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A novel solid-phase synthesis of cyclic guanidines

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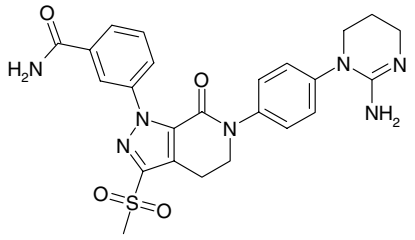
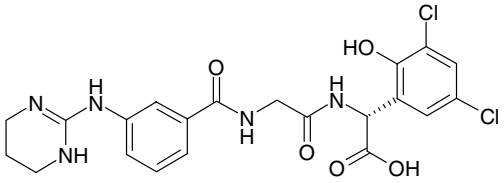
Abstract—We have developed a robust solid-phase approach to cyclic guanidines based on the Staudinger protocol. The synthetic sequence involves the reaction of the immobilized aza-Wittig reagents derived from the respective azidobenzoic acids with bifunctional amines. Convenient isolation and good yields of the desired products (34–84%) along with the diversity of the targeted molecules are distinctive features of the resultant library.

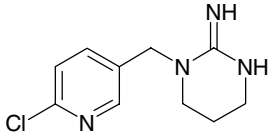
Guanidines are of considerable importance as physiologically active substances. The guanidine moiety is believed to mediate a variety of electrostatic interactions.[1] One of the proteolythic mechanisms involved in in vivo degradation of peptides is believed to be based on the terminal 'Arg-labeling' (*N*-End Rule).[2] Conformationally restricted guanidines are reported to display a broad spectrum of biological activities. Representative compounds include coagulation factor Xa inhibitors (A),[3] integrin $\alpha_V\beta_3$ (Vitronectin) antagonists (B),[4] and specific nicotinic $\alpha_4\beta_2$ agonists (C).[5]



A



B



C

There are a number of diverse routes to cyclic guanidines, however the search for a universal, high-yielding synthesis of these useful molecules is still ongoing.[6,7] In an effort to enrich the structural diversity of our internal screening libraries, we developed a novel solid support synthesis of compounds containing the cyclic guanidine moiety. Specifically, we selected a sequence based on the Staudinger reaction[8] to generate a polymer-bound aza-Wittig reagent of type **1**. Reagent **1** is readily converted into the respective carbodiimide **2** with a flexible alkyl chain bearing a terminal leaving group. Addition of amine and spontaneous cyclization of the resultant guanidine was expected to afford the desired molecule **3** (Scheme 1).

The synthetic sequence was performed on a solid support in order to (i) introduce diversity into the resulting library, and (ii) to minimize the loss of intermediates due to their water solubility or hydrolysis (Scheme 2). In the optimized reaction sequence, *m*- or *p*-azidobenzoic acid was immobilized on a bromo-Wang resin **4** to yield the expected polymer-bound esters **5** (1.72 mM/g loading, as determined by microanalysis for both *m*- and *p*-benzoic acids). Resin **5** was then treated with PPh_3

