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Regioselective double dehydrative cyclization route to construct polyheterocyclic skeletons consisting of 2,3-dihydroquinazolin-4(1*H*)-ones and 1,2-dihydropyrrolo[1,2-*a*]pyrazines†

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The $Sc(OTf)_3$-catalyzed reaction of 2-aminobenzamide with *N*-substituted pyrrole-2-carboxaldehyde proceeded well to give a tetracyclic skeleton consisting of dihydroquinazolin-4-one and 1,2-dihydropyrrolo[1,2-*a*]pyrazine *via* regioselective double cyclodehydrations where two heterocyclic rings (quinazolinone and pyrazine) were sequentially constructed through the formation of three C–N bonds.

Introduction

2,3-Dihydroquinazolin-4(1*H*)-one or its oxidized form, quinazolin-4(3*H*)-one, is a common heterocyclic moiety found in some bioactive natural substances such as evodiamine, rutaecarpine, tryptanthrin, and luotonin A (Fig. 1). Due to their diverse pharmacological functions[1] including anti-inflammatory,[2] anti-obesity,[3] and anticancer activities,[4] not surprisingly, numerous medicinal studies based on these scaffolds have been conducted through the synthesis of structural analogs in search for therapeutic agents with optimal activities.[5] Inspired by these precedents, we decided to construct a new polycyclic chemical motif bearing a quinazolinone (shown in the yellow box in Fig. 1) to investigate its effects under various biological conditions. Typically, several polycyclic systems fused with quinazolinone have been explored using 2-aminobenzamide **1a** and compounds having two electrophilic sites (Scheme 1a). Interestingly, different cyclization modes were observed depending on the substrates and the catalytic conditions. While the condensation of **1a** with **2** in the presence of $CuBr_2$ and K_2CO_3 provided **3**,[6] $AgNO_3$-catalyzed reaction of **1a** with 2-alkynylbenzaldehyde **4** afforded **5**.[7] Previously, we were able to construct a wide range of *N*-fused polycycles from **6** *via* an annulative functionalization strategy.[8] As a substrate possessing two electrophilic carbonyl groups instead of aldehyde and alkyne which can be seen in **2** and **4**, compound **6** was envisioned to serve as an annulation partner of **1a** (Scheme 1b).

At the outset, we expected that the condensation of **1a** with **6** would give rise to **8** or **9** as the N1 or N3 of the intermediate **7** formed as a consequence of chemoselective cyclodehydration of **6** with **1a** could participate in the second dehydrative cyclization. Herein, we report our results on the modular synthesis of **8** utilizing a regioselective double ring closure strategy.

Results and discussion

Reaction optimization for the synthesis of **8** or **9** was carried out with **1a** and **6a** (Table 1). When a mixture of **1a** and **6a** in EtOH was stirred in the presence of $Sc(OTf)_3$ (0.1 equiv.) at 100 °C, **8a** was isolated in 96% yield (entry 1). **9a** was not detected in the reaction mixture. X-ray crystallographic analysis unequivocally determined the chemical structure of **8a** (Fig. 2).[9] Lowering the catalyst loading to 0.05 equiv. slightly decreased the yield of **8a** (entry 2). The reaction at room temperature provided **7a** as a major product (entry 3). The chemical structure of **7a** was again firmly established by X-ray crystallographic analysis (Fig. 3).[10] The reaction at 80 °C or 120 °C led to inferior results (entries 4 and 5). Use of other metal triflates such as $In(OTf)_3$ and $Bi(OTf)_3$ furnished **8a** in lower yields (entries 6 and 7). The reaction with PTSA (0.1 equiv.) afforded **10a** (12%) as well as **8a** (69%) (entry 8). Overall, regioselective double cyclodehydration under the optimized conditions enabled us to construct three C–N bonds for the successive formation of quinazolinone and pyrazine. Notably, only two

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†Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR spectra of the synthesized compounds. CCDC 2430468 for **7a** and 2430469 for **8a**. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d5ob00580a

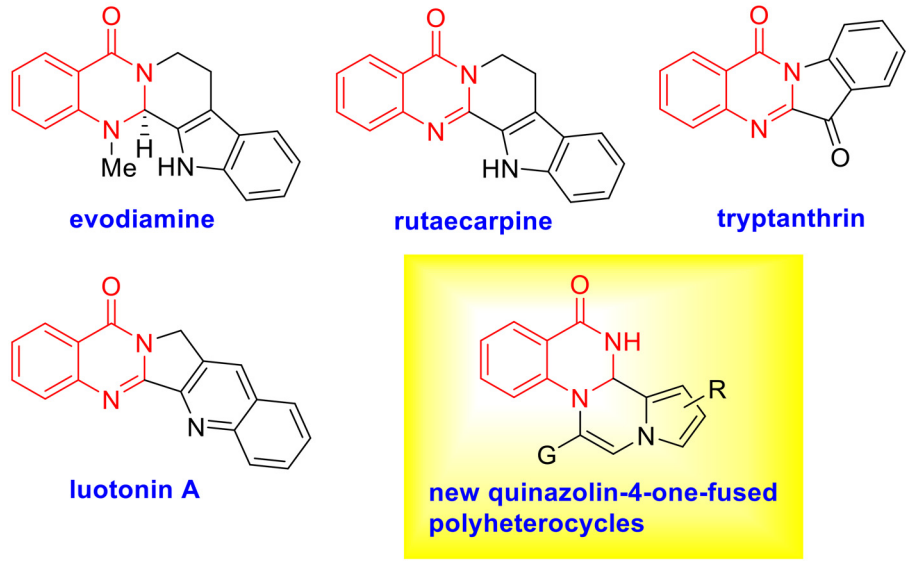
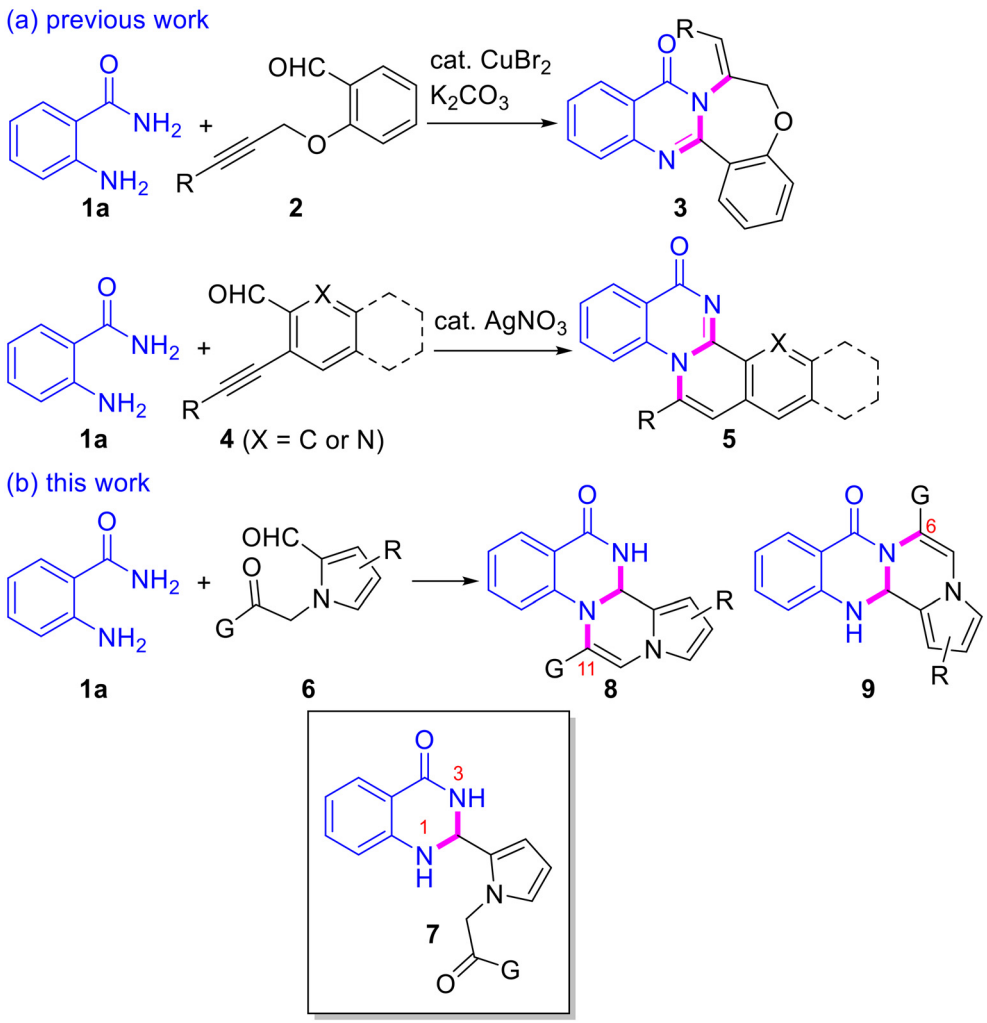
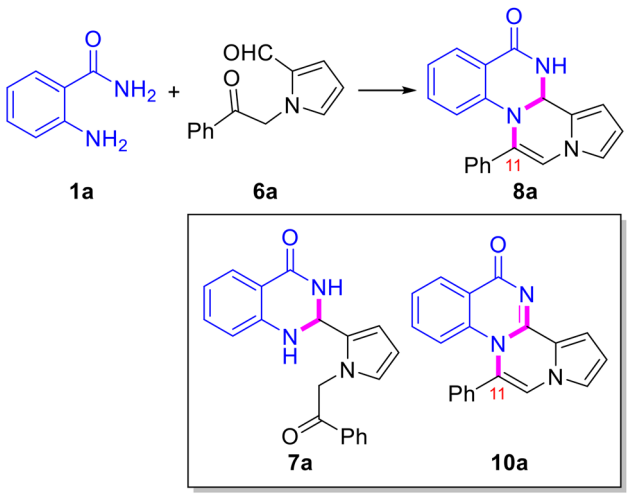


Fig. 1 Bioactive substances bearing (dihydro)quinazolin-4-one.



