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Microwave-Assisted *aza*-Friedel−Crafts Arylation of *N*-Acyliminium Ions: Expedient Access to 4-Aryl 3,4-Dihydroquinazolinones

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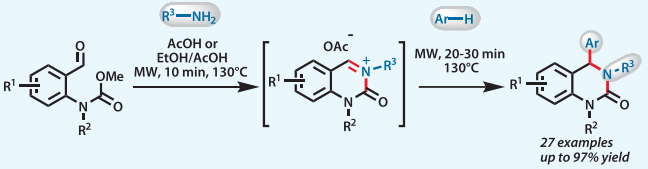
Supporting Information

ABSTRACT: A one-pot microwave-assisted *aza*-Friedel−Crafts arylation of *N*-acyliminium ions, generated in situ from *o*-formyl carbamates and different amines, is reported. This metal-free protocol provides rapid access to diverse 4-aryl 3,4-dihydroquinazolinones in excellent yield without any aqueous workup. A solvent-directed process for the selective *aza*-Friedel−Crafts arylation of electron-rich aryl/heteroaryl/butenyl-tethered *N*-acyliminium ions is also described.



INTRODUCTION

N-Acyliminium ions[1−5] are versatile electrophiles that provide direct access to α-substituted amino derivatives via the intra- or intermolecular addition of various nucleophiles. In particular, in situ-generated *N*-acyliminium ions have been widely exploited in the synthesis of bioactive nitrogen-containing heterocycles, especially in the preparation of alkaloid natural products.[1,2,6,7] Accordingly, the development of rapid, convenient, and high-yielding protocols for the selective intra- or intermolecular nucleophilic addition to cyclic *N*-acyliminium ions remains a field of considerable interest.[8−11] The C4-substituted quinazolinone framework is known to exhibit a wide range of biological properties. For example, SM-15811 is a potent Na^+/Ca^{2+} exchanger inhibitor,[12−14] proquazone is an anti-inflammatory drug,[15,16] and 4-disubstituted 3,4-dihydroquinazolinones are T-type channel selective calcium blockers with in vivo central nervous system efficacy in epilepsy and tremor models[17,18] (Figure 1). Finally, the 3,4-dihydroquinazolinones DPC 961 and DPC 083 and related analogs are potent human immunodeficiency virus non-nucleoside reverse transcriptase inhibitors.[19,20]

The known methods for the synthesis of 4-aryl substituted 3,4-dihydroquinazolinones include a two-step condensation of aldehyde, urea, and carboxylic acid,[21] and a three-step synthesis from *o*-amino acetophenones[12−14,17,18] and the organocatalytic asymmetric synthesis of trifluoromethyl 3,4-dihydroquinazolinones based on the *aza*-Friedel−Crafts reaction of indoles with cyclic *N*-acylketimines using a chiral phosphoric acid catalyst.[22] Xie and co-workers reported the enantioselective *aza*-Friedel−Crafts reaction of naphthols/phenols with cyclic *N*-acylketimines using a chiral quinine-squaramide catalyst.[23] Despite these elegant approaches, the existing methods require either lengthy reaction sequences or isolation of cyclic *N*-acylketimines, which limits their utility in the generation of diverse 3,4-dihydroquinazolinone libraries.

During the preparation of this manuscript, Chandrasekharam and co-workers reported a water-mediated multicomponent synthesis of 4-aryl substituted 3,4-dihydroquinazolinones under conventional heating.[24] However, it is important to highlight that the use of water as a reaction medium demanded long reaction times, and, in many cases, chromatographic purification was required, both of which detract from its appeal as a green protocol. Moreover, the scope of this method is restricted to indole and mono-functional amine nucleophiles, limiting its utility in library generation. In this context, an environmentally benign and expedient method for the rapid synthesis of 4-aryl 3,4-dihydroquinazolinone libraries is highly desirable.

As part of our ongoing research program, we recently reported a highly efficient solvent-directed diversity-oriented synthesis of skeletally diverse 3,4-dihydroquinazolinones scaffold libraries based on *N*-acyliminium ion chemistry under environmentally benign reaction conditions.[25−29] Our recent findings demonstrated that the intramolecular cyclization of aryl/heteroaryl tethered nucleophiles with *N*-acyliminium ions[27] leads to the formation of 3,4-dihydroquinazolinone-embedded polyheterocycles (Scheme 1). With the aim of developing an expedient approach to 4-aryl/heteroaryl

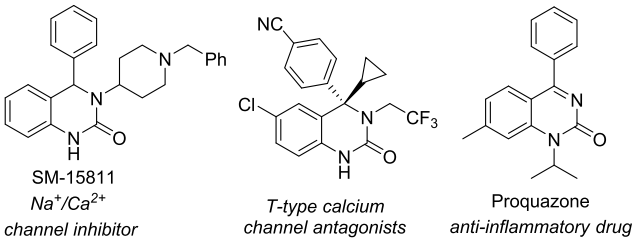


Figure 1. Structures of pharmaceutically important 4-aryl quinazolinones.

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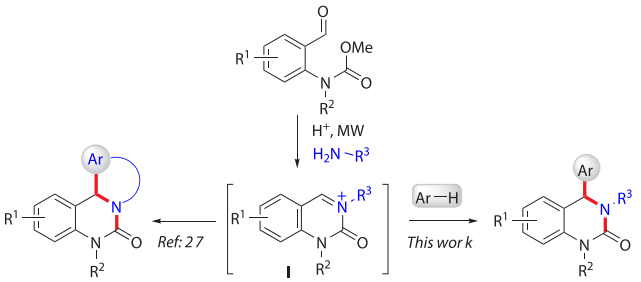
Scheme 1. Proposed Reaction Sequence for the *aza*-Friedel−Crafts Arylation of *N*-Acyliminium Ions

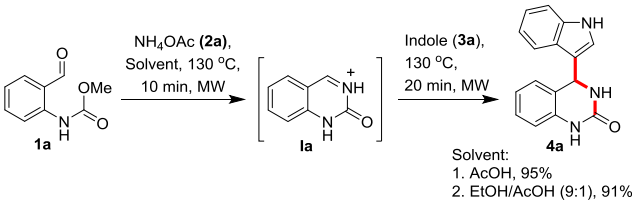


3,4-dihydroquinazolinones, we were encouraged to investigate the intermolecular functionalization of *N*-acyliminium ions (**I**) with indoles and arenes to produce 4-aryl 3,4-dihydroquinazolinone scaffold libraries based on a cascade imine/cyclization/*aza*-Friedel−Crafts reaction sequence. Herein, we present one-pot microwave-assisted metal-free sequential *N*-acyliminium ion/*aza*-Friedel−Crafts arylation that provides rapid access to 4-aryl/heteroaryl 3,4-dihydroquinazolinones from readily available precursors (Scheme 1).

RESULTS AND DISCUSSION

We started our investigation by optimization of the reaction conditions for the *aza*-Friedel−Crafts arylation of the *N*-acyliminium ion generated in situ from *o*-formyl carbamate **1a** and NH_4OAc **2a** (Scheme 2). We were pleased to observe that

Scheme 2. Optimization Studies for the *aza*-Friedel−Crafts Arylation of an *N*-Acyliminium Ion



the reaction proceeded in either AcOH or EtOH/AcOH as the solvent. The reaction between *o*-formyl carbamate **1a** and NH_4OAc **2a** (2 equiv) in AcOH under microwave heating at 130 °C for 10 min provided *N*-acyliminium ion intermediate **Ia** (confirmed by liquid chromatography/mass spectrometry (LC/MS)), which upon subsequent treatment with indole **3a** (1.3 equiv) and an additional 20 min of heating at 130 °C produced 4-indolyl 3,4-dihydroquinazolinone **4a** in excellent yield (95%). Similarly, the two-step reaction sequence in EtOH/AcOH (9:1) afforded dihydroquinazolinone **4a** in a slightly reduced yield (91%) under optimal protic solvent/Brønsted acid combinations (Scheme 2).

