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# Base Promoted Three-Component Annulation of 4-Diazoisochroman-3-imines with Dimethylsulfonium Ylides: Synthesis of Highly Functionalized Isochromeno[4,3-*c*]pyridazines

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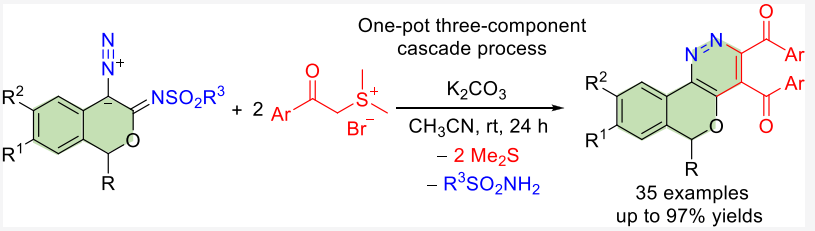


**ABSTRACT:** A novel method has been developed to synthesize a unique class of highly functionalized isochromeno[4,3-*c*]pyridazines. This reaction features an intermolecular functionalization of terminal nitrogen atom of diazo group of 4-diazoisochoman-3-imine with two dimethylsulfonium ylide components, followed by a base promoted 6-exo-trig cyclization step. Readily available starting materials, a broad substrate scope, and operationally simple, mild, and catalyst-free reaction conditions are the prominent features of this method.

## INTRODUCTION

Molecules containing pyridazine heterocycles have been in the limelight for the past two decades. They have numerous applications as chemo-luminescent materials,[1] photovoltaic materials,[2] ligands for heterogeneous catalysis,[3] nonlinear optical materials,[4] and in supramolecular chemistry.[5] Moreover, the pyridazine ring system has been considered as one of the best for drug design by GlaxoSmithKline, as incorporation of pyridazine ring into medically active drugs leads to the formation of new diazines having promising pharmacological activities.[6] Some examples of medicinally important pyridazine derivatives with various biological activities like anticancer, anti-inflammatory, anticonvulsant, antimicrobial, cytotoxic, and antifungal are shown in Figure 1.[7]

General methods for pyridazine ring construction includes annulation reactions between hydrazines and 1,4-dicarbonilic precursors,[8,9] functionalization of pyridazines via ortho metalation,[8,10] nucleophilic substitution,[8,11] or cross-coupling reactions (e.g., Sonogoshira, Stille, Suzuki reactions)[8,12] as well as a combination of cross-coupling and cyclization reactions.[8] Despite all of these methods, the immense importance of the pyridazine ring system demands the development of operationally simple and efficient approaches for their synthesis.

Diazo compounds are ambiphilic reagents intrinsically, as they possess an electrophilic terminal nitrogen atom and a nucleophilic carbon atom bonded to the diazo group.[13] In the past, research mainly focused on exploring the nucleophilic character of diazo compounds,[13] while the electrophilicity of their terminal nitrogen atom has been rarely explored.[13b,14] Considerable acquisition of Lewis basicity and electron density of terminal nitrogen atom of diazo compounds require highly reactive nucleophiles for their functionalization.[15] Dimethylsulfonium ylides have been highly ranked as strong nucleophilic reagents on Mayr's nucleophilicity scale.[16] In 2017−18, Doyle and co-workers demonstrated the nucleophilic addition of dimethylsulfonium ylides to electrophilic metal carbenes generated in situ from diazo-acetates/imides.[17] Recently, Xu's group reported a direct functionalization of the terminal nitrogen atom of $\alpha$-diazo-$\beta$-ketoesters/ketones by utilizing dimethylsulfonium ylides as nucleophiles under catalyst-free conditions (Scheme 1A).[18] This functionalization proceeds via the formation of zwitterionic intermediates, which are quite stable as compared to their azo-counterparts.[19]

We have been working on the chemistry of three different classes of stable cyclic diazo compounds, e.g., 3-diazoindolin-2-imines,[20a,b] 4-diazoisochroman-3-imines,[20c] and 4-diazoisoquinolin-3-ones,[20d] developed in our group. Previously, we utilized dimethylsulfoxonium ylides as active nucleophiles, which were added to electrophilic copper carbenes generated in situ from 3-diazoindolin-2-imines (Scheme 1B).[21] As a continuation of our

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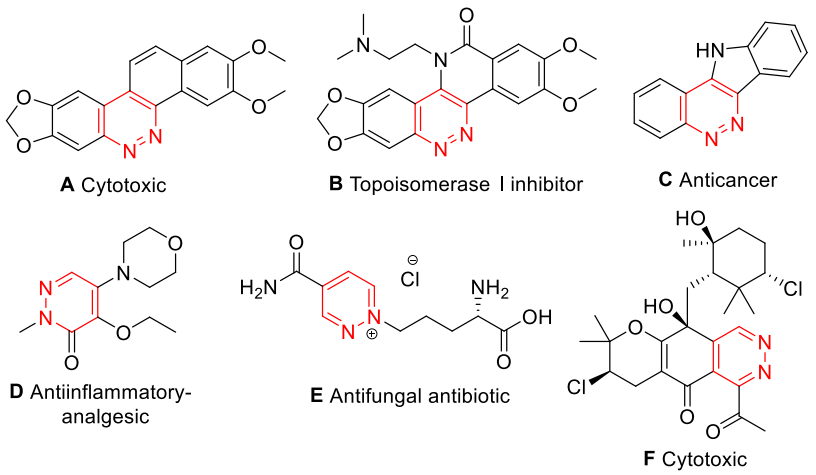
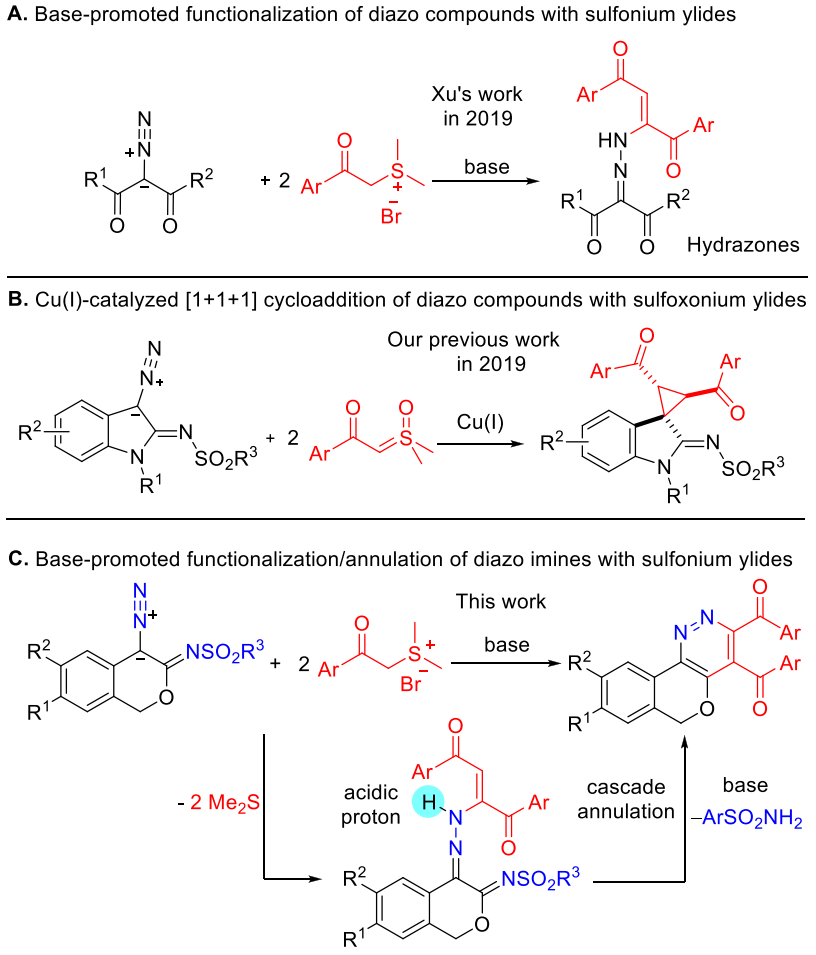



**Figure 1.** Biologically ative pyridazine derivatives.

**Scheme 1. Previous Work and Our Current Design**




works on diazo chemistry and inspired by the recent success of Xu and co-workers,[18] we envisioned that the functionalization of the terminal nitrogen atom of 4-diazoisochroman-3-imines with dimethylsulfonium ylides in the presence of a base would lead to the formation of hydrazones having a highly acidic proton (Scheme 1C). If an excess of base is present, removal of the acidic proton of hydrazone would generate a strong nucleophilic center, which would be added to the electrophilic carbon atom of 4-diazoisochroman-3-imines. Formation of a six-membered pyridazine ring and the presence of a good leaving group like tosyl at the electrophilic carbon atom of 4-diazoisochroman-3-imines should favor the cascade annulation step (Scheme 1C). The results of our successful effort in the catalyst-free environment are disclosed here.