Scheme 1 Synthetic approaches to construct quinazolinone-fused rings.

Table 1 Reaction optimization for the synthesis of **8a** [a]



Entry	Catalyst (equiv.)	Temp (°C)	Time (h)	Yield[b] (%) 7a	8a	10a
1	$Sc(OTf)_3$ (0.1)	100	2.5	0	96	0
2	$Sc(OTf)_3$ (0.05)	100	5	0	91	0
3	$Sc(OTf)_3$ (0.1)	rt	1	88	9	0
4	$Sc(OTf)_3$ (0.1)	80	4.5	0	92	0
5	$Sc(OTf)_3$ (0.1)	120	1.5	0	79	0
6	$In(OTf)_3$ (0.1)	100	4	0	84	1
7	$Bi(OTf)_3$ (0.1)	100	4.5	0	84	1
8	PTSA (0.1)	100	3	0	69	12

[a] A solution of **1a** (30 mg, 0.22 mmol), **6a** (1.2 equiv.), and catalyst in EtOH (3 mL) was stirred at the indicated temperature for the indicated time. [b] Isolated yield (%).

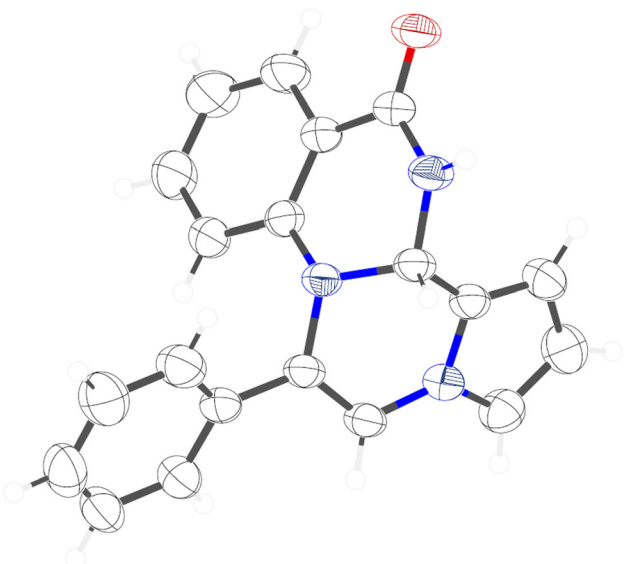


Fig. 2 Thermal ellipsoid plot for **8a** with 50% probability.

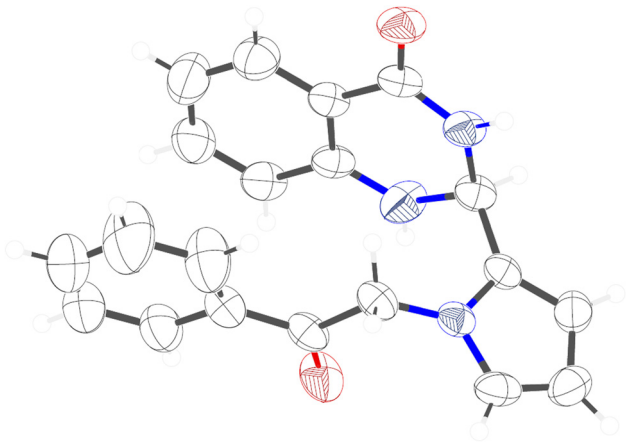


Fig. 3 Thermal ellipsoid plot for **7a** with 50% probability.

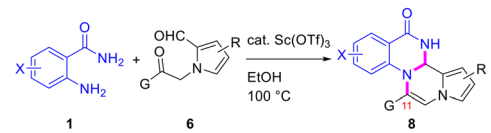
equivalents of water were generated as a byproduct of this atom-economical procedure.[11,12]

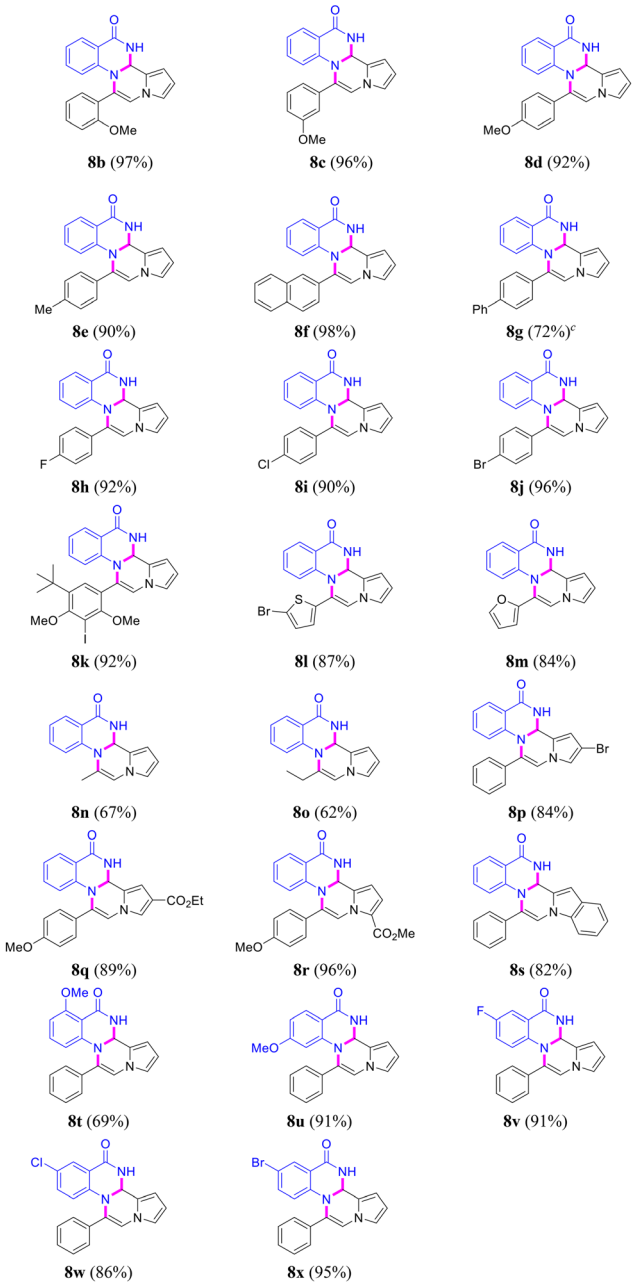
The reaction scope was then examined with several *N*-substituted pyrrole-2-carboxaldehydes **6** (Table 2). Many functional groups such as alkoxy, alkyl, aryl, or halogen were well tolerated under these conditions to furnish the corresponding products **8b–k** in excellent yields. Products **8l** and **8m** bearing heterocycles such as thiophene and furan were obtained in 87 and 84% yields, respectively. Products **8n** and **8o** having a methyl and an ethyl group at the C11 position were also isolated albeit in lower yields. When the substrates (**6p–6s**) derived from 4-bromopyrrole-2-carboxaldehyde, ethyl 5-formyl-1*H*-pyrrole-3-carboxylate, methyl 5-formyl-1*H*-pyrrole-2-carboxylate, and indole-2-carboxaldehyde were allowed to react with 2-aminobenzamide under the optimized conditions, the corresponding polycyclic *N*-fused products (**8p–8s**) were produced respectively. The reaction of some substituted 2-aminobenzamides possessing a methoxy or a halogen with **6a** delivered the corresponding products **8t–x** in good to excellent yields.

A scale-up experiment with **1a** (300 mg) was carried out to afford **8a** in 95% yield (Scheme 2a). Subjecting intermediate **7a** to the optimized conditions allowed dehydrative cyclization to form the dihydropyrazine moiety, leading to the tetracyclic *N*-fused structure **8a** (Scheme 2b). Based on this observation, the probable reaction mechanism was proposed, as shown in Scheme 3. Acid-catalyzed imine formation from the first dehydration reaction of **1a** with **6a** would produce **A**. Intramolecular nucleophilic addition of the adjacent amide to imine in **A** would give rise to **7a**. The subsequent regioselective attack by the N1 nitrogen of **7a** on the pendant carbonyl group followed by the loss of water (second dehydration) would provide **8a** *via* **B**.

Further derivatization of the resulting hybrid structure **8** to demonstrate the expandability of this scaffold is shown in Scheme 4. I_2-mediated oxidation of **8a** gave rise to **10a** in 80% yield. Catalytic hydrogenation of **8a** at 60 °C cleaved the dihydropyrazine ring to afford **11**. Base-promoted alkylation of **8a**

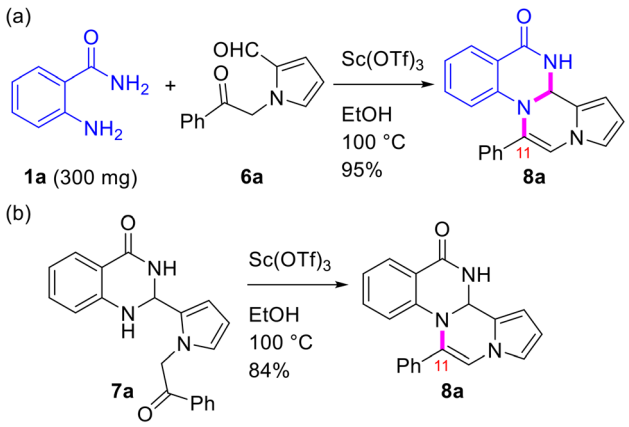
Table 2 Synthesis of **8b–x** [a,b]



