ELSEVIER

Small molecule inhibitors of ebola virus infection

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Ebola viruses are extremely virulent and highly transmissible. They are responsible for sporadic outbreaks of severe hemorrhagic fevers with human mortality rates of up to 90%. No prophylactic or therapeutic treatments in the form of vaccine, biologicals or small molecule, currently exist. Yet, a wealth of antiviral research on ebola virus is being generated and potential inhibitors have been identified in biological screening and medicinal chemistry programs. Here, we detail the state-of-the-art in small molecule inhibitors of ebola virus infection, with >60 examples, including approved drugs, compounds currently in clinical trials, and more exploratory leads, and summarize the associated *in vitro* and *in vivo* evidence for their effectiveness.

Introduction

The *Ebolavirus* genus is a member of the *Filoviridae* family of viruses of the *Mononegavirales* order [1] and includes five species. These have significant differences in terms of virulence and geographical distribution. For instance, *Reston Ebolavirus* (RESTV) is not pathogenic for humans, whereas *Zaire Ebolavirus* (EBOV) represents the most pathogenic form for humans, with lethality rates of up to 90% [2]. They are enveloped nonsegmented negative single-stranded RNA viruses, of a filamentous morphology [3].

The approximately 19 kb RNA genome of ebola viruses encodes seven genes that produce a nucleoprotein, three glycoproteins ($GP_{1,2}$, the membrane-bound surface protein responsible for entry, and soluble and small soluble glycoprotein: sGP and ssGP, respectively), four viral proteins (VP24, VP30, VP35 and VP40) and the viral RNA-dependent RNA polymerase. The matrix protein VP40 drives the formation of virus-like particles (VLP) [4,5] that, owing to $GP_{1,2}$ exposed on their surfaces, are presented to the host cell. The subsequent virus fusion and entry occur through a complex cascade of micropinocytosis–endocytosis [6–8], endosome trafficking [9,10] and proteolytic activation [11,12] steps, among others. This results in virions being internalized and the viral genome replicated. The virus infection is characterized by massive production of proinflammatory cytokines, severe host immunosuppression and rapid viremia, and often manifests in the form of a fulminant hemorrhagic fever [2,13,14].

The ease of ebola virus transmission from bodily fluids [15], the high virulence and rapid progression of infection, coupled with the high fatality rate, have prompted its classification as a hazard group 4 pathogen by the Advisory Committee on Dangerous Pathogens (ACDP). Despite several therapeutic options, including vaccines [2], monoclonal antibodies [16,17], recombinant proteins [18,19], antibody–interferon (IFN) combinations [20] and small interfering (si)RNA [21] having been developed and tested with success in nonhuman primate models of ebola virus infection, none is currently approved for use in humans. Additionally, because most of these approaches build on virus-specific designs, they are likely to have a limited spectrum of activity. The lack of therapy and the recent cases of ebola virus infection outside the African region have created a high level of public concern, and highlight the need to identify effective therapeutic agents targeting ebola viruses.

A large volume of biomedical research is devoted to the investigation of the molecular basis of ebola virus infection as a way to develop strategies to combat it. Here, we review the body of literature detailing the identification and characterization of small molecules acting as ebola virus infection inhibitors. The compounds identified from a systematic literature survey have been categorized based on their reported mechanism of anti-ebola virus

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action (e.g. inhibition of viral replication) and documented molecular mechanism (e.g. kinase inhibitor). When mechanistic information on their ebola virus inhibitory activity was not available, small molecules have been organized based on the type of their documented anti-ebola virus activity (e.g. *in vitro*). For each literature record, the most relevant molecular entities and associated data are described, as summarized in the supplementary material online. A total of 65 compounds belonging to more than 50 chemical classes, including approved drugs, antiviral agents in clinical trials, lead compounds, exploratory chemical probes and screening hits, are discussed.

Viral transcription modulators

T-705 (**favipiravir**, Fig. 1) was first described by Toyama Chemicals as a selective inhibitor of influenza virus replication with minimal cytotoxicity [22] and is currently in Phase III clinical trials for the treatment of influenza. **T-705** closely resembles naturally occurring primary nucleobases (Fig. 1). It was shown to inhibit the viral RNA-dependent RNA polymerase via an active metabolite and to induce a high rate of lethal RNA mutation [23–26]. Oestereich *et al*. showed that **T-705** was also effective at inhibiting ebola virus replication *in vitro* without any observed cytotoxicity under the experimental conditions used [27]. When dosed orally twice daily to type I IFN-α/β receptor knockout (IFNAR$^{-/-}$) mice, **T-705** was able to prevent mortality in 100% of the animals. Importantly, **T-705** treatment was started 6 days post infection (pi) and resulted in a significant production of ebola virus antibodies, indicating the occurrence of a virus-specific adaptive immune response [27]. Similar results (100% protection) were obtained by Smither *et al*. when administering oral **T-705** to (IFNAR$^{-/-}$) 129/Sv mice, 1 hour after aerosol ebola virus E718 infection [28].

BCX4430 (Fig. 1) is an adenosine analog rapidly metabolized to its 5′-monophosphate derivative, which in turn acts as a nonobligate RNA chain terminator upon incorporation into viral RNA but not human RNA or DNA [29]. **BCX4430** is active *in vitro* against ebola virus and multiple negative-sense RNA viruses and did not display any significant mutagenicity, as determined by the Ames assay. Its pharmacokinetic profile is reminiscent of that of a nucleotide, with the parent compound being rapidly cleared (Rat $t_{1/2}$ = 5 min) and the phosphorylated metabolites residing longer (Rat $t_{1/2}$ = 6.2 hours for the 5′-triphosphate-**BCX4430**) [29]. Intramuscular or oral, twice-daily administration of **BCX4430** to ebola virus-infected C57Bl/6 mice, 4 hours before infection, resulted in 100% and 90% survival, respectively. Further studies evaluating the ebola virus protection by **BCX4430** in nonhuman primates are reportedly ongoing [29].

