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Fused mesoionic heterocycles: synthesis of [1,2,3]triazolo[1,5-*a*]quinoline, [1,2,3]triazolo[1,5-*a*]quinazoline, [1,2,3]triazolo[1,5-*a*]quinoxaline and [1,2,3]triazolo[5,1-*c*]benzotriazine derivatives☆

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Abstract—General methods are descibed for the synthesis of mesoionic derivatives of [1,2,3]triazolo[1,5-*a*]quinoline, [1,2,3]triazolo[1,5-*a*]quinazoline, [1,2,3]triazolo[1,5-*a*]quinoxaline and [1,2,3]triazolo[5,1-*c*]benzotriazine.

1. Introduction

Many routes are available for the synthesis of monocyclic mesoionic compounds,[2] but reported methods for the preparation of ring fused analogues are more limited.[3] As part of a programme to develop Th2 selective immunosuppressive agents,[4] we describe in this work a concise entry into mesoionic [1,2,3]triazolo[1,5-*a*]quinolinium (**1**), [1,2,3]triazolo[1,5-*a*]quinazolinium (**2**), [1,2,3]triazolo[1,5-*a*]quinoxalinium (**3**) and [1,2,3]triazolo[5,1-*c*]benzotriazinium (**4**) ring systems (Fig. 1).

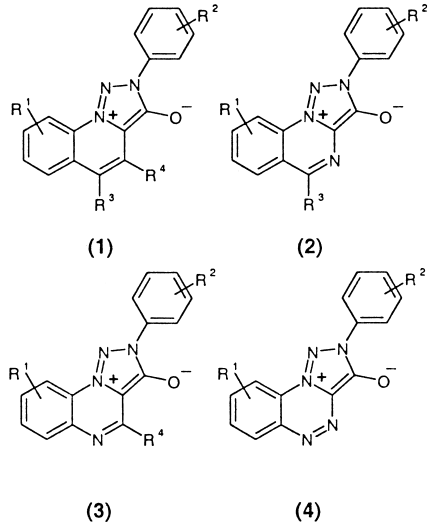
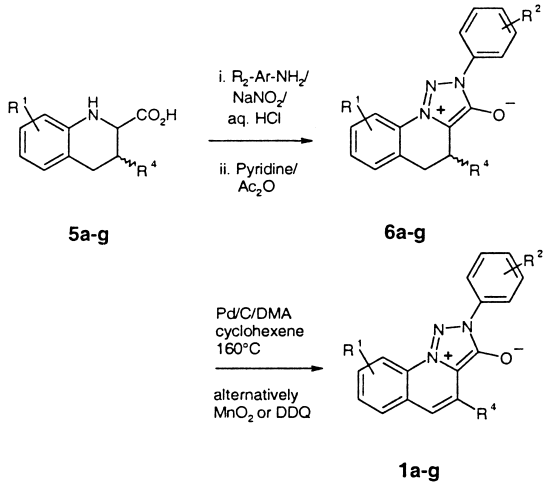


Figure 1.

Cyclodehydration procedures are often used for the



6a 28% **1a** 41% R^1=H, R^2=H, R^4=H
6b 50% **1b** 62% R^1=H, R^2=*p*-F, R^4=H
6c 50% **1c** 58% R^1=H, R^2=*p*-CF_3, R^4=H
6d 20% **1d** 44% R^1=H, R^2=*m*-CF_3, R^4=H
6e 36% **1e** 86% R^1=H, R^2=*p*-OCF_3, R^4=H
6f 24% **1f** 49% R^1=6,9-DiF, R^2=*p*-CF_3, R^4=H
6g 30% **1g** 91% R^1=H, R^2=6-Cl-(3-pyridinyl), R^4=Me

Scheme 1.

☆ See Ref. 1.

Keywords: fused mesoionic heterocycles; [1,2,3]triazolo[1,5-*a*]quinoline; [1,2,3]triazolo[1,5-*a*]quinazoline; [1,2,3]triazolo[5,1-*c*]benzotriazine; aryl hydrocarbon receptor (AhR).

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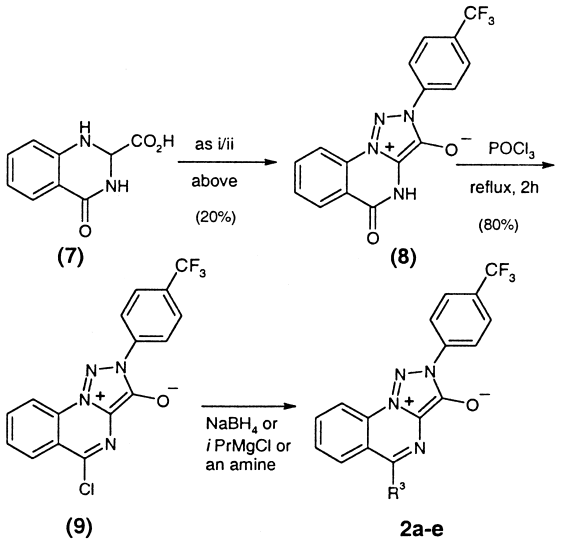
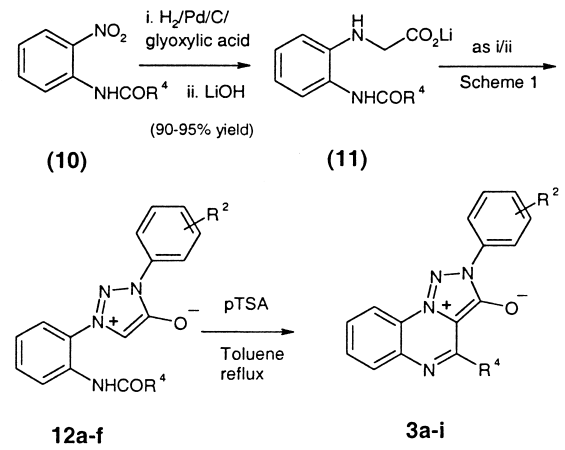


2a R^3 = H (33%)
2b R^3 = iPr (15%)
2c R^3 = morpholine (44%)
2d R^3 = piperidine (74%)
2e R^3 = pyrrolidine (86%)

Scheme 2.

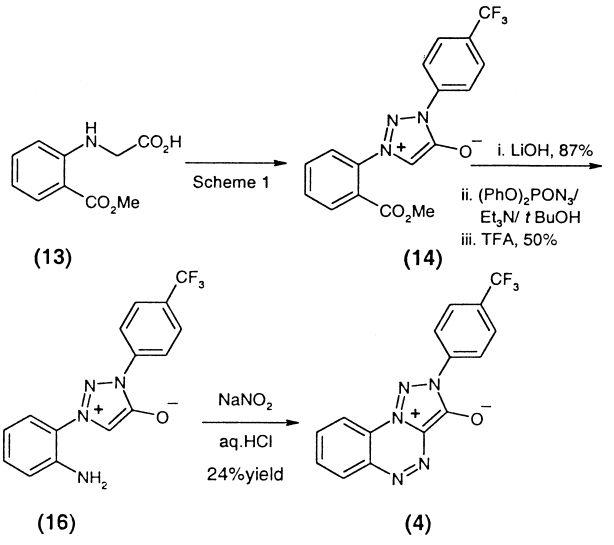
synthesis of mesoionic compounds and the few reported examples of mesoionic 1,3-dialkyl- and 1,3-diaryl-substituted 1,2,3-triazoles have been prepared by this general approach.[5] Analogous ring fused systems corresponding to (**1**)–(**4**) have not been previously described. We report herein preparative methods for these ring systems in



12a	26%	**3a**	51%	R^1=H, R^2=*p*-F, R^4=Me,
12b	23%	**3b**	53%	R^1=H, R^2=3,4-DiF-phenyl, R^4=Et
12c	55%	**3c**	16%	R^1=H, R^2=4-F,3-Me-phenyl, R^4=Me
12d	28%	**3d**	34%	R^1=H, R^2= *p*-Et, R^4=Me,
12e	20%	**3e**	45%	R^1=H, R^2=3-pyridinyl, R^4=Me
12f	21%	**3f**	59%	R^1=H, R^2=3,4-DiF-phenyl, R^4=Me,
		3g	19%*	R^1=H, R^2=*p*-CH_3, R^4=Me,
		3h	22%*	R^1=H, R^2=2-F,5-Me-phenyl, R^4=Me,
		3i	22%*	R^1=H, R^2=*p*-SCH_3, R^4=Me,

* yield from (**11**)

Scheme 3.



Scheme 4.

which the key ring fusion step is either formation of the triazolium ring (**1**) and (**2**) (Schemes 1 and 2) or formation of the quinazolium/triazinium ring (**3**) and (**4**) (Schemes 3 and 4). Compounds of this type are of interest because they are found to possess potent immunosuppressive properties and as such were of potential value for application in diseases known to possess an immune component.[4]

2. Results and discussion

For the preparation of the [1,2,3]triazolo[1,5-*a*]quinolinium ring system of (**1**), tetrahydroquinaldic acid (**5**)[6] was reacted with an aryl diazonium (prepared in situ from the corresponding aniline and sodium nitrite) to afford an intermediate triazine, which was isolated but then immediately treated with acetic anhydride in pyridine to effect cyclization to the triazolium hydroxide inner salt (**6**). Partially saturated compounds (**6**) could then be dehydrogenated by treatment with DDQ or MnO_2 or, more preferably, by treatment with palladium on charcoal in dimethylacetamide at 160°C. The choice of conditions for the dehydrogenation was determined by the presence or absence of groups sensitive to hydrogenolysis during treatment with palladium on charcoal. Whilst a hydrogen scavenger (cyclohexene) was added to the reaction, some substrates were still problematic (e.g. aromatic chlorides) and MnO_2 or DDQ proved a more suitable oxidant. Using one or other of these methods a range of analogues of (**1**) possessing various R^1–R^4 substituents was prepared in overall yields ranging from 10–30% (from **5**). The corresponding quinazolinium salts (**2**) were prepared by an analogous route starting from 4-oxo-1,2,3,4-tetrahydroquinazoline-2-carboxylic acid (**7**). Surprisingly, this simple compound (or related analogues) had not been reported previously, but could be simply accessed from anthranilamide and glyoxylic acid.[4] After cyclization, the resulting amide (**8**) can be converted into a chloroimine (**9**) by reaction with phosphorus oxychloride, and then reacted with nucleophiles to afford compounds (**2**). This reaction sequence was successful with sodium borohydride and also with amines, but less so with a Grignard

reagent; *iso*-propylmagnesium chloride affording only a 15% yield of product (**2b**).

[1,2,3]Triazolo[1,5-*a*]quinoxalinium (**3**) and [1,2,3]triazolo[5,1-*c*]benzotriazinium (**4**) ring systems were most expediently prepared from a preexisting 1,3-diaryl substituted triazolium hydroxide, making use of the nucleophilicty of this ring system to effect cyclization onto a pendant electrophilic substituent on the N1 aryl group (Schemes 3 and 4). Thus hydrogenation of acylated 2-nitroaniline (**10**) in the presence of glyoxylic acid gave an almost quantitative yield of the differentially functionalized phenylenediamine (**11**), through a sequence of steps involving reduction of the nitro group and in situ formation of the imine with glyoxylic acid, followed by hydrogenation of the imine. This reaction was routinely carried out on a 50 g scale. The carboxylic acid itself proved relatively unstable[7] but could be conveniently isolated and stored as a stable lithium salt. Treatment of this compound under the standard conditions with an aryl diazonium salt followed by acetic anhydride/pyridine gave the triazolium hydroxide (**12**). A variety of conditions were investigated for cyclization but the most successful and simplest to carry out was refluxing with *p*-toluenesulphonic acid in toluene.

An X-ray structure determination for compound **3b** illustrates the expected planar arrangement of the ring system (Fig. 2).[8,9] The C–O bond distance of 1.23A° is intermediate between a carbonyl C=O bond distance (1.20A°) and a carboxylate C–O$^-$ distance (1.25A°) in accordance with the proposed mesoionic nature of the triazolium oxide ring system.

By an analogous sequence of steps triazolium hydroxide (**16**) was prepared, with the aniline group being installed by a Curtius rearrangement in *t*-butanol solvent (Scheme 4). Diazotization of this aniline resulted in immediate cyclization to afford the [1,2,3]triazolo[5,1-*c*]benzotriazinium system of (**4**).

If the Curtius rearrangement is carried out in a non-nucleophilic solvent such as toluene, the intermediate isocyanate is trapped by the triazolium ring system to give the cyclic amide (**17**) (Scheme 5). Amide (**17**) can itself be converted into compounds of type (**3**) either by direct reaction with a

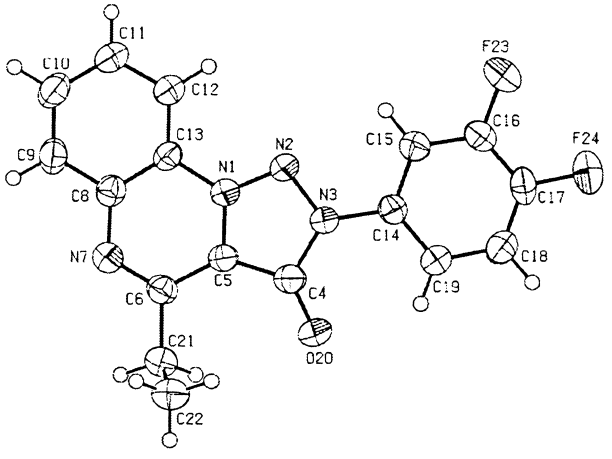
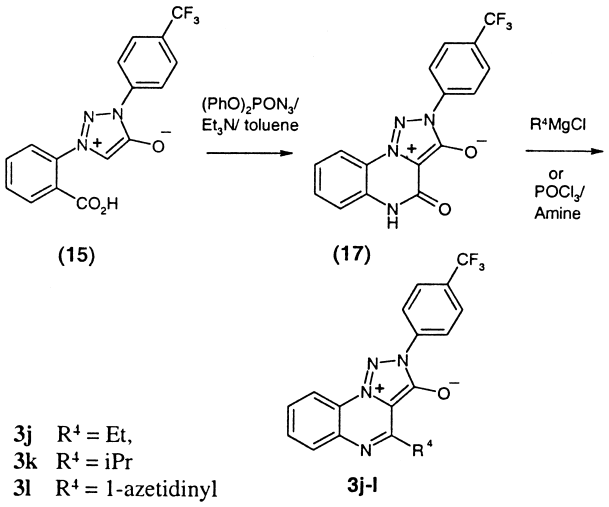


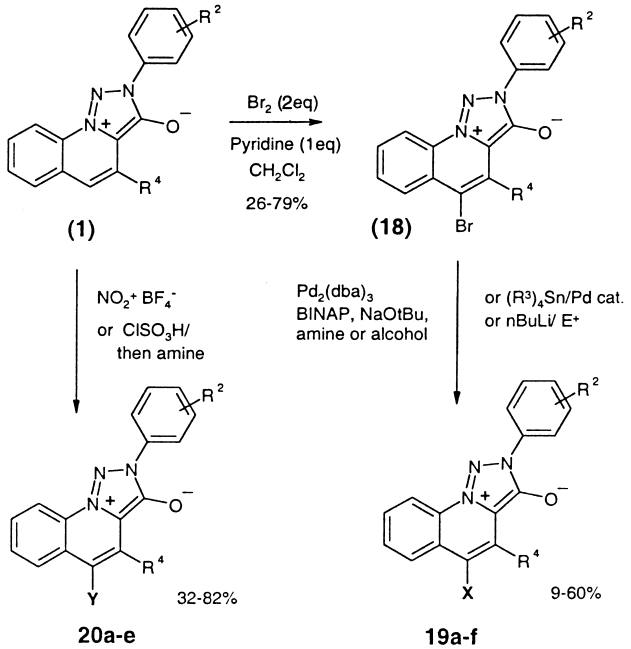
Figure 2. X-Ray structure of compound **3b.**



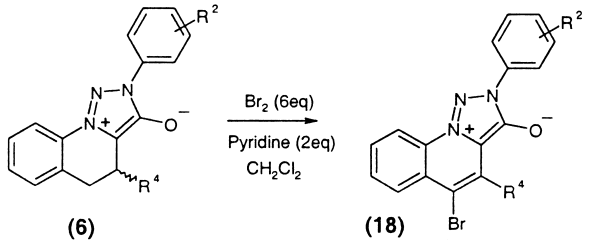
Scheme 5.

