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Cyclopenta[*g*]quinazolinone-based inhibitors of thymidylate synthase targeting α-folate receptor overexpressing tumours: synthetic approaches to 4-{*N*-[(6*RS*)-2-hydroxymethyl-4-oxo-3,4,7,8-tetrahydro-6*H*-cyclopenta[*g*]quinazolin-6-yl]-*N*-(prop-2-ynyl)amino}benzoic acid

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Abstract—An advanced intermediate for the synthesis of cyclopenta[*g*]quinazolinone-based antifolates such as (6*RS*)-CB300945 was prepared by a convergent methodology. The oxo-functionality required for the formation of the C-6–N-10 bond in **4** was introduced in the initial steps of the synthesis, then the tricyclic ring was constructed and finally the propargyl group was introduced using the (propargyl)$Co_2(CO)_6^+$ complex without the need to protect the N-3–H or 2-hydroxymethyl functionalities.

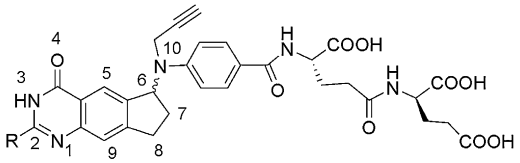
1. Introduction

Cyclopenta[*g*]quinazolinone-based antifolates have been reported as potent inhibitors of the thymidylate synthase (TS) enzyme[1–3] that is an established target in cancer chemotherapy.[4,5] It was also reported that certain compounds of this class could utilise the α-folate receptor (α-FR) to enter cells.[3,6,7] The α-folate receptor is overexpressed in many carcinomas,[8–11] and (6*RS*)-CB300638 (**1**), (6*RS*)-CB300945 (**2**) (Fig. 1) displayed selectivity for cells that express the α-FR (e.g., A431-FBP) over those without the α-FR (A431).[3] Both (6*RS*)-CB300638 (**1**) and (6*RS*)-CB300945 (**2**) are potent inhibitors of thymidylate synthase[3] (for (6*RS*)-CB300638 (**1**), L1210 TS $K_i$app=0.42 nM).[1,3]

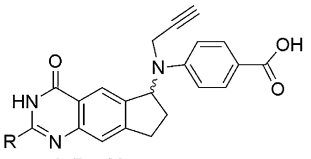
A linear multistep synthesis has been developed for the preparation of this class of compounds with the benzoic acid derivatives **3** and **4** (or their protected forms) being the crucial intermediates.[1–3] The first synthesis of **3** was achieved via the N-10-alkylation of a suitably protected glutamate derivative of **3** using propargyl bromide, followed by removal of the protecting groups and then enzymatic cleavage of the glutamyl residue.[1,12] Crystallographic analysis of a derivative of **3** provided an unequivocal confirmation of its structure.[12] Subsequently, compound **3** was prepared by a non-enzymatic route via a (propargyl)$Co_2(CO)_6^+$ complex[13] starting from 5-acetamido-6-bromoindan-1-one (**13**).[14,15]

2. Results

Access to 2-hydroxymethylcyclopenta[*g*]quinazolinone-based antifolates such as (6*RS*)-CB300945 (**2**) was gained via the intermediate **4** or its 2-hydroxymethyl ester protected form, prepared in a linear fashion via a multistep synthesis



1. (6*RS*)-CB300638, R = Me
2. (6*RS*)-CB300945, R = CH_2OH



3. R = Me
4. R = CH_2OH

Figure 1.

Keywords: Cyclopenta[*g*]quinazolinones; Dicobalt hexacarbonyl complex; Antifolates.
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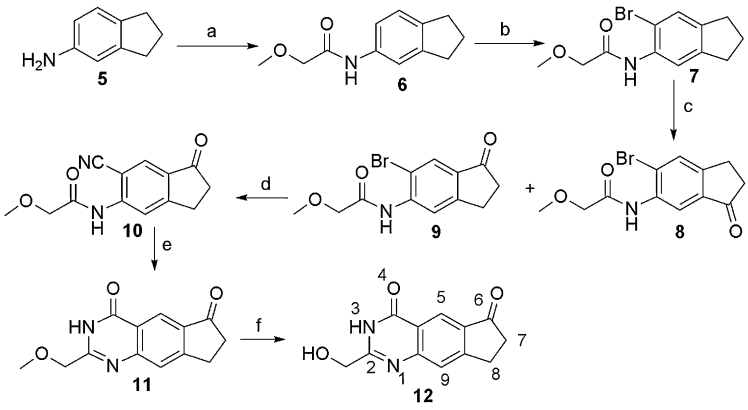


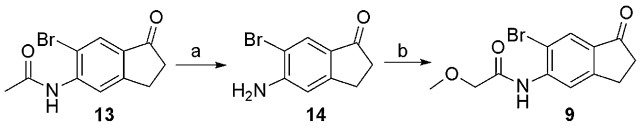
Scheme 1. Conditions: (a) methoxyacetyl chloride, DMF, pyridine, rt; (b) Br_2, AcOH; (c) CrO_3, AcOH; (d) $Zn(CN)_2$, $Pd_2(dba)_3$, dppf, DMA, 120 °C; (e) H_2O_2, NaOH, H_2O, EtOH, 0–55 °C; (f) 48% HBr, 120 °C.

using 5-amino-6-carboxyindane as the chemical starting point.[3] In this route, the cyclopenta[*g*]quinazolinone ring was first synthesised and the 2-hydroxymethyl substituent was protected either as an acetate or trimethylacetate ester.[3] Subsequent low yielding 6-oxo functionalisation facilitated the C-6–N-10 bond formation via a reductive amination reaction allowing the introduction of the *p*-aminobenzoate moiety. Finally, the *N*-10-propargyl group was introduced via a Nicholas reaction with (propargyl)$Co_2(CO)_6^+$.[3]

The promising biochemical profile of compound **2**[3] prompted us to search for a convergent route to **4** in order to establish an alternative synthetic pathway to (6*RS*)-CB300945 (**2**), and facilitate the preparation of additional cyclopenta[*g*]quinazolinone-based antifolates. We decided to investigate two approaches, and in both cases the oxo-functionality that is required for the formation of the C-6–N-10 bond was efficiently introduced in the initial steps of the synthesis (Schemes 1 and 3).

