SUPPORTING INFORMATION

Novel highly potent and selective nonsteroidal aromatase inhibitors: synthesis, biological evaluation and structure-activity relationships investigation

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S1
Chemistry. General Methods. All melting points were determined in open glass capillaries using a Büchi apparatus and are uncorrected. $^1$H and $^{13}$C NMR spectra were recorded on a Varian Gemini 300 spectrometer in CDCl$_3$ solutions, with Me$_4$Si as the internal standard. Mass spectra were recorded on a V.G. 7070 E spectrometer or on a Waters ZQ 4000 apparatus operating in electrospray (ES) mode. Silica gel (Merck, 230-400 mesh) was used for purification with flash chromatography. The purity of the tested compounds was determined by HPLC analysis, performed on a Jasco LC 1500 PU-1587; the column used was a Phenomenex Luna C18(2) $5\mu m$ 4.60 mm × 150 mm; elution conditions: mobile phase CH$_3$CN/H$_2$O 30/70; the flow-rate was 0.8 ml/min and the injection volume was 5 $\mu l$; peaks were detected at 250 nm and results were > 95% purity. Compounds were named following IUPAC rules as applied by AUTONOM, a PC software for systematic names in organic chemistry, Beilstein-Institut and Springer.

Synthesis of intermediate compounds 14, 15, 22, 29-38, 40, 41

2-(2-methyl-4-nitrophenoxy)benzoic acid (14). A mixture of o-chlorobenzoic acid (17.2 g, 0.11 mol), 2-methyl-4-nitrophenol (15 g, 0.11 mol), Cu (1.5 g), CuI (1.5 g) and K$_2$CO$_3$ (30 g) in 150 mL of nitrobenzene were heated at 170-180 °C for 8 h. The solvent was removed by steam distillation and the resulting suspension was filtered and acidified with HCl. The solid was filtered, washed with water and crystallised from ligroin, to obtain 15 g of 14, (50 %). Mp 151-153 °C. $^1$H NMR: $\delta$ 2.40 (s, 3H, CH$_3$), 7.00-8.10 (m, 7H, Ar).

4-Methyl-2-nitroanthen-9-one (15). 14 (15 g, 0.055 mol) was suspended in 100 mL of polyphosphoric acid and the mixture was heated at 120 °C for 6 h and then poured into ice. The solid was filtered, washed with water and crystallised from ligroin, to yield 9 g of 15 (64 %). Mp 214-216 °C. (Lit.$^1$ 218 °C). $^1$H NMR: $\delta$ 3.10 (s, 3H, CH$_3$), 7.20-8.40 (m, 6H, Ar).
4-Bromomethyl-2-nitroanthen-9-one (22). A mixture of 15 (3 g, 0.012 mol), N-bromosuccinimide (2.07 g, 0.012 mol) in the presence of a catalytic amount of benzoyl peroxide in 70 mL of CCl₄ was refluxed for 4 h and then hot filtered. The solvent was evaporated to dryness and the residue crystallized from ligroin, to give 2.8 g of the desired compound (72 %) which was used without further purification. ¹H NMR: δ 5.80 (s, 2H, CH₂Br), 7.40-8.50 (m, 6H, Ar).

2-(2-Methyl-5-nitro-phenylsulfanyl)benzoic acid (29). A mixture of 2-bromo-4-nitrotoluene (10.0 g, 0.05 mol), 2-mercaptobenzoic acid (7.1 g, 0.05 mol), Cu (1.0 g), CuI (1.0 g) and K₂CO₃ (4.55 g) in 150 mL of nitrobenzene were heated at 170-180 °C for 8 h. After steam distillation to remove the solvent, the resulting suspension was filtered and acidified with HCl. The solid was filtered, washed with water and crystallised from ligroin, to obtain 8.5 g of 29, (64 %). Mp 170-174 °C. ¹H NMR (DMSO): δ 2.35 (s, 3H, CH₃), 6.70-8.35 (m, 7H, Ar).

2-(2-Methyl-5-nitro-phenoxy)benzoic acid (30). Following the procedure described for 29, starting from 2-bromo-4-nitrotoluene (10.0 g, 0.05 mol) and salicylic acid (7.8 g, 0.05 mol), 9.4 g of 30 were obtained, (72 %). Mp 197-199 °C (ligroin). ¹H NMR: δ 2.40 (s, 3H, CH₂), 6.90-8.15 (m, 7H, Ar).

