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Synthesis and antiviral activity of novel 3-substituted pyrazolinium salts

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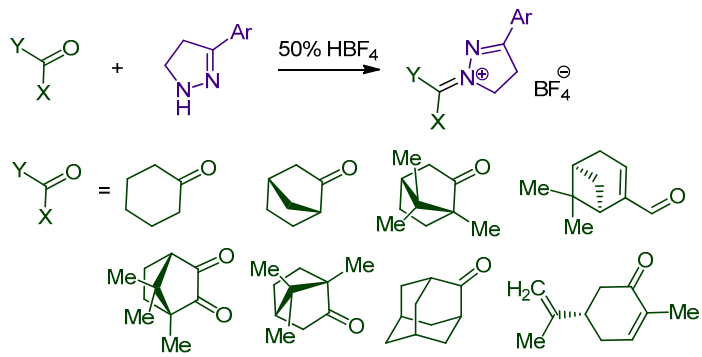


For the first time, convenient methods for the preparation of pyrazoline *N*-alkylidene salts based on terpene (camphor, camphorquinone, carvone) ketones, cage (adamantanone and norcamphor) ketones, and natural aldehydes (carvone and myrtenal) allowing the isolation of stable pyrazolinium salts in individual form were proposed. Optimization of the conditions for the synthesis of the target products was carried out. The antiviral activity of the synthesized salts was studied; among the tested compounds 1-bornylidene-3-phenylpyrazolinium tetrafluoroborate (IC_{50} 6.2 μM, SI 107) exhibited the greatest activity against influenza A/Puerto Rico/8/34 (H1N1) virus.

Keywords: adamantanone, camphor, camphorquinone, carvone, myrtenal, norcamphor, 2-pyrazoline, antiviral activity, influenza A (H1N1) virus.

Heterocyclic derivatives of natural carbonyl compounds are of great interest for organic and medicinal chemistry. Terpene aldehydes and ketones are isolated from natural sources in the form of individual stereoisomers with a known configuration, which makes it possible to use the derivatives obtained on their basis as chiral ligands[1] and organocatalysts.[2] Quite often, chemical modification and, in particular, the introduction of an N-heterocyclic fragment or an additional nitrogen-containing functional groups increases the biological activity of natural compounds. For example, natural camphor does not possess antiviral properties. However, its reaction with aminoethanol leads to the formation of imine **I**, which is highly active against a wide range of influenza A virus strains (H1N1, H3N2, H5N2) and influenza B virus and has low toxicity[3] (Fig. 1). Pyrazoles **II** and pyrazolones **III**, obtained from camphor (Fig. 1) and adamantanone (compound **IV**), are inhibitors of 11β-hydroxysteroid dehydrogenase type 1, an enzyme responsible for the direct and reverse conversion of cortisone to cortisol,[4] while tetrazolopyrimidines with a camphor fragment (e.g., compound **V**) are CNS stimulants.[5]

The combination of the (+)-camphor cage moiety with the isoxindole ring revealed effective inhibitors of orthopoxviruses,[6] including variola virus,[7] and viruses that cause hemorrhagic fever with renal syndrome.[8] (+)-Camphoric

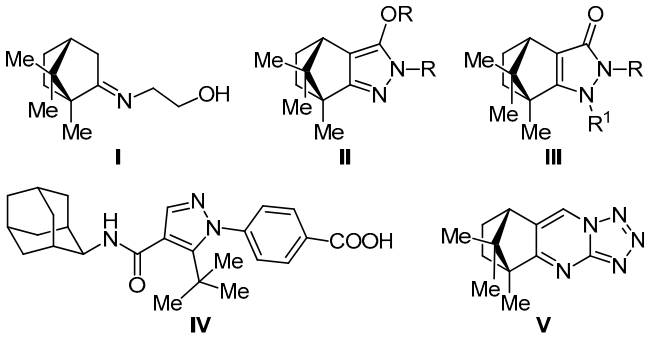


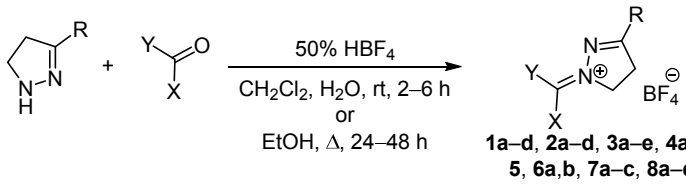
Figure 1. Nitrogen-containing and heterocyclic compounds **I**–**V** based on (+)-camphor and adamantanone.

acid based cyclic imides were active against flaviviruses,[9] nitrogen-containing polycyclic compounds based on this natural acid exhibited activity against influenza A (H1N1) virus.[10] Direct amination of camphor with secondary amines in the presence of $Fe(CO)_5$ leading to a mixture of *exo*/*endo* isomers was described;[11] it was shown that the reactions of natural cage ketones with *ortho*-substituted anilines occur with the cleavage of the natural framework.[12] Thus, the modification of natural ketones with nitrogen-containing groups and the study of the antiviral activity of the obtained heterocyclic compounds is one of the urgent directions in the field of organic and medicinal chemistry.[13]

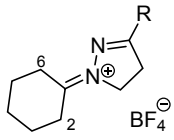
Enamines, which are formed by the reaction of secondary amines with carbonyl compounds, are widely employed in organic synthesis. The use of equivalent amounts of ammonium salts of strong non-nucleophilic acids as catalysts in the reactions of amines with C=N electrophiles leads to the formation of stable iminium salts.[14] It is known that the reaction of cyclic hydrazones, *NH*-unsubstituted 4,5-dihydro-1*H*-pyrazoles (2-pyrazolines), which are effectively secondary amines, with aromatic and heteroaromatic aldehydes leads to the formation of pyrazolinium salts.[15] The resulting arylidene salts are important synthons in organic reactions;[16] however, they are usually used in further chemical transformations without identification or isolation as individual substances. Analysis of the literature data showed that until now pyrazolinium salts based on natural and cage ketones have not been obtained. In this work, we proposed for the first time convenient preparative methods for the synthesis of pyrazoline alkylidene salts based on terpene ketones (camphor, camphorquinone, menthone, carvone), cage ketones (adamantanone and norcamphor), and natural aldehydes (carvone and myrtenal), which make it possible to isolate stable pyrazolinium salts in individual form (Scheme 1).

We started the development of the method by using mono-, bi-, and tricyclic ketones. Thus, we were the first to isolate and characterize *N*-alkylidenepyrazolinium salts **1a**–**d** by the reaction of cyclohexanone with 3-aryl-2-pyrazolines in CH_2Cl_2 (Scheme 1). The reaction proceeded under mild conditions (vigorous stirring in the CH_2Cl_2–H_2O two-phase system at room temperature) and led to the formation of 1-cyclohexylidene-3-arylpyrazolinium tetrafluoroborates **1a**–**d**.

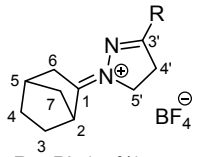
Scheme 1. General scheme for obtaining pyrazolinium salts **1a**–**d**, **2a**–**d**, **3a**–**e**, **4a**–**e**, **5**, **6a**,**b**, **7a**–**c**, **8a**–**d**



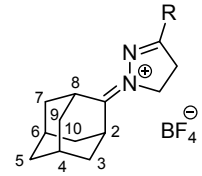
1a–**d**, **2a**–**d**, **3a**–**e**, **4a**–**e**, **5**, **6a**,**b**, **7a**–**c**, **8a**–**d**



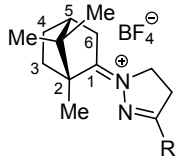
1a R = Ph (73%)
b R = 4-$MeOC_6H_4$ (52%)
c R = 4-ClC_6H_4 (38%)
d R = 4-MeC_6H_4 (44%)



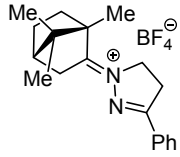
2a R = Ph (77%)
b R = 4-$MeOC_6H_4$ (65%)
c R = 4-ClC_6H_4 (49%)
d R = 4-MeC_6H_4 (33%)



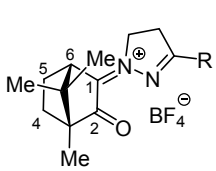
3a R = Ph (92%)
b R = 4-$MeOC_6H_4$ (47%)
c R = 4-ClC_6H_4 (51%)
d R = 4-MeC_6H_4 (56%)
e R = Me (78%)



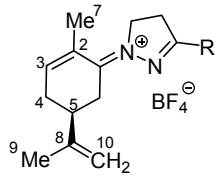
4a R = Ph (58%)
b R = 4-$MeOC_6H_4$ (54%)
c R = 4-ClC_6H_4 (45%)
d R = 4-MeC_6H_4 (30%)
e R = Me (68%)



