Bioorganic & Medicinal Chemistry Letters 20 (2010) 4816–4818

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

1-Methyl-1*H*-pyrrole-2-carbonitrile containing tetrahydronaphthalene derivatives as non-steroidal progesterone receptor antagonists

Jeffrey C. Kern [a,*], Eugene Terefenko [a], Eugene Trybulski [a], Thomas J. Berrodin [b], Jeffrey Cohen [b], Richard C. Winneker [b], Matthew R. Yudt [b], Zhiming Zhang [b], Yuan Zhu [b], Puwen Zhang [a,†]

[a] *Chemical Sciences, Pfizer Global Research and Development, 500 Arcola Road, Collegeville, PA 19426, USA*
[b] *Musculoskeletal Biology, Pfizer Global Research and Development, 500 Arcola Road, Collegeville, PA 19426, USA*

ARTICLE INFO

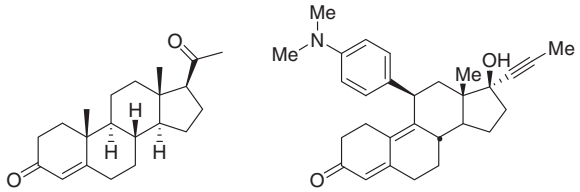
Article history:
Received 12 March 2010
Revised 17 June 2010
Accepted 21 June 2010
Available online 25 June 2010

Keywords:
Progesterone
Antagonist
Modulator
Tetrahydronaphthalene
Nuclear hormone
1-Methyl-1H-pyrrole-2-carbonitrile

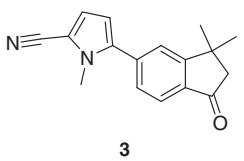
ABSTRACT

Non-steroidal 1-methyl-1*H*-pyrrole-2-carbonitrile containing tetrahydronaphthalenes and acyclic derivatives were evaluated as novel series of progesterone receptor (PR) antagonists using the T47D cell alkaline phosphatase assay. Moderate to potent PR antagonists were achieved with these scaffolds. Several compounds (e.g., **15** and **20**) demonstrated low nanomolar PR antagonist potency and good selectivity versus other steroid receptors.

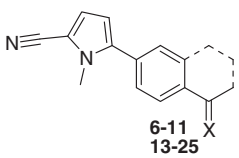
Progesterone (**1**) is an endogenous hormone that plays an important role in female reproduction. Synthetic progestins commonly used in oral contraceptives achieve efficacy via ovulation inhibition and thickening of the cervical mucus.[1] Progestin/estrogen combinations are also used in hormone replacement therapy. A selective progesterone receptor (PR) antagonist may be potentially used in female contraception[2] and for the treatment of various gynecological and obstetric diseases including hormone dependent cancers and non-malignant chronic conditions such as fibroids and endometriosis.[3,4] The therapeutic potential of PR antagonists has not yet been fully realized. Mifepristone (**2**), the only marketed PR antagonist, demonstrated activity at other steroid receptors such as the glucocorticoid (GR) and androgen (AR) receptors. Mifepristone (**2**) was nearly equipotent as an antagonist for both the PR and GR. This potentially limits its chronic use.[5] In the search for selective PR modulators, a number of non-steroidal PR scaffolds have been investigated.[6–10] We reported several chemical series that yielded potent PR modulators.[11–14] Several scaffolds incorporated a cyanopyrrole moiety which acts as a progesterone A-ring mimic from co-crystal structure analysis.[12] We have recently reported our efforts to combine the cyanopyrrole A-ring mimic with an indane core (e.g., **3**) that produced low nanomolar PR modulators.[15] As a continuation of this work, we expanded the indane core to that of tetrahydronaphthalenes (**6–11**) and their acyclic analogs (**13–25**) and examined the SAR of these new scaffolds as PR modulators. In this Letter, we describe the synthesis and in vitro structure–activity relationship of the new 1-methyl-1*H*-pyrrole-2-carbonitrile containing tetrahydronaphthalenes and acyclic derivatives.



