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# Synthesis of Squaric Acid Monoamides as Building Blocks for Drug Discovery

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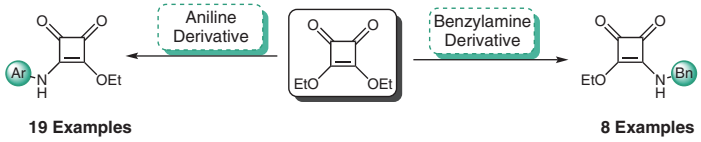



The Wren Group would like to dedicate this article to Tory May Wren who sadly passed away on the 28th October 2022. She is a constant source of inspiration for her dad (Stephen P. Wren).

Received: 03.07.2023
Accepted after revision: 03.08.2023
Published online: 04.08.2023 (Accepted Manuscript), 29.08.2023 (Version of Record)
DOI: 10.1055/a-2148-9518; Art ID: SO-2023-07-0043-L



**Abstract** Herein, we present a synthetic compound library comprising of 28 anilino and benzylamino monosquarate-amide derivatives. Members of this library were designed as bioisosteric replacements for groups such as the ubiquitous carboxylic acid moiety. Further to their synthesis, we have shown the potential of these chemical building blocks for the generation of additional novel compounds. This work forms part of our efforts aimed at the assembly of 96-well plates loaded with bioisosteric analogues that may be used to enrich drug discovery programs. The research presented in this work focuses on the chemistry of 3,4-dihydroxycyclobut-3-ene-1,2-dione, a known carboxylic acid bioisostere.

**Key words** squaric acid, squaramide, bioisostere, carboxylic acid, compound library

The carboxylic acid moiety is a ubiquitously recognised functional group in the sphere of organic chemistry. The importance of this group is easily justified both by its prevalence and the number of endogenous biological processes which rely on its intrinsic chemical nature.[1] Over 450 marketed drug compounds worldwide are known to possess a carboxylic acid group within their chemical structure. Such drug classes include nonsteroidal anti-inflamatory drugs (NSAIDs) (such as naproxen (**1**) and indomethacin (**2**)), anticoagulants, statins, betafucin (which contains fusidic acid (**3**)), β-lactam antibiotics, and GPR40 agonists to name but a few (Figure 1).[2–4]

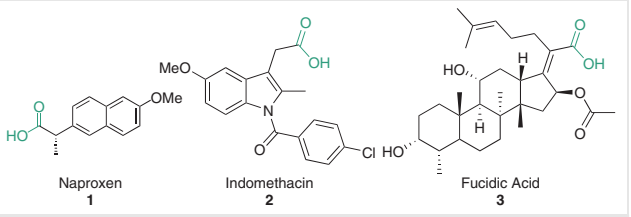



**Figure 1** Examples of marketed drug compounds featuring a carboxylic acid

Despite its prevalence, and often acting directly as a pharmacophore to invoke a biological response, the presence of this polar moiety can also confer significant drawbacks. One such pitfall involves extensive metabolism of the carboxylic acid functional group through glucoconjugation.[5] Another potential complication is a diminished ability to diffuse across biological membranes and this can be a particular issue in the context of developing agents which act on the central nervous system (CNS). In order for drugs to be CNS active they must successfully permeate the blood brain barrier, a highly lipophilic membrane which does not tolerate the charged carboxylate ion present at physiological pH.[6] Further, the presence of the carboxylic acid functionality can lead to idiosyncratic toxicity and result in a drug candidate being withdrawn from the market (for example, benoxaprofen).[7]

Frequently, replacement of the carboxylic acid motif or other structural units with a suitable surrogate or bioisostere (such as a squaramide) is undertaken in order to avoid suboptimal properties that may give rise to unsuitability for lead compound generation, or undesirable pharmacokinetic effects.[1,8] In this paper, we describe our con-

tinuing efforts to develop a toolbox of bioisosteric building blocks for use by the medicinal chemistry community. This work builds on our recent review of the synthesis of novel thiazolidinedione-containing derivatives used to replace carboxylic acid moieties in druglike structures.[9] Consultation of the literature, specifically works published by Lassalas and co-workers, highlighted 3,4-dihydroxycyclobut-3-ene-1,2-dione (squaric acid) as a recognised bioisostere for the carboxylic acid functionality.[10]