## RESULTS AND DISCUSSION

To verify our hypothesis, 4-diazoisochroman-3-imines **1a** and 2-oxo-2-phenylethyl sulfonium bromide **2a** (dimethylsulfonium



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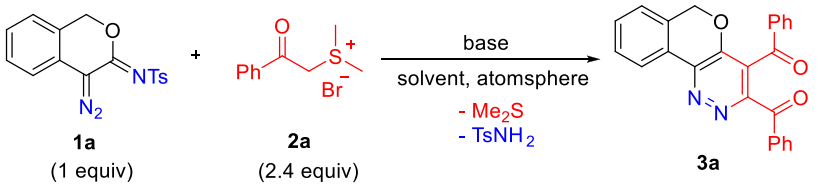
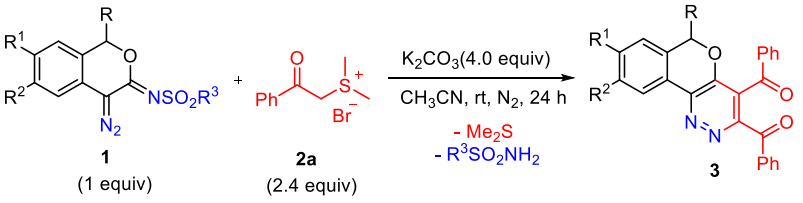
**Table 1. Optimization of Reaction Conditions**[a]

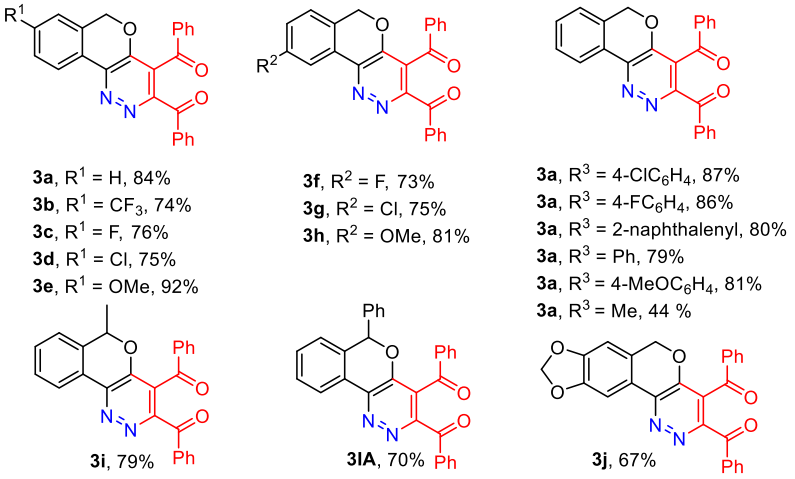



| entry | base (equiv) | solvent | temp (°C) | yield (%)[b] |
|---|---|---|---|---|
| 1[c] | $K_2CO_3$ (3.0) | $CH_3CN$ | rt | 46 |
| 2 | $K_2CO_3$ (3.0) | $CH_3CN$ | rt | 66 |
| 3 | $Na_2CO_3$ (3.0) | $CH_3CN$ | rt | ND |
| 4 | $K_3PO_4$ (3.0) | $CH_3CN$ | rt | 43 |
| 5 | $Et_3N$ (3.0) | $CH_3CN$ | rt | ND |
| 6 | DIPEA (3.0) | $CH_3CN$ | rt | ND |
| 7 | *t*-BuOK (3.0) | $CH_3CN$ | rt | 13 |
| 8[d] | none | $CH_3CN$ | rt | ND |
| 9 | $K_2CO_3$ (3.0) | DCE | rt | 8 |
| 10 | $K_2CO_3$ (3.0) | toluene | rt | 5 |
| 11 | $K_2CO_3$ (3.0) | THF | rt | 10 |
| 12 | $K_2CO_3$ (3.0) | DMSO | rt | 10 |
| 13 | $K_2CO_3$ (2.5) | $CH_3CN$ | rt | 51 |
| 14 | $K_2CO_3$ (3.5) | $CH_3CN$ | rt | 71 |
| 15 | $K_2CO_3$ (4.0) | $CH_3CN$ | rt | 82 |
| 16 | $K_2CO_3$ (4.5) | $CH_3CN$ | rt | 82 |
| 17 | $K_2CO_3$ (5.0) | $CH_3CN$ | rt | 71 |
| 18[e] | $K_2CO_3$ (4.0) | $CH_3CN$ | rt | 84 |
| 19[f] | $K_2CO_3$ (4.0) | $CH_3CN$ | rt | 46 |
| 20[e] | $Cs_2CO_3$ (4.0) | $CH_3CN$ | rt | trace |

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.24 mmol), 2 mL of solvent, $N_2$ atmosphere, 24 h reaction time. [b]Isolated yields. [c]Air atmosphere. [d]No base was used. [e]Dry acetonitrile was used. [f]Sulfonium bromide was replaced with corresponding sulfonium ylide, ND = not detected, rt = room temperature.

**Scheme 2. Substrate Scope of Diazo Compounds 1**




ylide precursor) were selected as model substrates. As our first trial, **1a** and **2a** were allowed to react in the presence of 3 equiv of potassium carbonate ($K_2CO_3$) base in acetonitrile solvent at room temperature under an air atmosphere (Table 1, entry 1). The color of the reaction mixture was instantly changed from yellow to purple, but a complex mixture formation was indicated



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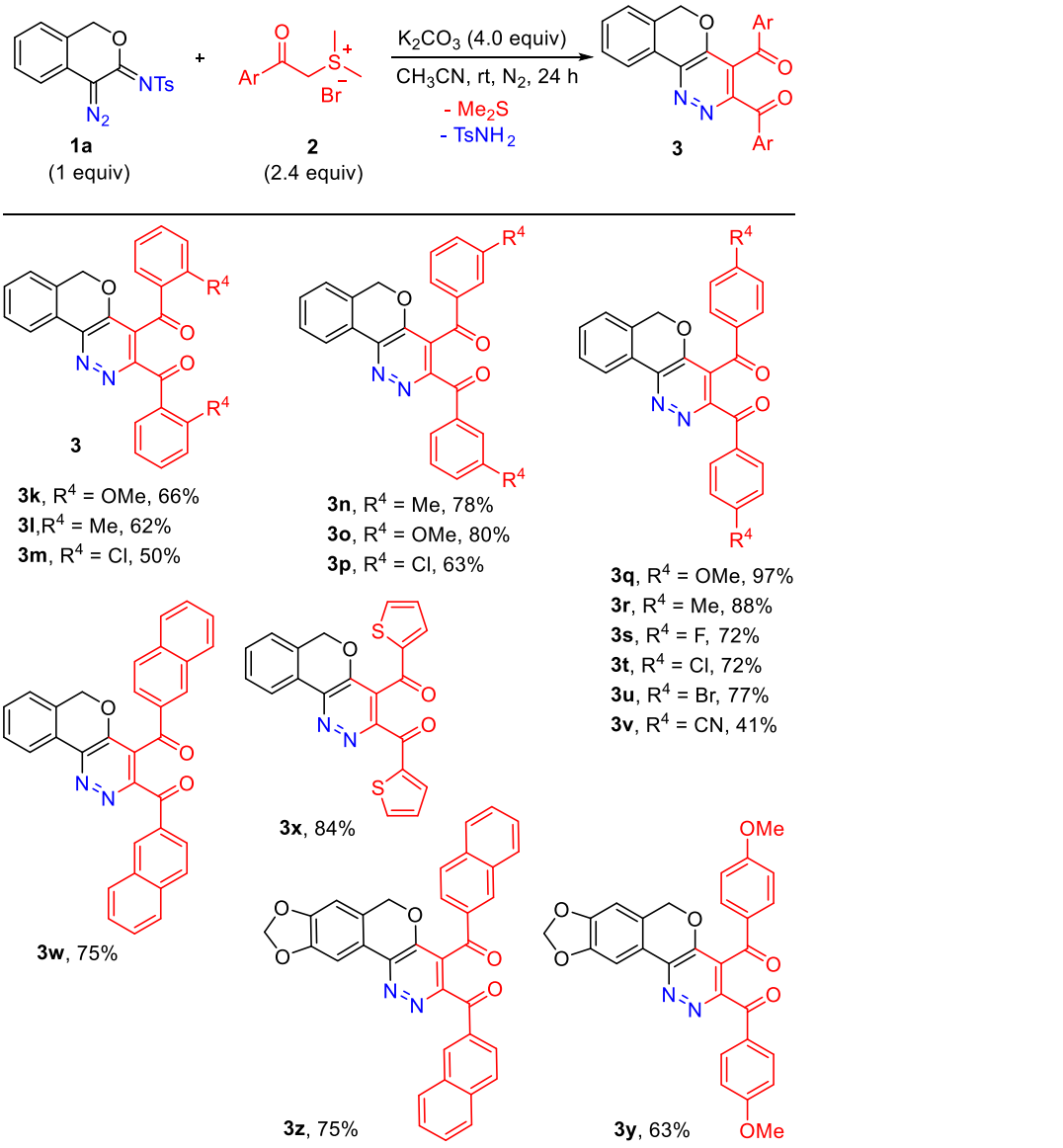
**Scheme 3. Substrate Scope of Sulfonium Salts 2**




