Tetrahedron 68 (2012) 534–543

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Preparation of 6-aminoquinazolin-4(3*H*)-ones via direct S_NAr on the quinazoline ring

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ARTICLE INFO

Article history:
Received 2 August 2011
Received in revised form 3 November 2011
Accepted 4 November 2011
Available online 19 November 2011

Keywords:
Direct S_NAr
Unactivated fluorides
Quinazolin-4-(3*H*)-one

ABSTRACT

The preparation of 6-aminoquinazolin-4(3*H*)-ones requires the use of platinum–metal group catalysis on the corresponding C-6-iodo or 6-bromo precursors. Herein, we report to our knowledge the first successful S_NAr reaction directly at the unactivated C-6 position of the quinazolin-4(3*H*)-one nucleus.

1. Introduction

Substituted quinazolines have been the focus of much research in recent years from pharmaceutical and academic groups, notably, as small molecule ATP-competitive kinase inhibitors.[1] At present, there are eight C-4-substituted quinazolines in late-stage clinical development (Fig. 1) amongst which *gefinitib*,[2] and *erlonitib*[3] are already commercialised for the treatment of non-small cell lung cancer and *lapatinib*,[4] for hormone-positive and HER2-positive advanced breast cancer (Fig. 1).[4]

During a recent discovery program, we became interested in exploring C-4-substituted quinazolines having substitution at C-6 and C-8 on the phenyl ring[5] but before starting synthetic work, we carried out a quick search of the existing literature to determine our freedom to operate. Inspection of the literature revealed that the C-4-substituted quinazoline family comprises more than 144,000 CAS members exemplified in 3843 patents to date (entry 1). Within this family, perhaps not surprisingly we discover that C-4,6,7-trisubstituted quinazolines are the most dominant representing 40,641 CAS members exemplified in 1999 patents (entry 6). If we limit the searches specifically to amine substitution at C-4 and ether substitution at C-6 and C-7, we find this particular family is responsible for more than 96% of all patents in this sub-family (entry 7). Finally, the C-4,6,8-trisubstituted family, with just 4352 CAS members exemplified in just 61 patents, is one of the least studied cores thus offering potentially more freedom to explore this chemical space. Moreover, the particular substitution pattern that we designed having a methyl substituent at C-2, C-6-amino substitution and any substitution at C-8 has no existing references (entry 9) (Table 1).[6]

With this knowledge in hand, we set about designing a valid route to the scaffold, which would allow us to vary preferentially all three key positions in an orthogonal manner. With so few references in the literature, we decided to employ Kepner-Tregoe[8] decision analysis in order to help us with route selection, recently employed by our process research and development colleagues at Avlon, Bristol.[9] We envisaged three routes to access the key synthon (**10**) having the potential to vary all key positions of the quinazoline nucleus, all based on a Niementowski cyclisation strategy.[10] Route A, possibly the longest of all routes, focused on manipulating 2-amino-isophthalic acid (**1**) as the starting material. Halogenation at C-4 followed by cyclisation following recognised cyclisation protocol[11,12] should afford intermediate **2** leaving a Buchwald–Hartwig amination followed by functional group transformation of the carboxyl functionality to a halogen atom via a standard functional group manipulation relying on the Curtius rearrangement. The key step for route B is dependant on a smooth *ortho*-halogenation of anthranilic acid derivative **5**. Electrophilic halogenation of *p*-disubstituted aminobenzenes in general is quite rare with seemingly only one reference[13] but if successful, we were confident the rest of the sequence would be straightforward. Based on existing literature an in-house chemistry experience, route C was possibly the least likely to succeed as its key step relied on direct amination at the unactivated C-6–F position of a quinazolin-4(3*H*)-one, for which there were no supporting references. However, if successful, this route would be arguably the most convergent allowing us to target the synthesis of

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doi:10.1016/j.tet.2011.11.008

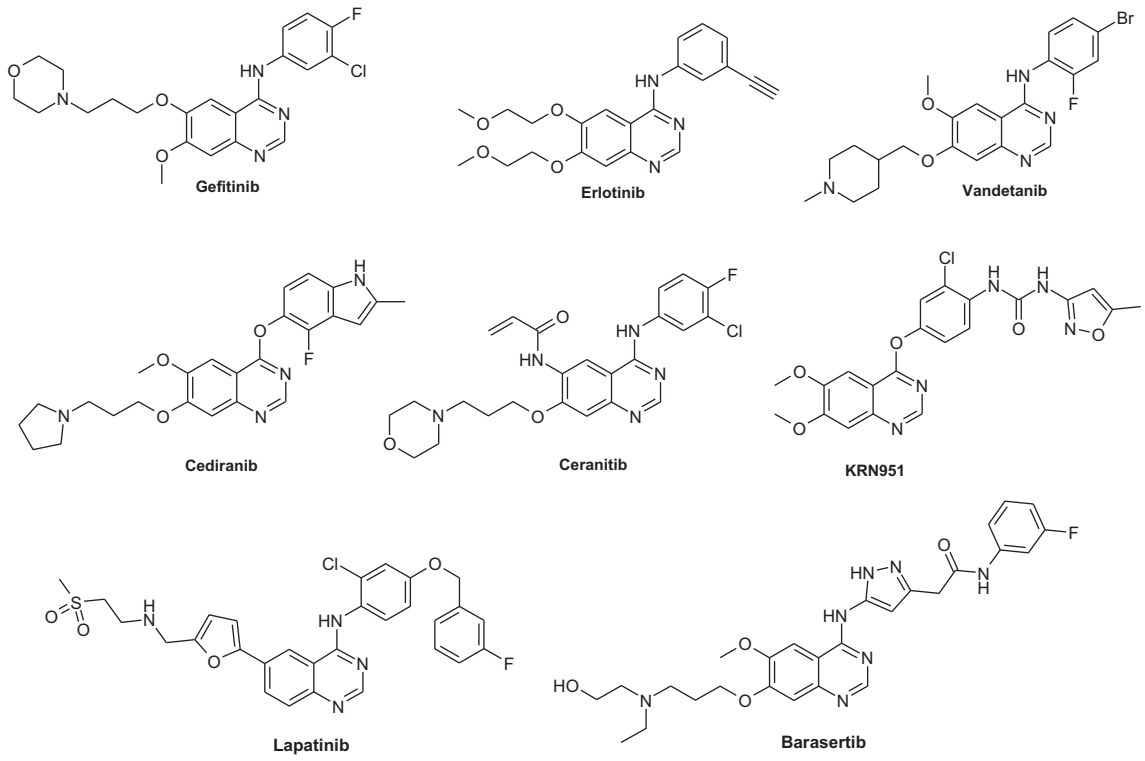


Fig. 1. A selection of C-4-substituted quinazolines on the market or in late-stage clinical trials.

Table 1
Current literature distribution of C-4-substituted quinazolines with two substituents on the phenyl ring A=any atom apart from H

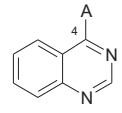
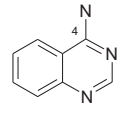
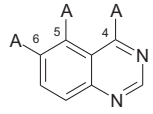
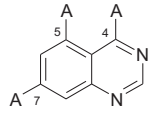
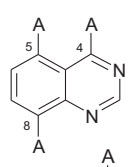
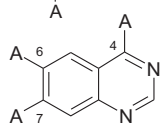
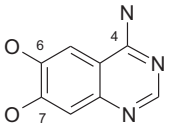
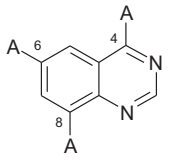
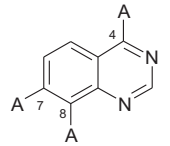
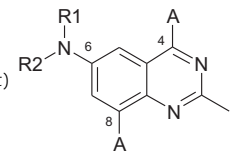
Entry	Substructure	CAS Nos	Total references/ patents	% Share of total references/ patent
1		144,293	12,845/3843	—
2		129,026	9754/2654	75.9/69.1
3		12,252	291/111	2.3/2.9
4		1111	131/87	1.0/2.3
5		426	210/142	1.6/3.7
6		40,641	8167/1999	63.6/52.0

Table 1 (*continued*)

Entry	Substructure	CAS Nos	Total references/ patents	% Share of total references/ patent
7		15,688	7840/1758	61.0/45.7 96.0/87.9[a]
8		4352	127/61	1.0/1.6
9		367	95/48	0.7/1.2
10 (Target)		0	0	—

[a] Refers specifically to percentage share of the C-4,6,7-trisubstituted family (entry 6).[6,7]

the most flexible intermediate in relation to the vectors that we wished to explore (Fig. 2).

From Table 2, we decided on the 'must haves' being the availability of a reasonable starting material and the tractability from that starting material to the final key synthon **10** as judged by both key vectors selectively, if successful with the S_NAr reaction at the unactivated C-6 position. Likewise route B also scored highly furnishing a similar bifunctional intermediate, albeit after considerably more steps. Route A was the least appealing as the amine group at C-6 was fixed early on in the sequence, therefore, permitting for linear variations from the C-8 position at the end of the sequence. In terms of SHE (safety, health and environment), the scoring of route C>B>A is a simple reflection on the number of steps required to effect the sequence reducing. Finally, in terms of 'added-value' or novelty, while efficient S_NAr reactions on the quinazoline nucleus are known, usually at the activated positions 2,4,5,7[16] and also recently at the unactivated C-8 position,[17] there are no references at the unactivated C-6 position of a quinazolin-4(3*H*)-one ring. Therefore, if successful, this would be worthy addition to the quinazoline literature as opposed to the other two routes, which even if successful, could be classed as standard functional group manipulation.

