Azaxanthones and azathioxanthones are effective sensitisers for europium and terbium luminescence

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Several azaxanthone and azathioxanthone sensitising chromophores have been incorporated into macrocyclic ligands and form well-defined Eu and Tb complexes in polar media. Excitation of the heterocyclic chromophore in the range 330 to 382 nm leads to modest amounts of aromatic fluorescence and relatively efficient metal-based luminescence, with absolute metal-based quantum yields of up to 24% in aqueous media.

Over the past twenty years, there has been much interest in the development of highly emissive lanthanide complexes incorporating an aromatic sensitising group to enhance efficient light absorption and promote energy transfer to the proximate Ln(III) ion. The stimulus for this work has been the utility of such complexes as optical probes or sensors in a wide variety of applications. The first uses were in heterogeneous bio-assays[1] and were followed by the introduction of single-component systems, based on europium cryptates.[2] Complexes of Eu(III) and Tb(III) are now used to good effect in a variety of high throughput assays and screening protocols, and several use time-resolved spectroscopy to enhance the signal to noise ratio in luminescence detection.[3]

Several recent reviews serve to highlight the key issues which have been addressed in optimising the design features of such systems.[4–10] The essential features of a ligand suitable for such applications may be summarised as follows: a small singlet–triplet energy separation minimising ligand fluorescence and allowing efficient inter-system crossing to populate the triplet state of the sensitiser; a high extinction coefficient for the sensitiser absorption band in the range 337–420 nm, facilitating single-photon excitation of biological samples; a fast energy transfer step leading to population of the lanthanide excited state, by selecting the triplet energy level of the sensitiser to lie at least 2,000 cm^{-1} above the emissive lanthanide excited state; a 7 to 9-coordinating ligand, preferably with at least one donor incorporated into the sensitising moiety to minimise the sensitiser–Ln^{3+} distance, that not only effectively shields the lanthanide(III) excited state from radiationless deactivation, involving vibrational and/or electronic energy transfer, but also inhibits quenching by electron transfer.

A very small number of single-component systems have been devised that meet these stringent design criteria for applications in biological media. Encouraging behaviour has been reported for terbium complexes of acyclic podands with phenolic amide donors,[11] for Eu and Tb complexes incorporating tetraazatriphenylene sensitisers[10,12,13] and for certain terpyridyl derivatives.[14] However, there remains considerable scope for improvement. Particular targets include maximising the product of ϕ_{em} and ε as well as minimising lanthanide excited state deactivation by electron transfer from electron rich donors.[12]

It is well known that aryl ketones are effective triplet sensitisers in organic photochemistry. Indeed, substituted acetophenones,[15] benzophenones[16] and acridones[17] have been incorporated into ligand structures to promote lanthanide sensitisation. In the case of the acridone systems studied, sensitisation of europium emission but not terbium was possible. Acridone fluorescence accounted for at least 80% of the emitted luminescence. Recent photophysical studies on 1-azaxanthone **1a**[18] and various thioxanthones **2a**[19] have been reported, suggesting that such aromatic ketones may be well suited to sensitise lanthanide luminescence. For example, **1a** has a triplet energy of 25,400 cm^{-1} and absorbs light around 335 nm in polar media, with an efficient intersystem crossing step ($\phi^{f}_{H_2O} = 0.01$, $\phi^{isc}_{H_2O} = 0.82$). The parent thioxanthone analogue absorbs around 375 nm with a slightly greater tendency to fluoresce. By replacing one phenyl group with a pyridine, possessing an α-methyl substituent, *e.g.* **1b**, **2b**, it was envisaged that binding to the lanthanide ion by the pyridyl N would be facilitated, with the alpha substituent allowing linkage to a suitable ligand framework. For example, the α-Me group may be easily converted into an α-CH_2Br derivative with *N*-bromosuccinimide prior to introduction into a suitable ligand.

The similarity in energy of azaxanthone nπ* and ππ* excited states[18] leads to a marked sensitivity of their photochemical properties to variation of solvent and substituent. A small library of substituted 1-azaxanthones and 1-azathioxanthones was therefore prepared, in order to analyse the effect of varying the nature and position of substituents in the benzenoid ring on both their singlet and triplet energies and their ability to fluoresce. Such a process informs the selection of the chromophore to be incorporated into the final octadentate ligand for lanthanide ion complexation. Herein, we report the outcome of the first phase of these studies and report on the photochemical behaviour of selected europium and terbium complexes of ligands incorporating some of these heterocyclic chromophores. A preliminary account of a related europium complex, bearing an azathioxanthone sensitiser has been communicated recently.[20]

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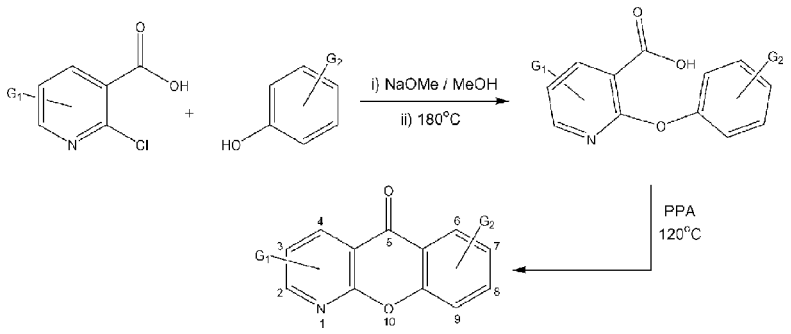


Scheme 1

1-Azaxanthone and 1-azathioxanthone synthesis and spectroscopic properties

The synthesis of 1-azaxanthones is most expeditiously addressed by a two-step process involving reaction of a substituted phenol (or thiophenol) with a 2-chloronicotinic acid derivative, followed by electrophilic cyclisation under acidic conditions,[21,22] (Scheme 1). *Ortho* and *para*-substituted phenols give rise to a single product whereas a *meta*-substituted phenol leads to formation of 6- and 8-substituted constitutional isomers. These may be separated by chromatography. The synthesis of compounds **1** to **16** was undertaken in this manner, using standard procedures.

The photophysical properties of 2-methyl-1-azaxanthone (**1b**), do not deviate significantly from those reported for 1-azaxanthone, **1a**.[18] The absorption spectrum of **1b** exhibited a small red shift in the longest wavelength band upon increasing solvent polarity, shifting from 329 nm (EPA) to 330 and 334 nm in MeOH and H_2O. Such behaviour is consistent with an increasing contribution from low-lying ππ* states, to the lowest energy transition which has predominantly nπ* character, as deduced for **1a**.[18] The extinction coefficient of the 330 nm band for **1b** in MeOH was measured in the presence of increasing amounts of water. It fell from 6,900 $M^{-1}cm^{-1}$ to approach a limiting value of 4,500 $M^{-1}cm^{-1}$ in 33% water–methanol. The reduction in the oscillator strength of the transition had been noted previously for **1a** to a similar extent. The low-temperature phosphorescence spectrum of **1b** (EPA glass, 77 K) possesses a highest energy band at 24,800 cm^{-1} (quoted in Table 1 as the 'zero–zero' transition, with the value corresponding to the *maximum* intensity of this band). Fine structure was observed, with three less intense bands separated by ~1650 cm^{-1}, typical of carbonyl vibration fine structure, (Fig. 1). Such behaviour is also consistent with the dominant nπ* character

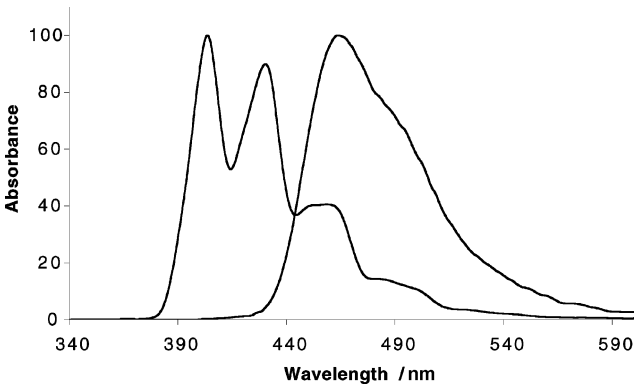


Fig. 1 Phosphorescence emission spectra for compounds **1b** and **10** (77 K, EPA glass), illustrating the vibrational fine structure for **1b** and the longer wavelength, less structured emission for **10**, associated with the enhanced 'ππ* character' of its triplet state.

Table 1 Photophysical properties of 2-methyl-1-azaxanthone derivatives

2-Me-azaxanthone derivative	λ_{max}/nm (ε; $M^{-1}cm^{-1}$)[a]	λ_{em}/nm (I_{em}^{rel})[b]	E_T/cm^{-1} [c]
1b[g]	330 (6,900)	405 (1)	24,800
	[350 (9,000)]	[490 (10)]	[23,250]
3a	328 (5,720)	392 (1.3)	24,900
4	336 (9,380)	409 (0.4)	24,600
5a	355 (4,845)	453 (320)	21,500
5b	341 (5555)	474 (40)	21,900
6	421 (8,800)	555[f] (1.6)	[d]
7	404 (8,000)	545[f] (1.2)	[d]
8	334 (11,140)	[d]	[d]
9	369 (20,176)	472 (505)	21,200
10	356 (18,000)	458 (515)	21,600
11	329 (9,780)	392 (1.3)	24,900

[a] MeOH, 295 K; triplet energies are quoted here as the observed *zero–zero* transition *i.e.* an intensity maximum and are subject to an error of ±400 cm^{-1}. [b] Relative fluorescence emission intensity in MeOH is given, referenced to the very weakly fluorescent derivative **1b**[e]. [c] 77 K in an Et_2O–isopentane–ethanol (EPA) frozen glass with typically a 100 μ delay. [d] No significant emission was detected. [e] Under these conditions, acridone (λ_{abs} 412 nm, $E_T = 21{,}050$ cm^{-1}) has a relative fluorescence emission intensity of 470. [f] This emission band was observed at room temperature in solution, but not at low temperature in the glass. At 77 K, fluorescence emission at 413 nm was observed (λ_{exc} 352 nm). [g] Values in square brackets refer to the *N*-oxide for which a very broad emission band was noted.

of this triplet state. This behaviour may be contrasted with that observed for the 8-amino-derivative, **10**. The lowest energy absorption band was observed at 356 nm and was more intense than the band at 330 nm (shoulder: Fig. 2). The triplet energy lowered to 21,600 cm^{-1} with no distinct vibrational fine structure and there was a 500-fold increase in room temperature relative fluorescence emission intensity. Taken together, such behaviour is consistent with conjugation of the exocyclic N lone pair, lowering the energy of the LUMO of **10** compared to **1b**, accompanied by a switch to predominant ππ* character in the singlet and triplet excited states. The bands at 330 and 356 nm presumably correspond to transitions with dominant nπ* and π–π* character. Similar observations have been reported when comparing the behaviour of benzophenone with 4,4-dimethylaminobenzophenone (Michler's ketone) in polar media.[24,25]

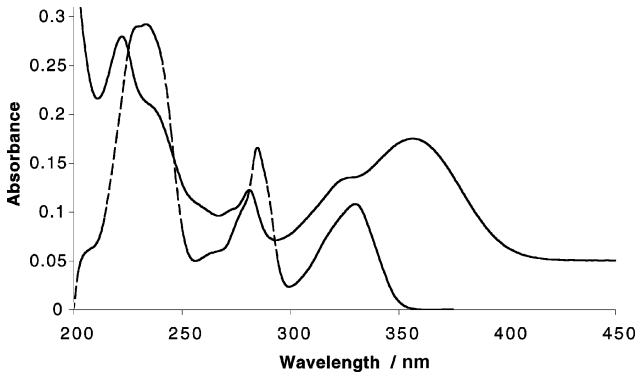
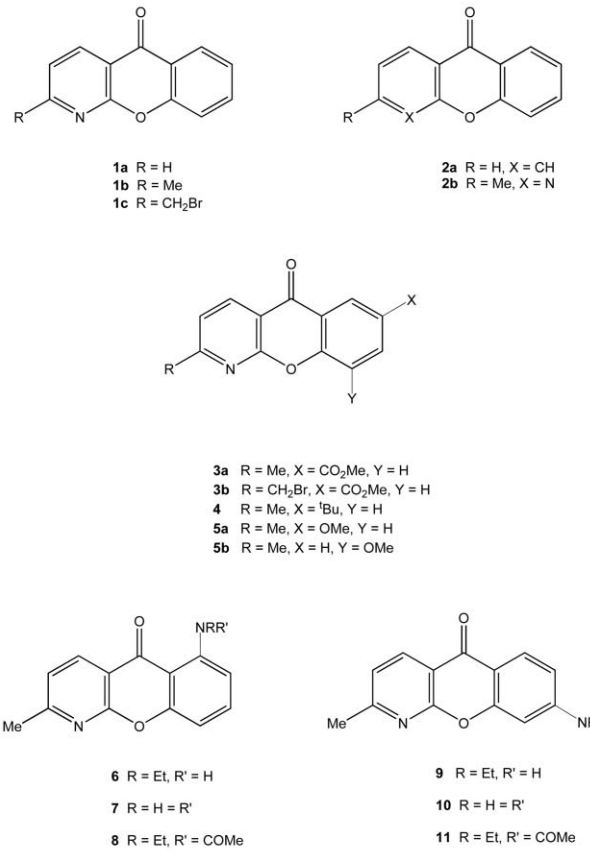


Fig. 2 Absorption spectra for compounds **1b** (lower) and **10** (295 K, MeOH).

The constitutionally isomeric methoxy derivatives **5a** and **5b** broadened and slightly shifted the lowest energy absorption band to the red, the effect being most distinct for the 7-substituted isomer, **5a**. This compound was also about 8 times more fluorescent than the 9-substituted isomer, **5b**, which was, in turn, 40 times more fluorescent than the parent **1b**. The 7-*tert*-butyl, **4**, and 7-carboxymethyl, **3b**, derivatives perturbed the singlet and triplet energies of the chromophore very little compared to **1b**. The *tert*-butyl derivative, **4**, was the least fluorescent of all the derivatives examined, consistent with its enhanced tendency to undergo radiationless deactivation of the singlet excited state, *via* internal conversion associated with the increased number of vibrational/rotational modes of the *tert*-butyl group.

The *ortho*-substituted series **6–8** presented quite different behaviour. The 6-substituted compounds exhibit no measurable low temperature phosphorescence. In their absorption spectra quite intense bands above 400 nm were observed for the amines **6** and **7** (λ_{max} 421 and 404 nm respectively), whereas for the amide **8** (lacking the ability to engage in significant N lone pair conjugation with the aryl moiety), the absorption band was not shifted compared to **1b**. At 77 K, a distinct fluorescent emission was defined at 489 nm for **6**. The room temperature emission spectra of **6** and **7** (but not **8**) revealed very broad and weak bands at 565 and 545 nm respectively. The relative intensity of this band decreased proportionately as the concentration of the solution was varied over the range 1 → 50 μM. A similar pattern of behaviour



was noted for the methoxy-derivatives **5a** and **5b** (very similar band widths and parallel diminution in emission intensity as concentration was reduced). A broad emission band was reported for 2-aminoxanthone in polar media, and was interpreted in terms of the formation of solvent-mediated formation of dimers or trimers—termed loosely as 'excimer-like aggregates of dynamic type',[26] this phenomenon having been previously postulated for various anthraquinone dyes.[27] Here, the variation in concentration was similar to that observed by these authors, but there seems no compelling reason to invoke molecular aggregation or clustering, mediated by the polar solvent, to explain the observed emission profile. The methoxy-substituted compounds **5a** and **5b** exhibited a long-lived phosphorescence at 77 K. Lifetimes of 1.0 and 0.85 seconds were measured and may be compared to a value of 2 ms for the parent **1a**, for which considerable nπ* character in the lowest energy triplet was deduced. The measured triplet energies of 21,500 and 21,900 cm^{-1} respectively are rather low triplet energy values and similar to those found for the amino derivatives **9** and **10**. They are too low to allow efficient Tb sensitisation at ambient temperature.

