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Scaffold Diversity through a Branching Double Annulation Cascade Strategy: An Iminium Induced One-pot Synthesis of Diverse Fused Tetrahydroisoquinoline (THIQ) Scaffolds

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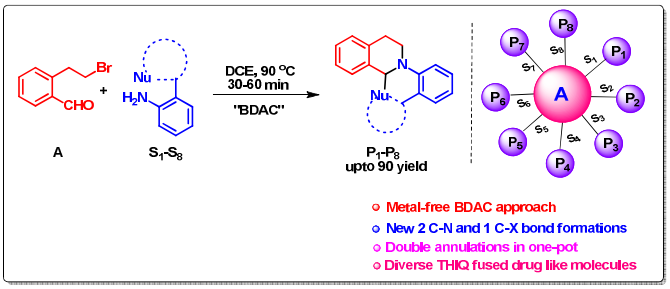


Abstract: A branching double annulation cascade (BDAC) strategy for diverse and complex fused THIQ scaffolds *via* a highly reactive iminium induced one-pot double cyclization sequence involving Pictect-Spengler type cyclization has been developed for the first time. The salient features of this protocol are direct and rapid access to unprecedented diverse fused THIQ skeletons, metal/catalyst free, cleaner reaction profile, good to excellent yields and convenient approach. This catalyst-free domino process facilitates the double annulation with variety of scaffold building agents *via* two C-N and one C-X (X = C, N, O) bonds 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]

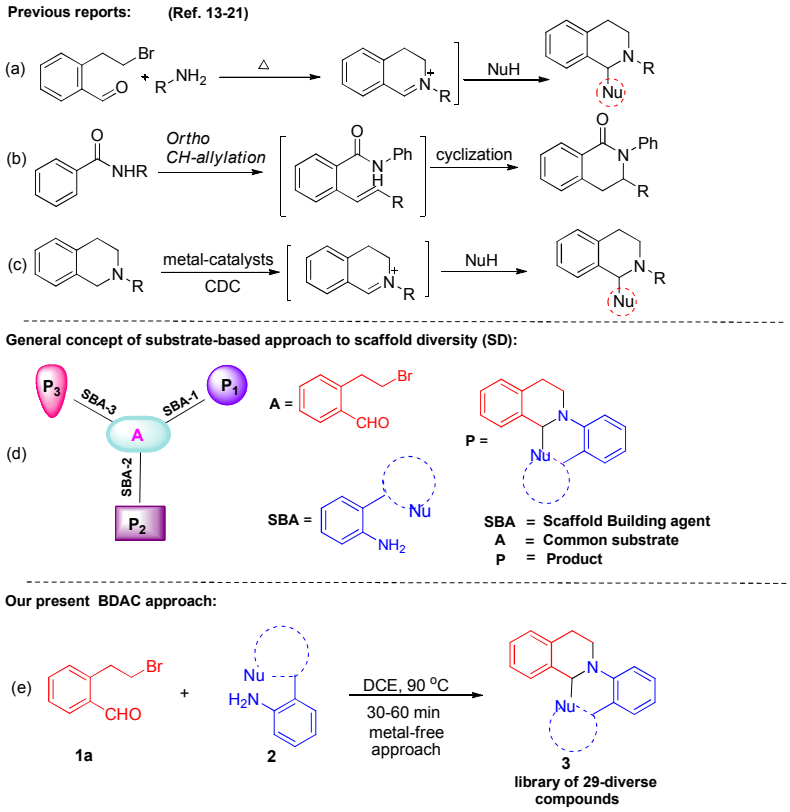
and cascade strategies.[2] Awestruck by the nature's ability to create structurally and functionally diverse pre-validated natural product libraries from a limited pool of simple building blocks and the demand for compound libraries with structural complexity and stereogenic centers[3] has led synthetic organic chemist to explore chemical space paradigm by taking the leads from natural products, which is highly challenging.[4] To meet this challenge, diversity oriented synthesis (DOS)[5] has emerged as an important tool which entails efficient synthesis of skeletally, stereochemically and functionally diverse libraries.[6] DOS by employing 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] have successfully demonstrated in creating diverse molecular scaffolds, which 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[13] type cyclization for accessing three dimensional privileged THIQ compounds as 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. Latest approaches to substituted THIQ involve metal catalysed *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 one-pot fashion.[12c,d] However, many of the previous reported approaches to construct complex THIQ derivatives often have limited skeletal diversity and require several steps, and hence there lies 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 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

Scheme 1. Different approaches for the synthesis of fused THIQ skeletons and our designed BDAC strategy.



intermediate for further diversification with wide range of SBAs **2** (Scheme 1e). THIQ 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 library containing unprecedented THIQ fused skeletons by using 2-(2-bromoethyl)benzaldehyde **1a** as a common substrate

and 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 biological important molecules (Figure 1).

