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# Synthesis and Structure-Activity Relationship Studies of 2,3-Dihydroimidazo[2,1-*a*]isoquinoline Analogs as Antitumor Agents

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5-Aryl-2,3-dihydroimidazo[2,1-*a*]isoquinolines were reported to have strong antitumor activity and one of the derivatives such as 5-[4'-(piperidinomethyl)phenyl]-2,3-dihydroimidazo[2,1-*a*] isoquinoline (1, SDZ 62-434) was found to be more effective than the clinical cytostatic agent edelfosine (2) in *in vitro* and *in vivo* assays. Currently SDZ 62-434 is in clinical trials in Europe. The structure-activity relationship studies of SDZ 62-434 showed that compounds with substitution on ring A were less active than the lead compound. Ring B in SDZ 62-434 was essential for the activity because compounds without B ring had no antitumor activity. Among the 3-arylisoquinolin-1-one derivatives, 3-[4'-(piperidinomethyl)phenyl] substituted analog had no antitumor activity but simple phenyl substituted compound, such as **4**, showed the most potent antitumor activity in various human tumor cell lines.

**Key words** : Imidazoisoquinolines, Antitumor, SDZ 62-434

## INTRODUCTION

5-Aryl-2,3-dihydroimidazo[2,1-*a*]isoquinolines were reported to have antitumor activity against a variety of murine and human tumor cell lines and in murine tumor models (Houlihan *et al.*, 1995a). These compounds were developed as platelet activating factor (PAF, 3) antagonists and some of these analogs were known to be potent noncharged PAF receptor antagonists (Houlihan *et al.*, 1993). It has been reported (Berdel *et al.*, 1987; Modest *et al.*, 1989; Munder *et al.*, 1990; Houlihan *et al.*, 1995b) that a number of charged PAF receptor antagonists, that is, compounds containing phospholipids, have antitumor activity through one or combination of the following mechanism, direct cytotoxicity (Berdel *et al.*, 1991), macrophage activation (Berdel *et al.*, 1980), changes in membrane structure and permeability (Noseda *et al.*, 1988; Dive *et al.*, 1990), alteration of signal transduction (Seewald *et al.*, 1990; Uberall *et al.*, 1991), and the rate of uptake by endocytosis (Bazill *et al.*, 1990; Workman *et al.*, 1991). Subsequently variety of PAF receptor antagonists have been evaluated for their antitumor activity and it has been found that a number of noncharged PAF receptor antagonists, that is, compounds without phospholipid moiety, also have antitumor activity (Houlihan *et al.*, 1995a). One of the typical noncharged PAF receptor antagonists, SDZ 62-434, is currently in clinical trials as a potential antitumor agent (Houlihan *et al.*, 1995c).

In this paper we report the findings on our structure-activity relationship studies where the imidazo[2,1-*a*] isoquinoline moiety (rings A, B, and C) and side chain in SDZ 62-434 are modified. Chlorine or methyl group was substituted on ring A (5, 6), and the tri-substituted double bond in ring B has been re-

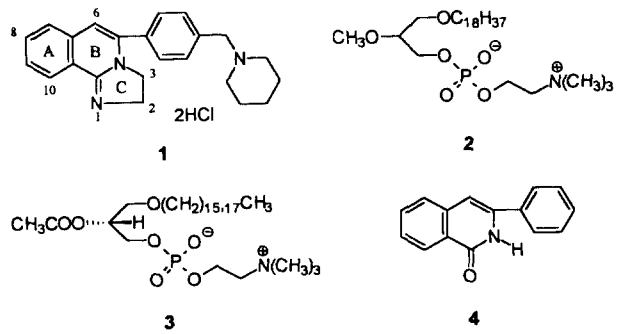


**Fig. 1.**

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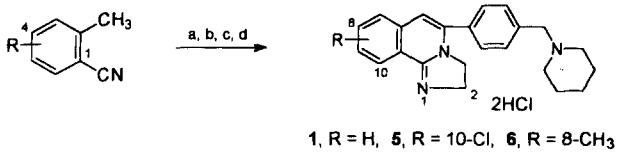
placed with carbonyl and methyl group (8, 9). The imidazo ring was replaced by its bioisosteres (4, 10-15).