by TLC analysis. As the reaction time was prolonged, the color of the reaction mixture was changed to deep red, and fortunately after 24 h, product **3a** was isolated in 46% yield. It is noteworthy that a hydrazone intermediate was not obtained or detected even by TLC after 24 h. The structure of **3a** was identified through HRMS, IR, and $^{1}H$ and $^{13}C$ NMR spectroscopic analysis and was later confirmed with X-ray single crystal analysis.[22] Delighted by this result, we focused on optimization of reaction conditions. While the reaction was performed under a nitrogen atmosphere, **3a** was isolated in an improved yield of 66% (Table 1, entry 2). When $K_2CO_3$ was replaced with other inorganic bases like $Na_2CO_3$ and $K_3PO_4$ under a $N_2$ atmosphere, the desired product **3a** was not observed with the former, while a lower yield was obtained with the latter (Table 1, entries 3 and 4). Tertiary amines $Et_3N$ and DIPEA were also employed as base, but only a trace amount of a visible yellow spot was detected by TLC while desired product **3a** was not detected (Table 1, entries 5 and 6). Potassium *tert*-butoxide gave a poor yield of **3a** with a complex mixture of inseparable side products, while there was no reaction when no base was used (Table 1, entries 7 and 8). $K_2CO_3$ turned out to be necessary and an ideal base for this reaction. Several other solvents like dichloroethane (DCE), toluene, tetrahydofuran (THF), and dimethyl sulfoxide (DMSO) were also screened, but a poor yield of **3a** was isolated in these cases (Table 1, entries 9−12). Once the base loading was decreased to 2.5 equiv, the yield decreased to 51% (Table 1, entry 13). Increasing the base loading from 3.5 equiv to 4.0 equiv improved the reaction, and **3a** was isolated in 71% and 82% yields, respectively (Table 1, entries 14 and 15). Further increasing the base loading to 4.5 equiv did not affect the reaction, while a further increment of base to 5.0 equiv dropped the yield of **3a** to 71% (Table 1, entries 16 and 17). When dried acetonitrile was used along with 4.0 equiv of base, a slight improvement in reaction was observed (Table 1, entry 18). While **2a** was replaced with its corresponding dimethylsulfonium ylide, the yield of **3a** was drastically decreased to 46% (Table 1, entry 19). This drop in yield suggested that a controlled and sequential supply of reactive sulfonium ylide is a key point in this transformation, as the yield was better using ylide precursor **2a**. When 4.0 equiv of $Cs_2CO_3$ were used to replace $K_2CO_3$, only a trace of the desired product was observed (Table 1, entry 20). Finally, optimal reaction conditions were established to be 4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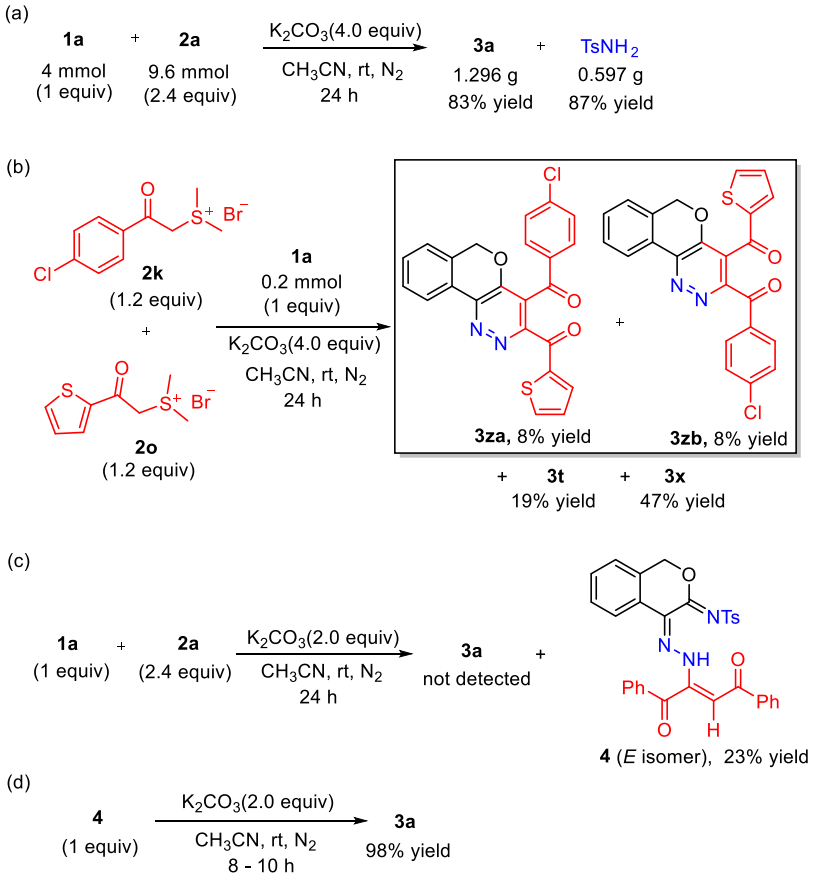
**Scheme 4. Gram Scale Reaction and Controlled Experiments**




equiv of $K_2CO_3$ base, dry acetonitrile solvent, 24 h of reaction time, a $N_2$ atmosphere, and room temperature (Table 1, entry 18).

After establishing the optimal reaction conditions, we focused on the substrate scope of 4-diazoisochroman-3-imines **1** (Scheme 2). The presence of electron-withdrawing groups like $CF_3$, F, and Cl at the 7 position of diazo compounds **1** slightly retarded the reaction, and the corresponding products **3b**−**3d** were isolated in 74−76% yields. The presence of an electron-donating group like $OCH_3$ at the 7 position gave the corresponding product **3e** in an excellent yield of 92%. A somewhat similar trend was observed for the substituents present at the 6 position of diazo compounds **1**, and corresponding products **3f**−**3h** were obtained in 73−81% yields. Substituent **R** at one position of diazo compound **3** could be a methyl or phenyl group, giving the corresponding products **3i** and **3IA** in 79% and 70% yields, respectively. When 6,7-dioxolo-4-diazoisochroman-3-imine **1j** was used for this transformation, the desired product **3j** was obtained in 67% yield. Diazo compounds **1** with various sulfonyl groups attached like 4-chlorobenzenesulfonyl, 4-fluorobenzenesulfonyl, 2-naphthalenesulfonyl, benzenesulfonyl,4-methoxybenzene-sulfonyl, and methylsulfonyl were also useful for these transformations. The highest yield of **3a** (87%) was obtained when diazo component **1k**, with a 4-chlorobenzenesulfonyl group attached, was used.

Subsequently the substrate scope of sulfonium ylides **2** was explored (Scheme 3). The presence of substituents at the *ortho* position of **2** had a significant effect on this reaction. When electron-donating groups like $OCH_3$ and $CH_3$ were present at the *ortho* position of **2**, the corresponding products **3k** and **3l** were isolated in 66% and 62% yields, respectively. Even a lower yield of product **3m** (50%) was obtained when an electron-withdrawing group (Cl) was present at the *ortho* position of **2**. The reaction was improved when both electron-donating and -withdrawing groups $CH_3$, $OCH_3$, and Cl were present at the meta position of **2**. Thus, the corresponding products **3n**−**3p** were isolated in 78%, 80%, and 63% yields, respectively. The presence of a substituent at the *para* position of **2** favored the formation of **3**. When electron-donating groups $OCH_3$ and $CH_3$ were present at the *para* position of **2**, the corresponding products **3q** and **3r** were obtained in excellent yields of 97% and 88%, respectively. The presence of halogens at the *para* position of **2** gave the desired products **3s**−**3u** in reasonable yields (72−77%). When a strong electron-withdrawing group like cyano was present at the *para* position of **2**, **3v** was obtained in a relatively lower yield of 41%. 2-Oxo-2-naphthalenylethyl sulfonium bromide **2n** and 2-oxo-2-thiophenylethyl sulfonium bromide **2o** were also feasible for these transformations to give corresponding products **3w** and **3x** in 75% and 84% yields, respectively. The reaction exhibited great potential when 6,7-dioxolo-4-diazoisochroman-3-imine **1j** was treated with 4-methoxy sulfonium bromide **2h** and 2-oxo-2-naphthalenylethyl sulfonium bromide **2n**. The corresponding products **3y** and **3z** were isolated in 63% and 75% yields, respectively. Aliphatic sulfonium salts like (2-methoxy-2-oxoethyl)- and (2-ethoxy-2-oxoethyl)-dimethylsulfonium bromides were also tried, but a very complex inseparable mixture formation was indicated by TLC even after 24 h.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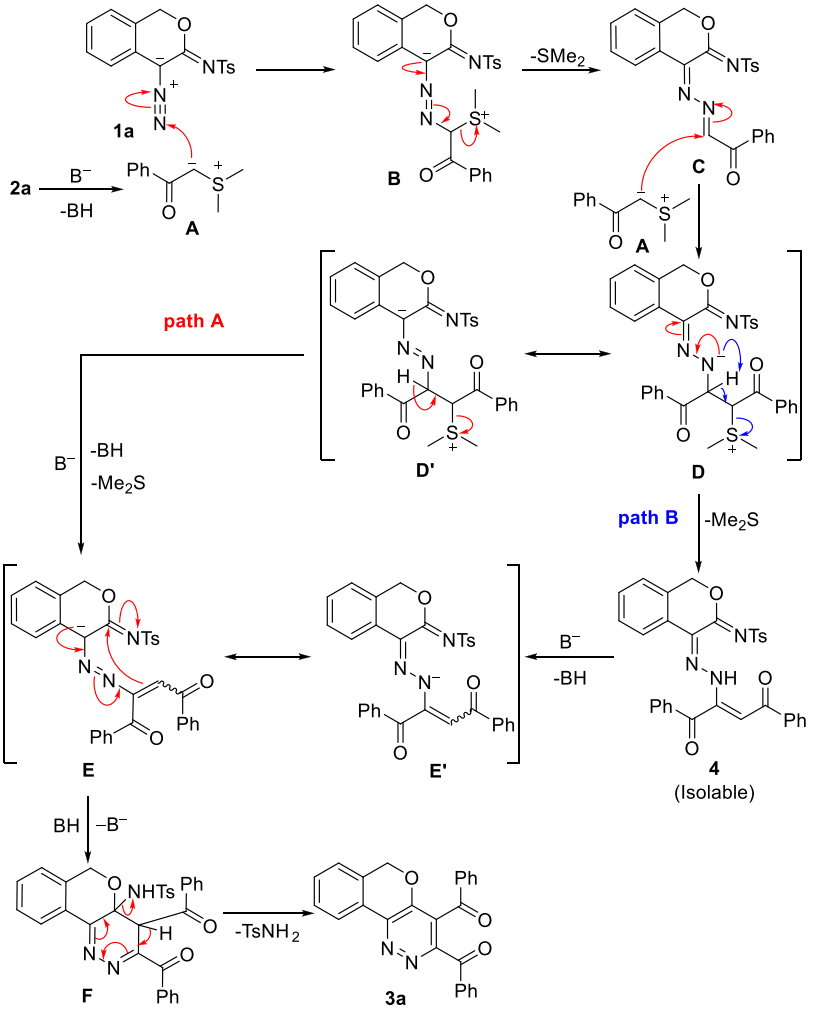
**Scheme 5. Plausible Mechanism**




