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Scaffold Diversity through a Branching Double-Annulation Cascade Strategy: Iminium-Induced One-Pot Synthesis of Diverse Fused Tetrahydroisoquinoline Scaffolds

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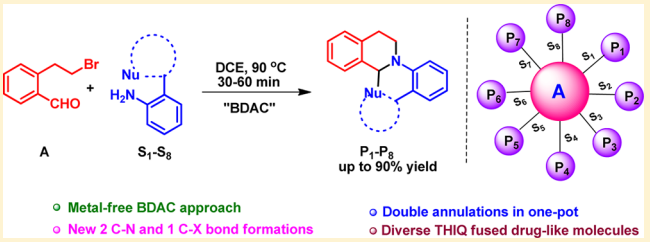
Supporting Information

ABSTRACT: A branching double-annulation cascade (BDAC) strategy for diverse and complex fused THIQ scaffolds via a highly reactive iminium-induced one-pot double-cyclization sequence involving Pictect−Spengler-type cyclization has been developed for the first time. The salient features of this protocol are that it allows direct and rapid access to unprecedented diverse fused THIQ skeletons, is metal/catalyst free, has a cleaner reaction profile, provides good to excellent yields, and is a convenient approach. This catalyst-free domino process facilitates the double annulation with a variety of scaffold building agents via two C−N and one C−X (X = C, N, O) bond formation in a single step under uniform reaction conditions. Furthermore, we reveal an unusual dual BDAC sequence leading to N−N-linked isoquinoline dimer.



INTRODUCTION

The pursuit of identification of new small molecule modulators for chemical genetics and drug discovery has led to synthesis of natural product based compounds, combinatorial synthesis of libraries,[1] and cascade strategies.[2] Awestruck by Nature's ability to create structurally and functionally diverse prevalidated natural product libraries from a limited pool of simple building blocks and led by the demand for compound libraries with structural complexity and stereogenic centers,[3] synthetic organic chemist have explored the chemical space paradigm by taking the lead from natural products, which is a highly challenging task.[4] To meet this challenge, diversity-oriented synthesis (DOS)[5] has emerged as an important tool that entails efficient synthesis of skeletally, stereochemically, and functionally diverse libraries.[6] DOS using folding[7]/branching pathways,[8] build/couple/pair (B/C/P) strategies,[9] structural variations in common substrates/building blocks,[10] and branching cascade approaches[11] has been successful in creating diverse molecular scaffolds that serve as biological probes and potential leads for drug discovery.

In connection with our broader interests in developing synthetic strategies for diverse and complex polyheterocycles involving cascade annulations[12] in a one-pot manner, herein we are pleased to disclose a cascade sequence involving a highly reactive iminium intermediate and further Pictet−Spengler-type[13] cyclization for accessing three-dimensional privileged THIQ compounds as a branching double-annulation cascade (BDAC).

Numerous strategies have been reported for the synthesis of THIQ such as Strecker lactamization/alkylations,[14] allylation−lactamization cascade,[15] Mukaiyama−Mannich lactamization/alkylations,[16] 1,3-dipolar cycloaddition reaction of azomethine imine,[17] and Grignard[18] as well as allyltrimethoxysilane[19] addition to imine as shown in Scheme 1a. The latest approaches to substituted THIQ involve metal-catalyzed *ortho* C−H allylation/cyclization (Scheme 1b),[20] cross-dehydrogenative coupling (CDC) reactions (Scheme 1c),[21] and redox-neutral reactions.[22] Recently, we have developed cascade strategies for the synthesis of THIQ in a one-pot fashion.[12c,d] However, many of the previous reported approaches to construct complex THIQ derivatives have limited skeletal diversity and require several steps, and hence, there is a need to develop efficient strategies for THIQ compounds. To address this challenge, we envisioned that the concept of branching cascade could be utilized, involving the reaction of a common substrate with different scaffold-building agents (SBAs), and Scheme 1d illustrates the general concept of a substrate-based approach to scaffold diversity, which we have utilized in the present strategy. To the best of our knowledge, the branching cascade pathway has not yet been reported for the synthesis of diverse and complex THIQ molecules. With this in mind, we have identified 2-(2-bromoethyl)benzaldehyde **1a** as a common substrate to generate highly reactive and versatile iminium intermediate for further diversification with wide range of SBAs **2** (Scheme 1e). THIQs, with a stereogenic center at the C1 position, occupy an important place among natural and unnatural compounds possessing valuable biological activities[23] and are precursors for synthesis of complex alkaloids.[14−16]

Herein, we report a novel BDAC strategy for rapid access to diverse molecular libraries containing unprecedented THIQ fused skeletons by using 2-(2-bromoethyl)benzaldehyde **1a** as a

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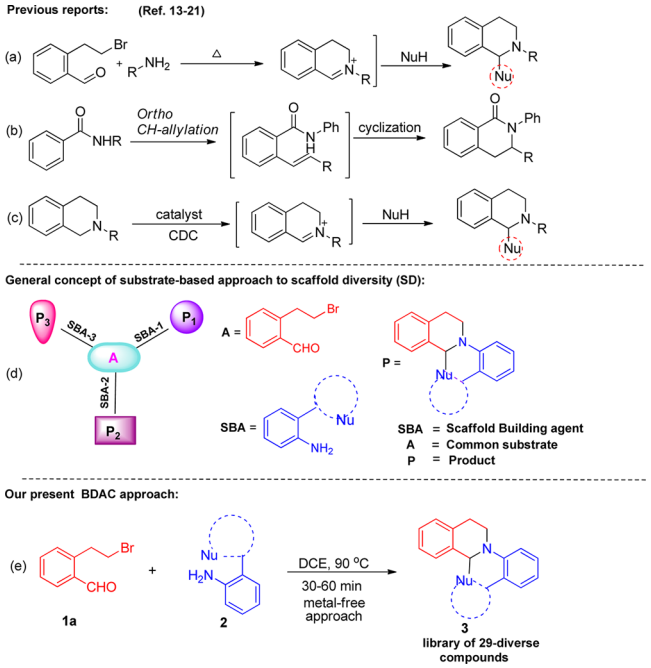
Scheme 1. Different Approaches for the Synthesis of Fused THIQ Skeletons and Our Designed BDAC Strategy

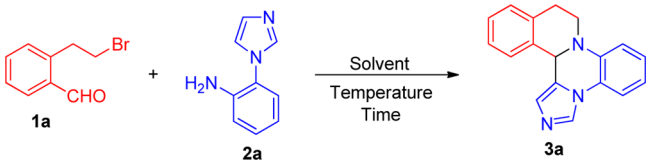


common substrate and a variety of *N*,*C*-, *N*,*O*-, and *N*,*N*-1,5-bisnucleophiles as SBAs. The synthesized molecules contain multiple privileged structures such as tetrahydroisoquinoline (coralydine I and (+) cripsin A II), imidazoquinoxaline (PPQ-102 III),[24] pyrroloquinoxaline (IV),[25] tetrazolo[1,5-*c*]-quinoxaline (V),[26] quinazolinone (rutaecapine VI),[27] and benzothiadiazinedioxide (IDRA-21 VII),[28] which form part of natural products and biologically important molecules (Figure 1).

RESULTS AND DISCUSSION

Toward this end, initially to check the feasibility of our branching cascade strategy we performed a model reaction of 2-(2-bromoethyl)benzaldehyde (**1a**) with 2-(2-aminophenyl)-imidazole (**2a**) under polar protic solvents such as MeOH and EtOH at various temperatures (Table 1, entries 1−4), which under reflux temperature in MeOH gave the desired product **3a** in 47% yield (Table 1, entry 2). Inspired by this result, and in order to increase the yield further, we screened the reaction under polar aprotic solvents such as acetonitrile and 1,4 dioxane, which afforded moderate yields of the products (20−53%, Table 1, entries 5−7). We continued our attempts to optimize the yield by performing the reaction in chlorinated solvents (Table 1, entries 8−10), and to our delight, DCE at reflux temperature provided the desired product in good yield (Table 1, entry10). After screening various solvents, we chose DCE as a solvent for further optimization studies. Increasing the reaction temperature to 90 °C resulted in a better yield of the product **3a** (75%) (Table 1,

Table 1. Optimization Conditions for the Synthesis of Fused Tetrahydroisoquinoline Compound 3a through BDAC[a]



entry	solvent	additive	*T* (°C)	time (min)	yield[b] (%)
1	MeOH		rt	120	45
2	MeOH		reflux	60	47
3	EtOH		rt	120	40
4	EtOH		reflux	60	42
5	CH_3CN		rt	90	20
6	CH_3CN		reflux	60	53
7	1,4-Dioxane		reflux	60	45
8	DCM		rt	90	42
9	DCE		rt	90	56
10	DCE		reflux	60	66
11	**DCE**		**90**	**30**	**75**[c]
12	DCE		100	30	65
13	DCE		90	30	66[d]
14	DCE	DBU	90	60	0
15	DCE	PTSA	90	60	70
16	DCE	Et_3N	90	60	68
17	DCE	M.S.	90	60	70[e]
18	DCE	Na_2SO_4	90	60	69

[a]Reaction conditions: **1a** (0.23 mmol), **2a** (0.23 mmol), and 1 mL of solvent. [b]Isolated yields after column chromatography. [c]No detrimental effect observed on reaction outcome by varying the concentration of reaction. [d]Unconventional microwave heating was used. [e]4 Å molecular sieves were used.

