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4,4-Dimethyl-1,2,3,4-tetrahydroquinoline-based PPARα/γ agonists. Part I: Synthesis and pharmacological evaluation

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Abstract—Type-2 diabetes (T2D) is a complex metabolic disease characterized by insulin resistance in the liver and peripheral tissues accompanied by a defect in pancreatic β-cell. Since their discovery three subtypes of Peroxisomes Proliferators Activated Receptors were identified namely PPARα, PPARγ and PPARβ/(δ). We were interested in designing novel PPARγ selective agonists and/or dual PPARα/γ agonists. Based on the typical topology of synthetic PPAR agonists, we focused our design approach on 4,4-dimethyl-1,2,3,4-tetrahydroquinoline as novel cyclic tail.

Type-2 diabetes (T2D) is a complex metabolic disease characterized by insulin resistance in the liver and peripheral tissues accompanied by a defect in pancreatic β-cell.[1] Because of excessive food intake and lack of physical activity that characterize the western life style, T2D is assumed to reach epidemic proportions.[2] According to the WHO, currently more than 151 million people suffer from diabetes worldwide and this number is expected to exceed 333 million by 2025.

At present, the treatment of T2D is directed toward the reduction of hyperglycemia by improving insulin secretion or reducing the insulin resistance of peripheral tissues. Most of these commonly used therapies have been developed through ignorance of any therapeutic target. Thus, considerable efforts were made to get better understanding of the disease's pathogenesis in order to identify more suitable therapeutic strategies.[3]

Since their discovery in 1990 by Isseman and Green[4] three subtypes of Peroxisomes Proliferators Activated Receptors were identified namely PPARα, PPARγ and PPARβ/(δ). PPARs belong to the family of nuclear receptors and act as ligand-activated transcription factors that govern numerous biological processes[5] including energy metabolism,[6] cell proliferation, skin development and inflammation.

Once the receptors of thiazolidinedione class of agents (TZD, e.g., Rosiglitazone, Fig. 1) and fibrates (e.g., Fenofibrate, Fig. 1) were identified, respectively, as PPARγ and PPARα, extensive studies were initiated to develop compounds that activate these receptors.[7]

The goals consisted in identifying second generation ligands that were more efficacious and that could potentially offer additional benefits to the patients. Thus dual-acting PPARα/γ agonists (e.g., Tesaglitazar, Fig. 1) were considered in this past few years as very attractive option in the treatment of dyslipidemic type-2 diabetes.[7,8]

As shown in Scheme 1, the ligand–protein interactions of typical PPAR agonists could be represented by a sim-

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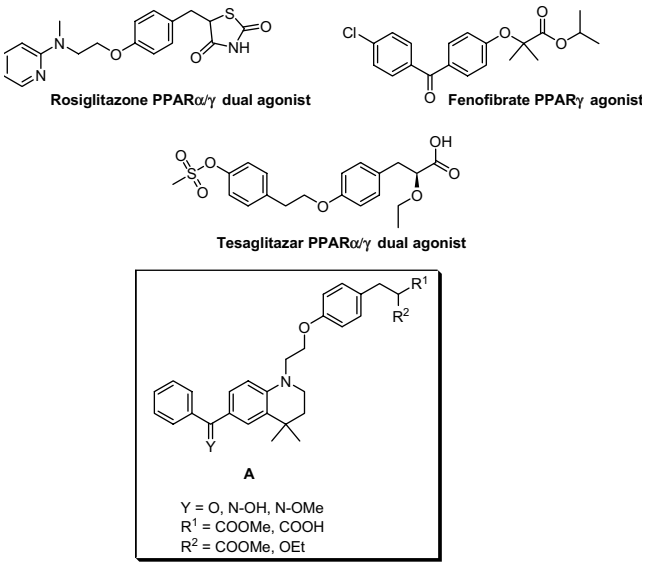
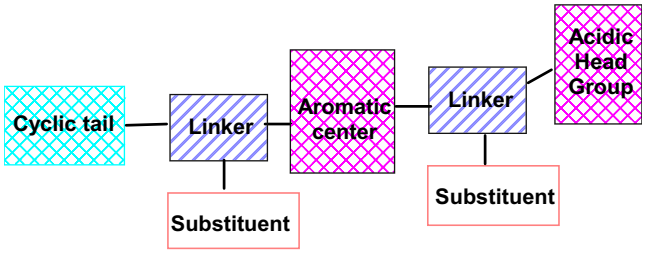


Figure 1. Structures of PPARγ selective agonist and two PPARα/γ dual agonists (both were aborted in clinical phase III) and general structure of our compounds A.

