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Solid-phase synthesis of [1,2,4]triazolo[3,4-*a*]phthalazine and tetrazolo[5,1-*a*]phthalazine derivatives

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Abstract—A general method is reported for the solid-phase synthesis of [1,2,4]triazolo[3,4-*a*]phthalazine and tetrazolo[5,1-*a*]phthalazine derivatives based on the cyclization of resin-bound chlorophthalazines **4** with various hydrazides or sodium azide. The resin-bound chlorophthalazines **4**, produced by nucleophilic aromatic substitution reaction of dichlorophthalazine with the secondary amine resins **2**, served as the key intermediate for subsequent triazolophthalazine resins **6** and tetrazolophthalazine resins **8**, which provided the desired products **7** and **9** in good yields and purities.

Solid-phase synthesis has emerged as a powerful technique in generating combinatorial libraries of small organic molecules useful for drug discovery.[1] Heterocyclic skeletons provide scaffolds on which pharmacophore can arrange to yield potent and selective drugs.[2] In this respect, phthalazine scaffold have shown its potential as a privileged structure for the generation of drug-like libraries in drug-discovery process.[3] Moreover, heterocyclic fused phthalazines have been found effective for the inhibitor of p38 MAP kinase,[4] selective binding of GABA receptor,[5] antianxiety drug,[6] antitumor agent,[7] high-affinity ligands to the $\alpha_2\delta$-1 subunit of calcium channel.[8] Therefore, many reports have been described in the solution-phase synthesis of heterocyclic fused phthalazine derivatives.[4–9] However, the solid-phase synthesis of heterocyclic fused phthalazines has been scarcely reported in the research field of drug-like library construction, as compared with their simple aromatic phthalazine derivatives. As a part of our research on drug discovery program, we needed to develop a facile and rapid solid-phase parallel approach for the construction of drug-like small organic molecules using various heterocycles.[10] Especially, we were interested in constructing heterocyclic fused phthalazine libraries on solid-phase to find novel hit compounds toward multiple biological targets.

Herein, we would like to report our finding about an efficient procedure for the synthesis of [1,2,4]triazolo[3,4-*a*]phthalazine and tetrazolo[5,1-*a*]phthalazine derivatives on solid-phase. The reaction sequence is illustrated in Scheme 1. We selected resin-bound chlorophthalazines **4** as the key intermediate for synthesis of these derivatives on solid-phase, since it can afford various heterocyclic fused phthalazine compounds and easily release final products from the solid support under 5% trifluoroacetic acid (TFA) condition.

As the first step, the resin-bound secondary amines **2** were prepared from acid sensitive methoxybenzaldehyde (AMEBA) resin and various primary amines by reductive amination in the presence of $NaBH(OAc)_3$ in DMF. Formation of the resin **2** was confirmed by the disappearance of the aldehyde carbonyl band at 1670 cm^{-1} by attenuated total reflection (ATR) FTIR on single beads. Resins **2** were then treated with 1,4-dichlorophthalazine **3** and triethylamine (TEA) in dimethylsulfoxide (DMSO) at 80 °C to give the resin-bound chlorophthalazines **4**. With the chlorophthalazine resin **4** in hand, we first examined the incorporation of resins **4** with substituted hydrazides **5** and TEA in xylene at 110 °C for the formation of [1,2,4]triazolo[3,4-*a*]phthalazine resins **6**. And subsequent treatment of the heterocyclic fused resins **6** with 5% TFA in DCM at rt for 3 h gave the desired

