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Appending zinc tetraphenylporphyrin with an amine receptor at β-pyrrolic carbon for designing a selective histamine chemosensor

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Adopting the rarely used β-functionalisation strategy in porphyrin-based sensor design, an amine receptive site is appended onto the zinc(II) porphyrin molecular framework affording a ditopic chemosensor **4**. The assembled chemosensor interacts selectively with histamine in toluene via a 'two-site' binding mode. Association constant of the complex evaluated from the respective UV–vis spectra is found to be $(2.32 \pm 0.57) \times 10^6$, which is approximately 4-fold greater than those complexes derived from **4** and nicotine/histidine. On the basis of a combined spectroscopic method and molecular modelling, the binding model of the porphyrin host and biogenic guest molecules is established. Our results clearly demonstrate the viability of the design and development of the porphyrin-based chemosensor by appending a receptor at the β-pyrrolic carbon of the porphyrin scaffold.

Keywords: zinc tetraphenylporphyrin; β-functionalisation; ditopic chemosensor; histamine sensing

1. Introduction

The construction of multi-functionalised molecular assemblies from well-defined building blocks has emerged as the research focusing area of supramolecular chemistry because of its great potential for medicinal applications and for the design of selective synthetic chemosensors targeting biologically relevant ions and molecules. Among all well-explored molecular scaffolds, porphyrins stand out elegantly as a judicious choice in this particular application (*1–3*). The covalent or non-covalent binding motifs bearing the porphyrin scaffold have gained importance in view of the crucial role of porphyrin assemblies in biological pigment systems. On the one hand, the multi-ligating sites present in the porphyrin scaffold offer an access to a variety of functionalisation possibilities. On the other hand, the intriguing photophysical properties associated with porphyrins warrant their exploitations in both colorimetric and fluorometric sensing. As a result, we have witnessed in recent years that numerous designs of porphyrin-based chemosensors have been known for the detection of cations, anions and biologically relevant small organic molecules. For instance, we reported the development of 5,10,15,20-tetraphenylporphyrin (TPP) as a mercury ion-selective optical sensor (*4*), while Yu and co-workers (*5*) exploited porphyrin-appended terpyridine as a chemosensor for cadmium. Operating on a metal ion-controlled photo-induced electron transfer mechanism in a zinc porphyrin–quinone dyad, an extremely exquisite design of a yttrium ion-selective fluorescence sensor was reported by Okamoto et al. (*6*). Metallo-porphyrins in cooperative with the H-bond donors incorporated into their *meso*-phenyl moieties create a well-defined cavity for binding anions (*7–9*). A clear division of labour exerted by a Zn-porphyrin–crown ether conjugate to interact intramolecularly with anions and cations, respectively, developed by Kim and Hong (*10*), was employed for visible sensing of sodium cyanide. Exploiting the principle of molecular recognition and manipulating the unique photophysical properties of porphyrins, D'Souza (*11*, *12*) developed a porphyrin-based chemosensor for hydroquinone and nicotine, respectively. Using an optode membrane protocol, based on fluorescence enhancement of a *meso–meso*-linked porphyrin dimer, determination of histidine in simulated serum samples was accomplished (*13*). Operating on a different sensing mechanism, selective detection of histidine in human serum samples by a zinc porphyrin conjugate with an appended pyrene was realised (*14*). Molecular recognition of carbohydrates by urea-appended porphyrins characterised by convergent multiple H-bonding sites was demonstrated by Kim and Hong (*15*). To expedite the synthesis, all the above-mentioned porphyrin-based sensory materials were assembled invariantly with four phenyl moieties incorporated into

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the C-5,10,15,20 of the host. Discriminative introduction of different phenyl moieties onto the *meso*-positions of a porphyrin structure framework not only suffers from its poor efficiency but also requires extensive purification efforts to fish out the desired precursor for the subsequent sensor assemble. In contrast, direct preparation of symmetrical tetra-*meso*-arylated porphyrins is a simple synthetic preparation; however, the resultant host may contain too many functionalities which could distract the subsequent sensor design. A seemingly neglected alternative approach by selective functionalisation warrants attention in the arena of sensor development. As demonstrated by us and others, symmetrical TPP can be functionalised at the β-pyrrolic carbon of the porphyrin with high selectivity and diverse variants (*16–18*). In this context, we have recently reported a novel dicarboxylate receptor based on a β-pyrrolic functionalisation strategy (*19*). To our knowledge, there is scarce literature known on porphyrin-based chemosensor development involving the appendage of receptive sites at its β-pyrrolic carbons. In response to this challenge, utilising a metal centre of the zinc porphyrin host as the first binding site, in this report, we describe the design and construction of a ditopic porphyrin-based chemosensor by appending the second binding site via the β-pyrrolic functionalisation strategy (Figure 1). In contrast to the traditional 'differential' *meso*-functionalisation approach, not only the involved preparative effort is considerably expedited, but also the viability of varying the second binding site of the chemosensor inherent with the new approach is substantially widened.