In 1991 and 1995, Huggins *et al*. first reported on the ability of two *S*-adenosylhomocysteine (SAH) hydrolase inhibitors, carbocyclic 3-deazaadenosine (**C-c3Ado**) and 3-deazaneplanocin A (**c3Nep**) (Fig. 1), to inhibit ebola virus replication *in vitro* [30,31], confirming their original broad antiviral profile [32]. Twice-daily dosing of **C-c3Ado** or **c3Nep** prolonged survival of SCID mice infected with the Mayinga strain of ebola virus [30,31] Further studies with **C-c3Ado** confirmed these initial results: when **C-c3Ado** was administered at day 0 or 1 pi, ebola virus-infected BALB/c mice were protected in a dose-dependent manner, with **C-c3Ado** doses ≥0.7 mg/kg/8 hours preventing mortality completely [33]. Survival and virus protection decreased with increased time between infection and start of treatment (90% versus 40% protection when **C-c3Ado** dosing started at days 2 and 3, respectively) [33]. Similar deterioration of efficacy because of delay in therapy start was obtained when administering **c3Nep**

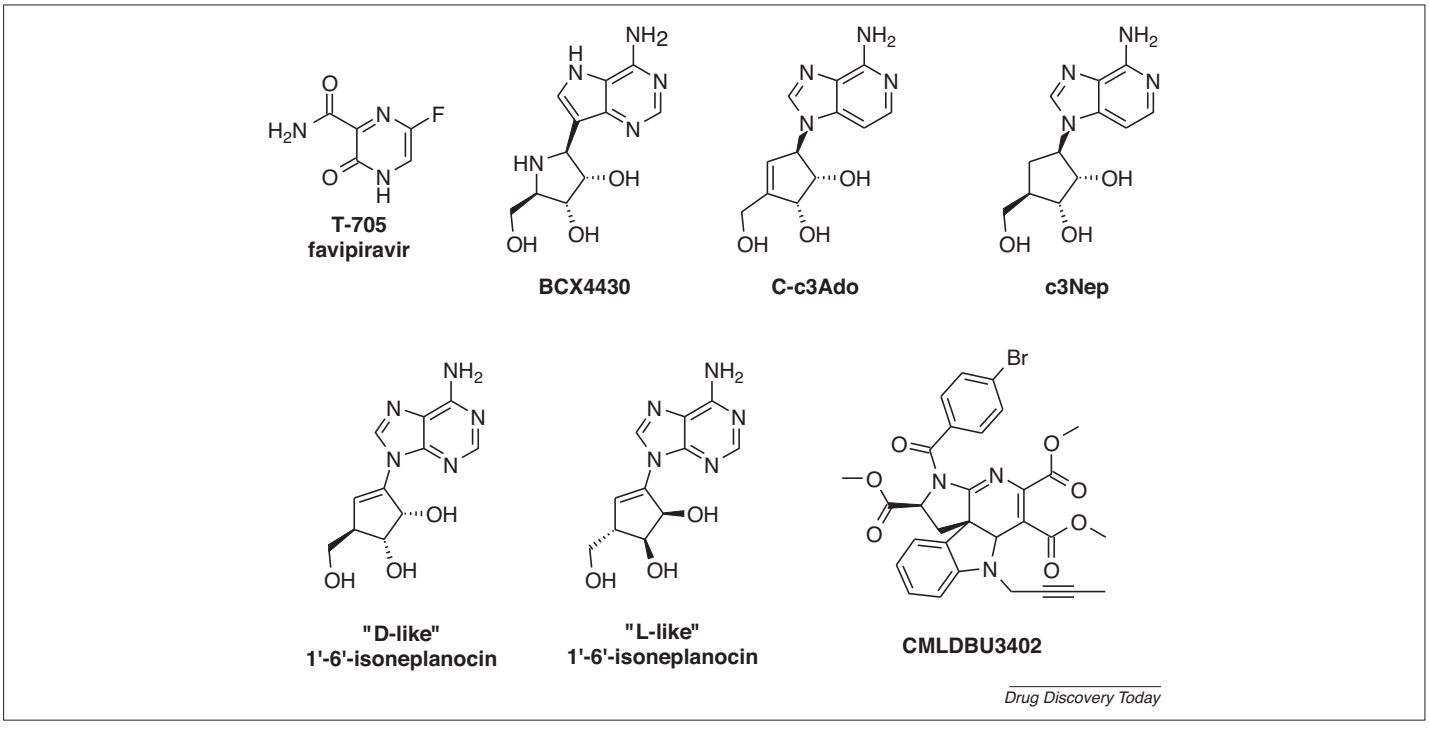

FIGURE 1

Viral transcription modulators with reported anti-ebola virus activity.

[34]. Ye and Schneller recently reported that the two enantiomers of C-1′/C-6′ isoneplanocin (‘**D-like**’ and ‘**L-like**’, Fig. 1) effectively inhibited ebola virus replication *in vitro* [35]. Despite their structural similarity to **c3Nep**, a difference in their ability to inhibit SAH hydrolase was observed (IC_{50} = 0.9 and 27 nM, for the **D-like** and **L-like** enantiomers, respectively). This difference notwithstanding, the two enantiomers had comparable activity against ebola virus [35]. The postulated link between SAH hydrolase inhibition and its indirect reduction of methylation of the 5′ cap of viral mRNA resulting in impaired ebola virus replication inspires further investigation. For instance, **c3Nep** administration massively increased interferon-α production in ebola virus-infected but not uninfected BALB/c mice [36]. This can reverse the suppression of innate antiviral responses, thus offering an additional mechanism of action for the class of SAH hydrolase inhibitors. Additionally, the role of any phosphorylated metabolites deriving from such nucleoside-like compounds, analogously to metabolic activation pathways for well-established antiviral therapies such as ribavirin [37], together with their pharmacokinetic and pharmacodynamics profiles, needs to be considered [38].

An indoline-based alkaloid-like derivative (**CMLDBU3402**, Fig. 1) originated from diversity-oriented synthesis was also found to significantly inhibit viral transcription and, thus, ebola virus infection in A549 cells [39].

Viral entry and fusion modulators

The first phase of ebola virus infection involves fusion of the viral and host cell membranes. Here, proteolysis of the ebola virus membrane glycoprotein ($GP_{1,2}$) has been shown to represent a necessary step [11]. Proteolytic degradation of ebola virus $GP_{1,2}$ was blocked *in vitro* by the unselective cysteine protease inhibitor **E-64d** [11] and **E-64** [40], the selective cathepsin B (CatB) inhibitors **CA-074** [11] and **CA-074Me** [12], the mixed CatB/L inhibitor **FY-DMK** [11] and the cathepsin L (CatL) inhibitor **Z-FY(t-Bu)-DMK** [12] (Fig. 2), resulting in reduced EBOV multiplication [11,12]. Confirming these initial findings, the cysteine and serine protease inhibitor **Leupeptin** and the CatL inhibitor **CID23631927** (Fig. 2) were able to reduce EBOV infection in macrophages [41] and human embryonic kidney 293T cells [42], respectively. Recently, an assay monitoring CatL-based degradation of ebola virus $GP_{1,2}$-derived peptides identified triazine derivatives **5705213** and **7402683** (Fig. 2) as CatL inhibitors that reduced host cell entry for pseudotyped viruses bearing ebola virus-$GP_{1,2}$ [43]. It remains to be seen whether protease inhibitors could have utility beyond an *in vitro* setting, because CatB and CatL activity has been shown not to be required for ebola virus replication *in vivo* [44].

