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**Original paper**

# Synthesis and diuretic activity of imidazo[2,1-b]thiazole acetohydrazones

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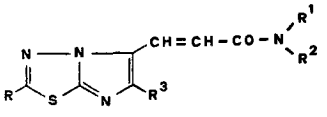
**Summary** — The synthesis of dimethylaminoacetohydrazones of 5-formylimidazo[2,1-b]thiazoles and thiazolines is reported. A potent diuretic activity was confirmed for the 2-methyl derivative bearing a phenyl ring at position 6 ($\mathbf{4}_l$).

**Résumé** — **Synthèse et activité diurétique d'acétohydrazones de dérivés de l'imidazo[2,1-b]thiazole.** *Synthèse de diméthylaminoacétohydrazones de formyl-5 imidazo[2,1-b]thiazoles et thiazolines. Une forte activité diurétique se manifeste lorsque le dérivé méthylé en 2 porte un noyau phényle en position 6* ($\mathbf{4}_l$).

**imidazo[2,1-b]thiazoles / hydrazones / diuretic activity**

## Introduction

Owing to our interest in heterocyclic medicinal chemistry, we have investigated the synthesis and the diuretic properties of a number of formylimidazo[2,1-b]thiazole dimethylaminoacetohydrazones. These derivatives have been designed bearing in mind two recently published reports: on the one hand, the anti-inflammatory [1, 2] and anti-secretory [3] activities of different acetohydrazones, on the other, the diuretic actions of the imidazothiadiazole acrylamides **1** [4, 5]. The new derivatives **4** (Scheme 1) widen the pharmacological spectrum of the acetohydrazones and show the effectiveness of changing the supporting moiety (bioisosteric cycle replacement) and of introducing a basic substituent on the acyl group. For an exhaustive review on bicyclic heterocyclic diuretics see ref. [6].



**1**

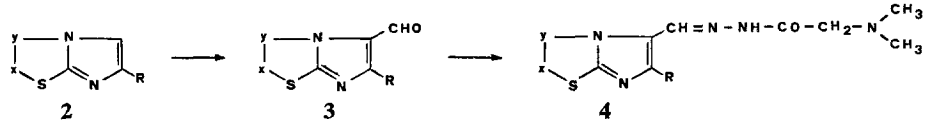
## Chemistry

The imidazo[2,1-b]thiazoles **2**, reacting under Vilsmeier conditions, afforded the 5-formyl derivatives **3** which, in turn, were treated with *N,N*-dimethylaminoacetohydrazide to yield the hydrazones **4**.

The new aldehydes $\mathbf{3}_{k-m}$ are described under experimental protocols, whereas the physical data concerning the hydrazones $\mathbf{4}_{a-m}$ are reported in Tables I and II.

## Pharmacological Results and Discussion

Table III shows, for each compound, the acute toxicity and the diuretic effect in rats at a given dose level. Evaluation of the diuretic activity of both the saturated compounds $\mathbf{4}_{f-j}$ and their unsaturated analogues ($\mathbf{4}_{a-e}$) shows that, among the 6-position substituents which were synthesized, a phenyl or substituted phenyl group was superior. This was confirmed by the results obtained with the analogues, 2- and 3-methyl derivatives ($\mathbf{4}_{l-m}$) which, considering the dose employed and the acute toxicity (*i.e.*, their therapeutic index), are obviously the most promising derivatives. For this reason, compounds $\mathbf{4}_{l-m}$ were chosen for more extensive evaluation of their diuretic activities. Table IV gives the results obtained in rats while Table V shows the effects of the same compounds in dogs. Taking into account the same dose levels in rats for the 0—6 h period, the salidiuretic effects of compounds $\mathbf{4}_l$ and $\mathbf{4}_m$ were comparable to that of furosemide, except for their greater kaluretic activity. In dogs, compound $\mathbf{4}_l$ is much more effective than $\mathbf{4}_m$. Although $\mathbf{4}_l$ is about as potent a salidiuretic agent as furosemide, it is less effective and displays no meritorious differences in its electrolyte excre-



