Tetrahedron xxx (2016) 1–7

Contents lists available at ScienceDirect

Tetrahedron

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

Reactivity and regioselectivity in the acylation of 2,4-diaminoquinazolines

Elina Marinho, M. Fernanda Proença *

Chemistry Department, University of Minho, Campos de Gualtar, 4710-057 Braga, Portugal

ARTICLE INFO

Article history:
Received 5 May 2016
Received in revised form 1 June 2016
Accepted 2 June 2016
Available online xxx

Keywords:
4-Aminoquinazolines
Acylation
Anhydrides
Isocyanates
Acyl chlorides

ABSTRACT

2-(2-Aminophenyl)quinazoline-4-amines were selectively acylated at the phenylamino group by anhydrides, isocyanates or acyl chlorides, at room temperature. A similar selectivity was obtained in the reaction with ethoxymethylene derivatives and orthoesters. Acylation of the exocyclic imino substituent in the quinazolino-quinazoline tetracyclic structure also occurred under mild conditions with acetic anhydride and isocyanates. Hydrolysis to release the aniline substituent was performed with concd HCl (1 equiv at 60 °C) and with 3 M NaOH (3 equiv, rt), leading to the formylated derivative or cleaving the acyl group in the heterocyclic amine.

1. Introduction

The quinazoline nucleus is an important pharmacophore, with a vast range of applications. The therapeutic activity depends on the position and nature of the substituents in their skeleton[1] and includes, among others, sedative and hypnotics, anti-hypertensive, antipsychotic, anticancer, anti-diabetic, antimicrobial, analgesic, antiviral, anti-depressant, anti-inflammatory, antitubercular, or anticonvulsant activity.[2] The synthetic strategies to prepare different quinazoline derivatives and their biological properties have been extensively documented in reviews[2e,2f,3] and monographs.[4] Numerous methods are based on the use of anilines or *o*-functionalized nitrobenzene.[3a,5]

The amide bond can be considered one of the most important functional groups, widely present in natural products, bioactive compounds or in natural/man-made materials.[6] It is estimated that more than 25% of the drugs currently on the market contain the amide group.[7] Several representative medications containing both the quinazoline and amide scaffolds are exemplified in Fig. 1. Amides can be prepared from a wide variety of precursors by a range of different reaction pathways but classical methods are still the most commonly used procedures by the pharmaceutical industry. Traditionally, amides have been prepared from the reaction of amines with activated carboxylic acids,[7,8] aldehydes,[9] anhydrides,[10] alkynes,[11] esters,[12] or alcohols.[13] Some of these methods use metal catalysts such as ruthenium[12a,13a] or lanthanide[9a] complexes, nickel,[9b] copper,[9d] $FeCl_2$,[10b] and also *N*-heterocyclic carbene.[13a,14]

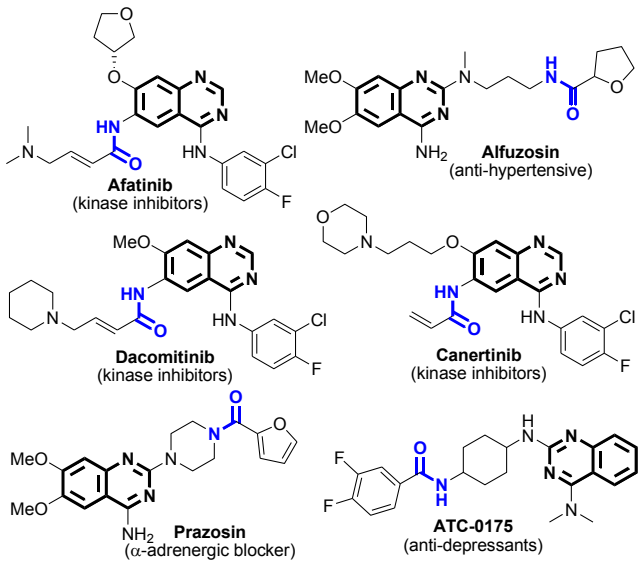


Fig. 1. Quinazoline-based bioactive compounds incorporating an amide unit.

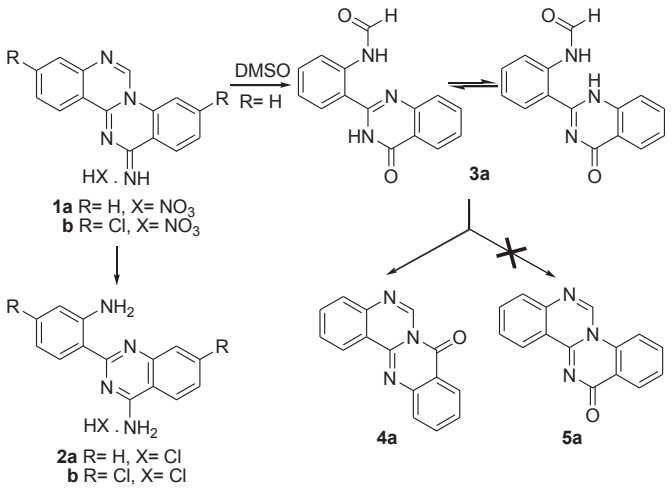
* Corresponding author. Tel.: +351 253 604379; fax: +351 253 604382; e-mail address: fproenca@quimica.uminho.pt (M.F. Proença).

http://dx.doi.org/10.1016/j.tet.2016.06.003
0040-4020/

In this work, a strategy was designed and implemented for the selective acylation of a substituted quinazoline incorporating two primary amines, one at the 4-position of the quinazoline nucleus and another in the aromatic substituent linked to the 2-position of the heterocycle. The high nucleophilicity of the aromatic amine when compared to the heterocyclic amine, makes it impossible to acylate the less reactive nitrogen atom without affecting the other amine function. These studies aimed at the selective acylation of each of these amino groups, maintaining the second primary amine available for further chemical transformations.

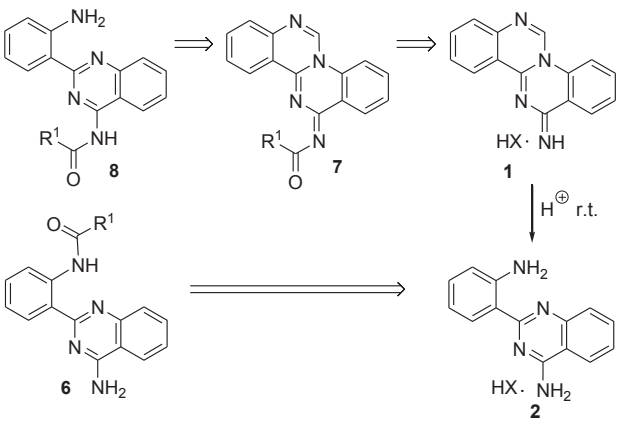
2. Results and discussion

Quinazolino[3,4-*a*]quinazolines **1** (Scheme 1), used as starting material, were easily prepared by a one-pot reaction involving anthranilonitriles and triethyl orthoformate in the presence of acid, following a procedure previously developed in our group.[15] Compound **1** was used as a precursor for 2-(2-amino)quinazolines **2**, isolated in excellent yield from methanol and hydrochloric acid, at room temperature.[16] Changing the solvent to DMSO and refluxing the solution for 5, 15 or 20 min, led to the formation of compound **4a** in 87–92%. This compound was erroneously identified as **5a** in our previous work,[15] but we could now isolate its precursor **3a**, slightly contaminated with **4a** (ca. 60% yield), when the solution of **1a** in DMSO was refluxed for one minute only. In the ^{1}H NMR spectrum of compound **3a** (0.006 M DMSO solution at 20 °C), besides the formyl proton (δ 8.36 ppm) and the corresponding N–H signal (δ 12.45 ppm) two broad singlets at δ 10.85 and 10.66 ppm (in a 3:1 molar ratio and integrating for a total of one proton) were assigned to each possible tautomer of the heterocyclic N–H. Compound **3a** was unstable in solution and progressively evolved to the cyclic structure **4a**.



