HETEROCYCLES, Vol. 93, No. 1, 2016, pp. 185 - 201. © 2016 The Japan Institute of Heterocyclic Chemistry
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# DIVERSITY-ORIENTED APPROACH TO 1,2,3,4-TETRAHYDROISOQUINOLINE-3-CARBOXYLIC ACID (TIC) DERIVATIVES†

**Sambasivarao Kotha,* Shilpi Misra, Nimita Gopal Krishna, Vijayalakshmi Bandi, Mohammad Saifuddin, and Nagaraju Devunuri**

Department of Chemistry, Indian Institute of Technology-Bombay, Powai, Mumbai-400076 India, Phone: +91-22-2576 7160, Fax: +91(22)-2572 7152; E-mail: srk@chem.iitb.ac.in

†This paper is dedicated to Prof. Lutz F. Tietze's on the occasion of his 75th birthday.

**Abstract** – A convenient method is reported for synthesizing various 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives and bis-armed acid derivatives by treating dibromo-*o*-xylylenes precursor with diethyl acetamidomalonate under basic conditions. Suzuki coupling reaction has been to expand this methodology. One of the structure revision of 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid into bis-armed amino acid is also reported.

## INTRODUCTION

The tetrahydroisoquinoline (THIQ, **2**) moiety is a useful structural element present in several alkaloids and active pharmaceutical ingredients.[1] Moreover, tetrahydroisoquinoline family of antitumour antibiotics constitutes a small, yet growing number of chemotherapeutic agents. 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (Tic) **3** is regarded as the surrogate of proline (Pro) and a rigid analogue of tyrosine (Tyr) or phenylalanine (Phe) **1** (Figure 1). The structure of Tic happens to be a core unit in many bioactive molecules like enzyme inhibitors, antagonists and $\delta$-opioid receptors with a broad spectrum of pharmacological activity.[2] These amino acids have far reaching impact in peptidomimetics since the nitrogen atom involved here is not a free proton donor. The protected nitrogen atom in Tic aids in the design of peptidomimetics. Moreover, Tic has widely been used to impart conformational constraint to the peptide chain and thus aids in modulating the pharmacological profile of a given peptide[3] and insertion of Tic in $\delta$-opioid receptors enhances their selectivity and binding affinity.[4] Therefore, it is useful to design simple and general strategies to generate diverse Tic derivatives from easily accessible starting materials.

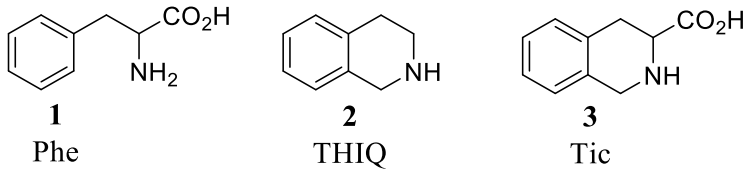
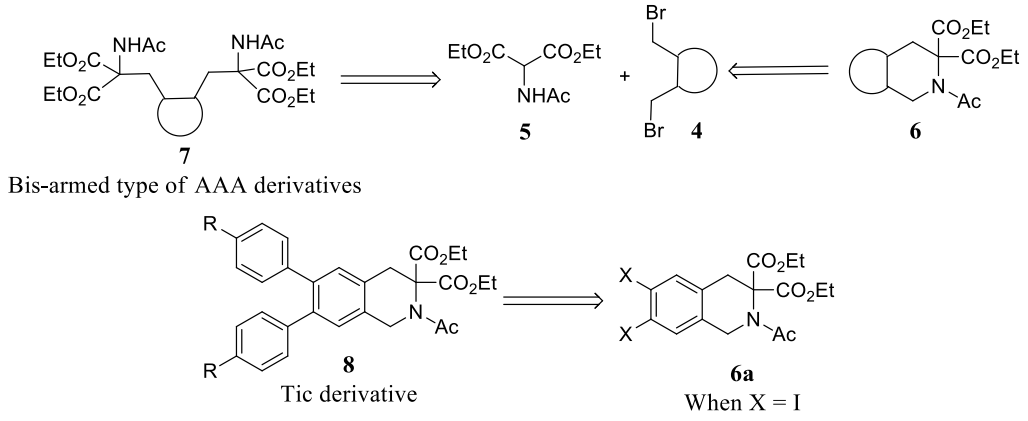



**Figure 1**. Structures of Phe, THIQ and Tic

## RESULTS AND DISCUSSION

In continuation of our efforts to design various Tic derivatives by building block approach,[5] we are interested in developing an alternate approach more suitable for the synthesis of a wide variety of modified Tic analogues involving diethyl acetamidomalonate (DEAM) as a glycine equivalent.

Herein, we disclose our detailed results for assembling functionalized Tic derivatives from $\alpha,\alpha'$-dibromo-*o*-xylylenes and DEAM **5** under base-catalyzed conditions. While testing the scope of reaction, we found that in some instances, bis-armed amino acid derivatives are formed as the exclusive product. Additionally, the ability of DEAM to deliver higher analogues of Tic derivatives has been exploited. Furthermore, halogenated Tic derivatives seem to be promising candidates for the synthesis of various functionalized Tic derivatives through the application of Suzuki-Miyaura (SM) cross-coupling reaction. The required dibromo derivatives were obtained, respectively, from the corresponding dimethyl aromatic compounds and aromatic diols under different bromination conditions as described in the literature.[6,7] Benzocycloalkane diols were assembled *via* a known literature procedure by our group which includes [2+2+2] cycloaddition reaction and reduction as key steps.[8] Alternatively, a bromomethylation strategy can also be adopted for the synthesis of the benzocycloalkane bromides.[9] The retrosynthetic analysis suggest that, the target structure **8** could be obtained from the compound **6a** using Suzuki-Miyaura coupling reaction. In a similar fashion compound **6** and **7** could be obtained starting from dibromo-*o*-xylylenes **4** and DEAM **5** (Scheme 1).

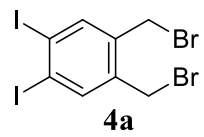
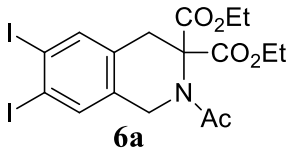
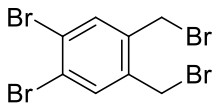
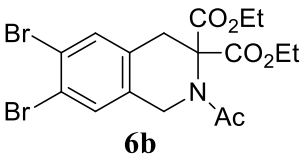
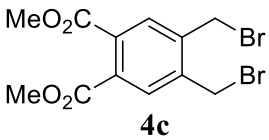
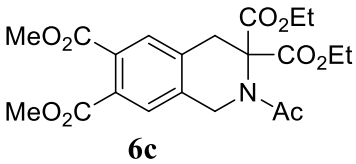
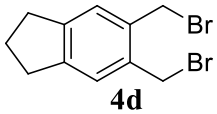
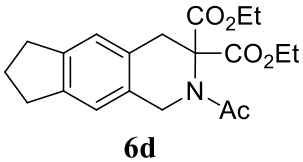
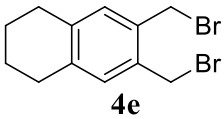
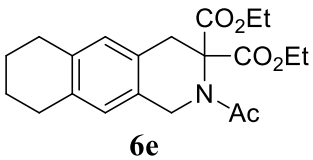
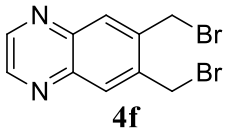
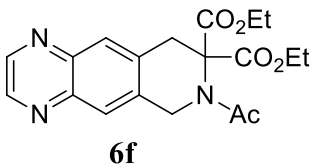


