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Solid-bound, proton-driven, fluorescent 'off–on–off' switches based on PET (photoinduced electron transfer)

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Dedicated to Fraser Stoddart

ABSTRACT

Anthracene-based, H^+-driven, 'off–on–off' fluorescent PET (photoinduced electron transfer) switches are immobilized on organic and inorganic polymeric solids in the form of Tentagel® and silica, respectively. The environment of the organic bead displaces apparent switching thresholds towards lower pH values whereas the $Si–O^-$ groups of silica electrostatically cause the opposite effect. These switches are ternary logic gate tags, one of which can be particularly useful in strengthening molecular computational identification (MCID) of small solid objects.

1. Introduction

Fluorescent versions of molecular switches[1] are particularly attractive because of their visibility and high sensitivity of detection with cheap instrumentation.[2] Importantly, predictive designs such as PET (photoinduced electron transfer)[3] are available for chemically-driven fluorescent switches. 'Off–on' and 'on–off' types are the simplest of these. Though the more complex 'off–on–off' behaviour can be discerned in the early literature,[4] it was recognized as such in 1996[5] and a robust design basis for it was proposed in terms of PET.[2,6] Several interesting extensions have been developed subsequently,[7] including Na^+-enabled,[7e] Ca^{2+}-enabled[7g] and Zn^{2+}-sharpened[7h] and H^+-driven versions. A novel self-assembled example has also been unveiled.[7i] Now we present solid-bound fluorescent 'off–on–off' switches for the first time.

Solid-bound, PET-based fluorescent switches are available[8] but those with more complex switching behaviour appear to be unknown, except for one recent case of two-input AND logic.[9] We recently showed how multi-valued logic[10] becomes useful for real-life application[9] of molecular computation,[11,12] in the field of (solid) object identification. Now we show that 'off–on–off' switches are interesting examples of multi-valued logic for potential use in this field where every new input–output logic pattern can give rise to a distinguishable tag for identification purposes. Indeed, each such gate can be combined pair-wise with others to create several more distinguishable tags.[9] The fact that computer engineers prefer solid-state systems[13] is another encouragement for us to transplant molecular logic from solution[11,12] for demonstration purposes.

2. Results and discussion

Fluorescent PET systems of the 'fluorophore–spacer–receptor' format have proved to be a straightforward way of designing sensors and switches.[2,3,6] This approach has the added strength of expandability, where additional modules can be co-opted to produce molecular systems of the 'receptor$_1$–spacer$_1$–fluorophore–spacer$_2$–receptor$_2$' and 'fluorophore–receptor$_1$–spacer$_1$–spacer$_2$–receptor$_2$' formats displaying binary logic[11] as well as 'off–on–off' switches.[5,7] While the latter is interesting as a direct sensor for a window of pH for instance, it is possible to view the 'off–on–off' behaviour as a multi-valued logic system (Table 1). The three levels of H^+ (low, medium and high) can be coded as digital states of 0, 1 and 2 for the input. As has been noted, ternary and higher levels of logic carry the weakness of sensitivity to error accumulation[14] and the strength of higher information density,[9] when compared with the far-better known binary version. Now we build a 'receptor$_1$–spacer$_1$–receptor$_2$–spacer$_2$–fluorophore–spacer$_3$–receptor$_3$–linker' system, which is attached via a peptide bond to Tentagel®[15] and silica[16] beads to produce **1** and **2**, respectively, which show excellent

Table 1
Multi-valued logic table for 'off–on–off' behaviour

Input (H^+)	Output (Fluor^n)
0 (low)	0 (low)
1 (medium)	1 (high)
2 (high)	0 (low)

