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Solid-phase synthesis of 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-thiones and 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-ones

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Abstract—An efficient approach for the synthesis of 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-thiones and 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-ones on solid phase has been developed. The reaction conditions were readily amenable and the products were obtained in good yields and purities after their cleavage from the resin.

1. Introduction

Since Merrifield introduced the concept of solid-phase synthesis,[1] solid-phase organic synthesis has become a powerful approach for the combinatorial and the parallel rapid synthesis of acyclic and heterocyclic compounds.[2] Substituted heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly useful as therapeutic agents. As a result, an increasing range and number of pharmaceutically useful heterocyclic compounds have been prepared using solid-phase methodology.[2] This approach permits the rapid synthesis of large numbers of individual compounds, as well as mixture-based combinatorial libraries in a short time frame and facilitates their use in high-throughput screening.[3] The design and synthesis of novel scaffolds as core structures for the library generation of small molecules on solid phase is an essential step in accessing a wide variety of structurally complex derivatives. Quinazoline compounds have been well-recognized for their pharmacological properties such as anticonvulsant,[4,5] sedative, antihypertensive,[6] vasodilator,[7] antiinflammatory,[8] antibiosis,[9] phosphodiesterase inhibitors,[10] and fibrinogen receptor antagonists.[11]

The imidazoquinazoline derivatives such as 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-thiones and 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-ones (Fig. 1) have been reported as biologically active inhibitors of (cCMP)-specific phosphodiesterase[12] and receptor tyrosine kinases.[13] The compounds were also useful for treating or mitigating cardiovascular diseases[12a,14] such as thrombosis, angina pectoris, hypertension, arteriosclerosis, and asthma.

As a part of our ongoing efforts directed towards the solid-phase synthesis of heterocyclic compounds and the generation of combinatorial libraries of organic compounds,[3] we report here an efficient approach for the solid-phase synthesis of 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]-quinazolin-2(3*H*)-thiones and 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-ones from 4-chloro-7-fluoro-6-nitroquinazoline scaffold as the core structure.[15]

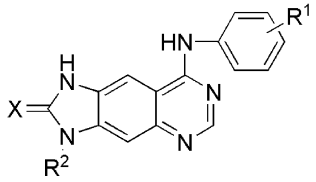

Figure 1. 3-Alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-thiones (X = S). 3-Alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-ones (X = O).

Keywords: Solid-phase synthesis; Imidazoquinazoline derivatives; Scaffold approach.
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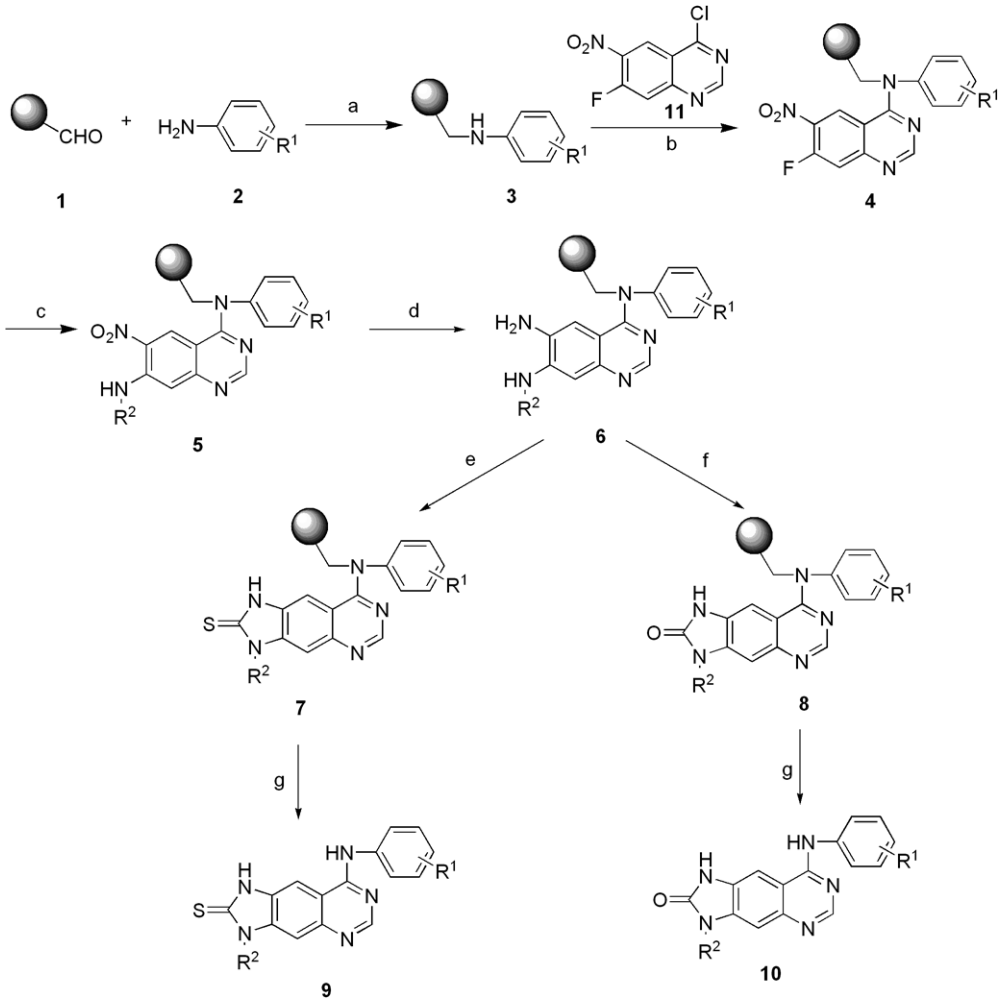
The parallel solid-phase synthesis of these compounds was carried out on the solid phase using the 'tea-bag' methodology. The reaction sequence is illustrated in Scheme 1.