To illustrate the invoked strategy, biologically relevant histamine was chosen as the bifunctional target molecule for optimising the complementary structural characteristics of the ditopic porphyrin-based chemosensor. Arguably, histamine is one of the most prominent biogenic amines in clinical and food chemistry (*20*). Furthermore, histamine acts as a neurohormone responsible for inducing

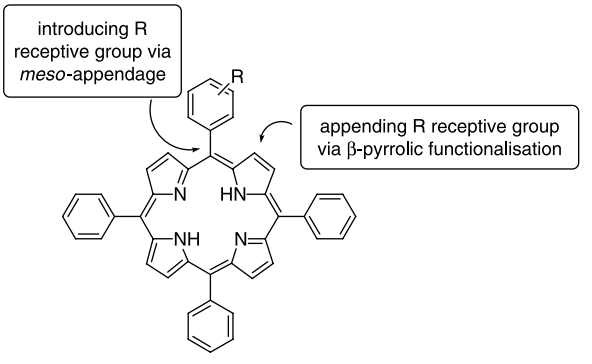


Figure 1. *Meso*-appendage vs. β-pyrrolic functionalisation strategy to assemble the porphyrin framework for the chemosensor design.

a variety of allergic reactions (*21*). The normal physiological concentration of histamine in human blood is 0.1–1 μM (*22*). Abnormal histamine concentration manifests itself via dysfunctional symptoms (such as gastric disorder, mastocytosis and chronic myelogenous leukaemia) (*23*). Chemosensing, characterised by its high selectivity and sensitivity and operative without the use of any instrument, is a promising avenue for the histamine assay. In this regard, Bao et al. (*24*) developed an engineered methylamine dehydrogenase-based biosensor for selective and sensitive detection of histamine. A molecular imprinting-based fluorescent histamine chemosensor using zinc(II) protoporphyrin as a functional monomer was fabricated to achieve the detection of histamine at 0.1–1 mM (*25*). In this study, we seek to exploit the β-pyrrolic functionalisation strategy to construct a ditopic chemosensor for binding histamine. The supramolecular binding interaction between the host and the guest is firmly established by a combined spectroscopic method and computational analysis. The distinct feature of such chemosensor design may open up an avenue to complement the current development of supramolecular porphyrin chemistry.

2. Experimental

2.1 Ethyl 2-(5-methyl-2-phenoxymethylcarboxylate)-5,10,15,20-tetraphenylporphyrin (3)

Compound **2** (300 mg) was first dissolved in $CHCl_3$ (30 ml) and demetallised by concentrated H_2SO_4 (98%, 1 ml) at room temperature for 10 min, and then was neutralised with sodium bicarbonate solution. The free porphyrin was extracted by $CHCl_3$ (3× 30 ml), dried with anhydrous magnesium sulphate and evaporated to dryness. The crude porphyrin was refluxed with ethyl 2-bromoacetate (75 mg) and excess K_2CO_3 in THF for 5 h. The reaction mixture was filtered and evaporated under vacuum, and the residue was purified by column chromatography over silica gel, using $CHCl_3$–petroleum ether (10:1) as the eluent. The pure product was recrystallised from $CHCl_3$–CH_3OH to afford compound **3** (134 mg, 40%) as a purple solid (m.p. 118–9°C). ^{1}H NMR (400 MHz; $CDCl_3$): δ 2.64 (2H, br s, inner NH), 0.77–0.80 (3H, t, $J = 7.2$ Hz, CH_3), 2.25 (3H, s, CH_3), 3.83–3.92 (2H, ABq, $J_{AB} = 3.6$ Hz, CH_2), 4.29 (2H, s, CH_2), 6.40–6.43 (1H, d, $J = 8.4$ Hz, 3′-H), 6.87–6.88 (1H, d, $J = 8.4$ Hz, 4′-H), 7.10–7.11 (1H, d, $J = 1.6$ Hz, 6′-H), 7.19–7.28 (3H, m, 20-$H_{m,p}$), 7.69–7.77 (9H, m, 5-, 10- and 15-$H_{m,p}$), 7.80–7.82 (1H, d, $J = 6.4$ Hz, 20-H_o), 8.04 (1H, s, 20-H_o), 8.21–8.29 (6H, m, 5-, 10- and 15-H_o), 8.63–8.64 (1H, d, $J = 4.8$ Hz, 13-H), 8.71–8.73 (1H, d, $J = 4.8$ Hz, 12-H), 8.80 (1H, s, 3-H), 8.80 and 8.82 (2H, ABq, $J_{AB} = 3.2$, 7- and 8-H), 8.83 (2H, ABq, $J_{AB} = 2.4$, 17- and 18-H). HR-MS (ESI) calcd for $C_{55}H_{41}N_4O_3$ $(M+1)^+$ requires 807.3329, found 807.3332.