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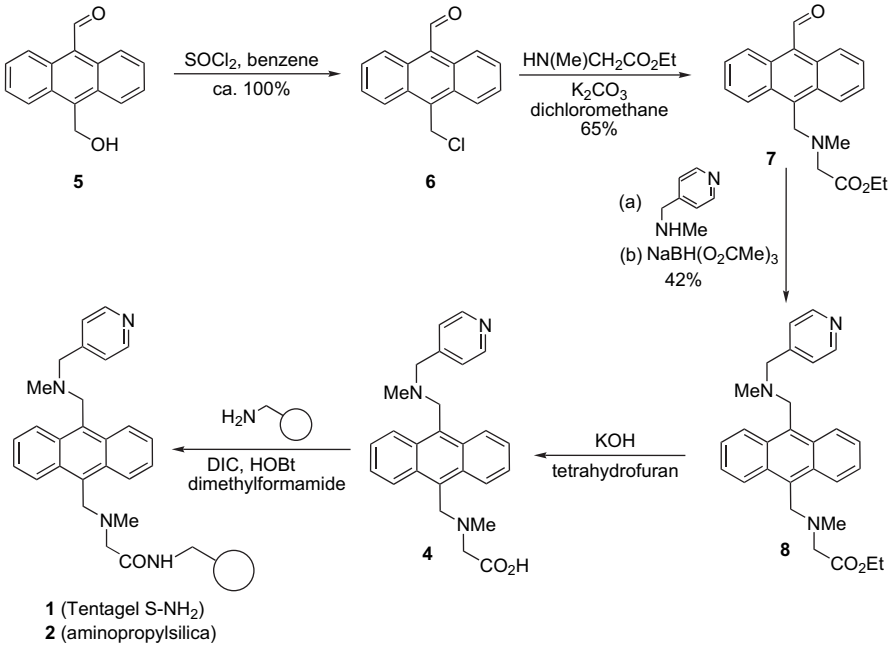
'off–on–off' behaviour. A simpler 'fluorophore–receptor$_1$–spacer$_1$–spacer$_2$–receptor$_2$' system linked to Tentagel® beads (**3**) also shows 'off–on–off' behaviour but in a less pronounced fashion.

For our current purpose, the essentials of a fluorescent 'off–on–off' system has a fluorophore such as anthracene, an amine receptor as a PET donor[17] and a pyridine receptor, which becomes a PET acceptor upon protonation.[18] Importantly, the protonated amine and the unprotonated pyridine are innocent bystanders as far as PET is concerned. Hence our aim is to synthesize **4**, which contains an extra amine group for synthetic convenience. Notably, **4** contains a carboxylic acid group for the peptide coupling step required for linking to the beads.

The synthesis of **1** and **2** begins with **5**,[19] which is converted into a benzylic chloride **6**. Nucleophilic attack of the amine group of sarcosine onto the chloro-substituted carbon in **6** produces **7**. This is converted into a Schiff base with 4-(*N*-methylaminomethyl)pyridine and reduced with NaBH(O$_2$CMe)$_3$[20] to produce **8**. Alkaline hydrolysis of the ethyl ester gives **4**, which is coupled with Tentagel S-NH$_2$® or aminopropylsilica using DIC and HOBt to give **1** or **2**, respectively.

Gratifyingly, the H$^+$-driven 'off–on–off' behaviour of **8** is carried over into its Tentagel®- and silica-bound versions, **1** and **2** (photographs in Fig. 1). Figure 2a,b and Table 2 provide more quantitative information on this phenomenon. It is noticeable that the pK_a values are depressed for **1** as compared to **8**. There are three reasons for this. (i) The anthracene fluorophore is very hydrophobic[24] and so it will self-regulate its position to occupy a similarly hydrophobic microenvironment[25] on the bead. The latter discourages electric charges, therefore the protonation of the amine receptors will be difficult hence lowering the pK_a. (ii) Each polymer bead contains multiple copies of the switch systems. As protonation of each receptor occurs, successive protonation will be more difficult as the density of electric charges is being built up. The low polarity of the bead environment means there will be strong repulsion between these positive charges. This makes full protonation of the fluorophore-appended receptors harder to achieve. (iii) When we note that only a 5% loading of switch systems has been grafted onto the beads, there are clearly many free amine groups on the bead, which are available for protonation. These are the groups, which are protonated initially due to their exposed



The UV–visible absorption spectrum of model ester **8** is affected slightly but significantly by H$^+$, as expected for anthracenemethylamine-based fluorescent PET switches.[21] This gives one observable pK_a value of 5.8, which corresponds to the amine (receptor$_2$) unit near the pyridine, given that literature values for 4-(dimethylaminomethyl)pyridine have an amine (corresponding to receptor$_2$) pK_a of 7.6 and a pyridine (corresponding to receptor$_1$) pK_a of 4.2[22] while *N*,*N*-dimethylglycine ethyl ester (corresponding to receptor$_3$) has a pK_a of 5.9.[23] In other words, the pK_a order tends to be: receptor$_2$>receptor$_3$>receptor$_1$.

The fluorescence of **8** in homogeneous solution shows typical H$^+$-driven 'off–on–off' behaviour with observable pK_a values of 4.1 and 1.5 (Table 1) for the 'off–on' and 'on–off' arms, corresponding to receptor$_3$ and receptor$_1$, respectively. It is expected from many previous studies[17,21] that the pK_a values determinable by fluorescence and by absorption for a given receptor within PET systems will be identical within experimental error. There is no perturbation of the emission wavelength or band shape during this process. The switching factors of both arms are very large, well over an order of magnitude.

nature compared to the amines attached to the fluorophore, as well as due to the electron withdrawing effect of the anthracene fluorophore. Thus a substantial positive charge density is built up on the bead surface before the protonation of fluorophore-appended receptors takes place. The latter process is therefore made more difficult, i.e., pK_a values are reduced.