Scheme 1. Ring-opening of compound **1**.

Studies on the reactivity of compounds **1** and **2**, in particular the acylation by anhydrides, isocyanates or ethyl chloroformate was expected to allow the regioselective formation of amides **6** or **8** from the exocyclic amino groups. The retrosynthetic analysis presented in Scheme 2 summarizes the strategy that was used for the synthetic approach: the more nucleophilic amino group of the aromatic ring in compound **2** would be acylated under mild conditions while the less reactive heteroaromatic amino substituent could be acylated in the tetracyclic structure **1**. Hydrolysis of **7** would release the aromatic amine leading to **8** and allowing further transformations of this more reactive nucleophile.



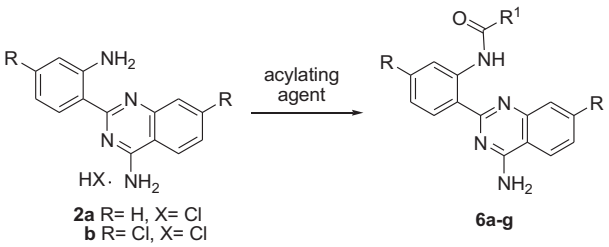
Scheme 2. Retrosynthetic approach for the regioselective acylation of quinazoline **2**.

Table 1 summarizes the selected experimental conditions for the monoacylation of 2-(2-aminophenyl)quinazolin-4-amine **2**, used as the hydrochloride.

Quinazolines **2a**,**b** were reacted with a eightfold excess of acetic anhydride in the presence of triethylamine (1 or 1.5 molar equivalents). Compounds **6a** and **6b** were isolated in 89% and 63% yield after, respectively, 1 h and 2 h at room temperature (Table 1, entries 1 and 2).

The reaction of **2a** with succinic anhydride was carried out in acetonitrile. The reagents were combined in a 1:2 molar ratio, in the presence of triethylamine. The product **6c** was isolated in 68% yield after 1 day at room temperature (entry 3). Similar experimental conditions were used for the reaction of **2a** with maleic anhydride (entry 4) with the immediate formation of **6d**, isolated in 79% yield. The use of ethanol as solvent also led to a very fast reaction, giving the same product in 73% yield.

Table 1
Selected experimental conditions for the reaction of compound **2** with anhydrides, isocyanates and ethyl chloroformate



Entry	Reagents (equiv)	Reactions conditions	R	R^1	Product (yield)
1	**2a**, Ac_2O (1:8)	NEt_3 (1 equiv), rt, 1 h	H	Me	**6a** (89%)
2	**2b**, Ac_2O (1:8)	NEt_3 (1.5 equiv), rt, 2 h	Cl	Me	**6b** (63%)
3	**2a**, succinic anhydride (1:2)	CH_3CN, NEt_3 (1 equiv), rt, 1 day	H	$CH_2CH_2CO_2H$	**6c** (68%)
4	**2a**, maleic anhydride (1:2)	CH_3CN, NEt_3 (1 equiv), rt, 1 min	H	$CH{=}CHCO_2H$	**6d** (79%)
5	**2a**, ClCOOEt (1:2)	CH_3CN, NEt_3 (1.5 equiv), rt, 8 h	H	OEt	**6e** HCl (74%)
6	**2a**, ClCOOEt (1:2)	CH_3CN, NEt_3 (3 equiv), rt, 8 h	H	OEt	**6e** (71%)
7	**2a**, C_6H_5NCO (1:1.2)	CH_3CN, NEt_3 (1.2 equiv), rt, 15 min	H	NHC_6H_5	**6f** (91%)
8	**2a**, $C_6H_{11}NCO$ (1:1.2)	CH_3CN, NEt_3 (1.2 equiv), rt, 10 min	H	NHC_6H_{11}	**6g** (52%)

Please cite this article in press as: Marinho, E.; Proença, M. F., Tetrahedron (2016), http://dx.doi.org/10.1016/j.tet.2016.06.003

The reaction of compound **2a** with ethyl chloroformate (1:2 molar ratio) was also performed in acetonitrile and triethylamine, at room temperature. The pure product was isolated after 8 h at room temperature and the amount of triethylamine that was used (1.5 or 3 molar equivalents) resulted in the hydrochloride of **6e** (74%), or the neutral species **6e** (71%), respectively (entries 5 and 6). The reaction with isocyanates (1.2 equiv) was also performed at room temperature and in the presence of triethylamine (1.2 equiv). The product was isolated after 15 min (**6f**, 91%, entry 7) or 10 min (**6g**, 52%, entry 8).

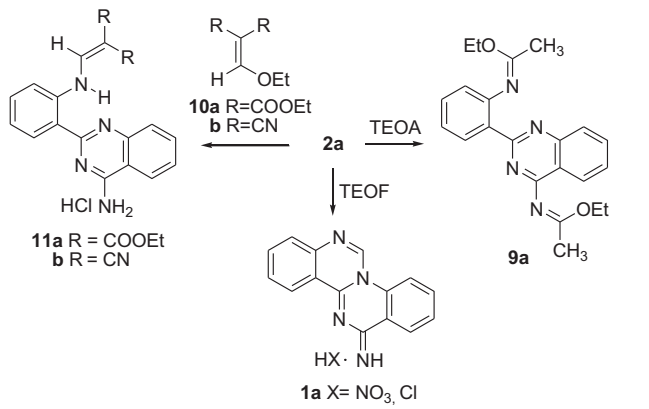
Attempts to induce intramolecular cyclization in **6a** by stirring an ethanolic solution of this compound with nitric acid, at room temperature, failed to lead to the substituted tetracyclic derivative. After one day, only the nitrate of the starting material was isolated in 94% yield. These conditions were previously used to generate compound **1** from the formyl derivative **6** (R^1=H).[16]

The acetimidate **9a** was also prepared (Table 2, entry 1) but the product could only be isolated in good yield (86%) when **2a** was reacted with a large excess of triethyl orthoacetate (TEOA) and the mixture was refluxed for 4.5 h. Decreasing the reaction time to one hour resulted in a decrease in the isolated yield of this product to 52%. An experiment to test the possibility of intramolecular cyclization was performed in the NMR tube, by adding nitric acid to a solution of **9a** in deuterated DMSO, at room temperature. The formation of compound **2a** was immediately detected and after 6 days the starting material completely evolved to this product.

The reaction of **2a** with 2 equiv of triethyl orthoformate (TEOF), led to the tetracyclic structure **1a**, isolated as the hydrochloride, after 15 h at room temperature (entry 2). The use of 1 equiv of TEOF and nitric acid, followed by reflux (1 day) led to the same product **1a**, isolated as the nitrate (entry 3).

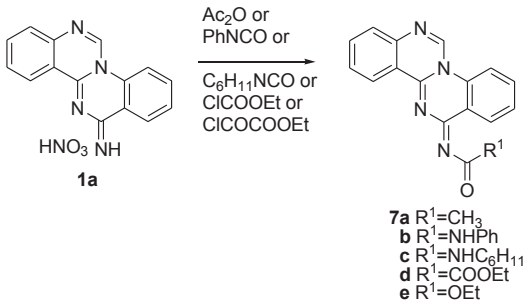
Ethoxymethylene compounds are known to react smoothly with amines, and this functional group can mimic the aldehyde, with elimination of the active methylene moiety, without the assistance of catalysts.[17] The aminomethylene derivatives **11a** and **11b** (Table 2) were prepared by combining the corresponding reagents in ethanol at 55 °C (3 days) or at 50 °C (4 days), respectively (entries 4 and 5). There was no evidence for the formation of the cyclic product under these experimental conditions.

