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Convenient synthesis of 2-(het)arylpyrrolidines via stable 1-pyrrolinium salts

Anna S. Melyashova [a], Andrey V. Smolobochkin [a], Almir S. Gazizov [a, *], Julia K. Voronina [a, b], Alexander R. Burilov [a], Michail A. Pudovik [a]

[a] Arbuzov Institute of Organic and Physical Chemistry, FRC Kazan Scientific Center, Russian Academy of Sciences, 420088, Arbuzova str., 8, Kazan, Russian Federation

[b] N. S. Kurnakov Institute of General and Inorganic Chemistry, RAS, 31 Leninsky Av., 119991, Moscow, Russian Federation

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ABSTRACT

The efficient method for the synthesis of 2-(het)aryl-substituted pyrrolidines possessing exocyclic carbon-carbon double bond via the Mannich-type reaction of stable 3-arylidene-1-pyrrolinium salts with different heterocyclic *C*-nucleophiles is proposed.

1. Introduction

Pyrrolidine core is a frequently occurring motif in many biologically active compounds, both natural and synthetic [1,2]. Moreover, recently published data indicates [3] that pyrrolidine ring is one of the most widespread heterocyclic scaffold in approved drugs. 2-(Het)aryl-substituted pyrrolidine derivatives are of a special interest since a range of approved drugs possessing this scaffold have appeared in recent years (antiviral drugs Velpatasvir [4], Daclatasvir [5], anti-cancer drugs Acalabrutinib [6], Larotrectinib [7], Fig. 1). As a result, development of methods for the synthesis of such compounds gain increasing importance. Approaches to 2-(hetero)arylpyrrolidines described so far can be divided into two main groups. The first one includes the (hetero) arylation of an existing pyrrolidine fragment and the second is based on the formation of pyrrolidine ring from acyclic precursors.

One of the promising methods for the synthesis of pyrrolidine derivatives within the first approach is the reaction of electrophilic 1-pyrrolines with nucleophiles. Different nucleophiles have been employed, thus allowing synthesis of pyrrolidines possessing phosphoryl fragment [8,9], various aliphatic [10–12] and aromatic [13,14] substituents. However, a thermal and chemical instability of many 1-pyrrolines even at room temperature, as well as their multi-stage synthesis [15,16], limits somewhat widespread usage of these compounds.

Earlier, we reported one-pot approach to 3-arylidene-1-pyrrolinium salts via tandem Mannich-type intramolecular cyclization/[1,3]-sigmatropic rearrangement of *N*-(4,4-diethoxybutyl)arylimines [17]. In contrast to parent 1-pyrroline, these compounds are solid substances that are stable at room temperature for an indefinitely long time. At the same time, they possess a key imine bond suitable for further modification. All of these renders 3-arylidene-1-pyrrolines valuable precursors for 2-substituted pyrrolidines synthesis. Interestingly, in spite of these compounds being known for a long time [18], their reactions with *C*-nucleophiles remain rather unexplored [10,11,17]. Recently, we have demonstrated that imine bond of 3-arylidene-1-pyrrolines is reactive towards some electron-rich arenes in acidic media hence providing easy access to 3-arylidene-2-arylpyrrolidines [19]. Similar reaction was reported later by Jana and coworkers [20], except that activation of C=N bond in this case was achieved via acetylation of imine nitrogen. Herein we report the extension of our methodology to heterocyclic *C*-nucleophiles and successful synthesis of various 2-(het)arylpyrrolidines.

* Corresponding author.
E-mail address: agazizov@iopc.ru (A.S. Gazizov).

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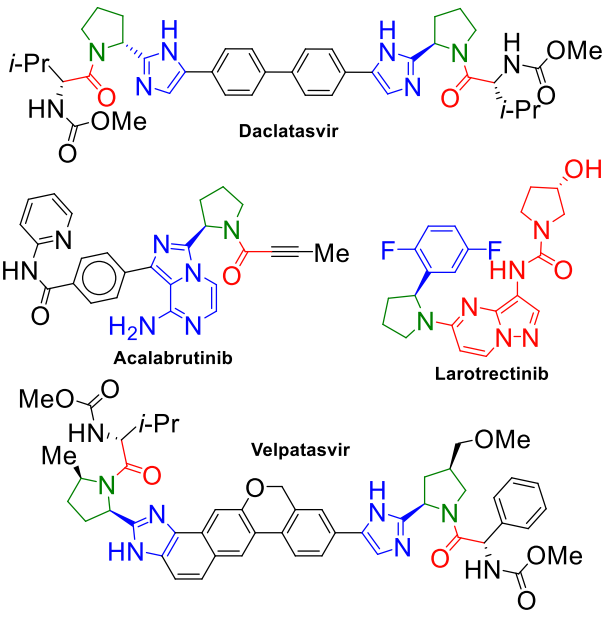


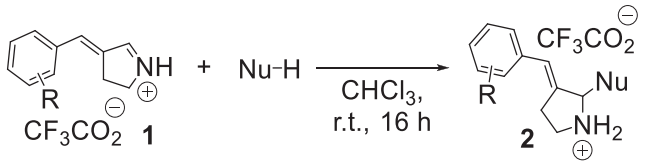
Fig. 1. 2-(Het)arylpyrrolidines of biological importance.

2. Results and discussion

We initiated our studies with the screening of the reaction conditions for the interaction of (*E*)-4-benzylidene-1-pyrrolinium trifluoroacetate **1a** with 4-hydroxy-6-methyl-2H-pyran-2-one (Scheme 1). First, we tried conditions previously found to be optimal for the interaction of 3-arylidine-1-pyrrolines with phenols [19], i.e., prolonged heating of reactants in benzene. The formation of target pyrrolidine **2a** was observed according to NMR spectra of reaction mixture, alongside with considerable amount of unidentified byproducts. Further studies revealed that byproducts formation is suppressed significantly when the reaction is carried out in chloroform solution at room temperature. Thus, these conditions were used for further experiments.

We next explored the scope of 1-pyrrolinium salts **1a-e** with different substituents in the phenyl moiety using the 4-hydroxy-6-methyl-2*H*-pyran-2-one as the model compound (Table 1, entries 1–5). Electron-donating methoxy group produced the corresponding product **2d** with fairly high yield. Electron-withdrawing fluorine and chlorine substituents were also well tolerated (Table 1, entries 2–4). At the same time, the presence of nitro group at the para-position of phenyl ring decreased the yield of the target compound drastically (Table 1, entry 5). The 1-pyrroline **1e** was obtained with 8% yield only, and most of the starting material was recovered from reaction mixture.

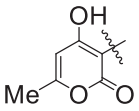
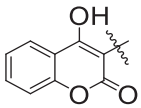
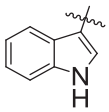
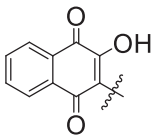
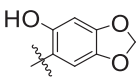
Next, the substrate scope was tested by utilizing different *C*-nucleophiles. The benzo annelated derivative of hydroxy-2*H*-pyran-2-one, 4-hydroxy-2*H*-chromen-2-one appeared to be much



1: R = H (a), 4-Cl (b), 3-F (c), 4-MeO (d), 4-NO_2 (e)

Scheme 1. Reaction of 1-pyrrolinium salts **1** with *C*-nucleophiles.

Table 1
Synthesis of 2-(het)arylpyrrolidines **2**.

