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Divergent 2-Chloroquinazolin-4(3*H*)-one Rearrangement: Twisted-Cyclic Guanidine Formation or Ring-Fused *N*-Acylguanidines via a Domino Process

Gang Yan,[a] Bereket L. Zekarias,[a] Xiaoyu Li,[a] Victor A. Jaffett,[b] Ilia A. Guzei[c] and Jennifer E. Golden*[a][b]

Abstract: A highly efficient 2-chloroquinazolin-4(3*H*)-one rearrangement was developed that predictably generates either twisted-cyclic or ring-fused guanidines in a single operation, depending on the presence of a primary versus secondary amine in the accompanying diamine reagent. Exclusive formation of twisted-cyclic guanidines results from pairing 2-chloroquinazolinones with secondary diamines. Use of primary amine-containing diamines permits a domino quinazolinone rearrangement/intramolecular cyclization, gated through (*E*)-twisted-cyclic guanidines, to afford ring-fused *N*-acylguanidines. This scalable, structurally tolerant transformation generated 55 guanidines and delivered twisted-cyclic guanidines with robust plasma stability and an abbreviated total synthesis of an antitumor ring-fused guanidine (4 steps, 55% yield).

Introduction

Guanidines are broadly used across multiple industries as catalysts, curing agents, organic superbases, artificial sweeteners, and agrochemicals.[1] Their pharmaceutical relevance is marked by an increased representation in approved drugs and bioactive molecules with a wide range of pharmacological and architectural diversity.[2] Notable examples include drugs such as zanamivir[3] **1**, famotidine[4] **2**, clonidine[5] **3**, and mizolastine[6] **4**, and numerous bioactive guanidines (**5**-**8**) in development also have been reported[7] (Figure 1). As such, tremendous interest has been devoted to constructing novel guanidine-containing frameworks, fostering the discovery of new synthetic methods and scaffolds with tunable properties. Herein, we report an unprecedented, divergent transformation involving a regiospecific rearrangement of 2-chloroquinazolin-4(3*H*)-ones **9** that predictably generates either antiviral twisted-cyclic guanidines **10** or antitumor ring-fused *N*-acylguanidines **11** in high yield.

Many methods exist for assembling cyclic guanidines **12** (Scheme 1A). Popular approaches include treating thioureas[7a, 7d, 8] **13** or Vilsmeier-like precursors[9] **14** with amines. Carbodiimides[10] are also common feedstocks, as exemplified by Pd-catalyzed cyclizations with vinylaziridines[11], or reports detailing Ti- or Pd-catalyzed, intermolecular cyclization reactions with diamines **16**.[12] Metal-catalyzed, intramolecular ring-closing reactions between guanidines **17** and an appended functional group have also been described.[13]

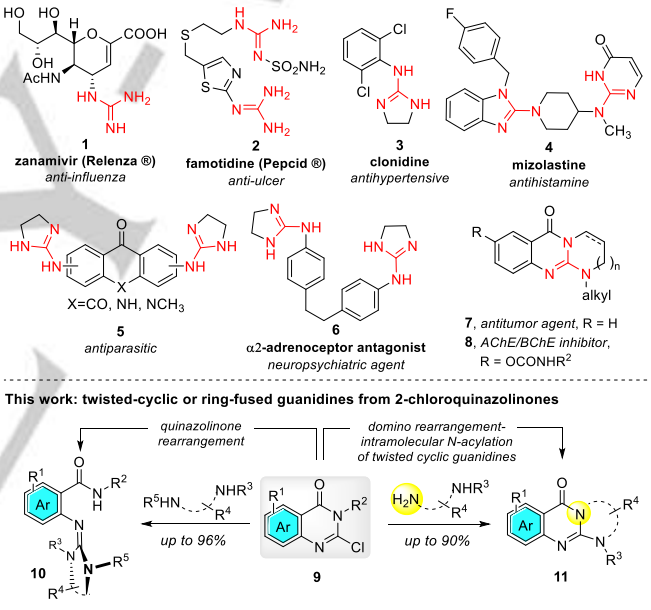

Figure 1. Drugs and bioactive molecules containing a guanidine motif (red), and our divergent, one-step synthesis of either twisted cyclic guanidines or ring-fused *N*-acylguanidines from 2-chloroquinazolinones

Fewer methods focus on ring-fused guanidines (Scheme 1B); however, this framework is a ring-fused aza-analog of the well-known quinazolinone privileged structure.[14] As bioactivity profiling of these newer guanidines emerges, interest has grown in their efficient assembly. For example, a radical cascade cyclization reaction[15] using azido-*N*-cyanobenzamides **18** has generated a series of investigational N^1-H guanidines **19**, while anthranilamide **20** was converted in seven steps to a series of N^1-substituted guanidines **22** with potent *in vivo* antitumor activity.[7b] In a separate study, isatoic anhydride **23** was transformed with isothiourea **24** into N^1-H guanidines **25**.[7c] Ultimately these intermediates were modified into cholinesterase inhibiting N^1-substituted guanidines over 8 total steps. Collectively, these

