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Synthesis of amino heterocycle aspartyl protease inhibitors

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Aspartyl proteases are important pharmacological targets. Historically aspartyl proteases have been commonly targeted with transition state derived peptidomimetics. The strategy to develop aspartyl protease inhibitors has undertaken a dramatic paradigm shift in the last 10 years. The pharmaceutical industry in 2005 disclosed several scaffolds or “head groups” that prompted the field to move beyond peptidomimetic derived inhibitors. Since the discovery of the first amino heterocycle aspartyl protease inhibitor, the amino hydantoin, industry and academia have positioned themselves for a foothold on the new molecular space, designing a variety of related “head groups”. Both the design and synthetic efforts involved in constructing these scaffolds are varied and complex. Here we highlight the synthetic strategies used to access these amino heterocycle scaffolds.

1. Introduction

Aspartyl proteases are important pharmacological targets. There are several aspartyl protease inhibitors that have entered the market place or have entered the clinical setting, treating diseases such as hypertension, Alzheimer’s disease, and HIV. Aliskiren (Tekturna©), an inhibitor of the aspartyl protease renin, was a first in class drug that entered the market in 2007 for treatment of hypertension. Aliskiren was developed from a transition state peptidomimetic strategy, and although the journey of drug to the marketplace was successful, it was a long exhaustive pathway to the clinic. The issues with undertaking a peptidomimetic approach to develop an inhibitor suitable for in vivo dosing, have been well documented, and further exemplified by the low oral bioavailability of Aliskiren. Lessons learnt from the peptidomimetic approach to develop Aliskiren were implemented in the development of HIV aspartyl protease inhibitors. Ten of these inhibitors, such as Lopinavir and Ritonavir, are all in the marketplace. Although these drugs underpin the success of the mimetic approach, the development of drugs treating HIV and hypertension was long and exhaustive, due to difficulties with complex syntheses and oral bioavailability. In addition, some of these drugs have issues with cytochrome P450 inhibition, P-gp efflux and possessed poor blood brain membrane permeability, which was a major issue in developing a beta-secretase inhibitor for the treatment of Alzheimer’s disease. This was well documented by Zhu. These examples ignited the pharmaceutical industry in the aspartyl protease inhibitor field into a flurry of activity. Each company positioned themselves for a foothold in the new molecular space. This activity resulted in the design of a plethora of novel amino

Figure 1. Nomenclature of the 5-, 6- and 7-membered 2-amino heterocycles presented in this review, and examples of this class that have entered into clinic trials.
heterocycle scaffolds (Figure 1) targeting aspartyl proteases, particularly beta-secretase (BACE-1). Several of these amino heterocycle BACE-1 inhibitors, such as AZD-3292 (also known as LY3314814), MK-8931 (or Verubecestat) and LY2886721 (Figure 1) have now entered clinical trials for treatment of Alzheimer’s disease.11

An overview of the development these amino heterocycle scaffolds targeting beta-secretase was undertaken by both Oehrlich et al.12 and Ghosh et al.,13 and demonstrates the immense effort and resources by both industry and academia to design novel scaffolds. The design of the new scaffolds by industry was not only to capture new molecular space, but as the research in this area evolved, it was clear that some of the scaffolds did not possess ideal physicochemical properties. One particular issue was the pKa of the basic amidine functionality that varied greatly and was dependent on atoms and functionality incorporated into the head group scaffold. The pKa of the head group was not only important for binding to the catalytic dyad, but for optimal pharmacokinetics and mediating off target activity, such as P-gp mediated efflux. The search for optimal physicochemical properties underpins the design of a variety of head groups described here and elsewhere.12-14

