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Synthesis and biological evaluation of 3-(azolylmethyl)-1*H*-indoles and 3-(α-azolylbenzyl)-1*H*-indoles as selective aromatase inhibitors

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Abstract

This present study identifies a number of azolyl-substituted indoles as potent inhibitors of aromatase. In the sub-series of 3-(azolylmethyl)-1*H*-indoles, four imidazole derivatives and their triazole analogues were tested. Imidazole derivatives **11** and **14** in which the benzyl moiety was substituted by 2-chloro and 4-cyano groups, respectively, were the most active, with IC_{50} values ranging between 0.054 and 0.050 μM. In the other sub-series, eight 3-(α-azolylbenzyl)-1*H*-indoles were prepared and tested. Compound **30**, the *N*-ethyl imidazole derivative, proved to be an aromatase inhibitor, showing an IC_{50} value of 0.052 μM. All target compounds were further evaluated against 17α-hydroxylase/C17,20-lyase to determine their selectivity profile.

Keywords: *Indole, azoles, inhibitor, aromatase, 17α-hydroxylase/C17,20-lyase, breast cancer, selective*

Introduction

Estrogens not only play a key role in normal expression of secondary sexual characteristics, and establishment and maintenance of pregnancy but are also involved in the natural history of breast cancer. A high proportion of breast cancer tumors are dependent upon estrogens for growth and respond to therapeutic measures designed to deplete circulating estrogens. Aromatase, a cytochrome P450 enzyme (P450 arom), catalyzes the biosynthesis of these estrogens from androgens. Activity of aromatase results in aromatization of the A ring of androgens with the concomitant loss of the C_{18} angular methyl group. So, the inhibition of the enzyme becomes a logical aim in breast cancer hormonotherapy [1,2].

The structurally diverse group of aromatase inhibitors are classically categorized into two major group: steroidal and non-steroidal derivatives; they appear to be different on their ability to interact with the enzyme [3,4]. A great number of steroidal compounds structurally related to the natural substrates (androstenedione or testosterone) have been developped. 4-Hydroxyandrostenedione (4-OHA) [5,6] was the first aromatase steroidal inhibitor to become available, and had high enzyme selectivity. But it had to be administered as a parental formulation due to its poor oral bioavailability. Other steroidal inhibitors, in addition to 4-OHA, have been also shown to cause inactivation of aromatase [7–11]. One of these, exemestane [11], has proved to be orally effective in postmenopausal women and reached the market in 1999. Steroidal inhibitors bind either very tightly or irreversibly to aromatase and then cause its inactivation [6,12].

Among the non-steroidal inhibitors, the most studied compounds were aminoglutethimide [AG, 3-(4-aminophenyl)-3-ethylpiperidine-2,6-dione] [13], 4-substituted anilines [14–16], imidazole antifungals and analogs[17,18]. AG, the first commercially

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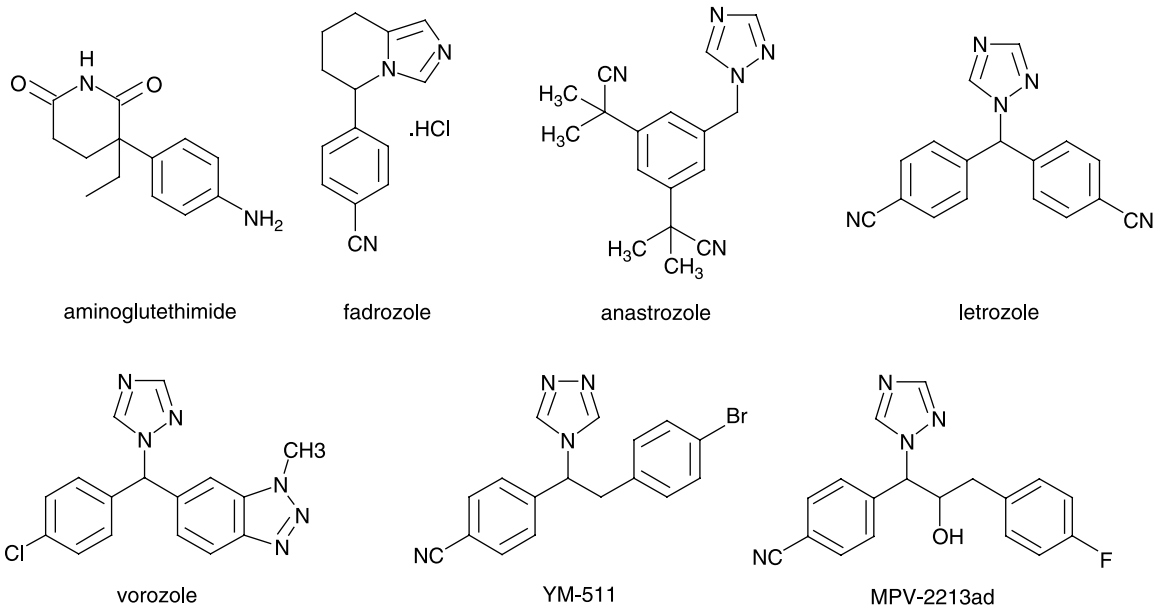


Figure 1. Structures of nonsteroidal inhibitors.

available non-steroidal inhibitor, was launched in 1981. However, the use of AG [19] has been limited due to (i) its lack of specificity - AG inhibits other cytochrome P450 enzymes such as P450scc and, P450c11 - and (ii) its intrinsic toxicity - main side-effects are lethargy, dizziness and skin rashes. Investigations of many research teams have resulted notably in the discovery of several heterocyclic azoles [20–23] such as fadrozole, anastrozole, letrozole, vorozole, YM-511 and MPV-2213ad (see Figure 1 for structures).

As shown in Table I, a major advance in potency is observed for these new non-steroidal aromatase inhibitors. The selectivity profile is also increased for fadrozole [24], vorozole [5], letrozole [26], anastrozole [27], YM-511 [28] and MPV-2213ad [29]. About their mechanism of action, it can be noted that they perturb the catalytic properties of the heme prosthetic group of aromatase [30].

In previous works [31–33], we initially prepared and evaluated 3-azolylmethylindoles and 3-(α-azolylbenzyl)indoles as potential aromatase inhibitors. 1-4-Fluorobenzyl-3-(1*H*-imidazol-1-ylmethyl)-1*H*-indole **ML60**, 1-ethyl-3-[(1*H*-imidazol-1-yl)(4-fluorophenyl)methyl]-1*H*-indole **PI19** and 1-ethyl-3-[(1*H*-imidazol-1-yl)(4-fluorophenyl)methyl]-2-methyl-1*H*-indole **CLE36** (see Figure 2 for structures) proved to be the most potent agents in inhibiting aromatization of androgens (androstenedione and, testosterone).

The present paper describes further structural optimizations in azolylmethyl-substituted indole series, namely the development of 1-substituted-3-(azolylmethyl)-1*H*-indoles and 1-substituted-3-(α-azolylbenzyl)-1*H*-indoles. Synthesis and structure-activity studies on the *in vitro* activity (inhibition of P450 arom) of compounds **11**–**18** and **30**–**37** are described in this paper. The most potent compounds were further evaluated for selectivity (inhibition of 17α-hydroxylase/C17,20-lyase).

