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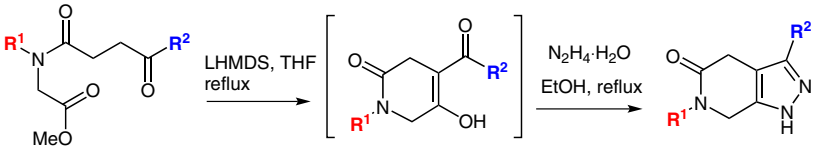
Synthesis of the Novel Tetrahydropyrazolo[3,4-*c*]pyridin-5-one Scaffold

Nicholas J. Howe*
Kevin Blades
Gillian M. Lamont

AstraZeneca Oncology Innovative Medicines, Mereside, Alderley Park, Macclesfield, Cheshire, SK10 4TG, UK
nick.howe@astrazeneca.com



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Abstract We report an efficient synthesis of the novel 1,4,6,7-tetrahydropyrazolo[3,4-*c*]pyridin-5-one scaffold with the potential for incorporation of alkyl or aryl substituents at the C-3 and N-6 positions. The route utilises a Dieckmann condensation to install the lactam ring, followed by a hydrazine cyclisation to build the fused pyrazole ring.

Key words pyrazole, lactam, Dieckmann condensation, hydrazine

Indazoles and azaindazoles are important heterocyclic cores for exploration as drug scaffolds.[1] In comparison with indazole (**1**) and, to a lesser extent, 6-azaindazole (**2**), the analogous fused pyrazole-lactam **3** is a significantly less lipophilic scaffold for structural elaboration, as demonstrated by their ClogP values[2] (Figure 1).

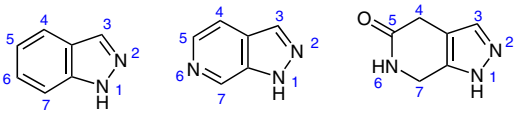


Figure 1 Generic indazole, 6-azaindazole and 1,4,6,7-tetrahydropyrazolo[3,4-*c*]pyridin-5-one scaffolds

Compounds based on core **3** should also have improved aqueous solubility compared with analogous compounds based on cores **1** and **2**, as a result of their reduced planarity.[3] Compounds with fused pyrazole-lactam cores are known to be biologically significant, and examples include Apixaban (**4**), which is an inhibitor of blood coagulation factor Xa,[4] and **5** (Figure 2), which was recently reported as having antitumour activity.[5] The synthesis of substituted 1,4,6,7-tetrahydropyrazolo[3,4-*c*]pyridin-5-one (**3**) was required for an AstraZeneca medicinal chemistry project and this paper describes how it was achieved.

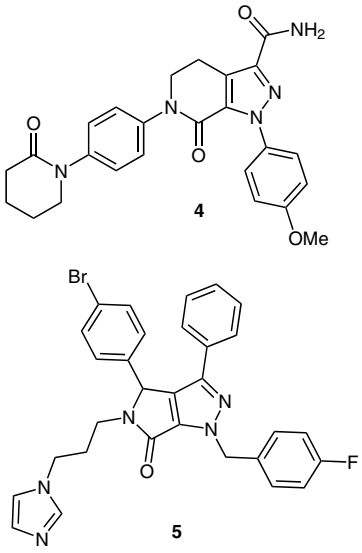
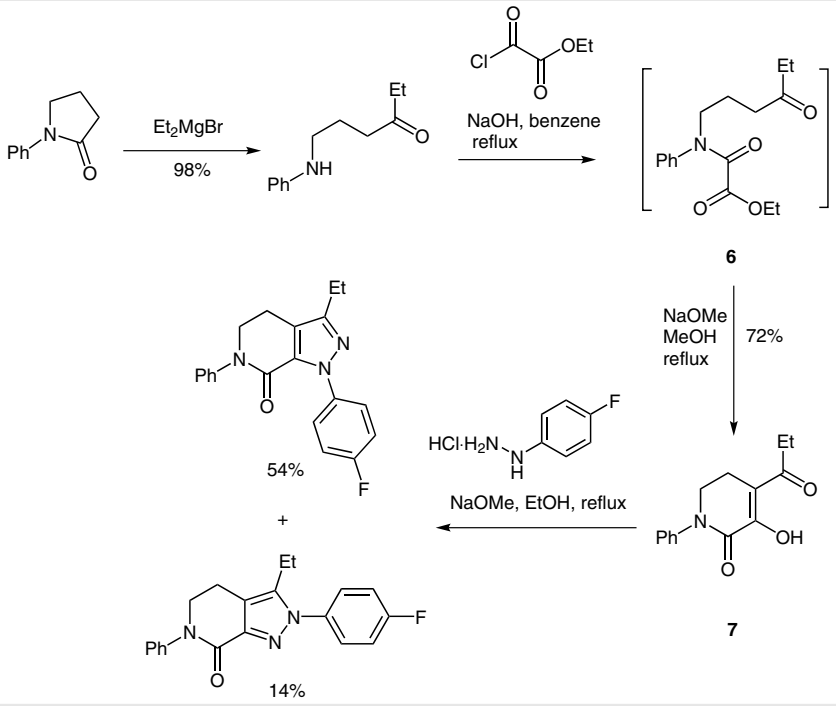


