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Synthesis of a 1,3,5-benzotriazepine-2,4-dione based library

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ABSTRACT

A library of benzotriazepines has been synthesised employing microwave-mediated synthesis, supported resins and parallel synthesis methodology.

Privileged structures are extremely important in drug discovery and new routes to known or novel scaffolds are desirable since they can lead to new bioactive drug-like molecules, and can be incorporated in libraries for fragment-based or high throughput screening.[1] Benzodiazepines (BZDs) are examples of privileged scaffolds in medicinal chemistry and are found in a number of known or investigational drugs including those targeting G-protein coupled receptors (GPCRs).[2] In many cases, for example for cholecystokinin-2 receptor (CCK_2) antagonists, it was found that the benzodiazepine needs to be enantiomerically pure for receptor subtype selectivity (over CCK_1),[3] whereas scaffold-hopping to an achiral benzotriazepine (BZT) structure led to effective CCK_2 antagonists, obviating the need for a stereoselective synthesis or resolution.[4] This approach has been extended to the development of selective BZT-based PTH-1 (parathyroid hormone-1 receptor) antagonists (Fig. 1).[5]

Given the dearth of 1,3,5-benzotriazepine-2,4-diones (1,3,5-BZT) in the chemical literature[4a] and the promising biological activity of the aforementioned CCK_2 antagonists, we report the synthesis of a novel library based on this scaffold employing mainly microwave[6] and amide coupling reactions.

The synthesis of the 1,3,5-BZT scaffold was achieved as shown in Scheme 1. The synthetic steps have been largely based on the previously reported synthesis of BZTs.[4a] However, we have since optimised the original chemistry and adapted it using microwave and supported reagent mediated methods, wherever feasible, to produce a number of novel BZTs devoid of the structural motifs required for notably CCK_2 binding (i.e. lacking a 3-substituted acetamide on the N-3 atom). The compounds hereafter may hence have interesting applications in medicinal chemistry, e.g. aimed at GPCR receptors.

N-Alkyl-1,2-diamines **3** were either available commercially or prepared as described previously.[3] Thus, nucleophilic aromatic substitution of 1-fluoro-2-nitrobenzene (**1**) with commercially available primary amines was performed in a microwave reactor and gave nitroanilines **2** in excellent yields. Reduction of the nitro group and subsequent alkylation with α-haloketones or α-haloesters gave *N*,*N*′-dialkyl-1,2-diamines **4**. In our experience, thermal-mediated synthesis provided a better synthetic route with higher yields. *N*,*N*′-Dialkyl-1,2-diamines **4** were further treated with freshly prepared phenyl isocyanatoformate (**5**) under microwave irradiation to give the N-3 unsubstituted BZTs **6**.[7] The yields for this step were comparable or slightly improved compared to the corresponding step performed under conventional heating. Substitution at the N-3 nitrogen was achieved by base-mediated (NaH or PS-BEMP = (polymer supported)-2-tert-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2 diazaphosphorine) alkylation[8] to produce the trisubstituted 1,3,5-BZTs **7** (Table 1).

When sodium hydride was used in base-mediated alkylations on the N-3 nitrogen, transesterification reactions were observed when the R^2 substituent was an alkoxide.[9] For example, when

