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Estrogen receptor ligands. Part 9: Dihydrobenzoxathiin SERAMs with alkyl substituted pyrrolidine side chains and linkers

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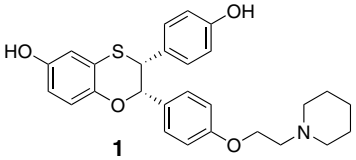
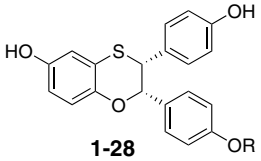
Abstract—A series of dihydrobenzoxathiin SERAMs with alkylated pyrrolidine side chains or alkylated linkers was prepared. Minor modifications in the side chain or linker resulted in significant effects on biological activity, especially in uterine tissue.

The clinical significance of the selective estrogen receptor modulators (SERMs) is well documented.[1] Recently, there has been much interest in the development of receptor subtype-selective SERMS.[2] Previous reports from this laboratory have reported the discovery of dihydrobenzoxathiins (e.g., **1**) as a novel class of Selective Estrogen Receptor Alpha Modulators (SERAMs).[3a–e] More recently, we have also described our initial studies on the side chain SAR of **1**, which were aimed at maintaining potency and selectivity while reducing oxidative metabolism of the side chain.[3d,e]



1



1-28

During the course of these studies, we found that the fused cyclopropyl analog **2** had excellent potency and subtype selectivity while retaining a uterine profile comparable to that of **1** (Table 1). However, like all of the bicyclic analogs that we examined,[3d] **2** appeared to be susceptible to metabolic oxidation of the side chain, as measured by an in vitro liver microsome assay.[4] Interestingly, the unsubstituted pyrrolidine analog **3** did not form a detectable cyanide adduct in this assay. However, **3** had a less favorable SERM profile than **1**, particularly with regard to uterine agonism/antagonism.

We therefore targeted analogs **4**–**16** for synthesis with the hope that we could find a pyrrolidine analog with an improved SERM profile that was less susceptible than **1** to oxidation. The requisite aminoalcohol side chain synthons **4a**–**16a** were prepared by a variety of methods as summarized below (Table 1 and Schemes 1–3).[5]

The first method, illustrated by the preparation of the 3-methyl analog **4a**, involved conversion of a chiral diacid, for example, **29**, to the corresponding imide **45** by sequential reaction with acetyl chloride (to form the anhydride), ethanolamine, and acetic anhydride (Scheme 1). As expected, some epimerization occurred during this sequence; imide **45** was obtained in only 71% ee.[6] For initial evaluation, this enantiomerically impure material was converted to the final product, dihydrobenzoxathiin **4**. However, it was possible to obtain enantiomerically pure **4a** by chiral HPLC separation of the enantiomers of **45**[6] followed by reduction of the

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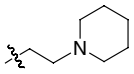
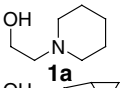
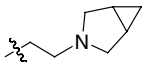
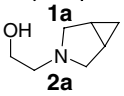
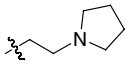
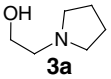
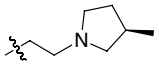
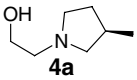
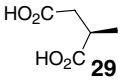
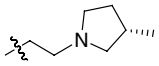
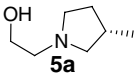
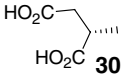
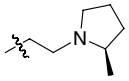
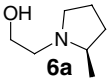
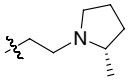
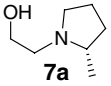
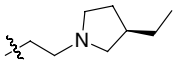
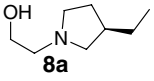
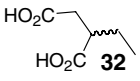
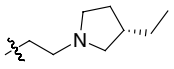
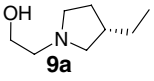
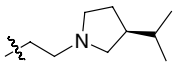
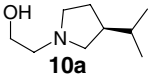
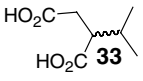
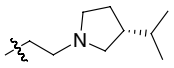
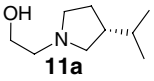
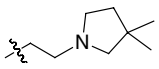
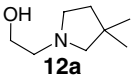
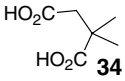
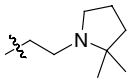
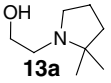
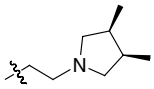
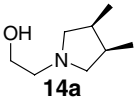
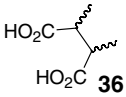
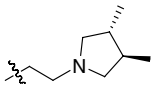
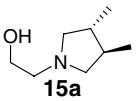
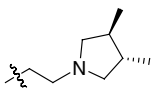
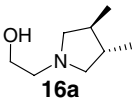
Table 1. Side chain preparation summary and biodata for alkylated pyrrolidine analogs

#	R	ER Binding (IC_{50}, nM)[9]			Cyanide adduct?[4]	MCF-7[10] IC_{50} (nM)	Uterine activity[11]		Side chain	Starting material[5]	Scheme (yield)[5]
		hERα	hERβ	β/α			%Ant.	%Ag.			
1		0.8	45	56	Yes	2.8	99	9	 **1a**	Commercial (Aldrich)	
2		0.7	136	194	Yes	2.6	86	8	 **2a**	See Ref. 4	
3		2.6	64	25	No	3.3	72	34	 **3a**	Commercial (Aldrich)	
4		3.0	161	54	No	0.9	106	−19	 **4a**	 **29**	1 (50)
5		1.0	50	50	No	1.0	85	8	 **5a**	 **30**	1 (48)
6		0.7	21	30	No	0.4	83	12	 **6a**	 **31**	2 (19)
7		0.8	48	60	No	0.5	22	65	 **7a**	**31**	2 (17)
8		0.9	24	27	—	1.6	31	63	 **8a**	 **32**	1 (26)
9		1.1	19	17	—	1.2	14	77	 **9a**	**32**	1 (26)
10		0.4	13	33	Yes	3.5	27	36	 **10a**	 **33**	1 (23)
11		0.3	13	43	Yes	3.8	34	46	 **11a**	**33**	1 (17)
12		1.0	45	45	Yes	0.7	78	2	 **12a**	 **34**	1 (11)
13		0.9	59	65	Yes	0.4	3	98	 **13a**	 **35**	3 (39)
14		0.7	73	104	No	0.5	75	22	 **14a**	 **36**	1 (7)
15		0.5	37	74	Weak	0.4	103	−10	 **15a**	**36**	1 (6)
16		0.4	22	55	No	—	52	39	 **16a**	**36**	1 (6)
—	Raloxifene	1.8	12	7	No	0.8	81	24	n/a	n/a	n/a
—	17β-Estradiol	1.3	1.1	1	—	—	—	100[11b]	n/a	n/a	n/a