Pergamon

Bioorganic & Medicinal Chemistry Letters 9 (1999) 1837–1842

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Synthesis and Structure-Activity Relationships of New Non-steroidal Progesterone Receptor Ligands

Ken-ichi Kurihara, Kiyoshi Tanabe, Yasuo Yamamoto, Rie Shinei, Keiichi Ajito, Tsuneo Okonogi

Drug Discovery, Pharmaceutical Research Center, Meiji Seika Kaisha, Ltd.,

760 Morooka-cho, Kohoku-ku, Yokohama 222-8567, Japan

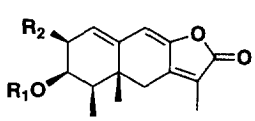
Received 24 March 1999; accepted 14 May 1999

Abstract:

In order to study structure-activity relationships, a series of new non-steroidal progesterone receptor ligands based on PF1092A [1] was synthesized with structural modifications (mostly introduction or removal of a methyl group) at the 3-, 4-, 5-, 7- or 9-position in the 6-acetoxy-4a, 5, 6, 7-tetrahydro-3, 4a, 5-trimethylnaphtho[2, 3-*b*]furan-2(4*H*)-one [2] skeleton. Critical positions for high binding affinity to the progesterone receptor were identified.

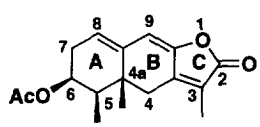
Introduction

PF1092A (**1a**), B (**1b**) and C (**1c**) [1] (Figure 1) were isolated from the culture extract of *Penicillium oblatum* as optically active sesquiterpenes possessing a ligularenolide [3] skeleton. PF1092A showed a high affinity for the progesterone receptor *in vitro*. Recently we synthesized (±)-PF1092A (**1a**) and a derivative (**2**) [2], and found that the optically active natural product has a two-fold higher affinity than the racemate for the receptor (Figure 1). In that report, we also established that the 6- or 7-position is important for binding to



(±)-PF1092A (1a) : R_1 = Ac, R_2 = OH
(±)-PF1092B (1b) : R_1 = H, R_2= OAc
(±)-PF1092C (1c) : R_1 = H, R_2 = OH
2 : R_1 = Ac, R_2= H

Figure 1



6-Acetoxy-4a, 5, 6, 7-tetrahydro-3, 4a, 5-trimethylnaphtho[2, 3-*b*]furan-2(4*H*)-one skeleton

Figure 2

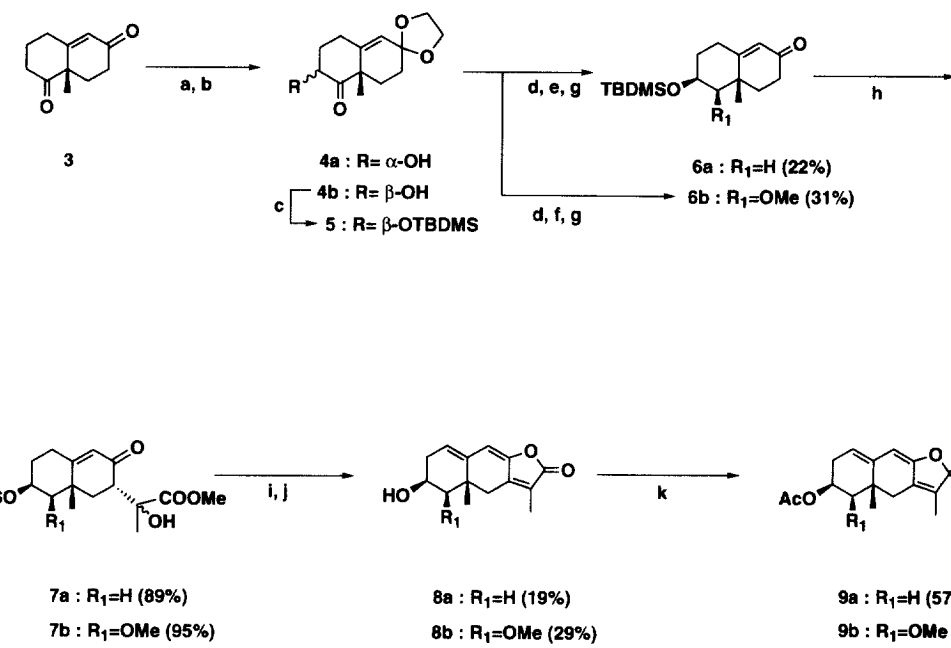
the progesterone receptor *in vitro*, and showed that derivatives having an acetoxyl group at the 6-position exhibit high affinity for the receptor. In this paper we describe the synthesis of a series of modified racemic derivatives **9a**, **9b**, **15**, **24a-d** retaining the 6-acetoxy-4a, 5, 6, 7-tetrahydro-3, 4a, 5-trimethylnaphtho[2, 3-*b*]furan-2(4*H*)-one skeleton (Figure 2), for further studies of the structure-activity relationships.