## CHEMISTRY

5-Aryl-2,3-dihydroimidazo[2,1-*a*]isoquinoline derivatives were synthesized by the procedure shown in Scheme 1. The 2-aryl-2(*1H*)-imidazolines, prepared from the appropriately substituted benzonitrile and (2-aminoethyl)ammonium *p*-toluenesulfonate at high temperature, were lithiated (Houlihan *et al.*, 1982) to the dilithio derivatives and then treated with an alkyl aryl ester to give a variable mixture of 5-aryl-2,3,5,6-tetrahydroimidazo[2,1-*a*]isoquinoline-5-ols and 5-aryl-2,3-dihydroimidazo[2,1-*a*]isoquinolines. Refluxing of this mixture in toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid afforded the 5-aryl-2,3-dihydroimidazo[2,1-*a*]isoquinolines. The HCl salt of these derivatives were prepared by treatment with acetyl chloride-methanol solution.

2,4-Dimethylbenzonitrile was prepared from 2,4-dimethylbenzoic acid and chlorosulfonylisocyanate in a single step process (Botteghi *et al.*, 1982) and 4-methoxy-2-methylbenzonitrile was made from 3-methyl-4-nitrophenol following a procedure as shown in Scheme 2. Attempts to convert 4-methoxy-2-methylbenzonitrile to a corresponding dihydroimidazo compound **7** was not successful. Compounds **8**, **9** were obtained by acylation of 2-(2-methylphenyl)-2(1H)-imidazoline.

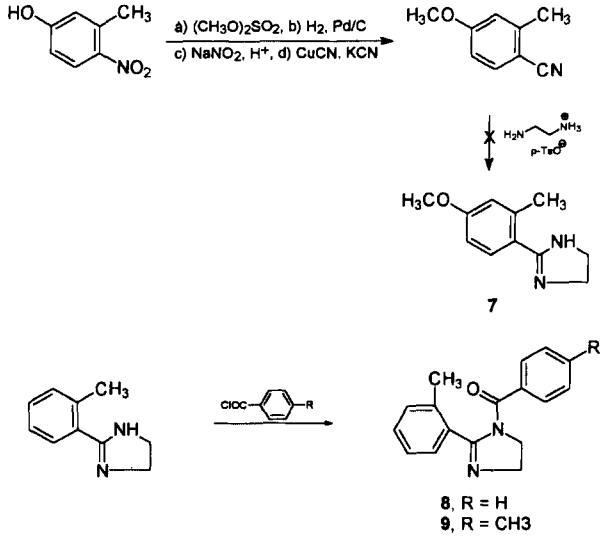
Substituted isoquinolines (**10-15**) were prepared by two different routes as shown in Scheme 3. 2-Methylbenzonitrile was converted to amide using hydrogen peroxide (Noller, 1943) followed by N-ethylation and the resulting N-ethyl amide was lithiated to the dilithio derivatives and then treated with an ester same way as in Scheme 1 to afford compounds **10-13**. Compounds **4**, **14** and **15** were prepared by a known method (Poindexter, 1982).



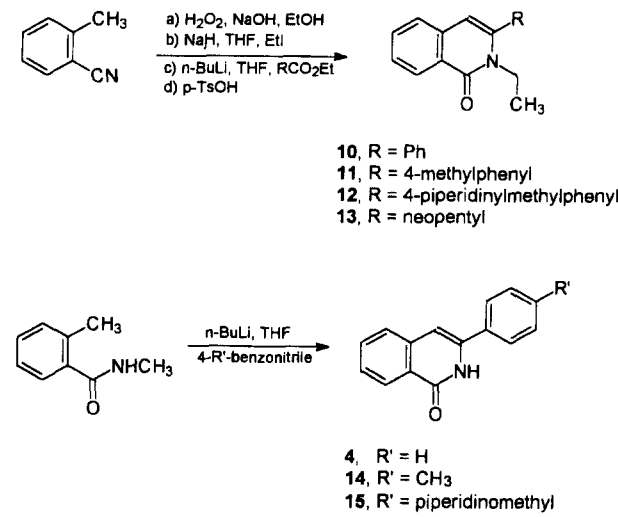

**1**, R = H, **5**, R = 10-Cl, **6**, R = 8-$CH_3$

a) $H_2NCH_2CH_2NH_2$.p-TsOH, b) n-BuLi, THF, ethyl 4'-(piperidinomethyl)benzoate, c) p-TsOH, d) HCl(g), MeOH

