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Tetrahedron Letters 44 (2003) 4077–4080

TETRAHEDRON LETTERS

New synthetic approaches to estrogen receptor modulators: imidazo[1,2-*a*]pyridines

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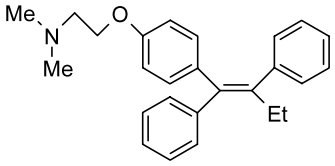
Received 28 February 2003; revised 31 March 2003; accepted 31 March 2003

Abstract—Constrained triarenes have been important templates for selective modulation of the estrogen receptor (ER). For our ER program, we sought an unexplored, synthetically accessible heterocyclic template capable of bearing a broad range of pharmacophores. Traditional approaches to these therapeutics such as raloxifene have relied on an alkoxy moiety to link the arene-based scaffold to the modulating amine group. Alternatively, aryl halide-mediated introduction of alkylene or aryl side chains has not been studied extensively. The synthetic incorporation of pharmacophoric side chains that are carbon-linked to a novel imidazopyridine-based ER recognition motif is disclosed.

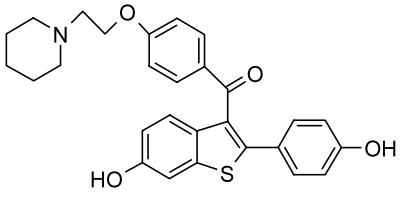
The genesis of triaryl template-based estrogen receptor (ER) modulators was realized in the 1960s with the discovery of the breast cancer therapeutic tamoxifen.[1] Constraint of this key non-steroidal ER recognition motif paved the way for the discovery of the benzothiophene raloxifene, an important second generation selective estrogen receptor modulator (SERM) for prevention of osteoporosis in menopausal women.[2] The human estrogen receptor, a member of the nuclear receptor superfamily of ligand-dependent transcription factors, experiences a conformational change upon ligand binding to initiate a cascade of regulatory events with its target genes.[1] The biological effects of estrogen are mediated by its two receptor subtypes, ERα and ERβ.[3]

Whilst the two hydroxy groups of raloxifene serve as anchors in ER's ligand binding domain, selective effects are attributed to interaction of the amine moiety with Asp-351. Synthetic approaches to these types of trioxygenated compounds utilize alkoxide-linked pharmacophoric amine groups. In our medicinal chemistry program, we aimed to introduce a variety of pharmacophores to a suitably-protected core using aryl halide intermediates. This strategy furnished novel carbon-linked moieties to a new, imidazopyridine-based ER recognition motif. To this end, the synthesis of ER binding imidazo[1,2-*a*]pyridines[4] (**1**) are disclosed herein.

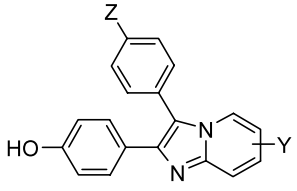
The mechanism of cyclocondensation of 2-aminopyridine with 2-haloketones to afford imidazopyridine cores has been studied by Hand and Paudler.[5] The imidazopyridine template has been employed to prepare potential pharmaceutical agents such as calcium channel blockers,[6] GABA modulators,[7] and cyclooxygenase-2 (COX-2) inhibitors.[8] For instance, synthesis of 2-(4-alkylsulfonylphenyl)-3-phenylimidazopyridines led to the discovery of potent, selective COX-2 inhibitors as promising anti-inflammatory agents.[8] Indomethacin-



