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Invited Review

Approaches to Carbocyclic Sialidase Inhibitors

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Summary. The crucial role played by carbohydrates in many physiological processes has made this class of compounds an interesting target for drug design. Consequently mimicking carbohydrates has been one of the most rapidly growing fields in synthetic organic chemistry in recent years, and particularly intense focus has been devoted to sialic acids and sialic acid metabolizing enzymes, including sialidases. Inhibition of the latter enzyme from influenza virus can be regarded as one of the most successful examples of structure-based drug design and high affinity inhibitors based on neuraminic acid have been developed. There is an ongoing search for inhibitors with improved physicochemical properties and among them, carbocyclic systems, where the ring oxygen of the carbohydrate is replaced by carbon, have become the center of interest. This review intends to give a brief overview over the structures and synthetic approaches which surfaced in the last decade.

Keywords. Sialidase inhibitors; Sialidase; Carbocycles; Influenza virus neuraminidase.

Introduction

Sialic acids are a group of about fifty derivatives [1] of the nine-carbon sugar *KDN* (2-keto-3-deoxy-D-*glycero*-D-*galacto*-nononic acid), the most well-known member of which is *N*-acetylneuraminic acid (*Neu5Ac*) (**1**) [2–4]. They are located mainly at the non-reducing terminus of an oligosaccharide chain, α-ketosidically linked commonly to galactose, *N*-acetylgalactosamine or another sialic acid of a given glycoconjugate, which itself is part of the outer cell membrane. Examples for the wide variety of functions played by sialic acid containing epitopes are participation in cellular recognition processes, influence on biophysical properties of a glycoconjugate or a cell, or protection of a cell from pathogen attachment or

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degradation. The ability of *N*-acetylneuraminic acid to act as receptor or substrate for pathogenic microorganisms like viruses or bacteria has led to an increased interest in sialidases, a class of enzymes that catalyze the cleavage of terminal residues from the glycan chain, thus modulating the sialic acid profile of the cell during infection processes [5, 6]. The significance of sialidases from several bacteria to pathogenesis has been shown [7], but the major target of drug design in sialidase inhibition has been the neuraminidase from influenza virus, an enzyme that facilitates the release of viral progeny from the infected cell by cleaving sialic acids from the host cell surface [8–10].

The mechanism of sialoside hydrolysis has been proposed to run through a flattened sialosyl-cation intermediate which is then trapped by water, a transition-state thought to be mimicked by *Neu5Ac2en* **2**, a classical sialidase inhibitor with an inhibition constant K_i in the low micromolar range (Fig. 1) [11]. Based on this lead structure, zanamivir (**3**) a highly potent and selective inhibitor of the sialidases from influenza virus A and B has been developed and is currently marketed under the tradename Relenza^{TM} (Fig. 2) [12, 13]. Shortcomings of **3** regarding the bioavailability of this highly polar molecule, have led to many successful attempts to replace the dihydropyran ring by the less polar carbocyclic cyclohexene ring [9, 14]. Oseltamivir (**4**), an equally potent inhibitor with better bioavailability which is administered as the ethyl ester prodrug, has meanwhile entered the market as Tamiflu^{TM} (Fig. 2A) [15, 16].

For this reason, interest to mimic neuraminic acid by carbocycles, be it as a transition-state analogue or a substrate analogue has greatly increased recently, and it seemed appropriate to prepare a review, which describes the synthetic effort towards sialidase inhibition based on carbocycles preceding, accompanying and following the development of **4**. There is, however, a constant input of information on inhibition of sialidases from the side of heterocyclic inhibitors [14], the chemistry of which cannot be included here. Therefore, whenever necessary, lead structures such as **2** will be mentioned (Fig. 2A).

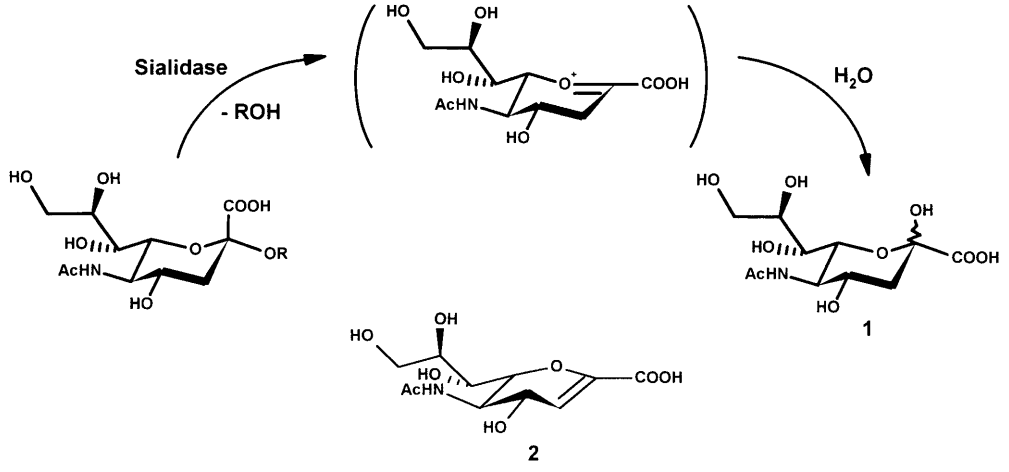

Fig. 1. The sialidase reaction with α-ketosidically linked *N*-acetylneuraminic acid as substrate, a proposed oxocarbenium ion intermediate which adds water to give *N*-acetylneuraminic acid (**1**). The transition-state analogue *Neu5Ac2en* **2** is thought to successfully mimic the oxocarbenium ion

