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# Transition-metal-free *N*-arylation: A general approach to aza-fused poly-heteroaromatics

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**Abstract**

A new and efficient method for the synthesis of various aza-fused poly-hetero aromatics has been described. This protocol includes an intermolecular condensation followed by metal-free base-promoted intramolecular C—N coupling reaction. The advantage of this one-pot transformation lies in the use of simple cyclic amidines-like compounds without prefunctionalization of the starting heterocycles.

## 1 | INTRODUCTION

Aza-fused poly heterocyclic frameworks are found in a large number of naturally occurring compounds that exhibit diverse biological properties.[1] In addition, the aza-fused polycyclic moieties are also found in pharmacological important compounds such as antidiabetic drug Sitagliptin, marketed Kinase-inhibitor Ponatinib, and insomnia management drug Zolpidem.[2] Among those, the aza-fused quinoxalines and quinazolines serve as an active pharmacophore for various therapeutic indications.[3] For instance, indolo[1,2,a]quinoxaline exhibits promising antifungal activities in vitro against the phytopathogenic fungi,[4] whereas pyrrolo[1,2,a]quinoxaline has been reported as second generation non-nucleoside reverse transcriptase inhibitor (NNRTI),[5] and Pyrazolo[1,5-a]quinazolines-based derivatives developed as noncamptothecin topoisomerase I inhibitors.[6] However, aza-fused quinoxaline and quinoazolines (Figure 1), eg, indolo[1,2,a]quinoxaline,[7] pyrrolo[1,2,a] quinoxaline,[8] pyrazolo [1,5-a]quinazolines,[9] triazolo [1,5-a] quinazolines,[10] indazolo [2,3-a]quinazolines,[11] and benzo[4,5]imidazo[1,2-a]quinazoline,[12] have not been regularly pursued as common core for medicinal chemistry activities, because of the lack of general and efficient methods for the synthesis of these compounds. Therefore, finding an efficient and general methodology in synthesizing these aza-fused heterocycles are highly desirable.

The commonly used protocols for the synthesis of these *N*-heterocyclic compounds involve an intramolecular-cyclization step *via* metal-catalyzed C—N bond formation.[13] In particular the *N*-arylation reactions are generally catalyzed mainly by Pd or Cu complexes with the help of expensive ligands often at elevated temperatures.[14,15] Additionally, if applied in the synthesis of active pharmaceuticals ingredients (API), the use of such transition-metal catalysts is controversial, since they may remain in the products as trace impurities, which have to be removed in tedious additional steps.

Hence, reaction protocols that enable the preparation of compounds through intramolecular C—N coupling

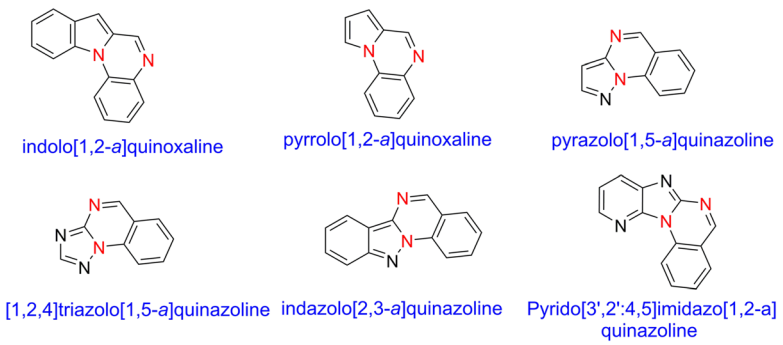


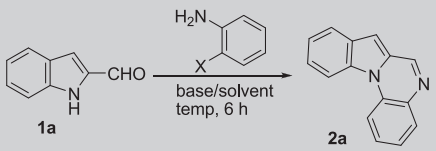

**FIGURE 1** AZU-fused polycyclic-heteroaromatics [Color figure can be viewed at wileyonlinelibrary.com]

reactions in the absence of transition metals are attractive and considered sustainable. In this context, various metal-free *N*-arylation reactions, including intramolecular ring-closing reactions to give heterocyclic products, have been studied with great interest in recently.[16] Diness and Fairlie et al reported catalyst-free *N*-arylation reaction in which fluorine is displaced from unactivated fluorobenzene by azoles or indoles under optimized reaction conditions.[17] More recently, Cao et al developed a mild and straightforward catalyst-free method for *N*-vinylation of azoles with (2,2-difluorovinyl)arenes in the presence of base.[18] In order to synthesize the aza-fused *N*-heterocyclic system (Scheme 1), herein, we wish to report a new cascade reaction which involves the sequential intermolecular condensation followed by aromatic nucleophilic substitution ($S_NAr$).

## 2 | RESULTS AND DISCUSSION

In order to find an optimized protocol, first we examined the reaction of 1*H*-indole-2-carbaldehyde (**1a**) and 2-fluoroaniline by using the medium $K_2CO_3$/DMF in 120°C (entry 1, Table 1). However, to our disappointment, only 40% of the cyclized product was formed. When the base was changed to CsF, indolo[1,2-a]quinoxaline was isolated in 50% yield (entry 2, Table 1). Encouraged by these results, different combinations of base/solvent were screened (entries 3-9, Table 1), and it was observed that