Starting from 4-(4-formyl-3-methoxyphenoxy)butyryl AM resin **1**, in the presence of $NaBH_3CN$ in DMF, an arylamine was attached to the resin by reductive amination. The resin-bound arylamine **3** was then reacted with 4-chloro-7-fluoro-6-nitroquinazoline **11** scaffold to yield the corresponding chemoselective resin-bound quinazoline **4**, which was then treated with an alkylamine to give resin-bound compound **5**. The resin-bound compound **6** was formed through the reduction of resin-bound compound **5** by tin chloride in DMF. Thionylation of resin-bound compound **6** with CS_2 in THF afforded resin-bound compound **7**. Carbonylation of resin-bound compound **6** with triphosgene in DCM afforded resin-bound compound **8**. The desired 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-thiones **9** or 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-ones **10** were obtained in good yield and purity after the cleavage of resin-bound compound **7** or **8** by using TFA/DCM (1:1). The products were characterized by electrospray LC–MS, ^1H NMR and ^{13}C NMR. The results are summarized in Table 1 (individual 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-thiones) and Table 2 (individual 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-nes).

From the results of Tables 1 and 2, the yields and purities of products **9** and **10** were found to depend on the nature of the substituent R^1 of arylamines **2**. Arylamines bearing electron-donating groups and aniline gave satisfactory results. However, arylamines with electron-withdrawing groups (4-trifluoromethylbenzenamine and 4-chlorobenzenamine; Table 1, entries 14 and 15) gave low yields. The steric effect was also examined. When *o*-methyl aniline was used as the first building block, it gave low yield (Table 1, entry 16). Thus, arylamines bearing electron-withdrawing groups or *ortho*-substituents were excluded from use as building blocks for



Scheme 1. Solid-phase synthesis of 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-thiones and 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-ones. Reagents and conditions: (a) $NaBH_3CN$ (10 equiv, 0.1 M) in DMF/AcOH (99:1), rt, 24 h; (b) 4-chloro-7-fluoro-6-nitroquinazoline **11** in THF (10 equiv, 0.1 M), Et_3N (10 equiv, 0.1 M), rt, 24 h, repeated; (c) R^2NH_2 (20 equiv, 0.2 M) in DCM, rt, 24 h; (d) $SnCl_2{\cdot}2H_2O$ (2 M) in DMF, rt, 24 h; (e) CS_2 (20 equiv, 0.2 M), DIEA (20 equiv, 0.2 M) in THF, rt, 24 h; (f) triphosgene (10 equiv, 0.1 M) in DCM, 38 °C, 12 h; (g) TFA/DCM = 1:1, rt, 1 h.

