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Traceless, Self-Cleaving Solid- and Solution-Phase Parallel Synthesis of 3,4,7-Trisubstituted 3,4-Dihydroquinoxalin-2-ones

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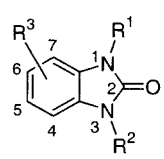
This article describes a new methodology for the parallel synthesis of 3,4-dihydroquinoxalin-2-ones containing three points of diversity. The synthesis begins with commercially available resin-bound α-amino acids as the source of the first diversity element and employs a combination of solid- and solution-phase chemistry to introduce the other two. The key step is an intramolecular cyclization and simultaneous traceless cleavage from the solid support to give a disubstituted 3,4-dihydroquinoxalin-2-one. The third substituent is introduced in solution by N-alkylation of the aniline nitrogen using a scavenger resin to dispose of excess reagent. All the reactions in the sequence take place at room temperature without the need to use strong acids or to maintain an inert atmosphere, thereby preserving the chiral integrity of the starting α-amino acid and facilitating the generation of libraries in a high-throughput parallel format.

Introduction

Combinatorial chemistry has become a powerful tool for the rapid generation of libraries of small organic molecules. Many of the advances in this field have been geared toward the discovery and optimization of new chemical leads as potential drug candidates. Not surprisingly then, the level of interest in combinatorial or parallel methods of synthesis of heterocyclic, "druglike" molecules has been and continues to be quite high.[1] Interestingly, most of these efforts deal primarily with either solid- or solution-phase chemistry, even though it has been recognized that each of these methodologies has its own limitations in terms of ease of automation, reproducibility, and versatility. To be able to synthesize compound libraries of increasing molecular complexity, it could be advantageous to develop methods that combine the expediency of solid-phase synthesis with the flexibility of solution-phase chemistry. We report such a hybrid strategy for the parallel synthesis of 3,4,7-trisubstituted 3,4-dihydroquinoxalin-2-ones.

The [6.6]-ring fused quinoxalinone system, **2**, like its [6,5]-fused benzimidazolone and [6,7]-fused 1,5-benzodiazepin-2-one homologues **1** and **3**, respectively, is a useful scaffold for the construction of small heterocycle libraries.[2]

Although not as extensively investigated as their higher benzodiazepine homologues, quinoxalinones have been shown to possess significant biological properties, including inhibition of aldose reductase[3] and PDGF receptor tyrosine kinase,[4] partial agonism and antagonism of the $GABA_A$/benzodiazepine receptor complex,[5] and antagonism of the AMPA[6] and angiotensin II[7] receptors. This level of biological activity has elicited an interest in these compounds, and recently several groups have reported new solid-phase synthetic approaches toward quinoxalinones.[8] Common features of these approaches are the construction of the quinoxalinone ring attached to a solid support through the C7 carbon and the subsequent acid-induced release of the product into solution. Notwithstanding the utility and broad scope of these strategies, a number of side reactions were observed during acid-induced cleavage of 3-substituted 3,4-dihydroquinoxalin-2-ones, including racemization of the C3 carbon and oxidation of the 3,4-carbon−nitrogen bond. It occurred to us that these side reactions could be avoided by developing an approach in which the 3,4-dihydroquinoxalinone scaffold would be formed and cleaved form the solid support under acid-free conditions. These requirements would be most readily satisfied by a strategy involving the intramolecular cyclization of an appropriately substituted resin-bound α-amino acid (cf. **5** in Scheme 1) and concurrent self-cleavage of the resulting 3,4-dihydroquinoxalinone from the solid support. Furthermore, such an approach would have the extra advantage of leaving no trace of the resin linker. Scheme 1 illustrates this strategy retrosynthetically.



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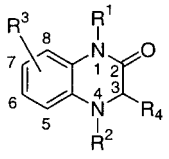

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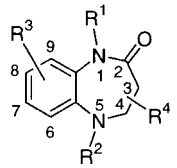

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Results and Discussion

The implementation of our synthetic approach is shown in Scheme 2. The Fmoc protecting group of commercially available *N*-α-Fmoc-amino acids **8** preloaded onto Wang resin was removed with 20% piperidine in dimethylforma-