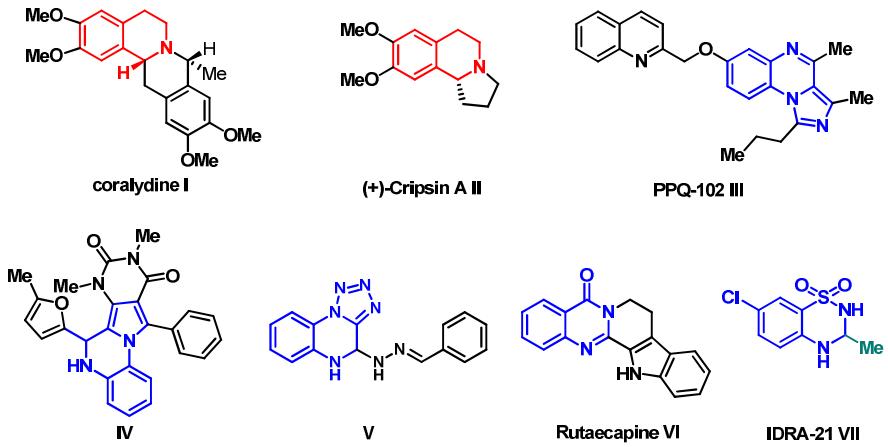


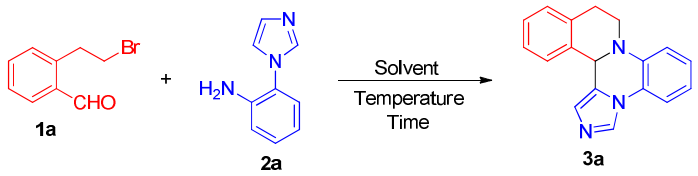
Figure 1. Naturally occurring THIQ alkaloids and representative examples of bioactive molecules containing our privileged motifs.

Results and Discussion:

To 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), of which under reflux temperature in MeOH gave the desired product **3a** albeit in 47% yield (Table 1, entry 2). Inspired by this result, in order to increase the yield further, we screened the reaction under polar aprotic solvents such as acetonitrile and 1,4 dioxane, which afforded the 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 having screened various solvents, we have chosen DCE as a solvent for further optimization studies. The increase in reaction temperature to 90 ^{o}C resulted in better yield of the product **3a** (75%) (Table 1, entry 11), however, further increase in temperature to 100 ^{o}C as well as the

unconventional microwave heating could not improve the yield of the product further (Table 1, entries 12 and 13). Our attempts to use additives like DBU, PTSA and Et_3N have failed to improve the yield of the product (Table 1, entries 14-16). Similarly, employing dehydrating agents like 4Å molecular sieves and Na_2SO_4 did not aid in enhancing the yields (Table 1, entries 17 and 18).

Table 1. Optimization conditions for the synthesis of fused tetrahydroisoquinoline compound 3a through BDAC [a]



