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PAPER

N^3-Alkylation during formation of quinazolin-4-ones from condensation of anthranilamides and orthoamides†

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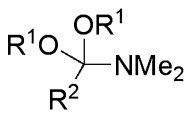
Dimethylformamide dimethylacetal (DMFDMA) is widely used as a source of electrophilic one-carbon units at the formate oxidation level; however, electrophilic methylation with this reagent is previously unreported. Reaction of anthranilamide with DMFDMA at 150 °C for short periods gives mainly quinazolin-4-one. However, prolonged reaction with dimethylformamide di(primary-alkyl)acetals leads to subsequent alkylation at N^3. 3-Substituted anthranilamides give 8-substituted 3-alkylquinazolin-4-ones. Condensation of anthranilamides with dimethylacetamide dimethylacetal provides 2,3-dimethylquinazolin-4-ones. In these reactions, the source of the N^3-alkyl group is the *O*-alkyl group of the orthoamides. By contrast, reaction with the more sterically crowded dimethylformamide di(isopropyl)acetal diverts the alkylation to the oxygen, giving 4-isopropoxyquinazolines, along with N^3-methylquinazolin-4-ones where the methyl is derived from *N*-Me of the orthoamides. Reaction of anthranilamide with the highly sterically demanding dimethylformamide di(*t*-butyl)acetal gives largely quinazolin-4-one, whereas dimethylformamide di(neopentyl)acetal forms a mixture of quinazolin-4-one and N^3-methylquinazolin-4-one. The observations are rationalised in terms of formation of intermediate cationic electrophiles (alkoxymethylidene-*N*,*N*-dimethylammonium) by thermal elimination of the corresponding alkoxide from the orthoamides. These are the first observations of orthoamides as direct alkylating agents.

Introduction

Dimethylformamide dimethylacetal (DMFDMA, dimethoxymethyldimethylamine, **1a**, Fig. 1) is a convenient electrophile to introduce one-carbon units at the formate oxidation level.[1] Condensation with primary amines and amides leads to *N*,*N*-dimethylformamidines and *N′*-acyl-*N*,*N*-dimethylformamides, respectively;[2] the latter can be cyclised to 1,2,4-triazoles with hydrazines and to 1,3,5-triazines with guanidines.[3] Methyl anthranilate condenses with **1a** to give methyl 2-(dimethylformamidino)benzoate, which, on treatment with primary amines, furnishes 3-alkylquinazolin-4-ones.[4] It also condenses with "active" methylene groups to form *N*,*N*-dimethylenamines. These enamines are excellent aldehyde equivalents in further synthesis, particularly of a wide range of heterocycles. For example, acetophenones condense with **1a** to give 3-dimethylaminopropenoylbenzenes; these conjugate electrophiles react with guanidines to form 4-arylpyrimidine-2-amines[1] and with arylhydrazines to form 1,4-diarylpyrazoles.[5] Condensation of **1a** with methyl groups on electron-deficient aromatic rings is also efficient and produces 2-arylenamines; again these are useful synthetic equivalents of arylacetaldehydes. The Ar-Me is particularly activated in methyl 2-methyl-3-nitrobenzoate and condensation with **1a** gives an enamine. Passage of this intermediate through a moist silica gel column hydrolyses the enamine and cyclises to 5-nitroisocoumarin, a key intermediate in the synthesis of 5-aminoisoquinolin-1-one,[6] an important inhibitor of poly(ADP-ribose)polymerases-1 and -2.[7] This process cannot



1a: R^1 = Me, R^2 = H
1b: R^1 = Et, R^2 = H
1c: R^1 = Bn, R^2 = H
1d: R^1 = R^2 = Me
1e: R^1 = Pr^i, R^2 = H
1f: R^1 = Bu^t, R^2 = H
1g: R^1 = CH_2Bu^t, R^2 = H

Fig. 1 Structures of orthoamides used in this study.

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be extended, as condensation of the starting ester with **1d** generates an alternative enamine, leading to 3-dimethylamino-1-methoxy-5-nitronaphthalene.[8] By contrast, reactions of **1** where the electrophilic centre is one of the methyl groups are virtually unknown; the formation of methyl esters from carboxylic acids is actually an incorporation of a nucleophilic MeO unit.

Synthetic approaches to quinazolin-4-ones lacking C^2- and N^3-substituents have mostly involved the introduction of the 2-C as a one-carbon electrophile to anthranilamides, although **1a** appears not to have been used for this purpose. The principal method is to heat the anthranilic acid to high temperatures (>180 °C) with formamide.[9,10] These quinazolin-4-ones can then be readily alkylated at 3-N with alkyl halides and potassium hydroxide in methanol[11] or under phase-transfer conditions.[10] Less-used routes to N^3-alkylquinazolin-4-ones include replacement of the whole [N^3-Ar] unit of 3-(2-cyanophenyl)quinazolin-4-ones with primary alkylamines (by initial nucleophilic attack on the carbonyl),[12] copper(I)-catalysed reaction of *N*-alkyl-2-iodobenzamides with formamidine,[13] photochemical rearrangements of 2-alkylcinnolinium-4-olates[14] and condensation of anthranilic acid with primary amines and orthoesters under Lewis acid catalysis[15,16] and with alkylisocyanides.[17] The way is therefore open to examine whether **1a** and its homologues can be used as a source of electrophilic one-carbon units to convert anthranilamides to 3-unsubstituted quinazolin-4-ones under milder conditions than required for the corresponding reaction with formamide; this study also included the effect of a diversity of substituents at the 3-position of the anthranilamide to test sensitivity to steric bulk *ortho* to the amine and to electron-withdrawing or electron-donating substituents which influence the nucleophilicity of this amine.

Results and discussion

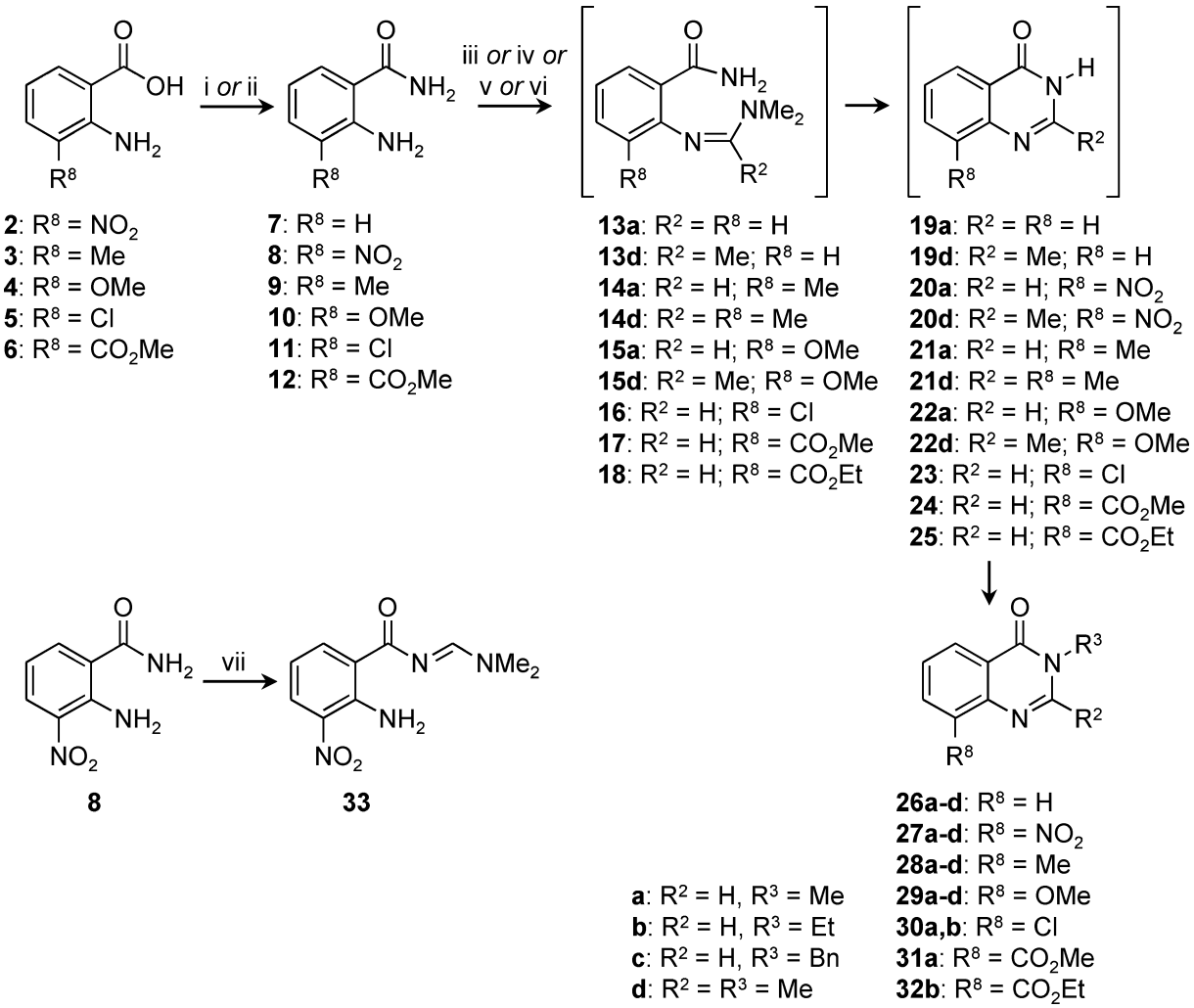
In an initial experiment (Scheme 1), heating anthranilamide **7** with three molar equivalents of **1a** in DMF at reflux for a short period (90 min) gave the expected quinazolin-4-one **19a** in 75% yield; in this process, the orthoamide **1a** is acting purely as a source of the 2-CH unit at the formate oxidation level. However, during purification, the material had to be separated from a less-polar contaminating product. Repeating the treatment of **7** with **1a** but for a longer time (16 h) led to complete consumption of the desired **19a** and conversion to the less-polar material, which was isolated in 95% yield. This was isolated and characterised by ^{1}H NMR spectroscopy as an *N*-methylquinazolin-4-one or as 4-methoxyquinazoline, with the observation of a signal integrating for three protons at δ 3.48. The structure was confirmed as 3-methylquinazolin-4-one **26a** by comparison with literature mp data[11] and by HMBC correlations between the methyl ^{1}H NMR signal at δ 3.48 and the 2-C signal at δ 148.41 and between the methyl protons and the 4-C signal at δ 160.64. The ^{13}C NMR spectrum had been previously assigned by reference to the ^{1}H spectrum using HSQC and HMBC data. The alternative structures 1-methylquinazolin-4-one and 1-methoxyquinazoline were inconsistent with these HMBC data. Thus **26a** appeared to arise from methylation of **19a** at N^3.

