4-Methyl- and 4-(Halophenyl)pyrimidinium (4-Halobenzoyl)methylides. Correlation of Structure, Stability, Reactivity, and Biological Activity

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For the first time in the cycloimminium ylide series, we present a theoretical and experimental study concerning the correlation between structure, stability, reactivity, and biological activity of 4-(R)-pyrimidinium (4-halobenzoyl)methylides (R = Me and 4-chlorophenyl; hal = X = F, Cl, Br, I; see **5** and **6** in *Scheme 1*). The 4-methylpyrimidinium (4-halobenzoyl)methylides **5** are relatively stable compounds, while the (4-chlorophenyl)-pyrimidinium (4-halobenzoyl)methylides **6** are more unstable. Their stability varies with the nature of the substituents at the ylide carbanion and pyrimidinium cation moieties as confirmed by quantum-chemical calculations. The latter also disclose the possibility to use pyrimidinium ylides as nucleophilic reagents as well as 1,3-dipoles in reactions with appropriate reagents. The experimental data obtained confirm the calculations concerning the nucleophilicity and reactivity of the ylides **5** and **6**. Moreover, the influence of microwave irradiation on the synthesis of the pyrimidinium salts **3** and **4** from pyrimidine and an organic halide is studied and reveals a remarkable reaction-rate increase under microwave irradiation as compared to classical conditions; this allows the general and facile synthesis of the salts **3** and **4** (*Scheme 1*, *Table 1*). The *in vitro* biological activity of the newly obtained 4-methylpyrimidine compounds is also tested. Some of them exhibit a remarkable activity against different microorganisms (germs and fungi) which allows to establish structure–activity correlations.

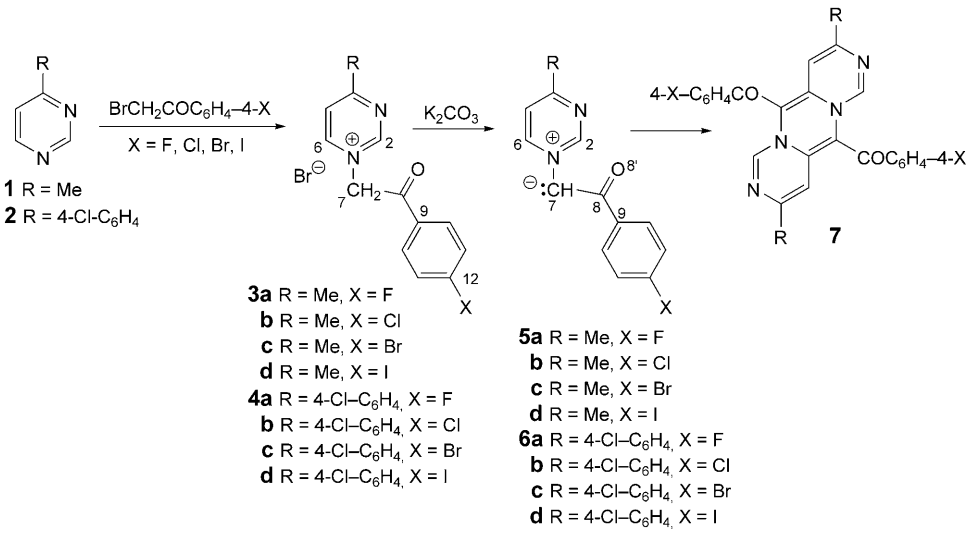
Introduction. – According to the literature [1–21], the chemistry of cycloimminium ylides is widely discussed due to their theoretical importance [1–17] as well as their practical applications (biological [18], acido-basic [19], semiconductor properties [20], *etc.*). In the case of cycloimminium (4-halobenzoyl)ylides (hal = X = F, Cl, Br, I), we did not find any systematic [1–21] study concerning the correlation between structure, stability, and biological activity.

The aim of this work was to study the correlation between structure, stability, reactivity, and biological activity in the series of cycloimminium (4-halobenzoyl)ylides.

Results and Discussion. – For the synthesis of new pyrimidinium ylides derived from 4-methylpyrimidine (**1**) and 4-(4-chlorophenyl)pyrimidine (**2**), we used the salt method described by *Kröhnke* [22]. Thus, the pyrimidinium salts **3a–d** and **4a–d**, prepared by treating **1** or **2** with 4-halophenacyl bromides (=2-bromo-1-(4-halophenyl)-ethanones), were subjected to alkali carbonates in aqueous solution to afford the corresponding pyrimidinium ylides **5a–d** and **6a–d** (*Scheme 1*).

A main disadvantage of the quaternization of pyrimidines **1** and **2** is the fact that under classical conditions (refluxing in a solvent), the reaction time is very long, 60 min for **1** and 5 days for **2**. Moreover, since only a few reports on the influence of microwave on the quaternization process of heterocycles are known [23–25], we decided to synthesize the desired cycloimminium salts by microwave heating. In *Table 1* a compar-

Scheme 1[1])



ison of the reaction results under microwave heating and under classical conditions is presented. Thus, both methods give comparable yields, but under microwave irradiation, reaction times decrease dramatically, from 60 min to 5 min, and from 5 days to 20 min, respectively.

Table 1. *Synthesis of Cycloimminium Salts under Microwave Heating and under Classical Conditions*

	Microwave heating			Classical conditions		
	Reaction time	Reaction temp. [°]	Yield [%]	Reaction time	Reaction temp. [°]	Yield [%]
3a	5 min	70	92	60 min	50	91
3b	5 min	70	94	60 min	50	94
3c	5 min	70	96	60 min	50	96
3d	5 min	70	89	60 min	50	90
4a	20 min	90	80	5 days	110	76
4b	20 min	90	70	5 days	110	68
4c	20 min	90	73	5 days	110	70
4d	20 min	90	65	5 days	110	67

To establish a correlation between structure, stability, and reactivity in the 4-(R)-pyrimidinium (4-halobenzoyl)methylide series, we performed a theoretical study by means of the general theory of perturbation limited to the frontier molecular orbitals [26–30]. Thus, the heat of formation (*Table 2*), the atomic charges, the coefficients of the atomic orbitals, and the values of the energy of the frontier molecular orbitals for ylides **5b** and **6b** (*Table 3*) were calculated with the PM3 [30] method (for the other ylides, the results are similar).