**TABLE 1** Synthesis of indolo[1,2-a]quinoxaline and derivatives[a]

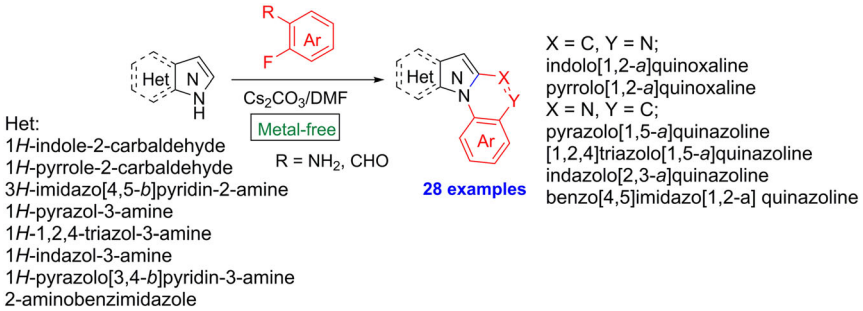



| Entry | X | Base | Temp, °C | Solvent | Yield, %[b] |
|---|---|---|---|---|---|
| 1 | F | $K_2CO_3$ | 120 | DMF | 40 |
| 2 | F | CsF | 120 | DMF | 50 |
| **3** | **F** | **$Cs_2CO_3$** | **120** | **DMF** | **88** |
| 4 | F | $Cs_2CO_3$ | 120 | Xylene | 15 |
| 5 | F | $Cs_2CO_3$ | 120 | DMSO | 45 |
| 6 | F | $K_3PO_4$ | 120 | DMF | 70 |
| 7 | F | NaO*t*-Bu | 120 | DMF | trace |
| 8 | F | $Na_2CO_3$ | 120 | DMF | 45 |
| 9 | F | $Cs_2CO_3$ | 120 | DMA | 75 |
| 10 | F | - | 120 | DMF | n.r. |
| 11 | Cl | $Cs_2CO_3$ | 120 | DMF | 20 |
| 12 | Br | $Cs_2CO_3$ | 120 | DMF | n.r. |
| 13 | I | $Cs_2CO_3$ | 120 | DMF | n.r. |
| 14[c] | F | $Cs_2CO_3$ | 120 | DMF | 70 |
| 15 | F | $Cs_2CO_3$ | 80 | DMF | n.r. |

[a]Reaction conditions: 2-fluoro aniline (0.450 mmol.), indole-2-carbaldehyde (0.450 mmol.), cesium carbonate (1.350 mmol), DMF (2 mL); 120°C, 6 h.

[b]isolated yield.

[c]cesium carbonate (0.900 mmol) was used. n. r. = no reaction.




**SCHEME 1** Synthesis of Aza-fused polycyclic heteroaromatics [Color figure can be viewed at wileyonlinelibrary.com]

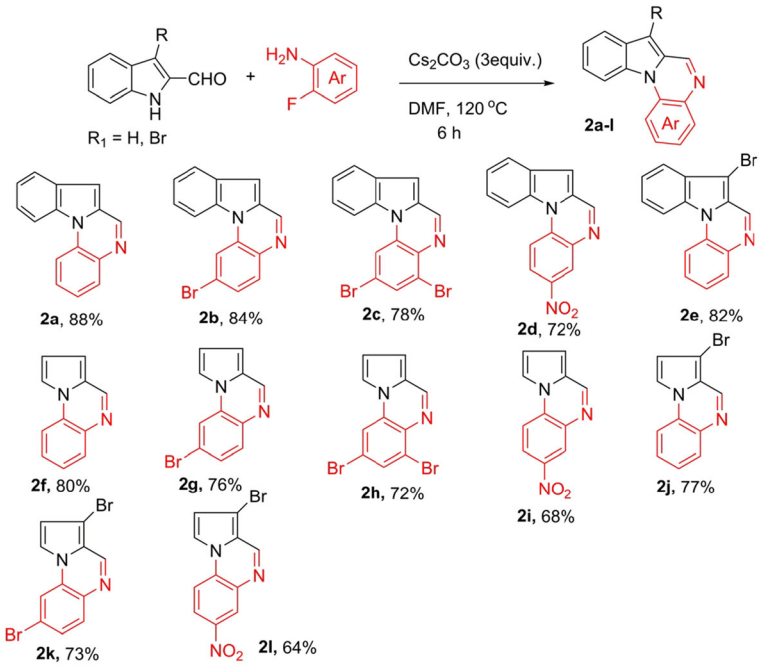
$Cs_2CO_3$ in DMF at 120°C gave the best results (88%) (entry 3, Table 1). When we changed the coupling partner from 2-fluoroaniline to 2-chloro aniline, only 20% product was isolated (entry 11, Table 1), while 2-bromo aniline and 2-iodo aniline (entry 12 and 13, Table 1) failed to produce any desired product under the optimized conditions. Using less equivalent of base (2 equiv.) has negative impact on the isolated yield (entry 14, Table 1). Also, the lowering of temperature from 120°C to 80°C reduced the yield of **2a** (entry 15, Table 1). Control experiments confirmed that in the absence of $Cs_2CO_3$, no product was formed (entry 10, Table 1).

With the optimized conditions in hand, next, we explored the scope with respect to 1*H*-indole-2-carbaldehyde and 1*H*-pyrrole-2-carbaldehyde (Table 2). This survey revealed that a range of 2-fluoroanilines bearing halo group like -Br or strong electron-withdrawing group like $-NO_2$ are good substrates for the cascade reaction under the optimized conditions to give indolo[1,2,a]quinoxalines (**2b-d**) in good yields (72%-84%). These functional groups can further be manipulated to achieve molecular complexity in designed biologically active compounds. The reaction was next briefly explored with respect to substitution of the formyl indole component. Bromo substitution at 3-positions of the indole ring was well tolerated which under the optimized conditions gave 7-bromoindolo [1,2-a]quinoxaline (**2e**) in good yield (82%).

After that, we performed the reaction on five-membered heterocyclic 1*H*-pyrrole-2-carbaldehyde with different 2-fluoroanilines, and reaction was smooth, and desired product pyrrolo[1,2-a]quinoxalines (**2f-l**) were isolated in good yields. Notably, the C—Br bonds of the substrates remained intact during all reactions, thus providing an additional handle for further functionalization of these products (**2g-h**, **2j-l**).