The question then arises as to the source and nature of the electrophilic methylating agent; does the methyl group come from O–Me or from N–Me of **1a**? This was addressed by repeating the condensation with the corresponding O–Et reagent, dimethylformamide diethylacetal (DMFDEA, **1b**). Reaction of **7** with **1b** in boiling DMF for 16 h led to the formation of the N^3-ethylquinazolin-4-one **26b** but in the lower yield of 52%. Thus it is clear that, with simple alkyl groups, the alkyl group introduced at N^3 arises from the *O*-alkyl groups in the reagent orthoamide and not from the *N*-alkyl groups.

Since our medicinal chemical interest is in quinazolinones related to **19–25**, *i.e.* with an 8-substituent, the effect of substitution at position-3 of the anthranilamide on the cyclocondensation to the quinazolin-4-ones and on the new N^3-alkylation of the putative intermediate 8-substituted quinazolin-4-ones was investigated. The substituents at the 3-position of the anthranilamides were chosen to be diverse in electronic effect, to explore the scope fully, ranging from the strongly electron-withdrawing nitro group in **8** to the electron-donating methoxy group in **10**, through a small alkyl in **9**, a halogen in **11** and an ester in **12**. The anthranilamides **8–12** were not commercially available but were synthesised from their corresponding benzoic acids **2–6**, as shown in Scheme 1. 3-Nitroanthranilic acid **2** was treated with thionyl chloride, followed by ammonia to give **8**, presumably *via* a benzoxathiazine-2,4-dione intermediate. This method failed for reactions of **3–6** but treatment with these anthranilic acids with 1,1′-carbonyldiimidazole at elevated temperature, followed by reaction of the intermediate (an *N*-acylimidazole or an isatoic anhydride) with ammonia furnished the anthranilamides **9–12** for the study. As for the parent anthranilamide **7**, treatment of **8–12** with excess **1a** in refluxing DMF for 16 h furnished the corresponding N^3-methylquinazolin-4-ones **27a**, **28a**, **29a**, **30a**, **31a** in very high yields. Similar reactions of **8–11** with **1b** gave the N^3-ethylquinazolin-4-ones **27b**, **28b**, **29b**, **30b** but generally in lower yields. The reaction of the methyl ester **12** with **1b** gave the ethyl ester **32b**, through transesterification with ethanol generated as a leaving group from the orthoamide during the condensation. The location of the new alkyl group at N^3 was confirmed in each case by HMBC correlation spectra.

Extending the scope of the new reaction to larger primary alkyl groups, heating **7–10** with the dibenzyl orthoamide **1c** gave the *N*-benzylquinazolin-4-ones **26c**, **27c**, **28c**, **29c**, generally in good yields, except for the nitro analogue **27c**. The condensation/alkylation can also be extended to introduce a alkyl substituent at the 2-position, which would require an acetamide acetal, rather than the formamide acetals used hitherto. Reaction of the anthranilamides **7–10** with dimethylacetamide dimethylacetal **1d** in boiling DMF gave moderate yields of the 2,3-dimethylquinazolin-4-ones **26d**, **27d**, **28d**, **29d**.

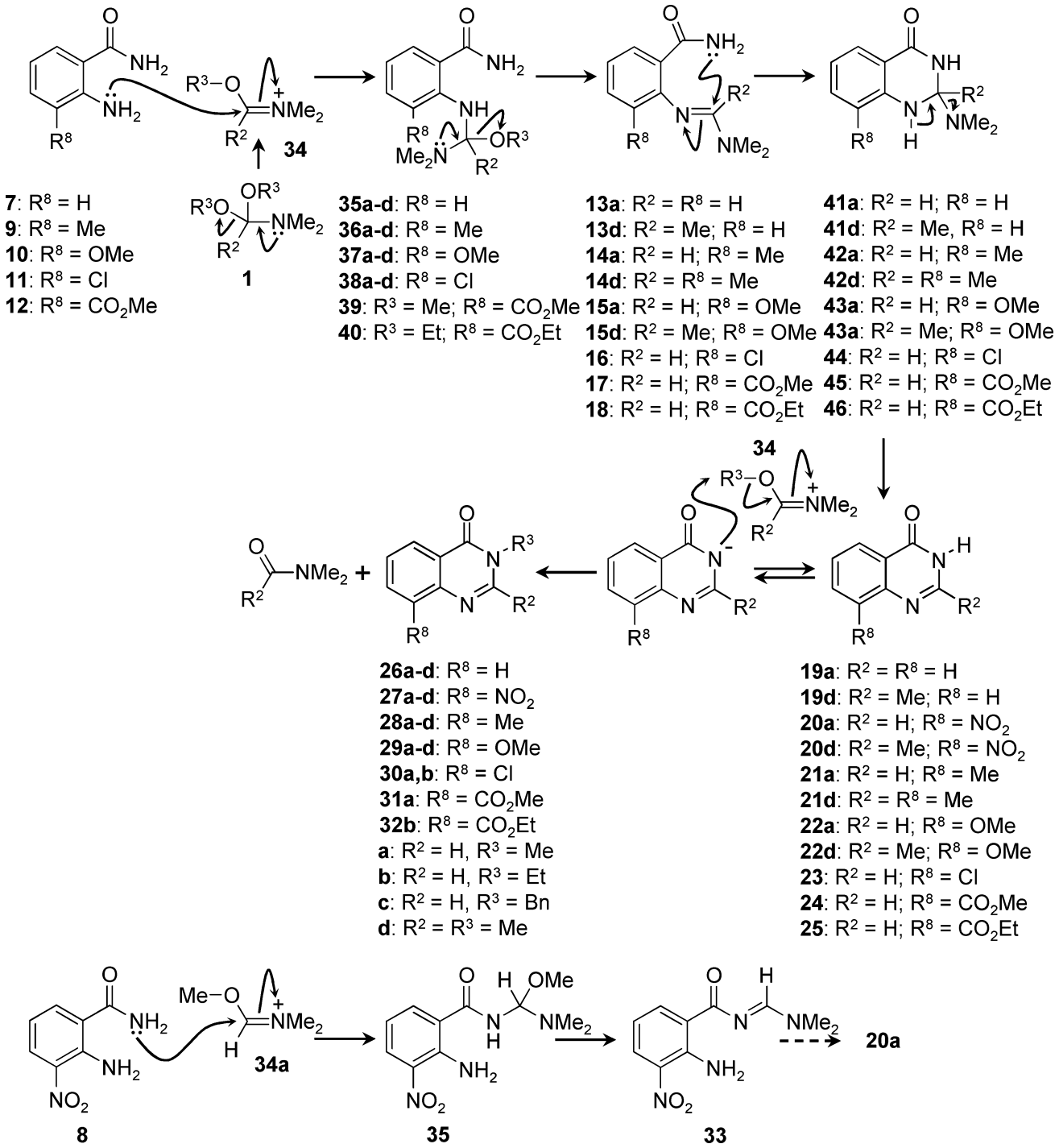
In each run with orthoformamides **1a–c**, formation of the intermediate quinazolin-4-ones **19a**, **21a**, **22a**,**23a** was detected by TLC at shorter time periods but no 8-nitroquinazolin-4-one **20a** was observed. This anomalous behaviour of the compounds containing the nitro group led to a study of the reaction of **8** with **1a** under milder conditions. Heating **8** with 1.2 molar equivalents of **1a** in boiling THF (*ca.* 65 °C, *cf.* 150 °C for refluxing DMF) gave a solid which was shown by ^{1}H and ^{13}C NMR spectroscopy to comprise a mixture of the acylformamidine **33**, with smaller amounts of **20a** and **27a** (Scheme 1). This experiment gives significant insights into the course and mechanism of the condensation forming the quinazolinone heterocycle and the alkylation at N^3.



Scheme 1 Formation of N^3-alkylquinazolin-4-ones **26a–d**, **27a–d**, **28a–d**, **29a–d**, **30a**, **b**, **31a**, **32b** by reaction of anthranilamides **7–12** with **1a–d**. *Reagents and conditions*: i, $SOCl_2$, NH_3; ii, *N*,*N*′-carbonyldiimidazole, NH_3; iii, **1a**, DMF, 150 °C; iv, **1b**, DMF, 150 °C; v, **1c**, DMF, 150 °C; vi, **1d**, DMF, 150 °C; vii, **1a**, THF, reflux.

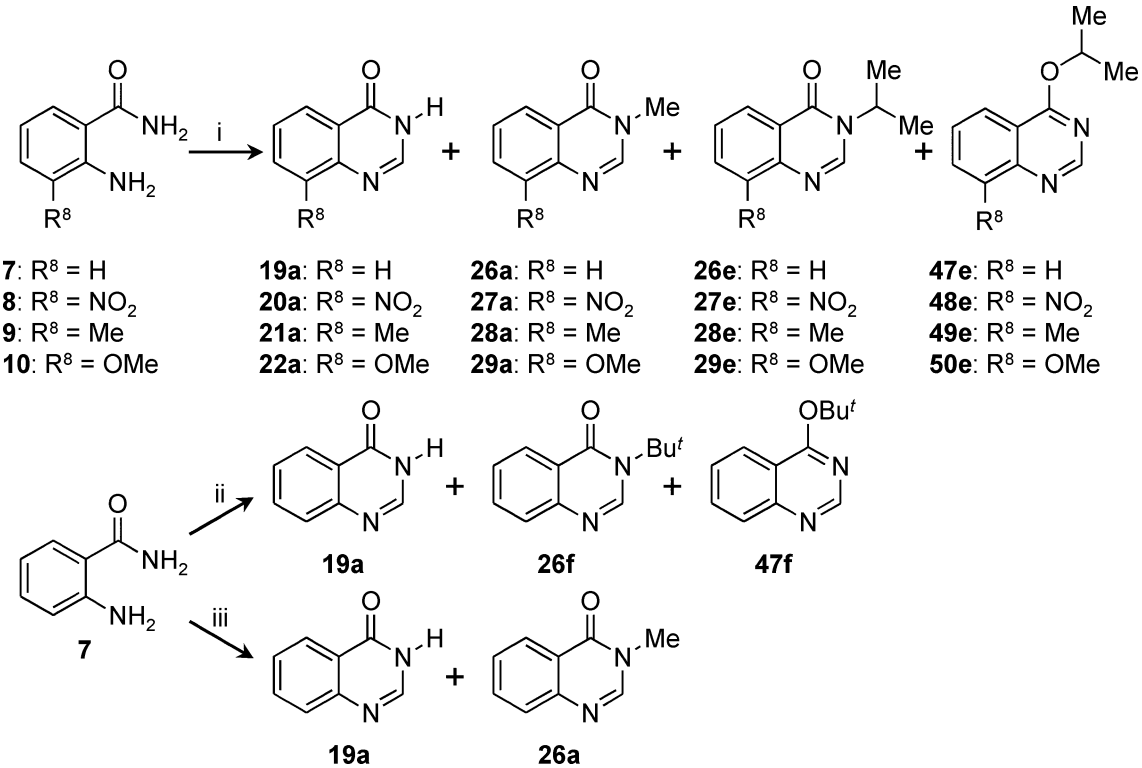
Scheme 2 shows our proposal for the mechanisms of these novel processes with orthoamides **1a–d** carrying primary O-alkyl groups. Thermal elimination of alkoxide from **1a–d** generates the alkoxyiminium ion **34**. In the parent anthranilamide **7** and in **9–11**, which lack electron-withdrawing substituents at the 3-position *ortho* to the aniline NH_2, this $ArNH_2$ is the more nucleophilic of the two nitrogens and attacks the sp^2-carbon of **34** to give tetrahedral intermediates **35–40**. Another elimination of alkoxide leads to formamidine intermediates **13–18**, where the sp^2 carbon is again the electrophile in the intramolecular reaction with the primary amide. Simple elimination of dimethylamine from the second tetrahedral intermediates **41–46** gives the quinazolin-4-ones **19**, **21–25**. The orthoamides **1** are basic and generate some of the corresponding anion. This quinazolin-4-one anion then attacks the cationic intermediate **34** at the O-alkyl group. This S_N2-like substitution is facilitated by DMF being an excellent leaving group. Thus the alkoxyiminium **34** can be electrophilic either at the central sp^2 carbon or at the sp^3 carbon of the O-alkyl group. The observation that **19a** can be isolated at short reaction times and that **21a**, **22a**, **23a**, **24a** can be seen by TLC in the reaction mixtures of longer treatment of **7**, **9–12** with **1a** confirms that the methylation occurs after the formation of the quinazolin-4-one ring and is, therefore, slower than the cyclocondensation step. The ethylation reactions are generally slower and lower-yielding than the methylations, consistent with steric crowding at the CH_2 group of the ethoxyiminium intermediate **34b**. No effect of the electronic nature (electron-donating, electron-neutral) of the 3-substituent in **7**,**9–12** is seen in the outcome of the reaction.