[1]) Arbitrary atom numberings; for systematic names, see *Exper. Part*.

From the calculated data listed in *Table 2*, two main conclusions concerning the stability can be drawn: *1*) The substituent R at C(4) of the pyrimidinium ring influences the stability, the 4-methylpyrimidinium ylides **5** being more stable than the 4-(4-chlorophenyl)pyrimidinium ylides **6**. *2*) The halogen atom at C(4) of the benzoyl group also influences the stability, in both series **5** and **6**, since the stability decreases with decreasing electronegativity of the halogen atom (F > Cl > Br > I).

Table 2. *Heat of Formation* [kcal/mol] *for 4-(R)-Pyrimidinium [4-(X)-Benzoyl]methylides* **5** *and* **6**

	X = F	X = Cl	X = Br	X = I
5 (R = Me)	−7.59	29.33	43.80	57.47
6 (R = 4-Cl-C_6H_4)	19.62	56.53	71.01	84.66

From the data of *Table 3*, the following is deduced: *1*) The ylide C-atoms, C(7) have a negative atomic charge, low but significant. *2*) The ylide N-atoms N(1) have a positive atomic charge, also low but significant, and smaller (in absolute value) than those of the ylide C-atoms. *3*) The ring C-atoms in α-position, *i.e.*, C(2) and C(6), have small negative atomic charges, both being low.

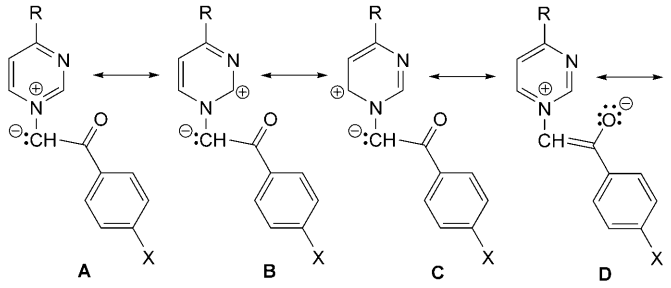
Table 3. *Coefficients of Atomic Orbitals* (p_z), *Total Atomic Charge* Q, *and Energies* [eV] *of Ylides* **5b** *and* **6b**. Arbitrary numbering of atoms (see *Scheme 1*)[1]).

		Energy [eV]	Coefficients of atomic orbitals (p_z)						
			N(1)(ylide)	C(7)(ylide)	C(2)	C(6)	N(3)	C(8)	O(8′)
5b	HOMO	−8.3671	+0.0617	−0.6659	+0.3602	+0.3413	−0.0904	−0.0991	+0.2706
	LUMO	−1.0739	−0.5202	+0.2825	+0.3280	+0.1735	+0.0826	+0.2600	−0.2435
	Q		+0.8276	−0.6947	−0.3717	−0.4103	+0.0318	+0.4183	−0.3953
6b	HOMO	−8.3072	+0.0819	−0.6014	+0.3343	+0.3055	−0.1137	−0.0923	+0.2411
	LUMO	−1.4167	−0.4739	+0.2885	+0.2151	+0.1729	+0.1783	+0.2179	−0.2145
	Q		+0.8266	−0.6835	−0.3731	−0.4092	+0.0379	+0.4177	−0.3903

The low total atomic charges indicate the delocalization of the anionic charge from the ylide C-atom center to the ylide substituent and of the positive charge from the ylide N-atom to the pyrimidine heterocycle as shown by **A**–**D** in *Scheme 2*. Consequently a relatively good stability is predicted for these ylides.

The significant negative atomic charge at the ylide C-atoms suggests that pyrimidinium ylides could be used as nucleophilic reagents in appropriate reactions. Also, the data from *Table 3* and *Scheme 2* show that the ylides **5** and **6** have a 1,2-dipolar structure (octet form, canonical structure **A**), a dipole which could accept a 1,3-dipolar structure (sextet form without double bond, canonical structures **B** and **C**). The 1,3-dipolar activity could involve either the 2- or 6-position of the pyrimidine ring – a regiochemical problem. However, position 6 is less electron-deficient (atomic charge *Q ca.* −0.4) than position 2 (atomic charge *Q ca.* −0.2), therefore more suitable for reaction with an electron-deficient dipolarophile. As in related cases [15][16], we expect that reactions of pyrimidinium (4-halobenzoyl)methylides with an electron-deficient dipolarophile should occur as an ordinary [3+2] dipolar cycloaddition leading to azabicyclic compounds at the 2- or 6-position.

Scheme 2



5a–d

The experimental data obtained confirm the theoretical data concerning the stability and reactivity. Thus, the new ylides **5a–d** and **6a–d** have indeed different stabilities according to the nature of their substituents. Thus, 4-methylpyrimidinium ylides **5** are moderately stable (for several days), while 4-(4-chlorophenyl)pyrimidinium ylides **6** underwent a rapid dimerization after their preparation (*via* a [3+3] dipolar cycloaddition) yielding an ylide **6**/dimer **7** mixture (within 24 h) (*Scheme 1*). The nucleophilicity of the pyrimidinium ylides **5** and **6** was established by their protonation with hydrochloric acid giving the appropriate pyrimidinium chloride salts **8** and **9**, respectively (*Scheme 3*).

Moreover, the ability of pyrimidinium (4-halobenzoyl)methylides **5** and **6** to react with an electron-deficient dipolarophile *via* a [3+2] dipolar cycloaddition was established by their reaction with methyl prop-2-ynoate which gave a mixture of pyrrolo[1,2-*c*]pyrimidine **11a**,**b** (cycloaddition at C(6) of **5b** or **6b**) and pyrrolo[1,2-*a*]pyrimidine **12a**,**b** (cycloaddition at C(2) of **5b** or **6b**), besides dimer **7** (*Scheme 3*). Concerning the regiochemical outcome, the isomers from the cycloaddition at the 2- and 6-positions of the pyrimidine ring were obtained with different rates, the cycloaddition at position 6 being favored (*Table 4*).