2.2 [2-(5-Methyl-2-phenoxymethylcarboxy)-5,10,15,20-tetraphenylporphyrinato]Zn(II) (4)

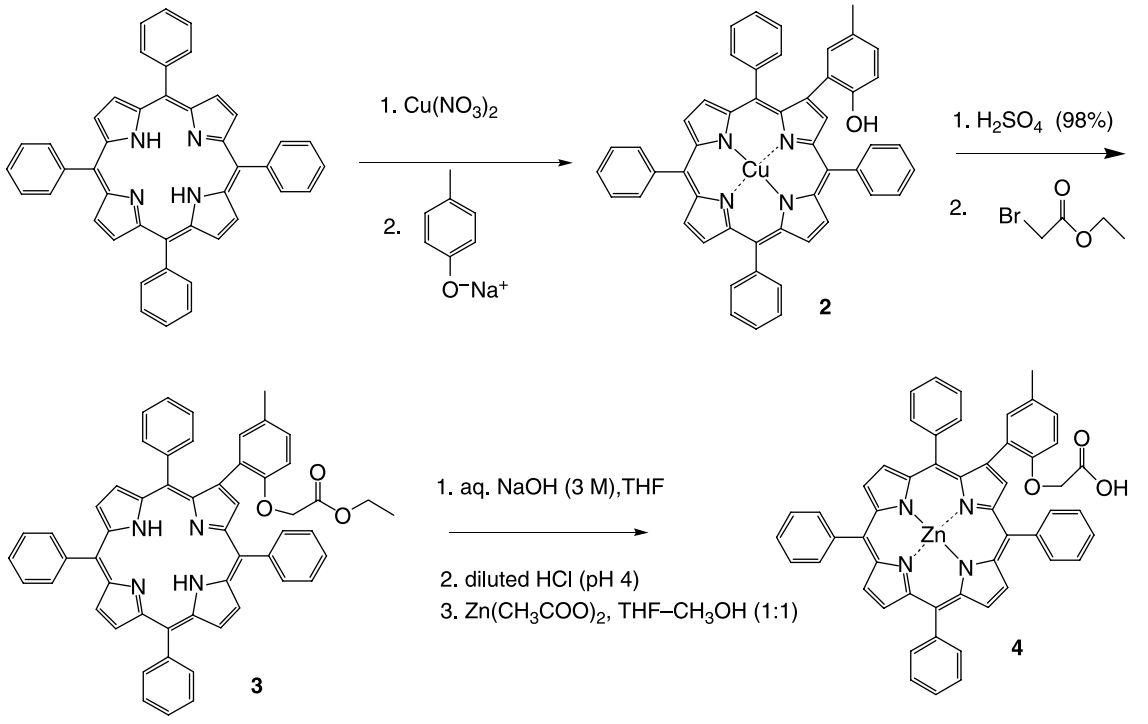
Compound **3** (100 mg) in THF (25 ml) was stirred and refluxed with aqueous NaOH solution (3 M, 10 ml) for 5 h. The reaction mixture was extracted with $CHCl_3$ (3× 20 ml). The combined organic layers were washed with saturated brine solution and distilled water successively, and then dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure, and the residue was then subjected to column chromatography over silica gel, using $CHCl_3$–CH_3OH (100:2) as the eluent. The organic solution of the desired fractions was combined, condensed and the pH adjusted to 4 by diluted HCl solution. The organic layer was collected, dried and evaporated to dryness to afford the free porphyrin as a solid. The solid was dissolved in THF–CH_3OH (1:1) and refluxed with excess $Zn(CH_3COO)_2{\cdot}2H_2O$ for 1 h. The mixture was washed with distilled water, and then dried over $MgSO_4$. After filtration, the solvent was removed under reduced pressure, and the residue was then recrystallised from $CHCl_3$–hexane to afford compound **4** (83.5 mg, 80%) as a purple solid (m.p. 232–3°C). ^{1}H NMR (400 MHz; $CDCl_3$): δ 2.28 (3H, s, CH_3), 4.01 (2H, br s, CH_2), 6.23 (1H, br s, 3′-H), 6.83 (2H, br s, 4′- and 6′-H), 7.17 (3H, br s, 20-$H_{m,p}$), 7.68 (9H, m, 5-, 10- and 15-$H_{m,p}$), 7.74 (2H, m, 20-H_o), 8.14–8.21 (6H, m, 5-, 10- and 15-H_o), 8.62 (1H, br s, 13-H), 8.78 (1H, br s, 12-H), 8.92 (5H, m, 3-, 7-, 8-, 17- and 18-H), COOH signal was not observed; HR-MS (ESI) calcd for $C_{53}H_{37}N_4O_3Zn$ $(M+1)^+$ requires 841.2135, found 841.2157.