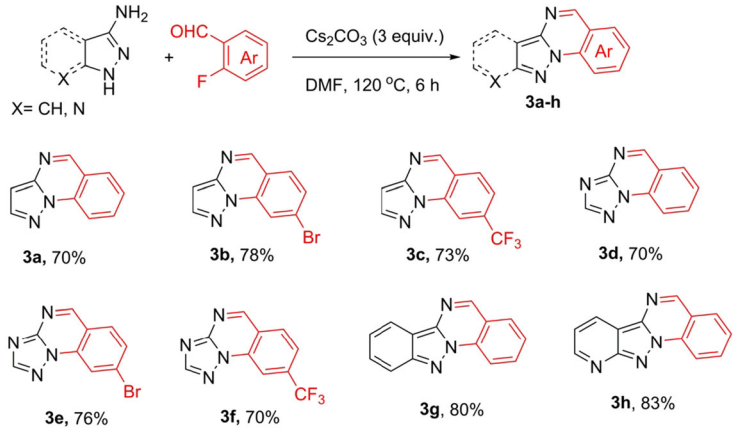
Inspired by the promising results above, we then focused on the synthesis of different classes of aza-fused quinazolines (Table 3). Under the optimized condition, we first investigated the reaction of five-membered heterocyclic 1*H*-pyrazol-3-amine with different 2-fluoro benzaldehyde. and the reaction was smooth, and the desired product pyrazolo[1,5-*a*]quinazolines (**3a-c**) were isolated in good yields (70%-78%). Further, to enhance the substrate scope, we performed the reaction with another five-membered heterocyclic compound 1*H*-1,2,4-triazol-3-amine with substituted 2-fluorobenzaldehydes and the aza-fused heterocyclic products [1,2,4]triazolo[1,5-a] quinazoline (**3d-f**) were isolated in good yields (70%-76%). The further extension of this reaction was then explored with 1*H*-indazol-3-amine and its 7-aza derivative. Both 1*H*-indazol-3-amine and 1*H*-pyrazolo[3,4-b] pyridin-3-amine underwent the reaction to give novel aza-fused polycyclic indazolo[2,3-a]quinazoline (**3g**) and 10-aza indazolo[2,3-a]quinazoline (**3h**) in very good yield (80%-83%).

**TABLE 2** Synthesis of Indolo[1,2-a]quinoxaline and derivatives[a]




[a]Reaction conditions: 2-fluoro aniline (0.450 mmol.), indole 2-carbaldehyde (0.450 mmol.), $CS_2CO_3$ (1.35 mmol.), DMF (2 mL), 120°C, 6 h.

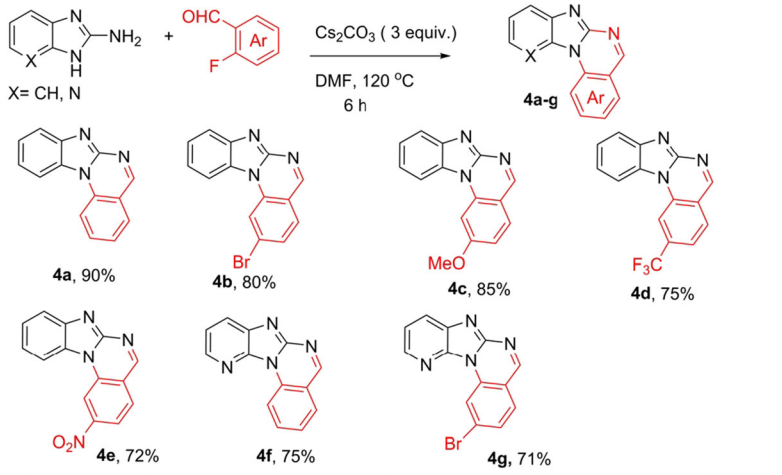
**TABLE 3** Synthesis of Aza-fused quinazoline derivatives[a]




[a] Reaction conditions: 1H-Pyrazol-3-amine(0.602 mmol), 2-fluoro benzalddehyde (0.602 mmol), $Cs_2CO_3$ (1.807 mmol), DMF( 2 mL), 120 °C, 6h.

[a]Reaction conditions: 1H-pyrazolo-3-amine (0.602 mmol.), 2-fluoro benzaldehyde (0.602 mmol.), $CS_2CO_3$ (1.807 mmol.), DMF (2 mL), 120°C, 6 h.

**TABLE 4** Synthesis of benzo[4,5]imidazo[1,2-a]quinozoline and derivatives[a]



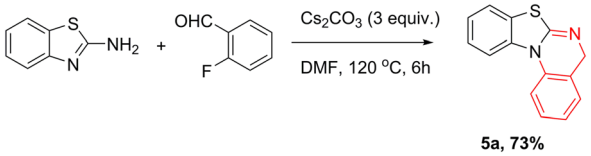

[a] Reaction conditions: 2-Amino benzimidazole (0.376 mmol), 2-fluoro benzaldehyde (0.375 mmol), $Cs_2CO_3$ (1.127 mmol), DMF( 2 mL), 120 °C, 6h.

[a]Reaction conditions: 2-amino benzimidazole (0.376 mmol.), 2-fluoro benzaldehyde (0.375 mmol.), $CS_2CO_3$ (1.127 mmol.), DMF (2 mL), 120°C, 6 h.

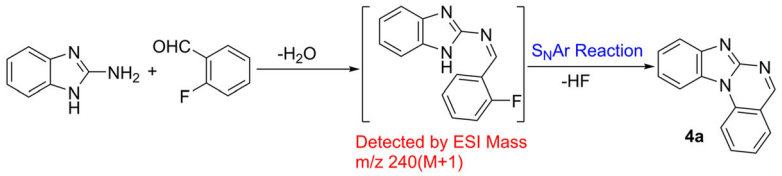
To further extend the scope, the optimized protocol was employed to obtain various benzo[4,5]imidazo[1,2-a]quinazolines from a broad range of substituted 2-fluorobenzaldehydes and 2-aminobenzimidazole.

