An efficient construction of quinazolin-4(3*H*)-ones under microwave irradiation

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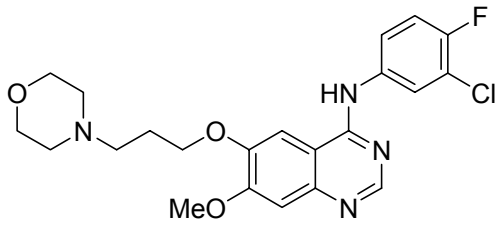
Abstract

The highly accelerated Niementowski synthesis of quinazolin-4(3*H*)-one and quinazolin-2,4-dione derivatives under microwave irradiation is reported. Compared to the conventional conditions, this new method shows the advantages of a good substrate tolerance, and a clean and rapid conversion. The method has been successfully applied for the construction of the key intermediate of iressa.

Keywords: Quinazolin-4(3*H*)-ones, microwave irradiation, Iressa

Introduction

Various quinazolin-4-ones, quinazolin-2,4-diones and their derivatives are well known to possess an array of physiological activities, e. g. anticancer, muscal relaxant, hypnotic, antiinflammatory, antineoplastic, diuretic, and antihypertensive activities, and are widely used in pharmaceuticals.[1] Examples include the anticancer compound trimetrexate, the sedative methaqualone, the alpha adrenergic receptor antagonist such as doxazosin and the antihypertensive agent ketanserin. As a consequence, they have been very attractive targets in synthetic chemistry in recent years. In particular, gefinitib, *i.e.* *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy) quinazolin-4-amine (traded as Iressa, ZD1839, see **Figure 1**) which can be synthesized by elaboration of 6-benzyloxy-7-methoxyquinazolin-4(3*H*)-one **9**, has been recognized as a tyrosine kinase inhibitor of the epidermal growth factor receptor and has been clinically used against cell lung cancer with ever increasing popularity.[2]



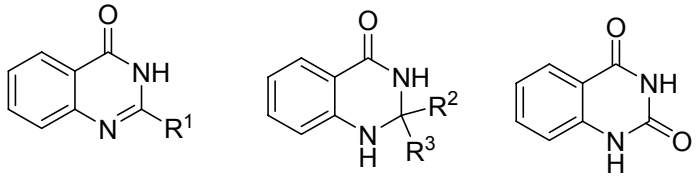
Iressa

Figure 1

In accordance with the significance of quinazolin-4(3*H*)-ones, various synthetic methods have been developed for the construction of this kind of fused heterocycles.[3,4] Many quinazolines can be prepared from 2-aminobenzaldehyde, 2-aminophenyl ketones or anthranilic acids. Typically, quinazolin-4(3*H*)-ones are prepared from an anthranilic acid or its derivative, e.g. 2-amimobenzonitrile and an amide under acidic catalytic conditions by heating them at 200 °C, termed as the Niementowski synthesis. A recent paper has reported a $Yb(OTf)_3$-catalyzed one-pot synthesis of quinazolin-4(3*H*)-ones from anthranilic acid, anilines and orthoesters (or formic acid) under solvent-free conditions.[5] The reaction was completed in several minutes and the temperature was lowered to 60 or 80 °C, providing good to excellent yields of the products, but the method seems to be restricted to the synthesis of 2-aryl substituted quinazolin-4(3*H*)-ones. Certainly, there are still many other possible variations. For example, 4*H*-3,1-benzoxazin-4-ones react with primary amines at or above room temperature to give a variety of 4-quinazolinones.[6] Although the reported methods are valuable in varying degree, some of them still suffer from limitations like unsatisfactory or variable yields, lengthy reaction time, unsatisfactory substrate tolerance and tedious work-up procedure. Benzoxazin-4-ones themselves have to be prepared from anthranilic acids and are rather moisture-sensitive, highly hygroscopic, and prone to deteriorate at higher temperatures. It is therefore of interest to develop a reliable synthetic strategy for the construction of such fused heterocycles.

