Pergamon

Tetrahedron Letters 40 (1999) 3881–3884

TETRAHEDRON
LETTERS

Novel Synthesis of Oxindole Quinazolines using Solid Phase Multiparallel Chemistry.

Laurent F. Hennequin, * Sylvie Piva-Le Blanc

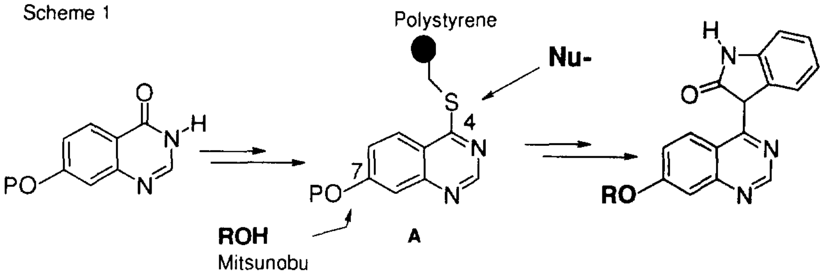
Zeneca Pharma, Centre de Recherches, Z.I. La Pompelle, BP401, 51064 Reims, France

Received 3 March 1999; accepted 26 March 1999

Abstract : A novel synthesis of oxindole quinazolines modified at the C4 and C7 positions via solid phase multiparallel chemistry is described. The C7 position of the quinazoline was modified by Mitsunobu reaction and the introduction of the key C4-oxindole ring was achieved at the final stage of the synthesis and constituted the cleavage step from the resin. Purification of the final products was easily achieved via SPE taking advantage of the mild basicity of the quinazoline nucleus.

Substituted quinazolines have proven to possess very attractive pharmacology as recently illustrated by several series of new cellular-signal-transduction inhibitors.[1-3] As part of a program devoted to the synthesis of oxindole quinazolines[1], a novel series of tyrosine kinase inhibitors, we wanted to investigate the modifications of the C4 and C7 positions of intermediate **A**. A multiparallel solid phase [4] approach was found to allow efficient variation of these two positions and to simplify purification of the target products. Our strategy was based on attaching a polystyrene resin[5] at the C4 position of the quinazoline nucleus to allow first the variation of the C7 position via Mitsunobu reaction on solid phase followed by the nucleophilic displacement of the resin by an oxindol ring to yield the desired products (Scheme 1).[1] In order to achieve this goal, we attached the polystyrene resin[5] at the C4 position of the quinazoline via a thioether linker that was anticipated to be stable during the Mitsunobu reaction and also under acidic conditions but could also act as a good leaving group for the nucleophilic introduction of the oxindole moiety.

