at 209.88 ppm for ketone group. Additionally, the mass spectrum from **4** showed a molecular ion (m/z) 330.13. It is important to mention that in this study was

not observed the dimer 1,1'-(ethane-1,2-diylbis(6-fluoro-1,5-dinitro-3-azabicyclo[3.3.1]non-6-ene-3,9-diyl))bis(propan-2-one) (compound **5**),

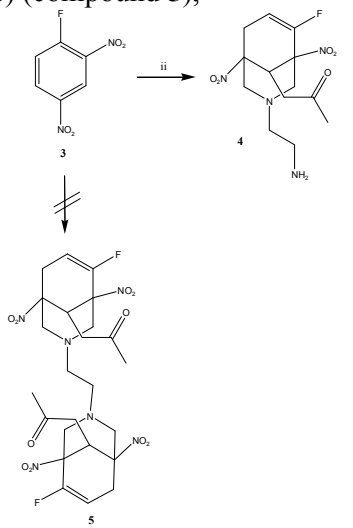


**Figure 2**. Synthesis of the 4-(3-(2-aminoethyl)-6-fluoro-1,5-dinitro-3-azabicyclo[3.3.1]non-6-en-9-yl)butan-2-one (**4**) using the multicomponent system [3,5-dinitrobenzoic acid (**3**), sodium ethoxide, ethylenediamine and formaldehyde [ii]). The compound 1,1'-(ethane-1,2-diylbis(6-fluoro-1,5-dinitro-3-azabicyclo[3.3.1]non-6-ene-3,9-diyl))bis(propan-2-one) (**5**)was not observed.

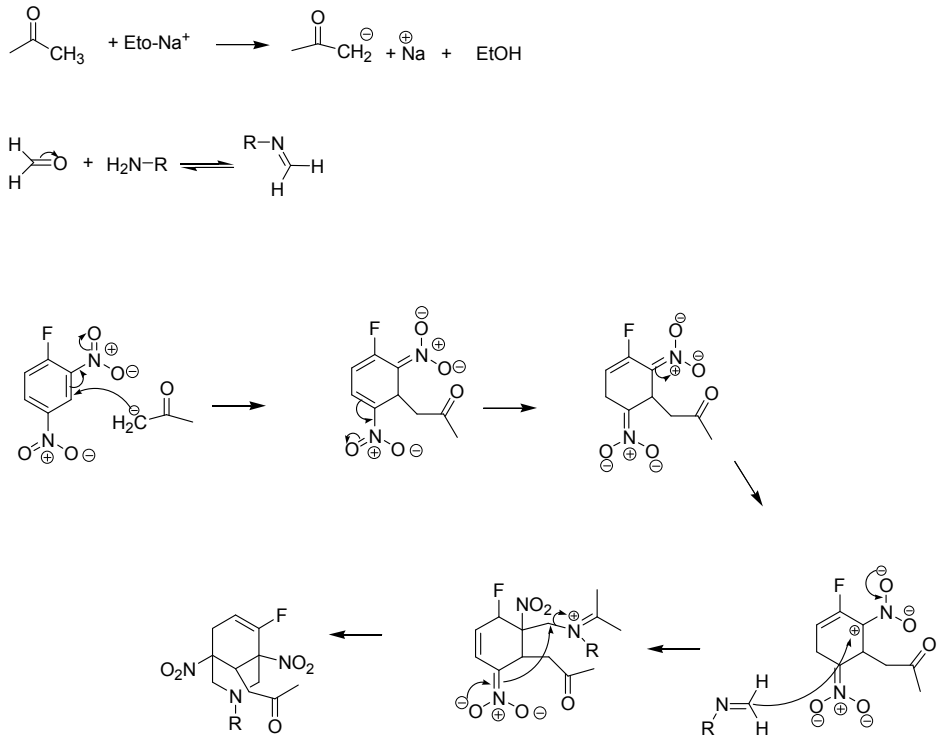


**Figure 3**. Mechanism of reaction involved in the synthesis of compound **4 (**4-(3-(2-aminoethyl)-6-fluoro-1,5-dinitro-3-azabicyclo[3.3.1]non-6-en-9-yl)butan-2-one).

