Pergamon

Tetrahedron 56 (2000) 7245–7253

TETRAHEDRON

Synthesis and Reactions of some 2-Vinyl-3*H*-quinazolin-4-ones

Anette Witt and Jan Bergman*

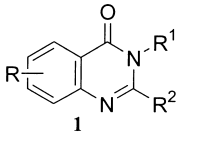
Unit for Organic Chemistry, Department of Biosciences, Karolinska Institute and Södertörn University College, Novum Research Park, SE-141 57 Huddinge, Sweden

Received 14 December 1999; revised 7 June 2000; accepted 22 June 2000

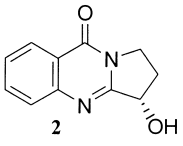
Abstract—A simple, high-yielding synthesis of 2-vinyl-3*H*-quinazolin-4-one, 2-(1-chlorovinyl)-3*H*-quinazolin-4-one and 2-(1-bromovinyl)-3*H*-quinazolin-4-one. The 2-vinylquinazolinones **11a** and **14** participate readily in nucleophilic addition reactions. Treatment with both carbon and nitrogen nucleophiles results in a clean conversion into a variety of 2-substituted 3*H*-quinazolin-4-one derivatives. The 2-(1-halovinyl)-3*H*-quinazolin-4-ones **11b** and **11c** reacted with carbon nucleophiles to give several derivatives of 2-substituted 3*H*-quinazolin-4-one, such as dihydrofurancarboxylic ethyl ester **23**.

Introduction

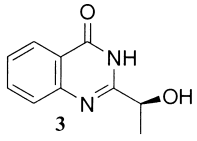
3*H*-Quinazolin-4-one **1** is a frequently encountered unit in natural products[1] such as *l*-vasicinone (**2**),[2] chrysogine (**3**)[3] and drugs[4] such as methaqualone (**4**),[5] febrifugine (**5**) and isofebrifugine (**6**). The latter two compounds are potent but toxic antimalaria drugs, the stereochemistry of which has recently been revised.[6] Molecules based on quinazoline and quinazolinone exhibit a multitude of interesting pharmacological activities,[7] including anticonvulsant, antibacterial and antidiabetic activity.[8,9]



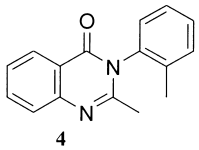
1



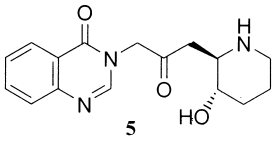
2



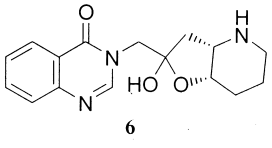
3



4



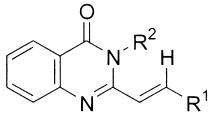
5



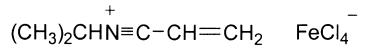
6

The most common synthetic method to 2-substituted 3*H*-quinazolin-4-one is based on the acylation–cyclisation of anthranilic acid (or a derivative, e.g. 2-aminobenzonitrile) and proceeds usually via an *o*-amidobenzamide intermediate.[10–12] Several other methods are available such as cathodic reduction of 2-nitrobenzonitrile.[13] Although the construction of the quinazolinone skeleton has been extensively described in the literature,[7,14] it is surprising to note that very few 2-vinyl derivatives of 3*H*-quinazolin-4-ones are known. In this paper we will discuss a simple, high-yielding synthesis of vinylquinazolinones **11a**–**c** and **14**. Furthermore the reactivity of compounds **11a**–**c** and **14** towards several nucleophiles to give 2-substituted 3*H*-quinazolin-4-one derivatives is reported.

Several 2-styrylquinazolin-4(3*H*)-ones **7** (R^1=C_6H_5) have been prepared since 1910[15] and some derivatives have been demonstrated to possess significant growth inhibitory activity against L1210 murine leukaemia cells.[9] In this context the recently developed anticancer drug CP-31398, N^1-{2-[(*E*)-2-(4-methoxy-phenyl)-vinyl]-quinazolin-4-yl}-*N*,*N*-dimethyl-propane-1,3-diamine, is also of interest.[16] Nevertheless very few derivatives of **7** (R^1=H) have been reported in the literature. Fuks[17] has given an example, where **7** (R^1=H, R^2=*i*-Pr) was prepared in a low yield by reacting the nitrilium salt **8** with methyl anthranilate and Skibo et al. has reported the preparation of 5,8-dihydroxy-2-vinyl-3*H*-quinazolin-4-one.[18] The parent compound **11a** however, has only been mentioned briefly in a patent.[19]



7

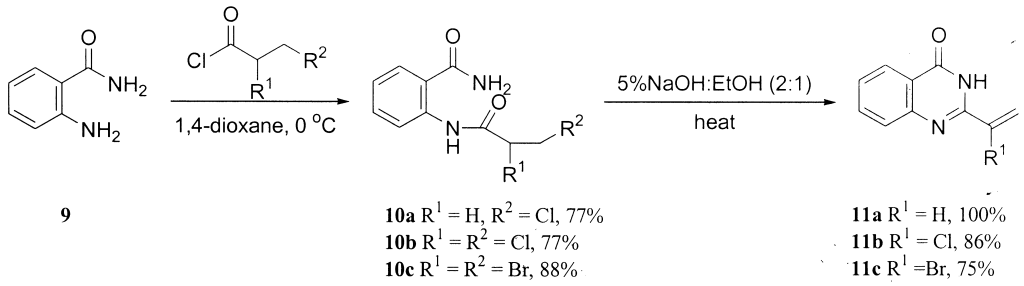


8

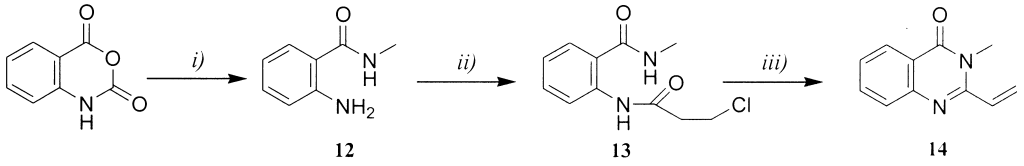
Keywords: cyclisation; Michael reactions; quinazolinones.

* Corresponding author. Tel.: +46-8-608-9204; fax: +46-8-711-68-69; e-mail: jabe@cnt.ki.se

0040–4020/00/$ - see front matter
PII: S0040-4020(00)00595-0



Scheme 1.



Scheme 2. (i) Methylamine in water 60%, rt, 67%. (ii) 3-Chloropropionyl chloride, 1,4-dioxane, 0°C, 75%. (iii) 0.5 M $Na_2CO_{3(aq)}$ in 10% MeOH, heat, 23%.

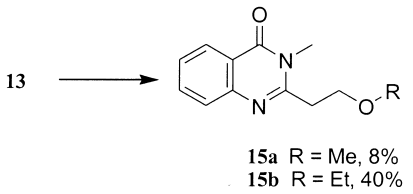
Results and Discussion

2-(3-Chloropropionylamino)-benzamide (**10a**) was readily obtained from anthranilamide (**9**) and 3-chloropropionyl chloride. Cyclisation and dehydrohalogenation of **10a** was effected conveniently with sodium hydroxide in aqueous ethanol to the desired product **11a** in an overall yield of 77% (Scheme 1). The halosubstituted vinylquinazolinones **11b** and **11c** were synthesised analogously in overall yields of 66%.

The *N*-substituted analogue of **11a**, **14**, was similarly prepared (Scheme 2). Thus methylamine in water was added to isatoic anhydride and the corresponding anthranilamide **12**[20] was treated with 3-chloropropionyl chloride to yield 2-(3-chloropropionylamino)-*N*-methyl-benzamide (**13**). Compound **13** underwent cyclisation in refluxing 0.5 M $Na_2CO_{3(aq)}$ containing 10% MeOH to **14**, which was isolated after separation on silica gel in an overall yield of 12%.

The low yield is due to the fact that the cyclisation of compound **13** was not straightforward and the methoxy adduct **15a** was also isolated along with the vinylquinazolinone **14** (Scheme 3). When **13** was treated with sodium hydroxide in aqueous ethanol the ethoxy adduct **15b** was the sole product.

The vinylquinazolinones **11a** and **14** were considered to be good acceptors in Michael type additions and in fact a variety of substituted alkylquinazolinones could be prepared



Scheme 3.