Several X-ray structures have provided insight into the binding mode of the amino heterocycle scaffold to aspartyl proteases. Figure 2 shows an example of the 2-amino heterocycle class (21 in Scheme 5), bound to the open flap form of BACE-1.5c Note that the flap is in a relatively open conformation similar to that of published apo structures, which is consistent with a number of amino heterocycle aspartyl protease inhibitors and is in contrast to the more closed flap confirmation that is seen with substrate based peptidomimetics. The X-ray structure (Figure 2) shows that the amino functionality interacts with the acid groups of the two catalytic aspartates in the catalytic dyad, while the 2-N forms a hydrogen bond with the protonated carboxylic acid aspartate. The 3-N that is generally alkylated on all amino heterocycle inhibitors, faces out of the binding cleft, and takes no part in binding affinity. This has allowed the replacement of the 3-N with other atoms such as O, S, and C. The 3-C has been exploited to provide a site of differentiation compared to the 3-N, for example dialkyl substituents. Although the 3-position does not take part in any direct binding, attaching the appropriate substituents to this position has allowed an indirect route to access other pockets in the binding cleft of aspartyl proteases. The 3-position is also critically important in mediating the pKa of the amidine functionality that interacts with the aspartyl residues in the catalytic dyad.

Both the S1 and S1’ pockets of the aspartyl proteases can be accessed from the 5-position of the 5-membered heterocycle 2. This carbon is usually differentially disubstituted which allows one substituent to protrude in the S1 pocket and another into the S1’ pocket. Given that this carbon is differentially disubstituted it creates a chiral centre, which adds to the synthetic complexity of this class of inhibitor. The group that is appended to the 5-C and enters the S1 pocket, also permits entry to the S3 pocket.

6- and 7- membered amino heterocycles, 3 and 4 respectively, bind in the same orientation to the 5- membered orthologues 2. The open flap binding confirmation of this class is conducive to accommodating larger heterocycles, given the additional endocyclic atoms face solvent space. The additional endocyclic atoms in the 6- and 7- membered systems enables extra chemical diversity to be installed in these positions. Although installing functionality in these positions is directed into solvent space, these positions are used to mediate pKa of the amidine group that interacts with the catalytic aspartyl amino acids. Additionally these positions are also used to install chiral cyclic ring systems that conformationally constrain and rigidify the 6- and 7- membered systems. Given the flexibility of these scaffolds, the structural diversity within this class of inhibitor is large and varied.

One aspect that underpins this research are the synthetic strategies that were undertaken to construct these head groups, some with highly functionalised architecture. Here we describe a summary of the synthetic strategies undertaken to access the 2-amino heterocycle head groups that were used as scaffolds to target specific aspartyl proteases.

This review will focus on the synthesis of the 5-, 6- and 7- membered scaffolds or head groups (2, 3, and 4 respectively) broadly depicted in Figure 1. In the literature this class of aspartyl protease inhibitor is referred to as the amino (or imino) hydantoin in the case of the 5-membered lactam system or the amino pyrimidine in the instance of the 6-membered lactam system. In this review, the IUPAC nomenclature convention will be used. For example, the amino hydantoin head group 2 will be referred to as the 2-amino 1H-imidazol-5(4H)-one.

2. 5-Membered heterocycles

One of the first amino heterocycles, the 6-amino 2,3,4,8-tetrahydroimidazo[1.5-a]pyrimidine 1 (Figure 1), was identified from a high throughput screen of BACE-1.5d Chemists quickly realised that truncating the tetrahydropyrimidine ring to produce the 2-amino 1H-imidazol-5(4H)-one 5b resulted in improved BACE-
1 potency across a range of analogues. The discovery of the 2-amino imidazol-5-(4H)-one head group 5 by Malamas et al. initiated the search for greater diversity among the amino heterocycle class.

2.1 2-Amino 1H-imidazol-5(4H)-one and surrogates

The pathway to access the imidazolone head group 5 has been predominantly through a benzilic acid rearrangement in the presence of a guanidine equivalent (Scheme 1). Entry to the diketone intermediate building block is depicted in Scheme 1 and 2. The most common method is starting from the alkyne using either KMnO₄ or Wacker type conditions, employing catalytic palladium in the presence of DMSO or oxygen at high temperature (Scheme 1). High yields are achieved in both cases if a diaryl alkyne is used. The alkyne is easily accessed via the Sonogashira reaction. This route is compatible with a diverse array of functional handles that allow late stage diversification, for entry to analogues shown in Scheme 5.