Tamoxifen



Raloxifene



1

Z = Ar, CH=CHR, C≡CR

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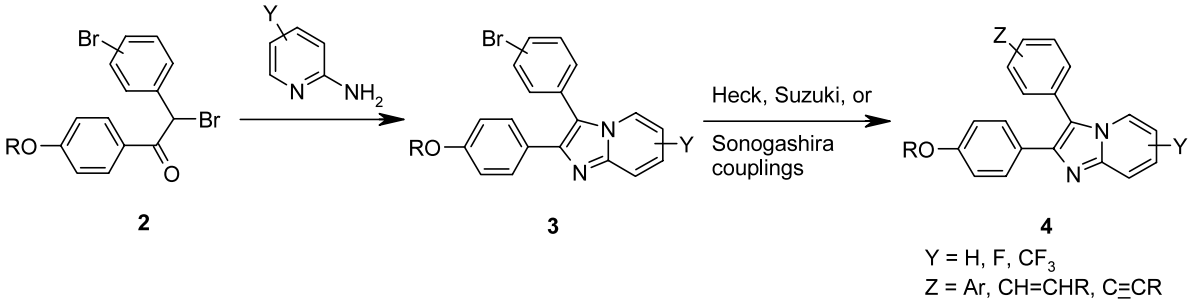
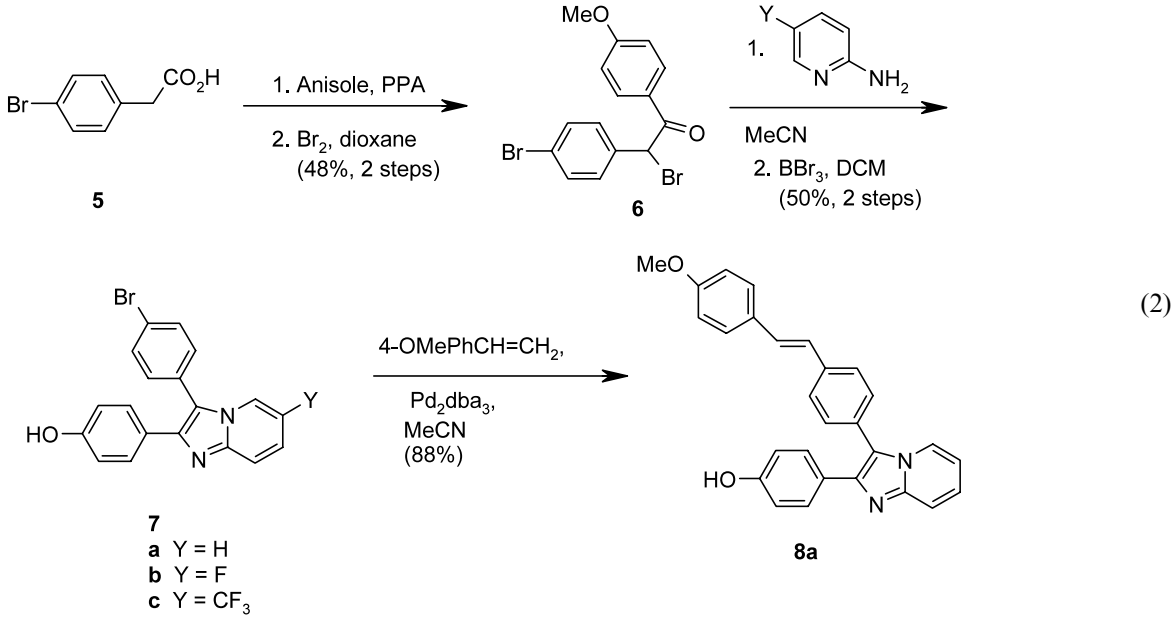


(1)

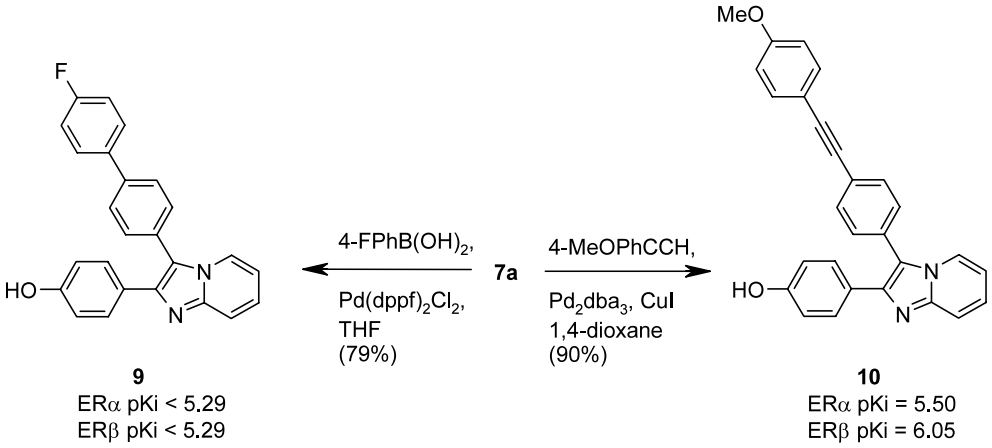
based anti-inflammatory agents have been synthesized as well.[9] The key, annulation step in the synthesis of our ER-targeted imidazopyridines required 2-aminopyridines and bromine-substituted benzoin-derived precursors **2** to furnish variably-substituted tetracyclic intermediates **3** (Eq. (1)). Synthetic details are presented below.