Entry	R	Nu	Cmpd	Yield, %[a]
1	H		**2a**	79
2	4-Cl		**2b**	90
3	3-F		**2c**	81
4	4-MeO		**2d**	84
5	4-NO_2		**2e**	8
6	H		**2f**	12
7	4-Cl		**2g**	28
8	3-F		**2h**	22
9	4-NO_2		**2i**	22
10	H		**2j**	83[b]
11	4-Cl		**2k**	91[b]
12	3-F		**2l**	76[b]
13	4-MeO		**2m**	45[b]
14	H		**2n**	82[c]
15	4-Cl		**2o**	86[c]
16	3-F		**2p**	85[c]
17	4-MeO		**2q**	85[c]
18	H		**2r**	97
19	4-Cl		**2s**	99
20	3-F		**2t**	61
21	4-MeO		**2u**	62
22	4-NO_2		**2v**	23
23	H		**2w**	71
24	4-Cl		**2x**	80
25	3-F		**2y**	58

[a] Isolated yield.
[b] Reaction conditions: $CHCl_3$, reflux, 24 h.
[c] Reaction conditions: benzene, reflux, 24 h.

less reactive toward 1-pyrrolinium salts **1**. The yields of the target compounds **2f-i** did not exceed 20–30% (Table 1, entries 6–9).

Similarly, indole reacted with 3-arylidyne1-pyrroliniums **1** at room temperature to give pyrrolidines **2j-m**, albeit in low yield. However, refluxing reactants in chloroform allowed to increase yield of target compounds up to 91% (Table 1, entries 10–13). Pyrrole appeared to be even less reactive. Thus, only prolonged refluxing in higher-boiling benzene provided target 2-(pyrrol-2-yl)-3-arylidenepyrrolidines **2n-q** (Table 1, entries 14–15).

Since both pyrrole and indole are basic, they are able to deprotonate starting pyrrolinium salts **1** in coarse of reaction forming equilibrium mixture of 1-pyrroline, 1-pyrrolinium, 1*H*-pyrrol-1-ium or 1*H*-indol-1-ium salts and pyrrole or indole themselves. The deprotonation of 1-pyrrolinium salt reduces electrophilicity of imine bond. Moreover, the formation of 1*H*-pyrrol-1-ium or 1*H*-indol-1-ium salts also decreases their reactivity towards electrophilic substitution. This may explain the lower reaction rates and harsher conditions required in case of these heterocycles. The difference in reactivity of pyrrole and indole may also be attributed to higher basicity of the former.

We also tested benzo[*d*][1,3]dioxol-5-ol (sesamol) and non-heterocyclic 2-hydroxynaphthalene-1,4-dione as *C*-nucleophiles in this reaction. Both of them reacted smoothly at room temperature to give 2-substituted pyrrolidines **2r-u** and **2w-y** with good to high yields (Table 1, entries 18–21 and 23–25). Again, nitro-substituted pyrrolidine **2v** was the exception, which was obtained with only 23% yield (Table 1, entry 22).

According to x-ray data [17], imine bond, double C=C bond and aromatic ring are fully conjugated in 3-arylidine-1-pyrrolines **1**. So, the presence of electron-donating groups in phenyl substituent should lower the partial charge on imine carbon. On the contrary, electron-withdrawing groups should increase it. As a result, the

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reactivity of 1-pyrrolinium salts **1d** and **1e** should be inverse to that observed in our experiments.

Quantum chemistry calculations were performed for nitro- and methoxy-substituted 1-pyrrolinium salts **1d,e** to justify these considerations. Initial structures taken from x-ray data were fully optimized at the B3LYP/6−311++G(2d,p) theory level. All optimizations were followed by frequency calculations at the same level of theory in order to check that optimized structures really correspond to true minima. All calculations have been performed with the Gaussian 16 package [21].

It is well-known that electrophile-nucleophile interactions are driven by electrostatic attraction between positive and negative charges (electrostatic control) and orbital overlap between the HOMO of nucleophile and the LUMO of electrophile (orbital control). Since it was hard to estimate a dominant factor in our case, we performed both Hirshfeld charges calculation and NBO analysis [22] for 1-pyrroliniums **1d,e**. Calculated Hirshfeld charges alongside with lowest unoccupied natural bond orbitals for both compounds are presented on Fig. 2.

The results obtained suggest that the positive charge is strongly delocalized in 1-pyrrolinium salt **1d** and the aromatic carbon atom next to hydroxyl group is the most positively charged. On the other hand, the delocalization in compound **1e** occurs to a lesser extent and the nitrogen atom of nitro group bears a largest charge in this case. This is in agreement with general electron-withdrawing nature of nitro substituent and electron-donating properties of methoxy group.

In accordance with our qualitative assumptions, imine carbon atom in nitro substituted 1-pyrroline **1e** is more positively charged than in methoxy substituted 1-pyrroline **1d**. Moreover, NBO analysis indicates that LUMO of salt **1e** is localized mainly on imine bond (−8.753 eV). At the same time, LUMO of 1-pyrroline **1d** is localized on aromatic carbon atom (−6.734 eV) and only the next higher-energy orbital is localized on the C═N bond (−5.169 eV). Considering energy difference of these orbitals (−8.753 vs −5.169 eV) and higher positive charge of imine carbon atom in case of compound **1e** (+0.223 vs + 0.196), imine bond in nitro-substituted pyrrolinium salt **1e** should be more prone to nucleophilic attack both in case of electrostatic and orbital control. Taking this into account, the low yield of pyrrolidine **2e** cannot be attributed to electronic effects of substituent.

Additionally, intermediates for the reaction of pyran-2-one with 1-pyrrolines **1d,e** were explored using quantum chemistry methods. Interestingly, obtained results suggest a strong interaction of nitrogen atom lone pair with positively charged carbon atom and formation of a four-membered azetidine ring during reaction. Thus, two intermediates with different orientation of pyran-2-one ring are possible for each case (Fig. 3). Calculated energies of intermediates relative to energies of reactants are given in Table 2. All calculations were performed at B3LYP/6−311++G(2d,p) theory level. According to the Hammond's postulate, these values can be closely approximated to energies of corresponding transition states. As seen from the table, intermediates with *exo*-orientation of pyran-2-one ring are about 2 kcal/mol lower in energy in each case. However, energy difference between intermediates *endo*-**INT-PYR-NO2**, *endo*-**INT-PYR-OMe** and *exo*-**INT-PYR-NO2**, *exo*-**INT-PYR-OMe** is much greater (≈7 kcal/mol). Again, obtained results indicate that methoxy-substituted pyrrolinium salt **1d** should be less reactive compared to its nitro-substituted counterpart **1e**.

We speculated that a low yield of compound **2e** may be due to the extremely poor solubility of starting pyrroline **1e**. So, not the interaction of 1-pyrroline **1e** with nucleophile, but a dissolution of starting material becomes a rate-limiting step of the reaction. Indeed, increasing the reaction time resulted in slightly improved yields of target compound, although a significant amount of unreacted pyrroline **1e** was still present in reaction mixture (Table 3). However, even after 3 months the yield was only 20%, and neither changing solvents nor refluxing allowed to improve it further.

Similarly, energies of intermediates for the reaction of pyrrolines **1d,e** with chromen-2-one have been calculated (Table 2). Energies of all intermediates in this case is 1−3 kcal/mol higher than those for pyran-2-one. According to Eyring equation, 1 kcal/mol difference in activation energy results in almost 6-fold difference in reaction rates at room temperature. Thus, lower reactivity of chromen-2-one compared to pyran-2-one towards 1-pyrrolines may be attributed to these energy differences.