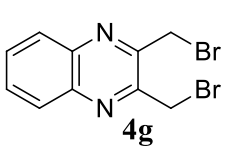
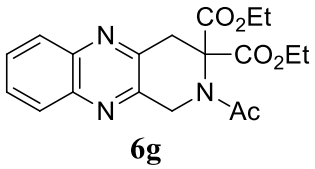
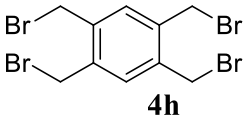
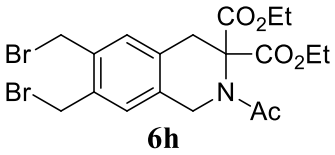
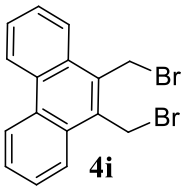
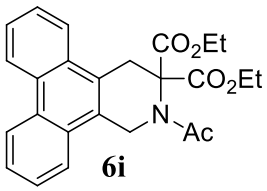
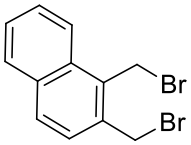
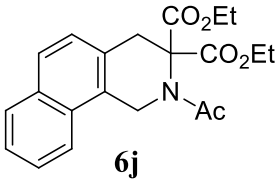
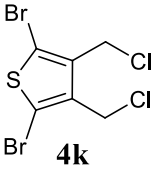
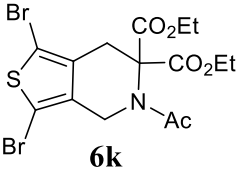
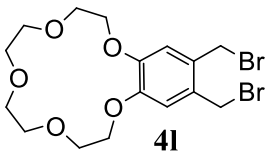
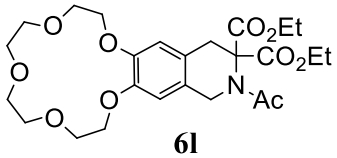

**Scheme 1**. Retrosynthetic approach to Tic and bis-armed type of AAA derivative

This work has been reported as a preliminary communication,[10a] and now we report the detailed experimental procedures with some additional examples. Also, we revised the structure of one of the earlier products.

Initially, dibromide **4a** was subjected to alkylation with DEAM **5** in the presence of $K_2CO_3$ using dry acetonitrile at 75 °C to obtain the corresponding Tic derivative **6a**. Although, limited reports are available regarding the usage of DEAM for the construction of unusual amino acid derivatives, its utility in the preparation of Tic derivatives needs further attention.[11] Various dibromo derivatives that have effectively undergone the base-catalyzed cyclization reaction with DEAM to prepare Tic derivatives (**6a-l**) are shown in Table 1. Our efforts also resulted an alternative and modular approach for synthesis of higher analogues of Tic derivative *i.e*. Sic derivative **6m** and Hic derivative **6n** (Table 2). Thus, the strategy employed here is complementary to the existing methods for the synthesis of higher analogues of Tic.[12]

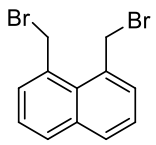
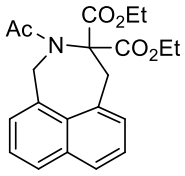
**Table 1**. Synthesis of TIC derivatives

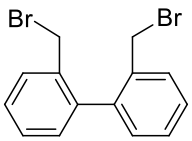
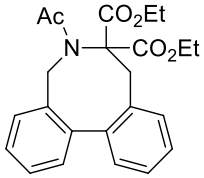
| Entry | Starting Material | Product | Condition | Yield% |
|---|---|---|---|---|
| 1 |  **4a** |  **6a** | A | 41[a] |
| 2 |  **4b** |  **6b** | A | 46[a] |
| 3 |  **4c** |  **6c** | A | 63[a] |
| 4 |  **4d** |  **6d** | B | 45[a] |
| 5 |  **4e** |  **6e** | B | 42[a] |
| 6 |  **4f** |  **6f** | B | 60[a] |

| | | | | |
|---|---|---|---|---|
| 7 |  **4g** |  **6g** | B | 75[a] |
| 8 |  **4h** |  **6h** | A | 54[a] |
| 9 |  **4i** |  **6i** | A<br>B | 45[a]<br>48[a] |
| 10 |  **4j** |  **6j** | B | 48[a] |
| 11 |  **4k** |  + **7d** **6k** | B | 56[a]+40 [b] |
| 12 |  **4l** |  **6l** | A | 75[a] |

Reaction conditions: **Condition A**: DEAM (1.0 equiv.), $K_2CO_3$ (5.0 equiv.), MeCN reflux, 24 h; **Condition B**: DEAM (0.9-1.1 equiv.), $K_2CO_3$ (3.5-6 equiv.), TBAHS[·] (0.2-1.0 equiv.), MeCN reflux, 11-22 h: [a] Isolated yield after column chromatography, [b] Compound **6k** was isolated along with compound **7d,** [·] TBAHS = Tetrabutylammonium hydrogen sulphate

**Table 2**. Synthesis of Sic and Hic derivatives

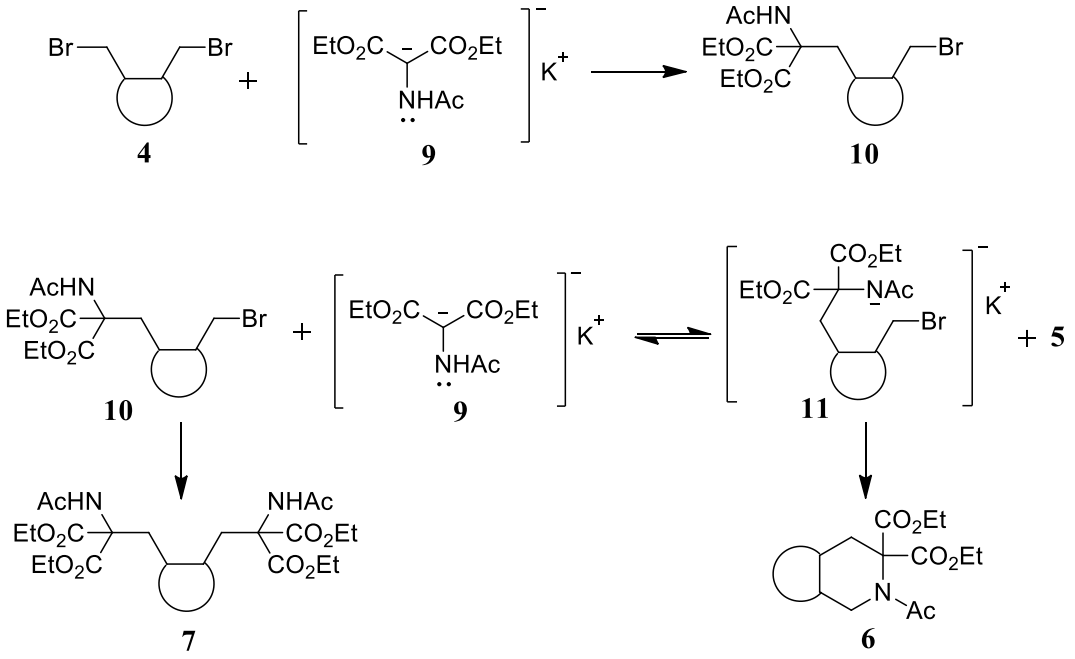
| Entry | Starting Material | Product | Condition | Yield% |
|---|---|---|---|---|
| 1 |  **4m** |  **6m** | A | 64[a] |

| | | | | |
|---|---|---|---|---|
| 2 |  **4n** |  **6n** | A | 64[a] |

Reaction conditions: **Condition A**: DEAM (1.0 equiv.), $K_2CO_3$ (5.0 equiv.), MeCN, reflux, 24 h
[a] Isolated yield after column chromatography

