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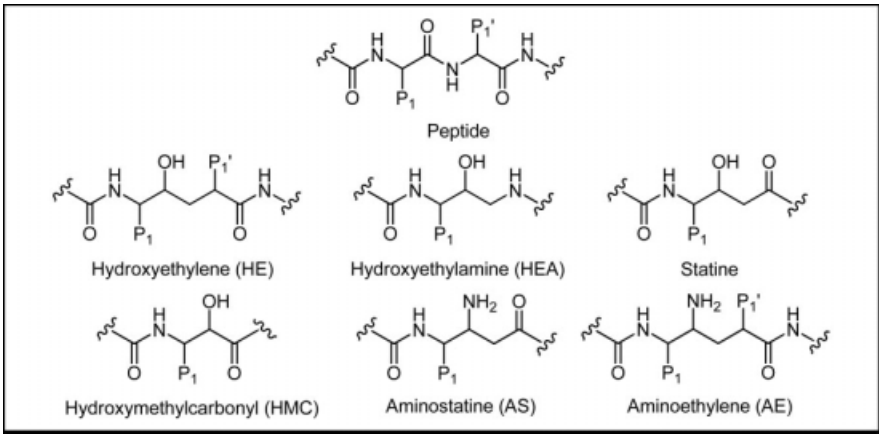

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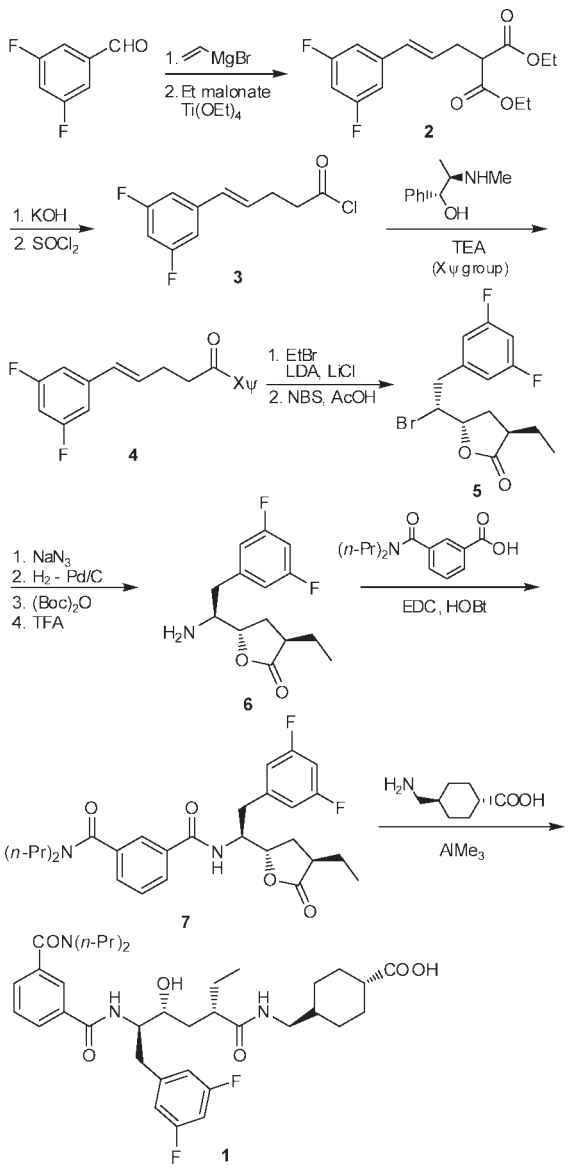
INTRODUCTION

Alzheimer's disease (AD), the neurodegenerative syndrome first described by Alois Alzheimer in 1906, affects more than 37 million people worldwide [1]. β-Amyloid cleaving enzyme-1 (BACE1) is an aspartyl protease isoform which is the principle neuronal protease responsible for the formation of Aβ fragments in the brain [2]. BACE1 is an excellent target for antiamyloid AD therapy and potent inhibitors of this enzyme have already been reported [3]. However, first generation inhibitors based on the peptidomimetic strategy showed problems related to the nature of their structure, such as blood-brain barrier crossing, poor oral bioavailability, and susceptibility to P-glycoprotein transport [4,5]. To overcome these difficulties, new nonpeptidomimetic β-secretase inhibitors were designed. After the discovery of the first nonpeptidomimetic inhibitors by Takeda Chemicals in 2001 [6], intensive efforts in research by both institutional and industrial laboratories resulted in the synthesis of hundreds of new generation inhibitors. We here review the synthesis of the most significant inhibitors, with particular emphasis on those developed by pharmaceutical companies.