Additionally, Hirshfeld charges calculation and NBO analysis

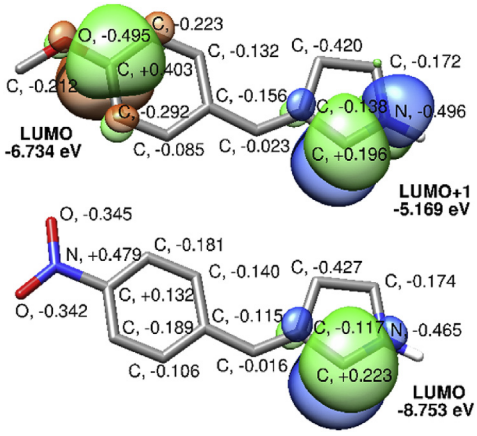

Fig. 2. Hirshfeld charges and natural bond orbitals of compounds **1d,e** as obtained from quantum chemistry calculations (B3LYP/6−311++G(2d,p), Gaussian 16).

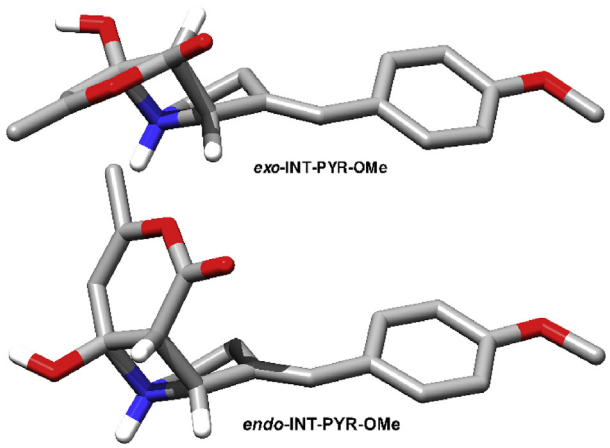

Fig. 3. Calculated geometries of intermediates for the reaction of pyran-2-one with 1-pyrroline **1d** (B3LYP/6−311++G(2d,p), Gaussian 16).

Table 2
Calculated energies of reaction intermediates.[a].

R	MeO	NO_2
	pyran-2-one	
endo-**INT-PYR**	30.56	23.22
exo-**INT-PYR**	28.68	21.41
	chromen-2-one	
endo-**INT-CHROM**	33.51	25.49
exo-**INT- CHROM**	29.73	22.07

[a] Relative to calculated energies of reactants.

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Table 3
Reaction of 1-pyrroline **1e** with pyran-2-one.

Entry	Reaction time	Solvent	Temperature	2e, %[a]	1e, %[a]
1	16 h	$CHCl_3$	r.t.	11	81
2	2 weeks	$CHCl_3$	r.t.	15	77
3	1 month	$CHCl_3$	r.t.	17	72
4	3 months	$CHCl_3$	r.t.	20	67
5	16 h	$CHCl_3$	reflux	15	79
6	72 h	benzene	reflux	19	78

[a] According to NMR data.

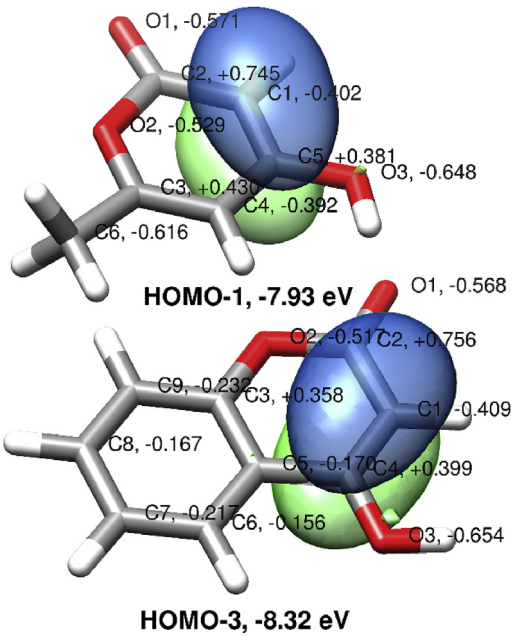

Fig. 4. Hirshfeld charges and natural bond orbitals of 4-hydroxy-6-methyl-2*H*-pyran-2-one and 4-hydroxy-2*H*-chromen-2-one as obtained from quantum chemistry calculations (B3LYP/6−311++G(2d,p), Gaussian 16).

were performed for optimized geometries of 4-hydroxy-6-methyl-2*H*-pyran-2-one and 4-hydroxy-2*H*-chromen-2-one (B3LYP/6−311++G(2d,p), Gaussian 16). Energy of occupied orbital located at C1 atom of 4-hydroxy-6-methyl-2*H*-pyran-2-one is −7.93 eV, whereas energy of occupied orbital located at C1 atom for 4-hydroxy-2*H*-chromen-2-one is lower and equals to −8.32 eV (Fig. 4). Although appropriate Hirshfeld charges are close to each other (−0.402 vs −0.409), difference in orbitals energy may also contribute to lower reactivity of chromen-2-one.

3. Conclusion

In conclusion, we have demonstrated an efficient method for the synthesis of various 2-(het)arylpyrrolidines starting from shelf-stable 3-arylidene-1-pyrrolinium salts. Both electron-rich *N*- and *O*-heterocycles may be introduced in pyrrolidine ring by simple metal-free procedure.

4. Experimental section

4.1. General information

^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 400 (working frequency 400.1 MHz for ^{1}H, 100.6 for ^{13}C), Avance 500 (working frequency 500.1 MHz for ^{1}H, 125.8 for ^{13}C) and Avance 600 (working frequency 600.1 MHz for ^{1}H, 150.9 for ^{13}C) spectrometers in $(CD_3)_2SO$, $CDCl_3$ and CD_3OD relative to the residual solvent protons. ESI-TOF mass spectra were recorded on a AmazonX (Bruker Daltonik GmbH) instrument. MALDI-TOF mass spectra were recorded on a Bruker ULTRAFLEX III TOF/TOF instrument (with 2,5-dihydroxybenzoic acid matrix) instrument. IR spectra were obtained with a Bruker Vector 22 spectrometer. Elemental analysis was performed on Carlo Erba EA 1108 instrument. Melting points were determined in glass capillaries with a Stuart SMP 10 apparatus. All solvents were purified and dried according to standard procedures.

4.2. General procedure for synthesis of 2-(het)aryl-3-arylidenepyrrolidines ***2a-i,r-y***

To a solution of 3-arylidine-1-pyrroline **1** (1.6 mmol) in chloroform (10 mL) appropriate C-nucleophile (1.6 mmol) was added. The reaction mixture was stirred at room temperature for 16 h. The precipitate was filtered off, washed with diethyl ether and dried in vacuum (0.1 torr, r.t., 3 h) to give target compounds **2a-i,r-y**.

4.3. General procedure for synthesis of 2-(indol-3-yl)-3-arylidenepyrrolidines ***2j-m***

To a solution of 3-arylidine-1-pyrroline **1** (1.6 mmol) in chloroform (10 mL) indole (0.19 g, 1.6 mmol) was added. The reaction mixture was refluxed for 24 h. The solvent was evaporated in vacuum, the residue washed thoroughly with hexane and dried in vacuum (0.1 torr, r.t., 3 h) to give target compounds **2j-m**.

4.4. General procedure for synthesis of 2-(pyrrol-2-yl)-3-arylidenepyrrolidines ***2n-q***

To a solution of 3-arylidine-1-pyrroline **1** (1.6 mmol) in benzene (10 mL) pyrrole (0.12 mL, 1.6 mmol) was added. The reaction mixture was refluxed for 24 h. The solvent was evaporated in vacuum, the residue washed thoroughly with diethyl ether and dried in vacuum (0.1 torr, r.t., 3 h) to give target compounds **2n-q**.

