# Efficient Solid-Phase Synthesis of 3-Substituted-5-Oxo-5*H*-Thiazolo[2,3-b]-Quinazoline-8-Carboxamides under Mild Conditions with Two Diversity Positions

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In continuation of our efforts to develop novel and efficient polymer-supported routes, leading to heterocyclic derivatives with potentially attractive pharmacological properties, we turned our attention to thiazolo[2,3,b]quinazolines. A survey of the literature revealed that a quinazoline ring fused with thiazole exhibits a wide range of biological activities,[1–3] including antifungal[4] and antibacterial activities.[4–6] Thiazolo[2,3,b]-quinazoline derivatives were also tested for their application as herbicides for the agricultural industry.[7]

To date, only solution-chemistry syntheses have been described. Narang et al.[5,8] reported the first synthetic route to thiazoloquinazolines in solution by refluxing the appropriate α-haloketones with 2-carbethoxy-phenylthiourea. Subsequently, Schadev et al.[1] used 2-aminobenzonitrile and 4-chloro-2-aminobenzonitrile with α-thiocyanoketones in the presence of hydrochloric acid to synthesize thiazolo[2,3,b]-quinazolines and Sharma et al.[9] condensed isatin with allyl isothiocyanate in the presence of aqueous alcoholic potassium hydroxide. Dhami et al.[5] condensed anthranilic acid with 2-chlorothiazole. Chern et al.[10] described a multistep route from 2-thioxo-1*H*,3*H*-quinazolin-4-one leading to 3-methyl-thiazolo[2,3-b]quinazolin-5-one, that was further derivatized. Although some of the routes described provided respectable yield, in all reported syntheses the conditions for cyclization of acyclic precursor were severe. The harsh conditions limited the diversity of accessible derivatives. Here we report the first solid-phase synthesis of thiazolo[2,3,b]quinazoline accomplished under mild conditions and amenable to high throughput/combinatorial synthesis.

Our solid-phase synthesis of thiazolo[2,3,b]quinazoline is based on the use of anthranilates and bromoketones as key building blocks and diversity elements. Anthranilates are versatile synthons providing access to diverse fused heterocyclic systems. Their application for polymer-supported syntheses of heterocycles is employed frequently and includes the synthesis of quinazolin-4-ones,[11–14] quinazoline-2,4-diones,[15–21] 4-hydroxyquinolin-2-ones,[22] 2-amino-benzooxazin-4-ones,[23] 2-thioxoquinazoline-4-ones,[24] 1,4-benzodiazepine-2,5-diones,[25–29] and pyrrolo[2,1-c][1,4]benzodiazepines.[30,31] We have used anthranilates for syntheses of quinazolin-4-ones[32] and recently 2-substituted-3-hydroxy-4(1*H*)-quinolinone-7-carboxamides.[33]

Our first effort to prepare thiazolo[2,3,b]quinazolines was based on a solid-supported synthesis of 2-thioxoquinazoline-4-ones using anthranilates as the key synthon. This was followed by alkylation with bromoketones and subsequent formation of the six-membered quinazolinone ring. Combination of these two types of building blocks allows for the preparation of thiazolo[2,3,b]quinazolines with two diversity positions: one on the carboxylic benzene ring and the second on position 3 of the thiazolo ring.

Briefly, Rink amide resin **1**, after cleavage of the Fmoc group, was acylated with commercially available 1-methyl-2-aminoterephtalate (Scheme 1). We chose to apply the same anthranilate component we employed in the synthesis of 2-substituted-3-hydroxy-4(1*H*)-quinlinon-7-carboxamides.[33] The aniline-type of amine **2** was reacted with Fmoc-NCS. Freshly prepared Fmoc-NCS, from KSCN and Fmoc-Cl in THF, provided superior results when compared to an expensive Fmoc-NCS obtained from a commercial source. After cleavage of the Fmoc group from the thiourea **3** by piperidine in DMF, spontaneous cyclization to 2-thioxo-quinazoline-4-ones **4** was observed. Finally, the intermediate **4** was alkylated with 2-bromo-4′-methyl-acetophenone to yield **5a**. All steps of the reaction sequence proceeded with very high yield and provided crude preparation of high purity (>95% as judged from HPLC traces). However, we were unsuccessful in closing the five-membered thiazole ring under mild conditions including $PPh_3$/iodine, TMS-Cl, and acid or base catalysis. Since, this sequence of chemical transformations represents a very efficient route leading to the synthesis of S-alkyl derivatives of 2-mercapto-3*H*-quinazolin-4-ones **6**, appealing compounds *per se*, we developed conditions for selective S-alkylation. While selective S-alkylation with bromoketone was complete in 1 h at ambient temperature, alkylation with benzylbromide required an overnight reaction time. The addition of a base or elevated temperature caused contamination by a N-alkyl side-product. The S-alkylated products **6** were isolated in high yield (>90%) and purity (>90%). Syntheses of analogous 2-thioxoquinazoline-4-one derivatives have already been reported.[34,35]