Figure 2 Biologically active compounds based on fused pyrazole-lactam scaffolds

Duplantier et al. described the synthesis of 4,5,6,7-tetrahydropyrazolo[3,4-*c*]pyridin-7-ones[6] (Scheme 1) proceeding via keto ester **6**, which underwent a Dieckmann condensation with sodium methoxide to give the vinylogous acid **7**, which then underwent cyclisation with an aryl hydrazine to give a mixture of the two 4,5,6,7-tetrahydropyrazolo[3,4-*c*]pyridin-7-one regioisomers. It should be noted that the authors only reported the synthesis of compounds bearing alkyl substituents at the C-3 position of the core.

We have been successful in developing a similar approach to the synthesis of 6,7-dihydro-1*H*-pyrazolo[3,4-*c*]-pyridin-5(4*H*)-ones **8** (Table 1). The success of this new route required finding reliable conditions for formation of the γ-keto acid intermediates **10**. Initial attempts focussed on reaction of an aryllithium species (derived from the aryl



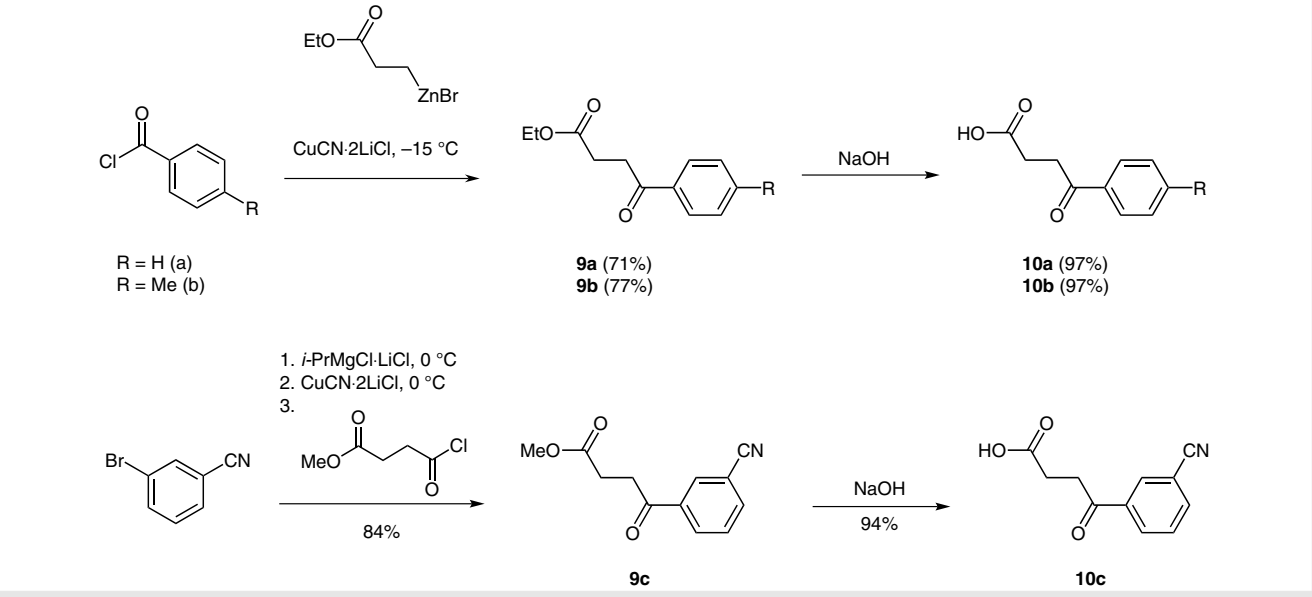
Scheme 1 Synthetic route to 4,5,6,7-tetrahydropyrazolo[3,4-*c*]pyridin-7-ones[6]