A gram scale reaction of diazo compound **1a** and sulfonium bromide **2a** was performed to demonstrate the practicality of this method. Reaction of 4 mmol of **1a** with 9.6 mmol of **2a** under standard conditions gave 1.296 g of product **3a** (83%), while 0.597 g of tosyl amine (87%) was also obtained as side product (Scheme 4a). In order to verify the sequential addition of two molecules of sulfonium bromides **2** to diazo compounds **1**, a crossover experiment of **1a** with **2k** and **2o** was performed. Luckily, we isolated both the cross products **3za** and **3zb** in a 1:1 ratio along with usual products **3t** and **3x** (Scheme 4b). Furthermore, to confirm our hypothesis of in situ formation of a hydrazone intermediate, a controlled experiment was performed to isolate it. When we decreased the base loading to 2 equiv in the model reaction between **1a** and **2a**, hydrazone **4** was isolated in 23% yield as the *E* isomer (Scheme 4c).[23] It was surprising to observe that the product **3a** was not even detected by TLC by using 2 equiv of base for 24 h and only a trace amount of **3a** was detected when the reaction time was prolonged to 48 h (Scheme 4c).

Moreover, when **4** was treated with 2 equiv of $K_2CO_3$ for 8 to 10 h in acetonitrile at room temperature, **3a** was isolated in 98% yield (Scheme 4d). This conversion suggests that hydrazone **4** should be the reaction intermediate generated in situ during the formation of **3**.

Based on our controlled experiments and literature report,[18] the following mechanism is proposed for the formation of **3a** and **4** (Scheme 5). First, dimethylsulfonium ylide **A** is generated from **2a** in the presence of a base. Then the nucleophilic addition of ylidic carbon to the electrophilic terminal nitrogen atom of **1a** leads to the formation of zwitter ionic intermediate **B**. Removal of dimethyl sulfide from **B** leads to the formation of **C**, which possesses a less sterically hindered aldimine moiety. The nucleophilic carbon of second molecule of ylide **A** adds to this aldimine carbon atom of **C** to form intermediate **D** with resonance structure **D′**. In the presence of an excess of base (Scheme 5, path A), **D′** undergoes an elimination to form **E** with the release of dimethyl sulfide. Subsequently, **E** undergoes a *6-exo-trig* cyclization to form intermediate **F**, which gives the final product **3a** by elimination of tosylamine. Alternatively (Scheme 5, path B), enamine **4** is generated from **D** through elimination of dimethyl sulfide and can be isolated if only 2 equiv of base are used. Excess base can promote the transformation of **4** to **3a** via intermediate **E** or its resonance structure **E′**.

In conclusion we have developed an efficient method to synthesize a novel class of highly functionalized isochromeno-[4,3-*c*]pyridazines through direct functionalization and cascade annulation of 4-diazoisochroman-3-imines with sulfonium salts. This reaction comprises a nucleophilic dimerization of in situ generated dimethylsulfonium ylides with diazo compounds, followed by a base promoted *6-exo-trig* cyclization/aromatization cascade process. Ease of preparation of starting materials, a broad substrate scope, and operationally simple and mild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reaction conditions in a catalyst-free environment are the merits of this reaction. As the isochroman and pyridazine ring system is an extensive part of biologically active compounds, these newly synthesized isochromeno[4,3-*c*]pyridazines may find their applications in medicinal chemistry in future.

## EXPERIMENTAL SECTION

**General Information.** Unless otherwise mentioned, all reactions were carried out under a nitrogen atmosphere. Solvents and reagents were purchased from commercial sources and used as received. Acetonitrile was distilled over sodium. Melting points were measured with a micro melting point apparatus. NMR spectra were obtained at 400 or 600 MHz for $^{1}$H NMR and 100 or 150 MHz for $^{13}$C NMR. $^{1}$H NMR chemical shifts were quoted in parts per million (ppm) referenced to 0.0 ppm for tetramethylsilane. $^{13}C\{^{1}H\}$ NMR spectra were obtained by using the same NMR spectrometers, and chemical shifts were reported in ppm referenced to the center line of a triplet at 77.00 ppm of $CDCl_3$. The following abbreviations are used to describe peak patterns as appropriate: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doblets, td = triplet of doublets, ddd = doublet of doublet of doublets, dt = doublet of triplets. Coupling constants *J* were reported in hertz (Hz). All high-resolution mass spectra (HRMS) data were recorded by using an ESI ionization on Quadrupole Time-of-Flight (Q-TOF) mass spectrometer. Flash column chromatography was performed employing 300−400 mesh silica gel. Thin layer chromatography (TLC) was performed on silica gel HSGF254.

Diazo compounds **1** were synthesized according to our published procedure.[20c] Sulfonium salts **2** were prepared according to the known procedure.[24]

**General Procedure for the Preparation of Compounds 3.** To an oven-dried Schlenk tube equipped with a magnetic stirrer bar were added 4-diazoisochroman-3-imine **1** (0.10 mmol), dimethyl (2-oxo-2-phenylethyl)sulfonium bromide **2** (0.24 mmol), and $K_2CO_3$ (0.40 mmol). The Schlenk tube was evacuated and backfilled with nitrogen three times. Freshly distilled acetonitrile (2.0 mL) was added to the Schlenk tube in the continuous flow of nitrogen. The resulting mixture was stirred vigorously at room temperature for 24 h. Diazo compound **1** was consumed completely, and a sole major product was indicated by TLC. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (petroleum ether (PE)/ethyl acetate (EA) = 6:1−3:1, v/v) to give pure products **3** as whitish solids.

**Preparation of Compound 3a at 4 mmol Scale (Gram Scale).** To an oven-dried 100 mL Schlenk tube equipped with a magnetic stirrer bar were added 4-diazoisochroman-3-imine **1a** (1.308 g, 4 mmol), dimethyl(2-oxo-2-phenylethyl)sulfonium bromide **2a** (2.507 g, 9.6 mmol), and $K_2CO_3$ (2.211 g, 16 mmol). The Schlenk tube was evacuated and backfilled with nitrogen three times. Freshly distilled acetonitrile (60 mL) was added to the Schlenk tube in the continuous flow of nitrogen. The resulting mixture was stirred vigorously at room temperature for 24 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (PE/EA = 3:1, v/v) to give pure products **3a**. Tosyl amine was also isolated as a side product.

**Procedure of the Cross over Controlled Experiment.** To an oven-dried Schlenk tube equipped with a magnetic stirrer bar were added 4-diazoisochroman-3-imines **1a** (0.20 mmol) and 1.2 equiv each of sulfonium bromide **2k** (0.24 mmol) and **2o** (0.24 mmol). A 4 equiv amount of $K_2CO_3$ (0.80 mmol) was added, and the Schlenk tube was evacuated and backfilled with nitrogen three times. Freshly distilled acetonitrile (3.0 mL) was added to the Schlenk tube in the continuous flow of nitrogen. The resulting mixture was stirred vigorously at room temperature for 24 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (PE/EA = 15:1−10:1, v/v) to give two cross products **3za** and **3zb** in a 1:1 ratio along with usual products **3t** and **3x**.

**Procedure for the Preparation of Hydrazone 4.** To an oven-dried Schlenk tube equipped with a magnetic stirrer bar were added 4-diazoisochroman-3-imine **1a** (0.20 mmol), dimethyl(2-oxo-2-phenylethyl)sulfonium bromide **2a** (0.48 mmol), and $K_2CO_3$ (0.40 mmol). The Schlenk tube was evacuated and backfilled with nitrogen three times. Freshly distilled acetonitrile (3.0 mL) was added to the Schlenk tube in the continuous flow of nitrogen. The resulting mixture was stirred vigorously at room temperature for 24 h. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel (PE/EA = 3:1, v/v) to give pure products **4** as a yellow solid.

*(6H-Isochromeno[4,3-c]pyridazine-3,4-diyl)bis(phenylmethanone) (**3a**).* White solid; $R_f$ = 0.20 (PE/EA = 5:1); Yield: 33 mg, 84%; Mp 202−205 °C; $^{1}$H NMR (600 MHz, $CDCl_3$) $\delta$ 8.62 (d, *J* = 7.2 Hz,1H), 8.15 (d, *J* = 7.8 Hz, 2H), 7.87 (d, *J* = 7.2 Hz, 2H), 7.62−7.59 (m, 2H), 7.54 (t, *J* = 7.2 Hz, 2H), 7.47−7.47 (m, 4H), 7.14 (d, *J* = 7.2 Hz, 1H), 5.33 (s, 2H); $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 191.7, 191.0, 155.9, 151.1, 146.7, 136.4, 135.4, 134.0, 133.7, 132.2, 131.7, 131.4, 129.5, 129.0, 128.8, 128.3, 127.0, 126.0, 124.5, 68.8; IR (film, $cm^{-1}$):3062, 2929, 2865, 1681, 1667, 1597, 1522, 1449, 1408, 1363, 1297, 1266, 1181, 1079, 951, 863, 761; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{16}N_2NaO_3$ 415.1053; Found 415.1050.