4.5. (E)-3-Benzylidene-2-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)pyrrolidin-1-ium trifluoroacetate (***2a***)

Beige solid, yield 502 mg, 97%; [Found: C, 57.41; H, 4.59; N 3.52. $C_{19}H_{18}F_3NO_5$ requires C, 57.43; H, 4.57; N 3.53%]; mp 166–167 °C; n_{max} (KBr) 1674, 798, 779 cm^{-1}; d_H (600 MHz DMSO-d_6) 2.23 (3H, s, CH_3), 2.97–3.09 (2H, m, CH_2), 3.35–3.49 (1H, m, CH_2), 3.59–3.69 (1H, m, CH_2), 5.39 (1H, s, CH), 6.14–6.16 (2H, m, CH), 6.17 (1H, s, CH_{Ar}), 7.25 (1H, t, *J* 7.2 Hz, CH_{Ar}), 7.30 (3H, m, CH_{Ar}), 8.31 (1H, s, OH), 8.55 (1H, br.s, NH_2^+), 9.54 (1H, br.s, NH_2^+); d_C (600 MHz, DMSO-d_6) 20.03, 29.58, 44.22, 57.79, 79.67, 95.67, 100.92, 120.58, 128.95, 130.40, 131.90, 132.00, 135.79, 139.66, 163.75, 164.01, 170.24; ESI, *m/z*: 284.2 [M-CF3COO$^-$]$^+$.

4.6. (E)-3-(4-chlorobenzylidene)-2-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)pyrrolidin-1-ium trifluoroacetate (***2b***)

Beige solid, yield 659 mg, 90%; [Found: C, 52.84; H, 3.98; Cl, 8.20; N 3.25. $C_{19}H_{17}ClF_3NO_5$ requires C, 52.85; H, 3.97; Cl, 8.21; N 3.24%]; mp 130–132 °C; n_{max} (KBr) 1664, 1590, 796, 777 cm^{-1}; d_H (600 MHz DMSO-d_6) 2.23 (3H, s, CH_3), 2.97–3.01 (1H, m, CH_2), 3.02–3.06 (1H, m, CH_2), 3.37–3.44 (1H, m, CH_2), 3.60–3.66 (1H, m, CH_2), 5.40 (1H, s, CH), 6.15 (1H, s, CH), 6.20 (1H, s, CH_{Ar}), 7.36 (2H, d, *J* 8.6 Hz, CH_{Ar}), 7.42 (2H, d, *J* 8.6 Hz, CH_{Ar}), 8.31 (1H, s, OH), 8.52 (1H, br.s, NH_2^+), 8.62 (1H, br.s, NH_2^+); d_C (600 MHz, DMSO-d_6) 20.03, 29.58, 44.22, 57.79, 79.67, 95.67, 100.92, 120.58, 128.95, 130.40,

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131.90, 132.00, 135.79, 139.66, 163.75, 164.01, 170.24; ESI, *m*/*z*: 318.2 [M-CF3COO$^-$]$^+$.

*4.7. (E)-3-(3-fluorobenzylidene)-2-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)pyrrolidin-1-ium trifluoroacetate (**2c**)*

White solid, yield 590 mg, 82%; [Found: C, 52.93; H, 4.14; N 3.39. $C_{19}H_{17}F_4NO_5$ requires C, 54.95; H 4.13,; N 3.37%]; mp 176–177 °C; n_{max} (KBr) 1674, 1584, 797, 767 cm^{-1}; d_H (600 MHz DMSO-d_6) 2.23 (3H, s, CH_3), 2.98–3.10 (2H, m, CH_2), 3.37–3.44 (1H, m, CH_2), 3.59–3.66 (1H, m, CH_2), 5.40 (1H, s, CH), 6.16–6.18 (1H, m, CH), 6.19 (1H, s, CH_{Ar}), 7.06–7.10 (1H, m, CH_{Ar}), 7.36–7.43 (1H, m, CH_{Ar}), 8.55 (1H, br.s, NH_2^+), 9.60 (1H, br.s, NH_2^+); d_C (600 MHz, DMSO-d_6) 20.03, 29.62, 45.20, 57.88, 95.94, 101.06, 114.19, 114.33, 115.02, 115.16, 120.67, 124.85, 130.87, 139.84, 140.47, 161.91, 163.52, 163.94, 170.53; ESI, *m*/*z*: 302.2 [M-CF3COO$^-$]$^+$.

*4.8. (E)-3-(4-methoxybenzylidene)-2-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)pyrrolidin-1-ium trifluoroacetate (**2d**)*

White solid, yield 610 mg, 84%; [Found: C, 56.20; H, 4.71; N 3.30. $C_{20}H_{20}F_3NO_6$ requires C, 54.21; H 4.72,; N 3.28%]; mp 166–167 °C; n_{max} (KBr) 1674, 1513, 797, 752 cm^{-1}; d_H (600 MHz DMSO-d_6) 2.23 (3H, s, CH_3), 2.92–3.03 (2H, m, CH_2), 3.59–3.65 (2H, m, CH_2), 3.76 (1H, s, CH_2), 5.36 (1H, s, CH), 6.07 (1H, s, CH), 6.18 (1H, s, CH_{Ar}), 6.92 (2H, d, *J* 8.4 Hz, CH_{Ar}), 7.26 (2H, s, *J* 8.4 Hz CH_{Ar}), 8.31 (1H, br.s, NH_2^+), 9.51 (1H, br.s, NH_2^+); d_C (600 MHz, DMSO-d_6) 20.02, 29.40, 45.20, 55.61, 57.82, 88.59, 95.68, 101.05, 114.44, 121.31, 129.48, 130.03, 135.73, 158.75, 163.87; ESI, *m*/*z*: 314.2 [M-CF3COO$^-$]$^+$.

*4.9. (E)-3-(4-nitrobenzylidene)-2-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)pyrrolidin-1-ium trifluoroacetate (**2e**)*

Yellowish solid, yield 60 mg, 8%; [Found: C, 51.58; H, 3.88; N 6.32. $C_{19}H_{17}F_3N_2O_7$ requires C, 51.59; H 3.87; N 6.33%]; mp 173–174 °C; n_{max} (KBr) 1676,1376, 857 cm^{-1}; d_H (600 MHz DMSO-d_6) 1.10 (3H, t, 7.0 Hz, CH_3, 3.05–3.14 (2H, m, CH_2), 3.20–3.24 (1H, m, CH_2), 3.32–3.49 (1H, m, CH_2), 5.22 (1H, d, 2.1 Hz, CH), 5.95–5.99 (1H, m, CH), 7.62 (2H, d, 8.8 Hz, CH_{Ar}), 8.21 (2H, d, *J* 8.8 Hz, CH_{Ar}), 9.03 (1H, br.s, NH_2^+), 9.56 (1H, br.s, NH_2^+) 11.67 (1H, br.s, OH); d_C (600 MHz, DMSO-d_6) 19.52, 19.91, 29.87, 44.24, 60.43, 89.14, 100.75, 104.57, 119.62, 123.38, 124.18, 124.70, 144.02, 146.08, 159.35, 162.02, 166.29, 167.87; ESI, *m*/*z*: 329.2 [M-CF3COO$^-$]$^+$.