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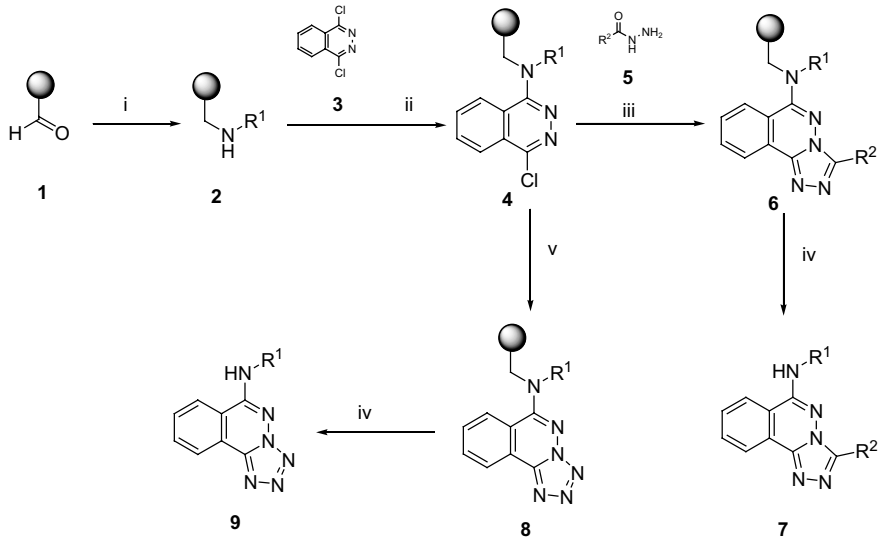
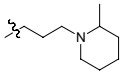


Scheme 1. Reagents and conditions: (i) R^1NH_2, $NaBH(OAc)_3$, AcOH, DMF, rt, 24 h; (ii) TEA, DMSO, 80 °C, 12 h; (iii) TEA, xylene, 110 °C, 24 h; (iv) TFA/DCM (5:95), rt, 3 h; (v) NaN_3, NMP, 120 °C, 24 h.

[1,2,4]triazolo[3,4-*a*]phthalazines **7**. As shown in Table 1, by using the sequence of reactions, we could obtain various [1,2,4]triazolo[3,4-*a*]phthalazines analogues in good four-step overall yields with high purities. In addition, Figure 1 shows the purity and LC/MS spectrum of representative product **7a**.[11]

For further investigation of potential of the resins **4**, we also examined the formation of tetrazolo[5,1-*a*]phthalazine derivatives **9** from the resin-bound chlorophthalazines **4** treated with NaN_3 in 1-methyl-2-pyrrolidinone (NMP) at 120 °C. The desired tetrazolo[5,1-*a*]phthalazines **9** were cleaved from the resins **8** with 5% TFA in DCM at rt for 3 h in good yields and purities as shown in Table 2. Figure 2 shows the purity and LC/MS spectrum of representative product **9a**.[12]

Table 2.

Product	R^1	Yield[a] (%)	Purity[b] (%)
9a		90	98
9b	Bn	65	100
9c	4-Cl–Bn	58	89
9d	2-Cl–Bn	49	83
9e	2-Me–Bn	78	93
9f	*n*-Pr	82	92
9g		64	59
9h		73	77

[a] Four-step overall yields from AMEBA resin **1** (loading capacity of the resin **1** is 1.2 mmol/g).
[b] All of the crude products were checked by LC/MS.

Table 1.

Product	R^1	R^2	Yield[a] (%)	Purity[b] (%)
7a		4-*tert*-Bu–Ph	73	97
7b		3-MeO–Ph	49	97
7c		3-F–Ph	57	95
7d		4-CF_3–Ph	41	90
7e		4-Cl–Ph	42	96
7f	Bn	Ph	62	82
7g	Bn	CH_2Ph	59	88
7h	4-Cl–Bn	2-Cl–Ph	40	74
7i	*n*-Pr	4-*tert*-Bu–Ph	61	92
7j	*n*-Pr	2-Cl–Ph	62	85

[a] Four-step overall yields from AMEBA resin **1** (loading capacity of the resin **1** is 1.2 mmol/g).
[b] All of the crude products were checked by LC/MS.