1, Progesterone **2**, Mifepristone



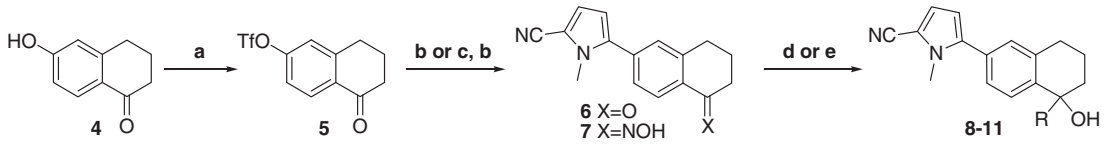
3



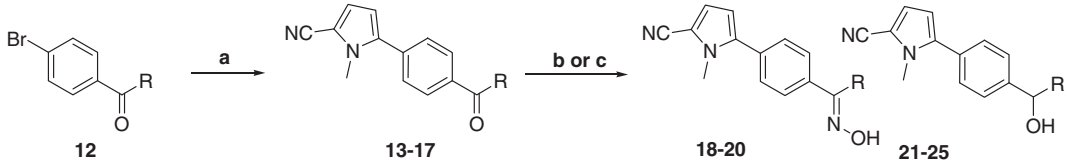
6-11
13-25

* Corresponding author. Address: Merck Research Laboratory, West Point, PA 19486, USA. Tel.: +1 610 505 8420.
E-mail addresses: Jkern75@hotmail.com (J.C. Kern), puwen.zhang@pharmaron.com (P. Zhang).
† Present address: Pharmaron Inc., 201E Jefferson St., Louisville, KY 40202, USA.

0960-894X/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2010.06.109

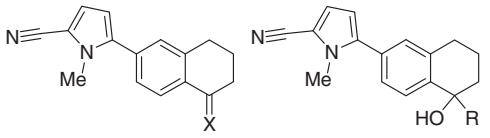


Scheme 1. Synthesis of 1-methyl-5-(5-oxo-5,6,7,8-tetrahydronaphthalen-2-yl)-1*H*-pyrrole-2-carbonitrile and derivatives. Reagents and conditions: (a) triflic anhydride, pyridine, 0 °C, 92%; (b) *N*-methyl-2-cyanopyrrole, LDA, $B(OiPr)_3$, THF, 0 °C, N_2; $Pd(PPh_3)_4$, Na_2CO_3, Glyme/H_2O, 80 °C, N_2, 43%; (c) $NH_2OH{\cdot}HCl$, NaOAc, EtOH/H_2O, 80 °C, 50%; (d) $NaBH_4$, MeOH, 0 °C, 40%; (e) RMgBr, THF, 0 °C, 60–80%.



Scheme 2. Synthesis of acyclic ketones and derivatives. Reagents and conditions: (a) *N*-methyl-2-cyanopyrrole, LDA, $B(OiPr)_3$, THF, 0 °C, N_2; $Pd(PPh_3)_4$, Na_2CO_3, Glyme/H_2O, 80 °C, N_2, 52–78%; (b) $NH_2OH{\cdot}HCl$, NaOAc, EtOH/H_2O, 80 °C, 46–83%; (c) $NaBH_4$, MeOH, 0 °C, 26–79%.

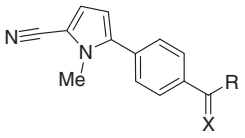
Table 1
PR alkaline phosphatase activities of tetrahydronaphthalene derivatives



Compd	X[a]	R[b]	PR alk. phos. IC_{50}[c] (nM)
6	O		28
7	NOH		33
8		H	7
9		CH_3	6
10		$CCCH_3$	10
11		Phenyl	35

[a] Oxime analog is of trans configuration.
[b] Compounds tested as racemates.
[c] 50% inhibitory concentration of tested compounds on 1 nM progesterone induced alkaline phosphatase activity in the human T47D breast carcinoma cell line. Values represent the average of at least duplicate determinations. The standard deviation for the assay was typically ±20% of the mean or less. Blanks indicate values not determined.