For the synthesis of thiazolo[2,3-b]quinazolin-5-ones, we modified the synthetic route and closed the thiazole ring first, followed by cyclization via amide bond formation. To prevent the spontaneous cyclization to 2-thioxoquinazoline-4-ones **4**, we cleaved the methyl ester of 1-methyl-2-aminoterephtalate **2** before the reaction with Fmoc-NCS (Scheme 2). Following cleavage of the resin-bound methyl-ester (**2**) using potassium trimethylsilanolate (TMSOK) in THF,[36] the carboxylic acid (**7**) was treated with a solution of Fmoc-NCS[37] in THF to yield Fmoc-protected thiourea (**8**). After subsequent treatment with 20% piperidine in DMF, a thiazole ring (**9**) was formed by a reaction with dichloromethane solution of 2-bromo-4′-methyl-acetophenone for 1 h.

Unfortunately, the product was accompanied by contaminants. We observed formation of two side products. Using

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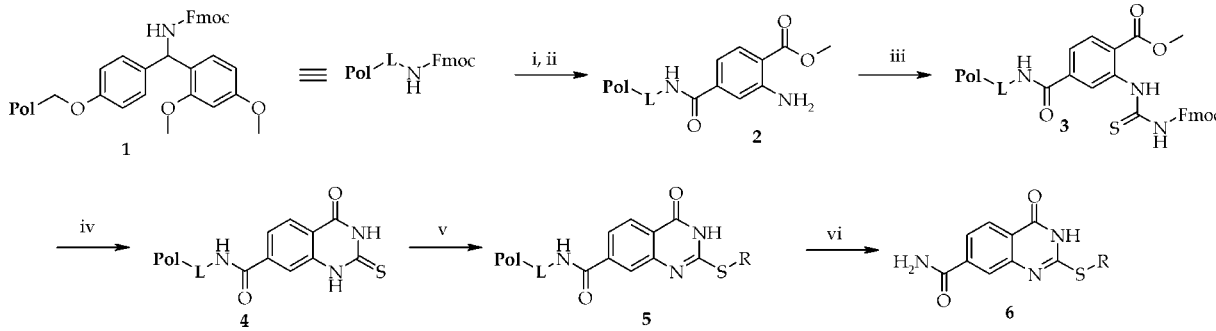
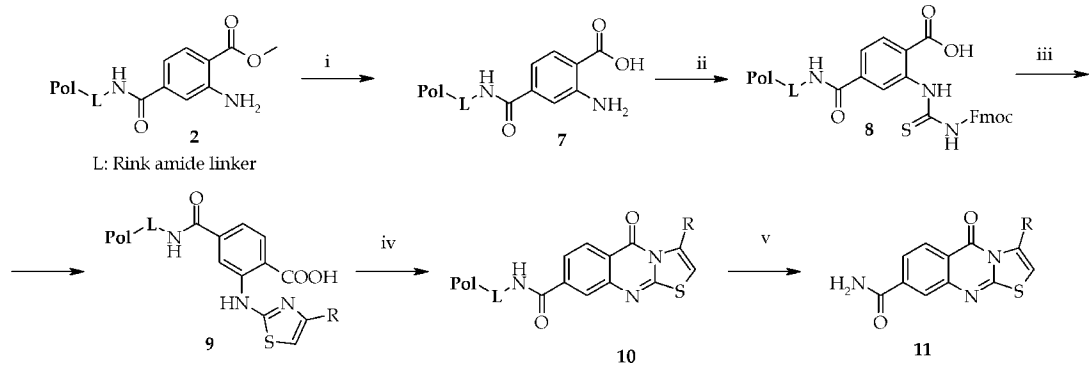
**Scheme 1.** Synthesis of 2-Alkylsulfanyl-4-oxo-3,4-dihydro-quinazoline-7-carboxylic Acid Amide[a]



[a] Reagents: (i) 20% piperidine/DMF, 20 min; (ii) 1-methyl-2-aminoterephtalate, DIC, HOBt, DCM, DMF, rt, overnight; (iii) Fmoc-NCS, THF, rt, 1 h; (iv) 20% piperidine/DMF, rt, 10 min; (v) 2-bromo-4′-methyl-acetophenone, toluene, rt, 1 h (**5a**); or benzylbromide, DCM, overnight (**5b**); 50% TFA/DCM, rt, 1 h.