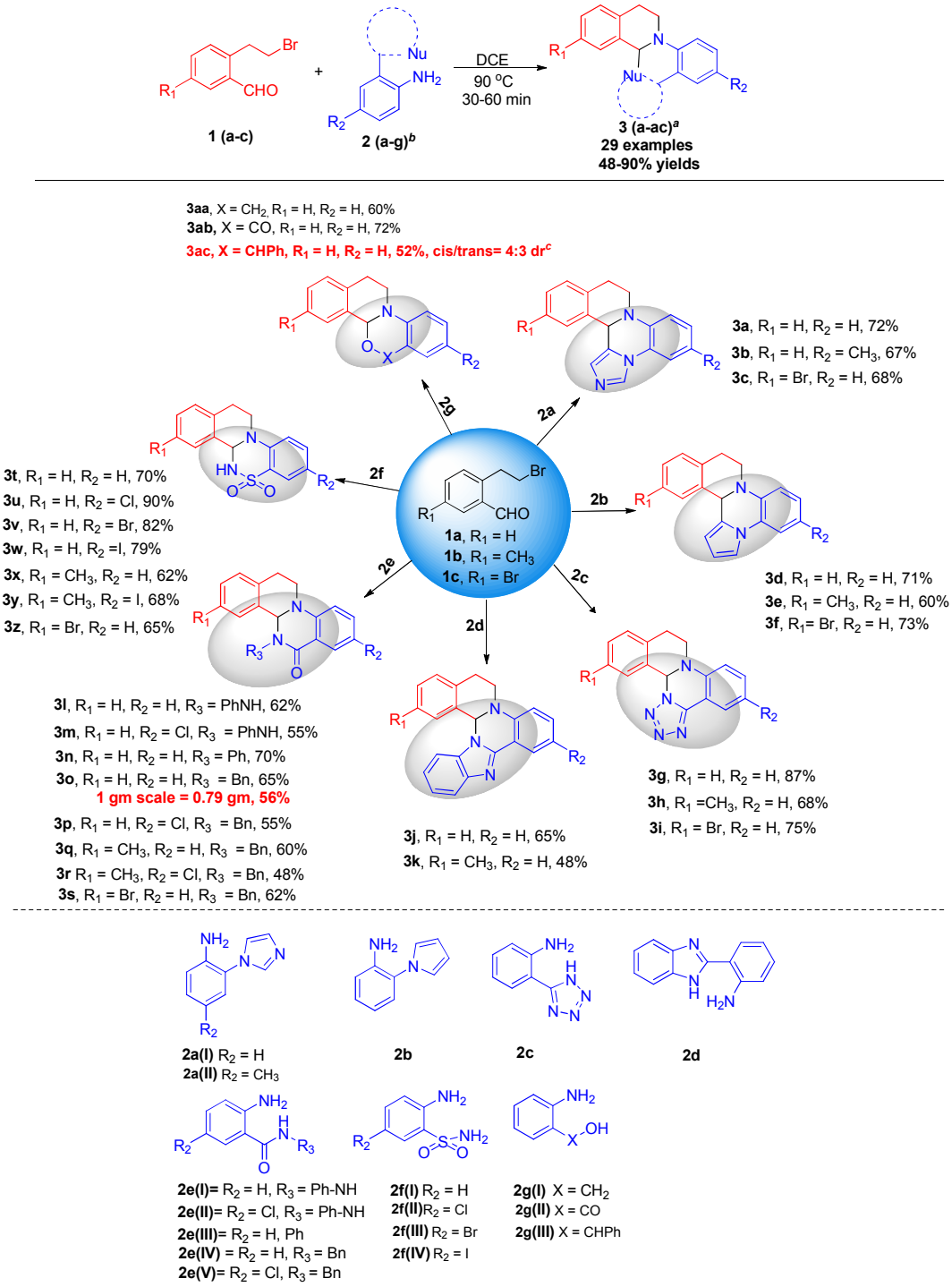
Entry	Solvent	Additive	Tempt °C	Time (min)	Yield (%)[b]
1	MeOH	-	rt	120	45
2	MeOH	-	reflux	60	47
3	EtOH	-	rt	120	40
4	EtOH	-	reflux	60	42
5	CH_3CN	-	rt	90	20
6	CH_3CN	-	reflux	60	53
7	1,4-Dioxane	-	reflux	60	45
8	DCM	-	rt	90	42
9	DCE	-	rt	90	56
10	DCE	-	reflux	60	66
11	**DCE**	-	**90**	**30**	**75**[c]
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] 4Å molecular sieves was used.

At the outset of this study, our efforts were directed towards design and synthesis of different *N,C*-, *N,O*-, and *N,N*-1,5-bisnucleophiles (Figure 2). With this pool of compounds (**2a-2h**) in hand, a series of annulation reactions were envisaged in order to achieve skeletal diversity. With the standard reaction conditions in hand, 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-3f**) in good yields (71-73%). The fact that the more nucleophilic pyrrole substituted SBA **2b** gave better yield than imidazole 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-3i,** 75-87%) and benzimidazoquinazolino-THIQs (**3j** and **3k,** 48% and 65%). Tetrazole based SBA **2c** was the best nucleophile, which afforded the excellent yields of the corresponding products among all heterocyclic SBAs. With an aim to functionally diversify the skeleton and for comparative study, we evaluated the reactivity of the amide as *N*,*N*-bisnucleophile, in our present strategy. To our surprise the reaction of variety of 2-aminobenzamides **2e** with **1a-1c** under standard conditions, afforded the corresponding products (**3l-3s**) 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 tetrahydrobenzothiadiazinoisoquinolino-6,6-dioxide which is a privileged scaffold present in several natural products of biological interest.[28] Accordingly, when we have reacted variety of 2-aminosulphonamides (**2f**) with **1a-1c**, afforded the products **3t-3z** in good to excellent yields (62-90%).