**Scheme 1.**




**Scheme 2.**




**Scheme 3.**

## RESULTS AND DISCUSSION

The most efficient way of optimizing activity of a lead structure is to follow Topliss decision tree approach. It was suggested that, according to this method, the initial synthesis of three substituted derivatives, namely the 4-Cl, 4-$CH_3$ and 4-$OCH_3$ compounds. Two of these sustituents were chosen but the compounds with Cl and $CH_3$ group on A ring, compounds **5**, **6** respectively, fail to improve the antitumor activity (Table). The result may indicate the limitation of Topliss decision tree approach to only an unfused benzene ring system. The synthesis of compounds with $OCH_3$ substituent is in progress to prove this point further.

We wanted to modify the ring B. It can be assumed that the ring B is holding the ring A and the two nitrogens in the imidazo moiety in a same plane. We designed compounds **8** and **9** to test the importance of this planarity. If you break the double bond in the ring B then the ring A and the imidazo group are not going to be in a same plane because of steric hinderance of 1,2-disubstituents of the ring A. The electronic nature of the double bond was mimicked by in-

**Table 1.** *In vitro* antitumor activity against human cell lines[a] ($ED_{50}$ μg/ml)

| Compound \ Cell line | A549 | SK-OV-3 | SK-MEL-2 | XF498 | HCT15 |
|---|---|---|---|---|---|
| 1 | 18 | 14 | 12 | 12 | 11 |
| 4 | 0.97 | 0.72 | 0.65 | 2.65 | 0.3 |
| 5 | na[b] | na | na | na | na |
| 6 | 15 | 17 | 8 | 11 | 18 |
| 8 | na | na | na | na | na |
| 9 | na | na | na | na | na |
| 10 | 15 | 30 | 24 | 18 | 14 |
| 11 | 18 | 28 | 18 | 15 | 20 |
| 12 | na | na | na | na | na |
| 13 | na | na | 28 | 26 | 17 |
| 14 | 9 | 6 | 5 | 14 | 3 |
| 15 | na | na | na | na | na |

[a]Tumor cell lines: A549 (human lung), SK-OV-3 (human ovarian), SK-MEL-2 (human melanoma), HCT 15 (human colon), XF 498 (human CNS)
[b]na represents $ED_{50}$>30

troducing carbonyl group in the place of the double bond. Compounds **8** and **9** did not show antitumor activity. Presumably the planarity of the ring A and the two nitrogens in the imidazo group are crucial to the activity.

Antitumor activity of N-ethylisoquinolin-1-one derivatives (compounds **10-13**), a hydrolyzed form of the double bond in the imidazo moiety of the lead compound **1**, were similar to the lead compound except compound **12**. This result implies that N-ethylisoquinolin-1-ones are bioisosteres of the imidazoisoquinolines. But in these series of compounds the ring B substituents seem to play an important role in the antitumor activity. Among the compounds tested for the antitumor activity, **4** showed the most potent activity (about 20 times more potent than the lead compound **1** against five different human tumor cell lines.

## CONCLUSION

The lower antitumor activity of compounds **5** and **6**, designed based on Topliss decision tree, than the lead compound **1** may indicate the limitation of Topliss decision tree approach to only an unfused benzene ring system. The planarity of the ring A and B and the hetero atoms in ring C are the important pharmacophore for the antitumor activity of substituted imidazoisoquinolines since the compounds **8** and **9** did not show antitumor activity. Substituted isoquinolin-1-ones are the bioisosteres of imidazoisoquinolines because compound **4** showed 20 times more potent antitumor activity than the lead compound **1** against various different human tumor cell lines.

## EXPERIMENTAL SECTION

### General

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use. Chromatography was performed using Merck 60, 70-230 mesh silica gel. Thin layer chromatography (TLC) was carried out using E. Merck Silica Gel 60 precoated plates. Melting points were determined by the capillary method on a Electrothermal IA9200 digital melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) data for $^1$H-NMR were taken on Bruker AC80 and Varian 300 spectrometers and are reported in δ (ppm) downfield from tetramethylsilane (TMS). The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, dd=double doublet, bs=broad singlet, bm=broad multiplet. Mass spectra (MS) were obtained on Shimazu GCMS QP2000A instrument applying an electron-impact ionization (EI) method. Infrared spectra (IR) were determined neat or in pressed KBr disks on a Perkin-Elmer 783 instrument and are reported in reciprocal centimeters. Ether denotes diethyl ether.