(Table 1). Some analogous additions in the 2- and 4-vinylpyridine[21] and 2-, 6- and 8-vinylpurine[22] series have been investigated previously. Likewise the sulfur nucleophile, 2-mercaptoethanol, had been added to 5,8-dihydroxy-2-vinyl-3*H*-quinazolin-4-one.[18]

The stabilised anion of diethyl acetamidomalonate reacted readily with **11a** or **14** in the presence of a slight excess of base to form the Michael adduct **16a** and **17a** respectively (Scheme 4, Table 1, entries 1 and 2). Compound **16a** crystallised readily from ethanol, while compound **17a** was isolated by column chromatography on silica gel as a colourless oil. Indole, as nucleophile, reacted at the 3-position with **11a** or **14** in refluxing acetic acid. The desired compounds **16b** and **17b** were obtained in good yields (Table 1, entries 3 and 4).

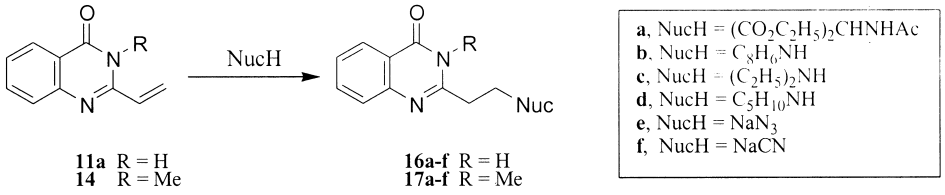
The first attempt to react **11a** or **14** with nitrogen nucleophiles failed using non-catalytic conditions. When a catalytic amount of acetic acid was added in methanol[21] the aminoquinazolinones **16c**,**d** and **17c**,**d** were isolated (Table 1, entries 5, 6, 7 and 8). Compounds **16c**,**d** have been prepared earlier by cyclisation of the corresponding 2-(3-aminopropionylamino)-benzamide with base in alcoholic solution.[23] The 2-vinylquinazolinones **11a** and **14** were also allowed to react with sodium azide and the expected products, **16e** and **17e**, were isolated by column chromatography on silica gel (Table 1, entries 9 and 10). Compounds **16f**[24] and **17f** could be similarly prepared (Table 1, entries 11 and 12).

The halosubstituted vinylquinazolinones **11b**,**c** were expected to be good acceptors in Michael type additions and should therefore after dehydrohalogenation give rise to various derivatives of **7**. However when **11b**,**c** were treated with carbon nucleophiles only cyanide as nucleophile gave the expected product **20** (Scheme 6). Hydrolysis of **20** gave a complex product pattern. However the expected acid **19** could be prepared by an alternative method (Scheme 5).

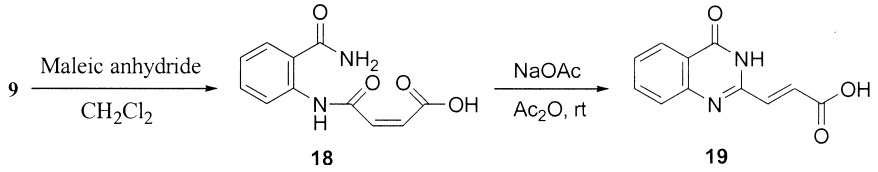
Table 1. Addition of nucleophiles

Entry	2-Vinyl-quinazolinone	Nucleophile	Reagent	Solvent	Time (h)	Yield (%)
1	**11a**	Diethyl acet-amidomalonate	Na	EtOH	3	80, **16a**
2	**14**	Diethyl acet-amidomalonate	NaH	THF	24	41, **17a**
3	**11a**	Indole	–	HOAc	4	95, **16b**
4	**14**	Indole	–	HOAc	4	75, **17b**
5	**11a**	Diethylamine	HOAc[a]	MeOH	20	49, **16c**
6	**14**	Diethylamine	HOAc[a]	MeOH	20	85, **17c**
7	**11a**	Piperidine	HOAc[a]	MeOH	20	84, **16d**
8	**14**	Piperidine	HOAc[a]	MeOH	20	100, **17d**
9	**11a**	Azide	–	THF/H_2O	20	48, **16e**
10	**14**	Azide	–	THF/H_2O	20	50, **17e**
11	**11a**	Cyanide	–	EtOH/H_2O	24	76, **16f**
12	**14**[b]	Cyanide	–	0.5 M Na_2CO_3[c]	1.5	23, **17f**

[a] Catalytic amount.
[b] One-pot synthesis starting with compound **13**.
[c] 0.5 M $Na_2CO_{3(aq)}$ in 10% MeOH was used as solvent.



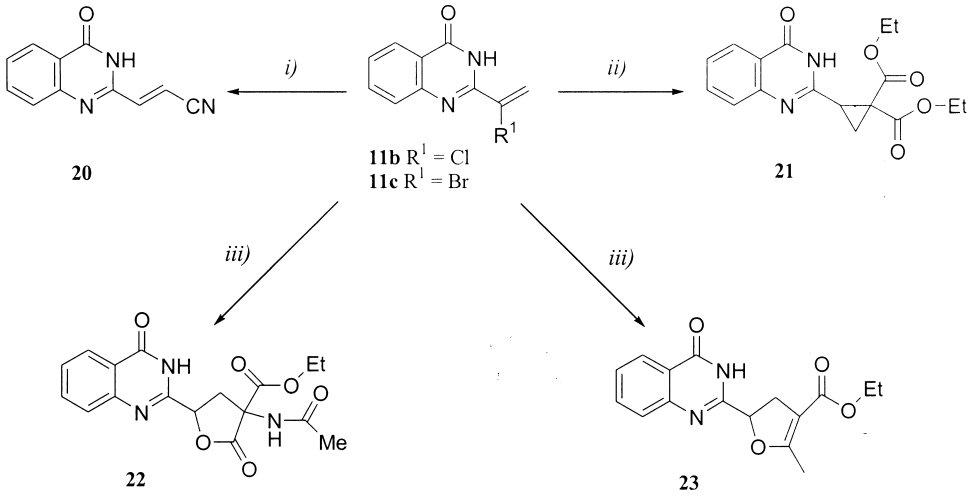
Scheme 4.



Scheme 5.

The acid **18**, readily prepared from anthranilamide (**9**) and maleic anhydride, was cyclised by sodium acetate in acetic anhydride to the desired acid **19** in an overall yield of 37% (Scheme 5). It might be added that Kulkarni[25] has described a synthesis, wherein **19** was prepared by condensation of 2-methyl-3*H*-quinazolin-4-one and chloral, followed by hydrolysis.

The stabilised anion of diethylmalonate reacted readily with **11b,c** in the presence of a slight excess of base to form the



Scheme 6. (i) NaCN, EtOH, water, heat, 66%. (ii) Diethylmalonate, NaH, dry THF, heat, 60%. (iii) Diethyl acetamido-malonate or ethyl acetoacetate, Na, EtOH, heat. **22** (53%) or **23** (5%).

cyclopropane derivative **21** (Scheme 6). A reasonable mechanism involves an initial Michael type addition followed by cyclisation. Various cyclopropane adducts from diethylmalonate have been prepared similarly.[26] The vinylquinazolinones **11b,c** were allowed to react with diethyl acetamidomalonate or ethyl acetoacetate, and the cyclisation products **22** and **23** were isolated. Two diastereomers of **22** were isolated by column chromatography on silica gel. Due to difficulties in the isolation of compound **23** by column chromatography on silica gel the yield was only 5%. Additional material was isolated in 40% yield and according to NMR and GC–MS there were at least two products, which probably are diastereomers of a cyclopropane adduct. Interestingly cyclopropane products and 2,3-dihydrofuran derivatives have been isolated after treatment of methyl (*E*)- and (*Z*)-2-bromo-4,4-dimethoxy-2-butenoates with base.[26b,27]

Experimental

NMR spectra were recorded in DMSO-d_6 solutions, unless otherwise stated, on a Bruker Avance DPX 300 spectrometer, operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C, respectively; δ values are given in ppm or, where indicated, on a JOEL (500 MHz) instrument. IR spectra were recorded on a Perkin–Elmer 1600 FT-IR instrument. Mass spectra were recorded on a Micromass Platform II spectrometer, using the direct-inlet system, or a Hewlett–Packard GC/MS system (HP 6890 series GC system/HP 5973 mass selective detector) equipped with a capillary column (HP-5MS column with 5% phenyl methyl siloxane) both operating in the electron impact (EI) mode at 70 eV. Fragments larger than 20% of the base peak are given. Element analyses were performed by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. HRMS analyses were performed by Sveriges Lantbruksuniversitet (SLU), Uppsala, Sweden. Melting points were determined on a Büchi Melting Point B-545 and are uncorrected. All solvents were purified by distillation or were HPLC grade. Column chromatography was done on silica gel 60 (230–400 mesh ASTM, Merck), TLC analyses were run on Merck Silica Gel 60 F_{254} plates.