Encouraged by the results, we envisioned to explore 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 C1 stereocenter, many research groups have focused on the introduction of a substituent at 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 *N*,*O*-1,5 bisnucleophile, which afforded the expected product **3ac** although in low stereoselectivity (*cis/trans* = 4:3) as a mixture



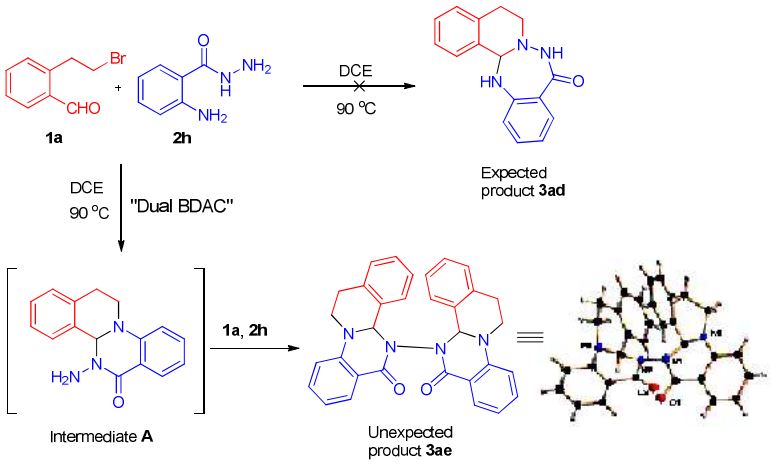
[a] Reactions were performed in DCE (1mL) with **1** (0.23 mmol), **2** (0.23 mmol) at 90 °C for 30-60 min. [b] **2a-2g** represent various *N,C*-, *N,O*- and *N,N*-1,5-bisnucleophiles as SBAs. [c] dr was determined by ^{1}H NMR spectroscopy.

Figure 2. Synthesis of various diverse fused tetrahydroisoquinoline compounds 3a-3ac through branching double annulation cascade (BDAC) strategy.

of inseparable diastereomers in 52% yield. The relative configuration of the major diastereomers was assigned to be cis based on NOE experiment. Our attempts to improve the diastereoselectivity by varying temperature, solvent system and concentration went in vein (see ESI). All 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 ESI for X-ray data of **3p** and **3t**).

In our present BDAC strategy, several diverse halo-substituted compounds have been synthesized, which could be utilized as versatile synthons for further diversification. The present BDAC strategy was proved to be very general and versatile by enabling 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 being weak nucleophile comparatively were the best among all 1,5-bisnucleophiles in terms of the reactivity and yield. The substituents such as Me and Br on common substrate **1** was non detrimental on reaction outcome and yield of the products (**3a-3ac**).

Scheme 2. Scope of BDAC strategy with 2-aminobenzohydrazide (2h).



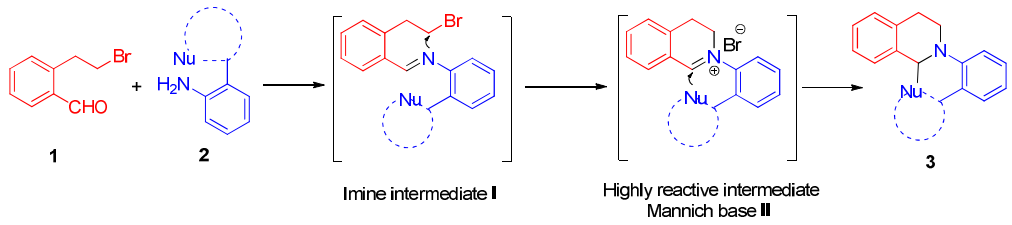
Further aiming to expand the diversity in the BDAC strategy, we envisioned that by using 2-aminobenzohydrazide (**2h**) as 1,6-bisnucleophile can result in 7-membered fused tetrahydrobenzotriazepino isoquinolinone skeleton. To our surprise, when we used 2-

aminobenzohydrazide (**2h**) as *N*,*N*-bisnucleophile, resulted in the dimer product **3ae** instead of expected compound **3ad** (Scheme 2), which was confirmed by spectral and X-ray crystal structure analyses (CCDC 1478494, see ESI 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 0.79 gm, 56% yield (Figure 2).

