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SAR studies of 6-aryl-1,3-dihydrobenzimidazol-2-ones as progesterone receptor antagonists☆

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Abstract—We have previously reported that the aryl substituted benzimidazolones, benzoxazinones, and oxindoles (e.g., **1**–**3**) are progesterone receptor (PR) antagonists and have recently disclosed that the nature of 5- and 6-aryl moieties played a critical role in PR functional activity in the oxindole and benzoxazinone templates. For example, replacing the phenyl group of PR antagonists **2** and **3** with a 5′-cyanopyrrol-2′-yl moiety switched their functional activity to PR agonist activity (**2a** and **3a**). These findings prompted us to examine if there is a similar effect of the 6-aryl moieties on the PR functional activity for the benzimidazolone template. Numerous analogs, such as **5**, showed potent PR antagonist activity with about a 10-fold increase in potency as compared to those reported earlier in the same series. More interestingly, pyrrole-containing benzimidazolones **24**–**27** remained as PR antagonists in contrast to the PR agonist activity switch for oxindole and benzoxazinone scaffolds when a 5′-cyanopyrrol-2′-yl group was installed as a pendant aryl group.

The progesterone receptor (PR) is a member of the superfamily of ligand-dependent transcription factors.[1] PR agonists play an important role in female reproduction and have been used extensively, often in combination with an estrogen, in contraceptives, and hormone therapy. In contrast, clinically successful PR antagonists remain scarce and their therapeutic potential has not yet been fully realized. A selective 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[3] and endometriosis.[4]

Clinically available steroidal PR antagonists, namely mifepristone,[5] demonstrated activity at other steroidal receptors, such as the glucocorticoid receptor (GR). Mifepristone was nearly equipotent as an antagonist for both PR and GR, and this potentially limited its chronic use. To search for more selective compounds, a number of non-steroidal PR antagonists have been identified.[6–10] Recently, we have disclosed several series of novel PR antagonists including 6-aryl benzimidazolones (e.g., **1**), 6-aryl benzoxazinones (e.g., **2**), and 5-aryl oxindoles (e.g., **3**).[10–12] The SAR trends brought out by these studies indicated that a pendent aryl ring substituted *para* to the *N*–H moiety and a lipophilic group at the position *ortho* to the *N*–H are critical for the compounds to elicit PR antagonist activity. Furthermore, we discovered that the nature of 6- and 5-aryl moieties played a critical role in PR functional activity for the benzoxazinone and oxindole templates in the human T47D cell alkaline phosphatase assay. For example, replacing the phenyl group of PR antagonists **2** and **3** with a 5′-cyanopyrrol-2′-yl moiety switched their functional activity from PR antagonism to PR agonist activity. The corresponding pyrrole-containing compounds **2a** and **3a** became potent PR agonists in the T47D cell alkaline phosphatase assay (EC_{50} values of 1.1 and 2.8 nM, respectively).[11] These findings prompted us to examine if there is a similar effect of 6-aryl moieties for the benzimidazolone scaffold on their PR functional activity. Thus, a number of benzimidazolone compounds with various 6-aryl groups, as well as with a selection of 1-position substituents, were prepared and these novel 6-aryl benzimidazolones were evaluated for PR functional activity in the alkaline phosphatase assay.

