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Solid Phase Synthesis of 2-Aminoquinazoline-Based Compounds‡

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A versatile method for the solid-phase synthesis of 2-aminoquinazoline-based derivatives, 3-substituted-3,4-dihydroquinazolin-2-amines and imidazoquinazolines, has been developed. They were obtained by treating the amino group of polymer-linked amino acids with 2-nitrobenzaldehyde followed by reduction of the nitro group to an amine. Cyclization of the resulting immobilized intermediates with cyanogen bromide followed by acidic/basic cleavage yielded the desired quinazoline-based compounds in high yields and purities.

Introduction

The potential for rapid lead generation by use of combinatorial libraries has prompted immense interest in the development of new solid-phase synthetic methodology. The preponderance of heterocyclic frameworks in historical samplings of known drug structures makes them an attractive target for combinatorial organic synthesis.[1,2] As part of our continuing effort to develop new solid-phase reactions[3] for synthesizing small organic molecules of medicinal importance, we required libraries based on 3-substituted-3,4-dihydroquinazolin-2-amines. Quinazolines derivatives are attractive targets because they form an important component of pharmacologically active compounds and are associated with a wide spectrum of biological activities ranging from anticonvulsant[4] and antibacterial to antidiabetic.[5] Quinazolines are also among the most potent of the protein kinase inhibitors that compete for binding at the ATP site.[6]

Wang and Hauske have described a solid-phase synthesis of 2-amino derivatized 3,4-dihydroquinazolines.[7] Treating polymer-supported cinnamyl iminophosphorane with arylisocyanate followed by exposure to a secondary amine afforded the desired quinazolines. It occurred to us that use of *o*-nitrobenzaldehyde and polymer-bound amines would give rise to an intermediate, which could be then directly cyclized with an appropriate reagent to give the desired compounds. In this article, we report a facile and efficient method for the solid-phase synthesis of 2-aminoquinazoline-based compounds from amino acids R^1 and 2-nitrobenzaldehydes R^2 as versatile building blocks.

Results and Discussion

Our strategy commenced with the traceless synthesis of 2-aminoquinazoline (Scheme 1) by directly anchoring 2-nitrobenzadehyde to the Rink amide AM resin (0.63 mmol/g) by reductive alkylation. The completion of loading was monitored by a negative Kaiser test and a positive chloranil test. This was followed by the reduction of the nitro group with $SnCl_2 \cdot 2H_2O$ to give an amine in high yield and purity. Cyclization was carried out in the presence of cyanogen bromide to give the desired immobilized quinazolines. Finally, cleavage was accomplished using 50% TFA in DCM, and the crude product (97% purity, as evident by HPLC) so obtained was purified using reverse phase HPLC to give 3,4 dihydroquinazoline-2-amine **4(a)** in high yield (>95%). The compound was characterized using NMR and ESMS. The traceless strategy was extended to other derivatives of 2-nitrobenzadehyde, which resulted in compounds based on **4** in high yields and purities (Table 1).

Next, to introduce combinatorial diversity, we decided to include nonproteogenic amino acids (Scheme 2) as an additional diversity between the Rink amide AM resin and 2-nitrobenzadehyde. Thus, in the first instance, polymer linked N^{ϵ}-amino caproic acid was condensed with 2-nitrobenzadehyde, followed by reduction of the nitro group. The resulting resin was then treated with BrCN, followed by acidic cleavage with 50% TFA/DCM. The final product, **8(a)**, was lyophilized and characterized by NMR and ESMS. Other nonproteogenic amino acids, such as *p*-amino benzoic acid, γ-amino butyric acid, and 3-amino benzoic acid, also resulted in the formation of 2-aminoquinazoline-based compounds, **8(a−d)**, as the only product in excellent yields and purities (Table 2).

In our next experiment, we introduced the α-amino acid alanine (Scheme 3), and interestingly, after cyclization with BrCN followed by acidic cleavage, we obtained a compound in 94% purity with a molecular weight of 202 Da instead of the desired mass of 219 Da. We envisaged that the free amine formed during the treatment with BrCN might react with the amide moiety of the resin-linked alanine residue to yield the cyclized product **12**. This was confirmed by ^1H NMR studies, and the product was found to be quinazoline-based fused tricyclic structure imidazoquinazolines (3-methyl-1,5-dihydroimidazo[2,1-*b*]quinazolin-2(3*H*)-one; prototype **12**) instead of the desired compound **13**. Thus, using the amino acid alanine, **12** is formed as a result of two sequential cyclizations from resin **10** (Scheme 3).