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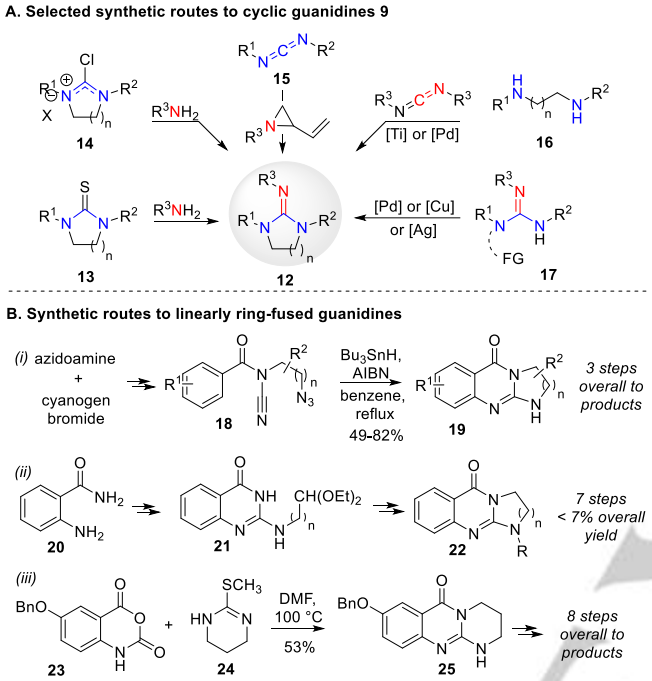
pioneering methods generated novel guanidines of diverse utility; however, all offer access to only one of the two classes of guanidines discussed here, and most still suffer from one or more challenges associated with elusive starting materials, reagent toxicity, limited substrate scope or poor overall yield. Therefore, new synthetic approaches to novel cyclic guanidines continue to be in high demand.

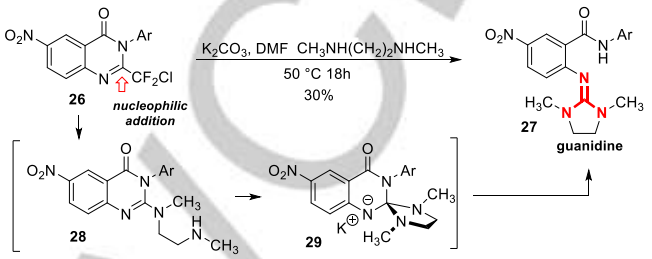


Scheme 1. Synthetic approaches to cyclic and linearly ring-fused guanidines

Results and Discussion

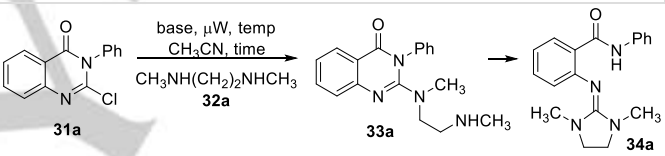
In the pursuit of structure-property relationships associated with a class of antiviral (*E*)-amidobenzamidines,[16] we explored several new quinazolinone starting materials, including 2-difluorochloromethylquinazolinone **26** (Scheme 2). When quinazolinone **26** was heated with N^1,N^2-dimethylethanediamine in the presence of potassium carbonate in DMF, a new scaffold, guanidine **27**, was isolated in a modest 30% yield. Increasing the reaction temperature to 120 °C further diminished the yield, but reaction analysis revealed the presence of intermediate 2-aminoquinzolinone **28**, likely resulting from a nucleophilic addition-elimination reaction at the imine-like carbon of the quinazolinone (red arrow), followed by a rare example of haloform extrusion (-CHF_2Cl). Cyclization to form spirocycle **29**, followed by ring opening, would afford the cyclic guanidine **27**.

Intrigued by this result, we sought to improve this transformation. Preparation of quinazolinone **26** was challenging due to the volatility and expense of difluorochloroacetyl chloride and the marginal yield of product obtained from **26** and other trifluoromethylquinazolinones. Given these issues and the prospect that the product likely resulted from a nucleophilic addition-elimination reaction, we assessed the viability of the commercially available 2-chloroquinazolin-4(3*H*)-one **31a** as a surrogate in the transformation. If successful, a variety of accessible substituted 2-chloroquinazolinones could be employed. For instance, **31a** (though commercial) was easily prepared in two steps in 85% yield from anthranilic acid and phenyl isothiocyanate.[14d] Pilot reactions using **31a** with N^1,N^2-dimethyl-1,2-ethanediamine **32a** were explored to identify ideal conditions for this transformation (Table 1).



