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Fused imidazoles as potential chemical scaffolds for inhibition of heat shock protein 70 and induction of apoptosis. Synthesis and biological evaluation of phenanthro[9,10-*d*]imidazoles and imidazo[4,5-*f*][1,10]phenanthrolines†

Alpa Patel,[a] Swee Y. Sharp,[b] Katelan Hall,[a] William Lewis,[a] Malcolm F. G. Stevens,[c] Paul Workman[b] and Christopher J. Moody*[a]

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The imidazole ring is widespread in biologically active compounds, and hence imidazole-containing scaffolds are useful starting points for drug discovery programmes. We report the synthesis of a series of novel imidazole-containing compounds fused with either phenanthrene or phenanthroline, which show enhanced growth inhibitory potency against human colon, breast and melanoma cancer cell lines, as well as evidence of inhibition of the molecular chaperone heat shock protein 70 (Hsp70) pathway in cells, as shown by depletion of downstream oncogenic client proteins of the Hsp90 chaperone pathway, and induction of apoptosis.

Introduction

The imidazole ring is widely represented amongst biologically active compounds, and is a component of the amino acid histidine, the nucleic acid base adenine, a range of natural products and secondary metabolites,[1] and a plethora of synthetic pharmaceutical agents, many of which have had major benefits for human health.[2,3] Thus cimetidine **1** was an early histamine H-2-receptor antagonist that inhibits gastric acid secretion, losartan **2** was the first angiotensin II receptor antagonist to be marketed and is used to treat hypertension, whilst fused imidazoles such as the proton pump inhibitor benzimidazole omeprazole **3** and the imidazotetrazine temozolomide **4** are used to block stomach acid secretion and as a first line treatment for glioblastoma mulltiforme respectively (Fig. 1).

More recent additions to the repertoire of bioactive imidazoles are the triarylimidazole p38α MAP-kinase inhibitor SB203580 **5**, and the related imidazole apoptozole **6** (Fig. 1).

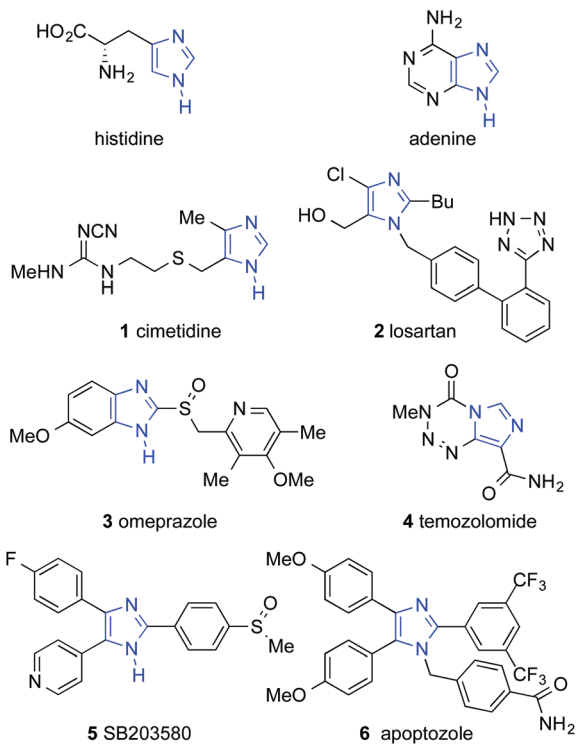

Fig. 1 Some biologically active imidazoles.

[a]*School of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, UK. E-mail: c.j.moody@nottingham.ac.uk*
[b]*Cancer Research UK Cancer Therapeutics Unit, Division of Cancer Therapeutics, The Institute of Cancer Research, Haddow Laboratories, London, SM2 5NG, UK*
[c]*School of Pharmacy, University of Nottingham, University Park, Nottingham, NG7 2RD, UK*

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In view of our interest in the heat shock protein (Hsp) molecular chaperones,[4,5] we became interested in the imidazole scaffold exhibited by apoptozole, and its reported biological activity. The compound **6** induced apoptosis in murine P19 embryonic carcinoma cells and was reported to bind to the heat shock proteins Hsp72 and Hsc70 as determined by surface plasmon resonance (SPR) using an apoptozole–biotin conjugate.[6] Based on molecular modeling, Shin and co-workers suggested that apoptozole binds to the ATP-ase domain of Hsc70.[7] More recently, the ability of apoptozole to induce apoptosis and to bind to Hsp70 was confirmed.[8,9] However, a very recent study was unable to find any experimental evidence that apoptozole binds to Hsp70 family members directly,[10] suggesting an indirect effect in cells on the Hsp70/Hsp90 chaperone pathway.

Heat shock proteins such as Hsp70 family members facilitate the folding, activity, stability and cellular translocation of newly synthesized polypeptides, as well as preventing the aggregation of unfolded mature proteins. The frequent overexpression of Hsps in many cancers supports the increasing interest in Hsps as targets for new molecular cancer therapeutics,[11] and precedence has been established by the clinical development and activity of inhibitors of the Hsp90 molecular chaperone.[12,13] There are at least eight Hsp70 family members, of which the two main cytoplasmic isoforms are the ubiquitously expressed Hsc70, and Hsp72, which is overexpressed as a response to stress factors.[14] Many human cancers and tumour cell lines show increased levels of Hsp70 family members, prompting the suggestion that this may contribute to the ability of these cells to evade apoptosis.[11] As a result, inhibition of Hsp70 has emerged in recent years as a promising strategy to target cancer, both as an individual approach and in conjunction with other heat shock proteins such as Hsp90.[15–21]

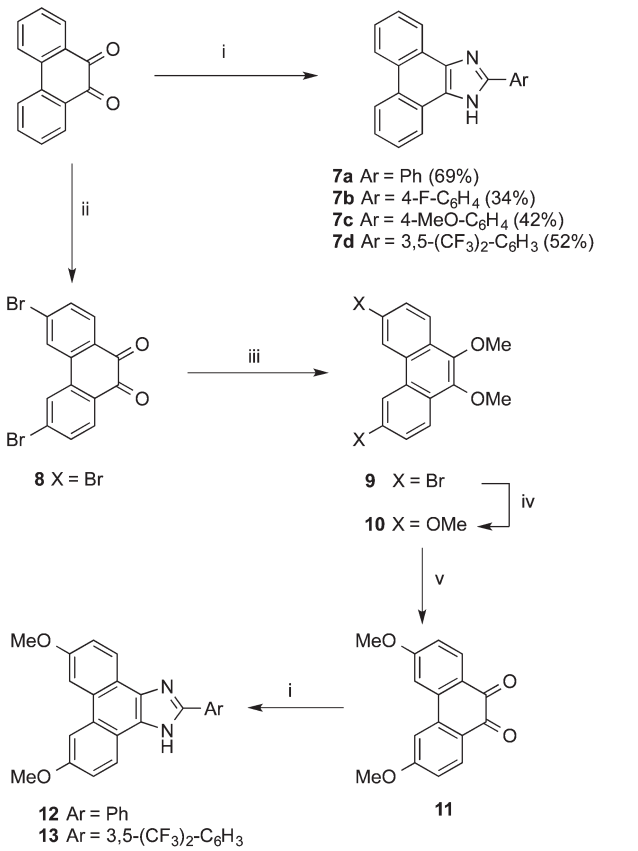
Here, we report the synthesis and evaluation for anticancer activity of a series of compounds based on a triarylimidazole core, analogous to apoptozole, but with the incorporation of a phenanthrene or phenanthroline ring system. We have shown that these compounds potently reduce the viability of human cancer cell lines, and deplete Hsp72 and Hsp27 as well as Hsp90 client proteins. In addition, the novel imidazo[4,5-*f*][1,10]phenanthrolines have emerged as a highly promising chemical scaffold for the induction of apoptosis.

Results and discussion

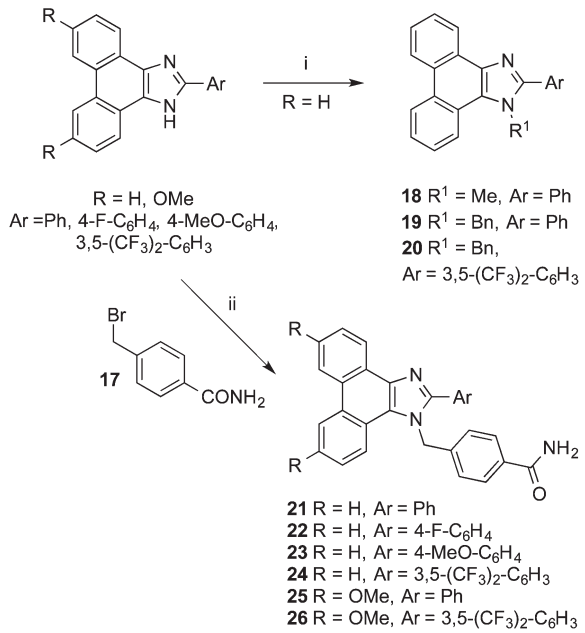
Phenanthro[9,10-*d*]imidazoles

Debus and Radziszewski independently reported the multicomponent synthesis of imidazoles in acidic conditions in the 19th century, using a diketone, ammonium acetate, aniline and an aldehyde.[22,23] In 2004, Wolkenberg and co-workers applied microwave irradiation to synthesize polysubstituted imidazoles using the same starting components, omitting an aniline so that the 2,4,5-trisubstituted imidazole was formed.[24] Therefore, these conditions were utilized to make several 2,4,5-triarylimidazoles, starting from phenanthrene-9,10-dione to yield the phenanthro[9,10-*d*]imidazole scaffolds **7** with variable substitution of the C-2 aryl ring (Scheme 1).

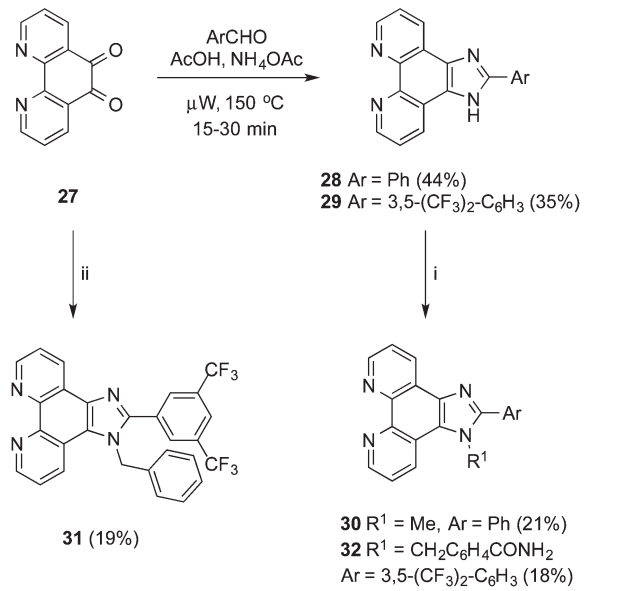
Functionalization of the phenanthrene ring was achieved by following MacLachlan and co-workers' procedure,[25] *via* initial bromination of phenanthrene-9,10-dione under radical conditions to give 3,6-dibromophenanthrene-9,10-dione **8**. Reduction of the *ortho*-quinone with sodium dithionite allowed Ullmann coupling of 3,6-dibromo-9,10-dimethoxyphenanthrene **9** to produce tetramethoxyphenanthrene **10** (Scheme 1). Oxidation with ammonium cerium(IV) nitrate afforded 3,6-dimethoxyphenanthrene-9,10-dione **11**, an appropriate precursor to imidazole synthesis using the multicomponent conditions described above. Dione **11** was utilized in the synthesis of the corresponding imidazoles with benzaldehyde to give **12** and 3,5-bis(trifluoromethyl)benzaldehyde for compound **13** (Scheme 1). For comparison and structure–activity relationship elaboration, the non-planar analogue of **7c**, 2-(4-methoxyphenyl)-4,5-phenyl-1*H*-imidazole **14**, was synthesized from benzil in 61% yield. To investigate the influence of substitution on the left hand side of the molecule, 2,4,5-tris-(4-trimethoxyphenyl)-1*H*-imidazole **15** was formed from 4,4′-



Scheme 1 Synthesis of phenanthro[9,10-*d*]imidazoles. Reagents and conditions: (i) ArCHO, AcOH, NH_4OAc, μW, 150 °C, 15 min. (ii) bromine, benzoyl peroxide, nitrobenzene, 110 °C, 16 h; (iii) $Na_2S_2O_4$, Me_2SO_4, Bu_4NBr, THF, water, rt, 45 min; (iv) NaOMe (25%), CuBr, EtOAc, toluene, 80 °C, 64 h; (v) $Ce(NH_4)_2(NO_3)_6$, MeCN, water, rt, 15 min.



Scheme 2 Alkylation of phenanthro[9,10-*d*]imidazoles. Reagents and conditions: (i) ^{t}BuOK, MeI or BnBr, THF, rt, 16 h to 3 days; (ii) ^{t}BuOK, **17**, THF, rt, 16 h to 3 days.



Scheme 3 Synthesis of imidazo[4,5-*f*][1,10]phenanthrolines. Reagents and conditions: (i) MeI or **17**, ^{t}BuOK or K_2CO_3, DMF or MeCN, rt, 16 h; (ii) 3,5-$(CF_3)_2C_6H_3CHO$, $BnNH_2$, AcOH, NH_4OAc, μW, 150 °C, 30 min.

dimethoxybenzil, and 2,4,5-tris-(4-trifluorophenyl)-1*H*-imidazole **16** from 4,4′-difluorobenzil.