The situation is different for the compounds bearing the electron-withdrawing nitro group. Heating **8** with **1a** at lower temperature allowed **33** to be isolated as an intermediate, whereas no formamidine could be isolated in the reaction of **7** with **1a** in boiling THF. This indicates that the nitro group deactivates the *ortho*-amine to such an extent that the amide-NH_2 becomes the more nucleophilic of the two NH_2 nitrogens. Condensation of **8** with **34** thus proceeds *via* attack of the weakly nucleophilic amide NH_2 at the sp^2 electrophilic centre. The tetrahedral intermediate **35** then collapses to form the acylformamidine **33**, which cyclises to form **20a**. Subsequent methylation forms **27a**. Two further experimental observations are pertinent. Firstly, **33** is unstable



Scheme 2 Proposed mechanisms for formation of intermediate quinazolin-4-ones **19–25** and product 3-(primary)alkylquinazolin-4-ones **26–32**, demonstrating that intermediates **34** (derived from orthoamides **1**) can be electrophilic formyl equivalents and electrophilic alkylating agents in the same reaction mixture.

to column chromatography, returning to **8** rather than cyclising to **20a**; this is consistent with the very low intramolecular nucleophilicity of the adjacent 2-NH_2, with intermolecular silica-bound water being more reactive. Secondly, **20a** was not shown as an intermediate by TLC (comparison with authentic standard prepared from **2** and formamide) at any stage of the two-step reaction at 150 °C. It was observed as a minor component of the mixture of products of reaction of **8** with limiting amount of **1a** at lower temperature. At the higher temperature with excess **1a**, it is clear that the cyclocondensation reaction is slowed significantly by the nitro group, such that the methylation (and, indeed, ethylation) reactions are now faster and intermediate **20a** is consumed as soon as it is formed. With only 1.2 equivalents of **1a** and the lower temperature, the supply of bifunctional electrophile



7: R^8 = H
8: R^8 = NO_2
9: R^8 = Me
10: R^8 = OMe

19a: R^8 = H
20a: R^8 = NO_2
21a: R^8 = Me
22a: R^8 = OMe

26a: R^8 = H
27a: R^8 = NO_2
28a: R^8 = Me
29a: R^8 = OMe

26e: R^8 = H
27e: R^8 = NO_2
28e: R^8 = Me
29e: R^8 = OMe

47e: R^8 = H
48e: R^8 = NO_2
49e: R^8 = Me
50e: R^8 = OMe

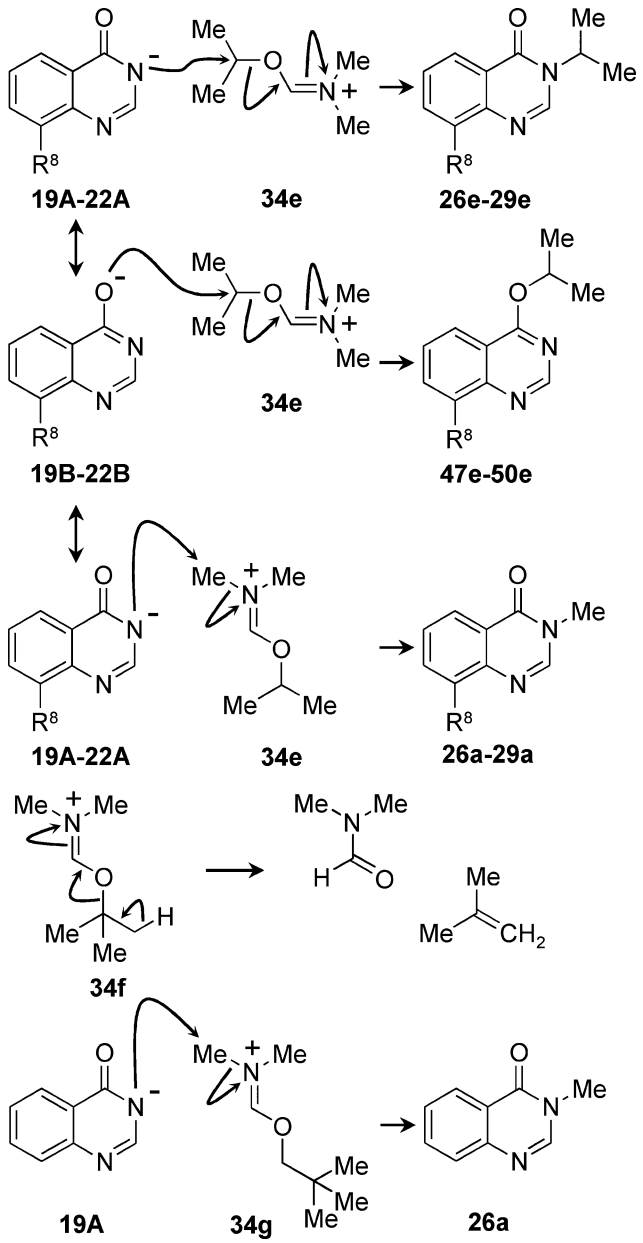
Scheme 3 Reaction of anthranilamides **7–10** with hindered orthoamides **1e–g**. *Reagents and conditions*: i, **1e**, DMF, 150 °C; ii, **1f**, DMF, 150 °C; iii, **1g**, DMF, 150 °C.

34a is exhausted, as formation of **26a** requires two equivalents thereof.

In contrast to the N^3-alkylations observed with orthoamides carrying unhindered primary alkoxy groups, Scheme 3 shows the anomalous products obtained from reactions of the anthranilamides **7–10** with orthoamides **1e–g**, carrying isopropoxy (secondary), *t*-butyl (tertiary) and neopentyloxy (hindered primary) groups, respectively. Reaction of anthranilamides **7**, **9**, **10** with **1e** at 150 °C for 24 h gave mixtures which were not chromatographically separable but which were analysed by ^{1}H and ^{13}C NMR. The component compounds were further identified by COSY, NOESY, HSQC and HMBC NMR and MS. A component of each mixture was the corresponding N^3-unsubstituted quinazolin-4-one **19a**, **21a**, **22a**. Also observed were the expected N^3-isopropylquinazolin-4-ones **26e**, **28e**, **29e**. The location of the isopropyl group at the 3-position in **26e**, **28e**, **29e** was confirmed for each example through HMBC cross-peaks connecting the isopropyl 2-H with 2-C and 4-C of the quinazolin-4-one and by NOE between 2-H and the isopropyl $(CH_3)_2$ and isopropyl CH protons. Less expected was the formation of the 4-isopropoxyquinazolines **47e**, **49e**, **50e** by alkylation at the harder nucleophile oxygen. Isomers **26e**, **28e**, **29e** and **47e**, **49e**, **50e** were formed in approximately equimolar amounts in each case. The structures of **47e**, **49e**, **50e** were confirmed by the more downfield ^{1}H chemical shifts of the isopropyl central protons δ 5.43–5.58) and the ^{13}C chemical shifts of the isopropyl central carbons (δ 69.84–70.01), compared to the corresponding values for **26e**, **28e**, **29e** (^{1}H δ 4.97–5.03; ^{13}C δ 45.09–46.19). For **49e**, an HMBC cross-peak was observed connecting the isopropyl 2-H with the quinazoline 4-C. More unexpected was the presence of the corresponding N^3-methylquinazolin-4-ones **26a**, **28a**, **29a** as the major components of the product mixtures. Similar reaction of the nitro analogue **8** with **1e**, followed by very careful chromatography, gave only a very small pure sample of **27e**.

Moving from the moderate steric demand of the isopropyl group to the severe crowding of the *t*-butyl unit, **7** was treated with five equivalents of **1f** at 150 °C for 24 h; this process furnished only the N^3-unsubstituted quinazolin-4-one **19a**, in high yield. When **19a** was re-subjected to the same reaction conditions with a further five equivalents of **1f** for a further 24 h, chromatography of the product mixture provided very small amounts of N^3-Bu^t-quinazolin-4-one **26f** and 4-Bu^{t}O-quinazoline **47f**, along with major recovery of unreacted **19a**. Although **1g** contains primary alkoxy groups, these are neopentyl, which should preclude both S_N1-like and S_N2-like electrophilic reactions. Treatment of **7** with **1g** afforded good yields of **19a** and, unexpectedly, the N^3-methylquinazolin-4-one **26a**.