### 2-[2'-(Methyl)phenyl]imidazoline

A mixture of *o*-tolunitrile (2.00 g, 17 mmol) and (2-aminoethyl)ammonium *p*-toluenesulfonate (3.96 g, 17 mmol) was refluxed for 6 h and allowed to cool to ca. 40°C then poured into $H_2O$ (50 ml). This mixture was treated with 6N NaOH (17 ml, 102 mmol) and allowed to stir at room temperature overnight. The resultant solid was filtered off, dissolved in $CH_2Cl_2$, washed with $H_2O$ (twice with 50 ml), filtered through Celite, and then evaporated *in vacuo* to give 1.90 g of a white solid (70%); mp 62-66°C; $^1$H-NMR ($CDCl_3$) 2.49 (s, 3H), 3.76 (s, 4H), 4.12 (bs, 1H), 7.05-7.53 (m, 4H)

### 2,4-Dimethylbenzonitrile

2,4-Dimethylbenzoic acid (0.50 g, 3.33 mmol) in $CH_2Cl_2$ (10 ml) was treated dropwise at refluxing temperature with a solution of chlorosulfonylisocyanate (0.495 g, 3.50 mmol) in $CH_2Cl_2$ (10 ml) with stirring over a period of 45 min. After the addition, heating was continued for 1 h to complete the evolution of $CO_2$ and added DMF (0.54 ml, 7.0 mmol) to the reaction mixture for 15 min. While cooling to 15-20°C, stirred for an additional 15 min, poured into ice-water. After the ice has melted, extracted with $CH_2Cl_2$, washed with $H_2O$ (x6), dried over $MgSO_4$, filtered, evaporated *in vacuo* to give 209.4 mg (48%); $^1$H-NMR ($CDCl_3$) 2.35 (s, 3H), 2.49 (s, 3H), 6.75-7.52 (m, 3H); IR (neat) 2280 $cm^{-1}$

**5-[4'-(Piperidinomethyl)phenyl]-2,3-dihydroimidazo[2,1-*a*]isoquinoline 2HCl (1)**

A stirred solution of 2-(*o*-methylphenyl)imidazoline (1.00 g, 6 mmol) in THF (20 ml) under Ar atmosphere was treated dropwise with 1.6 M n-BuLi in hexane (7.81 ml, 13 mmol) at ice-water bath temp., allowed to stir for 2h at 0°C. The mixture was cooled to -78°C, and treated dropwise with a solution of methyl 4-piperidinomethylbenzoate (1.75 g, 8 mmol) in THF (5 ml). After an additional 0.5 h at -78°C, the reaction mixture was allowed to warm to -10°C, treated with saturated $NH_4Cl$ solution. The mixture was then evaporated and treated with EtOAc and $H_2O$, the organic layer was separated, washed with $H_2O$, brine, dried ($MgSO_4$), and filtered, and the filtrate was evaporated *in vacuo* to give 2.71 g of a dark orange oil. A solution of this crude product (2.71 g) and *p*-toluenesulfonic acid (0.119 g, 0.625 mmol) in toluene (20 ml) was refluxed for 8 h with continuous removal of $H_2O$ (Dean-Stark trap). The toluene was removed *in vacuo,* and the residue was dissolved in $CH_2Cl_2$, washed with $H_2O$, saturated $NaHCO_3$ solution, and brine, dried ($MgSO_4$), filtered, and evaporated *in vacuo* to give the free base. The HCl salt was prepared by dissolving the free base in a mixture of MeOH (5 ml) and acetyl chloride (0.47 g, 12 mmol) at ice-water bath temp. and evaporated *in vacuo,* then crystallized from EtOH to give white powder (40%); mp 323-325°C; $^1$H-NMR (DMSO-$d_6$) 1.39 (q, 2H), 1.82 (m, 4H), 2.84 (q, 2H), 3.12 (m, 2H), 4.11 (t, 2H), 4.38 (d, 2H), 4.56 (t, 2H), 7.13 (s, 1H), 7.64-8.54 (m, 8H), 11.14 (bs, 2H).

Following the same procedure as described above for **1** and replacing 2-(*o*-methylphenyl)imidazoline with different imidazolines, the following compounds were made.