With the optimized reaction conditions in hand, we first explored the scope of the *aza*-Friedel−Crafts arylation of different cyclic *N*-acyliminium ions generated in situ from *o*-formyl carbamates **1b**−**1h** and NH_4OAc **2a** with indole **3a** in AcOH (Scheme 3). *N*-Acyliminium ions **1b**−**1h** derived from aldehydes **1b**−**1h** containing electron-donating/withdrawing and halogen substituents reacted smoothly with indole to afford the corresponding 4-indolyl 3,4-dihydroquinazolinones **4b**−**4f** in good to excellent yields (86−92%). The introduction of an *o*-substituent and *N*-1-benzyl substituent was also well-tolerated, giving 3,4-dihydroquinazolinones **4g** and **4h** in good yield. Next, the scope of the indole nucleophile was explored and indole derivatives containing electron-donating/withdrawing, and halogen substituents furnished the corresponding 4-indolyl 3,4-dihydroquinazolinones **4i**, **4j**, and **4n** in good to excellent yield (83−92%). Sterically hindered *o*-substituted indoles reacted smoothly, producing 3,4-dihydroquinazolinones **4k**−**4m** in good to excellent yield. The protocol also worked well with *N*-methylindole and 7-azaindole to afford 3,4-dihydroquinazolinones **4o** and **4p** in 84 and 90% yield, respectively (Scheme 3).

Next, to further expand the scope and applicability of microwave-assisted *aza*-Friedel−Crafts arylation of *N*-acyliminium ions, we investigated the effect of varying the arene and amine components (Scheme 4). Our protocol tolerated a wide range of amine nucleophiles, affording the corresponding 3,4-dihydroquinazolinone in up to 95% yield. Primary alkyl amines such as benzylamine **2a** and 2-thiophenemethylamine **2b** worked well to afford *N*-3-functionalized 3,4-dihydroquinazolinones **6a**, **6b** in excellent yields (>94%). A one-step three-component reaction between aldehyde **1a**, benzylamine **2b**, and indole **3a** afforded **6a** in reduced yield (85%) confirming that the two-step sequential approach is preferable. *N*-Acyliminium ions also reacted smoothly with 1,3-dimethoxybenzene **5a** to produce 4-aryl 3,4-dihydroquinazolinones **6c**−**6e** in moderate to good yields. It is important to highlight that the branched amine *N*-methyl 4-amino piperidine **2d** was efficiently transformed into **6e**, an analog of SM-15811 in satisfactory yield. Finally, *m*-cresol **5b** underwent chemoselective C-functionalization to produce **6f** in 52% yield (Scheme 4).

Next, we sought to expand the scope of the selective cascade arylation reaction using challenging amine nucleophiles bearing pendant electron-rich aryl/alkenyl moieties (**2e**−**2j**, Scheme 5). Gratifyingly, electron-rich aryl/heteroaryl/butenyl-tethered *N*-acyliminium ions were generated in situ from *o*-formyl carbamate and amines **2e**−**2h** in EtOH/AcOH (9:1) and reacted smoothly with indole **3a** to afford *N*-3-aryl/heteroaryl/butenyl-tethered 4-aryl 3,4-dihydroquinazolinones **7a**−**7d** in excellent yield (Scheme 5). However, with indole tethered *N*-acyliminium ions, intramolecular *aza*-Friedel−Crafts cyclization was more favored under the optimized reaction conditions. The *N*-acyliminium ion derived from 4-aminomethyl indole **2i** gave **7e** in 36% yield along with the polycyclic product **7e′**, whereas the tryptamine derivative gave only traces of **7f** (Scheme 5). It is important to highlight that by changing the solvent composition the reaction can be paused at the *N*-acyliminium ion stage, followed by selective functionalization at the C-4 position with an external indole nucleophile, despite the presence of a pendant electron-rich aryl, thiophene, indole, or alkene nucleophile. Thus, the two-step protocol using a minimum of acetic acid can effectively suppress competing intramolecular *aza*-Friedel−Crafts[27] and *aza*-Prins cyclization[28] reactions, allowing the selective C-4 functionalization by an indole nucleophile.

CONCLUSIONS

In conclusion, we have developed a highly efficient, metal-free microwave-assisted *aza*-Friedel−Crafts arylation of *N*-acyliminium ions. The solvent-directed selective *aza*-Friedel−Crafts arylation of challenging aryl/heteroaryl/butenyl-tethered *N*-acyliminium ions was achieved to produce 4-aryl 3,4-dihydroquinazolinones. This protocol offers a rapid and direct approach to generate polyfunctionalized 4-aryl 3,4-dihydro-

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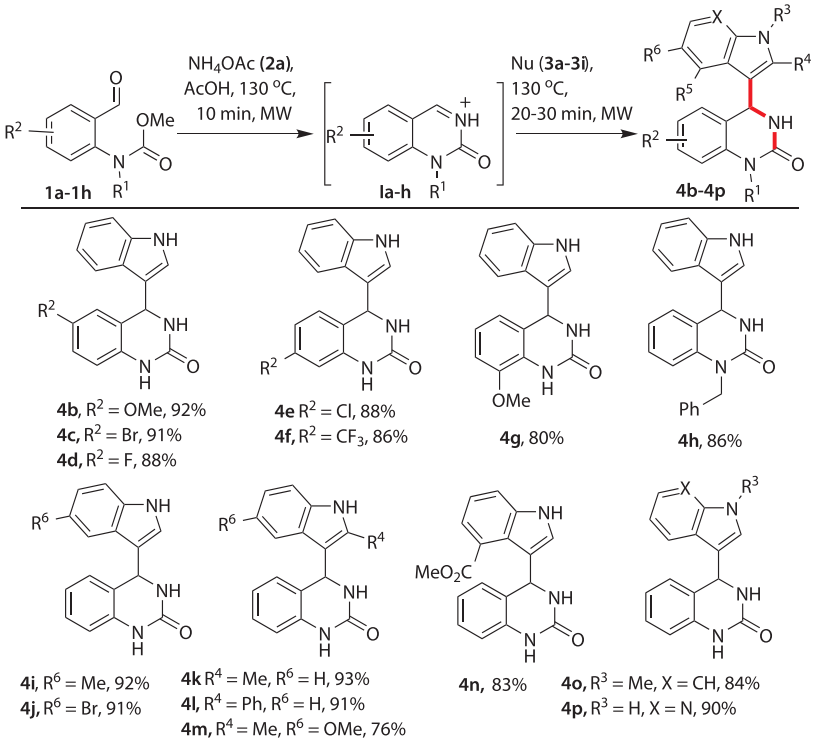
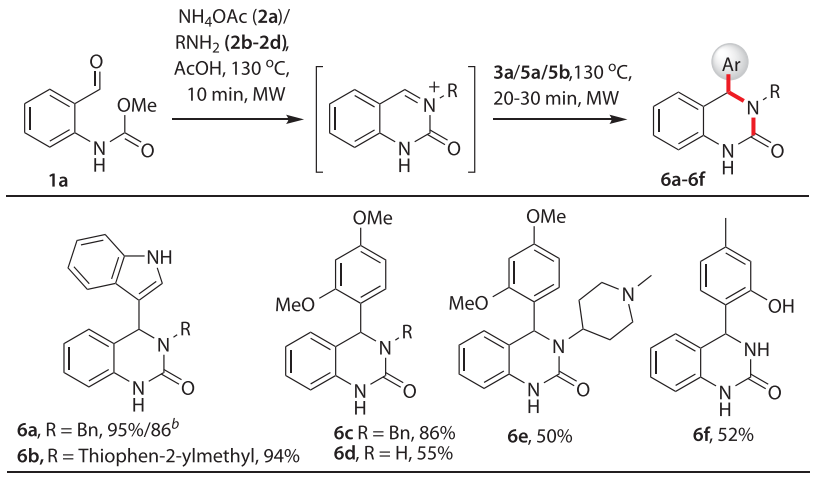
Scheme 3. Scope of *aza*-Friedel−Crafts Arylation of *N*-Acyliminium Ions with Indoles[a]



