Phosphinic acids: current status and potential for drug discovery

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Phosphinic acid derivatives exhibit diverse biological activities and a high degree of structural diversity, rendering them a versatile tool in the development of new medicinal agents. Pronounced recent progress, coupled with previous research findings, highlights the impact of this moiety in medicinal chemistry. Here, we highlight the most important breakthroughs made with phosphinates with a range of pharmacological activities against many diseases, including anti-inflammatory, anti-Alzheimer, antiparasitic, antihepatitis, antiproliferative, anti-influenza, anti-HIV, antimalarial, and antimicrobial agents. We also provide the current status of the corresponding prodrugs, drug-delivery systems, and drug applications of phosphinic acids in the clinical stage

Introduction and scope

The phosphinic acid chemistry story began with the pioneering work of August Wilhelm Hofmann in 1855 on methylphosphinic acid [1]. The broad biological applications of phosphinic acids are driven by their four combined features: tetrahedral transition state resemblance; ability to form electrostatic interactions;, hydrogen bonds; and the capacity to coordinate with diverse metal ions [2]. These unique features, combined with the ability to incorporate side chains of amino acids provided by these privileged structures, constitute a firm basis for the discovery of potent and selective bioactive molecules [3]. Such an approach has been successfully applied to design potent inhibitors of enzymes of medical interest [4,5]. Additionally, these classes of compound have shown a promising and expanding platform for agrochemicals and industrial applications, as well as ligands for transition metal complexes [6]. The steady growth in volume and diversity of this class of compounds in many areas of science has stimulated chemists to direct increased efforts to the development of innovative synthetic methods for their preparation, with particular attention paid to stereoselective synthesis [7].

On searching 'phosphinic acid' as a keyword in any chemistry database; a countless amount of literature references; journal articles; books; and patents appear as proof of its importance in chemical research; thus; it is impractical to survey the literature of phosphinic acids without narrowing the search to specific perspectives. In this respect; several excellent reviews on numerous aspects of the synthesis and applications of phosphinic acids have been published [2–7]. These reviews were devoted to physical; organic; and natural product perspectives; synthetic procedures; including asymmetric synthesis; and their activities as zinc metalloproteinase inhibitors [2–7]. Therefore; a more up-to-date and inclusive survey is required. In continuation of our research in exploring the utilization of phosphinic acids as a structural motif in medicinal chemistry [7]; here we provide a panoramic view of the multiple applications of phosphonic acids that exhibit biological activity alongside appropriate prodrug and drug case studies. We highlight significant advances in phosphinic acid-based molecules in terms of their biological activity and applications in the treatment of disease. We also present an overview of the current state of progress that has been made in terms of their prodrug; drug delivery; and drug applications currently in clinical development.

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https://doi.org/10.1016/j.drudis.2018.11.016

Biological and medicinal significance

Table 1 summarizes the chemical and pharmacological libraries of the most important phosphinic acid scaffolds (compounds **1–35** [8–54]) with a range of pharmacological activities towards several diseases, including anti-inflammatory, anti-Alzheimer, antiparasitic, antihepatitis, antiproliferative, anti-influenza, anti-HIV, and antimalarial compounds. These scaffolds are discussed further below.

Anti-inflammatory agents

The most important factor in accelerating inflammatory diseases is the imbalance between proteases and antiproteases [8]. One group of proteases released during inflammation is chymases, which have emerged as potential therapeutic targets that inhibit matrix destruction and tissue remodeling [8]. Therefore, it would be interesting to develop potent and selective chymase inhibitors for therapeutic use. With this objective, Greco *et al*. proposed a series of β-carboxamido-phosphonic acids **1a–e** as a modification of molecule **2** (JNJ-10311795) for obtaining potent inhibitors of human mast cell chymase (Table 1) [8,9]. Favorable rat pharmacokinetics data were obtained for **1b** (chymase IC_{50} = 3.5 nM), and compound **1c** (IC_{50} = 17 nM) was found to be orally bioavailable in rats (F = 39%), and orally efficacious in a hamster model of inflammation [9], outlining the potential of this class.

Anti-Alzheimer's agents

The latest and significant achievements in the therapeutic treatment of Alzheimer's disease (AD) have focused on using BACE1 as a key target for drug development [10]. One of the most potent BACE1 inhibitors is **OM00-3** (K_i = 0.3 nM), a second-generation inhibitor of BACE1 [10]. Manzenrieder *et al*. [10] reported the design and synthesis of a phosphinic dipeptide isostere of **OM00-3**, which acts as an inhibitor of human BACE1 and was developed by replacing the hydroxyethylene isostere of **OM00-3** with a phosphinic dipeptide isostere while retaining the amino acid sequence optimized for the hydroxyethylene isostere.

A series of pseudo phosphinic dipeptide (PDP) inhibitors (**3–5**) were screened as inhibitors of human BACE1 using **OM00-3** as a reference (IC_{50} = 6 nM). The phosphinic octapeptide **3** exhibited similar potency towards BACE1 (IC_{50} = 12 nM), whereas compound **4,** with an isophthalamide *N*-terminal mimetic, gave nanomolar range potency (IC_{50} = 360 nM). However, integration of the PDP isostere with the benzodiazepindione-*N*-terminal mimetic **5** did not improve the inhibitory potency (IC_{50} = 52 μM).

Antiparasitic agents

As part of efforts aimed at developing new chemotherapeutic agents effective against Chagas disease (a major parasitic disease worldwide caused by the protozoan *Trypanosoma cruzi*), it was hypothesized that the presence of the phosphinic acid moiety would mimic the tetrahedral transition state of trypanothione synthase (TryS), a typical C:N ligase enzyme. Ravashcino *et al*. [12] designed a series phosphinate derivatives (**6a–g**) and evaluated them against *T. cruzi* amastigotes and epimastigotes (Table 1). In this series of compounds, **6d** and **6e** were potent inhibitors against intracellular *T. cruzi* proliferation with IC_{50} values of 9.8 μM and 14.2 μM, respectively. The basic phosphinopeptide structure discovered by Ravashcino *et al*. constitutes a starting point for the development of easily accessible and optimized drugs.

Anti-HIV agents

The phosphinic acid scaffold has been used in anti-HIV-1 aspatic acid protease research as a noncleavable transition state analog that has provided highly potency analogs (**7–12**) [13–19]. The ψ-Phe-Pro inhibitors **7** and **8** exhibit low anti-HIV-1 activity, whereas the potency of compounds based on ψ-Phe-Phe modified structures are more selective than those based on ψ-Phe-Pro **9** and **10**. This might account for the cyclopentane ring in the P_1'-position that might not be an optimal mimic of the conformation of a normal proline residue undergoing pyramidalization at nitrogen during proteolysis. Moreover, elongation of inhibitor **9** to include, symmetrical to the P′ positions, a Val-Val sequence at the P_2 and P_3 positions, provided the potent inhibitor **10**. According to the rationale of the design of these inhibitors, a novel transition-state analog mimicking the scissile Phe-Pro has been incorporated into inhibitor **11**, which exhibits time-dependent inhibition of HIV protease (K_i = 8.2 nM). Interestingly, the insertion of a methyleneamino linker produced a nonhydrolyzable moiety that is likely to be zwitterionic near physiological pH. Furthermore, it appears that there is a strong pH dependency of HIV-1 protease inhibition for the phosphinate transition state analogs, with higher K_i values at pH 6.5 compared with pH 4.5, suggesting that the non-ionized phosphinic acid has the highest affinity for the protease.