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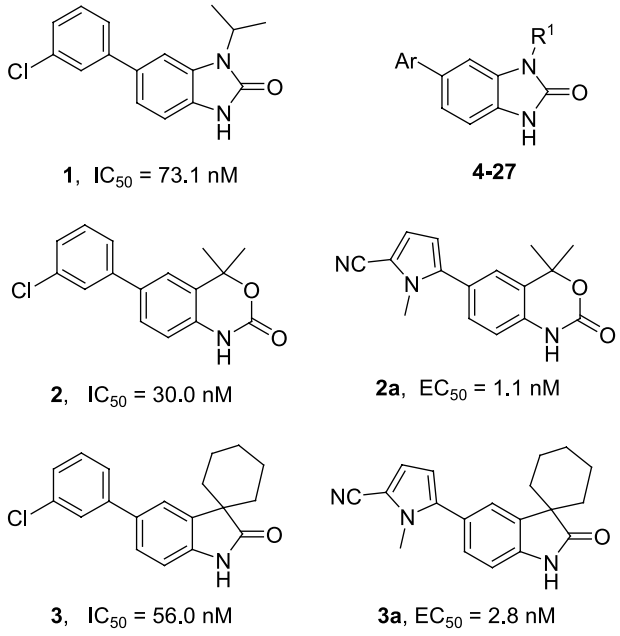
The synthesis and in vitro SAR of novel 6-aryl benzimidazolones (**4**–**27**) are the subjects of this report.



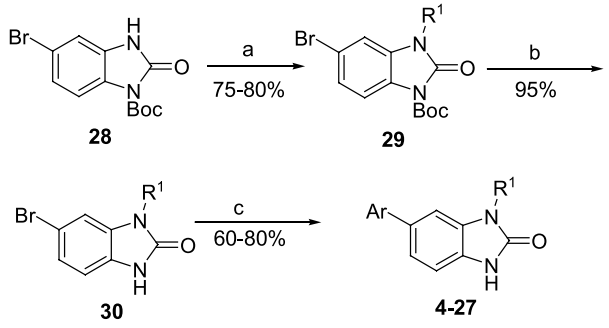
Chemistry

The preparation of the target compounds **4**–**27**, as shown in Scheme 1, was described previously.[12,13] In brief, alkylation of the BOC-protected benzimidazolones **28** to **29** easily took place by alkylation via a Mitsunobu protocol or for R^1 = Aryl by coupling with an appropriate aryl boronic acid via a copper (II) catalyzed procedure. Removal of protecting groups from benzimidazolones **29** under acidic conditions afforded **30**, which was cross-coupled with an appropriate aryl boronic acid to provide the desired 6-aryl benzimidazolones **4**–**27** in good yield.

Results and discussion

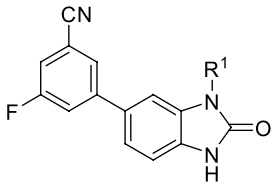
We have previously reported the preliminary SAR of the 6-aryl benzimidazolones, 6-aryl benzoxazinones, and 5-aryl oxindoles.[13–15] Similar SAR trends were observed for the benzimidazolone and oxindole scaffolds. However, the PR functional activities of the 6-aryl benzoxazinones were dependent on the nature of the pendant 6-aryl group and a few analogs showed modest PR agonist activity in the T47D cell alkaline phosphatase assay.[14] More recently, we have disclosed that 5- or 6-(5′-cyanopyrrol-2′-yl) substituted oxindoles and benzoxazinones were potent PR agonists when phenyl-based pendent aryl groups were replaced by a 5′-cyanopyrrol-2′-yl moiety.[11] In contrast, the corresponding SAR for the benzimidazolone template has not been fully examined and only a modest potency ($IC_{50} \sim 30$ nM) in the T47D alkaline phosphatase assay was achieved among the best compounds reported earlier.[13] To probe further the SAR of the benzimidazolone scaffold and improve upon the PR potency, a selection of 1-position substituents and different 6-aryl moieties was examined. These novel 6-aryl benzimidazolones were evaluated for PR antagonist activity in the T47D cell alkaline phosphatase assay and the results are listed in Tables 1 and 2.

