Synthesis J. L. Holmes et al. Paper

Synthesis of Novel Hydroxymethyl-Substituted Fused Heterocycles

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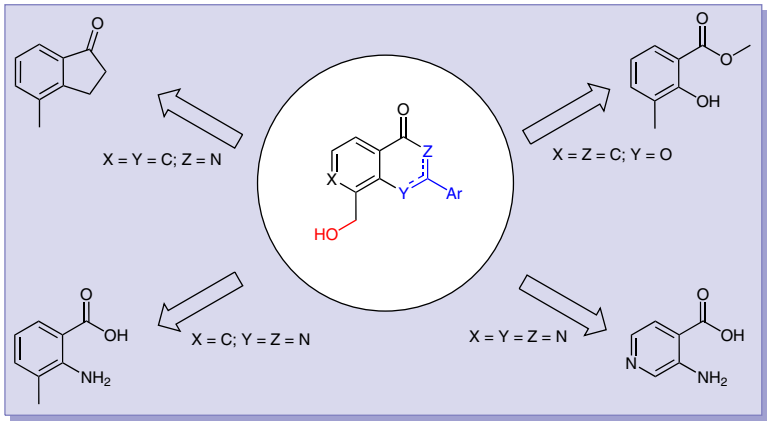


Received: 17.12.2015
Accepted after revision: 08.01.2016
Published online: 18.02.2016
DOI: 10.1055/s-0035-1561355; Art ID: ss-2015-t0725-op

Abstract Examples of hydroxymethylated analogues of heteroaryl cores such as quinazolin-4-ones, isoquinolin-1(2*H*)-ones, pyrido[3,4-*d*]pyrimidin-4(3*H*)-ones, chromen-4-ones and pyrrolo[2,1-*f*][1,2,4]triazin-4(3*H*)-ones are sparse or non-existent in the scientific literature. We have demonstrated that such compounds are accessible by using standard procedures from readily available raw materials.

Key words cross-coupling, fused-ring systems, heterocycles, quinazolinones, isoquinolinones, chromenones, triazinones

Fused heterocycles such as quinazolin-4-ones, isoquinolines and azaquinazolinone feature in a large number of pharmaceutical products and, as such, there is an extensive body of work in the literature describing their syntheses.[1]

As part of a drug discovery programme, we identified, *via* a high-throughput screen, a 2-phenylquinazolin-4-one (Figure 1) as a potential lead.[2] Further elaboration of this core revealed that increased potency could be achieved by substitution at the 8-position with a hydroxymethyl moiety. Closer examination of the crystal structure of AZ0926 (a potent inhibitor, Figure 1), bound in the target enzyme suggested that this was due to an interaction between the hydroxyl and a glutamate residue. We therefore needed to retain the hydroxymethyl functionality to maintain potency whilst investigating other parts of the molecule.

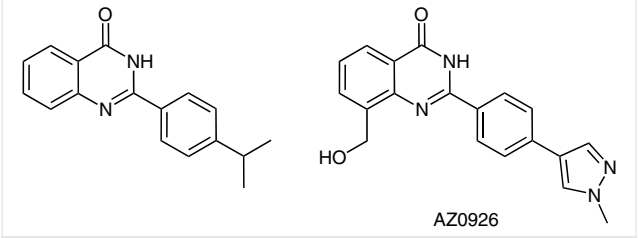


Figure 1 The 2-phenylquinazolin-4-one lead identified by high-throughput screening and optimised quinazolin-4-one AZ0926

Whilst the preparation of these fused heterocycles is well represented in the literature,[1] we were unable to find examples of 8-hydroxymethyl-substituted quinazolinones. We thus commenced a programme of work to develop synthetic routes to these motifs. This paper details the various strategies employed in the preparation of a range of novel hydroxymethyl-substituted quinazolinones and other fused heterocycles.

Our initial work centred on the development of a set of 8-(hydroxymethyl)quinazolin-4(3*H*)-ones. Quinazolinones are a class of fused heterocycles of considerable interest to

the pharmaceutical industry. Found in a range of drug substances (Figure 2), including anticonvulsants[3] such as centazolone, antiinflammatories,[4] antibacterials,[5] antimalarials (febrifugine)[6] and diabetic treatments (balaglitazone),[7] traditional syntheses involve condensation with anthranilic acids or amides,[8] whilst more recent methods have used copper-catalysed processes[9] to provide the 2-substituted and 2,3-substituted quinazolinones.

We initially began our syntheses of 8-(hydroxymethyl)quinazolin-4(3*H*)-ones **3** by using the traditional method of condensation between an aldehyde **2** and a substituted anthranilic amide derivative **1** (Scheme 1). Copper(II) chloride in DMSO was found to provide the best results with a range of aldehydes **2a**–**e** from our collection. Further derivatisation of compound **3e** using Suzuki–Miyaura cross coupling proved difficult, providing the target compounds in poor yield. In addition to this, the scope of the condensation step was limited to the availability of aldehydes. We decided therefore to explore routes that would provide us with a more versatile intermediate that could be functionalised in the 2-position at a late stage giving us access to a wide range of 8-hydroxymethyl quinazolinone analogues.