Since its first synthesis, in 1959, by Cohen and colleagues, there has been continuous interest into the chemistry of squaric acid and its functionalised nitrogenous derivatives (Figure 2).[11] Squaric acid is a highly versatile organic framework which can be derivatised extensively and has seen use in the fields of optoelectronic materials, inorganic dyes, organocatalysis, and in the development of new pharmaceuticals.[12–14]

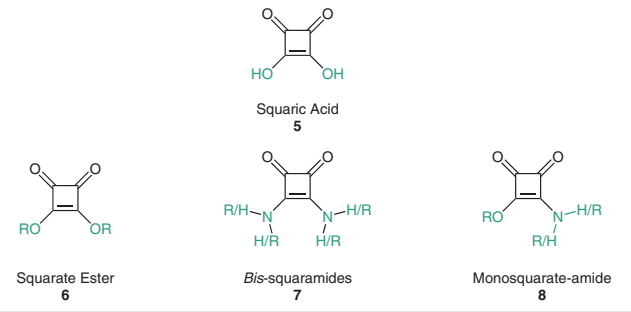



**Figure 2** Squaric acid and functionalised squaric acid derivatives

Squaric acid functionalised derivatives have been used in the field of medicinal chemistry. The majority of such structures usually fall into the class of bis-squaramides **7**, though some squarate esters **6** also are used clinically. One common clinically used example of a squarate ester is the dibutyl ester of squaric acid (SADBE).[15] SADBE is a known potent allergen and strong irritant and has been used in the treatment of *alopecia areata*. As a topical immunotherapy treatment it is a good alternative treatment method to patients with refractory alopecia who do not tolerate standard treatments, such as corticosteroids, phototherapy, topical Minoxidil, topical irritating agents, or immunosuppressives.[16,17]

Amino/nitrogen-functionalised squaric acid derivatives are far more common in the literature. Generally, the squaric acid core is chemically stable in an aqueous environment and therefore often stable *in vivo* (a largely aqueous environment). Other studies have revealed that where squaramides are used as isosteres for amino acids, they are often more resistant to decarboxylase action as they do not possess the nucleophilic nitrogen atom essential for the decarboxylation mechanism.[13] Squaric acid derivatives have been researched to combat a large multitude of different disease areas including, but not limited to, antibacterial, cytotoxic, antiprotozoal, and antiviral agents (Figure 3).[15] We commenced our investigations by targeting compounds that resemble **8** (where the squaric acid ring is functionalised once with a primary amine, and specifically, with the use of substituted anilines or benzylamines as library inputs).

Due to the poor solubility exhibited by squaric acid (**5**) in organic solvents, diethyl squarate (DES) (**14**, an example of **6**) was used as the precursor for all the following transformations.[18] We turned our attention to couple benzylamine (**15**) with diethyl squarate (**14**) by combining the two substrates in MeOH at room temperature. After 1 h the desired monosquarate-amide product **16** was isolated following purification, as a white solid, in 33% yield (Scheme 1). The structure of **16** was determined and confirmed by IR spectroscopy, NMR spectroscopy, and HRMS.

