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Mendeleev Commun., 2018, **28**, 592–594

Mendeleev Communications

A facile metal-free approach to *N*,*N'*-bis(1-oxidopyrimidin-4-yl)diamines with promising biological activity

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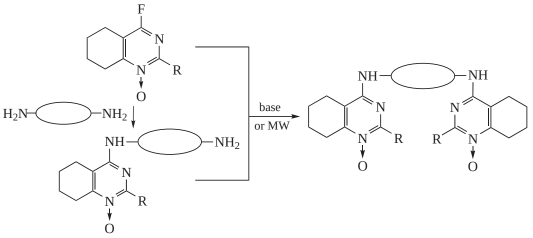
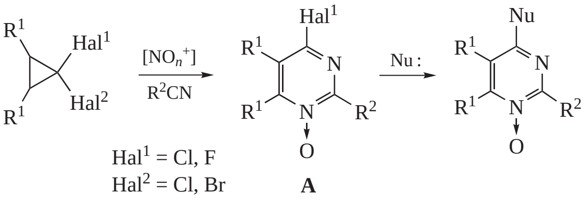
DOI: 10.1016/j.mencom.2018.11.009

Novel *N*-(1-oxidopyrimidin-4-yl)- and *N*,*N'*-bis(1-oxidopyrimidin-4-yl)diamines were prepared from 4-fluoropyrimidine *N*-oxides and diamines basing on S$_N$Ar reaction. One compound from this series possessed antiviral activity against tick-borne encephalitis virus (TBEV).



Pyrimidine derivatives are of high importance in living organisms and reveal a broad spectrum of biological activity.[1,2] Compounds containing two pyrimidine moieties are particularly challenging for drug design. Such structures are reported to possess, *e.g*., anti-inflammatory,[3] antiviral,[4] and antidiabetic[5] properties. Bis(pyrimidine) nucleotides may be used for presenting DNA sequence information outside of the double helix.[6] Bis(pyrimidines) have also found an application in the synthesis of macrocyclic ligands of pyrimidinophane type.[7,8] Though the *N*-oxide motif has been widely and successfully used in drug development,[9] until recently no bis(pyrimidine *N*-oxide) derivatives have been described due to their limited synthetic availability. The present work was aimed at the elaboration of a preparative synthesis of diamines equipped with pyrimidine *N*-oxide fragments and obtaining a series of novel compounds of this chemotype. Inhibition of tick-borne encephalitis virus (TBEV) reproduction was previously shown for structurally related pyrimidine *N*-oxides,[10] so anti-TBEV activity of the compounds obtained here was assessed to estimate how connection of these moieties with a linker affects their antiviral activity.

The main synthetic approach to bis(pyrimidines) is the reaction of halogen-substituted pyrimidines with diamines.[11,12] Recently we reported the synthesis of 4-halogenopyrimidine *N*-oxides **A** based on heterocyclization of 1,1-dihalogenocyclopropanes upon treatment with nitrating or nitrosating agents in the presence of nitriles[13–17] and their further modification with nucleophiles[10,18,19] (Scheme 1).



Scheme 1

Previously we have demonstrated the feasibility of the two-step approach to *N*,*N'*-bis(pyrimidinyl)diamines based on S$_N$Ar reactions of 4-fluoropyrimidine *N*-oxides.[20] To explore the scope and limitations of this approach, compounds **1a**,**b** were investigated in the reaction with a series of diamines containing open-chain, adamantane, or benzene moiety in the linker (Scheme 2). Two-fold excess of diamine was taken, and diisopropylethylamine (DIPEA) was used as a base (method A). In this way, a series of *N*-(pyrimidinyl)diamines **2a**–**i**, resulting from nucleophilic substitution employing single amino group, was obtained.[†] The reaction proceeded smoothly with all diamines except for less

