Scaffold Approach for Solid-Phase Synthesis of 2,3-Disubstituted 8-Arylamino-3*H*-imidazo[4,5-*g*]quinazolines

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Combinatorial chemistry has emerged as a powerful methodology for the preparation of libraries of small organic compounds to accelerate the drug discovery process.[1] 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 the 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 tricyclic fused scaffold incorporating the quinazoline and imidazo moiety, such as 8-arylamino-3*H*-imidazo[4,5-*g*]quinazolines (Figure 1), has displayed a broad range of biological activities, including inhibitions of the EGFR,[12,13] F16BPase,[14] EphB2,[15,16] erbB2,[13e] HER3, HER4,[13e] U251, HepG-2, Lox IMVI, MCF-7, Hs 578T, UMRC2, and Caki-1[17] cell growth.

As a part of our ongoing efforts directed toward 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 2,3-disubstituted 8-arylamino-3*H*-imidazo[4,5-*g*]quinazolines from a 4-chloro-7-fluoro-6-nitroquinazoline scaffold as the core structure.

The parallel solid-phase synthesis of 2,3-disubstituted 8-arylamino-3*H*-imidazo[4,5-*g*]quinazolines was carried out on the solid phase using the "tea-bag" methodology. The reaction sequence is illustrated in Scheme 1.

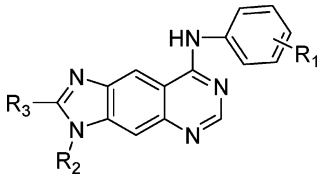

Figure 1. 8-Arylamino-3*H*-imidazo[4,5-*g*]quinazolines.

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 scaffold to yield the corresponding chemoselective resin-bound quinazoline **4**, which was then treated with an alkylamine to give resin-bound compound **5**. The imidazo ring of resin-bound compound **6** was formed through the reduction of the nitro group of resin-bound compound **5** with tin chloride and intramolecular cyclization with an alkylaldehyde in one step at 50 °C. Then the desired 2,3-disubstituted 8-arylamino-3*H*-imidazo[4,5-*g*]quinazoline **7** was obtained in good yield and purity after the cleavage of resin-bound compound **6** by using TFA/DCM (1:1). The products were characterized by electrospray LC−MS, ^{1}H NMR, and ^{13}C NMR. The results are summarized in Table 1.

From these results, the yields and purities of products were dependent 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) 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 making the 2,3-disubstituted 8-arylamino-3*H*-imidazo[4,5-*g*]quinazoline library. Excellent yield and purity of the product could also be obtained when propylamine was used instead of arylamine. However, for the purpose of biological screening, alkylamines were not used as building blocks for the library. The reaction of resin-bound arylamine **3** with 4-chloro-7-fluoro-6-nitroquinazoline 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 using both primary and secondary alkylamines but could not be substituted using arylamines. Successful reduction of the aromatic nitro group and intramolecular cyclization were accomplished by treatment of resin-bound compound **5** with tin chloride and an alkylaldehyde in one pot for 1 h at 50 °C. The results were good yield and high purity.

In conclusion, using 4-chloro-7-fluoro-6-nitroquinazoline scaffold as the core structure, we have demonstrated a novel

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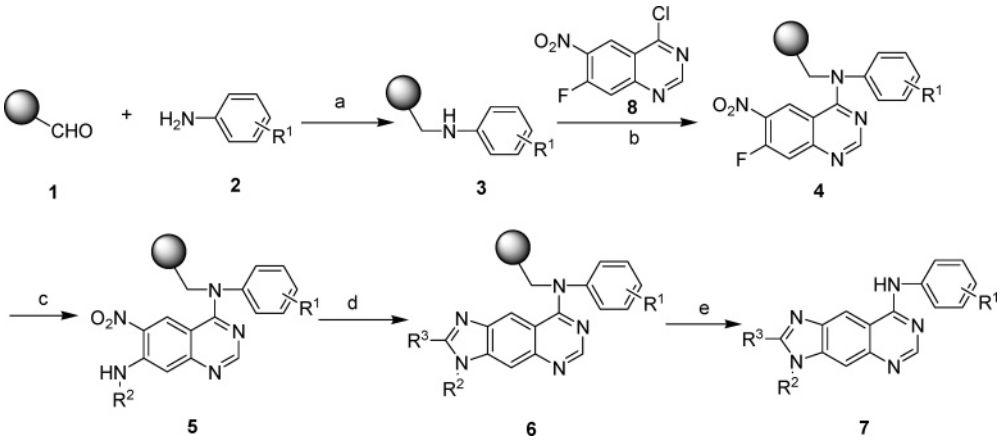
Scheme 1. Solid-Phase Synthesis of 2,3-Disubstituted 8-Arylamino-3*H*-imidazo[4,5-*g*]quinazolines **7**[a]



[a] 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 in THF (10 equiv, 0.1 M), Et_3N (10 equiv, 0.1 M), 24 h, repeat; (c) R^2NH_2 (20 equiv, 0.2 M) in DCM, 24 h; (d) R^3CHO (10 equiv, 0.1 M), $SnCl_2 \cdot 2H_2O$ (2 M) in DMF, 50 °C, 1 h; (e) TFA/DCM = 1:1, 1 h.

