Inhibition of Estrone Sulfate-induced Uterine Growth by Potent Nonestrogenic Steroidal Inhibitors of Steroid Sulfatase

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INTRODUCTION

E2 is the main steroid hormone supporting growth of tumors in patients with estrogen-sensitive breast cancer (1). In addition to the blockade of E2 action that can be achieved by the use of antiestrogens (2, 3), a complementary approach to reduce the effects of estrogens consists in the inhibition of steroidogenic enzymes involved in their synthesis (4). Thus, extensive work has focused over the years on the development of inhibitors of the steroidogenic enzymes, namely aromatase (5–7), 17β-HSDs (8, 9), and steroid sulfatase (10–12). Inhibition of aromatase has been shown to provide an efficient blockade of the synthesis of potent estrogens, estrone (E1), and E2 (13–16) but cannot block the effect of weak estrogen 5-diol (17–19). The enzymes steroid sulfatase and type 1 17β-HSD mediate the synthesis of 5-diol by the adrenal precursors DHEAS and dehydroepiandrosterone available in the circulation. In addition, transformation of sulfated steroid estrone sulfate (E1S), the most abundant C18 steroid in aged women, by steroid sulfatase and type 1 17β-HSD provides another major source of potent estrogens E1 and E2 in breast tissue (4, 20–22).

There is now evidence that an important amount of E2 in breast tumors originates from local transformation of E1S following the sulfatase pathway, whereas <10% results from the aromatization of androst-4-ene-3,17-dione and testosterone (23, 24). The same pathway accounts for the transformation of DHEAS into the estrogen C19 steroid 5-diol. Thus, inhibition of steroid sulfatase, the enzyme responsible for the conversion of DHEAS to dehydroepiandrosterone and E1S to E1, may allow reduction of estrogen levels in tumors and could represent a promising approach for the treatment of estrogen-sensitive breast cancer.

Some of the most efficient steroid sulfatase inhibitors developed were sulfamate derivatives (10–12). The first reported inhibitor in this series, estrone sulfamate (EMATE; Ref. 25, 26) is a very potent irreversible inhibitor, but it is also an estrogenic compound (27), thus having less than optimal characteristics for the therapy of estrogen-sensitive cancers. Purhot et al. (28) then investigated various A-ring substituted analogues of EMATE and found that the 2-methoxy derivative was nonestrogenic and yet a potent inhibitor. Studies reported previously by other groups have in fact indicated that the E2 metabolite 2-methoxy-E2 has reduced ER binding affinity (29) as well as interesting antiangiogenic, antiproliferative, apoptotic, anticancerogenic, and cytotoxic properties (30–35). Our group has shown previously that the combined effects of a benzyl (or tert-butylbenzyl) group at C17α and a sulfamate group at C3 of E2 provide an improved inhibition of steroid sulfatase activity (36, 37). These inhibitors, however, induced the proliferation of estrogen-sensitive ZR-75-1 cells, thus suggesting an estrogenic activity (38). We then concluded that the 2-methoxy analogues of these inhibitors might be nonestrogenic and possibly promising therapeutic agents for estrogen-sensitive cancers by targeting important actions: (a) the inhibition of steroid sulfatase; (b) the inhibition of ERα cell proliferation; and (c) the inhibition of tumor angiogenesis (Fig. 1). Herein, we present the chemical synthesis briefly, the steroid sulfatase in vitro and in vivo inhibitory activities, as well as an in vivo study on the estrogenic properties of these new steroidal inhibitors.

MATERIALS AND METHODS

Chemical Synthesis. Starting steroids 2-methoxyestrone (1) and 2-methoxy-3-O-benzylestra-1,3,5 (10)-trien-17β-ol (7) were purchased from Steraloids, Inc. (Newport, RI) or synthesized similarly as reported in literature (39). Target compounds 6 and 7, as well as intermediate compounds 3–5, were synthesized from 1 and 2 as exemplified in Fig. 2 with few modifications of the procedure used for the synthesis of 11–14 (37). Additional compounds 8–10 were synthesized using classical reduction or sulfamoylation reactions already reported in the preparation of similar compounds (37, 38, 40). The chemical structure of all compounds were fully characterized by infrared, NMR, and mass analysis, and the purity of tested compounds was determined by HPLC and found acceptable for biological assays with purities ranging from 97% to 99%. The next data reported for key compound 7 as well as the HPLC profile (Fig. 3) are representative of all compounds tested in our study. The full details of the experimental procedure and characterization will be available on request addressed to the corresponding author.