The absence of low-T phosphorescence and the very weak room-temperature fluorescence emission for **6–8** may be attributed to deactivation of the singlet and triplet excited states, *via* vibronic coupling involving an intramolecular hydrogen bond.[19] For compound **6**, direct support for this premise was found following analysis of the molecular structure by X-ray crystallography at 120 K (Fig. 3). The C(10)–N(2)–H(2) bond angle was found to be 117.8°, and observed torsion angles around the substituent were consistent with a planar N atom, allowing optimal overlap

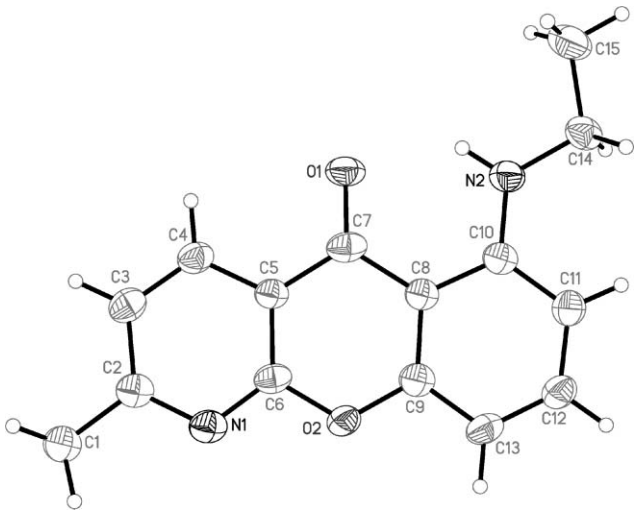
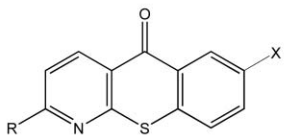


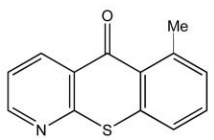
Fig. 3 Crystal and molecular structure of **6** (120 K), illustrating the intramolecular hydrogen bond (N2 · · · O1 distance is 2.676(3) Å), and showing the crystallographic numbering scheme.

of the N lone pair with the π-system. No evidence for any other hydrogen bonding interactions in the solid-state structure was found, involving either solvent (absent in the lattice) or an intermolecular interaction. The amide, **8**, also gave rise to no significant fluorescence at room temperature nor was any low-T phosphorescence observed. In this case, a weak intramolecular C–H · · · O interaction may be invoked to rationalise this behaviour. Such C–H · · · O interactions have been postulated previously to account for related cases of non-radiative deactivation, for example, those observed in the excited state chemistry of 6-methylthioxanthone.[19]

Given the behaviour observed with the 1-azaxanthone, a slightly different series of compounds was screened with the 1-azathioxanthones. It had previously been noted that introduction of a nitrogen atom into a xanthone[18,28] skeleton reduces the intensity of fluorescence and relatively weak fluorescence was therefore expected. The photophysical behaviour of the parent-2-methyl, **2b**, 6-carboxy-2-methyl **12** and four isomeric monomethyl derivatives **13–16** was studied, (Table 2). Much more subtle variations in singlet and triplet energies were noted. Alkyl-substitution in the 6-position (*i.e.* **4**) produced the most significant red shift in the absorption spectrum, with a parallel increase in the fluorescence emission wavelength (very weak at 440 nm) and a decrease in the triplet energy to 22,800 cm^{-1}. These values may be compared to those for **2b** (λ_{absc} 371 nm; λ_{em} = 425 nm; E_T = 23,700 cm^{-1}). Alkyl substitution in the 7, 8 or 9-position did not perturb the observed singlet and triplet energies significantly, nor did it affect the observed band intensities. The solvent dependence of the weak fluorescence emission of **2b** was studied to help probe the character of the singlet excited state. The broad and weak fluorescence emission band observed at room temperature shifted to the blue and became even less intense in solvents of lower polarity (Fig. 4). Indeed a structureless emission band was not observed in CH_2Cl_2, EtOAc, THF and toluene. Such behaviour is consistent with a slight enhancement of the ππ* character in the singlet excited state in more polar media. Low temperature phosphorescence emission was strong, and in every case examined, the vibrational fine structure observed was indicative of a significant nπ* character in the T_1 state.



12a R = Me, X = CO_2Me
12b R = CH_2Br, X = CO_2Me
13 R = H, X = Me



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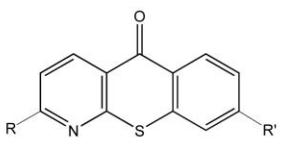
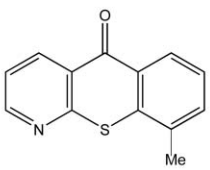


15a R = Me, R' = H
15b R = H, R' = Me



16

Implications for Eu^{3+}/Tb^{3+} sensitisation

Fluorescence emission for the 1-azaxanthones examined was weak unless donor N or O lone-pairs were introduced into the chromophore in the 7, 8 or 9 position. Such a substitution pattern also led to a significant lowering of the triplet energy, obviating their use for Tb sensitisation. Substitution in the 6-position tended to lead to fast radiationless deactivation of both singlet and triplet excited states, precluding the use of such systems for sensitised luminescence. Introduction of alkyl or carboxy groups perturbed the triplet energy much less and also did not enhance the tendency of the chromophore to fluoresce.

Table 2 Photophysical properties of 2-methyl-1-azathioxanthone derivatives

1-Axathioxanthone derivative	λ_{max}/m(ε, M^{-1} cm^{-1})[a]	λ_{em}/nm(I^{rel}_{em})[b]	E_T/cm^{-1}[c]
2b	371 (6,770)	425 (3.3)	23,700
12a	369 (5,360)	423 (0.7)	23,800
13	372 (5,790)	428 (3.6)	23,500
14	381 (5,350)	440[d]	22,800
15b	375 (5,450)	437 (1.0)	23,500
16	374 (5,760)	437 (5.1)	23,600

[a] MeOH, 295 K. [b] Relative fluorescence emission intensity, compared to compound **1b**. [c] 77 K in a 1 : 1 MeOH/EtCH glass (of 20,400 cm^{-1} for $^5D_4$ Tb excited state and 17,200 cm^{-1} for $^5D_0$ Eu excited state). In each case, vibrational fine structure was evident, although the emission bands were rather broad consistent with mainly 'nπ* character' in the triplet excited state. [d] Very weak.

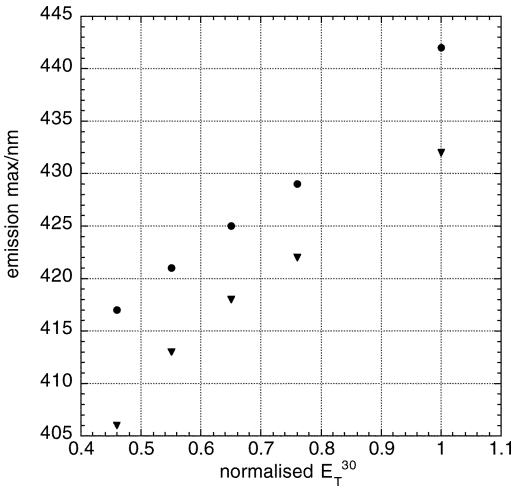


Fig. 4 Variation of the fluorescence emission band with the solvent polarity parameter, E_T^{30} (295 K) for 2-methyl-1-azathioxanthone, **15a**, and for the derived europium complex, [Eu.**20**]$^{3+}$.

For the 1-azathioxanthones, the singlet–triplet energy gap was smaller than that observed with azaxanthones, and typically were of the order of 3,500 cm^{-1}; triplet energies examined were typically close to 23,500 cm^{-1} (±500 cm^{-1}). This energy is well suited to Eu^{3+} sensitisation, but is at the practicable limit for Tb^{3+} (Tb: $^5D_4$ lies at 20,400 cm^{-1}), at least for room temperature applications. In order to assess the utility of these chromophores in sensitised emission, selected octadentate ligands were constructed incorporating the xanthone chromophores and the luminescence behaviour of their Eu^{3+} and Tb^{3+} complexes defined. Ligands **17**, **18** and **19** were prepared, and compared to the heptadentate ligand **20** which had been prepared earlier for anion-binding studies.[20] The synthesis of **17–19** followed established methodology[12] involving the intermediacy of the appropriate 2-bromomethyl derivative, prepared by radical bromination of the 2-methyl precursor with *N*-bromosuccinimide. Complexes of Eu and Tb were prepared using standard methods and were purified either by chromatography on alumina or by reverse-phase HPLC.

Measurements of the radiative rate constant for decay of lanthanide emission were made in H_2O and D_2O for each lanthanide complex, allowing an estimation of the complex hydration state by application of the well-known relationship between the number of bound water molecules and the difference in excited state quenching rates in the two media.[29] In every case, a hydration state close to one was found, consistent with the behaviour of related complexes.[6] These include a close analogue of **17**, where a 4-morpholino-substitued pyridine replaces the azaxanthone moiety.[30] Such behaviour is in accord with a complex structure in which the pyridyl N is bound to the lanthanide ion, generating a nine coordinate complex in which one water binds to cap a square anti-prismatic coordination geometry.[6] Further support for formation of the mono-aqua species came from the measurement of the relaxivities of selected Gd complexes. For example, with [Gd.**17**], a relaxivity of 2.94 mM^{-1}s^{-1} was measured (310 K, 60 MHz). At this field and frequency, such a value is in the range expected for Gd complexes of this molecular weight.[6]

Quantum yield measurements for the complexes were made using published procedures. For the complexes with azathioxanthone chromophores (Table 3), rather low values were found with the terbium complexes in aerated solution, consistent with the low measured radiative lifetimes. Much longer lifetimes were measured in degassed solution, consistent with competitive back energy transfer from the lanthanide excited state to the aryl triplet, enhancing its susceptibility to quenching by molecular oxygen. Many examples of this phenomenon have been reported,[6] where the gap between the aryl triplet and the Tb excited state is less than about 2,500 cm^{-1}. For the corresponding europium complexes,

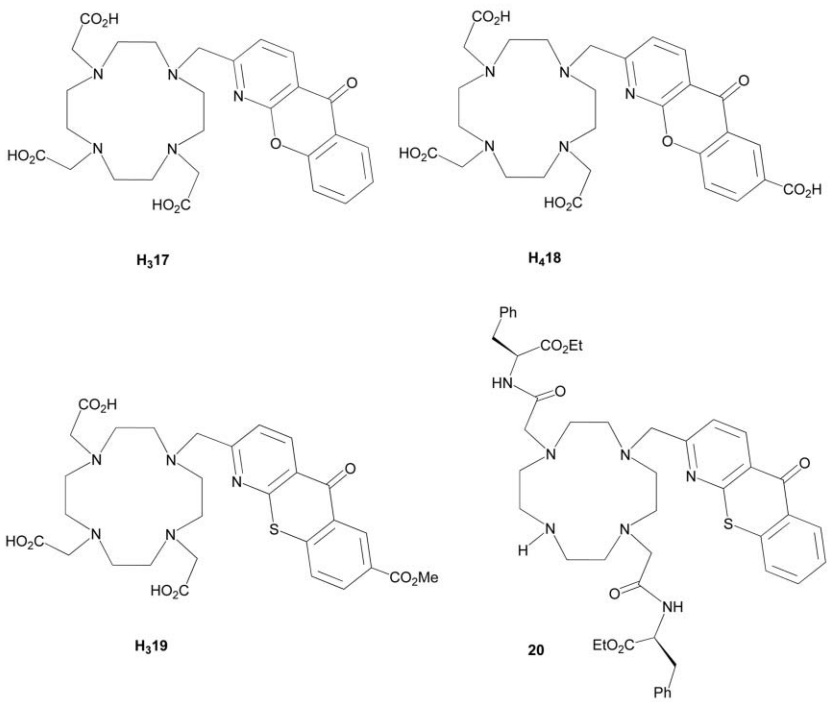


Table 3 Photophysical properties of Eu^{3+} and Tb^{3+} complexes of ligands **17**–**20** (H_2O, 295 K)

Complex	τ_{H_2O}/ms	τ_{D_2O}/ms	q	$\phi^{em}{}_{H_2O}$ (%)
[Eu. **17**][a,b]	0.57	2.02	1.2	6.9
[Tb. **17**]	1.82	2.73	0.6	24
[Eu. **18**][a]	0.60	2.08	1.1	8.0
[Tb. **18**]	1.89	2.88	0.64	12[e]
[Eu. **19**][c]	0.51	1.62	1.3	2.2
[Tb. **19**]	0.49	0.60	1.25	2.1
[Eu. **20**][d]	0.32	0.49	1.1	8.9
[Tb. **20**]	0.059	0.060	n/a	not measured
	(0.66)	(0.84)	(1.25)	(12)

[a] In each case, λ_{abs} = 336 nm; q values are subject to an estimated error of 25% and quantum yields are given as the mean of 3 observations (±20%). [b] For the corresponding complex [Gd.**17**], E_T = 24,950 cm^{-1} (77 K, 1 : 1 EtOH–MeOH glass). [c] λ_{exc} = 375 nm. [d] λ_{exc} = 382 nm; emission quantum yields (ϕ_f, %) for thioxanthone fluorescence were as follows: **20**: 4.4 (MeOH), 25 (H_2O); [Eu. **20**]: 44 (H_2O); [Tb. **20**]: 50 (H_2O); for the Tb complex, values in parentheses refer to a degassed sample. The lower lifetime of this Eu complex is due to quenching by the ring NH oscillator. [e] The lower quantum yield here compared to [Tb.**17**] may be related to less efficient inter-system crossing and/or enhanced vibrational deactivation of the azaxanthone singlet excited state.

[Eu.**19**] and [Eu.**20**]$^{3+}$ quantum yields were higher, but there was still a fairly significant fluorescence from the thioxanthone chromophore, as noted in the chromophore spectral studies discussed above (Fig. 5). Indeed, the quantum yield for ligand fluorescence was measured to be 44 and 50% in water for [Eu.**20**]$^{3+}$ and [Tb.**20**]$^{3+}$ respectively. Considerably less azathioxanthone fluorescence was observed in less polar media. Comparing the behaviour of [Tb.**20**]$^{3+}$ and [Eu.**20**]$^{3+}$ in water and methanol, for example, the ligand based fluorescence was 10 times less in the latter case. The fluorescence emission band also shifted to the blue as the solvent polarity diminished (Fig. 4); this effect correlated well with that observed for the parent chromophore **15a**. Evidently, the presence of the proximate lanthanide ion appears neither to perturb the facility of inter-system crossing in the xanthone entity significantly, nor to change the sensitivity of the energy of the nπ* and ππ* excited states to local solvation effects.