2-(3-Chloropropionylamino)-benzamide (10a). 3-Chloropropionyl chloride (13.3 g, 0.1 mol) was added to a solution of anthranilamide **9** (29.0 g, 0.2 mol) in 1,4-dioxane (80 mL) during 20 min at 0°C under a nitrogen atmosphere. The mixture was stirred at room temperature for 1 h and then diluted with water until precipitate appeared, which was collected and washed with water to give compound **10a** (18.3 g, 77%) as a white solid; mp 117–119°C; IR (KBr) 3387, 3171, 1696, 1623, 1584, 1522, 1447, 1390, 1290, 1122, 870, 758, 640 cm^{-1}; δ_H 2.83 (2H, t, *J*=6.1 Hz), 3.87 (2H, t, *J*=6.1 Hz), 7.12 (1H, dd, *J*=7.6, 7.4 Hz), 7.49 (1H, dd, *J*=7.9, 7.4 Hz), 7.73 (1H, s), 7.80 (1H, d, *J*=7.6 Hz), 8.27 (1H, s), 8.45 (1H, d, *J*=7.9 Hz), 11.78 (1H, s); δ_C 40.4 (t), 40.5 (t), 119.8 (s), 120.3 (d), 122.6 (d), 128.6 (d), 132.2 (d), 139.3 (s), 167.8 (s), 170.7 (s). The product thus obtained was used without further purification.

2-Vinyl-3*H*-quinazolin-4-one (11a). A mixture of **10a** (18.3 g, 81 mmol) in 5% NaOH (200 mL) and EtOH (100 mL) was heated to reflux for 5 min, whereupon the solution was allowed to cool for 15 min and then acidified with HOAc (20 mL). The resulting precipitate was collected and washed with water to give compound **11a** (14.0 g, 100%) as a white solid; mp 170–190°C (dec.); IR (KBr) 3185, 3060, 2928, 1682, 1578, 1468, 1342, 983, 944, 77 cm^{-1}; δ_H 5.81 (1H, dd, *J*=7.3, 4.6 Hz), 6.54–6.59 (2H, m), 7.47 (1H, ddd, *J*=8.1, 6.9, 1.2 Hz), 7.64 (1H, d, *J*=8.1 Hz), 7.78 (1H, ddd, *J*=7.8, 6.9, 1.5 Hz), 8.09 (1H, dd, *J*=7.8, 1.2 Hz), 12.27 (1H, s); δ_C 121.2 (s), 125.1 (t), 125.8 (d), 126.4 (d), 127.2 (d), 130.7 (d), 134.4 (d), 148.6 (s), 150.9 (s), 161.7 (s); MS (EI) *m*/*z* (rel. intensity) 173 (M^++1, 12%), 172 (M^+, 100), 146 (25), 119 (98), 90 (22), 54 (20), 44 (75); Anal. Calcd for $C_{10}H_8N_2O$: C, 69.76; H, 4.68; N, 16.27. Found: C, 69.64; H, 4.64; N, 16.16.

2-(2,3-Dichloropropionylamino)-benzamide (10b). Similarly prepared as compound **10a** using anthranilamide **9** and 2,3-dichloropropionyl chloride. Yield; 77%. Beige solid; mp 150–155°C (dec.); IR (KBr) 3369, 3174, 1678, 1642, 1584, 1519, 1396, 1296, 1122, 980, 871, 756, 644 cm^{-1}; δ_H (500 MHz) 4.08 (1H, dd, *J*=11.9, 5.0 Hz), 4.19 (1H, dd, *J*=11.9, 5.1 Hz), 5.16 (1H, dd, *J*=5.1, 5.0 Hz), 7.21 (1H, dd, *J*=7.8, 7.3 Hz), 7.54 (1H, ddd, *J*=8.3, 7.3, 1.0 Hz), 7.80 (1H, s), 7.84 (1H, dd, *J*=7.8, 1.0 Hz), 8.30 (1H, s), 8.44 (1H, d, *J*=8.3 Hz), 12.45 (1H, s); δ_C 46.3 (t), 59.2 (d), 120.3 (d), 120.6 (s), 123.5 (d), 128.6 (d), 132.3 (d), 138.4 (s), 164.6 (s), 170.4 (s). The product thus obtained was used without further purification.

2-(1-Chlorovinyl)-3*H*-quinazolin-4-one (11b). Similarly prepared as compound **11a** using the benzamide **10b**. Yield; 86%. Beige solid; mp 148–158°C (dec.); IR (KBr) 3438, 3179, 3049, 1670, 1581, 1448, 1341, 1154, 976, 960, 772 cm^{-1}; δ_H 6.06 (1H, d, *J*=2.3 Hz), 6.67 (1H, d, *J*=2.3 Hz), 7.45 (1H, ddd, *J*=7.9, 6.9, 1.1 Hz), 7.64 (1H, d, *J*=7.8 Hz), 7.74 (1H, ddd, *J*=8.1, 6.9, 1.4 Hz), 8.09 (1H, dd, *J*=8.1, 1.1 Hz); δ_C 121.1 (t), 121.5 (s), 125.9 (d), 126.3 (d), 127.3 (d), 133.6 (d), 135.0 (s), 148.8 (s), 151.9 (s), 164.8 (s); GC/MS (EI) *m*/*z* (rel. intensity) 208 (M^++2, 16%), 206 (M^+, 49), 171 (100). HRMS (EI) *m*/*z* Calcd for $C_{10}H_7N_2OCl$ 206.0247: found 206.0231.

2-(2,3-Dibromopropionylamino)-benzamide (10c). Similarly prepared as compound **10a** using anthranilamide **9** and 2,3-dibromopropionyl chloride. Yield; 88%. Light brown solid; mp 162–164°C (dec.); IR (KBr) 3382, 3188, 1668, 1582, 1521, 1398, 1300, 751, 641 cm^{-1}; δ_H 3.98 (2H, d, *J*=7.2 Hz), 5.01 (1H, t, *J*=7.2 Hz), 7.20 (1H, dd, *J*=7.6, 7.4 Hz), 7.54 (1H, dd, *J*=8.2, 7.4 Hz), 7.79–7.88 (2H, m), 8.35 (1H, s), 8.38 (1H, d, *J*=8.2 Hz), 12.24 (1H, s); δ_C 31.9 (t), 46.2 (d), 120.5 (s), 120.6 (d), 123.6 (d), 128.7 (d), 132.3 (d), 138.5 (s), 164.9 (s), 170.4 (s). The product thus obtained was used without further purification.

2-(1-Bromovinyl)-3*H*-quinazolin-4-one (11c). Similarly prepared as compound **11a** using the benzamide **10c**. Yield; 75%. Light yellow solid; mp 180–190°C (dec.); IR (KBr) 3180, 3046, 2919, 1666, 1604, 1469, 1342, 1153, 975, 914, 775 cm^{-1}; δ_H 6.45 (1H, d, *J*=3.5 Hz), 7.00 (1H, d, *J*=3.5 Hz), 7.55 (1H, dd, *J*=8.0, 7.1 Hz), 7.71 (1H, d, *J*=8.0 Hz), 7.84 (1H, ddd, *J*=8.1, 7.1, 1.2 Hz), 8.13 (1H,

d, J=8.1 Hz), 12.50 (1H, s); δ_C 121.2 (s), 123.0 (s), 125.9 (d), 127.3 (t), 127.6 (d), 127.8 (d), 134.8 (d), 147.8 (s), 149.2 (s), 161.7 (s); GC/MS (EI) *m*/*z* (rel. intensity) 252 (M^++2, 35%), 250 (36), 171 (100); Anal. Calcd for $C_{10}H_7N_2OBr$: C, 47.84; H, 2.81; N, 11.16. Found: C, 47.91; H, 2.88; N, 11.10.

2-Amino-*N*-methylbenzamide (12). Methylamine in water (40 mL, 60%) was added to isatoic anhydride (16.2 g, 0.1 mol), portionwise under stirring and controlling the CO_2 release. The reaction mixture was maintained at room temperature for 1 h. The solution was neutralised with 2 M HCl (~20 mL) and the resulting precipitate was collected and washed with water to give compound **12** (10.0 g, 67%) as a grey solid; mp 79–81°C (Lit.,[20b] mp 79–80°C); IR (KBr) 3424, 3306, 3068, 1619, 1587, 1538, 1309, 1159, 748 cm^{-1}; δ_H 2.71 (3H, d, J=4.5 Hz), 6.39 (2H, s), 6.48 (1H, ddd, J=8.0, 7.0, 1.0 Hz), 6.67 (1H, dd, J=8.3, 0.9 Hz), 7.10 (1H, ddd, J=8.3, 7.0, 1.3 Hz), 7.45 (1H, dd, J=8.0, 1.3 Hz), 8.17 (1H, d, J=3.6 Hz); δ_C 26.0 (q), 114.6 (d), 114.8 (s), 116.3 (d), 127.9 (d), 131.5 (d), 149.5 (s), 169.4 (s); MS (EI) *m*/*z* (rel. intensity) 151 (M^++1, 3%), 150 (M^+, 42), 120 (47), 119 (25), 92 (32), 65 (22), 44 (58), 40 (100).