Next, we turned our attention to increasing the molecular size in a bid to impart selectivity towards the target protein. Methylation of 1*H*-imidazoles was achieved by reaction with iodomethane with potassium *tert*-butoxide in THF. Analogous benzylation was successful with benzyl bromide as the alkylating agent under the same reaction conditions. Alternatively, compound **19** could also be made through a multicomponent reaction with benzylamine. The final alkylation was proposed due to the molecular modeling study cited by Shin *et al.*, which indicated that the benzamide oxygen of apoptozole could participate in a hydrogen bonding interaction with the Glu376 residue of the ATP binding pocket of Hsc70.[7] The commercially available 4-(bromomethyl)benzoic acid could be readily converted into 4-(bromomethyl)benzamide **17** to allow alkylation of the imidazole for the incorporation of a methylbenzamide moiety at N-1, analogous to apoptozole (Scheme 2). Apoptozole itself (**6**) was synthesized as a reference compound, by multicomponent synthesis of the 2,4,5-substituted imidazole followed by alkylation with **17**.

Imidazo[4,5-*f*][1,10]phenanthrolines

Following the promising results in the phenanthro[9,10-*d*]imidazole series (see below), we turned our attention to introducing heteroatoms within the tetracyclic ring system. 1,10-Phenanthroline is a readily available chemical that is commonly used as a chelating ligand for metal-catalyzed reactions. The ring system can be oxidized to phenanthroline-1,10-dione **27**, which in our case, provided a useful starting material for imidazole synthesis through the multicomponent pathway in acidic media (Scheme 3).

As with the previous series, alkylation of the imidazole nitrogen was attempted. This proved particularly difficult with compound **28**, possibly due to its poor solubility and high polar character, although methylation was possible to give **30**. Benzyl derivative **31** was synthesized through a multicomponent imidazole formation with benzylamine. Alkylation of **29** with 4-(bromomethylbenzamide) **17** to give **32** was successful as the bis(trifluoromethyl)phenyl ring provided improved solubility in organic solvents (Scheme 3).

The structures of apoptozole **6**, imidazole **14** and phenathroimidazole **18** were confirmed by X-ray crystallography (Fig. 2) that established that the aromatic rings are not coplanar in the non-constrained imidazoles **6** and **14**.

Biological evaluation

The imidazole library was evaluated for *in vitro* anticancer activity in the human colon cancer cell line HCT116 using the CellTiter-Blue® viability assay. In our hands, apoptozole **6** gave a GI_{50} of 7.0 μM in this assay. All of the fused phenanthro[9,10-*d*]-imidazoles tested showed potency equivalent to apoptozole, ranging from 3.5 to 11.2 μM (Table 1), with compound **7c** being twice as potent as apoptozole. Interestingly, non-planar compound **14** was found to be less active in the cell viability assay, whereas **15** and **16** both showed potency that was comparable to apoptozole and the phenanthro[9,10-*d*]imidazoles. Selected compounds were also evaluated in the breast cancer cell line MCF7 with compound **7c** showing similar activity in MCF7 cells when compared with HCT116 (Table 1).

Our previous studies showed that siRNA silencing of Hsp70 isoforms Hsp72 and Hsc70 resulted in depletion of Hsp90

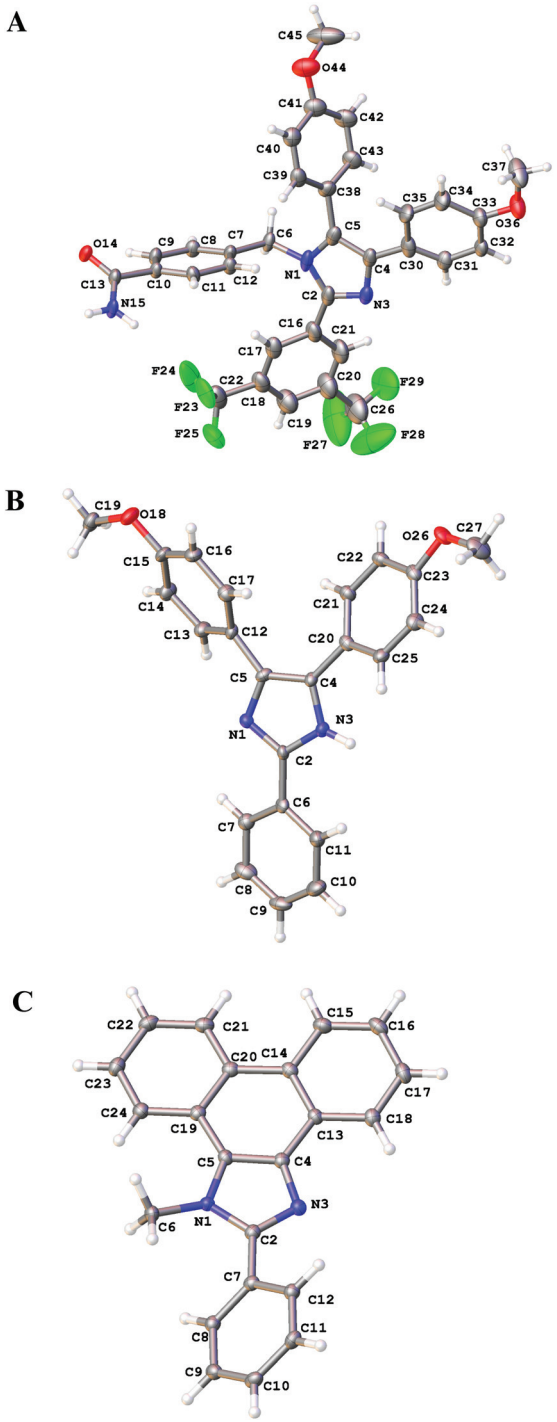


Fig. 2 X-Ray crystal structures of (A) apoptozole **6** (CCDC 1456778), (B) imidazole **14** (CCDC 1456780) and (C) phenathroimidazole **18** (CCDC 1456779).

client proteins and induction of apoptosis.[26] Compounds were therefore investigated for their effect on expression of the commonly studied Hsp90 client proteins, together with effects on the levels of Hsp72, Hsc70 and Hsp27, and also on cleaved PARP as a marker of apoptosis in HCT116 human colon carcinoma cells, as used previously.[26]

Imidazoles **7a**, **7c** and **16** showed varying degrees of depletion of Hsp72 and Hsc70 as well as Hsp27 over the period 48 hours and at concentrations of 5 and 10 × GI_{50} (Fig. 3). The greatest effects were seen for Hsp27 whereas no effects were seen on Hsc70. Hsp72 showed evidence of depletion by all compounds at 48 hours, particularly the most potent compound **7c**. Additionally, compounds **7a**, **7c** and **16** depleted oncogenic client proteins of Hsp90, namely, ERBB2, CRAF and CDK4. In addition, cleaved PARP was observed, indicative of apoptosis. The inactive 4,5-diphenyl-1*H*-imidazole **14**, which has a GI_{50} of >20 μM, did not show any detectable effects on Hsps, Hsp90 or cleaved PARP at the highest concentration tested.

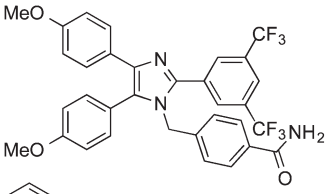
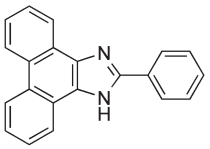
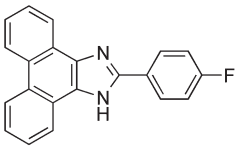
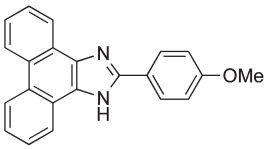
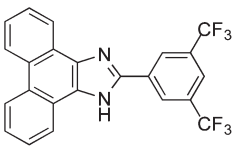
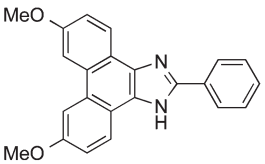
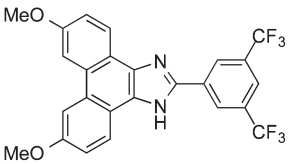
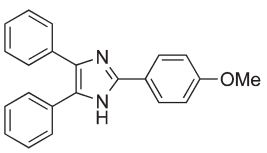
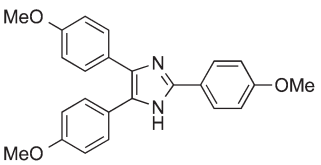
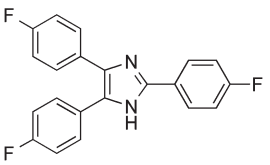
The Hsp90 inhibitor 17-*N*-allylamino-17-demethoxygeldanamycin (17-AAG)[27] was included as a control compound (Fig. 3A). As expected, 17-AAG caused induction of the heat shock pathway as shown by elevated expression of Hsp72 and Hsp27, whereas this was not seen with the imidazoles **7a**, **7c** and **16**. Both 17-AAG and compounds **7a**, **7c** and **16** caused depletion of Hsp90 client proteins, indicating that they blocked the function of the Hsp90 chaperone complex, consistent with our published results with siRNA silencing of Hsp72 and Hsc70.[26] The precise effects of the active imidazole compounds and 17-AAG varied between the Hsp90 client proteins studied.

Alkylation of the imidazole nitrogen gave compounds with differing activities in the cell viability assay in HCT116 colon, MCF7 breast and WM266.4 melanoma cells in the cell viability assay (Table 2). Methylation or benzylation results in comparable activity to the non-alkylated imidazole. However, introduction of the methylbenzamide group resulted in loss of activity for compounds **21** and **24**. Interestingly, analogues **22** and **23** retained potency in comparison to their non-alkylated precursors **7b** and **7c**, suggesting that functionalization of the C-2 aryl ring with a *para* substituent that can participate in hydrogen bonding may be important. Dimethoxyphenanthrene analogue **25** was found to be the most active benzamide derivative, with a GI_{50} of 3.40 μM in HCT116 cells. Unfortunately, the direct analogue of apoptozole **26**, where the two methoxyphenyl rings at the 4 and 5 positions of the imidazole are constrained into a phenanthrene system, was insoluble in our assay conditions.

Interestingly, imidazo[4,5-*f*][1,10]phenanthroline **28** showed almost an eighty-fold increase in potency when compared to apoptozole, with a GI_{50} of 0.09 μM in HCT116 cells and submicromolar values in WM266.4 and MCF7 cells (Table 2). Compound **28** also showed the desired effects on client protein depletion by Western blot (Fig. 4A). In addition, Hsp72 and Hsp27 protein levels were decreased over 48 hours, and there was clear evidence of apoptosis, as shown by PARP cleavage in HCT116 cells. Interestingly, analogues of the imidazo[4,5-*f*][1,10]phenanthroline **28** that are substituted at the C-2 aryl ring have recently been reported as DNA G-quadruplex binders,[28] although in the case of compound **28** itself we were unable to find evidence for such an interaction. Thus incubation of **28** with the 22 base human telomeric sequence AGGG $(TTAGGG)_3$ showed no change in ellipticity in its CD spectrum.

Despite the evidence of desired on-pathway biomarker changes, compound **28** was considered to have potential to be

Table 1 Cell growth viability assay results of 4,5-disubstituted imidazoles and phenanthro[9,10-*d*]imidazoles series against HCT116 (colon) and MCF7 (breast) human cancer cells, showing GI_{50} (μM) with standard error (SE)

		HCT116		MCF7	
Compound	Structure	GI_{50}/μM	SE/±μM	GI_{50}/μM	SE/±μM
6 (apoptozole)		7.0	0.5		
7a		7.6	0.3	>5	
7b		6.7	0.4		
7c		3.0	0.3	4.0	0.5
7d		7.3	1.2		
12		7.8	0.3		
13		11.2	1.5		
14		>20	4.7		
15		7.8	0.6		
16		9.5	0.6	>10	

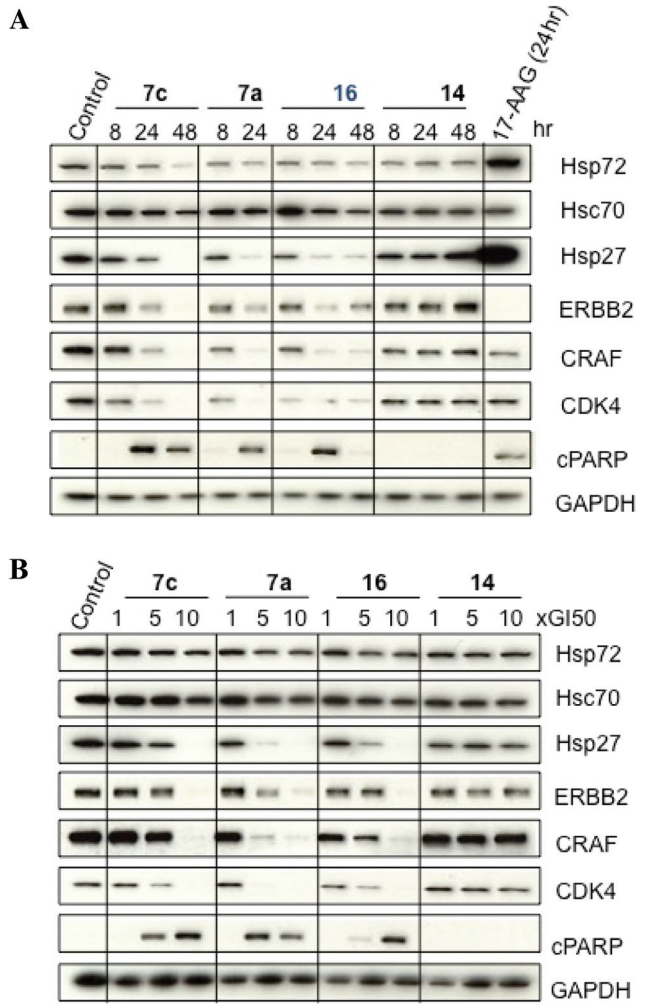


Fig. 3 Effects of imidazole compounds on expression of heat shock proteins, Hsp90 client proteins and cleaved PARP in HCT116 human colon cancer cells. Western blots of lysates of HCT116 human colon cancer cells treated with (A) 5 × GI_{50} concentrations of compounds **7a**, **7c**, **16** (non-planar compound) and the inactive compound **14** or the Hsp90 inhibitor 17-AAG or vehicle control for 8, 24 and 48 h or (B) multiples of GI_{50} of compounds for 24 h. GAPDH was used as loading control.

a highly non-selective small molecule inhibitor due to its low molecular weight, and it was thought that *N*-alkylation of this series of compounds might be a step towards gaining selectivity and reducing off-target effects when moving forward to *in vivo* studies. Pleasingly, although methylation of the imidazole nitrogen resulted in drop in potency (compound **30** *vs.* **28**), the *N*-methyl compound **30** is still more active than apoptozole. Unfortunately, 3,5-bis(trifluoromethyl)phenyl derivative **29** was too insoluble to test in our assay conditions, but the corresponding alkylated derivatives **31** and **32** showed at least a tenfold increase in activity in comparison to apoptozole in HCT116 cells (Table 2 and Fig. 4B). Structurally, compound **32** shares the N-1 and C-2 imidazole substituents with apoptozole, but differs in that the fused phenanthroline at C-4/C-5 results in a more planar structure.