*(8-(Trifluoromethyl)-6H-isochromeno[4,3-c]pyridazine-3,4-diyl)bis(phenylmethanone) (**3b**).* White solid; $R_f$ = 0.33 (PE/EA = 6:1); Yield: 34.1 mg, 74%; Mp 193−195 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.75 (d, *J* = 8.4 Hz, 1H), 8.14 (dd, *J* = 8.4 Hz, 1.2 Hz, 2H), 7.87−7.82 (m, 3H), 7.65−7.61 (m, 2H), 7.51−7.49 (m, 4H), 7.43 (s, 1H), 5.39 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 191.2, 190.7, 156.5, 151.4, 145.5, 136.2, 135.2, 134.2, 133.9, 133.8, 133.7 (q, $CF_3$, $^{2}J_{C-F}$ = 32.9 Hz), 132.1, 131.3, 128.99, 128.91, 128.3, 126.4 (q, $CF_3$, $^{3}J_{C-F}$ = 3.6 Hz), 125.0, 123.4 (q, $CF_3$, $^{1}J_{C-F}$ = 270.1 Hz), 121.7 (q, $CF_3$, $^{3}J_{C-F}$ = 3.7 Hz), 68.4; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ − 63.14 (s, 3F); IR (film, $cm^{-1}$): 3063, 2942, 2873, 1675, 1669, 1597, 1520, 1450, 1401, 1331, 1293, 1171, 1128, 1083, 955, 864, 779, 694; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{26}H_{16}F_3N_2O_3$ 461.1108; Found 461.1107.

*(8-Fluoro-6H-isochromeno[4,3-c]pyridazine-3,4-diyl)bis(phenylmethanone) (**3c**).* White solid; $R_f$ = 0.24 (PE/EA = 6:1); Yield: 31.2 mg, 76%; Mp 202−205 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.65−8.61 (m, 1H), 8.14 (dd, *J* = 8.4 Hz, 1.2 Hz, 2H), 7.87 (dd, *J* = 8.4 Hz, 1.2 Hz, 2H), 7.61 (td, *J* = 7.2 Hz, 1.6 Hz, 2H), 7.51−7.46 (m, 4H), 7.27−7.25 (m, 1H), 6.88 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 5.30 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 191.5, 190.8, 165.1 (d, C−F, $^{1}J_{C-F}$ = 253.0 Hz), 155.9, 150.5, 146.0, 136.3, 135.3, 134.2 (d, C−F, $^{3}J_{C-F}$ = 8.2 Hz), 134.0, 133.7, 131.4, 128.9, 128.8, 128.3, 127.2, 127.1, 127.0, 122.3 (d, C−F, $^{4}J_{C-F}$ = 3.1 Hz), 117.0 (d, C−F, $^{2}J_{C-F}$ = 22.0 Hz), 111.7 (d, C−F, $^{2}J_{C-F}$ = 23.3 Hz), 68.3 (d, C−F, $^{4}J_{C-F}$ = 2.2 Hz); $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ −105.81 to −105.87 (m); IR (film, $cm^{-1}$): 3067, 2933, 1675, 1659, 1595, 1449, 1368, 1268, 1208, 1109, 985, 924, 863, 719; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{16}FN_2O_3$ 411.1139; Found 411.1141.

*(8-Chloro-6H-isochromeno[4,3-c]pyridazine-3,4-diyl)bis(phenylmethanone) (**3d**).* White solid; $R_f$ = 0.31 (PE/EA = 6:1); Yield: 32 mg, 75%; Mp 213−215 °C; $^{1}$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.56 (d, *J* = 8.4 Hz, 1H), 8.13 (dd, *J* = 8.4 Hz, 1.2 Hz, 2H), 7.86 (dd, *J* = 8.4 Hz, 1.2 Hz, 2H), 7.62 (td, *J* = 7.6 Hz, 1.6 Hz, 2H), 7.53 (dd, *J* = 8.4 Hz, 2.0 Hz, 1H), 7.51−7.46 (m, 4H), 7.16 (d, *J* = 2.0 Hz, 1H), 5.29 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 191.5, 190.8, 156.0, 150.8, 146.0, 138.5, 136.3, 135.3, 134.1, 133.8, 133.2, 131.3, 129.9, 128.9, 128.8, 128.3, 127.1, 125.9, 124.7, 124.6, 68.2; IR (film, $cm^{-1}$): 3067, 2920, 2843, 1678, 1662, 1597, 1448, 1364, 1292, 1198, 1091, 978, 863, 778; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{25}H_{16}ClN_2O_3$ 427.0844; Found 427.0845.

*(8-Methoxy-6H-isochromeno[4,3-c]pyridazine-3,4-diyl)bis(phenylmethanone) (**3e**).* White solid; $R_f$ = 0.28 (PE/EA = 3:1); Yield: 39 mg, 92%; Mp 213−216 °C; $^{1}$H NMR (600 MHz, $CDCl_3$) $\delta$ 8.55 (d, *J* = 9.0 Hz, 1H), 8.15 (dd, *J* = 8.4 Hz, 1.8 Hz, 2H), 7.86 (dd, *J* = 8.4 Hz, 1.2 Hz, 2H), 7.61−7.58 (m, 2H), 7.48−7.45 (m, 4H), 7.06 (dd, *J* = 9.0 Hz, 2.4 Hz, 1H), 6.62 (d, *J* = 2.4 Hz, 1H), 5.27 (s, 2H), 3.87 (s, 3H). $^{13}C\{^{1}H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 191.8, 190.9, 162.9, 155.2, 150.1, 146.7, 136.5, 135.5, 133.8, 133.7, 133.5, 131.4, 128.9, 128.8, 128.2, 126.60, 126.56, 118.6, 115.3, 109.6, 68.7, 55.6; IR (film, $cm^{-1}$): 3058, 2938, 2843, 1679, 1659, 1611, 1515, 1449, 1398, 1367, 1212, 1157,


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1029, 958, 864, 721, 694; HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{26}H_{19}N_2O_4$ 423.1339; Found 423.1342.

*(9-Fluoro-6H-isochromeno[4,3-c]pyridazine-3,4-diyl)bis(phenylmethanone) (**3f**).* White solid; $R_f$ = 0.23 (PE/EA = 6:1); Yield: 30 mg, 73%; Mp 208−210 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.31 (dd, $J$ = 9.0 Hz, 2.4 Hz, 1H), 8.13 (dd, $J$ = 8.0 Hz, 1.2 Hz, 2H), 7.86 (dd, $J$ = 8.4 Hz, 1.2 Hz, 2H), 7.64−7.60 (m, 2H), 7.45 (t, $J$ = 7.6 Hz, 4H), 7.23 (dd, $J$ = 8.4 Hz, 2.8 Hz, 1H), 7.16−7.13 (m, 1H), 5.31 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 191.5, 190.8, 163.3 (d, C−F, $^1J_{C-F}$ = 247.0 Hz), 145.9 (d, C−F, $^4J_{C-F}$ = 2.9 Hz), 136.3, 135.2, 134.1, 133.8, 131.3, 128.9, 128.8, 128.3, 128.2, 128.1, 127.3 (d, C−F, $^4J_{C-F}$ = 3.3 Hz), 127.2, 126.5 (d, C−F, $^3J_{C-F}$ = 8.1 Hz), 119.3 (d, C−F, $^2J_{C-F}$ = 22.6 Hz), 111.3 (d, C−F, $^2J_{C-F}$ = 24.0 Hz), 68.5; $^{19}$F NMR (376 MHz, $CDCl_3$) $\delta$ − 110.40 to −110.46 (m); IR (film, $cm^{-1}$): 3062, 2916, 2843, 1685, 1669, 1595, 1449, 1356, 1266, 1175, 1087, 988, 876, 772, 716, 690; HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{25}H_{16}FN_2O_3$ 411.1139; Found 411.1138.

*(9-Chloro-6H-isochromeno[4,3-c]pyridazine-3,4-diyl)bis(phenylmethanone) (**3g**).* White solid; $R_f$ = 0.27 (PE/EA = 6:1); Yield: 32 mg, 75%; Mp 256−258 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.61 (d, $J$ = 2.0 Hz, 1H), 8.14 (dd, $J$ = 8.4 Hz, 1.2 Hz, 2H), 7.86 (dd, $J$ = 8.4 Hz, 1.2 Hz, 2H), 7.62 (td, $J$ = 6.8 Hz, 1.2 Hz, 2H), 7.52−7.47 (m, 5H), 7.10 (d, $J$ = 8.4 Hz, 1H) 5.30 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 191.4, 190.8, 156.2, 151.1, 145.8, 136.3, 135.8, 135.2, 134.1, 133.8, 132.1, 131.4, 129.8, 128.9, 128.8, 128.3, 127.6, 127.2, 125.9, 124.4, 68.4; IR (film, $cm^{-1}$): 3054, 2920, 2856, 1685, 1669, 1597, 1522, 1457, 1408, 1350, 1286, 1159, 1090, 962, 876, 739, 691; HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{25}H_{16}ClN_2O_3$ 427.0844; Found 427.0842.

*(9-Methoxy-6H-isochromeno[4,3-c]pyridazine-3,4-diyl)bis(phenylmethanone) (**3h**).* White solid; $R_f$ = 0.20 (PE/EA = 3:1); Yield: 34.2 mg, 81%; Mp 222−224 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.17−8.13 (m, 3H), 7.87 (dd, $J$ = 8.4 Hz, 1.6 Hz, 2H), 7.61 (td, $J$ = 7.6 Hz, 1.2 Hz, 2H), 7.51−7.46 (m 4H), 7.11−7.04 (m, 2H), 5.29 (s, 2H), 3.93 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 191.8, 190.9, 160.5, 155.9, 151.2, 146.6, 136.4, 135.3, 133.9, 133.7, 131.4, 128.9, 128.8, 128.3, 127.1, 127.0, 125.6, 123.9, 120.0, 107.4, 68.7, 55.7; IR (film, $cm^{-1}$): 3066, 2951, 2843, 1686, 1666, 1596, 1457, 1354, 1206, 1175, 1053, 963, 894, 741; HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{26}H_{19}N_2O_4$ 423.1339; Found 423.1341.