Microwave-assisted chemical synthesis is proving to be a powerful technique for increasing the output of chemical synthesis.[6] The advantages of the microwave method over classical techniques including a strikingly enhanced reaction rate, improved yields and cleaner products have been well documented.[7] There are also a few esoteric examples describing the benefits of using microwave irradiation for the construction of the quinazolin-4(3*H*)-one core.[8] For example, Besson[8c] has reported the microwave-mediated condensation of anthranilic acids with formamide, to give, via an *o*-amidine intermediate, quinazolin-4(3*H*)-ones. Recently, we are engaged in the use of microwave irradiation for the preparation of the usually uneasy attainable compounds such as diaryl ethers and diaryl sulfides.[9] In continuation of our interest in reactions where conventional heating was limited, with recent focus on the fused heterocyclic skeleton serving as building blocks for the preparation of compounds with pronounced pharmaceutical value like Iressa, we furthered our investigation on the use of microwave irradiation for

synthesizing diverse quinazolinones based on the modified Niementowski reaction. In this paper, we demonstrate that, under microwave irradiation, both anthranilic acids and anthranilamides react smoothly with a range of amides and ketones or urea leading to quinazolinone derivatives of high purity in moderate to excellent yields with a simple work-up. In the course of the work, three types of quinazolinone derivatives were obtained, namely 2-substituted quinazolin-4(3*H*)-ones **1**, 2,2-disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones **2** and 1*H*,3*H*-quinazolin-2,4-dione **3** (Figure 2).



1 **2** **3**

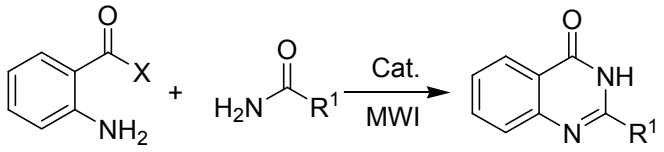
Figure 2

Results and Discussion

Our work was initiated with the reaction between anthranilamide **4a** and formamide **5a**. To optimize the reaction conditions, the irradiation power, the reactants ratio and reaction time were variably investigated. We were pleased to find that the reaction provided quinazolin-4(3*H*)-one **1a** in 93% yield after 5 min of irradiation at 300 W with the reactants ratio of **4a**:**5a** at 1:5 (Table 1, entry 1) in the presence of one equivalent of acetic acid. In comparison, a conventional thermal heating of this reaction at reflux in ethanol for 1h gave 86% yield of the product under acetic acid catalysis.[10] Encouraged by this result, the reactivity of other amides toward the Niementowski reaction was examined and the results are summarized in Table 1. The addition of less than a stoichiometric amount of the acid is helpful for the reaction. For formamide and acetamide **5b**, glacial acetic acid is strong enough to catalyze the reaction. But for benzamide **5c,** a stronger acid such as *p*-TsOH is necessary. As expected, **5b** demonstrated a much lower reactivity, probably due to steric hindrance. However, the moderate yield of **1b** could be achieved when the mole ratio of **4a**, **5b** and the acetic acid was 1:10:1 under microwave irradiation of 500 W for 20 min (Table 1, entry 2). Instead of an aliphatic amide, the aromatic substrate **5c** was employed to test the scope of the protocol. To our surprise, under comparable conditions as for **5a**, the 2-phenyl substituted **1c** was isolated in 63% yield after 10 min irradiation at 300 W with the addition of 0.04 equivalents of *p*-TsOH as the catalyst (Table 1, entry 3). Increasing the amount of the acid did not improve the yields significantly. Further, the Niementowski reaction could also be carried out for 2-cyanoacetamide **5d**, providing a satisfactory yield of the product **1d** under comparable conditions, yet at a much lower microwave output without any acid added in only 5 minutes (Table 1, entry 4).

We then switched to the use of the cheaper substrate anthranilic acid **4b** for the desired Niementowski reaction. The activities of **5a-c** were sequentially examined according to the comparable conditions for anthranilamide. We obtained the 2-substituted quinazolin-4(3*H*)-one products **1a-c** in 81%, 46%, and 17% yields, respectively. These were generally lower than that achieved in the case of anthranilamide, especially when the aromatic amide **5c** was used.

Table 1. Acid-catalyzed coupling of anthranilamide or anthranilic acid with amide under microwave irradiation[a]