ISOPHTHALAMIDE-BASED INHIBITORS

Elan Pharmaceuticals synthesized a variety of hydroxyethylene (HE) BACE1 inhibitors bearing the optimal isophthalamide *N*-terminus of the statin series and different C termini at the P1′ substituent. As an example, compound **1** inhibited BACE1 at 50 n*M* concentration [7]. Reaction of 3,5-difluorobenzaldehyde with vinylmagnesium bromide according to Orito [8] afforded 3-(3,5-difluorophenyl)-1-propen-3-ol which was treated with diethyl malonate in the presence of titanium tetraethoxide to give ethyl 4-(3,5-difluorophenyl)-3-butenoate **2**. Ester **2** underwent alkaline hydrolysis to the acid which was transformed into the corresponding acid chloride **3** with thionyl chloride. Coupling reaction of **3** with (1*R*,2*R*)-(-)-pseudoephedrine in the presence of triethylamine (TEA) and subsequent treatment of **4** with ethyl bromide in the presence of lithium diisopropylamide (LDA) and LiCl afforded a compound, which on treatment with *N*-bromosuccinimide (NBS) and AcOH at reflux underwent intramolecular lactonization to give **5**. The bromide was transformed to the corresponding azide by nucleophilic attack with sodium azide and concomitant inversion of the alpha chiral center. The azide was reduced with hydrogen in the presence of palladium as a catalyst and protected with bis-(*tert*-butoxycarbonyl)anhydride to give a compound, which then was treated with trifluoroacetic acid to afford **6**. *N*-Ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide (EDC)/1-hydroxy-benzotriazole (HOBt) amide coupling to the isophthalamide furnished the lactone **7**. Finally, **7** was ring-opened using trimethylaluminum and the required amine to provide **1** (Scheme 1) [7,9].

Scheme 1



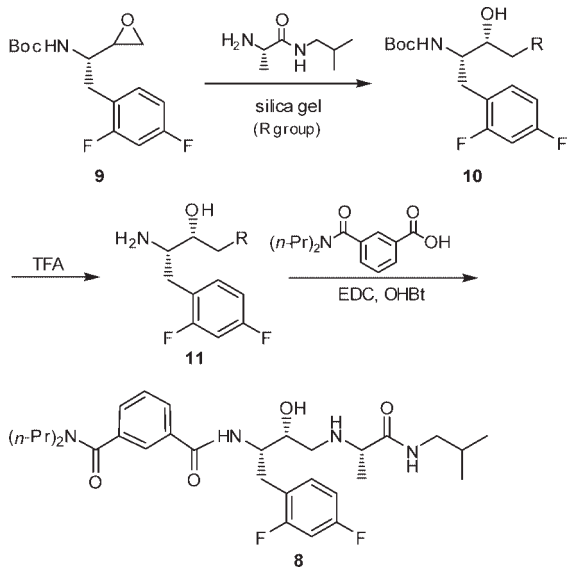
HE transition state-based inhibitor was replaced by an hydroxyethyl secondary amine (HEA) isosteric group in order to improve cell-to-enzyme potency. Compound **8** was a potent cellular inhibitor of Aβ production (more potent than the statin and the HE BACE inhibitors with comparable enzyme potency) [10]. The synthesis of **8** was accomplished starting from the erythro (*R*)-amino epoxide **9**, which was transformed into the Boc-protected amino alcohol **10**. Removal of the protecting group under TFA acidic conditions (**11**) and subsequent coupling reaction provided **8** (Scheme 2) [10].

Merck Research Laboratories synthesized HEA isosteres among potential HE motifs because of its lower molecular weight and one less amide bond. In addition, introduction of a sulfonamide group in a series of isophthalamides led to potent and selective BACE1 inhibitors [11–18].

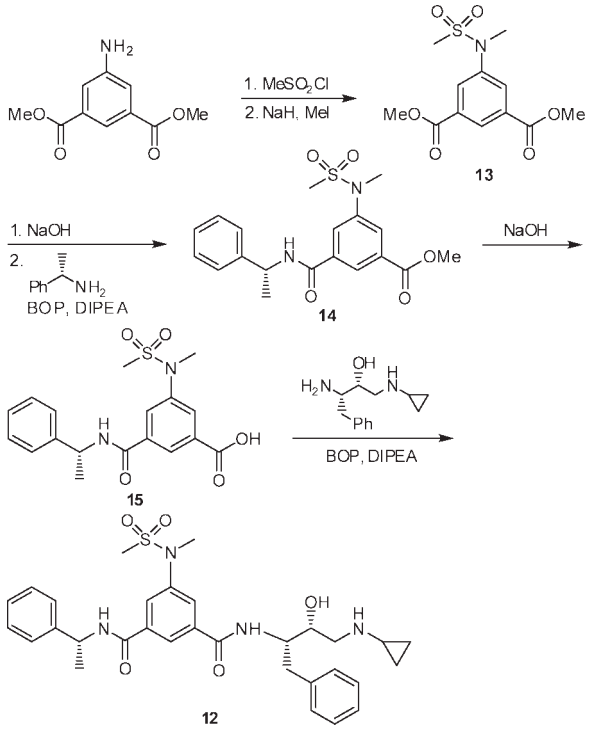
Compound **12** displayed excellent activity in both enzymatic (IC_{50} = 15 n*M*) and cell-based assays (IC_{50} = 29 n*M*), but showed moderate BACE1/BACE2 selectivity [12]. Isophthalamide **12** was prepared from 5-aminoisophthalic ester which was mesylated and then *N*-alkylated with methyl iodide to give **13**. Alkaline hydrolysis of **13** furnished the mono-ester which was coupled with (*R*)-α-methylbenzylamine in the presence of (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP)/*N*,*N*-diisopropylethylamine (DIPEA) to furnish **14**. Subsequent hydrolysis of the remaining ester, and amide coupling of **15** with 1-benzyl-3-cyclopropylamino-2-hydroxypropylamine gave **12** (Scheme 3) [12].