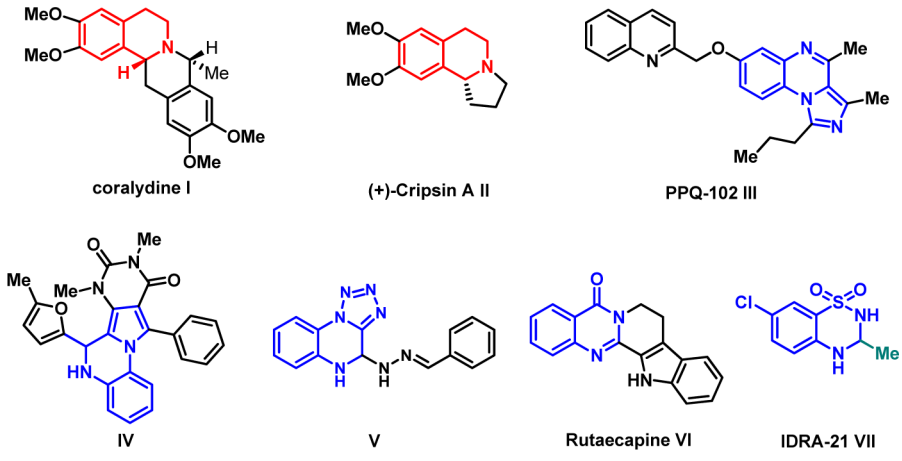


Figure 1. Naturally occurring THIQ alkaloids and representative examples of bioactive molecules containing our privileged motifs.

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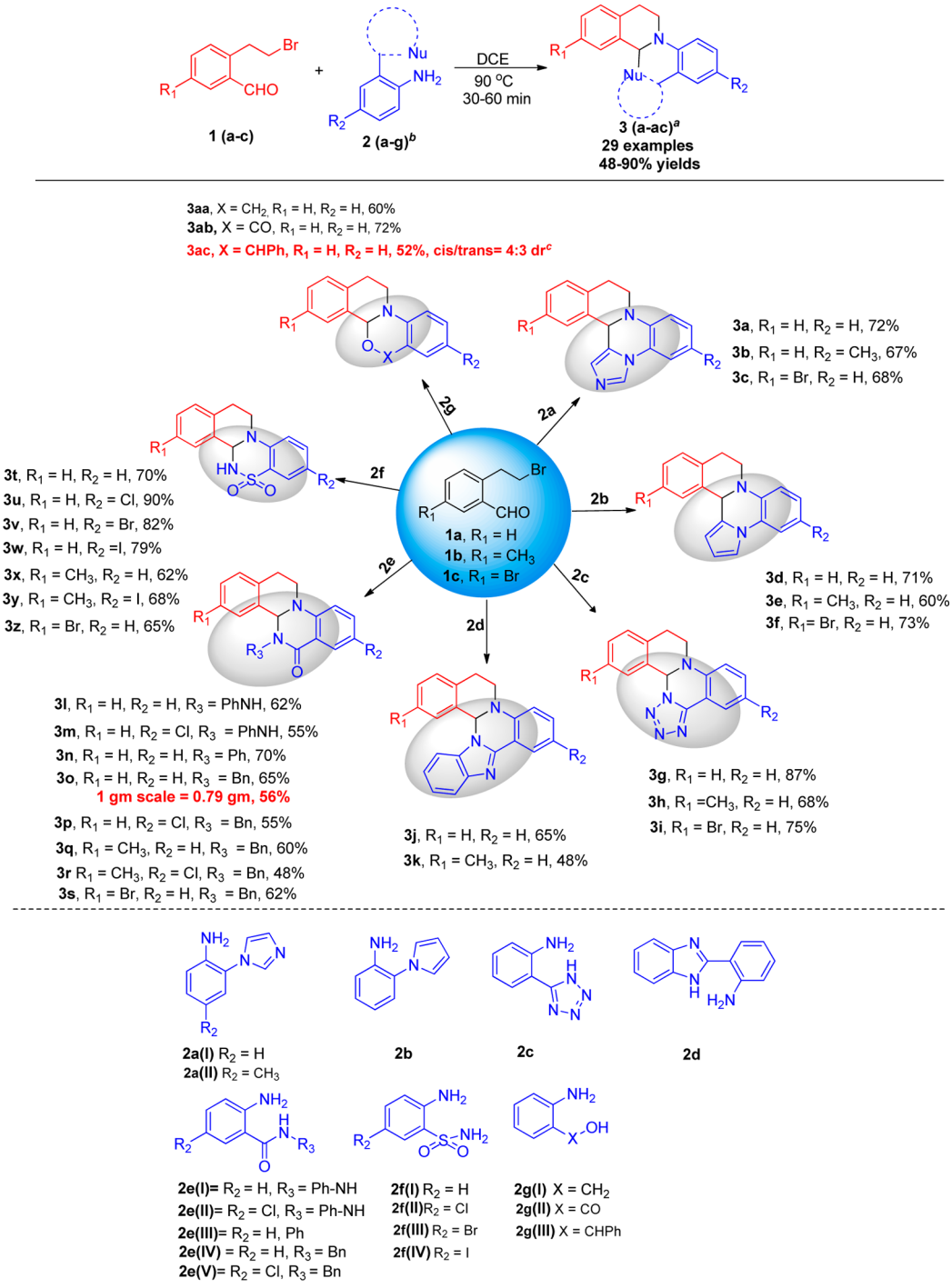

Figure 2. Synthesis of various diverse fused tetrahydroisoquinoline compounds **3a**–**ac** through a BDAC strategy. (a) Reactions were performed in DCE (1 mL) with **1** (0.23 mmol) and **2** (0.23 mmol) at 90 °C for 30–60 min. (b) **2a**–**g** represent various *N,C*-, *N,O*-, and *N,N*-1,5-bisnucleophiles as SBAs. (c) dr was determined by ^{1}H NMR spectroscopy.

entry 11); however, a further increase in temperature to 100 °C as well as unconventional microwave heating could not improve the yield of the product (Table 1, entries 12 and 13). Our attempts to use additives like DBU, PTSA, and Et_3N failed to improve the yield of the product (Table 1, entries 14–16). Similarly, employing dehydrating agents like 4 Å molecular sieves and Na_2SO_4 did not aid in enhancing the yields (Table 1, entries 17 and 18).

At the outset of this study, our efforts were directed toward design and synthesis of different *N,C*-, *N,O*-, and *N,N*-1,5-bisnucleophiles (Figure 2). With this pool of compounds (**2a**–**h**) in hand, a series of annulation reactions were envisaged in order to achieve skeletal diversity. Using the standard reaction conditions, we first subjected substituted imidazole-based *N,C*-bisnucleophiles **2a(I)** and **2a(II)** leading to corresponding products **3b** and **3c** in 67% and 68% yields. In addition, we have also employed 2-(1*H*-pyrrol-1-yl)aniline (**2b**) in our cascade annulation, resulting in pyrroloquinoxaline–THIQs (**3d**–**f**) in good yields (71–73%). The fact that the more nucleophilic pyrrole-substituted SBA **2b** gave a better yield than imidazole