A careful literature survey revealed imidazoquinazolines to be an interesting class of compounds, as one of the compounds, 1,5-dihydroimidazo[2,1-*b*]quinazolin-2-one (Ana-

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Scheme 1. Traceless Synthesis of 2-Amino Quinazoline on RAM Resin

Scheme 2. Synthesis of 2-Aminoquinazoline-Based Compounds Using Nonproteogenic Amino Acids

Scheme 3. Synthesis of Quinazoline-Based Compounds Using α-Amino Acids

Table 1. Compounds Based on Prototype **4** Synthesized on Rink Amide AM Resin

product	R^2	yield/purity %	t_R (min)	ESMS $(M + H)^+$
4(a)	−H	96/98	5.79	148.13
4(b)	6-chloro	95/97	9.72	182.20
4(c)	5-hydroxy	98/96	5.24	164.13
4(d)	3-methoxy	96/98	8.89	178.07
4(e)	4,5-dimethoxy	95/96	7.54	208.13

Table 2. Representative Compounds Based on Prototype **8** Synthesized on Rink Amide AM Resin

Products	Amino acids	(R^1)	Yield/Purity (%)	t_R (min)	ESMS $(M+H)^+$
8(a)	N^{ε}-Caproic acid	$(CH_2)_5$	96/98	7.57	261.33
(b)	p-amino benzoic acid		97/92	6.49	267.40
(c)	γ-amino butyric acid	$(CH_2)_3$	95/98	8.00	233.33
(d)	3-amino benzoic acid		98/93	8.42	267.40

grelide), is used clinically to reduce the elevated platelet counts and the risk of thrombosis in patients with thrombocythaemia in various myeloproliferative disorders (MPD).[8] This led us to explore our strategy with other amino acids, such as phenylalanine, leucine, isoleucine, and glycine, with the goal of studying the effect of other amino acids on the formation of quinazoline-based compounds. Under the given cleavage condition (50% TFA/DCM), we observed the formation of a mixture of tricyclic structure **12** and 2-aminoquinazoline **13** for phenylalanine, leucine, and isoleucine; however, an anomaly was observed for glycine, which

Table 3. Representative Compounds Based on Prototype **12** Synthesized on Wang resin using Basic Cleavage

Products	Amino acids	(R^1)	Yield/Purity (%)	t_R (min.)	ESMS $(M+H)^+$
12(a)	Ala	$-CH_3$	96/97	11.37	202.40
(b)	Phe	$-CH_2Ph$	95/98	15.68	278.60
(c)	Leu	$-CH_2CH(CH_3)_2$	96/95	15.69	244.40
(d)	Ile	$-CH(CH_3)CH_2CH_3$	97/98	14.63	244.40
(e)	Gly	-H	98/98	10.30	188.33
(f)	Met	$-(CH_2)_2SCH_3$	96/95	13.52	262.47
(g)	Gln (Trt)	$-CH_2)_2CONH(Trt)$	97/97	20.86	501.40
(h)	Asp (OBu^t)	$-CH_2COO(OBu^t)$	95/98	15.47	302.33
(i)	Val	$-CH(CH_3)_2$	97/96	13.50	230.33
(j)	Glu(OBu^t)	$-CH_2)_2COO(OBu^t)$	96/98	15.86	316.53
(k)	Lys (Boc)	$-(CH_2)_4NH(Boc)$	98/97	15.60	359.27
(l)	Thr (Bu^t)	$-CH(OBu^t)CH_3$	97/95	15.43	288.47
(m)	Ser (Bu^t)	$-CH_2O(Bu^t)$	99/96	16.17	274.67
(n)	Tyr (Bu^t)	O	98/98	18.64	350.73
(o)	Trp	N H	96/97	15.77	317.60

resulted in the formation of 2-aminoquinazoline **13** [2-amino-3-(2′-amino-2′-oxoethyl)-3,4-dihydroquinazolin-1-ium bromide]as the only major product. It was purified and characterized by NMR to establish its structural identity. Thus, using RAM resin and acidic cleavage conditions, α-amino acids except glycine predominantly gave imidazoquinazolines **12** along with **13**, present as a byproduct ranging from 0 to 40%.