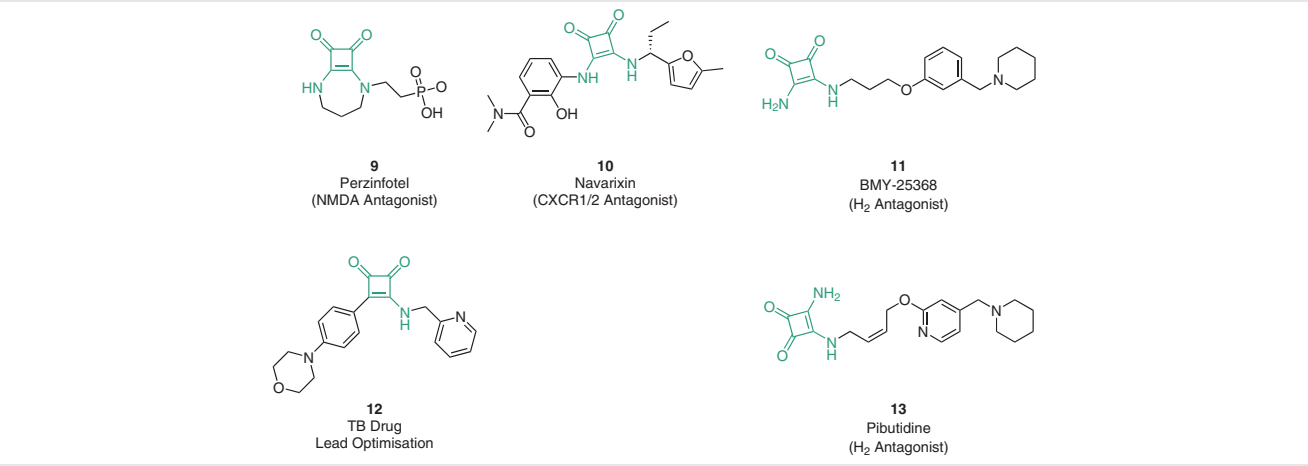
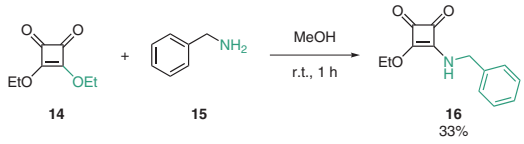
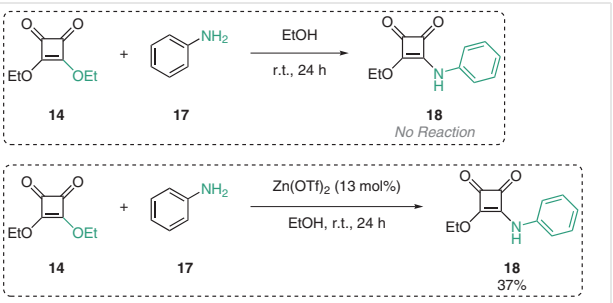



**Figure 3** Functionalised squaric acid medicinal agents




**Scheme 1** Coupling of diethyl squarate with benzylamine

With compound **16** in hand, attention then turned to accessing the aniline derivative **18**. Analysis of the reaction mechanism (which proceeds via nucleophilic addition then elimination) involves EtOH leaving as a byproduct of the reaction. Consequently, we exchanged the reaction solvent from MeOH to EtOH when trying to access the aniline scaffold. However, the attempted reaction failed to initiate, and no product formation was observed after 24 h (Scheme 2).

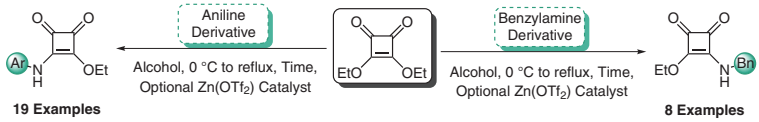


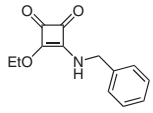
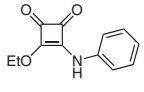