Less ligand fluorescence was evident in the emission spectra of the terbium complexes in water with integral azaxanthone sensitisers, *e.g.* [Tb.**17**] and [Tb.**18**] (Fig. 6)]. Such behaviour accords with the lower intrinsic fluorescence of the azaxanthone chromophores, **1b** and **3** (Table 1). The measured absolute quantum yield for [Tb.**17**] was 24%, which is quite a high value for a complex with one coordinated water molecule. Moreover, this high emission intensity and long emission lifetime was conserved in aqueous solutions containing added salts. For example, the terbium emission lifetime in [Tb.**17**] was 1.98 ms in 1 M aqueous sodium acetate solution buffered to pH4, and was invariant (±5%) over a period of 48 h.

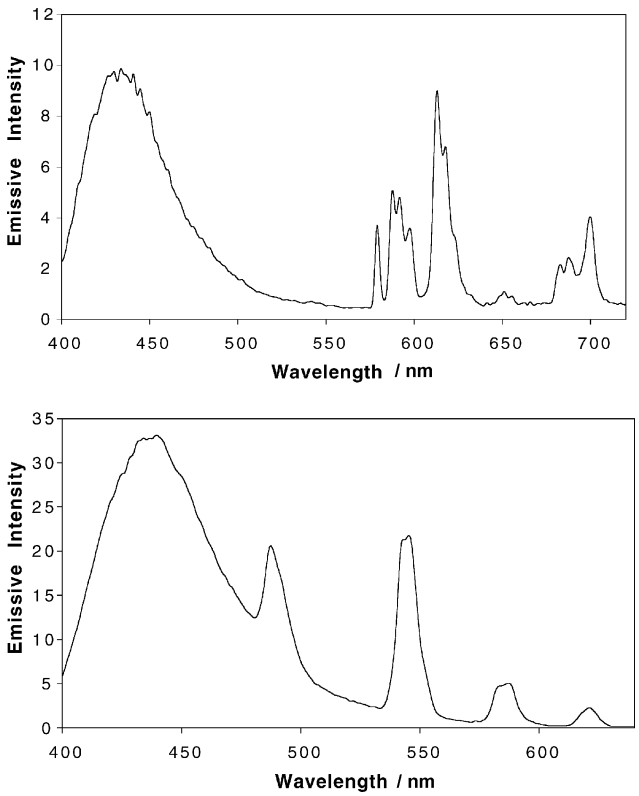


Fig. 5 Total emission spectra (aerated water, 295 K, λ_{exc} 375 nm) for [Ln.**19**] (Ln = Eu {upper}; Ln = Tb {lower}) showing the ligand fluorescence around 440 nm and the lanthanide emission bands to lower energy.

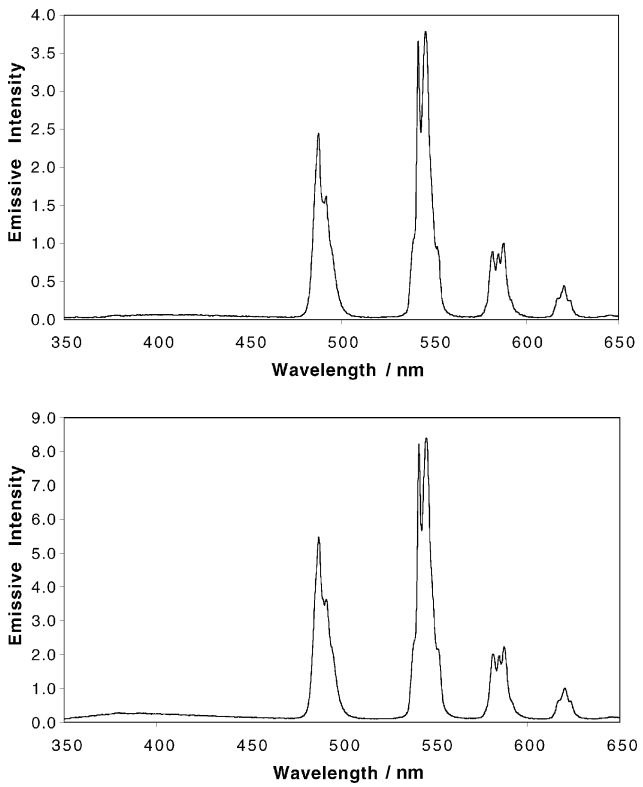


Fig. 6 Total emission spectra (aerated water, 295 K, λ_{exc} 334 nm) for [Tb.**17**] compared to [Tb.**18**]$^-$ (upper) showing the very low azaxanthone fluorescence, and the typical terbium emission pattern in each case.

Conclusions

Azaxanthone and thioxanthone chromophores are superior to acridone chromophores as sensitising moieties for Eu and Tb emission. In such systems, the most obvious synthetic strategy

allows the incorporation of a range of different substituents in the benzenoid ring. Alkoxy and amino-substituents tend to favour molecular fluorescence or lower the triplet energy to such an extent that Tb-sensitised emission becomes impracticable. Simple alkyl, acylamino or carboxy substituents do not perturb the chromophore triplet energy very much, allowing the identification of appropriate derivatives for conjugation to vectors for assays or for other molecular probe applications.

Experimental

General Procedures

All commercially available reagents were used as received, from their respective suppliers. Solvents were dried using an appropriate drying agent when required. Reactions requiring anhydrous conditions were carried out using Schlenk-line techniques under an atmosphere of dry argon. Water and H_2O refer to high purity water with conductivity $\leq$0.04 μS cm^{-1} obtained from the 'Purite$_{STILL}$ plus' purification system.

Thin-layer chromatography was carried out on neutral alumina plates (Merck Art 5550) or silica plates (Merck 5554) and visualised under UV (254 nm) or by staining with iodine. Preparative column chromatography was carried out using neutral alumina (Merck Aluminium Oxide 90, activity II-III, 70–230 mesh), presoaked in ethyl acetate, or silica (Merck Silica Gel 60, 230–400 mesh).

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 200 (^{1}H at 199.98 MHz, ^{13}C at 50.29 MHz), Varian Unity 300 (^{1}H at 299.91 MHz, ^{13}C at 75.41 MHz), Varian VXR 400 (^{1}H at 399.97 MHz, ^{13}C at 100.57 MHz), or a Bruker AMX 500 spectrometer. Spectra were referenced internally to the residual protio-solvent resonances. Electrospray mass spectra were recorded on a VG Platform II (Fisons instrument), operating in positive or negative ion mode as stated, with methanol as the carrier solvent. Accurate mass spectra were recorded using a Thermo Finnigan LTQ FT mass spectrometer. Melting points were recorded using a Köfler block and are uncorrected. UV/Vis absorbance spectra were recorded on a Perkin Elmer Lambda 900 UV/Vis/NIR spectrometer. Emission Spectra and Lifetimes were measured on a Fluorolog-3 and a Perkin Elmer LS55 luminescence spectrometer using FL Winlab software. All samples were contained in quartz cuvettes with a path length of 1 cm and measurements obtained relative to a reference of pure solvent contained in a matched cell.

Single crystal X-ray diffraction

Crystal structures were determined for **5a**, **5b**, **6** and **15a**. Data were collected using graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å) on a Bruker area detector diffractometer (Bruker SMART CCD 1 K or Bruker ProteumM with Bede Microsource), equipped with Cryostream N_2 open-flow cooling device.[31] In each case, series of narrow ω-scans (0.3°) at several ϕ-settings were carried out to cover approximately a sphere of data to a maximum resolution between 0.70 and 0.77 Å. Cell parameters were determined and refined using the SMART software,[32] and raw frame data were integrated using the SAINT program.[33] Structures were solved by direct methods and refined by full-matrix least squares on F^2 using SHELXTL software[34] (for structures of **5a**, **6** and **15a**) and full-matrix least squares on F using CRYSTALS[35] (for **5b**). Reflection intensities were corrected by numerical integration using SHELXTL software, based on crystal measurements and indexing of the faces[34] or by the multi-scan method, based on multiple scans of identical and Laue equivalent reflections (using the SADABS software).[36] Non-hydrogen atoms were refined with anisotropic displacement parameters and the hydrogen atoms were positioned geometrically and refined using a riding model. Crystallographic data (excluding structure factors) for the structures included herein have been deposited with the Cambridge Crystallographic Data Centre† CCDC reference numbers 296391–296394..

Excited state measurements

The lifetimes of the Tb and Eu complexes were measured by exciting the sample using a short pulse of light (336 nm) followed by the monitoring of the integrated intensity of light (546 nm for terbium, 613 nm for europium) emitted during a fixed gate time, t_g, after a delay time, t_d. At least 20 delay times were used covering 3 or more lifetimes. A gate time of 0.1 ms was employed, and the excitation and emission slits set to a bandpass of 10 nm and 2.5 nm respectively. The obtained exponential decay curves were fitted to the equation below, using Microsoft Excel,

$$I = A_0 + A_1\exp(-kt)$$

where:

I = intensity at time t after the flash

A_0 = intensity after the decay has finished

A_1 = pre-exponential factor

k = rate constant for decay of the excited state.

Quantum yield measurements were made relative to a standard,[12] $LnPh_3dpqC(CF_3SO_3)_3$, for each of the Tb^{3+} and Eu^{3+} complexes. For the standard and each of the unknowns, five solutions with absorbances between 0.02 and 0.1 were used. For each of these solutions the absorbance at the excitation wavelength and the total integrated emission was determined. A plot of total integrated emission against absorbance gave a straight line with slope Em./Abs. The unknown quantum yield was calculated using the equation below:

$$\Phi_x = \Phi_r \cdot \frac{slope_x}{slope_r} \cdot \left(\frac{n_x}{n_r}\right)^2$$

Since values for both the sample and reference compounds were recorded in water the refractive index term cancels out. Errors in quantum yield determinations can arise due to the inner filter effect or errors in the amount of absorbed light. These effects were minimised by only using samples with absorbances below 0.2. Errors in assessing the amount of light absorbed by each sample were minimised by choosing the excitation wavelength to be on a relatively flat area of the absorption curve and by using a small band-pass for excitation.

† CCDC reference numbers 296391–296394. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b601357k

Low temperature phosphorescence spectra of heterocyclic ligands and gadolinium(III) complexes were recorded to enable the triplet energy of the bound chromophore to be determined. An Oxford Instruments optical cryostat operating at 77 K was used with the samples dissolved in EPA (diethyl ether–isopentane–ethanol, 5 : 5 : 2) or EtOH–MeOH mixtures and contained in 10 mm cuvettes. The triplet energy was considered as the highest energy (shortest wavelength) observed phosphorescence band, corresponding to the 0–0 transition, using time-gated detection.

The longitudinal water proton relaxation rate was measured at 60 MHz using a Bruker Minispec mq spectrometer operating at 310 K, by means of a standard inversion-recovery technique. The data obtained was accurate to a reproducibility of ±1%. A correction was made for the diamagnetic contribution to allow the estimation of the paramagnetic relaxivity. The gadolinium concentration of the solution was measured in triplicate using a Perkin Elmer ICPOES (Inductively Coupled Plasma Optical Emission) spectrometer.

Synthesis

6-Methyl-2-phenoxynicotinic acid. Sodium (1.44 g, 62.6 mmol) was dissolved in dry MeOH (27 cm^3), followed by the addition of 6-methyl-2-chloronicotinic acid (5.09 g, 29.6 mmol) and phenol (13.27 g, 0.14 mol) under argon, forming a yellow solution. The MeOH was removed under reduced pressure, and the brown melt heated for 1 hour at 180 °C under argon with stirring. Upon cooling, the melt was treated with water (200 cm^3) forming a pale yellow suspension, which was washed with diethyl ether (3 × 200 cm^3). The aqueous layer was acidified with acetic acid to pH 4, yielding a fine white precipitate upon cooling which was collected *via* filtration, and after thorough drying yielded the *title compound* as a pale yellow solid (3.01 g, 44%), m.p. 134–136 °C (lit.[23] 155–156 °C). Found: C, 67.79; H, 4.74; N, 6.11%. $C_{13}H_{11}NO_3$ requires C, 68.11; H, 4.84; N, 6.11%. δ_H ($CDCl_3$) 2.40 (3H, s, CH_3), 7.03 (1H, d, *J* 7.8, $H^{5)}$), 7.18 (2H, d, *J* 7.6, $H^{2\prime}$), 7.29 (1H, t, *J* 7.6, $H^{4\prime}$), 7.44 (2H, t, *J* 7.6, $H^{3\prime}$), 8.41 (1H, d, *J* 7.8, H^4)10.6 (1H, br s OH); δ_C ($CDCl_3$, 125 MHz) 24.4 (CH_3), 110.0 (C^3), 119.4 (C^5), 121.8 ($C^{2\prime}$), 125.8 ($C^{4\prime}$), 129.6 ($C^{3\prime}$), 143.6 (C^4), 152.0 ($C^{1\prime}$), 160.2 (C^2), 163.2 (C^6), 164.7 (COOH); *m/z* ($ESMS^-$) 184 (M − COOH, 95%), 228 (M − H, 100%). HRMS (ES^+), found: 230.0809 [M + H]; $C_{13}H_{12}NO_3$ requires 230.0812.

2-Methyl-1-azaxanthone, 1b. Polyphosphoric acid (80 g) was added to 2-phenoxy-6-methylnicotinic acid (1.535 g, 6.7 mmol) and the reaction mixture heated at 120 °C for 20 hours under argon with stirring. The resulting light-brown liquid was cooled to room temperature and then slowly and carefully poured onto ice (200 g) with stirring until a homogeneous solution formed. The pH of the solution was then carefully adjusted to 12 by the addition of 50% aqueous KOH solution and the yellow crystals that formed upon cooling were removed *via* filtration. The product was recrystallised from toluene–petroleum ether (40–60 °C). The crystals that formed upon standing were filtered and dried thoroughly to yield the *title compound* as a pale yellow crystalline solid (1.23 g, 87%), m.p. 131–132 °C (lit.[23] 136–8 °C); R_f (SiO_2, DCM): 0.30. Found C, 73.9; H, 4.27; N, 6.73. $C_{13}H_9NO_2$ requires C, 73.9; H, 4.29; N, 6.63%. δ_H ($CDCl_3$) 2.71 (3H, s, CH_3), 7.30 (1H, d, *J* 7.8, H^3), 7.43 (1H, ddd, *J* 8,7, 0.9 H^7), 7.61 (1H, dd, *J* 8.4, 0.9, H^9), 7.77 (1H, ddd, *J* 8, 7, 1.5 H^8), 8.32 (1H, dd, *J* 8, 1.5, H^6), 8.60 (1H, d, *J* 7.8, H^4); δ_C ($CDCl_3$) 25.2 (CH_3), 114.3 ($C^{4\prime}$), 118.6 (C^9), 121.3 (C^3), 121.8 ($C^{6\prime}$), 124.7 (C^7), 126.7 (C^6), 135.5 (C^8), 137.4 (C^4), 155.8 ($C^{9\prime}$), 160.0 ($C^{1\prime}$), 165.2 (C^2), 177.7 (C^5); *m/z* ($ESMS^+$) 233.7 ([M + Na], 100%); HRMS (ES^+), found: 212.0707 [M + H], $C_{13}H_{10}NO_2$ requires 212.0706; UV-vis (H_2O) λ_{max} (ε/mol^{-1} dm^3 cm^{-1}) 289 (16,180) and 334 nm (8790).