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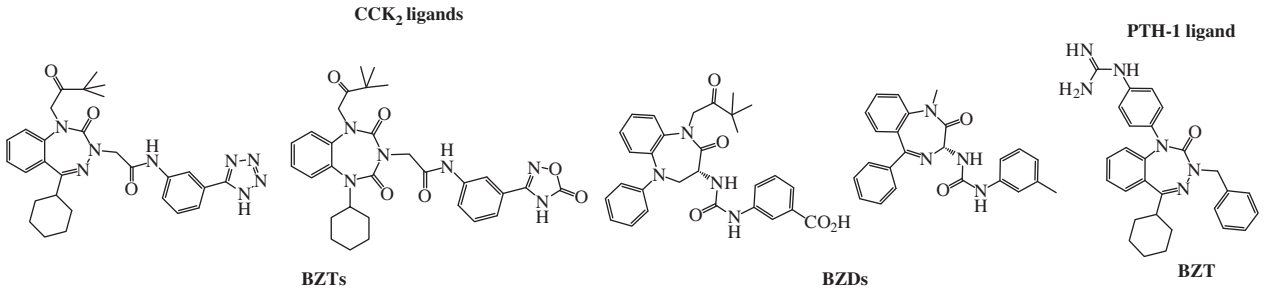
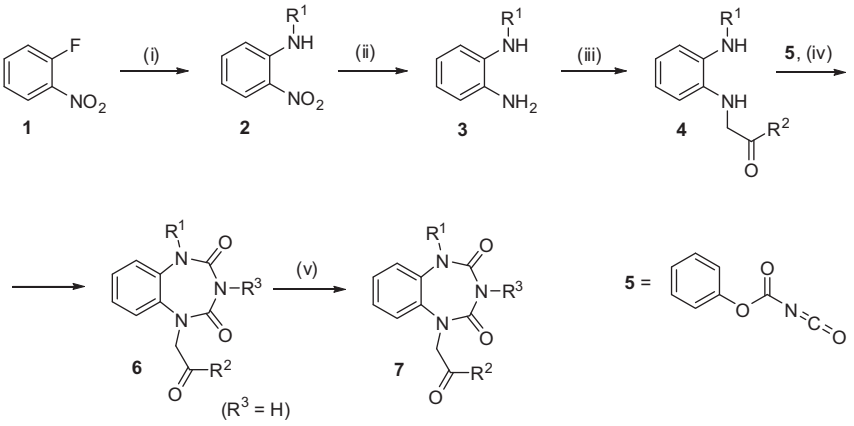
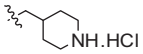
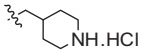


Figure 1. Bioactive benzodiazepine and benzotriazepine scaffolds.



Scheme 1. Synthesis of 1,3,5-BZTs. Reagents and conditions: (i) H_2N-R^1, Et_3N, MeCN, MW, 90-100%; (ii) 10% Pd/C, H_2 (1 atm), EtOH, rt, quant.; (iii) Br-CH_2COR^2, K_2CO_3, DMF, rt or 65 °C, 53-66%; (iv) DMA, MW; (v) NaH or PS-BEMP, X-R^3, where X = Cl, Br, I; DMF.

Table 1
Synthesis of a 1,3,5-BZT based library

Product	R^1	R^2	R^3	Yield[a] (%)
6a	*c*-C_6H_{11}	OBn	H	40
6b	*c*-C_6H_{11}	*t*-Bu	H	16
6c	Ph	OBn	H	59
6d	Ph	O*t*-Bu	H	51
6e	Ph	*t*-Bu	H	63
6f		*t*-Bu	H	42[b]
7a	*c*-C_6H_{11}	*t*-Bu	Me	67[c]
7b	Ph	OBn	CH_2CO*t*-Bu	97[c]
7c	Ph	OBn	CH_2-2-Py	98[c]
7d	Ph	*t*-Bu	Me	87[c]
7e	Ph	*t*-Bu	Et	63[c]
7f	Ph	*t*-Bu	Bn	79[c]
7g	Ph	*t*-Bu	CH_2-2-Py	52[c]
7h		*t*-Bu	Me	99[b]

[a] Yields refer to chromatographically isolated products of over 95% purity (NMR) for the last synthetic step.
[b] Overall yield over two steps.
[c] Yields refer to the reactions using PS-BEMP as base.