Scheme 1. Access to the 2-amino 1H-imidazol-5(4H)-one 5 via the diketone.

Alternative pathways to access the diketone are shown in Scheme 2. In one synthesis, Malamas et al. reacted an acid chloride with a benzyl phosphonium salt, to produce the ylide 6. This was followed by oxidation of the ylide 6 to yield the diketone 7. This route appeared more amenable to producing a diketone where one of the substituents is an alkyl group. Malamas et al. also employed a silyloxy ether 9, which was formed from the aldehyde 8. The anion of 9 was formed and reacted with an acid chloride and upon hydrolysis gave the diketone 7.

Other methods include reacting an activated dicarbonyl species, 11 or ethyl malonyl chloride with the appropriate equivalents of a carbon nucleophile, to yield the unsymmetrical diketones 10. Starting from aryl carboxylic acids is an attractive option given the number that are commercially available. Zhou et al. used phenylacetic acid derivatives 12 in a Friedel-Crafts like alkylation, and the methylene product 13 subsequently oxidised to give the diaryl diketone 14. While, Cumming et al. used benzoic acids to form the phenyl amide 15, which was activated to the chloro imidate, and on-reacted in an N-heterocyclic carbene catalyzed benzoin transformation to give the unsymmetrical diketone 16. All these methods to access the diketone offer different advantages depending on the functionality on the diketone substituents. These synthetic routes to synthesise the diketone are all geared towards ensuring diversity can be housed in the final amino imidazolone product.

The diketone is most commonly converted to the amino imidazolone 17 via reaction with the N-substituted guanidine in one step or with the N-substituted thiourea in two steps. The two step reaction is generally higher yielding than the one step procedure (Scheme 3). The N-3 substituent is then incorporated into the guanidine or thiourea. Installing the N-3 substituent post 2-amino imidazolone formation can be problematic with respect to regioselectivity.

Substitution can be installed on the N-1 substituent regioselectively following the route depicted in Scheme 4. Zhou et al. used a Ugi multicomponent reaction starting from simple building blocks to synthesise the benzyl protected intermediate 18. Hydrolysis of the benzyl imine and oxidative displacement of the thione gave the N-1 substituted product 19. Analogues with the N-1 substitution were found to be less active against BACE-1 than the N-3 substituted.
to the opposite face of the hindered chirality directing substituent, usually with excellent dr. The chiral DMF-DMA to methylate the N-3 position of the hydantoin closure is effected by addition of a substituted amine, to gain access selectively converted to the 2-thioamide, before conversion to the imidazolone.

Bucherer–Bergs reaction can also be used to gain entry to the imidazolone scaffold. The 4-phosphonate analogue 34, was generated by first using the disubstituted imine with isocyanate phosphane in a cycloaddition reaction to form the cyclic diazaphospholidinone 33, and in turn converted to the amino dihydro diazaphosphole 34 (Scheme 7).

2.2 Amino hydro-imidazoles

The pKa of the 2-amino-imidazolone was important for its interaction with the aspartates in the catalytic dyad and pharmacokinetics. To modulate the pKa, numerous other scaffolds were designed around the 2-amino-imidazolone scaffold. An obvious change was to install a sulfonyl or phosphonate group in place of the 4-carbonyl functionality on the imidazolone (Scheme 7). The synthesis of the 4-sulfonyl analogues started from the 2,2-disubstituted malonyl sulfonyl amide.

The research centered around exploring the removal of the 4-carbonyl group in the imidazolone scaffold in the heterocycles 35. This synthon was accessed from the halo acetamide which was converted to the 2-amino thioacetamide that was deprotected and cyclised in the one step (Scheme 6). These procedures enabled the synthesis of potent inhibitors targeting BACE-1 21, 23, 22 and plasminogen II and IV 24 (Scheme 5).

