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Solid-phase synthesis of 3,4-dihydro-2(1*H*)-quinazolinones and 3,4-dihydro-1*H*-quinazolin-2-thiones

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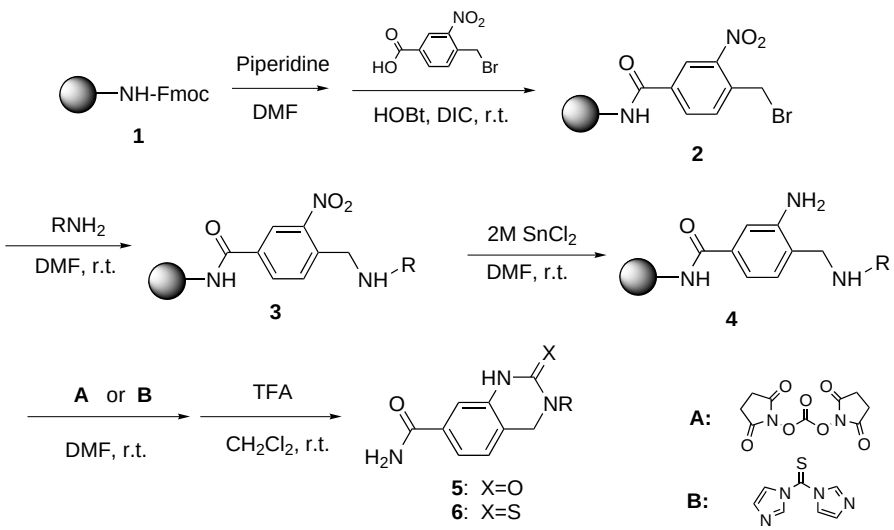
Abstract—The solid-phase synthesis of 3,4-dihydro-2(1*H*)-quinazolinones and 3,4-dihydro-1*H*-quinazolin-2-thiones is described. Starting from Rink resin, acylation with 4-bromomethyl-3-nitrobenzoic acid and amination with primary amines, reduction with tin chloride and cyclization, the desired 3,4-dihydro-2(1*H*)-quinazolinones and 3,4-dihydro-1*H*-quinazolin-2-thiones have been synthesized in good yield and high purity.

Solid-phase organic synthesis of heterocyclic compounds has become a focal point of combinatorial chemistry in the drug discovery process due to its speed and versatility at generating a large number of drug-like compounds.[1] A wide variety of quinazolinones have been shown to possess CNS depressant,[2] analgesic,[3] antibacterial,[4] and anti-HIV activities,[5] which allow this class of heterocyclic compounds to be of interest for combinatorial library synthesis. Due to their wide range of biological activities, a variety of synthetic routes leading to quinazolinones in solution phase have been well developed.[5] To date, only a few solid-phase syntheses of quinazolinones have been published.[6] However, a solid-phase synthesis of 3,4-dihydro-2(1*H*)-quinazolinones has not yet been reported. In this paper, we wish to describe a straightforward solid-phase synthesis to generate a diverse set of 3,4-dihydro-2(1*H*)-quinazolinones and 3,4-dihydro-1*H*-quinazolin-2-thiones. This method is mild, efficient, affords high yield and purity, and is suitable for automated parallel synthesis.



Scheme 1.

Keywords: combinatorial chemistry; solid-phase synthesis; 3,4-dihydro-2(1*H*)-quinazolinones; 3,4-dihydro-1*H*-quinazolin-2-thiones.
* Corresponding author. Tel.: 1-609-860-0700; fax: 1-609-860-0781; e-mail: qun.sun@pharma.com

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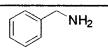
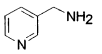
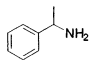
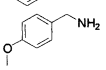
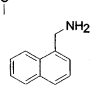
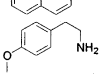
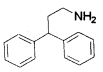
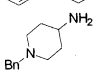
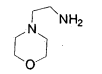
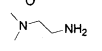
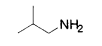
Table 1. Purity and yield of 3,4-dihydro-2(1*H*)-quinazolinones and 3,4-dihydro-1*H*-quinazolin-2-thiones