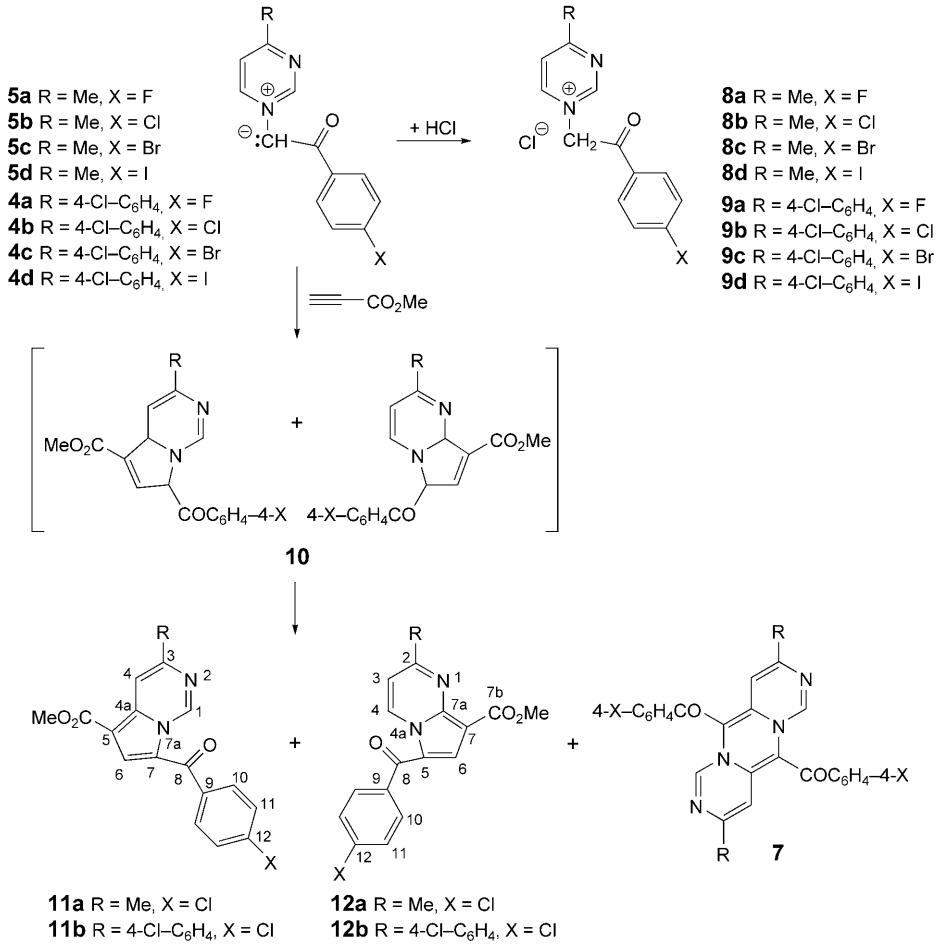
Table 4. *Yields of the Cycloadditions of the Pyrimidinium (4-Chlorobenzoyl)methylides* **5b** *or* **6b** *and Methyl Prop-2-yonate* (see *Scheme 3*)

	Cycloaddition at C(6)		Cycloaddition at C(2)		Dimer **7** [%]
	Cycloadduct	yield [%]	Cycloadduct	yield [%]	
5b (R = Me, X = Cl)	**11a**	31.5	**12a**	7	24.5
6b (R = 4-Cl-C_6H_4, X = Cl)	**11b**	37	**12b**	6	21

The structure of the new pyrimidine compounds was established by elemental and spectral analysis (IR, ^{1}H- and ^{13}C-NMR, COSY, HMQC, HMBC; see *Exper. Part*) as well as by their chemical transformations (see above).

The *in vitro* antimicrobial and antifungical activity of the new 4-methylpyrimidine derivatives **3a–d** and **5a–d** were tested having in view that in a previous study, related compounds have shown biological activity [18][31–33]. The biological tests were performed in rustless-steel cylinders by means of the diffusimetric method [33] which is

Scheme 3



based on the diffusion of the tested substances on the gelose surface (for bacteria) and *Sabouard* environment (for fungus *Candida albicans*). The cylinders were maintained for 24 h at 34° for bacteria and at 37° for *Candida*. The substances were tested in 5% (*v*/*v*) aqueous DMF solutions against a reference solvent sample. The inhibition diameter zone (in mm) of development of the microbial strain was measured. A compound is considered active [33] if the difference between its inhibition diameter zone and that of the reference sample is higher than 2 mm (3–4 mm, moderate activity; and up to 5 mm, high activity). Comparison of the obtained data (*Table 5*) leads to the following conclusions concerning the relation between structure and biological activity: *1*) The salts **3a**–**c** have a remarkably nonselective activity against *Gram*-positive and *Gram*-negative germs as well as against fungus *Candida albicans*. Salt **3d** is active only against *Staphylococcus aureus Oxford*. *2*) Ylide **5d** is active against *Gram*-positive and *Gram*-negative germs, while the other ylides are considered to be mostly inactive.

Table 5. In vitro *Antimicrobial and Antifungical Activity*[a]) *of 4-Methylpyrimidine Derivatives* **3** *and* **5**

	Staphylococcus aureus Oxford	*Bacillus subtilis*	*Escherichia coli*	*Bacillus proteus vulgaris*	*Candida albicans*
Reference sample	17	10	15	15	15
3a	*25*	*16*	*22*	*23*	*23*
3b	*23*	*15*	*18*	*20*	*21*
3c	*23*	*15*	*21*	*22*	*23*
3d	*23*	14	17	18	18
5a	17	*16*	17	17	15
5b	17	*16*	16	16	16
5c	15	*15*	17	17	16
5d	*23*	*15*	*20*	*19*	17

[a]) Activity expressed in mm of the inhibition diameter zone (see text).

Conclusions. – For the first time in the cycloimminium ylide series, a theoretical and experimental study concerning the correlation between structure, stability, reactivity, and biological activity of 4-(R)-pyrimidinium (4-halobenzoyl)methylides (R = methyl and 4-chlorophenyl, hal = F, Cl, Br, I) is presented. Quantum-chemical calculations and the experimental data show that the stability of these pyrimidinium methylides is dependent on the nature of the substituents at the ylide carbanion and pyrimidinium cation moieties. The quantum-chemical calculations predict the possibility of using pyrimidinium ylides as nucleophilic reagents as well as 1,3-dipoles in reactions with appropriate reagents. The nucleophilicity of pyrimidinium ylides is established by the formation of pyrimidinium chloride salts in the presence of hydrochloric adid, and their 1,3-dipole reactivity by the formation of [3 + 2] cycloadducts with the electron-deficient dipolarophile methyl prop-2-ynoate.