***Preparation of two fluoro-3-Aza-bicyclo[3.3.1]non-6-ene-steroid derivatives***

In this study, the compound **4** reacted with **2** using boric acid as catalyst (Method A) to form a fluoro-3-Aza-bicyclo[3.3.1]non-6-ene-nitroestrone (compound **6**).The $^{1}$H NMR spectrum of **6** shows signals at 1.00 ppm for methyl group bound to steroid nucleus; at 2.08 ppm for methyl group bound to ketone; at 1.22-2.06, 2.09-2.25, 2.75-2.80, 3.02 and 6.66-8.10 ppm for steroid moiety; at 2.74 and 2.83 ppm for methylene group bound to both 3-Aza-bicyclo[3.3.1]non-6-ene and ketone group; at 2.50-2.73, 2.88 and 3.62-6.40 for 3-Aza-bicyclo[3.3.1]non-6-ene; at 3.18 and 3.50 ppm for methylene groups bound to both amino groups; at 9.56 ppm for hydroxyl group.

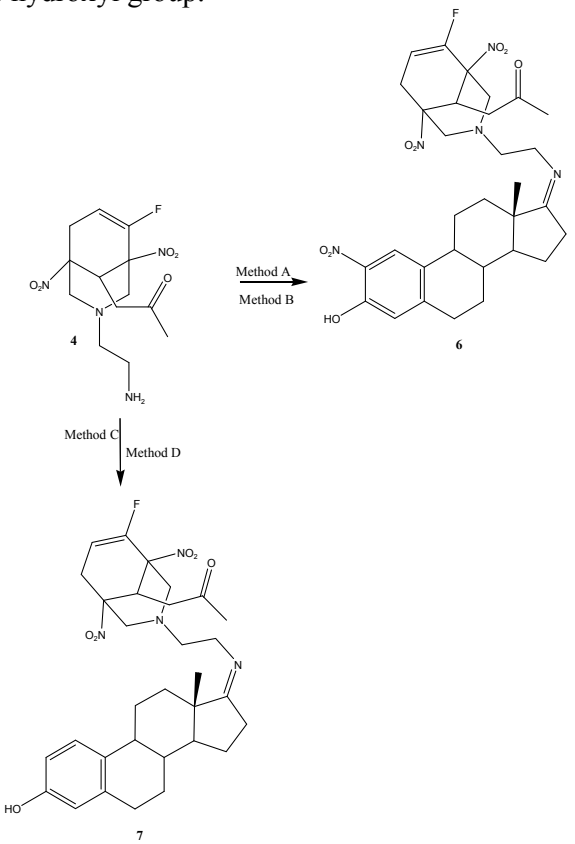



**Figure 4**.Synthesis of 4-(6-fluoro-)-2-nitroestrone-1,5-dinitro-3-azabicyclo- [3.3.1]non-6-en-9-yl)butan-2-one (**6**) using the multicomponent system (1-fluoro-2,4-dinitrobenzene,sodium ethoxide andformaldehyde) [Method A]. Also **6**was prepared via reaction of compound **2**with **4** [Method B]. After, the compound **4** reacted with estrone [Method C] in presence of boric acid to form the 1-{6-fluoro-estrone-1,5-dinitro-3-azabicyclo[3.3.1]non-6-en-9-yl}propan-2-one (**7**). Finally, **7**[Method D]was prepared using a multicomponent system (estrone-ethylenediamine, 1-fluoro-2,4-dinitrobenzene, sodium ethoxide and formaldehyde)

$^{13}$C NMR spectra showed chemical shifts at 15.74 ppm for methyl group bound to steroid nucleus; at 29.72 ppm for methyl group bound to ketone; at 21.94-26.00, 29.82-32.40, 33.90-37.62, 41.02-44.12, 54.30, 114.02-148.50 ppm for steroid moiety; at 32.46, 50.76, 55.17-110.34 and 155.02 ppm for 3-Aza-bicyclo[3.3.1]non-6-ene; at 50.84 and 54.24 ppm for both amino groups; at 37.92 ppm for methylene group bound to both 3-Aza-bicyclo[3.3.1]non-6-ene and ketone group; at 176.82 ppm for imino group; at 202.90 ppm for ketone group. Finally, the mass spectrum from **6** showed a molecular ion (m/z) 627.27. Also **6**was prepared via reaction of compound **2** with **4** [Method B]in presence of boric. It is important to mention, that yielding was higher in the Method B compared with method A.Finally, the RMN spectra were similar in both methods.

