Available online at www.sciencedirect.com
SCIENCE DIRECT®
European Journal of Pharmacology 461 (2003) 73–78
www.elsevier.com/locate/ejphar

CP8668, a novel orally active nonsteroidal progesterone receptor modulator with tetrahydrobenzindolone skeleton

Yuji Tabata*, Yumiko Iizuka, Rie Shinei, Ken-ichi Kurihara, Tsuneo Okonogi, Shigeru Hoshiko, Yasushi Kurata

Pharmaceutical Research Center, Meiji Seika Kaisha, Ltd., 760 Morooka-cho, Kohoku-ku, Yokohama 222-8567, Japan

Received 12 September 2002; received in revised form 17 December 2002; accepted 24 December 2002

Abstract

We investigated progestational activity of a new nonsteroidal compound, CP8668, ((4*aR*,5*R*,6*R*,7*R*)-7-methoxy-6-(*N*-propylaminocarbonyl)oxy-4*a*,5,6,7-tetrahydro-1,3,4*a*,5-tetramethylbenz[*f*]indol-2(4*H*)-one). CP8668 showed selective affinity for human progesterone receptor equal in strength to other steroidal progestins. CP8668 showed no significant affinity for human glucocorticoid receptor or human estrogen receptor and very weak affinity for rat androgen receptor. In endogeneous and exogeneous progesterone-dependent enzyme expression assays using human mammary carcinoma T47D, CP8668 showed mixed agonist–antagonist activity. However, in a rabbit endometrial transformation test, CP8668 showed good progestational activity following s.c. and p.o. administration. These results suggest that CP8668 is a selective and orally active progesterone receptor modulator, which shows mixed agonist–antagonist activity in in vitro transcription tests and agonist activity in endometrial transformation assays in rabbits, and that it is potentially a promising lead compound for a new type of orally active progesterone receptor modulator.

Keywords: CP8668; Progesterone receptor modulator, nonsteroidal; T47D; Endometrial transformation, rabbit; PF1092

1. Introduction

Progesterone, a steroid hormone, plays an important role in mammalian female reproduction during all stages of ovarian cycles and during pregnancy. Therefore, progestins, which are synthetic compounds with progestational activities, have many therapeutic uses, including a use as oral contraceptive agents, in hormone replacement therapy in combination with estrogens, assisted reproduction technology, and the treatment of gynecological disorders such as dysmenorrhea, endometriosis, and dysfunctional uterine bleeding caused by hormonal imbalances (Editorial, 1996).

Furthermore, mixed agonists–antagonists, which span the biological spectrum and are called progesterone receptor modulators or mesoprogestins, are also reported to offer potential applications in the treatment of endometrial disorders such as endometriosis, uterine myoma and dysfunctional uterine bleeding (Chwalisz et al., 2000, 2002; Elger et al., 2000).

Nevertheless, most steroidal progesterone receptor agonists possess cross-reactivity for other steroid receptors, and are often accompanied by side effects (Editorial, 1996). Thus, research on nonsteroidal progesterone receptor agonists has been promoted for the past several years (Pathirana et al., 1995; Combs et al., 1995; Zhi et al., 1999; Palmer et al., 2002; Zhang et al., 2002).

In the course of screening for nonsteroidal progesterone receptor ligands, we discovered PF1092A, B, and C in extracts of cell cultures of a rare fungus, *Penicillium oblatum* PF1092 (Tabata et al., 1997a,b). These compounds possess tetrahydronaphthofuranone skeletons. We then proceeded to synthesize derivatives and analogues of PF1092 (Kurihara et al., 1997, 1999; Tatsuta et al., 1997; Harimaya et al., 1997) and reported on the in vitro biological activities of preliminary derivatives of PF1092C (Tabata et al., 2001). In the report, we showed that these preliminary derivatives possess selective affinity for progesterone receptor, and that we can synthesize in vitro active progesterone receptor pure antagonists and mixed agonists–antagonists from PF1092C.