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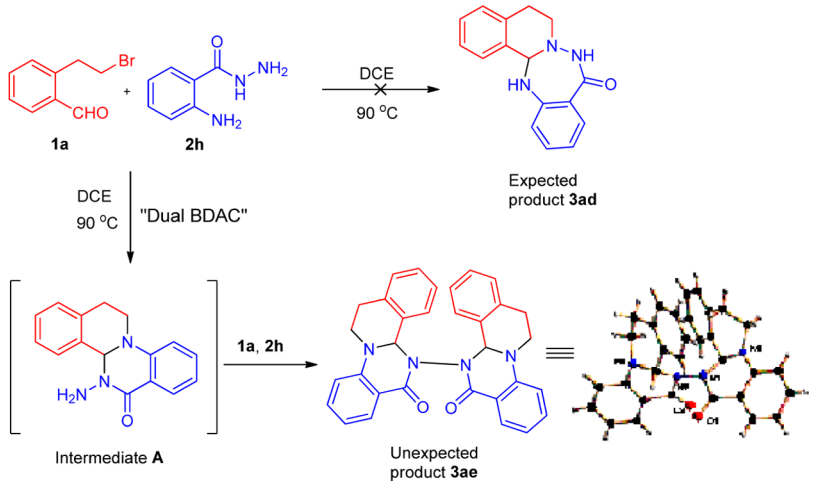
Scheme 2. Scope of BDAC Strategy with 2-Aminobenzohydrazide (2h)



substituted SBA **2a** is in agreement with our proposed concept. In our efforts to diversify the skeleton, we investigated azole-based *N,N*-bisnucleophiles such as **2c** and **2d**, which resulted in the corresponding products tetrazoloquinozalino-THIQs (**3g–i**, 75–87%) and benzimidazoquinazolino-THIQs (**3j** and **3k**, 48% and 65%). Tetrazole-based SBA **2c** was the best nucleophile, which afforded excellent yields of the corresponding products among all heterocyclic SBAs. With an aim of functionally diversifing the skeleton and for comparative study, we evaluated the reactivity of the amide as a *N,N*-bisnucleophile in our present strategy. To our surprise, the reaction of a variety of 2-aminobenzamides **2e** with **1a–c** under standard conditions afforded the corresponding products (**3l–s**) in good to high yields (48–70%). It is to be noted that these products could be diversified further for various applications. The successful employment of 2-aminobenzamides **2e** (**I–V**) prompted us to examine the 2-aminobenzenesulfonamides (**2f**) as a scaffold building agent for the synthesis of tetrahydrobenzothiadiazinoisoquinoline 6,6-dioxide, which is a privileged scaffold present in several natural products of biological interest.[28] Accordingly, when we reacted a variety of 2-aminosulfonamides (**2f**) with **1a–c** we obtained products **3t–z** in good to excellent yields (62–90%).

Encouraged by the results, we explored the nucleophilicity of oxygen in our present strategy by treatment of 2-aminobenzyl alcohol **2g(I)** and 2-aminobenzoic acid **2g(II)** with **1a**, which afforded **3aa** and **3ab** in 60 and 72% yields, respectively. Due to the ubiquity of THIQ-based natural products containing a C1 stereocenter, many research groups have focused on the introduction of a substituent at the C1 position in a stereogenic fashion and also on natural products containing two contiguous and 1,3 stereocenters. Our aim to introduce stereochemical diversity in our present strategy prompted us to examine the possibility of diastereoselectivity by employing the 1,3 stereocenter inducing SBAs. With this idea in mind, we selected the phenyl-substituted secondary alcohol **2g(III)** as the *N,O*-1,5 bisnucleophile, which afforded the expected product **3ac** but with low stereoselectivity (*cis*/*trans* = 4:3) as a mixture of inseparable diastereomers in 52% yield. The relative configuration of the major diastereomer was assigned as cis on the basis of NOE experiment. Our attempts to improve the diastereoselectivity by varying temperature, solvent system, and concentration were unsuccessful (see the SI). All of the compounds were confirmed by ^{1}H and ^{13}C spectroscopy and high-resolution mass spectrometry. Although the NMR spectroscopic data support the formation of fused privileged tetrahydroisoquinoline scaffolds **3**, the structures of **3p** and **3t** were unambiguously secured by X-ray crystal analyses (see the SI for X-ray data of 3p and 3t).

In our present BDAC strategy, several diverse halo-substituted compounds have been synthesized that could be utilized as versatile synthons for further diversification. The present BDAC strategy was proven to be very general and versatile by enabling a variety of SBAs with distinct nucleophilic centers to react with common precursor under unified reaction conditions. Overall, it was found that the *N,N*-bisnucleophiles afforded excellent yields compared to *N,C* and *N,O*-bisnucleophiles, and 2-aminobenzenesulfonamides (**2f**), though comparatively weak nucleophiles, were the best among all 1,5-bisnucleophiles in terms of the reactivity and yield. Substituents such as Me and Br on common substrate **1** did not affect the reaction outcome or yield of the products (**3a–ac**).

Further aiming to expand the diversity in the BDAC strategy, we envisioned that using 2-aminobenzohydrazide (**2h**) as the 1,6-bisnucleophile can result in a 7-membered fused tetrahydrobenzotriazepino isoquinolinone skeleton. To our surprise, when we used 2-aminobenzohydrazide (**2h**) as *N,N*-bisnucleophile we obtained the dimer product **3ae** instead of the expected compound **3ad** (Scheme 2), which was confirmed by spectral and X-ray crystal structure analyses (CCDC 1478494, see the SI for X-ray data of **3ae**). The formation of **3ae** can be explained by dual BDAC reactions involving transamination of **2h** with intermediate **A** with the elimination of hydrazine hydrobromide.

After having developed the BDAC strategy for the synthesis of diverse heterocyclic scaffolds, we envisaged that it would be appropriate to check the scalability of our BDAC strategy for the synthesis of fused tetrahydroisoquinoline compounds **3**. Accordingly, we performed the scale-up (1g scale) reaction for the synthesis of the product **3o**, resulting in a yield of 0.79 g, 56% (Figure 2).

Based on the literature reports[12c,d,29] and experimental studies (see the SI for experimental studies), we have formulated a plausible reaction mechanism for the synthesis of diverse fused tetrahydroisoquinoline derivatives as shown in Scheme 3. Initially, 2-(2-bromomethyl)benzaldehyde (**1**) and scaffold-building agent (SBA) **2** react to give an imine intermediate **I**, followed by an intramolecular alkylative

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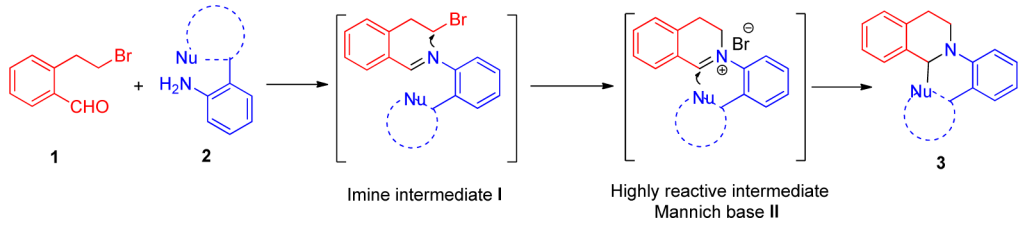
Scheme 3. Plausible Reaction Mechanism for the Synthesis of THIQ-Fused Compound 3



cyclization leading to reactive Mannich base **II**, which on further Pictet–Spengler-type[13] annulation affords the desired product **3** (Scheme 3).

In summary, we have successfully developed an advanced metal-free branching double-annulation cascade strategy for the synthesis of library of 29 new, complex, and diverse tetrahydroisoquinoline-fused derivatives by using a variety of *N,C*-, *N,O*-, and *N,N*-1,5-bisnucleophiles as SBAs and 2-(2-bromoethyl)benzaldehydes as a common precursor under uniform reaction conditions. The important features of the present protocol are that it is metal/catalyst-free, operationally simple, uses simple starting materials, and gives moderate to excellent yields. Moreover, the success of the gram-scale synthesis of fused THIQ makes this process useful for industrial applications. Undoubtedly, this protocol, which affords three-dimensional THIQ derivatives that are diverse in its coverage of chemical space, should prove useful for further scaffold innovation in a drug discovery program. Further, studies on enantioselective synthesis of these scaffolds are currently underway.

EXPERIMENTAL SECTION

General Considerations. IR spectra were recorded on an FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a 400 MHz spectrometer at 295 K in $CDCl_3$; chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) (δ_H = 0.00 ppm) or $CHCl_3$ (δ_H = 7.25 ppm). ^{13}C NMR spectra were recorded on 100 MHz spectrometer at rt in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [δ_C = 77.00 ppm (central line of triplet)]. The following abbreviations are used in the ^{1}H NMR: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, m = multiplet, and br s = broad singlet. The assignments of signals were confirmed by ^{1}H, ^{13}C CPD and DEPT spectra. High-resolution mass spectra (HR-MS) were recorded using a Q-TOF multimode source. Melting points were determined on an electrothermal melting point apparatus and are uncorrected. 2-(2-Bromoethyl)benzaldehyde (**1a–c**) were prepared by using known procedures. All of the bisnucleophiles such as *N,C*-, *N,O*-, and *N,N*-1,5-bisnucleophiles as SBAs (**2a–h**) were either prepared in the laboratory or purchased from commercial sources. Dry solvents such as MeOH, EtOH, and 1,4-dioxane were dried over sodium metal, and CH_3CN, DCM and DCE were dried over calcium hydride.