Scheme 4 provides our mechanistic rationale for these unusual observations. Intermediate cation **34e** is generated by elimination of isopropanol from **1e**. The quinazolinone anion can be represented in two mesomeric structures, **19A–22A** and **19B–22B**, showing that it has two potentially nucleophilic sites. When this meets simple primary alkoxy electrophiles **34a–d**, alkylation takes place exclusively at the softer and more nucleophilic nitrogen. However, the increased steric bulk of the secondary alkyl group drives some of the alkylation to the more sterically accessible but more weakly nucleophilic oxygen, giving the 4-isopropoxyquinazolines **47e–50e**, in addition to the *N*-alkylated products **26e–29e**. The secondary alkyl electrophile in **34e** may also be more "S_N1-like"/cationic in its reactivity, making it a harder electrophile with greater propensity to react at oxygen, whereas the corresponding



Scheme 4 Proposed mechanisms for formation of 3-isopropylquinazolin-4-ones **26e–29e**, 4-isopropoxyquinazolines **47e–50e** and 3-methylquinazolin-4-ones **26a–29a** from intermediate quinazolinone anions **19A–22A / 19B–22B** (derived from **7–10**) and electrophile **34e** (derived from **1e**); proposed mechanisms for formation of **26a** from **19A** and electrophile **34g** (derived from **1g**) and degradation of analogous electrophile **34f** (derived from **1f**).

primary alkyl intermediates **34a–d** may be more "S_N2-like" and softer in their electrophilic reactivity, reacting only with the softer nitrogen nucleophile. However, both reactions are slow, diverting the nucleophiles **19A–22A** to approach the alternative electrophilic site in **34e**, the intrinsically less electrophilic but less sterically encumbered *N*-methyl. This process generates an iminoester as the leaving group, in forming the 3-methylquinazolin-4-ones **26a–29a**. The steric bulk is increased further in intermediate cation **34g**. This can form readily by thermal elimination of neopentyl alcohol from **1g** but the remaining neopentyl alkyl group at the oxygen cannot react as an alkylating electrophile, either by S_N1 or S_N2 mechanisms. Thus the only electrophilic site in **34g** is the N-methyl, which alkylates anion **19A** to form **26a**. Intermediate **34f**, derived by elimination of Bu^{t}OH from orthoamide **1f**, may, at first sight, be expected to behave like intermediate cation **34g** and thus condense with **7** to give **19a**, which would then be methylated by the weak *N*-Me electrophile to give **26a**. However, by far the major product is **19a**, with traces of the *N*-Bu^t and *O*-Bu^t compounds **26f** and **47f**, with no *N*-methylation. This observation can be rationalised, as cationic intermediate **34f** has an alternative mode of decomposition through an elimination giving 2-methylpropene and DMF (Scheme 4). The lifetime of **34f** at 150 °C may be long enough to insert 2-C of the quinazoline, a rapid reaction at this temperature, but too short to allow it to persist long enough to carry out the slow methylation using the *N*-methyl groups. Interestingly, the tertiary alkyl group of **34f** should react in an "S_N1-like" manner, allowing it to alkylate the harder oxygen as well as the softer nitrogen nucleophiles of the quinazolinone.

Conclusions

In this paper, we report that dimethylformamide di(primary-alkoxy)acetals **1a–c** and dimethylacetamide dimethylacetal **1d** can eliminate one alkoxide thermally to generate cationic intermediates **34a–d** that can act as electrophiles at two sites. Firstly, the predictable cyclocondensation of anthranilamides **7–12** with **1** generates quinazolin-4-ones through attack on the central carbon, which is sp^2 in **34**. This cyclocondensation also takes place readily with **7** and the electrophilic sp^2-carbon of the corresponding cationic intermediates **34e–g**, derived from more sterically bulky diisopropoxy, di-*t*-butoxy and dineopentyl acetals **1e–g**. Secondly, nucleophilic attack also takes place at the alkoxy sp^3 carbon of unhindered primary intermediates **34a–d**, forming 3-alkylquinazolin-4-ones **26–32** from the N–H quinazolin-4-ones **19–25**. This second reaction of **1** as electrophilic alkylating agents is unprecedented. Increasing the steric bulk of the *O*-alkyl substituent in the cationic intermediates **34e**,**g** mitigates this second electrophile but reveals a third site, the *N*-methyl. Reaction of N–H quinazolin-4-one **19a** with these electrophiles gives the N^3-Me quinazolin-4-one **26a** as major products. These reactions provide a useful one-pot route to N^3-(primary-alkyl)quinazolin-4-ones and point to new applications of these orthoamides as electrophilic alkylating agents in heterocyclic and other chemistry.

Experimental

NMR spectra were recorded on Bruker Avance III 400 and 500 spectrometers of solutions in hexadeuteriodimethylsulfoxide, except as otherwise noted; coupling constants are given in Hz. Mass spectra were obtained using Bruker microTOF™ spectrometers in electrospray positive ion mode. IR spectra were obtained as KBr discs. The stationary phase for chromatography was silica gel. Melting points were determined using a Reichert-Jung Thermo Galen instrument and are uncorrected. Reactions were performed at ambient temperature, unless stated otherwise. The solvents were evaporated under reduced pressure. Solutions in organic solvents were dried with sodium sulfate. The brine was saturated.

2-Amino-3-nitrobenzamide (8)

2-Amino-3-nitrobenzoic acid **2** (5.1 g, 28 mmol) was suspended in tetrahydrofuran (50 mL). Thionyl chloride (5.0 g, 42 mmol) and dimethylformamide (100 μL) were added and the mixture was stirred for 16 h. This solution was added dropwise to aq. ammonia (35%, 200 mL). Filtration and drying gave **8** (4.02 g, 79%) as an orange solid: mp 240–242 °C (lit.[18] mp 234–235 °C); ν_{max} 3458, 3431, 3297, 3207, 1686, 1630, 1596, 1544, 1320 cm^{-1}; δ_H 6.66 (1 H, t, *J* 6.8, 5-H), 7.59 (1 H, br s, CONH), 7.94 (1 H, dd, *J* 6.0, 1.2, 6-H), 8.14 (1 H, br s, CONH), 8.17 (1 H, dd, *J* 6.8, 1.2, 4-H), 8.64 (2 H, br s, Ar-NH_2); δ_C (HSQC/HMBC) δ 113.67 (5-C), 118.82 (3-C), 129.40 (6-C), 132.13 (1-C), 136.41 (4-C), 146.03 (2-C), 169.93 (C═O).

2-Amino-3-methylbenzamide (9)

2-Amino-3-methylbenzoic acid **3** (2.93 g, 19.8 mmol) in dry dimethylformamide (78 mL) was treated with 1,1′-carbonyldiimidazole (3.14 g, 19.4 mmol) at 70 °C under argon for 1 h, after which aq. ammonia (35%, 49 mL) was added dropwise. The mixture was stirred for 16 h. The mixture was allowed to cool to 20 °C and diluted with ethyl acetate (100 mL). Washing (water (twice), brine (twice)), drying and evaporation gave **9** (2.14 g, 98%) as a white solid: mp 150–152 °C (lit.[19] mp 147–149 °C); ν_{max} 3468, 3392, 3353, 3190, 1641, 1608, 1569 cm^{-1}; δ_H 2.05 (3 H, s, Me), 6.35 (2 H, br s, Ar-NH_2), 6.41 (1 H, br t, *J* 7.6, 5-H), 6.89 (1 H, br s, CONH), 7.04 (1 H, d, *J* 6.8, 6-H), 7.34 (1 H, dd, *J* 8.0, 0.8, 4-H), 7.67 (1 H, br s, CONH); δ_C (HSQC/HMBC) 17.56 (Me), 113.59 (1-C), 114.17 (5-C), 122.99 (3-C), 126.61 (6-C), 132.67 (4-C), 148.21 (2-C), 171.73 (C═O).

2-Amino-3-methoxybenzamide (10)

2-Amino-3-methoxybenzoic acid **4** was treated with 1,1′-carbonyldiimidazole, as for the synthesis of **9**, to give **10** (80%) as a white solid: mp 139–141 °C (lit.[20] mp 140–141 °C); ν_{max} 3474, 3367, 3304, 3150, 1670, 1617, 1548 cm^{-1}; δ_H 3.77 (3 H, s, Me), 6.23 (2 H, br s, Ar-NH_2), 6.44 (1 H, t, *J* 8.0, 5-H), 6.85 (1 H, dd, *J* 7.6, 0.8, 6-H), 7.03 (1 H, br s, CONH), 7.16 (1 H, dd, *J* = 8.0, 1.2, 4-H), 7.67 (1 H, br s, CONH); δ_C (HSQC/HMBC) 55.53 (Me), 111.98 (6-C), 113.38 (3-C), 113.64 (5-C), 120.42 (4-C), 140.19 (1-C), 146.88 (2-C), 171.19 (C═O).

2-Amino-3-chlorobenzamide (11)

2-Amino-3-chlorobenzoic acid **5** was treated with 1,1′-carbonyldiimidazole, as for the synthesis of **9**, to give **11** (97%) as a white solid: mp 155–157 °C (lit.[21] mp 161–162 °C); ν_{max} 3436, 3398, 3277, 3222, 1640, 1607, 1573, 1542 cm^{-1}; δ_H 6.51 (1 H, t, *J* 8.0, 5-H), 6.66 (2 H, br s, Ar-NH_2), 7.26 (1 H, br s, CONH), 7.34 (1 H, dd, *J* 7.6, 1.2, 6-H), 7.53 (1 H, dd, *J* 8.0, 1.6, 4-H), 7.86 (1 H, br s, CONH); δ_C (HSQC/HMBC) 114.89 (1-C), 115.84 (5-C), 119.03 (3-C), 127.74 (6-C), 131.83 (4-C), 145.62 (2-C), 170.45 (C═O).

Methyl 2-amino-3-aminocarbonylbenzoate (12)

Methyl 2-amino-3-carboxybenzoate **6** was treated with 1,1′-carbonyldiimidazole, as for the synthesis of **9**, to give **12** (84%) as a white solid: mp 75–77 °C; ν_{max} 3455, 3437, 3285, 3200, 1682 (br), 1575 cm^{-1}; δ_H 3.78 (3 H, s, Me), 6.52 (1 H, t, *J* 7.8, 5-H), 6.99 (0.5 H, br s, CONH), 7.28 (1 H, br s, CONH), 7.61 (0.5 H, br s, CONH), 7.77 (1 H, dd, *J* 7.7, 1.6, 6-H), 7.87 (1 H, dd, *J* 7.9, 1.6, 4-H), 7.99 (2 H, br s, Ar-NH_2); δ_C (HSQC/HMBC) 51.63 (Me), 110.51 (1-C), 113.21 (5-C), 116.17 (3-C), 134.56 (6-C), 134.64 (4-C), 151.59 (2-C), 167.54 (CO_2Me), 170.72 ($CONH_2$); *m/z* 217.0619 (M + Na) ($C_9H_{10}N_2NaO_3$ requires 217.0589).

Quinazolin-4-one (19a)

2-Aminobenzamide **7** (500 mg, 3.7 mmol) in dimethylformamide (18 mL) was treated with **1a** (1.27 g, 10.6 mmol) at 150 °C for 1.5 h. Cooling, evaporation and chromatography (ethyl acetate/dichloromethane 1 : 4 → 2 : 3) gave **19a** (410 mg, 75%) as a white solid: mp 225–227 °C (lit.[22] mp 221–222 °C); δ_H 7.58 (1 H, ddd, *J* 8.1, 7.3, 1.1, 6-H), 7.72 (1 H, ddd, *J* 8.1, 1.2, 0.5, 8-H), 7.87 (1 H, ddd, *J* 8.2, 7.2, 1.6, 7-H), 8.15 (1 H, s, 2-H), 8.18 (1 H, ddd, *J* 8.0, 1.6, 0.4, 5-H), 12.3 (1 H, br, 3-H); δ_C (HSQC/HMBC) 122.64 (4a-C), 125.80 (5-C), 126.70 (6-C), 127.21 (8-C), 134.27 (7-C), 145.33 (8a-C), 148.77 (2-C), 160.68 (4-C).

