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The first AMPA receptor negative modulators based on the tetrahydroquinazoline scaffold

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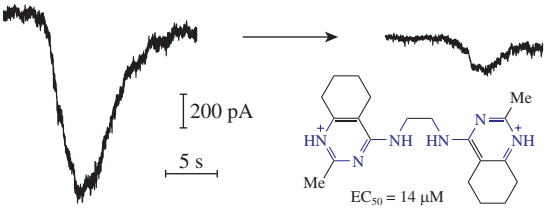
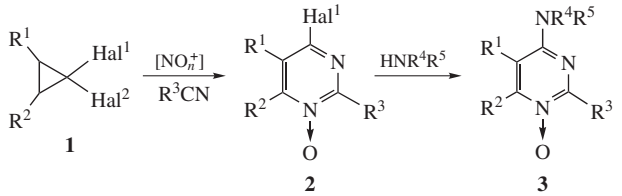
A convenient approach to novel symmetric bispyrimidine diamines comprises S_NAr reactions of 4-fluoropyrimidine *N*-oxide with alkane-α,ω-diamines with subsequent reduction of *N*-oxide function. The obtained substances were tested in patch-clamp experiments for the influence on the kainate-induced currents in Purkinje neurons and showed negative modulating effect.



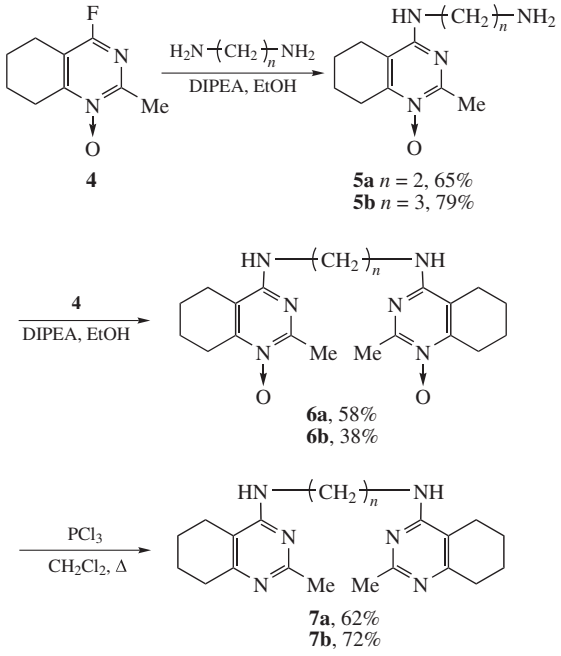
The AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) receptors are attractive targets for the treatment of various neurological disorders.[1–3] Their positive modulators can improve learning and memory formation while antagonists, negative modulators or reversible channel blockers, could be perspective agents, *e.g.* for the treatment of epilepsy.[4] Earlier we performed molecular modeling[5] and experimental studies[6] of highly active AMPA receptor potentiators. Here we present the synthesis of a novel series of bispyrimidine diamines and describe their action on the kainate-induced currents in Purkinje cells.

The most efficient approach to bispyrimidine diamines is based on S_NAr reactions of halogenopyrimidine derivatives, usually proceeding smoothly under mild conditions.[7] Previously (Scheme 1) we elaborated an efficient preparative method affording 4-amino-substituted pyrimidine derivatives **3**. 2-Alkylpyrimidine scaffold was constructed *via* three-component heterocyclization of dihalocyclopropanes **1** upon the treatment with nitrating or nitrosating reagents.[8] Subsequent S_NAr reactions of compound **2** (Hal^1 = F) with various primary and secondary amines afforded pyrimidine oxides **3** (see Scheme 1).[9]

In the present work we elaborated a convenient approach to bispyrimidine *N*,*N*′-dioxides **6**, the precursors of target compounds **7** (Scheme 2). Substitution of fluorine in 4-fluoropyrimidine *N*-oxide **4** was performed upon the treatment with the corresponding diamines in the presence of *N*,*N*-diisopropylethylamine (DIPEA). The attempt to obtain symmetric heterocycle **6a** in one stage from pyrimidine *N*-oxide **4** and ethylenediamine, taken in 2 : 1 ratio, led to the non-separable mixture of mono- and disubstitution products **5a** and **6a**. Using the excess of diamine in relation to pyrimidine *N*-oxide **4** led exclusively to the mono-substitution product **5a**. Subsequent reaction of isolated amine **5a** with an excess of **4** afforded bispyrimidine *N*,*N*′-dioxide **6a** in high preparative yield. This two-stage synthetic scheme was used to obtain homologue **6b**.[†]



Scheme 1



Scheme 2

[†] *General procedure for the preparation of compounds* **5a**,**b**. A mixture of pyrimidine *N*-oxide **4** (0.5 mmol), the corresponding diamine (1.0 mmol) and DIPEA (129 mg, 1.0 mmol) in ethanol (1 ml) was stirred at room temperature for 24 h. The solvent was evaporated *in vacuo*, the product was isolated *via* preparative column chromatography.