Analogues of **12** with both lower polar surface area and fewer H-bond donor/acceptor groups showed better pharmacodynamic and/or pharmacokinetic properties. Compound **16** was synthesized as S3-truncated analogue of **12**, and showed excellent binding activity [16]. An optimized synthesis of **16** is depicted in Scheme 4. Methyl 3-nitrobenzoate was treated with *N*-iodosuccinimide (NIS) in triflic acid (TfOH) to produce methyl 5-iodo-3-nitrobenzoate which was reduced to amine **17** with stannous chloride dihydrate. The aniline **17** was mesylated and then methylated with iodomethane in the presence of sodium hydride to give **18**. One-pot hydroindation/Suzuki coupling reaction furnished (*Z*)-methyl 3-(2-cyclopropylvinyl)-5-(*N*-methylmethylsulfonamido)-benzoate exclusively in 93% yield according to Oshima and coworkers [19]. The ester intermediate was then transformed into acid **19** by alkaline hydrolysis.

Scheme 2



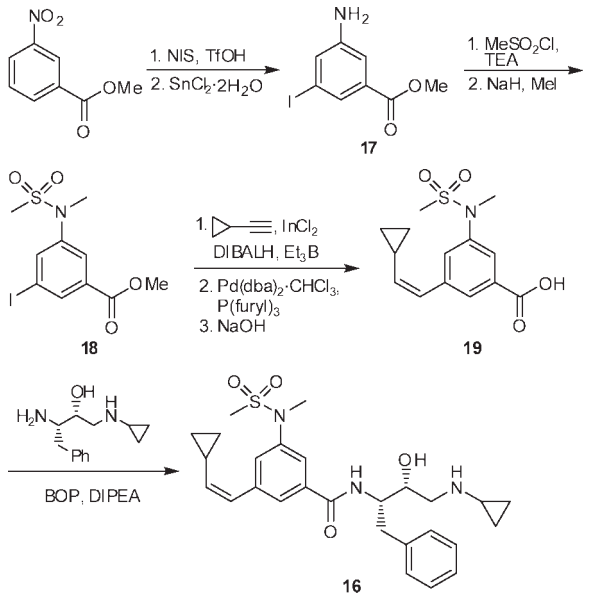
Scheme 3



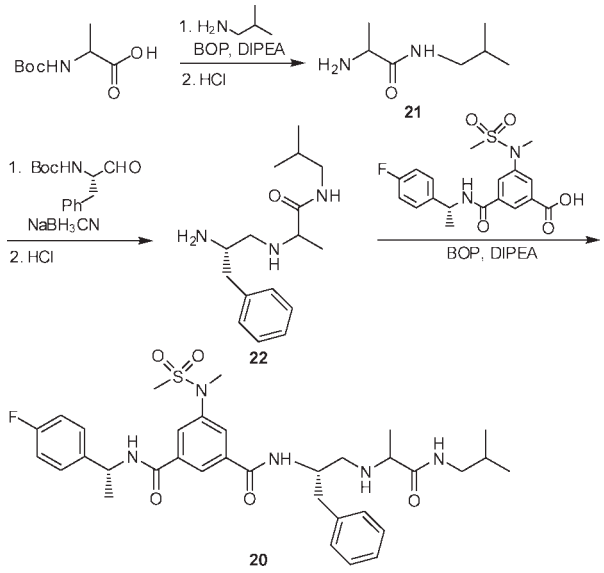
Reaction of **19** with the required amine in the presence of BOP and DIPEA afforded **16** [16].

Either small alkyl groups or longer hydrophilic substituents at the P1′ region produced compounds endowed with high BACE1 inhibitory potencies, and selectivity over BACE2 and human renin. Compound **20** was prepared by reaction of *iso*-butylamine with *N*-Boc-L-alanine and subsequent deprotection with gaseous HCl to afford *N-iso*-butylalaninamide (**21**). This compound was treated with *N*-Boc-L-phenylalanylaldheyde in the presence of sodium cyanoborohydride, and then deprotected with HCl to give **22**. Subsequent amide coupling of **22** with the appropriate benzoic acid in the presence of BOP and DIPEA afforded **20** (Scheme 5) [17].

