

Article

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

Duddu S. Sharada, Anand H Shinde, Srilaxmi M. Patel, and Shinde Vidyacharan

J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 11 Jul 2016Downloaded from <http://pubs.acs.org> on July 11, 2016

Just Accepted

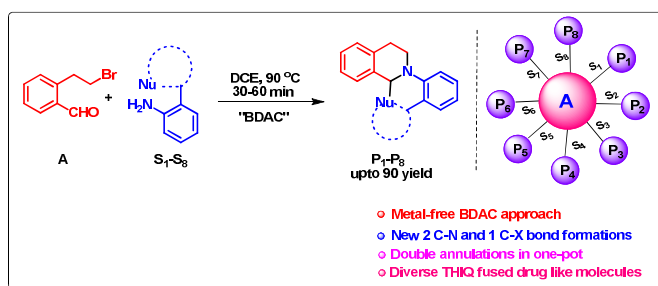
“Just Accepted” manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides “Just Accepted” as a free service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. “Just Accepted” manuscripts appear in full in PDF format accompanied by an HTML abstract. “Just Accepted” manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are accessible to all readers and citable by the Digital Object Identifier (DOI®). “Just Accepted” is an optional service offered to authors. Therefore, the “Just Accepted” Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the “Just Accepted” Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these “Just Accepted” manuscripts.

Scaffold Diversity through a Branching Double Annulation Cascade

Strategy: An Iminium Induced One-pot Synthesis of Diverse Fused Tetrahydroisoquinoline (THIQ) Scaffolds

Duddu S. Sharada,* Anand H. Shinde,[†] Srilaxmi M. Patel[†] and Shinde Vidyacharan

Department of Chemistry, Indian Institute of Technology Hyderabad (IITH), Kandi, Sangareddy, 502 285, Telangana, India. E-mail: sharada@iith.ac.in



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 Pictet-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 libraries¹

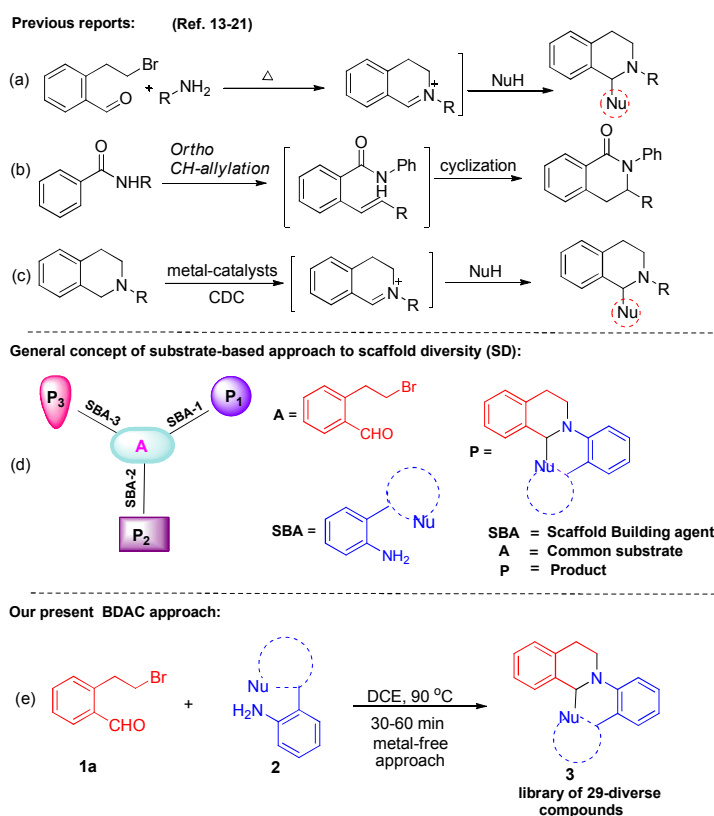
1
2
3 and cascade strategies.² Awestruck by the nature's ability to create structurally and functionally diverse
4 pre-validated natural product libraries from a limited pool of simple building blocks and the demand for
5 compound libraries with structural complexity and stereogenic centers³ has led synthetic organic chemist
6 to explore chemical space paradigm by taking the leads from natural products, which is highly
7 challenging.⁴ To meet this challenge, diversity oriented synthesis (DOS)⁵ has emerged as an important
8 tool which entails efficient synthesis of skeletally, stereochemically and functionally diverse libraries.⁶
9 DOS by employing folding⁷/branching pathways,⁸ build/couple/pair (B/C/P) strategies,⁹ structural
10 variations in common substrates/building blocks¹⁰ and branching cascade approaches¹¹ have successfully
11 demonstrated in creating diverse molecular scaffolds, which serve as biological probes and potential leads
12 for drug discovery.
13
14
15
16
17
18
19
20
21
22
23
24

25
26 In connection with our broader interests in developing synthetic strategies for diverse and complex
27 polyheterocycles involving cascade annulations¹² in a one-pot manner, herein, we are pleased to disclose
28 a cascade sequence involving a highly reactive iminium intermediate and further Pictet-Spengler¹³ type
29 cyclization for accessing three dimensional privileged THIQ compounds as branching double annulation
30 cascade (BDAC).
31
32
33
34
35
36

37 Numerous strategies have been reported for the synthesis of THIQ such as Strecker
38 lactamization/alkylations,¹⁴ allylation-lactamization cascade,¹⁵ Mukaiyama-Mannich lactamization/
39 alkylations,¹⁶ 1,3-dipolar cycloaddition reaction of azomethine imine¹⁷ and Grignard¹⁸ as well as
40 allyltrimethoxysilane¹⁹ addition to imine as shown in Scheme 1a. Latest approaches to substituted THIQ
41 involve metal catalysed *ortho* C-H allylation/cyclization (Scheme 1b),²⁰ cross-dehydrogenative coupling
42 (CDC) reactions (Scheme 1c),²¹ and redox-neutral reactions.²² Recently, we have developed cascade
43 strategies for the synthesis of THIQ in one-pot fashion.^{12c,d} However, many of the previous reported
44 approaches to construct complex THIQ derivatives often have limited skeletal diversity and require
45 several steps, and hence there lies a need to develop efficient strategies for THIQ compounds. To address
46 this challenge, we envisioned that the concept of branching cascade could be utilized, involving the
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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 activities²³ 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 (+) crispin 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).