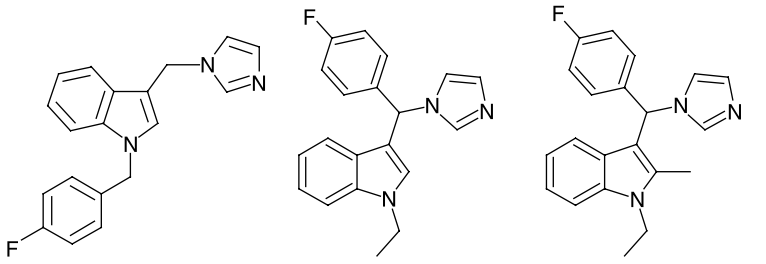
Table I. Inhibition of aromatase by major nonsteroidal inhibitors.

compound	P450 arom inhibition [23] IC_{50} (nM)	material
aminoglutethimide	3,800.000	Human placenta
MPV-2213ad	0,180.000	Human placenta
anastrozole	14.600	Human placenta
fadrozole	6.910	Human placenta
letrozole	0.390	Human placenta
vorozole	1.400	Rat granulosa cells
YM-511	0.125	Human placenta

Materials and methods

Chemistry

Instrumentation. Chemicals were purchased from Sigma-Aldrich. Compounds **3** and **20** were prepared according to reported methods [34,33]. Evaporations of final product solutions were done under vacuum with a rotatory evaporator. Column chromatography (CC) was carried out by using silica gel (silica gel 60, 63–200 mesh, E. Merck). Melting points were determined on a Tottoli-Büchi apparatus and are uncorrected. IR spectra (KBr or NaCl) were recorded as either neat (liquid or oil) or a KBr pellet (solids) on a Perkin-Elmer Paragon 1000 PC spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AC 250 (250 MHz) spectrometer, using DMSO d_6 as solvent. Chemical shifts are expressed in ppm (δ) downfield from internal TMS. Coupling constants J are expressed in Hz. Signals of protons exchangeable



ML60: IC_{50} = 0.072 μM **PI19**: IC_{50} = 0.057 μM **CLE36**: IC_{50} = 0.025 μM

Figure 2. Structures and aromatase inhibitory activities of compounds **ML60**, **PI19** and **CLE36**.

with D_2O are denoted by an asterisk (⋆). EI MS spectra were obtained on a Hewlett-Packard HP 5989A spectrometer (250°C, 70 eV).

*Synthesis of N-substituted 1H-3-indolecarbaldehydes **3**–**6***. A mixture of 1*H*-indole-3-carbaldehyde **2** (3.4 mmol) and K_2CO_3 (17 mmol) in dry acetone (15 mL) was stirred at room temperarure for 1 h. The corresponding benzyl chloride (4.1 mmol) was added and the reaction mixture was heated to reflux for 5 h. After filtration, the filtrate was evaporated. Water was added to the residue and the solution was extracted three times with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude product was purified by trituration to give the target compound.

*1-(2-Chlorobenzyl)-1H-3-indolecarbaldehyde (**3**)*. This compound was prepared from precursor **2**. Yield: 80%, brown crystals, mp 90–91°C (isopropyl ether). IR (KBr, cm^{-1}) 1656 (CO); ^{1}H NMR (DMSO d_6) δ 5.68 (s, 2H, CH_2), 7.0 (dd, J = 7.5, 1.6 Hz, 1H, H-6′), 7.30–7.44 (m, 4H, H-5, H-6, H-4′, H-5′), 7.54–7.61 (m, 2H, H-7, H-3′), 8.16–8.21 (m, 1H, H-4), 8.41 (s, 1H, H-2), 9.99 (s, 1H, CHO).

*1-(2-Fluorobenzyl)-1H-3-indolecarbaldehyde (**4**)*. This compound was prepared from precursor **2**. Yield: 88%, brown crystals, mp 95–97°C (diethyl ether). IR (KBr, cm^{-1}) 1665 (CO); ^{1}H NMR (DMSO d_6) δ 5.65 (s, 2H, CH_2), 7.63–7.66 (s, 1H, H-7), 7.17–7.46 (m, 6H, H-5, H-6, H-3′, H-4′, H-5′, H-6′), 8.15-8.18 (m, 1H, H-4), 8.44 (s, 1H, H-2), 9.99 (s, 1H, CHO).

*1-(3-Fluorobenzyl)-1H-3-indolecarbaldehyde (**5**)*. This compound was prepared from precursor **2**. Yield: 87%, brown solid, mp 105–107°C (isopropyl ether). IR (KBr, cm^{-1}) 1664 (CO); ^{1}H NMR (DMSO d_6) δ 5.61 (s, 2H, CH_2), 7.14–7.35 (m, 5H, H-5, H-6, H-2′, H-4′, H-6′), 7.42 (ddd, J = 7.9, 7.9, 6.1 Hz, 1H, H-5′), 7.62–7.66 (m, 1H, H-7), 8.14–8.18 (m, 1H, H-4), 8.53 (s, 1H, H-2), 9.99 (s, 1H, CHO).

*1-(4-Cyanobenzyl)-1H-3-indolecarbaldehyde (**6**)*. This compound was prepared from precursor **2**. Yield: 85%, brown solid, mp 153–155°C (isopropyl ether). IR (KBr, cm^{-1}) 2230 (CN), 1658 (CO); ^{1}H NMR (DMSO d_6) δ 5.71 (s, 2H, CH_2), 7.26–7.34 (m, 2H, H-5, H-6), 7.47 (d, J = 8.2 Hz, 2H, H-2′, H-6′), 7.56–7.60 (m, 1H, H-7), 7.86 (d, J = 8.2 Hz, 2H, H-3′, H-5′), 8.15–8.18 (m, 1H, H-4), 8.54 (s, 1H, H-2), 9.99 (s, 1H, CHO).

*Synthesis of 3-aroylindoles **21**–**23***. To a magnetically stirred suspension of $AlCl_3$ (10 mmol) in CH_2Cl_2 (20 mL) at 25°C was added 4-fluorobenzoyl chloride (10 mmol) and the mixture was stirred at the same temperature for 1 h. A solution of 5-bromo-1*H*-indole **19** or 5-bromo-1-ethyl-1*H*-indole **20** (10 mmol) in CH_2Cl_2 (10 mL) was added dropwise to the mixture at 25°C. After stirring for 24 h at 25°C, the reaction mixture was poured into ethyl acetate and ice water. The organic layer was separated, washed with water, and dried over Na_2SO_4. After evaporation of solvent, the crystalline residue was recrystallized in the appropriate solvent.

*5-Bromo-3-(4-fluorobenzoyl)-1H-indole (**21**)*. This compound was prepared from precursor **19**. Yield: 45%, fine white crystals, mp 250°C (ethyl acetate, decomposition). IR (KBr, cm^{-1}) 3157 (NH), 1596 (CO); ^{1}H NMR (DMSO d_6) δ 7.40 (dd, J = 8.9, 8.9 Hz, 2H, H-3″, H-5″), 7.44 (dd, J = 1.7, 8.6 Hz, 1H, H-6), 7.54 (d, J = 8.6 Hz, 1H, H-7), 7.92 (dd, J = 5.7, 8.7 Hz, 2H, H-2″, H-6″), 8.09 (d, J = 3.1 Hz, 1H, H-2), 8.43 (d, J = 1.7 Hz, 1H, H-4), 12.35 (s⋆, 1H, NH).