2-(3-Chloropropionylamino)-*N*-methylbenzamide (13). Similarly prepared as compound **10a** using the benzamide **12** and 3-chloropropionyl chloride. Yield; 75%. White solid; mp 140–141°C; IR (KBr) 3311, 3096, 2975, 1684, 1625, 1599, 1516, 1444, 1289, 758, 694 cm^{-1}; δ_H 2.79 (3H, d, J=4.5 Hz), 2.84 (2H, t, J=6.2 Hz), 3.87 (2H, t, J=6.2 Hz), 7.14 (1H, dd, J=7.7, 7.4 Hz), 7.48 (1H, ddd, J=8.3, 7.4, 1.0 Hz), 7.71 (1H, d, J=7.8 Hz), 8.39 (1H, d, J=8.3 Hz), 8.69 (1H, s), 11.48 (1H, s); δ_C 26.2 (q), 40.2 (t), 40.5 (t), 120.5 (d), 120.9 (s), 122.8 (d), 127.9 (d), 131.8 (d), 138.6 (s), 167.8 (s), 168.6 (s); MS (EI) *m*/*z* (rel. intensity) 242 (M^++2, 8%), 240 (M^+, 23), 150 (100), 146 (77), 120 (95), 119 (56), 92 (37), 90 (24), 65 (35), 63 (38), 55 (34), 44 (50). The product thus obtained was used without further purification.

3-Methyl-2-vinyl-3*H*-quinazolin-4-one (14) and 3-methyl-2-(2-methoxyethyl)-3*H*-quinazolin-4-one (15a). A mixture of **13** (3.28 g, 14 mmol) in 0.5 M Na_2CO_3 aqueous solution with 10% MeOH (70 mL) was heated to reflux for 1.5 h. The reaction mixture was neutralised with 2 M HCl and extracted with ethyl acetate (50 mL×3). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford a solid residue, which was purified by chromatography on a silica gel column (1:1, ethyl acetate in hexane as the eluent).

14 (r_f=0.48), 580 mg (23%) as a white solid; mp 123–125°C; IR (KBr) 3074, 3035, 1670, 1560, 1470, 1416, 1336, 1300, 1132, 932, 773, 694 cm^{-1}; δ_H 3.56 (3H, s), 5.79 (1H, dd, J=10.7, 1.9 Hz), 6.44 (1H, dd, J=16.6, 1.9 Hz), 7.01 (1H, dd, J=16.6, 10.7 Hz), 7.46 (1H, dd, J=8.0, 7.0 Hz), 7.62 (1H, d, J=8.0 Hz), 7.76 (1H, dd, J=7.9, 7.0 Hz), 8.08 (1H, dd, J=7.9, 1.3 Hz); δ_C 30.4 (q), 120.0 (s), 126.2 (t), 126.2 (d), 126.5 (d), 127.1 (d), 129.8 (d), 134.2 (d), 146.9 (s), 152.3 (s), 161.1 (s); MS (EI) *m*/*z* (rel. intensity) 187 (M^++1, 8%), 186 (M^+, 68), 185 (100), 68 (33), 44 (29), 42 (23), 40 (36); Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.84; H, 5.45; N, 15.08.

15a (r_f=0.30), 250 mg (8.4%) as a white solid; mp 87–88°C; IR (KBr) 3069, 2903, 1686, 1593, 1474, 1336, 1111, 1058, 967, 767, 693, 640 cm^{-1}; δ_H 3.09 (2H, t, J=7.0 Hz), 3.30 (3H, s), 3.52 (3H, s), 3.81 (2H, t, J=7.0 Hz), 7.45 (1H, dd, J=7.9, 7.3 Hz), 7.55 (1H, d, J=7.9 Hz), 7.75 (1H, ddd, J=8.0, 7.3, 1.2 Hz), 8.07 (1H, d, J=8.0 Hz); δ_C 30.0 (q), 34.2 (t), 58.2 (q), 69.0 (t), 119.8 (s), 126.1 (d), 126.2 (d), 126.6 (d), 134.1 (d), 146.7 (s), 155.7 (s), 161.3 (s); Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.86; H, 6.38; N, 12.69.

3-Methyl-2-(2-ethoxyethyl)-3*H*-quinazolin-4-one (15b). A mixture of **13** (5.35 g, 22 mmol) in 5% NaOH (60 mL) and EtOH (30 mL) was heated to reflux for 5 min. The solution was allowed to cool and then acidified with HOAc (10 mL). The solvent was concentrated under reduced pressure to a volume of 20 mL and poured on water (15 mL). The resulting precipitate was collected and purified by chromatography on a silica gel column (1:1, ethyl acetate in hexane as the eluent) to give compound **15b** (2.06 g, 40%) as a beige solid; mp 80–81°C; IR (KBr) 2976, 2864, 1690, 1598, 1474, 1338, 1111, 778, 696 cm^{-1}; δ_H 1.10 (3H, t, J=7.0 Hz), 3.09 (2H, t, J=7.0 Hz), 3.49 (2H, q, J=7.0 Hz), 3.53 (3H, s), 3.84 (2H, t, J=7.0 Hz), 7.45 (1H, dd, J=8.0, 7.1 Hz), 7.55 (1H, d, J=8.0 Hz), 7.75 (1H, dd, J=8.1, 7.1 Hz), 8.08 (1H, d, J=8.1 Hz); δ_C 15.1 (q), 30.0 (q), 34.5 (t), 65.5 (t), 66.9 (t), 119.7 (s), 126.1 (d), 126.2 (d), 126.6 (d), 134.1 (d), 146.7 (s), 155.7 (s), 161.2 (s). HRMS (EI) *m*/*z* Calcd for $C_{13}H_{16}N_2O_2$ 232.1212: found 232.1203.

2-Acetylamino-2-[2-(4-oxo-3,4-dihydroquinazolin-2-yl)-ethyl]-malonic acid diethyl ester (16a). Sodium (1.19 g, 52 mmol) was dissolved in EtOH (120 mL) at room temperature under a nitrogen atmosphere. Diethyl acetamidomalonate (11.38 g, 52 mmol) and the vinylquinazolinone **11a** (8.81 g, 51 mmol) were added and the reaction mixture was heated to reflux for 3 h. Water (40 mL) and HOAc (4 mL) were added and the clear solution was allowed to crystallise over night. White crystals were collected and washed with EtOH to give compound **16a** (16.0 g, 80%); mp 173–174°C; IR (KBr) 3265, 3032, 2892, 1748, 1674, 1640, 1613, 1529, 1467, 1260, 1188, 777 cm^{-1}; δ_H 1.14 (6H, t, J=7.1 Hz), 1.91 (3H, s), 2.47–2.63 (4H, m), 4.05–4.15 (4H, m), 7.43 (1H, ddd, J=8.0, 6.8, 1.2 Hz), 7.58 (1H, d, J=8.0 Hz), 7.75 (1H, ddd, J=8.0, 6.8, 1.2 Hz), 8.06 (1H, dd, J=8.0, 1.2 Hz), 8.33 (1H, s), 12.25 (1H, s); δ_C 13.8 (q), 22.2 (q), 28.9 (t), 29.7 (t), 61.7 (t), 65.5 (s), 120.8 (s), 125.7 (d), 125.9 (d), 126.6 (d), 134.2 (d), 148.7(s), 156.4 (s), 161.8 (s), 167.4 (s), 169.3 (s); Anal. Calcd for $C_{19}H_{23}N_3O_6$: C, 58.60; H, 5.95; N, 10.79. Found: C, 58.70; H, 6.06; N, 10.72.