Table 1. Individual 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-thiones **9**

Entry	Product	R^1	R^2	Yield[a] (%)	Purity[b] (%)
1	**9a**	4-CH_3O	$CH_3CH_2CH_2$	93	90
2	**9b**	4-CH_3O	$CH_3(CH_2)_2CH_2$	90	91
3	**9c**	4-CH_3O	$(CH_3)_2CH$	91	92
4	**9d**	4-CH_3O	$(CH_3)_2CHCH_2$	94	90
5	**9e**	4-CH_3O	$CH_3C_2H_5CH$	92	91
6	**9f**	4-CH_3O	C_6H_{11}	94	92
7	**9g**	4-CH_3O	$CH_3CH_2O(CH_2)_2CH_2$	93	92
8	**9h**	4-CH_3O	$CH_3OCH_2CH_2CH_2$	91	91
9	**9i**	4-CH_3	$(CH_3)_2CH$	93	94
10	**9j**	H	$(CH_3)_2CH$	90	95
11	**9k**	4-$(CH_3)_3C$	$(CH_3)_2CH$	92	92
12	**9l**	3,4-di(CH_3O)	$(CH_3)_2CH$	93	90
13	**9m**	4-F	$(CH_3)_2CH$	35	77
14	**9n**	4-Cl	$(CH_3)_2CH$	—[c]	—
15	**9o**	4-CF_3	$(CH_3)_2CH$	—[c]	—
16	**9p**	2-CH_3	$(CH_3)_2CH$	—[c]	—

[a] Percent yields are based on the weight of crude material and relative to the initial loading of the resin.
[b] The purity of the crude material was estimated based on analytical traces at 254 nm.
[c] The yield and purity were poor.

Table 2. Individual 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-ones **10**

Entry	Product	R^1	R^2	Yield[a] (%)	Purity[b] (%)
1	**10a**	4-CH_3O	$CH_3CH_2CH_2$	95	95
2	**10b**	4-CH_3O	$CH_3(CH_2)_2CH_2$	97	92
3	**10c**	4-CH_3O	$(CH_3)_2CH$	95	94
4	**10d**	4-CH_3O	$(CH_3)_2CHCH_2$	94	91
5	**10e**	4-CH_3O	$CH_3C_2H_5CH$	94	93
6	**10f**	4-CH_3O	$CH_2{=}CHCH_2$	95	84
7	**10g**	4-CH_3O	$CH_3CH_2O(CH_2)_2CH_2$	97	92
8	**10h**	4-CH_3O	$CH_3OCH_2CH_2CH_2$	94	89
9	**10i**	4-CH_3O	C_6H_{11}	92	92
10	**10j**	4-CH_3	$(CH_3)_2CH$	94	93
11	**10k**	H	$(CH_3)_2CH$	93	93
12	**10l**	4-$(CH_3)_3C$	$(CH_3)_2CH$	94	89
13	**10m**	3,4-di(CH_3O)	$(CH_3)_2CH$	94	90
14	**10n**	4-F	$(CH_3)_2CH$	30	74

[a] Percent yields are based on the weight of crude material and relative to the initial loading of the resin.
[b] The purity of the crude material was estimated based on analytical traces at 254 nm.

making 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-thiones and 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-ones library. The reaction of resin-bound arylamine **3** with 4-chloro-7-fluoro-6-nitroquinazoline **11** was highly chemoselective. Thus, only compound **4** was found by LC–MS and NMR once the resin-bound compound was cleaved. The fluoro group of resin-bound compound **4** could be substituted by both primary and secondary alkylamines but could not be substituted by arylamines. Successful reduction of aromatic nitro group and subsequent thionylation or carbonylation afforded the desired resin-bound products **9** or resin-bound products **10** in high yields and good purity.

In conclusion, using 4-chloro-7-fluoro-6-nitroquinazoline scaffold as core structure, we have demonstrated a novel approach for the parallel solid-phase synthesis of 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-thiones and 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-ones from common building blocks, such as arylamines (R^1), alkylamines (R^2), triphosgene or CS_2 (X). In addition, the reaction conditions are readily amenable to the synthesis of individual and mixture-based combinatorial libraries. The screening of 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-thiones and 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-ones in different assays for identification of active compounds will be reported in due course.