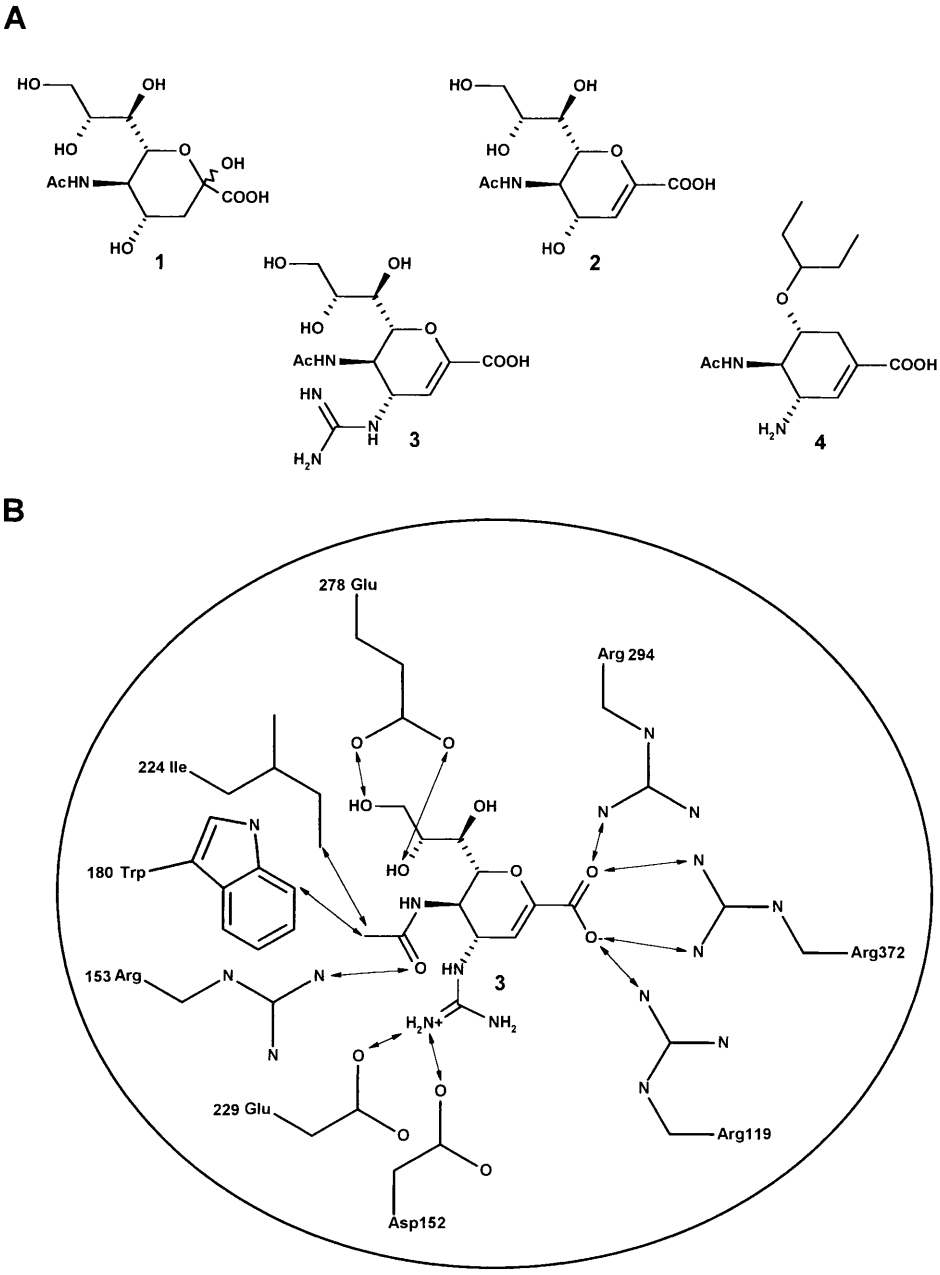

Fig. 2. **A**: Structures of *Neu5Ac* **1**, lead compound *Neu5Ac2en* **2** and the commercially available anti-influenza drugs zanamivir (**3**) and oseltamivir (**4**). **B**: Schematic representation of zanamivir (**3**) bound to the active site of influenza neuraminidase. Arrows represent interactions between functional groups of the inhibitor and amino acid side chains

Carbocyclic Sialidase Inhibitors

Aromatic systems

The emerging knowledge about the promising effects of neuraminidase inhibition in treatment of influenza infections initiated a variety of attempts to mimic

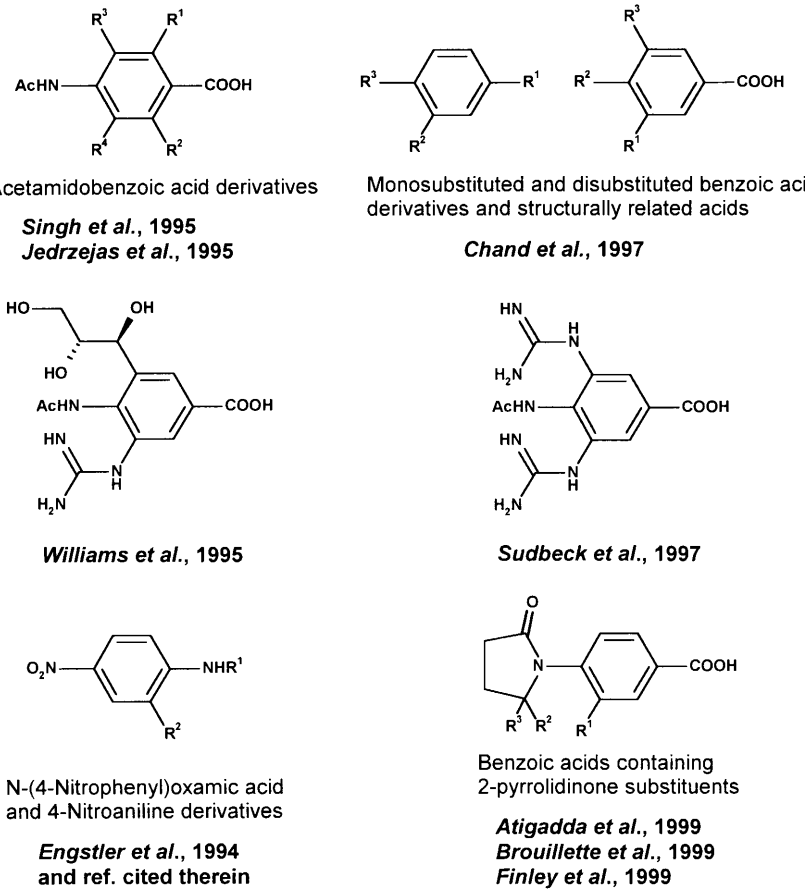

Fig. 3. Aromatic sialidase inhibitors (R^1, R^2, R^3 indicate different substituents in the respective study)

N-acetylneuraminic acid by derivatives of benzoic acid (Fig. 3) [17–25]. Most of the target molecules contain an acetamide or at least an amide in the 4-position of the ring thus simulating two important recognition motifs of sialidases: the acetamide and the acidic group which is negatively charged under physiological conditions, in a spatial arrangement resembling *Neu5Ac* [26] or *Neu5Ac2en* [27–29].