All small-scale dry reactions were carried out using standard syringe–septum techniques. Reactions were monitored by TLC on silica gel using a combination of petroleum ether and ethyl acetate as eluents. Reactions were generally run under argon atmosphere. Solvents were distilled prior to use; petroleum ether with a boiling range of 40–60 °C was used.

I. General Procedure 1: Preparation of Isochromans.[30] A mixture of the substituted phenylethyl alcohol (**i**) (4.97 mmol), chloromethyl methyl ether (7.046 mmol), and *N,N*-diisopropylethylamine (9.95 mmol) in dry dichloromethane (15 mL) was stirred under a nitrogen atmosphere for 2.5 h at rt. The reaction mixture was then washed with water and dried (Na_2SO_4), and the solvent was removed in vacuo. The crude MOM acetal (**ii**) was dissolved in dried acetonitrile and added to a cooled (0 °C) solution of trimethylsilyl trifluoromethanesulfonate (TMSOTf) (4.97 mmol). The reaction was carried out under nitrogen atmosphere for 3 h. The mixture was then quenched by the addition of l M $NaHCO_3$. The organic phase was washed with brine, dried with anhydrous sodium sulfate, and evaporated under reduced pressure. Purification by column chromatography afforded the corresponding substituted isochromans (SI).

*II. General Procedure 2: Preparation of 2-(2-Bromoethyl)-benzaldehydes **1a–1c**.*[30] To a solution of the substituted isochroman **iii** derivative (7.46 mmol) in acetonitrile (15 mL) was added $CuBr_2$ (8.95 mmol) under nitrogen atmosphere. The solution was refluxed for about 2 h and then cooled to room temperature. Water was added to the reaction mixture followed by extraction with ethyl acetate. The combined organic extracts were washed with brine, dried with anhydrous Na_2SO_4, filtered, concentrated, and then purified by silica gel column chromatography to afford the products **1a–c** in 68–74% yield (see the SI).

*III. General Procedure 3: Synthesis of Diverse Scaffold Containing Fused Tetrahydroisoquinolines **3a–ae** through BDAC Strategy.* 2-(2-Bromoethyl)benzaldehydes **1a–c** (50 mg, 0.23 mmol) and a variety of bisnucleophiles **2** (0.23 mmol) were taken in a 5 mL round-bottom flask, 1 mL of DCE was added, and the mixture was heated at 90 °C. After completion of the reaction (monitored by TLC), the DCE solvent was completely evaporated under reduced pressure. The reaction mixture was quenched by aq $NaHCO_3$ and extracted with ethyl acetate (2 × 20 mL). The combined organic layer was washed with brine solution and allowed to dry over anhydrous Na_2SO_4. The crude extract was purified by filtration through a silica gel (100–200 mesh) column using hexane and ethyl acetate as eluents to yield the desired product **3a–ae**.

*IV. General Procedure 4: Large-Scale Synthesis of Isoquinolino-quinazolinone **3o** through BDAC Strategy.* 2-(2-Bromoethyl)-benzaldehyde (**1a**) (1000 mg, 4.69 mmol) and *N,N*-bisnucleophile **2e(IV)** (790 mg, 4.69 mmol) were taken in a 25 mL round-bottom flask, 10 mL of DCE was added, and the mixture was heated at 90 °C. After completion of the reaction (monitored by TLC), the DCE solvent was completely evaporated under reduced pressure. The reaction mixture was quenched by aq $NaHCO_3$ and extracted with ethyl acetate (2 × 20 mL). The combined organic layer was washed with brine solution and allowed to dry over anhydrous Na_2SO_4. The crude extract was purified by filtration through a silica gel (100–200 mesh) column using hexane and ethyl acetate as eluents to yield the desired product **3o** in 56%, 790 mg.

*7,11b-Dihydro-6H-imidazo-6H-imidazo[1,5-a]isoquinolino[1,2-c]quinoxaline (**3a**):* brown solid (46 mg, 72%); mp 198–200 °C; IR (MIR-ATR, 4000–600 cm^{-1}) ν_{max} 3112, 2923, 2854, 1710, 1600, 1507, 1462, 1351, 1109, 746, 653; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.86 (d, J = 16.1 Hz, 1H), 3.21–3.28 (m, 1H), 3.36–3.40 (m, 1H), 3.97 (ddd, J_a = 12.5, J_b = 5.4 and J_c = 2.2 Hz, 1H), 5.53 (s, 1H), 6.92–6.97 (m, 2H), 7.05 (d, J = 7.8 Hz, 1H), 7.17–7.23 (m, 4H), 7.26–7.32 (m, 1H), 7.43 (dd, J_a = 7.8 and J_b = 1 Hz, 1H), 8.0 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.1, 43.7, 54.7, 114.7, 115.7, 119.7, 124.6, 124.7, 126.3, 126.9, 127.4, 127.52, 129.3, 131.5, 133.1, 133.9, 137.6; HR-MS (ESI$^+$) m/z calcd for $C_{18}H_{16}N_3^+$ [M + H$^+$] 274.1339, found: 274.1326.

*2-Methyl-7,11b-dihydro-6H-imidazo[1,5-a]isoquinolino[1,2-c]-quinoxaline (**3b**):* brown solid (45 mg, 67%); mp 177–180 °C; IR (MIR-ATR, 4000–600 cm^{-1}) ν_{max} = 3055, 2924, 2858, 1705, 1513, 1360, 816, 736, 651; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.82–2.87 (m, 1H), 3.19–3.24 (m, 1H), 3.28–3.35 (m, 1H), 3.87–

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3.92 (m, 1H), 5.45 (s, 1H), 6.94−6.96 (m, 2H), 7.01 (d, J = 1.5 Hz, 1H), 7.13−7.16 (m, 1H), 7.19−7.22 (m, 2H), 7.24−7.25 (m, 1H), 7.30−7.33 (m, 1H), 7.97 (d, J = 1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 27.1, 43.9, 54.9, 115.2, 116.3, 124.7, 124.8, 126.2, 126.9, 127.3, 127.4, 127.7, 129.3, 129.8, 131.5, 133.1, 134.0, 135.4; HR-MS (ESI$^+$) m/z calcd for $C_{19}H_{18}N_3^+$ = [M + H$^+$]: 288.1495, found 288.1482.

*10-Bromo-7,11b-dihydro-6H-imidazo[1,5-a]isoquinolino[1,2-c]-quinoxaline (**3c**):* brown solid (56 mg, 68%); mp 168−170 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3049, 2922, 1718, 1604, 1509, 1475, 1347, 1273, 813, 739, 651; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.78−2.82 (m, 1H), 3.2 (ddd, J_a = 16.9, J_b = 11.5 and J_c = 5.9 Hz, 1H), 3.42 (ddd, J_a = 13.2, J_b = 11.7 and J_c = 4.4 Hz, 1H), 4.02−4.07 (m, 1H), 5.56 (s, 1H), 6.92 (td, J_a = 7.7 and J_b = 1.2 Hz, 1H), 7.00−7.05 (m, 3H), 7.17−7.20 (m, 1H), 7.32 (dd, J_a = 8.3 and J_b = 1.5 Hz, 1H), 7.41−7.45 (m, 2H), 8.03 (d, J = 1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 43.9, 54.6, 114.8, 115.8, 119.8, 119.9, 124.4, 125.2, 126.1, 127.0, 129.7, 130.6, 131.0, 131.7, 132.9, 135.8, 136.7; HR-MS (ESI$^+$) m/z calcd for $C_{18}H_{15}BrN_3^+$ = [M + H$^+$] 352.0444, found 352.0430.

*7,11b-Dihydro-6H-isoquinolino[2,1-a]pyrrolo[2,1-c]quinoxaline (**3d**):* brown solid (45 mg, 71%); mp 120−122 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3052, 2902, 2829, 1506, 1337, 1288, 1221, 738, 701, 643; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.8 (d, J = 16.1 Hz, 1H), 3.19−3.27 (m, 1H), 3.31−3.38 (m, 1H), 3.90−3.95 (m, 1H), 5.46 (s, 1H), 6.07−6.08 (m, 1H), 6.32−6.34 (m, 1H), 6.84−6.88 (m, 1H), 6.97−6.99 (m, 1H), 7.05−7.20 (m, 5H), 7.31−7.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.1, 44.0, 56.2, 105.7, 110.0, 114.5, 115.1, 115.1, 119.7, 125.0, 126.0, 127.0, 127.5, 127.7, 128.5, 129.2, 134.2, 134.4, 137.6; HR-MS (ESI$^+$) m/z calcd for $C_{19}H_{17}N_2^+$ = [M + H$^+$] 273.1386, found 273.1382.

