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Original article

Structure–activity relationship studies of SEN12333 analogues: Determination of the optimal requirements for binding affinities at α7 nAChRs through incorporation of known structural motifs

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ABSTRACT

Alpha7 nicotinic acetylcholine receptors (nAChRs) have implications in the regulation of cognitive processes such as memory and attention and have been identified as a promising therapeutic target for the treatment of the cognitive deficits associated with schizophrenia and Alzheimer's disease (AD). Structure affinity relationship studies of the previously described α7 agonist SEN12333 (**8**), have resulted in the identification of compound **45**, a potent and selective agonist of the α7 nAChR with enhanced affinity and improved physicochemical properties over the parent compound (SEN12333, **8**).

1. Introduction

Neuronal nicotinic acetylcholine receptors (nAChRs) are a family of ligand-gated cation channels that have generated extensive interest as potential therapeutic targets for the treatment of cognitive disorders [1–3]. There exist multiple subtypes of nAChRs where each subtype is formed from either a homo- or heteropentameric combination of twelve possible subunits: α2–α10 and β2–β4. The homomeric α7 nAChR is one of the most commonly expressed nicotinic receptor subtypes in the human brain and is found in high levels of expression in regions associated with learning and memory such as the cerebral cortex and the hippocampus [4–6]. Experimental evidence supports the involvement of this receptor in schizophrenia and Alzheimer's disease (AD) [7,8]. Schizophrenia and AD are both chronic conditions with intense and devastating symptoms; modulators of the α7 nAChR have been extensively studied for the treatment of the cognitive deficits associated with these pathologies [4,6,9–11].

Schizophrenia is a disease defined by positive (hallucinations, delusions) and negative symptoms (reduced affect, low motivation, social withdrawal, disorganized thoughts) and cognitive impairments (learning and memory deficits, decreased attention) [12]. While positive symptoms are somewhat controlled with current medications, cognitive deficits and negative symptoms largely remain untreated. Examinations of the post-mortem brains of schizophrenic patients have revealed a reduction in α7 mRNA expression and concomitantly a reduction in the density of α7 nAChR protein [13–15]. Furthermore, polymorphisms within the α7 nAChR subunit gene *CHRNA7* have been associated with the auditory gating deficits in schizophrenia, a defect ordinarily normalized by nicotine and possibly underlying the high incidence of tobacco use among schizophrenic patients [16–18]. Selective α7

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nAChR agonists have shown excellent *in vivo* efficacy in the normalization of auditory gating in rats, indicating potential utility in the treatment of the cognitive deficits associated with schizophrenia [4,19,20].

A reduction in the expression of α7 nAChR protein has similarly been observed in the hippocampus of AD patients [21,22]. A component of β-Amyloid (Aβ) peptides, the characteristic neuritic plaques of AD thought to contribute to neurodegeneration, was found to interact with the α7 nAChR with picomolar affinity [23,24]. Exogenous nAChR agonist nicotine exhibits protective effects against the neurotoxicity of Aβ peptides, and this neuroprotection can be blocked through selective antagonism of α7 nAChRs [25]. Furthermore, utilization of siRNA transfection to inhibit α7 mRNA and protein expression, further exacerbated the toxicity of Aβ peptides in neuroblastoma SH-SY5Y cells [26]. As is consistent with such findings, selective activation of α7 nAChRs attenuated Aβ-induced cell death, and suggests a therapeutic application for α7 nAChR agonists in the treatment of AD [25,26].

Whilst α7 nAChR is a valid target with therapeutic application in schizophrenia and AD, few structural classes of selective α7 nAChR agonists have been identified, and reported ligands are primarily centred on anabaseine, quinuclidine, or diazabicyclic scaffolds [27]. One of the initial functionally α7-selective agents identified was partial agonist, dimethoxybenzylidene anabaseine (DMXB-A, **1**, Fig. 1), exhibiting only micromolar potency at α7 nAChRs with off-target activity at α4β2 nAChRs and 5-HT3 receptors [28,29]. In proof of concept trials for non-smoking schizophrenic patients, DMXB-A (**1**) exhibited an improvement in various neurocognitive measures and has progressed to Phase II studies, further providing a foundation for the therapeutic use of α7 agonists [2,30].

In relation to the pharmaceutical industry, various α7 nAChR agonists have entered clinical trials for use in the treatment of cognitive deficits of schizophrenia (CDS). An early example disclosed by AstraZeneca was the quinuclidine-derived spiro-oxazolidinone, AR-R17779 (**2**), a potent full agonist with several hundred-fold *in vitro* selectivity for rat α7 over rat α4β2 nAChRs [31]. Pharmacological profiling of AR-R17779 (**2**) *in vivo* demonstrated improvements in learning and memory in several rat models, in accordance with the expected cognition-enhancing properties of selective α7 nAChR agonists [32,33]. SR180711 (**3**) was reported by Sanofi-Aventis as a potent partial agonist of recombinant human α7 nAChRs. It displays over 250-fold selectivity for α7 over other nAChR subtypes and negligible affinity for 100 other receptors [34,35]. Phencyclidine induced cognitive deficits were shown to be normalized following SSR180711 (**3**) administration in mice which further supports the role of α7 nAChR agonists in treating CDS and AD [36,37]. SSR180711 (**3**) successfully entered Phase II clinical trials, however, studies were discontinued due to cataract development in subjects and a narrow therapeutic index. Additional examples of α7 nAChR agonists entering clinical trials for the treatment of CDS include TC-5619 (**4**, Phase II), ABT-107 (**5**, Phase I), and EVP-6124 (**6**, Phase III) [6,38–40]. Despite showing initial success, TC-5619 (**4**) and ABT-107 (**5**) have since been withdrawn from the clinic, however, EVP-6124 (**6**) has successfully progressed to Phase III clinical trials and suggests that α7 nAChR agonist can be safely targeted in the clinic. It is evident that known α7 ligands display relatively little structural diversity and have likely been developed through optimization of a common chemotype. The majority of these ligands therefore possess the same cross-reactivity with other sites, such as activity at hERG channels.

High-throughput screening by Siena Biotech and Wyeth led to the discovery of piperazine **7** (Fig. 2) as a novel chemotype with weak partial agonist activity at α7 nAChRs, further investigation of the piperazine, biaryl, and amide regions of compound **7** culminated in the discovery of SEN12333 (**8**) [41]. SEN12333 (**8**) is a potent and selective α7 nAChR agonist, displaying exceptional selectivity for α7 over other nAChR subtypes, 5-HT3 receptors, and hERG channels [41,42]. Aside from its favourable *in vitro* profile, SEN12333 also exhibited acceptable bioavailability and good brain penetration in rats [42]. Initial investigations of SEN12333 in animal models of episodic memory unveiled its ability to reverse both scopolamine- and MK-801-induced amnesia [41,42].

The development of SEN12333 (**8**) was centred on simultaneous improvement of potency and drug-like properties. Accordingly, only limited structure–activity relationships are evident for this class of α7 nAChR ligands. Modification of the morpholine functionality contained within compound **8** revealed branched acyclic amines to result in decreased potency while small, aliphatic azacycles appear to be optimal, however, few examples of these are reported [41]. Brief exploration into the replacement of the arylanilide with other aromatic moieties showed little effect on α7 nAChR activity, however, biaryls were generally preferred over

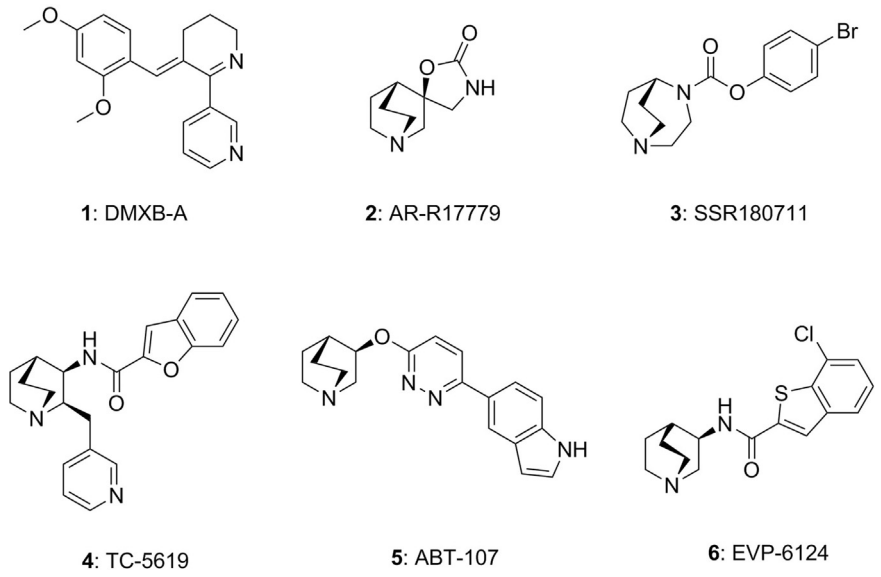


Fig. 1. Selected α7 nAChR agonists evaluated in preclinical and clinical studies.

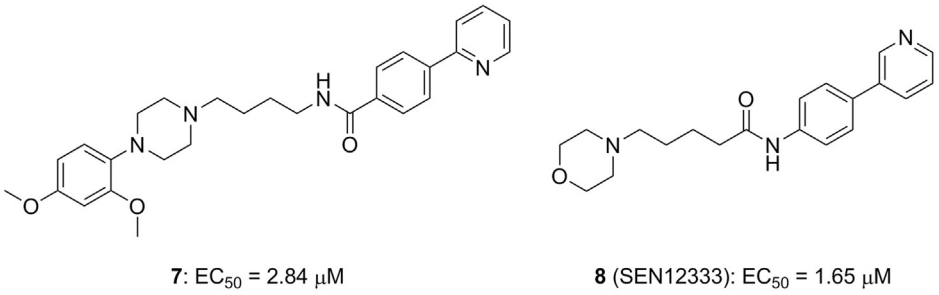


Fig. 2. Activity of SEN12333 (**8**) and its parent structure **7**, at α7 nAChRs in a fluorescence assay [40].

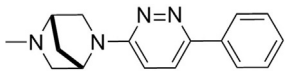
mono-aromatic groups [41]. Previous work within our laboratory examining the effect of contracted or elongated carbon chain linkers have identified the 4-carbon chain linker of compound **8** to be optimal for binding and functional activity at α7 nAChRs [43].

Further work by Haydar and co-workers examines the effect on the first ring of the biaryl system in SEN12333 (**8**) and details the development of a novel series of ligands (Series 3) which was developed from two known, previously studied series (Series 1 and 2), as shown in Fig. 3 [44]. Series 1 is representative of SEN12333 (**8**), whilst Series 2 described replacement of the amide moiety with urea functionality [45]. Series 2 generally exhibits enhanced potency at α7 nAChRs as compared to Series 1, however, it also demonstrated low selectivity particularly against the homologous α3 receptor, unfavourable hERG activity and substantial cytochrome P450 inhibition [45]. The development of Series 3 resulted in compounds with a good level of potency, improved selectivity, an optimal hERG profile and no cytochrome P450 inhibition [44]. Series 3 retains two hydrogen bond donors and therefore encompasses the possibility of additional interactions when compared to Series 1 and 2 [44].

At the same point in time, compound **9** (Fig. 4) was identified as a potent and selective α7 nAChR agonist [46]. Structure–activity relationship (SAR) studies revealed the 5-*N*-methyl, heteroaryl linker and the nature of terminal aryl group to be critical for affinity and agonist activity at α7 nAChRs.

The differences in the general scaffolds of SEN12333 (**8**) and compound **9** were noticed. It was postulated that compound **9** was somewhat of a truncated hybrid of SEN12333; whereby removal of the carbon chain linker and amide bond of SEN12333 (**8**) would result in a compound of high similarity to compound **9** (Fig. 5).

Herein we report our continued research into analogues of SEN12333 (**8**) to expand the SAR profile and identify more favourable pharmacophoric units for increased affinity. This was to



9: K_i = 9.3 nM
EC_{50} = 9.5 μM

Fig. 4. The structure of compound 9 and its activity against α7 nAChR in binding (K_i) and patch clamp (EC_{50}) assays [45].

be achieved by synthesizing hybrids of SEN12333 (**8**) through integration of functionalities present within compound **9** in addition to those seen in other known α7 nAChR agonists. This would allow us to not only determine which pharmacophoric units were optimal for the binding of SEN12333, but also to identify the optimal functionalities possible for binding of compound **9** and ascertain if the functionalities could be interchanged whilst maintaining affinity and selectivity.

The most striking difference between SEN12333 (**8**) and compound **9** appeared to be the choice of heterocycle comprising the basic centre of the molecule. Therefore this portion of the molecule was selected as the starting point for further SAR study with the synthesis of analogues **10**–**17** achieving this goal. Morpholine was replaced by small azacycles piperidine, 1-methylpiperazine, (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane and 2-oxa-6-azaspiro[3.3]heptane. These azacycles were chosen to represent a stepwise progression from the heterocycle contained within SEN12333 (**8**, morpholine) to that contained within compound **9** ((1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane). The 2-oxa-6-azaspiro[3.3]heptane moiety was also included due to its known structural similarities to morpholine and favourable physicochemical properties [47].

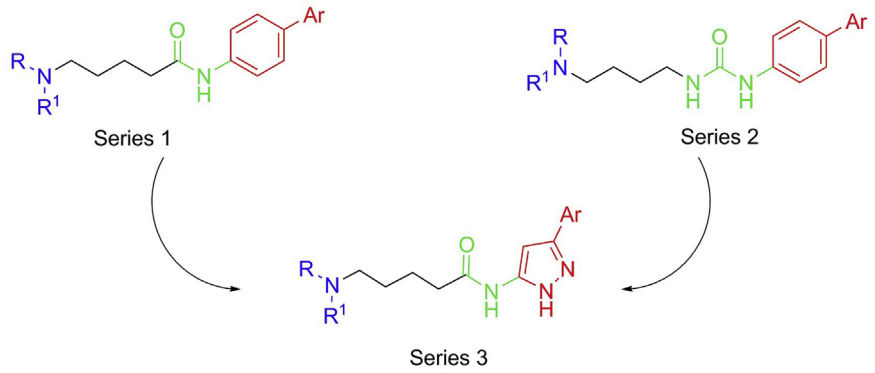


Fig. 3. Series 1, 2 and 3 with pharmacophoric elements: basic centre (blue), carbon chain (black), central linker (green) and biaryl system (red). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

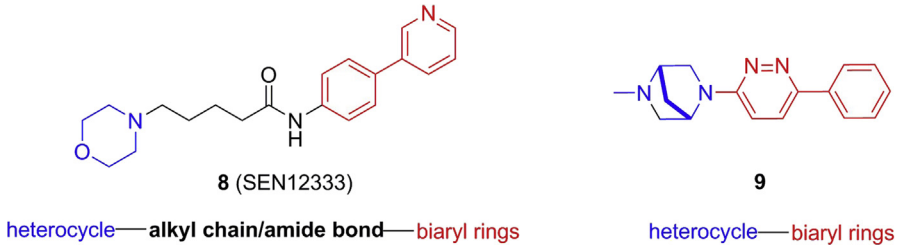


Fig. 5. Similarities between SEN12333 (**8**) and compound **9**.

Additionally, it offers the potential for varied hydrogen bonding interactions. Due to the convergent nature of their synthesis, with the phenyl pyridyl scaffold being constructed in the final step, we took the opportunity to prepare an analogous set of biphenyl-containing compounds. The two scaffolds allowed a simultaneous examination of the effect of the presence of the pyridine nitrogen within the terminal aromatic ring.

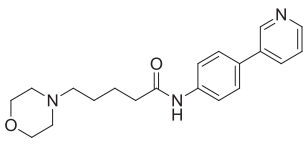
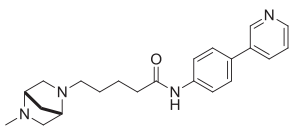
2. Results and discussion

2.1. Molecular modelling studies

While the α7 X-ray crystal structure is yet to be determined, crystals of α7 agonists bound to the extracellular domain of the homologous acetylcholine binding protein (AChBP) [48] have provided the template for the construction of homology models. Residues conserved from *Torpedo marmorata* at the α7 nAChR binding site include aromatic amino acids Tyr94 (loop A), Trp152 and Tyr154 (loop B), Tyr191 and Tyr199 (loop C) and Trp56 and Gln58 (loop D). Bridged cysteine residues Cys193 and Cys194 (loop C) are only present within α subunits and are known to interact with nicotinic ligands in the co-crystal of AChBP [48,49]. Molecular modelling methods [43] were applied to SEN12333 (**8**) and compound **14** in order to predict the key interactions and binding modes of the different aliphatic heterocyclic groups. The docking poses and the XP docking summary [50] reveal that proposed ligand **14**, containing the (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane core of agonist **9**, is predicted to be a much more potent binder at α7 receptors than SEN12333 (**8**) as indicated by its more negative GScore (Table 1).

The docking studies highlight the putative key interactions of compound **14** in a homology model for the human α7 receptor (Fig. 6). The basic amine in the 5-position of the (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane core of compound **14** is engaged in a hydrogen bond interaction with the indole nitrogen of Trp171, a known key interaction of the cationic centre of α7 agonists [51]. The (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane is also engaged with Tyr210, Trp77 and Tyr115. The essential bridged di-sulfide residues Cys212 and Cys213 are also shown to interact with the carbonyl functionality of compound **14**.

Table 1
G-scores of SEN12333 (**8**) and compound **14**.

Compound	Ligand	GScore
SEN12333 (**8**)		−5.14
14		−13.14

2.2. Synthetic chemistry and in vitro studies

The syntheses of analogues **10**–**17** are depicted in Scheme 1 and involved the initial conversion of 5-bromovaleric acid (**18**) to the corresponding acid chloride and subsequent treatment with 4-bromoaniline in the presence of triethylamine to give desired anilide **19** (91%). This last compound, in the presence of catalytic iodide, could be used to alkylate the appropriate amine to afford compounds **20**–**24** in good yields (51–93%). Morpholine, piperidine and 1-methylpiperazine were all readily available, however amine **25** was synthesized according to procedures previously described by our laboratory [52] and 2-oxa-6-azaspiro[3.3]heptane was synthesized according to procedures previously described by Carreira and co-workers [47]. Subjecting bromoarenes to Suzuki cross-coupling with either 3-pyridylboronic acid or phenylboronic acid gave the desired ligands **10**–**17** (70–90%). SEN12333 (**8**) was synthesized for direct comparison with the new analogues.

An alternative synthesis was also proposed in order to prepare the reverse-amide analogues of the newly synthesized compounds (Scheme 2). This began by alkylating the appropriate amine with bromide **28** to yield amines **29**–**31** (74–91%) followed by hydrazinolysis and amide bond formation to give compounds **32**–**34** (35–66% over two steps). Final Suzuki cross-coupling with either 3-pyridylboronic acid or phenylboronic acid gave the desired retro-amide ligands **37**–**42** (55–91%).

All newly synthesized compounds and SEN12333 (**8**) were subjected to competition binding measurements against racemic [^{3}H]epibatidine. The binding assays were performed using membrane homogenates of stably transfected HEK293 cells expressing rat α7, α4β2, or α3β4 nAChR subtype [53–55]. All compounds were selective for the α7 subtype over the α4β2 and α3β4 subtypes and a range of affinities were obtained. The results are summarized in Tables 2 and 3. The first series of compounds (Table 2), reveal replacement of the morpholine ring of SEN12333 (**8**) with a piperidine functionality as in analogue **10** to result in an increase in potency at α7 nAChRs; evident in the direct comparison of SEN12333 (**8**) and **10** (K_i: 670 nM vs 220 nM). Conversion to the biphenyl analogue of **10**, gave a compound (**11**) with similar potency (Table 2, entry 3). The use of the 1-methylpiperazine functionality (**12**) led to a dramatic loss of potency, this was partially restored in the corresponding biphenyl analogue **13**. The results of compound **10** and **12** are in agreement with work previously described by Haydaar and co-workers, however, these compounds were included in the present work for completeness of the study [41]. Interestingly incorporation of the (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane functionality as in compound **14** corresponded with a complete loss of potency at α_7 nAChRs, again, this was

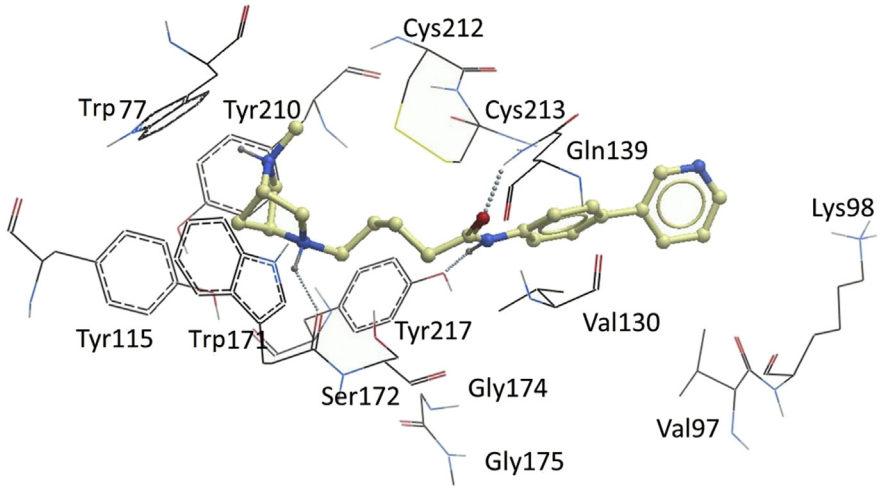
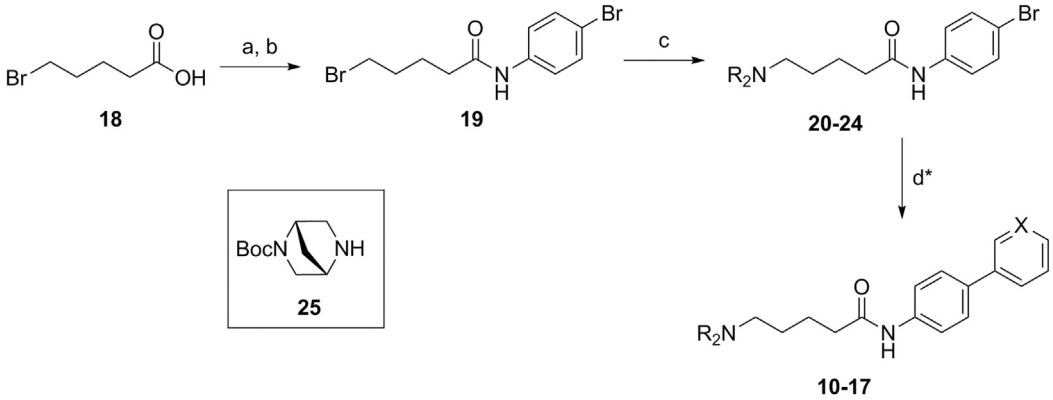
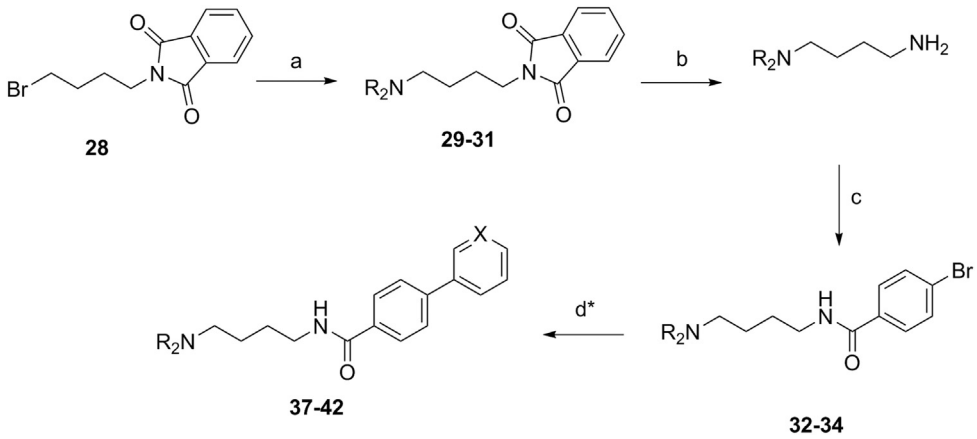


Fig. 6. Compound **14** docked into the active site of the AChBP.