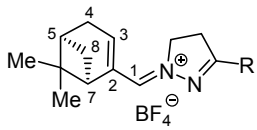
5 (89%)



6a R = Ph (76%)
b R = Me (82%)



7a R = 4-$MeOC_6H_4$ (28%)
b R = 4-ClC_6H_4 (22%)
c R = 4-MeC_6H_4 (31%)



8a R = Me (36%)
b R = 4-$MeOC_6H_4$ (27%)
c R = 4-ClC_6H_4 (29%)
d R = 4-MeC_6H_4 (15%)

In the high-resolution mass spectra in the positive ion mode of all the obtained products **1a**–**d**, peaks corresponding to the cationic fragments of the obtained compounds are recorded, whereas in the negative ion mode, the peaks of the tetrafluoroborate anion were registered. The IR spectra contain absorption bands characteristic of the C=N and C=N$^+$ bonds at 1594–1600 and 1641–1656 cm^{-1}. In the ^{1}H NMR spectra of compounds **1a**–**d**, the signals of the 2(6)-CH_2 protons of the cyclohexanone fragment are observed at 2.85–2.86 and 3.20–3.23 ppm, whereas the ^{13}C NMR spectrum reveals the signals of the C-1 atom of the cyclohexanone and C-3' atom of pyrazoline fragments at 174.4–176.0 and 180.9–183.6 ppm, respectively. The use of pyrazolines with substituents at position 5 (3,5,5-trimethyl-2-pyrazoline or 3-methyl-5-phenyl-2-pyrazoline) in this reaction did not lead to the formation of the target alkylidene salts.

The preparation of pyrazolinium salts **2a**–**d**, **3a**–**e** in reactions with cage ketones (norcamphor, adamantan-2-one) required a different solvent. The use of EtOH made it possible to increase the reaction temperature. The formation of the products (precipitation) began almost immediately; however, heating in EtOH under reflux was continued for 24 h to ensure the completeness of the process. In the ^{1}H NMR spectra of norcamphor derivatives **2a**–**c**, a doubled set of signals is observed, which indicates the formation of geometric *E*- and *Z*-isomers. In this case, the signals of the *ortho* protons of the aromatic substituent in the spectra of compounds **2a**–**c** lose their equivalence and are recorded in the form of adjacent doublets of equal intensity. In the ^{13}C NMR spectrum, for compound **2c** doubling of all, and for compound **2a**, *ortho*-aromatic, proton signals are also recorded.

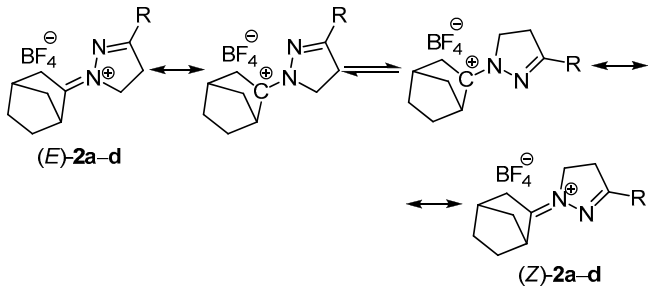
With an increase in the recording temperature to 60°C, both signal doubling and separation of the signals of aromatic *ortho* protons disappear, which indicates a facile transformation of the geometric isomers of the formed compounds into each other (Scheme 2).

The formation of adamantane derivatives **3a**–**e** takes place in the CH_2Cl_2–H_2O two-phase system in 30–50 min with good yields. The precipitation of products **3a**–**e** occurs immediately upon cooling the reaction mixture, which makes these reactions preparatively convenient.

For even more sterically hindered ketones (*R*,*R*)-(+)- and (*S*,*S*)-(–)-camphor, the reaction was carried out in EtOH with a twofold excess of 50% HBF_4. Increasing the reaction time to 48 h made it possible to obtain the target products **4a**–**e**, **5** in up to 89% yields (Scheme 1). In the ^{1}H NMR spectrum of compound **4c**, as in the ^{1}H NMR spectra of compounds **2a**–**d**, a doubling of signals due to the formation of both possible geometric *E*- and *Z*-isomers is observed.

The reaction of *NH*-unsubstituted 2-pyrazolines with camphorquinone proceeds in EtOH without heating. The formed salts **6a**,**b** precipitate from the reaction mixture within 20–30 min. The reaction proceeds regioselectively at the more accessible carbonyl group in position 3 of the bornane skeleton leading to the formation of compounds **6a**,**b**. The ^{1}H NMR spectra of these compounds contain

Scheme 2. Inversion of *E*–*Z* isomers of compounds **2a**–**d**



signals of the protons of the pyrazoline ring at 3.37–5.13 ppm. The upfield shift of the signals of the methyl group at the C-3* atom of compound **6a** (0.98 ppm), as compared to the signals of the corresponding carbon atom in the spectrum of salt **4a** (1.48 ppm), confirms the regioselectivity of the reaction. The ^{13}C NMR spectrum of product **6a** retains the signal of the carbonyl carbon atom C-2 at 197.7 ppm. The IR spectrum of this compound exhibits the characteristic intense band of vibrations of the carbonyl group at 1755 cm^{-1}. The most sterically hindered terpenoid, fenchone, containing three methyl substituents adjacent to the carbonyl group, does not react with *NH*-unsubstituted pyrazolines: even with prolonged heating under reflux in BuOH, only the tetrafluoroborate salt of 3-phenylpyrazoline was isolated from the reaction mixture.

Reactions with unsaturated aldehyde myrtenal and ketone carvone also occur in the CH_2Cl_2–H_2O two-phase system. As a result, salts **7a**–**c** (carvone derivatives) and **8a**–**d** (myrtenal derivatives) were obtained containing a terpenoid substituent at position 1 of the pyrazoline ring, as well as donor and acceptor substituents in the aromatic ring (Scheme 1). The low yields in these reactions, apparently, are caused by the fact that the target compounds were unstable and strongly resinified both during the reaction and during the isolation process. In all cases, the reactions of 1,3-unsaturated carbonyl natural compounds with *NH*-unsubstituted pyrazolines proceed regioselectively at the carbonyl group, without affecting the conjugated C=C double bond. This is confirmed by the presence of a signal at 6.94 ppm corresponding to a proton at the conjugated double bond in the spectra of ketone derivatives **7a**–**c** and signals of protons 3-CH and 1-CH at 7.51–7.66 and 8.44–8.54 ppm, respectively, in the spectra of aldehyde derivatives **8a**–**d**.

We performed a preliminary *in vitro* assessment of the antiviral action of some of the compounds obtained in this work against influenza A (H1N1) virus (Table 1). For comparison, data are given for the clinically used antiviral drug rimantadine, which has a cage structure. Among the tested compounds, compound **4a**, which is 1-bornylidene-3-phenylpyrazolinium tetrafluoroborate based on (+)-camphor, showed the greatest activity against influenza A/Puerto Rico/8/34 (H1N1) virus (IC_{50} 6.2 μM, SI 107). At the same time, its stereoisomer **5**, synthesized by us on the

* The numbering of the atoms in the bornyl fragment in the description of the spectra is carried out by analogy with other cyclic ketones: the atom bonded to the pyrazoline ring is designated as C-1.

basis of (–)-camphor, showed no activity at all. A pronounced antiviral activity was also found for compounds **1a**, **3b**, **7c** based on cyclohexanone, adamantanone, and norcamphor. Compound **4e** containing a methyl substituent in the pyrazoline ring was the least toxic among the (+)-camphor derivatives, and its half-maximal inhibitory concentration was 41 μM. It should be noted that, on the whole, the obtained compounds are of low toxicity, with the exception of compounds **1c** and **4c**, which contain a chlorine atom in the aromatic ring. The toxicity of pyrazolinium salts based on carvone was also higher compared to similar substances, but lower than that of the reference drug.

Our data on the biological properties of the synthesized compounds make it possible to conclude that further pharmacological studies of compound **4a** are promising and that it is important which enantiomer of the natural compound is used in the synthesis.

To conclude, we have obtained for the first time and characterized in an individual form pyrazolinium salts based on cyclic and cage ketones, including natural ones, which are of interest not only as intermediates for subsequent synthetic transformations, but also exhibiting activity against the influenza A (H1N1) virus, which makes further studies of the obtained compounds and their analogs and modification of their structure to obtain pharmacologically optimal products promising.