*10-Methyl-7,11b-dihydro-6H-isoquinolino[2,1-a]pyrrolo[2,1-c]-quinoxaline (**3e**):* brown solid (38 mg, 60%); mp 130−132 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3044, 2918, 2847, 1505, 1337, 1289, 1164, 741, 701, 610, 549; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H), 2.78 (d, J = 15.7 Hz, 1H), 3.17−3.25 (m, 1H), 3.34 (td, J_a = 12 and J_b = 3.9 Hz, 1H), 3.9−3.96 (m, 1H), 5.44 (s, 1H), 6.09 (d, J = 2.9 Hz, 1H), 6.34 (t, J = 3.2 Hz, 1H), 6.85−6.89 (m, 1H), 6.98−7.03 (m, 2H), 7.05−7.09 (m, 1H), 7.14 (s, 1H), 7.17 (dd, J_a = 2.7 and J_b = 1.7 Hz, 1H), 7.23 (s, 1H), 7.33 (dd, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 26.6, 44.1, 56.14, 105.7, 110.0, 114.4, 115.0, 115.1, 119.6, 124.9, 127.6, 127.8, 128.5, 129.0, 131.0, 134.1, 135.5, 137.6; HR-MS (ESI$^+$) m/z calcd for $C_{20}H_{19}N_2^+$ = [M + H$^+$] 287.1543, found 287.1539.

*10-Bromo-7,11b-dihydro-6H-isoquinolino[2,1-a]pyrrolo[2,1-c]-quinoxaline (**3f**):* brown solid (44 mg, 73%); mp 148−150 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3048, 2919, 2833, 1508, 1340, 1165, 741, 703, 657, 538; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 (d, J = 17.6, 1H), 3.16−3.24 (m, 1H), 3.38 (ddd, J_a = 13.1, J_b = 11.6 and J_c = 4.2 Hz, 1H), 3.99 (ddd, J_a= 13.2, J_b = 5.6 and J_c = 2.2 Hz, 1H), 5.47 (s, 1H), 6.13 (dd, J_a = 3.2 and J_b = 1.2 Hz, 1H), 6.36 (t, J = 3.2 Hz, 1H), 6.87 (td, J_a = 7.6 and J_b = 1.5 Hz, 1H), 6.96−6.99 (m, 2H), 7.05−7.09 (m, 1H), 7.18 (dd, J_a = 2.9 and J_b = 1.5 Hz, 1H), 7.26−7.29 (m, 1H), 7.32 (dd, J_a = 7.8 and J_b = 1.5 Hz, 1H), 7.42 (d, J = 1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.9, 44.1, 56.0, 106.2, 110.2, 114.5, 115.1, 115.2, 119.5, 119.8, 125.0, 127.0, 127.5, 130.1, 130.2, 130.8, 133.0, 136.7, 137.1; HR-MS (ESI$^+$) m/z calcd for $C_{19}H_{16}BrN_2^+$ = [M + H$^+$] 351.0491, found 351.0477.

*7, 11b-Dihydro-6H-isoquinolino[2,1-a]tetrazolo[1,5-c]-quinazoline (**3g**):* white solid (56 mg, 87%); mp 88−90 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3067, 2922, 2854, 1720, 1655, 1614, 1489, 1387, 1295, 1238, 1119, 1031, 749, 697, 649; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.94 (dt, J_a = 16.6 and J_b = 4.4 Hz, 1H), 3.19−3.27 (m, 1H), 3.53−3.61 (m, 1H), 3.92−3.98 (m, 1H), 6.88 (s, 1H), 7.08 (td, J = 7.6 Hz, 1H), 7.14−7.17 (t, J = 7.6 Hz, 2H), 7.20−7.22 (m, 1H), 7.28−7.35 (m, 2H), 7.47 (ddd, J_a = 8.4, J_b = 7.2 and J_c = 1.5 Hz, 1H), 8.03 (dd, J_a = 7.6 and J_b = 1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.8, 44.8, 72.0, 111.5, 116.2, 121.9, 126.3, 126.8, 127.7, 129.3, 129.4, 129.8, 133.4, 134.5, 143.7, 148.8; HR-MS (ESI$^+$) m/z calcd for $C_{16}H_{14}N_5^+$ = [M + H$^+$] 276.1244, found 276.1239.

*10-Methyl-7,11b-dihydro-6H-isoquinolino[2,1-a]tetrazolo[1,5-c]-quinazoline (**3h**):* white solid (43 mg, 68%); mp 170−172 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 2920, 1618, 1494, 1303, 1214, 1144, 1064, 747, 612; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 2.89 (dt, J_a = 16.9 and J_b = 4 Hz, 1H), 3.22(ddd, J_a = 16.5, J_b = 10.6 and J_c = 5.6 Hz, 1H), 3.54−3.61 (m, 1H), 3.95−4.01 (m, 1H), 6.89 (s, 1H), 7.04−7.15 (m, 5H), 7.45−7.49 (m, 1H), 8.04 (dd, J_a = 7.8 and J_b = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 25.3, 44.9, 72.1, 111.4, 115.9, 121.7, 126.4, 127.9, 129.2, 129.8, 130.3, 131.2, 133.4, 136.6, 143.6, 148.8; HR-MS (ESI$^+$) m/z calcd for $C_{17}H_{16}N_5^+$ = [M + H$^+$] 290.1400, found 290.1395.

*10-Bromo-7,11b-dihydro-6H-isoquinolino[2,1-a]tetrazolo[1,5-c]-quinazoline (**3i**):* white solid (46 mg, 75%); mp 192−195 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 1618, 1580, 1488, 1304, 1220, 1139, 816, 739; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.91 (dt, J_a = 17.1 and J_b = 3.9 Hz, 1H), 3.21 (ddd, J_a = 16.6, J_b = 10.5 and J_c = 5.6 Hz, 1H), 3.59 (ddd, J_a = 14.4, J_b = 10 and J_c = 4.9 Hz, 1H), 3.99−4.05 (m, 1H), 6.91 (s, 1H), 7.05 (d, J = 8.3, 1H), 7.09−7.16 (m, 2H), 7.41−7.52 (m, 3H), 8.06 (dd, J_a = 7.6 and J_b = 1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.1, 44.6, 71.4, 111.3, 116.0, 120.3, 122.1, 126.5, 130.4, 131.0, 132.1, 132.6, 133.3, 133.6, 143.1, 148.7; HR-MS (ESI$^+$) m/z calcd for $C_{16}H_{13}BrN_5^+$ = [M + H$^+$] 354.0349, found 354.0343.

*6,17a-Dihydro-5H-benzo[4,5]imidazo[1,2-c]isoquinolino[2,1-a]-quinazoline (**3j**):* white solid (49 mg, 65%); mp 188−190 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3054, 2921, 2851, 1613, 1479, 1449, 1226, 736, 642, 546; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.86 (d, J = 17.1 Hz, 1H), 3.45−3.62 (m, 1H), 3.76−3.81 (m, 1H), 4.32−4.45 (m, 1H), 7.16−6.74 (m, 7H), 7.47−7.25 (m, 4H), 7.88−7.86 (m, 1H), 8.14 (d, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 44.9, 69.5, 109.3, 119.7, 123.0, 123.2, 125.6, 126.2, 126.6, 128.7, 129.5, 131.9, 134.3, 134.2, 134.5, 135.45, 143.8; HR-MS (ESI$^+$) m/z calcd for $C_{22}H_{18}N_3^+$ = [M + H$^+$] 324.1495, found 324.1494.

*2-Methyl-6,17a-dihydro-5H-benzo[4,5]imidazo[1,2-c]-isoquinolino[2,1-a]quinazoline (**3k**):* white solid (36 mg, 48%); mp 178−180 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3049, 2920, 2851, 1613, 1479, 1267, 1218, 736, 699, 641, 543; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.04 (s, 3H), 2.83 (d, J = 14.7 Hz, 1H), 3.44−3.46 (m, 1H), 3.78−3.82 (m, 1H), 4.27−4.31 (m, 1H), 6.51−6.54 (m, 1H), 6.84−7.05 (m, 5H), 7.32−7.42 (m, 4H), 7.88 (d, J = 7.3 Hz, 1H), 8.14 (d, J = 7.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 23.5, 44.8, 69.3, 108.0, 109.1, 113.1, 119.5, 122.8, 123.0, 126.1, 129.3, 129.4, 131.8, 134.5, 136.3, 143.7; HR-MS (ESI$^+$) m/z calcd for $C_{23}H_{20}N_3^+$ = [M + H$^+$] 338.1652, found 338.1650.