During these studies, we noticed that the substituted heterocyclic aromatic dibromides behaved in a unique fashion under similar reaction conditions. In this context, reaction of chloro and methyl substituted quinoxaline dibromides (**4o**, **4p** and **4q**) with DEAM **5** failed to give the cyclized products, instead bis-armed amino acids (Table 3, **7a-c**) were the only significant products obtained. In contrast, unsubstituted quinoxaline dibromide **4g** gave Tic derivative **6g** as the exclusive product. On the other hand, the thiophene dibromide **4k** delivered the corresponding Tic derivative **6k** as well as the bis-armed amino acid derivative **7d**.

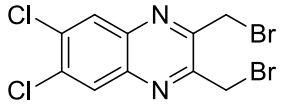
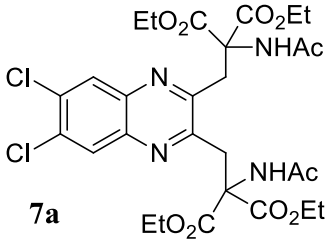
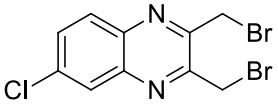
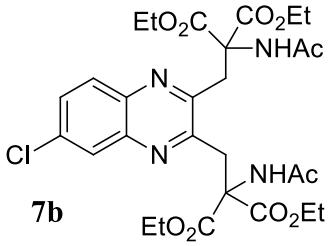
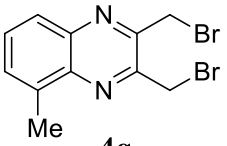
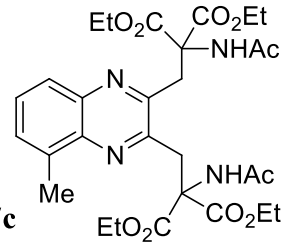
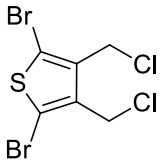
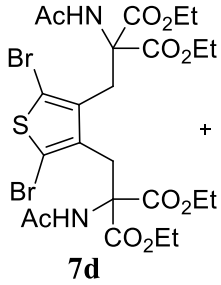
The proposed mechanism of the reaction is as shown in Scheme 2. In the first step, the dibromide **4** reacts with the carbanion **9** leading to the intermediate **10**. It is possible that another molecule of the carbanion **9** subsequently attacks the carbon terminus of the C-Br bond in the intermediate **10** leading to bis(monoalkylated) product **7**. In an alternate pathway, the carbanion **9** possibly attacks the hydrogen terminus of the acidic C-H bond in the intermediate **10** *via* proton transfer to the carbanion **9** and the intermediate **11** cyclizes to form the cyclized product **6**. Therefore, the reason for the formation of bis-armed quinoxaline derivative such as **7a, 7b and 7c** is probably the slow rate of intramolecular *N*-alkylation of **11** compared to intermolecular *C*-alkylation of **10**.



**Scheme 2**. Synthesis of bis(monoalkylated) product and dialkylated product

Liu and co-workers[13] have reported the involvement of some kind of electronic interactions in the 2,3-disubstituted quinoxaline sultines and 6,7-disubstituted quinoxalinosultines. Although both these quinoxaline systems are similar in structure and reactivity but their reaction products, however, differ.

**Table 3**. Synthesis of bis-armed type of AAA derivatives

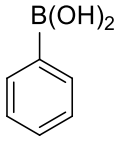
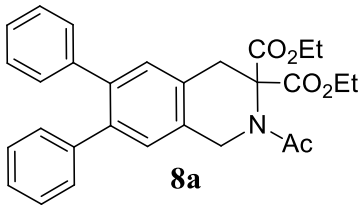
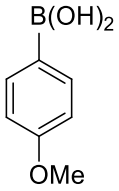
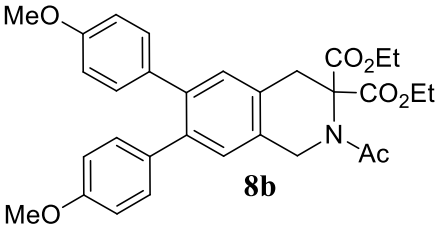
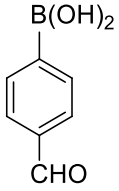
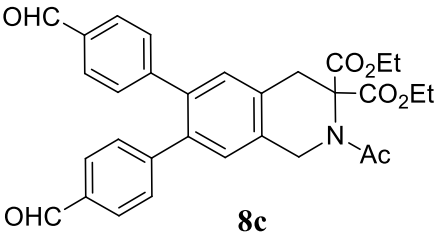
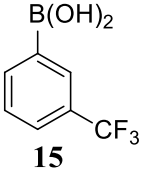
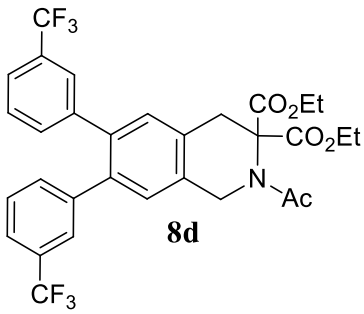
| Entry | Starting Material | Product | Yield% |
|---|---|---|---|
| 1 |  **4o** |  **7a** | 72 [a] [Ref 10b] |
| 2 |  **4p** |  **7b** | 70[a] |
| 3 |  **4q** |  **7c** | 63[a] |
| 4 |  **4k** |  + **6k**  **7d** | 40[a]+56 [b] |

Reaction conditions: Condition B: DEAM (1.0-2.0 equiv.), $K_2CO_3$ (3.5-6 equiv.), TBAHS (0.5-1.0 equiv.), MeCN, reflux, 15-22 h: [a]Isolated yield after column chromatography, [b]Compound **7d** was isolated along with compound **6k**

Having established the conditions for the synthesis of Tic derivatives and its higher analogues, we expanded the scope of the reaction to assemble functionalized Tic derivatives. The diiodo Tic derivative **6a** was found to be a suitable precursor for the functionalization of Tic derivative by the application of Suzuki-Miyaura (SM) cross-coupling.[14] In this regard, we prepared various SM

cross-coupled products by reaction of **6a** with various boronic acids in the presence [$Pd_2(dba)_3$] and Buchwald ligand[15] conditions (Table 4). Similarly, the Suzuki-Miyaura (SM) cross-coupling reaction of the substrate **7a** gave a complex mixture.