*4.10. (E)-3-Benzylidene-2-(4-hydroxy-2-oxo-2H-chromen-3-yl) pyrrolidin-1-ium trifluoroacetate (**2f**)*

Beige solid, yield 52 mg, 12%; [Found: C, 60.98; H, 4.20; N 3.21. $C_{22}H_{18}F_3NO_5$ requires C, 60.97; H 4.19,; N 3.23%]; mp 216–218 °C; n_{max} (KBr) 1656, 1516, 789, 755 cm^{-1}; d_H (600 MHz DMSO-d_6) 3.03–3.08 (2H, m, CH_2), 3.25–3.29 (1H, m, CH_2), 3.67–3.73 (1H, m, CH_2), 5.37–5.41 (1H, m, CH), 6.15–6.19 (1H, m, CH_{Ar}), 7.16–7.24 (3H, m, CH_{Ar}), 7.27–7.31 (2H, s, CH_{Ar}), 7.32–7.36 (2H, m, CH_{Ar}), 7.46–7.49 (1H, m, CH_{Ar}), 7.81–7.85 (1H, m, CH_{Ar}), 9.01 (1H, br.s, NH_2^+), 9.87 (1H, br.s, NH_2^+); d_C (600 MHz, DMSO-d_6) 29.52, 44.04, 61.55, 91.55, 116.46, 121.02, 122.85, 124.84, 127.12, 128.53, 128.94, 131.29, 137.31, 140.60, 154.44, 164.35, 174.02; ESI, *m*/*z*: 320.2 [M-CF3COO$^-$]$^+$.

*4.11. (E)-3-(4-chlorobenzylidene)-2-(4-hydroxy-2-oxo-2H-chromen-3-yl)pyrrolidin-1-ium trifluoroacetate (**2g**)*

Beige solid, yield 130 mg, 28%; [Found: C, 54.47; H, 3.65; Cl, 7.59; N 3.00. $C_{22}H_{17}ClF_3NO_5$ requires C, 56.48; H, 3.66; Cl, 7.58; N 2.99%]; mp 216–217 °C; n_{max} (KBr) 1650, 1603, 1518, 796, 755, 727 cm^{-1}; d_H (600 MHz DMSO-d_6) 3.00–3.09 (2H, m, CH_2), 3.38–3.45 (1H, m, CH_2), 3.65–3.74 (1H, m, CH_2), 5.40 (1H, s, CH), 6.16 (1H, s, CH), 7.16–7.22 (2H, m, CH_{Ar}), 7.32 (2H, d, *J* 8.5 Hz, CH_{Ar}), 7.38 (2H, d, *J* 8.6 Hz, CH_{Ar}), 7.45–7.49 (1H, m, CH_{Ar}), 7.81–7.85 (1H, m, CH_{Ar}), 9.05 (1H, br.s, NH_2^+), 9.31 (1H, br.s, NH_2^+); d_C (600 MHz, DMSO-d_6) 29.49, 44.02, 61.51, 91.64, 107.77, 116.45, 119.78, 122.85, 124.82, 128.87, 130.22, 131.31, 136.19, 141.77, 154.41, 173.92, 179.95; ESI, *m*/*z*: 354.2 [M-CF3COO$^-$]$^+$.

*4.12. (E)-3-(3-fluorobenzylidene)-2-(4-hydroxy-2-oxo-2H-chromen-3-yl)pyrrolidin-1-ium trifluoroacetate (**2h**)*

Beige solid, yield 107 mg, 22%; [Found: C, 58.43; H, 3.79; N 3.11. $C_{22}H_{17}F_4NO_5$ requires C, 58.54; H, 3.80; N 3.10%]; mp 207–208 °C; n_{max} (KBr) 1652, 1606, 1517, 788, 756 cm^{-1}; d_H (600 MHz DMSO-d_6) 3.03–3.13 (2H, m, CH_2), 3.40–3.52 (1H, m, CH_2), 3.66–3.76 (1H, m, CH_2), 5.41 (1H, s, CH), 6.18 (1H, s, CH), 7.02–7.08 (1H, m, CH_{Ar}), 7.09–7.16 (2H, m, CH_{Ar}), 7.17–7.23 (2H, m, CH_{Ar}), 7.33–7.41 (1H, m, CH_{Ar}), 7.45–7.51 (1H, m, CH_{Ar}), 9.07 (1H, br.s, NH_2^+), 9.27 (1H, br.s, NH_2^+); d_C (600 MHz, DMSO-d_6) 29.55, 40.48, 44.05, 61.47, 113.93, 114.42, 114.93, 116.47, 119.91, 122.88, 134.73, 124.84, 128.75, 130.80, 131.35, 139.06, 143.65, 155.41, 165.18, 173.56; ESI, *m*/*z*: 338.1 [M-CF3COO$^-$]$^+$.

*4.13. (E)-3-(4-nitrobenzylidene)-2-(4-hydroxy-2-oxo-2H-chromen-3-yl)pyrrolidin-1-ium trifluoroacetate (**2i**)*

Brown solid, yield 168 mg, 22%; [Found: C, 55.25; H, 3.57; N 5.86. $C_{22}H_{17}F_3N_2O_7$ requires C, 55.24; H, 3.58; N 5.86%]; mp 196–197 °C; n_{max} (KBr) 1651, 1602, 1517, 788, 756 cm^{-1}; d_H (500 MHz DMSO-d_6) 3.10–3.17 (2H, m, CH_2), 3.39–3.43 (1H, m, CH_2), 3.69–3.76 (1H, m, CH_2), 5.47 (1H, s, CH), 6.30–6.34 (1H, m, CH), 7.17–7.21 (2H, m, CH_{Ar}), 7.45–7.50 (1H, m, CH_{Ar}), 7.59 (2H, d, 8.9 Hz, CH_{Ar}), 7.83 (2H, d, 1.7 Hz, CH_{Ar}), 8.17 (2H, d, 8.9 Hz, CH_{Ar}), 9.19 (2H, br.s, NH_2^+); d_C (600 MHz, DMSO-d_6) 29.49, 44.02, 61.51, 91.64, 107.77, 116.45, 119.78, 122.85, 124.82, 128.87, 130.22, 131.31, 136.19, 141.77, 154.41, 173.92, 179.95; ESI, *m*/*z*: 365.2 [M-CF3COO$^-$]$^+$.

*4.14. (E)-3-Benzylidene-2-(1H-indol-3-yl)pyrrolidin-1-ium trifluoroacetate (**2j**)*

Beige solid, yield 516 mg, 83%; [Found: C, 64.92; H, 4.94; N 7.22. $C_{21}H_{19}F_3N_2O_2$ requires C, 64.94; H, 4.93; N 7.21%]; mp 111–113 °C; n_{max} (KBr) 1619, 1493, 798, 746, 721 cm^{-1}; d_H (600 MHz DMSO-d_6) 3.09–3.16 (1H, m, CH_2), 3.20–3.27 (2H, m, CH_2), 3.50–3.56 (1H, m, CH_2), 5.74 (1H, s, CH), 6.31 (1H, s, CH), 7.08 (1H, t, *J* 7.5 Hz, CH_{Ar}), 7.18 (1H, t, *J* 7.7 Hz, CH_{Ar}), 7.28 (2H, t, 7.1 Hz, CH_{Ar}), 7.37 (4H, dt, 7.4 Hz, CH_{Ar}), 7.47 (1H, d, 8.2 Hz, CH_{Ar}), 7.56 (1H, d, 2.7 Hz, CH_{Ar}), 7.63 (1H, d, 8.0 Hz, CH_{Ar}), 8.83 (1H, br.s, NH_2^+), 9.59 (1H, br.s, NH_2^+), 11.49 (1H, br.s, NH); d_C (600 MHz, DMSO-d_6) 29.24, 44.26, 60.04, 108.89, 112.53, 119.46, 119.81, 122.36, 125.09, 127.53, 127.76, 128.74, 129.06, 130.13, 133.14, 136.77, 136.96, 138.23; ESI, *m*/*z*: 275.2 [M-CF3COO$^-$]$^+$.