Scheme 2. Quinazolinone rearrangement leading to new cyclic guanidines

Table 1. Quinazolinone to cyclic guanidine reaction optimization [a]



entry	base	equiv. base	solvent	T/°C	time (h)	^{1}H NMR[b] conversion	yield[c] **36a**
1[d]	K_2CO_3	2	DMF	50	4	> 85%	66%
2[d]	K_2CO_3	2	CH_3CN	50	4	47%	45%
3[e]	K_2CO_3	3	CH_3CN	100	4	58%	53%
4	K_2CO_3	3	CH_3CN	100	1	78%	61%
5	K_2CO_3	3	CH_3CN	150	1	> 99%	71%
6	NEt_3	3	CH_3CN	100	1	80%	79%
7	NEt_3	3	CH_3CN	100	2	82%	81%
8	**NEt_3**	**3**	**CH_3CN**	**150**	**2**	**> 99%**	**93% (92%) (85%)[f]**

[a] Conditions: **31a** (0.2 mmol), **32a** (0.26 mmol), base, and solvent (2 mL) under microwave irradiation unless otherwise noted. [b] Calculated based on the consumption of **31a**. [c] NMR yield with 1,3,5-trimethoxybenzene as internal standard. Parenthetical value is isolated yield. [d] Thermal heating. [e] Sealed tube experiment. [f] 2 mmol scale reaction yield.

Under the conditions initially identified, the starting material was consumed in less than 4 h, as determined by TLC, and guanidine **34a** was observed in 66% yield with greater than 85% conversion by ^{1}H NMR (entry 1). The use of DMF complicated the workup, so acetonitrile was assessed, though comparatively this resulted in ~ 20% diminished yield and reduced conversion by ^{1}H NMR (entry 2). Yield and conversion were improved to 71% and >99%,

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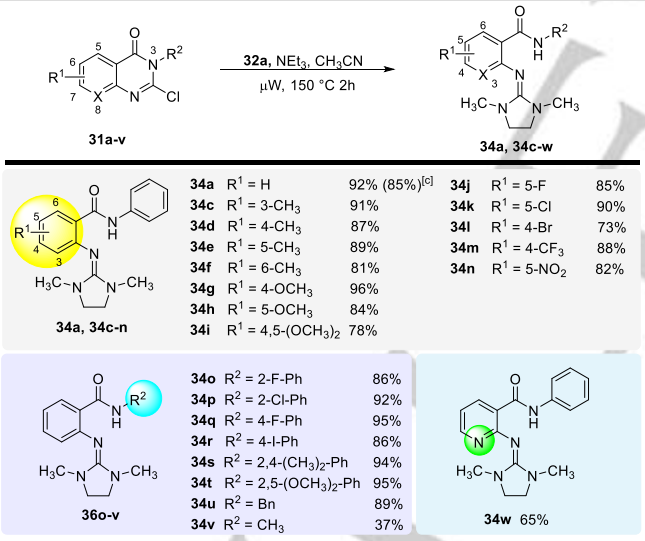
respectively, by increasing the stoichiometry of base (3 equiv.), switching to microwave irradiation, elevating the temperature to 150 °C and reducing the reaction time to 1 h (entries 3-5). Additionally, substituting triethylamine for K_2CO_3 at 100 °C for 1-2 h gave yields of 79% (entry 6) and 81% (entry 7), respectively. Finally, increasing temperature to 150 °C resulted in full conversion and an isolated yield of 92% of **34a** (entry 8). On a 2 mmol scale, **34a** was obtained in 85% yield (> 500 mg).

Notably, **33a** was not observed by ^{1}H NMR under any of these conditions, but when analogous pilot reactions were carried out in parallel between **31a** and *N*^{1},*N*^{2}-dimethyl-1,3-propanediamine **32b**, a significant quantity of the corresponding *N*^{1},*N*^{2}-dimethyl-1,3-propanediamine-appended quinazolinone **33b** was isolated in certain reactions (not shown). For example, with **31a** and K_2CO_3 (1 equiv. each), in CH_3CN at 50 °C for 3.5 h, **33b** was isolated in 95% yield without any evidence of desired guanidine **34b**. Fortunately, the optimized conditions determined for the two-carbon tethered diamine **32a**, when applied to the longer chain diamine **32b**, afforded guanidine **34b** in 85% yield. These conditions were then applied to a spectrum of substituted 2-choroquinazolinones and diamines to evaluate the sensitivity of the method to electronic and steric factors. We first examined effects of heteroatom incorporation or substituents on the quinazolinone core, along with *NH*-amide substituent changes, using 2-chloroquinazolinones **31a-v** (Table 2).