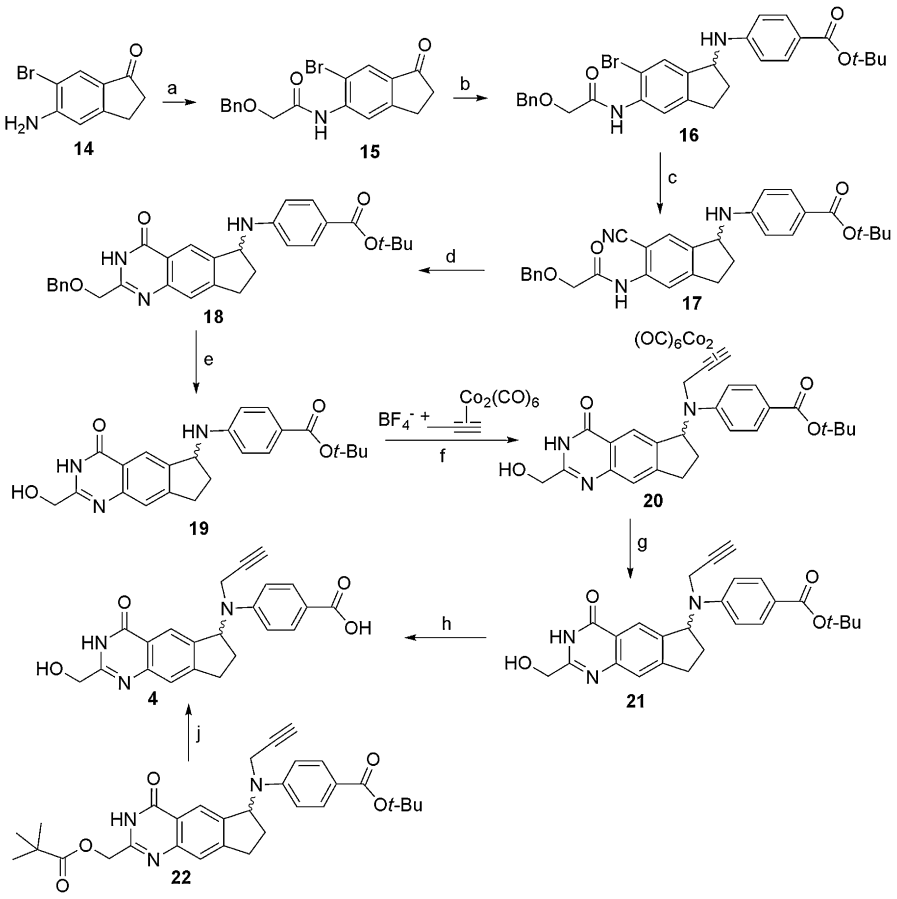
In the first approach, the aim was to first construct the tricyclic system (Scheme 1) and then introduce the *tert*-butyl 4-aminobenzoate moiety followed by the introduction of the propargyl group. The synthesis started with 5-aminoindane (**5**), which was converted into the methoxyacetamide derivative **6** by treatment with methoxyacetyl chloride in DMF using pyridine as base. Methoxyacetyl chloride was utilised since it was envisaged that the 2-hydroxymethyl substituent of the cyclopenta[*g*]quinazolinone ring could be generated at a later stage from the methoxymethyl group via a demethylation reaction. Bromination of **6** was accomplished using Br_2/AcOH, and oxidation of **7** was performed under conditions analogous to those utilised for the oxidation of its 2-acetamido counterpart.[13,14] The indan-1-one **9** was isolated as the major product (55%) of the oxidation reaction, and only a small amount (3%) of indanone **8** was obtained. Adopting the reaction conditions reported for the oxidation of 5-acetamido-6-bromoindane[15] resulted in obtaining the ketone **9** in a higher yield (72%).

For the assignment of the regiochemistry in the oxidation products **8** and **9** (Scheme 1), access to the indanone **9** was also gained via 5-amino-6-bromoindan-1-one (**14**), which was obtained from the known compound **13**[13–15] as shown in Scheme 2. The methoxyacetamido derivative **9** (Scheme 2) had an ^1H NMR identical to that of a sample synthesised as described in Scheme 1. In the next step, cyanation of the aryl bromide **9** was performed using $Zn(CN)_2$ in DMA under Pd-catalysis to afford **10** in 69% yield. The indanone derivative **10** was then cyclised to the 2-methoxymethylcyclopenta[*g*]quinazolinone **11** by treatment with H_2O_2 and NaOH in EtOH/H_2O. At this stage, prior to the construction of the C-6–N-10 bond, it was attempted to generate the 2-hydroxymethyl functionality by cleaving the methyl ether in **11** with a protic or a Lewis acid. Disappointingly, it was not possible to form **12** in a workable yield, since all the attempted conditions were either low yielding or completely unsuccessful. The highest yield (~20%) was obtained by heating **11** with 48% HBr at 120 °C for 3 h.



Scheme 2. Conditions: (a) 48% HBr, 70 °C; (b) methoxyacetyl chloride, DMF, pyridine, rt.