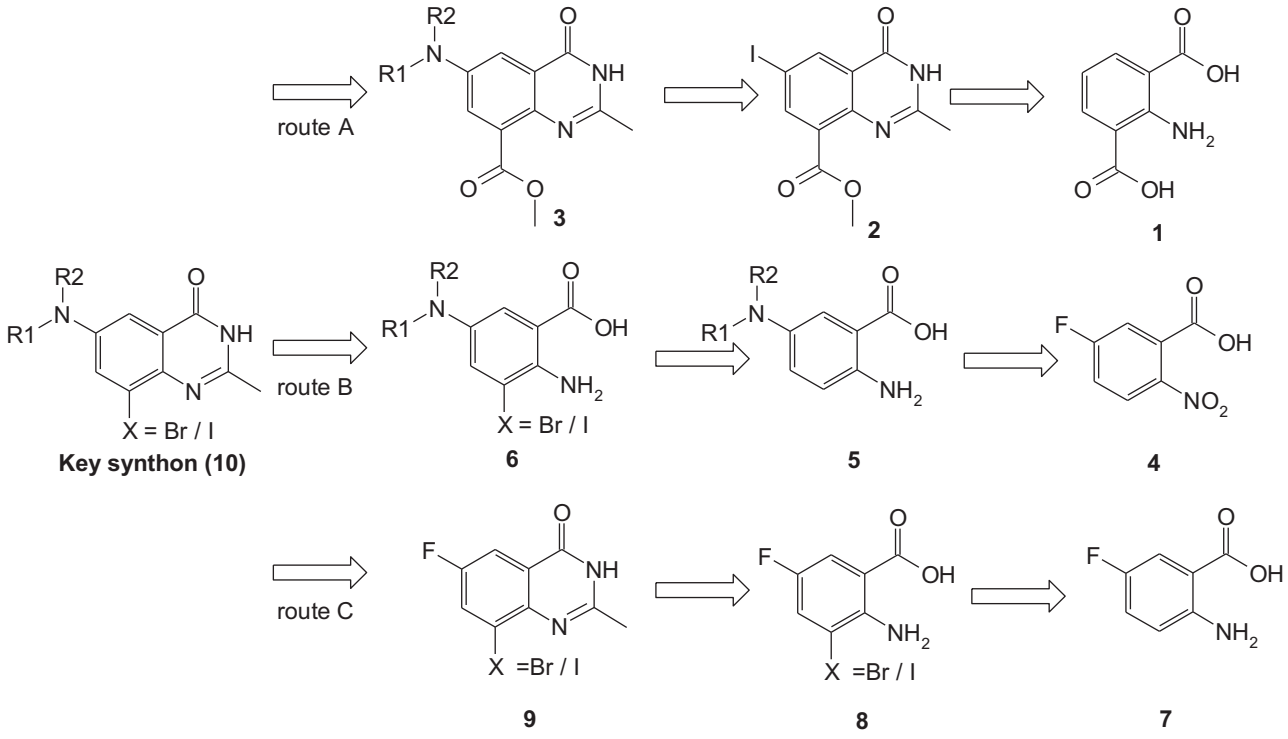


Fig. 2. Retrosynthetic analysis of key synthon.

Table 2
Our Kepner-Tregoe scoring of the three routes

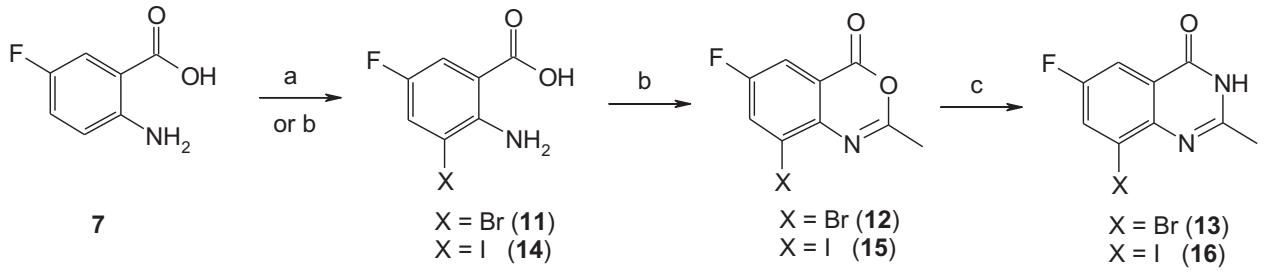
Factor	Route A	Route B	Route C
Tractability	OK	OK	OK
Readily-available SMs	OK	OK	OK
Few steps	3	7	8
Supporting literature	9	5	2
Orthogonality	3	3	8
Safety aspects	3	7	8
Added-value	5	3	7
Total	23	25	33

existing literature and in-house experience in the quinazoline field.[10] From that point, we scored the routes based on what we regarded as the key factors to a successful route. In terms of the number of steps, route A was the least appealing as starting from 2-amino-isophthalic acid, we envisaged a total of eight steps to get to synthon **1** compared to five steps for route B and four steps for route C. However, in terms of supporting literature, it was clear that route A seems like the most evident having more or less close analogies for each step reported. While route B seemed logical, the key step was going to control a selective electrophilic halogenation *ortho* to the aniline in the presence of another donor amine already in place at *para*, for which there are no supporting references. The key step for route C relied on an efficient S_NAr at the unactivated C-6–F of the quinazolin-4(3*H*)one ring, for which there are no supporting references. However, direct S_NAr on unactivated aryl fluorides[14] can be viewed as an acceptable strategy affording moderate to excellent yields of substituted product with notable successes in recent literature.[15] Route C scored highly for orthogonality as the intermediate 6-F–8-Br/I precursor (**9**) would allow us to explore

2. Results and discussion

Influenced by the results obtained from the Kepner-Tregoe analysis, we set about work on route C. The synthesis started from 4-fluoroanthranilic acid. Bromination using *N*-bromosuccinimide in refluxing AcOH and iodination using iodonium chloride under acidic conditions[18] afforded **11** and **14**, respectively. Cyclisation afforded **12**/**15**, which were transformed to the corresponding quinazolin-4(3*H*)-ones **13**/**16** using concd aqueous ammonia in a sealed tube.[19] Both processes were carried out without resorting to purification by silica gel chromatography (Scheme 1).

With the key synthons in hand, we set about validating the route by testing the S_NAr reaction using morpholine directly as the solvent. Before starting experimental work on **13** or **16**, we observed that direct S_NAr on 6-fluoroquinazolin-4(3*H*)-one was not possible resulting in only traces of desired compound despite prolonged periods of heating at 220 °C under microwave



Scheme 1. Synthesis of key synthon **1**. Reagents and conditions: (a) ICl, HCl (aq), H_2O, rt, 74%; (b) NBS, AcOH, rt, 66%; (c) Ac_2O, 140 °C, 93% (X=Br) 95% (X=I); (d) NH_4OH, 100 °C, 74% (X=Br), 84% (X=I).

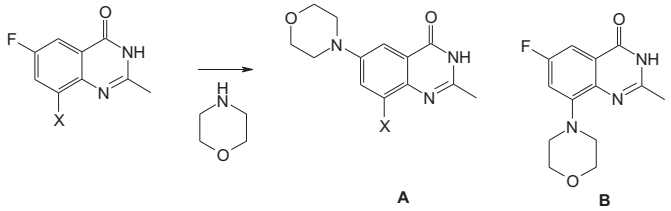
irradiation (entry 1). On the contrary and to our surprise the S_NAr reaction proceeded with, perhaps unexpectedly, competition at C-8 at 180 °C under microwave irradiation using **13** as the starting material (entry 2). In order to improve selectivity, we decided to study the effects of lowering the reaction temperature and heating for longer periods. The effects of lowering the temperature from 180 °C to 160 °C notably increased selectivity significantly from 1/1 to 2/1 in favour of the desired product (entry 3). We continued this study finally deducing we could achieve acceptable conversions with reasonable selectivity by operating the reaction at 120 °C for 6 days (entries 3–5 vs 6). Not surprisingly attempts to add a mineral base to irreversibly neutralise the mole of HF formed resulted in no conversion. We postulate that the substitution was discouraged due to the quantitative deprotonation of the quinazolin-4(3*H*)-one skeleton resulting in the thermodynamically-stable ion potassium salt. Reaction in neat morpholine or in presence of a tertiary base does not stop the reaction as deprotonation of the quinazolin-4(3*H*)-one is rather transient with the equilibrium lying towards the active non-protonated form (entry 7 vs entry 8). To further improve selectivity, we found that **16** was a superior substrate to **13** (entries 9–11) even if the rate of substitution was significantly decreased due to a weaker inductive effect (entries 2 and 3 vs entries 9 and 10). One of the key conclusions we deduced is that a relatively inert halogen atom inducing a weak inductive effect *meta* to the C–F bond is actually sufficient to allow the S_NAr reaction to take place with weak nucelophiles.[20]

In order to quickly confirm this hypothesis and that the fused pyrimidinone ring was playing no role in activating the C-6-F towards S_NAr, we applied similar reaction conditions to simple halogen substituted fluorobenzenes using morpholine as the solvent. From Table 3, it appears evident that the presence of a halogen atom at the *meta* position to the fluorine leaving group enhances greatly the rate of substitution compared to *ortho* position (entries 5–8 vs entries 2–4) with *para*-substitution exerting little affect (entries 9 and 10). We postulate that while evidently the inductive effect of having a halogen atom *ortho* to the leaving group is more important than at the *meta* position, the approach of the nucleophile on the *ipso* position is more sterically and electronically hindered explaining the higher conversions (entries 5–7 vs entries 2–4). It appears also clear, by the conversion rates, that the presence of the pyrimidinone ring is slowing down rather than accelerating the rate of substitution (Table 4, entry 7 vs Table 3, entry 3).