The major intention behind the use of the benzene template was, of course, to facilitate the chemistry of the inhibitors with a concomitant reduction of costs, and provide a more hydrophobic core which could be favourable regarding bioavailability. Without exception, all aromatic neuraminidase inhibitors shown in Fig. 3 are synthesized from aromatic precursors by standard chemical methods and most of the studies have been accompanied by X-ray crystallography and modeling [17]. In the studies of *Singh et al.* [18] and *Jedrzejas et al.* [19] substitutions at the benzene ring were carried out at all possible positions and an inhibitory activity of 1–10 μM (IC_{50}) [18] (later 2.5 μM [20]) towards influenza virus neuraminidase was reached with a guanidino group as R^3 (R^1, R^2, $R^4 = H$). Binding to the active site was demonstrated but the most promising compound was inactive in a mouse

model [20]. These investigations were extended by *Chand et al*. [20] by synthesizing a variety of monosubstituted and disubstituted benzoic acid derivatives as well as derivatives of the related phenylsulfonic acid, phenylsulfinic acid, and phenylphosphonic acid but the inhibitory potency was not improved. *Williams et al*. [21] identified the same benzoic acid derivative as inhibitor (IC_{50}: 8 μM) and provided evidence that attachment of the glycerol side chain at C5 hampers binding of the benzoic acid derivatives already containing a guanidino group at C3. Parallel studies by X-ray crystallography suggested the di-guanidino derivative to be promising but it turned out not to be (IC_{50}: 70 μM, *Sudbeck et al*. [22]) (Fig. 3).

Later studies included the knowledge about the potency of GS 4071 **4** in inhibition of the influenza neuraminidase and its structural features. For example, activity was retained when the acetamide moiety at C4 of the 3-guanidino benzoic acid was replaced by optimized cyclic 2-pyrrolidinone substituents [23, 24] (Fig. 3). Inhibition was improved to the submicromolar range [25] when the basic guanidine substituent was replaced by another basic but more hydrophobic 3-pentylamine substituent (*Finley et al*., 1999 [25] and *Atigatta et al*., 1999 [24], $R^1 = NHCH(CH_2CH_3)_2$, $R^2 = R^3 = CH_2OH$) (Fig. 3). However, the inhibition was considerably lower for influenza B neuraminidase than for the influenza A enzyme and the interest in benzoic acids somehow ceased compared to the olefinic and saturated rings although new derivatives are still reported [30]. Among the aromatic sialidase inhibitors the study of *Engstler et al*. [31] is a special case as it was directed towards bacterial sialidases rather than viral sialidases (Fig. 3). *N*-(4-Nitrophenyl)-oxamic acids ($R^1 = COCO_2H$) and 4-Nitroanilines ($R^1 = H$) were synthesized based on previous reports about the inhibition of the enzymes from influenza virus [32] and *Vibrio cholerae* [33] and mainly non-competitive inhibition was found [31].

Cyclohexene-based systems

The tremendous interest in synthesizing cyclohexene-based sialidase inhibitors was mainly ignited by the possibility to mimic *Neu5Ac2en* and its improved analogue zanamivir, while at the same time overcoming the pharmacological shortcomings of the latter compounds regarding bioavailability, a task which could not be accomplished with heterocyclic analogues of *Neu5Ac2en* **2** such as its phospha [34] or thia analogue [35] (Fig. 4).

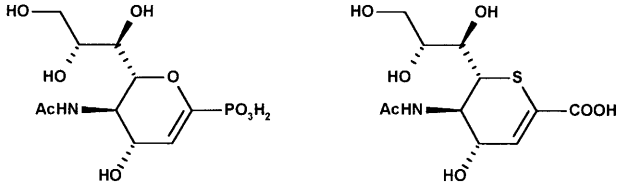

Fig. 4. Heterocyclic analogues of lead compound *Neu5Ac2en* **2**

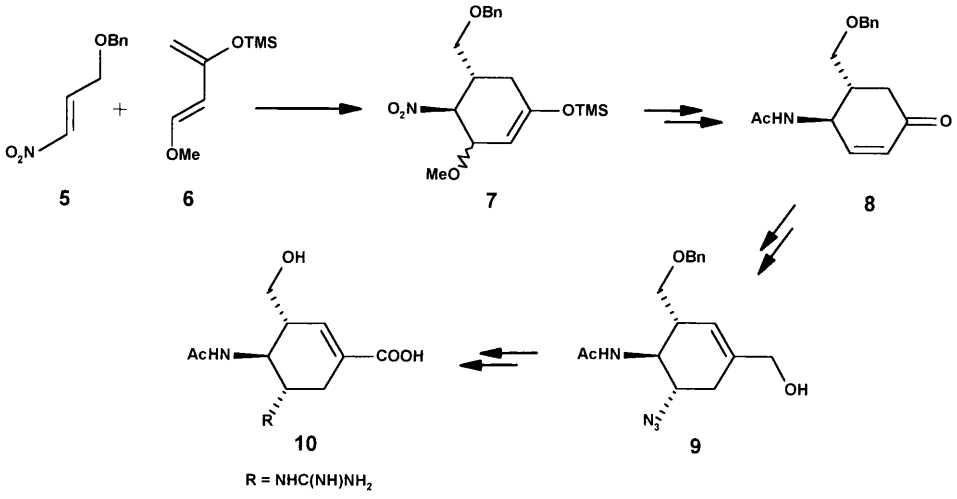

Fig. 5. Synthesis of a carbocyclic analogue of zanamivir with truncated side-chain by *Chandler et al.*, 1995 [36]

Chandler et al. [36] synthesized and investigated carbocyclic analogues of zanamivir starting with a *Diels-Alder* reaction of nitro olefine **5** and *Danishefsky*'s diene **6** to give carbocyclus **7** (Fig. 5). Conversion into the enone **8** followed by C-homologation and introduction of a second nitrogen led to the alcohol **9** which was transformed in few steps to slightly simplified zanamivir analogue **10** (Fig. 5).