Grignard reagent, or by conversion into an intermediate chloroimine and further reaction with a nucleophile, such as an amine. In general, because the yields for both Grignard addition to the amide and for the nucleophilic displacement of chloride are low (12–18%), this process is less efficient than the direct route through intermediates (**10**)–(**12**).

The facile reactivity of the intermediate triazolium hydroxides with electrophiles is reflected in the reactivity of the [1,2,3]triazolo[1,5-*a*]quinolinium hydroxides (**1**) (R^3=H) (Scheme 6). Treatment with bromine effects clean bromination at the 5-position. In fact, treatment of the dihydro analogue (**6**) with excess bromine (6 equiv.) and pyridine (2 equiv.) results in the one-pot oxidation/bromination to give compound (**18**) cleanly (Scheme 7).



Scheme 6. R^2=H, *m*-F, *p*-F, *p*-Cl, *m*-CF_3, *p*-CF_3, *p*-OCF_3, 6-Cl-(3-pyridinyl), 6-Me-(3-pyridinyl). R^4=H, Me. X=Me, OMe, 1-azetidinyl, 1-morpholinyl, Me_2CHOH, $NH(CH_2)_2OMe$. Y=NO_2, SO_2azetidine.



Scheme 7. R^2=*p*-CF_3, R^4=H 50%. R^2=*p*-CF_3, R^4=Me 50%.

The bromo compound itself can be lithiated and quenched with electrophiles, or can be subjected to palladium catalyzed coupling reactions (Scheme 6). Nitration of (**1**) (R^3=H) can also be effected cleanly by treatment with nitronium tetrafluoroborate in dichloromethane, and (although not illustrated) the nitro compound can be readily reduced and derivatized on the resulting aniline nitrogen. In a similar manner, chlorosulfonation and trapping of the in situ generated sulfonyl chloride with an amine affords the corresponding sulfonamide, as illustrated by the preparation of the azetidine sulfonamide in 32% yield.

3. Conclusion

In summary, concise routes are provided to fused tricyclic mesoionic triazolium hydroxide inner salts, many of which can be prepared on large scale and in relatively few steps. Examples of functionalization of these ring systems are provided and these intermediates can themselves provide the basis for further derivatization.

4. Experimental[1]

4.1. General

Melting points are uncorrected. Infrared spectra were recorded on a Perkin–Elmer 2000 FT spectrometer and spectra were recorded over the range 400–4000 cm^{-1} by Attenuated Total Reflectance (ATR). ^1H and ^{13}C NMR spectra were recorded on a Varian Unity Inova 300 spectrometer in the indicated solvent using TMS as internal standard. Mass spectra were recorded on an Agilant 100 MSD instrument.

4.2. Representative procedure for the preparation of 4,5-dihydro-3-hydroxy-2-aryl-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salts (6a–g)

4.2.1. 4,5-Dihydro-3-hydroxy-2-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (6c). To a stirred solution of 4-(trifluoromethyl)aniline (12.08 g, 75 mmol) in a mixture of water (150 ml), tetrahydrofuran (60 ml) and concentrated hydrochloric acid (20 ml) at 0 to −5°C was added portionwise a solution of sodium nitrite (5.43 g, 78 mmol) in water (50 ml). The solution was stirred 15 min at 0 to −5°C and then was added portionwise to a solution of 1,2,3,4-tetrahydro-quinoline-2-carboxylic acid (13.3 g, 75 mmol) in pyridine (150 ml) at 0 to −5°C. The solution was stirred for 1 h at 0 to −5°C and then was allowed to warm to room temperature. Water was added and the solution extracted with ethyl acetate (twice), dried over magnesium sulphate and concentrated in vacuo. To the residue was added pyridine (90 ml) then acetic anhydride (10 ml) and the solution was stirred for 1 h. The reaction mixture was diluted with diethyl ether and filtered to give the title compound (12.25 g, 50%) as a yellow solid; mp 216–218°C; [Found: C, 61.43; H, 3.67; N, 12.66. $C_{17}H_{12}F_3N_3O$ requires: C, 61.63; H, 3.65; N, 12.68%]; ν_{max} (neat) 1656, 1610, 1491, 1418, 1320, 1105, 1062, 845, 755 cm^{-1}; δ_H ($CDCl_3$) 8.40 (2H, d, *J*=8.7 Hz), 8.02 (1H, m), 7.76 (2H, d, *J*=8.7 Hz), 7.41 (3H, m), 3.08 (4H, m); δ_C ($CDCl_3$) 155.4, 139.1, 132.8, 130.0, 129.7, 129.3, 128.0, 126.3, 120.7 (2C), 117.0, 114.8, 24.8, 17.6, 126.3; *m/z* APCI (+ve) 332 ($[M+H]^+$).

4.2.2. 4,5-Dihydro-3-hydroxy-2-phenyl-[1,2,3]triazolo-[1,5-*a*]quinolinium hydroxide, inner salt (6a). Prepared by the general procedure described above using 1,2,3,4-tetrahydroquinoline-2-carboxylic acid (12 g, 0.067 mol) and aniline (6.31 g, 67.8 mmol) to give, after crystallization from ethyl acetate, the title compound (4.9 g, 28%) as a brown solid; mp 145–146°C; [Found: C, 72.74; H, 4.85; N, 15.96. $C_{16}H_{13}N_3O$ requires: C, 72.99; H, 4.98; N, 15.96%]; ν_{max} (neat) 1649, 1484, 1313, 1178, 1078, 1065, 754 cm^{-1}; δ_H ($CDCl_3$) 8.14 (2H, m), 8.01 (1H, m), 7.53 (2H, t, *J*=8 Hz), 7.40 (4H, m), 3.14 (2H, m), 3.08 (2H, m); δ_C ($CDCl_3$) 154.7, 136.1, 132.9, 129.8, 129.7, 129.4, 129.2, 128.1, 128.0, 121.5, 117.0, 114.9, 24.9, 17.9; *m/z* APCI (+ve) 264 ($[M+H]^+$).

4.2.3. 4,5-Dihydro-2-(4-fluorophenyl)-3-hydroxy-[1,2,3]-triazolo[1,5-*a*]quinolinium hydroxide, inner salt (6b). Prepared by the general procedure described above using 1,2,3,4-tetrahydroquinoline-2-carboxylic acid (23 g, 0.13 mol) and 4-fluoroaniline (13.4 ml, 0.14 mol) to give the title compound (18.3 g, 50%) as a yellow solid; mp 144–146°C; [Found: C, 68.57; H, 4.33; N, 14.70. $C_{16}H_{12}FN_3O$ requires: C, 68.32; H, 4.30; N, 14.94%]; ν_{max} (neat) 1635, 1617, 1603, 1509, 1489, 1216, 1151, 835, 759 cm^{-1}; δ_H ($CDCl_3$) 8.18 (2H, m), 7.99 (1H, m), 7.42 (3H, m), 7.18 (2H, m), 3.07 (4H, s); *m/z* APCI (+ve) 282 ($[M+H]^+$).

4.2.4. 4,5-Dihydro-3-hydroxy-2-(3-trifluoromethylphenyl)-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (6d). Prepared by the general procedure described above using 1,2,3,4-tetrahydro-quinoline-2-carboxylic acid (6.0 g, 40 mmol) and 3-trifluoromethylaniline (5.46 g, 40 mmol) to give the title compound (2.21 g, 20%) as a yellow solid; mp 182–184°C; [Found: C, 61.69; H, 3.60; N, 12.47. $C_{17}H_{12}F_3N_3O$ requires: C, 61.63 H, 3.65; N, 12.68%]; ν_{max} (neat) 1655, 1489, 1462, 1338, 1289, 1116, 1070, 898, 802, 763 cm^{-1}; δ_H ($CDCl_3$) 8.57 (1H, m), 8.46 (1H, s), 8.05 (1H, m), 7.64 (2H, m), 7.43 (3H, m), 3.08 (4H, s); δ_C ($CDCl_3$) 155.4, 136.9, 132.8, 131.6 (C, q, J_{C-F}=33 Hz), 129.9, 129.7, 129.7, 129.3, 128.0, 124.1 (CH, q, J_{C-F}=4 Hz), 123.9, 122.6, 117.6, 117.1 (CH, q, J_{C-F}=4 Hz), 114.6, 24.8, 17.7; *m/z* APCI (+ve) 332 ($[M+H]^+$).

4.2.5. 4,5-Dihydro-3-hydroxy-2-[4-(trifluoromethoxy)-phenyl]-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (6e). Prepared by the general procedure described

above using 1,2,3,4-tetrahydroquinoline-2-carboxylic acid (12 g, 67.8 mmol) and (4-trifluoromethoxy)aniline (12.01 g, 67.8 mmol) to give the title compound (8.44 g, 36%) as a cream solid; mp 163–165°C; [Found: C, 58.79; H, 3.30; N, 12.03. $C_{17}H_{12}F_3N_3O_2$ requires: C, 58.79; H, 3.48; N, 12.10%]; ν_{max} (neat) 1653, 1506, 1491, 1254, 1219, 1149, 752 cm^{-1}; δ_H ($CDCl_3$) 8.27 (2H, m), 8.00 (1H, m), 7.40 (5H, m), 3.07 (4H, s); δ_C ($CDCl_3$) 155.2, 148.1, 134.8, 132.9 129.83 129.7, 129.36, 128.0, 122.5, 121.6, 117.0, 114.6, 24.8, 17.7, 17.7; *m/z* APCI (+ve) 348 ($[M+H]^+$).

4.2.6. 6,9-Difluoro-4,5-dihydro-3-hydroxy-2-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (6f). Prepared by the general procedure described above using 5,8-difluoro-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (5.325 g, 25 mmol) and 4-(trifluoromethyl)aniline (4.03 g, 25 mmol) to give the title compound (2.65 g, 24%) as a tan solid; mp>260°C; [Found: C, 55.26; H, 2.77; N, 11.53. $C_{17}H_{10}F_5N_3O$ requires: C, 55.59; H, 2.74; N, 11.44%]; ν_{max} (neat) 1655, 1610, 1508, 1320, 1240, 1121, 1107, 849, 814 cm^{-1}; δ_H ($CDCl_3$) 8.39 (2H, d, J=8.7 Hz), 7.77 (2H, d, J=8.7 Hz), 7.20 (2H, m), 3.06 (4H, m); δ_C ($CDCl_3$) 156.5, 154.5, 149.84(C, d, J_{C-F}=255 Hz), 138.8, 129.7 (C, q, J_{C-F}= 36 Hz), 126.4 (C, d, J_{C-F}=4 Hz), 124.9, 122.7, 121.6 (C, dd, J_{C-F}=8, 6 Hz), 120.9, 120.4 (C, d, J_{C-F}=23.5 Hz), 117.2 (C, dd, J_{C-F}=16, 8 Hz), 117.0 (C, dd, J_{C-F}=16, 8 Hz), 114.9, 18.6, 17.05; *m/z* APCI (+ve) 368 ($[M+H]^+$).

4.2.7. 4,5-Dihydro-2-(6-chloro-3-pyridinyl)-3-hydroxy-4-methyl-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (6g). To a solution of 3-amino-6-chloropyridine (23.9 g, 0.188 mol) in tetrahydrofuran (100 ml), water (200 ml) and concentrated hydrochloric acid (40 ml) at 0°C was added a solution of $NaNO_2$ (13.0 g, 0.188 mol) in water (100 ml) dropwise maintaining a temperature of 0°C. 30 min after complete addition the mixture was added to a solution of 3-methyl-1,2,3,4-tetrahydroquinoline-2-carboxylic acid (30 g, 0.157 mol) in pyridine (150 ml) at 0°C maintaining the temperature below 5°C. After 1.5 h the mixture was partitioned between ethyl acetate and water. The organic layer was collected and dried over magnesium sulphate. The solution was partially concentrated in vacuo, diluted with further pyridine (50 ml) and treated with acetic anhydride (30 ml). The mixture was allowed to stand for 3 days. The solid which separated was washed with ethyl acetate then diethyl ether, then dried to afford the title compound (14.74 g, 30%); [Found: C, 60.99; H, 4.22; N, 16.68. $C_{16}H_{13}ClN_4O$ requires: C, 61.25; H, 4.19; N, 16.91%]; δ_H ($CDCl_3$) 9.20 (1H, m), 8.70 (1H, m), 8.01 (1H, m), 7.37–7.50 (4H, m), 3.46 (1H, m), 3.18 (1H, m), 2.85 (1H, m), 1.43 (3H, m); *m/z* APCI (+ve) 313 ($[M+H]^+$).