Table 1. Activity of the obtained compounds **1a–d**, **2a**,**b**,**d**, **3a–e**, **4a–c**,**e**, **5**, **7a–c**, and **8a–d** against influenza A/Puerto Rico/8/34 (H1N1) virus

Compound	CC_{50},* μM	IC_{50},** μM	SI***
1a	>950	60.5 ± 5.2	16
1b	>900	122 ± 10	7
1c	132 ± 8	86 ± 11	2
1d	>915	128 ± 15	7
2a	>920	110 ± 13	8
2b	>850	467 ± 41	2
2d	>880	580 ± 59	1
3a	>820	112 ± 13	7
3b	>760	27 ± 2.4	26
3c	>750	425 ± 49	1
3d	>790	344 ± 28	2
3e	>980	259 ± 29	4
4a	665	6.2 ± 1.1	107
4b	275	68 ± 12	4
4c	108 ± 5	77 ± 6	1
4e	660	41 ± 4	15
5	>820	385 ± 29	2
7a	196	37 ± 2.8	5
7b	202	82 ± 11	2
7c	218	13 ± 2	16
8a	430	40 ± 3	10
8b	207	80 ± 9.5	2
8c	750	45 ± 3.4	16
8d	210	84 ± 8.2	2
Rimantadine	51 ± 4	10 ± 2	5

* CC_{50} – half-maximal cytotoxic concentration, that is, the concentration of the test substance causing the death of 50% of the cells.
** IC_{50} – half-maximal inhibitory concentration, that is, the concentration of the test substance causing 50% inhibition of viral replication.
*** SI – selectivity index CC_{50}/IC_{50}.

Experimental

IR spectra were registered on a UR-20 spectrometer in petroleum jelly. ^{1}H and ^{13}C NMR spectra were acquired on an Agilent 400 MR spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ or DMSO-d_6, using the residual solvent signals (7.24 (^{1}H) and 77.0 (^{13}C) ppm for $CDCl_3$ and 2.50 (^{1}H) and 39.5 (^{13}C) ppm for DMSO-d_6) as internal standard. The NMR signals were assigned by analogy with the structures of similar compounds described in the literature. High-resolution mass spectra were recorded on an Agilent 7200 Accurate Mass Q-TOF mass spectrometer in full scan mode in *m*/*z* 0–500 range, EI ionization (70 eV) with direct sample introduction, as well as on a Bruker maXis device by electrospray ionization. Elemental analysis was performed on a Carlo Erba ER-20 CHN-analyzer. Monitoring of the reaction progress and assessment of the purity of synthesized compounds were done by TLC on a fixed layer of silica gel (Merck, Silufol plates, eluent PhH–EtOAc, 4:1).

The solvents used in the experiments were purified and absolutized according to routine methods.

Synthesis of alkylidene salts of pyrazolines 1a–d, 7a–c, 8a–d (General method). 50% Aqueous HBF_4 (0.25 ml/mmol) was added dropwise to a vigorously stirred solution of 3-arylpyrazoline in CH_2Cl_2 (10 ml). An equimolar amount of aldehyde or ketone was added in portions with stirring to the resulting salt solution. Stirring was continued for 2–6 h. The precipitated crystals were filtered off, washed with H_2O to pH 7, then with Et_2O. If no salt precipitation occurred, the organic layer was separated, washed with H_2O to pH 7, and concentrated to dryness. Upon addition of a small amount of EtOH, the salt crystallized.

Synthesis of alkylidene salts of pyrazolines 2a–d, 3a–e, 4a–e, 5, 6a,b (General method). 50% Aqueous HBF_4 (0.25 ml/mmol) was added dropwise to a vigorously stirred solution of 3-arylpyrazoline in EtOH (10 ml). An equimolar amount of aldehyde or ketone was added to the resulting salt solution in portions with stirring. The mixture was heated under reflux for 0.5–48 h. The crystals that precipitated were filtered off, washed with H_2O to pH 7, then with Et_2O. If no crystals precipitated, the reaction mixture was evaporated on a rotary evaporator, the resulting oil was crystallized using Et_2O. The resulting salts were recrystallized from EtOH.

1-Cyclohexylidene-3-phenyl-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (1a)[17] was obtained from 3-phenyl-

4,5-dihydro-1*H*-pyrazole (1.0 g, 6.8 mmol) and cyclohexanone (0.61 g, 6.8 mmol). Yield 1.6 g (73%), yellow crystals, mp 181–182°C. IR spectrum, ν, cm^{-1}: 1051, 1093 (BF_4), 1600, 1656 (C=N, $C=N^+$). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.66–1.69 (2H, m, 4-CH_2); 1.85–1.96 (4H, m, 3,5-CH_2); 2.85 (2H, t, *J* = 6.5, 2(6)-CH_2); 3.20 (2H, t, *J* = 5.8, 6(2)-CH_2); 3.76 (2H, t, *J* = 7.6, 4'-CH_2); 4.57 (2H, t, *J* = 7.3, 5'-CH_2); 7.61–8.04 (5H, m, H Ph). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 23.3 (C-3,5); 31.9 (C-4); 32.8 (C-2,6); 33.3 (C-4'); 51.0 (C-5'); 128.3 (C Ph); 129.0 (C Ph); 129.3 (C Ph); 134.0 (C Ar); 176.0 (C-1); 182.7 (C-3'). Found, *m*/*z*: 227.1545 $[M–BF_4]^+$. $C_{15}H_{19}N_2$. Calculated, *m*/*z*: 227.1543.

1-Cyclohexylidene-3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (1b) was obtained from 3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole (2.29 g, 13.0 mmol) and cyclohexanone (1.27 g, 13.0 mmol). Yield 2.3 g (52%), light-yellow crystals, mp 147–148°C. IR spectrum, ν, cm^{-1}: 1054, 1068 (BF_4), 1594, 1646 (C=N, $C=N^+$). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.71 (2H, t, *J* = 4.8, 4-CH_2); 1.91–1.99 (4H, m, 3,5-CH_2); 2.85 (2H, t, *J* = 6.0, 2(6)-CH_2); 3.21 (2H, t, *J* = 5.9, 6(2)-CH_2); 3.64 (2H, t, *J* = 7.6, 4'-CH_2); 3.87 (3H, s, OCH_3); 4.59 (2H, t, *J* = 7.3, 5'-CH_2); 6.95 (2H, d, *J* = 8.7, H Ar); 7.82 (2H, d, *J* = 8.7, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 23.3 (C-3,5); 24.9 (C-4); 31.9 (C-2,6); 32.6 (C-4'); 51.5 (C-5'); 55.2 (OCH_3); 114.2 (C Ar); 120.0 (C Ar); 130.8 (C Ar); 163.9 (C Ar); 174.4 (C-1); 180.9 (C-3'). Found, *m*/*z*: 257.1652 $[M–BF_4]^+$. $C_{16}H_{21}N_2O$. Calculated, *m*/*z*: 257.1648.

3-(4-Chlorophenyl)-1-cyclohexylidene-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (1c) was obtained from 3-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole (1.0 g, 5.5 mmol) and cyclohexanone (0.54 g, 5.5 mmol). Yield 0.57 g (29%), white powder, mp 186–187°C. IR spectrum, ν, cm^{-1}: 1051, 1093 (BF_4), 1600, 1656 (C=N, $C=N^+$). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.73 (2H, t, *J* = 5.4, 4-CH_2); 1.92–2.01 (4H, m, 3,5-CH_2); 2.86 (2H, t, *J* = 6.4, 6-CH_2); 3.23 (2H, t, *J* = 6.1, 2-CH_2); 3.67 (2H, t, *J* = 7.6, 4'-CH_2); 4.63 (2H, t, *J* = 7.6, 5'-CH_2); 7.47 (2H, d, *J* = 8.6, H Ar); 7.84 (2H, d, *J* = 8.6, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 23.7 (C-3,5); 25.2 (C-4); 32.4 (C-2); 33.2 (C-6); 33.4 (C-4'); 51.0 (C-5'); 126.8 (C Ar); 129.5 (C Ar); 130.3 (C Ar); 140.3 (C Ar); 174.7 (C-1); 183.6 (C-3'). Found, *m*/*z*: 261.1160 $[M–BF_4]^+$. $C_{15}H_{18}ClN_2$. Calculated, *m*/*z*: 261.1153.

1-Cyclohexylidene-3-(4-methylphenyl)-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (1d) was obtained from 3-(4-methylphenyl)-4,5-dihydro-1*H*-pyrazole (1.0 g, 6.25 mmol) and cyclohexanone (0.6 g, 6.25 mmol). Yield 0.9 g (44%), mp 176°C. IR spectrum, ν, cm^{-1}: 1034, 1054 (BF_4), 1597, 1641 (C=N, $C=N^+$). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.72 (2H, t, *J* = 5.3, 4-CH_2); 1.91–1.99 (4H, m, 3,5-CH_2); 2.40 (3H, s, CH_3); 2.85 (2H, t, *J* = 6.2, 2(6)-CH_2); 3.22 (2H, t, *J* = 6.1, 6(2)-CH_2); 3.64 (2H, t, *J* = 7.5, 4'-CH_2); 4.83 (2H, t, *J* = 7.6, 5'-CH_2); 7.36 (2H, d, *J* = 8.1, H Ar); 7.57 (2H, d, *J* = 8.2, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 23.3 (C-3,5); 25.3 (C-4); 31.9 (C-2); 32.9 (C-6); 33.4 (C-4'); 51.2 (C-5'); 41.4 (CH_3); 114.2 (C Ar); 129.0 (C Ar); 130.8 (C Ar); 138.9 (C Ar); 175.2 (C-1); 183.2 (C-3'). Found, *m*/*z*: 241.1695 $[M–BF_4]^+$. $C_{16}H_{21}N_2$. Calculated, *m*/*z*: 241.1699.