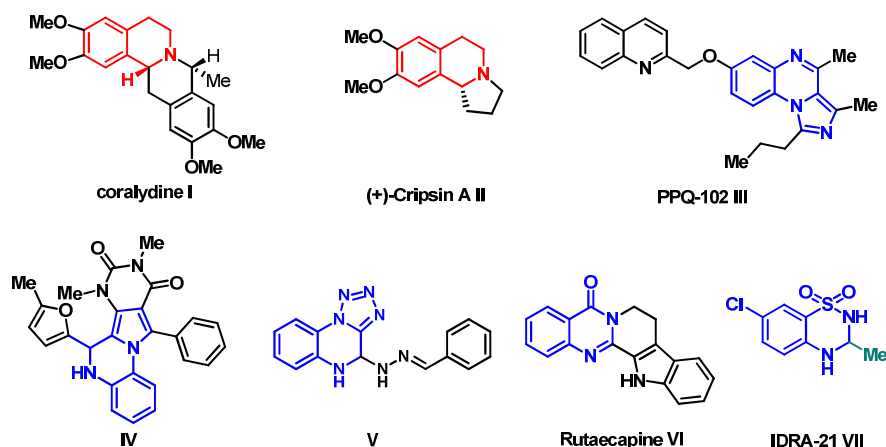


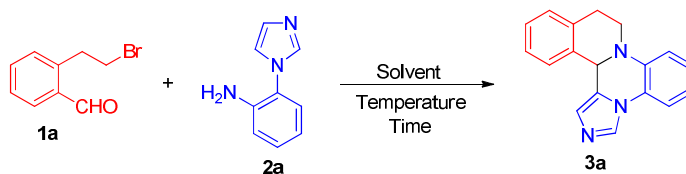
Figure 1. Naturally occurring THIQ alkaloids and representative examples of bioactive molecules containing our privileged motifs.

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, entry 10). After having screened various solvents, we have chosen DCE as a solvent for further optimization studies. The increase in reaction temperature to 90 °C resulted in better yield of the product **3a** (75%) (Table 1, entry 11), however, further increase in temperature to 100 °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 Et₃N have failed to improve the yield of the product (Table 1, entries 14-16). Similarly, employing dehydrating agents like 4Å molecular sieves and Na₂SO₄ 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



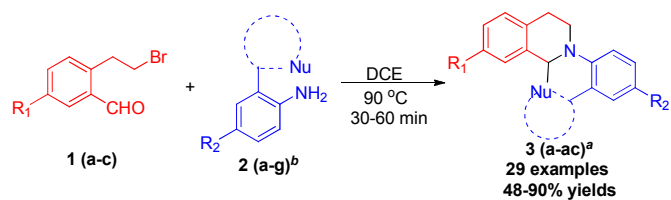
Entry	Solvent	Additive	Temp ^o C	Time (min)	Yield (%) ^b
1	MeOH	-	rt	120	45
2	MeOH	-	reflux	60	47
3	EtOH	-	rt	120	40
4	EtOH	-	reflux	60	42
5	CH ₃ CN	-	rt	90	20
6	CH ₃ CN	-	reflux	60	53
7	1,4-Dioxane	-	reflux	60	45
8	DCM	-	rt	90	42
9	DCE	-	rt	90	56
10	DCE	-	reflux	60	66
11	DCE	-	90	30	75^c
12	DCE	-	100	30	65
13	DCE	-	90	30	66 ^d
14	DCE	DBU	90	60	0
15	DCE	PTSA	90	60	70
16	DCE	Et ₃ N	90	60	68
17	DCE	M.S.	90	60	70 ^e
18	DCE	Na ₂ SO 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)**

1
2
3 leading to corresponding products **3b** and **3c** in 67% and 68% yields. In addition, we have also employed
4
5 2-(1*H*-pyrrol-1-yl)aniline (**2b**) in our cascade annulation resulting in pyrroloquinoxaline-THIQs (**3d-3f**) in
6
7 good yields (71-73%). The fact that the more nucleophilic pyrrole substituted SBA **2b** gave better yield
8
9 than imidazole substituted SBA **2a** is in agreement with our proposed concept. In our efforts to diversify
10
11 the skeleton, we investigated azole based *N,N*-bisnucleophiles such as **2c** and **2d**, which resulted in the
12
13 corresponding products tetrazoloquinoxalino-THIQs (**3g-3i**, 75-87%) and benzimidazoquinazolino-
14
15 THIQs (**3j** and **3k**, 48% and 65%). Tetrazole based SBA **2c** was the best nucleophile, which afforded the
16
17 excellent yields of the corresponding products among all heterocyclic SBAs. With an aim to functionally
18
19 diversify the skeleton and for comparative study, we evaluated the reactivity of the amide as *N,N*-
20
21 bisnucleophile, in our present strategy. To our surprise the reaction of variety of 2-aminobenzamides **2e**
22
23 with **1a-1c** under standard conditions, afforded the corresponding products (**3l-3s**) in good to high yields
24
25 (48-70%). It is to be noted that these products could be diversified further for various applications. The
26
27 successful employment of 2-aminobenzamides **2e** (**I-V**), prompted us to examine the 2-
28
29 aminobenzenesulfonamides (**2f**) as a scaffold building agent for the synthesis of
30
31 tetrahydrobenzothiadiazinoisoquinolino-6,6-dioxide which is a privileged scaffold present in several
32
33 natural products of biological interest.²⁸ Accordingly, when we have reacted variety of 2-
34
35 aminosulphonamides (**2f**) with **1a-1c**, afforded the products **3t-3z** in good to excellent yields (62-90%).
36
37
38
39

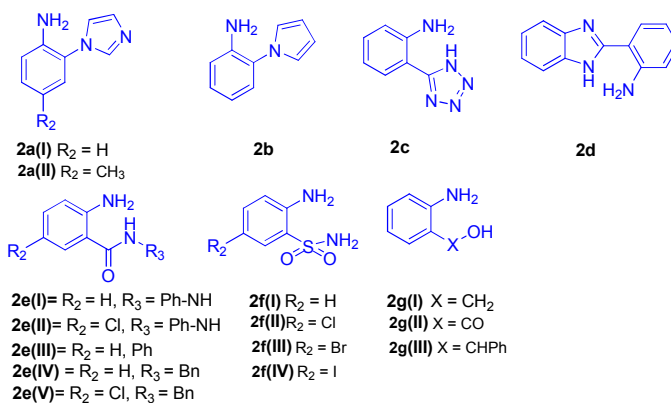
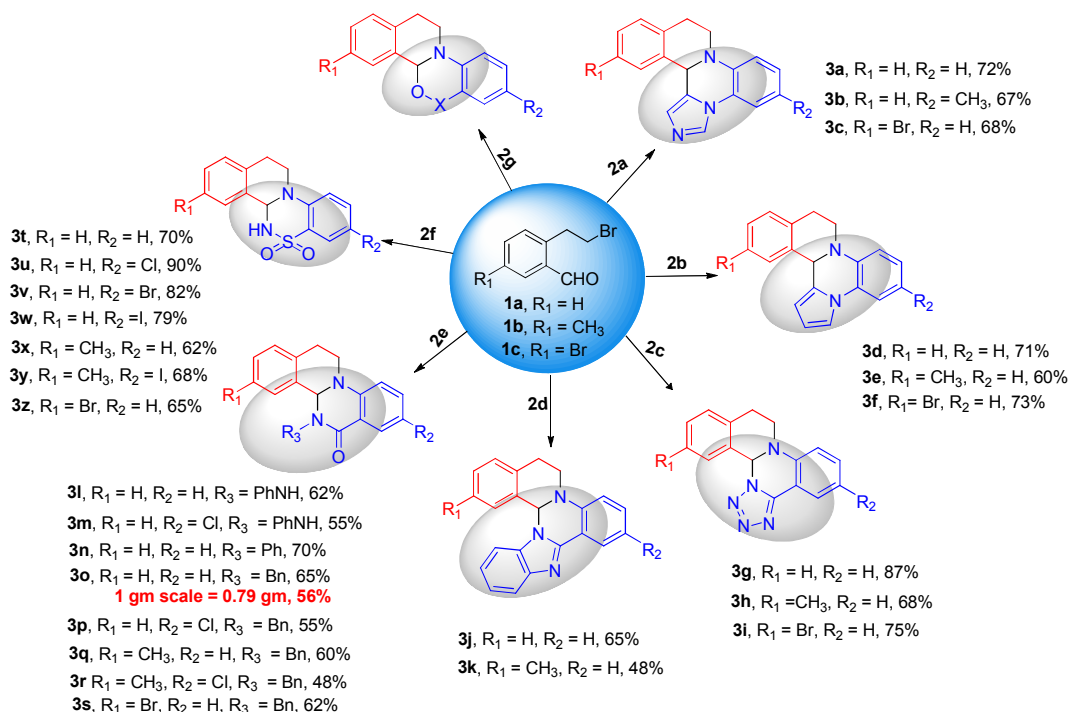
40 Encouraged by the results, we envisioned to explore the nucleophilicity of oxygen in our present
41
42 strategy, by treatment of 2-aminobenzyl alcohol **2g(I)** and 2-aminobenzoic acid **2g(II)** with **1a**, which
43
44 afforded **3aa** and **3ab** in 60 and 72% yields, respectively. Due to the ubiquity of THIQ based natural
45
46 products containing C1 stereocenter, many research groups have focused on the introduction of a
47
48 substituent at C1 position in a stereogenic fashion and also on natural products containing two contiguous
49
50 and 1,3 stereocenters. Our aim to introduce stereochemical diversity in our present strategy, prompted us
51
52 to examine the possibility of diastereoselectivity by employing the 1,3 stereocenter inducing SBAs. With
53
54 this idea in mind, we selected the phenyl substituted secondary alcohol **2g(III)** as *N,O*-1,5 bisnucleophile,
55
56 which afforded the expected product **3ac** although in low stereoselectivity (*cis/trans* = 4:3) as a mixture
57
58
59
60