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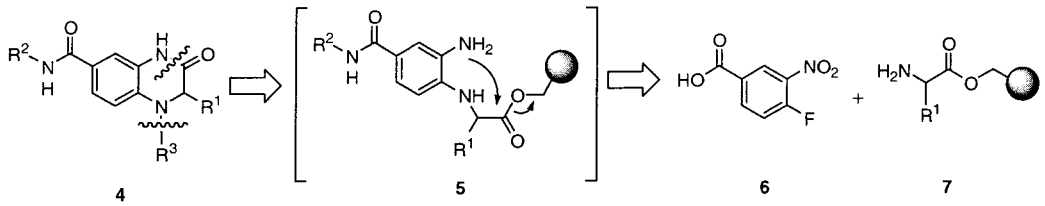
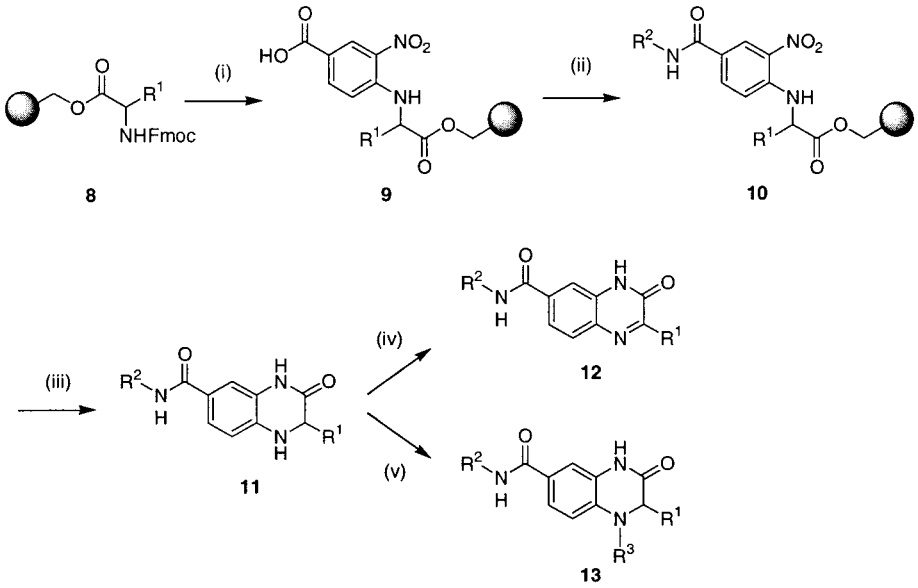
Scheme 1



Scheme 2[a]



[a] Reagents: (i) 20% piperidine, DMF, then (3-NO_2-4-F)-$PhCO_2H$, DIPEA, DMAP, DMF; (ii) R^2NH_2, HBTU, DIPEA, DMF; (iii) $SnCl_2 \cdot 2H_2O$, DMF; (iv) *p*-chloranil, DCM/DMF; (v) R^3CH_2Br, Cs_2CO_3, acetone.

mide (DMF). The resulting amines were then reacted with 4-fluoro-3-nitrobenzoic acid in the presence of diisopropylethylamine (DIPEA) and a catalytic amount of *N*,*N*-(dimethylamino)pyridine (DMAP) to give the 2-nitro-4-carboxyanilines **9** in both high yield (≥75%) and purity (≥95%), as determined by LC/MS analysis of the intermediates released from the resins upon treatment with a 20% solution of TFA in dichloromethane (DCM). The same results were obtained whether the ipso-fluoride displacement was performed at room temperature for 24 h or at 45 °C for 8 h.

The second element of diversity was introduced by amidation of the carboxyl group with a variety of amines using standard peptide coupling conditions, i.e., *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) and DIPEA in DMF. Interestingly, the chemical yield and purity of the resulting amides **10** were found to be dependent not only on the nature of the amine reagent but also on the nature of the resin-bound α-amino acid. Unhindered alkylamines, such as 3-fluorobenzylamine, consistently provided the highest yield and purity of amides with all of the supported substrates examined, whereas sterically hindered alkylamines, such as benzhydrylamine, were just as good as anilines bearing electron-donating substituents (e.g., 4-methoxyaniline). The side chain (R^1) of the starting α-amino acid also had a noticeable effect on the extent of the amidation. Indeed, carboxyanilines **9** prepared from resin-bound alanine (R^1 = Me) gave significantly higher yields of amides **10** than those obtained from resin-bound valine (R^1 = i-Pr) or leucine ($R^1 = Me_2CHCH_2$); carboxyanilines **9** generated from resin-bound phenylalanine ($R^1 = PhCH_2$) reacted to provide amides **10** in the lowest yields.[9]

The third step of our synthetic strategy was the most critical, for it required three discrete processes to occur in a concerted fashion and in high yield: (a) reduction of the aromatic nitro group, (b) nucleophilic addition of the resulting aniline onto the resin-bound ester carbonyl, and (c) elimination of the *p*-benzyloxy resin from the tetrahedral intermediate, freeing the product into solution. It was not totally apparent to us that a high yield could be obtained by intramolecular cyclization of a hindered aminoester such as **5** (Scheme 1) and concurrent cleavage of the quinoxalinone from the solid support. As discussed below, our concerns turned out to be unwarranted.

Treatment of resins **10** with $SnCl_2 \cdot 2H_2O$ in DMF at room temperature for 24 h delivered the 3,4-dihydroquinoxalin-2-ones **11** in solution.[10] The reaction workup was straightforward. The filtrates were collected in scintillation vials and concentrated in a centrifugal evaporator. The residues were partitioned between ethyl acetate and 5% aqueous NaOH and sonicated for 5−10 min. The organic layers were removed, dried over anhydrous Na_2SO_4, filtered into tared scintillation vials, and concentrated as described before.