[a]Isolated yield. All reactions were performed with 1 equiv *o*-formyl carbamate (**1b−1h**), 2 equiv NH_4OAc (**2a**) in 1 mL AcOH, 130 °C, MW, 10 min, and then 1.3 equiv indole (**3a−3i**) 130 °C, MW, 20−30 min.

Scheme 4. Scope of *aza*-Friedel−Crafts Arylation of *N*-Acyliminium Ions with Arenes[a,b]



[a]Isolated yield. Unless otherwise stated, reactions were performed with 1 equiv *o*-formyl carbamate (**1b−1h**), 2 equiv NH_4OAc (**2a**) and 1.3 equiv amine (**2b−2d**) in 1 mL AcOH, 130 °C, MW, 10 min, and then 1.3 equiv Nu (**3a**/**5a**/**5b**) 130 °C, MW, 20−30 min. [b]One-step reaction in AcOH, MW, 130 °C, 20 min.

quinazolinone libraries in excellent yields under environmentally benign reaction conditions and in a short reaction time. Moreover, the protocols utilize readily available and stable *o*-formyl carbamate precursors and are compatible with a broad scope of amine and aryl/heteroaryl nucleophiles. Further investigations to expand the scope of this approach and explore the biological activity of these compounds are underway in our laboratory.

EXPERIMENTAL SECTION

All reagents and solvents were obtained from commercial suppliers and used without further purification. The yields stated refer to homogenous and spectroscopically pure isolated material. Thin layer chromatography (TLC, 0.25 mm E. Merck silica plates, 60F-254) was used to assess reaction progress and the plates were visualized with 254 nm UV light. Silica gel chromatography was performed using E. Merck silica gel (60 Å pore size, particle size 40−63 nm). ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR spectra at 100 MHz. The

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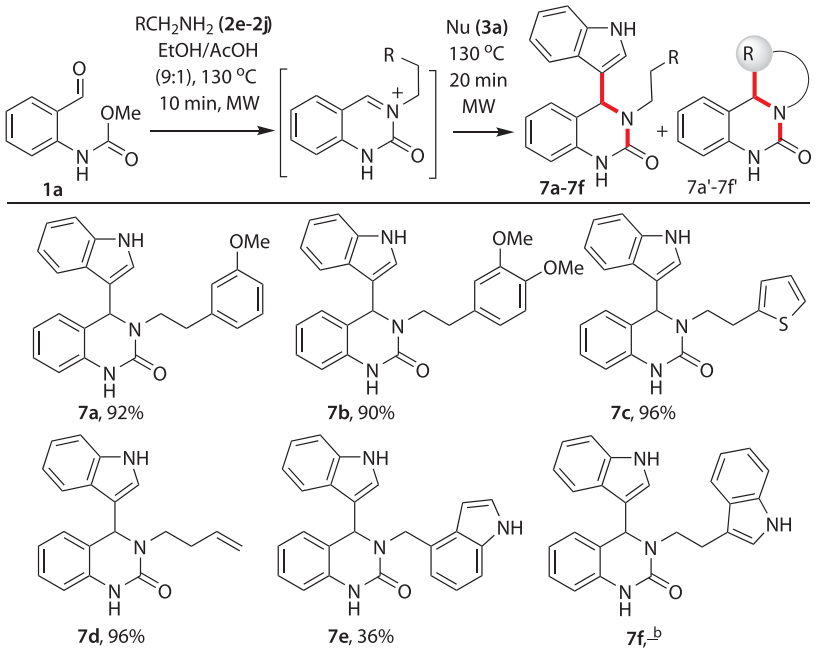
Scheme 5. Solvent-Directed Selective 4-Arylation of Aryl/Alkenyl Tethered *N*-Acyliminium Ions[a,b]



[a]Isolated yield. All reactions were performed with 1 equiv *o*-formyl carbamate (**1a**), 1.3 equiv amine (**2e**−**2j**) in 1 mL EtOH/AcOH (9:1), 130 °C, MW, 10 min, and then 1.5 equiv Nu (**3a**) 130 °C, MW, 20 min. [b]Product not isolated.

chemical shifts for ^{1}H NMR and ^{13}C NMR were referenced to tetramethylsilane via residual solvent signals (^{1}H, $CDCl_3$ at 7.26 ppm; ^{13}C, $CDCl_3$ at 77.16 ppm; ^{1}H, DMSO-d_6 at 2.45 ppm; ^{13}C, DMSO-d_6 at 39.43 ppm; ^{1}H, CD_3OD at 3.31 ppm; and ^{13}C, CD_3OD at 49.0 ppm). Microwave reactions were performed in an Initiator single mode reactor producing controlled irradiation at 2450 MHz and the temperature was monitored using the built-in online IR sensor. LC/MS was performed on an instrument equipped with a CP-Sil 8 CB capillary column (50 × 3.0 mm^2, particle size 2.6 μm, pore size 100 Å) operating at an ionization potential of 70 eV using a CH_3CN/H_2O gradient (0.05% HCOOH). High-resolution mass values were determined using a 7-T hybrid ion trap and a time of flight detector and an electrospray ionization source. All reactions were performed in sealed Pyrex microwave-transparent process vials designed for 0.5−2 mL reaction volumes, unless otherwise stated.

Preparation of *o*-Formyl Carbamates. The required known compounds **1a**−**1h** were prepared from the corresponding amino alcohols following the literature procedure.[25,26]

General Procedure A. *One-Pot, Two-Step Preparation of 4-Aryl 3,4-Dihydroquinazolinones (**4a**−**4p** and **6a**−**6f**) Exemplified by **4a**.* A 0.5−2 mL Pyrex process vial was charged with aldehyde **1a** (40 mg, 224 μmol), NH_4OAc **2a** (34 mg, 448 μmol), and acetic acid (1 mL). The vial was sealed and subjected to microwave irradiation at 130 °C for 10 min, after which indole (**3a**, 34 mg, 290 μmol) was added. The vial was re-sealed and heated by microwave at 130 °C for 20 min, and thereafter the reaction mixture was concentrated in vacuo. Silica gel chromatography (2−5% MeOH in dichloromethane (DCM) or 30−85% EtOAc in *n*-pentane) provided the title compound as a white solid (56 mg, 95%).