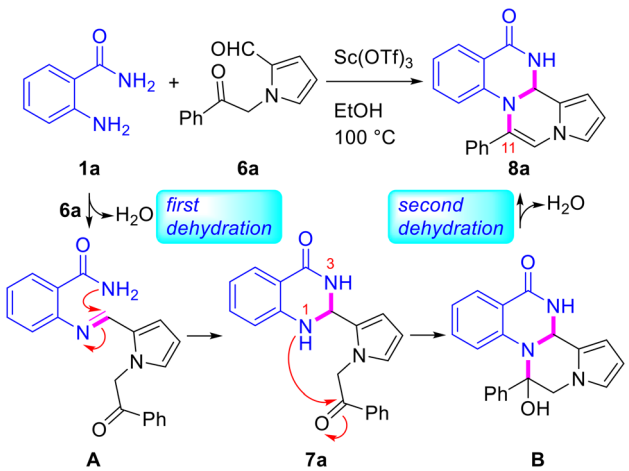


[a] A solution of **1a** (0.22 mmol), **6** (1.2 equiv.), and $Sc(OTf)_3$ (0.1 equiv.) in EtOH (3 mL) was stirred at 100 °C for the indicated time. [b] Isolated yield (%). [c] **6g** (1.7 equiv.) was used.

with three different alkylating agents led to **12**, **13**, and **14** in good yields, respectively. The Mannich reaction of **13** with formaldehyde and morpholine delivered **15**.[13]



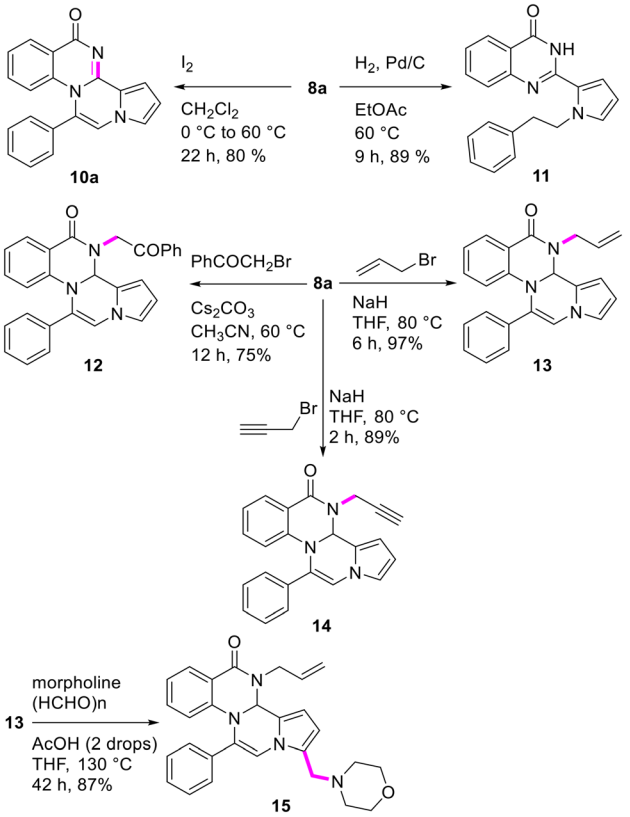
Scheme 2 Scale-up and control experiments.



Scheme 3 Proposed reaction mechanism.

Conclusions

In summary, a highly efficient approach to construct a novel dihydroquinazolin-4-one skeleton fused with 1,2-dihydropyrrolo[1,2-*a*]pyrazine was established from the $Sc(OTf)_3$-catalyzed reaction of 2-aminobenzamide with *N*-substituted pyrrole-2-carboxaldehyde, where regioselective double cyclodehydrations enabled the consecutive construction of two heterocyclic rings (quinazolinone and pyrazine) through the formation of three C–N bonds. Given the growing importance of quinazolinone-containing heterocyclic scaffolds in pharmaceutical sciences,[14] our double dehydrative cyclization protocol to construct the quinazolinone–pyrrolopyrazine hybrid should be useful for the expansion of the heterocyclic chemical space associated with this motif. Further synthetic efforts to explore new *N*-fused heterocyclic chemical scaffolds for biological evaluation are currently being pursued in our laboratory and the results will be reported soon.



Scheme 4 Derivatization.

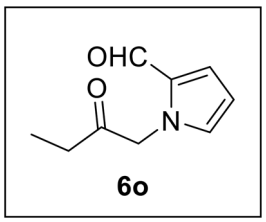
Experimental section

General methods

Unless specified, all reagents and starting materials were purchased from commercial sources and used as received without purification. "Concentrated" refers to the removal of volatile solvents *via* distillation using a rotary evaporator. "Dried" refers to pouring onto or passing through anhydrous magnesium sulfate followed by filtration. Flash chromatography was performed using silica gel (230–400 mesh) with hexanes, ethyl acetate, and dichloromethane as the eluents. All reactions were monitored by thin-layer chromatography on 0.25 mm silica plates (F-254) visualized under UV light. Melting points were measured using a capillary melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz NMR spectrometer and were described as chemical shifts, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant in hertz (Hz), and number of protons. HRMS data were measured using an electrospray ionization (ESI) and Q-TOF mass analyzer. X-ray crystal structures of **7a** and **8a** were determined using a SuperNova, Dual, Cu at home/near, AtlasS2 diffractometer.

General procedure for the synthesis of 6 .[15] To a stirred solution of pyrrole-2-carboxaldehyde (500 mg, 5.258 mmol) in CH_3CN (18 mL) were added K_2CO_3 (1.5 equiv.) and 2-bromoacetophenone (1.2 equiv.) at room temperature. After being stirred at room temperature for 24 h, the reaction mixture was concentrated under reduced pressure, diluted with ethyl acetate (30 mL) and washed with water (30 mL). The water layer was extracted with ethyl acetate (30 mL) one more time. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was purified by trituration with a mixed solvent (hexanes/ethyl acetate/dichloromethane = 30 : 1 : 2 or 10 : 1 : 2) to give **6a** (952.9 mg, 85%).

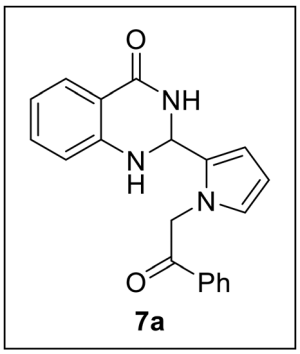
*1-(2-Oxobutyl)-1H-pyrrole-2-carbaldehyde (**6o**).*



Yellow gum (760.9 mg, 88%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.48 (s, 1H), 7.01–6.96 (m, 1H), 6.86 (s, 1H), 6.31 (t, J = 5.6 Hz, 1H), 5.09 (s, 2H), 2.53 (q, J = 7.2 Hz, 2H), 1.11 (t, J = 7.2 Hz, 3H); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$) δ 204.6, 179.9, 132.4, 131.5, 124.8, 110.3, 57.4, 33.2, 7.4; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_9H_{12}NO_2$ 166.0863, found 166.0868.

Synthesis of 7a. A mixture of **1a** (0.22 mmol, 1.0 equiv.), **6a** (1.2 equiv.) and $Sc(OTf)_3$ (0.1 equiv.) in EtOH (3 mL) was stirred at room temperature for 1 h. The reaction mixture was suction-filtered and washed with EtOH to yield **7a**. Additional purification of the filtrate by silica gel column chromatography (hexane : ethyl acetate : dichloromethane = 2 : 1 : 2) afforded **7a** along with **8a**. Overall, **7a** was obtained (61.0 mg, 88%) as an ivory solid along with **8a** (6.3 mg, 9%) as an ivory solid. The X-ray crystal structure of **7a** was obtained *via* dissolution of the compound in a mixed solvent (tetrahydrofuran/ethyl alcohol, 1 : 1) and slow evaporation of the solvent at room temperature.

*2-(1-(2-Oxo-2-phenylethyl)-1H-pyrrol-2-yl)-2,3-dihydroquinazolin-4(1H)-one (**7a**).*



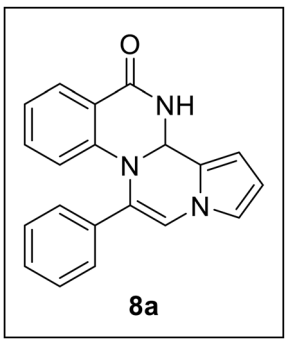
Ivory solid, mp: 214.3–214.9 °C (61.0 mg, 88%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.01–7.97 (m, 2H), 7.90 (s, 1H), 7.67 (t, J = 7.6 Hz, 1H), 7.59–7.53 (m, 3H), 7.22–7.18 (m, 1H), 6.86 (s, 1H), 6.79–6.76 (m, 1H), 6.70 (d, J = 8.0 Hz, 1H), 6.66 (t, J = 7.6 Hz, 1H), 6.12 (dd, J = 3.6, 1.6 Hz, 1H), 6.00 (t, J = 3.2 Hz, 1H), 5.86–5.72 (m, 3H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 194.8,

163.9, 148.0, 134.9, 133.8, 133.2, 131.0, 128.9, 128.0, 127.3, 124.7, 117.5, 115.3, 114.9, 108.9, 106.5, 60.6, 53.5; **HRMS** (ESI-QTOF) *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{18}N_3O_2$ 332.1394, found 332.1399.

General procedure for the synthesis of 8. A mixture of **1a** (0.22 mmol, 1.0 equiv.), **6a** (1.2 equiv.), and $Sc(OTf)_3$ (0.1 equiv.) in EtOH (3 mL) was stirred at 100 °C (heating mantle was used) for 2.5 h. The reaction was carried out in a 7 mL sealed vial. After the reaction mixture was cooled down to rt, the precipitate was suction-filtered and washed with EtOH to afford **8a**. Additional purification of the filtrate by silica gel column chromatography (hexane : ethyl acetate : dichloromethane = 2 : 1 : 2) furnished **8a**. Overall, **8a** was obtained in 96% yield (66.0 mg) as an ivory solid. X-ray crystal structure of **8a** was obtained *via* dissolution of the compound in a mixed solvent (acetone/ethyl alcohol, 1 : 1) and slow evaporation of the solvent at room temperature.