3aa, X = CH₂, R₁ = H, R₂ = H, 60%

3ab, X = CO, R₁ = H, R₂ = H, 72%

3ac, X = CHPh, R₁ = H, R₂ = H, 52%, cis/trans = 4:3 dr^c



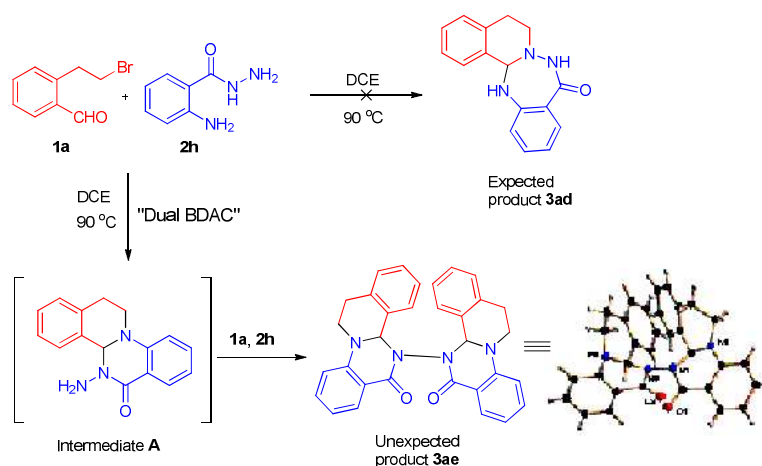
^a Reactions were performed in DCE (1mL) with **1** (0.23 mmol), **2** (0.23 mmol) at 90 °C for 30-60 min. ^b **2a-2g** represent various *N,C*-, *N,O*- and *N,N*-1,5-bisnucleophiles as SBAs. ^c dr was determined by ¹H NMR spectroscopy.

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 ^1H 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**).



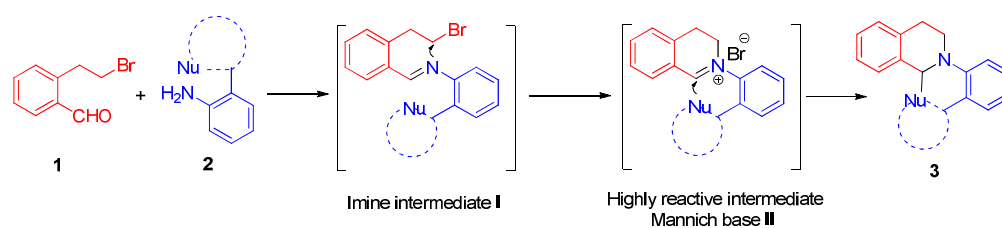
Further aiming to expand the diversity in the BDAC strategy, we envisioned that by using 2-aminobenzohydrazide (**2h**) as 1,6-bisnucleophile can result in 7-membered fused tetrahydrobenzotriazepino isoquinolinone skeleton. To our surprise, when we used 2-

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-Spengler¹³ 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

1
2
3 affords three dimensional THIQ derivatives which are diverse in its coverage of chemical space, should
4 prove useful for further scaffold innovation in drug discovery program. Further, studies on
5 enantioselective synthesis of these scaffolds are currently under way.
6
7
8

9
10 We gratefully acknowledge Council of Scientific and Industrial Research (CSIR), New Delhi, India
11 and Indian Institute of Technology Hyderabad (IITH) for financial support. AHS, SMP and SV thank to
12 UGC, New Delhi, India for the award of research fellowship.
13
14

15 16 **Experimental Section**

17 18 **General Considerations**

19
20 IR spectra were recorded on a FTIR spectrophotometer. ¹H NMR spectra were recorded on 400 MHz
21 spectrometer at 295 K in CDCl₃; chemical shifts (δ ppm) and coupling constants (Hz) are reported in
22 standard fashion with reference to either internal standard tetramethylsilane (TMS) ($\delta_{\text{H}} = 0.00$ ppm) or
23 CHCl₃ ($\delta_{\text{H}} = 7.25$ ppm). ¹³C NMR spectra were recorded on 100 MHz spectrometer at RT in CDCl₃;
24 chemical shifts (δ ppm) are reported relative to CHCl₃ [$\delta_{\text{C}} = 77.00$ ppm (central line of triplet)]. In the
25 1HNMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q =
26 quartet, qui = quintet, m = multiplet and br s. = broad singlet. The assignments of signals were confirmed
27 by ¹H, ¹³C CPD, and DEPT spectra. High-resolution mass spectra (HR-MS) were recorded using Q-TOF
28 multimode source. Melting points were determined on an electro thermal melting point apparatus and are
29 uncorrected. 2-(2-bromoethyl)benzaldehyde (**1a-1c**) were prepared by using known procedures. All the
30 bisnucleophiles such as *N,C*-, *N,O*- and *N,N*-1,5-bisnucleophiles as a SBAs (**2a-2h**) which were either
31 prepared in the laboratory or purchased from commercial sources. All the dry solvents such as, MeOH,
32 EtOH and 1,4-Dioxane were dried over sodium metal and CH₃CN, DCM and DCE were dried over
33 calcium hydride.
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50

51
52 All small scale dry reactions were carried out using standard syringe-septum technique. Reactions
53 were monitored by TLC on silica gel using a combination of petroleum ether and ethyl acetate as eluents.
54
55
56
57
58
59
60

1
2
3 Reactions were generally run under argon atmosphere. Solvents were distilled prior to use; petroleum
4 ether with a boiling range of 40 to 60 °C was used.