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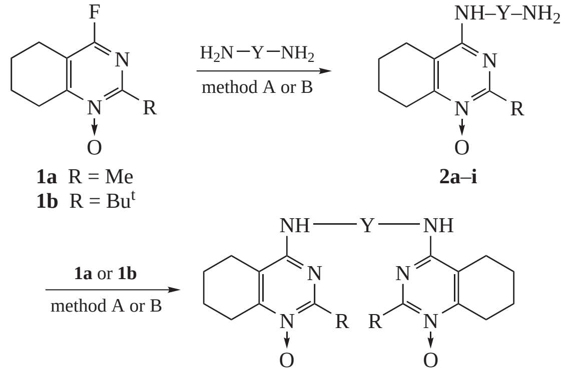
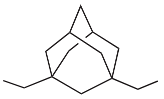
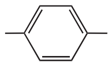
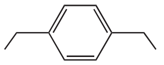
[†] *General procedure for the preparation of* N-*tetrahydroquinazolinyldiamines* **2a**–**g**,**i**. A mixture of pyrimidine *N*-oxide (0.5 mmol), corresponding diamine (1.0 mmol) and DIPEA (129 mg, 1.0 mmol) in ethanol (1 ml) was stirred at room temperature for 24 h. The solvent was evaporated *in vacuo*, the product was purified by column chromatography.

N*-(2-Methyl-1-oxido-5,6,7,8-tetrahydroquinazolin-4-yl)butane-1,4-diamine* **2c**. Yield 45 mg (36%), colourless oil, R_f 0.1 (MeOH). ^{1}H NMR (400.0 MHz, CDCl$_3$) δ: 1.44–1.57 (m, 2H, CH$_2$, diamine), 1.60–1.73 (m, 2H, CH$_2$, diamine), 1.72–1.84 (m, 4H, 2CH$_2$, cy-Hex), 2.27 (br. t, 2H, CH$_2$, cy-Hex, $^3J_{HH}$ 6.2 Hz), 2.60 (s, 3H, Me), 2.75 (t, 2H, CH_2NH$_2$, $^3J_{HH}$ 6.8 Hz), 2.89 (br. t, 2H, CH$_2$, cy-Hex, $^3J_{HH}$ 6.0 Hz), 3.46 (dt, 2H, CH_2NH, $^3J_{HH}$ 5.3 Hz, $^3J_{HH}$ 6.8 Hz), 5.05 (br. t, 1H, NH, $^3J_{HH}$ 5.3 Hz). ^{13}C NMR (100.6 MHz, CDCl$_3$) δ: 20.2 (Me), 20.9 (CH$_2$, cy-Hex), 21.0 (CH$_2$, cy-Hex), 22.2 (CH$_2$, cy-Hex), 24.5 (CH$_2$, cy-Hex), 26.9 (CH$_2$), 30.7 (CH$_2$), 41.1 (CH$_2$N), 41.6 (CH$_2$N), 111.6 (C^{4a}), 151.7 (C^4), 153.1 (C^{8a}), 154.7 (C^2). HRMS (ESI$^+$, 70 eV), m/z: 251.1858 [M+H]$^+$ (calc. for C$_{13}$H$_{22}$N$_4$O, m/z: 251.1866).



1a R = Me
1b R = Bu^t
2a–i
3a–i

2, **3**	R	Y	Yield of **2** (%)	Yield of **3** (%)
a	Me	$(CH_2)_2$	65 (A),[20] 61 (B)	58 (A),[20] 55 (B)
b	Me	$(CH_2)_3$	79 (A)[20]	38 (A)[20]
c	Me	$(CH_2)_4$	36 (A)	48 (A)
d	Bu^t	$(CH_2)_2$	35 (A)	52 (A)
e	Bu^t	$(CH_2)_3$	47 (A)	35 (A)
f	Bu^t	$(CH_2)_4$	46 (A)	48 (A)
g	Bu^t		50 (A)	38 (A)
h	Me		49 (B)	48 (B)
i	Me		54 (A)	53 (B)

Scheme 2 *Reagents and conditions*: method A, DIPEA, EtOH, ~20 °C, 24 h; method B, MW, MeCN, 75 °C, 40 min.

nucleophilic *p*-phenylenediamine. In the latter case, a large amount of the starting diamine remained unchanged, and the isolation of product **2h** was complicated. Compound **2h** was successfully obtained using the microwave assistance (method B). When the optimal 2 : 1 ratio of **1a** and *p*-phenylenediamine was taken, the resulting mixture was free of the starting diamine, and product **2h** could be easily isolated.[‡] It should be noted that under the microwave irradiation the reaction time could be significantly reduced and no application of a base was necessary. Under these conditions, products **2a–i** can be in principle obtained in yields comparable with those provided by method A, as it is demonstrated by the reaction of **1a** with ethylenediamine.