3. Results and discussion

3.1 Porphyrin receptor synthesis

The readily accessible TPP was chosen as the starting material for building up ditopic chemosensor **4** (i.e. ZnTPP-β-phenoxyacetic acid; Scheme 1). Employing the synthetic protocol developed by us, the β-pyrrolic-functionalised 2-substituted cresol Cu porphyrin **2** was obtained in about 50% overall yield from TPP (*16*). Demetallation of **2** by treatment with concentrated sulphuric acid followed by alkylating the appended phenol with ethyl bromoacetate and potassium carbonate gave rise to the corresponding ethyl ester **3** in 40% yield. Liberation of the free carboxylic acid as a potential H-bonding site was achieved by base hydrolysis and subsequent careful acidification with dilute hydrochloric acid. Insertion of zinc metal to confer the host with the axial ligating site was achieved by refluxing the metal-free β-substituted porphyrin with zinc acetate in 1:1 methanol–THF for 1 h, affording ditopic chemosensor **4** in 80% overall yield.

In the prevalent porphyrin-based chemosensor design, sensing is often accomplished by utilising metal axial coordination and suitable receptors at the ring periphery via *meso*-appendage. In the present study, we have successfully designed a porphyrin-based optical chemosensor for



Scheme 1. Synthetic route for chemosensor **4**.

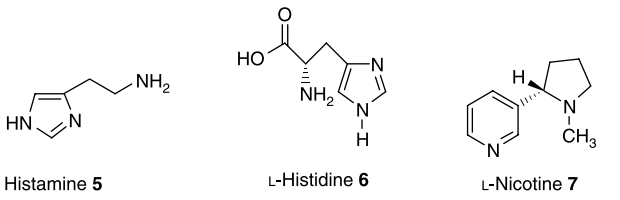


Figure 2. The structure of potential diamine guests of chemosensor **4**.

selective detection of histamine and related compounds in toluene solution. The unique structural feature of chemosensor **4** allows us to modulate its binding potential through (1) the selective incorporation of a phenoxyacetic acid moiety onto the porphyrin molecular platform via β-pyrrolic carbon providing the first binding site for amine, (2) axial ligation of zinc porphyrin as the second binding site for the imidazole entity of histamine and (3) a combined visible and fluorescence method to evaluate the 'two-site' recognition mechanism of the sensor and the guest. It is noteworthy that the π–π interaction between the β-appended *ortho*-phenoxyacetic acid moiety and one of the *meso*-bound phenyl rings in **4** confers the sensor with a certain degree of rigidity which may enhance its binding selectivity towards potential guests (vide infra).

3.2 Binding characteristics of chemosensor 4 towards bifunctional guests

A cursory examination of the chelating capacity of **4** reveals that cooperative influence of its two receptive sites (i.e. zinc ion and carboxylic acid) should exert binding affinity to terminal diamines such as histamine, histidine and nicotine (Figure 2). Due to the solubility constraint of chemosensor **4**, all binding experiments described in this paper were performed in toluene solution.

The binding of the alkaloids/amino acid, **5**–**7**, to the newly synthesised chemosensor porphyrin **4** was examined by UV–vis absorption, fluorescence, ^{1}H NMR and HR-MS spectral methods. To start our study, UV–vis absorption titration binding experiments performed at room temperature showed that both the Soret band and Q bands of **4** underwent a red shift as histamine was added (Figure 3). Red shifts of 8 and 6 nm, respectively, for the Q bands and the Soret band of **4** were found when histamine was introduced. Clear isosbestic points were observed, which is indicative of the existence of two states through the formation of a 1:1 complex. Non-linear fittings of the experimental data allow the evaluation of the corresponding binding constant of the complex. To substantiate the contribution of the carboxylic acid group of the host as the essential H-bond donor to bind the amine terminus of histamine, porphyrin **3** bearing an ester functionality instead of the acid moiety was used as the controlled compound. As deduced from the corresponding UV–vis titration curves (Figure S9, Supporting Information), a much weaker association constant for **3** and histamine complex was obtained [i.e. $(8.74 \pm 3.29) \times 10^5$]. When the chemosensor was allowed to interact with histidine and nicotine individually, it resulted in similar changes in the UV–vis spectra of **4** (Figures S3–S7, Supporting Information). Serving as an effective axial Lewis acidic ligating group, Zn metal centre of metallo-porphyrin **4** can coordinate strongly with pyridine, imidazole or aliphatic amines in organic non-polar solvents (*26*, *27*). On the basis of the UV–vis titration curves of **4** with 1-aminopropane, imidazole, 2-phenylethylamine and the bifunctional guests **5**–**7**, their respective association constants were evaluated**.** As the spectral variation in the Q bands of the host triggered by the guest was more prominent than that in the Soret band, we were able to compute the association constants with high reliability. The results are compiled