Side chain truncation was accepted to facilitate synthesis and significant retention of activity was found, although the guanidino group was not advantageous over amino such as in zanamivir [36]. *Kim et al.* [15] synthesized oseltamivir GS4104 **4** (prodrug: ethyl ester) and derivatives including double bond regioisomers, and obtained inhibition of influenza neuraminidase A and B comparable to zanamivir (Fig. 6).

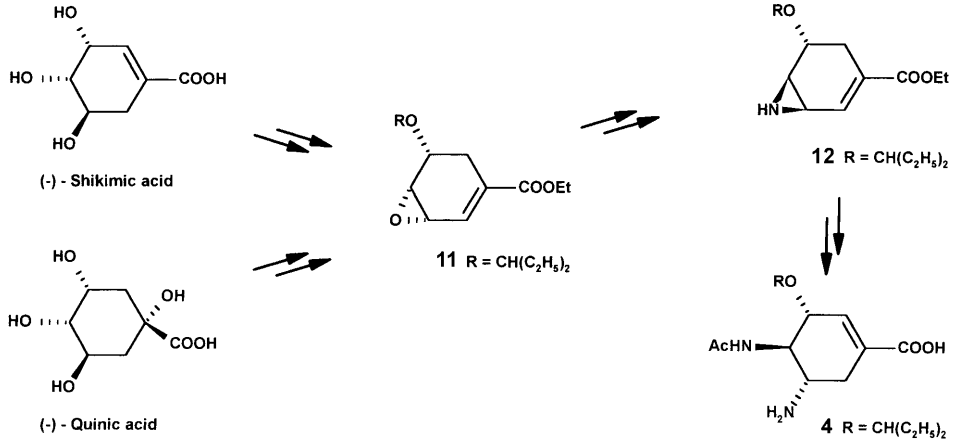

Fig. 6. Synthetic strategy towards GS4104 by *Kim et al.*, 1997 [15]; *Rohloff et al.*, 1998 [37]; *Karpf* and *Trussardi*, 2001 [38]

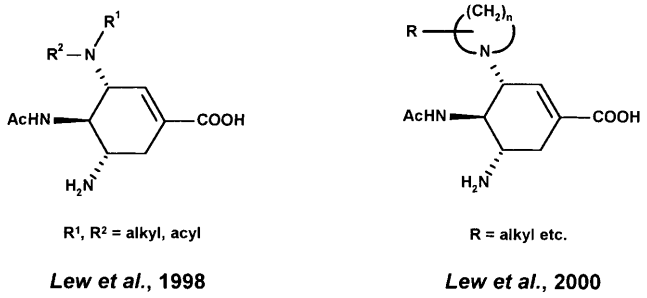

Fig. 7. GS 4104 analogues modified at C-3 synthesized by *Lew et al*., 1998 [40] and 2000 [41]

Pharmacological advantages were considerable and the compound is meanwhile marketed as its ethyl ester prodrug Tamiflu. The first synthesis of GS 4104 [15], its improved versions [37, 38] and syntheses of analogues [39] utilized the chiral pool and started from (-)-quinic acid or (-)-shikimic acid which were converted into epoxides of type **11** to allow introduction of two nitrogens via aziridines **12** and subsequent ring opening with azide [15, 37] or amines [38] (Fig. 6).

Two additional studies by *Lew et al*. [40, 41] (Fig. 7) sought to further improve activity by introducing alkylamine- or acylamide- [40] as well as cyclic amine substituents [39]. Several compounds, for instance a piperidine substituent at C3 produced excellent inhibition, however, no improvement could be reached compared to GS 4104 [39].

Important information regarding the double bond orientation was provided by *Vorwerk et al*. [42] by synthesizing and investigating the carbocyclic analogue **19** of *Neu5Ac2en*, and its isomer **18** (Fig. 8).

The approach based essentially on earlier chemical syntheses and, last but not least, on the natural biosynthesis of neuraminic acid. *N*-Acetyl-D-mannosamine was selectively protected to give **13**, the carbon chain was elongated in an indium-mediated reaction with bromo methacrylate and the branched 9-carbon sugar **14** was converted into ketone **15**. Radical cyclization furnished cyclohexanes of type **16** and, after elimination of water, the cyclohexene **17**. Isomerization to the corresponding *Neu5Ac2en* analogues failed and consequently the double bonds of **18** and **19** had to be created by hydrogenation, introduction of a leaving group and elimination (Fig. 8). Inhibition of influenza-A neuraminidase was 40 fold increased (20 μM, IC_{50}) with the Carba-*Neu5Ac2en* **18** having the double bond in the GS 4104 orientation and interestingly, comparatively strong inhibition of the neuraminidase from *Salmonella typhimurium* was found [42].

Another *Diels-Alder* strategy followed by *Kerrigan et al*. provided access to compounds of type **28** and **29**, in racemic form [43] (Fig. 9).

Cycloaddition of nitro-acrylamide **20** and diene **21** gave the enol ether **22** as the major product, which was readily converted into the corresponding ketone. Ethoxyvinylation and ozonolysis gave the mixture of α-hydroxy esters **23**. Finally, elimination and hydrolysis yielded access to cyclohexenecarboxylic acids **24** and **25** as racemates [43]. A similar strategy starting from the *Diels-Alder* pair nitroethene **26** and diene **27** provided the racemic mixtures of cyclohexenecarboxylic acids **28** and