Substituted benzo[4,5]imidazo[1,2-a]quinazolines are most commonly synthesized by inconvenient multistep methods[19]; thus the reported protocols do not meet the demand in structure activity relationship (SAR) study. Recently, Ma et al reported the base promoted synthesis of benzimidazo[1,2-a]quinolines.[20] However, the reported method did not apply with 7-aza derivative of 2-aminobenzimidazole. Thus, to enhance the scope of this method, we examined the cascade reaction by using 2-aminobenzimidazole/3H-imidazo[4,5-b]pyridin-2-amine with different substituents of 2-fluorobenzaldehydes. A variety of both electron-withdrawing and electron-donating substituents were well tolerated, and the results are summarized in Table 4.

The use of simple 2-fluoro benzaldehyde in this cascade reaction resulted the desired product (Table 4, 4**a**) in 90% yield. When we performed the reaction with




**SCHEME 2** Synthesis of 5H-benzo[4,5]thiazolo[3,2-a] quinazoline [Color figure can be viewed at wileyonlinelibrary.com]




**SCHEME 3** Proposed Mechanism [Color figure can be viewed at wileyonlinelibrary.com]

electron donating groups like -OMe substituted 2-flourobenzaldehyde, yield of desired product (**4c**) was isolated in excellent yield (85%). As expected in case of strong electron withdrawing groups like —$CF_3$ and —$NO_2$, the isolated yields were slightly reduced (**4d and 4e,** 75%, 72%). The 3*H*-imidazo [4,5-*b*]pyridin-2-amine was also condensed with 2-fluoro benzaldehyde and 4-bromo 2-fluoro benzaldehyde which lead to the novel aza-fused compounds (**4f-4g**) in good yields (75%-71%).

Finally, we performed the reaction with 2-aminobenzothiazole and 2-fluoro benzaldehyde; the aza-fused novel heterocyclic compound 5*H*-benzo[4,5] thiazolo[3,2-a]quinazoline[21] (**5a**) was obtained in good yield 73% under the optimized conditions (Scheme 2).

Based on these experimental findings, we put forward a tentative mechanistic proposal as depicted in Scheme 3. Here, the first step involves the formation of imine followed by $S_NAr$ reaction which leads to the desired product.

## 3 | CONCLUSIONS

In summary, we have developed an efficient and environmentally benign method for the synthesis of unique aza-fused polycyclic quinoxaline and quinazolines from readily available starting materials under metal-free conditions. The method is amenable to structural variation of both reaction partners and consequently serves as a useful alternative to existing routes to indolo[1,2-a] quinoxalines, pyrrolo[1,2-a]quinoxalines, pyrazolo[1,5-a] quinazolines, triazolo[1,5-a] quinazolines, indazolo[2,3-a] quinazolines, benzimidazo[1,2-a] quinazolines, and 5H-benzo[4,5]thiazolo[3,2-a]quinazoline. Due to its manipulation ease, low-cost, and benign character, the new synthetic protocol described appears promising for large-scale applications. Further exploration of this reaction in preparing biologically relevant compounds is currently underway.

## 4 | EXPERIMENTAL SECTION

### 4.1 | General information

All purchased chemicals were used without further purification. All reactions were performed under air atmosphere. Analytical thin layer chromatography was performed using TLC precoated silica gel 60F254 MERCK (20 × 20 cm). TLC plates were visualized by exposing UV light or by iodine vapors or immersion in ninhydrin followed by heating on a hot plate. Organic solutions were concentrated by rotary evaporation on BUCHI-Switzerland, R-120 rotary evaporator and vacuum pump V-710. Flash column chromatography was performed on Merck flash silica gel 230 to 400 mesh size. Melting points of solid compounds were determined on BUCHI-B-545-Switzerland melting point apparatus. $^1$H and $^{13}$C NMR spectra were recorded with BRUCKER 500 and 400-MHz NMR instruments. Proton and carbon magnetic resonance spectra ($^1$H NMR and $^{13}$C NMR) were recorded using tetramethylsilane (TMS) in the solvent of $CDCl_3$ as the internal standard ($^1$H NMR: TMS at 0.00 ppm, $CHCl_3$ at 7.24 ppm; $^{13}$C NMR: $CDCl_3$ at 77.0 ppm) or were recorded using TMS in the solvent of DMSO-$d_6$ as the internal standard ($^1$H NMR: TMS at 0.00 ppm, DMSO at 2.50 ppm;$^{13}$C NMR: DMSO at 40.0 ppm) or were recorded using TMS in the solvent of Acetone-$d_6$ as the internal standard ($^1$H NMR: TMS at 0.00 ppm, Acetone at 2.09 ppm;$^{13}$C NMR: Acetone at 29.9 ppm, 206.7 ppm). Mass spectra were recorded with VARIAN GC-MS-MS instrument. HRMS spectra were recorded with LCMS-QTOF Module No. G6540 A (UHD) instrument.

#### 4.1.1 | Supporting information

Copies of $^1$H and $^{13}$C NMR spectra of all the compounds.

#### 4.1.2 | Synthesis of Indolo[1,2-a] quinoxaline and derivatives

An oven-dried round bottom flask was charged with a stirring bar, 2-fluoro aniline (0.450 mmol.), indole-2-carbaldehyde (0.450 mmol.), cesium carbonate (1.351 mmol), and dry DMF, and then reaction mixture was stirred at 120°C under nitrogen atmosphere. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured into the ice cold water and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine solution (20 mL × 2) dried over $Na_2SO_4$ and concentrated under reduced pressure. The crude product was purified by

column chromatography (acetone: hexane) to yield the desired product.