2-Methyl-1-azaxanthone-*N*-oxide. 2-Methyl-1-azaxanthone (45 mg, 213 μmol) was dissolved in trifluoroacetic acid (TFA) (400 μL) and H_2O_2 (100 μL, 37%) and the resulting solution boiled under reflux for 4 hours. A further two additions of TFA (400 μL) and H_2O_2 (100 μL, 37%) were made at 4 hour intervals and then the reaction was evaporated to dryness under reduced pressure. The residue was taken up in aqueous $NaHCO_3$ (10 cm^3) and extracted with CH_2Cl_2 (2 × 10 cm^3). The combined organics were washed with aqueous NaCl solution (10 cm^3), dried (Na_2SO_4), filtered and evaporated under reduced pressure to give the crude compound as a yellow solid. Subsequent purification *via* column chromatography (silica, CH_2Cl_2 to 2% EtOH) yielded the title compound (24 mg, 106 μmol, 50%) as a pale yellow solid, R_f 0.33 (silica, 3% EtOH:CH_2Cl_2), m.p. 191–2 °C. Found: C, 66.2; H, 4.15; N, 5.83%; $C_{13}H_9NO_3.H_2O$ requires C, 66.1; H, 4.27; N, 5.93%.

δ_H(*$CDCl_3$*). 8.32 (d, 1H, *J* 7.9 Hz, H^6), 8.09 (d, 1H, *J* 8.2 Hz, H^4), 7.88–7.80 (m, 2H, $H^{8,9}$), 7.51 (t, 1H, H^7), 7.34 (d, 1H, *J* 8.2 Hz, H^3), 2.74 (s, 3H, CH_3).

δ_C (*$CDCl_3$*). 176.2 (C^5), 155.2 (C^2), 155.1 ($C^{1\prime}$), 154.9 ($C^{9\prime}$), 136.3 (C^8), 126.9 (C^6), 126.0 (C^7), 122.7 (C^4), 121.3 ($C^{6\prime}$), 120.7 (C^3), 119.1 (C^9), 117.5 ($C^{4\prime}$), 18.9 (CH_3).

(*m/z*) $ESMS^+$ 228 ($[M + H]^+$, 5%), 250 ($[M + Na]^+$, 100%), 477 ($[2M + Na]^+$, 20%).

Found: (ES^+) 250.0473; $C_{13}H_9NO_3Na$ requires 250.0475, $[M + Na]^+$.

2-Bromomethyl-1-azaxanthone, 1c. 2-Methyl-1-azaxanthone (0.200 g, 0.947 mmol) was dissolved in CCl_4 (10 cm^3) and the reaction heated to 80 °C under argon. *N*-Bromosuccinimide (NBS) (85 mg, 0.475 mmol, 0.5 eq.) was added along with benzoyl peroxide (3 mg) with stirring and the reaction mixture was stirred at room temperature under argon, using a tungsten lamp for activation. The reaction was monitored using TLC (SiO_2, toluene–CH_2Cl_2–MeOH, 48.5 : 48.5 : 3) and ^1H NMR. After 8 hours and the addition of 2 equivalents of NBS and benzoyl peroxide, the crude reaction mixture was allowed to cool to room temperature and then filtered. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel (toluene–DCM, 80 : 20) to yield the *title compound* as a white crystalline solid (0.102 g, 0.35 mmol, 37%), m.p. 169–171 °C; R_f (SiO_2, toluene–dichloromethane–MeOH, 48.5 :48.5 : 3): 0.67. Found C, 53.9; H, 2.74; N, 4.85%. $C_{13}H_8NO_2Br$ requires: C, 53.8; H, 2.78; N, 4.83%. δ_H ($CDCl_3$) 4.61 (2H, s, CH_2Br), 7.45 (1H, ddd, *J* 8,7.2, 1.0, H^7), 7.58 (1H, d, *J* 8, H^3), 7.62 (1H, d, *J* 8, H^9), 7.80 (1H, ddd, *J* 8,7.2,1.6, H^8), 8.31 (1H, d, *J* 8, H^6), 8.72 (1H, d, *J* 8, H^4); δ_C ($CDCl_3$) 32.3 (CH_2Br), 116.1 ($C^{4\prime}$), 118.6 (C^9), 120.9 (C^3), 121.7 ($C^{6\prime}$), 125.0 (C^7), 126.8 (C^6), 135.9 (C^8), 138.8 (C^4), 155.8 ($C^{9\prime}$), 158.8 ($C^{1\prime}$), 162.1 (C^2), 177.2 (C^5); *m/z* ($ESMS^+$) 290.1 ([M + H], 100%), 312.1 ([M + Na], 20%). HRMS (ES^+) found: 289.9817 [M + H], $C_{13}H_9BrNO_2$ requires 289.9811.

2-(4-Methoxycarbonylphenoxy)-6-methylnicotinic acid. Sodium methoxide (660 mg, 12.2 mmol) was dissolved in dry MeOH (5 cm^3) with stirring, followed by methyl-4-hydroxybenzoate (4.26 g, 28 mmol) and 6-methyl-2-chloronicotinic acid (1.0 g, 5.9 mmol). The methanol was removed under reduced pressure and the reaction heated for 24 hours at 180 °C with stirring. The reaction mixture was left to cool to ~120 °C and poured onto ice (~40 g) to give a white suspension, which was treated with diethyl ether (3 × 50 cm^3). The separated aqueous solution was acidified with acetic acid yielding a pale yellow precipitate, which was filtered, washed with water and dried thoroughly to yield the *title compound* as a white crystalline solid (1.005 g, 60%), m.p. 118–120 °C. Found C, 59.2; H, 4.52; N, 4.49. $C_{15}H_{13}NO_5.H_2O$ requires C, 59.0; H, 4.95; N, 4.59%. δ_H ($CDCl_3$) 2.41 (3H, s, $^1CH_3$), 3.91 (3H, s, OCH_3), 7.02 (1H, d, *J* 8, H^5), 7.18 (2H, d, *J* 9, $H^{2\prime}$), 8.07 (2H, d, *J* 9, $H^{3\prime}$), 8.32 (1H, d, *J* 8, H^4); δ_C ($CDCl_3$) 24.4 (CH_3), 52.3 (OCH_3), 111.3 (C^3), 119.3 (C^5), 121.0 ($C^{2\prime}$), 126.6 ($C^{4\prime}$), 131.4 ($C^{3\prime}$), 143.4 (C^4), 157.6 ($C^{1\prime}$), 160.6 (C^2), 163.2 (C^6), 166.7 ($COOCH_3$), 168.2 (COOH); *m/z* ($ESMS^-$) 242 ([M − COOH], 75%), 286 ([M − H], 100%); HRMS (ES^+) found: 288.0869 [M + H], $C_{15}H_{13}NO_5$ requires 288.0866.

7-Methoxycarbonyl-2-methyl-1-azaxanthone, 3a. Polyphosphoric acid (70 g) was added to 2-(4-methoxycarbonylphenoxy)-6-methylnicotinic acid (0.90 g, 3.1 mmol) and the reaction mixture heated at 120 °C for 18 hours under argon with stirring. The resulting brown liquid was cooled to room temperature and then slowly and carefully poured into a beaker containing cold MeOH (100 cm^3) with stirring until a homogeneous solution formed. The solution was carefully adjusted to an apparent pH of approximately 7 by the addition of 10% aqueous KOH solution. The resulting white suspension was extracted with chloroform (3 × 50 cm^3) and the solvent removed from the combined organic washings to yield the *title compound* as a pale yellow crystalline solid (0.428 g, 1.6 mmol, 51%), m.p. 194–196 °C; R_f (SiO_2, toluene–dichloromethane–MeOH, 48.5 : 48.5 : 3): 0.30. Found C, 66.5; H, 4.14; N, 5.13%. $C_{15}H_{11}NO_4$ requires C, 66.9; H, 4.12; N, 5.20%.

δ_H ($CDCl_3$) 2.73 (3H, s, CH_3), 3.98 (3H, s, OCH_3), 7.24 (1H, d, *J* 9, H^3), 7.65 (1H, d, *J* 9, H^9), 8.41 (1H, d, *J* 9, H^8), 8.61 (1H, d, *J* 9, H^4), 9.0 (1H, s, H^6); δ_C ($CDCl_3$) 25.2 (CH_3), 52.6 (OCH_3), 114.4 ($C^{4\prime}$), 118.9 (C^9), 121.4 ($C^{6\prime}$), 121.8 (C^3), 126.8 (C^7), 129.2 (C^6), 136.0 (C^8), 137.6 (C^4), 158.3 ($C^{9\prime}$), 160.0 ($C^{1\prime}$), 165.72 (CO_2Me), 165.75 (CN), 176.9 (*keto*); *m/z* ($ESMS^+$) 291.8 ([M + Na], 100%), 269.7 ([M + H], 25%); HRMS (ES^+), found: 270.0760 [M + H], $C_{15}H_{12}NO_4$ requires 270.0761; UV-vis (H_2O) λ_{max} (ε/mol^{-1} dm^3 cm^{-1}) 288 (12,860) and 334 nm (5720).

7-Methoxycarbonyl-2-bromomethyl-1-azaxanthone, 3b. 7-Methoxycarbonyl-2-methyl-1-azaxanthone (0.215 g, 0.798 mmol) was dissolved in a mixture of CCl_4 and MeCN (2 : 1 ratio, 10 cm^3) and the reaction heated to 80 °C under argon. NBS (71 mg, 0.399 mmol, 0.5 eq.) was added along with AIBN (~2 mg) with stirring and the reaction monitored using TLC (SiO_2, EtOAc–hexane, 50 : 50) and ^1H NMR. After 4 days and the addition of 7 equivalents of NBS and AIBN the reaction was halted and the crude reaction mixture allowed to cool to room temperature before being filtered. The solvent was removed under reduced pressure and the residue purified by column chromatography on silica gel (hexane–EtOAc, 50 : 50) to yield the *title compound* as a white crystalline solid (0.140 g, 0.40 mmol, 50%), m.p. 156–158 °C; R_f (SiO_2, EtOAc–hexane, 50 : 50): 0.65. Found C, 49.4; H, 3.34; N, 4.07%. $C_{15}H_{10}NO_4Br.H_2O$ requires C, 49.2; H, 3.30; N, 3.83%.

δ_H ($CDCl_3$) 3.98 (3H, s, OCH_3), 4.62 (2H, s, CH_2Br), 7.62 (1H, d, *J* 8, H^3), 7.68 (1H, d, *J* 8.5, H^9), 8.44 (1H, dd, *J* 8.5, H^8), 8.74 (1H, d, *J* 8, H^4), 9.00 (1H, d, *J* 2,H^6); δ_C ($CDCl_3$) 32.3 (CH_2Br), 52.8 (OCH_3), 116.2 ($C^{4\prime}$), 119.2 (C^9), 121.5 ($C^{6\prime}$), 121.6 (C^3), 127.3 (C^7), 129.4 (C^6), 136.6 (C^8), 139.0 (C^4), 158.4 ($C^{9\prime}$), 159.8 ($C^{1\prime}$), 162.7 (C^2), 165.8 (CO_2Me), 176.7 (C^5); *m/z* ($ESMS^+$) 348.1 ([M + H], 100%), 370.1 ([M + Na], 30%).

6-Methyl-2-(4′-*tert*-butylphenoxy)nicotinic acid. To a solution of sodium (1.03 g, 44.6 mmol) dissolved in dry MeOH (25 ml) was added 2-chloro-6-methylnicotinic acid (3.62 g, 21.1 mmol) and 4-*tert*-butylphenol (15.17 g, 101.0 mmol) and the mixture stirred for 10 min. MeOH was removed *in vacuo* to afford a viscous orange oil which was heated for 2 h at 180 °C with stirring. After cooling, the cream coloured gum was treated with H_2O (200 cm^3) and washed successively with Et_2O (3 × 200 cm^3). The aqueous solution was acidified to pH 5 with acetic acid and the off white precipitate that formed collected by filtration and washed with H_2O. The crude product was recrystallised from CH_2Cl_2–hexane and dried ($MgSO_4$) to afford 6-methyl-2-4′-*tert*-butylphenoxynicotinic acid as a white powder (4.60 g, 16.1 mmol, 76%), m.p. 179–181 °C. Found: C, 71.28; H, 6.76; N, 4.96%. $C_{17}H_{19}NO_3$ requires: C, 71.56; H, 6.71; N, 4.91%. δ_H (300 MHz, $CDCl_3$), 1.38 (9H, s, $C(CH_3)_3$), 2.45 (3H, s, CH_3), 7.05 (1H, d, *J* 7.8, H^3), 7.14 (2H, d, *J* 8.8, $H^{2\prime}$), 7.46 (2H, d, *J* 8.8, $H^{3\prime}$), 8.43 (1H, d, *J* 7.8, H^4); δ_C ($CDCl_3$), 24.68 (CH_3), 31.68 ($C(CH_3)_3$), 34.79 ($C(CH_3)_3$), 110.25 (C^5), 119.64 (C^3), 121.20 ($C^{2\prime}$), 126.76 ($C^{3\prime}$), 143.79 (C^4), 148.92 ($C^{4\prime}$), 149.81 ($C^{1\prime}$), 160.46 (C^2), 163.46 (C^6), 164.84 (COOH); *m/z* ($ESMS^+$) 286 ([M + H], 25%), 308 ([M + Na], 100%); HRMS (ES^+), found: 308.1256 [M + Na]; $C_{17}H_{19}NO_3Na$ requires 308.1257.

2-Methyl-1-aza-7-*tert*-butylxanthone, 4. Polyphosphoric acid (80 g) was added to 6-methyl-2-4′-*tert*-butylphenoxynicotinic acid (1.91 g, 6.96 mmol) and the reaction heated at 120 °C for 20 h. The light brown mixture was poured whilst still hot onto crushed ice (300 g) and carefully basified to pH 12 by addition of KOH. The yellow precipitate was collected by filtration and the crude product recrystallised from CH_2Cl_2 and dried ($MgSO_4$). Removal of all solvents *in vacuo* afforded yellow crystals of the title product (1.57 g, 5.88 mmol, 88%), m.p. 117–119 °C. Found: C, 76.3; H, 6.38; N, 5.23%. $C_{17}H_{17}NO_2$ requires: C, 76.4; H, 6.41; N, 5.24%. δ_H (300 MHz, $CDCl_3$), 1.39 (9H, s, $C(CH_3)_3$), 2.70 (3H, s, CH_3), 7.28 (1H, d, *J* 7.9, H^3), 7.54 (1H, d, *J* 8.7, $H^{6\prime}$), 7.82 (1H, dd, *J* 8.7, $H^{5\prime}$), 8.28 (1H, d, *J* 2.4, $H^{3\prime}$), 8.59 (1H, d, *J* 7.9, H^4); δ_C ($CDCl_3$), 25.34 (CH_3), 31.57 ($C(CH_3)_3$), 35.06 ($C(CH_3)_3$), 114.47 (C^5), 118.34 (C^3), 121.23 ($C^{2\prime}$), 122.63 ($C^{6\prime}$), 133.62 ($C^{3\prime}$), 137.64 ($C^{5\prime}$), 148.10 (C^4), 154.03 ($C^{4\prime}$), 160.22 ($C^{1\prime}$), 165.15 (C^2), 165.15 (C^6), 178.00 (CO); *m/z* ($ESMS^+$) 290 ([M + Na], 35%), 557 ([2M + Na], 100%); HRMS (ES^+) 290.1152 [M + Na]; $C_{17}H_{17}NO_2Na$ requires: 290.1152.