It was envisaged that we could obtain this desired versatility if we could first prepare a 2-chloroquinazoline such as compound **9** (Scheme 2). Our route to 2-chloroquinazolinones started with the commercially available anthranilic acid **5**, which was converted into amide **6** by using standard coupling conditions. Cyclisation to provide imide **7** followed by chlorination provided us with the desired chloroquinazolinone **8**. Hydrolysis and regioselective displacement of the chloro with piperazine derivatives followed by

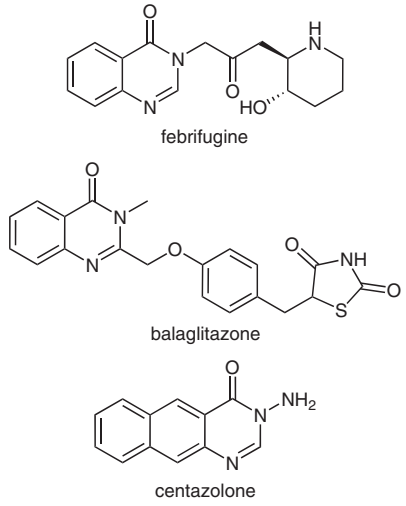
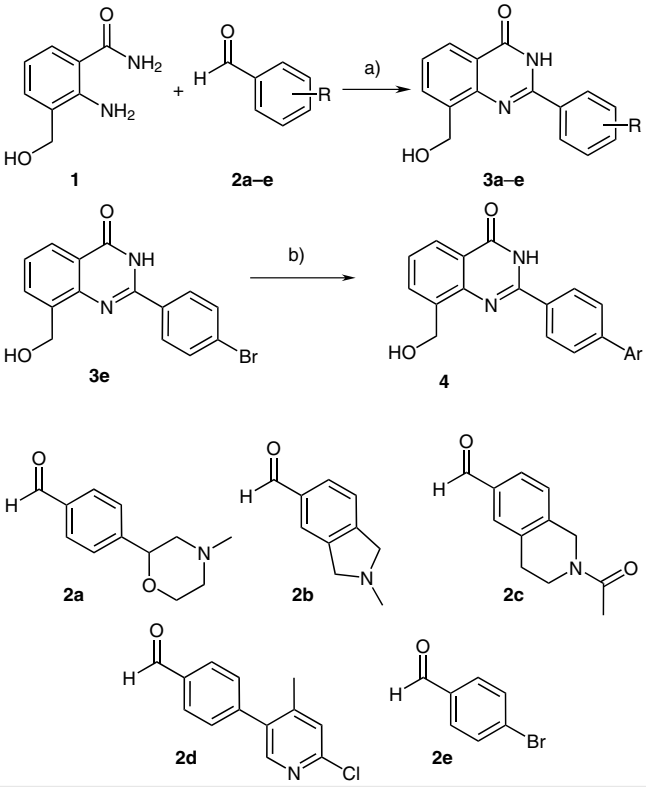
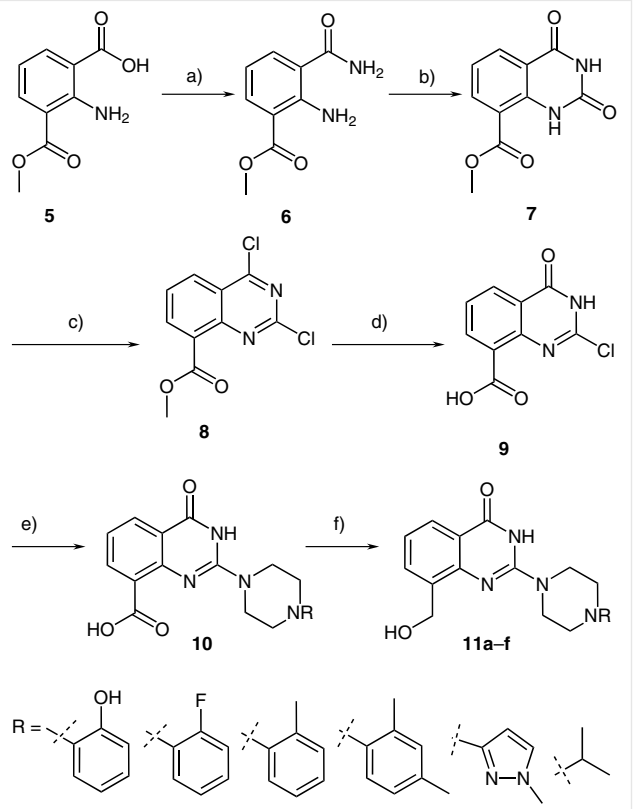