Listed in Table 1 are compounds **4**–**10** substituted with various lipophilic groups at the 1-position, while maintaining a consistent 6-aryl group (3′-cyano-5′-fluorophenyl). Compounds **4** and **7** that were substituted with an acyclic isopropyl and 3-pentyl, respectively, exhibited a similar PR antagonist potency and had IC_{50} values of about 29 nM. Interestingly, the constrained cyclobutyl and cyclopentyl analogs **5** and **6** were the most potent ones with IC_{50} values of 3.3 and 5.7 nM, respectively, suggesting that an appropriate rigid ring at the 1-position in this series was preferred. Increasing the cycloalkyl ring size to a cyclohexyl moiety (**8**) caused a ~20-fold reduction in PR antagonist potency over the



Scheme 1. 6-Aryl-1,3-dihydro-benzimidazol-2-ones. Reagents and conditions: (a) R^1OH, DEAD, Ph_3P, THF, rt or $Cu(OAc)_2$, $ArB(OH)_2$, CH_2Cl_2, rt, N_2; (b) CH_2Cl_2, TFA, rt; (c) $ArB(OH)_2$, $Pd(Ph_3P)_4$, K_2CO_3, toluene, $EtOH/H_2O$, 90 °C.

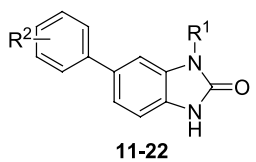
Table 1. Inhibition of progesterone induced alkaline phosphatase activity in T47D cells: SAR at the 1-position



Compound	R^1	PR Alk. Phos. IC_{50} (nM)[a]
4	*i*-C_3H_7	29.6
5	*c*-C_4H_7	3.3
6	*c*-C_5H_9	5.7
7	3-C_5H_{11}	29.0
8	*c*-C_6H_{11}	83.6
9	Phenyl	137.3
10	3′-Chlorophenyl	3000

[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.

Table 2. Inhibition of progesterone induced alkaline phosphatase activity in T47D cells: SAR of 6-aryl groups



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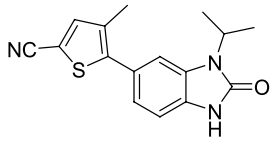

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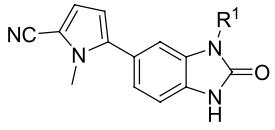

24-27

Compound	R^1	R^2	PR Alk. Phos. IC_{50} (nM)[a]
11	*i*-C_3H_7	2′-F	412.3
12	*i*-C_3H_7	3′-F	77.9
13	*i*-C_3H_7	4′-F	295.4
14	*i*-C_3H_7	3′-F, 4′-F	206.6
15	*i*-C_3H_7	3′-Cl, 4′-F	105.6
16	*i*-C_3H_7	3′-CN, 4′-F	60.3
17	*i*-C_3H_7	3′-Cl, 5′-Cl	100.0
18	*c*-C_4H_7	3′-F, 4′-F	175.4
19	*c*-C_4H_7	3′-Cl, 4′-F	106.0
20	*c*-C_5H_9	3′-F, 4′-F	96.8
21	*c*-C_5H_9	3′-Cl, 4′-F	134.7
22	3-C_5H_{11}	3′-Cl, 4′-F	425.6
23	*i*-C_3H_7		24.8
24	*i*-C_3H_7		4.7[b]
25	*c*-C_4H_7		10.9[b]
26	*c*-C_5H_9		5.6[b]
27	3-C_5H_{11}		11.7[b]

[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] In this assay, compounds **24**–**27** showed weak agonist activity in the absence of 1 nM progesterone (agonist mode) at 3000 nM.

1-cyclobutyl congener **5**. The 1-phenyl analog **9** was marginally less potent than its cyclohexyl analog **8**. However, introducing an extra 3-chlorine atom on the 1-phenyl moiety (**10**) caused a drastic reduction in PR potency when compared to its des-chlorine analog **9**.