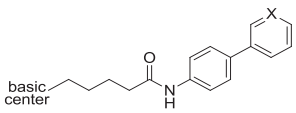
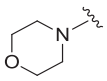
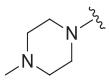
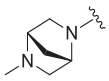
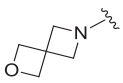
Scheme 1. Reagents and conditions: (a) $(COCl)_2$, rt, 45 min; (b) 4-bromoaniline, Et_3N, CH_2Cl_2, −78 °C to rt, 4 h, 91% yield over 2 steps; (c) appropriate amine, NaI, Et_3N, DMF, reflux, 16 h, 51–93%; (d) $Pd(PPh_3)_4$, appropriate boronic acid, MeCN/sat. aq. Na_2CO_3 (1:1), reflux, 18 h, 70–90%; * when amine **25** was used additional deprotection and methylation steps were performed as follows; HCl (4 M in 1,4-dioxane), MeOH, rt, 2 h; (d) 37% aq. HCOH, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, rt, 18 h, 48–53% over two steps.



Scheme 2. Reagents and conditions: (a) appropriate amine, NaI, Et_3N, THF, reflux, 16 h, 74–91%; (b) $NH_2NH_2 \cdot H_2O$, EtOH, reflux, 1 h; (c) 4-bromobenzoyl chloride, Et_3N, CH_2CH_2, −78 °C to rt, 2 h, 35–66% over two steps; (d) $Pd(PPh_3)_4$, appropriate boronic acid, MeCN/sat. aq. Na_2CO_3 (1:1), reflux, 18 h, 55–91%; * when amine 25 was used additional deprotection and methylation steps were performed as follows; HCl (4 M in 1,4-dioxane), MeOH, rt, 2 h; (d) 37% aq. HCOH, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, rt, 18 h, 58–62% over two steps.

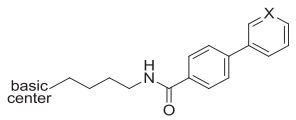
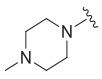
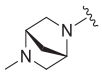
somewhat restored in the analogous biphenyl compound **15**. This is in direct contrast to our molecular modelling results, and suggests the α7 homology model is not predictive of binding affinity at α7 nAChRs for this series of compounds. Incorporation of the slightly larger 2-oxa-6-azaspiro[3.3]heptane functionality (**16** and **17**), similarly resulted in a loss of potency at α7 receptors. The physicochemical properties, calculated 1−octanol-water partition coefficient (cLogP), polar surface area (PSA) and ligand lipophilicity

Table 2
Binding affinities of basic centre exploration of SEN12333 (**8**).

Ligand			Binding affinity K_i (nM)[a,b]			Physicochemical properties		
								
Compound	Basic centre	X	α7	α4β2	α3β4	LogP[c]	PSA	LLE[d]
SEN12333 (**8**)		N	670 ± 119	>10,000	>10,000	2.25	53.93	3.92
10		N	220 ± 30	>10,000	>10,000	3.46	44.7	3.20
11		CH	190 ± 30	>10,000	2600 ± 200	4.79	32.34	1.93
12		N	9330	DNC	313,000	1.32	47.94	3.71
13		CH	1620	DNC	88,100	2.65	35.58	3.14
14		N	>10,000	>10,000	>100,000	1.07	47.94	ND
15		CH	3200 ± 100	>10,000	>10,000	2.41	35.58	3.08
16		N	>10,000	>10,000	>50,000	2.40	53.93	2.32
17		CH	>10,000	>10,000	>50,000	3.73	41.57	1.04

[a] Competition binding assays were carried out in membrane homogenates of stably transfected cells or rat forebrain tissue as described previously. The nAChRs were labelled with [^{3}H]-epibatidine. The K_d values (nM) for [^{3}H]-epibatidine used for calculating K_i values were 0.3 for $\alpha_3\beta_4$, 0.04 for $\alpha_4\beta_2$ and 1.8 for α_7. K_i values are the mean ± SEM of three to six independent measurements. For low binding affinity compounds, estimated K_i value ranges were provided.
[b] DNC = does not converge.
[c] Calculated using ChemDraw12.0.
[d] ND = not determined.

Table 3
Binding affinities of basic centre exploration in reverse amide series.

Ligand			Binding affinity K_i (nM)[a,b]			Physicochemical properties		
								
Compound	Basic centre	X	α7	α4β2	α3β4	LogP[c]	PSA	LLE[d]
37		N	1400 ± 200	>10,000	>50,000	3.15	44.70	2.70
38		CH	410 ± 80	>10,000	>10,000	4.49	32.34	1.90
39		N	>10,000	>10,000	>10,000	1.00	47.94	ND
40		CH	5400 ± 700	>10,000	>100,000	2.35	35.58	2.92
41		N	>10,000	>10,000	>10,000	0.76	47.94	3.38
42		CH	6100 ± 500	>10,000	>10,000	2.11	35.58	3.10

[a] Competition binding assays were carried out in membrane homogenates of stably transfected cells or rat forebrain tissue as described previously. The nAChRs were labelled with [^{3}H]-epibatidine. The K_d values (nM) for [^{3}H]-epibatidine used for calculating K_i values were 0.3 for $\alpha_3\beta_4$, 0.04 for $\alpha_4\beta_2$ and 1.8 for α_7. K_i values are the mean ± SEM of three to six independent measurements. For low binding affinity compounds, estimated K_i value ranges were provided.
[b] DNC = does not converge.
[c] Calculated using ChemDraw12.0.
[d] ND = not determined.

efficiency (LLE) of all newly synthesized compounds are also shown in Table 2. Drug lipophilicity is reportedly changing less over time in comparison to other physical properties and suggests it to be a key drug-like property [56,57]. The success of a lead in drug development is therefore largely affected by its lipophilicity and accordingly, the role of LogP in influencing drug potency, pharmacokinetics and toxicity has been recognized for numerous years [57]. All compounds in the current study display predicted values clog$P$ < 5, defined by Lipinski to be a requirement for desirable drug-like and physicochemical properties, all compounds also exhibited acceptable PSA values [58]. The recent development of a novel index known as ligand lipophilicity efficient (LLE) has served as an important guide in the process of lead optimization, and also as a flag for selection of preclinical candidates [59]. LLE is

defined as:

$$LLE = pIC_{50}(\text{or } pK_i) - cLogP$$

A typical oral drug with cLogP of 2.5 and potency within the range of 1–10 nM suggests a target LLE of 5–7 or greater. The advantages of high *in vivo* potency are low total doses in humans and decreased adventitious compound related toxicity [59]. In essence, the target objective for molecule optimization is to enhance potency without simultaneously elevating lipophilicity. Whilst all compounds **8** and **10**–**17** display acceptable cLog*P* values the calculation of their LLE values confers some interesting results. Piperidine containing analogues **10** and **11** respectively display a 3 and 3.5 fold increase in affinity relative to SEN12333 (**8**), however, their LLE values are much lower, 3.2 and 1.9 respectively. This is a direct result of their increased cLogP values (3.46 and 4.79 respectively vs 2.25 of **8**) and is particularly evident in the more lipophilic **11**. Interestingly, while compound **12** is a much weaker binder at α7 receptors (K_i = 9330 nM), its low cLogP value results in an LLE value similar to that of SEN12333 (**8**) (3.70 vs 3.92 respectively). Though compound **12** is unsuitable for further development due to its low binding affinity, the importance of lipophilicity is highlighted. The importance of binding affinity upon LLE values and drug-likeness is evident in compounds **14** and **15**. Whilst these compounds display acceptable cLogP values, their extremely low binding affinities diminish their LLE values and renders them unsuitable for further development.

The binding affinities of the reverse amide hybrid series as summarized in Table 3 were generally less potent than their counterparts in Table 2, thus indicating the original amide bond orientation of SEN12333 (**8**) to be favourable for α7 binding. This is evident in the direct comparison of data obtained for compounds **37** with **10** and **38** with **11**, despite the similar cLog*P* values between amide and reverse amide hybrids. A similar trend was seen with piperidine being the favoured aliphatic heterocycle and biphenyl compounds were consistently more potent than their phenylpyridyl counterparts. In terms of binding affinity, the results indicate piperidine to be the optimal functionality for the basic centre portion of SEN12333 (**8**) and suggest that structural features of the basic centre of lead compound **9** cannot be transposed onto SEN12333 (**8**). It was postulated that substitution with a slightly branched, larger heterocycle and the introduction of a second potential site of protonation on the heterocycle leads to this decrease in potency. Consistent with our results from Table 2 the PSA and LLE values of compounds **37**–**42** were included. Again, the importance of lipophilicity is highlighted with the most potent compound of the series **38** returning an LLE value of only 1.90 as a result of its increased lipophilicity. Despite the low binding affinity of **42**, its extremely low cLog*P* value results in its LLE being an acceptable 3.38, even though it is unsuitable for further development.

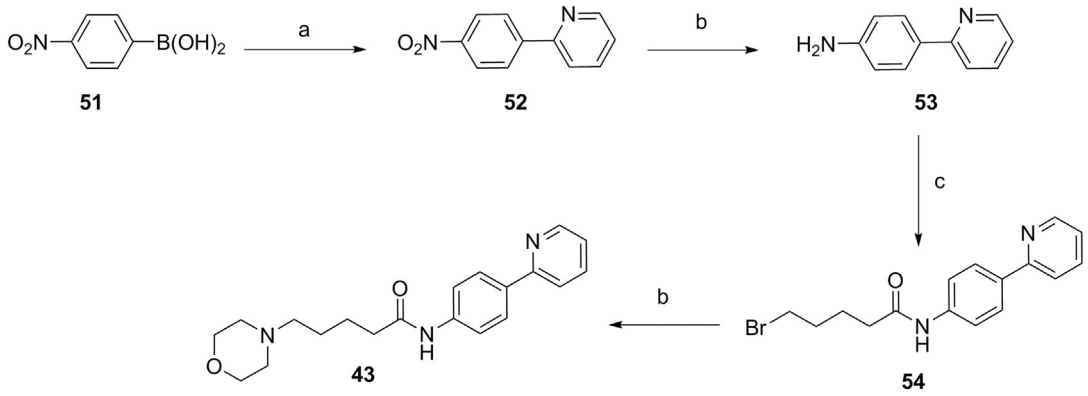
We then turned our attention to the SAR exploration of the biaryl moiety of SEN12333 (**8**). Compounds **43** and **44** examine the effect of the position of the pyridine nitrogen within the terminal aromatic ring. Compounds **45** and **46** respectively explore the incorporation of a fluorine atom, a known bioisostere of hydrogen [60], onto the terminal aromatic ring of SEN12333 (**8**) and the replacement of pyridine with indole, previously described to exhibit excellent human liver microsome stability in similar compounds (>97% remaining after 30 min incubation) [46]. We sought to potentially improve the biological properties of SEN12333 (**8**) and also to enhance the hydrogen bonding capacity of the terminal aromatic ring through incorporation of these motifs. Hybrid compound **47** explores the direct transposition of the biaryl moiety of lead compound **9** onto SEN12333 (**8**). Compounds **48**–**50** involve the incorporation of a phenyl-substituted-pyrazole ring as the biaryl motif of SEN12333 (**8**), in order to potentially enhance the hydrogen bonding capacity of the biaryl system within the α_7 active site [44].

The synthesis of compound **43** required a revised synthesis in order to successfully incorporate the 2-pyridine moiety (Scheme 3). Following the procedure of Baran and co-workers [61], boronic acid **51** was reacted with pyridine to afford the 2-substituted pyridine **52** in 27% yield. Subsequent hydrogenation afforded aniline **53** (87%), which, in a manner similar to that described above, could be reacted with the acid chloride formed from acid **18**, to afford amide **54** (85% from acid over two steps). Final iodide assisted displacement of the bromide contained within compound **54** with morpholine afforded target compound **43** (74%).

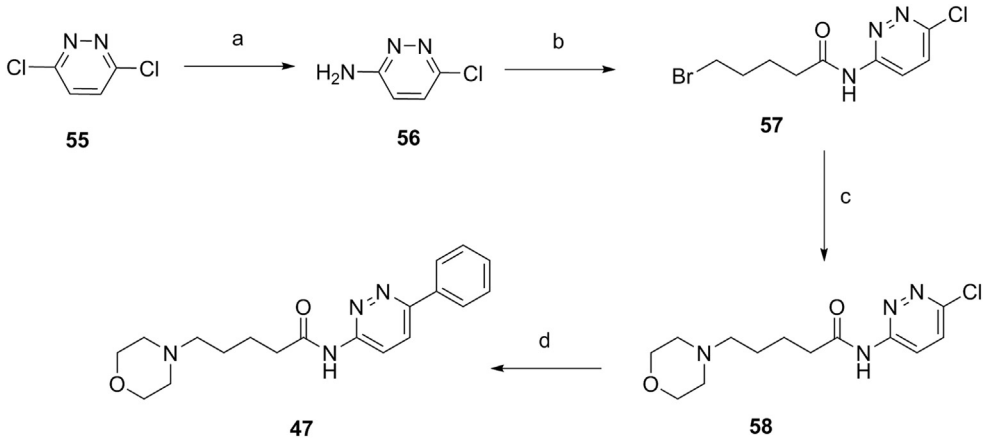
Compounds **44**–**46** were synthesized in an analogous manner to that described in Scheme 1 from bromide **20** using the appropriate boronic acid (57–72%). Pyridazine analogue **47** could be synthesized from starting material **55**, which underwent monosubstitution to afford aniline **56** (66%) followed by amide formation in a manner similar to that described above and thus providing compound **57** (20% over two steps, Scheme 4). Iodide assisted morpholine substitution (62%) provided amine **58** which, followed by Suzuki cross-coupling with phenylboronic acid, afforded the target pyridazine containing analogue **47** (63%).

Pyrazole containing analogues **48**–**50** were synthesized as depicted in Scheme 5 [62]. Methyl benzoate (**59**) was treated with the anion derived from acetonitrile to afford compound **60** (63%), which could then be reacted with hydrazine to form pyrazole **61** (80%). The amine contained within pyrazole **61** could then be used to form amide **60** (74%) and finally amine displacement as utilized earlier afforded analogues **48**–**50** (56–62%)

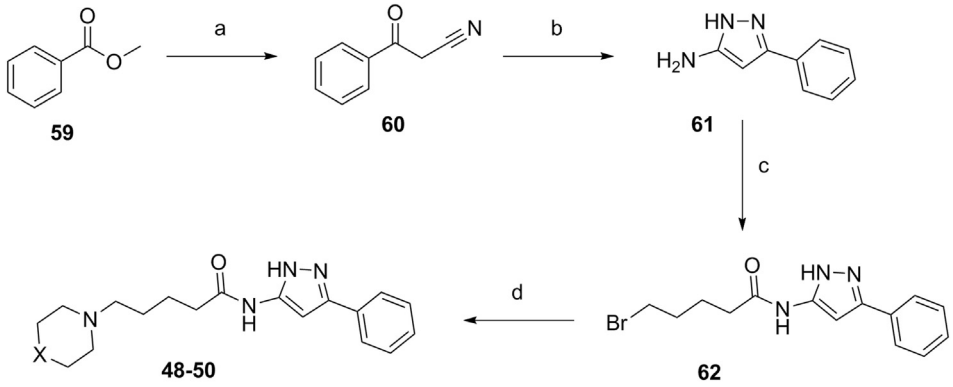
In the competition binding assay, compounds **43**–**50** showed a range of affinities and all compounds were selective for the α7 subtype over the α4β2 and α3β4 subtypes (Table 4). Compounds **43** and **44** containing the 2- and 4-position pyridine nitrogen both display a 2-fold increased potency over the lead SEN12333 (**8**) and importantly an increase in their LLE values. This indicates that currently the pyridine nitrogen of **8** is in the least favourable position within the terminal aromatic ring and suggests the potential of further development of compounds **43** and **44**. Upon conserving the 3-position of the pyridine nitrogen and incorporating the electronegative 2-fluorine substituent as in compound **45**, a dramatic increase in potency and LLE is seen as compared to SEN12333 (**8**) (85 nM vs 670 nM respectively). Introduction of the 5-indolyl moiety (**46**) was well tolerated and led to increased potency relative to compound **8**, suggesting the additional H-bonding possibilities of indole **46** are favourable and that the biaryl moiety can be extended without sacrificing potency. However, the increased lipophilicity of compound **46** results in a somewhat diminished LLE value. Hybrid compound **47** containing the biaryl ring system of compound **9** exhibited a complete loss of potency at α7 receptors, indicating that the structural features of compound **9** cannot be incorporated into SEN12333 (**8**). The development of such hybrids is catastrophic for α7 binding affinity. Incorporation of the prominent 5-phenyl-1*H*-pyrazole moiety resulted in a severe loss of potency at α7 receptors evident in direct comparison of compounds **48** and SEN12333 (**8**). This drop in potency was restored by incorporation of the more favourable aliphatic heterocycle piperidine (**49**). Consistent with our SAR results from the basic centre exploration of SEN12333 (**8**), incorporation of the 1-methylpiperazine functionality was unfavourable and resulted in a loss of potency at α7 receptors (**50**). While compound **49** displays a similar binding affinity to SEN12333 (**8**), its increased lipophilicity lowers its LLE value as compared to **8** (2.29 vs 3.92 respectively). Additionally, the comparison of compound **49** with **38** suggests that the phenyl to pyrazolyl swap has minimal potency penalty but offers a



Scheme 3. Synthesis of compound **43**. Reagents and conditions: (a) pyridine, trifluoroacetic acid, $AgNO_3$, $K_2S_2O_8$, CH_2Cl_2, H_2O, rt, 24 h, 27%; (b) H_2 (1 atm), Pd/C, MeOH, 18 h, rt, 87%; (c) (i) 5-bromovaleric acid, $(COCl)_2$, rt, 1 h (ii) 53, Et_3N, CH_2Cl_2, −78 °C to rt, 10 h, 85%; (d) morpholine, NaI, Et_3N, THF, reflux, 16 h, 74%.



Scheme 4. Synthesis of compound **47**. Reagents and conditions: (a) NH_4OH, μwave, 120 °C, 300 W, 30 min, 66%; (b) (i) 5-bromovaleric acid, $(COCl)_2$, rt, 1 h (ii) 56, Et_3N, CH_2Cl_2, −78 °C to rt, 10 h, 20%; (c) morpholine, NaI, Et_3N, DMF, reflux, 16 h, 62%; (d) $Pd(PPh_3)_4$, phenylboronic acid, MeCN/sat. aq. Na_2CO_3 (1:1), reflux, 18 h, 63%.

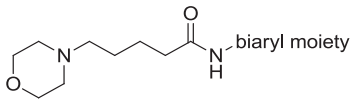
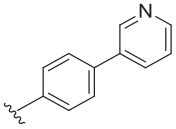
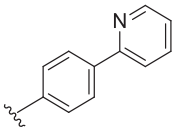
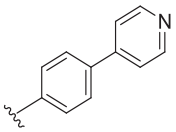
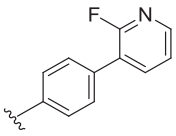
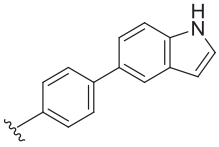
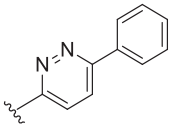
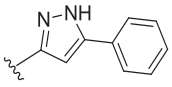
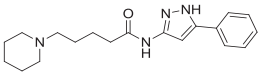
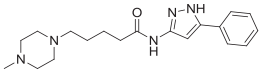


Scheme 5. Synthesis of pyrazole containing analogues **48**–**50**. Reagents and conditions: (a) NaH, MeCN, PhMe, reflux, 18 h, 63%; (b) $NH_2NH_2 \cdot H_2O$, CH_3COOH, EtOH, reflux, 18 h, 80%; (c) (i) 5-bromovaleric acid, $(COCl)_2$, rt, 1 h (ii) 60, Et_3N, CH_2Cl_2, −78 °C to rt, 10 h, 74%; (d) appropriate amine, NaI, Et_3N, THF, reflux, 16 h, 56–62%.

lipophilicity benefit.

The structures described thus far have focused on the development of hybrids of SEN12333 (**8**) by incorporating elements of compound **9** onto the SEN12333 (**8**) scaffold. This has resulted in a more comprehensive SAR study of SEN12333 (**8**) being developed. We then turned our attention to synthesizing hybrids of compound **9**; to expand its SAR and better compare binding data with that obtained for SEN12333 (**8**) analogues. This was to be achieved by altering the heterocycle comprising the basic centre of the molecules while still retaining the more truncated structure that distinguishes these two lead compounds. Similar to the previous work with SEN12333 (**8**), (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane was replaced by small azacycles morpholine, piperidine and 1-methylpiperazine. These azacycles were selected as again they represent the stepwise regression from the (1*S*,4*S*)-2,5-diazabicyclo [2.2.1]heptane heterocycle contained within compound **9** to the

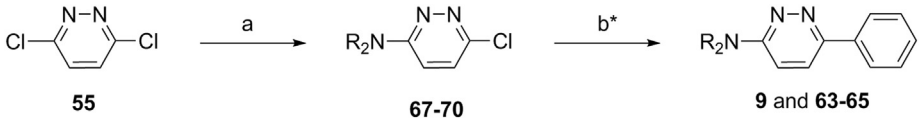
Table 4
Binding affinities of biaryl moiety exploration analogues of SEN12333 (**8**).

Ligand		Binding affinity K_i (nM)[a,b]			Physicochemical properties		
							
Compound	Biaryl moiety	α7	α4β2	α3β4	LogP[c]	PSA	LLE[d]
SEN12333 (**8**)		670 ± 119	>10,000	>10,000	2.25	53.93	3.92
43		330 ± 80	>10,000	>10,000	2.46	53.93	4.02
44		350 ± 90	>10,000	>10,000	2.25	53.93	4.21
45		85 ± 10	>10,000	>10,000	2.48	53.93	4.59
46		310 ± 30	>10,000	>10,000	3.57	53.6	2.94
47		>10,000	>10,000	>10,000	2.39	66.29	1.65
48		2600 ± 300	>10,000	>10,000	2.96	65.96	2.63
49		660 ± 70	>50,000	>10,000	3.89	56.73	2.29
50		>10,000	>10,000	>10,000	1.74	59.97	2.85

[a] Competition binding assays were carried out in membrane homogenates of stably transfected cells or rat forebrain tissue as described previously. The nAChRs were labelled with [^{3}H]-epibatidine. The K_d values (nM) for [^{3}H]-epibatidine used for calculating K_i values were 0.3 for α3β4, 0.04 for α4β2 and 1.8 for α7. K_i values are the mean ± SEM of three to six independent measurements. For low binding affinity compounds, estimated K_i value ranges were provided.
[b] DNC = does not converge.
[c] Calculated using ChemDraw12.0.
[d] ND = not determined.

morpholine ring contained within SEN12333 (**8**). The synthesis of compound **9** and analogues **63**–**65** is shown in Scheme 6 and begins with mono-chloride substitution of pyridazine **55** with various amines to afford compounds **67**–**70** (37–83%). Suzuki cross-coupling of the remaining chloride with phenylboronic acid afforded analogues **63**–**65** (59–78%). 5-Indolyl analogue **66** was synthesized analogously so as to draw comparisons with previously tested SEN12333 (**8**) hybrid **46**.