4.3. Representative procedure for the preparation of 3-hydroxy-2-aryl-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salts (1) using palladium on charcoal

4.3.1. 3-Hydroxy-2-[4-(trifluoromethyl)phenyl]-[1,2,3]-triazolo[1,5-*a*]quinolinium hydroxide, inner salt (1c). A solution of 4,5-dihydro-3-hydroxy-2-[4-(trifluoromethyl) phenyl]-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (**6c**, 9.6 g, 28.9 mmol) and 10% palladium on carbon (1 g) in a mixture of dimethylacetamide (100 ml) and cyclohexene (100 ml) was heated in an oil bath at 140°C for 48 h. After allowing to cool, the solution was diluted with a mixture of water and ethyl acetate and filtered through Celite. The organic layer was separated, dried over magnesium sulphate and concentrated in vacuo. Purification by chromatography on silica gel (ethyl acetate) gave the title compound (5.54 g, 58%) as a yellow solid; mp 174–176°C; ν_{max} (neat) 1659, 1611, 1313, 1107, 1086, 1064, 839, 749 cm^{-1}; [Found: C, 62.20; H, 3.14; N, 12.59. $C_{17}H_{10}F_3N_3O$ requires: C, 62.01; H, 3.06; N, 12.76%]; δ_H ($CDCl_3$) 8.48 (3H, m), 7.80 (1H, dd, J=7.9, 1.3 Hz), 7.77 (2H, d, J=8.7 Hz), 7.73–7.64 (2H, m), 7.63 (1H, d, J=9.1 Hz), 7.24 (1H, d, J=9.1 Hz); *m/z* APCI (+ve) 330 ($[M+H]^+$).

4.3.2. 3-Hydroxy-2-phenyl-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (1a). Prepared from 4,5-dihydro-3-hydroxy-2-phenyl-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (**6a**, 4.1 g, 15.5 mmol) to give the title compound (1.7 g, 41%) as a yellow solid; mp 153–155°C; [Found: C, 73.78; H, 4.33; N, 16.12. $C_{16}H_{11}N_3O$ requires: C, 73.55; H, 4.24; N, 16.08%]; ν_{max} (neat) 1655, 1492, 1460, 1401, 1319, 1136, 761 cm^{-1}; δ_H ($CDCl_3$) 8.53 (1H, dd, J=8, 1.3 Hz), 8.12 (2H, m), 7.81 (1H, dd, J=7.6, 1.8 Hz), 7.68 (2H, m), 7.67 (1H, d, J=9.3 Hz), 7.36 (2H, d, J=8.3 Hz), 7.24 (2H, d, J=9.2 Hz); δ_C ($CDCl_3$) 153.4, 136.5, 130.3, 129.2, 129.2 (2C), 129.0, 128.7, 127.7, 127.6, 121.2 (2C), 119.7, 118.8, 117.1, 115.8; *m/z* APCI (+ve) 262 ($[M+H]^+$).

4.3.3. 2-(4-Fluorophenyl)-3-hydroxy-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (1b). Prepared from 4,5-dihydro-2-(4-fluorophenyl)-3-hydroxy-[1,2,3]triazolo-[1,5-*a*]quinolinium hydroxide, inner salt (**6b**, 1 g, 3.5 mmol) to give the title compound (0.615 g, 62%) as a yellow solid; mp 184–186°C; ν_{max} (neat) 1671, 1505, 1405, 1222, 1134, 1097, 838, 795, 764, 750 cm^{-1}; [Found: C, 68.76; H, 3.60; N, 15.06. $C_{16}H_{10}F_3N_3O$ requires: C, 68.81; H, 3.61; N, 15.05%]; δ_H ($CDCl_3$) 8.53 (1H, m), 8.26 (2H, m), 7.83 (1H, m), 7.70 (3H, m), 7.26 (3H, m); δ_c ($CDCl_3$) 153.6, 139.3, 130.1, 129.5, 129.4, 128.8, 127.9, 126.4, 126.3, 126.3, 126.3, 120.6, 120.2, 119.0, 116.9, 115.9; *m/z* APCI (+ve) 280 ($[M+H]^+$).

4.3.4. 3-Hydroxy-2-[3-(trifluoromethyl)phenyl]-[1,2,3]-triazolo[1,5-*a*]quinolinium hydroxide, inner salt (1d). Prepared from 4,5-dihydro-3-hydroxy-2-(3-trifluoromethyl phenyl)-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (**6d**, 4.08 g, 12.3 mmol) to give the title compound (1.78 g, 44%) as a yellow solid; mp 168–169°C; ν_{max} (neat) 1656, 1464, 1342, 1112, 1070, 802, 753 cm^{-1}; [Found: C, 62.44; H, 3.11; N, 12.68. $C_{17}H_{10}F_3N_3O$ requires: C, 62.01; H, 3.06; N, 12.76%]; δ_H ($CDCl_3$) 8.64 (1H, dt, J=6.7, 1.9 Hz), 8.56 (2H, m), 7.84 (1H, dd, J=7.7, 1.5 Hz), 7.70 (5H, m), 7.29 (1H, d, J=8.7 Hz); δ_c ($CDCl_3$) 153.5, 137.0, 131.7 (C, q, J_{C-F}=33 Hz), 130.2, 129.8, 129.5, 129.3, 128.8, 127.9, 123.9 (C, q, J_{C-F}=4 Hz), 123.8, 120.2, 119.0, 117.6 (C, q, J_{C-F}=4 Hz), 116.9, 116.0,131.7; *m/z* APCI (+ve) 330 ($[M+H]^+$).

4.3.5. 3-Hydroxy-2-[4-(trifluoromethoxy)phenyl]-[1,2,3]-triazolo[1,5-*a*]quinolinium hydroxide, inner salt (1e). Prepared from 4,5-dihydro-3-hydroxy-2-[4-(trifluoro-

methoxy) phenyl)-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (**6e**, 5 g, 14.4 mmol) to give the title compound (4.3 g, 86%) as a yellow solid. Mp 155–156°C; ν_{max} (neat) 1675, 1500, 1402, 1259, 1215, 1153, 1102, 796, 751 cm^{-1}; [Found: C, 59.34; H, 3.00; N, 12.36. $C_{17}H_{10}F_3N_3O_2$ requires: C, 59.14; H, 2.92; N, 12.17%]; δ_H ($CDCl_3$) 8.54 (1H, m), 8.36 (2H, m), 7.84 (1H, m), 7.70 (3H, m), 7.40 (2H, m), 7.28 (1H, m); δ_c ($CDCl_3$) 153.3, 147.9, 135.0, 130.2, 129.4, 129.2, 128.8, 127.8, 122.4, 121.7, 121.5, 120.1, 119.4, 118.9, 117.0, 115.9; *m/z* APCI (+ve) 346 ($[M+H]^+$).

4.3.6. 6,9-Difluoro-3-hydroxy-2-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolo[1,5-*a*]quinolinium, hydroxide inner salt (1f). A solution 6,9-difluoro-4,5-dihydro-3-hydroxy-2-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (**6f**, 2 g, 5.4 mmol) and DDQ (1.86 g, 8.2 mmol) in toluene (150 ml) was refluxed for 14 h. Purification by chromatography on silica gel (ethyl acetate/iso-hexane 2:1) followed by recrystallization from ethyl acetate gave the title compound (0.98 g, 49%) as yellow needles; mp 243–245°C; [Found: C, 55.52; H, 2.18; N, 11.65. $C_{17}H_8F_5N_3O$ requires: C, 55.90; H, 2.21; N, 11.50%]; δ_H ($CDCl_3$) 8.49 (2H, m), 7.81 (2H, m), 7.75 (1H, m), 7.37 (3H, m); *m/z* APCI (+ve) 366 ($[M+H]^+$).

4.3.7. 2-(6-Chloro-3-pyridinyl)-3-hydroxy-4-methyl-[1,2,3]-triazolo[1,5-*a*]quinolinium hydroxide, inner salt (1g). 4,5-Dihydro-2-(6-chloro-3-pyridinyl)-3-hydroxy-4-methyl-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (**6g**, 11.2 g, 35.8 mmol) was dissolved in chloroform (50 ml) and manganese dioxide (11 g) was added. The mixture was refluxed for 24 h. Further manganese dioxide (10 g, 115 mmol) was added and the mixture refluxed for a further 30 h. The mixture was filtered through Celite and concentrated in vacuo to give the title compound (10.2 g, 91%); mp 250–251°C; ν_{max} (neat) 1655, 1459, 1384, 1332, 1120, 1100, 1067, 831, 749 cm^{-1}; [Found: C, 61.59; H, 3.58; N, 17.76. $C_{16}H_{11}ClN_4O$ requires: C, 61.84; H, 3.57; N, 18.03%]; δ_H ($CDCl_3$) 9.31 (1H, dd, J=2.8, 0.5 Hz), 8.76 (1H, dd, J=8.7, 2.7 Hz), 8.48 (1H, m), 7.74 (1H, m), 7.65 (2H, m), 7.50 (1H, dd, J=8.8, 0.6 Hz), 7.00 (1H, s), 2.78 (3H, s); *m/z* APCI (+ve) 311($[M+H]^+$).

4.3.8. 4-Oxo-1,2,3,4-tetrahydroquinazoline-2-carboxylic acid (7). To a stirred solution of anthranilamide (45 g, 0.33 mol) in methanol (900 ml) was added glyoxylic acid monohydrate (30.6 g, 0.33 mol) and the reaction mixture was refluxed for 1 h. The solution was cooled to 0 to −5°C for several hours, then filtered to give the title compound (28.1 g) as a white solid; mp 184–185°C; [Found: C, 56.25; H, 3.99; N, 14.64. $C_9H_8N_2O_3$ requires: C, 56.25; H, 4.20; N, 15.58%]; ν_{max} (neat) 1710, 1687, 1603, 1606, 1518, 1237 cm^{-1}; δ_H (DMSO-d_6) 7.57 (1H, d, J=7.9 Hz), 7.24 (1H, ddd, J=8.3, 7.1, 1.4 Hz), 7.16 (1H, s), 6.78 (1H, d, J=7.7 Hz), 6.68 (1H, dd, J=14.9, 1.1 Hz), 4.96 (1H, dd, J=4.2, 2.7 Hz); δ_C (DMSO-d_6) 172.1, 163.1, 147.06, 133.2, 127.2, 117.3, 114.9, 114.4, 63.4; *m/z* APCI (+ve) 193 ($[M+H]^+$).

4.3.9. 4,5-Dihydro-3-hydroxy-5-oxo-2-[4-(trifluoromethyl)-phenyl]-[1,2,3]triazolo[1,5-*a*]quinazolinium hydroxide, inner salt (8). To a stirred solution of 4-(trifluoromethyl)-aniline (16.1 g, 0.1 mol) in a mixture of water (145 ml), tetrahydrofuran (65 ml) and concentrated hydrochloric acid (35 ml) at 0 to −5°C was added portionwise a solution of sodium nitrite (7.25 g, 0.105 mol) in water (80 ml). The solution was stirred 15 min at 0° to −5°C and then was added portionwise to a solution of 4-oxo-1,2,3,4-tetrahydroquinazoline-2-carboxylic acid (19.2 g, 0.1 mol) in pyridine (145 ml) and water (100 ml) at 0° to −5°C. The solution was stirred for 1 h then allowed to warm to room temperature. The solid was filtered, washed with water and then azeotroped with toluene. To the residue was added pyridine (180 ml) then acetic anhydride (25 ml) and the solution was stirred for 1 h. The reaction mixture was diluted with diethyl ether and filtered to give the title compound (6.8 g, 20%) as a yellow solid; mp>250°C; [Found: C, 55.50; H, 2.75; N, 15.79. $C_{16}H_{13}N_3O$ requires: C, 55.47; H, 2.62; N, 16.18%]; ν_{max} (neat) 1709, 1661, 1610, 1516, 1319, 1304, 1119, 848, 759 cm^{-1}; δ_H (DMSO-d_6) 12.90 (1H, br s), 8.50 (2H, m), 8.33 (1H, m), 8.28 (1H, m), 8.03 (3H, m), 7.83 (1H, m); *m/z* APCI (+ve) 347 ($[M+H]^+$).

4.3.10. 5-Chloro-3-hydroxy-2-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolo[1,5-*a*]quinazolinium hydroxide, inner salt (9). A solution of 4,5-dihydro-3-hydroxy-5-oxo-2-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolo[1,5-*a*]quinazolinium hydroxide, inner salt (**8**, 1.76 g, 5 mmol) in phosphorus oxychloride (20 ml) was refluxed for 2 h before being concentrated in vacuo. The residue was quenched with water then basified with solid sodium hydrogen carbonate. The solution was extracted with ethyl acetate (twice), dried over magnesium sulphate and concentrated in vacuo. The solid was washed with ethyl acetate to give the title compound (1.48 g, 80%) as a yellow solid; mp>250°C; [Found: C, 52.66; H, 2.15; N, 15.18. $C_{16}H_8ClF_3N_3O$ requires: C, 52.69; H, 2.21; N, 15.36%]; ν_{max} (neat) 1600, 1556, 1327, 1166, 1122 cm^{-1}; δ_H ($CDCl_3$) 8.39 (1H, m), 8.12 (2H, m), 8.00 (3H, m), 7.69 (1H, m), 7.64 (1H, m); δ_C ($CDCl_3$) 165.4, 143.5, 136.6, 134.1 (C, q, J_{C-F}=33 Hz), 132.7, 130.2, 129.4, 127.3, 126.2 (2C), 124.2, 122.0, 121.6, 114.5, 112.3; *m/z* APCI (+ve) 365 ($[M+H]^+$).

