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5-Aryl indanones and derivatives as non-steroidal progesterone receptor modulators

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ABSTRACT

Novel 5-aryl indanones, inden-1-one oximes, and inden-1-ols were synthesized and evaluated as progesterone receptor (PR) modulators using the T47D cell alkaline phosphatase assay. Both PR agonists and antagonists were achieved with appropriate 3- and 5-substitution from indanones and inden-1-ols while inden-1-one oximes provided only PR antagonists. Several compounds such as **10** and **11** demonstrated potent in vitro PR agonist potency similar to that of steroidal progesterone (**1**). In addition, a number of compounds (e.g., **12**, **13**, **17**, **18**) showed potent PR antagonist activity indicating the indanones and derivatives are promising PR modulator templates.

Progesterone (**1**) is an endogenous hormone which 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 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] However, steroidal progestins and antiprogestins are often associated with undesirable side effects due to the direct interactions with other steroid receptors such as the glucocorticoid receptor (GR) and androgen receptor (AR), as well as potential effects of steroidal metabolites. The only clinically available PR antagonist, mifepristone, demonstrates activity at other nuclear receptors with nearly equipotent activity at the glucocorticoid receptor (GR), which 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.[11–13] One of the most successful scaffolds is the 5′-cyanopyrrol-2-yl substituted benzoxazinone (i.e., **2**) which led to the discovery of the clinically efficacious PR agonist, tanaproget (**3**). Recently, we reported the co-crystal structure of the PR ligand binding domain (LBD) and tanaproget.[12] The crystal structure revealed that tanaproget binds to the same site as steroidal progesterone in the PR LBD with the 3-keto moiety from progesterone aligning together with the cyano group from tanaproget while the C- and D-rings of progesterone overlay with the benzoxazine-2-thione group.[12,14] To exploit the findings from the co-crystal and design structurally novel PR ligands, the carbonyl motif of the D-ring region of progesterone was combined with the cyanopyrrole A-ring mimic of tanaproget to produce the more simplified indanone scaffold, exemplified by compound **4**. In this Letter, we describe the synthesis and in vitro structure–activity relationship of the indanones and their derivatives.

The preparation of **4**,[15] a representative indanone, is shown in Scheme 1. Friedel–Crafts acylation of anisole with 3-methylbut-2-enoyl chloride **5** and simultaneous demethylation to give phenol **6** was achieved under microwave conditions. Cyclization of phenol **6** using aluminum chloride was conducted in *o*-dichlorobenzene with conventional heating to afford indanone **7**, which was converted to triflate **8** with triflic anhydride in pyridine. The target compound **4** was obtained by palladium catalyzed coupling of **8** with in situ generated *N*-methyl-2-cyanopyrrole boronate. Further elaboration of the carbonyl group of indanone is shown in Scheme 2. Conversion of the indanone **4** into inden-1-one oxime **13** was readily achieved with hydroxyl amine. Reduction with sodium

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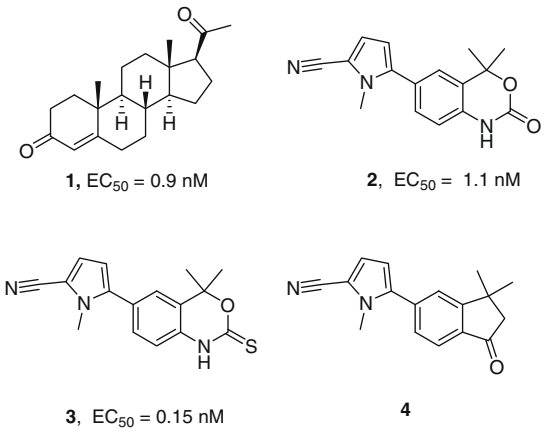
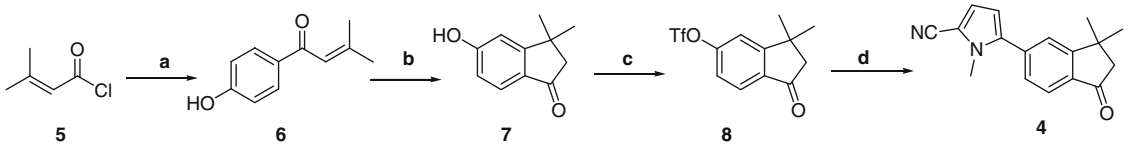
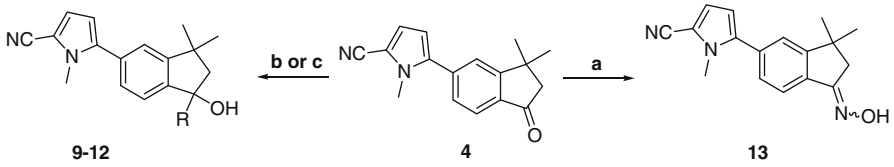


borohydride in methanol or addition of an appropriate Grignard reagent to indanone **4** provided the corresponding secondary and tertiary inden-1-ols **9–12**. Other analogs reported herein were prepared in a similar fashion.