4-Methyl-1-nitrothioxanthen-9-one (31). Starting from 29 (5.0 g, 0.017 mol), following the same procedure described for compound 15, 2.7 g of 31 were obtained (59 %). Mp 171-173 °C (Lit. mp 171 °C). ¹H NMR: δ 2.30 (s, 3H, CH₂), 7.10-7.80 (m, 6H, Ar).

4-Bromomethyl-1-nitrothioxanthen-9-one (32). Using the procedure described for 22, 1.11 g of compound 32 (79 %) were obtained from 31 (1.18 g, 0.0043 mol) as oily compound which was used without further purification. ¹H NMR: δ 4.50 (s, 2H, CH₂Br), 7.10-7.90 (m, 6H, Ar).

1-Methyl-(2-phenoxy-4-nitro)benzene (33). 30 (0.8 g, 0.0017 mol) was heated 3 h at 220 °C in presence of a catalytic amount of Cu. After cooling, the compound was dissolved in CH₂Cl₂ and washed with NaHCO₃ saturated solution and H₂O. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (toluene/petroleum ether 9:1), to obtain 0.55 g (80 %) of 33, as oily compound. ¹H NMR: δ 2.40 (s, 3H, CH₂), 7.00-7.80 (m, 8H, Ar).
1-Methyl-(4-nitro-2-phenylsulfanil)benzene (34). Using the procedure described for 33, 0.30 g of 34 (73 %) were obtained as oily compound (Lit. \( ^3 \) mp 65-68 °C) starting from 29 (0.5 g, 0.0017 mol). 
\(^1\)H NMR: \( \delta \) 2.40 (s, 3H, \( CH_3 \)), 7.10-7.40 (m, 8H, \( Ar \))

1-Bromomethyl-(2-phenoxy-4-nitro)benzene (35). Using the procedure described for compound 22, 35 (0.4 g, 70 %) was obtained from 33 (0.55 g, 0.0024 mol) as oily compound which was used without further purification. \(^1\)H NMR: \( \delta \) 4.62 (s, 2H, \( CH_2 Br \)), 7.10-7.90 (m, 8H, \( Ar \)).

1-Bromomethyl-(4-nitro-2-phenylsulfanil)benzene (36). Using the procedure described for compound 22, 36 (0.56 g, 80 %) was obtained from 34 (0.42 g, 0.0017 mol) as oily compound which was used without further purification. \(^1\)H NMR: \( \delta \) 4.67 (s, 2H, \( CH_2 Br \)), 7.24-8.18 (m, 8H, \( Ar \)).

2-Tolyoxybenzene (37). Using the procedure described for 33, 0.36 g (73 %) of 37 were obtained as oily compound (Lit. \( ^4 \) bp 134-135 °C) starting from 2-o-tolyloxybenzoic acid \( ^5 \) (2 g, 0.0028 mol); purified by flash chromatography (toluene/petroleum ether 9:1). \(^1\)H NMR: \( \delta \) 2.49 (s, 3H, \( CH_3 \)), 7.00-7.50 (m, 9H, \( Ar \)).

1-Bromomethyl-2-phenoxybenzene (38). Using the procedure described for compound 22, 38 (0.5 g, 80 %) was obtained from 37 (0.35 g, 0.002 mol) as oily compound which was used without further purification. \(^1\)H NMR: \( \delta \) 4.42 (s, 2H, \( CH_2 Br \)), 6.80-8.10 (m, 9H, \( Ar \)).

8-Methyl-5-nitro-9-oxa-1-azaanthracen-10-one (40). A solution of 39 (2.9 g, 0.014 mol) in \( H_2 SO_4 \) (80 mL) was treated with fuming HNO\( _3 \) (0.58 mL, 0.014 mol) in 5 mL of \( H_2 SO_4 \), keeping the temperature between 0 and 5 °C. The reaction mixture was stirred for 1 h at room temperature and poured into ice. The separated solid was collected by filtration and purified by flash chromatography (toluene/acetone 4:1). 1.6 g (60 %) of 40 was obtained: mp 168-171 °C. \(^1\)H NMR: \( \delta \) 2.75 (s, 3H, \( CH_3 \)), 7.60-9.10 (m, 5H, \( Ar \)).

8-Bromomethyl-5-nitro-9-oxa-1-azaanthracen-10-one (41). Using the procedure described for compound 22, 41 (0.59 g, 70 %) was obtained from 40 (0.65 g, 0.0025 mol) as oily compound which was used without further purification. \(^1\)HNMR: \( \delta \) 4.92 (s, 2H, \( CH_2 Br \)), 7.48-9.20 (m, 5H, \( Ar \)).
References