The subsequent treatment of isolated amines **2a–g** with a small excess of the corresponding pyrimidine *N*-oxide **1a**,**b** (1 : 1.2 ratio) smoothly afforded symmetrical *N*,*N'*-bis(pyrimidinyl)diamines **3a–g** (see Scheme 2).[§] Nevertheless, no reaction of phenyl-containing heterocycle **2h** with fluoropyrimidine *N*-oxide **1a** was observed under standard conditions (method A). The reflux of the reaction mixture afforded bis(pyrimidinyl)diamine **3h**, yet higher conversion (60% *vs*. 30%) was achieved using a microwave assistance.[¶] The latter method was also used to access compounds **3a** and **3i**.

As mentioned above, bis(pyrimidines) are promising compounds for biological studies. Earlier we have found that deoxygenated derivatives of **3a**,**b** demonstrated a moderate activity as negative modulators of AMPA receptors. Further studies of this kind are also planned for compounds **3g–i**.

Extending the results of our previous studies on antiviral activity of 4-aminopyrimidine *N*-oxides,[10] we performed herein the same assessment for the prospective analogues with bulky substituents in 2- and 4-positions of pyrimidine cycle. For this study we selected *N*-(1-oxidopyrimidin-4-yl)diamines **2e**,**g** and *N*,*N'*-bis(1-oxidopyrimidin-4-yl)diamines **3e**,**g** bearing *tert*-butyl and adamantyl fragments; for comparison, less sterically hindered analogue **3b** was also investigated. The activity of these compounds against TBEV strain Absettarov in the plaque reduction assay was estimated.[21] Compound **2g** showed a moderate anti-TBEV activity (EC_{50} = 9±3 μM), while other compounds did not inhibit TBEV reproduction at 50 μM concentration. Cytotoxicity of **2g** was assessed in PEK cells on days 1 (CC_{50} = 176.8 μM) and 7 (CC_{50} = 88.4 μM). Thus, it may be preliminary concluded that in the case of mononuclear pyrimidine *N*-oxides bulky substituents are favourable for antiviral activity (compound **2g**) showing a good agreement with previously obtained data.[10] Loss of antiviral activity in the linked dimers **3b**,**e**,**g** allows one to suggest that pyrimidine *N*-oxide moiety of previously published **2**-like compounds[10] is unlikely to be buried in the E protein binding pocket, but should be exposed to the external space.

In summary, we have elaborated an efficient metal-free two-step synthetic approach to bis(1-oxidopyrimidin-4-yl)diamines, and some of them as well as their derivatives could be further studied as AMPA receptor modulators. This new type of compounds also provides new information about possible binding modes of pyrimidine *N*-oxide inhibitors of TBEV reproduction.

This work was supported by the Russian Foundation for Basic Research (grant no. 18-03-00651) (synthesis of hetero-

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[‡] *4-(4-Aminophenylamino)-2-methyl-5,6,7,8-tetrahydroquinazoline 1-oxide* **2h**. A mixture of 4-fluoropyrimidine *N*-oxide **1a** (1 mmol, 180 mg) and *p*-phenylenediamine (0.5 mmol, 54 mg) in MeCN (2 ml) was microwave irradiated at 75 °C for 40 min. The solvent was evaporated *in vacuo*. The product was isolated by column chromatography. Yield 66 mg (49%), brown oil, R_f 0.63 (MeOH). ^{1}H NMR (400.0 MHz, $CDCl_3 + CD_3OD$) δ: 1.71–1.82 (m, 4H, 2CH$_2$, cy-Hex), 2.36–2.41 (m, 2H, CH$_2$, cy-Hex), 2.51 (s, 3H, Me), 2.77–2.84 (m, 2H, CH$_2$, cy-Hex), 6.59–6.64 (m, 2H, 2CH, Ar, $^3J_{HH}$ 8.6 Hz), 7.17–7.23 (m, 2H, 2CH, Ar, $^3J_{HH}$ 8.6 Hz, $^4J_{HH}$ 1.5 Hz). ^{13}C NMR (100.6 MHz, $CDCl_3 + CD_3OD$) δ: 19.8 (Me), 20.6 (CH$_2$, cy-Hex), 20.7 (CH$_2$, cy-Hex), 22.2 (CH$_2$, cy-Hex), 24.4 (CH$_2$, cy-Hex), 113.0 (C^{4a}), 115.5 (2CH, Ar), 123.7 (2CH, Ar), 129.3 (C, Ar), 143.2 (C, Ar), 151.2 (C^4), 153.7 (C^{8a}), 154.9 (C^2). HRMS (ESI$^+$, 70 eV), *m/z*: 271.1553 [M + H]$^+$ (calc. for $C_{15}H_{18}N_4O$, *m/z*: 271.1553).