General Procedure B. *One-Pot, Two-Step Preparation of 4-Aryl 3,4-Dihydroquinazolinones (**7a**−**7e**) Exemplified by **7b**.* A 0.5−2 mL Pyrex process vial was charged with aldehyde **1a** (40 mg, 224 μmol), amine **2f** (53 mg, 290 μmol), and ethanol/acetic acid (9:1, 1 mL). The vial was sealed and subjected to microwave irradiation at 130 °C for 10 min, after which indole (**3a**, 39 mg, 334 μmol) was added. The vial was re-sealed and heated by microwave at 130 °C for 20 min, and thereafter the reaction mixture was concentrated in vacuo. Silica gel chromatography (2−5% MeOH in DCM or 55−70% EtOAc in *n*-pentane) provided the title compound as a white solid (85 mg, 90%).

*4-(1H-Indol-3-yl)-3,4-dihydroquinazolin-2(1H)-one (**4a**).*[24] Prepared following the general procedure (**A**), starting from aldehyde **1a** (40 mg, 224 μmol), amine **2a** (34 mg, 448 μmol), and nucleophile **3a** (34 mg, 290 μmol). Yield: 56 mg (95%); white solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.99−10.90 (m, 1H), 9.27−9.22 (m, 1H), 7.50 (d, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 8.1 Hz, 1H), 7.18−7.14 (m, 2H), 7.11−7.02 (m, 2H), 6.96−6.87 (m, 2H), 6.86−6.81 (m, 1H), 6.79−6.73 (m, 1H), 5.80 (d, *J* = 2.2 Hz, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 154.1, 137.6, 137.1, 127.9, 127.0, 125.3, 123.5, 122.2, 121.6, 121.2, 119.6, 119.0, 118.7, 114.0, 112.0, 50.9. High resolution mass spectrometry HRMS (electrospray ionization, ESI): calcd for $C_{18}H_{17}N_4O$ $[M + MeCN + H]^+$ 305.1402; found 305.1418. TLC (SiO_2): R_f = 0.06 (60% EtOAc in *n*-pentane).

*4-(5-Methoxy-2-methyl-1H-indol-3-yl)-3,4-dihydroquinazolin-2(1H)-one (**4b**).* Prepared following the general procedure (**A**), starting from aldehyde **1b** (40 mg, 191 μmol), amine **2a** (29 mg, 376 μmol), and nucleophile **3a** (29 mg, 248 μmol). Yield: 52 mg (92%); white solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.98 (d, *J* = 2.5 Hz, 1H), 9.12 (d, *J* = 1.9 Hz, 1H), 7.66−7.48 (m, 1H), 7.37 (m, 1H), 7.18 (d, *J* = 2.5 Hz, 1H), 7.11 (m 1H), 7.07 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 6.94 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 1H), 6.73 (dd, *J* = 8.7, 2.7 Hz, 1H), 6.56 (d, *J* = 2.7 Hz, 1H), 5.79 (d, *J* = 2.3 Hz, 1H), 3.58 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 153.9, 153.7, 136.7, 130.8, 124.9, 123.0, 122.9, 121.2, 119.2, 118.6, 118.2, 114.4, 112.9, 112.2, 111.6, 55.2, 50.6. HRMS (ESI):

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calcd for $C_{19}H_{19}N_4O_2$ [M + MeCN + H]$^+$ 335.1508; found 335.1517. TLC (SiO_2): R_f = 0.13 (5% MeOH in DCM).

*6-Bromo-4-(1H-indol-3-yl)-3,4-dihydroquinazolin-2(1H)-one (**4c**).* Prepared following the general procedure (**A**), starting from aldehyde **1c** (40 mg, 155 μmol), amine **2a** (24 mg, 311 μmol), and nucleophile **3a** (47 mg, 292 μmol). Yield: 48 mg (91%); white solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.19−10.92 (m, 1H), 9.56−9.44 (m, 1H), 7.50 (d, J = 7.9 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.35−7.31 (m, 1H), 7.28 (dd, J = 8.5, 2.3 Hz, 1H), 7.25 (d, J = 2.5 Hz, 1H), 7.13−7.05 (m, 2H), 7.00−6.93 (m, 1H), 6.81 (d, J = 8.5 Hz, 1H), 5.92−5.82 (m, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 153.3, 136.7, 136.6, 130.3, 129.0, 124.7, 124.3, 123.3, 121.3, 119.0, 118.8, 117.7, 115.7, 112.0, 111.8, 50.1. HRMS (ESI): calcd for $C_{18}H_{16}BrN_4O$ [M + MeCN + H]$^+$ 383.0507; found m/z 383.0516. TLC (SiO_2): R_f = 0.15 (5% MeOH in DCM).

*6-Fluoro-4-(1H-indol-3-yl)-3,4-dihydroquinazolin-2(1H)-one (**4d**).* Prepared following the general procedure (**A**), starting from aldehyde **1d** (40 mg, 203 μmol), amine **2a** (31 mg, 402 μmol), and nucleophile **4a** (31 mg, 265 μmol). Yield: 50 mg (88%); white solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.01 (s, 1H), 9.31 (s, 1H), 7.65−7.48 (m, 1H), 7.48−7.31 (m, 1H), 7.24 (s, 1H), 7.22−7.19 (m, 1H), 7.13−7.04 (m, 1H), 7.01−6.92 (m, 2H), 6.91−6.82 (m, 1H), 6.82−6.75 (m, 1H), 5.84 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 156.4 (d, $^1J_{CF}$ = 236.1 Hz), 153.2, 136.3, 133.3 (d, $^4J_{CF}$ = 1.9 Hz), 124.3, 123.1 (d, $^3J_{CF}$ = 7.0 Hz), 122.8, 120.8, 118.7, 118.3, 117.1, 114.4 (d, $^3J_{CF}$ = 7.7 Hz), 113.9 (d, $^2J_{CF}$ = 22.7 Hz), 112.50 (d, $^2J_{CF}$ = 23.6 Hz), 111.3, 49.9. HRMS (ESI): calcd for $C_{16}H_{13}FN_4O$ [M + H]$^+$ 282.1043; found 282.1054. TLC (SiO_2): R_f = 0.16 (5% MeOH in DCM).

*7-Chloro-4-(1H-indol-3-yl)-3,4-dihydroquinazolin-2(1H)-one (**4e**).* Prepared following the general procedure (**A**), starting from aldehyde **1e** (40 mg, 187 μmol), amine **2a** (29 mg, 376 μmol), and nucleophile **3a** (29 mg, 248 μmol). Yield: 49 mg (88%); white solid. ^{1}H NMR (CD_3OD, 400 MHz): δ 7.41 (m, 1H), 7.35 (m, 1H), 7.19 (s, 1H), 7.09 (ddd, J = 8.2, 7.0, 1.1 Hz, 1H), 6.94 (ddd, J = 8.0, 7.0, 1.1 Hz, 1H), 6.88 (d, J = 2.0 Hz, 1H), 6.82 (dd, J = 8.3, 0.9 Hz, 1H), 6.76 (dd, J = 8.3, 2.0 Hz, 1H), 5.92 (s, 1H). ^{13}C NMR (CD_3OD, 100 MHz): δ 153.8, 139.4, 137.4, 132.3, 128.9, 125.4, 123.9, 121.8, 121.4, 121.1, 119.7, 119.3, 118.2, 113.6, 112.3, 50.7. HRMS (ESI): calcd for $C_{18}H_{16}ClN_4O$ [M + MeCN + H]$^+$ 339.1013; found 339.1029. TLC (SiO_2): R_f = 0.09 (5% MeOH in DCM).