Scheme 4



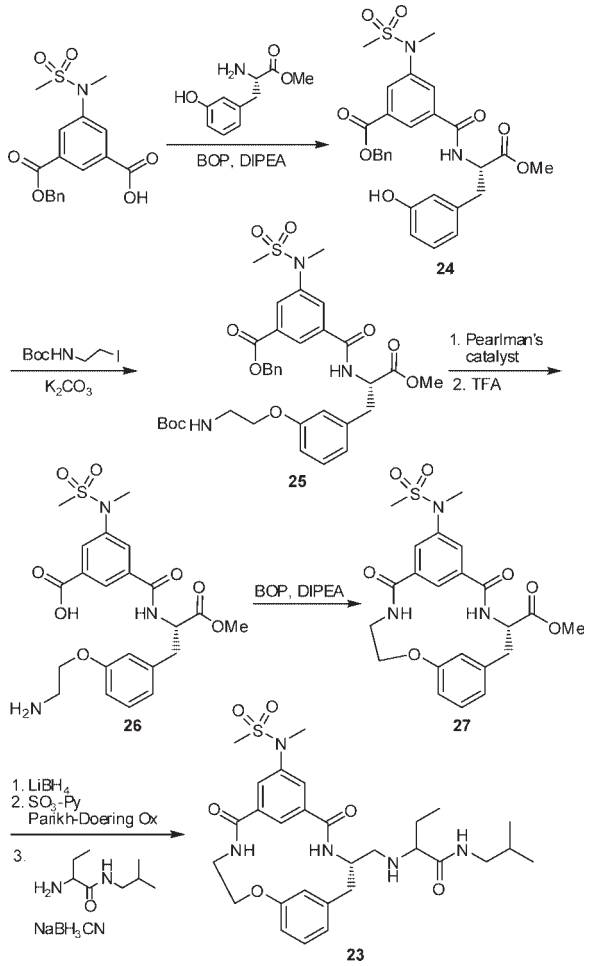
Scheme 5



X-ray crystallographic data of the **12**/BACE1 complex revealed the presence of space in proximity of the P1 and P3 groups. This observation prompted the design of macrocycles that would link these groups in an isophthalamide-based inhibitor. Macrocyclic **23**, which also incorporated a ψ[CH_2NH]-reduced amide bioisosteric group, exhibited high inhibitory potency (IC_{50} = 32 n*M*, assayed as 1:1 diastereomeric mixture); however, in the cell-based assay **23** was significantly less potent (IC_{50} = 5.4 μ*M*) [18]. Compound **23** was synthesized by reaction of 3-(*N*-methyl-methansulfonamido)-5-benzyloxycarbonylbenzoic acid with 3-tyrosine methyl ester in the presence of BOP and DIPEA to produce phenol **24** which was alkylated to **25** with *tert*-butyl (2-iodoethyl)carbamate. Deprotection of the benzyl ester using Pearlman's catalyst, followed by removal of the amino Boc protecting group afforded the corresponding *seco*-acid **26**. This acid underwent macrocyclization to **27** in the presence of BOP reagent and DIPEA. Subsequent two-steps transformation of **27** into the corresponding aldehyde and final reductive amination with (*S*)-2-amino-*N-iso*-butylbutanamide afforded **23** (Scheme 6) [18].

Efforts to improve potency culminated in the synthesis of macrocycle **28** as a single diastereomer. As BACE1 inhibitor, **28** (IC_{50} = 4 n*M*) was 8-fold more potent than **23**, and showed significantly improved

Scheme 6

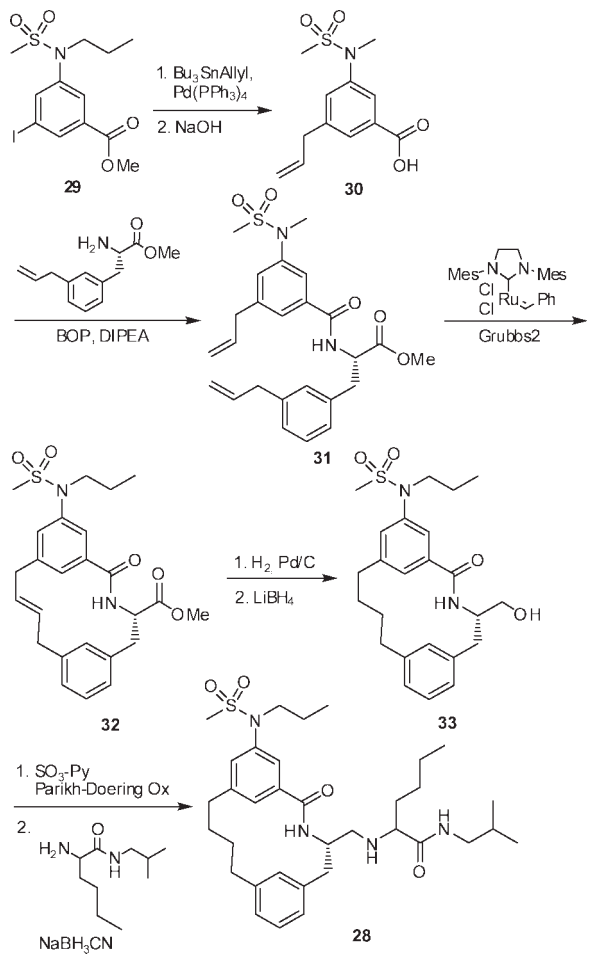


apparent permeability. An elegant synthesis of **28** is depicted in Scheme 7. Allylation of the iodoarene **29** under Stille conditions and subsequent hydrolysis of the methyl ester provided benzoic acid **30**. This acid was coupled with (*S*)-3-allyl phenylalanine to furnish the precursor **31**. Macrocyclization was accomplished through metathesis reaction using second-generation Grubbs catalyst. Hydrogenation of the *E*-olefin **32** and subsequent reduction of the ester using $LiBH_4$ provided alcohol **33**. The latter compound underwent Parikh-Doering oxidation, and finally reductive amination with *N*-isobutyl-L-norleucinamide to afford **28** [18].