Table 2
PR alkaline phosphatase activity of acyclic ketones and oximes in T47D cells



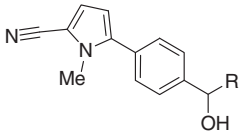
Compd	X[a]	R	PR alk. phos. IC_{50}[b] (nM)
13	O	CH_3	800
14	O	C_2H_5	115
15	O	$C(CH_3)_3$	3
16	O	Thien-2-yl	266
17	O	Phenyl	300
18	NOH	CH_3	108
19	NOH	C_2H_5	17
20	NOH	$C(CH_3)_3$	3

[a] Oxime analogs are of trans configuration.
[b] 50% inhibitory concentration of tested compounds on 1 nM progesterone induced alkaline phosphatase activity in the human T47D breast carcinoma cell line. Values represent the average of at least duplicate determinations. The standard deviation for the assay was typically ±20% of the mean or less. Blanks indicate values not determined.

The preparation of the tetrahydronaphthalenone (**6**), tetrahydronaphthalenone oxime (**7**), and tetrahydronaphthalenols (**8–11**) is shown in Scheme 1. Synthesis of triflate **5** from commercially available phenol **4** was carried out using triflic anhydride in pyridine. The target compound **6** was obtained by palladium catalyzed coupling of **5** with in situ generated *N*-methyl-2-cyanopyrrole boronate. Compound **7** was achieved by first reacting trifate **5** with hydroxylamine, followed by palladium catalyzed coupling with in situ generated *N*-methyl-2-cyanopyrrole boronate. Treatment of compound **6** with either sodium borohydride or an appropriate Grignard reagent gave secondary alcohol **8** or tertiary alcohols **9**–**11**, respectively. The synthesis of the acyclic derivatives is shown in Scheme 2. Starting with commercially available aryl bromides generically represented by **12**, palladium catalyzed coupling with in situ generated *N*-methyl-2-cyanopyrrole boronate yielded ketone derivatives **13–17**. Treatment of the ketones **13–15** with hydroxylamine provided oxime derivatives **18–20**. Addition of an appropriate Grignard to ketones **13–17** provided benzyl alcohol derivatives **21–25**.

All compounds were tested in an alkaline phosphatase assay using the T47D breast carcinoma cell line. The tetrahydronaphthalenone and its oxime and alcohol derivatives **6–11** are shown in Table 1. These compounds all displayed PR antagonist functional activity. The tetrahydronaphthalenone **6** and oxime **7** were equipo-

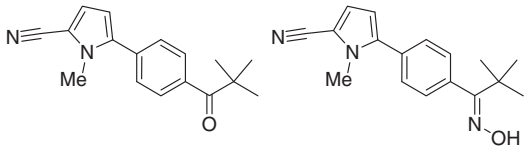
Table 3
PR alkaline phosphatase activity of acyclic benzyl alcohols in T47D cells



Compd[a]	R	PR alk. phos. IC_{50}[b] (nM)
21	CH_3	36
22	C_2H_5	27
23	$C(CH_3)_3$	24
24	Thien-2-yl	47
25	Phenyl	118

[a] Compounds tested as racemates.
[b] 50% inhibitory concentration of tested compounds on 1 nM progesterone induced alkaline phosphatase activity in the human T47D breast carcinoma cell line. Values represent the average of at least duplicate determinations. The standard deviation for the assay was typically ±20% of the mean or less.

