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NEW SELECTIVE NONSTEROIDAL AROMATASE INHIBITORS: SYNTHESIS AND INHIBITORY ACTIVITY OF 2, 3 or 5-(α-AZOLYLBENZYL)-1*H*-INDOLES

Marc Le Borgne,*[a] Pascal Marchand,[a] Bénédicte Delevoye-Seiller,[a] Jean-Michel Robert,[a] Guillaume Le Baut,[a] Rolf W. Hartmann,[b] and Martina Palzer[b]

[a]*Laboratoires de Chimie Thérapeutique et de Chimie Organique, Faculté de Pharmacie, 1, rue Gaston Veil, F-44035 Nantes, France and* [b]*Fachrichtung 12.1 Pharmazeutische und Medizinische Chemie, Universität des Saarlandes, P.O. Box 15 11 50, D-66041 Saarbrücken, Germany*

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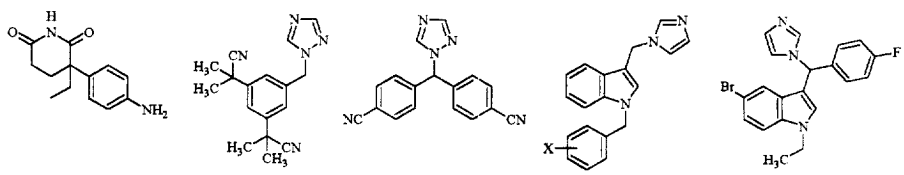
Abstract: Six azolyl substituted indoles were synthesized and tested for their activity to inhibit two P450 enzymes: P450 arom and P450 17α. It was observed that the introduction of α-imidazolylbenzyl chain at carbon 3 or 5 on indole nucleus led to very active molecules. Compounds **22**, **23** and especially **33** demonstrate very high potential against P450 arom. Under our assay conditions of high substrate concentration the IC_{50} are 0.057, 0.0785 and 0.041 μM, respectively. These compounds are moderate inhibitors against P450 17α.

Introduction

Nonsteroidal aromatase inhibitors are known to prevent the conversion of androgens to estrogens by inhibiting P450 aromatase enzyme and play a significant role in the treatment of estrogen dependent diseases, e.g. advanced breast cancer in postmenopausal patients.[1] For two decades aminoglutethimide (**1**) was the unique agent used clinically. However, this drug lacks selectivity and potency for aromatase, and possesses serious side effects, e.g., CNS depression, neutropenia, rash. Recently two highly active inhibitors, anastrozole (**2**) and letrozole (**3**), were launched in several countries (e.g., UK, France). In the UK, anastrozole is currently being used in preference to aminoglutethimide. These third generation aromatase inhibitors, which act as reversible competitive inhibitors, have potency and high selectivity for this enzyme, are well tolerated and could be also used in premenopausal women.[2]



1 **2** **3** **4**: X = 2-Cl **5**: X = 4-CN **6**

The present work is a follow up of our past efforts to design new aromatase inhibitors in indole series that has produced few potentially active 3-(azolylmethyl)-1*H*-indoles and 3-(α-azolylbenzyl)-1*H*-indoles: compounds **4**, **5** and, **6**.[3] These inhibitors consisted of an indole moiety for specific binding in the active site of aromatase and an azole for interacting with iron atom at the centre of the haem group of the enzyme. These encouraging results prompted us to carry out further investigations. In this communication, we report the synthetic pathways to the 2, 3 and 5-(α-azolylbenzyl)indoles and their biological evaluation against P450 arom and P450 17α enzymes.

* Fax: +33 (0)2 40 41 28 76; E-mail: Marc.Leborgne@sante.univ-nantes.fr

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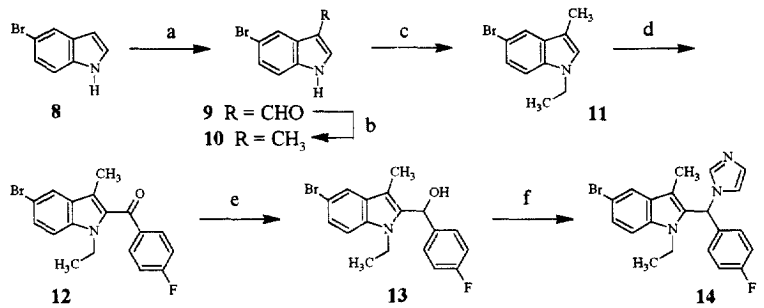
Chemistry