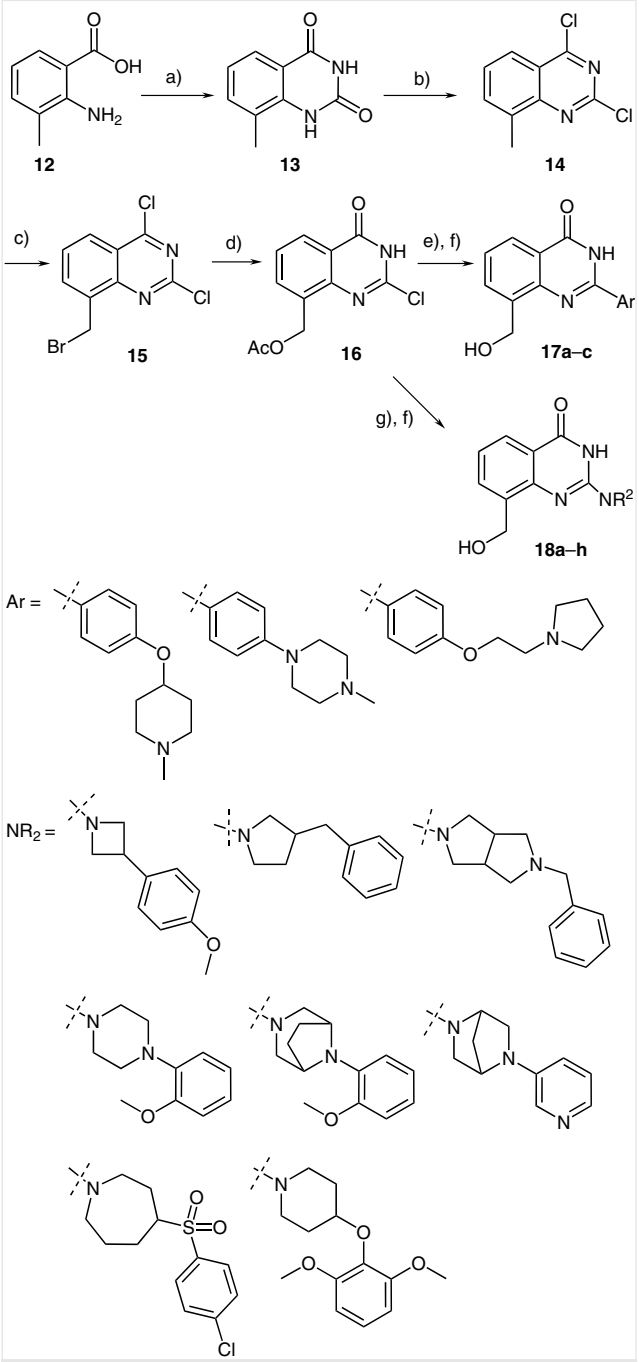
Figure 2



Scheme 1 *Reagents and conditions*: (a) $FeCl_3$, H_2O, benzaldehyde, 44%; (b) $ArB(OR)_2$, Cs_2CO_3, $Pd(PPh_3)_4$, dioxane, H_2O, 145 °C (microwave), 14% (Ar = 2-methyl-3-pyridine).



Scheme 2 *Reagents and conditions*: (a) HATU, NH_4OH, DIPEA, DMF, r.t., quant; (b) CDI, K_2CO_3, DMF, 90 °C, 76%; (c) $POCl_3$, 100 °C, quant; (d) KOH, H_2O, 105 °C; (e) DIPEA, MeCN, 4-R-substituted piperazine, 80 °C; (f) LAH, THF, r.t., 13–29% over 3 steps. HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate; CDI = 1,1′-carbonyldiimidazole.



Scheme 3 *Reagents and conditions*: (a) urea, NMP, 150 °C, 74%; (b) $POCl_3$, 100 °C, 79%; (c) NBS, AIBN, EtOAc, 65 °C, 78%; (d) CsOAc, NMP/H_2O, r.t., 70%; (e) $Pd(PPh_3)_4$, Cs_2CO_3, ArX, dioxane, H_2O, 100 °C; (f) K_2CO_3, MeOH, 50 °C, 30–98% over 2 steps; (g) DIPEA, DMF, 100 °C, HNR_2.

lithium aluminium hydride reduction afforded the desired (hydroxymethyl)quinazolinones **11a–f** (Scheme 2).

Although material was initially produced in this manner (Scheme 2), the yields were low, especially the reduction step. The solubility of the acid intermediates **9** and **10** was also poor, making isolation difficult. To avoid the final LAH reduction whilst improving the solubility of our intermediates in organic solvents, we devised an expedient and reliable route to a protected 8-(hydroxymethyl)quinazolinone **16** from a cheap and readily available anthranilic acid **12** (Scheme 3). Multi-gram quantities of **12** were stocked in-house which would allow for scale-up as the project progressed.

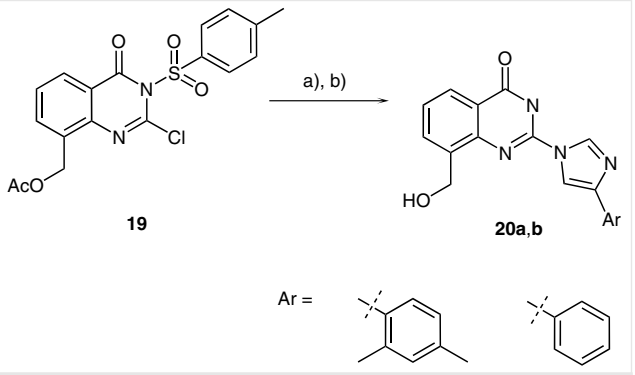
Anthranilic acid **12** was converted into the benzylic bromide **15** using standard procedures (Scheme 3).[2] Nucleophilic substitution and simultaneous hydrolysis of the 4-chloro motif with CsOAc afforded the acetylated precursor **16**. This latter transformation was initially conducted with KOAc, but yields were variable. Investigation into this step revealed that by switching to CsOAc in NMP/H_2O, yields were much improved and the reaction was less capricious. The results of this study are shown in Table 1. Acetate **16** was then manipulated to provide either 2-amino- or 2-aryl-substituted quinazolinones **17** or **18** *via* chloride displacement by using a range of amines or Suzuki–Miyaura coupling, respectively, as shown in Scheme 3.

Table 1 Conditions for Conversion of **15** into **16**

Base	Solvent	Temp (°C)	Time (h)	Conv. (%)[a]
KOAc	MeCN	70	2	30
KOAc	acetone	70	2	5
KOAc	DMF	50	2	40
KOAc	DMF	25	24	20
KOAc	NMP	50	2	50
KOAc	NMP/H_2O	25	16	50
NaOAc	NMP	50	2	no product
CsOAc	DMF	50	2	50
CsOAc	NMP	50	2	50
CsOAc	NMP/H_2O	50	4	70

[a] As measured by peak area (UPLC).