Since both quinazoline-based compounds are pharmacologically important prototypes, we decided to establish a general method for synthesizing tricyclic prototype **12** selectively on solid phase in quantitative yields. We envisaged that use of Wang resin as the polymer support (Scheme 3) would provide an ester linkage, which may in turn facilitate the complete cyclization of intermediates **11** to imidazoquinazolines **12**. To test our hypothesis, several proteogenic amino acids were used for the synthesis of imidazoquinazoline-based compounds **12** using Wang resin as the solid support.

At the final step, each batch of the resin **11** was divided equally into two parts and subjected to acidic as well as basic cleavages separately. Treatment of resins **11** with 50% TFA/DCM resulted in the formation of imidazoquinazoline derivatives **12** in excellent yields (>95%) and purities (>85%), as evident from ^1H and ^{13}C NMR of 2′-(2-oxo-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-3-yl) acetic acid. However, anomalies were observed with resins **11** derived from methionine, lysine, glutamine, valine, and leucine; they resulted in mixtures of imidazoquinazolines **12** (50−70%) and 2-aminoquinazolines **14** (10−40%). In addition, glycine failed to cyclize under the given acidic conditions and resulted in the formation of **14** [2-amino-3-(carboxymethyl)-3,4-dihydroquinazolin-1-ium bromide] as the only product. Its structural identity was established using ^1H NMR.

On the contrary, treatment of resins **11** with 25% diisopropylamine/dichloromethane mixture for 12 h at room temperature gave **12** (Table 3) as the only product in excellent yields (>95%) and purities (95−100%). Interestingly, under these conditions, the amino acids for which anomalies were observed under acidic conditions also resulted in the formation of imidazoquinazoline **12** as the only product in quantitative yields. The compounds were characterized using HPLC, ESMS, and ^1H NMR.

Thus, imidazoquinazolines **12** can be obtained selectively from α-amino acids using Wang resin and base-catalyzed cyclative cleavage strategy, whereas 2-aminoquinazolines **8** can be derived from nonproteogenic amino acids using RAM resin and acid-catalyzed cleavage strategy.

Conclusions

In summary, we have developed a versatile approach for the solid-phase synthesis of 3-substituted-3,4-dihydroquinazolin-2-amines and imidazoquinazolines from the polymer-linked proteogenic/nonproteogenic amino acids and 2-nitrobenzaldehydes. This method may potentially be used for the generation of large libraries of quinazolines-based compounds using an automated synthesizer.

Experimental Section

(1) General. Rink amide AM resin (1% divinylbenzene, 100−200 mesh, 0.63 mmol/g substitution), Wang resin (1% divinylbenzene, 100−200 mesh, 0.63 mmol/g substitution), and amino acids were purchased from Novabiochem, Switzerland. *N*-Hydroxybenzotrizaole HOBt was purchased from Janseen Chemica, Belgium. *O*-Nitrobenzaldehyde, *N*,*N*′-diisopropylcarbodiimide, piperidine, and trifluoroacetic acid were purchased from Aldrich. 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 of 5-mL capacity, which were shaken on an orbital shaker IKA-Vibrax-VXR. The ^1H and ^{13}C NMR spectra were obtained on 300-MHz spectrometer, and chemical shifts were reported in ppm (δ) relative to TMS. Because of solubility properties, the solvents used were DMSO-d_6 and CD_3OD. RP-HPLC analysis of crude products was carried out on Agilent liquid chromatograph using a 5-μm, 4.8 × 150-mm C-18 reverse-phase column with a linear gradient of 0−100% (Tables 1−3) ACN in water (v/v) over 25 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) technique.