The products were analyzed for purity and identity by LC/MS and ^1H NMR. The purity of the 3,4-dihydroquinoxalinones **11** was consistently high, ranging from 77% to 97%, whereas the overall yield for the three steps was dependent

Table 1. Disubstituted 3,4-Dihydroquinoxalin-2-ones

compound	(chirality)-R^1	R^2	purity (%)	yield (%)	MW	MS ($ES^{-/+}$) *m/z*
11a	(L)-Me	4-MeO−Ph−	97	66	311.34	312
11b	(L)-Me	Ph_2CH−	96	56	371.44	370
11c	(L)-Me	3-F−$PhCH_2$−	94	55	313.33	312
11d	(L)-i-Pr	4-MeO−Ph−	97	54	339.39	340
11e	(L)-i-Pr	Ph_2CH−	87	61	399.49	400
11f	(L)-i-Pr	3-F−$PhCH_2$−	94	66	341.39	340
11g	(D)-i-Pr	3-F−$PhCH_2$−	91	23	341.39	342
11h	(L)- Me_2CHCH_2−	4-MeO−Ph-	87	52	353.42	352
11i	(L)- Me_2CHCH_2−	Ph_2CH−	92	56	413.52	412
11j	(L)- Me_2CHCH_2−	3-F−$PhCH_2$−	86	56	355.41	354
11k	(L)-$PhCH_2$−	4-MeO−Ph−	93	24	387.44	386
11l	(L)-$PhCH_2$−	Ph_2CH−	77	32	447.54	446
11m	(L)-$PhCH_2$−	3-F−$PhCH_2$−	80	32	389.43	388
11n	(L)-Pro[R^1−$(CH_2)_3$−R^3]	3-F−$PhCH_2$−	92	47	339.37	338

Table 2. Trisubstituted 3,4-Dihydroquinoxalin-2-ones

compound	(chirality)-R^1	R^2	R^3	purity (%)	yield (%)	MW	MS (ES^-) *m/z*
13a	(L)-Me	4-MeO−Ph-	CH_3−	96	77	325.37	324
13b	(L)-Me	Ph_2CH−	2-NO_2−$PhCH_2$−	87	56	506.56	505
13c	(L)-Me	3-F−$PhCH_2$−	3,5-$(MeO)_2PhCH_2$−	85	78	463.51	462
13d	(L)-i-Pr	4-MeO−Ph−	CH_3−	96	66	353.42	352
13e	(L)-i-Pr	Ph_2CH−	2-NO_2−$PhCH_2$−	78	57	534.62	533
13f	(L)-i-Pr	3-F−$PhCH_2$−	3,5-$(MeO)_2PhCH_2$−	84	92	491.56	490
13g	(D)-i-Pr	3-F−$PhCH_2$−	3,5-$(MeO)_2PhCH_2$−	73	52	491.56	490
13h	(L)-Me_2CHCH_2−	4-MeO−Ph−	CH_3−	83	76	367.45	366
13i	(L)-Me_2CHCH_2−	Ph_2CH−	2-NO_2−$PhCH_2$−	75	39	548.64	547
13j	(L)-Me_2CHCH_2−	3-F−$PhCH_2$−	3,5-$(MeO)_2PhCH_2$−	74	72	505.59	504
13k	(L)-$PhCH_2$−	4-MeO−Ph−	CH_3−	84	72	401.47	400
13l	(L)-$PhCH_2$−	Ph_2CH−	2-NO_2−$PhCH_2$−	67	32	582.66	581
13m	(L)-$PhCH_2$−	3-F−$PhCH_2$−	3,5-$(MeO)_2PhCH_2$−	74	40	539.61	538

on the nature of the starting α-amino acid and ranged from 23% to 66% (Table 1). The low yields obtained with phenylalanine were mostly due to incomplete amidation in the second step; the resulting 7-carboxylic acid substituted 3,4-dihydroquinoxalinone was removed during the isolation protocol.

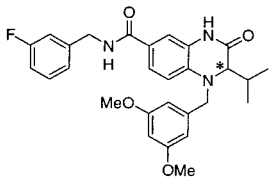
In all the examples examined, no trace of byproducts arising from oxidation of the 3,4-carbon−nitrogen bond were detected, as expected from an acid-free, self-cleaving reaction step. Notwithstanding this observation, the 3,4-dihydroquinaxolin-2-ones **11** could be easily and cleanly oxidized to the corresponding quinoxalinones **12** with a small excess of *p*-chloranil at room temperature (Scheme 2).

To incorporate a third element of diversity, we studied the alkylation of the aniline nitrogen in solution phase. To this end, a representative 3,7-disubstituted 3,4-dihydroquinoxalinone **11** was treated with different combinations of base (NaH, K_2CO_3, Cs_2CO_3, Et_3N), alkylating agent, and solvent (DMSO, DMF, acetone), at room temperature or 45 °C, and for varying amounts of time. The progress of these reactions was monitored by LC/MS. The conditions that provided the best overall results, both in terms of yield and purity of the N4-alkylated products, were 3 equiv of Cs_2CO_3 and 5 equiv of alkyl halide in acetone at room temperature for 8 h.[11] Several different workup protocols were examined for their reproducibility and adaptability to a high-throughput format. The one selected consisted of diluting the reaction mixtures with dichloromethane, washing the organic solutions with aqueous HCl to remove inorganic salts, and then treating them with tris(2-aminoethyl)amine polystyrene scavenger resin to simultaneously remove any excess of alkylating agent and acid. The solutions were then filtered and concentrated, and the crude products were purified by parallel flash chromatography on silica gel-filled SPE cartridges to afford 3,4,7-trisubstituted 3,4-dihydroquinoxalin-2-ones **13** in 67−96% purity and 32−92% yield; 13 different analogues were prepared in parallel (Table 2).

