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PIPERIDINE-RENIN INHIBITORS COMPOUNDS WITH IMPROVED PHYSICOCHEMICAL PROPERTIES

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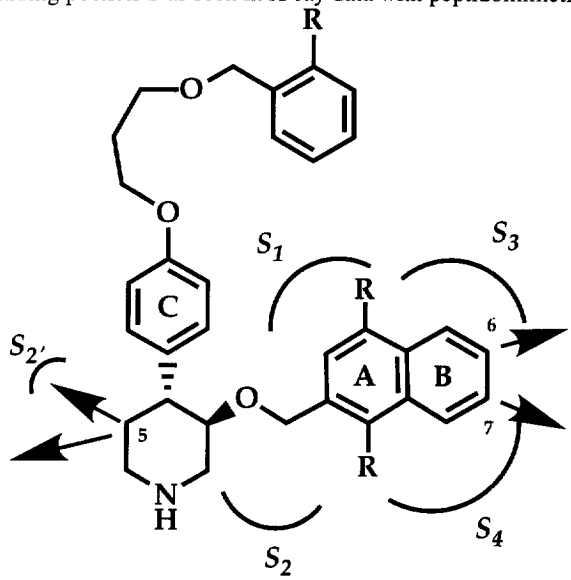
Abstract: Piperidine renin inhibitors with heterocyclic core modifications or hydrophilic attachments show improved physical properties (lower lipophilicity, improved solubility). Tetrahydroquinoline derivative ***rac*-30** with a molecular weight of 517 and a log $D_{(pH\ 7.4)}$ of 1.9 displays potent and long lasting blood pressure lowering effects after oral administration to sodium depleted conscious marmosets.

The highly potent piperidine renin inhibitors **1**[1] (Figure 1) are compounds of high lipophilicity and insufficient water solubility. Modifications of the core structure as well as hydrophilic extensions attached at suitable positions might transform poorly soluble compounds into analogues with more favorable physical properties. Transformation of the first aromatic ring (A) of the naphthyl moiety into an electron poor analogue has proven unfavorable (data not shown). This finding could be rationalized by the X-ray structural data

Figure 1. Design of potential hydrophilic attachments to piperidine renin inhibitors.
(Positions of binding pockets S as seen in X-ray data with peptidomimetic inhibitors are indicated).



1a, R= H; 1b, R= OMe
(active antipode shown as determined in Ref. 1)