In a further study, we synthesized an orally active tetrahydrobenzindolone-type progesterone receptor modula-

* Corresponding author. Tel.: +81-45-545-3113; fax: +81-45-545-3193.
E-mail address: yuji_tabata@meiji.co.jp (Y. Tabata).

0014-2999/03/$ - see front matter © 2003 Elsevier Science B.V. All rights reserved.
doi:10.1016/S0014-2999(02)02958-8

tor, CP8668, from PF1092C. This paper describes the pharmacology of CP8668 in in vitro and in vivo assays and the possibility of tetrahydrobenzindolone-type compounds as lead compounds for oral active progesterone receptor modulators.

2. Materials and methods

2.1. Materials

CP8668 ((4*aR*,5*R*,6*R*,7*R*)-7-Methoxy-6-(*N*-propylaminocarbonyl)oxy-4*a*,5,6,7-tetrahydro-1,3,4*a*,5-tetramethylbenz[*f*]indol-2(4*H*)-one) was synthesized from PF1092C ((4*aR*,5*R*,6*R*,7*S*)-6,7-dihydroxy-4*a*,5,6,7-tetrahydro-3,4*a*,5-trimethylnaphtho [2,3-*b*]furan-2(4*H*)-one) at our laboratory. The purity of CP8668 was confirmed to be over 98% by high performance liquid chromatography analysis (Shimadzu CHROMATOPAC C-R4A). PF1092C was purified from extracts of cell cultures of the rare fungus, *P. oblatum PF1092*, at the same location. Progesterone (4-pregnene-3,20-dione) was purchased from Junsei Chemical. Testosterone (4-androsten-17β-ol-3-one), 17β-estradiol (3,17α-dihydroxy-1,3,5[10]-estratriene) and medroxyprogesterone acetate (MPA, 6α-methyl-17α-hydroxyprogesterone acetate) were purchased from Wako. Dexamethasone (9α-fluoro-16α-methyl-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione) and RU486 (11β-[4-dimethylamino]phenyl-17β-hydroxy-17-[1-propynyl]estra-4,9-dien-3-one) were purchased from Sigma. [1,2,6,7,-^{3}H(*N*)]-Progesterone (specific activity: 3589 GBq/mmol), [17α-methyl-^{3}H]-mibolerone (4-esteren-7α,17α-dimethyl-17β-ol-3-one) (specific activity: 3145 GBq/mmol), and [2,4,6,7,-^{3}H(*N*)]-estradiol (specific activity: 2664 GBq/mmol) were purchased from NEN™ Life Science Products [1,2,4-^{3}H]-Dexamethasone (specific activity: 1590 GBq/mmol) was purchased from Amersham Pharmacia Biotech.

2.2. Cell cultures

T47D human breast carcinoma cells, IM-9 human lymphoma cells, and MCF-7 human breast carcinoma cells were purchased from the American Type Culture Collection (ATCC). T47D human breast cancer cells and MCF-7 human breast carcinoma cells were cultured in Dulbecco's Modified Eagle Medium (DMEM, Gibco) containing 10% fetal bovine serum. IM-9 human lymphoma cells were cultured in an RPMI 1640 medium containing 10% fetal bovine serum. The cloned T47D cells to which pMAMneo-LUC plasmid (Clontech) was transfected (T47D-pMAMneo-LUC cells) were cultured in DMEM containing 10% fetal bovine serum and 600 μg/ml G418 (Meiji Seika Kaisha). All cell lines were cultured at 37 °C with 5% CO_2.