Scheme 1

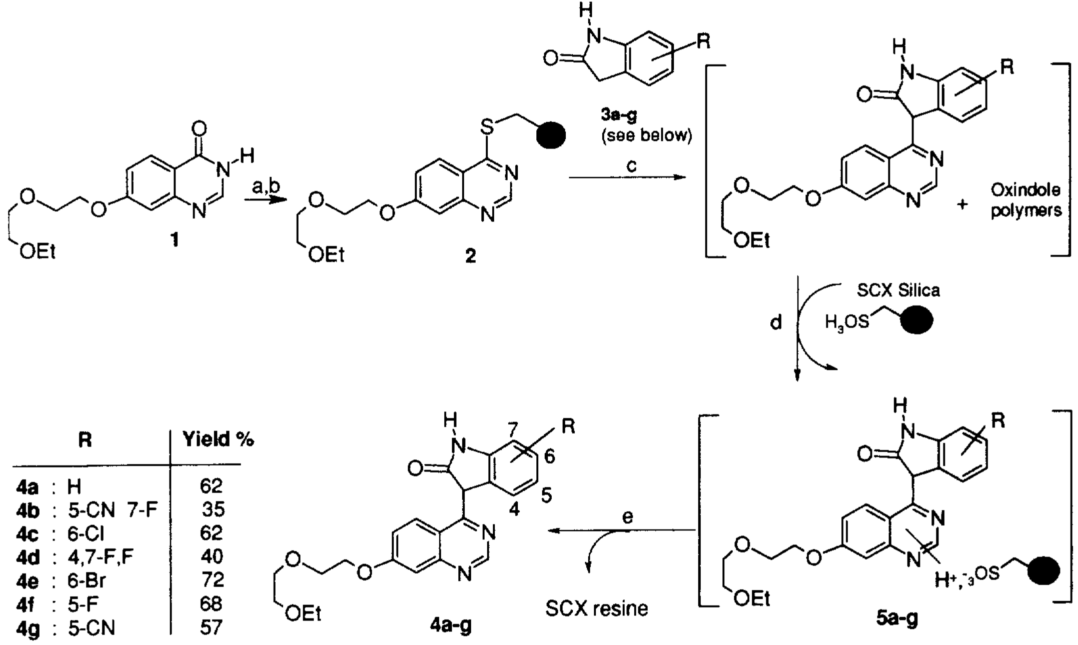


In order to test the coupling of the quinazoline on the resin and its cleavage via nucleophilic displacement by oxindoles, quinazolinone **1**[6] was treated with phosphorus pentasulfide in pyridine at 110°C to give the corresponding thioquinazolone (Scheme 2) which was then reacted with Merrifield resin[5] in DMF in the presence of DBU to give the resin supported quinazoline **2** in excellent yield (based on resin weight increase). Introduction of the oxindoles was achieved by coupling the sodium anion of oxindoles **3a-g** (preformed by reaction with NaH in DMSO) with **2** in DMSO at 100°C.[8] Due to the propensity of oxindoles to polymerise under such coupling conditions, a large excess of the anions of oxindoles **3a-g** (10 equiv.) had to be used to achieve a complete and rapid conversion to the desired oxindole quinazolines **4a-g**. Under these conditions, the work up and

0040-4039/99/$ - see front matter © 1999 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(99)00638-3

purification of **4a-g** by conventional precipitation or chromatographic methods were not satisfactory. So we exploited the mild basicity of the quinazoline nucleus of **4a-g** and purified the product by solid phase extraction (SPE).[9,10]

Scheme 2



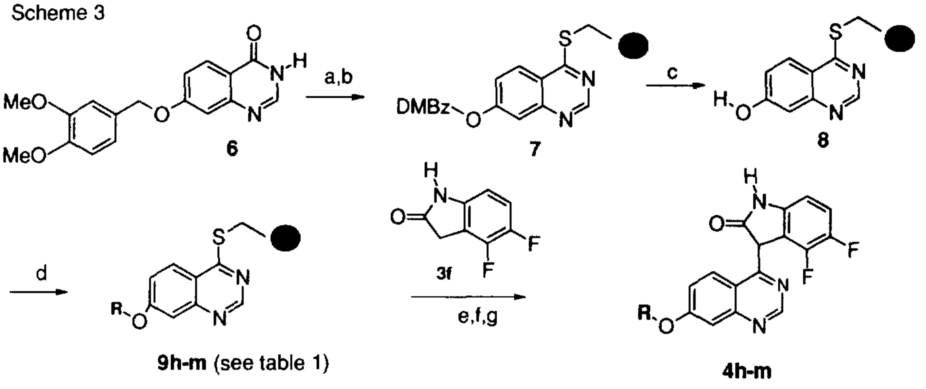
	R	Yield %
4a	H	62
4b	5-CN 7-F	35
4c	6-Cl	62
4d	4,7-F,F	40
4e	6-Br	72
4f	5-F	68
4g	5-CN	57

a) P_4S_{10}, pyridine 110°C 72% b) Merrifield, DBU, DMF c) **3a-g** (10 eq.), NaH, DMSO 100°C
d) 1) filtration through SCX silica ; 2) washing with CH_2Cl_2 / MeOH e) 2% NH_3 in MeOH /CH_2Cl_2 (1/1)

