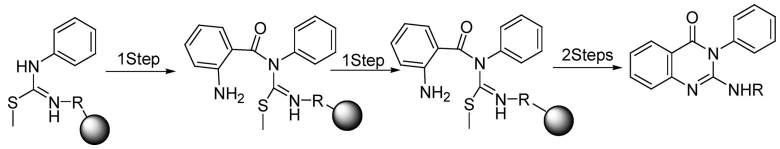
JOURNAL OF combinatorial CHEMISTRY

Article

Solid-Phase Synthesis of 2-Aminoquinazolinone Derivatives with Two- and Three-Point Diversity

Bijoy Kundu, Pankaj Partani, Srinivas Duggineni, and Devesh Sawant

J. Comb. Chem., **2005**, 7 (6), 909-915• DOI: 10.1021/cc0500699 • Publication Date (Web): 09 September 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

Solid-Phase Synthesis of 2-Aminoquinazolinone Derivatives with Two- and Three-Point Diversity

Bijoy Kundu,* Pankaj Partani, Srinivas Duggineni, and Devesh Sawant

Medicinal Chemistry Division, Central Drug Research Institute, Lucknow 226 001, India

Received May 30, 2005

A versatile solid-phase method for the synthesis of various substituted 2-amino-4(3*H*)-quinazolinones with two- and three-point diversity is described. The synthesis commenced with the generation of polymer-bound *S*-methylisothiourea followed by N-acylation with different substituted *o*-nitrobenzoic acid. Finally, reduction of the nitro group triggered intramolecular cyclization via formation of guanidine to afford 2-amino-4(3*H*)-quinazolinone and its derivatives in high yields and purities.

Introduction

Polymer-supported combinatorial chemistry has become a highly powerful tool in drug discovery. The technique has encouraged chemists to evolve new synthetic approaches suitable for the preparation of solid-phase combinatorial libraries. During the past decade, combinatorial chemistry has provided access to chemical libraries based on privileged structures.[1] Among privileged structures, heterocyclic structures have received special attention because they belong to a class of compounds with proven utility in medicinal chemistry.[2] In recent years, the field of solid-phase heterocyclic chemistry has rapidly expanded, and numerous preparations have been reported.[3] As part of our continuing effort to develop new solid-phase strategies for synthesizing N-rich heterocycles based on 2-aminoquinazoline[4] derivatives, we required libraries based on 2-aminoquinazolinones for lead generation against a variety of disease targets. Quinazolinones have been reported to possess a vast range of biological activity.[1]

A careful survey of the literature revealed that solid-phase synthesis of quinazolinones with a free amino group at position 2 has not yet been reported, although there are several reports in the literature dealing with solid-phase synthesis of 2-amino derivatized quianzolin-4(3*H*)-ones. In one of the earliest strategies, synthesis of 2-amino derivatized quianzolin-4(3*H*)-ones was carried out either by the cyclocondensation of anthranilic acids with amino acids and aldehydes[5] or by aza-Wittig-mediated annulation involving *o*-azido benzoic acid.[6] Other methods reported involved reaction of resin-bound *o*-anilino derivative with aryl isothiocyanate, followed by either treatment of resulting thioureas with amines in the presence of Mukaiyama's[7a] reagent or treatment of thioureas with secondary amines in the presence of DIC[7b] to afford resin-bound guanidines. Finally, acid-catalyzed cyclative cleavage strategies were applied to give quinazolinones in high yield. In addition to this, three groups have described strategies for the synthesis of quinazolinones based on isatoic anhydride. Gopalsamy et al.[8a] treated isatoic anhydride with pseudothioureas that led to the formation of a quinazolinone ring on the resin and subsequent cleavage with TFA-liberated quinazolinones. A similar strategy was reported by Yang and Kaplan[8b] in which resin-bound isothioureas (connected via S) after treatment with isatoic anhydride produced 2-amino derivatized quinazolinones in a single step. In yet another strategy, Zhang and co-workers[8c] initially prepared N-substituted benzamide by treating isatoic anhydride with primary amines and then reacting with polystyrene triphenylphosphine to produce resin-bound immunophosphoranes. This, upon treatment with isocyanates, produced 2-amino derivatized quinazolinones.

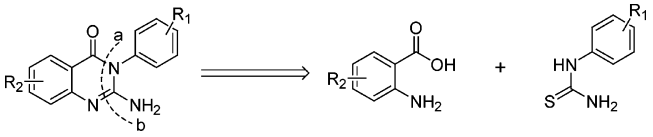


Figure 1. Retrosynthetic pathway for the synthesis of 2-amino-quinazolinones.

We directed our efforts toward the development of a novel solid-phase strategy for 2-aminoquinazolinone derivatives based on following two-tier objectives: (1) that the strategy would be applicable to both 2-aminoquinazolinones and 2-amino derivatized quinazolinones, and (2) that it would avoid the reliance of isatoic anhydrides in favor of more accessible building blocks amenable to parallel solid-phase synthesis. In the first instance, we decided to analyze the retrosynthetic approach for the synthesis of 2-aminoquinazolinones with the emphasis on the formation of cyclic guanidines present in the quinazolinone ring (Figure 1).

Retrosynthetic analysis revealed that the most efficient route to 2-aminoquinazolinones would employ condensation of thioureas/isothioureas with anthranilic acids. However, on the basis of this approach, two different synthetic routes are possible for the solid-phase synthesis of the title compounds.

In one of the routes (route A, Figure 2), the title compounds can be obtained by the condensation of polymer-bound anthranilic acid linked via an ester bond to the resin with isothioureas, followed by intramolecular cyclization. In

* Corresponding author. Phone: +91-0522-2212411-18, ext. 4383. Fax: +91-0522-2223405, 2223938. E-mail: bijoy_kundu@yahoo.com.