Compounds **7a**,**b** were prepared *via* the PCl_3 reduction of dioxides **6a**,**b** employing the method, previously reported for derivatives containing one pyrimidine oxide moiety (Scheme 2).[10,‡] The reaction proceeded smoothly, giving the products of simultaneous reduction of two *N*-oxide moieties, dimeric tetrahydroquinazoline derivatives **7a**,**b**. Note that the isolation procedure, modified for these compounds, afforded the target heterocycles in analytically pure form without additional purification.

Compounds **7a** and **7b** were tested in patch-clamp experiments for their influence on the kainate-induced currents recorded for the Purkinje cell extracted from the rat cerebellum.[11,§] Both compounds revealed moderate negative modulating effects: **7a** having shorter linker is more active with 14 μM EC_{50} (the concentration causing 50% decrease of kainate-induced currents) while **7b** showed EC_{50} above 50 μM (Figure 1). Figure 1(*b*) demonstrates the decrease in kainate-induced currents after the application of 50 μM **7a**. The recovery of the initial current in the control experiment after the wash-out stage confirms the correctness of the results.

Being rather strong bases analogous to compounds having similar π-system (*e.g.*, pK_a of *N*,2,5,6-tetramethylpyrimidine-4-amine[12] is 8.14) compounds **7** could also block AMPA receptor currents possibly similarly to ketamine bound in the ionic pore. It should be noted that N(1) nitrogen atom is preferably protonated according to quantum chemical calculations (on MP2 theory level with cc-pVTZ basis set) which give energy difference 8.5 kcal mol^{-1} as compared to N(3)-protonated form.

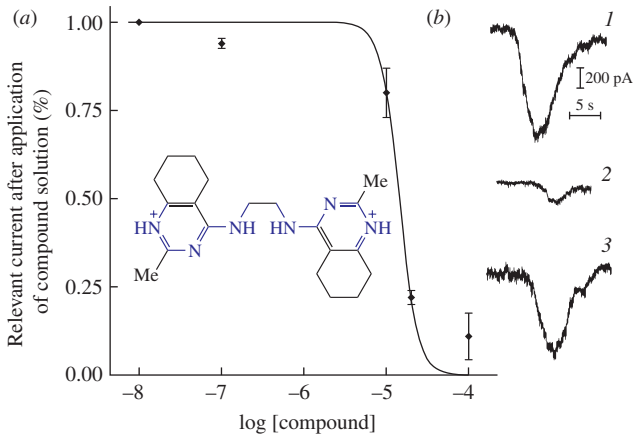


Figure 1 (*a*) The results of electrophysiological studies of compound **7a** were approximated with the Hill equation to obtain pEC_{50} = 4.8 ± 0.1. (*b*) Change in the membrane conductance: (*1*) control experiment, (*2*) after the **7a** (50 μM) application and (*3*) the recovery of the initial conductance after the thorough wash-out.

The obtained data on bioactivity may form the basis for the development of novel AMPA receptor modulators. Suggested synthetic approach opens great opportunities for further structural optimization of bis(pyrimidine) derivatives including the variation of the length and the nature of the linker and the substituents in the pyrimidine core that is useful for the synthesis of libraries of compounds with predicted bioactivity.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.07.028.

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N-*(2-Methyl-1-oxido-5,6,7,8-tetrahydroquinazolin-4-yl)ethane-1,2-diamine* **5a**. Yield 72 mg (65%), yellowish oil, R_f = 0.05 (MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.71–1.84 (m, 4H, $2CH_2$, Cy), 2.33 (br.t, 2H, CH_2, Cy, $^3J_{HH}$ 5.5 Hz), 2.60 (s, 3H, Me), 2.88 (br.t, 2H, CH_2, Cy, $^3J_{HH}$ 5.5 Hz), 2.94 (t, 2H, CH_2NH$_2$, $^3J_{HH}$ 5.9 Hz), 3.51 (dt, 2H, CH_2NH, $^3J_{HH}$ 5.9 Hz, $^3J_{HH}$ 5.5 Hz), 5.29 (br.s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.2 (Me), 20.8 (CH_2, Cy), 21.0 (CH_2, Cy), 22.1 (CH_2, Cy), 24.5 (CH_2, Cy), 41.0 (CH_2NH_2), 43.2 (CH_2NH), 112.0 (C^{4a}), 151.9 (C^4), 153.2 (C^{8a}), 154.6 (C^2). HRMS (ESI, 70 eV), *m/z*: 223.1558 [M+H]$^+$ (calc. for $C_{11}H_{18}N_4O$, *m/z*: 223.1553).