Table 2
Selected experimental conditions for the reaction of **2a** with ethoxymethylene compounds and orthoesters



Entry	Reagents (equiv)	Conditions	Product (yield)
1	**2a**, TEOA (1:25)	Reflux, 4.5 h	**9a** (86%)
2	**2a**, TEOF (1:2)	rt, 15 h	**1a** HCl (79%)
3	**2a**, TEOF (1:1)	HNO_3, reflux, 1 day	**1a** HNO_3 (85%)
4	**2a**, **10a** (1:1)	EtOH, 55 °C, 3 days	**11a** (65%)
5	**2a**, **10b** (1:1.2)	EtOH, 50 °C, 4 days	**11b** (63%)

The presence of the exocyclic imine nitrogen in **1a** was previously reported to lead to **7a**–**b**[15] in acetic anhydride or phenyl isocyanate, respectively, at room temperature in the presence of triethylamine (Scheme 3). In this work, compound **1a** was further reacted with cyclohexylisocyanate (1:3 molar ratio), and 1.2 equiv of triethylamine. The product **7c** was isolated in 90% yield after two daysat 50 °C.

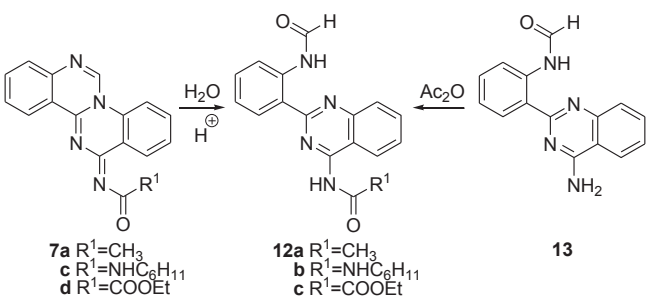


Scheme 3. Reaction of compound **1a** with acylating agents.

The reaction with ethyl chlorooxalate (2 equiv) was initially carried out using 2 equiv of triethylamine at room temperature. After 10 min, the solid isolated was a mixture of the hydrochloride of **1a** and the product **7d**. Increasing the amount of triethylamine (3 equiv) and the reaction time to 55 min, led to the pure product **7d** in 84% yield.

The reaction with ethyl chloroformate was initially performed from the nitrate of **1a**, in acetonitrile. An excess of the acylating agent was always used (3, 4.5 and 6 equiv) together with the same amount of triethylamine or pyridine, at room temperature or in an ice bath. The unreacted reagent **1a** was always isolated in 70–96% yield after 15 min to 5 days. The product **7e** could only be isolated from a solution of the neutral compound **1a** in a 1:1 mixture of ethanol:water, upon addition of 2 equiv of ethyl chloroformate, at room temperature. Immediate isolation of the solid product resulted in only 14% yield but increasing the reaction time to 15 min further decreased the yield to 10%. In both cases, the solid that precipitated from the mother liquor was identified as a complex mixture.

The possibility to open the pyrimidine ring in compound **7** maintaining the acyl group in the exocyclic amine was initially tested for compound **7a** (R^1=CH_3), in water and in the presence of 1 equiv of TFA. After 17 h at room temperature, the solid product was identified as **12a** (isolated quantitatively) (Scheme 4). Decreasing the reaction time to 8 h led to the same product in 93% yield. Increasing the acid strength (conc. HCl, 1 equiv) with warming at 60 °C for 1 h led also to **12a** (85%). The structure of compound **12a** was further confirmed by its synthesis from **13** in the presence of an eightfold excess of acetic anhydride in acetonitrile and 1 equiv of triethylamine. After three days at 50 °C, when



Scheme 4. Acid-catalyzed hydrolysis of compounds **7a**, **7c** and **7e**.

the starting material was no longer identified by TLC, the product **12a** was isolated in 83% yield.

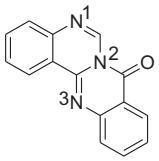
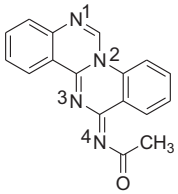
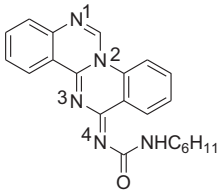
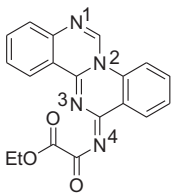
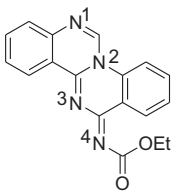
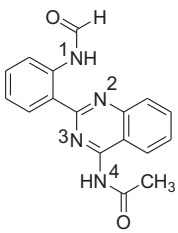
Hydrolysis of **7c** and **7d** was performed under similar reaction conditions (1 equiv of concd HCl) and the corresponding products **12b** and **12c** were quantitatively isolated after one hour at 60 °C.

Cleavage of the formyl group, maintaining the acyl moiety, was attempted in base, considering that acidic conditions failed to achieve this goal. When a suspension of **12a** in 3 M of NaOH was stirred at room temperature, the solid isolated after 18 h was identified as product **13** (87%). In this case, cleavage of the acetyl group was occurring preferably.

Considering that this experiment failed to generate the desired product, the evolution of compound **12a** was followed by ^{1}H NMR spectroscopy, in acid medium. A solution of **12a** (3.4 mg) in DMSO-d_6 (600 μL) and TFA (5 μL), was kept at room temperature for 19 h. As the reaction mixture was stable under these conditions, the NMR tube was warmed at 60 °C. After 19 h, the presence of a mixture of compounds **12a**, **2a**, acetic acid (δ_H 1.90 ppm) and formic acid (δ_H 8.12 ppm) in a 1.5:0.4:1.5:0.4 ratio could be identified. After seven days, the evolution to compound **2a** (present in the protonated form) was complete and remained stable after 14 days. This study showed that heating in the presence of acid does not allow the selective cleavage of the formyl group.

All compounds were characterized by the usual analytical and spectroscopic techniques and a selection was also studied by ^{15}N/^{1}H HMBC correlation spectra (Table 3). All the tetracyclic compounds **7** exhibit high chemical shifts (δ 210.7–257.5 ppm) for the N1 and N3 nitrogen atoms and a considerably lower chemical shift was assigned to N2 (δ 159.0–164.9 ppm). A similar pattern was observed for compound **4a**, but in this case N3 shows a chemical shift of δ 184.2 ppm, approximately 25 ppm higher when compared to the same N atom in compounds **7**. This is likely to reflect the electron-withdrawing effect of the adjacent carbonyl group, absent in the analogous tetracyclic compounds. For the bicyclic structure **12a**, the chemical shift of N2 and N3 is compatible with the presence of an aromatic pyrimidine system and that of N1 and N2 confirm their incorporation in the amide bond.

Table 3
Data for ^{15}N chemicals shifts by HMBC correlation to ^{1}H NMR signals, obtained in DMSO-d_6 solution

Compound		δ N_1	δ N_2	δ N_3	δ N_4
	**4a**	256.56	184.23	221.75	—
	**7a**	251.65	160.21	210.70	273.90
	**7c**	—	159.03	—	—
	**7d**	257.50	164.90	—	—
	**7e**	—	160.82	—	—
	**12a**	134.96	264.54	245.15	138.56

3. Conclusions

In summary, the diaminoquinazoline **2** was selectively acylated in the aromatic amino group by anhydrides, isocyanates and acyl chlorides. The reaction is equally selective with orthoesters and ethoxymethylene cyanoacetate or malononitrile. The products were isolated in 52–91% yield by simple filtration from the reaction medium. Intramolecular cyclization of the acylated derivatives was never observed. The less nucleophilic imine nitrogen in the tetracyclic quinazoline **1** was also acylated in 84–90% yield by reaction with acetic anhydride or isocyanates. The reaction with ethyl chloroformate required an extensive search for the most convenient experimental conditions and the isolated yield of the acylated product never exceeded 14%. Hydrolysis of the modified quinazoline **1** to release the aromatic amino group was attempted in aqueous HCl and in NaOH leading only to the formylated amine with eventual cleavage of the acyl substituent in the heterocyclic amine or the recovery of the starting diaminoquinazoline **2**.

