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Solid-phase synthesis of fused [2,1-*b*]quinazolinone alkaloids

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Abstract—Solid-phase synthesis of fused [2,1-*b*]quinazolinone alkaloids has been developed for the preparation of vasicinone and deoxyvasicinone by two approaches. The derivative of polymer-supported *p*-nitrophenyl carbonate was attached to anthranilic acid and then coupled with various bromo-lactams. This resin-linked bromo intermediate upon acetylation, hydrolysis and resin cleavage gave the cyclized [2,1-*b*]quinazolinones (vasicinone). Alternatively, resin-linked azido-benzoic acids were coupled with bromo-substituted lactams followed by cyclization in an aza-Wittig reductive cyclization process giving the bromo-substituted quinazolinone intermediates, with subsequent acetylation, hydrolysis and resin cleavage affording the fused [2,1-*b*]quinazolinones.

Combinatorial chemistry has become an extremely powerful technique for the generation of drug-like small organic molecule libraries in medicinal chemistry programmes.[1] Solid-phase organic synthesis (SPOS) is especially useful in creating large numbers of hit and lead compounds[2] in combinatorial libraries for use in high-throughput screening.[3] As a result, an increasing range and number of pharmaceutically useful heterocyclic compounds have been prepared.[4] In this investigation, we have developed new solid-phase strategies for synthesizing nitrogen-containing heterocyclic compounds based on fused [2,1-*b*]quinazolinones, employing Wang resin and polymer-supported (PS) 4-nitrophenyl carbonate linkers.

Vasicinone is a fused [2,1-*b*]quinazolinone alkaloid isolated from the aerial parts of *Adhatoda vacica* (family: Acanthacea; Sanskrit-Vasaka), which is an evergreen subherbaceous bush used extensively in indigenous medicine for treatment of colds, coughs, bronchitis and asthma.[5] The related alkaloids, (±)-vasicinone **1**, (±)-vasicine **3**, (±)-vasicinolone **4** and deoxyvasicinone **5** have also been isolated from the above types of plants[6] (Fig. 1).

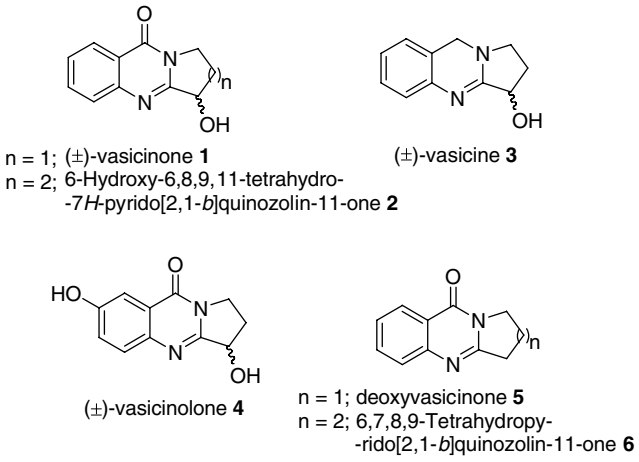

Figure 1.

The synthesis of vasicinone and deoxyvasicinone has been reported,[7] however, most methods were targeted towards the preparation of a racemate, including carbonylation catalyzed by palladium,[8] coupling *O*-methyl butyrolactam with anthranilic acid[9] and an intramolecular aza-Wittig reaction using PPh_3 and PBu_3.[10] (±)-Vasicinone has also been synthesized from deoxyvasicinone by bromination with NBS followed by acetylation with NaOAc–AcOH and lead tetraacetate free radical oxidation.[9] Notably, (3*S*)-(−)-vasicinone has been claimed to have better bronchodilation activity than the racemic form and has been recently synthesized[10] via asymmetric hydroxylation using the Davis reagent. In this laboratory we have developed a chemoenzymatic method employing a lipase-catalyzed resolution process of racemic vasicinone.[11] Recently, another

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approach was developed by Argade and co-workers[12] employing (*S*)-acetoxysuccinic anhydride as one of the starting materials. However, there are no reports of solid-phase synthesis for these compounds. Therefore, in this letter we report two strategies for the solid-phase synthesis of fused [2,1-*b*]quinazolinones for the first time. This will allow the method to be used for the production of libraries, as different anthranilic acid and azido benzoic acid derivatives could be anchored to the solid support and coupled to a diverse range of C-ring precursors.