The final test of this methodology required demonstration that the chiral integrity of the starting α-amino acid had been maintained throughout all four synthetic steps. To address this issue, the sequence of reactions described above was repeated with both Fmoc-L-valine and Fmoc-D-valine Wang resins as the starting materials. The resulting 3,4,7-trisubstituted 3,4-dihydroquinoxalin-2-ones **13f** and **13g** were then analyzed by chiral HPLC and found to be optically pure. The calculated enantiomeric excess (ee) and measured optical rotation for each enantiomer are given in Figure 1.

Conclusions

A new methodology for the parallel synthesis of 3,4,7-trisubstituted 3,4-dihydroquinoxalin-2-ones has been developed using a combination of solid- and solution-phase steps. The approach employs commercially available resin-bound α-amino acids as the starting materials, leaves no trace of the resin linker, and preserves the chiral integrity of the products. Furthermore, the results obtained with proline (cf. **11n**, Table 1), an amino acid possessing a secondary amino group, indicate that N-alkylated α-amino acids can also be used as starting building blocks, thereby offering an alternative way of introducing the quinoxalinone N4-substituent. In addition to alkyl halides, acyl halides and isocyanates may



13f, g

Compound	Starting Resin	ee (%)[a]	$[\alpha]_D$ [b]
13f	Fmoc-*L*-Val-Wang	98	+26.1°
13g	Fmoc-*D*-Val-Wang	99	-32.8°

[a]Calculated using LC areas (retention times: **13f**=10.1 min; **13g**=11.2 min)

[b]Specific rotations at 25°C in $CHCl_3$. **13f**: c=0.93; **13g:** c=1.27

Figure 1.

also be used to derivatize such nitrogen, allowing an even higher degree of molecular diversity.

Experimental Section

Materials and Methods. Wang resin (styrene−1% DVB copolymer, 100−200 mesh) was obtained from NovaBiochem (catalog no. 01-64-0014) or Chem-Impex (catalog no. 01927). Tris(2-aminoethyl)amine polystyrene scavenger resin was obtained from Argonaut Technologies (catalog no. 800228). Solvents were purchased from EM Science, J. T. Baker, Mallinckrodt, or Aldrich and were anhydrous and/or HPLC grade. Reactions were performed in individual polypropylene tubes (Pharmacia Biotech, catalog no. 17-0435-01 or BioRad, catalog no. 732-1010), scintillation vials (Wheaton Scientific-VWR, catalog no. 986541), or amber jars (Qorpak-VWR, catalog no. 7930). Stirring/mixing was achieved by gentle 360° rotation on a Glas-Col rotator. Filtrations and washings were carried out on a multiport vacuum manifold (Supelco Visiprep, catalog no. 5-7030). Solvent evaporation was performed on a GeneVac Atlas HT-8 centrifugal evaporator. Crude products were purified by parallel chromatography using Supelclean LC-Si SPE cartridges (Supelco, catalog no. 5-7051). Purity and molecular parent ion identity were determined on a Hewlett-Packard HP1100 LC/MSD instrument using a Zorbax Eclipse XDB-C8 column (4.6 mm × 150 mm, 3.5 μm, catalog no. 935967-906), a 10 mM aqueous ammonium acetate/acetonitrile mobile phase (95:5 to 10:90 v/v gradient, with 0.1% acetic acid as a modifier and a 5.0 min run time), a flow rate of 2.0 mL/min with a splitter to 0.4 mL/min post-column; UV detection at 254 nm, and atmospheric-pressure electrospray ionization (API-ES) in either a negative or positive mode. Chiral HPLC analysis was performed on a Beckman Gold HPLC using a 4.6 mm × 250 mm, 5.0 μm, Chiralcel OD column (J. T. Baker, catalog no. 7195) and UV detection at 220 nm. The structures of the final products were confirmed by ^{1}H NMR on a Varian Gemini-300 instrument; chemical shifts are reported in ppm downfield from internal tetramethylsilane. Chemical yields of compounds prepared on a solid support and cleaved with TFA were calculated based on the molecular weight of their trifluoroacetate salts; all yields reported are corrected for purity. Compounds names were generated with the Chemistry 4-D Draw software from ChemInnovation Software, Inc. (San Diego, CA).

Procedure for the Synthesis of Resins 9. The synthesis of 4-[(carboxyethyl)amino]-3-nitrobenzoic acid (**9a**) illustrates this general procedure. Fmoc-Ala-Wang resin **(8a)** (Chem-Impex, catalog no. 04163, lot no. 1903-0897-01, 1.5 g, 0.77 mmol) was placed in a 30 mL amber jar and swollen with DMF (5 mL). A solution of 20% piperidine in DMF (15 mL) was added, and the suspension was mixed for 20 min. The resin was filtered and washed with DMF (3 × 20 mL each). This Fmoc-deprotection step was repeated once more. Then, a solution of 4-fluoro-3-nitrobenzoic acid (1.4 g, 7.7 mmol) in DMF (15 mL) was added to the resin, followed by DIPEA (1.3 mL, 7.7 mmol) and a catalytic amount of DMAP dissolved in DMF (1 mL). The suspension was mixed at room temperature for 24 h, filtered through a 30 mL fritted funnel, washed successively with DMF, 2-propanol, and DCM (3 × 20 mL each), and dried under vacuum. An aliquot of this resin (0.4 g) was placed in a 12 mL fritted tube and treated with 20% TFA in DCM (6 mL) for 20 min. The filtrate was collected in a tared scintillation vial, and the resin was washed with DCM (5 mL). The combined filtrate and washing was concentrated to dryness to obtain **9a** (64 mg, 99% pure by HPLC, 75% yield). ^{1}H NMR (DMSO-d_6/D_2O): δ 1.45 (3H, d, J = 6.8 Hz), 4.44 (1H, q, J = 6.5 Hz), 7.00 (1H, d, J = 9.3 Hz), 7.95 (1H, d, J = 8.9 Hz), 8.59 (1H, s). MS (ES^-): m/z 253 (M − H), 367 (M + 113).

