Tetrahedron 68 (2012) 3098–3102

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

Synthesis of condensed tetrahydroimidazo[1,2-*a*]quinazoline-1,5-dione derivatives

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ARTICLE INFO

Article history:
Received 8 November 2011
Received in revised form 13 January 2012
Accepted 31 January 2012
Available online 5 February 2012

Keywords:
2-Aminobenzamide
Aminoacid
Cyclization
Triethyl orthoformate
Quinazoline

ABSTRACT

Heating of *N*-{2-[(R-amino)carbonyl]phenyl}prolinamides in triethyl orthoformate solution was found to give 6-R-5,6,6a,8,9,10,10a,11-octahydropyrrolo[1′,2′:3,4]imidazo[1,2-*a*]quinazoline-5,11-diones. Similar reaction of *N*-{2-[(R-amino)carbonyl]phenyl}thiazolidine-4-carboxamides afforded 6-R-5,6,6a,10,10a,11-hexahydrothiazolo[3′,4′:3,4]imidazo[1,2-*a*]quinazoline-5,11-diones. The relative configuration of C-6a and C-10a centres of the tetracyclic compounds obtained was assigned as trans on the basis of X-ray crystallographic study.

1. Introduction

Fused 4-quinazolinone core is a motif found in many natural alkaloids and a number of synthetic drugs (for recent reviews see Refs. 1–4). Among them compounds with partially or completely hydrogenated heterocyclic rings are of particular interest for biology and medicine.[5] During the course of our research[6–10] on pyrrolo[1,2-*a*]quinazolines chemistry we have paid attention to their aza-analogues, namely imidazo[1,2-*a*]quinazolines. Literature analysis revealed that in contrast to the corresponding aromatic derivatives[11] hydrogenated imidazo[1,2-*a*]quinazolines are relatively rare.[12–15] Except a singular case,[12] the only known approach to this core involves reduction of the appropriate heterocyclic guanidinium salt precursors obtained through a stepwise imidazole ring annulation to quinazoline derivatives.[13–15] Thus, development of new methods for the synthesis of hydrogenated imidazo[1,2-*a*]quinazolines warrants further investigations. In particular, it looks reasonable to prepare the core through direct introduction of the bridgehead sp^3 carbon atom (3a-C). It could be achieved by reaction of a suitable precursor with orthoformic acid derivatives like triethyl orthoformate, DMFDMA etc. Noteworthy, a similar approach was employed previously for the synthesis of tricyclic derivatives from 9 to 12 membered tri-[16–23] and tetraazacycloalkanes[24–28] as well as for the transformation of cyclohexane-1,3,5-triamine derivatives into the triazaadamantane skeleton.[29–31] The applicability of this concept to imidazoquinazoline system construction has been examined and the results are reported herein.

2. Results and discussion

Prolinamides **6a**–**d** (Scheme 1) were suggested as suitable precursors for the cyclization. They were obtained readily through acylation of 2-aminobenzamides **3a**–**d** with the mixed anhydride of *N*-Boc-proline generated in situ, followed by deprotection of the intermediate compounds **4a**–**d**. A two-step protocol without isolation of intermediates **4** was developed. It provided the target compounds **6** in 70–85% yields as the hydrochloride salts. It should be noted that certain proline–anthranilic acid di- and tripeptide analogues have been used recently in the synthesis of *circumdatin* family alkaloids.[32–35] In those cases appropriate amides were prepared in a similar manner starting from either *N*-Boc-[34,35] or *N*-Cbz-proline.[32,33]

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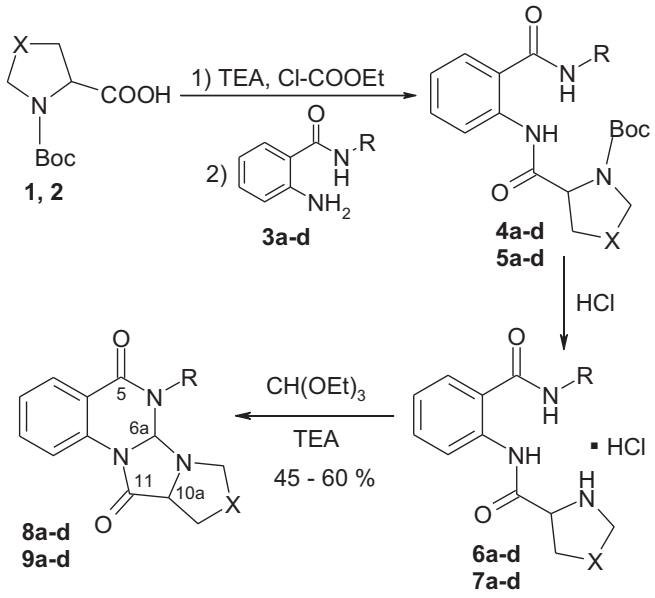
doi:10.1016/j.tet.2012.01.096



Scheme 1. For X and R assignment see the Table 1.

Table 1
Compounds **6**–**9**

No.	X	R	No.	X	R
6a	CH_2	Me	**8a**	CH_2	Me
6b	CH_2	Et	**8b**	CH_2	Et
6c	CH_2	$PhCH_2$	**8c**	CH_2	$PhCH_2$
6d	CH_2	Ph	**8d**	CH_2	Ph
7a	S	Me	**9a**	S	Me
7b	S	Et	**9b**	S	Et
7c	S	$PhCH_2$	**9c**	S	$PhCH_2$
7d	S	Ph	**9d**	S	Ph

Cyclization of the amides **6** into the target core was studied. It was found that heating compounds **6a**–**d** in a triethyl orthoformate solution afforded pyrrolo[1′,2′:3,4]imidazo[1,2-*a*]quinazoline derivatives **8a**–**d**. It is noteworthy that for the related cyclizations reported[16–31] the use of triethyl orthoformate resulted in low yields or no reaction[16–18,31] and required long time heating at high temperatures[16] sometimes even in autoclave.[31] So the more reactive DMFDMA was usually used to perform the reaction satisfactorily.[17–31] In the present case the use of triethyl orthoformate appeared to be suitable furnishing compounds **8** in 45–60% yield after 5–6 h at reflux temperature.