Competition binding assays of the newly synthesized hybrids of compound **9** are summarized in Table 5. It was immediately evident that the potency trend for the basic centre of compound **9** was in contradiction to that of SEN12333, (**8**). Aliphatic azacycles morpholine and piperidine which corresponded to potency and selectivity for compounds of similar structure to SEN12333 (**8**) were the less active in the series of truncated hybrids (**63** and **64**). Incorporation of 1-methylpiperazine (**65**) marginally restored potency at



Scheme 6. Reagents and conditions: (a) appropriate amine, DIPEA, DMF, reflux, 17 h, 37–83%; (b) $Pd(PPh_3)_4$, phenylboronic acid, MeCN/sat. aq. Na_2CO_3 (1:1), reflux, 18 h, 59–78%; * when amine **25** was used an additional deprotection and methylation steps were performed as follows; HCl (4 M in 1,4-dioxane), MeOH, rt, 2 h; (d) 37% aq. HCOH, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, rt, 18 h, 66% over two steps.

α7 receptors; however, compound **65** interestingly was the only compound to show any potency for the α4β2 receptors. The most potent compound of the series was compound **9** thus suggesting that the (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane functionality is the optimal heterocycle for the binding and selectivity of the synthesized compounds which possess this truncated structure. This is further highlighted by the excellent LLE value of compound **9**. Incorporation of the 5-indolyl moiety into the truncated scaffold resulted in hybrid **66**, previously shown to improve the potency of SEN12333 hybrid – **46** (Table 4), here resulted in a complete loss of potency at α7 receptors.

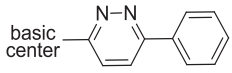
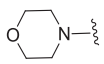
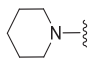
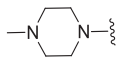
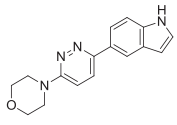
The final set of hybrids synthesized investigated the necessity of the pyridazine moiety within compound **9** (general structure 2) and the consequence of incorporating the biphenyl or phenyl-pyridyl motif originally associated with SEN12333 (**8**) (general structure 1). The synthesis of analogues **72**–**79** began with a Buchwald–Hartwig amination between an appropriate amine and 1,4-dibromobenzene (**80**) or, in the case of using piperidine as the amine, a Cu(II) mediated coupling to afford compounds **81**–**84** (47–82%) (Scheme 7). A subsequent Suzuki cross-coupling with the appropriate boronic acid led to the target compounds **72**–**79** (70–90%).

In consistency with our results of the previous truncated series (Table 5), small unsubstituted azacycles morpholine and piperidine are not tolerated for compounds bearing the scaffold of general structure 2, the results are summarized in Table 6. This is evident in the dramatic loss of potency of compounds **72**–**75**. Similar to the results of Table 5, introduction of the 1-methylpiperazine functionality (**76** and **77**) marginally restored potency. The most potent compounds of this series were **78** and **79** containing the (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane functionality. Interestingly, in accordance with the SEN12333-hybrids (Tables 2 and 3), the biphenyl compounds were of enhanced potency as compared to their corresponding phenyl-pyridyl counterparts. While compound **79** was considerably more potent than compound **78**, the high cLog*P* value of compound **79** has resulted in its LLE value being below that of compound **78**. For compounds containing the general structure 2, it can be concluded that potency at α7 receptors is largely dependent on the aliphatic heterocyclic ring, alteration of this to a smaller, unsubstituted heterocycle results in a striking loss of potency at α7 receptors irrespective of the biaryl ring system. Substitution of the biaryl ring system of compound **9** (general structure 2) with that of SEN12333 (general structure 1) was well tolerated and suggests that these ring systems can be interchanged on these smaller truncated hybrids.

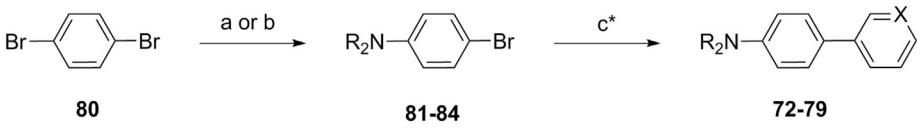
2.3. Functional activity of selected compounds

Several of the α7 receptor ligands described were selected, based upon their binding profiles and LLE values, for evaluation in functional activity studies. The aim of these studies was to determine the agonist activity of the selected synthesized ligands at the

Table 5
Binding affinities of basic centre exploration of truncated analogues.

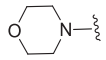
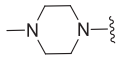
Ligand		Binding affinity K_i (nM)[a,b]			Physicochemical properties		
basic center: 							
Compound	Basic centre	α7	α4β2	α3β4	cLog*P*[c]	PSA	LLE[d]
63		>10,000	>100,000	>1,000,000	1.78	37.19	1.67
64		>10,000	>10,000	>10,000	3.18	27.96	ND
65		4070	417	>10,000	2.36	31.20	ND
9		5.9 ± 0.6	>30,000	>50,000	2.50	31.20	5.73
66		>10,000	>10,000	>10,000	1.79	49.22	ND

[a] Competition binding assays were carried out in membrane homogenates of stably transfected cells or rat forebrain tissue as described previously. The nAChRs were labelled with [^{3}H]-epibatidine. The K_d values (nM) for [^{3}H]-epibatidine used for calculating K_i values were 0.3 for $\alpha_3\beta_4$, 0.04 for $\alpha_4\beta_2$ and 1.8 for α_7. K_i values are the mean ± SEM of three to six independent measurements. For low binding affinity compounds, estimated K_i value ranges were provided.
[b] DNC = does not converge.
[c] Calculated using ChemDraw12.0.
[d] ND = not determined.



Scheme 7. Reagents and conditions (a) appropriate amine, $Pd_2(dba)_3$, ±-BINAP, toluene, reflux, 15 min then 80, KOtBu, reflux, 16 h; (b) $Cu(OAc)_2 \cdot H_2O$, 4-bromophenylboronic acid, piperidine, 4 Å MS, CH_2Cl_2, 20 h, rt, 58% (c) $Pd(PPh_3)_4$, appropriate boronic acid, MeCN/sat. aq. Na_2CO_3 (1:1), reflux, 18 h, 70–90%; * when amine 25 was used an additional deprotection and methylation steps were performed as follows; HCl (4 M in 1,4-dioxane), MeOH, rt, 2 h; (d) 37% aq. HCOH, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$, rt, 18 h, 54–61%% over two steps.

Table 6
Binding affinities of SEN12333 (**8**)-hybrid-truncated analogues.

Ligand			Binding affinity K_i (nM)[a,b]			Physicochemical properties		
basic center — X								
Compound	Basic centre	X	α7	α4β2	α3β4	LogP[c]	PSA	LLE[d]
72		N	>10,000	DNC	>10,000	2.10	24.83	1.50
73		CH	>10,000	>10,000	>10,000	3.49	12.47	ND
74		N	>10,000	>10,000	>10,000	3.48	15.6	ND
75		CH	>10,000	>10,000	>10,000	4.87	3.24	ND
76		N	9400 ± 1800	>10,000	>10,000	2.66	18.84	2.37
77		CH	7700 ± 800	>10,000	>10,000	4.05	6.48	1.06
78		N	140 ± 40	>10,000	>10,000	2.80	18.84	4.05
79		CH	34 ± 10	>10,000	>10,000	4.19	6.48	3.28

[a] Competition binding assays were carried out in membrane homogenates of stably transfected cells or rat forebrain tissue as described previously. The nAChRs were labelled with [^{3}H]-epibatidine. The K_d values (nM) for [^{3}H]-epibatidine used for calculating K_i values were 0.3 for $\alpha_3\beta_4$, 0.04 for $\alpha_4\beta_2$ and 1.8 for α_7. K_i values are the mean ± SEM of three to six independent measurements. For low binding affinity compounds, estimated K_i value ranges were provided.
[b] DNC = does not converge.
[c] Calculated using ChemDraw12.0.
[d] ND = not determined.

α7 receptor. The ligands included in the functional activity studies were compounds **44**, **45**, **46**, hybrid compounds **78** and **79**. SEN12333 (**8**) and lead agonist **9** were also included as references to directly correlate SAR as a result of modifying these leads. To determine their agonistic activity at α7 receptors, the selected compounds were evaluated in a fluorescent calcium assay using a GH4C1 cell line expressing rat α7 receptors. The results are summarized in Table 7.

The EC_{50} of SEN12333 (**8**) was determined to be 687 nM, corresponding to its binding affinity (K_i = 670 nM). Compound **44** which contains the pyridine nitrogen at the 4-position within the terminal aromatic ring, previously displayed a 2-fold increase in binding affinity compared to SEN12333 (**8**) (K_i = 350 vs 670 nM). In the functional assay, compound **44** exhibited comparable potency (EC_{50} = 522 nM) to SEN12333 (**8**), indicating that the 4-position of the pyridine nitrogen within the terminal aromatic ring is favourable for both binding affinity and agonist potency. Compound **45**, incorporating the electronegative fluorine atom, previously displayed an 8-fold increase in binding affinity compared to SEN12333 (**8**) (K_i = 85 nM vs 670 nM). Compound **45** additionally demonstrated an EC_{50} of 145 nM, a dramatic improvement in functional activity compared to SEN12333 (**8**), which may result from attenuation of pyridine basicity, the addition of another hydrogen-bond acceptor or by increasing the torsional angle between the heteroaromatics. Considering the increased potency of **45**, this region of the molecule could be targeted for further examination. Compound **46** containing the 5-indolyl motif, previously demonstrated a 2-fold improvement in binding affinity compared to SEN12333 (**8**) (K_i = 310 nM vs 670 nM). However, in studies of agonist potency, compared to SEN12333 (**8**), compound **46** displayed comparable agonist activity at the α7 receptor, with an EC_{50} of 997 nM, suggesting the extension of the indolyl motif into the hydrophobic pocket is similarly tolerated for agonist activity. Lead agonist **9** (K_i = 5.9 nM) was the most potent compound of the series with an EC_{50} of 25 nM. Analogues **78** and **79** examined the incorporation of the biaryl motif initially associated with SEN12333 (**8**). These compounds maintained binding affinity at the α7 receptor (K_i = 140 and 34 nM respectively), however, this was diminished compared to the lead compound **9**. These compounds additionally maintained agonist activity at the α7 receptor, *albeit* below that of lead agonist

Table 7
The functional activities of selected compounds.

Compound	EC_{50} (nM)[a]
SEN12333 (**8**)	687
44	522
45	145
46	997
78	126
79	253
9	25

[a] Compounds were tested for agonist activity on the α7nAChR in a fluorescent calcium assay using a GH4C1 cells stably expressing rat α7 nAChR. To determine EC_{50} values, all compounds were tested at 0.03, 0.1, 0.3, 1, 3 and 10 μM (n = 3) except for compound **9** which was tested (n = 3) at 0.001–0.3 μM. Replicates have been factored in each datapoint, the error is contained in the datapoints.

9. Compound **78**, containing the phenyl-pyridyl motif, displayed an EC_{50} of 126 nM. Although this is diminished compared to the lead **9**, this is still a 5-fold increase in agonist activity compared to SEN12333 (**8**) (EC_{50} 687 nM). Interestingly, biphenyl containing compound **79**, displayed higher binding affinity ($K_i = 34$ nM) than the related **78**, but exhibited somewhat diminished potency ($EC_{50} = 253$ nM).

2.4. Electrophysiology

Two compounds, SEN12333 (**8**) and compound **45**, were tested for agonist activity on the α7 nicotinic acetylcholine receptor (α7 nAChR) in manual patch-clamp electrophysiology using GH4C1 cells stably expressing rat α7 nAChR. The results are summarized in Table 8 and Fig. 7. Both SEN12333 and **45** are full agonists and more potent than the endogenous agonist, acetylcholine (ACh). The potency in electrophysiology is much lower for these agonists than in the binding and fluorescence assays (300- to 600-fold less potent), which is a well-established phenomenon with reported agonists. For example, compound (**9**) and its analogues showed 200- to 1000-fold drop-offs from binding to electrophysiology [45]. Consistent with the binding and fluorescence data, compound **45** was at least as potent as SEN12333 by electrophysiology.

3. Conclusion

In conclusion, the synthesis and SAR analysis within two structurally distinct series of α7 agonists (represented by SEN12333 and compound **9**) have been described. Hybrids of both lead compounds have been synthesized and the functional groups interchanged to gain greater insight into the requirements of these two agonists for α7 receptor binding. We have identified two analogues of SEN12333, compound **44** and **45**, which are respectively of a 2- and 8-fold increase in affinity relative to SEN12333. Both compounds exhibit acceptable predicted log*P* values and display the potential for further development of the series. After investigating whether compound **9** represents a truncated version of SEN12333 (**8**), it was concluded that the functional groups of the two structures cannot be interchanged and maintain potency at α7 receptors, particularly in relation to the aliphatic heterocycle. The divergent SAR between the series suggests there may be a different binding mode for the basic heterocycles. Biaryl ring substitution of compound **9** with those present in SEN12333 (**8**) was the only functional group exchange tolerated as evident in compounds **78** and **79**.

4. Experimental section

4.1. General synthetic details

Reactions were conducted under a positive pressure of dry nitrogen or argon, unless otherwise stated. Temperatures quoted as 0 °C and −78 °C were achieved with cooling baths of ice-water and dry ice-acetone, respectively. Acetonitrile, dichloromethane, 1,2-dichloroethane, methanol, and triethylamine were distilled from calcium hydride. Tetrahydrofuran and diethyl ether were dried over sodium wire and distilled from sodium benzophenone ketyl. Ethanol, *n*-propanol and pyridine were distilled from calcium hydride and stored over activated 3 Å molecular sieves. Crude tosyl chloride (~10 g) was dissolved in chloroform (25 mL), filtered and diluted with hexanes (125 mL) to precipitate impurities. The solution was then filtered, clarified with activated charcoal and concentrated under reduced pressure to give analytically pure material (~7 g). All reagents were purchased from either Sigma Aldrich Chemical Company, Matrix Scientific, Boron Molecular, or Tokyo Chemical Industry Co and used without further purification. Melting point determinations were measured on either a Gallenkamp melting point apparatus or Optimelt Automated Melting Point System and are recorded uncorrected. Infrared absorption spectra were run as Nujol (KBr) mulls for solids using a BIO-RAD FT-IR spectrophotometer/DRIFTS A 4000–400 cm^{-1} or as thin films on sodium chloride (NaCl) plates for oils using either Shimadzu FTIR-8400S Bruker Alpha-E FT-IR spectrometers. ^1H and ^{13}C NMR spectra were acquired at 300 ± 1 K using either a Bruker Avance DP 282 (300 MHz), DP X400 (400 MHz) or DPX500 (500 MHz). ^1H chemical shifts are reported relative to residual non-deuterated solvent resonance or tetramethylsilane. Data are reported as chemical shifts (δ_H ppm), relative integral, multiplicity (s = singlet; br s = broad singlet; app. br s = apparent broad singlet; d = doublet; dd = doublet of doublets; t = triplet; dt = doublet of triplets; q = quartet; quin = quintet; m = multiplet range), coupling constants (*J*, Hz) and assignments are made where unambiguous. ^{13}C chemical shifts are reported relative to the internal perdeuterated solvent resonance and are specified as quaternary (C), methine (aryl or CH), methylene (CH_2) or methyl (CH_3). Residual acid in deuterated chloroform was removed prior to use by filtering through a pad of basic alumina. Low-resolution mass spectra were recorded on a Finnigan LCQ mass spectrometer. High-resolution mass spectra were recorded by the Mass Spectrometry Unit of the School of Chemistry, University of Sydney. Positive electrospray ionisation (ESI) and atmospheric pressure chemical ionisation (APCI) utilized methanol and/or dichloromethane. The purity of all new compounds was ≥95% based on C, H and N analyses conducted at the Department of Chemistry and Biomolecular Sciences,

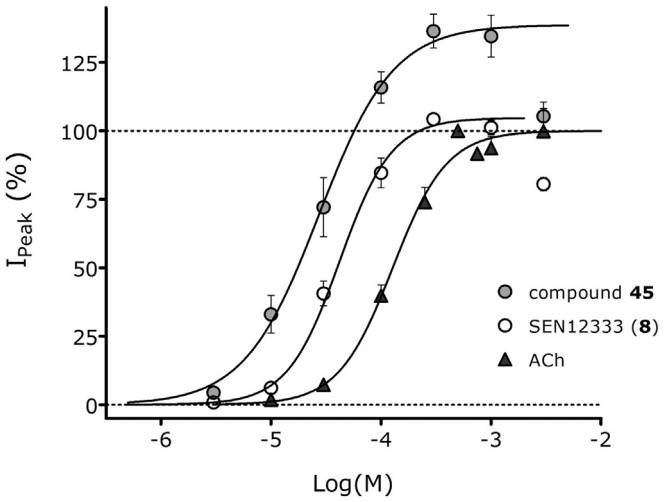


Fig. 7. Electrophysiology studies of SEN12333 (**8**), compound **45** and ACh.

Table 8
Electrophysiology studies of SEN12333 (**8**), compound **43** and ACh.

Compound	EC_{50} (μM)	n_H	Efficacy (%)
ACh	127.6	1.76	100
SEN12333 (**8**)	42	1.83	104.3
45	27.3	1.28	136.5

SEN12333 (**8**) and compound **45**, were tested for agonist activity on the α7 nAChR in manual patch-clamp electrophysiology using GH4C1 cells stably expressing rat α7 nAChR. The manual patch-clamp recordings used the fast application add-on Dynaflow® system. To determine EC_{50} values, the compounds were tested at 3 μM, 10 μM, 30 μM, 100 μM, 300 μM, 1 mM and 3 mM (n = 5). Peak currents were normalized to saturating acetylcholine. Replicates have been factored in each datapoint, the error is therefore contained in the datapoints.

Macquarie University, Sydney, Australia. Analytical thin layer chromatography was carried out using aluminium backed silica gel 60 F_{254} (0.2 mm) Merck KGaA sheets and plates were visualized under a UV lamp at $\lambda = 254$ nm. Plates were routinely stained with phosphomolybdic acid (5% solution in absolute ethanol). Flash column chromatography employed Merck Kieselgel 60 (230–400 mesh) silica gel. Solvents for flash column chromatography were distilled prior to use and are quoted as volume/volume mixtures where applicable.

4.1.1. General procedure 1 for the synthesis of ω-bromo-N-(4-bromophenyl)alkanamides [43]

The appropriate ω-bromoalkanoic acid (1 mmol) was suspended in oxalyl chloride (*ca*. 2 mL), stirred at ambient temperature for 45 min, and the excess oxalyl chloride evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL), cooled to −78 °C, and treated dropwise with a solution of 4-bromoaniline (1.1 mmol) and triethylamine (1.1 mmol) in CH_2Cl_2 (11 mL). The mixture was warmed to ambient temperature, stirred for 4 h, and CH_2Cl_2 (50 mL) was added. The solution was washed with H_2O (50 mL), hydrochloric acid (1 M; 50 mL), saturated aqueous sodium hydrogencarbonate (50 mL), brine (50 mL), dried ($MgSO_4$), filtered, and the solvent evaporated under reduced pressure to give the crude amides.

*4.1.1.1. 5-Bromo-N-(4-bromophenyl)pentanamide (**19**) [43].* Subjecting 5-bromopentanoic acid (**18**) to general procedure 1 gave, after purification by flash chromatography on silica eluting with hexane-ethyl acetate (70:30), amide **19** (0.91 mmol, 91%) as a colourless solid; mp 165–167 °C; νmax/cm^{-1} 3303, 1660, 1591, 1522, 1394, 818; δ_H (300 MHz, $CDCl_3$) 7.41 (4H, m), 7.22 (1H, br s), 3.43 (2H, t, *J* 9.2 Hz), 2.38 (2H, t, *J* 9.2 Hz), 1.91–1.84 (4H, m); δ_C (75 MHz, $CDCl_3$) 171.2, 137.5, 132.1, 121.3, 116.4, 58.2, 37.0, 25.4, 23.2; *m/z* (APCI) 255 ($[M-Br]^-$, 100).

4.1.2. General procedure 2 for the synthesis of N-(4-bromophenyl)-ω-morpholinoalkanamides [43]

A solution of amide **19** (1.0 mmol) in DMF (10 mL) was treated with sodium iodide (1.0 mmol), triethylamine (1.0 mmol) and the appropriate amine (1.1 mmol), and heated at reflux for 16 h. After cooling to ambient temperature, the solution was partitioned between H_2O (100 mL) and ethyl acetate (100 mL), the layers separated, and the aqueous layer extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were washed with H_2O (100 mL), brine (100 mL), dried ($MgSO_4$), filtered, and the solvent evaporated under reduced pressure to give crude amides.

*4.1.2.1. N-(4-Bromophenyl)-5-morpholinopentanamide (**20**) [43].* Subjecting compound **19** to general procedure 2, using morpholine as the amine source, gave, after purification by flash chromatography on silica eluting with ethyl acetate, compound **20** (0.85 mmol, 85%) as a colourless solid; mp 147–148 °C; νmax/cm^{-1} 2939, 1665, 1590, 1531, 1488, 1395, 1302, 1246, 1114, 1070, 1007, 825; δ_H (300 MHz, $CDCl_3$) 7.54 (1H, br s), 7.42 (4H, m), 3.74 (4H, t, *J* 4.4 Hz), 2.51–2.36 (8H, m), 1.77 (2H, m), 1.61 (2H, m); δ_C (75 MHz, $CDCl_3$) 171.4, 137.2, 132.0, 121.5, 116.7, 66.7, 58.4, 53.7, 37.4, 25.8, 23.3; *m/z* (+ESI) 341 ($[M+H]^+$, 100).

*4.1.2.2. N-(4-Bromophenyl)-5-(piperidin-1-yl)pentanamide (**21**).* Subjecting amide **19** to general procedure 2 using THF as the solvent and piperdine as the amine source, the crude amide was obtained and purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (90:9:1) to give compound **21** (1.0 g, 82%) as a colourless solid; mp 123–124 °C; νmax/cm^{-1} 2934, 1739, 1665, 1592, 1535, 1489, 1394, 824; δ_H (300 MHz, $CDCl_3$) 8.09 (1H, br s), 7.38 (4H, m), 2.36–2.27 (8H, m), 1.69 (2H, m), 1.58–1.51 (6H, m), 1.41 (2H, m); δ_C (75 MHz, $CDCl_3$) 171.8, 137.2, 131.9, 121.8, 116.8, 58.8, 54.7, 37.3, 26.2, 25.9, 24.3, 23.7; *m/z* (+ESI) 339 ($[M+H]^+$, 80); Found: C, 56.67; H, 7.04; N, 8.22. Calc for $C_{16}H_{23}BrN_2O$: C, 56.64, H, 6.83; N, 8.26%

*4.1.2.3. N-(4-Bromophenyl)-5-(4-methylpiperazin-1-yl)pentanamide (**22**) [41].* Subjecting compound **19** to general procedure 2 using THF as the solvent and *N*-methyl piperazine as the amine source, the crude amide was obtained and purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (90:9:1) to give compound **22** (1.84 g, 51%) as a colourless solid; mp 99–100 °C; νmax/cm^{-1} 2933, 1738, 1665, 1587, 1529, 1499, 1387, 824; δ_H (200 MHz, $CDCl_3$) 7.56 (1H, br s), 7.41 (4H, br m), 2.49–2.33 (12H, m), 2.29 (3H, s), 1.80–1.57 (4H, m); δ_C (125 MHz, $CDCl_3$) 171.4, 137.2, 132.0, 121.6, 116.8, 57.0, 54.9, 53.1, 46.0, 37.4, 26.2, 23.5; *m/z* (+ESI) 355 ($[M+H]^+$, 100).