4 **5** **1**

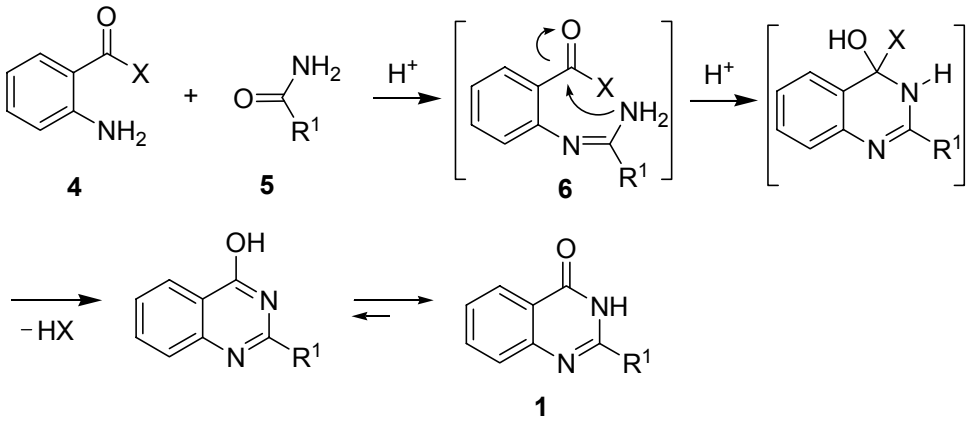
4a. X = NH_2; **4b**: X = OH; **1a**, **5a**: R^1 = H; **1b**, **5b**: R^1 = Me; **1c**, **5c**: R^1 = Ph; **1d**, **5d**: R^1 = CH_2CN

Entry	**4**	**5**	Substrates ratio (**4**:**5**)	Cat. (equiv.)	Power (W)	Time (min)	Product[b]	Yield of **1**[c] (%)
1	**4a**	**5a**	1:5	HOAc (1.0)	300	5	**1a**	93
2	**4a**	**5b**	1:10	HOAc (1.0)	500	20	**1b**	77
3	**4a**	**5c**	1:5	*p*-TsOH (0.04)	300	10	**1c**	63
4	**4a**	**5d**	1:1	none	60	5	**1d**	78
5	**4b**	**5a**	1:5	HOAc (1.0)	300	5	**1a**	81
6	**4b**	**5b**	1:10	HOAc (1.0)	500	20	**1b**	46
7	**4b**	**5c**	1:5	*p*-TsOH (0.04)	300	10	**1c**	17

[a] Reaction of 1 mmol scale, MW power and reaction time as specified.
[b] All products were identified on the basis of their NMR and IR spectra.
[c] Isolated yield based on **4**

Mechanistically, the reaction may proceed via an *o*-amidine intermediate **6** as illustrated in Scheme 1. The first step in this reaction involves the acid catalyzed formation of intermediate **6** by reaction of the amino group in anthranilamide or anthranilic acid with the carbonyl group of the amide, followed by the nucleophilic attack of the nitrogen nucleophile at the carboxylic or

amido carbonyl group which is activated by protonation to produce the product **1** upon elimination of amine or water or two molecules of water.



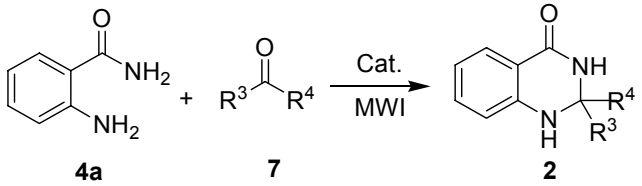
Scheme 1

Encouraged by this success, we became interested in applying this protocol for other carbonyl compounds, such as ketones. Due to the superior performance in the Niementowski reaction, anthranilamide **4a** was selected as the substrate and was subjected to reaction with different kinds of ketones **7** (Table 2). As a result, different 2,2-disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones **2** were obtained in yields ranging from 66 to 95% (Table 2, entries 1-4). This indicates a dramatic reduction in reaction time as compared with the conventional thermal process.[4g,4h] The use of an aliphatic ketone gave excellent isolated yields, and with cyclohexanone the reaction proceeded equally well, providing the 2-spiro substituted 2,3-dihydroquinazolin-4(1*H*)-one **2c**. However, application of benzophenone afforded **2d** with a low yield of 66% even though the irradiation time was prolonged to 20 min (Table 2, entry 4). To the best of our knowledge, there is no report on the Niementowski reaction using an electronically unfavorable substrate like benzophenone under classical heating conditions.

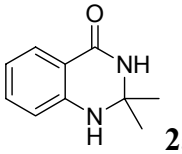
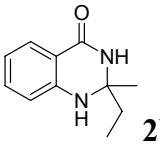
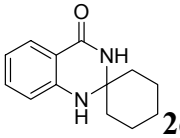
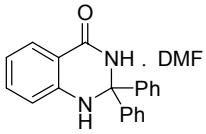
It's interesting that **2d** was isolated as a complex with one molecule of DMF, which is probably formed via the intermolecular hydrogen bond.

