Support from the Forschungsinstitut für Molekulare Pharmakologie is gratefully acknowledged. M.S. was supported by the DFG Graduiertenkolleg GRK 80 "Modellstudien". The authors thank Wolfgang Bermel for helpful discussions regarding the setup of the TROSY experiments, Hartmut Oschkinat for his continuous encouragement, and Karen Zierler for carefully reading the manuscript.

[1] K. Wüthrich, *NMR of Proteins and Nucleic Acids*, Wiley, New York, **1986**.
[2] a) G. T. Montelione, G. Wagner, *J. Magn. Reson.* **1990**, *87*, 183 – 188; b) L. E. Kay, M. Ikura, R. Tschudin, A. Bax, *J. Magn. Reson.* **1990**, *89*, 496 – 514; c) G. M. Clore, A. M. Gronenborn, *Prog. Nucl. Magn. Reson. Spectrosc.* **1991**, *23*, 43 – 92; d) M. Sattler, J. Schleucher, C. Griesinger, *Prog. Nucl. Magn. Reson. Spectrosc.* **1999**, *34*, 93 – 158.
[3] L. P. McIntosh, F. W. Dahlquist, *Q. Rev. Biophys.* **1990**, *23*, 1 – 38.
[4] a) K. H. Gardner, L. E. Kay, *Biol. Magn. Reson.* **1999**, *16*, 27 – 74; b) B. T. Farmer II, R. A. Venters, *Biol. Magn. Reson.* **1999**, *16*, 75 – 120.
[5] a) K. Pervushin, R. Riek, G. Wider, K. Wüthrich, *Proc. Natl. Acad. Sci. USA* **1997**, *94*, 12366 – 12371; b) K. Pervushin, *Q. Rev. Biophys.* **2000**, *33*, 161 – 197.
[6] A. Arora, L. K. Tamm, *Curr. Opin. Struct. Biol.* **2001**, *11*, 540 – 547.
[7] a) A. Arora, F. Abildgaard, J. H. Bushweller, L. K. Tamm, *Nat. Struct. Biol.* **2001**, *8*, 334 – 338; b) C. Fernandez, K. Adeishvili, K. Wüthrich, *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 2358 – 2363; c) C. Fernandez, C. Hilty, S. Bonjour, K. Adeishvili, K. Pervushin, K. Wüthrich, *FEBS Lett.* **2001**, *504*, 173 – 178.
[8] a) J. K. Lanyi, *Biochim. Biophys. Acta.* **2000**, *1460*, 1 – 3 and references cited therein; b) U. Haupts, J. Tittor, D. Oesterhelt, *Annu. Rev. Biophys. Biomol. Struct.* **1999**, *28*, 367 – 99; c) D. Oesterhelt, *Curr. Opin. Struct. Biol.* **1998**, *8*, 489 – 500; d) D. Oesterhelt, W. Stoeckenius, *Nature (London), New Biol.* **1971**, *233*, 149 – 152.
[9] a) J. Wess, *FASEB J.* **1997**, *11*, 346 – 354; b) H. G. Dohlman, J. Thorner, M. G. Caron, R. J. Lefkowitz, *Annu. Rev. Biochem.* **1991**, *60*, 653 – 688.
[10] K. Palczewski, T. Kumasaka, T. Hori, C. A. Behnke, H. Motoshima, B. A. Fox, I. Le Trong, D. C. Teller, T. Okada, R. E. Stenkamp, M. Yamamoto, M. Miyano, *Science* **2000**, *289*, 739 – 745.
[11] H. Luecke, B. Schobert, H.-T. Richter, J.-P. Cartailler, J. K. Lanyi, *J. Mol. Biol.* **1999**, *291*, 899 – 911.
[12] a) H. Patzelt, A. S. Ulrich, H. Egbringhoff, P. Dux, J. Ashurst, B. Simon, H. Oschkinat, D. Oesterhelt, *J. Biomol. NMR* **1997**, *10*, 95 – 106; b) M. Kolbe, PhD thesis, Ludwig-Maximilians-University Munich, **2001**.
[13] M. Seigneuret, J. M. Neumann, J. L. Rigaud, *J. Biol. Chem.* **1991**, *266*, 10066 – 10069.