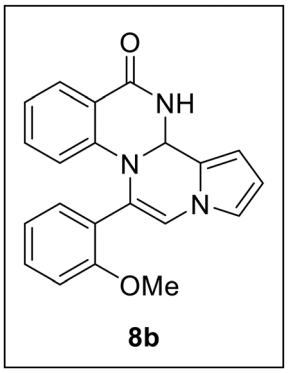
Scale-up experiment. A mixture of **1a** (2.20 mmol, 1.0 equiv.), **6a** (1.2 equiv.), and $Sc(OTf)_3$ (0.1 equiv.) in EtOH (30 mL) was stirred at 100 °C (heating mantle was used) for 5.5 h. After the reaction mixture was cooled down to rt, the precipitate was suction-filtered and washed with EtOH to give **8a**. Additional purification of the filtrate by silica gel column chromatography (hexane : ethyl acetate : dichloromethane = 2 : 1 : 2) afforded **8a**. Overall, **8a** was obtained in 95% yield (658.9 mg) as an ivory solid.

*11-Phenyl-3b,4-dihydro-5H-pyrrolo[2',1':3,4]pyrazino[1,2-a]quinazolin-5-one (**8a**).*



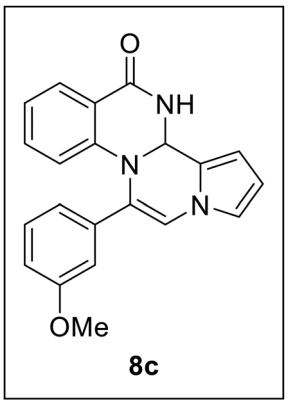
Ivory solid, mp: 265.0–265.8 °C (66.0 mg, 96%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.09 (d, J = 4.8 Hz, 1H), 8.08 (s, 1H), 7.76–7.68 (m, 3H), 7.44 (t, J = 7.6 Hz, 2H), 7.34 (t, J = 7.2 Hz, 1H), 7.13 (t, J = 7.6 Hz, 1H), 6.96 (s, 1H), 6.82 (t, J = 7.6 Hz, 1H), 6.23 (d, J = 8.4 Hz, 1H), 6.12 (s, 1H), 6.07 (s, 1H), 5.75 (d, J = 4.4 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 161.7, 145.6, 134.1, 133.3, 129.2, 128.7, 128.6, 128.2, 127.6, 124.5, 119.9, 118.8, 118.3, 117.7, 115.9, 109.7, 105.3, 64.1; **HRMS** (ESI-QTOF) *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{16}N_3O$ 314.1288, found 314.1281.

*11-(2-Methoxyphenyl)-3b,4-dihydro-5H-pyrrolo[2',1':3,4]pyrazino[1,2-a]quinazolin-5-one (**8b**).*



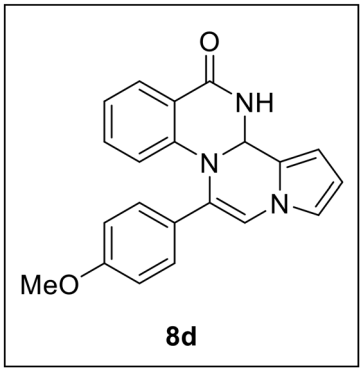
Ivory solid, mp: 259.3–259.8 °C (73.5 mg, 97%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.90 (d, J = 3.6 Hz, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.68 (s, 1H), 7.53 (d, J = 7.6 Hz, 1H), 7.31 (t, J = 7.6 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 7.04–7.01 (m, 2H), 6.97 (t, J = 7.2 Hz, 1H), 6.88 (t, J = 7.2 Hz, 1H), 6.23 (d, J = 8.0 Hz, 1H), 6.13–6.09 (m, 2H), 5.89 (d, J = 3.6 Hz, 1H), 3.71 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 162.4, 156.5, 145.2, 132.4, 129.6, 129.2, 127.4, 126.0, 125.6, 121.8, 121.0, 120.8, 120.3, 118.8, 117.6, 111.6, 109.4, 105.8, 63.6, 55.4, 55.0; **HRMS** (ESI-QTOF) *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{18}N_3O_2$ 344.1394, found 344.1392.

*11-(3-Methoxyphenyl)-3b,4-dihydro-5H-pyrrolo[2',1':3,4]pyrazino[1,2-a]quinazolin-5-one (**8c**).*



Ivory solid, mp: 271.6–272.2 °C (72.5 mg, 96%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.07 (d, J = 3.6 Hz, 1H), 8.09 (s, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.29–7.25 (m, 2H), 7.17–7.12 (m, 1H), 6.95–6.90 (m, 2H), 6.82 (t, J = 7.2 Hz, 1H), 6.25 (d, J = 8.4 Hz, 1H), 6.12 (t, J = 3.2 Hz, 1H), 6.06 (s, 1H), 5.73 (d, J = 4.0 Hz, 1H), 3.78 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 161.8, 159.9, 145.7, 135.6, 133.4, 130.4, 128.64, 128.58, 127.6, 120.0, 118.8, 118.7, 117.6, 117.0, 115.9, 113.8, 109.8, 109.7, 105.4, 64.2, 55.3; **HRMS** (ESI-QTOF) *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{18}N_3O_2$ 344.1394, found 344.1391.

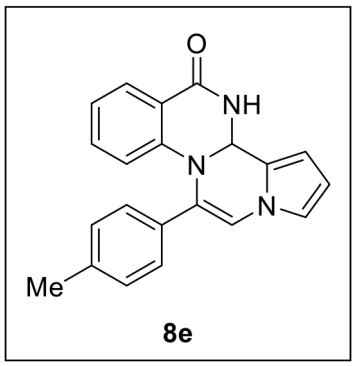
*11-(4-Methoxyphenyl)-3b,4-dihydro-5H-pyrrolo[2',1':3,4]pyrazino[1,2-a]quinazolin-5-one (**8d**).*



8d

Ivory solid, mp: 225.0–225.3 °C (69.7 mg, 92%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.06 (d, J = 4.8 Hz, 1H), 7.92 (s, 1H), 7.72 (d, J = 7.2 Hz, 1H), 7.63 (d, J = 8.8 Hz, 2H), 7.13 (t, J = 7.8 Hz, 1H), 7.00 (d, J = 8.4 Hz, 2H), 6.93 (s, 1H), 6.81 (t, J = 7.2 Hz, 1H), 6.24 (d, J = 8.0 Hz, 1H), 6.09 (t, J = 2.8 Hz, 1H), 6.04 (s, 1H), 5.72 (d, J = 4.8 Hz, 1H), 3.78 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 161.7, 159.3, 145.7, 133.2, 128.8, 128.5, 127.6, 126.3, 126.0, 119.9, 118.5, 117.7, 116.5, 116.0, 114.6, 109.4, 105.0, 64.2, 55.2; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{21}H_{18}N_3O_2$ 344.1394, found 344.1394.

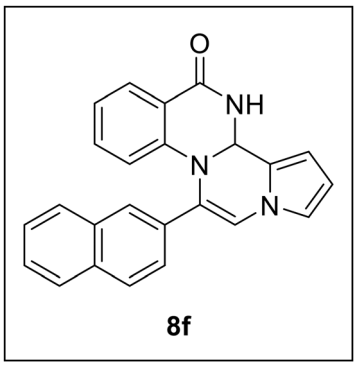
*11-(p-Tolyl)-3b,4-dihydro-5H-pyrrolo[2',1':3,4]pyrazino[1,2-a]quinazolin-5-one (**8e**).*



8e

Pale yellow solid, mp: 259.1–259.8 °C (64.8 mg, 90%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.08 (d, J = 5.2 Hz, 1H), 8.00 (s, 1H), 7.72 (dd, J = 7.6, 1.2 Hz, 1H), 7.59 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 7.15–7.10 (m, 1H), 6.94 (s, 1H), 6.84–6.79 (m, 1H), 6.22 (d, J = 8.4 Hz, 1H), 6.10 (t, J = 3.2 Hz, 1H), 6.06 (s, 1H), 5.72 (d, J = 4.8 Hz, 1H), 2.32 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 161.8, 145.7, 137.7, 133.3, 131.2, 129.8, 128.8, 128.6, 127.6, 124.5, 119.9, 118.7, 117.7, 117.5, 116.0, 109.6, 105.2, 64.2, 20.9; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{21}H_{18}N_3O$ 328.1444, found 328.1442.

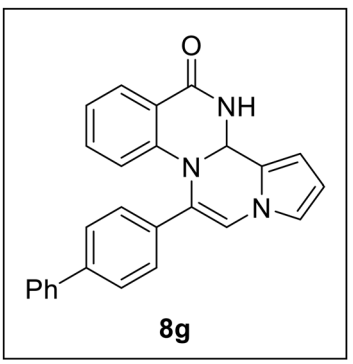
*11-(Naphthalen-2-yl)-3b,4-dihydro-5H-pyrrolo[2',1':3,4]pyrazino[1,2-]quinazolin-5-one (**8f**).*



8f

Ivory solid, mp: 279.9–280.6 °C (78.0 mg, 98%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.15 (d, J = 4.8 Hz, 1H), 8.25 (s, 1H), 8.15 (s, 1H), 8.01 (d, J = 8.8 Hz, 1H), 7.96–7.90 (m, 3H), 7.75 (d, J = 7.2 Hz, 1H), 7.53–7.48 (m, 2H), 7.09 (t, J = 7.6 Hz, 1H), 7.00 (s, 1H), 6.81 (t, J = 7.6 Hz, 1H), 6.27 (d, J = 8.0 Hz, 1H), 6.14 (t, J = 2.8 Hz, 1H), 6.10 (s, 1H), 5.82 (d, J = 4.4 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 161.9, 145.8, 133.40, 133.35, 132.7, 131.6, 129.0, 128.81, 128.75, 128.2, 127.7, 126.8, 126.4, 123.6, 122.1, 120.0, 119.1, 119.0, 117.8, 116.0, 109.9, 105.5, 64.2; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{24}H_{18}N_3O$ 364.1444, found 364.1449.