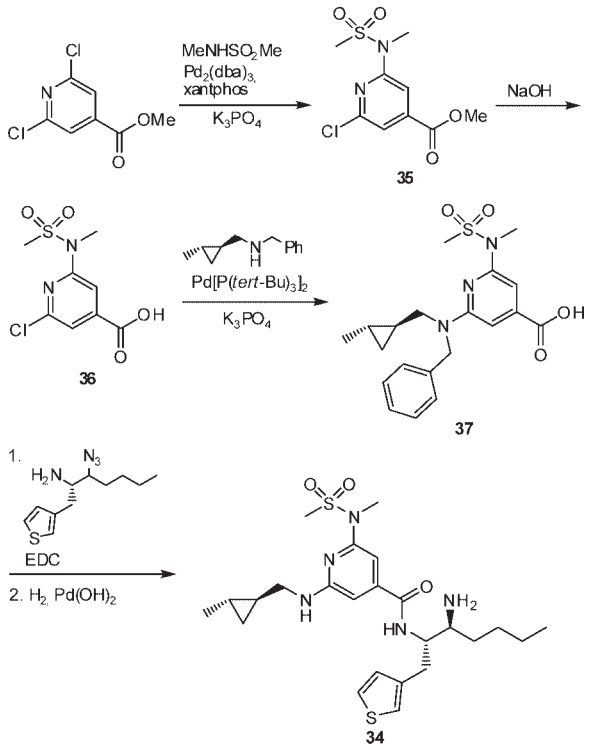
ISONICOTINAMIDES

In an effort to improve CNS penetration and pharmacokinetic stability of BACE1 inhibitors, Merck discovered a series of highly potent and selective isonicotinamides [20–22]. The improvement in potency was due to the incorporation of a *trans*-methyl-cyclopropane P3 that could be responsible for enhanced van der Waals contacts within the context of a 10s-loop down BACE1 conformation. Noncapped compound **34** displayed potent activity in both BACE1 (IC_{50} = 11 n*M*) and sAPP_NF cellular (IC_{50} = 38 n*M*) assays. Compound **34** was synthesized by reaction of methyl 2,6-dichloroisonicotinate with *N*-methyl methylsulfonamide in the presence of tris(dibenzylideneacetone)di-palladium(0) ($Pd_2(dba)_3$) and 9,9-dimethyl-4,5-bis (diphenylphosphino)xanthene (xantphos) to afford the intermediate arylsulfonamide **35**. Amide **35** underwent alkaline hydrolysis to afford the corresponding carboxylic acid **36**. Cross coupling reaction of **36** with *trans*-1-methyl-2-benzylaminomethylcyclopropane in the presence of palladium(0)tributyl-phosphine (Pd/P(*tert*-Bu)$_3$) gave **37**. Aminoacid **37** was coupled with the amino azide in the presence of *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDC), and then hydrogenated with concomitant deprotection to provide **34** (Scheme 8) [20].

Scheme 7



Scheme 8



GUANIDINES

Guanidines were also reported as β-secretase inhibitors [28–38]; among these, indoleacetic acid acyl guanidine **44** inhibited BACE at <0.1 μ*M* concentration [38]. Compound **44** was obtained from 3,5-dichloro-4-aminobenzonitrile which was treated with sodium hexamethyldisilazane (NaHMDS) and acetyl chloride to form **45** which was reduced to benzylamine with lithium aluminum hydride. Amine **46** was treated with *N*-Boc-*S*-methylisothiourea in the presence of trifluoroacetic anhydride (TFAA) and DIPEA to give *tert*-butyl *N*-4-acetamido-3,5-dichlorobenzylcarbamidoyl-carbamate (**47**). This compound was coupled with 6-bromoindole-3-acetic acid in the presence of HATU and DIPEA to give **48**, which after deprotection with TFA afforded **44** (Scheme 10) [38].