*5-(Phenylamino)-12,13-dihydro-4bH-isoquinolino[2,1-a]-quinazolin-6(5H)-one (**3l**):* white solid (50 mg, 62%); mp 196−198 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3260, 3032, 2922, 2853, 1655, 1599, 1472, 1267, 741, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.75 (dd, J_a = 16.9 and J_b = 4.6, 1H), 3.26−3.35 (m, 1H), 3.65 (ddd, J_a = 14.4, J_b = 12 and J_c = 5.4 Hz, 1H), 4.25 (dd, J_a = 14.4 and J_b = 5.1 Hz, 1H), 5.98 (s, 1H), 6.84−6.87 (m, 1H), 6.92 (t, J = 7.3 Hz, 1H), 7.01−7.04 (m, 4H), 7.09−7.15 (m, 2H), 7.22−7.26 (m, 2H), 7.31 (s, 1H), 7.38−7.42 (m, 1H), 7.53 (d, J = 7.3 Hz, 1H), 7.9 (dd, J_a = 7.8 and J_b = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 44.8, 75.1, 113.6, 114.2, 117.2, 119.5, 121.8, 126.2, 126.4, 128.2, 129.0, 129.3, 129.4, 134.0, 134.2, 135.3, 146.7, 147.5, 163.1; HR-MS (ESI$^+$) m/z calcd for $C_{22}H_{20}N_3O^+$ = [M + H$^+$] 342.1601, found 342.1595.

*8-Chloro-5-(phenylamino)-12,13-dihydro-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one (**3m**):* white solid (48 mg, 55%); mp 125−127 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3263, 2916, 2754, 1657, 1488, 1248, 1099, 900, 739, 691, 643, 591; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74 (dd, J_a = 16.9 and J_b = 4.6 Hz, 1H), 2.72−2.77 (m, 1H), 3.22−3.31 (m, 1H), 3.61−3.68 (m, 1H), 4.17−4.22 (m, 1H), 5.96 (s, 1H), 6.92−6.93 (m, 2H), 6.99−7.02 (m, 2H), 7.11−7.22 (m, 2H), 7.23−7.25 (m, 2H), 7.31−7.34 (m, 1H), 7.44 (br. s, 1H), 7.53 (d, J = 7.3 Hz, 1H), 7.86−7.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.3, 45.0, 75.2, 114.1, 115.1, 118.4, 121.8, 124.8, 126.3, 126.4, 128.4, 128.9, 129.0, 129.4, 133.8, 133.9, 135.0, 146.1, 146.5, 162.1; HR-MS (ESI$^+$) m/z calcd for $C_{22}H_{19}ClN_3O^+$ = [M + H$^+$] 376.1211, found 376.1204.

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*5-Phenyl-12,13-dihydro-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one (**3n**):* white solid (54 mg, 70%); mp 92−94 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3065, 1667, 1598, 1462, 1378, 1326, 1275, 755, 695, 662; ^1H NMR (400 MHz, $CDCl_3$) δ 2.83 (dd, J_a = 17.1 and J_b = 4.4, 1H), 3.26−3.29 (m, 1H), 3.72 (ddd, J_a = 14.7, J_b = 11.2 and J_c = 5.9 Hz, 1H), 4.20−4.26 (m, 1H), 6.16 (s, 1H), 6.85−6.89 (m, 1H), 6.98 (d, J = 8.3 Hz, 1H), 7.03−7.08 (m, 2H), 7.13−7.16 (m, 1H), 7.19−7.23 (m, 1H), 7.32−7.40 (m, 4H), 7.48−7.50 (m, 2H), 7.99 (dd, J_a = 7.8 and J_b = 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 45.1, 75.3, 114.1, 119.2, 119.7, 125.1, 125.9, 126.2, 127.2, 128.2, 128.9, 129.1, 129.9, 133.8, 134.4, 135.6, 141.7, 147.4, 162.8; HR-MS (ESI^+) m/z calcd for $C_{22}H_{19}N_2O^+$ = [M + H^+] 327.1492, found 327.1486.

*5-Benzyl-12, 13-dihydro-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one (**3o**):* white solid (52 mg, 65%); mp 158−160 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3030, 2917, 1648, 1601, 1475, 1261, 744, 697; ^1H NMR (400 MHz, $CDCl_3$) δ 2.29 (dd, J_a = 16.9 and J_b = 3.7 Hz, 1H), 3.13−3.04 (m, 1H), 3.48 (ddd, J_a = 14.1, J_b = 11.1 and J_c = 5.6 Hz, 1H), 3.98 (dd, J_a = 13.7 and J_b = 5.4 Hz, 1H), 4.36 (d, J = 15.2 Hz, 1H), 5.72−5.85 (m, 2H), 6.82−6.88 (m, 2H), 6.99−7.01 (m, 1H), 7.13−7.19 (m, 2H), 7.22−7.35 (m, 7H), 7.95 (dd, J_a = 7.8 and J_b = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 44.6, 49.7, 71.7, 113.7, 118.5, 119.4, 119.8, 125.9, 126.2, 127.5, 127.7, 128.3, 128.7, 129.3, 129.5, 133.4, 134.8, 137.3, 147.5, 163.5; HR-MS (ESI^+) m/z calcd for $C_{23}H_{21}N_2O^+$ = [M + H^+] 341.1648, found 341.1644.

*5-Benzyl-8-chloro-12,13-dihydro-4bH-isoquinolino[2,1-a]-quinazolin-6(5H)-one (**3p**):* white solid (48 mg, 55%); mp 210−212 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3062, 2920, 1652, 1476, 1259, 737, 699, 639; ^1H NMR (400 MHz, $CDCl_3$) δ 2.71 (dd, J_a = 17.1 and J_b = 3.9 Hz, 1H), 3.03−3.11 (m, 1H), 3.5 (ddd, J_a = 14.2, J_b = 11 and J_c = 5.6 Hz, 1H), 3.95 (dd, J_a = 13.7 and J_b = 5.4 Hz, 1H), 4.35 (d, J = 15.2 Hz, 1H), 5.64−5.68 (m, 2H), 6.82 (d, J = 8.8 Hz, 1H), 7.02 (d, J = 6.8 Hz, 1H), 7.15−7.21 (m, 2H), 7.23−7.32 (m, 7H), 7.91 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.4, 44.7, 49.8, 71.7, 104.9, 109.8, 115.2, 124.7, 125.8, 126.4, 127.6, 127.7, 128.5, 128.7, 129.1, 129.3, 133.3, 134.5, 136.9, 146.0, 162.4; HR-MS (ESI^+) m/z calcd for $C_{23}H_{20}ClN_2O^+$ = [M + H^+] 375.1259, found 375.1250.

*5-Benzyl-3-methyl-12,13-dihydro-4bH-isoquinolino[2,1-a]-quinazolin-6(5H)-one (**3q**):* white solid (47 mg, 60%); mp 158−160 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3032, 2917, 1647, 1603, 1476, 1384, 1264, 1169, 818, 738, 698; ^1H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 2.66 (dd, J_a = 16.6 and J_b = 4.4 Hz, 1H), 3.08 (d, J = 6.4 Hz, 1H), 3.49 (ddd, J_a = 14.2, J_b = 11.2 and J_c = 5.9 Hz, 1H), 4.01 (dd, J_a = 13.9 and J_b = 5.6 Hz, 1H), 4.34 (d, J = 15.7 Hz, 1H), 5.64 (s, 1H), 5.74 (s, 1H), 6.83−6.92 (m, 3H), 6.99−7.02 (m, 2H), 7.27−7.34 (m, 6H), 7.97 (dd, J_a = 7.8 and J_b = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 24.1, 44.7, 49.9, 71.8, 113.6, 118.4, 119.3, 126.4, 127.5, 127.7, 128.7, 129.0, 129.1, 129.5, 131.6, 133.4, 135.8, 137.3, 147.5, 163.5; HR-MS (ESI^+) m/z calcd for $C_{24}H_{23}N_2O^+$ = [M + H^+] 355.1805, found 355.1799.

