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Novel heterocyclic thyromimetics. Part 2☆

Helmut Haning,* Ulrich Mueller, Gunter Schmidt, Carsten Schmeck, Verena Voehringer, Axel Kretschmer and Hilmar Bischoff

Bayer HealthCare AG, Bayer Schering Pharma Global Drug Discovery, D-42096 Wuppertal, Germany

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Abstract—Novel heterocyclic thyromimetics are presented carrying carboxy-substituted benzofurans or sulfur containing heterocycles, as replacements for the amino acid side chain of T3. Potent agonists were identified in both series. SAR trends are examined and found to be mostly consistent with previously published thyromimetics. The lack of isoform selectivity demonstrated with isoform-selective transient THR transfection assays has been confirmed by corresponding in vivo studies.

Cardiovascular diseases continue to be the number one cause of mortality in the western world. Aberrant lipoprotein profiles have been well established as a risk factor contributing to the morbidity of these maladies. The natural thyroid hormones (TH) T4 **1** and T3 **2** play an important role in the regulation of multiple physiological endpoints such as brain development, energy homeostasis and control of cholesterol levels through interaction with thyroid hormone receptors (THR), members of the nuclear hormone receptor superfamily. The different physiological functions of the thyroid hormones are mediated by different receptor subtypes, THRα and THRβ, with distinct tissue distribution. The natural hormones T4 and T3 cannot therapeutically be used due to their cardiac side effects such as tachycardia and arrhythmia. Molecules mimicking only the beneficial effects of the thyroid hormones on these processes and lacking their cardiac side effects potentially could find therapeutic use in a number of conditions such as obesity, atherosclerosis and dyslipidemia.

Selective and therapeutically useful thyromimetic action therefore can be based either on receptor selectivity or specific tissue targeting. Over the last years great improvements have been made in the design and understanding of THRβ selective agonists.[2] In addition the concept of liver targeting has also been demonstrated with the liver targeted conjugation of T3 with bile acid[3] and demonstration of liver selective activity of L-94901 **3** that can at least in part be attributed to liver selective nucleic transport.[4]

Recently we have demonstrated that incorporation of heterocycles into the biphenyl ether framework of the natural hormones leads to a valuable addition in the chemical diversity of synthetic thyromimetic agents and can also form the basis for THRβ selective molecules.[1]

Since it has been demonstrated that changes either in the outer ring of the biphenyl ether skeleton

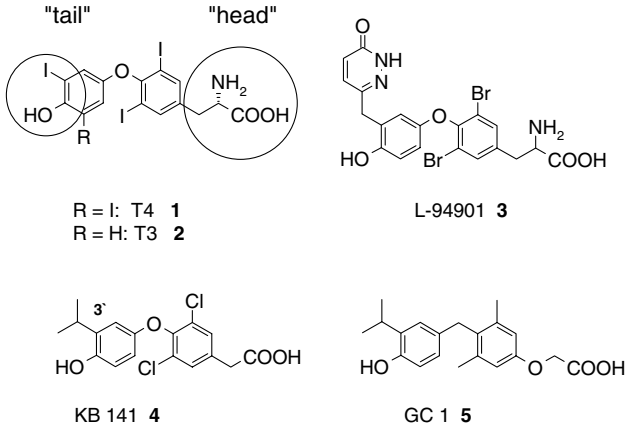

Figure 1. Thyroidhormones T4 **1** and T3 **2**, L-94901 **3**, KB141 **4**.

Keywords: Thyromimetics; Benzofuranes; Thiazinane-2,4-dione.
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* Corresponding author. Fax: +49 202 364160; e-mail: Helmut.Haning@bayerhealthcare.com