In the second approach, we were planning to first form the C-6–N-10 bond, then construct the tricyclic scaffold and generate the 2-hydroxymethyl functionality, and finally introduce the propargyl group via a (propargyl)$Co_2(CO)_6^+$ complex (Scheme 3) in a fashion similar to that reported for the synthesis of **3**.[13] The synthesis started with 5-amino-6-bromoindan-1-one (**14**) (Schemes 2 and 3), which was converted into **15** by treatment with benzyloxyacetyl chloride in DMF. By using benzyloxyacetyl chloride it was anticipated that the 2-hydroxymethyl substituent could be generated by the Pd-catalysed hydrogenolysis of the benzyl (Bn) group. Next the C-6–N-10 bond was formed by the reductive amination of the ketone **15** with *tert*-butyl 4-aminobenzoate.[16] For this transformation, the highest yield (85%) was obtained when the reductive amination reaction was performed using decaborane in methanol/dichloromethane.[3,13,17] Cyanation of the aryl bromide **16** was achieved by heating with copper(I) cyanide in 1-methyl-2-pyrrolidinone (NMP) at 150 °C. Cyclisation of **17** to give the cyclopenta[*g*]quinazolinone derivative **18** was effected by treatment with H_2O_2 and NaOH in EtOH/H_2O. Hydrogenolysis of the benzyloxymethyl ether **18** was performed



Scheme 3. Conditions: (a) benzyloxyacetyl chloride, DMF, pyridine, rt; (b) *tert*-butyl 4-aminobenzoate, 4-toluenesulfonic acid, $NaBH_3CN$, AcOH or *tert*-butyl 4-aminobenzoate, CH_2Cl_2/MeOH, decaborane; (c) CuCN, NMP, 150 °C; (d) H_2O_2, NaOH, H_2O, EtOH, 0–55 °C; (e) EtOH, 10% Pd/C, 50 °C; (f) CH_2Cl_2, DME, *i*-Pr_2NEt, rt; (g) $Fe(NO_3)_3$, EtOH, rt; (h) TFA/CH_2Cl_2, rt; (j) (i) TFA/CH_2Cl_2, rt; (ii) 1 N NaOH, MeOH/H_2O, rt.

in EtOH using 10% Pd/C to afford the 2-hydroxymethyl substituted cyclopenta[*g*]quinazolinone **19**. It should be noted that heating of the reaction mixture at 50 °C for several hours was required for the hydrogenolysis to take place. The propargyl group was next introduced on the N-10-position by reacting **19** with (propargyl)$Co_2(CO)_6^+BF_4^-$ followed by demetallation (Scheme 3).[13,18] The propargylated derivative **21** was obtained in 53% yield from **19** without the need to protect the N-3–H and 2-hydroxymethyl functionalities. Finally, the *tert*-butyl ester was cleaved with TFA to afford the benzoic acid derivative **4** as a racemic mixture, as it was confirmed by chiral HPLC that indicated two peaks (t_R=10.75, 12.27 min) for compound **4** in a ratio 1:1. As expected, the ^{1}H NMR of **4** was identical to that of a sample derived from the known compound **22**[3] by TFA and alkaline cleavage of the *tert*-butyl and trimethylacetate esters, respectively (Scheme 3).[3]

In summary, two new synthetic approaches to **4** were investigated, and a new convergent route to **4** was established. The oxo-functionality required for the formation of the C-6–N-10 bond in **4** was efficiently introduced in the initial steps of the synthesis, and the benzyloxymethyl ether was used to mask the hydroxymethyl functionality, which was generated after the introduction of the *p*-aminobenzoate moiety and the formation of the cyclopenta[*g*]quinazolinone ring. Subsequently, the *N*-10-propargyl substituent was introduced utilising the (propargyl)$Co_2(CO)_6^+$ as an electrophilic propargyl synthon without the need to protect the N-3–H or 2-hydroxymethyl functionalities.

3. Experimental

3.1. General

Thin layer chromatography (TLC) was performed on precoated sheets of silica $60F_{254}$ (Merck Art 5735) and visualised under UV light. Merck silica 60 (Art 15111) was used in flash column chromatography. Column chromatography was also performed on a FlashMaster personal unit (Jones Chromatography) using isolute silica columns. Petrol refers to light petroleum (bp 60–80 °C). Electrospray ionisation (ESI) mass spectra were recorded using a TSQ 700 triple quadrupole mass spectrometer (Finnigan MAT) fitted with an electrospray ionisation source (Analytica). Proton NMR spectra were recorded using a Bruker AC250 spectrometer at 250 MHz. Field strengths are expressed in units of δ (ppm) relative to tetramethylsilane as an internal standard, and peak multiplicities are designated as follows: s, singlet; d, doublet; dd, doublet of doublets; dm, doublet of multiplets; t, triplet; q, quartet, br s, broad singlet, m, multiplet. High performance liquid chromatography (HPLC) analyses were performed using a Waters system. The system used a model 510 solvent delivery system, model 680 automated gradient controller, model U6K injector and model M-490 programmable wavelength detector set to monitor at 230

and 280 nm. Retention times were determined on a Trivector Trilab 3000 multichannel chromatography data system. Chiral separations were performed on a 25 cm×0.46 cm Astec cyclobond I (cyclodextrin β) column (Astec, Advanced Separation Technologies Ltd., UK) and eluted isocratically with different ratios of (25 mM Na_2HPO_4/25 mM NaH_2PO_4, 1:1 v/v)/CH_3CN and a flow rate of 1 mL/min. LCMS analysis was conducted using gradient elution (MeOH/0.1% HCO_2H in H_2O) and a Supelco Discovery C18 HPLC column (5 cm×0.46 cm, 5 μm). Samples were injected using a Gilson 215 liquid handler. The HPLC system employed a Thermoseparations P4000 quaternary pump and UV 2000 detector operating at 254 nm. HPLC eluent passed directly into an LCQ ion trap mass spectrometer (Finnigan LCQ) operating in electrospray ionisation mode. Fast atom bombardment (FAB) mass spectra were determined with VG ZAB-SE spectrometer. Melting points were determined on a Kofler block and are uncorrected. Elemental analyses were determined by C.H.N. Analysis Ltd., Leicester, UK or Warwick Analytical Service, University of Warwick Science Park, Coventry, UK.