The crude mixture resulting from the C4 displacement reaction was passed through acidic SCX sulfonic silica.[9] By virtue of the strong interaction between the quinazoline nitrogens and the sulfonic acid function of the silica, the expected products **4a-g** were retained on the column whilst the excess of oxindoles and oxindole polymers were washed through. After washing the SCX column with methylene chloride/MeOH, pure **4a-g** were displaced from the silica by washing with a 2% solution of NH_3 in MeOH/CH_2Cl_2.[8] After removal of the solvents by evaporation, the oxindole quinazolines **4a-g** were isolated in excellent yields (scheme 2) and purity (>90%) as measured by NMR and MS. Only C-alkylation products were isolated, as previously observed in solution chemistry. [1] Due to the ease of handling of these resins and the efficiency of the SPE technique, it was even possible to run the seven reactions and purifications in parallel in a day.

Having validated the chemistry at the C4 position, and to enable modifications at both the C4 and C7 positions of the quinazoline ring, the C7 hydroxy group of **6** was protected as the dimethoxybenzyl moiety because of the mild acid lability of this protecting group (Scheme 3). The quinazolinone **6** was reacted with P_4S_{10} as above to give the corresponding thione which was in turn coupled to the Merrifield resin to give **7**.[8] Cleavage of the dimethoxybenzyl group was quantitatively achieved by treatment with TFA in methylene chloride (1/2) to give **8** without cleavage at the thiobenzyl site. Introduction of a range of C7 side chains was carried out under Mitsunobu conditions, using a large excess (10 eq.) of alcohol (ROH), DEAD and PPh_3 to achieve complete and rapid conversion.[8] This reaction worked very well and was successful with a large range of alcohols, differing in their lipophilicity, basicity, aromaticity and size as illustrated by a selection shown in Table 1. Filtration of the resin and washing with methylene chloride led to the supported derivatives **9h-m** and illustrated clearly the advantage of a resin based approach to achieve a rapid and simple separation of the desired products from side products such as triphenylphosphine, triphenylphosphine oxide or DEAD derivatives. The completion of these reactions was monitored by ^{13}C NMR of the resins.[8] In addition, we reacted aliquots of resins **8** and **9h-m** with sodium methoxide[8,11,12] to generate the corresponding 4-methoxyquinazoline, easily analysed by NMR. The absence of 4-methoxy-7-dimethoxybenzylquinazoline in the crude product of step c) and 4-methoxy-7-hydroxy-quinazoline in step d) was indicative of the completeness of the reaction. The introduction of the C4 oxindole moiety was achieved as previously described by coupling the sodium anion of **3f** (10 eq) with **9h-m** .

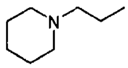
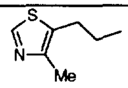
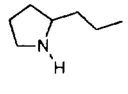
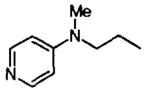
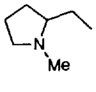
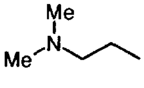
Scheme 3



a) P_4S_{10} pyridine, 110°C, 67% b) Merrifield, DBU, DMF c) TFA / CH_2Cl_2 (1/2), RT d) ROH (10 eq.), Ph_3P (10eq.), DEAD (10eq.), THF, 2Hr e) NaH, DMF f) SCX silica filtration g) NH_3 , MeOH, CH_2Cl_2

The reaction products were purified by SPE followed by the displacement of the expected products **4h-m** from SCX column[9] using a solution of ammonia in methanol.[8] Evaporation led to **4h** and **j-m** in excellent yields and purity (>95%) (Table 1).[9] In the case of **4i** the Mitsunobu reaction failed probably due to intramolecular cyclisation of the activated Mitsunobu intermediate to form the corresponding fused bicyclo-[3-2-0]-azaheptane.[13]

Table 1

	R	yield %*		R	yield %*
4h		53	4k		67
4i		0	4l		62
4j		60	4m		46

* calculated over steps d,e,f,g and based on the theoretical charge of the resin.