*(6-Methyl-6H-isochromeno[4,3-c]pyridazine-3,4-diyl)bis(phenylmethanone)(**3i**).* White solid; $R_f$ = 0.20 (PE/EA = 6:1); Yield: 32.2 mg, 79%; Mp 165−167 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 8.65−8.63 (m, 1H), 8.16 (dd, $J$ = 7.2 Hz, 1.2 Hz, 2H), 7.87 (dd, $J$ = 8.4 Hz, 1.2 Hz, 2H), 7.62−7.59 (m, 2H), 7.55−7.53 (m, 2H), 7.49−7.46 (m, 4H), 7.15−7.13 (m, 1H), 5.50 (q, $J$ = 7.2 Hz, 1H), 1.49 (d, $J$ = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 191.8, 191.1, 155.9, 149.9, 146.5, 136.7, 136.5, 135.5, 133.9, 133.6, 132.1, 131.4, 129.2, 128.9, 128.7, 128.2, 127.5, 125.0, 124.5, 124.4, 75.8, 22.9; IR (film, $cm^{-1}$): 3064, 2979, 1667, 1597, 1449, 1404, 1354, 1291, 1256, 1180, 1079, 960, 906, 856, 733; HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{26}H_{19}N_2O_3$ 407.1390; Found 407.1389.

*(6-Phenyl-6H-isochromeno[4,3-c]pyridazine-3,4-diyl)bis(phenylmethanone) (**3IA**).* Light green solid, $R_f$ = 0.27 (PE/EA = 6:1); Yield: 33 mg, 70%; Mp 115−117 °C $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.74 (d, $J$ = 7.6 Hz, 1H), 8.12 (dd, $J$ = 7.2 Hz, 1.2 Hz, 2H), 7.64−7.50 (m, 6H), 7.48−7.44 (m, 2H), 7.31- 7.28 (m, 3H), 7.23−7.19 (m, 2H), 7.08 (d, $J$ = 7.6 Hz, 1H), 6.99 (d, $J$ = 7.6 Hz, 2H), 6.41 (bs, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 191.8, 190.9, 155.9, 149.7, 146.8, 138.1, 136.2, 135.4, 133.7, 133.6, 133.5, 132.1, 131.1, 129.6, 129.1, 128.8, 128.7, 128.6, 128.2, 127.9, 127.7, 126.4, 126.0, 124.5, 80.3; IR (film, $cm^{-1}$): 3063, 2978, 1666, 1597, 1519, 1449, 1399, 1292, 1074, 943, 862, 732, 693; HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{31}H_{21}N_2O_3$ 469.1547; Found 469.1547.

*(6H-[1,3]Dioxolo[4′,5′:6,7]isochromeno[4,3-c]pyridazine-3,4-diyl)bis(phenylmethanone) (**3j**).* White solid; $R_f$ = 0.22 (PE/EA = 4:1); Yield: 29.4 mg, 67%; Mp 205−207 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.14 (dd, $J$ = 8.4 Hz, 1.2 Hz, 2H), 8.03 (s, 1H), 7.87 (dd, $J$ = 8.0 Hz, 1.2 Hz, 2H), 7.63−7.58 (m, 2H), 7.50−7.46 (m, 4H), 6.57 (s, 1H), 6.09 (s, 2H), 5.23 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 191.8, 190.9, 155.4, 151.3, 150.4, 149.0, 146.6, 136.4, 135.4, 133.9, 133.6, 131.4, 128.9, 128.8, 128.2, 127.1, 126.5, 120.3, 104.6, 104.4, 101.9, 68.8; IR (film, $cm^{-1}$):3058, 2903, 2854, 1674, 1668, 1596, 1457, 1357, 1268, 1174, 1037, 937, 875, 735; HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{26}H_{17}N_2O_5$ 437.1132; Found 437.1132.

*(6H-Isochromeno[4,3-c]pyridazine-3,4-diyl)bis((2-methoxyphenyl)methanone) (**3k**).* White solid; $R_f$ = 0.30 (PE/EA = 3:1); Yield: 30 mg, 66%; Mp 209−211 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.56 (dd, $J$ = 6.4 Hz, 2.8 Hz, 1H), 8.06 (dd, $J$ = 8.0 Hz, 2.0 Hz, 1H), 7.55−7.45 (m, 5H), 7.14−7.12 (m, 1H), 7.09−7.06 (m, 1H), 7.03−6.91 (m, 3H), 5.30 (s, 2H), 3.72 (s, 3H), 3.56 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 193.4, 189.5, 159.8, 158.9, 154.9, 149.9, 146.3, 135.3, 133.5, 131.8, 131.6, 131.1, 130.8, 129.6, 129.2, 127.2, 126.7, 125.8, 124.4, 124.1, 120.9, 120.4, 112.2, 111.8, 68.6, 55.8, 55.7; IR (film, $cm^{-1}$): 3071, 2943, 2843, 1673, 1661. 1597, 1465, 1366, 1305, 1253, 1162, 1020, 953, 868, 754; HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{27}H_{21}N_2O_5$ 453.1445; Found 453.1445.

*(6H-Isochromeno[4,3-c]pyridazine-3,4-diyl)bis(o-tolylmethanone) (**3l**).* White solid; $R_f$ = 0.26 (PE/EA = 6:1); Yield: 26.2 mg, 62%; Mp 158−160 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.58−8.55 (m, 1H), 7.58−7.51 (m, 3H), 7.48−7.38 (m, 3H), 7.33 (d, $J$ = 7.6 Hz, 1H), 7.26−7.18 (m, 3H), 7.15−7.13 (m, 1H), 5.34 (s, 2H), 2.74 (s, 3H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 194.9, 193.1, 156.2, 150.7, 146.8, 140.7, 138.7, 136.3, 135.3, 132.8, 132.3, 132.1, 131.7, 131.6, 131.5, 131.2, 131.1, 129.4, 127.6, 126.1, 125.7, 125.3, 124.5, 124.4, 68.8, 21.7, 20.7; IR (film, $cm^{-1}$): 3067, 3015, 2927, 2869, 1682, 1669, 1600, 1570, 1458, 1362, 1293, 1256, 1073, 951, 866, 736; HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{27}H_{21}N_2O_3$ 421.1547; Found 421.1545.

*(6H-Isochromeno[4,3-c]pyridazine-3,4-diyl)bis((2-chlorophenyl)methanone)(**3m**).* White solid; $R_f$ = 0.19 (PE/EA = 6:1); Yield: 23 mg, 50%; Mp 128−130 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.57−8.55 (m, 1H), 7.95 (dd, $J$ = 7.6 Hz,1.6 Hz, 1H), 7.56 (dd, $J$ = 7.6 Hz,1.6 Hz, 1H), 7.54−7.51 (m, 2H), 7.49−7.35 (m, 6H), 7.16−7.14 (m, 1H), 5.39 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 193.1, 189.6, 154.0, 150.9, 147.1, 136.8, 134.7, 133.8, 133.7, 132.6, 132.3, 132.2, 131.7, 131.4, 130.6, 130.1, 129.5, 127.6, 127.0, 126.6, 126.0, 124.6, 124.4, 68.9; IR (film, $cm^{-1}$): 3049, 2920, 2852, 1691, 1683, 1588, 1435, 1411, 1364, 1301, 1202, 1055, 952, 862, 746; HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{25}H_{15}Cl_2N_2O_3$ 461.0454; Found 461.0457.

*(6H-Isochromeno[4,3-c]pyridazine-3,4-diyl)bis(m-tolylmethanone)(**3n**).* White solid; $R_f$ = 0.30 (PE/EA = 6:1); Yield: 33 mg, 78%; Mp 82−84 °C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 8.62−8.60 (m, 1H), 7.96 (dt, $J$ = 7.6 Hz, 1.6 Hz, 1H), 7.91 (t, $J$ = 1.6 Hz, 1H), 7.71 (bs, 1H), 7.62 (dt, $J$ = 7.6 Hz, 1.6 Hz, 1H), 7.57−7.50 (m, 2H), 7.43−7.41 (m, 2H), 7.39−7.33 (m, 2H), 7.16−7.13 (m, 1H), 5.32 (s, 2H), 2.40 (s, 3H), 2.39 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 191.8, 191.2, 156.0, 151.1, 146.6, 138.7, 137.9, 136.3, 135.4, 134.9, 134.5, 132.1, 131.7, 131.6, 129.4, 129.2, 128.7, 128.6, 128.1, 127.0, 126.4, 126.0, 124.4, 124.3, 68.8, 21.3, 21.2; IR (film, $cm^{-1}$): 3067, 2921, 2860, 1682, 1668, 1602, 1460, 1407, 1363, 1302, 1171, 967, 796, 734; HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{27}H_{21}N_2O_3$ 421.1547; Found 421.1547.

*(6H-Isochromeno[4,3-c]pyridazine-3,4-diyl)bis((3-methoxyphenyl)methanone)(**3o**).* White solid; $R_f$ = 0.23 (PE/EA = 5:1); Yield: 36.2 mg, 80%; Mp 98−100 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 8.61 (dd, $J$ = 7.2 Hz, 1.8 Hz, 1H), 7.78 (dt, $J$ = 7.2 Hz, 1.2 Hz, 1H), 7.61 (q, $J$ = 1.2 Hz, 1H), 7.54−7.52 (m, 2H), 7.49 (t, $J$ = 1.8 Hz, 1H), 7.39−7.32 (m, 3H), 7.17−7.13 (m, 3H), 5.33 (s, 2H), 3.85 (s, 3H), 3.82 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 191.4, 190.7, 160.0, 159.5, 155.8, 151.1, 146.7, 137.7, 136.6, 132.1, 131.7, 129.8, 129.4, 129.2, 126.9, 126.0, 124.7, 124.4, 122.2, 120.75, 120.73, 114.7, 112.5, 68.8, 55.5, 55.4; IR (film, $cm^{-1}$): 3072, 2940, 2836, 1683, 1667, 1596, 1486, 1463, 1364, 1274, 1195, 1039, 970, 862, 765; HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{27}H_{21}N_2O_5$ 453.1445; Found 453.1446.