*5-Benzyl-8-chloro-3-methyl-12,13-dihydro-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one (**3r**):* white solid (41 mg, 48%); mp 152−155 °C; 48% yield; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 2912, 2753, 1649, 1454, 1255, 1103, 889, 809, 732, 698, 640, 589, 539; ^1H NMR (400 MHz, $CDCl_3$) δ 2.27 (s, 3H), 2.66 (dd, J = 16.9 and 4.6, 1H), 3.01−3.09 (m, 1H), 3.48 (ddd, J_a = 14.2, J_b = 11.2 and J_c = 5.9 Hz, 1H), 3.94 (dd, J_a = 13.7 and J_b = 5.9 Hz, 1H), 4.32 (d, J = 15.2 Hz, 1H), 5.61 (s, 1H), 5.72 (d, J = 12.2 Hz, 1H), 6.8 (d, J = 8.8 Hz, 1H), 6.9−6.92 (m, 1H), 6.99−7.01 (m, 2H), 7.24−7.33 (m, 6H), 7.91 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 24.0, 44.8, 50.0, 71.8, 115.1, 119.6, 124.6, 126.3, 127.6, 127.7, 128.7, 129.1, 129.2, 129.3, 131.3, 133.2, 136.0, 137.0, 146.0, 162.4; HR-MS (ESI^+) m/z calcd for $C_{24}H_{22}ClN_2O^+$ = [M + H^+] 389.1415, found 389.1408.

*5-Benzyl-3-bromo-12,13-dihydro-4bH-isoquinolino[2,1-a]-quinazolin-6(5H)-one (**3s**):* white solid (43 mg, 62%); mp 128−130 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3340, 3057, 2919, 1647, 1603, 1477, 1260, 1167, 816, 734, 697, 629, 546; ^1H NMR (400 MHz, $CDCl_3$) δ 2.64 (dd, J_a = 17.1 and J_b = 4.9 Hz, 1H), 3.07−3.11 (m, 1H), 3.5 (ddd, J_a = 14.4, J_b = 11.5 and J_c = 5.9 Hz, 1H), 4.07 (dd, J_a = 14.2 and J_b = 5.9 Hz, 1H), 4.3 (d, J = 15.7 Hz, 1H), 5.6 (s, 1H), 5.81 (d, J = 15.2 Hz, 1H), 6.86−6.89 (m, 3H), 7.26−7.36 (m, 8H), 7.96 (dd, J_a = 7.8 and J_b = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 44.3, 50.1, 71.4, 113.4, 118.2, 119.6, 119.9, 127.6, 127.7, 128.6, 128.8, 129.62, 130.9, 131.4, 133.5, 133.6, 136.9, 146.9, 163.1; HR-MS (ESI^+) m/z calcd for $C_{23}H_{20}BrN_2O^+$ = [M + H^+] 419.0754, found 419.0746.

*4b,5,12,13-Tetrahydrobenzo[5,6]thiadiazino[3,4-a]isoquinoline 6,6-dioxide (**3t**):* white solid (47 mg, 70%); mp 218−220 °C; 70% yield; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3231, 2922, 2853, 1597, 1481, 1449, 1318, 1274, 1158, 748, 662, 610, 556; ^1H NMR (400 MHz, $CDCl_3$) δ 2.98−3.14 (m, 2H), 3.46 (ddd, J_a = 12.3, J_b = 8.2 and J_c = 4.4 Hz, 1H), 3.86 (dt, J_a = 12.5 and J_b = 5.3 Hz, 1H), 4.77 (d, J = 12.7 Hz, 1H), 5.98 (d, J = 13.2 Hz, 1H), 6.97 (t, J = 7.6 Hz, 1H), 7.03 (d, J = 8.3 Hz, 1H), 7.20−7.23 (m, 1H), 7.30−7.33 (m, 2H), 7.45 (ddd, J_a = 8.6, J_b = 7.1 and J_c = 1.5 Hz, 1H), 7.6 (dd, Ja = 5.4 and J_b = 3.9 Hz, 1H), 7.78 (dd, Ja = 7.8 and J_b = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.0, 43.8, 68.5, 116.1, 119.4, 125.3, 125.4, 127.1, 127.7, 128.3, 128.7, 131.7, 133.5, 135.0, 144.5; HR-MS (ESI^+) m/z calcd for $C_{15}H_{15}N_2O_2S^+$ = [M + H^+] 287.0849, found 287.0845.

*8-Chloro-4b,5,12,13-tetrahydrobenzo[5,6][1,2,4]thiadiazino[3,4-a]isoquinoline 6,6-dioxide (**3u**):* white solid (69 mg, 90%); mp 198−200 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3222, 3065, 2925, 2849, 1597, 1478, 1322, 1160, 734, 666, 621, 554; ^1H NMR (400 MHz, $CDCl_3$) δ 3.0−3.1 (m, 2H), 3.46 (ddd, J_a = 12.2, J_b = 8.1 and J_c = 4.6 Hz, 1H), 3.78−3.84 (m, 1H), 4.93 (d, J = 12.7 Hz, 1H), 5.95 (d, J = 12.7 Hz, 1H), 7.0 (d, J = 8.8 Hz, 1H), 7.21−7.23 (m, 1H), 7.31−7.38 (m, 3H), 7.57 (dd, J_a = 5.1 and J_b = 3.7 Hz, 1H), 7.7 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.9, 44.0, 68.3, 117.8, 124.3, 124.7, 125.9, 127.2, 127.7, 128.3, 128.8, 131.2, 133.6, 134.8, 143.1; HR-MS (ESI^+) m/z calcd for $C_{15}H_{14}ClN_2O_2S^+$ = [M + H^+] 321.0459, found 321.0454.

*8-Bromo-4b,5,12,13-tetrahydrobenzo[5,6][1,2,4]thiadiazino[3,4-a]isoquinoline 6,6-dioxide (**3v**):* white solid (70 mg, 82%); mp 200−202 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3411, 3027, 2837, 2720, 2253, 2128, 1644, 1593, 1476, 1322, 1164, 1005, 820, 758, 617, 561; ^1H NMR (400 MHz, $CDCl_3$) δ 2.98−3.10 (m, 2H), 3.43−3.47 (td, J_a = 8.2 and J_b = 4.2 Hz, 1H), 3.78−3.83 (m, 1H), 4.95 (d, J = 12.7 Hz, 1H), 5.93 (d, J = 12.7 Hz, 1H), 6.93 (d, J = 9.3 Hz, 1H), 7.21−7.24 (m, 1H), 7.30−7.35 (m, 2H), 7.47−7.5 (m, 1H), 7.54−7.57 (m, 1H), 7.82 (d, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.9, 43.9, 68.4, 111.2, 117.8, 126.3, 127.3, 127.6, 127.8, 128.3, 128.9, 131.2, 134.8, 136.4, 143.4; HR-MS (ESI^+) m/z calcd for $C_{15}H_{14}BrN_2O_2S^+$ = [M + H^+] 364.9954, found 364.9948.

*8-Iodo-4b,5,12,13-tetrahydrobenzo[5,6][1,2,4]thiadiazino[3,4-a]-isoquinoline 6,6-dioxide (**3w**):* white solid (76 mg, 79%); mp 210−212 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3419, 1649, 1402, 1175, 1006, 821, 759, 618, 568; ^1H NMR (400 MHz, $CDCl_3$) δ 2.55−2.61 (m, 1H), 2.96−3.13 (m, 1H), 3.47 (ddd, J_a = 12.1, J_b = 7.5 and J_c = 4.4 Hz, 1H), 3.77−3.83 (m, 1H), 5.9 (d, J = 12.2 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 7.20−2.22 (m, 1H), 7.29−7.38 (m, 2H), 7.55−7.57 (m, 1H), 7.64 (dd, J_a = 8.8 and J_b = 2 Hz, 1H), 7.98 (d, J = 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.9, 43.8, 68.3, 79.9, 117.9, 126.7, 127.3, 127.6, 128.3, 128.9, 131.3, 133.4, 134.8, 142.0, 143.9; HR-MS (ESI^+) m/z calcd for $C_{15}H_{14}IN_2O_2S^+$ = [M + H^+] 412.9815, found 412.9809.

*3-Methyl-4b,5,12,13-tetrahydrobenzo[5,6][1,2,4]thiadiazino[3,4-a]isoquinoline 6,6-dioxide (**3x**):* white solid (41 mg, 62%); mp 228−230 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3205, 2918, 2851, 1715, 1594, 1450, 1319, 1156, 741, 664, 559; ^1H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.96−3.04 (m, 2H), 3.42 (ddd, J_a = 12.3, J_b = 8.2 and J_c = 4.2 Hz, 1H), 3.83 (dt, J_a = 12.1 and J_b = 5.2 Hz, 1H), 4.78 (d, J = 12.7 Hz, 1H), 5.92 (d, J = 13.2 Hz, 1H), 6.94−6.96 (m, 1H), 7.05−7.14 (m, 3H), 7.40−7.46 (m, 2H), 7.76 (dd, J_a = 7.8 and J_b = 1.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 28.6, 43.9, 68.6, 116.1, 119.4, 125.3, 125.4, 128.2, 129.6, 131.4, 131.8, 133.5, 136.9, 144.6; HR-MS (ESI^+) m/z calcd for $C_{16}H_{17}N_2O_2S^+$ = [M + H^+] 301.1005, found 301.1001.