Based on the literature reports[12c,d, 29] and experimental studies (see ESI 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-bromoethyl)benzaldehydes (**1a**) and scaffold-building agents (SBAs) **2** react to give an imine intermediate **I**, followed by an intramolecular alkylative cyclization leading to reactive Mannich base **II** which on further Pictet-Spengler[13] type annulation affords the desired product **3** (Scheme 3).

Scheme 3. Plausible reaction mechanism for the synthesis of THIQ fused compound 3.



In summary, we have successfully developed an advanced metal-free double annulation branching cascade (BDAC) 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 a SBAs and 2-(2-bromoethyl)benzaldehydes as a common precursor under uniform reaction conditions. The important features of the present protocol are metal and catalyst-free, operational simplicity, use of simple starting materials and moderate to excellent yields. Moreover, the success of gram-scale synthesis of fused THIQ make this process useful for industrial applications. Undoubtedly, this protocol which

affords three dimensional THIQ derivatives which are diverse in its coverage of chemical space, should prove useful for further scaffold innovation in drug discovery program. Further, studies on enantioselective synthesis of these scaffolds are currently under way.

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Experimental Section

General Considerations

IR spectra were recorded on a FTIR spectrophotometer. ^{1}H NMR spectra were recorded on 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)]. In the 1HNMR, the following abbreviations were used throughout: 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 Q-TOF multimode source. Melting points were determined on an electro thermal melting point apparatus and are uncorrected. 2-(2-bromoethyl)benzaldehyde (**1a**-**1c**) were prepared by using known procedures. All the bisnucleophiles such as *N,C*-, *N,O*- and *N,N*-1,5-bisnucleophiles as a SBAs (**2a**-**2h)** which were either prepared in the laboratory or purchased from commercial sources. All the 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 technique. 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 to 60 ˚C was used.

(I) General Procedure 1: Preparation of isochromans.[30]

A mixture of the substituted phenylethyl alcohol (**i**) (4.97 mmol), chloromethylmethyl ether (7.046 mmol) and *N,N*-diisopropylethylamine (9.95 mmol) in dry dichloromethane (15 mL) was stirred under nitrogen atmosphere for 2.5 h at rt. The reaction mixture was then washed with water, dried (Na_2SO_4) and the solvent was removed in vaccuo. The crude MOM acetal (**ii**) was dissolved in dried acetonitrile and added to cooled (0 ^oC) solution of trimethylsilyl trifluoromethanesulfonate (TMSOTf) (4.97 mmol). The reaction was carried out under nitrogen atmosphere for 3h. Then the mixture was quenched by the addition of l M $NaHCO_3$. The organic phase was washed with brine, dried with anhydrous sodium sulphate and evaporated under reduced pressure. Purification by column chromatography afforded corresponding substituted isochromans (see ESI).

(II) General procedure 2: Preparation of 2-(2-bromoethyl)benzaldehydes (1a-1c).[30]

To a solution of the substituted isochroman **iii** (7.46 mmol) derivatives in acetonitrile (15 mL), $CuBr_2$ (8.95 mmol) was added under nitrogen atmosphere. The solution was refluxed for about 2h and then cooled to room temperature. The reaction mixture was added water, extracted with ethyl acetate. The combined organic extracts were washed with brine and dried with anhydrous Na_2SO_4, filtered and concentrated and then purified by silica gel column chromatography to afford the products (**1a-1c)** in 68-74% yield (see ESI).

(III) General procedure 3: Synthesis of diverse scaffold containing fused tetrahydroisoquinolines (3a-3ae) through BDAC strategy: 2-(2-Bromoethyl)benzaldehydes (**1a-c**) (50 mg, 0.23 mmol) and variety of bisnucleophiles **2** (0.23 mmol) were taken in a 5 mL round bottom flask and added 1 mL of DCE heated at 90 ^oC. 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-3ae**.

(IV) General procedure 4: Large scale synthesis of isoquinolinoquinazolinone 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 and added 10 mL of DCE heated at 90 ^oC. 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.

