Total synthesis of asperlicin C, circumdatin F, demethylbenzomalvin A, demethoxycircumdatin H, sclerotigenin, and other fused quinazolinones†

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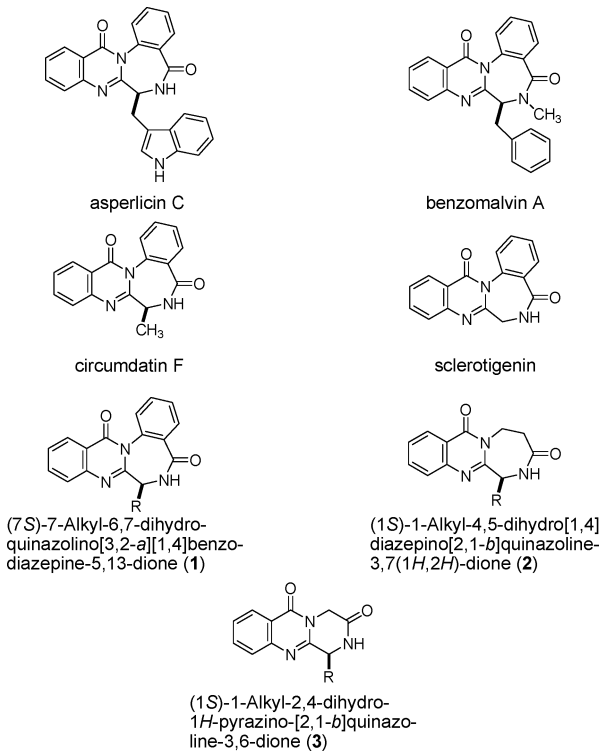
Using scandium triflate and microwaves, the direct double dehydrocyclization of anthranilate-containing tripeptides was achieved, affording the total syntheses of (i) quinazolino[3,2-*a*]-benzodiazepinediones (**1a–f**), (ii) diazepino[2,1-*b*]quinazolinediones (**2a–e**), and (iii) pyrazino[2,1-*b*]quinazolinediones (**3a–e**) with good overall isolated yields (23–43%, 37–47% and 31–56%, respectively). Among the quinazolino[3,2-*a*]benzodiazepinediones synthesized, **1a** (sclerotigenin), **1b** (circumdatin F), and **1f** (asperlicin C) are natural products.

Introduction

Many natural products are heterocyclic compounds, and a good number of them are quinazolinone alkaloids.[1] Due in part to its wide range of useful pharmacological properties, the structure of quinazolinone has been extensively utilized as a valuable scaffold for drug discovery in medicinal chemistry. Some synthetic quinazolinones, such as Raltitrexed, Ispinesib and Tempostatin, have been on the market or are currently in clinical trials for cancer treatment. In recent years, more natural products with the quinazolinone core structure have been isolated and purified.[1] These alkaloids in general fall into two families: with the quinazolinone fused to a benzodiazepinedione, as in asperlicin C, or to a diketopiperazine, as in fumiquinazoline F. Among them, natural products consisting of two anthranilic acids (Abz) and an amino acid condensed together forming the quinazolino[3,2-*a*][1,4]-benzodiazepine core unit have been isolated from various microorganisms. These include asperlicins A–E from *Aspergillus alliaceus*,[2] benzomalvins A–C from *Penicillium* sp,[3] circumdatins A–H from *Aspergillus ochraceus*,[4] and sclerotigenin from *Penicillium sclerotigenum* and *Penicillium commune*;[5] a number of them are biologically active (*e.g.*, circumdatin H is an inhibitor of the mammalian mitochondrial respiratory chain, with an IC_{50} value of 1.5 μM[4a]). We recently reported the use of metal triflates to facilitate total syntheses of the conformationally constrained quinazolino[3,2-*a*][1,4]-benzodiazepines and pyrazino[2,1-*b*]quinazolinones.[6] On the basis of our previous findings, in this full paper, we extend our synthetic protocol to the structurally diverse members: (i) quinazolino[3,2-*a*]benzodiazepinediones (**1a–f**), (ii) diazepino[2,1-*b*]quinazolinediones (**2a–e**), and (iii) pyrazino[2,1-*b*]quinazolinediones (**3a–e**). Among **1a–f** synthesized, sclerotigenin (**1a**, R = H), circumdatin F (**1b**, R = CH_3), and asperlicin C (**1f**, R = CH_2indole) are natural products.



In the literature, there have been three synthetic strategies primarily developed for the preparation of quinazolinobenzodiazepines (**1**). The Snider, Thomas, and Eguchi groups separately reported the employment of a powerful Staudinger/intramolecular aza-Wittig tandem reaction, known as the Eguchi protocol,[7] for the total synthesis of sclerotigenin (**1a**), circumdatin F (**1b**), asperlicin C (**1f**) and benzomalvin A.[7] Though it provided a direct route to heterocyclic natural products, this protocol nevertheless suffered from the limited solubility of the benzodiazepine in conventional solvents and the formation of the bis-adduct upon acylation reaction. With a 2.5% overall yield, Witt and Bergman afforded a six-step total synthesis of circumdatin F (**1b**) by adopting the Ganesan procedure

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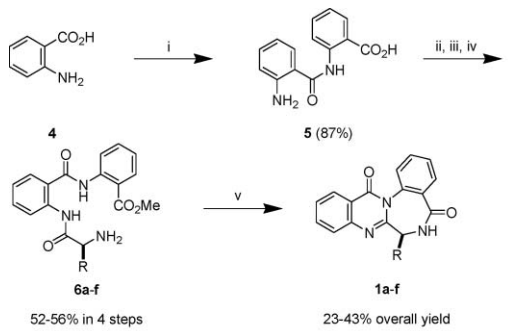
(triphenylphosphine, iodine and a tertiary amine) in which the formation of an iminobenzoxazine intermediate was the key step.[8] In addition, Bock's group completed the first total syntheses of asperlicins C and E, featuring a regioselective annulation of benzodiazepinedione with anthranilic acid.[9] From the synthesis point of view, both the Eguchi and the Ganesan protocols are two important methods exploited for the construction of quinazolinone rings. Most recently, Liu and co-workers achieved syntheses of racemic quinazolinobenzodiazepines (**1**) using a one-pot domino procedure that owes its success to microwave heating at 230 °C.[10] All of these aforementioned experimental procedures, however, either required a number of synthetic steps or proceeded with long reaction times and low to moderate yields; hence, alternative reagents and efficient reaction conditions to facilitate the direct transformation to the quinazolinones are to be of great value.