0960-894X/99/$ - see front matter
PII: S0960-894X(99)00275-9

Synthesis

To obtain derivatives modified at the 5-position (Scheme 1), commercially available (±)-Wieland-Mischer ketone (**3**) was selectively ketalized at the enone by the use of $(CH_2OTMS)_2$ with TMSOTf [4], and hydroxylated with *m*-CPBA *via* the silyl-enol ether, followed by treatment with TBAF (α : β=1 : 7) [5].

Scheme 1



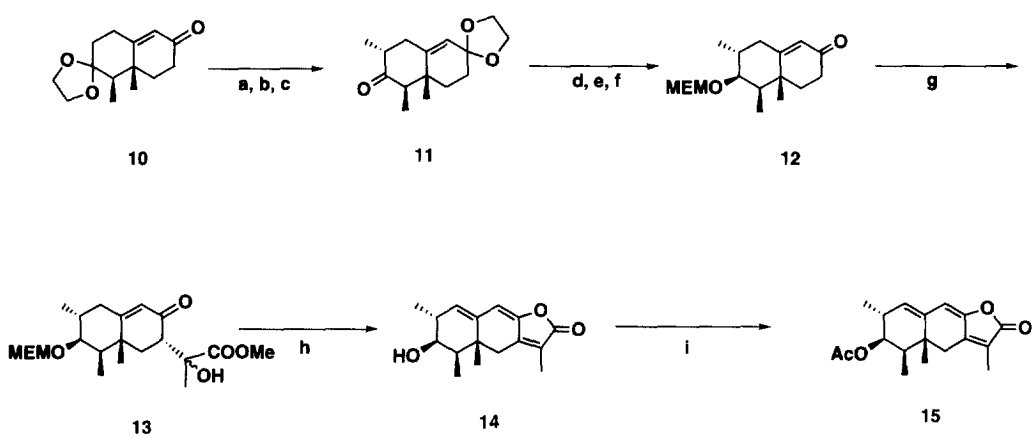
Modification of A ring (1)

a: $(CH_2OTMS)_2$ (3.0 eq), TMSOTf (0.02 eq), CH_2Cl_2 (92%), b: (1) TMSCl (1.5 eq), LDA (1.5 eq), THF (2) *m*-CPBA (1.3 eq), $NaHCO_3$ (3.9 eq), hexane (3) 1.0M TBAF (1.5 eq), THF (α : β = 1 : 7) (81%), c: TBDMSCl (1.2 eq), imidazole (2.4 eq), DMF (95%), d: $LiAlH_4$ (1.5 eq), THF (79%), e: (1) NaH (4.0 eq), CS_2 (2.0 eq), MeI (2.0 eq), THF (2) *n*-Bu_3SnH (1.1 eq), AIBN (0.1 eq), toluene, f: MeOTf (7.8 eq), 2,6-di-*t*-butylpyridine (8.2 eq), CH_2Cl_2, g: *p*-TsOH (0.2 eq), acetone, h: methyl pyruvate (2.0 eq), LDA (1.7 eq), $ZnCl_2$ (1.7 eq), THF, i: *p*-TsOH (3.3 eq), toluene, j: 1.0M TBAF (1.7 eq), THF, k: AcCl (5.5 eq), 4-DMAP (7.1 eq), CH_2Cl_2.