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Scheme 7. Synthetic pathways to access the 3-amino-2,5-dihydro-1,2,4-thiadiazole 1,1-dioxide 31 and 3-amino-2,5-dihydro-2,4-diazaphospholidinone 34 scaffolds.

Scheme 8. Synthetic pathways to generate the 2-amino-4-methyl-4H-imidazole 39, 4-amino-2,5-dihydro-1H-imidazole 42, 5-amino-3,4-dihydro-2H-pyrrole 45, and 4-amino-2,5-dihydrothiazole 47 head groups.

Scheme 9. Syntheses of the 4-amino-2H-imidazole 51 head group.

Scheme 10. Synthesis of the 3-amino-2,5-dihydro-1,2,4-oxadiazole 56 scaffold.

Scheme 12. Synthetic pathways to access the 2-amino-5,6-dihydropyrimidin-4-one head groups 70 and 74.

Scheme 13. Synthetic route to access 3-amino 5,6-dihydro-2H-1,2,4-thiadiazine 1,1-dioxide 80 and 3-amino 1-(methylimino)-5,6-dihydro-2H-1,2,4-thiadiazine 1-oxide 81.

Ginman et al. also demonstrated that the 3-nitrogen can be removed completely to give the 5-amino 3,4-dihydro-2H-pyrrole 45. The 3,4-dihydro-2H-pyrrole 45 was generated starting from aryl aldehyde 43 that was subjected to a Stetter reaction. Next a lithiated arene attacks the ketone to form the intermediate 44 that is subsequently ring closed under strong acidic conditions. Finally conversion to the 3,4-dihydro-2H-pyrrol-5-amine 45 was undertaken via the thioamide. Entry to the 2,5-dihydrothiazol-4-amine 47 was via a lithiated arene attack of an aryl nitrile. The resulting imine 46 was reacted with the 2-mercaptoacetate to give the cyclic amide en-route to the amino dihydrothiazole 47. These procedures enabled the synthesis of the potent inhibitors 48 and 49 that target BACE-1 (Scheme 8).
In a successful attempt to prevent off target hERG activity the 4-amino-2H-imidazole scaffold 51 was designed (Scheme 9). One synthesis started from the multicomponent reaction of a ketone with an α-oxo acetate in the presence of ammonia to give the intermediate 50, which was converted to the amino imidazole 51 in two steps. The second pathway, started by reacting a ketone with a dithiooxamide to give the 2-amino-3-thiomidazole 52. This scaffold was well positioned to install diversity at the 3-position via a Kumada reaction, and led to the structural diversity seen in the potent BACE-1 inhibitor 53.

2.3 3-Amino 2,5-dihydro-1,2,4-oxadiazole

The N-substitution on the guanidine moiety was also maintained in the 2,5-dihydro-1,2,4-oxadiazol-3-amine head group (Scheme 10). To synthesise this scaffold, Dillard et al. started from the reaction of ketone 54 with bis TMS carbodiimide to give the NCyano imine 55. This intermediate was reacted with the N-substituted hydroxylamine to give the oxadiazole 56. Zhu et al. used a different approach starting from the α-substituted benzyl isothiocyanate 57. The α-centre of this intermediate was brominated and then on-reacted with N-methyl hydroxylamine to give the 3-thio oxadiazole 58 and subsequently the 3-amino 1,2,4-oxadiazole 59. These reaction sequences were used to produce the potent BACE-1 inhibitor 59 (Scheme 10).

