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Novel solid-phase synthesis of 2,6-disubstituted 4(3*H*)-quinazolinones for combinatorial library generation

Csaba Wéber,* Attila Bielik, Györgyi I. Szendrei and István Greiner

Chemical and Biotechnological Research and Development, Gedeon Richter Ltd, PO Box 27, H-1475 Budapest, Hungary

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Abstract—A novel procedure for the synthesis of 6-alkoxy-2-amino-4(3*H*)-quinazolinones from 2,4-dichloro-6-hydroxyquinazoline, amines and alcohols using Wang resin is described.

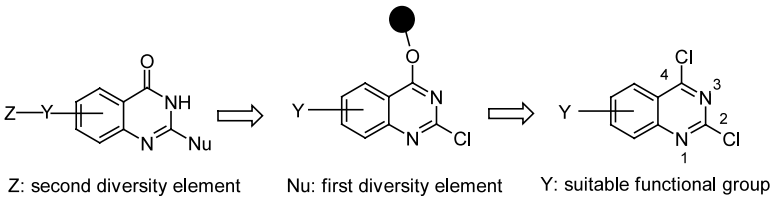
2-Amino-4(3*H*)-quinazolinones are of pharmacological interest as histamine H2-antagonists,[1] antibacterial[2] and antihypertensive[3] agents. Antimicrobial,[4] anticonvulsant,[5] antitumor[6] and potential antiinflammatory[7] activities of 4(3*H*)-quinazolinones have also been disclosed. Some 2-amino-4(3*H*)-quinazolinones have been isolated from natural products.[8] In the course of our efforts directed towards the solid-phase synthesis of structurally diverse heterocycles having potential biological activity, we have developed a method for the preparation of compounds containing this structural element.

There have been a number of syntheses reported of 4(3*H*)-quinazolinone derivatives on solid support.[9–11] More recently Yang and co-workers[12] described a solid-phase synthesis approach to this type of compound. This two-step method is based on the acylation of resin-bound thiourea by isatoic anhydride, followed by cleavage of the product via an intramolecular cyclization. All of these procedures have two common features. The first one is that the diversity of the benzene ring of the molecule derives from substituted anthranilic acids. The second one is that the cyclization occurs under solid-phase conditions.

There have been a number of combinatorial chemistry applications reported of trichlorotriazines,[13,14] di- and trichloropyrimidines[15,16] and dichloropurines.[17–19] The common feature of these methods is the selective replacement of the halogens by nucleophiles.

Our approach is based on 2,4-dichloroquinazoline derivatives having a functional group (Y) on the benzene ring available for further modification on solid support. The two chlorines at C-2 and C-4 can be replaced selectively by nucleophiles. This type of compound can be coupled to solid supports at C-4 via a nucleophilic linker, while the second nucleophile (the first diversity element) can be introduced into C-2 (Scheme 1). The second diversity element (Z) can be coupled via the functional group of the benzene ring (Y).

Following the retrosynthetic strategy, amines and alcohols were used as building blocks and 2,4-dichloro-6-



Scheme 1.

Keywords: 4(3*H*)-quinazolinones; solid phase; Mitsunobu.

* Corresponding author. Fax: 36 1 4326002; e-mail: cs.weber@richter.hu

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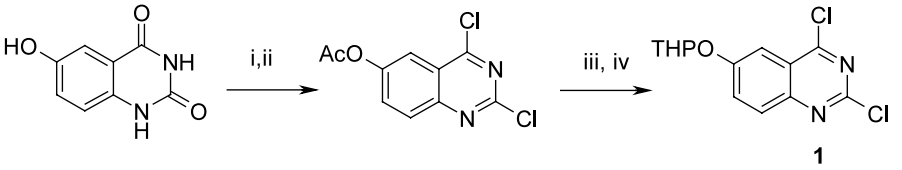
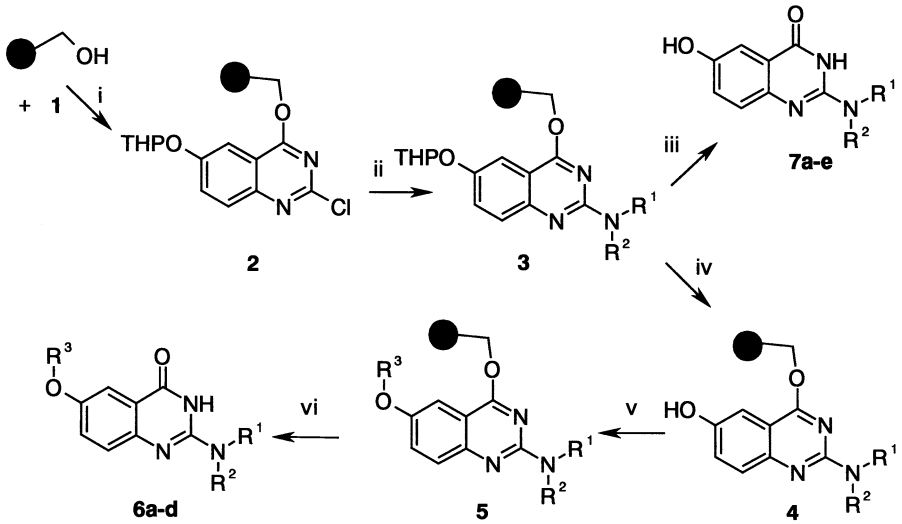
hydroxyquinazoline† as the core structure. The protected form of the core was prepared from 6-hydroxy-2,4(1*H*,3*H*)-quinazolinedione[20] in four steps (Scheme 2).