By using a haploid genetic screen, Carette *et al.* identified the endo/lysosomal cholesterol transporter protein Niemann–Pick C1 (NPC1) as a key host element required for ebola virus cellular entry [10]. Here, impairment of NPC1 function (NPC1 phenotype) by genetic manipulation resulted in complete resistance to ebola virus infection *in vitro* and *in vivo*. Treatment with **U18666A** [45] and **imipramine** [46] (Fig. 3), two agents known to induce a NPC1 phenotype, probably via targeting of the NPC1 pathway directly [46] or acid sphingomyelinase (ASMase) inhibition [47], respectively, reduced ebola virus infectivity *in vitro*. Interestingly, this reduced infectivity was ebola virus specific, because the entry of other viruses was not affected [10]. In line with these findings, a concomitant study by Côté *et al.* discovered piperazine derivative **3.47** (Fig. 3) as an effective inhibitor of cellular entry by viruses pseudotyped with EBOV-$GP_{1,2}$ [48] and biochemical experiments revealed that **3.47** inhibited binding of EBOV $GP_{1,2}$ to NPC1. Furthermore, an affinity-labeling agent based on **3.47** cross-linked directly with NPC1, indicating NPC1 as the target protein [48,49].

Selective estrogen receptor (ER) modulators **clomiphene** and **toremiphene** (Fig. 3) showed potent *in vitro* inhibition of ebola virus infection in a screen of US Food and Drug Administration (FDA)-approved drugs [50]. Dosing of **clomiphene** and **toremiphene** to ebola virus-challenged C57Bl/6 mice 1 hour pi (60 mg/kg) yielded survival rates of 90% and 50%, respectively, at day 28 pi. The observed *in vitro* antiviral effects of **clomiphene** and **toremiphene** were independent of ER expression [50] but were affected by NPC1 overexpression [51]. Similarly to **U18666A**, **clomiphene** and **toremiphene**, several cationic amphiphilic small molecules (e.g. **Ro 48-8071** and **terconazole**, Fig. 3) strongly inhibited ebola virus infection *in vitro* [51]. These compounds induced cholesterol accumulation in endosomes, a typical trait of the NPC1 phenotype, and ebola virus entry inhibition was reduced by NPC1 overexpression. Remarkably and by contrast with what has been observed with **3.47**, none of the tested cationic

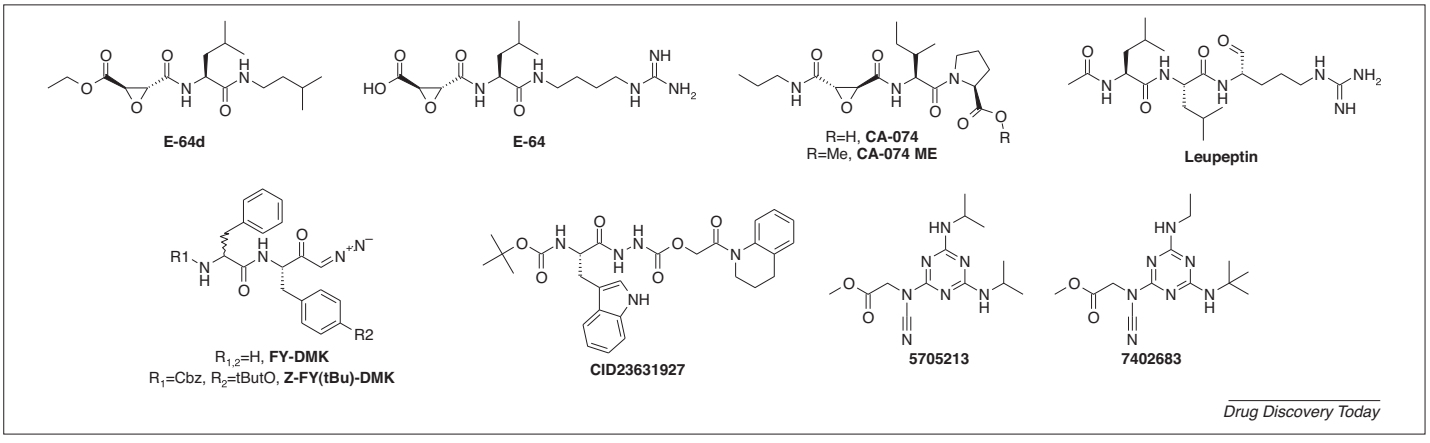

FIGURE 2

Protease inhibitors with reported anti-ebola virus activity.

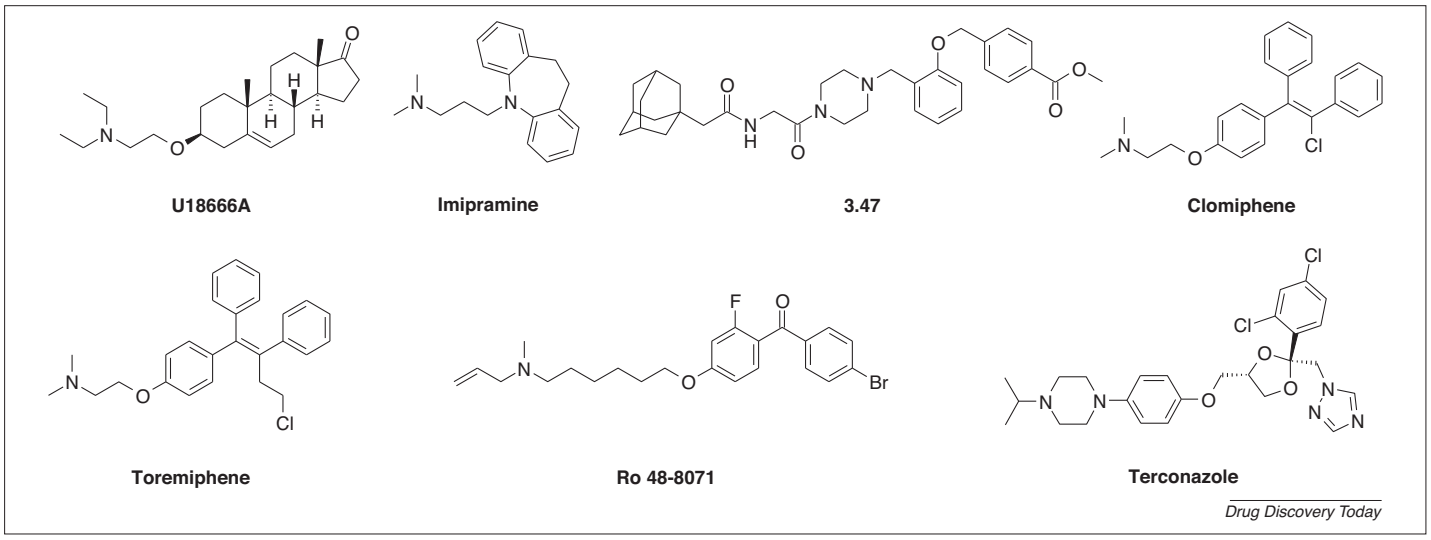

FIGURE 3

Niemann–Pick C1 (NPC1)-dependent, small-molecule ebola virus inhibitors.

amphiphiles disrupted binding of ebola virus-$GP_{1,2}$ to NPC1, indicating yet an additional way of NPC1 pathway interference [51].