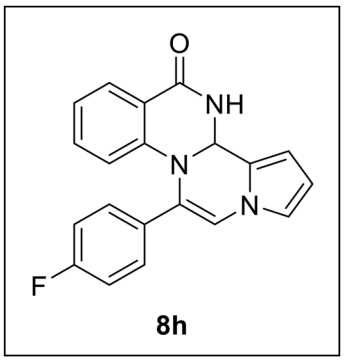
*11-([1,1'-Biphenyl]-4-yl)-3b,4-dihydro-5H-pyrrolo[2',1':3,4]pyrazino[1,2-a]quinazolin-5-one (**8g**).*



8g

Brown solid, mp: 273.9–274.1 °C (62.1 mg, 72%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.10 (d, J = 4.8 Hz, 1H), 8.15 (s, 1H), 7.82–7.75 (m, 4H), 7.73 (t, J = 7.6 Hz, 3H), 7.48 (t, J = 7.6 Hz, 2H), 7.37 (t, J = 7.6 Hz, 1H), 7.18–7.13 (m, 1H), 6.97 (s, 1H), 6.83 (t, J = 7.6 Hz, 1H), 6.29 (d, J = 8.0 Hz, 1H), 6.13 (t, J = 3.0 Hz, 1H), 6.08 (s, 1H), 5.76 (d, J = 5.6 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 161.7, 145.7, 139.7, 139.4, 133.4, 133.2, 129.0, 128.7, 128.3, 127.7, 127.6, 127.4, 126.6, 125.0, 120.0, 118.8, 118.5, 117.7, 115.9, 109.8, 105.4, 64.2; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{26}H_{20}N_3O$ 390.1601, found 390.1605.

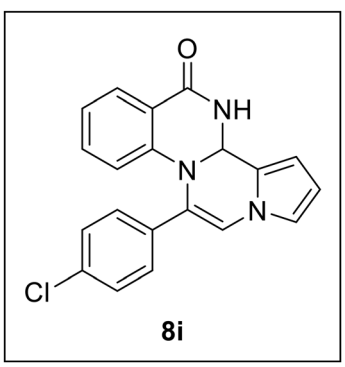
*11-(4-Fluorophenyl)-3b,4-dihydro-5H-pyrrolo[2',1':3,4]pyrazino [1,2-a]quinazolin-5-one (**8h**).*



8h

Brown solid, mp: 256.9–257.5 °C (67.4 mg, 92%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.12 (d, J = 4.8 Hz, 1H), 8.05 (s, 1H), 7.77–7.72 (m, 3H), 7.28 (t, J = 8.8 Hz, 2H), 7.14 (t, J = 7.2 Hz, 1H), 6.95 (s, 1H), 6.83 (t, J = 7.2 Hz, 1H), 6.22 (d, J = 8.4 Hz, 1H), 6.12 (t, J = 2.8 Hz, 1H), 6.08 (s, 1H), 5.77 (d, J = 4.8 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 163.2, 161.7, 160.7, 145.5, 133.4, 130.6 (J = 3.0 Hz), 128.5, 127.9, 127.7, 126.6 (J = 9.0 Hz), 120.1, 118.8, 118.2, 116.8 (J = 191.0 Hz), 116.2 (J = 22.0 Hz), 109.8, 105.4, 64.1; **^{19}F NMR** (376 MHz, DMSO-d_6) δ −113.7; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{20}H_{15}FN_3O$ 332.1194, found 332.1198.

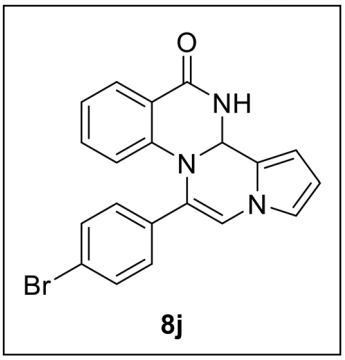
*11-(4-Chlorophenyl)-3b,4-dihydro-5H-pyrrolo[2',1':3,4]pyrazino [1,2-a]quinazolin-5-one (**8i**).*



8i

Brown solid, mp: 294.5–294.8 °C (69.1 mg, 90%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.11 (d, J = 4.4 Hz, 1H), 8.14 (s, 1H), 7.76–7.69 (m, 3H), 7.49 (d, J = 8.8 Hz, 2H), 7.15 (t, J = 7.6 Hz, 1H), 6.95 (s, 1H), 6.84 (t, J = 7.6 Hz, 1H), 6.20 (d, J = 8.4 Hz, 1H), 6.12 (s, 1H), 6.07 (s, 1H)z, 5.75 (d, J = 4.8 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 161.7, 145.5, 133.4, 133.1, 132.5, 129.2, 128.6, 127.7, 127.6, 126.2, 120.2, 119.0, 118.9, 117.8, 115.8, 110.0, 105.6, 64.1; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{20}H_{15}ClN_3O$ 348.0898, found 348.0898.

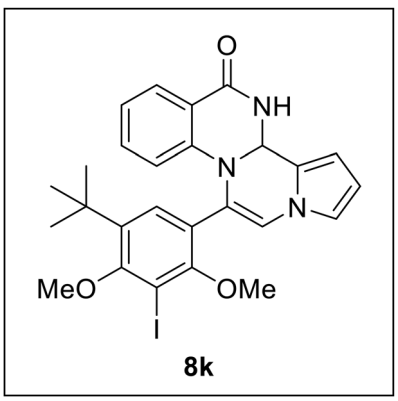
*11-(4-Bromophenyl)-3b,4-dihydro-5H-pyrrolo[2',1':3,4]pyrazino [1,2-a]quinazolin-5-one (**8j**).*



8j

Ivory solid, mp: 286.4–287.1 °C (83.4 mg, 96%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.09 (d, J = 4.4 Hz, 1H), 8.16 (s, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.67–7.61 (m, 4H), 7.16 (t, J = 7.6 Hz, 1H), 6.94 (s, 1H), 6.84 (t, J = 7.6 Hz, 1H), 6.20 (d, J = 8.0 Hz, 1H), 6.12 (s, 1H), 6.07 (s, 1H), 5.75 (d, J = 4.4 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 161.6, 145.5, 133.43, 133.38, 132.1, 128.6, 127.7, 127.6, 126.5, 121.0, 120.1, 119.0, 118.9, 117.7, 115.8, 109.9, 105.6, 64.1; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{20}H_{15}BrN_3O$ 392.0393, found 392.0398.

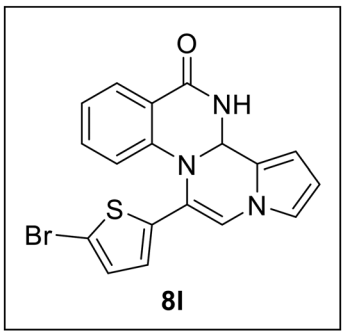
*11-(5-(tert-Butyl)-3-iodo-2,4-dimethoxyphenyl)-3b,4-dihydro-5H-pyrrolo[2',1':3,4]pyrazino[1,2-a]quinazolin-5-one (**8k**).*



8k

Yellow gum (112.1 mg, 92%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.92 (d, J = 3.6 Hz, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.66 (s, 1H), 7.36 (s, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.05 (s, 1H), 6.92 (t, J = 7.6 Hz, 1H), 6.29 (d, J = 8.4 Hz, 1H), 6.16–6.11 (m, 2H), 5.96 (d, J = 3.6 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 1.22 (s, 9H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 164.1, 161.0, 156.9, 144.2, 140.6, 132.0, 130.3, 128.4, 125.5, 123.4, 123.0, 122.3, 121.9, 121.1, 118.1, 110.6, 110.1, 106.6, 92.5, 64.1, 62.3, 60.4, 35.1, 31.1; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{26}H_{27}IN_3O_3$ 556.1092, found 556.1094.

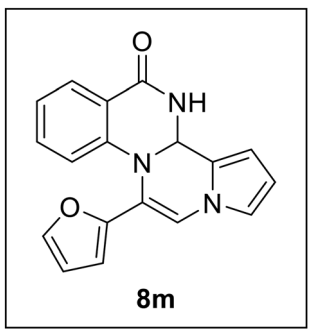
*11-(5-Bromothiophen-2-yl)-3b,4-dihydro-5H-pyrrolo[2′,1′:3,4]pyrazino[1,2-a]quinazolin-5-one (**8l**).*



8l

Dark brown solid, mp: 250.2–251.0 °C (76.6 mg, 87%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.09 (d, J = 4.8 Hz, 1H), 7.97 (s, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.27–7.22 (m, 3H), 6.93 (s, 1H), 6.89 (t, J = 7.6 Hz, 1H), 6.48 (d, J = 8.4 Hz, 1H), 6.10 (t, J = 3.0 Hz, 1H), 6.06 (s, 1H), 5.74 (d, J = 4.8 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 161.6, 145.6, 140.8, 133.5, 131.9, 128.3, 127.7, 123.6, 120.7, 119.0, 118.1, 117.6, 115.7, 111.0, 110.0, 106.0, 64.0; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{18}H_{13}BrN_3OS$ 397.9957, found 397.9961.

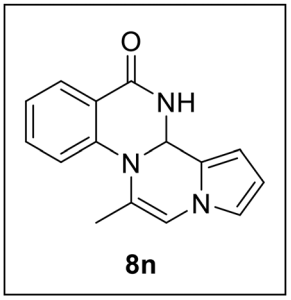
*11-(Furan-2-yl)-3b,4-dihydro-5H-pyrrolo[2′,1′:3,4]pyrazino[1,2-a]quinazolin-5-one (**8m**).*



8m

Ivory solid, mp: 248.6–249.4 °C (56.2 mg, 84%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.06 (d, J = 4.8 Hz, 1H), 7.82 (s, 1H), 7.78 (s, 1H), 7.73 (d, J = 7.2 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 7.00 (s, 1H), 6.87 (t, J = 7.6 Hz, 1H), 6.58 (s, 1H), 6.54 (d, J = 3.2 Hz, 1H), 6.40 (d, J = 8.4 Hz, 1H), 6.10 (t, J = 2.8 Hz, 1H), 6.06 (s, 1H), 5.73 (d, J = 4.8 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 161.7, 148.6, 146.0, 143.4, 133.4, 128.2, 127.6, 121.2, 120.4, 119.2, 117.9, 116.9, 115.5, 112.2, 109.7, 108.1, 105.8, 64.0; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{18}H_{14}N_3O_2$ 304.1081, found 304.1076.

