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New adamantane-containing compounds targeting rimantadine-resistant influenza virus A/PR/8/34: molecular design, synthesis and SAR study

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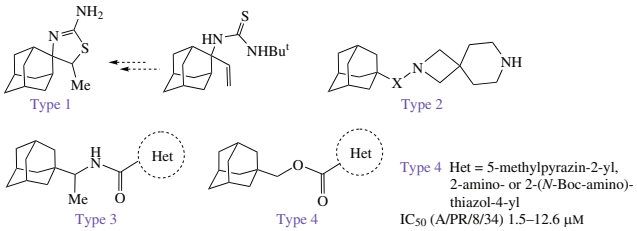
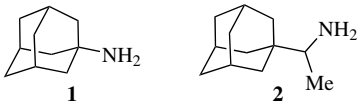
Four types of adamantane-containing compounds were designed by modifying molecules with proven activity against resistant influenza A viral strains or mutated M2 channel of the virion envelope. Three series were obtained, excluding 5′-methyl-5′*H*-spiro[adamantane-2,4′-thiazol]-2′-amine, since no intramolecular cyclization of 1-*tert*-butyl-3-(2-vinyladamantan-2-yl)thiourea occurred in the reaction with HBr or bromine. 2,7-Diazaspiro[3.5]nonane comprising derivatives of adamantane and new series of rimantadine amides have manifested high cytotoxicity, while acceptable selectivity was observed for ester analogues of the latter, and three novel esters demonstrated potent antiviral activity (IC_{50} = 1.5–12.6 μM *vs*. 67 μM for rimantadine) against the rimantadine-resistant influenza virus A/PR/8/34.



Keywords: adamantane derivatives, spiro compounds, isothioureas, heterocyclization, molecular docking, rimantadine resistant influenza virus, structure–activity relationship (SAR).

Design of new antiviral agents is complicated by the emergence of drug resistance in viruses. Thus, the vast majority of influenza A viruses are currently resistant to the action of amantadine **1** and rimantadine **2**, blockers of proton transport through ion channels formed by the wild type (WT) M2 protein of the virion envelope.[1–3] Despite attempts to overcome this problem, both by scaffold replacement and/or other modifications in molecules **1** and **2**, the development of drugs that are not susceptible to the resistance mechanisms remains a challenge (see reviews[3–9] and some recent examples[10–16]). Rational design of such compounds is complicated, because the data on the role of possible binding regions in M2 protein of inhibitors of resistant viral strains is constantly being refined (for details, see ref. 17 and citations therein). The activity of the most potent current M2 channel inhibitors of resistant virus strains is in the one- or two-digit micromolar concentration range, and only a few compounds have an acceptable toxicological profile.[3–16] Under these circumstances, the accumulation and analysis of new SAR data take on special significance. In the present work, for such a study, we proposed several different structural types of adamantane-containing compounds obtained by modifying molecules with proven activity against resistant viral strains or mutated M2 channel (Figures 1–3).



1 **2**

Based on the data on the high activity of spirane **3** against the WT influenza A virus[18] and the proven blocking of the S31N M2 channel of the mutant virus for compound **4**,[17] we proposed a hybrid structure **5** (see Figure 1). The results of computer molecular docking performed as described earlier[19–21] (see Online Supplementary Materials, Figure S1) predict efficient interaction of spirane **5** with both rimantadine binding sites, main and peripheral, of the S31N M2 mutant channel, which is in accordance with the new methodology of the design of its inhibitors according to data reported.[17]

Fragments of spiranes **6**, **7** (known M2 WT channel blockers[22,23]) were used in the design of a conformationally restricted analogue of compound **8**[24] capable of inhibiting both WT and rimantadine-resistant S31N M2 mutant channels (see

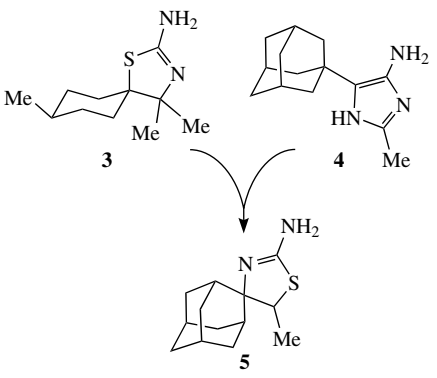


Figure 1 Proposed structural hybrid of molecules **3** and **4** – compound **5**.