**5-[4'-(Piperidinomethyl)phenyl]-10-chloro-2,3-dihydroimidazo[2,1-*a*]isoquinoline 2HCl (5)**

Obtained as a yellow powder (25%); mp 296-298°C; $^1$H-NMR (DMSO-$d_6$) 1.38 (q, 2H), 1.81 (m, 4H), 2.81 (q, 4H), 2.28 (s, 3H), 4.05 (t, 2H), 4.38 (d, 2H), 4.50 (t, 2H), 7.14 (s, 1H), 7.44-8.59 (m, 7H), 11.96 (s, 2H); FAB MS *m/z* (relative intensity) 378.3 (M+)

**5-[4'-(Piperidinomethyl)phenyl]-8-methyl-2,3-dihydroimidazo[2,1-*a*]isoquinoline 2HCl (6)**

Obtained as a yellow powder (45%); mp >340°C; $^1$H-NMR (DMSO-$d_6$) 1.38 (q, 2H), 1.80 (m, 4H), 2.82 (q, 4H), 4.03 (t, 2H), 4.38 (d, 2H), 4.44 (t, 2H), 7.36 (s, 1H), 7.65-7.99 (m, 7H), 9.83 (s, 1H), 11.36 (bs, 1H).

**2-[2'-(Methyl)phenyl]-3-benzoyl-2(*1H*)-imidazoline (8)**

To a stirred solution of 2-(2'-methylphenyl)imidazoline (300 mg, 1.88 mmol) in $CH_2Cl_2$ (10 ml) was added, at ice-water bath temp., triethylamine (208.7 mg, 2.06 mmol) followed by benzoyl chloride (263.5 mg, 1.88 mmol). The reaction mixture was allowed to warm to room temperature, diluted with $CH_2Cl_2$ (10 ml), washed with $H_2O$, dried ($MgSO_4$), filtered, evaporated *in vacuo*. The product was purified by flash chromatography to afford 435 mg of an oil (88%); $^1$H-NMR ($CDCl_3$) 2.26 (s, 3H), 4.09 (t, 4H), 6.83-7.46 (m, 9H).

**2-[2'-(Methyl)phenyl]-3-[4'-(methyl)benzoyl]-2(*1H*)-imidazoline (9)**

Obtained as a yellow solid (95%); mp 85 -88°C; $^1$H-NMR ($CDCl_3$) 2.24 (s, 3H), 2.26 (s, 3H), 4.09 (t, 4H), 6.88-7.50 (m, 8H).

**N-Ethyl-3-phenylisoquinolin-1-one (10)**

In a 500 ml round-bottomed flask were placed of o-tolunitrile (20 g, 170.8 mmol), 30-35% $H_2O_2$ (68.2 ml, 592.7 mmol), EtOH (200 ml), and 6N NaOH (6.8 ml), allowed to stand for 12 h, maintained at 50°C for 3 h. The mixture, while still warm, was neutralized with 5% $H_2SO_4$, cooled to room temperature, extracted with $CH_2Cl_2$, dried ($MgSO_4$), filtered, evaporated *in vacuo* to give 20 g of white solid (100%); $^1$H-NMR ($CDCl_3$) 2.50 (s, 3H), 5.72 (bs, 2H), 7.19-7.49 (m, 4H).

A stirred solution of *o*-toluamide (30 g, 0.22 mol) in THF (300 ml) was treated with NaH (8.81 g, 0.22 mol) at ice-water bath temp. under Ar atmosphere, allowed to stir for 1h, slowly added a solution of ethyl iodide (41.18 g, 0.26 mol) in THF (200 ml) for 12 h at room temperature, filtered, washed with $CH_2Cl_2$, brine, dried ($MgSO_4$), filtered, evaporated *in vacuo* to give 37.09 g of off-white solid. (100%, monoethyl amide contents >80% by $^1$H-NMR); $^1$H-NMR ($CDCl_3$) 1.27 (t, 3H), 2.45 (s, 3H), 3.49 (q, 2H), 5.74 (bs, 1H), 7.24-7.54 (m, 4H).