10.1021/cc0500699 CCC: $30.25
Published on Web 09/09/2005

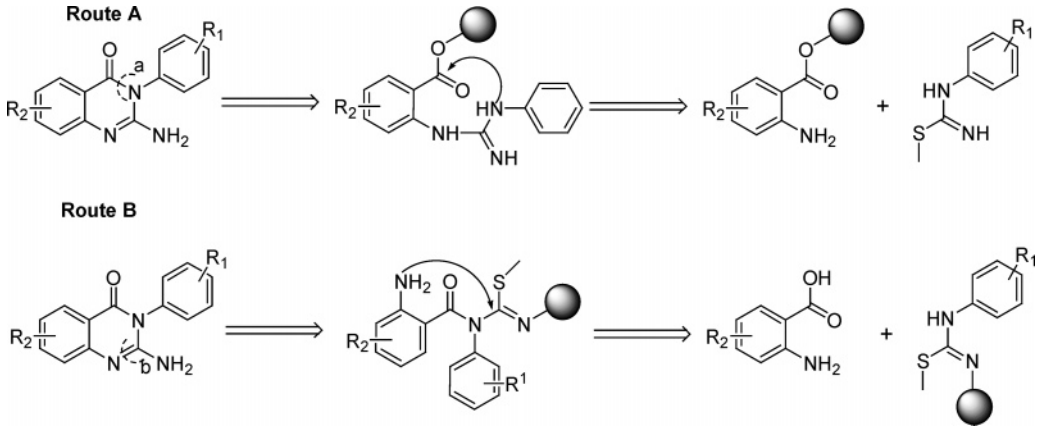
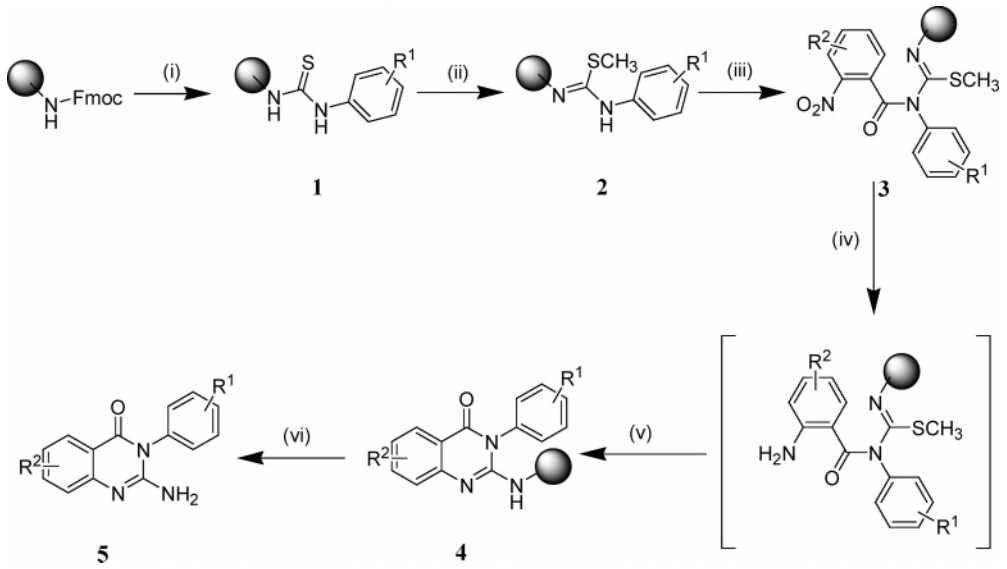


Figure 2. Two possible synthetic pathways for 2-aminoquinazolinones on solid support.

Scheme 1. Traceless Synthesis of 2-Amino-4(3*H*)-quinazolinones[a]



[a] (i) 25% Piperidine/DMF, isothiocynates/DCM, o/n, rt; (ii) 2 M CH_3 in DMF, 2 h, 3 cycles; (iii) *o*-nitrobenzoic acids, HOBt/TBTU/DIPEA, 6 h, rt; HOBt/DIC, 12 h, rt; (iv) 1 M $SnCl_2 \cdot 2H_2O$, DMF, 5 h; (v) DMF, 80 °C, 5 h; (vi) 50% TFA/DCM, 2 h.

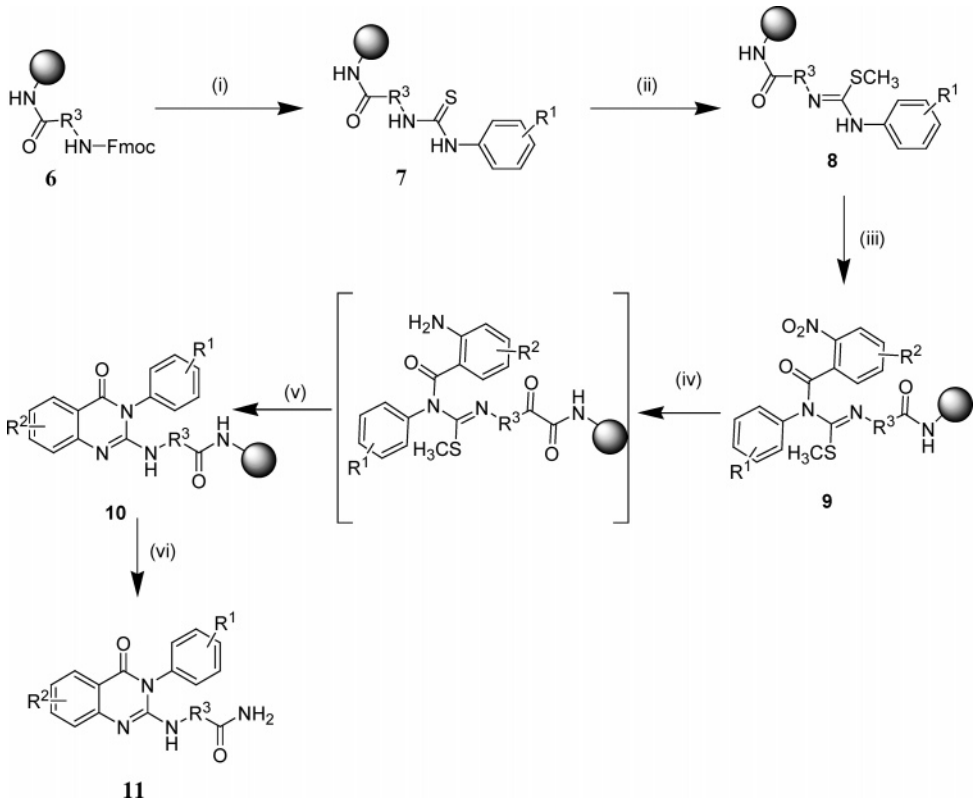
addition, concomitant cyclization during the condensation between anthranilic acids and isothioureas would release products from the resin, leading to lower yields or more elaborate purification. In contrast, in route B (Figure 2), the title compounds can be obtained by the condensation of the resin-bound isothioureas linked through one of the NHs with *o*-nitrobenzoic acid using the standard coupling reagents used for amide bond formation, followed by reduction of the nitro group to achieve intramolecular cyclization. Of these two routes, we preferred to work with route B because it would lead to the synthesis of both 2-aminoquinazolinones and 2-amino derivatized quinazolinones, whereas route A would yield only 2-aminoquinazolinones. In this Article, we describe a versatile method for the synthesis of 2-amino-quinazolinones and their derivatives using amino acids, isothioureas, and *o*-nitrobenzoic acid.