*8-Iodo-3-methyl-4b,5,12,13-tetrahydrobenzo[5,6][1,2,4]-thiadiazino[3,4-a]isoquinoline 6,6-dioxide (**3y**):* white solid (64 mg, 68%); mp 218−220 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3217, 2921, 2854, 1469, 1322, 1273, 1160, 929, 798, 730, 665; ^1H NMR

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(400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.92−3.05 (m, 2H), 3.41 (ddd, J_a = 12.3, J_b = 8.4 and J_c = 4.2 Hz, 1H), 3.78−3.83 (m, 1H), 4.88 (d, J = 12.7 Hz, 1H), 5.9 (d, J = 12.7 Hz, 1H), 6.81 (d, J = 9.3 Hz, 1H), 7.09−7.14 (m, 2H), 7.38 (s, 1H), 7.66 (dd, J_a = 8.8 and J_b = 2 Hz, 1H), 7.99 (d, J = 2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 28.5, 43.9, 68.4, 79.9, 117.9, 126.7, 128.0, 128.2, 129.7, 131.0, 131.7, 133.5, 137.1, 142.0, 143.9; HR-MS (ESI$^+$) m/z calcd for $C_{16}H_{16}IN_2O_2S^+$ = [M + H$^+$] 426.9972, found 426.9962.

*3-Bromo-4b,5,12,13-tetrahydrobenzo[5,6][1,2,4]thiadiazino[3,4-a]isoquinoline 6,6-dioxide (**3z**):* white solid (54 mg, 65%); mp 228−230 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3213, 2924, 2852, 1706, 1598, 1478, 1319, 1161, 738, 548; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90−2.96 (m, 2H), 3.36 (ddd, J_a = 12.5, J_b = 7.8 and J_c = 4.6 Hz, 1H), 3.74−3.79 (m, 1H), 4.83 (d, J = 12.7 Hz, 1H), 5.81 (d, J = 13.2 Hz, 1H), 6.87−6.92 (m, 1H), 7.01 (dd, J_a = 10.3 and J_b = 8.8 Hz, 2H), 7.34−7.40 (m, 2H), 7.64−7.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.6, 43.7, 67.9, 116.4, 119.8, 120.7, 125.4, 125.5, 130.0, 130.7, 131.9, 133.6, 133.9, 144.2; HR-MS (ESI$^+$) m/z calcd for $C_{15}H_{14}BrN_2O_2S^+$ = [M + H$^+$] 364.9954, found 364.9951.

*4b,6,12,13-Tetrahydrobenzo[4,5][1,3]oxazino[2,3-a]isoquinoline (**3aa**):* white solid (33 mg, 60%); mp 115−117 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3035, 2933, 2897, 2838, 1602, 1491, 1455, 1389, 1287, 1228, 1193, 1154, 1056, 1029, 946, 749, 664; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.91 (dt, J_a = 15.9 and J_b = 3.5 Hz, 1H), 3.14 (ddd, J_a = 16, J_b = 10.6 and J_c = 5.1 Hz, 1H), 3.44−3.58 (m, 2H), 4.96 (d, J = 15.2 Hz, 1H), 5.22 (d, J = 14.7 Hz, 1H), 5.41 (s, 1H), 6.95−7.02 (m, 2H), 7.11 (d, J = 7.8 Hz, 1H), 7.17−7.28 (m, 4H), 7.45 (dd, J_a= 5.4 and J_b = 3.9 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.8, 46.2, 68.3, 84.4, 121.2, 121.7, 1245.0, 126.3, 126.4, 127.3, 128.3, 128.7, 133.4, 135.3, 146.0; HR-MS (ESI$^+$) m/z calcd for $C_{16}H_{14}N^+$ = [[M + H$^+$]-H_2O]: 220.1120, found 220.1113.

*12,13-Dihydrobenzo[4,5][1,3]oxazino[2,3-a]isoquinolin-6(4bH)-one (**3ab**):* white solid (43 mg, 72%); mp 115−117 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 1720, 1607, 1484, 1467, 1399, 1331, 1292, 1229, 752; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.1 (t, J_a = 5.9, J_b = 5.9 Hz, 2H), 3.46−3.52 (m, 1H), 3.71−3.76 (m, 1H), 6.14 (s, 1H), 7.11−7.13 (m, 2H), 7.26−7.24 (m, 1H), 7.33−7.36 (m, 2H), 7.55−7.59 (m, 2H), 8.11 (dd, J = 7.8 Hz, 1.5, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.0, 43.6, 85.7, 117.0, 117.2, 122.0, 127.0, 128.4, 128.6, 129.3, 130.0, 131.0, 134.7, 135.1, 150.0, 165.1; HR-MS (ESI$^+$) m/z calcd for $C_{16}H_{14}NO_2^+$ = [M + H$^+$] 252.1019, found 252.1008.

*6-Phenyl-4b,6,12,13-tetrahydrobenzo[4,5][1,3]oxazino[2,3-a]-isoquinoline (**3ac**):* brown solid (35 mg, 52%); mp 60−62 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3029, 2925, 2834, 1659, 1601, 1487.44, 1455, 1391, 1221, 1146, 939, 747, 699, 644; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.85−2.99 (m, 2H), 3.18−3.23 (m, 2H), 3.55−3.60 (m, 2H), 3.71−3.72 (m, 1H), 3.98 (t, J = 5.9 Hz, 1H), 5.36 (s, 1H), 5.68 (s, 1H), 6.04 (s, 1H), 6.21 (s, 1H), 6.74 (d, J = 7.8 Hz, 1H), 6.85−6.88 (m, 1H), 6.97−7.05 (m, 3H), 7.15−7.16 (m, 4H), 7.21−7.25 (m, 4H), 7.29−7.32 (m, 2H), 7.33−7.43 (m, 4H), 7.43−7.51 (m, 7H); ^{13}C, HMBC, HSQC NMR (100 MHz, $CDCl_3$) δ 29.7 (t, $-CH_2-$), 29.9 (t, $-CH_2-$), 46.1 (t, $-CH_2-$), 47.0 (t, $-CH_2-$), 77.07 (d, −CH−), 78.2 (d, −CH−), 81.5 (d, −CH−), 84.4 (d, −CH−), 120.9 (d, Ar-CH), 121.0 (d, Ar-CH), 121.7 (s, Ar-C), 121.8 (d, Ar-CH), 122.0 (d, Ar-CH), 125.8 (s, Ar-C), 126.3 (d, Ar-CH), 126.4 (d, Ar-CH), 127.3 (d, Ar-CH), 127.6 (d, Ar-CH), 127.9 (d, Ar-CH), 128.0 (d, 2C, Ar-CH), 128.0 (d, 2C, Ar-CH), 128.1 (d, Ar-CH), 128.2 (d, 2C, Ar-CH), 128.3 (s, Ar-C), 128.4 (d, 2C, Ar-CH), 128.5 (d, Ar-CH), 128.5 (d, 2C, Ar-CH), 128.8 (d, 2C, Ar-CH), 129.1 (d, Ar-CH), 129.4 (d, 2C, Ar-CH), 130.3 (s, Ar-C), 133.4 (s, Ar-C), 135.1 (s, Ar-C), 135.4 (s, Ar-C), 141.8 (s, Ar-C), 142.4 (s, Ar-C), 146.4 (s, Ar-C).

*12,12′,13,13′-Tetrahydro[5,5′-biisoquinolino[2,1-a]quinazoline]-6,6′(4bH,4′bH)-dione (**3ae**):* white solid (45 mg, 38%); mp 230−232 °C; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 2903, 1722, 1606, 1466, 1398, 1294, 1241, 1160, 1119, 1032, 951, 750, 697, 639; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90−2.93 (m, 2H), 3.45−3.62 (m, 2H), 6.48 (s, 1H), 7.32−7.49 (m, 1H), 7.50−7.53 (m, 3H), 7.81−7.91 (m, 3H), 8.33−8.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.0, 45.0, 72.7, 118.7, 120.3, 121.7, 125.9, 127.7, 128.1, 128.9, 129.6, 130.6, 133.9, 136.4, 150.0, 166.6; HR-MS (ESI$^+$) m/z calcd for $C_{32}H_{27}N_4O_2^+$ = [M + H$^+$] 499.2129, found 499.2127.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01096.

Experimental procedures and characterization for all new compounds; NMR spectra (PDF)
X-ray data for **3p** (CIF)
X-ray data for **3t** (CIF)
X-ray data for **3ae** (CIF)

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Notes

The authors declare no competing financial interest.

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