A number of 6-aryl benzimidazolones, as depicted in Table 2, were prepared to probe the SAR of substitution on the 6-aryl group. 3′-Fluorophenyl analog **12** was more potent than its 2′- and 4′-fluorophenyl congeners **11** and **13** in the T47D alkaline phosphatase assay. This result was consistent with the SAR trend observed from the benzoxazinone and oxindole scaffolds in that an electron-withdrawing group was preferred at the 3′-position of a pendant phenyl group.[14,15] 3′,4′- and 3′,5′-Disubstituted analogs **14**, **15**, and **17** had modest PR antagonist potency and were marginally less potent than their 3′-fluorophenyl analog **12**. The 3′-cyano-4′-fluorophenyl analog **16** maintained its potency and was comparable to its analog **12**. In contrast to the 3′-cyano-5′-fluorophenyl analog **4**–**6**, the *N*-cyclobutyl and *N*-cyclopentyl groups did not increase antagonist potency over *N*-isopropyl for 3′, 4′-disubstituted phenyl analogs (compare **18**–**21** with **14** and **15**). These six compounds had similar PR antagonist potency with IC_{50} values in the range of 96–206 nM. The 6-(thien-2′-yl) analog **23** had PR antagonist potency comparable to its 6-(3′-cyano-5′-fluorophenyl) analog **4** (IC_{50} 24.8 nM vs 29.6 nM, respectively).

Interestingly, the 5′-cyano-1′-methylpyrrol-2′-yl group that led to the PR agonist activity in the benzoxazinone and oxindole templates did not execute the same for the corresponding benzimidazolones **24**–**27**.[16] The 5′-cyanopyrrol-2′-yl containing benzimidazolones remained as potent PR antagonists. For example, benzimidazolone **24** was about 5-fold more potent than its 6-(3′-cyano-5′-fluorophenyl) and 6-(thien-2′-yl) analogs **4** and **23**. Other 6-(5′-cyanopyrrol-2′-yl) containing compounds **25**–**27** also showed good PR antagonist potency (IC_{50} 5.6–12 nM). In addition, these compounds had high binding affinity in a progesterone receptor competition binding assay using T47D cells. For example, compound **25** had an IC_{50} value of 7 nM in this assay.

In summary, we have examined a selection of 1-position substituents and different 6-aryl moieties for the benzimidazolone scaffold. Numerous analogs, such as **5**, showed potent PR antagonist activity in the T47D cell alkaline phosphatase assay with a 10-fold increase in PR antagonist potency as compared to those reported earlier in the same series. Furthermore, pyrrole-containing benzimidazolones **24**–**27** remained as PR antagonists in contrast to the PR agonist functional activity switch for oxindole and benzoxazinone scaffolds when a 5′-cyanopyrrol-2′-yl group was substituted at the 6-position.

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16. Analytical data for **5-(3-isopropyl-2-oxo-2,3-dihydro-1*H*-benzimidazol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (24)**. A white solid: ^{1}H NMR (DMSO-d_6) δ 11.0 (s, 1H), 7.34 (d, 1H, J = 0.9 Hz), 7.11–7.05 (m, 2H), 7.03 (d, 1H, J = 4.0 Hz), 6.31 (d, 1H, J = 4.0 Hz), 4.64 (m, 1H), 3.72 (s, 3H), 1.46 (d, 6H, J = 6.7 Hz). HRMS (ESI) *m/z* calcd for $C_{16}H_{16}N_4O+H^+$, 281.1397. Found $[M+H]^+$, 281.1386. **5-(3-Cyclopentyl-2-oxo-2,3-dihydro-1*H*-benzimidazol-5-yl)-1-methyl-1*H*-pyrrole-2-carbonitrile (26)**. A white solid: ^{1}H NMR (DMSO-d_6) δ 11.0 (s, 1H), 7.23 (d, 1H, J = 1.17 Hz), 7.12–7.08 (m, 2H), 7.03 (d, 1H, J = 4.0 Hz), 6.31 (d,1H, J = 4.0 Hz), 4.76 (q, 1H, J = 8.6 Hz), 3.72 (s, 3H), 2.10–2.05 (m, 2H), 1.90–1.89 (m, 4H), 1.66–1.62 (m, 2H). HRMS (ESI) *m/z* calcd for $C_{18}H_{18}N_4O+H^+$, 307.1553. Found $[M+H]^+$, 307.1551.