On the other hand, the pK_a values are enhanced for **2** as compared to **8**. Of the three reasons discussed above, points (ii) and (iii) are as valid as ever. Point (i) is less applicable since the silica lattice is composed of significant dipoles. However, the dominant effect in the silica environment is due to the significant proportion of Si–O$^-$ groups at the surface.[26] These will concentrate protons locally and also electrostatically stabilize protonated amines of the switch molecules. Hence, the enhancement of the pK_a values can be understood. Similar explanations are available for dielectric and charge effects of detergent micelles on the pK_a values of amine-based sensors.[27]

We note the switching factors of both arms of the 'off–on–off' profile are very large for both **1** and **2**, showing that the bead environments are not retarding the PET rates at all. The relatively

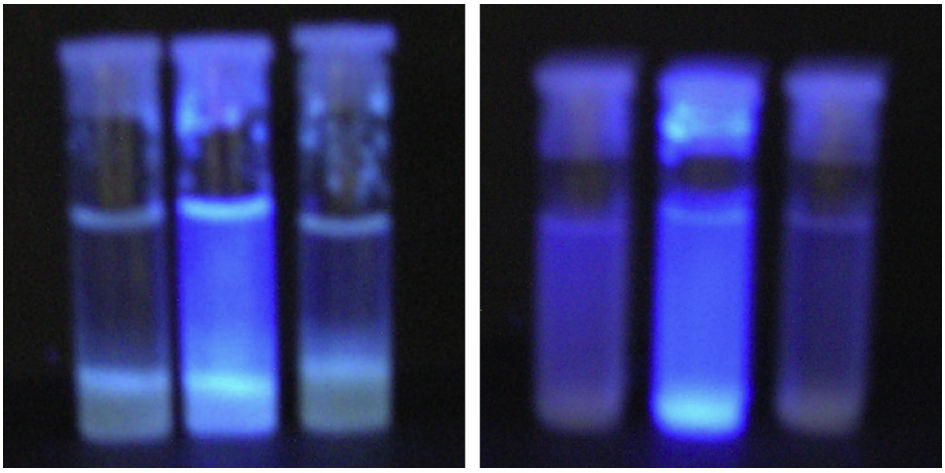


Figure 1. Photographs of **1** (Tentagel®; left photo) and **2** (silica; right photo) excited at 366 nm. The left, middle and right vials in each set are held at high (**1**: 7 and **2**: 8), medium (**1**: 2 and **2**: 4.5) and low (**1**: 0 and **2**: 1) pH values, respectively.

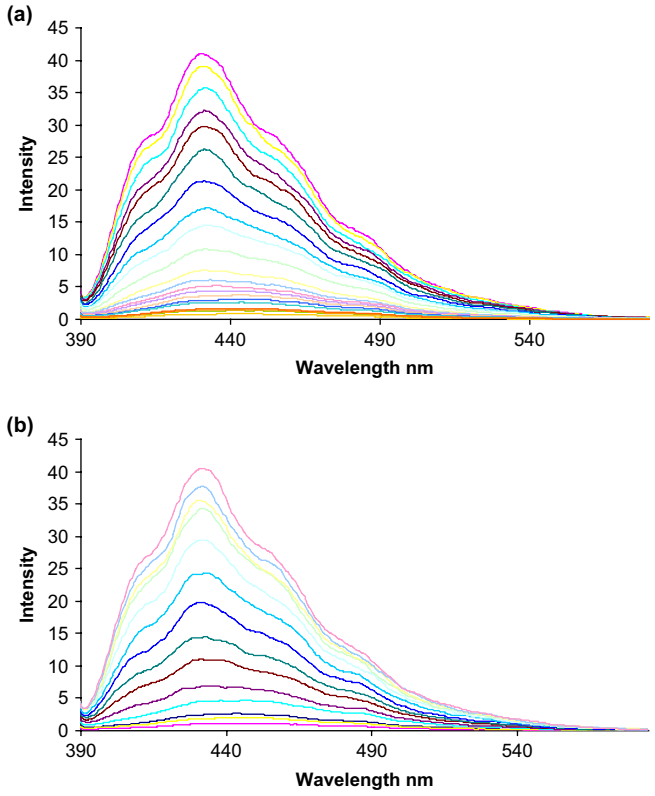
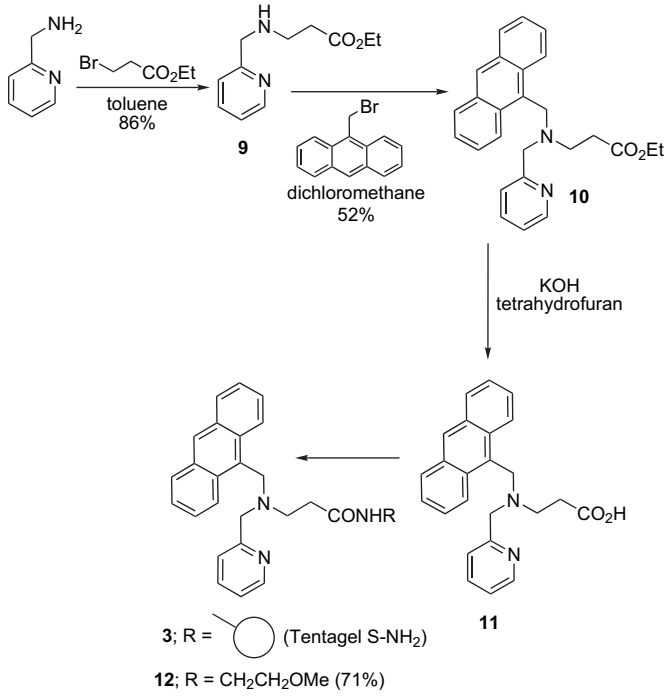