2-(4-Methoxyphenoxy)-6-methylnicotinic acid. Sodium (1.44 g, 62.6 mmol) was dissolved in dry MeOH (27 cm^3), followed by the addition of 6-methyl-2-chloronicotinic acid (5.09 g, 29.6 mmol) and 4-methoxyphenol (17.50 g, 0.14 mol) under argon, forming a

yellow solution. The solvent was removed under reduced pressure, and the brown melt heated for 22 hours at 190 °C under argon with stirring. The melt was treated with water (200 cm^3) producing a pale yellow suspension, which was washed with diethyl ether (3 × 200 cm^3). The aqueous layer was acidified with acetic acid to pH 4, yielding a fine white precipitate upon cooling. This was collected by filtration, and dried thoroughly to yield the *title compound* as a pale yellow solid (3.51 g, 46%), m.p. 138–139 °C. Found: C, 64.8; H, 5.05; N, 5.48%. $C_{14}H_{13}NO_4$ requires C, 64.8; H, 5.06; N, 5.40%. δ_H ($CDCl_3$) 2.40 (3H, s, CH_3), 3.85 (3H, s, OCH_3), 6.95 (2H, dd, *J* 6.8, 2.2, $H^{3\prime}$), 7.02 (1H, d, *J* 7.8, H^5), 7.11 (2H, dd, *J* 6.8, 2.2, $H^{2\prime}$), 8.41 (1H, d, *J* 7.8, H^4); δ_C ($CDCl_3$, 125 MHz) 24.4 (CH_3), 55.6 (OCH_3), 109.7 (C^3), 114.6 ($C^{3\prime}$), 119.3 (C^5), 122.8 ($C^{2\prime}$), 143.6 (C^4), 145.1 ($C^{1\prime}$), 157.3 ($C^{4\prime}$), 160.4 (C^2), 163.2 (C^6), 164.3 (COOH); *m/z* ($ESMS^+$) 282.1 ([M + Na], 100%). HRMS (ES^+), found: 282.0734 [M + Na]; $C_{14}H_{13}NO_4Na$ requires 282.0737.

7-Methoxy-2-methyl-1-azaxanthone, 5a. 2-(4-Methoxyphenoxy)-6-methylnicotinic acid (2.00 g, 7.71 mmol) was dissolved in polyphosphoric acid (60 g) forming a yellow thick solution that was heated for 20 hours at 120 °C under argon resulting in a brown melt. After cooling, the melt was dissolved in cold concentrated sodium hydroxide solution (200 cm^3). The pH of the yellow solution was adjusted to 8 by further addition of concentrated NaOH solution, forming a fine yellow precipitate. The product was extracted into diethyl ether (3 × 100 cm^3), and the solvent removed under reduced pressure. The product was recrystallised using ethanol, and the solid that formed on standing was collected and dried to yield the *title compound* as pale yellow crystals (548 mg, 30%), m.p. 170–171 °C. Found: C, 69.5; H, 4.61; N, 5.85%. $C_{14}H_{11}NO_3$ requires C, 69.7; H, 4.60; N, 5.80%. δ_H ($CDCl_3$) 2.71 (3H, s, CH_3), 3.93 (3H, s, OCH_3), 7.30 (1H, d, *J* 8.0, H^3), 7.37 (1H, dd, *J* 9.2, 3.0, H^8), 7.55 (1H, d, *J* 9.2, H^9), 7.67 (1H, d, *J* 3.0, H^6), 8.60 (1H, d, *J* 8.0, H^4); δ_C ($CDCl_3$, 125 MHz) 25.1 (CH_3), 56.0 (OCH_3), 105.9 (C^6), 119.6 ($C^{4\prime}$), 119.9 (C^9), 121.0 (C^3), 122.0 ($C^{6\prime}$), 125.3 (C^8), 137.3 (C^4), 150.4 ($C^{9\prime}$), 156.5 (C^7), 159.8 ($C^{1\prime}$), 165.0 (C^2), 177.4 (C^5); *m/z* ($ESMS^+$) 242.1 ([M + H], 30%), 264.1 ([M + Na], 40%), 505.2 ([2M + Na], 100%), 746.1 ([3M + Na], 50%). HRMS (ES^+), found: 264.0632 [M + Na]; $C_{14}H_{11}NO_3Na$ requires 264.0631. The structure was confirmed by single crystal X-ray diffraction.‡

7-Methoxy-2-methyl-1-azaxanthone-*N*-oxide. 7-Methoxy-2-methyl-1-azaxanthone (55 mg, 0.23 mmol) was dissolved in TFA (0.4 ml) and H_2O_2 (0.1 ml, 30%) forming an orange solution which was refluxed at 125 °C under argon. Two further additions of TFA (0.4 ml) and H_2O_2 (0.1 ml, 30%) were made at two hour intervals, and the reaction mixture refluxed for 16 hours. After cooling the orange brown solution, the solvents were removed under reduced pressure yielding an orange brown solid. The crude product was dissolved in aqueous $NaHCO_3$ solution (10 cm^3), and washed with dichloromethane (2 × 10 cm^3), and the combined organics were then washed with aqueous NaCl (10 cm^3) and dried (Na_2SO_4). The resulting solution was filtered and the solvent removed under reduced pressure yielding an orange solid. The crude product was purified by column chromatography (silica, DCM → DCM–EtOH 97 : 3) yielding the *title compound* as a pale orange crystalline solid (40 mg, 68%), m.p. 220–222 °C. δ_H ($CDCl_3$) 2.72 (3H, s, CH_3), 3.91 (3H, s, OCH_3), 7.33 (1H, d, *J* 8.2, H^3), 7.41 (1H, dd, *J* 9.2, 3.2, H^8), 7.74 (1H, d, *J* 3.2, H^9), 7.74 (1H, d, *J* 9.2, H^6), 8.12 (1H, d, *J* 8.2, H^4); *m/z* ($ESMS^+$) 258 (M + H, 100%), 280 (M + Na, 65%). HRMS (ES^+), found: 258.0761 [M + H]; $C_{14}H_{12}NO_4$ requires 258.0761.

2-(2-Methoxyphenyl)-6-methylnicotinic acid. Sodium (1.44 g, 62.6 mmol) was dissolved in dry MeOH (27 cm^3), followed by the addition of 6-methyl-2-chloronicotinic acid (5.09 g, 29.6 mmol) and 2-methoxyphenol (15.50 cm^3, 0.14 mol) under argon, forming a dark green solution. The MeOH was removed under reduced pressure, and the dark green melt heated for 40 hours at 155 °C under argon with stirring. The melt was treated with water (200 cm^3) producing a pale yellow suspension, which was washed with diethyl ether (3 × 200 cm^3). The aqueous layer was then acidified with acetic acid to pH 4, yielding a fine white precipitate upon cooling. The product was extracted using ethyl acetate (3 × 200 cm^3) and the solvent removed under reduced pressure, through drying yielded the *title compound* as a pale yellow solid (4.52 g, 60%), m.p. 160–161 °C. Found: C, 64.7; H, 5.05; N, 5.36%. $C_{14}H_{13}NO_4$ requires C, 64.8; H, 5.06; N, 5.40%. δ_H ($CDCl_3$) 2.42 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 7.03 (1H, dd, *J* 8.0, 1.5, $H^{3\prime}$), 7.04 (1H, d, *J* 7.5, H^5), 7.06 (1H, td, *J* 8.0, 1.5, $H^{5\prime}$), 7.29 (1H, td, *J* 8.0, 1.5, $H^{4\prime}$), 7.45 (1H, dd, *J* 8.0, 1.5, $H^{6\prime}$), 8.41 (1H, d, *J* 7.5, H^4); δ_C ($CDCl_3$, 125 MHz) 24.7 (CH_3), 56.1 (OCH_3), 110.3 (C^3), 112.6 ($C^{3\prime}$), 119.8 (C^5), 121.0 ($C^{5\prime}$), 124.4 ($C^{6\prime}$), 127.1 ($C^{4\prime}$), 141.3 ($C^{1\prime}$), 143.8 (C^4), 151.4 ($C^{2\prime}$), 160.3 (C^2), 163.1 (C^6), 164.9 (COOH); *m/z* ($ESMS^-$) 214 ([M − COOH], 60%), 258 ([M − H], 100%). HRMS (ES^-), found: 258.0768 [M − H]; $C_{14}H_{12}NO_4$ requires 258.0772.

9-Methoxy-2-methyl-1-azaxanthone, 5b. 2-(2-Methoxyphenol)-6-methylnicotinic acid (2.50 g, 9.6 mmol) was dissolved in polyphosphoric acid (60 g) forming a yellow thick solution, and heated for 20 hours at 120 °C under argon resulting in a brown melt. Upon cooling, the melt was dissolved in cold concentrated sodium hydroxide solution (200 cm^3). The pH of the yellow solution was adjusted to 8 by the further addition of concentrated aqueous NaOH solution, forming a fine yellow precipitate. The product was extracted into diethyl ether (3 × 100 cm^3), dried (K_2CO_3), and the solvent removed under reduced pressure. The product was recrystallised using ethanol, and the solid that formed upon standing was collected and dried to yield the *title compound* as pale yellow crystals (480 mg, 21%), m.p. 183–185 °C. Found: C, 68.5; H, 4.59; N, 5.67. $C_{14}H_{11}NO_3.0.25H_2O$ requires C, 68.4; H, 4.73; N, 5.70%. δ_H ($CDCl_3$) 2.73 (3H, s, CH_3), 4.05 (3H, s, OCH_3), 7.29 (1H, dd, *J* 8.0, 1.5, H^8), 7.31 (1H, d, *J* 8.0, H^3), 7.35 (1H, t, *J* 8.0, H^7), 7.87 (1H, dd, *J* 8.0, 1.5, H^6), 8.60 (1H, d, *J* 8.0, H^4); δ_C ($CDCl_3$, 125 MHz) 25.4 (CH_3), 56.6 (OCH_3), 114.3 ($C^{4\prime}$), 116.3 (C^7), 117.5 (C^6), 121.6 (C^3), 122.9 ($C^{9\prime}$), 124.5 (C^8), 137.5 (C^4), 146.4 ($C^{6\prime}$), 149.3 (C^9), 160.1 ($C^{1\prime}$), 165.6 (C^2), 178.0 (C^5); *m/z* ($ESMS^+$) 242 ([M + H], 70%), 264 ([M + Na], 75%), 505 ([2M + Na], 100%), 746 ([3M + Na], 10%). HRMS (ES^+),

‡ C_{14} H_{11} N O_3, M_r = 241.24, Monoclinic ($P2_1/n$), a = 12.191(2) Å, b = 3.8876(8) Å, c = 22.922(4) Å, β = 90.223(6)°, Z = 4, μ = 0.105 mm^{-1} D_{calc} = 1.475 Mg m^{-3}, T = 120(2) K, 2132 independent reflections [R(int) = 0.1274], R_1 = 0.0620, wR_2 = 0.1416 [I > 2sigma(I)]. CCDC 296392. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b601357k

found: 242.0812 [M + H]; $C_{14}H_{12}NO_3$ requires 242.0812. The structure was confirmed by single crystal X-ray diffraction.§

2-[(3-(*N*-Acetyl-*N*-ethylamino)phenoxy]-6-methylnicotinic acid. 2-Chloro-6-methylnicotinic acid (2.88 g, 16.7 mmol) was added to a stirred solution of 3-(*N*-acetyl-*N*-ethylamino)phenol (3.0 g, 16.7 mmol) in NaOMe solution (2 M, 16.8 cm^3) and stirred for 5 minutes at room temperature under an argon atmosphere. The solvents were removed under reduced pressure and the residue dissolved in DMF (15 cm^3). K_2CO_3 (1.16 g, 8.4 mmol) and CuI (0.1 g, 0.5 mmol) were added to the mixture and the resulting suspension heated at 140 °C for 12 hours, monitoring the reaction using tlc. Upon completion, the reaction was cooled to room temperature and the solvents removed under reduced pressure. The residue was taken up in water (150 cm^3) and filtered. The aqueous solution was acidified with aqueous HCl (1 M) and the resulting precipitate collected *via* filtration and dried thoroughly. Recrystallisation from MeOH yielded the title compound as a colourless solid, (3.5 g, 64%), m.p. 159–60 °C.

δ_H 8.32 (d, 1H, *J* 7.8 Hz, H^4), 7.43 (t, 1H, $H^{5\prime}$), 7.16 (d, 1H, *J* 7.8 Hz, $H^{6\prime}$), 7.01 (d, 1H, *J* 8.1 Hz, $H^{4\prime}$), 7.00 (s, 1H, $H^{2\prime}$), 6.99 (d, 1H, *J* 7.8 Hz, H^5), 3.76 (q, 2H, *J* 7.1 Hz, CH_2), 2.37 (s, 3H, CH_3), 1.92 (s, 3H, $COCH_3$), 1.12 (t, 3H, *J* 7.1 Hz, CH_2CH_3).

δ_C 170.7 ($C{=}O_{(acid)}$), 167.4 ($C{=}O_{(amide)}$), 162.5 (C^6), 160.7 (C^2), 154.2 ($C^{1\prime}$), 143.3 (C^4), 130.5 ($C^{5\prime}$), 124.4 ($C^{4\prime}$), 122.3 ($C^{2\prime}$), 121.0 ($C^{6\prime}$), 118.9 (C^5), 111.4 (C^3), 44.0 (CH_2), 24.4 (CH_3), 22.8 ($CO\mathit{C}H_3$), 13.1 ($CH_2\mathit{C}H_3$). $ESMS^-$ (*m*/*z*) 313 ($[M - H]^-$, 100%). HRMS (ES^+) 337.1151; $C_{17}H_{18}N_2O_4Na$ requires 337.1159, [M + $Na]^+$). Found: C, 64.8; H, 5.76; N, 8.78%; $C_{17}H_{18}N_2O_4$ requires C, 64.9; H, 5.77; N, 8.91%.

***N*-Substituted-1-azaxanthones.** 2-[(3-(*N*-Acetyl-*N*-ethylamino)-phenoxy]-6-methylnicotinic acid (2.0 g, 6.4 mmol) was added to PPA (100 g) and heated at 120 °C under an argon atmosphere with stirring for 16 hours. The resulting viscous solution was poured onto ice (300 g) and stirred until a homogeneous solution formed. The solution was then basified to pH 12 using aqueous KOH (50%) and the yellow precipitate that formed upon cooling was isolated *via* filtration. The resulting brown solid consisted of a mixture of three major products which were separated by column chromatography (silica, $CHCl_3$ 1 to 5% MeOH) and recrystallised from the stated solvent.

6-Ethylamino-2-methyl-1-azaxanthone, 6. (130 mg, 0.5 mmol, 8%) recrystallised from MeOH, m.p. 142–144 °C.

δ_H 9.31 (br s, 1H, NH), 8.46 (d, 1H, *J* 7.9 Hz, H^4), 7.47 (t, 1H, H^8), 7.22 (d, 1H, *J* 7.9 Hz, H^3), 6.68 (d, 1H, *J* 8.8 Hz, H^7), 6.47 (d, 1H, *J* 8.5 Hz, H^9), 3.31 (q, 2H, *J* 7.2 Hz, CH_2), 2.67 (s, 3H, CH_3), 1.38 (t, 3H, *J* 7.2 Hz, $CH_2\mathit{C}H_3$). δ_C 180.1 (C^5), 164.2 (C^2), 159.5 ($C^{1\prime}$), 157.5 ($C^{9\prime}$), 151.9 (C^6), 136.61 (C^4), 136.57 (C^8), 120.7 (C^3), 114.6 ($C^{4\prime}$), 106.4 ($C^{6\prime}$), 104.5 (C^7), 102.7 (C^9), 37.8 (CH_2), 25.0 (CH_3), 14.4 ($CH_2\mathit{C}H_3$).