### 4.1.3 | Indolo[1,2-a]quinoxaline(2a)

[8a] Orange solid; m.p.: 110°C to 112°C; $^1$H NMR (500 MHz, acetone-$d_6$) δ 9.06 (s, 1H), 8.69 (dd, $J$ = 15.6, 8.3 Hz, 2H), 8.05 (d, $J$ = 7.8 Hz, 1H), 7.98 (d, $J$ = 8.1 Hz, 1H), 7.73 (t, $J$ = 7.0 Hz, 1H), 7.61 (t, $J$ = 7.2 Hz, 1H), 7.50 (dd, $J$ = 15.0, 7.3 Hz, 2H), 7.35 (s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 147.9, 135.9, 132.6, 130.4, 129.8, 129.1, 128.7, 124.4, 124.1, 122.9, 122.7, 114.9, 114.6, 100.9; HRMS (ESI): m/z Calcd. for $C_{15}H_{11}N_2$ $[M + H]^+$ : 219.0917; found: 219.0916.

### 4.1.4 | 2-Bromoindolo[1,2-a]quinoxaline (2b)

Yellow solid; m.p.: 155 to 157°C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.52 (d, $J$ = 1.8 Hz, 1H), 8.30 (d, $J$ = 8.7 Hz, 1H), 7.92 (d, $J$ = 8.0 Hz, 1H), 7.77 (d, $J$ = 8.5 Hz, 1H), 7.54 (t, $J$ = 7.4 Hz, 1H), 7.47 (dd, $J$ = 8.5, 1.8 Hz, 1H), 7.42 (t, $J$ = 7.5 Hz, 1H), 7.11 (s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 148.2, 134.9, 132.6, 131.7, 131.5, 129.5, 129.2, 127.3, 124.9, 123.2, 123.1, 122.1, 117.9, 114.1, 101.6. HRMS (ESI): m/z Calcd. for $C_{15}H_{10}BrN_2$ $[M + H]^+$ : 298.0022; found: 298.0031.

### 4.1.5 | 2,4-Dibromoindolo[1,2-a] quinoxaline (2c)

Yellow solid; m.p.: 214°C to 215°C; $^1$H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.59 (d, $J$ = 1.8 Hz, 1H), 8.35 (d, $J$ = 8.8 Hz, 1H), 8.01 (d, $J$ = 8.1 Hz, 1H), 7.88 (d, $J$ = 1.8 Hz, 1H), 7.64 (m, 1H), 7.51 (dd, $J$ = 14.4, 6.7 Hz, 1H), 7.23 (s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 150.9, 136.5, 132.5, 131.7, 131.5, 129.5, 129.2, 128.0, 125.5, 123.2, 123.1, 122.1, 119.26, 112.8, 103.7. HRMS (ESI): m/z Calcd. for $C_{15}H_9Br_2N_2$ $[M + H]^+$ : 374.9127; found:374.9132.

### 4.1.6 | 3-Nitroindolo [1,2-a]quinoxaline (2d)

Yellow solid; m.p.: above 230°C; $^1$H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.85 (d, $J$ = 2.3 Hz, 1H), 8.54 (d, $J$ = 9.1 Hz, 1H), 8.49 (dd, $J$ = 9.2, 2.3 Hz, 1H), 8.43 (d, $J$ = 8.6 Hz, 1H), 8.03 (d, $J$ = 8.1 Hz, 1H), 7.67 (t, $J$ = 7.5 Hz, 1H), 7.56 (d, $J$ = 7.6 Hz, 1H), 7.29 (s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 150.0, 143.3, 135.8, 135.5, 132.9, 129.6, 129.4, 128.8, 125.8, 124.0, 123.6, 123.5, 115.0, 114.5, 103.5. HRMS (ESI): m/z Calcd. for $C_{15}H_{10}N_3O_2$ $[M + H]^+$ : 264.0768; found: 264.0797.

### 4.1.7 | 7-Bromoindolo[1,2-a]quinoxaline (2e)

Yellow solid; m.p.: 184°C to 187°C; $^1$H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 8.44 (dd, $J$ = 8.4, 3.1 Hz, 2H), 8.04 (d, $J$ = 7.9 Hz, 1H), 7.96 (d, $J$ = 8.1 Hz, 1H), 7.63(m, 2H), 7.55(m, 1H), 7.47 (t, $J$ = 7.6 Hz, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 145.0, 135.5, 131.2, 130.1, 129.6, 129.0, 127.4, 125.1, 124.2, 123.1, 120.3, 114.5, 114.4. HRMS (ESI): m/z Calcd. for $[M + H]^+$ : $C_{15}H_{10}BrN_2$ $[M + H]^+$ : 298.0022; found: 298.0029.

### 4.1.8 | Pyrrolo[1,2-a]quinoxaline (2f)

[8a] Yellow solid; m.p.: 130°C to 132°C $^1$H NMR (400 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.93 (d, $J$ = 8.0 Hz, 1H), 7.89 (s, 1H), 7.81 (d, $J$ = 8.1 Hz, 1H), 7.48 (t, $J$ = 7.7 Hz, 1H), 7.39 (t, $J$ = 7.6 Hz, 1H), 6.88 (d, $J$ = 3.6 Hz, 1H), 6.84 (s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 145.3, 135.1, 129.7, 129.5, 128.0, 126.3, 125.3, 114.6, 114.3, 113.8, 108.0. HRMS (ESI): m/z Calcd. for $C_{11}H_9N_2$ $[M + H]^+$ : 169.0760; found: 169.0772.