Styryl-appended target **8a** was prepared as follows (Eq. (2)). Friedel–Crafts acylation of anisole by polyphosphoric acid-activated 4-bromophenylacetic acid (**5**)[10] and bromination in dioxane[11] of this acetophenone intermediate furnished α-bromoketone **6**. The bis-electrophile **6** was cyclo-condensed with variably-substituted 2-aminopyridines in acetonitrile to isolate key bromoarene intermediates **7a–c** (for **7c**, ERα SPA binding $pK_i = 6.50$, ERβ SPA binding $pK_i = 5.00$; for estradiol, ERα $pK_i = 8.70$, ERβ $pK_i = 8.56$). Since one initiative of our synthesis was to introduce a variety of moieties at the bromine-containing position of **7a–c**, feasibility of methyl ether unmasking using harsh boron tribromide was studied and effected prior to palladium-mediated carbon–carbon bond formation toward products exemplified by **8a** (ERα $pK_i = 5.50$; ERβ $pK_i = 5.95$). Thus, methyl ether deprotection and Heck coupling of the resultant phenol with 4-methoxystyrene proceeded smoothly to **8a**. Experimental details for conversion of **6** to **8a** are included.[12] The versatility of this general strategy renders the intermediates **7a–c** suitable for Suzuki and Sonogashira couplings as well (Eq. (3), products **9**[13] and **10**[14]).

In summary, we have described a practical, five-step synthesis of novel, estrogen-receptor binding imidazo[1,2-*a*]pyridines. As an application of this chemistry, key bromoarene intermediates **7a–c** were carried forward to biologically interesting ER modulators such as **8a**. Given the facility of the Heck, Suzuki, and Sonogashira couplings with the phenolic intermediates **7a–c**, these aryl bromides offer promise for metal-directed homologation using Stille and Buchwald methodologies as well. These transformations will be studied in due course. The synthesis of potential pharmacophoric side chains that are carbon-linked[15] to the imidazopyridine core represents a general methodology that may be applicable to a number of triarene-type ER modulator templates.



(2)



9
ERα pKi < 5.29
ERβ pKi < 5.29

10
ERα pKi = 5.50
ERβ pKi = 6.05

(3)

Acknowledgements

We thank Dr. David W. Gray of GlaxoSmithKline Discovery Research Biology for biological data.