*5-Bromo-1-ethyl-3-(4-fluorobenzoyl)-1H-indole (**22**)*. This compound was prepared from precursor **20**. Yield: 80%, brown crystals, mp 155–157°C (diiso-propyl ether/MeOH). IR (KBr, cm^{-1}) 1616 (CO); ^{1}H NMR (DMSO d_6) δ 1.42 (t, J = 7.2 Hz, 3H, CH_3), 4.36 (q, J = 7.2 Hz, 2H, CH_2), 7.42 (dd, J = 8.8, 8.8 Hz, 2H, H-3″, H-5″), 7.50 (dd, J = 2.0, 8.7 Hz, 1H, H-6), 7.69 (d, J = 8.7 Hz, 1H, H-7), 7.93 (dd, J = 5.6, 8.8 Hz, 2H, H-2″, H-6″), 8.19 (s, 1H, H-2), 8.45 (d, J = 2.0 Hz, 1H, H-4).

*5-Bromo-3-(2,4-dichlorobenzoyl)-1-ethyl-1H-indole (**23**)*. This compound was prepared from precursor **20**. Yield: 91%, pink solid, mp 147–149°C (diisopropyl ether/MeOH). IR (KBr, cm^{-1}) 1630 (CO). ^1H NMR (DMSO d_6) δ 1.57 (t, J = 7.2 Hz, 3H, CH_3), 4.48 (q, J = 7.2 Hz, 2H, CH_2), 7.60 (dd, J = 1.8, 8.9 Hz, 1H, H-6), 7.62 (dd, J = 1.8, 8.2 Hz, 1H, H-5″), 7.68 (d, J = 8.2 Hz, 1H, H-6″), 7.72 (d, J = 8.9 Hz, 1H, H-7), 7.74 (d, J = 1.8 Hz, 1H, H-3″), 7.96 (s, 1H, H-2), 8.64 (d, J = 1.8 Hz, 1H, H-4).

*Synthesis of N-substituted 3-aroylindoles **24** and **25***. A mixture of 5-bromo-3-(4-fluorobenzoyl)-1*H*-indole **21** (2.50 mmol) and Cs_2CO_3 (5 mmol) in acetonitrile (15 mL) was heated to reflux for 2 h. 2-Chlorobenzyl chloride or 4-fluorobenzyl chloride (2.80 mmol) was added and the reaction mixture was heated to reflux for 1 h. Then, it was filtered and the filtrate was evaporated. To the residue was added water and the solution was extracted three times with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude product was triturated from isopropyl ether to give **24** or **25**.

*5-Bromo-1-(2-chlorobenzyl)-3-(4-fluorobenzoyl)-1H-indole (**24**)*. This compound was prepared from precursor **21**. Yield: 98%, brown solid (isopropyl ether/CH_2Cl_2), mp 150–151°C. IR (KBr, cm^{-1}) 1632 (CO); ^1H NMR (DMSO d_6) δ 5.70 (s, 2H, CH_2), 6.83 (d, J = 7.3 Hz, 1H, H-6′), 7.25–7.38 (m, 2H, H-4′, H-5′), 7.37–7.52 (m, 4H, H-6, H-7, H-3″, H-5″), 7.56 (d, J = 7.6 Hz, 1H, H-3′), 7.94 (dd, J = 5.8 Hz, 8.4 Hz, 2H, H-2″, H-6″), 8.33 (s, 1H, H-2), 8.48 (s, 1H, H-4).

*5-Bromo-3-(4-fluorobenzoyl)-1-(4-fluorobenzyl)-1H-indole (**25**)*. This compound was prepared from precursor **21**. Yield: 93%, white solid, mp 150–152°C (isopropyl ether). IR (KBr, cm^{-1}) 1629 (CO). ^1H NMR (DMSO d_6) δ 5.58 (s, 2H, CH_2), 7.19 (dd, J = 8.8, 8.8 Hz, 2H, H-3′, H-5′), 7.38–7.43 (m, 2H, H-2′, H-6′), 7.43 (dd, J = 8.8, 8.8 Hz, 2H, H-3″, H-5″), 7.45 (dd, J = 1.9, 8.8 Hz, 1H, H-6), 7.59 (d, J = 8.8 Hz, 1H, H-7), 7.95 (dd, J = 5.6, 8.8 Hz, 2H, H-2″, H-6″), 8.42 (s, 1H, H-2), 8.45 (d, J = 1.9 Hz, 1H, H-4).

*Synthesis of carbinol derivatives **7–10** and **26–29***. A solution of sodium borohydride (12.6 mmol) in methanol (10 mL) was added dropwise to a solution of the appropriate indole-3-carbaldehyde **3–6** or ketone derivative **22–25** (4.2 mmol) in methanol (10 mL). The reaction mixture was stirred at room temperature for 1 h. Water (30 mL) was added and the solution was extracted three times with diethyl ether. The combined organic layers were dried (Na_2SO_4) and the solvent was carefully evaporated leaving the desired crude product.

*1-(2-Chlorobenzyl)-3-hydroxymethyl-1H-indole (**7**)*. This compound was prepared from precursor **3**. Yield: 82%, white solid, mp 85–87°C (isopropyl ether). IR (KBr, cm^{-1}) 3380 (OH); ^1H NMR (DMSO d_6) δ 4.70 (d, J = 5.4 Hz, 2H, CH_2), 4.89 (t*, J = 5.4 Hz, 1H, OH), 5.51 (s, 1H, CH_2), 6.76 (dd, J = 7.5, 1.6 Hz, 1H, H-6′), 7.05–7.18 (m, 2H, H-5, H-6), 7.25 (ddd, J = 7.5, 7.5, 1.3 Hz, 1H, H-5′), 7.31–7.41 (m, 3H, H-2, H-7, H-4′), 7.55 (dd, J = 7.8, 1.3 Hz, 1H, H-3′), 7.68 (m, 1H, H-4).

*1-(2-Fluorobenzyl)-3-hydroxymethyl-1H-indole (**8**)*. This compound was prepared from precursor **4**. Yield: 88%, yellow oil. IR (NaCl, cm^{-1}) 3390 (OH). ^1H NMR (DMSO d_6) δ 4.70 (d, J = 5.4 Hz, 2H, CH_2), 4.91 (t*, J = 5.4 Hz, 1H, OH), 5.47 (s, 2H, CH_2), 7.05–7.38 (m, 6H, H-5, H-6, H-3′, H-4′, H-5′, H-6′), 7.39 (s, 1H, H-2), 7.46–7.52 (m, 1H, H-7), 7.66–7.69 (m, 1H, H-4).

*1-(3-Fluorobenzyl)-3-hydroxymethyl-1H-indole (**9**)*. This compound was prepared from precursor **5**. Yield: 66%, white solid, mp 63–65°C (isopropyl and diethyl ethers, cyclohexane). IR (KBr, cm^{-1}) 3388 (OH); ^1H NMR (DMSO d_6) δ 4.68 (d, J = 5.4 Hz, 2H, CH_2), 4.86 (t*, J = 5.4 Hz, 1H, OH), 5.43 (s, 2H, CH_2), 7.03–7.17 (m, 5H, H-5, H-6, H-2′, H-4′, H-6′), 7.38 (ddd, J = 8.0, 8.0, 6.1 Hz, 1H, H-5′), 7.45 (s, 1H, H-2), 7.45–7.48 (m, 1H, H-7), 7.64–7.67 (m, 1H, H-4).