**Scheme 2** Coupling of aniline to DES with and without $Zn(OTf)_2$

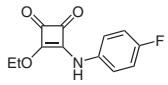
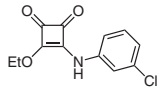
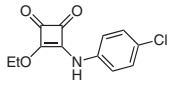
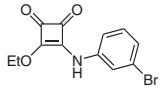
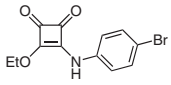
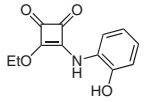
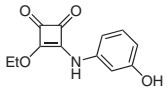
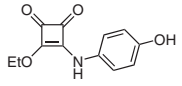
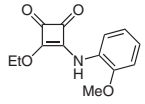
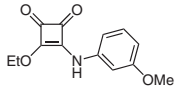
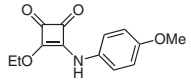
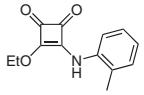
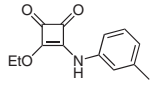
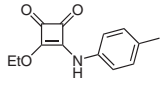
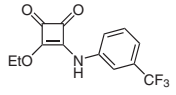
This reaction failure was attributed to the poor nucleophilicity of aniline as compared to benzylamine. Consultation of the literature revealed that, in many cases, a Lewis acid catalyst is introduced into the reaction which serves to coordinate to the carbonyl oxygens.[19] The presence of such a Lewis acid draws electron density away from the planar carbonyl carbons making them more electrophilic and the compounds more susceptible to substitution. Furthermore, the cationic zinc species can act as a steric block and (as a result of its coordination) prevents nucleophilic attack of the amine directly onto the carbonyl oxygens. With the inclusion of the $Zn(OTf)_2$ catalyst, loaded at 13 mol%, the desired aniline scaffold was yielded as an off-white solid in a 37% yield (Scheme 2). Ethyl alcohol is the only reaction solvent that we have evaluated to date. This decision was based on literature precedent.[20–23] While this is not an excellent yield, $Zn(OTf)_2$ was chosen as a suitable catalyst following literature precedent published by Taylor *et al.*[19] We are in the process of screening a series of potential Lewis acid catalysts in an effort to increase the yield of product.

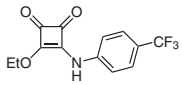
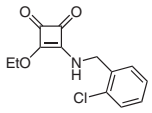
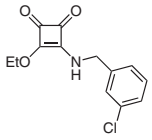
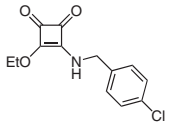
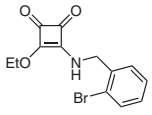
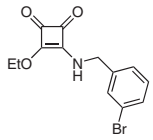
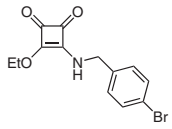
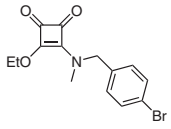
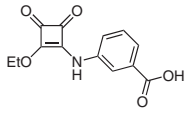
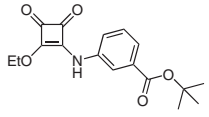
Inspired by our own success in yielding the unsubstituted analogues **16** and **18** we sought to generate a monosubstituted compound library by adding functionality to access further derivatives. Simple, yet functionalised, anilines and benzylamines were chosen on the basis of low cost and ability for varied substrate scope. This chemistry proved to have extensive substrate scope (Table 1). The isolated compounds listed in Table 1 were all initially attempted without the presence of the $Zn(OTf)_2$ catalyst. If the reaction failed to initiate after a period of 24 h, then the reaction was restarted, and the catalyst was included. Table 1 shows the reaction conditions used and associated yields for the compound library generation plus an assessment of each reaction product's novelty. In cases where the reaction failed to show significant consumption of the reacting amine the reaction was brought to reflux to try and drive the reaction forward. In many cases, and with TLC monitoring, heating the reaction at reflux for prolonged periods did not cause any further consumption of the starting amine and hence did not increase product yield. Overall, we have not only generated novel composition of matter for some of the monosquarate-amides, but we have also shown an improved yield for the synthesis of compound **25** (compared to a previous route).[24]