Over the past 4 years, inhibitors of cyclin-dependent kinases (CDKs) have emerged as a potential therapeutic window for HIV treatment [20]. Therefore, Orfi *et al*. [20] synthesized the **12** phosphinic analog of the sulfonamide **LDC000067**, one of the most potent CDK9 inhibitors known to date [21]. Phosphinic acid **12** was slightly less potent than **LDC000067** as a CDK9 inhibitor (IC_{50} = 142 nM versus 44 nM for **LDC000067**) but exhibited high specificity for the CDK9/CycT1 complex.

Anti-hepatitis viral agents

Since the first report of hepatitis C virus (HCV) infection during the 1980s, it has been considered a serious public health issue. Hepacivirin (NS3/4A) protease inhibitors have provided positive proof of concept in clinical trials. In recent years, phosphinic acids have been investigated as carboxylate isosteres and have been shown to be potent inhibitors of hepacivirin [21]. Clarke *et al*. reported the synthesis and biological evaluation of a series of cyclic phosphinic acids (**13** and **14**) and their acyclic analog (**15**), which is structurally similar to ciluprevir [21,22]. Development of compounds **13a–f**, **14a–c,** and **15a–u** was achieved by a focused structure–activity relationship (SAR) study that explored the substituent and conformationally constraining effects. Interestingly, saturation of the macrocyclic benzyl phosphinic acids exhibited a significant increase in replicon activity (**14a–c** versus **13a–c**). Moreover, all alkyl phosphinic acids (e.g., **15a–c**), as well as disubstituted benzyl phosphinic acids (e.g., **15s–u**), showed poor bioavailability. No improvement in inhibitory potency was observed by insertion of electron-donating (Me and OMe groups) or electron-withdrawing substituents (Cl, F, and Br groups) at the 8-position of the quinolone ring. In addition, the *ortho*-substituted analogs resulted in improvement of replicon activity compared

TABLE 1

Examples of phosphinic acids with a range of pharmacological activities towards many diseases

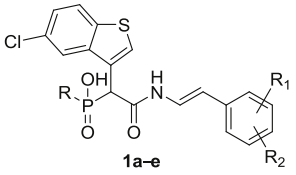
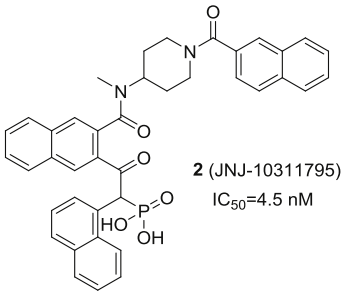
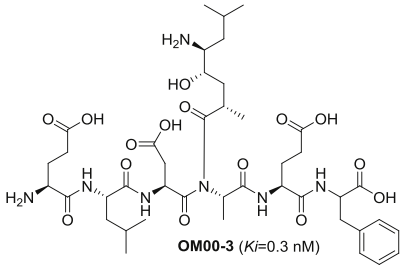
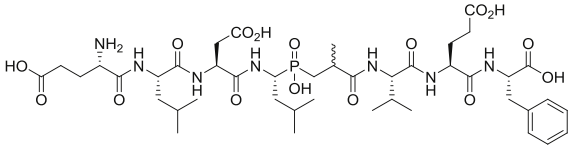
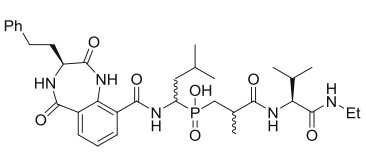
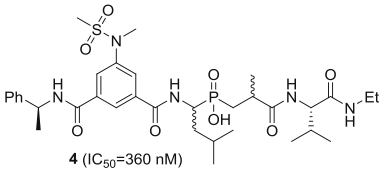
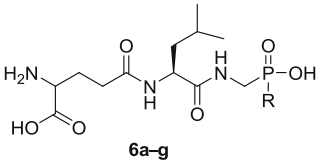
Significance	Examples	Refs
Anti-inflammatory agents	 **1a–e** **1a.** R=Me, R_1=H, R_2=H, IC_{50}=50 nM **1b.** R=Me, R_1=3-Cl, R_2=H, IC_{50}=3.5 nM **1c.** R=Me, R_1=3-Cl, R_2=5-F, IC_{50}=17 nM **1d.** R=Me, R_1=3-F, R_2=4-F, IC_{50}=58 nM **1e.** R=Et, R_1=3-F, R_2=4-F, IC_{50}=165 nM  **2** (JNJ-10311795) IC_{50}=4.5 nM	[8,9]
Anti-Alzheimer's agents	 **OM00-3** (*Ki*=0.3 nM)  **3** (IC_{50}=12 nM)  **5** (IC_{50}=52 μM)  **4** (IC_{50}=360 nM)	[10,11]
Antiparasitic agents	 **6a–g** **6a:** R=CH_3, IC_{50}>50 μM **6b**: R=CH_2CH_3, IC_{50}>50 μM **6c**: R=CH_2CHCH_2, IC_{50}>50 μM **6d**: R=$CH_2(CH_2)_2CH_3$, IC_{50}>50 μM **6e**: R=$CH_2(CH_2)_3CH_3$, IC_{50}=14.2 μM **6f** : R=$CH_2(CH_2)_4CH_3$, IC_{50}>50 μM **6g**: R=$CH_2(CH_2)_5CH_3$, IC_{50}>50 μM	[12]

TABLE 1 (*Continued*)

