Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 1661–1663

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Synthesis and Biological Activity of Phenoxyphenyl Oxamic Acid Derivatives Related to L-Thyronine

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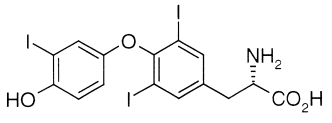
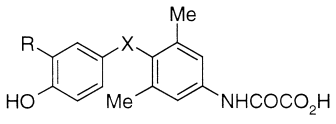
Received 11 April 2000; accepted 19 May 2000

Abstract—The synthesis of substituted phenoxyphenyl oxamic acid derivatives related to L-thyronine (L-T_3) is described. The in vitro and in vivo cholesterol lowering and cardiovascular effects of these compounds are presented and discussed.

Triiodothyronine (L-T_3) **1** and related analogues have been shown to lower cholesterol levels in animal models[1] and man.[2] This property results from the action of thyroid hormone on its liver nuclear receptors to stimulate the synthesis of low density lipoprotein (LDL) receptors[3] as well as the synthesis of several lipolytic enzymes.[4] However, these agents are not used therapeutically due to adverse cardiac side effects, which arise either directly by acting on cardiac receptors or indirectly through an increase in metabolic rate.[5] Recently we described a series of diaryl ether containing oxamic acid derivatives such as **2** that shows a large separation between lipid lowering activity and cardiovascular side effects and selectivity for activation of thyroid hormone β receptor (TRβ) compared to TRα.[6] As previously shown, these compounds have an unusual structure–activity profile in that replacement of the 3,5-diiodo groups with methyl groups resulted in comparable or enhanced potency and improved in vivo activity. In the previous report,[6a] investigation of the structure–activity profile at the 3′-position was limited. Herein we report the results of the synthesis and testing of a variety of 3′-alkyl and 3′-aryl derivatives **3**.



1 (L-T_3)



2, X = O, R = *i*Pr
3, X = O, R = alkyl, aryl, cycloalkyl
4a, X = S, R = *c*-C_6H_{11}
4b, X = SO_2, R = *c*-C_6H_{11}

Chemistry Results

Compounds **3d** and **3f**–**3j** were prepared as described in Scheme 1. Nucleophilic aromatic substitution reaction of iodophenol **6** with *p*-chloronitrobenzene **7** led to the key diphenyl ether derivative **8**. Suzuki coupling[7] of **8** with arylboronic acids (**9**) produced the 3′-aryl analogues **10**. Demethylation of **10** with boron tribromide followed by nitro group reduction generated the phenols **11**. Reaction of **11** with dimethyl oxalate led to the corresponding oxamate esters, which underwent alkaline hydrolysis to yield the final compounds **3**. The 3′-phenyl-4′-deshydroxy analogue **5** was prepared analogously starting with the reaction of commercially available 3-phenylphenol with **7**, followed by nitro group reduction, treatment with dimethyl oxalate and alkaline hydrolysis.

Compounds **3a**–**c** and **3e** were prepared from the starting hydroquinones **12** as shown in Scheme 2. Selective protection of the less hindered hydroxyl group with *t*-butyldimethylchlorosilane, followed by methylation of the

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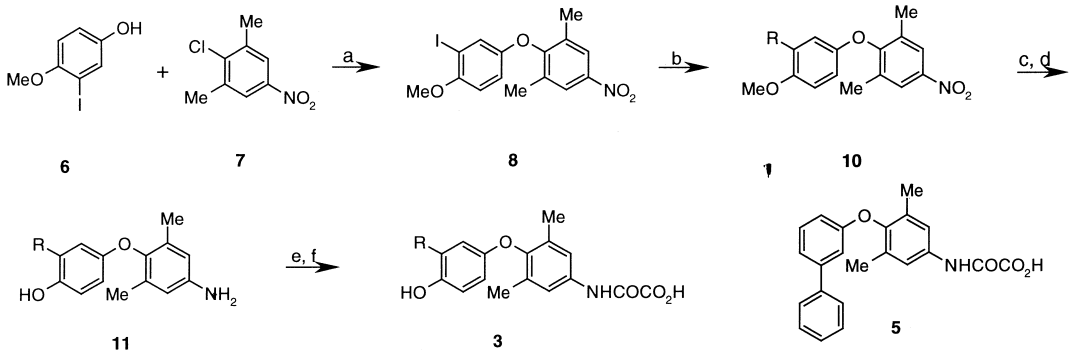
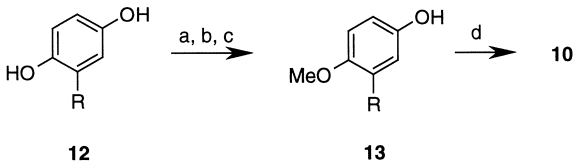