Table 2. Effect of 2-chloroquinazolinone modification on guanidine formation[a][b]



34a	R^1 = H	92% (85%)[c]	**34j**	R^1 = 5-F	85%
34c	R^1 = 3-CH_3	91%	**34k**	R^1 = 5-Cl	90%
34d	R^1 = 4-CH_3	87%	**34l**	R^1 = 4-Br	73%
34e	R^1 = 5-CH_3	89%	**34m**	R^1 = 4-CF_3	88%
34f	R^1 = 6-CH_3	81%	**34n**	R^1 = 5-NO_2	82%
34g	R^1 = 4-OCH_3	96%			
34h	R^1 = 5-OCH_3	84%			
34i	R^1 = 4,5-$(OCH_3)_2$	78%			
34o	R^2 = 2-F-Ph	86%			
34p	R^2 = 2-Cl-Ph	92%			
34q	R^2 = 4-F-Ph	95%			
34r	R^2 = 4-I-Ph	86%			
34s	R^2 = 2,4-$(CH_3)_2$-Ph	94%			
34t	R^2 = 2,5-$(OCH_3)_2$-Ph	95%			
34u	R^2 = Bn	89%			
34v	R^2 = CH_3	37%			

[a] Conditions: **31** (0.2 mmol), **32a** (0.26 mmol), NEt_3 (0.6 mmol) and CH_3CN (2 mL). [b] Isolated yields, averaged from two independent experiments. [c] 2 mmol scale.

Substitutions on the phenyl ring core of the quinazolinone structure were also well tolerated. A methyl group at any of one of the C8 – C5 positions of the quinazolinone core afforded the corresponding guanidine products **34c-f** in good yield (81–91%). Installation of an electron donating methoxy group at C7 and/or C6 position of the substrate core rearranged successfully, affording the desired products **34g-i** in 78% – 96% yield. Substrates bearing electron withdrawing substituents also fared well, permitting a range of halogens, or trifluoromethyl or nitro group substituents at the C4 or C5 product position (**34j-n**, 73%–90%). Quinazolinones with amide substituted *N*^{3}-phenyl rings afforded corresponding guanidines in high yield (**34o-t**). While the *N*^{3}-methyl amide substrate only gave 37% of guanidine **34v**, rearrangements leading to the *N*-benzyl **34u** (89%) and pyridyl derivatives **34w** (65%) were more productive.

An X-ray crystal structure of **34a** (Figure 2A) revealed a twisted and bent guanidine moiety relative to the core phenyl ring, resulting in a dihedral angle of 54.41° between the two components (Figure 2B).[1k, 17] An intramolecular hydrogen bond, formed between the amide-*N*^{1}*H* and the imine-like nitrogen atom (*N*^{2}) of the guanidine was apparent (distance = 1.96 Å), and distances between the amide-*N*^{1}*H* and the C17 and C18 *N*-methyl groups (Figure 2C) were determined which became relevant for asymmetrical diamine-derived analogs, discussed below (Table 3).

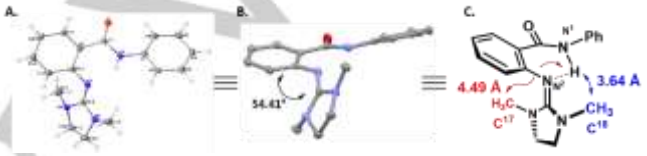


Figure 2. A. Molecular drawing of **34a** shown with 50% probability ellipsoids, CCDC 1965267. B. Alternate X-ray rendering of **34a** showing dihedral angle between the guanidine moiety and core phenyl ring. C. ChemDraw depiction of **34a** geometry with relative distances between guanidine substituents and amide-*NH*.

Further changes in diamine structure led to multiple discoveries. As already noted, diamines **32a** and **32b** afforded cyclic guanidines **34a** and **34b**, respectively, in high yield (85-92%). Seven-membered cyclic guanidines could not be obtained when using *N*^{1},*N*^{2}-dimethyl-1,4-butanediamine, presumably due to energetically unfavorable formation of a 7-membered intermediate (data not shown). Increasing steric bulk of the diamine *N*-substituents reduced the yield of the corresponding guanidines, as seen with *N*^{1},*N*^{2}-diethyldiamine **32c** or *N*^{1},*N*^{2}-dibenzyldiamine **32d** which gave **34x** and **34y** in 74% and 24% yield, respectively (Table 3). Asymmetrically substituted *N*^{1},*N*^{2}-alkylmethyl-1,2-ethanediamines **32e-h** were also evaluated in the reaction, revealing a formation of (*E*)-guanidines **34z-34cc** in good yield (62-80%). Each product showed a strong NOE between the larger R^1 group and the *NH*-amide compared to a weaker NOE between the guanidine *N*-methyl substituent and the *NH*-amide proton. The specificity was attributed to reduced steric interactions when the larger *N*-substituent occupies a region of space further away from the core phenyl ring, accommodated by the (*E*)-configuration. The observed NOE data was consistent with relative distances observed between the *N*-guanidine substituents and the amide-*NH* in the X-ray structure of **34a** (Fig. 2C). Branched diamines were also successfully incorporated. Reaction of **31a** with (±)-*trans*-*N*^{1},*N*^{2}-dimethylcyclohexane-1,2-diamine **32i** afforded (±)-*trans*-**34dd** in 68% yield while *(S)*-*N*^{1},*N*^{2}-dimethylpropane-1,2-diamine **32j** gave (*S*)-**34ee** as a mixture of *E* and *Z* isomers in 84% yield. The installation of a C8-methyl