Entry	R-NH_2	Product (X=O)	Purity[a]	Yield[b]	Entry	Product (X=S)	Purity[a]	Yield[b]
1		**5a**	71%	92%	**12**	**6a**	87%	88%
2		**5b**	95%	95%	**13**	**6b**	78%	91%
3		**5c**	76%	85%	**14**	**6c**	89%	81%
4		**5d**	70%	86%	**15**	**6d**	79%	72%
5		**5e**	85%	70%	**16**	**6e**	66%	75%
6		**5f**	75%	73%	**17**	**6f**	69%	79%
7		**5g**	72%	81%	**18**	**6g**	60%	79%
8		**5h**	60%	100%	**19**	**6h**	72%	97%
9		**5i**	95%	71%	**20**	**6i**	82%	89%
10		**5j**	92%	89%	**21**	**6j**	60%	80%
11		**5k**	90%	71%	**22**	**6k**	80%	83%

a: Purity was determined by HPLC analysis of crude products. Products show satisfactory NMR and MS data, which are consistent with the proposed structure.
b: The crude yields were based on weight of crude samples and were relative to the initial loading.

As outlined in Scheme 1, the polystyrene-Rink-NH_2 resin was initially prepared from the polystyrene-Rink-NH-Fmoc using a standard procedure.[7,8] The resulting Rink-NH_2 resin was treated with 4 equiv. of 4-bromomethyl-3-nitrobenzoic acid in the presence of 4 equiv. of 1,3-diisopropylcarbodiimide (DIC) and 4 equiv. of 1-hydroxy-benzotriazole hydrate (HOBt) in DMF. The mixture was agitated at room temperature for 5 h to give resin **2**, which is commonly used as a photocleavable linker in solid-phase synthesis.[7] However, in our case, resin **2** was applied as a scaffold rather than a photocleavable linker. Amination of bromide resin **2** was performed with 10 equiv. of primary amine in DMF, followed by reduction with 2 M tin chloride to afford resin **4**, which was split into two portions for the next cyclization reaction. Quality control of resin **4** was performed by cleavage of the scaffold from resin (TFA) and subsequent analysis (LC/MS).

One portion of resin **4** was treated with *N*,*N*′-disuccinimidyl carbonate **A** at room temperature overnight. After cleavage with TFA in CH_2Cl_2 for 1 h, the desired product **5** was obtained. Meanwhile, the other portion was treated with 1,1′-thiocarbonyldiimidazole **B** under the same conditions to obtain the desired product **6**. The purity of the products was determined by RP-HPLC and ranged from 60 to 95% (Table 1). The correct molecular weight was confirmed by mass spectrometry (LC–MS with an electrospray sample inlet system). Structures were further confirmed by ^1H and ^{13}C NMR spectroscopy.[9]

In summary, we have developed a new and straightforward solid-phase synthesis of 3,4-dihydro-2(1*H*)-quinazolinones and 3,4-dihydro-1*H*-quinazolin-2-thiones in good yield and high purity. This methodology could be ideally suited for the construction of large combinatorial libraries.