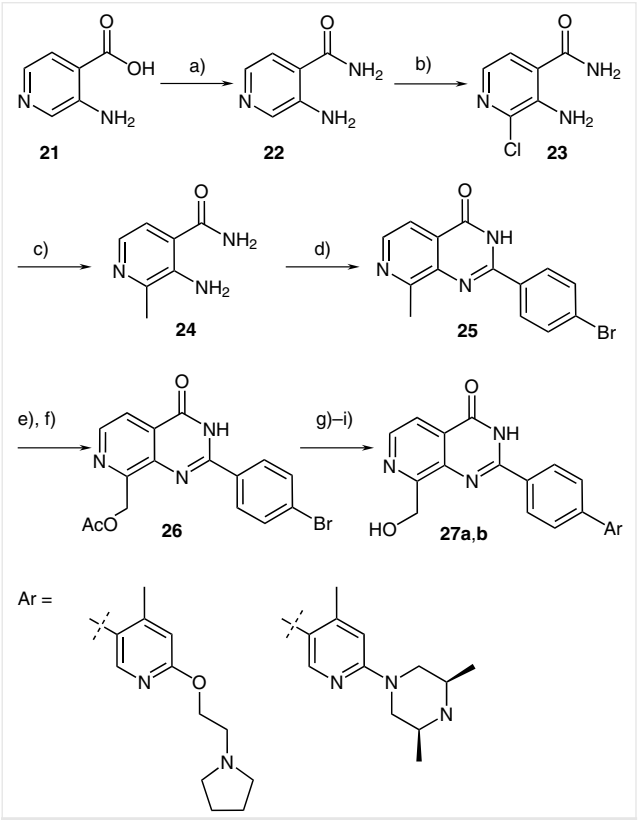
A wide range of non-aromatic nitrogen nucleophiles from azetidines through to diazepanes were introduced in this manner. We were however, unable to introduce less nucleophilic five-membered heterocycles such as imidazoles by using these conditions. We explored protecting the free quinazolinone NH group by using a tosyl protecting group and found, to our delight, that it was now possible to prepare the desired imidazoles **20** (Scheme 4). Acetate deprotection by using standard basic conditions furnished the novel 8-(hydroxymethyl)quinazolinone products.



Scheme 4 *Reagents and conditions*: (a) 4-aryl-1*H*-imidazole, DIPEA, DMA, sodium methanesulfinate, 80 °C; (b) K_2CO_3, MeOH, 50 °C, 7–13% over 2 steps.

With the 8-hydroxymethylquinazolin-4-ones in hand, our attention turned to analogues of alternative fused heterocyclic cores. We next explored the synthesis of pyrido[3,4-*d*]pyrimidin-4(3*H*)-ones or 'azaquinazolinones'. Literature syntheses of pyrido[3,4-*d*]pyrimidin-4(3*H*)-ones or azaquinazolinones typically use similar approaches to those used for quinazolinones, e.g. condensation with azaanthranilates[10] or copper-catalysed coupling of a urea with a bromoisonicotinic acid.[11] Despite a significant number of known examples,[10–12] we were unable to find any examples of 8-hydroxymethyl-substituted azaquinazolinones in the literature.

Our approach to the synthesis of the desired azaquinazolinones followed a similar route to our quinazolinone synthesis. We converted the readily available pyridine **21**, which was in plentiful supply in our stores, into our desired azaquinolinones **27** in nine steps as shown in Scheme 5.



Scheme 5 *Reagents and conditions*: (a) NH_4Cl, HATU, DMF, 87%; (b) concd HCl, H_2O_2, r.t., 27%; (c) $Pd(OAc)_2$, RuPhos, K_2CO_3, $B(OMe)_3$, toluene, 100 °C, 86%; (d) $Ga(OTf)_3$ (10 mol%), 4-bromobenzaldehyde, DMSO, 85 °C, then DDQ, r.t., 66%; (e) *m*CPBA, CH_2Cl_2, 65%; (f) Ac_2O, 120 °C, 30%; (g) $[Pd(dppf)_2Cl_2]\cdot CH_2Cl_2$, KOAc, bis(pinacolato)diboron, DME, 85 °C, 85%; (h) ArBr, $[Pd(dtbpf)Cl_2]$, K_3PO_4, DMF/H_2O; (i) K_2CO_3, MeOH, 65–74% over 2 steps.

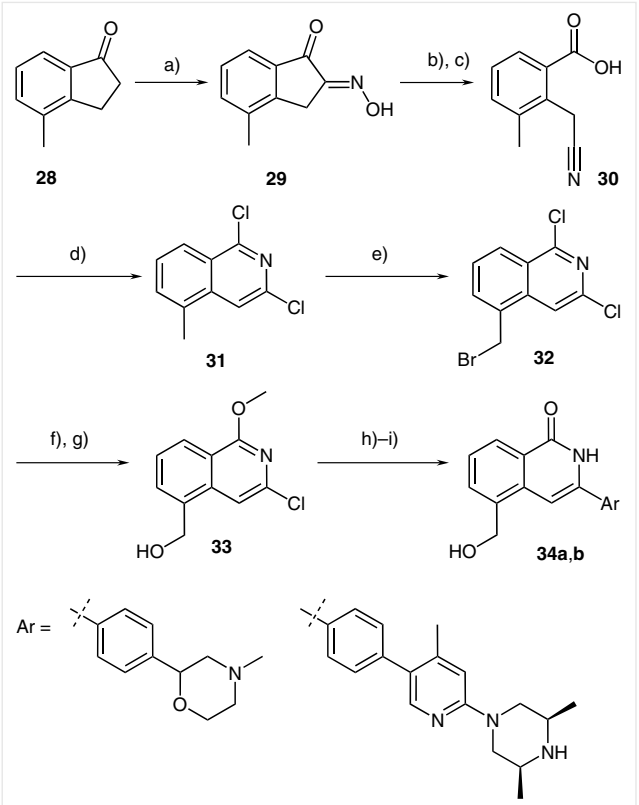
Amidation and chlorination[13] provided the 2-chloropyridine **23**, which was converted into the corresponding 2-methylpyridine **24** by Suzuki–Miyaura cross coupling (Scheme 5). Condensation of this intermediate with bromobenzaldehyde in the presence of catalytic gallium triflate[14] provided the azaquinazolinone core **25**. We initially attempted this reaction by using copper(II) chloride in DMSO, as this had been successful in the synthesis of the quinazolinone series. Unfortunately, although we did observe the desired product, we also observed undesired side products which rendered purification difficult. The combi-