All compounds were tested in an alkaline phosphatase assay using the T47D breast carcinoma cell line. The indanones and their oxime derivatives **4, 13–16** are shown in Table 1. Compounds **4** and **14** demonstrated that the mode of PR functional activity is dependant upon the 3-position substitution of the indanones. The unsubstituted indanone **14** is a PR antagonist with an IC_{50} of 34 nM, and the 3,3-dimethyl substituted indanone **4** is a potent PR agonist (EC_{50} = 10 nM). This result indicated that combining the tanaproget scaffold with progesterone to form the non-steroidal indanone template is a valid approach for novel PR ligands, however the potency of resultant compound **4** was reduced compared to that of either progesterone (**1**) or tanaproget (**3**). Encouraged by the findings of indanones **4** and **14**, we decided to further expand this template and explore the SAR of related analogs. The oxime compounds **13, 15**, and **16** were prepared and evaluated. In contrast to the indanones, the oxime derivatives remained as PR antagonists regardless of their 3-position substitution (Table 1). There is, however, an increase in potency in the oxime derivatives with the installation of 3-methyl groups. The 3,3-dimethyl analog **13** (IC_{50} = 14 nM) is fourfold more potent than the mono-methyl analog **16** and 10-fold more potent than the unsubstituted oxime **15**. Examination of the functional activity of inden-1-ols (**9, 17, 18**) indicated that they follow the same SAR trend as that of the indanones. Both the unsubstituted and 3-mono-methyl substituted inden-1-ols (**17, 18**) are potent PR antagonists with IC_{50} values of 10 and 18 nM, respectively. Similar to indanone **4**, the dimethyl substituted inden-1-ol (**9**) resulted in a functional switch to that of a PR agonist with an EC_{50} of 19 nM. To further explore the alcohol template, several 1-position substituted derivatives were prepared. As shown in Table 2, both methyl and ethyl substituted

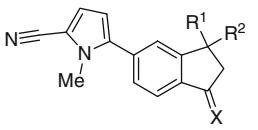


Scheme 1. Synthesis of 5-(3,3-dimethyl-1-oxo-2,3-dihydro-1*H*-inden-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile. Reagents and conditions: (a) anisole, $AlCl_3$, CH_2Cl_2, 100 °C, 15 min, microwave, 46%; (b) $AlCl_3$, *o*-dichlorobenzene, 150 °C, 32%; (c) triflic anhydride, pyridine, 0 °C, 85%; (d) *N*-methyl-2-cyanopyrrole, LDA, $B(OiPr)_3$, THF, 0 °C, N_2; $Pd(PPh_3)_4$, Na_2CO_3, glyme/H_2O, 80 °C, N_2, 55%.



Scheme 2. Synthesis of inden-1-ol and inden-1-one oxime from indanone **4**. Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, NaOAc, EtOH/H_2O, 80 °C, 55%; (b) $NaBH_4$, MeOH, 0 °C, 51%; (c) RMgBr, THF, 0 °C, 24–50%.

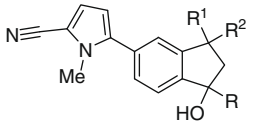
Table 1
PR alkaline phosphatase activities of indanones and inden-1-one oximes



Compd	R^1	R^2	X[a]	PR Alk. Phos. EC_{50}[b] (nM)	PR Alk. Phos. IC_{50}[c] (nM)
14	H	H	O	>3000	34
4	CH_3	CH_3	O	10	
15	H	H	NOH	>3000	132
16	H	CH_3	NOH	>3000	65
13	CH_3	CH_3	NOH	>3000	14

[a] Oxime analogs predominantly trans configuration (>90%).
[b] 50% Effective concentration of tested compounds on alkaline phosphatase activity in the human T47D breast carcinoma cell line.
[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.