The synthesis of the target compound **14** is described in Scheme I and consisted in introduction of α-imidazolylbenzyl chain at carbon 2 on indole nucleus. 5-Bromo-3-formylindole **9** was obtained according to the reaction conditions of Vilsmeier-Haack,[4] using $POCl_3$/DMF and H_2O/NaOH. The aldehyde is then reduced by $LiAlH_4$/THF[4,5] to yield **10**. Alkylation[6] of **10** using NaH/ethyliodide in DMF led to 1-substituted indole derivative **11**. Friedel-Crafts acylation[7] of **11** yielded **12** that, on $NaBH_4$ reduction,[5] afforded **13**. Treatment of the carbinol **13** with 1,1'-carbonyldiimidazole[8] (CDI) in THF gave the azole derivative **14**.

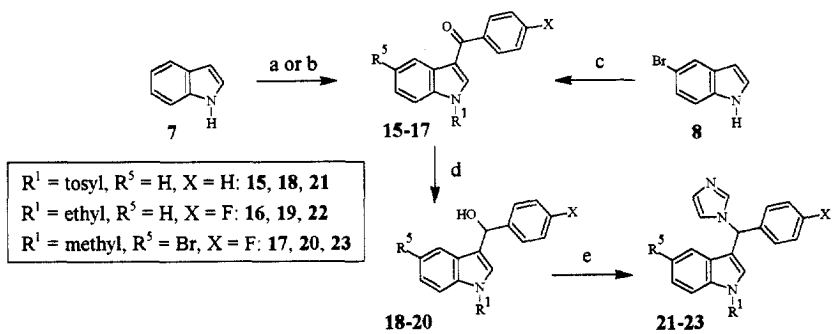
Scheme I



Reagents and conditions: (a) i. $POCl_3$/DMF; ii. H_2O/NaOH, 98%; (b) $LiAlH_4$/THF, 78%; (c) NaH/C_2H_5I/DMF, 92%; (d) $AlCl_3$/4-F-C_6H_4COCl/CH_2Cl_2, 55%; (e) $NaBH_4$/CH_3OH, 98%; (f) CDI/THF, 74%.

In the second series of compounds, we targeted the introduction of an α-azolylbenzyl sidechain at carbon 3 on indole nucleus (Scheme II). 3-Benzoyl-1-tosylindole **15**, precursor to **21**, was prepared by treatment of indole with Mg/CH_3I/benzoyl chloride in diethyl ether, at 0°C to room temperature,[9] followed by alkylation using K_2CO_3/tosyl chloride in acetone. A direct acylation of indole by Friedel-Crafts procedure[10] was attempted and the 4-fluorobenzoyl derivative **16** was isolated in a slightly better yield than by Oddo reaction (21% instead of 12%). Similar alkylation using K_2CO_3/ethyliodide in acetone afforded compound **16**. In case of 5-bromoindole **8**, we started by *N*-alkylation with NaH/methyl iodide in DMSO, followed by a Friedel-Crafts acylation[7] affording **17** in a more satisfactory yield (60%). The ketones **15-17** were finally reduced by $NaBH_4$ in methanol and the alcohols **18-20**, so obtained, were treated with CDI in THF to afford compounds **21-23**.

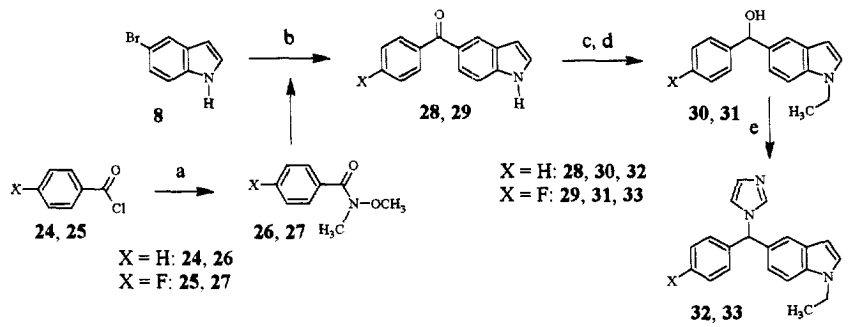
Scheme II



Reagents and conditions: (a) i. Mg/CH_3I/diethyl ether/C_6H_5COCl/CH_2Cl_2, 12%; ii. K_2CO_3/acetone/4-CH_3-$C_6H_4SO_2Cl$, 88%; (b) i. $AlCl_3$/4-F-C_6H_4COCl/CH_2Cl_2, 21%; ii. K_2CO_3/C_2H_5I/acetone, 78%; (c) i. NaH/CH_3I/DMSO, 99%; ii. $AlCl_3$/4-F-C_6H_4COCl/CH_2Cl_2, 60%; (d) $NaBH_4$/CH_3OH, 64-98%; (e) CDI/THF, 27-34%.