2. Typical procedure for the synthesis of 3-(3-methoxypropyl)-8-(4-methoxyphenylamino)-1*H*-imidazo[4,5-*g*]-quinazoline-2(3*H*)-thione (9h)

To the 4-(4-formyl-3-methoxyphenoxy)butyryl AM resin **1** (220 mg, 0.2 mmol sealed within a polypropylene mesh packet) was added 4-methoxybenzenamine (10 equiv, 0.1 M), $NaBH_3CN$ (10 equiv, 0.1 M) in anhydrous DMF/HOAC (99:1). The mixture was shaken for 24 h at room temperature. The resin was then washed with DMF (3 times), DCM (3 times), and MeOH (3

times). The resulting resin-bound compound **3** was coupled with 4-chloro-7-fluoro-6-nitroquinazoline **11** (10 equiv, 0.1 M) using triethylamine (10 equiv, 0.1 M) in anhydrous THF at room temperature for 24 h. The resin was washed with DMF (3 times), DCM (3 times), and MeOH (3 times). This procedure was repeated. Resin-bound compound **4** was reacted with 3-methoxypropan-1-amine (20 equiv, 0.2 M) in DCM for 24 h at room temperature. The resin was washed with DMF (3 times), DCM (3 times), and MeOH (3 times) to afford resin-bound compound **5**. The resin-bound compound **6** was formed through the reduction of resin-bound compound **5** with $SnCl_2{\cdot}2H_2O$ (2 M) in DMF. After being washed with DMF (3 times), DCM (3 times), and MeOH (3 times), the resin-bound compound **6** was then thionylated with CS_2 (20 equiv, 0.2 M), DIEA (20 equiv, 0.2 M) in THF to afford the resin-bound compound **7**. After being washed with DMF (3 times), DCM (3 times), and MeOH (3 times), the resin-bound compound **7** was treated with TFA/DCM = 1:1 at room temperature for 1 h and the solvent was removed under the reduced pressure. The pure product compound **9h** was obtained after a flash column purification with eluant EtOAc.

3-(3-Methoxypropyl)-8-(4-methoxyphenylamino)-1*H*-imidazo[4,5-*g*]quinazoline-2(3*H*)-thione (**9h**) LC–MS (ESI) *m*/*z* 396.4 ($M+H^+$). ^{1}H NMR (500 MHz, DMSO-d_6) 13.32 (1H, br s), 9.74 (1H, s), 8.29–8.44 (2H, m), 7.67–7.69 (2H, m), 7.63 (1H, s), 6.95–6.97 (2H, m), 4.34–4.37 (2H, t, $J = 6.9$ Hz), 3.77 (3H, s), 3.38–3.40 (2H, t, $J = 6.0$ Hz), 3.24 (3H, s), 1.98–2.03 (2H, m). ^{13}C NMR (125 MHz, DMSO-d_6) 172.47, 157.83, 155.65, 152.98, 146.29, 137.29, 132.22, 130.45, 124.28, 113.54, 111.21, 105.11, 101.19, 68.82, 57.77, 55.17, 40.61, 27.27.

3. Typical procedure for the synthesis of 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-ones (10)

The preparation of resin-bound compound **6** was the same as the procedure for the synthesis of 3-alkyl-8-arylamino-1*H*-imidazo[4,5-*g*]quinazolin-2(3*H*)-thiones. The resin-bound compound **6** was carbonylated with triphosgene (10 equiv, 0.1 M) in refulxing DCM for 12 h to afford resin-bound compound **8**. After being washed with DMF (3 times), DCM (3 times), and MeOH (3 times), the resin-bound compound **8** was treated with TFA/DCM = 1:1 at room temperature for 1 h and the solvent was removed under the reduced pressure to afford the crude product. After a flash column purification with eluant EtOAc/EtOH = 95:5, compound **10** was obtained. All the compounds were characterized with LC–MS (ESI), ^{1}H NMR, and ^{13}C NMR, and the spectroscopic datas of the products are consistent with their structures.

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