The microwave-promoted reaction of 4-(R)-pyrimidine with an organic halide shows a remarkable rate enhancement as compared to standard heating conditions, thus allowing a rapid, facile, and general synthesis of cycloimminium salts from N-heterocycles and organic halides.

The *in vitro* biological assays with the new pyrimidine compounds show that some of them have a remarkable activity against different microorganisms (germs and fungi). Correlation between structure and biological activity allows to draw the following conclusions: *1*) Salts are more active that ylides. *2*) The influence of the halogen atom at C(4) of the benzoyl moiety is different in the series of the salts and of the ylides: in the series of the pyrimidine salts, the F-derivative has an excellent antimicrobial and antifungal activity (nonselective), while in the series of the pyrimidinium ylides, the I-derivative has a good antimicrobial (but no antifungal) activity.

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Experimental Part

General. The 4-(X)-phenacyl bromides, 4-methylpyrimidine, and methyl prop-2-ynoate were purchased from *Aldrich* (Germany). Flash chromatography (FC): silica gel *60 (Aldrich*, Germany*)*. Solvent systems for FC and TLC: CH_2Cl_2/MeOH 99.5 : 0.5 (*A*), CH_2Cl_2/acetone 98 : 2 (*B*). Microwave irradiation: monomode reactor *Star-2*

(50 W), *CHEM Corporation*. UV/VIS Spectra: *Hitachi-U-2010* spectrometer, MeCN solns.; λ_{max} in nm. IR Spectra: *Jasco 660-C* spectrometer; in KBr; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Bruker-Avance-400-DRX* instrument (400 MHz); δ values rel. to Me_4Si in ppm, J in Hz. M.p.: *Meltemp-II* apparatus; uncorrected. The quantum-chemical calculations were performed with the HyperChem (vs. 5.02) software for *Windows 95* (*Hypercub, Inc.*, Gainsville, USA).

Pyrimidinium Salts **3a**–**d**, *Classical Conditions: General Procedure A (G.P. A).* To a soln. of 2-bromo-1-(4-halophenyl)ethanone (5 mmol) in Et_2O (20 ml), 4-methylpyrimidine (5 ml, 5 mmol) was added dropwise within 20 min. The soln. was stirred at r.t. for 5 days. The obtained pyrimidinium salt was filtered and dried *in vacuo*.

Pyrimidinium Salts **4a**–**d**, *Classical Conditions: General Procedure B (G.P. B).* A soln. of 4-(4-chlorophenyl)pyrimidine (0.9525 g, 5 mmol) and 2-bromo-1-(4-halophenyl)ethanone (5 mmol) in toluene (20 ml) was heated to reflux under stirring for 5 days. The obtained pyrimidinium salt was filtered off, dried *in vacuo*, and then purified by recrystallization from Et_2O.

Pyrimidinium Salts, Microwave Heating: General Procedure C (G.P.C). Caution! It is hazardous to heat a reaction mixture by microwave rapidly. Typical procedure for the synthesis of cycloimminium salts: The N-heterocycle (5 mmol) and the organic halide (5 mmol) were added to toluene (20 ml) in a tube (*Pyrex* glass or quartz). The tube was then placed in the microwave cell (one or both cells of the *Star* reactor can be used) and heated for the appropriate time while stirring (stirring is desirable but can be replaced by continuously bubbling N_2 (or air) through the mixture). After completion of the heating cycle, the tube was cooled to r.t. and the cycloimminium salt filtered off and purified by recrystallization from an appropriate solvent.

Pyrimidinium Ylides: General Procedure D (G.P.D). A soln. of the pyrimidinium salt (1 mmol) H_2O/EtOH 1:1 (50 ml) was treated with 40% aq. K_2CO_3 soln. The ylide was filtered off, washed with a great amount of H_2O, and dried *in vacuo*. No further purification was required.

Pyrimidinium Chlorides by Reaction of Pyrimidinium Ylides with Hydrochloric Acid: General Procedure E (G.P. E). The pyrimidinium ylide (0.5 mmol) in H_2O was treated with dil. (1:1) aq. HCl soln., which gave the pyrimidinium chloride. The salt was filtered, washed with a large amount of H_2O and dried *in vacuo*. No further purification was required.

Cycloaddition Reactions: General Procedure F (G.P.F). To a soln. of the cycloimminium salt (10 mmol) and methyl prop-2-ynoate (15 mmol) in MeCN (10 ml) under N_2, Et_3N (11 mmol) in MeCN (15 ml) was added dropwise over 4 days while stirring. The resulting mixture was treated with H_2O, the precipitate filtered *in vacuo* and washed thoroughly with H_2O, and the dried crude product first recrystallized from MeOH and then purified by FC (silica gel, adequate eluent). The product was then washed with an appropriate solvent.

1-[2-(4-Fluorophenyl)-2-oxoethyl]-4-methylpyrimidinium Bromide (**3a**). According to the *G.P. A* and *C*, with 2-bromo-1-(4-fluorophenyl)ethanone (1.085 g): Yield 91%. Yellow crystals. M.p. 174–176°. IR: 3100–3050 (C–H(arom.)), 1700 (C=O), 1640, 1600, 1500, 1405 (C=C, C=N(arom.)). ^{1}H-NMR ((D_6)DMSO)[1]): 9.80 (*s*, H–C(2)); 8.75–8.55 (*d*, J=6.0, H–C(5)); 9.40–9.25 (*d*, J=6.0, H–C(6)); 6.50 (*s*, CH_2(7)); 8.40–8.10 (*d*, J=9.0, 2 H, H–C(10)); 7.55–7.35 (*t*, J=9.0, J(H,F)=3.0, 2 H, H–C(11)); 3.20 (*s*, Me–C(4)). Anal. calc. for $C_{13}H_{12}BrFN_2O$ (311.15): C 50.16, H 3.85, N 9.00; found: C 51.02, H 3.90, N 8.92.