**Table 4.** Expansion of Tic derivatives using Suzuki-Miyura coupling reaction

| Entry | Starting Material | Boronic acid | Product | Yield% |
|---|---|---|---|---|
| 1 | **6a** |  **12** |  **8a** | 30[a] |
| 2 | **6a** |  **13** |  **8b** | 49[a] |
| 3 | **6a** |  **14** |  **8c** | 48[a] |
| 4 | **6a** |  **15** |  **8d** | 50[a] |

Reaction conditions: **Condition A**: [$Pd_2(dba)_3$] (1.5 mol%), Boronic acids (2.5 equiv.), aqueous $Na_2CO_3$ (5 equiv.), Buchwald ligand (XPhos) (10 mol%), THF/toluene/water: [a] Isolated yield after column chromatography

## CONCLUSION

In conclusion, a modular approach has been devised to highly functionalized Tic derivatives using DEAM. This strategy provides a unique opportunity to assemble higher analogues of Tic in an easy manner. Highly functionalized Tic derivatives may find important applications in bioorganic and medicinal chemistry. Therefore, we also studied Suzuki–Miyaura (SM) cross-coupling to assemble densely

functionalized Tic derivatives. To the best of our knowledge, unique examples describing different behavioral pattern of heterocyclic aromatic dibromides is described with DEAM. In some of the examples, heterocyclic aromatic dibromides gave selectively one product over the other possible products.

## EXPERIMENTAL

**General:** Melting points were recorded with a Labhosp or Veego melting point apparatus. Boiling points refer to the bath temperatures. Infrared (IR) spectra were recorded with an Nicolet Impact-400 FT IR spectrometer in KBr/$CHCl_3$/$CCl_4$. $^1$H (300 and 400 MHz), $^{13}$C (75.4 and 100.6 MHz) NMR spectroscopic data were determined at room temperature with AV 400 (Bruker), AMX-400 (Varian), or VXR-300S (Varian) spectrometers in $CDCl_3$, coupling constants (J values) are given in Hertz (Hz). High-resolution mass measurements were carried out using a Micromass Q-Tof spectrometer. Analytical thin layer chromatography (TLC) was performed on (10 × 5 cm) glass plates coated with Acme's silica gel G or GF 254 (containing 13% calcium sulfate as a binder). Silica gel was coated on the glass plates using the "Sandwich Technique". Chromatography was performed with Acme's silica gel (100–200 mesh) using double spray bellows for the application of pressure; the column was typically eluted with ethyl acetate/petroleum ether mixture. DEAM used here was purchased from Aldrich Chemical Co., Inc. (Milwaukee, WI, USA). Anhydrous MeCN was prepared by doing distillation over $CaH_2$.

**General procedure for the synthesis of Tic, Sic and Hic derivatives:**

To a stirred solution of finely powdered potassium carbonate (5 equiv.) and DEAM (1 equiv.) in anhydrous MeCN (15 mL, 1.5 mol%) was added aromatic dibromide (1 equiv.). The reaction mixture was stirred at 75 °C for 24 h under the continuous flow of nitrogen. At the conclusion of the reaction (TLC monitoring), the reaction mixture was cooled and filtered through the Celite pad. The filtrate was evaporated under reduced pressure and the crude product was purified by silica gel column chromatography.

**Diethyl 2-acetyl-6,7-diiodo-1,2-dihydroisoquinoline-3,3-dicarboxylate (6a)**

To a stirred suspension of potassium carbonate (1.3 g, 9.65 mmol) and DEAM (419 mg, 1.93 mmol) in anhydrous MeCN (20 mL) was added 1,2-bis(bromomethyl)-4,5-diiodobenzene (**4a**) (1 g, 1.93 mmol) to give a white solid **6a** (450 mg, 41%). $R_f$ = 0.28 (silica gel, 50% EtOAc-petroleum ether); Mp 110 °C; IR (KBr): 1094, 1302, 1652, 1746, 2854, 2982 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.20 (t, $J$ = 7.17 Hz, 6H), 2.26 (s, 3H), 3.32 (s, 2H), 4.16-4.19 (m, 4H), 4.56 (s, 2H), 7.68 (s, 2H); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ = 14.0, 22.5, 36.4, 46.7, 62.3, 67.5, 106.1, 106.7, 134.1, 134.2, 136.7, 138.3, 167.5, 171.0; HRMS (Q-Tof): *m/z* calcd for $C_{17}H_{20}I_2NO_5$ $[M+H]^+$ 571.9431; found 571.9438.

**Diethyl 2-acetyl-6,7-dibromo-1,2-dihydroisoquinoline-3,3-dicarboxylate (6b)**

To a stirred suspension of potassium carbonate (159 mg, 1.15 mmol) and DEAM (50 mg, 0.23 mmol) in anhydrous MeCN (10 mL) was added 1,2-dibromo-4,5-bis(bromomethyl)benzene (**4b**) (100 mg, 0.23 mmol) to give a white solid **6b** (50 mg, 46%). $R_f$ = 0.38 (silica gel, 50% EtOAc-petroleum ether); IR (KBr): 1021, 1266, 1664, 1743, 2854, 2928 $cm^{-1}$; Mp = 123-125 °C; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 1.20 (t, $J$ = 7.13 Hz, 6H), 2.27 (s, 3H), 3.36 (s, 2H), 4.18-4.21 (m, 4H), 4.60 (s, 2H), 7.45 (s, 2H); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): $\delta$ = 14.0, 22.5, 36.6, 47.0, 62.3, 67.6, 123.5, 123.9, 131.2, 132.9, 133.4, 133.5, 167.5, 171.0; HRMS (Q-Tof): *m/z* calcd for $C_{17}H_{20}Br_2NO_5$ $[M+H]^+$ 475.9708; found 475.9708.

**Diethyl 2-acetyl-6,7-dibromo-1,4-dihydroisoquinoline-3,3-dicarboxylate (6c)**

To a stirred suspension of potassium carbonate (121 mg, 0.88 mmol) and DEAM (26 mg, 0.12 mmol) in anhydrous MeCN (5 mL) was added compound **4c** (50 mg, 0.11 mmol) to give a white solid **6c** (42 mg, 63%). $R_f$ = 0. 36 (silica gel, 60% EtOAc-petroleum ether); Mp 142 °C; IR (KBr): 632, 1650, 1728, 2993, 3040 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 1.19 (t, $J$ = 5 Hz, 6H), 2.27 (s, 3H), 3.48 (s, 2H), 3.90 (d, $J$ = 1.6 Hz, 6H), 4.11-4.19 (m, 4H), 4.72 (s, 2H), 7.54 (d, $J$ = 7 Hz, 2H); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): $\delta$ = 14.0, 22.5, 37.1, 47.5, 52.9, 62.4, 67.6, 127.0, 128.6, 131.1, 131.6, 135.7, 135.9, 167.5, 167.6, 171.2; HRMS (Q-Tof): *m/z* calcd for $C_{21}H_{25}NNaO_9$ $[M+Na]^+$ 458.1418; found 458.1422.