A siRNA screening for kinome gene products revealed mitogen-activated protein kinase (MAPK), phosphoinositide 3 kinases (PI3K) and calcium/calmodulin kinases (CAMK2) as cell proteins that are significantly related to EBOV infectivity [52]. Accordingly, the PI3K inhibitor **LY294002** and CAMK2 inhibitor **KN-93** (Fig. 4) effectively reduced ebola virus infection in Vero E6 cells, when tested at 50 mM concentration [52]. Furthermore, a series of pyridinyl imidazole inhibitors of p38 MAPK (e.g. **SB202190** and **p38inK III**, Fig. 4) inhibited viral entry in dendritic cells [53]. In line with the proinflammatory function of MAPK, dosing of the MAPK inhibitors resulted in much-reduced cytokine and chemokine release upon ebola virus infection, an important feature to minimize ebola virus virulence.

Given that protein phosphorylation regulates several protein–protein interactions that are relevant to endosome formation and endocytosis of viruses, Kolokoltsov *et al.* tested the broad tyrosine kinase inhibitor **genistein** and the epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor **tyrphostin AG1478** (Fig. 4) for their anti-ebola virus activity. Both compounds concentration-dependently inhibited ebola virus infection to host cells and displayed a high degree of antiviral synergy when dosed in combination [54]. Furthermore, the c-Abl1 tyrosine kinase was shown to phosphorylate and activate VP40, a key matrix protein involved in the transport of the viral genome–protein complex to the cell surface and subsequent budding [55]. Consequently, c-Abl1 kinase inhibitors **nilotinib** and **imatinib** (Fig. 4) reduced the release of virus-like particles and significantly inhibited EBOV replication *in vitro* [55]. By contrast, dephosphorylation of VP30, a component of the ebola virus nucleocapsid complex, resulted in sustained ebola virus transcription. **Okadaic acid** (Fig. 4) inhibits protein phosphatases 1 (PP1) and 2A (PP2A), which together with PP2C, are responsible for VP30 dephosphorylation, and significantly blocked ebola virus growth *in vitro* [56].

Perturbation of cell signaling processes, as shown in the above protein kinase examples, can affect the complex process of viral entry. Results with the multiple ion channel blockers **amiodarone**, **dronedarone** and the L-type calcium channel blocker **verapamil** (Fig. 5) support this notion. All three agents were shown to inhibit ebola virus $GP_{1,2}$-mediated cell entry [57]. Interestingly, in the same experiments, T-type calcium and potassium blockers had no effect. Consistently with the viral entry results, **amiodarone** concentration-dependently reduced EBOV infection in EAhy cells [57]. In this context, **rottlerin** (Fig. 5), a potent large conductance potassium channel ($BK_{Ca^{2+}}$) opener, a reported mitochondrial uncoupler [58] and an ambiguous protein kinase C (PKC) inhibitor [59], has also been demonstrated to inhibit ebola virus-like particle entry to MDCK cells [60].

The process of ebola virus entry and fusion to host cells requires dynamic trafficking of viral payloads via endocytosis and, as such, is dependent on a functional cytoskeleton. Here, the microtubule-stabilizer taxol enhanced ebola virus entry, whereas the microtubule-disrupting agents **nocodazole** and **colchicine** (Fig. 6) significantly impaired it [61]. Additionally, intact and functional actin filaments are required for ebola virus infectivity, as indicated by the EBPV inhibitory effects of actin-specific reagents **cytochalasin B** and **D**, **latrunculin A** and **jasplakinolide** [61] (Fig. 6).

The ebola virus GPs represent a key recognition element for viral maturation and are crucial mediators of viral budding. Their structure and function are dependent on their glycosylation profile. For instance, treatment with **tunicamycin** (Fig. 7) an *N*-linked glycosylation suppressor, decreased EBOV infection of HeLa cells by >90% [62]. Moreover, a series of imino sugars (**IHVR11029**, **IHVR17028** and **IHVR19029**; Fig. 7) was recently reported to inhibit endoplasmic reticulum (ER) α-glucosidase I, a deglycosylating enzyme required for proper folding and maturation of nascent proteins. Importantly, the three imino sugars yielded 50–80% survival when administered to EBOV-challenged C57Bl/6 mice 4 hours pi [63].

Mudhasani *et al.* performed a high content image-based screening for inhibitors of Rift Valley fever virus (RVFV) to HeLa cells [64]. Among the hits that were subsequently screened for additional antiviral activity, **G202-0362** (Fig. 8) proved to be the most

