Tetrahedron 64 (2008) 5139–5146

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

New strategies for the synthesis of heteroannulated 2-pyridinones, substituted 2-quinolinones and coumarins from dehydroamino acid derivatives

Maria João R.P. Queiroz *, Ana S. Abreu, Ricardo C. Calhelha, M. Solange D. Carvalho, Paula M.T. Ferreira *

Centro de Química, Universidade do Minho, Campus de Gualtar, 4710-057 Braga, Portugal

ARTICLE INFO

Article history:
Received 31 January 2008
Received in revised form 13 March 2008
Accepted 17 March 2008
Available online 21 March 2008

Keywords:
Dehydroamino acids
Suzuki coupling
Intramolecular cyclizations
Heteroannulated 2-pyridinones
2-Quinolinones
Coumarins

ABSTRACT

Several heteroannulated pyridinones were prepared from the methyl esters of *N*-Boc-β,β-diheteroaryldehydroalanines by treatment with acetic acid. The latter were obtained by a bis-Suzuki coupling of a β,β-dibromodehydroalanine with heteroarylboronate compounds. The products were obtained in good yields and the cyclization reaction involves the nucleophilic attack of one of the heteroaromatic rings on the carbonyl of the Boc group. The scope of this reaction was extended to the *Z*-isomer of *N*-Boc-β-heteroaryldehydrophenylalanines to give 4-phenylpyridinones. A tandem Suzuki coupling–cyclization protocol was developed for the synthesis of 2-quinolinones and coumarins. Thus, β-brominated dehydroamino acids were reacted with 2-(pinacolboronate)aniline or phenol in a one-pot Suzuki coupling followed by lactamization or lactonization to give the corresponding 3-amino-2-quinolinones or 3-aminocoumarins in good to high yields. This type of strategy was also applied to the synthesis of 2-quinolinones and coumarins linked in position-3 to amino acids, using as starting materials brominated dehydropeptides.

1. Introduction

Ring fused 2-pyridinones involving the nitrogen atom have been used as lead compounds for the preparation of several type of drugs such as selective anticancer agents,[1] antiviral agents[2] or inhibitors of Aβ-peptide aggregation, which play an important role in amyloid formation in Alzheimer's disease.[3]

Several thieno[2,3-*b*]pyridine-6(7*H*)-ones were prepared by Berger et al. from substituted methyl 2-aminothiophene-3-carboxylates and phenylacetyl chloride to give amides that subsequently cyclized using potassium hexamethyldisilazide in THF at low temperatures. These thienopyridinones were designed by a bioisosteric approach with 3-phenyl-4-hydroxy-quinolin-2-(1*H*)-one by replacement of the benzene nucleus by thiophene and are cytoprotectants and inhibitors of the glycine binding to the *N*-Methyl-D-aspartate (NMDA) receptor.[4]

A series of 2-quinolinones have been synthesized from substituted anilines and diethylmalonate in diphenylether at 250 °C and, were evaluated as non-nucleoside HIV-1 inhibitors of reverse transcriptase, some of them showing activity against drug-resistant mutants.[5]

Heck et al.[6] prepared 2-quinolinones from 2-iodoanilines and dimethyl maleate using $Pd(OAc)_2$ and NEt_3. Recently, Cho and Kim used a similar approach to obtain the same type of quinolinones from 2-iodoanilines and dialkyl itaconates.[7]

The coumarin moiety is present in several natural products exhibiting a broad range of biological activities, including anticancer[8] and anti-HIV.[9] Coumarins have also been used as luminescent probes,[10] photostable laser dyes[11] and triplet sensitizers.[12]

Larock and Kadnikov reported the synthesis of coumarins[13] and 2-quinolinones[14] by palladium-catalyzed carbonylative annulation of internal alkynes with *o*-iodophenols or *o*-iodoanilines.

More recently, Cachi et al. prepared 4-aryl-2-quinolinones[15] and 4-arylcoumarins[16] from *o*-bromocinnamamide or alkyl 3-(*o*-hydroxyaryl)acrylates and aryl iodides and bromides using $Pd(OAc)_2$ and a molten tetra(*n*-butyl)ammonium acetate/tetra(*n*-butyl)ammonium bromide. These domino processes involve in the first case sequential catalytic cycles of a Heck reaction followed by an intramolecular Buchwald–Hartwig C–N bond forming reaction and in the second case a Heck reaction and a nucleophilic attack of the OH group in the carbonyl of the ester.

In the course of our long experience in dehydroamino acid chemistry and metal-mediated reactions, we have synthesized

* Corresponding authors.
E-mail addresses: mjrpq@quimica.uminho.pt (M.J.R.P. Queiroz), pmf@quimica.uminho.pt (P.M.T. Ferreira).

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.03.057

a large variety of new heterocyclic compounds. Thus, by reacting β-bromo or β,β-dibromodehydroamino acid derivatives with aryl or heteroarylboronic acids or boronates under Suzuki cross-coupling conditions we were able to prepare β,β-disubstituted dehydroamino acids, which were successfully cyclized to thienoindoles, benzo[*b*]thienopyrroles and indoles using an unprecedent metal-assisted C–N intramolecular cyclization.[17–19]

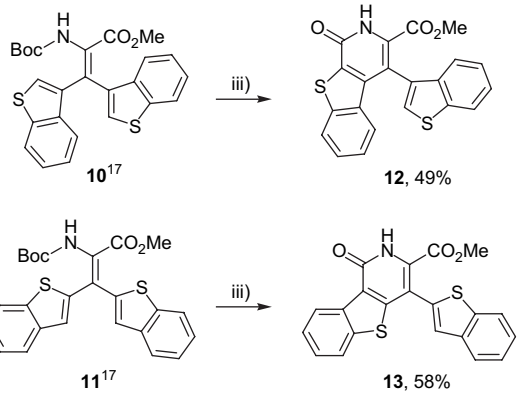
Here, we report an important method for the synthesis of new heteroannulated 2-pyridinones and substituted 2-quinolinones and coumarins using Suzuki and Suzuki–Miyaura cross-couplings[20] and intramolecular cyclizations, taking advantage of the reactivity of the amino acid protecting groups. Although several palladium-catalyzed reactions have been used in the synthesis of heterocycles,[21] to our knowledge this is the first time this strategy was successfully applied to dehydroamino acids and dehydropeptides.

2. Results and discussion

Several new β,β-bis-heteroaryldehydroalanines were prepared by a bis-Suzuki cross-coupling of β,β-dibromodehydroalanine **1**, earlier prepared by us,[22] with heteroarylboronated compounds, in good to excellent yields (Scheme 1). The conditions used for the coupling of potassium 3-trifluoroboratethiophene were those described by Molander and Fumagalli in a palladium-catalyzed Suzuki cross-coupling of potassium aryl and heteroaryltrifluoroborates with alkenyl bromides.[23] The other Suzuki couplings were carried out using conditions earlier developed by us.[19]

The coupling products **2**–**5** were treated with acetic acid in DMF at 160 °C (Scheme 1). Compounds **2** and **3** afforded the heteroannulated 2-pyridinones **6** and **7** in good yields, by nucleophilic attack of position-2 of the thiophene or furan rings on the carbonyl of the Boc group with loss of *t*-BuOH. This constitutes, as far as our knowledge, a new method for the synthesis of this type of compounds. When compounds **4** and **5** were subjected to the same conditions, no lactamization occurred and the only products obtained were the very unstable free amines **8** and **9** resulting from cleavage of the Boc group (Scheme 1). This can be due to the fact that position-3 is not so nucleophilic as position-2 in furan and thiophene rings.

Having these results in hand, we decided to apply the same methodology to our previously synthesized β,β-bis(benzo[*b*]thienyl)dehydroalanines **10** and **11**.[17] The corresponding heteroannulated 2-pyridinones **12** and **13** were obtained in good yields (Scheme 2) due to the fact that in the benzo[*b*]thiophene ring position-2 and 3 reacted almost in the same way.



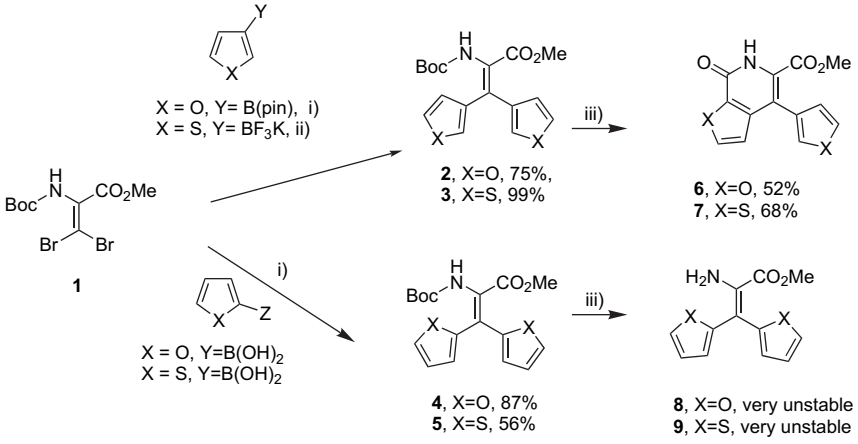
Scheme 2. (iii) 10 equiv CH_3COOH, DMF, 160 °C.