3-Methylquinazolin-4-one (26a)

Amide **7** (500 mg, 3.7 mmol) in dimethylformamide (16 mL) was treated with **1a** (1.3 g, 11 mmol) at 150 °C for 16 h. Cooling, evaporation and chromatography (ethyl acetate/petroleum ether, 2 : 3 → ethyl acetate) gave **26a** (560 mg, 95%) as a white solid: mp 98–100 °C (lit.[11] mp 105 °C); ν_{max} 1670, 1614 cm^{-1}; δ_H 3.55 (3 H, s, Me), 7.60 (1 H, ddd, *J* 8.1, 7.2, 1.2, 6-H), 7.73 (1 H, ddd, *J* 8.2, 1.2, 0.5, 8-H), 7.87 (1 H, ddd, *J* 8.2, 7.1, 1.6, 7-H), 8.43 (1 H, ddd, *J* 8.0, 1.5, 0.5, 5-H), 8.34 (1 H, s, 2-H); δ_C (HSQC/HMBC) 33.49 (Me), 121.43 (4a-C), 125.82 (5-C), 126.91 (6-C), 127.12 (8-C), 134.09 (7-C), 148.10 (8a-C), 148.41 (2-C), 160.64 (4-C).

3-Ethylquinazolin-4-one (26b)

Amide **7** (500 mg, 3.7 mmol) in dimethylformamide (16 mL) was treated with **1b** (1.3 g, 11 mmol) at 150 °C for 16 h. Cooling, evaporation and chromatography (ethyl acetate/petroleum ether 1 : 4 → 1 : 1) gave **26b** (330 mg, 52%) as a white solid: mp 110–112 °C (lit.[12] mp 99–101 °C); ν_{max} 1676, 1613 cm^{-1}; δ_H 1.27 (3 H, t, *J* 7.5, Me), 3.99 (2 H, q, *J* 7.5, CH_2), 7.52 (1 H, t, *J* 8.0, 6-H), 7.66 (1 H, d, *J* 8.0, 8-H), 7.80 (1 H, br t, *J* 7.5, 7-H), 8.15 (1H, br d, *J* 8.0, 5-H), 8.41 (1 H, s, 2-H); δ_C (HSQC/HMBC) 14.49 (Me), 41.19 (CH_2), 121.57 (4a-C), 125.94 (5-C), 126.92 (6-C), 127.13 (8-C), 134.15 (7-C), 147.84 (8a-C), 147.99 (2-C), 159.97 (4-C).

3-Phenylmethylquinazolin-4-one (26c)

Amide **7** (200 mg, 1.5 mmol) was stirred at 150 °C with **1c** (2.00 g, 7.3 mmol) in dimethylformamide (8.0 mL) for 24 h. Evaporation and chromatography (ethyl acetate/petroleum ether 1 : 4 → 7 : 1) gave **26c** (286 mg, 82%) as a white solid: mp 117–119 °C; (lit.[16] mp 118–120 °C); ν_{max} 1674, 1604 cm^{-1}; δ_H 5.20 (2 H, s, CH_2), 7.29–7.38 (5 H, m, Ph-H_5); 7.55 (ddd, *J* 8.0, 7.0, 1.1, 6-H), 7.69 (1 H, brd, *J* 8.0, 8-H), 7.84 (1 H, ddd, *J* 8.1, 7.0, 1.5, 7-H), 8.15 (1 H, dd, *J* 8.0, 1.2, 5-H), 8.58 (1 H, s, 2-H); δ_C (HSQC/HMBC) 48.84 (CH_2), 121.64 (4a-C), 126.11 (8-C), 127.19 (6-C), 127.26 (5-C), 127.64 and 128.64 (Ph 2,3,5,6-C_4), 127.67 (Ph 4-C), 134.43 (7-C), 136.85 (Ph 1-C), 147.91 (8a-C), 148.01 (2-C), 160.09 (4-C); *m/z*

495.1777 (2 M + Na) ($C_{30}H_{24}N_4NaO_2$ requires 495.1806); 259.0848 (M + Na) ($C_{15}H_{12}N_2NaO$ requires 259.0847), 237.1043 (M + H) ($C_{15}H_{13}N_2O$ requires 237.1029).

2,3-Dimethylquinazolin-4-one (26d)

Amide **7** (200 mg, 1.47 mmol) was stirred at 150 °C with **1d** (783 mg, 5.9 mmol) in dimethylformamide (8.0 mL) for 2 d. Evaporation and chromatography (CH_2Cl_2 → CH_2Cl_2/EtOAc 4 : 1) gave **26d** (30 mg, 12%) as a white solid: mp 110–112 °C (lit.[12] mp 108–109 °C); ν_{max} 1671, 1600 cm^{-1}; δ_H 2.57 (3 H, s, 2-Me), 3.53 (3 H, s, 3-Me), 7.46 (1 H, ddd, *J* 8.0, 6.8, 0.8, 6-H), 7.56 (1 H, brd, *J* 8.0 Hz, 8-H), 7.77 (1 H, ddd, *J* 8.4, 7.2, 1.6 Hz, 7-H), 8.09 (1 H, dd, *J* 8.0, 1.2 Hz, 5-H); δ_C (HSQC/HMBC) 23.15 (2-Me), 30.52 (3-Me), 119.70 (4a-C), 126.05 (6-C), 126.12 (5-C), 126.41 (8-C), 134.09 (7-C), 155.60 (2-C), 161.27 (4-C).

3-Methyl-8-nitroquinazolin-4-one (27a)

Amide **8** was treated with **1a**, as for the synthesis of **19a** except that the chromatographic eluant was ethyl acetate/petroleum ether (1 : 4 → 1 : 1), to give **27a** (93%) as a pale yellow solid: mp 165–167 °C (lit.[23] mp 157 °C); ν_{max} 1697, 1614, 1604, 1526, 1366 cm^{-1}; δ_H 3.49 (3 H, s, Me), 7.63 (1 H, t, *J* 8.6, 6-H), 8.26 (1 H, dd, *J* 8.0, 1.6, 7-H), 8.34 (1 H, dd, *J* 8.0, 1.6, 5-H), 8.47 (1 H, s, 2-H); δ_C (HSQC/HMBC) 33.86 (Me), 122.83 (4a-C), 126.56 (5-C), 127.58 (6-C), 129.64 (7-C), 139.85 (8-C), 146.45 (8a-C), 150.97 (2-C), 159.31 (4-C).

3-Ethyl-8-nitroquinazolin-4-one (27b)

Amide **8** was treated with **1b**, as for the synthesis of **26b**, to give **27b** (89%) as a pale yellow solid: mp 143–145 °C (lit.[24] mp 143–144 °C); ν_{max} 1683, 1526, 1379 cm^{-1}; δ_H 1.27 (3 H, t, *J* 7.2, Me), 3.98 (2 H, q, *J* 7.2, CH_2), 7.64 (1 H, t, *J* 7.6, 6-H), 8.26 (1 H, dd, *J*8.0, 1.6, 7-H), 8.35 (1 H, dd, *J* 8.0, 1.2, 5-H), 8.53 (1 H, s, 2-H); δ_C (HSQC/HMBC) 14.20 (Me), 41.74 (CH_2), 123.00 (4a-C), 126.61 (5-C), 127.63 (6-C), 129.76 (7-C), 139.74 (8-C), 146.47 (8a-C), 150.43 (2-C), 158.69 (4-C); *m/z* 242.0535 (M + Na) ($C_{10}H_9N_3NaO_3$ requires 242.0542), 220.0719 (M + H) ($C_{10}H_{10}N_3O_3$ requires 220.0722).

8-Nitro-3-(phenylmethyl)quinazolin-4-one (27c)

Amide **8** (200 mg, 1.1 mmol) was stirred at 150 °C with **1c** (1.2 g, 4.4 mmol) in dimethylformamide (4.0 mL) for 5 d. Evaporation and chromatography (ethyl acetate/petroleum ether 1 : 1) gave **27c** (190 mg, 61%) as pale yellow crystals: mp 189–191 °C; ν_{max} 1691, 1602, 1527, 1356 cm^{-1}; δ_H ($(CD_3)_2SO$) 5.27 (2 H, s, CH_2), 7.36 (5 H, m, Ph-H_5), 7.76 (1 H, t, *J* 8.0, 6-H), 8.38 (1 H, dd, *J* 8.0, 1.2, 7-H), 8.44 (1 H, dd, *J* 8.0, 1.6, 5-H), 8.78 (1 H, s, 2-H); δ_H ($CDCl_3$) 5.21 (2 H, s, CH_2), 7.35 (5 H, m, Ph-H_5), 7.58 (1 H, t, *J* 8.0, 6-H), 8.09 (1 H, dd, *J* 8.0, 1.5, 7-H), 8.23 (1 H, s, 2-H), 8.53 (1 H, dd, *J* 8.0, 1.5, 5-H); δ_C (HSQC/HMBC) ($CDCl_3$) 50.07 (CH_2), 123.74 (4a-C), 126.54 (6-C), 128.24 and 129.18 (Ph 2,3,5,6-C_4), 128.52 (7-C), 128.71 (Ph 4-C), 131.08 (5-C), 134.71 (Ph 1-C), 140.46 (8a-C), 146.63 (8-C), 148.60 (2-C), 159.42 (4-C); *m/z* 585.1460 (2 M + Na) ($C_{30}H_{22}N_6NaO_6$ requires 585.1493), 304.0686 (M + Na) ($C_{15}H_{11}N_3NaO_3$ requires 304.0693), 282.0879 (M + H) ($C_{15}H_{12}N_3O_3$ requires 282.0873).

2,3-Dimethyl-8-nitroquinazolin-4-one (27d)

2-Amino-3-nitrobenzamide **8** (200 mg, 1.1 mmol) was stirred at 150 °C with **1d** (441 mg, 3.3 mmol) in dimethylformamide (4.0 mL) for 5 d. Evaporation and chromatography (dichloromethane) gave **27d** (180 mg, 75%) as a pale yellow solid: mp 178–179 °C (lit.[25] mp 175 °C); δ_H ($(CD_3)_2SO$) 2.64 (3 H, s, 2-Me), 3.60 (3 H, s, 3-Me), 7.66 (1 H, t, *J* 8.0, 6-H), 8.30 (1 H, dd, *J* 7.6, 1.6, 7-H), 8.39 (1 H, dd, *J* 8.0, 1.6, 5-H); δ_H ($CDCl_3$) 2.65 (3 H, s, 2-Me), 3.63 (3 H, s, 3-Me), 7.48 (1 H, t, *J* 8.0, 6-H), 8.00 (1 H, dd, *J* 7.8, 1.4, 7-H), 8.43 (1 H, dd, *J* 8.0, 1.5, 5-H); δ_H (HSQC/HMBC) ($CDCl_3$) 24.06 (2-Me), 31.30 (3-Me), 121.85 (4a-C), 125.31 (6-C), 128.04 (7-C), 130.82 (5-C), 139.73 (8a-C), 146.29 (8-C), 157.42 (2-C), 160.72 (4-C); *m/z* 242.0521 (M + Na) ($C_{10}H_9N_3NaO_3$ requires 242.0542), 220.0748 (M + H) ($C_{10}H_{10}N_3O_3$ requires 220.0722).