3.1.1. 5-Methoxyacetamidoindane (6). To a solution of 5-aminoindane (4.66 g, 35.0 mmol) in anhydrous DMF (26 mL) was slowly added methoxyacetyl chloride (5.70 g, 52.50 mmol) followed by pyridine (8.5 mL, 105.0 mmol). The red solution was stirred at room temperature for 3.5 h under argon, then it was partitioned between EtOAc (200 mL) and 1 M HCl (120 mL). The organic layer was washed with more 1 M HCl (120 mL), brine (100 mL), dried (Na_2SO_4) and concentrated in vacuo. The residue was triturated with diethyl ether; the white precipitate was collected by filtration, washed with diethyl ether (10 mL) and dried to afford the title compound (5.93 g, 83%), mp 104–105 °C; ^{1}H NMR (250 MHz, $CDCl_3$) 2.06 (m, 2H, 2-CH_2), 2.87 (m, 4H, 1-CH_2 and 3-CH_2), 3.50 (s, 3H, OCH_3), 4.00 (s, 2H, 2-CH_2OMe), 7.22 (m, 2H, 6-H, 7-H), 7.52 (s, 1H, 4-H), 8.18 (s, 1H, CONH); MS (ESI, *m/z*) 206 [$(M+H)^+$, 100%]; found C, 70.10; H, 7.38; N, 6.81; $C_{12}H_{15}NO_2$ requires C, 70.22; H, 7.37; N, 6.82%.

3.1.2. 6-Bromo-5-methoxyacetamidoindane (7). A mixture of 5-methoxyacetamidoindane (5.50 g, 0.027 mol) and glacial acetic acid (25 mL) was cooled in an ice-water bath (~10 °C). Bromine (1.5 mL, 0.029 mol) was then added dropwise over a 20 min period while the temperature was kept between 10 and 15 °C. The reaction mixture was stirred for a further hour, then poured into an ice-water bath (100 mL) and the reaction flask washed with a further portion of water (70 mL). The precipitate was collected by filtration, washed with water (150 mL) and dried in vacuo over P_2O_5 to afford the title compound (6.98 g, 91%), mp 84–86 °C; ^{1}H NMR (250 MHz, $CDCl_3$) 2.09 (m, 2H, 2-CH_2), 2.88 (m, 4H, 1-CH_2 and 3-CH_2), 3.55 (s, 3H, OCH_3), 4.04 (s, 2H, 2-CH_2OMe), 7.34 (s, 1H) and 8.22 (s, 1H) (4-H, 7-H), 8.83 (s, 1H, CONH); MS (ESI, *m/z*) 284, 286 [$(M+H)^+$, 98%, 100%]; found C, 50.62; H, 4.93; N, 4.92; Br, 28.05; $C_{12}H_{14}BrNO_2$ requires C, 50.72; H, 4.97; N, 4.93; Br, 28.12%.

3.1.3. 6-Bromo-5-methoxyacetamidoindan-1-one (9). *Method A*: to a solution of 6-bromo-5-methoxyacetamidoindane (0.85 g, 3.0 mmol) in glacial acetic acid (7 mL) heated to 55 °C was added dropwise a solution of CrO_3 (1.2 g, 12.0 mmol) in aqueous glacial acetic acid (7 mL; 1:1 v/v) over a 15 min period. The reaction mixture was then stirred at this temperature for 45 min. The reaction mixture was cooled in an ice-bath, then isopropanol (4 mL) was added and the mixture was stirred at this temperature for 10 min before being concentrated in vacuo. The black residue was broken up with a spatula with the aid of water and then partitioned between water (50 mL) and EtOAc (150 mL). The aqueous layer was extracted with further EtOAc (2×40 mL); the combined extracts were dried (Na_2SO_4), and concentrated in vacuo to give an off-white residue. Purification by column chromatography on silica (5% EtOAc in dichloromethane) afforded in order of elution: *6-bromo-5-methoxyacetamidoindan-1-one* (**9**) as a white solid, which was further purified by trituration with EtOAc/hexanes (1:5 v/v): 0.50 g (55%), mp 162–163 °C; ^{1}H NMR (250 MHz, $CDCl_3$) 2.72 (m, 2H, 2-CH_2), 3.11 (m, 2H, 3-CH_2), 3.57 (s, 3H, OCH_3), 4.09 (s, 2H, 2-CH_2OMe), 7.95 (s, 1H) and 8.65 (s, 1H) (4-H, 7-H), 9.27 (s, 1H, CONH); MS (ESI, *m/z*) 298, 300 [$(M+H)^+$, 100%, 97%]; found: C, 48.13; H, 3.99; N, 4.70; Br, 26.95; $C_{12}H_{12}BrNO_3$ requires C, 48.34; H, 4.06; N, 4.70; Br, 26.80%, followed by *6-bromo-5-methoxyacetamidoindan-3-one* (**8**) as a solid, which was further purified by trituration with EtOAc/hexanes (1:5 v/v): 0.026 g, (3%), mp 149–151 °C; ^{1}H NMR (250 MHz, $CDCl_3$) 2.71 (m, 2H, 2-CH_2), 3.01 (m, 2H, 1-CH_2), 3.56 (s, 3H, OCH_3), 4.08 (s, 2H, 2-CH_2OMe), 7.73 (s, 1H) and 8.71 (s, 1H) (4-H, 7-H), 8.97 (s, 1H, CONH); MS (ESI, *m/z*) 298, 300 [$(M+H)^+$, 100%, 98%]; found: C, 47.95; H, 3.96; N, 4.59; Br, 26.63; $C_{12}H_{12}BrNO_3$ requires C, 48.34; H, 4.06; N, 4.70; Br, 26.80%.

Method B:[15] to a solution of 6-bromo-5-methoxyacetamidoindane (5.00 g, 17.62 mmol) in AcOH (30 mL) was added a solution of CrO_3 (6.00 g, 60.00 mmol) in H_2O (12 mL) ensuring that the temperature remained between 25 and 30 °C. The mixture was stirred at room temperature for 30 min, then a further portion of CrO_3 (0.50 g, 5.00 mmol) in H_2O (2.5 mL) was added and the mixture was stirred at room temperature for 1 h. H_2O (3×50 mL) was added with 2 min of stirring between additions resulting in the product crystallising from solution. The mixture was cooled to 0 °C and the crude product collected by filtration and dried in vacuo over P_2O_5. The residue was purified by column chromatography eluting with 4% EtOAc in CH_2Cl_2 to yield the desired product as a white solid (3.78 g, 72%).