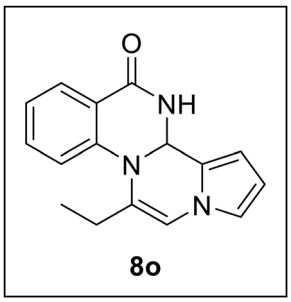
*11-Methyl-3b,4-dihydro-5H-pyrrolo[2′,1′:3,4]pyrazino[1,2-a]quinazolin-5-one (**8n**).*



8n

Yellow solid, mp: 210.9–211.5 °C (37.1 mg, 67%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.19 (s, 1H), 8.63–8.60 (m, 1H), 8.30–8.24 (m, 1H), 8.06–8.01 (m, 2H), 7.61 (t, J = 2.0 Hz, 1H), 7.35 (s, 1H), 6.87 (d, J = 2.0 Hz, 2H), 6.82 (d, J = 1.6 Hz, 1H), 4.11 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 162.9, 143.3, 132.1, 127.6, 125.3, 124.8, 124.1, 123.8, 120.2, 117.0, 108.3, 106.3, 104.9, 62.6, 17.3; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{15}H_{14}N_3O$ 252.1131, found 252.1131.

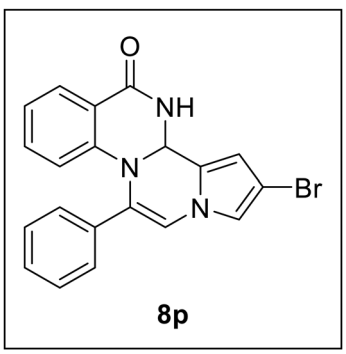
*11-Ethyl-3b,4-dihydro-5H-pyrrolo[2′,1′:3,4]pyrazino[1,2-a]quinazolin-5-one (**8o**).*



8o

Ivory solid, mp: 206.4–207.0 °C (36.4 mg, 62%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.09 (d, J = 7.6 Hz, 1H), 7.50 (t, J = 7.2 Hz, 1H), 7.32 (t, J = 7.2 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 6.73 (s, 1H), 6.27–6.16 (m, 3H), 6.12 (s, 1H), 5.99 (s, 1H), 2.32–2.21 (m, 1H), 2.08–1.97 (m, 1H), 0.89 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 163.8, 143.6, 132.4, 129.8, 128.6, 126.0, 125.7, 124.6, 119.6, 117.6, 109.1, 106.1, 103.6, 63.9, 23.7, 11.7; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{16}H_{16}N_3O$ 266.1288, found 266.1283.

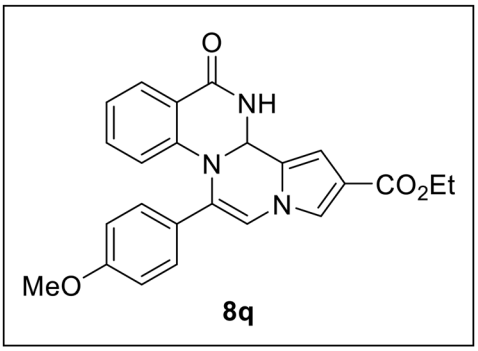
*2-Bromo-11-phenyl-3b,4-dihydro-5H-pyrrolo[2′,1′:3,4]pyrazino[1,2-a]quinazolin-5-one (**8p**).*



8p

Ivory solid, mp: 275.3–275.5 °C (72.4 mg, 84%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.10 (d, J = 4.8 Hz, 1H), 8.01 (s, 1H), 7.74 (dd, J = 7.6, 1.6 Hz, 1H), 7.69 (d, J = 7.2 Hz, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.36 (t, J = 7.6 Hz, 1H), 7.19–7.12 (m, 2H), 6.85 (t, J = 7.6 Hz, 1H), 6.23 (d, J = 8.4 Hz, 1H), 6.12 (s, 1H), 5.79 (d, J = 4.8 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 161.5, 145.2, 133.6, 133.4, 129.7, 129.5, 129.3, 128.6, 127.7, 124.7, 120.3, 118.3, 117.7, 117.4, 116.0, 107.4, 96.8, 63.5; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{20}H_{15}BrN_3O$ 392.0393, found 392.0393.

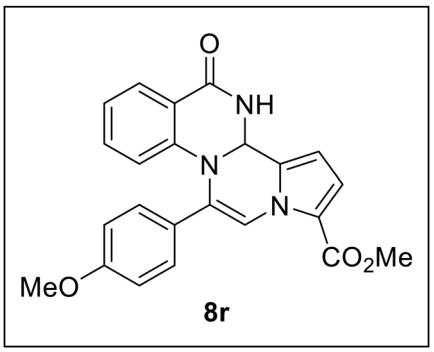
*Ethyl 11-(4-methoxyphenyl)-5-oxo-3b,4-dihydro-5H-pyrrolo[2′,1′:3,4]pyrazino[1,2-a]quinazoline-2-carboxylate (**8q**).*



8q

Ivory solid, mp: 279.0–279.5 °C (81.5 mg, 89%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.12 (d, J = 4.8 Hz, 1H), 7.93 (s, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 8.8 Hz, 2H), 7.58 (s, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 8.8 Hz, 2H), 6.85 (t, J = 7.6 Hz, 1H), 6.36 (s, 1H), 6.25 (d, J = 8.4 Hz, 1H), 5.80 (d, J = 4.8 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), 3.79 (s, 3H), 1.22 (t, J = 7.2 Hz, 3H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 163.3, 161.7, 159.9, 145.2, 133.4, 131.5, 129.8, 127.7, 126.5, 125.7, 123.0, 120.4, 117.7, 116.3, 116.2, 115.6, 114.8, 105.4, 63.5, 59.5, 55.3, 14.4; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{24}H_{22}N_3O_4$ 416.1605, found 416.1601.

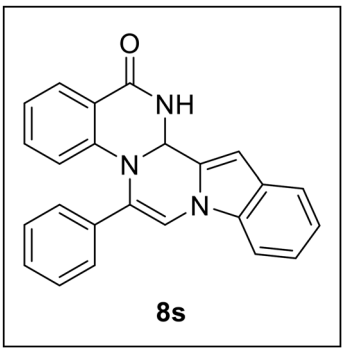
*Methyl 11-(4-methoxyphenyl)-5-oxo-3b,4-dihydro-5H-pyrrolo[2′,1′:3,4]pyrazino[1,2-a]quinazoline-1-carboxylate (**8r**).*



8r

Ivory solid, mp: 268.8–269.6 °C (85.1 mg, 96%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.19 (d, J = 4.8 Hz, 1H), 8.25 (s, 1H), 7.73 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 8.8 Hz, 2H), 7.15 (t, J = 7.6 Hz, 1H), 7.04 (d, J = 8.8 Hz, 2H), 6.92 (d, J = 4.0 Hz, 1H), 6.84 (t, J = 7.6 Hz, 1H), 6.25 (d, J = 8.4 Hz, 1H), 6.20 (d, J = 4.0 Hz, 1H), 5.83 (d, J = 4.8 Hz, 1H), 3.80–3.77 (m, 6H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 161.5, 160.6, 160.0, 144.7, 134.6, 133.5, 131.0, 127.7, 126.6, 125.6, 120.4, 120.0, 118.3, 117.6, 116.1, 114.9, 114.6, 105.7, 63.7, 55.3, 51.5; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{23}H_{20}N_3O_4$ 402.1449, found 402.1448.

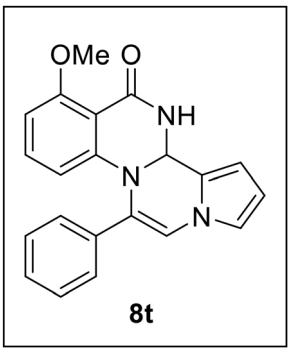
*8-Phenyl-1,15b-dihydro-2H-indolo[2′,1′:3,4]pyrazino[1,2-a]quinazolin-2-one (**8s**).*



8s

Ivory solid, mp: 300.6–301.2 °C (65.3 mg, 82%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.28 (d, J = 5.2 Hz, 1H), 8.57 (s, 1H), 7.91–7.85 (m, 3H), 7.74 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.35 (t, J = 7.2 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.15–7.08 (m, 2H), 6.80 (t, J = 7.6 Hz, 1H), 6.53 (s, 1H), 6.28 (d, J = 8.4 Hz, 1H), 5.94 (d, J = 4.4 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 161.9, 146.1, 135.3, 134.2, 134.1, 133.5, 129.2, 128.1, 128.0, 127.8, 127.7, 124.3, 122.8, 121.3, 121.1, 120.0, 117.4, 116.2, 115.8, 110.2, 100.1, 64.0; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{24}H_{18}N_3O$ 364.1444, found 364.1445.