Table 4
Nuclear receptor antagonist cross-activities of **2**, **15**, and **20**



15 **20**

Compd	PR IC_{50}[a] (nM)	ER IC_{50}[b] (nM)	AR IC_{50}[b] (nM)	GR IC_{50}[b] (nM)	MR IC_{50}[b] (nM)
2	0.2	5000	6.9	0.6	590
15	3	NA[c]	100	NA	NA
20	3	NA	165	NA	NA

[a] 50% inhibitory concentration of tested compounds on 1 nM progesterone induced alkaline phosphatase activity in the human T47D breast carcinoma cell line. Values represent the average of at least duplicate determinations. The standard deviation for the assay was typically ±20% of the mean or less.
[b] Experimental values represented the average of at least duplicate determinations. The standard deviation for these assays was typically ±30% of mean or less. See reference for details.
[c] Not active up to 10 μM concentration.

tent with an IC_{50} of 28 nM and 33 nM, respectively. The tetrahydronaphthalenols also displayed good PR antagonist potency. Unsubstituted (**8**) or 1-methyl (**9**) or 1-propargyl (**10**) analogs showed good PR antagonist potency with an IC_{50} of 6–10 nM. Compound **11**, with a phenyl substitution resulted in several fold reduction in potency.

In an effort to examine the SAR of acyclic analogs, the saturated ring was excised to yield compound **13**. Compared to the tetrahydronaphthalenone analog **6**, the acyclic methyl ketone **13** was nearly 30-fold less potent. Additional ketone analogs were prepared and demonstrated a broad range of PR antagonist potency (Table 2). The ethyl, thienyl, and phenyl substituted ketone analogs were weaker PR antagonists with IC_{50} values of 115–300 nM. Surprisingly, the *t*-butyl group (**15**) substantially increased PR antagonist potency with an IC_{50} = 3 nM which was over 30-fold more potent than the methyl and ethyl analogs (Table 2).[16] Conversion of ketones **13–15** into oximes gave compounds **18–20** which were also PR antagonists. The oximes exhibited a similar SAR trend as that of their ketone analogs with the *t*-butyl analog being most potent. However, the methyl and ethyl oxime analogs **18** and **19** were more potent than the corresponding ketones **13** and **14**. The PR antagonist potency of benzyl alcohols **21–25** is listed in Table 3. These compounds showed moderate PR antagonist potency (IC_{50} 24–118 nM). In contrast to the SAR of their ketone and oxime analogs, 1-substitution (R) in the alcohol series did not significantly impact the PR antagonist potency. The *t*-butyl analog **23** was similar in potency to the methyl (**21**) and ethyl (**22**) derivatives.

Compounds **15** and **20** were evaluated for their selectivity against other steroid receptors by using a Gal4-DNA binding domain (DBD)-hormone receptor ligand binding domain (LBD) one- or two-hybrid assay for each receptor[17] (Table 4). Compared to the steroidal PR antagonist mifepristone (**2**), both compounds **15** and **20** are more selective for the PR over other steroid receptors. Although these compounds showed moderate antagonist activity at the AR, they displayed no activity at the ER, GR, or MR in this assay. This suggests that these novel PR antagonists will likely have less GR-related side effects.

In summary, 1-methyl-1*H*-pyrrole-2-carbonitrile containing tetrahydronaphthalenones and analogs were evaluated as PR antagonists. From these scaffolds, a number of PR antagonists with low nanomolar in vitro potency were identified, most notably acyclic ketone **15** and oxime **20**. Compounds **15** and **20** also demonstrated good in vitro selectivity for the PR over other steroid receptors with an improved selectivity profile compared to mifepristone.

Acknowledgment

We thank Drs. Ronald Magolda, Richard Lyttle, and Magid Abou-Gharbia for support and the assistance of Department of Analytical Chemistry for analytical data.