[14] M. Salzmann, K. Pervushin, G. Wider, H. Senn, K. Wüthrich, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 13585 – 13590.
[15] M. Salzmann, G. Wider, K. Pervushin, H. Senn, K. Wüthrich, *J. Am. Chem. Soc.* **1999**, *121*, 844 – 848.
[16] V. Sklenar, M. Piotto, R. Leppik, V. Saudek, *J. Magn. Reson. Ser. A* **1993**, *102*, 241 – 245.
[17] a) A. G. Palmer, J. Cavanagh, P. E. Wright, M. Rance, *J. Magn. Reson.* **1991**, *93*, 151 – 170; b) L. E. Kay, P. Keifer, T. Saarinen, *J. Am. Chem. Soc.* **1992**, *114*, 10663 – 10665.
[18] K. V. Pervushin, G. Wider, K. Wüthrich, *J. Biomol. NMR* **1998**, *12*, 345 – 348.
[19] M. J. Pettei, A. P. Yudd, K. Nakanishi, R. Henselman, W. Stoeckenius, *Biochemistry* **1977**, *16*, 1955 – 1959; b) G. S. Harbison, S. O. Smith, J. A. Pardoen, C. Winkel, J. Lugtenburg, J. Herzfeld, R. Mathies, R. G. Griffin, *Proc. Natl. Acad. Sci. USA* **1984**, *81*, 1706 – 1709; c) S. O. Smith, A. B. Myers, J. A. Pardoen, C. Winkel, P. P. J. Mulder, J. Lugtenburg, R. Mathies, *Proc. Natl. Acad. Sci. USA* **1984**, *81*, 2055 – 2059; d) P. Scherrer, M. K. Mathew, W. Sperling, W. Stoeckenius, *Biochemistry* **1989**, *28*, 829 – 834.
[20] a) J. P. Loria, M. Rance, A. G. Palmer III, *J. Magn. Reson.* **1999**, *141*, 180 – 184; b) P. Permi, A. Annila, *J. Biomol. NMR* **2001**, *20*, 127 – 133.
[21] S. Grzesiek, A. Bax, *J. Biomol. NMR* **1993**, *3*, 185 – 204.
[22] J. Cavanagh, W. J. Fairbrother, A. G. Palmer III, N. J. Skelton, *Protein NMR Spectroscopy*, Academic Press, San Diego **1996**.
[23] a) H. Belrhali, P. Nollert, A. Royant, C. Menzel, J. P. Rosenbusch, E. M. Landau, E. Pebay-Peyroula, *Structure Fold. Des.* **1999**, *7*, 909 – 917; b) L. O. Essen, R. Siegert, W. D. Lehmann, D. Oesterhelt, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 11673 – 11678.
[24] N. A. Farrow, R. Muhandiram, A. U. Singer, S. M. Pascal, C. M. Kay, G. Gish, S. E. Shoelson, T. Pawson, J. D. Forman-Kay, L. E. Kay, *Biochemistry* **1994**, *33*, 5984 – 6003.
[25] a) D. Fushman, R. Weisemann, H. Thüring, H. Rüterjans, *J. Biomol. NMR* **1994**, *4*, 61 – 78; b) M. R. Gryk, R. Abseher, B. Simon, M. Nilges, H. Oschkinat, *J. Mol. Biol.* **1998**, *280*, 879 – 896.
[26] S. Spera, A. Bax, *J. Am. Chem. Soc.* **1991**, *113*, 5490 – 5492.
[27] P. Luginbühl, T. Szyperski, K. Wüthrich, *J. Magn. Reson. Ser. B* **1995**, *109*, 229 – 233.
[28] G. Zhu, Y. Xia, K. H. Sze, X. Yan, *J. Biomol. NMR* **1999**, *14*, 377 – 381.
[29] A. Bax, S. Grzesiek in *NMR of Proteins* (Eds.: G. M. Clore, A. M. Gronenborn), CRC Press, Boca Raton, FL, **1993**, pp. 36.
[30] a) M. Ikura, A. Bax, G. M. Clore, A. M. Gronenborn, *J. Am. Chem. Soc.* **1990**, *112*, 9020 – 9022; b) T. Frankiel, C. Bauer, M. D. Carr, B. Birdsall, J. Feeney, *J. Magn. Reson.* **1990**, *90*, 229.