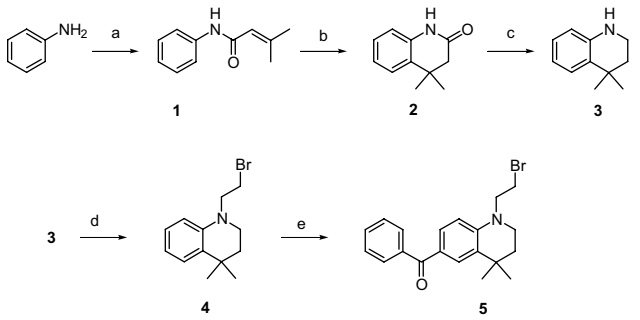


Scheme 1. General structure of typical synthetic PPAR agonist.

plified topological representation.[9] The acidic head group, known as carboxylic acid or 2,4-thiazolidinediones, is involved in up to four hydrogen bounds with the receptor. This part is crucial for PPAR activation. The central aromatic moiety is located in a hydrophobic pocket while the cyclic tail tolerates more polar substituents.

In this course, we were interested in designing novel PPARγ selective agonists and/or dual PPARα/γ agonists. Based on the typical topology of synthetic PPAR agonists, we focused our design approach on 4,4-dimethyl-1,2,3,4-tetrahydroquinoline as novel cyclic tail[10] (general formula A, Fig. 1). In this paper, we report the synthesis and the biological evaluation of the first derivatives we obtained: the malonate series which is a selective PPARγ agonist and the dual-acting PPARα/γ agonists which show the required α-ethoxy-β-phenyl-propionic acid moiety.

The 4,4-dimethyl-1,2,3,4-tetrahydroquinoline was prepared according to the synthetic sequence outlined in Scheme 2. Aniline was treated with 3,3-dimethyl-acryloyl chloride to give amide **1** which was cyclized under the Friedel–Crafts conditions. The best conditions for this key step were identified by using $AlCl_3$ (4 equiv)



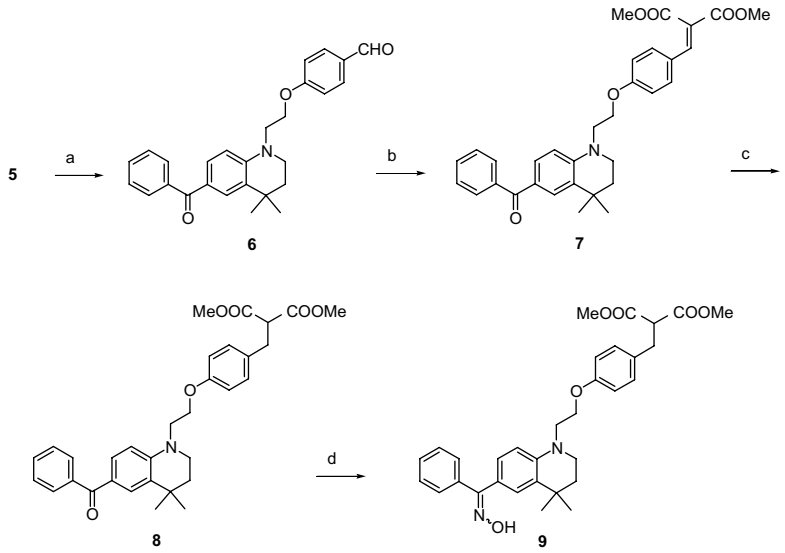
Scheme 2. Reagents and conditions: (a) 3,3-dimethyl-acryloyl chloride, pyridine, 97%; (b) $AlCl_3$, CH_2Cl_2, 90%; (c) BH_3·THF, toluene, 100%; (d) i) bromoacetyl bromide, Et_3N, THF; ii) BH_3·THF, toluene, 75%; (e) benzoyl chloride, $TiCl_4$, 1,2-dichloroethane, 71%.

and the reaction performed in dry dichloromethane. The reduction of the lactam **2** using BH_3·THF complex finally afforded the desired moiety **3** which is globally obtained in 87% yield.