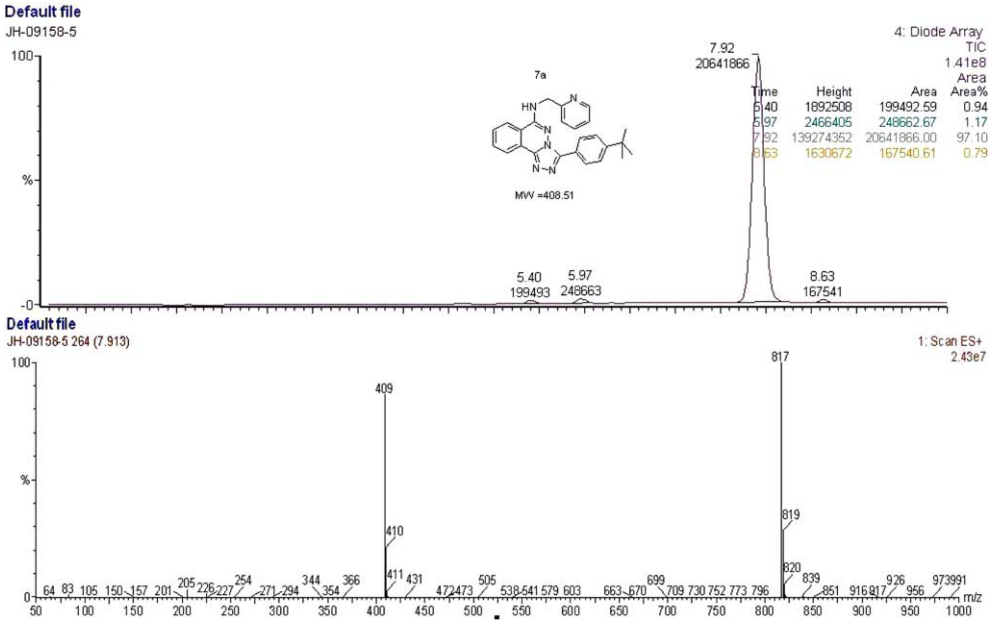


Figure 1. LC/MS spectrum of representative product **7a**.

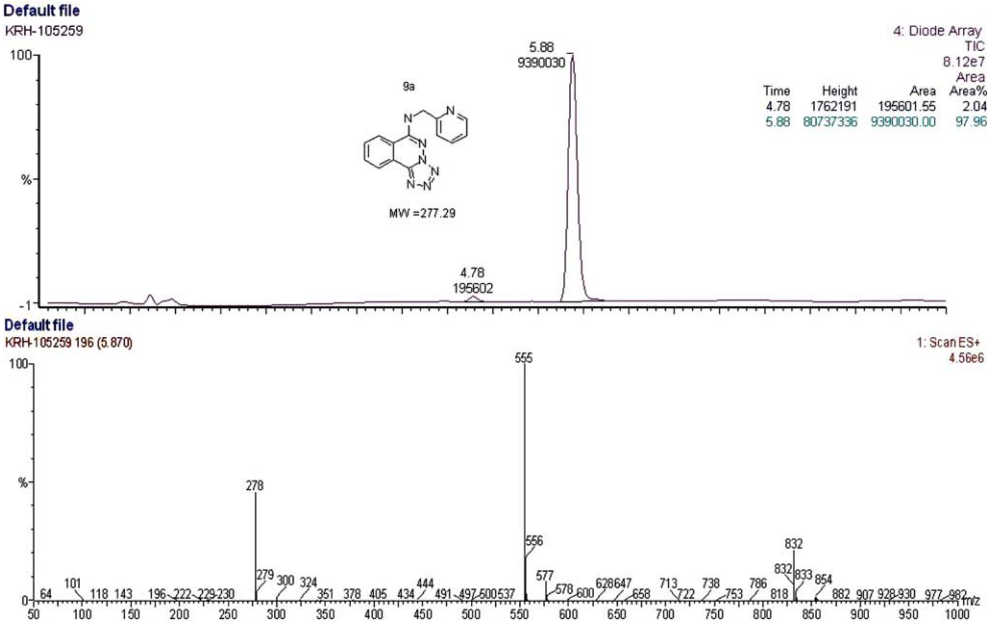


Figure 2. LC/MS spectrum of representative product **9a**.