Procedure for the Synthesis of Resins 10. The synthesis of 2-({4-[*N*-(4-methoxyphenyl)carbamoyl]-2-nitrophenyl}-amino)propanoic acid (**10a**) illustrates this general procedure. Resin **9a** (1.1 g, 0.56 mmol) was placed in a 30 mL amber jar and swollen with DMF (5 mL). A solution of HBTU (0.84 g, 2.2 mmol) in DMF (10 mL) was added, followed by DIPEA (0.38 mL, 2.2 mmol) and a catalytic amount of DMAP dissolved in DMF (1 mL). The suspension was mixed at room temperature for 15 min and then treated with a solution of 4-methoxyaniline (0.69 g, 5.6 mmol) in DMF (5 mL). The mixture was stirred at room temperature for 4 h and filtered, and the resin was successively washed with DMF, 2-propanol, and DCM (3 × 20 mL each) and dried under vacuum. An aliquot of this resin (0.35 g) was placed in a 12 mL fritted tube and treated with 20% TFA in DCM (6 mL) for 20 min. The filtrate was collected in a tared scintillation vial, and the resin was washed with DCM (5 mL). The combined filtrate and washing was concentrated to dryness to obtain **10a (**78 mg, 84% pure by LC/MS, 77% yield). ^{1}H NMR (DMSO-d_6): δ 1.49 (3H, d, J = 6.8 Hz), 3.74 (3H, s), 4.54 (1H, q, J = 6.8 Hz), 6.92 (2H, d, J = 8.9 Hz), 7.12 (1H, d, J = 9.3 Hz), 7.64 (2H, d, J = 8.9 Hz), 8.12 (1H, d, J = 9.2 Hz), 8.77 (1H, d, J = 6.5 Hz), 8.80 (1H, s), 10.1 (1H, s). MS (ES^-): m/z 358 (M − H), 472 (M + 113).

Synthesis of 3,4-Dihydroquinoxalinones (11). The preparation of *N*-(4-methoxyphenyl)[2-methyl-3-oxo(1,2,4-trihydroquinoxalin-6-yl)]carboxamide (**11a**) illustrates this general procedure. Resin **10a** (0.75 g, 0.38 mmol) was placed in a

20 mL scintillation vial and swollen with DMF (3 mL). A solution of $SnCl_2 \cdot 2H_2O$ (0.86 g, 3.8 mmol) in DMF (6 mL) was added. The vial was closed with a PTFE-lined cap and stirred at room temperature for 24 h. The resin was filtered through a 12 mL fritted tube, and the filtrate was collected in a 20 mL scintillation vial. The solvents were evaporated, and the viscous orange oil that remained was sonicated with EtOAc (10 mL) and 5% aqueous NaOH (8 mL) for 5−10 min. The resulting mixture was poured into a 60 mL separatory funnel and washed with water (15 mL). The organic phase was decanted, dried with Na_2SO_4, filtered into a tared 20 mL scintillation vial, and concentrated to dryness to obtain **11a** (80 mg, 97% pure by LC/MS, 66% yield). ^{1}H NMR (DMSO-d_6): δ 1.29 (3H, d, J = 6.4 Hz), 3.73 (3H, s), 3.90 (1H, q, J = 6.5 Hz), 6.58 (1H, s), 6.71 (1H, d, J = 7.9 Hz), 6.90 (2H, d, J = 8.9 Hz), 7.35 (1H, s), 7.47 (1H, d, J = 8.3 Hz), 7.62 (2H, d, J = 8.8 Hz), 9.79 (1H, s), 10.4 (1H, s). MS (ES$^+$): m/z 312 (M + H).

Synthesis of Quinoxalinones (12) by Oxidation of 3,4-Dihydroquinoxalinones (11). The synthesis of *N*-[(3-fluorophenyl)methyl][2-(methylethyl)-3-oxo(4-hydroquinoxalin-6-yl)]carboxamide (**12f**) illustrates this general procedure. Dihydroquinoxalin-2-one (**11f**) (53 mg, 0.16 mmol) was placed in a scintillation vial and suspended in DCM (5 mL). A solution of tetrachloro-1,4-benzoquinone (*p*-chloranil, 50 mg, 0.2 mmol) in DMF (1 mL) was added to the vial dropwise. The mixture was stirred at room temperature for 3 h and concentrated to dryness. The solid residue was taken up in 20% EtOAc in hexane (4 mL) and loaded onto a 1.0 g silica gel-filled SPE cartridge conditioned with the same eluent. The first 10 mL of eluent was discarded, and the product was then eluted with 100% EtOAc (10 mL) and collected in a tared scintillation vial. Evaporation of the solvent provided **12f** (46 mg, 88% pure by LC/MS, 74% yield). ^{1}H NMR (DMSO-d_6): $\boldsymbol{\delta}$ 1.13 (6H, d, J = 3.7 Hz), 3.49 (1H, m), 4.50 (2H, d, J = 5.8 Hz), 7.12 (3H, m), 7.38 (1H, m), 7.78 (3H, m), 9.26 (1H, t, J = 5.4 Hz), 12.5 (1H, s). MS (ES$^+$): m/z 340 (M + H).