$ESMS^+$ (*m*/*z*) 255 ($[M + H]^+$, 50%), 277 ($[M + Na]^+$, 100%), 531 ($[2M + Na]^+$, 70%).

Found: C, 66.1; H, 5.77; N, 10.0%; $C_{15}H_{14}N_2O_2{\cdot}H_2O$ requires C, 66.2; H, 5.92; N, 10.3%. The structure was confirmed by single crystal X-ray diffraction.¶

8-*N*-Ethylamino-2-methyl-1-azaxanthone, 9. (410 mg, 1.6 mmol, 25%) recrystallised from toluene, m.p. 177–178 °C.

δ_H 8.54 (d, 1H, *J* 7.9 Hz, H^4), 8.06 (d, 1H, *J* 8.8 Hz, H^6), 7.23 (d, 1H, *J* 7.9 Hz, H^3), 6.59 (dd, 1H, *J* 8.8, 2.1 Hz, H^7), 6.54 (d, 1H, *J* 2.1 Hz, H^9), 3.28 (q, 2H, *J* 7.2 Hz, CH_2), 2.67 (s, 3H, CH_3), 1.33 (t, 3H, *J* 7.2 Hz, $CH_2\mathit{C}H_3$).

δ_C 176.0 (C^5), 163.5 (C^2), 160.1 ($C^{1\prime}$), 158.4 ($C^{9\prime}$), 154.4 (C^8), 137.1 (C^4), 128.1 (C^6), 120.7 (C^3), 114.7 ($C^{4\prime}$), 112.2 ($C^{6\prime}$), 112.0 (C^7), 96.9 (C^9), 38.1 (CH_2), 25.0 (CH_3), 14.5 ($CH_2\mathit{C}H_3$). $ESMS^+$ (*m*/*z*) 255 ($[M + H]^+$, 15%), 277 ($[M + Na]^+$, 40%), 532 ($[2M + Na]^+$, 100%). HRMS (ES^+) 277.0946; $C_{15}H_{14}N_2O_2Na$ requires 277.0945, $[M + Na]^+$. Found: C, 69.9; H, 5.80; N, 10.8%; $C_{15}H_{14}N_2O_2{\cdot}0.25H_2O$ requires C, 69.6; H, 5.65; N, 10.8%.

8-(*N*-Acetyl-*N*-ethylamino)-2-methyl-1-azaxanthone, 11. (490 mg, 1.7 mmol, 26%) recrystallised from EtOH, m.p. 180–182 °C.

δ_C 8.60 (d, 1H, *J* 7.9 Hz, H^4), 8.36 (d, 1H, *J* 8.4 Hz, H^6), 7.41 (d, 1H, *J* 2.0 Hz, H^9), 7.34 (d, 1H, *J* 7.9 Hz, H^3), 6.25 (dd, 1H, *J* 8.4, 2.0 Hz, H^7), 3.85 (q, 2H, *J* 7.1 Hz, CH_2), 2.73 (s, 3H, CH_3), 1.98 (s, 3H, $COCH_3$), 1.17 (t, 3H, *J* 7.1 Hz, $CH_2\mathit{C}H_3$).

δ_C 176.6 (C^5), 169.4 (NC=O), 165.5 (C^2), 160.0 ($C^{1\prime}$), 156.1 ($C^{9\prime}$), 149.2 (C^8), 137.4 (C^4), 128.3 (C^6), 124.5 (C^7), 121.7 (C^3), 120.8 ($C^{6\prime}$), 117.6 (C^9), 114.3 ($C^{4\prime}$), 44.4 (CH_2), 25.2 (CH_3), 23.0 ($CO\mathit{C}H_3$), 13.4 ($CH_2\mathit{C}H_3$). $ESMS^+$ (*m*/*z*) 297 ($[M + H]^+$, 30%), 319 ($[M + Na]^+$, 100%), 615 ($[2M + Na]^+$,70%). Found: C, 68.5; H, 5.38; N, 9.41%; $C_{17}H_{16}N_2O_3$ requires C, 68.9; H, 5.44; N, 9.45%.

6-(*N*-Acetyl-*N*-ethylamino)-2-methyl-1-azaxanthone, 8. Acetyl chloride (13.5 μL, 190 μmol) was added dropwise to a stirred solution of 6-ethylamino-2-methyl-1-azaxanthone (48 mg, 190 μmol) in ethyl acetate (10 cm^3) under an argon atmosphere. Following the addition, the reaction was stirred at room temperature for a further 4 hours during which time a yellow precipitate formed. The solvents were removed under reduced pressure to give a pale yellow solid. The solid residue was suspended in $CHCl_3$ (15 cm^3) and quickly washed with saturated $NaHCO_3$ solution (5 cm^3). The organic solvents were dried (K_2CO_3), filtered and evaporated under reduced pressure to give the title compound (55 mg, 98%) as a pale yellow solid, which was recrystallised from ethanol. m.p. 171–173 °C. Found: C, 68.7; H, 5.47; N, 9.44%; $C_{17}H_{16}N_2O_3$ requires C, 68.9; H, 5.44; N, 9.45%.

δ_H ($CDCl_3$) Major diastereoisomer (~80%) 8.53 (d, 1H, *J* 7.9 Hz, H^4), 7.80 (t, 1H, H^8), 7.67 (d, 1H, *J* 8.5 Hz, H^9), 7.31 (d, 1H, *J* 7.9 Hz, H^3), 7.20 (d, 1H, *J* 7.6 Hz, H^7), 4.31 (dq, 1H, *J* 13.9, 7.3 Hz, CH_2), 3.22 (dq, 1H, *J* 13.9, 7.3 Hz, CH_2), 2.71 (s, 3H, CH_3), 1.76 (s, 3H, $COCH_3$), 1.10 (t, 3H, *J* 7.3 Hz, $CH_2\mathit{C}H_3$)

δ_C ($CDCl_3$) Major diastereoisomer only 176.2 (C^5), 169.5 ($C{=}O_{(amide)}$), 165.4 (C^2), 159.0 ($C^{1\prime}$), 157.3 ($C^{9\prime}$), 142.3 (C^6), 137.6 (C^4), 135.0 (C^8), 127.0 (C^7), 121.6 (C^3), 119.4 (C^9), 118.2 ($C^{6\prime}$), 114.8

§ C_{14} H_{11} N O_3, M_r = 241.24, Monoclinic ($P2_1$), *a* = 3.8200(6) Å, *b* = 9.5681(16) Å, *c* = 14.756(2) Å, β = 93.579(4)°, *Z* = 2, μ = 0.106 mm^{-1} D_{calc} = 1.488 $Mg\,m^{-3}$, *T* = 120(2) K, 1380 independent reflections [*R*(int) = 0.027], R_1 = 0.0276, wR_2 = 0.0297 [*I* > 2sigma(*I*)] CCDC 296391. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b601357k

¶ C_{15} H_{14} N_2 O_2, M_r = 254.28, Monoclinic ($P2_1/c$), *a* = 4.5840(3) Å, *b* = 11.1889(7) Å, *c* = 24.2034(15) Å, β = 90.953(3)°, *Z* = 4, μ = 0.092 mm^{-1} D_{calc} = 1.361 Mg/m^3, *T* = 120(2) K, 2722 independent reflections [*R*(int) = 0.1251], R_1 = 0.0560, wR_2 = 0.1174 [*I* > 2sigma(*I*)]. CCDC 296393. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b601357k

($C^{4'}$), 43.8 (CH_2), 25.1 (CH_3), 22.7 ($CO\mathit{C}H_3$), 12.9 ($CH_2\mathit{C}H_3$). ESMS$^+$ (*m*/*z*) 297 ([M + H]$^+$, 30%), 319 ([M + Na]$^+$,100%), 615 ([2M + Na]$^+$, 70%). HRMS (ES$^+$) 319.1052; $C_{17}H_{16}N_2O_3Na$ requires 319.1053, [M + Na]$^+$.

2-(1-Azaxanthonylmethyl)-1,4,7-tris(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane. 1,4,7-Tris(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (0.127 g, 0.246 mmol) was combined with 2-bromomethyl-1-azaxanthone (70 mg, 0.243 mmol) and Cs_2CO_3 (83 mg, 0.255 mmol) and dry acetonitrile was added (5 cm^3). The reaction mixture was heated to reflux (85 °C) under argon with stirring for 16 hours and the reaction monitored by TLC to confirm that all the brominated starting material had been consumed. The solvent was removed under reduced pressure and DCM (50 cm^3) added and the solvent again removed under reduced pressure. The resulting solid was dissolved in a small volume of DCM (5 cm^3) and the solution filtered to remove any solid CsBr. The crude mixture purified by column chromatography on alumina (DCM–MeOH, 99.5 : 0.5) to yield the *title compound* as a pale-yellow crystalline solid (0.152 g, 0.21 mmol, 86%), m.p. >250 °C; R_f (SiO_2, DCM–MeOH, 95 : 5): 0.51; δ_H ($CDCl_3$) 1.46 (27H, s, t-Bu), 3.15 (16H, m br, cyclen ring), 3.45 (2H, s, acetate CH_2), 3.59 (4H, s, 2 × acetate CH_2's), 4.59 (2H, s, CH_2), 7.45 (1H, t, *J* 8, H^7), 7.53 (1H, d, *J* 8, H^3), 7.60 (1H, d, *J* 8, H^9), 7.77 (1H, t, *J* 8, H^8), 8.31 (1H, d, *J* 8, H^6), 8.67 (1H, d, *J* 8, H^4); *m*/*z* (ESMS$^+$) 746.4 ([M + Na], 100%), 724.4 ([M + H], 20%). HRMS (ES$^+$), found: 724.4279 [M + H]; $C_{39}H_{58}N_5O_8$ requires 724.4280.

2-(1-Azaxanthonylmethyl-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane, 17. A mixture of trifluoroacetic acid (1 cm^3) in DCM (0.5 cm^3) was added to 2-(1-azaxanthonylmethyl)-1,4,7-tris(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (0.107 g, 0.148 mmol) and the reaction mixture left under argon for 48 hours at room temperature. The solvents were removed under reduced pressure and a small volume of DCM (3 × 5 cm^3) was added and removed, again under reduced pressure to yield the *title compound* as a pale-orange crystalline solid (69 mg, 0.124 mmol, 84%), m.p. >250 °C; R_f (SiO_2, DCM–MeOH, 95 : 5): 0.50; δ_H (CD_3CN) 2.75–3.27 (16H, m br, cyclen ring), 3.36 (2H, s, acetate CH_2), 3.77 (4H, s, 2 × acetate CH_2's), 4.51 (2H, s, CH_2), 7.48 (1H, t, *J* 8, H^7), 7.51 (1H, d, *J* 8, H^3), 7.73 (1H, d, *J* 8, H^9), 7.87 (1H, t, *J* 8, H^8), 8.20 (1H, d, *J* 8, H^6), 8.58 (1H, d, *J* 8, H^4). *m*/*z* (ESMS$^+$) 556.2 (M + H, 100%), 578.2 (M + Na, 15%). HRMS (ES$^+$), found: 556.2398 [M + H]; $C_{27}H_{34}N_5O_8$ requires 556.2402.

[Tb.17]. 2-Methyl-1-azaxanthone-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane (40 mg, 71 μmol) was added to $TbCl_3.6H_2O$ (27 mg, 72 μmol) and the solids dissolved in a MeOH–H_2O mixture (1 : 1, 3 cm^3). The solution was then carefully adjusted to an apparent pH of approximately 5.5 by the addition of 10% aqueous NaOH and the reaction heated at 55 °C under argon for 16 hours. The reaction was followed by TLC (DCM–MeOH, 70 : 30) and upon completion the pale yellow solution was adjusted to an apparent pH of approximately 10 by the addition of aqueous $NaHCO_3$ solution and the resulting white precipitate removed *via* a fine syringe filter. The solvents were removed under reduced pressure and the residue purified by column chromatography on alumina (DCM–MeOH, 50 : 50) to yield the *title compound* as a white crystalline solid (10 mg, 14 μmol, 20%), m.p. >250 °C; δ_H (D_2O, 500 MHz, 298 K) multiple resonances from δ − 440 to +400 ppm, indicating the presence of 2 major paramagnetically shifted species, exchanging slowly on the ^{1}H NMR timescale; *m*/*z* (ESMS$^+$) 734.2 (M + Na, 100%); HRMS (ES$^+$), found: 734.1248 (M + Na), $C_{27}H_{30}N_5O_8TbNa$ requires 734.1241; λ_{abs} (H_2O): 336 nm; τ_{H_2O}: 1.82 ms; τ_{D_2O}: 2.73 ms; ϕ_{H_2O}: 0.24.

[Eu.17]. 2-(1-Azaxanthonylmethyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane (10 mg, 18 μmol) was added to $Eu(OAc)_3.3H_2O$ (5.9 mg, 18 μmol) and the solids dissolved in a MeOH–H_2O mixture (1 : 1, 3 cm^3). The solution was then carefully adjusted to an apparent pH of approximately 5.5 by the addition of 10% aqueous NaOH and the reaction heated at 55 °C under argon for 16 hours. The reaction was followed by TLC (DCM–MeOH, 70 : 30) and upon completion the pale yellow solution was adjusted to an apparent pH of approximately 10 by the addition of aqueous $NaHCO_3$ solution and the resulting white precipitate removed *via* a fine syringe filter. The solvents were removed from the clear colourless solution under reduced pressure to yield the *title compound* as a pale yellow crystalline solid (11 mg, 15.6 μmol, 87%), m.p. >250 °C; δ_H (D_2O, 500 MHz, 298 K) multiple resonances from δ − 24 to +40 ppm, indicating the presence of at least 2 diamagnetically shifted components, exchanging slowly with respect to the ^{1}H NMR timescale; *m*/*z* (ESMS$^+$) 726.1 ([M + Na], 100%); HRMS (ES$^+$), found: 726.1188 [M + Na], $C_{27}H_{30}N_5O_8EuNa$ requires 726.1185; λ_{abs} (H_2O): 336 nm; τ_{H_2O}: 0.57 ms; τ_{H_2O}: 2.02 ms; ϕ_{H_2O}: 0.069.

[Gd.17]. The Gd complex was prepared in an analogous manner to the Tb complex. m.p. >250 °C; *m*/*z* (ESMS$^+$) 733.0 (M + Na, 100%); HRMS (ES$^+$), found: 733.1228 [M + Na], $C_{27}H_{30}N_5O_8GdNa$ requires 733.1228; r_{1p} (H_2O, 310 K, 60 MHz) = 2.94 mM^{-1} s^{-1}.

7-Methoxycarbonyl-2-(1-azaxanthonylmethyl)-1,4,7-tris(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane. 1,4,7-Tris(*tert*-butoxycarbonyl-methyl)-1,4,7,10-tetraazacyclododecane (92 mg, 0.178 mmol) was combined with 7-methoxycarbonyl-2-bromomethyl-1-azaxanthone (62 mg, 0.178 mmol) and K_2CO_3 (0.025 g, 0.181 mmol) and dry acetonitrile (5 cm^3) was added. The reaction mixture was heated to reflux (80 °C) under argon with stirring for 16 hours and the reaction monitored by TLC to confirm that all the brominated starting material had been consumed. The solvent was removed under reduced pressure and DCM (50 cm^3) added and the solvent again removed under reduced pressure. The resulting solid was dissolved in a small volume of DCM (5 cm^3) and the solution filtered to remove any solid KBr. The crude mixture purified by column chromatography on silica gel (DCM–EtOH, 99 : 1) to yield the *title compound* as a 50 : 50 mixture of two distinct stereoisomers in the form of a pale-yellow foam (0.076 g, 0.097 mmol, 54%), m.p. >250 °C; R_f (Alumina, DCM–EtOH, 97 : 3): 0.40/0.60.