4.3.11. 3-Hydroxy-2-[4-(trifluoromethyl)phenyl]-[1,2,3]-triazolo[1,5-*a*]quinazolinium hydroxide, inner salt (2a). To a solution of 5-chloro-3-hydroxy-2-[4-(trifluoromethyl)-phenyl]-[1,2,3]triazolo[1,5-*a*]quinazolinium hydroxide, inner salt (**9**, 1 g, 2.7 mmol) in ethanol (150 ml) was added sodium borohydride (1.04 g, 27 mmol) and the reaction mixture was stirred for 2 h. The solution was quenched with ammonium chloride solution, extracted with ethyl acetate (twice), dried over magnesium sulphate and concentrated in vacuo. The residue was recrystallized from methanol to give the title compound (0.33 g, 37%) as a yellow solid; mp>250°C; [Found: C, 58.28; H, 2.89; N, 16.76. $C_{16}H_9F_3N_4O$ requires: C, 58.19; H, 2.75; N, 16.96%]; ν_{max} (neat) 1606, 1556, 1421, 1323, 1171, 1115 cm^{-1}; δ_H (DMSO-d_6) 9.08 (1H, s), 8.40 (2H, m), 8.28 (2H, m), 8.16 (2H, m), 7.95 (1H, m), 7.79 (1H, m); *m/z* APCI (+ve) 331 ($[M+H]^+$).

4.3.12. 3-Hydroxy-5-(1-methylethyl)-2-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolo[1,5-*a*]quinazolinium hydroxide, inner salt (2b). To a solution of 5-chloro-3-hydroxy-2-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolo[1,5-

a]quinazolinium hydroxide, inner salt (**9**, 1 g, 2.7 mmol) in tetrahydrofuran (150 ml) was added dropwise isopropyl magnesium chloride (3.4 ml, 2 M solution in tetrahydrofuran) and the solution was stirred overnight. The solution was quenched with ammonium chloride solution, extracted with dichloromethane (twice), dried over magnesium sulphate and concentrated in vacuo. Purification by chromatography on silica gel (acetone/methanol 10:1) followed by recrystallization from ethyl acetate gave the title compound (0.15 g) as a white solid; mp 255°C; [Found: C, 61.02; H, 4.04; N, 14.81. $C_{19}H_{15}F_3N_4O$ requires: C, 61.29; H, 4.06; N, 15.05%]; δ_H (DMSO-d_6) 8.27 (1H, m), 8.17 (3H, m), 8.10 (2H, m), 7.90 (1H, m), 7.77 (1H, m), 2.99 (1H, m), 1.41 (6H, m); *m/z* APCI (+ve) 373 ($[M+H]^+$).

4.3.13. 3-Hydroxy-5-(morpholinyl)-2-[4-(trifluoromethyl)-phenyl]-[1,2,3]triazolo[1,5-*a*]quinazolinium hydroxide, inner salt (2c). A solution of 5-chloro-3-hydroxy-2-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolo[1,5-*a*]quinazolinium hydroxide, inner salt (**9**, 0.5 g, 1.37 mmol) in morpholine (10 ml) was refluxed for 30 min. The solution was concentrated in vacuo and chromatographed on silica gel (acetone/methanol 10:1) followed by recrystallization from ethyl acetate gave the title compound (0.25 g, 44%) as a pale yellow solid; mp>250°C; [Found: C, 57.76; H, 3.93; N, 16.34. $C_{20}H_{16}F_3N_5O_2$ requires: C, 57.83; H, 3.88; N, 16.86%]; ν_{max} (neat) 1611, 1602, 1554, 1508, 1323, 1132, 1110, 752 cm^{-1}; δ_H ($CDCl_3$) 8.44 (1H, d, *J*=8.0 Hz), 8.14 (2H, m), 7.97(2H, m), 7.93 (1H, d, *J*=8.0 Hz), 7.69 (1H, m), 7.64 (1H, m), 3.74 (4H, m), 3.43 (4H, m); δ_C ($CDCl_3$) 165.4, 140.5, 137.9, 133.2 (C, q, J_{C-F}=33 Hz), 133.1, 132.9, 132.3, 131.9, 129.6, 129.4, 127.1, 125.2 (2C), 124.3, 122.1, 121.5, 114.2, 66.6, 50.1, 133.2; *m/z* APCI (+ve) 416 ($[M+H]^+$).

4.3.14. 3-Hydroxy-5-(piperidinyl)-2-[4-(trifluoromethyl)-phenyl]-[1,2,3]triazolo[1,5-*a*]quinazolinium hydroxide, inner salt (2d). A solution of 5-chloro-3-hydroxy-2-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolo[1,5-*a*]quinazolinium hydroxide, inner salt (**9**, 0.5 g, 1.37 mmol) in piperidine (10 ml) was refluxed for 30 min. The solution was concentrated in vacuo and chromatographed on silica gel (dichloromethane/methanol 15:1). The product was stirred in diethyl ether and filtered to give the title compound (0.42 g, 74%) as a pale yellow solid; mp>250°C; [Found: C, 60.72; H, 4.37; N, 16.94. $C_{21}H_{18}F_3N_5O$ requires: C, 61.01; H, 4.39; N, 16.94%]; ν_{max} (neat) 1612, 1601, 1502, 1451, 1324, 1164, 1132, 1105, 855, 751 cm^{-1}; δ_H ($CDCl_3$) 8.49 (1H, d, *J*=8.0 Hz), 8.13 (2H, m), 8.09 (1H, d, *J*=8.0 Hz), 7.76 (1H, m), 7.94 (2H, m), 3.35 (4H, m), 7.68 (1H, m), 1.57 (6H, m); *m/z* APCI (+ve) 414 ($[M+H]^+$).

4.3.15. 3-Hydroxy-5-(pyrrolidinyl)-2-[4-(trifluoromethyl)-phenyl]-[1,2,3]triazolo[1,5-*a*]quinazolinium hydroxide, inner salt (2e). A solution of 5-chloro-3-hydroxy-2-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolo[1,5-*a*]quinazolinium hydroxide, inner salt (**9**, 0.5 g, 1.37 mmol) in pyrrolidine (10 ml) was refluxed for 30 min. The solution was concentrated in vacuo and chromatographed on silica gel (dichloromethane: methanol/15:1). The product was stirred in diethyl ether and filtered to give the title compound (0.47 g, 86%) as a pale yellow solid; mp>250°C; [Found: C, 60.28; H, 4.04; N, 17.36. $C_{20}H_{16}F_3N_5O$ requires: C, 60.15; H, 4.09; N, 17.54%]; δ_H (DMSO-d_6) 8.56 (1H, m), 8.12 (1H, m), 8.06 (2H, m), 7.92 (2H, m), 7.79 (1H, m), 7.69 (1H, m), 3.56 (4H, m), 1.91 (4H, m); *m/z* APCI (+ve) 400 ($[M+H]^+$).

4.3.16. [2-(Acetylamino)phenyl]amino acetic acid, lithium salt (11a). A solution of 2-nitroacetanilide (50 g, 0.277 mol) in methanol (1 l) was stirred with 10% palladium on charcoal (10 g) under an atmosphere of hydrogen (5 bar). Once hydrogen uptake had ceased a solution of glyoxylic acid monohydrate (26.2 g, 0.28 mol) in water (100 ml) was added and the mixture rehydrogenated at 5 bar. Once hydrogen uptake had ceased the mixture was filtered rapidly and lithium hydroxide monohydrate (11.96 g, 0.28 mol) in water (100 ml) was added. The solution was concentrated to a volume of ca 100 ml in vacuo. The lithium salt was precipitated by addition of acetone and dried in vacuo to afford the title compound as a colourless powder (56.2 g); δ_H (DMSO-d_6) 7.06 (2H, m), 6.55 (2H, m), 3.37 (2H, s), 2.08 (3H, s); δ_C (MeOH-d^4/D_20) 202.4, 173.8, 144.6, 129.1, 128.2, 124.1, 118.1, 113.4, 23.4; *m/z* APCI (+ve) 209 ($[M+H]^+$).

4.3.17. [2-(Propionylamino)phenyl]amino acetic acid, lithium salt (11b). A solution of 2-nitrophenylpropionamide (25 g, 0.129 mol) in methanol (500 ml) was stirred with 10% palladium on charcoal (5 g) under an atmosphere of hydrogen (5 bar). Once hydrogen uptake had ceased a solution of glyoxylic acid monohydrate (12.2 g, 0.13 mol) in water (100 ml) was added and the mixture rehydrogenated at 5 bar. Once hydrogen uptake had ceased the mixture was filtered rapidly and lithium hydroxide monohydrate (5.55 g, 0.13 mol) in water (100 ml) was added. The solution was concentrated to a volume of ca 50 ml in vacuo. The lithium salt was precipitated by addition of acetone and dried in vacuo to afford the title compound as a colourless powder (28 g); δ_H (DMSO-d_6) 9.25 (1H, s), 6.47 (2H, t, *J*=8.1 Hz), 6.42 (2H, d, *J*=8.5 Hz), 7.04–6.94 (2H, m), 5.10 (1H, s), 3.21 (2H, s), 2.32 (2H, q, *J*=7.6 Hz), 1.10 (3H, t, *J*=7.6 Hz); δ_C (DMSO-d_6) 172.5, 171.7, 143.2, 126.7, 126.5, 123.0, 114.5, 110.7, 48.1, 28.8, 10.0; *m/z* APCI (+ve) 223 ($[M+H]^+$).

4.3.18. 1-(2-Acetylamino)phenyl-3-(4-fluorophenyl)-4-hydroxy-[1,2,3]triazolium hydroxide, inner salt (12a). To a solution of 4-fluoroaniline (9.47 ml, 0.1 mol) in water (120 ml), tetrahydrofuran (60 ml) and concentrated hydrochloric acid (30 ml) at −5°C was added a solution of $NaNO_2$ (7.25 g, 0.105 mol) in water (60 ml) dropwise maintaining a temperature of less than 0°C. Once addition was complete the solution was stirred for a further 30 min at 0°C then added portionwise to a solution of 2-(acetylamino)phenylamino acetic acid, lithium salt (21.4 g, 0.1 mol) in pyridine (200 ml) at −5°C maintaining a temperature of less than 0°C. The mixture was stirred below 0°C for 2 h before being partitioned between ethyl acetate and water. The layers were separated and the aqueous extracted with ethyl acetate. The combined organics were dried over magnesium sulphate then concentrated in vacuo until only pyridine remained (ca 30 ml volume). To the pyridine solution was added acetic anhydride (50 ml) and the solution was allowed to stir for 1 h. The reaction mixture was concentrated in vacuo and azeotroped with toluene. The resulting semi-solid was

triturated with ether and collected, then washed with diethyl ether and dried in vacuo to afford the title compound (8.0 g, 26%); mp 228–230°C; [Found: C, 60.65; H, 4.18; N, 17.94. $C_{16}H_{13}FN_4O_2$ requires: C, 60.53; H, 4.20; N, 17.94%]; ν_{max} (neat) 1661, 1600, 1541, 1498, 1299, 1227, 832, 773 cm^{-1}; δ_H ($CDCl_3$) 8.90 (1H, s), 8.34 (1H, d, J=7.5 Hz), 8.00 (2H, m), 7.56 (1H, t, J=7.9 Hz), 7.45 (1H, m), 7.30 (1H, m), 7.13 (2H, m), 6.96 (1H, s), 2.19 (3H, s); δ_C ($CDCl_3$) 169.3, 162.9, 160.9, 157.4, 132.4, 131.6, 127.3, 125.1, 125.0, 123.0, 122.9, 116.1, 116.0, 109.1, 24.3; m/z APCI (+ve) 313($[M+H]^+$).

4.3.19. 2-(4-Fluorophenyl)-3-hydroxy-4-methyl-[1,2,3]-triazolo[1,5-*a*]quinoxalinium hydroxide, inner salt (3a). To 1-(2-acetylamino)phenyl-3-(4-fluorophenyl)-4-hydroxy-[1,2,3]triazolium hydroxide, inner salt (**12b**, 7.47 g, 24 mmol) in toluene (200 ml) was added *p*-toluenesulphonic acid monohydrate (4.83 g, 25 mmol) and the mixture was heated with azeotropic removal of water for 8 h. The reaction mixture was concentrated in vacuo and partitioned between dichloromethane and sodium hydrogen carbonate solution. The organic layer was collected and dried over magnesium sulphate, then concentrated in vacuo. Chromatography on silica eluting with 49:1 dichloromethane/methanol followed by recrystallization from ethyl acetate gave the title compound (3.58 g, 51%) as pale yellow needles. Mp 198°C; [Found: C, C, 65.22; H, 3.75; N, 18.86. $C_{16}H_{11}FN_4O$ requires: C, 65.30; H, 3.77; N, 19.04%]; ν_{max} (neat) 1677, 1500, 1227, 1131, 1095, 832, 765 cm^{-1}; δ_H ($CDCl_3$) 8.30 (1H, m), 8.16 (2H, m), 7.94 (2H, m), 7.71 (1H, m), 7.60 (1H, m), 7.21 (2H, m), 2.92 (3H, m); δ_C ($CDCl_3$) 162.8, 160.8, 155.5, 153.7, 139.9, 132.0 (C, d, J_{C-F}=3 Hz), 130.9, 129.4, 128.2, 124.0, 123.0, 122.9, 116.3, 116.1, 114.8, 113.0, 20.9; m/z APCI (+ve) 295($[M+H]^+$).

4.3.20. 3-(3,4-Difluorophenyl)-4-hydroxy-1-(2-propionylamino)phenyl-[1,2,3]triazolium hydroxide, inner salt (12b). To a solution of 3,4-difluoroaniline (2.83 g, 22 mmol) in water (15 ml) and concentrated hydrochloric acid (8 ml) at −5°C was added a solution of $NaNO_2$ (1.59 g, 23 mmol) in water (15 ml) dropwise maintaining a temperature of less than 0°C. Once addition was complete the solution was stirred for a further 15 min at 0°C then added portionwise to a solution of 2-(propionylamino) phenylamino acetic acid, lithium salt (5 g, 22 mmol) in pyridine (50 ml) at −5°C maintaining a temperature of less than 0°C. The mixture was stirred below 0°C for 1 h then allowed to warm to room temperature. The mixture was partitioned between ethyl acetate and water, the layers separated and the aqueous extracted with ethyl acetate. The combined organics were dried over magnesium sulphate then concentrated in vacuo until only pyridine remained (ca 25 ml volume). To the pyridine solution was added acetic anhydride (8 ml) and the solution was allowed to stir for 14 h. The reaction mixture was concentrated in vacuo and azeotroped with toluene. The resulting semi-solid was triturated with ether and collected, then washed with ethyl acetate and dried in vacuo to afford the title compound (1.76 g, 23%); mp 178–180°C; [Found: C, 59.42; H, 4.17; N, 16.28. $C_{16}H_{13}FN_4O_2$ requires: C, 59.30; H, 4.10; N, 16.27%]; ν_{max} (neat) 1655, 1600, 1518, 1474, 1289, 1270, 755 cm^{-1}; δ_H ($CDCl_3$) 8.39 (1H, d, J=8.7 Hz), 8.31 (1H, s, br), 8.09 (1H, ddd, J=11.1, 7.3, 2.6 Hz), 7.91 (1H, m), 7.59 (1H, m), 7.46 (1H, dd, J=8.1, 1.5 Hz), 7.32 (2H, m), 7.00 (1H, s), 2.36 (2H, q, J=7.6 Hz), 1.18 (3H, t, J=7.6 Hz); m/z APCI (+ve) 345($[M+H]^+$).