Table 2
1,3,5-BZT based library

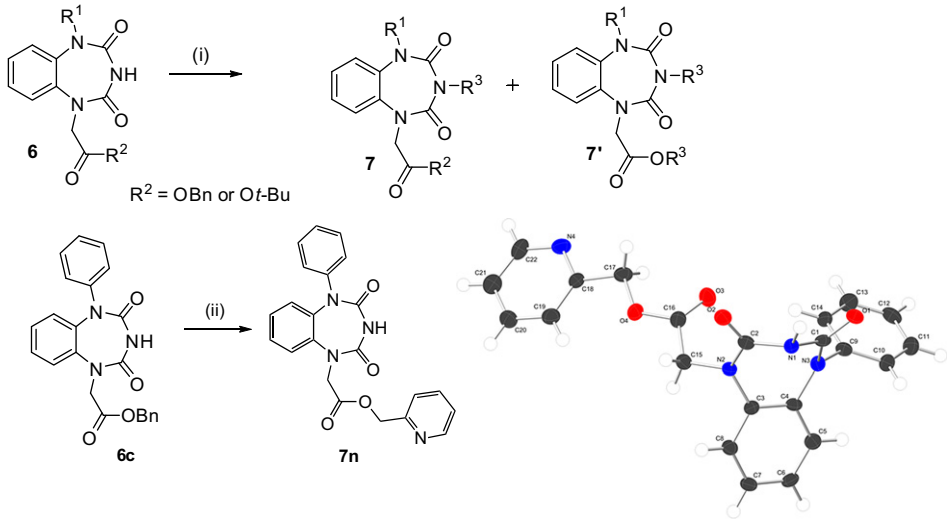
Substrate	Product	R^1	R^2	R^3	Yield[a] (%)
6a	**7i**	*c*-C_6H_{11}	OBn	Me	56
6a	**7i′**	*c*-C_6H_{11}	OMe	Me	31
6a	**7j**	*c*-C_6H_{11}	OBn	CH_2-2-Py	48
6a	**7j′**	*c*-C_6H_{11}	CH_2-2-Py	CH_2-2-Py	n/i[b]
6d	**7k**	Ph	O*t*-Bu	Me	80
6d	**7k′**	Ph	OMe	Me	19
6c	**7l**	Ph	OBn	Bn	92
6c	**7m**	Ph	OMe	Me	39
6c	**7m′**	Ph	OMe	Me	35
6c	**7n**	Ph	O-CH_2-2-Py	H	84
6c	**7n′**	Ph	O-CH_2-2-Py	O-CH_2-2-Py	n/i[b]

The products of the transesterification reactions.
[a] Yields refer to chromatographically isolated products of over 95% purity (NMR) for the last synthetic step.
[b] Not isolated.

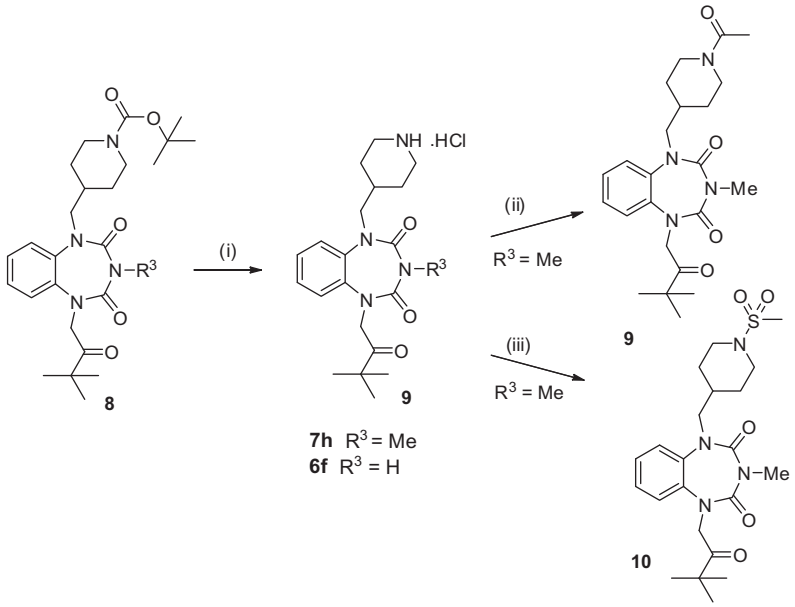
iodomethane was reacted with the sodium salt of **6a**, a methyl ester **7i′** (Table 2) was isolated in 31% yield, as well as the Bn ester **7i** in 56% yield (Scheme 2). In one instance, a cross-esterified primary imide was isolated as the major product of the reaction (**7n**, Table 2), an X-ray structure of which is shown, confirming such a rearrangement (Scheme 2). These reactions were found, however, to be somewhat capricious and we are, at present, investigating the mechanism of this rearrangement. When PS-BEMP was used as the base, no cross-esterification was observed with the compounds containing an ester function, and the expected alkylated products were obtained in 97% (**7b**, Table 1) and 98% yields (**7c**, Table 1), respectively.