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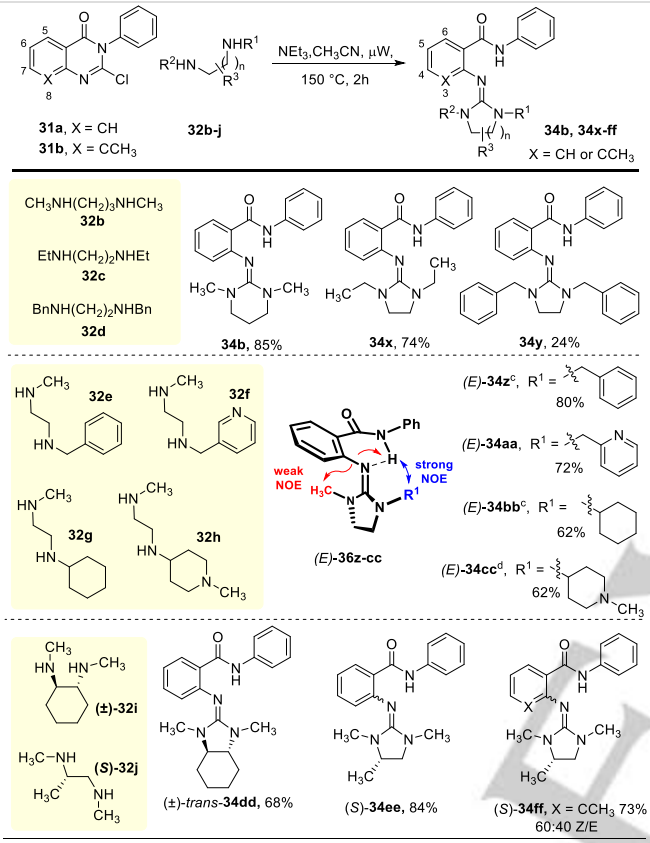
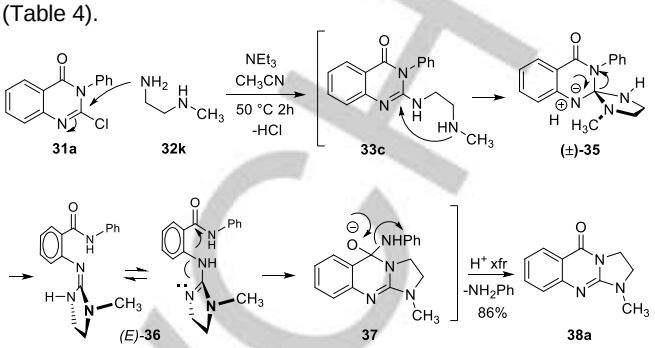
substituent on the quinazolinone core (**31b**) led to a 73% yield of (*S*)-**34ff** in a 60:40 ratio of Z/E isomers. Generally, these reactions were high yielding for a variety of regional structural changes and electronic influences, and exclusive cyclic (*E*)-guanidine formation occurred when a disparity in diamine *N*-substituent size was introduced.

Table 3. Effects of altering diamine structure on cyclic guanidine formation[a][b]



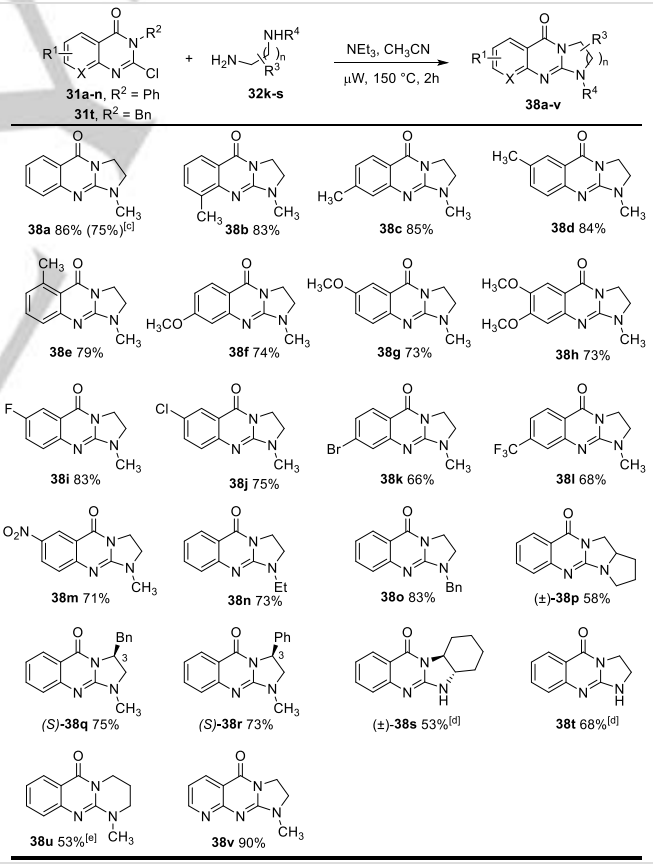
[a] Reaction conditions: **31a** or **31b** (0.2 mmol), **32** (0.26 mmol), NEt_3 (0.6 mmol) and CH_3CN (2 mL). [b] Isolated yields, averaged from two independent experiments. [c] Used di-HCl salt form of diamine **32** and NEt_3 (1 mmol). [d] Used tri-HCl salt form of the diamine **32** and NEt_3 (1.2 mmol).