On the other hand, the 1-{6-fluoro-estrone-1,5-dinitro-3-azabicyclo[3.3.1]non-6-en-9-yl}propan-2-one (**7**) was prepared via reaction of compound **4** reacted with estrone [Method C] using boric acid as catalyst. The $^{1}$H NMR spectrum of **7** shows signals at 1.00 ppm for methyl group bound to steroid nucleus; at 2.08 ppm for methyl group bound to ketone; at 1.22-2.06, 2.09-2.26, 2.60, 2.75-2.80 and 6.66-7.42 ppm for steroid moiety; at 2.74 and 2.83 ppm for methylene groups bound to both 3-Aza-bicyclo[3.3.1]non-6-ene and ketone group; at 2.50, 2.73, 2.88, 3.62-4.32 and 6.40 for 3-Aza-bicyclo[3.3.1]non-6-ene; at 3.18 and 3.50 ppm for methylene groups bound to both amino groups; at 5.56 ppm for hydroxyl group.$^{13}$C NMR spectra showed chemical shifts at 15.76 ppm for methyl group bound to steroid nucleus; at 29.72 ppm for methyl group bound to ketone; at 37.94 ppm for methylene group bound to both 3-Aza-bicyclo[3.3.1]non-6-ene and ketone group; at 21.96-29.06, 32.42, 33.91-37.62, 41.02-43.32, 54.29, 112.61-153.97 ppm for steroid moiety; at 32.48, 50.75, 55.16-110.34 and 155.02 ppm for 3-Aza-bicyclo[3.3.1]non-6-ene; at 50.88 and 54.24 ppm for both amino groups; at 176.88 ppm for imino group; at 202.90 ppm for ketone group. Finally, the mass spectrum from **7** showed a molecular ion (m/z) 582.28.

***Method D:***

The 1-{6-fluoro-estrone-1,5-dinitro-3-azabicyclo[3.3.1]non-6-en-9-yl}propan-2-one (**7**) was prepared using a multicomponent system (estrone-ethylenediamine, 1-fluoro-2,4-dinitrobenzene, sodium ethoxide and formaldehyde)[Method D]. It is important to mention, that yielding was higher in the Method C compared with method D.Finally, the RMN spectra were similar in both methods.

***Physicochemical parameters evaluation***

There are several structure-activity studies which suggest that some physicochemical factors are involved in the activity of several compounds, such as hydrogen bond donor groups. (HBD) and hydrogen bond acceptor groups (HBA) may exert also changes on some biological system[xxii]. In this regard, these physicochemical descriptors have been evaluated using some pharmacophore models[xxiii,xxiv]; It is important to mention that pharmacophores are generally used to evaluate some chemical characteristics that are related with the biological activity of several molecules; therefore, in this study a theoretical study was carried out using a pharmacophore model[xxv]. The theoretical results (Figure 5, Table 1) showed several hydrogen bond acceptor groups for compound **2** (fluor, ketone, nitro) and a hydrogen bond donor group (amino); for compound **6**several hydrogen bond acceptor groups (imino, nitro and ketone groups); and a hydrogen bond donor group (hydroxyl).