bromide through lithium–bromine exchange with *n*-BuLi) with succinic anhydride to go straight to the desired γ-keto acid.[7]

This approach did not yield the desired product, so, after attempting a palladium-catalysed approach,[8] our attention turned to the reaction of an organometallic species with an acid chloride to form the desired ketone. Organolithium species were deemed too reactive and incompatible with the desired functionalities (e.g., ester, nitrile) so we investigated the use of organocuprate species. These were prepared by transmetallation of an organozinc or organomagnesium species using commercial copper cyanide–lithium chloride complex.[9]

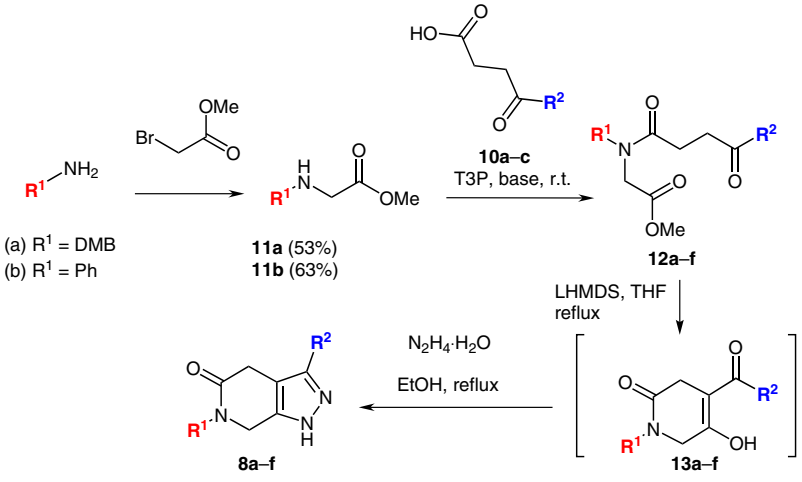
The cuprate derived from (3-ethoxy-3-oxopropyl)zinc bromide reacted with benzoyl chloride or 4-methylbenzoyl chloride to give the corresponding γ-keto esters in 71 and 77% yield, respectively (Scheme 2). Reaction of this same alkylcuprate with 3-cyanobenzoyl chloride, however, failed to give any γ-keto ester. An alternative method was used in this case; the aryl Grignard of 3-bromobenzonitrile was formed, transmetallated with CuCN·2LiCl and subsequently reacted with methyl 4-chloro-4-oxobutanoate to give the desired γ-keto ester in 84% yield. This method is suited to electron-deficient aryl bromides such as 3-bromobenzonitrile. However, more electron-rich aryl bromides (e.g., bromobenzene or 4-bromotoluene) are less suited to this method because they undergo bromine–magnesium exchange only very slowly.[10]

With the γ-keto esters **9** in hand, the corresponding γ-keto acids **10** were formed by base hydrolysis and were then coupled using propanephosphonic cycloanhydride (T3P) with amino esters **11** to give amide products **12**. Due to its reduced nucleophilicity, methyl 2-(phenylamino)acetate required two equivalents of acid and overnight stirring for the reaction to proceed, but even then the yield of **12f** was moderate (63%; Table 1). Intermediates **12** were then subjected to a Dieckmann condensation with LHMDS at reflux. The resulting vinylogous acid intermediates **13** were then heated to reflux with hydrazine in ethanol to give 6,7-dihydro-1*H*-pyrazolo[3,4-*c*]pyridin-5(4*H*)-ones **8**. The combined yields for these two final steps varied from 66% (**8e**) to 21% (**8f**). The Dieckmann condensations generally gave just one major product; however, the cyclisation with methyl 2-(4-oxo-*N*,4-diphenylbutanamido)acetate gave an equal amount of an unknown regioisomer, which could not be separated from desired **13f**. Upon reaction with hydrazine, **8f** precipitated out of the reaction mixture. The hydrazine reactions were generally complete within 24 h; however, cyclisation of the intermediate hydrazones proceeded more slowly when electron-withdrawing substituents were present (Table 1, **8c** and **8f**). The final cyclisation was also attempted with vinylogous acid **13a** and methyl- and arylhydrazines (Table 2). The reaction with methylhydrazine gave an inseparable mixture of regioisomers, but it is assumed that **14a** is the major regioisomer by analogy to the reactions of phenylhydrazine and 2-pyridylhydrazine,