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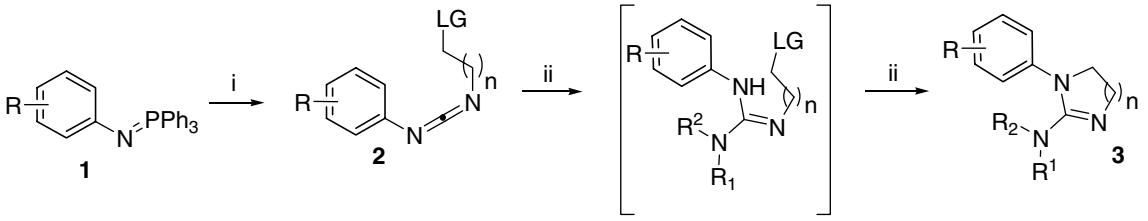
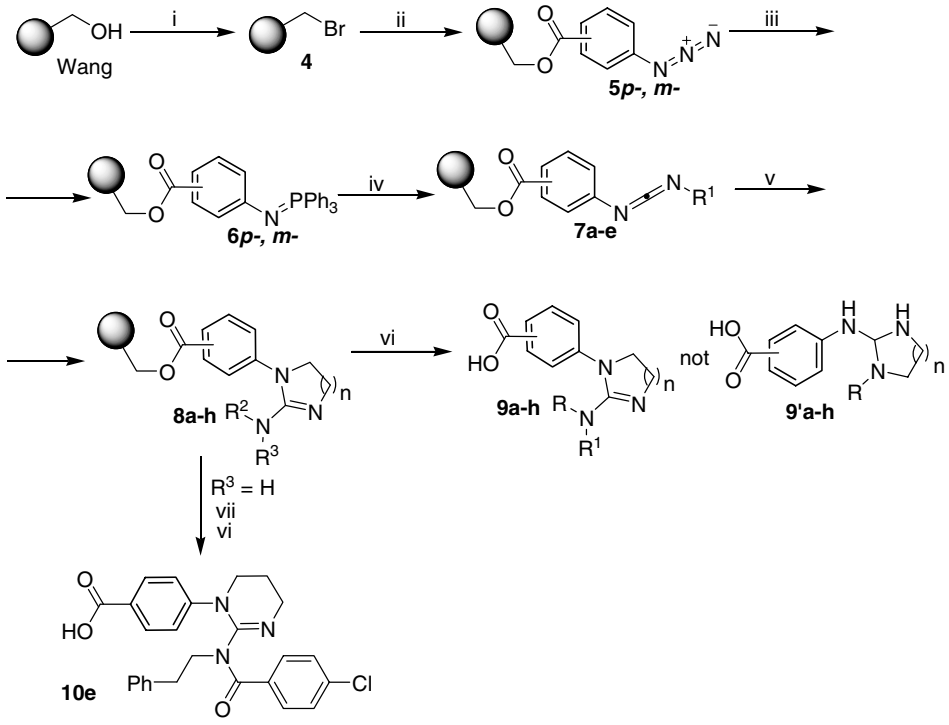


Scheme 1. Reagents: (i) O=C=N–$(CH_2)_n$LG; (ii) R^1R^2NH; LG = leaving group.

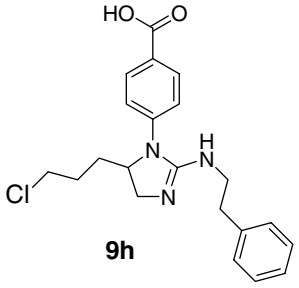


Scheme 2. Reagents and conditions: Ph_3P/CBr_4, DMF, rt; (ii) *m*- or *p*-azidobenzoic acid, Cs_2CO_3, DMF, 60 °C, 48 h; (iii) Ph_3P, THF, rt, 1 h; (iv) R^1NCO, THF, rt, 12–72 h; (v) $R^1 = (CH_2)_nHaI$; primary or secondary aliphatic amines, THF, rt, 4 h; (vi) 10% TFA in DCM, rt, 1 h; (vii) 4-Cl-C_6H_4COCl, 4 equiv, 0.25 N, DIPEA 4 equiv, 0.25 N, THF, rt, 4 h.

in THF at room temperature to afford the expected immobilized aza-Wittig products **6**. Polymer bound compounds **6** were subsequently reacted with 2-chloroethyl- or 3-chloropropropyl isocyanates in THF, followed by the reaction of the resulting carbodiimides **7a**–**d** with primary or secondary aliphatic amines to yield resins **8a**–**g**. These were cleaved with a 10% solution of TFA in CH_2Cl_2 to furnish the targeted cyclic amidines **9a**–**g** in 72–95% isolated yields. Additionally, immobilized cyclic guanidine **8e** was further acylated at the exocyclic nitrogen and cleaved with TFA to yield compound **10e** containing an additional diversity point.