4. Experimental section

4.1. General methods

All compounds were fully characterized by elemental analysis and spectroscopic data. The NMR spectra were recorded at room temperature, on a Varian Unity Plus (1H: 300 MHz, 13C: 75 MHz), or on a Bruker Avance III 400 (1H: 400 MHz, 13C: 100 MHz) including the 1H–13C and 1H–15N correlation spectra (HMQC and HMBC). Deuterated DMSO was used as solvent. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet and br, broad. The coupling constants J, are reported in hertz (Hz). IR spectra were recorded on a FTIR Bomem MB 104 using Nujol mulls and NaCl cells. All reactions were monitored by thin layer chromatography (TLC) using silica gel 60 F254 (Merck). The melting points were determined on a Stuart SMP3 melting point apparatus and are uncorrected. Elemental analyses were performed on a LECO CHNS-932 instrument.

4.2. Synthesis of *N*-(2-(4-oxo-3,4-dihydroquinazolin-2-yl) phenyl) formamide 3a

DMSO (100 μL) was added to the nitrate of 13*H*-quinazoline[3,4-*a*]quinazolin-13-imine **1a** (0.04 g; 0.12 mmol) and the reaction

mixture was refluxed for 1 min. The white solid that precipitated after addition of water was filtered and washed with water. The product (0.02 g) was identified by ^{1}H NMR as *N*-(2-(4-oxo-3,4-dihydroquinazolin-2-yl)phenyl) formamide **3a** slightly contaminated with **4a**. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.45 (br s, 1H), 10.85 (br s, 0.75H), 10.66 (br s, 0.25H), 8.36 (s, 1H), 8.32 (d, J=8.0 Hz, 1H), 8.16 (dd, J=1.2, 8.0 Hz, 1H), 7.84 (td, J=1.2, 8.0 Hz, 1H), 7.79 (td, J=1.2, 8.0 Hz, 1H), 7.78 (d, J=8.0 Hz, 1H), 7.74 (d, J=8.0 Hz, 1H), 7.54 (td, J=1.2, 8.0 Hz, 1H), 7.52 (td, J=1.2, 8.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.12, 160.40, 152.51, 147.99, 136.30, 134.51, 134.38, 131.17, 129.72, 127.38, 126.83, 125.70, 122.48, 122.48, 121.55. IR (Nujol mull): 3180, 1650, 1609, 1579, 1528 cm^{-1}.

4.3. General procedure for the synthesis of amides 6a–d

A yellow suspension of compound **2a**, triethylamine (1–3 M equiv) and anhydride (2–8 M equiv), in acetonitrile or without solvent was stirred at room temperature for 5 min (**6d**), 50 min (**6a**), 2 h (**6b**) or 1 day (**6c**). The solid was filtered and washed with water, leading to the pure product.

*4.3.1. N-[2-(4-Aminoquinazolin-2-yl)phenyl] acetamide **6a**.* White solid, 89%. Mp 229–231 °C. IR (Nujol mull) 3400, 3317, 3213, 1671, 1645, 1627, 1604, 1589, 1578, 1544, 1504 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.63 (s, 1H), 8.61 (d, J=1.5 Hz, 1H), 8.57 (d, J=8.4 Hz, 1H), 8.30 (d, J=8.1 Hz, 1H), 8.12 (br s, 2H), 7.83 (t, J=7.2 Hz, 1H), 7.77 (d, J=7.2 Hz, 1H), 7.53 (td, J=1.5, 8.4 Hz, 1H), 7.42 (td, J=1.5, 8.4 Hz, 1H), 7.15 (td, J=1.5, 8.1 Hz, 1H), 2.24 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.19, 161.58, 160.61, 148.39, 139.84, 133.64, 130.82, 130.36, 126.95, 125.94, 123.78, 122.89, 122.10, 119.65, 112.68, 25.26. Anal. Calcd for $C_{16}H_{14}N_4O\cdot0.6H_2O$: C, 66.46; H, 5.31; N, 19.38. Found: C, 66.69; H, 5.36; N, 19.14.

*4.3.2. N-[2-(4-Amino-7-chloroquinazolin-2-yl)-5-chlorophenyl]acetamide **6b**.* White solid, 63%. Mp>300 °C. IR (Nujol mull) 3445, 3332, 3204, 1667, 1650, 1619, 1600, 1589, 1576, 1544, 1536 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.31 (s, 1H), 8.64 (d, J=2.1 Hz, 1H), 8.57 (d, J=8.7 Hz, 1H), 8.29 (d, J=8.7 Hz, 1H), 8.10 (br s, 2H), 7.79 (t, J=1.8 Hz, 1H), 7.55 (dd, J=2.1, 8.7 Hz, 1H), 7.20 (dd, J=2.1, 8.7 Hz, 1H), 2.26 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ=168.59, 161.25, 160.72, 148.38, 140.60, 138.14, 135.31, 131.90, 126.15, 125.69, 125.57, 121.80, 121.31, 118.89, 111.25, 25.02. Anal. Calcd for $C_{16}H_{12}N_4O\cdot0.3H_2O$: C, 54.49; H, 3.61; N, 15.89. Found: C, 54.51; H, 3.62; N, 15.92.

*4.3.3. 4-{[2-(4-Aminoquinazolin-2-yl)phenyl] amino}-4-oxobutanoic acid **6c**.* White solid, 68%. Mp 214–216 °C. IR (Nujol mull) 3411, 3337, 3245, 1770, 1719, 1665, 1648, 1611, 1579, 1536, 1505 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.72 (br s, 1H), 12.13 (s, 1H), 8.60 (dd, J=1.2, 8.4 Hz, 1H), 8.57 (d, J=8.4 Hz, 1H), 8.29 (d, J=8.4 Hz, 1H), 8.09 (br s, 2H), 7.85 (td, J=1.2, 8.4 Hz, 1H), 7.78 (d, J=8.4 Hz, 1H), 7.54 (td, J=1.2, 8.4 Hz, 1H), 7.42 (td, J=1.2, 8.4 Hz, 1H), 7.15 (td, J=1.2, 8.0 Hz, 1H), 2.78 (t, J=6.9 Hz, 2H), 2.60 (t, J=6.9 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.74, 169.99, 161.60, 160.62, 148.36, 139.80, 133.61, 130.83, 130.36, 126.85, 125.93, 123.72, 122.86, 122.04, 119.65, 112.68, 32.31, 28.92. Anal. Calcd for $C_{18}H_{16}N_4O_3\cdot1/3H_2O$: C, 63.14; H, 4.92; N, 16.37. Found: C, 63.16; H, 4.70; N, 16.25.

*4.3.4. 4-{[2-(4-Aminoquinazolin-2-yl)phenyl] amino}-4-oxobut-2-enoic acid **6d**.* Yellow solid, 79%. Mp 190–193 °C. IR (Nujol mull) 3472, 3324, 3224, 1775, 1626, 1602, 1575, 1539 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.08 (br s, 1H), 13.09 (s, 1H), 8.64 (dd, J=1.2, 8.0 Hz, 1H), 8.61 (d, J=8.0 Hz, 1H), 8.27 (d, J=8.0 Hz, 1H), 8.10 (br s, 2H), 7.83 (td, J=1.2, 8.4 Hz, 1H), 7.71 (d, J=8.0 Hz, 1H), 7.53 (td, J=1.2, 8.0 Hz, 1H), 7.47 (td, J=1.2, 8.0 Hz, 1H), 7.22 (td, J=1.2, 8.4 Hz, 1H), 6.73 (d, J=12 Hz, 1H), 6.37 (d, J=12 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ=166.66, 163.36, 161.63, 160.39, 148.12, 139.35, 133.83, 129.07, 133.63, 130.99, 130.39, 126.79, 126.05, 123.70, 123.17, 122.88, 119.97, 112.70. Anal. Calcd for $C_{18}H_{14}N_4O_3\cdot0.25H_2O$: C, 63.80; H, 4.32; N, 16.54. Found: C, 63.85; H, 4.14; N, 16.54.