Results and discussion

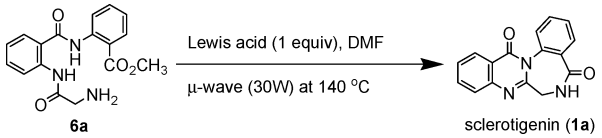
We envisioned that our strategy of using metal triflates to access quinazolinones should be useful to construct compounds such as **1–3** so that the molecular diversity of quinazolinone-based molecules may be explored. For the work presented in this paper, we first began our experiments by synthesizing quinazolino[3,2-*a*]benzodiazepinediones (**1a–f**) and optimizing their preparation. Our route to natural and unnatural **1a–f** is shown in Scheme 1. Since the natural product sclerotigenin (**1a**) gave the lowest isolated yield among the quinazolino[3,2-*a*]benzodiazepinediones (**1**) synthesized in our recent preliminary communication,[6a] in this full paper, we decided to choose **1a** as our synthetic target on which to optimize the reaction conditions, including screening for the optimization of metal triflates and solvents. At first, we selected nine metal triflates available in our laboratory, and carried out the screening to identify the most effective Lewis acids that efficiently facilitate the formation of the ring structure **1a** from its open-chain tripeptide precursor (**6a**). This precursor, Gly-Abz-Abz-OMe **6a**, was readily prepared in a straightforward manner: a direct coupling of anthranilic acid **4** with isatoic anhydride in heated water to generate Abz-Abz **5** with a high isolated yield (87%), which was subsequently converted to its methyl ester (80% yield) in hot acidic methanol, followed by condensing with Cbz-Gly in the presence of EDC (84% yield), and finally deprotection



i) isatoic anhydride, H_2O, reflux, 2 h; ii) H_2SO_4/MeOH (1:25, v/v) reflux, 5 d, 80%; iii) Cbz-L-amino acid, EDC CH_2Cl_2, rt, 2-6 h, 78-86%; iv) H_2,Pd(OH)$_2$/C, rt, MeOH, 0.5 h, 91-97%; v) Sc(OTf)$_3$, DMF, 10-15 min, μ-wave (30W) at 140 °C, 44-78%

Scheme 1 Synthesis of 7-substituted quinazolino[3,2-*a*]benzodiazepinediones (**1a–f**).

Table 1 Screening of Lewis acid catalysts for dehydrative cyclization of Gly-Abz-Abz-OMe (**6a**) to sclerotigenin (**1a**)



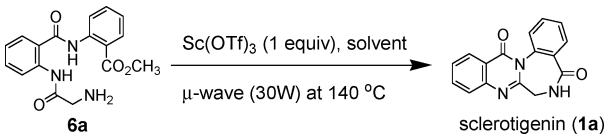
Entry	Lewis acid	Reaction time/min	Isolated yield (%)
1	$Al(OTf)_3$	60	23
2	$Cu(OTf)_2$	N.R.[a]	—
3	$La(OTf)_3$	20	25
4	$Mg(OTf)_2$	50	20
5	$Sc(OTf)_3$	10	61
6	$Sm(OTf)_3$	20	39
7	$Sn(OTf)_2$	10	50
8	$Yb(OTf)_3$	10	39
9	$Zn(OTf)_2$	15	7

[a] No reaction.

by catalytic hydrogenation (96% yield) to afford the desired Gly-Abz-Abz-OMe **6a** (56% isolated yield in four steps). With the aid of metal triflates, we then employed microwaves[11] to deliberately facilitate the concomitant double dehydrocyclization reaction as the last step in the total synthesis. Therefore, compound **6a** was treated with all nine metal triflates in DMF by microwaves with the temperature controlled at 140 °C, to see if the dehydrative cyclization would successfully achieve **1a**.

Table 1 summarises the screening results and, among metal triflates tested, $Sc(OTf)_3$ showed the best activity with the shortest reaction time (10 min) and the highest isolated yield (61%, entry 5). Table 1 shows that the catalytic activities of the triflates greatly depend on the associated cation. The Lewis acids $Al(OTf)_3$, $La(OTf)_3$, $Mg(OTf)_2$, $Sm(OTf)_3$, $Sn(OTf)_2$, $Yb(OTf)_3$ and $Zn(OTf)_2$ were moderately effective (longer reaction time or lower yield), but $Cu(OTf)_2$ was totally inactive. No sclerotigenin **1a** was formed in the absence of Lewis acid. The solvent effect was investigated (Table 2), and DMF was found to be the best choice

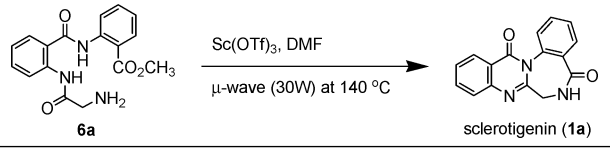
Table 2 Optimization of solvents used for dehydrative cyclization of Gly-Abz-Abz-OMe (**6a**) to sclerotigenin (**1a**)



Entry	Solvent	b.p./°C	Reaction time/min	Isolated yield (%)
1	*o*-Xylene	143	N.R.[a]	—
2	Anisole	154	N.R.[a]	—
3	DMF	155	10	61
4	DMF[b]	155	N.R.[a]	—
5	Diglyme	162	N.R.[a]	—
6	Diglyme[c]	162	N.R.[a]	—
7	DMSO	189	5	58
8	HMPA	232	5	21
9	[bdmim][NTf_2]	—	N.R.[a]	—

[a] No reaction was observed after 10 min reaction time. [b] Instead of $Sc(OTf)_3$, triflic acid (1 equiv.) was used as a Brønsted protic acid. [c] Ionic liquid [bdmim][NTf_2] (10%, v/v) was added to attempt to promote the microwaved reaction.

Table 3 Optimization in stoichiometry of the $Sc(OTf)_3$ catalyst used for dehydrative cyclization of Gly-Abz-Abz-OMe (**6a**) to sclerotigenin (**1a**)



Entry	$Sc(OTf)_3$/equiv.	Reaction time/min	Isolated yield (%)
1	1	10	61
2	0.5	15	54
3	0.2	60	44

(entry 3). We also found that the dehydrocyclization reaction did not need to be performed in anhydrous solvent; that is, the straight use of on-the-shelf DMF as the reaction medium sufficed. Moreover, the amount of $Sc(OTf)_3$ used in the reaction was tested (Table 3), and 1 mol equiv. proved to be the most practical stoichiometry in terms of reaction time and isolated yield (entry 1). This direct formation of **1a** from **6a** is attractive simply because the construction of two rings could be concomitantly prepared in one reaction step.

The successful preparation of **1a** using metal triflates allowed us to pursue further the total syntheses of more complex target compounds with greater diversity (**1b–f**, Table 4). The results in Table 4 show that compounds **1b–f**, including the natural products circumdatin F (**1b**) and asperlicin C (**1f**), were readily synthesized with good yields in 10–15 min by $Sc(OTf)_3$ and microwaves from their linear tripeptides **6b–f**. In the case of **1e**, which has a constrained proline ring, a low isolated yield was obtained (44%, entry 4). Under the experimental conditions, circumdatin F (**1b**) gave the highest isolated yield (78%, entry 1). The overall yields for **1a–f** in this five-step total synthesis were 23–43%.