*4.15. (E)-3-(4-chlorobenzylidene)-2-(1H-indol-3-yl)pyrrolidin-1-ium trifluoroacetate (**2k**)*

Beige solid, yield 630 mg, 91%; [Found: C, 59.66; H, 4.30; Cl, 8.37; N 6.62. $C_{21}H_{18}ClF_3N_2O_2$ requires C, 59.65; H, 5.29; Cl, 8.38; N 6.63%]; mp 143–144 °C; n_{max} (KBr) 1626, 798, 746 cm^{-1}; d_H (600 MHz DMSO-d_6) 3.07–3.14 (1H, m, CH_2), 3.18–3.27 (1H, m, CH_2), 3.41–3.49 (1H, m, CH_2), 3.51–3.57 (1H, m, CH_2), 5.31 (1H, s, CH), 5.75 (1H, s, CH), 7.07 (1H, t, 7.5 Hz, CH_{Ar}), 7.18 (1H, t, *J* 7.6 Hz, CH_{Ar}), 7.39 (1H, d, *J* 8.4 Hz, CH_{Ar}), 7.43 (1H, t, 8.2 Hz, CH_{Ar}), 7.47 (2H, d, 8.2 Hz, CH_{Ar}), 7.56 (1H, d, 2.7 Hz, CH_{Ar}), 7.62 (2H, d, 2.8 Hz, CH_{Ar}), 8.88 (1H, br.s, NH_2^+), 9.69 (1H, br.s, NH_2^+), 11.48 (1H, br.s, NH); d_C

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(600 MHz, DMSO-d_6) 29.23, 44.22, 60.02, 108.78, 112.53, 119.42, 119.81, 122.35, 123.88, 126.11, 127.56, 129.03, 130.47, 132.24, 135.70, 136.95, 130.42; ESI, *m*/*z*: 309.2 [M-CF3COO$^-$]$^+$.

4.16. (E)-3-(3-fluorobenzylidene)-2-(1H-indol-3-yl)pyrrolidin-1-ium trifluoroacetate (**2l**)

Beige solid, yield 455 mg, 70%; [Found: C, 62.05; H, 4.48; N 6.89. $C_{21}H_{18}F_4N_2O_2$ requires C, 62.07; H, 4.46; N 6.89%]; mp 116–118 °C; n_{max} (KBr) 1582, 1489, 836, 798, 746 cm^{-1}; d_H (600 MHz DMSO-d_6) 3.10–3.18 (1H, m, CH_2), 3.22–3.32 (1H, m, CH_2), 3.42–3.49 (1H, m, CH_2), 3.52–3.58 (1H, m, CH_2), 5.76 (1H, s, CH), 6.33 (1H, s, CH), 7.06–7.13 (2H, m, CH_{Ar}), 7.16–7.23 (2H, m, CH_{Ar}), 7.42 (1H, q, 7.2 Hz, CH_{Ar}), 7.48 (1H, d, 8.1 Hz, CH_{Ar}), 7.56 (1H, d, 2.7 Hz, CH_{Ar}), 7.63 (1H, d, 8.0 Hz, CH_{Ar}), 8.94 (1H, br.s, NH_2^+), 9.85 (1H, br.s, NH_2^+), 11.52 (1H, br.s, NH); d_C (600 MHz, DMSO-d_6) 29.29, 44.21, 59.98, 101.41, 108.76, 112.52, 114.39, 114.53, 115.06, 115.20, 119.42, 119.42, 119.80, 122.33, 123.94, 124.96, 126.14, 130.90, 130.96, 136.95, 139.22, 139.27, 140.30, 158.44, 158.64, 158.85, 159.60, 161.94, 163.56; ESI, *m*/*z*: 392.2 [M-CF3COO$^-$]$^+$.

4.17. (E)-3-(4-methoxybenzylidene)-2-(1H-indol-3-yl)pyrrolidin-1-ium trifluoroacetate (**2m**)

Beige solid, yield 288 mg, 43%; [Found: C, 63.16; H, 5.07; N 6.69. $C_{22}H_{21}F_3N_2O_3$ requires C, 63.15; H, 5.06; N 6.70%]; mp 131–132 °C; n_{max} (KBr) 1674, 1512, 799, 746 cm^{-1}; d_H (600 MHz DMSO-d_6) 2.96–3.02 (1H, m, CH_2), 3.05–3.11 (1H, m, CH_2), 3.41–3.48 (1H, m, CH_2), 3.51–3.56 (1H, m, CH_2), 3.76 (3H, s, OCH_3), 5.71 (1H, s, CH), 6.24 (1H, s, CH), 6.94 (2H, d, *J* 8.6 Hz, CH_{Ar}), 7.07 (2H, d, 7.4 Hz, CH_{Ar}), 7.17 (1H, t, 7.8 Hz, CH_{Ar}), 7.30 (2H, d, 8.7 Hz, CH_{Ar}), 7.45–7.48 (1H, m, CH_{Ar}), 7.54 (1H, d, 2.6 Hz, CH_{Ar}), 7.62 (1H, d, 8.0 Hz, CH_{Ar}), 8.81 (1H, br.s, NH_2^+), 9.63 (1H, br.s, NH_2^+), 11.46 (1H, br.s, NH); d_C (600 MHz, DMSO-d_6) 29.11, 44.20, 55.63, 59.96, 109.05, 112.51, 114.52, 119.46, 119.74, 122.27, 124.54, 126.20, 127.46, 129.45, 130.10, 135.65, 136.97, 150.92; ESI, *m*/*z*: 305.2 [M-CF3COO$^-$]$^+$.

4.18. (E)-3-Benzylidene-2-(1H-pyrrol-2-yl)pyrrolidin-1-ium trifluoroacetate (**2n**)

Beige solid, yield 472 mg, 82%; [Found: C, 60.36; H, 5.05; N 8.27. $C_{17}H_{17}F_3N_2O_3$ requires C, 60.35; H, 5.06; N 8.28%]; mp 132–133 °C; n_{max} (KBr) 1675, 798, 746 cm^{-1}; d_H (600 MHz DMSO-d_6) 2.98–3.05 (1H, m, CH_2), 3.07–3.15 (1H, m, CH_2), 3.43–3.50 (2H, m, CH_2)) 5.45 (1H, s, CH), 6.11 (1H, s, CH), 6.25 (1H, s, CH_{Ar}), 6.29 (1H, s, CH_{Ar}), 6.90 (1H, s, CH_{Ar}), 7.25–7.31 (2H, m, CH_{Ar}), 7.37–7.42 (3H, m, CH_{Ar}), 9.03 (1H, br.s, NH_2^+), 9.70 (1H, br.s, NH_2^+), 11.08 (1H, br.s, NH); d_C (600 MHz, DMSO-d_6) 29.90, 44.04, 60.54, 110.13, 120.38, 125.21, 125.45, 127.85, 128.79, 129.07, 136.62, 137.97, 158.75, 158.96; ESI, *m*/*z*: 225.2 [M-CF3COO$^-$]$^+$.

4.19. (E)-3-(4-chlorobenzylidene)-2-(1H-pyrrol-2-yl)pyrrolidin-1-ium trifluoroacetate (**2o**)

Brown solid, yield 89 mg, 14%; [Found: C, 54.80; H, 4.31; Cl, 9.49; N 7.54. $C_{17}H_{16}ClF_3N_2O_2$ requires C, 54.78; H, 4.33; Cl, 9.51; N 7.52%]; mp 129–130 °C; n_{max} (KBr) 1593, 1492, 797, 772 cm^{-1}; d_H (600 MHz DMSO-d_6) 2.94–3.03 (1H, m, CH_2), 3.07–3.14 (1H, m, CH_2), 3.41–3.51 (2H, m, CH_2)) 5.42 (1H, s, CH), 6.09 (1H, s, CH), 6.25 (1H, d, 10.8 Hz, CH_{Ar}), 6.90 (1H, s, CH_{Ar}), 7.32 (1H, s, CH_{Ar}), 7.38 (2H, d, 8.6 Hz, CH_{Ar}), 7.44 (2H, d, 8.2 Hz, CH_{Ar}), 9.22 (1H, br.s, NH_2^+), 9.95 (1H, br.s, NH_2^+); d_C (600 MHz, DMSO-d_6) 28.87, 43.91, 60.54, 108.49, 110.27, 120.39, 124.10, 125.00, 129.04, 130.51, 132.30, 135.54, 139.24; ESI, *m*/*z*: 259.1 [M-CF3COO$^-$]$^+$.