*4.1.2.4. 4-Bromo-N-((1S,4S)-tert-butyl5-(2,5-diazabicyclo[2.2.1]heptane-2-carboxylate)butyl)benzamide (**23**).* Subjecting compound **19** to general procedure 2 using THF as the solvent and **25** as the amine source, the crude amide was obtained and purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (90:9:1) to give compound **23** (0.19 g, 84%) as a tan oil; $[\alpha]_D^{25}$ −19.4 (0.7, $CHCl_3$); ν_{max}/cm^{-1} 2931, 1666, 1590, 1531, 1488, 1393, 1364, 1328, 1246, 1100, 1007, 826; δ_H (500 MHz, $CDCl_3$) 8.06 (1H, br s), 7.42 (2H, d, *J* 8.5 Hz), 7.37 (2H, d, *J* 8.5 Hz), 4.29 (0.5H, br s), 4.19 (0.5H, br s), 3.74–3.40 (2H, m), 3.10 (1H, d, *J* 9.0 Hz), 2.88 (0.5H, d, *J* 9.5 Hz), 2.81 (0.5H, d, *J* 9.0 Hz), 2.57–2.43 (3H, m), 2.33 (2H, t, *J* 7.5 Hz), 1.78–1.61 (4H, m), 1.50–1.43 (11H, m) (mixture of rotamers); δ_C (125 MHz, $CDCl_3$) 171.6, 154.5, 154.3, 137.4, 131.9, 121.5, 116.6, 79.6, 79.5, 61.4, 60.8, 60.3, 60.1, 57.8, 56.8, 54.2, 53.6, 49.8, 48.9, 37.3, 36.2, 35.5, 28.79, 28.73, 28.6, 23.4 (mixture of rotamers); *m/z* (APCI) 396 ($[M-C_4H_9]^+$, 100) 254 ($[M-C_{10}H_{17}N_2O_2]^+$, 80) 452 ($[M+H]^+$, 100); Found: MH^+ 452.15389 $C_{21}H_{36}BrN_3O_3$ + H requires 452.15488.

*4.1.2.5. N-(4-Bromophenyl)-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl) pentanamide (**24**).* Subjecting compound **19** to general procedure 2, using 2-oxa-6-azaspiro[3.3]heptane as the amine source, gave the crude amide. Purification by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (92:8.5:0.5) yielded amide **24** (0.63 g, 74%) as a colourless solid; mp 125–127 °C; ν_{max}/cm^{-1} 2937, 1734, 1690, 1524, 1502, 1475, 1248, 1106, 892; δ_H (500 MHz, $CDCl_3$) 7.48 (1H, br s), 7.43–7.39 (4H, m), 4.72 (4H, s), 3.32 (4H, s), 2.39 (2H, t, *J* 7.5 Hz), 2.34 (2H, t, *J* 7.5 Hz), 1.72 (2H, quin, *J* 7.5 Hz), 1.4 (2H, quin, *J* 7.5 Hz); δ_C (125 MHz, $CDCl_3$) 171.2, 137.2, 132.1, 121.5, 116.9, 81.5, 64.0, 59.2, 39.2, 37.5, 27.2, 23.2; *m/z* (ESI) 353, 355 ($[M+H]^+$, 100); Found: C, 54.11; H, 5.55; N, 7.80. Calc for $C_{16}H_{21}BrN_2O_2$: C, 54.40, H, 5.99; N, 7.93%

4.1.3. General procedure 3 for the synthesis of morpholino-N-(4-(pyridin-3-yl)phenyl)alkanamides [43]

A suspension of the appropriate amide (1.0 mmol) and pyridine-3-boronic acid (1.1 mmol) were suspended in acetonitrile-aqueous sodium carbonate (1:1, 0.4 M, 10 mL) and deoxygenated with bubbling argon at ambient temperature. A catalytic amount of $Pd(PPh_3)_4$ (0.05 mmol, 5 mol%) was added, and the mixture heated at reflux for 18 h. The reaction was partitioned between ethyl acetate (30 mL) and saturated aqueous sodium carbonate (30 mL), the layers separated, and the aqueous layer extracted with ethyl acetate (2 × 30 mL). The combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$), filtered, and the solvent evaporated under reduced pressure to give the crude product.

*4.1.3.1. 5-Morpholino-N-(4-(pyridin-3-yl)phenyl)pentanamide (**8**, SEN12333) [43].* Subjecting compound **20** to general procedure 3 gave, after purification by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (90:9:1), compound **8** (0.83 mmol, 83%) as an off-white solid; mp 112–114 °C; νmax/cm^{-1} 2954, 1669, 1599, 1532, 1474, 1289, 1184, 1115, 805, 711; δ_H (300 MHz, $CDCl_3$) 8.79 (1H, s), 8.54 (1H, d, *J* 4.6 Hz), 8.20 (1H, br s), 7.83 (1H, d, *J* 7.9 Hz), 7.65 (2H, d, *J* 8.5 Hz), 7.50 (2H, d, *J* 8.5 Hz), 7.33 (1H, m), 3.69 (4H, t, *J* 6.0 Hz), 2.45–2.35 (8H, m), 1.76 (2H, m), 1.58 (2H, m); δ_C (75 MHz, $CDCl_3$) 171.6, 148.2, 148.2, 138.5, 136.2, 134.2, 133.3, 127.7, 123.8, 120.5, 66.8, 58.5, 53.7, 37.4, 25.9, 23.5; *m*/*z* (+ESI) 340 ($[M+H]^+$, 100).

*4.1.3.2. 5-(Piperidin-1-yl)-N-(4-(pyridin-3-yl)phenyl)pentanamide (**10**).* Subjecting compound **21** to general procedure 3, the crude amide was obtained and purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (93:6.5:0.5) to give compound **10** (0.12 g, 71%) as a colourless solid; mp 117–118 °C; νmax/cm^{-1} 2932, 1668, 1599, 1530, 1473, 1375, 1116; δ_H (500 MHz, $CDCl_3$) 8.82 (1H, d, *J* 2.0 Hz), 8.56 (1H, dd, *J* 1.0, 4.5 Hz), 7.88 (1H, br s), 7.84 (1H, dt, *J* 1.5, 8.0 Hz), 7.64 (2H, d, *J* 8.5 Hz), 7.5 (2H, d, *J* 8.5 Hz), 7.34 (1H, dd, *J* 5.0, 8.0 Hz), 2.43–2.32 (8H, m), 1.76 (2H, m), 1.62–1.55 (6H, m), 1.42 (2H, m); δ_C (125 MHz, $CDCl_3$) 171.7, 148.3, 148.2, 138.4, 136.2, 134.2, 133.6, 127.8, 123.7, 120.7, 59.0, 54.8, 37.6, 26.5, 26.1, 24.5, 23.9; *m*/*z* (+ESI) 169 ($[M-C_{11}H_9N_2]$, 100); (APCI) 253 ($[M-C_5H_{10}N]^+$, 100); Found: C, 74.66; H, 8.24; N, 12.29. Calc for $C_{21}H_{27}N_3O$: C, 74.74, H, 8.06; N, 12.45%

*4.1.3.3. N-([1,1′-Biphenyl]-4-yl)-5-(piperidin-1-yl)pentanamide (**11**).* Subjecting compound **21** to general procedure 3 using phenylboronic acid, the crude amide was obtained and purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (90:9:1) to give compound **11** (0.15 g, 52%) as a colourless solid; mp 109–111 °C; νmax/cm^{-1} 2933, 1654, 1596, 1532, 1488, 1395, 826; δ_H (500 MHz, $CDCl_3$) 7.58–7.53 (4H, m), 7.42–7.39 (4H, m), 7.31 (1H, m), 2.44–2.37 (8H, m), 1.78 (2H, m), 1.65–1.59 (6H, m), 1.45 (2H, m) NH proton not observed; δ_C (125 MHz, $CDCl_3$) 171.5, 140.9, 137.5, 132.1, 128.9, 127.7, 127.2, 127.0, 120.7, 58.9, 54.8, 37.5, 26.4, 26.0, 24.5, 23.9; *m*/*z* (APCI) 252 ($[M-C_5H_{10}N]$, 100), 168 ($[M-C_{11}H_9N_2]^+$, 95), 337 ([M+H], 80); Found: C, 78.74; H, 8.01; N, 8.23. Calc for $C_{22}H_{28}N_2O$: C, 78.53, H, 8.39; N, 8.33%

*4.1.3.4. 5-(4-Methylpiperazin-1-yl)-N-(4-(pyridin-3-yl)phenyl)pentanamide (**12**) [41].* Subjecting compound **22** to the general procedure 3 gave, after purification by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (90:9:1) compound **12** (0.28 g, 57%) as a colourless solid; mp 144–146 °C; νmax/cm^{-1} 3551, 2945, 2803, 1740, 1653, 1532, 1425, 1289, 843; δ_H (500 MHz, $CDCl_3$) 8.82 (1H, d, *J* 1.5 Hz), 8.56 (1H, dd, *J* 1.5, 4.5 Hz), 7.84 (1H, dt, *J* 2.0, 8.0 Hz), 7.63 (2H, d, *J* 8.5 Hz), 7.54 (2H, d, *J* 8.5 Hz), 7.35 (1H, dd, *J* 5.0, 8.0 Hz), 2.43–2.34 (12H, m), 2.27 (3H, s), 1.80–1.74 (2H, m), 1.62–1.56 (2H, m) NH proton not observed; δ_C (125 MHz, $CDCl_3$) 171.3, 148.3, 148.0, 138.1, 136.0, 134.0, 132.1, 127.7, 123.6, 120.4, 58.1, 55.1, 53.3, 46.1, 37.5, 26.4, 23.6; *m*/*z* (+ESI) 353 ($[M+H]^+$, 100).

*4.1.3.5. N-([1,1′-Biphenyl]-4-yl)-5-(4-methylpiperazin-1-yl)pentanamide (**13**).* Subjecting **22** to the general procedure 3 using phenylboronic acid gave, after purification by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (85:13.5:1.5) **13** (0.34 mmol, 68%) as a colourless solid; mp 147.5–148.9 °C; νmax/cm^{-1} 3552, 2942, 2805, 1738, 1656, 1596, 1532, 1372, 1216, 834, 762; δ_H (500 MHz, $CDCl_3$) 7.59 (2H, d, *J* 8.5 Hz), 7.56–7.53 (4H, m), 7.42 (2H, t, *J* 6.0 Hz), 7.32 (1H, t, *J* 6.0 Hz), 2.47–2.38 (12H, m), 2.28 (3H, s), 1.78–1.74 (2H, m), 1.63–1.58 (2H, m); δ_C (125 MHz, $CDCl_3$) 171.4, 140.6, 137.4, 137.2, 128.9, 127.7, 127.2, 127.0, 120.4, 58.1, 55.1, 53.3, 46.1, 37.6, 26.4, 23.7; *m*/*z* (+ESI) 352 ($[M+H]^+$, 100); Found: C, 75.10; H, 8.37; N, 11.86. Calc for $C_{22}H_{29}N_3O$: C, 75.18, H, 8.32; N, 11.96%

*4.1.3.6. 5-((1S,4S)-tert-Butyl5-(2,5-diazabicyclo[2.2.1]heptane-2-carboxylate)-N-(4-(pyridin-3-yl)phenyl)pentanamide (**26**).* Subjecting compound **23** to general procedure 3 the crude residue was obtained and purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (90:9.5:0.5) to give compound **26** (0.17 g, 93%) as a colourless oil; $[a]_D^{25}$ −25.1 (1.0, $CHCl_3$); νmax/cm^{-1} 2974, 1687, 1598, 1529, 1474, 1397, 1328, 1250, 1103; δ_H (400 MHz, $CDCl_3$) 8.81 (1H, br s), 8.56 (1H, d, *J* 4.8 Hz), 7.84 (1H, d, *J* 7.6 Hz), 7.65 (2H, d, *J* 8.4 Hz), 7.53 (2H, d, *J* 8.4 Hz), 7.34 (1H, dd, *J* 4.8, 7.6 Hz), 4.34 (0.5H, s), 4.22 (0.5H, s), 3.54–3.44 (2H, m), 3.14 (1H, d, *J* 6.8 Hz), 2.95 (0.5H, d, *J* 9.2 Hz), 2.88 (0.5H, d, *J* 9.2 Hz), 2.63–2.56 (2H, m), 2.42 (2H, t, *J* 7.6 Hz), 1.83–1.76 (4H, m), 1.68 (1H, m), 1.54 (2H, quin, *J* 7.6 Hz), 1.45 (9H, s) (mixture of rotamers); δ_C (100 MHz, $CDCl_3$) 171.5, 154.3, 148.4, 148.2, 138.4, 136.2, 134.2, 133.5, 127.8, 123.7, 120.5, 79.6, 79.5, 61.6, 60.9, 60.4, 60.3, 57.8, 56.8, 54.2, 53.6, 49.7, 48.7, 37.6, 36.4, 35.6, 28.7, 23.5 (mixture of rotamers); *m*/*z* (ESI) 451 ($[M+H]^+$, 100), 253 ($[M-C_{10}H_{17}N_2O_2]^+$, 63), 395 ($[M-C_4H_9]^+$, 34); Found: MH^+ 451.27040 $C_{26}H_{34}N_4O_3$ + H requires 451.27092.

*4.1.3.7. 5-((1S,4S)-tert-Butyl5-(2,5-diazabicyclo[2.2.1]heptane-2-carboxylate)-N-[1,1'-biphenyl]-4-carboxamide (**27**).* Subjecting compound **23** to general procedure 3 using phenylboronic acid the crude residue was obtained and purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (92:7.5:0.5) to give compound **27** (0.1 g, 59%) as a colourless oil; $[a]_D^{25}$ −22.3 (1.0, $CHCl_3$); νmax/cm^{-1} 2916, 1668, 1598, 1529, 1486, 1405, 1165; δ_H (500 MHz, $CDCl_3$) 7.60–7.54 (6H, m), 7.42 (2H, d, *J* 7.5 Hz), 7.32 (1H, d, *J* 7.5 Hz), 4.34 (0.5H, s), 4.21 (0.5H, s), 3.54 (0.5H, d, *J* 10.0 Hz), 3.48–3.44 (1.5H, m), 3.14 (1H, t, *J* 9.0 Hz), 2.94 (0.5H, d, *J* 9.5 Hz), 2.89 (0.5H, d, *J* 9.5 Hz), 2.62–2.55 (1.5H, m), 2.47 (0.5H, d, *J* 9.5 Hz), 2.40 (2H, t, *J* 7.5 Hz), 1.83–1.76 (4H, m), 1.70 (0.5H, d, *J* 9.0 Hz), 1.54 (0.5H, d, *J* 9.5 Hz), 1.54 (2H, quin, *J* 7.5 Hz), 1.45 (9H, s), NH proton not observed (mixture of rotamers); δ_C (100 MHz, $CDCl_3$) 171.4, 154.5, 154.4, 140.7, 137.4, 137.2, 128.9, 127.7, 127.2, 127.0, 120.3, 79.6, 79.5, 61.5, 60.9, 60.4, 60.2, 57.9, 56.8, 54.2, 53.6, 49.7, 48.7, 37.6, 36.4, 35.6, 28.8, 28.7, 23.5 (mixture of rotamers); *m*/*z* (ESI) 472 ($[M+Na]^+$, 100), 252 ($[M-C_{10}H_{17}N_2O_2]^+$, 85), 394 ($[M-C_4H_9]^+$, 34); Found: MNa^+ 472.25675 $C_{27}H_{35}N_3O_3$ + Na requires 472.25761.

4.1.4. General procedure 5 for N-methylation of ((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pentanamides

A solution of the appropriate *N*-Boc protected pentanamide (1.0 mmol) in methanol (0.1 M) was treated with hydrogen chloride gas in dioxane (5.0 mmol) and stirred at room temperature for 2 h. The solvent was then removed under a steam of nitrogen gas and the residue partitioned between hydrochloric acid (1 M, 20 mL) and CH_2Cl_2 (50 mL), the aqueous layer was further extracted with CH_2Cl_2 (20 mL) and then basified to pH 14 with addition of aqueous sodium hydroxide (3 M, *ca* 10 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic extracts dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The free amine was then suspended in $ClCH_2CH_2Cl$ (0.1 M) and treated with aqueous formaldehyde (37%, 1.5 mmol) and $NaBH(OAc)_3$ (5 mmol) and the resulting mixture stirred at ambient temperature for 17–20 h. The reaction was quenched with addition of aqueous sodium hydroxide (3 M, 5 mL) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered and the solvent

evaporated to give the crude residue.

*4.1.4.1. 5-((1S,4S)-5-Methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)-N-(4-(pyridin-3-yl)phenyl)pentanamide (**14**).* Subjecting compound **26** to general procedure 5 the crude residue was obtained and purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (88:11.5:0.5) to give methylated amine **14** (0.05 g, 48% over two steps) as a colourless oil; $[a]_D^{25}$ −21.5 (1.0, $CHCl_3$); ν_{max}/cm^{-1} 2929, 1668, 1597, 1525, 1473, 1425, 1288, 1250, 1182, 1001, 845; δ_H (500 MHz, $CDCl_3$) 8.81 (1H, d, *J* 1.5 Hz), 8.55 (1H, dd, *J* 1.5, 4.5 Hz), 7.99 (1H, br s), 7.84 (1H, dt, *J* 2.0, 8.0 Hz), 7.66 (2H, d, *J* 8.5 Hz), 7.52 (2H, d, *J* 8.5 Hz), 7.34 (1H, dd, *J* 5.0, 8.0 Hz), 3.23 (1H, s), 3.17 (1H, s), 2.82 (1H, d *J* 10.0 Hz), 2.71 (1H, dd, *J* 2.5, 10.0 Hz), 2.66–2.60 (2H, m), 2.51 (2H, m), 2.42 (2H, t, *J* 7.5 Hz), 2.36 (3H, s), 1.79 (2H, quin, *J* 7.5 Hz), 1.69 (2H, m), 1.54 (2H, quin, *J* 7.5H); δ_C (125 MHz, $CDCl_3$) 171.7, 148.4, 148.2, 138.4, 136.2, 134.2, 133.5, 127.8, 123.7, 120.5, 63.7, 62.4, 57.1, 56.6, 53.5, 41.6, 37.5, 33.6, 28.5, 23.6; *m*/*z* (APCI) 253 ($[M-C_6H_{11}N_2]^+$, 100), 169 ($[M-C_{11}H_{19}N_2O]^+$, 68), 365 ($[M+H]^+$, 24); Found: MH^+ 365.23377 $C_{22}H_{28}N_4O$ + H requires 365.23414.

*4.1.4.2. N-([1,1′-Biphenyl]-4-yl)-5-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)pentanamide (**15**).* Subjecting compound **27** to general procedure 5 the crude residue was obtained and purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (85:14:1) to give methylated amine **15** (0.06 g, 50% over two steps) as a colourless oil; $[a]_D^{25}$ −24.7 (1.0, $CHCl_3$); ν_{max}/cm^{-1} 2910, 1670, 1587, 1529, 1480, 1428, 1165, 809; δ_H (500 MHz, $CDCl_3$) 8.32 (1H, br s), 7.62 (2H, d, *J* 8.5 Hz), 7.54 (4H, t, *J* 9.0 Hz), 7.40 (2H, t, *J* 7.5 Hz), 7.3 (1H, t, *J* 7.5 Hz), 3.32 (1H, s), 3.18 (1H, s), 2.92 (1H, d, *J* 10.0 Hz), 2.72–2.60 (3H, m), 2.49 (2H, m), 2.40 (2H, t, *J* 7.5 Hz), 2.36 (3H, s), 1.79–1.69 (4H, m), 1.54 (2H, m); δ_C (125 MHz, $CDCl_3$) 171.9, 140.7, 137.8, 136.9, 128.9, 127.6, 127.1, 126.9, 120.3, 63.6, 62.1, 57.0, 56.7, 53.4, 41.8, 37.3, 33.1, 28.2, 23.6; *m*/*z* (ESI) 364 ($[M+H]^+$, 100); Found: MH^+ 364.23859 $C_{23}H_{29}N_3O$ + H requires 364.23889.

*4.1.4.3. N-(4-(Pyridin-3-yl)phenyl)-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pentanamide (**16**).* Subjecting amide **24** to the general procedure 3 gave the crude residue which was purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (90:9:1) to give pentanamide **16** (0.29 g, 70%) as a yellow oil; νmax/cm^{-1} 3673, 2925, 1738, 1598, 1535, 1365, 1215; δ_H (400 MHz, $CDCl_3$) 8.78 (1H, d, *J* 1.6 Hz), 8.53 (1H, dd, *J* 1.6, 4.8 Hz), 8.39 (1H, br s), 7.81 (1H, m), 7.62 (2H, d, *J* 8.4 Hz), 7.49 (2H, d, *J* 8.4 Hz), 7.32 (1H, dd, *J* 4.8, 7.6 Hz), 4.68 (4H, s), 3.27 (4H, s), 2.37–2.33 (4H, m), 1.70 (2H, quin, *J* 7.6 Hz), 1.36 (2H, quin, *J* 7.6 Hz); δ_C (100 MHz, $CDCl_3$) 171.6, 148.1, 147.9, 138.6, 136.2, 134.2, 133.3, 127.6, 123.7, 120.5, 81.4, 63.9, 59.2, 39.1, 37.3, 27.2, 23.3; *m*/*z* (ESI) 352 ($[M+H]^+$, 100), 725 ($[2M+Na]^+$, 43); Found: MH^+ 352.01969. $C_{21}H_{25}N_3O$ + H requires 352.20250.