Conclusion

We have identified a series of phenanthro[9,10-*d*]imidazoles that show *in vitro* potency against HCT116 human cancer cell lines that is equivalent to or greater than apoptozole, a reported inhibitor of Hsp70 and inducer of apoptosis in cancer cells. In addition, imidazo[4,5-*f*][1,10]phenanthrolines, readily obtained in a single step from phenanthroline-1,10-dione, have emerged as a highly promising chemical scaffold for apoptosis induction, with at least a ten-fold increase in potency when compared to apoptozole in a cell viability assay. Both series of compounds have also demonstrated cellular biomarker activity consistent with inhibition of Hsp70 family members Hsc70 and Hsp72, including depletion of Hsp90 client proteins together with induction of apoptosis,[15] although we have no direct evidence of binding to Hsp70. Nevertheless, irrespective of the precise molecular mechanism of action, the novel imidazo[4,5-*f*][1,10]phenanthrolines reported herein appear to have potential for further investigation as therapeutic agents that induce apoptosis in cancer cells.

Experimental section

Chemistry

General information. Commercially available reagents were used without further purification unless otherwise stated, including anhydrous *N*,*N*-dimethylformamide, methanol and ethyl acetate. Dichloromethane and tetrahydrofuran were freshly distilled from calcium hydride and sodium-benzophenone ketyl, respectively, according to standard procedures. Toluene was purged with nitrogen over activated alumina towers. Water refers to deionized water, and ether refers to diethyl ether. Light petroleum refers to the fraction with boiling point range 40–60 °C.

Reactions were routinely carried out under a nitrogen or argon atmosphere. Microwave reactions were conducted using a focused (300 W) microwave reactor with an IR temperature sensor. Analytical thin layer chromatography was carried out on aluminum-backed plates coated with silica gel 60 F_{254} and visualized under UV light at 254 nm and/or 360 nm. Flash column chromatography was carried out using Aldrich 60 Å silica gel with the eluent specified.

Melting points were measured using a digital melting point apparatus, and are uncorrected. High and low resolution mass spectra were recorded on a time-of-flight instrument using Electrospray Ionization (ESI). Infrared spectra were recorded over the range 4000–600 cm^{-1} using an FT-IR spectrometer, either as a solution in chloroform or as a solid in Attenuated Total Reflectance (ATR) mode. NMR spectra were recorded at 400 MHz for ^{1}H NMR and corresponding 100 MHz for ^{13}C NMR. Chemical shifts are quoted in parts per million (ppm), and are referenced to residual protonated solvent as an internal standard. Multiplicity abbreviations used: s singlet d doublet, t triple, q quartet, m multiplet. Coupling constants *J* are quoted in Hertz (Hz). Assignments were made with the use

Table 2 Cell growth viability assay results of alkylated phenanthro[9,10-*d*]imidazoles and of imidazo[4,5-*f*][1,10]phenanthrolines against HCT116 (colon), WM266.4 (melanoma) and MCF7 (breast) human cancer cells, showing GI_{50} (μM) with standard error (SE)

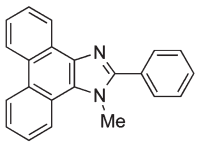
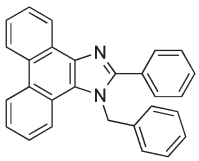
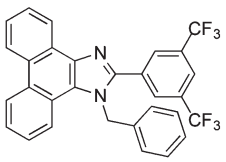
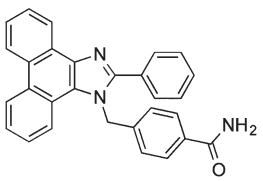
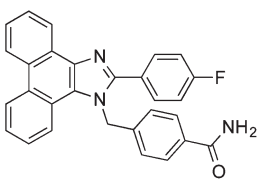
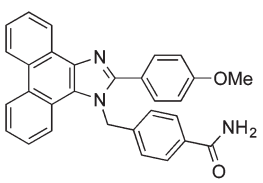
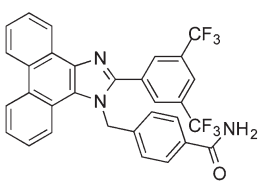
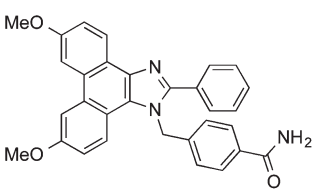
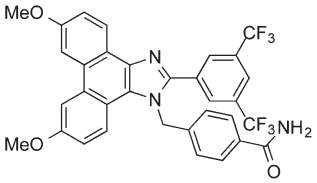
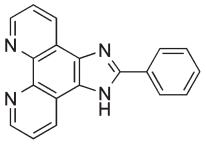
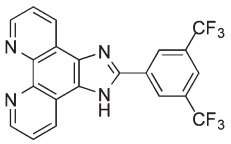
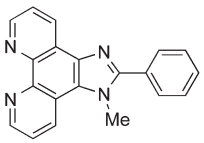
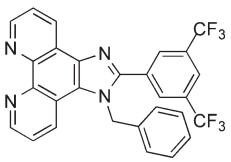
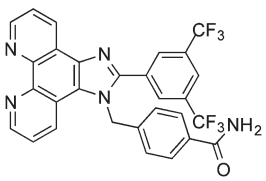
		HCT116		WM266.4		MCF7	
Compound	Structure	GI_{50}/μM	SE/±μM	GI_{50}/μM	SE/±μM	GI_{50}/μM	SE/±μM
18		9.4	0.5				
19		6.8	1.4				
20		>20					
21		>20					
22		5.9	1.1	>5		>10	
23		5.5	1.0	>5		>10	
24		>20					
25		3.4	1.0	>5		>10	

Table 2 *(Contd.)*

Compound	Structure	HCT116		WM266.4		MCF7	
		GI_{50}/μM	SE/±μM	GI_{50}/μM	SE/±μM	GI_{50}/μM	SE/±μM
26		Insoluble					
28		0.09	0.01	0.32	0.10	0.69	0.11
29		Insoluble					
30		2.6	0.04				
31		0.5	0.2	2.9	0.3	2.8	0.8
32		0.7	0.3	2.5	0.07	2.3	0.5

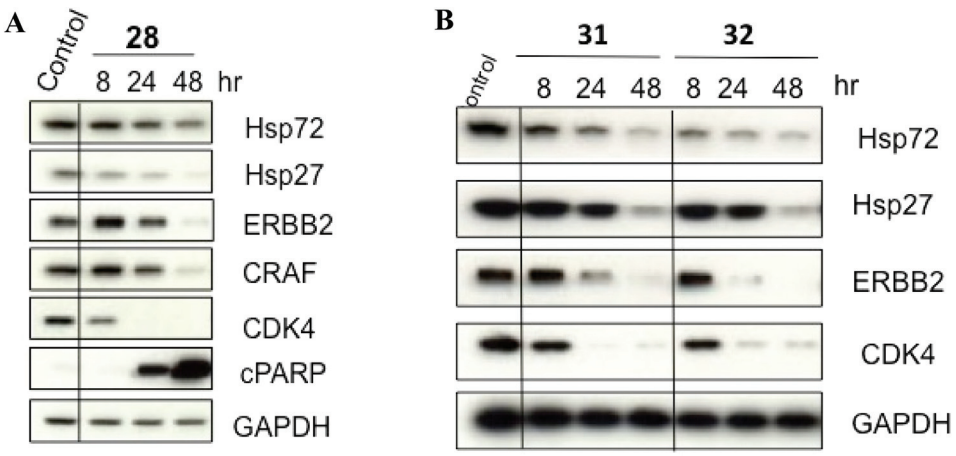


Fig. 4 Western blot of lysates of HCT116 human colon cancer cells treated with (A) compound **28** at 5 × GI_{50} for 8, 24 and 48 h, and (B) with 5 × GI_{50} concentrations of compounds **31** or **32** for 8, 24 and 48 h. GAPDH was used as loading control.

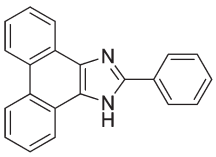
of DEPT spectra as well as COSY, HMQC and HMBC correlation techniques. LCMS was used to determine purity of compounds, with purity ≥95% unless otherwise stated, as measured by the area under curve (AUC) of the UV trace at 254 nm.

Experimental procedures

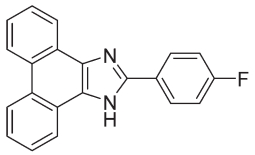
General procedure 1: synthesis of trisubstituted imidazoles. A 35 mL microwave vial was charged with 1,2-diketone (0.5–5 mmol), aryl aldehyde (1.2 eq.), ammonium acetate (10 eq.) and glacial acetic acid (6410 mL). The mixture was heated at 150 °C for 15–30 min under microwave irradiation (300 W). Following reaction completion by TLC, the mixture was cooled to room temperature and added slowly to ammonium hydroxide (35%; 30 mL). The resulting precipitate was collected by filtration and purified by flash column chromatography, recrystallization or trituration to give the product.

General procedure 2a: alkylation of 1*H*-imidazoles. In an oven-dried flask, a solution of trisubstituted imidazole (0.5–1 mmol) in THF or DMF (10 mL $mmol^{-1}$) was treated with potassium *tert*-butoxide (2 eq.) and the mixture stirred for 5 min The alkylating agent (2–5 eq.) was added and the mixture stirred at ambient temperature for 16 h to 3 days. Once the reaction was complete, as judged by TLC, the mixture was added to water (20–100 mL) and extracted with ethyl acetate (3 × 10–50 mL). The combined organic extracts were washed with saturated brine (20–100 mL), dried ($MgSO_4$) and concentrated onto silica. Purification by flash column chromatography and trituration gave the product.

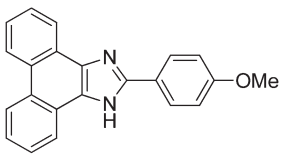
General procedure 2b: alkylation of 1*H*-imidazoles. General procedure **2a** was applied with the following changes: potassium *tert*-butoxide was replaced with potassium carbonate (2 eq.), and THF or DMF was replaced with acetonitrile (10 mL $mmol^{-1}$).