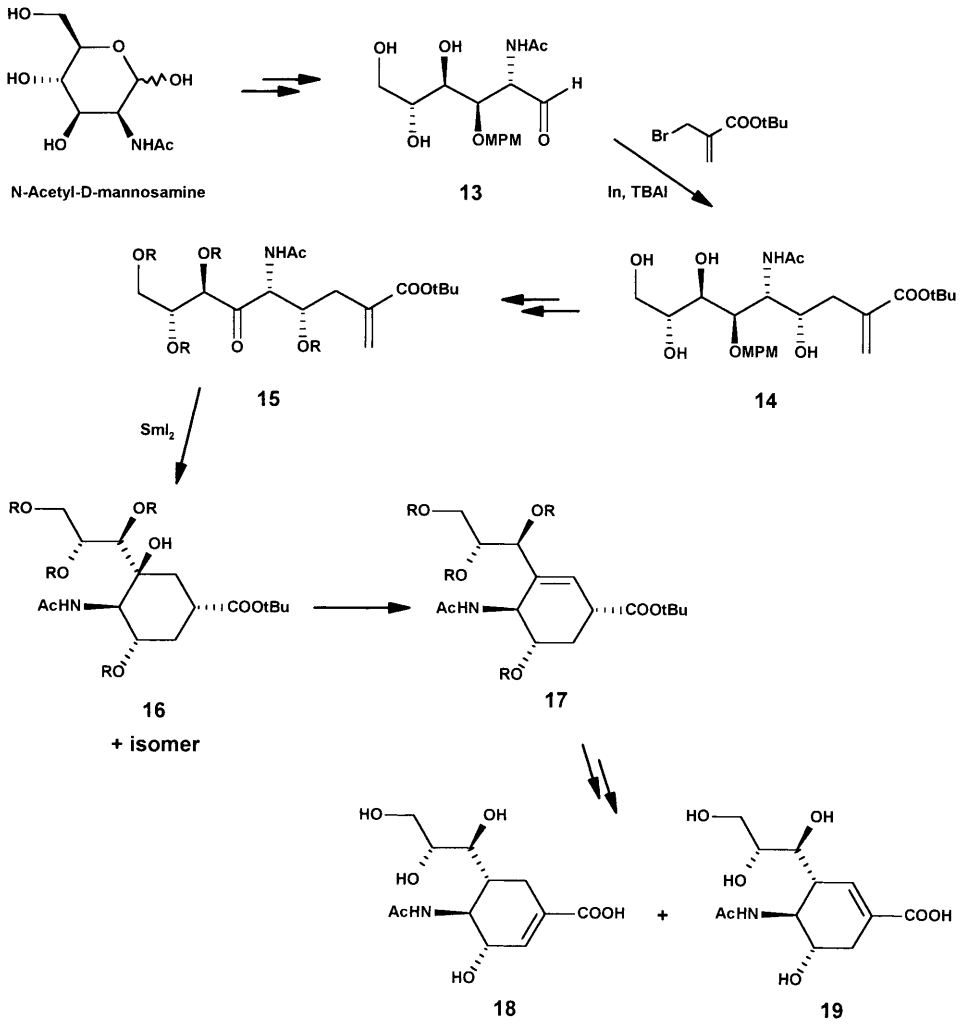

Fig. 8. Synthesis of *Carba-Neu5Ac2en* by *Vorwerk* and *Vasella*, 1998 (MPM = methoxyphenylmethyl, R = *MOM* = methoxymethyl) [42]

29 [44] (Fig. 9). All compounds exhibited some selectivity towards the influenza A enzyme with IC_{50} values as low as 17 nM for **28**. The results obtained by *Vasella et al.* with analogues of neuraminic acid [45] and *Neu5Ac2en* [32] containing a phosphonate moiety instead of a carboxylate group inspired us to develop a synthesis which gives access to phosphonate containing analogues of GS 4104 (*Streicher et al.* [46]) (Fig. 10).

Phosphonate monoesters retain a negative charge under physiological conditions and thus our systems allow modifications in proximity to the negative charge such as an aglycon mimic. We started from D- and L-xylose respectively, which we converted into the corresponding enantiomeric 3-Azido-1.2-*O*-isopropylidene-xylofuransyl-5-triflates **30** and **34** according to well established procedures [47] (Fig. 10). Substitution of the triflate by tetraethyl methylenediphosphonate anions [48–50] provided 6-carbon sugars **31** and **35** which can be cyclized to the D- and L-xylo configured azido-cyclohexenephosphonates **32** and **36** [45, 51] (Fig. 10). Selective modifications combined with azide reduction, *N*-acylation and ester

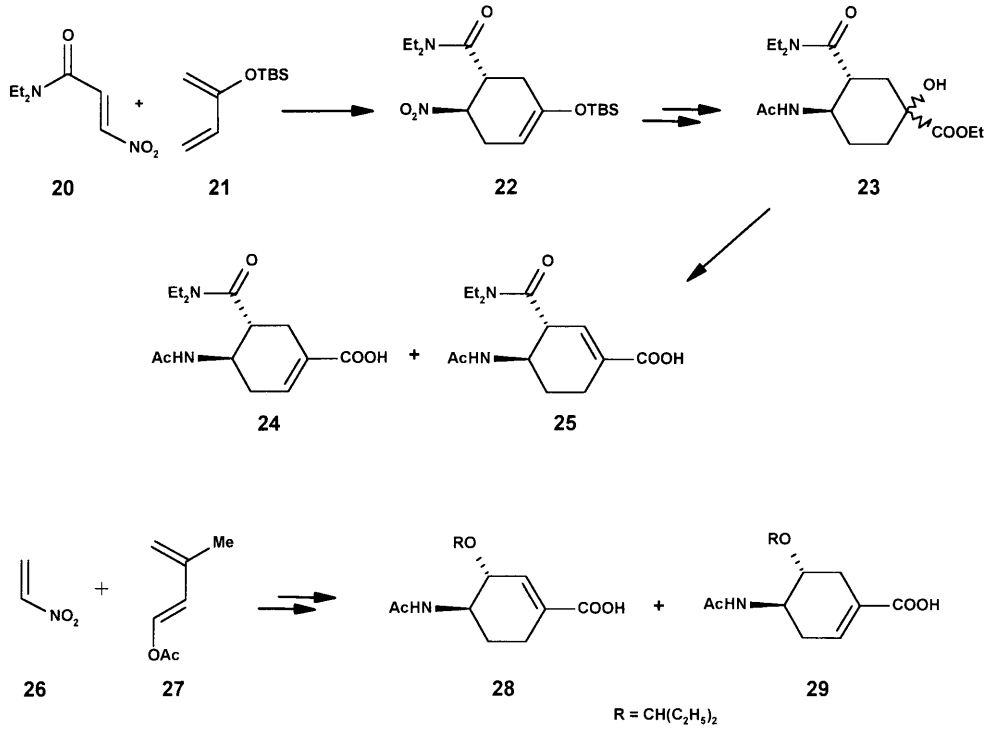

Fig. 9. *Diels-Alder* approach to sialidase inhibitors by *Kerrigan et al.*, 2001 (TBS = ^{t}butyldimethylsilyl) [43, 44]

