Polycyclic N-Benzamido Imides with Potent Activity against Vaccinia Virus

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The synthesis and antiviral activity of a series of novel polycyclic analogues of the orthopoxvirus egress inhibitor tecovirimat (ST-246) is presented. Several of these compounds display sub-micromolar activity against vaccinia virus, and were more potent than cidofovir (CDV). The more active compounds were about 10-fold more active than CDV, with minimum cytotoxic concentrations above 100 μM. Chemical manipulations of the two carbon–carbon double bonds present in the compounds were carried out to further explore the structure–activity relationships of these new polycyclic imides. Hydrogenation of the two carbon–carbon double bonds decreases antiviral activity, whereas either cyclopropanation or epoxidation of the double bonds fully eliminates the antiviral activity.

Introduction

Poxviruses, double-stranded DNA viruses that replicate entirely in the cytoplasm, are the largest known animal viruses.[1] The most famous members of the poxvirus family are variola virus, the causative agent of smallpox, and vaccinia virus, which shares over 97% amino acid sequence identity with variola, is used in the variola virus vaccine, and is widely used as a model poxvirus in the laboratory.[2]

Smallpox is a devastating, highly transmissible, infectious disease with high morbidity and up to 40% mortality. Following a global, intensive immunization campaign with the vaccinia virus vaccine, the World Health Organization (WHO) declared the worldwide eradication of smallpox in 1980. Three years later, variola virus stocks were either supposedly destroyed or submitted to one of the two WHO-approved laboratories situated at the US Center for Disease Control and Prevention (CDC) in Atlanta and at the Russian State Research Center of Virology and Biotechnology in Novosibirsk.[3]

The successful global immunization campaign resulted in a decreased demand for the development of therapies against variola virus because pharmaceutical companies had little interest in developing drugs for a disease that had already been eradicated. However, owing to recent worldwide political developments, variola is nowadays widely regarded as one of the most significant bioterrorist threats.[4] In fact, the CDC has placed variola virus at the top of the high-threat agents list (category A)[5] because the impact of a smallpox pandemic in the human population today would be even more catastrophic than during the last century as a result of the vaccination programs being suspended, mainly because the vaccinia virus vaccines have substantial side effects.[6] Moreover, there is also a natural public threat arising from the emergence of zoonotic poxvirus infections such as the monkeypox virus, a virus that produces a disease in man that closely resembles smallpox, though less frequently fatal. Monkeypox exists naturally in Africa and several cases are reported in the US every year.[7] The bioterrorist threat, the growing concern about zoonotic infections, and the side effects of vaccines have re-established the need for efficient safe therapies for poxvirus infections.

Recently, several compounds have been identified that inhibit various steps in poxvirus infection, including DNA synthesis and virion morphogenesis.[8] The drugs currently recommended for short-term prophylaxis, adverse vaccination reactions, and emergency treatment against smallpox are cidofovir (CDV) and tecovirimat (ST-246; Figure 1).

CDV is an acyclic phosphonate derivative of cytosine that targets viral DNA polymerases. It has a broad-spectrum antivi-
eral activity, proving to be effective against many poxviruses and herpesviruses. However, the low oral bioavailability of CDV and potential nephrotoxicity associated with its intravenous administration would be an issue in the case of a bioterrorist attack. Prodrugs of CDV have been prepared that significantly enhance its oral bioavailability.

Tecovirimat, a new, potent, orally active antipoxviral agent recently disclosed by SIGA laboratories, features a polycyclic hydrocarbon moiety and an N-benzamido substituent. It targets the F13L protein of vaccinia virus, a membrane component required for the formation of extracellular viral particles. Tecovirimat was shown to inhibit the growth of multiple orthopoxviruses in cell cultures, including two strains of variola virus. In addition, tecovirimat has demonstrated significant antiviral activity in various animal models of the poxvirus disease, including the complete protection of golden-mantled ground squirrels from lethal doses of monkeypox virus and protection of nonhuman primates from variola virus in lesional disease models. The agent demonstrated favorable safety, tolerability, and pharmacokinetics in a double-blind, randomized, placebo-controlled phase I ascending-dose study in healthy human volunteers. These and other results support the use of tecovirimat to prevent smallpox disease in nonvaccinated individuals, as a postexposure therapeutic for use in nonsymptomatic individuals exposed to variola virus, as a treatment for confirmed smallpox infection, and as an adjuvant to vaccination with the smallpox vaccine. Recently, it has received both orphan drug designation and fast-track status from the US Food and Drug Administration (FDA), supporting development of tecovirimat for the prevention and treatment of smallpox infections.