4.20. (E)-3-(3-fluorobenzylidene)-2-(1H-pyrrol-2-yl)pyrrolidin-1-ium trifluoroacetate (**2p**)

Brown solid, yield 514 mg, 85%; [Found: C, 57.31; H, 4.53; N 7.85. $C_{17}H_{16}F_4N_2O_2$ requires C, 57.30; H, 4.53; N 7.86%]; mp 162–164 °C; n_{max} (KBr) 1583, 799, 723 cm^{-1}; d_H (600 MHz DMSO-d_6) 2.99–3.06 (1H, m, CH_2), 3.10–3.17 (1H, m, CH_2), 3.39–3.51 (2H, m, CH_2), 5.48 (1H, s, CH), 6.10 (1H, s, CH), 6.25 (1H, s, CH_{Ar}), 6.30 (1H, s, CH_{Ar}), 6.90 (1H, s, CH_{Ar}), 7.10–7.15 (1H, m, CH_{Ar}), 7.16–7.23 (1H, m, CH_{Ar}), 7.40–7.45 (1H, m, CH_{Ar}), 9.44 (1H, br.s, NH_2^+), 11.13 (1H, br.s, NH_2^+); d_C (600 MHz, DMSO-d_6) 28.95, 44.01, 60.51, 108.57, 110.22, 114.50, 114.64, 115.03, 115.22, 120.44, 124.33, 125.01. 128.79, 130.92, 130.98, 139.05, 139.10, 139.88, 158.67, 158.88 159.08, 159.26, 161.92, 163.53; ESI, *m*/*z*: 243.2 [M-CF3COO$^-$]$^+$.

4.21. (E)-3-Benzylidene-2-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)pyrrolidin-1-ium trifluoroacetate (**2r**)

White solid, yield 500 mg, 97%; [Found: C, 62.01; H, 4.08; N 3.15. $C_{23}H_{18}F_3NO_5$ requires C, 62.02; H, 4.07; N 3.14%]; mp 160–161 °C; n_{max} (KBr) 1672, 798, 746 cm^{-1}; d_H (600 MHz DMSO-d_6) 3.05–3.15 (2H, m, CH_2), 3.38–3.48 (1H, m, CH_2), 3.68–3.77 (1H, m, CH_2), 5.54 (1H, s, CH), 6.21–6.25 (1H, m, CH), 7.23–7.25 (1H, m, CH_{Ar}), 7.28–7.37 (4H, m, CH_{Ar}), 7.74 (1H, td, *J* 7.5 Hz, 1.3 Hz, CH_{Ar}), 7.83 (1H, td, 7.5 Hz, 1.4 Hz, CH_{Ar}), 7.99 (2H, ddd, 6.9 Hz, 5.1 Hz, 1.3 Hz, CH_{Ar}), 8.80 (1H, br.s, NH_2^+), 9.39 (1H, br.s, NH_2^+); d_C (600 MHz, DMSO-d_6) 29.61, 45.17, 58.86, 99.98, 113.91, 121.61, 126.02, 126.24, 127.30, 128.57, 128.90, 131.44, 132.73, 133.86, 134.85, 137.11, 139.55, 156.81, 158.31, 165.51, 167.96, 183.02; ESI, *m*/*z*: 322.2 [M-CF3COO$^-$]$^+$.

4.22. (E)-3-(4-chlorobenzylidene)-2-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)pyrrolidin-1-ium trifluoroacetate (**2s**)

White solid, yield 493 mg, 99%; [Found: C, 57.55; H, 3.58; Cl, 7.41; N 2.91. $C_{23}H_{17}ClF_3NO_5$ requires C, 57.57; H, 3.57; Cl, 7.39; N 2.92%]; mp 169–170 °C; n_{max} (KBr) 1680, 796 cm^{-1}; d_H (600 MHz DMSO-d_6) 3.01–3.12 (2H, m, CH_2), 3.13–3.18 (1H, m, CH_2), 3.36–3.43 (1H, m, CH_2), 5.53 (1H, s, CH), 7.32 (2H, d, 8.4 Hz, CH_{Ar}), 7.38 (2H, d, 8.4 Hz, CH_{Ar}), 7.73 (1H, t, *J* 7.6 Hz, CH_{Ar}), 7.81 (1H, t, 7.4 Hz, CH_{Ar}), 7.99 (2H, t, 8.7 Hz, CH_{Ar}), 8.80 (1H, br.s, NH_2^+), 9.38 (1H, br.s, NH_2^+); d_C (600 MHz, DMSO-d_6) 29.59, 31.16, 45.11, 59.05, 113.63, 120.37, 126.02, 126.27, 128.90, 129.76, 130.30, 131.52, 131.73, 132.46, 132.65, 134.01, 134.82, 136.07, 140.78, 206.90; ESI, *m*/*z*: 366.2 [M-CF3COO$^-$]$^+$.

4.23. (E)-3-(3-fluorobenzylidene)-2-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)pyrrolidin-1-ium trifluoroacetate (**2t**)

White solid, yield 295 mg, 61%; [Found: C, 59.60; H, 3.71; N 3.03. $C_{23}H_{17}F_4NO_5$ requires C, 59.62; H, 3.70; N 3.02%]; mp 141–142 °C; n_{max} (KBr) 1678, 782 cm^{-1}; d_H (600 MHz DMSO-d_6) 3.05–3.18 (2H, m, CH_2), 3.34–3.44 (2H, m, CH_2), 5.54 (1H, s, CH), 6.23 (1H, s, CH), 7.05 (1H, t, 8.8 Hz, CH_{Ar}), 7.13 (2H, dd, 16.3 Hz, 9.3 Hz, CH_{Ar}), 7.37 (1H, q, *J* 7.7 Hz, CH_{Ar}), 7.72 (1H, t, 7.5 Hz, CH_{Ar}), 7.79–7.83 (1H, m, CH_{Ar}), 7.95–8.01 (1H, m, CH_{Ar}), 8.80 (1H, br.s, NH_2^+), 9.37 (1H, br.s, NH_2^+); d_C (600 MHz, DMSO-d_6) 29.64, 45.09, 59.12, 113.49, 113.95, 114.89, 120.49, 124.76, 126.02, 126.26, 130.77, 130.83, 132.39, 134.09, 134.81, 139.60, 141.12, 158.38, 158.83, 161.90, 163.51, 172.89, 172.94, 180.97, 183.27; ESI, *m*/*z*: 350.2 [M-CF3COO$^-$]$^+$.