Whether or not any racemization had taken place at the amino acid was examined through ^{1}H NMR spectroscopy in the presence of europium(III) tris[3-(heptafluoropropyl hydroxymethylene)-(+)-camphorate], (+)-Eu(hfc)$_3$, as a chiral shift reagent.[12] The results in Fig. 1 clearly show that, as representative examples, synthetic **1b** (circumdatin F) and **1c** are stereochemically pure and essentially free of racemization. This nicely suggests that, under our experimental conditions, the $Sc(OTf)_3$-promoted dehydrocyclization reaction appeared to preserve chirality during the total synthesis of optically active quinazolinobenzodiazapines (**1**).[13]

We extended our protocol further by broadening its scope in synthesis to prepare new compounds with greater molecular diversity: diazepino[2,1-*b*]quinazolinediones (**2a–e**) and pyrazino[2,1-*b*]quinazolinediones (**3a–e**). Adopting a similar approach, starting compounds β-alanine (**7**) and glycine methyl ester (**10**) were incorporated in a straightforward manner to construct the desired **2a–e** and **3a–e**, respectively (Schemes 2 and 3). To our delight, the key $Sc(OTf)_3$-catalyzed dehydrocyclization reactions of **9a–e** and **12a–e** tripeptides proceeded smoothly and required very short reaction times (1–3 min) to afford the target products **2a–e** and **3a–e** with good to high isolated yields (67–86% and 49–86%, respectively) (Tables 5 and 6). In our hands, compounds **2c**

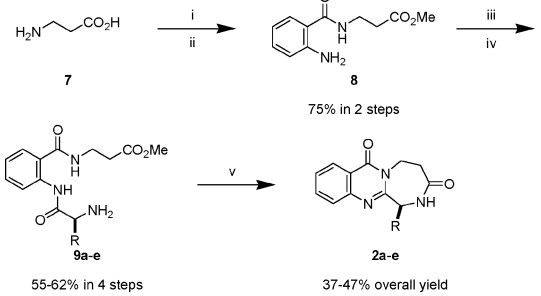


Fig. 1 ^{1}H NMR (400 MHz) spectra of the highlighted (a) methyl protons of synthetic circumdatin F (**1b**) prepared from L-Ala (top) and D,L-Ala (bottom), and (b) aryl proton of the target compound **1c** prepared from L-Leu (top) and D,L-Leu (bottom) in $CDCl_3$ after the addition of 0.132 and 0.59 equiv., respectively, of the chiral shift reagent (+)-Eu(hfc)$_3$.

i) isatoic anhydride, TEA, EtOAc, reflux, 2 h; ii) Cbz-L-amino acid, EDC, CH_2Cl_2, rt, 0.5-1 h, 78-86%; iii) $SOCl_2$, MeOH, 0 °C to rt, 1 h; iv) H_2, $Pd(OH)_2$/C, rt, MeOH, 0.5 h, 90-96%; v) $Sc(OTf)_3$, DMF, 1-3 min, μ-wave (30W) at 140 °C, 67-86%.

Scheme 2 Synthesis of 1-substituted diazepino[2,1-*b*] quinazolinediones (**2a–e**)

Table 4 Quinazolino[3,2-*a*]benzodiazepinediones (**1b–f**) prepared from $Sc(OTf)_3$-promoted dehydrocyclization of linear tripeptides, X-Abz-Abz-OMe (**6b–f**), in DMF at 140 °C by microwaves[a]

Entry	X	R	Product	Reaction time/min	Isolated yield (%)
1	L-Ala	H	**1b** (circumdatin F)	15	78
2	L-Leu	CH_3	**1c**	10	46
3	L-Phe	CH_2Ph	**1d** (demethylbenzomalvin A)	15	61
4	L-Pro	$(CH_2)_3$	**1e** (demethoxycircumdatin H)	10	44
5	L-Trp	CH_2indole	**1f** (asperlicin C)	15	68

[a] Reaction conditions: tripeptide, 30 mg; $Sc(OTf)_3$, 1 equiv.; DMF, 0.3 mL. Individual microwave-assisted reactions were carried out in a reaction vessel and temperature-controlled at 140 °C using a commercial CEM Discover instrument (CEM Corporation, Matthews, NC, USA). 30 W microwave power was applied throughout the reaction period.

Table 5 Diazepino[2,1-*b*]quinazolinediones (**2a–e**) prepared from $Sc(OTf)_3$-promoted dehydrocyclization of linear tripeptides, X-Abz-β-Ala-OMe (**9a–e**), in DMF at 140 °C with microwaves[a]

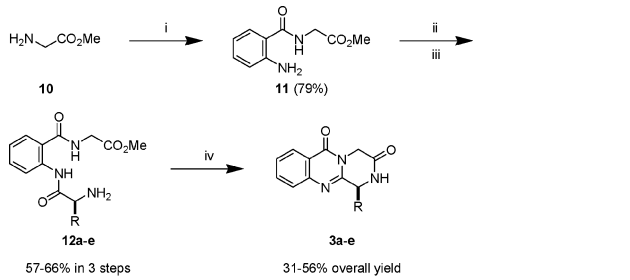
Entry	X	R	Product	Reaction time/min	Isolated yield (%)
1	Gly	H	**2a**	1	67
2	L-Ala	CH_3	**2b**	1	80
3	L-Phe	CH_2Ph	**2c**	3	86
4	L-Pro	$(CH_2)_3$	**2d**	1	70
5	L-Trp	CH_2indole	**2e**	3	71

[a] Reaction conditions: tripeptide, 30 mg; $Sc(OTF)_3$, 1 equiv.; DMF, 0.3 mL. Individual microwave-assisted reactions were carried out in a reaction vessel and temperature-controlled at 140 °C using a commercial CEM Discover instrument (CEM Corporation, Matthews, NC, USA). 30 W microwave power was applied throughout the reaction period.

Table 6 Pyrazino[2,1-*b*]quinazolinediones (**3a–e**) prepared from $Sc(OTf)_3$-promoted dehydrocyclization of linear tripeptides, X-Abz-Gly-OMe (**12a–e**), in DMF at 140 °C with microwaves[a]

Entry	X	R	Product	Reaction time/min	Isolated yield (%)
1	Gly	H	**3a**	1	86
2	L-Ala	CH_3	**3b**	1.5	84
3	L-Phe	CH_2Ph	**3c**	2	73
4	L-Pro	$(CH_2)_3$	**3d**	2	49
5	L-Trp	CH_2indole	**3e**	2	76

[a] Reaction conditions: tripeptide, 30 mg: $Sc(OTf)_3$, 1 equiv.; DMF, 0.3 mL. Individual microwave-assisted reactions were carried out in a reaction vessel and temperature-controlled at 140 °C using a commercial CEM Discover instrument (CEM Corporation, Matthews, NC, USA). 30 W microwave power was applied throughout the reaction period.



i) isatoic anhydride, TEA, EtOA, reflux, 2 h; ii) Cbz-L-amino acid, EDC, H_2Cl_2, rt, 0.5-1 h, 80-89%; iii) H_2, $Pd(OH)_2$/C, rt, MeOH, 15-30 min, 88-96%; iv) $Sc(OTf)_3$, DMF, 1-2 min, μ-wave (30W) at 140 °C, 49-86%

Scheme 3 Synthesis of 1-substituted pyrazino[2,1-*b*] quinazolinediones (**3a–e**)

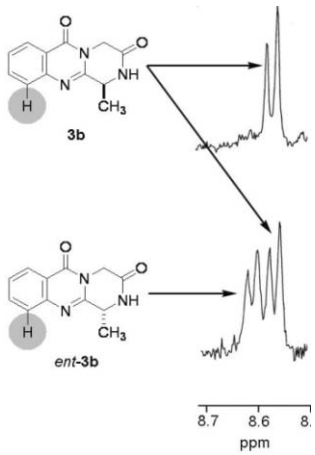


Fig. 3 ^{1}H NMR (400 MHz) spectra of the highlighted aryl proton of the target compound **3b** prepared from L-Ala (top) and D,L-Ala (bottom) in $CDCl_3$ after the addition of 2.80 equiv. of the chiral shift reagent (+)-Eu(hfc)$_3$.