4.4. General procedure for the synthesis of carbamate 6e

Ethylchloroformate (2 M equiv) was added to a suspension of compound **2a** in acetonitrile (1 mL). After 20 min, triethylamine (1.5–3 M equiv) was added to the mixture. The reaction mixture was stirred at room temperature for 8 h. The solid was filtered and washed with acetonitrile, leading to the pure product.

*4.4.1. Ethyl [2-(4-aminoquinazolin-2-yl)phenyl] carbamate hydrochloride **6e**.* Beige solid, 74%. Mp>300 °C. IR (Nujol mull) 3264, 3056, 1734, 1654, 1630, 1608, 1590, 1569, 1537 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 14.18 (s, 1H), 9.83 (br s, 2H), 9.64 (br s, 1H), 8.55 (d, J=8.4 Hz, 1H), 8.03 (td, J=1.2, 8.4 Hz, 1H), 7.92 (d, J=8.4 Hz, 1H), 7.85 (d, J=8.4 Hz, 1H), 7.83 (d, J=8.4 Hz, 1H), 7.73 (td, J=8.4 Hz, 1H), 7.60 (td, J=1.2, 8.4 Hz, 1H), 7.29 (td, J=8.4 Hz, 1H), 4.01 (q, J=7.2 Hz, 2H), 1.12 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.19, 158.87, 153.81, 140.36, 137.39, 136.16, 132.32, 130.71, 127.89, 124.96, 123.33 (2C), 121.93, 120.08, 111.45, 60.68, 14.47. Anal. Calcd for $C_{17}H_{17}N_4O_2Cl.0\cdot2H_2O$: C, 58.60; H, 5.04; N, 16.08. Found: C, 58.37; H, 5.05; N, 16.34.

*4.4.2. Ethyl [2-(4-aminoquinazolin-2-yl)phenyl] carbamate **6e**(free base).* Pink solid, 71%. Mp 175–178 °C. IR (Nujol mull) 3440, 3343, 3252, 1707, 1650, 1624, 1596, 1578, 1547, 1501 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.35 (s, 1H), 8.60 (dd, J=1.2, 8.1 Hz, 1H), 8.32 (dd, J=1.2, 8.1 Hz, 1H), 8.28 (dd, J=1.2, 8.4 Hz, 1H), 8.08 (br s, 2H), 7.85 (td, J=1.2, 8.1 Hz, 1H), 7.66 (dd, J=1.2, 8.1 Hz, 1H), 7.53 (td, J=1.2, 8.1 Hz, 1H), 7.44 (td, J=1.2, 8.1 Hz, 1H), 7.11 (td, J=1.2, 8.1 Hz, 1H), 4.18 (q, J=7.2 Hz, 2H), 1.29 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 161.65, 160.66, 153.37, 148.12, 139.96, 133.70, 131.05, 130.43, 126.51, 125.97, 123.78, 122.40, 121.35, 118.22, 112.72, 60.32, 14.54. Anal. Calcd for $C_{17}H_{16}N_4O_2\cdot0.4H_2O$: C, 64.70; H, 5.38; N, 17.76. Found: C, 64.62; H, 5.09; N, 17.49.

4.5. General procedure for the synthesis of ureas 6f and 6g

Isocyanate (1.2 M equiv) and triethylamine (1.2 M equiv) were added to a suspension of compound **2a** in acetonitrile. The reaction mixture was stirred at room temperature for 10 min (**6g**) or 15 min (**6f**). The solid was filtered and washed with water, leading to the pure product.

*4.5.1. 1-[2-(4-Aminoquinazolin-2-yl)phenyl]-3-phenylurea **6f**.* White solid, 91%. Mp 240–242 °C. IR (Nujol mull) 3498, 3391, 3286, 1659, 1650, 1611, 1595, 1548 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.57 (s, 1H), 9.48 (s, 1H), 8.58 (dd, J=1.2, 8.0 Hz, 1H), 8.27 (d, J=8.0 Hz, 1H), 8.21 (d, J=8.0 Hz, 1H), 8.09 (br s, 2H), 7.94 (d, J=8.0 Hz, 1H), 7.82 (td, J=1.2, 8.0 Hz, 1H), 7.55 (dd, J=1.2, 8.8 Hz, 2H), 7.52 (t, J=8.0 Hz, 1H), 7.40 (td, J=2.0, 8.0 Hz, 1H), 7.28 (td, J=1.2, 8.4 Hz, 2H), 7.08 (td, J=1.2, 8.0 Hz, 1H), 6.98 (td, J=1.2, 8.4 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.44, 160.54, 152.52, 149.00, 140.54, 140.00, 133.28, 130.34, 130.29, 128.60 (2C), 127.67, 125.65, 123.50, 123.32, 121.95, 120.86, 120.82, 119.09 (2C), 112.60. Anal. Calcd for $C_{21}H_{17}N_5O\cdot0.1H_2O$: C, 70.60; H, 4.87; N, 19.61. Found: C, 70.57; H, 4.92; N, 19.43.

*4.5.2. 1-(2-(4-Aminoquinazolin-2-yl)phenyl)-3-cyclohexylurea **6g**.* Yellow solid, 52%. Mp 202–204 °C. IR (Nujol mull) 3490, 3299, 3179, 1630, 1569, 1545, 1503 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.00 (s, 1H), 8.49 (dd, J=1.6, 8.0 Hz, 1H), 8.23 (d, J=8.0 Hz, 1H), 8.20 (d, J=8.0 Hz, 1H), 8.05 (s, 2H), 7.94 (d, J=8.0 Hz, 1H), 7.81 (td, J=1.6, 8.0 Hz, 1H), 7.50 (td, J=1.6, 8.0 Hz, 1H), 7.31 (td, J=1.6, 8.0 Hz,

Please cite this article in press as: Marinho, E.; Proença, M. F., Tetrahedron (2016), http://dx.doi.org/10.1016/j.tet.2016.06.003

1H), 6.98 (td, *J*=1.6, 8.0 Hz, 1H), 6.94 (d, *J*=8.4 Hz, 1H), 3.46–3.53 (m, 1H), 1.83–1.88 (m, 2H), 1.69–1.72 (m, 2H), 1.56–1.62 (m, 1H), 1.21–1.33 (m, 5H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.36, 160.75, 154.45, 149.18, 141.38, 133.29, 130.28, 130.25, 127.73, 125.56, 123.50, 122.69, 120.31, 119.99, 112.54, 48.39, 33.36 (2C), 25.37, 24.92 (2C). Anal. Calcd for $C_{21}H_{23}N_5O$: C, 69.77; H, 6.46; N, 19.38. Found: C, 69.82; H, 6.46; N, 19.32.