Next, attention was focused on the reaction with urea and the results are given in Table 3. As can be seen, both **4a** and **4b** can be used, affording 1*H*,3*H*-quinazolin-2,4-dione **3** in good yields. Compound **3** has been reported to be a key precursor for the synthesis of reversible inhibitors of the gastric (H^+/K^+)-ATPase.[11] Again, **4a** exhibited a greater activity towards the cyclocondensation. Since urea undergoes decomposition at high temperatures, the reaction had to be performed in solvents such as DMSO.

Table 2. Acid-catalyzed coupling of anthranilamide with ketones under microwave irradiation[a]



4a **7** **2**

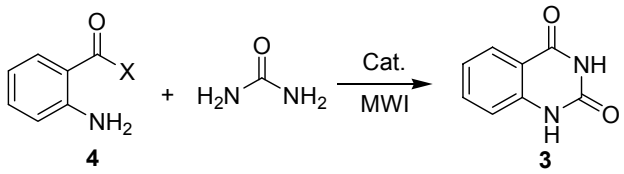
Entry	Ketone **7**	Substrates ratio (**4**:**7**)	Cat. (equiv.)	Power (W)	Time (min)	Product[b]	Yield of **2**[c] (%)
1		1:40	*p*-TsOH (0.02)	60	5	 **2a**	91
2		1:20	*p*-TsOH (0.02)	60	5	 **2b**	95
3		1:5	none	300	10	 **2c**	91
4		1:5	*p*-TsOH (0.08)	300	20	 **2d·DMF**	66

[a] Reaction on 1 mmol scale, MW power and reaction time as specified.
[b] All products were identified on the basis of their NMR and IR spectra.
[c] Isolated yield based on **4**

Having established the advantages of the microwave irradiation approach for the construction of the quinazoline core, we decided to apply the protocol for the synthesis of the key intermediate of Iressa (Scheme 2). Thus, 5-benzyloxy-4-methoxy-2-aminobenzamide **8**, prepared from isovanillin according to a known procedure,[12] was reacted with formamide in the presence of one equivalent of acetic acid under microwave irradiation at 300 W for 5 min, providing the 6,7-disubstituted quinazolin-4(3*H*)-one **9** in 87% isolated yield. Compared to the thermal heating method, which utilized the 6-benzyloxy-7-methoxyquinazolin-4(3*H)*-one and formamide which required 5h of heating at 190 °C, the developed method gave a significant reduction in reaction time.[13] Treatment of **9** with an excess amount of phosphoryl chloride yielded the 4-chloro substituted quinazoline **10** in 68% yield, which was further converted to the 4-anilino substituted **11** by reaction with 3-chloro-4-fluoroaniline in 93% yield. Debenzylation of **11** was smoothly accomplished upon hydrogenolysis over Pd/C in ethanol wherein the deprotected product **12** was

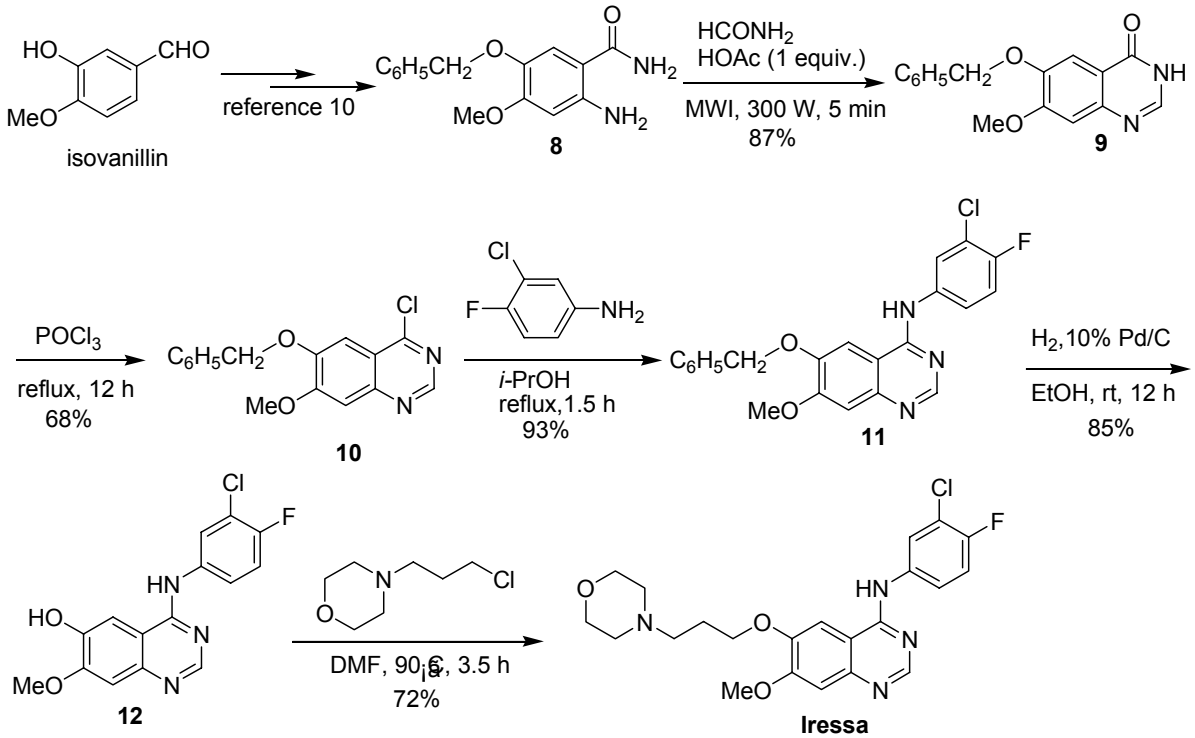
obtained in 85% yield. Finally, the 6-OH substituted quinazoline **12** was subjected to etherification with 4-(3-chloropropyl)morpholine[14] upon heating at 90 °C in DMF for 3.5 h in the presence of a mild base, providing 72% yield of Iressa as a pale yellow solid.

