Pergamon

Bioorganic & Medicinal Chemistry Letters 11 (2001) 2747–2750

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Synthesis and Progesterone Receptor Antagonist Activities of 6-Aryl Benzimidazolones and Benzothiazolones†

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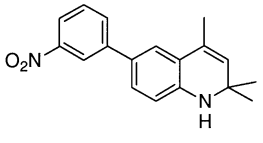
Received 30 May 2001; accepted 6 August 2001

Abstract—Novel 6-aryl benzimidazolones and benzothiazolones were prepared and examined as bioisosteres of the recently reported 6-aryl dihydroquinolines (**1**) for progesterone receptor (PR) antagonist activities. PR antagonist activities increased when compounds **9c**–**f** possessed a more lipophilic group at position-1 and pendent aryl moiety *para* to NH moiety. Furthermore, conversion of carbonyl moiety of **9e**,**f** to the thio-carbonyl led to benzoimidazolethiones **15a**,**b** with significantly improved potency and binding affinity.

The progesterone receptor (PR) is one of the steroid receptors that constitute a subclass of structurally related intracellular gene regulators known as 'ligand dependent transcription factors'.[1] PR agonists are known to play an important role in women's health and have been used extensively in female contraception and hormone replacement therapy. On the other hand, the therapeutic potential of PR antagonists has not yet been fully realized. A selective PR antagonist is potentially useful for the treatment of hormone dependent cancers,[2] nonmalignant chronic conditions such as uterine fibroids,[3] and endometriosis.[4] However, many steroidal PR antagonists, such as mifepristone, cross-react with other steroid receptors such as glucocorticoid and androgen receptors, thus preventing their chronic use. The therapeutic opportunities presented by PR antagonists led us to search for novel, selective, nonsteroidal PR antagonists. Several classes of the nonsteroidal PR antagonists,[5–8] including 6-aryl dihydroquinolines such as **1**,[8b] have been reported. In this report, we discuss the synthesis and SAR of novel PR antagonists 6-aryl benzimidazolones (**5**–**16**) and benzothiazolones (e.g., **17a**,**b**).

Synthesis

6-(3-Nitrophenyl) benzimidazolone (**5**) was prepared as illustrated in Scheme 1. Acylation and nitration of 4-bromoaniline followed by reduction yielded the acety-



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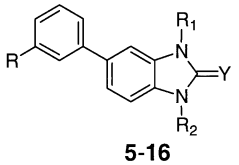
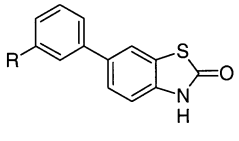


5-16

R = Cl, NO_2; R_1 = H, Me, Et, *i*-C_3H_7, Bn; R_2 = H, Bn; Y = O, S



17a, b

R = Cl, NO_2

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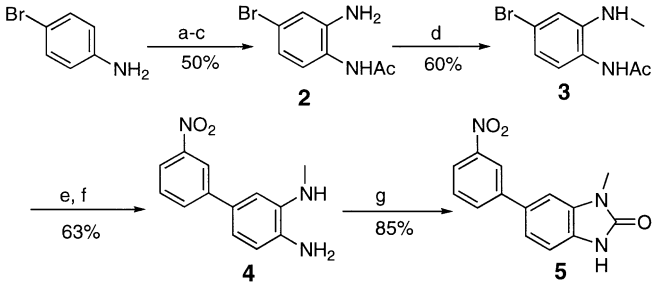
†Presented in preliminary form at XVI International Symposium on Medicinal Chemistry, Bologna, Italy, 18–22 September 2000.