7
8 **(I) General Procedure 1: Preparation of isochromans.**³⁰

9
10 A mixture of the substituted phenylethyl alcohol (**i**) (4.97 mmol), chloromethylmethyl ether (7.046
11 mmol) and *N,N*-diisopropylethylamine (9.95 mmol) in dry dichloromethane (15 mL) was stirred under
12 nitrogen atmosphere for 2.5 h at rt. The reaction mixture was then washed with water, dried (Na₂SO₄) and
13 the solvent was removed in vacuo. The crude MOM acetal (**ii**) was dissolved in dried acetonitrile and
14 added to cooled (0 °C) solution of trimethylsilyl trifluoromethanesulfonate (TMSOTf) (4.97 mmol). The
15 reaction was carried out under nitrogen atmosphere for 3h. Then the mixture was quenched by the
16 addition of 1 M NaHCO₃. The organic phase was washed with brine, dried with anhydrous sodium
17 sulphate and evaporated under reduced pressure. Purification by column chromatography afforded
18 corresponding substituted isochromans (see ESI).
19
20
21
22
23
24
25
26
27
28
29

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

31
32 To a solution of the substituted isochroman **iii** (7.46 mmol) derivatives in acetonitrile (15 mL), CuBr₂
33 (8.95 mmol) was added under nitrogen atmosphere. The solution was refluxed for about 2h and then
34 cooled to room temperature. The reaction mixture was added water, extracted with ethyl acetate. The
35 combined organic extracts were washed with brine and dried with anhydrous Na₂SO₄, filtered and
36 concentrated and then purified by silica gel column chromatography to afford the products (**1a-1c**) in 68-
37 74% yield (see ESI).
38
39
40
41
42
43
44
45

46 **(III) General procedure 3: Synthesis of diverse scaffold containing fused tetrahydroisoquinolines**

47 **(3a-3ae) through BDAC strategy:** 2-(2-Bromoethyl)benzaldehydes (**1a-c**) (50 mg, 0.23 mmol) and
48 variety of bisnucleophiles **2** (0.23 mmol) were taken in a 5 mL round bottom flask and added 1 mL of
49 DCE heated at 90 °C. After completion of the reaction (monitored by TLC), the DCE solvent was
50 completely evaporated under reduced pressure. The reaction mixture was quenched by aq. NaHCO₃ and
51 extracted with ethyl acetate (2 × 20 mL). The combined organic layer was washed with brine solution and
52
53
54
55
56
57
58
59
60

1
2
3 allowed to dry over anhydrous Na₂SO₄. The crude extract was purified by filtration through a silica gel
4 (100-200 mesh) column using hexane and ethyl acetate as eluents to yield the desired product **3a-3ae**.
5
6

7
8 **(IV) General procedure 4: Large scale synthesis of isoquinolinoquinazolinone 3o through BDAC**
9 **strategy.**
10

11
12 2-(2-Bromoethyl)benzaldehyde (**1a**) (1000 mg, 4.69 mmol) and *N,N*-bisnucleophile **2e(IV)** (790 mg, 4.69
13 mmol) were taken in a 25 mL round bottom flask and added 10 mL of DCE heated at 90 °C. After
14 completion of the reaction (monitored by TLC), the DCE solvent was completely evaporated under
15 reduced pressure. The reaction mixture was quenched by aq. NaHCO₃ and extracted with ethyl acetate (2
16 × 20 mL). The combined organic layer was washed with brine solution and allowed to dry over
17 anhydrous Na₂SO₄. The crude extract was purified by filtration through a silica gel (100-200 mesh)
18 column using hexane and ethyl acetate as eluents to yield the desired product **3o** in 56%, 790 mg.
19
20
21
22
23
24
25
26
27

28 **Spectroscopic data of all unknown compounds: 7,11b-Dihydro-6H-imidazo-6H-imidazo[1,5-**
29 **a]isoquinolino[1,2-c]quinoxaline (3a):** Brown solid (46 mg, 72%); mp 198–200 °C; IR (MIR-ATR,
30 4000–600 cm⁻¹): ν_{\max} = 3112, 2923, 2854, 1710, 1600, 1507, 1462, 1351, 1109, 746, 653; ¹H NMR (400
31 MHz, CDCl₃) 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 =
32 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
33 (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); ¹³C NMR (100 MHz,
34 CDCl₃) 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,
35 131.5, 133.1, 133.9, 137.6; HR-MS (ESI⁺) *m/z* calculated for C₁₈H₁₆N₃⁺ = [M+H⁺]: 274.1339; found:
36 274.1326.
37
38
39
40
41
42
43
44
45
46
47
48

49 **2-Methyl-7,11b-dihydro-6H-imidazo[1,5-a]isoquinolino[1,2-c]quinoxaline (3b):** Brown solid (45 mg,
50 67%); mp 177–180 °C; IR (MIR-ATR, 4000–600 cm⁻¹): ν_{\max} = 3055, 2924, 2858, 1705, 1513, 1360, 816,
51 736, 651; ¹H NMR (400 MHz, CDCl₃) δ ppm = 2.32 (s, 3H), 2.82–2.87 (m, 1H), 3.19–3.24 (m, 1H),
52 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),
53
54
55
56
57
58
59
60

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 $\text{C}_{19}\text{H}_{18}\text{N}_3^+$ = $[\text{M}+\text{H}^+]$: 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}): $\nu_{\text{max}} = 3049, 2922, 1718, 1604, 1509, 1475, 1347, 1273, 813, 739, 651$; ^1H 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 $\text{C}_{18}\text{H}_{15}\text{BrN}_3^+ = [\text{M}+\text{H}^+]$: 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}): $\nu_{\text{max}} = 3052, 2902, 2829, 1506, 1337, 1288, 1221, 738, 701, 643$; ^1H 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 $\text{C}_{19}\text{H}_{17}\text{N}_2^+ = [\text{M}+\text{H}^+]$: 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}): $\nu_{\text{max}} = 3044, 2918, 2847, 1505, 1337, 1289, 1164, 741, 701, 610, 549$; ^1H 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,

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

CDCl₃) 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 C₂₀H₁₉N₂⁺ = [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 °C; IR (MIR-ATR, 4000–600 cm⁻¹): ν_{\max} = 3048, 2919, 2833, 1508, 1340, 1165, 741, 703, 657, 538; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₉H₁₆BrN₂⁺ = [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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₆H₁₄N₅⁺ = [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; ¹H NMR (400 MHz, CDCl₃) 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 $\text{C}_{17}\text{H}_{16}\text{N}_5^+ = [\text{M}+\text{H}^+]$: 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 °C; IR (MIR-ATR, 4000–600 cm^{-1}): $\nu_{\text{max}} = 1618, 1580, 1488, 1304, 1220, 1139, 816, 739$; ^1H 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 $\text{C}_{16}\text{H}_{13}\text{BrN}_5^+ = [\text{M}+\text{H}^+]$: 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 °C; IR (MIR-ATR, 4000–600 cm^{-1}): $\nu_{\text{max}} = 3054, 2921, 2851, 1613, 1479, 1449, 1226, 736, 642, 546$; ^1H 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 $\text{C}_{22}\text{H}_{18}\text{N}_3^+ = [\text{M}+\text{H}^+]$: 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 °C; IR (MIR-ATR, 4000–600 cm^{-1}): $\nu_{\text{max}} = 3049, 2920, 2851, 1613, 1479, 1267, 1218, 736, 699, 641, 543$; ^1H 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