2.4 2-Amino 4,5-dihydrooxazole and thiazole

In ongoing efforts to generate BACE-1 inhibitors with improved CNS penetration, P-gp efflux and hERG, the head group was altered by several groups to a 2-amino 4,5-dihydrooxazole or 2-amino 4,5-dihydrothiazole scaffold (62 and 63). This change altered the pKa of the oxazine head group, in examples 64, 65, and 66, which was sufficient to ameliorate all of the aforementioned properties, while retaining potent BACE-1 activity. The general scheme to synthesise the 4,5-dihydrooxazole 62 and 4,5-dihydrothiazole 63 class of inhibitor started with a ketone 60 that was converted to the methylene 61 using a Wittig reaction or a Tebbe approach to enter the S3 pocket of the aspartyl protease, similar to that shown in Figure 2. Interestingly, McKittrick et al. used a novel approach to enter the S3 sub-pocket of renin exploiting the N3-substituent, shown in compound 76. Here, the N-substitution is readily installed with the N-Boc-N'-substituted thiourea reagent, but can be installed post dihydropyrimidin-4-one formation using a base and an aliphatic halide or via a Mitsunobu reaction using an alcohol (not shown).

The direct sulfonamide and imino sulfonamide analogues of the 2-amino dihydro pyrimdin-4-one, 70 and 74 respectively, were also produced utilising the sulfonamide chemistry. Here, the sulfonamide imine 77 was reacted with either deprotonated PMB protected methyl sulfonamide or sulfonamide to afford 78 and 79 respectively. The sulfonamide and PMB groups were removed and then cyanogen bromide used to commit cyclization, to give either the sulfone and sulfanilamide systems, 80 and 81 respectively. This synthesis was used to produce the sulfanilamide analogue 82 which possessed potent BACE-1 activity (Scheme 13). The phosphonate analogue of 80 was also generated by Zhu et al. The synthesis of the 4, 4-disubstituted analogue started from the β-amino
phosphate 83 that was coupled to the N-Boc N-methyl thiourea followed by Boc deprotection to afford 84. Similarly the 5 substituted analogue 86 was prepared from the β-amino phosphate 85. Here, 85 was reacted with thiophosgene, followed by amine deprotection to afford 86. Similarly the 5 substituted analogue 86 was prepared from the β-amino phosphate 85. Here, 85 was reacted with thiophosgene, followed by amine deprotection to afford 86. The resulting cyclised thiourea was converted to the 1,2,3,4-tetrahydro-1,5,2-diazaphosphinine 2-oxide 86 with use of ammonium hydroxide under oxidative conditions (Scheme 14). All 4 scaffolds (80, 81, 84 and 86) were found to exhibit similar activity against BACE-1 compared to direct analogues of the progenitor 74, 24, 35b.

3.2. 2-Amino 3,4,5,6-tetrahydropyridines

In several scaffolds the nitrogen adjacent to the amino group was replaced with a disubstituted carbon (Scheme 15). The aim of these head groups was to modulate the pKa of the amidine functionality to ablate P-gp activity, and to assist with BBB permeability to target BACE-1. Although, P-gp activity was abrogated and the potency against BACE-1 in vitro was comparable to 75, no pharmacological response in vivo was observed.36 The synthesis of these scaffolds both utilised the sulfonamide chemistry. For 88, this started with nucleophilic addition of a metalated functionalised methyl sulfone to the sulfonamide imine 77. The sulfonamide group was removed from the resulting product 87, and enabled an AlMe₃ mediated cyclization of the amine to the nitrile, to afford 88. The synthesis of the tetrahydro pyridine 92, started with a Reformatsky like addition of a zinc species to the sulfonamide imine 89 to give 90. The sulfonamide group was removed and the amine protected with a DMB group, via reductive amination and subsequently reacted with a functionalised acryloyl chloride. This intermediate 91 was positioned for metathesis reaction using the second generation Grubb’s catalyst to afford the cyclised tetrahydropyridine 92. The 3-cyclopropyl group was next installed over 4 steps, and the 2-hydroxy converted to the 2-amine over these steps to give the tetrahydropyridine 93. These synthetic pathways led to the potent inhibitors of BACE-1, 9435a and 9536(Scheme 15).

3.3 Amino 5,6-dihydro-oxazine, thiazine and orthologues

Similar to the five membered dihydrooxazole and thiazole head groups (62 and 63), the 6-membered oxazine and thiazines were constructed to improve PK and CNS penetration while maintaining BACE-1 potency. A plethora of analogues harbouring these head groups were created,17 many of them possessing improved CNS penetration, 37a, 37c, 37h leading to the potent BACE-1 inhibitors 96 and 97 (Scheme 16).
Scheme 16. Synthetic routes to produce the amino dihydro-oxazine, thiazine and oxadiazine head groups.