0960-894X/01/$ - see front matter
PII: S0960-894X(01)00554-6

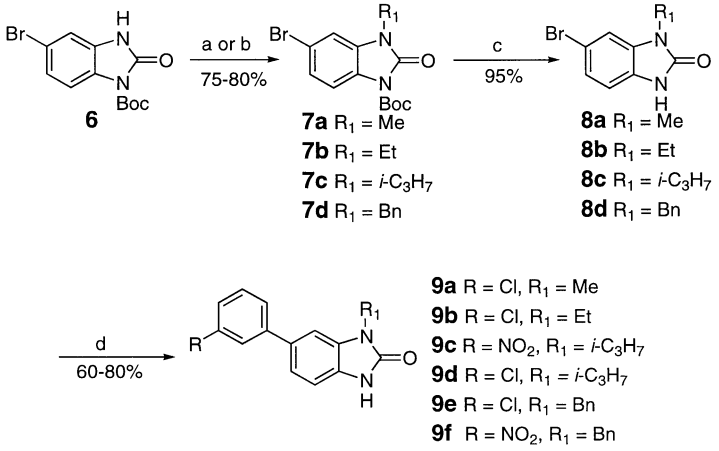
lated *o*-phenylenediamine **2**. Selective methylation of **2** via a reductive alkylation protocol[9] afforded the alkylated *o*-phenylenediamine **3**. Coupling of **3** with 3-nitrophenyl boronic acid via a palladium catalyzed Suzuki reaction and removal of acetyl moiety under an acidic condition gave the desired *o*-phenylenediamine **4**. Ring closure of **4** with 1,1′-carbonyl diimidazole provided the target compound **5** in good yield.

6-Aryl benzimidazolones **9a**–**f** and their 5-substituted congeners **13a**,**b** were more conveniently prepared from the selectively protected benzimidazolones **6**[10] and **10**[10] as depicted in Schemes 2 and 3, respectively. Alkylation of **6** or **10**, using a standard alkylation procedure or a Mitsunobu protocol, provided **7** or **11**. Removal of the protecting groups from benzimidazolones **7** and **11** using TFA or isopropylamine gave compounds **8** or **12**. The cross-coupling of **8** or **12** with an appropriate aryl boronic acid provided 6-aryl benzimidazolones **9a**–**f** or 5-aryl benzimidazolones **13a**,**b** in good yields.[11]

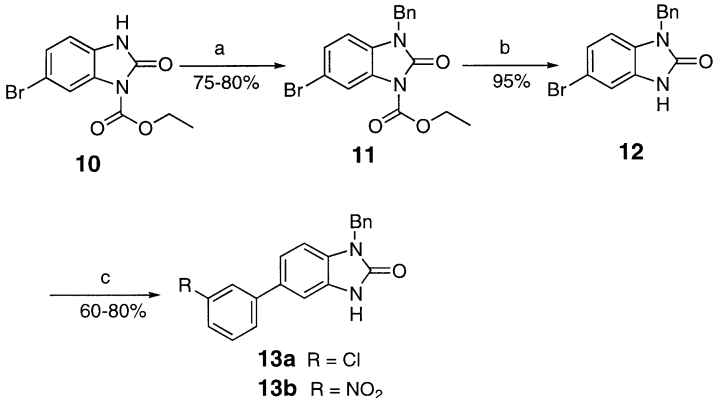
6-Aryl benzothiazol-2-ones and benzimidazole-2-thiones **15**–**17**[11] were prepared as illustrated in Scheme 4. Briefly, 6-aryl benzimidazole-2-thiones **15a**,**b** and 5-aryl benzimidazole-2-thione **16** were prepared by heating a mixture of their corresponding benzimidazolones and Lawesson's reagents at reflux in toluene. 6-Aryl benzothiazol-2-ones **17a**,**b** were prepared from com-



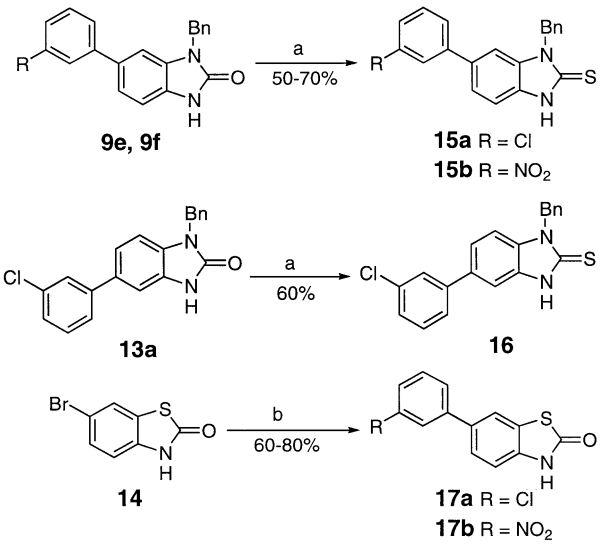
Scheme 1. Reagents and conditions: (a) Ac_2O, reflux; (b) concd HNO_3; (c) Fe, $AcOH/H_2O$; (d) $CH(OEt)_3$, reflux, EtOH, $NaBH_4$; (e) $ArB(OH)_2$, $Pd(Ph_3P)_4$, K_2CO_3, toluene, $EtOH/H_2O$, 85 °C; (f) 1 N HCl, reflux; (g) CDI, THF.