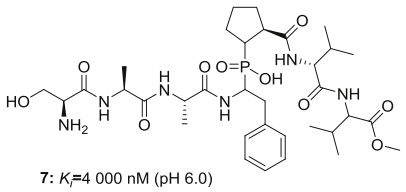
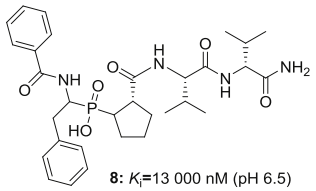
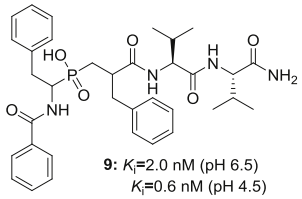
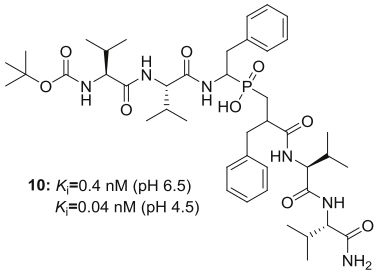
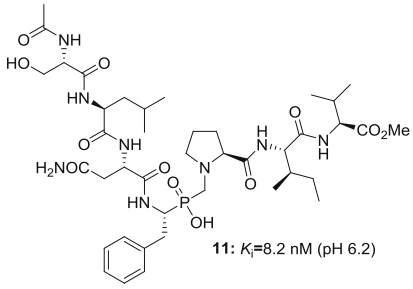
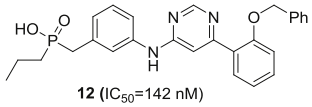
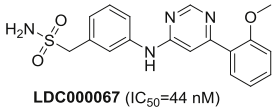
Significance	Examples	Refs
Anti-HIV agents	 **7:** K_i=4 000 nM (pH 6.0) K_i=120 nM (pH 3.6)  **8:** K_i=13 000 nM (pH 6.5) K_i=450 nM (pH 4.5)  **9:** K_i=2.0 nM (pH 6.5) K_i=0.6 nM (pH 4.5)  **10:** K_i=0.4 nM (pH 6.5) K_i=0.04 nM (pH 4.5)  **11:** K_i=8.2 nM (pH 6.2)  **12** (IC_{50}=142 nM)  **LDC000067** (IC_{50}=44 nM)	[13–20]

TABLE 1 (*Continued*)

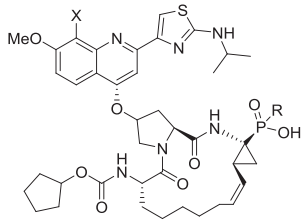
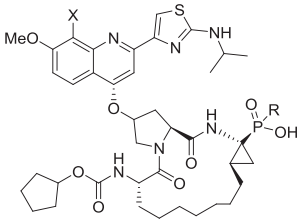
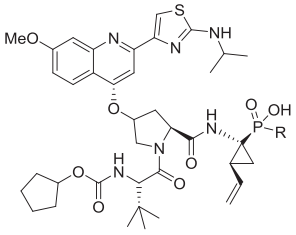
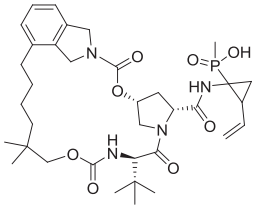
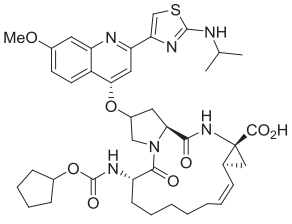
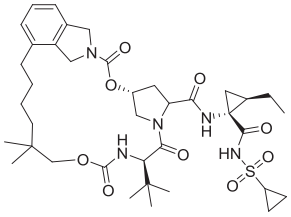
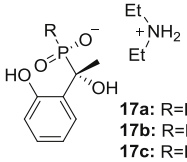
Significance	Examples	Refs
Anti-hepatitis viral agents	 **13a: R=Bn, X=H** (IC_{50}=6 nM, EC_{50}=5 nM); **13b: R=2-Cl-Bn, X=H** (IC_{50}=3 nM, EC_{50}=5 nM); **13c: R=2-MeOBn, X=H** (IC_{50}=3 nM, EC_{50}=7 nM); **13d: R=2,6-F_2-Bn, X=H** (IC_{50}=4 nM, EC_{50}=10 nM); **13e: R=2,6-F_2-Bn, X=F** (IC_{50}=11 nM, EC_{50}=43 nM); **13f: R=2,6-F_2-Bn, X= Br** (IC_{50}=3 nM, EC_{50}=70 nM).  **14a: R= Bn, X=H** (IC_{50}=3 nM, EC_{50}=10 nM); **14b:R= 2-Cl-Bn, X=H** (IC_{50}=1 nM, EC_{50}=5 nM); **14c: R=2-MeOBn, X=H** (IC_{50}=3 nM, EC_{50}=9 nM).   **16** *Ki*[a] = 24 nM **15a: R=Me** (IC_{50}=6 nM, EC_{50}=69 nM); **15b: R=Et** (IC_{50}=8 nM, EC_{50}=390 nM); **15c: R=*n*-Bu** (IC_{50}=8 nM, EC_{50}=49 nM); **15d: R=*i*-Pr** (IC_{50}=8.6 nM, EC_{50}=3080 nM); **15e: R=Ph** (IC_{50}=44 nM, EC_{50}=2650 nM); **15f: R=Bn** (IC_{50}=9 nM, EC_{50}=180 nM); **15g: R=2-Cl-Bn** (IC_{50}=6 nM, EC_{50}=311 nM); **15h: R=2-Me-Bn** (IC_{50}=6 nM, EC_{50}=47 nM); **15i: R=2-F-Bn** (IC_{50}=4 nM, EC_{50}=170 nM); **15j: R=3-F-Bn** (IC_{50}=8 nM, EC_{50}=239 nM); **15k: R=4-F-Bn** (IC_{50}=7 nM, EC_{50}=284 nM); **15l: R=2-OMe-Bn** (IC_{50}=6 nM, EC_{50}=48 nM); **15m: R=3-OMe-Bn** (IC_{50}=7 nM, EC_{50}=540 nM); **15n: R=4-OMe-Bn**(IC_{50}=10 nM, EC_{50}=460 nM); **15o: R=2-Me-Bn** (IC_{50}=8 nM, EC_{50}=146 nM); **15p: R=3-Me-Bn** (IC_{50}=8 nM, EC_{50}=331 nM); **15q: R= 4-Me-Bn** (IC_{50}=15 nM, EC_{50}= 860 nM); **15r: R=2,6-F_2-Bn** (IC_{50}=4 nM, EC_{50}=74 nM); **15s: R=2,6-Me_2-Bn** (IC_{50}=63 nM, EC_{50}=7700 nM); **15t: R=2F,6Cl-Bn** (IC_{50}=6 nM, EC_{50}=120 nM); **15u: R=2F,6CF_3-Bn** (IC_{50}=6 nM, EC_{50}=340 nM).  **Ciluprevir** IC_{50}[b]=1 nM, EC_{50}[c]=1 nM  **MK-7009** *Ki*[a]=0.06 nM [a] Inhibition of the full-length HCV–NS3/4A protease measured by the inhibition constants (*Ki* values). [b] IC_{50} determined by enzymatic assay using an HCV genotype 1b NS3/4A protein. [c] EC_{50} determined by cell based assay using Huh-luc cells harboring subgenomic HCV genotype 1b replicon.	[21–23]
Anti-influenza agents	 **17a:** R=Ph **17b:** R=Me, EC_{50}=28 μM **17c:** R=Et	[24]

TABLE 1 (*Continued*)