*4-(1H-Indol-3-yl)-7-(trifluoromethyl)-3,4-dihydroquinazolin-2(1H)-one (**4f**).* Prepared following the general procedure (**A**), starting from aldehyde **1f** (40 mg, 162 μmol), amine **2a** (25 mg, 324 μmol), and nucleophile **3a** (25 mg, 213 μmol). Yield: 46 mg (86%); white solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.17−10.91 (m, 1H), 9.85−9.48 (m, 1H), 7.54−7.48 (m, 1H), 7.45−7.41 (m, 1H), 7.41−7.36 (m, 1H), 7.28−7.22 (m, 1H), 7.20−7.14 (m, 2H), 7.14−7.05 (m, 2H), 6.99−6.93 (m, 1H), 5.94 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 152.7, 137.5, 136.3, 127.9 (q, $^2J_{CF}$ = 31.8 Hz), 127.2, 125.7 (q, $^4J_{CF}$ = 1.2 Hz), 123.6 (q, $^1J_{CF}$ = 272.1 Hz), 124.3, 123.0, 120.9, 118.6, 118.4, 116.9, 115.95 (q, $^3J_{CF}$ = 4.5 Hz), 111.3, 109.5 (q, $^3J_{CF}$ = 4.2 Hz), 49.9. HRMS (ESI): calcd for $C_{19}H_{16}F_3N_4O$ [M + MeCN + H]$^+$ 373.1276; found 373.1281. TLC (SiO_2): R_f = 0.15 (5% MeOH in DCM).

*4-(1H-Indol-3-yl)-8-methoxy-3,4-dihydroquinazolin-2(1H)-one (**4g**).* Prepared following the general procedure (**A**), starting from aldehyde **1g** (40 mg, 191 μmol), amine **2a** (29 mg, 376 μmol), and nucleophile **3a** (29 mg, 248 μmol). Yield: 45 mg (80%); white solid. ^{1}H NMR ($CDCl_3$/CD_3OD, 400 MHz): δ 7.31−7.24 (m, 1H), 7.23−7.16 (m, 1H), 7.03 (s, 1H), 6.97−6.90 (m, 1H), 6.82−6.76 (m, 1H), 6.68−6.64 (m, 2H), 6.46−6.37 (m, 1H), 5.82 (s, 1H), 3.76 (s, 3H). ^{13}C NMR ($CDCl_3$/CD_3OD, 100 MHz): δ 156.2, 146.5, 138.3, 126.1, 126.0, 124.2, 123.1, 122.9, 122.5, 120.0, 119.7, 117.8, 56.3, 52.5. HRMS (ESI): calcd for $C_{19}H_{19}N_4O_2$ [M + MeCN + H]$^+$ 335.1508; found 335.1524. TLC (SiO_2): R_f = 0.16 (5% MeOH in DCM).

*1-Benzyl-4-(1H-indol-3-yl)-3,4-dihydroquinazolin-2(1H)-one (**4h**).* Prepared following the general procedure (**A**), starting from aldehyde **1h** (40 mg, 149 μmol), amine **2a** (23 mg, 298 μmol), and nucleophile **3a** (23 mg, 196 μmol). Yield: 45 mg (86%); white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.34 (s, 1H), 7.66−7.49 (m, 1H), 7.42−7.29 (m, 6H), 7.25−7.17 (m, 1H), 7.15−7.05 (m, 3H), 6.98−6.90 (m, 1H), 6.88−6.81 (m, 2H), 6.00 (s, 1H), 5.55 (s, 1H), 5.29 (d, J = 16.6 Hz, 1H), 5.21 (d, J = 16.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 155.5, 137.8, 137.6, 137.0, 128.8, 128.3, 127.1, 126.9, 126.6, 125.4, 124.0, 123.4, 122.7, 122.4, 120.2, 119.7, 117.0, 114.3, 111.7, 51.0, 46.2. HRMS (ESI): calcd for $C_{23}H_{20}N_3O$ [M + MeCN + H]$^+$ 354.1606; found 354.1606. TLC (SiO_2): R_f = 0.13 (5% MeOH in DCM).

*4-(5-Methyl-1H-indol-3-yl)-3,4-dihydroquinazolin-2(1H)-one (**4i**).* Prepared following the general procedure (**A**), starting from aldehyde **1a** (40 mg, 224 μmol), amine **2a** (34 mg, 441 μmol), and nucleophile **3b** (38 mg, 290 μmol). Yield: 57 mg (92%); yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.87 (s, 1H), 9.29 (s, 1H), 7.36−7.33 (m, 1H), 7.31−7.26 (m, 1H), 7.20−7.17 (m, 1H), 7.16−7.10 (m, 2H), 7.01−6.87 (m, 3H), 6.84−6.78 (m, 1H), 6.10−5.68 (m, 1H), 2.35 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 153.8, 137.2, 135.1, 127.5, 126.9, 126.5, 125.2, 123.2, 122.8, 121.9, 120.8, 118.8, 117.5, 113.6, 111.3, 50.5, 21.4. HRMS (ESI): calcd for $C_{19}H_{19}N_4O$ [M + MeCN + H]$^+$ 319.1559; found m/z 319.1575. TLC (SiO_2): R_f = 0.16 (5% MeOH in DCM).

*4-(5-Bromo-1H-indol-3-yl)-3,4-dihydroquinazolin-2(1H)-one (**4j**).* Prepared following the general procedure (**A**), starting from aldehyde **1a** (40 mg, 224 μmol), amine **2a** (34 mg, 441 μmol), and nucleophile **3c** (57 mg, 291 μmol). Yield: 70 mg (91%); white solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.17 (br s, 1H), 9.29 (br s, 1H), 7.67 (d, J = 1.9 Hz, 1H), 7.33 (d, J = 8.6 Hz, 1H), 7.21−7.14 (m, 2H), 7.11−7.08 (m, 1H), 6.93 (d, J = 7.5 Hz, 1H), 6.85 (dd, J = 8.0, 1.2 Hz, 1H), 6.79 (ddd, J = 7.5, 7.5, 1.2 Hz, 1H), 5.80 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 153.7, 137.2, 135.4, 127.7, 126.7, 126.5, 124.8, 123.7, 121.5, 121.4, 121.0, 118.1, 113.7, 111.4, 50.1. HRMS (ESI): calcd for $C_{18}H_{16}BrN_4O$ [M + MeCN + H]$^+$ 383.0507; found 383.0502. TLC (SiO_2): R_f = 0.16 (5% MeOH in DCM).

*4-(2-Methyl-1H-indol-3-yl)-3,4-dihydroquinazolin-2(1H)-one (**4k**).* Prepared following the general procedure (**A**), starting from aldehyde **1a** (40 mg, 224 μmol), amine **2a** (34 mg, 441 μmol), and nucleophile **3d** (38 mg, 290 μmol). Yield: 58 mg (93%); white solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.93 (s, 1H), 9.28 (s, 1H), 7.34−7.26 (m, 1H), 7.26−7.20 (m, 1H), 7.11 (m, 1H), 7.01−6.96 (m, 1H), 6.89−6.81 (m, 2H), 6.77−6.72 (m, 2H), 5.95 (s, 1H), 2.46 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 153.7, 137.7, 135.8, 133.2, 127.9, 127.0, 126.7, 121.9, 121.2, 120.5, 118.8, 113.9, 113.7, 110.9, 49.9, 11.8. HRMS (ESI): calcd for $C_{19}H_{19}N_4O$ [M + MeCN + H]$^+$ 319.1551; found 319.1559. TLC (SiO_2): R_f = 0.16 (5% MeOH in DCM).