Method C: to a solution of 5-amino-6-bromoindan-1-one (**14**) (0.113 g, 0.5 mmol) in anhydrous DMF (1 mL) was slowly added methoxyacetyl chloride (0.081 g, 0.70 mmol) followed by pyridine (0.20 mL, 2.5 mmol). The reaction mixture was stirred at room temperature for 2 h under argon, then it was partitioned between EtOAc (50 mL) and 1 M HCl (30 mL). The organic layer was washed with further 1 M HCl (30 mL), brine (30 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (5% EtOAc in dichloromethane) afforded the ketone **9** (0.073 g) as white solid.

3.1.4. 6-Cyano-5-methoxyacetamidoindan-1-one (10). To a solution of 6-bromo-5-methoxyacetamidoindan-1-one (3.77 g, 12.65 mmol) in anhydrous DMA (75 mL) was

added $Zn(CN)_2$ (0.91 g, 7.71 mmol), $Pd_2(dba)_3$ (0.49 g, 0.54 mmol) and dppf (0.57 g, 1.08 mmol). The mixture was heated at 120 °C for 2 h under argon, then cooled to room temperature and partitioned between EtOAc (300 mL) and 2 M NH_4OH (250 mL). The organic extract was washed with brine (250 mL), dried (Na_2SO_4) and the solvent removed in vacuo. The residue was purified by column chromatography eluting with 10% EtOAc in CH_2Cl_2 to yield the desired product as a white solid (2.13 g, 69%), mp 170 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.76 (m, 2H, 2-CH_2), 3.23 (m, 2H, 3-CH_2), 3.59 (s, 3H, CH_3), 4.11 (s, 2H, OCH_2), 8.00 (s, 1H, 7-H), 8.72 (s, 1H, 4-H), 9.26 (br s, 1H, NH); MS (ESI, *m/z*) 245 [(M+H)$^+$, 100%]; found C, 63.64; H, 4.90; N, 11.40; $C_{13}H_{12}N_2O_3$ requires C, 63.93; H, 4.95; N, 11.47%.

3.1.5. 2-Methoxymethyl-3,4,7,8-tetrahydro-6*H*-cyclopenta[*g*]quinazolin-4,6-dione (11). To a mixture of 6-cyano-5-methoxyacetamidoindan-1-one (2.00 g, 8.20 mmol), EtOH (25 mL), H_2O (5.25 mL) and 30% H_2O_2 (7.25 mL) cooled in an ice-bath was added granulated NaOH pellets (0.55 g, 13.42 mmol). The mixture was stirred at room temperature for 15 min, then slowly heated to 55 °C until a homogeneous solution was obtained before being allowed to cool to room temperature. The solvent was removed in vacuo and the residue was suspended in H_2O (300 mL), then heated to 50 °C for 5 min. The solution was again cooled to room temperature and acidified to pH 4 with 1 M HCl. The resulting precipitate was collected by filtration and dried in vacuo over P_2O_5 to yield the desired product as a white solid (1.93 g, 96%), mp 257–259 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 2.71 (m, 2H, 7-CH_2), 3.24 (m, 2H, 8-CH_2), 3.37 (s, 3H, CH_3), 4.36 (s, 2H, 2-CH_2), 7.76 (s, 1H, 9-H), 8.28 (s, 1H, 5-H); MS (FAB, *m/z*) 245 [(M+H)$^+$, 100%]; HRMS: measured 245.0933; calculated for $C_{13}H_{13}N_2O_3$ (M+H)$^+$: 245.0926.

3.1.6. 5-Amino-6-bromoindan-1-one (14). A solution of 5-acetamido-6-bromoindan-1-one[13–15] (2.85 g, 10.60 mmol) in 48% HBr (90 mL) was placed in an oil bath preheated to 70 °C. The mixture was stirred at this temperature for 1.5 h, then cooled in an ice-bath and diluted with aqueous NaOH (1 M, 50 mL). The pH was then adjusted to ~5 with aqueous NaOH (50% w/w). The brown solid was collected by filtration, washed with water, and dried in vacuo over P_2O_5. Purification by column chromatography (8% EtOAc in CH_2Cl_2) gave an orange solid. This solid was triturated with 30% hexane in diethyl ether to obtain a pale brown solid (1.80 g, 75%), mp 209–211 °C (lit.[15] 199–200 °C; prepared by alkaline amide hydrolysis); ^{1}H NMR (250 MHz, $CDCl_3$) 2.65 (m, 2H, 2-CH_2), 2.99 (m, 2H, 3-CH_2), 4.65 (br s, 2H, NH_2), 6.73 (s, 1H) and 7.86 (s, 1H) (4-H and 7-H); MS (ESI, *m/z*) 226, 228 [(M+H)$^+$, 100%]; found: C, 47.59; H, 3.49; N, 6.11; Br, 35.16; C_9H_8BrNO requires C, 47.82; H, 3.57; N, 6.20; Br, 35.34%.

3.1.7. 5-Benzyloxyacetamido-6-bromoindan-1-one (15). To a stirred solution of 5-amino-6-bromoindan-1-one (1.70 g, 7.5 mmol) in anhydrous DMF (15 mL) was added slowly benzyloxyacetyl chloride (2.07 g, 11.25 mmol) followed by pyridine (3.0 mL, 37.5 mmol). The reaction mixture was stirred at room temperature for 18 h under argon and then partitioned between EtOAc (200 mL) and 1 M HCl (150 mL). The aqueous layer was extracted with further EtOAc (100 mL) and the combined extracts were washed with 1 M HCl (100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (40% EtOAc in hexane and then 2% EtOAc in CH_2Cl_2/hexane (9:1 v/v)) afforded a yellow solid. This solid was reprecipitated from CH_2Cl_2/hexane to obtain a pale yellow solid (2.07 g, 75%), mp 120 °C; ^{1}H NMR (250 MHz, $CDCl_3$) 2.72 (m, 2H, 2-CH_2), 3.10 (m, 2H, 3-CH_2), 4.18 (s, 2H) and 4.72 (s, 2H) (PhCH_2 and OCH_2CO), 7.39 (m, 5H, *Ph*CH_2), 7.95 (s, 1H) and 8.65 (s, 1H) (4-H and 7-H), 9.39 (s, 1H, CONH); MS (ESI, *m/z*) 396, 398 [(M+Na)$^+$, 50%]; 374, 376 [(M+H)$^+$, 100%]; found: C, 57.53; H, 4.23; N, 3.71; Br, 21.35; $C_{18}H_{16}BrNO_3$ requires C, 57.77; H, 4.31; N, 3.74; Br, 21.35%.