Solution-Phase Synthesis of Trisubstituted 3,4-Dihydroquinoxalinones (13). The synthesis of (1,2-dimethyl-3-oxo-1,2,4-trihydroquinoxalin-6-yl)-*N*-(4-methoxy-phenyl)carboxamide (**13a**) illustrates this general procedure. Dihydroquinoxalinone (**11a**) (25 mg, 0.08 mmol) was placed in a 20 mL scintillation vial with a magnetic stirring bar and suspended in acetone (3 mL). Solid Cs_2CO_3 (78 mg, 0.24 mmol) was added to the suspension, followed by iodomethane (25.0 μL, 0.4 mmol). The mixture was stirred at room temperature for 8 h, diluted with DCM (8 mL), and poured into a 60 mL separatory funnel. The organic solution was washed with water (20 mL) and then with 20% aqueous HCl until neutral pH was reached. The organic layer was decanted, dried with Na_2SO_4, and filtered into a 12 mL fritted tube containing tris(2-aminoethyl)amine polystyrene scavenger resin (0.25 g, 1.2 mmol). Triethylamine (112.0 μL, 0.8 mmol) was added, and the mixture was stirred at room temperature overnight. The suspension was filtered, and the filtrate was collected in a scintillation vial and concentrated to dryness. The residue was taken up in 20% EtOAc in hexane (3 mL), the suspension was briefly sonicated and then loaded onto a 1 g silica gel-filled SPE cartridge conditioned with the same eluent. The first 10 mL of the eluent was discarded, and the product was then eluted with 20% MeOH in EtOAc (10 mL) and collected in a tared scintillation vial. The solvents were evaporated to afford **13a** (20 mg, 96% pure by LC/MS, 77% yield). ^{1}H NMR (DMSO-d_6): δ 1.31 (3H, d, J = 6.7 Hz), 3.34 (3H, s), 3.74 (3H, s), 3.95 (1H, q, J = 6.4 Hz), 6.68 (1H, s), 6.80 (1H, d, J = 8.2 Hz), 6.92 (2H, d, J = 8.6 Hz) 7.60 (4H, m), 9.84 (1H, s). MS (ES$^-$): m/z 324 (M − H).

The following compounds were synthesized using the above procedure.

***N*-(Diphenylmethyl){2-methyl-1-[(2-nitrophenyl)methyl]-3-oxo(1,2,4-trihydro-quinoxalin-6-yl)}carboxamide (13b).** Obtained 33 mg, 87% pure by LC/MS, 56% yield. ^{1}H NMR (DMSO-d_6): δ 1.38 (3H, d, J = 6.5 Hz), 4.16 (1H, q, J = 6.3 Hz), 5.50 (2H, m), 6.28 (1H, d, J = 8.8 Hz), 6.81 (2H, m), 7.68−7.09 (15H, m), 8.23 (1H, d, J = 8.3 Hz), 8.85 (1H, d, J = 8.3 Hz). MS (ES$^-$): m/z 505 (M − H).

{1-[(3,5-Dimethoxyphenyl)methyl]-2-methyl-3-oxo(1,2,4-trihydroquinoxalin-6-yl)}-*N*-[(3-fluorophenyl)methyl]carboxamide (13c). Obtained 43 mg, 85% pure by LC/MS, 78% yield. ^{1}H NMR (DMSO-d_6): δ 1.34 (3H, d, J = 6.3 Hz), 3.67 (6H, s), 4.08 (1H, m), 4.42 (2H, d, J = 5.4 Hz), 5.08 (2H, m), 6.37 (3H, m), 6.78 (2H, d, J = 8.2 Hz), 7.09 (3H, m), 7.40 (3H, m), 8.77 (1H, m). MS (ES$^-$): m/z 462 (M − H).

***N*-(4-Methoxyphenyl)[1-methyl-2-(methylethyl)-3-oxo-(1,2,4-trihydroquinoxalin-6-yl)]carboxamide (13d).** Obtained 24 mg, 96% pure by LC/MS, 66% yield. ^{1}H NMR (DMSO-d_6/D_2O): δ 0.84 (6H, m), 1.98 (1H, m), 3.32 (3H, s), 3.71 (4H, m), 6.83 (4H, m), 7.60 (4H, m), 9.83 (1H, s). MS (ES$^-$): m/z 352 (M − H).