*(6H-Isochromeno[4,3-c]pyridazine-3,4-diyl)bis((3-chlorophenyl)methanone)(**3p**).* White solid; $R_f$ = 0.26 (PE/EA = 6:1); Yield: 29 mg, 63%; Mp 186−189 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 8.62−8.61 (m, 1H), 8.14 (t, $J$ = 1.8 Hz, 1H), 8.09−8.07 (m, 1H), 7.85−7.84 (m, 1H), 7.71−7.69 (m, 1H), 7.59−7.54 (m, 4H), 7.45−7.42 (m, 2H), 7.16−7.15 (m, 1H), 5.35 (s, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 190.4, 189.6, 155.3, 151.1, 147.0, 137.9, 136.8, 135.3, 134.6, 133.9, 133.7, 132.4, 131.7, 131.2, 130.2, 129.6, 128.7, 127.1, 126.5, 125.7, 124.6,


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124.5, 68.9; IR (film, $cm^{-1}$): 3067, 2929, 1684, 1668, 1569, 1521, 1461, 1408, 1364, 1300, 1256, 1202, 1079, 963, 879, 767, 726; HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{25}H_{15}Cl_2N_2O_3$ 461.0454; Found 461.0457.

*(6H-Isochromeno[4,3-c]pyridazine-3,4-diyl)bis((4-methoxyphenyl)methanone)(**3q**).* White solid; $R_f$ = 0.25 (PE/EA = 3:1); Yield: 44 mg, 97%; Mp 114−116 °C; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.61−8.59 (m, 1H), 8.17 (d, $J$ = 8.8 Hz, 2H), 7.83 (d, $J$ = 8.8 Hz, 2H), 7.57−7.49 (m, 2H), 7.15−7.13 (m, 1H), 6.96−6.93 (m, 4H), 5.31 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 190.2, 189.2, 164.21, 164.16, 156.5, 151.0, 146.5, 133.9, 131.9, 131.7, 131.4, 129.7, 129.6, 129.4, 128.3, 127.0, 126.4, 126.2, 124.4, 124.3, 114.1, 113.6, 68.8, 55.53, 55.51; IR (film, $cm^{-1}$): 3080, 2936, 2840, 1674, 1660, 1597, 1510, 1460, 1408, 1364, 1260, 1172, 1079, 974, 868, 772; HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{27}H_{21}N_2O_5$ 453.1445; Found 453.1441.

*(6H-Isochromeno[4,3-c]pyridazine-3,4-diyl)bis(p-tolylmethanone)(**3r**).* White solid; $R_f$ = 0.27 (PE/E.A = 6:1); Yield: 37 mg, 88%; Mp 236−238 °C; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.62−8.60 (m, 1H), 8.06 (d, $J$ = 8.4 Hz, 2H), 7.77−7.75 (m, 2H), 7.57−7.50 (m, 2H), 7.26−7.26 (m, 4H), 7.15−7.13 (m, 1H), 5.32 (s, 2H), 2.424 (s, 3H), 2.415 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 191.3, 190.4, 156.2, 151.0, 146.6, 145.0, 144.7, 134.1, 132.9, 132.0, 131.7, 131.6, 129.5, 129.4, 129.1, 129.0, 127.1, 126.1, 124.44, 124.37, 68.7, 21.83, 21.81; IR (film, $cm^{-1}$): 3032, 2921, 2841, 1678, 1661, 1605, 1460, 1411, 1363, 1298, 1180, 1078, 974, 867, 738; HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{27}H_{21}N_2O_3$ 421.1547; Found 421.1547.

*(6H-Isochromeno[4,3-c]pyridazine-3,4-diyl)bis((4-fluorophenyl)methanone)(**3s**).* White solid; $R_f$ = 0.29 (PE/EA = 6:1); Yield: 31 mg, 72%; Mp 152−154 °C; $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 8.62−8.60 (m, 1H), 8.24 (dd, $J$ = 9.0 Hz, 5.4 Hz, 2H), 7.88 (dd, $J$ = 8.4 Hz, 4.8 Hz, 2H), 7.58−7.53 (m, 2H), 7.17−7.14 (m, 5H), 5.34 (s, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 190.1, 189.2, 166.3 (d, C−F, $^1J_{C-F}$ = 255.1 Hz), 155.8, 151.1, 146.8, 134.3 (d, C−F, $^3J_{C-F}$ = 9.4 Hz), 132.9 (d, C−F, $^4J_{C-F}$ = 1.8 Hz), 132.3, 131.7, 131.68, 131.65, 129.6, 126.8, 125.9, 124.5, 116.1 (d, C−F, $^2J_{C-F}$ = 22.2 Hz), 115.5 (d, C−F, $^2J_{C-F}$ = 21.7 Hz), 68.9; IR (film, $cm^{-1}$): 3075, 2916, 2869, 1671, 1662, 1595, 1506, 1412, 1362, 1297, 1243, 1153, 1070, 972, 851, 772; $^{19}F$ NMR (376 MHz, $CDCl_3$) $\delta$ −103.08 to −103.16 (m), −103.24 to −103.32 (m); HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{25}H_{15}F_2N_2O_3$ 429.1045; Found 429.1046.

*(6H-Isochromeno[4,3-c]pyridazine-3,4-diyl)bis((4-chlorophenyl)methanone) (**3t**).* White solid; $R_f$ = 0.31 (PE/EA = 6:1); Yield: 33.2 mg, 72%; Mp 253−255 °C; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.62−8.60 (m, 1H), 8.15 (d, $J$ = 8.8 Hz, 2H), 7.79 (d, $J$ = 8.4 Hz, 2H), 7.59−7.54 (m, 2H), 7.47−7.45 (m, 4H), 7.17−7.15 (m, 1H), 5.34 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 190.5, 189.6, 155.5, 151.1, 146.9, 140.6, 140.5, 134.7, 133.5, 132.9, 132.4, 131.7, 130.3, 129.6, 129.3, 128.7, 126.6, 125.8, 124.5, 68.9; IR (film, $cm^{-1}$): 3062, 2925, 2860, 1684, 1662, 1586, 1457, 1409, 1362, 1266, 1177, 1091, 974, 864, 763; HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{25}H_{15}Cl_2N_2O_3$ 461.0454; Found 461.0454.

*(6H-Isochromeno[4,3-c]pyridazine-3,4-diyl)bis((4-bromophenyl)methanone) (**3u**).* White solid; $R_f$ = 0.28 (PE/EA = 6:1); Yield: 42.2 mg, 77%; Mp 250−252 °C; $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 8.60 (d, $J$ = 6.6 Hz, 1H), 8.06 (d, $J$ = 7.8 Hz, 2H), 7.71 (d, $J$ = 8.4 Hz, 2H), 7.64−7.55 (m, 6H), 7.15 (d, $J$ = 6.6 Hz, 1H), 5.34 (s, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 190.7, 189.7, 155.5, 151.1, 146.9, 135.2, 133.9, 132.9, 132.4, 132.2, 131.7, 130.3, 129.6, 129.41, 129.39, 126.6, 125.8, 124.5, 124.4, 68.9; IR (film, $cm^{-1}$): 3071, 2946, 2841, 1678, 1668, 1583, 1457, 1363, 1264, 1173, 1068, 973, 862, 767; HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{25}H_{15}Br_2N_2O_3$ 548.9444; Found 548.9442.

*4,4′-(6H-Isochromeno[4,3-c]pyridazine-3,4-dicarbonyl)dibenzonitrile (**3v**).* White solid; $R_f$ = 0.22 (PE/EA = 5:1); Yield: 18.2 mg, 41%; Mp 292−294 °C; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.63−8. 61 (m, 1H), 8.28 (d, $J$ = 8.4 Hz, 2H), 7.95 (d, $J$ = 8.4 Hz, 2H), 7.83−7.79 (m, 4H), 7.60−7.58 (m, 2H), 7.19−7.17 (m, 1H), 5.37 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 190.3, 189.6, 154.7, 151.2, 147.2, 139.0, 138.3, 132.85, 132.81, 132.1, 131.8, 131.6, 129.8, 129.1, 126.3, 125.4, 124.7, 124.6, 117.9, 117.7, 117.2, 116.9, 69.1; IR (film, $cm^{-1}$): 3101, 2933, 2843, 2228, 1691, 1683, 1597, 1412, 1364, 1261, 1199, 1079, 975, 866, 773; HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{27}H_{15}N_4O_3$ 443.1139; Found 443.1141.

