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European Journal of Pharmaceutical Sciences 24 (2005) 421–431
EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES
www.elsevier.com/locate/ejps

Synthesis and pharmacological profile of non-peptide vasopressin antagonists

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Received 28 July 2004; received in revised form 24 November 2004; accepted 16 December 2004

Abstract

Recently we presented a series of 6-ethyl and 6-benzylthieno[2,3-b][1,4]thiazine derivatives with relaxing effects on vascular smooth muscle and terminal ileum. In this report the synthesis of further thieno[2,3-b][1,4]thiazine derivatives and related compounds with a thieno[2,3-b][1,4]thiazepine or thieno[3,2-b][1,4]thiazine ring system is described. The pharmacological effect of the agents was tested in isolated smooth (terminal ileum, pulmonary artery, aortic rings, myometrial strips) and heart (papillary muscle, spontaneously beating right atrium) muscle preparations of the guinea pig. Contractions were measured isometrically, and smooth muscle preparations were either precontracted with high K^+ (60 or 90 mM KCl containing nutrient solution) or with agonists, while papillary muscles were electrically stimulated (1 Hz). The vasopressin antagonistic activity of the test compounds was tested in isolated papillary muscles in which the V_{1A}-receptor subtype is located. The biphasic response to vasopressin was antagonized, dependent on the chemical structure of the test compound. Thieno[3,2-b][1,4]thiazines were more potent than thieno[2,3-b][1,4]thiazine and thieno[2,3-b][1,4]thiazepine compounds. In addition, substitution of a methyl substituted terminal benzyl ring instead of a phenyl- or dichlorobenzoyl moiety attenuated the vasopressin antagonistic effect.

Keywords: Thienothiazines; Thienothiazepines; Vasopressin antagonism; Smooth muscle; Papillary muscle; Guinea pig

1. Introduction

The anterior pituitary hormone vasopressin plays an important role in various regulatory effects such as fluid and electrolyte homeostasis and blood pressure, depending on the tissue and the vasopressin receptor subtype to which it binds. So far four vasopressin receptor subtypes V_{1A}, V_{1B}, V_2 and V_3 have been identified (Birnbaumer et al., 1992; Lolait et al., 1992; Morel et al., 1992; De Keyzer et al., 1994; Sugimoto et al., 1994; Thibonnier et al., 1994). The V_{1A} subtype is located e.g. in vascular smooth muscle cells, cardiomyocytes, hepatocytes and platelets as has been shown by radioligand binding experiments (Thibonnier and Roberts, 1985; Phillips et al., 1990; Howl et al., 1991; Serradeil-Le Gal et al., 1995). Via binding to V_{1A} vasopressin causes potent vasoconstriction. The V_{1B} subtype was found in the anterior pituitary, pancreatic β-cells and adrenal medulla (Jard et al., 1986; Lee et al., 1995; Grazzini et al., 1996) and there it stimulates release of hormones and mediators. The V_2 subtype is present in the kidney (Guillon et al., 1982; Jans et al., 1989), being responsible for water retention, but there are also extrarenal V_2 or V_2-like receptors that are involved in vascular and clotting factor responses (Serradeil-Le Gal, 2001). Consequently the effects of vasopressin may also contribute to pathophysiological states like congestive heart failure, liver cirrhosis, renal disease and many others (Mah and Hofbauer, 1987; Laszlo et al., 1991; Naitoh et al., 1994; Thibonnier et al., 2002). There is ample evidence that vasopressin is a component of the neurohormonal response to congestive heart

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0928-0987/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejps.2004.12.008

failure, and that it might play a role in the development, progression and worsening of this disease. It could be shown that non-peptide vasopressin antagonists are able to improve the fluid status, osmotic balance and hemodynamics of patients with congestive heart failure (Thibonnier, 2003). This new therapeutic approach led researchers to develop non-peptide vasopressin receptor antagonists, which have the advantage of oral application.

Examples for synthetized non-peptide V_{1A} antagonists are OPC-21268 (Yamamura et al., 1991) and SR 49059 (Serradeil-Gal et al., 1993), whereas conivaptan (Tahara et al., 1997; Burnier et al., 1999; Yatsu et al., 1999; Matsuhisha et al., 2000) and YM471 (Tsukada et al., 2002) are potent non-selective V_{1A}/V_2 vasopressin receptor antagonists.

Preliminary data of aromatically substituted 6-ethyl- and 6-benzyl-2,3-dihydro-1H-thieno[2,3-b][1,4]thiazines suggest vasopressin receptor antagonistic activity of the compounds (personal communication, master theses). The 6-ethyl derivatives showed more potent relaxing effects on smooth muscle preparations than the 6-benzyl analogues. In this paper we present some 6-ethyl- and 6-benzyl-2,3-dihydro-1H-thieno[2,3-b][1,4]thiazines, showing that the ethyl group in position 6 on the thienothiazine ring is responsible for the potent relaxing effects. Furthermore these results prompted us to modify the ring system and synthesize some new 2-benzyl-4,5,6,7-tetrahydrothieno[2,3-b][1,4]thiazepines and 3,4-dihydro-2H-thieno[3,2-b][1,4] thiazines and to investigate their effects on smooth and heart muscle preparations.