A stirred solution of crude N-ethyl *o*-toluamide (1 g, 5.93 mmol, monoethyl amide contents >80%) in THF (20 ml) was treated dropwise with 1.6 M n-BuLi (7.41 ml, 11.86 mmol) at ice-water bath temp. under Ar atmosphere, allowed to stir for 2 h at the same temp., added a solution of methyl benzoate (968.8 mg, 7.12 mmol) in THF (2 ml) at -78°C, stirred for 1 h at -78°C, warmed to -10°C, quenched with saturated $NH_4Cl$, extracted with EtOAc, brine, dried ($MgSO_4$), filtered, evaporated *in vacuo* to give 1.95 g of crude product. A solution of this crude product (1.95 g) and *p*-TsOH (112.7 mg, 0.593 mmol) in toluene (30 ml) was refluxed for ca. 8h with continuous removal of $H_2O$ (Dean-Stark trap). The toluene was removed *in vacuo*, and the residue was dissolved in EtOAc, washed with $H_2O$, saturated $NaHCO_3$ solution, and brine, dried

($MgSO_4$), filtered, and evaporated in vacuo to give 1.7 g of solid. It was purified by flash chromatography, recrystallized from ethyl acetate to afford yellow solid (40%); mp 78-81°C; $^1$H-NMR ($CDCl_3$) 1.15 (t, 3H), 4.00 (q, 2H), 6.38 (s, 1H), 7.34-8.51 (m, 9H).

**N-Ethyl-3-[4'-(methyl)phenyl]isoquinolin-1-one (11)**

Obtained as a white solid (53%); mp 124-125°C; $^1$H-NMR ($CDCl_3$) 1.14 (t, 3H), 2.42 (s, 3H), 4.00 (q, 2H), 6.36 (s, 1H), 7.32-8.50 (m, 8H).

**N-Ethyl-3-[4'-(piperidinomethyl)phenyl]isoquinolin-1-one HCl (12)**

Obtained as a yellow powder (34%); mp 298.5-300.5°C; $^1$H-NMR ($CDCl_3$) 1.15 (t, 3H), 1.65 (b, 2H), 1.92 (b, 3H), 2.66 (bq, 3H), 3.50 (bd, 2H), 3.99 (q, 2H), 4.18 (d, 2H), 6.36 (s, 1H), 7.37-8.66 (m, 8H).

**N-Ethyl-3-neopentyl-isoquinolin-1-one (13)**

Obtained as a dark yellow oil (26%); $^1$H-NMR ($CDCl_3$) 1.02 (s, 9H), 1.25 (t, 3H), 2.65 (s, 2H), 4.28 (q, 2H), 6.31 (s, 1H), 7.28-8.44 (m, 4H).

**3-Phenylisoquinolin-1-one (4)**

A stirred solution of N-methyl-*o*-tolunitrile (0.5 g, 3.35 mmol) in THF (20 ml) under Ar was treated dropwise with 1.6 M n-BuLi in hexane (4.2 ml, 6.70 mmol) at ice-water bath temp., allowed to stir for 2 h at the same temp. The mixture was then cooled to -65°C, and treated dropwise with a solution of benzonitrile (431.5 mg, 4.19 mmol) in THF (1.5 ml). After an additional 0.5 h at -65°C, the reaction mixture was allowed to warm to room temperature, treated with saturated $NH_4Cl$ solution. The mixture was then evaporated *in vacuo* and diluted with EtOAc and $H_2O$, the organic layer was separated, washed with $H_2O$, brine, dried ($MgSO_4$), and filtered, and the filtrate was evaporated *in vacuo*, recrystallized from EtOH to give 259.4 mg of white solid (35%).; mp 198-200°C; $^1$H-NMR ($CDCl_3$) 6.89 (s, 1H), 7.40-8.46 (m, 9H), 10.44 (bs, 1H).

**3-[4'-(Methyl)phenyl]isoquinolin-1-one (14)**

Obtained as a white solid (38%).; mp 223-227°C; $^1$H-NMR ($CDCl_3$) 2.42 (s, 3H), 6.72 (s, 1H), 7.35-8.45 (m, 8H), 10.35 (bs, 1H).

**3-[4'-(Piperidinomethyl)phenyl]isoquinolin-1-one HCl (15)**

Obtained as a yellow solid after crystalization from ethanol (48%).; mp 175-177°C; $^1$H-NMR ($CDCl_3$) 1.52 (b, 6H), 2.42 (b, 4H), 3.67 (s, 2H), 6.77 (s, 1H), 7.35-8.45 (m, 8H), 10.98 (bs, 1H).

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