New adamantane derivatives containing monoterpene fragments in their structure and investigation of their antipox activity

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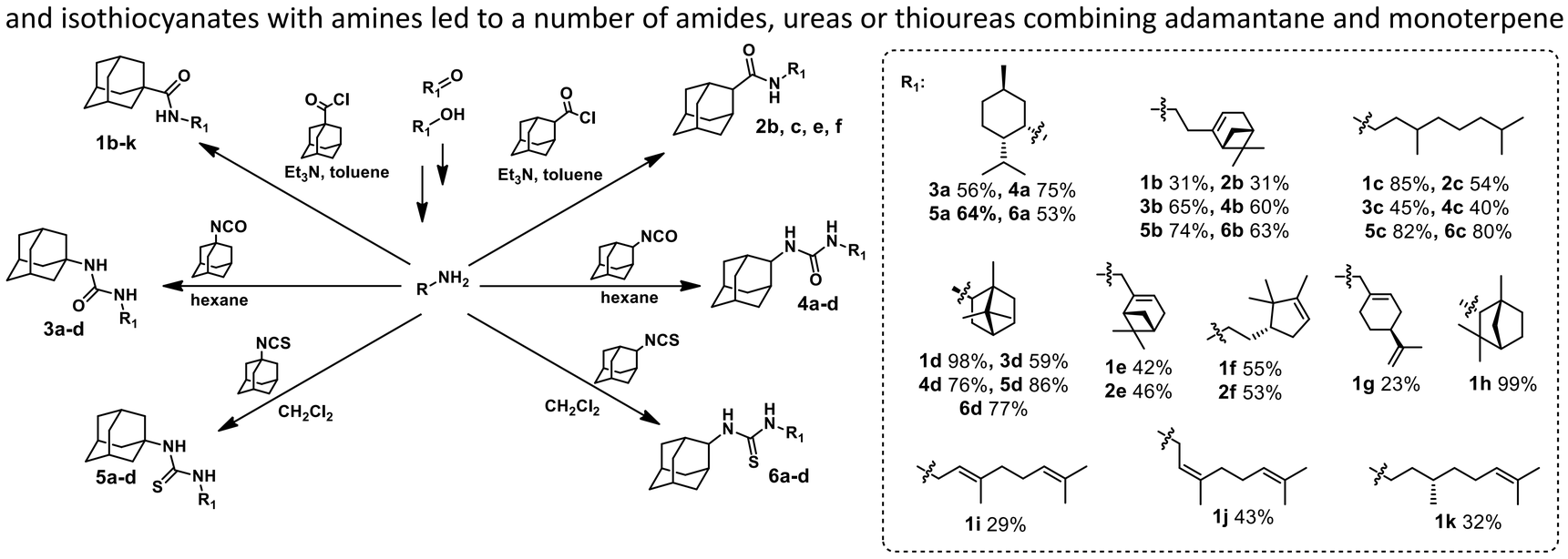
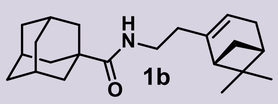
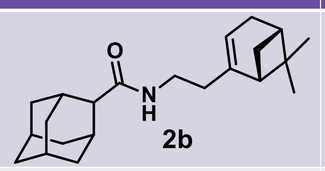
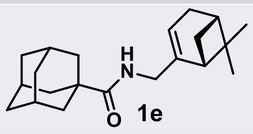
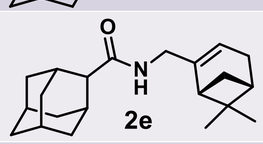
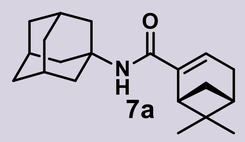
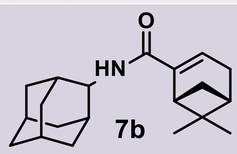
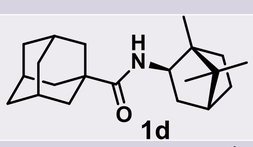
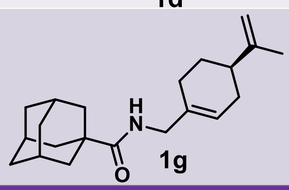
Since, WHO declared eradication of natural smallpox in 1980, Independent Advisory Group on Public Health Implications of Synthetic Biology Technology Related to Smallpox report to the WHO Director-General noted the need to continue developing new low molecular weight agents against variola virus because of a number of reasons, such as discounted vaccination, possibility of smallpox spreading from permafrost solid, bioterrorism, potential danger of other orthopoxviruses circulating in animal population [1].

Despite a number of adamantane derivatives is known to demonstrate antiviral activity, only few adamantane derivatives showed activity against vaccinia virus [2]. On the other hand, monoterpene derivatives demonstrate various biological activities, in particular some camphor derivatives were found being active against vaccinia virus [3]. To find new agents to be active against orthopoxviruses we synthesized a different adamantane derivatives containing monoterpene fragments in their structure [4, 5]. For this purpose a wide number of monoterpene amines was obtained starting from corresponding alcohols or carbonyl compounds. Isocyanates, isothiocyanates containing 1- or 2- substituted adamantane fragment were obtained as well. Combination of carboxylic acids chlorides or isocyanates and isothiocyanates with amines led to a number of amides, ureas or thioureas combining adamantane and monoterpene fragments in their structure.



Amides **1b-k**, **2b,c,e,f**, **7a,b, 8a,b**, **9a,b** were tested against vaccinia virus, it was shown that the derivatives of bicyclic (pinene and bornane) monoterpenes possess a most potent antipox activity. For derivatives **1b**, **1e**, **2b**, **2e**, **7b** antiviral activity against cowpox virus and ectromelia virus was shown as well.

Compound	CC_{50}, μM	IC_{50}, μM	SI	Compound	CC_{50}, μM	IC_{50}, μM	SI
 1b	750.2±84.6	1.8±0.2	417	 2b	372.5±97.7	4.4±0.1	85
 1e	1908.6±101.4	1.7±0.2	1123	 2e	1225.9±143.9	4.6±0.2	267
 7a	7.9±0.9	0.7±0.1	11	 7b	811.5±110.5	2.5±0.1	325
 1d	316.7±39.3	10.6±0.7	30	**Cidofovir**	475.3±30.1	40.0±1.2	12
 1g	319.0±39.6	12.3±0.8	26	**Tecovirimat**	1276±202	0.01±0.003	127600

Compound	CC_{50}, μM (M±SD, n=3)	cowpox virus		ectromelia virus	
		IC_{50}, μM (M±SD, n=3)	SI	IC_{50}, μM (M±SD, n=3)	SI
1b	750.2±84.6	4.1±0.6	183	1.6±0.6	469
1e	1908.6±101.4	4.7±0.2	406	2.7±0.2	707
2b	372.5±97.7	12.5±0.1	30	9.5±0.1	39
2e	1225.9±143.9	15.0±0.2	82	12.6±0.2	97
7b	811.5±110.5	7.2±0.2	113	1.7±0.2	477

CC_{50} is the cytotoxic concentration causing 50% cell death in an uninfected monolayer; IC_{50} is the inhibitory concentration ensuring 50% cell survival in a virus-infected monolayer; as M ± SD, where M is the mean, and SD is the standard deviation; n = 3 is the number of CC_{50} and IC_{50} measurements; SI is the drug selectivity index (CC_{50}/IC_{50})

References:
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