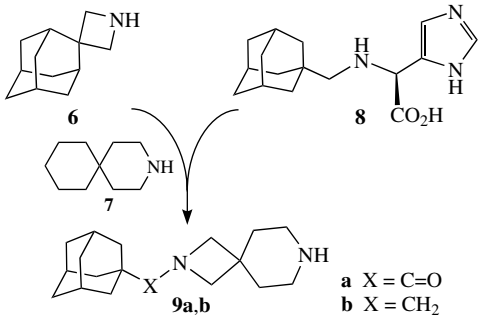


Figure 2 Structures of known molecules **6**,[22] **7**,[23] **8**[24] and spiranes **9a**,**b** obtained in this work.

Figure 2). In the proposed molecules **9a**,**b** their overall length and the distance between the adamantane residue and the terminal basic nitrogen atom are close to those of molecule **8**. Molecular modeling predicts a favorable location of both compounds **9a**,**b** (regardless of the basicity of the central nitrogen atom) in the main and peripheral binding sites of rimantadine in S31N M2 mutant channel (see Figures S2 and S3).

The structures of two other series of putative antivirals were proposed on the basis of data[25–27] that a modification of the primary amine of amantadine or rimantadine in some cases resulted in potent activity against the S31N mutation. In our previous work,[27] SAR study for compounds of general formula **10** and **11** revealed a clear dependence on the linker length (amides **10a–c** are more active than their homologs **11a–c**) and on the position of the nitrogen atom in the pyridine ring. To further study the influence of lipophilicity, basicity of nitrogen atoms and other characteristics on activity, it seemed logical to obtain broad series of isosteric analogs of molecules **10** and **11**. In the present work, we studied several rimantadine amides containing substituted and unsubstituted aromatic heterocycles with two heteroatoms of general formula **12**. A similar series of non-chiral molecules with ester linker (structural type **13**) was also proposed for synthesis (see Figure 3).

To obtain the target spirane **5**, it was planned to use the previously elaborated preparatively convenient procedure for intramolecular cyclization of cycloalkenylthioureas.[28–31] For this purpose, compound **14** (obtained from adamantan-2-one according to the method reported[32]) was converted to the hydrochloride of 2-vinyladamantane-2-amine **15** and then transformed to thiourea derivative **16** (Scheme 1). The latter was treated with HBr to anticipate the intramolecular cyclization (*cf.* ref. 28); unfortunately, no conversion of the original substrate was observed. An attempt to carry out the reaction with bromine[28] led to highly complex mixture of products, in which no product

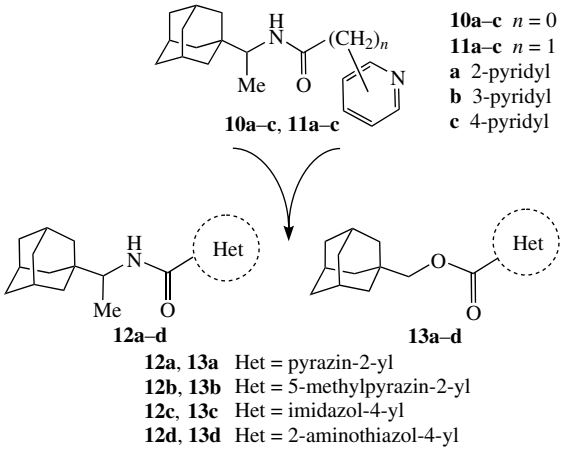
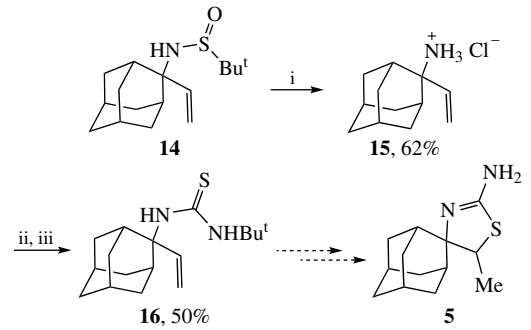


Figure 3 Structures of series **12** and **13**.