Scheme 2 Synthesis of γ-keto acid intermediates **10**

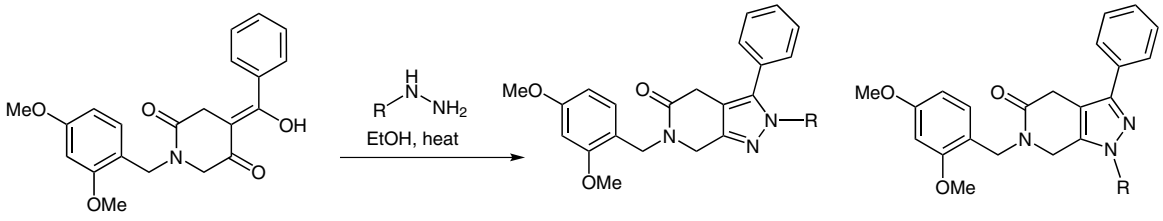
Table 1 Synthetic Route to 6,7-Dihydro-1*H*-pyrazolo[3,4-*c*]pyridin-5(4*H*)-ones **8**



Entry	R^1	R^2	Isolated yield (%)		
			12	**13**	**8**
a	DMB[a]	Ph	88	74	71
b	DMB[a]	4-MeC_6H_4	83	54	82
c	DMB[a]	3-NCC_6H_4	82	70	58
d	DMB[a]	Me[b]	98	57	88
e	Pr[c]	Ph	85	79	83
f	Ph	Ph	63	50	43

[a] DMB = 2,4-dimethoxybenzyl.
[b] Commercial levulinic acid was used.
[c] Commercial methyl 2-(propylamino)acetate was used.

Table 2 Reaction of Vinylogous Acid **13a** with Substituted Hydrazines



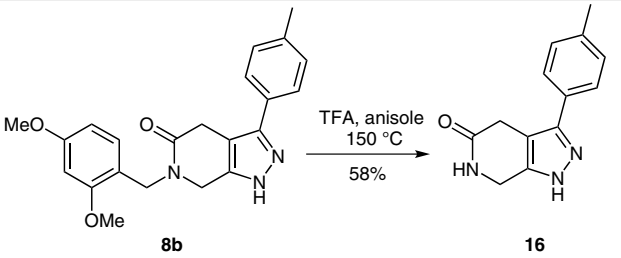
13a **14** **15**

Entry	R	Yield of **14** (%)	Yield of **15** (%)
a	Me	54[a]	14[a]
b	Ph	60[b]	11[c]
c	2-pyridyl	78[b]	negligible

[a] Regioisomers not separable; the ratio was determined based on ^{1}H NMR spectroscopic analysis.
[b] Isolated and the structure was confirmed by ROESY NMR.
[c] Determined by LC–MS analysis.

where it was possible to isolate the major regioisomer and this was confirmed in both cases as the 2-substituted pyrazole (Table 2, **14b** and **14c**). It is postulated that when the R^2 group is phenyl, as in **13a**, the vinylogous acid exists predominantly as the tautomer shown in Table 2, which may explain the regioselectivity observed on reaction with substituted hydrazines.

To allow the potential for further derivatisation[11] of the 1,4,6,7-tetrahydropyrazolo[3,4-*c*]pyridin-5-one core, it was demonstrated that the DMB protecting group could be removed by heating **8b** with trifluoroacetic acid to give the N-H lactam **16** in 58% yield (Scheme 3).