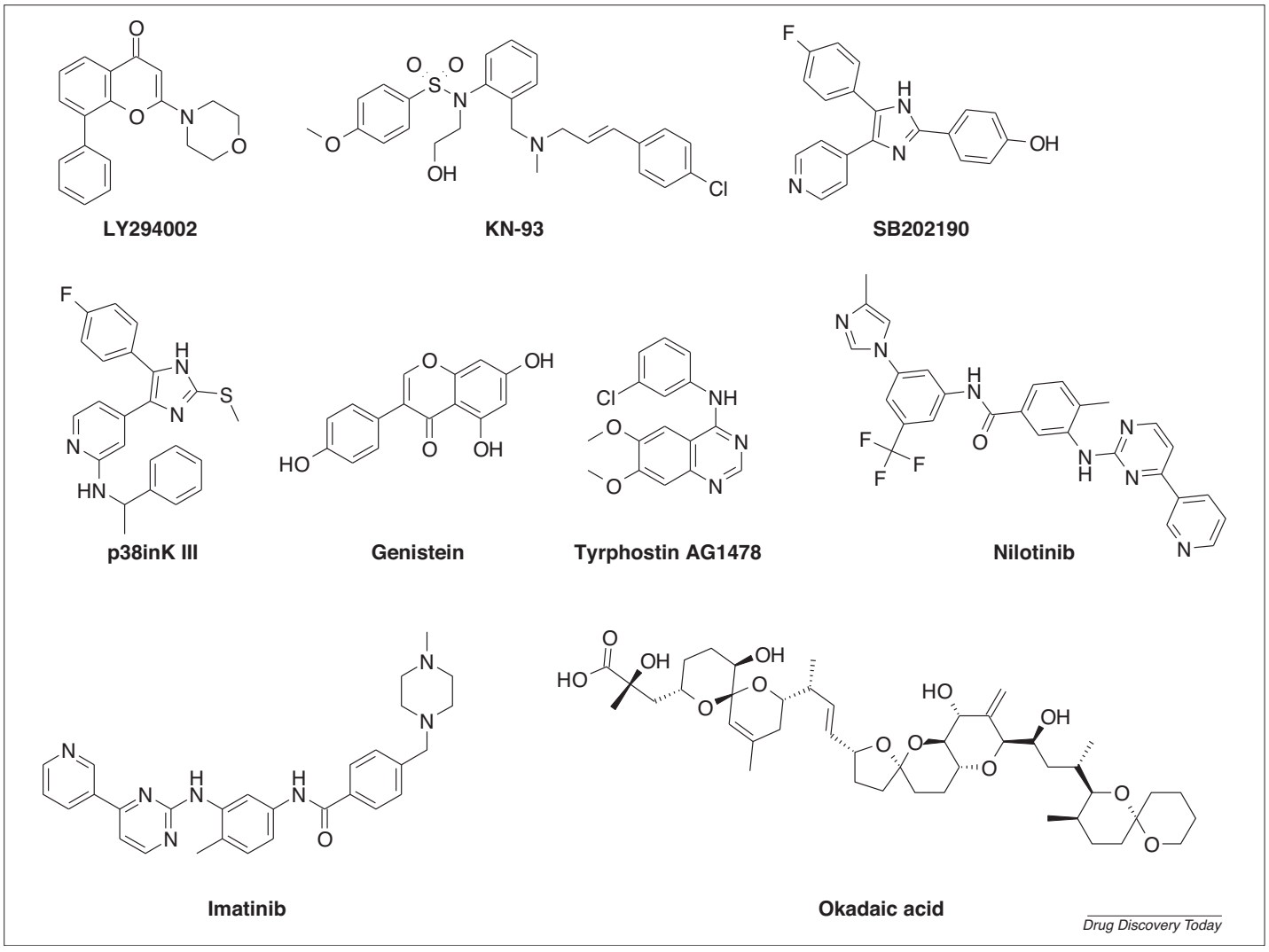

FIGURE 4

Kinase and phosphatase inhibitors with reported anti-ebola virus activity.

potent against ebola virus infection (EC_{50}: 16.1 mM). Interestingly, additional mechanistic studies using RVFV indicated that **G202-0362** affected viral budding from the Golgi to the cell surface [64]. Another two compounds found to impair ebola virus budding directly, **4** and **5** (Fig. 8), were determined to inhibit the interaction between the VP40 PPxY late budding domains and the host Nedd4 E3 ubiquitin ligase [65]. Benzodiazepine derivative **7** (Fig. 8) was also shown to inhibit EBOV infection in Vero E6 cells and mechanistic experiments indicated that it directly binds ebola virus $GP_{1,2}$ [66], normally required for initiating virus budding and entry.

Small molecule ebola virus modulators *in vitro*

Several different chemotypes have shown to affect ebola virus-related biology and impair ebola virus infection *in vitro*, as summarized in Fig. 9. These include the heat shock protein 90 (HSP90)

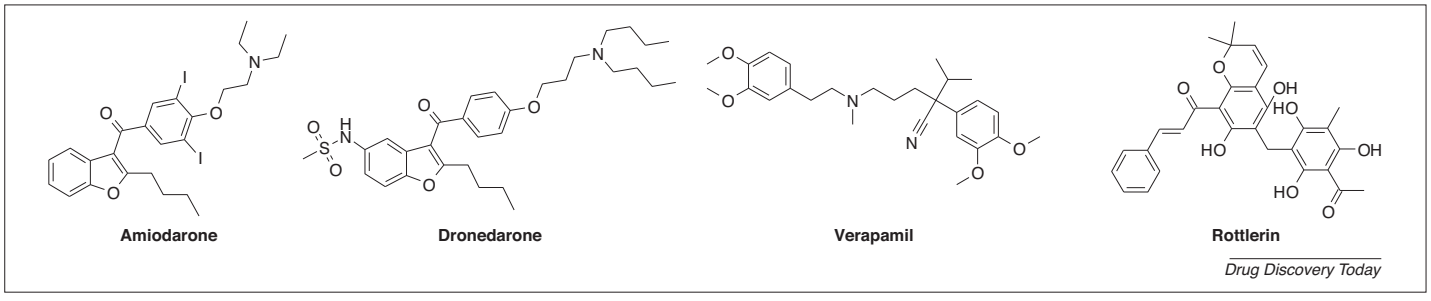

FIGURE 5

Ion channel modulators with reported anti-ebola virus activity.