Figure 2. Fluorescence emission spectra of **1** as a function of pH. The excitation wavelength is 368 nm. pH values in order of increasing intensity at 431 nm: (a) 6.7, 6.2, 5.6, 5.4, 5.1, 4.9, 4.7, 4.5, 4.4, 4.2, 4.0, 3.8, 3.7, 3.5, 3.3, 3.2, 3.0, 2.8, 2.6, 2.5 and 2.3; (b) 0.1, 0.2, 0.4, 0.5, 0.6, 0.7, 0.9, 1.0, 1.2, 1.4, 1.5, 1.7, 1.8, and 2.0.

flexible structure of the switch molecule appears to permit good solvation in spite of the hydrophobic nature of the anthracene unit. The 4-substitution of the pyridyl unit also aids solvation (see later concerning **3**). Therefore **1** and **2** will be very suitable for use as MCID logic tags (Fig. 3).

While the 'receptor$_1$–spacer$_1$–receptor$_2$–spacer$_2$–fluorophore–spacer$_3$–receptor$_3$' system is clearly successful, there would be an elegance if a 'fluorophore–receptor$_1$–spacer$_1$–spacer$_2$–receptor$_2$' system could perform the same function. In other words, and more specifically, can a simpler switch structure (**3**) be as successful as **1**, for instance?

The synthesis of **3** is as follows. The first step is a nucleophilic attack of the amine group of 2-aminomethylpyridine onto the bromo-substituted carbon of 2-ethylbromopropionate to give **9**. This is then followed by a second nucleophilic attack of the amine **9** onto the bromo-substituted carbon of bromomethylanthracene. Products resulting from the attack of the pyridine are not seen. Alkaline hydrolysis of **10** results in **11**. Compound **11** is coupled with Tentagel S-NH$_2$® using DIC and HOBt to give **3**. A model compound **12** is then synthesized by reacting **11** with 2-methoxyethylamine, DCC and HOBt.



Again, small but significant H^+-induced changes are found in the UV–visible absorption spectrum[21] of model compound **12**. This gives one observable pK_a value of 6.5 for the amine group. The moderate fluorescence 'off–on–off' behaviour of **12** in homogeneous solution gives pK_a values of 6.3 and 2.8 for the 'off–on' and 'on–off' arms, corresponding to amine and pyridine units, respectively. Indeed, the switch factors for both arms are significantly smaller (by nearly a factor of 10) than in the case of **8**. The crowded nature of **8**'s functional groups and the subsequent repulsion of

Table 2
Photochemical and acidity parameters of fluorescent 'off–on–off' PET switches **1**, **2**, **8**, **3** and **12**

Compound		λ_{Ex}	λ_{Em}	Switch factor	pK_a	Gradient	R^2
1	'Off–on'	375	431	52	3.4	1.04	0.9957
	'On–off'	375	431	39	1.1	1.45	0.9940
2	'Off–on'	375	431	20	5.7	1.03	0.9936
	'On–off'	375	431	20	3.1	0.87	0.9919
8	'Off–on'	375	431	50	4.1	1.02	0.9885
	'On–off'	375	431	20	1.5	1.49	0.9983
3	'Off–on'	370	424	2.1	4.6	0.67	0.9895
	'On–off'	370	424	2.6	2.2	1.67	0.9880
12	'Off–on'	370	421	5.2	6.3	1.02	0.9870
	'On–off'	370	421	2.8	2.8	1.52	0.9887