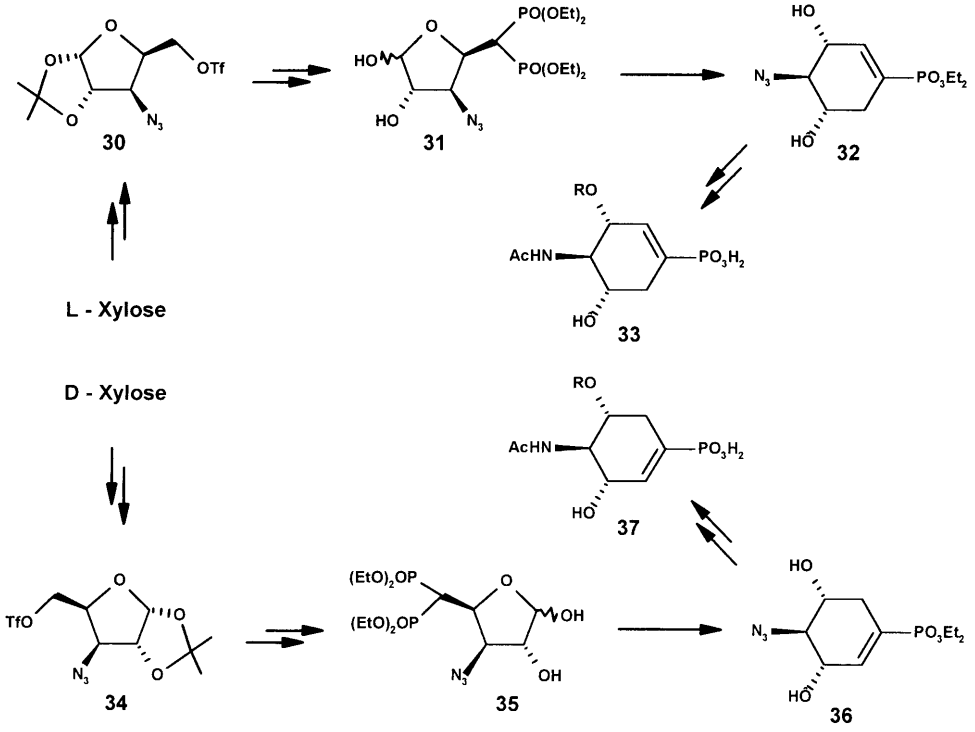

Fig. 10. Synthesis of isomeric cyclohexenephosphonates *via* mirrored synthesis form enantiomeric xylofuranoses by *Streicher et al.*, 2001 [46], 2002 (R = H, CH–CH_2CH_2) [51]

cleavage provide access to a virtually unlimited number of inhibitors such as the phosphonic acids **33** and **37** (Fig. 10). We tested a selection of compounds and found moderate inhibition of three bacterial sialidases [51].

The number of screened analogues of GS 4104 was recently catapulted into a new dimension by the combinatorial approach of *Hochgürtel et al.* [52] who created a sortiment of neuraminidase inhibitors under the selection pressure of the target enzyme itself (Fig. 11).

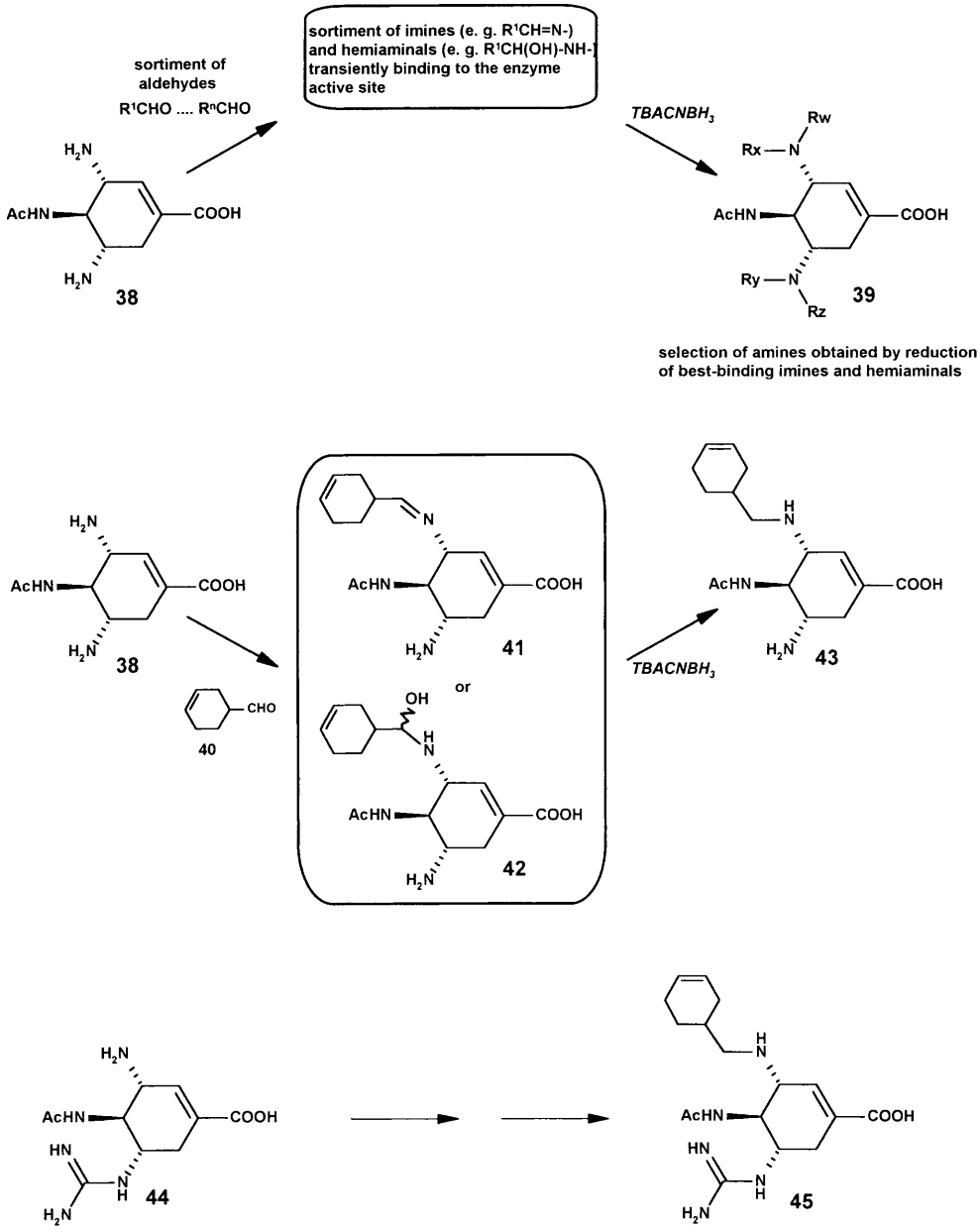

Fig. 11. High affinity inhibitors of neuraminidase by screening of *in vitro* virtual combinatorial sortiments, *Hochgürtel et al.*, 2002 ($TBACNBH_3$ = tetrabutylammoniumcyanoborohydride) [52]