SIGA has disclosed structure–activity relationships on ST-246, mainly regarding the effects of the substitution of the aromatic ring. However, few efforts were made with regard to the replacement of the tricyclononene subunit (Figure 2). Herein we report the synthesis and potent antiviral activity of several ST-246 analogues containing a pentacyclo[6.4.0.0^2,10.03,7.04,9]dodeca-5,11-diene moiety. To the best of our knowledge, these are the first biologically active compounds featuring this pentacyclic framework. We also report the synthesis and evaluation of several analogues of ST-246 containing a tricyclo[3.3.0.0^3,7]octane (bisnoradamante) skeleton. Note that although ST-246 and several analogues studied by SIGA had the two carbonyl groups of the imide moiety of the molecule attached to methylene carbon atoms, the compounds herein feature the carbonyl groups attached to quaternary carbon atoms (Figure 3).

Synthesis of compounds 3a–j was accomplished in two steps through condensation of an acyl hydrazide with the known bisnoradamantane anhydride (1), followed by thermally induced dehydratation of the carboxylic acids 2a–j to the N-benzamido imides 3a–j (Scheme 1).

On the other hand, starting from diester 4, hydrolysis and dehydration led to anhydride 5 in very high yield. Reaction of 5 with a series of acyl hydrazides in ethanol led to the corresponding mixtures of acids 6 and benzamido imides 7. Heating of these mixtures in toluene or xylene at reflux for 24 h led to the required imides 7 in good overall yields (Scheme 2).

To explore the structure–activity relationship (SAR) of these new polycyclic imides further we carried out chemical manipu-
Reactions of the two carbon–carbon double bonds of 7. Reaction of 7a, 7k, and 7s with an excess of dimethyldioxirane in acetone led to the corresponding diepoxides 8a, 8k, and 8s in high yields (Scheme 2). The stereoselectivity of the epoxidation reaction was unequivocally established for 8s by X-ray crystallography (Figure 4).[21]

Catalytic hydrogenation of 7a and 7d led to 9a and 9d, respectively, in nearly quantitative yields. The reduction of the two carbon–carbon double bonds of 7b was accompanied by hydrogenolysis of the C–Br bond, leading to 9e in quantitative yield. Finally, we explored the double cyclopropanation of the dienes. Because several attempts to achieve the cyclopropanation of 7a failed, we carried out the cyclopropanation of anhydride 5 that led to anhydride 10. Reaction of 10 with selected acyl hydrazides, followed by thermally induced dehydration of the carboxylic acids 11, led to N-benzamido imides 12a,k,l,m,o,p in good overall yields (Scheme 3). The stereoselectivity of the cyclopropanation reaction was unequivocally established by X-ray crystallography (Figure 5).[21]

The structures of all new compounds were confirmed by elemental analysis and/or accurate mass measurement, as well as IR, ¹H NMR, ¹³C NMR, and mass spectral data. Moreover, the structural features of 3e, 8s, and 10 were further confirmed by X-ray crystallography (Figure 6).[21] Interestingly, in 3e and in 8s, the plane of the benzamido substituent is essentially orthogonal to the plane of the imide group.

For the compounds of general structure 3, 7, 8, 9, and 12, CPE (cytopathic effect) reduction assays were performed to determine the antiviral activity against a broad panel of DNA and RNA viruses, that is, herpes simplex virus type 1 and type 2, and vaccinia virus (evaluated in infected human embryonic lung fibroblast (HEL) cells); feline coronavirus and feline herpesvirus (in Crandell–Rees Feline Kidney cells); vesicular stomatitis virus, Coxsackie B4 virus and respiratory syncytium virus (in HeLa cells); parainfluenza-3 virus, reovirus-1, Sindbis virus, and Punta Toro virus (tested in Vero cells); and influenza virus (in Madin–Darby canine kidney cells).[22]

In studying the SAR of several analogues of ST-246, Bailey et al. have previously found that electron-withdrawing substituents are beneficial for the antiviral activity.
tution on the meta or para position of the N-benzamido sub-
stituent provided the most potent inhibitors of orthopoxvi-
rus.[10, 15] We observed the same trend in our bisnoradamantane
derivatives, the p-nitro (3c) and 4-pyridyl (3f) derivatives being
the only active compounds against vaccinia virus (Table 1). For
these reasons we only synthesized derivatives of
8a.k.s and bicsyclopropyl derivatives 12a.k.m.o.p showed EC50 >
100 μM. The number of independent tests is given in parentheses.