(2) General Procedure for Preparation of Prototype 4. The Fmoc groups of the Rink amide AM resin 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 × 5 mL). The resin so obtained was treated with *o*-nitrobenzaldehydes (10-fold) in trimethylorthoformate for 3 h at room temperature. The resin was then filtered and treated with 1% AcOH solution of trimethylorthoformate and $NaCNBH_3$ (10-fold) for 2 h at room temperature. The resin was filtered and washed successively with MeOH (3 × 2 mL), DMF (3 × 2 mL), DCM (3 × 2 mL), and ether (3 × 2 mL) and finally dried in vacuo to give **1**. Completion of the reaction was confirmed by a negative Kaiser test and positive chloranil test. The nitro group of resin **1** was reduced to amine with 2 M $SnCl_2 \cdot 2H_2O$ in DMF (1 mL) for 5 h at room temperature. Thereupon the resin was 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 to give **2**. Next, the resin **2** was treated with cyanogen bromide (10-fold) in DMF/EtOH (2:1) mixture for 16 h at room temperature. The resin was successively washed with DMF (3 × 2 mL), EtOH (3 × 2 mL), MeOH (3 × 2 mL), DCM (3 × 2 mL), and ether (3 × 2 mL) and dried in vacuo to give **3**. The resulting resin **3** was subjected to acidic cleavage with a mixture of 50% TFA in DCM (1 mL) for 2 h at room temperature. The resulting mixture was filtered, and the filtrate was evaporated to dryness in vacuo. The residue was freeze-dried after dissolving in ^{t}BuOH/water (4:1) to give the desired compounds based on prototype **4**.

2-Amino-3,4-dihydroquinazolin-1-ium Bromide 4(a) (Table 1). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.48 (s, 2H, CH_2Ph), 6.97 (d, 1H, J = 6.0 Hz, ArH), 7.08 (t, 1H, J = 7.5 Hz, ArH), 7.18 (d, 1H, J = 9.0 Hz, ArH), 7.25 (t, 1H, J = 7.5 Hz, ArH), 7.59 (s, 2H, NH_2), 8.35 (s, 1H, NH), 10.61 (s, 1H, $^+$NH).

2-Amino-6-chloro-3,4-dihydroquinazolin-1-ium Bromide 4(b) (Table 1). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.51 (s, 2H, CH_2Ph), 6.96 (d, 1H, J = 8.2 Hz, ArH), 7.17 (m, 1H, ArH), 7.29 (m, 1H, ArH), 7.72 (s, 2H, NH_2), 8.43 (s, 1H, NH), 10.87 (s, 1H, $^+$NH).

(3) General Procedure for Preparation of Prototype 8. The Fmoc groups of the Rink amide AM resin 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 × 5 mL). The resin so obtained was coupled with Fmoc-protected nonproteogenic amino acids (10-fold) by using HOBt (10-fold), DIC (10-fold), and DMF (1 mL) as solvent for 16 h at room temperature. The resin was filtered and 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 the resulting resin 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 × 5 mL). The resin so obtained was treated with *o*-nitrobenzaldehydes (10-fold) in trimethylorthoformate for 3 h at room temperature. The resin was then filtered and treated with 1% AcOH solution of trimethylorthoformate and $NaCNBH_3$ (10-fold) for 2 h at room temperature. The resin was filtered and washed successively with MeOH (3 × 2 mL), DMF (3 × 2 mL), DCM (3 × 2 mL), and ether (3 × 2 mL) and, finally, dried in vacuo to give **5**. Completion of the reaction was confirmed by a negative Kaiser test and positive chloranil test. The nitro group of resin **5** was reduced to amine with 2 M $SnCl_2 \cdot 2H_2O$ in DMF (1 mL) for 5 h at room temperature. Thereupon the resin was 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 to give **6**. Next, the resin **6** was treated with cyanogen bromide (10-fold) in DMF/EtOH (2:1) mixture for 16 h at room temperature. The resin was successively washed with DMF (3 × 2 mL), EtOH (3 × 2 mL), MeOH (3 × 2 mL), DCM (3 × 2 mL), and ether (3 × 2 mL) and dried in vacuo to give **7**. The resulting resin **7** was subjected to acidic cleavage with a mixture of 50% TFA in DCM (1 mL) for 2 h at room temperature. The resulting mixture was filtered, and the filtrate was evaporated to dryness in vacuo. The residue was freeze-dried after dissolving in ^{t}BuOH/water (4:1) to give the desired compounds based on prototype **8**.