nation of gallium triflate with DDQ in DMSO furnished the desired azaquinazolinone core in higher yield. Bromination using NBS and AIBN, as used in the synthesis of the quinazolinones, failed to give appreciable quantities of the desired benzylic bromide. The reaction proceeded very slowly, and when heated further, yielded mainly the dibrominated product. Installation of the 8-hydroxymethyl moiety to give **26** was achieved instead *via* the Boekelheide reaction.[15] Functionalisation of the pendant aromatic ring was realised through borylation and Suzuki–Miyaura cross coupling with several aryl halides. Final deprotection, as before, furnished our examples of 8-(hydroxymethyl)azaquinazolinones **27**.

We next turned to the synthesis of 8-(hydroxymethyl)isoquinolin-1(2*H*)-one derivatives. Many known syntheses of isoquinolinones involve lithiation of an *ortho*-methylphenylamide.[16] Alternate syntheses include a recent rhodium-catalysed C–H activation with vinyl esters.[17] A rhodium-catalysed approach has been used to make MIDA boronates of isoquinolinones,[18] which has led to a variety of substituted isoquinolinones. However, to our knowledge, no 5-hydroxymethyl-substituted analogues have appeared in the literature.

Our approach to the synthesis was a modification of a literature strategy which involved the condensation of an acid with a benzylic nitrile.[19] The starting material for our synthesis was 4-methylindenone (**28**) which was converted to isoquinolinone **34** in ten steps (Scheme 6). The indenone **28** was converted into the corresponding keto oxime **29**, which was hydrolysed by using sodium hydroxide. Subsequent dehydration of the oxime with tosyl chloride furnished benzylic nitrile **30**. Cyclisation and chlorination using a combination of PCl_5 and $POCl_3$ provided the methylisoquinoline **31**. With this material in hand, we were able to brominate the benzylic position as before, and displace the bromide in **32** with acetate by using the CsOAc conditions developed for the quinazolinone synthesis (Scheme 3). Unfortunately, concomitant hydrolysis of the 2-chloro functionality did not occur in this series. So the product of acetylation was subsequently treated with NaOMe in MeOH to give compound **33**. Diversity was then introduced at the 3-position by using Suzuki–Miyaura cross coupling. Final deprotection by using HCl at 80 °C successfully delivered the desired 5-(hydroxymethyl)isoquinolines **34** (Scheme 6).

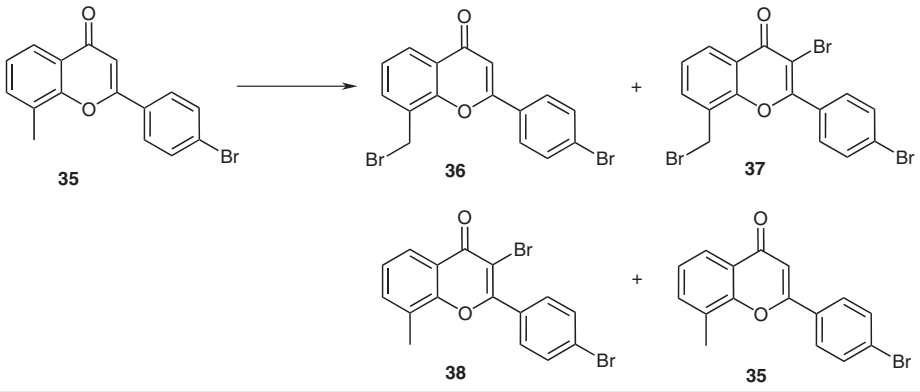
Our initial approach to the synthesis of 8-(hydroxymethyl)chromen-4-ones (Scheme 7) followed a strategy similar to that used for the quinazolinones and isoquinolines. Benzylic bromination of a key intermediate **35** with NBS and AIBN was expected to provide us with a substrate that could be further manipulated to yield a diverse range of (hydroxymethyl)chromenones. Unfortunately, bromination was capricious and frequently led to a mixture of products which became even more problematic on gram scales.



Scheme 6 *Reagents and conditions*: (a) *n*-butyl nitrite, concd HCl, r.t., 70%; (b) 2 M NaOH, 50 °C; (c) TsCl, 80 °C, 99% over 2 steps; (d) PCl_5, $POCl_3$, 0 °C to r.t., 70%; (e) NBS, AIBN, EtOAc, reflux, 75%; (f) CsOAc (7 equiv), H_2O, NMP, 60 °C; (g) NaOMe in MeOH, 60 °C, 75% over 2 steps; (h) $[Pd(dtbpf)Cl_2]$, K_3PO_4, dioxane, H_2O, $ArB(OH)_2$, 80 °C; (i) 6 M HCl, 80 °C, 22–45%.

Although it was possible to isolate the desired chromenone **36**, the poor yield meant that a more reliable route was sought.

An alternative approach was found and we were able to produce a number of chromenones in an eight-step sequence from the commercially available phenol **39** (Scheme 8).[20] Bromination of **40** was carried out with NBS and AIBN as before. The bromine was displaced with methoxide to give the substrate for the condensation reaction to provide diketone **42**. Cyclisation to yield the chromenone core was effected in AcOH with HBr and proceeded in two stages. Monitoring of the reaction by using LCMS revealed that displacement of the pendant methoxide with bromine occurred at 80 °C; an increase in temperature to 100 °C induced cyclisation. The bromine was subsequently displaced with acetate to afford chromenone **43**. As in previous examples, the final steps involved Suzuki–Miyaura cross coupling or Buchwald coupling and deprotection, yielding **44** in yields ranging from 22–42% over the two steps.