Scheme 17. Synthetic routes to produce the amino dihydro-oxazine and thiazine scaffolds.

16 is shown that possesses a cyclopropyl group at the 5,6 position of the thiazine. Here, Woltering et al.\textsuperscript{36} produced the starting chiral cyclopropyl amide 104 from an intramolecular carbenoid cyclopropanation induced by a chiral ligated Rh catalyst. 104 was then subjected to a Hoffmann rearrangement followed by basic hydrolysis to generate the amino alcohol 105, which was treated with tert-butylisothiocyanate to yield the thiourea 106. This intermediate was cyclised under Appel conditions followed by deprotection under strongly acidic conditions to generate the chiral 2-amino 5,6-dihydro-thiazine 107 (Scheme 16). Another iteration on the dihydro-oxazine head group, was the 3-amino 5,6-dihydro-1,2,4-oxadiazine 111. To synthesise this scaffold, Zhu et al.\textsuperscript{38} produced the oxathiazolidine 109 from cyclisation of the \( \beta \)-amino alcohol 108. After replacing the Boc protection with an allyl, addition of a substituted hydroxylamine gave the ring opened product 110. After protecting group removal, addition of cyanogen bromide yielded the 5,6-dihydro-1,2,4-oxadiazine 111 (Scheme 16).\textsuperscript{38}

Ginman et al. focused on refining the dihydro-oxazine/thiazine core to address permeability and hERG activity, while maintaining BACE-1 potency. To do this, a series of head groups were generated where the sulfur or oxygen heteroatom were placed in different positions around the 6-membered head group,\textsuperscript{25} shown in Scheme 17. The 4-amino 5,6-dihydro-oxazine and thiazine variant 114 can be accessed via condensation of a ketone 54 with either a thiol or alcohol amide 112 under acidic conditions to form the lactam 113.
This intermediate was converted to the 4-amino 5,6-dihydro-oxazine/thiazine 114 in two steps (Scheme 17). The synthesis of the 3-amino 2,6-dihydro-oxazine 118 or thiazine 121 head groups started from the amino alcohol 116. To access the amino alcohol 116, a ketone 54 was reacted with KCN and (NH₄)₂CO₃ in Bucherer-Bergs reaction to form the hydantoin 115, which was hydrolysed, followed by reduction to afford the amino alcohol 116. The amino alcohol 116 was then employed in their synthesis of the 2,6-dihydrooxazine head group 118. Here, the amino alcohol 116 was reacted with chloroacetyl chloride and cyclised on addition with base to form the morpholinone 117. Conversion of the amide to the amidine in two steps gave the 3-amino 2,6-dihydro 118 (Scheme 17).

To access the 3-amino 2,6-dihydro-thiazine 121, the amino alcohol 116 was converted to the alkyl sulphate by treatment with chlorosulfonic acid followed by a Wenker reaction to afford the aziridine 119. Aziridine ring opening and expansion with methyl 2-mercaptoproacetate gave the 6-membered lactam 120, which was followed by a 2 step conversion to the 3-amino 2,6-dihydro-thiazine 121 (Scheme 17). These methods only produced the racemic 3-amino 2,6-dihydro-thiazine, and chiral chromatography was required to produce the enantiopure product.

To produce the 2,6-dihydro-oxazine head group 118 in a stereoselective manner, the sulfanilamide methodology was again employed. Starting from the earlier described β-amino alcohol 98, that was accessed from the sulfanilamide 72, 98 was treated with 2-chloroacetyl chloride, followed by addition of potassium tert-butoxide, yielding the cyclic intermediate 122. The amide functionality was then transformed into the amidine to give 123 in two steps via the corresponding thioamide. This stereoselective synthesis allowed entry to the potent BACE-1 and BACE-2 inhibitors, 124 and 125 respectively (Scheme 17).