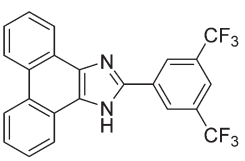
2-Phenyl-1H-phenanthro[9,10-d]imidazole ***7a.*** Prepared by general procedure 1 from phenanthrene-9,10-dione (300 mg, 1.44 mmol) and benzaldehyde (175 μL, 1.73 mmol). Purification by recrystallization from dichloromethane–methanol (1 : 1) gave the *title compound* as a beige solid (294 mg, 69%); mp 323–324 °C (lit.,[1] mp 322–324 °C); (Found: M + H^+, 295.1217. $C_{21}H_{14}N_2$ + H^+ requires 295.1230); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3606, 3459, 3007, 1602, 1474, 1242, 824; δ_H (400 MHz; DMSO-d_6) 8.86 (1 H, d, *J* 8.4, ArH), 8.83 (1 H, d, *J* 8.4, ArH), 8.61 (1 H, d, *J* 8.0, ArH), 8.57 (1 H, d, *J* 8.0, ArH), 8.33 (2 H, dd, *J* 8.4, 1.2, ArH), 7.76 (1 H, t, *J* 7.4, ArH), 7.73 (1 H, t, *J* 7.4, ArH), 7.65–7.59 (4 H, m, ArH), 7.50 (1 H, t, *J* 7.4, ArH); δ_C (100 MHz; DMSO-d_6) 149.6 (C), 137.5 (C), 130.9 (C), 129.7 (CH), 129.4 (CH), 128.17 (C), 128.15 (C), 128.1 (C), 127.6 (CH), 127.54 (CH), 127.46 (C), 126.6 (CH), 125.8 (CH), 125.7 (CH), 124.6 (CH), 124.2 (CH), 122.9 (C), 122.5 (CH), 122.4 (CH); *m*/*z* (ESI) 295 (M + H^+, 100%). Data are consistent with those reported in literature.[29]



2-(4-Fluorophenyl)-1H-phenanthro[9,10-d]imidazole ***7b.*** Prepared by general procedure 1 from phenanthrene-9,10-dione (500 mg, 2.40 mmol) and 4-fluorobenzaldehyde (254 μL, 2.64 mmol). Purification by recrystallization from hexane–dichloromethane (1 : 2) gave the *title compound* as a colourless solid (251 mg, 34%); mp 214–215 °C; (Found: M + H^+, 313.1143. $C_{21}H_{13}FN_2$ + H^+ requires 313.1136); ν_{max} ($CHCl_3$)/cm^{-1} 3459, 3010, 1609, 1525, 1483, 1455, 1428, 1240, 1158, 1100, 842; δ_H (400 MHz; DMSO-d_6) 8.87 (1 H, d, *J* 8.0, ArH), 8.83 (1 H, d, *J* 8.0, ArH), 8.59 (1 H, d, *J* 8.0, ArH), 8.53 (1 H, d, *J* 8.0, ArH), 8.37 (1 H, d, *J* 8.8, ArH), 8.35 (1 H, d, *J* 8.8, ArH), 7.76 (1 H, t, *J* 7.2, ArH), 7.72 (1 H, t, *J* 7.2, ArH), 7.66–7.61 (2 H, m, ArH), 7.46 (2 H, t, *J* 8.8, ArH); δ_C (100 MHz; DMSO-d_6) 163.2 (d, *J* 245, CF), 148.7 (C), 137.4 (C), 128.8 (d, *J* 8, CH), 128.17 (C), 128.01 (C), 127.64 (CH), 127.56 (CH), 127.53 (C), 127.50 (C), 127.4 (C), 125.8 (CH), 125.64 (CH), 124.57 (CH), 124.2 (CH), 122.9 (C), 122.4 (CH), 122.3 (CH), 116.5 (d, *J* 21, CH); *m*/*z* (ESI) 313 (M + H^+, 100%).

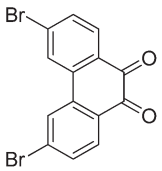


2-(4-Methoxyphenyl)-1H-phenanthro[9,10-d]imidazole ***7c.*** Prepared by general procedure 1 from phenanthrene-9,10-dione (300 mg, 1.44 mmol) and 4-methoxybenzaldehyde (193 μL, 1.58 mmol). Purification by recrystallization from ethanol gave the *title compound* as a beige solid (196 mg, 42%); mp 265–266 °C (lit.,[30] mp 265–266 °C); (Found: M + H^+, 325.1331. $C_{22}H_{16}N_2O$ + H^+ requires 325.1335); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3608, 1602, 1559, 1484, 1178, 839; δ_H (400 MHz; DMSO-d_6) 13.30 (1 H, s, NH), 8.85 (1 H, d, *J* 8.4, ArH), 8.83 (1 H, d, *J* 8.4, ArH), 8.60 (1 H, d, *J* 8.0, ArH), 8.54 (1 H, d, *J* 8.0, ArH), 8.27 (2 H, d, *J* 8.4, ArH), 7.74 (1 H, t, *J* 7.4, ArH), 7.72 (1 H, t, *J* 7.4, ArH), 7.62 (2 H, t, *J* 7.4, ArH), 7.17 (2 H, d, *J* 8.4, ArH), 3.87 (3 H, s, Me); δ_C (100 MHz; DMSO-d_6) 160.7 (C), 149.8 (C), 137.4 (2 × C), 128.2 (CH), 128.0 (C), 127.93 (C), 127.87 (C), 127.52 (CH), 127.48 (CH), 125.6 (CH), 125.5 (CH), 124.5 (CH), 124.2 (CH), 123.5 (C), 122.9 (C), 122.3 (2 × CH), 114.9 (CH), 55.8 (Me); *m*/*z* (ESI) 325 (M + H^+, 100%).

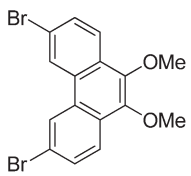


2-(3,5-Bis(trifluoromethyl)phenyl)-1H-phenanthro[9,10-d]imidazole ***7d.*** Prepared by general procedure 1 from phenanthrene-

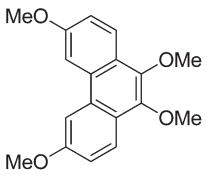
9,10-dione (1.00 g, 4.80 mmol) and 3,5-bis(trifluoromethyl)-benzaldehyde (871 μL, 5.28 mmol). Purification by flash chromatography, eluting with light petroleum–ethyl acetate (9 : 1), followed by trituration with ether (20 mL) gave the *title compound* as a colourless solid (1.08 g, 52% yield, 63% purity); mp 307–308 °C; (Found: M + H^+, 431.0959. $C_{23}H_{12}F_6N_2$ + H^+ requires 431.0977); ν_{max} ($CHCl_3$)/cm^{-1} 3451, 3012, 1621, 1427, 1280, 1184, 1144, 1094, 1016, 896, 847; δ_H (400 MHz; acetone-d_6) 12.98 (1 H, s, NH), 8.90 (3 H, br s, ArH), 8.85 (1 H, d, *J* 8.0, ArH), 8.75 (1 H, d, *J* 8.0, ArH), 8.38 (1 H, d, *J* 7.4, ArH), 8.13 (1 H, s, ArH), 7.76 (1 H, t, *J* 7.4, ArH), 7.72–7.67 (3 H, m, ArH); δ_C (100 MHz; acetone-d_6) 146.8 (C), 138.9 (C), 134.0 (2 × C), 132.7 (q, *J* 33, C), 129.8 (C), 129.3 (C), 129.2 (C), 128.3 (C), 128.1 (CH), 127.9 (CH), 126.91 (CH), 126.87 (CH), 126.7 (CH), 126.5 (CH), 124.9 (CH), 124.5 (q, *J* 270, CF_3), 124.4 (CH), 123.3 (CH), 122.7 (CH), *m*/*z* (ESI) 431 (M + H^+, 100%).



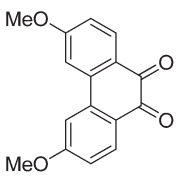
3,6-Dibromophenanthrene-9,10-dione ***8***. Phenanthrene-9,10-dione (5.00 g, 24.0 mmol) was dissolved in nitrobenzene (48 mL) and treated with benzoyl peroxide (582 mg, 2.40 mmol) followed by the slow addition of bromine (2.52 mL, 49.2 mmol). The mixture was heated at 110 °C for 16 h, cooled to room temperature and diluted with ethanol (100 mL). The resulting precipitate was collected by filtration to give the first crop, and the filtrate concentrated. The residue was triturated with ethanol (50 mL) and filtered to give a second crop, which was combined with the first to give the *title compound* as a light brown solid (6.73 g, 77%); mp 283–285 °C (lit.,[31] mp 281–284 °C); (Found: M + H^+, 386.8639. $C_{14}H_6{}^{79}Br_2O_2$ + H^+ requires 386.8627); λ_{max} (MeOH)/nm 331 (log ε 3.46); ν_{max} ($CHCl_3$)/cm^{-1} 3012, 1681, 1587, 1548, 1289, 923, 831; δ_H (400 MHz; DMSO-d_6) 8.63 (2 H, br s, ArH), 7.91 (2 H, d, *J* 8.4, ArH), 7.75 (2 H, dd, *J* 8.4, 1.4, ArH); δ_C (100 MHz; DMSO-d_6) 177.6 (C), 135.9 (C), 132.7 (CH), 130.8 (CH), 130.7 (C), 130.0 (C), 127.7 (CH); *m*/*z* (ESI) 388 (M + H^+, 100%).



3,6-Dibromo-9,10-dimethoxyphenanthrene ***9***. 3,6-Dibromophenanthrene-9,10-dione **8** (300 mg, 0.82 mmol) was suspended in THF–water (1 : 1; 14 mL) and treated with tetrabutylammonium bromide (106 mg, 0.33 mmol) and sodium dithionite (571 mg, 3.28 mmol). The reaction mixture was stirred at room temperature for 15 min, dimethyl sulfate (543 μL, 5.74 mmol) added slowly and the mixture stirred for an additional 15 min. Ice (10 g) was added and the reaction mixture stirred for 15 min, and then extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with water (30 mL) and saturated brine (30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography, eluting with cyclohexane–dichloromethane (1 : 1), gave the *title compound* as a cream solid (262 mg, 81%); mp 152–153 °C (lit.,[25] mp 162–163 °C); (Found: M + H^+, 393.9191. $C_{16}H_{12}{}^{79}Br_2O_2$ + H^+ requires 393.9199); ν_{max} ($CHCl_3$)/cm^{-1} 3010, 2843, 1615, 1591, 1486, 1346, 1312, 1122, 1095, 986; δ_H (400 MHz; $CDCl_3$) 8.65 (2 H, d, *J* 1.8, ArH), 8.10 (2 H, d, *J* 8.8, ArH), 7.73 (2 H, dd, *J* 8.8, 1.8, ArH), 4.08 (6 H, s, Me); δ_C (100 MHz; $CDCl_3$) 143.8 (C), 130.6 (CH), 128.9 (C), 128.2 (C), 125.4 (CH), 124.0 (CH), 120.5 (C), 61.0 (Me); *m*/*z* (ESI) 394/396/398 (M + H^+, 8/16/8%). Data are consistent with those reported in literature.[25]

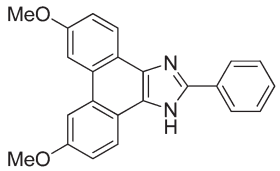


3,6,9,10-Tetramethoxyphenanthrene ***10***. Copper(I) bromide was purified prior to use by stirring in glacial acetic acid for 16 h, filtering and triturating with ethanol and ether. 3,6-Dibromo-9,10-dimethoxyphenanthrene **9** (3.02 g, 7.62 mmol) was suspended in ethyl acetate–toluene (1 : 1; 8 mL) and treated slowly with a solution of sodium methoxide (25%; 64 mL, 305 mmol). Copper(I) bromide (218 mg, 1.52 mmol) was added and the resulting mixture heated at 80 °C for 64 h. The reaction mixture was added to water (100 mL) and extracted with dichloromethane (3 × 75 mL). The combined organic extracts were dried ($MgSO_4$), concentrated onto silica gel and purified by flash chromatography, eluting with light petroleum–ethyl acetate (9 : 1) to give the *title compound* as a cream solid (1.95 g, 86%); mp 73–74 °C (lit.,[25] mp 74–76 °C); (Found: M + Na^+, 321.1103. $C_{18}H_{18}O_4$ + Na^+ requires 321.1097); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2939, 2838, 1608, 1509, 1449, 1431, 1370, 1356, 1319, 1258, 1240, 1173, 1116, 1073, 1036, 990; δ_H (400 MHz; $CDCl_3$) 8.14 (2 H, d, *J* 9.0, ArH), 7.93 (2 H, d, *J* 2.2, ArH), 7.30–7.27 (2 H, m, ArH), 4.07 (6 H, s, Me), 4.02 (6 H, s, Me); δ_C (100 MHz; $CDCl_3$) 157.7 (C), 142.3 (C), 129.3 (C), 124.0 (C), 123.8 (CH), 116.5 (CH), 104.7 (CH), 61.0 (Me), 55.6 (Me); *m*/*z* (ESI) 321 (M + Na^+, 100%). Data are consistent with those reported in literature.[25]

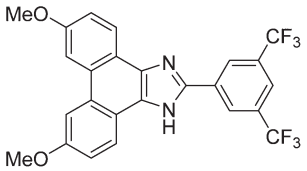


3,6-Dimethoxyphenanthrene-9,10-dione ***11***. 3,6,9,10-Tetramethoxyphenanthrene **10** (330 mg, 1.11 mmol) was dissolved in acetonitrile (6 mL) and treated with a solution of ammonium cerium(IV) nitrate (1.21 g, 2.21 mmol) in acetonitrile (15 mL). Water (45 mL) was added slowly and the resulting precipitate collected by filtration and triturated with

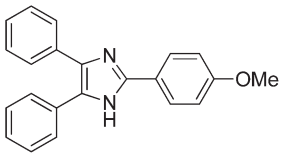
ethanol to give the *title compound* as a yellow solid (236 mg, 79%); mp 228–229 °C (lit.,[25] mp 226–230 °C); (Found: M + Na^+, 291.0640. $C_{16}H_{12}O_4$ + Na^+ requires 291.0628); λ_{max} (MeOH)/nm 349 ($\log \varepsilon$ 5.35); ν_{max} ($CHCl_3$)/cm^{-1} 3011, 2843, 1670, 1595, 1566, 1344, 1324, 1313, 1247; δ_H (400 MHz; $CDCl_3$) 8.17 (2 H, d, *J* 8.6, ArH), 7.35 (2 H, d, *J* 2.0, ArH), 6.95 (2 H, dd, *J* 8.6, 2.0, ArH), 3.97 (6 H, s, Me); δ_C (100 MHz; $CDCl_3$) 179.0 (C), 165.6 (C), 137.5 (C), 133.3 (CH), 125.1 (C), 114.3 (CH), 109.8 (CH), 55.9 (Me); *m*/*z* (ESI) 291 (M + Na^+, 100%). Data are consistent with those reported in literature.[25]