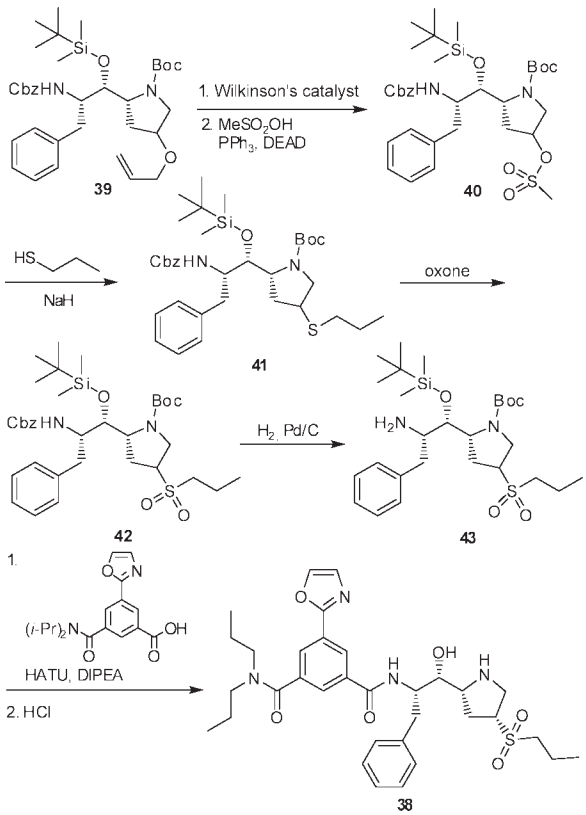
High-throughput screening (HTS) of Wyeth's compound library by means of a FRET assay identified acylguanidines as a new class of BACE1 inhibitors (*i.e.*, **49**: BACE1 IC_{50} = 3.7 μ*M*) [28]. Wyeth synthesized analogues **50–52** which were potent BACE1 inhibitors.

With the exception of **49**, these compounds were generally highly selective for BACE1 over cathepsin and

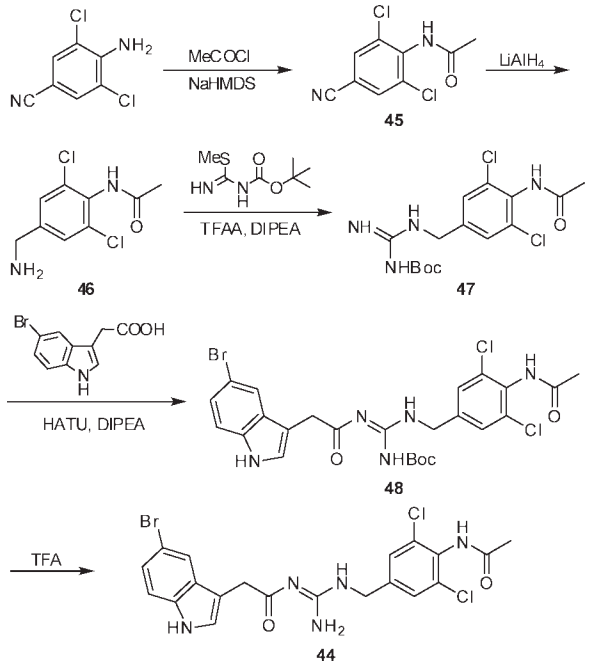
HETEROCYCLIC DERIVATIVES

Bristol-Myers Squibb synthesized heterocyclic derivatives, *i.e.*, pyrrolidine, pyrrolidinone, and azepinone compounds as β-secretase inhibitors [23–27]. Compound **38** inhibited BACE1 at concentration <0.1 μ*M* [26]. Compound **38** was obtained by treatment of the starting pyrrolidine derivative with rhodium tris(triphenylphosphine) chloride (Wilkinson's catalyst) to afford (2*R*,4*R*)-*tert*-butyl 2-((1*S*,2*S*)-2-benzyloxycarbonyl)-1-(*tert*-butyl dimethylsilyloxy)-3-phenylpropyl)-4-hydroxypyrrolidine -1-carboxylate (**39**). This compound was transformed into the corresponding mesylate by reaction with methanesulfonic acid in the presence of triphenylphosphine and diethyl azodicarboxylate, and then treated with sodium propanethiolate to give the 4-propylthiopyrrolidine derivative **41**. After oxidation of sulfur to sulfone with oxone (**42**), the Cbz protecting group was removed by catalytic reduction with hydrogen (Pd/C) to give **43**. Coupling the amino group of **43** with 3-dipropylaminocarbonyl-5-oxazol-2-yl-benzoic acid in the presence of *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU) and DIPEA gave a compound which was deprotected with 4*N* HCl to provide **38** (Scheme 9) [26].