2.3. Steroid receptor binding assay

Each steroid receptor binding assay method was described by Tabata et al. (2001). In brief, cytosol containing steroid receptors was prepared from different cell lines or organs of various species (human progesterone receptor from T47D, rat androgen receptor from rat prostate, human glucocorticoid receptor from IM-9 and human estrogen receptor from MCF-7). An experimental procedure for rat androgen receptor was in accordance with the Guidelines for Animal Experimentation approved by the Pharmaceutical Research Center of Meiji Seika Kaisha. Each cell and organ was homogenized in appropriate preservation buffer and centrifuged at 100,000 × *g* for 30 min. The resulting supernatant (cytosol) was stored at − 80 °C until use. Cytosol was incubated with the corresponding radioligand for the corresponding incubation time ([1,2,6,7,-^{3}H(*N*)]-progesterone for 1 h for human progesterone receptor, [17α-methyl-^{3}H]-mibolerone for 24 h for rat androgen receptor, [1,2,4-^{3}H]-dexamethasone for 24 h for human glucocorticoid receptor and [2,4,6,7,-^{3}H(*N*)]-estradiol for 20 h for estrogen receptor). Following the incubation, cold dextran-coated charcoal solution was added to the reaction mixture. Following the incubation at 4 °C for 10 min and centrifugation at 5000 × *g*, the radioactivity of the supernatant was determined with Aquasol-2 (Packard Instrument) using a liquid scintillation counter (Beckman LS6500). Nonspecific binding was defined as the binding observed when 10 μM of corresponding cold steroid was added to the reaction mixture.

2.4. Progesterone-dependent endogeneous luciferase expression assay

The progesterone-dependent modulation of gene transcription was examined using a luciferase assay with stable transfected T47D-pMAMneo-LUC cells. The assay was

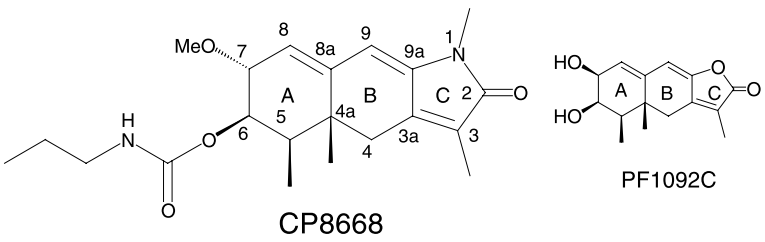

Fig. 1. Structures of CP8668 and PF1092C.

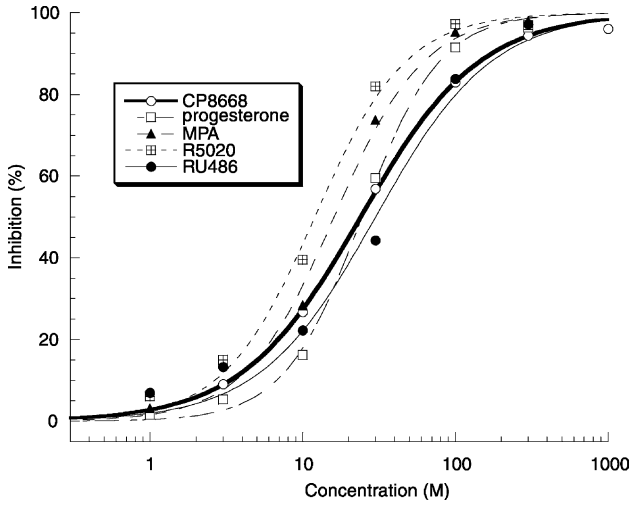

Fig. 2. Inhibitory effects of CP8668 on [^{3}H]-progesterone binding to human progesterone receptor. The reaction mixtures, containing [1,2,6,7-^{3}H(*N*)] progesterone, T47D cytosol, and tested compounds, were incubated for 1 h at 4 °C. Radioactivity of the supernatant was measured with a liquid scintillation counter. The data shown are representative of three independent experiments, all of which provided similar results.

performed as previously described (Tabata et al., 2001). In brief, the growth medium for T47D-pMAMneo-LUC cells was replaced with phenol red-free DMEM containing 5% fetal bovine serum treated with dextran-coated charcoal. After 24 h of cultivation, the cells were plated in 96-well plates at 50,000 cells/well. After 8 h of cultivation, the test compounds were added to each well to achieve the appropriate compound concentration. After 16 h of cultivation, 100 μl of Luc Lite (Packard) solution was added to each well and mixed. After 15 min of incubation at room temperature, luminescence was measured using an ARVO (Perkin-Elmer) luminometer. All data points were measured in triplicate.