Scheme 2. Reagents and conditions: (a) BnBr, KI, K_2CO_3, MeCN, 80 °C or MeI, K_2CO_3, MeCN, rt; (b) R_1OH, DEAD, Ph_3P, THF, rt; (c) CH_2Cl_2, TFA, rt; (d) $ArB(OH)_2$, $Pd(Ph_3P)_4$, K_2CO_3, toluene, $EtOH/H_2O$, 90 °C.



Scheme 3. Reagents and conditions: (a) BnBr, KI, K_2CO_3, MeCN, 80 °C; (b) isopropylamine, THF, rt; (c) $ArB(OH)_2$, $Pd(Ph_3P)_4$, K_2CO_3, toluene, $EtOH/H_2O$, 90 °C.



Scheme 4. Reagents and conditions: (a) Lawesson's reagent, toluene, reflux; (b) $ArB(OH)_2$, $Pd(Ph_3P)_4$, K_2CO_3, toluene, $EtOH/H_2O$, 90 °C.

mercially available 6-bromo benzothiazol-2-one (**14**) and 3-nitro and 3-chloro phenyl boronic acids using Suzuki coupling conditions.

Results and Discussion

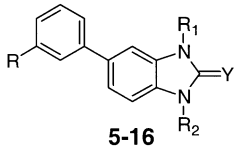
6-Aryl dihydroquinolines such as **1** (Table 1) were recently reported as nonsteroidal PR antagonists.[8] In an effort to improve the potency of 6-aryl dihydroquinolines as PR antagonists, we examined various replacements for the dihydroquinoline core. Benzimidazolones and benzothiazolones were among the first scaffolds examined. The compounds were evaluated for their ability to inhibit progesterone induced PRE-luciferase activity in CV-1 cells[12] and/or inhibit progesterone stimulated alkaline phosphatase activity in a T47D human breast carcinoma cell line.[13,14] The progesterone receptor binding affinity of the novel compounds was measured as previously reported.[12,13]

As shown in Table 1, 6-aryl 1-substituted benzimidazolones such as **9c–f** showed moderate PR antagonist activity in the PRE-luciferase assay or in the alkaline phosphatase assay. The potency of these compounds was markedly affected by the substituent (R_1) at position-1 as demonstrated by 6-aryl benzimidazolones **5** and **9a–f**. As size of substituent R_1 increased from methyl and ethyl to isopropyl and benzyl, the potency of the compounds improved. These results suggested that a lipophilic group or steric bulk at the position-1 is favored.

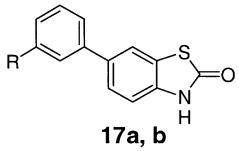
The 1-substituted 5-aryl benzimidazolones **13a**,**b** are at least 6 times less potent than their 6-aryl congeners (**9e**,**f**) in their PR activity and binding affinity. This finding indicates that the favored position of pendent aryl moiety is *para* to NH group.