A halogen metal exchange strategy[11,12] was employed to prepare two 5-acylindole derivatives **28** and **29** (Scheme III). 5-Bromoindole was first converted to 1-potassio derivative and then subjected to bromo-lithium exchange using *tert*-butyllithium (*tert*-BuLi) in THF at -78°C. The metalated species was then reacted with suitable Weinreb amide[13] to prepare regiospecific 5-substituted indoles **28** and **29**. *N*-Ethylation of indole nitrogen using NaH/ethyliodide followed by reduction[12] of the carbonyl group resulted into alcohol derivatives **30** and **31**. Treatment of **30** and **31** with CDI, as described earlier, afforded **32** and **33**.

Scheme III



Reagents and conditions: (a) CH_3O-NH-CH_3.HCl/$CHCl_3$/pyridine, 91 and 95%; (b) KH/THF/*tert*-BuLi, 54 and 45%; (c) NaH/DMF/C_2H_5I, 97 and 76%; (d) $NaBH_4$/CH_3OH, 97 and 94%; (e) CDI/THF, 62 and 42%.

Results and Discussion

The target compounds[14] were tested for *in vitro* inhibitory activity against P450 arom[15,16] and P450 17α.[17] The corresponding results are summarized in Table 1. The compound **14**, with the α-imidazolylbenzyl chain at carbon 2 of indole nucleus, exerted a slight inhibition of P450 arom: IC_{50} = 0.238 μM. Among the second group of compounds, the tosyl derivative **21** was found to be a weak inhibitor (IC_{50} = 5.4 μM). Removal of the bromine atom resulted in reduced activity: the RP of **22** is 324.6 instead of 357.1 for **6**. It was observed that the replacement of ethyl chain (compound **6**, IC_{50} = 0.0518 μM) by methyl group leads to a less potent compound **23** (IC_{50} = 0.0785 μM). Among 5-substituted indole derivatives, the results indicate that **33** was a better inhibitor of aromatase than **32**. In fact, the introduction of a fluoro substituent led to a significant enhancement in inhibitory activity against aromatase as is seen with compound **33**: IC_{50} = 0.041 μM.

All target compounds were also tested *in vitro* for their inhibitory activity against P450 17α to assess the selectivity profile. It was observed that only 5-substituted indole derivatives **32** and **33** showed greater than 35% inhibition at a concentration of 2.5 μM. The level of androgen biosynthesis inhibitory activity of azolyl-substituted indoles was moderate in comparaison to their estrogen biosynthesis inhibitory activity: P450 17α IC_{50} of **33**, the most potent P450 arom inhibitor, was 60-fold higher.

In conclusion, we have described the syntheses of imidazolyl substituted indoles and pharmacological studies have shown that compounds **22**, **23** and **33** were highly potent as aromatase inhibitors. We are continuing to explore the indole scaffold as skeleton of our molecules for inhibiting P450 arom. Further biological evaluation is currently undergoing to confirm their selectivity profile by testing them against P450 18[16] and P450 scc.[15,16] *In vivo* P450 arom inhibitory activity will also be performed.[18] The full details of the structure-activity relationships, chemical synthesis, molecular modeling and pharmacological studies of this novel series of compounds will be the subject of future publications from these laboratories.

Table 1. *In Vitro* Activity of 2, 3 or 5-(α-AZOLYLBENZYL)-1*H*-INDOLES

Compound	P450 arom		P450 17α
	IC_{50} (μM)[a]	RP[b]	% inhibition[c]
4[3]	0.054	342.6	62.8
5[3]	0.05	370	15.4
6[3]	0.0518	357.1	3.7
14	0.238	77.7	30.2
21	5.4	3.4	31.1
22	0.057	324.6	25.5
23	0.0785	235.7	3.8
32	0.205	90.2	77.3
33	0.041	451.2	52.2

[a]IC_{50} is the concentration of inhibitor required to give 50% inhibition. Concentration of testosterone: 2.5 μM. The given values are mean values of at least three experiments. The deviations were within ±5%. [b]Relative potency, calculated from the IC_{50} values and related to AG (IC_{50} of AG: 18.5 μM). [c]Concentration of progesterone: 25 μM. Concentration of inhibitor: 2.5 μM. Under identical experimental conditions ketoconazole caused an inhibition of 70%. All values are the mean of at least 2 determinations.

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