δ_H ($CDCl_3$, 300 MHz) 1.44 (27H, s, t-Bu), 3.16 (16H, m br, cyclen ring), 3.44 (2H, s, acetate CH_2), 3.58 (4H, s, 2 × acetate CH_2's), 3.97 (3H, s, OCH_3), 4.59 (2H, s, CH_2), 7.51 (1H, d, *J* 8, H^3), 7.68 (1H, d, *J* 8.5, H^9), 8.40 (1H, dd, *J* 8.5, H^8), 8.68 (1H, d, *J* 8, H^4), 8.98 (1H, s, H^6); *m*/*z* (ESMS$^+$) 804.8 ([M + Na], 100%), 782.2 ([M + H], 25%).

7-Carboxy-2-(1-azaxanthonylmethyl)-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane, 18. 7-Methoxycarbonyl-2-(1-azaxanthonylmethyl)-1,4,7-tris(*tert*-butoxycarbonylmethyl)-1,4,7,10-tetraazacyclododecane (60 mg, 77 μmol) was suspended in HCl (6 M, 4 cm^3) and the reaction mixture heated to reflux (100 °C) under argon with stirring for 16 hours. The acid was removed under reduced pressure to yield the *title compound* as a pale-yellow solid (46 mg, 77 μmol, 100%), m.p. >250 °C; δ_H (D_2O, 200 MHz) 3.16 (16H, m br, cyclen ring), 3.44 (2H, s, acetate CH_2), 3.58 (4H, s, 2 × acetate CH_2's), 4.59 (2H, s, CH_2), 7.49 (1H, d, *J* 8, H^3), 7.61 (1H, d, *J* 8.5, H^9), 8.15 (1H, dd, *J* 8.5, H^8), 8.36 (1H, s, H^6), 8.49 (1H, d, *J* 8, H^4); *m*/*z* (ESMS$^+$) 600.7 ([M + H], 100%).

[Tb.18]. 7-Carboxy-2-methyl-1-azaxanthone-1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane (42 mg, 70 μmol) was dissolved in H_2O (2 cm^3) and a solution of $TbCl_3.6H_2O$ (34 mg, 91 μmol) in H_2O (1 cm^3) added. The solution was then carefully adjusted to a pH of approximately 5.5 by the addition of 10% aqueous KOH solution and the reaction heated at 90 °C under argon for 16 hours. The reaction was followed by TLC (DCM–MeOH, 70 : 30) and upon completion the pale yellow solution was adjusted to a pH of approximately 10 by the addition of aqueous $NaHCO_3$ solution and the resulting white precipitate removed *via* a fine syringe filter. The solvents were removed from the clear colourless solution under reduced pressure to yield the *title compound* as a white crystalline solid (37 mg, 49 μmol, 70%), m.p. >250 °C; δ_H (D_2O, 500 MHz, 298 K) multiple resonances from δ −440 to +400 ppm, indicating the presence of 2 major paramagnetically shifted isomers, exchanging slowly on the ^1H NMR timescale; *m*/*z* (ESMS$^-$) 754.1 ([M − H], 100%); λ_{abs} (H_2O): 336 nm; τ_{H_2O}: 1.89 ms; τ_{H_2O}: 2.88 ms; ϕ_{H_2O}: 0.12.

2-(4′-Methyloxycarbonylphenylthio)-6-methylnicotinic acid. To a stirred solution of methyl-4-thiobenzoate (5 g, 29.7 mmol) and 2-chloro-6-methylnicotinic acid (4.25 g, 24.8 mmol) in DMF (28 ml) was added copper(I) bromide (220 mg, 1.53 mmol) and the resulting mixture was heated at 120 °C for 10 minutes. K_2CO_3 (5.21 g, 37.7 mmol) was added, followed by DMF (20 ml). The reaction mixture was heated to 150 °C overnight and then allowed to cool down. After being diluted by water (150 ml), the resulting solution was washed with ether (4 × 150 ml). The pH of the solution was adjusted to 4 by addition of acetic acid. The precipitated product was collected by filtration and dried under reduced pressure to yield the *title compound* as a pale yellow solid (4.8, 64%), m.p. 190–192 °C; (found C, 59.23; H, 4.25; N, 4.47. $C_{15}H_{13}NO_4S$ requires C, 59.39; H, 4.32; N, 4.62%); δ_H (DMSO, 500 MHz) 2.23 (3H, s, CH_3), 3.86 (3H, s, OCH_3), 7.11 (1H, d, *J* 7.8, H^5), 7.61 (2 H, d, *J* 8.1, $H^{2'}$, $H^{6'}$), 7.95 (2H, d, *J* 8.1, $H^{3'}$, $H^{5'}$), 8.13 (1H, d, *J* 7.8, H^4); δ_C (DMSO, 125 MHz) 24.7 (CH_3), 52.9 (OCH_3), 120.3 (C^5), 121.4 (C^3), 129.9 ($C^{4'}$), 129.9 ($C^{3'}$, $C^{5'}$), 135.5 ($C^{2'}$, $C^{6'}$), 138.4 ($C^{1'}$), 140.1 (C^4), 159.4 (C^2), 162.1 (C^6), 166.6 ($COOCH_3$), 167.7 (COOH); *m*/*z* (ESMS$^-$) 302 ([M − H]$^-$, 100%).

7-Methoxycarbonyl-2-methyl-1-azathioxanthone, 12a. A mixture of 2-(4′-methoxycarbonylphenylthio)-6-methylnicotinic acid (4 g, 13.2 mmol) and polyphosphoric acid (120 ml) was heated to 120 °C and vigorously stirred for 24 h. The reaction was allowed to cool down to room temperature and was diluted by dry methanol (300 ml). The reaction mixture was heated under reflux for a further 16 h. The majority of the methanol was removed under reduced pressure to give a sticky syrup, which was diluted by water to give 1000 ml of solution. The pH of the solution was adjusted to 8 by the addition of NaOH pellets and was extracted with $CHCl_3$ (3 × 300 ml). The solvent was removed under reduced pressure to yield the *title compound* as a pale greenish solid (3.25 g, 86%), sublimes 190–194 °C; (found C, 62.4; H, 3.71; N, 4.81. $C_{15}H_{11}NO_3S$ requires C, 63.4; H, 3.89; N, 4.91%); δ_H ($CDCl_3$) 2.69 (3H, s, CH_3), 3.99 (3H, s, OCH_3), 7.32 (1H, d, *J* 8.0, H^3), 7.70 (1H, d, *J* 8.5, H^9), 8.25 (1H, dd, *J* 8.5, 2.0, H^8), 8.58 (1H, d, *J* 8.0, H^4), 8.88 (1H, d, J 2.0, H^6); δ_C ($CDCl_3$, 125 MHz) 25.2 (CH_3), 52.7 (OCH_3), 122.7 (C^3), 124.4 ($C^{4'}$), 127.0 (C^9), 128.8 ($C^{6'}$), 129.0 (C^7), 131.7 (C^6), 132.8 (C^8), 138.1 (C^4), 142.6 ($C^{9'}$), 157.8 ($C^{1'}$), 164.3 (C^2), 166.2 ($COOCH_3$), 180.1 (C^5); *m*/*z* (ESMS$^+$) 286 ([M + H]$^+$, 30%), 308 ([M + Na]$^+$, 100%), 593 ([2M + Na]$^+$, 15%).

2-Bromomethyl-7-methoxycarbonyl-1-azathioxanthone, 12b. *N*-Bromosuccinimide (NBS) (175 mg, 0.98 mmol) and dibenzoyl peroxide (10 mg, 0.04 mmol) were added to a solution of 7-methoxycarbonyl-2-methylazathioxanthone (500 mg, 1.75 mmol) in CCl_4 (30 ml). The reaction mixture was heated under reflux for 2 h after which NBS (175 mg, 0.98 mmol) and dibenzoyl peroxide (10 mg, 0.04 mmol) were added again. The reaction mixture was heated under reflux for further 34 h. Further additions of dibenzoyl peroxide were made at 4 h (10 mg, 0.04 mmol), 6.5 h (10 mg, 0.04 mmol), 9.5 h (20 mg, 0.08 mmol), 24 h (10 mg, 0.04 mmol) and 29.5 h (10 mg, mmol) after the reaction start. Further additions of NBS (90 mg, 0.51 mmol) were made at 24 h and 29.5 h after the reaction start. The reaction mixture was allowed to cool down, filtered and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica (gradient elution: CH_2Cl_2–toluene 1 : 1 to 2% CH_3OH–49% CH_2Cl_2–49% toluene) to yield the *title compound* as a light yellow solid (90 mg, 25%), R_f 0.42 (silica, 2% MeOH: 49% toluene: 49% CH_2Cl_2), sublimes 186–190 °C; (found C, 49.2; H, 2.70; N, 3.84. $C_{15}H_{10}BrNO_3S$ requires C, 49.5; H, 2.77; N, 3.85%); δ_H ($CDCl_3$, 500 MHz) 4.00 (3H, s, CH_3), 4.61 (2H, s, CH_2), 7.61 (1H, d, *J* 8.5, H^3), 7.71 (1H, d, *J* 8.5, H^9), 8.28 (1H, dd, *J* 8.5, 1.5, H^8), 8.82 (1H, d, *J* 8.5, H^4), 9.20 (1H, d, *J* 1.5, H^6); δ_C ($CDCl_3$, 125 MHz) 32.4 (CH_2), 52.8 (CH_3), 122.3 (C^3), 125.8 ($C^{4'}$), 127.1 (C^9), 128.9 ($C^{6'}$), 129.2 (C^7), 131.8 (C^6), 133.2 (C^8), 139.3 (C^4), 142.3 ($C^{9'}$), 157.8 ($C^{1'}$), 161.5 (C^2), 166.1 ($COOCH_3$), 179.8 (C^5); *m*/*z* (ESMS$^+$) 364 ([M + H]$^+$, 20%), 386 ([M + Na]$^+$, 100%), 749 ([2M + Na]$^+$, 55%).

1-(7-Methoxycarbonyl-2-methyl-1-azathioxanthone)-4,7,10-tris-*tert*-butoxycarbonylmethyl-1,4,7,10-tetraazacyclododecane. A solution of 2-bromomethyl-7-methoxycarbonyl-1-azathioxanthone (90 mg, 0.25 mmol), 1,4,7-tris-*tert*-butoxycarbonylmethyl-1,4,7,10-tetraazacyclododecane (130 mg, 0.25 mmol) and Cs_2CO_3 (84 mg, 0.26 mmol) in acetonitrile (5 ml) was heated under reflux for 20 h. The solvent was removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (20 ml), filtered and the solvent was removed under reduced pressure again. The residue was dissolved in CH_2Cl_2 (20 ml), the suspension was filtered to remove the salts and the solvent was removed under reduced pressure. The residue was purified by chromatography on alumina (gradient elution: CH_2Cl_2 to 2% CH_3OH–CH_2Cl_2) to yield the *title compound* as a brown glass (60 mg, 30%), R_f 0.48 (alumina, 5% MeOH–CH_2Cl_2). δ_H ($CDCl_3$, 500 MHz) 1.32 (18 H, s, CH_3), 1.59 (9H, s, CH_3), 2.05–3.90 (24H, br m, CH_2 ring, CH_2CO, CH_2),

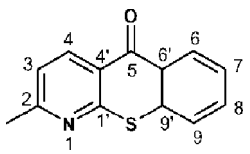
3.99 (3H, s, OCH_3), 7.44 (1H, d, *J* 8.5, H^9), 7.52 (1H, d, *J* 8.2, H^3), 8.26 (1H, dd, *J* 8.5, 1.5, H^8), 8.81 (1H, d, *J* 8.2, H^4), 9.21 (1H, d, H^6); δ_C ($CDCl_3$, 125 MHz) 21.6 (CH_2), 28.3 (CH_3), 52.9 (OCH_3), 49.5–58.2 (CH_2 ring, CH_2CO), 82.4 (C^{tbutyl}), 123.0 (C^3), 125.4 ($C^{4\prime}$), 126.3 (C^9), 128.8 ($C^{6\prime}$), 129.1 (C^7), 131.8 (C^6), 133.2 (C^8), 138.9 (C^4), 142.3 ($C^{9\prime}$), 158.4 ($C^{1\prime}$), 164.5 (C^2), 166.0 (COOMe), 173.2 (COO*t*Bu), 179.9 (C^5); *m/z* ($ESMS^+$) 798 ([M + H]$^+$, 20%), 820 ([M + Na]$^+$, 100%). Found: (ES^+) 820.3926 ($C_{41}H_{59}N_5O_9SNa$ requires 820.3926, [M + Na]$^+$).

[Tb.19]. A solution of 1-(7-methoxycarbonyl-2-methyl-1-azathioxanthone)-4,7,10-tris-*tert*-butoxycarbonylmethyl-1,4,7,10-tetraazacyclododecane (80 mg, 0.10 mmol) in TFA (3 ml) and CH_2Cl_2 (0.2 ml) was stirred at room temperature for 18 h. The solvents were removed under reduced pressure. The residue was repeatedly (3×) dissolved in CH_2Cl_2 and the solvent removed under reduced pressure. The residue was analysed by ^{1}H NMR spectroscopy. The residue was dissolved in water (8 ml) and MeOH (3 ml) and $TbCl_3.6H_2O$ (45 mg, 0.12 mmol) was added. The pH of the solution was adjusted to 5.5 by the addition of 1M KOH solution. The reaction mixture was stirred at 65 °C overnight. The pH dropped to 2.8 and was adjusted back to 5.5 and the mixture was stirred at 65 °C for a further 10 h. Methanol was removed under reduced pressure and the remaining solution was diluted with water (10 ml). The reaction mixture was filtered. Water was removed by freeze-drying and the residue was purified by HPLC to yield the *title compound* (15 mg, 13%). Found: (ES^-) 784.1078 ($C_{29}H_{31}N_5O_9STb$ requires: 784.1091, [M − H]$^-$). λ_{abs}(MeOH) 372 nm; ε(MeOH) 5360 M^{-1} cm^{-1}, $\tau_{Tb}(H_2O)$ 0.49 ms, $\tau_{Tb}(D_2O)$ 0.62ms; ϕ_{Tb} (H_2O) = 0.021.

[Eu.19]. A solution of 1-(7-methoxycarbonyl-2-methyl-1-azathioxanthone)-4,7,10-tris-*tert*-butoxycabonylmethyl-1,4,7,10-tetraazacyclododecane (60 mg, 0.076 mmol) in TFA (2 ml) and CH_2Cl_2 (0.1 ml) was stirred at room temperature for 18 h. The solvents were removed under reduced pressure. The residue was repeatedly (3×) dissolved in CH_2Cl_2 and the solvent removed under reduced pressure. The residue was analysed by ^{1}H NMR spectroscopy. The residue was dissolved in water (5 ml) and MeOH (2 ml) and $EuCl_3.6H_2O$ (30 mg, 0.082 mmol) was added. The pH of the solution was adjusted to 5.5 by the addition of 1M KOH solution. The reaction mixture was stirred at 65 °C overnight. The pH dropped to 3.5 and was adjusted back to 5.5 and the mixture was stirred at 65 °C for further 10 h. Methanol was removed under reduced pressure and the remaining solution was diluted with water (10 ml). The reaction mixture was filtered. Water was removed by freeze drying and the residue was purified by HPLC to yield the *title compound* (10 mg, 17%). Found: (ES^-) 778.10605 ($C_{29}H_{31}EuN_5O_9S$ requires 778.10604, [M − H]$^-$). λ_{abs}(MeOH) 372 nm; ε(MeOH) 5360 M^{-1} cm^{-1}, $\tau_{Eu}(H_2O)$ 0.51 ms, $\tau_{Eu}(D_2O)$ 1.62ms; ϕ_{Eu} (H_2O) = 0.022.