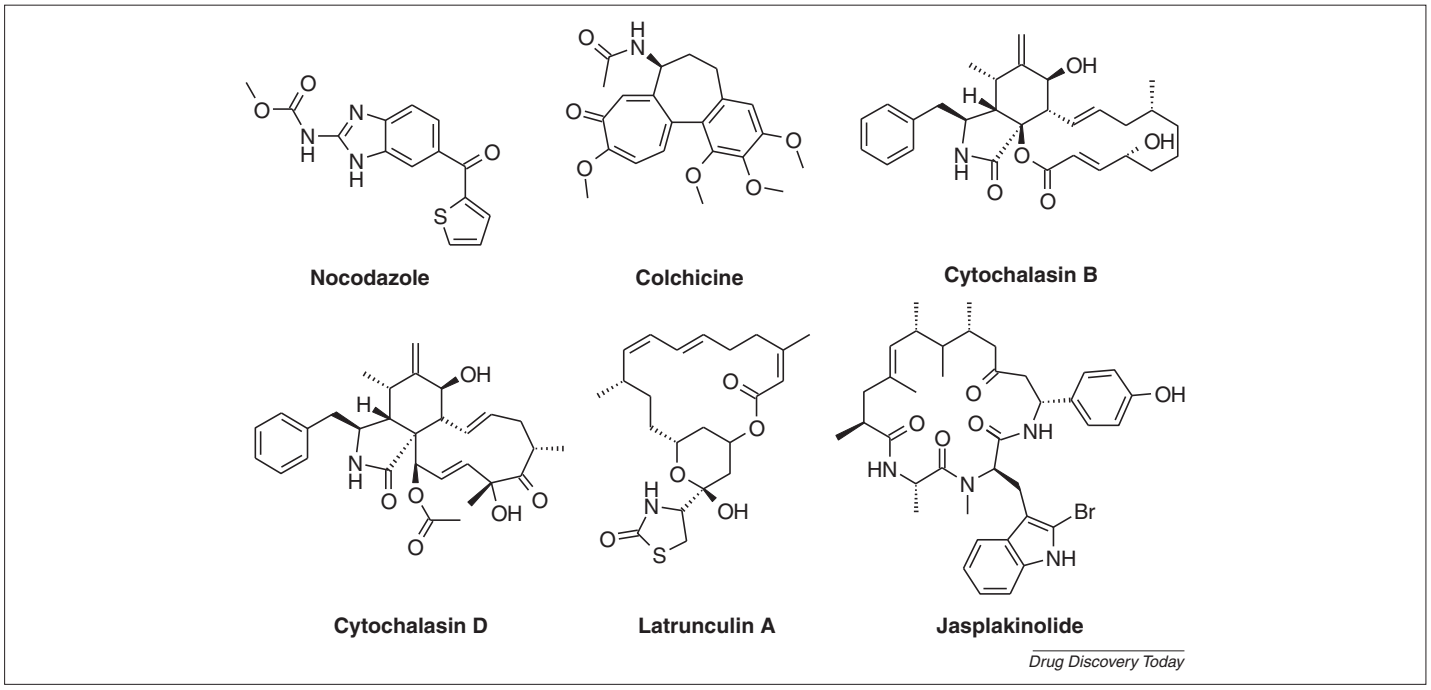

FIGURE 6

Microtubule and actin modulators with reported anti-ebola virus activity.

inhibitor **17-AAG** [67], the sodium/potassium-transporting ATPase subunit alpha-1 (ATP1A1) inhibitor **ouabain** (probably affecting the function of ebola virus VP24 [68]) the 11beta-hydroxysteroid dehydrogenase inhibitor **glycyrrhizic acid** [69], the specific vacuolar ATPase (V-ATPase) inhibitors **bafilomycin A1** and **concanamycin A**, because of their alkalinizing effect on the endosome [12,61,70] and the nonspecific V-ATPase inhibitor and RAB5A GTPase activator **vacuolin-1** [47,71]. Furthermore, **retinazone** (Fig. 9) was shown to covalently bind glucocorticoid response elements and disrupt EBOV infection [72], whereas isoxazole derivative **8j** (Fig. 9) inhibited EBOV $GP_{1,2}$-pseudotyped HIV particles entry in 293T cells (IC_{50} = 2.5 mM) [73]. Lastly, in a drug-repurposing effort, Madrid *et al.* screened 1012 FDA-approved drugs for their antiviral effect against several viral pathogens, including ebola viruses [74]. Among the compounds able to inhibit pseudotype viral entry, **amiodaquin**, **diphenoxylate**, **diphenylpyraline** and **ketotifen** (Fig. 9) also displayed the ability to inhibit ebola virus replication [74].

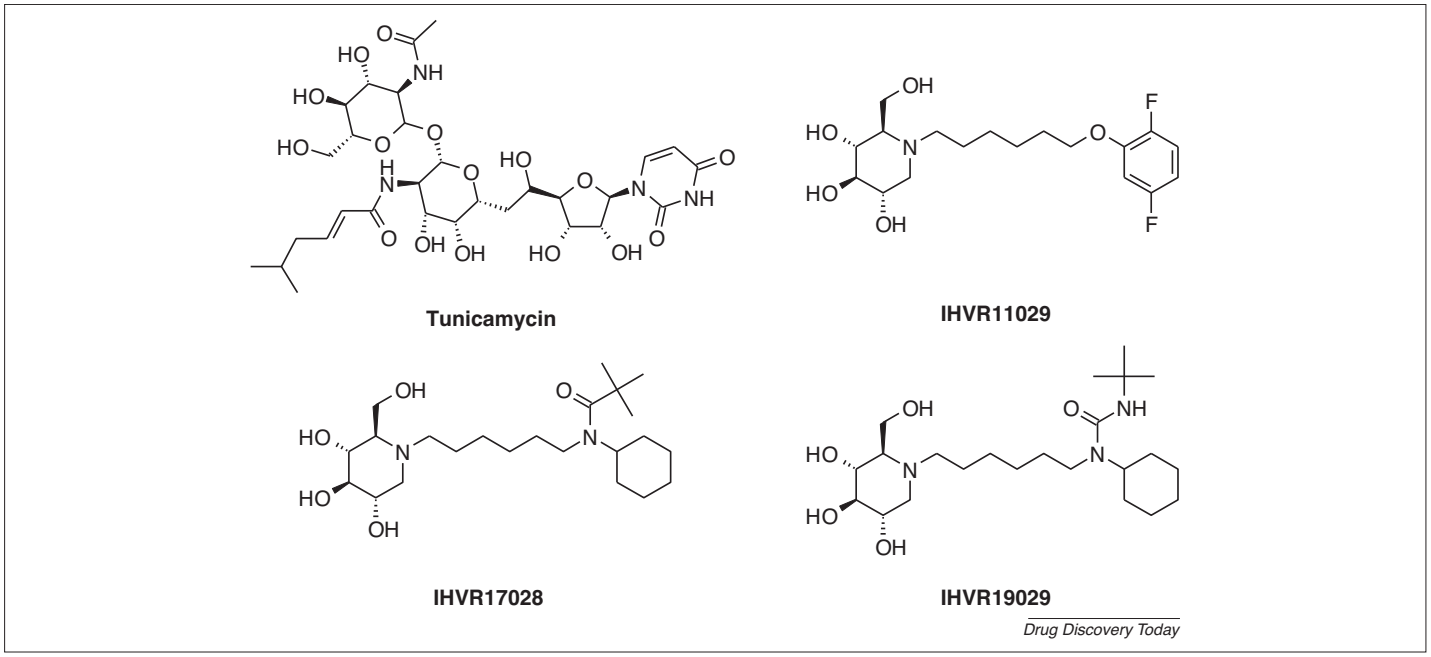

FIGURE 7

Glycosylation modulators with reported anti-ebola virus activity.