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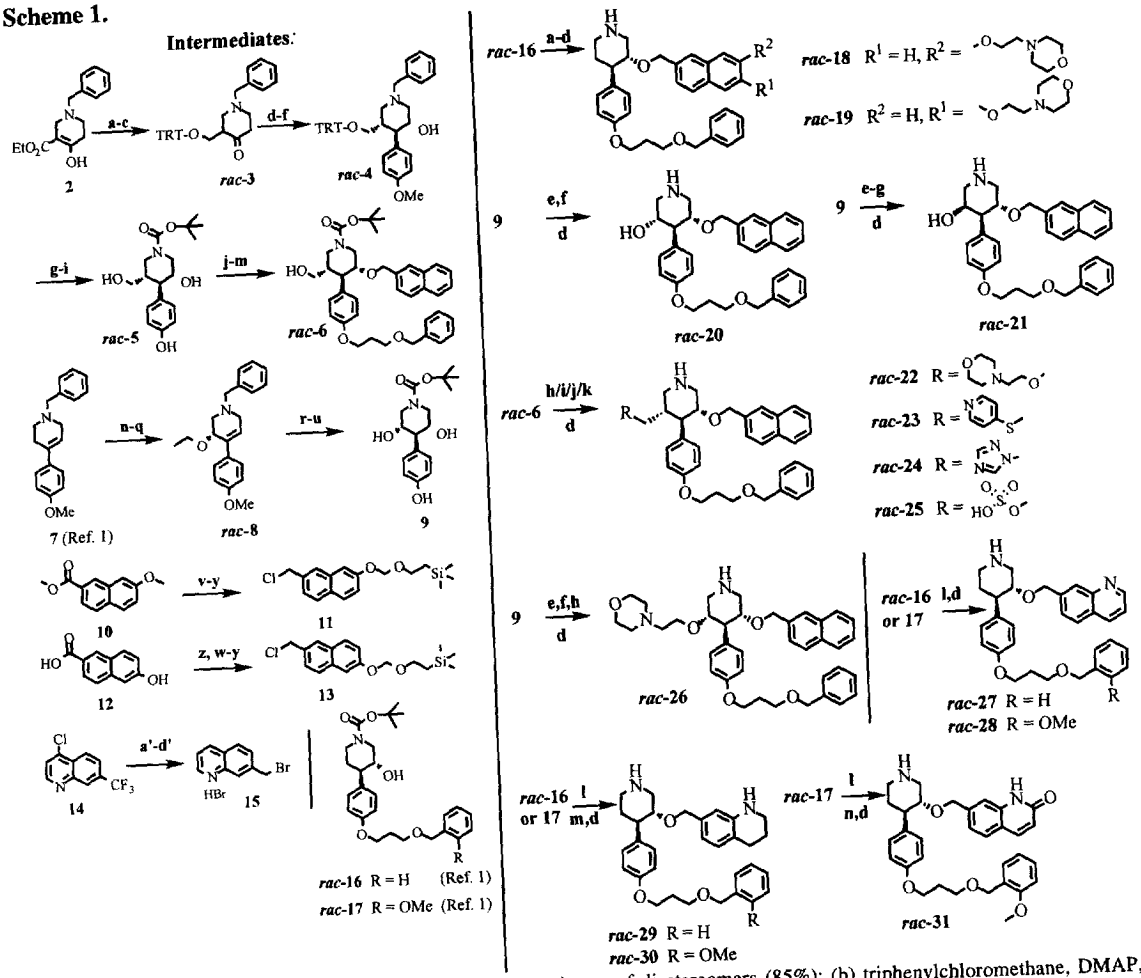
PII: S0960-894X(99)00196-1

Scheme 1.