Results and Discussion

In the first instance, we decided to develop a traceless synthesis for 2-aminoquinazolinones on Rink amide AM resin; the synthetic strategy is depicted in Scheme 1. Our synthesis commenced with the synthesis of resin-bound thioureas **1** obtained by treating resin-bound amine with isothiocyanates. Resin **1** was then converted to corresponding *S*-methyl isothiourea **2** by reacting with methyl iodide. The remaining NH in the isothiourea **2** was next coupled with *o*-nitrobenzoic acid to give N-acylated product **3**. Reduction of the nitro functionality in **3** furnished resin-bound cyclized quinazolinone **4**. Finally, the product was cleaved under acidic conditions (50% TFA/DCM), and the residue was purified by column chromatography to furnish the desired product **5**. The efficacy of our traceless strategy was demonstrated by synthesizing eight compounds with two-point diversity (Table 1).

Attempts to synthesize 2-aminoquinozolinones from alkyl and benzyl isothiocyanates were not successful due to failure in the N-acylation of the isothioureas. This was evident from the analysis of the cleaved product after the acylation step by HPLC and ESMS, which showed the presence of isothioureas as the major product. This may be attributed to 1,3-prototropic tautomerism in isothioureas;[9] however, this phenomenon was not observed during the N-acylation of the isothioureas obtained from phenyl isothiocyanates. Next, to introduce combinatorial diversity, we decided to include amino acids as an additional diversity between the Rink amide AM resin and isothiocyanates (Scheme 2). Thus, the

Scheme 2. Solid Phase Synthesis of 2-Aminoquinazolinone Derivatives with Three-Point Diversity[a]



[a] (i) 25% Piperidine/DMF, isothiocynates/DCM, o/n, rt; (ii) 2 M CH_3I in DMF, 2 h, 3 cycles; (iii) *o*-nitrobenzoic acids, HOBt/TBTU/DIPEA, 6 h, rt; HOBt/DIC, 12 h, rt; (iv) 1 M $SnCl_2 \cdot 2H_2O$, DMF, 5 h; (v) DMF, 80 °C, 5 h; (vi) 50% TFA/DCM, 2 h.

Table 1. Physicochemical Characteristic of 2-Aminoquinazolinones with Two-Point Diversity

entry	R^1	R^2	ESMS (M + H)	% yield (crude/ isolated[a])	t_R[b] (min)	HPLC purity[c] at 220 nm (%)
5a	H	H	238.00	92/80	12.986	92
5b	H	8-Cl	272.13	96/85	13.406	100
5c	H	7-Cl	272.07	93/82	13.255	94
5d	H	6-OCH_3	268.21	90/79	12.184	89
5e	CH_3	H	252.18	94/81	13.985	92
5f	CH_3	8-Cl	286.13	98/83	14.011	99
5g	CH_3	7-Cl	286.07	91/80	14.425	92
5h	CH_3	6-OCH_3	282.13	89/77	13.001	85

[a] Compounds obtained after purification from the silica gel chromatography. [b] Retention time on HPLC (C18 reversed-phase column; 150 × 4.8 mm; 5 μm) with a linear gradient of 0−100% CH_3CN in water over 35 min, flow rate of 1.0 mL/min, and UV detection at 220/254 nm. [c] Purity of crude products obtained after cleavage from the resin.

synthesis commenced with the treatment of polymer-linked amino acids **6** with isothiocyanates, followed by S-methylation using CH_3I. The resulting resin-bound isothioureas **8** were then coupled with *o*-nitrobenzoic acid in the presence of TBTU/HOBt and DIC/HOBt to give **9**. The nitro group in the resin **9** was reduced with $SnCl_2 \cdot 2H_2O$, followed by heating to give resin-bound quinazolinones **10**. The final product was cleaved with 50% TFA/DCM, and the residue after purification was analyzed by HPLC, NMR, and ESMS. Interestingly, our strategy did not work with naturally occurring α-amino acids because it led to the formation of 2-aminoimidazolidin-4-ones, as described earlier by Houghten et al.[10a] and Wang et al.[10b]

The scope and limitation of our strategy (Scheme 2) for synthesizing 2-amino derivatized quinazolinones was established by generating a mini library of 24 compounds using three amino acids, two isothiocyanates, and four *o*-nitrobenzoic acids. The crude products after the acidolytic cleavage from the resin were purified on silica gel chromatography using EtOAc/hexane as an eluant to furnish 2-amino derivatized quinazolinones **11**.

The compounds were isolated in excellent yields (Table 2) ranging from 77 to 85%. The electron-withdrawing and -donating substitution on *o*-nitrobenzoic acid had no significant effect on the yield and purity of the final compound. All compounds were characterized using HPLC, ESMS, and ^1H NMR.

Conclusions

In summary, we have developed a versatile approach for the solid-phase synthesis of both 2-aminoquinazolinones and 2-amino derivatized quinazolinones. The method can be used for the generation of large libraries of quinazolinones using an automated synthesizer.