Spectroscopic data of all unknown compounds: ***7,11b-Dihydro-6H-imidazo-6H-imidazo[1,5-a]isoquinolino[1,2-c]quinoxaline*** **(3a):** Brown solid (46 mg, 72%); mp 198−200 ^oC; IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3112, 2923, 2854, 1710, 1600, 1507, 1462, 1351, 1109, 746, 653; ^1H NMR (400 MHz, $CDCl_3$) δ ppm = 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 ppm = 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* calculated 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 ^oC; IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3055, 2924, 2858, 1705, 1513, 1360, 816, 736, 651; ^1H NMR (400 MHz, $CDCl_3$) δ ppm = 2.32 (s, 3H), 2.82−2.87 (m, 1H), 3.19−3.24 (m, 1H), 3.28− 3.35 (m, 1H), 3.87−3.92 (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 ppm = 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* calculated 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%); 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 ppm = 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 ppm = 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* calculated 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 ppm = 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 ppm = 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* calculated 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 ppm = 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 ppm = 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* calculated 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%); m.p. 148−150 ^oC; IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3048, 2919, 2833, 1508, 1340, 1165, 741, 703, 657, 538; ^1H NMR (400 MHz, $CDCl_3$) δ ppm = 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 ppm = 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* calculated 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 ^oC; IR (MIR-ATR, 4000−600 cm^{-1}) ν_{max} = 3067, 2922, 2854, 1720, 1655, 1614, 1489, 1387, 1295, 1238, 1119, 1031, 749, 697, 649; ^1H NMR (400 MHz, $CDCl_3$) δ ppm = 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 ppm = 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* calculated 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 ^oC; IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2920, 1618, 1494, 1303, 1214, 1144, 1064, 747, 612; ^1H NMR (400 MHz, $CDCl_3$) δ ppm = 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 ppm = 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* calculated 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%); 192−195 ^{o}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 ppm = 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 ppm = 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* calculated 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%); m.p. 188−190 ^{o}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 ppm = 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 ppm = 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* calculated 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%); m.p. 178−180 ^{o}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 ppm = 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

ppm = 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* calculated 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; ^1H NMR (400 MHz, $CDCl_3$) δ ppm = 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 ppm = 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* calculated 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; ^1H NMR (400 MHz, $CDCl_3$) δ ppm = 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 ppm = 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* calculated for $C_{22}H_{19}ClN_3O^+ = [M+H^+]$: 376.1211; found: 376.1204.

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 ppm = 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 ppm = 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* calculated 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 ^{o}C; IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3030, 2917, 1648, 1601, 1475, 1261, 744, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 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 ppm = 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* calculated 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 ^{o}C; IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3062, 2920, 1652, 1476, 1259, 737, 699, 639; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 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 ppm = 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* calculated 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 ^{o}C; IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3032, 2917, 1647, 1603, 1476, 1384, 1264, 1169, 818, 738, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 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 ppm = 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* calculated 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; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 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 ppm = 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* calculated 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%); 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; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 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 ppm = 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* calculated 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; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 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 ppm = 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* calculated 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 ^{o}C; IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3222, 3065, 2925, 2849, 1597, 1478, 1322, 1160, 734, 666, 621, 554; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 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 ppm = 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* calculated 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 ^{o}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; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 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 ppm = 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* calculated 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 ^{o}C; IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3419, 1649, 1402, 1175, 1006, 821, 759, 618, 568; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 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 ppm = 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* calculated 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 ^{o}C; IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3205, 2918, 2851, 1715, 1594, 1450, 1319, 1156, 741, 664, 559; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 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 ppm = 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* calculated 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 ^{o}C; IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3217, 2921, 2854, 1469, 1322, 1273, 1160, 929, 798, 730, 665; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm = 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 ppm = 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* calculated 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 ^{o}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 ppm = 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 ppm = 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* calculated 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 ppm = 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 ppm = 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* calculated 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 ppm = 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 ppm = 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* calculated 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 ppm = 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 ppm = 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 ^{o}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 ppm = 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 ppm = 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* calculated for $C_{32}H_{27}N_4O_2^+ = [M+H^+]$: 499.2129; found: 499.2127.

Supporting Information

Experimental procedures and characterization for all new compounds, copies of NMR spectra, and CIF files (for **3p**, **3t** and **3ae**) provided. This material is available free of charge via the Internet at http://pubs.acs.org.

Author Contributions

†AHS and SMP contributed equally.

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