The general approach for the solid-phase synthesis of 6-alkoxy-2-amino-4(3*H*)-quinazolinones is shown in Scheme 3. Wang resin[21] was deprotonated by BuLi in THF and was then reacted with **1** to give **2**. Reaction of **2** with secondary amines in DMF at 100°C afforded resin-bound 2-aminoquinazolines **3**. These compounds were cleaved from the resin to give **7**. We observed that alkyl and cyclic secondary amines gave the substituted 6-hydroxy-4(3*H*)-quinazolinone derivatives in high yield and excellent purity (Table 1, entries 1–3). On the other hand primary or aryl amines yielded the desired product in only trace amounts even under aggressive conditions (70 h with a 15-fold excess of amine) (Table 1, entries 4 and 5). In these multicomponent products the 2-chloro-6-hydroxy-4(3*H*)-quinazolone derivative was detected. The second step of diversification was achieved by removing the THP (tetrahydropyran-2-yl) group of **3** with $BF_3{\cdot}Et_2O$ in the presence of thiophenol (PhSH) in THF followed by alkylation of the resulting phenol with alcohols under Mitsunobu conditions.[22–24] Our experimental results with diethyl azodicarboxylate (DEAD)/triphenylphosphine (PPh_3) were in accordance with the observations made by Krchnák et al.[25] They found that fast addition of undiluted DEAD to the reaction mixture resulted in the formation of a side product, the corresponding ethyl ether. We could not fully avoid this side product using diluted reagents and slow addition. However, the experiments carried out with diisopropyl azodicarboxylate DIAD/PPh_3 worked well providing the expected ethers of primary and secondary alcohols without isopropyl ether impurity. The final products were cleaved from the resin with 20% TFA in CH_2Cl_2 (Table 1, entries 6–9).

A representative set of 4(3*H*)-quinazolinones synthesized by this approach is summarized in Table 1. As shown, most compounds gave a fair overall yield and good to excellent purity.



Scheme 2. *Reagents and conditions*: (i) Ac_2O, pyridine, reflux, 3 h, 94% (ii) $POCl_3$, $PhNEt_2$, reflux, 2 h, 72% (iii) MeOMgCl, MeOH, THF, reflux, 3 h, 91% (iv) 3,4-dihydro-2*H*-pyran, THF, cat. H_2SO_4, reflux, 84%.



Scheme 3. *Reagents and conditions*: (i) 2.2 equiv. BuLi, 3 equiv. **1**, rt, 5 h; (ii) 5 equiv., HNR^1R^2, DMF, 24 h, 100°C; (iii) 20% TFA/DCM (iv) 1 equiv. $BF_3{\cdot}Et_2O$, PhSH, THF, rt, 1 h; (v) 10 equiv. PPh_3, 10 equiv. DIAD, 10 equiv. R^3OH, rt, 16 h; (vi) 20% TFA/DCM.

† Physical and spectroscopic data for compound **1** (Scheme 2) and their precursors: **6-Acetoxy-2,4(1*H*,3*H*)-quinazolindione**: mp 321–324°C; ^{1}H NMR (DMSO-d_6, TMS) δ 2.28 (s, 3H), 7.20 (d, 1H, J=8.7 Hz), 7.42 (dd, 1H, J=8.7 Hz and 2.7 Hz), 7.61 (d, 1H, J=2.7 Hz), 11.27 (br s, 2H); MS (EI) 220 (M^+). **6-Acetoxy-2,4-dichloroquinazoline**: mp 143–144°C; ^{1}H NMR ($CDCl_3$, TMS) δ 2.40 (s, 3H), 7.74 (dd, 1H, J=9.3 Hz and 2.4 Hz), 8.00 (d, 1H, J=2.4 Hz), 8.03 (d, 1H, J=9.3 Hz); MS (EI) 256 (M^+). **2,4-Dichloro-6-hydroxyquinazoline**: mp 171–172°C; ^{1}H NMR (DMSO-d_6, TMS) δ 7.42 (d, 1H, J=2.4 Hz), 7.69 (dd, 1H, J=9.3 Hz and 2.4 Hz), 7.93 (d, 1H, J=9.3 Hz), 10.96 (s, 1H); MS (EI) 214 (M^+). **2,4-Dichloro-6-(tetrahydropyran-2-yloxy)quinazoline**: mp 116–117°C; ^{1}H NMR ($CDCl_3$, TMS) δ 1.58–1.84 (m, 3H), 1.91–2.13 (m, 3H), 3.64–3.74 (m, 1H), 3.80–3.92 (m, 1H), 5.65 (t, 1H, J=3.3 Hz), 7.71 (dd, 1H, J=9.0 Hz and 2.7 Hz), 7.76 (d, 1H, J=2.7 Hz), 7.92 (d, 1H, J=9.0 Hz); MS (EI): 298 (M^+).