The same approach was applied to the synthesis of heteroannulated pyridinones **16**, **18** and **20** from β-thienyl or benzo[*b*]-thienyldehydrophenylalanines **15**, **17** and **19** increasing the scope of this reaction (Scheme 3). However, the product yields were slightly lower when compared with those obtained for compounds **7**, **12** and **13**.

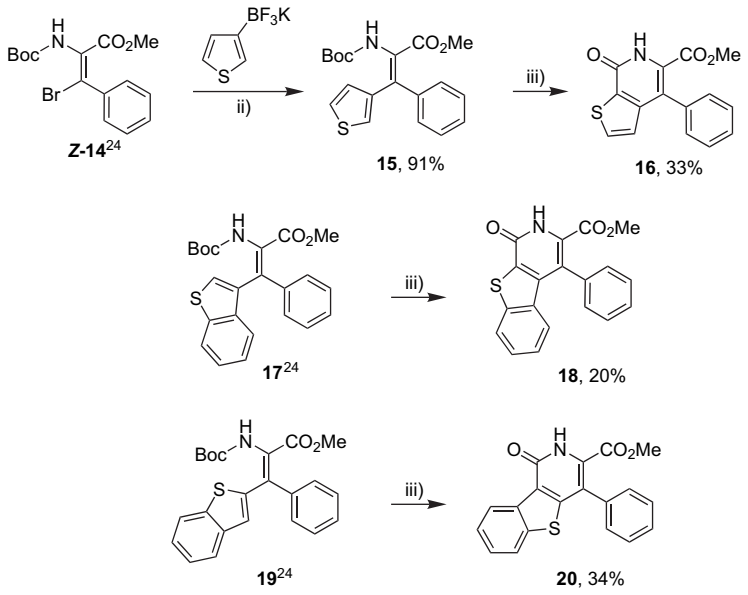
The β-brominated dehydroamino acids were also used as precursors of 2-quinolinones. Thus, by reacting the former with 2-(pinacolboronate)aniline, we were able to obtain compounds **21**, **22**, **24** and **25** in a tandem one-pot Suzuki cross-coupling and lactamization, which occur by nucleophilic attack of the NH_2 on the carbonyl of ester group with loss of methanol (Table 1).

The β,β-dibromodehydroalanine **1** gave quinolinone **21** as major product, after a bis-Suzuki coupling and lactamization and quinolinone **22** as minor product, possibly resulting from the reduction of one of the vinyl-Pd-Br species (Entry 1, Table 1).

Compound ***E*-23** gave with identical conditions but using 1.3 equiv of 2-(pinacolboronate)aniline the corresponding quinolinone **24** in an excellent yield (entry 2, Table 1). Using the conditions already applied by us in Suzuki couplings of sterically hindered substrates (condition C, namely 2-(dicyclohexylphosphane)biphenyl as ligand and $Ba(OH)_2 \cdot 8H_2O$ as base),[18] the 2-quinolinone **25** was obtained from ***E*-14** in 50% yield with cleavage of the Boc group (entry 3, Table 1). This may due to the use of a stronger base and higher temperature.

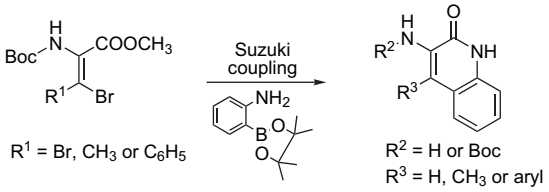


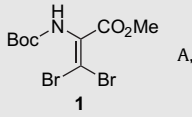
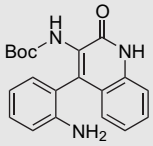
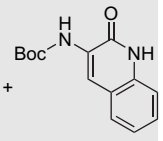
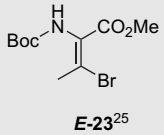
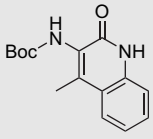
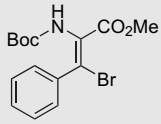
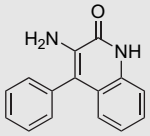
Scheme 1. (i) 20 mol % $PdCl_2(dppf) \cdot CH_2Cl_2$ (1:1), 1.4 equiv Cs_2CO_3, THF/H_2O (1:1); (ii) 4 mol % $PdCl_2(dppf) \cdot CH_2Cl_2$ (1:1), 6 equiv K_2CO_3, toluene/H_2O (2.7:1); (iii) 10 equiv CH_3COOH, DMF, 160 °C.



Scheme 3. (ii) 2 mol % $PdCl_2(dppf)\cdot CH_2Cl_2$ (1:1), 6 equiv K_2CO_3, toluene/H_2O (2.7:1); (iii) 10 equiv CH_3COOH, DMF, 160 °C.

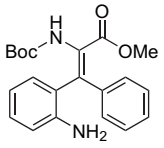
Table 1
Synthesis of substituted 2-quinolinones by one-pot Suzuki coupling and lactamization



Entry	Dehydroamino acid	Conditions	2-Quinolinones (%)
1	 **1**	A, 3 h	 **21**, 70% +  **22**, 10%
2	 ***E*-23**[25]	B, 3 h	 **24**, 97%
3	 ***E*-14**[24]	C, 1 h	 **25**, 50%

A: 5 equiv 2-(pinacolboronate)aniline, 20 mol % $PdCl_2(dppf)\cdot CH_2Cl_2$ (1:1), 1.4 equiv Cs_2CO_3, THF/H_2O (1:1), 90 °C.
B: 1.3 equiv 2-(pinacolboronate)aniline, 10 mol % $PdCl_2(dppf)\cdot CH_2Cl_2$ (1:1), 1.4 equiv Cs_2CO_3, THF/H_2O (1:1), 90 °C.
C: 1.3 equiv 2-(pinacolboronate)aniline, 5 mol % $Pd(OAc)_2$, 20 mol % 2-(dicyclohexylphosphane)biphenyl, 3 equiv $Ba(OH)_2\cdot 8H_2O$, dioxane, 120 °C.

Compound ***Z*-14** was also reacted with 2-(pinacolboronate)aniline using conditions B and only gave the Suzuki coupling product **26** in 51% yield.



26

Using a similar methodology, it was also possible to obtain several substituted coumarins using 2-(pinacolboronate)phenol as coupling component (Table 2).

When β,β-dibromodehydroalanine **1** was used as coupling component (entry 1, Table 2), we have obtained the coumarin **27** in good yield, adding a $KHSO_4$ 1 M solution to acidify the reaction mixture. In this case, the product resulting from elimination of a bromine atom was not isolated as observed in the reaction of compound **1** with 2-(pinacolboronate)aniline.

Coumarins **28** and **29** were obtained from compounds ***E*-23** and ***E*-14**, respectively, in excellent yields (entries 2 and 3, Table 2). Compound ***E*-30**, gave coumarin **31** in good yield with cleavage of the 4-nitrobenzyloxycarbonyl group [Cbz(NO_2)].

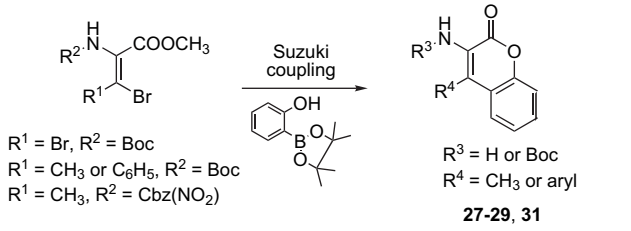
We have also tried this reaction with β-brominated dehydrodipeptides **32**[26] and **33**, which were obtained by bromination of the corresponding dehydrodipeptides with *N*-bromosuccinimide (NBS) followed by treatment with triethylamine. Compound **32** reacted with 2-(pinacolboronate)phenol to give coumarin **34** in 53% yield. The 2-quinolinone **35** was obtained in 60% yield by reacting the dehydrodipeptide **33** with 2-(pinacolboronate)aniline (Scheme 4).

These results show that brominated dehydropeptides are also good substrates for this type of reactions giving interesting coumarins and 2-quinolinones linked in position-3 to an amino acid derivative.