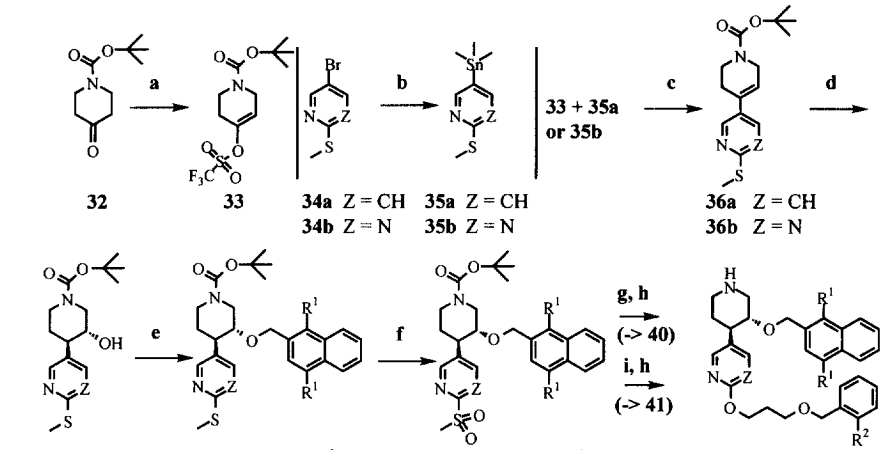


Intermediates: *Reagents :* (a) $NaBH_4$, MeOH, r.t., 18 h, mixture of diastereomers (85%); (b) triphenylchloromethane, DMAP, pyridine, r.t., 48 h, mixture of diastereomers (96%); (c) $(COCl)_2$, DMSO, CH_2Cl_2 , Et_3N, -70°C (93%); (d) 4-iodoanisole, *n*-BuLi, TBME, -70°C-r.t. (87%); (e) $POCl_3$, pyridine, 60°C, 18 h (72 %); (f) i. BH_3xTHF, THF, r.t., 18 h, ii. sodium percarbonate, H_2O, 60°C, 3 h (71%); (g) BBr_3 , CH_2Cl_2 , 0°C-r.t., 18 h (98%); (h) H_2 , Pd/C (10%), MeOH, r.t., 18 h (95%); (i) Boc_2O, DMF, Et_3N, 0°C-r.t., 48 h (78%); (j) benzyl-3-bromopropyl ether, K_2CO_3, butan-2-one, 100°C, 48 h (91%); (k) triphenylchloromethane, DMAP, pyridine, r.t., 18 h (83%); (l) 2-bromomethyl-naphthalene, NaH, DMF, 0°C-r.t., 4 h (81%); (m) $(CF_3CO)_2O$, CF_3COOH, CH_2Cl_2, 0°C. 30 sec, then Et_3N, MeOH, 0 °C (97%) (compare Ref. 2); (n) i. HBr, aq. 48%, toluene, r.t., ii. NaBr, Br_2, dioxane/H_2O (compare Ref. 3); (o) NaOH, 0°C-r.t., dioxane/H_2O; (p) BuLi, THF, reflux (compare Ref. 4); (q) NaH, EtI, THF, r.t/35°C (*n*-q, 42%); (r) i. $NaBH_4$, BF_3xOEt_2, DME, 15°C, ii. KOH aq., 15°C, iii. H_2O_2 aq. (30 wt-%), 70°C (65%); (s) BBr_3, CH_2Cl_2, 40°C (91 %); (t) H_2-Pd/C, MeOH, r.t. (97%); (u) Boc_2O, $NaHCO_3$, dioxane/H_2O, r.t. (91%); (v) i. BBr_3, $MeCl_2$, 0°C-r.t., 5 h, ii. MeOH, r.t. (90%); (w) $ClCH_2OCH_2CH_2SiMe_3$, $NEt(iPr)_2$, CH_2Cl_2, 0°C-r.t., 6 h (quant.); (x) $LiAlH_4$, ether, 0°C-r.t. (quant., 83%); (y) PPh_3, CCl_4, MeCN, 0°C-r.t., 1 h (72-73%); (z) MeOH, HCl, reflux, 3 h (87%); (a') H_2, 5% Pd/C, MeOH, r.t. (82%); (b') 30% oleum, 150°C, then MeOH, reflux (98%); (c') sodium dihydrido-bis-(2-methoxyethoxy)aluminate, THF, -20°C (85%); (d') 30% HBr/AcOH, 70°C (98%).

Compounds 18-31: *Reagents:* (a) **11** or **13**, NaH, DMF, r.t. (85-86%); (b) 0.14N HCl (gas)/MeOH, 5°C-r.t., 1.5 h (77-85%); (c) 4-(2-chloro-ethyl)-morpholine hydrochloride, K_2CO_3, DMF, 60°C, 18 h (quant.); (d) 2N HCl (gas)/MeOH, CH_2Cl_2, 2-3 h, 40°C (40-80%); (e) benzyl-3-bromopropyl ether, K_2CO_3, 2-butanone, reflux, r.t. (89%); (f) 2-naphthyl-methyl bromide, NaH, DMF, r.t. (33%); (g) i. Ph_3P, HCOOH, diethylazodicarboxylate, THF, r.t, ii. KOH (5 eq.), MeOH, r.t. (86%); (h) 4-(2-chloro-ethyl)-morpholine hydrochloride, NaH (excess), DMF, 50°C, 18 h (33-52%); (i) 4,4'-dithiopyridine, tributyl phosphine, pyridine, reflux, 72 h (82%); (j) i. mesyl chloride, Et_3N, THF, 0°C-r.t., 2 h (quant.), ii. 1,2,4-triazole, NaH, DMF, 0°C-r.t., 2 h; then mesylate of ***rac-6***, DMF, 100°C, 18 h (77%); (k) SO_3/Et_3N, pyridine, r.t., 36 h (90%); (l) **15**, NaH, DMF, r.t. (86-94%); (m) $NiCl_2$, $NaBH_4$, MeOH, 0°C-r.t. (60-77%); (n) i. *m*-CPBA, $CHCl_3$, r.t. (quant.), ii. CH_2Cl_2, K_2CO_3, H_2O, TsCl (80%).