1-(Bicyclo[2.2.1]hept-2-ylidene)-3-phenyl-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (2a), mixture of *E*- and *Z*-isomers, was obtained from 3-phenyl-4,5-dihydro-1*H*-pyrazole (1.7 g, 11.6 mmol) and norcamphor (1.2 g, 11.0 mmol). Yield 2.9 g (81%), white powder, mp 200–201°C. IR spectrum, ν, cm^{-1}: 1046, 1091 (BF_4), 1594, 1695 (C=N, $C=N^+$). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.38–1.41 (1H, m, 3-CH_2); 1.56–1.85 (4H, m, 4,7-CH_2); 2.04–2.09 (1H, m, 3-CH_2); 2.58–2.97 (3H, m, 5-CH, 6-CH_2); 3.51 (0.5H, br. s, 2-CH); 3.75–3.79 (2H, m, 4'-CH_2); 3.91–3.93 (0.5H, m, 2-CH); 4.37–4.65 (2H, m, 5'-CH_2); 7.61 (2H, t, *J* = 7.6, H Ph); 7.72 (1H, t, *J* = 7.5, H Ph); 7.99 (1H, d, *J* = 7.9, H Ph); 8.02 (1H, d, *J* = 7.6, H Ph). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 24.4 (C-4); 25.9 (C-4'); 34.2 (C-3); 36.0 (C-5); 41.2 (C-7); 45.9 (C-6); 51.1 (C-2); 51.8 (C-5'); 128.4 (C Ph); 128.9 (C Ph); 129.2 (C Ph); 129.6 (C Ph); 134.2 (C Ph); 176.0 (C-3'); 187.8 (C-1) Found, *m*/*z*: 239.1551 $[M–BF_4]^+$. $C_{16}H_{19}N_2$. Calculated, *m*/*z*: 239.1543.

1-(Bicyclo[2.2.1]hept-2-ylidene)-3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (2b), mixture of *E*- and *Z*-isomers, was obtained from 3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole (1.12 g, 6.4 mmol) and norcamphor (0.7 g, 6.4 mmol). Yield 1.47 g (65%), white powder, mp 206–208°C. IR spectrum, ν, cm^{-1}: 1015, 1057 (BF_4), 1608, 1703 (C=N, $C=N^+$). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.38–1.40 (1H, m, 3-CH_2); 1.52–1.78 (4H, m, 4,7-CH_2); 2.02–2.04 (1H, m, 3-CH_2); 2.55–2.92 (3H, m, 5-CH, 6-CH_2); 3.46–3.49 (0.5H, m, 2-CH); 3.72–3.79 (2H, m, 4'-CH_2); 3.85 (0.5H, br. s, 2-CH); 3.87 (3H, s, OCH_3); 4.30–4.58 (2H, m, 5'-CH_2); 7.16 (2H, d, *J* = 8.8, H Ar); 7.95 (1H, d, *J* = 8.8, H Ar); 7.98 (1H, d, *J* = 8.8, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 24.9 (C-4); 25.9 (C-4'); 33.8 (C-3); 35.8 (C-5); 41.1 (C-7); 45.5 (C-6); 51.1 (C-2); 51.8 (C-5'); 56.0 (OCH_3); 115.0 (C Ar); 120.6 (C Ar); 131.4 (C Ar); 164.0 (C Ar); 175.1 (C-3'); 186.0 (C-1). Found, *m*/*z*: 269.1648 $[M–BF_4]^+$. $C_{17}H_{21}N_2O$. Calculated, *m*/*z*: 269.1648.

1-(Bicyclo[2.2.1]hept-2-ylidene)-3-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (2c) was obtained from 3-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole (1.15 g, 6.4 mmol) and norcamphor (0.7 g, 6.4 mmol). Yield 1.13 g (49%), white powder, mp 246–248°C. IR spectrum, ν, cm^{-1}: 1010, 1060 (BF_4), 1597, 1698 (C=N, $C=N^+$). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.34–1.36 (1H, m, 3-CH_2); 1.55–1.85 (4H, m, 4,7-CH_2); 2.03–2.06 (1H, m, 3-CH_2); 2.55–2.98 (3H, m, 5-CH, 6-CH_2); 3.47–3.50 (0.5H, m, 1-CH); 3.71–3.74 (2H, m, 4'-CH_2); 3.89–3.91 (0.5H, m, 1-CH); 4.34–4.63 (2H, m, 5'-CH_2); 7.69 (2H, d, *J* = 8.5, H Ar); 7.99 (1H, d, *J* = 8.5, H Ar); 8.05 (1H, d, *J* = 8.8, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 24.6 (C-4); 25.1 (C-4); 25.9 (C-4'); 26.1 (C-4'); 34.3 (C-3); 34.5 (C-3); 36.1 (C-5); 36.2 (C-5); 40.7 (C-7); 41.5 (C-7); 46.0 (C-6); 46.1 (C-6); 51.4 (C-2); 52.1 (C-5'); 127.5 (C Ar); 129.9 (C Ar); 130.0 (C Ar); 131.1 (C Ar); 131.2 (C Ar); 139.2 (2C Ar); 175.3 (C-3'); 175.7

(C-3'); 188.1 (C-1); 188.5 (C-1). Found, *m*/*z*: 272.1070 $[M–HBF_4]^+$. $C_{16}H_{17}ClN_2$. Calculated, *m*/*z*: 272.1075.

1-(Bicyclo[2.2.1]hept-2-ylidene)-3-(4-methylphenyl)-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (2d) was obtained from 3-(4-methylphenyl)-4,5-dihydro-1*H*-pyrazole (0.6 g, 3.7 mmol) and norcamphor (0.4 g, 3.6 mmol). Yield 0.4 g (33%), white powder, mp 190–191°C. IR spectrum, ν, cm^{-1}: 1011, 1056 (BF_4), 1594, 1704 (C=N, $C=N^+$). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.66–1.73 (4H, m, 3,4,7-CH_2); 1.89 (1H, d, *J* = 10.4, 3-CH_2); 1.92–2.00 (1H, m, 4-CH_2); 2.40 (3H, s, CH_3); 2.51 (1H, d, *J* = 19.4, 6-CH_2); 2.72 (1H, s, 5-CH); 2.87 (1H, d, *J* = 19.1, 6-CH_2); 3.61–3.70 (2H, m, 4'-CH_2); 3.93 (1H, d, *J* = 4.0, 2-CH); 4.44–4.50 (2H, m, 5'-CH_2); 7.27 (2H, d, *J* = 8.6, H Ar); 7.75 (2H, d, *J* = 8.0, H Ar). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 22.1 (CH_3); 25.5 (C-4); 26.2 (C-4'); 34.1 (C-3); 36.5 (C-5); 40.1 (C-7); 40.6 (C-6); 46.5 (C-2); 51.1 (C-5'); 125.7 (C Ar); 129.3 (C Ar); 130.2 (C Ar); 145.3 (C Ar); 175.6 (C-3'); 188.0 (C-1). Found, *m*/*z*: 252.1621 $[M–HBF_4]^+$. $C_{17}H_{20}N_2$. Calculated, *m*/*z*: 252.1622.

1-(Adamantan-2-ylidene)-3-phenyl-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (3a) was obtained from 3-phenyl-4,5-dihydro-1*H*-pyrazole (2.36 g, 16.1 mmol) and adamantan-2-one (2.42 g, 16.1 mmol). Yield 5.38 g (92%), white-yellow powder, mp 243–244°C. IR spectrum, ν, cm^{-1}: 1025, 1045 (BF_4), 1596, 1651 (C=N, $C=N^+$). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.92 (2H, s, 4,6-CH); 2.04 (4H, s,) and 2.19–2.22 (6H, m, $5CH_2$); 3.20 (1H, s, 2-CH); 3.75 (2H, t, *J* = 7.5, 4'-CH_2); 4.02 (1H, s, 8-CH); 4.60 (2H, t, *J* = 7.5, 5'-CH_2); 7.61 (2H, t, *J* = 7.6, H Ph); 7.72 (1H, t, *J* = 7.6, H Ph); 8.03 (2H, d, *J* = 8.0, H Ph). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 26.3 (C-4,6); 33.3 (C-4'); 34.8 (C-5); 36.7 (C-3); 37.7 (C-7); 38.4 (C-9,10); 38.6 (C-8,2); 50.8 (C-5'); 128.3 (C Ar); 129.0 (C Ar); 129.4 (C Ar); 134.0 (C Ar); 176.3 (C-3'); 187.6 (C-1). Found, *m*/*z*: 279.1848 $[M–BF_4]^+$. $C_{19}H_{23}N_2$. Calculated, *m*/*z*: 279.1856.