2. Materials and methods

2.1. Chemistry

2.1.1. General methods

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian UnityPlus-300 (300 MHz). Chemical shifts are reported in δ values (ppm) relative to Me_4Si line as internal standard and J values are reported in Hertz. Mass spectra were obtained by a Shimadzu GC/MS QP 1000 EX or Hewlett Packard (GC: 5890; MS: 5970) spektrometer. The obtained elemental analysis results were within ±0.4% of the theoretical values for the formulas given. Column chromatography was performed using silica gel 60, 70–230 mesh ASTM (Merck). Solutions in organic solvents were dried over anhydrous sodium sulfate.

*2.1.1.1. (2-Benzyl-4,5,6,7-tetrahydrothieno[2,3-b][1,4]thiazepin-4-yl)(4-nitrophenyl)methanone (**8**).* A solution of **7** in anhydrous methylene chloride (40 ml) was treated with triethylamine (1.04 g, 10 mmol) followed by 4-nitro benzoic acid chloride (1.9 g, 10 mmol) under argon atmosphere. After stirring at room temperature for 3 h the reaction mixture was washed with water, 5% sodium hydrogen carbonate solution and brine. The dried and evaporated organic layer was recrystallized from ethanol to yield 3.3 g (80%) of an olive solid, mp 153 °C. ^{1}H NMR ($CDCl_3$): δ = 2.27–2.43 (m, 2H, $SCH_2C\mathbf{H}_2$), 2.74–2.88 (m, 2H, SCH_2), 3.75 (s, 2H, phenyl CH_2), 3.33–4.77 (m, 2H, NCH_2), 6.00 (s, 1H, thiophene H), 6.74–6.86 (m, 2H, aromat. H), 7.09–7.21 (m, 3H, aromat. H), 7.42 (B-part of an AB-system, J = 8.8 Hz, 2H), 8.02 (A-part of an AB-system, J = 8.8 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ = 32.6, 33.0, 36.1, 45.8, 123.0, 125.0, 126.8, 127.9, 128.3, 128.4, 138.8, 142.3, 143.5, 145.3, 148.0, 167.2 (1 C could not be detected). MS: *m/z* 91 (100%), 150 (27%), 260 (25%), 410 (59%). Anal. $C_{21}H_{18}N_2O_3S_2$.

*2.1.1.2. (4-Aminophenyl)(2-benzyl-4,5,6,7-tetrahydrothieno[2,3-b][1,4]thiazepin-4-yl)methanone (**9**).* A solution of **8** in a mixture of glacial acetic acid (100 ml), methanol (7 ml) and water (7 ml) was warmed up to 70 °C. Then iron powder (3.92 g, 70 mmol) was added in portions. After stirring the reaction mixture at 70 °C for 1 h it was poured onto ice water. The crude product was recrystallized from ethyl acetate to yield 3.41 g (90%) of a solid, mp 163 °C. ^{1}H NMR ($CDCl_3$): δ = 2.18–2.38 (m, 2H, $SCH_2C\mathbf{H}_2$), 2.65–2.82 (m, 2H, SCH_2), 3.81 (s, 2H, CH_2 phenyl), 3.88 (s, 2H, NH_2), 3.31–4.30 (m, 2H, NCH_2), 6.11 (s, 1H, thiophene H), 6.84–6.98 (m, 2H, aromat. H), 6.46 (B-part of an AB-system, J = 8.5 Hz, 2H), 7.15 (A-part of an AB-system, J = 8.5 Hz, 2H), 7.08–7.32 (m, 3H, aromat. H). ^{13}C NMR ($CDCl_3$): δ = 32.6, 33.2, 36.2, 45.7, 113.5, 124.3, 125.5, 125.8, 126.5, 128.2, 128.4, 130.1, 139.1, 141.9, 147.3, 148.3, 169.3. MS: *m/z* 120 (100%), 261 (14%), 380 (9%). Anal. $C_{21}H_{20}N_2OS_2$.

*2.1.1.3. 3,4-Dihydro-2H-thieno[3,2-b][1,4]thiazine (**13**).* To a solution of **12** (0.684 g, 4 mmol) in absolute tetrahydrofuran (20 ml) a 1.0 M solution of lithium aluminium hydride (4 ml, 4 mmol) in tetrahydrofuran was added dropwise under argon atmosphere. After stirring at room temperature for 4 h ethyl acetate (2–3 ml) was added carefully and the mixture stirred for further 20 min. By-products were removed by filtration of the reaction mixture through aluminium oxide 90 and eluting with tetrahydofuran. The filtrate was concentrated at room temperature and immediately transformed to **14**. MS: *m/z* 102 (52%), 115 (25%), 129 (23%), 142 (56%), 157 (100%).

*2.1.1.4. 3,4-Dihydro-2H-thieno[3,2-b][1,4]thiazin-4-yl(4-nitrophenyl)methanone (**14**).* The concentrated solution of **13** was treated with triethylamine (0.56 ml, 4 mmol) followed by 4-nitro benzoic acid chloride (0.74 g, 4 mmol), diluted in 4 ml tetrahydrofuran. After stirring at room temperature for 6 h the reaction mixture was evaporated and the residue diluted in ethyl acetate. The organic layer was washed with 5% sodium hydrogen carbonate solution and water, dried and evaporated. The product was purified by crystallisation from dimethylformamide/water (7 + 3) to yield 1.0 g (82%) of a solid, mp 197–198 °C. ^{1}H NMR (d_6-DMSO/$CDCl_3$): δ = 3.17–3.29 (m, 2H, NCH_2), 3.93–4.06 (m, 2H, SCH_2),