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*4-(2-Phenyl-1H-indol-3-yl)-3,4-dihydroquinazolin-2(1H)-one (**4l**).* Prepared following the general procedure (**A**), starting from aldehyde **1a** (40 mg, 224 μmol), amine **2a** (34 mg, 441 μmol), and nucleophile **3e** (56 mg, 290 μmol). Yield: 69 mg (91%); yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.43 (s, 1H), 9.35 (d, J = 1.9 Hz, 1H), 7.81−7.73 (m, 2H), 7.63−7.55 (m, 2H), 7.54−7.47 (m, 1H), 7.45−7.41 (m, 1H), 7.37−7.32 (m, 1H), 7.29−7.24 (m, 1H), 7.17−7.05 (m, 2H), 6.98−6.91 (m, 1H), 6.89 (dd, J = 8.0, 1.1 Hz, 1H), 6.70 (m, 1H), 6.61−6.54 (m, 1H), 5.99 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 153.8, 137.6, 136.8, 136.8, 132.6, 129.3, 129.2, 128.5, 128.1, 126.7, 126.5, 122.0, 121.6, 121.3, 120.3, 119.3, 114.0, 113.5, 111.8, 50.5. HRMS (ESI): calcd for $C_{24}H_{21}N_4O$ [M + MeCN + H]$^+$ 381.1715; found 381.1730. TLC (SiO_2): R_f = 0.20 (5% MeOH in DCM).

*4-(5-Methoxy-1H-indol-3-yl)-3,4-dihydroquinazolin-2(1H)-one (**4m**).* Prepared following the general procedure (**A**) starting from aldehyde **1a** (40 mg, 224 μmol), amine **2a** (34 mg, 441 μmol), and nucleophile **3f** (47 mg, 292 μmol). Yield: 52 mg (76%); pink solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.76 (s, 1H), 9.34 (d, J = 1.9 Hz, 1H), 7.17 (d, J = 8.7 Hz, 1H), 7.15−7.09 (m, 1H), 7.01−6.96 (m, 1H), 6.90−6.85 (m, 1H), 6.81−6.74 (m, 3H), 6.65 (dd, J = 8.7, 2.5 Hz, 1H), 5.90 (d, J = 1.7 Hz, 1H), 3.64 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 153.8, 153.2, 137.8, 133.8, 130.8, 127.9, 127.2, 127.1, 121.8, 121.3, 114.0, 113.8, 111.4, 109.5, 101.7, 55.5, 49.9, 11.9. HRMS (ESI): calcd for $C_{20}H_{21}N_4O_2$ [M + MeCN + H]$^+$ 349.1665; found 349.1669. TLC (SiO_2): R_f = 0.16 (5% MeOH in DCM).

*Methyl 3-(2-oxo-1,2,3,4-Tetrahydroquinazolin-4-yl)-1H-indole-4-carboxylate (**4n**).* Prepared following the general procedure (**A**), starting from aldehyde **1a** (40 mg, 224 μmol), amine **2a** (34 mg, 441 μmol), and nucleophile **3g** (51 mg, 291 μmol). Yield: 60 mg (83%); white solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.46 (s, 1H), 9.28 (s, 1H), 7.75−7.66 (m, 2H), 7.27−7.20 (m, 1H), 7.19−7.14 (m, 1H), 7.03−6.97 (m, 1H), 6.93−6.88 (m, 1H), 6.87−6.83 (m, 1H), 6.84−6.73 (m, 2H), 6.27 (d, J = 2.5 Hz, 1H), 3.93 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 168.7, 154.1, 137.8, 137.6, 127.6, 126.9, 126.4, 123.1, 122.8, 122.6, 122.3, 121.1, 120.3, 118.8, 117.0, 113.8, 52.2, 49.8. HRMS (ESI): calcd for $C_{18}H_{16}N_3O_3$ [M + H]$^+$ 322.1192; found 322.1202. TLC (SiO_2): R_f = 0.17 (5% MeOH in DCM).

4-(1-Methyl-1*H*-indol-3-yl)-3,4-dihydroquinazolin-2(1*H*)-one (4o).[24] Prepared following the general procedure (**A**), starting from aldehyde **1a** (40 mg, 224 μmol), amine **2a** (34 mg, 441 μmol), and nucleophile **3h** (38 mg, 290 μmol). Yield: 52 mg (84%); white solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.27 (d, J = 1.9 Hz, 1H), 7.56 (m, 1H), 7.40 (m, 1H), 7.21 (t, J = 2.2 Hz, 1H), 7.15 (s, 1H), 7.17−7.07 (m, 1H), 7.13−7.06 (m, 1H), 6.99 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 7.00−6.93 (m, 1H), 6.86 (dd, J = 8.0, 1.2 Hz, 1H), 6.78 (m, 1H), 5.82 (d, J = 2.2 Hz, 1H), 3.74 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 153.7, 137.1, 127.6, 127.2, 126.5, 125.3, 121.7, 121.3, 120.8, 119.4, 118.8, 117.6, 113.7, 109.8, 50.2, 32.3. HRMS (ESI): calcd for $C_{19}H_{19}N_4O$ [M + MeCN + H]$^+$ 319.1559; found m/z 319.1567. TLC (SiO_2): R_f = 0.08 (60% EtOAc in n-pentane).

*4-(1H-Pyrrolo[2,3-b]pyridin-3-yl)-3,4-dihydroquinazolin-2(1H)-one (**4p**).* Prepared following the general procedure (**A**), starting from aldehyde **1a** (40 mg, 224 μmol), amine **2a** (34 mg, 441 μmol), and nucleophile **3i** (34 mg, 288 μmol). Yield: 53 mg (90%); white solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.53 (s, 1H), 9.31 (s, 1H), 8.19 (d, J = 4.6 Hz, 1H), 7.85 (d, J = 7.9 Hz, 1H), 7.33−7.26 (m, 2H), 7.17−7.08 (m, 1H), 7.05−6.95 (m, 2H), 6.91−6.84 (m, 1H), 6.83−6.78 (m, 1H), 6.07−5.61 (m, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 153.7, 148.9, 142.7, 137.1, 127.7, 127.3, 126.6, 123.3, 121.3, 121.0, 117.2, 117.2, 115.2, 113.7, 50.5. HRMS (ESI): calcd for $C_{15}H_{13}N_4O$ [M + H]$^+$ 265.1089; found 265.1076. TLC (SiO_2): R_f = 0.09 (5% MeOH in DCM).

*3-Benzyl-4-(1H-indol-3-yl)-3,4-dihydroquinazolin-2(1H)-one (**6a**).*[24] Prepared following the general procedure (**A**), starting from aldehyde **1a** (40 mg, 224 μmol), amine **2b** (36 mg, 336 μmol), and nucleophile **3a** (34 mg, 290 μmol). Yield: 75 mg (95%); yellow solid. ^{1}H NMR ($CDCl_3$/CD_3OD, 400 MHz): δ 11.14 (d, J = 2.5 Hz, 1H), 9.70 (s, 1H), 7.53−7.48 (m, 1H), 7.47−7.45 (m, 1H), 7.44−7.35 (m, 3H), 7.34−7.27 (m, 3H), 7.15−7.07 (m, 2H), 7.04−6.94 (m, 2H), 6.92 (dd, J = 8.0, 1.1 Hz, 1H), 6.78 (m, 1H), 5.75 (s, 1H), 5.17 (d, J = 15.5 Hz, 1H), 3.77 (d, J = 15.4 Hz, 1H). ^{13}C NMR ($CDCl_3$/CD_3OD, 100 MHz): δ 155.8, 138.5, 138.3, 136.6, 129.5, 128.9, 128.7, 128.3, 128.1, 126.1, 124.7, 123.0, 122.8, 122.5, 120.3, 119.9, 117.0, 114.7, 112.6, 56.5, 47.8. HRMS (ESI): calcd for $C_{23}H_{20}N_3O$ [M + H]$^+$ 354.1606; found 354.1613. TLC (SiO_2): R_f = 0.20 (40% EtOAc in n-pentane).