**Diethyl 2-acetyl-4,6,7,8-tetrahydrocyclopentaisoquinoline-3,3-dicarboxylate (6d)**

To a stirred suspension of potassium carbonate (681 mg, 4.9 mmol), TBAHS (132 mg, 0.4 mmol) and DEAM (188 mg, 0.86 mmol) in anhydrous MeCN (20 mL) was added compound **4d** (250 mg, 0.82 mmol) to give a white solid **6d** (132 mg, 45%). $R_f$ = 0.42 (silica gel, 50% EtOAc-petroleum ether); Mp 182-184 °C; IR (KBr): 3257, 2986, 1746, 1643, 1517, 1274, 1213, 1018, 749 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 1.17 (t, $J$ = 7.03 Hz, 6H), 2.05 (quintet, $J$ = 3.4 Hz, 2H), 2.28 (s, 3H), 2.86 (t, $J$ = 3.4 Hz, 4H), 3.37 (s, 2H), 4.15 (q, $J$ = 7.1 Hz, 4H), 4.63 (s, 2H), 7.01 (s, 2H); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): $\delta$ = 14.0, 22.5, 25.5, 32.6, 37.6, 48.2, 61.9, 68.3, 122.1, 123.7, 130.0, 130.5, 143.6, 144.1, 168.1, 170.9; HRMS (Q-Tof): *m/z* calcd for $C_{20}H_{26}NO_5$ $[M+H]^+$ 360.1811; found 360.1799.

**Diethyl 2-acetyl-1,2,6,7,8,9-hexahydrobenzoisoquinoline-3,3-dicarboxylate (6e)**

To a stirred suspension of potassium carbonate (262 mg, 1.9 mmol) and DEAM (75.6 mg, 0.35 mmol) in anhydrous MeCN (15 mL) was added compound **4e** (100 mg, 0.32 mmol) to give a white solid **6e** (49.5 mg, 42%). $R_f$ = 0.43 (50% EtOAc-petroleum ether); Mp 90-92 °C; IR (KBr): 3054, 2986, 1742, 1659, 1421, 1265, 1095, 1061, 743 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 1.17 (t, $J$ = 7.1 Hz, 6H), 1.77 (m, 4H), 2.26 (s, 3H), 2.71 (m, 4H), 3.34 (s, 2H), 4.15 (q, $J$ = 7.1 Hz, 4H), 4.61 (s, 2H), 6.84 (s, 2H); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): $\delta$ = 14.0, 22.5, 23.2, 29.18, 29.2, 37.2, 47.8, 61.9, 68.3, 126.6, 128.2, 129.2, 129.7,

136.4, 136.8, 168.1, 171.0; HRMS (Q-Tof): *m/z* calcd for $C_{21}H_{28}NO_5$ $[M+H]^+$ 374.1967; found 374.1962.

**Diethyl 7-acetyl-6,7-dihydropyrido[4,3-*g*]quinoxaline-8,8(9*H*)-dicarboxylate (6f)**

To a stirred suspension of potassium carbonate (306 mg, 2.2 mmol), TBAHS (54 mg, 0.15 mmol) and DEAM (72.2 mg, 0.33 mmol) in dry MeCN (15 mL) was added compound **4f** (100 mg, 0.32 mmol) to give a pale yellow semi-solid **6f** (70 mg, 60%). $R_f$ = 0.28 (80% EtOAc-petroleum ether); IR (neat): 3020, 2401, 2346, 1744, 1657, 1522, 1399, 1216, 1029, 909, 760 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 1.17 (t, $J$ = 7.1 Hz, 6H), 2.36 (s, 3H), 3.68 (s, 2H), 4.17 (q, $J$ = 7.1 Hz, 4H), 4.93 (s, 2H), 7.95 (d, $J$ = 6.0 Hz, 2H), 8.85 (s, 2H); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): $\delta$ = 14.1, 22.6, 37.8, 47.9, 62.3, 68.1, 126.5, 127.9, 135.5, 135.9, 142.4, 142.7, 145.4, 145.5, 167.8, 170.8; HRMS (Q-Tof): *m/z* calcd for $C_{19}H_{22}N_3O_5$ $[M+H]^+$ 372.1559; found: 372.1567.

**Diethyl 2-acetyl-1,2-dihydropyridoquinoxaline-3,3-dicarboxylate (6g)**

To a stirred suspension of potassium carbonate (153 mg, 1.1 mmol), TBAHS (54 mg, 0.16 mmol) and DEAM (62 mg, 0.28 mmol) in anhydrous MeCN (15 mL) was added compound **4g** (100 mg, 0.32 mmol) to give a white solid **6g** (87 mg, 75%). $R_f$ = 0.32 (40% EtOAc-petroleum ether); Mp 114-118 °C; IR (KBr) 3054, 2986, 1746, 1666, 1421, 1265, 1059, 1023, 747 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ = 1.18 (t, $J$ = 6.9 Hz, 6H), 2.36 (s, 3H), 3.85 (s, 2H), 4.19 (q, $J$ = 6.9 Hz, 4H), 5.04 (s, 2H), 7.76-7.79 (m, 2H), 8.02-8.09 (m, 2H); $^{13}C$ NMR (75.4 MHz, $CDCl_3$): $\delta$ = 13.9, 22.6, 39.5, 50.3, 62.5, 67.8, 128.9, 129.1, 130.3, 141.7, 148.5, 167.3, 171.4; HRMS (Q-Tof): *m/z* calcd for $C_{19}H_{22}N_3O_5$ $[M+H]^+$ 372.1559; found 372.1563.

**Diethyl 2-acetyl-6,7-bis(bromomethyl)-1,2-dihydroisoquinoline-3,3-dicarboxylate (6h)**

To a stirred suspension of potassium carbonate (380 mg, 2.75 mmol) and DEAM (120 mg, 0.55 mmol) in anhydrous MeCN (15 mL) was added compound **4h** (250 mg, 0.55 mmol) to give a white solid **6h** (150 mg, 54%). $R_f$ = 0.44 (silica gel, 50% EtOAc-petroleum ether); Mp = 120 °C; IR (KBr): 1061, 1266, 1666, 1746, 2983, 3056 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 1.17 (t, $J$= 7.02 Hz, 6H), 2.29 (s, 3H), 3.41 (s, 2H), 4.12-4.20 (m, 4H), 4.61 (s, 4H), 4.67 (s, 2H), 7.18 (s, 2H); $^{13}C$ NMR (75.4 MHz, $CDCl_3$): $\delta$ = 14.0, 22.4, 29.3, 29.4, 37.0, 47.4, 62.1, 67.7, 128.8, 130.4, 133.7, 133.8, 135.8, 136.2, 167.6, 171.0; HRMS (Q-Tof): *m/z* calcd for $C_{19}H_{24}NO_5Br_2$ $[M+H]^+$ 504.0021; found 503.9997.

**Diethyl 2-acetyl-1,2-dihydrodibenzoisoquinoline-3,3-dicarboxylate (6i)**

To a stirred suspension of potassium carbonate (41 mg, 0.30 mmol) and DEAM (13.0 mg, 0.06 mmol) in anhydrous MeCN (10 mL) was added 9,10-dibromomethylphenanthrene **4i** (25 mg, 0.06 mmol) to give a white solid **6i** (13 mg, 45%). $R_f$ = 0.61 (silica gel, 50% EtOAc-petroleum ether); Mp 184-188 °C; IR

(KBr): 1069, 1303, 1670, 1734, 3079 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 1.14 (t, $J$ = 7.1 Hz, 6H), 2.44 (s, 3H), 3.95 (s, 2H), 4.14-4.19 (m, 4H), 5.15 (s, 2H), 7.67-7.69 (m, 4H), 7.85-7.78 (m, 1H), 8.10-8.12 (m, 1H), 8.71-8.75 (m, 2H); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): $\delta$ = 14.0, 22.7, 32.6, 45.8, 62.3, 67.3, 122.0, 123.1, 123.5, 123.6, 124.5, 126.2, 126.8, 126.9, 127.3, 128.4, 129.8, 129.9, 130.0, 168.0, 172.4; HRMS (Q-Tof): *m/z* calcd for $C_{25}H_{26}NO_5$ $[M+H]^+$ 420.1811; found 420.1800.