*4.1.4.4. N-([1,1′-Biphenyl]-4-yl)-5-(2-oxa-6-azaspiro[3.3]heptan-6-yl)pentanamide (**17**).* Subjecting amide **24** to the general procedure 3 using phenylboronic acid gave the crude residue which was purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (92:7.5:0.5) to give pentanamide **17** (0.088 g, 90%) as a colourless solid; mp 1089–111; νmax/cm^{-1} 3729, 2927, 1740, 1662, 1597, 1531, 1408, 1355, 1331, 1237; δ_H (500 MHz, $CDCl_3$) 7.75 (1H, br s), 7.58–7.53 (4H, m), 7.43–7.37 (4H, m), 7.32 (1H, t, *J* 7.5 Hz), 4.70 (4H, s), 3.38 (4H, s), 2.42 (2H, t, *J* 7.5 Hz), 2.35 (2H, t, *J* 7.5 Hz), 1.72 (2H, quin, *J* 7.5 Hz), 1.45 (2H, quin, *J* 7.5 Hz); δ_C (125 MHz, $CDCl_3$) 171.3, 140.6, 137.4, 137.2, 128.9, 127.7, 127.2, 126.9, 120.3, 81.4, 63.7, 59.0, 38.8, 37.4, 26.8, 23.3; *m*/*z* (ESI) 351 ($[M+H]^+$, 100), 723 ($[2M+Na]^+$, 33); Found: C, 75.52; H, 7.39 N, 7.88. Calc for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99%

*4.1.4.5. 2-(4-(Piperidin-1-yl)butyl)isoindoline-1,3-dione (**29**).* *N*-(4-Bromobutyl)phthalimide (**28**) (2.0 g, 7.09 mmol) was suspended in THF (64 mL) and treated with sodium iodide (1.06 g, 7.09 mmol), triethylamine (0.99 mL, 7.09 mmol) and piperidine (0.77 mL, 7.79 mmol). The mixture was then heated at reflux for 16 h. After cooling to ambient temperature, the solvent was removed *in vacuo* and the residue partitioned between H_2O (100 mL) and $CHCl_3$ (100 mL). The aqueous layer was further extracted with $CHCl_3$ (100 mL) and the organic extracts combined, dried (MgSO4), filtered, and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica eluting with ethyl acetate to give phthalimide **29** (1.52 g, 74%) as a colourless solid; mp 73–74 °C; νmax/cm^{-1} 2933, 2765, 1711, 1395, 1367, 1215, 1040; δ_H (300 MHz, $CDCl_3$) 7.82–7.80 (2H, m), 7.70–7.67 (2H, m), 3.68 (2H, t, *J* 6.9 Hz), 2.32–2.26 (6H, m), 1.66 (2H, m), 1.56–1.46 (6H, m), 1.39 (2H, m); δ_C (75 MHz, $CDCl_3$) 168.5, 133.9, 132.2, 123.2, 59.0, 54.7, 38.0, 26.8, 26.1, 24.5, 24.4; *m*/*z* (APCI) 287 ($[M+H]^+$, 83); Found: C, 71.42; H, 8.06; N, 9.78. Calc for $C_{17}H_{22}N_2O$: C, 71.30, H, 7.74; N, 9.78%

*4.1.4.6. 2-(4-(4-Methylpiperazin-1-yl)butyl)isoindoline-1,3-dione (**30**).* *N*-(4-Bromobutyl)phthalimide (**28**) (2.0 g, 7.09 mmol) was suspended in THF (64 mL) and treated with sodium iodide (1.06 g, 7.09 mmol), triethylamine (0.99 mL, 7.09 mmol) and *N*-methyl piperazine (0.86 mL, 7.09 mmol). The mixture was then heated at reflux for 16 h. After cooling to ambient temperature, the solvent was removed *in vacuo* and the residue partitioned between H_2O (100 mL) and $CHCl_3$ (100 mL). The aqueous layer was further extracted with $CHCl_3$ (100 mL) and the organic extracts combined, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica eluting with ethyl acetate to give phthalimide **30** (1.94 g, 91%) as a colourless solid; mp 71–72 °C; νmax/cm^{-1} 2794, 1707, 1394, 1164, 1041; δ_H (300 MHz, $CDCl_3$) 7.83–7.81 (2H, m), 7.72–7.69 (2H, m), 3.70 (2H, t, *J* 6.4 Hz), 2.43–2.33 (10H, m), 2.26 (3H, s), 1.69 (2H, m), 1.52 (2H, s); δ_C (75 MHz, $CDCl_3$) 168.6, 134.0, 132.2, 123.3, 58.1, 55.2, 53.3, 46.2, 38.0, 26.7, 24.4; *m*/*z* (APCI) 302 ($[M+H]^+$, 100); Found: C, 67.82; H, 7.64; N, 13.84. Calc for $C_{17}H_{23}N_3O_2$: C, 67.75, H, 7.69; N, 13.94%

*4.1.4.7. (1S,4S)-tert-Butyl-5-(4-(1,3-dioxoisoindolin-2-yl)butyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**31**).*
N-(4-Bromobutyl)phthalimide (**28**) (0.32 g, 1.15 mmol) was suspended in THF (11 mL) and treated with sodium iodide (0.17 g, 1.15 mmol), triethylamine (160 μL, 1.15 mmol) and **157** (0.25 g, 1.26 mmol). The mixture was then heated at reflux for 16 h. After cooling to ambient temperature, the solvent was removed *in vacuo* and the residue partitioned between H_2O (100 mL) and $CHCl_3$ (100 mL). The aqueous layer was further extracted with $CHCl_3$ (100 mL) and the organic extracts combined, dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica eluting with ethyl acetate to give phthalimide **31** (0.35 g, 76%) as an off-white solid; $[a]_D^{25}$ −22.8 (0.9, $CHCl_3$); νmax/cm^{-1} 3129, 1689, 1419, 1320, 890; δ_H (500 MHz, $CDCl_3$) 7.83–7.82 (2H, m), 7.71–7.69 (2H, m), 4.31 (0.5H, s), 4.19 (0.5H, s), 3.69 (2H, t, *J* 7.0 Hz), 3.50 (0.5H, d, *J* 10.0 Hz), 3.45–3.41 (1.5H, m), 3.41 (1H, t, *J* 10.0 Hz), 2.92 (0.5H, d, *J* 9.5 Hz), 2.85 (0.5H, d, *J* 9.5 Hz), 2.58–2.52 (2.5H, m), 2.43 (0.5H, d, *J* 9.5 Hz), 1.78–1.63 (4H, m), 1.51–1.41 (11H, m) (mixture of rotamers); δ_C (125 MHz, $CDCl_3$) 168.6, 154.4, 154.3, 134.0, 132.3, 123.3, 79.4, 79.3, 61.4, 60.9, 60.21, 60.16, 57.9, 56.9, 54.0, 53.4, 49.8, 48.7, 38.0, 36.5, 35.6, 28.7, 26.7, 26.6 (mixture of rotamers); *m*/*z* (ESI) 400 ($[M+H]^+$, 100); Found: MH^+ 400.22329 $C_{22}H_{29}N_3O_4$ + H

requires 400.22363.

*4.1.4.8. 4-Bromo-N-(4-(piperidin-1-yl)butyl)benzamide (**32**).* Phthalimide **29** (0.85 g, 2.97 mmol) was suspended in anhydrous ethanol (30 mL) and treated with hydrazine monohydrate (0.72 mL, 14.85 mmol). The mixture was heated under reflux for 2 h and then cooled to room temperature, filtered, and the filtrate evaporated under reduced pressure. The remaining residue was suspended in hydrochloric acid (1 M; 50 mL) and heated under reflux for 1 h. After cooling to room temperature, the mixture was filtered and the filtrate washed with CH_2Cl_2 (50 mL). The aqueous layer was basified to pH 14 with addition of aqueous sodium hydroxide (3 M), and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent removed *in vacuo* to give crude amine which was used directly in the next step without further purification or characterization due to its volatile nature.

4-Bromobenzoyl chloride (0.52 g, 2.39 mmol) was suspended in CH_2Cl_2 (15 mL) and cooled to 0 °C. A solution of crude amine (2.97 mmol) and triethylamine (0.33 mL, 2.39 mmol) in CH_2Cl_2 (15 mL) was added dropwise and stirring continued at 0 °C for 0.5 h. The mixture was then allowed to reach room temperature and stirring continued for a further 2 h. CH_2Cl_2 (50 mL) was added and the solution washed with saturated aqueous sodium carbonate (50 mL), saturated aqueous ammonium chloride (50 mL), H_2O (50 mL) then brine (50 mL). The organic layer was then dried ($MgSO_4$), filtered, and the solvent removed under reduced pressure to give the crude residue. Purification by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (90:9:1), gave amide **32** (0.99 g, 50% over two steps) as a colourless solid; mp 112–113 °C; νmax/cm^{-1} 3316, 2932, 1742, 1632, 1536; δ_H (300 MHz, $CDCl_3$) 7.62 (2H, d, *J* 8.4 Hz), 7.53 (2H, d, *J* 8.4 Hz), 3.43 (2H, q, *J* 5.4 Hz), 2.34–2.30 (6H, m), 1.66–1.50 (8H, m), 1.40 (2H, m); δ_C (75 MHz, $CDCl_3$) 166.9, 134.1, 131.8, 128.8, 125.9, 58.7, 54.7, 40.2, 27.5, 25.9, 24.7, 24.5; *m*/*z* (APCI) 185 ([M−$C_9H_{19}N_2$]$^+$, 100), 339 ([M+H], 42); Found: C, 56.69; H, 6.97; N, 8.25. Calc for $C_{16}H_{23}BrN_2O$: C, 56.64, H, 6.83; N, 8.26%

*4.1.4.9. 4-Bromo-N-(4-(4-methylpiperazin-1-yl)butyl)benzamide (**33**).* Phthalimide **30** (1.20 g, 3.98 mmol) was suspended in anhydrous ethanol (40 mL) and treated with hydrazine monohydrate (0.97 mL, 19.9 mmol). The mixture was heated under reflux for 2 h and then cooled to room temperature, filtered, and the filtrate evaporated under reduced pressure. The resulting residue was suspended in hydrochloric acid (1 M; 50 mL) and heated under reflux for 1 h. After cooling to room temperature, the mixture was filtered and the filtrate washed with CH_2Cl_2 (50 mL). The aqueous layer was basified to pH 14 with addition of aqueous sodium hydroxide (3 M), and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude amine which was used directly in the next step without further purification or characterization due to its volatile nature.

4-Bromobenzoyl chloride (0.18 g, 0.8 mmol) was suspended in CH_2Cl_2 (10 mL) and cooled to 0 °C. A solution of crude the amine (0.87 mmol) and triethylamine (0.11 mL, 0.8 mmol) in CH_2Cl_2 (10 mL) was added dropwise and stirring continued at 0 °C for 0.5 h. The mixture was then allowed to reach room temperature and stirring continued for a further 2 h. CH_2Cl_2 (50 mL) was added and the solution washed with saturated aqueous sodium carbonate (50 mL), saturated aqueous ammonium chloride (50 mL), H_2O (50 mL) then brine (50 mL). The organic layer was then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give the crude residue. Purification by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (90:9:1), gave amide **33** (0.3 g, 35%) as a colourless solid; mp 121–123 °C; νmax/cm^{-1} 2940, 2794, 1636, 1590, 1544, 1482, 1284, 1164, 1011; δ_H (300 MHz, $CDCl_3$) 7.61 (2H, d, *J* 8.1 Hz), 7.54 (2H, d, *J* 8.1 Hz), 3.43 (2H, t, *J* 6.0 Hz), 2.39–2.35 (10H, m), 2.42 (3H, s), 1.65–1.59 (4H, m), NH proton not observed; δ_C (75 MHz, $CDCl_3$) 166.8, 134.0, 131.8, 128.7, 125.9, 58.0, 55.1, 53.3, 46.1, 40.2, 27.5, 24.6; *m*/*z* (APCI) 354 ([M+H]$^+$, 100); Found: C, 54.18; H, 7.06; N, 11.56. Calc for $C_{16}H_{24}BrN_3O$: C, 54.24, H, 6.83; N, 11.86%

*4.1.4.10. (1S,4S)-tert-Butyl 5-(4-(4-bromobenzamido)butyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**34**).* Phthalimide **31** (0.40 g, 1.12 mmol) was suspended in anhydrous ethanol (12 mL) and treated with hydrazine monohydrate (273 μL, 5.62 mmol). The mixture was heated under reflux for 2 h and then cooled to room temperature, filtered, and the filtrate evaporated under reduced pressure. The remaining residue was suspended in hydrochloric acid (1 M; 50 mL) and heated under reflux for 1 h. After cooling to room temperature, the mixture was filtered and the filtrate washed with CH_2Cl_2 (50 mL). The aqueous layer was basified to pH 14 with addition of aqueous sodium hydroxide (3 M), and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude amine which was used directly in the next step without further purification or characterization.

4-Bromobenzoyl chloride (0.25 g, 1.12 mmol) was suspended in CH_2Cl_2 (10 mL) and cooled to 0 °C. A solution of the crude amine (1.12 mmol) and triethylamine (156 μL, 0.8 mmol) in CH_2Cl_2 (10 mL) was added dropwise and stirring continued at 0 °C for 0.5 h. The mixture was then allowed to reach room temperature and stirring continued for a further 2 h. CH_2Cl_2 (50 mL) was added and the solution washed with saturated aqueous sodium carbonate (50 mL), saturated aqueous ammonium chloride (50 mL), H_2O (50 mL) and brine (50 mL). The organic layer was then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give the crude residue. Purification by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (93:6.5:0.5), gave amide **34** (0.33 g, 66% over two steps) as a tan oil; $[a]_D^{25}$ −22.6 (1.0, $CHCl_3$); νmax/cm^{-1} 2938, 1678, 1591, 1531, 1492, 1387, 1330, 1245, 1105, 1010, 826; δ_H (500 MHz, $CDCl_3$) 7.61 (2H, d, *J* 8.5 Hz), 7.53 (2H, d, *J* 8.5 Hz), 4.31 (0.5H, s), 4.19 (0.5H, s), 3.5 (0.5H, d, *J* 10.5 Hz), 3.44–3.40 (3.5H, m), 3.12 (1H, t, *J* 8.0 Hz), 2.88 (0.5H, d, *J* 9.5 Hz), 2.83 (0.5H, d, *J* 9.5 Hz), 2.60–2.52 (2.5H, m), 2.43 (0.5H, d, *J* 9.5 Hz), 1.71 (1H, d, *J* 9.5 Hz), 1.68–1.64 (3H, m), 1.53 (2H, m), 1.44 (9H, s), NH peak not observed (mixture of rotamers); δ_C (125 MHz, $CDCl_3$) 166.8, 154.4, 154.3, 134.0, 131.8, 128.7, 126.0, 61.3, 60.7, 60.2, 60.1, 57.7, 56.7, 53.8, 53.3, 49.6, 48.6, 40.1, 36.4, 35.6, 28.7, 27.5, 27.4, 26.9 (mixture of rotamers); *m*/*z* (ESI) 454, 452 ([M+H]$^+$, 100); Found: MH$^+$ 452.15429 $C_{21}H_{30}BrN_3O_3$ + H requires 452.15429.

*4.1.4.11. N-(4-(Piperidin-1-yl)butyl)-4-(pyridin-3-yl)benzamide (**37**).* Subjecting compound **32** to general procedure 3 gave, after purification by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (95:4.5:0.5) compound **37** (0.126 g, 63%) as a colourless solid; mp 115–117 °C; νmax/cm^{-1} 3315, 2932, 1739, 1639, 1546, 1366, 1305, 1216; δ_H (300 MHz, $CDCl_3$) 8.87 (1H, d, *J* 2.1 Hz), 8.62 (1H, dd, *J* 1.5, 4.8 Hz), 7.91 (1H, t, *J* 2.1 Hz), 7.87 (2H, d, *J* 8.4 Hz), 7.64 (2H, d, *J* 8.4 Hz), 7.39 (1H, dd, *J* 4.8, 8.78 Hz), 6.95 (1H, br s), 3.50 (2H, q, *J* 6.0 Hz), 2.37–2.32 (6H, m), 1.69–1.51 (8H, m), 1.42 (2H, m); δ_C (75 MHz, $CDCl_3$) 167.3, 149.2, 148.5, 140.7, 135.8, 134.8, 134.5, 128.0, 127.3, 123.8, 58.8, 54.7, 40.1, 27.6, 25.9, 24.7, 24.5; *m*/*z* (APCI) 182 ([M−$C_{11}H_8N$]$^+$, 100), 253 ([M−$C_5H_{10}N$]$^+$, 35); Found: C, 74.38; H, 8.37; N, 12.41. Calc for $C_{21}H_{27}N_3O$: C, 74.74, H, 8.06; N, 12.45%

*4.1.4.12. N-(4-(Piperidin-1-yl)butyl)-[1,1′-biphenyl]-4-carboxamide (**38**).* Subjecting compound **32** to general procedure 3 using

phenylboronic acid gave, after purification by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (95:4.5:0.5) compound **38** (0.19 g, 67%) as a colourless solid; mp 129–131 °C; νmax/cm^{-1} 3327, 2932, 1632, 1541, 1304, 852; δ_H (400 MHz, $CDCl_3$) 7.83 (2H, d, *J* 8.8 Hz), 7.64 (2H, d, *J* 8.8 Hz), 7.61 (2H, d, *J* 7.2 Hz), 7.46 (2H, t, *J* 7.2 Hz), 7.36 (1H, m), 3.49 (2H, q, *J* 6.4 Hz), 2.37–2.34 (6H, m), 1.70–1.62 (4H, m), 1.58–1.53 (4H, m), 1.41 (2H, m), NH proton not observed; δ_C (100 MHz, $CDCl_3$) 167.5, 144.1, 140.3, 133.8, 129.0, 128.0, 127.6, 127.3, 127.2, 58.7, 54.7, 40.0, 27.6, 25.8, 24.5, 24.4; *m/z* (APCI) 181 ($[M-C_{12}H_9]^+$, 100), 252 ($[M-C_5H_{10}N]^+$, 38); Found: C, 78.01; H, 8.68; N, 8.32. Calc for $C_{22}H_{28}N_2O$: C, 78.53, H, 8.39; N, 8.33%

*4.1.4.13. N-(4-(4-Methylpiperazin-1-yl)butyl)-4-(pyridin-3-yl)benzamide (**39**).* Subjecting compound **33** to the general procedure 3 gave, after purification by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (95:4.5:0.5) compound **39** (0.05 mmol, 55%) as a colourless solid; mp 113–115 °C; νmax/cm^{-1} 3295, 2939, 2798, 1737, 1638, 1545, 1458, 1371, 1301, 1216, 1164, 1012; δ_H (500 MHz, $CDCl_3$) 8.82 (1H, d, *J* 2.0 Hz), 8.60 (1H, dd, *J* 1.5, 5.0 Hz), 7.87–7.83 (3H, m), 7.60 (2H, d, *J* 8.0 Hz), 7.36 (1H, dd, *J* 5.0, 8.0 Hz), 6.89 (1H, br s), 3.46 (2H, q *J* 6.5 Hz), 2.38–2.35 (10H, m), 2.22 (3H, s), 1.68–1.58 (4H, m); δ_C (125 MHz, $CDCl_3$) 167.3, 149.2, 148.4, 140.8, 135.7, 134.7, 134.5, 127.9, 127.3, 123.8, 58.1, 55.1, 53.3, 46.2, 40.2, 27.6, 24.7; *m/z* (APCI) 182 ($[M-C_9H_{20}N_3]^+$, 100), 253 ($[M-C_5H_{11}N_2]^+$, 37); Found: C, 71.49; H, 8.31; N, 15.81. Calc for $C_{21}H_{28}N_4O$: C, 71.56, H, 8.01; N, 15.9%

*4.1.4.14. N-(4-(4-Methylpiperazin-1-yl)butyl)-[1,1′-biphenyl]-4-carboxamide (**40**).* Subjecting compound **33** to the general procedure 3 using phenylboronic acid gave, after purification by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (95:4.5:0.5) compound **40** (0.057 mmol, 71%) as a colourless solid; mp 132–133 °C; νmax/cm^{-1} 3320, 2932, 2791, 1741, 1632, 1543, 1485, 1372, 1166; δ_H (500 MHz, $CDCl_3$) 7.82 (2H, d, *J* 8.0 Hz), 7.62 (2H, d, *J* 8.0 Hz), 7.58 (2H, d, *J* 7.5 Hz), 7.44 (2H, t, *J* 7.5 Hz), 7.37 (1H, t, *J* 7.5 Hz), 6.79 (1H, br s), 3.47 (2H, q, *J* 6.5 Hz), 2.60–2.36 (10H, m), 2.25 (3H, s), 1.68–1.59 (4H, m); δ_C (125 MHz, $CDCl_3$) 167.6, 144.2, 140.2, 133.8, 129.0, 128.1, 127.6, 127.30, 127.29, 58.1, 55.1, 53.2, 46.0, 40.1, 27.6, 24.6; *m/z* (APCI) 181 ($[M-C_9H_{20}N_3]^+$, 100), 252 ($[M-C_5H_{11}N_2]^+$, 37); Found: C, 75.17; H, 8.36; N, 11.87. Calc for $C_{22}H_{29}N_3O$: C, 75.18, H, 8.32; N, 11.95%

*4.1.4.15. (1S,4S)-tert-Butyl-5-(4-(4-(pyridin-3-yl)benzamido)butyl)-2,5-diazabicyclo[2.2.1] heptane-2-carboxylate (**35**).* Subjecting compound **34** to general procedure 3 the crude residue was obtained and purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (95:4.5:0.5) to give the desired amide **35** (0.12 g, 89%) as a colourless oil; $[a]_D^{25}$ −20.3 (1.0, $CHCl_3$); ν_{max}/cm^{-1} 2935, 1688, 1547, 1409, 1103, 859; δ_H (500 MHz, $CDCl_3$) 8.84 (1H, d, *J* 2.0 Hz), 8.6 (1H, dd, *J* 1.5, 4.5 Hz), 7.89 (1H, t, *J* 2.0 Hz), 7.89 (2H, d, *J* 8.5 Hz), 7.86 (2H, d, *J* 8.5 Hz), 7.37 (1H, dd, *J* 4.5, 8.0 Hz), 6.93 (1H, br s), 4.31 (0.5H, s), 4.19 (0.5H, s), 3.49–3.45 (4H, m), 3.13 (1H, m), 2.91 (0.5H, d, *J* 9.0 Hz), 2.84 (0.5H, d, *J* 9.0 Hz), 2.62–2.54 (2.5H, m), 2.45 (0.5H, d, *J* 0.5H), 1.74–1.68 (4H, m), 1.56 (2H, m), 1.43 (9H, s) (mixture of rotamers); δ_C (125 MHz, $CDCl_3$) 167.2, 154.4, 154.3, 149.2, 148.4, 140.8, 135.7, 134.64, 134.55, 127.9, 127.3, 123.77, 79.6, 79.5, 61.3, 60.7, 60.19, 60.10, 57.8, 56.7, 53.8, 53.4, 49.7, 48.6, 40.1, 36.4, 35.6, 28.6, 27.5, 26.9 (mixture of rotamers); *m/z* (ESI) 923 ($[2M+Na]^+$, 100); Found: MH^+ 451.27035 $C_{26}H_{34}N_4O_3$ + Na requires 451.27092.

*4.1.4.16. (1S,4S)-tert-butyl-5-(4-([1,1′-biphenyl]-4-ylcarboxamido) butyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**36**).* Subjecting compound **34** to general procedure 3 using phenylboronic acid the crude amide was obtained and purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (95:4.5:0.5) to give the desired amide **36** (0.11 g, 80%) as a colourless oil; $[a]_D^{25}$ −17.5 (1.0, $CHCl_3$); ν_{max}/cm^{-1} 3279, 2914, 1689, 1546, 1486, 1408, 1327, 1105, 858; δ_H (500 MHz, $CDCl_3$) 7.82 (2H, d, *J* 8.5 Hz), 7.63 (2H, d, *J* 8.5 Hz), 7.59 (2H, d, *J* 7.5 Hz), 7.44 (2H, t, *J* 7.5 Hz), 7.37 (1H, t, *J* 7.5 Hz), 6.86 (1H, br s), 4.32 (0.5H, s), 4.19 (0.5H, s), 3.53–3.43 (4H, m), 3.12 (1H, t, *J* 8.5 Hz), 2.91 (0.5H, d, *J* 9.5 Hz), 2.85 (0.5H, d, *J* 9.5 Hz), 2.62–2.54 (2.5H, m), 2.45 (0.5H, d, *J* 9.5 Hz), 1.75 (1H, d, *J* 9.5 Hz), 1.70–1.62 (3H, m), 1.56 (2H, br s), 1.44 (9H, s) (mixture of rotamers); δ_C (125 MHz, $CDCl_3$) 167.5, 154.4, 154.3, 144.2, 140.2, 133.7, 129.0, 128.1, 127.5, 127.28, 127.25, 79.6, 79.4, 61.2, 60.7, 60.2, 60.1, 57.8, 56.7, 53.8, 53.3, 49.6, 48.6, 40.1, 36.4, 35.6, 28.6, 27.5, 26.9 (mixture of rotamers); *m/z* (ESI) 921 ($[2M+Na]^+$, 100); Found: MH^+ 450.27531 $C_{27}H_{35}N_3O_3$ + Na requires 450.27567.