obtained with **1a**[1] showing a strong positive edge to face interaction of Phe_{117} of the active site of renin with this aromatic ring. It is, however, not possible to see strong interactions of the second aromatic ring (B) of the naphthalene unit with the enzyme, which suggests, that structural modifications might be possible. Inspection of the enzyme environment does not give arguments for or against a replacement of the 4-phenyl moiety (C) by more hydrophilic heterocyclic analogues. The 4-phenyl moiety is involved in a number of intermolecular aromatic interactions e.g. with Trp_{39}, Tyr_{75} and Phe_{112}. Thus, a prediction, which carbon atoms should be

Scheme 2.



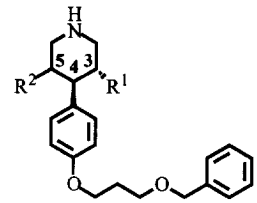
Reagents: (a) 1) LDA, THF; 2) $PhN(SO_2CF_3)_2$, -78°C to r.t. (85%) (Ref. 5); (b) **34a** (Ref. 6) or **34b** (Ref. 7), hexamethyldistannane, $(PPh_3)_4Pd$, BHT, dioxane, reflux (77%, **35a**; 75%, **35b**); (c) $(PPh_3)_4Pd$, BHT, LiCl, DME, reflux (66%, **36a**; 74%, **36b**); (d) i. BH_3xTHF (excess), DME, r.t., ii. $Na_2CO_3x1.5H_2O_2$, H_2O, 50°C (21%, ***rac*-37a**; 25%, ***rac*-37b**); (e) 2-(bromomethyl)-naphthalene or 2-(chloromethyl)-1,4-dimethoxy-naphthalene (Ref. 1), NaH, DMF, r.t. (78-85%); (f) *m*-CPBA, CH_2Cl_2, r.t. (71-80%); (g) ***rac*-39a** or ***rac*-39b**, ROH, KOtBu, THF, r.t. (48-51%), (ROH: 3-benzyloxy-propanol, 3-(2-methoxybenzyloxy)-propanol (prepared from 2-methoxy-benzylchloride and propyleneglycol with NaH, THF at r.t. (88%)); (h) $ZnBr_2$, CH_2Cl_2, r.t. (37-95%) (compare Ref. 8); (i) ***rac*-39c** or ***rac*-39d**, ROH, NaH, DMF, r.t. (52-62%), (ROH: 3-benzyloxy-propanol, 3-(2-methoxybenzyloxy)-propanol).

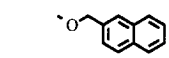
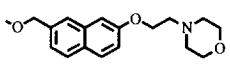
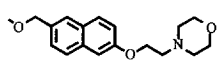
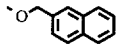
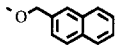
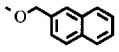
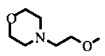
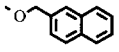
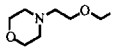
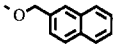
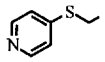
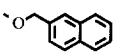
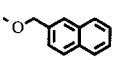
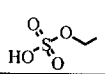
replaced by heteroatoms, was not possible. The selection of positions for the introduction of hydrophilic extensions, however, is rather straightforward. Position 5 of the piperidine ring as well as positions 6 and 7 in the naphthalene unit have exit vectors pointing towards bulk water (see Figure 1). An equatorial exit vector at position 5 (3,4-trans-, 4,5-trans-piperidine) is preferred. Axial substituents at position 5 (3,4-trans-, 4,5-cis-piperidine) point towards the flap region. Larger equatorial substituents at position 5 of the piperidine ring might even reach the former S_2' pocket. Due to the flap movement induced by the piperidine inhibitors, the 4-phenyl ring separates the S_1 from the S_2' pocket, a task formerly performed by the side chain of Tyr_{75}.