Furthermore, the sequence was successfully extended to the cysteine derived acid **2** (Scheme 1). Thus the corresponding amides **7a**–**d** were obtained through the same two-step procedure. Their reaction with triethyl orthoformate occurred similarly leading to thiazolo[3′,4′:3,4]imidazo[1,2-*a*]quinazoline derivatives **9a**–**d**. It should be also emphasized that both compounds **8** and **9** are representatives of novel hitherto unknown heterocyclic cores.

The structures of the prepared compounds **6**–**9** were confirmed by ^1H and ^{13}C NMR spectroscopic analysis. Among the spectral data the signals of 6a-H and 6a-C observed in ^1H and ^{13}C NMR spectra of compounds **8**,**9** at 5.6–5.8 and 89–91 ppm, respectively, deserve to be mentioned as the most remarkable attributes of the tetracyclic system formed. Moreover, the cyclization turned out to proceed diastereoselectively yielding the products **8**,**9** with definite relative configuration of the two stereocenters, 6a-C and 10a-C. In order to assign the relative configuration unambiguously an X-ray crystallographic study was carried out for derivative **9c** (Fig. 1). It revealed clearly the hydrogen atoms at positions 6a and 10a to be trans.

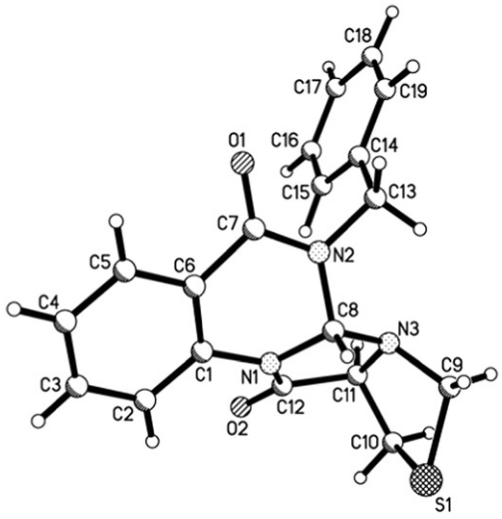


Fig. 1. X-ray molecular structure of compound **9c** with the atom numbering used in the crystallographic analysis.

Following the analogy the same relative configuration was assigned throughout the series of compounds **8a**–**d**, **9a**–**d**. Thus they should be formulated as the racemates of the pair of enantiomeric structures **A** and **B** (Fig. 2).

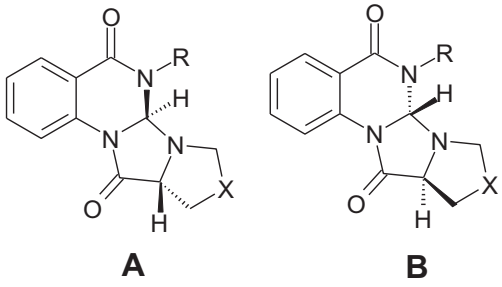


Fig. 2. The relative configuration of compounds **8a**–**d**, **9a**–**d**.

According to the crystal data the central imidazolone ring is planar (with precision of 0.02 Å). Pyrimidine and thiazole moieties are condensed with it in cis-like manner and are arranged trans in respect of each other. The nitrogen atoms N(1) and N(2) are almost planar; the sums of the bonds angles centred on them are 358.0° and 359.0°, respectively. The atom N(3) is pyramidal; the sum of the bonds angles around it is 333.2°. The pyrimidine moiety adopts a chair conformation with the atom C(8) deviated from the least-squared plane of the rest of the atoms of the ring at 0.61 Å. The following puckering parameters[36] have been calculated: S=0.66, Θ=51.7°, Ψ=8.3°. Simultaneously, the thiazole fragment is in the envelope conformation. Deviation of the S(1) atom from the least-squared plane of the rest atoms of the ring is 0.89 Å.

In conclusion, the present research has resulted in a novel approach to condensed hydrogenated imidazo[1,2-*a*]quinazolines. Its main concept is to bring in the bridgehead sp^3 one-carbon unit into appropriate acyclic precursor thus forming both pyrimidine and imidazole rings at once. Anthranilic acid based dipeptide analogues **6**,**7** have been established as suitable precursors, and triethyl orthoformate has been shown to be apt source of the desired carbon. The method is believed to offer a good alternative to the known approaches.[12–15] Also it should be noted that proline–anthranilic acid and related dipeptide analogues have already been utilized in the synthesis of naturally occurring fused 4-quinazolinones.[32–35] However in all those cases a carboxylic

carbon atom of the proline residue in the starting material became 2-C atom of the quinazoline moiety in the product. The present cyclization displays another reactivity of these dipeptide analogues thus extending their synthetic potential.

3. Experimental

3.1. General

2-Aminobenzamides **3a**–**d** were prepared according to the described procedures.[37–40] *N*-Boc aminoacids **1**,**2** were either commercially available or prepared as reported.[41] Other reagents were commercially available. All melting points were determined in open capillary tubes in a Thiele apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 500 spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C) in DMSO-d_6 or $CDCl_3$ solutions. Chemical shifts (δ) are given in parts per million downfield from internal Me_4Si. *J* values are in Hertz. The purity of all compounds obtained was checked by ^{1}H NMR and LC/MS on an Agilent 1100 instrument.