4.3.21. 2-(3,4-Difluorophenyl)-4-ethyl-3-hydroxy-[1,2,3]-triazolo[1,5-*a*]quinoxalinium hydroxide, inner salt (3b). To 3-(3,4-difluorophenyl)-4-hydroxy-1-(2-propionylamino)-phenyl-[1,2,3]triazolium hydroxide, inner salt (**12b**, 1.56 g, 4.5 mmol) in toluene (120 ml) was added *p*-toluenesulphonic acid monohydrate (0.95 g, 5 mmol) and the mixture was heated with azeotropic removal of water for 40 h. The reaction mixture was concentrated in vacuo and partitioned between dichloromethane and sodium hydrogen carbonate solution. The organic layer was collected and dried over magnesium sulphate then concentrated in vacuo. Chromatography on silica eluting with 49:1 dichloromethane/methanol followed by recrystallization from ethyl acetate gave the title compound (0.79 g, 53%) as pale yellow crystals; mp 160–162°C; [Found: C, 62.56; H, 3.44; N, 17.08. $C_{17}H_{12}F_2N_4O$ requires: C, 62.58; H, 3.71; N, 17.17%]; ν_{max} (neat) 1672, 1509, 1500, 1262, 1113, 864, 859, 755 cm^{-1}; δ_H ($CDCl_3$) 8.35 (1H, d, J=8.2 Hz), 8.19 (1H, ddd, J=11.4, 7.1, 2.4 Hz), 8.03 (1H, m), 7.74 (1H, t, J=7.7 Hz), 7.99 (1H, d, J=8.4 Hz), 7.63 (1H, t, J=7.7 Hz), 7.32 (1H, q, J=9.1 Hz), 3.31 (1H, q, J=7.5 Hz), 1.47 (3H, t, J=7.5 Hz); δ_C ($CDCl_3$) 160.4, 153.3, 150.2 (C, dd, J_{C-F}=250, 13 Hz), 149.5 (C, dd, J_{C-F}=250, 13 Hz), 140.1, 132.2 (C, dd, J_{C-F}=8, 4 Hz), 131.0, 129.7, 128.3, 123.9, 117.9, 117.7, 116.7 (C, dd, J_{C-F}=6, 4 Hz), 114.8, 112.8, 110.6, 110.4, 27.7, 12.2, 116.7; m/z APCI (+ve) 327($[M+H]^+$).

4.3.22. 1-(2-Acetylamino)phenyl-3-(4-fluoro-3-methylphenyl)-4-hydroxy-[1,2,3]triazolium hydroxide, inner salt (12c). Prepared from 4-fluoro-3-methylaniline (6.26 g, 50 mmol) in water (60 ml), tetrahydrofuran (30 ml), concentrated hydrochloric acid (15 ml), $NaNO_2$ (3.63 g, 52 mmol) in water (30 ml), 2-(acetylamino)phenylamino acetic acid, lithium salt (10.7 g, 50 mmol) in pyridine (100 ml), and acetic anhydride (25 ml) to afford the title compound (9.02 g, 55%); mp 201–202°C; [Found: C, 62.30; H, 4.65; N, 16.89. $C_{17}H_{15}FN_4O_2$ requires: C, 62.57; H, 4.63; N, 17.17%]; ν_{max} (neat) 1708, 1685, 1649, 1540, 1491, 1467, 1287, 1243, 761, 735 cm^{-1}; δ_H ($CDCl_3$) 8.97 (1H, s, br), 8.34 (1H, d, br, J=7.9 Hz), 7.80 (2H, m), 7.57 (1H, m), 7.44 (1H, dd, J=8.1, 1.5 Hz), 7.26 (1H, m), 7.26 (1H, s), 7.06 (1H, t, J=8.9 Hz), 6.95 (1H, s), 2.29 (3H, d, J=1.9 Hz), 2.20 (3H, s); m/z APCI (+ve) 327 ($[M+H]^+$).

4.3.23. 2-(4-Fluoro-3-methyl)phenyl-3-hydroxy-4-methyl-[1,2,3]triazolo[1,5-*a*]quinoxalinium hydroxide, inner salt (3c). Prepared from **12c** (6.60 g, 20 mmol) and *p*-toluenesulphonic acid (4.10 g, 21 mmol) in toluene (200 ml) to give, after recrystallization from ethyl acetate, the title compound (1.00 g, 16%) as a yellow solid. Mp 203–205°C; [Found: C, 66.16; H, 4.27; N, 18.25. $C_{17}H_{13}FN_4O$ requires: C, 66.23; H, 4.25; N, 18.17%]; ν_{max} (neat) 1665, 1496, 1224, 1120, 826, 761, 754 cm^{-1}; δ_H ($CDCl_3$) 8.36 (1H, dd, J=8.3, 1.3 Hz), 8.05 (1H, dd, J=6.8, 2.4 Hz), 7.97 (1H, dd, J=8.3, 1.2 Hz), 7.94 (1H, m), 7.74 (1H, ddd, J=8.3, 7.2, 1.3 Hz), 7.63 (1H, m), 2.96 (3H, s), 7.17 (1H, t, J=8.9 Hz), 2.39 (3H, s); m/z APCI (+ve) 309 ($[M+H]^+$).

4.3.24. 1-(2-Acetylamino)phenyl-3-(4-ethylphenyl)-4-hydroxy-[1,2,3]triazolium hydroxide, inner salt (12d). Prepared from 4-ethylaniline (6.05 g, 50 mmol) in water (60 ml), tetrahydrofuran (20 ml), concentrated hydrochloric acid (15 ml), $NaNO_2$ (3.63 g, 52 mmol) in water (30 ml), 2-(acetylamino) phenylamino acetic acid, lithium salt (10 g, 47 mmol) in pyridine (100 ml), and acetic anhydride (15 ml) to afford the title compound (4.3 g, 28%); mp 162–163°C; [Found: C, 67.20; H, 5.50; N, 17.18. $C_{18}H_{18}N_4O_2$ requires: C, 67.07; H, 5.63; N, 17.38%]; ν_{max} (neat) 1686, 1649, 1638, 1473, 1294, 770, 761 cm^{-1}; δ_H ($CDCl_3$) 9.17 (1H, s, br), 8.33 (1H, d, J=8.5 Hz), 7.83 (2H, d, J=8.4 Hz), 7.55 (1H, m), 7.42 (1H, m), 7.26 (3H, m), 6.90 (1H, s), 2.66 (2H, q, J=7.6 Hz), 2.19 (3H, s), 1.25 (3H, t, J=7.6 Hz); m/z APCI (+ve) 323($[M+H]^+$).

4.3.25. 2-(4-Ethylphenyl)-3-hydroxy-4-methyl-[1,2,3]-triazolo[1,5-*a*]quinoxalinium hydroxide, inner salt (3d). Prepared from **12d** (4.0 g, 12.4 mmol) and *p*-toluenesulphonic acid (2.6 g, 13.7 mmol) in toluene (150 ml) to give the compound title compound (1.265 g, 34%) as a yellow solid; mp 176–178°C; [Found: C, 71.28; H, 5.09; N, 18.12. $C_{18}H_{16}N_4O$ requires: C, 71.04; H, 5.30; N, 18.41%]; ν_{max} (neat) 1577, 1502, 1314, 1132, 1111, 832, 773 cm^{-1}; δ_H ($CDCl_3$) 8.34 (1H, d, J=8.5 Hz), 8.04 (2H, m), 7.88 (1H, d, J=7.9 Hz), 7.65 (1H, t, J=7.8 Hz), 7.54 (1H, t, J=7.8 Hz), 7.36 (2H, m), 2.89 (3H, s), 2.73 (2H, m), 1.29 (3H, t, J=7.8 Hz); δ_C ($CDCl_3$) 155.6, 153.7, 144.4, 139.8, 133.6, 130.6, 129.3, 128.6, 128.0, 124.2, 121.1, 114.8, 113.0, 28.5, 20.9, 15.4; m/z APCI (+ve) 305 ($[M+H]^+$).

4.3.26. 1-(2-Acetylamino)phenyl-4-hydroxy-[3-(3-pyridinyl)-1,2,3]triazolium hydroxide, inner salt (12e). Prepared from 3-aminopyridine (9.40 g, 0.1 mol) in water (120 ml), tetrahydrofuran (60 ml), concentrated hydrochloric acid (30 ml), $NaNO_2$ (7.25 g, 0.105 mol) in water (60 ml), 2-(acetylamino) phenylamino acetic acid, lithium salt (21.4 g, 0.1 mol) in pyridine (200 ml), and acetic anhydride (25 ml) to afford the title compound (5.8 g, 20%); mp 190°C; [Found: C, 60.24; H, 4.10; N, 23.45. $C_{15}H_{13}N_5O_2$ requires: C, 60.01; H, 4.44; N, 23.72%]; ν_{max} (neat) 1703, 1656, 1637, 1601, 1546, 1468, 1424, 1366, 759 cm^{-1}; δ_H (DMSO-d_6) 9.77 (1H, s), 9.25 (1H, m), 8.64 (1H, m), 8.44 (1H, m), 7.90 (1H, m), 7.71 (1H, m), 7.63 (2H, m), 7.50 (1H, s), 7.40 (1H, m), 2.02 (3H, s); δ_C ($CDCl_3$) 169.7, 157.7, 148.8, 141.5, 132.6, 132.4, 131.7, 127.6, 127.5, 125.4, 125.1, 123.5, 109.5, 24.1; m/z APCI (+ve) 296 ($[M+H]^+$).

4.3.27. 3-Hydroxy-4-methyl-2-(3-pyridinyl)-[1,2,3]triazolo[1,5-*a*]quinoxalinium hydroxide, inner salt (3e). Prepared from **12e** (5.40 g, 18 mmol) and *p*-toluenesulphonic acid (6.60 g, 35 mmol) in toluene (300 ml) to give, after recrystallization from ethyl acetate the title compound (2.31 g, 45%) as pale orange crystals; mp 205°C; [Found: C, 64.67; H, 3.79; N, 24.96. $C_{15}H_{11}N_5O$ requires: C, 64.97; H, 4.00; N, 25.26%]; δ_H ($CDCl_3$) 9.40 (1H, m), 8.66 (1H, m), 8.62 (1H, m), 8.34 (1H, d, J=8.2 Hz), 7.96 (1H, d, J=8.2 Hz), 7.74 (1H, t, J=7.3 Hz), 7.64 (1H, t, J=7.3 Hz), 7.49 (1H, dd, J=8.2, 4.7 Hz), 2.97 (3H, s); δ_C ($CDCl_3$) 155.4, 154.0, 148.8, 142.0, 140.0, 132.8, 131.2, 129.5, 128.4, 127.8, 124.0, 123.7, 114.9, 112.9, 20.9; m/z APCI (+ve) 278 ($[M+H]^+$).

4.3.28. 1-(2-Acetylamino)phenyl-3-(3,4-difluorophenyl)-4-hydroxy-[1,2,3]triazolium hydroxide, inner salt (12f). Prepared from 3,4-difluoroaniline (12.9 g, 0.1 mol) in water (120 ml), tetrahydrofuran (60 ml), concentrated hydrochloric acid (30 ml), $NaNO_2$ (7.25 g, 0.105 mol) in water (60 ml), 2-(acetylamino)phenylamino acetic acid, lithium salt (21.4 g, 0.1 mol) in pyridine (200 ml), and acetic anhydride (25 ml) to afford the title compound (7.05 g, 21%); mp 209°C; [Found: C, 57.94; H, 3.67; N, 16.71. $C_{16}H_{12}F_2N_4O_2$ requires: C, 58.18; H, 3.66; N, 16.96%]; ν_{max} (neat) 1706, 1656, 1599, 1514, 1283, 1273, 848, 760 cm^{-1}; δ_H ($CDCl_3$) 9.76 (1H, s), 8.24 (1H, ddd, J=12.1, 7.5, 2.5 Hz), 7.94 (1H, m), 7.88 (1H, d, J=8.2 Hz), 7.66 (1H, m), 7.70 (1H, m), 7.40 (1H, m), 7.48 (1H, s), 2.00 (3H, s); m/z APCI (+ve) 331($[M+H]^+$).

4.3.29. 2-(3,4-Difluorophenyl)-3-hydroxy-4-methyl-[1,2,3]-triazolo[1,5-*a*]quinoxalinium hydroxide, inner salt (3f). Prepared from **12f** (6.50 g, 19.7 mmol) and *p*-toluenesulphonic acid (4.12 g, 21.7 mmol) in toluene (500 ml). Recrystallization of the product from ethyl acetate to gave the title compound (3.65 g, 59%) as pale yellow needles; mp 201°C; [Found: C, 60.95; H, 3.15; N, 17.77. $C_{16}H_{10}F_2N_4O$ requires: C, 61.04; H, 3.23; N, 17.94%]; ν_{max} (neat) 1668, 1505, 1435, 1376, 1340, 1266, 1119, 828, 770, 762 cm^{-1}; δ_H ($CDCl_3$) 8.37 (1H, m), 8.19 (1H, m), 8.06 (1H, m), 7.99 (1H, m), 7.79 (1H, m), 7.66 (1H, m), 7.35 (1H, m), 2.96 (3H, s); δ_C ($CDCl_3$) 155.4, 153.6, 150.2 (C, dd, J_{C-F}=250, 14 Hz), 149.5 (C, dd, J_{C-F}=250, 14 Hz), 140.0, 132.2, 131.1, 129.5, 128.3, 123.9, 116.7 (C, dd, J_{C-F}=6, 4 Hz), 114.8, 113.2, 110.5, 110.36, 20.9; m/z APCI (+ve) 313 ($[M+H]^+$).