1-[2-(4-Chlorophenyl)-2-oxoethyl]-4-methylpyrimidinium Bromide (**3b**). According to the *G.P. A* and *C*, with 2-bromo-1-(4-chlorophenyl)ethanone (1.168 g): Yield 94%. Orange crystals. M.p. 178–179°. IR: 3100–3050 (C–H(arom.)), 1700 (C=O), 1640, 1600, 1550, 1500, 1460, 1405 (C=C, C=N(arom.)). ^{1}H-NMR ((D_6)DMSO)[1]): 9.70 (*s*, H–C(2)); 8.35–8.25 (*d*, J=6.0, H–C(5)); 9.20–9.10 (*d*, J=6.0, H–C(6)); 6.50 (*s*, CH_2(7)); 8.20–7.50 (*d*, J=9.0, 2 H, H–C(10)); 7.70–7.50 (*d*, J=9.0, 2 H, H–C(11)); 2.90 (*s*, Me–C(4)). Anal. calc. for $C_{13}H_{12}BrClN_2O$ (327.61): C 47.63, H 3.66, N 8.54; found: C 47.80, H 3.72, N 8.39.

1-[2-(4-Bromophenyl)-2-oxoethyl]-4-methylpyrimidinium Bromide (**3c**). According to the *G.P. A* and *C*, with 2-bromo-1-(4-bromophenyl)ethanone (1.39 g): Yield 96%. Yellow-orange crystals. M.p.: 166–167°. IR: 3100–3050 (C–H(arom.)), 2980 (C–H(aliph.)), 1698 (C=O), 1625, 1575, 1460 (C=C, C=N(arom.)). ^{1}H-NMR ((D_6)DMSO)[1]): 9.60 (*s*, H–C(2)); 8.30–8.25 (*d*, J=5.6, H–C(5)); 9.16–9.11 (*d*, J=5.6, H–C(6)); 6.45 (*s*, CH_2(7)); 7.85–7.70 (*m*, 4 H, H–C(10), H–C(11)); 2.80 (*s*, Me–C(4)). Anal. calc. for $C_{13}H_{12}Br_2N_2O$ (372.06): C 41.97, H 3.25, N 7.53; found: C 41.80, H 3.30, N 7.30.

1-[2-(4-Iodophenyl)-2-oxoethyl]-4-methylpyrimidinium Bromide (**3d**). According to the *G.P. A* and *C*, with 2-bromo-1-(4-iodophenyl)ethanone (1.67 g): Yield 89%. Yellow needles. M.p. 204–205°. IR: 3100–3050 (C–H(arom.)), 1695 (C=O), 1640, 1580, 1490, 1455, 1415 (C=C, C=N(arom.)). ^{1}H-NMR ((D_6)DMSO)): 9.65 (*s*, H–C(2)); 8.35–8.20 (*d*, J=6.0, H–C(5)); 9.30–9.15 (*d*, J=6.0, H–C(6)); 6.45 (*s*, CH_2(7)); 8.15–8.00 (*d*, J=9.0, 2 H, H–C(10)); 7.90–7.75 (*d*, J=9.0, 2 H, H–C(11)); 2.90 (*s*, Me–C(4)). Anal. calc. for $C_{13}H_{12}BrIN_2O$ (419.06): C 37.26, H 2.88, N 6.68; found: C 37.22, H 2.63, N 6.51.

4-(4-Chlorophenyl)-1-[2-(4-fluorophenyl)-2-oxoethyl]pyrimidinium Bromide (**4a**). According to the *G.P. B* and *C*, with 2-bromo-1-(4-fluorophenyl)ethanone (1.085 g): Yield 80%. White crystals. M.p. 183–185°. IR: 1626*s*

(C=O); 1693, 1590, 1462, 1092 (*s–m*, C=C, C=N(arom.)); 833*s–m* (C–H(arom.), def.); 482*w*(C–Cl); 2910*w* (C–H(aliph.)); 3031 (C–H(arom.), def). ^{1}H-NMR ((D$_6$)DMSO^1): 9.85 (*s*, H–C(2)); 9.48–9.46 (*d*, *J* = 6.8, H–C(6)); 9.06–9.05 (*d*, *J* = 6.8, H–C(5)); 8.51–8.49 (*d*, *J* = 8.0, 2 H, H–C(2′)); 8.23–8.2 (*t*, *J*(H,F) = 3.6, *J* = 8.0, 2 H, H–C(10)); 7.80–7.78 (*d*, *J* = 8.0, 2 H, H–C(3′)); 7.55–7.5 (*t*, *J*(H–F) = 8.8, *J* = 8.0, 2 H, H–C(11)). ^{13}C-NMR ((D$_6$)DMSO^1): 188.67 (C(8)=O); 167.35 (C(4)); 164.25 (C(12)); 154.12 (C(2)); 153.00 (C(6)); 139.63 (C(9)); 131.89 (C(1′)); 131.57 (C(4′)); 131.47 (C(10)); 131.29 (C(2′)); 129.92 (C(3′)); 117.94 (C(5)); 116.17 (C(11)); 62.12 (C(7)). Anal. calc. for $C_{18}H_{13}BrClFN_2O$ (407.65): C 53.03, H 3.21, N 6.87; found: C 52.96, H 3.32, N 6.79.

4-(4-Chlorophenyl)-1-[2-(4-chlorophenyl)-2-oxoethyl]pyrimidinium Bromide (**4b**). According to the *G.P. B* and *C*, with 2-bromo-1-(4-chlorophenyl)ethanone (1.1675 g). Yield 70%. Yellowish crystals. M.p. 228–230°. IR: 1630*s* (C=O); 1698, 1590, 1454, 1341, 1092 (*s–m*, C=C, C=N(arom.)); 821, 762 (*s–m*, C–H(arom.), def.); 484*w* (C–Cl); 2926*w* (C–H(aliph.)); 3029 (C–H(arom.), def.). ^{1}H-NMR ((D$_6$)DMSO)^1): 9.8 (*s*, H–C(2)); 9.43–9.41 (*d*, *J* = 6.4, H–C(6)); 9.04–9.02 (*d*, *J* = 6.4, H–C(5)); 8.51–8.49 (*d*, *J* = 8.4, 2 H, H–C(2′)); 8.14–8.12 (*d*, *J* = 8.0, 2 H, H–C(10)); 7.82–7.76 (*m*, 4 H, H–C(11), H–C(3′)). ^{13}C-NMR ((D$_6$)DMSO)^1): 189.11 (C(8)=O); 167.41 (C(4)); 154.15 (C(2)); 153.01 (C(6)); 139.66 (C(9)); 139.39 (C(12)); 131.85 (C(1′)); 131.44 (C(4′)); 130.73 (C(2′)); 129.95 (C(10)); 129.62 (C(3′)); 129.06 (C(11)); 117.95 (C(5)); 62.15 (C(7)). Anal. calc. for $C_{18}H_{13}BrN_2OCl_2$ (424.10): C 50.97, H 3.08, N 6.60; found: C 51.03, H 3.12, N 6.52.