The desired alcohol **4b** was isolated by silica gel chromatography, and **4b** was converted to **5** by reaction with TBDMSCl and imidazole in DMF. Reduction of the ketone **5** with $LiAlH_4$ in THF selectively afforded the *cis* -alcohol with respect to the methyl group. Radical reduction *via* xanthate [6] afforded **6a**, whereas methylation [7] with MeOTf in the presence of 2, 6-di-*tert*-butylpyridine led to **6b**. Compounds **7a, b** were derived from compound **6a, b** with methyl pyruvate *via* aldol condensation in the presence of $ZnCl_2$ [8] in THF. The tricyclic alcohols **8a, b** were obtained by treatment of **7a, b** with *p*-TsOH in toluene at reflux followed by deprotection of the TBDMS group with TBAF. Acetylation afforded the required **9a** and **9b**.

Modification of the 7-position of the tetrahydronaphthofuranone skeleton was performed by utilizing the racemic compound **10** [2) 9) 10)] (Scheme 2). Compound **11** was obtained by 70% $HClO_4$ treatment of **10** to remove the ketal group and then selective protection with $(CH_2OTMS)_2$, followed by methylation with MeI in the presence of LDA. Compound **11** was converted to **12** by reduction with $LiBH_4$ in THF followed by deketalization and introduction of the 2-methoxyethoxymethyl (MEM) group. Compound **12** was led to the alcohol **14** in the same manner as used for the conversion of **6** to **8**. Acetylation afforded the required compound **15**.

Scheme 2

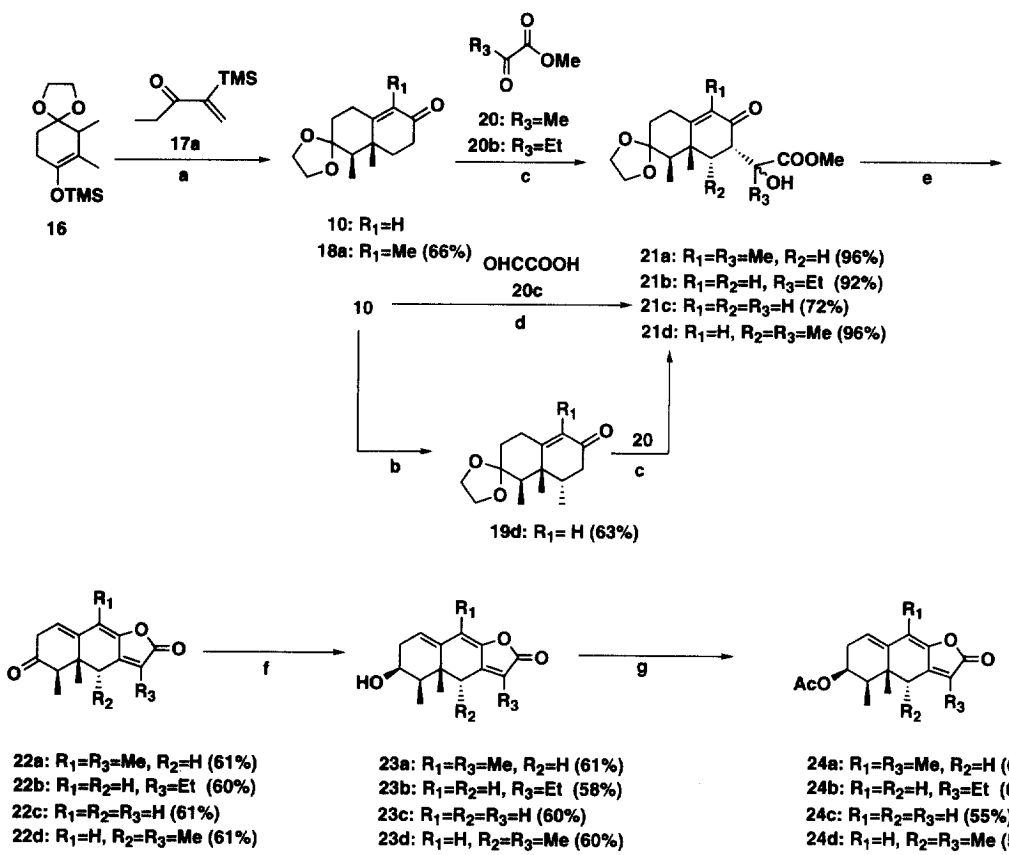


Modification of A ring (2)