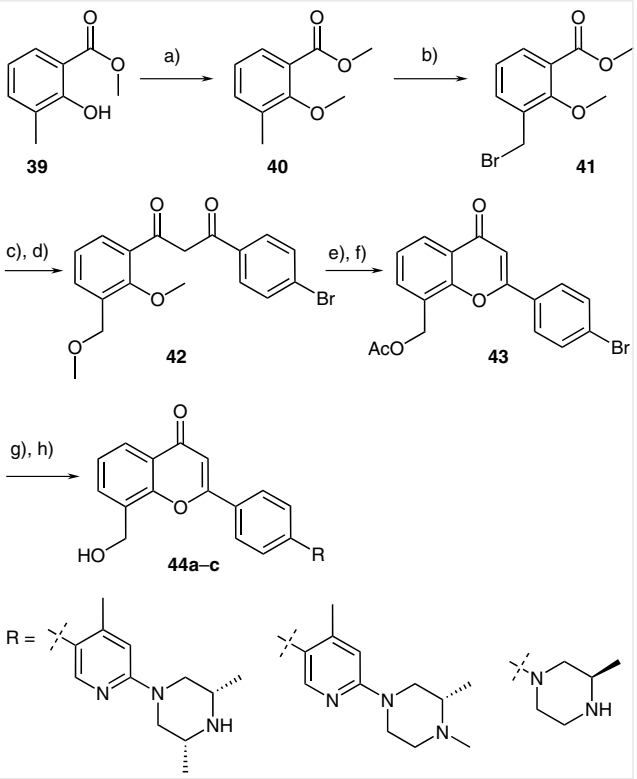
Scheme 7 *Reagents and conditions*: NBS, AIBN, EtOAc, reflux.

Despite numerous examples of pyrrolo[2,1-*f*][1,2,4]triazine-4(3*H*)-one cores in the literature,[21,22] we found no examples of 7-hydroxymethyl-substituted 'triazinones'. Typical literature[22] approaches to the triazinone core involve base cyclisation of an amidopyrroloamide. We employed similar chemistry using aminopyrrole **45** as the starting material to form the triazinone **47** in two steps (Scheme 9).[2] Key precursor **50** was easily accessed in three further steps.[2]

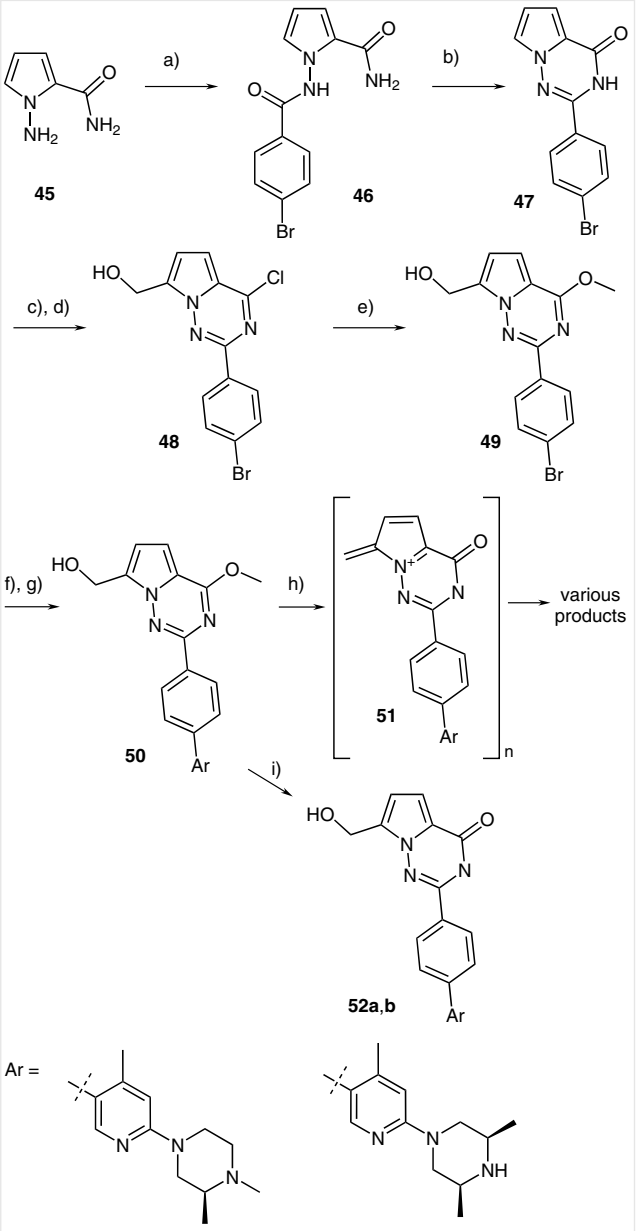
The final methoxy-deprotection step was initially conducted by using dilute acid and gentle heating, but this led to elimination of the hydroxy group and a variety of products *via* suspected intermediate **51**. To avoid formation of this unwanted byproduct, an alternate deprotection protocol, using sodium thiomethoxide in DMF at a temperature between 50 and 70 °C (depending on the compound), provided the desired product **52** in good yield (Scheme 9).

A range of novel hydroxymethyl-substituted fused heterocycles has been prepared as part of a medicinal chemistry programme. Despite many of these cores being prevalent in the literature, there are few examples, if any, of hydroxymethyl-substituted analogues. We have successfully developed routes to access such compounds and, using this chemistry, we have been able to prepare an extensive number of novel analogues.