*1-(4-Cyanobenzyl)-3-hydroxymethyl-1H-indole (**10**)*. This compound was prepared from precursor **6**. Yield: 93%, white solid, mp 60–62°C (isopropyl ether). IR (KBr, cm^{-1}) 3560 (OH), 2220 (CN); ^1H NMR (DMSO d_6) δ 4.68 (d, J = 5.4 Hz, 2H, CH_2), 4.88 (t*, J = 5.4 Hz, 1H, OH), 5.53 (s, 2H, CH_2), 7.03–7.16 (m, 2H, H-5, H-6), 7.35 (d, J = 8.2 Hz, 2H, H-2′, H-6′), 7.42 (d, J = 7.9 Hz, 1H, H-7), 7.45 (s, 1H, H-2), 7.66 (d, J = 7.4 Hz, 1H, H-4), 7.81 (d, J = 8.2 Hz, 2H, H-3′, H-5′).

*5-Bromo-1-ethyl-3-[(4-fluorophenyl) (hydroxy) methyl]-1H-indole (**26**)*. This compound was prepared from precursor **22**. Yield: 88%, white solid, mp 162–164°C (isopropyl ether). IR (KBr, cm^{-1}) 3164 (OH). ^1H NMR (DMSO d_6) δ 1.34 (t, J = 7.2 Hz, 3H, CH_3), 4.18 (q, J = 7.2 Hz, 2H, CH_2), 5.80 (d*, J = 4.5 Hz, 1H, OH), 5.97 (d, J = 4.5 Hz, 1H, CH), 7.18 (dd, J = 8.8, 8.8 Hz, 2H, H-3″, H-5″), 7.24 (dd, J = 1.9, 8.6 Hz, 1H, H-6), 7.25 (s, 1H, H-2), 7.45 (d, J = 8.6 Hz, 1H, H-7), 7.50 (dd, J = 5.7, 8.8 Hz, 2H, H-2″, H-6″), 7.66 (d, J = 1.9 Hz, 1H, H-4).

*5-Bromo-3-[(2,4-dichlorophenyl) (hydroxy) methyl]-1-ethyl-1H-indole (**27**)*. This compound was prepared from precursor **23**. Yield: 78%, white solid,

mp 120–122°C (isopropyl ether). IR (KBr, cm^{-1}) 3232 (OH). ^{1}H NMR (DMSO d_6) δ 0.85 (t, J = 7.0 Hz, 3H, CH_3), 4.16 (q, J = 7.0 Hz, 2H, CH_2), 6.01 (d⋆, J = 4.9 Hz, 1H, OH), 6.20 (d, J = 4.9 Hz, 1H, CH), 7.06 (s, 1H, H-2), 7.28 (dd, J = 1.9, 8.7 Hz, 1H, H-6), 7.47 (d, J = 8.7 Hz, 1H, H-7), 7.55 (dd, J = 8.3 Hz, 1H, H-5″), 7.60 (d, J = 2.1 Hz, 1H, H-3″), 7.78 (d, J = 1.9 Hz, 1H, H-4), 7.84 (d, J = 8.3 Hz, 1H, H-6″).

*5-Bromo-1-(2-chlorobenzyl)-3-[(4-fluorophenyl)(hydroxy)methyl]-1H-indole (**28**)*. This compound was prepared from precursor **24**. Yield: 93%, brown solid, mp 101–103°C (isopropyl ether). IR (KBr, cm^{-1}) 3274 (OH); ^{1}H NMR (DMSO d_6) δ 5.51 (s, 2H, CH_2), 5.85 (d⋆, J = 4.5 Hz, 1H, OH), 5.99 (d, J = 4.5 Hz, 1H, CH), 6.75 (d, J = 7.3 Hz, 1H, H-6′), 7.15-7.55 (m, 8H, H-2, H-6, H-7, H-3′, H-4′, H-5′, H-3″, H-5″), 7.50 (dd, J = 5.9, 7.2 Hz, 2H, H-2″, H-6″), 7.67 (d, J = 1.7 Hz, 1H, H-4).

*5-Bromo-1-(4-fluorobenzyl)-3-[(4-fluorophenyl)(hydroxy)methyl]-1H-indole (**29**)*. This compound was prepared from precursor **25**. Yield: 95%, white solid, mp 125–127°C (cyclohexane). IR (KBr, cm^{-1}) 3114 (OH); ^{1}H NMR (DMSO d_6) δ 5.40 (s, 2H, CH_2), 5.85 (d⋆, J = 4.5 Hz, 1H, OH), 5.99 (d, J = 4.5 Hz, 1H, CH), 7.14–7.24 (m, 5H, H-6, H-3′, H-5′, H-3″, H-5″), 7.28 (dd, J = 5.9 Hz, 8.6 Hz, 2H, H-2′, H-6′), 7.38 (s, 1H, H-2), 7.45 (d, J = 8.8 Hz, 1H, H-7), 7.51 (dd, J = 5.8, 8.5 Hz, 2H, H-2″, H-6″), 7.67 (d, J = 1.7 Hz, 1H, H-4).

*Synthesis of imidazole derivatives **11**–**14**, **30**, **31**, **34** and **35***. A solution of the appropriate carbinol derivative **7**–**10** or **26**–**29** (3.70 mmol) and CDI (3.70 mmol) in dry THF (20 mL) was stirred at room temperature for 3 h. The reaction mixture was partitioned between H_2O and diethyl ether and extracted three times with diethyl ether. The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by CC (CH_2Cl_2:EtOH = 19:1).

*1-(2-Chlorobenzyl)-3-(1H-imidazol-1-ylmethyl)-1H-indole (**11**)*. This compound was prepared from precursor **7**. Yield: 42%, white solid, mp 45–47°C (isopropyl ether). ^{1}H NMR (DMSO d_6) δ 5.38 (s, 2H, CH_2), 5.54 (s, 2H, CH_2), 6.80 (dd, J = 7.5, 1.8 Hz, 1H, H-6′), 6.88 (s, 1H, H_{imide}), 7.06–7.20 (m, 2H, H-5, H-6), 7.20 (s, 1H, H_{imide}), 7.28 (m, 1H, H-5′), 7.35 (m, 1H, H-4′), 7.43 (d, J = 8.0 Hz, 1H, H-7), 7.55 (dd, J = 7.8, 1.3 Hz, 1H, H-3′), 7.59 (s, 1H, H-2), 7.62 (d, J = 7.7 Hz, 1H, H-4), 7.80 (s, 1H, H_{imide}).

*1-(2-Fluorobenzyl)-3-(1H-imidazol-1-ylmethyl)-1H-indole (**12**)*. This compound was prepared from precursor **8**. Yield: 42%, white solid, mp 65–68°C (isopropyl ether). ^{1}H NMR (DMSO d_6) δ 5.38 (s, 2H, CH_2), 5.51 (s, 2H, CH_2), 6.91 (s, 1H, H_{imide}), 7.06–7.41 (m, 6H, H-5, H-6, H-3′, H-4′, H-5′, H-6′), 7.21 (s, 1H, H_{imide}), 7.53 (d, J = 8.1 Hz, 1H, H-7), 7.61 (s, 1H, H-2), 7.63 (d, J = 7.7 Hz, 1H, H-4), 7.82 (s, 1H, H_{imide}).