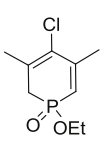
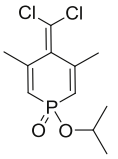
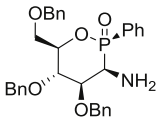
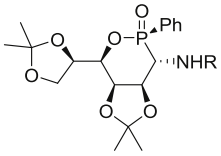
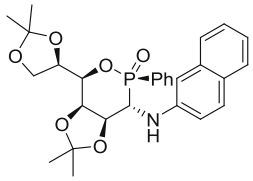
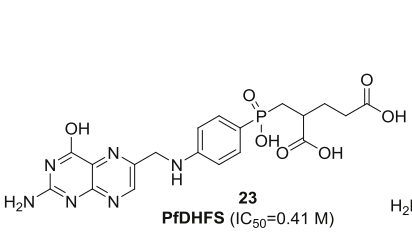
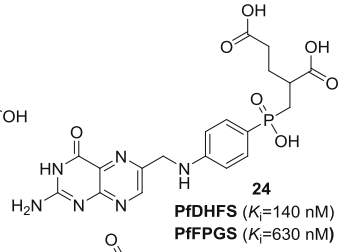
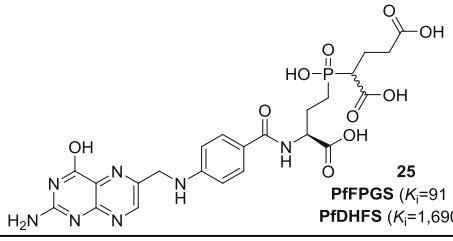
Significance	Examples	Refs
Antiproliferative agents	 **18** (IC_{50}=38.1 μM)  **19** (IC_{50}=29.2 μM)  ***(2S,3S,4S,5S,6R)*-20** EC_{50}=16.3 ± 0.1μM  ***(2S,3S,4S,5R, 6R)*-21a–d** **21a:** R=C_6H_5,IC_{50}=10.29 μM **21b:** R=4-MeC_6H_4, IC_{50}=5.50 μM **21c:** R=1-naphthyl, IC_{50}=5.74 μM **21d:** R=$C_6H_5CH_2$, IC_{50}=14.80 μM  ***(2S,3S,4S,5R, 6R)*–22** Gli4 (EC_{50}=5.22 μM) Gli7 (EC_{50}=2.33 μM)	[25–27]
Antimalarial agents	 **23** **PfDHFS** (IC_{50}=0.41 M)  **24** **PfDHFS** (K_i=140 nM) **PfFPGS** (K_i=630 nM)  **25** **PfFPGS** (K_i=91 nM) **PfDHFS** (K_i=1,690 nM)	[28–31]

TABLE 1 (*Continued*)

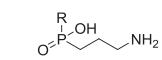
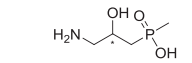
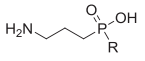
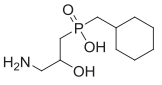
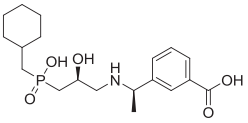
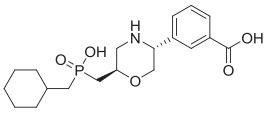
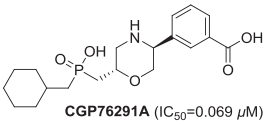
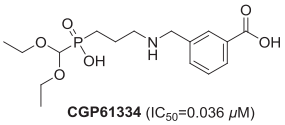
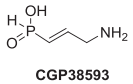
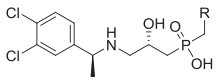
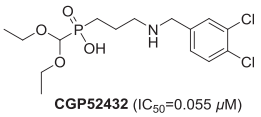
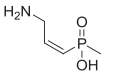
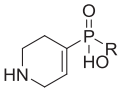
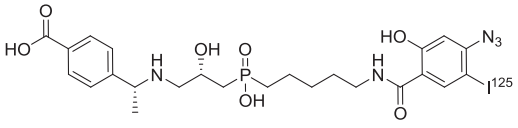
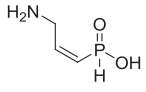
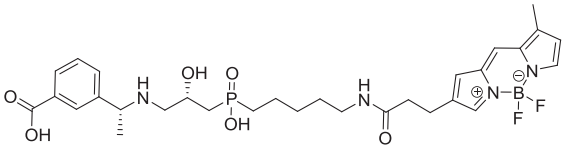
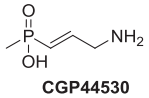
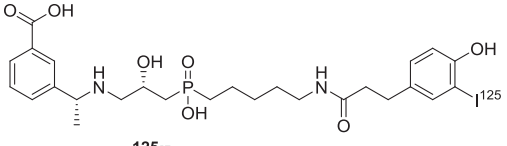
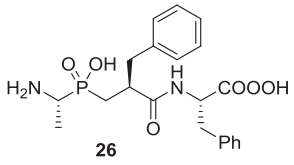
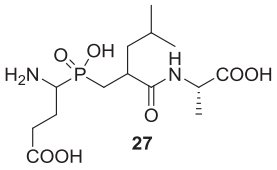
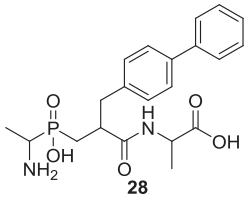
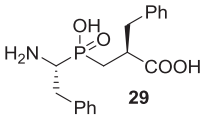
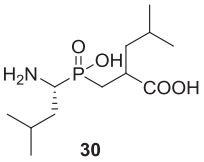
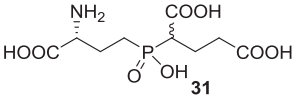
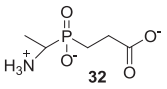
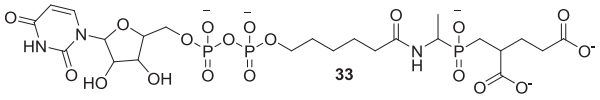
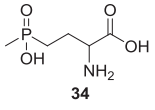
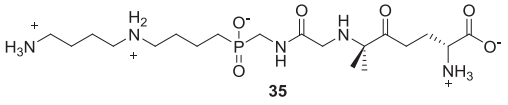
Significance	Examples	Refs
Neural activity	 R=H, **CGP27492** (IC_{50}=0.005 μM) R=Me, **CGP35024** (IC_{50}=0.0163 μM) R=CHF_2, **CGP47656** (IC_{50}=0.29 μM)  **(*R,S*): CGP34938** (IC_{50}=0.077 μM) **(*S*): CGP44532** (IC_{50}=0.152 μM) **(*R*): CGP44533** (IC_{50}=0.045 μM)  R = *n*-Bu, **CGP36742** (IC_{50}=38 μM) R = Bn, **CGP46381** (IC_{50}=10 μM) R = $CH(OEt)_2$, **CGP35348** (IC_{50}=27 μM)  **CGP49311A** (IC_{50}=5 μM)  **CGP5699A** (IC_{50}=0.002 μM)  **CGP76290A** (IC_{50}=0.00185 μM)  **CGP76291A** (IC_{50}=0.069 μM)  **CGP61334** (IC_{50}=0.036 μM)  **CGP38593** (IC_{50}=7.68 μM)  R=Cyclohexyl, **CGP54626** (IC_{50}=0.0044 μM) R=Phenyl, **CGP55845** (IC_{50}=0.0057 μM)  **CGP52432** (IC_{50}=0.055 μM)  **CGP70523** (IC_{50}=38 μM)  R=Me, **TPMPA** (K_B=2.1 μM) R=Et, **TPEPA**  **[^{125}I] CGP71872** (IC_{50}=2.4 nM)  **CGP70522** (IC_{50}>300 μM)  **NVP-AAJ415** (IC_{50}=22 nM)  **CGP44530** (IC_{50}=5.35 μM)  **[^{125}I] CGP64213** (IC_{50}=1.2 nM)	[32–38]