3.2. Prolinamides 6a–d and thiazolidine-4-carboxamides 7a–d. General procedure

Ethyl chloroformate (0.86 g, 8.0 mmol) was added to a stirred solution of appropriate acid **1**,**2** (8.0 mmol) and triethylamine (0.81 g, 8.0 mmol) in anhydrous dioxane (20 mL) and the stirring was continued for 30 min maintaining the temperature below 15 °C by external cooling. Then the appropriate benzamide **3a**–**d** (7.5 mmol) was added and the mixture was heated at reflux for 2 h. After cooling the solvent was evaporated in vacuo, the residue was triturated with water and filtered to give crude derivatives **4a**–**d**, **5a**–**d**. This crude material was dissolved in *i*-PrOH (15 mL) containing conc hydrochloric acid (1.3 mL) and the solution obtained was heated at 50–60 °C until a gas evolution had ceased (1.5–2 h). Upon cooling the precipitate formed was filtered yielding pure compounds **6a**–**d**, **7a**–**d** as the hydrochloride salts. The *i*-PrOH filtrate was evaporated to dryness in vacuo and the residue was recrystallized from anhydrous acetonitrile to give a further portion of **6a**–**d**, **7a**–**d**···HCl.

*3.2.1. N-{2-[(Methylamino)carbonyl]phenyl}-prolinamide hydrochloride (**6a**).* Yield 1.73 g (82%); White crystals; mp 250–251 °C; δ_H (DMSO-d_6) 1.91–1.97 (2H, m, 4-CH_2), 2.01–2.08 (1H, m, 3-H), 2.33–2.39 (1H, m, 3-H), 2.77 (3H, d, *J*=4.5, CH_3), 3.18–3.26 (2H, m, 5-CH_2), 4.41–4.47 (1H, m, 2-H), 7.22 (1H, t, *J*=8.5, 4-H_{Ar}), 7.51 (1H, t, *J*=8.5, 5-H_{Ar}), 7.76 (1H, d, *J*=8.5, 6-H_{Ar}), 8.13 (1H, d, *J*=8.5, 3-H_{Ar}), 8.73 (1H, br s, NH·HCl), 8.82 (1H, q, *J*=4.5, N*H*-Me), 10.31 (1H, br s, NH·HCl), 11.68 (1H, s, CONH); δ_C (DMSO-d_6) 24.0 (4-C), 26.7 (CH_3), 29.5 (3-C), 45.8 (5-C), 60.6 (2-C), 122.2 (6-C_{Ar}), 123.8 (2-C_{Ar}), 124.5 (4-C_{Ar}), 128.8 (3-C_{Ar}), 132.1 (5-C_{Ar}), 137.6 (1-C_{Ar}), 167.1 (CONH), 168.7 (CONH); ν_{max}(KBr) 3331, 3293, 2895, 1678, 1588, 1540, 1520, 1454, 1396, 1336, 1246, 798, 765 cm^{-1}; found: C, 55.10; H, 6.67; N, 14.63; Cl, 12.40. $C_{13}H_{17}N_3O_2$·HCl requires C, 55.03; H, 6.39; N, 14.81; Cl, 12.49.

*3.2.2. N-{2-[(Ethylamino)carbonyl]phenyl}-prolinamide hydrochloride (**6b**).* Yield 1.74 g (78%); Beige crystals; mp 175–176 °C; δ_H (DMSO-d_6) 1.12 (3H, t, *J*=7.5, CH_3), 1.901–0.98 (2H, m, 4-CH_2), 2.01–2.07 (1H, m, 3-H), 2.32–2.38 (1H, m, 3-H), 3.23–3.30 (2H, m, 2 NCH_2), 4.41–4.47 (1H, m, 2-H), 7.22 (1H, t, *J*=8.0, 4-H_{Ar}), 7.51 (1H, t, *J*=8.0, 5-H_{Ar}), 7.76 (1H, d, *J*=8.5, 6-H_{Ar}), 8.12 (1H, d, *J*=8.5, 3-H_{Ar}), 8.73 (1H, br s, NH·HCl), 8.83 (1H, s, CONH), 10.33 (1H, br s, NH·HCl), 11.64 (1H, s, CONH); δ_C (DMSO-d_6) 15.0 (CH_3), 24.0 (4-C), 29.5 (3-C), 34.6 (CH_2CH_3), 45.8 (5-C), 60.5 (2-C), 122.3 (6-C_{Ar}), 124.1 (2-C_{Ar}), 124.5 (4-C_{Ar}), 128.8 (3-C_{Ar}), 132.0 (5-C_{Ar}), 137.6 (1-C_{Ar}), 167.1 (CONH), 168.0 (CONH); ν_{max}(KBr) 3312, 2974, 2877, 1695, 1684, 1591, 1538, 1520, 1455, 1447, 1332, 1244, 999, 803, 769 cm^{-1}; found: C, 56.28; H, 6.65; N, 14.20; Cl, 11.75. $C_{14}H_{19}N_3O_2$·HCl requires C, 56.47; H, 6.77; N, 14.11; Cl, 11.91.

