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# SYNTHESIS OF 3-METHYL-7-[2-(DIMETHYLAMINOETHYL)OXIMINO]-5-ARYLCYCLOPENTA [F] BENZOXAZOLINONES, POTENTIAL LIGANDS OF THE $5HT_{1D}$ RECEPTORS

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**ABSTRACT**: The synthesis of 3-methyl-7-[2-(dimethylaminoethyl)oximino]-5-arylcyclopenta[f] benzoxazolinones, potential ligands of the $5HT_{1D}$ receptors is described through a 4 steps reaction strategy from 3-methyl -6-acetyl benzoxazolinone.

In man,the neurotransmitter serotonin (5-hydroxytryptamine, 5-HT, Figure 1) occurs in most tissues of the body . The large family of 5HT receptors provides important therapeutical targets.[1] Thus, 5HT has been implicated in some diseases like disorders of the central nervous system and migraine.[2] The $5HT_{1D}$ recognition site is one of the discovered

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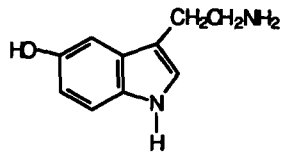
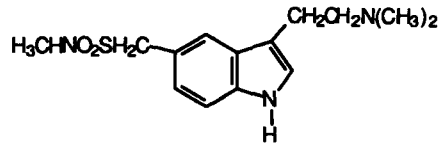
$5HT_1$ subtypes. It's interest in the area of migraine therapy increased with the introduction of the anti-migrainous drug sumatriptan (see Figure 1)which is one of the most potent and selective 5-$HT_{1D}$ receptor agonists.[3] However, some of sumatriptan's clinical side effects may be related to a lack of vascular selectivity.

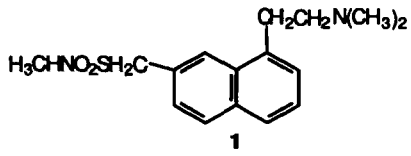
Our interest in the research of serotonin receptors ligands have focused on the synthesis of broad number of compounds of different chemical classes[4,5] that have high affinity for 5HT receptors and that can act as agonists or antagonists. For example, a program was initiated in our laboratories with the objective of identifying novel series of potent 5HT ligands. Thus, some benzoxazolinonic derivatives have revealed interesting properties toward the $5HT_{1A}$ and $5HT_{2A}$ recognition sites.[6] On the other hand , knowing that naphthalene is a stable bioisostere of the indole ring,[7] one of our strategies involved this bioisosteric replacement of the indole nucleus of the 5-$HT_{1D}$ agonist sumatriptan[8] and the study of compound1(Figure1) for 5-$HT_{1D}$ affinity and vascular selectivity . In fact, 1 is a brain $5HT_{1D}$ agonist that interact selectively with the sapheneous vein.




Serotonin



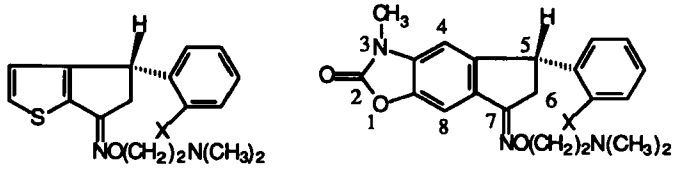

Sumatriptan




1

**Figure 1**

Recently,[9] a new original chemical family of highly selective 5HT$_{1D}$ agonists was described with the oxime ethers **2a-b** (Figure 2) that showed higher potency and better selectivity profile than sumatriptan . A considerable interest has so evinced for the variation of the thienyl ring moiety of these compounds and it occured to us that the replacement of this aromatic portion by the 5HT benzoxazolinonic pharmacophore (Compounds **3a-b** in figure **2**) should be of interest.