Received: March 15, 2002 [Z 380]

The First Orally Active Low Molecular Weight Agonists for the LH Receptor: Thienopyr(im)idines with Therapeutic Potential for Ovulation Induction

N. C. R. van Straten,*[a] G. G. Schoonus-Gerritsma,[a] R. G. van Someren,[a] J. Draaijer,[a] A. E. P. Adang,[a] C. M. Timmers,[b] R. G. J. M. Hanssen,[c] and C. A. A. van Boeckel[a]

KEYWORDS:

G-protein-coupled receptors · medicinal chemistry · nitrogen heterocycles · receptors · structure – activity relationships

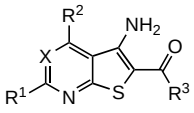
The gonadotropins, a class of glycoproteins with an average molecular weight of 30 kD, play a pivotal role in human reproduction. Follicle stimulating hormone (FSH), for example, causes ovarian follicle maturation in women and is involved in spermatogenesis in men. Luteinizing hormone (LH) is responsible for ovulation induction in women and controls testosterone production in men. Finally, human choriogonadotropin (hCG) maintains the early stages of a pregnancy.[1] All gonadotropins consist of a common α subunit and a hormone-specific

[a] *Dr. N. C. R. van Straten, G. G. Schoonus-Gerritsma, R. G. van Someren, J. Draaijer, Dr. A. E. P. Adang, Prof. Dr. C. A. A. van Boeckel*
Lead Discovery Unit
N.V. Organon
PO Box 20
5340 BH Oss (The Netherlands)
Fax: (+31) 4126-63508
E-mail: nicole.vanstraten@organon.com
[b] *Dr. C. M. Timmers*
Dept. of Medicinal Chemistry
N.V. Organon (The Netherlands)
[c] *Dr. R. G. J. M. Hanssen*
Dept. of Pharmacology
Research and Development
N.V. Organon (The Netherlands)

β subunit that are noncovalently linked. Both FSH and LH are produced in the pituitary and act on particular G-protein-coupled receptors (GPCRs) expressed in the gonads. FSH receptors (FSHR) are found on granulosa cells (♀) and Sertoli cells (♂), whereas LH receptors (LHR) are present on Theca cells (♀) and Leydig cells (♂).

Binding of LH to the LHR stimulates the Theca and Leydig cells to produce testosterone (Figure 1). Subsequently, testosterone is converted into estradiol in the female granulosa cell by the cytochrome P450 enzyme aromatase, which is generated after activation of the FSHR by FSH.[2] Gonadotropins are used clinically in infertility treatment in assisted reproductive therapy for oocyte maturation and ovulation induction. Current methods such as in vitro fertilization use either urinary or recombinant gonadotropins.[3] A major drawback in the clinical application of these hormones is the required parenteral (intramuscular or subcutaneous) administration by injection. Low molecular weight (LMW) agonists on the other hand have the potential to become orally active drugs, which display enhanced patient convenience and compliance. During the past decade, the discovery of LMW modulators for receptors that are normally triggered by high molecular weight (HMW) endogenous ligands (for example, peptides and proteins) has been a great challenge for medicinal chemists. The identification of LMW agonists has met with limited success. Recently, Merck scientists reported the first orally active LMW agonist for the human insulin receptor tyrosine kinase,[4] a molecule that mimics the mode of action of the 51 amino acid containing peptide insulin. Up to now, no orally active LMW agonists for either of the gonadotropin receptors have been described.[5, 6]

We here disclose the first class of orally active low molecular weight agonists (structures **1** and **2**, Scheme 1) for the luteinizing hormone receptor, with Org 41841 (**1v**) the most potent. Compound **1v** showed an EC_{50} value (the effective concentration that causes 50% of the maximum response) of 20 nM on a cell line that expressed the human luteinizing hormone receptor (hLHR), and in vivo efficacy in mice after oral administration.[7]



1 : X = N

1a : X = N, R^1 = SMe, R^2 = Ph, R^3 = OEt

1v : X = N, R^1 = SMe, R^2 = 3-OMe-Ph, R^3 = NH*t*Bu (Org 41841)

2 : X = CH

Scheme 1. *General structures of LH receptor agonistic thienopyri(mi)dines* ***1*** *and* ***2****.*

The high-throughput screening program run by Organon on the hLHR employs a Chinese hamster ovary (CHO) cell line that stably expresses the hLHR and the cyclic-AMP-response-element (CRE) – luciferase-reporter construct and has revealed thieno[2,3-*d*]pyrimidine **1a** (EC_{50} = 1.4 μM) as a selective hLHR agonist with no activity on hFSHR, human corticotropin-releasing factor I receptor, and human thyroid stimulating hormone receptor. Synthesis of the hit compound **1a** was accomplished with a literature procedure by using a slight modification in reaction conditions to improve yield and ease of purification. Thus, Biginelli-type condensation of *S*-methylisothiourea (**3a**, R^1 = SMe) with benzaldehyde (**4a**, R^2 = Ph) and ethyl cyanoacetate (**5**) in the presence of K_2CO_3 gave pyrimidone **6a**.[8] Subsequent treatment of **6a** with $POCl_3$ (→**7a**), base-mediated nucleophilic substitution, and concomitant cyclization[9] furnished hit compound **1a** (R^1=SMe, R^2 = Ph, R^3 = OEt) in an overall yield of 49%. This synthetic sequence, outlined in Scheme 2, includes ester hydrolysis and subsequent amide or ester formation (steps d and e, respectively) and was also applied for the preparation of analogues **1b**–**v** (Table 1).