3,8-Dimethylquinazolin-4-one (28a)

Amide **9** was treated with **1a**, as for the synthesis of **26a** except that the chromatographic eluant was ethyl acetate/petroleum ether (1 : 4 → 3 : 7), to give **28a** (0.41 g, 71%) as a white solid: mp 151–153 °C; ν_{max} 1667, 1612, 1574 cm^{-1}; δ_H 2.52 (3 H, s, 8-Me), 3.49 (3 H, s, 3-Me), 7.39 (1 H, t, *J* 7.5, 6-H), 7.64 (1 H, ddq, *J* 8.0, 2.5, 0.5, 7-H), 7.97 (1 H, brd, *J* 8.0, 5-H), 8.35 (1 H, s, 2-H); δ_C (HSQC/HMBC) 17.02 (8-Me), 33.43 (3-Me), 121.35 (4a-C), 123.48 (5-C), 126.38 (6-C), 134.38 (7-C), 135.26 (8-C), 146.57 (8a-C), 147.37 (2-C), 160.85 (4-C); *m/z* 371.1450 (2 M + Na) ($C_{20}H_{20}N_4NaO_2$ requires 371.1478), 197.0680 (M + Na) ($C_{10}H_{10}N_2NaO$ requires 197.0691), 175.0874 (M + H) ($C_{10}H_{11}N_2O$ requires 175.0871).

3-Ethyl-8-methylquinazolin-4-one (28b)

Amide **9** was treated with **1b**, as for the synthesis of **26b** except that the chromatographic eluant was ethyl acetate/petroleum ether (1 : 4), to give **28b** (45%) as a white solid: mp 67–69 °C; ν_{max} 1678, 1607, 1574, 1456 cm^{-1}; δ_H 1.25 (3 H, t, *J* 7.2, CH_2CH_3), 2.50 (3 H, s, 8-Me), 3.96 (2 H, q, *J* 7.2, CH_2), 7.36 (1 H, t, *J* 7.6, 6-H), 7.63 (1 H, br d, *J* 7.2, 7-H), 7.96 (1 H, br d, *J* 8.0, 5-H), 8.39 (1 H, s, 2-H); δ_C (HSQC/HMBC) 14.47 (CH_2CH_3), 16.97 (8-Me), 41.10 (CH_2), 121.53 (4a-C), 123.61 (5-C), 126.40 (6-C), 134.43 (7-C), 135.28 (8-C), 146.47 (8a-C), 146.80 (2-C), 160.20 (4-C); *m/z* 211.0846 (M + Na) ($C_{11}H_{12}N_2NaO$ requires 211.0847), 189.1033 (M + H) ($C_{11}H_{13}N_2O$ requires 189.1028).

8-Methyl-3-phenylmethylquinazolin-4-one (28c)

Amide **9** was treated with **1c**, as for the synthesis of **26c** except that the chromatographic eluant was ethyl acetate/petroleum ether (1 : 9 → 7 : 1), to give **28c** (83%) as pale buff solid: mp 143–145 °C; ν_{max} 1673, 1603 cm^{-1}; δ_H 2.54 (3 H, s, 8-Me), 5.20 (2 H, s, CH_2), 7.28-7.36 (5 H, m, Ph-H_5), 7.43 (1 H, t, *J* 8.0, 6-H), 7.69 (1 H, dd, *J* 7.6, 1.6, 7-H), 7.99 (1 H, dd, *J* 8.0, 0.8, 5-H), 8.59 (1 H, s, 2-H); δ_C (HSQC/HMBC) 17.03 (Me), 48.79 (CH_2), 121.58 (4a-C), 123.76 (5-C) 126.69 (6-C), 127.61 and 128.62 (Ph 2,3,5,6-C_4), 127.64 (Ph 4-C), 134.74 (7-C), 135.47 (8-C), 136.86 (Ph 1-C), 146.37 (8a-C), 147.02 (2-C), 160.31 (4-C); *m/z* 523.2085 (2 M + Na) ($C_{32}H_{28}N_4Na_1O_2$ requires 523.2104), 273.0985 (M + Na) ($C_{16}H_{14}N_2Na_1O_1$ requires 273.0998), 251.1186 (M + H) ($C_{16}H_{15}N_2O_1$ requires 251.1179).

2,3,8-Trimethylquinazolin-4-one (28d)

Amide **9** (50 mg, 0.33 mmol) was stirred at 150 °C with **1d** (133 mg, 1.0 mmol) in dimethylformamide (1.5 mL) for 90 h. Evaporation and chromatography (ethyl acetate/petroleum ether 1 : 4) gave **27d** (18.9 mg, 38%) as a white solid: mp 104–108 °C (lit.[26] mp 107 °C); δ_H ($(CD_3)_2SO$) 2.14 (3 H, s, 8-Me), 2.65 (3 H, s, 2-Me), 3.59 (3 H, s, 3-Me), 7.40 (1 H, t, *J* 8.0, 6-H), 7.68 (1 H, ddq, *J* 8.0, 1.2, 0.5, 7-H), 8.00 (1 H, dd, *J* 8.0, 1.2, 5-H); δ_H ($CDCl_3$) 2.56 (3 H, s, 8-Me), 2.59 (3 H, s, 2-Me), 3.59 (3 H, s, 3-Me), 7.28 (1 H, t, *J* 7.5, 6-H), 7.72 (1 H, brd, *J* 7.5, 7-H), 8.07 (1 H, brd, *J* 7.5, 5-H); δ_C (HSQC/HMBC) ($CDCl_3$) 17.13 (8-Me), 23.76 (2-Me), 30.90 (3-Me), 120.07 (4a-C), 124.31 (5-C), 125.75 (7-C), 134.53 (7-C), 135.09 (8-C), 145.84 (8a-C), 152.90 (2-C), 162.65 (4-C). *m/z* 399.1828 (2 M + Na) ($C_{22}H_{24}N_4NaO_2$ requires 399.1782), 211 (M + Na), 189 (M + H).

8-Methoxy-3-methylquinazolin-4-one (29a)

Amide **10** was treated with **1a**, as for the synthesis of **26a** except that the chromatographic eluant was ethyl acetate, to give **29a** (64%) as a white solid: mp 177–179 °C (lit.[9] mp 172 °C); ν_{max} 1677, 1602, 1548 cm^{-1}; δ_H 3.47 (3 H, s, 3-Me), 3.88 (3 H, s, OMe), 7.31 (1 H, dd, *J* 8.0, 1.2, 7-H), 7.41 (1 H, t, *J* 8.0, 6-H), 7.66 (1 H, dd, *J* 8.0, 1.2, 5-H), 8.23 (1 H, s, 2-H); δ_C (HSQC/HMBC) 33.42 (3-Me), 55.96 (OMe), 114.63 (5-C), 116.79 (7-C), 122.52 (4a-C), 127.23 (6-C), 138.70 (8a-C), 146.97 (2-C), 154.48 (8-C), 160.50 (4-C).

3-Ethyl-8-methoxyquinazolin-4-one (29b)

Amide **10** was treated with **1b**, as for the synthesis of **26b** except that the chromatographic eluant was ethyl acetate/petroleum ether (1 : 4) → EtOAc, to give **29b** (43%) as a white solid: mp 115–116 °C (lit.[9] mp 108 °C); ν_{max} 1680, 1604, 1570 cm^{-1}; δ_H 1.24 (3 H, t, *J* 6.8 Hz, CH_2CH_3), 3.89 (3 H, s, OMe), 3.96 (2 H, q, *J* 6.8, CH_2), 7.32 (1 H, dd, *J* 8.0, 1.2, 7-H), 7.42 (1 H, t, *J* 8.0, 6-H), 7.67 (1 H, dd, *J* 8.0, 1.2, 5-H), 8.32 (1 H, s, 2-H); δ_C (HSQC/HMBC) 14.44 (CH_2CH_3), 41.16 (CH_2), 55.99 (OMe), 114.73 (5-C), 116.91 (7-C), 122.68 (4a-C), 127.26 (6-C), 138.59 (8a-C), 146.39 (2-C), 154.49 (8-C), 159.85 (4-C).

8-Methoxy-3-phenylmethylquinazolin-4-one (29c)

Amide **10** was treated with **1d**, as for the synthesis of **26c** except that the chromatographic eluant was ethyl acetate/petroleum ether (2 : 3 → 7 : 1), to give **29c** (72%) as a white solid: mp 121–123 °C (lit.[9] mp 118 °C); ν_{max} 1688, 1605, 1570, 1483 cm^{-1}; δ_H (COSY) 3.90 (3 H, s, OMe), 5.20 (2 H, s, CH_2), 7.28–7.35 (5 H, m, Ph-H_5), 7.38 (1 H, slightly br dd, *J* 8.0, 1.3, 7-H), 7.47 (1 H, t, *J* 8.0, 6-H), 7.69 (1 H, dd, *J* 8.0, 1.3 Hz, 5-H), 8.51 (1 H, s, 2-H); δ_C (HSQC/HMBC) 48.82 (CH_2), 56.00 (OMe), 114.96 (7-C), 117.01 (5-C), 122.73 (4a-C), 127.60 (Ph 2,4,6-C_3), 127.65 (6-C), 128.64 (Ph 3,5-H_2), 136.85 (Ph 1-C), 138.42 (8a-C), 146.61 (2-C), 154.55 (8-C), 160.00 (4-C); *m/z* 555 (2 M + Na), 289.0984 (M + Na) ($C_{16}H_{14}N_2NaO_2$ requires 289.0953), 267 (M + H).

2,3-Dimethyl-8-methoxyquinazolin-4-one (29d)

Amide **10** (95 mg, 0.57 mmol) was stirred at 150 °C with **1d** (230 mg, 1.7 mmol) in dimethylformamide (2.3 mL) for 24 h. Evaporation and chromatography (ethyl acetate/methanol 19 : 1) gave **29d** (28 mg, 24%) as a white solid: mp 133 °C (lit.[27] mp 133–136 °C); δ_H 2.63 (3 H, s, 2-Me), 3.59 (3 H, s, 3-Me), 3.95 (3 H, s, OMe), 7.36 (1 H, dd, *J* 8.0, 1.2, 7-H), 7.44 (1 H, t, *J* 8.0, 6-H), 7.70 (1 H, dd, *J* 8.0, 1.2, 5-H); δ_C (HSQC/HMBC) 23.19 (2-Me), 30.60 (3-Me), 55.74 (*O*-Me), 114.35 (7-C), 117.07 (5-C), 120.73 (8-C), 126.27 (6-C), 137.68 (8a-C), 154.21 (4a-C), 161.15 (4-C); *m/z* 205.0976 (M + H) ($C_{11}H_{13}N_2O_2$ requires 205.0977).