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12. Compound **8a** was synthesized from **6** as follows: A solution of **6** (1.92 g, 4.99 mmol) and 2-aminopyridine (0.52 g, 1.1 equiv.) in MeCN (100 mL) was heated at 90°C for 18 h. The solution was evaporated and the crude product was purified over silica gel-60 via medium pressure liquid chromatography (MPLC; EtOAc/DCM) to afford 0.99 g (52% yield) of a fine off-white powder. A solution of this product (0.65 g, 1.7 mmol) in DCM (65 mL) was cooled to −20°C in a MeOH/ice bath. Under nitrogen, BBr_3 was added slowly (10 mL of 1.0 M DCM, 5.9 equiv.). After 2 h the reaction mixture was warmed to rt (4 h), and quenched with MeOH (50 mL). The reaction was concentrated, filtered through silica gel (EtOAc/DCM) and evaporated to give **7a** (0.60 g, 97% yield) as a pale yellow/red powder. A 16×125 mm screw-capped vial was charged with **7a** (30 mg, 82 μmol), tris(dibenzylidineacetone)dipalladium (7.5 mg, 0.09 equiv.), tris-*o*-tolylphosphine (4.5 mg, 0.18 equiv.), then evacuated and back-filled with nitrogen. 4-Methoxystyrene (14 μL, 1.2 equiv.), Et_3N (25 μL, 2 equiv.), DMF (0.5 mL), and MeCN (1 mL) were delivered via syringe and the mixture stirred at 85°C for 7 h, cooled, and evaporated. The crude product was purified over silica gel via MPLC (EtOAc/DCM) to yield 2-(hydroxyphenyl)-3-(4-{[*E*]-2-[4-methoxyphenyl]ethenyl}phenyl)imidazo[1,2-*a*]pyridine (**8a**, 30.7 mg, 88% yield) as a dark yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.50 (s, 1H), 8.07–8.05 (d, 1H), 7.75–7.73 (d, 2H), 7.61 (s, 1H), 7.59–7.56 (d, 2H), 7.47–7.41 (m, 4H), 7.34–7.30 (d, 1H), 7.29–7.25 (t, 1H), 7.21–7.17 (d, 1H), 6.97–6.95 (d, 2H), 6.87–6.84 (t, 1H), 6.69–6.68 (d, 2H), 3.77 (s, 3H). IR (neat, cm^{-1}): 3028, 2958, 2929, 2851, 1725, 1656, 1633, 1607, 1510, 1487, 1442, 1391, 1344, 1249, 1173, 1105, 1026, 838, 754. MS (high-resolution, M+H$^+$): $C_{28}H_{22}N_2O_2$, calculated 419.1759; observed, 419.1759.
13. For **9**: A 16×125 mm screw-capped vial was charged with **7a** (30 mg, 82 μmol), (1,1′-bis(diphenylphosphino)ferrocene)palladium chloride (6.2 mg, 0.1 equiv.), K_2CO_3 (22.7 mg, 2 equiv.), 4-fluorophenylboronic acid (23 mg, 2 equiv.), then evacuated and back-filled with nitrogen and THF (2.5 mL). The reaction mixture was stirred at 65°C for 18 h, cooled, concentrated and diluted with EtOAc (75 mL). The organic layer was washed with brine (100 mL), and dried over $MgSO_4$, and evaporated. The crude product was purified over silica gel via MPLC (EtOAc/DCM) to afford 2-(hydroxyphenyl)-3-(4′-fluoro-1,1′-biphenyl-4-yl)imidazo[1,2-*a*]pyridine (**9**, 24.6 mg, 79% yield) as a white flaky solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.52 (s, 1H), 8.10–8.07 (d, 1H), 7.89–7.82 (m, 4H), 7.65–7.62 (d, 1H), 7.58–7.55 (d, 2H), 7.47–7.44 (d, 2H), 7.37–7.26 (m, 3H), 6.90–6.85 (t, 1H), 6.72–6.69 (d, 2H). IR (neat, cm^{-1}): 1161, 1528, 1508, 1486, 1440, 1390, 1345, 1274, 1237, 1161, 1102, 1024, 1006, 825, 753. MS (high-resolution, M+H$^+$): $C_{25}H_{17}FN_2O$, calculated, 381.1403; observed, 381.1425.
14. For compound **10**: A 16×125 mm screw-capped vial was charged with **7a** (30 mg, 82 μmol), tris(dibenzylideneacetone)dipalladium(0) (15.0 mg, 0.2 equiv.), triphenylphosphine (806 mg, 0.4 equiv.), and copper(I) iodide (3.1 mg, 0.2 equiv.), and then evacuated and back-filled with nitrogen. A solution of 1-ethynyl-4-methoxybenzene (53.3 μL, 5 equiv.), Et_3N (50.0 μL, 4.3 equiv.), and 1,4-dioxane

(0.5 mL) were delivered via syringe, and the mixture stirred at 110°C for 16 h. The reaction mixture was cooled, concentrated, and then diluted with EtOAc (50 mL). The solution was washed twice with brine (50 mL), and dried over $MgSO_4$. The crude reaction mixture was purified over silica gel via MPLC (MeOH/DCM) to yield 2-(hydroxyphenyl)-3-(4-{[4-methoxyphenyl]ethynyl}phenyl)imidazo-[1,2-*a*]pyridine (**10**, 62 mg, 90% yield) as a white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.56 (s, 1H), 8.13–8.10 (d, 1H), 7.71–7.69 (d, 2H), 7.66–7.63 (d, 1H), 7.56–7.51 (m, 4H), 7.42–7.39 (d, 2H), 7.35–7.30 (t, 1H), 7.03–7.00 (d, 2H), 6.93–9.89 (t, 1H), 6.73–6.70 (d, 2H), 3.81 (s, 3H). IR (neat, cm^{-1}): 2962, 2926, 1649, 1603, 1510, 1441, 1393, 1258, 1172, 1139, 1091, 1021, 797, 755. MS (high-resolution, $M+H^+$): $C_{28}H_{20}N_2O_2$, calculated, 417.1603; observed, 417.1625.

15. For an example of a carbon-linked basic side chain to a naphthimidazole core, see: Kuo, S.-C.; Ibuka, T.; Huang, L.-J.; Lien, J.-C.; Yean, S.-R.; Huang, S.-C.; Lednicer, D.; Morris-Natschke, S.; Lee, K.-H. *J. Med. Chem.* **1996**, *39*, 1447.