(entry 3, Table 5) and **3a** (entry 1, Table 6) gave the highest yield (86%). The overall yields for the syntheses of **2a–e** and **3a–e** were 37–47% and 31–56% in a total of five and four reaction steps, respectively. Chiral resolution experiments by ^{1}H NMR in the presence of (+)-Eu(hfc)$_3$ in $CDCl_3$ unambiguously showed that, using **2b** and **3b** as illustrative examples, new quinazolinones **2** and **3** synthesized in this work are enantiopure and free of noticeable racemization (Fig. 2 and 3).[13] This unambiguously demonstrates that, under our experimental conditions, the chirality is preserved (including during the $Sc(OTf)_3$-promoted dehydrocyclization reaction) throughout the synthesis of quinazolindiones **2a–e** and **3a–e**. The successful application of our synthetic protocol to access various fused quinazolinones **1–3** demonstrates the utility of this new method. Both the synthetic scheme and the chiral ^{1}H NMR

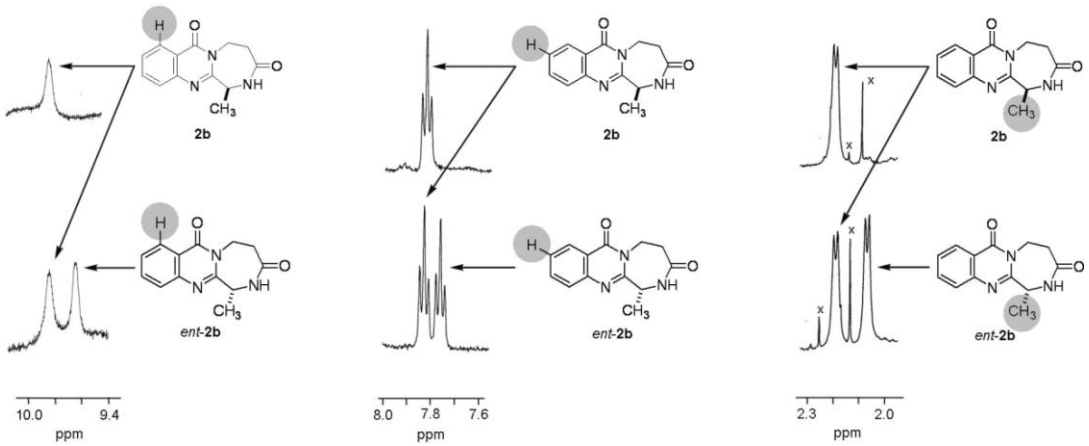


Fig. 2 ^{1}H NMR (400 MHz) spectra of the highlighted aryl and methyl protons of the target compound **2b** prepared from L-Ala (top) and D,L-Ala (bottom) in $CDCl_3$ after the addition of 1.26 equiv. of the chiral shift reagent (+)-Eu(hfc)$_3$.

procedure depicted in this work should be effective means of preparing and characterizing constrained, quinazolinone-based peptidomimetics.

Conclusions

In conclusion, the total syntheses of sclerotigenin (**1a**), circumdatin F (**1b**) and asperlicin C (**1f**) natural products, and their analogous compounds (**1c–e**) were achieved in five steps with 23–43% overall isolated yields starting from anthranilic acid. Using the synthetic approaches developed in this report, structurally similar diazepino[2,1-*b*]quinazolinones (**2a–e**) and pyrazino[2,1-*b*]quinazolinones (**3a–e**) were readily synthesized with good overall isolated yields of 37–47% and 31–56%, respectively. In continuously exploring the search for natural and synthetic quinazolinone compounds that produce useful pharmacological activities and other tailored properties, the compounds with a quinazolinone ring fused with α- and β-amino acids prepared in this work shall provide a convenient entry to new quinazolinone entities.

Experimental section

Gerneral

Flash chromatography was performed on silica gel (230–400 mesh). TLC was carried out on aluminium-backed silica plates precoated with silica (0.2 mm), which were developed using standard visualizing agents, such as UV fluorescence and iodine. Unless otherwise indicated, all reactions were carried out without the aid of dry nitrogen or argon. NMR spectra were recorded on a Bruker AVANCE DPX 400 at 400 MHz (^{1}H) and 100.6 MHz (^{13}C), both in $CDCl_3$ unless otherwise stated. Chemical shifts are quoted in parts per million (ppm). Melting points were determined on a Fargo MP-2D apparatus (Taiwan, ROC) and are uncorrected. Solvents and reagents were obtained from commercial sources and were used without further purification.

General procedure for the total synthesis of quinazolino[3,2-*a*][1,4]benzodiazepines (1a–f). A suspension of isatoic anhydride (2.5 g, 15.3 mmol) and anthranilic acid **4** (2.3 g, 16.8 mmol) in water (50 mL) was refluxed for 2 h and then cooled. The solid product was filtered, washed with water, and dried to obtain Abz-Abz **5** (3.4 g, 87% yield) as a pale yellow powder with excellent purity.

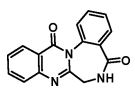
To a solution of sulfuric acid (2 mL) in methanol (50 mL) was added Abz-Abz **5** (2 g, 7.8 mmol). The reaction mixture was heated at reflux for 5 d and then cooled. The solution was concentrated under reduced pressure to give a brown oil and poured into water (20 mL). The pH was adjusted to 8 with 10% NaOH in an ice bath and then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to afford a brown residue, and purified by flash chromatography (ethyl acetate–hexane = 1 : 7) to give the desired methyl ester (1.67 g, 80% yield) as a light yellow solid.

For tripeptide preparation, EDC (1.1 equiv.) was added to a solution of the aforementioned methyl ester (1.1 equiv.) and *N*-Cbz-protected L-amino acid (100 mg) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at ambient temperature for 2–6 h. The mixture was washed with 10% citric acid (3 × 5 mL) and dried (Na_2SO_4), concentrated under reduced pressure to afford a solid residue and further purified by flash chromatography (ethyl acetate–hexane = 1 : 5–1 : 8) to give the desired product Cbz-X-Abz-Abz-OMe (X= L-amino acid) (78–86% yield) as white solids.