1-[2-(4-Bromophenyl)-2-oxoethyl]-4-(4-chlorophenyl)pyrimidinium Bromide (**4c**). According to the *G.P. B* and *C*, with 2-bromo-1-(4-bromophenyl)ethanone (1.39 g). Yield 73%. Colorless crystals. M.p. 246–247°. IR: 1628*s* (C=O); 1698, 1587, 1453, 1081 (*s–m*, C=C, C=N(arom.)); 830*s* (C–H(arom.), def.); 482*w* (C–Cl); 2919*w* (C–H(aliph.), 3040*w* (C–H(arom.)). ^{1}H-NMR ((D$_6$)DMSO)^1): 9.84 (*s*, H–C(2)); 9.47–9.45 (*d*, *J* = 6.8, H–C(6)); 9.06–9.04 (*d*, *J* = 6.8, H–C(5)); 8.51–8.49 (*d*, *J* = 8.4, 2 H, H–C(2′)); 8.05–8.03 (*d*, *J* = 8.0, 2 H, H–C(10)); 7.91–7.89 (*d*, *J* = 8.0, 2 H, H–C(11)); 7.80–7.78 (*d*, *J* = 8.4, 2 H, H–C(3′)); 6.54 (*s*, CH$_2$(7)). ^{13}C-NMR ((D$_6$)DMSO)^1): 189.36 (C(8)=O); 167.38 (C(4)); 154.11 (C(2)); 153.00 (C(6)); 139.65 (C(9)); 132.17 (C(1′)); 131.99 (C(2′)); 131.47 (C(4′)); 130.72 (C(10)); 129.94 (C(3′)); 129.60 (C(11)); 128.66 (C(12)); 117.95 (C(5)); 62.13 (C(7)). Anal. calc. for $C_{18}H_{13}Br_2ClN_2O$ (468.57): C 46.14, H 2.79, N 5.98; found: C 46.04, H 2.83, N 5.82.

4-(4-Chlorophenyl)-1-[2-(4-iodophenyl)-2-oxoethyl]pyrimidinium Bromide (**4d**). According to the *G.P. B* and *C*, with 2-bromo-1-(4-iodophenyl)ethanone (1.67 g). Yield 65%. Colorless crystals. M.p. 253–255°. ^{1}H-NMR ((D$_6$)DMSO)^1): 9.73 (*s*, H–C(2)); 9.35–9.33 (*d*, *J* = 6.4, H–C(6)); 9.00–8.98 (*d*, *J* = 6.4, H–C(5)); 8.51–8.49 (*d*, *J* = 8.4, 2 H, H–C(2′)); 8.11–8.09 (*d*, *J* = 8.0, 2 H, H–C(10)); 7.87–7.85 (*d*, *J* = 8.0, 2 H, H–C(3′)); 7.83–7.80 (*d*, *J* = 8.0, 2 H, H–C(11)); 6.38 (*s*, CH$_2$(7)). ^{13}C-NMR ((D$_6$)DMSO)^1): 182.62 (C(8)=O); 167.43 (C(4)); 154.17 (C(2)); 153.03 (C(6)); 139.69 (C(9)); 132.39 (C(1′)); 131.50 (C(4′)); 130.73 (C(2′)); 130.03 (C(10)); 129.64 (C(3′)); 129.52 (C(11)); 117.93 (C(5)); 103.68 (C(12)); 62.01 (C(7)). Anal. calc. for $C_{18}H_{13}BrClIN_2O$ (515.58): C 41.93, H 2.54, N 5.43; found: C 41.86, H 2.62, N 5.38.

4-Methylpyrimidinium 2-(4-Fluorophenyl)-2-oxoethylide (**5a**). According to *G.P. D*, with **3a** (0.311 g, 1.0 mmol). Yield 97%. Brown-red crystals. M.p. 164–166°. IR: 3050 (C–H(arom.)), 2980 (C–H(aliph.)), 1705–1650 (br. band with 2 peaks at 1700; C=O, dimer), 1660 (C=O, ylide), 1610, 1580, 1515, 1430 (C=C, C=N(arom.)). Anal. calc. for $C_{13}H_{11}FN_2O$ (230.24): N 12.17; found N 12.09.

4-Methylpyrimidinium 2-(4-Chlorophenyl)-2-oxoethylide (**5b**). According to *G.P. D*, with **3b** (0.328 g, 1.0 mmol). Yield 98%. Brown crystals. M.p. 148–151°. IR: 3050 (C–H(arom.)), 2980 (C–H(aliph.)), 1705–1650 (br. band with 2 peaks at 1700; C=O, dimer), 1660 (C=O, ylide), 1600, 1570, 1490, 1405 (C=C, C=N(arom.)). Anal. calc. for $C_{13}H_{11}ClN_2O$ (246.70): N 11.35; found N 11.19.

4-Methylpyrimidinium 2-(4-Bromophenyl)-2-oxoethylide (**5c**). According to *G.P. D*, with **3c** (0.372 g, 1.0 mmol). Yield 99%. Red crystals. M.p. 138–140°. IR: 3050 (C–H(arom.)), 2980 (C–H(aliph.)), 1705–1650 (br. band with 2 peaks at 1705; C=O, dimer), 1670 (C=O, ylide), 1590, 1490, 1455, 1400 (C=C, C=N(arom.)). Anal. calc. for $C_{13}H_{11}BrN_2O$ (291.15): N 9.62; found N 9.45.