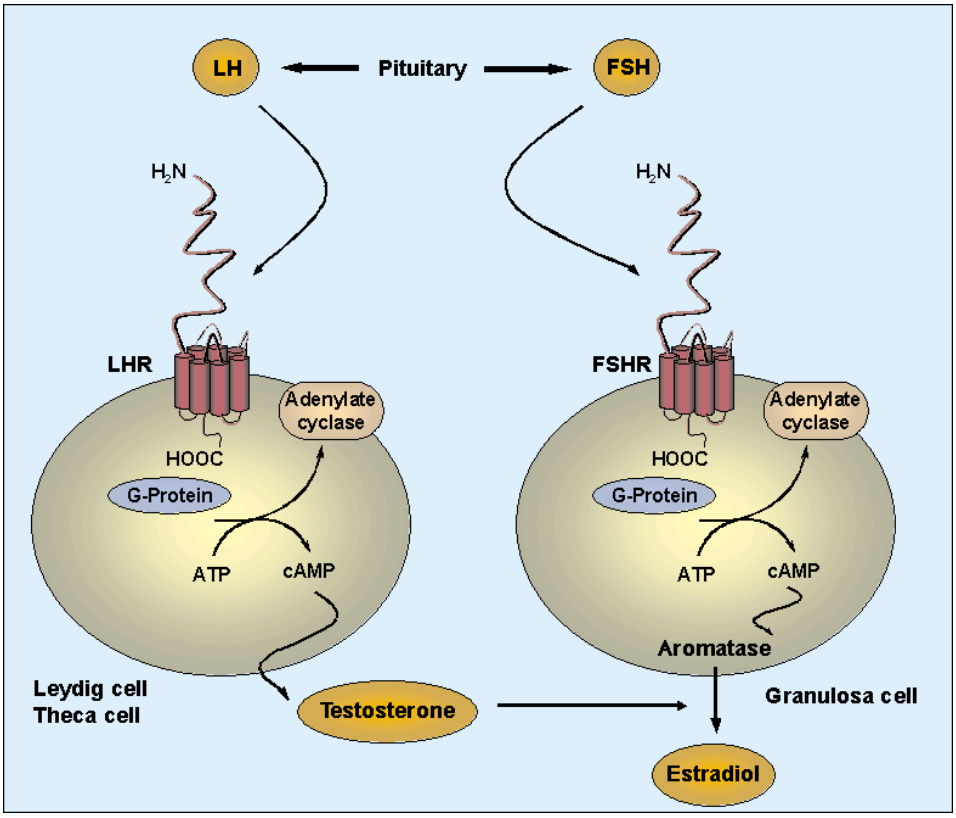
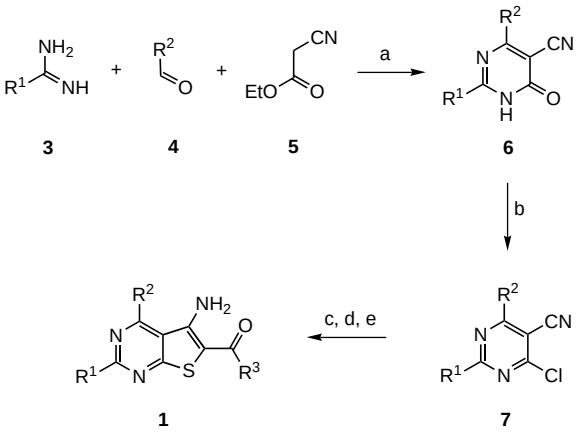


Figure 1. *Production of testosterone and estradiol by activation of the LH receptor and FSH receptor, respectively.*

1439-4227/02/03/10 $ 20.00+.50/0 ChemBioChem **2002**, No. 10



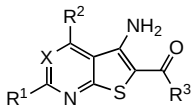
Scheme 2. *Synthesis of thieno[2,3-*d*]pyrimidines with the general structure* ***1****. a)* ***3:4:5*** *= 1:4:2, K_2CO_3 (1.1 equiv), EtOH, 60 °C, 5 h; b) $POCl_3$/dioxane (3:4 (v/v)), 80 °C, 3 h; c) ethyl 2-mercaptoacetate (1.1 equiv), NaOEt (1.6 equiv), EtOH, 50 °C, 3 h, 5 – 50 % over three steps. For R^3 = OEt: d) LiOH (20 equiv), dioxane/water (9:1 (v/v)), RT, 16 h, quant; e) amine or alcohol (1.2 equiv),* N,N*-diisopropylethylamine (5 equiv), bromotripyrrolidinophosphoniumhexafluorophosphate (1.5 equiv), CH_2Cl_2, RT, 16 h, 14 – 90 %.*

