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Tetrahedron Letters 45 (2004) 8049–8051
Tetrahedron Letters

Novel parallel synthesis of *N*-(4-oxo-2-substituted-4*H*-quinazolin-3-yl)-substituted sulfonamides

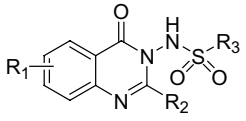
Yuefen Zhou,* Douglas E. Murphy, Zhongxiang Sun and Vlad E. Gregor*

Department of Medicinal Chemistry, Anadys Pharmaceuticals Inc., 3115 Merryfield Row, San Diego, CA 92121, USA

Received 23 July 2004; revised 27 August 2004; accepted 30 August 2004
Available online 21 September 2004

Abstract—A general method was developed to synthesize a class of *N*-(4-oxo-2-substituted-4*H*-quinazolin-3-yl)-substituted sulfonamides in moderate to good yield. This new method can be applied in both single compound and parallel synthesis. About 90 compounds with a variety of substituents were synthesized using this method in a parallel fashion.

Quinazolinone derivatives are known to possess hypnotic, diuretic, anti-hypertensive, anti-bacterial, anti-viral, anti-inflammatory, bronchodilator, anti-HIV, and tuberculostatic activity.[1] In search of anti-infective agents, we became interested in synthesizing various 3-sulfonamide-substituted quinazolinone derivatives (**1**).



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A general synthetic method of broad scope that would allow for the rapid generation of compounds on a small scale in a solution-phase parallel fashion was essential to our program. To date, there are only a few examples of the title compounds (**1**) reported. The reported synthesis of the title compounds (**1**) involves the sulfonylation of 3-amino-quinazolinones (**2**) with arylsulfonyl chlorides in refluxing benzene or ethanol in the presence of a base, such as pyridine or NaOH, with yields ranging from 58% to 66% (Scheme 1).[2a–c]

In our initial efforts we attempted to use the existing method (Scheme 1) to make the title compounds (**1**) in both direct and parallel fashion. The key 3-aminoquinazolinone intermediates (**2**) were prepared in good yield according to the literature method[2a] as shown in Scheme 2.

Initially, the reactions of **2** with various sulfonyl chlorides were tried in refluxing benzene in the presence of pyridine as base, and with pyridine alone as both base and solvent at 80 °C on a 100 μmol scale. Some reactions were not always reproducible in our hands. These results led to the development of a versatile method that allowed the title compounds (**1**) to be synthesized efficiently with various substituents in parallel fashion on a μmol scale.

A new strategy was therefore planned, where benzoxazinones (**4**) and substituted sulfonyl hydrazides (**5**) would condense to give the title compounds (**1**). The sulfonyl hydrazides (**5**) were conveniently prepared from the corresponding sulfonyl chlorides and hydrazine.[2d] The first attempt was to treat an equivalent amount of **4a** (R_1 = 6-F, R_2 = Ph) with *p*-nitrobenzenesulfonyl hydrazide (**5a**) on a 200 μmol scale in anhydrous pyridine (1 mL). No desired product was detected by LC–MS after heating at 100 °C overnight. When the solvent

Keywords: 3-Sulfonamide-substituted quinazolinones; Parallel synthesis.
* Corresponding authors. Tel.: +1 858 530 3693/3646; fax: +1 858 530 3644; e-mail addresses: yzhou@anadyspharma.com; vgregor@anadyspharma.com