3.1.8. *tert*-Butyl 4-[*N*-(5-(2-benzyloxy-ethanoylamino)-6-bromoindan-1-yl)amino]-benzoate (16). *Method A*: to a round-bottom flask containing 5-benzyloxyacetamido-6-bromoindan-1-one (0.750 g, 2.0 mmol), 4-toluenesulfonic acid (0.030 g), *tert*-butyl 4-aminobenzoate[16] (0.540 g, 2.8 mmol) was added anhydrous DME (24 mL). An Aldrich azeotropic distillation apparatus containing molecular sieves (3 Å) was fitted to the reaction flask, which was then placed in an oil bath preheated to 115 °C. The mixture was stirred at this temperature for 3.5 h under argon, then cooled to room temperature. A solution of $Na(CN)BH_3$ in THF (1 M; 2.8 mL, 2.8 mmol) was then added followed by AcOH (0.094 mL). The reaction mixture was stirred at room temperature for 2.5 h, then it was partitioned between EtOAc (200 mL) and saturated aqueous $NaHCO_3$ (150 mL). The aqueous layer was extracted with further EtOAc (100 mL) and the combined extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (EtOAc/petroleum ether (1:1 v/v)) afforded a yellow solid. This solid was reprecipitated from EtOAc/hexane to obtain the desired compound as a pale yellow solid (0.233 g, 21%), mp 150–151 °C; ^{1}H NMR (250 MHz, $CDCl_3$,) 1.56 (s, 9H, $C(CH_3)_3$), 1.92 (m, 1H) and 2.63 (m, 1H) (2-CH_2 indanyl), 2.82–3.00 (m, 2H, 3-CH_2 indanyl), 4.15 (s, 2H) and 4.71 (s, 2H) (PhCH_2 and OCH_2CO), 4.24 (d, J=8.1 Hz, 1H, N^{10}–H), 5.02 (m, 1H, 1-CH indanyl), 6.64 (d, J=8.7 Hz, 2H, 3,5-ArH), 7.39 (m, 5H, *Ph*CH_2), 7.50 (s, 1H) and 8.33 (s, 1H) (4-H and 7-H), 7.85 (d, J=8.7 Hz, 2H, 2,6-ArH), 9.06 (s, 1H, CONH); MS (ESI, *m/z*) 575, 573 [(M+Na)$^+$, 100%, 98%]; found: C, 63.03; H, 5.65; N, 5.04; Br, 14.46; $C_{29}H_{31}BrN_2O_4$ requires C, 63.16; H, 5.67; N, 5.08; Br, 14.49%.

Method B: to a solution of 5-benzyloxyacetamido-6-bromoindan-1-one (3.45 g, 9.22 mmol) in anhydrous methanol (330 mL) and CH_2Cl_2 (40 mL) was added *tert*-butyl 4-aminobenzoate (1.94 g, 10.05 mmol) followed by decaborane (0.310 g). The reaction mixture was stirred at room temperature overnight before being concentrated in vacuo. Purification by column chromatography (40% EtOAc in petroleum ether (60–80 °C)) afforded the desired product: 4.30 g, (85%).

3.1.9. *tert*-Butyl 4-[*N*-(5-(2-benzyloxy-ethanoylamino)-6-cyanoindan-1-yl)amino]-benzoate (17). To a stirred solution of *tert*-butyl 4-[*N*-(5-(2-benzyloxy-ethanoylamino)-6-bromoindan-1-yl)amino]-benzoate (0.210 g, 0.38 mmol)

in anhydrous NMP (2.2 mL) was added CuCN (0.068 g, 0.76 mmol). The reaction flask was placed in an oil bath preheated to 150 °C and it was stirred at this temperature for 3 h under argon. The mixture was then allowed to cool to room temperature and poured into a mixture of aqueous ammonia (2 mL) and ice-water (5 mL). This mixture was stirred at room temperature for 5 min, the brown precipitate was then collected by filtration and washed with water. This precipitate was then suspended in CH_2Cl_2 (70 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification of the residue by column chromatography, eluting with 35% EtOAc in hexane, afforded a brown solid (0.084 g, 45%), mp 194–195 °C; ^{1}H NMR (250 MHz, $CDCl_3$) 1.55 (s, 9H, $C(CH_3)_3$), 1.95 (m, 1H) and 2.64 (m, 1H) (2-CH_2 indanyl), 2.99 (m, 2H, 3-CH_2 indanyl), 4.13 (s, 2H) and 4.72 (s, 2H) (Ph*CH*$_2$ and O*CH*$_2$CO), 4.22 (d, *J*=8.1 Hz, 1H, N^{10}–H), 5.05 (m, 1H, 1-CH indanyl), 6.65 (d, *J*=8.7 Hz, 2H, 3,5-ArH), 7.39 (m, 5H, *Ph*CH_2), 7.54 (s, 1H) and 8.37 (s, 1H) (4-H and 7-H), 7.86 (d, *J*=8.7 Hz, 2H, 2,6-ArH), 9.06 (s, 1H, CONH); MS (ESI, *m*/*z*) 520 [(M+Na)$^+$, 100%]; found: C, 72.26; H, 6.26; N, 8.41; $C_{30}H_{31}N_3O_4$ requires C, 72.41; H, 6.28; N, 8.44%.