Based on the structure of GS 4104 known to contain all necessary functionalities for high affinity inhibition of influenza virus neuraminidase, a GS 4104 analogous scaffold **38**, having two amino groups at positions 3 and 5, was synthesized. The scaffold was reacted with a sortiment of n aldehydes (10 fold excess) in the presence of an equimolar amount of neuraminidase active sites and the variety of possible imines (n for reaction of one amine per scaffold molecule, n^2 for both amines) and hemiaminals ($2n$ for one amine, $4n^2$ for both) was reduced, after brief incubation, to the corresponding amines with tetrabutylammonium cyanoborohydride (Fig. 11). The equilibrium of this dynamic sortiment of transiently formed imines and hemiaminals is shifted towards the compounds with highest affinity for the target the formation of which is thus amplified at least by the factor 100 [52]. The conditions were optimized in such a way that only the amplified structures could be detected, the resulting amines were identified with HPLC-MS and then chemically resynthesized. This "*in vitro* virtual screening" [53] selected strongly binding imines like **41** and hemiaminals like **42**, formed by the reaction of scaffold **38** with aldehyde **40** (Fig. 11). The amines obtained after reduction were, however, sufficiently related to allow the identification of several high affinity inhibitors such as **43** (1.64 μM). This meant a 20 fold enhancement of inhibition compared to the scaffold molecule **38**, a factor which was confirmed even when an improved scaffold molecule **44** (352 nM) was used as starting point, to after screening, give **45** (16 nM) (Fig. 11) [52].

Saturated systems

Saturated carbocylic neuraminic acid mimics synthesized for the purposes of neuraminidase inhibition can roughly be divided into two groups, the first of which is displayed in Fig. 12: the first group contains a six-membered ring scaffold and

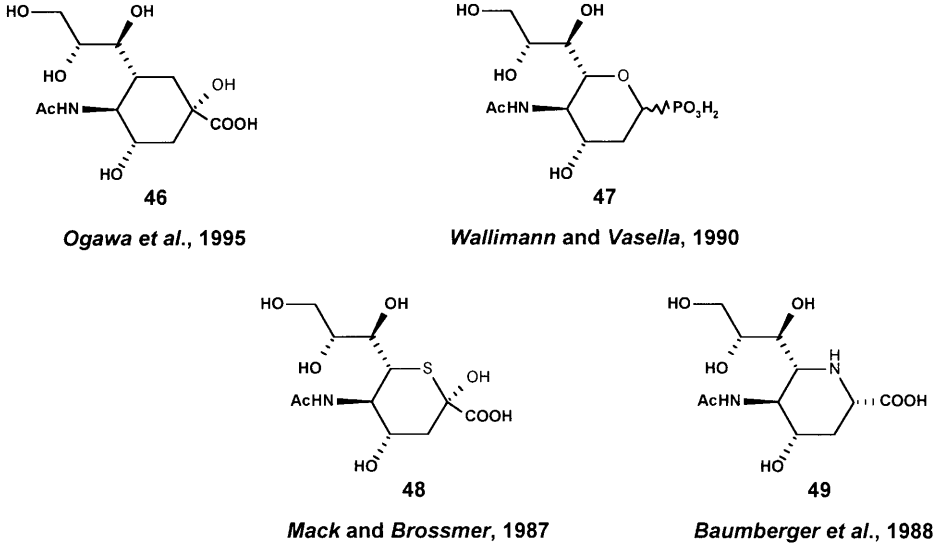

Fig. 12. Sialidase inhibitors based on saturated six-membered ring scaffolds, synthesized by *Ogawa et al.* [54], *Wallimann* and *Vasella* [45], *Mack* and *Brossmer* [35], *Baumberger et al.* [55]

mimics the chair conformation of neuraminic acid itself, *e.g.* **46** [54], like it has been done before with phosphonate containing analogues like **47** [45], with 6-thia neuraminic acid **48** [35], and with the 6-amino-analogue **49** [55] (Fig. 12).

Ogawa et al. [54] prepared the 6a-Carba-neuraminic acid **46** in a multistep synthesis starting from **51**, readily available from the endo adduct **50** of the *Diels-Alder* reaction of acrylic acid and furan to provide the carbocyclic scaffold. Deprotection and oxidation to the ketone allowed *Horner-Emmons* homologation to give a mixture of alkenes **52**, the (*Z*)-isomer of which was reduced to the corresponding alcohols, protected and then *cis*-hydroxylated to give a separable mixture of diols including **53**. Protective group modifications followed by oxidation gave the ketone **54** which was reacted with vinylmagnesium bromide to yield the epimeric mixture of tertiary alcohols **55**. Protection, ozonolysis, and oxidation followed by activation of ring carbon 4 allowed introduction of azide to give **56** and the molecule could be converted in few remaining steps into protected 6a-*Carba-Neu5Ac* **46** (Fig. 13). The deprotected acid showed weak inhibition against the sialidase from *Streptococcus sp.* [54].