8b **16**

Scheme 3 Deprotection of 2,4-dimethoxybenzyl protecting group

We have developed an efficient route[12–14] to a novel tetrahydropyrazolo[3,4-*c*]pyridin-5-one scaffold. This approach allows for alkyl or aryl substituents to be incorporated at the C-3 and N-6 positions. Further structural diversity can be achieved by the use of suitable protection on the lactam nitrogen, such as the DMB group. This allows the N-1/N-2 and N-6 positions on this scaffold to be further elaborated, once the core has been constructed.

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379504.

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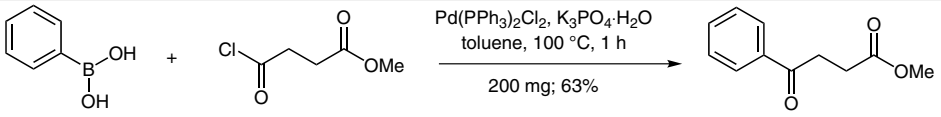

Scheme 4 γ-Keto ester formation by palladium catalysis[8]

(8) Wang, Y.; Przyuski, K.; Roemmele, R. C.; Hudkins, R. L.; Bakale, R. P. *Org. Process Res. Dev.* **2013**, *17*, 846; Pd-catalysed coupling gave the desired γ-keto ester in 63% yield (Scheme 4); however, on 10-fold scale-up to 13 mmol, the yield dropped to 39%. We were unable to obtain a robust, scalable procedure by using this methodology.

(9) (a) For transmetallation of ArMg species with CuCN·2LiCl, see: Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 3333. (b) For transmetallation of ArZn species with CuCN·2LiCl, see: Kneisel, F. F.; Dochnahl, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 1017.

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(11) For conditions for lactam N-alkylation and N-arylation, see Ref. 6. For the conversion of silyl-protected lactams into N-alkyl cyclic imines, see: Hua, D. H.; Miao, S. W.; Bharathi, S. N.; Katsuhira, T.; Bravo, A. A. *J. Org. Chem.* **1990**, *55*, 3682.

(12) **Formation of γ-Keto Esters; Typical Procedure for Ethyl 4-Oxo-4-phenylbutanoate(9a)**: A multi-necked round-bottomed flask was dried with a hot-air gun under vacuum and then purged with nitrogen and cooled. To this flask was added (3-ethoxy-3-oxopropyl)zinc(II) bromide (0.5 M in THF, 7.50 mL, 3.75 mmol), which was cooled to –15 °C under nitrogen. Benzoyl chloride (0.419 mL, 3.57 mmol) was added followed by copper(I) dilithium dichloride cyanide (1 M in THF, 3.75 mL, 3.75 mmol). The reaction mixture was warmed to r.t. and stirred at this temperature for 3 h. The reaction was quenched by addition of sat. aq NH_4Cl (80 mL) and filtered. The filtrate was extracted with EtOAc (2 × 50 mL) and the combined organics were washed with brine (40 mL), dried ($MgSO_4$), filtered, and concentrated under vacuum to afford an orange oil (900 mg). The crude product was purified by flash silica chromatography (EtOAc–heptane, 0 to 30%). Pure fractions were evaporated to dryness to afford ethyl 4-oxo-4-phenylbutanoate (0.53 g, 71%) as a colourless liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.2 Hz, 3 H), 2.76 (t, *J* = 6.7 Hz, 2 H), 3.31 (t, *J* = 6.7 Hz, 2 H), 4.16 (q, *J* = 7.1 Hz, 2 H), 7.43–7.50 (m, 2 H), 7.53–7.60 (m, 1 H), 7.95–8.01 (m, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.2, 28.4, 33.4, 60.6, 128.1, 128.6, 133.2, 136.7, 172.9, 198.1. HRMS: *m*/*z* calcd for $C_{12}H_{14}O_3$: 206.0943; found: 206.0926.