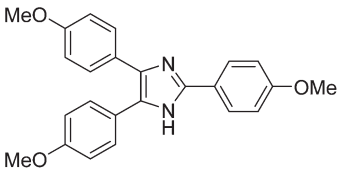
6,9-Dimethoxy-2-phenyl-1H-phenanthro[9,10-d]imidazole ***12***. Prepared by general procedure 1 from 3,6-dimethoxyphenanthrene-9,10-dione **11** (150 mg, 0.56 mmol) and benzaldehyde (62 μL, 0.61 mmol). Purification by flash chromatography, eluting with light petroleum–ethyl acetate (3 : 1), followed by trituration with ether (15 mL) gave the *title compound* as a pale yellow solid (100 mg, 51%); mp 273–274 °C; (Found: M + H^+, 355.1434. $C_{23}H_{18}N_2O_2$ + H^+ requires 355.1441); ν_{max} ($CHCl_3$)/cm^{-1} 3462, 3006, 1731, 1624, 1594, 1548, 1468, 1456, 1408, 1389, 1173, 1031; δ_H (400 MHz; DMSO-d_6) 13.25 (1 H, s, NH), 8.48 (2 H, d, 8.4, ArH), 8.28 (2 H, dd, *J* 8.4, 1.2, ArH), 8.24 (1 H, br s, ArH), 8.21 (1 H, br s, ArH), 7.59 (2 H, t, *J* 7.2, ArH), 7.48 (1 H, t, *J* 7.2, ArH), 7.44 (1 H, d, *J* 8.4, ArH), 7.39 (1 H, d, *J* 8.4, ArH), 4.03 (6 H, s, Me); δ_C (100 MHz; DMSO-d_6) 157.1 (C), 157.0 (C), 148.1 (C), 135.7 (C), 130.6 (C), 128.9 (2 × CH), 128.8 (C), 128.4 (C), 126.5 (C), 125.9 (CH), 123.5 (CH), 123.3 (CH), 121.6 (C), 117.1 (C), 116.5 (CH), 116.4 (CH), 106.9 (CH), 106.4 (CH), 55.6 (Me), 55.5 (Me); *m*/*z* (ESI) 355 (M + H^+, 100%).



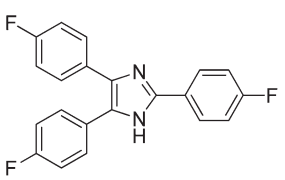
2-(3,5-Bis(trifluoromethyl)phenyl)-6,9-dimethoxy-1H-phenanthro[9,10-d]imidazole ***13***. Prepared by general procedure 1 from 3,6-dimethoxyphenanthrene-9,10-dione **11** (150 mg, 0.56 mmol) and 3,5-bis(trifluoromethyl)benzaldehyde (101 μL, 0.61 mmol). Purification by flash chromatography, eluting with light petroleum–ethyl acetate (85 : 15), followed by trituration with dichloromethane (10 mL) gave the *title compound* as a yellow solid (221 mg, 56%); mp 256–257 °C; (Found: M + H^+, 491.1199. $C_{25}H_{16}F_6N_2O_2$ + H^+ requires 491.1189); λ_{max} (CH_2Cl_2)/nm 390 ($\log \varepsilon$ 5.58), 369 (5.53); ν_{max} ($CHCl_3$)/cm^{-1} 3454, 1624, 1600, 1467, 1361, 1280, 1175, 1143; δ_H (400 MHz; DMSO-d_6) 13.55 (1 H, br s, NH), 8.83 (2 H, s, ArH), 8.39 (2 H, br s, ArH), 8.19 (2 H, br s, ArH), 8.15 (1 H, s, ArH), 7.39 (2 H, d, *J* 7.6, ArH), 4.01 (6 H, s, Me); δ_C (100 MHz; DMSO-d_6) 157.5 (C), 157.4 (C), 144.8 (C), 136.0 (C), 132.9 (C), 131.0 (q, *J* 33, C), 129.4 (C), 128.8 (C), 127.4 (C), 127.3 (C), 125.7(CH), 125.6 (CH), 123.5 (CH), 123.3 (q, *J* 271, CF_3), 121.6 (CH), 116.7 (C), 116.5 (CH), 116.4 (CH), 107.1 (CH), 106.5 (CH), 55.6 (Me); *m*/*z* (ESI) 491 (M + H^+, 100%).



2-(4-Methoxyphenyl)-4,5-diphenyl-1H-imidazole ***14***. Prepared by general procedure 1 from benzil (300 mg, 1.43 mmol) and 4-methoxybenzaldehyde (174 μL, 1.43 mmol). Purification by recrystallization from hexane–ethanol (1 : 4) gave the *title compound* as a colourless solid (285 mg, 61%); mp 233–234 °C (lit.,[32] mp 234 °C); (Found: M + H^+, 327.1483. $C_{22}H_{18}N_2O$ + H^+ requires 327.1492); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3449, 3011, 2839, 1615, 1506, 1464, 1254, 1177, 1032, 835; δ_H (400 MHz; DMSO-d_6) 12.49 (1 H, s, NH), 8.01 (2 H, d, *J* 8.8, ArH), 7.54 (2 H, d, *J* 7.6, ArH), 7.49 (2 H, d, *J* 7.6, ArH), 7.43 (2 H, t, *J* 7.2, ArH), 7.36 (1 H, t, *J* 7.2, ArH), 7.30 (2 H, t, *J* 7.2, ArH), 7.21 (1 H, t, *J* 7.2, ArH), 7.04 (2 H, d, *J* 8.8, ArH), 3.82 (3 H, s, Me); δ_C (100 MHz; DMSO-d_6) 159.4 (C), 146.6 (C), 136.7 (C), 135.3 (C), 131.2 (C), 128.6 (CH), 128.3 (CH), 128.1 (CH), 127.6 (CH), 127.0 (CH), 126.7 (CH), 126.43 (C), 126.39 (CH), 123.1 (C), 114.1 (CH), 55.2 (Me); *m*/*z* (ESI) 327 (M + H^+, 100%).

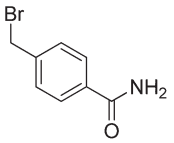


2,4,5-Tri(4-methoxyphenyl)-1H-imidazole ***15***. Prepared by general procedure 1 from 4,4′-dimethoxybenzil (250 mg, 0.92 mmol) and benzaldehyde (124 μL, 1.02 mmol). Purification by flash chromatography, eluting with light petroleum–ethyl acetate (2 : 3), followed by trituration with ether (10 ml) gave the *title compound* as a cream solid (249 mg, 70%); mp 184–185 °C (lit.,[33] mp 183–184 °C); (Found: M + H^+, 387.1702. $C_{24}H_{22}N_2O_3$ + H^+ requires 387.1703); ν_{max} ($CHCl_3$)/cm^{-1} 3450, 3011, 2962, 2839, 1616, 1520, 1499, 1466, 1441, 1295, 1248, 1176, 1034, 836; δ_H (400 MHz; DMSO-d_6) 7.99 (2 H, d, *J* 8.6, ArH), 7.46 (2 H, d, *J* 8.6, ArH), 7.40 (2 H, d, *J* 8.6, ArH), 7.04–6.99 (4 H, m, ArH), 6.87 (2 H, d, *J* 8.6, ArH), 3.81 (3 H, s, Me), 3.80 (3 H, s, Me), 3.74 (3 H, s, Me); δ_C (100 MHz; DMSO-d_6) 159.2 (C), 158.6 (C), 157.8 (C), 144.9 (C), 136.0 (C), 129.6 (CH), 128.1 (CH), 128.0 (C), 126.5 (CH), 123.7 (C), 123.3 (2 × C), 114.0 (2 × CH), 113.6 (CH), 55.2 (2 × Me), 55.0 (Me); *m*/*z* (ESI) 357 (M + H^+, 100%).

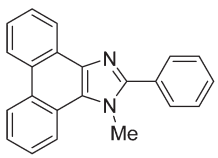


2,4,5-Tri(4-fluorophenyl)-1H-imidazole ***16***. Prepared by general procedure 1 from 4,4′-difluorobenzil (300 mg,

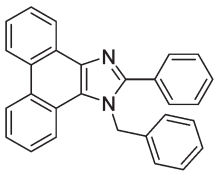
1.22 mmol) and 4-fluorobenzaldehyde (117 μL, 1.22 mmol). Purification by recrystallization from hexane–ethanol (1 : 2) gave the *title compound* as a colourless solid (183 mg, 43%); mp 245–246 °C (lit.,[34] mp 162–164 °C); (Found: C, 72.1; H, 3.7; N, 8.0. $C_{21}H_{13}F_3N_2$ requires C, 72.0; H, 3.7; N, 8.0%); (Found: M + H^+, 351.1097. $C_{21}H_{13}F_3N_2$ + H^+ requires 351.1104); ν_{max} ($CHCl_3$)/cm^{-1} 3447, 2974, 1602, 1518, 1497, 1439, 1240, 1157, 1094, 841; δ_H (400 MHz; DMSO-d_6) 12.73 (1 H, br s, NH), 8.10 (1 H, d, *J* 9.0, ArH), 8.09 (1 H, d, *J* 9.0, ArH), 7.53 (2 H, d, *J* 8.8, ArH), 7.52 (2 H, d, *J* 8.8, ArH), 7.33 (2 H, t, *J* 9.0, ArH), 7.32–7.12 (4 H, m, ArH); δ_C (100 MHz; DMSO-d_6) 162.2 (d, *J* 244, CF), 161.7 (d, *J* 244, CF), 161.1 (d, *J* 242, CF), 144.7 (C), 136.2 (C), 131.4 (d, *J* 3, C), 130.6 (d, *J* 7, CH), 128.9 (d, *J* 9, CH), 127.31 (d, *J* 3, C), 127.30 (d, *J* 8, CH), 127.1 (C), 126.9 (d, *J* 3, C), 115.73 (d, *J* 22, CH), 115.68 (d, *J*, 21, CH), 115.1 (d, *J* 21, CH); *m*/*z* (ESI) 351 (M + H^+, 100%).



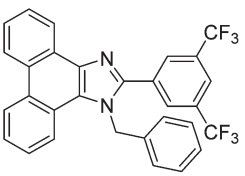
4-(Bromomethyl)benzamide ***17***. 4-(Bromomethyl)benzoic acid (2.50 g, 11.6 mmol) was suspended in ethyl acetate (45 mL) and treated with thionyl chloride (1.27 mL, 17.4 mmol). The mixture was heated at 75 °C for 15 h, cooled and concentrated under reduced pressure. The residue was dissolved in dichloromethane (45 mL), cooled to 0 °C and ammonium hydroxide (35%; 1.13 mL, 23.3 mmol) added slowly. The mixture was stirred at 0 °C for 15 min and then quenched with water (45 mL). The resulting precipitate was filtered, washed with water (50 mL) and dried under vacuum to give the *title compound* as a colourless solid (2.22 g, 89%); mp 181–182 °C (lit.,[35] mp 185–187 °C); (Found: M + Na^+, 235.9684. $C_8H_8{}^{79}BrNO$ + Na^+ requires 235.9681); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3521, 1734, 1697, 1611, 1421, 1371, 1315, 1286, 1171, 1089; δ_H (400 MHz; DMSO-d_6) 7.99 (1 H, br s, NH), 7.84 (2 H, d, *J* 8.4, ArH), 7.51 (2 H, d, *J* 8.4, ArH), 7.40 (1 H, br s, NH), 4.73 (2 H, s, CH_2); δ_C (100 MHz; DMSO-d_6) 167.3 (C), 141.1 (C), 134.1 (C), 129.1 (CH), 127.8 (CH), 33.5 (CH_2); *m*/*z* (ESI) 235/237 (M + Na^+, 98/100%). Data are consistent with those reported in literature.[36]



1-Methyl-2-phenyl-1H-phenanthro[9,10-d]imidazole ***18***. Prepared by general procedure 2 from 2-phenyl-1*H*-phenanthro[9,10-*d*]imidazole **7a** (200 mg, 0.68 mmol) and iodomethane (85 μL, 1.36 mmol) in THF (7 mL). Purification by flash chromatography, eluting with light petroleum–ethyl acetate (4 : 1), followed by trituration with ether (15 mL) gave the *title compound* as a colourless solid (135 mg, 64%); mp 184–185 °C (lit.,[37] mp 185–186 °C); (Found: M + H^+, 309.1388. $C_{22}H_{16}N_2$ + H^+ requires 309.1386); ν_{max} ($CHCl_3$)/cm^{-1} 3069, 3008, 2960, 1613, 1576, 1532, 1473, 1462, 1422, 1380, 1329, 1028; δ_H (400 MHz; DMSO-d_6) 8.97 (1 H, d, *J* 8.0, ArH), 8.86 (1 H, d, *J* 8.0, ArH), 8.60 (2 H, t, *J* 7.2, ArH), 7.88 (2 H, d, *J* 6.0, ArH), 7.76–7.62 (7 H, m, ArH), 4.30 (3 H, s, Me); δ_C (100 MHz; DMSO-d_6) 152.1 (C), 136.6 (C), 130.2 (C), 129.7 (CH), 129.4 (CH), 128.7 (CH), 128.2 (C), 127.5 (C), 127.4 (C), 127.3 (CH), 127.1 (CH), 126.9 (C), 125.4 (CH), 125.1 (CH), 124.5 (CH), 123.6 (CH), 123.2 (C), 121.9 (CH), 121.3 (CH), 36.0 (Me); *m*/*z* (ESI) 309 (M + H^+, 100%).