All compounds have been synthesized in racemic form according to Schemes 1 and 2.

Compounds ***rac*-18** and ***rac*-19** bearing morpholino-ethoxy extensions at the 6 and 7 positions of the naphthyl moiety showed only a minor reduction of potency in comparison to the reference compound ***rac*-1** (IC_{50} values against recombinant human renin, Table 1). The all equatorial 5-hydroxy compound ***rac*-20**

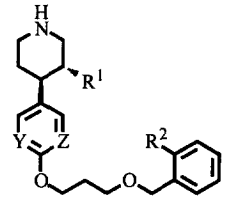
Table 1. **IC_{50} values (against purified recombinant human renin (Note 9) and human plasma renin[10]), clog P[11] and log Kw (log $D_{(HPLC, pH\ 7.4)}$)[12] values of piperdine renin inhibitors bearing hydrophilic extensions.**

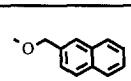
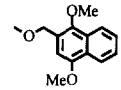
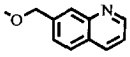
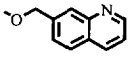
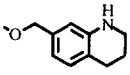
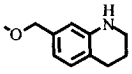
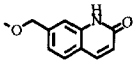
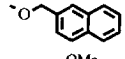
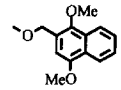
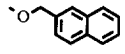
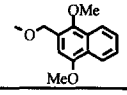


Comp.	R^1	R^2	Stereo-chemistry C(4)-C(5)	IC_{50} (nM) (rec. h. renin)	IC_{50} (nM) (human plasma renin)	Ratio IC_{50} (plasma) / IC_{50} (rec. h. ren.)	clogP (Ref. 11)	logKw ($logD_{HPLC}$) (Note 12)
rac-**1a** (Ref. 1)		H	- -	5.0	$1.3x10^3$	$2.6x10^2$	6.2	n.d.
rac-**18**		H	- -	12	$1.3x10^2$	11	6.2	5.6
rac-**19**		H	- -	22	$1.4x10^3$	64	6.2	n.d.
rac-**20**		HO	*trans*	6.4	$1.4x10^3$	$2.2x10^2$	5.0	4.9
rac-**21**		HO	*cis*	9.0	$1.0x10^4$	$1.1x10^3$	5.0	n.d.
rac-**26**			*trans*	1.8	$3.8x10^2$	$2.1x10^2$	6.0	n.d.
rac-**22**			*trans*	3.3	$1.6x10^2$	48	5.7	n.d.
rac-**23**			*trans*	0.4	$4.9x10^2$	$1.2x10^3$	7.2	5.8
rac-**24**			*trans*	0.92	$1.9x10^2$	$2.1x10^2$	4.9	n.d.
rac-**25**			*trans*	2.3	$1.9x10^3$	$8.4x10^2$	n.d.	n.d.

displayed a potency comparable to ***rac*-1a**, whereas its epimer ***rac*-21** was found to be less potent by only a factor of 2. This result excludes significant unfavorable interactions of the inhibitor with the flap region. Compounds ***rac*-22** and ***rac*-26** with morpholino-ethoxy extensions as equatorial substituents at position 5 of the piperidine ring displayed an increase in potency by a factor of two and three, respectively. All 4 morpholino-ethoxy compounds showed a solubility of at least 3 mg/ml in water as

Table 2. IC_{50} values (against purified recombinant human renin (Note 9) and human plasma renin[10]), clog P[11] and log Kw (log $D_{(HPLC, pH\ 7.4)}$)[12] values of piperdine renin inhibitors with hydrophilic core modifications.