1-(Adamantan-2-ylidene)-3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (3b) was obtained from 3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole (1.5 g, 8.5 mmol) and adamantan-2-one (1.27 g, 8.5 mmol). Yield 1.58 g (47%), white powder, mp 218–219°C. IR spectrum, ν, cm^{-1}: 1033, 1051 (BF_4), 1599, 1655 (C=N, $C=N^+$). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.91 (2H, s, 4,6-CH); 2.03–2.05 (4H, m) and 2.15–2.21 (6H, m, $5CH_2$); 3.18 (1H, s, 2-CH); 3.70 (2H, t, *J* = 8.0, 4'-CH_2); 3.87 (3H, s, OCH_3); 4.00 (1H, s, 7-CH); 4.57 (2H, t, *J* = 8.1, 5'-CH_2); 7.15 (2H, d, *J* = 8.8, H Ar); 8.01 (2H, d, *J* = 8.8, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 26.3 (C-4,6); 33.1 (C-4'); 34.9 (C-5); 36.5 (C-3); 37.5 (C-7); 38.3 (C-9,10); 38.5 (C-8,2); 50.8 (C-5'); 55.8 (OCH_3); 114.8 (C Ar); 120.6 (C Ar); 131.2 (C Ar); 163.8 (C Ar); 175.4 (C-3'); 186.1 (C-1). Found, *m*/*z*: 309.1971 $[M–BF_4]^+$. $C_{20}H_{25}N_2O$. Calculated, *m*/*z*: 309.1961.

1-(Adamantan-2-ylidene)-3-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (3c) was obtained from 3-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole (1.5 g, 8.3 mmol) and adamantan-2-one (1.24 g, 8.3 mmol). Yield 1.69 g (51%), white powder, mp 107–107.5°C. IR spectrum, ν, cm^{-1}: 1010, 1056 (BF_4), 1607, 1671 (C=N, $C=N^+$). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.97 (2H, s, 4,6-CH); 2.12–2.27 (10H, m, $5CH_2$); 3.20 (1H, s, 2-CH); 3.73 (2H, t, *J* = 7.6, 4'-CH_2); 4.12 (1H, s, 8-CH); 4.67 (2H, t, *J* = 7.8, 5'-CH_2); 7.28 (2H, d, *J* = 8.6, H Ar); 7.78 (2H, d, *J* = 8.6, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 26.3 (C-4,6); 33.4 (C-4'); 34.8 (C-5); 36.8 (C-3); 37.7 (C7); 38.5 (C-9,10); 38.6 (C-2,8); 50.9 (C-5'); 127.2 (C Ar); 129.5 (C Ar); 130.8 (C Ar); 138.8 (C Ar); 175.4 (C-3'); 188.4 (C-1). Found, *m*/*z*: 312.1382 $[M–HBF_4]^+$. $C_{19}H_{21}ClN_2$. Calculated, *m*/*z*: 312.1388.

1-(Adamantan-2-ylidene)-3-(4-methylphenyl)-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (3d) was obtained from 3-(4-methylphenyl)-4,5-dihydro-1*H*-pyrazole (1.0 g, 6.2 mmol) and adamantan-2-one (0.93 g, 6.2 mmol). Yield 1.31 g (56%), white powder, mp 213–215°C. IR spectrum, ν, cm^{-1}: 1021, 1054 (BF_4), 1598, 1697 (C=N, $C=N^+$). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 2.04 (2H, s, 4,6-CH); 2.19 (2H, s,) and 2.25–2.34 (8H, m, $5CH_2$); 2.43 (3H, s, CH_3); 3.27 (1H, s, 2-CH); 3.74 (2H, t, *J* = 8.0, 4'-CH_2); 4.19 (1H, s, 8-CH); 4.60 (2H, t, *J* = 7.8, 5'-CH_2); 7.70 (2H, d, *J* = 8.2, H Ar); 8.05 (2H, d, *J* = 8.2, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 21.8 (C-4,6); 26.7 (C-4'); 27.3 (C-5); 33.6 (C-3); 35.3 (C-7); 37.1 (C-9); 38.0 (C-10); 38.8 (C-8); 39.0 (C-2); 46.8 (C-5'); 51.2 (CH_3); 126.0 (C Ar); 129.4 (C Ar); 130.4 (C Ar); 145.1 (C Ar); 176.5 (C-3'); 187.6 (C-1). Found, *m*/*z*: 293.2016 $[M–BF_4]^+$. $C_{20}H_{25}N_2$. Calculated, *m*/*z*: 293.2012.

1-(Adamantan-2-ylidene)-3-methyl-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (3e) was obtained from 3-methyl-4,5-dihydro-1*H*-pyrazole (1.0 g, 11.9 mmol) and adamantan-2-one (1.65 g, 11.0 mmol). Yield 2.6 g (78%), white powder, mp 212–213°C. IR spectrum, ν, cm^{-1}: 1040, 1068 (BF_4), 1644, 1673 (C=N, $C=N^+$). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.91 (2H, s, 4,6-CH); 2.07–2.23 (10H, m, $5CH_2$); 2.26 (3H, s, CH_3); 3.05 (1H, s, 2-CH); 3.31 (2H, t, *J* = 7.8, 4'-CH_2); 3.93 (1H, s, 8-CH); 4.43 (2H, t, *J* = 7.8, 5-CH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 16.6 (C-4,6); 26.5 (C-4'); 35.3 (C-5); 37.1 (C-3); 37.2 (C-7); 38.1 (C-9); 38.7 (C-10); 38.9 (C-2,8); 46.8 (C-5'); 50.0 (CH_3); 180.6 (C-3'); 188.2 (C-1). Found, *m*/*z*: 217.1703 $[M–BF_4]^+$. $C_{14}H_{21}N_2$. Calculated, *m*/*z*: 217.1699.

3-Phenyl-1-((1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylidene)-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (4a) was obtained from 3-phenyl-4,5-dihydro-1*H*-pyrazole (4.9 g, 33.5 mmol) and (+)-camphor (5.1 g, 33.5 mmol). Yield 7.04 g (58%), white powder, mp 240–241°C. IR spectrum, ν, cm^{-1}: 1047, 1066 (BF_4), 1602, 1666 (C=N, $C=N^+$). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.93 (3H, s, 9-CH_3); 0.98 (3H, s, 8-CH_3); 1.37 (1H, t, *J* = 8.7, 4-CH_2); 1.48 (3H, s, 10-CH_3); 1.73 (1H, t, *J* = 9.5, 4-CH_2); 1.92–1.93 (2H, m, 3-CH_2); 2.22 (1H, s, 5-CH); 2.57 (1H, d, *J* = 20.2) and 3.17 (1H, d, *J* = 19.2, 6-CH_2); 3.67 (2H, t, *J* = 7.8, 4'-CH_2); 4.49–4.56 (2H, m, 5'-CH_2); 7.60–7.72 (3H, m, H Ph); 7.99 (2H, d, *J* = 7.7, H Ph). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 13.6 (C-8); 18.4 (C-9); 19.8 (C-10); 25.9 (C-4); 31.6 (C-2); 32.6 (C-4'); 43.4 (C-5); 52.0 (C-3); 52.7 (C-7); 57.5 (C-6); 59.5 (C-5'); 128.3 (C Ar); 128.9 (C Ar); 129.4 (C Ar); 133.9 (C Ar); 176.1

(C-3'); 188.0 (C-1). Found, *m*/*z*: 281.2013 $[M–BF_4]^+$. $C_{19}H_{25}N_2$. Calculated, *m*/*z*: 281.2012.

3-(4-Methoxyphenyl)-1-((1*R*,4*R*)-1,7,7-trimethylbicyclo-[2.2.1]hept-2-ylidene)-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (4b) was obtained from 3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole (3.0 g, 17.0 mmol) and (+)-camphor (2.6 g, 17.1 mmol). Yield 3.7 g (54%), light-gray powder, mp 231–233°C. IR spectrum, ν, cm^{-1}: 1038, 1056 (BF_4), 1609, 1677 (C=N, $C=N^+$). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.96 (3H, s, 9-CH_3); 1.01 (3H, s, 8-CH_3); 1.52 (3H, s, 10-CH_3); 1.56–1.57 (1H, m, 4-CH_2); 1.87–1.95 (3H, m, 3,4-CH_2); 2.21–2.22 (1H, m, 5-CH); 2.58–2.63 (1H, d, *J* = 19.8) and 3.05–3.10 (1H, d, *J* = 19.3, 6-CH_2); 3.60–3.69 (2H, m, 4'-CH_2); 4.47–4.65 (2H, m, 5'-CH_2); 6.96 (2H, d, *J* = 8.8, H Ar); 7.80 (2H, d, *J* = 8.8, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 13.7 (C-8); 18.4 (C-9); 19.8 (C-10); 25.8 (C-4); 31.6 (C-2); 32.3 (C-4'); 43.4 (C-5); 51.9 (C-3); 52.7 (C-7); 55.7 (OCH_3); 57.3 (C-6); 60.0 (C-5'); 114.9 (C Ar); 120.6 (C Ar); 131.1 (C Ar); 163.8 (C Ar); 175.3 (C-3'); 186.3 (C-1). Found, *m*/*z*: 311.2120 $[M–BF_4]^+$. $C_{20}H_{27}N_2O$. Calculated, *m*/*z*: 311.2118.