**2** **3** **4**

**Scheme 1**

**Table I.** Dimethylaminoacetohydrazones $\underline{4}_{a-m}$.

| Compound | Starting material | x | y | R | Formula (mw) | Mp (°C) | Solvent |
|---|---|---|---|---|---|---|---|
| $\underline{4}_a$ | $\underline{3}_a$ (7) | CH | CH | Cl | $C_{10}H_{12}ClN_5OS$ (285.8) | 183–185 | EtOH |
| $\underline{4}_b$ | $\underline{3}_b$ (7) | CH | CH | $CH_3$ | $C_{11}H_{15}N_5OS$ (265.3) | 174–175 | EtOH |
| $\underline{4}_c$ | $\underline{3}_c$ (7) | CH | CH | $C_6H_5$ | $C_{16}H_{17}N_5OS$ (327.4) | 160–161 | EtOH |
| $\underline{4}_d$ | $\underline{3}_d$ (8) | CH | CH | $C_6H_4Cl(p)$ | $C_{16}H_{16}ClN_5OS$ (361.8) | 225–227 | EtOH |
| $\underline{4}_e$ | $\underline{3}_e$ (8) | CH | CH | $C_6H_4CH_3(p)$ | $C_{17}H_{19}N_5OS$ (341.4) | 212–215 | EtOH |
| $\underline{4}_f$ | $\underline{3}_f$ (7) | $CH_2$ | $CH_2$ | Cl | $C_{10}H_{14}ClN_5OS$ (287.2) | 120–125 | Toluene |
| $\underline{4}_g$ | $\underline{3}_g$ (7) | $CH_2$ | $CH_2$ | $CH_3$ | $C_{11}H_{17}N_5OS$ (267.4) | 128–130 | Toluene |
| $\underline{4}_h$ | $\underline{3}_h$ (7) | $CH_2$ | $CH_2$ | $C_6H_5$ | $C_{16}H_{19}N_5OS$ (329.4) | 174–175 | Toluene |
| $\underline{4}_i$ | $\underline{3}_i$ (8) | $CH_2$ | $CH_2$ | $C_6H_4Cl(p)$ | $C_{16}H_{18}ClN_5OS$ (363.9) | 187–188 | Toluene |
| $\underline{4}_j$ | $\underline{3}_j$ (8) | $CH_2$ | $CH_2$ | $C_6H_4CH_3(p)$ | $C_{17}H_{21}N_5OS$ (343.4) | 203–204 | Toluene |
| $\underline{4}_k$ | $\underline{3}_k$ | C-$CH_3$ | CH | $CH_3$ | $C_{12}H_{17}N_5OS$ (279.4) | 177–178 | Toluene |
| $\underline{4}_l$ | $\underline{3}_l$ | C-$CH_3$ | CH | $C_6H_5$ | $C_{17}H_{19}N_5OS$ (341.4) | 204–205 | Toluene |
| $\underline{4}_m$ | $\underline{3}_m$ | CH | C-$CH_3$ | $C_6H_5$ | $C_{17}H_{19}N_5OS$ (341.4) | 110–113 | Toluene |

tion profile. In conclusion, the present biological data on compound $\mathbf{4}_l$ indicate that it is a new type of potent high ceiling diuretic which also appears to be safe, as measured by its acute toxicity.

## Experimental protocols

### Chemistry

The melting points are uncorrected. Elemental analyses (C, H, N) were performed by Dr. V. Nuti (University of Pisa) and determined values are within 0.4% of the theoretical ones. Bakerflex plates (silica-gel IB2-F) were used for TLC and Kieselgel 60 (Merck) for column chromatography. The eluent was a mixture of acetone/petroleum ether/30% $NH_4OH$ in different proportions (*e.g.*, 70/29/1). The IR were recorded in nujol on a Perkin—Elmer 298 and the $^1H$ NMR in $CDCl_3$ on a Varian EM-390 (90 MHz) using TMS as an internal standard.

*Synthesis of the aldehydes* $\mathbf{3}_{k-m}$

The Vilsmeier reagent was prepared by dropping $POCl_3$ (9.2 g, 0.06 mol) into a stirred and cooled solution of DMF (4.38 g, 0.06 mol) in $CHCl_3$ (6 ml). 0.03 mol of 2,6-dimethylimidazo[2,1-b]thiazole $\mathbf{2}_k$ (submitted for publication) or 2-methyl-6-phenylimidazo[2,1-b]thiazole $\mathbf{2}_l$ [9] or 3-methyl-6-phenylimidazo[2,1-b]thiazole $\mathbf{2}_m$ [10] were dissolved in 40 ml of $CHCl_3$ and slowly added to the stirred and cooled Vilsmeier reagent. After 1 h at room temperature, the mixture was refluxed for 5 h, the solvent eliminated under reduced pressure, and the residue oil poured onto ice. Dilute $NH_4OH$ was slowly added to complete the precipitation (pH $\simeq$ 6) and the crude aldehyde was recovered by filtration with a yield of *ca.* 65%.