This Cbz-protected tripeptide was then deprotected by catalytic hydrogenation. To a solution of tripeptide (100 mg) in methanol (30 mL) was added a catalytic amount of 20% $Pd(OH)_2/C$ and a balloon of hydrogen. This deprotection reaction by hydrogenation was allowed to proceed until the protected tripeptide was completely consumed (0.5 h). The reaction mixture was filtered and concentrated under reduced pressure to give the product **6a–f** as a colorless solid (91–97% yield).

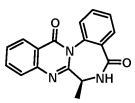
To a microwave reaction vessel was added **6a–f** (30 mg), $Sc(OTf)_3$ (1 equiv.) and DMF (0.3 mL). The vessel was placed inside a CEM Discover single-mode microwave synthesizer equipped with a magnetic stirrer, where it was exposed to microwaves at 140 °C (30 W) for 10–15 min. After reaction the DMF was removed under reduced pressure and the mixture was poured into water (5 mL). The solution was extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to afford a brown residue, and finally purified by flash column chromatography (ethyl acetate–hexane = 1 : 1–1 : 5) to obtain the desired quinazolino[3,2-*a*][1,4]benzodiazepine products **1a–f** (44–78% yield) as white solids.

6,7-Dihydroquinazolino[3,2-*a*][1,4]benzodiazepine-5,13-dione (sclerotigenin)



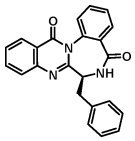
White solid, mp 308–310 °C; δ_H (400 MHz; DMSO-d_6) 4.00 (1H, dd, J = 15.4, 6.6 Hz, NCH_2), 4.18 (1H, dd, J = 15.4, 5.1 Hz, NCH_2), 7.58-7.65 (4H, m, ArH), 7.71 (1H, d, J = 8.0 Hz, ArH), 7.79 (1H, d, J = 7.4 Hz, ArH), 7.89 (1H, t, J = 7.6 Hz, ArH), 8.18 (1H, d, J = 7.7 Hz, ArH), 8.89 (1H, t, J = 5.3 Hz, NH); δ_C (100 MHz; DMSO-d_6) 46.4, 121.2, 127.1, 127.3, 127.8, 128.7, 129.0, 129.6, 130.8, 130.9, 133.6, 135.4, 146.3, 155.0, 161.2, 167.2; FAB-HRMS m/z $[M + H]^+$ calcd for $C_{16}H_{12}O_2N_3$ 278.0930, found 278.0927.

(7*S*)-6,7-Dihydro-7-methylquinazolino[3,2-*a*][1,4]-benzodiazepine-5,13-dione (circumdatin F)



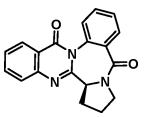
White solid, mp 261–263 °C; δ_H (400 MHz; $CDCl_3$) 1.74 (3H, t, J = 6.8 Hz, CH_3), 4.43 (1H, quin, J = 6.4 Hz, NCH), 6.40 (1H, d, J = 5.6 Hz, NH), 7.56-7.66 (4H, m, ArH), 7.75-7.82 (2H, m, ArH), 8.00 (1H, dd, J = 7.2, 1.2 Hz, ArH), 8.34 (1H, d, J = 7.9 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 15.4, 50.2, 121.5, 127.4, 127.5, 127.8, 128.5, 129.4, 130.0, 130.8, 131.4, 133.7, 134.9, 146.2, 155.2, 161.8, 168.4; FAB-HRMS m/z $[M + H]^+$ calcd for $C_{17}H_{14}O_2N_3$ 292.1086, found 292.1090.

(7*S*)-7-Benzyl-6,7-dihydroquinazolino[3,2-*a*][1,4]-benzodiazepine-5,13-dione



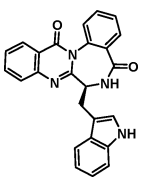
White solid, mp 140–142 °C; δ_H (400 MHz; $CDCl_3$) 3.30 (1H, dd, J = 14.4, 8.4 Hz, $PhCH_2$), 3.69 (1H, dd, J = 14.8, 5.6 Hz, $PhCH_2$), 4.40 (1H, q, J = 6.0 Hz, NCH), 7.20-7.34 (5H, m, ArH), 7.39-7.47 (2H, m, ArH), 7.57-7.66 (4H, m, ArH), 7.87 (1H, d, J = 7.6 Hz, ArH), 8.04 (1H, d, J = 6.0 Hz, NH), 8.10 (1H, d, J = 7.6 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 36. 1, 55.3, 120.8, 127.1, 127.3, 127.6, 127.8, 128.4, 128.5, 128.8, 129.7, 130.1, 130.4, 131.1, 133.2, 134.6, 137.1, 153.7, 161.2, 168.7; FAB-HRMS m/z [M + H]$^+$ calcd for $C_{23}H_{18}O_2N_3$ 368.1399, found 368.1390.

(7*S*)-6,7-Dihydro-7-hexahydropyrrolo[1′,2′:1,2] quinazolino[3,2-*a*][1,4]-benzodiazepine-5,13-dione



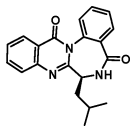
White solid, mp 228–230 °C; δ_H (400 MHz; $CDCl_3$) 2.06-2.19 (2H, m, CH_2), 2.29-2.45 (1H, m, CH_2), 3.16-3.21 (1H, m, CH_2), 3.58-3.65 (1H, m, CH_2), 3.77-3.82 (1H, m, CH_2), 4.55 (1H, d, J = 7.6 Hz, NCH), 7.50-7.61 (5H, m, ArH, NH), 7.70-7.81 (2H, m, ArH), 8.0 (1H, d, J = 7.7 Hz, ArH), 8.0 (1H, dd, J = 8.0, 0.92 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 23.6, 26.9, 46.4, 58.8, 121.5, 127.4, 127.5, 127.5, 128.3, 128.6, 129.9, 130.7, 132.3, 133.2, 134.7, 146.0, 153.6, 161.6, 164.4; FAB-HRMS m/z [M + H]$^+$ calcd for $C_{20}H_{18}O_2N_3$ 318.1368, found 318.1243.