TABLE 1 (*Continued*)

Significance	Examples	Refs
Inhibitors of metalloproteinase	 **26** Inhibitor of aminopeptidase-N/CD13  **27** Inhibitor aminopeptidase A  **28** Neprilysin inhibition, *Ki* (1.2 nM)  **29** Inhibitor of leucine aminopeptidases  **30** Inhibitors of leucine aminopeptidase  **31** Inhibitor of human glutamate carbioxypeptidase II  **32** D-alanine—D-alanine ligase  **33** D-glutamate-adding enzymes (MurD)  **34** Glutamine synthetase  **35** Glutathionylspermidine synthetase	[39–54]

with the *meta*- and *para*-substituted analogs. IC_{50} values were determined by enzymatic assays using an HCV genotype 1b hepacivirin. EC_{50} values were determined by cell-based assays using Huh-luc cells harboring subgenomic HCV genotype 1b replicon. Additionally, Pompei *et al*. [23] synthesized the phosphinic acid analog **16** of the clinically evaluated compound **MK-7009** and tested its effect on hepacivirin inhibition.

Anti-influenza agents

The rapid spread of annual influenza epidemics is felt globally each year and affects ~15% of the world's population [24]. Given the large economic burden in the form of hospitalization and productivity loss, intensive research is underway to discover new antiviral molecules to overcome this recurring public health problem [24]. Thus, Khorshin and Pozdeev reported the preparation of α,γ-dihydroxyphosphinates **17** as a new class of protective agents against influenza virus A subtype H3N2 [24]. The antiviral activity of products **17a–c** were evaluated in *vitro* in Madin–Darby canine kidney (MDCK) cells infected with H3N2, and showed disappointing results for **17a** and **17c**, whereas the most active derivative **17b** (EC_{50} = 28 μM) was four to five times less potent compared with the commercial anti-influenza drug rimantadine (EC_{50} = 5.0 μM) [24]. However, the phosphinates **17a–c** exhibited substantial protective activity in tests performed *in vivo* after inoculation of influenza virus A/Aichi/2/68 (H3N2) in mice.

Antiproliferative agents

Many types of organophosphorus compound have been reported to show anticancer activity [25,26]. In this respect, the Keglevich group reported the evaluation of a series of *P*-heterocycles, the dihydrophosphinine oxides **18** and **19**, as antitumor agents [25]. The antiproliferative activities of these structures were tested against an NCI-60 cell line panel of human malignant cells. High efficacy with total growth inhibitory concentrations in the 60 tumor cell lines were obtained for **18** and **19**, with IC_{50} values of 38.1 μM and 29.2 μM, respectively [25].

To develop a new antiglioma therapy, Clarion and coworkers designed and synthesized the oxaphosphinane **20**, which was tested for its antiproliferative activity against glioblastoma (EC_{50} = 16.3 *m*M) and is expected to be a therapeutic compound in preclinical glioma models [26]. This series of *C*-glycoside mimetics was extended to heptopyranoses **21a–d** (*D*-glycero-*D*-talo- and *D*-glycero-*D*-galactopyranose analogs) [27]. These com-

pounds were evaluated against glioma cancer cell lines, generating new therapeutic perspectives against glioblastoma. The ability of the heptopyranose analog **22** to inhibit the invasion and migration of cancer cells was also investigated. This compound showed potent antiproliferative properties on Gli4 (EC_{50} = 5.22 *m*M) and Gli7 (EC_{50} = 2.33 *m*M), suggesting new therapeutic perspectives against glioblastoma [27].

Antimalarial agents

New inhibitors are urgently needed in the face of drug resistance to therapeutics and prophylactics against malaria caused by *Plasmodium falciparum*. Accordingly, Coward and Yang designed and synthesized several arylphosphinic acid derivatives (**23–25**) as possible PfDHFS-FPGS inhibitors, by introducing a phosphinic group [28–31].

The biological evaluation of compounds **23–25** showed potent inhibition of *Escherichia coli* glutamate DHFS-FPGS-catalyzed ligation reactions [28–31]. The reduced 7,8-dihydroderivative **23** inhibited *Pf*DHFS activity with an IC_{50} of 0.41 μM, whereas **24** showed good affinity for *Pf*DHFS and *Pf*FPGS, with K_i values of 140 nM and 630 nM, respectively [28–31]. An assessment of the reduced 7,8-dihydroderivative **25** showed that its inhibition of *Pf*FPGS (K_i = 91 nM) was 19 times less than that of *Pf*DHFS (K_i = 1690 nM) [31].

Neural activity

A massive boost to GABA research came from studies of phosphinic analogs of GABA that bind effectively to these receptors. A range of 3-aminopropyl phosphinic acid analogs of baclofen has been synthesized and evaluated, including **CGP27492** and its methyl analog (**CGP35024**), which are three- to sevenfold more potent than the active *R*-isomer of baclofen. Other phosphinic acid-based agonists have been described, such as **CGP47656**, **CGP44532**, its (*R*)-enantiomer **CGP44533**, and the racemate **CGP34938** [48,49]. The design of selective and high-affinity $GABA_B$ receptor antagonists has been important in establishing the significance and isolation of the $GABA_B$ receptor genes. In 1987, the discovery of the first $GABA_B$ receptor antagonist, the phosphonic acid analog of baclofen, called phaclofen, was reported by Kerr *et al.* [50]. Subsequent findings of antagonists were reported, but most of these agents exhibited relatively low affinity for the receptor [51].

The significant breakthrough and improvement in antagonist selectivity and affinity to ~10 000 times higher values than previous antagonists stemmed from introducing a benzyl substituent to existing molecules, such as **CGP5699A**, **CGP54626**, **CGP55845**, **CGP76290A**, **CGP52432**, **CGP61334**, and **CGP76291A** [52–54]. Some high-affinity $GABA_B$-receptor antagonists have also been developed with specific radioactivity, such as **[^{125}I] CGP64213** (IC_{50} = 1.2 nM) and **[^{125}I] CGP71872** (IC_{50} = 2.4 nM), or with photoaffinity and fluorescence, such as **NVP-AAJ415** (IC_{50} = 22 nM) [52]. The $GABA_C$ receptor has distinct pharmacology, physiology, and subunit composition compared with the $GABA_A$ and $GABA_B$ receptors. The structures and pharmacological data for a series of GABAc receptor agonists and antagonists are given in Table 1 [53]. **TPMPA** and **TPEPA** are still the most selective $GABA_C$ receptor antagonists reported to date [54].