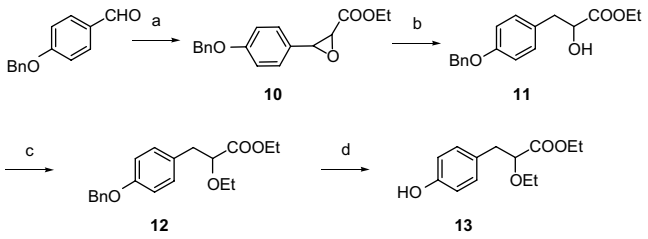
All conditions tested for classical *N*-alkylation of secondary amine **3** were unsuccessful and led us to carry out the introduction of bromoethyl chain in two steps. Treatment of **3** with bromoacetyl bromide provided an intermediate bromo-amide which was directly reduced with BH_3·THF complex and yielded **4** in 75%. Benzoylation of **4** using classical Friedel–Crafts conditions finally afforded **5** as a central building block. Preparation of the lead structures **8**–**9** consisted in the functionalization of this key intermediate as described in Scheme 3. The first step was the alkylation of 4-hydroxy-benzaldehyde in the presence of potassium carbonate. The Knoevenagel condensation of dimethyl malonate on the resulting aldehyde **6** followed by the reduction of double bound yielded the first desired compound **8**. Treatment with hydroxylamine hydrochloride in pyridine finally gave the oxime analog **9** in mixture 50/50 *Z*/*E* isomers.

The synthesis of the α-ethoxy-β-phenyl-propionic acid derivatives was based on the same general strategy and required the preparation of the corresponding phenol **13**.

Scheme 4 describes the pathway followed for the racemic preparation of this key synthon. This synthesis was based on the regioselective reduction of the epoxide **10** obtained after treatment of commercially available 4-benzyloxy-benzaldehyde under the Darzens reaction conditions. According to the procedure described by Hutchins et al.,[11] the reduction of the epoxide **10** was performed by $NaBH_3CN$ in the presence of a catalytic amount of BF_3:Et_2O in THF. In this condition, the α-hydroxy-ester **11** was synthesized in 67% yield. The ether formation of the secondary alcohol **11** with ethyl iodide was more challenging because of favored formation of the elimination by-product. Therefore, a study conduced on the nature of base, solvent and on the temperature of the formation of intermediary ethanolate was carried out. The best conditions were identified by using sodium hydride in DMF at −50 °C. In this condition, the prod-



Scheme 3. Reagents and conditions: (a) 4-hydroxy-benzaldehyde, K_2CO_3, DMF, 65%; (b) dimethyl malonate, piperidine, AcOH, toluene, 66%; (c) H_2 (2 bars), Pd/C, 1,4-dioxane/MeOH, 67%; (d) HO–NH_2·HCl, pyridine, 73%.



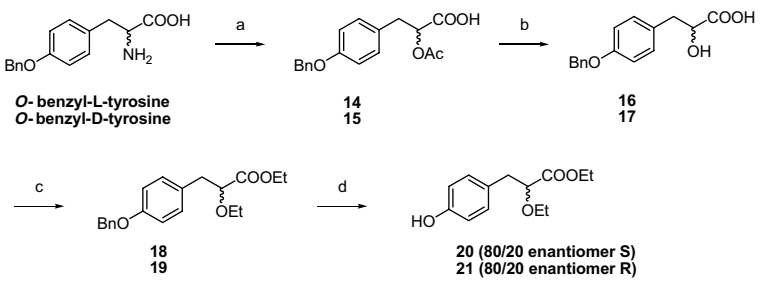
Scheme 4. Reagents and conditions: (a) ethyl chloroacetate, EtONa, EtOH, 93%; (b) $NaBH_3CN$, $BF_3{\cdot}Et_2O$, pH < 7, THF, 67%; (c) NaH, EtI, DMF, −50 °C to rt, 82%; (d) H_2, Pd/C, EtOH, 100%.

uct **12** was obtained in 82% yield, that is, to say 18% of residual by-product. Finally, hydrogenation of the benzyl protecting group yielded quantitatively the desired racemic phenol **13**.