*1-(3-Fluorobenzyl)-3-(1H-imidazol-1-ylmethyl)-1H-indole (**13**)*. This compound was prepared from precursor **9**. Yield: 92%, white solid, mp 62–65°C (cyclohexane). ^{1}H NMR (DMSO d_6) δ 5.37 (s, 2H, CH_2), 5.47 (s, 2H, CH_2), 6.88 (s, 1H, H_{imide}), 7.04–7.16 (m, 5H, H-5, H-6, H-2′, H-4′, H-6′), 7.20 (s, 1H, H_{imide}), 7.34–7.43 (m, 1H, H-5′), 7.49 (d, J = 8.2 Hz, 1H, H-7), 7.60 (d, J = 7.7 Hz, 1H, H-4), 7.66 (s, 1H, H-2), 7.81 (s, 1H, H_{imide}); IR (KBr, cm^{-1}) 1086.

*1-(4-Cyanobenzyl)-3-(1H-imidazol-1-ylmethyl)-1H-indole (**14**)*. This compound was prepared from precursor **10**. Yield: 60%, white solid, mp 102–104°C (isopropyl ether). IR (KBr, cm^{-1}) 2229 (CN); ^{1}H NMR (DMSO d_6) δ 5.38 (s, 2H, CH_2), 5.57 (s, 2H, CH_2), 6.89 (s, 1H, H_{imide}), 7.04–7.16 (m, 2H, H-5, H-6), 7.21 (s, 1H, H_{imide}), 7.36 (d, J = 8.2 Hz, 2H, H-2′, H-6′), 7.45 (d, J = 8.1 Hz, 1H, H-7), 7.60 (d, J = 7.6 Hz, 1H, H-4), 7.65 (s, 1H, H-2), 7.81 (s, 1H, H_{imide}), 7.83 (d, J = 8.2 Hz, 2H, H-3′, H-5′).

*5-Bromo-1-ethyl-3-[(4-fluorophenyl)(1H-imidazol-1-yl)methyl]-1H-indole (**30**)*. This compound was prepared from precursor **26**. Yield: 71%, white solid, mp 143–145°C (isopropyl ether). ^{1}H NMR (DMSO d_6) δ 1.33 (t, J = 7.2 Hz, 3H, CH_3), 4.22 (q, J = 7.2 Hz, 2H, CH_2), 6.97 (s, 1H, H_{imide}), 7.12 (s, 1H, CH), 7.14 (s, 1H, H-2), 7.20 (s, 1H, H_{imide}), 7.24–7.30 (m, 2H, H-3″, H-5″), 7.30–7.34 (m, 4H, H-4, H-6, H-2″, H-6″), 7.54 (d, J = 8.6 Hz, 1H, H-7), 7.75 (s, 1H, H_{imide}).

*5-Bromo-3-[(2,4-dichlorophenyl)(1H-imidazol-1-yl)methyl]-1-ethyl-1H-indole (**31**)*. This compound was prepared from precursor **27**. Yield: 66%, white solid, mp 138–140°C (isopropyl ether/EtOH). ^{1}H NMR (DMSO d_6) δ 1.32 (t, J = 7.1 Hz, 3H, CH_3), 4.21 (q, J = 7.1 Hz, 2H, CH_2), 6.91 (d, J = 8.4 Hz, 1H, H-6″), 6.99 (s, 1H, H_{imide}), 7.07 (s, 1H, H-2), 7.15 (s, 1H, H_{imide}), 7.27 (s, 1H, CH), 7.34 (dd, J = 8.8, 8.8 Hz, 1H, H-6), 7.49 (d, J = 1.7 Hz, 1H, H-4), 7.52 (dd, J = 2.1, 8.4 Hz, 1H, H-5″), 7.56 (d, J = 8.8 Hz, 1H, H-7), 7.71 (s, 1H, H_{imide}), 7.75 (d, J = 2.1 Hz, 1H, H-3″).

*5-Bromo-1-(2-chlorobenzyl)-3-[(4-fluorophenyl)(1H-imidazol-1-yl)methyl]-1H-indole (**34**)*. This compound was prepared from precursor **28**. Yield: 71%, white crystals, mp 145°C (isopropyl ether/MeOH, decomposition). ^{1}H NMR (base) (DMSO d_6) δ 5.55 (s, 2H, CH_2), 6.70 (d, J = 7.1 Hz, 1H, H6′), 6.99 (s, 1H, H_{imide}), 7.21 (s, 1H, H_{imide}), 7.17–7.42 (m, 11H, H-2, H-4, H-6, H-7, H-4′, H-5′, H-2″, H-3″, H-5″, H-6″,

CH), 7.53 (d, J = 7.6 Hz, 1H, H-3′), 7.77 (s, 1H, H_{imide}).

*5-Bromo-1-(4-fluorobenzyl)-3-[(4-fluorophenyl)(1H-imidazol-1-yl)methyl]-1H-indole (**35**)*. This compound was prepared from precursor **29**. Yield: 80%, white solid, mp 140–142°C (cyclohexane/diethyl ether). ^{1}H NMR (DMSO d_6) δ 5.50 (s, 2H, CH_2), 6.99 (s, 1H, H_{imide}), 7.15–7.33 (m, 12H, H-2, H-4, H-6, H-2′, H-3′, H-5′, H-6′, H-2″ H-3″ H-5″ H-6″, CH), 7.21 (s, 1H, H_{imide}), 7.47 (d, J = 8.7 Hz, 1H, H-7), 7.77 (s, 1H, H_{imide}).

*Synthesis of triazole derivatives **15**–**18**, **32**, **33**, **36** and **37***. Thionyl chloride (11.8 mmol) was dropped into an ice-cooled solution of 1*H*-1,2,4-triazole (47.2 mmol) in dry acetonitrile (30 mL). The mixture was stirred at room temperature for 1 h, then filtered. This solution was added dropwise to a solution of the appropriate carbinol derivative **7**–**10** or **26**–**29** (3.0 mmol) in dry acetonitrile (10 mL). After addition, the mixture was stirred at room temperature for 2 h, then filtered and concentrated. The residue was dissolved in CH_2Cl_2. The organic solution was washed with brine, dried over Na_2SO_4, filtered, and evaporated to provide the crude product. This mixture was purified by CC (CH_2Cl_2:EtOH = 19:1). In the case of compounds **15** and **16**, appropriate eluates were collected and evaporated to give the corresponding regioisomers.

*1-(2-Chlorobenzyl)-3-(1H-1,2,4-triazol-1-ylmethyl)-1H-indole (**15a**)*. This compound was prepared from precursor **7**. Yield: 74%, pale yellow crystals, mp 65–66°C (cyclohexane/CH_2Cl_2). ^{1}H NMR (DMSO d_6) δ 5.54 (s, 2H, CH_2), 5.60 (s, 2H, CH_2), 6.81 (d, J = 7.5 Hz, 1H, H-6′), 7.07–7.12 (m, 1H, H-5), 7.15–7.20 (m, 1H, H-6), 7.24–7.30 (m, 1H, H-5′), 7.33–7.38 (m, 1H, H-4′), 7.43 (d, J = 8.1 Hz, 1H, H-7), 7.55 (d, J = 7.8 Hz, 1H, H-3′), 7.60 (s, 1H, H-2), 7.67 (d, J = 7.7 Hz, 1H, H-4), 7.97 (s, 1H, $H_{triazole}$), 8.64 (s, 1H, $H_{triazole}$).