Experimental Section

General. Rink amide AM resin (1% divinylbenzene, 100−200 mesh, 0.63 mmol/g substitution) and amino acids were purchased from Novabiochem, Switzerland. *N*-Hydroxybenzotriazole (HOBt) and 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluranium tetrafluoroborate (TBTU) were purchased from Janseen Chemica, Belgium. Isothiocynates and *o*-nitrobenzoic acids were purchased from Lancaster and

Table 2. Physicochemical Characteristic of 2-Aminoquinazolinones with Three-Point Diversity

entry	R^1	R^2	R^3	ESMS (M + H)	% yield (crude/isolated[a])	t_R[b] (min)	HPLC purity[c] 220 nm (%)
11a	H	H	$-(CH_2)_2-$	309.20	90/80	14.024	89
11b	H	8-Cl	$-(CH_2)_2-$	342.87	97/81	14.148	100
11c	H	7-Cl	$-(CH_2)_2-$	343.13	92/80	14.051	91
11d	H	6-OCH_3	$-(CH_2)_2-$	339.07	88/71	13.134	84
11e	CH_3	H	$-(CH_2)_2-$	323.13	94/81	14.019	94
11f	CH_3	8-Cl	$-(CH_2)_2-$	357.07	96/83	15.394	100
11g	CH_3	7-Cl	$-(CH_2)_2-$	357.13	91/80	15.302	92
11h	CH_3	6-OCH_3	$-(CH_2)_2-$	353.07	89/77	14.208	84
11i	H	H	$-(CH_2)_3-$	323.20	91/79	14.289	87
11j	H	8-Cl	$-(CH_2)_3-$	357.13	95/82	13.401	98
11k	H	7-Cl	$-(CH_2)_3-$	357.13	93/84	14.449	92
11l	H	6-OCH_3	$-(CH_2)_3-$	353.13	88/77	13.768	85
11m	CH_3	H	$-(CH_2)_3-$	337.20	93/80	14.087	89
11n	CH_3	8-Cl	$-(CH_2)_3-$	371.07	95/83	14.345	100
11o	CH_3	7-Cl	$-(CH_2)_3-$	371.20	90/79	15.094	93
11p	CH_3	6-OCH_3	$-(CH_2)_3-$	367.07	87/75	14.102	82
11q	H	H	$-(CH_2)_5-$	351.20	91/80	15.563	87
11r	H	8-Cl	$-(CH_2)_5-$	385.07	97/78	14.288	94
11s	H	7-Cl	$-(CH_2)_5-$	385.13	91/79	16.320	90
11t	H	6-OCH_3	$-(CH_2)_5-$	381.00	87/74	13.156	80
11u	CH_3	H	$-(CH_2)_5-$	365.20	93/80	14.080	89
11v	CH_3	8-Cl	$-(CH_2)_5-$	399.00	92/83	14.616	96
11w	CH_3	7-Cl	$-(CH_2)_5-$	399.13	90/78	14.783	89
11x	CH_3	6-OCH_3	$-(CH_2)_5-$	395.00	87/75	13.627	81

[a] Compounds obtained after purification from the silica gel chromatography. [b] Retention time on HPLC (C18 reversed-phase column; 150 × 4.8 mm; 5 μm) with a linear gradient of 0−100% CH_3CN in water over 35 min, flow rate of 1.0 mL/min, and UV detection at 220/254 nm. [c] Purity of crude products obtained after cleavage from the resin.

Sigma-Aldrich Chemical Co. Anhydrous solvents were used for reactions. All other reagents were obtained from commercial sources and were used without further purification. The reactions were carried out in polypropylene syringes (5-mL capacity) with frit, which were shaken on an orbital shaker IKA Vibrax-VXR. The ^1H and ^{13}C NMR spectra were obtained on a 300-MHz spectrometer, and chemical shifts were reported in parts per million (δ) relative to TMS. All spectra were recorded at 25 °C. Because of solubility properties, the solvent used was DMSO-d_6. RP-HPLC analysis of crude products was carried out on an Agilent liquid chromatograph using a 5-μm, 4.8 × 150 mm, C-18, reversed-phase column with a linear gradient of 0−100% acetonitrile in water (v/v) over 35 min. The flow rate was 1.0 mL/min, and UV detection was observed at 220/254 nm. Mass spectra were recorded using electron spray ionization (ESI).

General Experimental Procedure for 2-Aminoquinazolinones. The Fmoc groups of Rink amide AM resin (0.063 mmol; 100 mg) were removed by treating with 25% piperidine in DMF (1 mL) twice for 5 and 25 min. The resin was filtered and washed with DMF (9 × 2 mL). The resin so obtained was coupled with isothiocynates (10 equiv) in anhydrous DCM as solvent for 16 h at room temperature to afford resin-bound thiourea **1**. The resin was filtered; washed successively with DMF (9 × 2 mL), MeOH (3 × 2 mL), DCM (3 × 2 mL), and ether (3 × 2 mL); and, finally, dried in vacuo. Completion of the reaction was confirmed by a negative Kaiser test. The resin-bound thiourea was treated three times with 2 M solution of methyl iodide (1 mL) in DMF for 2 h each to obtain resin-bound isothiourea **2**. The resin was filtered; washed successively with DMF (3 × 2 mL), MeOH (3 × 2 mL), DCM (3 × 2 mL), and ether (3 × 2 mL); and, finally, dried in vacuo. The resin so obtained was coupled with *o*-nitrobenzoic acid (5 equiv) by using TBTU (3 equiv), HOBt (3 equiv), DIPEA (6 equiv), and DMF (1.2 mL) as solvent for 6 h at room temperature. The resin was filtered and washed with DMF (9 × 2 mL). The resin so obtained was again treated with *o*-nitrobenzoic acid (5 equiv) by using HOBt (5 equiv), DIC (5 equiv), and DMF (1.2 mL) as solvent for 12 h at room temperature. The resin was filtered; washed successively with DMF (3 × 2 mL), MeOH (3 × 2 mL), DCM (3 × 2 mL), and ether (3 × 2 mL); and, finally, dried in vacuo. The nitro group of resin **3** was reduced to amine with 1 M $SnCl_2 \cdot 2H_2O$ in DMF (1 mL) for 5 h at room temperature. The resin was washed with DMF (9 × 2 mL), suspended in 1.2 mL of DMF, and heated at 80 °C for 8 h. The resin was filtered; washed successively with DMF (3 × 2 mL), MeOH (3 × 2 mL), DCM (3 × 2 mL), and ether (3 × 2 mL); and, finally, dried in vacuo. The final compounds were cleaved from the resin using 50% TFA/DCM for 2 h at room temperature. The excess TFA mixture was evaporated, and the residue was freeze-dried after dissolving in *t*-BuOH/water (4:1). The crude products were purified by column chromatography on silica gel using EtOAc/hexane as an eluant to give the desired quinazolinones.