a: 70%$HClO_4$, CH_2Cl_2 (75%), b: $(CH_2OTMS)_2$ (3.0 eq), TMSOTf (0.02 eq), CH_2Cl_2, c: LDA (1.1 eq), MeI (2.5 eq), THF, d: $LiBH_4$ (1.5 eq), THF, e: *p*-TsOH (0.02 eq), acetone (40% from step b), f: MEMCl (2.0 eq), *i*-Pr_2NH (2.0 eq), CH_2Cl_2 (85%), g: methyl pyruvate (2.0 eq), LDA (1.7 eq), $ZnCl_2$ (1.7 eq), THF(75%) , h: *p*-TsOH (0.5 eq), benzene (30%), i: AcCl (2.5 eq), 4-DMAP (4.0 eq), CH_2Cl_2 (55%).

To obtain derivatives modified at the 3-, 4- or 9-position (namely the B or C-ring) of the tetrahydronaphthofuranone skeleton, we employed compound **16** as a starting material (Scheme 3).

Scheme 3



Modification of B and C rings

a: (1) 2.0M MeLi (2.3 eq), DME, (2) NaOMe (1.1 eq), MeOH, b: (1) DDQ (1.5 eq), toluene, (2) Me_2CuLi (2.0 eq), Et_2O, c: LDA (1.7 eq), $ZnCl_2$ (1.7 eq), THF, d: (1)1N NaOH, EtOH, (2) $TMSCHN_2$ (1.5 eq), e: *p*-TsOH (1.0 eq), toluene, f: $NaBH_4$ (2.0 eq), MeOH, g: AcCl (3.0 eq), 4-DMAP (6.0 eq), CH_2Cl_2.

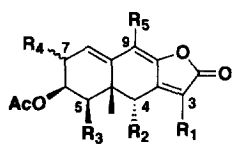
To obtain the 9-methylated compound, **16**[10] was coupled with the Michael acceptor **17a**[11] in the presence of MeLi in DME, followed by cyclization with NaOMe to afford **18a**. For conversion at the 4-position, **19d** was obtained by dehydrogenation of **10** with DDQ followed by introduction of the methyl group *via* Michael addition. This methylation proceeded with *trans*-selectivity with respect to the other methyl groups. These

compounds **18a** and **19d** were led to **21a** and **21d**, respectively, with methyl pyruvate *via* aldol condensation in the presence of $ZnCl_2$ in THF. To obtain the 3-position modifications, **21b, c** were synthesized *via* aldol condensation of **10** with **20b, c**, respectively, and then esterification with $TMSCHN_2$ in the case of **21c**. Compounds **21a-d** were converted to the cyclic compounds **22a-d** by treatment with *p*-TsOH in toluene. Selective reduction of **22a-d** with $NaBH_4$ in MeOH provided **23a-d**, which were acetylated to afford **24a-d**. The new racemic derivatives **9a-b**, **15**, **24a-d** were subjected to assay of progesterone receptor-binding affinity.

Receptor-Binding Affinity and Discussion

The receptor-binding affinities of **24a** and **24b** were markedly reduced compared with that of **1a** (Table 1), suggesting that the receptor's binding pocket has little latitude to accommodate increased bulkiness of the ligand at positions 3 and 9. This is consistent with the high affinity of **24c**, in which the replacement of 3-Me of **2** (or 3-Et of **24b**) with H causes no loss of affinity. On the other hand, introduction of a methyl group at position 4 (**24d**) only slightly decreased the binding affinity.