4.3.30. 3-Hydroxy-4-methyl-2-(4-methylphenyl)-[1,2,3]-triazolo[1,5-*a*]quinoxalinium hydroxide, inner salt (3g). Prepared from 4-toluidine (10 g, 93 mmol) and 2-(acetylamino) phenyl amino acetic acid, lithium salt (20 g, 93 mmol) to give the title compound (5.31 g, 19%) as a beige solid; mp 192–193°C; [Found: C, 70.27; H, 4.78; N, 19.50. $C_{17}H_{14}N_4O$ requires: C, 70.33; H, 4.86; N, 19.30%]; ν_{max} (neat) 1675, 1578, 1505, 1475, 1440, 1395, 1373, 820, 760 cm^{-1}; δ_H (DMSO-d_6) 8.34 (1H, m), 7.98 (2H, m), 7.92 (1H, m), 7.90 (1H, m), 7.70 (1H, m), 7.38 (2H, d, J=8.2 Hz), 2.75 (3H, s), 2.38 (3H, s); δ_C ($CDCl_3$) 155.7, 153.8, 139.9, 138.1, 133.5, 130.7, 129.8, 129.4, 128.1, 124.3, 121.1, 114.9, 113.1, 21.2, 20.9; m/z APCI (+ve) 291 ($[M+H]^+$).

4.3.31. 2-(2-Fluoro-5-methylphenyl)- 3-hydroxy-4-methyl-[1,2,3]triazolo[1,5-*a*]quinoxalinium hydroxide, inner salt (3h). Prepared from 2-fluoro-5-methylaniline (1.58 ml, 14 mmol) and 2-(acetylamino)phenylamino acetic acid, lithium salt (3.0 g, 14 mmol) to give the title compound (0.95 g, 22%) as a yellow solid; mp 231–232°C; [Found: C, 66.16; H, 3.98; N, 18.20. $C_{17}H_{13}FN_4O$ requires: C, 66.23; H, 4.25; N, 18.17%]; ν_{max} (neat) 1677, 1500, 1371, 1128, 821, 765 cm^{-1}; δ_H ($CDCl_3$) 8.29 (1H, d, J=8.2 Hz), 7.96 (1H, d, J=8.2 Hz), 7.72 (1H, t, J=7.7 Hz), 7.59 (1H, t, J=7.7 Hz), 7.47 (1H, m), 7.29 (1H, m), 7.21 (1H, t, J=9.0 Hz), 2.96 (3H, s), 2.43 (3H, s); δ_C ($CDCl_3$) 155.7 (C), 140.0 (C), 134.7 (C), 132.0 (CH), 131.0 (CH), 129.5 (CH), 128.4 (CH), 128.2 (CH), 116.8 (CH), 115.0

(CH), 20.9 (CH_3), 20.7 (CH_3); *m/z* APCI (+ve) 309 ($[M+H]^+$).

4.3.32. 3-Hydroxy-4-methyl-2-(4-methylthiophenyl)-[1,2,3]-triazolo[1,5-*a*]quinoxalinium hydroxide, inner salt (3i). Prepared from 4-methythioaniline (1.74 ml, 12.7 mmol) and 2-(acetylamino) phenylamino acetic acid, lithium salt (3.0 g, 14 mmol) to give the title compound (0.99 g, 22%) as a yellow solid; mp 198–199°C; [Found: C, 63.53; H, 4.18; N, 17.37; S, 9.95. $C_{17}H_{14}N_4OS$ requires: C, 63.34; H, 4.38; N, 17.38; S, 9.95%]; ν_{max} (neat) 1662, 1491, 1396, 1376, 821, 769 cm^{-1}; δ_H ($CDCl_3$) 8.36 (1H, m), 8.12 (2H, m), 7.98(1H, m), 7.74 (1H, m), 7.63 (1H, m), 7.40 (2H, m), 2.96 (3H, s), 2.55 (3H, s); δ_C ($CDCl_3$) 155.6, 153.7, 139.9, 138.9, 133.0, 130.8, 129.4, 128.1, 126.8, 126.8, 124.1, 121.2, 114.8, 113.0, 76.9, 20.9, 15.7; *m/z* APCI (+ve) 323 ($[M+H]^+$).

4.3.33. 4-Hydroxy-1-(2-methoxycarbonylphenyl)-3-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolium hydroxide, inner salt (14). To a stirred solution of 4-(trifluoromethyl)-aniline (4.2 g, 26 mmol) in a mixture of water (50 ml), tetrahydrofuran (20 ml) and concentrated hydrochloric acid (10 ml) at 0 to −5°C, was added portionwise a solution of sodium nitrite (1.91 g, 27 mmol) in water (20 ml). The solution was stirred 15 min at 0 to −5°C and was then added portionwise to a solution of methyl 2-(carboxymethyl-amino)benzoate (**13**, 5 g, 24 mmol) in pyridine (50 ml) and water (10 ml) at 0 to −5°C. The solution was stirred for 1 h at 0°C and then for 1 h at 0–10°C. The mixture was diluted with ethyl acetate and the organics separated, dried over magnesium sulphate and concentrated in vacuo to ca 30 ml volume. To the residue was added acetic anhydride (10 ml) and the solution was stirred for 1 h. The reaction mixture was concentrated in vacuo, azeotroping twice with toluene. The product was chromatographed on silica (ethyl acetate then ethyl acetate/ethanol 10:1). Crystallization from ethyl acetate/isohexane gave the title compound (1.50 g, 17%) as a colourless solid; mp 149–150°C; [Found: C, 56.48; H, 3.32; N, 11.58. $C_{17}H_{12}F_3N_3O_3$ requires: C, 56.20; H, 3.33; N, 11.57%]; δ_H ($CDCl_3$) 8.32 (2H, d, *J*=8.50 Hz), 8.07 (1H, dd, *J*=7.4, 1.8 Hz), 8.0–7.69 (4H, m), 7.61 (1H, dd, *J*=7.5, 1.5 Hz), 7.01 (1H, s), 3.79 (3H, s); δ_C ($CDCl_3$) 164.8, 157.9, 138.7, 135.8, 133.0, 131.7, 131.4, 129.6 (C, q, J_{C-F}=34 Hz), 127.6, 126.4 (C, q, J_{C-F}=4 Hz), 126.2, 123.8 (C, q, J_{C-F}=272 Hz), 120.7, 109.3, 52.9, 52.9; *m/z* APCI (+ve) 364 ($[M+H]^+$).

4.3.34. 1-(2-Carboxyphenyl)-4-hydroxy-3-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolium hydroxide, inner salt (15). To a stirred solution of 4-hydroxy-1-(2-methoxycarbonyl phenyl)-3-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolium hydroxide, inner salt (**14**, 4.55 g, 12.5 mmol) in tetrahydrofuran (50 ml) and methanol (15 ml) was added a solution of sodium hydroxide (0.60 g, 15 mmol) in water (15 ml). After 30 min the solution was acidified with aqueous potassium hydrogen sulphate solution and extracted with ethyl acetate. The organics were concentrated in vacuo and azeotroped to dryness with toluene to give the title compound (3.8 g, 87%) as a colourless solid; mp>265°C; [Found: C, 54.48; H, 2.62; N, 11.49. $C_{16}H_{10}F_3N_3O$ requires: C, 55.02; H, 2.89; N, 12.03%]; δ_H (DMSO-d_6) 8.32 (2H, d, *J*=8.7 Hz), 8.01 (1H, m), 7.96(2H, d, *J*=8.7 Hz), 7.88–7.77 (3H, m), 7.66 (1H, d *J*=1.3 Hz); *m/z* APCI (+ve) 350 ($[M+H]^+$).

4.3.35. 1-(2-Aminophenyl)-4-hydroxy-3-(4-trifluoromethylphenyl)-3H-[1,2,3]triazolium hydroxide, inner salt (16). To 1-(2-carboxyphenyl)-4-hydroxy-3-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolium hydroxide, inner salt (**15**, 1 g, 2.86 mmol) in *t*-butanol (50 ml) was added triethylamine (0.94 ml, 6.7 mmol) and diphenylphosphoryl azide (1.29 g, 4.7 mmol). The mixture was heated to 80°C for 18 h. The reaction mixture was concentrated in vacuo and suspended in dichloromethane (10 ml), then trifluoroacetic acid (10 ml) was added. After 30 min the mixture was concentrated in vacuo and partitioned between ethyl acetate and aqueous sodium hydrogen carbonate solution. The organics were collected and dried over magnesium sulphate then concentrated in vacuo. The resulting yellow solid was recrystallized from ethyl acetate to give the title compound (0.461 g, 50%); mp 198°C; [Found: C, 55.42; H, 3.15; N, 17.05. $C_{15}H_{11}F_3N_4O$ requires: C, 56.25; H, 3.46; N, 17.49%]; ν_{max} (neat) 1652, 1633, 1614, 1320, 1110, 1069, 846, 743 cm^{-1}; δ_H ($CDCl_3$) 8.31 (2H, m), 7.75 (2H, m), 7.34 (2H, m), 7.03 (1H, s), 6.90 (2H, m), 4.46 (2H, br s); δ_C ($CDCl_3$) 157.89, 140.53, 138.67, 131.77, 126.45 (C, q, J_{C-F}=7 Hz), 124.91, 122.49, 120.73, 118.71, 117.92, 108.51; *m/z* APCI (+ve) 321 ($[M+H]^+$).

4.3.36. 3-Hydroxy-2-(4-trifluoromethylphenyl)-[1,2,3]-triazolo[5,1-*c*][1,2,4]benzotriazinium hydroxide, inner salt (4). To 1-(2-aminophenyl)-4-hydroxy-3-(4-trifluoromethylphenyl)-3*H*-[1,2,3]triazolium hydroxide, inner salt (**16**, 0.1 g, 0.3 mmol) in water (3.2 ml), tetrahydrofuran (1 ml) and concentrated hydrochloric acid (0.52 ml) at −5°C was added a solution of $NaNO_2$ (21 mg, 0.3 mmol) in water (0.8 ml) dropwise. After 10 min the mixture was allowed to warm to room temperature and the resulting solid was collected by filtration. The solid was then stirred in boiling ethanol (20 ml) for 5 min before being collected by filtration to afford the title compound as a yellow powder (0.024 g, 23%); mp 317–318°C; [Found: C, 54.32; H, 2.38; N, 21.04. $C_{15}H_8F_3N_5O$ requires: C, 54.39; H,2.43; N, 21.14%]; ν_{max} (neat) 1700, 1611, 1579, 1483, 1321, 1105, 779 cm^{-1}; δ_H (DMSO-d_6) 8.58 (1H, m), 8,51 (1H, m), 8.46 (2H, d, *J*=8.5 Hz), 8.12 (1H, dd), 8.09 (1H, m), 8.06 (2H, d, *J*=8.5 Hz); *m/z* APCI (+ve) 332($[M+H]^+$).

4.3.37. 3-Hydroxy-4-oxo-2-[4-(trifluoromethyl)phenyl]-4,5-dihydro-[1,2,3]triazolo[1,5-*a*]quinoxalinium hydroxide, inner salt (17). To a stirred solution of 1-(2-carboxyphenyl)-4-hydroxy-3-[4-(trifluoromethyl)phenyl]-[1,2,3]-triazolium hydroxide, inner salt (**15**, 1.2 g, 3.4 mmol) in anhydrous toluene (40 ml) and triethylamine (1.2 ml, 8.6 mmol) was added diphenylphosphorylazide (1.2 ml, 5.5 mmol) and the mixture stirred at room temperature for 14 h. The mixture was then heated at 75°C for 20 min. Dichloromethane (40 ml) was added and the mixture allowed to cool. The precipitate was filtered and washed with dichloromethane followed by ethyl acetate then diethyl ether, and dried in vacuo to give the title compound (1.05 g) as a colourless solid; mp>300°C; [Found: C, 55.10; H, 2.39; N, 15.59. $C_{16}H_9F_3N_4O_2$ requires: C, 55.50; H, 2.62; N, 16.18%]; δ_H (DMSO-d_6) 11.68 (1H, s), 8.40 (2H, d, *J*=8.7 Hz), 8.25 (1H, dd, *J*=8.7, 1.3 Hz), 8.01(2H, d,

J=8.7 Hz), 7.64 (1H, td, J=7.8, 1.5 Hz), 7.36 (2H, m); m/z APCI (+ve) 347 ($[M+H]^+$).

4.3.38. 4-Ethyl-3-hydroxy-2-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolo[1,5-*a*]quinoxalinium hydroxide, inner salt (3j). To a stirred suspension of 3-hydroxy-4-oxo-2-[4-(trifluoromethyl)phenyl]-4,5-dihydro-[1,2,3]triazolo[1,5-*a*]-quinoxalinium hydroxide, inner salt (**17**, 0.90 g, 2.6 mmol) in toluene (150 ml) at 75°C was added a solution of ethylmagnesium chloride (3 M in diethyl ether, 3 ml). After 5 min the reaction was quenched with water (3 ml) and the product extracted with ethyl acetate and concentrated in vacuo. Chromatography on silica (dichloromethane/diethyl ether, 4:1) followed by recrystallization from ethyl acetate: isohexane gave the title compound (0.109 g) as colourless needles; mp 181°C; [Found: C, 60.20; H, 3.34; N, 15.50. $C_{18}H_{13}F_3N_4O$ requires: C, 60.34; H, 3.66; N, 15.64%]; ν_{max} (neat) 1674, 1328, 1103, 1509, 851, 765 cm^{-1}; δ_H ($CDCl_3$) 8.42 (2H, d, J=8.8 Hz), 8.36 (1H, m), 8.00 (1H, m), 7.80 (2H, d, J=8.8 Hz), 7.76 (1H, m), 7.74 (1H, m), 3.33 (2H, q, J=7.5 Hz), 1.47 (3H, t, J=7.5 Hz); δ_C ($CDCl_3$) 160.4, 153.6, 140.3, 138.7, 131.1, 129.8, 129.6 (C, q, J_{C-F}=33 Hz), 129.5, 128.3, 126.5 (C, q, J_{C-F}=4 Hz), 124.0, 123.7 (C, q, J_{C-F}=272 Hz), 120.5, 114.9, 112.9, 27.7, 12.2; m/z APCI (+ve) 359 ($[M+H]^+$).