A series of thieno[2,3-*b*]pyridines with general structure **2** was synthesized by the method depicted in Scheme 3. Thus, α,β-unsaturated ketones of general structure **9**, obtained by aldol condensation of ketones **8** with aldehydes **4**, were condensed with 2-cyanothioacetamide to give thiopyridones **10**. Nucleophilic substitution followed by cyclization, saponification, and amide formation provided thieno[2,3-*b*]pyridines **2a** – **g** in satisfactory overall yields.[10]

All thienopyrimidines **1b** – **v** and thienopyridines **2a** – **g** were tested in the CHO – hLHR assay by using luciferase as a functional read out.[11] The resulting EC_{50} values are delineated in Table 1. As shown for the thienopyrimidine series, introduction of a *meta* substituent on the phenyl ring in the R^2 group is tolerated, whereas *para* substitution gives rise to loss of activity (see analogues **1b** and **1c**). Replacement of the phenyl ring in R^2 with a heteroaromatic group yields compounds with EC_{50} values in the low micromolar range (analogues **1g** – **i**). Furthermore, enlargement of the *S*-Me group to an *S*-pentyl group had a detrimental effect on potency (analogue **1d**). Use of amidines instead of isothiourea (R^1 = alkyl, aryl) in the preparation of the thienopyrimidine series provided inactive compounds in the case of R^1 = alkyl (for example, analogue **1k**), whereas potencies in the submicromolar range were observed for derivatives with R^1 = (hetero)aryl (analogues **1l** – **n**). Finally, it was established that hydrolysis of the ethyl ester leads to deterioration of activity (analogue **1o**), whereas replacement of the ester moiety with an amide group turned out to be crucial to obtain potencies in the 10 – 100-nanomolar range, with analogue **1v** the most potent LHR agonist.

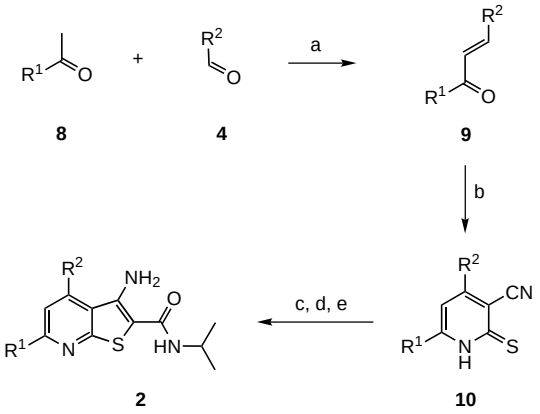
It is of interest to note that the thienopyridine series **2** follows the same structure – activity relationships (SAR) seen in the thienopyrimidine series. For example, heteroaromatic groups can be introduced with retention of activity (analogues **2c**, **e**, **f**) and amides (analogues **2f**, **g**) prove to be more potent than the corresponding esters. However, overall activities in the thieno-

Table 1. *EC_{50} values for analogues* ***1a – v*** *and* ***2a – g*** *on CHO – hLHR(luc) assay.[a]*