4.6. Synthesis of *N*-[13*H*-quinazolino[3,4-*a*]quinazolin-13-ylidene] cyclohexylurea 7c

Cyclohexylisocyanate (0.11 g; 0.87 mmol; 115 μL; 3 M equiv) and triethylamine (1.2 M equiv) were added to a yellow suspension of compound **2a** (0.09 g; 0.29 mmol) in acetonitrile (2 mL). The reaction mixture was stirred at 50 °C. After 2 days, the reaction was complete by TLC. The white solid was filtered and washed with water leading to the pure product *N*-[13*H*-quinazolino[3,4-*a*]quinazolin-13-ylidene] cyclohexylurea **7c** The presence of the exocyclic imine nitrogen in **1a** was previously reported to lead to **7a**–**b**[15] in acetic anhydride or phenyl isocyanate, respectively, at room temperature in the presence of triethylamine (Scheme 3). In this work, compound **1a** was further reacted with cyclohexylisocyanate (1:3 molar ratio), and 1.2 equiv of triethylamine. The product **7c** was isolated in 90% yield after two days at 50 °C. 3277, 1635, 1604, 1545, 1521 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.39 (s, 1H), 8.42 (dd, *J*=1.2, 8.0 Hz, 1H), 8.41 (d, *J*=8.0 Hz, 1H), 8.20 (dd, *J*=1.2, 8.0 Hz, 1H), 7.87 (td, *J*=1.2, 8.0 Hz, 1H), 7.81 (td, *J*=1.6, 8.0 Hz, 1H), 7.75 (d, *J*=8.0 Hz, 1H), 7.65 (td, *J*=1.2, 8.0 Hz, 1H), 7.61 (t, *J*=8.0 Hz, 1H), 6.96 (d, *J*=8.4 Hz, 1H), 3.56–3.63 (m, 1H), 1.88–1.91 (m, 2H), 1.70–1.73 (m, 2H), 1.54 (m, 1H), 1.12–1.31 (m, 5H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.38, 150.48, 146.37, 144.02, 139.48, 135.06, 134.55, 132.84, 128.41, 128.08, 127.25, 126.47, 125.80, 120.61, 119.30, 115.32, 48.30, 32.90, 25.36, 24.72. Anal. Calcd for $C_{22}H_{21}N_5O$: C, 71.13; H, 5.71; N, 18.86. Found: C, 71.31; H, 5.86; N, 19.01.

4.7. Synthesis of ethyl oxo[13*H*-quinazolino[3,4-*a*]quinazolin-13-ylideneamino]acetate 7d

Triethylamine (185 μL; 3 M equiv) was added to a yellow suspension of compound **1a** (0.11 g, 0.44 mmol) in acetonitrile (1 mL) followed by ethyl chlorooxalate (0.12 g; 0.88 mmol; 100 μL; 2 M equiv). The beige suspension was stirred at room temperature. After 40 min, the TLC show absence of starting material, and the yellow solid precipitate was filtered and washed with a mixture of water and acetonitrile. The product was identified as ethyl oxo [13*H*-quinazolino[3,4-*a*]quinazolin-13-ylideneamino] acetate **7d** (0.13 g; 0.37 mmol; 84%). Mp 224–226 °C. IR (Nujol mull): 1731, 1650, 1623, 1595, 1565, 1541, 1509 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.73 (s, 1H), 8.69 (d, *J*=8.0 Hz, 1H), 8.47 (dd, *J*=1.2, 8.0 Hz, 1H), 8.41 (dd, *J*=1.2, 8.0 Hz, 1H), 7.98–8.05 (m, 2H), 7.90 (d, *J*=8.0 Hz, 1H), 7.77–7.81 (m, 2H), 4.15 (q, *J*=7.2 Hz, 2H), 1.14 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ=172.19, 163.02, 158.12, 147.73, 144.42, 139.27, 135.64, 135.27, 134.70, 129.10, 129.04, 127.59, 127.46, 126.18, 120.12, 117.97, 116.10, 61.17, 13.88. Anal. Calcd for $C_{19}H_{14}N_4O_3$: C, 65.88; H, 4.08; N, 16.18. Found: C, 65.93; H, 4.08; N, 16.15.

4.8. Synthesis of ethly *N*-[13*H*-quinazolino[3,4-*a*]quinazolin-13-ylidene]carbamate 7e

Ethyl chloroformate (0.05 g; 0.42 mmol; 40 μL; 2 M equiv) was added to a yellow suspension of compound **1a** (0.05 g; 0.21 mmol) in water:ethanol (1:1.1 mL). The mixture was stirred at room temperature leading immediately to a homogeneous solution and shortly after, to a white solid precipitate. The solid was filtered and washed with water–ethanol to give ethyl *N*-[13*H*-quinazolino[3,4-a]quinazolin-13-ylidene]carbamate **7e** (0.01 g; 0.03 mmol; 14%). Mp 248–250 °C. A second crop was isolated from the mother liquor and identified as a complex mixture. IR (Nujol mull): 1695, 1630, 1601, 1543 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.47 (s, 1H), 8.47 (d, *J*=8.4 Hz, 1H), 8.45 (d, *J*=8.4 Hz, 1H), 8.21 (dd, *J*=1.2, 8.4 Hz, 1H), 7.92 (td, *J*=1.2, 8.4 Hz, 1H), 7.88 (td, *J*=1.2, 8.4 Hz, 1H), 7.80 (d, *J*=8.4 Hz, 1H), 7.65–7.72 (m, 2H), 4.22 (q, *J*=7.2 Hz, 2H), 1.30 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ=163.70, 152.96, 147.61, 144.35, 139.55, 135.59, 135.22, 133.89, 129.01, 128.75, 127.60, 126.77, 126.12, 120.47, 118.50, 115.87, 61.24, 14.83. Anal. Calcd for $C_{18}H_{14}N_4O_2$: C, 67.90; H, 4.44; N, 17.60. Found: C, 68.01; H, 4.51; N, 17.79.

4.9. Synthesis of ethyl *N*-[2-(2-{[1-ethoxyethylidene]amino} phenyl)quinazolin-4-yl]ethanimidoate 9a

Triethyl orthoacetate (1 mL) was added 2-(2-aminophenyl) quinazolin-4-amine hydrochloride **2a** (0.06 g; 0.22 mmol). The reaction mixture was refluxed for 4.5 h. Partial removal of the liquid reagent in the rotary evaporator led to a solid precipitate. The dark yellow solid was identified as ethyl *N*-[2-(2-{[1-ethoxyethylidene] amino}phenyl)quinazolin-4-yl] ethanimidoate **9a** (0.07 g; 0.19 mmol; 86%). Mp 108–110 °C. IR (Nujol mull) 1692, 1666, 1615, 1598, 1567, 1542 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.02 (dd, *J*=1.2, 8.0 Hz, 1H), 7.92 (td, *J*=1.2, 8.0 Hz, 1H), 7.88 (dd, *J*=1.2, 8.0 Hz, 1H), 7.84 (dd, *J*=1.2, 8.0 Hz, 1H), 7.61 (td, *J*=1.2, 8.0 Hz, 1H), 7.38 (td, *J*=1.2, 8.0 Hz, 1H), 7.13 (td, *J*=1.2, 8.0 Hz, 1H), 6.79 (dd, *J*=1.2, 8.0 Hz, 1H), 4.39 (q, *J*=7.2 Hz, 2H), 4.00 (q, *J*=7.2 Hz, 2H), 1.97 (s, 3H), 1.79 (s, 3H), 1.37 (t, *J*=7.2 Hz, 3H), 1.08 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 165.41, 163.77, 161.69, 160.47, 150.74, 148.21, 133.95, 130.87, 130.25, 130.02, 127.66, 126.99, 124.92, 122.23, 121.85, 117.14, 60.62, 60.77, 17.17, 17.14, 14.00. Anal. Calcd for $C_{22}H_{24}N_4O_2 \cdot 0.4H_2O$: C, 68.64; H, 6.23; N, 14.86. Found: C, 68.86; H, 6.53; N, 14.60.