2-Acetylamino-2-[2-(3-methyl-4-oxo-3,4-dihydroquinazolin-2-yl)-ethyl]-malonic acid diethyl ester (17a). Diethyl acetamidomalonate (380 mg, 1.7 mmol) dissolved in dry THF (5 mL) was added to a suspension of NaH (42 mg, 1.8 mmol) in dry THF (5 mL) at room temperature under a nitrogen atmosphere. After 15 min the vinylquinazolinone **14** (293 mg, 1.6 mmol) in dry THF (5 mL) was added and the mixture allowed to stand at room temperature

over night. The mixture was quenched with HOAc (0.2 mL) and concentrated under reduced pressure to afford a yellow oil, which was purified by chromatography on silica gel column (4:1, ethyl acetate in hexane as the eluent) to give compound **17a** (260 mg, 41%) as a colourless oil; IR (neat) 3368, 2979, 1738, 1668, 1599, 1474, 1201, 1013, 775, 698 cm^{-1}; δ_H ($CDCl_3$) 1.24 (6H, t, *J*=7.1 Hz), 2.04 (3H, s), 2.78–2.90 (4H, m), 3.60 (3H, s), 4.16–4.28 (4H, m), 6.93 (1H, s), 7.44 (1H, dd, *J*=7.8, 6.9 Hz), 7.59 (1H, d, *J*=7.8 Hz), 7.69 (1H, ddd, *J*=8.2, 6.9, 1.5 Hz), 8.22 (1H, dd, *J*=8.2, 1.2 Hz); δ_C ($CDCl_3$) 13.9 (q), 23.0 (q), 30.0 (t), 30.2 (t), 30.3 (q), 62.7 (t), 65.6 (s), 120.1 (s), 126.4 (d), 126.6 (d), 126.8 (d), 134.0 (d), 146.9 (s), 155.6 (s), 162.3 (s), 167.7 (s), 169.4 (s); Anal. Calcd for $C_{20}H_{25}N_3O_6$: C, 59.54; H, 6.25; N, 10.42. Found: C, 59.46; H, 6.34; N, 10.32.

2-[2-(1*H*-Indol-3-yl)-ethyl]-3*H*-quinazolin-4-one (16b). A mixture of the vinylquinazolinone **11a** (1.02 g, 5.9 mmol) and indole (0.79 g, 6.7 mmol) in HOAc (6 mL) was heated to reflux for 4 h. A white precipitate was collected and washed with EtOH to give compound **16b** (1.62 g, 95%); mp 302–303°C; IR (KBr) 3176, 3043, 2918, 1682, 1613, 1469, 1335, 1231, 1072, 770, 732 cm^{-1}; δ_H 2.95–3.01 (2H, m), 3.15–3.22 (2H, m), 6.96 (1H, dd, *J*=7.9, 7.0 Hz), 7.06 (1H, dd, *J*=8.0, 7.0 Hz), 7.15 (1H, d, *J*=2.0 Hz), 7.33 (1H, d, *J*=8.0 Hz), 7.44 (1H, ddd, *J*=7.9, 7.0, 1.0 Hz), 7.60–7.65 (2H, m), 7.76 (1H, ddd, *J*=8.1, 7.0, 1.5 Hz), 8.09 (1H, dd, *J*=8.1, 1.1 Hz), 10.79 (1H, s), 12.28 (1H, s); δ_C 22.7 (t), 35.7 (t), 111.4 (d), 113.3 (s), 118.2 (d), 118.5 (d), 120.8 (s), 121.0 (d), 122.4 (d), 125.7 (d), 125.9 (d), 126.8 (d), 127.0 (s), 134.3 (d), 136.2 (s), 148.9 (s), 157.3 (s), 161.9 (s); MS (EI) *m*/*z* (rel. intensity) 290 (M^++1, 3%), 289 (M^+, 15), 130 (100), 44 (47), 40 (33); Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.22; N, 14.52. Found: C, 74.64; H, 5.31; N, 14.44.

2-[2-(1*H*-Indol-3-yl)-ethyl]-3-methyl-3*H*-quinazolin-4-one (17b). Similarly prepared as compound **16b** using the vinylquinazolinone **14**. Yield; 75%. White solid; mp 185–186°C; IR (KBr) 3262, 1665, 1588, 1470, 1340, 1232, 1008, 742 cm^{-1}; δ_H 3.20 (4H, s), 3.52 (3H, s), 6.97 (1H, dd, *J*=7.9, 7.1 Hz), 7.07 (1H, dd, *J* =7.9, 7.1 Hz), 7.24 (1H, d, *J*=2.2 Hz), 7.35 (1H, d, *J*=7.9 Hz), 7.47 (1H, ddd, *J*=7.9, 7.0, 1.0 Hz), 7.58 (1H, d, *J*=7.9 Hz), 7.66 (1H, d, *J*=7.9 Hz), 7.78 (1H, ddd, *J*=8.1, 7.0, 1.4 Hz), 8.11 (1H, dd, *J*=8.1, 1.0 Hz), 10.82 (1H, s); δ_C 21.8 (t), 29.9 (q), 35.3 (t), 111.4 (d), 113.5 (s), 118.3 (d), 118.3 (d), 119.8 (s), 120.9 (d), 122.6 (d), 126.2 (d), 126.2 (d), 126.8 (d), 127.1 (s), 134.1 (d), 136.3 (s), 147.0 (s), 157.5 (s), 161.4 (s); Anal. Calcd for $C_{19}H_{17}N_3O$: C, 75.23; H, 5.65; N, 13.85. Found: C, 75.19; H, 5.77; N, 13.81.

2-(2-Diethylaminoethyl)-3*H*-quinazolin-4-one (16c). Diethylamine (149 mg, 2 mmol) and HOAc (0.1 mmol) were added to a mixture of the vinylquinazolinone **11a** (175 mg, 1 mmol) in MeOH (10 mL). The solution was heated to reflux over night. After evaporation, the residue was recrystallised from hexane to give compound **16c** (123 mg, 49%) as white crystals; mp 115–117°C (Lit.,[23] mp 122°C); IR (KBr) 3172, 3034, 2974, 2799, 1682, 1618, 1466, 1320, 1206, 1067, 904, 776 cm^{-1}; δ_H 0.93 (6H, t, *J*=7.1 Hz), 2.48 (4H, q, *J*=7.1 Hz), 2.70 (2H, t, *J*=6.9 Hz), 2.83 (2H, t, *J*=6.9 Hz), 7.43 (1H, dd, *J*=8.0, 7.0 Hz), 7.57 (1H, d, *J*=8.0 Hz), 7.75 (1H, ddd, *J*=7.9, 7.0, 1.2 Hz), 8.06 (1H, dd, *J*=7.9, 1.3 Hz); δ_C 11.9 (q), 32.0 (t), 46.1 (t), 49.8 (t), 120.8 (s), 125.7 (d), 125.9 (d), 126.7 (d), 134.9 (d), 149.0 (s), 156.9 (s), 161.8 (s).

2-(2-Diethylaminoethyl)-3-methyl-3*H*-quinazolin-4-one (17c). Diethylamine (distilled from CaH_2, 149 mg, 2 mmol) and HOAc (0.1 mmol) were added to a mixture of the vinylquinazolinone **14** (190 mg, 1 mmol) in MeOH (10 mL). The solution was heated to reflux over night. After evaporation, the residue was dissolved in ice-water (~20 mL). The aqueous solution was made basic with 2 M NaOH and extracted with ethyl acetate (25 mL×2). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give compound **17c** (225 mg, 85%) as a yellow oil; IR (neat) 2970, 1674, 1599, 1474, 1421, 1338, 1011, 774, 697 cm^{-1}; δ_H ($CDCl_3$) 1.05 (6H, t, *J*=7.1 Hz), 2.60 (4H, q, *J*=7.1 Hz), 2.96 (4H, s), 3.62 (3H, s), 7.39 (1H, dd, *J*=7.9, 6.9 Hz), 7.59 (1H, d, *J*=7.9 Hz), 7.67 (1H, ddd, *J*=8.0, 6.9, 1.3 Hz), 8.21 (1H, dd, *J*=8.0, 0.8 Hz); δ_C ($CDCl_3$) 12.3 (q), 31.0 (q), 34.0 (t), 47.6 (t), 50.6 (t), 120.6 (s), 126.7 (d), 127.1 (d), 127.2 (d), 134.4 (d), 147.6 (s), 156.5 (s), 162.9 (s); Anal. Calcd for $C_{15}H_{21}N_3O$: C, 69.47; H, 8.16; N, 16.20. Found: C, 69.56; H, 8.04; N, 16.11.

2-(2-Piperidin-1-yl-ethyl)-3*H*-quinazolin-4-one (16d). Similarly prepared as compound **16c** using the vinylquinazolinone **11a** and piperidine. Yield; 84%. Compound **16d** was recrystallised from ethyl acetate to yield an analytically pure substance. White solid; mp 148–149°C (Lit.,[23] mp 148°C); IR (KBr) 3168, 3100, 2933, 2745, 1680, 1620, 1609, 1468, 1248, 894, 769 cm^{-1}; δ_H 1.31–1.40 (2H, m), 1.40–1.53 (4H, m), 2.35–2.45 (4H, m), 2.66–2.81 (4H, m), 7.43 (1H, dd, *J*=8.0, 7.2 Hz), 7.57 (1H, d, *J*=8.0 Hz), 7.75 (1H, ddd, *J*=8.0, 7.2, 1.0 Hz), 8.06 (1H, dd, *J*=8.0, 0.6 Hz), 12.24 (1H, s); δ_C 24.0 (t), 25.6 (t), 31.8 (t), 53.6 (t), 55.8 (t), 120.8 (s), 125.6 (d), 125.9 (d), 126.7 (d), 134.2 (d), 148.9 (s), 156.7 (s), 161.7 (s).