Analogue	X	R^1	R^2	R^3	EC_{50} [μM]
1a	N	SMe	Ph	OEt	1.4 ± nd[b]
1b	N	SMe	3-Br-Ph	OEt	1.5 ± 0.2
1c	N	SMe	4-Br-Ph	OEt	> 10
1d	N	S-*n*-pentyl	3-Br-Ph	OEt	> 10
1e	N	SEt	Ph	OEt	1.9 ± 3.4
1f	N	SCH_2Ph	Ph	OEt	3.6 ± nd
1g	N	SMe	4-pyridyl	OEt	2.7 ± 0.1
1h	N	SMe	3-furoyl	OEt	1.0 ± 0.3
1i	N	SMe	3-thienyl	OEt	0.46 ± 0.1
1j	N	SMe	3-OMe-Ph	OEt	0.12 ± 0.01
1k	N	Me	3-thienyl	OEt	> 10
1l	N	4-pyridyl	3-furoyl	OEt	1.6 ± 0.08
1m	N	2-thienyl	3-thienyl	OEt	0.15 ± 0.01
1n	N	Ph	Ph	OEt	0.16 ± 0.04
1o	N	SMe	Ph	OH	6.9 ± 1.7
1p	N	SMe	Ph	OCH_2adamant-1-yl	3.7 ± 0.9
1q	N	SMe	Ph	O-(3-OMePh)	1.2 ± 0.03
1r	N	SMe	Ph	O-cyclohexyl	0.15 ± 0.01
1s	N	SMe	Ph	N-*n*-heptyl	3.6 ± 0.4
1t	N	SMe	Ph	NCH_2thien-2-yl	0.13 ± 0.02
1u	N	2-thienyl	3-thienyl	NH*i*Pr	0.07 ± 0.01
1v (Org 41841)	N	SMe	3-OMe-Ph	NH*t*Bu	0.02 ± 0.005
2a	CH	Ph	Ph	OEt	0.98 ± 0.16
2b	CH	2-naphthyl	Ph	OEt	> 10
2c	CH	2-furoyl	Ph	OEt	2.7 ± 0.2
2d	CH	Ph	3-OMe-Ph	OEt	0.53 ± 0.03
2e	CH	2-thienyl	2-thienyl	OEt	0.58 ± 0.03
2f	CH	2-thienyl	Ph	NH*i*Pr	0.18 ± 0.01
2g	CH	Ph	3-OMe-Ph	NH*i*Pr	0.16 ± 0.02

[a] CHO-K1 cells that stably express the hLHR and the CRE – luciferase reporter construct were suspended in 96-well plates and stimulated at 37 °C with the LH agonistic compound. After 4 h, Luclite was added and luciferase activity was measured on a Topcount (Packard) apparatus.[11] [b] nd = not determined.



Scheme 3. *Synthesis of thieno[2,3-b]pyridines of general structure* ***2****. a)* ***8:4*** *= 1:1.1, NaOH (1.2 equiv), MeOH, RT, 2 h, 91 – 100 %; b) 2-cyanothioacetamide (1.1 equiv), NaOMe (0.3 equiv), MeOH, reflux, 16 h, 11 – 39 %; c) ethyl chloroacetate (1.2 equiv), NaOEt (1.6 equiv), EtOH, RT, 3 h, 41 – 99 %. For R^3 = OEt: d) LiOH (20 equiv), dioxane/water (9:1 (v/v)), RT, 16 h, quant; e) amine (1.5 equiv),* N,N*-diisopropylethylamine (5 equiv),* O*-(benzotriazol-1-yl)*-N,N,N′,N′*-tetramethyluronium tetrafluoroborate (1.1 equiv), CH_2Cl_2, RT, 16 h, 13 – 62 %.*

pyridine series are lower than in the corresponding thienopyrimidine series, which indicates the importance of the nitrogen atom at position 3 of the scaffold (analogue **1n** versus **2a**).

LHR agonist **1v** (Org 41841),[12] with the potency-enhancing 3-OMe-Ph and NH*t*Bu groups at positions 4 and 6 of the thienopyrimidine scaffold, respectively, was chosen for further pharmacological profiling, the results of which are depicted in Table 2. Thus, Org 41841 was tested in vitro on mouse Leydig cells with testosterone as the functional read out and revealed an EC_{50} value of 0.43 μM.[7, 13] In vivo efficacy was measured in an ovulation induction model by using urinary FSH-primed immature mice (50 mg kg^{-1}, p.o.), which resulted in an average of 40% ovulating animals.[7]

Table 2. *Pharmacological profiling of LHR agonist Org 41841 (analogue **1v**).*

Assay (read out)	Result
mouse Leydig cells (testosterone)[a]	EC_{50}: 0.43 μM
in vivo ovulation induction in mice (% ovulating animals)[b]	40% ovulating animals

[a] Leydig cells were isolated from male mice. Testosterone production was measured after stimulation of the LHR with an LHR agonistic compound.[7, 13] [b] Immature female mice were primed with urinary FSH, treated with Org 41841 (50 mg kg^{-1}, orally) and approximately 48 h later treated with an LHR agonistic compound. The animals were killed after LHR agonist treatment and the number of ova in the oviduct was microscopically assessed.[7]

In conclusion, we have demonstrated that heterocycles of the general structures **1** and **2** are low molecular weight agonists for the luteinizing hormone receptor and mimic the mode of action of the high molecular weight endogenous ligand LH. Initial SAR for this class of compounds could be deduced and more than 50-fold improvement in potency was achieved through substitutions. Moreover, Org 41841 is the first example known to date of a LMW agonist for a gonadotropin receptor that shows in vivo efficacy after oral administration. Since our compounds are not able to displace ^{125}I-labeled LH, we assume that the binding position is located in the evolutionarily conserved monoamine-related binding pocket of the seven-helical transmembrane domain[14] rather than in the large extracellular domain where the native HMW ligand LH interacts with the receptor. Alternative transmembrane binding sites for synthetic GPCR antagonists (so-called 'insurmountable' antagonists) are reported frequently in the literature, for example, in the case of angiotensin receptor antagonists.[15]

Org 41841 can be used as a starting point for further optimization, which could eventually lead to a selective, orally active drug for ovulation induction in assisted reproductive therapy. Further progress in this area will be reported in due course.