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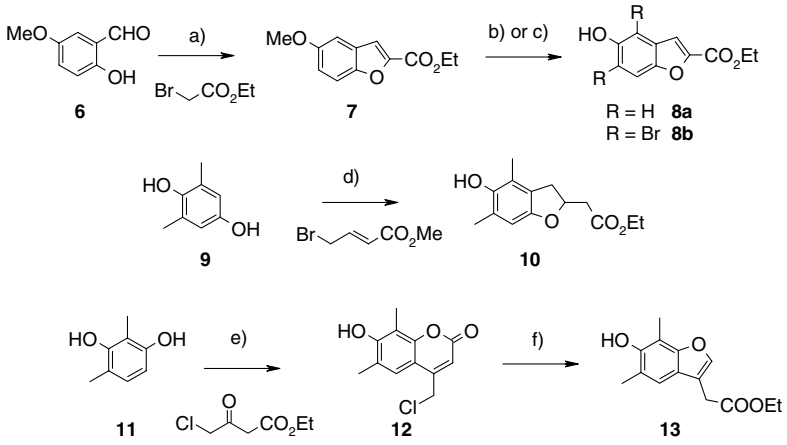
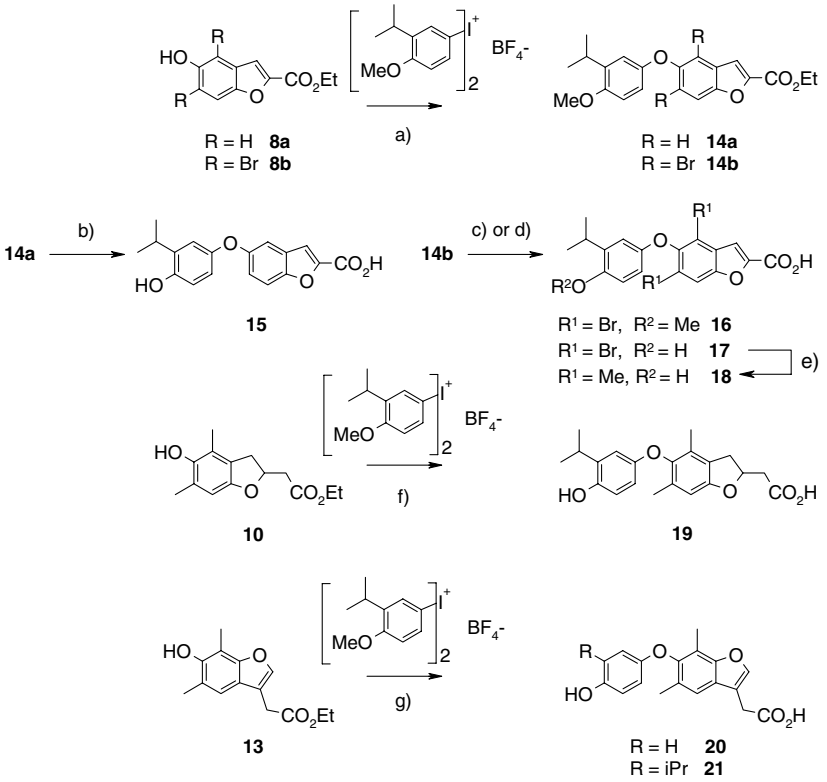
(exemplified by analogues of KB 141 **4** with diverse substituents in the 3′ position) or in the head group (exemplified by GC 1 **5**) can lead to enhanced selectivity, we wanted to explore the incorporation of heterocycles into the head group to expand the diversity in thyromimetic scaffolds. This work expands on recent disclosures in the field of bicyclic thyroid hormone receptor agonists[5] (Fig. 1).