Table 1. Relative progesterone receptor-binding affinities of the newly synthesized compounds



Compound	R_1	R_2	R_3	R_4	R_5	RBA*
1a	Me	H	Me	β-OH	H	1.0
2	Me	H	Me	H	H	0.8
9a	Me	H	H	H	H	0.08
9b	Me	H	OMe	H	H	0.7
15	Me	H	Me	α-Me	H	1.6
24a	Me	H	Me	H	Me	0.07
24b	Et	H	Me	H	H	0.2
24c	H	H	Me	H	H	1.2
24d	Me	Me	Me	H	H	0.8

For clarity, substituents which differ from those of other compounds are shown in boxes.

*Relative binding affinity
= IC_{50} of 1a / IC_{50} of test compound at the human Pg receptor

The methyl group at the 5-position of **1a** appears to play an important role, since its removal (**9a**) resulted in a large decrease of binding affinity, while its replacement with OMe resulted in a small decrease.

It is noteworthy that replacement of 7β-OH of **1a** with 7α-Me (**15**) resulted in an increase of binding affinity. This suggests that further modification of the basic skeleton of PF1092 at the 7-position could be an attractive strategy to obtain derivatives with higher binding affinity for the progesterone receptor.

Acknowledgments

We thank Mr. Y. Tabata and Miss. Y. Iizuka for evaluation of binding affinity to progesterone receptor.

References and Note

1a) Tabata, Y.; Miike, N.; Hatsu, M.; Kurata, Y.; Yaguchi, T.; Someya, A.; Miyadoh, S.; Hoshiko, S.; Tsuruoka, T.; Omoto, S.; *J. Antibiot.* **1997**, 50, 304~308.

1b) Tabata, Y.; Hatsu, M.; Kurata, Y.; Miyajima, K.; Tani, H.; Sasaki, T.; Kodama, Y.; Tsuruoka, T.; Omoto, S.; *J. Antibiot.* **1997**, 50, 309~313.

2a) Kurihara, K.; Tanabe, K.; Shinei, R.; Okonogi, T.; Ohtsuka, Y.; Omoto, S.; Yasuda, S.; Tatsuta, K.; *J. Antibiot.* **1997**, 50, 360~362.

2b) Kurihara, K.; Shinei, R.; Tanabe, K.; Yamamoto, Y.; Ajito, K.; Miyazima, K.; Tabata, Y.; Yasuda, S.; Tatsuta, K.; Okonogi, T.; (Meiji Seika Kaisha, Ltd.) WO-Patent. **1997**, WO97/30040.

3a) Tanahashi, Y.; Ishizaki, Y.; Takahashi, T.; Tori, K.; *Tetrahedron Letters.* **1968**, 3739~3742.

3b) Ishizaki, Y.; Tanahashi, Y.; Takahashi, T. ; Tori, K.; *Tetrahedron.* **1970**, 26, 5387~5393.

4) Hwu, J. R.; Wetzel, J. M.; *J. Org. Chem.* **1985**, 50, 3946~3948.

5) Rubottom, G. M.; Vazeques, M. A.; Pelegrina, D. R.; *Tetrahedron Letters.* **1974**, 4319~4322.

6) Barton, D. H. R.; McCombie, S. W.; *J. Chem. Soc., Perkin I.* **1975**, 1574~1585.

7) Kurihara, K.; Kikuchi, N.; Akiyama, Y.; Usui, T.; (Meiji Seika Kaisha, Ltd.) JP Patent. **1995**, tokuganhei 7-112181.

8) House, H. O.; Crumrine, D. S.; Teranishi, A. Y.; Olmstead, H. D.; *J. Am. Chem. Soc.* **1973**, 95, 3310~3324.

9a) Yamakawa, K.; Izuta, I.; Oka, H.; Sakaguchi, R.; Kobayashi, M.; Satoh, T.; *Chem. Pharm. Bull.* **1979**, 27, 331~340.

9b) Yamakawa, K.; Kobayashi, M.; Hinata, S.; Satoh, T.; *Chem. Pharm. Bull.* **1980**, 28, 3265~3274.

10) Bohlmann, F.; Otto, W.; *Liebigs Ann. Chem.* **1982**, 186~190.

11) This compound was prepared by means of a similar procedure in the following reference. Boeckmann, Jr. R. K.; Blum, D. M.; Ganem, B.; Halvey, N.; *Org. Synth.* **1978**, 58, 152.