Peptides 1990
E. Giralt and D. Andreu (Eds.)

Vasopressin analogs as strong uterotonic inhibitors

Zdenko Procházka, Miroslava Žertová, Tomislav Barth, Jiřina Slaninová, Lenka Maletínská, Ivo Bláha and Michal Lebl

Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Siences, 166 10 Prague 6, Czechoslovakia

Solid phase methodology on benzhydrylamine or *p*-methylbenzhydrylamine resin with Boc-strategy was used for the synthesis of sixteen analogs of vasopressin with D-homoarginine (D-Har) in position 8 and *p*- or *o*-alkyl and *p*-alkoxy-substituted D- or L-phenylalanine in position 2. Prepared analogs belong either to the amino series [1] (with Cys in position 1) or the deamino series [2] (with ß-mercaptopropionic acid (Mpa) in position 1).

H-X-Y-Phe-Gln-Asn-Cys-Pro-D-Har-Gly-NH_2

I-X	X = Cys	Y = See Table 1
XI-XVI	X = Mpa	Y = See Table 1

For the side-chain protection we have used: nitro (D-Har)-, 4-methylbenzyl (Cys, Mpa) and 2,4-dichlorobenzyl (Tyr). Protected amino acids were coupled by DCC and HOBt in dimethylformamide. Side-chain protecting groups were cleaved simultaneously with the peptide from the resin by liquid HF. Sulfhydryl group oxidation was performed by potassium ferricyanide and analogs were purified by HPLC. Synthesis of analogues with alkylphenylalanine in position 2 was performed using this amino acid in the racemic forms and appropriate diastereoisomers were separated by HPLC at the end of synthesis. Identification of L- or D-amino acid was performed by digestion with L-amino acid oxidase. Besides that, in all cases the value of k in HPLC on reversed phase was always lower for the L-diastereoisomer. For the formation of both diastereoisomers only 1.1 equivalent of protected racemic amino acid was used. Biological activities of the analogs are given in Table 1. [D-Har^8]vasopressin (I) and [Mpa^1,D-Har^8]vasopressin (XI) were found to have lower antidiuretic activity and were also found to be weak agonists in the uterotonic test in vitro. Substitution in position 2 led to a substantial decrease of antidiuretic activity. Pressor activity of analogs with substituted position 2 was either very low (II, V, VI) or very low inhibitory activity appeared (IX, X, XIII, XV, XVI). Most interesting were results of the uterotonic activity. Weak uterotonic agonists I and XI were transformed by modification of position 2 to rather potent uterotonic inhibitors. In the amino series *p*-ethylphenylalanine and in the deamino series *p*-methyl- and *p*-ethyl-phenylalanine of D-configuration were found superior in producing an inhibitor. This is consistent with the findings of previous structure-activity studies [3].

Table 1 *Biological activites (rat) of amino (I-X) and deamino (XI-XVI) vasopressin analogs (I.U./mg) with different modification in the position 2*

Compound	(R)	Uterotonic in vitro	Pressor	Antidiuretic
	AVP	17	412	465
	dDAVP	5	0.5	100%dDAVP
I	L-Tyr	0.9	–	1%dDAVP
II	L-Tyr(Me)	pA_2=7.70	0.04	–
III	D-Tyr(Me)	pA_2=7.90	–	–
IV	L-Tyr(Et)	pA_2=7.20	–	–
V	L-Phe(pMe)	pA_2=6.85	0.04	<0.1%dDAVP
VI	D-Phe(pMe)	pA_2=7.78	0.04	<0.1%dDAVP
VII	L-Phe(oMe)	pA_2=6.40	–	–
VIII	D-Phe(oMe)	pA_2=7.78	–	–
IX	L-Phe(pEt)	pA_2=7.40	pA_2=6.5	<0.1%dDAVP
X	D-Phe(pEt)	pA_2=8.15	pA_2=6.5	<0.1%dDAVP
XI	L-Tyr	0.8	0.28	5%dDAVP
XII	L-Tyr(Me)	pA_2=8.10	0	–
XIII	L-Phe(pMe)	pA_2=7.50	pA_2=6.2	<1%dDAVP
XIV	D-Phe(pMe)	pA_2=8.20	0	<1%dDAVP
XV	L-Phe(pEt)	pA_2=8.00	pA_2=6.2	<1%dDAVP
XVI	D-Phe(pEt)	pA_2=8.30	pA_2=6.35	<1%dDAVP

References

1. Žertová, M., Procházka, Z., Bláha, I., Barth, T., Slaninová, J., Maletínská, L. and Lebl, M., Coll. Czech. Chem. Commun., 56(1991), in press.
2. Žertova, M., Procházka, Z., Barth, T., Slaninová, J., Škopková J., Bláha, I. and Lebl, M., Coll. Czech. Chem. Commun., 56(1991), in press.
3. Jošt, K., Brtník, F. and Lebl, M. (Eds.) Handbook of Neurohypophyseal Hormone Analogs, Vol. I, II. CRC Press, Boca Raton, FL, 1987.