We were also curious to see if introduction of an activating mesomeric group at C-8 would significantly increase the reaction rate. Therefore, we transformed the C-8–Br to the C-8–CN in excellent yield using a MAOS (microwave-assisted organic synthesis) palladium catalysed cyanation process recently communicated by Pitts et al.[21] However, to our surprise the presence of a C-8–CN group did not increase the reaction rate and we also observed a significant problem of addition of morpholine onto the C-8–CN group (Scheme 2).

Although the approach was adequate for the introduction of secondary amine nucleophiles, this approach could not be used for alkoxides due to deprotonation and inactivation of the quinazoline ring towards substitution. Therefore, we decided to protect the N-3 position with a PMB (*p*-methoxybenzyl) group with the knowledge that we should be able to deprotect the group with relative ease.[22] Selective N-protection of **16** was achieved using a slight excess of PMB-Cl in refluxing acetone overnight in the presence of potassium carbonate to afford **21** in good yield (Scheme 3, Table 5).

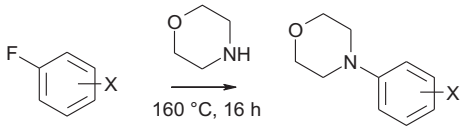
Table 3
Optimisation study using morpholine as the solvent. N/A=not applicable



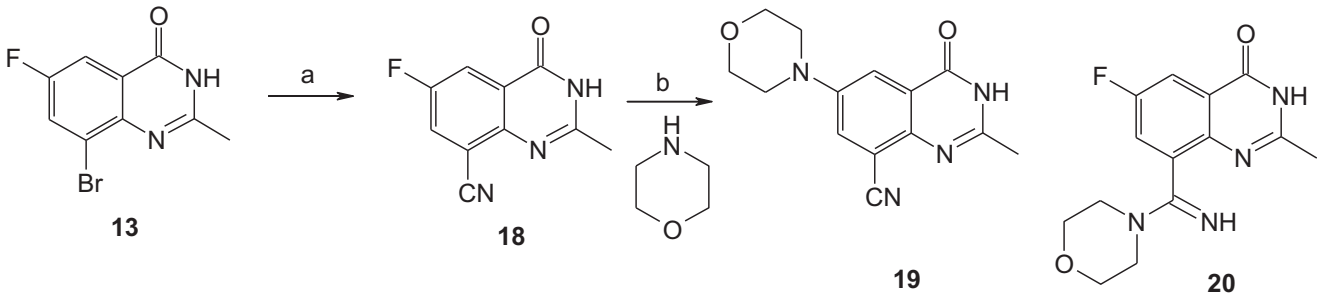
Entry	X	Temperature/time	% Conv.[b]	% A[b]	% B[b]
1	H	180–220 °C/16 h	0	—	N/A
2[a]	Br	180 °C/2 h	89	58	42
3	Br	160 °C/16 h	64	64	36
4	Br	140 °C/2 days	84	69	31
5	Br	130 °C/3 days	90	70	30
6	Br	120 °C/6 days	91	72	28
7	Br	Et_3N/120 °C/3 days	76	68	32
8	Br	K_2CO_3/120 °C/3 days	0	—	—
9[a]	I	180 °C/2 h	29	63	37
10	I	160 °C/3 days	60	77	23
11 (Cpd 17)	I	140 °C/6 days	93	84[c]	16

[a] Reaction performed under microwave irradiation.
[b] Figures determined by analytical LCMS.
[c] Isolated yield.

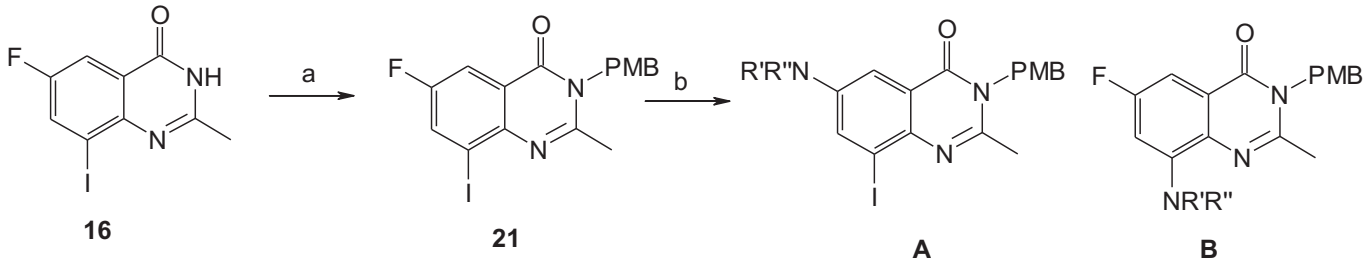
Table 4
The % S_NAr conversion as judged by LCMS on simple halogen substituted fluorobenzenes



Entry	X	% Conversion
1	H	0
2	2-F	33
3	2-Br	0
4	2-I	0
5	3-F	82
6	3-Cl	74
7	3-Br	79
8	3-I	44
9	4-F	0
10	4-Br	0



Scheme 2. Reagents and conditions: (a) $Zn(CN)_2$, $Pd_2(dba)_3$, xantphos, DMA, 160 °C, microwave, 10 min, 76%; (b) morpholine, 140 °C, 2 days, 78% conversion (**19** (65%); **20** (35%)).



Scheme 3. Reagents and conditions: (a) PMB-Cl, K_2CO_3, acetone, reflux, 16 h, 85%; (b) R′R″NH, 140 °C, 3 days.

Table 5
Effect of varying the amine on yield and conversion after 3 days at 140 °C

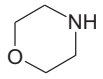
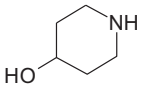
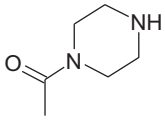
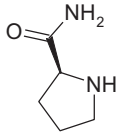
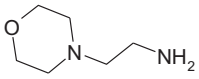
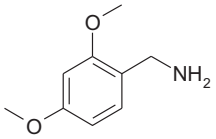
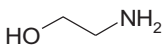
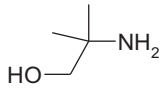
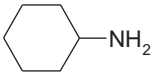
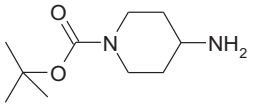
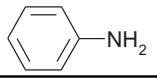
Entry (compound)	Compound	Amine	% A[a]	% B
1	**22**		68	12
2	**23**		78	9[c]
3	**24**		68	7[c]
4	**25**[b]		21	N/D
5	**26**		43	N/D
6	**27**		45	N/D
7	**28**		41	N/D
8	**29**		17	N/D

Table 5 (*continued*)

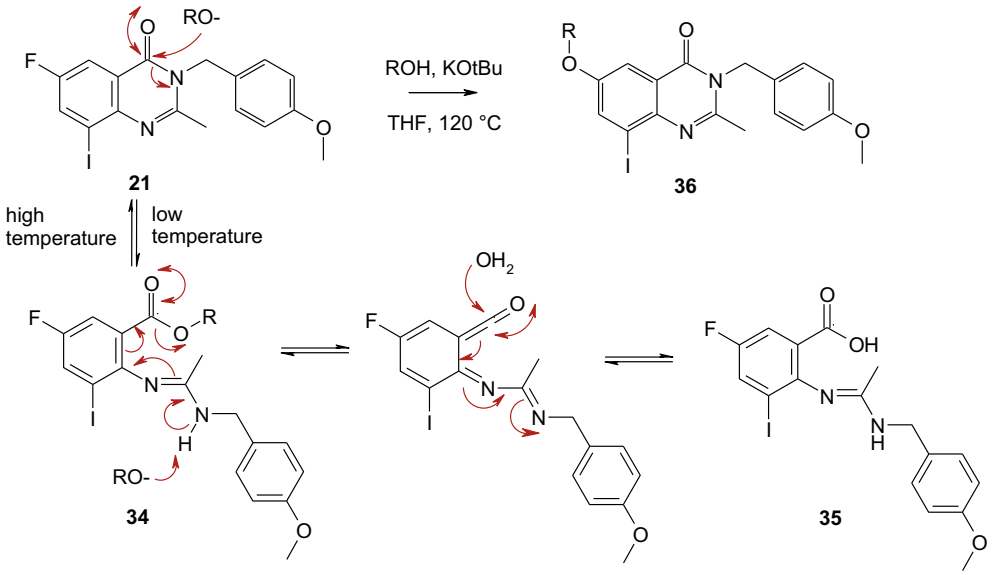
Entry (compound)	Compound	Amine	% A[a]	% B
9	**30**		14[c]	N/D
10	**31**		16[c]	N/D
11	**32**		39	N/D
12	**33**		N/D	N/D

N/D=not detected.
[a] Isolated yield.
[b] Reaction mixture heated at 180 °C for 3 days.
[c] Reaction mixtures not isolated.