8-Chloro-3-methylquinazolin-4-one (30a)

Amide **11** was treated with **1a**, as for the synthesis of **26a**, to give **30a** (63%) as a white solid: mp 160–162 °C (lit.[14] mp 158–159 °C); ν_{max} 1672, 1609 cm^{-1}; δ_H 3.49 (3 H, s, Me), 7.46 (1 H, t, *J* 7.8, 6-H), 7.92 (1 H, dd, *J* 7.8, 1.3, 5-H), 8.07 (1 H, dd, *J* 8.0, 1.2, 7-H), 8.45 (1 H, s, 2-H); δ_C (HSQC/HMBC) 33.69 (Me), 123.13 (4a-C), 125.03 (5-C), 127.25 (6-C), 130.66 (7-C), 134.17 (8-C), 144.58 (8a-C), 149.27 (2-C), 160.12 (4-C).

8-Chloro-3-ethylquinazolin-4-one (30b)

Amide **11** was treated with **1b**, as for the synthesis of **26b** except that the chromatographic eluant was ethyl acetate/petroleum ether (1 : 4 → 3 : 7), to give **30b** (58%) as a white solid: mp 127–128 °C (lit.[24] mp 123–123.5 °C); ν_{max} 1679, 1607 cm^{-1}; δ_H 1.26 (3 H, t, *J* 7.2, CH_2CH_3), 3.98 (2 H, q, *J* 7.2, CH_2), 7.47 (1 H, t, *J* 8.0, 6-H), 7.93 (1 H, dd, *J* 7.6, 1.2, 7-H), 8.08 (1 H, dd, *J* 8.0, 1.6, 5-H), 8.49 (1 H, s, 2-H); δ_C (HSQC/HMBC) 14.31 (CH_2CH_3), 41.49 (CH_2), 123.29 (4a-C), 125.16 (5-C), 127.29 (6-C), 130.69 (7-C), 134.23 (8-C), 144.48 (8a-C), 148.72 (2-C), 159.48 (4-C).

Methyl 3-methyl-4-oxoquinazoline-8-carboxylate (31a)

Amide **12** was treated with **1a**, as for the synthesis of **27a**, to give **31a** (66%) as a white solid: mp 180–182 °C; ν_{max} 1740, 1681, 1610 cm^{-1}; δ_H 3.48 (3 H, s, 3-Me), 3.86 (3 H, s, OMe), 7.54 (1 H, t, *J* 7.6, 6-H), 7.95 (1 H, dd, *J* 7.6, 1.6, 7-H), 8.26 (1 H, dd, *J* 8.0, 1.6, 5-H), 8.38 (1 H, s, 2-H); δ_C (HSQC/HMBC) 33.57 (3-Me), 52.33 (OMe), 121.90 (4a-C), 126.36 (5-C), 128.54 (6-C), 130.65 (7-C), 133.32 (8-C), 145.35 (8a-C), 149.14 (2-C), 160.14 (4-C); MS *m/z* 219.0777 (M + H) ($C_{11}H_{11}N_2O_3$ requires 219.0769).

Ethyl 3-ethyl-4-oxoquinazoline-8-carboxylate (32b)

Amide **12** was treated with **1b**, as for the synthesis of **7a** except that the chromatographic eluant was ethyl acetate/petroleum ether (3 : 7 → 1 : 1), to give **32b** (40%) as a white solid: mp 113–115 °C; ν_{max} 1727, 1672, 1606 cm^{-1}; δ_H 1.26–1.32 (6 H, m, 2 × Me), 3.97 (2 H, q, *J* 7.2, 3-CH_2), 4.30 (2 H, q, *J* 7.2, OCH_2), 7.55 (1 H, t, *J* 7.6, 6-H), 7.94 (1 H, dd, *J* 7.6, 1.6, 7-H), 8.26 (1 H, dd, *J* 8.0, 1.6, 5-H), 8.43 (1 H, s, 2-H); δ_C (HSQC/HMBC) 14.09 (3-CH_2CH_3), 14.34 (OCH_2CH_3), 41.34 (3-CH_2), 61.05 (OCH_2), 122.03 (4a-C), 126.39 (5-C), 128.47 (6-C), 131.04 (7-C), 133.12 (8-C), 145.19 (8a-C), 148.53 (2-C), 159.51 (4-C), 166.68 (CO_2); *m/z* 269.0939 (M + Na) ($C_{13}H_{14}N_2NaO_3$ requires 269.0902), 247.1132 (M + H) ($C_{13}H_{15}N_2O_3$ requires 247.1083).

***N′*-(2-Amino-3-nitrobenzoyl)-*N*,*N*-dimethylformamidine (33)**

Amide **8** (200 mg, 1.1 mmol) was heated under reflux with **1a** (157 mg, 1.3 mmol) in tetrahydrofuran (4.0 mL) for 16 h. The

evaporation residue, in ethyl acetate, was washed with water. The combined aq. washings were then extracted thrice with ethyl acetate. The combined organic extracts were dried. Evaporation gave an orange solid (221 mg). ^{1}H NMR showed that the solid comprised **20a** (19% yield), **27a** (21% yield) and **33** (52% yield). Spectroscopic data for **33**: δ_H (COSY/NOESY) 3.13 (3 H, d, *J* 0.5, Me *trans* to formamidine-H), 3.23 (3 H, s, Me *cis* to formamidine-H), 6.67 (1 H, br t, *J* 8.0, 5-H), 8.22 (1 H, dd, *J* 8.5, 4-H), 8.61 (1 H, br s, N=CH), 8.62 (1 H, m, 6-H); δ_C (HSQC/HMBC) 35.38 (Me *trans* to formamidine-H), 41.19 (Me *cis* to formamidine-H), 113.53 (5-C), 121.14 (1-C), 130.54 (4-C), 132.26 (3-C), 140.39 (6-C), 147.31 (2-C), 160.35 (N=CH), 176.82 (C=O).

Reaction of 7 with 1e

2-Aminobenzamide **7** (200 mg, 1.47 mmol) was stirred at 150 °C with **1e** (1.29 g, 7.3 mmol) in dimethylformamide (8.0 mL) for 24 h. Further **1e** (773 mg, 4.4 mmol) was added and the mixture was stirred at 150 °C for 24 h. Evaporation gave a colourless oil, which was shown by ^{1}H NMR to comprise **19a**, **26a**, 3-(prop-2-yl)quinazolin-4-one **26e** and 4-(prop-2-yloxy)quinazoline **47e** (1.4 : 2.3 : 1.4 : 1.0): δ_H (**19a**) 7.53 (1 H, brt, *J* 8, 6-H), 7.67 (1 H, brd, *J* 8, 8-H), 7.81 (1 H, brt, *J* 8, 7-H), 8.13 (1 H, brd, *J* 7.5, 5-H), 8.09 (1 H, s, 2-H), 12.5 (1 H, br, 3-H); δ_C (HSQC/HMBC) (**19a**) 121.58 (4a-C), 123.24 (5-C), 126.8 (6-C), 127 (8-C), 134.32 (7-C), 148 (8a-C), 147.42 (2-C), 160.65 (4-C); δ_H (**26a**) 3.50 (3 H, s, 3-Me), 7.53 (1 H, brt, *J* 8, 6-H), 7.67 (1 H, brd, *J* 8, 8-H), 7.81 (1 H, brt, *J* 8, 7-H), 8.15 (1 H, dd, *J* 7.0, 1.0, 5-H), 8.37 (1 H, s, 2-H); δ_C (HSQC/HMBC) (**26a**) 33.85 (3-Me), 121.45 (4a-C), 125.84 (5-C), 126.8 (6-C), 127 (8-C), 134.21 (7-C), 148.13 (8a-C), 148.44 (2-C), 160.65 (4-C); δ_H (**26e**) 1.436 (6 H, d, *J* 7.0, CH*Me*$_2$), 5.00 (1 H, septet, *J* 7.0, C*H*Me$_2$), 7.53 (1 H, brt, *J* 8, 6-H), 7.67 (1 H, brd, *J* 8, 8-H), 7.81 (1 H, brt, *J* 8, 7-H), 8.15 (1 H, dd, *J* 7.0, 1.0, 5-H), 8.47 (1 H, s, 2-H); δ_C (HSQC/HMBC) (**26e**) 21.17 (CH*Me*$_2$), 45.09 (*C*HMe$_2$), 121.40 (4a-C), 125.83 (5-C), 126.8 (6-C), 127 (8-C), 134.12 (7-C), 148 (8a-C), 145.35 (2-C), 159.7 (4-C); δ_H (**47e**) 1.436 (6 H, d, *J* 6.4, CH*Me*$_2$), 5.58 (1 H, septet, *J* 6.0, C*H*Me$_2$), 7.52 (1 H, brt, *J* 7.5, 6-H), 7.90 (1 H, brd, *J* 8, 8-H), 7.93 (1 H, brt, *J* 8, 7-H), 8.15 (1 H, dd, *J* 7.0, 1.0, 5-H), 8.78 (1 H, s, 2-H); δ_C (HSQC/HMBC) (**47e**) 21.53 (CH*Me*$_2$), 70.01 (*C*HMe$_2$), 116.1 (4a-C), 126 (5-C), 126.8 (6-C), 127.4 (8-C), 134.00 (7-C), 150.54 (8a-C), 153.34 (2-C), 165.5 (4-C); *m*/*z* 189.1018 (**26e**/**47e** + H) ($C_{11}H_{13}N_2O$ requires 189.1028), 147.0546 (**19a** + H) ($C_8H_7N_2O$ requires 147.0558).

Reaction of 8 with 1e; synthesis of 8-nitro-3-(prop-2-yl)quinazolin-4-one (27e)

2-Amino-3-nitrobenzamide **8** (25 mg, 0.14 mmol) was stirred at 150 °C with **1e** (115 mg, 0.66 mmol) in DMF (0.55 mL) for 4 d. Evaporation and chromatography (ethyl acetate/petroleum ether 1 : 4) gave **27e** (0.7 mg, 3%) as a pale yellow solid: mp 165–167 °C; δ_H 1.50 (6 H, d, *J* 6.8, 2 × Me), 5.03 (1 H, septet, *J* 6.8, C*H*Me$_2$), 7.74 (1 H, t, *J* 8.0, 6-H), 8.36 (1 H, dd, *J* 8.0, 1.6, 7-H), 8.45 (1 H, dd, *J* 8.0, 1.6, 5-H), 8.67 (1 H, s, 2-H); *m*/*z* 489.1461 (2 M + Na) ($C_{22}H_{22}N_6NaO_6$ requires 489.1499), 256.0685 (M + Na) ($C_{11}H_{11}N_3NaO_3$ requires 256.0693), 234.0890 (M + H) ($C_{11}H_{12}N_3O_3$ requires 234.0873).