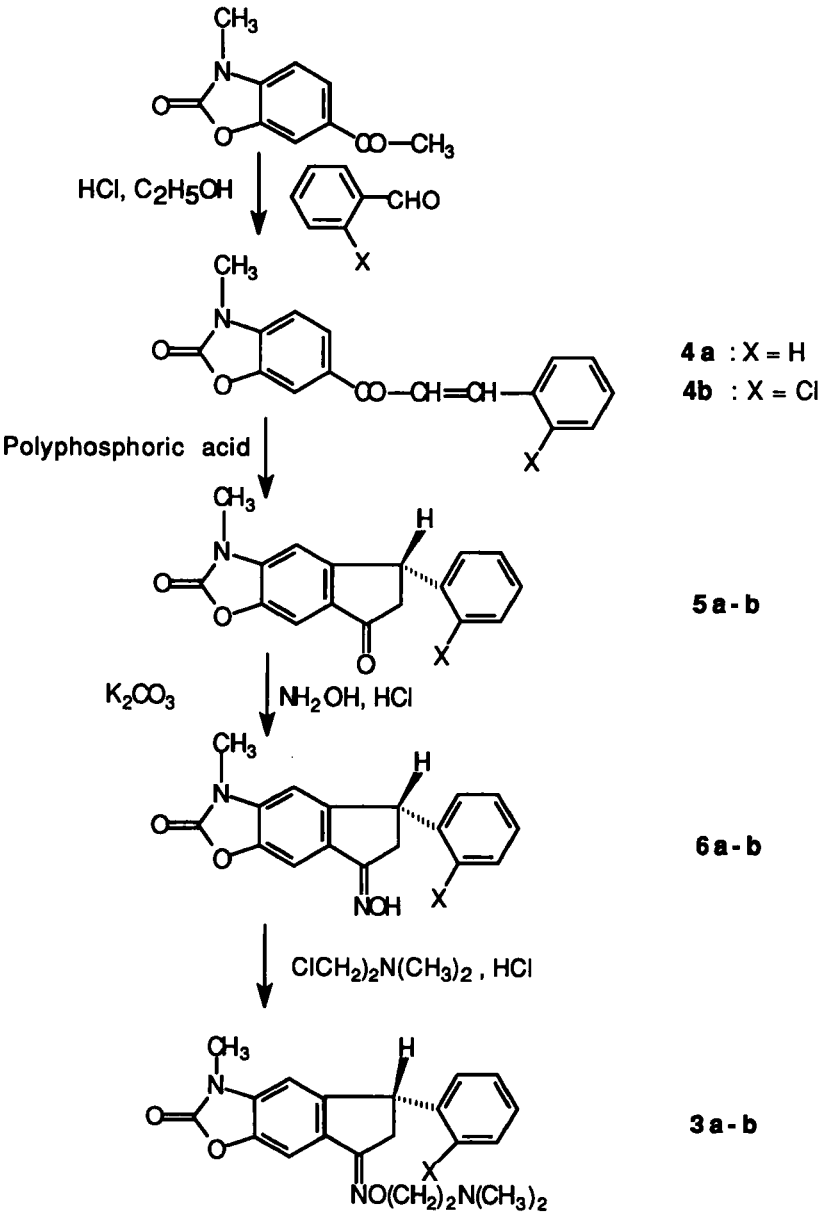

**2a** : X = H
**2b** : X = Cl

**3a** : X = H
**3b** : X = Cl

**Figure 2**

Therefore we embarked on a general approach to such benzoxazolinonic derivatives and herein we report the results of our investigation.

The synthesis (Scheme 1) used 6-acetyl-3-methyl benzoxazolinone[10] as starting material. By reaction with benzaldehyde under crotonisation conditions, in acidic medium (gazeous HCl), the chalcones **4a-b** were obtained with a higher yield (65-75%) compared with those obtained by use of NaOH as catalyst[11] (35% yield). These chalcones led with a moderate yield (30-40%) to the indanones **5a-b** by heating in polyphosphoric acid.[12] To access to the corresponding oximes **6a-b**, reaction with hydroxylamine hydrochloride in the presence of potassium carbonate[13] (65% yield) or sodium acetate (45% yield) in an hydroalcoolic medium was performed




**Scheme 1**

Configurations of oximes **6a-b** was determined by NOESY NMR spectroscopy. In the case of **6a**, a coupling observed between the OH proton and the H-6a cyclanic one seemed to indicate a preferential antistereochemistry whereas in the case of the chloro analogue **6b**, coupling observed between the OH proton and the H-8 aromatic one indicated a preferential syn stereochemistry. For both compounds, coupling values of the H-5 cyclanic proton indicated a preferential pseudo equatorial configuration for the phenyl ring in this position. To access to the target compounds **3a-b,** etherification of the oximes with use of an excess of $Ag_2O$ [14] and 2-chlorodimethylaminoethane in THF was successful with a moderate yield (30%). Finally , the simplest condition[15] was heating one equivalent of the oxime with 6 equivalent of the amine hydrochloride, in acetonitrile or dioxane, in the presence of 8 equivalents of $K_2CO_3$. The biological characteristics of **3a-b** are presently under study.