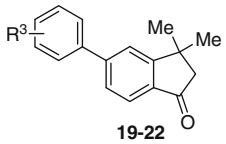
Table 2
PR alkaline phosphatase activity of inden-1-ols in T47D cells



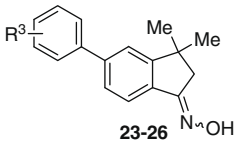
Compd[a]	R^1, R^2	R	PR Alk. Phos. EC_{50}[b] (nM)	PR Alk. Phos. IC_{50}[c] (nM)
17	H, H	H	>3000	10
18	H, CH_3	H	>3000	18
9	CH_3, CH_3	H	19	
10	CH_3, CH_3	CH_3	1	
11	CH_3, CH_3	C_2H_5	2	
12	CH_3, CH_3	$CCCH_3$	>3000	3

[a] Compounds tested as racemates or a mixture of diastereomers.
[b] 50% Effective concentration of tested compounds on alkaline phosphatase activity in the human T47D breast carcinoma cell line.
[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 3
Inhibition of progesterone induced alkaline phosphatase activity in T47D cells. SAR of phenyl indanones and oximes.



19-22



23-26

Compd[a]	R^3	PR Alk. Phos. IC_{50}[b] (nM)
19	3′-CN	195
20	3′-Cl	66
21	3′-Cl, 4′-Cl	79
22	3′-Me	225
23	3′-CN	317
24	3′-Cl	490
25	3′-Cl, 4′-Cl	456
26	3′-Me	316

[a] Oxime analogs predominantly trans configuration (>90%).
[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.

alcohols **10** and **11** are potent PR agonists (EC_{50} = 1 and 2 nM) which had similar in vitro potency to that of endogenous progesterone (**1**, 0.9 nM). However, extending the 1-substitution further to a propargyl group (**12**) resulted in a complete PR functional activity switch to that of a potent PR antagonist (IC_{50} = 3 nM). The PR functional activity therefore, can be modulated at both the 1- and 3-positions, making the inden-1-ol a good scaffold to achieve both potent PR agonists as well as antagonists. In our earlier reports,[11,16,17] the type of aryl substitution at the 6-position and 7-position, respectively, from benzoxazinone and benzoxazepinone templates, affects the PR functional activity. The 5′-cyanopyrrol-2-yl group elicits PR agonist activity using several chemical templates. To examine the impact of replacing the 5′-cyanopyrrol-2-yl moiety from the indanones and oximes, a number of 5-phenyl substituted indanone and oxime derivatives were prepared (Table 3). Not surprisingly, the phenyl substituted indanones (**19–22**, IC_{50} 66–225 nM) were all PR antagonists indicating that the 5′-cyanopyrrol-2-yl group played an important role in the PR agonist activity of the 3,3-dimethyl indanone **4**. The phenyl based oxime analogs (**23–26**) remain PR antagonists but are much less potent than the cyanopyrrole derivative **13**.

In summary, combining the cyanopyrrole moiety from tanaproget with the carbonyl motif of the D-ring region of progesterone to form the indanone template is a valid approach to develop PR modulators. Utilizing this approach, a number of novel 5-(5′-cyanopyrrol-2-yl) substituted indanones, inden-1-one oximes, and inden-1-ols were prepared that had modest to potent PR activity. Both PR agonists and antagonists were achieved with appropriate choices of 1-, 3-, and 5-substitutions. Notably, inden-1-ols **10** and **11** had low nanomolar in vitro potency in the T47D cell alkaline phosphatase assay similar to that of steroidal progesterone.

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15. *Analytical data for 5-(3,3-dimethyl-1-oxo-2,3-dihydro-1H-inden-5-yl)-1-methyl-1H-pyrrole-2-carbonitrile* (**4**). A white solid: ^{1}H NMR (DMSO-d_6) 7.86 (dd, *J* = 1.4 Hz, 0.6 Hz, 1H), 7.68 (dd, *J* = 7.9 Hz, 0.5 Hz, 1H), 7.59 (dd, *J* = 7.9 Hz, 1.6 Hz, 1H), 7.10 (d, *J* = 4.2 Hz, 1H), 6.53 (d, *J* = 4.2 Hz, 1H), 3.79 (s, 3H), 2.61 (s, 2H), 1.42 (s, 6H). HRMS: calcd for $C_{17}H_{16}N_2O+H^+$, 265.13354; found (ESI

$[M+H]^+$), 265.1332; Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.16; H, 6.27; N, 10.58.

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