3. Conclusions

We have developed new and efficient strategies for the synthesis of heteroannulated 2-pyridinones, substituted 2-

Table 2
Synthesis of substituted coumarins by one-pot Suzuki coupling and lactonization



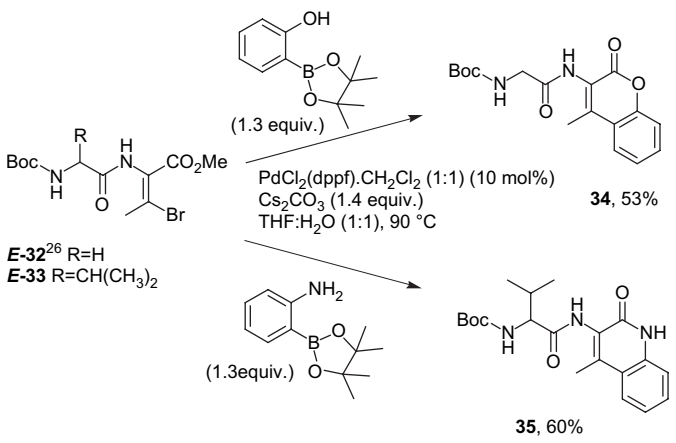
Entry	Dehydroamino acid	Conditions	Coumarins (%)
1	**1**	A, 3 h 30 min	**27**, 60%
2	***E*-23**	B, 3 h	**28**, 99%
3	***E*-14**	B, 3 h	**29**, 97%
4	***E*-30**[26]	B, 7 h	**31**, 47%

A: 5 equiv 2-(pinacolboronate)phenol, 20 mol % $PdCl_2(dppf)\cdot CH_2Cl_2$ (1:1), 1.4 equiv Cs_2CO_3, THF/H_2O (1:1), 90 °C.
B: 1.3 equiv 2-(pinacolboronate)phenol, 10 mol % $PdCl_2(dppf)\cdot CH_2Cl_2$ (1:1), 1.4 equiv Cs_2CO_3, THF/H_2O (1:1), 90 °C.

quinolinones and coumarins using brominated dehydroamino acids as building blocks. As far as our knowledge, it is the first time that these compounds were prepared using Suzuki cross-couplings of aryl or heteroarylboron compounds with β-bromo or β,β-dibromodehydroamino acids followed by intramolecular cyclization. The latter occurs by nucleophilic attack either by the substituents (NH_2 or OH) on the carbonyl of the ester or by the heteroaromatic ring on the carbonyl of the Boc group.

The tandem one-pot Suzuki coupling and intramolecular cyclization methodology, which takes advantage of the presence of an ester as carboxylic acid protecting group, was also applied successfully to brominated dehydropeptides giving coumarins and 2-quinolinones linked to amino acids.

The new compounds obtained are heteroannulated 2-pyridinones, 2-quinolinones and coumarins, and therefore may have several interesting biological applications.



Scheme 4.

4. Experimental

4.1. Suzuki couplings

*4.1.1. Boc-ΔAla[β,β-bis-(fur-3-yl)]-OMe (**2**)*

To a solution of *N-tert*-butoxycarbonyl-,β,β-dibromodehydroalanine [Boc-ΔAla(β,β-Br)-OMe] **1**[22] (150 mg, 0.418 mmol) in 4 mL of THF/H_2O (1:1), the 3-(pinacolboronate)furan (5 equiv), Cs_2CO_3 (1.4 equiv) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (1:1) (20 mol %) were added and the mixture was heated at 90 °C for 4 h. THF was removed under reduced pressure and the residue was dissolved in ethyl acetate (25 mL). The organic layer was washed with water and brine (2×10 mL each), dried over $MgSO_4$ and evaporated at reduced pressure to give an oil. Column chromatography using solvent gradient from neat petroleum ether to 40% diethyl ether/petroleum ether gave compound **2** (104 mg, 75%) as a yellow solid, mp 157–159 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9H, CH_3Boc), 3.68 (s, 3H, OCH_3), 6.21 (br s, 1H, NH), 6.31 (m, 1H, ArH), 6.51 (br s, 1H, ArH), 7.35 (m, 1H, ArH), 7.39 (m, 1H, ArH), 7.43 (m, 1H, ArH), 7.47(m, 1H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 28.1 [C(*C*H_3)$_3$], 52.1 (OCH_3), 81.3 [O*C*(CH_3)$_3$], 110.5 (CH), 111.1 (CH), 115.9 (C), 123.0 (C), 123.3 (C), 124.4 (C), 141.5 (CH), 142.9 (CH), 143.3 (CH), 143.5 (CH), 152.6 (C=O), 166.3(C=O); MS (FAB) *m*/*z* (%) 335 (M^++2), 334 (M^++1), 333 (M^+); HRMS *m*/*z* [M^++H] calcd for $C_{17}H_{20}NO_6$ 334.1291, found 334.1288.

*4.1.2. Boc-ΔAla[β,β-bis-(thien-3-yl)]-OMe (**3**)*

To a solution of compound **1** (101 mg, 0.280 mmol) in 2.05 mL of toluene/H_2O (2.7:1), potassium 3-thiophene trifluoroborate (3.5 equiv), K_2CO_3 (6 equiv) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (4 mol %) were added, and the mixture was heated at 90 °C for 3 h 30 min. Toluene was removed under reduced pressure and the residue was dissolved in ethyl acetate (25 mL). The organic layer was washed with water and brine (2×10 mL each), dried over $MgSO_4$ and evaporated at reduced pressure to give an oil. Column chromatography using solvent gradient from neat petroleum ether to 40% diethyl ether/petroleum ether gave compound **3** (101 mg, 99%) as a brown solid, mp 124–126 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9H, CH_3Boc), 3.61 (s, 3H, OCH_3), 6.23 (br s, 1H, NH), 6.87 (dd, *J*=5.0 and 1.2 Hz, 1H, ArH), 7.08 (dd, *J*=5.0 and 1.2 Hz, 1H, ArH), 7.14 (dd, *J*=3.0 and 1.2 Hz, 1H, ArH), 7.20 (dd, *J*=3.0 and 1.2 Hz, 1H, ArH), 7.26 (dd, *J*=5.0 and 3.0 Hz, 1H, ArH), 7.36 (dd, *J*=5.0 and 3.0 Hz, 1H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 28.1 [C(*C*H_3)$_3$], 52.1 (OCH_3), 81.4 [O*C*(CH_3)$_3$], 122.7 (C), 124.2 (CH), 125.2 (CH), 126.0 (CH), 126.5 (CH), 128.2 (CH), 128.4 (CH), 138.4 (C), 139.6 (C), 152.6 (C=O), 166.5 (C=O); MS (FAB) *m*/*z* 367 (M^++2), 366 (M^++1), 365 (M^+); HRMS [M^++H] *m*/*z* calcd for $C_{17}H_{20}NO_4S_2$ 366.0834, found 366.0827.

*4.1.3. Boc-ΔAla[β,β-bis-(fur-2-yl)]-OMe (**4**)*

To a solution of compound **1** (150 mg, 0.418 mmol) in 4 mL of THF/H_2O (1:1), fur-2-ylboronic acid (8 equiv), Cs_2CO_3 (1.4 equiv) and $PdCl_2(dppf)\cdot CH_2Cl_2$ (1:1) (20 mol %) were added, and the mixture was heated at 90 °C for 3 h. THF was removed under reduced pressure and the residue was dissolved in ethyl acetate

(25 mL). The organic layer was washed with water and brine (2×10 mL each), dried over $MgSO_4$ and evaporated at reduced pressure to give an oil. Column chromatography using solvent gradient from neat petroleum ether to 40% diethyl ether/petroleum ether gave compound **4** (121 mg, 87%) as an oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 9H, CH_3Boc), 3.68 (s, 3H, OCH_3), 6.34 (br d, J=3.3 Hz, 1H, ArH), 6.38 (br d, J=3.3 Hz, 1H, ArH), 6.42–6.43 (m, 1H, ArH), 6.46–6.48 (m, 1H, ArH), 7.44 (d, J=1.8 Hz, 1H, ArH), 7.54 (d, J=1.8 Hz, 1H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 28.1 [C(CH_3)$_3$], 52.3 (OCH_3), 81.8 [$OC(CH_3)_3$], 110.9 (CH), 111.0 (CH), 111.7 (CH), 112.5 (CH), 126.7 (C), 142.7 (CH), 142.9 (CH), 144.1 (C), 148.8 (C), 150.6 (C), 152.0 (C=O), 165.4 (C=O); MS (FAB) m/z 335 (M^++2), 334 (M^++1), 333 (M^+), 233 (M^+−Boc); HRMS [M^++H] m/z calcd for $C_{17}H_{20}NO_6$ 334.1291, found 334.1285.