General procedure for the preparation of compounds **6a**,**b**. A mixture of pyrimidine *N*-oxide **4** (0.6 mmol), the corresponding (tetrahydroquinazolinyl)diamine **5** (0.5 mmol) and DIPEA (129 mg, 1.0 mmol) in ethanol (1 ml) was stirred at room temperature for 24 h. The solvent was evaporated *in vacuo*, the product was isolated *via* preparative column chromatography.

N,N′-*Bis(2-methyl-1-oxido-5,6,7,8-tetrahydroquinazolin-4-yl)ethane-1,2-diamine* **6a**. Yield 133 mg (58%), yellowish oil, R_f = 0.1 (MeOH). ^{1}H NMR (400 MHz, CD_3OD) δ: 1.66–1.79 (m, 8H, $4CH_2$, Cy), 2.28 (br.t, 4H, $2CH_2$, Cy, $^3J_{HH}$ 5.5 Hz), 2.57 (s, 6H, 2Me), 2.82 (br.t, 4H, $4CH_2$, Cy, $^3J_{HH}$ 5.6 Hz), 3.71 (br.s, 4H, 2CH_2NH). ^{13}C NMR (100 MHz, CD_3OD) δ: 20.3 (2Me), 20.7 ($2CH_2$, Cy), 20.9 ($2CH_2$, Cy), 22.4 ($2CH_2$, Cy), 24.5 ($2CH_2$, Cy), 41.8 ($2CH_2$N), 112.4 (2C^{4a}), 152.9 (2C^{8a}), 153.3 (2C^4), 154.7 (2C^2). HRMS (ESI, 70 eV), *m/z*: 385.2367 [M+H]$^+$ (calc. for $C_{20}H_{28}N_6O_2$, *m/z*: 385.2347).

‡ *General procedure for the preparation of compounds* **7a**,**b**. Phosphorus trichloride (1.2 mmol, 165 mg, 0.1 ml) was added to a solution of compound **6** (0.3 mmol) in CH_2Cl_2 (1 ml). The mixture was refluxed for 2 h and poured into the equal volume of icy water. The organic layer was separated, and the water layer was extracted with CH_2Cl_2 (3×1 ml). The combined organic layers were washed with aqueous $NaHCO_3$. The water layers were combined and extracted with CH_2Cl_2 again (3×1 ml). The last CH_2Cl_2 extracts contained the target compound. The solvent was evaporated *in vacuo* to give pure product.

N,N′-*Bis(2-methyl-5,6,7,8-tetrahydroquinazolin-4-yl)ethane-1,2-diamine* **7a**. Yield 66 mg (62%), white crystals, mp 173 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.75–1.82 (m, 8H, $4CH_2$, Cy), 2.19 (br.t, 4H, $2CH_2$, Cy, $^3J_{HH}$ 5.2 Hz), 2.48 (s, 6H, 2Me), 2.64 (br.t, 4H, $4CH_2$, Cy, $^3J_{HH}$ 5.2 Hz), 3.71–3.80 (m, 4H, 2CH_2NH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.0 (2Me), 22.2 ($4CH_2$, Cy), 25.9 ($2CH_2$, Cy), 31.7 ($2CH_2$, Cy), 42.2 ($2CH_2$N), 108.7 (2C^{4a}), 161.1 (2C^{8a}), 161.3 (2C^4), 163.7 (2C^2). HRMS (ESI, 70 eV), *m/z*: [M+H]$^+$ 353.2447 (calc. for $C_{20}H_{28}N_6$, *m/z*: 353.2448).

§ For cell isolation, a selected region of the rat brain was cut into slices 0.4–0.6 mm thick followed by the incubation in buffer solution for 1 h. Then, the slices were transferred to the fresh buffer solution and incubated about 20 min. The slices were incubated at 34 °C and pre-gassed with 100% O_2. Finally, the slices were mechanically dissociated into individual cells using Pasteur pipettes.

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