In examples where *N*-Boc-protected piperidin-4-ylmethyl was chosen as an R^1 substituent at the N-1 nitrogen, further modifications on the nitrogen of the piperidine ring were possible after an initial Boc-deprotection. Compounds **8** (see Supplementary data) were hence treated with a HCl solution in 1,4-dioxane to afford quantitative yields of **6f** and **7h** as hydrochloride salts (Scheme 3). Compound **7h** was then reacted with representative acid chlorides and sulfonyl chlorides to give compounds **9** and **10**, respectively.

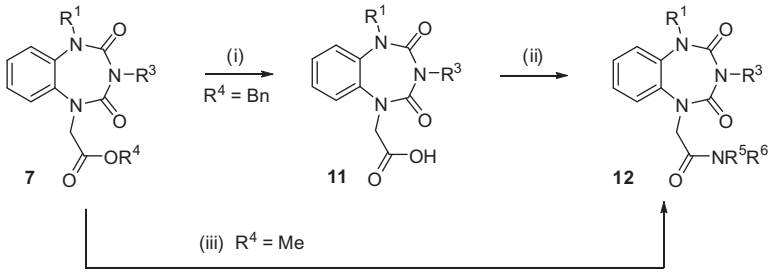
Compound **7** (Scheme 4) containing a Bn ester as the R^4 substituent at the N-5 nitrogen were transformed into carboxylic acids



Scheme 2. Cross-esterification reactions. Reagents and conditions: (i) NaH, X-R^3, where X = Cl, Br, I; DMF; (ii) NaH, 2-Br-CH_2-Py·HBr; and DMF. The crystal structure of **7n** is shown (CCDC 856222).



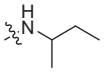
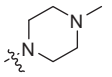
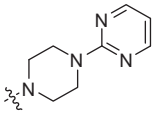
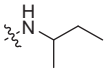
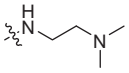
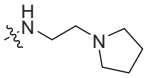
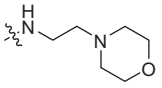
Scheme 3. Modifications of the R^1 substituents at the N-1 nitrogen. Reagents and conditions: (i) 4 M HCl in 1,4-dioxane, CH_2Cl_2, rt, quant.; (ii) AcCl, Et_3N, CH_2Cl_2, rt, 62%; (iii) $MeSO_2Cl$, Et_3N, CH_2Cl_2, rt, 79%.