As part of our reaction assessment, we also evaluated diamines containing at least one primary amine. Notably, we did not observe expected *NH*-cyclic guanidine analogs, but rather discovered the formation of linear, *ring-fused N*-acylguanidines in high yield under the optimized conditions. For example, treatment of **31a** with diamine **32k** afforded 86% yield of ring-fused guanidine **38a** (Scheme 3). Mechanistically, we proposed that diamine (**32k**) attacked 2-chloroquinazolinone **31a** to form aminoquinazolinone **33c**. Intramolecular cyclization of the pendant amine on the electrophilic imine-like carbon of **33c** afforded a spirocycle (±)-**35** that, upon ring opening, forms cyclic (*E*)-guanidine **36**. As we have shown, the (*E*)-configuration is favored when the guanidine nitrogen atoms bear substituents of unequal size, and this configuration is necessary for intramolecular cyclization. Intramolecular nucleophilic addition of the guanidine-*NH* of (*E*)-**36** to the amide moiety generates a 6.6.5-tricyclic intermediate **37** that, following extrusion of aniline, affords a ring-fused *N*-acylguanidine **38a**. The scope of this transformation was investigated, revealing successful reactions for a spectrum of quinazolinone core substitutions and diamines (Table 4).



Scheme 3. Proposed mechanism for the novel formation of ring-fused *N*-acylguanidines from primary amines and 2-chloroquinazolinones.

Table 4. Yield and scope of rearrangement affording ring-fused guanidines[a][b]



[a] Conditions unless otherwise noted: **31** (R^2 = Ph, 0.2 mmol), **32** (0.26 mmol), NEt_3 (0.6 mmol) and CH_3CN (2 mL). [b] Isolated yields, averaged from two independent experiments. [c] 2 mmol scale. [d] Used 3.0 equiv. of diamine (0.6 mmol). [e] Used **31t** (R^2 = Bn).

Ring-fused guanidines **38a**-**m** derived from *N*-methylethane-1,2-diamine **32k** and variously substituted 2-chloroquinazolinones