4.1.4. Boc-ΔAla[β,β-bis-(thien-2-yl)]-OMe (**5**)

To a solution of compound **1** (150 mg, 0.418 mmol) in (4 mL) THF/H_2O (1:1), thien-2-ylboronic acid (8 equiv), Cs_2CO_3 (1.4 equiv) and $PdCl_2$(dppf)·CH_2Cl_2 (1:1) (20 mol %) were added, and the mixture was heated at 90 °C for 7 h. THF was removed under reduced pressure and the residue was dissolved in ethyl acetate (25 mL). The organic layer was washed with water and brine (2×10 mL each), dried over $MgSO_4$ and evaporated at reduced pressure to give an oil. Column chromatography using solvent gradient from neat petroleum ether to 30% diethyl ether/petroleum ether gave compound **5** (85.0 mg, 56%) as an oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 9H, CH_3Boc), 3.60 (s, 3H, OCH_3), 6.43 (br s, 1H, NH), 6.97–7.11 (m, 4H, ArH), 7.36 (dd, J=5.0 and 1.5 Hz, 1H, ArH), 7.44 (dd, J=5.0 and 1.5 Hz, 1H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 28.1 [C(CH_3)$_3$], 52.2 (OCH_3), 81.7 [$OC(CH_3)_3$], 119.6 (C), 125.9 (C), 126.5 (CH), 127.2 (2×CH), 128.2 (CH), 128.4 (CH), 130.1 (CH), 140.2 (C), 140.5 (C), 152.5 (C=O), 165.9 (C=O); MS (FAB) m/z 367 (M^++2), 366 (M^++1), 365 (M^+); HRMS [M^++H] m/z calcd for $C_{17}H_{20}NO_4S_2$ 366.0834, found 366.0850.

4.2. General procedure for the synthesis of 2-pyridinones

In a Schlenk tube containing a solution of compounds **2**, **3**, **10**,[17] **11**,[17] **15**, **17**[24] or **19**[24] in dry DMF (0.1 M), glacial acetic acid (10 equiv) was added and the mixture was stirred under Ar at 160 °C for several hours. After cooling, ethyl acetate (30 mL) was added and the solution was washed with water and brine (2×10 mL each), dried over $MgSO_4$ and the removal of solvent under reduced pressure gave an oil.

4.2.1. Methyl 4-(fur-3-yl)-6H-furo[2,3-c]pyridin-7-one-5-carboxylate (**6**)

Compound **6** was prepared from compound **2** (100 mg, 0.300 mmol) according to the general procedure described above and heating for 5 h 30 min. Column chromatography using solvent gradient from diethyl ether to 50% chloroform/diethyl ether gave compound **6** (42.0 mg, 52%) as a beige solid, mp 204–205 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (s, 3H, OCH_3), 6.48 (dd, J=2.4 and 0.6 Hz, 1H, ArH), 6.65 (d, J=1.8 Hz, 1H, ArH), 7.54–7.56 (m, 2H, ArH), 7.80 (d, J=1.8 Hz, 1H, ArH), 9.89 (br s, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 53.0 (OCH_3), 108.4 (CH), 112.2 (CH), 112.7 (C), 118.7 (C), 125.7 (C), 135.6 (C), 141.2 (CH), 142.7 (CH), 144.9 (C), 148.9 (CH), 151.7 (C=O), 161.8 (C=O); MS m/z 259 (M^+), 244 (M^+−CH_3), 215 (M^+−44), 69 (M^+−190); HRMS m/z M^+ calcd for $C_{13}H_9NO_5$ 259.0481, found 259.0483.

4.2.2. Methyl 4-(thien-3-yl)-thieno[2,3-c]pyridin-7-one-5-carboxylate (**7**)

Compound **7** was prepared from compound **3** (87.0 mg, 0.238 mmol) according to the general procedure described above and heating for 5 h 30 min. The oil obtained was washed with diethyl ether and compound **7** (47.0 mg, 68%) was obtained as a beige solid, mp 198–200 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.74 (s, 3H, OCH_3), 7.00 (d, J=5.4 Hz, 1H, ArH), 7.07 (dd, J=5.1 and 1.5 Hz, 1H, ArH), 7.25–7.27 (m, 2H, ArH), 7.44 (dd, J=5.1 and 3.0 Hz, 1H, ArH), 7.71 (d, J=5.4 Hz, 1H, ArH), 9.45 (br s, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 53.1 (OCH_3), 118.3 (C), 124.2 (CH), 125.2 (CH), 126.1 (CH), 126.3 (C), 129.0 (CH), 133.6 (C), 133.7 (CH), 135.0 (C), 147.3 (C), 157.2 (C=O), 162.2 (C=O); MS (EI) m/z 291 (M^+), 231 (M^+−COOMe), 69(M^+−222); HRMS m/z M^+ calcd for $C_{13}H_9NO_3S_2$ 291.0024, found 291.0026.

4.2.3. H-ΔAla[β,β-bis-(fur-2-yl)]-OMe (**8**)

Compound **8** was prepared from Boc-ΔAla-[β,β-bis-(fur-2-yl)]-OMe **4** (0.340 mmol, 113 mg) according to the general procedure described above and heating for 5 h giving the unstable compound **8** (78.0 mg, 98%) as an oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.65 (s, 3H, OCH_3), 5.22 (br s, 2H, NH_2), 6.10 (dd, J=3.3 Hz, 1H, ArH), 6.25 (dd, J=3.3 and 0.9 Hz, 1H, ArH), 6.42–6.44 (m, 2H, ArH), 7.43 (dd, J=1.8 and 0.9 Hz, 1H, ArH), 7.49 (dd, J=1.8 and 0.9 Hz, 1H, ArH).

4.2.4. H-ΔAla[β,β-bis-(thien-2-yl)]-OMe (**9**)

Compound **9** was prepared from Boc-ΔAla-[β,β-bis-(thien-2-yl)]-OMe **5** (0.328 mmol, 120.0 mg) according to the general procedure described above and heating for 3 h 30 min giving the unstable compound **9** (80.0 mg, 92%) as an oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.59 (s, 3H, OCH_3), 4.46 (br s, 2H, NH_2), 6.87 (dd, J=3.6 and 1.2 Hz, 1H, ArH), 6.97 (dd, J=5.3 and 3.6 Hz, 1H, ArH), 7.05 (dd, J=5.3 and 3.6 Hz, 1H, ArH), 7.12 (dd, J=3.6 and 1.2 Hz, 1H, ArH), 7.29 (dd, J=5.3 and 1.2 Hz, 1H, ArH), 7.33 (dd, J=5.3 and 1.2 Hz, 1H, ArH).

4.2.5. Methyl 4-(benzothien-3-yl)-2H-benzothieno[2,3-c]pyridin-1-one-3-carboxylate (**12**)

Compound **12** was prepared from compound **10**[17] (100 mg, 0.215 mmol) according to the general procedure described above and heating for 5 h. Column chromatography using solvent dichloromethane gave compound **12** (40.0 mg, 48%) as a white solid, mp 287–288 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.58 (s, 3H, OCH_3), 6.54 (br d, J=8.4 Hz, 1H, ArH), 7.00–7.05 (m, 1H, ArH) 7.29–7.45 (m, 5H, ArH), 7.93 (br d, J=8.4 Hz, 1H, ArH), 8.02 (br d, J=8.4 Hz, 1H, ArH), 9.93 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 53.3 (OCH_3), 116.5 (C), 122.4 (CH), 123.0 (CH), 123.4 (CH), 124.8 (CH), 125.0 (CH), 125.1 (CH), 125.2 (CH), 125.4 (CH), 127.8 (CH), 128.2 (C), 130.5 (C), 135.4 (C), 135.9 (C), 139.0 (C), 139.4 (C), 140.9 (C), 142.5 (C), 157.6 (C=O), 161.9 (C=O); MS (EI) m/z 391 (M^+), 331, 302; HRMS m/z calcd for $C_{21}H_{13}NO_3S_2$ 391.0337, found 391.0330.

4.2.6. Methyl 4-(benzothien-2-yl)-2H-benzothieno[3,2-c]pyridin-1-one-3-carboxylate (**13**)

Compound **13** was prepared from compound **11**[17] (100 mg, 0.215 mmol) according to the general procedure described above and heating for 2 h. Column chromatography using dichloromethane gave compound **13** (49.0 mg, 63%) as a beige solid, mp 255–256 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H, OCH_3), 7.40–7.61 (m, 5H, ArH), 7.81 (d, J=8.0 Hz, 1H, ArH), 7.87–7.93 (m, 2H, ArH), 8.95 (d, J=8.0 Hz, 1H, ArH), 9.72 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 53.5 (OCH_3), 114.6 (C), 121.9 (CH), 122.3 (CH), 124.1 (CH), 124.6 (CH), 125.0 (CH), 125.4 (CH), 125.91 (CH), 125.94 (CH), 126.7 (C), 127.0 (CH), 127.5 (C), 136.0 (C), 136.1 (C), 139.4 (C), 139.9 (C), 140.8 (C), 153.8 (C), 157.4 (C=O), 161.4 (C=O). Anal. Calcd for $C_{21}H_{13}NO_3S_2$: C, 64.43; H, 3.35; N, 3.58; S, 16.38. Found: C, 64.06; H, 3.51; N, 3.59; S, 16.34.