**Scheme 2.** Preparation of Nonsubstituted Carboxamides[a]



[a] Reagents: (i) TMSOK, THF, rt, 1 h; (ii) Fmoc-NCS, THF, rt, 1 h; (iv) 20% piperidine/DMF, rt, 10 min; (iii) 2-bromo-4′-methyl-acetophenone, DCM, rt, 1 h; (iv) DIC, HOBt, DCM, DMF, rt, overnight; (v) 50% TFA/DCM, rt, 1 h.

2-bromo-4′-methyl-acetophenone in DCM, we detected 15% of 2-thioxoquinazoline-4-ones, similar to the previous synthetic route (Scheme 1) where the ester was not cleaved (compound **4**). The side-product **4** was subsequently alkylated by 2-bromo-4′-methyl-acetophenone to yield a S-alkyl derivative **5**. Thus, cleavage of the methyl ester did not completely prevent the cyclization to quinazolinone. To suppress this side-reaction, we shortened the removal of the Fmoc group to 10 min. We also evaluated Fmoc deprotection with TBAF in THF in order to minimize the cyclizaton. However, the resulting product was not clean. The reaction conditions for the subsequent addition of bromoketones were optimized by changing concentration, solvents, and reaction temperature. In a polar environment such as DMF, we obtained about 7% of **9** and 93% of **5** (as judged by the LC traces of the crude products) and in a nonpolar solvent, such as toluene, the ratio changed to 92% of **9** and 8% of **5**. The modification of temperature or concentration did not yield any improvement. Thus, for further experiments we used toluene as the solvent for reactions with bromoketones.

Gratifyingly, the cyclization to thiazolo[2,3,b]quinazolines (**10**) proceeded under mild conditions using DIC/HOBt at room temperature overnight. The product **11** was cleaved from the polymer support using 50% TFA in DCM for 30 min.

To evaluate the scope and the limitations of this route, we prepared a small set of model compound **11**. A set of commercially available bromoketones was evaluated and 3-substituted-5-oxo-5*H*-thiazolo[2,3-b]quinazoline-8-carboxamides **11** were prepared. Five phenylbromo-ketones were

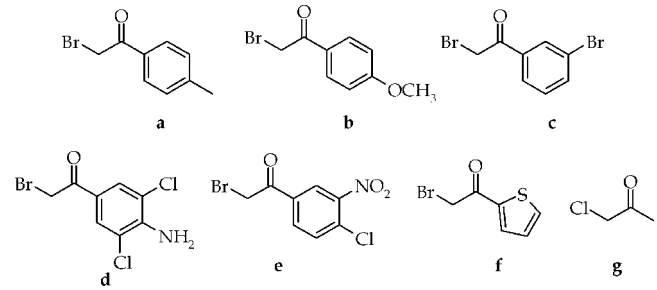


**Figure 1.** Bromoketones used for the synthesis of 5-oxo-3-substituted-5*H*-thiazolo[2,3-b]quinazoline-8-carboxylic acid amides.

**Table 1.** Analytical Data of Thiazolo[2,3-b]quinazolin-5-ones (**11**)

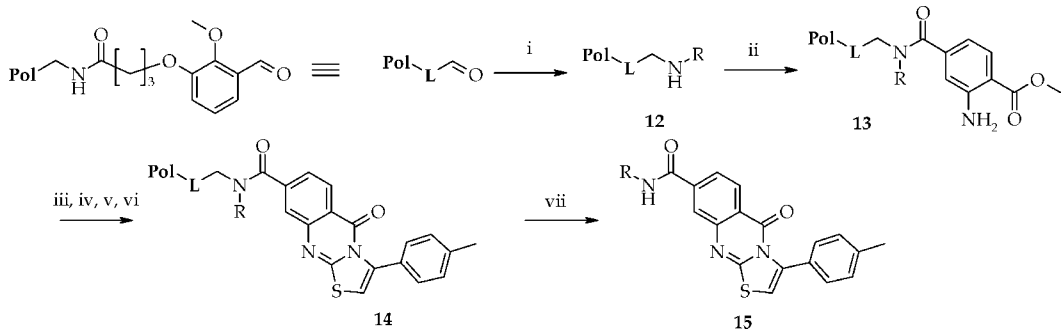
| entry | haloketone | Rt | MS | crude yield | crude purity |
|---|---|---|---|---|---|
| 1 | a | 6.25 | 336 | 87% | 96% |
| 2 | b | 6.35 | 352 | 70% | 85% |
| 3 | c | 6.50 | 401 | 42% | 77% |
| 4 | d | 6.13 | 406 | 63% | 96% |
| 5 | e | 6.43 | [a] | 90% | 88% |
| 6 | f | 5.27 | 328 | 63% | 98% |
| 7 | g | 4.15 | 260 | 52% | 50% |