**Diethyl 3-acetyl-3,4-dihydrobenzoisoquinoline-2,2-dicarboxylate (6j)**

To a stirred suspension of potassium carbonate (230 mg, 1.7 mmol), TBAHS (80 mg, 0.24 mmol) and DEAM (94 mg, 0.43 mmol) in anhydrous MeCN (20 mL) was added compound **4j** (150 mg, 0.48 mmol) to give a white solid **6j** (84 mg, 48%). $R_f$ = 0.22 (silica gel, 30% EtOAc-petroleum ether); Mp 154-158 $^oC$; IR (KBr) 3054, 2987, 1742, 1671, 1421, 1265, 1048, 1023, 739 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 1.07 (t, $J$ = 7.1 Hz, 6H), 2.34 (s, 3H), 3.86 (s, 2H), 4.12 (q, $J$ = 7.1 Hz, 4H), 4.84 (s, 2H), 7.22 (d, $J$ = 8.4 Hz, 1H), 7.48-7.52 (m, 1H), 7.55-7.59 (m, 1H), 7.74 (d, $J$ = 8.5 Hz, 1H), 7.83 (d, $J$ = 7.6 Hz, 1H), 8.04 (d, $J$ = 8.5 Hz, 1H); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): $\delta$ = 13.9, 22.6, 32.6, 48.5, 62.2, 68.0, 122.9, 124.1, 126.1, 126.9, 127.8, 127.9, 128.8, 129.5, 130.9, 132.9, 168.1, 171.6; HRMS (Q-Tof): *m/z* calcd for $C_{21}H_{24}NO_5$ $[M+H]^+$ 370.1654; found 370.1660.

**Diethyl 5-acetyl-1,3-dibromo-4,5-dihydrothienopyridine-6,6-dicarboxylate (6k)**

To a stirred suspension of potassium carbonate (147 mg, 1.06 mmol) and DEAM (78 mg, 0.36 mmol) in anhydrous MeCN (5 mL) was added compound **4k** (60 mg, 0.18) to give a white solid **6k** (47.8 mg, 56%). $R_f$= 0.61 (silica gel, 40% EtOAc-petroleum ether); Mp 144-147 °C; IR (KBr) 3049, 2986, 1742, 1679, 1265, 1023, 744 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 1.28 (t, $J$ = 7.2 Hz, 6H), 2.1 (s, 3H), 3.89 (s, 2H), 4.27 (q, $J$ = 7.2 Hz, 4H), 4.54 (s, 2H); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): $\delta$ = 14.1, 22.7, 33.2, 45.5, 62.5, 68.1, 106.5, 107.9, 132.7, 133.3, 167.2, 171.9; HRMS (Q-Tof): *m/z* calcd for $C_{15}H_{18}NO_5Br_2S$ $[M+H]^+$ 481.9272; found 481.9281.

**Diethyl 16-acetyl-2,3,5,6,8,9,11,12,15,18-decahydro-[1,4,7,10,13]pentaoxacyclopenta decino[2,3]-isoquinoline-dicarboxylate (6l)**

To a stirred suspension of potassium carbonate (217 mg, 1.57 mmol) and DEAM (57 mg, 0.26 mmol) in anhydrous MeCN (10 mL) was added compound **4l** (100 mg, 0.26 mmol) to give white semi-solid **6l** (72 mg, 75%). $R_f$ = 0.35 (neutral $Al_2O_3$, 100% $CHCl_3$); IR (KBr): 740, 1266, 1670, 1743, 2989, 3054 $cm^{-1}$; $^1H$-NMR (400 MHz, $CDCl_3$): $\delta$ =1.15 (t, $J$ = 7.1 Hz, 6H), 2.24 (s, 3H), 3.30 (s, 2H), 3.72 (s, 8H), 3.89 (d, $J$ = 4.1 Hz, 4H), 4.06 (d, $J$ = 3.7 Hz, 4H), 4.12 (t, $J$ = 7.2 Hz, 4H), 4.57 (s, 2H), 6.62 (d, $J$ = 3.6 Hz, 2H); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): $\delta$ = 14.0, 22.5, 29.7, 37.0, 47.6, 61.9, 62.8, 68.1, 69.1, 69.2, 69.5, 69.6, 70.4, 71.0, 111.9, 113.5, 124.8, 124.9, 148.4, 148.6, 167.9, 171.1; HRMS (Q-Tof): *m/z* calcd for

$C_{25}H_{35}NNaO_{10}$ $[M+Na]^+$ 532.2163; found 532.2153.

**Diethyl 2-acetyl-1,2-dihydronaphthoazepine-3,3-dicarboxylate (6m)**

To a stirred suspension of potassium carbonate (131 mg, 0.95 mmol) and DEAM (41.2 mg, 0.19 mmol) in anhydrous MeCN (10 mL) was added dibromo compound **4m** (62 mg, 0.19 mmol) to give a white solid **6m** (47 mg, 64%). $R_f$ = 0.37 (silica gel, 50% EtOAc-petroleum ether); Mp 124-126 °C; IR (KBr): 1046, 1303, 1652, 1744, 2983 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 1.01 (bt, 6H), 2.28 (s, 3H), 3.81 (s, 2H), 3.93-4.06 (bm, 4H), 5.12 (bs, 2H), 7.21-7.40 (m, 4H), 7.78-7.73 (m, 2H); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): $\delta$ = 13.5, 22.5, 42.1, 51.5, 61.7, 72.1, 125.5, 125.9, 126.3, 128.8, 129.2, 129.5, 131.8, 132.8, 134.3, 135.0, 167.7, 171.0; HRMS (Q-Tof): *m/z* calcd for $C_{21}H_{24}NO_5$ $[M+H]^+$ 370.1654 found 370.1641.

**Diethyl 6-acetyl-5,6-dihydrodibenzoazocine-7,7-dicarboxylate (6n)**

To a stirred suspension of potassium carbonate (138 mg, 1.0 mmol) and DEAM (43.4 mg, 0.20 mmol) in anhydrous MeCN (10 mL) was added 2,2'-bis(bromomethyl)biphenyl **4n** (70 mg, 0.20 mmol) to give a white solid **6n** (52 mg, 64%). $R_f$ = 0.40 (silica gel, 50% EtOAc-petroleum ether); Mp 139 °C; IR (KBr): 1058, 1266, 1404, 1654, 1744, 2985, 3058 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 1.22 (t, $J$= 7.16 Hz, 3H), 1.32 (t, $J$= 7.16 Hz, 3H), 2.45 (s, 3H), 2.93 (1/2ABq, $J$= 16.0 Hz, 1H), 3.43 (1/2ABq, $J$ = 16.0 Hz, 1H), 3.79 (1/2ABq, $J$ = 15.58 Hz, 1H), 4.20-4.40 (m, 4H), 4.74 (1/2ABq, $J$ = 15.50 Hz, 1H), 7.26-7.46 (m, 8H); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): $\delta$ = 14.0, 14.3, 22.7, 38.4, 47.7, 61.8, 62.0, 70.2, 128.0, 128.1, 128.6, 128.7, 129.0, 129.1, 129.5, 131.4, 134.2, 136.0, 140.7, 141.6, 166.9, 168.3, 172.4; HRMS (Q-Tof): *m/z* calcd for $C_{23}H_{25}NNaO_5$ $[M+Na]^+$ 418.1630; found 418.1647.