In methanol–water (1:1; v/v). Model compounds **8** and **12** were used at 10^{-5} M. pK_a values were determined with the aid of equation:[17,21] $\log[(I_{F\,max}-I_F)/(I_F-I_{F\,min})]=\mathrm{pH}-\mathrm{p}K_a$, the linear gradient (the coefficient of pH) of which is ideally 1. The observed gradients for the 'off–on' arms mostly fit this. In the case of **3** the noticeably smaller gradient can be understood from the various environments the switches inhabit on the beads. The cases which are larger than unity are concerned with high acidities, where the glass pH electrode is less reliable.[31] Switch factor=$I_{F\,max}/I_{F\,min}$. R^2 is the parameter for the goodness of linear fit.

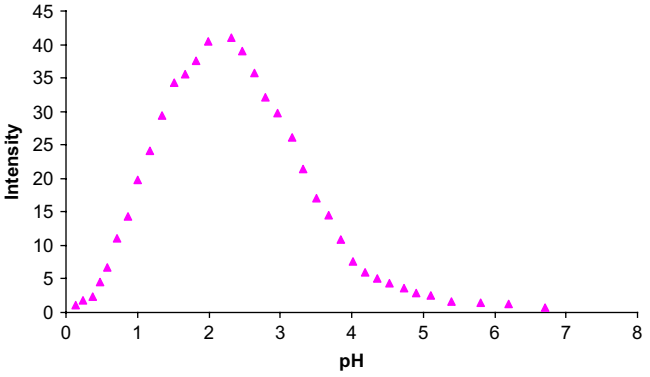


Figure 3. Fluorescence intensity (at 431 nm)–pH profile for **1**.

solvent molecules is probably the reason for the reduced rates of PET. PET rates within sensors and switches are known to be retarded in relatively apolar environments.[28–30]

Transplantation to the Tentagel® environment (**3**) displays further retarded PET rates leading to yet smaller switch factors. The pK_a values are decreased further as well (Table 2). So the more apolar environment of the organic polymer bead is taking its toll, as well as the effects of the population of the switch molecules among a larger population of more exposed amines on each bead. Furthermore, the amine group in **3** is surrounded by an anthracene unit, a 2-pyridyl group and the bead surface. In contrast, **1** and **2** possess methylamines, which are more easily solvated. Also, the 2-pyridyl group of **3** is in a congested zone and quite difficult to solvate. Again, the contrast of the 4-pyridyl group in **1** and **2** is telling. Therefore **3** is less clear-cut than **1** as an 'off–on–off' switch and thus less easy to use as a MCID logic tag. However, it must be pointed out that the MCID method can harness both large and small switching factors.[9]

3. Conclusions

We can conclude that H^+-driven, PET-based fluorescent 'off–on–off' switches can be transplanted onto Tentagel® and silica beads with some change in the characteristics but without loss of performance in favourable cases. These are ready for use in molecular computational identification (MCID) schemes.

4. Experimental section

4.1. General

^{1}H NMR spectra were recorded on a General Electric QE300 or GN-Ω 500 instrument. Mass spectra were recorded at 70 eV on an AEI-MS 902 spectrometer using a heated inlet system. Electrospray mass spectra were recorded using a VG Quattro II Triple Quadrupole Mass Spectrometer. IR spectra were recorded on a Perkin–Elmer 983G spectrometer. Electronic absorption spectra were recorded on a Perkin–Elmer Lambda 9 UV–vis–NIR spectrometer. Fluorescence emission spectra were recorded on Perkin–Elmer LS-5B luminescence spectrometer, with a fibre optic accessory being used for bead samples. Measurements of pH were determined using a Cranwell CR99 pH meter.

4.1.1. 10-(Chloromethyl)-9-anthraldehyde, ***6***

Compound **5**[19] (1.0 g, 4.2 mmol) was suspended into benzene (30 ml) with thionyl chloride (1 ml, 12.72 mmol) and heated at reflux for 2 h. The solvent was removed to leave a crude brown solid (1.07 g, yield: 100%), which was used without further purification. ^{1}H NMR ($CDCl_3$) 300 MHz δ 11.45 (s, C*H*O, 1H), 8.89 (d, Ant*H*, 2H, J=7.7 Hz), 8.42 (d, Ant*H*, 2H, J=9.8 Hz), 7.67 (m, Ant*H*, 4H), 5.60 (s, CH_2Cl, 2H).