Scheme 1. Synthesis of 3′–aryl derivatives **3d–j**. R is defined in Table 1. Reagents: (a) NaH, DMF, 120 °C; (b) $RB(OH)_2$ (**9**), $PdCl_2(dppf)$, K_3PO_4, DME; (c) BBr_3; (d) H_2, 10% Pd/C, EtOH or H_2NNH_2, 10% Pd/C, EtOH; (e) Dimethyl oxalate, 120°C; (f) NaOH.



Scheme 2. Synthesis of intermediates for **3a–c** and **3e**. R is defined in Table 1. Reagents: (a) $Me_3CSi(Me)_2Cl$; (b) Me_2SO_4, K_2CO_3; (c) 6 N HCl; (d) **7**, NaH.

more hindered hydroxyl group and de-silylation produced the phenols **13**. Reaction of **13** with 4-chloro-3,5-dimethylnitrobenzene **7** generated **10**, which was elaborated to the final compounds as outlined in Scheme 1.

The sulfur containing analogues **4a** and **4b** were prepared as described in Scheme 3. Nucleophilic aromatic substitution reaction of 2-cyclohexyl-4-mercaptophenol (**14**)[8] with **7** led to thioether **15**. Hydrogenation of nitro compound **15** produced the intermediate aniline, which was condensed with dimethyl oxalate to yield **16**. Alkaline hydrolysis of **15** led to thioether product **4a**. Sulfone **4b** was prepared by MCPBA oxidation of the intermediate oxamate ester, followed by alkaline hydrolysis.

Biological Results

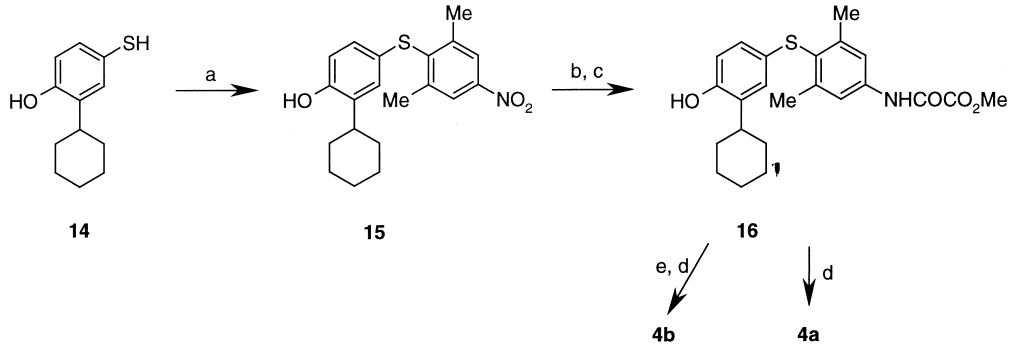
Compounds **3a–j**, **4a**,**b** and **5** were tested in vitro for competitive binding to the L-T_3 receptor of intact rat liver nuclei and the results are summarized in Table 1. Among the 3′-alkyl derivatives, the ethyl (**3b**) and isopropyl (**2**) were more active than the methyl analogue (**3a**), which is consistent with the structure–activity profile of previously reported L-T_3 analogues.[9,10]