Scheme 1 *Reagents and conditions*: i, HCl·dioxane, 0–20 °C, 10 min; ii, $CSCl_2$, $NaHCO_3$, H_2O, EtOAc, 3–20 °C, 30 min; iii, Bu^tNH_2, EtOAc, 20 °C, 12 h.

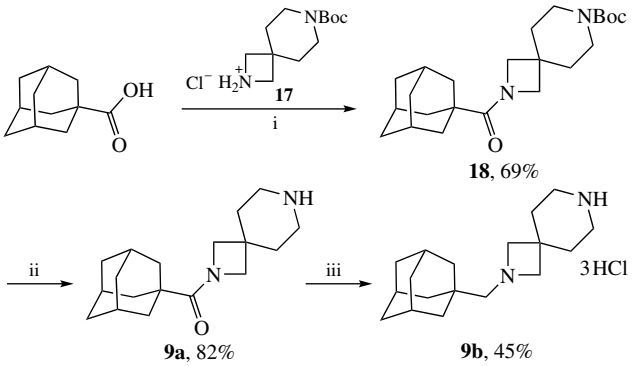
of intramolecular cyclization (the precursor of target molecule **5**) was detected. Thus, unlike similar *N*-*tert*-butyl-*N*-(cyclohex-2-en-1-yl)thioureas,[28] the bulkier adamantane analog did not undergo the transformation, and the synthesis of 5′-methyl-5′*H*-spiro[adamantane-2,4′-thiazol]-2′-amine **5** requires another synthetic scheme.

The target compounds **9a**,**b** were synthesized *via* the amidation of adamantane-1-carboxylic acid with commercially available spirocyclic amine hydrochloride **17** using DIPEA/EDCI/DMAP system (Scheme 2). The obtained amide **18** was further deprotected and neutralized to the free base **9a**. Reduction of the latter gave 2-(adamantan-1-ylmethyl)-2,7-diazaspiro[3.5]-nonane **9b** as trihydrochloride.

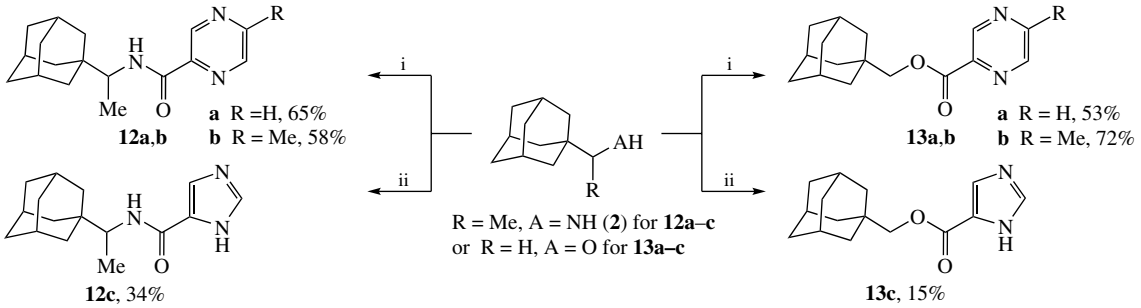
The synthesis of heterocyclic derivatives of rimantadine **2** and 1-adamantylmethanol was carried out by standard amidation or esterification of the corresponding acids using various carbodiimides (Scheme 3). Pyrazine-containing compounds **12a**,**b** and **13a**,**b** were obtained in the presence of EDCI/DMAP in acceptable yields. Similar reactions for imidazole-4-carboxylic acid using the DCC/DMAP or EDCI/DMAP systems did not occur, but with the use of HBTU/*N*-methylmorpholine (NMM) the target products **12c** and **13c** were obtained, albeit with low yields.

Aminothiazole derivatives **12d** and **13d** were prepared in good yields from 2-(*tert*-butoxycarbonylamino)thiazole-4-carboxylic acid **19**[33] with the use of EDCI/DMAP and DDC/DMAP systems, respectively, followed by deprotection and neutralization of the intermediate compounds **20** and **21** (Scheme 4).