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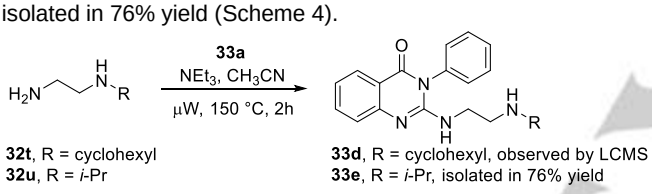
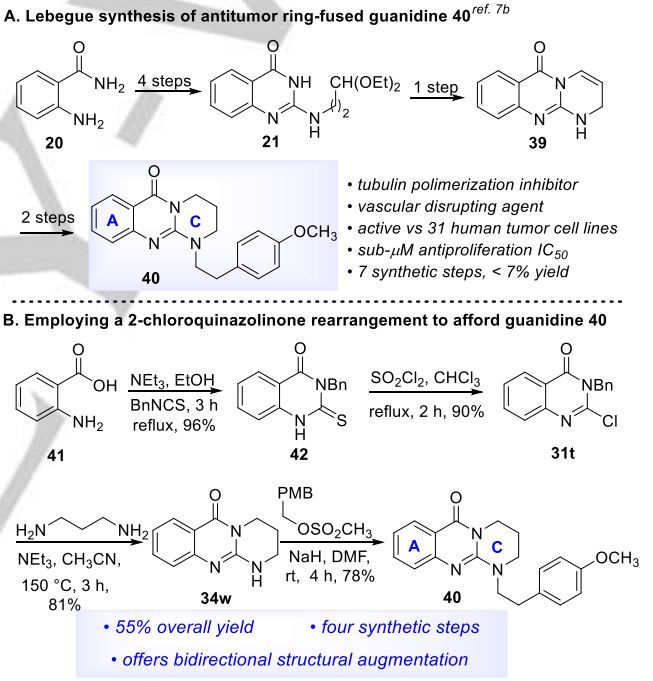
(**31a-m**) were obtained in 66–86% yield. Ring-fused guanidines with N^1-Et (**38n**), N^1-Bn (**38o**) and tetracyclic guanidine (±)-**38p** were obtained in good yield when differentially substituted diamines were employed. Other highlights included the incorporation of chiral diamines, generating the corresponding C3-substituted products **38q** (75%) and **38r** (73%). Ring-fused N^1-H-guanidines devoid of an N^1-alkyl substituent were also generated when tethered primary amines were used. Specifically, N^1-H tricyclic guanidine **38s** and tetracyclic guanidine **38t** were obtained in 53% and 68% yield, respectively, though in these cases, yields were improved when three equivalents of the diamine was used. Synthesis of the 6.6.6-tricylic system of **38u** was initially achieved in 23% yield from *N*-methyl-1,3-propanediamine and **31a**; however, we anticipated that the phenyl appendage on the amide-like nitrogen of the quinazoline core may sterically interfere with the reaction. To test this, **31a** was replaced in the reaction with *N*-benzyl derivative **31t**, revealing a 30% improvement in yield of **38u**. In accord with the proposed mechanism and Table 3 results from diamines bearing bulky *N*-substituents, use of *N*-cyclohexylethane-1,2-diamine **32t** or *N*-isopropylethane-1,2-diamine **32u** did not afford ring-opened or ring-fused guanidines. In fact, these reactions revealed elusive yet informative intermediates **33d** and **33e**, the latter of which was isolated in 76% yield (Scheme 4).



Scheme 4. Characterization and isolation of unrearranged 2-aminoquinazolinone intermediates.

The utility of this method was further demonstrated for each of the two accessible guanidine structural classes. Plasma stability is one optimization parameter in our antiviral medicinal chemistry program.[16a] Mouse plasma stability of ~65% has been generally observed for a series of benzamidines, and we questioned the stability of the benzamidine functionality towards enzymatic hydrolysis *in vivo*. As the twisted-cyclic guanidines described herein are structural isosteres of our lead benzamidines, we tested the stability of select guanidine analogs and observed improved mouse plasma stability ranging from 78-100%. Given that these compounds have yet to be optimized for antiviral inhibition, we were pleased to observe a marked improvement in plasma stability compared to the corresponding amidine predecessors. These compounds are now part of a separate antiviral development arm that will be part of a future publication. The transformation was also advantageous in building bioactive, ring-fused guanidines. For instance, compound **40** is a tubulin polymerization inhibitor, vascular disrupting agent, and inhibited growth of 31 human cancer cell lines representing nine cancer cell types (Scheme 5A).[7b] We speculate that the synthesis of **40**, accomplished in < 7% overall yield and requiring 7 steps from anthranilamide **20**, has possibly impeded structure-activity relationship (SAR) exploration. We recognized that **40** might be more efficiently prepared and analogs thereof may be more expediently explored using the 2-chloroquinazolinone rearrangement. To assess this approach, the requisite *N*-benzyl-2-chloroquinazolinone **31t** was generated from anthranilic acid **41** in 86% yield over 2 steps (Scheme 6B). In the key rearrangement step, **31t** was treated with 1,3-diaminopropane (10 equiv.) to afford N^1-H tricyclic guanidine **34w** in 81% yield after microwave irradiation at 150 °C for 3 hours. Subsequent *N*-alkylation of **34w** with 4-methoxyphenethyl methanesulfonate afforded the desired guanidine **40** in 78% yield. Thus, guanidine **40** was obtained in four steps and 55% overall yield. Based on the previous substrate scope investigation in Table 3, this method permits SAR investigation of the terminal rings (rings A and C) of this guanidine scaffold, possibly revealing new development opportunities. Furthermore, all of the compounds between the two guanidine classes prepared by this method have been submitted for extensive screening to elucidate additional activity of interest.



Scheme 5. A. Reported synthesis of antitumor ring-fused *N*-acyl guanidine **40** and (B) a high-yielding, analog-enabling total synthesis of **40** using our domino 2-choroquinazolinone rearrangement/intramolecular cyclization.