**Table 1** Overview of Synthetic Reactions Used to Yield Monosquarate-amide Derivatives



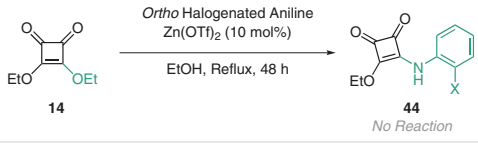

| Compound ID | Structure | Solvent | Temp | Time (h) | Catalyst presence | Yield (%) | Is product novel? |
|---|---|---|---|---|---|---|---|
| 16 |  | MeOH | r.t. | 1 | no | 33 | no[24] |
| 18 |  | EtOH | r.t. | 4 | 13 mol% | 37 | no[20] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 19 |  | EtOH | r.t. | 12 | 20 mol% | 75 | no (patent)[21] |
| 20 |  | EtOH | r.t. | 14 | 10 mol% | 26 | yes |
| 21 |  | EtOH | r.t. | 4 | 10 mol% | 60 | no (patent)[22] |
| 22 |  | EtOH | r.t. | 8 | 10 mol% | 64 | no[25] |
| 23 |  | EtOH | r.t. | 1 | 10 mol% | 66 | no[19] |
| 24 |  | EtOH | r.t. | 24 | no | 44 | no[26] |
| 25 |  | EtOH | 0 °C to r.t. | 24 | no | 54 | no[24] |
| 26 |  | EtOH | 0 °C to r.t. | 12 | no | 45 | yes |
| 27 |  | EtOH | r.t. | 24 | 13 mol% | 18 | yes |
| 28 |  | EtOH | r.t. | 24 | 13 mol% | 94 | yes |
| 29 |  | EtOH | r.t | 36 | 13 mol% | 49 | no[20] |
| 30 |  | EtOH | r.t | 50 | no | 29 | no[27] |
| 31 |  | EtOH | r.t | 48 | no | 89 | no[27] |
| 32 |  | EtOH | r.t | 12 | no | 75 | no[27] |
| 33 |  | EtOH | r.t | 10 | no | 54 | no (patent)[28] |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 34 |  | EtOH | r.t | 40 | 20 mol% | 48 | no[23] |
| 35 |  | EtOH | r.t | 48 | 10 mol% | 38 | yes |
| 36 |  | EtOH | r.t | 48 | no | 25 | yes |
| 37 |  | EtOH | reflux | 24 | no | 99 | yes |
| 38 |  | EtOH | r.t | 4 | no | 34 | yes |
| 39 |  | EtOH | 0 °C to r.t | 5 | no | 57 | yes |
| 40 |  | EtOH | r.t | 24 | no | 41 | yes |
| 41 |  | EtOH | r.t | 24 | no | 91 | yes |
| 42 |  | EtOH | reflux | 6 | 20 mol% | 31 | yes |
| 43 |  | EtOH | reflux | 5 | no | 48 | yes |

It can be witnessed that the coupling of DES (**14**) with one equivalent of amine leads to the generation of the corresponding monosquarate-amides in moderate to excellent yield (Table 1). Compound **37** was obtained in 99% yield, but these refluxing conditions have not yet proved to be transferable to the reactions run at room temperature. This series of compounds exhibit significant halide functionalisation as well as the presence of some electron-donating and electron-withdrawing groups (e.g., hydroxy, tolyl and trifluoromethyl derivatives **24**–**26**, **30**–**32**, and **33**, **34** respectively). Also, current research being conducted within our group is centered on extending this compound library to incorporate anilines adorned with fused ring systems and carbonyl-containing functional groups that are suitably protected.

It should be noted, however, that coupling reactions between **14** and *ortho*-halogenated aniline derivatives failed to proceed even when re-attempted with the inclusion of $Zn(OTf)_2$ and heating at reflux for a period of 48 h (see **44**, Scheme 3). The failure in these instances has been attributed both to the poor nucleophilicity of the anilines and the physical parameter of steric crowding. In the case of *ortho*-halogenated benzylamine derivatives (**35** and **38**), the reactions did yield the desired monosquarate-amides, presumably due to the fact that the requisite amines are sufficiently nucleophilic.