4.2.7. Boc-(Z)-ΔPhe[β-(thien-3-yl)]-OMe (**15**)

To a solution of compound ***Z*-14**[24] (200 mg, 0.560 mmol) in 4.1 mL toluene/H_2O (2.7:1), the potassium 3-thiophene trifluoroborate (1.3 equiv), K_2CO_3 (6 equiv) and $PdCl_2$(dppf)·CH_2Cl_2 (1:1) (2 mol %) were added, and the mixture was heated at 90 °C for

3 h 30 min. Toluene was removed under reduced pressure and the residue was dissolved in ethyl acetate (25 mL). The organic layer was washed with water and brine (2×10 mL each), dried over $MgSO_4$ and evaporated at reduced pressure to give an oil. Column chromatography using solvent gradient from neat petroleum ether to 30% diethyl ether/petroleum ether gave compound **15** (0.183 g, 91%) as a yellow solid, mp 128–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 9H, CH_3Boc), 3.50 (s, 3H, OCH_3), 6.23 (br s, 1H, NH), 7.06 (dd, J=5.3 and 1.2 Hz, 1H, ArH), 7.14–7.18 (m, 3H, ArH), 7.29–7.36 (m, 4H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 28.1 [C(CH_3)$_3$], 51.9 (OCH_3), 81.3 [OC(CH$_3$)$_3$], 125.2 (C), 125.9 (CH), 126.9 (CH), 127.9 (CH), 128.0 (2×CH), 128.4 (CH), 129.0 (2×CH), 139.2 (C), 139.7 (C), 152.8 (C=O), 166.4 (C=O); MS (FAB) m/z 361 (M^++2), 360 (M^++1), 359 (M^+); HRMS m/z [M^++H] calcd for $C_{19}H_{22}NO_4S$ 360.1270, found 360.1275.

4.2.8. Methyl 4-phenyl-6H-thieno[2,3-c]pyridin-7-one-5-carboxylate (*16*)

Compound **16** was prepared from compound **15** (143 mg, 0.398 mmol) according to the general procedure described above and heating for 4 h. Column chromatography using diethyl ether gave compound **16** as a yellow solid (37.0 mg, 33%), mp 181–183 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.67 (s, 3H, OCH_3), 6.89 (d, J=5.4 Hz, 1H, ArH), 7.26–7.30 (m, 2H, ArH), 7.45–7.48 (m, 3H, ArH), 7.69 (d, J=5.4 Hz, 1H, ArH), 9.46 (br s, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 52.8 (OCH_3), 123.3 (C), 125.8 (C), 126.1 (CH), 128.0 (CH), 128.2 (2×CH), 129.2 (2×CH), 133.6 (CH), 135.8 (C), 147.2 (C), 157.3 (C=O), 162.3 (C=O); MS (FAB) m/z 287 (M^++2), 286 (M^++1), 285 (M^+); HRMS m/z [M^++H] calcd for $C_{15}H_{12}NO_3S$ 286.0538, found 286.0536.

4.2.9. Methyl 4-phenyl-2H-benzothieno[2,3-c]pyridin-1-one-3-carboxylate (*18*)

Compound **13** was prepared from compound **17** (196 mg, 0.479 mmol) according to the general procedure described above and heating for 5 h. The crude was washed with diethyl ether giving compound **18** (31.0 mg, 20%) as a yellow solid, mp 266–268 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.69 (s, 3H, OCH_3), 6.48 (d, J=8.4 Hz, 1H, ArH), 7.09 (t, J=8.1 Hz, 1H, ArH), 7.33–7.37 (m, 2H, ArH), 7.44 (t, J=8.1 Hz, 1H, ArH), 7.53–7.57 (m, 3H, ArH), 7.93 (d, J=8.4 Hz, 1H, ArH), 9.94 (br s, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 53.0 (OCH_3), 123.4 (CH), 123.8 (C), 124.9 (CH), 125.9 (CH), 126.3 (C), 127.7 (CH), 128.5 (CH), 128.8 (2×CH), 129.3 (2×CH), 135.7 (C), 135.78 (C), 135.81 (C), 140.7 (C), 142.5 (C), 157.6 (C=O), 162.0 (C=O); MS (FAB) m/z 337 (M^++2), 336 (M^++H), 335 (M^+), 304 (M^+−OMe); HRMS m/z [M^++H] calcd for $C_{19}H_{14}NO_3S$ 336.0694, found 336.0692.

4.2.10. Methyl 4-phenyl-2H-benzothieno[3,2-c]pyridin-1-one-3-carboxylate (*20*)

Compound **20** was prepared from compound **19** (113 mg, 0.287 mmol) according to the general procedure described above and heating for 4 h. The crude was washed with diethyl ether giving compound **20** (33.0 mg, 34%) as a beige solid, mp 282–284 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H, OCH_3), 7.38–7.40 (m, 2H, ArH), 7.48–7.59 (m, 5H, ArH), 7.80 (d, J=7.6 Hz, 1H, ArH), 8.97 (br d, J=7.2 Hz, 1H, ArH), 9.78 (br s, 1H, NH); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 53.1 (OCH_3), 121.8 (CH), 122.4 (C), 125.6 (C), 125.8 (CH), 126.0 (CH), 126.9 (CH), 128.5 (2×CH), 128.6 (C), 128.7 (CH), 129.1 (2×CH), 129.3 (C), 135.6 (C), 136.1 (C), 140.1 (C), 157.7 (C=O), 161.8 (C=O); MS (FAB) m/z 337 (M^++2), 336 (M^++1), 335 (M^+); HRMS m/z [M^++H] calcd $C_{19}H_{14}NO_3S$ 336.0694, found 336.0687.

4.3. General procedures for the synthesis of 3,4-disubstituted 2-quinolinones and coumarins

Procedure 1. To a solution of compound **1**,[22] ***E*-14**,[24] ***E*-23**,[25] ***E*-30**,[26] ***E*-32**[26] or ***E*-33** in THF/H_2O (1:1), 2-(pinacolboronate)aniline or 2-(pinacolboronate)phenol, Cs_2CO_3 (1.4 equiv) and $PdCl_2$(dppf)·CH_2Cl_2 (1:1) were added and the mixture was heated at 90 °C. THF was removed under reduced pressure and the residue was dissolved in ethyl acetate (25 mL). The organic layer was then washed with water and brine (2×10 mL each), dried over $MgSO_4$ and evaporated at reduced pressure to give an oil.

Procedure 2. A dried Schlenk tube was charged under Ar with dry dioxane (3 mL), ***E*-14** (0.500 mmol), $Pd(OAc)_2$ (5 mol %), 2-(dicyclohexylphosphino)biphenyl (20 mol %), $Ba(OH)_2·8H_2O$ (3 equiv) and 2-(pinacolboronate)aniline (1.3 equiv). The mixture was heated at 100 °C for 1 h. Water and ethyl acetate were added, the phases were separated, and the aqueous phase was extracted with more ethyl acetate. The organic phases were collected, dried ($MgSO_4$), filtered and the solvent was evaporated at reduced pressure to give a brown oil, which was subjected to column chromatography.

4.3.1. 3-(tert-Butoxycarbonyl)amino-4-(2-aminophenyl)quinolin-2-one (*21*) and 3-(tert-butoxycarbonyl)aminoquinolin-2-one (*22*)

2-Quinolinones **21** and **22** were prepared from compound **1** (72.0 mg, 0.200 mmol), 5 equiv of 2-(pinacolboronate)aniline and 20 mol % $PdCl_2$(dppf)·CH_2Cl_2 (1:1) according to general procedure 1 and heating for 3 h. Crystallization from ethyl acetate gave a brown solid **21** (47.0 mg, 70%), mp 200–202 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 9H, CH_3Boc), 3.80 (br s, 2H, NH_2), 6.51 (br s, 1H, NHBoc), 6.84–6.89 (m, 2H, ArH), 7.03 (dd, J=8.1 and 1.5 Hz, 1H, ArH), 7.09–7.14 (m, 1H, ArH), 7.22–7.32 (m, 2H, ArH), 7.39–7.47 (m, 2H, ArH), 12.38 (br s, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 28.0 [C(CH_3)$_3$], 80.4 [OC(CH$_3$)$_3$], 116.1 (CH), 116.3 (CH), 118.5 (CH), 119.7 (C), 120.5 (C), 122.8 (CH), 126.4 (C), 127.0 (CH), 129.48 (CH), 129.51 (CH), 129.8 (CH), 136.5 (C), 142.2 (C), 144.4 (C), 153.3 (C=O), 161.1 (C=O); MS (FAB) m/z 353 (M^++2), 352 (M^++1) 351 (M^+); HRMS m/z 352.1664 [M^++H] (calcd $C_{20}H_{22}N_3O_3$ 352.1661). Column chromatography of the remaining residue using solvent gradient from neat petroleum ether to 20% diethyl ether/petroleum ether gave 2-quinolinone **22** (5.0 mg, 10%) as a brown solid, mp 178–180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.58 (s, 9H, CH_3Boc), 7.22–7.27 (m, 1H, ArH), 7.33–7.46 (m, 2H, ArH), 7.57 (d, J=7.8 Hz, 1H, ArH), 7.77 (s, 1H, NHBoc), 8.44 (s, 1H, β-CH), 11.53 (br s, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 28.3 [C(CH_3)$_3$], 81.2 [OC(CH$_3$)$_3$], 115.4 (CH), 119.3 (CH), 120.9 (C), 123.4 (CH), 127.3 (CH), 127.9 (CH), 128.4 (C), 133.2 (C), 152.7 (C=O), 158.7 (C=O); MS (FAB) m/z 261 (M^++1), 260 (M^+), 205 (M^+−C(CH$_3$)$_3$); HRMS m/z [M^++H] calcd for $C_{14}H_{17}N_2O_3$ 261.1239, found 261.1244.