(7*S*)-6,7-Dihydro-7-((indol-2-yl)methyl)quinazolino[3,2-*a*][1,4]-benzodiazepine-5,13-dione (asperlicin C)



White solid, mp 313–314 °C; δ_H (400 MHz; DMSO-d_6) 3.36-3.44 (1H, m, indolyl-CH_2), 3.66 (1H, dd, J = 14.8, 4.8 Hz, indolyl-CH_2), 4.39-4.41 (1H, m, NCH), 6.92 (1H, t, J = 7.6 Hz, ArH), 7.02 (1H, t, J = 7.6 Hz, ArH), 7.32-7.34 (2H, m, ArH), 7.52-7.70 (6H, m, ArH), 7.85 (4H, d, J = 8.0 Hz, ArH), 7.91 (1H, d, J = 7.2 Hz, ArH), 8.20 (1H, d, J = 8.0 Hz, ArH), 8.92 (1H, d, J = 6.4 Hz, ArH), 10.87 (1H, bs, NH); δ_C (100 MHz; DMSO-d_6) 25.6, 57.1, 110.0, 111.6, 118.5, 119.2, 121.1, 122.2, 124.7, 127.1, 127.3, 127.7, 127.8, 128.7, 129.0, 130.9, 131.4, 132.6, 135.1, 136.2, 147.2, 155.9, 161.3, 167.6; FAB-HRMS m/z [M + H]$^+$ calcd for $C_{25}H_{19}O_2N_4$ 407.1508, found 407.1502.

(7*S*)-6,7-Dihydro-7-isobutylquinazolino[3,2-*a*][1,4]-benzodiazepine-5,13-dione



White solid, mp 227–229 °C; δ_H (400 MHz; $CDCl_3$) 0.90 (3H, d, J = 6.5 Hz, CH_3), 1.00 (3H, d, J = 6.5 Hz, CH_3), 1.86-2.04 (2H, m, CH_2), 2.14-2.21 (1H, m, CH), 4.20 (1H, q, J = 2.4 Hz, NCH), 6.66 (1H, d, J = 6.5 Hz, NH), 7.49-7.81 (6H, m, ArH), 7.96 (1H, d, J = 7.4 Hz, ArH), 8.29 (1H, d, J = 7.8 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 22.2, 233, 24.6, 38.3, 52.6, 121.7, 127.6, 127.8, 128.0, 128.6, 129.2, 130.0, 131.0, 131.5, 133.7, 135.0, 146.4, 154.9, 161.9, 168.1; FAB-HRMS m/z [M + H]$^+$ calcd for $C_{20}H_{20}O_2N_3$ 334.1556, found 334.1613.

General procedure for the total synthesis of diazepino[2,1-*b*]quinazolinediones (2a–e)

To a round-bottom flask containing methanol (50 mL) and β-alanine **7** (1 g, 11.2 mmol) at 0 °C was added slowly thionyl chloride (2.5 equiv.). The progress of the reaction was monitored by TLC. After the completion of the reaction (1 h), the mixture solution was evaporated (to remove methanol and excess thionyl chloride) and then lyophilized to afford the product methyl β-alaninate HCl (91% yield).

A suspension of isatoic anhydride (2.5 g, 15.3 mmol), methyl β-alaninate HCl (2.3 g, 16.8 mmol), and triethylamine (3.13 mL) in ethyl acetate (50 mL) was refluxed for 2 h and then cooled. The solid precipitate was filtered off and the organic layer was extracted with aqueous KOH. The resulting organic solution was then evaporated to obtain the crude product, and purified by flash chromatography (dichloromethane–methanol = 150 : 1) to afford the desired product **8** (82% yield).

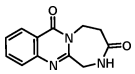
For tripeptide preparation, EDC (1.2 equiv.) was added to a solution of **8** (1.1 equiv.) and *N*-Cbz-protected L-amino acid (100 mg) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at ambient temperature for 0.5–1 h. The mixture was washed with 10% citric acid (3 × 5 mL), dried (Na_2SO_4), and concentrated under reduced pressure to afford a solid residue, which was further purified by flash chromatography (ethyl acetate–hexane = 1 : 1) to give Cbz-X-Abz-β-Ala-OMe (X= L-amino acid) (78–86% yield).

This Cbz-protected tripeptide was then deprotected by catalytic hydrogenation. To a solution of tripeptide (100 mg) in methanol (30 mL) was added a catalytic amount of 20% $Pd(OH)_2/C$ and a balloon of hydrogen. This deprotection reaction by hydrogenation was allowed to proceed until the protected tripeptide was completely consumed (15–30 min). The reaction mixture was filtered and concentrated under reduced pressure to give the product **9a–e** as a colorless solid (90–96% yield).

To a microwave reaction vessel was added **9a–e** (30 mg), $Sc(OTf)_3$ (1 equiv.) and DMF (0.3 mL). The vessel was placed inside a CEM Discover single-mode microwave synthesizer equipped with a magnetic stirrer, where it was exposed to microwaves at 140 °C (30 W) for 1–3 min. After reaction the DMF was removed under reduced pressure to afford a brown residue, and finally purified by flash column chromatography (dichloromethane–methanol = 40 : 1) to obtain the desired

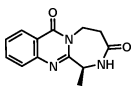
diazepino[2,1-*b*]quinazolinediones **2a–e** (67–86% yield) as white solids.

2*H*-[1,4]Diazepino[2,1-*b*]quinazoline-3,7-(1*H*,4*H*,5*H*)-dione



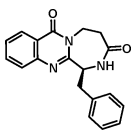
White solid, mp 250–253 °C; δ_H (400 MHz; DMSO-d_6) 2.66 (2H, t, J = 6 Hz, $COCH_2$), 4.41 (2H, d, $CONHCH_2$), 4.49 (2H, t, J = 6 Hz, NCH_2), 7.54 (1H, t, J = 7.4 Hz, ArH), 7.65 (1H, d, J = 8.2 Hz, ArH), 7.83 (1H, t, J = 7.6, Hz, ArH), 8.13 (2H, m, ArH and CONH); δ_C (100 MHz, DMSO-d_6) 35.1, 36.7, 45.8, 120.6, 126.6, 127.3, 127.3, 134.7, 147.1, 155.0, 160.5, 170.1; FAB-HRMS m/z [M + H]$^+$ calcd for $C_{12}H_{11}O_2N_3$ 229.0851, found 229.0930.

(1*S*)-1-Methyl-2*H*-[1,4]diazepino[2,1-*b*]quinazoline-3,7-(1*H*,4*H*,5*H*)-dione



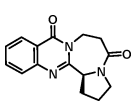
White solid, mp 289–291; δ_H (400 MHz; DMSO-d_6) 1.5 (3H, d, J = 6.4 Hz, CH_3), 2.81 (1H, d, J = 18.3 Hz, COC*H*H), 4.20 (1H, t, J = 12.6 Hz, NC*H*H), 4.90 (1H, dd, J = 14.8, 3.52 Hz, NC*H*H), 5.21-5.22 (1H, m, CONHC*H*), 7.54 (1H, t, J = 7.6 Hz, ArH), 7.67 (1H, d, J = 8.1 Hz, ArH), 7.83 (1H, t, J = 7.6 Hz, ArH), 7.89 (1H, s, CONH), 8.14 (1H, d, J =7.8 Hz, ArH); δ_C (100 MHz; DMSO-d_6) 16.9, 35.0, 35.6, 47.9, 120.6, 126.6, 127.2, 127.6, 134.7, 146.8, 156.9, 160.7, 169.9; FAB-HRMS m/z [M + H]$^+$ calcd for $C_{13}H_{13}O_2N_3$ 243.1008, found 243.1086.