All materials were sourced from commercial suppliers and used as provided. Reaction progress was monitored by Waters Aquity UPLC with Waters 3100 Mass detection or TLC using glass plates pre-coated with 0.25 mm 300–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Visualisation was by exposure to UV light. Flash column chromatography was performed using pre-loaded Silicycle columns containing silica gel (60 Å pore size, standard grade) and an Isco Combi-Flash Companion. Reverse phase chromatography was performed using pre-loaded RediSep Rf cartridges containing C18 silica and a Teledyne Isco Combi-Flash Rf. Details of preparative HPLC purification are contained within the experimental information where relevant. The HRMS was performed using a Thermo LTQ-FT/Accela/CTC/PDA with Acquity 50 × 2.1 C18 CSH 1.7 µm columns at 40 °C. NMR spectra were obtained on Bruker AV400, Drx500 and AV700 MHz systems using DMSO-d_6, $CDCl_3$ or CD_3OD and are reported relative to a protiated solvent signal or tetramethylsilane.



Scheme 8 *Reagents and conditions*: (a) MeI, K_2CO_3, acetone, reflux, 57%; (b) AIBN, NBS, MeCN, 80 °C, 80%; (c) NaOMe, MeOH, MeCN, 65 °C, quant; (d) 4-bromoacetophenone, NaH, dioxane, 80 °C, 41%; (e) HBr, AcOH, 80 °C, 1 h, then 100 °C, 2 h, quant; (f) NaOAc, DMF, 100 °C, 87%; (g) $ArB(OH)_2$, $Pd(PPh_3)_4$, Cs_2CO_3, dioxane, 85 °C *or* $Pd_2(dba)_3$, BINAP, Na*t*-OBu, 110 °C, toluene; (h) MeOH, K_2CO_3, 50 °C, 13–42% over 2 steps.



Scheme 9 *Reagents and conditions*: (a) Et_3N, 4-BrC_6H_4COCl, MeCN, r.t., 89%; (b) NH_4OH, 100 °C, 53%; (c) $POCl_3$, DMF, 95 °C; (d) $NaBH_4$, THF, 0 °C, 85%; (e) NaOMe, MeOH, 60 °C, 98%; (f) $[Pd(dppf)_2Cl_2]$, KOAc, bis(pinacolato)diboron, dioxane; (g) ArBr, $[Pd(dtbpf)Cl_2]$, K_3PO_4, DMF, 105 °C; (h) 2–6 M HCl or TMSCl; (i) NaSMe, DMF, 50–70 °C, 29–64%.

Quinazolin-4(3*H*)-ones 11a–f; General Procedure

2-Chloro-4-oxo-3,4-dihydroquinazoline-8-carboxylic acid (634 mg, 2.82 mmol) was added to amine (2.82 mmol) and DIPEA (0.64 mL, 3.67 mmol) in MeCN. The resulting suspension was heated at 80 °C for 7 hours during which time further additions of DIPEA and solvent were made to help drive the reaction to completion. The reaction mixture was concentrated and the resulting residue acidified with 2 M HCl in dioxane (25 mL). MeOH (10 mL) was added and the mixture stirred for 1 hour. The mixture was filtered and the solid collected and dried to provide the desired product as a light brown/beige powder as the HCl salt. This material was used with no further purification.

Lithium aluminum hydride (5.69 mL, 5.69 mmol) (1 M solution in THF) was added dropwise to the acid (1.90 mmol) in THF (10 mL) at ambient temperature under nitrogen. The resulting suspension was stirred at 50 °C for 3 hours, cooled to ambient temperature and quenched by the addition of sat. aqueous ammonium chloride (100 mL). The mixture was extracted into EtOAc (3 × 150 mL) and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated to provide the crude product as a yellow gum. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 50 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH_3) and MeCN as eluents. Pure fractions were evaporated to dryness to afford the desired compounds.

8-(Hydroxymethyl)-2-[4-(2-hydroxyphenyl)piperazin-1-yl]quinazolin-4(3*H*)-one (11a)

The above method was used to provide the target **11a** as a colourless solid; yield: 89 mg (62%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.98–3.05 (m, 4 H), 3.75–3.82 (m, 4 H), 4.80 (d, *J* = 5.3 Hz, 2 H), 5.07 (t, *J* = 5.3 Hz, 1 H), 6.73–6.78 (m, 1 H), 6.92 (dd, *J* = 1.3, 7.8 Hz, 1 H), 7.14–7.22 (m, 1 H), 7.70 (d, *J* = 7.1 Hz, 1 H), 7.78–7.87 (m, 1 H), 9.02 (s, 1 H), 11.43 (br s, 1 H).

^{13}C NMR (176 MHz, DMSO-d_6): δ = 44.99, 49.73, 59.15, 115.60, 116.35, 118.89, 119.39, 121.59, 123.20, 123.85, 130.85, 136.45, 139.38, 139.48, 147.15, 150.15, 163.14.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{21}N_4O_3$: 353.16082; found 353.16077.

Quinazolin-4(3*H*)-ones 17a–c; General Procedure

$Pd(PPh_3)_4$ (139 mg, 0.12 mmol) was added to a degassed mixture of (2-chloro-4-oxo-3,4-dihydroquinazolin-8-yl)methyl acetate (**16**; 149 mg, 0.59 mmol), boronic acid/ester ArX (0.65 mmol, 1.1 equiv) and Cs_2CO_3 (388 mg, 1.19 mmol) in dioxane (4 mL) and H_2O (3 mL). The resulting suspension was degassed and stirred at 100 °C for 3 hours under a nitrogen atmosphere. The reaction mixture was cooled to 50 °C and K_2CO_3 (164 mg, 1.19 mmol) and MeOH (3 mL) were added. The mixture was stirred at 50 °C for 2 hours and then allowed to cool to ambient temperature. The reaction mixture was filtered and the filtrate was concentrated to provide the crude product. Purification by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 50 mm diameter, 100 mm length) using decreasingly polar mixtures of H_2O (containing 1% NH_3) and MeCN as eluents provided the desired compounds.