**General Procedure for the synthesis of bis-armed amino acid derivatives:**

To a stirred suspension of finely powdered potassium carbonate (3.5-6.0 equiv.), TBAHS (0.5-1.0 equiv.) and DEAM (1.0-2.0 equiv.) in dry MeCN (15 mL) was added aromatic dibromide (1 equiv.). The resulting heterogeneous reaction mixture was stirred at 75 °C for 15-22 h under nitrogen. At the conclusion of the reaction (TLC monitoring), the reaction mixture was cooled and filtered with the aid of a Celite pad. The filtrate was evaporated under reduced pressure and the crude product was purified by neutral alumina column chromatography.

**Tetraethyl-2,2'-(6,7-dichloroquinoxaline)bis(methylene)bis(2-acetamidomalonate) (7a)**

To a stirred suspension of potassium carbonate (197 mg, 1.4 mmol), TBAHS (26.5 mg, 0.08 mmol) and DEAM (84.6 mg, 0.39 mmol) in anhydrous MeCN (15 mL) was added compound **4o** (100 mg, 0.26 mmol) to give a pale yellow solid **7a** (122 mg, 72%). $R_f$ = 0.26 (silica gel, 50% EtOAc-petroleum ether); Mp = 98-102 °C; IR (KBr): 3055, 2986, 1743, 1678, 1266, 1017, 740 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$):

$\delta$ = 1.23 (t, $J$ = 7.2 Hz, 12H), 1.95 (s, 6H), 4.14 (s, 4H), 4.27 (m, 8H), 7.01 (s, 2H), 8.00 (s, 2H); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ = 14.1, 23.2, 36.7, 63.1, 65.5, 129.0, 134.3, 138.7, 153.5, 167.6, 169.6; HRMS (Q-Tof): *m/z* calcd for $C_{28}H_{35}N_4O_{10}Cl_2$ $[M+H]^+$ 657.1730; found 657.1714.

**Tetraethyl 2,2'-(6-chloroquinoxaline)bis(methylene)bis(2-acetamidomalonate) (7b)**

To a stirred suspension of potassium carbonate (284 mg, 2.05 mmol), TBAHS (23.2 mg, 0.06 mmol) and DEAM (112 mg, 0.51 mmol) in anhydrous MeCN (20 mL) was added compound **4p** (120 mg, 0.34 mmol) to give a pale yellow solid **7b** (148 mg, 70%). $R_f$ = 0.3 (silica gel, 50% EtOAc-petroleum ether); Mp 134-136 °C; IR (KBr): 3384, 2947, 2835, 1653, 1451, 1028 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.23 (m, 12H), 1.94 (s, 6H), 4.11 (s, 2H), 4.12 (s, 2H), 4.27 (m, 8H), 7.01 (s, 1H), 7.02 (s, 1H), 7.61 (d, $J$ = 8.8 Hz, 1H), 7.81 (d, $J$ = 8.8 Hz, 1H), 7.87 (s, 1H); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ = 11.5, 20.5, 34.1, 60.3, 62.9, 124.7, 127.0, 127.9, 132.8, 135.9, 137.6, 149.7, 150.6, 165.0, 166.8; HRMS (Q-Tof): *m/z* calcd for $C_{28}H_{36}N_4O_{10}Cl$ $[M+H]^+$ 623.2120; found 623.2102.

**Tetraethyl 2,2'-(5-methylquinoxaline)bis(methylene)bis(2-acetamidomalonate) (7c)**

To a stirred suspension of potassium carbonate (251.28 mg, 1.82 mmol), TBAHS (20.5 mg, 0.06 mmol) and DEAM (98 mg, 0.45 mmol) in anhydrous MeCN (20 mL) was added 2,3-bis(bromomethyl)-5-methylquinoxaline **4q** (100 mg, 0.30 mmol) to give pale yellow semi-solid **7c** (114 mg, 63%). $R_f$ = 0.3 (silica gel, 50% EtOAc-petroleum ether); IR (KBr): 3686, 3617, 3020, 2977, 2400, 1724, 1602, 1520, 1477, 1424, 1216, 1046 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.2 (m, 12H), 2.79 (s, 3H), 2.81 (s, 3H), 2.9 (s, 3H), 4.05 (s, 2H), 4.09 (s, 2H), 4.23 (m, 8H), 7.73 (s, 1H), 7.74 (s, 1H), 7.68-7.83 (m, 1H), 7.95 (d, $J$ = 8.4 Hz, 1H), 8.17 (t, $J$ = 7.6 Hz, 1H); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ = 14.0, 17.3, 28.0, 28.1, 39.2, 39.3, 63.1, 69.2, 126.8, 128.9, 130.9, 133.2, 133.4, 137.7, 143.2, 147.9, 166.7, 174.5; HRMS (Q-Tof): *m/z* calcd for $C_{29}H_{39}N_4O_{10}$ $[M+H]^+$ 603.2510; found 603.2519.

**Tetraethyl 2,2'-(2,5-dibromothiophene)bis(methylene)bis(2-acetamidomalonate) (7d)**

To stirred suspension of potassium carbonate (147 mg, 1.06 mmol) and DEAM (78 mg, 0.36 mmol) in anhydrous MeCN (5 mL) was added compound **4k** (60 mg, 0.18 mmol) to give white solid **7d** (50 mg, 40%). $R_f$ = 0.39 (silica gel, 40% EtOAc-petroleum ether); Mp 150-151 °C; IR (KBr): 3055, 2987, 2109, 1740, 1682, 1266, 1059, 1023, 740 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.24-1.29 (m, 12H), 1.99 (s, 3H), 2.07 (s, 3H), 3.63 (s, 2H), 3.85 (s, 2H), 4.15-4.31 (m, 8H), 6.50 (s, 1H), 6.75 (s, 1H); $^{13}$C NMR (100.6 MHz, $CDCl_3$): $\delta$ = 14.0, 14.1, 23.3, 23.7, 32.9, 33.4, 62.8, 63.2, 65.4, 66.0, 112.3, 114.6, 132.8, 134.2, 167.0, 167.7, 169.6, 169.7; HRMS (Q-Tof): *m/z* calcd for $C_{24}H_{33}N_2O_{10}Br_2S$ $[M+H]^+$ 699.0223; found 699.0248.