1
2
3 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,
4
5 136.3, 143.7; HR-MS (ESI⁺) *m/z* calculated for C₂₃H₂₀N₃⁺ = [M+H⁺]: 338.1652; found: 338.1650.
6
7

8 **5-(Phenylamino)-12,13-dihydro-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one (3l):** White solid (50
9 mg, 62%); mp 196–198 °C; IR (MIR-ATR, 4000–600 cm⁻¹): ν_{\max} = 3260, 3032, 2922, 2853, 1655, 1599,
10 1472, 1267, 741, 697; ¹H NMR (400 MHz, CDCl₃) δ ppm = 2.75 (dd, J_a = 16.9 and J_b = 4.6, 1H),
11 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,
12 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),
13 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 =
14 1.5 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ ppm = 24.4, 44.8, 75.1, 113.6, 114.2, 117.2, 119.5, 121.8,
15 126.2, 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*
16 calculated for C₂₂H₂₀N₃O⁺ = [M+H⁺]: 342.1601; found: 342.1595.
17
18
19
20
21
22
23
24
25
26
27

28 **8-Chloro-5-(phenylamino)-12, 13-dihydro-4bH-isoquinolino[2, 1-a]quinazolin-6(5H)-one (3m):** White
29 solid (48 mg, 55%); mp 125–127 °C; IR (MIR-ATR, 4000–600 cm⁻¹): ν_{\max} = 3263, 2916, 2754, 1657,
30 1488, 1248, 1099, 900, 739, 691, 643, 591; ¹H NMR (400 MHz, CDCl₃) δ ppm = 2.74 (dd, J_a = 16.9 and
31 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,
32 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),
33 7.44 (br. s, 1H), 7.53 (d, J = 7.3 Hz, 1H), 7.86–7.87 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ ppm = 24.3,
34 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,
35 135.0, 146.1, 146.5, 162.1; HR-MS (ESI⁺) *m/z* calculated for C₂₂H₁₉ClN₃O⁺ = [M+H⁺]: 376.1211; found:
36 376.1204.
37
38
39
40
41
42
43
44
45
46
47

48 **5-Phenyl-12,13-dihydro-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one (3n):** White solid (54 mg, 70%);
49 mp 92–94 °C; IR (MIR-ATR, 4000–600 cm⁻¹): ν_{\max} = 3065, 1667, 1598, 1462, 1378, 1326, 1275, 755,
50 695, 662; ¹H NMR (400 MHz, CDCl₃) δ ppm = 2.83 (dd, J_a = 17.1 and J_b = 4.4, 1H), 3.26–3.29 (m, 1H),
51 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),
52 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),
53
54
55
56
57
58
59
60

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 $\text{C}_{22}\text{H}_{19}\text{N}_2\text{O}^+ = [\text{M}+\text{H}^+]$: 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}): $\nu_{\text{max}} = 3030, 2917, 1648, 1601, 1475, 1261, 744, 697$; ^1H 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 $\text{C}_{23}\text{H}_{21}\text{N}_2\text{O}^+ = [\text{M}+\text{H}^+]$: 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}): $\nu_{\text{max}} = 3062, 2920, 1652, 1476, 1259, 737, 699, 639$; ^1H 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 $\text{C}_{23}\text{H}_{20}\text{ClN}_2\text{O}^+ = [\text{M}+\text{H}^+]$: 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}): $\nu_{\text{max}} = 3032, 2917, 1647, 1603, 1476, 1384, 1264, 1169, 818, 738, 698$; ^1H 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–

1
2
3 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
4 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,
5
6
7 131.6, 133.4, 135.8, 137.3, 147.5, 163.5; HR-MS (ESI^+) m/z calculated for $\text{C}_{24}\text{H}_{23}\text{N}_2\text{O}^+ = [\text{M}+\text{H}^+]$:
8 355.1805; found: 355.1799.
9

10
11
12 **5-Benzyl-8-chloro-3-methyl-12,13-dihydro-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one (3r):** White
13 solid (41 mg, 48%); mp 152–155 °C; 48% yield; IR (MIR-ATR, 4000–600 cm^{-1}): $\nu_{\text{max}} = 2912, 2753,$
14
15 1649, 1454, 1255, 1103, 889, 809, 732, 698, 640, 589, 539; ^1H NMR (400 MHz, CDCl_3) δ ppm = 2.27 (s,
16
17 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,
18
19 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, $J = 12.2$
20
21 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, $J =$
22
23 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,
24
25 126.3, 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^+)
26
27 m/z calculated for $\text{C}_{24}\text{H}_{22}\text{ClN}_2\text{O}^+ = [\text{M}+\text{H}^+]$: 389.1415; found: 389.1408.
28
29
30
31

32
33 **5-Benzyl-3-bromo-12,13-dihydro-4bH-isoquinolino[2,1-a]quinazolin-6(5H)-one (3s):** White solid (43
34 mg, 62%); 128–130 °C; IR (MIR-ATR, 4000–600 cm^{-1}) $\nu_{\text{max}} = 3340, 3057, 2919, 1647, 1603, 1477, 1260,$
35
36 1167, 816, 734, 697, 629, 546; ^1H NMR (400 MHz, CDCl_3) δ ppm = 2.64 (dd, $J_a = 17.1$ and $J_b = 4.9$ Hz,
37
38 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 $J_b =$
39
40 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),
41
42 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,
43
44 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,
45
46 133.6, 136.9, 146.9, 163.1; HR-MS (ESI^+) m/z calculated for $\text{C}_{23}\text{H}_{20}\text{BrN}_2\text{O}^+ = [\text{M}+\text{H}^+]$: 419.0754; found:
47
48 419.0746.
49
50
51

52
53 **4b,5,12,13-Tetrahydrobenzo[5,6]thiadiazino[3,4-a]isoquinoline 6,6-dioxide (3t):** White solid (47 mg,
54 70%); mp 218–220 °C; 70% yield; IR (MIR-ATR, 4000–600 cm^{-1}): $\nu_{\text{max}} = 3231, 2922, 2853, 1597, 1481,$
55
56 1449, 1318, 1274, 1158, 748, 662, 610, 556; ^1H NMR (400 MHz, CDCl_3) δ ppm = 2.98–3.14 (m, 2H),
57
58
59
60

1
2
3 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, $J =$
4 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,
5 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, $J_a = 5.4$ and $J_b = 3.9$
6 1H), 7.78 (dd, $J_a = 7.8$ and $J_b = 1.5$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ ppm = 29.0, 43.8, 68.5,
7 116.1, 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
8 calculated for $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}_2\text{S}^+ = [\text{M}+\text{H}^+]$: 287.0849; found: 287.0845.
9
10
11
12
13
14
15