*3.2.3. N-{2-[(Benzylamino)carbonyl]phenyl}-prolinamide hydrochloride (**6c**).* Yield 2.19 g (81%); White crystals; mp 228–229 °C; δ_H (DMSO-d_6) 1.91–1.98 (3H, m, 3-H, 4-CH_2), 2.31–2.35 (1H, m, 3-H), 3.19–3.25 (2H, m, 5-CH_2), 4.42–4.48 (3H, m, 2-H, NCH_2Ph), 7.22–7.27 (2H, m, 4-H_{Ar}, H_{Ph}), 7.30–7.38 (4H, m, 4H_{Ph}), 7.53 (1H, t, *J*=7.5, 5-H_{Ar}), 7.84 (1H, d, *J*=7.5, 6-H_{Ar}), 8.10 (1H, d, *J*=7.5, 3-H_{Ar}), 8.73 (1H, br s, NH·HCl), 9.40 (1H, t, *J*=4.0, CO*NH*CH_2), 10.27 (1H, br s, NH·HCl), 11.52 (1H, s, CONH); δ_C (DMSO-d_6) 24.0 (4-C), 29.5 (3-C), 43.1 (CH_2Ph), 45.8 (5-C), 60.5 (2-C), 122.6 (6-C_{Ar}), 124.2 (2-C_{Ar}), 124.7 (4-C_{Ar}), 127.3 (4-C_{Ph}), 127.8 (3,5-C_{Ph}), 128.6 (3-C_{Ar}), 128.8 (2,6-C_{Ph}), 132.2 (5-C_{Ar}), 137.6 (1-C_{Ar}), 139.6 (1-C_{Ph}), 167.2 (CONH), 168.3 (CONH); ν_{max}(KBr) 3280, 1682, 1594, 1531, 1455, 1323, 1307, 1244, 750, 700 cm^{-1}; found: C, 63.18; H, 6.25; N, 11.63; Cl, 9.99. $C_{19}H_{21}N_3O_2$·HCl requires C, 63.42; H, 6.16; N, 11.68; Cl, 9.85.

*3.2.4. N-[2-(Anilinocarbonyl)phenyl]prolinamide hydrochloride (**6d**).* Yield 2.05 g (79%); White crystals; mp 169–170 °C; δ_H (DMSO-d_6) 1.80–1.86 (2H, m, 4-CH_2), 2.02–2.06 (1H, m, 3-H), 2.26–2.30 (1H, m, 3-H), 3.13–3.21 (2H, m, 5-CH_2), 4.40–4.44 (1H, m, 2-H), 7.09 (1H, t, *J*=7.5, 4-H_{Ph}), 7.33 (3H, m, 2,6-H_{Ph}, 4-H_{Ar}), 7.55 (1H, t, *J*=8.0, 5-H_{Ar}), 7.70–7.78 (4H, m, 3,5-H_{Ph}, 3,6-H_{Ar}), 8.61 (1H, br s, NH·HCl), 10.11 (1H, br s, NH·HCl), 10.44 (1H, s, CONH), 10.81 (1H, s, CONH); δ_C (DMSO-d_6) 22.8 (4-C), 29.8 (3-C), 46.0 (5-C), 59.9 (2-C), 120.7 (2,6-C_{Ph}), 124.1 (6-C_{Ar}), 124.2 (4-C_{Ar}), 125.4 (4-C_{Ph}), 128.8 (2-C_{Ar}), 129.0 (3,5-C_{Ph}), 129.4 (3-C_{Ar}), 131.6 (5-C_{Ar}), 135.9 (1-C_{Ar}), 139.6 (1-C_{Ph}), 166.6 (CONH), 167.4 (CONH); ν_{max}(KBr) 2992, 1688, 1593, 1556, 1341, 1256, 759, 712, 689 cm^{-1}; found: C, 62.56; H, 5.80; N, 12.21; Cl, 10.15. $C_{18}H_{19}N_3O_2$·HCl requires C, 62.52; H, 5.83; N, 12.15; Cl, 10.25.

*3.2.5. N-{2-[(Methylamino)carbonyl]phenyl}-thiazolidine-4-carboxamide hydrochloride (**7a**).* Yield 1.70 g (75%); White crystals; mp 189–190 °C; δ_H (DMSO-d_6) 2.79 (3H, d, *J*=4.5, CH_3), 3.34 (1H, dd, J^2=11.5, J^3=6.5, 5-H), 3.52 (1H, dd, J^2=11.5, J^3=7.5, 5-H), 4.30–4.36 (2H, m, 2-CH_2), 4.79 (1H, dd, J^3=6.5, J^3=7.5, 4-H), 7.25 (1H, t, *J*=8.0, 4-H_{Ar}), 7.53 (1H, t, *J*=8.0, 5-H_{Ar}), 7.77 (1H, d, *J*=8.0, 6-H_{Ar}), 8.11 (1H, d, *J*=8.0, 3-H_{Ar}), 8.80 (1H, q, *J*=4.5, N*H*-Me), 10.22 (2H, br s, NH·HCl), 11.75 (1H, s, CONH); δ_C (DMSO-d_6) 26.8 (CH_3), 33.4 (5-C), 48.8 (2-C), 63.7 (4-C), 122.5 (6-C_{Ar}), 124.4 (2-C_{Ar}), 124.7 (4-C_{Ar}), 128.8 (3-C_{Ar}), 132.0 (5-C_{Ar}), 137.3 (1-C_{Ar}), 165.5 (CONH), 168.5 (CONH); ν_{max}(KBr) 3322, 1697, 1605, 1530, 1459, 1394, 1332, 1288, 1239, 955, 779, 743 cm^{-1}; found: C, 47.54; H, 5.10; N, 13.90; Cl, 11.73; S, 10.42. $C_{12}H_{15}N_3O_2S$·HCl requires C, 47.76; H, 5.34; N, 13.92; Cl, 11.75; S, 10.62.