4.1.2. [(10-Formyl-anthracen-9-ylmethyl)-methyl-amino]-acetic acid ethyl ester, ***7***

Compound **6** (0.50 g, 2.00 mmol) and sarcosine ethyl ester hydrochloride (0.60 g, 3.90 mmol) were refluxed overnight in dichloromethane (10 ml) in the presence of anhydrous potassium carbonate (5.00 g). The reaction mixture was cooled, potassium carbonate was filtered off and washed with dichloromethane. The filtrate was then concentrated to yield a brown residue, which was separated by column chromatography on silica using dichloromethane as the eluent. The brown oil obtained solidified upon standing (0.42 g, yield: 65%), mp=56 °C. Found: $C_{21}H_{21}NO_3$ C, 74.76; H, 6.02; N, 4.18. Required for: $C_{21}H_{21}NO_3$ C, 75.20; H, 6.31; N, 4.18. ^{1}H NMR ($CDCl_3$) 300 MHz δ 11.45 (s, C*H*O, 1H), 8.90 (d, Ant*H*, 2H, J=8.3 Hz), 8.75 (d, Ant*H*, 2H, J=6.4 Hz), 7.69–7.58 (m, Ant*H*, 4H), 4.78 (s, CH_2, 2H), 4.21 (q, N($CH_2CO_2CH_2CH_3$), 2H, J=7.2 Hz), 3.46 (s, CH_2, 2H), 2.56 (s, NCH_3, 3H), 1.26 (t, N($CH_2CO_2CH_2CH_3$), 3H, J=7.1 Hz). ^{13}C NMR ($CDCl_3$) 125 MHz δ 194.0, 171.2, 138.3, 134.1, 133.5, 131.2, 130.9, 130.1, 128.3, 127.2, 126.0, 125.7, 125.2, 124.2, 123.9, 60.5, 57.2, 53.4, 51.7, 41.8, 14.3. IR (ν_{max}) KBr 3437, 2980, 1728, 1673, 1200, 750 cm^{-1}. m/z (%) (EI) 336 (M^++H, 10), 335 (M^+, 44), 262 (32), 248 (15), 220 (27), 219 (100), 218 (13), 191 (90), 192 (19), 189 (76), 188 (15), 187 (10).

4.1.3. (Methyl-{10-[(methyl-pyridin-4-ylmethyl-amino)-methyl]-anthracen-9-ylmethyl}amino)-acetic acid ethyl ester, ***8***

Compound **7** (0.25 g, 0.75 mmol) and methyl-pyridin-4-ylmethylamine (0.09 g, 0.75 mmol) were charged to a round bottom flask. 1,2-Dichloroethane (3 ml) was added and the mixture treated with sodium triacetoxyborohydride[20] (0.24 g, 1.13 mmol). The reaction mixture was stirred at room temperature for two days under an N_2 (g) atmosphere. The reaction was quenched by addition of saturated sodium hydrogen carbonate solution (20 ml) and the aqueous layer was extracted with ethyl acetate (3×10 ml). The organic extracts were combined, dried over magnesium sulfate and the solvent removed. The residue was loaded onto flash silica and eluted with dichloromethane–ethyl acetate 80:20 v/v to yield a yellow brown solid (0.14 g, yield: 42%), mp=98 °C. Found: $C_{28}H_{31}N_3O_2$ 441.2404. Required for: $C_{28}H_{31}N_3O_2$ 441.2416. ^{1}H NMR ($CDCl_3$) 300 MHz δ 8.61 (m, Ant*H*, 4H), 8.47 (d, Ar*H*, 2H, J=5.1 Hz), 7.58 (m, Ant*H*, 4H), 7.19 (d, Ar*H*, 2H, J=5.4 Hz), 4.75 (s, CH_2, 2H), 4.60

(s, CH_2, 2H), 4.24 (q, N($CH_2CO_2CH_2CH_3$), 2H, J=7.2 Hz), 3.65 (s, CH_2, 2H), 3.44 (s, CH_2, 2H), 2.52 (s, CH_3, 3H), 2.32 (s, CH_3, 3H), 1.29 (t, N($CH_2CO_2CH_2CH_3$), 3H, J=7.1 Hz). ^{13}C NMR ($CDCl_3$) 125 MHz δ 171.8, 150.1, 150.0, 149.3, 131.6, 131.5, 131.1, 130.8, 126.0, 125.8, 125.7, 124.2, 60.8, 57.8, 54.6, 52.2, 42.8, 42.2, 31.3, 14.7. IR (ν_{max}) KBr 3436, 2978, 2840, 1737, 1191, 750 cm^{-1}. m/z (%) (EI) 442 (M^++H, 7), 441 (M^+, 16), 326 (56), 325 (90), 235 (10), 232 (23), 219 (38), 205 (44), 204 (70), 191 (100), 189 (41), 165 (15), 135 (68), 122 (49), 121 (17), 107 (12), 92 (30), 65 (15).