***N*-(Diphenylmethyl){2-(methylethyl)-1-[(2-nitrophenyl)methyl]-3-oxo(1,2,4-trihydroquinoxalin-6-yl)}carboxamide (13e).** Obtained 54 mg, 78% pure by LC/MS, 57% yield. ^{1}H NMR (DMSO-d_6): δ 0.95 (6H, m), 2.10 (1H, m), 3.86 (1H, d, J = 5.9 Hz), 5.52 (2H, m), 6.28 (1H, d, J = 8.7 Hz), 7.31−6.89 (14H, m), 7.60 (3H, m), 8.23 (1H, d, J = 8.1 Hz), 8.83 (1H, d, J = 8.7 Hz). MS (ES$^-$): m/z 533 (M − H).

{(2S)-1-[(3,5-Dimethoxyphenyl)methyl]-2-(methylethyl)-3-oxo(1,2,4-trihydro-quinoxalin-6-yl)}-*N*-[(3-fluorophenyl)-methyl]carboxamide (13f). Obtained 132 mg, 84% pure by LC/MS, 92% yield. ^{1}H NMR (DMSO-d_6): δ 0.94 (6H, m), 2.04 (1H, m), 3.67 (6H, s), 3.80 (1H, d, J = 5.5 Hz), 4.42 (2H, d, J = 5.0 Hz), 4.94 (1H, d, J = 15.6 Hz), 5.27 (1H, d, J = 15.6 Hz), 6.41 (3H, m), 6.85 (2H, d, J = 5.8 Hz), 7.07 (3H, m), 7.38 (3H, m), 8.74 (1H, t, J = 5.0 Hz). MS (ES$^-$): m/z 490 (M − H).

{(2R)-1-[(3,5-Dimethoxyphenyl)methyl]-2-(methylethyl)-3-oxo(1,2,4-trihydroquinoxalin-6-yl)}-*N*-[(3-fluorophenyl-)methyl]carboxamide (13g). Obtained 42 mg, 73% pure by LC/MS, 52% yield. ^{1}H NMR (DMSO-d_6): δ 0.93 (6H, m), 2.05 (1H, m), 3.67 (6H, s), 3.80 (1H, d, J = 5.9 Hz), 4.42 (2H, d, J = 5.4 Hz), 4.94 (1H, d, J = 15.7 Hz), 5.27 (1H, d, J = 15.7 Hz), 6.40 (3H, m), 6.84 (2H, d, J = 4.1 Hz), 7.09 (3H, m), 7.38 (3H, m), 8.76 (1H, t, J = 5.8 Hz). MS (ES$^-$): m/z 490 (M − H).

***N*-(4-Methoxyphenyl)[1-methyl-2-(2-methylpropyl)-3-oxo(1,2,4-trihydroquinoxalin-6-yl)]carboxamide (13h).** Obtained 47 mg, 83% pure by LC/MS, 76% yield. ^{1}H NMR (DMSO-d_6): δ 0.89 (6H, d, J = 3.2 Hz), 1.43 (2H, m), 1.81 (1H, m), 3.33 (3H, s), 3.74 (3H, s), 3.91 (1H, m), 6.72 (1H, s), 6.85 (3H, m), 7.62 (4H, m), 9.82 (1H, s). MS (ES$^-$): *m*/*z* 366 (M − H).

***N*-(Diphenylmethyl){2-(2-methylpropyl)-1-[(2-nitrophenyl)methyl]-3-oxo(1,2,4-trihydroquinoxalin-6-yl)}-carboxamide (13i).** Obtained 42 mg, 75% pure by LC/MS, 39% yield. ^{1}H NMR (DMSO-d_6): δ 0.92 (6H, d, J = 6.4 Hz), 1.56 (2H, m), 1.83 (1H, m), 4.09 (1H, t, J = 6.1 Hz), 5.51 (2H, m), 6.29 (1H, d, J = 8.4 Hz), 7.25 (17H, m), 8.23 (1H, d, J = 8.2 Hz), 8.86 (1H, d, J = 8.6 Hz). MS (ES$^-$): *m*/*z* 547 (M − H).

{1-[(3,5-Dimethoxyphenyl)methyl]-2-(2-methylpropyl)-3-oxo(1,2,4-trihydro-quinoxalin-6-yl)}-*N*-[(3-fluorophenyl)-methyl]carboxamide (13j). Obtained 79 mg, 74% pure by LC/MS, 72% yield. ^{1}H NMR (DMSO-d_6): δ 0.90 (6H, d, J = 5.9 Hz), 1.46 (2H, m), 1.87 (1H, m), 3.67 (6H, s), 4.02 (1H, t, J = 5.8 Hz), 4.42 (2H, d, J = 5.26), 5.08 (2H, m), 6.37 (3H, m), 6.77 (1H, s), 6.83 (1H, d, J = 7.9 Hz), 7.07 (3H, m), 7.39 (3H, m), 8.76 (1H, m). MS (ES$^-$): *m*/*z* 504 (M − H).

***N*-(4-Methoxyphenyl)[1-methyl-3-oxo-2-benzyl(1,2,4-trihydroquinoxalin-6-yl)]carboxamide (13k).** Obtained 31 mg, 84% pure by LC/MS, 72% yield. ^{1}H NMR (DMSO-d_6): δ 2.91 (2H, d, J = 5.3 Hz), 3.31 (3H, s), 3.74 (3H, s), 4.25 (1H, m), 7.72−6.66 (13H, m), 9.79 (1H, s). MS (ES$^-$): *m*/*z* 400 (M − H).