2-Amino-3-(6′-amino-6′-oxohexyl)-3,4-dihydroquinazolin-1-ium Bromide 8(a) (Table 2). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.27 (m, 2H, CH_2), 1.51 (m, 2H, CH_2), 1.62 (m, 2H, CH_2), 2.05 (t, 2H, J = 7.2 Hz, CH_2CO), 3.42 (t, 2H, J = 7.5 Hz, CH_2N), 4.59 (s, 2H, CH_2Ph), 6.71 (s, 2H, CNH_2), 6.96 (d, 1H, J = 9 Hz, ArH), 7.08 (t, 1H, J = 7.5 Hz, ArH), 7.17(d, 1H, J = 9 Hz, ArH), 7.27 (t, 1H, J = 7.5 Hz, ArH), 7.95 (s, 2H, $CONH_2$), 10.79 (s, 1H, $^+$NH).

2-Amino-3-[4′-(amino carbonyl)phenyl]-3,4-dihydroquinazolin-1-ium Bromide 8(b) (Table 2). ^{1}H NMR (300 MHz, CD_3OD): δ = 4.55 (s, 2H, CH_2Ph), 7.20 (m, 3H, 3× ArH), 7.37 (m, 2H, 2× ArH), 7.56(d, 1H, J = 7.2 Hz, ArH), 7.94 (d, 2H, J = 8.7 Hz, 2× ArH).

2-Amino-3-(4′-amino-4′-oxobutyl)-3,4-dihydroquinazolin-1-ium Bromide 8(c) (Table 2). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.82 (t, 2H, J = 6.6 Hz, CH_2), 2.17 (t, 2H, J = 6.9 Hz, CH_2CO), 3.43 (t, 2H, J = 6.9 Hz, CH_2N), 4.58 (s, 2H, CH_2Ph), 6.95 (d, 1H, J = 9 Hz, ArH), 7.08 (t, 1H, J = 7.5 Hz, ArH), 7.17(d, 1H, J = 6 Hz, ArH), 7.26 (t, 1H, J = 7.5 Hz, ArH), 7.51 (s, 2H, $CONH_2$), 8.04 (s, 2H, CNH_2), 10.75 (s, 1H, $^+$NH).

(3) General Procedure for Preparation of Prototype 12 and 13 on RAM Resin. The Fmoc groups of Rink amide AM resin 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 × 5 mL). The resin so obtained was coupled with Fmoc-protected proteogenic amino acids (10-fold) by using HOBt (10-fold), DIC (10-fold), and DMF (1 mL) as solvent for 16 h at room temperature. The resin was filtered and 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 the resulting resin 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 × 5 mL). The resin so obtained was treated with *o*-nitrobenzaldehydes (10-fold) in trimethylorthoformate for 3 h at room temperature. The resin was then filtered and treated with 1% AcOH solution of trimethylorthoformate and $NaCNBH_3$ (10-fold) for 2 h at room temperature. The resin was filtered and washed successively with MeOH (3 × 2 mL), DMF (3 × 2 mL), DCM (3 × 2 mL), and ether (3 × 2 mL) and, finally, dried in vacuuo to give **9**. Completion of the reaction was confirmed by a negative Kaiser test and positive chloranil test. The nitro group of resin **9** was reduced to amine with 2M $SnCl_2 \cdot 2H_2O$ in DMF (1 mL) for 5 h at room temperature. Thereupon the resin was 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 to give **10**. Next, the resin **10** was treated with cyanogen bromide (10-fold) in DMF/EtOH (2:1) mixture for 16 h at room temperature. The resin was successively washed with DMF (3 × 2 mL), EtOH (3 × 2 mL), MeOH (3 × 2 mL), DCM (3 × 2 mL), and ether (3 × 2 mL) and dried in vacuo to give **11**. The resulting

resin **11** was then subjected to acidic cleavage with a mixture of 50% TFA in DCM (1 mL) for 2 h at room temperature. The resulting mixture was filtered, and the filtrate was evaporated to dryness in vacuo. The residue was freeze-dried after dissolving in ^{t}BuOH/water (4:1) to give the desired compounds based on prototypes **12** and **13**.

3-Methyl-1,5-dihydroimidazo[2,1-*b*]quinazoline-2(3*H*)-one (Prototype 12). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.11 (d, 3H, J = 6.9 Hz, CH_3), 1.26 (d, 3H, J = 6.9 Hz, CH_3, enantiomer), 3.77 (m, 1H, COCHN), 4.43 (d, 1H, J = 13.8 Hz, CH_2Ph), 4.56 (d, 1H, J = 13.8 Hz, CH_2Ph), 5.39 (s br, 1H, NH), 6.95 (d, 1H, J = 7.8 Hz, ArH), 7.02 (t, 1H, J = 7.5 Hz, ArH), 7.16 (d, 1H, J = 7.5 Hz, ArH), 7.22 (t, 1H, J = 7.6 Hz, ArH).