[§] *General procedure for the preparation of bis(tetrahydroquinazolinyl)-diamines* **3a–g**. A mixture of pyrimidine *N*-oxide **1** (0.6 mmol), corresponding *N*-tetrahydroquinazolinyldiamine **2** (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 by column chromatography.

N,N'-Bis(2-methyl-1-oxido-5,6,7,8-tetrahydroquinazolin-4-yl)butane-1,4-diamine **3c**. Yield 119 mg (48%), colourless oil, R_f 0.5 (MeOH). ^{1}H NMR (400.0 MHz, $CDCl_3$) δ: 1.69–1.80 (m, 12H, 4CH$_2$, cy-Hex + 2CH$_2$, diamine), 2.42–2.48 (m, 4H, 2CH$_2$, cy-Hex), 2.55 (s, 6H, 2Me), 2.74–2.82 (m, 4H, 2CH$_2$, cy-Hex), 3.53–3.62 (m, 4H, 2C*H*$_2$NH). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ: 20.3 (2Me), 20.8 (2CH$_2$, cy-Hex), 20.9 (2CH$_2$, cy-Hex), 22.6 (2CH$_2$, cy-Hex), 24.5 (2CH$_2$, cy-Hex), 26.3 (2CH$_2$), 42.2 (2CH$_2$N), 112.7 (2C^{4a}), 152.6 (2C), 154.0 (2C), 155.4 (2C). HRMS (ESI$^+$, 70 eV), *m/z*: 413.2660 [M + H]$^+$ (calc. for $C_{22}H_{32}N_6O_2$, *m/z*: 413.2670).

[¶] *General procedure for the preparation of bis(tetrahydroquinazolinyl) diamines* **3h**,**i**. A mixture of pyrimidine *N*-oxide **1** (0.6 mmol) and *N*-tetrahydroquinazolinyldiamine **2** (0.5 mmol) in ethanol (1 ml) was microwave irradiated at 75 °C for 40 min. After cooling, the solvent was evaporated *in vacuo*, the product was isolated by column chromatography.

N,N'-Bis(2-methyl-1-oxido-5,6,7,8-tetrahydroquinazolin-4-yl)benzene-1,4-diamine **3h**. Yield 103 mg (48%), brown oil, R_f 0.63 (MeOH). ^{1}H NMR (400.0 MHz, $CDCl_3 + CD_3OD$) δ: 1.73–1.85 (m, 8H, 4CH$_2$, cy-Hex), 2.47–2.52 (m, 4H, 2CH$_2$, cy-Hex), 2.57 (s, 6H, 2Me), 2.80–2.85 (m, 4H, 2CH$_2$, cy-Hex), 7.51 (s, 4H, 4CH, Ar). ^{13}C NMR (100.6 MHz, $CDCl_3 + CD_3OD$) δ: 23.7 (Me), 24.61 (CH$_2$, cy-Hex), 24.62 (CH$_2$, cy-Hex), 26.2 (CH$_2$, cy-Hex), 28.5 (CH$_2$, cy-Hex), 117.8 (2C^{4a}), 125.8 (4CH, Ar), 138.4 (2C, Ar), 154.8 (2C^4, Ar), 158.1 (2C^{8a}), 158.8 (2C^2). HRMS (ESI$^+$, 70 eV), *m/z*: 433.2340 [M + H]$^+$ (calc. for $C_{24}H_{28}N_6O_2$, *m/z*: 433.2347).

cycles **2a**–**f** and **3a**–**f**) and the Russian Science Foundation (grant no. 17-15-01455) (synthesis of heterocycles **2g**–**i** and **3g**–**i**). TBEV sample was kindly provided by Professor Galina G. Karganova. BSL-3 facilities, virus isolation, and virus & cell collection maintenance were supported by the state research funding for Institute of Poliomyelitis and Viral Encephalitides, M. P. Chumakov Federal Scientific Center for Research and Development of Immune-Biological Products, Russian Academy of Sciences. Authors are grateful to Dr. Liubov I. Kozlovskaya for continuous support and discussions.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.11.009.

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Received: 1st June 2018; Com. 18/5596