The results in Table 3 demonstrate clearly the advantage of protecting the N-3 position. Displacement with morpholine proceeds in half of the time while retaining the same selectivity (85/15). As expected, unhindered secondary amine nucleophiles gave the best results (entries 1–3) apart from L-prolinamide (entry 4), which gave a particularly poor yield even at higher temperatures presumably due to reduced basicity and increased steric hindrance due to the presence of the C-2-carboxamide functionality. Unhindered primary amines also reacted in acceptable yields (entries 5–7). Not surprisingly, very hindered primary amines (entries 8–10) reacted very slowly but heteroaromatic bases, such as imidazole gave acceptable conversions (entry 11) and aromatic amines (e.g., aniline, entry 12) gave only traces of substituted product.

After having demonstrated the amine substrate scope for **21**, we turned our attention to the introduction of other nucleophiles.

Initially, we focused on introducing alkoxides but after the first experiments, only traces of the desired product (**36**) were detected. In fact after much experimentation, only the ring-opened by-product (**35**) was detected despite operating the reaction under anhydrous conditions. Surprised by this result, we proposed that the side product was possibly the kinetic product, which would have a strong thermodynamic driving force to re-cyclise to the quinazolinone to re-afford the starting material. We postulate that



the enhanced lability of the carbonyl of the quinazolinone could be explained by the stabilisation of the negative charge by the resulting amidine moiety after ring opening. The intermediate ester (**34**), the most probable by-product, was never detected by LCMS, therefore, we assumed the ester **34** was quickly hydrolysing to the acid possibly via a reactive ketene intermediate during analysis affording the acid **35**.

In order to confirm the theory, we simply increased the operating temperature from 80 °C to 120 °C. To our satisfaction, at 120 °C, all the starting material was transformed to the desired product (**36**) and only traces of **35** were detected. We quickly evaluated the substrate scope with ethereal side chains often employed to improve physicochemical properties of quinazolines (entries 1–3 after deprotection). Perhaps surprisingly, we also successfully introduced phenyl ether substitution (entry 4) with a satisfactory yield. However, attempts to introduce carbon or amide nucleophiles (entries 5 and 6) failed and sulfur nucleophiles afforded no selectivity (Table 6).

3. Conclusion

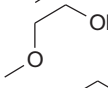
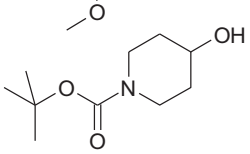
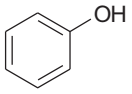
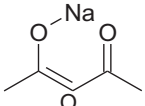
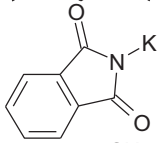
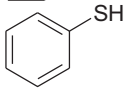
In conclusion, we have demonstrated an efficient and orthogonal route to access a poorly studied quinazoline template that highlights a novel direct S_NAr at the unactivated C-6 position of the quinazoline ring. In addition, we managed to show that a halogen atom *meta* to the fluorine leaving group exerts a sufficient inductive effect to permit the substitution under standard laboratory conditions.

4. Experimental

4.1. General methods

^1H and ^{13}C NMR spectra were recorded on a Bruker Biospin AVANCE 500 spectrometer. Chemical shifts are reported as δ values downfield from internal TMS in appropriate organic solutions. The purity and the structures of the products were confirmed by LCMS on a Waters 2690 photodiode array detector system using the following conditions: Column, Symmetry C-18; Solvent A, water 0.1% formic acid; Solvent B, CH_3CN; flow rate, 2.5 ml/min; run time, 4.5 min; gradient, from 0 to 100% solvent B; mass detector, micromass ZMD. Preparative LCMS was carried out using Waters 600 Pumps linked to a Waters 2700 Sample Manager and a Waters

Table 6
Results obtained with other nucleophiles

Entry	Compound	Nucleophile	% Yield
1	**37**		51
2	**38**		70
3	**39**		42
4	**40**		51
5	**41**		—
6	**42**		—
7	**43**		Mixture

Isolated yields.

micromass ZMD mass detector. Samples are routinely filtered and injected at concentrations of around 50 mg of expected product per ml of DMF. All strength measurements are carried out as follows: in a 2 ml vial, precisely ca. 10 mg of the compound is added. We add precisely ca. 2 mg of the reference compound (maleic acid). This mixture is dissolved in a mixture of DMSO-d_6 (0.55 ml) and CD_3COOD (5 drops). This mixture is warmed if necessary to obtain a complete dissolution. A proton spectrum is recorded with a long pulse delay (8 s) in order to obtain a quantitative measurement. Strength is calculated using the formula below:

$$\text{Force} = \frac{\text{Ic} \times \text{wr} \times \text{Mc} \times n\text{Hr}}{\text{Ir} \times \text{wc} \times \text{Mr} \times n\text{Hc}} \times \text{PR}$$

where: I=Integration; w=weight; M=Molecular weight; n=Number of proton in the studied signal; c=Compound; r=Reference; PR=Reference purity.

All small scale S_NAr reactions were carried out in 2 ml capacity microwave pressure tubes with a magnetic stirrer bar.

*4.1.1. 2-Amino-3-bromo-5-fluorobenzoic acid (**11**).* *N*-Bromosuccinimide (631 mg, 3.55 mmol) was added portionwise to a stirred solution of 2-amino-5-fluorobenzoic acid (**7**, 500 mg, 3.22 mmol) dissolved in acetic acid (5 ml) and the reaction mixture was stirred overnight at room temperature. The resulting precipitate was collected by filtration, washed with petroleum ether (20 ml) and dried to a constant weight to afford 2-amino-3-bromo-5-fluorobenzoic acid (**11**, 501 mg, 66.4%) as a clear beige solid, which was used without further purification: LCMS (t_R=1.35 min, purity=100%), ESI m/z, no ion detected; ^{1}H NMR (DMSO-d_6) δ (ppm) 6.76 (br s, 2H), 7.55 (dd, J=3.0 Hz, J_{H-F}=9.4 Hz, 1H), 7.71 (dd, J=3.0 Hz, J_{H-F}=7.8 Hz, 1H), 12.72 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 109.4 (d, J_{C-F}=7.1 Hz); 111.1 (d, J_{C-F}=7.1 Hz), 116.2 (d, J_{C-F}=22.1 Hz), 124.9 (d, J_{C-F}=24.8 Hz), 145.1, 151.4 (d, J_{C-F}=235.3 Hz), 168.1 (d, J_{C-F}=2.7 Hz).

*4.1.2. 6-Fluoro-8-bromo-2-methyl-4H-3,1-benzoxazin-4-one (**12**).* 2-Amino-3-bromo-5-fluorobenzoic acid (472 mg, 2.02 mmol) in Ac_2O (4 ml) was stirred at reflux (140 °C) for 2 h. The reaction mixture was allowed to cool to room temperature. The reaction mixture was concentrated to dryness and diluted with ethyl acetate (10 ml). The reaction mixture was concentrated to dryness to give the desired 8-bromo-6-fluoro-2-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one (**12**, 490 mg, 94%) as a pale brown solid, which was used without further purification: LCMS (t_R=3.42 min, purity=100%), ESI$^+$ m/z, no ion detected; ^{1}H NMR (DMSO-d_6), δ (ppm): 2.44 (s, 3H), 7.89 (dd, 1H, J=2.7 Hz, J_{H-F}=7.8 Hz), 8.25 (dd, 1H, J=2.7 Hz, J_{H-F}=8.2 Hz); ^{13}C NMR (DMSO-d_6), δ (ppm) 21.1, 112.9 (d, J_{C-F}=23.9 Hz), 119.1 (d, J_{C-F}=9.7 Hz), 121.6 (d, J_{C-F}=9.7 Hz), 127.7 (d, J_{C-F}=26.5 Hz), 141.0 (d, J_{C-F}=2.7 Hz), 159.4 (d, J_{C-F}=1.8 Hz), 159.6 (d, J_{C-F}=250.3 Hz), 168.6.

