Addition/Correction

Highly Potent 1,4-Benzo-thiazine Derivatives as K$^+$-Channel Openers

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Additions and Corrections

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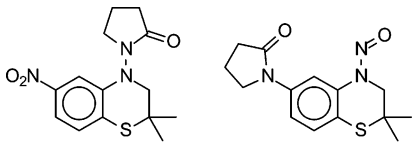
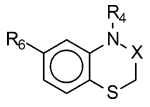
Violetta Cecchetti,* Vincenzo Calderone, Oriana Tabarrini, Stefano Sabatini, Enrica Filipponi, Lara Testai, Roberto Spogli, Enrica Martinotti, and Arnaldo Fravolini: Highly Potent 1,4-Benzothiazine Derivatives as K_{ATP}-Channel Openers.

Pages 3670−3679. The structure of compound **4a**, referred to as 2,2-dimethyl-6-nitro-4-(2-oxo-1-pyrrolidinyl)-3,4-dihydro-2*H*-1,4-benzothiazine (original **4a**), was found to be incorrect. The structure and biological activity should correspond instead to the structure of 2,2-dimethyl-4-nitroso-6-(2-oxo-1-pyrrolidinyl)-3,4-dihydro-2*H*-1,4-benzothiazine (revised **4a**).



It was unexpectedly obtained from 6-amino-2,2-dimethyl-4-nitroso-3,4-dihydro-2*H*-1,4-benzothiazine, which is a side product formed in the reduction of 6-nitro-4-nitrosobenzothiazine derivative **17** to the 4-amino-6-nitro derivative **19** (see Scheme 3, page 3673). This evidence was discovered during an in-depth conformational study of this class of highly potent $K_{ATP}CO_S$, which also included X-ray analyses. Details of the study will be published separately, and the crystallographic data of revised **4a** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 271510).

Page 3672. In Table 1, the row **4a** should read R_4 = NO and R_6 = 2-oxo-1-pyrrolidinyl. In Table 2, the structure was misdrawn. The correct structure for Table 2 is shown below:



Page 3676. In lines 20−21, first column, the chemical name in the pararaph heading should be replaced with "**2,2-Dimethyl-4-nitroso-6-(2-oxo-1-pyrrolidinyl)-3,4-dihydro-2*H*-1,4-benzothiazine Revised 4a.**" The authentic derivative **4a** (original **4a**) was synthesized, as depicted in Scheme 3 (page 3673), and its analytical data and vasorelaxant activity are reported below. 2,2-Dimethyl-6-nitro-4-(2-oxo-1-pyrrolidinyl)-3,4-dihydro-2*H*-1,4-benzothiazine (original **4a**) was prepared using the procedure described for **3a**, starting from 4-amino-6-nitrobenzothiazine **19**. It was purified by column chromatography, eluting with cyclohexane/EtOAc (1:1): yield 58%; mp 135−137 °C; ^{1}H NMR δ 1.49 and 1.52 (each 3H, s, CH_3), 2.15−2.70 (4H, m, CH_2CH_2N and CH_2CO), 3.33 and 3.78 (each 1H, d, J = 11.6 Hz, CH_2), 3.48−3.61 and 3.62−3.75 (each 1H, m, CH_2CH_2N), 7.14 (1 H, d, J = 8.5 Hz, H-8), 7.43 (1 H, d, J = 2.3 Hz, H-5), 7.60 (1 H, dd, J = 2.3 and 8.5 Hz, H-7); MS *m/z* (rel intens) 307 (47), 277 (3), 264 (8), 222 (45), 207 (100), 194 (10), 181 (6), 161 (13), 135 (13).

The vasorelaxant activity of the original **4a**, evaluated in aortic rings precontracted with 20 mM KCl (as reported in the Experimental Section), is E_{max} = 100%, $pIC_{50} \pm SEM = 9.84 \pm 0.15$. Thus, the pharmacological behavior found for the original **4a** is in perfect agreement with the SAR delineated for this $K_{ATP}CO$ benzothiazine class, unlike what was previously shown by the revised **4a** because of its peculiar structure. In particular, it can now be observed that the original **4a** exhibits a potency comparable to that of **4d** (pIC_{50} = 9.13), and this is in agreement with the nearly equivalent potencies shown by the analogous couple **3a** and **3d** (pIC_{50} = 6.91 and 7.06, respectively). While, the revised **4a** showed a potency (pIC_{50} = 6.42) that was unexpectedly much lower than that of **4d.** Moreover, revised **4a** showed a dramatic decrease in potency when compared with **4c** (∼4.5 log units) while the original **4a** is only 1 log unit less potent than **4c**; this difference in potency is substantially comparable to those exhibited by **3a** vs **3c** (∼1 log unit) and **6a** vs **6c** (∼2 log units).

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