8-(Hydroxymethyl)-2-[4-(1-methylpiperidin-4-yloxy)phenyl]quinazolin-4(3*H*)-one (17a)

The above method was used to provide the target **17a** as a colourless solid; yield: 116 mg (54%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.91 (dtd, *J* = 3.6, 8.0, 12.0 Hz, 2 H), 2.00–2.11 (m, 2 H), 2.29–2.39 (m, 5 H), 2.67–2.76 (m, 2 H), 4.37 (br s, 1 H), 4.42–4.51 (m, 1 H), 5.09 (s, 2 H), 7.07 (d, *J* = 8.9 Hz, 2 H), 7.42 (t, *J* = 8.0 Hz, 1 H), 7.68 (d, *J* = 6.3 Hz, 1 H), 8.03 (t, *J* = 8.9 Hz, 2 H), 8.23 (dd, *J* = 1.4, 8.0 Hz, 1 H), 10.21 (br s, 1 H).

^{13}C NMR (176 MHz, DMSO-d_6): δ = 30.42, 45.73, 52.26, 58.89, 72.05, 115.48, 120.11, 123.84, 124.77, 125.60, 129.50, 131.28, 139.17, 145.68, 150.93, 159.85, 162.39.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{24}N_3O_3$: 366.18122; found 366.18127.

Quinazolin-4(3*H*)-ones 18a–k; General Procedure

DIPEA (0.30 mL, 1.70 mmol) was added in one portion to (2-chloro-4-oxo-3,4-dihydroquinazolin-8-yl)methyl acetate (**16**; 101 mg, 0.40 mmol) and amine HNR_2 (0.40 mmol) in DMF (3 mL). The resulting solution was stirred at 100 °C for 30–60 minutes. K_2CO_3 (273 mg, 1.98 mmol) and MeOH (5 mL) were added and the mixture was stirred overnight at 50 °C. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 50 mm diameter, 100 mm length) using decreasingly polar mixtures of H_2O (containing 1% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the desired products.

8-(Hydroxymethyl)-2-[3-(4-methoxyphenyl)azetidin-1-yl]quinazolin-4(3*H*)-one (18a)

The above method was used to provide the target **18a** as a colourless solid; yield: 75 mg (37%).

^{1}H NMR (500 MHz, DMSO-d_6): δ = 3.75 (s, 3 H), 3.81–3.95 (m, 1 H), 4.03 (dd, *J* = 6.4, 8.6 Hz, 2 H), 4.48 (t, *J* = 8.6, 2 H), 4.78 (s, 2 H), 6.87–6.98 (m, 2 H), 7.07–7.19 (m, 1 H), 7.27–7.38 (m, 2 H), 7.58–7.73 (m, 1 H), 7.83 (dd, *J* = 1.7, 7.9 Hz, 1 H).

^{13}C NMR (176 MHz, DMSO): δ = 32.80, 55.06, 57.83, 59.33, 114.00, 116.61, 121.34, 123.98, 127.98, 130.79, 133.95, 136.06, 147.46, 151.53, 158.14, 162.76.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{20}N_3O_3$: 338.14992; found 338.14972.

Quinazolin-4(3*H*)-ones 20a,b; General Procedure

DIPEA (0.15 mL, 0.88 mmol) was added to the imidazole (0.29 mmol, 1 equiv) in DMA (6 mL) and the mixture was stirred for 10 minutes. (2-Chloro-4-oxo-3-tosyl-3,4-dihydroquinazolin-8-yl)methyl acetate (**19**; 118 mg, 0.29 mmol) and sodium methanesulfinate (30 mg, 0.29 mmol) were added and the mixture stirred for 72 hours at 80 °C. The temperature was reduced to 50 °C and K_2CO_3 (100 mg, 0.72 mmol) in MeOH (3 mL) was added. The mixture was stirred overnight. The reaction mixture was filtered and concentrated *in vacuo*. The crude product was purified by preparative HPLC (Waters XBridge Prep C18 OBD column, 5µ silica, 19 mm diameter, 100 mm length) using decreasingly polar mixtures of H_2O (containing 1% NH_3) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford the desired compounds.

8-(Hydroxymethyl)-2-(4-phenyl-1*H*-imidazol-1-yl)quinazolin-4(3*H*)-one (20b)

The above method was used to provide the target **20b** as a colourless solid; yield: 12 mg (13%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.98 (s, 2 H), 7.23–7.31 (m, 1 H), 7.34 (t, *J* = 7.5 Hz, 1 H), 7.38–7.47 (m, 2 H), 7.77 (d, *J* = 6.9 Hz, 1 H), 7.89 (dd, *J* = 1.3, 8.2 Hz, 2 H), 7.94–8.00 (m, 1 H), 8.42 (d, *J* = 1.2 Hz, 1 H), 8.63 (d, *J* = 1.2 Hz, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 59.21, 112.56, 120.54, 123.45, 124.20, 124.59, 126.82, 128.57, 129.85, 133.72, 136.12, 137.66, 141.06, 146.82, 147.59, 167.62.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{15}N_4O_2$: 319.11895; found 319.11893.

Further experimental details and compound data are available in the Supporting Information.

Acknowledgments

We would like to thank Rebecca Burton, Gemma Mayers, Caroline McMillan, Nia Lock, Howard Beeley and Paul Davey for purification, NMR and mass spectrometry assistance.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1561355.

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