3.4 5-Amino-1,6-dihydropyrazin-2(3H)-one and 3-amino-piperazin-2-one

Another variation on the dihydro oxazine theme to mediate the pKa of the amidine functionality of the head group, was to insert an amide at various positions, giving rise to either a 5-amino-1,6-dihydropyrazin-2(3H)-one 128 or a 3-amino-piperazin-2-one 131. It was found that the 5-amino dihydropyrazin-2(3H)-one (128) compared to other head groups (for example 95 and 124) possess similar potent BACE-1 inhibitory activity, however the 3-amino-piperazin-2-one scaffold (131) was 10 fold less potent (Scheme 18). To form the 1,6-dihydropyrazinone 128, Trabanco-Suarez et al. started by reacting the ketone 54 with trimethylsilyl cyanide in the presence of ammonia to form the intermediate nitrile. The nitrile was hydrolysed under acidic conditions, followed by treatment with thionyl chloride to form the amino ester 126. The reaction of 126 with chloroacetyl chloride followed by methyamine induced cyclisation to the piperazine-dione 127. Conversion of the amide functionality to the amidine in two steps gave the desired compound 128 (Scheme 18).

The synthesis of the 3-amino-piperazin-2-one head group 131 was initiated from the amino alcohol 116 which was converted to the protected amino aldehyde 129 employing Dess-Martin periodinane. The N-methyl group was introduced by reductive amination followed by acylation and in situ cyclisation with ethyl oxalate to the piperazine-2,3-dione 130. Finally, the piperazinedione was O-methylated using Me₃OBF₄ followed by conversion to the amidine after treatment with NH₃ in the presence of NH₄Cl to give 131 (Scheme 18).

3.5 2-Amino-pyrimidin-4(3H)-one

Yonezawa et al. generated the pyrimidin-4-one 134, a sp² hybridised form of the 5,6-dihydropyrimidin-4-one 70 in an attempt to improve the binding affinity to BACE-1. It was found the sp² character was not well tolerated, resulting in low µM inhibition of BACE-1. To generate such a scaffold, the cyclopropanoic acid 132 was converted to the β-ketoester 133 under Masamune conditions. The ketoester 133 was treated with guanidine carbonate in the presence of sodium ethoxide followed by selective methylation of the lactam nitrogen affording the 2-amino-pyrimidin-4(3H)-one 134 (Scheme 18).

Scheme 18. Synthesis of the 5-amino-1,6-dihydropyrazin-2(3H)-one 128, 3-amino-piperazin-2-one 131 and 2-amino-pyrimidin-4(3H)-one 134 head groups.
4. 7-Membered heterocycles

The binding orientation of the amino heterocycle class in the substrate binding cleft of aspartyl protease inhibitors is not only conducive to 5- and 6-membered systems, but can also accommodate 7-membered systems, as seen by the BACE-1 activity comparison between 124 (Scheme 17) and 151 (Scheme 20), and the head group comparison study performed by Woltering et al.36

7.1 2-Amino-4,5,6,7-tetrahydro-1,3-thiazepine

Woltering et al. generated a 4,5-cyclopropyl fused 4,5,6,7-tetrahydro-1,3-thiazepine 142 to introduce a degree of conformational restriction to improve BACE-1 affinity. To access this scaffold, the initial steps involved the formation of intermediate amino alcohol 139. This began with a Regitz diazo transfer reaction of allyl ester 135 to afford the allyl α- diazoester 136, which was cyclised to the lactone intermediate using an intramolecular carbenoid cyclopropanation induced by a chiral ligated Rh catalyst, followed by ring opening to form the amide 105. Hoffmann rearrangement of 105 to a carbamate 137 followed by homologation of the alcohol over several steps gave the ester 138. Reduction and saponification produced the amino alcohol 139 (Scheme 19). Alternatively, the amino alcohol 139 could be generated by a cyclopropanation reaction of buten-3-ol in the presence of an aromatic nitrile 140 using Ti(OiPr)₄ and a hindered Grignard. With the amino alcohol 139 now in hand, the amine was converted to a thiourea 141 using tBuNCS, and cyclisation was performed using Appel reaction conditions. Finally, the tBu group was removed under acidic conditions to give the 4,5,6,7-tetrahydro-thiazepine 142. Using this synthesis, compound 143 was generated and was shown to have an IC₅₀ of 26 nM against BACE-1 and 11 nM against BACE-2 (Scheme 19). It was noted that the addition of the cyclopropyl group had no effect on BACE-1 activity.36