Reaction of 9 with 1e

2-Amino-3-methylbenzamide **9** was treated with **1e**, as for the reaction of **7** with **1e**, to give a colourless oil, which was shown by ^{1}H NMR to comprise **21a**, **28a**, 8-methyl-3-(prop-2-yl)quinazolin-4-one **28e** and 8-methyl-1-(prop-2-yloxy)quinazoline **49e** (2.9 : 2.2 : 1.3 : 1.0): δ_H (**21a**) 2.5 (3 H, s, 8-Me), 7.38 (1 H, m, 6-H), 7.64 (1 H, brd, *J* 8, 7-H), 7.92 (1 H, m, 5-H), 8.11 (1 H, s, 2-H), 12.25 (1 H, br, 3-H); δ_C (HSQC/HMBC) (**21a**) 17.23 (8-Me), 122.56 (4a-C), 123.5 (5-C), 126.14 (6-C), 134.62 (7-C), 146.58 (8a-C), 147 (2-C), 135.2 (8-C), 161.00 (4-C); δ_H (**28a**) 2.5 (3 H, s, 8-Me), 3.48 (3 H, s, 3-Me), 7.38 (1 H, m, 6-H), 7.64 (1 H, brd, *J* 8, 7-H), 7.92 (1 H, m, 5-H), 8.35 (1 H, s, 2-H); δ_C (HSQC/HMBC) (**28a**) 33.44 (3-Me), 17.03 (8-Me), 121.35 (4a-C), 123.5 (5-C), 126.37 (6-C), 134.36 (7-C), 135.2 (8-C), 146.58 (8a-C), 147.36 (2-C), 160.86 (4-C); δ_H (**28e**) 1.42 (6 H, d, *J* 7.0, CH*Me*$_2$), 2.5 (3 H, s, 8-Me), 4.99 (1 H, septet, *J* 6.8, C*H*Me$_2$), 7.38 (1 H, m, 6-H), 7.64 (1 H, brd, *J* 8, 7-H), 7.92 (1 H, m, 5-H), 8.48 (1 H, s, 2-H); δ_C (HSQC/HMBC) (**28e**) 17.09 (8-Me), 21.53 (CH*Me*$_2$), 45.99 (*C*HMe$_2$), 121.3 (4a-C), 123.87 (5-C), 126.42 (6-C), 134.43 (7-C), 135.2 (8-C), 145.85 (8a-C), 144.3 (2-C), 159.63 (4-C); δ_H (**49e**) 1.41 (6 H, d, *J* 6.0, CH*Me*$_2$), 2.5 (3 H, s, 8-Me), 5.43 (1 H, septet, *J* 6.2, C*H*Me$_2$), 7.49 (1 H, dd, *J* 8.0, 7.5, 6-H), 7.73 (1 H, dd, *J* 7.0, 1.0, 7-H), 7.92 (1 H, brd, *J* 8.0, 5-H), 8.78 (1 H, s, 2-H); δ_C (HSQC/HMBC) (**49e**) 16.94 (8-Me), 21.20 (CH*Me*$_2$), 69.84 (*C*HMe$_2$), 115.92 (4a-C), 120.75 (5-C), 126.37 (6-C), 133.65 (7-C), 135.5 (8-C), 149.44 (8a-C), 153.31 (2-C), 165.78 (4-C); *m*/*z* 203.1178 (**28e**/**49e** + H) ($C_{12}H_{15}N_2O$ requires 203.1184), 175.0868 (**28a** + H) ($C_{10}H_{11}N_2O$ requires 175.0871), 161.0709 (**21a** + H) ($C_9H_9N_2O$ requires 161.0715).

Reaction of 10 with 1e

2-Amino-3-methoxybenzamide **10** was treated with **1e**, as for the reaction of **7** with **1e**, to give a colourless oil, which was shown by ^{1}H NMR to comprise **22a**, **29a**, 8-methoxy-3-(prop-2-yl)quinazolin-4-one **29e** and 8-methyl-1-(prop-2-yloxy)quinazoline **50e** (1.0 : 2.6 : 1.4 : 1.2): δ_H (**22a**) 3.892 (3 H, s, OMe), 7.35 (1 H, brd, *J* 8.0, 7-H), 7.45 (1 H, t, *J* 8.0, 6-H), 7.66 (1 H, dd, *J* 8.0, 1.0, 5-H), 8.20 (1 H, s, 2-H), 12.2 (1 H, br, 3-H); δ_C (HSQC/HMBC) (**22a**) 55.85 (OMe), 123.5 (4a-C), 114.89 (5-C), 116.92 (7-C), 127.28 (6-C), 138.00 (8a-C), 147.0 (2-C), 154.4 (8-C), 160.52 (4-C); δ_H (**29a**) 3.49 (3 H, s, 3-Me), 3.898 (3 H, s, OMe), 7.35 (1 H, brd, *J* = 8.0 Hz, 7-H), 7.45 (1 H, t, *J* = 8.0 Hz, 6-H), 7.690 (1 H, dd, *J* = 8.5, 1.0 H, 5-H), 8.31 (1 H, s, 2-H); δ_C (HSQC/HMBC) (**29a**) 33.42 (3-Me), 55.91 (OMe), 114.72 (5-C), 116.76 (7-C), 122.50 (4a-C), 127.28 (6-C), 138.66 (8a-C), 147.02 (2-C), 154.46 (8-C), 160.52 (4-C); δ_H (**29e**) 1.43 (6 H, d, *J* 6.0, CH*Me*$_2$), 3.901 (3 H, s, OMe), 4.97 (1 H, septet, *J* 7.0, C*H*Me$_2$), 7.35 (1 H, brd, *J* 8.0, 7-H), 7.45 (1 H, t, *J* 8.0, 6-H), 7.691 (1 H, dd, *J* 8.5, 1.0, 5-H), 8.39 (1 H, s, 2-H); δ_C (HSQC/HMBC) (**29e**) 21.16 (CH*Me*$_2$), 46.19 (*C*HMe$_2$), 55.85 (OMe), 116.52 (5-C), 114.89 (7-C), 122.50 (4a-C), 127.28 (6-C), 138.01 (8a-C), 143.90 (2-C), 154.4 (8-C), 159.60 (4-C); δ_H (**50e**) 1.42 (6 H, d, *J* 7.0, CH*Me*$_2$), 3.95 (3 H, s, OMe), 5.55 (1 H, septet, *J* 6.0, C*H*Me$_2$), 7.39 (1 H, dd, *J* 8.0, 1.0, 7-H), 7.56 (1 H, dd, *J* 8.5, 7.5, 6-H), 7.64 (1 H, dd, *J* 8.5, 1.2, 5-H), 8.72 (1 H, s, 2-H); δ_C (HSQC/HMBC) (**50e**) 21.55 (CH*Me*$_2$), 56.0 (OMe), 69.91 (*C*HMe$_2$), 112.88 (7-C), 114.09 (5-C), 116.92 (4a-C), 127.53 (6-C), 142.29 (8a-C), 152.92 (2-C), 155.4

(8-C), 165.39 (4-C); *m/z* 241.0945 (**29e/50e** + Na) ($C_{12}H_{14}N_2NaO_2$ requires 241.0953), 219.1130 (**29e/50e** + H) ($C_{12}H_{15}N_2O_2$ requires 219.1134), 191.0817 (**29a** + H) ($C_{10}H_{11}N_2O_2$ requires 191.0820), 177.1658 (**22a** + H) ($C_9H_9N_2O_2$ requires 177.0664).

Reaction of 7 with 1f: quinazolin-4-one (19a), 3-(1,1-dimethylethyl)quinazolin-4-one (26f) and 4-(1,1-dimethylethoxy)quinazoline (47f)

Amide **7** (200 mg, 1.5 mmol) was stirred at 150 °C with **1g** (1.49 g, 7.3 mmol) in dimethylformamide (8.0 mL) for 24 h. Evaporation and chromatography (ethyl acetate/petroleum ether 1 : 4) gave **19a** (170 mg, 79%), with data as above. This material (160 mg, 1.1 mmol) was stirred at 150 °C with **1g** (1.49 g, 7.3 mmol) in ethyl acetate (8.0 mL) for 24 h. Evaporation and chromatography (ethyl acetate/petroleum ether 4 : 1) gave crude 4-(1,1-dimethylethoxy)quinazoline **26f** (3.0 mg, 1.4%) as a colourless gum: δ_H (COSY/NOESY) 1.75 (9 H, s, Bu^t), 7.68 (1 H, ddd, *J* 8.2, 6.6, 1.5, 6-H), 7.91 (1 H, brd, *J* 8 Hz, 8-H), 7.94 (1 H, ddd, *J* 8.4, 6.6, 1.5, 7-H), 8.13 (1 H, ddd, *J* 8.2, 1.4, 0.6, 5-H), 8.79 (1 H, s, 2-H); δ_C (HSQC/HMBC) 27.84 (Me_3), 82.80 (CMe_3), 117.00 (4a-C), 123.57 (5-C), 127.19 (6-C), 127.36 (8-C), 133.67 (7-C), 150.49 (8a-C), 153.74 (2-C), 165.65 (4-C); *m/z* 203.1179 (M + H) ($C_{12}H_{15}N_2O$ requires 203.1184). Further elution gave 3-(1,1-dimethylethyl)quinazolin-4-one **47f** (21 mg, 9%), as a pale yellow solid: mp 75–78 °C (lit.[4] mp 68-74 °C); δ_H (COSY/NOESY) 1.74 (9 H, s, Bu^t), 7.57 (1 H, ddd, *J* 8.1, 7.2, 1.2, 6-H), 7.70 (1 H, brd, *J* 8, 8-H), 7.94 (1 H, ddd, *J* 8.2, 7.1, 1.6, 7-H), 8.21 (1 H, ddd, *J* 8.0, 1.5, 0.4, 5-H), 8.47 (1 H, s, 2-H); δ_C (HSQC/HMBC) 27.99 (Me_3), 60.47 (CMe_3), 122.39 (4a-C), 126.14 (5-C), 126.58 (8-C), 126.75 (6-C), 134.10 (7-C), 145.18 (2-C), 147.20 (8a-C), 161.14 (4-C); *m/z* 203.1185 (M + H) ($C_{12}H_{15}N_2O$ requires 203.1184). Further elution gave recovered **19a** (67 mg, 41%), with properties as above.

Reaction of 7 with 1g

2-Aminobenzamide **7** (200 mg, 1.47 mmol) was stirred at 150 °C with **1g** (1.69 g, 7.3 mmol) in dimethylformamide (8.0 mL) for 24 h. Evaporation and chromatography (ethyl acetate/petroleum ether 1 : 1) gave a colourless gum, which was shown by ^{1}H NMR to comprise **19a** and **26a** (10 : 1).

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