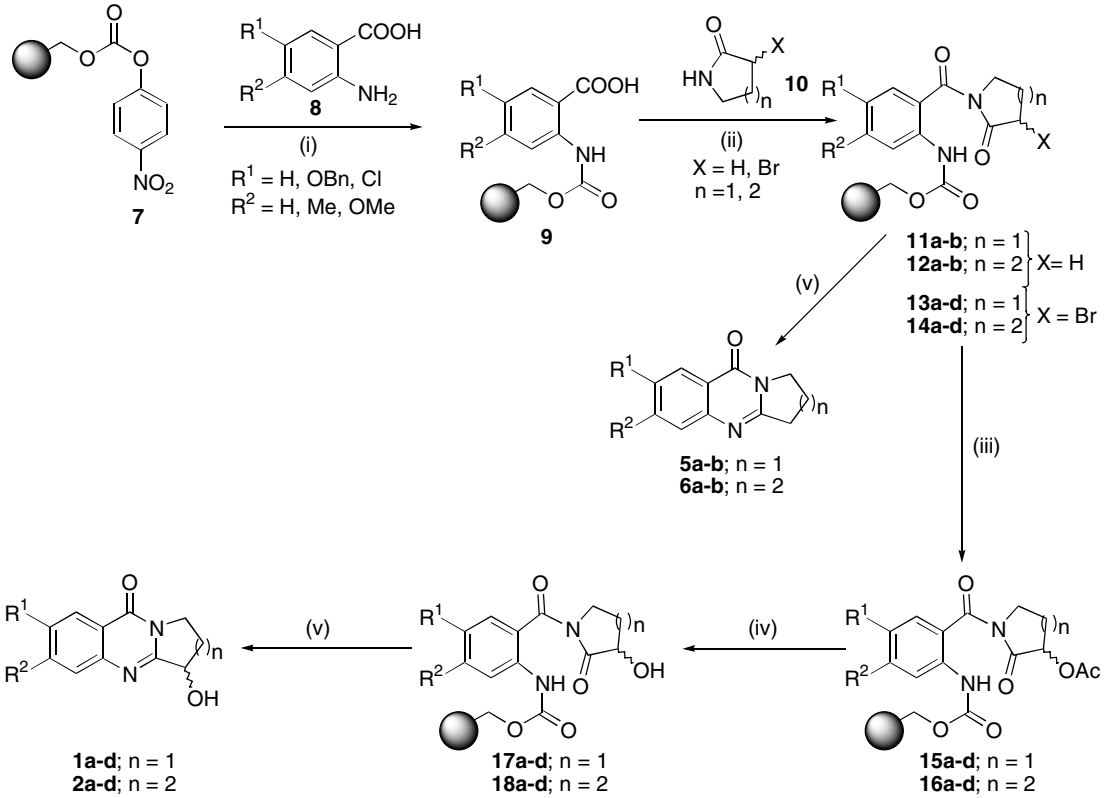
Table 1. Yields and molecular ions observed for fused [2,1-*b*]-quinazolinones

Entry	R^1	R^2	*n*	Yield (%)[a]	EIMS[b]
1a	H	H	1	88	202
1b	Me	H	1	85	216
1c	OMe	OBn	1	85	338
1d	H	Cl	1	88	236
2a	H	H	2	86	216
2b	Me	H	2	84	230
2c	OMe	OBn	2	85	352
2d	H	Cl	2	87	250
5a	H	H	1	90	186
5b	OMe	OBn	1	88	322
6a	H	H	2	87	200
6b	OMe	OBn	2	90	336
27a	OMe	OH	1	82	248
27b	OMe	OH	2	80	262