[1] a) J. H. Dorrington, D. T. Armstrong, *Recent Prog. Horm. Res.* **1979**, *35*, 301 – 342; b) R. M. Sharp, *Clin. Endocrinol. (Oxford, UK)* **1990**, *33*, 787 – 807.

[2] For a review, see: G. F. Erickson, D. A. Magoffin, C. A. Dyer, C. Hofeditz, *Endocr. Rev.* **1985**, *6*, 371 – 399.

[3] a) V. Insler, *Int. J. Fertility* **1988**, *33*, 85 – 97; b) D. Navot, Z. Rosenwalks, *J. In Vitro Fert. Embryo Transf.* **1988**, *5*, 3 – 13; c) J. H. Morse, J. W. Lustbader, J. W. Harrington, R. E. Canfield, *Am. J. Reprod. Immunol. Microbiol.* **1988**, *17*, 134 – 140.

[4] a) B. Zhang, G. Salituro, D. Szalkowski, L. Zhihua, Y. Zhang, I. Royo, D. Vilella, M. T. Diez, F. Pelaez, C. Ruby, R. L. Kendall, X. Mao, P. Griffin, J. Calaycay, J. R. Zierath, J. V. Heck, R. G. Smith, D. E. Moller, *Science* **1999**, *284*, 974 – 977; b) H. B. Wood, Jr., R. Black, G. Salituro, D. Szalkowski, Z. Li, Y. Zhang, D. E. Moller, B. Zhang, A. B. Jones, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1189 – 1192; c) K. Liu, D. Szalkowski, Z. Li, V. Ding, G. Kwei, S. Huskey, D. E. Moller, J. V. Heck, B. B. Zhang, A. B. Jones, *J. Med. Chem.* **2000**, *43*, 3487 – 3494.

[5] LMW nonpeptide agonists for peptide-binding GPCRs: a) E. E. Sugg, *Annu. Rep. Med. Chem.* **1997**, *32*, 277 – 283; b) S. Perlman, J. T. Schambye, R. A. Rivero, W. J. Greenlee, S. A. Hjorth, T. W. Schwartz, *J. Biol. Chem.* **1995**, *270*, 1493 – 1496; c) S. Perlman, C. M. Costa-Neto, A. A. Miyakawa, H. T. Schambye, S. A. Hjorth, A. C. M. Paiva, R. A. Rivero, W. J. Greenlee, T. W. Schwartz, *Mol. Pharmacol.* **1997**, *51*, 301 – 311; d) C. J. Aquino, D. R. Armour, J. M. Berman, L. S. Birkemo, R. A. E. Carr, D. K. Croom, M. Dezube, R. W. Dougherty, Jr., G. N. Ervin, M. K. Grizzle, J. E. Head, G. C. Hirst, M. K. James, M. F. Johnson, L. J. Miller, K. L. Queen, T. J. Rimele, D. N. Smith, E. E. Sugg, *J. Med. Chem.* **1996**, *39*, 562 – 569; e) T. M. Wilson, B. R. Henke, T. M. Momtahen, P. L. Myers, E. E. Sugg, R. J. Unwalla, D. K. Croom, R. W. Dougherty, M. K. Grizzle, M. F. Johnson, K. L. Queen, T. J. Rimele, J. D. Yingling, M. K. James, *J. Med. Chem.* **1996**, *39*, 3030 – 3034; f) R. P. Nargund, A. A. Patchett, M. A. Bach, M. G. Murphy, R. G. Smith, *J. Med. Chem.* **1998**, *41*, 3103 – 3127; g) S. P. Rohrer, E. T. Birzin, R. T. Mosley, S. C. Berk, S. M. Hutchins, D.-M. Shen, Y. Xiong, E. C. Hayes, R. P. Parmar, F. Foor, S. W. Mitra, S. J. Degrado, M. Shu, J. M. Klopp, S.-J. Cai, A. Blake, W. W. S. Chan, A. Pasternak, L. Yang, A. A. Patchett, R. G. Smith, K. T. Chapman, J. M. Schaeffer, *Science* **1998**, *282*, 737 – 740.