Comp.	Y	Z	R^1	R^2	IC_{50} (nM) (rec. h. renin)	IC_{50} (nM) (human plasma renin)	ratio IC_{50} (plasma) / IC_{50} (rec. h. ren.)	clogP (Ref. 11)	logKw ($logD_{HPLC}$) (Note 12)
rac-1a (Ref. 1)	CH	CH		H	5.0	$1.3x10^3$	$2.6x10^2$	6.2	n.d.
rac-1b (Ref. 1)	CH	CH		MeO	0.087	12	$1.4x10^2$	6.1	5.4
rac-27	CH	CH		H	12	$8.1x10^2$	68	4.9	n.d.
rac-28	CH	CH		MeO	4.0	$1.6x10^2$	40	4.8	n.d.
rac-29	CH	CH		H	5.1	$3.3x10^2$	65	5.1	n.d.
rac-30	CH	CH		MeO	0.67	37	55	5.0	3.8
rac-31	CH	CH		MeO	8.0	$1.1x10^2$	14	3.6	3.9
rac-40a	N	CH		H	$5.9x10^2$	$7.1x10^3$	12	5.2	5.1
rac-40b	N	CH		MeO	0.50	$1.1x10^2$	$2.2x10^2$	5.1	4.7
rac-41a	N	N		H	$8.2x10^2$	$8.2x10^3$	10	4.3	4.4
rac-41b	N	N		MeO	10	$1.6x10^2$	16	4.3	4.1

dihydrochlorides, but the calculated lipophilicity values of the neutral bases remained comparable to that of ***rac*-1a**. The potency against human plasma renin, a parameter which takes into account plasma protein binding and thus represents a better estimation of activity in vivo, increased to the 100 nM range. The only exception being ***rac*-19**. Compounds ***rac*-23** and ***rac*-24** were designed to interact with the S_2' pocket, both show subnanomolar in vitro potency; but so far no X-ray data could be obtained to verify their binding mode. Heterocyclic modifications of the 4-phenyl moiety were accompanied with substantial potency reductions in all cases (Table 2). The more hydrophilic pyrimidine derivatives ***rac*-41a** and ***rac*-41b** showed the most substantial potency reductions in comparison to reference compounds ***rac*-1a** and ***rac*-1b**, but as expected a rather small ratio IC_{50} (plasma) / IC_{50} (rec. h. ren.). Within the series of hydrophilic modifications in the second ring of the

naphthyl unit, the quinolone ***rac*-31**, the compound with the lowest clog P, showed a potency reduction of about a factor of 100 in comparison to ***rac*-1b**. The tetrahydroquinoline compound ***rac*-29**, however, was equipotent to ***rac*-1a** and its o-methoxy analogue ***rac*-30** was found to be 10 times less potent than ***rac*-1b**. It showed an IC_{50} value of 37 nM against human plasma renin. Its physical properties: aqueous solubility as dihydrochloride of more than 3 mg/ml, distribution coefficients log Kw (log $D_{(HPLC, pH\ 7.4)}$)[12] = 3.8 and log $D_{(pH\ 7.4)}$[13] = 1.9 together with a molecular weight of 517 make it a truly interesting candidate for further evaluation.

Compound ***rac*-30** was tested for oral activity in conscious, sodium-depleted chronically instrumented freely moving marmosets. It produced a pronounced and long-lasting reduction in MAP in a dose dependent manner when given as a single dose at 1 and 3 mg/kg p.o. The maximal fall in MAP was observed 8.5 hours after administration of the compound at the 3 mg/kg dose with a maximum decrease in MAP of -19 mm Hg and a value of -10 mm Hg after 20 hours. These data compare well with those reported for other potent orally active renin inhibitors.[14-19] The synthesis of ***(R,R)*-30**, the active antipode of ***rac*-30**, and its blood pressure effects after p.o. administration to conscious sodium depleted marmosets and squirrels monkeys will be reported in due time.