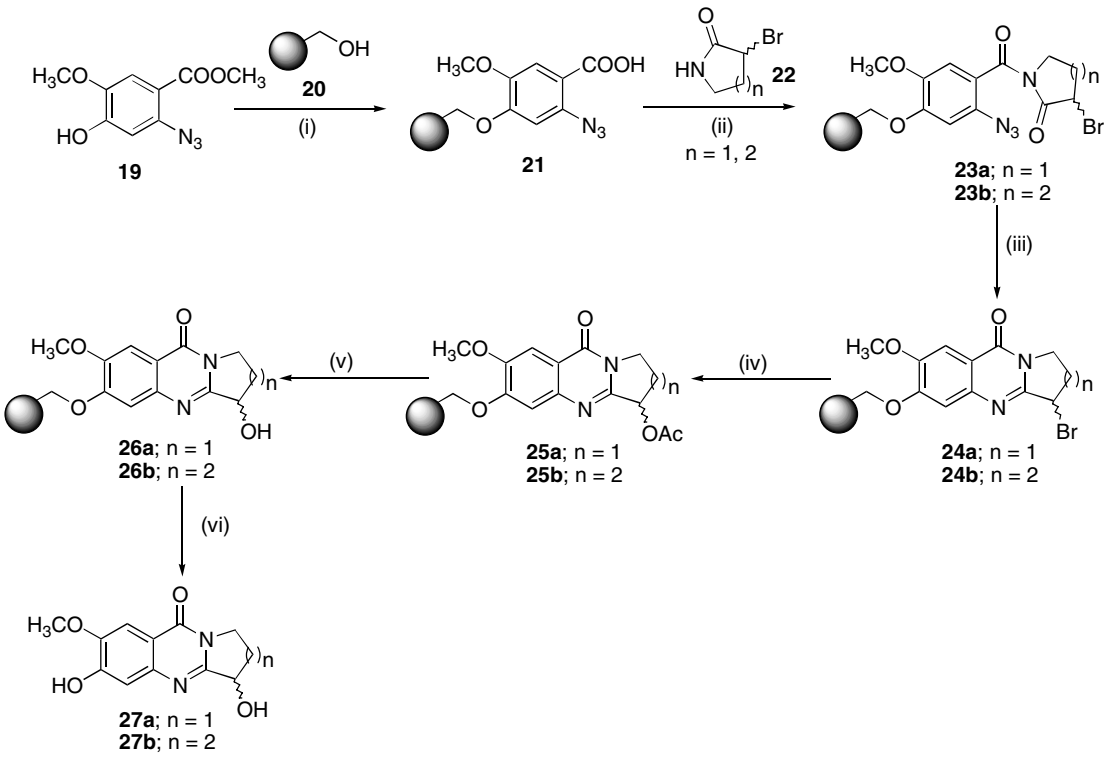
[a] Based on initial loading of the Wang resin and PS-*p*-nitrophenyl carbonate.
[b] Parent ion observed as (M^+).

A stirred solution of anthranilic acid **8** was coupled to the PS-*p*-nitrophenyl carbonate **7** using 1-hydroxybenzotriazole (HOBt) and diisopropylethylamine (DIPEA) in DMF–CH_2Cl_2 (1:2) to give **9**. Then, **9** was coupled to various lactams **10**[13] utilizing dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 to afford **11** and **13**. Bromides **13** were reacted with potassium acetate and catalytic 18-crown-6-ether in dry CH_3CN at reflux for 6 h or DMF at room temperature for 8 h to afford acetates **15**. These upon deacetylation with K_2CO_3 in THF–MeOH (1:1) gave **17**. Finally, **11** and **17** were treated with 50% TFA–CH_2Cl_2 (1:1) to effect cleavage from the resin followed by cyclization to produce [2,1-*b*]quinazolinones **1**[15] and **5**[16] in good yields as shown in Table 1. Similarly, (Scheme 2) the Wang resin was attached to methyl-2-azido-4-hydroxy-5-methoxybenzoate under Mitsunobu conditions,[14a,b] this upon hydrolysis and coupling with **22** gave **23** as indicated by IR spectra, which showed a strong azide stretching vibration in the range 2115 cm^{-1}. Azides **23** were cyclized by an aza-Wittig mediated reductive cyclization using triphenylphosphine (TPP) in dry toluene to give **24**. Intermediate **24** was converted into **27**[17] by employing reactions similar to those described in Scheme 1. These transformations were monitored by FT-IR spectroscopy of the resin beads.

In a typical synthesis, a suspension of PS-*p*-nitrophenyl carbonate **7** (1.00 g, 0.93 mmol/g, 100–200 mesh and 1% DVB) in CH_2Cl_2–DMF (2:1, 10 mL) was stirred for 30 min, then a solution of anthranilic acid **8** (0.64 g,



Scheme 1. Reagents and conditions: (i) HOBt, DIPEA, CH_2Cl_2–DMF (2:1), 6 h, rt; (ii) DCC, DMAP, CH_2Cl_2, 0 °C, 12 h, rt; (iii) KOAc, 18-crown-6-ether, CH_3CN, 80 °C, 6 h or DMF, 8 h, rt; (iv) K_2CO_3, THF–MeOH (1:1), rt, 6 h; (v) TFA, CH_2Cl_2 (1:1), 2 h.