Table 3. Acid-catalyzed coupling of anthranilamide/anthranilic acid with urea under microwave irradiation[a]



Entry	**4**	Solvent	Cat. (equiv.)	Power (W)	Time (min)	Yield[b] of **3** (%)
1	**4a**	DMSO	HOAc (1)	300	5	88
2	**4b**	DMSO	HOAc (1)	300	10	66

[a] Reaction on 1 mmol scale. With the substrates ratio of **4a** to urea 1:4. Reaction time as specified.
[b] Isolated yield based on **4**. The structure **3** was ascertained by IR and NMR data.



Scheme 2. Synthesis of Iressa.

Experimental Section

General Procedures. All materials were of commercial quality and were used as received. Melting points were uncorrected. The product purities were determined by GC-MS analysis. GC-MS data was acquired on a TOP series GC8000 with a FINNIGAN-VOYAGER mass selective detector. NMR data were acquired on a Bruker 500 or a Varian 400 spectrometers. ^{1}H and ^{13}C chemical shifts (δ) are reported in ppm relative to TMS as internal standard. Coupling constants (J) are given in Hz. A modified domestic microwave oven adopted for refluxing was used for all the investigations and the reactions were monitored by thin layer chromatography coated with silica gel.

General procedure for synthesis of quinazolin-4(3*H*)-one. To the mixture of anthranilamide (0.68 g, 5 mmol) and an appropriate amide (50 mmol) was added 5 mmol of acetic acid, and the mixture was heated under microwave irradiation at 500 Watt for a few minutes. After the reaction was finished, the resulting mixture was poured into ice-cooled water and stirred for 30 min. The precipitation was filtered, and the filter cake washed with water to yield target molecules.

Quinazolin-4(3*H*)-one (1a). Yield, 93 %, white solid in a purity higher than 99%, mp 215-216 °C (lit.[8], 216 °C). ^{1}H NMR (DMSO-d$_6$) δ 7.53 (t, J = 7.25 Hz, 1H), 7.67 (d, J = 8.15 Hz, 1H), 7.82 (m, 1H), 8.09~8.13 (m, 2H), 12.24 (s, 1H, NH); GC-MS *m/z* 146 (M$^+$).

2-Methylquinazolin-4(3*H*)-one (1b). Yield, 77 %, white solid in a purity higher than 98%, mp 238-240 °C (lit.[15], 240 °C). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 2.35 (s, 3H), 7.45 (m, 1H), 7.57 (d, J = 8.10 Hz, 1H,), 7.76 (m, 1H), 8.08 (d, J = 7.75 Hz, 1H), 12.2 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 21.96, 121.15, 126.19, 126.37, 127.10, 134.79, 149.48, 154.78, 162.24; GC-MS *m/z* 160 (M$^+$).

2-Phenylquinazolin-4(3*H*)-one (1c). Yield, 63 %, white solid in a purity of 98.6%, mp 242-246 °C (lit.[16], 246 °C). ^{1}H NMR (DMSO-d$_6$) δ 7.56 (m, 4H), 7.75 (d, J = 7.25 Hz, 1H), 7.84 (m, 1H), 8.18 (m, 3H), 12.55 (s, 1H, NH); GC-MS *m/z* 222 (M$^+$).