3-Methyl-2-(2-piperidin-1-yl-ethyl)-3*H*-quinazolin-4-one (17d). Similarly prepared as compound **17c** using the vinylquinazolinone **14** and piperidine (distilled from CaH_2). Yield; 100%. Light yellow oil; IR (neat) 2934, 2854, 1674, 1599, 1474, 1422, 1338, 1118, 1012, 773, 698 cm^{-1}; δ_H ($CDCl_3$) 1.40–1.53 (2H, m), 1.58–1.68 (4H, m), 2.47–2.63 (4H, m), 2.85–2.98 (2H, m), 2.98–3.10 (2H, m), 3.63 (3H, s), 7.41 (1H, dd, *J*=8.1, 6.9 Hz), 7.60 (1H, d, *J*=8.1 Hz), 7.69 (1H, dd, *J*=8.1, 6.9 Hz), 8.23 (1H, dd, *J*=8.1, 1.4 Hz); δ_C ($CDCl_3$) 24.3 (t), 25.9 (t), 30.7 (q), 33.0 (t), 54.7 (t), 56.1 (t), 120.4 (s), 126.6 (d), 126.9 (d), 127.0 (d), 134.2 (d), 147.3 (s), 155.9 (s), 162.6 (s); Anal. Calcd for $C_{16}H_{21}N_3O$: C, 70.82; H, 7.80; N, 15.48. Found: C, 70.67; H, 7.89; N, 15.32.

2-(2-Azidoethyl)-3*H*-quinazolin-4-one (16e). Sodium azide (0.34 g, 5.2 mmol) dissolved in water (5 mL) was added to a stirred solution of the vinylquinazolinone **11a** (0.58 g, 3.4 mmol) in THF (25 mL). After 1 h at room temperature the solution was heated to 60°C over night. The solution was acidified with 10% HCl and then diluted with water (50 mL). The aqueous phase was extracted with ethyl acetate (2×50 mL). The combined extracts were dried

(Na_2SO_4) and concentrated under reduced pressure to afford a solid residue, which was purified by chromatography on silica gel column (1:1, ethyl acetate in hexane as the eluent, r_f=0.38) to give compound **16e** (0.35 g, 48%) as a white solid; mp 152–153°C; IR (KBr) 3170, 3033, 2972, 2914, 2087, 1677, 1614, 1469, 1253, 883, 780, 690 cm^{-1}; δ_H 2.90 (2H, t, *J*=6.6 Hz), 3.77 (2H, t, *J*=6.6 Hz), 7.47 (1H, dd, *J*=7.9, 7.1 Hz), 7.60 (1H, d, *J*=7.9 Hz), 7.78 (1H, ddd, *J*=8.1, 7.1, 1.4 Hz), 8.08 (1H, dd, *J*=8.1, 1.3 Hz), 12.27 (1H, s); δ_C 33.9 (t), 47.5 (t), 120.9 (s), 125.7 (d), 126.3 (d), 126.8 (d), 134.4 (d), 148.5 (s), 154.6 (s), 161.6 (s); MS (EI) *m*/*z* (rel. intensity) 216 (M^++1, 1%), 215 (M^+, 8) 187 (73), 186 (38), 160 (82), 132 (33), 120 (28), 119 (100), 92 (31), 90 (28), 77 (24), 64 (22), 63 (23), 44 (59), 43 (72), 41 (30), 40 (65); Anal. Calcd for $C_{10}H_9N_5O$: C, 55.81; H, 4.21; N 32.54. Found: C, 56.02; H, 4.28; N, 32.64.

3-Methyl-2-(2-azidoethyl)-3*H*-quinazolin-4-one (17e). Similarly prepared as compound **16e** using the vinylquinazolinone **14** and sodium azide to give compound **17e**, which was purified by chromatography on silica gel column (1:1, ethyl acetate in hexane as the eluent, r_f=0.52). Yield; 50%. White solid; mp 65–67°C; IR (KBr) 2936, 2101, 1666, 1603, 1477, 1295, 1132, 956, 779, 697 cm^{-1}; δ_H 3.16 (2H, t, *J*=6.3 Hz), 3.52 (3H, s), 3.82 (2H, t, *J*=6.3 Hz), 7.48 (1H, ddd, *J*=8.0, 7.0, 1.0 Hz), 7.59 (1H, d, *J*=8.0 Hz), 7.79 (1H, ddd, *J*=8.0, 7.0, 1.5 Hz), 8.11 (1H, dd, *J*=8.0, 1.1 Hz); δ_C 29.6 (q), 33.7 (t), 47.0 (t), 119.8 (s), 126.2 (d), 126.4 (d), 126.7 (d), 134.2 (d), 146.5 (s), 155.2 (s), 161.2 (s); MS (EI) *m*/*z* (rel. intensity) 230 (M^++1, <0.1%), 229 (M^+, 2) 185 (39), 174 (35), 146 (23), 77 (22), 69 (29), 57 (27), 55 (32), 45 (22), 44 (82), 43 (81), 42 (25), 41 (43), 40 (100). In contrast to the azide **16e** the azide **17e** was to unstable to allow elemental analysis.

3-(4-Oxo-3,4-dihydroquinazolin-2-yl)-propionitrile (16f). The vinylquinazolinone **11a** (0.52 g, 3.0 mmol) was added to a solution of sodium cyanide (0.30 g, 6.1 mmol) in EtOH (20 mL) and water (5 mL). The reaction mixture was heated to reflux over night and then quenched with 2 M HCl. After evaporation, the solid residue was taken up in saturated $NaHCO_3$/ethyl acetate (1:1). The aqueous phase was extracted with ethyl acetate (25 mL×4), the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to give compound **16f** (0.46 g, 76%). Compound **16f** was recrystallised from ethanol to yield an analytically pure substance. White solid; mp 225°C (dec.) (Lit.,[21] mp 243.5°C); IR (KBr) 3171, 3042, 2982, 2246, 1686, 1626, 1605, 1470, 1418, 1339, 1252, 905, 773, 688, 638 cm^{-1}; δ_H 2.94–2.99 (4H, m), 7.48 (1H, dd, *J*=8.2, 7.0 Hz), 7.62 (1H, d, *J*=8.2 Hz), 7.79 (1H, ddd, *J*=8.1, 7.0, 1.5 Hz), 8.09 (1H, dd, *J*=8.1, 1.2 Hz), 12.31 (1H, s); δ_C 13.4 (t), 29.5 (t), 120.1 (s), 121.0 (s), 125.8 (d), 126.5 (d), 126.9 (d), 134.5 (d), 148.4 (s), 154.3 (s), 161.5 (s).

3-(3-Methyl-4-oxo-3,4-dihydroquinazolin-2-yl)-propionitrile (17f). A mixture of **13** (0.72 g, 3.0 mmol) in 0.5 M Na_2CO_3 aqueous solution (25 mL) was heated to reflux. When the mixture became clear sodium cyanide (0.24 g, 4.9 mmol) and methanol (3 mL) were added, whereupon the solution was refluxed for 1.5 h and allowed to cool to room temperature before quenching with 2 M HCl. The resulting precipitate was collected after 48 h and washed with water. The solid residue was purified by chromatography on a silica gel column (1:1, ethyl acetate in hexane as eluent, r_f=0.20) to give compound **17f** (0.15 g, 23%) as a white solid; mp 197–199°C; IR (KBr) 2946, 2249, 1671, 1609, 1472, 1422, 1327, 1137, 779, 698 cm^{-1}; δ_H 2.95 (2H, t, *J*=6.7 Hz), 3.25 (2H, t, *J*=6.7 Hz), 3.52 (3H, s), 7.49 (1H, ddd, *J*=8.0, 6.9, 1.0 Hz), 7.61 (1H, d, *J*=8.0 Hz), 7.79 (1H, ddd, *J*=8.1, 6.9, 1.5 Hz), 8.11 (1H, d, *J*=8.1, 1.1 Hz); δ_C 13.3 (t), 29.3 (t), 29.4 (q), 119.8 (s), 120.5 (s), 126.2 (d), 126.6 (d), 126.8 (d), 134.3 (d), 146.4 (s), 154.8 (s), 161.1 (s); Anal. Calcd for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.78; H, 5.21; N, 19.75.