Conclusions

Herein we describe a highly efficient rearrangement of 2-chloroquinazolin-4(3*H*)-ones that generates either twisted-cyclic or ring-fused *N*-acylguanidines in a single operation. Moreover, the reaction pathway is exquisitely controlled by the presence of a primary versus secondary amine in the diamine reagent with which the 2-chloroquinazolinone is paired. Use of secondary diamines afford exclusively twisted-cyclic guanidines while diamines bearing at least one primary amine generate twisted-cyclic guanidines *in situ* that subsequently undergo intramolecular

ring closure to afford ring-fused *N*-acylguanidines. Both reaction pathways showed broad structural substrate tolerance, generating 32 novel twisted-cyclic guanidines in up to 96% yield and 23 ring-fused *N*-acylguanidines in up to 90% yield. The transformation benefits from demonstrated scalability and the use of accessible and diversely substituted starting materials which are commercially obtained or derived from anthranilic acid in two high-yielding steps. Twisted-cyclic guanidines have found utility in our antiviral program, offering exceptional plasma stability compared to our related benzamidine scaffold. The method was also deployed in the expedient synthesis of a known antitumor agent containing the ring-fused *N*-acylguanidine scaffold. Hence, the desired ring-fused guanidine **40** was synthesized in only four steps and in 55% yield which is three steps shorter and with an 8-fold increase in yield compared to the published report.[7b] The divergent yet tractable nature of this transformation to generate two distinct classes of bioactive guanidines with high efficiency is expected to facilitate the development of new guanidine-containing frameworks.

Experimental Section

For a detailed description of the synthesis of starting materials and final products, see the Supporting Information.

2-((1,3-dimethylimidazolidin-2-ylidene)amino)-*N*-phenylbenzamide (34a) To a microwave vial was added 2-chloroquinazolin-4(3*H*)-one (**31a**, 51 mg, 0.2 mmol), *N*,*N*'-dimethylethylenediamine (**32a**, 0.03 mL, 0.26 mmol), NEt_3 (0.085 mL, 0.6 mmol) and CH_3CN (2 mL). After heating the mixture under microwave irradiation at 150 °C for 2 h, the cooled mixture was diluted with CH_2Cl_2 (20 mL) and washed with saturated $NaHCO_3$ solution (15 mL). The aqueous layer was then washed with CH_2Cl_2 (20 mL). The combined organic layer was dried with $MgSO_4$, filtered and purified by flash column. Eluent: 40% - 60% ethyl acetate/hexane; yield: 57 mg, 92%; white solid, m.p. 165-167 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.33 (s, 1H), 8.27 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.78 – 7.67 (m, 2H), 7.33 (t, *J* = 7.9 Hz, 2H), 7.30 – 7.23 (m, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 7.01 – 6.92 (m, 1H), 6.83 (dd, *J* = 8.2, 2.1 Hz, 1H), 3.41 (s, 4H), 2.75 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.4, 157.4, 148.3, 139.6, 131.5, 131.1, 129.0, 124.1, 123.3, 122.9, 120.5, 120.1, 48.5, 35.3. HRMS (ESI) m/z for $C_{18}H_{21}N_4O^+$ $(M+H)^+$, 309.1710 (Calc.), found 309.1713.

1-methyl-2,3-dihydroimidazo[2,1-*b*]quinazolin-5(1*H*)-one (38a) Following the procedure for **34a**, used **31a** (51 mg, 0.2 mmol), *N*-methylethylenediamine (**32k**, 0.023 mL, 0.26 mmol), NEt_3 (0.085 mL, 0.6 mmol) and CH_3CN (2 mL). Eluent: 50% - 95% ehyl acetate/hexane; yield: 35 mg, 86%; white solid, m.p. 177-178 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.56 (ddd, *J* = 8.5, 7.0, 1.6 Hz, 1H), 7.39 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.16 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 4.21 – 4.11 (m, 2H), 3.70 – 3.61 (m, 2H), 3.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3, 153.1, 151.0, 134.4, 126.6, 124.9, 122.7, 117.8, 47.1, 40.5, 31.9. HRMS (ESI) m/z for $C_{11}H_{12}N_3O^+$ $(M+H)^+$, 202.0975 (Calc.), found 202.0977.

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Conflicts of interest

There are no conflicts to declare.

Keywords: guanidine • twisted guanidine• quinazolinone • rearrangement • ring-fused guanidine

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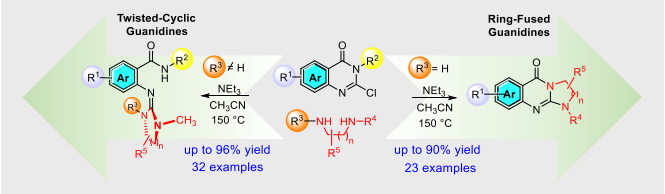

Two distinct guanidine structural classes were generated selectively via a 2-chloroquinazolinone rearrangement. The reaction either arrests at the twisted-cyclic guanidine stage or gives ring-fused *N*-acylguanidines via a domino rearrangement/intramolecular cyclization, depending on diamine substitution.

KEYWORDS: guanidine; domino; rearrangement; acylguanidine

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Divergent 2-Chloroquinazolin-4(3*H*)-one Rearrangement: Twisted-Cyclic Guanidine Formation or Ring-Fused *N*-Acylguanidines via a Domino Process