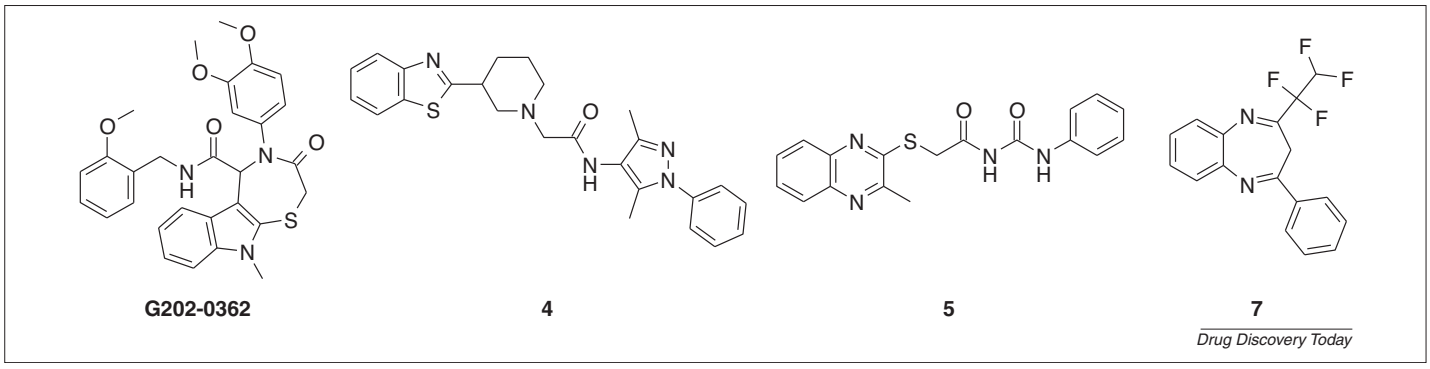

FIGURE 8

Budding modulators with reported anti-ebola virus activity.

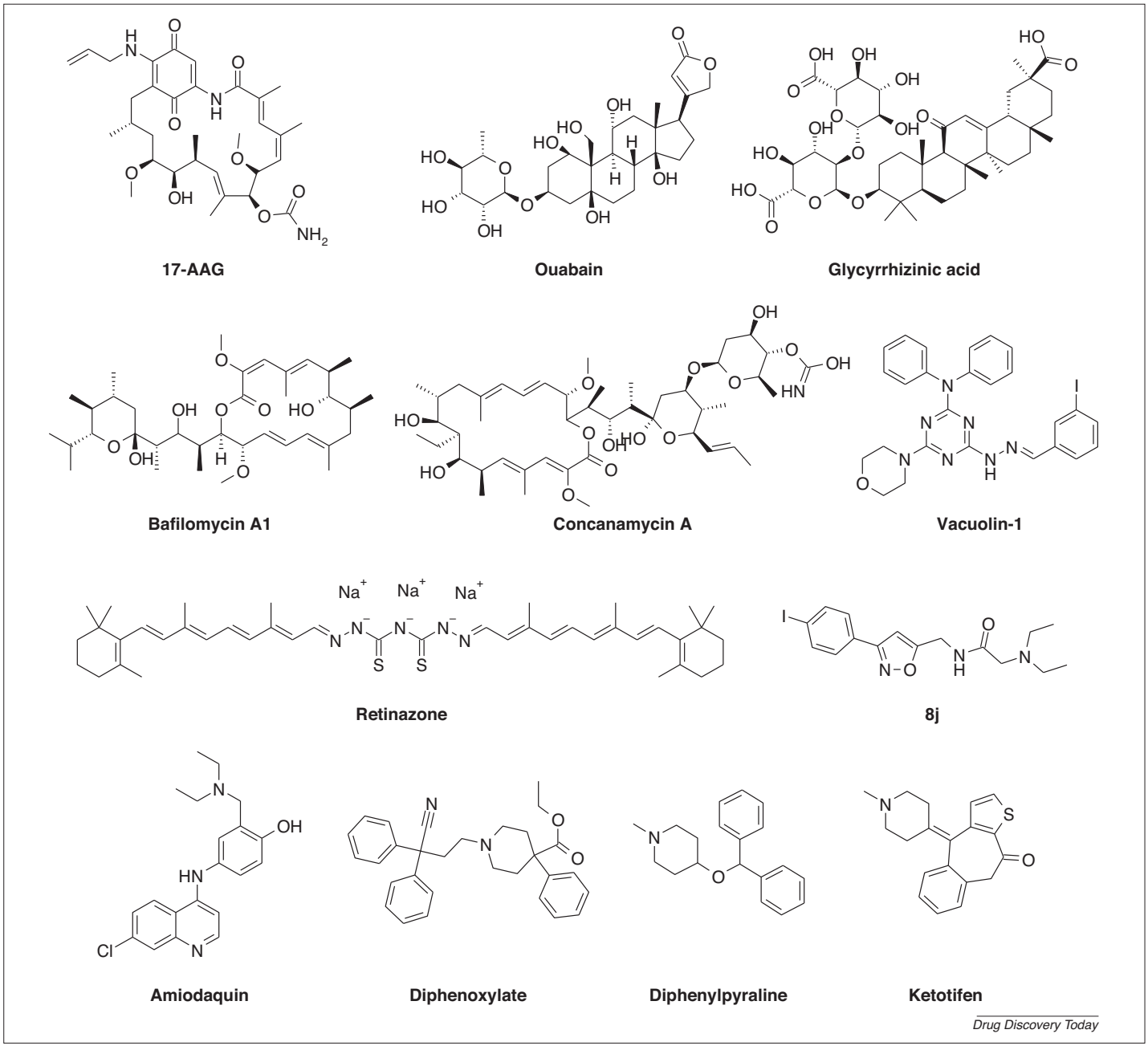

FIGURE 9

Diverse small molecules with reported anti-ebola virus activity *in vitro*.

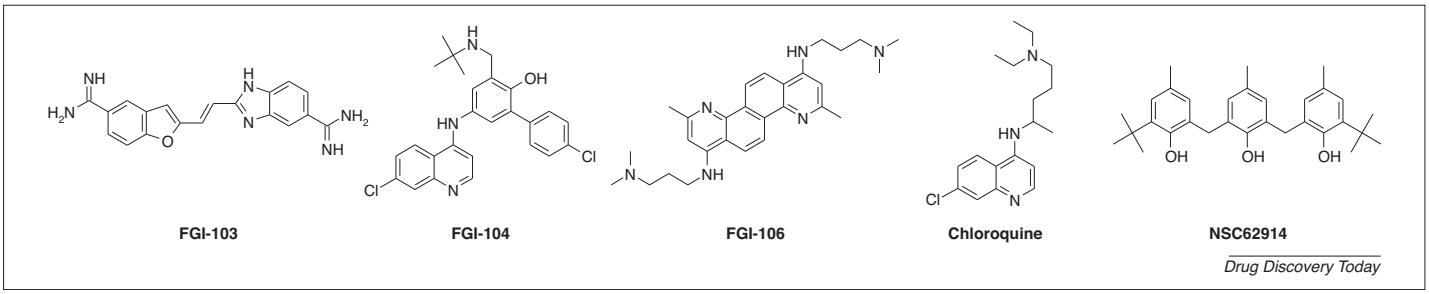

FIGURE 10

Diverse small molecules with reported anti-ebola virus activity *in vivo*.