4.3.2. 3-(tert-Butoxycarbonyl)amino-4-methylquinolin-2-one (*24*)

2-Quinolinone **24** was prepared from compound ***E*-23** (60.0 mg, 0.200 mmol), 1.3 equiv of 2-(pinacolboronate)aniline and 10 mol % $PdCl_2$(dppf)·CH_2Cl_2 (1:1) according to general procedure 1 described above and heating for 3 h. Crystallization from ethyl acetate/petroleum ether gave compound **24** as a brown solid (53.0 mg, 97%), mp 211–213 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 9H, CH_3Boc), 2.47 (s, 3H, CH_3), 7.08 (br s, 1H, NHBoc), 7.22–7.27 (m, 1H, ArH), 7.36–7.46 (m, 2H, ArH), 7.72 (d, J=7.8 Hz, 1H, ArH), 12.11 (br s, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 15.7 (CH_3), 28.2 [C(CH_3)$_3$], 80.7 [OC(CH$_3$)$_3$], 116.1 (CH), 121.3 (C), 122.8 (CH), 124.7 (CH), 125.4 (C), 129.2 (CH), 135.3 (C), 139.1 (C), 153.6 (C=O), 160.8 (C=O); MS (FAB) m/z 276 (M^++2), 275 (M^++1), 274 (M^+); HRMS m/z [M^++H] calcd for $C_{15}H_{19}N_2O_3$ 275.1396, found 275.1397.

4.3.3. 3-Amino-4-phenylquinolin-2-one (*25*)

2-Quinolinone **25** was prepared from compound ***E*-14** (175 mg, 0.500 mmol) according to general procedure 2 and heating for 1 h. Column chromatography using solvent gradient from pure petroleum ether to diethyl ether gave compound **25** as a brown solid (59.0 mg, 50%), mp 238–240 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.37 (br s, 2H, NH_2), 7.08–7.11 (m, 2H, ArH), 7.26–7.32 (m, 1H, ArH), 7.38–

7.42 (m, 3H, ArH), 7.46–7.52 (m, 1H, ArH), 7.56–7.62 (m, 2H, ArH), 11.78 (br s, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 115.6 (CH), 122.1 (C), 122.2 (C), 122.7 (CH), 124.0 (CH), 125.6 (CH), 128.2 (CH), 129.5 (2×CH), 129.7 (2×CH), 132.1 (C), 133.4 (C), 134.8 (C), 159.2 (C=O); MS *m*/*z* 236 (M^+), 235 (M^+-1), 217 (M^+-19), 190 (M^+-46); HRMS *m*/*z* M^+ calcd for $C_{15}H_{12}N_2O$ 236.0950, found 236.0952.

4.3.4. Boc-(Z)-ΔPhe[β-(2-aminophenyl)]-OMe (**26**)

Compound **26** was prepared from ***Z*-14** (100 mg, 0.280 mmol), 1.3 equiv of 2-(pinacolboronate)aniline and 10 mol % $PdCl_2(dppf)\cdot CH_2Cl_2$ (1:1) according to general procedure 1 described above and heating for 2 h 30 min. Column chromatography using solvent gradient from pure petroleum ether to 50% diethyl ether in petroleum ether gave compound **26** (53.0 mg, 51%), mp 149–151 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.45 (s, 9H, CH_3Boc), 3.59 (s, 3H, OCH_3), 3.86 (br s, 2H, NH_2), 6.01 (br s, 1H, NH), 6.69–6.76 (m, 2H, ArH), 6.88 (br d *J*=7.5 Hz, 1H, ArH), 7.12–7.19 (m, 3H, ArH), 7.26–7.30 (m, 3H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 28.1 [C(CH_3)$_3$], 52.0 (OCH_3), 81.3 [O*C*(CH_3)$_3$], 115.8 (CH), 118.3 (CH), 122.5 (C), 126.9 (C), 127.9 (CH), 128.2 (2×CH), 128.6 (2×CH), 129.2 (C), 129.6 (CH), 131.1 (CH), 139.1 (C), 143.9 (C), 153.1 (C=O), 166.2 (C=O); MS (FAB) *m*/*z* 370 (M^++2), 369 (M^++1), 251 (M^+-118); HRMS *m*/*z* [M^++H] calcd $C_{21}H_{25}N_2O_4$ 369.1814, found 369.1822.

4.3.5. 3-(tert-Butoxycarbonyl)amino-4-(2-hydroxyphenyl)-coumarin (**27**)

Coumarin **27** was prepared from compound **1** (72.0 mg, 0.200 mmol), 5 equiv of 2-(pinacolboronate)phenol and 20 mol % $PdCl_2(dppf)\cdot CH_2Cl_2$ (1:1) according to general procedure 1 and heating for 3 h 30 min. After removing THF under reduced pressure, the residue was dissolved in ethyl acetate (25 mL). The organic layer was washed with a solution of 1 M $KHSO_4$, water and brine (2×10 mL each), dried over $MgSO_4$ and evaporated at reduced pressure to give an oil. Crystallization from diethyl ether gave a brown solid **27** (43.0 mg, 61%), mp 194–196 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 1.36 (s, 9H, CH_3Boc), 7.03–7.12 (m, 2H, ArH), 7.19–7.32 (m, 3H, ArH), 7.38–7.44 (m, 2H, ArH), 7.59–7.64 (m, 1H, ArH), 8.54 (br s, 1H, NH); ^{13}C NMR (75.4 MHz, acetone-d_6) δ 28.2 [C(CH_3)$_3$], 80.1 [O*C*(CH_3)$_3$], 117.1 (CH), 117.2 (CH), 120.6 (CH), 120.9 (C), 121.0 (C), 123.6 (C), 125.0 (CH), 128.3 (CH), 130.9 (CH), 131.3 (CH), 131.8 (CH), 146.5 (C), 153.1 (C), 154.3 (C), 155.0 (C), 159.5 (C); MS (FAB) *m*/*z* 355 (M^++2), 354 (M^++1), 353 (M^+); HRMS *m*/*z* [M^++H] calcd $C_{20}H_{20}NO_5$ 354.1341, found 354.1342.

4.3.6. 3-(tert-Butoxycarbonyl)amino-4-methylcoumarin (**28**)

Compound **28** was prepared from ***E*-23** (100 mg, 0.340 mmol), 1.3 equiv of 2-(pinacolboronate)phenol and 10 mol % $PdCl_2(dppf).CH_2Cl_2$ (1:1) according to general procedure 1 described above and heating for 3 h 30 min. Column chromatography using solvent gradient from 50% dichloromethane in petroleum ether to neat dichloromethane gave compound **28** (93.0 mg, 99%) as a beige solid, mp 137–139 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 9H, CH_3Boc), 2.40 (s, 3H, CH_3), 6.60 (br s, 1H, NH), 7.29–7.35 (m, 2H, ArH), 7.46–7.51 (m, 1H, ArH), 7.64 (dd, *J*=8.1 and 1.5 Hz, 1H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 15.4 (CH_3), 28.1 [C(CH_3)$_3$], 81.2 [O*C*(CH_3)$_3$], 116.6 (CH), 120.8 (C), 121.0 (C), 124.6 (CH), 124.9 (CH), 130.5 (CH), 141.8 (C), 150.8 (C), 153.1 (C), 159.8 (C); MS *m*/*z* 275 (M^+), 201 ($M^+-(CH_3)_3CO$), 175 (M^+–Boc), 146 (M^+-129); HRMS *m*/*z* M^+ calcd for $C_{15}H_{17}NO_4$ 275.1158, found 275.1152.