2-Amino-3-(2′-amino-2′-oxoethyl)-3,4-dihydroquinazolin-1-ium Bromide (Prototype 13). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.13 (s, 2H, CH_2Ph), 4.51 (s, 2H, CH_2-CO), 6.98 (d, 1H, J = 7.8 Hz, ArH), 7.08 (t, 1H, J = 7.2 Hz, ArH), 7.16 (d, 1H, J = 7.2 Hz, ArH), 7.28 (t, 1H, J = 7.5 Hz, ArH), 7.43 (s, 1H, $CONH_2$), 7.74 (s, 1H, $CONH_2$), 8.06 (s, 2H, CNH_2), 11.05 (s, 1H, $^+$NH).

(4) General Procedure for Preparation of Prototype 12 and 14 on WANG Resin Using Acidic Cleavage. The Wang resin was coupled with Fmoc-protected proteogenic amino acids (4-fold) by using Boc_2O (4-fold), pyridine (4-fold), DMAP (0.2-fold), and DCM (1 mL) as solvent for 16 h at 0 °C. The resin was filtered and washed successively with MeOH (3 × 2 mL), DCM (3 × 2 mL), and ether (3 × 2 mL) and, finally, dried in vacuo. The Fmoc groups of the resulting resin 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 × 5 mL). The resin so obtained was treated with *o*-nitrobenzaldehydes (10-fold) in trimethylorthoformate for 3 h at room temperature. The resin was then filtered and treated with 1% AcOH solution of trimethylorthoformate and $NaCNBH_3$ (10-fold) for 2 h at room temperature. The resin was filtered and washed successively with MeOH (3 × 2 mL), DMF (3 × 2 mL), DCM (3 × 2 mL), and ether (3 × 2 mL) and, finally, dried in vacuo to give **9**. Completion of the reaction was confirmed by a negative Kaiser test and positive chloranil test. The nitro group of resin **9** was reduced to amine with 2 M $SnCl_2 \cdot 2H_2O$ in DMF (1 mL) for 5 h at room temperature. Thereupon the resin was 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 to give **10**. Next, the resin **10** was treated with cyanogen bromide (10-fold) in DMF/EtOH (2:1) mixture for 16 h at room temperature. The resin was successively washed with DMF (3 × 2 mL), EtOH (3 × 2 mL), MeOH (3 × 2 mL), DCM (3 × 2 mL), and ether (3 × 2 mL) and dried in vacuo to give **11**. The resulting resin **11** was then subjected to acidic cleavage with a mixture of 50% TFA in DCM (1 mL) for 2 h at room temperature. The resulting mixture was filtered, and the filtrate was evaporated to dryness in vacuo. The residue was freeze-dried after dissolving in ^{t}BuOH/water (4:1) to give the desired compounds based on prototypes **12** and **14**.

2′-(2-Oxo-1,2,3,5-tetrahydroimidazo[2,1-*b*]quinazolin-3-yl) Acetic Acid (Prototype 12). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.86 (dd, 1H, J =5.1 Hz, J = 17.7 Hz, CH_2), 2.97 (dd, 1H, J = 4.2 Hz, J = 17.7 Hz, CH_2), 4.33 (t, 1H, J = 4.5 Hz, COCHN), 4.54 (d, 1H, J = 14.1 Hz, CH_2-Ph), 4.69 (d, 1H, J = 14.1 Hz, CH_2Ph), 7.09 (d, 1H, J = 8.1 Hz, ArH), 7.15 (t, 1H, J = 7.5 Hz, ArH), 7.22 (d, 1H, J = 7.2 Hz, ArH), 7.31 (t, 1H, J = 7.3 Hz, ArH), 12.25 (s br, 1H, COOH).