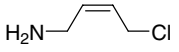
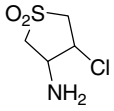
All crude materials (see Table 1) were collected, concentrated in vacuo and purified by HPLC to yield the desired materials in 95–99% purities, as measured by both UV (254 nm) and ELSD. We found that in general, the outcome of the synthetic sequence did not depend on the nature of the haloalkyl chain. Specifically, both 2-chloroethyl- and 3-chloropropyl derivatives afforded comparable yields of the targeted molecules. In addition, primary and secondary amines prompted a robust cyclization step and good yields of cyclic guanidines **9**. For the derivatives of primary amines, a characteristic splitting of the exocyclic CH_2 and NH groups ($J \sim 3$ Hz) has been observed confirming the expected chemical structures **9**.[9]

An alternative reaction sequence to prepare **9d**,**e** provided considerably lower yields of the targeted guanidines. Thus, the treatment of carbodiimides **7** derived from primary amines with in situ generated 2-chloro-

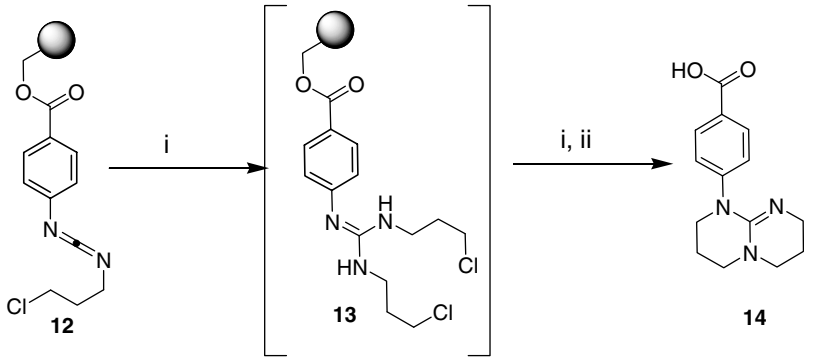


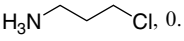
9h

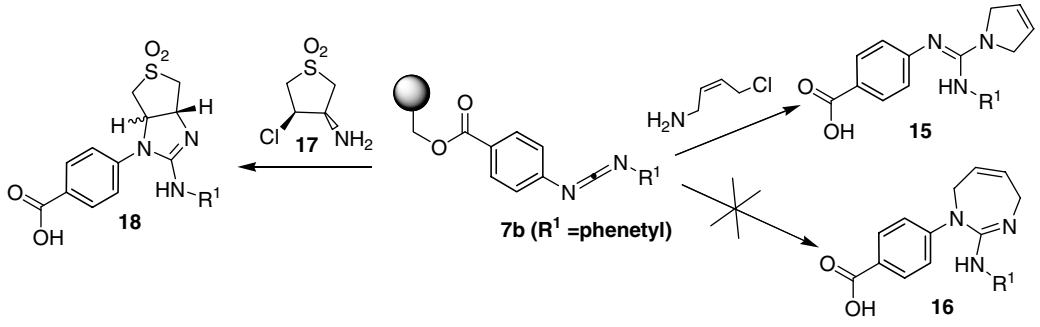
Table 1. Synthesis of cyclic guanidines **9a–h**, **10e**, **14**, **15**, **18**