4.24. (E)-3-(4-methoxybenzylidene)-2-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)pyrrolidin-1-ium trifluoroacetate (**2u**)

Beige solid, yield 472 mg, 62%; [Found: C, 60.61; H, 4.25; N 2.96. $C_{24}H_{20}F_3NO_6$ requires C, 60.63; H, 4.34; N 2.95%]; mp 186–187 °C;

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n_{max} (KBr) 1678, 1615, 798, 784 cm^{-1}; d_H (600 MHz $CDCl_3$) 2.94–3.05 (1H, m, CH_2), 3.06–3.18 (1H, m, CH_2), 3.29–3.49 (1H, m, CH_2), 3.53–3.62 (1H, m, CH_2), 5.32 (1H, s, CH), 5.78–5.84 (3H, m, OMe), 6.20 (1H, q, 2.4 Hz, CH_{Ar}), 6.54 (2H, s, CH_{Ar}), 6.67 (2H, s, CH_{Ar}), 7.20–7.29 (3H, m, CH_{Ar}), 7.30–7.37 (2H, m, CH_{Ar}), 8.43 (1H, br.s, NH_2^+), 10.10 (1H, br.s, NH_2^+); d_C (600 MHz, DMSO-d_6) 29.41, 44.83, 55.56, 109.13, 111.51, 114.38, 119.68, 120.91, 123.09, 125.90, 126.44, 126.56, 126.62, 128.52, 129.88, 131.09, 132.41, 133.72, 134.59, 134.93, 155.76, 158.52, 160.03, 160.06, 181.75, 183.10, 185.05, 185.24 186.16; ESI, *m/z*: 362.2 $[M\text{-}CF3COO^-]^+$.

4.25. (E)-3-(4-nitrobenzylidene)-2-(3-hydroxy-1,4-dioxo-1,4-dihydronaphthalen-2-yl)pyrrolidin-1-ium trifluoroacetate (**2v**)

Beige solid, yield 180 mg, 23%; [Found: C, 59.31; H, 3.51; N 5.70. $C_{23}H_{70}F_3N_2O_7$ requires C, 56.33; H, 3.49; N 5.71%]; mp 160–162 °C; n_{max} (KBr) 1678, 1645, 798, 784 cm^{-1}; d_H (400 MHz $CDCl_3$) 3.10–3.18 (2H, m, CH_2), 3.39–3.44 (1H, m, CH_2), 3.71–3.80 (1H, m, CH_2), 5.58 (1H, s, CH), 6.18 (1H, s, CH_{Ar}), 7.57 (2H, d, 8.7 Hz, CH_{Ar}), 7.70–7.77 (2H, m, CH_{Ar}), 7.85–7.89 (1H, m, CH_{Ar}), 7.94–7.99 (1H, m, CH_{Ar}), 8.16 (2H, d, 8.7 Hz, CH_{Ar}), 8.91 (1H, br.s, NH_2^+), 9.20 (1H, br.s, NH_2^+); d_C (600 MHz, DMSO-d_6) 30.05, 44.49, 60.66, 109.44, 109.23, 111.35, 118.28, 119.21, 121.03, 124.08, 125.67, 125.94, 127.43, 129.42, 131.29, 134.23, 139.42, 143.98, 145.82, 146.28, 156.36; ESI, *m/z*: 377.2 $[M\text{-}CF3COO^-]^+$.

4.26. (E)-3-Benzylidene-2-(5-hydroxybenzo[d][1,3]dioxol-4-yl) pyrrolidin-1-ium trifluoroacetate (**2w**)

White solid, yield 465 mg, 71%; [Found: C, 58.69; H, 4.44; N 3.40. $C_{20}H_{18}F_3NO_5$ requires C, 58.68; H, 4.43; N 3.42%]; mp 138–139 °C; n_{max} (KBr) 1675, 798, 784 cm^{-1}; d_H (600 MHz $CDCl_3$) 2.99–3.05 (1H, m, CH_2), 3.09–3.10 (1H, m, CH_2), 3.38–3.43 (1H, m, CH_2) 3.47–3.54 (1H, m, CH_2), 5.46 (1H, s, CH), 5.97 (2H, s, CH_{Ar}), 6.15 (1H, s, CH_{Ar}), 6.59 (1H, s, CH_{Ar}), 6.86 (1H, s, CH_{Ar}), 7.25–7.31 (1H, m, CH_{Ar}), 7.33–7.48 (1H, m, CH_{Ar}), 8.64 (1H, br.s, NH_2^+), 9.70 (1H, br.s, NH_2^+), 10.20 (1H, br.s, OH),; d_C (600 MHz, DMSO-d_6) 29.33, 44.63, 61.85, 98.20, 101.70, 109.19, 113.15, 124.77, 127.74, 128.74, 129.03, 136.71, 139.06, 140.46, 148.99, 151.75, 158.15, 158.41, 158.61, 159.16; ESI, *m/z*: 296.2 $[M\text{-}CF3COO^-]^+$.

4.27. (E)-3-(4-chlorobenzylidene)-2-(5-hydroxybenzo[d][1,3] dioxol-4-yl)pyrrolidin-1-ium trifluoroacetate (**2x**)

White solid, yield 423 mg, 80%; [Found: C, 54.14; H, 3.85; Cl, 8.00; N 3.15. $C_{20}H_{17}ClF_3NO_5$ requires C, 54.13; H, 3.86; Cl, 7.99; N 3.16%]; mp 140–141 °C; n_{max} (KBr) 1674, 797, 776 cm^{-1}; d_H (600 MHz $CDCl_3$) 2.97–3.09 (1H, m, CH_2), 3.08–3.14 (1H, m, CH_2), 3.38–3.43 (1H, m, CH_2) 3.47–3.53 (1H, m, CH_2), 5.45 (1H, s, CH), 5.97 (2H, s, CH_{Ar}), 6.15 (1H, s, CH_{Ar}), 6.58–6.61 (1H, m, CH_{Ar}), 6.86 (1H, s, CH_{Ar}), 7.37–7.40 (2H, m, CH_{Ar}), 7.41–7.45 (2H, m, CH_{Ar}), 8.58 (1H, br.s, NH_2^+), 9.59 (1H, br.s, NH_2^+), 10.09 (1H, br.s, OH),; d_C (600 MHz, DMSO-d_6) 29.32, 44.65, 61.95, 79.66, 98.18, 101.75, 109.26, 113.01, 123.60, 129.01, 130.48, 132.23, 135.61, 140.07, 140.31, 149.07, 151.67; ESI, *m/z*: 330.2 $[M\text{-}CF3COO^-]^+$.

4.28. (E)-3-(3-fluorobenzylidene)-2-(5-hydroxybenzo[d][1,3] dioxol-4-yl)pyrrolidin-1-ium trifluoroacetate (**2y**)

White solid, yield 397 mg, 58%; [Found: C, 56.20; H, 4.02; N 3.27. $C_{20}H_{17}F_4NO_5$ requires C, 56.21; H, 4.01; N 3.28%]; mp 150–151 °C; n_{max} (KBr) 1674, 1615, 797, 768 cm^{-1}; d_H (600 MHz $CDCl_3$) 2.97–3.07 (1H, m, CH_2), 3.11–3.18 (1H, m, CH_2), 3.38–3.43 (1H, m, CH_2) 3.48–3.55 (1H, m, CH_2), 5.47 (1H, s, CH), 5.97 (2H, s, CH_{Ar}), 6.17 (1H, s, CH_{Ar}), 6.59 (1H, c, CH_{Ar}), 6.86 (1H, s, CH_{Ar}), 7.11 (1H, td, 8.8 Hz, 2.2 Hz, CH_{Ar}), 7.20 (2H, d, 8.7 Hz, CH_{Ar}), 7.42 (1H, q, 7.4 Hz, CH_{Ar}), 8.63 (1H, br.s, NH_2^+), 9.68 (1H, br.s, NH_2^+), 10.18 (1H, br.s, OH),; d_C (600 MHz, DMSO-d_6) 29.37, 44.64, 61.42, 98.19, 101.73, 109.28, 112.99, 114.42, 114.56, 115.06, 116.20, 123.67, 124.98, 130.90, 139.17, 140.49, 140.93, 151.73, 158.33, 161.93, 163.64, 166.27; ESI, *m/z*: 314.2 $[M\text{-}CF3COO^-]^+$.

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Appendix. Supplementary data

Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.tet.2019.130681. These data include MOL files and InChiKeys of the most important compounds described in this article.

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