*2,6-Dimethyl-5-formylimidazo[2,1-b]thiazole* $\mathbf{3}_k$. $C_8H_8N_2OS$ (180.2); mp 158—59°C (EtOH); $\nu_{max}$ ($cm^{-1}$): 1640, 1320, 1260, 890. $\delta$ (ppm): 2.45 (3H, d, $CH_3$-2, $J$ = 1.5 Hz); 2.60 (3H, s, $CH_3$-6); 8.01 (1H, q, *H*-3, $J$ = 1.5 Hz); 9.82 (1H, s, C*H*O).

*2-Methyl-5-formyl-6-phenylimidazo[2,1-b]thiazole* $\mathbf{3}_l$. $C_{13}H_{10}N_2OS$ (242.3); mp 172—75°C (EtOH); $\nu_{max}$ ($cm^{-1}$): 1630, 1320, 850, 705. $\delta$ (ppm): 2.48 (3H, s, $CH_3$); 7.55 (3H, m, ar.); 7.82 (2H, m, ar.); 8.16 (1H, q, *H*-3, $J$ = 1.5 Hz); 9.95 (1H, s, C*H*O).

*3-Methyl-5-formyl-6-phenylimidazo[2,1-b]thiazole* $\mathbf{3}_m$. $C_{13}H_{10}N_2OS$ (242.3); mp 167—69°C (EtOH); $\nu_{max}$ ($cm^{-1}$): 1665, 1340, 1270, 700. $\delta$ (ppm): 2.82 (3H, d, $CH_3$, $J$ = 1.5 Hz); 6.58 (1H, q, *H*-2, $J$ = 1.5 Hz); 7.54 (3H, m, ar.); 7.78 (2H, m, ar.); 9.80 (1H, s, C*H*O).

*Synthesis of the dimethylaminoacetohydrazones* $\mathbf{4}_{a-m}$

The aldehyde $\mathbf{3}_{a-m}$ (4 mmol) was dissolved in 30 ml of EtOH and refluxed for 10 min with *N,N*-dimethylaminoacetohydrazide hydrochloride (4.5 mmol) dissolved in 5 ml of $H_2O$. The hydrochloride thus formed was separated, dissolved in $H_2O$ and treated with dilute $NH_4OH$ to yield the hydrazone $\mathbf{4}_{a-m}$ as free base (*ca.* 80%) which was crystallized as reported in Table I. Compound $\mathbf{4}_m$ was previously purified by column chromatography. The spectroscopic data for compounds $\mathbf{4}_{a-m}$ are reported in Table II.

### Pharmacology

*Diuretic activity in rats*

Four rats (Charles River—Calco, Como, Italy) were orally administered distilled water (25 ml/kg) containing the compound being tested, which had previously been suspended in Tween 80 (1% v/v with respect to water). Urine excreted during the 6 h following the treatment was collected in order to measure the sodium concentration by means of atomic absorption. The ratio of the mEq/100 g of body weight of the treated animals to the corresponding ratio of the control animals (treated with the vehicle alone) was calculated: the mean values obtained are reported in Table III.

For the determination of the excreted urinary volumes and electrolytes (Table IV), 3 groups of 2 animals were treated as in the previous test, but at the 3rd h were intubated with an additional amount of distilled water (25 ml/kg).

*Diuretic activity in dogs*

Four male beagles weighing 10—13 kg were housed in an air-conditioned room and received commercial diet and water *ad libitum*. Two days before the treatment, urine was collected by means of a catheter, measured and analyzed. The mean values of volumes and electrolytes thus obtained were used as a control (Table V). On day 3 the lower dose was administered p.o. and urine excreted during the first 2 h was collected and analyzed separately from that excreted during the subsequent 4 h. On day 6, the dogs received the second dose (5 mg/kg) of the same compound and the new data were registered. The same experiment was repeated with the second compound under consideration and then with furosemide included as usual for comparative purposes.