*3.2.6. N-{2-[(Ethylamino)carbonyl]phenyl}-thiazolidine-4-carboxamide hydrochloride (**7b**).* Yield 1.71 g (72%); White crystals; mp 202–204 °C; δ_H (DMSO-d_6) 1.14 (3H, t, *J*=7.5, CH_3), 3.30–3.40 (3H, m, 5-H, CH_2CH_3), 3.52 (1H, dd, J^2=11.5, J^3=7.5, 5-H), 4.29–4.37 (2H, m, 2-CH_2), 4.80 (1H, dd, J^3=6.5, J^3=7.5, 4-H), 7.25 (1H, t, *J*=8.5, 4-H_{Ar}), 7.53 (1H, t, *J*=8.5, 5-H_{Ar}), 7.77 (1H, d, *J*=8.5, 6-H_{Ar}), 8.10 (1H, d, *J*=8.5, 3-H_{Ar}), 8.30 (1H, t, *J*=4.5, *NH*CH_2), 10.93 (2H, br s, NH·HCl), 11.72 (1H, s, CONH); δ_C (DMSO-d_6) 15.0 (CH_3), 33.4 (5-C), 34.6 (CH_2CH_3), 48.8 (2-C), 63.6 (4-C), 122.5 (6-C_{Ar}), 124.6 (2-C_{Ar}), 124.7 (4-C_{Ar}), 128.8 (3-C_{Ar}), 131.9 (5-C_{Ar}), 137.3 (1-C_{Ar}), 165.4 (CONH), 167.9 (CONH); ν_{max}(KBr) 3299, 1698, 1542, 1522, 1508, 1456, 1413, 1295, 1246, 1149, 876, 761, 670, 662 cm^{-1}; found: C, 49.50; H, 5.55; N, 13.42; Cl, 11.03; S, 10.14. $C_{13}H_{17}N_3O_2S$·HCl requires C, 49.44; H, 5.74; N, 13.30; Cl, 11.23; S, 10.15.

*3.2.7. N-{2-[(Benzylamino)carbonyl]phenyl}-thiazolidine-4-carboxamide hydrochloride (**7c**).* Yield 2.30 g (81%); White crystals; mp 191–192 °C; δ_H (DMSO-d_6) 3.27 (1H, dd, J^2=11.0, J^3=6.0, 5-H), 3.41 (1H, dd, J^2=11.0, J^3=7.0, 5-H), 4.27–4.33 (2H, m, 2-CH_2),

4.46–4.52 (2H, m, CH_2Ph), 4.77 (1H, dd, J^3=6.0, J^3=7.0, 4-H), 7.27 (2H, m, H_{Ph}, 4-H_{Ar}), 7.31–7.41 (4H, m, 4H_{Ph}), 7.56 (1H, t, J=8.0, 5-H_{Ar}), 7.83 (1H, d, J=8.0, 6-H_{Ar}), 8.12 (1H, d, J=8.0, 3-H_{Ar}), 9.38 (1H, t, J=5.5, $NHCH_2$), 10.33 (2H, br s, NH·HCl), 11.60 (1H, s, CONH); δ_C (DMSO-d_6) 33.4 (5-C), 43.2 (CH_2Ph), 48.7 (2-C), 63.5 (4-C), 122.8 (6-C_{Ar}), 124.7 (2-C_{Ar}), 124.9 (4-C_{Ar}), 127.3 (4-C_{Ph}), 127.8 (3,5-C_{Ph}), 128.8 (2,6-C_{Ph}), 128.9 (3-C_{Ar}), 132.1 (5-C_{Ar}), 137.2 (1-C_{Ar}), 139.6 (1-C_{Ph}), 165.5 (CONH), 168.1 (CONH); ν_{max}(KBr) 3280, 1682, 1594, 1531, 1454, 1323, 1244, 750, 700 cm^{-1}; found: C, 57.29; H, 5.27; N, 11.36; Cl, 9.57; S, 8.67. $C_{18}H_{19}N_3O_2S$·HCl requires C, 57.21; H, 5.33; N, 11.12; Cl, 9.38; S, 8.48.

*3.2.8. N-[2-(Anilinocarbonyl)phenyl]thiazolidine-4-carboxamide hydrochloride (**7d**).* Yield 2.02 g (74%); White crystals; mp 171–172 °C; δ_H (DMSO-d_6) 3.28 (1H, dd, J^2=11.5, J^3=6.5, 5-H), 3.48 (1H, dd, J^2=11.5, J^3=7.5, 5-H), 4.27–4.33 (2H, m, 2-CH_2), 4.73 (1H, dd, J^3=6.5, J^3=7.5, 4-H), 7.11 (1H, t, J=7.0, 4-H_{Ph}), 7.31–7.39 (3H, m, 4-H_{Ar}, 2,6-H_{Ph}), 7.58 (1H, t, J=7.5, 5-H_{Ar}), 7.74–7.81 (3H, m, 6-H_{Ar}, 3,5-H_{Ph}), 7.86 (1H, d, J=7.5, 3-H_{Ar}), 10.27 (2H, br s, NH·HCl), 10.50 (1H, s, CONH), 11.05 (1H, s, CONH); δ_C (DMSO-d_6) 33.6 (5-C), 49.1 (2-C), 63.6 (4-C), 120.9 (2,6-C_{Ph}), 124.0 (6-C_{Ar}), 124.3 (4-C_{Ar}), 125.4 (4-C_{Ph}), 128.4 (2-C_{Ar}), 129.1 (3,5-C_{Ph}), 129.4 (3-C_{Ar}), 131.7 (5-C_{Ar}), 135.9 (1-C_{Ar}), 139.6 (1-C_{Ph}), 165.7 (CONH), 166.6 (CONH); ν_{max}(KBr) 3266, 1679, 1644, 1549, 1540, 1489, 1447, 1330, 1260, 760, 745 cm^{-1}; found: C, 56.20; H, 4.74; N, 11.44; Cl, 9.70; S, 8.71. $C_{17}H_{17}N_3O_2S$·HCl requires C, 56.12; H, 4.99; N, 11.55; Cl, 9.74; S, 8.81.