In conclusion, we describe in this paper a very easy and efficient multiparallel synthesis of oxindole quinazolines. The use of solid phase chemistry allowed easy modification of the C7 substituent illustrating the advantage of solid phase chemistry over solution chemistry in reactions such as Mitsunobu. Introduction of the C4 oxindole ring by nucleophilic displacement of the thioether linker was a key step in our strategy and also represented the step of cleavage from the resin. Purification of the final compounds was achieved by Solid Phase Extraction using a sulfonic acid silica by taking advantage of the greater basicity of the products formed compared with the impurities. Further development of this chemistry is ongoing.

References and notes

1) Thomas, A.P.; Hennequin, L.F.; Lohmann, J.J.; Ple, P. WO 9742187 A1 971113. Unequivocal proof of carbon-carbon attachement and structure was proven by ^{1}H, ^{13}C NMR, NOE effects and cross chemistry (unpublished data).

2) Thompson, A.M.; Murray, D.K.; Elliott, W.L.; Fry, D.W.; Nelson, J.A.; Hollis-Showalter, H.D.; Roberts, B.J.; Vincent, P.W.; Denny, W.A. *J.Med. Chem.* **1997**, *40*, 3915-3925

3) Takase, Y.; Saeki, T.; Watanabe, N.; Adachi, H.; Souda, S.; Saito, I. *J.Med. Chem.* **1994,** *37*, 2106-2111

4) See complete issue of Chem Review 1997, 97, issue 2

5) Merrifield resin Bachem® D1245 1.24 mmol/g

6) 1 was prepared by reaction of the sodium salt of ethoxyethoxyethanol with 6-fluoro quinazolinone [7] (110°C, 30hrs, Alcohol (4 eq.), NaH (4 eq.), DMF, 84%.

7) Rewcastle, G.W.; Palmer, B.D.; Bridges, A.J.; Showalter, H.D.; Sun L.; Nelson, J.; McMichael, A.; Kraken, A.J.; Fry, D.W., Denny, W.A. *J. Med. Chem.* **1996,** *39*, 918-928