3.1.10. *tert*-Butyl 4-{*N*-[(6*RS*)-2-benzyloxymethyl-4-oxo-3,4,7,8-tetrahydro-6*H*-cyclopenta[*g*]quinazolin-6-yl]-amino}benzoate (18). To a stirred, ice-bath cooled mixture of *tert*-butyl 4-[*N*-(5-(2-benzyloxy-ethanoylamino)-6-cyanoindan-1-yl)amino]-benzoate (3.77 g, 7.59 mmol), EtOH (70 mL) and H_2O (11 mL) was added 30% H_2O_2 (8.05 mL) followed by granulated NaOH pellets (0.640 g, 16.0 mmol). The reaction mixture was stirred at 0 °C for 10 min, then placed in an oil bath preheated to 55 °C and stirred at this temperature for 1 h. The solvents were then removed in vacuo; the residue was treated with H_2O (80 mL) and the pH was adjusted to ~5 with 1 M HCl. The pale yellow solid was collected by filtration, washed with H_2O and dried in vacuo over P_2O_5 (3.56 g, 95%), mp 194–195 °C; ^{1}H NMR (250 MHz, DMSO-d_6) 1.52 (s, 9H, $C(CH_3)_3$), 1.90 (m, 1H) and 2.62 (m, 1H) (7-CH_2), 2.90–3.17 (m, 2H, 8-CH_2), 4.43 (s, 2H) and 4.60 (s, 2H) (Ph*CH*$_2$ and O*CH*$_2$C=N), 5.18 (q, *J*=7.4 Hz, 1H, 6-CH), 6.79 (d, *J*=8.8 Hz, 2H, 3′,5′-ArH), 6.87 (d, *J*=8.0 Hz, 1H, *N*^{10}–H), 7.34 (m, 5H, *Ph*CH_2), 7.54 (s, 1H) and 7.92 (s, 1H) (5-H and 9-H), 7.68 (d, *J*=8.9 Hz, 2H, 2′,6′-ArH), 12.20 (s, 1H, CONH); MS (ESI, *m*/*z*) 520 [(M+Na)$^+$, 90%], 498 [(M+H)$^+$, 100%]; found: C, 72.13; H, 6.25; N, 8.38; $C_{30}H_{31}N_3O_4$ requires C, 72.41; H, 6.28; N, 8.44%.

3.1.11. *tert*-Butyl 4-{*N*-[(6*RS*)-2-hydroxymethyl-4-oxo-3,4,7,8-tetrahydro-6*H*-cyclopenta[*g*]quinazolin-6-yl]amino}benzoate (19). To a solution of *tert*-butyl 4-{*N*-[(6*RS*)-2-benzyloxymethyl-4-oxo-3,4,7,8-tetrahydro-6*H*-cyclopenta[*g*]quinazolin-6-yl]amino}benzoate (1.40 g, 2.8 mmol) in EtOH (150 mL) was added 10% Pd/C (0.665 g). The mixture was stirred at 45 °C for 3 h, then more catalyst (0.200 g) was added and stirring was continued at 50 °C for 6 h. The catalyst was removed by filtration, washed with EtOH and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography, eluting with 8% methanol in EtOAc, gave a white solid (0.679 g, 60%), mp 265–266 °C; ^{1}H NMR (250 MHz, DMSO-d_6) 1.52 (s, 9H, $C(CH_3)_3$), 1.88 (m, 1H) and 2.57 (m, 1H) (7-CH_2), 2.90–3.17 (m, 2H, 8-CH_2), 4.38 (d, *J*=6.0 Hz, 2H, 2-*CH*$_2$OH), 5.17 (m, 1H, 6-CH), 5.54 (t, *J*=6.1 Hz, 1H, CH_2*OH*), 6.79 (d, *J*=8.8 Hz, 2H, 3′,5′-ArH), 6.91 (d, *J*=7.8 Hz, 1H, *N*^{10}–H), 7.51 (s, 1H) and 7.91 (s, 1H) (5-H and 9-H), 7.68 (d, *J*=8.8 Hz, 2H, 2′,6′-ArH), 11.83 (s, 1H, CONH); MS (ESI, *m*/*z*) 408 [(M+H)$^+$, 65%], 352 [(M−^{t}Bu)$^+$, 100%], 215 (60%); found: C, 67.41; H, 6.20; N, 10.17; $C_{23}H_{25}N_3O_4$ requires C, 67.80; H, 6.18; N, 10.31%.