In conclusion, we have demonstrated an efficient syn-thesis of [1,2,4]triazolo[3,4-*a*]phthalazines **7** and tetrazolo[5,1-*a*]phthalazines **9** using chlorophthalazine resins **4**. The chlorophthalazines **4** served as the key intermediate for the subsequent cyclization with various hydrazides or NaN_3 to provide the desired [1,2,4]triazolo[3,4-*a*]phthalazines **7** or tetrazolo[5,1-*a*]phthalazines **9** derivatives in good four-step overall yields and purities.

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11. *General procedure for the synthesis of [1,2,4]triazolo[3,4-a]phthalazines*: To a suspension of AMEBA resin **1** (10 g, 12 mmol, loading 1.2 mmol/g, 100–200 mesh, 1% DVB, Novabiochem) in DMF containing 1% AcOH were added successively 2-(aminomethyl)pyridine (3.7 mL, 36 mmol) and $NaBH(OAc)_3$ (7.6 g, 36 mmol). The reaction mixture was shaken at room temperature for 24 h, followed by washes with DMF (× 2), DCM (× 2), MeOH (× 2). The resulting resin **2a** was treated with 1,4-dichlorophthalazine (4.8 g, 24 mmol) and TEA (3.3 mL, 24 mmol) in DMSO at 80 °C for 12 h, followed by washes with DMF (× 2), DCM (× 2), MeOH (× 2). Chlorophthalazine resin **4a** (100 mg, 0.12 mmol) was cyclized with 4-*tert*-butylphenylhydrazide (69 mg, 0.36 mmol) in xylene in the presence of TEA (0.050 mL, 0.36 mmol) at 110 °C for 24 h to give [1,2,4]triazolo[3,4-*a*]phthalazine resin **5a**. Resin **5a** was cleaved with 5% TFA/DCM cocktail solution to give the corresponding desired product **7a**. *3-(tert-Butylphenyl)-6-(pyridin-2-ylmethylamino)[1,2,4]-triazolo[3,4-a]phthalazine* (**7a**): ^{1}H NMR (500 MHz, CD_3OD): δ 8.40 (br, 1H), 8.37 (m, 1H), 8.16 (m, 1H), 7.84–7.80 (m, 3H), 7.74–7.73 (m, 1H), 7.66 (m, 1H), 7.40 (m, 1H) 7.34–7.33 (m, 2H), 7.20 (m, 1H), 4.70 (s, 2H), 1.27 (s, 9H); ^{13}C NMR (125 MHz, CD_3OD): δ 158.3, 153.0, 151.8, 148.2, 147.9, 142.7, 137.4, 132.8, 130.9, 127.1, 125.1, 123.6, 123.1, 123.0, 122.9, 122.3, 121.1, 118.7; LC/MS (ESI) *m/z* 409 $(M+H)^+$.
12. *6-(Pyridin-2-ylmethylamino)tetrazolo[5,1-a]phthalazine* (**9a**): ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.09 (m, 1H), 8.75–8.73 (m, 1H), 8.58–8.51 (m, 2H), 8.18 (m, 1H), 8.11–8.07 (m, 2H), 7.84 (m, 1H), 7.66 (m, 1H), 5.80 (br, 1H), 4.99 (d, 2H, J = 5.6 Hz); ^{13}C NMR (125 MHz, DMSO-d_6): δ 156.8, 154.0, 146.1, 142.5, 140.6, 134.6, 133.0, 125.4, 124.9, 124.7, 124.1, 122.3, 120.5, 44.8; LC/MS (ESI) *m/z* 278 $(M+H)^+$.