Table 1. Individual 2,3-Disubstituted 8-Arylamino-3*H*-imidazo[4,5-*g*]quinazolines

entry	product	R^1	R^2	R^3	yield[a] (%)	purity[b] (%)	MW (found)[c]
1	**7a**	4-CH_3O	$CH_3CH_2OCH_2CH_2CH_2$	$(CH_3)_2CHCH_2$	90	98	434.6 ($[M + H]^+$)
2	**7b**	4-CH_3O	$CH_3CH_2CH_2CH_2$	$(CH_3)_2CH$	95	90	390.6 ($[M + H]^+$)
3	**7c**	4-CH_3O	C_6H_{11}	$(CH_3)_2CH$	91	96	416.5 ($[M + H]^+$)
4	**7d**	3,4-di(CH_3O)	$CH_3CH_2CH_2CH_2$	$(CH_3)_2CH$	93	92	420.5 ($[M + H]^+$)
5	**7e**	3,4-di(CH_3O)	$CH_3OCH_2CH_2CH_2$	$(CH_3)_2CH$	88	96	436.5 ($[M + H]^+$)
6	**7f**	3,4-di(CH_3O)	$CH_3OCH_2CH_2CH_2$	$CH_3CH_2CH_2$	85	94	436.6 ($[M + H]^+$)
7	**7g**	4-$(CH_3)_3C$	$CH_3CH_2CH_2$	CH_3CH_2	87	91	388.6 ($[M + H]^+$)
8	**7h**	4-$(CH_3)_3C$	$CH_3OCH_2CH_2CH_2$	$(CH_3)_2CH$	86	91	432.7 ($[M + H]^+$)
9	**7i**	4-$(CH_3)_3C$	$CH_3CH_2CH_2$	$(CH_3)_2CHCH_2$	85	92	416.7 ($[M + H]^+$)
10	**7j**	4-$(CH_3)_3C$	$CH_3OCH_2CH_2CH_2$	$CH_3CH_2CH_2$	86	94	432.6 ($[M + H]^+$)
11	**7k**	4-CH_3	$CH_3CH_2CH_2$	$(CH_3)_2CHCH_2$	89	95	374.6 ($[M + H]^+$)
12	**7l**	4-CH_3	$(CH_3)_2CH$	$CH_3CH_2CH_2$	87	91	360.5 ($[M + H]^+$)
13	**7m**	4-CH_3	$CH_3CH_2CH_2$	CH_3CH_2	84	90	346.6 ($[M + H]^+$)
14	**7n**	H	$(CH_3)_2CH$	$(CH_3)_2CH$	89	90	346.5 ($[M + H]^+$)
15	**7o**	H	C_6H_{11}	$CH_3CH_2CH_2$	82	92	386.6 ($[M + H]^+$)
16	**7p**	2-CH_3	$(CH_3)_2CH$	CH_3CH_2	24	82	346.5 ($[M + H]^+$)
17	**7q**	4-F	$CH_3CH_2CH_2CH_2$	$(CH_3)_2CH$	12	72	378.6 ($[M + H]^+$)

[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 on the basis of analytical traces at 214 nm. [c] Confirmed by mass spectra (ESI).

approach for the parallel solid-phase synthesis of 2,3-disubstituted 8-arylamino-3*H*-imidazo[4,5-*g*]quinazolines from common building blocks, such as arylamines (R^1), alkylamines (R^2), and alkylaldehydes (R^3). In addition, the reaction conditions are readily amenable to the synthesis of individual and mixture-based combinatorial libraries. The preparation of a library containing 1000 ($10R^1 \times 10R^2 \times 10R^3$) different 2,3-disubstituted 8-arylamino-3*H*-imidazo[4,5-*g*]quinazolines and its screening using different assays for identification of active compounds will be reported in due course.

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Supporting Information Available. The preparation of scaffold 4-chloro-7-fluoro-6-nitroquinazolin; general procedure for the synthesis of 2,3-disubstituted 8-arylamino-3*H*-imidazo[4,5-g]quinazolines; copies of LC−MS data of all compounds; and ^1H and ^{13}C NMR spectra of **7a**, **7e**, **7h**, **7i**, **7k**, **7l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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