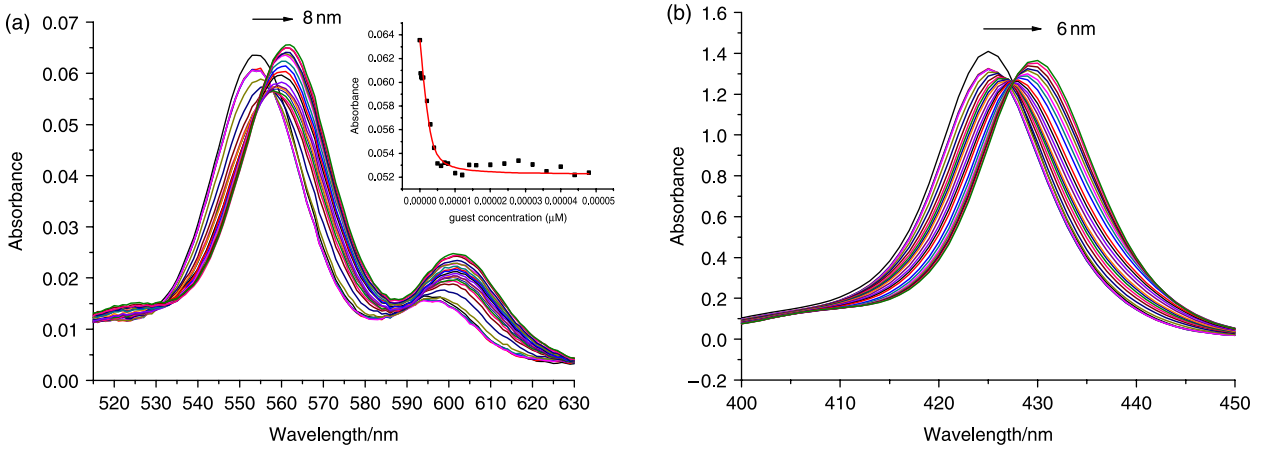


Figure 3. UV–vis titration of **4** with histamine in toluene: (a) changes in the Q bands, inset is the titration data point and the non-linear least-square fitting curve, and (b) changes in the Soret band.

Table 1. Association constants of ZnTTP and ZnTPP-β-phenoxyacetic acid (**4**) with amines[a].

Run	Porphyrin host	Guest	K (M^{-1})[b] (R^2)	Reference
1	Zn(T-*p*-CH_3PP)[c]	Pyridine	3.3×10^3	(*26*)
2	Zn(T-*p*-CH_3PP)	Butylamine	1.9×10^4	(*26*)
3	Porphyrin **4**	Propylamine	$(6.37 \pm 0.72) \times 10^5$ (0.9778)	This work
4	ZnTPP	Imidazole	5.4×10^4	(*26*)
5	Porphyrin **4**	Imidazole	$(3.30 \pm 0.96) \times 10^5$ (0.8481)	This work
6	Porphyrin **4**	2-Phenylethylamine	$(1.25 \pm 0.12) \times 10^6$ (0.9914)	This work
7	Porphyrin **4**	Histamine (**5**)	$(2.32 \pm 0.57) \times 10^6$ (0.9469)	This work
8	Porphyrin **4**	Histidine (**6**)	$(5.57 \pm 0.53) \times 10^5$ (0.9745)	This work
9	Porphyrin **4**	Nicotine (**7**)	$(6.67 \pm 0.49) \times 10^5$ (0.9743)	This work

[a] Conditions: 298 K, in toluene.
[b] Deduced from the changes in the Q bands of the UV–vis spectra of **4** in the titration experiments.
[c] [*meso*-Tetrakis(*p*-methylphenyl)porphyrinato]zinc(II).

in Table 1 and relevant association constants of similar systems in the literature are cited for comparison.