Scheme 2. Reagents and conditions: (i) (a) TPP, DIAD, NMP, 16 h, rt; (b) 1 N NaOH, 1,4-dioxane, 100 °C, 12 h; (ii) DCC, DMAP, CH_2Cl_2, 12 h, 0 °C–rt; (iii) TPP, toluene, 3 h, rt; (iv) KOAc, 18-crown-6-ether, CH_3CN, 80 °C, 6 h or DMF, 8 h, rt; (v) K_2CO_3, THF–MeOH (1:1), 6 h, rt; (vi) TFA, CH_2Cl_2, (1:1) 1 h, rt.

4.70 mmol), HOBt (0.38 g, 2.80 mmol), DIPEA (0.97 mL, 5.50 mmol) in CH_2Cl_2–DMF (2:1, 10 mL) was added to the swollen resin and the mixture stirred at rt for 6 h. The derivatized resin **9** was then filtered, rinsed with DMF (2×15 mL), CH_2Cl_2 (2×15 mL), MeOH (2×15 mL), ether (2×15 mL) and dried in vacuo. To a suspension of resin **9** in CH_2Cl_2 (10 mL), DCC (0.77 g, 3.72 mmol) and DMAP (8 mg) were added at 0 °C and the reaction allowed to stir at the same temperature for 30 min. Lactam **10** (0.61 g, 3.72 mmol) in CH_2Cl_2 (5 mL) was added to the above reaction mixture, which was slowly stirred at rt for 12 h to gives **11** and **13**. This resin was then filtered and washed with CH_2Cl_2 (2×15 mL), MeOH–water (9:1, 2×15 mL), MeOH (2×15 mL) and ether (2×15 mL) and then dried in vacuo. To a suspension of resin **13** in dry CH_3CN (15 mL) or DMF (10 mL) was added KOAc (0.73 g, 7.44 mmol), and a catalytic amount of 18-crown-6-ether and the reaction mixture was slowly stirred at 80 °C for 6 h, or in DMF at rt for 8 h. On cooling, resin **15** was filtered, washed with CH_3CN (2×15 mL), DMF (2×15 mL), MeOH–water (8:2, 2×15 mL), MeOH (2×15 mL), CH_2Cl_2 (2×15 mL) and ether (2×15 mL) and then dried in vacuo. To resin **15** in THF–MeOH (1:1, 10 mL), K_2CO_3 was added (0.39 g, 2.80 mmol) and the slurry was stirred at rt for 6 h. The derivatized resin was then filtered and washed with water (2×15 mL), THF (2×15 mL), MeOH (2×15 mL), CH_2Cl_2 (2×15 mL) and ether (2×15 mL), then dried in vacuo. Finally, a suspension of resin **17** or **11** in (10 mL) TFA–CH_2Cl_2 (1:1) was stirred at rt for 2 h. This procedure was repeated to ensure a complete cleavage of the product from the resin. The combined supernatant was saturated with aqueous $NaHCO_3$ solution, the organic layer was then separated and dried over Na_2SO_4. This, upon evaporation in vacuo, afforded crude products **1** and **5**, which were purified by column chromatography (silica gel, 60–120 mesh) employing ethyl acetate–hexane (6:4).

In conclusion, we have demonstrated a solid-phase synthesis of fused [2,1-*b*]quinazolinones, namely vasicinone and deoxyvasicinone, for the first time. One of the methods involves a resin attached to an amino functionality while the other is an aza-Wittig reductive cyclization process. These methodologies are amenable to the generation of libraries with diversity in both the A- and C-rings to afford the fused [2,1-*b*]quinazolinones.