3.3. Pyrrolo[1′,2′:3,4]imidazo[1,2-*a*]quinazoline-5,11-diones 8a–d and thiazolo[3′,4′:3,4]imidazo[1,2-*a*]quinazoline-5,11-diones 9a–d. General procedure

A solution of the corresponding compounds **6a–d**, **7a–d**···HCl (4.0 mmol) and triethylamine (0.41 g, 4.0 mmol) in triethyl orthoformate (10 mL) was heated at reflux for 5–6 h. After cooling the triethyl orthoformate was removed in vacuo, the residue was dissolved in ethyl acetate (30 mL), washed with water (2×10 mL) and dried (Na_2SO_4). The extract was evaporated and the solid residue was recrystallized from a suitable solvent to yield derivatives **8a**, **8c**, **9a–d**. In the case of compounds **8b**, **8d** the residue after the evaporation remained oily. It was taken up in $CHCl_3$ (5 mL) and purified by column chromatography on silica ($CHCl_3$/MeOH, 9:1). Evaporation of the appropriate fractions afforded compounds **8b**, **8d**.

*3.3.1. 6-Methyl-5,6,6a,8,9,10,10a,11-octahydro-pyrrolo[1′,2′:3,4]imidazo[1,2-a]quinazoline-5,11-dione (**8a**).* Yield 0.61 g (59%); Yellowish powder; mp 87–88 °C (from EtOH); δ_H (DMSO-d_6) 1.72–1.78 (1H, m, 10-H), 1.84–1.90 (1H, m, 10-H), 2.05–2.11 (1H, m, 9-H), 2.13–2.21 (1H, m, 9-H), 3.03 (3H, s, CH_3), 3.06–3.10 (1H, m, 8-H), 3.21–3.27 (1H, m, 8-H), 3.95 (1H, dd, J=5.0, J=8.5, 10a-H), 5.77 (1H, s, 6a-H), 7.28 (1H, t, J=8.0, 3-H), 7.55 (1H, t, J=8.0, 2-H), 7.76 (1H, d, J=8.0, 1-H), 7.93 (1H, d, J=8.0, 4-H); δ_C (DMSO-d_6) 25.3 (9-C), 27.9 (CH_3), 29.3 (10-C), 55.5 (8-C), 64.4 (10a-C), 90.5 (6a-C), 120.9 (1-C), 121.4 (4a-C), 126.0 (3-C), 128.3 (4-C), 133.3 (2-C), 135.1 (12a-C), 162.4 (5-CO), 172.8 (11-CO); ν_{max}(KBr) 2928, 2853, 1743, 1724, 1655, 1489, 1473, 1339, 1320, 1191, 1092, 796, 774, 701 cm^{-1}; found: C, 65.36; H, 5.65; N, 16.29. $C_{14}H_{15}N_3O_2$ requires C, 65.36; H, 5.88; N, 16.33.

*3.3.2. 6-Ethyl-5,6,6a,8,9,10,10a,11-octahydro-pyrrolo[1′,2′:3,4]imidazo[1,2-a]quinazoline-5,11-dione (**8b**).* Yield 0.61 g (56%); R_f ($CHCl_3$/MeOH, 9:1) 0.90; Yellowish powder; mp 92–93 °C; δ_H (DMSO-d_6) 1.16 (3H, t, J=7.0, CH_3), 1.70–1.74 (1H, m, 10-H), 1.79–1.85 (1H, m, 10-H), 1.98–2.04 (1H, m, 9-H), 2.12–2.16 (1H, m, 9-H), 3.06–3.11 (1H, m, 8-H), 3.19–3.25 (1H, m, 8-H), 3.58–3.62 (1H, m, CH_2CH_3), 3.65–3.69 (1H, m, CH_2CH_3), 4.00–4.04 (1H, m, 10a-H), 6.07 (1H, s, 6a-H), 7.37 (1H, t, J=8.0, 3-H), 7.64 (1H, t, J=8.0, 2-H), 7.72 (1H, d, J=8.0, 1-H), 7.94 (1H, d, J=8.0, 4-H); δ_C (DMSO-d_6) 13.9 (CH_3), 25.4 (9-C), 29.2 (10-C), 36.0 (CH_2CH_3), 55.7 (8-C), 64.4 (10a-C), 89.6 (6a-C), 121.1 (1-C), 121.9 (4a-C), 126.0 (3-C), 128.3 (4-C), 133.3 (2-C), 135.1 (12a-C), 161.8 (5-CO), 173.0 (11-CO); ν_{max}(KBr) 1723, 1647, 1489, 1468, 1422, 1304, 1190, 1096, 766, 696 cm^{-1}; found: C, 66.38; H, 6.28; N, 15.28. $C_{15}H_{17}N_3O_2$ requires C, 66.40; H, 6.32; N, 15.49.

*3.3.3. 6-Benzyl-5,6,6a,8,9,10,10a,11-octahydro-pyrrolo[1′,2′:3,4]imidazo[1,2-a]quinazoline-5,11-dione (**8c**).* Yield 0.64 g (48%); White powder; mp 166–167 °C (from dioxane); δ_H (DMSO-d_6) 1.58–1.64 (1H, m, 10-H), 1.67–1.73 (1H, m, 10-H), 1.94–1.98 (1H, m, 9-H), 2.04–2.08 (1H, m, 9-H), 2.76–2.82 (1H, m, 8-H), 2.99–3.05 (1H, m, 8-H), 3.85 (1H, dd, J=4.0, J=8.5, 10a-H), 4.77 (1H, d, J=15.0, CH_2Ph), 4.87 (1H, d, J=15.0, CH_2Ph), 6.03 (1H, s, 6a-H), 7.20–7.23 (1H, m, H_{Ph}), 7.25–7.34 (4H, m, 4H_{Ph}), 7.39 (1H, t, J=8.0, 3-H), 7.66 (1H, t, J=8.0, 2-H), 7.73 (1H, d, J=8.0, 1-H), 7.97 (1H, d, J=8.0, 4-H); δ_C (DMSO-d_6) 25.2 (9-C), 29.2 (10-C), 44.6 (CH_2Ph), 55.6 (8-C), 64.4 (10a-C), 89.9 (6a-C), 121.2 (1-C), 121.7 (4a-C), 126.1 (3-C), 127.2 (4-C_{Ph}), 127.8 (3,5-C_{Ph}), 128.6 (4-C), 128.9 (2,6-C_{Ph}), 133.6 (2-C), 135.3 (12a-C), 138.7 (1-C_{Ph}), 162.3 (5-CO), 172.9 (11-CO); ν_{max}(KBr) 1715, 1697, 1649, 1637, 1489, 1429, 1417, 1404, 1320, 1233, 1138, 1089, 766, 738, 703 cm^{-1}; found: C, 71.93; H, 5.75; N, 12.60. $C_{20}H_{19}N_3O_2$ requires C, 72.05; H, 5.74; N, 12.60.