4-Methylpyrimidinium 2-(4-Iodophenyl)-2-oxoethylide (**5d**). According to *G.P. D*, with **3d** (0.428 g, 1.0 mmol). Yield 97%. Orange-yellow crystals. M.p. 131–134°. IR: 3050 (C–H(arom.)), 2980 (C–H(aliph.)), 1705–1650 (br. band with 2 peaks at 1705; C=O, dimer), 1670 (C=O, ylide), 1600, 1490, 1400 (C=C, C=N(arom.)). Anal. calc. for $C_{13}H_{11}IN_2O$ (338.15): N 8.28; found N 8.20.

4-(4-Chlorophenyl)pyrimidinium 2-(4-Fluorophenyl)-1-oxoethylide (**6a**). According to *G.P. D*, with **4a** (0.407 g, 1.0 mmol). Yield 98%. Red-orange crystals. M.p. 165–168°. UV: 504. IR: 1634 (*s*, br. C=O); 1679, 1586, 1487, 1087 (*s–m*, C=C, C=N(arom.)); 821*s* (C–H(arom.), def.); 498*w* (C–Cl); 3058*w* (C–H(arom.)); 2923*w* (C–H(aliph.)). Anal. calc. for $C_{18}H_{12}ClFN_2$ (326.75): N 8.57; found N 8.49.

4-(4-Chlorophenyl)pyrimidinium 2-(4-Chlorophenyl)-2-oxoethylide (**6b**). According to *G.P. D*, with **4b** (0.424 g, 1.0 mmol). Yield 99%. Red crystals. M.p. 148–150°. UV: 506.5. IR: 1632*s* (br. C=O); 1680, 1586,

1093 (*s–m*, C=C, C=N(arom.)); 833*s* (C–H(arom.), def.); 497*w* (C–Cl); 3056*w* (C–H(arom.)); 2925*w* (C–H(aliph.)). Anal. calc. for $C_{18}H_{12}Cl_2N_2O$ (343.20): N 8.16; found N 8.09.

4-(4-Chlorophenyl)pyrimidinium 2-(4-Bromophenyl)-2-oxoethylide (**6c**). According to *G.P. D*, with **4c** (0.468 g, 1.0 mmol). Yield 97%. Red-orange crystals. M.p. 153–156°. UV: 507. IR: 1629*s* (br., C=O); 1679, 1582, 1455, 1092 (*s–m*, C=C, C=N(arom.)); 830*s* (C–H(arom.), def.); 496*w* (C–Cl); 3050*w* (C–H(arom.)); 2920*w* (C–H(aliph.)). Anal. calc. for $C_{18}H_{12}OBrClN_2$ (387.66): N 7.23; found: N 7.14.

4-(4-Chlorophenyl)pyrimidinium 2-(4-Iodophenyl)-2-oxoethylide (**6d**). According to *G.P. D*, with **4d** (0.515 g, 1.0 mmol). Yield 92%. Red-orange crystals. M.p. 163–166°. UV: 508. IR: 1624*s* (br., C=O); 1679, 1584, 1453, 1092 (*s–m*, C=C, C=N(arom.)); 834*s* (C–H(arom.), def.); 494*w* (C–Cl); 3048*w* (C–H(arom)); 2922*w* (C–H(aliph.)). Anal. calc. for $C_{18}H_{12}ClIN_2O$ (434.66): N 6.44; found: N 6.36.

1-[2-(4-Fluorophenyl)-2-oxoethyl]-4-methylpyrimidinium Chloride (**8a**). According to *G.P. E*, with **5a** (0.115 g, 0.5 mmol). Yield 91%. Yellow crystals. M.p. 162–164°.

1-[2-(4-Chlorophenyl)-2-oxoethyl]-4-methylpyrimidinium Chloride (**8b**). According to *G.P. E*, with **5b** (0.123 g, 0.5 mmol). Yield 93%.Yellowish crystals M.p. 166–168°.

1-[2-(4-Bromophenyl)-2-oxoethyl]-4-methylpyrimidinium Chloride (**8c**). According to *G.P. E*, with **5c** (0.145 g, 0.5 mmol). Yield 92%. Colorless crystals. M.p. 154–156°.

1-[2-(4-Iodophenyl)-2-oxoethyl]-4-methylpyrimidinium Chloride (**8d**). According to *G.P. E*, with **5d** (0.169 g, 0.5 mmol). Yield 90%. Colorless crystals. M.p. 194–195°.

4-(4-Chlorophenyl)-1-[2-(4-fluorophenyl)-2-oxoethyl]pyrimidinium Chloride (**9a**). According to *G.P. E*, with **6a** (0.163 g, 0.5 mmol). Yield 91%. Yellowish crystals. M.p. 178–180°.

4-(4-Chlorophenyl)-1-[2-(4-chlorophenyl)-2-oxoethyl]pyrimidinium Chloride (**9b**). According to *G.P. E*, with **6b** (0.171 g, 0.5 mmol). Yield 92%. Yellow crystals. M.p. 211–214°.

4-(4-Chlorophenyl)-1-[2-(4-bromophenyl)-2-oxoethyl]pyrimidinium Chloride (**9c**). According to *G.P. E*, with **6c** (0.193 g, 0.5 mmol). Yield 91%. Yellow–orange crystals. M.p. 207–209°.

4-(4-Chlorophenyl)-1-[2-(4-iodophenyl)-2-oxoethyl]pyrimidinium Chloride (**9d**). According to *G.P. E*, with **6d** (0.217 g, 0.5 mmol). Yield 91%. Yellow crystals. M.p. 237–239°.

Methyl 3-Methyl-7-(4-chlorobenzoyl)pyrrolo[1,2-c]pyrimidine-5-carboxylate (**11a**). According to *G.P. F*, with **3b** (3.721 g, 10 mmol). Washing with acetone and subsequent FC (silica gel, column 13×2 cm, *B*) gave yellow cubic crystals. M.p. 195°. IR: 1730*s* (C=O, ester); 1645*s* (C=O, ketone); 1590, 1515, 1470, 1450, 1405 (*s–m*, C=C, C=N(arom.)); 1220, 1110*s* (C–O–C); 2950*w* (C–H(aliph.)). ^{1}H-NMR ($CDCl_3$)[1]): 10.48 (*s*, H–C(1)); 8.04 (*s*, H–C(4)); 7.78 (*s*, H–C(6)); 7.78 (*d*, *J*=8, 2 H, H–C(10)); 7.50 (*d*, *J*=8, 2 H, H–C(11)); 3.91 (*s*, COOMe); 2.63 (*s*, Me). ^{13}C-NMR ($CDCl_3$)[1]): 183.86 (C(8)=O); 163.92 (*C*OOMe); 152.59 (C(1)); 148.88 (C(3)); 140.62 (C(12)); 138.46 (C(4a)); 137.35 (C(9)); 130.37 (C(10)); 129.76 (C(4)); 128.93 (C(11)); 121.78 (C(7)); 117.80 (C(6)); 105.40 (C(5)); 51.51 (MeO), 23.91 (Me). Anal. calc. for $C_{17}H_{13}ClN_2O_3$ (328.75): N 8.52; found: N 8.50.