Metalloprotease inhibitors

Many approaches have been applied to the design and preparation of novel potent inhibitors of different metalloenzymes, including aminopeptidase N, glutamine synthetase, glutathione synthetase, glutathionylspermidine synthetase, D-Ala-D-Ala ligase, and leucine aminopeptidase (compounds **26–35**) [39–54]. Most of these inhibitors have exhibited significant inhibitory effects and, thus, the development of promising drugs might be expected in the future.

Phosphinic prodrug and drug delivery applications

Fosinopril: an ACE inhibitor prodrug

Phosphinic acid derivatives exhibit a good record for the modulation of physiological and pathological procedures bearing a well-tolerated bioisosteric replacement, with no noticeable toxic effects. Nevertheless, the use of phosphinates as drugs presents a challenge with respect to their drug delivery. At physiological pH, phosphinates are negatively charged and, because of their polarity, are unable to penetrate cell membranes. To overcome this problem, esters can be used as prodrugs [55]. A representative example of a phosphinate prodrug is fosinopril **36**, an antihypertensive drug with excellent oral bioavailability (Fig. 1) [56]. Fosi-

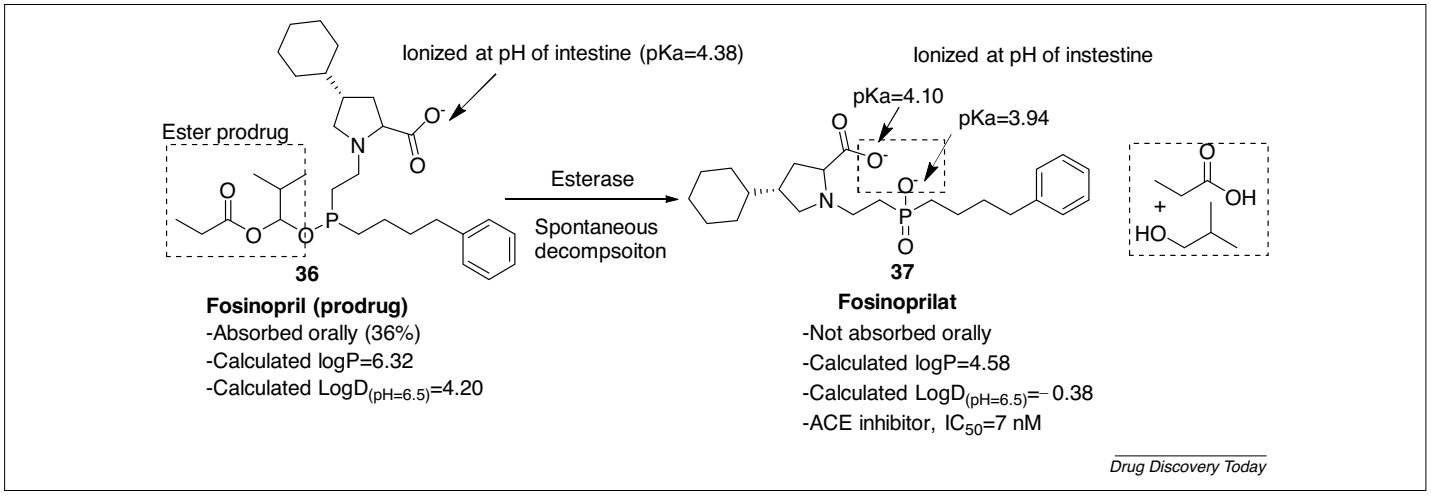


FIGURE 1

Structures and bioconversion pathway of fosinopril.

nopril sodium **36** was discovered during the mid-1980s and launched by E.R. Squibb & Sons (now Bristol-Myers Squibb) in 1991. This drug undergoes hydrolysis in human plasma, intestine, and liver followed by spontaneous decomposition to afford propionic acid and isobutyl alcohol as nontoxic by-products with the free acid **37**, which is the inhibitor of ACE that causes a decrease in blood pressure [57]. The ester prodrug has a greater distribution coefficient than the parent drug, and this increased lipophilicity correlates well with the bioavailability data (Fig. 1) [58,59]. The significant dual (renal and hepatic) route of elimination and a prolonged elimination half-life (~12 h) of fosinoprilat demonstrated its benefits as an efficient alternative to established oral antihypertensive agents for the treatment of idiopathic hypertension [57].

Osteotropic prodrugs for the prevention of osteomyelitis

Osteomyelitis is a morbid infectious skeletal disease that is accompanied by a decrease in bone density and necrosis [60]. The delivery of bioactive moieties from prodrugs to poorly vascularized sites of infection is often required to achieve a therapeutic outcome for antiosteoporosis drugs [61]. Bisphosphonates have been used clinically over the past half-century to treat metabolic bone diseases because of their ability to inhibit hydroxyapatite dissolution [61]. In this context, Houghton *et al*. studied the affinity of bisphosphonated dioxolenone **38** and 2-acyloxyhydrocinnamate **39a–c** for bone and their ability to release their parent antibiotic drug once bound to bone, by *in vivo* evaluation against *Staphylococcus aureus* in a rat model of osteomyelitis (Fig. 2) [62]. Phosphinylmethylphosphinates **38** and **39a**,**b** were shown to be highly bound to bone, being taken up at 35–76% over 1 h, with the exception of compound **39c**, which demonstrated no binding affinity. According to their assessment, these fluoroquinolone bisphosphonates function as efficient organ (bone)-directed antibiotic prodrugs in line with their intended rational drug design.

Folylpolyglutamate inhibitors: anticancer prodrugs

Folylpolyglutamate synthetase (FPGS) is an enzyme that catalyzes the synthesis of folate and antifolate poly(γ-glutamate) metabolites, and it has been considered as a potential target for anticancer drug design [63]. In this context, Coward *et al*. designed the phosphinic acids **40a–d** as FPGS inhibitors (Fig. 3). The phosphinic acid **40a** is the most potent inhibitor of FPGS *in vitro* described to date (K_i = 3.1 ± 0.5 nM) [64]. Unfortunately, when it was used as inhibitor of CCRF-CEM cells, it was completely ineffective because of its polarity and inability to penetrate cell membranes [64]. To overcome this transport barrier, Coward *et al*. adapted and investigated the ester analogs **40b–d** as prodrugs [65]. The prodrugs **40b–d** were evaluated in Chinese hamster ovary cells, but were ineffective in all cell lines [66].