8) The procedures described are typical and representative for the preparation of **2**, **4**, **6**, **7**, **8**, **9**. Typical procedure: A suspension of Merrifield resin (9.77g, 12.1 mmol) in DMF(200ml) was stirred at ambient temperature for 15 min. Dimethoxylbenzylthione (4.77g, 14.5 mmol) in DMF(50ml) was added and the mixture was stirred until complete dissolution. DBU (2.17ml, 14.5 mmol) was added and the mixture was stirred for 24hrs. The resin was filtered, washed with DMF (3X) followed by CH_2Cl_2 (4X) followed by MeOH/THF 1/1 (3X) and dried under vacuum overnight to give **7** (13.1g) (theoretical 13.3 g). **7** : ^{13}C NMR ($CDCl_3$) 33.5 (SCH_2-Resin); 55.87 (2C, OMe); 70.47 (OCH_2Ph).
7 (12gr) Was stirred in CH_2Cl_2 (100ml) for 15min. TFA (50ml) was added and stirring continued for 5hrs. The resin was filtered, washed with CH_2Cl_2 (4X) followed by MeOH/THF 2/1 (2X) and dried under vacuum overnight to give **8** (10g). **8** : ^{13}C NMR (C_4D_8O) 33.88 (SCH_2Ph).
8 (200mg) was suspended in anhydrous THF (3ml). 2-Hydroxyethylpiperidine (0.25ml, 10eq) and PPh_3 (480mg, 10eq) were added. After complete dissolution DEAD (0.29ml, 10eq) in THF (2ml) was added dropwise. The suspension was stirred 1hr at ambient temperature. The resin was filtered, washed successively with CH_2Cl_2 (5X); MeOH (2X); CH_2Cl_2 (2X); MeOH/CH_2Cl_2 1/1 (2X); THF (2X) and dried under vacuum to give **9h** (231mg). **9h** : ^{13}C NMR ($CDCl_3$) δ 24.1 ($\underline{C}H_2$); 25.9 (2C, $\underline{C}H_2$); 40.3 ($\underline{C}H_2S$); 55.03 (2C, $\underline{C}H_2N$); 57.8 (CH_2N); 66.5 (CH_2O).
A solution of **3h** (1.84g, 10.9 mmol) in DMSO (9ml) was added to a suspension on NaH (0.438g, 10.98 mmol) (prewashed with pentane) in DMSO (9ml). **9h** (200mg) was suspended in DMSO (2ml) and stirred for 15min. After stirring for 30min, the solution of oxindole was poured onto the suspension of resin and the mixture was heated at 100°C under N_2 for 3.5 hrs. After cooling, saturated NH_4Cl (10ml) was added followed by water (1ml) and the mixture was extracted with EtOAc. The organic layer was washed with water to pH=6 and dried over $MgSO_4$. The organic layer was filtered and poured onto an SCX (IST1.9gr) column preconditioned with MeOH. The column was washed with EtOAc (2X) followed by CH_2Cl_2 (2X) and CH_2Cl_2/MeOH 1/1 (2X). A solution of 1% NH_3 in CH_2Cl_2/MeOH 1/1 was then passed through the column and the fractions containing **4h** were collected and evaporated to give **4h** (47mg; 53 %). In some cases small amounts (<10%) of quinazolone resulting from an uncompleted reaction contaminated the final product. **4h** ^{1}H NMR (DMSO, CF_3COOD) δ 1.4 (m, 1H); 1.72 (m, 3H); 1.86 (m, 2H); 3.05 (t, 2H, J = 11.5hz); 3.5 (4H, m); 4.6 (t, 2H, J = 4hz); 6.77 (dd, 1H, J=8.8 and 4 hz); 7.13 (dt, 1H, J = 10.4 and 8.8hz); 7.25(s, 1H); 7.28 (d, 1H, J = 9.4hz); 8.01 (t, 1H, J = 9.4hz); 8.72 (s, 1H). MS-ESI : 425 [MH]+.

9) Cartridge IST Isolute® SCX part N° 9530-0100 particle size 40-70 μM.

10) D.P. Curran, *Angew. Chem. Int. Ed.* **1998,** *37*, 1174-1196.

11) **8** (200mg) was added to a solution of MeONa (freshly prepared from Na and anhydrous MeOH) in THF (4ml) and the mixture was stirred for 2hrs at 65°C. After cooling and evaporating, the residue was partitioned between saturated NH_4Cl (5ml) and EtOAc (pH of aqueous layer adjusted to 7 with 2N HCl). The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to give 4-methoxy-7-hydroxyquinazoline (32mg; quant.). ^{1}HNMR (DMSO) δ 4.1 (s, 3H); 7.1 (d, 1H); 7.2 (dd, 1H); 8.0 (d, 1H); 8.65 (s, 1H). MS-ESI : 177 [MH]+. The same procedure applied to **9h** (100mg) gave 4-methoxy-7-piperidinethoxyquinazoline (18 mg; quant.). ^{1}HNMR (DMSO) δ 4.1 (s, 3H); 4.3 (t, 2H); 2.75 (t, 2H). MS-ESI: 290[MH]+.

12) The conversion of the C-4 supported thioether quinazoline into the corresponding C4-alkoxy derivatives had been shown to be almost quantitative by reacting a series of alkoxides with the resins (Unpublished data).

13) Sammes, P.; Smith, S. *J. Chem. Soc. Perkin Trans I*, **1984**, 2415-2419