References and notes

1. Yuzpe, A. A. *J. Reprod. Med.* **2002**, *47*, 967.
2. Brown, A.; Cheng, L.; Lin, S.; Baird, D. T. *J. Clin. Endocrinol. Metab.* **2002**, *87*, 63.
3. Kettel, L. M.; Murphy, A. A.; Morales, A. J.; Ulmann, A.; Baulieu, E. E.; Yen, S. S. *Fertil. Steril.* **1996**, *65*, 23.
4. Murphy, A. A.; Kettel, L. M.; Morales, A. J.; Roberts, V. J.; Yen, S. S. *J. Clin. Endocrinol. Metab.* **1993**, *76*, 513.
5. Brogden, R. N.; Goa, K. L.; Faulds, D. *Drugs* **1993**, *45*, 384.
6. Combs, D. W.; Reese, K.; Cornelius, L. A. M.; Gunnet, J. W.; Cryan, E. V.; Granger, K. S.; Jordan, J. J.; Demarest, K. T. *J. Med. Chem.* **1995**, *38*, 4880.
7. Kurihara, K.; Tanabe, K.; Yamamoto, Y.; Shinei, R.; Ajito, K.; Okonogi, T. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1837.
8. Zhi, L.; Tegley, C. M.; Pio, B.; Edwards, J. P.; Motamedi, M.; Jones, T. K.; Marschke, K. B.; Mais, D. E.; Risek, B.; Schrader, W. T. *J. Med. Chem.* **2003**, *46*, 4104.
9. Jain, N.; Allan, G.; Linton, O.; Tannenbaum, P.; Chen, X.; Xu, J.; Zhu, P.; Gunnet, J.; Demarest, K.; Lundeen, S.; Murray, W.; Sui, Z. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3977.
10. Wang, Y.; Duraiswami, C.; Madauss, K. P.; Tran, T. B.; Williams, S. P.; Deng, S.; Graybill, T. L.; Hammond, M.; Jones, D. G.; Grygielko, E. T.; Bray, J. D.; Thompson, S. K. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 4916.
11. Collins, M. A.; Hudak, V.; Bender, R.; Fensome, A.; Zhang, P.; Miller, L.; Winneker, R. C.; Zhang, Z.; Zhu, Y.; Cohen, J.; Unwalla, R. J.; Wrobel, J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2185.
12. Fensome, A.; Bender, R.; Chopra, R.; Cohen, J.; Collins, M. A.; Hudak, V.; Malakian, K.; Lockhead, S.; Olland, A.; Svenson, K.; Terefenko, E. A.; Unwalla, R. J.; Wilhelm, J. M.; Wolfrom, S.; Zhu, Y.; Zhang, Z.; Zhang, P.; Winneker, R. C.; Wrobel, J. *J. Med. Chem.* **2005**, *48*, 5092.
13. Zhang, P.; Terefenko, E. A.; Fensome, A.; Wrobel, J.; Winneker, R.; Lundeen, S.; Marschke, K. B.; Zhang, Z. *J. Med. Chem.* **2002**, *45*, 4379.
14. Zhang, P.; Kern, J. C.; Terefenko, E. A.; Trybulski, E. J. US Patent 20070066628A1; US Patent 7,319,152.
15. Kern, J. C.; Terefenko, E.; Trybulski, E.; Berrodin, T. J.; Cohen, J.; Winneker, R. C.; Yudt, M. R.; Zhang, Z.; Zhu, Y.; Zhang, P. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6666.
16. Analytical data for 5-[4-(2,2-dimethylpropanoyl)phenyl]-1-methyl-1*H*-pyrrole-2-carbonitrile (**15**). A white solid: ^{1}H NMR (DMSO-d_6) 7.83 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 8.5 Hz, 2H), 7.07 (d, J = 4.0 Hz, 1H), 6.47 (d, J = 4.0 Hz, 1H), 3.77 (s, 3H), 1.31 (s, 9H). HRMS: calcd for $C_{17}H_{18}N_2O + H^+$, 267.14919; found (ESI, $[M+H]^+$), 267.1494.
17. Sadowski, I.; Bell, B.; Broad, P.; Hollis, M. *Gene* **1992**, *118*, 137.