*4.1.3. 8-Bromo-6-fluoro-2-methylquinazolin-4(3H)-one (**13**).* A suspension of 8-bromo-6-fluoro-2-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one (**12**, 466 mg, 1.81 mmol) in concd aqueous NH_3 (28% v/v, 8 ml) was stirred at reflux (100 °C) for 1.5 h. The reaction mixture was concentrated. The resulting precipitate was collected by filtration, washed with water (20 ml) and dried to a constant weight to afford 8-bromo-6-fluoro-2-methylquinazolin-4(3*H*)-one (**14**, 342 mg, 73.7%) as a pale white solid, which was used without further purification: (t_R=2.40 min, purity=100%), ESI$^+$ m/z, no ion detected; ^{1}H NMR (DMSO-d_6), δ (ppm) 2.39 (s, 3H), 7.80 (dd, J=3.0 Hz, J_{H-F}=8.2 Hz, 1H), 8.13 (dd, J=2.7 Hz, J_{H-F}=8.2 Hz, 1H), 12.54 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 21.6, 110.7 (d, J_{C-F}=23.0 Hz), 122.9 (d, J_{C-F}=9.7 Hz), 123.0 (d, J_{C-F}=8.8 Hz), 126.5 (d, J_{C-F}=26.6 Hz), 143.9 (d, J_{C-F}=2.7 Hz), 155.3 (d, J_{C-F}=1.8 Hz), 159.0 (d, J_{C-F}=247.7 Hz), 161.1 (d, J_{C-F}=3.5 Hz); HRMS m/z (ESI$^+$) calculated for $C_9H_7N_2BrF$: 256.97203; found: 256.97205.

*4.1.4. 2-Amino-5-fluoro-3-iodobenzoic acid (**14**).* A solution of iodine monochloride (14.2 ml, 283.6 mmol) in water (170 ml) and concd HCl (40.0 ml) at 0 °C (iodine monochloride was added to the aqueous hydrochloric acid solution at 0 °C, then used immediately), was added to a stirred solution of 2-amino-5-fluorobenzoic acid (**7**, 40.0 g, 257.9 mmol) dissolved in water (300 ml) and in concd HCl (25.0 ml). The reaction mixture was shielded from light and stirred over a period of 2 days at room temperature. The resulting precipitate was collected by filtration, washed with water (30 ml) and dried to a constant weight to afford 2-amino-5-fluoro-3-iodobenzoic acid (**14**, 57.0 g, 79%) as a pale brown solid: LCMS (t_R=0.87 min, purity=100%), ESI$^-$ m/z, 280 (M−H)$^-$; ^{1}H NMR (DMSO-d_6) 7.56 (d, J=3.0 and 8.6 Hz, 1H), 7.82 (dd, J=3.0 and 7.6 Hz, 1H); ^{13}C NMR (DMSO-d_6), δ (ppm): 86.2 (d, J_{C-F}=8.0 Hz); 110.3 (d, J_{C-F}=7.1 Hz); 117.2 (d, J_{C-F}=22.1 Hz); 131.5 (d, J_{C-F}=24.8 Hz); 147.8; 152.3 (d, J_{C-F}=J=236.2 Hz); 168.5 (d, J_{C-F}=2.7 Hz); HRMS m/z (ESI$^+$) calculated for $C_7H_5O_2NFI$: 280.93435; found: 280.93212.

*4.1.5. 6-Fluoro-8-iodo-2-methyl-4H-3,1-benzoxazin-4-one (**15**).* 2-Amino-5-fluoro-3-iodobenzoic acid (**14**, 57.0 g, 202.8 mmol) in Ac_2O (181 ml, 1622.6) was stirred at reflux (140 °C) for 2 h. The reaction mixture was allowed to cool to room temperature. The reaction mixture was concentrated to dryness. The reaction mixture was diluted with ethyl acetate (500 ml) and the reaction mixture was concentrated to dryness to give the desired 6-fluoro-8-iodo-2-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one (**15**, 61.4 g, 99%) as a pale brown solid, which was used without further purification: LCMS (t_R=3.42 min, purity=100%), ESI$^+$ m/z, no ion detected; ^{1}H NMR (DMSO-d_6), δ (ppm): 2.44 (s, 3H); 7.88 (dd, J=3.0 Hz, J_{H-F}=8.0 Hz, 1H); 8.35 (dd, J=2.7 Hz, J_{H-F}=8.0 Hz, 1H).

*4.1.6. 8-Iodo-6-fluoro-2-methylquinazolin-4(3H)-one (**16**).* A suspension of 6-fluoro-8-iodo-2-methyl-4*H*-benzo-[*d*][1,3]oxazin-4-one (**15**, 61.4 g, 201.28 mmol) in concd aqeous NH_3 (28% v/v, 330 ml) was stirred at reflux (100 °C) for 2 h. The reaction mixture was filtered, the resulting precipitate was washed with water (400 ml) and dried to a constant weight to afford 6-fluoro-8-iodo-2-methylquinazolin-4(3*H*)-one (**16**, 56.5 g, 92%) as an off white solid: (t_R=2.10 min, purity=90%), ESI$^-$ m/z, 303 (M−H)$^-$. ^{1}H NMR (DMSO-d_6), δ (ppm) 2.39 (s, 3H); 7.80 (dd, J=3.0 Hz, J_{H-F}=8.2 Hz, 1H); 8.27 (dd, J=3.0 Hz, J_{H-F}=8.0 Hz, 1H); 12.49 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 21.6, 101.0 (d, J_{C-F}=8.0 Hz), 110.8 (d, J_{C-F}=22.1 Hz), 121.2 (d, J_{C-F}=8.8 Hz), 132.0 (d, J_{C-F}=25.7 Hz), 145.1 (d, J_{C-F}=1.8 Hz), 154.5 (d, J_{C-F}=1.8 Hz), 158.8 (d, J_{C-F}=248.6 Hz), 160.8 (d, J_{C-F}=3.5 Hz); HRMS m/z (ESI$^+$) calculated for $C_9H_7ON_2FI$: 304.95816; found: 304.95807.

*4.1.7. 8-Iodo-2-methyl-6-(morpholin-4-yl)quinazolin-4(3H)-one (**17**).* 6-Fluoro-8-iodo-2-methylquinazolin-4(3*H*)-one (**16**, 56.5 g, 185.8 mmol) and morpholine (553 ml, 6317.8 mmol) were heated at 129 °C over a period of 5 days. The reaction mixture was concentrated to dryness, diluted with water (500 ml). The resulting precipitate was collected by filtration, washed with water (5×50 ml) and dried to a constant weight to afford 8-iodo-2-methyl-6-morpholinoquinazolin-4(3*H*)-one (17, 58.8 g, 84%) as a pale white solid; LCMS (t_R=1.98 min, purity=100%), ESI$^+$ m/z, 372 (M+H)$^+$; ^{1}H NMR (DMSO-d_6), δ (ppm) 2.35 (s, 3H), 3.19 (t, J=4.8 Hz, 4H), 3.74 (t, J=4.8 Hz, 4H); 7.42 (d, J=2.9 Hz, 1H), 7.99 (d, J=2.9 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 21.4, 47.89, 65.8, 100.8, 108.6, 121.0, 132.3, 141.5, 149.5, 151.7, 161.3; HRMS m/z (ESI$^+$) calculated for $C_{13}H_{14}O_2N_3I$: 372.02035; found: 372.02029.

*4.1.8. 6-Fluoro-2-methyl-4-oxo-1,4-dihydroquinazoline-8-carbonitrile (**18**).* To a solution of 8-bromo-6-fluoro-2-methyl-

quinazolin-4(3*H*)-one (**13**, 100 mg, 0.39 mmol) in DMF (1 ml), was successively added *N*1,*N*1,*N*2,*N*2-tetramethylethane-1,2-diamine (0.012 ml, 0.08 mmol), dicyanozinc (0.015 ml, 0.23 mmol), tris(dibenzylideneacetone)dipalladium (17.81 mg, 0.02 mmol) and (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis-(diphenylphosphine) (2.251 mg, 3.89 μmol). The reaction tube was sealed, sparged with argon and heated to 160 °C over a period of 200 s in the microwave reactor. The resulting suspension was filtered and the filtrate was concentrated to dryness. The resulting liquid was diluted with water (we obtain a suspension) and triturated with diethyl ether to give a solid, which was collected by filtration and dried under vacuum to give 6-fluoro-2-methyl-4-oxo-3,4-dihydroquinazoline-8-carbo-nitrile (**18**, 60 mg, 76%) as a clear beige solid, which was used without further purification; LCMS (t_R=1.53 min, purity=98%), ESI$^-$ *m*/*z*, 202.0 (M−H)$^-$; ^{1}H NMR (DMSO-d_6), δ (ppm) 2.41 (s, 3H), 8.08 (dd, *J*=3.0 Hz, J_{H-F}=8.2 Hz, 1H), 8.37 (dd, *J*=3.0 Hz, J_{H-F}=8.2 Hz, 1H); 12.70 (br s, 1H); ^{13}C NMR (DMSO-d_6) 22.5, 102.0, 114.8, 115.2, 115.3, 138.9, 159.0, 162.9, 166.3; HRMS *m*/*z* (ESI$^+$) calculated for $C_{10}H_6ON_3F$: 204.05677; found: 204.05670.