*4-(1H-Indol-3-yl)-3-(thiophen-2-ylmethyl)-3,4-dihydroquinazolin-2(1H)-one (**6b**).* Prepared following the general procedure (**A**), starting from aldehyde **1a** (40 mg, 224 μmol), amine **2c** (33 mg, 292 μmol), and nucleophile **3a** (34 mg, 290 μmol). Yield: 76 mg (94%); white solid. ^{1}H NMR ($CDCl_3$/CD_3OD, 400 MHz): δ 7.44 (m, 1H), 7.38 (m, 1H), 7.35 (s, 1H), 7.31 (dd, J = 4.8, 1.6 Hz, 1H), 7.14−7.07 (m, 2H), 6.99−6.95 (m, 2H), 6.95−6.91 (m, 1H), 6.91−6.86 (m, 2H), 6.79 (m, 1H), 5.86 (s, 1H), 5.29 (dd, J = 15.5, 0.9 Hz, 1H), 4.07 (d, J = 15.5 Hz, 1H). ^{13}C NMR ($CDCl_3$/CD_3OD, 100 MHz): δ 156.1, 141.8, 139.4, 137.3, 129.8, 129.1, 128.7, 128.4, 127.2, 127.1, 126.0, 123.9, 123.8, 123.3, 121.3, 120.9, 117.5, 115.6, 113.6, 57.1, 43.7. HRMS (ESI): calcd for $C_{21}H_{18}N_3OS$ [M + H]$^+$ 360.1171; found 360.1168. TLC (SiO_2): R_f = 0.16 (5% MeOH in DCM).

*3-Benzyl-4-(2,4-dimethoxyphenyl)-3,4-dihydroquinazolin-2(1H)-one (**6c**).* Prepared following the general procedure (**A**) but with 30 min of heating in the second step, starting from aldehyde **1a** (40 mg, 224 μmol), amine **2b** (36 mg, 336 μmol), and nucleophile **5a** (40 mg, 289 μmol). Yield: 72 mg (86%); yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.96 (s, 1H), 7.51 (m, 5H), 7.45−7.40 (m, 1H), 7.30 (m, 1H), 7.22−7.15 (m, 1H), 7.08−6.93 (m, 2H), 6.77−6.57 (m, 2H), 6.05 (s, 1H), 5.62 (d, J = 15.1 Hz, 1H), 4.01 (s, 6H), 3.93 (d, J = 15.1 Hz, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 160.1, 157.0, 153.4, 137.8, 136.4, 128.4, 127.9, 127.7, 127.4, 127.1, 125.9, 122.9, 121.6, 121.1, 113.6, 105.7, 98.6, 55.6, 55.2, 54.6, 46.8. HRMS (ESI): calcd for $C_{23}H_{23}N_2O_3$ [M + H]$^+$ 375.1709; found 375.1711. TLC (SiO_2): R_f = 0.26 (40% EtOAc in n-pentane).

*4-(2,4-Dimethoxyphenyl)-3,4-dihydroquinazolin-2(1H)-one (**6d**).* Prepared following the general procedure (**A**) but with 30 min of heating in the second step, starting from aldehyde **1a** (40 mg, 224 μmol), amine **2a** (34 mg, 441 μmol), and nucleophile **5a** (40 mg, 289 μmol). Yield: 35 mg (55%); white solid. ^{1}H NMR (DMSO-d_6, 400 MHz,): δ 9.21 (s, 1H), 7.17−7.07 (m, 1H), 7.05−6.95 (m, 3H), 6.86−6.79 (m, 2H), 6.64−6.59 (m, 1H), 6.54−6.48 (m, 1H), 5.80 (d, J = 2.4 Hz, 1H), 3.86 (s, 3H), 3.76 (s, 3H). ^{13}C NMR (DMSO-d_6, 400 MHz,): δ 159.4, 156.2, 153.6, 136.7, 127.3, 127.2, 125.8, 124.9,

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121.2, 120.6, 113.3, 104.6, 98.1, 55.2, 54.8, 50.2. HRMS (ESI): calcd for $C_{18}H_{20}N_3O_3$ [M + MeCN + H]$^+$ 326.1505; found 326.1508. TLC (SiO_2): R_f = 0.21 (5% MeOH in DCM).

*4-(2,4-Dimethoxyphenyl)-3-(1-methylpiperidin-4-yl)-3,4-dihydroquinazolin-2(1H)-one (**6e**).* Prepared following the general procedure (**A**) but with 30 min of heating the second step, starting from aldehyde **1a** (40 mg, 224 μmol), amine **2d** (33 mg, 289 μmol), and nucleophile **5a** (68 mg, 492 μmol). Yield: 43 mg (50%); white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47 (s, 1H), 7.24−7.20 (m, 2H), 7.08−6.96 (m, 1H), 6.86−6.76 (m, 1H), 6.65−6.58 (m, 1H), 6.40−6.31 (m, 1H), 6.29 (dd, *J* = 8.5, 2.4 Hz, 1H), 5.95 (s, 1H), 4.41−4.14 (m, 1H), 3.84 (s, 3H), 3.67 (s, 3H), 2.95 (d, *J* = 10.7 Hz, 1H), 2.79 (d, *J* = 11.7 Hz, 1H), 2.24 (s, 3H), 2.21−1.97 (m, 4H), 1.59 (d, *J* = 12.1 Hz, 1H), 1.45 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.0, 155.3, 154.9, 135.0, 127.5, 127.0, 125.3, 125.0, 123.2, 121.8, 113.3, 104.4, 98.2, 55.2, 55.0, 54.9, 54.8, 52.2, 51.4, 45.2, 29.4, 28.7, 21.8. HRMS (ESI): calcd for $C_{22}H_{28}N_3O_3$ [M + H]$^+$ 382.2131; found 382.2132. TLC (SiO_2): R_f = 0.23 (10% MeOH in DCM).

*4-(4-Hydroxy-2-methylphenyl)-3,4-dihydroquinazolin-2(1H)-one (**6f**).* Prepared following the general procedure (**A**) but with 30 min in heating the second step, starting from aldehyde **1a** (40 mg, 224 μmol), amine **2a** (33 mg, μmol), and nucleophile **5b** (31 mg, 289 μmol). Yield: 30 mg (52%); white solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.62 (s, 1H), 9.15 (s, 1H), 7.07 (t, *J* = 7.9 Hz, 2H), 6.95 (s, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 6.81−6.74 (m, 2H), 6.63 (s, 1H), 6.55 (d, *J* = 7.8 Hz, 1H), 5.79 (d, *J* = 2.3 Hz, 1H), 2.17 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 154.0, 153.4, 137.5, 137.0, 128.5, 127.5, 126.9, 126.3, 121.9, 120.9, 119.9, 115.9, 113.6, 50.7, 20.7. HRMS (ESI): calcd for $C_{15}H_{15}N_2O_2$ [M + H]$^+$ 255.1143; found 255.1134. TLC (SiO_2): R_f = 0.22 (5% MeOH in DCM).