2-Methoxy-3-sulfamoyloxy-17α-benzylestra1,3,5 (10)-trien-17β-ol (7). White solid; infrared (KBr): 3395 (OH and NH); 1H NMR (CDCl3): 0.98 (s, 18-CH3); 1.3–2.4 (14H), 2.68 and 2.94 (2d of AB-system, J = 13.2 Hz, CH2Ph), 2.82 (m, 6-CH3), 3.89 (s, OCH3), 4.96 (s, OSO2NH2), 6.96 (s, 4-CH), 7.06 (s, 1-CH), 7.33 (m, CH2Ph), 13C NMR (CDCl3): 14.44 (18-C), 23.27 (15-C), 26.36 and 27.28 (7- and 11-C), 28.62 (6-C), 31.36 (12-C), 33.7 (16-C), 39.11 (8-C), 42.33 (1-C), 44.34 (9-C), 46.69 (13-C), 49.53 (14-C), 56.35 (OCH3), 82.98 (17-C), 110.44 (1-C), 124.06 (4-C), 126.36 (5’-C), 128.14 (3’ and 5’-C), 130.19 (5-C), 131 (2’ and 6’-C), 136.8 (10-C), 138.12 (1’-C), 142 (11-C), 146 (12-C), 149.93 (13-C), 156.35 (OCH3).
140.41 (3-C), 148.93 (2-C); LRMS for C_{26}H_{33}NO_{5}S: 489.6 m/z; HPLC purity = 97.2% (C-18 Nova Pak column, H_{2}O: methanol/30:70).

Steroid Sulfatase Assays (in Vitro Studies). HEK-293 cells (American Type Culture Collection, Rockville, MD), transiently transfected with a sulfatase expression vector (pCMV-sulfa), were used as the source of steroid sulfatase activity. The pCMV-sulfa was constructed by insertion of a cDNA fragment, downstream of the CMV promoter of the pCMV vector, kindly provided by Dr. M. B. Mathews (Cold Spring Harbor Laboratories, Cold Spring Harbor, NY). The cDNA fragment was obtained by screening of a human placenta cDNA library (Clontech Laboratories Inc., Palo Alto, CA) using the incomplete cDNA fragment kindly provided by Dr. L. J. Shapiro (Howard Hughes Medical Institute, Los Angeles, CA) as probe. Transfection of the expression vector was performed by the calcium phosphate procedure using 10 μg of recombinant plasmid/10^6 cells. The cells were initially plated at 10^5 cells/cm² in Falcon culture flasks and grown in DMEM containing 10% (volume for volume) fetal bovine serum supplemented with 2 mM L-glutamine, 1 mM sodium pyruvate, 100 IU penicillin/ml, and 100 μg of streptomycin sulfate/ml. For assay, the HEP-293 cells transfected with steroid sulfatase activity were prepared by repeated freezing (~80°C), thawing (five times), and homogenization using a Dounce homogenizer. The enzymatic reaction was carried out at 37°C for the transformation of [^{3}H]E_{1}S into [^{3}H]E_{1} in 1.25 ml of each phase (organic: [^{3}H]E_{1} and aqueous: [^{3}H]E_{1}S) were recorded by liquid scintillating counting with a Beckman LS8001 (Irvin, CA). The results are reported as a percentage (%) of inhibition at appropriate concentrations.

Studied Sulfatase and Estrogenicity Assays (in Vivo Studies). Female BALB/c mice (BALB/cAnCtBR) weighing 18–20 grams were obtained from Charles River, Inc. (St-Constant, Québec, Canada) and housed four to five per cage in a temperature (22 ± 3°C) and light (12 h/day, lights on at 7h15) controlled environment. The mice were fed rodent chow and tap water ad libitum. The animals were OVX under isoflurane anesthesia via bilateral flank incisions and randomly assigned to groups of 8–10 animals. Ten mice were kept intact (INT) as control. To exert an estrogenic effect and stimulate an estrogen-sensitive parameter as uterus, E_{1}S is converted into E_{1} and then into E_{2} under the catalytic activities of the enzymes steroid sulfatase and type 1 17β-HSD, respectively. Mice in the intact and OVX control groups received the vehicle alone (8% ethanol-0.4% methylcellulose) during the 9-day period. The possible estrogenic activity (Fig. 5) of tested compounds was evaluated after their administration by subcutaneous (s.c.) injection [100 μg, s.c., once daily (ID)] alone to OVX female mice for 9 days. For the evaluation of the inhibition of steroid sulfatase activity (Figs. 6–8), the tested compounds were administered as suspension in 8% ethanol-0.4% methylcellulose to OVX mice for 9 days (1, 10, or 100 μg s.c. or oral (p.o.), ID, from day 2 to 10 of the study). The mice were simultaneously treated with E_{1}S [2 μg s.c., twice daily (BID)] from day 5 to 10 of the study. The tested compounds were also administered to OVX mice treated simultaneously with E_{1}S (0.06 μg s.c., BID) from day 5 to 10 of the study (Fig. 6). This was needed to ensure that the effect observed on the uterine weight does not result from an antiestrogenic effect instead of the inhibition of steroid sulfatase. On day 11, the mice were sacrificed by exsanguination followed by cervical dislocation. Uterus from mice were rapidly dissected, weighed, and kept in 10% buffered formalin for further histological studies.
Table 1. *In vitro* inhibition of steroid sulfatase activity (homogenates of transfected HEK-293 cells) by 2-methoxy derivatives and reference inhibitors