2-Cyanomethylquinazolin-4(3*H*)-one (1d). Yield, 78 %, white solid in a purity higher than 97%, mp 242 °C (lit.[17], 242-243 °C). ^{1}H NMR (DMSO-d$_6$) δ 4.18 (s, 2H), 7.53 (m, 1H), 7.68 (m, 1H), 7.82 (m, 1H), 8.11 (d, J = 7.80 Hz, 1H), 12.46 (s, 1H, NH); GC-MS *m/z* 185 (M$^+$).

General procedure for the synthesis of 2,2-disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones 2. To a mixture of anthranilamide (0.68 g, 5 mmol) and *p*-toluenesulfonic acid (17 mg, 0.1 mmol) was added the required ketone. The mixture was heated under microwave irradiation at 60 Watt for 5 min. The excess of ketone was removed under reduced pressure and the residues were washed with ether to afford target molecules.

2,2-Dimethyl-2,3-dihydroquinazolin-4(1*H*)-one (2a). Yield, 91%, white solid in a purity higher than 99%, mp 178-180 °C (lit.[4g], 183-184 °C). ^{1}H NMR (500 MHz, DMSO-d$_6$) δ 1.56 (s, 6H), 3.5 (br, 1H, NH), 6.4 (br, 1H, NH), 6.62 (d, J = 8.04 Hz, 1H), 6.83 (m, 1H), 7.29 (m, 1H), 7.88

(m, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 29.52, 67.36, 114.36, 114.77, 116.97, 127.72, 133.72, 147.62, 163.61; GC-MS *m/z* 176 (M^+).

2-Ethyl-2-methyl-2,3-dihydroquinazolin-4(1*H*)-one (2b). Yield, 95%, white solid in a purity higher than 98%, mp 178-180 °C (lit.[18], 184-186 °C). ^{1}H NMR ($CDCl_3$) δ 0.99 (t, *J* = 7.15 Hz, 3H), 1.49 (s, 3H), 1.80 (m, 2H), 3.80 (br, 1H, NH), 6.49 (br, 1H, NH), 6.62 (d, *J* = 7.25 Hz, 1H), 6.80 (t, *J* = 7.20 Hz, 1H), 7.28 (m, 1H), 7.87 (m, 1H); GC-MS *m/z* 190 (M^+).

1'*H*-spiro[cyclohexane-1,2'-quinazolin]-4'(3'*H*)-one (2c). Yield, 91%, white solid in a purity higher than 98%, mp 226 °C (lit.[18], 224-225 °C). ^{1}H NMR ($CDCl_3$) δ 1.25-1.42 (m, 2H), 1.54-1.63 (m, 6H), 1.73-1.74 (t, *J* = 6.35 Hz, 2H), 6.62 (d, *J* = 7.50 Hz, 2H), 6.80 (t, *J* = 8.10 Hz, 1H), 7.21 (m, 1H), 7.56 (d, *J* = 7.50 Hz, 1H), 7.91 (s, 1H); GC-MS *m/z* 216 (M^+).

2,2-Diphenyl-2,3-dihydroquinazolin-4(1*H*)-one coupled with DMF (2d·DMF). Yield, 66%, white solid, mp 138-142 °C. ^{1}H NMR ($CDCl_3$) δ 2.88 (s, 3H), 2.95 (s, 3H), 5.20 (br, 1H, NH), 6.47 (s, 1H, NH), 6.70 (d, *J* = 8.05 Hz, 1H), 6.79 (s, 1H), 7.26 (m, 1H), 7.32-7.35 (m, 6H), 7.40-7.42 (m, 4H), 7.80 (m, 1H), 8.00 (s, 1H).

Typical procedure for 1*H*,3*H*-quinazolin-2,4-dione 3 (Table 3, entry 1). To a mixture of anthranilamide (0.68 g, 5 mmol) and urea (1.20 g, 20 mmol) were added 5 mL of DMSO and acetic acid (5 mmol). The mixture was heated under microwave irradiation at 300 Watt for 5 min. After completion of the reaction, the mixture was poured into ice-cooled water and stirred for 30 min. The solid was filtered by suction, washed with cold water and dried at vacuum to afford the compound **3** in 88% yield as a white solid in 98% purity, mp > 280 °C (lit.[19], 342-343 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.18 (m, 2H), 7.63 (m, 1H), 7.89 (d, *J* = 9.75 Hz, 1H), 11.14 (s, 1H, NH), 11.29 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 114.84, 115.85, 122.84, 127.47, 135.47, 141.39, 150.84, 163.37; GC-MS *m/z* 162 (M^+).