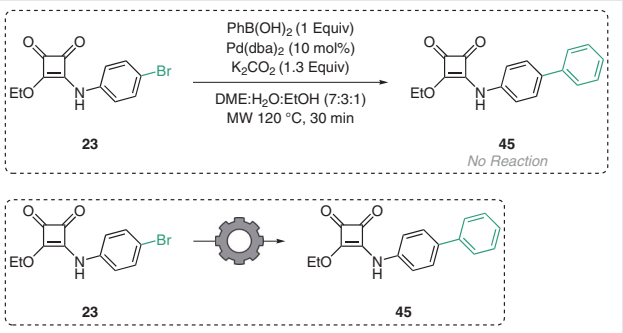

**Scheme 3** Reactions of diethyl squarate with *ortho* halogenated anilines

In all cases, where reactions yielded the desired products, they existed as amorphous solids when free of reaction solvent. The crude products were purified via column chromatography over silica gel without any aqueous workup being conducted. After accessing the purified compound, derivatives which were prepared using $Zn(OTf)_2$ were subjected to an aqueous workup to remove any transition-metal impurities.

With a significant series of analogues in hand, we began to explore the use of some of them in further chemical reactions in order to provide proof-of-concept applications for these versatile building blocks.

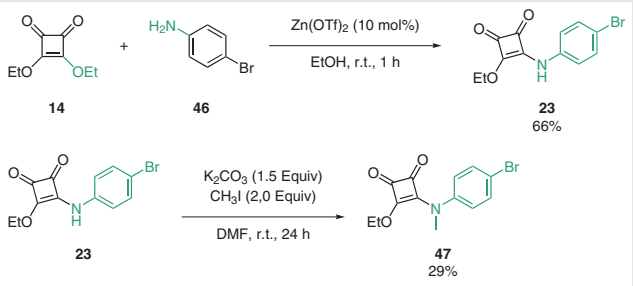
Brominated analogues are often targeted in synthetic studies due to their ability to act as substrates in cross-coupling reactions.[29,30] Thus, we attempted to use substrate **23** in a novel Suzuki cross-coupling reaction. For simplicity, $PhB(OH)_2$ was selected as a model coupling partner, $Pd(dba)_2$ as the palladium catalyst, and $K_2CO_3$ as the accompanying base. A three-component solvent mixture comprising of DME, $H_2O$, and EtOH, was used in the reaction. Unfortunately, after heating at 120 °C for 30 min, with microwave irradiation, no discernable product was detected by TLC and $^1H$ NMR spectroscopy (Scheme 4). We are currently studying alternative reaction conditions aimed at the discovery of a suitable methodology that allows the Pd-catalysed coupling of squaric acid derivatives (**45**, see Scheme 4).

Our intention to develop methods that demonstrate further functionality can be attached to our library compounds was exemplified by the addition of a Me group to the 'amidic' N**H**. Whilst being a relatively straightforward procedure, this reaction provided proof of concept that the synthesised substrates can afford more complex structural features.




**Scheme 4** Attempted Suzuki cross-coupling reaction utilising a synthesised derivative

The methyl adduct **47** was successfully obtained as a white solid in a 29% yield. It was isolated following the dissolution of **23** (which was prepared from **14** and **46**) and $K_2CO_3$ in DMF. Following dissolution and allowing 30 min for deprotonation, 2 equiv of MeI were added dropwise to the reaction mixture. After allowing the reaction to proceed for 24 h, the desired product was isolated the following aqueous workup, trituration with $Et_2O$ and column chromatography (eluting with 50% EtOAc in hexane; see Scheme 5).