<table>
<thead>
<tr>
<th>Compound</th>
<th>C3-group</th>
<th>C2-group</th>
<th>C17α-group</th>
<th>Inhibition (%) at 30 nM</th>
<th>Inhibition (%) at 300 nM</th>
<th>Inhibition (%) at 3000 nM</th>
<th>IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Phenol</td>
<td>Methoxy</td>
<td>tert-Butyl-benzyl</td>
<td>52</td>
<td>86</td>
<td>95</td>
<td>28 ± 9</td>
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<tr>
<td>5</td>
<td>Phenol</td>
<td>Methoxy</td>
<td>Benzyl</td>
<td>0</td>
<td>15</td>
<td>63</td>
<td>0.002</td>
</tr>
<tr>
<td>6</td>
<td>Sulfamate</td>
<td>Methoxy</td>
<td>tert-Butyl-benzyl</td>
<td>99</td>
<td>99</td>
<td>99</td>
<td>0.004 ± 0.002</td>
</tr>
<tr>
<td>7</td>
<td>Sulfamate</td>
<td>Methoxy</td>
<td>Benzyl</td>
<td>99</td>
<td>99</td>
<td>99</td>
<td>0.024 ± 0.008</td>
</tr>
<tr>
<td>8</td>
<td>Phenol</td>
<td>Methoxy</td>
<td>H</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.70 ± 0.16</td>
</tr>
<tr>
<td>9</td>
<td>Sulfamate</td>
<td>Methoxy</td>
<td>Ketone</td>
<td>89</td>
<td>98</td>
<td>98</td>
<td>99</td>
</tr>
<tr>
<td>10</td>
<td>Sulfamate</td>
<td>Methoxy</td>
<td>H</td>
<td>80</td>
<td>97</td>
<td>97</td>
<td>99</td>
</tr>
<tr>
<td>11</td>
<td>Phenol</td>
<td>H</td>
<td>tert-Butyl-benzyl</td>
<td>91</td>
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<tr>
<td>12</td>
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</tr>
<tr>
<td>14</td>
<td>Sulfamate</td>
<td>H</td>
<td>Benzyl</td>
<td>99</td>
<td>99</td>
<td>99</td>
<td>0.030 ± 0.003</td>
</tr>
</tbody>
</table>

*Inhibition of the transformation of [3H]E1S (100 μM) to [3H]E1.*

* See Fig. 2 for the chemical structures of tested compounds.

* Error estimated at ± 5%.

Fig. 4. Effects of increasing concentration of compounds 3, 6, 7, 9, 13, and E1S on enzymatic activity of steroid sulfatase transfected in HEK-293 cells (see “Materials and Methods” for details). The results are expressed as a percentage of transformation of [3H]E1S into [3H]E1. Data points represent the mean values ± SE from triplicate incubations.