[a] No significant ion current detected.

selected that contain various combinations of electron-withdrawing as well as electron-donating substituents. One heterocyclic bromoketone and chloroacetone were also included (Figure 1). Yield and purity of all products are summarized in Table 1.

To introduce diversity position on the phenyl ring, we prepared *N*-derivatized carboxamides (**14**) using the BAL

**Scheme 3.** Preparation of N-Derivatized Carboxamides[a]




[a] Reagents: (i) amine, 10% HOAc/DMF, overnight, $NaBH(OAc)_3$, 5h; (ii) 1-methyl-2-aminoterephtalate, DIC, HOBt, DCM, DMF, rt, overnight; (iii) TMSOK, THF, rt, 1 h; (iv) Fmoc-NCS, THF, rt, 1 h; (v) 20% piperidine/DMF, rt, 10 min; (vi) 2-bromo-4′-methyl-acetophenone, toluene, rt, 1 h; (vii) DIC, HOBt, DCM, DMF, rt, overnight; (viii) 50% TFA/DCM, rt, 1 h.

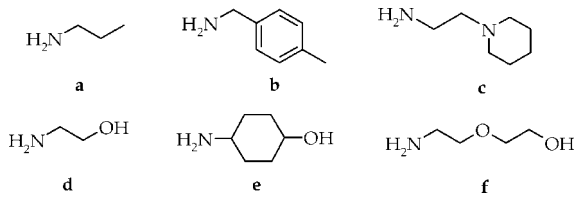



**Figure 2.** Amines for the second diversity position.

linker[38] immobilized to aminomethyl resin. Polymer-supported secondary amines (**12**) were prepared using the procedure described in the first diversity step.[39] Resin-bound products **14** were obtained following the same chemical transformations and the same procedures used for unsubstituted amide (**10**) (Scheme 3).

The outcome of the reaction sequence was evaluated for a set of six amines (Figure 2); *n*-propyl and benzyl amines were included as representative examples of amines without any side-chain functional group, and target compounds were obtained in high purity. In the case of polymer-supported ethanolamine (**13d**), *trans*-4-aminocyclohexanol (**13e**), and 2-(2-amino-ethoxy)-ethanol (**13f**), we observed acylation of hydroxy group by 1-methyl-2-aminoterephtalate (about 10% of the double acylated side product, HPLC). In the following step, the ester of the side product was saponified. Therefore, it was not necessary to protect the hydroxy group before the acylation.

After completion of the solid-supported synthesis, the thiazoloquinazolines were cleaved from the resin by 50% TFA in DCM. Because the reaction sequence resulted in high yield and provided crude products of high purity, it enabled very simple isolation of target compounds. After evaporation of TFA, residual oil was sonified for 5 min in diethylether. Precipitated products were collected by filtration or centrifugation, washed with fresh diethylether, and dried. This simple procedure removed any minor impurities detected in the crude products as they remained dissolved in diethylether during sonification. The purity of thiazoloquinolinones was consistently high (Table 2) as judged from the analytical HPLC traces (integration of diode array 200–450 nm traces). The exception was compound **15c**, which did not precipitate in ether and was purified by HPLC.