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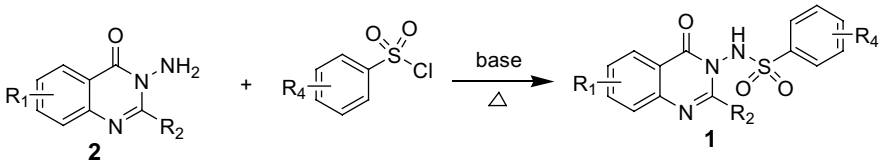
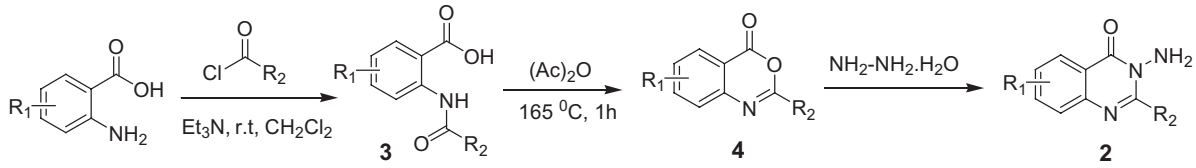
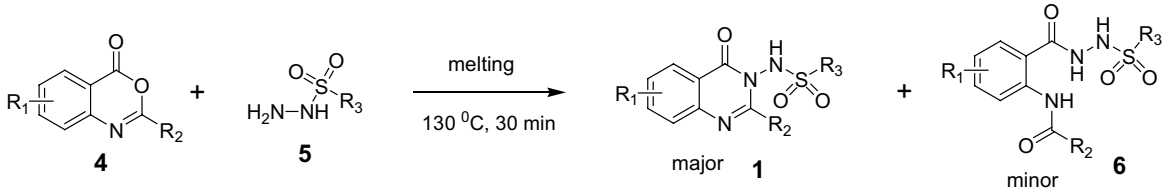
doi:10.1016/j.tetlet.2004.08.183



Scheme 1.



Scheme 2.



Scheme 3.

was changed to glacial acetic acid, the reaction gave the desired product **1a** (R_1 = 6-F, R_2 = Ph, R_3 = 4-NO_2-Ph) with <20% conversion as indicated by LC–MS. Under these conditions, a number of new 3-sulfonamide-substituted quinazolinone derivatives (**1**) were synthesized in very low yield. Some reactions failed to give any desired products at all; therefore, efforts are taken to improve both yield and reaction scope.

The next attempt consisted of combining **4a** and **5a** devoid of solvent, followed by heating to 160 °C (oil bath), allowing the resulting melt to stir under a N_2 atmosphere for 15 min. LC–MS analysis of the reaction mixture indicated formation of the desired product (**1a**) in <20% yield along with multiple side products. Reducing the melting temperature to 130 °C while keeping other conditions constant increased the conversion to 50% (LC–MS). By extending the reaction time to 30 min, the purity of the desired product increased to greater than 80% as indicated by LC–MS without work-up or purification. This improved method was applied to the parallel synthesis of a variety of new quinazolinone derivatives (**1**)[3] (Scheme 3).

Four 6-fluoro-benzoxazinone intermediates (**4**) and 22 sulfonyl hydrazides (**5**) were synthesized using the methods described above. The remaining challenge was to determine if the parallel synthesis of the title compounds (**1**) under the melt conditions described above could be performed. The MiniBlock™ XT system[3] made this strategy possible. This system allows for up to 24 reactions to run simultaneously under a N_2 atmosphere. Using multiple systems, 88 reactions were performed in parallel utilizing the four 6-fluoro-benzoxazinones (**4**) and the 22 sulfonyl hydrazides (**5**) on a 200 μmol scale to give the desired 3-sulfonamide-substituted quinazolinones (**1**). The results are listed in Table 1.

Table 1. Synthesis of 2-substituted, 3-sulfonamide-substituted quinazolinones (**1**)[a]

R_3	R_2 (% yield[b])			
	Phen-ethyl	Bn	Ph	2-Thiophene-methylene
4-CO_2H-Ph	98	81	67	99
4-NHCOMe-Ph	99	94	58	99
4-OCF_3-Ph	96	90	81	74
3,4-Di-Cl-Ph	83	85	40	29
4-CF_3-Ph	90	92	87	45
4-CN-Ph	90	88	51	73
4-Cl-Ph	90	90	68	49
Bn	82	96	45	79
3-NO_2-4-Cl-Ph	92	89	55	24
3-CO_2H-Ph	99	98	98	83
5′-(*N*-Thiophen-2-yl-methyl-benzamide)	83	72	37	51
4-^{i}Pr-Ph	86	76	64	32
4-OMe-Ph	85	90	73	71
3,4-Di-F-Ph	92	89	98	75
2-Cl-Ph	95	70	60	80
3,4-Di-OMe-Ph	86	69	90	63
3,5-Di-Cl-Ph	95	92	53	50
4-F-Ph	95	98	99	78
4-NO_2-Ph	95	81	99	97
4-^{t}Bu	92	82	44	50
2,4-Di-Cl-5-Me-Ph	57	17	26	<5
2,4-Di-Cl-Ph	<5	8	15	52