**Table II.** IR and $^1H$ NMR data for the hydrazones $\underline{4}_{a-m}$.

| Compound | $\nu_{max.}$ ($cm^{-1}$) | $\delta$(ppm): th = thiazole thn = thiazoline |
|---|---|---|
| $\underline{4}_a$ | 1675,1300, 1240,1150 | 2.36(6H,s,$CH_3NCH_3$);3.15(2H,s,$CH_2$);7.06(1H,d,th,J=4.5Hz);8.32(1H,s,CH); 8.50(1H,d,th,J=4.5Hz);10.25(1H,broad s,NH) |
| $\underline{4}_b$ | 1675,1610, 1300,1260 | 2.38(6H,s,$CH_3NCH_3$);2.43(3H,s,$CH_3$);3.15(2H,s,$CH_2$);6.91(1H,d,th,J=4.5 Hz);8.40(1H,s,CH);8.43(1H,d,th,J=4.5Hz);10.19(1H,broad s,NH) |
| $\underline{4}_c$ | 1670,1285, 1255,1150 | 2.32(6H,s,$CH_3NCH_3$);3.11(2H,s,$CH_2$);6.90(1H,d,th,J=4.5Hz);7.40(3H,m,ar); 7.68(2H,m,ar);8.45(1H,s,CH);8.51(1H,d,th,J=4.5Hz);10.25(1H,broad s,NH) |
| $\underline{4}_d$ | 1675,1290, 1235,1150 | 2.42(6H,s,$CH_3NCH_3$);3.20(2H,s,$CH_2$);6.98(1H,d,th,J=4.5Hz);7.50(2H,d,ar, J=8.5Hz);7.70(2H,d,ar,J=8.5Hz);8.58(1H,s,CH);8.60(1H,d,th,J=4.5Hz); 10.30(1H,broad s,NH) |
| $\underline{4}_e$ | 1675,1370, 1285,1160 | 2.35(6H,s,$CH_3NCH_3$);2.41(3H,s,$C_6H_4CH_3$);3.13(2H,s,$CH_2$);6.90(1H,d,th, J=4.5Hz);7.30(2H,d,ar,J=8.5Hz);7.58(2H,d,ar,J=8.5Hz);8.41(1H,s,CH); 8.55(1H,d,th,J=4.5Hz);10.05(1H,broad s,NH) |
| $\underline{4}_f$ | 1685,1290, 1240,1165 | 2.35(6H,s,$CH_3NCH_3$);3.13(2H,s,$CH_2$);3.85(2H,t,thn,J=7.5Hz);4.60(2H,t, thn,J=7.5Hz);8.08(1H,s,CH);10.25(1H,broad s,NH) |
| $\underline{4}_g$ | 1675,1610, 1370,1260 | 2.25(3H,s,$CH_3$);2.32(6H,s,$CH_3NCH_3$);3.10(2H,s,$CH_2$);3.81(2H,t,thn,J=7.5 Hz);4.54(2H,t,thn,J=7.5Hz);8.10(1H,s,CH);10.08(1H,broad s,NH) |
| $\underline{4}_h$ | 1690,1600, 1300,1255 | 2.31(6H,s,$CH_3NCH_3$);3.08(2H,s,$CH_2$);3.80(2H,t,thn,J=7.5Hz);4.60(2H,t, thn,J=7.5Hz);7.38(3H,m,ar);7.57(2H,m,ar);8.20(1H,s,CH);10.17(1H, broad s,NH) |
| $\underline{4}_i$ | 1690,1300, 1250,830 | 2.33(6H,s,$CH_3NCH_3$);3.10(2H,s,$CH_2$);3.86(2H,t,thn,J=7.5Hz);4.63(2H,t, thn,J=7.5Hz);7.40(2H,d,ar,J=8.5Hz);7.65(2H,d,ar,J=8.5Hz);8.24(1H,s, CH);10.15(1H,broad s,NH) |
| $\underline{4}_j$ | 1670,1585, 1540,1250 | 2.34(6H,s,$CH_3NCH_3$);2.40(3H,s,$C_6H_4CH_3$);3.12(2H,s,$CH_2$);3.87(2H,t,thn, J=7.5Hz);4.66(2H,t,thn,J=7.5Hz);7.29(2H,d,ar,J=8.5Hz);7.53(2H,d,ar, J=8.5Hz);8.20(1H,s,CH);10.08(1H,broad s,NH) |
| $\underline{4}_k$ | 1675,1300, 1250,1170 | 2.35(6H,s,$CH_3NCH_3$);2.40(3H,s,$CH_3$-6);2.42(3H,d,$CH_3$-2,J=1.5Hz);3.13(2H, s,$CH_2$);8.10(1H,q,th,J=1.5Hz);8.32(1H,s,CH);10.11(1H,broad s, NH) |
| $\underline{4}_l$ | 1655,1595, 1530,1325 | 2.32(6H,s,$CH_3NCH_3$);2.43(3H,d,$CH_3$,J=1.5Hz);3.11(2H,s,$CH_2$);7.40(3H,m, ar);7.65(2H,m,ar);8.17(1H,q,th,J=1.5Hz);8.38(1H,s,CH);10.20(1H,s,NH) |
| $\underline{4}_m$ | 1690,1570, 1225,1155 | 2.32(6H,s,$CH_3NCH_3$);2.85(3H,d,$CH_3$,J=1.5Hz);3.10(2H,s,$CH_2$);6.45(1H,q,th, J=1.5Hz);7.45(3H,m,ar);7.65(2H,m,ar);8.28(1H,s,CH);10.0(1H,broad s,NH) |