*4.1.4.17. N-(4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl) butyl)-4-(pyridin-3-yl)benzamide (**41**).* Subjecting compound **35** to general procedure 5 the crude residue was obtained and purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (88:11:1) to give methylated amine **41** (0.08 g, 58% over two steps) as a colourless oil; $[a]_D^{25}$ −17.6 (1.0, $CHCl_3$); ν_{max}/cm^{-1} 2930, 1665, 1582, 1525, 1425, 1289, 1250, 1184, 1005, 845; δ_H (500 MHz, $CDCl_3$) 8.85 (1H, d, *J* 2.0 Hz), 8.61 (1H, dd, *J* 1.5, 5.0 Hz), 7.98 (2H, d, *J* 8.5 Hz), 7.89 (1H, dt, *J* 1.5, 8.0 Hz), 7.64 (2H, d, *J* 8.5 Hz), 7.38 (1H, dd, *J* 4.0, 8.0 Hz), 3.63 (1H, s), 3.51 (2H, m), 3.47 (1H, s), 3.22 (1H, d, *J* 11.0 Hz), 3.08 (1H, d, *J* 11.0 Hz), 2.96 (1H, dd, *J* 2.5, 11.0 Hz), 2.89 (2H, m), 2.76–2.70 (3H, m), 2.51 (3H, s), 1.71 (4H, m), NH proton not observed; δ_C (125 MHz, $CDCl_3$) 167.3, 149.2, 148.2, 140.8, 135.8, 134.6, 134.3, 128.1, 127.3, 123.8, 63.6, 62.5, 56.5, 55.8, 52.7, 41.1, 39.3, 33.6, 26.9, 25.0; *m/z* (ESI) 365 ($[M+H]^+$, 100); Found: MH^+ 365.23366 $C_{22}H_{28}N_4O$ + H requires 365.23414.

*4.1.4.18. N-(4-((1S,4S)-5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl) butyl)-[1,1′-biphenyl]-4-carboxamide (**42**).* Subjecting compound **36** to general procedure 5 the crude residue was obtained and purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (88:11:1) to give methylated amine **42** (0.075 g, 62% over two steps) as a colourless oil; $[a]_D^{25}$ −25.8 (1.0, $CHCl_3$); ν_{max}/cm^{-1} 3306, 2910, 1710, 1509, 1462, 1408, 1318, 1106, 923; δ_H (500 MHz, $CDCl_3$) 7.84 (2H, d, *J* 8.5 Hz), 7.64 (2H, d, *J* 8.5 Hz), 7.60 (2H, d, *J* 7.5 Hz), 7.45 (2H, t, *J* 7.5 Hz), 7.37 (1H, t, *J* 7.5 Hz), 7.05 (1H, br s), 3.48 (2H, m), 3.33 (1H, s), 3.20 (1H, s), 2.88 (1H, d, *J* 10.0 Hz), 2.76–2.64 (3H, m), 2.57–2.52 (2H, m), 2.37 (3H, s), 1.74–1.66 (4H, m), 1.59 (2H, m); δ_C (125 MHz, $CDCl_3$) 167.6, 144.2, 140.2, 133.8, 129.0, 128.1, 127.6, 127.31, 127.25, 63.6, 62.2, 56.7, 56.2, 53.1, 41.4, 40.0, 33.7, 27.5, 26.7; *m/z* (ESI) 364 ($[M+H]^+$, 100); Found: MH^+ 364.23840 $C_{23}H_{29}N_3O$ + H requires 364.23889.

*4.1.4.19. 2-(4-Nitrophenyl)-pyridine (**52**) [63].* To a solution of pyridine (323 μL, 4.0 mmol) in dichloromethane (20 mL) was added trifluoroacetic acid (308 μL, 4.0 mmol) followed by 4-nitrophenylboronic acid (**51**) (2.0 g, 12.0 mmol). Water (12 mL) was then added, followed by silver(I) nitrate (0.14 g, 0.8 mmol) in water (8 mL). Potassium persulfate (3.2 g, 12.0 mmol) was then added and the solution was stirred vigorously at room temperature and monitored by thin-layer chromatography analysis of the organic layer. After 3 h, a second addition of solid silver(I) nitrate (0.14 g, 0.8 mmol) and potassium persulfate (3.2 g, 12.0 mmol) was added. After stirring for 24 h, the reaction was diluted with dichloromethane (70 mL) and washed with aqueous sodium hydroxide (2 M; 50 mL). The layers were separated, and the aqueous layer was extracted with dichloromethane (2 × 50 mL), the organic extracts were combined, dried ($MgSO_4$), filtered, and evaporated *in*

vacuo. Purification by flash chromatography on silica eluting with hexane-ethyl acetate (1:1) gave compound **52** (0.22 g, 27%) as a yellow solid; mp 131–133 °C (lit mp 131–132 °C); ν_{max}/cm^{-1} 1583, 1516, 1435, 1347, 856; δ_H (500 MHz, $CDCl_3$) 8.75 (1H, d, *J* 4.5 Hz), 8.32 (2H, d, *J* 8.5 Hz), 8.18 (2H, d, *J* 8.5 Hz), 7.84–7.81 (2H, m), 7.34 (1H, m); δ_C (125 MHz, $CDCl_3$) 155.0, 150.3, 148.3, 145.4, 137.3, 127.8, 124.3, 123.7, 121.4; *m*/*z* (ESI) 154 ($[M-NO_2]^+$, 100).

*4.1.4.20. 4-(Pyridin-2-yl)aniline (**53**) [64,65].* A solution of compound **52** (0.2 g, 1.03 mmol) in methanol (10 mL) was treated with 10% palladium on carbon (20 mg) and subjected to a hydrogen atmosphere. The mixture was stirred for a further 18 h and then filtered through a pad of Celite®. The pad was washed with methanol (50 mL) and the combined filtrates evaporated *in vacuo* to give the crude residue which was purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (95:4.5:0.5) to give amine **53** (0.15 g, 87%) as a brown solid; mp 89–92 °C (lit mp 94–95 °C); ν_{max}/cm^{-1} 3333, 3210, 1606, 1586, 1519, 1294, 1181; δ_H (500 MHz, $CDCl_3$) 8.62 (1H, dt, *J* 1.0, 5.0 Hz), 7.83 (2H, d, *J* 8.5 Hz), 7.68–7.61 (2H, m), 7.11 (1H, m) 6.75 (2H, d, *J* 8.5 Hz), 3.83 (2H, br s); δ_C (125 MHz, $CDCl_3$) 157.6, 149.5, 147.5, 136.6, 129.8, 128.1, 121.0, 119.4, 115.2; *m*/*z* (ESI) 171 ($[M+H]^+$, 100).

*4.1.4.21. 5-Bromo-N-(4-(pyridin-2-yl)phenyl)pentanamide (**54**).* 5-bromovaleric acid (0.14 g, 0.75 mmol) was suspended in oxalyl chloride (*ca*. 2 mL), stirred at ambient temperature for 45 min, and the excess oxalyl chloride evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL), cooled to −78 °C, and treated dropwise with a solution of amine **53** (0.14 g, 0.82 mmol) and triethylamine (115 μL, 0.82 mmol) in CH_2Cl_2 (10 mL). The mixture was warmed to ambient temperature, stirred for 10 h, and CH_2Cl_2 (70 mL) was added. The solution was washed with H_2O (50 mL), hydrochloric acid (1 M; 50 mL), saturated aqueous sodium hydrogencarbonate (50 mL), brine (50 mL), dried ($MgSO_4$), filtered, and the solvent evaporated under reduced pressure to give the crude amide which was purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (98:1.5:0.5) to give amide **54** (0.21 g, 85%) as a colourless solid; mp 97–98 °C; ν_{max}/cm^{-1} 3230, 1718, 1543, 1418, 1375, 1214, 907, 814; δ_H (500 MHz, $CDCl_3$) 8.67 (1H, d, *J* 5.0 Hz), 7.98 (2H, d, *J* 8.5 Hz), 7.76–7.70 (2H, m), 7.64 (2H, d, *J* 8.5 Hz), 7.21 (1H, t, *J* 5.5 Hz), 3.46 (2H, t, *J* 7.0 Hz), 2.43 (2H, t, *J* 7.0 Hz), 2.01–1.87 (4H, m), NH proton not observed; δ_C (125 MHz, $CDCl_3$) 170.6, 156.9, 149.8, 138.7, 137.7, 127.6, 120.1, 120.3, 119.9, 115.3, 36.8, 33.3, 32.2, 24.1; *m*/*z* (ESI) 333, 335 ($[M+H]^+$, 100); Found: C, 57.74; H, 5.29; N, 8.43. Calc for $C_{16}H_{17}BrN_2O$: C, 57.67, H, 5.14; N, 8.41%

*4.1.4.22. 5-Morpholino-N-(4-(pyridin-2-yl)phenyl)pentanamide (**43**).* A solution of amide **54** (0.1 g, 0.3 mmol) in THF (5 mL) was treated with sodium iodide (0.046 g, 0.3 mmol), triethylamine (42 μL, 0.3 mmol) and morpholine (64 μL, 0.34 mmol), and heated at reflux for 16 h. After cooling to ambient temperature, the solvent was removed under reduced pressure and the residue partitioned between H_2O (50 mL) and ethyl acetate (70 mL). The layers were separated, and the aqueous layer extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered, and the solvent evaporated under reduced pressure to give the crude residue which was purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (90:9:1) to give amide **43** (0.073 g, 74%) as a colourless solid; mp 155–156.0 °C; ν_{max}/cm^{-1} 3302, 2915, 1658, 1598, 1466, 1118, 782; δ_H (500 MHz, $CDCl_3$) 8.65 (1H, d, *J* 5.0 Hz), 7.96 (2H, d, *J* 8.5 Hz), 7.74–7.68 (2H, m), 7.62 (2H, d, *J* 8.5 Hz), 7.58 (1H, br s), 7.19 (1H, t, *J* 6.5 Hz), 3.69 (4H, t, *J* 4.5 Hz), 2.42–2.34 (8H, m), 1.77 (2H, quin, *J* 7.5 Hz), 1.59 (2H, quin, *J* 7.5 Hz); δ_C (125 MHz, $CDCl_3$) 171.3, 156.9, 149.7, 138.9, 136.9, 135.3, 127.7, 122.0, 120.3, 119.9, 67.1, 58.7, 53.9, 37.6, 26.2, 23.5; *m*/*z* (ESI) 340 ($[M+H]^+$, 100); Found: C, 70.74; H, 7.37; N, 12.37. Calc for $C_{20}H_{25}N_3O_2$: C, 70.77, H, 7.42; N, 12.38%

*4.1.4.23. 5-Morpholino-N-(4-(pyridin-4-yl)phenyl)pentanamide (**44**).* Subjecting compound **20** to general procedure 3 using 4-pyridineboronic acid, the crude residue was obtained and purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (92:7.5:0.5) to give pentanamide **44** (0.067 g, 57%) as a colourless solid; mp 103–104 °C; ν_{max}/cm^{-1} 2949, 1689, 1596, 1525, 1292, 1116, 814; δ_H (400 MHz, $CDCl_3$) 8.64 (1H, br s), 7.67–7.59 (6H, m), 7.49 (2H, d, *J* 4.4 Hz), 3.71 (4H, t, *J* 4.4 Hz), 2.44–2.36 (8H, m), 1.79 (2H, quin, *J* 7.6 Hz), 1.60 (2H, quin, *J* 7.6 Hz); δ_C (100 MHz, $CDCl_3$) 171.4, 150.3, 147.7, 139.1, 133.8, 127.8, 121.4, 120.3, 67.1, 58.6, 53.9, 37.6, 26.1, 23.5; *m*/*z* (ESI) 340 ($[M+H]^+$, 100); Found: C, 63.74; H, 7.87; N, 11.39. Calc for $C_{20}H_{25}N_3O_2 + 2H_2O$: C, 63.98, H, 7.79; N, 11.19%

*4.1.4.24. N-(4-(2-fluoropyridin-3-yl)phenyl)-5-morpholinopentanamide (**45**).* Subjecting amide **20** to general procedure 3 using 2-fluoro-3-pyridineboronic acid, the crude residue was obtained and purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (92:7.5:0.5) to give pentanamide **45** (0.12 g, 72%) as a colourless solid; mp 129–130 °C; ν_{max}/cm^{-1} 2953, 1664, 1599, 1527, 1437, 1397, 1249, 1116; δ_H (500 MHz, $CDCl_3$) 8.17 (1H, d, *J* 5.0 Hz), 7.85 (1H, m), 7.63 (2H, d, *J* 8.5 Hz), 7.54 (2H, d, *J* 8.5 Hz), 7.41 (1H, br s), 7.26 (1H, m), 3.71 (4H, t, *J* 4.5 Hz), 2.44–2.37 (8H, m), 1.77 (2H, quin, *J* 8.0 Hz), 1.61 (2H, quin, *J* 8.0 Hz); δ_C (125 MHz, $CDCl_3$) 171.3, 160.5 (d, $^1J_{C\text{-}F}$ 238.8 Hz), 146.2 (d, $^3J_{C\text{-}F}$ 13.8 Hz), 140.5 (d, $^3J_{C\text{-}F}$ 5 Hz), 138.3, 129.63, 129.60, 123.4 (d, $^2J_{C\text{-}F}$ 28.8 Hz), 122.0, 120.0, 67.1, 58.7, 53.9, 37.6, 26.2, 23.5; *m*/*z* (ESI) 358 ($[M+H]^+$, 100); Found: C, 67.27; H, 6.82; N, 11.58. Calc for $C_{20}H_{24}FN_3O_2$: C, 67.21, H, 6.77; N, 11.76%

*4.1.4.25. N-(4-(1H-indol-5-yl)phenyl)-5-morpholinopentanamide (**46**).* Subjecting amide **20** to general procedure 3 using 5-indolylboronic acid, the crude residue was obtained and purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (90:9:1) to give pentanamide **46** (0.14 g, 81%) as a colourless solid; mp 205–206 °C; ν_{max}/cm^{-1} 3290, 1663, 1597, 1470, 1318, 1114, 807, 734; δ_H (500 MHz, DMSO-d_6) 11.09 (1H, br s), 9.88 (1H, s), 7.76 (1H, s), 7.65 (2H, d, *J* 9.0 Hz), 7.58 (2H, d, *J* 9.0 Hz), 7.44 (1H, d, *J* 8.5 Hz), 7.37–7.35 (2H, m), 6.46 (1H, t, *J* 2.0 Hz), 3.56 (4H, t, *J* 4.5 Hz), 2.32–2.27 (8H, m), 1.62 (2H, quin, *J* 7.5 Hz), 1.47 (2H, quin, *J* 7.5 Hz); δ_C (125 MHz, DMSO-d_6) 171.1, 137.7, 136.5, 135.2, 131.0, 128.2, 126.7, 125.9, 120.1, 119.4, 117.6, 111.7, 101.4, 66.2, 58.0, 53.4, 36.2, 25.5, 23.0; *m*/*z* (ESI) 378 ($[M+H]^+$, 100); Found: C, 73.22; H, 7.21; N, 11.13. Calc for $C_{23}H_{27}N_3O_2$: C, 73.18, H, 7.21; N, 11.13%

*4.1.4.26. 6-Chloropyridazin-3-amine (**56**) [66].* To a thick-wall borosilicate glass vial was added 3,6-dichloropyridazine (**55**) (1.5 g, 10.1 mmol) and ammonium hydroxide solution (5 mL; NH_3 content: 28–30%). The vial was sealed and placed in the microwave reactor for 30 min at 120 °C (power: 300 W). After cooling, the precipitate that deposited was filtered off, washed with ethyl acetate-hexane (3:7) and dried to give amine **56** (0.86 g, 66%) as a yellow solid; mp decomposition >206 °C (lit mp 229–232 °C); ν_{max}/cm^{-1} 3147, 1643, 1596, 1455, 1055, 838; δ_H (200 MHz, DMSO) 7.36 (1H, d, *J* 10.0 Hz), 6.84 (1H, d, *J* 10.0 Hz), 6.61 (2H, br s); δ_C (75 MHz, DMSO) 160.2, 145.0, 128.9, 117.5; *m*/*z* (ESI) 130 ($[M+H]^+$, 100).

*4.1.4.27. 5-Bromo-N-(6-chloropyridazin-3-yl)pentanamide (**57**).* 5-bromovaleric acid (**18**) (0.46 g, 2.6 mmol) was suspended in

oxalyl chloride (*ca.* 2 mL), stirred at ambient temperature for 45 min, and the excess oxalyl chloride evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL), cooled to −78 °C, and treated dropwise with a solution of amine **56** (0.3 g, 2.3 mmol) and triethylamine (355 μL, 2.6 mmol) in CH_2Cl_2 (20 mL). The mixture was warmed to ambient temperature, stirred for 10 h, and CH_2Cl_2 (100 mL) was added. The solution was washed with H_2O (70 mL), saturated aqueous ammonium chloride (70 mL), saturated aqueous sodium hydrogencarbonate (70 mL), brine (70 mL), dried ($MgSO_4$), filtered, and the solvent evaporated under reduced pressure to give the crude amide. The orange residue was suspended in methanol and the resulting solid filtered off and dried to give amide **57** (0.13 g, 20%) as a colourless solid; mp decomposition >169 °C; ν_{max}/cm^{-1} 3191, 1690, 1582, 1515, 1409, 1141, 1088, 735; δ_H (300 MHz, $CDCl_3$) 10.5 (1H, br s), 8.66 (1H, d, *J* 9.0 Hz), 7.58 (1H, d, *J* 9.0 Hz), 3.48 (2H, t, *J* 6.0 Hz), 2.71 (2H, t, *J* 6.0 Hz), 2.01–1.92 (4H, m); δ_C (75 MHz, $CDCl_3$) 173.1, 155.0, 152.0, 130.9, 122.2, 36.7, 33.1, 32.1, 23.9; *m*/*z* (ESI) 292 ($[M+H]^+$, 100); Found: C, 36.97; H, 3.68; N, 14.06. Calc for $C_9H_{11}BrClN_3O$: C, 36.95, H, 3.79; N, 14.36%

*4.1.4.28. N-(6-chloropyridazin-3-yl)-5-morpholinopentanamide (**58**).* A solution of amide **57** (0.1 g, 0.34 mmol) in DMF (8 mL) was treated with sodium iodide (0.051 g, 0.34 mmol), triethylamine (50 μL, 0.34 mmol) and morpholine (33 μL, 0.38 mmol), and heated at reflux for 19 h. After cooling to ambient temperature, the solution was partitioned between H_2O (50 mL) and ethyl acetate (50 mL), the layers separated, and the aqueous layer extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with H_2O (100 mL), brine (50 mL), dried ($MgSO_4$), filtered, and the solvent evaporated under pressure to give the crude residue which was purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (90:9:1) to give amide **58** (0.061 g, 62%) as a colourless solid; mp decomposition >152 °C; ν_{max}/cm^{-1} 2937, 1686, 1588, 1518, 1406, 1136, 1116, 866; δ_H (300 MHz, $CDCl_3$) 10.47 (1H, br s), 8.61 (1H, d, *J* 9.0 Hz), 7.52 (1H, d, *J* 9.0 Hz), 3.71 (4H, t, *J* 6.0 Hz), 2.70 (2H, t, *J* 6.0 Hz), 2.47–2.41 (6H, m), 1.78 (2H, m), 1.65 (2H, m); δ_C (75 MHz, $CDCl_3$) 173.5, 155.3, 151.7, 130.3, 121.8, 66.9, 58.5, 53.8, 37.4, 25.8, 23.3; *m*/*z* (ESI) 299 ($[M+H]^+$, 100); Found: C, 52.55; H, 6.46; N, 18.69. Calc for $C_{13}H_{19}ClN_4O_2$: C, 52.26, H, 6.41; N, 18.75%

*4.1.4.29. 5-Morpholino-N-(6-phenylpyridazin-3-yl)pentanamide (**47**).* Subjecting amide **58** to general procedure 3 using phenylboronic acid gave, after purification by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (90:9:1) compound **47** (0.027 g, 63%) as a colourless solid; mp decomposition >220 °C; ν_{max}/cm^{-1} 2942, 1679, 1590, 1519, 1406, 1218, 1147, 1120, 866; δ_H (500 MHz, $CDCl_3$) 10.46 (1H, br s), 8.65 (1H, d, *J* 9.0 Hz), 8.02 (2H, d, *J* 7.0 Hz), 7.91 (1H, d, *J* 9.0 Hz), 7.54–7.48 (3H, m), 3.67 (4H, t, *J* 4.5 Hz), 2.79 (2H, t, *J* 7.5 Hz), 2.37–2.34 (6H, m), 1.82 (2H, quin, *J* 7.5 Hz), 1.61 (2H, quin, *J* 7.5 Hz); δ_C (125 MHz, $CDCl_3$) 173.4, 156.4, 154.9, 136.2, 129.9, 129.2, 126.8, 126.3, 119.7, 67.1, 58.7, 53.9, 37.6, 26.1, 23.5; *m*/*z* (ESI) 363 ($[M+Na]^+$, 100); Found: C, 67.10; H, 7.24; N, 16.53. Calc for $C_{19}H_{24}N_4O_2$: C, 67.04, H, 7.11; N, 16.46%

*4.1.4.30. 3-Oxo-3-phenylpropanenitrile (**60**) [67].* A cooled (0 °C) solution of methyl benzoate (**59**) (7.0 g, 51.4 mmol) in toluene (60 mL) was treated portionwise with sodium hydride (60% dispersion in mineral oil, 4.08 g, 102.8 mmol). The mixture was allowed to warm to room temperature and treated dropwise with a solution of acetonitrile (13.5 mL, 257.0 mmol) in toluene (15 mL). The mixture was heated at reflux for 18 h during which time a thick precipitate formed. The mixture was cooled (0 °C), quenched by addition of hydrochloric acid (3 M; 30 mL) and then partitioned between ethyl acetate (150 mL) and H_2O (100 mL). The aqueous layer was further extracted with ethyl acetate (2 × 70 mL) and the combined organic extracts washed with brine (150 mL), dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The crude residue was then purified by flash chromatography on silica eluting with hexane-ethyl acetate (1:1) to give nitrile **60** (4.7 g, 63%) as a colourless solid; mp 79–81 °C (lit mp 81–82 °C); ν_{max}/cm^{-1} 2950, 2837, 1690, 1427, 1365, 1210, 847; δ_H (500 MHz, $CDCl_3$) 7.92 (2H, d, *J* 8.0 Hz), 7.66 (1H, t, *J* 7.5H), 7.52 (2H, t, *J* 8.0 Hz), 4.10 (2H, s); δ_C (125 MHz, $CDCl_3$) 187.3, 134.9, 134.4, 129.3, 128.6, 114.0, 29.5.

*4.1.4.31. 3-Phenyl-1H-pyrazol-5-amine (**61**) [68].* A solution of compound **60** (3.5 g, 24.1 mmol) in absolute ethanol (50 mL) was treated with hydrazine monohydrate (2.5 mL, 48.3 mmol) and glacial acetic acid (2.4 mL, 38.6 mmol) and heated at reflux for 18 h. The mixture was allowed to cool to ambient temperature and the solvent removed under reduced pressure. The residue was suspended between CH_2Cl_2 (100 mL) and hydrochloric acid (1M; 100 mL), the aqueous layer was further extracted with CH_2Cl_2 (50 mL) and then basified to pH 12 with addition of aqueous sodium hydroxide (3 M; *ca* 40 mL). The aqueous layer was then extracted with CH_2Cl_2 (3 × 100 mL) and the basified organic extracts combined, dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude residue which was purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (90:9.5:0.5) to give amine **61** (3.06 g, 80%) as an off-white solid; mp 144–145 °C (lit mp 145–146 °C); ν_{max}/cm^{-1} 3205, 1571, 1510, 758, 693; δ_H (500 MHz, $CDCl_3$) 7.55 (2H, d, *J* 7.0 Hz), 7.36 (2H, t, *J* 7.0 Hz), 7.30 (1H, t, *J* 7.0 Hz), 5.90 (1H, s), 3NH protons not observed; δ_C (125 MHz, $CDCl_3$) 154.5, 145.9, 130.5, 129.0, 128.4, 125.6, 90.5; *m*/*z* (ESI) 160 ($[M+H]^+$, 100).