The binding affinity of the monotopic ZnTPP receptor towards nitrogen-containing guest molecules increases in the order pyridine > 1-aminobutane > imidazole, in line with their respective basicity (*27*). It is interesting to observe that, by incorporating an additional receptive site in porphyrin **4**, complexes possessing higher binding constant resulted from the new host and the monofunctional guests. Presumably, the additional β-appended phenyl group present could increase the hydrophobic environment of the host, thus favouring stronger binding. The substantial enhancement in binding constants observed between **4** and propylamine/2-phenylethylamine over imidazole appears to be more than that reflected from their pK_a values (Table 1, entries 3, 5 and 6). Apparently, additional interactions may exist between the alkyl/aryl group of the guests and porphyrin **4**. We speculated that the propyl group of propylamine could stretch into the π–π hydrophobic sheath created by the peripheral phenyl groups of the porphyrin. It is noteworthy that the binding constant of **4**–2-phenylethylamine complex is compared favourably to that of **4**–histamine, suggesting that the stability gained arising from the additional interaction between the phenyl ring of the guest and the host is quite substantial. Conceivably, the additional receptive site of the host endowed by its phenoxyacetic acid lingering group can form H-bonding with suitable guest molecules. Using imidazole as the control compound in our sensing system, the stronger binding interaction observed between the host and the three bifunctional guests can be attributed to the presence of H-bonding (Table 1, entries 7–9). Computational study confirms this supposition and provides insight into the binding mode between 2-phenylethylamine and porphyrin **4** (vide infra). Exhibiting the highest binding constant with histamine, porphyrin **4** can be regarded as a chemosensor capable of recognising this important biogenic alkaloid. Corroborating evidence on the binding model of the complexes is provided by molecular modelling.

To shed light on the binding model between various guests (histamine, histidine, nicotine and 2-phenylethylamine) and porphyrin **4**, their corresponding binding structures were optimised at the B3LYP/6-31+G(d) level. In all three optimised structures of the complexes between host **4** and the three di-nitrogen guests, three interactions are found in the two binding sites of the host: (1) two H-bondings are formed between the acidic hydrogen in the phenoxyacetic group and the terminal amine group in the guest as well as between the carbonyl oxygen in the phenoxyacetic group and the aliphatic hydrogen adjacent to the terminal amine; (2) the imidazole/pyridine moiety of the guest molecules is ligated axially with zinc porphyrin. The 'three-point' interactions in the host–guest structure are expected to be very rigid and thus the binding affinities of porphyrin **4** for guests **5**–**7** should be large. At the B3LYP/6-31+G(d) level, the binding energy between porphyrin **4** and guests **5**–**7** ranged from 80 to 210 kJ/mol. This binding energy, included with zero-point correction and thermal correction at 298 K, was calculated as the electronic energy of the binding structures relative to free host and guest molecules. The binding energies obtained in the theoretical predictions are in line with the significantly large binding constants measured for porphyrin **4** and guests **5**–**7**. In contrast, the molecular modelling revealed that the phenyl ring of 2-phenylethylamine can serve as a π facial acceptor to interact with the phenoxymethylcarboxyl group of the host as shown in Figure 4, leading to the formation of the fairly stable complex (*28*). As reflected in its binding constant, this additional H–π interaction is comparable to that of the normal hydrogen bonding.

3.3 Fluorescence titrations with guest molecules

On excitation at 420 nm, porphyrin **4** emits between 550 and 690 nm with two maxima at 607 and 650 nm. Careful examination of the fluorescence titration curves of **4** with various guests reveals their intriguing features.

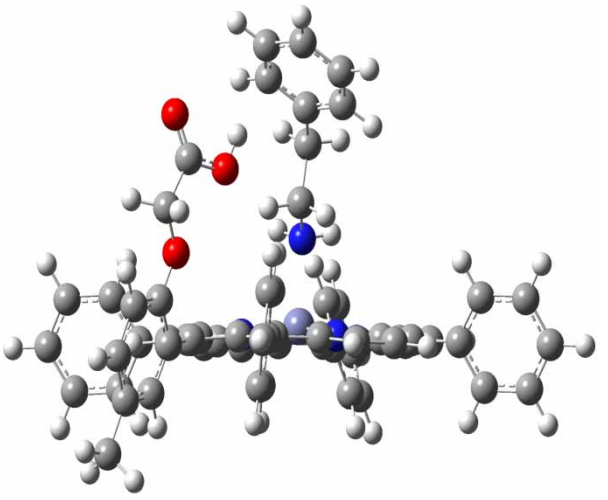


Figure 4. The optimised structure of porphyrin **4** and 2-phenylethylamine derived from molecular modelling.

The spectral changes of **4** caused by the guests can be clearly divided into two different categories according to their number of interaction sites to the host. Addition of bifunctional guest molecules capable of 'two-site' binding exemplified by histamine causes a distinct blue shift (~3 nm) and gradual signal enhancement of the 607 nm peak and reduction of the 650 nm peak of **4**. Furthermore, an isoemissive point at 635 nm of the titration spectral curves is apparent, reminiscent of the findings in UV–vis spectroscopy (vide supra), indicating the presence of only one equilibrium in solution (Figure 5(a)). Similar spectral features are observed for porphyrin **4** binding with either histidine or nicotine (Supporting Information). In contrast, the addition of monofunctional guest molecules, such as 1-aminopropane and 2-phenylethylamine, characterised by their 'one-site' binding capacity can trigger fluorescence signal enhancement on both fluorescence peaks of **4** (Figure 5(b)). While imidazole was introduced into the host, quenching of both peaks was observed (Figure S5). Quenching with imidazole could be attributed to the hydrogen bonding of N—H of imidazole with oxygen of the appended carboxylic acid group, which can cause PET-type quenching.