**Table III.** Diuretic activity and acute toxicity of the hydrazones $4_{a-m}$ in rats.

| Compound | Dose (mg/kg) | Diuretic effect[a] | $LD_{50}$ p.o. and i.p. (mg/kg) |
|---|---|---|---|
| $4_a$ | 20 | 120 | 1500, 250 |
| $4_b$ | | n.s. | 1500, 600 |
| $4_c$ | 5 | 310 | 600, 600 |
| $4_d$ | 20 | 170 | > 1000, > 1000 |
| $4_e$ | 5 | 130 | > 3000, > 3000 |
| $4_f$ | 20 | 130 | > 1000, 600 |
| $4_g$ | | n.s. | > 1000, > 1000 |
| $4_h$ | 10 | 230 | > 3000, > 1000 |
| $4_i$ | 20 | 230 | 800, 600 |
| $4_j$ | 20 | 120 | 800, 600 |
| $4_k$ | 10 | 180 | 1000, 600 |
| $4_l$ | 1 | 300 | > 3000, > 3000 |
| $4_m$ | 0.5 | 250 | > 3000, > 3000 |
| Furosemide | 10 | 490 | |
| Hydroflumethiazide | 5 | 260 | |
| Spironolactone | 20 | 360 | |
| Acetazolamide | 2.5 | 200 | |

[a] Increase of sodium excretion expressed as a percentage in comparison to control = 100; n.s. = not significant.

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**Table IV.** Excreted urinary volumes and electrolytes in rats (mean ± SEM).

| Compound | Dose (mg/kg) | Urinary volume (ml) [a] / Body weight (kg) | | Ion (mEq) [b] / Body weight (kg) | |
|---|---|---|---|---|---|
| $4_l$ | 2.5 | 26.5 ± 0.42 | 16.7 ± 1.22 | 1.32 ± 0.15; 0.48 ± 0.01 | 0.06 ± 0.01; 0.35 ± 0.02 |
| $4_l$ | 10 | 34.5 ± 1.30 | 16.4 ± 1.54 | 2.24 ± 0.06; 0.66 ± 0.09 | 0.15 ± 0.01; 0.33 ± 0.03 |
| $4_m$ | 2.5 | 33.3 ± 1.20 | 13.6 ± 0.52 | 2.03 ± 0.15; 0.93 ± 0.05 | 0.14 ± 0.02; 0.33 ± 0.04 |
| $4_m$ | 10 | 32.6 ± 0.75 | 14.7 ± 2.43 | 2.55 ± 0.71; 1.04 ± 0.12 | 0.16 ± 0.03; 0.25 ± 0.02 |
| Furosemide | 10 | 36.5 ± 0.83 | 10.7 ± 0.87 | 1.82 ± 0.33; 1.02 ± 0.05 | 0.03 ± 0.01; 0.13 ± 0.02 |
| Control | — | 20.3 ± 1.21 | 10.5 ± 0.95 | 0.24 ± 0.01; 0.38 ± 0.02 | 0.05 ± 0.01; 0.20 ± 0.01 |

[a] 0—3 h and 3—6 h, respectively.
[b] $Na^+$; $K^+$ for the period 0—3 h and 3—6 h, respectively.