[a] All of the products (R_1 = 6-F) <90% pure by ELSD were purified by reverse-phase HPLC in automated fashion using Waters MS-triggered purification system using CH_3CN and H_2O as eluting solvents.
[b] The yields are estimated by HPLC (ELSD) from LC–MS results of the reaction mixture before HPLC purification.

The scope of this reaction is fairly broad, where R_2 and R_3 can be alkyl and substituted aromatic/hetero-aromatic groups. The methodology can be applied in either a direct[4] or parallel fashion, giving moderate to good yields of the products.[5]

During the development of this procedure, a major impurity, 2-benzoylamino-*N*-(4-fluoro-benzenesulfonamido)-5-fluoro-benzamide (**6a**; R_1 = 4-F, R_2 = Ph and R_3 = 4-F-Ph) was isolated after purification.[6] The isolation of **6a** suggests that the melt reaction may initially proceed via this intermediate, followed by ring closure upon extended heating to form the title compound (**1**). To test this hypothesis, a stepwise approach was explored. An equivalent amount of **4b** (R_1 = 6-F, R_2 = 2-thiophenemethylene) and benzenesulfonylhydrazide were combined and dissolved in anhydrous DMF (0.4 M). The mixture was shaken at room temperature for 22 h to give the ring-opened compound **6b** (R_1 = 4-F, R_2 = 2-thiophenemethylene, R_3 = Ph) as the major product along with less than 5% of the cyclized product **1b** (R_1 = 6-F, R_2 = 2-thiophenemethyl, R_3 = Ph). This mixture was heated at 80 °C for 20 h to give the cyclized product **1b** in 78% isolated yield after column chromatography purification. These results support our hypothesis about the possible mechanism of the melt reaction, and warrants further investigation of this method.

In summary, a novel, general and efficient method for the synthesis of a variety of new 2-substituted, 3-sulfonamide-substituted quinazolinone derivatives in both direct and parallel fashion was developed. By demonstrating the broad application of this chemistry, this methodology may be very useful in organic synthesis.