4.3.7. 3-(tert-Butoxycarbonyl)amino-4-phenylcoumarin (**29**)

Coumarin **29** was prepared from compound ***E*-14** (122 mg, 0.340 mmol), 1.3 equiv of 2-(pinacolboronate)phenol and 10 mol % $PdCl_2(dppf)\cdot CH_2Cl_2$ (1:1) according to general procedure 1 described above and heating for 3 h. Column chromatography using solvent gradient from neat petroleum ether to 40% diethyl ether/petroleum ether gave compound **29** (111 mg, 97%) as a white solid, mp 153–154 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.28 (s, 9H, CH_3Boc), 6.14 (br s, 1H, NH), 7.18–7.22 (m, 1H, ArH), 7.29–7.33 (m, 1H, ArH), 7.37–7.40 (m, 3H, ArH), 7.45–7.54 (m, 4H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 27.8 [C(CH_3)$_3$], 80.8 [O*C*(CH_3)$_3$], 116.7 (CH), 120.1 (C), 120.7 (C), 124.4 (CH), 127.1 (CH), 128.5 (2×CH), 128.68 (2×CH), 128.72 (CH), 130.9 (CH), 133.0 (C), 145.9 (C), 151.8 (C), 152.2 (C), 159.9 (C); MS (FAB) *m*/*z* 338 (M^++1), 282 (M^++1−(CH_3)$_3$C), 238 (M^++1−Boc); HRMS *m*/*z* [M^++H] calcd for $C_{20}H_{20}NO_4$ 338.1392, found 338.1394.

4.3.8. 3-Amino-4-methylcoumarin (**31**)

Coumarin **31** was prepared from compound ***E*-30** (110 mg, 0.290 mmol), 1.3 equiv of 2-(pinacolboronate)phenol and 10 mol % $PdCl_2(dppf)\cdot CH_2Cl_2$ (1:1) according to general procedure 1 and heating for 7 h. Column chromatography using a solvent gradient from neat petroleum ether to 40% diethyl ether/petroleum ether gave compound **31** (24.0 mg, 47%) as a yellow solid, mp 104–106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.24 (s, 3H, CH_3), 4.18 (br s, 2H, NH_2), 7.24–7.33 (m, 3H, ArH), 7.46–7.50 (m, 1H, ArH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 11.7 (CH_3), 116.4 (CH), 118.8 (C), 121.7 (C), 122.5 (CH), 124.5 (CH), 126.9 (CH), 128.9 (C), 148.5 (C), 159.0 (C); MS (EI) *m*/*z* 175 (M^+), 146 (M^+-29); HRMS M^+ *m*/*z* calcd for $C_{10}H_9NO_2$ 175.0633, found 175.0632.

4.3.9. Boc-Val-Z-ΔAbu-OMe

Boc-Val-*Z*-ΔAbu-OMe was prepared from Boc-Val-Thr-OMe (3.14 g, 10 mmol), *tert*-butylpyrocarbonate (Boc_2O) (2.18 g, 10 mmol) and 4-dimethylaminopyridine (DMAP) (122 mg, 1 mmol,), according to the procedure described by us elsewhere.[27] Boc-Val-*Z*-ΔAbu-OMe (2.39 g, 76%) was obtained as white solid, mp 107.5–108.0 °C from diethyl ether/*n*-hexane; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (d, *J*=6.9 Hz, 3H, γ-CH_3Val), 1.02 (d, *J*=6.9 Hz, 3H, γ-CH_3Val), 1.43 (s, 9H, CH_3Boc), 1.75 (d, *J*=7.2 Hz, 3H, γ-CH_3ΔAbu), 2.13–2.25 (m, 1H, β-CHVal), 3.73 (s, 3H, OCH_3), 4.05–4.12 (m, 1H, α-CHVal), 5.18 (d, *J*=8.4 Hz, 1H, NHVal), 6.80 (q, *J*=7.2 Hz, 1H, β-CHΔAbu), 7.61 (s, 1H, NHΔAbu); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 14.5 (γ-CH_3ΔAbu), 17.7 (γ-CH_3Val), 19.2 (γ-CH_3Val), 28.2 [C(CH_3)$_3$], 30.7 (β-CHVal), 52.2 (OCH_3), 60.0 (α-CHVal), 80.0 [O*C*(CH_3)$_3$], 126.0 (C), 134.5 (β-CHΔAbu), 155.9 (C), 164.7 (C), 170.2 (C). Anal. Calcd for $C_{15}H_{26}N_2O_5$: C, 57.31; H, 8.34; N, 8.91. Found: C, 57.34; H, 8.15; N, 8.86.

4.3.10. Boc-Val-ΔAbu(β-Br)-OMe (***Z*- and *E*-33**)

Boc-Val-*Z*-ΔAbu-OMe (1.57 g, 5 mmol) was reacted with NBS (0.900 g, 5 mmol) followed by treatment with triethylamine (2.5 equiv) according to the procedure described by us elsewhere[26] giving Boc-Val-ΔAbu(β-Br)-OMe (1.88 g, 96%) as a 1:1 mixture of *E* and *Z*-isomer. Column chromatography using solvent gradient from neat petroleum ether to 40% diethyl ether/petroleum ether gave Boc-Val-*Z*-ΔAbu(β-Br)-OMe (***Z*-33**) as a white solid, mp 137.5–138.0 °C from diethyl ether/*n*-hexane; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (d, *J*=6.9 Hz, 3H, γ-CH_3Val), 1.07 (d, *J*=6.9 Hz, 3H, γ-CH_3Val), 1.45 (s, 9H, CH_3Boc), 2.16–2.27 (m, 1H, β-CHVal), 2.57 (s, 3H, γ-CH_3ΔAbu), 3.79 (s, 3H, OCH_3), 3.94–4.09 (m, 1H, α-CHVal), 5.05 (d, *J*=8.7 Hz, 1H, NHVal), 7.75 (s, 1H, NHΔAbu); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 17.6 (γ-CH_3Val), 19.1 (γ-CH_3Val), 24.7 (γ-CH_3ΔAbu), 28.3 [C(CH_3)$_3$], 30.5 (β-CHVal), 52.5 (OCH_3), 59.5 (α-CHVal), 80.2 [O*C*(CH_3)$_3$], 125.2 (C), 126.7 (C), 155.8 (C=O), 162.8 (C=O), 170.1 (C=O). Anal. Calcd for $C_{15}H_{25}BrN_2O_5$: C, 45.81; H, 6.41; N, 7.12. Found: C, 45.80; H, 6.32; N, 7.27. Boc-Val-*E*-Δ-Abu(β-Br)-OMe (***E*-33**) was obtained as a white solid, mp 158.5–159.0 °C from diethyl ether/*n*-hexane; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (d, *J*=6.9 Hz, 3H, γ-CH_3Val), 0.99 (d, *J*=6.9 Hz, 3H, γ-CH_3Val), 1.42 (s, 9H, CH_3Boc), 2.08–2.19 (m, 1H, β-CHVal), 2.35 (s, 3H, γ-CH_3ΔAbu), 3.78 (s, 3H, OCH_3), 3.99–4.04 (m, 1H, α-CHVal), 5.28

(d, J=8.4 Hz, 1H, NHVal), 8.27 (s, 1H, NHΔAbu); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 18.0 (γ-CH_3Val), 19.1 (γ-CH_3Val), 25.6 (γ-CH_3ΔAbu), 28.2 [C(CH_3)$_3$], 30.5 (β-CHVal), 52.2 (OCH_3), 59.7 (α-CHVal), 80.4 [O*C*(CH_3)$_3$], 122.9 (C), 126.0 (C), 156.2 (C=O), 164.0 (C=O), 170.5 (C=O). Anal. Calcd for $C_{15}H_{25}BrN_2O_5$: C, 45.81; H, 6.41; N, 7.12. Found: C, 45.75; H, 6.38; N, 7.28.

4.3.11. *tert*-Butyl 2-(4-methyl-2-oxo-2H-chromen-3-ylamino)-2-oxoethylcarbamate (**34**)

Compound **34** was prepared from ***E*-32**[26] (90.0 mg, 0.260 mmol) according to general procedure 1 described above and heating for 3 h. Column chromatography using 50% diethyl ether/petroleum ether gave compound **34** (45.0 mg, 53%) as an oil. Crystallization from diethyl ether/petroleum ether gave a white solid, mp 110–111 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.47 (s, 9H, CH_3Boc), 2.35 (s, 3H, γ-CH_3ΔAbu), 4.04 (d, J=5.1 Hz, 2H, CH_2Gly), 5.52 (br s, 1H, NHGly), 7.28–7.34 (m, 2H, ArH), 7.47–7.52 (m, 1H, ArH), 7.65 (d, J=8.4 Hz, 1H, ArH), 8.21 (br s, 1H, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 15.5 (γ-CH_3ΔAbu), 28.2 [C(*C*H_3)$_3$], 44.7 (CH_2Gly), 80.5 [O*C*(CH_3)$_3$], 116.7 (CH), 119.9 (C), 120.4 (C), 124.7 (CH), 125.2 (CH), 131.1 (CH), 144.7 (C), 151.2 (C), 156.1 (C), 159.5 (C), 168.8 (C); MS (FAB) m/z 334 (M^++2), 333 (M^++1), 332 (M^+), 307 (M^+−25), 289 (M^+−(CH_3)$_3$), 277 (M^+−(CH_3)$_3$C); HRMS m/z [M^++H] calcd for $C_{17}H_{21}N_2O_5$ 333.1450, found 333.1451.