***N*-(3-carboxy-acryloyl)-anthranilamide (18).** Maleic anhydride (7.94 g, 81 mmol) was added to a mixture of anthranilamide **9** (10.01 g, 74 mmol) in dichloromethane (130 mL) at 40°C and within 1–2 min a new yellow precipitate was formed. Stirring was continued for 0.5 h and the resulting precipitate was collected to give **18** (16.19 g, 94%) as a yellowish solid; mp 180–182°C; IR (KBr) 3443, 3355, 3229, 1717, 1671, 1584, 1540, 1402, 1252, 972, 840, 748 cm^{-1}; δ_H 6.26 (1H, d, *J* =12.0 Hz), 6.55 (1H, d, *J*=12.0 Hz),7.16 (1H, ddd, *J*=7.9, 7.2, 0.8 Hz), 7.51 (1H, ddd, *J*=8.3, 7.2, 1.2 Hz), 7.74 (1H, s), 7.82 (1H, dd, *J*=7.9, 1.2 Hz), 8.28 (1H, s), 8.45 (1H, d, *J*=8.3 Hz), 11.93 (1H, s), 12.97 (1H, s); δ_C 120.1 (s), 120.5 (d), 123.0 (d), 128.6 (d), 129.1 (d), 132.2 (d), 133.5 (d), 139.0 (s), 163.4 (s), 166.5 (s), 170.5 (s). The product thus obtained was used without further purification.

3-(4-Oxo-3,4-dihydroquinazolin-2-yl)-acrylic acid (19). A mixture of **18** (2.34 g, 10 mmol) and NaOAc (0.51 g, 6.2 mmol) in acetic anhydride (15 mL) was stirred at room temperature over night and then poured into water (75 mL). Stirring was continued for 3–4 h and the resulting precipitate was collected to give compound **19** (0.84 g, 39%) as a yellow solid; mp 256–258°C (dec.) (Lit.,[25] mp 262–263°C); IR (KBr) 3436, 3202, 1692, 1651, 1589, 1470, 1339, 1183, 981, 764, 623 cm^{-1}; δ_H 7.05 (1H, d, *J*=15.8 Hz), 7.26 (1H, d, *J*=15.8 Hz), 7.53 (1H, dd, *J*=8.0, 7.1 Hz), 7.69 (1H, d, *J*=8.0 Hz), 7.82 (1H, dd, *J*=7.9, 7.1 Hz), 8.11 (1H, d, *J*=7.9 Hz), 12.52 (1H, s); δ_C 121.7 (s), 125.9 (d), 127.3 (d), 127.7 (d), 129.0 (d), 134.6 (d), 135.9 (d), 148.3 (s), 149.5 (s), 161.5 (s), 166.4 (s).

3-(4-Oxo-3,4-dihydroquinazolin-2-yl)-acrylonitrile (20). The halosubstituted vinylquinazolinone **11c** (0.50 g, 2.0 mmol) was added to a solution of sodium cyanide (0.20 g, 4.1 mmol) in EtOH (20 mL) and water (5 mL). The reaction mixture was heated to reflux over night and then quenched with 2 M HCl. The resulting precipitate was collected to give the conjugated nitrile **20** (0.26 g, 66%) as a brown solid; mp 240°C (dec.); IR (KBr) 3424, 3178, 3062, 2925, 2224, 1666, 1469, 1277, 1144, 964, 770 cm^{-1}; δ_H 6.95 (1H, d, *J*=16.5 Hz), 7.31 (1H, d, *J*=16.5 Hz), 7.58 (1H, dd, *J*=7.9, 7.0 Hz), 7.71 (1H, d, *J*=7.9 Hz), 7.86 (1H, ddd, *J*=8.0, 7.0, 1.5 Hz), 8.14 (1H, dd, *J*=8.0, 1.3 Hz), 12.57 (1H, s); δ_C 106.7 (d), 117.2 (s), 121.8 (s), 126.0 (d), 127.7 (d), 127.8 (d), 134.8 (d), 142.7 (d), 147.9 (s), 148.3 (s), 161.2 (s); Anal. Calcd for $C_{11}H_7N_3O$: C, 67.00; H, 3.58; N, 21.31. Found: C, 66.65; H, 4.25; N, 20.88.

2-(4-Oxo-3,4-dihydroquinazolin-2-yl)-cyclopropane-1,1-dicarboxylic acid diethyl ester (21). Diethylmalonate (390 mg, 2.4 mmol) was added to a suspension of NaH (60 mg, 2.5 mmol) in dry THF (13 mL) at room temperature under a nitrogen atmosphere. After 15 min was the halo-substituted vinylquinazolinone **11b** (420 mg, 2.0 mmol) in dry THF (7 mL) added and the mixture was heated to reflux for 3 h. The mixture was quenched with diluted HOAc and concentrated under reduced pressure to afford compound **21** (400 mg, 60%) as a light brown solid; IR (KBr) 3424, 2979, 1737, 1674, 1610, 1471, 1208, 769, 630 cm^{-1}; δ_H 0.80 (3H, t, *J*=7.1 Hz), 1.20 (3H, t, *J*=7.1 Hz), 1.76 (1H, dd, *J*=8.7, 4.6 Hz), 2.25 (1H, dd, *J*=7.0, 4.6 Hz), 2.99 (1H, dd, *J*=8.7, 7.0 Hz), 3.87 (2H, q, *J*=7.1 Hz), 4.17 (2H, q, *J*=7.1 Hz), 7.36–7.52 (2H, m), 7.74 (1H, ddd, *J*=8.1, 6.9, 1.4 Hz), 8.06 (1H, dd, *J*=8.1, 1.4 Hz), 12.60 (1H,s); δ_C 13.5 (q), 13.9 (q), 18.1 (t), 27.9 (d), 37.9 (s), 60.8 (t), 61.8 (t), 120.9 (s), 125.8 (d), 126.2 (d), 126.5 (d), 134.4 (d), 148.0 (s), 152.7 (s), 161.6 (s), 165.2 (s), 168.3 (s); GC/MS (EI) *m/z* (rel. intensity) 331 (M^++1, 1%), 330 (M^+, 8), 285 (23), 284 (100), 239 (27), 210 (20), 184 (84); Anal. Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.64; H, 5.36; N, 8.29.

3-Acetylamino-2-oxo-5-(4-oxo-3,4-dihydroquinazolin-2-yl)-tetrahydro-furan-3-carboxylic acid ethyl ester (22). Sodium (60 mg, 2.6 mmol) was dissolved in EtOH (20 mL) at room temperature under a nitrogen atmosphere. Diethyl acetamidomalonate (590 mg, 2.7 mmol) and the halosubstituted vinylquinazolinone **11c** (580 mg, 2.3 mmol) were added and the reaction mixture was heated to reflux for 3 h. Water (3 mL) and HOAc (0.3 mL) were added and the reaction mixture was concentrated under reduced pressure to afford a beige oil, which was purified by chromatography on a silica gel column (9:1, ethyl acetate in hexane as the eluent).

first diastereoismer (r_f=0.46, 100% ethyl acetate), 320 mg (39%) as a white solid; mp 197–199°C; IR (KBr) 3394, 3086, 2974, 1795, 1736, 1679, 1610, 1371, 1296, 1216, 1168, 1071, 778 cm^{-1}; δ_H 1.27 (3H, t, *J*=7.1 Hz), 1.98 (3H, s), 2.98 (1H, dd, *J*=13.6, 9.4 Hz), 3.24 (1H, dd, *J*=13.6, 7.3 Hz), 4.27 (2H, q, *J*=7.1 Hz), 5.52 (1H, dd, *J*=9.4, 7.3 Hz), 7.57 (1H, dd, *J*=7.8, 7.0 Hz), 7.70 (1H, d, *J*=7.8 Hz), 7.85 (1H, ddd, *J*=8.1, 7.0, 1.5 Hz), 8.14 (1H, dd, *J*=8.1, 1.2 Hz), 8.92 (1H, s), 12.25 (1H, s); δ_C 13.7 (q), 21.9 (q), 36.2 (t), 62.8 (t), 63.8 (s), 76.0 (d), 121.7 (s), 125.9 (d), 127.5 (d), 127.5 (d), 134.7 (d), 147.7 (s), 152.2 (s), 161.2 (s), 166.6 (s), 169.8 (s), 170.3 (s); MS (EI) *m/z* (rel. intensity) 360 (M^++1, 63%), 359 (M^+, 84), 300 (41), 286 (50), 256 (52), 200 (28), 184 (39), 183 (46), 173 (100), 147 (49), 43 (71); Anal. Calcd for $C_{17}H_{17}N_3O_6$: C, 56.82; H, 4.77; N, 11.69. Found: C, 56.74; H, 4.83; N, 11.65.