Table 1. In vitro competitive binding to the L-T_3 receptor of intact nuclei

Compound	R	IC_{50}(nM)[a]
1		1.1
2	*i*Pr	0.19[b]
3a	Me	5.4
3b	Et	0.25
3c	*c*-C_6H_{11}	2.2
3d	Ph	1.9
3e	*o*-CI-C_6H_4	0.17
3f	*m*-CI-C_6H_4	0.64
3g	*m*-F-C_6H_4	1.9
3h	*m*-CF_3-C_6-H_4	0.92
3i	*p*-CF_3-C_6H_4	14
3j	*p*-Me-C_6H_4	9.0
4a	*c*-C_6H_{11}	2.0
4b	*c*-C_6H_{11}	1.9
5		32

[a]The IC_{50} value is the concentration of compound which inhibits 50% of bound [^{125}I]-L-T_3 at the rat hepatic L-T_3 receptor as previously described and represents the mean of two or more assays using 6 to 8 concentrations of compound per assay. See ref 6.
[b]See ref 6.

The cyclohexyl analogue (**3c**) had affinity comparable to the phenyl analogue (**3d**), with IC_{50}'s of 2.2 and 1.9 nM respectively. The *o*-chlorophenyl analogue (**3e**, 0.17 nM) was the most active compound in the series, the *meta*-substituted analogues **3f–h** showed good activity (0.64–



Scheme 3. Synthesis of sulfur analogues **4a** and **4b**. Reagents: (a) **7**, NaH, DMF; (b) H_2, 10% Pd/C; (c) Dimethyl oxalate, 120 °C; (d) NaOH; (e) mCPBA.

Table 2. Effects in vivo on cardiovascular activity in rats after 7 days treatment

Per cent difference from vehicle treated controls					
Compound	Dose	Heart weight	Heart rate	% of initial developed tension	
				At 20 pulses/min	At 40 pulses/min
1	100 μg/kg	+38.9[a]	+52.5[a]	+18.2[a]	+12.7[a]
3c	25 mg/kg	+4.4	+6.3	+7.6[a]	+12.6[a]
3d	25 mg/kg	−3.1	−8.5	+3.7	−0.7

[a] $p < 0.05$ versus vehicle according to Student's *t*-test.

1.9 nM) and the *para*-substituted derivatives **3i**,**j** were the least active (14 and 9.0 nM), suggesting that the binding subsite is not deep enough to optimally accommodate *para* substituents. The 4′-deshydroxy analogue **5** was substantially less active than the corresponding 4-hydroxy compound **3d**.

Replacement of the diaryl ether oxygen in **3c** with sulfur (**4a**) or sulfonyl (**4b**) led to comparable affinity consistent with earlier reported studies.[9]

Compounds **3a**–**j**, **4a**,**b** and **5** were tested in hypercholesterolemic rats at 20 μg/kg po for 7 days as described previously.[6] The rats were made hypercholesterolemic by maintaining them ad libitum on a water and high cholesterol diet containing 1.5% cholesterol and 0.5% cholic acid. Only compounds **3c** and **3d** showed significant reduction in cholesterol (42 and 49%, respectively) relative to control animals. This activity is comparable to the results previously found for **2**, which at 25 μg/kg po lowered cholesterol by 54%.[6a] Compounds **3c** and **3d** were next tested for cardiovascular side effects. Previously it was found that the cardiovascular effects normally attributable to excess exposure of thyroid hormone, such as increased heart weight, chronotropy and inotropy, could be reproduced in rats.[6d] To test for the lack of cardiac effects, atrial heart rate, atrial tension and heart weight were determined after administration of the compounds to rats at 25 mg/kg po for 7 days as previously described.[6] Although **3c** had significant cardiovascular activity, **3d** showed no effects (Table 2). By comparison, L-T_3(**1**) produces cardiovascular effects at a dose of 100 μg/kg.[6]

Thus compound **3d** was found to have the desired biological profile, showing potent lipid lowering effects and no cardiovascular side effects with over a 1000-fold separation between the two effects. The 3′-phenyl analogues described here extend the structure–activity profile of the oxamic acid series of thyrominetics beyond the previously reported 3′-benzyl and benzoyl derivatives [6a] and provide additional insights into the structural properties needed for potent in vitro activity and the desired in vivo profile.

Acknowledgements

The authors wish to thank Drs. Cynthia Fink and Paivi Kukkola for helpful discussions and Ms. Fatima DeSousa for the preparation of this manuscript.

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