3.1.12. *tert*-Butyl 4-{*N*-[(6*RS*)-2-hydroxymethyl-4-oxo-3,4,7,8-tetrahydro-6*H*-cyclopenta[*g*]quinazolin-6-yl]-*N*-(prop-2-ynyl)amino}benzoate (21). To a round-bottomed flask containing (propargyl)$Co_2(CO)_6^{\ddagger}BF_4^-$[13,19] (0.390 g, 0.95 mmol) under argon was added anhydrous dichloromethane (14 mL), a nearly clear solution was obtained. To this solution a suspension of *tert*-butyl 4-{*N*-[(6*RS*)-2-hydroxymethyl-4-oxo-3,4,7,8-tetrahydro-6*H*-cyclopenta[*g*]-quinazolin-6-yl]amino}benzoate (0.285 g, 0.71 mmol) in anhydrous CH_2Cl_2 (14 mL) and DME (20 mL) was added in one portion. The mixture was stirred at room temperature for 10 min under argon, then diisopropylethylamine (0.14 mL) was added and stirring was continued at room temperature for 20 min. The reaction mixture was then partitioned between EtOAc (350 mL) and brine (100 mL). The organic layer was washed with 10% aqueous citric acid (100 mL) and brine (100 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by chromatography (silica isolute 20 g, 70 mL column), on elution with 70% EtOAc in CH_2Cl_2, gave a red solid (0.391 g, 76%), mp 190 °C (dec); ^{1}H NMR (250 MHz, DMSO-d_6) 1.52 (s, 9H, $C(CH_3)_3$), 2.24 (m, 1H) and 2.60 (m, 1H) (7-CH_2), 2.96–3.25 (m, 2H, 8-CH_2), 4.37 (d, *J*=5.9 Hz, 2H, 2-*CH*$_2$OH), 4.58 (d, *J*=17.2 Hz, 1H) and 4.73 (d, *J*=17.2 Hz, 1H) (N^{10}–CH_2), 5.55 (t, *J*=6.2 Hz, 1H, CH_2O*H*), 5.80 (t, *J*=7.7 Hz, 1H, 6-CH), 6.68 (s, 1H, propargyl H), 7.01 (d, *J*=8.8 Hz, 2H, 3′,5′-ArH), 7.56 (s, 1H) and 7.76 (s, 1H) (5-H and 9-H), 7.79 (d, *J*=9.8 Hz, 2H, 2′,6′-ArH), 11.83 (s, 1H, CONH). To a solution of this material (0.380 g, 0.52 mmol) in EtOH (65 mL) was added $Fe(NO_3)_3\cdot 9H_2O$ (2.60 g, 6.5 mmol). The mixture was stirred at room temperature for 2.5 h, brine (~200 mL) was then added into the reaction mixture that was extracted with EtOAc (3×150 mL). The combined organic extracts were washed with brine (120 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography, eluting with 5% MeOH in EtOAc, gave an off-white solid (0.161 g, 70%), mp 195–197 °C; ^{1}H NMR (250 MHz, DMSO-d_6,) 1.52 (s, 9H, $C(CH_3)_3$), 2.17 (m, 1H) and 2.55 (m, coincides with solvent peak, 1H) (7-CH_2), 2.90–3.20 (m, 3H, C≡CH, 8-CH_2), 3.87 (d, *J*=18.7 Hz, 1H) and 4.10 (d, *J*=18.7 Hz, 1H) (N^{10}–CH_2), 4.38 (d, *J*=5.8 Hz, 2H, 2-*CH*$_2$OH), 5.56 (br t, 1H, CH_2*OH*), 5.78 (t, *J*=8.7 Hz, 1H, 6-CH), 7.02 (d, *J*=9.0 Hz, 2H, 3′,5′-ArH), 7.55 (s, 1H) and 7.80 (s, 1H) (5-H and 9-H), 7.76 (d, *J*=9.8 Hz, 2H, 2′,6′-ArH), 11.82 (s, 1H, CONH); MS (ESI, *m*/*z*) 468 [(M+Na)$^+$, 60%], 446 [(M+H)$^+$, 50%], 390 [(M−^{t}Bu)$^+$, 70%], 215 (100%); found: C, 69.63; H, 6.13; N, 9.31; $C_{26}H_{27}N_3O_4$ requires C, 70.09; H, 6.11; N, 9.43%.

3.1.13. 4-{*N*-[(6*RS*)-2-Hydroxymethyl-4-oxo-3,4,7,8-tetrahydro-6*H*-cyclopenta[*g*]quinazolin-6-yl]-*N*-(prop-2-ynyl)amino}benzoic acid (4). *Method A*: a solution of

tert-butyl 4-{*N*-[(6*RS*)-2-hydroxymethyl-4-oxo-3,4,7,8-tetrahydro-6*H*-cyclopenta[*g*]quinazolin-6-yl]-*N*-(prop-2-ynyl)-amino}benzoate (0.050 g, 0.11 mmol) in CH_2Cl_2 (1 mL) and TFA (2.4 mL) was stirred at room temperature for 1 h. The solvents were then removed in vacuo and the residue was treated with water (8 mL). The pH was adjusted to ~10 with 1 N NaOH (a clear solution was obtained) and then to ~4 with 1 M HCl, resulting in the product precipitating from solution. The white precipitate was collected by filtration, washed with water and dried in vacuo over P_2O_5 to give the desired compound as a white solid (0.037 g, 88%), mp 173 °C (decomposed); ^{1}H NMR (250 MHz, DMSO-d_6) 2.26 (m, 1H, 7-CH_2), 2.90–3.15 (m, 3H, C≡CH, 8-CH_2), 3.85 (d, J=18.3 Hz, 1H) and 4.10 (d, J=18.3 Hz, 1H) (N^{10}–CH_2), 4.38 (s, 2H, 2-CH_2OH), 5.56 (br s, 1H, 2-CH_2OH), 5.78 (t, J=8.3 Hz, 1H, 6-CH), 7.03 (d, J=9.0 Hz, 2H, 3′,5′-ArH), 7.55 (s, 1H) and 7.83 (s, 1H) (5-H and 9-H), 7.81 (d, J=8.5 Hz, 2H, 2′,6′-ArH); MS (ESI, *m*/*z*) 390 [$(M+H)^+$, 100%], 215 (20%); found: C, 61.53; H, 5.04; N, 9.57; $C_{22}H_{19}N_3O_4 \cdot 2.1H_2O$ requires C, 61.86; H, 5.44; N, 9.84%.

Method B: a solution of *tert*-butyl 4-{*N*-[(6*RS*)-2-(2,2-dimethylpropionyloxymethyl)-4-oxo-3,4,7,8-tetrahydro-6*H*-cyclopenta[*g*]quinazolin-6-yl]-*N*-(prop-2-ynyl)amino}benzoate (**22**)[3] (0.150 g, 0.28 mmol) in CH_2Cl_2 (2 mL) and TFA (6 mL) was stirred at room temperature for 1 h. The solvents were removed in vacuo, the residue was triturated with ether and the precipitate was collected by filtration and suspended in water (5 mL) and MeOH (3 mL). A solution of aqueous NaOH (1 N; 1.1 mL, 1.1 mmol) was then added and the reaction mixture was stirred at room temperature for 8 h. The pH of the solution was then adjusted to ~5 with 1 M HCl and the white precipitate was collected by filtration, washed with water and dried in vacuo over P_2O_5 to give the desired product **4** (0.086 g, 79%).

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