2-Amino-3-phenyl-3*H*-quinazolin-4-one [5a]. ^1H NMR (300 MHz, $CDCl_3$): δ 8.15 (d, 1H, J = 7.8 Hz, ArH), 7.66−7.55 [m(o), 4H, ArH], 7.37−7.31 [m(o), 3H, ArH], 7.22 (t, 1H, J = 7.8 Hz, ArH), 4.96 (brs, 2H, 2 × NH).

2-Amino-8-chloro-3-phenyl-3*H*-quinazolin-4-one [5b]. ^1H NMR (300 MHz, DMSO-d_6): δ 7.90 (d, 1H, J = 7.5 Hz, ArH), 7.84 (d, 1H, J = 7.5 Hz, ArH), 7.62−7.52 [m(o), 3H, ArH], 7.40 (d, 2H, J = 7.2 Hz, ArH), 7.18 (t, 1H, J = 7.8 Hz, ArH), 7.01 (brs, 2H, 2 × NH).

2-Amino-7-chloro-3-phenyl-3*H*-quinazolin-4-one [5c]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.90 (d, 1H, J = 8.4 Hz, ArH), 7.58−7.56 [m(o), 3H, ArH], 7.39 (d, 2H, J = 6.9 Hz, ArH), 7.31 (s, 1H, ArH), 7.19 (d, 1H, J = 8.4 Hz, ArH), 6.87 (brs, 2H, 2 × NH).

2-Amino-6-methoxy-3-phenyl-3*H*-quinazolin-4-one [5d]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.60−7.52 [m(o), 3H, ArH], 7.36−7.22 [m(o), 5H, ArH], 6.12 (brs, 2H, 2 × NH), 3.78 (s, 3H, OCH_3).

2-Amino-3-*p*-tolyl-3*H*-quinazolin-4-one [5e]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.09 (dd, 1H, J = 7.8, 1.2 Hz, ArH), 7.62 (t, 1H, J = 8.4, 1.5 Hz, ArH), 7.43−7.32 [m(o), 3H, ArH], 7.23−7.16 [m(o), 3H, ArH], 5.48 (brs, 2H, 2 × NH), 2.45 (s, 3H, CH_3).

2-Amino-8-chloro-3-*p*-tolyl-3*H*-quinazolin-4-one [5f]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.12 (d, 1H, J = 7.8 Hz, ArH), 7.89 (d, 1H, J = 7.8 Hz, ArH), 7.42 (d, 2H, J = 7.8 Hz, ArH), 7.27−7.18 [m(o), 3H, ArH], 6.89 (brs, 2H, 2 × NH), 2.35 (s, 3H, CH_3).

2-Amino-7-chloro-3-*p*-tolyl-3*H*-quinazolin-4-one [5g]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (d, 1H, J = 8.7 Hz, ArH), 7.53 (s, 1H, ArH), 7.44 (d, 2H, J = 7.8 Hz, ArH), 7.34 (d, 1H, J = 8.4 Hz, ArH), 7.28 (d, 2H, J = 7.8 Hz, ArH), 5.16 (brs, 2H, 2 × NH), 2.48 (s, 3H, CH_3).

2-Amino-6-methoxy-3-*p*-tolyl-3*H*-quinazolin-4-one [5h]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.62 (d, 2H, J = 7.8 Hz, ArH), 7.40−7.28 [m(o), 3H, ArH], 7.10 (d, 2H, J = 8.0 Hz, ArH), 5.68 (brs, 2H, 2 × NH), 3.85 (s, 3H, OCH_3), 2.19 (s, 3H, CH_3).

General Experimental Procedure for 2-Amino Derivatized Quinazolinones. The Fmoc groups of Rink amide AM resin (0.063 mmol; 100 mg) were removed by treating with 25% piperidine in DMF (1 mL) twice for 5 and 25 min. The resin was filtered and washed with DMF (9 × 2 mL). The resin so obtained was coupled with Fmoc amino acids (5 equiv) by using HOBt (5 equiv), DIC (5 equiv), and DMF (1.2 mL) as solvent for 16 h at room temperature. The resin was filtered; washed successively with DMF (3 × 2 mL), MeOH (3 × 2 mL), DCM (3 × 2 mL), and ether (3 × 2 mL); and, finally, dried in vacuo. Completion of the reaction was confirmed by a negative Kaiser test. The Fmoc groups of amino acids were removed by treating with 25% piperidine in DMF (1 mL) twice for 5 and 25 min. The resin was filtered and washed with DMF (9 × 2 mL). The resin was further handled as described in the General Experimental Procedure for 2-Aminoquinazolinones (see above).

3-(4-Oxo-3-phenyl-3,4-dihydroquinazolin-2-ylamino)-propionamide [11a]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.90 (d, 1H, J = 7.8 Hz, ArH), 7.66−7.51 [m(o), 4H, ArH], 7.33 [d(o), 4H, ArH, CONH], 7.14 (t, 1H, J = 7.8 Hz, ArH), 6.82 (brs, 1H, CONH), 5.79 (brs, 1H, NH), 3.47 (q, 2H, J = 5.7 Hz, CH_2), 2.32 (t, 2H, J = 6.3 Hz, CH_2).

3-(8-Chloro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-ylamino)-propionamide [11b]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.03 (d, 1H, J = 7.8 Hz, ArH), 7.81 (d, 1H, J = 7.8 Hz, ArH), 7.46 (t, 1H, J = 8.0 Hz, ArH), 7.39−7.32 [m(o), 4H, ArH, CONH], 7.24 (d, 2H, J = 6.8 Hz, ArH), 7.07 (brs, 1H, CONH), 5.78 (brs, 1H, NH), 3.71 (t, 2H, J = 6.0 Hz, CH_2), 2.41 (t, 2H, J = 6.0 Hz, CH_2).