*(6H-Isochromeno[4,3-c]pyridazine-3,4-diyl)bis(naphthalen-2-ylmethanone)(**3w**).* White solid; $R_f$ = 0.24 (PE/EA = 6:1); Yield: 37 mg, 75%; Mp 140−142 °C; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.83 (s, 1H), 8.66 (dd, $J$ = 7.2 Hz, 1.6 Hz, 1H), 8.32 (d, $J$ = 1.6 Hz, 1H), 8.14 (dd, $J$ = 8.8 Hz, 1.6 Hz, 1H), 8.04 (dd, $J$ = 8.8 Hz, 1.6 Hz, 1H), 7.95 (t, $J$ = 8.4 Hz, 2H), 7.89−7.84 (m, 4H), 7.62−7.48 (m, 6H), 7.13 (d, $J$ = 6.8 Hz, 1H), 5.32 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 191.7, 190.7, 156.3, 151.3, 146.8, 136.1, 135.8, 134.7, 133.9, 132.5, 132.2, 132.1, 131.8, 131.6, 130.1, 129.8, 129.5, 128.9, 128.8, 128.1, 127.8, 127.9, 127.7, 126.8, 126.6, 126.1, 125.8, 124.5, 124.4, 123.8, 68.8; IR (film, $cm^{-1}$): 3058, 2925, 2852, 1681, 1661, 1625, 1595, 1467, 1409, 1364, 1300, 1197, 1076, 973, 889, 734; HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{33}H_{21}N_2O_3$ 493.1547; Found 493.1550.

*(6H-Isochromeno[4,3-c]pyridazine-3,4-diyl)bis(thiophen-2-ylmethanone) (**3x**).* White solid; $R_f$ = 0.22 (PE/EA = 4:1); Yield: 34 mg, 84%; Mp 132−134 °C; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.66−8.63 (m, 1H), 8.38 (dd, $J$ = 4.0 Hz, 1.2 Hz, 1H), 7.82 (dd, $J$ = 4.8 Hz, 1.2 Hz, 1H), 7.74 (dd, $J$ = 4.8 Hz, 1.2 Hz, 1H), 7.59−7.54 (m, 2H), 7.45 (dd, $J$ = 4.0 Hz, 1.2 Hz, 1H), 7.21−7.16 (m, 2H), 7.11 (dd, $J$ = 4.8 Hz, 4.0 Hz, 1H), 5.28 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 183.1, 180.9, 153.7, 151.3, 147.4, 143.6, 139.3, 137.7, 137.6, 134.8, 133.7, 132.3, 131.8, 129.5, 128.4, 127.9, 125.9, 124.53, 124.52, 68.9; IR (film, $cm^{-1}$): 3071, 2919, 2852, 1653, 1633, 1524, 1411, 1366, 1266, 1199, 1050, 913, 848, 761; HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{21}H_{13}N_2O_3S_2$ 405.0362; Found 405.0366.

*(6H-[1,3]Dioxolo[4′,5′:6,7]isochromeno[4,3-c]pyridazine-3,4-diyl)bis((4-methoxyphenyl)methanone) (**3y**).* White solid; $R_f$ = 0.21 (PE/EA = 5:1); Yield: 31.3 mg, 63%; Mp 244−246 °C; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.17 (d, $J$ = 8.8 Hz, 2H), 8.03 (s, 1H), 7.83 (d, $J$ = 8.8 Hz, 2H), 6.94 (2d, $J$ = 8.8 Hz, 4H), 6.58 (s, 1H), 6.09 (s, 2H), 5.22 (s, 2H), 3.88 and 3.87 (2s, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 190.3, 189.2, 164.2, 164.1, 156.0, 151.1, 150.2, 148.9, 146.4, 133.9, 131.4, 129.8, 129.7, 128.4, 127.0, 126.6, 126.4, 120.5, 114.1, 113.6, 104.6, 104.4, 101.9, 68.7, 55.54, 55.52; IR (film, $cm^{-1}$): 3071, 2961, 2843, 1669, 1660, 1597, 1457, 1356, 1261, 1167, 1034, 935, 878, 767; HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{28}H_{21}N_2O_7$ 497.1343; Found 497.1341.

*(6H-[1,3]Dioxolo[4′,5′:6,7]isochromeno[4,3-c]pyridazine-3,4-diyl)bis(naphthalen-2-ylmethanone) (**3z**).* White solid; $R_f$ = 0.26 (PE/EA = 6:1); Yield: 40.2 mg, 75%; Mp 174−176 °C; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.82 (s, 1H), 8.32 (s, 1H), 8.12 (dd, $J$ = 8.8 Hz, 1.6 Hz, 1H), 8.09 (s, 1H), 8.03 (dd, $J$ = 8.8 Hz, 1.6 Hz, 1H), 7.96 and 7.94 (2d, $J$ = 8.8 Hz, 2H), 7.89−7.85 (m,4H), 7.61 and 7.59 (2d, $J$ = 7.2 Hz, 2H), 7.53 and 7.50 (2d, $J$ = 7.2 Hz, 2H), 6.56 (s, 1H), 6.09 (s, 2H), 5.22 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 191.8, 190.7, 155.8, 151.3, 150.5, 149.0, 146.7, 136.1, 135.8, 134.6, 133.9, 132.7, 132.5, 132.2, 131.5, 130.1, 129.8, 128.9, 128.8, 128.1, 127.9, 127.7, 127.1, 126.8, 126.7, 126.6, 125.8, 123.9, 120.4, 104.7, 104.4, 102.0, 68.8; IR (film, $cm^{-1}$): 3057, 2908, 2267, 1677, 1661, 1595, 1457, 1358, 1247, 1173, 1037, 928, 816, 735; HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{34}H_{21}N_2O_5$ 537.1445; Found 537.1449.

*(4-(4-Chlorobenzoyl)-6H-isochromeno[4,3-c]pyridazin-3-yl)-(thiophen-2-yl)methanone (**3za**).* White solid; $R_f$ = 0.21 (PE/EA = 6:1); Yield: 7 mg, 8%; Mp 212−214 °C; $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 8.65 (dd, $J$ = 6.6 Hz, 1.8 Hz, 1H), 8.41 (dd, $J$ = 3.6 Hz, 1.2 Hz, 1H), 7.82 (dd, $J$ = 4.8 Hz, 1.2 Hz, 1H), 7.78 (d, $J$ = 8.4 Hz, 2H), 7.58−7.53 (m,2H), 7.47−7.44 (m, 2H), 7.21−7.19 (m, 1H), 7.15 (d, $J$ = 6.6 Hz, 1H), 5.34 (s, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$ 190.2, 181.1, 154.2, 151.3, 147.2, 140.3, 139.1, 137.8, 137.7, 134.8, 132.4, 131.7, 130.0, 129.6, 129.3, 127.9, 126.3, 125.9, 124.6, 124.5, 68.9; IR (film, $cm^{-1}$): 3068, 2934, 2854, 1678, 1635, 1587, 1463, 1368, 1264, 1171, 1091, 971, 843, 770; HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{23}H_{14}ClN_2O_3S$ 433.0408; Found 433.0407.

*(3-(4-Chlorobenzoyl)-6H-isochromeno[4,3-c]pyridazin-4-yl)-(thiophen-2-yl)methanone (**3zb**).* White solid; $R_f$ = 0.19 (PE/EA = 5:1); Yield: 7 mg, 8%; Mp 208−210 °C; $^1H$ NMR (600 MHz, $CDCl_3$) $\delta$ 8.61−8.59 (m, 1H), 8.13 (d, $J$ = 8.4 Hz, 2H), 7.75 (dd, $J$ = 5.4 Hz, 1.2 Hz, 1H), 7.57−7.55 (m, 2H), 7.52 (dd, $J$ = 3.6 Hz, 1.2 Hz, 1H), 7.46 (d,


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$J$ = 8.4 Hz, 2H), 7.18−7.16 (m,1H), 7.46 (t, $J$ = 4.2 Hz, 1H), 5.39 (s, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, $CDCl_3$) $\delta$189.6, 183.0, 155.1, 151.1, 147.1, 143.5, 140.4, 135.2, 134.2, 133.8, 132.7, 132.3, 131.7, 130.0, 129.6, 129.2, 128.7, 128.5, 126.3, 125.9, 124.5, 68.9; IR (film, $cm^{-1}$): 3062, 2916, 2860, 1665. 1652, 1586, 1411, 1364, 1265, 1175, 1077, 970, 865, 769, 727; HRMS (ESI) $m/z$: $[M + H]^+$ Calcd for $C_{23}H_{14}ClN_2O_3S$ 433.0408; Found 433.0410.

*N-((3E,4Z)-4-(2-((Z)-1,4-Dioxo-1,4-diphenylbut-2-en-2-yl)-hydrazono)isochroman-3-ylidene)-4-methylbenzenesulfonamide (4).* Yellow solid; $R_f$ = 0.27 (PE/EA = 3:1); Yield: 26 mg, 23%; Mp 208−210 °C; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 14.74 (s, 1H), 8.13 (d, $J$ = 8.0 Hz, 2H), 8.00 (d, $J$ = 7.6 Hz, 2H), 7.80 (d, $J$ = 7.2 Hz, 2H), 7.63−7.60 (m, 1H), 7.55−7.48 (m, 3H), 8.13 (t, $J$ = 7.6 Hz, 2H), 7.35 (d, $J$ = 8.0 Hz, 2H), 7.28−7.24 (m, 1H), 7.12−7.05 (m,2H), 6.87 (d, $J$ = 7.6 Hz, 1H), 6.25 (s, 1H), 5.41 (s, 2H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) $\delta$ 191.5, 189.4, 155.9, 154.4, 143.7, 138.1, 138.0, 135.5, 134.1, 132.4, 129.6, 129.3, 129.25, 129.21, 129.0, 128.9, 128.5, 128.4, 127.9, 125.9, 123.6, 123.5, 96.8, 70.8, 21.7; IR (film, $cm^{-1}$); 3326, 3054, 2988, 2912, 1679, 1667, 1611, 1584, 1467, 1397, 1266, 1066, 963, 878, 750; HRMS (ESI) $m/z$: $[M + Na]^+$ Calcd for $C_{32}H_{25}N_3O_5SNa$ 586.1407; Found 586.1406.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02204.

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

### Accession Codes

CCDC 2013407−2013408 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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### Notes

The authors declare no competing financial interest.

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