Methyl 4-(3-Cyanophenyl)-4-oxobutanoate(9c): To dried glassware was added 3-bromobenzonitrile (400 mg, 2.20 mmol) in anhydrous THF (5 mL) under nitrogen. This was cooled to –10 °C and isopropylmagnesium lithium chloride (1.3 M in THF, 2.54 mL, 3.30 mmol) was added over 10 min. The mixture was stirred at 0 °C for 3 h, monitoring for completion of magnesiation by LC-MS of NH_4Cl solution-quenched aliquots. Transmetallation was carried out by addition of copper(I) dilithium dichloride cyanide (1 M in THF, 3.74 mL, 3.74 mmol) at 0 °C, with stirring at this temperature for 10 min and then the mixture was cooled to –50 °C under nitrogen and methyl 4-chloro-4-oxobutanoate (0.418 mL, 3.30 mmol) in anhydrous THF (2 mL) was added. The reaction was stirred at –50 °C for 10 min and then warmed to r.t. gradually overnight. The reaction mixture was quenched by addition of sat. aq NH_4Cl (30 mL) and then extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with water (20 mL), brine (20 mL), dried ($MgSO_4$), filtered and concentrated under vacuum to afford a brown oil (1.0 g). The crude product was purified by flash silica chromatography (EtOAc–heptane, 0 to 100%). Pure fractions were evaporated to dryness to afford methyl 4-(3-cyanophenyl)-4-oxobutanoate (395 mg, 84%) as a white foamy solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.80 (t, *J* = 6.5 Hz, 2 H), 3.30 (t, *J* = 6.5 Hz, 2 H), 3.71 (s, 3 H), 7.59–7.65 (m, 1 H), 7.85 (dt, *J* = 7.7, 1.4 Hz, 1 H), 8.20 (dt, *J* = 7.9, 1.4 Hz, 1 H), 8.24–8.28 (m, 1 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 27.9, 33.5, 51.9, 113.4, 117.9, 129.7, 131.8, 132.0, 136.1, 137.4, 173.0, 196.1. HRMS: *m*/*z* calcd for $C_{12}H_{11}NO_3$: 217.0739; found: 217.0753.

(13) **Dieckmann Condensation and Subsequent Hydrazine Cyclisation; Typical Procedure for 3-Phenyl-6-propyl-6,7-dihydro-1*H*-pyrazolo[3,4-*c*]pyridin-5(4*H*)-one (8e)**: (i) Lithium bis(trimethylsilyl)amide (1 M in THF, 1.46 mL, 1.46 mmol) was added to a solution of methyl 2-(4-oxo-4-phenyl-*N*-propylbutanamido)acetate (386 mg, 1.32 mmol) in anhydrous THF (4 mL) under nitrogen. The reaction mixture was heated at reflux for 30 min. After cooling to r.t., the reaction was diluted with 1 M citric acid (20 mL) and CH_2Cl_2 (50 mL). The organics were washed with brine (50 mL), dried ($MgSO_4$), filtered, and the crude product was purified by flash silica chromatography (MeOH–CH_2Cl_2, 0 to 8%). Pure fractions were evaporated to dryness to afford 4-benzoyl-5-hydroxy-1-propyl-1,6-dihydropyridin-2(3*H*)-one (**13e**; 272 mg, 79%) as a pale-yellow oil, which solidified on standing. (ii) Hydrazine hydrate (0.097 mL, 2.01 mmol) was added to a solution of 4-benzoyl-5-hydroxy-1-propyl-1,6-dihydropyridin-2(3*H*)-one (260 mg, 1.00 mmol) in ethanol (5 mL). The reaction was heated to reflux for 24 h. After cooling to r.t., the solvent was removed under vacuum to afford a pale-brown solid, which was triturated with EtOAc–Et_2O (1:1), filtered, and dried to afford 3-phenyl-6-propyl-6,7-dihydro-1*H*-pyrazolo[3,4-*c*]pyridin-5(4*H*)-one (213 mg, 83%) as a beige powder. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 0.88 (t, *J* = 7.4 Hz, 3 H), 1.53–1.67 (m, 2 H), 3.37–3.47 (m, 2 H), 3.62 (t, *J* = 1.9 Hz, 2 H), 4.54 (s, 2 H), 7.25–7.78 (m, 5 H), 13.17 (s, 1 H). ^{13}C NMR (176 MHz, DMSO-d_6 + CD_3CO_2D): δ = 11.0, 19.5, 29.8, 45.0, 48.5, 107.9, 125.7, 127.5, 128.8, 130.6, 139.2, 140.5, 166.5. HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{18}N_3O$: 256.1450; found: 256.1460.

(14) For full experimental procedures and analytical data, please refer to the Supporting Information.