Enkephalinase inhibitors: management of pain prodrugs

Research on dual inhibitors of aminopeptidase *N* (APN) and neprilysin (NEP) as new analgesics represents an attractive goal for drug discovery towards pain management [67]. The prodrug based on a phosphinic acid derivative, **RB-3007**, has been successfully applied in this context and it appears to be a promising therapeutic agent with antinociceptive action in nanomolar range and longer duration of action compared with **RB-101** (Fig. 4) [68–70].

Drug delivery surfactants

With increasing numbers of drugs being developed with poor solubility characteristics (BCS class 2), drug delivery systems are increasingly being investigated to improve the therapeutic index and pharmacological effects of candidate drugs [71]. Among several promising new drug delivery systems, drug encapsulation in catanionic vesicles appears to be an efficient approach for pharmaceutical applications. These systems have recently attracted attention because they are easily formulated in aqueous solutions by mixing cationic and anionic surfactants that are relatively cheap and simple to use, thus being appropriate for production on an industrial scale. Furthermore, such systems show high thermodynamical stability and, therefore, can be stored for several years at room temperature in the lyophilized form without any degradation [72]. Using renewable resources, Blanzat *et al*. designed, synthesized, and studied the action of stable vesicles of a biocompatible and nontoxic sugar-derived tricatenar catanionic surfactant, TriCat, for drug vectorization (Fig. 5) [73].

TriCat exhibits the ability to retain drugs in the aqueous cavity of the vesicles for more than 30 h, which is among the highest probe-entrapment capabilities. Hence, tricatenar catanionic surfactants could be a promising new type of delivery system, in which the drug is easily entrapped during spontaneous surfactant self-assembly in water.

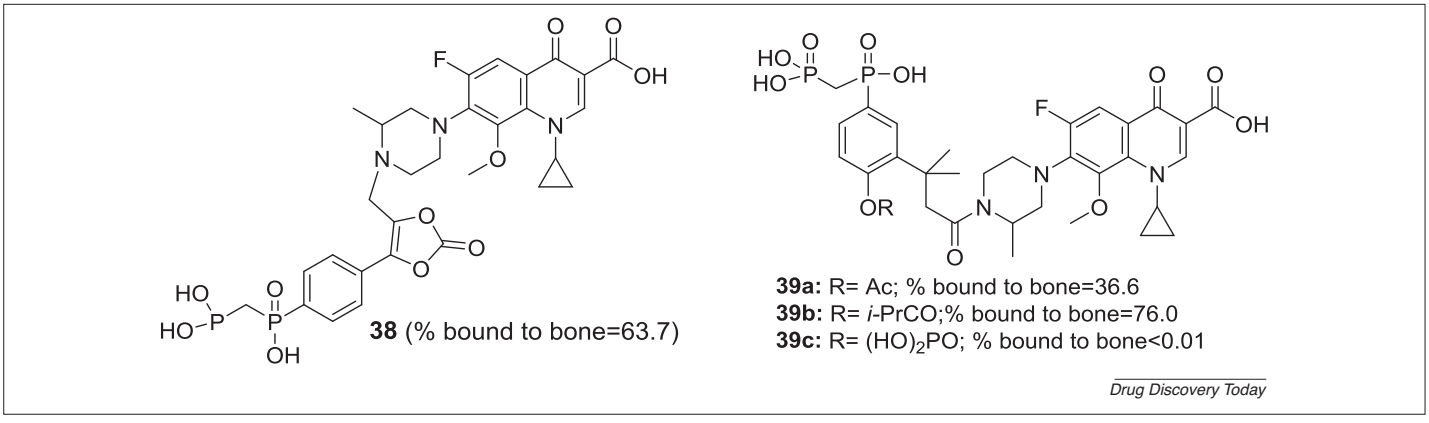


FIGURE 2

Structures of bisphosphonated 2-acyloxyhydrocinnamates **38** and **39a–c** as osteotropic prodrugs.

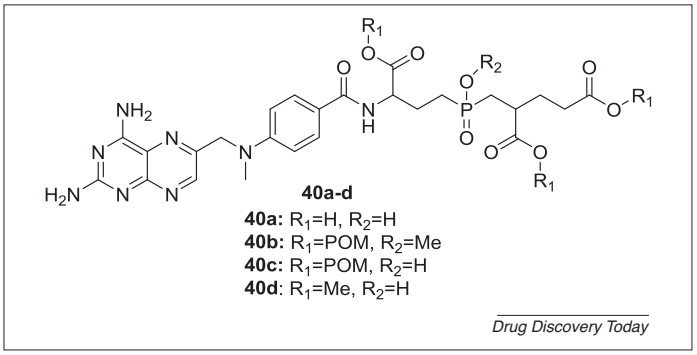


FIGURE 3

Structure of the pseudopeptide ester prodrugs **40a**–**d**.

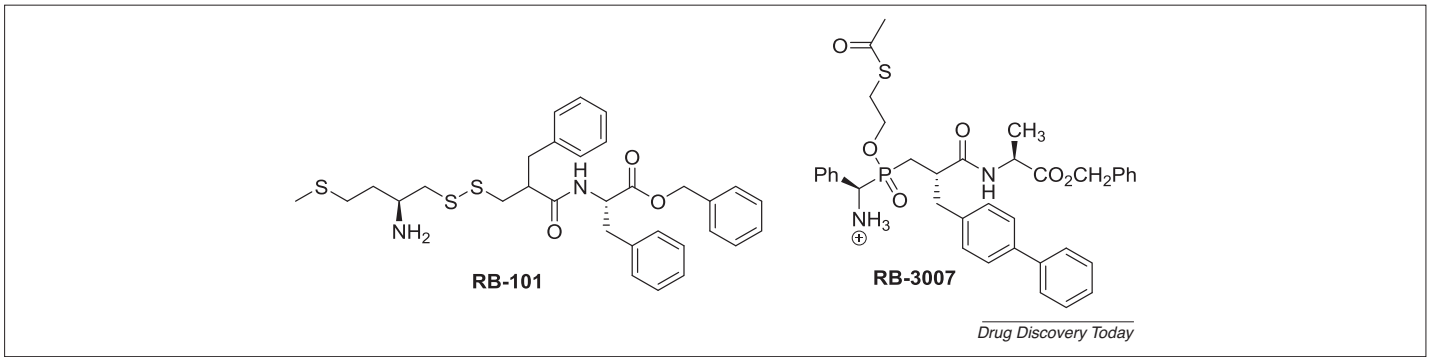


FIGURE 4

Dual NEP/APN inhibitors RB-101 and RB-3007.

Phosphinic acid drug applications

There are several phosphinic based drugs currently in clinical trials. The structures of some representative examples are shown in Fig. 6. Lesogaberan, developed by AstraZeneca, aims to treat gastroesophageal reflux (GERD), Fosdevirine has been developed towards HIV, **SGS-742** for AD, and **GS-9256** against HCV. Each of these important representatives are dealt with in turn in the following section.