RESULTS AND DISCUSSION

*In Vitro Study (Steroid Sulfatase Inhibitory Activity).* The inhibition of steroid sulfatase activity by 2-methoxylated compounds 3, 5–10 and reference compounds 11–14 was investigated in homogenate of transfected HEK-293 cells transforming E1S to E1 (Table 1) following a procedure reported previously (37). In the phenol series, the 2-methoxy-E2 (8) does not inhibit steroid sulfatase activity. In the case of other 2-methoxy derivatives 3 and 5, the methoxy group at C2 is responsible for a reduced inhibitory action compared with that of the parent compounds 11 and 12. This is probably caused by the activating effect induced by the ortho-positioning of the methoxy group, resulting in lower acidity of the phenolic group at C3. Thus, at a concentration of 300 nM, compounds 3 and 5 with a tert-butylbenzyl or a benzyl group at C-17α inhibited 86 and 15% of the enzyme activity, respectively, whereas their analogues 11 and 12 without a 2-methoxy group were more potent with 97 and 66% inhibitions. These differences were even more pronounced in the test run with the same compounds at a concentration of 30 nM. In the sulfamate series, all of the sulfamate derivatives inhibited >80% of the enzyme activity at 30 nM. At this concentration, the use of a tert-butylbenzyl (or benzyl) group at C17α provided a stronger inhibition of the enzyme, and the potency of inhibitors 6 and 7 was found higher than that of 2-methoxy-EMATE (9) or 2-methoxy-E2-3-O-sulfamate (10). Thus, our first observation (37, 38) about the complementarity of the inhibitory effects of a sulfamate group at C3 and a suitable hydrophobic group at C17 was confirmed here again with the 2-methoxylated compounds. Moreover, compounds 6, 7, 13, and 14 with two inhibiting groups fully inhibited (99%) enzymatic activity and were more active compared with their analogues without the sulfamate group at C3, namely compounds 3, 5, 11, and 12.

The methoxy derivatives 3, 6, 7, and 9 and the reference inhibitor 13 (37) were next tested at various concentrations to determine the IC50 for inhibition of steroid sulfatase activity. The results presented in Fig. 4 illustrate that all of these compounds are potent inhibitors of the enzyme. In our test, the IC50 of 2-methoxy-EMATE (9) was 1.7 nM, whereas compounds 6, 7, and 13 with the two inhibiting groups tert-butylbenzyl (or benzyl) and sulfamate were much more potent (IC50 = 0.04, 0.024, and 0.03 nM). The nonsulfamoylated inhibitor 3 was also a good inhibitor with an IC50 in the range of 30 nM. Although the introduction of the methoxy group at C2 resulted in a decrease of the inhibitory activity, this decrease can however be considered as small. Indeed, the IC50 of the reference inhibitor 13 and its 2-methoxy analogue 6 were 0.03 and 0.04 nM, respectively. In a previous test performed by Purohit et al. (28), the IC50 of 2-methoxy-EMATE (9) in placental microsomes was found to be 7-fold beyond that of EMATE. Rather interestingly, with an IC50 of 0.024 nM, compound 7 was apparently the best inhibitor of steroid sulfatase within those tested in our assay. Compound 7 was also tested on type 1 17β-hydroxysteroid dehydrogenase, and no inhibition of E1 into E2 transformation was observed at the two concentrations of 0.1 and 0.008 nM.
Deprivation of estrogens. When administered to OVX mice, E1 S in vivo gated inhibitory (antisulfatase) activities of tested compounds were investigated versus experimental studies focusing on antisulfatase and estrogenic activities.

In Vivo Studies. Estrogenic, antiestrogenic, and steroid sulfatase inhibitory (antisulfatase) activities of tested compounds were investigated in vivo using the OVX mouse model. As shown in Figs. 5–8, ovariectomy induces a 70% decrease of uterine weight because of deprivation of estrogens. When administered to OVX mice, E1 S is converted in the uterine tissue into E1 by the steroid sulfatase and then into E2 by type 1 17β-hydroxysteroid dehydrogenase. The increase of uterine weight, an estrogen-sensitive tissue, then reflected the formation of active estrogens from E1 S.

To discriminate between the estrogenic or nonestrogenic activities of a series of steroid sulfatase inhibitors, compounds 7, 12, 14, EMATE, and ICI 164,384 were injected s.c. to OVX female mice in the absence of treatment with E1 S (Fig. 5). No significant response or estrogenic stimuli of the uterus was observed with the pure antiestrogen ICI 164,384 (42). However, with a Ki of 11 μM, this was a weak inhibitor. The effect of ICI 164,384 in OVX mice simultaneously treated with E1 S (30 and 91% at 10 and 100 μg) is predominantly attributable to its antiestrogenic activity, rather than to antisulfatase activity. In contrast to other tested inhibitors, compound 7, the 2-methoxy derivative of 14, reduced by >84% the uterine growth induced by E1 S at both doses of 10 and 100 μg. A similar inhibitory effect (72%) was also observed following the administration of compound 7 at a lower dose of 1 μg, s.c. (Fig. 8). This later compound was also tested at a 100-μg dose administered p.o., and the inhibition achieved was the same as obtained with a 10-μg dose injected s.c. (83 and 80%, respectively). In summary, the in vivo experiments with the uterine weight model clearly prove that the synthesized compound 7 has no antiestrogenic activity and is a nonestrogenic potent inhibitor of steroid sulfatase activity, both following parenteral and p.o. administration.