*4.1.4.32. 5-Bromo-N-(5-phenyl-1H-pyrazol-3-yl)pentanamide (**62**).* 5-bromovaleric acid (1.24 g, 6.8 mmol) was suspended in oxalyl chloride (*ca.* 5 mL), stirred at ambient temperature for 45 min, and the excess oxalyl chloride evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL), cooled to −78 °C, and treated dropwise with a solution of compound **61** (1.2 g, 7.5 mmol) and triethylamine (1.05 mL, 7.5 mmol) in CH_2Cl_2 (20 mL). The mixture was warmed to ambient temperature, stirred for 10 h, and CH_2Cl_2 (150 mL) was added. The solution was washed with H_2O (100 mL), hydrochloric acid (1 M; 100 mL), saturated aqueous sodium hydrogencarbonate (100 mL), brine (100 mL), dried ($MgSO_4$), filtered, and the solvent evaporated under reduced pressure to give the crude amide which was purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (95:4.5:0.5) to give amide **62** (1.6 g, 74%) as an off white solid. Due to the unstable nature of amide **62** it was used directly in the next step without further characterisation.

*4.1.4.33. 5-Morpholino-N-(5-phenyl-1H-pyrazol-3-yl)pentanamide (**48**).* Subjecting compound **62** to general procedure 2 using THF as the solvent, the crude amide was obtained and purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (92:8.5:1.5) to give compound **48** (0.12 g, 59%) as a colourless solid; mp 158–160 °C; ν_{max}/cm^{-1} 3218, 2949, 1664, 1578, 1547, 1492, 1115, 1008; δ_H (500 MHz, $CDCl_3$) 8.66 (1H, s), 7.62 (2H, d, *J* 7.5 Hz), 7.41 (2H, t, *J* 7.5 Hz), 7.35 (1H, t, *J* 7.5 Hz), 6.83 (1H, br s), 3.70 (4H, t, *J* 4.5 Hz), 2.41–2.38 (6H, m), 2.35 (2H, t, *J* 7.5 Hz), 1.75 (2H, quin, *J* 7.5 Hz), 1.56 (2H, quin, *J* 7.5 Hz), one NH peak not observed; δ_C (100 MHz, $CDCl_3$) 171.0, 129.2, 128.8, 125.6, 93.6, 67.0, 58.6, 53.9, 36.8, 26.0, 23.4, pyrazole peaks not observed; *m*/*z* (ESI) 329 ($[M+H]^+$, 100); Found: C, 65.89; H, 7.32; N, 16.92. Calc for $C_{18}H_{24}N_4O_2$: C, 65.83; H, 7.37; N, 17.06%

*4.1.4.34. N-(5-Phenyl-1H-pyrazol-3-yl)-5-(piperidin-1-yl)pentanamide (**49**).* Subjecting compound **62** to general procedure 2 using THF as the solvent and piperidine as the amine source, the crude amide was obtained and purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (92:8.5:1.5) to give compound **49** (0.11 g, 56%) as a colourless solid; mp 163–164 °C; ν_{max}/cm^{-1} 3239, 2932, 1658, 1577, 1550, 1492, 959; δ_H (500 MHz, $CDCl_3$) 9.20 (1H, br s), 7.65 (2H, d, *J* 7.5 Hz), 7.41 (2H, t, *J* 7.5 Hz), 7.33 (1H, t, *J* 7.5 Hz), 6.83 (1H, br s), 2.40–2.36 (8H, m), 1.71 (2H, quin, *J* 7.5 Hz), 1.60–1.54 (6H, m), 1.42 (2H, m), one NH peak not observed; δ_C (125 MHz, $CDCl_3$) 171.5, 146.4, 130.5, 129.1, 128.5, 125.7, 93.5, 58.7, 54.7, 36.8, 26.3, 25.8, 24.4, 23.7, one pyrazole peak not observed; *m/z* (ESI) 327 ($[M+H]^+$, 100); Found: C, 66.20; H, 8.47; N, 16.24. Calc for $C_{19}H_{26}N_4O + H_2O$: C, 66.25; H, 8.19; N, 16.27%

*4.1.4.35. 5-(4-Methylpiperazin-1-yl)-N-(5-phenyl-1H-pyrazol-3-yl) pentanamide (**50**).* Subjecting compound **62** to general procedure 2 using THF as the solvent and 1-methylpiperazine as the amine source, the crude amide was obtained and purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (92:8.5:1.5) to give compound **50** (0.14 g, 62%) as a colourless solid; mp 162–164 °C; ν_{max}/cm^{-1} 3222, 3198, 2942, 2813, 1661, 1579, 1543, 1457, 1109; δ_H (500 MHz, $CDCl_3$) 8.9 (1H, br s), 7.63 (2H, d, *J* 7.5 Hz), 7.40 (2H, t, *J* 7.5 Hz), 7.33 (1H, t, *J* 7.5 Hz), 6.84 (1H, br s), 2.45–2.34 (12H, m), 2.56 (3H, s), 1.72 (2H, quin, *J* 7.5 Hz), 1.56 (2H, quin, *J* 7.5 Hz), one NH peak not observed; δ_C (125 MHz, $CDCl_3$) 171.2, 145.3, 130.4, 129.1, 128.7, 125.7, 93.7, 58.0, 55.0, 53.2, 46.1, 36.7, 26.2, 23.5, one pyrazole peak not observed; *m/z* (ESI) 705 ($[2M+Na]^+$, 100), 342 ($[M+H]^+$, 100); Found: C, 63.72; H, 8.52; N, 19.54. Calc for $C_{19}H_{26}N_4O + H_2O$: C, 63.48; H, 8.13; N, 19.48%

*4.1.4.36. 4-(6-chloropyridazin-3-yl)morpholine (**283**) [69].* To a solution of 3,6-dichloropyridazine (**67**) (1.0 g, 6.7 mmol) in DMF (67 mL) was added *N*,*N*-diisopropylethylamine (1.29 mL, 7.38 mmol) and morpholine (0.58 mL, 6.7 mmol). The mixture was heated at reflux for 17 h and after cooling to room temperature, partitioned between ethyl acetate (200 mL) and H_2O (100 mL). The aqueous layer was further extracted with ethyl acetate (2 × 80 mL) and the combined organic layers then further washed with H_2O (200 mL), brine (200 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give the crude product. Purification by flash chromatograph on silica eluting with ethyl acetate yielded the desired pyridazine **67** (1.1 g, 83%) as a yellow solid; mp 132–135 °C (lit mp 132.5–134.5 °C); ν_{max}/cm^{-1} 2985, 2924, 1582, 1527, 1454, 1266, 1164, 1123, 927, 821, 765; δ_H (300 MHz, $CDCl_3$) 7.22 (1H, d, *J* 9.0 Hz), 6.89 (1H, d, *J* 9.0 Hz), 3.82 (4H, t, *J* 6.0 Hz), 3.58 (4H, t, *J* 6.0 Hz); δ_C (75 MHz, $CDCl_3$) 159.3, 147.4, 128.9, 115.3, 66.4, 45.4; *m/z* (APCI) 200 ($[M+H]^+$, 100).

*4.1.4.37. 3-Chloro-6-(piperidin-1-yl)pyridazine (**68**) [69].* To a solution of 3,6-dichloropyridazine (**55**) (0.3 g, 2.0 mmol) in DMF (20 mL) was added *N*,*N*-diisopropylethylamine (377 μL, 2.2 mmol) and piperidine (200 μL, 2.0 mmol). The mixture was heated at reflux for 17 h and after cooling to room temperature, partitioned between ethyl acetate (100 mL) and H_2O (100 mL). The aqueous layer was further extracted with ethyl acetate (2 × 80 mL) and the combined organic layers then further washed with H_2O (200 mL), brine (200 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give the crude product. Purification by flash chromatograph on silica eluting with hexane-ethyl acetate (7:2) yielded the desired pyridazine **68** (0.29 g, 72%) as an off white solid; mp 75–77 °C (lit mp 74–76 °C); ν_{max}/cm^{-1} 3050, 2928, 2854, 1587, 1529, 1479, 1438, 1263, 1249, 1213, 1171, 1004, 923, 830; δ_H (500 MHz, $CDCl_3$) 7.14 (1H, d, *J* 9.5 Hz), 6.88 (1H, d, *J* 9.5 Hz), 3.60 (4H, t, *J* 5.5 Hz), 1.69–1.65 (6H, m); δ_C (125 MHz, $CDCl_3$) 159.1, 146.0, 128.5, 115.2, 46.3, 25.3, 24.4; *m/z* (APCI) 198 ($[M+H]^+$, 100).

*4.1.4.38. 3-Chloro-6-(4-methylpiperazin-1-yl)pyridazine (**69**) [69].* To a solution of 3,6-dichloropyridazine (**55**) (1.0 g, 6.7 mmol) in DMF (67 mL) was added *N*,*N*-diisopropylethylamine (1.29 mL, 7.38 mmol) and 1-methylpiperazine (744 μL, 6.7 mmol). The mixture was heated at reflux for 17 h and after cooling to room temperature, partitioned between ethyl acetate (200 mL) and H_2O (70 mL). The aqueous layer was further extracted with ethyl acetate (2 × 50 mL) and the combined organic layers then further washed with H_2O (100 mL), brine (100 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give the crude product. Purification by flash chromatograph on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (95:4.5:0.5) yielded the desired pyridazine **69** (0.88 g, 62%) as a pale yellow solid; mp 108–109 °C (lit mp 106–107 °C); ν_{max}/cm^{-1} 3780, 2953, 2927, 1443, 1258, 1168, 1143, 613; δ_H (500 MHz, $CDCl_3$) 7.12 (1H, d, *J* 9.5 Hz), 6.89 (1H, d, *J* 9.5 Hz), 3.64 (4H, t, *J* 5.0 Hz), 2.51 (4H, t, *J* 5.0 Hz), 2.34 (3H, s); δ_C (125 MHz, $CDCl_3$) 159.2, 147.0, 128.8, 115.3, 54.7, 46.3, 45.2; *m/z* (APCI) 213 ([M+H], 100).

*4.1.4.39. (1S, 4S)-tert-Butyl 5-(6-chloropyridazin-3-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**70**) [46].* To a solution of 3,6-dichloropyridazine (0.11 g, 0.76 mmol) in DMF (7.5 mL) was added *N*,*N*-diisopropylethylamine (145 μL, 0.83 mmol) and amine **25** (0.15 g, 0.76 mmol). The mixture was heated at reflux for 14 h and after cooling to room temperature, partitioned between ethyl acetate (200 mL) and H_2O (70 mL). The aqueous layer was further extracted with ethyl acetate (2 × 50 mL) and the combined organic layers then further washed with H_2O (100 mL), brine (100 mL) then dried ($MgSO_4$), filtered and the solvent removed under reduced pressure to give the crude product. Purification by flash chromatograph on silica eluting with hexane-ethyl acetate (1:1) yielded compound **70** (0.09 g, 37%) as a colourless solid; $[a]_D^{25}$ −50.9 (1.0, $CHCl_3$); mp dec >195 °C; νmax/cm^{-1} 3029, 2914, 1507, 1423, 1289, 1258, 1172, 1103, 842; δ_H (400 MHz, $CDCl_3$) 7.20 (1H, d, *J* 9.2 Hz), 6.59 (1H, d, *J* 9.2 Hz), 5.08 (0.6H, s), 4.93 (0.4H, s), 4.70 (0.6H, s), 4.57 (0.4H, s), 3.54 (1H, m), 3.45–3.37 (3H, m), 1.97 (2H, m), 1.44 (9H, m) (mixture of rotamers); δ_C (75 MHz, $CDCl_3$) 157.1, 154.3, 146.4, 129.1, 115.1, 80.1, 57.2, 56.8, 56.4, 55.9, 55.6, 52.9, 52.5, 37.7, 37.1, 28.5 (mixture of rotamers); *m/z* (APCI) 254 ($[M-C_4H_9]^+$, 100), 311 ($[M+H]^+$, 20).

*4.1.4.40. 4-(6-Phenylpyridazin-3-yl)morpholine (**63**) [69].* Subjecting **67** to general procedure 3 using phenyl boronic acid, the crude residue was obtained and purified by flash chromatography on silica eluting with ethyl acetate-hexane (2:1) to give pyridazine **63** (0.14 g, 61%) as a colourless solid; mp 153–154 °C (lit mp 153–155 °C); νmax/cm^{-1} 2854, 1594, 1451, 1432, 1378, 1263, 1238, 1120, 930, 831, 784, 746, 697; δ_H (500 MHz, $CDCl_3$) 8.0 (2H, d, *J* 7.5 Hz), 7.67 (1H, d, *J* 9.5 Hz), 7.47 (2H, t, *J* 7.5 Hz), 7.4 (1H, m), 6.97 (1H, d, *J* 9.5 Hz), 3.87 (4H, t, *J* 5.0 Hz), 3.67 (4H, t, *J* 5.0 Hz); δ_C (125 MHz, $CDCl_3$) 159.1, 151.7, 136.6, 128.84, 128.75, 126.0, 125.5, 112.8, 66.6, 45.4; *m/z* (APCI) 242 ($[M+H]^+$, 100).

*4.1.4.41. 3-Phenyl-6-(piperidin-1-yl)pyridazine (**64**).* Subjecting compound **68** to general procedure 3 using phenyl boronic acid, the crude residue was obtained and purified by flash chromatography on silica eluting with ethyl acetate-hexane (1:1) to give pyridazine **64** (0.16 g, 68%) as a colourless solid; mp 120–121 °C; νmax/cm^{-1} 2934, 2851, 1592, 1541, 1430, 1248, 1128, 923, 745, 694; δ_H (500 MHz, $CDCl_3$) 8.0 (2H, d, *J* 7.5 Hz), 7.62 (1H, d, *J* 9.5 Hz), 7.46 (2H, t, *J* 7.5 Hz), 7.39 (1H, t, *J* 7.5 Hz), 6.98 (1H, d, *J* 9.5 Hz), 3.71 (4H, m), 1.71 (6H, br s, signals overlapping); δ_c (125 MHz, $CDCl_3$) 159.1, 150.5, 137.1, 128.9, 128.6, 125.9, 125.2, 113.0, 46.4, 25.6, 24.8; *m/z* (APCI)

240 ([M+H]$^+$, 100); Found: C, 75.07; H, 7.13; N, 17.90. Calc for $C_{15}H_{17}N_3$: C, 75.28, H, 7.16; N, 17.56%

*4.1.4.42. 3-(4-Methylpiperazin-1-yl)-6-phenylpyridazine (**65**) [70].* Subjecting compound **69** to general procedure 3 using phenyl boronic acid, the crude residue was obtained and purified by flash chromatography on silica eluting with ethyl acetate-hexane (1:1) to give pyridazine **65** (0.14 g, 59%) as a colourless solid; mp 120–122 °C (lit mp 121–122 °C); νmax/cm^{-1} 2927, 1592, 1443, 1236, 1117, 985; δ_H (300 MHz, $CDCl_3$) 8.0 (2H, d, *J* 6.9 Hz), 7.65 (1H, d, *J* 9.6 Hz), 7.49–7.39 (3H, m), 6.98 (1H, d, *J* 9.6 Hz), 3.74 (4H, t, *J* 5.1 Hz), 2.56 (4H, t, *J* 5.1 Hz), 2.36 (3H, s); δ_c (75 MHz, $CDCl_3$) 159.1, 151.3, 136.9, 128.9, 128.8, 126.0, 125.3, 113.0, 54.8, 46.4, 45.2; *m*/*z* (APCI) 255 ([M+H]$^+$, 100).

*4.1.4.43. (1S, 4S)-tert-butyl 5-(6-phenylpyridazin-3-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**71**) [46].* Subjecting compound **70** to general procedure 3 using phenyl boronic acid, the crude residue was obtained and purified by flash chromatography on silica eluting with ethyl acetate-hexane (1:1) to give pyridazine **71** (0.18 g, 78%) as a colourless solid; mp 208–210 °C; $[a]_D^{25}$ −67.4 (1.0, $CHCl_3$); ν_{max}/cm^{-1} 1650, 1489, 1476, 1452, 1209, 1186, 809, 627; δ_H (500 MHz, $CDCl_3$) 7.98 (2H, d, *J* 7.0 Hz), 7.63 (1H, t, *J* 7.5 Hz), 7.45 (2H, t, *J* 7.5 Hz), 7.38 (1H, t, *J* 7.5 Hz), 6.67 (1H, d, *J* 9.0 Hz), 5.16 (0.6H, s), 5.01 (0.4H, s), 4.71 (0.6H, s), 4.57 (0.4H, s), 3.61 (1H, m), 3.53–3.42 (3H, m), 1.99 (2H, m), 1.43 (9H, m) (mixture of rotamers); δ_c (125 MHz, $CDCl_3$) 156.9, 156.7, 154.3, 150.7, 136.9, 128.9, 128.6, 125.8, 125.4, 112.8, 112.7, 80.0, 79.9, 57.3, 57.1, 56.6, 56.4, 55.7, 55.4, 53.0, 52.6, 37.6, 37.1, 28.6, 28.5 (mixture of rotamers); *m*/*z* (ESI) 353 ([M+H]$^+$, 100).

*4.1.4.44. (1S, 4S)-2-Methyl-5-(6-phenylpyridazin-3-yl)-2,5-diazabicyclo[2.2.1]heptane (**9**) [46].* Subjecting compound **71** to general procedure 5 the crude residue was obtained and purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (92:7.5:0.5) to give methylated amine **9** (0.03 g, 66% over two steps) as a colourless solid; mp 137–138 °C; $[a]_D^{25}$ −49.7 (1.0, $CHCl_3$); ν_{max}/cm^{-1} 2853, 1709, 1594, 1545, 1460, 1435, 1360, 1219, 1028, 834, 746, 695; δ_H (500 MHz, $CDCl_3$) 7.97 (2H, d, *J* 7.0 Hz), 7.6 (1H, d, *J* 9.0 Hz), 7.44 (2H, t, *J* 7.0 Hz), 7.36 (1H, t, *J* 7.0 Hz), 6.66 (1H, d, *J* 9.0 Hz), 3.62 (1H, d, *J* 9.5 Hz), 3.61 (1H, s), 3.44 (1H, dd, *J* 2.0, 9.5 Hz), 2.97 (1H, dd, *J* 2.0, 10.0 Hz), 2.73 (1H, d, *J* 10.0 Hz), 2.41 (3H, s), 2.24 (1H, s), 2.03 (1H, d, *J* 9.5 Hz), 1.87 (1H, d, *J* 10.0 Hz); δ_C (125 MHz, $CDCl_3$) 156.8, 150.3, 137.1, 128.9, 128.5, 125.8, 125.2, 112.7, 62.9, 60.4, 57.8, 51.1, 41.1, 35.9; *m*/*z* (ESI) 267 ([M+H]$^+$, 100).

*4.1.4.45. 4-(6-(1H-indol-6-yl)pyridazin-3-yl)morpholine (**66**).* Subjecting **67** to general procedure 3 using 5-indolylboronic acid, the crude residue was obtained and purified by flash chromatography on silica eluting with ethyl acetate-hexane (1:1) to give pyridazine **66** (0.11 g, 74%) as a colourless solid; mp decomposition >160 °C; νmax/cm^{-1} 3305, 1541, 1340, 1262, 1241, 1175, 1107, 1071, 936, 810, 727, 540; δ_H (500 MHz, DMSO-d_6) 11.2 (1H, s), 8.18 (1H, s), 7.97 (1H, d, *J* 9.5 Hz), 7.84 (1H, dd, *J* 2.0, 8.5 Hz), 7.48 (1H, d, *J* 8.5 Hz), 7.38 (1H, t, *J* 3.0 Hz), 7.33 (1H, d, *J* 9.5 Hz), 6.51 (1H, t, *J* 4.0 Hz); 3.76 (4H, t, *J* 4.5 Hz), 3.58 (4H, t, *J* 4.5 Hz); δ_C (125 MHz, DMSO-d_6) 158.8, 152.3, 136.2, 131.5, 128.7, 126.2, 125.1, 119.3, 117.7, 113.7, 111.7, 101.8; 65.9, 45.1; *m*/*z* (ESI) 281 ([M+H]$^+$, 100); Found: C, 68.56; H, 5.71; N, 19.77. Calc for $C_{16}H_{16}N_4O$: C, 68.55, H, 5.75; N, 19.99%

*4.1.4.46. 4-(4-Bromophenyl)morpholine (**81**).* A solution of tris(dibenzylideneacetone)dipalladium(0) (0.093 g, 0.1 mmol) and (±)-BINAP (0.13 g, 0.21 mmol) in toluene (7 mL) was degassed with argon for 10 min and then heated at 110 °C for 15 min. The reaction mixture was allowed to cool to room temperature before potassium *tert*-butoxide (0.53 g, 4.73 mmol), 1,4-dibromobenzene (**80**) (0.6 g, 2.54 mmol) and morpholine (332 μL, 3.82 mmol) were added. The resulting mixture was heated at reflux for 16 h, cooled to room temperature and filtered through a pad of Celite®, the pad was further washed with toluene (30 mL) and the combined filtrates evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica eluting with hexane-ethyl acetate (6:1) gave the desired amine **81** (0.19 g, 47%) as a colourless solid; mp 110–111 °C; νmax/cm^{-1} 2965, 2857, 2831, 1589, 1495, 1259, 1236, 1120, 923, 818; δ_H (300 MHz, $CDCl_3$) 7.35 (2H, d, *J* 9.0 Hz), 6.78 (2H, d, *J* 9.0 Hz), 3.84 (4H, t, *J* 6.0 Hz), 3.11 (4H, t, *J* 6.0 Hz); δ_C (75 MHz, $CDCl_3$) 150.3, 132.0, 117.4, 112.3, 66.8, 49.3; *m*/*z* (APCI) 242/244 ([M+H]$^+$, 68/100).

*4.1.4.47. 1-(4-Bromophenyl)piperidine (**82**) [71,72].* A suspension of 4-bromophenylboronic acid (0.3 g, 1.5 mmol), copper(II) acetate monohydrate (0.03 g, 0.15 mmol) and powdered 4 Å molecular sieves (0.56 g) in CH_2Cl_2 (10 mL) was stirred at room temperature for 5 min. Piperidine (74 μL, 0.74 mmol) was then added and the resulting mixture sealed and stirred under an atmosphere of air at room temperature for 20 h. The reaction mixture was filtered through a pad of Celite® and the solvent removed under reduced pressure to give the crude residue. Purification by flash chromatography on silica eluting with hexane-ethyl acetate (7:2) yielded amine **82** (0.1 g, 58%) as a colourless solid; mp 73–74 °C (lit mp 72–73 °C); νmax/cm^{-1} 2937, 2816, 1588, 1496, 1246, 1221, 1127, 807, 537; δ_H (500 MHz, $CDCl_3$) 7.31 (2H, d, *J* 9.0 Hz), 6.79 (2H, d, *J* 9.0 Hz), 3.12 (4H, t, *J* 5.5 Hz), 1.69 (4H, quin, *J* 5.5 Hz), 1.58 (2H, m); δ_C (125 MHz, $CDCl_3$) 151.3, 131.9, 118.1, 111.2, 50.6, 25.8, 24.3; *m*/*z* (APCI) 240, 242 ([M+H]$^+$, 100).