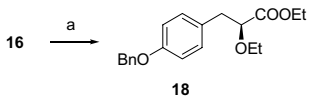
The challenge to carry out the preparation of **13** enantiomers lie in effecting complete control of inversion or retention of the stereogenic center under conditions that do not induce any epimerization. According to the well-known procedure of conversion of α-aminoacids into the corresponding α-hydroxy-acids,[12] we based our first enantioselective strategy on the conversion of the commercially available *O*-benzyl-tyrosines. As described in Scheme 5, treatment with isoamylnitrite in a mixture of acetic acid and chloroform provided the corresponding acetates **14** and **15** in good yield. Saponification using an aqueous solution of lithium hydroxyde generated quantitatively α-hydroxy-acids **16** and **17**. The previously established conditions of etherification were then applied to form the ester–ether **18** and **19**. Both of them were finally hydrogenated in order to provide both desired enantiomers **20** and **21**. The enantiomeric purity of **20** and **21** was evaluated by capillary electrophoresis. Unfortunately, both enantiomers showed only 60% enantiomeric excess.

In order to avoid epimerization potentially due to the hard basic conditions of etherification,[13] we then revised this step in neutral medium. As described in Scheme 6, classical esterification of **16** generated the hydroxy ester which was then alkylated using the procedure of halogenophile-assisted glycosilation.[14] Also treatment with ethyliodide and silver oxide (I) at reflux of Et_2O provides the supposed **18** in excellent yield.

Enantiomeric excess was then determinated by capillary electrophoresis[15] and was estimated at 60% again. To confirm the retention of stereogenic center under the conditions of conversion of *O*-benzyl-tyrosines, we fur-



Scheme 5. Reagents and conditions: (a) *i*-$C_5H_{11}ONO$, AcOH/$CHCl_3$, 85–87%; (b) LiOH 0.1 N, THF/H_2O, 100%; (c) NaH, EtI, DMF, −50 °C to rt, 57–60%; (d) H_2, Pd/C, EtOH, 100%.

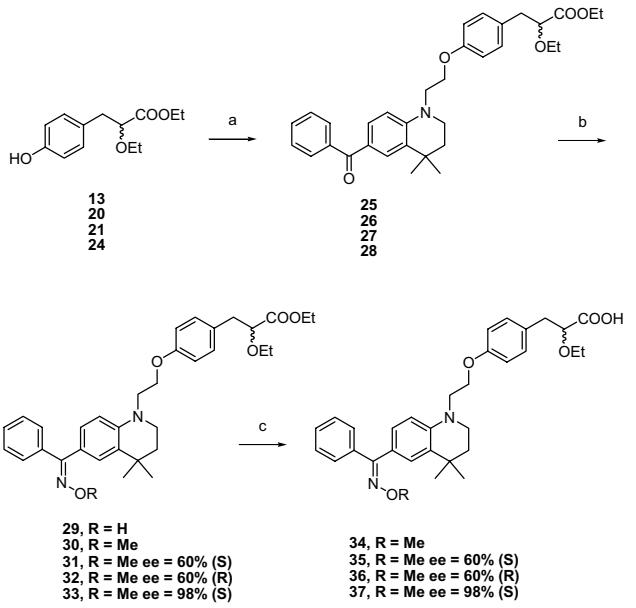


Scheme 6. Reagents and conditions: (a) i—$SOCl_2$, EtOH, 84%; ii—EtI, Ag_2O, Et_2O, 79%.

ther examinated the enantiomeric purity of **16** and **17**. We were disappointed to obtain the same result of 60% ee. In conclusion, conversion of *O*-benzyl-tyrosines into corresponding α-hydroxy-acids led to an 80/20 mixture of enantiomers but the alkylation under both basic and neutral conditions retained the configuration. In the sight of the disappointing results and in order to obtain enantiomerically pure **16** (*S*), we decided to follow the literature by reducing the 4-hydroxyphenyl pyruvic acid with (+)-DIP-Cl to afford **22** in 98% ee and 92% chemical yield. Selective protection of the phenol could be accomplished by reacting **22** with benzyl chloride in ethanol in the presence of K_2CO_3 during 18 h. The resulting compound was immediately treated with aqueous NaOH to effect hydrolysis of benzyl ester. Acidification of the reaction mixture induced precipitation of the product which was isolated by filtration. This latter was recrystallized in isopropanol to give the desired product **23** in 98% ee and 76% overall yield. The final ester–ether was then obtained in 3 steps under previous conditions in 98% ee and 60% chemical yield (Scheme 7).[13]