4.10. Synthesis of diethyl ({[2-(4-aminoquinazolin-2-yl) phenyl]amino}methylene) malonate hydrochloride 11a

Diethyl 2-(ethoxymethylene)malonate (0.09 g; 0.37 mmol; 1 M equiv; 76 μL) was added to a yellow suspension of 2-(2-aminophenyl)quinazolin-4-amine hydrochloride **2a** (0.10 g; 0.37 mmol) in ethanol (1 mL). The reaction mixture was stirred at 55 °C. After 3 days the yellow solid was filtered and washed with diethyl ether leading to the hydrochloride of diethyl ({[2-(4-aminoquinazolin-2-yl)phenyl]amino}methylene) malonate **11a** (0.10 g; 0.24 mmol; 65%). Mp 209–211 °C. IR (Nujol mull) 3445, 3331, 3147, 1706, 1649, 1622, 1574, 1562, 1530 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.02 (d, *J*=13.5 Hz, 1H), 9.95 (br s, 1H), 8.96 (br s, 1H), 8.47 (d, *J*=13.8 Hz, 1H), 8.50 (d, *J*=8.1 Hz, 1H), 8.20 (d, *J*=8.1 Hz, 1H), 8.12 (d, *J*=8.1 Hz, 1H), 8.03 (t, *J*=8.1 Hz, 1H), 7.70–7.76 (m, 3H), 7.36 (m, 1H), 4.22 (q, *J*=6.9 Hz, 2H), 4.12 (q, *J*=6.9 Hz, 2H), 1.24 (t, *J*=7.2 Hz, 6H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.21, 165.00, 162.01, 157.07, 150.35, 141.51, 139.64, 136.15, 133.98, 131.19, 127.97, 124.75, 124.02, 121.44, 120.44, 116.88, 111.44, 95.37, 59.92, 59.76, 14.29, 14.22. Anal. Calcd for $C_{22}H_{23}N_4O_4Cl$: C, 59.65; H, 5.25; N, 12.65. Found: C, 59.50; H, 5.02; N, 12.47.

4.11. Synthesis of ({[2-(4-aminoquinazolin-2-yl)phenyl] amino}methylene) malononitrile hydrochloride 11b

(Ethoxymethylene)malononitrile (0.04 g; 0.29 mmol; 1.2 equiv) was added to a yellow suspension of 2-(2-aminophenyl)quinazolin-4-amine hydrochloride **2a** (0.06 g; 0.24 mmol) in ethanol (2 mL). The reaction mixture was stirred at 50 °C. After 4 days the yellow solid was filtered and washed with diethyl ether leading to the hydrochloride of ({[2-(4-aminoquinazolin-2-yl)phenyl]amino} methylene)malononitrile **11b** (0.05 g; 0.15 mmol; 63%). Mp 217–219 °C. IR (Nujol mull): 3351, 2222, 1700, 1642, 1609,

Please cite this article in press as: Marinho, E.; Proença, M. F., Tetrahedron (2016), http://dx.doi.org/10.1016/j.tet.2016.06.003

1563 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 13.09 (br s, 1H), 9.07 (br s, 1H), 8.96 (br s, 1H), 8.81 (d, J=13.2 Hz, 1H), 8.37 (d, J=8.0 Hz, 1H), 8.32 (br s, 1H), 8.04 (d, J=8.0 Hz, 1H), 8.03 (d, J=8.0 Hz, 1H), 7.76 (d, J=8.0 Hz, 1H), 7.62–7.69 (m, 2H), 7.40 (t, J=8.0 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.17, 158.63, 156.43, 139.61, 138.47, 135.13, 134.08, 132.67, 130.93, 127.28, 124.94, 124.22, 122.68, 117.83, 114.57 (2C), 112.08, 53.59. Anal. Calcd for $C_{18}H_{13}N_6Cl$: C, 61.91; H, 3.76; N, 24.10. Found: C, 61.91; H, 3.94; N, 24.22.

4.12. Synthesis of *N*-(2-(2-formamidophenyl)quinazolin-4-yl) acetamide 12a

TFA (17 μL; 1 equiv) was added to a white suspension of compound **7a** (0.06 g; 0.22 mmol) in water (1 mL) leading immediately to a yellow suspension. The mixture was stirred at room temperature. After 17 h, the yellow solid was filtered and washed with water leading to the pure product *N*-(2-(2-formamidophenyl)quinazolin-4-yl)acetamide **12a** (0.07 g; 0.22 mmol; 100%). Mp 246–248 °C. IR (Nujol mull): 3325, 3286, 3176, 1722, 1660, 1630, 1595, 1549 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 13.21 (s, 1H), 11.01 (s, 1H), 8.65 (d, J=8.4 Hz, 2H), 8.63 (s, 1H), 8.54 (d, J=8.4 Hz, 1H), 7.97–8.00 (m, 2H), 7.71 (t, J=8.4 Hz, 1H), 7.48 (td, J=2.0, 8.4 Hz, 1H), 7.22 (t, J=8.4 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.35, 160.45, 158.44, 155.05, 151.07, 138.89, 134.69, 131.46, 130.25, 128.38, 127.20, 123.59, 123.07, 123.03, 121.08, 113.48, 25.13. Anal. Calcd for $C_{17}H_{14}N_4O_2$: C, 66.65; H, 4.62; N, 18.29. Found: C, 66.74; H, 4.68; N, 18.47.

4.13. Synthesis of *N*-{2-[2-(formylamino)phenyl]quinazolin-4-yl}-*N*′-cyclohexylurea 12b

Concentrated HCl (12 μL; 1 M equiv) was added to a white suspension of compound **7c** (0.06 g; 0.15 mmol) in water (1 mL). The reaction mixture was stirred at 60 °C. After 1 h, the yellow solid was filtered and washed with water leading to the pure product *N*-{2-[2-(formylamino)phenyl]quinazolin-4-yl}-*N*′-cyclohexylurea **12b** (0.06 g; 0.15 mmol; 100%). Mp 238–240 °C. IR (Nujol mull): 3220, 3145, 3102, 1680, 1621, 1581, 1548, 1503 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 12.90 (s, 1H), 10.17 (s, 1H), 8.63 (d, J=8.4 Hz, 1H), 8.60 (s, 1H), 8.51 (d, J=8.4 Hz, 1H), 8.40 (d, J=8.4 Hz, 1H), 8.04 (d, J=8.4 Hz, 1H), 7.97 (t, J=8.4 Hz, 1H), 7.69 (t, J=8.4 Hz, 1H), 7.51 (t, J=8.4 Hz, 1H), 7.25 (t, J=8.4 Hz, 1H), 3.69–3.73 (m, 1H), 1.96–1.98 (m, 2H), 1.70–1.73 (m, 2H), 1.59–1.61 (m, 1H), 1.24–1.38 (m, 5H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 160.30, 158.07, 156.40, 152.12, 149.24, 138.24, 133.95, 130.93, 129.66, 127.75, 126.84, 123.38, 122.74, 122.61, 120.67, 112.39, 48.04, 32.28 (2C), 24.89, 23.87 (2C). Anal. Calcd for $C_{22}H_{23}N_5O_2$: C, 67.84; H, 5.96; N, 17.98. Found: C, 67.93; H, 6.01; N, 17.91.