Entry	Compound	Substitution of benzene ring	R^1	R^2R^3NH	M+1 (Da) retention time (254 nm) (min)	Crude purity UV 254 nm/ELSD (%)[a]	Yield[b] (%)
1	**9a**	*p*	$(CH_2)_3Cl$	1-Phenylpiperazine	365, 2.67	91/99	82
2	**9b**	*m*	$(CH_2)_3Cl$	1-Phenylpiperazine	365, 2.63	92/99	84
3	**9c**	*p*	$(CH_2)_2Cl$	Bn, H	296, 2.53	80/99	68
4	**9d**	*p*	$(CH_2)_3Cl$	Bn, H	310, 2.61	93/99	76
5	**9e**	*p*	$(CH_2)_2Cl$	$PhCH_2CH_2$, H	310, 2.65	85/99	65
6	**9f**	*p*	$(CH_2)_3Cl$	$PhCH_2CH_2$, H	324, 2.72	93/99	74[9]
11	**9g**	*p*	$(CH_2)_3Cl$	All, H	260, 2.13	95/99	80
8	**10e**	*p*	$PhCH_2CH_2$	$(CH_2)_2Br$	448, 2.93	90/98	52
7	**9e**	*p*	$PhCH_2CH_2$	$(CH_2)_2Br$	310, 2.63	61/87	48
9	**9d**	*p*	Bn	$(CH_2)_3Cl$, H	310, 2.61	55/92	53
10	**9h**	*p*	$PhCH_2CH_2$	$CH_2CHCl(CH_2)_3Cl$	386, 3.02	50/90	34
12	**14**	*p*	$(CH_2)_3Cl$	$(CH_2)_3Cl$, H	260, 2.08	70/90	49
13	**15**	*p*	Bn		322, 2.68 574, 3.16	70/85 10/15	37
14	**18**	*p*	$PhCH_2CH_2$		400, 2.57 400, 3.29	14/10 57/85	62[10]

[a] LC/MS spectra were recorded with a PE SCIEX API 150EX MS equipped with a turboion source, Shimadzu 10ADVP separation module with a UV (λ_{max} 215 and 254 nm) and ELSD detectors, using a C_{18} column (Inertsil ODS-3, 3 μm, 2×50 mm), elution started with water/acetonitrile (95:5, v/v) and ended with acetonitrile/water (95:5, v/v) and used a linear gradient at a flow rate of 0.5 mL/min and an analysis cycle time of 7 min.
[b] Isolated yields after prep-HPLC (purity >95%).



Scheme 3. Reagents and conditions: (i)  , 0.15 N, 8 equiv, DIPEA 0.15 N, 8 equiv in THF/DCM 1:1, rt, 18 h; (ii) 10% TFA in DCM, 30 min.



Scheme 4.

ethyl or 3-chloropropyl amines resulted in ca. 15–20% yield reduction for products **9**, probably due to low stability of chloro-substituted amines (Table 1, compare entries 5 and 7, 4 and 9). Reaction of a 2,5-dichloropent-

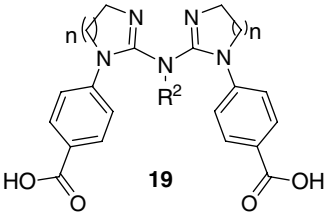


Figure 1.

ylamine (Table 1, entry 10) afforded the product **9h** of the 2-Cl substitution, with the 5-Cl substituent unmodified. Notably, the presence of a 3-chloropropyl chain in both isocyanate and amine moieties led to product **14** (Table 1, entry 12). This product is likely to be the result of a double addition of the amine to aza-Wittig reagent yielding **13** followed by a spontaneous cyclization of **13** to a bicyclic guanidine structure **14** (Scheme 3).

Reaction of **7b** derived from phenethylamine with *cis*-4-chloro-2-butenylamine furnished derivative **15** instead of **16** (Scheme 4). This outcome could be explained by the unfavorable thermodynamics for the formation of unsaturated seven-membered system in **16**. Similar observations were reported in the literature.[11] Reaction of **7b** with compound **17**[12] yielded the respective bicyclic derivative of imidazoline **18** in a 62% isolated yield (preparative HPLC, Table 1, entry 14).[13a,b]

In an effort to further optimize this solid-phase reaction protocol, we analyzed minor components of the reaction mixtures after TFA cleavage. Based on analytical data, structure **19** was assigned to the main side products (Fig. 1, content in crude mixtures 1–5% by UV 254 nm detection). These are likely to result from the cross-reaction of the amidines **8** derived from primary amines with the respective carbodiimides **7** under the reaction conditions.