The interesting inhibitory potency of furanose derivative like **57** [56] (Fig. 14) provoked interest in a second group of saturated systems: inhibitors containing a five-membered ring. Besides pyrrolidine derivatives (*e.g.* **58**), which have been subject to combinatorial approaches [57], compound BCX-1812 (**59**) [58],

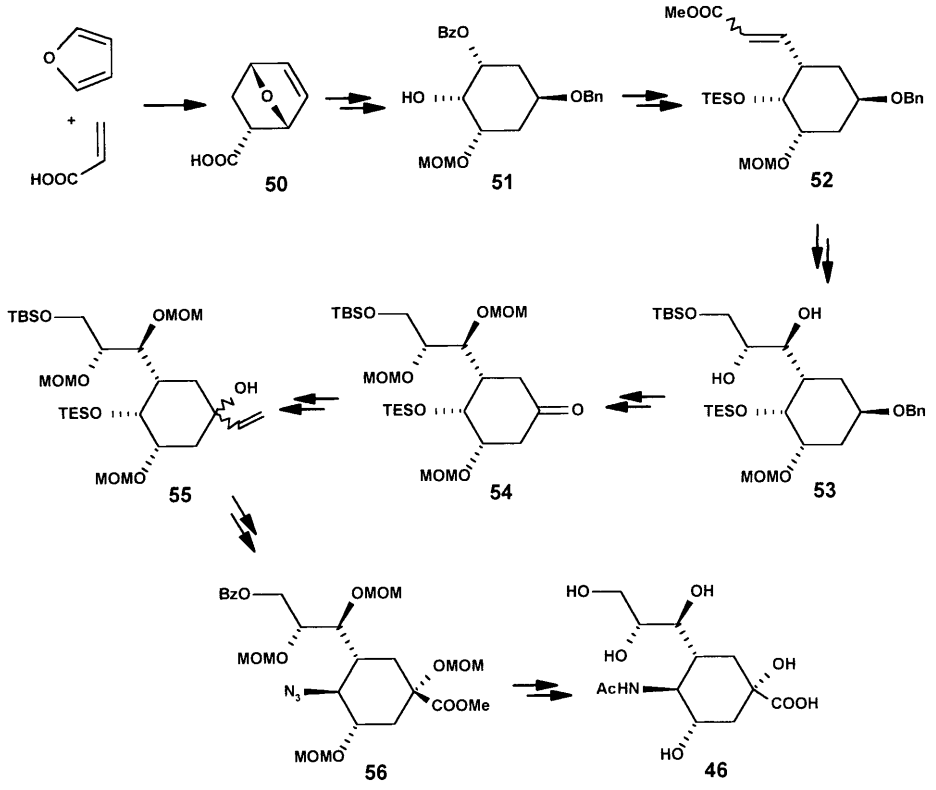

Fig. 13. Multistep synthesis of Carba-neuraminic acid by *Ogawa et al.*, 1995 (TES = triethylsilyl) [54]

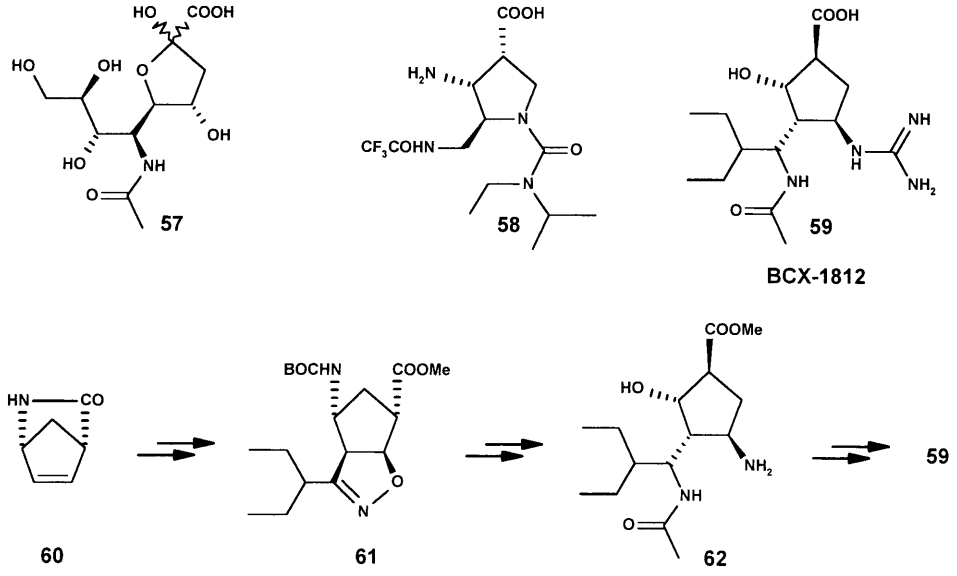

Fig. 14. Synthesis of highly potent inhibitor BCX-1812 by *Babu et al.*, 2000 [58] and heterocyclic lead compounds

a substituted cyclopentane ring, has the prospect of becoming the third commercially available neuraminidase inhibitor to treat influenza [9, 58, 59].

The structure was optimized in several cycles of synthesis and screening of complex mixtures, both enantiomeric and diastereomeric, by crystallography [58]. The final compound was synthesized by *Babu et al.* [58] starting from the commercially available lactam **60**, which was methanolyzed and *N*-protected followed by cycloaddition of 2-ethyl-butyronitrile oxide to give the isoxazoline **61** (Fig. 14). After reduction and *N*-deprotection the amine was converted into the guanidino group and the ester was cleaved to give target compound **59** (BCX-1812). The potency was shown to be equal or better than zanamivir (**3**) and oseltamivir (**4**) and with equally good bioavailability compared to the latter and similar behaviour in influenza treatment [58, 59].

Carbocyclic Sialylmimetics in the Inhibition of Lectins and Sialyltransferases

Not only have sialidases been targeted by carbocyclic analogues of neuraminic acids, there are two more classes of protein which have attracted increased attention in recent years: sialyltransferases and sialic acid binding lectins. Indeed, the neuraminic acid mimicking moieties in some of the most potent sialyltransferase inhibitors synthesized are carbocyclic and could, at least in principle, inhibit sialidases [60–62] (for a review see Ref. [63]). The recognition of sialosides as natural substrates by sialidases however, cannot be compared to the recognition of the natural donor substrate *CMP-Neu5Ac* by sialyltransferases, a recognition which utilizes mainly the *CMP*-part of the molecule. This fact is also reflected by the inhibitory potency of cytidinediphosphate (*CDP*), which lacks a sialic acid mimic [64].

Consequently, some inhibitors of the latter enzymes contain highly degenerate sialylmimetics, which provide additional polar or hydrophobic interactions, thus contributing effectively to affinity but do not fit into sialidase inhibitors reviewed here.

The same in the case in some lectin ligands synthesized to inhibit binding between a distinct lectin and its natural sialic acid ligand. For example, some of the best inhibitors of *E*-selectin designed to block *E*-selectin-sialyl *Lewis x* binding are cyclohexyllactic acid [65] or phenyllactic acid [66] residues. As such, they are carbocycles mimicking neuraminic acid but cannot be regarded as useful in sialidase inhibition and therefore are included elsewhere [14, 67–69].

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