4.3.39. 3-Hydroxy-4-(1-methylethyl)-2-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolo[1,5-*a*]quinoxalinium hydroxide, inner salt (3k). To a stirred suspension of 3-hydroxy-4-oxo-2-[4-(trifluoromethyl)phenyl]-4,5-dihydro-[1,2,3]triazolo[1,5-*a*]quinoxalinium hydroxide, inner salt (**17**, 0.30 g, 0.87 mmol) in toluene (25 ml) at 80°C was added a solution of isopropylmagnesium chloride (2 M in diethyl ether, 2.5 ml). After 10 min the reaction was quenched with water and the product extracted with ethyl acetate and concentrated in vacuo. Chromatography on silica (diethyl ether/isohexane, 1:1) and washing with ether gave the title compound (0.05 g) as a yellow powder; mp 167°C; [Found: C, 61.35; H, 4.43; N, 14.76. $C_{19}H_{15}F_3N_4O$ requires: C, 61.29; H, 4.06; N, 15.05%]; ν_{max} (neat) 1672, 1612, 1502, 1316, 1068, 845, 761 cm^{-1}; δ_H (DMSO-d_6) 8.43 (3H, m), 8.02 (3H, m), 7.86 (1H, m), 7.78 (1H, m), 3.94 (1H, m), 1.37 (6H, d, J=6.9 Hz); m/z APCI (+ve) 373 ($[M+H]^+$).

4.3.40. 4-Azetidinyl-3-hydroxy-2-[4-(trifluoromethyl)-phenyl]-[1,2,3]triazolo[1,5-*a*]quinoxalinium hydroxide, inner salt (3l). A solution of 3-hydroxy-4-oxo-2-[4-(trifluoromethyl)phenyl]-4,5-dihydro-[1,2,3]triazolo[1,5-*a*]-quinoxalinium hydroxide, inner salt (**17**, 2.17 g, 6.3 mmol) in phosphorus oxychloride (30 ml) was refluxed for 2 h before being concentrated in vacuo. The residue was quenched with aqueous sodium hydrogen carbonate solution and extracted with dichloromethane, dried over magnesium sulphate and concentrated in vacuo to give crude 4-chloro-3-hydroxy-2-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolo[1,5-*a*]quinoxalinium hydroxide, inner salt (1.80 g). To a stirred solution of this compound (0.5 g) in dichloromethane (10 ml) was added azetidine (1 ml). The mixture was stirred for 1 h at room temperature then concentrated in vacuo. Chromatography on silica followed by crystallization from ethyl acetate/isohexane gave the title compound as fine needles (0.10 g); mp 216–217°C; [Found: C, 58.92; H, 3.55; N, 18.18. $C_{19}H_{14}F_3N_5O$ requires: C, 59.22; H, 3.66; N, 18.17%]; δ_H (DMSO-d_6) 8.36 (2H, d), 8.19 (1H, m), 7.79 (2H, m), 7.64 (1H, m), 7.56 (1H, m), 7.27 (1H, m), 4.55 (4H, m), 2.45 (2H, m); m/z APCI (+ve) 386 ($[M+H]^+$).

4.3.41. 5-Bromo-3-hydroxy-2-phenyl-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (18a). To a solution of 3-hydroxy-2-phenyl-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (**1a**, 1.2 g, 4.6 mmol) in dichloromethane (100 ml) was added pyridine (0.36 ml, 4.6 mmol) then bromine (0.48 ml, 9.3 mmol) and stirred for 1 h. The reaction mixture was partitioned between ethyl acetate and sodium hydrogen carbonate solution. The organic layer was separated, dried over magnesium sulphate and concentrated in vacuo. Purification by chromatography on silica gel (dichloromethane/ethyl acetate 8:1 then ethyl acetate) followed by a diethyl ether wash gave the title compound (1.0 g, 64%) as a yellow solid; mp 246–249°C; [Found: C, 56.88; H, 2.98; N, 12.34. $C_{16}H_{10}BrN_3O$ requires: C, 56.49; H, 2.96; N, 12.35%]; ν_{max} (neat) 1656, 1648, 1492, 1461, 1404, 810, 749 cm^{-1}; δ_H ($CDCl_3$) 8.55 (1H, m), 8.19 (3H, m), 7.99 (1H, s), 7.77 (2H, m), 7.58 (2H, m), 7.44 (1H, m); δ_C ($CDCl_3$) 152.5, 136.3, 130.6, 130.3, 129.8, 129.2, 128.8, 127.9, 126.4, 121.3, 120.3, 118.7, 116.0, 113.1; m/z APCI (+ve) 340, 342 ($[M+H]^+$).

4.3.42. 5-Bromo-2-(4-fluorophenyl)-3-hydroxy-[1,2,3]-triazolo[1,5-*a*]quinolinium hydroxide, inner salt (18b). Prepared from 2-(4-fluorophenyl)-3-hydroxy-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (**1b**, 3 g, 10.7 mmol) to give the title compound (1.0 g, 26%) as a yellow solid; mp>250°C; [Found: C, 53.38; H, 2.48; N, 11.77. $C_{16}H_9BrFN_3O$ requires: C, 53.65; H, 2.53; N, 11.73%]; ν_{max} (neat) 1677, 1668, 1507, 1404, 1226, 1141, 831, 776 cm^{-1}; δ_H ($CDCl_3$) 8.53 (1H, m), 8.20 (3H, m), 7.98 (1H, s), 7.78 (2H, m), 7.23 (2H, m); m/z APCI (+ve) 358, 360 ($[M+H]^+$).

4.3.43. 5-Bromo-2-(4-chlorophenyl)-3-hydroxy-[1,2,3]-triazolo[1,5-*a*]quinolinium hydroxide, inner salt (18c). Prepared from 2-(4-chlorophenyl)-3-hydroxy-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (3.8 g, 12.9 mmol) to give the title compound (3.67 g, 79%) as a yellow solid; mp 238–240°C; [Found: C, 57.30; H, 2.33; N, 10.96. $C_{16}H_9BrClN_3O$ requires: C, 57.30; H, 2.42; N, 11.22%]; ν_{max} (neat) 1664, 1493, 1401, 1332, 834, 812, 763 cm^{-1}; δ_H ($CDCl_3$) 8.55 (1H, m), 8.22 (3H, m), 7.99 (1H, s), 7.78 (2H, m), 7.51 (2H, m); m/z APCI (+ve) 374, 376, 378 ($[M+H]^+$).

4.3.44. 5-Bromo-3-hydroxy-2-(3-trifluoromethylphenyl)-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (18d). Prepared from 3-hydroxy-2-(3-trifluoromethylphenyl)-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (**1e**, 0.85 g, 2.46 mmol) to give the title compound (0.39 g, 37%) as a yellow solid; mp 205–206°C; [Found: C, 50.15; H, 2.18; N, 10.15. $C_{17}H_9BrF_3N_3O$ requires: C, 50.02; H, 2.22; N, 10.29%]; ν_{max} (neat) 1665, 1452, 1445, 1341, 1324, 1169, 1112, 795, 761 cm^{-1}; δ_H ($CDCl_3$) 8.59 (2H, m), 8.52 (1H, s), 8.22 (1H, m), 7.97 (1H, s), 7.83 (2H, m), 7.64 (2H, m); δ_C ($CDCl_3$) 152.5, 136.8, 131.7 (C, q, J_{C-F}=33 Hz), 130.5, 130.4, 130.1, 129.9, 128.9, 126.5, 124.2 (C, q, J_{C-F}=4 Hz), 123.8, 123.6 (C, q,

J_{C-F}=272 Hz), 120.1, 118.8, 117.6 (C, q, J_{C-F}=4 Hz), 116.1, 113.7, 131.7, 123.6, 124.2; *m/z* APCI (+ve) 408, 410 ($[M+H]^+$).

4.3.45. 5-Bromo-3-hydroxy-2-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (18e). (a) Prepared from 3-hydroxy-2-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (**1c**, 1.0 g, 3 mmol) to give the title compound (0.56 g, 45%) as a yellow solid.

(b) Prepared from 4,5-dihydro-3-hydroxy-2-(4-trifluoromethylphenyl)-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (**6c**, 8.7 g, 26 mmol), bromine (8.1 ml, 157 mmol) and pyridine (4.25 ml, 53 mmol) to give the title compound as a yellow solid (5.30 g, 50%); mp 187–188°C; [Found: C, 49.88; H, 2.06; N, 10.09. $C_{17}H_9BrF_3N_3O$ requires: C, 50.02; H, 2.22; N, 10.29%]; ν_{max} (neat) 1676, 1615, 1514, 1321, 1112, 1104, 1065, 843, 758 cm^{-1}; δ_H ($CDCl_3$) 8.57 (1H, m), 8.47 (2H, m), 8.21 (1H, m), 7.99 (1H, s), 7.80 (4H, m); δ_C ($CDCl_3$) 152.6, 139.0, 130.5, 130.4, 130.1, 129.3 (C, q, J_{C-F}=33 Hz), 128.9, 126.5, 126.4, 126.4 (C, q, J_{C-F}=4 Hz), 124.9, 123.8 (C, q, J_{C-F}=275 Hz), 122.7, 120.5, 120.1, 118.9, 116.0, 113.7; *m/z* APCI (+ve) 408, 410 ($[M+H]^+$).

4.3.46. 5-Bromo-3-hydroxy-2-[4-(trifluoromethoxy)phenyl]-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (18f). Prepared from 3-hydroxy-2-[4-(trifluoromethoxy)-phenyl]-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (**1e**, 2.3 g, 6.6 mmol) to give the title compound (1.0 g, 38%) as a yellow solid; mp 202–204°C; [Found: C, 47.98; H, 1.99; N, 9.91. $C_{17}H_9BrF_3N_3O_2$ requires: C, 48.14; H, 2.14; N, 9.91%]; ν_{max} (neat) 1671, 1501, 1249, 1218, 1156, 858, 764 cm^{-1}; δ_H ($CDCl_3$) 8.55 (1H, m), 8.33 (2H, m), 8.21 (1H, m), 7.98 (1H, s), 7.78 (2H, m), 7.40 (2H, m); δ_C ($CDCl_3$) 152.5, 148.1, 134.7, 130.6, 130.5, 130.0, 129.0, 126.5, 122.5, 121.8, 120.4 (C, q, J_{C-F}=257 Hz), 120.2, 118.8, 116.0, 113.6; *m/z* APCI (+ve) 424, 426 ($[M+H]^+$).

4.3.47. 3-Hydroxy-5-methoxy-2-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (19a). A solution of 5-bromo-3-hydroxy-2-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (**18e**, 1.5 g, 3.7 mmol), tris(dibenzylideneacetone)-dipalladium (67.5 mg, 0.07 mmol), (*R*)-(+)-2,2-bis(diphenylphosphino)-1,1-binaphthyl (0.138 g, 0.22 mmol), 7 M ammonia in methanol (10 ml) and sodium *t*-butoxide (0.5 g, 5.2 mmol) in toluene (30 ml) was heated at 80°C in a sealed tube for 14 h. Purification by chromatography on silica gel (dichloromethane/ethyl acetate 3:1) followed by recrystallization from ethyl acetate gave the title compound (0.25 g, 19%) as a yellow solid; mp 212–213°C; [Found: C, 60.19; H, 3.30; N, 11.62. $C_{18}H_{12}F_3N_3O_2$ requires: C, 60.17; H, 3.37; N, 11.70%]; ν_{max} (neat) 1655, 1610, 1560, 1515, 1416, 1319, 1100, 840, 763 cm^{-1}; δ_H ($CDCl_3$) 8.48 (2H, d, *J*=8.7 Hz), 8.45 (1H, d, *J*=8.4 Hz), 8.17 (1H, d, *J*=8.0 Hz), 7.76 (2H, d, *J*=8.7 Hz), 7.73 (1H, d, *J*=7.4 Hz), 7.67 (1H, t, *J*=7.6 Hz), 6.87 (1H, s), 4.02 (3H, s); δ_C ($CDCl_3$) 153.2, 150.0, 139.5, 130.5, 130.1, 129.0, 128.9, 128.8, 126.2 (C, q, J_{C-F}=4 Hz), 123.9, 123.9 (C, q, J_{C-F}=274 Hz), 122.7, 120.6, 119.3, 115.8, 92.4, 56.2; *m/z* APCI (+ve) 360 ($[M+H]^+$).

4.3.48. 5-(1-Azetidinyl)-3-hydroxy-4-methyl-2-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide inner salt (19b). A solution of 5-bromo-3-hydroxy-4-methyl-2-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (**18e**, 0.7 g, 1.7 mmol), tris(dibenzylideneacetone)dipalladium (30 mg, 0.03 mmol), (*R*)-(+)-2,2-bis(diphenylphosphino)-1,1-binaphthyl (62 mg, 0.1 mmol), azetidine (0.34 ml, 5 mmol) and sodium tertiary butoxide (0.22 g, 2.3 mmol) in toluene (20 ml) was heated in a sealed tube at 80°C overnight. Purification by chromatography on silica gel (dichloromethane/ethyl acetate 4:1) followed by recrystallization from ethyl acetate gave the title compound (0.30 g, 46%) as an orange solid; [Found: C, 63.11; H, 4.42; N, 14.09. $C_{21}H_{17}F_3N_4O$ requires: C, 63.31; H, 4.30; N, 14.06%]; ν_{max} (neat) 1648, 1610, 1409, 1320, 1098, 844, 767 cm^{-1}; δ_H ($CDCl_3$) 8.49 (2H, d, *J*=8.5 Hz), 8.43 (1H, dd, *J*=7.8, 1.1 Hz), 7.98 (1H, dd, *J*=8.2, 1.2 Hz), 7.75 (2H, d, *J*=8.5 Hz), 7.56 (2H, m), 4.33 (4H, s, br), 2.78 (3H, s), 2.34 (2H, quin, *J*=7.4 Hz); δ_C ($CDCl_3$) 153.8, 140.6, 139.6, 129.2, 128.6 (C, q, J_{C-F}=33 Hz), 128.0, 127.6, 126.1, 124.9, 124.0 (C, q, J_{C-F}=273 Hz), 123.3, 120.5, 119.6, 116.2, 113.0, 58.2, 17.8, 12.7; *m/z* APCI (+ve) 399($[M+H]^+$).

4.3.49. 3-Hydroxy-5-(4-morpholinyl)-2-[4-(trifluoromethoxy)phenyl]-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (19c). Prepared from 5-bromo-3-hydroxy-2-[4-(trifluoromethoxy) phenyl]-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (1.4 g, 3.3 mmol) to give the title compound (0.602 g, 42%) as a yellow solid; mp 231–232°C; [Found: C, 58.31; H, 3.90; N, 13.18. $C_{21}H_{17}F_3N_4O_3$ requires: C, 58.61; H, 3.98; N, 13.02%]; ν_{max} (neat) 1655, 1505, 1256, 1151, 901, 768, 761 cm^{-1}; δ_H ($CDCl_3$) 8.56 (1H, m), 8.35 (2H, m), 8.14 (1H, m), 7.73 (2H, m), 7.39 (2H, d, *J*=9.0 Hz), 7.26 (1H, s), 3.99 (4H, m), 3.12 (4H, m); *m/z* APCI (+ve) 431 ($[M+H]^+$).