4.3.12. *tert*-Butyl 3-methyl-1-(4-methyl-2-oxo-1,2-dihydroquinolin-3-ylamino)-1-oxobutan-2-ylcarbamate (**35**)

Compound **35** was prepared from ***E*-33** (100 mg, 0.254 mmol) according to general procedure 1 described above and heating for 4 h 30 min. Column chromatography using chloroform gave compound **35** (57.0 mg, 60%) as a beige solid, mp 229–231 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.92 (d, J=6.6 Hz, 3H, γ-CH_3Val), 0.98 (d, J=6.6 Hz, 3H, γ-CH_3Val), 1.39 (s, 9H, CH_3Boc), 2.02–2.09 (m, 1H, β-CHVal), 2.23 (s, 3H, γ-CH_3ΔAbu), 3.97–4.03 (m, 1H, α-CHVal), 6.84 (d, J=8.7 Hz, 1H, NHVal), 7.18–7.23 (m, 1H, ArH), 7.30 (d, J=8.1 Hz, 1H, ArH), 7.45–7.50 (m, 1H, ArH), 7.74 (d, J=8.1 Hz, 1H, ArH), 9.26 (br s, 1H, NH), 11.88 (br s, 1H, NH); ^{13}C NMR (75.4 MHz, DMSO-d_6) δ 14.7 (γ-CH_3ΔAbu), 18.3 (γ-CH_3Val), 19.5 (γ-CH_3Val), 28.2 [C(*C*H_3)$_3$], 30.3 (β-CHVal), 60.3 (α-CHVal), 78.1 [O*C*(CH_3)$_3$], 115.2 (CH), 119.7 (C), 122.0 (CH), 125.0 (CH), 125.7 (C), 129.6 (CH), 136.6 (C), 140.6 (C), 155.7 (C), 159.0 (C), 170.9 (C); MS (FAB) m/z 375 (M^++2), 374 (M^++1), 373 (M^+), 318 (M^+−(CH_3)C), 175 (M^+−Boc–Val–CO); HRMS m/z [M^++H] calcd for $C_{20}H_{28}N_3O_4$ 374.2080, found 374.2079.

Acknowledgements

Foundation for the Science and Technology (FCT)—Portugal and FEDER (European Communautaire fund), for financial support through Centro de Química of Univ. Minho, Project POCI/QUI/59407/2004, for a post-doc. grant awarded to A.S.A. (SFRH/BPD/24548/2005) and for a Ph.D. grant awarded to R.C.C. (SFRH/BD/29274/2006) was acknowledged.

References and notes

1. (a) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888–3890; (b) Comins, D. L.; Nolan, J. M. *Org. Lett.* **2001**, *3*, 4255–4257.
2. Josien, H.; Curran, D. P. *Tetrahedron* **1997**, *53*, 8881–8886.
3. Thorsett, E. D.; Latimer, L. H. *Curr. Opin. Chem. Biol.* **2000**, *4*, 377–382.
4. Buchstaller, H.-P.; Siebert, C. D.; Steinmetz, R.; Frank, I.; Berger, M. L.; Gottschlich, R.; Leibrock, J.; Krug, M.; Steinhilber, D.; Noe, C. R. *J. Med. Chem.* **2006**, *49*, 864–871.
5. Freeman, G. A.; Andrews, C. W., III; Hopkins, A. L.; Lowell, G. S.; Schaller, L. T.; Cowan, J. R.; Gonzales, S. S.; Koszalka, G. W.; Hazen, R. J.; Boone, L. R.; Ferris, R. G.; Creech, K. L.; Roberts, G. B.; Short, S. A.; Weaver, K.; Reynolds, D. J.; Milton, J.; Ren, J.; Stuart, D. I.; Stammers, D. K.; Chan, J. H. *J. Med. Chem.* **2004**, *47*, 5923–5936.
6. Cortese, N. A.; Zielger, C. B.; Hrnjez, B. J.; Heck, R. F. *J. Org. Chem.* **1978**, *43*, 2953–2958.
7. Cho, C. S.; Kim, J. U. *Tetrahedron Lett.* **2007**, *48*, 3775–3778.
8. (a) Hecht, S. S.; Kenney, P. M. J.; Wang, M.; Trushin, N.; Agarwal, S.; Rao, A. V.; Upadhyaya, P. *Cancer Lett.* **1999**, *137*, 123–130; (b) Georgieva, M. C.; Konstantinov, S. M.; Berger, M. R. *Cancer Lett.* **2002**, *182*, 163–174.
9. (a) Palmer, C. J.; Josephs, J. L. *J. Chem. Soc., Perkin Trans. 1* **1995**, 3135–3152; (b) Kucherenko, A.; Flavin, M. T.; Boulanger, W. A.; Khilevich, A.; Shone, R. L.; Rizzo, J. D.; Sheinkman, A. K.; Xu, Z.-Q. *Tetrahedron Lett.* **1995**, *36*, 5475–5478.
10. Murata, C.; Masuda, T.; Todoroki, K.; Yoshida, H.; Nohta, H.; Yamaguchi, M.; Takadate, A. *Chem. Pharm. Bull.* **2005**, *53*, 750–758.
11. Jusinski, L. E.; Taatjes, C. A. *Rev. Sci. Instrum.* **2001**, *72*, 2837–2838.
12. Raviv, U.; Klein, J. *Polym. Adv. Technol.* **1998**, *9*, 825–830.
13. (a) Kadnikov, D. V.; Larock, R. C. *Org. Lett.* **2000**, *2*, 3643–3646; (b) Kadnikov, D. V.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 9423–9432.
14. Kadnikov, D. V.; Larock, R. C. *J. Org. Chem.* **2004**, *69*, 6772–6780.
15. Battistuzzi, G.; Bernini, R.; Cachi, S.; De Salve, I.; Fabrizi, G. *Adv. Synth. Catal.* **2007**, *349*, 297–302.
16. Battistuzzi, G.; Cachi, S.; De Salve, I.; Fabrizi, G.; Parisi, L. M. *Adv. Synth. Catal.* **2005**, *347*, 308–312.
17. Abreu, A. S.; Silva, N. O.; Ferreira, P. M. T.; Queiroz, M.-J. R. P.; Venanzi, M. *Eur. J. Org. Chem.* **2003**, 4792–4796.
18. Abreu, A. S.; Ferreira, P. M. T.; Queiroz, M.-J. R. P.; Ferreira, I. C. F. R.; Calhelha, R. C.; Estevinho, L. M. *Eur. J. Org. Chem.* **2005**, 2951–2957.
19. Abreu, A. S.; Castanheira, E. M. S.; Ferreira, P. M. T.; Queiroz, M.-J. R. P. *Tetrahedron* **2007**, *63*, 2215–2222.
20. For a recent review, see: Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633–9695.
21. (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127–2198; (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644–4680; (c) Kálai, T.; Jeko, J.; Berente, Z.; Hideg, K. *Synthesis* **2006**, *3*, 439–446.
22. Abreu, A. S.; Silva, N. O.; Ferreira, P. M. T.; Queiroz, M.-J. R. P. *Tetrahedron Lett.* **2003**, *44*, 3377–3379.
23. Molander, G. A.; Fumagalli, T. *J. Org. Chem.* **2006**, *71*, 5743–5747.
24. Abreu, A. S.; Ferreira, P. M. T.; Monteiro, L. S.; Queiroz, M.-J. R. P.; Ferreira, I. C. F. R.; Calhelha, R. C.; Estevinho, L. M. *Tetrahedron* **2004**, *60*, 11821–11828.
25. Silva, N. O.; Abreu, A. S.; Ferreira, P. M. T.; Monteiro, L. S.; Queiroz, M.-J. R. P. *Eur. J. Org. Chem.* **2002**, 2524–2528.
26. Ferreira, P. M. T.; Monteiro, L. S.; Pereira, M. G.; Ribeiro, L.; Sacramento, J.; Silva, L. *Eur. J. Org. Chem.* **2007**, 5934–5949.
27. Ferreira, P. M. T.; Maia, H. L. S.; Monteiro, L. S.; Sacramento, J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3697–3703.