2.5. Progesterone-dependent endogenous alkaline phosphatase expression assay

The progesterone-dependent modulation of alkaline phosphatase expression was examined using T47D. The assay was performed as previously described (Tabata et al., 2001). In brief, the growth medium was replaced with phenol red-free DMEM containing 5% fetal bovine serum treated with dextran-coated charcoal. After 24 h of cultivation, the cells were plated in 96-well plates at 25,000 cells/well. After 24 h of cultivation, the test compounds were added to each well to achieve the appropriate compound concentration. After 20 h of cultivation, the medium was removed and the cells were washed with 200 μl of Dulbecco's phosphate-buffered saline without calcium and magnesium (PBS(−)). The plates were kept at −80 °C for 15 min, and then thawed at room temperature. This freeze-and-thaw cycle was repeated once again. After 5 min of incubation at room temperature, 50 μl of PBS(−) and 30 μl of CSPD™ chemiluminescent substrate solution (Great EscApe™ SEAP Detection kit, Clontech) was added to each well and mixed. After 30 min of incubation at room temperature, luminescence was measured with an ARVO (Perkin-Elmer) luminometer.

2.6. Rabbit endometrial transformation test

The experimental procedure for the rabbit endometrial transformation test complied with the Guidelines for Animal Experimentation approved by the Pharmaceutical Research Center of Meiji Seika Kaisha. Immature female rabbits, weighing 800–1100 g, were used. All rabbits were primed with estrogen for 6 days, and then administered with 0, 5, or 10 mg/kg/day (s.c.), or with 0, 2.5, 5, or 10 mg/kg/day (p.o.) of CP8668 dissolved in MIGYOL 812 Neutral Oil (Mitsuba Trading) for 5 consecutive days to determine progestational activity. All rabbits were sacrificed on the day following the final administration of test compound or progesterone. The uteri were excised, weighed, and fixed in buffered formalin, and 2- to 3-mm sections were cut with a razor blade. Transversal slices from each of the right and left uterine horns were prepared, stained with haematoxylin and eosin, and examined histologically. The extent of endometrial transformation was recorded as a progestational effect in accordance with the method previously described (McPhail, 1934).

3. Results

3.1. Binding affinity of CP8668 to progesterone receptor and other steroid receptors

CP8668 possesses a tetrahydrobenzindolone skeleton synthesized from PF1092C in a series of steps (Fig. 1). In the progesterone receptor binding assay, CP8668 inhibited [^{3}H]-progesterone binding to human progesterone receptor dose-dependently with an IC_{50} value of 30 ± 7 nM (mean ±

Table 1
Relative binding affinity of CP8668 for steroid receptors

	hPR progesterone = 100	rAR testosterone = 100	hGR dexamethasone = 100	hER 17β-estradiol = 100
CP8668	92 ± 20	0.25 ± 0.04	< 0.07	< 0.007
RU486	72 ± 26	14 ± 2	65 ± 21	< 0.007
MPA	147 ± 37	33 ± 3	16 ± 3	< 0.007

Relative binding affinity (RBA) was calculated as follows: (mean of IC_{50} values of the standard steroidal compound/IC_{50} value of the test compound) × 100. The results represent means ± S.D. (three experiments).