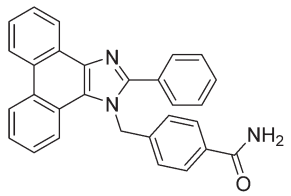


1-Benzyl-2-phenyl-1H-phenanthro[9,10-d]imidazole ***19***. Phenanthrene-9,10-dione (250 mg, 1.20 mmol) was suspended in glacial acetic acid (6 mL) and ammonium acetate (463 mg, 6.00 mmol), benzylamine (144 μL, 1.32 mmol) and benzaldehyde (133 μL, 1.32 mmol) were added. The mixture was heated at 150 °C for 15 min under microwave irradiation (300 W), cooled to room temperature and added to water (20 mL). The aqueous solution was extracted with ethyl acetate (3 × 10 mL), and the combined organic extracts were washed with saturated brine (20 mL), dried ($MgSO_4$) and concentrated onto silica. Purification by flash chromatography, eluting with light petroleum–ethyl acetate (3 : 1), followed by trituration with ether (10 mL) gave the *title compound* as a colourless solid (96 mg, 21%); mp 239–240 °C (lit.,[38] mp 241 °C); (Found: M + H^+, 385.1698. $C_{28}H_{20}N_2$ + H^+ requires 385.1699); ν_{max} ($CHCl_3$)/cm^{-1} 3068, 3011, 2968, 1605, 1531, 1512, 1498, 1474, 1455, 1426, 1391, 1265; δ_H (400 MHz; DMSO-d_6) 8.92 (1 H, d, *J* 8.2, ArH), 8.86 (1 H, d, *J* 8.2, ArH), 8.66 (1 H, dd, *J* 8.2, 1.2, ArH), 8.10 (1 H, dd, *J* 8.2, 1.2, ArH), 7.78–7.71 (3 H, m, ArH), 7.67 (1 H, td, *J* 7.6, 1.2, ArH), 7.59–7.54 (4 H, m, ArH), 7.49 (1 H, td, *J* 7.2, 1.2, ArH), 7.34 (2 H, t, *J* 7.6, ArH), 7,26 (1 H, t, *J* 7.2, ArH), 7.13 (2 H, d, *J* 7.6, ArH), 5.96 (2 H, s, CH_2); δ_C (100 MHz; DMSO-d_6) 152.6 (C), 137.14 (C), 137.08 (C), 130.2 (C), 129.7 (CH), 129.3 (CH), 129.1 (CH), 128.8 (CH), 128.3 (C), 127.7 (C), 127.5 (CH), 127.4 (CH), 126.9 (CH), 126.8 (C), 126.4 (C), 125.7 (CH), 125.4 (CH), 125.1 (CH), 124.3 (CH), 123.6 (CH), 122.4 (C), 121.9 (CH), 121.2 (CH), 50.0 (CH_2); *m*/*z* (ESI) 385 (M + H^+, 100%).

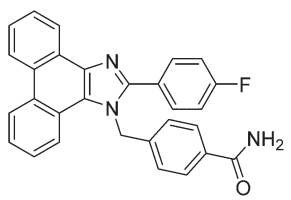


1-Benzyl-2-(3,5-bis(trifluoromethyl)phenyl)-1H-phenanthro[9,10-d]imidazole ***20***. Prepared by general procedure 2 from 2-(3,5-bis(trifluoromethyl)phenyl)-1*H*-phenanthro[9,10-*d*]imidazole **7d** (200 mg, 0.46 mmol) and benzyl bromide (111 μL, 0.93 mmol) in THF (5 mL). Purification by flash chromato-

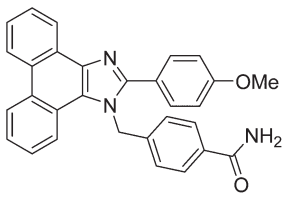
graphy, eluting with light petroleum–ethyl acetate (9 : 1), followed by trituration with ether gave the *title compound* as a colourless solid (108 mg, 45%); mp 215–216 °C; (Found: M + H^+, 521.1433. $C_{30}H_{18}F_6N_2$ + H^+ requires 521.1447); ν_{max} ($CHCl_3$)/cm^{-1} 2361, 1455, 1396, 1353, 1280, 1186, 1144, 1038, 905, 850; δ_H (400 MHz; acetone-d_6) 8.96 (1 H, d, *J* 8.8, ArH), 8.87 (1 H, d, *J* 8.0, ArH), 8.79 (1 H, dd, *J* 8.0, 1.4, ArH), 8.36 (2 H, br s, ArH), 8.21 (1 H, d, *J* 8.8, ArH), 8.19 (1 H, s, ArH), 7.78 (1 H, t, *J* 7.2, ArH), 7.71 (1 H, t, *J* 7.6, ArH), 7.63 (1 H, t, *J* 7.6, ArH), 7.52 (1 H, t, *J* 7.6, ArH), 7.45 (2 H, t, *J* 7.6, ArH), 7.39–7.34 (3 H, m, ArH), 6.11 (2 H, s, CH_2); δ_C (100 MHz; acetone-d_6) 150.7 (C), 139.0 (C), 137.9 (C), 134.2 (C), 132.6 (q, *J* 34, C), 130.6 (CH), 130.5 (CH), 130.4 (C), 130.3 (CH), 129.4 (C), 129.0 (C), 128.9 (CH), 128.3 (CH), 128.0 (CH), 127.0 (q, *J* 270, CF_3), 126.9 (CH), 126.8 (CH), 126.5 (CH), 125.3 (CH), 124.4 (CH), 123.83 (C), 123.78 (C), 123.4 (CH), 122.5 (CH), 51.7 (CH_2); *m*/*z* (ESI) 521 (M + H^+, 100%).



*1-(4-Carboxamidobenzyl)-2-phenyl-1H-phenanthro[9,10-d]imidazole **21**.* Prepared by general procedure 2b from 2-phenyl-1*H*-phenanthro[9,10-*d*]imidazole **7a** (200 mg, 0.68 mmol) and 4-(bromomethyl)benzamide **17** (175 mg, 0.82 mmol). Purification by flash chromatography, eluting with light petroleum–ethyl acetate (1 : 4) followed by recrystallization from dichloromethane–methanol (1 : 1) gave the *title compound* as a colourless solid (16 mg, 6%); mp 280–281 °C; (Found: M + H^+, 428.1752. $C_{29}H_{21}N_3O$ + H^+ requires 428.1757); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3607, 3012, 1682, 1602, 1540, 1474, 1458, 1368, 1239; δ_H (400 MHz; DMSO-d_6) 8.92 (1 H, d, *J* 8.0, ArH), 8.86 (1 H, d, *J* 8.0, ArH), 8.67 (1 H, d, *J* 8.0, ArH), 8.05 (1 H, d, *J* 8.0, ArH), 7.92 (1 H, br s, NH), 7.82 (2 H, d, *J* 8.2, ArH), 7.78–7.66 (4 H, m, ArH), 7.59–7.55 (4 H, m, ArH), 7.47 (1 H, t, *J* 8.0, ArH), 7.33 (1 H, br s, NH), 7.21 (2 H, d, *J* 8.2, ArH), 6.00 (2 H, s, CH_2); δ_C (100 MHz; DMSO-d_6) 167.4 (C), 152.6 (C), 140.3 (C), 137.2 (C), 133.6 (C), 130.1 (2 × C), 129.7 (CH), 129.3 (CH), 128.8 (CH), 128.3 (CH), 127.7 (C), 127.4 (CH), 127.0 (C), 126.8 (CH), 126.3 (C), 125.8 (CH), 125.4 (CH), 125.1 (CH), 124.4 (CH), 123.6 (CH), 122.4 (C), 122.0 (CH), 121.1 (CH), 49.9 (CH_2); *m*/*z* (ESI) 428 (M + H^+, 65%).

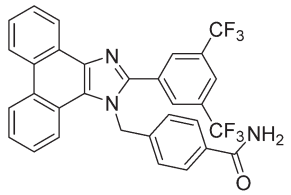


*1-(4-Carboxamidobenzyl)-2-(4-fluorophenyl)-1H-phenanthro[9,10-d]imidazole **22**.* Prepared by general procedure 2 from 2-(4-fluorophenyl)-1*H*-phenanthro[9,10-*d*]imidazole **7b** (200 mg, 0.64 mmol) and 4-(bromomethyl)benzamide **17** (206 mg, 0.96 mmol) in THF (6 mL). The mixture was added to water (20 mL), and the resulting precipitate filtered to give the first crop of product. The filtrate was extracted with ethyl acetate (3 × 10 mL) and the combined organic extracts washed with saturated brine (20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was adsorbed onto silica and purified by flash chromatography, eluting with light petroleum–ethyl acetate (1 : 4), followed by trituration with ether to give a second crop. Both crops were combined to give the *title compound* as a colourless solid (124 mg, 43% yield, 91% purity); mp 300–301 °C; (Found: M + H^+, 446.1673. $C_{29}H_{20}FN_3O$ + H^+ requires 446.1663); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3491, 3291, 3152, 1683, 1615, 1567, 1532, 1474, 1414, 1162; δ_H (400 MHz; DMSO-d_6) 8.93 (1 H, d, *J* 8.0, ArH), 8.87 (1 H, d, *J* 8.0, ArH), 8.66 (1 H, dd, *J* 8.0, 1.4, ArH), 8.05 (1 H, d, *J* 8.0, ArH), 7.91 (1 H, br s, NH), 7.80 (2 H, d, *J* 8.0, ArH), 7.77–7.74 (3 H, m, ArH), 7.68 (1 H, td, *J* 8.0, 1.4, ArH), 7.58 (1 H, td, *J* 8.0, 1.4, ArH), 7.49 (1 H, td, *J* 8.0, 1.4, ArH), 7.41 (2 H, t, *J* 8.0, ArH), 7.33 (1 H, br s, NH), 7.21 (2 H, d, *J* 8.0, ArH), 5.98 (2 H, s, CH_2); δ_C (100 MHz; DMSO-d_6) 167.4 (C), 162.9 (d, *J* 245, CF), 151.7 (C), 140.2 (C), 137.1 (C), 133.7 (C), 131.4 (d, *J* 9, CH), 128.4 (CH), 127.7 (2 × C), 127.4 (CH), 127.0 (CH), 126.7 (C), 126.6 (d, *J* 4, C), 126.3 (C), 125.8 (CH), 125.4 (CH), 125.2 (CH), 124.4 (CH), 123.6 (CH), 122.3 (C), 122.0 (CH), 121.1 (CH), 115.9 (d, *J* 22, CH), 49.1 (CH_2); *m*/*z* (ESI) 446 (M + H^+, 91%).

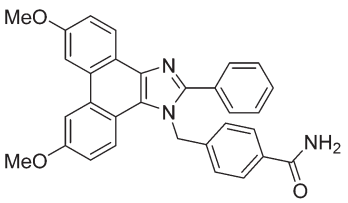


*1-(4-Carboxamidobenzyl)-2-(4-methoxyphenyl)-1H-phenanthro[9,10-d]imidazole **23**.* Prepared by general procedure 2 from 2-(4-methoxyphenyl)-1*H*-phenanthro[9,10-*d*]imidazole **7c** (200 mg, 0.62 mmol) and 4-(bromomethyl)benzamide **17** (198 mg, 0.92 mmol) in DMF (6 mL). Purification by flash chromatography, eluting with dichloromethane–methanol (9 : 1), followed by trituration with dichloromethane (10 mL) gave the *title compound* as a colourless solid (42 mg, 15% yield, 67% purity); mp 297–298 °C; (Found: M + H^+, 458.1850. $C_{30}H_{22}N_3O_2$ + H^+ requires 458.1863); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3513, 3319, 3164, 3012, 1686, 1606, 1568, 1476, 1417, 1298, 1264, 1184, 950; δ_H (400 MHz; DMSO-d_6) 8.93 (1 H, d, *J* 8.4, ArH), 8.86 (1 H, d, *J* 8.4, ArH), 8.66 (1 H, d, *J* 8.4, ArH), 8.04 (1 H, d, *J* 8.4, ArH), 7.92 (1 H, br s, NH), 7.82 (1 H, d, *J* 8.0, ArH), 7.75 (1 H, t, *J* 7.6, ArH), 7.69–7.63 (3 H, m, ArH), 7.56 (1 H, t, *J* 7.8, ArH), 7.48 (1 H, t, *J* 7.8, ArH), 7.33 (1 H, s, NH), 7.21 (2 H, d, *J* 8.4, ArH), 7.10 (2 H, d, *J* 8.4, ArH), 5.98 (2 H, s, CH_2), 3.82 (3 H, s, Me); δ_C (100 MHz; DMSO-d_6) 167.5 (C), 160.4 (C), 152.7 (C), 140.5 (C), 137.1 (C), 133.7 (C), 130.8 (CH), 128.4 (CH), 128.3 (C), 127.7 (C), 127.4 (CH), 127.0 (CH), 126.8 (C), 126.2 (C), 125.7 (CH), 125.4 (CH), 125.1 (CH), 124.4 (CH), 123.6 (CH), 122.5 (C), 122.3 (C), 122.1 (CH),

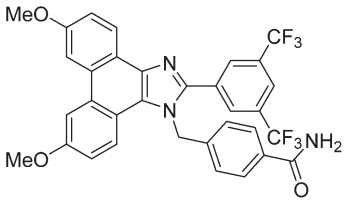
121.1 (CH), 114.3 (CH), 55.4 (Me), 50.0 (CH_2); *m*/*z* (ESI) 458 (M + H^+, 100%).