(1*S*)-1-(Phenylmethyl)-2*H*-[1,4]diazepino[2,1-*b*]quinazoline-3,7-(1*H*,4*H*,5*H*)-dione



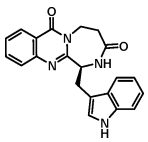
White solid, mp 207–209 °C; δ_H (400 MHz; $CDCl_3$) 2.75-3.00 (2H, m, Phe-CH*H* and COC*H*H), 3.20 (1H, dd, J = 14.8, 9.1 Hz, Phe-CH*H*), 3.75 (1H, dd, J = 14.8, 4.8 Hz, COC*H*H), 4.01 (1H, td, J = 14.3, 3.4 Hz, NC*H*H), 5.09-5.13 (1H, m, CONHC*H*), 5.27 (1H, dt, J = 15.2, 4.2 Hz, NC*H*H), 7.28-7.40 (5H, m, ArH), 7.53 (1H, td, J = 8, 1.2 Hz, ArH), 7.74-7.82 (2H, m, ArH), 8.30 (1H, d, J = 8.0 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 35.0, 35.5, 37.6, 54.2, 120.7, 127.0, 127.5, 127.5, 127.7, 129.1, 129.1, 129.2, 129.3, 134.5, 135.9, 146.6, 153.4, 161.1, 170.1; FAB-HRMS m/z [M + H]$^+$ calcd for $C_{19}H_{17}O_2N_3$ 319.1321, found 319.1355.

(1*S*)-Hexahydropyrrolo[1′,2′:1,2][1,4]diazepino[2,1-*b*]quinazoline-3,7-(1*H*,4*H*,5*H*)-dione



White solid, mp 250–253 °C; δ_H (400 MHz; DMSO-d_6) δ 1.79-1.97 (2H, m, NCH_2CH_2), 2.15-2.23 (1H, m, NCH_2CH_2CHH), 2.52-2.60 (1H, m, COCH*H*), 2.82 (1H, d, J = 18.3 Hz, COCH*H*), 2.92-3.01 (1H, m, NCH_2CH_2CHH), 3.39-3.46 (1H, m, NCH*H*), 3.53-3.61 (1H, m, NCH*H*), 4.19(1H, td, J = 12.8, 2.2 Hz, CNCH*H*), 4.92 (1H, d, J = 6.4 Hz, CNCH*H*), 5.45 (1H, t, J = 6.4 Hz, CONCH), 7.55 (1H, t, J = 7.4 Hz, ArH), 7.67 (1H, d, J = 8. 1 Hz, ArH), 7.83 (1H, td, J = 7.4, 1.5 Hz, ArH), 8.14 (1H, d, J = 8.0 Hz, ArH); δ_C (100 MHz; DMSO-d_6) 22.2, 29.0, 35.4, 35.9, 48.2, 56.5, 120.7, 126.6, 127.4, 127.6, 134.7, 146.7, 154.8, 160.6, 167.0; FAB-HRMS m/z [M + H]$^+$ calcd for $C_{15}H_{15}O_2N_3$ 269.1164, found 269.1243.

(1*S*)-1-(1*H*-Indol-3-ylmethyl)-2*H*-[1,4]diazepino[2,1-*b*]quinazoline-3,7-(1*H*,4*H*,5*H*)-dione



White solid, mp 306–309 °C; δ_H (400 MHz; DMSO-d_6) 2.53-2.57 (1H, m, COC*H*H), 2.81 (1H, d, J = 18.2, COCH*H*), 3.27-3.33 (1H, m, indolyl-CH*H*), 3.62 (1H, dd, J = 14.8, 5.2 Hz, indolyl-C*H*H), 4.23 (1H, t, J = 12.4 Hz, NC*H*H), 4.89 (1H, dd, J = 14.8, 4.2 Hz, NC*H*H), 5.31-5.34 (1H, m, CONHC*H*), 7.01 (1H, t, J = 7.4 Hz, ArH), 7.08 (1H, t, J = 7.2 Hz, ArH), 7.36 (1H, d, J = 8.0 Hz, N_{ind}-CH), 7.44 (1H, s, N_{ind}-H), 7.53-7.59 (2H, m, ArH), 7.75 (1H, d, J = 7.7 Hz, ArH), 7.85 (1H, t, J = 7.7 Hz, ArH), 8.16 (1H, d, J = 8.0 Hz, ArH), 10.90 (1H, s, CONH); δ_C (DMSO-d_6; 100 MHz) 26.4, 34.9, 35.7, 52.5, 110.1, 111.6, 118.6, 118.9, 120.6, 121.2, 124.9, 126.6, 127.3, 127.5, 127.6, 134.7, 136.4, 146.8, 156.4, 160.7, 169.9; FAB-HRMS m/z [M + H]$^+$ calcd for $C_{21}H_{18}O_2N_4$ 358.1430, found 358.1508.

General procedure for the total synthesis of pyrazino[2,1-*b*]quinazolinediones (3a–e)

A suspension of isatoic anhydride (1 g, 6.1 mmol), methyl glycinate HCl **10** (767 mg, 6.1 mmol), and triethylamine (3.13 mL) in ethyl acetate (50 mL) was refluxed for 2 h and then cooled. The solid precipitate was filtered off and the organic layer was extracted with aqueous KOH. The resulting organic solution was then evaporated to afford the desired product **11** (79% yield).

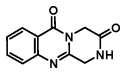
For tripeptide preparation, EDC (1.2 equiv.) was added to a solution of **11** (1.1 equiv.) and *N*-Cbz-protected L-amino acid (100 mg) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at ambient temperature for 0.5–1 h. The mixture was washed with 10% citric acid (3 × 5 mL) and dried (Na_2SO_4), concentrated under reduced pressure to afford a solid residue, which was further purified by flash chromatography (ethyl acetate–hexane = 1 : 1) to give Cbz-X-Abz-Gly-OMe (X= L-amino acid) (80–89% yield).

This Cbz-protected tripeptide was then deprotected by catalytic hydrogenation. To a solution of tripeptide (100 mg) in methanol (30 mL) was added a catalytic amount of 20% $Pd(OH)_2/C$ and a balloon of hydrogen. This deprotection reaction by hydrogenation was allowed to proceed until the protected tripeptide was completely consumed (15–30 min). The reaction mixture was filtered and concentrated under reduced pressure to give the product **12a–e** as the colorless solid (88–96% yield).

To a microwave reaction vessel was added **12a–e** (30 mg), $Sc(OTf)_3$ (1 equiv.) and DMF (0.3 mL). The vessel was placed inside a CEM Discover single-mode microwave synthesizer

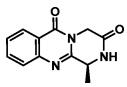
equipped with a magnetic stirrer, where it was exposed to microwaves at 140 °C (30 W) for 1–2 min. After reaction the DMF was removed under reduced pressure to afford a brown residue, and finally purified by flash column chromatography (dichloromethane–methanol = 40 : 1) to obtain the desired pyrazino[2,1-*b*]quinazolinediones **3a–e** (49–86% yield) as white solids.