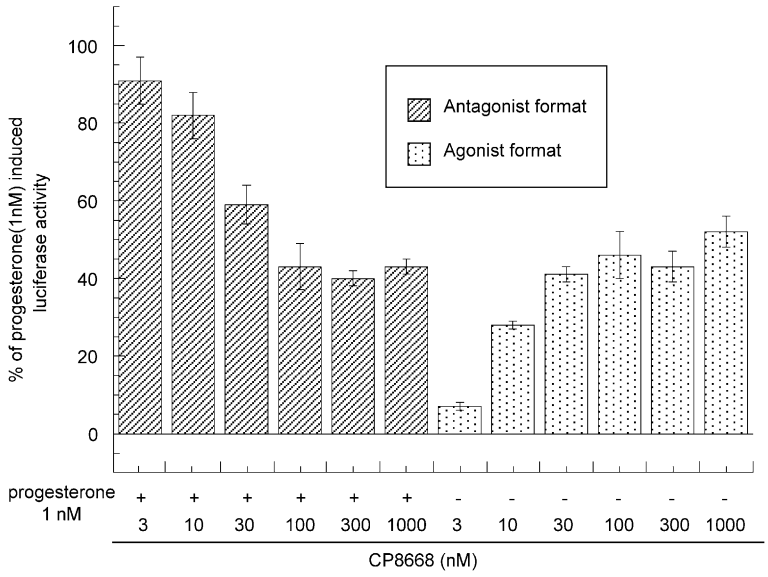

Fig. 3. Modulation of exogeneous luciferase expression in T47D-pMAMneo-LUC by CP8668. The indicated concentration of test compounds was added to T47D-pMAMneo-LUC and incubated at 37 °C for 16 h with progesterone (1 nM, antagonist format) or without progesterone (agonist format). Luciferase expression was estimated by measuring luminescence. The results represent the relative activity to 1 nM of progesterone (the means ± S.D. of three replicates). The data shown are representative of several experiments providing similar results.

S.D. from three independent experiments), or almost equal to those of other steroidal progesterone receptor ligands (Fig. 2). To verify its selectivity to progesterone receptor, we examined CP8668 in another steroid receptor binding assay (Table 1). CP8668 displayed a marked selectivity for human progesterone receptor, showing a much lower binding affinity to rat androgen receptor than testosterone, RU486, or MPA, and showing no significant binding to human glucocorticoid receptor or human estrogen receptors.

3.2. In vitro progesterone-dependent enzyme expression activity

We evaluated CP8668 in a progesterone-dependent exogeneous alkaline phosphatase expression assay using a T47D human breast cancer cell line, and a progesterone-dependent endogeneous luciferase expression assay using T47D transfected with the plasmid pMAMneo-LUC. In both enzyme expression assays, CP8668 was tested in the

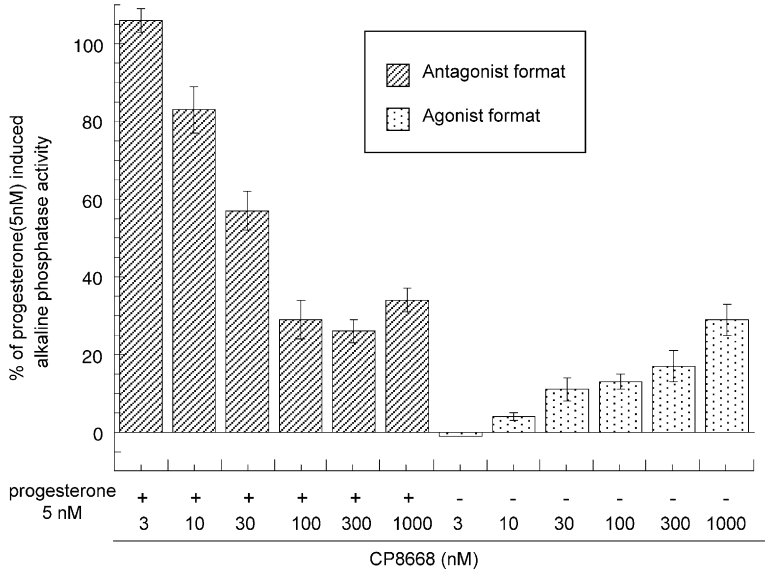

Fig. 4. Modulation of progesterone-dependent endogeneous alkaline phosphatase expression by CP8668. The indicated concentrations of test compounds were added to T47D and incubated at 37 °C for 20 h with progesterone (5 nM antagonist format) or without progesterone (agonist format). Alkaline phosphatase expression was estimated by measuring luminescence. The results represent the relative activity to 5 nM of progesterone (the means ± S.D. of three replicates). The data shown are representative of several experiments providing similar results.