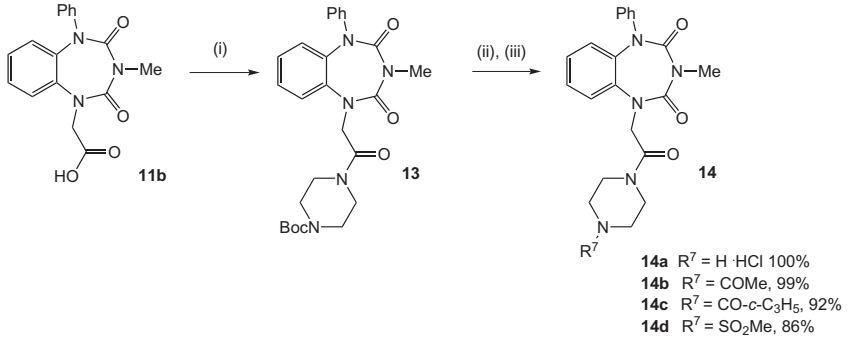
Scheme 4. Modifications at the N-5 nitrogen. Reagents and conditions: (i) TFA, CH_2Cl_2, rt, quant. or H_2, Pd/C, EtOH, EtOAc, quant.; (ii) HNR^5R^6, EDCI, HATU, DMAP, and DMF; (iii) HNR^5R^6, MW, 150 °C, 30 min.

11 and subsequently converted into secondary or tertiary amides **12**. Initial trial reactions indicated that neither EDCI nor HATU alone gave satisfactory conversion into the product (<50%), nor did increasing the amount of either reagent; however, combining the two gave much higher yields. This was, hence, used for the parallel coupling sequence without any further optimisation or alter-

Table 3
Synthesis of amide substituted BZTs

Substrate	Product	R^1	R^3	NR^5R^6	Yield[a] (%)
7b	**11a**	Ph	CH_2COt-Bu	—	100
7k	**11b**	Ph	Me	—	100
7i	**11c**	*c*-C_6H_{11}	Me	—	100
11a	**12a**	Ph	CH_2COt-Bu		18[b]
7k′	**12b**	Ph	Me		61[c]
11b	**12c**	Ph	Me		72[d]
11b	**12d**	Ph	Me		48[d]
11b	**12e**	Ph	Me		64[d]
7i	**12f**	*c*-C_6H_{11}	Me		57[c]
7i	**12g**	*c*-C_6H_{11}	Me		51[c]
11c	**12h**	*c*-C_6H_{11}	Me		82[e]
11c	**12i**	*c*-C_6H_{11}	Me		36[d]
11c	**12j**	*c*-C_6H_{11}	Me		84[d]
11c	**12k**	*c*-C_6H_{11}	Me		44[d]
11c	**12l**	*c*-C_6H_{11}	Me		46[d]

[a] Yields refer to chromatographically isolated products of over 95% purity (NMR) for the last synthetic step.
[b] Yields refer to the reactions using PS-CDI as the coupling reagent.
[c] Yields refer to the reactions performed neat in an appropriate amine.
[d] Yields refer to the reactions using HATU/EDCI as the coupling reagent.
[e] Yields refer to the reactions using $SOCl_2$ as a reagent.



Scheme 5. Further modifications at the N-5 nitrogen. Reagents and conditions: (i) Boc-piperazine, EDCI, HATU, DMAP, DMF, 84%; (ii) 4 M HCl in 1,4-dioxane, CH_2Cl_2, rt, quant.; (iii) acid chloride or methanesulfonyl chloride, Et_3N, CH_2Cl_2.

ation of the conditions. Moreover, the attempted use of PS-supported CDI as a coupling agent, gave very low yields (**12a**, Table 3). Another versatile method using $SOCl_2$ for acid activation was employed successfully for the amide synthesis (**12h**). Methyl esters **7′** could also be converted directly into amides **12** using microwave heating and an appropriate amine as a reagent/solvent (for example, compounds **12b**, **12f** and **12g**). Lewis acid mediated amidations were not attempted although these could represent a useful strategy for the amidation reaction.[10]

In an attempt to incorporate piperazine-functionalised substituents at N-5, the carboxylic acid **11b** was reacted with *N*-Boc-piperazine using our previous amide coupling conditions to give

13. Deprotection and further modification on the piperazine nitrogen yielded target compounds **14** (Scheme 5).

In conclusion, a chemically diverse library of 1,3,5-BZTs have been synthesised using a combination of thermal and microwave mediated chemistry.

Acknowledgements

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Supplementary data

Supplementary data (experimental details and analytical data for the compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.025.

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