3-(4-Chlorophenyl)-1-((1*R*,4*R*)-1,7,7-trimethylbicyclo-[2.2.1]hept-2-ylidene)-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (4c), mixture of *E*- and *Z*-isomers (1:3 ratio), was obtained from 3-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole (1.08 g, 6.0 mmol) and (+)-camphor (0.9 g, 6.0 mmol). Yield 1.04 g (45%), white powder, mp 230–231°C. IR spectrum, ν, cm^{-1}: 1058, 1087 (BF_4), 1596, 1677 (C=N, $C=N^+$). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.97 (3H, s, *Z*-9-CH_3); 0.99 (1H, s, *E*-9-CH_3); 1.02 (3H, s, *Z*-8-CH_3); 1.02 (1H, s, *E*-8-CH_3); 1.44 (1H, s, *E*-10-CH_3); 1.53 (3H, s, *Z*-10-CH_3); 1.54–1.56 (0.33H, m, *E*-4-CH_2); 1.58–1.61 (1H, m, *Z*-4-CH_2); 1.87–2.00 (4H, m, *E*+*Z*-4-CH_2, *E*+*Z*-3-CH_2); 2.18 (0.33H, s, *E*-5-CH); 2.22 (1H, s, *Z*-5-CH); 2.57 (1H, d, *J* = 19.9, *Z*-6-CH_2); 2.77 (0.33H, d, *J* = 20.7, *E*-6-CH_2); 3.07 (1H, d, *J* = 19.0, *Z*-6-CH_2); 3.25 (0.33H, d, *J* = 18.3, *E*-6-CH); 3.47–3.84 (2.66H, m, *E*+*Z*-4'-CH_2); 4.51–4.79 (2.66H, m, *E*+*Z*-5'-CH_2); 7.47–7.49 (2.66H, m, *E*+*Z*-H Ar); 7.80 (2H, d, *J* = 8.3, *Z*-H Ar); 7.84 (0.66H, d, *J* = 8.4, *E*-H Ar). Found, *m*/*z*: 315.1627 $[M–BF_4]^+$. $C_{19}H_{24}ClN_2$. Calculated, *m*/*z*: 315.1623.

3-(4-Methylphenyl)-1-((1*R*,4*R*)-1,7,7-trimethylbicyclo-[2.2.1]hept-2-ylidene)-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (4d) was obtained from 3-(4-methylphenyl)-4,5-dihydro-1*H*-pyrazole (1.0 g, 6.2 mmol) and (+)-camphor (0.95 g, 6.2 mmol). Yield 0.73 g (30%), white powder, mp 248–249°C. IR spectrum, ν, cm^{-1}: 1054, 1091 (BF_4), 1598, 1679 (C=N, $C=N^+$). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.97 (3H, s, 9-CH_3); 1.01 (3H, s, 8-CH_3); 1.53 (3H, s, 10-CH_3); 1.58 (1H, br. s, 4-CH_2); 1.94–1.97 (3H, m, 3,4-CH_2); 2.22 (1H, s, 5-CH); 2.43 (3H, s, C<u>H</u>$_3$Ar); 2.61 (1H, d, *J* = 19.8) and 3.07 (1H, d, *J* = 20.9, 6-CH_2); 3.60–3.69 (2H, m, 4'-CH_2); 4.48–4.67 (2H, m, 5'-CH_2); 7.30 (2H, d, *J* = 8.1, H Ar); 7.73 (2H, d, *J* = 8.1, H Ar). Found, *m*/*z*: 295.2170 $[M–BF_4]^+$. $C_{20}H_{27}N_2$. Calculated, *m*/*z*: 295.2169.

3-Methyl-1-((1*R*,4*R*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylidene)-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (4e) was obtained from 3-methyl-4,5-dihydro-1*H*-pyrazole (1.6 g, 19.0 mmol) and (+)-camphor (2.8 g, 18.4 mmol). Yield 3.9 g (68%), white powder, mp 177.5–178°C. IR spectrum, ν, cm^{-1}: 1047, 1066 (BF_4), 1602, 1666 (C=N, $C=N^+$). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.88 (3H, s, CH_3); 0.93 (3H, s, CH_3); 1.30–1.34 (4H, m, 4-CH_2, CH_3); 1.63 (1H, t, *J* = 9.8, 4-CH_2); 1.90–1.92 (2H, m, 5-CH); 2.15–2.18 (1H, m, 3-CH); 2.82 (3H, s, CH_3); 2.42–2.47 (1H, d, *J* = 20.2) and 3.07–3.12 (1H, d, *J* = 21.5, 6-CH_2); 3.17 (2H, t, *J* = 7.7, 4'-CH_2); 4.26–4.34 (2H, m, 5-CH_2). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 13.5 (C-8); 16.5 (C-9); 18.3 (C-10); 19.7 (CH_3); 25.7 (C-4); 31.5 (C-2); 36.4 (C-4'); 43.2 (C-5); 51.8 (C-3); 52.3 (C-7); 57.5 (C-6); 59.2 (C-5'); 181.2 (C-3'); 187.9 (C-1). Found, *m*/*z*: 219.1853 $[M–BF_4]^+$. $C_{14}H_{23}N_2$. Calculated, *m*/*z*: 219.1856.

3-Phenyl-1-((1*S*,4*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ylidene)-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (5) was obtained from 3-phenyl-4,5-dihydro-1*H*-pyrazole (0.96 g, 6.5 mmol) and (–)-camphor (1.0 g, 6.5 mmol). Yield 2.06 g (89%), white powder, mp 143.5–144°C. IR spectrum, ν, cm^{-1}: 1025, 1046 (BF_4^-), 1550, 1569 (C=N, $C=N^+$). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.93 (3H, s, 9-CH_3); 0.98 (3H, s, 8-CH_3); 1.37 (1H, t, *J* = 8.7, 4-CH_2); 1.48 (3H, s, 10-CH_3); 1.73 (1H, t, *J* = 9.5, 4-CH_2); 1.92–1.94 (2H, m, 3-CH); 2.22 (1H, s, 5-CH); 2.57 (1H, d, *J* = 20.2) and 3.17 (1H, d, *J* = 19.2, 6-CH_2); 3.67 (2H, t, *J* = 7.8, 4'-CH_2); 4.49–4.56 (2H, m, 5'-CH_2); 7.60–7.72 (3H, m, H Ph); 7.99 (2H, d, *J* = 7.7, H Ph). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 13.6 (C-8); 18.4 (C-9); 19.8 (C-10); 25.7 (C-4); 31.6 (C-2); 32.6 (C-4'); 43.4 (C-5); 52.0 (C-3); 52.7 (C-7); 57.5 (C-6); 59.5 (C-5'); 128.3 (C Ar); 128.9 (C Ar); 129.4 (C Ar); 133.9 (C Ar); 176.1 (C-3'); 188.0 (C-1). Found, *m*/*z*: 281.2012 $[M–BF_4]^+$. $C_{19}H_{25}N_2$. Calculated, *m*/*z*: 281.2012.

3-Phenyl-1-((1*R*,4*R*)-4,7,7-trimethyl-3-oxobicyclo[2.2.1]-hept-2-ylidene)-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (6a) was obtained from 3-phenyl-4,5-dihydro-1*H*-pyrazole (3.84 g, 26.3 mmol) and camphorquinone (4.37 g, 26.3 mmol). Yield 7.5 g (76%), light-yellow powder, mp 200–201°C. IR spectrum, ν, cm^{-1}: 1056 (BF_4^-), 1556, 1681 (C=N, $C=N^+$), 1755 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.98 (3H, s, 10-CH_3); 1.10 (3H, s, 8-CH_3); 1.12 (3H, s, 9-CH_3); 1.79–1.93 (2H, m, 4,5-CH_2); 2.02–2.08 (1H, m, 4-CH_2); 2.23–2.37 (1H, m, 5-CH_2); 3.78 (1H, d, *J* = 5.0, 6-CH); 3.75–3.87 (2H, m, 4'-CH_2); 4.70–4.79 (1H, m) and 5.06–5.13 (1H, m, 5'-CH_2); 7.51 (2H, t, *J* = 7.6, H Ph); 7.65 (1H, t, *J* =7.4, H Ph); 7.97 (2H, d, *J* = 7.7, H Ph). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 8.6 (C-10); 17.0 (C-8); 21.4 (C-9); 23.5 (5-C), 28.9 (C-4); 34.7 (C-4'); 45.6 (C-7); 53.1 (C-3,5'); 59.3 (C-6); 127.5 (C Ar); 128.9 (C Ar); 129.6 (C Ar); 134.9 (C Ar); 166.9 (C-1); 183.2 (C-3'); 197.7 (C-2). Found, %: C 59.46; H 6.10; N 7.44. $C_{19}H_{23}BF_4N_2O$ Calculated, %: C 59.71; H 6.07; N 7.33.