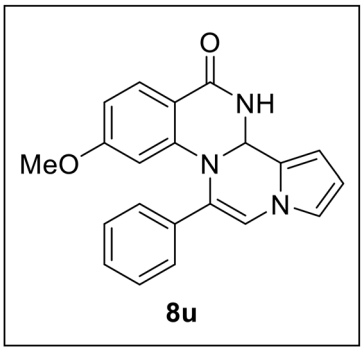
*6-Methoxy-11-phenyl-3b,4-dihydro-5H-pyrrolo[2′,1′:3,4]pyrazino[1,2-a]quinazolin-5-one (**8t**).*



8t

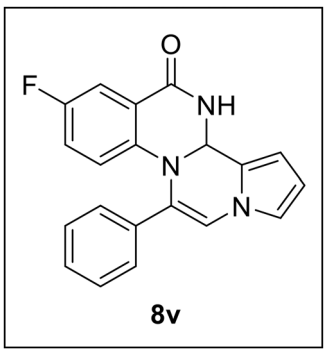
Pale yellow solid, mp: 313.3–313.6 °C (52.3 mg, 69%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.66 (d, J = 5.6 Hz, 1H), 7.99 (s, 1H), 7.66 (d, J = 7.2 Hz, 2H), 7.42 (t, J = 7.6 Hz, 2H), 7.36–7.28 (m, 1H), 7.03 (t, J = 8.0 Hz, 1H), 6.93 (s, 1H), 6.48 (d, J = 8.4 Hz, 1H), 6.12–6.09 (m, 1H), 6.07 (s, 1H), 5.86 (d, J = 8.0 Hz, 1H), 5.59 (d, J = 5.6 Hz, 1H), 3.70 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 160.3, 160.1, 147.8, 134.2, 133.2, 129.1, 128.1, 124.6, 118.7, 117.7, 109.7, 109.6, 109.0, 107.4, 105.3, 104.9, 63.7, 55.7; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{21}H_{18}N_3O_2$ 344.1394, found 344.1398.

*8-Methoxy-11-phenyl-3b,4-dihydro-5H-pyrrolo[2′,1′:3,4]pyrazino [1,2-a]quinazolin-5-one (**8u**).*



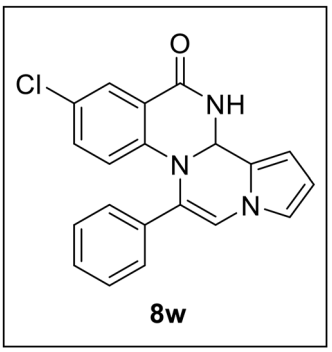
Ivory solid, mp: 278.6–279.4 °C (68.7 mg, 91%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.90 (d, J = 4.8 Hz, 1H), 8.04 (s, 1H), 7.72–7.65 (m, 3H), 7.44 (t, J = 7.6 Hz, 2H), 7.34 (t, J = 7.2 Hz, 1H), 6.96 (s, 1H), 6.42 (d, J = 8.8 Hz, 1H), 6.12 (t, J = 2.8 Hz, 1H), 6.05 (s, 1H), 5.74 (d, J = 4.4 Hz, 1H), 5.68 (s, 1H), 3.45 (s, 3H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 163.0, 161.6, 147.0, 134.1, 129.7, 129.2, 128.73, 128.68, 128.2, 124.6, 118.8, 118.3, 110.9, 109.7, 105.2, 101.9, 64.4, 55.0; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{21}H_{18}N_3O_2$ 344.1394, found 344.1393.

*7-Fluoro-11-phenyl-3b,4-dihydro-5H-pyrrolo[2′,1′:3,4]pyrazino [1,2-a]quinazolin-5-one (**8v**).*



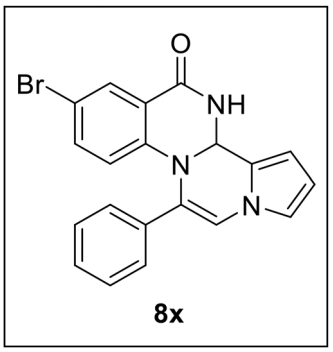
Ivory solid, mp: 239.6–240.5 °C (78.5 mg, 91%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.26 (d, J = 4.8 Hz, 1H), 8.07 (s, 1H), 7.70 (d, J = 7.6 Hz, 2H), 7.47–7.41 (m, 3H), 7.34 (t, J = 7.2 Hz, 1H), 7.05 (td, J = 8.8, 3.2 Hz, 1H), 6.96 (d, J = 0.8 Hz, 1H), 6.24 (dd, J = 8.8, 4.4 Hz, 1H), 6.13 (t, J = 3.2 Hz, 1H), 6.08 (d, J = 2.8 Hz, 1H), 5.77 (d, J = 4.8 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 160.9, 157.3, 155.0, 142.2, 133.9, 129.2, 128.4 (J = 32.0 Hz), 128.1, 124.5, 120.3 (J = 23.0 Hz), 119.0 (J = 6.0 Hz), 118.9, 118.3, 117.8 (J = 7.0 Hz), 113.4 (J = 23.0 Hz), 109.8, 105.6, 64.1; **^{19}F NMR** (376 MHz, DMSO-d_6) δ −123.2; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{20}H_{15}FN_3O$ 332.1194, found 332.1195.

*7-Chloro-11-phenyl-3b,4-dihydro-5H-pyrrolo[2′,1′:3,4]pyrazino [1,2-a]quinazolin-5-one (**8w**).*



Ivory solid, mp: 268.9–269.6 °C (65.9 mg, 86%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.28 (d, J = 4.8 Hz, 1H), 8.11 (s, 1H), 7.71 (s, 1H), 7.69 (s, 1H), 7.65 (d, J = 2.4 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 7.35 (t, J = 7.6 Hz, 1H), 7.22 (dd, J = 8.8, 2.4 Hz, 1H), 6.97 (s, 1H), 6.24 (d, J = 8.8 Hz, 1H), 6.13 (t, J = 3.2 Hz, 1H), 6.08 (s, 1H), 5.79 (d, J = 4.8 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 160.6, 144.5, 133.6, 133.0, 129.3, 128.3, 128.2, 126.8, 124.4, 124.1, 119.1, 119.0, 118.6, 117.9, 109.8, 105.6, 64.1; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{20}H_{15}ClN_3O$ 348.0898, found 348.0895.

*7-Bromo-11-phenyl-3b,4-dihydro-5H-pyrrolo[2′,1′:3,4]pyrazino [1,2-a]quinazolin-5-one (**8x**).*

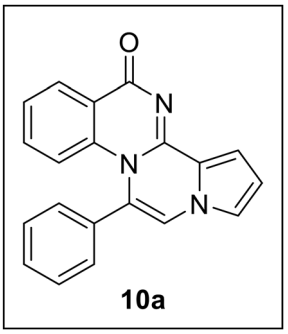


Ivory solid, mp: 265.0–265.2 °C (82.0 mg, 95%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 9.29 (d, J = 4.4 Hz, 1H), 8.12 (s, 1H), 7.78 (d, J = 1.6 Hz, 1H), 7.70 (d, J = 7.6 Hz, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.37–7.31 (m, 2H), 6.97 (s, 1H), 6.18 (d, J = 8.8 Hz, 1H), 6.15–6.11 (m, 1H), 6.09 (s, 1H), 5.80 (d, J = 4.8 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 160.5, 144.9, 135.8, 133.6, 129.7, 129.3, 128.34, 128.31, 128.2, 124.4, 119.4, 119.0, 118.6, 118.3, 111.6, 109.8, 105.6, 64.1; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{20}H_{15}BrN_3O$ 392.0393, found 392.0390.

Synthesis of 10a. To a solution of **8a** (0.10 mmol, 1.0 equiv.) in dichloromethane (3 mL) was added I_2 (3.0 equiv.) at 0 °C. After being stirred at 80 °C (heating mantle was used) for 21.5 h, the reaction mixture was cooled down to rt and washed with aq. sodium thiosulfate solution (3 mL). The aqueous layer was extracted with dichloromethane (3 mL) one more time. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate/dichloro-

methane = 1 : 4 : 2) to afford **10a** (23.9 mg, 80%) as a yellow solid.

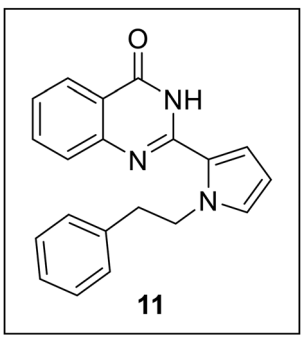
*11-Phenyl-5H-pyrrolo[2′,1′:3,4]pyrazino[1,2-a]quinazolin-5-one (**10a**).*



Yellow solid, mp: 297.1–297.5 °C (23.9 mg, 80%); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.31 (d, J = 7.6 Hz, 1H), 7.60 (d, J = 3.6 Hz, 1H), 7.42–7.38 (m, 3H), 7.37 (s, 1H), 7.36–7.33 (m, 2H), 7.32–7.28 (m, 2H), 7.19 (dd, J = 8.4, 7.2 Hz, 1H), 6.81 (d, J = 8.8 Hz, 1H), 6.74 (s, 1H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 168.4, 149.1, 137.9, 134.1, 131.1, 129.7, 129.2, 128.1, 127.1, 126.3, 126.1, 123.5, 122.2, 121.3, 120.9, 116.6, 115.4, 114.1; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{20}H_{14}N_3O$ 312.1131, found 312.1138.

Synthesis of 11. A mixture of **8a** (0.10 mmol, 1.0 equiv.) and 10% Pd/C (7 mg) in ethyl acetate (2 mL) was stirred under a H_2 balloon atmosphere at 60 °C (heating mantle was used) for 9 h. Then, the reaction mixture was cooled down to rt and filtered to remove the catalyst. The filtrate was concentrated *in vacuo*, which was triturated with a mixed solvent (hexane/dichloromethane = 5 : 1) to afford **11** (26.8 mg, 89%) as an ivory solid.

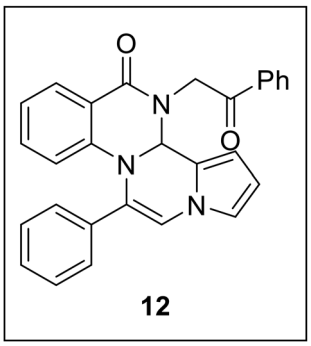
*2-(1-Phenethyl-1H-pyrrol-2-yl)quinazolin-4(3H)-one (**11**).*



Ivory solid, mp: 201.8–202.3 °C (26.8 mg, 89%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.03 (s, 1H), 8.11 (d, J = 8.0 Hz, 1H), 7.80 (t, J = 7.6 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.44 (t, J = 7.6 Hz, 1H), 7.30–7.24 (m, 3H), 7.23–7.16 (m, 3H), 7.10 (s, 1H), 6.14 (s, 1H), 4.79 (t, J = 7.6 Hz, 2H), 3.05 (t, J = 7.6 Hz, 2H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 161.9, 148.9, 146.6, 138.7, 134.6, 129.6, 128.8, 128.3, 126.8, 126.3, 125.9, 125.7, 123.0, 120.5, 115.3, 107.9, 50.3, 37.8; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{20}H_{18}N_3O$ 316.1445, found 316.1445.