16
17 **8-Chloro-4b,5,12,13-tetrahydrobenzo[5,6][1,2,4]thiadiazino[3,4-*a*]isoquinoline 6,6-dioxide (3u)**: White
18 solid (69 mg, 90%); mp 198–200 °C; IR (MIR-ATR, 4000–600 cm^{-1}): $\nu_{\text{max}} = 3222, 3065, 2925, 2849,$
19 1597, 1478, 1322, 1160, 734, 666, 621, 554; ^1H NMR (400 MHz, CDCl_3) δ ppm = 3.0–3.1 (m, 2H), 3.46
20 (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, $J =$
21 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 $J_b =$
22 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,
23 124.3, 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
24 for $\text{C}_{15}\text{H}_{14}\text{ClN}_2\text{O}_2\text{S}^+ = [\text{M}+\text{H}^+]$: 321.0459; found: 321.0454.
25
26
27
28
29
30
31
32
33
34

35 **8-Bromo-4b,5,12,13-tetrahydrobenzo[5,6][1,2,4]thiadiazino[3,4-*a*]isoquinoline 6,6-dioxide (3v)**: White
36 solid (70 mg, 82%); mp 200–202 °C; IR (MIR-ATR, 4000–600 cm^{-1}): $\nu_{\text{max}} = 3411, 3027, 2837, 2720,$
37 2253, 2128, 1644, 1593, 1476, 1322, 1164, 1005, 820, 758, 617, 561; ^1H NMR (400 MHz, CDCl_3) δ ppm
38 = 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, $J = 12.7$
39 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),
40 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 =
41 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-
42 MS (ESI⁺) m/z calculated for $\text{C}_{15}\text{H}_{14}\text{BrN}_2\text{O}_2\text{S}^+ = [\text{M}+\text{H}^+]$: 364.9954; found: 364.9948.
43
44
45
46
47
48
49
50
51
52

53 **8-Iodo-4b,5,12,13-tetrahydrobenzo[5,6][1,2,4]thiadiazino[3,4-*a*]isoquinoline 6,6-dioxide (3w)**: White
54 solid (76 mg, 79%); mp 210–212 °C; IR (MIR-ATR, 4000–600 cm^{-1}): $\nu_{\text{max}} = 3419, 1649, 1402, 1175,$
55 1006, 821, 759, 618, 568; ^1H NMR (400 MHz, CDCl_3) δ ppm = 2.55–2.61 (m, 1H), 2.96–3.13 (m, 1H),
56
57
58
59
60

1
2
3 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
4 = 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 $J_b = 2$
5 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,
6 126.7, 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
7 $\text{C}_{15}\text{H}_{14}\text{IN}_2\text{O}_2\text{S}^+ = [\text{M}+\text{H}^+]$: 412.9815; found: 412.9809.
8
9

10
11
12
13
14 **3-Methyl-4b,5,12,13-tetrahydrobenzo[5,6][1,2,4]thiadiazino[3,4-*a*]isoquinoline 6,6-dioxide (3x):** White
15 solid (41 mg, 62%); mp 228–230 °C; IR (MIR-ATR, 4000–600 cm^{-1}): $\nu_{\text{max}} = 3205, 2918, 2851, 1715,$
16 $1594, 1450, 1319, 1156, 741, 664, 559$; ^1H NMR (400 MHz, CDCl_3) δ ppm = 2.36 (s, 3H), 2.96–3.04 (m,
17 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
18 = 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),
19 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,
20 116.1, 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
21 for $\text{C}_{16}\text{H}_{17}\text{N}_2\text{O}_2\text{S}^+ = [\text{M}+\text{H}^+]$: 301.1005; found: 301.1001.
22
23
24
25
26
27
28
29
30
31
32

33 **8-Iodo-3-methyl-4b,5,12,13-tetrahydrobenzo[5,6][1,2,4]thiadiazino[3,4-*a*]isoquinoline 6,6-dioxide (3y):**
34 White solid (64 mg, 68%); mp 218–220 °C; IR (MIR-ATR, 4000–600 cm^{-1}): $\nu_{\text{max}} = 3217, 2921, 2854,$
35 $1469, 1322, 1273, 1160, 929, 798, 730, 665$; ^1H NMR (400 MHz, CDCl_3) δ ppm = 2.36 (s, 3H), 2.92–
36 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,
37 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, $J_a = 8.8$
38 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,
39 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
40 calculated for $\text{C}_{16}\text{H}_{16}\text{IN}_2\text{O}_2\text{S}^+ = [\text{M}+\text{H}^+]$: 426.9972; found: 426.9962.
41
42
43
44
45
46
47
48
49
50

51 **3-Bromo-4b,5,12,13-tetrahydrobenzo[5,6][1,2,4]thiadiazino[3,4-*a*]isoquinoline 6,6-dioxide (3z):** White
52 solid (54 mg, 65%); mp 228–230 °C; IR (MIR-ATR, 4000–600 cm^{-1}): $\nu_{\text{max}} = 3213, 2924, 2852, 1706,$
53 $1598, 1478, 1319, 1161, 738, 548$; ^1H NMR (400 MHz, CDCl_3) δ ppm = 2.90–2.96 (m, 2H), 3.36 (ddd, J_a
54 = 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,
55
56
57
58
59
60

1
2
3 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);
4
5 ^{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,
6
7 131.9, 133.6, 133.9, 144.2; HR-MS (ESI⁺) m/z calculated for $\text{C}_{15}\text{H}_{14}\text{BrN}_2\text{O}_2\text{S}^+ = [\text{M}+\text{H}^+]$: 364.9954;
8
9 found: 364.9951.

10
11
12 **4b,6,12,13-Tetrahydrobenzo[4,5][1,3]oxazino[2,3-*a*]isoquinoline (3aa)**: White solid (33 mg, 60%); mp
13
14 115–117 °C; IR (MIR-ATR, 4000–600 cm^{-1}): $\nu_{\text{max}} = 3035, 2933, 2897, 2838, 1602, 1491, 1455, 1389,$
15
16 1287, 1228, 1193, 1154, 1056, 1029, 946, 749, 664; ^1H NMR (400 MHz, CDCl_3) δ ppm = 2.91 (dt, $J_a =$
17
18 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,
19
20 $J = 15.2$ 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),
21
22 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,
23
24 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
25
26 (ESI⁺) m/z calculated for $\text{C}_{16}\text{H}_{14}\text{N}^+ = [[\text{M}+\text{H}^+]-\text{H}_2\text{O}]$: 220.1120; found: 220.1113.

27
28
29
30
31 **12,13-Dihydrobenzo[4,5][1,3]oxazino[2,3-*a*]isoquinolin-6(4*b*H)-one (3ab)**: White solid (43 mg, 72%);
32
33 mp 115–117 °C; IR (MIR-ATR, 4000–600 cm^{-1}): $\nu_{\text{max}} = 1720, 1607, 1484, 1467, 1399, 1331, 1292, 1229,$
34
35 752; ^1H 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–
36
37 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,
38
39 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,
40
41 122.0, 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
42
43 for $\text{C}_{16}\text{H}_{14}\text{NO}_2^+ = [\text{M}+\text{H}^+]$: 252.1019; found: 252.1008.