4.1.4. (Methyl-{10-[(methyl-pyridin-4-ylmethyl-amino)-methyl]-anthracen-9-ylmethyl}amino)-acetic acid, **4**

Compound **8** (0.14 g, 0.30 mmol) was dissolved in tetrahydrofuran (10 ml) to which potassium hydroxide (0.04 g, 0.60 mmol) dissolved in methanol (2 ml) and water (2 ml) was added. The solution was stirred at 60 °C for 4 h, after cooling and evaporation the residue was dissolved in water and precipitated out with drop-wise addition of acetic acid to yield a yellow solid.

4.1.5. Compound **4** grafted onto Tentagel S-$NH_2^®$ beads with 5% loading, **1**

To a 50 ml round bottom flask were added Tentagel S-$NH_2^®$ beads (0.5 g; 0.15 mm diameter, 0.9 mmol amine/g), **4** (0.0093 g, 0.023 mmol), HOBt (0.0345 g, 0.23 mmol), DIC (0.30 ml, 1.92 mmol) and dimethylformamide (20 ml). The reaction vessel was agitated for 3 h. The beads were washed sequentially with dimethylformamide (×2), dimethylformamide–methanol (×2) and methanol (×2).

4.1.6. Compound **4** grafted onto APS beads with 5% loading, **2**

Same procedure as for **1** but aminopropylsilica beads (0.5 g, 0.015 mm diameter, 0.9 mmol amine/g) were used instead of Tentagel S-$NH_2^®$ beads.

4.1.7. Ethyl 3-[(2′-pyridylmethyl)amino]propanoate, **9**

Ethyl-3-bromopropionate (0.56 g, 0.003 mol) was dissolved in toluene (30 ml). 2-Aminomethylpyridine (1.58 ml, 0.015 mol) was added and allowed to stir overnight. The solution was filtered and extracted with 0.1 M sodium hydrogen carbonate. The organic phase was dried over anhydrous sodium sulfate and the solvent removed yielding a clear oil (yield: 86%). ^{1}H NMR ($CDCl_3$) 300 MHz δ 8.57 (d, 1H, Ar–H, J=6 Hz), 7.62 (t, 1H, Ar–H, J=8 Hz), 7.31 (d, 1H, Ar–H, J=8 Hz), 7.13 (t, 1H, Ar–H, J=6 Hz), 4.12 (q, 2H, OCH_2CH_3, J=7 Hz), 3.92 (s, 2H, Ar–CH_2), 2.93 (t, 2H, NCH_2CH_2, J=6 Hz), 2.54 (t, 2H, NCH_2CH_2, J=7 Hz), 1.24 (t, 3H, OCH_2CH_3, J=7 Hz). ^{13}C NMR ($CDCl_3$) 75 MHz δ 14.3, 32.7, 45.0, 55.0, 60.0, 122.0, 128.0, 137.0, 149.0, 156.0, 172.0. IR (ν_{max}) KBr 3398, 2982, 1729, 1593, 1444, 1183, 763 cm^{-1}.

4.1.8. Ethyl 3-[(9′-anthrylmethyl)(2″-pyridylmethyl)amino]-propanoate, **10**

Compound **9** (0.26 g, 1.2 mmol), 9-bromomethylanthracene (0.34 g, 1.2 mmol) and anhydrous potassium carbonate (2 g) were refluxed overnight in dichloromethane (30 ml). The solution was allowed to cool, potassium salts were filtered off and the solvent was removed giving a yellow oil. After loading onto a column of flash silica the product, a yellow solid, was eluted with a ether–hexane mixture in the ratio 90:10 v/v (yield: 52%), mp 111 °C. ^{1}H NMR ($CDCl_3$) 300 MHz δ 8.46 (m, 4H, Ar–H), 7.97 (d, 2H, Ar–H, J=7 Hz), 7.50 (m, 5H, Ar–H), 7.24 (d, 1H, Ar–H, J=7 Hz), 7.06 (m, 1H, Ar–H), 4.63 (s, 2H, Ar–CH_2), 3.86 (q, 2H, OCH_2, J=7 Hz), 3.81 (s, 2H, Ar(py)–CH_2), 3.01 (t, 2H, NCH_2CH_2, J=7 Hz), 2.58 (t, 2H, NCH_2CH_2, J=7 Hz), 1.00 (t, 3H, OCH_2CH_3, J=7 Hz). ^{13}C NMR ($CDCl_3$) 75 MHz δ 14.4, 33.4, 50.9, 51.4, 60.2, 60.7, 122.2, 123.8, 125.2, 125.6, 125.7, 128.1, 129.4, 130.0, 131.7, 131.8, 136.5, 148.8, 160.4, 172.8. IR (ν_{max}) KBr 3437, 2921, 1732, 1589, 1320, 1181, 1027, 758, 733 cm^{-1}. m/z (%) (ES): 421 (M+Na^+, 20), 399 (M+H^+, 100).