Table 1.

Entry	Compound	NR^1R^2	R^3	Yield (%)[a]	Purity (%)[b]
1	**7a**	Piperidin-1-yl	–	75	99
2	**7b**	Morpholin-4-yl	–	69	94
3	**7c**	Bis(*n*-butyl)amino	–	74	88
4	**7d**	*n*-Hexylamino	–	–	15
5	**7e**	*N*-Methylphenylamino	–	–	12
6	**6a**	Piperidin-1-yl	Methyl	57	97
7	**6b**	Piperidin-1-yl	Ethyl	71	98
8	**6c**	Piperidin-1-yl	Isopropyl	67	92
9	**6d**	Piperidin-1-yl	2-Methylbutyl	62	96

[a] The overall yield was determined by weight based on the loading of **2**. The yields refer to compounds purified by flash chromatography.

[b] The purities of the crude products were determined by HPLC–MS at 254 nm. The structures of the purified products were confirmed by ^{1}H NMR and MS spectroscopy. **Compound 7a**: ^{1}H NMR (DMSO-d_6, TMS) δ 1.50–1.78 (br m, 6H), 3.58–3.70 (br m, 4H), 7.21 (dd, 1H, J=8.9 Hz and 2.6 Hz), 7.28 (d, 1H, J=2.6 Hz), 7.40 (d, 1H, J=8.9 Hz), 9.94 (br s, 1H); MS (EI) 245 (M^+). **Compound 7b**: ^{1}H NMR (DMSO-d_6, TMS) δ 3.69–3.84 (br m, 8H), 7.29 (dd, 1H, J=9.0 Hz and 3.0 Hz), 7.34 (d, 1H, J=3.0 Hz), 7.81 (d, 1H, J=9.0 Hz), 10.20 (br s, 1H); MS (EI) 247 (M^+). **Compound 7c**: ^{1}H NMR (DMSO-d_6, TMS) δ 0.91 (t, 6H, J=7.2 Hz), 1.26–1.40 (m, 4H), 1.49–1.62 (m, 4H), 3.55 (t, 4H, J=7.5 Hz), 7.20 (dd, 1H, J=9.0 Hz and 3.0 Hz), 7.28 (d, 1H, J=3.0 Hz), 7.44 (d, 1H, J=9.0 Hz), 9.82 (br s, 1H); MS (EI) 289 (M^+). **Compound 7d**: MS (EI) 261 (M^+). **Compound 7e**: MS (EI) 267 (M^+). **Compound 6a**: ^{1}H NMR (MeOH-d_4, TMS) δ 1.70–1.85 (br m, 6H), 3.70–3.80 (br m, 4H), 3.89 (s, 3H), 7.41 (dd, 1H, J=9.0 Hz and 2.7 Hz), 7.50–7.56 (m, 2H); MS (EI) 259 (M^+). **Compound 6b**: ^{1}H NMR (DMSO-d_6, TMS) δ 1.34 (t, 3H, J=6.9 Hz), 1.48–1.66 (br m, 6H), 3.49–3.60 (br m, 4H), 4.05 (q, 2H, J=6.9 Hz), 7.15–34 (m, 3H), 11.23 (s, 1H); MS (EI) 273(M^+). **Compound 6c**: ^{1}H NMR (DMSO-d_6, TMS) δ 1.28 (d, 6H, J=6.0 Hz), 1.46–1.68 (br m, 6H), 3.50–3.62 (br m, 4H), 4.54–4.68 (m, 1H), 7.11–7.34 (m, 3H), 11.22 (s, 1H); MS (EI) 287 (M^+). **Compound 6d**: ^{1}H NMR (MeOH-d_4, TMS) δ 0.98 (t, 3H, J=7.2 Hz), 1.04 (d, 3H, J=6.6 Hz), 1.22–1.36 (m, 1H), 1.52–1.78 (m, 7H), 1.78–1.97 (m, 1H), 3.60–3.74 (m, 4H), 3.76–3.92 (m, 2H), 7.24 (dd, 1H, J=9.0 Hz and 3.0 Hz), 7.35 (d, 1H, J=9.0 Hz), 7.46 (d, 1H, J=3.0 Hz); MS (EI) 315 (M^+).

Our approach is especially attractive for combinatorial synthesis due to the wide range of commercially available alcohols and secondary amines which can be used as diversity elements. Considering the fact that it is the enol–ether form of 4(3*H*)-quinazolinone that is coupled to solid support allows us to use Mitsunobu conditions without alkylation of *N*-3 or C4-*O*.

In summary, we have developed a new solid-phase method for the synthesis of 2,6-disubstituted-4(3*H*)-quinazolinones. Simple and mild reaction conditions and the huge number of commercially available building blocks permit us to synthesize large combinatorial libraries.

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