*1-(2-Chlorobenzyl)-3-(4H-1,2,4-triazol-4-ylmethyl)-1H-indole (**15b**)*. This compound was prepared from precursor **7**. Yield: 6%, white solid, mp 130°C (diisopropyl ether). ^{1}H NMR (DMSO d_6) δ 5.47 (s, 1H, CH_2), 5.55 (s, 1H, CH_2), 6.83 (d, J = 7.1 Hz, 1H, H-6′), 7.08–7.22 (m, 2H, H-5, H-6), 7.25–7.31 (m, 1H, H-5′), 7.33–7.39 (m, 1H, H-4′), 7.44 (d, J = 8.1 Hz, 1H, H-7), 7.55 (d, J = 7.8 Hz, 1H, H-3′), 7.62 (s, 1H, H-2), 7.66 (d, J = 7.6 Hz, 1H, H-4), 8.62 (s, 2H, $H_{triazole}$).

*1-(2-Fluorobenzyl)-3-(1H-1,2,4-triazol-1-ylmethyl)-1H-indole (**16a**)*. This compound was prepared from precursor **8**. Yield: 29%, brown solid, mp 121–123°C (diisopropyl ether/CH_2Cl_2). ^{1}H NMR (DMSO d_6) δ 5.50 (s, 2H, CH_2), 5.58 (s, 2H, CH_2), 7.05–7.42 (m, 6H, H-5, H-6, H-3′, H-4′, H-5′, H-6′), 7.52 (d, J = 8.2 Hz, 1H, H-7), 7.61 (s, 1H, H-2), 7.65 (d, J = 7.7 Hz, 1H, H-4), 7.96 (s, 1H, $H_{triazole}$), 8.64 (s, 1H, $H_{triazole}$).

*1-(2-Fluorobenzyl)-3-(4H-1,2,4-triazol-4-ylmethyl)-1H-indole (**16b**)*. This compound was prepared from precursor **8**. Yield: 24%, yellow crystals, mp 118–120°C (diisopropyl ether/CH_2Cl_2). ^{1}H NMR (DMSO d_6) δ 5.46 (s, 2H, CH_2), 5.51 (s, 2H, CH_2), 7.07–7.39 (m, 6H, H-5, H-6, H-3′, H-4′, H-5′, H-6′), 7.53 (d, J = 8.0 Hz, 1H, H-7), 7.64 (s, 1H, H-2), 7.65 (d, J = 7.8 Hz, 1H, H-4), 8.62 (s, 2H, $H_{triazole}$).

*1-(3-Fluorobenzyl)-3-(1H-1,2,4-triazol-1-ylmethyl)-1H-indole (**17**)*. This compound was prepared from precursor **9**. Yield: 65%, white solid, mp 135–137°C (cyclohexane). ^{1}H NMR (DMSO d_6) δ 5.48 (s, 2H, CH_2), 5.59 (s, 2H, CH_2), 7.05–7.20 (m, 5H, H-5, H-6, H-2′, H-4′, H-6′), 7.35–7.43 (m, 1H, H-5′), 7.50 (d, 1H, H-7, $\mathcal{J}$ = 8.0 Hz), 7.65 (d, 1H, H-4, $\mathcal{J}$ = 7.60 Hz), 7.68 (s, 1H, H-2), 7.96 (s, 1H, $H_{triazole}$), 8.65 (s, 1H, $H_{triazole}$).

*1-(4-Cyanobenzyl)-3-(1H-1,2,4-triazol-1-ylmethyl)-1H-indole (**18**)*. This compound was prepared from precursor **10**. Yield: 63%, white solid, mp 104–106°C (isopropyl ether). IR (KBr, cm^{-1}) 2226; ^{1}H NMR (DMSO d_6) δ 5.58 (s, 2H, CH_2), 5.60 (s, 2H, CH_2), 7.08–7.17 (m, 2H, H-5, H-6), 7.37 (d, J = 8.1 Hz, 2H, H-2′, H-6′), 7.45 (d, J = 7.9 Hz, 1H, H-7), 7.64–7.68 (m, 2H, H-2, H-4), 7.83 (d, J = 8.1 Hz, 2H, H3′, H-5′), 7.97 (s, 1H, $H_{triazole}$), 8.65 (s, 1H, $H_{triazole}$).

*5-Bromo-1-ethyl-3-[(4-fluorophenyl)(1H-1,2,4-triazol-1-yl)methyl]-1H-indole (**32**)*. This compound was prepared from precursor **26**. Yield: 67%, white solid, mp 126–128°C (isopropyl ether/EtOH). ^{1}H NMR (DMSO d_6) δ 1.33 (t, J = 7.20 Hz, 3H, CH_3), 4.22 (q, J = 7.20 Hz, 2H, CH_2), 7.22–7.27 (m, 3H, H-2, H-3″, H-5″), 7.28–7.35 (m, 2H, H-6, CH), 7.37–7.42 (m, 2H, H-2″, H-6″), 7.43 (d, J = 1.50 Hz, 1H, H-4), 7.54 (d, J = 8.70 Hz, 1H, H-7), 8.08 (s, 1H, $H_{triazole}$), 8.67 (s, 1H, $H_{triazole}$).

*5-Bromo-3-[(2,4-dichlorophenyl)(1H-1,2,4-triazol-1-yl)methyl]-1-ethyl-1H-indole (**33**)*. This compound was prepared from precursor **27**. Yield: 30%, white solid, mp 124–126°C (acetonitrile). ^{1}H NMR (DMSO d_6) δ 1.33 (t, J = 7.2 Hz, 3H, CH_3), 4.22 (q, J = 7.2 Hz, 2H, CH_2), 7.18 (s, 1H, H-2), 7.22 (d, J = 8.5 Hz, 1H, H-6″), 7.33 (dd, J = 1.8, 8.7 Hz, 1H, H-6), 7.48 (s, 1H, CH), 7.49–7.57 (m, 3H, H-4, H-7, H-5″), 7.76 (d, J = 2.0 Hz, 1H, H-3″), 8.11 (s, 1H, $H_{triazole}$), 8.69 (s, 1H, $H_{triazole}$).

*5-Bromo-1-(2-chlorobenzyl)-3-[(4-fluorophenyl)(1H-1,2,4-triazol-1-yl)methyl]-1H-indole (**36**)*. This compound was prepared from precursor **28**. Yield: 70%, pale yellow crystals, mp 145–147°C (MeOH/CH_2Cl_2). ^{1}H NMR (DMSO d_6) δ 5.56 (s, 2H, CH_2), 6.73

(d, J = 6.5 Hz, 1H, H-6′), 7.23-7.47 (m, 11H, H-2, H-4, H-6, H-7, H-4′, H-5′, H-2″, H-3″, H-5″, H-6″, CH), 7.53 (d, J = 7.6 Hz, 1H, H-3′), 8.10 (s, 1H, $H_{triazole}$), 8.71 (s, 1H, $H_{triazole}$).

*5-Bromo-1-(4-fluorobenzyl)-3-[(4-fluorophenyl)(1H-1,2,4-triazol-1-yl)methyl]-1H-indole (**37**)*. This compound was prepared from precursor **29**. Yield: 85%, white solid, mp 163–165°C (cyclohexane). ^{1}H NMR (DMSO d_6) δ 5.45 (s, 2H, CH_2), 7.17 (dd, J = 8.7, 8.7 Hz, 2H, H-3′, H-5′), 7.24–7.30 (m, 4H, H-2′, H-6′, H-3″, H-5″), 7.28 (dd, J = 1.8, 8.7 Hz, 1H, H-6), 7.38–7.45 (m, 5H, H-2, H-4, H-2″, H-6″, CH), 7.48 (d, J = 8.6 Hz, 1H, H-7), 8.09 (s, 1H, $H_{triazole}$), 8.69 (s, 1H, $H_{triazole}$).