Experimental Section

Synthesis of 2a: A mixture of anhydride 1 (103 mg, 0.50 mmol), 4-
trifluoromethylbenzoic acid hydrazide (102 mg, 0.50 mmol), and a
drop of diisopropylethylamine in absolute EtOH (2 mL) was heated
under reflux for 5 h. Upon cooling to room temperature, H2O
(0.2 mL) was added. The precipitate was collected by filtration and
washed with cold EtOH (2 × 2 mL) to give compound 2a as a white
solid (176 mg, 86% yield); mp: 256–257 °C; 1H NMR (500 MHz,
[1] [D6]DMSO): δ = 1.15 (s, 6H, CH3), 1.60 (dd, J = 8.0, J = 3.5 Hz, 2H)
and 1.72 (dd, J = 8.0, J = 3.5 Hz, 2H) (2(8)-H, and 4(6)-H); 1.80 (d,
J = 8.0 Hz, 2H) and 1.87 (d, J = 8.0 Hz, 2H) (2(8)-H, and 4(6)-H); 9.52
(s, 1H, NHCO-C6H5), 10.53 (s, 1H, NHCO-Ar), 11.82 ppm (br s, 1 H,
NH); 13C NMR (100.6 MHz, [1] [D6]DMSO): δ = 13.7 (C3, C7)-CH3,
47.1 (C, C3(7)), 55.7 (CH2) and 56.0 (CH2) (C2(8) and C4(6)), 57.1 (C)
and 58.0 (C1 and C5), 123.9 (C, q, Jc-f = 272.2 Hz, CF3), 125.4

Table 1. Antiviral activity and cytotoxicity in vaccinia-virus-infected HEL
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cells.

| Compound | Antiviral EC50 [μM]a | Minimum cytotoxic concentration [μM]a |
|----------|---------------------|-------------------------------------|
| 3a       | >100                | >100                                |
| 3b       | 100                 | >100                                |
| 3c       | 45                  | >100                                |
| 3d       | >100                | >100                                |
| 3e       | 100                 | >100                                |
| 3f       | 45                  | >100                                |
| 3g       | >100                | >100                                |
| 3h       | >100                | >100                                |
| 3i       | >100                | >100                                |
| 3j       | >100                | >100                                |
| 7a       | 1.2 (n = 3)         | >100                                |
| 7b       | 7.3 (n = 3)         | >100                                |
| 7c       | 3.0 (n = 2)         | >100                                |
| 7d       | 8.3 (n = 3)         | >100                                |
| 7f       | >100                | >100                                |
| 7k       | 0.48 (n = 2)        | 100                                 |
| 7l       | 0.60 (n = 2)        | 100                                 |
| 7m       | 0.16 (n = 2)        | 100                                 |
| 7n       | 0.82 (n = 2)        | 100                                 |
| 7o       | 3 (n = 2)           | >100                                |
| 7p       | 48 (n = 2)          | >100                                |
| 7q       | 16 (n = 2)          | >100                                |
| 7r       | 16 (n = 2)          | >100                                |
| 7s       | >100                | 100                                 |
| 7t       | >20                 | >100                                |
| 7u       | 32 (n = 2)          | >100                                |
| 7v       | 13.7 (n = 3)        | >100                                |
| 7w       | >100                | >100                                |
| 7x       | >100                | >100                                |
| ST-246   | 0.065 (n = 3)       | >100                                |
| Cidofovir| 5.7 (n = 3)         | >250                                |

[a] Compound concentration required to decrease virus-induced cytopa-
thogenicity by 50%. (b) Compound concentration required to cause a
microscopically detectable alteration of normal cell morphology. Diepoxides
8a.k.s and bicsyclopropyl derivatives 12a.k.m.o.p showed EC50 >
100 μM. The number of independent tests is given in parentheses.
(CH, q, J = 3.8 Hz, Ar-C3(5)), 128.4 (CH, Ar-C2(6)), 131.4 (C, q, J = 3.19 Hz, Ar-C4), 136.6 (C, Ar-C1), 164.2 (C, Ar-CO). 170.9 (C, COOH). 173.6 ppm (C, CS-CONH); IR (KBr): ν = 3400–2850 (max. at 3271, 3188, 3003, 2971, 2891, 2872), 1715, 1678, 1629, 1500, 1479, 1328, 1307, 1168, 1122, 1065, 851, 702, 689 cm⁻¹; MS (El, 70 eV): m/z (%): 410 (1) [M]⁺, 393 (2) [M–OH]⁺, 337 (8), 207 (97) [C₆H₄–O–CO]*, 189 (22), 173 (100) [CF₃–C–H₂–CO]*, 161 (53) [CF₃–H₃–C–CO]*, 145 (41), [CF₃–C–H]⁺, 133 (25), 121 (24); Anal. calcld for C₈H₇F₃N₂O₅·0.25acetone: C 59.55, H 3.62, N 6.10, F 13.48%. 

Compounds 2b–i were prepared in a similar manner to 2a; full experimental data for these compounds are given in the Supporting Information.