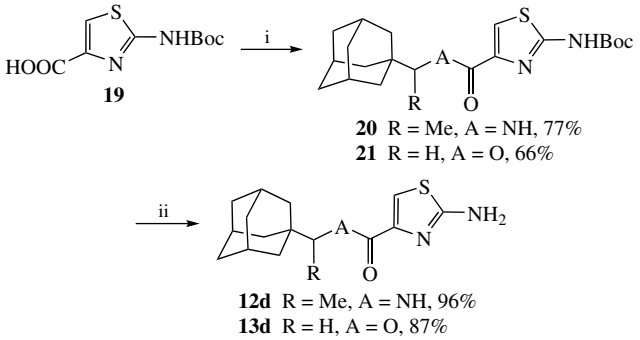
Primary screening of the antiviral activity of amide **9a**, amine **9b** (as trihydrochloride), amides **12a–d** (as racemates), esters **13a–d** and synthetic precursors **18**, **20** (as racemate) and **21** was carried out on the rimantadine-resistant strain of influenza virus A/Puerto Rico/8/34(H1N1) by assessing the cytoprotective



Scheme 2 *Reagents and conditions*: i, EDCI, DIPEA, DMAP (cat.), 20 °C, 16 h; ii, CF_3COOH, CH_2Cl_2, 20 °C, 16 h, then $NaHCO_3$ (sat.), H_2O; iii, $LiAlH_4$, THF, 20 °C, 16 h, then NaOH (15% aq.), then HCl (5% in EtOH), Et_2O.



Scheme 3 *Reagents and conditions*: i, pyrazine-2-carboxylic acid (for **12a** and **13a**) or 5-methylpyrazine-2-carboxylic acid (for **12b** and **13b**), DCC, DIPEA (for **12a**,**b**), DMAP (cat.), CH_2Cl_2, 20 °C, 24 h; ii, imidazole-4-carboxylic acid, HBTU, NMM, DMF, 20 °C, 24 h.



Scheme 4 *Reagents and conditions*: i, rimantadine, EDCI, DIPEA, DMAP (cat.) (for **20**) or 1-adamantylmethanol, DCC, DMAP (for **21**), CH_2Cl_2, 20 °C, 16 h; ii, TFA, CH_2Cl_2, 20 °C, 16 h, then $NaHCO_3$ (aq.).

activity with detection of the cytopathic effect using the MTT reagent on MDCK (dog kidneys) cells (for description of the procedures, see refs. 34, 35 and Online Supplementary Materials). Rimantadine **2** and its amides **10a–c** (see Figure 3)[27] were used as control compounds (to note, the activity and cytotoxicity of the latter were studied using resistant A/Puerto Rico/8/34(H1N1) virus,[27] which determined the choice of this strain in the present work). Activity against influenza virus was expressed as the concentration at which 50% inhibition of virus propagation in MDCK cells occurs (IC_{50}) and cytotoxicity was expressed as the concentration of a compound resulting in a 50% reduction in cell culture viability (CC_{50}). Selectivity index (SI) was calculated as the ratio of CC_{50} to IC_{50}. The results are shown in Tables 1 and 2 (for clarity of the SAR analysis, see also Tables S1 and S2).

As can be seen from Table 1, the IC_{50} values for adamantane-containing spirocyclic amide **9a** and its amine analogue **9b** are in the low micromolar concentration range. However, it is difficult to unambiguously interpret these data as a greater antiviral activity compared to rimantadine due to the high toxicity (lack of selectivity) of compounds **9a**,**b**. This fact was not expected, since there is evidence that incorporating spiro diamine motifs can reduce the cytotoxicity of the resulting molecules,[36] and, in addition, lead compound **6** (see Figure 1) has a very good toxicological profile.[22]

In the series **12a–d**, **13a–d** and **20**, **21**, three compounds with IC_{50} values about 10 μM were identified and several

Table 1 Antiviral activity and cytotoxicity of spiranes **9a**,**b** and **18**.

Compound	Influenza virus H1N1, IC_{50}[a]/μM	MDCK CC_{50}[a]/μM	SI
9a	12.8 ± 1.1	16.6 ± 1.4	1
9b[b]	4.4 ± 0.4	4.6 ± 0.4	1
18	84.9 ± 7.2	150 ± 12	2
2	67 ± 6	400 ± 20	6

[a]Mean values ± SD from two independent experiments. [b]As trihydrochloride.