*4.1.4.48. 1-(4-Bromophenyl)-4-methylpiperazine (**83**) [73].* A solution of tris(dibenzylideneacetone)dipalladium(0) (0.04 g, 0.084 mmol) and (±)-BINAP (0.10 g, 0.16 mmol) in toluene (10 mL) was degassed with argon for 10 min and then heated at 110 °C for 15 min. The reaction mixture was allowed to cool to room temperature before potassium *tert*-butoxide (0.44 g, 3.94 mmol), 1.4-dibromobenzene (**80**) (0.5 g, 2.12 mmol) and 1-methylpiperazine (260 μL, 2.34 mmol) were added. The resulting mixture was heated at reflux for 16 h, cooled to room temperature and filtered through a pad of Celite®, the pad was further washed with toluene (30 mL) and the combined filtrates evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica eluting with hexane-ethyl acetate (3:1) gave the desired amine **83** (0.16 g, 50%) as a colourless solid; mp 81–83 °C; νmax/cm^{-1} 2940, 2814, 1568, 1456, 1245, 1220, 1107, 930; δ_H (500 MHz, $CDCl_3$) 7.33 (2H, d, *J* 9.0 Hz), 6.79 (2H, d, *J* 9.0 Hz), 3.19 (4H, t, *J* 5.0 Hz), 2.57 (4H, t, *J* 5.0 Hz), 2.35 (3H, s); δ_C (125 MHz, $CDCl_3$) 150.4, 132.0, 117.8, 111.9, 55.1, 49.1, 46.3; *m*/*z* (ESI) 255/257 ([M+H]$^+$, 70/100).

*4.1.4.49. (1S, 4S)-tert-Butyl 5-(4-bromophenyl)-2,5-diazabicyclo [2.2.1]heptane-2-carboxylate (**84**).* A solution of tris(dibenzylideneacetone)dipalladium(0) (0.034 g, 0.037 mmol) and (±)-BINAP (0.046 g, 0.074 mmol) in toluene (10 mL) was degassed with argon for 10 min and then heated at 110 °C for 15 min. The reaction mixture was allowed to cool to room temperature before potassium *tert*-butoxide (0.19 g, 1.71 mmol), 1,4-dibromobenzene (**80**) (0.22 g, 0.92 mmol) and **157** (0.2 g, 1.01 mmol) were added. The resulting mixture was heated at reflux for 16 h, cooled to room temperature and filtered through a pad of Celite®, the pad was further washed with toluene (30 mL) and the combined filtrates evaporated under reduced pressure to give the crude product. Purification by flash chromatography on silica eluting with hexane-ethyl acetate (3:1)

gave the desired amine **84** (0.27 g, 82%) as a colourless solid; mp 210–211 °C; $[a]_D^{25}$ −22.0 (0.5, $CHCl_3$); νmax/cm^{-1} 3543, 2965, 1693, 1592, 1496, 1406, 1365, 1167, 1105; δ_H (400 MHz, $CDCl_3$) 7.29 (2H, d, *J* 8.4 Hz), 6.42 (2H, d, *J* 8.4 Hz), 4.62 (0.6H, s), 4.48 (0.4H, s), 4.33 (1H, s), 3.54 (1H, d, *J* 8.8 Hz), 3.45 (0.5H, d, *J* 9.6 Hz), 3.39–3.36 (1.5H, m), 3.16 (0.6H, d, *J* 8.8 Hz), 3.07 (0.4H, d, *J* 8.4 Hz), 1.99–1.87 (2H, m), 1.43 (9H, m) (mixture of rotamers); δ_C (100 MHz, $CDCl_3$) 154.2, 145.9, 132.1, 114.1, 108.6, 108.4, 57.4, 57.3, 57.0, 56.96, 56.47, 51.4, 51.1, 37.9, 37.4, 28.7, 28.6 (mixture of rotamers); *m*/*z* (ESI) 353/355 ([M+H], 61/100); Found MH^+ 353.08620, 355.08412 $C_{16}H_{21}BrN_2O_2$ + H requires 353.08647, 355.08647; Found: C, 54.49; H, 6.00; N, 7.55. Calc for $C_{16}H_{21}BrN_2O_2$: C, 54.40, H, 5.99; N, 7.93%

*4.1.4.50. 4-(4-(Pyridin-3-yl)phenyl)morpholine (**72**).* Subjecting compound **81** to general procedure 3, the crude residue was obtained and purified by flash chromatography on silica eluting with ethyl acetate-hexane (2:1) to give amine **72** (0.085 g, 56%) as a colourless solid; mp 162–163 °C; νmax/cm^{-1} 2970, 2846, 1609, 1350, 1259, 921, 823; δ_H (300 MHz, $CDCl_3$) 8.82 (1H, s), 8.52 (1H, d, *J* 6.0 Hz), 7.84 (1H, m), 7.52 (2H, d, *J* 9.0 Hz), 7.34 (1H, dd, *J* 6.0, 9.0 Hz), 7.00 (2H, d, *J* 9.0 Hz), 3.88 (4H, t, *J* 6.0 Hz), 3.22 (4H, t, *J* 6.0 Hz); δ_C (75 MHz, $CDCl_3$) 151.2, 147.6, 147.4, 136.4, 133.9, 128.8, 127.9, 123.7, 115.9, 66.9, 48.9; *m*/*z* (APCI) 241 ($[M+H]^+$, 100); Found: C, 74.86; H, 6.81; N, 11.29. Calc for $C_{15}H_{16}N_2O$: C, 74.97, H, 6.71; N, 11.66%

*4.1.4.51. 4-([1,1′-biphenyl]-4-yl)morpholine (**73**) [74].* Subjecting compound **81** to general procedure 3 using phenylboronic acid, the crude residue was obtained and purified by flash chromatography on silica eluting with ethyl acetate-hexane (6:1) to give amine **73** (0.093 g, 72%) as a colourless solid; mp 179–180 °C; νmax/cm^{-1} 2837, 1607, 1490, 1259, 1234, 1121, 927, 820, 761, 692; δ_H (500 MHz, $CDCl_3$) 7.57–7.53 (4H, m), 7.41 (2H, t, *J* 8.0 Hz), 7.29 (1H, t, *J* 8.0 Hz), 6.99 (2H, d, *J* 7.0 Hz), 3.89 (4H, t, *J* 5.0 Hz), 3.21 (4H, t, *J* 5.0 Hz); δ_C (125 MHz, $CDCl_3$) 150.7, 141.0, 132.9, 128.9, 128.0, 126.69, 126.67, 115.9, 67.1, 49.4; *m*/*z* (APCI) 240 ($[M+H]^+$, 100).

*4.1.4.52. 3-(4-(Piperidin-1-yl)phenyl)pyridine (**74**).* Subjecting compound **82** to general procedure 3, the crude residue was obtained and purified by flash chromatography on silica eluting with hexane-ethyl acetate (2:1) to give amine **74** (0.05 g, 72%) as a colourless solid; mp 134–136 °C; νmax/cm^{-1} 2934, 1606, 1244, 1130, 802, 711; δ_H (500 MHz, $CDCl_3$) 8.82 (1H, d, *J* 2.0 Hz), 8.50 (1H, dd, *J* 2.0, 5.0 Hz), 7.83 (1H, dt, *J* 2.0, 8.5 Hz), 7.49 (2H, d, *J* 8.5 Hz), 7.31 (1H, m), 7.02 (2H, d, *J* 8.5 Hz), 3.24 (4H, t, *J* 5.5 Hz), 1.73 (4H, quin, *J* 5.5 Hz), 1.61 (2H, m); δ_C (125 MHz, $CDCl_3$) 152.0, 147.9, 147.5, 136.6, 133.7, 127.88, 127.82, 123.6, 116.5, 50.3, 25.8, 24.5; *m*/*z* (ESI) 239 ($[M+H]^+$, 100); Found: C, 80.53; H, 7.71; N, 11.63. Calc for $C_{16}H_{18}N_2$: C, 80.63, H, 7.61; N, 11.75%

*4.1.4.53. 1-([1,1′-Biphenyl]-4-yl)piperidine (**75**) [75].* Subjecting compound **82** to general procedure 3 using phenylboronic acid, the crude residue was obtained and purified by flash chromatography on silica eluting with hexane-ethyl acetate (95:5) to give amine **75** (0.05 g, 71%) as a colourless solid; mp 122–123 °C; νmax/cm^{-1} 2937, 2850, 1607, 1490, 1241, 820, 760, 692; δ_H (500 MHz, $CDCl_3$) 7.56 (2H, d, *J* 7.5 Hz), 7.5 (2H, d, *J* 9.0 Hz), 7.39 (2H, t, *J* 7.5 Hz), 7.26 (1H, t, *J* 7.5 Hz), 7.0 (2H, d, *J* 9.0 Hz), 3.21 (4H, t, *J* 5.5 Hz), 1.73 (4H, quin, *J* 5.5 Hz), 1.60 (2H, m); δ_C (125 MHz, $CDCl_3$) 151.6, 141.2, 131.8, 128.8, 127.8, 126.6, 126.4, 116.6, 50.6, 25.9, 24.5; *m*/*z* (ESI) 238 ($[M+H]^+$, 100).

*4.1.4.54. 1-Methyl-4-(4-(pyridin-3-yl)phenyl)piperazine (**76**).* Subjecting compound **83** to general procedure 3, the crude residue was obtained and purified by flash chromatography on silica eluting with hexane-ethyl acetate (2:1) to give piperazine **76** (0.048 g, 63%) as a colourless solid; mp 110–111 °C; νmax/cm^{-1} 2939, 2843, 2799, 1609, 1525, 1477, 1450, 1291, 1243, 1161, 1147, 1006, 919, 826; δ_H (400 MHz, $CDCl_3$) 8.82 (1H, dd, *J* 0.8, 2.4 Hz), 8.51 (1H, dd, *J* 1.6, 4.8 Hz), 7.82 (1H, ddd, *J* 1.6, 2.4, 7.9 Hz), 7.50 (2H, d, *J* 9.2 Hz), 7.31 (1H, dd, *J* 4.8, 5.6 Hz), 7.01 (2H, d, *J* 9.2 Hz), 3.28 (4H, t, *J* 5.2 Hz), 2.59 (4H, t, *J* 5.2 Hz), 2.36 (3H, s); δ_C (100 MHz, $CDCl_3$) 151.2, 148.0, 147.7, 136.5, 133.7, 128.6, 127.9, 123.6, 116.2, 55.2, 48.8, 46.3; *m*/*z* (ESI) 254 ($[M+H]^+$, 100); Found MH^+ 254.16540 $C_{16}H_{19}N_3$ + H requires 254.16572.

*4.1.4.55. 1-([1,1′-Biphenyl]-4-yl)-4-methylpiperazine (**77**).* Subjecting compound **83** to general procedure 3 using phenylboronic acid, the crude residue was obtained and purified by flash chromatography on silica eluting with hexane-ethyl acetate (2:1) to give piperazine **77** (0.055 g, 74%) as a colourless solid; mp 113–114 °C; νmax/cm^{-1} 2940, 2846, 2837, 2791, 1735, 1607, 1527, 1491, 1292, 1243, 1163, 1008, 921, 821; δ_H (400 MHz, $CDCl_3$) 7.48 (2H, d, *J* 8.8 Hz), 7.44 (2H, d, *J* 7.2 Hz), 7.32 (2H, t, *J* 7.2 Hz), 7.20 (1H, d, *J* 7.2 Hz), 6.92 (2H, d, *J* 8.8 Hz), 3.20 (4H, t, *J* 5.2 Hz), 2.53 (4H, t, *J* 5.2 Hz), 2.29 (3H, s); δ_C (100 MHz, $CDCl_3$) 150.7, 141.1, 132.4, 128.8, 127.9, 126.7, 126.6, 116.2, 55.3, 49.0, 46.3; *m*/*z* (ESI) 253 ($[M+H]^+$, 100); Found MH^+ 253.17017 $C_{17}H_{20}N_2$ + H requires 253.17047.

*4.1.4.56. (1S, 4S)-tert-Butyl 5-(4-(pyridin-3-yl)phenyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**85**).* Subjecting compound **84** to general procedure 3 gave, after purification by flash chromatography on silica eluting with hexane-ethylacetate (1:1) compound **85** (0.053 g, 52%) as a colourless solid; mp 179–180 °C; $[a]_D^{25}$ −25.0 (1.0, $CHCl_3$); νmax/cm^{-1} 2918, 1692, 1609, 1525, 1474, 1402, 1322, 1184, 1166, 1102, 813; δ_H (500 MHz, $CDCl_3$) 8.81 (1H, s), 8.49 (1H, d, *J* 4.5 Hz), 7.81 (1H, d, *J* 7.5 Hz), 7.47 (2H, t, *J* 9.0 Hz), 7.30 (1H, dd, *J* 4.5, 8.0 Hz), 6.65 (2H, d, *J* 8.0 Hz), 4.67 (0.6H, s), 4.52 (0.4H, s), 4.44 (1H, s), 3.60 (1H, m), 3.52 (0.5H, d, *J* 10.0 Hz), 3.45–3.39 (1.5H, m), 3.27 (0.6H, d, *J* 9.0 Hz), 3.18 (0.4H, d, *J* 8.5 Hz), 2.01–1.92 (2H, m), 1.43 (9H, m) (mixture of rotamers); δ_C (125 MHz, $CDCl_3$) 154.2, 147.8, 147.4, 146.8, 136.6, 133.3, 128.2, 16.0, 125.81, 123.6, 113.0, 79.9, 79.8, 57.4, 57.3, 57.2, 57.0, 56.8, 56.5, 51.7, 51.3, 37.9, 37.5, 28.7, 28.6 (mixture of rotamers); *m*/*z* (ESI) 352 ($[M+H]^+$, 100); Found MH^+ 352.20195 $C_{21}H_{25}N_3O_2$ + H requires 352.20250.

*4.1.4.57. (1S, 4S)-tert-Butyl 5-([1,1′-biphenyl]-4-yl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (**86**).* Subjecting compound **84** to general procedure 3 using phenylboronic acid gave, after purification by flash chromatography on silica eluting with hexane-ethylacetate (3:1) compound **86** (0.059 g, 58%) as a colourless solid; mp 156–157 °C; $[a]_D^{25}$ −20.0 (1.0, $CHCl_3$); νmax/cm^{-1} 2950, 1695, 1491, 1405, 1365, 1186, 1167, 1103; δ_H (400 MHz, $CDCl_3$) 7.57 (2H, d, *J* 8.0 Hz), 7.51 (2H, t, *J* 8.4 Hz), 7.42 (2H, t, *J* 8.0 Hz), 7.28 (1H, m), 6.66 (2H, d, *J* 8.0 Hz), 4.69 (0.6H, s), 4.53 (0.4H, s), 4.46 (1H, s), 3.64 (1H, d, *J* 8.4 Hz), 3.56 (0.4H, d, *J* 9.6 Hz), 3.50–3.40 (1.6H, m), 3.84 (0.6H, d, *J* 8.4 Hz), 3.20 (0.4H, d, *J* 8.8 Hz), 2.04–1.93 (2H, m), 1.46 (9H, m) (mixture of rotamers); δ_C (100 MHz, $CDCl_3$) 154.3, 146.3, 129.7, 129.5, 128.8, 128.2, 126.4, 126.2, 112.9, 112.8, 79.8, 79.7, 57.5, 57.4, 57.2, 57.0, 56.9, 56.5, 51.6, 51.2, 37.9, 37.5, 28.7, 28.6; *m*/*z* (ESI) 373 ($[M+Na]^+$, 100); Found MNa^+ 373.18865 $C_{22}H_{26}N_2O_2$ + Na requires 373.18920.

*4.1.4.58. (1S, 4S)-2-Methyl-5-(4-(pyridin-3-yl)phenyl)-2,5-diazabicyclo[2.2.1]heptane (**78**).* Subjecting compound **85** to general procedure 5, the crude residue was obtained and purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (90:9.5:0.5) to give methylated amine **78** (0.03 g, 61% over two steps) as a colourless oil; $[a]_D^{25}$ −14.6 (1.0, $CHCl_3$); ν_{max}/cm^{-1} 2877, 1608, 1525, 1476, 1370; δ_H (400 MHz, $CDCl_3$) 8.81 (1H, d, *J* 1.6 Hz), 8.47 (1H, dd, *J* 1.2, 4.4 Hz), 7.81 (1H, dt, *J* 8.0 Hz), 7.46 (2H, d,

J 8.8 Hz), 7.29 (1H, dd, *J* 4.8, 7.6 Hz), 6.65 (2H, d, *J* 8.8 Hz), 4.26 (1H, s), 3.51 (1H, s), 3.41–3.37 (2H, m), 2.98 (1H, dd, *J* 2.0, 9.6 Hz), 2.66 (1H, d, *J* 9.2 Hz), 2.39 (3H, s), 2.01 (1H, d, *J* 9.2 Hz), 1.91 (1H, d, *J* 9.6 Hz); δ_C (100 MHz, $CDCl_3$) 147.7, 147.2, 147.1, 136.8, 133.3, 128.0, 125.4, 123.6, 113.0, 63.1, 59.0, 58.2, 52.0, 40.7, 36.6; *m/z* (ESI) 266 ($[M+H]^+$, 100); Found: MH^+ 266.16517 $C_{17}H_{19}N_3$ + H requires 266.16572.

*4.1.4.59. 2-([1,1′-Biphenyl]-4-yl)-5-methyl-2,5-diazabicyclo[2.2.1] heptane (**79**).* Subjecting compound **86** to general procedure 5, the crude residue was obtained and purified by flash chromatography on silica eluting with CH_2Cl_2-methanol-aqueous ammonia (90:9.5:0.5) to give methylated amine **79** (0.02 g, 54% over two steps) as a colourless oil; $[a]_D^{25}$ −16.5 (1.0, $CHCl_3$); ν_{max}/cm^{-1} 2914, 1609, 1527, 1487, 1365, 823; δ_H (500 MHz, $CDCl_3$) 7.54 (2H, d, *J* 7.5 Hz), 7.47 (2H, d, *J* 8.5 Hz), 7.38 (2H, t, *J* 8.5 Hz), 7.24 (1H, t, *J* 9.0 Hz), 6.63 (2H, d, *J* 8.5 Hz), 4.25 (1H, s), 3.51 (1H, s), 3.42–3.37 (2H, m), 2.98 (1H, dd, *J* 2.0, 9.8 Hz), 2.67 (1H, d, *J* 9.5 Hz), 2.39 (3H, s), 2.0 (1H, d, *J* 9.5 Hz), 1.91 (1H, d, *J* 9.5 Hz); δ_C (125 MHz, $CDCl_3$) 146.5, 141.4, 129.1, 128.8, 128.0, 126.3, 126.0, 112.9, 63.1, 58.9, 58.2, 51.9, 40.5, 36.7; *m/z* (ESI) 265 ([M+H], 100); Found: MH^+ 265.16993$C_{18}H_{20}N_2$ + H requires 265.17047.

4.2. Docking studies (Table 9)

Table 9
Summary of XP [50] docking results for SEN12333 (**8**) and **14**.

XP term[a]	Compound	
	SEN12333 (**8**)	**14**
GScore	−5.14	−13.14
LipophilicEvdW	−4.48	−4.61
PhobEn	−0.9	−2.7
PhobEnHB	0	0
HBond	−1.14	−1.11
Electro	−0.57	−1.19
Sitemap	−0.25	−0.27
PiCat	0	−4.12
LowMW	−0.37	−0.28
Penalties	4.69	1.64
Rot Penalties	0.49	0.49

[a] Description of XP terms. GScore: total Glide score; LipophilicEvdW: ChemScore lipophilic pair term and fraction of the total protein-ligand vdW energy; PhobEn: Hydrophobic enclosure reward; HBond: ChemScore H-bond pair term; Electro: Electrostatic rewards; Sitemap: Sitemap ligand/receptor non-H-bonding polar/hydrophobic and hydrophobic/hydrophilic complementarity terms; PiCat: Reward for cat-π interactions; LowMW: Reward for ligands with low molecular weight; Penalties: Polar atom burial and desolvation penalties, and penalty for intra-ligand contacts; RotPenal: Rotatable bond penalty.

4.3. Binding affinity studies of α7 ligands

Tissue culture medium and antibiotics were obtained from Invitrogen Corp (Carlsbad, California). Foetal bovine serum was purchased from Gemini Bio-products (West Sacramento, California). [^{3}H] ± EB was obtained from PerkinElmer Life and Analytical Sciences (Boston, Massachusetts). Three cell lines, KX$\alpha_3\beta_4$R2, KX$\alpha_4\beta_2$R2 and KXα_7R1, which express defined rat nAChR subtypes, were established previously by stably transfecting HEK293 cells with rat nAChR subunit genes [53–55,76].

These cell lines were maintained in minimum essential medium (MEM) supplemented with 10% foetal bovine serum, 100 U/mL penicillin G, 100 mg/mL streptomycin and selective antibiotics at 37 °C with 5% CO_2 in a humidified incubator. Membrane preparation procedures and binding assays were described previously [53–55,76]. Briefly, cultured cells at >80% confluence were removed from their flasks (80 cm^2) with a disposable cell scraper and placed in 10 mL of 50 mM Tris·HCl buffer (pH 7.4, 4 °C). The cell suspension was centrifuged at 10,000 × *g* for 5 min and the pellet was collected. The cell pellet was then homogenised in 10 mL buffer with a polytron homogenizer and centrifuged at 36,000 *g* for 10 min at 4 °C. The membrane pellet was resuspended in fresh buffer, and aliquots of the membrane preparation were used for binding assays. The concentrations of [^{3}H]EB used in competition binding assays were ~500 pM for $\alpha_3\beta_4$ and $\alpha_4\beta_2$ nAChRs and ~2 nM for α_7 nAChRs. Nonspecific binding was assessed in parallel incubations in the presence of 300 μM nicotine. Bound and free ligands were separated by vacuum filtration through Whatman GF/C filters treated with 0.5% polyethylenimine. The filter-retained radioactivity was measured by liquid scintillation counting. Specific binding was defined as the difference between total binding and nonspecific binding. Data from competition binding assays were analysed using Prism 5.

4.4. Functional activity studies of selected α7 ligands

All compounds were tested for agonist activity on the α7 nAChR in a fluorescent calcium assay using a GH4C1 cells stably expressing rat α7 nAChR. To determine EC_{50} values, all compounds were tested at 0.03, 0.1, 0.3, 1, 3 and 10 μM (n = 3) except for compound **9** which was tested (n = 3) at 0.001–0.3 μM Fluo4 Direct Dye from Molecular Probes was used and the assay was performed on a Perkin Elmer CellLux high throughput fluorescent plate reader. A baseline read was recorded prior to addition of compound. Peak/Base (P/B) ratios were calculated. Values >1.00 indicate agonist activity (shown in orange). GraphPad Prism, Version 4.03 was used to produce dose response curves for each compound and calculate the EC50 for agonist activity at rat α7 nAChR. Replicates have been factored in each datapoint, the error is contained in the datapoints, as opposed to calculating each replicate as a dose response and getting the error on the EC50.

4.5. Electrophysiology studies of SEN12333 (**8**) and compound **45**

Two compounds, SEN12333 (**8**) and compound **45**, were tested for agonist activity on the α7 nicotinic acetylcholine receptor (α7 nAChR) in manual patch-clamp electrophysiology using GH4C1 cells stably expressing rat α7 nAChR. The manual patch-clamp recordings used the fast application add-on Dynaflow® system. To determine EC_{50} values, the compounds were tested at 3 μM, 10 μM, 30 μM, 100 μM, 300 μM, 1 mM and 3 mM (n = 5). Peak currents were normalized to saturating acetylcholine. Replicates have been factored in each datapoint, the error is contained in the datapoints, as opposed to calculating each replicate as a dose response and getting the error on the EC50.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2015.03.025.

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