2-Amino-3-(carboxy methyl)-3,4-dihydroquinazolin-1-ium Bromide (Prototype 14). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 4.31 (s, 2H, CH_2N), 4.57 (s, 2H, CH_2Ph), 6.99 (d, 1H, J = 7.8 Hz, ArH), 7.09 (d, 1H, J = 7.5 Hz, ArH), 7.14 (t, 1H, J = 6.6 Hz, ArH), 7.29 (t, 1H, J = 7.5 Hz, ArH), 8.16 (s, 2H, NH_2), 11.11 (s, 1H, $^+$NH).

(5) General Procedure for Preparation of Prototype 12 on WANG Resin Using Base-Catalyzed Cyclative Cleavage. The Wang resin was coupled with Fmoc protected proteogenic amino acids (4-fold) by using Boc_2O (4-fold), pyridine (4-fold), DMAP (0.2-fold), and DCM (1 mL) as solvent for 16 h at 0 °C. The resin was filtered and washed successively with MeOH (3 × 2 mL), DCM (3 × 2 mL), and ether (3 × 2 mL) and, finally, dried in vacuo. The Fmoc groups of the resulting resin 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 × 5 mL). The resin so obtained was treated with *o*-nitrobenzaldehydes (10-fold) in trimethylorthoformate for 3 h at room temperature. The resin was then filtered and treated with 1% AcOH solution of trimethylorthoformate and $NaCNBH_3$ (10-fold) for 2 h at room temperature. The resin was filtered and washed successively with MeOH (3 × 2 mL), DMF (3 × 2 mL), DCM (3 × 2 mL), and ether (3 × 2 mL) and, finally, dried in vacuo to give **9**. Completion of the reaction was confirmed by a negative Kaiser test and positive chloranil test. The nitro group of resin **9** was reduced to amine with 2 M $SnCl_2 \cdot 2H_2O$ in DMF (1 mL) for 5 h at room temperature. Thereupon the resin was 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 to give **10**. Next, the resin **10** was treated with cyanogen bromide (10-fold) in DMF/EtOH (2:1) mixture for 16 h at room temperature. The resin was successively washed with DMF (3 × 2 mL), EtOH (3 × 2 mL), MeOH (3 × 2 mL), DCM (3 × 2 mL), and ether (3 × 2 mL) and dried in vacuo to give **11**. The resulting resin **11** was then subjected to basic cleavage with a mixture of 25% diisopropylamine in DCM (1 mL) for 12 h at room temperature. The resulting mixture was filtered, and the filtrate was evaporated to dryness in vacuo. The residue was freeze-dried after dissolving in ^{t}-BuOH/water (4:1) to give the desired compounds based on prototypes **12.** The ^{1}H NMR of compounds, for example, **12a**,**b**,**c**,**e** (Table 3) obtained using diisopropylamine-catalyzed cyclative cleavage showed the presence of residual diisopropylamine; however, after digesting with dichloromethane, only a negligible amount of diisopropylamine could be seen in the ^{1}H NMR, as in the case of **12**(**a**) and **12**(**e**) (Table 3).

3-(Phenyl methyl)-1,5-dihydroimidazo[2,1-*b*]quinazoline-2(3*H*)-one 12(b) (Table 3). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 2.99 (dd, 1H, J = 4.3 Hz, J = 14.4 Hz,

CHCH_2Ph), 3.18 (dd, 1H, $J = 4.1$ Hz, $J = 14.4$ Hz, CHCH_2-Ph), 4.12 (s, 1H, COCHN), 4.41 (s, 2H, CH_2Ph), 6.89 (d, 1H, $J = 6.0$ Hz, ArH), 7.00 (t, 1H, $J = 7.5$ Hz, ArH), 7.09 (d, 1H, $J = 6.0$ Hz, ArH), 7.20 (s br, 6H, 6× ArH).

3-(2′-Methyl propyl)-1,5-dihydroimidazo[2,1-*b*]quinazoline-2(3*H*)-one 12(c) (Table 3). ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.25$ (d, 6H, $J = 6.3$ Hz, Me_2CH), 1.65 (t, 2H, $J = 6.3$ Hz, CHCH_2), 1.88 (m, 1H, Me_2C*H*), 3.83 (t, 1H, $J = 5.8$ Hz, COCHN), 4.49 (d, 1H, $J = 13.8$ Hz, CH_2-Ph), 4.66 (d, 1H, $J = 13.8$ Hz, CH_2Ph), 6.99 (d, 1H, $J = 8.1$ Hz, ArH), 7.03 (d, 1H, $J = 7.8$ Hz, ArH), 7.17 (d, 1H, $J = 8.1$ Hz, ArH), 7.23 (d, 1H, $J = 7.5$ Hz, ArH).