### 4.1.9 | 8-Bromopyrrolo[1,2-a]quinoxaline (2g)

Yellow solid; m.p.: 177°C to 179°C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.95 (s, 1H), 7.81 (s, 1H), 7.75 (d, $J$ = 8.3 Hz, 1H), 7.47 (d, $J$ = 8.1 Hz, 1H), 6.84 (d, $J$ = 5.6 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 145.9, 139.2, 131.4, 129.4, 128.4, 125.2, 121.0, 116.9, 114.6, 114.4, 107.9. HRMS (ESI): m/z Calcd. for $C_{11}H_8N_2Br$ $[M + H]^+$ : 246.9866; found: 246.9876.

### 4.1.10 | 6,8-Dibromopyrrolo[1,2-a] quinoxaline (2h)

Yellow solid; m.p.: 205°C to 207°C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.81 (s, 1H), 7.92 (s, 1H), 7.82 (d, $J$ = 5.7 Hz, 2H), 6.90 (d, $J$ = 9.5 Hz, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 146.4, 139.5, 131.7, 128.5, 127.8, 126.9, 120.6, 116.6, 115.4, 115.2, 108.7. HRMS (ESI): m/z Calcd. for $C_{11}H_7N_2Br_2$ $[M + H]^+$ : 326.8971; found: 326.8962.

### 4.1.11 | 7-Nitropyrrolo[1,2-a]quinoxaline (2i)

Yellow solid; m.p.: 165°C to 167°C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.85 (s, 1H), 8.40 (d, $J$ = 9.1 Hz, 1H), 8.01 (s, 1H), 7.97 (d, $J$ = 9.0 Hz, 1H), 7.02 (d, $J$ = 9.0 Hz, 2H). $^{13}$C NMR (100 MHz, $CDCl_3$) δ 147.6, 143.9, 135.0, 132.1, 125.9, 124.6, 122.1, 117.0, 115.9, 115.3, 109.1. HRMS (ESI): m/z Calcd. for $C_{11}H_8N_3O_2[M + H]^+$ : 214.0611; found: 214.0625.

### 4.1.12 | 3-Bromopyrrolo[1,2-a]quinoxaline (2j)

Yellow solid; m.p.: 154°C to 155°C; $^1$H NMR (400 MHz, $CDCl_3$) δ 9.52 (s, 1H), 9.41 (s, 1H), 8.04 (m, 1H), 7.81(s, 1H), 7.75(d, $J$ = 8.2 Hz, 1H), 7.47(d, $J$ = 8.7 Hz, 1H), 6.85 (s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 148.5, 137.2, 131.4, 129.4, 128.4, 125.2, 121.0, 116.9, 115.3, 113.2, 102.1; HRMS (ESI): m/z Calcd. for $C_{11}H_8N_2Br$ [M + H]$^+$ : 246.9866; found: 246.9872.

### 4.1.13 | 3,8-Dibromopyrrolo[1,2-a] quinoxaline (2k)

Yellow solid; m.p.: 198°C to 199°C; $^1$H NMR (400 MHz, $CDCl_3$) δ 9.45(s, 1H), 9.33(s, 1H), 7.92(s, 1H), 7.81(d, $J$ = 7.9 Hz, 2H), 6.88(s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 148.8, 139.8, 131.4, 129.4, 128.4, 125.2, 116.9, 114.6, 114.4, 112.1, 107.9. HRMS (ESI): m/z Calcd. for $C_{11}H_7N_2Br_2$ [M + H]$^+$ : 326.8971; found: 326.8980.

### 4.1.14 | 3-Bromo-7-nitropyrrolo[1,2-a] quinoxaline (2l)

Yellow solid; m.p.: 159°C to 162°C; $^1$H NMR (500 MHz, $CDCl_3$) δ 9.44 (s, 1H), 9.35 (s, 1H), 7.63 (m, 2H), 7.09 (t, $J$ = 8.6 Hz, 1H), 6.96 (s, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 149.0, 144.0, 139.3, 133.0, 130.4, 129.5, 124.0, 123.5, 122.8, 114.1, 101.8. HRMS (ESI): m/z Calcd. for $C_{11}H_7N_3BrO_2$ [M + H]$^+$ : 291.9716; found: 291.9722.

### 4.1.15 | Pyrazolo[1,5-a]quinazoline (3a)

[9b] White solid; m.p.: $^1$H NMR (500 MHz, $CDCl_3$) δ 8.87 (s, 1H), 8.46 (d, $J$ = 8.4 Hz, 1H), 8.10 (d, $J$ = 2.1 Hz, 1H), 7.92 (dd, $J$ = 7.9, 0.7 Hz, 1H), 7.88 (m, 1H), 7.53 (m, 1H), 6.82 (d, $J$ = 2.1 Hz, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 151.7, 145.7, 142.7, 136.3, 134.1, 128.4, 125.2, 118.4, 114.6, 99.8. HRMS (ESI): m/z Calcd. for $C_{10}H_8N_3$ [M + H]$^+$ : 170.0713; found: 170.0729.

### 4.1.16 | 8-Bromopyrazolo[1,5-a] quinazoline (3b)

Yellow solid; m.p.: 150°C to 152°C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.69 (s, 1H), 8.11 (d, $J$ = 2.0 Hz, 1H), 7.80 (d, $J$ = 8.4 Hz, 1H), 7.67 (dd, $J$ = 8.4, 1.8 Hz, 1H), 6.83 (d, $J$ = 2.1 Hz, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 157.6, 146.6, 143.21, 138.2, 135.2, 128.9, 126.6, 123.4, 119.0, 113.0. HRMS (ESI): m/z Calcd. for $C_{10}H_7BrN_3$ [M + H]$^+$ : 247.9818; found: 247.9835.