Pharmacology

Inhibition of human placental aromatase (in Vitro). The compounds were tested for aromatase inhibitory activity according to the procedure of Thompson and Siiteri [35]. The microsomal fraction of freshly delivered human term placenta provided the source of the aromatase enzyme and [1β,2β-^{3}H]testosterone was used as substrate [36].

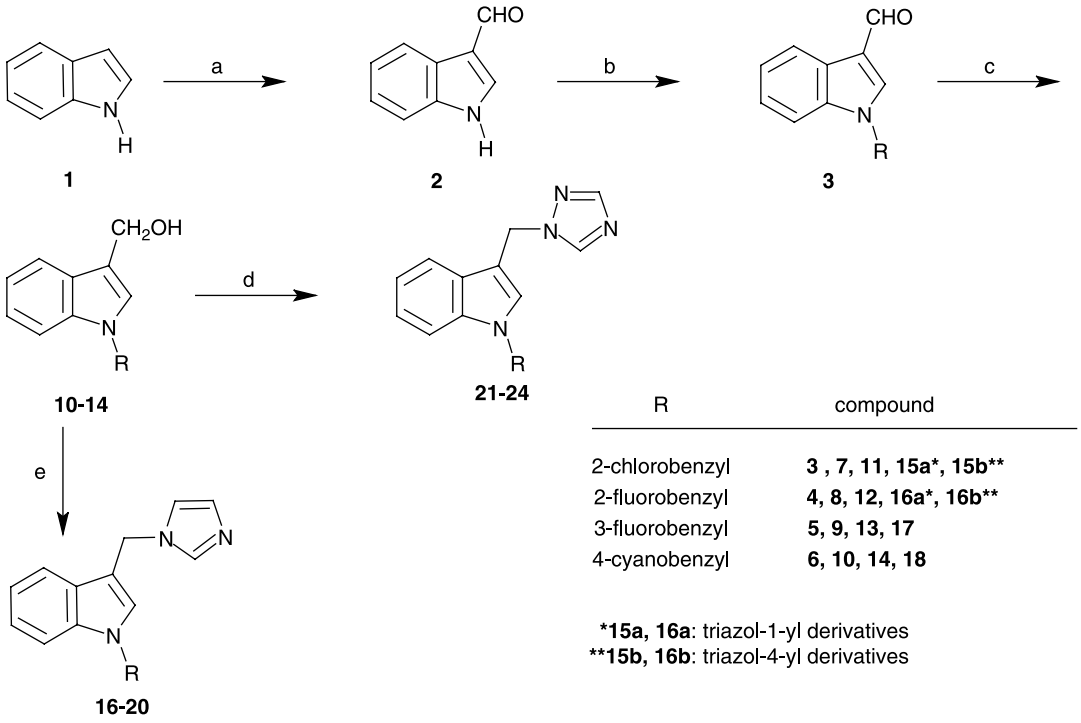
Inhibition of rat testicular P450 17α (in Vitro). Rat testicular microsomes were used as source of the enzyme, and nonlabeled progesterone served as substrate. The separation of the steroids was accomplished using the procedure recently described by Sergejew and Hartmann [37].

Results and discussion

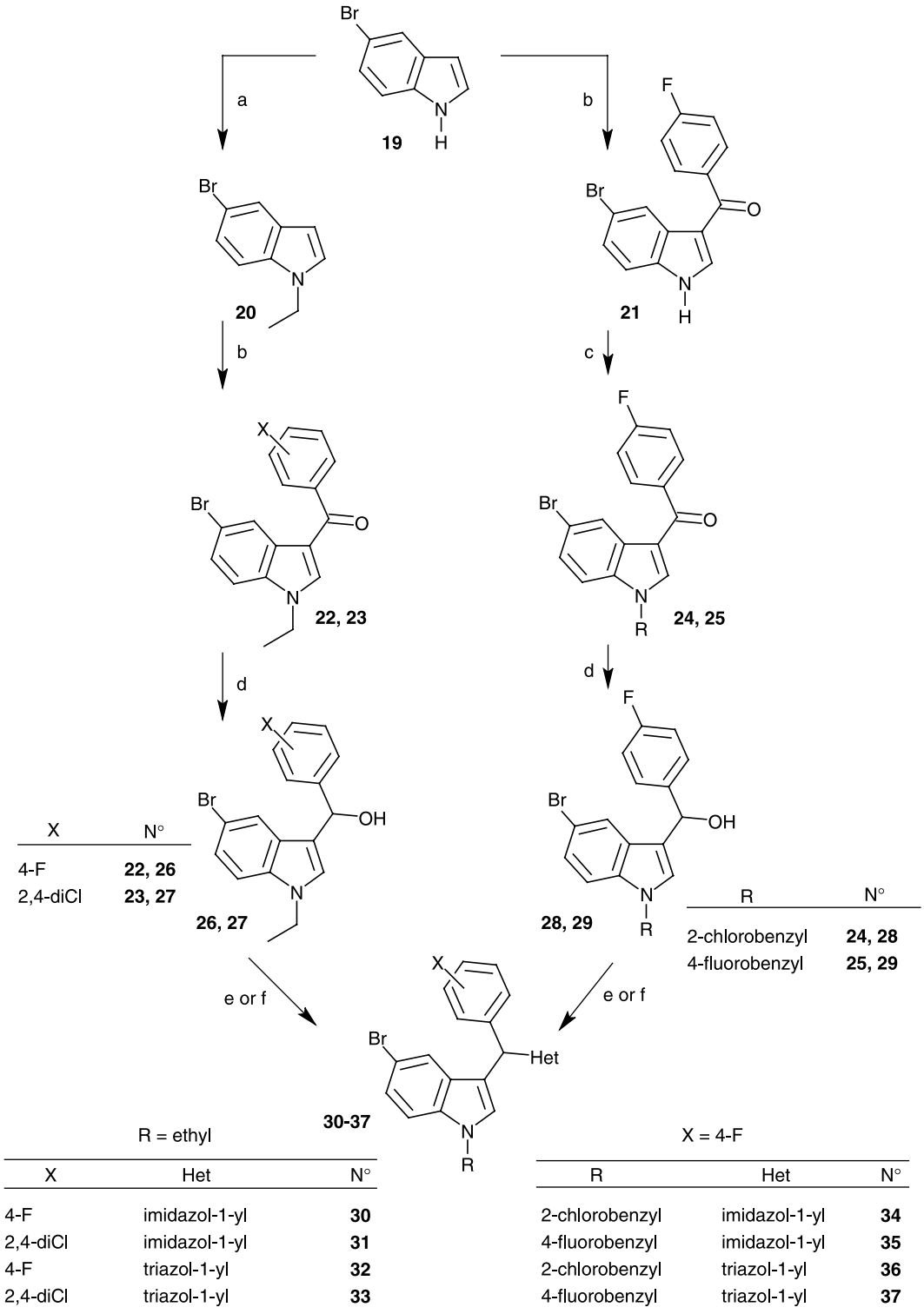
Chemistry

3-(Azolylmethyl)-1*H*-indoles incorporating differently substituted R groups were synthesized from indole-3-carbaldehyde **2** (see Scheme 1). *N*-Substitution of indole-3-carbaldehyde **2** with benzyl chlorides, using potassium carbonate in acetone, afforded the *N*-substituted indole derivatives **3**–**6**. Reduction of the carbonyl group was carried out by using sodium borohydride [38] in methanol and provided **7**–**10**. The synthesis of imidazolyl-substituted compounds **11**–**14** was achieved by the direct reaction of the carbinols **7**–**10** with 1,1′-carbonyldiimidazole (CDI) in THF [39], *via* decarboxylation of the carbamate intermediate. The triazolyl-substituted compounds **15**–**18** were prepared by the direct reaction of the corresponding carbinols with sulfinylditriazole (SDT) [40], which was readily generated from triazole and $SOCl_2$ in acetonitrile.