To demonstrate the role of porphyrin **4** as a chemosensor for histamine, we monitored the intensity ratio of two fluorescence peaks as a function of alkaloids and histidine concentration. Figure 6 displays such plots derived from the binding of **4** with histamine, histidine and nicotine. A rough linear relationship was obtained for the emission peak ratio against the concentration of these bifunctional guest molecules. From the slope of these straight lines, it is apparent that the chemosensor is most sensitive to histamine, corroborating with the highest binding constant of the complex.

3.4 ^{1}H NMR and HR-MS data in support of the binding model

To shed light on the binding mode of the complex, the interaction between receptor **4** and histamine was investigated by ^{1}H NMR spectroscopy. Upon binding to porphyrin **4**, the C-2 proton of the imidazole residue of histamine undergoes a shielding of ~0.37 ppm, while the C-5 imidazolyl proton of histamine experiences less shielding (0.06 ppm). On the other hand, the formation of H-bond between the terminal amino group of histamine and the peripheral carboxylic acid group of the receptor induces a slight upfield shift of the α-protons and the β-protons to amino terminal of histamine by 0.15 and 0.03 ppm, respectively (Figure S1, Supporting Information).

Convincing evidence on the 1:1 binding mode of the complex of **4** and histamine was obtained by the

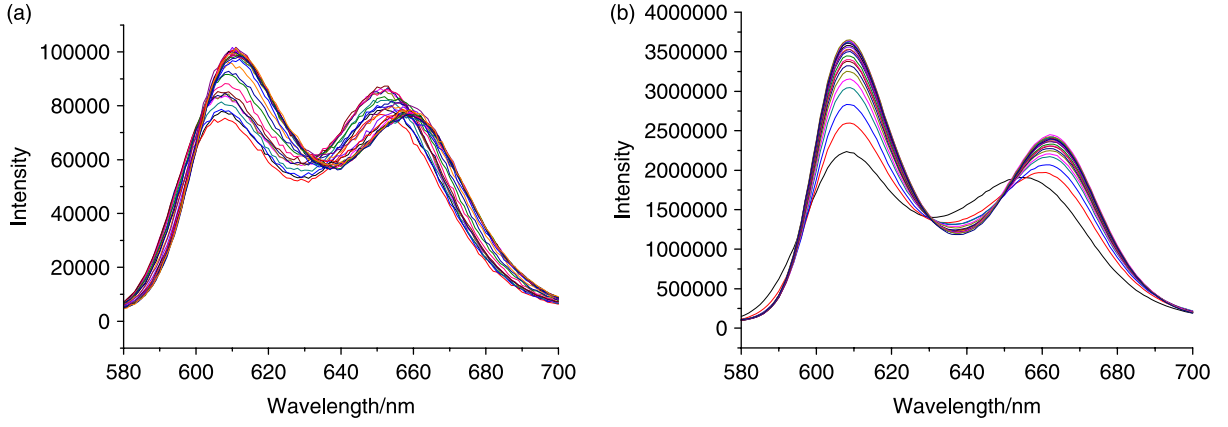


Figure 5. Fluorescence emission spectra of ZnTPP-β-phenoxyacetic acid (**4**) change upon the addition of (a) histamine and (b) propylamine. ZnTPP-β-phenoxyacetic acid (**4**) concentration, 3.0×10^{-6} M (in toluene); ligand concentrations 1.0×10^{-7} to 1.0×10^{-5} M. The excitation wavelength was 425 nm.

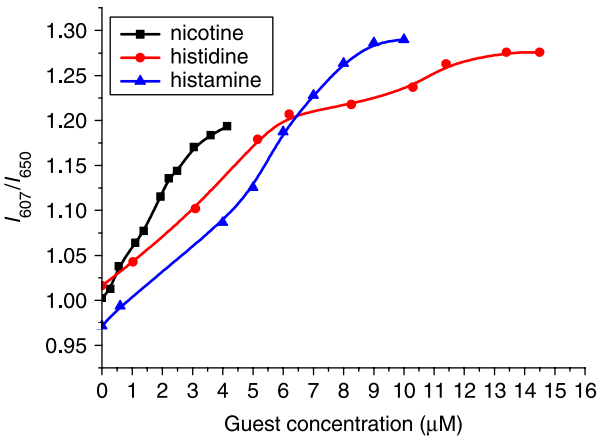


Figure 6. The intensity ratio of the emission bands, I_{607}/I_{650}, of **4** as a function of the concentration of histamine, histidine and nicotine.

observation of a high-resolution mass spectrum peak of $[M]^+$ of *m/z* 951.2878 from the ESI-HR-MS method. By overlaying the experimental spectrum of the complex with the theoretically required counterpart as shown in Figure 7, a perfect match of all isotopic peaks both in the peak position and in intensity becomes apparent. Thus, a selective binding of porphyrin **4** to histamine has been firmly established.