2*H*-Pyrazino[2,1-*b*]quinazoline-3,6-(1*H*,4*H*)-dione



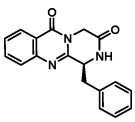
White solid, mp 274–276 °C; δ_H (400 MHz; DMSO-d_6) 4.43 (2H, d, J = 2.4 Hz, NCH_2), 4.53 (2H, s, $COCH_2$), 4.76 (2H, s, CH_2), 7.53 (1H, t, J = 7.6 Hz, ArH), 7.64 (1H, d, J = 8.1 Hz, ArH), 7.84 (1H, td, J = 7.6, 1.2 Hz, ArH), 8.14 (1H, d, J = 7.9 Hz, ArH), 8.6 (1H, s, CONH); δ_C (100 MHz; DMSO-d_6) 44.8, 44.9, 119.9, 126.4, 126.9, 127.0, 134.9, 147.3, 150.3, 160.0, 166.2; FAB-HRMS m/z [M + H]$^+$ calcd for $C_{11}H_{10}O_2N_3$ 215.0695, found 215.077.

(1*S*)-1-Methyl-2*H*-pyrazino[2,1-*b*]quinazoline-3,6-(1*H*,4*H*)-dione



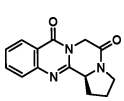
White solid, mp 239–240 °C; $[\alpha]_D^{20}$ = −44.2° (c 1.0, DMSO); δ_H (400 MHz; $CDCl_3$) 1.74 (3H, d, J = 6.9 Hz, CH_3), 4.70 (1H, q, J = 6.8 Hz, CONHC*H*), 4.76 (2H, s, CH_2), 6.78 (1H, s, NH), 7.52 (1H, t, J = 7.5 Hz, ArH), 7.68 (1H, d, J = 8.0 Hz, ArH), 7.78 (1H, td, J = 7.2, 1.5 Hz, ArH), 8.29 (1H, dd, J = 8.0, 1.4 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 20.6, 44.9, 51.7, 120.3, 127.1, 127.6, 127.6, 135.0, 147.3, 151.3, 160.9, 166.5; FAB-HRMS m/z [M + H]$^+$ calcd for $C_{12}H_{12}O_2N_3$ 230.0930, found 230.0930.

(1*S*)-1-(Phenylmethyl)-2*H*-pyrazino[2,1-*b*]quinazoline-3,6-(1*H*,4*H*)-dione



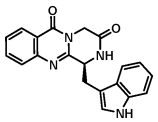
White solid, mp 230–231 °C; $[\alpha]_D^{20}$ = −105.9° (c 1.0, DMSO); δ_H (400 MHz; $CDCl_3$) 3.25-3.49 (3H, m, Phe-CH_2 and NC*H*H), 4.62 (1H, d, J = 18.8 Hz, NC*H*H), 4.91-4.94 (1H, m, CONCH), 7.05-7.10 (2H, m, ArH), 7.23-7.29 (3H, m, ArH), 7.53 (1H, t, J = 7.5 Hz, ArH), 7.73 (1H, d, J = 8.0 Hz, ArH), 7.82 (1H, td, J = 8.2, 2.1 Hz, ArH), 8.27 (1H, d, J = 7.9, Hz, ArH); δ_C (100 MHz; $CDCl_3$) 42.9, 44.5, 57.5, 120.1, 127.1, 127.4, 127.5, 128.2, 129.3, 130.0, 134.7, 135.1, 147.3, 150.1, 160.6, 166.5; FAB-HRMS m/z [M + H]$^+$ calcd for $C_{18}H_{16}O_2N_3$ 306.1243, found 306.1243.

(1*S*)-Hexahydropyrrolo[1′,2′:1,2]pyrazino[2,1-*b*]quinazoline-3,6-(1*H*,4*H*)-dione



White solid, mp 220–222 °C; $[\alpha]_D^{20}$ = −36.8° (c 1.0, DMSO); δ_H (400 MHz; DMSO-d_6) 1.89-2.01 (1H, m, $CONCH_2CHH$), 2.11-2.19 (1H, m, $CONCH_2CHH$), 2.43-2.62 (2H, m, $CONCHCH_2$), 2.63-2.66 (1H, m, CONCHC*H*H), 3.36 (2H, overlap with H_2O, $CONCH_2CH_2$), 3.68 (1H, t, J = 11 Hz, NCH), 4.45 (1H, dd, J = 20.0, 2.4 Hz, COC*H*H), 4.89 (1H, dd, J = 17.2, 2.5 Hz, COCH*H*), 7.58 (1H, td, J = 8.4, 1.8 Hz, ArH), 7.72 (1H, dd, J = 8.1, 2.0 Hz, ArH), 7.85-7.89 (1H, m, ArH), 8.16 (1H, d, J = 7.8 Hz, ArH); δ_C (100 MHz; $CDCl_3$) 20.8, 37.2, 39.1, 44.8, 45.9, 88.6, 120.3, 126.5, 127.6, 135.0, 146.9, 152.2, 159.9, 163.4; FAB-HRMS m/z [M + H]$^+$ calcd for $C_{14}H_{13}O_2N_3$ 255.1008, found 255.0930.

(1*S*)-1-(1*H*-Indol-3-ylmethyl)-2*H*-pyrazino[2,1-*b*]quinazoline-3,6-(1*H*,4*H*)-dione



White solid, mp 256–258 °C; $[\alpha]_D^{20}$ = −33.5° (c 1.0, DMSO); δ_H (400 MHz; DMSO-d_6) 2.84 (1H, d, J = 18.0 Hz, COC*H*H), 3.25 (1H, dd, J = 14.5, 4.4 Hz, indolyl-CH*H*), 3.42 (1H, dd, J = 14.4, 5.2 Hz, indolyl-C*H*H), 4.19 (1H, d, J = 18.0 Hz, COC*H*H), 4.80 (1H, q, J = 4.2 Hz, CONHC*H*), 6.59 (1H, t, J = 7.6 Hz, ArH), 6.94-6.98 (2H, m, ArH), 7.02 (1H, d, J = 2.3 Hz, N_{ind}-CH), 7.31 (1H, d, J = 8.3 Hz, ArH), 7.53 (1H, t, J = 7.9 Hz, ArH), 7.75 (1H, d, J = 8.0 Hz, ArH), 7.88 (1H, t, J = 7.8 Hz, ArH), 8.03 (1H, d, J = 7.9 Hz, ArH), 8.66 (1H, d, J = 3.4 Hz, N_{ind}-H), 11.00 (1H, s, CONH); δ_C (100 MHz; DMSO-d_6) 30.9, 32.5, 44.3, 56.5, 79.4, 107.7, 111.6, 117.7, 118.6, 119.7, 121.3, 125.3, 126.2, 126.9, 127.0, 127.2, 134.9, 136.1, 147.3, 151.9, 159.7, 164.9; FAB-HRMS m/z [M + H]$^+$ calcd for $C_{20}H_{17}O_2N_4$ 345.1352, found 345.1358.

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