Table 2
Effects of CP8668 in rabbit endometrial transformation tests

	Daily dose for 5 days (mg/kg)	Route	Number of animals	Progestational index, McPhail unit 0–4 (mean ± S.D.)
Vehicle	–	s.c.	3	0.0 ± 0.0
Progesterone	0.1	s.c.	3	4.0 ± 0.0
CP8668	5	s.c.	3	3.6 ± 0.5
	10	s.c.	3	4.0 ± 0.0
Vehicle	–	p.o.	2	0.0
Progesterone	0.15	s.c.	3	3.9 ± 0.2
CP8668	2.5	p.o.	4	1.0 ± 0.8
	5	p.o.	4	2.3 ± 1.1
	10	p.o.	4	3.2 ± 0.1

absence and presence of progesterone (i.e., in the agonist and antagonist formats, respectively). CP8668 partially inhibited progesterone-dependent enzyme expression in the antagonist format of both assays and induced enzyme expression in the agonist format of both assays, although the agonist activity was partial and gradual in comparison to that of progesterone (Figs. 3 and 4). In the antagonist format of both assays, RU486 inhibited progesterone-dependent enzyme expression dose-dependently and completely at the concentration of 10 nM (data not shown).

3.3. In vivo progestational activity in rabbit endometrial transformation tests

A rabbit endometrial transformation test was used to evaluate the in vivo progestational activity of CP8668. The results are shown in Table 2. Estrogen-primed immature rabbits administered for 5 days with progesterone demonstrated an elevated McPhail index. Daily s.c. administration of CP8668 clearly induced this progesterone-dependent transformation of the uterus to the same degree as progesterone, although maximum effects require higher doses than progesterone. These results suggest that CP8668 demonstrates maximum progestational activity in this endometrial transformation test. Through oral administration of CP8668, a dose-dependent progestational effect was also observed.

4. Discussion

In the course of screening for nonsteroidal progesterone receptor ligands, we discovered PF1092 compounds (Tabata et al., 1997a,b). Preliminary derivatives of PF1092C (of the tetrahydronaphthofuranone type) showed good selectivity for progesterone receptor and antagonist or mixed agonist–antagonist activity in vitro (Tabata et al., 2001). Based on these results, we attempted to synthesize active progesterone receptor modulators from PF1092C in vivo, thereby discovering the tetrahydrobenzindolone-type progesterone receptor modulator CP8668. The tetrahydrobenzindolone skeleton is chemically more stable than the tetrahydronaphthofuranone skeleton of PF1092C. CP8668 possesses alkoxy and carbamoyl groups at positions 6 and 7, the positions that have significant implications for affinity and modulating effects for progesterone receptor.

In the binding assay for steroid receptor, CP8668 showed an affinity for human progesterone receptor as strong as other steroidal progestins, and better selectivity than MPA or RU486. This level of selectivity for progesterone receptor is identical to that of the tetrahydronaphthofuranone-type modulator that we previously reported (Tabata et al., 2001). These results demonstrate that this type of structural difference at position 1 on the C ring between the two skeletons is not as critical to features concerning affinity and selectivity.