4-(3´-Chloro-4´-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy)quinazoline (Iressa).[20] yellow solid, mp > 250 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.00 (m, 2H), 2.35 (t, *J* = 6.5 Hz, 4H), 2.48 (t, *J* = 6.5 Hz, 2H), 3.58 (t, *J* = 4.5 Hz, 4H), 3.94 (s, 3H), 4.18 (t, *J* = 6.5 Hz, 2H), 7.22 (s, 1H), 7.45 (m, 1H), 7.80 (m, 2H), 8.12 (m, 1H), 8.50 (s, 1H), 9.57 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): 25.86, 53.38, 54.92, 55.77, 66.14, 67.08, 102.76, 107.18, 108.88, 116.29, 118.56, 122.17, 123.33, 137.00, 146.90, 148.24, 152.50, 153.95, 154.41, 156.02.

Conclusions

We have developed a convenient microwave-assisted synthesis of 2-substituted quinazolin-4(3*H*)-ones **1**, 2,2-disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones **2** and 1*H,*3*H*-quinazolin-2,4-dione **3**. The method offers several advantages including good to high yields, cleaner products, a dramatic reduction in reaction time and an easy experimental work-up procedure. The synthesis of an important anticancer drug, Iressa, has been accomplished on the basis of the construction of the key intermediate **9** using our microwave heating protocol.

Acknowledgements

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References

1. For a recent review, see: Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627.
2. (a) Camirand, A.; Zakikhani, M.; Young, F.; Pollak, M. *Breast Cancer Res*. **2005**, *7*, R570. (b) Baselga, J.; Averbuch, S. D. *Drugs* **2000**, *60*, 33. (c) Kim, R.; Toge, T.; *Surgery Today* **2004**, *34*, 293.
3. For synthesis of quinazolin-4(3*H*)-ones, see: (a) Yoo, C. L.; Fettinger, J. C.; Kurth, M. J. *J. Org. Chem*. **2005**, *70*, 6941. (b) Kamal, A.; Reddy, K. S.; Prasad, B. R.; Babu, A. H.; Ramana, A. V. *Tetrahedron Lett.* **2004**, *45*, 6517. (c) Alexandre, F. R.; Berecibar, A.; Wrigglesworth, R.; Besson, T. *Tetrahedron* **2003**, *59*, 1413. (d) Shimizu, M.; Oishi, A.; Taguchi, Y.; Gama, Y.; Shibuya, I. *Chem. Pharm. Bull.* **2002**, *50*, 426. (e) Shalaby, A. A.; Ei-Khamry, A. M. A.; Shiba, S. A.; Ahmed, A. A. A. E. *Arch. Pharm. Pharm. Med. Chem.* **2000**, *333*, 365. (f) Stevenson, T. M.; Kazmierczak, F.; Leonard, N. J. *J. Org. Chem.* **1986**, *51*, 616.
4. For synthesis of quinazolin-2,4-diones, see: Connolly, T. J.; McGary, P.; Sukhtankar, S. *Green Chem.* **2005**, *7*, 586. (b) Schwinn, D.; Glatz, H.; Bannwarth, W. *Helv. Chim. Acta* **2003**, *86*, 188. (c) Shao, H.; Colucci, M.; Tong, S.; Zhang, H.; Castelhano, A. L. *Tetrahedron Lett*. **1998**, *39*, 7235. (d) Gordeev, M. F.; Hui, H. C.; Gordon, E. M.; Patel, D. V. *Tetrahedron Lett*. **1997**, *38*, 1729. (e) Gouilleux, L.; Fehrentz, J. A.; Winternitz, F.; Martinez, J. *Tetrahedron Lett.* **1996**, *37*, 7031. (f) Buckman, B. O.; Mohan, R. *Tetrahedron Lett.* **1996**, *37*, 4439. (g) Larsen, S. D.; Connell, M. A.; Cudahy, M. M.; Evans, B. R.; May, P. D.; Meglasson, M. D.; O'Sullivan, T. J.; Schostarez, H. J.; Sih, J. C.; Stevens, F. C.; Tanis, S. P.; Tegley, C. M.; Tucker, J. A.; Vaillancourt, V. A.; Vidmar, T. J.; Watt, W.; Yu, J. H. *J. Med. Chem.* **2001**, *44*, 1217. (h) Klemm, L. H.; Weakley, T. J. R.; Gilbertson, R. D.; Song, Y. H. *J. Heterocycl. Chem.* **1998**, *35*, 1269. (i) Sharma, S. D.; Kaur, V. *Synthesis* **1989**, 677.
5. Wang, L.; Xia, J.; Qin, F.; Qian, C.; Sun, J. *Synthesis* **2003**, 1241.
6. (a) Parkanyi, C.; Yuan, H. L.; Stromberg, B. H. E.; Evenzahav, A. *J. Heterocycl. Chem*. **1992**, *29*, 749. (b) Errede, L. A.; MeBrady, J. J.; Qien, H. T. *J. Org. Chem.* **1977**, *42*, 656.
7. For some recent reviews on this topic, see: (a) Roberts, B. A.; Strauss, C. R. *Acc. Chem. Res.* **2005,** *38*, 653. (b) E. l. Ashry, E. S. H.; Ramadan, E.; Kassem, A. A. *Adv. Heterocycl. Chem.* **2005**, *88*, 1. (c) Molteni, V.; Ellis, D. A. *Curr. Org. Synth.* **2005**, *2*, 333. (d) Desai, B.; Kappe, C. O. *Top. Curr. Chem.* **2004**, *242*, 177. (e) de la Hoz, A.; Diaz-Ortiz, A.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164. (f) Kappe, C. O. *Angew. Chem. Int. Ed.* **2004**,