3-Methyl-1,5-dihydroimidazo[2,1-*b*]quinazoline-2(3*H*)-one 12(a) (Table 3). ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 1.32$ (d, 3H, $J = 7.2$ Hz, CH_3), 3.97 (m, 1H, COCHN), 4.49 (d, 1H, $J = 13.8$ Hz, CH_2Ph), 4.63 (d, 1H, $J = 13.8$ Hz, CH_2Ph), 7.02 (d, 1H, $J = 8.1$ Hz, ArH), 7.09 (t, 1H, $J = 7.3$ Hz, ArH), 7.20 (d, 1H, $J = 7.5$ Hz, ArH), 7.27 (t, 1H, $J = 7.5$ Hz, ArH).

1,5-Dihydroimidazo[2,1-*b*]quinazoline-2(3*H*)-one 12(e) (Table 3). ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 3.93$ (s, 2H, CH_2N), 4.55 (s, 2H, CH_2Ph), 7.00 (d, 1H, $J = 9.0$ Hz, ArH), 7.07 (t, 1H, $J = 7.5$ Hz, ArH), 7.19 (d, 1H, $J = 6.0$ Hz, ArH), 7.25 (t, 1H, $J = 7.5$ Hz, ArH).

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Supporting Information Available. Spectra for representative compounds listed in Tables 1 and 2 and for prototypes 12-14. This material is available free of charge via the Internet at http;//pubs.acs.org.

References and Notes

(1) Brase, S.; Gil, G.; Knepper, K. *Bioorg. Med. Chem. Lett.* **2002**, *10*, 2415.

(2) Krchnak, V.; Holladay, M. W. *Chem. Rev.* **2002**, *102*, 61.

(3) (a) Kesarwani, A. P.; Srivastava, G. K.; Rastogi, S. K.; Kundu. B. *Tetrahedron Lett.* **2002**, *43*, 5579. (b) Batra, S.; Rastogi, S. K.; Kundu, B.; Patra, A.; Bhaduri, A. P. *Tetrahedron Lett*. **2000**, *41*, 5971. (c) Srinivasan, T.; Gupta, P.; Kundu, B. *Tetrahedron Lett*. **2001**, *42*, 5993. (d) Rastogi, S. K.; Gupta, P.; Srinivasan, T.; Kundu, B. *Mol. Diversity* **2000**, *5*, 91. (e) Tripathi, R. P.; Rastogi, S. K.; Kundu, B.; Saxena, J. K.; Reddy, V. J. M.; Srivastva, S.; Chandra, S.; Bhaduri, A. P. *Comb. Chem. High Throughput Screening* **2001**, *4*, 237. (f) Gupta, P.; Singh, S. K.; Pathak, A.; Kundu B. *Tetrahedron* **2002**, *58*, 10469. (g) Rastogi, S. K.; Srivastava, G. K.; Singh, S. K.; Grover, R.; Roy, R.; Kundu, B. *Tetrahedron Lett*. **2002**, *43*, 8327.

(4) Mannschreck, A.; Koller, H.; Stuhler, G.; Davies, M. A.; Traber, J. *Eur. J. Med. Chem*. **1984**, *19*, 381.

(5) Molamas, M. S.; Miller J. *J. Med. Chem.* **1991**, *34*, 1492.

(6) (a) Fry, D. W. *Expert Opin. Invest. Drugs* **1994**, *3*, 577. (b) Gibson, K. H.; Grundy, W.; Godfrey, A. A.; Woodburn, J. R.; Asthon, S. E.; Curry, B. J.; Scarlett, L.; Barker, A. J.; Brown, D. S. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2723. (c) Myers, M. R.; Setzer, N. N.; Spada, A. P.; Zulli, A. L.; Hsu, C. Y. J.; Zilberstein, A.; Johnson, S. E.; Hook, L. E.; Jacoski, M. V. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 417.

(7) Wang, F.; Hauske, J. R. *Tetrahedron Lett*. **1997**, *38*, 8651.

(8) Spencer, C. M.; Brogden, R. N. *Drugs* **1994**, *47*, 809.

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