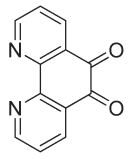
1-(4-Carboxamidobenzyl)-2-(3,5-bis(trifluoromethyl)phenyl)-1H-phenanthro[9,10-d]-imidazole ***24***. Prepared by general procedure 2 from 2-(3,5-bis(trifluoromethyl)phenyl)-1*H*-phenanthro[9,10-*d*]imidazole **7d** (200 mg, 0.46 mmol) and 4-(bromomethyl)benzamide **17** (199 mg, 0.93 mmol) in DMF (5 mL). Purification by flash chromatography, eluting with dichloromethane–methanol (19 : 1), followed by trituration with dichloromethane (10 mL) gave the *title compound* as a colourless solid (22 mg, 8%); mp 312–313 °C; (Found: M + H^+, 564.1492. $C_{31}H_{20}F_6N_3O$ + H^+ requires 564.1505); ν_{max} ($CHCl_3$)/cm^{-1} 3688, 3414, 3010, 1680, 1602, 1353, 1280, 1186, 1145, 904; δ_H (400 MHz; DMSO-d_6) 8.93 (1 H, d, *J* 8.4, ArH), 8.86 (1 H, d, *J* 8.4, ArH), 8.66 (1 H, d, *J* 8.4, ArH), 8.04 (1 H, d, *J* 8.4, ArH), 7.92 (1 H, br s, NH), 7.82 (1 H, d, *J* 8.0, ArH), 7.75 (1 H, t, *J* 7.6, ArH), 7.69–7.63 (3 H, m, ArH), 7.56 (1 H, t, *J* 7.8, ArH), 7.48 (1 H, t, *J* 7.8, ArH), 7.33 (1 H, s, NH), 7.21 (2 H, d, *J* 8.4, ArH), 7.10 (2 H, d, *J* 8.4, ArH), 5.98 (2 H, s, CH_2), 3.82 (3 H, s, Me); δ_C (100 MHz; DMSO-d_6) 167.3 (C), 149.6 (C), 139.9 (C), 137.4 (C), 133.6 (C), 132.5 (C), 130.8 (q, *J* 32, C), 129.8 (CH), 128.7 (C), 128.4 (CH), 127.9 (C), 127.6 (CH), 127.3 (CH), 127.2 (C), 126.6 (C), 126.1 (CH), 125.9 (q, *J* 270, CF_3), 125.6 (CH), 124.5 (CH), 123.7 (CH), 123.4 (CH), 123.3 (CH), 122.1 (CH), 121.7 (C), 121.3 (CH), 50.3 (CH_2); *m*/*z* (ESI) 564 (M + H^+, 100%).



1-(4-Carboxamidobenzyl)-6,9-dimethoxy-2-phenyl-1H-phenanthro[9,10-d]imidazole ***25***. Prepared by general procedure 2 from 6,9-dimethoxy-2-phenyl-1*H*-phenanthro[9,10-*d*]imidazole **12** (200 mg, 0.56 mmol) and 4-(bromomethyl)benzamide **17** (181 mg, 0.85 mmol) in THF (6 mL). The reaction mixture was added to water (20 mL) and the resulting precipitate collected by filtration and triturated with ethyl acetate (10 mL) followed by ether (10 mL) to give the *title compound* as a colourless solid (69 mg, 25% yield, 86% purity); mp 286–288 °C (decomp.); (Found: M + H^+, 488.1966. $C_{31}H_{25}N_3O_3$ + H^+ requires 488.1969); ν_{max} ($CHCl_3$)/cm^{-1} 3690, 3608, 1678, 1602, 1559, 1508, 1466, 1372, 1240; δ_H (400 MHz; DMSO-d_6) 8.55 (1 H, d, *J* 8.8, ArH), 8.27 (1 H, d, *J* 2.4, ArH), 8.20 (1 H, d, *J* 2.4, ArH), 7.94 (1 H, d, *J* 8.8, ArH), 7.92 (1 H, br s, NH), 7.82 (2 H, d, *J* 8.0, ArH), 7.69–7.67 (2 H, m, ArH), 7.54–7.52 (3 H, m, ArH), 7.41 (1 H, dd, *J* 8.8, 2.4, ArH), 7.33 (1 H, br s, NH), 7.19 (2 H, d, *J* 8.0, ArH), 7.15 (1 H, dd, *J* 8.8, 2.4, ArH), 5.94 (2 H, s, CH_2), 4.01 (3 H, s, Me), 3.94 (3 H, s, Me); δ_C (100 MHz; DMSO-d_6) 167.4 (C), 157.4 (C), 156.6 (C), 151.6 (C), 140.4 (C), 135.9 (C), 133.6 (C), 130.3 (2 × C), 129.6 (C), 129.5 (CH), 129.2 (CH), 128.8 (CH), 128.6 (C), 128.3 (CH), 125.4 (CH), 125.2 (C), 123.5 (CH), 122.6 (CH), 121.5 (C), 117.0 (CH), 115.8 (CH), 107.5 (CH), 106.1 (CH), 55.53 (Me), 55.45 (Me), 49.8 (CH_2); *m*/*z* (ESI) 488 (M + H^+, 100%).

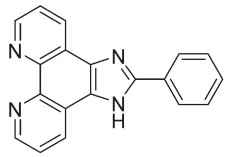


1-(4-Carboxamidobenzyl)-6,9-dimethoxy-2-(3,5-bis(trifluoromethyl)phenyl)-1H-phenanthro[9,10-d]imidazole ***26***. 2-(3,5-Bis-(trifluoromethyl)phenyl)-6,9-dimethoxy-1*H*-phenanthro[9,10-*d*]-imidazole **13** (250 mg, 0.51 mmol) was dissolved in THF (5 mL) and potassium bis(trimethylsilyl)amide (0.7 M; 1.46 mL, 1.02 mmol) was added. The mixture was stirred for 5 min, treated with 4-(bromomethyl)benzamide **17** (546 mg, 2.55 mmol) and stirred at room temperature for 2 days. The mixture was added to water (20 mL) and extracted with ethyl acetate (3 × 15 mL). The combined organic extracts were washed with saturated brine (20 mL), dried (Na_2SO_4) and concentrated onto silica. Purification by column chromatography, eluting with light petroleum–ethyl acetate (2 : 3) followed by trituration with ether (10 mL) gave the *title compound* as a colourless solid (36 mg, 11% yield, 94% purity); mp 319–320 °C; (Found: M + H^+, 624.1701. $C_{33}H_{23}F_6N_3O_3$ + H^+ requires 624.1716); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3607, 3440, 3011, 1666, 1619, 1602, 1468, 1355, 1240, 1174, 1127, 1100, 1032; δ_H (400 MHz; DMSO-d_6) 8.59 (1 H, d, *J* 8.8, ArH), 8.30 (1 H, d, *J* 2.4, ArH), 8.30 (3 H, br s, ArH), 8.23 (1 H, d, *J* 2.4, ArH), 8.01 (1 H, d, *J* 8.8, ArH), 7.,97 (1 H, br s, NH), 7.88 (2 H, d, *J* 8.8, ArH), 7.43 (1 H, dd, *J* 8.8, 2.4, ArH), 7.37 (1 H, br s, NH), 7.29 (2 H, d, *J* 8.8, ArH), 7.20 (1 H, dd, *J* 8.8, 2.4, ArH), 5.99 (2 H, s, CH_2), 4.04 (3 H, s, Me), 3.97 (3 H, s, Me); δ_C (100 MHz; DMSO-d_6) 167.3 (C), 157.7 (C), 157.0 (C), 148.5 (C), 140.0 (C), 136.1 (C), 133.6 (C), 133.1 (CH), 132.6 (C), 130.8 (q, *J* 33, C), 130.1 (C), 129.5 (CH), 128.8 (C), 128.4 (CH), 126.3 (C), 125.6 (CH), 123.6 (CH), 123.0 (q, *J* 271, CF_3), 122.7 (CH), 121.2 (C), 117.0 (CH), 116.7 (C), 115.9 (CH), 107.7 (CH), 106.2 (CH), 55.6 (Me), 55.5 (Me), 50.2 (CH_2); *m*/*z* (ESI) 624 (M + H^+, 40%).

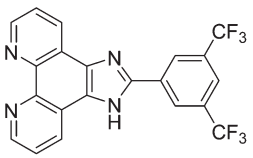


1,10-Phenanthroline-5,6-dione ***27***. An ice-cold solution of concentrated sulfuric acid (5 mL) and concentrated nitric acid

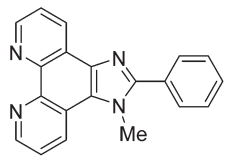
(2.5 mL) was added dropwise to 1,10-phenanthroline (500 mg, 2.77 mmol) and potassium bromide (495 mg, 4.16 mmol). The mixture was heated at 110 °C for 3 h, cooled to room temperature and added to ice-water (20 mL). The solution was neutralized to pH 7 by the careful addition of saturated sodium hydroxide, and the resulting suspension was extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure, and the residue triturated with ether (30 mL) to give the *title compound* as a yellow solid (719 mg, 81%); mp 260–261 °C (lit.,[39] mp 259–260 °C); (Found: M + H^+, 233.0326. $C_{12}H_6N_2O_2$ + Na^+ requires 233.0321); λ_{max} (CH_2Cl_2)/nm 309 (log ε 3.12), 375 (2.79); ν_{max} ($CHCl_3$)/cm^{-1} 2981, 1704, 1690, 1580, 1566, 1461, 1421, 1316, 1297, 1115, 1012, 927; δ_H (400 MHz; $CDCl_3$) 9.14 (2 H, dd, *J* 4.8, 1.8, ArH), 8.53 (2 H, dd, *J* 7.8, 1.8, ArH), 7.61 (2 H, dd, *J* 7.8, 4.8, ArH); δ_C (100 MHz; $CDCl_3$) 178.6 (C), 156.4 (CH), 152.9 (C), 137.3 (CH), 128.0 (C), 125.6 (CH); *m*/*z* (ESI) 233 (M + Na^+, 89%). Data are consistent with those reported in literature.[39]



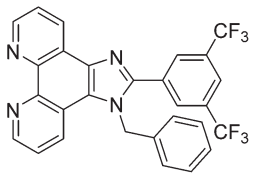
2-Phenyl-1H-imidazo[4,5-f][1,10]phenanthroline ***28***. Prepared by general procedure 1 from 1,10-phenanthroline-5,6-dione **27** (150 mg, 0.71 mmol) and benzaldehyde (79 μL, 0.79 mmol). Purification by trituration with ether (10 mL) followed by dichloromethane (10 mL) gave the *title compound* as a pale yellow solid (92 mg, 44%); mp 390–392 °C (decomp.) (lit.,[40] mp 380 °C); (Found: M + H^+, 297.1133. $C_{19}H_{12}N_4$ + H^+ requires 297.1135); ν_{max} ($CHCl_3$)/cm^{-1} 3691, 3454, 3063, 2964, 1602, 1563, 1545, 1476, 1455, 1398, 1350, 1067, 1028; δ_H (400 MHz; DMSO-d_6) 13.77 (1 H, s, NH), 9.05 (2 H, dd, *J* 4.2, 1.4, ArH), 8.94 (2 H, dd, *J* 8.0, 1.4, ArH), 8.30 (2 H, d, *J* 8.0, ArH), 7.86–7.83 (2 H, m, ArH), 7.63 (2 H, t, *J* 8.0, ArH), 7.53 (1 H, t, *J* 7.2, ArH); δ_C (100 MHz; DMSO-d_6) 150.8 (C), 148.1 (CH), 143.6 (2 × C), 130.1 (2 × C), 129.9 (2 × CH), 129.2 (CH), 126.4 (CH), 123.5 (CH); *m*/*z* (ESI) 297 (M + H^+, 100%).



2-(3,5-Bis(Trifluoromethyl)phenyl)-1H-imidazo[4,5-f][1,10]-phenanthroline ***29***. Prepared by general procedure 1 from 1,10-phenanthroline-5,6-dione **27** (500 mg, 2.38 mmol) and 3,5-bis (trifluoromethyl)benzaldehyde (470 μL, 2.85 mmol). Purification by recrystallization from cyclohexane–ethyl acetate (1 : 2) gave the *title compound* as a cream solid (356 mg, 35% yield, 91% purity); mp 236–237 °C; (Found: M + H^+, 433.0900. $C_{21}H_{10}F_6N_4$ + H^+ requires 433.0882); ν_{max} ($CHCl_3$)/cm^{-1} 3115, 2972, 1603, 1568, 1509, 1402, 1367, 1280, 1184, 1142, 1071, 981, 901; δ_H (400 MHz; acetone-d_6) 8.95 (4 H, br s, ArH), 8.89 (2 H, s, ArH), 7.99 (1 H, s, ArH), 7.66 (2 H, br s, ArH); δ_C (100 MHz; acetone-d_6) 149.1 (CH), 147.0 (C), 145.4 (C), 137.7 (C), 133.9 (C), 132.7 (q, *J* 33, C), 131.4 (CH), 129.0 (C), 127.5 (CH), 124.6 (CH), 124.3 (q, *J* 270, CF_3), 123.2 (CH); *m*/*z* (ESI) 433 (M + H^+, 100%).