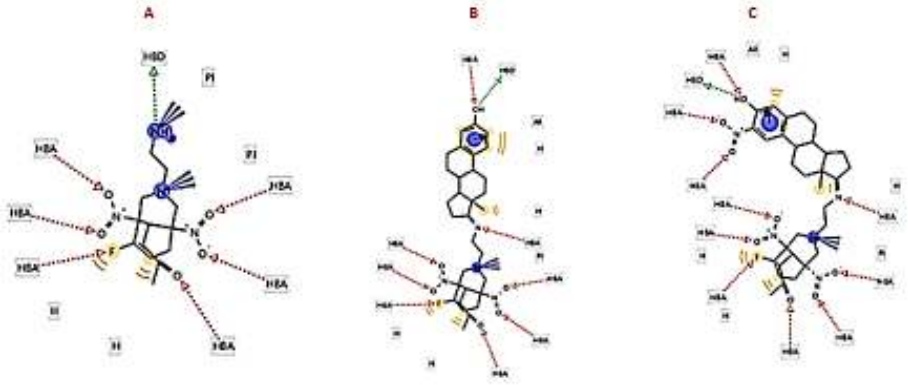



**Figure 5**. Scheme represents a pharmacophore from compounds **2** (A), **6** (B) and **7** (C) using the LigandScout software. The model involves a methyl group (yellow) hydrogen bond acceptors (HBA, red), hydrogen bond donor (HBD, green) and a positive ionizable (PI).

Another results shown some hydrogen bond acceptor groups for compound **7** (imino, nitro and ketone) and a hydrogen bond donor group (hydroxyl).Analyzing these results and other reports about Lipinski's rule which indicates that both HBD and HBA can condition some pharmacokinetic process of drugs in the human body[xxvi]; these data suggest that compounds **6** or **7**could have the ability of penetrate some barrier biological of human body

**Table 1**. Physicochemical parameters involved in the chemical structure of compounds **2**,**6** and **7**.

| Parameter | Compound **2** | Compound **6** | Compound **7** |
|---|---|---|---|
| Rotable | 8 | 11 | 10 |
| cLog | 0.14 | 4.79 | 4.888 |
| TPSA | 149.95 | 208.33 | 156.20 |
| HBA | 6 | 10 | 8 |
| HBD | 1 | 1 | 1 |

Hydrogen bond acceptor (HBA); hydrogen bond donator (HBD); topological polar surface area (TPSA);partition coefficient (cLog).

However, it is noteworthy that the rule does not predict if a compound could be pharmacologically active; therefore, other type of studies must be carried out to determine the interaction between some compounds with several biological targets such as proteins or enzymes.

**Acknowledgements**
None

## Experimental

### *General methods*

The estrone-ethylenediaminewas prepared by a previously reported method[xxvii]. In addition, all the reagents used in this study were purchased from Sigma-Aldrich Sigma-Aldrich Co., Ltd. The melting point for compounds was evaluated on an Electrothermal (900 model). Infrared spectra (IR) were determined using KBr pellets on a Perkin Elmer Lambda 40 spectrometer.$^{1}$H and $^{13}$C NMR (nuclear magnetic resonance) spectra were recorded on a Varian VXR300/5 FT NMR spectrometer at 300 and 75.4 MHz (megahertz) in $CDCl_3$ (deuterated chloroform) using TMS (tetramethylsilane) as an internal standard. EIMS (electron impact mass spectroscopy) spectra were determined using a Finnigan Trace Gas Chromatography Polaris Q-Spectrometer. Elementary analysis data were determined from a Perkin Elmer Ser. II CHNS/02400 elemental analyzer.

### *Chemical synthesis***.**

**(13S,Z)-17-((2-aminoethyl)imino)-13-methyl-2-nitro-7,8,9,11,12,13,14,15,16,17-deca-hydro-6H-cyclopenta[a]phenanthren-3-ol (2)**