Methyl 3-(4-Chlorophenyl)-7-(4-chlorobenzoyl)pyrrolo[1,2-c]pyrimidine-5-carboxylate (**11b**). According to *G.P. F*, with **4b** (4.68 g, 10 mmol). Washing with MeOH and subsequent FC (silica gel, column 13×2 cm, *A*) gave yellowish crystalline plates. M.p. 209–210°. IR: 1711*s* (C=O, ester); 1622*s* (C=O, ketone); 1523, 1477, 1443, 1404 (*s–m*, C=C, C=N(arom.)); 1209, 1090*s* (C–O–C); 2952*w* (C–H(aliph.)); 429*s* (C–Cl). ^{1}H-NMR ($CDCl_3$)[1]): 10.53 (*s*, H–C(1)); 8.56 (*s*, H–C(4)); 8.11–8.09 (*d*, *J*=8.8, 2 H, H–C(10)); 7.81–7.79 (*d*, *J*=8.4, 2 H, H–C(2′)); 7.78 (*s*, H–C(6)); 7.57–7,55 (*d*, *J*=7.6, H–C(3)); 7.53–7.51 (*d*, *J*=8.4, 2 H, H–C(3′)); 7.48–7.46 (*d*, *J*=8.8, 2 H, H–C(11)); 3.94 (*s*, COOMe). ^{13}C-NMR ($CDCl_3$)[1]): 183.88 (C(8)=O); 163.79 (*C*OOMe); 148.82 (C(4a)); 140.73 (C(1)); 140.70 (C(1′)); 138.57 (C(3)); 137.13 (C(12)); 136.37 (C(9)); 134.83 (C(4′)); 130.36 (C(2′)); 129.73 (C(6)); 129.20 (C(11)); 128.94 (C(3′)); 128.16 (C(10)); 122.13 (C(5)); 108.39 (C(4)); 106.93 (C(7)); 51.65 (Me). Anal. calc. for $C_{22}H_{14}Cl_2N_2O_3$ (425.27): N 6.59; found: N 6.52.

Methyl 2-Methyl-5-(4-chlorobenzoyl)pyrrolo[1,2-a]pyrimidine-7-carboxylate (**12a**). According to *G.P. F*, with **3b** (3.7206 g, 10 mmol). Washing with acetone and subsequent FC (silica gel, column 13×2 cm, *A*) gave yellowish needles. M.p. 187°. IR: 1730*s* (C=O, ester); 1645*s* (C=O, ketone); 1590, 1515, 1470, 1450, 1405 (*s–m*, C=C, C=N(arom.)); 1220, 1110*s* (C–O–C); 2950*w* (C–H(aliph.)). ^{1}H-NMR ($CDCl_3$)[1]): 7.70 (*d*, *J*=7.5, H–C(4)); 5.82 (*d*, *J*=7.5, H–C(3)); 8.24 (*s*, H–C(6)); 7.78 (*d*, *J*=8, 2 H, H–C(10)); 7.47 (*d*, *J*=8, 2 H, H–C(11)); 3.84 (*s*, COOMe); 3.73 (*s*, Me). ^{13}C-NMR ($CDCl_3$)[1]): 194.12 (C(8)=O); 166.41 (*C*OOMe); 164.21 (C(7a)); 142.31 (C(2)); 138.17 (C(12)); 137.82 (C(5)); 135.01 (C(4)); 134.27 (C(3)); 130.68 (C(10)); 128.83 (C(11)); 128.69 (C(6)); 111.04 (C(7)); 51.86 (MeO); 29.75 (Me). Anal. calc. for $C_{17}H_{13}ClN_2O_3$ (328.75): N 8.52; found: N 8.50.

Methyl 2-(4-Chlorophenyl)-5-(4-chlorobenzoyl)pyrrolo[1,2-a]pyrimidine-7-carboxylate (**12b**). According to *G.P. F*, with **4b** (4.68 g, 10 mmol). Washing with MeOH and subsequent FC (silica gel, column 13×2 cm, *A*) gave

yellow needles. M.p. 237–238°. IR: 1711*s* (C=O, ester); 1622*s* (C=O, ketone); 1523, 1477, 1443, 1404 (*s*–*m*, C=C, C=N(arom.)); 1252, 1136*s* (C–O–C); 2952*w* (C–H(aliph.)); 429*s* (C–Cl). ^{1}H-NMR ($CDCl_3$)[1]): 10.12–10.10 (*d*, *J* = 7.6, H–C(4)); 8.24–8.22 (*d*, *J* = 8.4, 2 H, H–C(10)); 7.99 (*s*, H–C(6)); 7.80–7.78 (*d*, *J* = 8.4, 2 H, H–C(2′)); 7.57–7.55 (*d*, *J* = 7.6, H–C(3)); 7.53–7.48 (m, 4 H, H–C(11), H–C(3′)); 3.97 (*s*, COOMe). ^{13}C-NMR ($CDCl_3$)[1]): 184.38 (C(8)=O); 163.43 (*C*OOMe); 156.90 (C(2)); 144.86 (C(7a)); 138.42 (C(1′)); 137.85 (C(9)); 137.14 (C(12)); 136.24 (C(4)); 134.67 (*C*(4′)); 131.01 (C(6)); 130.36 (C(2′)); 129.80 (C(3′)); 129.23 (C(10)); 128.92 (C(11)); 119.04 (C(7)); 107.53 (C(3)); 105.85 (C(5)); 51.72 (Me). Anal. calc. for $C_{22}H_{14}Cl_2N_2O_3$ (425.27): N 6.59; found: N 6.51.

Note. The synthesis of compounds **3c** and **5c**, as well as of **11a** and **12a** were published in [17] and [15], resp.

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