***N*-(Diphenylmethyl){1-[(2-nitrophenyl)methyl]-3-oxo-2-benzyl(1,2,4-trihydro-quinoxalin-6-yl)}carboxamide (13l).** Obtained 33 mg, 67% pure by LC/MS, 32% yield. ^{1}H NMR (DMSO-d_6): δ 3.05 (2H, m), 4.50 (1H, t, J = 4.7 Hz), 5.48 (2H, m), 6.28 (1H, d, J = 8.8 Hz), 7.57−6.81 (22H, m), 8.23 (1H, d, J = 5.4 Hz), 8.81 (1H, d, J = 8.4 Hz). MS (ES$^-$): *m*/*z* 581 (M − H).

{1-[(3,5-Dimethoxyphenyl)methyl]-3-oxo-2-benzyl(1,2,4-trihydroquinoxalin-6-yl)}-*N*-[(3-fluorophenyl)methyl]carboxamide (13m). Obtained 32 mg, 74% pure by LC/MS, 40% yield. ^{1}H NMR (DMSO-d_6): δ 2.98 (2H, s), 3.67 (6H, s), 4.33 (1H, t, J = 3.79 Hz), 4.43 (2H, d, J = 5.4 Hz), 5.10 (2H, m), 6.38 (3H, m), 6.68 (1H, s), 6.80 (1H, d, J = 8.2 Hz), 7.47−7.04 (11H, m), 8.75 (1H, t, J = 5.4 Hz). MS (ES$^-$): *m*/*z* 538 (M − H).

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Supporting Information Available. LC/MS chromatograms and ^{1}H NMR spectra of compounds **9a, 10a, 11a, 11n, 12f,** and **13a**−**m** and chiral HPLC chromatograms of **13f** and **13g**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Netzi, A.; Ostrech, J. M.; Houghten, R. A. *Chem. Rev*. **1997**, *97*, 449−472.
(2) (a) Wei, G. P.; Phillips, G. B. *Tetrahedron Lett.* **1998**, *39*, 179−182. (b) Pan, P.-C.; Sun, C.-M. *Tetrahedron Lett.* **1999**, 6443−6446. (c) Schwarz, M. K.; Tumelty, D.; Gallop, M. A. *Tetrahedron Lett.* **1998**, *39*, 8397−8400. (d) Lee, J.; Gauthier, D.; Rivero, R. A. *J. Org. Chem.* **1999**, *64*, 3060−3064.
(3) Sarges, R.; Lyga, J. W. *J. Heterocycl. Chem.* **1988**, *25*, 1475−1479.
(4) Gazit, A.; App, H.; McMahon, G.; Chen, J.; Levitzki, A.; Bohmer, F. D. *J. Med. Chem.* **1996**, *39*, 2170−2177.
(5) (a) TenBrink, R. E.; Im, W. B.; Sethy, V. H.; Tang, A. H.; Carter, D. B. *J. Med. Chem.* **1994**, *37*, 758−768. (b) Jacobsen, E. J.; TenBrink, R. E.; Stelzer, L. S.; Belonga, K. L.; Carter, D. B.; Im, H. K.; Im, W. B.; Sethy, V. H.; Tang, A. H.; VonVoigtlander, P. F.; Petke, J. D. *J. Med. Chem.* **1996**, *39*, 158−175. (c) Jacobsen, E. J.; Stelzer, L. S.; TenBrink, R. E.; Belonga, K. L.; Carter, D. B.; Im, H. K.; Im, W. B.; Sethy, V. H.; Tang, A. H.; VonVoigtlander, P. F.; Petke, J. D.; Zhong, W.-Z.; Mickelson, J. W. *J. Med. Chem.* **1999**, *42*, 1123−1144.
(6) Ohmori, J.; Sasamata-Shimizu, M.; Okada, M.; Sakamoto, S. *J. Med. Chem.* **1997**, *40*, 2053−2063.
(7) Kim, K. S.; Qian, L.; Bird, J. E.; Dickinson, K. E. J.; Moreland, S.; Schaeffer, T. R.; Waldron, T. L.; Delaney, C. L.; Weller, H. N.; Miller, A. V. *J. Med. Chem.* **1993**, *36*, 2335−2342.
(8) (a) Lee, J.; Murray, W. V.; Rivero, R. A. *J. Org. Chem.* **1997**, *62*, 3874−3879. (b) Morales, G. A.; Corbett, J. W.; DeGrado, W. F. *J. Org. Chem.* **1998**, *63*, 1172−1177. (c) Zaragoza, F.; Stephensen, H. *J. Org. Chem.* **1999**, *64*, 2555−2557. (d) Krchnak, V.; Szabo, L.; Vagner, J. *Tetrahedron Lett*. **2000**, *41*, 2835−2838. (e) Schwarz, M. K.; Gallop, M. A. Benzofused Heterocycles via Solid-Phase S_NAR Reactions. In *Solid-Phase Organic Synthesis*; Burgess, K., Ed.; John Wiley & Sons: New York, 2000; pp 81−117.
(9) The yield of amides **10** generated from resin-bound phenylalanine could be improved by repeating the amidation step one more time.
(10) Similar results were obtained at 45 °C for 8 h.
(11) A larger excess of base and/or alkyl halide combined with heat (e.g., 45 °C, 12 h) provided variable amounts of a bis-alkylated product, as determined by LC/MS.

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