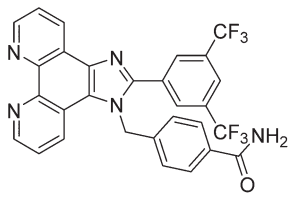


1-Methyl-2-phenyl-1H-imidazo[4,5-f][1,10]phenanthroline ***30***. Prepared by general procedure 2 from 2-phenyl-1*H*-imidazo[4,5-*f*][1,10]phenanthroline **28** (200 mg, 0.67 mmol) and iodomethane (84 μL, 1.35 mmol) in DMF (7 mL). Purification by flash chromatography, eluting with dichloromethane–methanol (19 : 1), and recrystallization from dichloromethane–methanol (1 : 1) gave the *title compound* as a pale orange solid (43 mg, 21%); mp 246–247 °C; (Found: M + H^+, 311.1292. $C_{20}H_{14}N_4$ + H^+ requires 311.1291); λ_{max} (MeOH)/nm 315 (log ε 5.08), 410 (4.49); ν_{max} ($CHCl_3$)/cm^{-1} 3012, 2971, 1602, 1524, 1474, 1454, 1424, 1239, 924, 850; δ_H (400 MHz; DMSO-d_6) 9.68 (1H, dd, *J* 8.2, 1.2, ArH), 9.47 (1 H, d, *J* 6.0, ArH), 9.20 (1 H, dd, *J* 4.4, 1.8, ArH), 9.08 (1 H, dd, *J* 8.2, 1.8, ArH), 8.43 (1 H, t, *J* 6.8, ArH), 8.26 (2 H, dt, *J* 6.8, 1.2, ArH), 8.09 (1 H, dd, *J* 8.2, 4.4, ArH), 7.66 (2 H, t, *J* 6.8, ArH), 7.60 (1 H, tt, *J* 6.8, 1.2, ArH), 5.26 (3 H, s, Me); δ_C (100 MHz; DMSO-d_6) 152.7 (C), 149.3 (CH), 147.1 (CH), 139.2 (CH), 138.2 (2 × C), 134.8 (4 × C), 130.7 (CH), 130.5 (CH), 129.2 (CH), 129.1 (C), 126.5 (CH), 125.0 (CH), 124.4 (CH), 54.5 (Me); *m*/*z* (ESI) 311 (M + H^+, 100%).

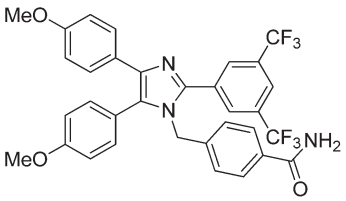


1-Benzyl-2-(3,5-bis(trifluoromethyl)phenyl)-1H-imidazo[4,5-f]-[1,10]phenanthroline ***31***. 1,10-Phenanthroline-5,6-dione **27** (200 mg, 0.95 mmol) was suspended in glacial acetic acid (2 mL) and ammonium acetate (147 mg, 1.90 mmol), 3,5-bis (trifluoromethyl)benzaldehyde (188 μL, 1.14 mmol) and benzylamine (125 μL, 1.14 mmol) were added. The mixture was heated at 100 °C for 18 h, cooled to room temperature and added slowly to ammonium hydroxide (35%; 15 mL). The solution was extracted with dichloromethane (3 × 15 mL) and the combined organic extracts dried (Na_2SO_4) and concentrated under reduced pressure. Recrystallization from cyclohexane–ethyl acetate (1 : 1) followed by trituration with ether (10 mL) gave the *title compound* as a colourless solid (93 mg, 19% yield, 91% purity); mp 234–235 °C; (Found: M + H^+, 523.1354. $C_{28}H_{16}F_6N_4$ + H^+ requires 523.1352); ν_{max} ($CHCl_3$)/cm^{-1} 2962, 1603, 1565, 1499, 1455, 1397, 1352, 1280, 1186, 1145, 1056, 1027, 906, 848; δ_H (400 MHz; DMSO-d_6) 9.08 (1 H, dd, *J* 4.2, 1.6, ArH), 8.99–8.97 (2 H, m, ArH), 8.48 (1 H, dd, *J* 8.4, 1.6,

ArH), 8.33 (1 H, s, ArH), 8.31 (2 H, s, ArH), 7.84 (1 H, dd, *J* 8.0, 4.2, ArH), 7.65 (1 H, dd, *J* 8.4, 4.2, ArH), 7.39–7.31 (3 H, m, ArH), 7.21 (2 H, d, *J* 7.6, ArH), 7.21 (2 H, d, *J* 7.6, ArH), 6.00 (2 H, s, CH_2); δ_C (100 MHz; DMSO-d_6) 150.7 (C), 148.8 (CH), 147.8 (CH), 144.2 (C), 143.9 (C), 136.2 (C), 135.9 (C), 132.1 (C), 130.9 (q, *J* 33, C), 129.8 (2 × CH), 129.3 (CH), 129.0 (CH), 127.9 (CH), 126.2 (C), 125.6 (CH), 123.8 (CH), 123.5 (CH), 123.3 (C), 123.0 (q, *J* 272, CF_3), 122.9 (CH), 119.2 (C), 50.2 (CH_2); *m*/*z* (ESI) 523 ($M + H^+$, 100%).



1-(4-Carboxamidobenzyl)-2-(3,5-bis(trifluoromethyl)phenyl)-1H-imidazo[4,5-f][1,10]-phenanthroline ***32****.* Prepared by general procedure 2b from 2-(3,5-bis(trifluoromethyl)phenyl)-1*H*-imidazo[4,5-*f*][1,10]phenanthroline **29** (200 mg, 0.46 mmol) and 4-(bromomethyl)benzamide **17** (119 mg, 0.56 mmol). Purification by flash chromatography, eluting with dichloromethane–methanol (9 : 1) and recrystallization from methanol gave the *title compound* as a colourless solid (47 mg, 18% yield, 86% purity); mp 183–184 °C; (Found: $M + H^+$, 566.1413. $C_{29}H_{17}F_6N_5O + H^+$ requires 566.1410); ν_{max} ($CHCl_3$)/cm^{-1} 2964, 1682, 1590, 1398, 1352, 1280, 1266, 1186, 1146, 906; δ_H (400 MHz; DMSO-d_6) 9.08 (1 H, dd, *J* 4.4, 1.8, ArH), 8.99 (1 H, t, *J* 1.8, ArH), 8.98 (1 H, t, *J* 1.8, ArH), 8.45 (1 H, dd, *J* 8.4, 1.4, ArH), 8.33 (3 H, br s, ArH), 7.96 (1 H, br s, NH), 7.87–7.82 (3 H, m, ArH), 7.64 (1 H, dd, *J* 8.4, 4.4, ArH), 7.37 (1 H, br s, NH), 7.30 (2 H, d, *J* 8.4, ArH), 6.05 (2 H, s, CH_2); δ_C (100 MHz; DMSO-d_6) 167.3 (C), 150.8 (C), 148.8 (CH), 147.8 (CH), 144.2 (C), 143.9 (C), 139.4 (C), 136.0 (C), 133.7 (C), 132.0 (C), 130.9 (q, *J* 33, C), 129.9 (CH), 129.8 (CH), 129.0 (CH), 128.4 (CH), 126.1 (C), 125.6 (CH), 123.8 (CH), 123.6 (CH), 123.3 (C), 123.0 (q, *J* 272, CF_3), 122.9 (CH), 119.1 (C), 50.1 (CH_2); *m*/*z* (ESI) 566 ($M + H^+$, 57%).



1-(4-Carboxamidobenzyl)-2-(3,5-bis(trifluoromethyl)phenyl)-4,5-di(4-methoxyphenyl)-1H-imidazole (apoptozole) ***6****.* (a) 2-(3,5-Bis(trifluoromethyl)phenyl)-4,5-di(4-methoxyphenyl)-1*H*-imidazole was prepared by general procedure 1 from 4,4′-dimethoxybenzil (500 mg, 1.85 mmol) and 3,5-bis(trifluoromethyl)benzaldehyde (335 μL, 2.03 mmol). Purification by flash chromatography, eluting with light petroleum–ethyl acetate (4 : 1), followed by trituration with ether (20 mL) gave 2-(3,5-bis(trifluoromethyl)phenyl)-4,5-di(4-methoxyphenyl)-1*H*-imidazole as a cream solid (641 mg, 70%); mp 219–220 °C; (Found: $M + H^+$, 493.1360. $C_{25}H_{18}F_6N_2O_2 + H^+$ requires 493.1345); ν_{max} ($CHCl_3$)/cm^{-1} 3441, 3006, 2963, 2839, 1615, 1519, 1490, 1356, 1280, 1250, 1182, 1143, 1033, 836; δ_H (400 MHz; DMSO-d_6) 13.01 (1 H, br s, NH), 8.68 (2 H, s, ArH), 8.06 (1 H, br s, ArH), 7.50–7.46 (4 H, m, ArH), 7.04 (2 H, d, *J* 8.0, ArH), 6.90 (2 H, d, *J* 8.0, ArH), 3.80 (3 H, s, Me), 3.76 (3 H, s, Me); δ_C (100 MHz; DMSO-d_6) 159.1 (C), 158.2 (C), 141.8 (C), 137.3 (C), 132.7 (C), 130.9 (q, *J* 32, C), 129.7 (CH), 128.7 (C), 128.3 (CH), 127.2 (C), 124.9 (CH), 123.3 (q, *J* 270, CF_3), 122.9 (C), 120.7 (CH), 114.2 (CH), 113.7 (CH), 55.2 (Me), 55.0 (Me); *m*/*z* (ESI) 493 ($M + H^+$, 100%).

(b) 1-(4-Carboxamidobenzyl)-2-(3,5-bis(trifluoromethyl)-phenyl)-4,5-di(4-methoxyphenyl)-1*H*-imidazole (apoptozole) **6** was prepared by general procedure 2 from 2-(3,5-bis(trifluoromethyl)phenyl)-4,5-di(4-methoxyphenyl)-1*H*-imidazole (200 mg, 0.41 mmol) and 4-(bromomethyl)benzamide **17** (130 mg, 0.61 mmol) in THF (4 mL). Purification by flash chromatography, eluting with light petroleum–ethyl acetate (2 : 3) gave the *title compound* as a colourless solid (143 mg, 56%); mp 191–192 °C; (Found: $M + H^+$, 626.1851. $C_{33}H_{25}F_6N_3O_3 + H^+$ requires 626.1873); ν_{max} ($CHCl_3$)/cm^{-1} 3531, 3415, 3003, 2964, 2840, 1680, 1615, 1588, 1520, 1491, 1358, 1280, 1250, 1183, 1143, 1033, 903, 836; δ_H (400 MHz; CD_3OD) 8.17 (2 H, s, ArH), 8.01 (1 H, s, ArH), 7.75 (2 H, d, *J* 8.4, ArH), 7.42 (2 H, d, *J* 8.8, ArH), 7.26 (2 H, d, *J* 8.8, ArH), 6.97 (2 H, d, *J* 8.8, ArH), 6.95 (2 H, d, *J* 8.4, ArH), 6.82 (2 H, d, *J* 8.8, ArH), 5.27 (2 H, s, CH_2), 3.81 (3 H, s, Me), 3.76 (3 H, s, Me); δ_C (100 MHz; CD_3OD) 171.6 (C), 162.1 (C), 160.5 (C), 146.0 (C), 142.5 (C), 140.2 (C), 134.5 (C), 134.4 (C), 133.7 (CH), 133.3 (q, *J* 33, C), 132.5 (C), 130.4 (CH), 129.7 (CH), 129.4 (CH), 127.7 (C), 127.3 (CH), 124.7 (q, *J* 270, CF_3), 123.8 (CH), 123.2 (C), 115.8 (CH), 114.9 (CH), 56.0 (Me), 55.8 (Me), 49.4 (CH_2); *m*/*z* (ESI) 626 ($M + H^+$, 100%). Data are consistent with those published in literature.[6]

Biology

Cell lines. The human cancer cell lines HCT116 (colon), WM266.4 (melanoma) and MCF7 (breast) were obtained from the American Type Culture Collection (LGC Promochem, UK). Cells were grown in DMEM/10% FCS, 2 mM glutamine and non-essential amino acids in 5% CO_2. Cells were free of Mycoplasma contamination (Venor GeM kit, Minerva Biolabs, Germany). HCT116 cells have been used in previous studies on the Hsp70 pathway.[26]

In vitro **cell viability assay.** The CellTiter-Blue® viability assay (Promega, USA) provides a homogenous, fluorometric method for estimating the number of viable cells. It uses the dark blue indicator dye resazurin to measure the metabolic capacity of cells that is an indicator of cell viability. Viable cells are able to reduce resazurin into resorufin (pink) that is highly fluorescent. Briefly, cells (6×10^3 cells per mL) were seeded into 384-well plates and were incubated for 24 h. Compounds (at a range of concentrations) were added using the ECHO liquid handler (Labcyte, USA) and then left at 37 °C for 96 h. Titer blue reagent was added to each well and left at 37 °C for 3–4 h. Fluorescence was measured using the Envision Multi-

label Plate Reader (Perkin Elmer, UK). The GI_{50} was determined as the concentration required to cause 50% inhibition, and data are reported as the mean ± SE of three replicates.

Western blotting. HCT116 cells were treated with either 5 × GI_{50} of compounds for 8, 24 and 48 h or multiples of GI_{50} for 24 h. Cell lysates were prepared and proteins were then immunoblotted and detected by enhanced chemiluminescence.[41] Antibodies to Hsps were from Stressgen and those for ERBB2, CRAF, CDK4, cleaved PARP and GAPDH were from Abcam, BD Bioscience, Santa Cruz, Cell Signaling and Chemicon, respectively.

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