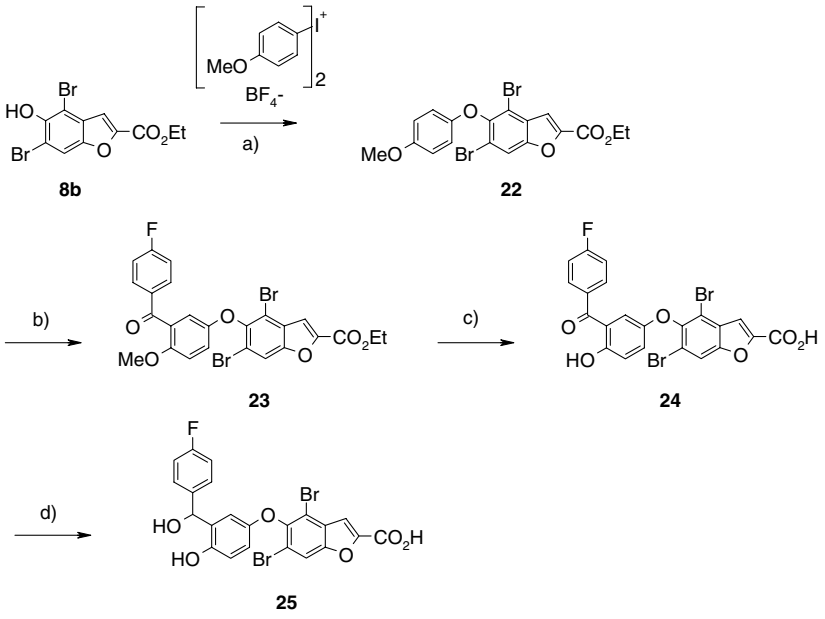
The principal tolerance of the THR ligand binding pocket to altered head groups has long been established.[6] In our studies we focused on benzofurans and sulfur containing heterocycles as amino acid replacements. The syntheses of our new heterocyclic thyromimetics are exemplified in Schemes 1–4. The syntheses of the heterocyclic fragments used for the construction of the biaryl ether framework are shown in Scheme 1.



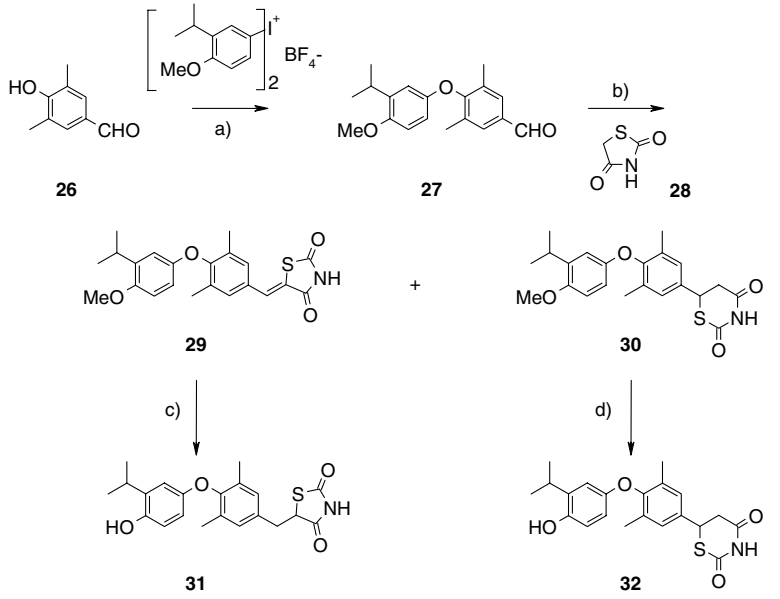
Scheme 1. Synthesis of benzofuran fragments. Reagents and conditions: (a) K_2CO_3, DMF, 80 °C (33%); (b) BBr_3, DCM, rt (39%); (c) i—BBr_3, DCM, rt (39%); ii—Br_2, HOAc, 50 °C (21%); (d) i—$ZnCl_2$ (1.7 equiv) *n*-heptane, reflux; ii—EtOH, concd H_2SO_4, reflux (6%); (e) concd H_2SO_4, rt (87%); (f) i—0.1 N NaOH, reflux (69%); ii—H_2SO_4 (cat.), EtOH, reflux, 16 h (75%).



Scheme 2. Synthesis of benzofuran thyromimetics. Reagents and conditions: (a) Cu bronze, NEt_3, DCM, 0 °C–rt, 16h; (b) BBr_3, DCM, −78 °C–rt (10%); (c) EtOH, NaOH (90%); (d) i—BBr_3, DCM, −78 °C–rt (90%); ii—EtOH, NaOH (85%); (e) i—$Sn(Me)_4$, $Pd(PPh_3)_4$, Tol, reflux (46%); ii—BBr_3, DCM, −78 °C–rt (90%); iii—EtOH, NaOH (85%); (f) i—Cu bronze, DCM, NEt_3 (17%); ii—$AlCl_3$, DCM, rt, 6 h, EtSH (49%), iii—NaOH (72%); (g) i—Cu bronze, DCM, NEt_3 (42%); ii—$AlCl_3$, DCM, rt, 6 h, EtSH (73%); iii—NaOH (72%) (yields refer to **21**).