Two types of functional assays (an endogeneous luciferase assay and an exogeneous alkaline phosphatase assay) were used to confirm the effects of CP8668 on progesterone-dependent enzyme expression. In endogeneous and exogeneous progesterone-dependent enzyme expression assays, we demonstrated that CP8668 was a mixed agonist–antagonist. The enzyme expression induced by CP8668 increased more gradually than that induced by progesterone, although its binding affinity for progesterone receptor is comparable to that of progesterone. However, other tetrahydrobenzindolone-type compounds with progestational activity did not always show these differences between the results of binding assay and enzyme expression assay (data not shown). Thus, this may indicate the characteristic activities of CP8668. We confirmed that the potentials of tetrahydrobenzindolone-type compounds could be controlled by chemical modifications at positions 6 and 7 on the tetrahydrobenzindolone skeleton same as when on the tetrahydronaphthofuranone skeleton (data not shown).

In the rabbit endometrial transformation tests, CP8668 showed good progestational activity following s.c. and p.o. administration. Progestational efficacies of CP8668 observed in this experiment with s.c. administration are the same as those by progesterone. Such progestational effects are inconsistent with in vitro mixed agonist–antagonist effects. The difference between in vitro activity on breast cancer cells and in vivo activity on endometrium is one of the striking features of CP8668. This feature is seen in some of other tetrahydrobenzindolone-type derivatives (data not shown). Recently, Chwalisz et al. (2002) reported progesterone receptor ligands with mixed agonist–antagonist activity as a potential therapeutic concept in endometriosis. We also reported that CP8816, an advanced derivative of CP8668, demonstrated inhibitory effects on uterine epithelial cell growth and the incidence of uterine adenomyosis in mice (Mori et al., 2002). Our tetrahydrobenzindolone-type progesterone receptor modulators may provide a good starting point for research on the pharmaceutical treatment of endometrial disease.

In conclusion, this report identifies CP8668 as showing selective progesterone receptor mixed agonist–antagonist activity in in vitro enzyme expression assays and agonist activity in in vivo rabbit endometrial transformation tests,

and demonstrates that tetrahydrobenzindolone-type compounds represent potential pharmacophores for in vivo orally active progesterone receptor modulators. Other aspects of the pharmacological activity of advanced derivatives having a tetrahydrobenzindolone skeleton and a detailed structure–activity relationship will be reported elsewhere.

References

Chwalisz, K., Brenner, R.M., Fuhrmann, U.U., Hess-Stumpp, H., Elger, W., 2000. Antiproliferative effects of progesterone antagonists and progesterone receptor modulators on the endometrium. Steroids 65, 741–751.

Chwalisz, K., Garg, R., Brenner, R.M., Schubert, G., Elger, W., 2002. Selective progesterone receptor modulators (SPRMs). A novel therapeutic concept in endometriosis. Ann. N .Y. Acad. Sci. 955, 373–388.

Combs, D.W., Reese, K., Phillips, A., 1995. Nonsteroidal progesterone receptor ligands. 1. 3-Aryl-1-benzoyl-1,4,5,6-tetrahydropyridazines. J. Med. Chem. 38, 4878–4879.

Editorial, 1996. This editorial covers the meeting of European Progestin Club. Moderation of meeting: Schindler, A.E. Participants: Campagnoli, C., Druckmann, R., Huber, J., Pasqualini, J.R., Schweppe, K.W., Thijssen, J.H.H., Correspondence and reprint requests: Pasqualini, J.R. Progestins: present and future. J. Steroid Biochem. Mol. Biol. 59, 357–363.

Elger, W., Bartley, J., Schneider, B., Kaufmann, G., Schubert, G., Chwalisz, K., 2000. Endocrine pharmacological characterization of progesterone antagonists and progesterone receptor modulators with respect to PR-agonistic and antagonistic activity. Steroids 65, 713–723.

Harimaya, K., Magome, E., Tabata, Y., Sasaki, T., Tsuruoka, T., 1997. Chemical conversion of PR toxin into new eremophilanolides as progesterone receptor ligands. Sci. Rep. Meiji Seika Kaisha 36, 19–27.