[6] Recently LMW agonists for the FSHR were disclosed: N. El Tayer, A. Reddy, D. Buckler, S. Magar, WO 00/08015 and US 6 235 755; H. Shroff, A. Reddy, N. El Tayer, N. Brugger, C. Jorand-Lebrun, WO 01/87287; R. Scheuerman, S. D. Yanofsky, C. P. Holmes, D. Maclean, B. Ruhland, R. W. Barrett, J. E. Wrobel, W. Kao, A. Gopalsamy, F. Sum, B. Hu, J. F. Rogers, J. W. Jetter, WO 02/09706.

[7] G. G. Gerritsma, N. C. R. van Straten, A. E. P. Adang, WO 00/61586.

[8] S. M. Hussain, A. A. El-Barbary, S. A. Mansour, *J. Heterocycl. Chem.* **1985**, *22*, 169 – 171.

[9] a) S. Kohra, Y. Tominaga, A. Hososmi, *J. Heterocycl. Chem.* **1988**, *25*, 959 – 968; b) A. A. Santilli, D. H. Kim, S. V. Wanser, *J. Heterocycl. Chem.* **1971**, *8*, 445 – 453; c) H. Cho, Y. Ohnaka, M. Hayashimatsu, M. Ueda, K. Shima, *Tetrahedron Lett.* **1986**, *27*, 6377 – 6380; d) S. Tumkevicius, *Liebigs Ann.* **1995**, *9*, 1703 – 1705.

[10] a) S. A. Abdel-Hady, M. A. Badawy, Y. A. Ibrahim, *Sulfur Lett.* **1989**, *9*, 101 – 108; b) H. Vieweg, V. Hanfeld, S. Leistner, G. Wagner, *Pharmazie* **1989**, *44*, 639 – 640; c) H. Vieweg, U. Krasselt, N. Böhm, J. Prantz, G. Wagner, *Pharmazie* **1990**, *45*, 731 – 733; d) H. Vieweg, G. Wagner, *Pharmazie* **1991**, *46*, 51 – 52.

[11] a) A. Brasier, J. Tate, J. Habener, *BioTechniques* **1989**, *7*, 1116 – 1122; b) O. Benzakour, C. Kanthou, U. Dennehy, *Biochem. J.* **1995**, *309*, 385 – 387.

[12] Characteristic analytical data for Org 41841: $R_f = 0.32$ (silica gel, 3:2, heptane/ethyl acetate (v/v); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.45$ (t, 1H, $J =$ 6.0 Hz), 7.18 – 7.07 (m, 3H), 5.95 (br s, 2H), 5.21 (br s, 1H), 3.87 (s, 3H), 2.65 (s, 3H), 1.45 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 169.8$, 167.3, 165.1, 162.5, 159.9, 144.7, 137.7, 130.1, 120.9, 117.8, 116.7, 113.8, 96.6, 55.5, 52.1, 29.1, 14.4 ppm; ESI MS: $[M + H^+]$ 403.0.

[13] B. M. J. L. Mannaerts, J. H. Kloosterboer, A. H. W. M. Schuurs, in *Neuroendocrinology of reproduction* (Eds.: R. Rolland, M. J. Heineman, N. Naaktgeboren, J. Schoemaker, H. Vemer, W. N. P. Willemsen) **1987**, 49 – 58, Elsevier Science Publishers B. V., Amsterdam.

[14] Detailed molecular modeling studies of the presented LMW LHR agonists will be published in due course by J. Kelder and M. Kouwijzer, Department of Molecular Design and Informatics, N. V. Organon.

[15] a) T. W. Schwartz, U. Gether, H. T. Schambye, S. A. Hjorth, *Curr. Pharm. Des.* **1995**, *1*, 325 – 342; b) L. Hunyady, T. Balla, K. J. Catt, *Trends Pharmacol. Sci.* **1996**, *17*, 135 – 140; c) C. E. Elling, T. W. Schwartz, *EMBO J.* **1996**, *15*, 6213 – 6219; d) B. C. VanWagenen, L. D. Artmann, L. G. Hammerland, B. C. P. Hung, J. Johnston, K. Krapcho, C. Levinthal, M. A. Logan, S. T. Moe, A. L. Mueller, R. Simin, D. L. Smith, L. Storjohann, T. M. Stormann, *Society for Neuroscience* **1998**, *24*, 576.

Received: March 19, 2002 [Z 381]