4. Conclusion

In contrast to the traditional *meso*-functionalisation approach, in this study, we report the expeditious construction of a ditopic porphyrin-based chemosensor by incorporating a receptor at its β-pyrrolic carbon. A selective histamine chemosensor is efficiently developed. Interestingly, the juxtaposition of an additional phenyl moiety at the β-pyrrolic carbon with one of the *meso*-phenyl groups of the porphyrin allows the formation of a π–π hydrophobic sheath, which, on the one hand, can enhance the rigidity of the host and, on the other hand, can accommodate the 'hydrophobic tail' of the guest such as propylamine. The strategy is proven to be highly efficient and potentially versatile. In principle, other substituted phenyl group(s) with multi-receptive sites can be appended on the tetraphenylporphyrin scaffold at its β-pyrrolic position. Exploration along this direction in chemsensor development is in progress.

Supplementary Information

General experimental procedures and copies of ^{1}H and ^{13}C NMR spectra of compounds **3** and **4**; ^{1}H NMR of the complex of **4**–histamine in comparison with the spectra of **4** and histamine; ESI-HR-MS spectrum of the complex of **4**–histamine; UV–vis spectrophotometric and fluorometric titration curves of **4** towards various guest

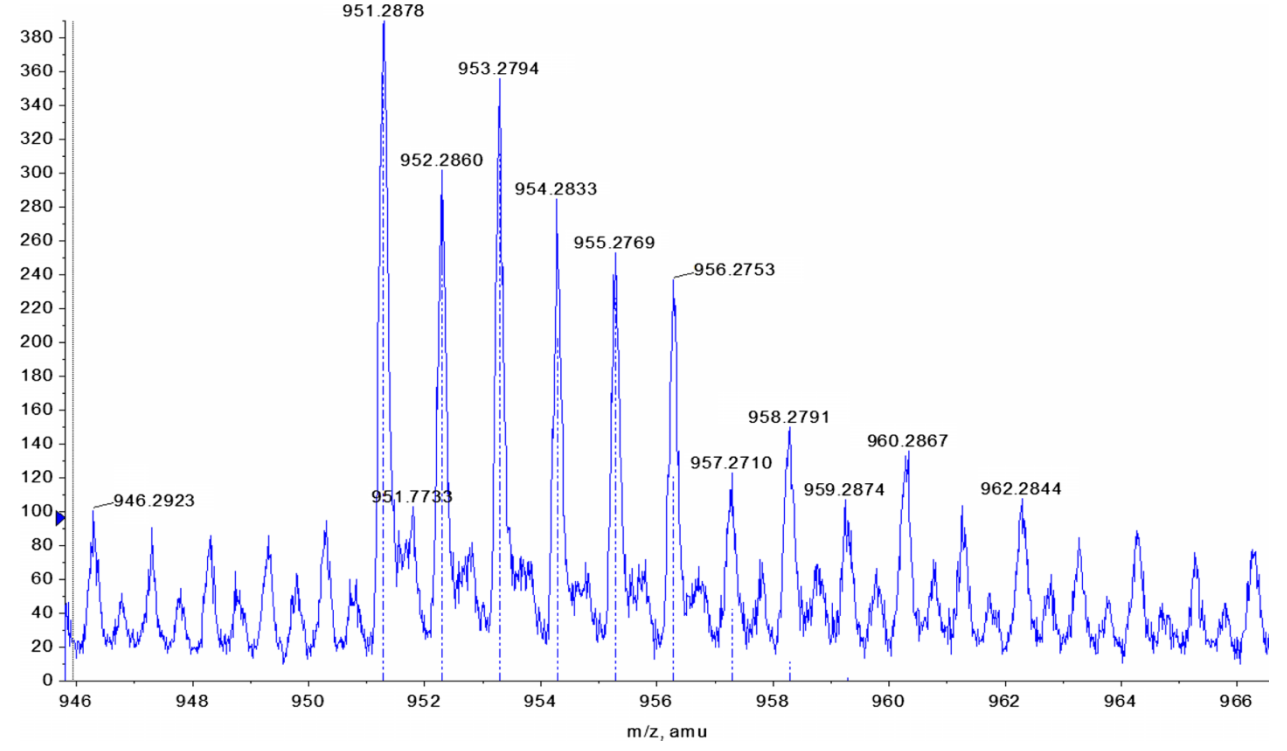


Figure 7. ESI-HR-MS of porphyrin **4**–histamine complex (solid lines) and the corresponding simulated spectrum (dotted lines).

molecules; UV–vis spectrophotometric titration curves of **4a** towards histamine.

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