3-Methyl-1-(4,7,7-trimethyl-3-oxobicyclo[2.2.1]hept-2-ylidene)-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (6b) was obtained from 3-methyl-4,5-dihydro-1*H*-pyrazole (1.68 g, 20.0 mmol) and camphorquinone (3.32 g, 20.0 mmol). Yield 5.2 g (82%), white powder, mp 176–

177°C. IR spectrum, ν, cm^{-1}: 1056 (BF_4^-), 1556, 1681 (C=N, C=N^+), 1755 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.96 (3H, s, 8-CH_3); 1.10 (3H, s, 9-CH_3); 1.11 (3H, 10-CH_3); 1.83–1.93 (2H, m, 4-CH); 2.05–2.08 (1H, m, 5-CH_2); 2.23–2.34 (1H, m, 5-CH_2); 2.43 (3H, s, CH_3); 3.37–3.39 (1H, m) and 3.52–3.57 (1H, m, 4'-CH_2); 3.67 (1H, d, *J* = 5.0, 6-CH); 4.58–4.62 (1H, m) and 4.89–4.93 (1H, m, 5'-CH_2). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 8.9 (C-8); 17.2 (C-6); 17.3 (C-10); 21.8 (C-9); 23.6 (C-6); 29.2 (C-4'); 39.4 (C-5); 45.8 (C-7); 53.4 (C-1); 53.6 (C-5'); 59.6 (C-4); 167.4 (C-2); 189.2 (C-3'); 198.1 (C-3). Found, *m*/*z*: 233.1656 $[M–BF_4]^+$. $C_{14}H_{21}N_2O$. Calculated, *m*/*z*: 233.1648.

1-(5-Isopropenyl-2-methylcyclohex-2-en-1-ylidene)-3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (7a) was obtained from 3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole (1.5 g, 8.5 mmol) and *S*-(+)-carvone (1.28 g, 8.5 mmol). Yield 0.93 g (28%), orange powder, mp 165–167°C. IR spectrum, ν, cm^{-1}: 1017, 1057 (BF_4), 1517, 1562, 1604 (C=N, C=N^+). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.75 (3H, s, 9-CH_3); 2.28–2.30 (1H, m, 5-CH); 2.38 (3H, s, 7-CH_3); 2.50–2.52 (1H, m) and 2.67–2.71 (1H, m, 6-CH_2); 2.81–3.01 (2H, m, 4-CH_2); 3.62 (2H, t, *J* = 8.2, 4'-CH_2); 3.85 (3H, s, OCH_3); 4.71 (2H, t, *J* = 8.2, 5'-CH_2); 4.88 (1H, s) and 4.91 (1H, s, 10-CH_2); 6.94 (1H, d, *J* = 4.3, 3-CH); 7.01 (2H, d, *J* = 8.8, H Ar); 7.83 (2H, d, *J* = 8.8, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.1 (C-9); 24.1 (C-7); 31.4 (C-6); 31.7 (C-4); 35.9 (C-4'); 39.8 (C-5); 52.8 (C-5'); 55.5 (OCH_3); 112.1 (C-10); 114.8 (C Ar); 120.6 (C-2); 130.1 (C Ar); 131.0 (C Ar); 144.8 (C-8); 154.7 (C-3); 164.1 (C Ar); 166.9 (C-3'); 173.5 (C-1). Found, *m*/*z*: 309.1954 $[M–BF_4]^+$. $C_{20}H_{25}N_2O$. Calculated, *m*/*z*: 309.1961.

3-(4-Chlorophenyl)-1-(5-isopropenyl-2-methylcyclohex-2-en-1-ylidene)-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (7b) was obtained from 3-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole (1.5 g, 8.3 mmol) and *S*-(+)-carvone (1.25 g, 8.3 mmol). Yield 0.74 g (22%), yellow powder, mp 138–140°C. IR spectrum, ν, cm^{-1}: 1009, 1058 (BF_4), 1560, 1606, 1645 (C=C, C=N, C=N^+). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.73 (3H, s, 9-CH_3); 2.27–2.31 (1H, m, 5-CH); 2.37 (3H, s, 7-CH_3); 2.51–2.53 (1H, m) and 2.68–2.71 (1H, m, 6-CH_2); 2.84–3.01 (2H, m, 4-CH_2); 3.52 (2H, t, *J* = 7.8, 4'-CH_2); 4.71–4.73 (2H, m, 5'-CH_2); 4.81 (1H, s) and (1H, s, 10-CH_2); 6.94 (1H, d, *J* = 4.2, 3-CH); 7.40 (2H, d, *J* = 8.2, H Ar); 7.73 (2H, d, *J* = 8.3, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.1 (C-9); 24.1 (C-7); 31.4 (C-6); 31.9 (C-4); 36.0 (C-4'); 39.7 (C-5); 52.8 (C-5'); 112.2 (C-10); 126.9 (C Ar); 129.5 (C-2); 130.0 (C Ar); 130.2 (C Ar); 140.0 (C-8); 144.7 (C-3); 156.2 (C Ar); 168.7 (C-3'); 173.3 (C-1). Found, *m*/*z*: 313.1469 $[M–BF_4]^+$. $C_{19}H_{22}ClN_2$. Calculated, *m*/*z*: 313.1466.

1-(5-Isopropenyl-2-methylcyclohex-2-en-1-ylidene)-3-(4-methylphenyl)-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (7c) was obtained from 3-(4-methylphenyl)-4,5-dihydro-1*H*-pyrazole (1.0 g, 6.2 mmol) and *S*-(+)-carvone (0.94 g, 6.2 mmol). Yield 0.6 g (25%), yellow powder, mp 165–167°C. IR spectrum, ν, cm^{-1}: 1048, 1057 (BF_4), 1560 1606, 1646 (C=C, C=N, C=N^+). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.74 (3H, s, 9-CH_3); 2.30–2.32 (1H, m, 5-CH); 2.41 (6H, s, 7-CH_3, C$\underline{H}_3$Ar); 2.53–2.55 (1H, m) and 2.72–2.76 (1H, m, 6-CH_2); 2.90–3.06 (2H, m, 4-CH_2); 3.59–3.62 (2H, m, 4'-CH_2); 4.68–4.71 (2H, m, 5'-CH_2); 4.85 (1H, s) and 4.86 (1H, s, 10-CH_2); 6.94 (1H, d, *J* = 4.9, 3-CH); 7.26 (2H, d, *J* = 7.8, H Ar); 7.71 (2H, d, *J* = 7.6, H Ar). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 20.1 (C-9); 21.7 (C-7); 24.1 (CH_3); 31.4 (C-6); 31.8 (C-4); 36.0 (C-4'); 39.8 (C-5); 52.7 (C-5'); 112.1 (C-10); 125.7 (C Ar); 128.8 (C Ar); 129.0 (C-2); 129.8 (C Ar); 130.2 (C-8); 144.9 (C-3); 155.4 (C Ar); 167.9 (C-3'); 174.1 (C-1). Found, *m*/*z*: 293.2018 $[M–BF_4]^+$. $C_{20}H_{25}N_2$. Calculated, *m*/*z*: 293.2012.

1-[((1*R*,5*S*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)-methylidene]-3-phenyl-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (8a) was obtained from 3-methyl-4,5-dihydro-1*H*-pyrazole (1.5 g, 10.3 mmol) and myrtenal (1.6 g, 10.6 mmol). Yield 1.3 g (36%), orange powder, mp 149–150°C. IR spectrum, ν, cm^{-1}: 1032, 1060 (BF_4), 1567, 1592, 1633 (C=C, C=N, C=N^+). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.86 (3H, s, 9-CH_3); 1.21–1.27 (1H, m, 8-CH_2); 1.45 (3H, s, 10-CH_3); 2.23 (1H, s, 5-CH); 2.58–2.63 (1H, m, 8-CH_2); 2.73–2.76 (2H, m, 4-CH_2); 3.64 (2H, s, 4'-CH_2); 3.72 (1H, s, 7-CH); 4.85 (2H, s, 5'-CH_2); 7.53–7.56 (3H, m, H Ph); 7.66 (1H, t, *J* = 7.4, 3-CH); 7.87 (2H, d, *J* = 6.8, H Ph); 8.54 (1H, s, 1-CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.1 (C-10); 25.7 (C-9); 30.8 (C-4); 31.8 (C-8); 35.3 (C-4'); 37.3 (C-6); 39.0 (C-5); 42.6 (C-7); 54.2 (C-5'); 127.8 (C Ar); 128.7 (C Ar); 129.1 (C Ar); 134.0 (C-2); 142.9 (C Ar); 156.8 (C-3); 175.0 (C-1); 175.9 (C-3'). Found, *m*/*z*: 279.1861 $[M–BF_4]^+$. $C_{19}H_{23}N_2$. Calculated, *m*/*z*: 279.1856.