*4.1.9. 2-Methyl-6-(morpholin-4-yl)-4-oxo-1,4-dihydro-quinazoline-8-carbonitrile (**19**).* 6-Fluoro-2-methyl-4-oxo-3,4-dihydroquinazoline-8-carbo-nitrile (**18**, 49 mg, 0.24 mmol) and morpholine (0.63 ml, 7.2 mmol) were sealed into a microwave tube. The reaction was degassed and heated at 160 °C for 16 h. The reaction mixture was cooled to room temperature and purified by preparative LCMS to afford 2-methyl-6-(morpholin-4-yl)-4-oxo-1,4-dihydro-quinazoline-8-carbonitrile (**19**, 42 mg, 65%): LCMS (t_R=1.43 min, purity=98%), ESI$^+$ *m*/*z*, 271.3 (M+H)$^+$; ^{1}H NMR (DMSO-d_6) δ 1.36 (s, 3H), 3.22−3.29 (m, 4H), 3.72−3.78 (m, 4H), 7.63 (d, 1H), 8.01 (d, 1H), 12.39 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 25.1, 47.6, 102.6, 114.7, 115.5, 120.6, 123.5, 141.1, 146.0, 158.7, 168.8; HRMS *m*/*z* (ESI$^+$) calculated for $C_{14}H_{15}O_2N_4$: 271.11895; found: 271.11888.

*4.1.10. 6-Fluoro-8-iodo-3-(4-methoxybenzyl)-2-methyl-quinazolin-4(3H)-one (**21**).* *p*-Methoxybenzyl chloride (0.535 ml, 3.95 mmol) was added to a suspension of 6-fluoro-8-iodo-2-methylquinazolin-4(3*H*)-one (**16**, 1 g, 3.29 mmol) and potassium carbonate (0.909 g, 6.58 mmol) in acetone (20 ml) and the resulting suspension was stirred at 60 °C for 24 h. The mixture was evaporated and absorbed on silica gel. The crude product was purified by flash chromatography on silica gel eluting with 5−15% ethyl acetate in petroleum ether. The solvent was evaporated to dryness to afford 6-fluoro-8-iodo-3-(4-methoxybenzyl)-2-methyl-quinazolin-4(3*H*)-one (**19**, 1.130 g, 81%) as a clear white solid; LCMS (t_R=3.87 min, purity=100%), ESI$^+$ *m*/*z*, 425.2 (M+H)$^+$; ^{1}H NMR (DMSO-d_6) δ (ppm) 2.54 (s, 1H), 3.73 (s,1H), 5.30 (s, 1H), 6.91 (d, *J*=8.65 Hz, 2H), 7.18 (d, *J*=8.59 Hz, 2H), 7.89 (dd, J_{ortho}=2.84 Hz, J_{H-F}=8.31 Hz, 1H), 8.32 (dd, J_{ortho}=2.85 Hz, J_{H-F}=8.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 23.59, 46.68, 55.45, 101.69, 111.95 (J_{C-F}=23 Hz), 114.54, 120.82, 128.22, 128.34, 144.26 (J_{C-F}=24.77 Hz), 155.78, 158.58 (J_{C-F}=248.56 Hz), 158.93, 160.51, 161.25; HRMS *m*/*z* (ESI$^+$) calculated for $C_{17}H_{14}O_2N_2FI$: 425.00785; found: 425.00745.

*4.1.11. 8-Iodo-3-(4-methoxybenzyl)-2-methyl-6-morpholino-quinazolin-4(3H)-one (**22a**) and 6-fluoro-3-(4-methoxybenzyl)-2-methyl-8-(morpholin-4-yl)quinazolin-4(3H)-one (**22b**).* A solution of 6-fluoro-8-iodo-3-(4-methoxybenzyl)-2-methylquinazolin-4(3*H*)-one (**21**, 52.6 mg, 0.12 mmol) in morpholine (400 μl, 4.57 mmol) was stirred under argon at 140 °C over weekend. After 3 days, the reaction mixture was cooled to room temperature and purified preparative LCMS to afford 8-iodo-3-(4-methoxybenzyl)-2-methyl-6-morpholinoquinazolin-4-(3*H*)-one (**22a**, 42 mg, 68%) as a yellow solid: LCMS (t_R=1.98 min, purity=100%), ESI$^+$ *m*/*z*, 492.3 (M+H)$^+$; ^{1}H NMR (DMSO-d_6) δ (ppm) 2.49 (s, 1H), 3.26 (m, 4H), 3.73 (s, 1H), 3.79 (m, 4H), 5.28 (s, 2H), 6.91 (d, *J*=8.7 Hz, 2H), 7.14 (d, *J*=8.6 Hz, 2H), 7.48 (d, *J*=2.7 Hz, 1H), 8.06 (d, *J*=2.7 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 23.36, 46.45, 48.29, 55.44, 66.29, 101.43, 109.50, 114.53, 120.71, 128.22, 128.63, 132.93, 140.12, 150.35, 152.90, 158.85, 161.50; HRMS *m*/*z* (ESI$^+$) calculated for $C_{21}H_{22}O_3N_3I$: 492.07004; found: 492.07023; and 6-fluoro-3-(4-methoxybenzyl)-2-methyl-8-morpholino-quinazolin-4(3*H*)-one (**22b**, 6.0 mg, 12%) LCMS (t_R=1.78 min, purity=100%), ESI$^+$ *m*/*z*, 384.4 (M+H)$^+$; ^{1}H NMR (DMSO-d_6) δ (ppm) 8.32 (dd, J_1=2.85 Hz, J_2=8.0 Hz, 1H), 7.89 (m, 1H), 7.18 (d, *J*=8.59 Hz, 2H), 6.91 (d, *J*=8.65 Hz, 2H), 5.30 (s, 1H), 3.73 (s, 1H), 2.54 (s, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 24.15, 46.85, 51.95, 55.95, 66.93, 103.16 (*J*=23.6 Hz), 110.33 (*J*=26.5 Hz), 115.05, 122.83 (*J*=10.2 Hz), 122.87, 128.79, 129.01, 150.79 (*J*=9.4), 152.51, 159.39, 162.15−160.09 (J_{C-F}=243.26 Hz), 162.19; HRMS *m*/*z* (ESI$^+$) calculated for $C_{21}H_{22}O_3N_3F$: 384.16397; found: 384.16384.

*4.1.12. 6-(4-Hydroxypiperidin-1-yl)-8-iodo-3-(4-methoxy-benzyl)-2-methylquinazolin-4(3H)-one (**23**).* A solution of 6-fluoro-8-iodo-3-(4-methoxybenzyl)-2-methylquinazolin-4(3*H*)-one (**21**, 52 mg, 0.12 mmol) in piperidin-4-ol (62.0 mg, 0.61 mmol) was stirred at 140 °C over weekend. The reaction mixture was purified by preparative LCMS to afford 6-(4-hydroxypiperidin-1-yl)-8-iodo-3-(4-methoxybenzyl)-2-methylquinazolin-4(3*H*)-one (23, 46 mg, 78%) as a yellow solid: LCMS (t_R=2.70 min, purity=100%), ESI$^+$ *m*/*z*, 506.3 (M+H)$^+$; ^{1}H NMR (DMSO-d_6) δ (ppm) 1.47 (m, 2H), 1.83 (m, 2H), 2.98 (td, *J*=9.9 Hz, 2H), 3.55 (m, 3H), 3.74 (s, 3H), 4.72 (d, *J*=4.2 Hz, 1H), 5.27 (s, 2H), 6.90 (d, *J*=8.7 Hz, 2H), 7.13 (d, *J*=8.6 Hz, 2H), 7.45 (d, *J*=2.7 Hz, 1H), 8.01 (d, *J*=2.7 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 22.86, 33.38, 45.86, 45.96, 54.97, 65.55, 100.95, 109.16, 114.05, 120.34, 127.75, 128.22, 132.87, 138.93, 149.65, 151.97, 158.37, 161.02; HRMS *m*/*z* (ESI$^+$) calculated for $C_{22}H_{25}O_3N_3I$: 506.09351; found: 506.09314.

*4.1.13. 6-(4-Acetylpiperazin-1-yl)-8-iodo-3-(4-methoxy-benzyl)-2-methylquinazolin-4(3H)-one (**24**).* A solution of 6-fluoro-8-iodo-3-(4-methoxybenzyl)-2-methylquinazolin-4(3*H*)-one (17, 50 mg, 0.12 mmol) in 1-(piperazin-1-yl)ethanone (76 mg, 0.59 mmol) was stirred at 140 °C for 3 days. The reaction mixture was purified by preparative LCMS to afford 6-(4-acetylpiperazin-1-yl)-8-iodo-3-(4-methoxybenzyl)-2-methylquinazolin-4(3*H*)-one (**24**, 33.0 mg, 53%) as a yellow foam; LCMS (t_R=2.67 min, purity=100%), ESI$^+$ *m*/*z*, 533.3 (M+H)$^+$; ^{1}H NMR (DMSO-d_6) δ (ppm) 2.06 (d, *J*=11.6 Hz, 3H), 2.49 (s, 3H), 3.23 (m, 2H), 3.30 (m, 2H), 3.59 (m, 4H), 3.72 (s, 3H), 5.28 (s, 2H), 6.90 (d, *J*=8.7 Hz, 2H), 7.14 (d, *J*=8.6 Hz, 2H), 7.48 (d, *J*=2.7 Hz, 1H), 8.07 (d, *J*=2.7 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 21.11, 22.90, 40.41, 45.10, 45.98, 47.64, 47.86, 54.98, 98.99, 100.98, 109.49, 114.06, 120.25, 127.76, 128.15, 133.86, 139.49, 149.41, 152.40, 158.38, 160.94; HRMS *m*/*z* (ESI$^+$) calculated for $C_{22}H_{25}O_3N_3I$: 533.09659; found: 533.09641.