7.2 2-Amino-4,5,6,7-tetrahydro-1,3-oxazepine

The synthesis of the 4,5,6,7-tetrahydro-1,3-oxazepine head group 147 by Kusakabe et al. began with the hydroboration of the chiral butenyl sulfonamide 144 to form the amino alcohol 145. The sulfonamide was then removed and the benzoyl thiourea formed. This allowed for an EDCI mediated cyclisation to the 7-membered oxazepine 146. Deprotection of the benzoyl group over three steps yielded the 2-amino-4,5,6,7-tetrahydro-1,3-oxazepine 147 (Scheme 19).45

Scheme 19. Synthesis of the 2-amino-4,5,6,7-tetrahydro-1,3-thiazepine and the 2-amino-4,5,6,7-tetrahydro-1,3-oxazepine scaffolds.

Scheme 20. Synthesis of the 3-amino-2,5,6,7-tetrahydro-1,4-oxazepine and the 5-amino-2,3,6,7-tetrahydro-1,4-oxazepine head groups.
7.2 3-Amino-2,5,6,7-tetrahydro-1,4-oxazepine and the 5-amino
2,3,6,7-tetrahydro-1,4-oxazepine

The pathway to access 2,5,6,7-tetrahydro-1,4-oxazepine involved
the reduction of a sulfonamide ester 148 to form a sulfonamide
alcohol, which was selectively alkylated with BrCH₂CN to form the
sulfonamide nitrite 149. The sulfonamide 149 was deprotected,
followed by AlMe₃ mediated cyclisation to yield the oxazepine 150
(Scheme 20). Following this method, Woltering et al. generated
the potent BACE-1 inhibitor 151 (Scheme 20). Dineen et al.
formed the 2,3,6,7-tetrahydro-1,4-oxazepine head group 154
starting from keto 60. The ketone 60 was treated with a Mesityl
and a strong base followed by TMSN₃ to form the azide 152. The
TMS group was then removed and the azide reduced to the β-
amino alcohol. The alcohol was when selectively alkylated via
a conjugation reaction with acrylonitrile to the cyano ether 153.
The cyano ether 153 was then cyclised using AlMe₃ to the 5-amino
2,3,6,7-tetrahydro-1,4-oxazepine 154. By this method, Dineen et
al. synthesised the BACE-1 inhibitor 155 which was shown to have an
IC₅₀ of 1 nM. In general the 7-membered systems exhibited
similar biochemical BACE-1 activity to their direct 6-membered
counterparts.

5. Conclusions

Here we have provided a snapshot of the immense effort that
has been invested in the synthesis of the amino heterocycle
of aspartyl protease inhibitor. Some 300 publications and
patents have been published or filed respectively since the
initial disclosure of this inhibitor class in 2005, demonstrating
the evolving diversity in the head group and functionality that
has been incorporated into this scaffold.

A large majority of the literature surrounding the amino
heterocycle class is geared toward targeting BACE-1 and BACE-
2, indicating that these scaffolds are under utilised in targeting
other pharmacologically relevant aspartyl proteases, such as
HIV protease for treating AIDS, renin for hypertension, and
certain plasminogen for treating malaria, and cathepsin D as an emerging cancer
target. Several of the amino heterocycles shown in this
review that target BACE-1, are progressing through clinical
trials for treating Alzheimer’s disease. It is foreseen that the
amino heterocycle class will be heavily utilised in aspartyl
protease drug discovery programs well into the future.

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