A solution of 2-nitroestrone (180 mg 0.57 mmol), ethylenediamine (90 µl; 1.50 mmol), boric acid (50 mg, 0.80 mmol), and 5 ml of methanol was stirring for 72 h at room temperature. The mixture obtained was dried under reduced pressure and purified by crystallization using the methanol:water:hexane (4:1:1) system; yielding 56 %; m.p. 210-212 $^{o}$C; IR ($V_{max}$, $cm^{-1}$) 3400, 3380, 3320, and 1540: $^{1}$H NMR (300 MHz, Chloroform-*d*) $\delta_H$: 1.00 (s, 3H), 1.22-3.00 (m, 15H), 3.10-3.50 (m, 4H), 6.10 (broad, 3H), 6-66-8.10 (m, 2H) ppm. 15.72, 21.94, 25.76, 26.00, 29.82, 32.44, 33.90, 37.62, 41.00, 41.05, 44.10, 54.14, 54.26, 114.02, 124.68, 132.30, 133.80, 146.22, 148.50, 176.82 ppm. EI-MS m/z: 357.20. Anal. Calcd. for $C_{20}H_{27}N_3O_3$: C, 67.20; H, 7.61; N, 11.76; O, 13.43. Found: C, 67.14; H, 7.57.

**1-[3-(2-aminoethyl)-6-fluoro-1,5-dinitro-3-azabicyclo[3.3.1]non-6-en-9-yl]propan-2-one (4)**

A solution of 1-fluoro-2,4-dinitrobenzene (100 µl, 0.79 mmol), ethylenediamine (90 µl; 1.50 mmol), sodium ethoxide (60 µl, 0.76 mmol), and 5 ml of formaldehyde was stirring for 72 h to reflux. The mixture obtained was dried under reduced pressure and purified by crystallization using the methanol:water (4:1) system;yielding 44 %; m.p. 172-174 $^{o}$C; IR ($V_{max}$, $cm^{-1}$) 3382, 1705, and 1542: $^{1}$H NMR (300 MHz, Chloroform-*d*) $\delta_H$: 1.04 (broad, 2H), 2.10 (s, 3H), 2.50 (m, 1H), 2.66 (m, 2H), 2.73 (m, 1H), 2.74-2.82 (m, 2H), 2.88 (m, 1H), 3.06 (m, 2H), 3.60-4.32 (m, 4H), 6.38 (d, 1H, J = 3.97 Hz) ppm. $^{13}$C NMR (500 MHz, Chloroform-*d*) $\delta_C$: 29.72, 32.44, 37.94, 39.40, 50.72, 55.12, 57.94, 58.25, 89.77, 91.90, 110.37, 155.02, 209.88 ppm. EI-MS m/z: 330.13. Anal. Calcd. for $C_{13}H_{19}FN_4O_5$: C, 47.27; H, 5.80; F, 5.75; N, 16.96; O, 24.22. Found: C, 47.22; H, 5.76.

**1-{6-fluoro-3-[2-({7-hydroxy-11a-methyl-8-nitro-2H,3H,3aH,3bH,4H,5H,9bH,10H, 11H-cyclopenta[a]phenanthren-1-ylidene}amino)ethyl]-1,5-dinitro-3-azabicyclo[3.3.1] non-6-en-9-yl}propan-2-one (6)**

***Method A:***

A solution of compound **2**(200 mg, 0.56 mmol),1-fluoro-2,4-dinitrobenzene (80 µl, 0.63 mmol),sodium ethoxide (60 µl, 0.76 mmol), and 5 ml of formaldehyde was stirring for 72 h to reflux. The mixture obtained was dried under reduced pressure and purified by crystallization using the methanol:water (4:1) system;yielding 56 %; m.p. $^{o}$C; 178-180; IR ($V_{max}$, $cm^{-1}$) 3402, 3320, 1707, and 1540: $^{1}$H NMR (300 MHz, Chloroform-*d*) $\delta_H$: 1.00 (s, 3H), 1.22-2.06 (m, 7H), 2.08 (s, 3H), 2.09-2.25 (m, 4H), 2.50-2.73 (m, 2H), 2.74 (m, 1H), 2.75-2.80 (m, 3H), 2.83 (m, 1H), 2.88 (m, 1H), 3.02 (m, 4H), 3.18-3.50 (m, 4H), 3.62-4.32 (m, 4H), 6.40 (d, 1H, J = 3.97 Hz), 6.66-8.10 (m, 2H), 9.56 (broad, 1H) ppm. $^{13}$C NMR (500 MHz, Chloroform-*d*) $\delta_C$: 15.74, 21.94, 25.78, 26.00, 29.72, 29.82, 32.40, 32.46, 33.90, 37.62, 37.92, 41.02, 44.12, 50.76, 50.84, 54.24, 54.30, 55.17, 57.97, 89.77, 91.92, 110.34, 114.02, 124.68, 132.33, 133.82, 146.22, 148.50, 155.02, 176.82, 202.90ppm. EI-MS m/z: 627.27. Anal. Calcd.for $C_{31}H_{38}FN_5O_8$: C, 59.32; H, 6.10; F, 3.03; N, 11.16; O, 20.39. Found: C, 59.28; H, 6.06.