## EXPERIMENTAL PART

Melting points were taken on a BÜCHI 570 capillary apparatus and are uncorrected. Infrared spectra were obtained from a PERKIN-ElMER 297 spectrophotometer on KBr paths. Elemental analyses were carried out by CNRS Center Vernaison, France. The results are within ± 0.40 % of the theoretical values. $^1$H-NMR spectra were recorded on WP 80 SY or AC 300 BRÜKER spectrometers. Chemical shifts were recorded in ppm (d) from an internal tetramethylsilane standard in deuteriochloroform or deuteriodimethyl sulfoxide. Coupling constants (J) are reported in hertz, and the following abreviations are used : s, singulet ; d, doublet ; t, triplet ; m, multiplet .

**General procedure for the Synthesis of 3-Methyl-6-(3-arylpropenoyl)benzoxazolinones (4).**

6-acetyl benzoxazolinone (9.6g ; 0.05 mol)was dissolved in a

saturated ethanolic solution of gazeous HCl (250 ml). Appropriate aromatic aldehyde (0.055 mol) was then added dropwise. The reaction medium was stirred at roome temperature for an required time. The solid obtained was filtered under vacuum, washed with water , dried and purified by recrystallization.

**4a** : Yield : 65% (from toluene), reaction time : 30 h. , mp 207-209°C, NMR ($CDCl_3$, 300MHz) δ : 8.00 (dd, J = 1.5 and 8.2 Hz, 1H) ; 7.90 (d, J=1.5 Hz, 1H) ; 7.85 (d, J = 15.60 Hz, 1H) ; 7.55 (d, J= 15.60 Hz, 1H) ; 7.65 and 7.45 (m, 5H) ; 7.05 (s, 1H) ; 3.50 (s,3H). Anal. Calcd for $C_{17}H_{13}NO_3$ : C, 73.10 ; H, 4.69 ; N, 5.01 . Found : C, 72.69 ; H, 4.61 ; N, 4.99 .

**4b** : Yield : 74% (from toluene), reaction time : mp 215-219°C, NMR (DMSO-$d_6$ , 300MHz) δ : 8.30-8.05 (m, 5H) ; 7.60 (m, 1H) ; 7.55 and 7.45 (m, 3H) ; 3.40 (s,3H). . Anal. Calcd for $C_{17}H_{12}ClNO_3$ : C, 65.08 ; H, 3.86 ; N, 4.46 . Found : C, 65.24 ; H, 3.67 ; N, 4.52 .

**General procedure for the Synthesis of 3-Methyl-7-oxo-5-arylcyclopenta[f]benzoxazolinones (5).**

Appropriate compound **(4)** (0.015 mol) was added dropwise to hot (120°C) polyphosphoric acid (34 g).The reaction medium was stirred at this temperature for 1H30 and then quenched with ice water. The solid obtained was filtered under vacuum, washed with water and stirred in refluxing chloroform (35 ml) for 2 h. After filtration and evaporation of the organic phase , the residue was washed three times with ethanol. After evaporation of the combined ethanol filtrates, the residue was purified recrystallization.

**5a** : Yield : 30% (from ethanol), mp 161°C, NMR ($CDCl_3$, 80MHz) δ : 7.60 (s, 1H) ; 7.60-7.10 (m, 5H) ; 6.80 (s, 1H) ; 4.60 (dd, J = 3.7 and 7.9 Hz, 1H) ; 3.40 (s,3H) ; 3.30 (dd, J =

7.9 and 19 Hz, 1H) ; 2.20 (dd, J = 3.7 and 19 Hz, 1H). Anal. Calcd for $C_{17}H_{13}NO_3$ : C, 73.10 ; H, 4.69 ; N, 5.01 . Found : C, 72.99 ; H, 4.75 ; N, 4.96.

**5b :** Yield : 40% (from cyclohexane), mp 157-158°C, NMR (DMSO-$d_6$ , 300MHz) δ : 7.60 (s, 1H) ; 7.50 (d, J= 6.64 Hz, 1H) ; 7.30 (m, 2H) ; 7.15 (s, 1H) ; 7.00 (s, 1H) ; 5.10 (m, 1H) ; 3.30 (s, 3H) ; 3.25 (m, 1H) ; 2.25 (m, 1H). Anal. Calcd for $C_{17}H_{12}ClNO_3$ : C, 65.08 ; H, 3.86 ; N, 4.46 . Found : C, 65.01 ; H, 3.86 ; N, 4.51.