3-(7-Chloro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-ylamino)-propionamide [11c]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, 1H, J = 8.4 Hz, ArH), 7.59−7.54 [m(o), 3H, ArH], 7.33 [d(o), 3H, J = 7.2 Hz, ArH], 7.22 (brs, 1H, CONH), 7.13 (d, 1H, J = 8.7 Hz, ArH), 6.68 (brs, 1H, CONH), 5.89 (brs, 1H, NH), 3.27 (t, 2H, J = 6.6 Hz, CH_2), 2.01 (t, 2H, J = 7.2 Hz, CH_2).

3-(6-Methoxy-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-ylamino)-propionamide [11d]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.60−7.53 [m(o), 3H, ArH], 7.33−7.30 [m(o), 6H, ArH, CONH], 6.80 (brs, 1H, CONH), 5.58 (t, 1H, J = 5.1 Hz, NH), 3.79 (s, 3H, OCH_3), 3.45 (q, 2H, J = 6.0 Hz, CH_2), 2.31 (t, 2H, J = 6.6 Hz, CH_2).

3-(4-Oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-ylamino)-propionamide [11e]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.89 (d, 1H, J = 7.8 Hz, ArH), 7.62 (t, 1H, J = 7.5 Hz, ArH), 7.39−7.31 [m(o), 4H, ArH, CONH], 7.20 (d, 2H, J = 7.5 Hz, ArH), 7.13 (t, 1H, J = 7.5 Hz, ArH), 6.83 (brs, 1H, CONH), 5.77 (brs, 1H, NH), 3.45 (q, 2H, J = 5.7 Hz, CH_2), 2.40 (s, 3H, CH_3), 2.32(t, 2H, J = 6.3 Hz, CH_2).

3-(8-Chloro-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-ylamino)-propionamide [11f]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.03 (d, 1H, J = 7.8 Hz, ArH), 7.82 (d, 1H, J = 7.8 Hz, ArH), 7.36−7.19 [m(o), 5H, ArH], 4.37 (t, 2H, J = 6.3 Hz, CH_2), 3.01 (t, 2H, J = 6.0 Hz, CH_2), 2.37 (s, 3H, CH_3).

3-(7-Chloro-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-ylamino)-propionamide [11g]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.88 (d, 1H, J = 8.4 Hz, ArH), 7.38−7.34 [m(o), 3H, ArH], 7.30 (brs, 1H, CONH), 7.20 (d, 2H, J = 7.8 Hz, ArH), 7.14 (d, 1H, J = 8.4 Hz, ArH), 6.82 (brs, 1H, CONH), 5.99 (t, 1H, J = 5.4 Hz, NH), 3.47 (q, 2H, J = 6.0 Hz, CH_2), 2.40 (s, 3H, CH_3), 2.32 (t, 2H, J = 6.6 Hz, CH_2).

3-(6-Methoxy-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-ylamino)-propionamide [11h]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.40−7.34 [m(o), 6H, ArH, CONH], 7.22 (d, 2H, J = 7.8 Hz, ArH), 6.95 (brs, 1H, CONH), 6.05 (brs, 1H, NH), 3.80 (s, 3H, OCH_3), 3.38 (overlapped with water, 2H, CH_2), 2.41 (s, 3H, CH_3), 2.35 (t, 2H, J = 6.0 Hz, CH_2).

4-(4-Oxo-3-phenyl-3,4-dihydroquinazolin-2-ylamino)-butyramide [11i]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.89 (d, 1H, J = 7.8 Hz, ArH), 7.64−7.54 [m(o), 4H, ArH], 7.36−7.26 [m(o), 4H, ArH, CONH], 7.12 (t, 1H, J = 7.8 Hz, ArH), 6.70 (brs, 1H, CONH), 5.76 (t, 1H, J = 5.4 Hz, NH), 3.28 (overlapped with water, 2H, CH_2), 2.02 (t, 2H, J = 7.2 Hz, CH_2), 1.75−1.66 (m, 2H, CH_2).

4-(8-Chloro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-ylamino)-butyramide [11j]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.17 (d, 2H, J = 7.8 Hz, ArH), 7.95 (d, 1H, J = 7.8 Hz, ArH), 7.82 (d, 1H, J = 7.8 Hz, ArH), 7.70 (brs, 1H, CONH), 7.39−7.32 [m(o), 4H, ArH, CONH], 7.19 (t, 1H, J = 7.8 Hz, ArH), 7.09 (d, 1H, J = 7.5 Hz, ArH), 5.51 (brs, 1H, NH), 4.14 (t, 2H, J = 7.8 Hz, CH_2), 2.37 (t, 2H, J = 6.0 Hz, CH_2), 1.88 (m, 2H, CH_2).

4-(7-Chloro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-ylamino)-butyramide [11k]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.87 (d, 1H, J = 8.4 Hz, ArH), 7.59−7.51 [m(o), 3H, ArH], 7.36−7.31 [m(o), 3H, ArH], 7.23 (brs, 1H, CONH), 7.13 (d, 1H, J = 8.4 Hz, ArH), 6.69 (brs, 1H, CONH), 5.98 (t, 1H, J = 5.1 Hz, NH), 3.37−3.28 [over-

lapped with water, 2H, CH_2], 2.02 (t, 2H, $J = 7.5$ Hz, CH_2), 1.75−1.69 (m, 2H, CH_2).

4-(6-Methoxy-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-ylamino)-butyramide [11l]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.87 (d, 2H, $J = 7.8$ Hz, ArH), 7.57 (d, 1H, $J = 7.8$ Hz, ArH), 7.29 (brs, 1H, CONH), 7.16−7.04 [m(o), 4H, ArH], 6.68 (brs, 1H, CONH), 6.59 (t, 1H, $J = 7.8$ Hz, ArH), 5.46 (brs, 1H, NH), 3.89 (s, 3H, OCH_3), 3.26 (q, 2H, $J = 6.6$ Hz, CH_2), 2.18 (t, 2H, $J = 7.2$ Hz, CH_2), 1.68 (m, 2H, CH_2).