**Table V.** Excreted urinary volumes (ml) and electrolytes (mEq) in dogs.

| Compound | Dose (mg/kg) | Urinary volume | | $Na^+$ | | $K^+$ | | $Cl^-$ | |
|---|---|---|---|---|---|---|---|---|---|
| Control | — | 24.9 ± 1.9 | 30.6 ± 2.1 | 2.65 ± 0.40 | 2.82 ± 0.42 | 0.33 ± 0.11 | 0.38 ± 0.09 | 2.42 ± 0.22 | 2.76 ± 0.25 |
| $4_l$ | 1 | 99.0 ± 2.8 | 76.5 ± 15.9 | 18.21 ± 2.44 | 5.60 ± 0.26 | 1.51 ± 0.56 | 0.54 ± 0.12 | 20.98 ± 1.53 | 8.26 ± 2.81 |
| Control | — | 28.6 ± 2.0 | 31.8 ± 2.3 | 2.70 ± 0.28 | 2.76 ± 0.40 | 0.62 ± 0.14 | 0.33 ± 0.10 | 2.45 ± 0.23 | 2.74 ± 0.37 |
| $4_l$ | 5 | 232.0 ± 21.9 | 121.8 ± 10.7 | 24.02 ± 2.98 | 11.26 ± 1.42 | 3.35 ± 0.81 | 0.39 ± 0.19 | 33.25 ± 1.65 | 8.61 ± 1.48 |
| Control | — | 27.0 ± 1.8 | 29.4 ± 1.8 | 2.65 ± 1.45 | 2.72 ± 0.45 | 0.26 ± 0.08 | 0.46 ± 0.21 | 2.57 ± 0.25 | 2.51 ± 0.22 |
| $4_m$ | 1 | 35.6 ± 3.9 | 39.3 ± 3.3 | 4.17 ± 0.50 | 4.45 ± 0.22 | 0.36 ± 0.09 | 0.62 ± 0.25 | 4.69 ± 0.29 | 5.33 ± 0.44 |
| Control | — | 29.3 ± 1.5 | 25.9 ± 2.4 | 2.27 ± 0.18 | 2.73 ± 0.28 | 0.73 ± 0.13 | 0.66 ± 0.09 | 2.33 ± 0.18 | 2.36 ± 0.27 |
| $4_m$ | 5 | 62.8 ± 3.4 | 59.6 ± 13.6 | 6.60 ± 1.01 | 5.32 ± 0.80 | 1.63 ± 0.17 | 1.74 ± 0.18 | 5.31 ± 0.49 | 5.07 ± 0.46 |
| Control | — | 24.8 ± 1.6 | 26.3 ± 2.1 | 2.81 ± 0.44 | 3.10 ± 0.58 | 0.35 ± 0.11 | 0.43 ± 0.15 | 2.12 ± 0.24 | 2.42 ± 0.29 |
| Furosemide | 1 | 81.8 ± 13.8 | 49.5 ± 10.2 | 20.88 ± 6.14 | 4.89 ± 0.69 | 0.86 ± 0.36 | 0.93 ± 0.46 | 15.47 ± 4.81 | 4.33 ± 1.09 |
| Control | — | 26.8 ± 1.1 | 27.8 ± 1.1 | 3.20 ± 0.45 | 2.24 ± 0.20 | 0.52 ± 0.07 | 0.65 ± 0.14 | 2.26 ± 0.15 | 2.45 ± 0.24 |
| Furosemide | 5 | 338.0 ± 31.5 | 87.0 ± 6.3 | 57.15 ± 7.98 | 6.31 ± 2.68 | 6.78 ± 0.83 | 1.60 ± 0.30 | 22.47 ± 2.95 | 30.09 ± 1.59 |

Values are means ± SEM for the period 0—2 h and 2—6 h, respectively.