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15. Compound **1a**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.38 (d, 1H, $J = 8.24$ Hz), 7.83–7.72 (m, 2H), 7.62–7.52 (m, 1H), 5.35–5.14 (m, 2H), 4.58–4.37 (m, 1H), 4.23–4.05 (m, 1H), 2.87–2.63 (m, 1H), 2.56–2.34 (m, 1H); EIMS *m*/*z* 202 (M^+); HRMS calcd for $C_{11}H_{10}N_2O_2$ 202.0742, found 202.0745.
16. Compound **5a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.24 (dd, 1H, $J = 1.5$, 8.3 Hz), 7.70–7.57 (m, 2H), 7.52–7.38 (m, 1H), 4.21–4.16 (t, 2H, $J = 7.5$ Hz), 3.18–3.12 (t, 2H, $J = 7.5$ Hz), 2.34–2.24 (m, 2H); EIMS *m*/*z* 186 (M^+); HRMS calcd for $C_{11}H_{10}N_2O$ 186.0793, found 186.0789.
17. Preparation of compound **27a**: To a solution of methyl-2-azido-4-hydroxy-5-methoxybenzoate **19** (0.39 g, 4.00 mmol) in NMP (15 mL) was added Wang resin **20** (1 g, 0.8–1.0 mmol/g, 4-benzyloxybenzyl alcohol, polymer-supported; polystyrene, 2% crosslinked, 200–400 mesh), TPP (1.05 g, 4.00 mmol), DIAD (0.79 mL, 4.00 mmol) and the reaction mixture was slowly stirred at rt for 16 h. The derivatized resin was filtered, rinsed with THF (2×15 mL), MeOH (2×15 mL) and dried in vacuo. This resin-coupled ester was hydrolyzed with 1 N NaOH (5 mL) in 1,4-dioxane (10 mL) and refluxed for 12 h. Filtration, washing with water (3×15 mL), water–dioxane (1:9, 3×15 mL), MeOH (3×15 mL), CH_2Cl_2 (3×15 mL) and ether (3×15 mL) then drying in vacuo gave resin **21**. To a suspension of **21** in CH_2Cl_2 (10 mL), DCC (0.83 g, 4.00 mmol) and DMAP (8 mg) were added at 0 °C and the reaction allowed to stir at the same temperature for 30 min. Bromo-lactam **22** (0.67 g, 4.00 mmol) in CH_2Cl_2 (5 mL) was added, and the reaction mixture was slowly stirred at rt for 12 h to give **23a**. This resin was then filtered and washed with CH_2Cl_2 (2×15 mL), MeOH–water (9:1, 2×15 mL), MeOH (2×15 mL) and ether (2×15 mL) and then dried in vacuo. To resin **23a** in dry toluene (10 mL) was added TPP (1.31 g, 5.00 mmol) and the mixture allowed stirred for 5 h at rt to give reductive cyclized product **24a**. The resin was filtered, and washed with toluene (2×15 mL), CH_2Cl_2 (2×15 mL) and ether (2×15 mL), then dried in vacuo. To a suspension of resin **24a** in dry CH_3CN (15 mL) or DMF (10 mL) was added KOAc (0.79 g, 8.00 mmol) and a catalytic amount of 18-crown-6-ether and the reaction mixture was slowly stirred at 80 °C for 6 h, or in DMF at rt for 8 h. On cooling, resin **25a** was filtered, washed with CH_3CN (2×15 mL), DMF (2×15 mL), MeOH–water (8:2, 2×15 mL), MeOH (2×15 mL), CH_2Cl_2 (2×15 mL) and ether (2×15 mL), and then dried in vacuo. To resin **25a** in THF–MeOH (1:1, 10 mL), K_2CO_3 (0.42 g, 3.00 mmol) was added and the mixture was stirred at rt for 6 h. The derivatized resin **26a** was then filtered and washed with water (2×15 mL), THF (2×15 mL), MeOH (2×15 mL), CH_2Cl_2 (2×15 mL) and ether (2×15 mL), then dried in vacuo. Finally, a suspension of resin **26a** in (10 mL) TFA–CH_2Cl_2 (1:1) was stirred at rt for 1 h. This procedure was repeated to ensure a complete cleavage of the product from the resin. The combined supernatant was saturated with aqueous $NaHCO_3$ solution, the organic layer was then separated and dried over Na_2SO_4. This upon evaporation in vacuo afforded the crude product, which was purified by column chromatography (silica gel, 60–120 mesh) with ethyl acetate–methanol (95:5) to give **27a** in good yields as shown in Table 1. ^{1}H NMR (200 MHz, $CDCl_3$+DMSO) δ 7.47 (s, 1H), 7.02 (s, 1H), 5.34–5.31 (d, 1H, $J = 5.72$ Hz), 4.36–4.25 (m, 1H), 4.14–4.01 (m, 3H), 3.96 (s, 3H), 2.89–2.73 (m, 1H), 2.57–2.47 (m, 1H); EIMS *m*/*z* 248 (M^+); HRMS calcd for $C_{12}H_{12}N_2O_4$ 248.2368, found 248.2371.