4.3.50. 3-Hydroxy-5-(2-methoxyethylamino)-2-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (19d). A solution of 5-bromo-3-hydroxy-2-[4-(trifluoromethyl) phenyl]-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (**18e**, 1.0 g, 2.4 mmol), tris(dibenzylideneacetone)dipalladium (0.045 g, 0.05 mmol), (*R*)-(+)-2,2-bis(diphenylphosphino)-1,1-binaphthyl (0.092 g, 0.15 mmol), 2-methoxyethylamine (0.55 g, 7.3 mmol) and sodium tertiary butoxide (0.33 g, 3.4 mmol) in toluene (20 ml) was heated at 80°C overnight. Purification by chromatography on silica gel (dichloromethane/ethyl acetate 1:1–1:3) followed by a diethyl ether wash gave the title compound (0.59 g, 60%) as a yellow solid; mp>250°C; [Found: C, 59.48; H, 4.36; N, 13.81. $C_{20}H_{17}F_3N_4O_2$ requires: C, 59.70; H, 4.26; N, 13.92%]; ν_{max} (neat) 1643, 1604, 1555, 1510, 1419, 1330, 1107, 846, 764 cm^{-1}; δ_H ($CDCl_3$) 8.58 (1H, d, *J*=8.4 Hz), 8.51 (2H, d, *J*=8.5 Hz), 7.87 (1H, d, *J*=7.7 Hz), 7.78 (2H, d, *J*=8.5 Hz), 7.76 (1H, t, *J*=7.5 Hz), 7.70 (1H, t, *J*=7.5 Hz), 3.78 (2H, s), 3.47 (3H, s); *m/z* APCI (+ve) 403 ($[M+H]^+$).

4.3.51. 2-(4-Chlorophenyl)-3-hydroxy-5-methyl-1,2,3]-triazolo[1,5-*a*]quinolinium hydroxide, inner salt (19e). A solution of 5-bromo-2-(4-chlorophenyl)-[3-hydroxy 1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt

(**18c**, 0.438 g, 1.17 mmol), trans-benzyl(chloro)bis (triphenylphosphine)palladium (II) (30 mg, 0.04 mmol) and tetramethyltin (5 ml) in anhydrous dimethylformamide (30 ml) was heated under nitrogen at 60°C for 14 h. The mixture was cooled, diluted with ethyl acetate, washed with water and dried over magnesium sulphate. Concentration in vacuo and chromatography on silica afforded the title compound (0.294 g, 32%); mp 213°C; [Found: C, 65.89; H, 3.67; N, 13.48. $C_{17}H_{12}ClN_3O$ requires: C, 65.92; H, 3.91; N, 13.57%]; ν_{max} (neat) 1672, 1491, 1408, 1326, 1146, 1094, 824, 752 cm^{-1}; δ_H ($CDCl_3$) 8.55 (1H, m), 8.27 (2H, m), 7.94 (1H, m), 7.69–7.76 (2H, m), 7.50 (3H, m), 2.60 (3H, s); δ_C ($CDCl_3$) 135.2, 133.0, 130.1, 129.3, 129.2, 129.1, 128.1, 127.5, 125.7, 122.2, 118.7, 116.2, 116.0, 18.8; *m/z* APCI (+ve) 310/312 ($[M+H]^+$).

4.3.52. 3-Hydroxy-5-[(1-hydroxy-1-methyl)ethyl]-2-[4-(trifluoromethyl)phenyl]-1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (19f). To a stirred solution of 5-bromo-3-hydroxy-2-[4-(trifluoromethyl)phenyl]-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (**18e**, 0.50 g, 1.2 mmol) in anhydrous tetrahydrofuran (60 ml) at −70°C, was added *n*-butyllithium solution (2.5 M, 1.1 ml). After 10 min acetone (0.1 ml, 1.4 mmol) was added and the solution allowed to warm to room temperature. The solution was quenched with 1N aq. hydrochloric acid solution and extracted with ethyl acetate. The extracts were dried (magnesium sulphate), concentrated and chromatographed on silica gel (dichloromethane/ethyl acetate, 10%) to afford the title compound as a yellow powder (0.040 g, 9%); mp 205–6°C; [Found: C, 61.77; H, 3.99; N, 10.84. $C_{20}H_{16}F_3N_3O_2$ requires: C, 62.01; H, 4.16; N, 10.85%]; δ_H ($CDCl_3$) 8.54 (1H, m), 8.46 (2H, d, *J*=8.5 Hz), 7.82 (3H, m), 7.71 (2H, m), 7.17 (2H, d, *J*=9.0 Hz), 1.77 (6H, s); *m/z* APCI (+ve) 388 ($[M+H]^+$).

4.3.53. 2-(6-Chloropyridin-3-yl)-3-hydroxy-4-methyl-5-nitro-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (20a). To a stirred suspension of 2-(6-chloropyridin-3-yl)-3-hydroxy-4-methyl-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (**1g**, 13.2 g, 42.6 mmol) in dichloromethane (500 ml) was added 0.5 M nitronium tetrafluoroborate solution in sulfolane (85 ml) at room temperature over a period of 1 min. After 1 h additional nitronium tetrafluoroborate solution (9 ml) was added. After a further 1 h the mixture was poured into sodium hydrogen carbonate solution and extracted with dichloromethane. The combined organic extracts were washed with aqueous sodium hydrogen carbonate solution, dried and concentrated in vacuo. The residue was diluted with water and the precipitated solid filtered and dried. Chromatography on silica (dichloromethane/methanol 1%) and recrystallization from acetone afforded the title compound as a yellow powder (12.60 g, 82%); mp 230–232°C; [Found: C, 53.98; H, 3.03; N, 19.67. $C_{16}H_{10}ClN_5O_3$ requires: C, 54.02; H, 2.83; N, 19.69%]; δ_H ($CDCl_3$) 9.25 (1H, d, *J*=2.7 Hz), 8.68 (1H, dd, *J*=8.8, 2.8 Hz), 8.56 (1H, m), 7.81 (3H, m), 7.53 (1H, d, *J*=8.8 Hz), 2.84 (3H, s); *m/z* APCI (+ve) 356/358 ($[M+H]^+$).

4.3.54. 3-Hydroxy-2-[3-(trifluoromethyl)phenyl]-5-nitro-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (20b). Prepared from 3-hydroxy-2-[3-(trifluoromethyl)phenyl]-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (**1d**, 0.25 g, 0.76 mmol) in dichloromethane (20 ml) and 0.5 M nitronium tetrafluoroborate solution in sulfolane (4 ml). Recrystallization from ethyl acetate afforded the title compound (0.182 g, 64%); mp>250°C; [Found: C, 54.16; H, 2.49; N, 14.75. $C_{17}H_9F_3N_4O_3$ requires: C, 54.55; H, 2.42; N, 14.97%]; ν_{max} (neat) 1681, 1592, 1536, 1495, 1445, 1307, 1108, 801, 771 cm^{-1}; δ_H ($CDCl_3$) 8.89 (1H, m), 8.74 (1H, s), 8.68 (1H, m), 8.57 (1H, m), 8.44 (1H, s), 7.89 (2H, m), 7.70 (2H, m); *m/z* APCI (+ve) 375 ($[M+H]^+$).

4.3.55. 2-(4-Chlorophenyl)-3-hydroxy-5-nitro-[1,2,3]-triazolo[1,5-*a*]quinolinium hydroxide, inner salt (20c). Prepared from 2-(4-chlorophenyl)-3-hydroxy-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (1.0 g, 3.38 mmol) in dichloromethane (75 ml) and 0.5 M nitronium tetrafluoroborate solution in sulfolane (12 ml). Chromatography on silica gel (dichloromethane/ethyl acetate 5%) and recrystallization from dichloromethane afforded the title compound (0.655 g, 57%); mp 285°C; [Found: C, 56.25; H, 2.56; N, 16.59. $C_{16}H_{19}ClN_4O_3$ requires: C, 56.40; H, 2.66; N, 16.44%]; δ_H ($CDCl_3$) 8.83 (1H, m), 8.66 (2H, m), 8.23 (2H, m), 7.93 (2H, m), 7.58 (2H, m); *m/z* APCI (+ve) 340/342 ($[M+H]^+$).

4.3.56. 3-Hydroxy-4-methyl-2-(6-methylpyridin-3-yl)-5-nitro-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (20d). Prepared from 3-hydroxy-4-methyl-2-(6-methyl-3-pyridinyl)-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (0.30 g, 1 mmol) in dichloromethane (10 ml) and 0.5 M nitronium tetrafluoroborate solution in sulfolane (4 ml). Chromatography on silica (dichloromethane/methanol 2%) and recrystallization from ethyl acetate afforded the title compound as an orange powder (0.15 g, 43%); mp 202–204°C; [Found: C, 60.55; H, 3.87; N, 20.62. $C_{17}H_{13}N_5O_3$ requires: C, 60.89; H, 3.91; N, 20.89%]; δ_H ($CDCl_3$) 9.25 (1H, d, *J*=2.5 Hz), 8.55 (1H, m), 8.48 (1H, dd, *J*=8.5, 2.5 Hz), 7.80 (3H, m), 7.35 (1H, d, *J*=8.5 Hz), 2.84 (3H, s), 2.66 (3H, s); *m/z* APCI (+ve) 336 ($[M+H]^+$).

4.3.57. 5-(Azetidin-1-ylsulfonyl)- 2-(3-fluorophenyl)-3-hydroxy-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (20e). A solution of 2-(3-fluorophenyl)-3-hydroxy-[1,2,3]triazolo[1,5-*a*]quinolinium hydroxide, inner salt (0.50 g, 1.8 mmol) in chlorosulphonic acid (5 ml) was stirred at room temperature for 60 h. The mixture was dripped onto ice and the precipitated product filtered and dried. The product was redissolved in tetrahydrofuran (5 ml) and treated with azetidine (5 ml). The solution was stirred at room temperature for 30 min then concentrated in vacuo. Chromatography on silica eluting with ethyl acetate, followed by recrystallization (ethyl acetate) gave the title compound as a yellow solid (0.20 g, 32%); mp>250°C; [Found: C, 57.18; H, 3.88; N, 13.65, S 8.06. $C_{19}H_{15}FN_4O_3S$ requires: C, 57.28; H, 3.80; N, 14.06, S 8.05%]; ν_{max} (neat) 1655, 1492, 1451, 1416, 1345, 1164, 822, 664 cm^{-1}; δ_H ($CDCl_3$) 8.98 (1H, s), 8.14 (2H, m), 8.08 (1H, dd, *J*=8.4, 1.3 Hz), 8.01 (1H, d, *J*=9.2 Hz), 7.82 (1H, d, *J*=9.2 Hz), 7.54 (1H, m), 7.30 (1H, d, *J*=9.2 Hz), 7.14 (1H, m), 3.93 (4H, t, *J*=7.0 Hz), 2.16 (2H, quintet, *J*=7.7 Hz); *m/z* APCI (+ve) 399 ($[M+H]^+$).

References

1. It should be noted that many of the compounds described in this paper have been found to be very potent ligands for the aryl hydrocarbon receptor. The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor that mediates many of the biological and toxicological effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, dioxin) and related chemicals. Given the known toxic potential of such ligands, extreme caution should be exercised when handling compounds within this and related series of compounds. An example where AhR mediated toxicity has been observed with related compounds can be found in: MacKenzie, A. R.; Brooks, S. *Chem. Ber* **1998**, *34* (12), 18.
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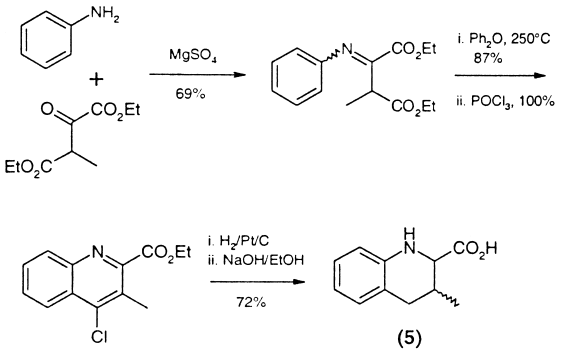
6. The preparation of tetrahydroquinaldic acids (**5**) is illustrated by the following synthetic sequence:



(5)

7. Cyclization of the parent carboxylic acid occurs on standing to afford 2-methyl-[1*H*]-benzimidazol-1-acetic acid.
8. X-Ray crystal data for **3b**: space group: triclinic, *P*-1, (No. 2). The compound is crystallized from ethylacetate with two molecules in the unit-cell. Unit-cell parameters: a=8.091(1), b=9.445(1), c=9.873(1) Å, α=78.31(1), β=81.79(1), γ=79.58(1)°, V=722.2(2) Å^3, Z=2. D_x=1.501(1) g/cm^3, F(000)=336. μ(Mo Kα)=1.16 cm^{-1}. Crystal dimensions 0.11×0.17×0.26 mm. A total of 2403 independent reflections [$F2>4\sigma(F^2)$] was refined to give R=0.040, R_w=0.044 for 218 parameters ($w=1/(\sigma^2F_o^2+(0.0300)F_o^2)$). $(\Delta/\sigma)_{max}$=0.0004, $\Delta\rho_{max}$=0.16 eÅ^{-3}, $\Delta\rho_{min}$=−0.15 eÅ^{-3}, $\Delta\rho_{mean}$=0.04 eÅ^{-3}. GOF=0.882. The X-ray intensity data of AR-C124721XX were collected at room temperature with an Enraf–Nonius κ-CCD diffractometer equipped with graphite monochromator and Mo Kα radiation. The Denzo-SMN Software Package was used for the unit-cell determination and reduction of the data set. The structure was solved by direct methods and refined with full-matrix least squares based on F, taking advantage of the MaXus software package. The non-H atoms were refined anisotropically whereas the H-atom positions were verified from Fourier electron density calculations and supplied with isotropic thermal displacement factors, U(iso)=0.05 Å^2. No absorption correction was applied.
9. All X-ray crystallographic data has been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC-178446.