4.14. Synthesis of Ethyl ({2-[2-(formylamino)phenyl] quinazolin-4-yl}amino)(oxo) acetate 12c

Concentrated HCl (14 μL; 1 equiv) was added to a white suspension of compound **7e** (0.06 g; 0.17 mmol) in water (1 mL). The reaction mixture was stirred at 60 °C. After 1 h, the yellow solid was filtered and washed with water leading to the pure product ethyl ({2-[2-(formylamino)phenyl]quinazolin-4-yl}amino)(oxo)acetate **12c** (0.06 g; 0.17 mmol; 100%). Mp 242–244 °C. IR (Nujol mull): 3321, 3279, 3177, 1733, 1680, 1666, 1599, 1551, 1521, 1501 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 12.69 (s, 1H), 12.15 (s, 1H), 8.63 (d, J=8.0 Hz, 1H), 8.61 (s, 1H), 8.47 (d, J=8.4 Hz, 1H), 8.40 (d, J=8.0 Hz, 1H), 8.18 (d, J=8.4 Hz, 1H), 8.06 (t, J=8.0 Hz, 1H), 7.77 (td, J=1.2, 8.4 Hz, 1H), 7.51 (td, J=1.2, 8.4 Hz, 1H), 7.25 (t, J=8.0 Hz, 1H), 4.21 (q, J=7.2 Hz, 2H), 1.17 (t, J=7.2 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.10, 160.77, 160.64, 158.68, 155.68, 150.09, 138.57, 135.33, 131.83, 130.54, 128.17 (2C), 123.88, 123.10, 122.65, 121.04, 113.62, 62.33, 13.66. Anal. Calcd for $C_{19}H_{16}N_4O_4$: C, 62.62; H, 4.43; N, 15.38. Found: C, 62.69; H, 4.34; N, 15.41.

Acknowledgements

We gratefully acknowledge the financial support by the University of Minho and FCT through the Portuguese NMR network (RNRMN), the Project F-COMP-01-00124-FEDER-022716 (ref. FCT PEst-C/QUI/UI0686/2011) FEDER- COMPETE, and a PhD grant awarded to E.M. (SFRH/BD/73659/2010).

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.06.003.

References and notes

1. Foucourt, A.; Bernard-Dubouilh, C.; Chosson, E.; Corbière, C.; Buquet, C.; Iannelli, M.; Leblond, B.; Marsais, F.; Besson, T. *Tetrahedron* **2010**, *66*, 4495–4502 and references therein.
2. (a) Seijas, J. A.; Vásquez-Tato, M. P.; Martínez, M. M. *Tetrahedron Lett.* **2000**, *41*, 2215–2217 and references therein; (b) Alvarado, M.; Barceló, M.; Carro, L.; Masaguer, C. F.; Raviña, E. *Chem. Biodiversity* **2006**, *3*, 106–117; (c) Aly, M. M.; Mohamed, Y. A.; El-Bayouki, K. A. M.; Basyouni, W. M.; Abbas, S. Y. *Eur. J. Med. Chem.* **2010**, *45*, 3365–3373; (d) Maurya, H.; Verma, R.; Alam, S.; Pandey, S.; Pathak, V.; Sharma, S.; Srivastava, K. K.; Negi, A. S.; Gupta, A. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5844–5849; (e) Khan, I.; Ibrar, A.; Abbas, N.; Saeed, A. *Eur. J. Med. Chem.* **2014**, *76*, 193–244 and references therein; (f) Ugale, V. G.; Bari, S. B. *Eur. J. Med. Chem.* **2014**, *80*, 447–501; (g) Chaudhari, C.; Siddiki, S. M. A. H.; Tamura, M.; Shimizu, K. *RSC Adv.* **2014**, *4*, 53374–53379.
3. (a) Connolly, D. J.; Cusack, D.; O'Sullivan, T. P.; Guiry, P. J. *Tetrahedron* **2005**, *61*, 10153–10202; (b) Martins, M. A. P.; Frizzo, C. P.; Moreira, D. N.; Buriol, L.; Machado, P. *Chem. Rev.* **2009**, *109*, 4140–4182 and references therein; (c) Wang, D.; Gao, F. *Chem. Cent. J.* **2013**, *7*, 95 1–15.
4. (a) Alawode, O. E.; Naganaboina, V. K.; Liyanage, T.; Desper, J.; Rayat, S. *Org. Lett.* **2014**, *16*, 1494–1497; (b) Mendoza-Martínez, C.; Correa-Basurto, J.; Nieto-Meneses, R.; Marquez-Navarro, A.; Aguilar-Suarez, R.; Montero-Cortes, M. D.; Nogueda-Torres, B.; Suarez-Contreras, E.; Galindo-Sevilla, N.; Rojas-Rojas, A.; Rodriguez-Lezama, A.; Hernandez-Luis, F. *Eur. J. Med. Chem.* **2015**, *96*, 296–307; (c) Yan, Y.; Xu, Y.; Niu, B.; Xie, H.; Liu, Y. *J. Org. Chem.* **2015**, *80*, 5581–5587; (d) Quintero, C.; Valderrama, M.; Becerra, A.; Daniliucb, C. G.; Rene, S.; Rojas, R. S. *Org. Biomol. Chem.* **2015**, *13*, 6183–6193.
5. (a) Portela-Cubillo, F.; Scott, J. S.; Walton, J. C. *J. Org. Chem.* **2009**, *74*, 4934–4942; (b) Yin, P.; Liu, N.; Deng, Y.-X.; Chen, Y.; Deng, Y.; He, L. *J. Org. Chem.* **2012**, *77*, 2649–2658.
6. Patel, O. P. S.; Anand, D.; Maurya, R. K.; Yadav, P. P. *Green Chem.* **2015**, *17*, 3728–3732.
7. Lanigan, R. M.; Starkov, P.; Sheppard, T. D. *J. Org. Chem.* **2013**, *78*, 4512–4523.
8. (a) Lundberg, H.; Adolfsson, H. *ACS Catal.* **2015**, *5*, 3271–3277; (b) Wangngae, S.; Duangkamol, C.; Pattarawarapan, M.; Phakhodee, W. *RSC Adv.* **2015**, *5*, 25789–25793.
9. (a) Seo, S.; Marks, T. J. *Org. Lett.* **2008**, *10*, 317–319; (b) Allen, C. L.; Davulcu, S.; Williams, J. M. J. *Org. Lett.* **2010**, *12*, 5096–5099; (c) Liu, X.; Jensen, K. F. *Green Chem.* **2012**, *14*, 1471–1474; (d) Ghosh, S. C.; Ngiam, J. S. Y.; Seayad, A. M.; Tuan, D. T.; Chai, C. L. L.; Chen, A. *J. Org. Chem.* **2012**, *77*, 8007–8015; (e) Leow, D. *Org. Lett.* **2014**, *16*, 5812–5815.
10. (a) Naik, S.; Bhattacharjya, G.; Talukdar, B.; Patel, B. K. *Eur. J. Org. Chem.* **2004**, 1254–1260; (b) Li, Y.; Ma, L.; Jia, F.; Li, Z. *J. Org. Chem.* **2013**, *78*, 5638–5646; (c) Marinho, E.; Proença, M. F. *Synthesis* **2015**, *47*, 1623–1632.
11. (a) Chan, W. K.; Ho, C.-M.; Wong, M.-K.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 14796–14797; (b) Mak, X. Y.; Ciccolini, R. P.; Robinson, J. M.; Tester, J. W.; Danheiser, R. L. *J. Org. Chem.* **2009**, *74*, 9381–9387.
12. (a) Gnanaprakasam, B.; Milstein, D. *J. Am. Chem. Soc.* **2011**, *133*, 1682–1685; (b) Morimoto, H.; Fujiwara, R.; Shimizu, Y.; Morisaki, K.; Ohshima, T. *Org. Lett.* **2014**, *16*, 2018–2021.
13. (a) Chen, C.; Zhang, Y.; Hong, S. H. *J. Org. Chem.* **2011**, *76*, 10005–10010; (b) Liu, X.; Jensen, K. F. *Green Chem.* **2013**, *15*, 1538–1541.
14. Vora, H. U.; Rovis, T. *J. Am. Chem. Soc.* **2007**, *129*, 13796–13797.
15. Marinho, E.; Aráujo, R.; Proença, F. *Tetrahedron* **2010**, *66*, 8681–8689.
16. Marinho, E.; Proença, M. F. *RSC Adv.* **2016**, *6*, 6138–6143.
17. Marinho, E. R.; Proença, F. P. *Arkivoc* **2009**, *xvi*, 346–361 and references therein.