Lesogaberan: drug for the treatment of GERD

The phosphinic acid, lesogaberan (AZD3355), was an experimental drug candidate developed by AstraZeneca and is currently in Phase 2II clinical trials as a GERD inhibitor, offering a new empirical approach to the management of reflux disease [74–76]. Previous studies demonstrated that lesogaberan successfully controlled the transient lower esophageal sphincter relaxation in dogs and humans, which is a primary cause of GERD [77–79]. Pharmacodynamic studies have shown that lesogaberan also reduced the mean number of reflux events (by 36% at 0.8 mg/kg as a single dose) [80]. Similar results were obtained in a Phase II study in patients with GERD, where it showed significant clinical efficacy at this dose as an add-on therapy for 4 weeks [81]. These dose-finding studies on GERD symptoms were extended to demonstrate that there is a dose dependency in the range of 30–240 mg twice daily [82]. A ran-

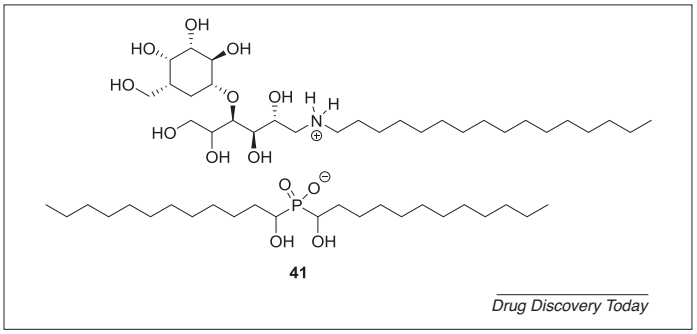


FIGURE 5

Structure of the tricatenar cationic surfactant, 1-*N*-hexydecylammonium-1-deoxyactitol-bis(R-hydroxydodecylphosphinate) **41**.

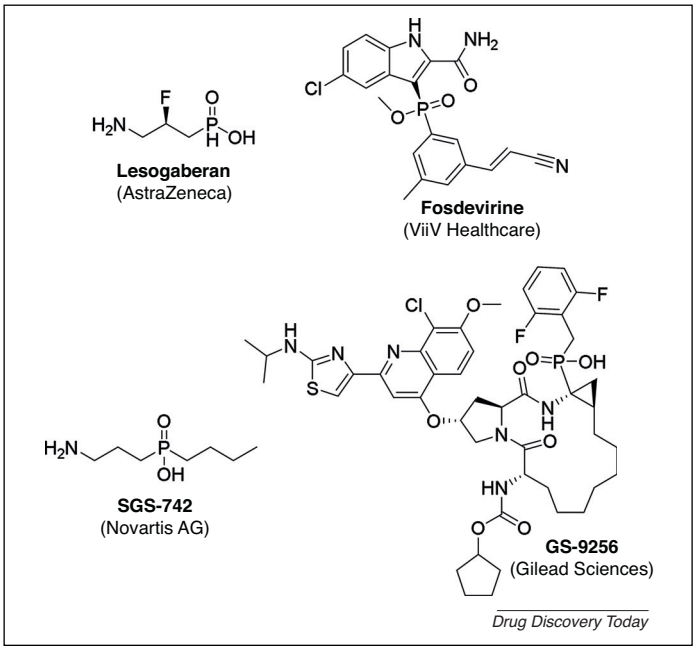


FIGURE 6

Representative phosphinic acid drugs in clinical trials.

domized, double-blind, placebo-controlled study was performed with 244 adult patients with GERD symptoms. Subjects were given lesogaberan or placebo at a twice-daily dose of 65 mg, during a 4-week treatment period; 16% of the lesogaberan group responded compared with 8% of the placebo group. Lesogaberan was also well tolerated during the study [83]. The major advantage of lesogaberan is that it offers a wide dosing range with an acceptable central nervous system safety margin [84,85].

SGS742: drug for the treatment of AD

SGS-742 has been developed by Novartis and was licensed to Saegis (acquired by Lundbeck in 2006) for the potential treatment of mild cognitive impairment and AD [86,87]. In May 2004, Saegis began enrollment in Phase II clinical trials of **SGS-742** as a memory-improving agent in patients with AD alongside the treatment of patients with succinic semialdehyde dehydrogenase deficiency [88].

Fosdevirine: drug for the treatment of HIV

Fosdevirine (**GSK 2248761** or **IDX899**) is a potent NNRTI of HIV-1 with low nanomolar activity that is currently in Phase II clinical trials [89]. It is being developed by ViiV Healthcare, a specialist HIV company established by GlaxoSmithKline (GSK) and Pfizer. Fosdevirine showed excellent antiviral efficacy *in vitro* against K103N and Y181C single reverse transcriptase mutants [90]. Additionally, FDV effectively decreased plasma HIV-1 RNA levels and increased lymphocyte counts [91]. A series of studies was performed that indicated a favorable safety profile and predictable pharmacokinetic properties [92,93].

In a Phase IIb clinical trial involving treating 20 patients for 4 weeks, five patients experienced seizures after completion of at least 4 weeks of treatment [94]. The high incidence of seizures could not be explained by background seizure incidence or risk because of concomitant medication [95]. Thus, in February 2011, the US Food and Drug Administration (FDA) placed a hold on the trials.

GS-9256: drug for the treatment of HCV

GS-9256 is a macrocyclic HCV-hepacivirin inhibitor with reasonable potency as monotherapy (HCV RNA reductions of 2.7 $\log^{10}$) [96,97]. Several Phase II studies for treatment-naive patients with genotype 1 HCV have been performed by using direct-acting antivirals of the hepacivirin inhibitor **GS-9256** along with tegobuvir (a non-nucleoside NS5 B polymerase inhibitor) as a dual therapy or together with ribavirin or PEG-IFN alfa/RBV [98–100]. Based on the virological response, quadruple therapy (tegobuvir/GS-9256/PEG-IFN/RBV) enabled the researchers to shorten the period of antiviral therapy with additive antiviral activity.

Concluding remarks and future perspectives

In this review, we have provided an overview of recent progress associated with phosphinic acid derivatives in the arena of medicinal chemistry and highlighted their novel applications in the design of prodrugs, drugs, and drug delivery systems. The behavior of the phosphinic group mimics the tetrahedral transition state of the carbon atom by being an isostere of the scissile amide bond in peptide substrates and this continues to be a valuable guiding principle in the design of diverse phosphinic-based compounds with pharmaceutical applications. These compounds have been used in the treatment of HIV, HCV, and AD, and as anti-inflammatory, antiparasitic, and antiproliferative agents. Beyond their important medicinal role, phosphinic acid scaffolds have found useful prodrug applications against osteoporosis, as well as anticancer, antinociceptive, and antihypertensive treatments. Furthermore, there has been con-

siderable progress made in their use in drug delivery to deliver the target drug to the right place with an appropriate concentration. Other significant attributes of these molecules are as drug applications for diverse therapeutic implementation (AD, GERD, HCV, and AIDS) with promising clinical applicability. It is expected that the next stage of the journey will take advantage of current knowledge to use phosphinic acids in future rational drug design campaigns.

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