1 μM.4 After a preliminary evaluation of the biodisponibility of the tested compounds, the benzyl derivative 7 was selected for additional in vivo studies focusing on antisulfatase and estrogenic activities.

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In the experiment reported in Fig. 6, E1 S or E1 were injected s.c. to OVX mice simultaneously to the administration of the selected inhibitor 7 at the daily dose of 100 μg. The uterine weight increase induced by E1 S was strongly inhibited (84%) by the nonestrogenic steroid sulfatase inhibitor 7, whereas the uterine weight induced by E1 was not significantly decreased (14%, nonsignificant). These results obtained with E1 and E1 S clearly demonstrate that compound 7 does not act as an antiestrogen (by blocking ER) but rather is a potent steroid sulfatase inhibitor efficiently blocking the transformation of E1 S into active estrogens.

As shown in Fig. 7, the inhibitors 12, 14, and EMATE (all without a methoxy group) reported previously did not reduce uterine weight when compared with control (OVX + E1 S), thus indicating their estrogenic properties. The administration of a nonestrogenic steroid sulfatase inhibitor should block estrogen synthesis from E1 S, and, correspondingly, the uterine weight increase induced by E1 S will be prevented. Nevertheless, an estrogenic inhibitor of the steroid sulfatase can itself exert an inhibitory action on steroid sulfatase (reducing uterine weight), but, simultaneously, it stimulates the growth of the uterus. In the same experiment, the antiestrogen ICI 164,384 induces a dose-dependent decrease of the uterine weight. Santner and Santen have reported previously the inhibition of estrone sulfatase by the antiestrogen ICI 164,384 in rat mammary tumors (42). However, with a Ki of 11 μM, this was a weak inhibitor. The effect of ICI 164,384 in OVX mice simultaneously treated with E1 S (30 and 91% at 10 and 100 μg) is predominantly attributable to its antiestrogenic activity, rather than to antisulfatase activity. In contrast to other tested inhibitors, compound 7, the 2-methoxy derivative of 14, reduced by >84% the uterine growth induced by E1 S at both doses of 10 and 100 μg. A similar inhibitory effect (72%) was also observed following the administration of compound 7 at a lower dose of 1 μg, s.c. (Fig. 8). This later compound was also tested at a 100-μg dose administered p.o., and the inhibition achieved was the same as obtained with a 10-μg dose injected s.c. (83 and 80%, respectively). In summary, the in vivo experiments with the uterine weight model clearly prove that the synthesized compound 7 has no antiestrogenic activity and is a nonestrogenic potent inhibitor of steroid sulfatase activity, both following parenteral and p.o. administration.

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4 V. Lua-The, unpublished data.
The results obtained from our in vivo study are in agreement with previous reports indicating that EMATE is an estrogens compound that could not be used in the treatment of estrogen-sensitive cancers (27, 28). Our results also demonstrate that the reversible inhibitor 17α-benzyl-E2 (12) and the irreversible inhibitor 3-O-sulfamate-17α-benzyl-E2 (14) are both estrogenic in the O VX mouse model (uterine weight). At the opposite and more interestingly, the 3-O-sulfamate-2-methoxy-17α-benzyl-E2 (7), which is the 2-methoxylated analogue of 14, was found to be a potent steroid sulfatase inhibitor, nonestrogenic, and without antiestrogenic activity (no effect mediated by ER). This compound reverses very efficiently the uterine weight stimulation normally induced by E1S after its transformation into active estrogens by blocking the steroid sulfatase. Compound 7 is also a potent in vitro inhibitor of steroid sulfatase with an IC50 of 0.024 nM for the transformation of E1S to E1 in homogenate of transfected HEK-293 cells. Because of the combined effects of the sulfamate and benzyl (or tert-butylbenzyl) groups introduced at C3 and C17α (37), the potency of 6 and 7 are comparable with that of the parent compound without the 2-methoxy group. Because it was shown previously that estrogen metabolite 2-methoxy-E2 (8) has low binding affinity for the estrogen receptor, exerts cytotoxic action in cancer cell cultures, and inhibits tumor angiogenesis (29–35, 43), we thus expect that the target 2-methoxylated inhibitors reported above might conserve some of these properties in addition to their very potent inhibition of steroid sulfatase. Additional studies will however be necessary to confirm this point as well as to focus on the use of these inhibitors in the therapy of estrogen-sensitive cancers.

ACKNOWLEDGMENTS

We thank Richard Labrecque and Yvon Fréchette for useful discussions about some aspects of the chemical synthesis. We also thank Mei Wang and Guy Reimnitz for their contribution in performing the enzymatic assays.

REFERENCES

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