References and notes

1. (a) Wilson, L. J.; Morris, T. W.; Wu, Q.; Renick, P. J.; Parker, C. N.; Davis, M. C.; McKeever, H. D.; Hershberger, P. M.; Switzer, A. G.; Shrum, G.; Sunder, S.; Jones, D. R.; Soper, S. S.; Dobson, R. L. M.; Burt, T.; Morand, K. L.; Stella, M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1149–1152; (b) Párkányi, C.; Yuan, H. L.; Strömberg, B. H. E.; Evenzahav, A. *J. Heterocycl. Chem.* **1992**, *29*, 749–753, and references cited therein; (c) Raffa, D.; Daidone, G.; Schillaci, D.; Maggio, B.; Plescia, F. *Pharmazie* **1999**, *54*(4), 251–254; (d) Kumar, A.; Singh, S.; Saxena, A.; Shanker, K. *Ind. J. Chem.* **1988**, *27B*, 443–447; (e) Jiang, J. B.; Hesson, D. P.; Dusak, B. A.; Dexter, D. L.; Kang, G. J.; Hamel, E. *J. Med. Chem.* **1990**, *33*, 1721–1728; (f) Desai, N. C.; Ghatt, J. J.; Shah, B. R.; Undavia, N. K.; Trivedi, P. B. *IL Farmaco* **1996**, *51*(5), 361–366.
2. (a) Zahran, M. A. *J. Ind. Chem. Soc.* **2000**, *77*(10), 494–496; (b) Ammar, Y. A. *Oret. J. Chem.* **1990**, *6*(3), 165–169; (c) Gupta, D. P.; Ahmad, S.; Kumar, A.; Shanker, K. *Ind. J. Chem.* **1988**, *27B*(11), 1060–1062; (d) Friedman, L.; Litle, R. L.; Reichle, W. R. *Org. Synth.* **1960**, *40*, 93.
3. General experimental procedure for parallel synthesis of *N*-(4-oxo-2-substituted-4*H*-quinazolin-3-yl)-substituted sulfonamides (**1**): Caution: It is not recommended to perform this reaction on a larger scale than shown here due to the potential uncontrollable decomposition of the sulfonyl hydrazides. The stepwise process using DMF as a solvent, described above may have the potential for a safe scale-up. The reaction should be carried out behind a safety shield. The benzoxazinones (0.2 mmol) and the sulfonyl-hydrazides (0.2 mmol) were mixed as solids. The reaction mixtures were heated in parallel at 130 °C under a nitrogen atmosphere for 30 min in MiniBlock™ XT systems (supplied from Mettler-Toledo AutoChem Inc.). After cooling, the solids were dissolved in $CHCl_3$ (4 mL) and washed with water (2 mL), aq $NaHCO_3$ (2 × 2 mL) and water (2 mL) sequentially by liquid–liquid extraction. The organic layers were dried and the resulting crude products were further purified by reverse-phase HPLC in automated fashion. Selected analytical data for **1c** (R_1 = 6-F, R_2 = 2-thiophenemethylene, R_3 = 4-OMe-Ph) are listed below: 10.8 mg, 12.1% isolated yield after HPLC purification with 100% HPLC purity by ELSD. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.84 (3H, s), 4.23 (1H, d, J = 16 Hz), 4.67 (1H, d, J = 16 Hz), 6.96 (2H, m), 7.06 (2H, d, J = 9.6 Hz), 7.40 (1H, dd, J = 4.4, 1.6 Hz), 7.56 (1H, d, J = 9.6 Hz), 7.69 (4H, m), 11.47 (1H, s). ^{13}C NMR (400 MHz, DMSO-d_6): δ 35.21, 56.60, 111.85, 115.08, 122.43, 124.40, 126.15, 127.51, 130.63, 130.89, 131.20, 137.45, 143.33, 156.80, 158.80, 159.54, 161.99, 163.83. LC–MS (ES+): m/z = 446.1 $[M+H]^+$. Anal. Calcd for $C_{20}H_{16}FN_3O_4S_2$: C, 53.92; H, 3.62; N, 9.43. Found: C, 53.85; H, 3.62; N, 9.46.
4. Example for single compound large-scale reaction: **1d** (R_1 = 6-F, R_2 = Bn, R_3 = 4-NHCOMe-Ph), reaction scale: 1.6 mmol, isolated yield: 71% after recrystallization (3:1 hexanes/EtOAc). LC–MS (ES+): m/z = 467.1 $[M+H]^+$.
5. The isolated yield after HPLC purification (range from 1% to 99% with average isolated yield of 38%) was much lower than the yield estimated by HPLC (ELSD) from LC–MS results, partially because the purification method was set in such a way to accommodate a variety of products (**1**) in an automated fashion giving the high throughput we desired, but with the disadvantage of losing an amount of product in many cases.
6. Analytical data for **6a**: LC–MS (ES+): m/z=432.2 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.27 (2H, t, J = 8.8 Hz), 7.44 (1H, t, J = 5.2 Hz), 7.53 (2H, t, J = 7.6 Hz), 7.60–7.64 (2H, m), 7.74 (2H, d, J = 6.8 Hz), 7.87 (2H, dd, J = 8.4, 5.2 Hz), 8.50 (1H, dd, J = 9.2, 5.6 Hz), 10.23 (1H, br s), 11.12 (1H, br s), 11.37 (1H, br s).