**General procedure for SM cross-coupling reaction in the presence of [$Pd_2(dba)_3$] and Buchwald ligand**

In a typical reaction procedure, the diiodo Tic derivative (1 equiv.) **6a** was reacted with an appropriate boronic acid (2.5 equiv.), Buchwald ligand (5 mol%) and $Na_2CO_3$ (5 equiv.) in presence of THF/toluene/water (1:1:1) at 80 $^oC$ for 15-20 min followed by addition of [$Pd_2(dba)_3$] (1.5 mol%). At the conclusion of the reaction (TLC monitoring), the reaction mixture was poured into water and aqueous phase was extracted with EtOAc (3 × 25 mL). The combined organic layer was washed with water, brine and dried over $Na_2SO_4$. Evaporation of solvent under reduced pressure gave the crude compound which was purified by silica gel column chromatography. Elution of the column with EtOAc-petroleum ether mixture gave the cross-coupled product.

**Diethyl 2-acetyl-6,7-diphenyl-1,2-dihydroisoquinoline-3,3-dicarboxylate (8a)**

Phenylboronic acid **12** (24 mg, 0.20 mmol), aqueous $Na_2CO_3$ (42.4 mg, 0.40 mmol) and Buchwald ligand (10 mol%, 2 mg) were added to a solution of **6a** (50 mg, 0.08 mmol) in THF/toluene/water (1:1:1, 9 mL), and the resulting reaction mixture was degassed for 15 min. [$Pd_2(dba)_3$] (1.2 mg, 1.5 mol%) was then added to obtain a white solid **8a** (12 mg, 30%). $R_f$ = 0.34 (silica gel, 50% EtOAc-petroleum ether); IR (KBr): 1021, 1261, 1397, 1747, 1966, 2855, 2924; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 1.19 (t, $J$= 7.17 Hz, 6H), 2.35 (s, 3H), 3.51 (s, 2H), 4.18-4.22 (m, 4H), 4.77 (s, 2H), 7.06-7.09 (m, 4H), 7.19-7.22 (m, 8H); $^{13}C$ NMR (75.4 MHz, $CDCl_3$): $\delta$ = 14.0, 22.5, 37.2, 47.7, 62.0, 68.1, 126.7, 128.0, 128.3, 129.8, 129.9, 131.3, 131.7, 139.9, 140.2, 140.8, 167.9, 171.2; HRMS (Q-Tof): *m/z* calcd for $C_{29}H_{30}NO_5$ $[M+H]^+$ 472.2124; found 472.2107.

**Diethyl 2-acetyl-6,7-bis(4-methoxyphenyl)-1,2-dihydroisoquinoline-3,3-dicarboxylate (8b)**

4-Methoxyphenylboronic acid **13** (30 mg, 0.20 mmol), aqueous $Na_2CO_3$ (42.4 mg, 0.40 mmol) and Buchwald ligand (2.0 mg 10 mol%) were added to a solution of diiodo Tic derivative **6a** (50 mg, 0.08 mmol) in THF/toluene/water (1:1:1, 9 mL), and the resulting reaction mixture was degassed for 15 min. [$Pd_2(dba)_3$] (1.2 mg, 1.5 mol%) was then added to obtain a white solid **8b** (22 mg, 49%). $R_f$ = 0.29 (silica gel, 50% EtOAc-petroleum ether); IR (KBr): 1028, 1296, 1395, 1609, 1741, 2837, 2982 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 1.18 (t, $J$= 7.17 Hz, 6H), 2.30 (s, 3H), 3.48 (s, 2H), 3.78 (s, 6H), 4.17-4.21 (m, 4H), 4.75 (s, 2H), 6.75 (d, $J$= 7.33 Hz, 4H), 6.98-7.04 (m, 4H), 7.16 (d, $J$= 3.97 Hz, 2H); $^{13}C$ NMR (75.4 MHz, $CDCl_3$): $\delta$ = 14.0, 22.5, 37.1, 47.7, 55.2, 62.0, 68.1, 113.5, 128.2, 129.8, 130.8, 131.3, 133.3, 139.4, 139.7, 158.5, 167.9, 171.1; HRMS (Q-Tof): *m/z* calcd for $C_{31}H_{34}NO_7$ $[M+H]^+$ 532.2335; found 532.2335.

**Diethyl 2-acetyl-6,7-bis(4-formylphenyl)-1,2-dihydroisoquinoline-3,3-dicarboxylate (8c)**

4-Formylphenylboronic acid **14** (45 mg, 0.30 mmol), aqueous $Na_2CO_3$ (64 mg, 0.60 mmol) and Buchwald

ligand (10 mol%, 3.8 mg) were added to a solution of diiodo Tic derivative **6a** (70 mg, 0.12 mmol) in THF/toluene/water (1:1:1, 9 mL), and the resulting reaction mixture was degassed for 15 min. $[Pd_2(dba)_3]$ (1.6 mg, 1.5mol%) was then added to obtain a white solid **8c** (30 mg, 48%). $R_f$ = 0.18 (silica gel, 50% EtOAc-petroleum ether); IR (KBr): 1063, 1209, 1394, 1605, 1703, 1747, 2853, 2982; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.21 (t, $J$ = 7.17 Hz, 6H), 2.33 (s, 3H), 3.54 (s, 2H), 4.18-4.23 (m, 4H), 4.80 (s, 2H), 7.22-7.28 (m, 6H), 7.73-7.75 (m, 4H), 9.97 (s, 2H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 14.0, 22.2, 27.8, 37.0, 47.6, 62.2, 67.9, 128.3, 129.9, 130.4, 132.8, 133.0, 135.0, 138.6, 138.9, 146.5, 167.8, 171.2, 191.8; HRMS (Q-Tof): *m/z* calcd. for $C_{31}H_{30}NO_7$ $[M+H]^+$ 528.2022; found 528.2025.

**Diethyl 2-acetyl-6,7-bis(3-(trifluoromethyl)phenyl)-1,2-dihydroisoquinoline-3,3-dicarboxylate (8d)**

3-(Trifluoromethyl)phenylboronic acid **15** (48 mg, 0.25 mmol), aqueous $Na_2CO_3$ (53 mg, 0.50 mmol) and Buchwald ligand (10 mol%, 2.4 mg) were added to a solution of diiodo Tic derivative **6a** (60 mg, 0.10 mmol) in THF/toluene/water (1:1:1, 9 mL), and the resulting reaction mixture was degassed for 15 min. $[Pd_2(dba)_3]$ (1.4 mg, 1.5 mol-%) was then added to obtain a white solid **8d** (32 mg, 50%). $R_f$ = 0.35 (silica gel, 40% EtOAc-petroleum ether); IR (KBr): 1075, 1266, 1331, 1664, 1735, 2854, 2986, 3054 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 1.21 (t, $J$ = 7.13 Hz, 6H), 2.32 (s, 3H), 3.54 (s, 2H), 4.20-4.23 (m, 4H), 4.80 (s, 2H), 7.21 (d, $J$ = 7.21 Hz, 2H), 7.26-7.36 (m, 6H), 7.48 (d, $J$ = 7.53 Hz, 2H); $^{13}$C NMR (75.4 MHz, $CDCl_3$): $\delta$ = 14.0, 22.5, 37.0, 47.5, 62.1, 67.9, 123.8, 126.5, 128.2, 128.6, 128.7, 129.7, 130.5, 130.9, 132.5, 132.8, 133.0, 138.4, 138.7, 140.8, 167.8, 171.1; HRMS (Q-Tof): *m/z* calcd for $C_{31}H_{28}NO_5F_6$ $[M+H]^+$; 608.1872; found 608.1868.

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derivative **7a**.

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