Scheme 3. Synthesis of benzoyl thyromimetics. Reagents and conditions: (a) Cu bronze, NEt_3, DCM, 0 °C–rt, 16 h (20%); (b) $TiCl_4$, 4-F-benzoylchloride (2.5 equiv), molsieves, DCM, rt (46%); (c) i—$AlCl_3$, EtSH (16 equiv), DCM, rt (72%); ii—NaOH, EtOH, rt (84%); (d) $NaBH_4$, MeOH, 0 °C (92%).



Scheme 4. Synthesis of thiazoline thyromimetics. Reagents and conditions: (a) Cu bronze, NEt_3, DCM, 0 °C–rt, 16 h (93%); (b) **28**, piperidine, benzoic acid, Tol, reflux (62% **29**, 12% **30**); (c) i—BBr_3, DCM, rt (26%); ii—Pd/C, H_2 4 bar, dioxane (54%); (d) BBr_3, DCM, rt (79%).

The benzofuran moieties **8**, **10** and **13** were synthesized either starting from the corresponding dihydroxy-benzaldehyde **6**,[7] from a substituted dihydrochinone **9** or following a sequence involving a coumarine rearrangement (**11**–**13**).[8]

The synthesis of the benzofuran derivatives was achieved via classical copper–bronze mediated coupling reactions of the respective hydroxybenzofuran with 3-substituted bis-(4-methoxy-phenyl)iodonium-tetra-fluoroborates (Scheme 2).[9]

The bromine atoms adjacent to the biphenyl ether bridge can be exchanged for methyl groups **18** using $Sn(Me)_4$.[10] Deprotection of the phenol is typically achieved with BBr_3 or $AlCl_3$/EtSH.

Incorporation of benzoyl type substituents in the 3′-position is achieved via Friedel–Crafts acylation (Scheme 3).

In addition to fused heterocyclic systems, we also investigated heterocycles attached via a spacer as substitutes

for the amino acid head group in the natural hormones. Syntheses are depicted in Scheme 4.

Condensation of the aromatic aldehyde **27** under basic conditions gave the rearranged thiazinane-2,4-dione **30** as side product in addition to the desired product **29**. Compounds **29** and **31** are closely related to a series of heterocyclic thyromimetics described by Ebisawa et al. and later Hashimoto et al.[11] and also Scanlan[12] as potent thyroid hormone receptor agonists. The corresponding congener of **31** carrying two ^{i}Pr-groups on the inner ring **33** was synthesized from the corresponding hydroxybenzaldehyde with the appropriate substitution pattern.

Several SAR trends are apparent comparing the analogues shown in Table 1. Potency was determined in a HEP-G2 whole cell assay containing both receptor isoforms.[1] As anticipated, substituents ortho to the central ether bond on the inner ring are required for activity as the derivative **15** is inactive.

Hydrogen bond donor capacity on the outer ring is also an essential component of these heterocyclic TR agonists demonstrated by the inactivity of **16**. Increasing the steric bulk of the ortho substituents from H as in **15** to methyl as in **18** to bromine as in **12** increases the thyromimetic potency consistent with long established trends in THR SAR and leads to potent single digit nanomolar THR agonists in this benzofuran series.

A benzoyl substituent on the outer ring like in **24** is tolerated however with reduced activity compared to ^{i}Pr-derivative **17**. Reduction of the carbonyl group in **24** to the corresponding alcohol **25** results in tenfold increased potency; this SAR trend is also present in the series of oxamic acid thyromimetics that spawned CGS 26214.[6a]

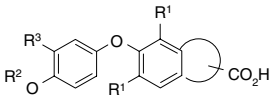
Due to the relatively weak activity no attempt was made on enantiomeric separation of the alcohol.