Kurihara, K., Tanabe, K., Shinei, R., Okonogi, T., Ohtsuka, Y., Omoto, S., Yasuda, S., Tatsuta, K., 1997. Synthesis of (±)-PF1092A, B, and C; new nonsteroidal progesterone receptor ligands. J. Antibiot. 50, 360–362.

Kurihara, K., Tanabe, K., Yamamoto, Y., Shinei, R., Ajito, K., Okonogi, T., 1999. Synthesis and structure–activity relationships of new nonsteroidal progesterone receptor ligands. Bioorg. Med. Chem. Lett. 9, 1837–1842.

McPhail, M.K., 1934. The assay of progestin. J. Physiol., 145–156.

Mori, T., Kurata, Y., Tabata, Y., Niho, N., Matsuda, M., Zhou, Y.F., 2002. Priming effects of novel nonsteroidal progesterone receptor modulators CP8816 and CP8863 on the development of adenomyosis in the mouse uterus. Life Sci. 71, 527–535.

Palmer, S., Campen, C.A., Allan, G.F., Rybczynski, P., Haynes-Johnson, D., Hutchins, A., Kraft, P., Kiddoe, M., Lai, M.T., Lombardi, E., Pedersen, P., Hodgen, G., Combs, D.W., 2002. Nonsteroidal progesterone receptor ligands with unprecedented receptor selectivity. J. Steroid Biochem. Mol. Biol. 75, 33–42.

Pathirana, C., Stein, R.B., Berger, T.S., Fenical, W., Ianiro, T., Mais, D.E., Torres, A., Goldman, M.E., 1995. Nonsteroidal human progesterone receptor modulators from the marine alga *Cymopolia barbata*. Mol. Pharmacol. 47, 630–635.

Tabata, Y., Miike, N., Hatsu, M., Kurata, Y., Yaguchi, T., Someya, A., Miyadoh, S., Hoshiko, S., Tsuruoka, T., Omoto, S., 1997a. PF1092A, B and C, new nonsteroidal progesterone receptor ligands produced by *Penicillium oblatum*: I. Taxonomy of producing strain, fermentation, isolation and biological activities. J. Antibiot. 50, 304–308.

Tabata, Y., Hatsu, M., Kurata, Y., Miyajima, K., Tani, M., Sasaki, T., Kodama, Y., Tsuruoka, T., Omoto, S., 1997b. PF1092A, B and C, new nonsteroidal progesterone receptor ligands produced by *Penicillium oblatum*: II. Physico-chemical properties and structure elucidation. J. Antibiot. 50, 309–313.

Tabata, Y., Iizuka, Y., Kashiwa, J., Takei Masuda, N., Shinei, R., Kurihara, K., Okonogi, T., Hoshiko, S., Kurata, Y., 2001. Fungal metabolite, PF1092 compounds and their derivatives, are nonsteroidal and selective progesterone receptor modulators. Eur. J. Pharmacol. 430, 159–165.

Tatsuta, K., Yasuda, S., Kurihara, K., Tanabe, K., Shinei, R., Okonogi, T., 1997. Total synthesis of progesterone receptor ligands, (−)-PF1092A, B, and C. Tetrahedron Lett. 38, 1439–1442.

Zhang, P., Terefenko, E.A., Fensome, A., Zhang, Z., Zhu, Y., Cohen, J., Winneker, R., Wrobel, J., Yardley, J., 2002. Potent nonsteroidal progesterone receptor agonists: synthesis and SAR study of 6-aryl benzoxazines. Bioorg. Med. Chem. Lett. 12, 787–790.

Zhi, L., Tegley, C.M., Marschke, K.B., Mais, D.E., Jones, T.K., 1999. 5-Aryl-1,2,3,4-tetrahydrochromeno[3,4-*f*]quinolin-3-ones as a novel class of nonsteroidal progesterone receptor agonists: effect of A-Ring modification. J. Med. Chem. 42, 1466–1472.