Lead structures were finally synthesized according to the sequence outlined in Scheme 8. Phenols **13**, **20**, **21** and **24** coupled the key intermediates **5** using potassium carbonate in DMF. Treatment of the resulting benzophenones **25**, **26**, **27** and **28** with the hydroxylamine hydrochloride or methoxylamine hydrochloride generated the corresponding oximes in good yield. The saponification of the ester by an aqueous solution of lithium hydroxide in THF finally afforded the desired acids **34**, **35**, **36** and **37**.[16]

Compounds were characterized by determining the binding affinity to human PPARγ using a competitive binding assay with [^{3}H]Rosiglitazone, appropriate radioligand for PPARγ. The binding profiles of compounds were compared to the profiles of two references, Rosiglitazone and Tesaglitazar. Functional activity was measured in a transient transfection assay using

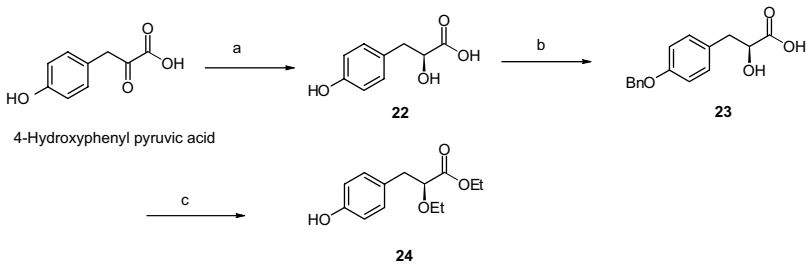


Scheme 8. Reagents and conditions: (a) **5**, K_2CO_3, DMF, 44–59%; (b) RO–NH_2·HCl, pyridine, 69–83%; (c) LiOH 0.1 N, THF/H_2O, 60–64%.

pGAL4hPPARα and pGAL4hPPARγ. The results are given in Table 1.

Compounds **8** and **9** (dimethyl malonate) were poorly PPARα agonists. The oxime analog **9** shows a partial PPARγ activation (74% against 140% **8**). No binding was observed on PPARγ LBD radiolabeled with Rosiglitazone.

An ether–ester substituent replacing the diester function leads to the very partial PPARα agonists without lost PPARγ agonist property. No difference on efficacy was observed between the oxime and oxime–ether compounds (**29** and **30**). Paradoxically, the compound **31** did not show amelioration of their efficacy or their potency on human PPARγ gene reporter. Moreover, no change on PPARα and PPARγ activation was shown with the acid-ether compound **34**. The (*S*)-**37** (ee = 98%) compound presented a 10-fold decrease on their PPARα efficacy compared to racemic compound **34**. A decrease of 10-fold on PPARγ activation was obtained with enantiomer **36** without any significant difference for PPARα activation.



Scheme 7. Reagents and conditions: (a) (+)-DIP-Cl, THF/Et_3N, 92%; (b) i) BnCl, K_2CO_3, EtOH; ii) NaOH, H_2O; iii) *i*-PrOH, 70% within 3 steps; (c) i) $SOCl_2$, EtOH; ii) EtI, Ag_2O, Et_2O; iii) H_2, Pd/C, EtOH, 60% within 3 steps.

Table 1. Activity of compounds in cell-based transactivation assay against human PPAR

Compound	Binding PPARγ K_i (nM)	Transactivation EC_{50}[a] (nM) (% activity)[b]	
		hPPARα	hPPARγ
Rosiglitazone	8	10,000 (15)	4 (100)
Tesaglitazar	18	414 (89)	37 (76)
8	10,000	Na	152 (140)
9	10,000	Na	195 (74)
29	618	189 (33)	48 (100)
30	10,000	30 (45)	19 (113)
31	10,000	29 (66)	14 (185)
34	48	12 (53)	11 (167)
35	>10,000	29 (66)	14 (185)
36	89	194 (52)	65 (107)
(*S*)-**37**	18	114 (63)	7.85 (95)

[a] Values are means of three experiments (na, not active).

[b] Refer to maximal activity obtained with each compound expressed in percentage of maximal activity of Rosiglitazone at 10^{-6} M for PPARγ and of WY 14,643[17] at 10^{-5} M for PPARα.