6-Methyl-2-thiophenoxynicotinic acid. 2-Chloro-6-methyl-nicotinic acid (5.00 g, 29.2 mmol) and thiophenol (3.80 g, 34.5 mmol), were dissolved in DMF (30 cm^3) with stirring, followed by CuBr (0.25 g, 17.5 mmol), and K_2CO_3 (6.00 g, 43.5 mmol). The reaction was heated for 15 minute at 130 °C followed by 18 hour at 150 °C generating a light yellow solution. The mixture was cooled down and treated with water (170 cm^3) to give a yellow suspension, which was washed with ether (3 × 80 cm^3). The aqueous solution was acidified with acetic acid yielding a very light yellow precipitate upon cooling, which was filtered, washed with water and dried thoroughly to yield the *title compound* as a pale yellow, crystalline solid (5.90 g, 83%), m.p. 170–2 °C. Found C, 63.7; H, 4.44; N, 5.60; S, 13.0% $C_{13}H_{11}NO_2S$ requires C, 63.7; H, 4.49; N, 5.73; S, 13.1%. δ_H ($CDCl_3$) 13.40 (1H, br s, –OH), 8.13 (1H, d, *J* 8 Hz, H^4), 7.42–7.52 (5H, m, $H^{2\prime-6\prime}$), 7.09 (1H, d, *J* 8 Hz, H^5), 2.23 (3H, s, CH_3); δ_c ($CDCl_3$) 24.8 (CH_3), 119.8 (C^5), 121.4 (C^4), 129.6 (C^3), 130.1 ($C^{3\prime,5\prime}$), 131.8 ($C^{1\prime}$), 136.1 ($C^{2\prime,6\prime}$), 139.9 ($C^{4\prime}$), 160.4 (C^2), 160.8 (C^6), 167.4 (COOH); *m/z* ($ESMS^+$) 246 [M + H], 268 [M + Na].

2-Methyl-1-azathioxanthone, 15a. Polyphosphoric acid (60 cm^3) was added to 6-methyl-2-thiophenoxynicotinic acid (5.50 g 22.4 mmol) and the mixture heated at 120 °C for 4 hours under argon with stirring. The resulting brown liquid was cooled to room temperature and then slowly poured onto cold concentrated aqueous sodium hydroxide solution (300 cm^3) with vigorous stirring. The light yellow precipitate that formed was collected *via* filtration. The product was recrystallised from warm EtOH. The crystals that formed upon standing were filtered and dried thoroughly to yield the *title compound* as a yellow crystalline solid (4.61 g, 90%) %), m.p. 145–7 °C. Found C, 68.4; H, 3.95; N, 6.17; S, 14.0%. $C_{13}H_9NOS$ requires C, 68.7; H, 3.89; N, 6.10; S, 14.0%. δ_H ($CDCl_3$) 8.73 (1H, d, *J* 8.2 Hz, H^4), 8.60 (1H, d, *J* 8 Hz, H^6), 7.65 (2H, m, $H^{8,9}$), 7.48 (1H, m, H^7), 7.31 (1H, d, *J* 8.2 Hz, H^3), 2.70 (3H, s, CH_3); δ_c ($CDCl_3$) 25.2 (CH_3), 121.7 (C^3), 124.8 (C^7), 127.3 (C^9), 127.5 (C^6), 129.6 ($C^{9\prime}$), 130.4 (C^4), 133.5 (C^8), 137.5 ($C^{6\prime}$), 138.5 ($C^{4\prime}$), 158.0 ($C^{1\prime}$), 162.1 (C^2), 181.0 (C^5); *m/z* ($ESMS^+$) 228 [M + H], 250 [M + Na], 477 [2M + Na]. The structure was confirmed by single crystal X-ray diffraction.*



2-(4′-Methylthiophenoxy)nicotinic acid. 2-Chloronicotinic acid (4.57 g, 29.2 mmol), 4-methylthiophenol (4.22 g, 34.5 mmol), were dissolved in DMF (30 cm^3) with stirring, followed by CuBr (0.25 g, 17.5 mmol), and K_2CO_3 (6.00 g, 43.5 mmol). The reaction was heated for 15 minutes at 130 °C followed by 18 hours at 150 °C to form a light yellow solution. The mixture was cooled and treated with water (170 cm^3) to give a yellow suspension, which was washed with ether (3 × 80 cm^3). The aqueous solution was acidified with acetic acid yielding a very light yellow precipitate upon cooling, which was filtered, washed with water and dried thoroughly to yield the *title compound* as a white crystalline solid (6.14 g, 87%), m.p. 190–192 °C. Found C, 63.5; H, 4.50; N, 5.64; S, 13.1 $C_{13}H_{11}NO_2S$ requires C, 63. 7; H, 4.49; N, 5.73; S, 13.1%. δ_H ($CDCl_3$) 13.60 (1H, br s, –OH), 8.41 (1H, d, *J* 7.5 Hz, H^6), 8.20 (1H, d, *J* 7.5 Hz, H^5), 7.38 (2H, m, $H^{3\prime,5\prime}$), 7.20 (3H, m, $H^{4,2\prime,6\prime}$), 2.31 (3H, s, CH_3); δ_c ($CDCl_3$) 20.2 (CH_3), 120.2 ($C^{4\prime}$), 123.2 (C^5),

* C_{13} H_9 N O S, M_r = 227.27, Monoclinic ($P2_1$), a = 3.8693(5) Å, b = 12.3848(16) Å, c = 10.4698(13) Å, β = 95.015(2)°, Z = 2, μ = 0.296 mm^{-1} D_{calc} = 1.510 Mg m^{-3}, T = 120(2) K, 2632 independent reflections [R(int) = 0.0551], R_1 = 0.0634, wR_2 = 0.1510 [I > 2sigma(I)]. CCDC 296394. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b601357k

127.7 (C^3), 130.5 ($C^{3',5'}$), 136.3 ($C^{2',6'}$), 139.6 ($C^{1'}$), 140.0 (C^4), 152.9 (C^6), 162.1 (C^2), 167.4 (COOH); *m/z* ($ESMS^+$) 246 [M + H], 268 [M + Na].

7-Methyl-1-azathioxanthone, 13. Polyphosphoric acid (60 cm^3) was added to 2-4′-methylthiophenoxy-nicotinic acid (5.50 g 22.4 mmol) and the mixture heated at 120 °C for 4 hours under argon with stirring. The resulting a brown liquid was cooled to room temperature and then slowly poured onto cold concentrated aqueous sodium hydroxide solution (300 cm^3) with vigorous stirring and the light green precipitate that formed was removed *via* filtration. The product was recrystallised from warm EtOH. The crystals that formed upon standing were filtered and dried thoroughly to yield the *title compound* as a yellow microcrystalline solid (4.32 g, 87%), m.p. 139–41 °C. Found C, 68.6; H, 4.07; N, 5.89; S, 13.9%; $C_{13}H_9NOS$ requires C, 68.7; H, 3.95; N, 6.17; S, 14.1%. δ_H ($CDCl_3$) 8.85 (1H, d, *J* 7.9 Hz, H^2), 8.72 (1H, d, *J* 7.9 Hz, H^4), 8.50 (1H, s, H^6), 7.78 (1H, d, *J* 8.2 Hz, H^9), 7.63 (2H, m, $H^{3,8}$), 3.29 (3H, s, CH_3); δ_c ($CDCl_3$) 22.9 (CH_3), 123.1 (C^3), 127.5 ($C^{9'}$), 128.2 (C^7), 129.5 ($C^{6'}$), 129.6 (C^9), 130.0 (C^8), 136.3 (C^6), 138.7 (C^4), 139.4 ($C^{4'}$), 156.9 ($C^{1'}$), 159.7 (C^2), 179.8 (C^5); *m/z* ($ESMS^+$) 228 [M + H], 250 [M + Na].

2-(2′-Methylthiophenoxy)nicotinic acid. This was prepared as described above for the *para* isomer to yield the *title compound* as a pale yellow, crystalline solid (6.02 g, 85%), m.p. 166–8 °C. Found C, 64.1; H, 4.29; N, 5.39; S,12.8%; $C_{13}H_{11}NO_2S$ requires: C, 63.7; H, 4.49; N, 5.73; S, 13.1%. δ_H ($CDCl_3$) 13.55 (1H, br s, –OH), 8.36 (1H, d, *J* 7.2 Hz, H^6), 8.22 (1H, d, *J* 7.2 Hz, H^5), 7.45 (1H, d, *J* 7.6 Hz, $H^{6'}$), 7.34 (2H, m, $H^{3',5'}$), 7.20 (2H, m, $H^{4,4'}$) 2.20 (3H, s, CH_3); δ_c ($CDCl_3$) 21.5 (CH_3), 120.3 ($C^{2'}$), 127.2 (C^5), 131.1 (C^3), 131.6 ($C^{4',5'}$), 137.0 ($C^{6'}$), 137.2 ($C^{3'}$), 143.2 ($C^{1'}$), 143.7 (C^4), 153.6 (C^6), 162.0 (C^2), 167.4 (COOH); *m/z* ($ESMS^+$) 246 [M + H], 268 [M + Na].

9-Methyl-1-azathioxanthone, 16. This was prepared as described for the isomer above yield the *title compound* as a light yellow crystalline solid (4.73 g, 95%), m.p. 135–7 °C. Found: C, 68.8; H, 3.97; N, 6.24; S, 13.9%; $C_{13}H_9NOS$ requires: C, 68.7; H, 3.95; N, 6.17; S, 14.1%. δ_H ($CDCl_3$) 8.92 (1H, dd, *J* 8, 1.8 Hz, H^2), 8.74 (1H, dd, *J* 8, 1.8 Hz, H^4), 8.34 (1H, dd, *J* 8, 2 Hz, H^6), 7.76 (1H, dd, *J* 8, 2 Hz, H^8), 7.67 (1H, t, *J* 8 Hz, H^3), 7.54 (1H, t, *J* 8 Hz, H^7), 2.52 (3H, s, CH_3); δ_c ($CDCl_3$) 20.1 (CH_3), 123.8 (C^3), 126.0 ($C^{4'}$), 127.3 (C^7), 127.8 (C^6), 129.1 ($C^{6'}$), 135.0 (C^8), 135.2 (C^9), 136.6 ($C^{9'}$), 138.1 (C^4), 157.2 (C^2), 158.9 ($C^{1'}$), 181.4 (C^5); *m/z* ($ESMS^+$) 228 [M + H], 250 [M + Na].

2-(3′-Methylthiophenoxy)nicotinic acid. This was prepared as described above for the *para* isomer yielding the *title compound* as a pale yellow crystalline solid (6.02 g, 85%), m.p. 160–2 °C. Found C, 63.9; H, 4.45; N, 5.26; S, 13.3%; $C_{13}H_{11}NO_2S$ requires C, 63.7; H, 4.49; N, 5.73; S, 13.1%. δ_H ($CDCl_3$) 13.60 (1H, br s, –OH), 8.41 (1H, d, *J* 7.9 Hz, H^6), 8.20 (1H, d, *J* 7.9 Hz, H^4), 7.28 (5H, m, $H^{5,2',3',4',6'}$) 2.23 (3H, s, CH_3); δ_c ($CDCl_3$) 21.7 (CH_3), 120.1 ($C^{5'}$), 122.0 (C^5), 129.7 ($C^{3'}$), 130.2 ($C^{3,4'}$), 134.0 ($C^{6'}$), 137.3 ($C^{2'}$), 138.7 ($C^{1'}$), 139.8 (C^4), 153.2 (C^6), 158.1 (C^2), 167.4 (COOH); *m/z* ($ESMS^+$) 246 [M + H], 268 [M + Na].

6-Methyl-1-azathioxanthone, 14 and 8-methyl-1-azathioxanthone, 15b. Polyphosphoric acid (60 cm^3) was added to 2-3′-methylthiophenoxy-nicotinic acid (5.50 g 22.4 mmol) and the mixture heated at 120 °C for 4 hours under argon with stirring. The resulting a brown liquid was cooled to room temperature and then slowly poured onto cold concentrated aqueous sodium hydroxide solution (300 cm^3) with vigorous stirring and the light grey precipitates that formed were removed *via* filtration. The product was washed with water and dried thoroughly to yield a 1 : 1 mixture (obtained from ^{1}H-NMR) of the *title compounds* as a light yellow powder. Products were separated by column chromatography (silica, toluene–CH_2Cl_2–EtOAc 45 : 45 : 10), Pure fractions were combined together and the solvents removed by reduced pressure. Products were recrystallised from warm EtOH, to yield the *given compound* as a light yellow crystalline solid.

6-Methyl-1-azathioxanthone, 14. Yield 0.41 g (8%) m.p. 184–186 °C. Found C, 69.1; H, 4.04; N, 6.02.; S, 13.8%; $C_{13}H_9NOS$ requires: C, 68.7; H, 3.95; N, 6.17; S, 14.1%. δ_H ($CDCl_3$) 8.81 (1H, dd, *J* 8 Hz, H^2), 8.79 (1H, d, *J* 8 Hz, H^4), 8.34 (1H, m, H^9), 7.42 (2H, m, $H^{2,7}$), 7.31 (2H, m, $H^{3,8}$), 2.23 (3H, s, CH_3); δ_c ($CDCl_3$) 22.3 (CH_3), 122.5 (C^3), 126.2 (C^8), 127.1 ($C^{4'}$), 128.7 (C^7), 129.8 (C^9), 138.8 ($C^{1'}$), 139.1 (C^2), 142.3 ($C^{6'}$), 152.7 (C^4), 159.2 ($C^{4'}$), 180.8 (C^5); *m/z* ($ESMS^+$) 228 [M + H], 250 [M + Na].

8-Methyl-1-azathioxanthone, 15b. Yield 0.56 g (11%) m.p. 126–128 °C. Found C, 68.7; H, 3.99; N, 5.81.; S, 14.1%; $C_{13}H_9NOS$ requires C, 68.7; H, 3.95; N, 6.17; S, 14.1%. δ_H ($CDCl_3$) 8.72 (1H, d, *J* 8 Hz, H^2), 8.66 (1H, d, *J* 8 Hz, H^4), 7.52 (1H, s, H^9), 7.50 (1H, d, *J* 7.9 Hz, H^6), 7.41 (1H, t, *J* 8 Hz, H^3), 7.30 (1H, d, *J* 7.9 Hz, H^7) 2.88 (3H, s, CH_3); δ_c ($CDCl_3$) 24.5 (CH_3), 121.8 (C^3), 125.5 (C^6), 128.3 ($C^{1'}$), 130.7 (C^7), 131.6 (C^9), 131.8 ($C^{9'}$), 138.3 (C^4), 138.8 ($C^{6'}$), 142.4 (C^8), 153.3 (C^2), 157.8 ($C^{4'}$) 182.1 (C^5); *m/z* ($ESMS^+$) 228 [M + H], 250 [M + Na].

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