### 4.1.17 | 8-(Trifluoromethyl)pyrazolo[1,5-a] quinazoline (3c)

Yellow solid; m.p.: Above 230°C; $^1$H NMR (400 MHz, $CDCl_3$) δ 8.86 (s, 1H), 8.72 (s, 1H), 8.09 (d, $J$ = 1.9 Hz, 1H), 8.01 (d, $J$ = 8.2 Hz, 1H), 7.70 (d, $J$ = 8.1 Hz, 1H), 6.82 (d, $J$ = 2.0 Hz, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 149.8, 144.8, 142.6, 142.4, 128.3, 127.3, 120.4, 118.9, 111.6, 99.8, 95.4. HRMS (ESI): m/z Calcd. for $C_{11}H_7F_3N_3$ [M + H]$^+$ : 238.0587; found: 238.0614.

### 4.1.18 | [1,2,4]Triazolo[1,5-a]quinazoline (3d)

[16j] White solid; m.p.: 173°C to 175°C; $^1$H NMR (400 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.88 (s, 1H), 8.42 (d, $J$ = 8.4 Hz, 1H), 8.08 (dd, $J$ = 8.0, 0.7 Hz, 1H), 7.91 (ddd, $J$ = 8.5, 7.3, 1.3 Hz, 1H), 7.59 (m, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 157.6, 154.1, 153.1, 135.9, 135.2, 128.9, 126.6, 119.0, 115.3. HRMS (ESI): m/z Calcd. for $C_9H_7N_4$ [M + H]$^+$ : 171.0665; found: 171.0678.

### 4.1.19 | 8-Bromo-[1,2,4]triazolo[1,5-a] quinazoline (3e)

Yellow solid; m.p.: 158°C to 160°C; $^1$H NMR (400 MHz, $CDCl_3$) δ 9.33 (s, 1H), 8.84 (s, 1H), 8.10 (s, 1H), 7.79 (s, 1H), 7.55 (d, $J$ = 7.4 Hz, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 162.2, 158.4, 153.8, 135.6, 135.1, 129.6, 126.6, 118.8, 114.5. HRMS (ESI): m/z Calcd. for $C_9H_6BrN_4$ [M + H]$^+$ : 248.9771; found: 248.9772.

### 4.1.20 | 8-(Trifluoromethyl)-[1,2,4] triazolo[1,5-a]quinazoline (3f)

Yellow solid; m.p.: Above 230°C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.34 (s, 1H), 8.77 (s, 1H), 8.46 (d, $J$ = 8.2 Hz, 1H), 7.77 (d, $J$ = 8.2 Hz, 1H), 7.69 (s, 1H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 158.0, 151.1, 147.6, 135.0, 134.2,

129.2, 121.3, 118.9, 113.3, 111.0. HRMS (ESI): m/z Calcd. for $C_{10}H_6F_3N_4$ $[M + H]^+$ : 239.0539; found: 239.0541.

### 4.1.21 | Indazolo[2,3-a]quinazoline (3g)

Yellow solid; m.p.: 159°C to 162°C; $^1$H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H), 8.85 (d, $J$ = 8.6 Hz, 1H), 8.32 (d, $J$ = 8.3 Hz, 1H), 8.12 (d, $J$ = 8.0 Hz, 1H), 8.03 (m, 1H), 7.96 (d, $J$ = 8.7 Hz, 1H), 7.73 (m, 1H), 7.62 (m, 1H), 7.36 (t, $J$ = 8.3 Hz, 1H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 148.7, 147.3, 138.7, 134.4, 132.9, 127.8, 127.2, 125.6, 120.8, 119.2, 119.1, 115.8, 115.2, 114.2. HRMS (ESI): m/z Calcd. for $C_{14}H_{10}N_3$ $[M + H]^+$ : 220.0869; found: 220.0900.

### 4.1.22 | Pyrido[2′,3′:3,4]pyrazolo[1,5-a]quinazoline (3h)

Yellow solid; m.p.: 175°C to 177°C; $^1$H NMR (500 MHz, Acetone-$d_6$) δ 9.40 (s, 1H), 8.95 (d, $J$ = 8.1 Hz, 1H), 8.86 (d, $J$ = 8.4 Hz, 1H), 8.72 (d, $J$ = 8.2 Hz, 1H), 8.45 (d, $J$ = 8.0 Hz, 1H), 8.25 (t, $J$ = 7.8 Hz, 1H), 7.93 (t, $J$ = 7.6 Hz, 1H), 7.40 (dd, $J$ = 8.2, 4.2 Hz, 1H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 161.2, 155.6, 149.0, 140.8, 131.6, 130.5, 129.2, 122.6, 121.8, 119.4, 118.2, 116.1, 109.9. HRMS (ESI): m/z Calcd. for $C_{13}H_9N_4$ $[M + H]^+$ : 221.0822; found: 221.0828.

### 4.1.23 | Benzo[4,5]imidazo[1,2-a]quinazoline (4a)

[20] Pale yellow solid; m.p.: 226°C to 228°C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.37 (s, 1H), 8.77 (d, $J$ = 8.4 Hz, 1H), 8.66 (m, 1H), 8.29 (dd, $J$ = 7.8, 1.4 Hz, 1H), 8.09 (ddd, $J$ = 8.7, 7.3, 1.5 Hz, 1H), 7.97 (m, 1H), 7.63 (m, 1H), 7.57 (m, 2H). HRMS (ESI): m/z Calcd. for $C_{14}H_{10}N_3$ $[M + H]^+$ : 220.0869; found: 220.0889.