Small molecule ebola virus modulators *in vivo*

Screening of the National Cancer Institute compound library (NCI, Frederick, MD) using an EBOV variant that expresses GFP (GFP-EBOV) in a fluorescence-based high-throughput assay identified **FGI-103** (Fig. 10) as an effective EBOV replication inhibitor (EC_{90}: 330 nM) with no overt *in vitro* cytotoxicity at the compound concentration range tested and an *in vivo* 50% lethal intraperitoneal (ip) dose greater than than 200 mg/kg [75]. Prophylactic administration (1 hour before ebola virus infection) of **FGI-103** to C57Bl/6 mice resulted in 100% protection. Therapeutic administration (1–5 days pi) yielded dose- and administration time-dependent protection, with a therapeutic window of less than 2 days. Ongoing studies are aiming at delineating the antiviral mechanism of action of **FGI-103** [75]. In 2009, the same research group at Functional Genetics Inc. was issued a patent covering 4-amino-quinoline derivatives (Fig. 10) as methods of inhibiting viral infection [76]. One such derivative, **FGI-104** (Fig. 10), an analog of the antimalarial drug **amodiaquine** (cf. Figs 9 and 10), exhibited broad-spectrum antiviral activity *in vitro*, including ebola virus, Hepatitis B (HBV) and C (HCV), and Cowpox viruses, among others [77]. In a prophylactic mouse model of ebola virus infection, a 10 mg/kg dose of **FGI-104** (2 hours before infection) yielded a 100% survival rate. Mechanistic studies with HCV and HBV material indicated that FGI-104 does not interfere with viral replication [77].

Using a GFP-EBOV-based high-throughput-screening assay, Aman *et al.* identified a diazachrysene derivative (**FGI-106**, Fig. 10) with significant *in vitro* antiviral activity (EBOV EC_{90}: 0.6 mM) and limited cytotoxicity in VERO E6 cells (CC_{50}: 10 mM) [78]. When administered ip 1 hour before infection to C57Bl/6 mice, **FGI-106** showed a dose-dependent decrease in mortality rate with a 5 mg/kg dose offering 100% survival. **FGI-106** also conferred protection when used in a therapeutic setting, although mortality increased with time of first dose [78]. The mechanism of antiviral action of **FGI-106** has not been elucidated. However, based on the wide antiviral *in vitro* profile reported for **FGI-106** (inhibiting replication of both negative and positive-strand RNA viruses), the authors speculate that it might target a host factor or pathway that is conservatively used by different viruses for replication [78]. Interestingly, **FGI-106** analogs with 3-(morpholin-4-yl)propan-1-amine side chains and 2,8-des-methyl-diazachrysene scaffold (**FGI-106-a** and **FGI-106-b**, Table S1 in the supplementary material online) also exhibited ebola virus inhibition *in vitro* [79,80].

Chloroquine (Fig. 10) emerged as one of the best *in vitro* ebola virus inhibitors following a drug-repurposing screening [74]. Follow-up *in vivo* studies revealed that **chloroquine** was the only tested drug able to reduce mortality significantly (90% survival rate at day 13 pi) when dosed at 90 mg/kg 4 hours before infection [74]. **Chloroquine** has been shown to exert multiple biological actions in cells, notably endosomal trafficking interference, all likely to contribute to its observed antiviral effect [74].

Chemical screening for EBOV inhibitors identified triphenolic derivative **NSC62914** (Fig. 10) as an effective inhibitor of EBOV infection in Vero E6 cells [81]. **NSC62914** displayed marked antioxidant properties, similar to known reactive oxygen species scavengers. In a prophylaxis study, 2 mg/kg **NSC62914** 1 hour before infection protected C57Bl/6 from EBOV infection (80% survival rate). The same dose was less effective in a therapeutic model, yielding 50% survival when administered to EBOV-challenged C57Bl/6 mice 1 day pi, with the 5 mg/kg dose decreasing survival even further, possibly because of compound toxicity [81].

Concluding remarks

Despite the wide public concern associated with ebola virus infection, it is comforting to witness the continuous advances made in dissecting crucial mechanisms of ebola virus infection and the identification of potential therapeutic targets. Likewise, the promising preclinical results obtained from existing experimental antiviral agents [28] or approved medicaments [50,74] in the small-molecule space seem to indicate opportunities to tackle ebola viruses beyond vaccines [2], biologicals [16–20] and RNA interference [21]. Importantly, the manifest ability of the immune system to counteract ebola virus infection, as from asymptomatic individuals [82] or antiviral treatment [27], represents a crucial resource to harness further. Still, several important challenges need to be resolved. First, the translational potential of the preclinical findings highlighted here needs to be verified. Even ebola virus hemorrhagic fever (EHF) models as advanced as those in nonhuman primates do not completely recapitulate the immunological aspects of ebola virus infection, and there is considerable difference in treatment efficacy across different animal models of ebola virus infection [83]. Here, rodent species are easier to protect from ebola virus infection compared with higher species, particularly humans, and their true predictive power to a clinical situation needs to be assessed. Likewise, the relevance of *in vivo* treatment results using rodent-adapted ebola virus forms, and that of *in vitro* data using vesicular stomatitis virus particles, needs to be evaluated in greater details. Second, the optimal window of efficacy for any ebola virus therapeutic needs to be defined. All the various vaccines and biologicals, as well as the small molecules described

here, have been administered to animals very close in time to the given ebola virus challenge. Although this might still provide protection benefits for personnel at risk of infection, their prophylactic and therapeutic potential for wider use remain unclear.

Small molecule-based, oral treatment of ebola virus infections is of particular appeal in remote outbreak settings, because the logistical challenges associated with it are reduced compared with biologicals or intravenous treatment in general. Effective, small-molecule antiviral agents have been successfully discovered and developed for a large range of viruses. Here, nucleoside derivatives and their ability to impair virus transcription might offer an important therapeutic option. Alternatively, small molecules targeting the process of virus entry could yield treatment options that are less susceptible to virus mutations. The current study represents the first systematic analysis of small molecules reported to inhibit ebola virus infection. As the gathered data were sparse and unstructured, we believe that this article could serve as a useful survey for researchers, especially medicinal chemists, embarking on ebola virus infection projects to evaluate available chemical matters and anti-ebola virus mechanistic hypotheses.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drudis.2014.12.010.

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