Synthesis of 12. A mixture of **8a** (0.10 mmol, 1.0 equiv.), phenacyl bromide (2.0 equiv.), and cesium carbonate (1.5 equiv.) in acetonitrile (3 mL) was stirred at 60 °C (heating mantle was used) for 12 h. The reaction mixture was concentrated *in vacuo*, diluted with dichloromethane (2 mL), and washed with water (2 mL). The water layer was extracted with dichloromethane (2 mL) one more time. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product. The reaction mixture was diluted with a small amount of EtOH, suction-filtered, and washed with EtOH to yield **12**. Additional purification of the filtrate by silica gel column chromatography (hexane : ethyl acetate : dichloromethane = 10 : 1 : 2) afforded **12**. Overall, **12** was obtained (30.9 mg, 75%) as a beige solid.

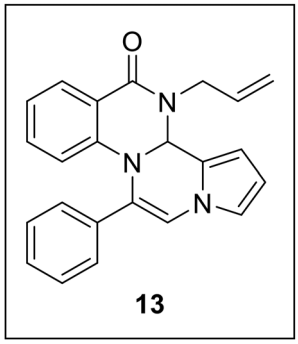
*4-(2-Oxo-2-phenylethyl)-11-phenyl-3b,4-dihydro-5H-pyrrolo[2′,1′:3,4]pyrazino[1,2-a]quinazolin-5-one (**12**).*



Beige solid, mp: 215.6–216.0 °C (30.9 mg, 75%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.15 (s, 1H), 8.09 (d, J = 7.6 Hz, 2H), 7.79–7.67 (m, 4H), 7.58 (t, J = 7.6 Hz, 2H), 7.49 (t, J = 7.6 Hz, 2H), 7.37 (t, J = 7.6 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.00 (s, 1H), 6.85 (t, J = 7.6 Hz, 1H), 6.32 (s, 1H), 6.27 (d, J = 8.4 Hz, 1H), 6.15 (s, 1H), 6.03 (s, 1H), 5.69 (d, J = 17.6 Hz, 1H), 4.83 (d, J = 18.0 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 193.6, 160.9, 145.8, 135.0, 133.9, 133.7, 133.4, 129.3, 128.9, 128.5, 128.3, 128.0, 127.8, 126.9, 124.4, 120.1, 119.1, 118.7, 117.3, 115.6, 109.8, 105.8, 69.5, 52.9; **HRMS** (ESI-QTOF) m/z $[M + H]^+$ calcd for $C_{28}H_{22}N_3O_2$ 432.1707, found 432.1710.

Synthesis of 13. After a mixture of **8a** (0.10 mmol, 1.0 equiv.), allyl bromide (4.0 equiv.), and sodium hydride (2.0 equiv.) in THF (3 mL) was stirred at 80 °C (heating mantle was used) for 6 h, the reaction mixture was cooled down to rt, quenched with water (2 mL), and extracted with dichloromethane (2 mL). The water layer was extracted with dichloromethane (2 mL) one more time. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product, which was triturated with a mixed solvent (hexane/dichloromethane = 5 : 1) to afford **13** (32.8 mg, 97%) as an ivory solid.

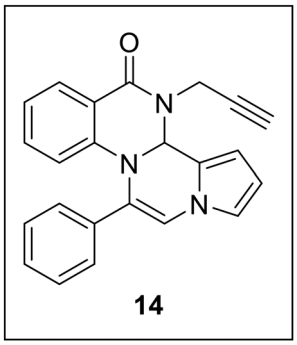
*4-Allyl-11-phenyl-3b,4-dihydro-5H-pyrrolo[2′,1′:3,4]pyrazino[1,2-a]quinazolin-5-one (**13**).*



Ivory solid, mp: 185.8–186.0 °C (32.8 mg, 97%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.16 (s, 1H), 7.76 (d, J = 6.8 Hz, 1H), 7.73 (d, J = 7.6 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.35 (t, J = 7.2 Hz, 1H), 7.18–7.13 (m, 1H), 6.98 (s, 1H), 6.85 (t, J = 7.6 Hz, 1H), 6.25 (d, J = 8.4 Hz, 1H), 6.14–6.10 (m, 1H), 6.09 (s, 1H), 6.06–5.94 (m, 1H), 5.80 (s, 1H), 5.38 (d, J = 17.2 Hz, 1H), 5.23 (d, J = 10.0 Hz, 1H), 4.81 (dd, J = 16.0, 4.8 Hz, 1H), 3.87 (dd, J = 16.0, 6.0 Hz, 1H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 160.6, 145.7, 133.9, 133.4, 133.3, 129.3, 128.7, 128.3, 127.9, 126.6, 124.3, 120.3, 119.1, 118.8, 117.5, 117.2, 115.7, 109.8, 105.6, 68.3, 47.5; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{23}H_{20}N_3O$ 354.1601, found 354.1607.

Synthesis of 14. A mixture of **8a** (0.10 mmol, 1.0 equiv.), propargyl bromide (4.0 equiv.) and sodium hydride (2.0 equiv.) in THF (3 mL) was stirred at 80 °C (heating mantle was used) for 2 h; then the reaction mixture was cooled down to rt, quenched with water (2 mL), and extracted with dichloromethane (2 mL). The water layer was extracted with dichloromethane (2 mL) one more time. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product, which was triturated with a mixed solvent (hexane/dichloromethane = 5 : 1) to afford **14** (30.1 mg, 89%) as a yellow solid.

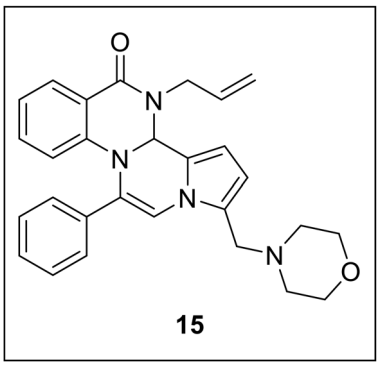
*11-Phenyl-4-(prop-2-yn-1-yl)-3b,4-dihydro-5H-pyrrolo[2′,1′:3,4]pyrazino[1,2-a]quinazolin-5-one (**14**).*



Yellow solid, mp: 141.5–141.9 °C (30.1 mg, 89%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.21 (s, 1H), 7.81 (d, J = 6.8 Hz, 1H), 7.79–7.71 (m, 3H), 7.44 (t, J = 7.2 Hz, 2H), 7.35 (t, J = 7.2 Hz, 1H), 7.22 (t, J = 7.2 Hz, 1H), 6.98 (s, 1H), 6.90 (t, J = 7.6 Hz, 1H), 6.31 (d, J = 8.0 Hz, 1H), 6.12 (s, 1H), 5.97 (s, 1H), 5.93 (s, 1H), 5.57–5.47 (m, 2H); **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ 201.4, 159.6, 145.5, 133.82, 133.79, 129.8, 129.4, 129.0, 128.7, 126.2, 124.7, 120.7, 118.3, 118.0, 117.0, 116.2, 110.5, 106.5, 97.9, 89.0, 67.9; **HRMS** (ESI-QTOF) m/z [M + H]$^+$ calcd for $C_{23}H_{18}N_3O$ 352.1444, found 352.1442.

Synthesis of 15. A mixture of **13** (0.09 mmol, 1.0 equiv.), morpholine (10.0 equiv.), paraformaldehyde (16.0 equiv.), and acetic acid (2 drops) in THF (3 mL) was stirred at 130 °C (heating mantle was used) for 42 h. The reaction mixture was concentrated *in vacuo*, diluted with dichloromethane (2 mL), and washed with aq. sodium bicarbonate solution (2 mL). The aqueous layer was extracted with dichloromethane (2 mL) one more time. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product, which was purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane = 3 : 1 : 2) to afford **15** (33.5 mg, 87%) as a pale yellow gum.

*4-Allyl-1-(morpholinomethyl)-11-phenyl-3b,4-dihydro-5H-pyrrolo[2′,1′:3,4]pyrazino[1,2-a]quinazolin-5-one (**15**).*



Pale yellow gum (33.5 mg, 87%); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.08 (s, 1H), 7.79–7.71 (m, 3H), 7.47 (t, J = 7.2 Hz, 2H), 7.36 (t, J = 7.2 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 6.84 (t, J = 7.2 Hz, 1H), 6.23 (d, J = 8.4 Hz, 1H), 6.03–5.95 (m, 3H), 5.76 (s, 1H), 5.38 (d, J = 17.2 Hz, 1H), 5.23 (d, J = 10.4 Hz, 1H), 4.79 (d, J = 12.8 Hz, 1H), 3.87 (dd, J = 16.0, 5.6 Hz, 1H), 3.60 (d, J = 14.4 Hz, 1H), 3.52 (s, 5H), 2.38–2.16 (m, 4H); **^{13}C{^{1}H} NMR** (100 MHz, DMSO-d_6) δ 160.6, 145.7, 134.1, 133.3, 133.1, 129.3, 128.32, 128.28, 127.8, 127.3, 127.1, 124.4, 120.3, 117.6, 117.4, 117.1, 115.5, 110.4, 104.4, 68.3, 66.4, 52.7, 52.5, 47.5; **HRMS** (ESI-QTOF) m/z [M + Na]$^+$ calcd for $C_{28}H_{28}N_4O_2Na$ 475.2104, found 475.2109.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

The data supporting this article have been included as part of the ESI.†

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