**Scheme 5** Conducted methylation of a synthesised analogue with MeI

In summary, we have managed to assemble an initial library of monosquarate-amide building blocks derived from DES and a series of functionalised aniline and benzylamine precursors. We have demonstrated a proof-of-concept progress that compounds of this class can act as substrates in further chemical transformations. These innovations are continuing within our laboratory. We are looking to further extend this platform technology with the main goal of assembling 96-well plates of proprietary building blocks bearing biosisosteric replacements for the carboxylic acid moiety and other groups. Our continuing studies on the formation of novel analogues of marketed drugs will be reported on in due course.

## Conflict of Interest

The authors declare no conflict of interest.

## Acknowledgment

We thank Mr Reece Bristow and Mr James Scanlon (two previous undergraduate students working within the Wren Group) very much for their hard work establishing some preliminary results for this work. Our extensive gratitude is offered to both Mr Arran Solomonsz and Mr Antony Wozniak from Asynt Ltd. for the supply of glassware and heating utilities. We are also very grateful to Steve Brough, and the rest of the team at Key Organics Ltd. for their support and their supply of *tert*-butyl 3-aminobenzoate (which was used in this research to synthesise derivative **37** and **38**).

## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-2148-9518.

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(31) Experimental procedures are detailed in the Supporting Information. Two example syntheses are given here.
**Compound 26**
To 3,4-diethoxycyclobut-3-ene-1,2-dione (500 mg, 0.43 mL, 2.94 mmol, 1 equiv) dissolved in EtOH (15 mL) at 0 °C was added 4-hydroxyaniline (321 mg, 2.94 mmol, 1 equiv) in EtOH (10 mL). The reaction was allowed to warm to r.t. and stirred for 12 h before being concentrated under reduced pressure and purified via column chromatography (5% MeOH in DCM). The desired compound was obtained as a tan solid (311 mg, 45%); mp 208–213 °C. FTIR: $\nu_{max}$ = 3695 (NH), 3212 (OH stretch), 2982 (CH aromatic), 1807 (CH alkyl), 1728 (C=O) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 10.56 (s, 1 H), 9.42 (s, 1 H), 7.14 (s, 2 H), 6.75–6.69 (m, 2 H), 4.72 (q, *J* = 7.1 Hz, 2 H), 1.44–1.32 (m, 3 H). $^{13}C$ NMR (101 MHz, acetone-$d_6$): δ = 155.6, 131.2, 122.5, 116.5, 70.3, 16.1. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{12}H_{11}NO_4Na$: 256.0580; found: 256.0603.
**Compound 41**
To 3,4-diethoxycyclobut-3-ene-1,2-dione (500 mg, 0.43 mL, 2.94 mmol, 1 equiv) dissolved in EtOH (7 mL) was added 1-(4-bromophenyl)-*N*-methylmethanamine (588 mg, 0.59 mL, 2.94 mmol, 1 equiv) dropwise. The reaction was then stirred at r.t. for 24 h before being concentrated under reduced pressure and purified via column chromatography (55% EtOAc–hexane). The product was obtained as a white solid (870 mg, 91%); mp 110–114 °C. FTIR: $\nu_{max}$ = 2988 (NH), 2928 (CH aromatic), 1802 (CH alkyl), 1703 (C=O), 1591 (CO) $cm^{-1}$. $^1H$ NMR (400 MHz, DMSO-$d_6$): δ = 7.59 (d, *J* = 8.4 Hz, 2 H), 7.28 (d, *J* = 8.4 Hz, 2 H), 4.75 (s, 1 H), 4.67 (p, *J* = 6.8 Hz, 2 H), 4.52 (s, 1 H), 3.05 (d, *J* = 63.5 Hz, 3 H), 1.35 (q, *J* = 7.3 Hz, 3 H). $^{13}C$ NMR (151 MHz, DMSO-$d_6$): δ = 188.8, 181.6, 176.5, 171.4, 134.9, 131.7, 130.3, 130.2, 121.2, 69.2, 53.0, 36.0, 15.5. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{14}H_{15}{}^{81}BrNO_3$: 326.02298; found: 326.0203.