*4-(1H-Indol-3-yl)-3-(3-methoxyphenethyl)-3,4-dihydroquinazolin-2(1H)-one (**7a**).* Prepared following the general procedure (**B**), starting from aldehyde **1a** (40 mg, 224 μmol), amine **2e** (43 mg, 290 μmol), and nucleophile **3a** (39 mg, 334 μmol). Yield: 82 mg (92%); off-white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.33−8.20 (m, 1H), 7.99 (s, 1H), 7.56 (m, 1H), 7.34 (m, 1H), 7.20−7.13 (m, 3H), 7.13−7.04 (m, 2H), 6.91−6.86 (m, 1H), 6.79 (ddd, *J* = 14.3, 7.7, 1.1 Hz, 2H), 6.74 (dd, *J* = 7.9, 2.1 Hz, 2H), 6.67−6.63 (m, 1H), 5.59 (s, 1H), 4.01 (ddd, *J* = 14.0, 9.0, 5.0 Hz, 1H), 3.66 (s, 3H), 3.22 (ddd, *J* = 13.8, 8.7, 7.1 Hz, 1H), 2.95 (ddd, *J* = 13.2, 9.0, 7.1 Hz, 1H), 2.71 (ddd, *J* = 13.4, 8.6, 5.0 Hz, 1H). δ ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.7, 154.1, 141.3, 136.7, 135.7, 129.6, 128.2, 126.8, 125.4, 122.8, 122.6, 122.1, 121.6, 121.3, 120.3, 119.4, 117.5, 114.3, 113.8, 112.2, 111.6, 56.9, 55.2, 47.3, 34.6. HRMS (ESI): calcd for [M + H]$^+$ 398.1869; found 398.1873. TLC (SiO_2): R_f = 0.13 (50% EtOAc in *n*-pentane).

*3-(3,4-Dimethoxyphenethyl)-4-(1H-indol-3-yl)-3,4-dihydroquinazolin-2(1H)-one (**7b**).* Prepared following the general procedure (**B**), starting from aldehyde **1a** (40 mg, 224 μmol), amine **2f** (53 mg, 290 μmol), and nucleophile **3a** (39 mg, 334 μmol). Yield: 85 mg (90%); white solid. ^{1}H NMR ($CDCl_3$/CD_3OD, 400 MHz): δ 7.33−7.24 (m, 2H), 7.21−7.13 (m, 1H), 7.03−6.95 (m, 1H), 6.96−6.87 (m, 2H), 6.85−6.76 (m, 1H), 6.71−6.53 (m, 4H), 6.50−6.36 (m, 2H), 5.40 (s, 1H), 3.70−3.56 (m, 4H), 3.47 (s, 3H), 3.07−2.87 (m, 1H), 2.73−2.61 (m, 1H), 2.52−2.37 (m, 1H). ^{13}C NMR ($CDCl_3$/CD_3OD, 100 MHz): δ 154.6, 148.9, 147.6, 137.1, 135.4, 132.4, 128.2, 127.0, 125.4, 123.6, 122.5, 122.2, 121.8, 121.0, 119.8, 119.0, 116.5, 113.9, 112.3, 111.9, 111.7, 57.2, 56.0, 55.7, 47.6, 33.9. HRMS (ESI): calcd for $C_{26}H_{26}N_3O_3$ [M + H]$^+$ 428.1974; found 428.1977. TLC (SiO_2): R_f = 0.10 (50% EtOAc in *n*-pentane).

*4-(1H-Indol-3-yl)-3-(2-(thiophen-2-yl)ethyl)-3,4-dihydroquinazolin-2(1H)-one (**7c**).* Prepared following the general procedure (**B**), starting from aldehyde **1a** (40 mg, 224 μmol), amine **2g** (37 mg, 290 μmol), and nucleophile **3a** (39 mg, 334 μmol). Yield: 80 mg (96%); light yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.32−8.24 (m, 1H), 8.15 (s, 1H), 7.58 (m, 1H), 7.35 (m, 1H), 7.21−7.13 (m, 2H), 7.14−7.03 (m, 3H), 6.94−6.85 (m, 2H), 6.83−6.70 (m, 3H), 5.67 (s, 1H), 4.01 (ddd, *J* = 13.3, 8.4, 5.2 Hz, 1H), 3.34−3.15 (m, 2H), 3.00−2.84 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.1, 141.8, 136.7, 135.6, 128.2, 127.1, 126.8, 125.4, 125.3, 123.8, 122.9, 122.7, 122.2, 121.5, 120.4, 119.4, 117.5, 113.9, 111.6, 57.2, 47.5, 28.5. HRMS (ESI): calcd for $C_{22}H_{29}N_3OS$ [M + H]$^+$ 374.1327; found 374.1324. TLC (SiO_2): R_f = 0.15 (50% EtOAc in pentane).

*3-(But-3-en-1-yl)-4-(1H-indol-3-yl)-3,4-dihydroquinazolin-2(1H)-one (**7d**).* Prepared following the general procedure (**B**), starting from aldehyde **1a** (40 mg, 224 μmol), amine **2h** (21 mg, 290 μmol), and nucleophile **3a** (39 mg, 334 μmol). Yield: 68 mg (96%); off-white solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.32 (s, 1H), 8.05 (s, 1H), 7.63 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.35 (m, 1H), 7.22−7.14 (m, 2H), 7.09 (m, 2H), 7.01 (ddd, *J* = 7.7, 1.5, 0.7 Hz, 1H), 6.85−6.72 (m, 2H), 5.88 (s, 1H), 5.78 (m, 1H), 5.15−4.88 (m, 2H), 3.91 (ddd, *J* = 13.9, 8.7, 6.4 Hz, 1H), 3.04 (ddd, *J* = 14.2, 8.6, 5.9 Hz, 1H), 2.47−2.35 (m, 1H), 2.33−2.20 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.2, 136.7, 135.7, 135.6, 128.2, 126.8, 125.4, 122.7, 122.6, 122.1, 121.5, 120.3, 119.4, 117.6, 116.7, 113.9, 111.6, 56.4, 44.7, 32.2. HRMS (ESI): calcd for [M + H]$^+$ 318.1606; found 318.1606. TLC (SiO_2): R_f = 0.2 (50% EtOAc in *n*-pentane).

*3-((1H-Indol-4-yl)methyl)-4-(1H-indol-3-yl)-3,4-dihydroquinazolin-2(1H)-one (**7e**).* Prepared following the general procedure (**B**), starting from aldehyde **1a** (40 mg, 224 μmol), amine **2i** (42 mg, 290 μmol), and nucleophile **3a** (39 mg, 334 μmol). Yield: 32 mg (36%); off-white solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.13 (d, *J* = 13.2 Hz, 2H), 9.66 (s, 1H), 8.28 (s, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.42−7.23 (m, 4H), 7.05 (m, 3H), 6.90 (m, 4H), 6.68 (m, 1H), 6.45 (s, 1H), 5.60 (s, 1H), 5.50 (d, *J* = 15.0 Hz, 1H), 3.83 (d, *J* = 15.0 Hz, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 152.9, 137.1, 136.3, 136.2, 128.4, 127.8, 127.1, 126.7, 125.3, 124.7, 124.0, 121.6, 121.3, 121.2, 121.0, 119.2, 119.0, 118.5, 116.3, 113.6, 112.1, 111.0, 99.8, 54.6, 44.7. HRMS (ESI): calcd for [M + H]$^+$ 393.1715; found 393.1729. TLC (SiO_2): R_f = 0.1 (50% EtOAc in *n*-pentane).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b02298.

Copies of ^{1}H and ^{13}C NMR spectra for all compounds (PDF)

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Notes

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