44
45
46 **6-Phenyl-4b,6,12,13-tetrahydrobenzo[4,5][1,3]oxazino[2,3-*a*]isoquinoline (3ac)**: brown solid (35 mg,
47
48 52%); mp 60–62 °C ; IR (MIR-ATR, 4000–600 cm^{-1}): $\nu_{\text{max}} = 3029, 2925, 2834, 1659, 1601, 1487.44,$
49
50 1455, 1391, 1221, 1146, 939, 747, 699, 644; ^1H NMR (400 MHz, CDCl_3) δ ppm = 2.85–2.99 (m, 2H),
51
52 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,
53
54 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),
55
56 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 ,
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

HMBC, HSQC NMR (100 MHz, CDCl₃) δ ppm = 29.7 (t, -CH₂-), 29.9 (t, -CH₂-), 46.1 (t, -CH₂-), 47.0 (t, -CH₂-), 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; ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₃₂H₂₇N₄O₂⁺ = [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.

References

- 1) (a) Walsh, D. P.; Chang, Y. T. *Chem. Rev.* **2006**, *106*, 2476–2530. (b) Ahn, Y. H.; Chang, Y. T. *Acc. Chem. Res.* **2007**, *40*, 1025–1033. (c) Cragg G. M.; Grothaus P. G.; Newman, D. L. *Chem. Rev.* **2009**, *109*, 3012–3043. (d) Newman D. J.; Cragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461–477.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
- 2) (a) Zhou, L.; Li, Z.; Zou, Y.; Wang, Q.; Sanhueza, I. A.; Schoenebeck, F.; Goeke, A. *J. Am. Chem. Soc.* **2012**, *134*, 20009-20012. (b) Cruz, F. A.; Chen, Z.; Kurtoic, S. I.; Dong, V. *M. Chem. Commun.* **2016**, *52*, 5836-5839. (c) Jiao, Z. W.; Tu, Y. Q.; Zhang Q.; Liu, W.X.; Zhang, S. Y.; Wang, S. H.; Zhang, F. M.; Jiang, S. *Nat. Commun.* **2015**, doi: 10.1038/ncomms8332. (d) Bakthadoss, M.; Kannan, D.; Srinivasan, J.; Vinayagam, V. *Org. Biomol. Chem.* **2015**, *13*, 2870-2874. (e) Bakthadoss, M.; Kannan, D. *RSC Adv.* **2014**, *4*, 11723-11731. (f) Bakthadoss, M.; Devaraj, A.; Kannan, D. *Eur. J. Org. Chem.* **2014**, 1505-1513.
- 3) Teague, S. J.; Davis, A. M.; Leeson, P. D.; Oprea, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 3743-3748.
- 4) (a) Renner, S.; Otterlo, W. V.; Seoane, M. D.; Möcklinghoff, S.; Hofmann, B.; Wetzel, S.; Schuffenhauer, A.; Ertl, P.; Oprea, T. A.; Steinhilber, D.; Brunsveld, L.; Rauh, D.; Waldmann, H. *Nat. Chem. Biol.* **2009**, *5*, 585-592. (b) Burke, M. D.; Berger, E. M.; Schreiber, S. L. *Science* **2003**, *302*, 613-618. (c) Galloway W. R. J. D.; Spring, D. R. *Expert Opin Drug Discov.* **2009**, *4*, 467-472.
- 5) Schreiber, S. L.; *Science* **2000**, *287*, 1964-1969.
- 6) (a) Morton, D.; Leach, S.; Cordier, C.; Warriner, S.; Nelson, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 104-109. (b) Kumagai, N.; Muncipinto, G.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 3635-3638. (c) Burke, M. D.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 46-58. (d) O'Connor, C. J.; Beckmann, H. S.; Spring, D. R. *Chem. Soc. Rev.* **2012**, *41*, 4444-4456.
- 7) (a) Oguri H.; Schreiber, S.L. *Org. Lett.* **2005**, *7*, 47-50. (b) Wang, Z.; Castellano, S.; Kinderman, S. S.; Argueta, C. E.; Beshir, A. B.; Fenteany, G.; Kwon, O. *Chem. Eur. J.* **2011**, *17*, 649-654.
- 8) (a) Robbins, D.; Newton, A. F.; Gignoux, C.; Legeay, J. C.; Sinclair, A.; Rejzek, M.; Stockman, R. A. *Chem. Sci.* **2011**, *2*, 2232-2235. (b) Schreiber, S. L. *Nature* **2009**, *457*, 153-154

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
- 9) (a) Marcaurelle, L. A.; Comer, E.; Dandapani, S.; Duvall, J. R.; Gerard, B.; Kesavan, S.; Mulrooney, C. A. *J. Am. Chem. Soc.* **2010**, *132*, 16962–16976. (b) Morton, D.; Leach, S.; Cordier, C.; Warriner, S.; Nelson, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 104–109. (c) Kwon, O.; Park, S. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 13402–13404.
- 10) (a) Patil, N. T.; Mutyala, A. K.; Lakshmi, P. G.; Raju, P. V.; Sridhar, B. *Eur. J. Org. Chem.* **2010**, 1999–2007. (b) Kumar K.; Waldmann, H. *Angew. Chem. Int. Ed.* **2009**, *48*, 1740–1752.
- 11) (a) Patil, N. T.; Shinde, V. S.; Sridhar, B. *Angew. Chem. Int. Ed.* **2013**, *52*, 2251–2255. (b) Liu, W.; Khedkar, V.; Baskar, B.; Schürmann, M.; Kumar, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 6900–6905. (c) Garcia-Castro, M.; Kremer, L.; Reinkemeier, C. D.; Unkelbach, C.; Strohmman, C.; Ziegler, S.; Kumar, K. *Nat. Commun.* **2015**, doi: 10.1038/ncomms7516.
- 12) (a) Vidyacharan, S.; Murugan, A.; Sharada, D. S. *J. Org. Chem.*, **2016**, *81*, 2837–2848. (b) Vidyacharan, S.; Shinde, A. H.; Satpathi, B.; Sharada, D. S. *Green Chem.* **2014**, *16*, 1168–1175. (c) Vidyacharan, S.; Sagar, A.; Sharada, D. S. *Org. Biomol. Chem.* **2015**, *13*, 7614–7618. (d) Shinde, A. H.; Archith, N.; Malipatel, S.; Sharada, D. S. *Tetrahedron Lett.* **2014**, *55*, 6821–6826. (e) Shinde, A. H.; Vidyacharan, S.; Sharada, D. S. *Org. Biomol. Chem.* **2016**, *14*, 3207–3211. (f) Sagar, A.; Babu, V. N.; Sharada, D. S. *RSC Adv.* **2015**, *5*, 29066–29071. (g) Shinde, A. H.; Vidyacharan, S.; Sharada, D. S. *Tetrahedron Lett.* **2014**, *55*, 3064–3069.
- 13) Pictet, A.; Spengler, T. *Chem. Ber.* **1911**, *44*, 2030–2036.
- 14) Dhanasekaran, S.; Suneja, A.; Bisai, V.; Singh, V. K. *Org. Lett.* **2016**, *18*, 634–637.
- 15) Dhanasekaran, S.; Bisai, V.; Unhale, R. A.; Suneja, A.; Singh, V. K. *Org. Lett.* **2014**, *16*, 6068–6071.
- 16) Dhanasekaran, S.; Kayet, A.; Suneja, A.; Bisai, V.; Singh, V. K. *Org. Lett.* **2015**, *17*, 2780–2783.
- 17) (a) Hashimoto, T.; Kimura, H.; Kawamata, Y.; Maruoka, K. *Nat. Chem.* **2011**, *3*, 642–646. (b) Hashimoto, T.; Maeda, Y.; Omote, M.; Nakatsu, H.; Maruoka, K. *J. Am. Chem. Soc.*