### 4.1.24 | 2-Bromobenzo[4,5]imidazo[1,2-a]quinazoline (4b)

[20] Pale yellow solid; m.p.: above 230°C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.37 (s, 1H), 8.83 (s, 1H), 8.70 (d, $J$ = 8.5 Hz, 1H), 8.26 (d, $J$ = 8.3 Hz, 1H), 7.98 (d, $J$ = 7.4 Hz, 1H), 7.92 (d, $J$ = 8.3 Hz, 1H), 7.60 (m, 2H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 158.6, 142.9, 137.5, 131.9, 129.0, 128.2, 124.8, 123.5, 120.0, 117.3, 117.0, 114.8. HRMS (ESI): m/z Calcd. For $C_{14}H_9BrN_3$ $[M + H]^+$ : 297.9975; found: 297.9976.

### 4.1.25 | 2-Methoxybenzo[4,5]imidazo[1,2-a]quinazoline (4c)

[20] Pale yellow solid; m.p.: 225°C to 226°C; $^1$H NMR (400 MHz, Acetone-$d_6$) δ 9.27 (s, 1H), 8.71 (d, $J$ = 8.5 Hz, 1H), 8.47 (d, $J$ = 9.1 Hz, 1H), 8.28 (d, $J$ = 7.0 Hz, 1H), 8.10 (m, 1H), 7.67 (dd, $J$ = 7.5, 3.2 Hz, 2H), 7.45 (d, $J$ = 7.4 Hz, 1H), 7.16 (dd, $J$ = 9.1, 2.5 Hz, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 157.8, 156.4, 144.5, 137.4, 136.57, 134.8, 128.9, 130.0, 124.8, 120.7, 118.0, 115.1, 114.2, 113.0, 56.1. HRMS (ESI): m/z Calcd. for $C_{15}H_{12}N_30$ $[M + H]^+$ :250.0975; found: 250.0979.

### 4.1.26 | 2-(Trifluoromethy)benzo[4,5]imidazo[1,2-a]quinazoline (4d)

Pale yellow solid; m.p.: above 230°C; $^1$H NMR (400 MHz, Acetone-$d_6$) δ 9.44 (s, 1H), 8.91 (s, 1H), 8.63 (m, 1H), 8.56 (d, $J$ = 8.1 Hz, 1H), 8.02 (d, $J$ = 7.7 Hz, 2H), 7.64 (m, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 160.2, 145.7, 138.8, 136.2, 135.9, 133.4, 130.9, 127.1, 126.0, 124.8, 122.9, 122.8, 122.2, 116.5, 113.7. HRMS (ESI): m/z Calcd. for $C_{15}H_9F_3N_3$ $[M + H]^+$ : 288.0743; found: 288.0746.

### 4.1.27 | 2-Nitrobenzo[4,5]imidazo[1,2-a]quinazoline (4e)

Pale yellow solid; m.p.; above 230°C $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.24

(s, 1H), 8.62 (m, 2H), 8.14 (m, 2H), 7.90 (m, 2H), 7.54 (t, $J$ = 7.5 Hz, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 159.7, 150.6, 149.0, 148.7, 143.8, 135.4, 130.3, 129.0, 127.5, 125.3, 123.0, 121.1, 119.1, 114.2. HRMS (ESI): m/z Calcd. for $C_{14}H_9N_4O_2$ $[M + H]^+$ : 265.0720; found: 265.0721.

### 4.1.28 | Pyrido[3′,2′:4,5]imidazo[1,2-a]quinazoline (4f)

Pale yellow solid; m.p.: above 230°C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.39 (s, 1H), 8.99 (dd, $J$ = 8.3, 1.3 Hz, 1H), 8.69 (m, 1H), 8.28 (dd, $J$ = 7.9, 1.0 Hz, 1H), 8.10 (m, 1H), 7.68 (t, $J$ = 7.5 Hz, 1H), 7.52 (dd, $J$ = 8.3, 4.7 Hz, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 160.2, 154.4, 146.6, 144.3, 135.5, 130.5, 128.7, 125.3, 125.1, 122.7, 121.5, 118.1, 114.9. HRMS (ESI): m/z Calcd. for $C_{13}H_9N_4$ $[M + H]^+$ : 221.0822; found: 221.0821.

### 4.1.29 | 2-Bromopyrido[3′,2′:4,5] imidazo[1,2-a]quinazoline (4g)

Pale yellow solid; m.p.: above 230°C; $^1$H NMR (400 MHz, DMSO-$d_6$) δ 9.12 (s, 1H), 9.04 (d, $J$ = 2.8 Hz, 1H), 8.59 (t, $J$ = 4.1 Hz, 1H), 8.25 (m, 1H), 8.00 (dd, $J$ = 8.5, 5.1 Hz, 1H), 7.96 (d, $J$ = 4.7 Hz, 1H), 7.55 (dd, $J$ = 8.0, 4.8 Hz, 1H). $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 164.2, 159.1, 142.6, 138.5, 138.1, 135.6, 131.6, 126.8, 122.7, 120.3, 115.4, 115.0, 114.1. HRMS (ESI): m/z Calcd. for $C_{13}H_8BrN_4$ $[M + H]^+$ : 298.9927; found: 298.9932.

### 4.1.30 | 5*H*-Benzo[4,5]thiazolo[3,2-a] quinazoline (5a)

Yellow solid; m.p.: 131°C to 133°C; $^1$H NMR (400 MHz, $CDCl_3$) δ 7.57 (t, $J$ = 7.9 Hz, 2H), 7.46 (t, $J$ = 7.7 Hz, 1H), 7.30 (t, $J$ = 7.5 Hz, 2H), 7.15 – 7.07 (m, 3H), 4.71 (s, 2H). $^{13}$C NMR (125 MHz, $CDCl_3$) δ 167.5, 161.9, 160.0, 152.0, 129.7, 129.6, 126.0, 124.4, 121.7, 120.8, 118.8, 115.6, 115.4, 43.2. HRMS (ESI): m/z Calcd. for $C_{14}H_{11}N_2S$ $[M + H]^+$ : 239.0638; found: 239.0642.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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