4.1.9. 3-[(9′-Anthrylmethyl)(2″-pyridylmethyl)amino]propanoic acid, **11**

Compound **10** (0.55 g, 1.4 mmol) was dissolved in tetrahydrofuran (20 ml). Sodium hydroxide (0.55 g, 14 mmol) was dissolved in water–methanol (20 ml/4 ml) and added to the reaction mixture. The solution was stirred overnight at which point the solvent was evaporated off yielding a yellow solid. The solid was dissolved in water and the solution was neutralized using glacial acetic acid. The resulting yellow precipitate was filtered and washed with water (yield: 78%), mp 170 °C. ^{1}H NMR ($CDCl_3$) 300 MHz δ 8.47 (d, 1H, Ar–H, J=8 Hz), 8.39 (s, 1H, Ar–H), 8.19 (d, 2H, Ar–H, J=8 Hz), 7.96 (d, 2H, Ar–H, J=8 Hz), 7.48 (m, 5H, Ar–H), 7.14 (m, 1H, Ar–H), 6.88 (d, 1H, Ar–H, J=8 Hz), 4.77 (s, 2H, Ar–CH_2), 3.96 (s, 2H, –Ar(py)–CH_2), 3.09 (t, 2H, NCH_2CH_2, J=6 Hz), 2.55 (t, 2H, NCH_2CH_2, J=6 Hz). ^{13}C NMR ($CDCl_3$) 125 MHz δ 32.1, 50.3, 51.1, 58.3, 122.5, 123.4, 124.1, 125.0, 126.4, 127.0, 128.6, 129.2, 131.3, 131.4, 136.8, 14.7, 156.9, 173.7. IR (ν_{max}) KBr 3436, 1591, 1384, 1189, 776, 735, 602 cm^{-1}. m/z (%) (ES): 371 (M+H^+, 100), 339 (95).

4.1.10. N1-(2‴-methoxyethyl)-3-[(9′-anthrylmethyl)(2″-pyridylmethyl)amino] propanamide, **12**

Compound **11** (0.148 g, 0.4 mmol), DCC (0.099 g, 0.48 mmol) and HOBt (0.06 g, 0.15 mmol) were dissolved in dichloromethane at 0 °C. 2-Methoxyethylamine (0.032 ml, 0.36 mmol) was added at 0 °C and stirred for 1 h and then at room temperature overnight. The suspension was filtered and the filtrate evaporated. The resulting yellow oil was dissolved in ethyl acetate and washed with sodium hydrogen carbonate (×2) and saturated brine. The solvent was evaporated producing a yellow oil (yield: 71%). ^{1}H NMR ($CDCl_3$) 500 MHz δ 8.57 (d, 1H, Ar–H, J=5 Hz), 8.38 (s, 1H, Ar–H), 8.19 (d, 2H, Ar–H, J=9 Hz), 7.97 (d, 2H, Ar–H, J=10 Hz), 7.63 (m, 1H, Ar–H), 7.44 (m, 4H, Ar–H), 7.26 (d, 1H, Ar–H, J=8 Hz), 7.19 (m, 1H, Ar–H), 4.60 (s, 2H, Ar–CH_2), 3.93 (s, 2H, Ar(py)–CH_2), 3.23 (s, 3H, OCH_3), 3.02 (t, 2H, NCH_2CH_2C, J=6 Hz), 2.87 (t, 2H, NCH_2CH_2O, J=6 Hz), 2.84 (t, 2H, NCH_2CH_2O, J=6 Hz), 2.38 (t, 2H, NCH_2CH_2C, J=6 Hz). ^{13}C NMR ($CDCl_3$) 75 MHz δ 32.6, 34.9, 50.3, 51.0, 58.5, 60.4, 70.9, 121.9, 123.7, 124.4, 124.9, 126.1, 127.2, 128.0, 130.0, 132.2, 132.4, 137.0, 150.0, 159.0, 172.1. IR (ν_{max}) KBr 3421, 2930, 2117, 1653, 1558, 1448, 1122, 889, 734 cm^{-1}. m/z (%) (CI): 192 (5), 428 (M+H^+, 100), 429 (27).

4.1.11. Compound **11** grafted onto Tentagel S-$NH_2^®$ beads with 5% loading, **3**

Same procedure as for **1** but **11** was used instead of **4** in the same molar quantities.

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