1-[((1*R*,5*S*)-6,6-Dimethylbicyclo-[3.1.1]hept-2-en-2-yl)-methylidene]-3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (8b) was obtained from 3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazole (1.5 g, 8.5 mmol) and myrtenal (1.28 g, 8.5 mmol). Yield 0.93 g (27%), brown powder, mp 145–146°C. IR spectrum, ν, cm^{-1}: 1035, 1060 (BF_4), 1567, 1603, 1628 (C=C, C=N, C=N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.82 (3H, s, 9-CH_3); 1.21–1.23 (1H, m, 8-CH_2); 1.63 (3H, s, 10-CH_3); 2.19 (1H, s, 5-CH); 2.53–2.58 (1H, m, 8-CH_2); 2.70–2.74 (2H, m, 4-CH_2); 3.54 (2H, t, *J* = 7.9, 4'-CH_2); 3.68 (1H, t, *J* = 4.3, 7-CH); 3.89 (3H, s, OCH_3); 4.79 (2H, t, *J* = 7.9, 5'-CH_2); 7.02 (2H, d, *J* = 8.9, H Ar); 7.51 (1H, br. s, 3-CH); 7.79 (2H, d, *J* = 8.9, H Ar); 8.44 (1H, s, 1-CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.3 (C-10); 25.9 (C-9); 31.0 (C-4); 31.7 (C-8); 35.3 (C-4'); 37.7 (C-6); 39.2 (C-5); 42.8 (C-7); 54.5 (CH_3O); 55.9 (C-5'); 114.8 (C Ar); 120.4 (C Ar); 131.2 (C Ar); 142.2 (C-2); 155.4 (C Ar); 161.0 (C-3); 164.5 (C-1); 175.4 (C-3'). Found, *m*/*z*: 309.1958 $[M–BF_4]^+$. $C_{20}H_{25}N_2O$. Calculated, *m*/*z*: 309.1961.

3-(4-Chlorophenyl)-1-[((1*R*,5*S*)-6,6-dimethylbicyclo-[3.1.1]hept-2-en-2-yl)methylidene]-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (8c) was obtained from 3-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazole (1.0 g, 5.5 mmol) and myrtenal (0.83 g, 5.5 mmol). Yield 0.64 g (29%), orange powder, mp 151–152°C. IR spectrum, ν, cm^{-1}: 1011, 1061 (BF_4), 1569, 1592, 1663 (C=C, C=N, C=N^+). ^{1}H NMR

spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.86 (3H, s, 9-CH_3); 1.23–1.25 (1H, m, 8-CH_2); 1.45 (3H, s, 10-CH_3); 2.24 (1H, s, 5-CH); 2.60–2.64 (1H, m, 8-CH_2); 2.76 (2H, m, 4-CH_2); 3.63 (2H, t, *J* = 7.7, 4'-CH_2); 3.68 (1H, t, *J* = 5.6, 7-CH); 4.85 (2H, t, *J* = 8.1, 5'-CH_2); 7.52 (2H, d, *J* = 8.4, H Ar); 7.59 (1H, s, 3-CH); 7.81 (2H, d, *J* = 8.4, H Ar); 8.52 (1H, s, 1-CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.3 (C-10); 25.9 (C-9); 31.0 (C-4,8); 35.5 (C-4'); 37.8 (C-6); 39.2 (C-5); 42.7 (C-7); 54.6 (C-5'); 126.6 (C Ar); 129.7 (C Ar); 130.1 (C Ar); 140.7 (C-2); 143.1 (C Ar); 157.0 (C-3); 162.8 (C-1); 175.4 (C-3'). Found, *m*/*z*: 313.1475 [M–BF_4]+. $C_{19}H_{22}BF_4N_2$. Calculated, *m*/*z*: 313.1466.

1-[((1*R*,5*S*)-6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl]-methylidene}-3-(4-methylphenyl)-4,5-dihydro-1*H*-pyrazolium tetrafluoroborate (8d) was obtained from 3-(4-methylphenyl)-4,5-dihydro-1*H*-pyrazole (1.0 g, 6.2 mmol) and myrtenal (0.93 g, 6.2 mmol). Yield 0.35 g (15%), yellow powder, mp 149–150°C. IR spectrum, ν, cm^{-1}: 1010, 1050 (BF_4), 1584 1608, 1635 (C=C, C=N, C=N$^+$). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.86 (3H, s, 9-CH_3); 1.23–1.25 (1H, m, 8-CH_2); 1.45 (3H, s, 10-CH); 2.23 (1H, s, 5-CH); 2.47 (3H, s, CH_3Ar); 2.59–2.61 (1H, m, 8-CH_2); 2.74–2.76 (2H, m, 4-CH_2); 3.60 (2H, t, *J* = 7.7, 4'-CH_2); 3.70 (1H, t, *J* = 5.5, 7-CH); 4.83 (2H, t, *J* = 8.1, 5'-CH_2); 7.36 (2H, d, *J* = 8.1, H Ar); 7.57 (1H, br. s, 3-CH); 7.75 (2H, d, *J* = 8.4, H Ar); 8.52 (1H, s, 1-CH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.3 (C-10); 21.8 (CH_3); 25.9 (C-9); 31.0 (C-4); 31.9 (C-8); 35.4 (C-4'); 37.8 (C-6); 39.3 (C-5); 42.9 (C-7); 54.4 (C-5'); 125.3 (C Ar); 128.9 (C Ar); 130.0 (C Ar); 143.0 (C-2); 145.6 (C Ar); 156.4 (C-3); 161.8 (C-1); 176.1 (C-3'). Found, *m*/*z*: 293.2019 [M–BF_4]$^+$. $C_{20}H_{25}N_2$. Calculated, *m*/*z*: 293.2012.

The study of cytotoxicity of the obtained compounds 1a–d, 2a,b,d, 3a–e, 4a–c,e, 5, 7a–c, and 8a–d. In order to test the toxicity on cell culture, a series of two-fold dilutions with a concentration of 300 to 4 μg/ml in Eagle's MEM supportive medium were prepared from the studied compounds. MDCK cells (ATCC CCL-34) were placed into the wells of 96-well cell culture plates and incubated until 90% monolayer was formed. The prepared dilutions were added to the wells of the plates and incubated for 72 h at 36°C in a 5% CO_2. Then, the methyltetrazolium (MTT) assay was performed on 96-well plates.[18] The cells were washed 2 times with saline (0.9% NaCl) and 100 μl/well of MTT solution (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-tetrazolium bromide) at a concentration of 0.5 μg/ml in Eagle's MEM supportive medium. The plates were incubated for 1 h at 36°C, after which the liquid was removed and DMSO (0.1 ml) was added to the wells. After dissolution of the precipitate, the optical density of the cells was measured on a ThermoMultiskan FC spectrophotometer (ThermoFisher Scientific, USA) at a wavelength of 540 nm. Based on the obtained data, the CC_{50}, that is, the concentration of the compound leading to the death of 50% of the cells in culture, was calculated.

The study of the antiviral activity of the synthesized compounds 1a–d, 2a,b,d, 3a–e, 4a–c,e, 5, 7a–c, and 8a–d against influenza A viruses. Evaluation of the antiviral activity of the compounds was carried out using a test for reduction of the degree of virus-specific cytopathic effect. The experiments used influenza A/Puerto Rico/8/34 (H1N1) viruses. MDCK cells were seeded into wells of 96-well cell culture plates and incubated until 90% monolayer was formed. The studied compounds in the range of concentrations were added to the cells in the wells of the plate and incubated for 1 h at 36°C in a 5% CO_2. Then, the cells were infected with the virus at a dose of 0.01 $TCID_{50}$ per cell. The cells were incubated for 72 h at 36°C in a 5% CO_2, after which the analysis of cell viability was carried out using the MTT assay, as described above. Based on the obtained data, a 50% inhibitory concentration was calculated for each compound, that is, a concentration that reduces the degree of viral cell destruction by 50%. Based on the obtained data, the selectivity index (SI), the ratio of CC_{50} to IC_{50}, was calculated for each compound.

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