4-(4-Oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-ylamino)-butyramide [11m]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.78 (d, 1H, $J = 8.4$ Hz, ArH), 7.64 (t, 1H, $J = 7.8$ Hz, ArH), 7.41−7.31 [m(o), 4H, ArH and CONH], 7.26−7.18 [m(o), 3H, ArH], 6.87 (brs, 1H, CONH), 5.90 (brs, 1H, NH), 3.58 (t, 2H, $J = 6.2$ Hz, CH_2), 2.34 (s, 3H, CH_3), 2.21 (t, 2H, $J = 6.6$ Hz, CH_2), 1.83 (m, 2H, CH_2).

4-(8-Chloro-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-ylamino)-butyramide [11n]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.27 (brs, 1H, CONH), 7.16 (d, 2H, $J = 7.8$ Hz, ArH), 7.10 (d, 2H, $J = 8.1$ Hz, ArH), 6.79 (s, 1H, CONH), 6.49 (d, 1H, $J = 6.6$ Hz, ArH), 6.32 (t, 1H, $J = 6.9$ Hz, ArH), 6.09 (d, 1H, $J = 9.6$ Hz, ArH), 4.68 (brs, 1H, NH), 3.49 (q, 2H, $J = 6.3$ Hz, CH_2), 2.27 (s, 3H, CH_3), 2.11 (t, 2H, $J = 6.9$ Hz, CH_2), 1.81−1.76 (m, 2H, CH_2).

4-(7-Chloro-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-ylamino)-butyramide [11o]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, 1H, $J = 8.4$ Hz, ArH), 7.38 [t(o), 3H, $J = 7.8$ Hz, ArH], 7.17−7.09 [m(o), 3H, ArH], 6.03 (brs, 1H, CONH), 5.38 (brs, 1H, CONH), 4.52 (brs, 1H, NH), 3.48 (q, 2H, $J = 6.0$ Hz, CH_2), 2.26 (t, 2H, $J = 6.0$ Hz, CH_2), 1.91−1.82 (m, 2H, CH_2).

4-(6-Methoxy-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-ylamino)-butyramide [11p]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.68 (d, 1H, $J = 7.8$ Hz, ArH), 7.53−7.42 [m(o), 4H, ArH], 7.27 (brs, 1H, CONH), 7.15 (d, 2H, $J = 7.8$ Hz, ArH), 6.47 (brs, 1H, CONH), 5.49 (brs, 1H, NH), 3.87 (s, 3H, OCH_3), 3.28 (t, 2H, $J = 6.6$ Hz, CH_2), 2.29 (t, 2H, $J = 6.0$ Hz, CH_2), 1.94−1,85 (m, 2H, CH_2).

6-(4-Oxo-3-phenyl-3,4-dihydroquinazolin-2-ylamino)-hexanoic Acid Amide [11q]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.96 (d, 1H, $J = 7.2$ Hz, ArH), 7.75 (t, 1H, $J = 6.9$ Hz, ArH), 7.63−7.60 [m(o), 4H, ArH], 7.41 (d, 2H, $J = 6.6$ Hz, ArH), 7.28 (t, 1H, $J = 6.6$ Hz, ArH), 7.23 (brs, 1H, CONH), 6.70 (brs, 1H, CONH), 5.80 (t, 1H, $J = 6.6$ Hz, NH), 3.65 (q, 2H, $J = 7.5$ Hz, CH_2), 2.02 (t, 2H, $J = 7.2$ Hz, CH_2), 1.65−1.45 [m(o), 4H, 2 × CH_2], 1.33−1.19 (m, 2H, CH_2).

6-(8-Chloro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-ylamino)-hexanoic Acid Amide [11r]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.39−7.34 [m(o), 2H, ArH, CONH], 7.25 [d(o), 4H, $J = 7.8$ Hz, ArH], 6.70 (brs, 1H, CONH), 6.53 (d, 1H, $J = 6.3$ Hz, ArH), 6.36 (t, 1H, $J = 8.4$ Hz, ArH), 6.08 (d, 1H, $J = 9.6$ Hz, ArH), 3.47 (q, 2H, $J = 6.3$ Hz, CH_2), 2.05 (t, 2H, $J = 6.9$ Hz, CH_2), 1.57−1.48 [m(o), 4H, 2 × CH_2), 1.30−1.28 (m, 2H, CH_2).

6-(7-Chloro-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-ylamino)-hexanoic Acid Amide [11s]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.89 (d, 1H, $J = 8.4$ Hz, ArH), 7.62−7.53 [m(o), 3H, ArH], 7.43 (s, 1H, ArH), 7.35 (d, 2H, $J = 6.6$ Hz, ArH), 7.22 (brs, 1H, CONH), 7.17 (d, 1H, $J = 8.7$ Hz, ArH), 6.68 (brs, 1H, CONH), 6.15 (brs, 1H, NH), 3.31 (q, 2H, $J = 6.3$ Hz, CH_2), 2.01 (t, 2H, $J = 7.2$ Hz, CH_2), 1.51−1.42 [m(o), 4H, 2 × CH_2], 1.22−1.15 (m, 2H, CH_2).

6-(6-Methoxy-4-oxo-3-phenyl-3,4-dihydroquinazolin-2-ylamino)-hexanoic Acid Amide [11t]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.63−7.52 [m(o), 4H, ArH, CONH], 7.42 (d, 2H, $J = 9.0$ Hz, ArH), 7.34−7.24 [m(o), 4H, ArH, CONH], 5.48 (brs, 1H, NH), 3.86 (s, 3H, OCH_3), 3.40 (q, 2H, $J = 6.3$ Hz, CH_2), 2.20 (t, 2H, $J = 7.2$ Hz, CH_2), 1.72−1.55 [m(o), 4H, 2 × CH_2], 1.33−1.25 (m, 2H, CH_2).

6-(4-Oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-ylamino)-hexanoic Acid Amide [11u]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.97 (d, 1H, $J = 7.8$ Hz, ArH), 7.78 (t, 1H, $J = 8.1$ Hz, ArH), 7.67 (d, 2H, $J = 7.8$ Hz, ArH), 7.42 (d, 2H, $J = 7.8$ Hz, ArH), 7.35−7.28 [m(o), 4H, ArH, CONH], 6.71 (brs, 1H, CONH), 6.05 (brs, 1H, CONH), 3.43 (overlapped with water, 2H, CH_2), 2.42 (s, 2H, CH_2), 2.02 (t, 2H, $J = 7.2$ Hz, CH_2), 1.49−1.44 [m(o), 4H, 2 × CH_2), 1.23−1.22 (m, 2H, CH_2).