Scheme 9



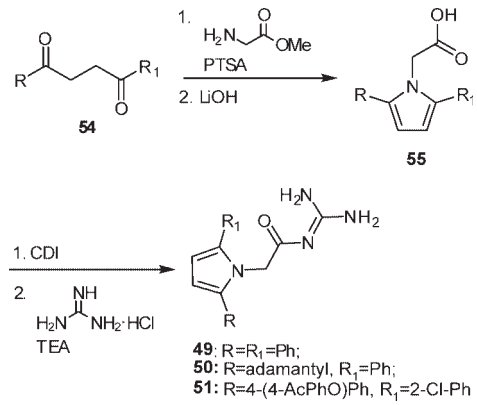
Scheme 10



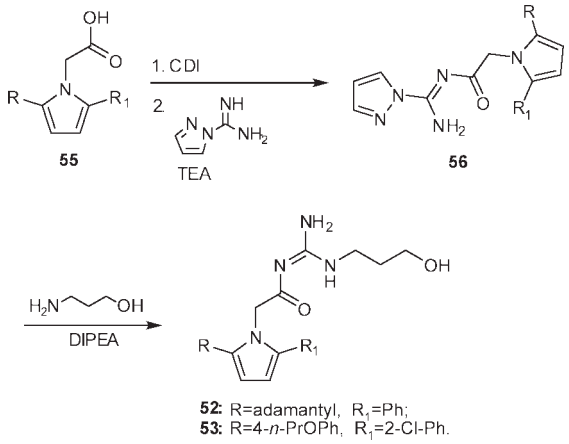
pepsin ($IC_{50} > 50$ μ*M*). Compounds **49–53** were synthesized from the 1,4-diones **54** which were coupled with glycine methyl ester followed by alkaline hydrolysis to give different 2-(2,5-disubstituted-1*H*-pyrrol-1- yl)-acetic acids **55**. Activation of the acid with 1,1′-carbonyldiimidazole (CDI) and subsequent reaction with guanidine hydrochloride gave **49–51** (Scheme 11). The substituted acylguanidines **52** and **53** were prepared by reaction of the corresponding pyrroleacetic acid **55** with 1*H*-pyrazole-1-carboximidamide in the presence of CDI and subsequent displacement of the pyrazole leaving group of **56** with 3-amino-1-propanol (Scheme 12) [28].

Janssen Pharmaceuticals applied for 2-amino-3,4-dihydropyrido[3,4-*d*]pyrimidines which showed K_i values in the submicromolar range of concentration [37].

Scheme 11



Scheme 12



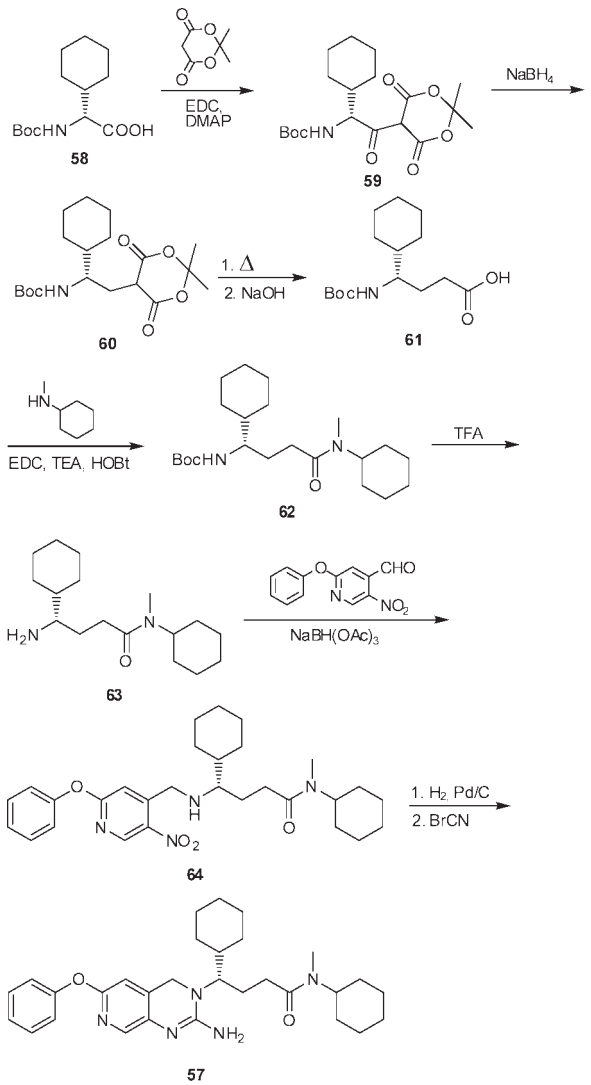
Johnson & Johnson Pharmaceuticals also focused SAR development on 2-amino-3,4-dihydroquinazoline [35]. The *S*-enantiomer **57** inhibited BACE1 with $K_i = 11$ n*M* (as racemate $K_i = 30$ n*M*). This compound exhibited excellent potency in a cellular assay, and additionally, lowered β-amyloid$_{1–40}$ in plasma by 40–70% in rats after per oral administration. Compound **57** was prepared from (*R*)-cyclohexylglycine **58** (>97% e.e.) which was treated with Meldrum's acid in the presence of EDC and 4-(dimethylamino)pyridine (DMAP) to afford **59**. $NaBH_4$ reduction of the ketone functionality provided **60** which underwent thermolysis in boiling toluene to give a lactam which was transformed into acid **61** by alkaline hydrolysis. Compound **61** was coupled with cyclohexylmethylamine in the presence of EDC, TEA, and HOBt to give amide **62**. After acidic cleavage of **62**, reaction of amine **63** with 2-phenoxy-5-nitropyridin-4-carboxaldehyde in the presence of sodium triacetoxyborohydride gave the nitroaminoalkyl intermediate **64** which was reduced to amine with hydrogen in the presence of palladium on carbon, and then cyclized to **57** with cyanogen bromide (Scheme 13) [35].