In summary, we have developed a robust solid-phase approach to cyclic guanidines based on the Staudinger protocol. The synthetic sequence involves the reaction of the immobilized aza-Wittig reagents derived from the respective azidobenzoic acids with bifunctional amines. Convenient isolation and good yields of the desired products (34–84%) along with the diversity of the targeted molecules are distinctive features of the resultant library.

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9. Wang resin 50 g (2 mmol/g, 0.1 mol) was treated with 0.5 mol of Ph_3P and 0.5 mol of CBr_4 in DMF (up to total volume of 500 mL) at room temperature for 4 h and washed with DCM×2, DMF×2, IPA×2, DCM×2, IPA, DCM, hexanes and dried overnight on liophilizer.[14] The obtained resin was treated with 21.6 g (132 mmol) of 4-azidobenzoic acid, 70 mmol of Cs_2CO_3, and 70 mmol of KI in 200 mL of dry DMF at 60 °C for 48 h (periodical passing away of formed CO_2 was needed). Washing procedure was as follows: DMF×2, DMF–H_2O 1:1×2, H_2O×4, IPA×2, DCM, IPA, DCM, IPA. The obtained resin **5** was kept overnight on a filter with a vacuum pump, and then dried on high vacuum for 48 h. The yield was 62.4 g (64.5 theoretically). Treatment of resin 5 with 0.4 N solution of Ph_3P in dry THF for 2 h followed by washing with THF×2, DCM, MeOH, DCM, and hexanes afforded the azo-Wittig resin **6** in quantitative yield. Cleavage of this resin with 10% TFA in DCM for 30 min followed with LC–MS analysis showed *p*-azo-Wittig benzoic acid with excellent 99+% (by UV 254 nm) purity. Resin **6** was treated overnight with 5 equiv of 0.4 N solution of 3-chloropropylisocyanate in dry THF at room temperature, shortly washed with dry THF and reacted with 0.25 N (5 equiv) solution of phenetyl amine in THF for 18 h. After careful washing with DMF, H_2O, DMF, (MeOH–DCM)×5, hexanes, drying, and cleavage with 10% TFA in DCM for 30 min crude material showed 93% (UV 254 nm) purity by LC–MS analysis. After concentrating the obtained solution in vacuo, the remaining material was purified by prep HPLC to give the desired compound **9f** as a white solid. Yield 74%. ^{1}H NMR, δ, ppm (DMSO-d_6): 13.2 (br s, 1H), 8.44 (t, $J = 2.9$ Hz, 1H), 8.00 (d, $J = 8.4$ Hz, 2H), 7.20–7.41 (m, 6H), 6.98 (t, $J = 5.9$ Hz, 1H), 3.63 (t, $J = 5.9$ Hz, 2H), 3.40 (dt, $J = 2.9$, 5.9 Hz, 2H), 3.29–3.86 (m, 2H), 2.72–2.78 (m, 2H), 2.00–2.08 (m, 2H); ^{13}C NMR, δ, ppm: 166.7, 152.1, 144.4, 138.5, 131.2, 130.6, 129.0, 128.5, 127.5, 126.6, 49.6, 42.3, 38.6, 34.2, 20.9. ESI-TOF, MH+: found 324.1703, calcd 324.1706.
10. Selected analytical data for **18**: ^{1}H NMR, δ, ppm (DMSO-d_6, 2% TFA): 8.88 (s, 1H), 7.76 (d, $J = 8.8$ Hz, 2H), 7.44 (d, $J = 8.8$ Hz, 2H), 7.15–7.25 (m, 5H), 3.43–3.49 (m, 4H), 3.36–3.40 (m, 2H), 3.31 (t, $J = 7.2$ Hz, 2H), 2.72 (t, $J = 7.2$ Hz, 2H); ^{13}C NMR, δ, ppm: 167.8, 155.4, 145.5,

140.1, 131.1, 129.3, 129.0, 126.8, 123.4, 117.2, 73.0, 70.4, 70.4, 60.9, 41.3, 36.3; ESI-TOF found 400.1332, calcd 400.1326.
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