- 1
2
3 **2010**, *132*, 4076–4077. (c) Hashimoto, T.; Omote, M.; Maruoka, K. *Angew. Chem. Int. Ed.*
4
5 **2011**, *50*, 3489–3492.
6
7
8 18) (a) Davis, F. A.; Mohanty, P. K.; Burns, D. M.; Andemichael, Y. W. *Org. Lett.* **2000**, *2*,
9 3901–3903. (b) Amat, M.; Elias, V.; Llor, N.; Subrizi, F.; Molins, E.; Bosch, J. *Eur. J. Org.*
10 *Chem.* **2010**, 4017–4026.
11
12
13
14 19) Itoh, T.; Miyazaki, M.; Fukuoka, H.; Nagata, K.; Ohsawa, A. *Org. Lett.* **2006**, *8*, 1295–1297.
15
16
17 20) Li, J. J.; Mei, T. S.; Yu, J. Q. *Angew. Chem.* **2008**, *120*, 6552–6555.
18
19
20 21) For selected CDC methods see: (a) Schweitzer-Chaput, B.; Klussmann, M. *Eur. J. Org.*
21 *Chem.* **2013**, *2013*, 666–671. (b) Ueda, H.; Yoshida, K.; Tokuyama, H. *Org. Lett.* **2014**, *16*,
22 4194–4197. (c) Baslé, O.; Li, C.-J. *Org. Lett.* **2008**, *10*, 3661–3663. (d) Dhineshkumar, J.;
23 Lamani, M.; Alagiri, K.; Prabhu, K. R. *Org. Lett.* **2013**, *15*, 1092–1095. (e) Alagiri, K.;
24 Devadig, P.; Prabhu, K. R. *Chem. Eur. J.* **2012**, *18*, 5160–5164. (f) Chen, Q.; Zhou, J.;
25 Wang, Y.; Wang, C.; Liu, X.; Xu, Z.; Lin, L.; Wang, R. *Org. Lett.* **2015**, *17*, 4212–4215. (g)
26 Huo, C.; Xie, H.; Wu, M.; Jia, X.; Wang, X.; Chen, F.; Tang, J. *Chem. Eur. J.* **2015**, *21*,
27 5723–5726.
28
29
30
31
32
33
34
35
36 22) (a) Zhang, C.; De, C. K.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2008**, *130*, 416–417. (b)
37 Murarka, S.; Zhang, C.; Konieczynska, M. D.; Seidel, D. *Org. Lett.* **2009**, *11*, 129–132. (c)
38 Murarka, S.; Deb, I.; Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2009**, *131*, 13226–13227.
39
40
41
42 23) (a) Aalla, S.; Gilla, G.; Bojja, Y.; Anumula, R. R.; Vummenthala, P. R.; Padi, P. R. *Org.*
43 *Process Res. Dev.* **2012**, *16*, 682–686. (b) Breschi, M. C.; Calderone, V.; Digiaco, M.;
44 Martelli, A.; Martinotti, E.; Minutolo, S. F.; Rapposelli, S.; Balsamo, A. *J. Med. Chem.*
45 **2004**, *47*, 5597–5600. (c) Jin, Y. C., Lee, Y. S., Kim, Y. M., Seo, H. G., Lee, J. H., Kim, H.
46 J.; Chang, K. C. *J. Pharmacol. Exp. Ther.* **2009**, *330*, 440–448. (d) Liu, W.; Liu, S.; Jin, R.;
47 Guo, H.; Zhao, J. *Org. Chem. Front.* **2015**, *2*, 288–299. (e) Wright, A. E.; Forleo, D. A.;
48 Gunawardana, G. P.; Gunasekera, S. P.; Koehn F. E.; McConnell, O. J. *J. Org. Chem.* **1990**,
49 *55*, 4508–4512. (f) Möcklinghoff, S.; Otterlo, W. V.; Rose, R.; Fuchs, S.; Zimmermann, T.
50
51
52
53
54
55
56
57
58
59
60

- 1
2
3 J.; Seoane, M. D.; Waldmann, H.; Ottmann, C.; Brunsveld, L. *J. Med. Chem.* **2011**, *54*, 2005-
4
5 2011.
6
7
8 24) Malamas, M. S.; Stange, H.; Schindler, R.; Lankau, H. J.; Grunwald, C.; Langen, B.; Fan, K.
9
10 *Y. Bioorg. Med. Chem. Lett.* **2012**, *22*, 5876–5884.
11
12 25) Sharma, M.; Pandey Snyder, D. S.; Tradtrantip, L.; Yao, C.; Kurth, M. J.; Verkman, A. S. *J.*
13
14 *Med. Chem.* **2011**, *54*, 5468–5477.
15
16 26) Yanagihara, Y.; Kasai, H.; Kawashima, T.; Shida, T. *Jpn. J. Pharmacol.* **1988**, *48*, 91–101.
17
18 27) (a) Sharma, M.; Pandey, S.; Chauhan, K.; Sharma, D.; Kumar, B.; Chauhan, P. M. *J. Org. Chem.*
19
20 **2012**, *77*, 929–937. (b) Ghosh, S. K.; Nagarajan, R. *RSC Adv.* **2016**, *6*, 27378-27387.
21
22
23 28) Phillips, D.; Sonnenberg, J.; Arai, A. C.; Vaswani, R.; Krutzik, P. O.; Kleisli, T.;
24
25 Chamberlin, A. R. *Bioorg. Med. Chem.* **2002**, *10*, 1229–1248.
26
27
28 29) (a) For iminium ion formation see: Yang, R.; Gao, Z.-F.; Zhao, J. Y.; Li, W.-B.; Zhou, L.;
29
30 Miao, F. *J. Agric. Food Chem.* **2015**, *63*, 1906-1914. (b) We have performed the reaction of
31
32 2-(2-bromoethyl)benzaldehyde (**1a**) with aniline under DCE solvent to give the 2-phenyl-
33
34 3,4-dihydroisoquinolin-2-ium bromide salt, which was characterised by the ¹H and ¹³C
35
36 NMR, thus supporting the proposed mechanism.
37
38
39 30) Zhou, M. Y.; Kong, S. S.; Zhang, L. Q.; Zhao, M.; Duan, J. A.; Ou-yang, Z.; Wang, M.
40
41 *Tetrahedron Lett.*, **2013**, *54*, 3962–3964.
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60