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8. General procedures for preparation of 3,4-dihydro-2(1*H*)-quinazolinones and 3,4-dihydro-1*H*-quinazolin-2-thiones: **Deprotection of Fmoc group**: Polystyrene-Rink-NH-Fmoc resin (2.5 g, 2.30 mmol) was suspended in 20% piperidine in DMF (30 mL) and agitated at room temperature for 2 h. The reaction mixture was filtered and the resin was washed [(DMF, MeOH, CH_2Cl_2) (3×30 mL each)] and dried in vacuum to afford a fresh PS-Rink-NH_2 resin. **Acylation with a carboxylic acid**: The above PS-Rink-NH_2 resin (2.30 mmol) was suspended in DMF (30 mL), followed by the addition of 4-bromomethyl-3-nitrobenzoic acid (2.15 g, 9.2 mmol), DIC (1.44 mL, 9.2 mmol) and HOBt (1.25 g, 9.2 mmol) at room temperature. The reaction mixture was agitated for 12 h at room temperature. Then the resin was filtered, washed [(DMF, MeOH, CH_2Cl_2) (3×30 mL each)] and dried. **Amination of bromide 2**: The above resin was split to 12 portions and each portion (1 equiv.) was suspended in DMF (2 mL), followed by the addition of the selected primary amine (10 equiv.) at room temperature. The reaction mixture was agitated overnight at room temperature. Then the resin was filtered, washed [(DMF, CH_2Cl_2) (3×2 mL each)] and dried. **Reduction with tin chloride**: To the above resin was added 2 M $SnCl_2$ in DMF (2 mL) and agitated for 24 h at room temperature. Then the resin was filtered, washed [(DMF, CH_2Cl_2) (3×2 mL each)] and dried for the next step. **Cyclization of resin 4**: The above resin was split into two portions and one portion (1.0 equiv.) was suspended in DMF (1.5 mL), followed by the addition of **A** (8.0 equiv.) at room temperature. The reaction mixture was agitated overnight at room temperature. The resin was then filtered, washed [(DMF, MeOH, CH_2Cl_2) (3×2 mL each)] and dried for cleavage. **Cleavage with TFA**: The above resin was suspended in CH_2Cl_2 (0.75 mL), followed by the addition of TFA (0.75 mL) at room temperature. The reaction mixture was agitated for 1 h at room temperature. Then the resin was filtered, washed with CH_2Cl_2 (2×1 mL each) and the filtrate evaporated to afford the desired 3,4-dihydro-2(1*H*)-quinazolinones **5**. The synthesis of the desired 3,4-dihydro-1*H*-quinazolin-2-thiones **6** was performed using the same procedure of cyclization of resin **4** with **B** instead of **A**, followed by cleavage with TFA.
9. Analytical data for compound **5e**: ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.56 (s, 1H), 8.22 (m, 1H), 7.97 (m, 1H), 7.90 (dd, $J=1.7$, 7.4 Hz, 1H), 7.86 (m, 1H), 7.52 (m, 4H), 7.31 (m, 1H), 7.29 (s, br, 2H), 7.05 (d, $J=4.4$ Hz, 1H), 5.03 (s, 2H), 4.34 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 168.4, 154.0, 138.4, 135.2, 134.4, 133.2, 129.5, 129.0, 127.3, 127.2, 126.8, 126.4, 126.3, 124.4, 121.3, 120.7, 113.7, 48.2, 48.0; MS (ESI) m/z for $C_{20}H_{17}N_3O_2$ (MH^+): 332. Compound **6h**: ^{1}H NMR (400 MHz, CD_3OD): δ 7.28 (m, 8H), 7.10 (d, $J=1.52$ Hz, 1H), 6.99 (d, $J=7.9$ Hz, 1H), 5.52 (m, 1H), 4.28 (s, 2H), 4.10 (s, 2H), 3.35 (m, 3H), 2.89 (m, 2H), 1.94 (m, 4H); ^{13}C NMR (100 MHz, CD_3OD): δ 178.5, 170.4, 135.3, 134.9, 131.2, 130.2, 129.4, 125.8, 122.5, 121.9, 112.6, 61.2, 55.1, 51.8, 43.3, 25.5; MS (ESI) m/z for $C_{21}H_{24}N_4OS$ (MH^+): 381; HPLC profile generated on an Eclipse XDB-C18 rapid resolution 4.6×50 mm column with a gradient of 85:15 to 10:90 of 0.1% TFA:acetonitrile with 0.1% TFA and UV detection at 260 nm.