3-(α-Azolylbenzyl)-1*H*-indoles were obtained by two synthetic routes as depicted in Scheme 2. A Friedel Crafts procedure [41,42], using $AlCl_3$ catalysis, was employed to give the *N*-ethyl-3-aroylindole derivatives **22** and **23**. A direct acylation of 5-bromo-1*H*-indole **19** was attempted, with 4-fluorobenzoyl chloride; it gave 3-acylindole derivative **21**, in moderate yield. *N*-Substitution of **21** was achieved with benzyl chlorides, using Cs_2CO_3 in



Scheme 1. Synthetic route to 3-azolylmethyl-1*H*-indoles **11**–**14**. Reagents: (a) see reference [34]; (b) K_2CO_3, acetone, RCl; (c) $NaBH_4$, methanol; (d) CDI, THF; (e) SDT, CH_3CN.



Scheme 2. Synthetic route to 3-(azolylbenzyl)-1*H*-indoles **30**–**37**. Reagents: (a) see reference [33]; (b) $AlCl_3$, CH_2Cl_2, ArCOCl; (c) $CsCO_3$, CH_3CN, R_1Cl; (d) $NaBH_4$, methanol; (e) CDI, THF; (f) SDT, CH_3CN.

acetonitrile, and gave 3-aroyl-1-benzyl-1*H*-indoles **24** and **25** in excellent yields. Then the corresponding alcohols **28** and **29** were obtained by using $NaBH_4$ in methanol. Introduction of the imidazole and triazole moieties was achieved with CDI and SDT, leading to compounds **30**–**37**.

Biological results

The ability of compounds under investigation to inhibit aromatase was investigated. The IC_{50} values and the potencies of the compounds, relative to AG, are given in Tables II and III. The reference standard used was aminoglutethimide, with an IC_{50} value of 18.5 μM.

Table II. Inhibition of P450 arom and P450 17α by 3-(azolylmethyl)-1*H*-indoles **11**–**18**.

compound	R	Het	P450 arom		P450 17α
			IC_{50} (μM)[a]	RP[b]	% inhibition[c]
11	2-chlorobenzyl	imidazol-1-yl	0.054	342.6	62.8
12	2-fluorobenzyl	imidazol-1-yl	0.124	149.2	55.5
13	3-fluorobenzyl	imidazol-1-yl	0.082	225.6	70.2
14	4-cyanobenzyl	imidazol-1-yl	0.050	370.0	15.4
15a	2-chlorobenzyl	triazol-1-yl	0.173	106.9	9.3
15b	2-chlorobenzyl	triazol-4-yl	3.500	5.3	0.0
16a	2-fluorobenzyl	triazol-1-yl	0.420	44.0	0.0
16b	2-fluorobenzyl	triazol-4-yl	7.220	2.6	0.5
17	3-fluorobenzyl	triazol-1-yl	0.307	60.3	14.4
18	4-cyanobenzyl	triazol-1-yl	0.141	131.2	1.8

[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. All values are the mean of at least 2 determinations.

In the sub-series of 3-(azolylmethyl)-1*H*-indoles, all imidazole derivatives **11**–**14** were more active than their triazole analogues **15**–**18**. Triazol-4-yl derivatives **15b** and **16b** showed the lowest inhibitory potencies ($IC_{50} > 3.5$ μM). The presence of a chloro substituent in the ortho position of the N-benzyl moiety gave a positive result (compare compound **11** with respect to compound **12**). The presence of a fluorine atom at position 3 of the N-benzyl substituent improved the antiaromatase activity: compound **13** is 1.5 times more active than parent compound **12**. Imidazole derivative **14** in which the benzyl moiety was substituted by a 4-cyano group, was the most active, with an IC_{50} value of 0.050 μM. All compounds of this sub-series did not exhibit any significant inhibitory activity on rat testicular P450 17α. The highest percentage inhibition value found was 70 with compound **13** at the concentration of 2.5 μM. IC_{50} value was only calculated in the case of percentage inhibition value superior to 85%.

Table III shows the in vitro data of the antiaromatase activity of 3-(α-azolylbenzyl)-1*H*-indoles **30**–**37**. The N-ethyl derivative **30** showed an IC_{50} value of 0.052 μM and this imidazole derivative was the best inhibitor of this sub-series. Further structure-activity study regarding the presence of a 2,4-dichlorophenyl substituent did not improve activity (compound **30** compared with **31**). The replacement of the N-ethyl chain of compound **30** by the N-halobenzyl moiety (2-chloro or 4-fluoro) gave negative results for compounds **32** and **33**. The triazole derivative **34** was 19 times less active than its imidazole analogue **30**. Other triazole analogues **35**–**37** were less active than parent molecules **31**–**33**. As found with the first sub-series, all 3-(α-azolylbenzyl)-1*H*-indoles **30**–**37** were poor P450 17α inhibitors, with no significant percentage inhibition values (< 3.7).

In order to evaluate the *in vivo* efficacy, the effect of select 3-(azolylmethyl)-1*H*-indoles and 3-(α-azolylbenzyl)-1*H*-indoles on the androgen-stimulated uterine growth will be determined. In juvenile female rats, androstedione treatment strongly stimulates uterine weight. This effect is due to ovarian aromatization of the androgen and can be dose-dependently antagonized by aromatase inhibitors such as compounds **14** and **30**. Thus the antiuterotrophic activity could give further biological data to continue our research. Furthermore we are doing molecular modelling

Table III. Inhibition of P450 arom and P450 17α by 3-(α-azolylbenzyl)-1*H*-indoles **30**–**37**.

compound	R	X	Het	IC_{50} (μM)[a]	RP[b]	% inhibition[c]
30	ethyl	4-F	imidazol-1-yl	0.052	357.1	3.7
31	ethyl	2,4-diCl	imidazol-1-yl	0.333	55.6	0.7
32[d]	2-chlorobenzyl	4-F	imidazol-1-yl	0.964	19.2	1.6
33	4-fluorobenzyl	4-F	imidazol-1-yl	0.623	29.7	0.0
34	ethyl	4-F	triazol-1-yl	0.980	18.9	0.9
35	ethyl	2,4-diCl	triazol-1-yl	4.400	4.2	0.0
36	2-chlorobenzyl	4-F	triazol-1-yl	<25	-	0.0
37	4-fluorobenzyl	4-F	triazol-1-yl	7.1	2.6	1.0

[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. All values are the mean of at least 2 determinations. [d] Tested as nitrate.

studies on compound **14** and **30** to better understand their interactions in the active site of P450 arom and then to be able to design new non steroidal aromatase inhibitors.

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