43, 6250. (g) Ersmark, K.; Larhed, M.; Wannberg, J. *Curr. Opin. Drug Discov. Dev.* **2004**, *7*, 417. (h) Hayes, B. L. *Aldrichchimica Acta* **2004**, *37*, 66.

8. (a) Mizuno, T.; Iwai, T.; Ishino, Y. *Tetrahedron Lett.* **2004**, *45*, 7073. (b) Mizuno, T.; Ishino, Y. *Tetrahedron* **2002**, *58*, 3155. (c) Alexandre, F. R.; Berecobar, A.; Besson, T. *Tetrahedron Lett*. **2002**, *43*, 3911. (d) Orfi, L.; Waczek, F.; Pato, J.; Varga, I.; Hegymegi-Barakonyi, B.; Houghten, R. A.; Keri, G. *Curr. Med. Chem*. **2004**, *11*, 2549. (e) Montazeri N.; Rad-Moghadam, K. *Phosphorus Sulfur Silicon Relat. Elem.* **2004**, *179*, 2533.
9. (a) Li, F.; Meng, Q. Q.; Chen, H. S.; Li, Z. M.; Wang, Q. R.; Tao, F. G. *Synthesis* **2005**, 1305. (b) Li, F.; Wang, Q. R.; Ding, Z. B.; Tao, F. G. *Org. Lett.* **2003**, *5*, 2169.
10. Stevenson, T. M.; Kazmierczak, F.; Leonard, N. J. *J. Org. Chem.* **1986**, *51*, 616.
11. Ife, M. R. J.; Brown, T. H.; Blurton, P.; Keeling, D. J.; Leach, C. A.; Meeson, M. L.; Parsons, I. E.; Theobald, C. J. *J. Med. Chem*. **1995,** *38***,** 2763**.**
12. Althuis, T. H.; Hess, J. J. *J. Med. Chem.* **1977**, *20*, 146.
13. Matsuno, K.; Ushiki, J.; Seishi, T.; Ichimura, M.; Giese N. A.; Yu, J. C.; Takahashi, S.; Oda, S.; Nomoto, Y. *J. Med. Chem.* **2003,** *46,* 4910.
14. Murty, M. S. R.; Jyothirmai, B.; Krishna, P. R.; Yadav, J. S. *Synth. Commun.* **2003**, *33*, 2483.
15. Etter, M. C. *J. Chem. Soc. Perkin Trans. 2* **1983**, 115.
16. Imai, Y.; Sato, S.; Takasawa, R.; Ueda, M. *Synthesis* **1981**, 35.
17. Sumitomo Chem. *DE 2005933*, **1970**; *Chem. Abstr*. **1970**, *74*, 65585.
18. Shi, D.; Shi, C.; Wang, J.; Rong, L.; Zhuang, Q.; Wang, X. *J. Heterocycl. Chem.* **2005**, *42*, 173.
19. Pakrashi, S. C.; Chattopadhyay, S.; Chakravarty, A. K. *J. Org. Chem.* **1976**, *41*, 2108.
20. Seimbille, Y.; Phelps, M. E.; Czernin, J.; Silverman, D. H. S. *J. Label. Compd. Radiopharm.* **2005**, 48, 829.