OTHER COMPOUNDS

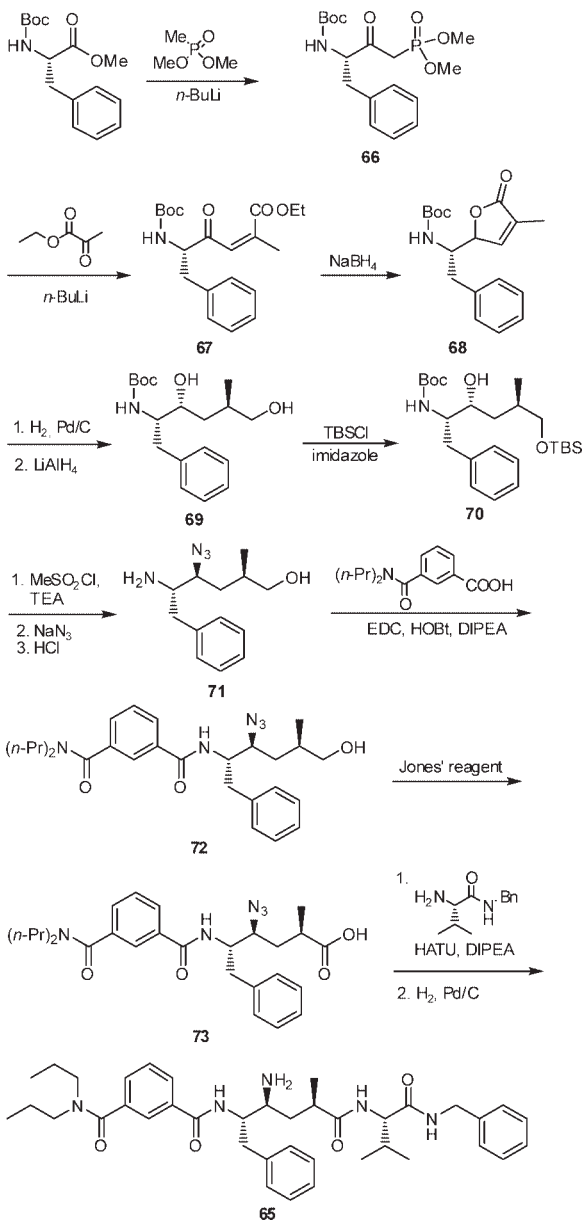
Sunesis Pharmaceuticals considered the primary amine group as a possible bioisostere of the hydroxyl group present in HE-containing BACE1 inhibitors [39]. Replacement of the HE motif with the aminoethylene bioisostere afforded compounds endowed with slightly reduced enzymatic inhibitory activity but distinctly improved cell potency (the *S*-isomer was preferred for activity). Incorporation of a benzyl P_1 substituent (*i.e.*, **65**) resulted in a net increase in inhibitory potency relative to the isobutyl analogues. Compound **65** was synthesized from *N*-Boc-L-phenylalanine methyl ester which was treated with dimethyl methylphosphonate in the

presence of *n*-butyl lithium to provide the corresponding phosphonate **66**. Reaction of crude **66** with ethyl pyruvate and *n*-butyl lithium gave ethyl (5*S*,2*Z*)-2-methyl-[5-(*tert*-butoxycarbonyl)amino]-4-oxo-6-phenyl-hex-2-enonate (**67**). Sodium borohydride reduction of **67** with concomitant intramolecular cyclization gave 2,5-dihydrofuran-2-one **68**. This compound was reduced to tetrahydrofuran-2-one with hydrogen in the presence of palladium over carbon, and then with lithium aluminum hydride to furnish (2*S*,3*R*,5*R*)-2-*tert*-butoxycarbonylamino-1-phenyl-5-methylhexan-3,6-diol (**69**). The diol was subsequently treated with *tert*-butyl-dimethylsilyl chloride (TBSCl) and imidazole (**70**), and then with methanesulfonyl chloride and triethylamine to furnish the corresponding methanesulfonate. Introduction of the azido group by displacing the methanesulfonate with sodium azide, and cleavage of both protecting groups with hydrochloric acid resulted in aminoalcohol **71** which was coupled with *N*,*N*-dipropyl isophthalamic acid in the presence of ECD, HOBt and DIPEA to form **72**. Oxidation of **72** to acid **73** with Jones' reagent (chromium trioxide and sulfuric acid) and further elaboration as above reported provided **65** (Scheme 14) [39].

Scheme 13



Scheme 14



CONCLUSION

Three-dimensional structural information for BACE1 in complex with a variety of inhibitors has led to great

strides in the development of new effective agents for the treatment of AD. Both academia and pharmaceutical companies focused their efforts to develop new synthetic strategies for the synthesis of potent BACE1 inhibitors, such as isophthalamides, isonicotinamides, heterocycles and other derivatives, which showed improved drug properties when compared with first generation peptidic inhibitors. These synthetic routes may serve as useful tools for medicinal chemists in discovering new AD therapeutics.

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