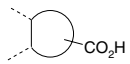
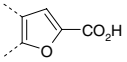
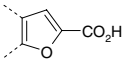
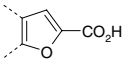
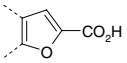
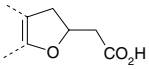
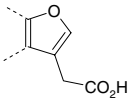
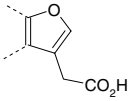
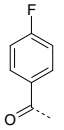
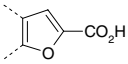
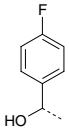
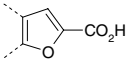
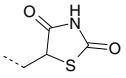
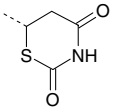
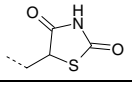
The regioisomeric benzofuran headgroup as represented in the compounds **20** and **21** was investigated. The incorporation of a methylene spacer between the benzofuran and the carboxylic acid leads to the highly potent subnanomolar THR ligand **21** (EC_{50} = 0.3 nM). A lipophilic substituent like the ^{i}Pr-group on the outer ring as in **21** is required for activity since the unsubstituted derivative **20** exhibits only weak activity. In addition, a saturated fused heterocycle was examined, also giving rise to a potent THR agonist **19**.

In the series of non-fused agonists extremely potent thyromimetics were found with 6- **31** as well as with 5-membered **32** heterocyclic moieties. The replacement of the methyl groups in **32** on the inner ring by isopropyl as in derivative **33** leads to a significant loss in activity.

THR isoform selectivity was examined for the most potent compounds **21**, **31** and **32** using an isoform selective transient transactivation assay as previously described.[1]

Table 1. EC_{50} data for compounds **15–33**



Compound	R^1	R^2	R^3		EC_{50} (nM)
15	H	H	*i*-Pr		1000
16	Br	Me	*i*-Pr		1000
17	Br	H	*i*-Pr		7
18	Me	H	*i*-Pr		110
19	Me	H	*i*-Pr		5.1
20	Me	H	H		1000
21	Me	H	*i*-Pr		0.3
24	Br	H			210
25	Br	H			22
31	Me	H	*i*-Pr		0.08
32	Me	H	*i*-Pr		0.06
33	*i*-Pr	H	*i*-Pr		70

Unfortunately, none of the selected heterocyclic compounds demonstrated selective activity for THR β.

In addition, thyromimetic activity was determined in vivo for the ethyl ester of compound **21** which is readily converted to the corresponding acid in vivo after oral administration. Once daily oral treatment of NMRI mice over a period of 7 days led to a non-linear dose dependent reduction of cholesterol of 32–41% beginning

at a dose of 0.1 mg/kg.[13] On the other hand, a pronounced increase of the heart weight of 12–27% could be demonstrated for this compound in a dose dependent manner beginning at 0.1 mg/kg in a mouse model for cardiac effects,[14] thus confirming the lack of in vitro selectivity.

In conclusion we have expanded the chemical diversity of potent thyromimetic agents with heterocyclic substituents in the head group. Picomolar agonists have been synthesized and their selective isoform activation has been determined. The lack of isoform selectivity has been confirmed with corresponding in vivo studies demonstrating thyromimetic activity on cholesterol homeostasis as well as on cardiac function in a similar dose range.

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13. NMRI mice (8–10 animals per group) were orally treated once daily by gavage (vehicle: solutol/ethanol/water 10:10:80) with doses of 0.1, 0.3, 1.0 and 3.0 mg/kg with the ethyl ester of compound **21** over a period of 7 days. At the end of the study blood was retroorbitally collected and serum cholesterol and triglyceride concentration levels were enzymatically determined using commercially available test kits (Boehringer Mannheim, Germany) and an autoanalyzer (EPOS 5060, Eppendorf Gerätebau, Hamburg, Germany). Serum cholesterol reductions of 32%, 34%, 39% and 41% versus control were determined.
14. C57BL/6J mice (10-12 animals per group) were orally treated once daily by gavage (vehicle: solutol/ethanol/water 10:10:80) with doses of 0.1, 0.3 and 3.0 mg/kg with the ethyl ester of compound **21** over a period of 11 days. At the end of the study heart rate was determined using a computerized non-invasive tail cuff system (TSE Systems GmbH, Bad Homburg, Germany). Animals were sacrificed and heart weight was determined. Increases in heart weight of 12%, 17% and 27% were determined, respectively.