*3.3.4. 6-Phenyl-5,6,6a,8,9,10,10a,11-octahydro-pyrrolo[1′,2′:3,4]imidazo[1,2-a]quinazoline-5,11-dione (**8d**).* Yield 0.59 g (46%); Clean yellow oil; R_f ($CHCl_3$/MeOH, 9:1) 0.74; δ_H ($CDCl_3$) 1.69–1.78 (2H, m, 10-CH_2), 2.06–2.18 (2H, m, 9-CH_2), 2.73–2.77 (1H, m, 8-H), 2.79–2.84 (1H, m, 8-H), 4.02 (1H, dd, J=5.5, J=7.0, 10a-H), 6.14 (1H, s, 6a-H), 7.24 (2H, d, J=7.5, 2,6-H_{Ph}), 7.32–7.40 (2H. m. 3-H, 4-H_{Ph}), 7.46 (2H, t, J=7.5, 3,5-H_{Ph}), 7.63 (1H, t, J=8.0, 2-H), 7.90 (1H, d, J=8.0, 1-H), 8.15 (1H, d, J=8.0, 4-H); δ_C ($CDCl_3$) 25.2 (9-C), 28.4 (10-C), 54.2 (8-C), 64.5 (10a-C), 90.8 (6a-C), 119.6 (1-C), 121.5 (4a-C), 125.9 (3-C), 128.3 (4-C), 128.9 (4-C_{Ph}), 129.4 (3,5-C_{Ph}), 130.1 (2,6-C_{Ph}), 133.2 (2-C), 134.9 (12a-C), 138.4 (1-C_{Ph}),163.4 (5-CO), 172.2 (11-CO); ν_{max}(KBr) 1718, 1665, 1654, 1598, 1522, 1490, 1432, 1325, 750, 693 cm^{-1}; found: C, 71.32; H, 5.33; N, 13.20. $C_{19}H_{17}N_3O_2$ requires C, 71.46; H, 5.37; N, 13.16.

*3.3.5. 6-Methyl-5,6,6a,10,10a,11-xehahydro-thiazolo[3′,4′:3,4]imidazo[1,2-a]quinazoline-5,11-dione (**9a**).* Yield 0.56 g (51%); White powder; mp 184–185 °C (from acetonitrile); δ_H (DMSO-d_6) 3.08 (3H, s, CH_3), 3.33 (1H, dd, J^2=10.5, J^3=8.0, 10-H), 3.41 (1H, dd, J^2=10.5, J^3=1.5, 10-H), 4.21 (1H, d, J=11.0, 8-H), 4.38 (1H, dd, J=1.5, J=8.0, 10a-H), 4.58 (1H, d, J=11.0, 8-H), 5.90 (1H, s, 6a-H), 7.39 (1H, t, J=8.0, 3-H), 7.66 (1H, t, J=8.0, 2-H), 7.84 (1H, d, J=8.0, 1-H), 7.95 (1H, d, J=8.0, 4-H); δ_C (DMSO-d_6) 27.9 (CH_3), 37.1 (10-C), 61.5 (8-C), 67.7 (10a-C), 89.5 (6a-C), 120.2 (1-C), 120.8 (4a-C), 126.3 (3-C), 128.5 (4-C), 133.6 (2-C), 134.3 (12a-C), 161.9 (5-CO), 170.4 (11-CO); ν_{max}(KBr) 1728, 1651, 1489, 1471, 1429, 1409, 1374, 1323, 1281, 1230, 1112, 1045, 948, 751, 687 cm^{-1}; found: C, 56.60; H, 4.93; N, 15.38; S, 11.78. $C_{13}H_{13}N_3O_2S$ requires C, 56.71; H, 4.76; N, 15.26; S, 11.65.

*3.3.6. 6-Ethyl-5,6,6a,10,10a,11-xehahydro-thiazolo[3′,4′:3,4]imidazo [1,2-a]quinazoline-5,11-dione (**9b**).* Yield 0.68 g (59%); White powder; mp 188, 189 °C (from toluene); δ_H (DMSO-d_6) 1.20 (3H, t, J=6.0, CH_3), 3.33 (1H, dd, J^2=12.0, J^3=7.0, 10-H), 3.42 (1H, dd, J^2=12.0, J^3=1.0, 10-H), 3.56–3.60 (1H, m, CH_2CH_3), 3.70–3.74 (1H, m, CH_2CH_3), 4.25 (1H, d, J=12.0, 8-H), 4.41 (1H, dd, J=7.0, J=1.0, 10a-H), 4.59 (1H, d, J=12.0, 8-H), 6.08 (1H, s, 6a-H), 7.39 (1H, t, J=8.0, 3-H), 7.66 (1H, t, J=8.0, 2-H), 7.77 (1H, d, J=8.0, 1-H), 7.95 (1H, d, J=8.0, 4-H); δ_C (DMSO-d_6) 14.1 (CH_3), 36.2 (CH_2CH_3), 36.9 (10-C), 61.7 (8-C), 67.8 (10a-C), 89.1 (6a-C), 120.5 (1-C), 121.4 (4a-C), 126.3 (3-C), 128.4 (4-C), 133.6 (2-C), 134.2 (12a-C), 161.4 (5-CO), 170.4 (11-CO); ν_{max}(KBr) 2928, 2853, 1748, 1734, 1716, 1697, 1683, 1669, 1653, 1489, 1473, 1427, 1390, 1122, 756, 724, 687 cm^{-1};

found: C, 58.20; H, 5.37; N, 14.50; S, 10.86. $C_{14}H_{15}N_3O_2S$ requires C, 58.11; H, 5.23; N, 14.52; S, 11.08.