Table 2 Antiviral activity and cytotoxicity of new rimantadine and 1-adamantylmethanol derivatives.

Compound	Influenza virus H1N1, IC_{50}[a]/μM	MDCK CC_{50}[a]/μM	SI	Compound	Influenza virus H1N1, IC_{50}[a]/μM	MDCK CC_{50}[a]/μM	SI
12a	38.5 ± 3.1	110 ± 10	3	**13a**	>400	>400	–
12b	36.7 ± 2.8	73.5 ± 6.1	2	**13b**	12.6 ± 1.0	105 ± 8	8
12c	>400	>400	–	**13c**	46.5 ± 3.3	400 ± 16	8
12d	36.0 ± 2.9	64.8 ± 5.2	2	**13d**	3.4 ± 0.2	15.7 ± 1.1	5
20	81.4 ± 6.9	210 ± 8.4	3	**21**	1.5 ± 0.1	8.5 ± 0.3	6
10a[27]	13	83	6	**10c**[27]	7.7	>1000	>130
10b[27]	100	>1000	>10	**2**	67 ± 6	400 ± 20	6

[a]Mean values ± SD from two independent experiments (literature mean values for compounds **10a–c** are given for comparison).

interesting structure–activity relationships were revealed (Table 2).

The IC_{50} value of pyrazine derivative **12a** is intermediate between those of pyridine prototypes **10a** and **10b**,[27] while SI value decreased noticeably. Both the replacement of the pyrazine ring in compound **12a** with an imidazole residue (**12c**) and the modification of the linker (**13a**) lead to a loss of activity. This clearly demonstrates that not only the basicity but the suitable location of at least one nitrogen atom in the protein is important in providing antiviral properties. With the exception of the pair **12a**–**13a**, the activity (and selectivity) of 1-adamantylmethanol esters is higher than that for the corresponding rimantadine derivatives (see Table 2). In addition to the differences in molecular shape, the achirality of compounds **13** may contribute to an increase in antiviral effect.

Noteworthy is a sharp rise in activity in the pair **13a** → **13b**, which is achieved by addition of methyl group at the pyrazine cycle (see Table 2). Another active compound with a substituent in the aromatic ring is aminothiazole derivative **13d** (slight decrease in selectivity may be due to the ability of aminothiazole group to form toxic metabolites in cells[37]). The *tert*-butyloxycarbonylated analogue of **13d**, compound **21**, also exhibits very high activity with an IC_{50} value forty times lower than that of rimantadine **2** and five times lower than that for amide **10c**, although with less SI compared to the latter. If, according to the original logic of structural design, the high antiviral activity of compounds **13d** and **21** is associated with blocking the S31N-mutant M2 channel of the rimantadine-resistant influenza virus, then the endocyclic nitrogen atom appears to play an important role in this, since the exocyclic nitrogen atom in compound **21** is not basic. Obviously, other factors may also affect the inhibition of mutant M2 channel, and different molecular targets of antiviral action of the new compounds cannot be excluded. Additional studies of the viroporin activity and the stage of intervention to virus life cycle are required for elucidation of the exact mechanism of antiviral action of the obtained esters.

In general, to address the rimantadine resistance problem, in the present work we have proposed four structural types of adamantane-containing compounds. Three series were obtained and the primary screening demonstrated that adamantane derivatives with 2,7-diazaspiro[3.5]nonane group and new rimantadine amides turned out to be cytotoxic to infected and uninfected cells. An acceptable selectivity was observed for ester analogs of the latter, for which several interesting structure–activity relationships were revealed. Three novel esters **13b**, **13d** and **21**, which are achiral, structurally simple and exhibit potent antiviral activity against the rimantadine-resistant influenza virus A/PR/8/34, are promising for further research. A more detailed understanding of the exact mechanism of the antiviral action of these esters, as well as our previously obtained amide of rimantadine **10c** with a good toxicological profile[27] will allow to understand more accurately the observed structure–activity relationships, which is important for the development of more potent inhibitors of the rimantadine-resistant influenza virus.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7570.

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