second diastereoisomer (r_f=0.31, 100% ethyl acetate), 120 mg (14%) as a white solid; mp 216–219°C; IR (KBr) 3366, 2980, 1780, 1749, 1681, 1620, 1469, 1206, 1058, 772 cm^{-1}; δ_H 0.98 (3H, t, *J*=7.1 Hz), 1.98 (3H, s), 2.83 (1H, dd, *J*=13.8, 9.0 Hz), 3.39 (1H, dd, *J*=13.8, 5.1 Hz), 4.00–4.12 (2H, m), 5.67 (1H, dd, *J*=9.0, 5.1 Hz), 7.55 (1H, ddd, *J*=7.9, 6.9, 1.1 Hz), 7.67 (1H, d, *J*=7.9 Hz), 7.83 (1H, ddd, *J*=8.1, 6.9, 1.5 Hz), 8.13 (1H, dd, *J*=8.1, 1.2 Hz), 8.89 (1H, s), 12.51 (1H, s); δ_C 13.4 (q), 21.9 (q), 35.7 (t), 62.4 (t), 62.8 (s), 74.8 (d), 121.5 (s), 125.9 (d), 127.1 (d), 127.3 (d), 134.6 (d), 147.8 (s), 152.9 (s), 161.4 (s), 167.0 (s), 170.1 (s), 170.3 (s); Anal. Calcd for $C_{17}H_{17}N_3O_6$: C, 56.82; H, 4.77; N, 11.69. Found: C, 56.75; H, 4.86; N, 11.55.

2-Methyl-5-(4-oxo-3,4-dihydroquinazolin-2-yl)-4,5-dihydro-furan-3-carboxylic acid ethyl ester (23). Similarly prepared as compound **22** using the halosubstituted vinylquinazolinone **11b** (420 mg, 2.0 mmol) and ethyl acetoacetate (130 mg, 2.3 mmol). The precipitate was purified by chromatography on a silica gel column (1:1, ethyl acetate in hexane as the eluent, r_f=0.39) to yield compound **23** (30 mg, 5%) as a white solid; mp 152–154°C; IR (KBr) 3449, 3181, 2925, 1680, 1648, 1607, 1468, 1226, 1080, 772 cm^{-1}; δ_H 1.21 (3H, t, *J*=7.1 Hz), 2.20 (3H, s), 3.10–3.37 (2H, m), 4.11 (2H, q, *J*=7.1 Hz), 5.53 (1H, dd, *J*=8.1, 10.9 Hz), 7.53 (1H, ddd, *J*=7.9, 7.0, 1.0 Hz), 7.68 (1H, d, *J*=7.9 Hz), 7.82 (1H, ddd, *J*=8.1, 7.0, 1.5 Hz), 8.12 (1H, dd, *J*=8.1, 1.2 Hz), 12.46 (1H, s); δ_C 13.7 (q), 14.3 (q), 33.3 (t), 59.2 (t), 79.4 (d), 101.6 (s), 121. 5 (s), 125.8 (d), 127.0 (d), 127.3 (d), 134.5 (d), 148.0 (s), 154.2 (s), 161.6 (s), 164.7 (s), 166.6 (s); GC/MS (EI) *m/z* (rel. intensity) 301 (M^++1, 4%), 300 (M^+, 22), 255 (44), 239 (100), 211 (68), 185 (24); Anal. Calcd for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 64.11; H, 5.41; N, 9.26.

References

1. Johne, S. *Prog. Chem. Org. Nat. Prod.* **1984**, *46*, 159–229.
2. Eguchi, S.; Suzuki, T.; Okawa, T.; Matsushita, Y.; Yashima, E.; Okamoto, Y. *J. Org. Chem.* **1996**, *61*, 7316–7319.
3. (a) Bergman, J.; Brynolf, A. *Tetrahedron* **1990**, *46*, 1295–1310. (b) Bergman, J. *J. Chem. Res. (S)* **1997**, 224.
4. Johne, S. In *Supplements to the 2nd Edition of Rodd's Chemistry of Carbon Compounds*, Ansell, M. F. Ed.; Elsevier: Amsterdam, 1995; Vol. IV I/J, pp 223–240.
5. Kacker, I. K.; Zaheer, S. H. *J. Indian Chem. Soc.* **1951**, *28*, 344–346.
6. (a) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H.; Kim, H-S.; Wataya, Y. *J. Org. Chem.* **1999**, *64*, 6833–6841. (b) Takaya, Y.; Tasaka, H.; Chiba, T.; Uwai, K.; Tanitsu, M.-A.; Kim, H.-S.; Wataya, Y.; Miura, M.; Takeshita, M.; Oshima, Y. *J. Med. Chem.* **1999**, *42*, 3163–3166. (c) Uesato, S.; Kuroda, Y.; Kato, M.; Fujiwara, Y.; Hase, Y.; Fujita, T. *Chem. Pharm. Bull.* **1998**, *46*, 1–5. (d) Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H. *Tetrahedron Lett.* **1999**, *40*, 2175–2178.
7. Armarego, W. L. F. *Adv. Heterocycl. Chem.* **1979**, *24*, 1–62.
8. Mayer, J. P.; Lewis, G. S.; Curtis, M. J.; Zhang, J. *Tetrahedron Lett.* **1997**, *38*, 8445–8448.
9. Jiang, J. B.; Hessan, D. P.; Dusak, B. A.; Dexter, D. L.; Kang, G. J.; Hamel, E. *J. Med. Chem.* **1990**, *33*, 1721–1728.
10. (a) von Niementowski, St. *J. Prakt. Chem.* **1895**, *51*, 564–572. (b) Bogert, M. T.; Gotthelf, A. H. *J. Am. Chem. Soc.* **1900**, *22*, 522–535. (c) Meyer, J. F.; Wagner, E. C. *J. Org. Chem.* **1943**, *8*, 239–252.
11. Bandgar, B. P. *Synth. Commun.* **1997**, *27*, 2065–2068.
12. Filachione, E. M.; Lengel, J. H.; Fisher, C. H. *J. Am. Chem. Soc.* **1944**, *66*, 494–496.
13. Estrada, E.; Rieker, A. *Z. Naturforsch* **1994**, *49b*, 1566–1568.
14. Larksarp, C.; Alper, H. *J. Org. Chem.* **2000**, *65*, 2773–2777 (references cited therein).

15. Bogert, M. T.; Beal, G. D.; Amend, C. G. *J. Am. Chem. Soc.* **1910**, *32*, 1654–1664.
16. Foster, B. A.; Coffey, H. A.; Morin, M. J.; Rastinejad, F. *Science* **1999**, *286*, 2507–2510.
17. Fuks, R. *Eur. Polym. J.* **1973**, *9*, 835–845.
18. (a) Dempcy, R. O.; Skibo, E. B. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1427–1434. (b) Dempcy, R. O.; Skibo, E. B. *Bioorg. Med. Chem.* **1993**, *1*, 39–43.
19. German Pat. 1,170,144 (to BASF), 1964.
20. (a) Staiger, P. R.; Wagner, E. C. *J. Org. Chem.* **1953**, *18*, 1427–1439. (b) Weddige, A.; Körner, M. *J. Prakt. Chem.* **1887**, *36*, 141–165.
21. (a) Reich, H. E.; Levine, R. *J. Am. Chem. Soc.* **1955**, *77*, 4913–4915. (b) Magnus, G.; Levine, R. *J. Am. Chem. Soc.* **1956**, *78*, 4127–4130.
22. (a) Överås, A. T.; Bakkestuen, A. K.; Gundersen, L.-L. *Acta Chem. Scand.* **1997**, *51*, 1116–1124. (b) Liu, F.; Dalhus, B.; Gundersen, L.-L.; Rise, F. *Acta Chem. Scand.* **1999**, *53*, 269–279.
23. Ahmed, A.; Narang, K. S.; Nath Ray, J. *J. Indian Chem. Soc.* **1938**, *15*, 152–159.
24. Yanai, M.; Kinoshita, T.; Takeda, S. *Chem. Pharm. Bull.* **1968**, *16*, 972–976.
25. Kulkarni, P. V. *J. Indian Chem. Soc.* **1942**, *19*, 180–182.
26. (a) Hjelt, E. *Chem. Ber.* **1884**, *17*, 2833–2835. (b) Takei, H.; Fukuda, Y.; Sugaya, K.; Taguchi, T.; Kawara, T. *Chem. Lett.* **1980**, 1307–1310.
27. Farina, F.; Maestro, M. C.; Martin, M. V.; Soria, M. L. *Tetrahedron* **1987**, *43*, 4007–4014.