**General procedure for the Synthesis of 3-Methyl-7-hydroxyimino-5-arylcyclopenta[f]benzoxazolinones (6).**

Appropriate indanone **(5)** was dissolved in methanol (73 ml) and water (1ml). $K_2CO_3$ (2.8g ; 0.02 mol) and hydroxylamine hydrochloride (2.8g ; 0.04 mol) were then added. The reaction medium was refluxed for the required time and then quenched with ice water. The solid obtained was filtered under vacuum, washed with water and dried before recrystallization.

**6a :** Yield : 60% (from toluene), reaction time : 3h, mp 219-221°C, NMR (DMSO-$d_6$ , 300MHz) δ : 10.95 (s,1H) ; 7.45 (s, 1H) ; 7.30 (m, 2H) ; 7.25 (m, 1H) ; 7.15 (m, 2H) ; 6.90 (s, 1H) ; 4.55 (dd, J = 3.7 and 8.8 Hz, 1H) ; ; 3.35 (dd, J = 8.8 and 18.7 Hz, 1H) ; 3.25 (s,3H) ; 2.70 (dd, J = 3.7 and 18.7 Hz, 1H). Anal. Calcd for $C_{17}H_{14}N_2O_3$ : C, 69.38 ; H, 4.79 ; N, 9.52 . Found : C, 69.09 ; H, 4.93 ; N, 9.27 .

**6b** :Yield : 65% (from toluene), reaction time : 2h, mp 240-242°C, NMR (DMSO-$d_6$ , 300MHz) δ : 10.95 (s,1H) ; 7.50 (s, 1H) ; 7.45 (s, 1H) ; 7.30 (m, 2H) ; 7.00 (s, 1H) ; 6.90 (s, 1H) ; 4.95 (dd, J = 5.7 and 9.1 Hz, 1H) ; ; 3.45 (dd, J = 9.1 and 18.4 Hz, 1H) ; 3.30 (s,3H) ; 2.60 (dd, J = 5.7 and 18.4 Hz, 1H). Anal. Calcd for $C_{17}H_{13}ClN_2O_3$ : C, 62.10 ; H, 3.98 ; N, 8.52 . Found : C, 62.06 ; H, 3.91 ; N, 9.34 .

**General procedure for the Synthesis of 3-Methyl-7-[2-(dimethylaminoethyl)oximino]-5-arylcyclopenta [f] benzoxazolinones (3).**

Appropriate oxime **(6)** (0.03 mol) was dissolved in a suitable solvent (acetonitrile or dioxane ; 30ml). N-(2-chloroethyl)-N,N-dimethylamine hydrochloride (2.75g, 0.019 mol) was then added. After filtration and evaporation of the organic phase , the residue was dissolved in HCl 1M. The so obtained aqueous solution was washed with ethylacetate and made basic with a 30% aqueous solution of NaOH. The oximinoether was extracted with ethylacetate. After evaporation of the combined organic phases, the residue was purified by recrystallization.

**3a** : Yield : 30% (from 95° ethanol), reaction time : 60h in acetonitrile, mp 181-186°C, NMR ($CDCl_3$ , 300MHz) δ : 7.55 (s,1H) ; 7.35-7.10 (m, 5H) ; 6.60 (s, 1H) ; 4.45 (dd, J = 4.2 and 8.7 Hz, 1H) ; 4.30 (t, J=5.7 Hz, 2H), 3.50 (dd, J = 8.7 and 19 Hz, 1H) ; 3.30 (s,3H) ; 2.85 (dd, J = 4.2 and 19 Hz, 1H), 2.70 (t, J=5.7 Hz, 2H) ; 2.35 (s, 6H). Anal. Calcd for $C_{21}H_{23}N_3O_3$ : C, 69.02 ; H, 6.34 ; N, 11.49 . Found : C, 69.12 ; H, 6.42 ; N, 11.41 .

**3b** : Yield : 41% (from acetonitrile), reaction time : 100h in dioxane, mp 131-132°C, NMR (DMSO-$d_6$ , 300MHz) δ : 7.45 (m, 2H) ; 7.25 (m, 2H) ; 7.00 (s, 1H) ; 6.90 (m, 1H) ; 4.95 (m, 1H) ; 4.20 (m, 2H), 3.45 (dd, J = 9 and 19 Hz, 1H) ; 3.30 (s,3H) ; 2.65 (m, 1H), 2.55 (t, J=5.6 Hz, 2H) ; 2.15 (s, 6H). Anal. Calcd for $C_{21}H_{22}ClN_3O_3$ : C, 63.07 ; H, 5.55 ; N, 10.51. Found : C, 62.67 ; H, 5.52 ; N, 10.55 .

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