*4.1.14. 1-[8-Iodo-3-(4-methoxybenzyl)-2-methyl-4-oxo-3,4-dihydroquinazolin-6-yl]-L-prolinamide (**25**).* A solution of 6-fluoro-8-iodo-3-(4-methoxybenzyl)-2-methylquinazolin-4(3*H*)-one (**21**, 50 mg, 0.12 mmol) and (*S*)-pyrrolidine-2-carboxamide (67.3 mg, 0.59 mmol) in NMP (0.1 ml) was stirred at 140 °C for 2 days. Further (*S*)-pyrrolidine-2-carboxamide (67.3 mg, 0.59 mmol) was added to the mixture and the reaction mixture was heated at 180 °C overnight. The reaction mixture was purified by preparative LCMS to afford (*S*)-1-(8-iodo-3-(4-methoxybenzyl)-2-methyl-4-oxo-3,4-dihydro-quinazolin-6-yl)pyrrolidine-2-carboxamide (**25**, 13.0 mg, 21%) as a yellow solid: LCMS (t_R=2.52 min, purity=98%), ESI$^+$ *m*/*z*, 519.23 (M+H)$^+$; ^{1}H NMR (DMSO-d_6) δ (ppm) 1.99 (m, 3H), 2.24 (m, 1H), 2.46 (s, 2H), 3.59 (m, 1H), 3.72 (s, 3H), 4.05 (d, *J*=8.0 Hz, 1H), 5.28 (d, *J*=16.6 Hz, 2H), 6.90 (d, *J*=8.6 Hz, 2H), 7.08 (d, *J*=2.6 Hz, 1H), 7.12 (d, *J*=8.4 Hz, 2H), 7.51 (d, *J*=2.5 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 23.26, 23.92, 31.56, 46.36, 48.85, 55.44, 62.73−61.84, 101.20, 106.43, 114.53, 120.95, 128.19, 128.69, 129.52, 137.75, 146.28,

150.99, 158.81, 161.19, 174.95; HRMS m/z (ESI^+) calculated for $C_{22}H_{25}O_3N_3I$: 519.08876; found: 519.08887.

*4.1.15. 8-Iodo-3-(4-methoxybenzyl)-2-methyl-6-{[2-(morpholin-4-yl)ethyl]amino}quinazolin-4(3H)-one (**26**).* A solution of 6-fluoro-8-iodo-3-(4-methoxybenzyl)-2-methylquinazolin-4(3*H*)-one (**21**, 50 mg, 0.12 mmol) in 2-morpholinoethanamine (400 μl, 3.05 mmol) was stirred under argon at 160 °C over weekend. The reaction mixture was purified by preparative LCMS to afford 8-iodo-3-(4-methoxybenzyl)-2-methyl-6-(2-morpholinoethylamino)-quinazolin-4(3*H*)-one (**26**, 26.0 mg, 41%) as a clear yellow solid: LCMS (t_R=2.80 min, purity=99%), ESI^+ m/z, 535.36 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ (ppm) 2.44 (m, 7H), 2.52 (m, 2H), 3.20 (dd, J=6.2, 12.0 Hz, 2H), 3.59 (m, 4H), 3.72 (s, 4H), 5.27 (s, 2H), 6.17 (t, J=5.2 Hz, 1H), 6.88 (d, J=8.7 Hz, 2H), 7.13 (2d, J=2.8, 8.69 Hz, 3H), 7.76 (d, J=2.5 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 23.18, 40.37, 46.33, 53.75, 55.44, 57.18, 66.54, 100.99, 104.65, 114.51, 121.37, 128.18, 128.83, 131.25, 137.89, 148.65, 150.75, 158.82, 161.42; HRMS m/z (ESI^+) calculated for $C_{23}H_{28}O_3N_4I$: 535.12006; found: 535.11969.

*4.1.16. 6-[(2,4-Dimethoxybenzyl)amino]-8-iodo-3-(4-meth-oxybenzyl)-2-methylquinazolin-4(3H)-one (**27**).* A solution of 6-fluoro-8-iodo-3-(4-methoxybenzyl)-2-methylquinazolin-4(3*H*)-one (**21**, 52.9 mg, 0.12 mmol) and (2,4-dimethoxyphenyl)methanamine (0.094 ml, 0.62 mmol) in NMP (0.1 ml) was stirred at 140 °C for 3 days. The reaction mixture was purified by preparative LCMS to afford 6-(2,4-dimethoxybenzylamino)-8-iodo-3-(4-methoxybenzyl)-2-methylquinazolin-4(3*H*)-one (**27**, 32 mg, 44%) as a clear yellow solid: LCMS (t_R=3.38 min, purity=100%), ESI^+ m/z, 572.32 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ (ppm) 2.43 (s, 3H), 3.72 (s, 6H), 3.84 (s, 3H), 4.19 (d, J=5.6 Hz, 2H), 5.23 (s, 2H), 6.48 (m, 1H), 6.58 (d, J=2.2 Hz, 1H), 6.67 (t, J=5.9 Hz, 1H), 6.89 (d, J=8.5 Hz, 2H), 7.09 (m, 3H), 7.74 (d, J=2.4 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 23.04, 55.43, 55.52, 55.86, 98.70, 100.88, 104.84, 114.50, 118.69, 121.26, 128.15, 128.36, 128.77, 129.07, 137.90, 148.53, 150.74, 158.33, 158.79, 160.13, 161.40; HRMS m/z (ESI^+) calculated for $C_{26}H_{27}O_4N_3I$ 572.10408; found: 572.10449.

*4.1.17. 6-[(2-Hydroxyethyl)amino]-8-iodo-3-(4-methoxy-benzyl)-2-methylquinazolin-4-(3H)-one (**28**).* A solution of 6-fluoro-8-iodo-3-(4-methoxybenzyl)-2-methylquinazolin-4(3*H*)-one (**21**, 52.9 mg, 0.12 mmol) and 2-aminoethanol (0.038 ml, 0.62 mmol) in NMP (0.1 ml) at 140 °C for 31 h. The reaction mixture was purified by preparative LCMS to afford 6-(2-hydroxyethylamino)-8-iodo-3-(4-methoxy-benzyl)-2-methylquinazolin-4(3*H*)-one (**28**, 24.0 mg, 41%) as a clear yellow solid: LCMS (t_R=2.48 min, purity=100%), ESI^+ m/z, 466.29 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ (ppm) 2.44 (s, 3H), 3.16 (q, J=5.8 Hz, 2H), 3.57 (q, J=5.3 Hz, 2H), 3.72 (s, 3H), 4.78 (t, J=5.1 Hz, 1H), 5.26 (s, 2H), 6.29 (t, J=5.6 Hz, 1H), 6.90 (d, J=8.7 Hz, 2H), 7.13 (m, 3H), 7.74 (d, J=2.6 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 23.17, 45.76, 46.32, 55.44, 59.64, 100.98, 104.43, 114.51, 121.38, 128.19, 128.84, 131.25, 137.76, 148.81, 150.67, 158.81, 161.48; HRMS m/z (ESI^+) calculated for $C_{19}H_{21}O_3N_3I$: 466.06221; found: 466.06210.

*4.1.18. 6-[(1-Hydroxy-2-methylpropan-2-yl)amino]-8-iodo-3-(4-methoxybenzyl)-2-methylquinazolin-4(3H)-one (**29**).* A solution of 6-fluoro-8-iodo-3-(4-methoxybenzyl)-2-methylquinazolin-4(3*H*)-one (**21**, 50 mg, 0.12 mmol) and 2-amino-2-methylpropan-1-ol (0.056 ml, 0.59 mmol) in NMP (0.1 ml) was stirred at 140 °C for 3 days. Further 2-amino-2-methylpropan-1-ol (0.056 ml, 0.59 mmol) was added and the reaction mixture was heated at 200 °C for 2 days. The reaction mixture was purified by preparative LCMS to afford 6-(1-hydroxy-2-methylpropan-2-ylamino)-8-iodo-3-(4-methoxybenzyl)-2-methylquinazolin-4(3*H*)-one (**29**, 10 mg, 17%) as a clear yellow solid. LCMS (t_R=2.79 min, purity=100%), ESI^+ m/z, 494.33 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ (ppm) 1.27 (s, 6H), 2.44 (s, 3H), 3.43 (d, J=5.1 Hz, 2H), 3.72 (s, 3H), 4.88 (m, 1H), 5.26 (s, 2H), 5.75 (s, 1H), 6.90 (d, J=8.6 Hz, 2H), 7.13 (d, J=8.6 Hz, 2H), 7.32 (d, J=2.5 Hz, 1H), 7.82 (d, J=2.5 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 23.27, 24.35, 46.34, 54.86, 55.51, 67.88, 100.49, 107.04, 114.59, 121.00, 128.26, 128.92, 134.03, 137.86, 147.39, 151.00, 158.83, 161.47; HRMS m/z (ESI^+) calculated for $C_{21}H_{24}O_3N_3I$: 494.09351; found: 493.09363.