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References and Notes

1. Vieira, E.; Binggeli, A.; Breu, V.; Bur, D.; Fischli, W.; Güller, R.; Hirth, G.; Märki, H.P.; Müller, M.; Oefner, C.; Scalone, M.; Stadler, H.; Wilhelm, M.; Wostl, W. *Bioorg. & Med. Chem. Lett.* **1999**, *9*, 1397.
2. Krainer, E.; Naider, F.; Becker, J. *Tetrahedron Letters* **1993**, *34*, 1713-1716.
3. Lyle, R.E.; Krueger, W.E. *J. Org. Chem.* **1965**, *30*, 394-396.
4. Lyle, R.E.; Krueger, W.E. *J. Org. Chem.* **1967**, *32*, 2873-2876.
5. Wustrow, D.J.; Wise, L.D. *Synthesis* **1991**, , 993-995.
6. Testaferri, L.; Tiecco, M.; Tingoli, M.; Bartoli, D.; Massoli, A. *Tetrahedron* **1985**, *41*, 1373-1384.
7. McOmie, J.F.W.; White, I.M. *J. Chem. Soc.* **1953**, , 3129-3131.
8. Nigam, S.C.; Mann, A.; Taddei, M.; Wermuth, C.-G. *Synthetic Communications* **1989**, *19*, 3139-3142.
9. For assay conditions see Ref. 1. The IC_{50} values depicted are mean values of 2-5 independent determinations.
10. For assay conditions see: Fischli, W.; Clozel, J.-P.; El Amrani, K.; Wostl, W.; Neidhart, W.; Stadler, H.; Branca, Q. *Hypertension* **1991**, *18*, 22-31. The IC_{50} values depicted are mean values of 2-3 independent determinations.
11. Leo, A.J. *Chem. Rev.* **1993**, *93*, 1281-1306.
12. The log Kw values were determined by HPLC measurements (20 mM MOPS buffer pH 7.4; column: LC-ABZ 150x46 mm with LC-ABZ precolumn 20x46 mm) as described in: Van de Waterbeemd, H.; Kansy, M.; Wagner, B.; Fischer, H. Lipophilicity Measurement by Reversed-Phase High Performance Liquid Chromatography (RP-HPLC). In *Lipophilicity in Drug Research and Toxicology*; Pliska, V.; Testa, B.; van de Waterbeemd, H., Eds.; Verlag Chemie: Weinheim, **1995**; pp. 71-87.
13. The log D value of ***rac*-30** was determined in octanol/water by the standard shake flask method at pH 7.4.
14. Raddatz, P. *Exp. Opin. Ther. Patents* **1994**, *4*, 489-504.
15. Raddatz, P. *Exp. Opin. Ther. Patents* **1994**, *4*, 1347-1359.
16. Maibaum, J.; Rasetti, V.; Rüeger, H.; Cohen, N.C.; Göschke, R.; Mah, R.; Rahuel, J.; Grütter, M.; Cumin, F.; Wood, J.M. in *Medicinal Chemistry: Today and Tomorrow. Proceedings of the AFMS Int. Med. Chem. Symposium, Tokyo 1995;* Yamazaki, M. (Ed.), Blackwell Science UK, **1997**, p. 155-163.
17. Maibaum, J.; Cohen, N.C.; Rahuel, J.; Schell, Ch.; Baum, H.-P.; Rigollier, P.; Schilling, W.; Wood, J.M. *XVth EFMC International Symposium on Medicinal Chemistry; Edinburgh (UK), 6-10 September* **1998** (Poster presentation).
18. Maibaum, J.; Stutz, S.; Göschke, R.; Rigollier, P.; Yamaguchi, Y.; Schilling, W.; Wood, J.M. *XVth EFMC International Symposium on Medicinal Chemistry; Edinburgh (UK), 6-10 September* **1998** (Poster presentation).
19. Göschke, R.; Rasetti, V.; Cohen, N.C.; Rahuel, J.; Grütter, M.; Stutz, S.; Rüeger, H.; Fuhrer, W.; Wood, J.M.; Maibaum, J. *XVth EFMC International Symposium on Medicinal Chemistry; Edinburgh (UK), 6-10 September* **1998** (Poster presentation).