***Method B:***

A solution of compound **4** (200 mg, 0.58 mmol), 2-nitroestrone (180 mg, 0.57 mmol), boric acid (50 mg, 0.80 mmol) and 5 ml of methanol was stirring for 72 h at room temperature.The mixture obtained was dried under reduced pressure and purified by crystallization using the methanol:water (4:1) system; yielding 65 %. In addition, similar $^{1}$H NMR and $^{13}$C NMR data were obtained compared with method A product.

**1-{6-fluoro-3-[2-({7-hydroxy-11a-methyl-2H,3H,3aH,3bH,4H,5H,9bH,10H,11H-cyclopenta[a]phenanthren-1-ylidene}amino)ethyl]-1,5-dinitro-3-azabicyclo[3.3.1]non-6-en-9-yl}propan-2-one (7)**

***Method C:***

A solution of compound **4** (200 mg, 0.58 mmol), estrone (180 mg, 0.66 mmol), boric acid (50 mg, 0.80 mmol) and 5 ml of methanol was stirring for 72 h at room temperature. The mixture obtained was dried under reduced pressure and purified by crystallization using the methanol:water (4:1) system; yielding 68 %;m.p. 128-130$^{o}$C;IR ($V_{max}$, $cm^{-1}$) 3400, 3322, 1705, and 1540: $^{1}$H NMR (300 MHz, Chloroform-*d*) $\delta_H$: 1.00 (s, 3H), 1.22-2.06 (m, 7H), 2.08 (s, 3H), 2.09-2.26 (m, 4H), 2.50 (m, 1H), 2.60 (m, 1H), 2.73 (m, 1H), 2.74 (m, 1H), 2.75-2.80 (m, 3H), 2.83 (m, 1H), 2.88 (m, 1H), 3.18-3.50 (m, 4H), 3.62-4.32 (m, 4H), 5.56 (broad, 1H), 6.40 (d, 1H, J = 3.97 Hz), 6.56-7.42 (m, 3H) ppm. $^{13}$C NMR (500 MHz, Chloroform-*d*) $\delta_C$: 15.74, 21.96, 25.79, 26.00, 29.06, 29.72, 32.41, 32.48, 33.91, 37.62, 37.94, 41.02,

43.32, 50.75, 50.88, 54.24, 54.29, 55.17, 57.97, 89.77, 91.92, 110.34, 112.61, 114.85, 125.64, 130.74, 135.38, 153.97, 155.02, 176.88, 202.90ppm. EI-MS m/z: 582.28. Anal. Calcd.for $C_{31}H_{39}FN_4O_6$: C, 63.90; H, 6.75; F, 3.26; N, 9.62; O, 16.48. Found: C, 63.86; H, 6.70.

***Method D:***

A solution of estrone-ethylenediamine(200 mg, 0.56 mmol), 1-fluoro-2,4-dinitrobenzene (80 µl, 0.63 mmol), sodium ethoxide (60 µl, 0.76 mmol), and 5 ml of formaldehyde was stirring for 72 h to reflux.The mixture obtained was dried under reduced pressure and purified by crystallization using the methanol:water (4:1) system; yielding 44 %; Finally, similar $^{1}H$ NMR and $^{13}C$ NMR data were obtained compared with method C product.

***Physicochemical parameters evaluation***

The parameters hydrogen bond acceptor (HBA), hydrogen bond donator (HBD), topological polar surface area (TPSA) and partition coefficient (cLog) of compound 5, 6, anastrozole and exemestane were evaluated using LigandScout software 4.3[xxviii].

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