*4.1.19. 6-(1H-Imidazol-1-yl)-8-iodo-3-(4-methoxybenzyl)-2-methylquinazolin-4(3H)-one (**32**).* A solution of 6-fluoro-8-iodo-3-(4-methoxybenzyl)-2-methylquinazolin-4(3*H*)-one (**21**, 52.4 mg, 0.12 mmol) and 1*H*-imidazole (57 mg, 0.84 mmol) in NMP (0.1 ml) was stirred at 160 °C for 72 h. The reaction mixture was purified by preparative LCMS to afford 6-(1*H*-imidazol-1-yl)-8-iodo-3-(4-methoxybenzyl)-2-methylquinazolin-4(3*H*)-one (**32**, 24 mg, 39%) as a clear beige solid: LCMS (t_R=2.65 min, purity=100%), ESI^+ m/z, 473.24 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ (ppm) 2.56 (s, 3H), 3.73 (s, 3H), 5.32 (s, 2H), 6.91 (d, J=8.7 Hz, 2H), 7.14 (s, 1H), 7.19 (d, J=8.6 Hz, 2H), 7.96 (s, 1H), 8.31 (d, J=2.5 Hz, 1H), 8.46 (s, 1H), 8.68 (d, J=2.5 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 23.24, 46.26, 54.99, 101.61, 114.08, 117.02, 118.12, 120.39, 127.84, 130.14, 135.23, 135.82, 145.17, 156.02, 158.47, 160.78; HRMS m/z (ESI^+) calculated for $C_{20}H_{18}O_2N_4I$: 473.04690; found: 473.04745.

*4.1.20. 8-Iodo-6-methoxy-3-(4-methoxybenzyl)-2-methyl-quinazolin-4(3H)-one (**37**).* Potassium *tert*-butoxide (88 mg, 0.87 mmol) was added in one portion to a stirred solution of methanol (0.035 ml, 0.86 mmol) dissolved in anhydrous THF (1 ml) under argon at room temperature for 30 min and the mixture was added to the solution of 6-fluoro-8-iodo-3-(4-methoxybenzyl)-2-methylquinazolin-4(3*H*)-one (**21**, 110.5 mg, 0.26 mmol) in THF (0.25 ml) under argon. The mixture was heated at 120 °C overnight. The reaction mixture was purified by preparative LCMS to afford 8-iodo-6-methoxy-3-(4-methoxybenzyl)-2-methylquinazolin-4(3*H*)-one (58 mg, 51%) as a clear yellow solid; LCMS (t_R=3.79 min, purity=100%), ESI^+ m/z, 437.3 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ (ppm) 2.50 (s, 3H), 3.72 (s, 3H), 3.88 (s, 3H), 5.29 (s, 2H), 6.90 (d, J=8.7 Hz, 2H), 7.15 (d, J=8.7 Hz, 2H), 7.57 (d, J=2.8 Hz, 1H), 7.96 (d, J=2.8 Hz, 1H); ^{13}C NMR δ (ppm) 23.44, 46.54, 55.47, 56.61, 97.46, 108.41, 113.32, 123.54, 125.39, 129.95, 131.16, 144.04, 157.42, 158.88, 159.69, 160.21; HRMS m/z (ESI^+) calculated for $C_{18}H_{17}O_3N_2I$: 437.02784; found: 437.02321.

*4.1.21. 8-Iodo-3-(4-methoxybenzyl)-6-(2-methoxyethoxy)-2-methylquinazolin-4(3H)-one (**38**).* A solution of 6-fluoro-8-iodo-3-(4-methoxybenzyl)-2-methylquinazolin-4(3*H*)-one (50 mg, 0.12 mmol) and sodium 2-methoxyethanolate (116 mg, 0.24 mmol) in NMP (0.1 ml) was stirred at 120 °C for 1 h. The reaction mixture was purified by preparative LCMS to afford 8-iodo-3-(4-methoxybenzyl)-6-(2-methoxyethoxy)-2-methylquinazolin-4(3*H*)-one (40 mg, 70%) as a clear brown solid: LCMS (t_R=3.02 min, purity=100%), ESI^+ m/z, 481.27 $(M+H)^+$; ^1H NMR (DMSO-d_6) δ (ppm) 2.51 (s, 3H), 3.31 (s, 3H), 3.69 (m, 2H), 3.72 (s, 3H), 4.23 (m, 2H), 5.29 (s, 2H), 6.90 (d, J=8.7 Hz, 2H), 7.15 (d, J=8.6 Hz, 2H), 7.58 (d, J=2.8 Hz, 1H), 7.97 (d, J=2.8 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 23.44, 46.56, 55.45, 58.54, 68.20, 70.52, 99.38, 101.42, 108.56, 114.53, 120.67, 128.28, 128.49, 133.76, 141.71, 153.92, 157.20, 158.88, 161.33; HRMS m/z (ESI^+) calculated for $C_{20}H_{21}O_4N_2I$: 480.05405; found: 480.05127.

*4.1.22. tert-Butyl 4-(8-iodo-3-(4-methoxybenzyl)-2-methyl-4-oxo-3,4-dihydroquinazolin-6-yloxy)piperidine-1-carboxylate (**39**).* Potassium *tert*-butoxide (79 mg, 0.71 mmol) was added portionwise to a stirred solution of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (149 mg, 0.74 mmol) dissolved in anhydrous DME (1 ml) under argon at room temperature for 30 min and the mixture (0.3 ml)

was added to the solution of 6-fluoro-8-iodo-3-(4-methoxybenzyl)-2-methylquinazolin-4(3*H*)-one (**21**, 50 mg, 0.12 mmol) and the reaction mixture was stirred at 120 °C 3 h. The reaction mixture was purified by preparative LCMS to afford *tert*-butyl 4-(8-iodo-3-(4-methoxybenzyl)-2-methyl-4-oxo-3,4-dihydro-quinazolin-6-yloxy)piperidine-1-carboxylate (**39**, 32 mg, 45%) as a clear yellow solid: LCMS (t_R=3.98 min, purity=100%), ESI$^+$ *m*/*z*, 606.42 (M+H)$^+$; ^{1}H NMR (DMSO-d_6) δ (ppm) 1.41 (s, 9H), 1.56 (m, 2H), 1.91 (m, 2H), 2.50 (s, 3H), 3.23 (s, 2H), 3.65 (m, 2H), 3.72 (s, 3H), 4.76 (m, 1H), 5.28 (s, 2H), 6.90 (d, *J*=8.6 Hz, 2H), 7.15 (d, *J*=8.6 Hz, 2H), 7.62 (d, *J*=2.7 Hz, 1H), 7.99 (d, *J*=2.7 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 23.44, 28.43, 46.56, 55.45, 73.24, 79.14, 101.47, 110.36, 114.53, 120.84, 128.29, 128.47, 134.74, 141.76, 153.99, 154.29, 155.63, 158.88, 161.30; HRMS *m*/*z* (ESI$^+$) calculated for $C_{27}H_{33}O_5N_3I$: 606.14594; found: 606.14600.

*4.1.23. 8-Iodo-3-(4-methoxybenzyl)-2-methyl-6-phenoxy-quinazolin-4(3H)-one (**40**).* A solution of 6-fluoro-8-iodo-3-(4-methoxybenzyl)-2-methylquinazolin-4(3*H*)-one (51 mg, 0.12 mmol) and sodium phenolate (27.9 mg, 0.24 mmol) in NMP (0.2 ml) at 120 °C for 5 h. The reaction mixture was purified by preparative LCMS to afford 8-iodo-3-(4-methoxybenzyl)-2-methyl-6-phenoxy-quinazolin-4(3*H*)-one (**40**, 32 mg, 51%) as a clear brown solid: LCMS (t_R=3.73 min, purity=100%), ESI$^+$ *m*/*z*, 499.30 (M+H)$^+$; ^{1}H NMR (DMSO-d_6) δ (ppm) 2.53 (s, 3H), 3.72 (s, 3H), 5.27 (s, 2H), 6.90 (d, *J*=8.7 Hz, 2H), 7.16 (2d, J_1=8.68 Hz, J_2=7.97 Hz, 4H), 7.27 (t, *J*=7.4 Hz, 1H), 7.49 (m, 3H), 8.09 (d, *J*=2.7 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ (ppm) 23.71, 46.79, 55.61, 101.97, 113.20, 114.70, 120.35, 120.99, 125.35, 128.48, 130.98, 135.57, 143.34, 155.21, 161.34, 159.07, 156.15, 155.98; HRMS *m*/*z* (ESI$^+$) calculated for $C_{23}H_{20}O_3N_2I$: 499.05131; found: 499.05164.

Acknowledgements

The authors would like to thank senior analysts Christian Delvare, Paul Davey, Becky Burton, Julie Demeritt and Madeleine Vickers for their support.

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