6-Aryl benzimidazole-2-thiones **15a**,**b** and 5-aryl benzimidazole-2-thione **16** were prepared and evaluated in the T-47D alkaline phosphatase assay.[13] From Table 1, 1-benzyl 6-aryl benzimidazole-2-thiones **15a**,**b** showed potent PR antagonist activity and their potency

Table 1. Activity and binding data of 6-aryl benzimidazolones and their analogues as PR antagonists



5-16



17a, b

Compd	R	R_1	R_2	Y	PRE-luciferase IC_{50} (nM)[a]	Alk. phos. IC_{50} (nM)[a]	PR binding K_i (nM)[a]
Mifepristone					0.3	0.2	1.1
1					42	41.0	20.0
5	NO_2	Me	H	O	1529.0	1000.0	>10,000
9a	Cl	Me	H	O	1370.0	1000.0	>10,000
9b	Cl	Et	H	O	928	1000.0	ND[b]
9c	NO_2	*i*-C_3H_7	H	O	106.0	29.2	~1000
9d	Cl	*i*-C_3H_7	H	O	135.7	73.1	525.0
9e	Cl	Bn	H	O	412.0	112.8	521.0
9f	NO_2	Bn	H	O	257.3	62.0	714.0
13a	Cl	H	Bn	O	3061.0	>10,000	3127.0
13b	NO_2	H	Bn	O	>10,000	>10,000	>10,000
15a	Cl	Bn	H	S	ND	17.0	150.0
15b	NO_2	Bn	H	S	ND	10.0	30.0
16	Cl	H	Bn	S	ND	>10,000	ND
17a	Cl				265.0	460.7	127.0
17b	NO_2				326.0	83.8	332.0

[a]Experimental values represent the average of at least duplicate determinations.[12–14] The standard deviations for these assays were typically ±20% of mean or less.
[b]ND, not determined.

improved at least 6-fold over their benzimidazol-2-one congeners (**9e**,**f**) in the alkaline phosphatase assay. The similar binding affinities of **15b** and dihydroquinoline **1** indicate that an appropriately substituted benzimidazole-2-thione core is a good bioisostere for dihydroquinoline core. Similar to the SAR trend observed in the 6-aryl benzimidazolones, the 5-substituted benzimidazole-2-thione congener **16** did not elicit any significant activity as a PR antagonist.

Changing the *N*-alkyl moiety to sulfur atom at position-1 resulted in 6-aryl benzothiazolones **17a**,**b** with similar potency and PR binding compared to 6-aryl benzimidazolones **9e**,**f**. The activity of 6-aryl benzothiazolones **17a**,**b** might be attributable to the lipophilic nature of sulfur atom at position-1. This result was consistent with the observation, described above, that a lipophilic group is preferred at position-1.

In summary, a number of novel 6-aryl benzimidazolones and benzothiazolones were examined as PR antagonists. The SAR trends unveiled from this study indicate that a lipophilic group at position-1 of the benzimidazolone nuclei and the pendent aryl ring substituted *para* to the N–H moiety are critical for the compounds' ability to elicit good PR antagonist activity. Furthermore, replacement of a carbonyl moiety with a thio-carbonyl group at position-2 significantly improved potency and binding affinity of 6-aryl benzimidazole-2-thiones. These findings proved valuable in the design of our next generation of more potent PR antagonists, which will be the subject of future disclosure.

Acknowledgements

We are grateful for the assistance of the Department of Analytical Chemistry of Wyeth-Ayerst Research for elemental analyses, NMR and mass spectroscopy data.