6-(8-Chloro-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-ylamino)-hexanoic Acid Amide [11v]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.23 (brs, 1H, CONH), 7.17 (d, 2H, $J = 8.1$ Hz, ArH), 7.10 (d, 2H, $J = 7.8$ Hz, ArH), 6.70 (brs, 1H, CONH), 6.49 (d, 1H, $J = 6.6$ Hz, ArH), 6.33 (t, 1H, $J = 7.5$ Hz, ArH), 6.05 (d, 1H, $J = 6.3$ Hz, ArH), 3.47 (q, 2H, $J = 6.6$ Hz, CH_2), 2.27 (s, 3H, CH_3), 2.04 (t, 2H, $J = 7.2$ Hz, CH_2), 1.58−1.47 [m(o), 4H, 2 × CH_2), 1.29−1.27 (m, 2H, CH_2).

6-(7-Chloro-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-ylamino)-hexanoic Acid Amide [11w]. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.03 (d, 1H, $J = 7.8$ Hz, ArH), 7.48−7.41 [m(o), 3H, ArH], 7.17−7.09 [m(o), 3H, ArH], 6.53 (brs, 1H, CONH), 5.79 (brs, 1H, CONH), 5.28 (brs, 1H, NH), 3.19 (q, 2H, $J = 6.6$ Hz, CH_2), 2.29 (s, 3H, CH_3), 2.16 (t, 2H, $J = 6.6$ Hz, CH_2), 1.68−1.57 [m(o), 4H, 2 × CH_2), 1.20−1.18 (m, 2H, CH_2).

6-(6-Methoxy-4-oxo-3-*p*-tolyl-3,4-dihydroquinazolin-2-ylamino)-hexanoic Acid Amide [11x]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, 1H, $J = 7.4$ Hz, ArH), 7.37 [t(o), 3H, $J = 8.0$ Hz, ArH], 7.25 (d, 1H, $J = 7.8$ Hz, ArH), 7.15 (d, 2H, $J = 7.8$ Hz, ArH), 6.65 (brs, 1H, CONH), 5.47 (brs, 1H, CONH), 4.25 (t, 1H, $J = 5.4$ Hz, NH), 3.84 (s, 3H, OCH_3), 3.38 (q, 2H, $J = 6.6$ Hz, CH_2), 2.18 (t, 2H, $J = 7.5$ Hz, CH_2), 1.68−1.58 (m, 2H, CH_2), 1.54−1.46 (m, 2H, CH_2), 1.36−1.25 (m, 2H, CH_2).

Acknowledgment. This is CDRI Communication No. 6814.

Supporting Information Available. ^{1}H NMR spectra of compounds **5a**−**e**, **5g**, **11a**, **11d**−**11g**, **11i**−**k**, **11n**−**o**, **11r**−**s**, and **11u**−**v**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893−930.

(2) (a) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555−600. (b) Fruchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17−42. (c) Nefzi, A.; Ostresh, J. M.; Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449−472. (d) Frazen, R. G. *J. Comb. Chem*. **2000**, *2*, 195−214.

(3) (a) Dolle, R. E. *J. Comb. Chem.* **2003**, *6*, 693−753. (b) Krchnak, V.; Hollabay, M. W. *Chem. Rev.* **2002**, *101*, 61−91. (c) Kundu, B.; Sawant, D.; Chhabra, R. *J. Comb. Chem.* **2005**, *7*, 317−321. (d) Ganesan, A. *Drug Discovery Today* **2002**, *7*, 47−55. (e) Kundu, B. *Curr. Opin. Drug Discovery Dev.* **2003**, *6*, 815−826. (f) Brase, S.; Gil, C.; Knepper, K. *Bioorg. Med. Chem. Lett.* **2002**, *10*, 2415−2437. (g) Brase, S.; Kirchhoff, J. H.; Kobberling, J. *Tetrahedron* **2003**, *59*, 885−939.

(4) (a) Srivastava, G. K.; Kesarwani, A. P.; Grover, R. K.; Roy, R.; Srinivasan, T.; Kundu, B. *J. Comb. Chem.* **2003**, *5*, 769−774. (b) Kesarwani, A. P.; Grover, R. K.; Roy, R.; Kundu, B. *Tetrahedron* **2005**, *61*, 629−635. (c) Grover, R. K.; Kesarwani, A. P.; Srivastava, G. K.; Kundu, B.; Roy, R. *Tetrahedron* **2005**, *61*, 5011−5018.

(5) Mayer, J. M.; Lewis, G. S.; Curtis, M. J.; Zhang, J. *Tetrahedron Lett.* **1997**, *38*, 8445−8448.

(6) Villalgordo, J. M.; Orbrecht, D.; Chucholowsky, A. *Synlett* **1998**, 1405−1407.

(7) (a) Yu, Y.; Ostresh, J. M.; Houghten, R. A. *J. Org. Chem.* **2002**, *67*, 5831−5834. (b) Kesarwarni, A. P.; Srivastava, G. K.; Rastogi, S. K.; Kundu, B. *Tetrahedron lett.* **2002**, *43*, 5579−5581.

(8) (a) Gopalsamy, A.; Yang, H. *J. Comb. Chem.* **2000**, *2*, 378−381. (b) Yang, R.-Y.; Kaplan, A. *Tetrahedron lett*. **2000**, *41*, 7005−7008. (c) Zhang, W.; Mayer, J. P.; Hall, S. E.; Weigel, J. A. *J. Comb. Chem.* **2001**, *3*, 255−256.

(9) Durant, G. J.; Ganellin, C. R.; Parsons, M. E. *Agents Actions* **1977**, *7*, 39−43.

(10) (a) Yu, Y.; Ostresh, J. M.; Houghten, R. A. *Tetrahedron* **2002**, *58*, 3349−3353. (b) Wang, X.; Dixon, S.; Yao, N.; Kurth, M. J.; Lam, K. S. *Tetrahedron Lett.* **2005**, *46*, 5747−5750.

CC0500699