Analysis of $^1$H NMR spectra of compound **15e** prepared from 4-aminocyclohexanol revealed the presence of two sets of signals for the amide protons and the aromatic anthranilate

**Table 2.** Analytical Data of Thiazolo[2,3-b]quinazolin-5-ones (**15**)

| entry | amine | Rt | MS | crude yield | crude purity |
|---|---|---|---|---|---|
| 1 | a | 7.75 | 378 | 70% | 98% |
| 2 | b | 9.08 | 440 | 70% | 99% |
| 3 | c | 5.98 | 447 | 96% | 85% |
| 4 | d | 6.00 | 380 | 87% | 98% |
| 5 | e | 6.52 | 434 | 40% | 98% |
| 6 | f | 6.07 | 424 | 90% | 97% |

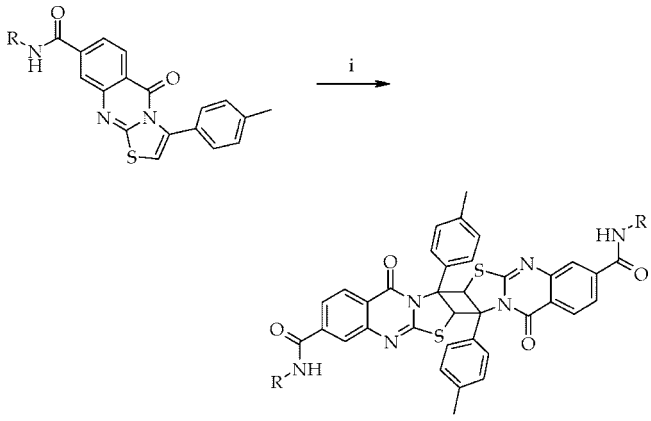
protons, corresponding presumably to two diasteroisomers, caused by epimerization during the reductive alkylation.[40]

Crude products with purities of <95% (compounds **11b**, **11c**, **11d**, **11g**, and **15c**) were purified by HPLC. Unexpectedly, our results demonstrated that the target compounds were not stable and we detected formation of a side-product. Analysis of HPLC-purified samples revealed the presence of a new component, formed by the transformation of the target product. We isolated the newly formed compound synthesized from thiazolo[2,3-b]quinazolin-5-one **15d**. The MS spectrum showed an *m/z* signal corresponding to a dimer of **15d** (ESI-MS $m/z = 759$, $[M_{dimer} + H]^+$). Both the $^1$H and $^{13}$C NMR spectra were very similar to the target compound **15d**, with the exception of the thiazole proton and two thiazole C4 and C5 carbons. The chemical shift of the proton moved from $\delta = 7.16$ ppm to $\delta = 5.14$ ppm. The $^{13}$C NMR spectrum revealed that a chemical shift of the C4 and C5 thiazole carbons $\delta = 136.9$ and 109.2 ppm moved to $\delta = 83.9$ and 51.7 ppm. This shift indicated transformation of the thiazole ring. Hetcor spectra of **15d** confirmed that $\delta = 7.16$ ppm thiazole proton was attached to $\delta = 109.2$ carbon, and hetcor spectra of the dimer showed proton $\delta = 5.14$ ppm attached to 51.7 ppm carbon. The analytical data suggested formation of a dimer (Scheme 4).

To independently demonstrate the formation of the dimer, we mixed solutions of thiazolo[2,3-b]quinazolin-5-ones **15b** and **15d** in DMSO and 10 mM ammonium acetate in water. After two days, LCMS traces revealed the presence of six compounds corresponding to thiazolo[2,3-b]quinazolin-5-ones ($R_t = 6.00$ min for **15d** and $R_t = 9.08$ min for **15b**), and a dimer of **15d** and **15b** with $R_t$ 6.60 min and 9.8 min, respectively. The last two peaks at $R_t$ 8.5 and 9.0 min corresponded to hetero-dimers as interpreted from MS spectra.

To address the cause of dimerization we prepared two solutions of thiazolo-quinazolinone **15d** and exposed one

**Scheme 4.** Formation of Dimers[a]



[a] Reagents: (i) DMSO, MeCN, water, hv, overnight.

solution to UV-light overnight while the other solution was maintained in the dark. We detected 25% of dimer in the first sample and no traces of the dimer in the second. This experiment proved that the dimerization in solution is caused by UV irradiation and the target compound is stable in solution when not exposed to UV light.

In conclusion, we have developed an efficient solid-phase synthesis of thiazolo[2,3,b]quinazolines with two diversity positions where all reaction steps were completed under mild conditions. A potential side-reaction, cyclization to 2-thioxo-quinazoline-4-ones, was suppressed by the selection of toluene as the reaction solvent. The quantitative conversion of all reaction steps resulted in high yields of all crude target products. Isolated yields, after simple purification by precipitation with ether, were only influenced by the solubility of the target compounds in diethylether. Unexpectedly, exposure of thiazolo[2,3,b]quinazolines solution to UV light caused dimerization.

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**Supporting Information Available.** Details of experimental procedures and spectroscopic data for new compounds. This information is available free of charge via the Internet at http: //pubs.acs.org.

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