*3.3.7. 6-Benzyl-5,6,6a,10,10a,11-hexahydro-thiazolo[3′,4′:3,4]imidazo[1,2-a]quinazoline-5,11-dione (**9c**).* Yield 0.88 g (63%); White powder; mp 166–167 °C (from dioxane); δ_H (DMSO-d_6) 3.26 (1H, dd, J^2=12.5, J^3=7.5, 10-H), 3.39 (1H, dd, J^2=12.5, J^3=1.0, 10-H), 4.09 (1H, d, J=11.5, 8-H), 4.19 (1H, d, J=11.5, 8-H), 4.26 (1H, dd, J=7.5, J=1.0, 10a-H), 4.86 (2H, s, CH_2Ph), 6.11 (1H, s, 6a-H), 7.22–7.28 (1H, m, H_{Ph}), 7.33–38 (4H, m, $4H_{Ph}$), 7.42 (1H, t, J=7.5, 3-H), 7.69 (1H, t, J=7.5, 2-H), 7.81 (1H, d, J=7.5, 1-H), 8.00 (1H, d, J=7.5, 4-H); δ_C (DMSO-d_6) 36.8 (10-C), 44.8 (CH_2Ph), 61.6 (8-C), 67.8 (10a-C), 89.4 (6a-C), 120.5 (1-C), 121.2 (4a-C), 126.4 (3-C), 127.3 (4-C_{Ph}), 127.7 (3,5-C_{Ph}), 128.7 (4-C), 128.9 (2,6-C_{Ph}), 133.8 (2-C), 134.5 (12a-C), 138.6 (1-C_{Ph}), 162.0 (5-CO), 170.3 (11-CO); ν_{max}(KBr) 1722, 1654, 1488, 1473, 1428, 1417, 1318, 1132, 1103, 766, 754, 731, 717, 699 cm^{-1}; found: C, 64.92; H, 4.70; N, 12.16; S, 9.09. $C_{19}H_{17}N_3O_2S$ requires C, 64.94; H, 4.88; N, 11.96; S, 9.12.

*3.3.8. 6-Phenyl-5,6,6a,10,10a,11-hexahydro-thiazolo[3′,4′:3,4]imidazo[1,2-a]quinazoline-5,11-dione (**9d**).* Yield 0.63 g (47%); Beige crystals; mp 159–160 °C (from toluene); δ_H (DMSO-d_6) 3.20 (1H, dd, J^2=12.0, J^3=8.0, 10-H), 3.36 (1H, dd, J^2=12.0, J^3=1.0, 10-H), 3.66 (1H, d, J=11.5, 8-H), 4.01 (1H, d, J=11.5, 8-H), 4.33 (1H, dd, J=8.0, J=1.0, 10a-H), 6.56 (1H, s, 6a-H), 7.38–7.48 (6H, m, 3-H, $5H_{Ph}$), 7.73 (1H, t, J=8.0, 2-H), 7.89 (1H, d, J=8.0, 1-H), 8.01 (1H, d, J=8.0, 4-H); δ_C (DMSO-d_6) 36.8 (10-C), 61.2 (8-C), 67.6 (10a-C), 90.6 (6a-C), 120.6 (1-C), 121.4 (4a-C), 126.4 (3-C), 128.1 (4-C_{Ph}), 128.8 (4-C), 129.3 (3,5-C_{Ph}), 130.0 (2,6-C_{Ph}), 134.0 (2-C), 134.7 (12a-C), 138.0 (1-C_{Ph}), 162.0 (5-CO), 170.5 (11-CO); ν_{max}(KBr) 1728, 1668, 1656, 1488, 1468, 1421, 1383, 1327, 1156, 1119, 1112, 1087, 758, 747, 699, 687 cm^{-1}; found: C, 64.33; H, 4.55; N, 12.63; S, 9.50. $C_{18}H_{15}N_3O_2S$ requires C, 64.08; H, 4.48; N, 12.45; S, 9.50.

3.4. X-ray crystal structure determination of compound 9c

Intensities of 19,055 reflections (4737 independent, R_{int}=0.030) were measured with 'Xcalibur-3' diffractometer operating in the ω-2θ scan mode, $2\theta_{max}$=60°, and using graphite monochromated Mo Kα radiation (λ=0.71073 Å). Crystal data: $C_{19}H_{17}N_3O_2S$, M_r=351.42, orthorhombic, a=9.6597 Å, b=9.9254 Å, c=16.955 Å, V=1625.6 $Å^3$, T=100 K, space group $P2_12_12_1$, Z=4, μ(Mo Kα)=0.218 mm^{-1}. The structure was solved by direct method with the SHELXTL program package.[42] Positions of hydrogen atoms were located from electron difference density maps and refined isotropically. Full-matrix least-squares refinement against F^2 in anisotropic approximation for non-hydrogen atoms using 4713 reflections was converged to wR_2=0.069, R_1=0.030 [for 4085 reflections with $F>4\sigma(F)$], S=0.865. Full crystallographic parameters (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication number CCDC 848856. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0) 223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

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