It is noteworthy that no correlation between EC_{50} values obtained from transactivation PPARγ tests and K_i values from binding tests, could suggest that these derivatives have a binding site different from the Rosiglitazone binding site.

The partial PPARγ gene reporter response of compound **9** (74%) suggests a different capacity for this derivative to induce recruitment on the co-activator/co-repressor on PPARγ, as compared to those observed with Rosiglitazone. Complementary experiments, especially in vivo assay, are ongoing to study with more precision, the impact of these new partial PPARγ agonist compounds in animal model of type-2 diabetes and metabolic syndrome, mainly in terms of anti-diabetic properties and potential side effects like edema formation and weight gain.

The 4,4-dimethyl-1,2,3,4-tetrahydroquinoline-based compounds are effective PPARγ selective agonists and dual-acting agonists of PPARα and PPARγ. Their pharmacological profiles translate very well into activity in human cells in vitro in terms of transactivation.

Finally, structural variations of the lead derivatives **9** (as PPARγ partial agonist) and **37** (as PPARα/γ dual agonist) are under investigations. That way we wish to modulate activity especially toward more potent PPARγ partial agonist with potentially PPARα residual agonist.

Acknowledgments

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15. Fused-silica capillary column, 70 cm × 50 μm, applied voltage, −15 kV, buffer 100 mM of phosphoric acid (EtOH) 3 N, pH 3.0, 5 mM. β-Cyclodextrin SBE and 15 mM. β-Cyclodextrin trimethyl, detection at 214 nm, temperature 25 °C, concentration 200 ppm.

16. Compound **8**: Red oil; MS (IS) *m*/*z* = 530 (M+H); 552 (M+Na); Anal. Calcd for $C_{32}H_{35}NO_6$: C, 72.57; H, 6.66; N, 2.64. Found: C, 72.18; H, 6.71; N, 2.55.
Compound **9**: Yellow foam; MS (IS) *m*/*z* = 545 (M+H); 527 (M−H_2O); Anal. Calcd for $C_{32}H_{36}N_2O_6$: C, 70.57; H, 6.66; N, 5.14. Found: C, 70.44; H, 6.58; N, 4.99.
Compound **29**: Yellow foam; MS (IS) *m*/*z* = 545 (M+H); 567 (M+Na); Anal. Calcd for $C_{33}H_{40}N_2O_5$: C, 72.77; H, 7.40; N, 5.14. Found: C, 72.85; H, 7.44; N, 5.30.
Compound **30**: Yellow oil; MS (IS) *m*/*z* = 559 (M+H); 581 (M+Na); Anal. Calcd for $C_{34}H_{42}N_2O_5$: C, 73.09; H, 7.58; N, 5.01. Found: C, 72.87; H, 7.42; N, 4.95.
Compound **31**: Yellow oil; MS (IS) *m*/*z* = 559 (M+H); 581 (M+Na); Anal. Calcd for $C_{34}H_{42}N_2O_5$: C, 73.09; H, 7.58; N, 5.01. Found: C, 72.92; H, 7.55; N, 4.90.
Compound **34**: White oil; MS (IS) *m*/*z* = 531 (M+H); 553 (M+Na); Anal. Calcd for $C_{32}H_{38}N_2O_5$: C, 72.43; H, 7.22; N, 5.28. Found: C, 72.62; H, 7.31; N, 5.22.
Compound **35**: White oil; MS (IS) *m*/*z* = 531 (M+H); 553 (M+Na); Anal. Calcd for $C_{32}H_{38}N_2O_5$: C, 72.43; H, 7.22; N, 5.28. Found: C, 72.49; H, 7.15; N, 5.60.
Compound **36**: White oil; MS (IS) *m*/*z* = 531 (M+H); 553 (M+Na); Anal. Calcd for $C_{32}H_{38}N_2O_5$: C, 72.43; H, 7.22; N, 5.28. Found: C, 72.81; H, 7.61; N, 5.55.
Compound **37**: White oil; MS (IS) *m*/*z* = 531 (M+H); 553 (M+Na); Anal. Calcd for $C_{32}H_{38}N_2O_5$: C, 72.43; H, 7.22; N, 5.28. Found: C, 72.38; H, 7.39; N, 5.54.
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