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11. Analytical data of our potent PR antagonists. **6-(3-Chloro-phenyl)-1-isopropyl-1,3-dihydro-benzoimidazol-2-one** (**9d**). A white solid: mp 164–165 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.9 (s, 1H), 7.7 (bs, 1H), 7.65 (d, 1H, J = 7.8 Hz), 7.51 (s, 1H), 7.46 (t, 1H, J = 7.9 Hz), 7.38 (m, 1H), 7.29 (d, 1H, J = 8.1 Hz), 7.04 (d, 1H, J = 8.1 Hz), 4.65 (m, 1H), 1.48 (d, 6H, J = 6.9 Hz). MS (ES) m/z ([M−H]$^-$, 285. Anal. calcd for $C_{16}H_{15}ClN_2O$: C, 67.02; H, 5.27; N, 9.77. Found: C, 67.40; H, 5.40; N, 9.43. **1-Benzyl-6-(3-chloro-phenyl)-1,3-dihydro-benzoimidazol-2-one** (**9e**). A white solid: mp 168–169 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.0 (s, 1H), 7.66 (t, 1H, J = 2.05 Hz), 7.58–7.5 (m, 1H), 7.45 (t, 2H, J = 8.18 Hz), 7.37–7.22 (m, 7 H), 7.08 (d, 1H, J = 8.18 Hz), 5.1 (s, 2H); MS (ES) m/z [M−H]$^-$, 333. Anal. calcd for $C_{20}H_{15}ClN_2O{\cdot}0.4\ H_2O$: C, 70.24; H, 4.66; N, 8.19. Found: C, 70.27; H, 4.56; N, 8.00. **1-Benzyl-6-(3-nitrophenyl)-1,3-dihydro-benzoimidazol-2-one** (**9f**). A white solid: mp 202–203 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.2 (s, 1H), 8.38 (t, 1H, J = 1.97 Hz), 8.15 (dd, 1H, J = 7.83, 1.97 Hz), 8.80 (d, 1H, J = 7.83 Hz), 7.72 (t, 1H, J = 7.83 Hz), 7.56 (bs, 1H), 7.43–7.22 (m, 6H), 7.13 (d, 1H, J = 7.83 Hz), 5.1 (s, 2H); MS (ES) m/z [M−H]$^-$, 344. Anal. calcd for $C_{20}H_{15}N_3O_3{\cdot}0.25\ H_2O$: C, 68.66; H, 4.46; N, 12.01. Found: C, 68.42; H, 4.44; N, 11.77. **1-Benzyl-6-(3-chlorophenyl)-1,3-dihydro-2*H*-benzimidazole-2-thione** (**15a**). A yellow solid: mp 211–212 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 12.99 (s, 1H), 7.70 (t, 1H, J = 1.7 Hz), 7.64 (m, 1H), 7.58–7.61 (m, 1H), 7.25–7.54 (m, 9H), 5.59 (s, 2H); MS (ESI) m/z [M−H]$^-$, 349. Anal. calcd for $C_{20}H_{15}ClN_2S$: C, 68.46; H, 4.31; N, 7.98. Found: C, 68.07; H, 4.23; N, 7.88. **1-Benzyl-6-(3-nitrophenyl)-1,3-dihydro-2*H*-benzimidazole-2-thione** (**15b**). A yellow solid: mp 244–245 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.08 (s, 1H), 8.43 (s, 1H), 8.20 (dd, 1H, J = 8.2, 1.7 Hz), 8.12 (d, 1H, J = 7.8 Hz), 7.72–7.78 (m, 2H), 7.62 (d, 1H, J = 8.3 Hz), 7.25–7.43 (m, 6H), 5.62 (s, 2H); MS (ESI) m/z [M−H]$^-$, 360. Anal. calcd for $C_{20}H_{15}ClN_2S{\cdot}0.2\ H_2O$: C, 65.81; H, 4.25; N, 11.51. Found: C, 65.56; H, 4.11; N, 11.29. **6-(3-Chloro-phenyl)-3*H*-benzothiazol-2-one** (**17a**). A white solid: mp 195–196 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.95 (s, 1H), 7.96 (d, 1H, J = 1.17 Hz), 7.7 (t, 1H, J = 1.76 Hz), 7.62–7.59 (m, 2H), 7.46 (t, 1H, J = 7.65 Hz), 7.4–7.38 (m, 1H), 7.18 (d, 1H, J = 8.24 Hz); MS (EI) m/z (M^+), 261. Anal. calcd for $C_{13}H_8ClNOS{\cdot}0.75\ H_2O$: C, 56.73; H, 3.48; N, 5.09. Found: C, 56.98; H, 3.11; N, 4.98. **6-(3-Nitro-phenyl)-3*H*-benzothiazol-2-one** (**17b**). A brown solid: mp 276–277 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.0 (s, 1H), 8.44 (t, 1H, J = 2.7 Hz), 8.21–8.08 (m, 3H), 7.78–7.69 (m, 2H), 7.24 (d, 1H, J = 9.23 Hz); MS (ES) m/z [M−H]$^-$, 271. Anal. calcd for $C_{13}H_8N_2O_3S{\cdot}0.25\ H_2O$: C, 56.41; H, 3.09; N, 10.12. Found: C, 56.48; H, 3.11; N, 9.99.
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