Synthesis of 3a: A suspension of acid 2a (155 mg, 0.38 mmol) in xylene (5 mL) was heated under reflux for 24 h in Dean–Stark apparatus. The solution was concentrated in vacuo to give compound 3a as a white solid (146 mg, 99% yield). An analytical sample of 3a was obtained by crystallization from CH₂Cl₂/pentane; mp: 217–218°C; ¹H NMR (500 MHz, D₂DMSO): δ = 1.22 (s, 6 H, CH₃), 1.84–1.89 (complex signal, 4 H, 6(10)-H and 9(11)-H), 1.93–1.98 (complex signal, 4 H, 6(10)-H and 9(11)-H), 7.96 (d, J = 8.0 Hz, 2 H, Ar-3(5)-H), 8.11 (d, J = 8.0 Hz, 2 H, Ar-2(6)-H), 11.39 ppm (s, 1 H, NH); ¹³C NMR (100 MHz, D₂DMSO): δ = 15.6 (CH) and 15.7 (CH) (C7 and C8), 30.9 (C) and 51.1 (C and C8 and C9), 53.8 (C, C15), 54.3 (CH) and 54.5 (CH) (C6(10) and C9(11)), 123.7 (C, q, J = 272.2 Hz, CF₂), 125.8 (CH, q, J = 3.8 Hz, Ar-C3(5)), 128.6 (CH, Ar-C2(6)), 132.3 (C, q, J = 3.2 Hz, Ar-C4, 134.8 (C, Ar-C1), 163.6 (C, Ar-CONH), 173.8 ppm (C, Ar-C2(4)); IR (KBr): ν = 3328, 3061, 2928, 1722, 1704, 1480, 1407, 1328, 1270, 1244, 1163, 1134, 1077, 1017, 854, 822, 774, 702 cm⁻¹; MS (El, 70 eV): m/z (%): 412 (2) [M]⁺, 393 (4) [M–F]⁻, 348 (19), 347 (100) [M–CF₃]⁻, 173 (80) [CF₃–C–H₂–CO]*, 154 (13), 153 (26), 152 (20), 145 (35) [CF₃–C–H]⁻; Anal. calcld for C₈H₇F₃N₂O₅·0.5H₂O: C 62.71, H 3.83, N 6.65, F 14.53, found: C 62.61, H 3.98, N 6.55, F 14.38.

Like compound 7a, derivatives 7b–d, f, k–u were prepared in a similar manner to 7a; full experimental data for these compounds are given in the Supporting Information.

Synthesis of 8a: An excess of a solution of dimethylxiranate (63 mg, 3.8 mmol) in acetone (1.5 mL) was added to solid compound 7a (70 mg, 0.71 mmol) and the solution was stirred overnight at room temperature. The solvent was evaporated in vacuo to give compound 8a as a white solid (75 mg, 99% yield). An analytical sample of 8a was obtained by crystallization from acetone. Mp: > 290°C (dec.); ¹H NMR (500 MHz, D₂DMSO): δ = 2.14 (br s, 2 H, 11-H and 12-H), 3.31 (br s, 4 H, 6(10)-H and 13(17)-H), 3.36 (br s, 2 H) and 3.43 (br s, 2 H) (7(9)-H and 14(16)-H), 7.95 (d, J = 8.3 Hz, 2 H, Ar-3(5)-H), 8.11 (d, J = 8.3 Hz, 2 H, Ar-2(6)-H), 11.62 ppm (s, 1 H, NH); ¹³C NMR (100 MHz, D₂DMSO): δ = 38.4 (CH) and 39.0 (CH) (C11 and C12), 47.3 (CH) and 47.7 (CH) (C7(9) and C14(16)), 54.8 (CH) and 55.1 (CH) (C6(10) and C13(17)), 59.2 (C, C15), 123.7 (C, q, J = 272.8 Hz, CF₂), 125.9 (CH, q, J = 3.8 Hz, Ar-C3(5)), 128.8 (CH, Ar-C2(6)), 132.5 (C, q, J = 31.8 Hz, Ar-C4), 134.3 (C, Ar-C1), 163.4 (C, Ar-CONH), 171.0 ppm (C, C2(4)); IR (KBr): ν = 3248, 3047, 2918, 2895, 1792, 1791, 1731, 1521, 1497, 1497, 1398, 1326, 1305, 1268, 1247, 1163, 1133, 1115, 1100, 1065, 852, 845, 823, 695 cm⁻¹; MS (El, 70 eV): m/z (%): 444 (4) [M]⁺, 393 (4) [M–F]⁻, 173 (100) [CF₃–C–H₂–CO]*, 145 (29) [CF₃–C=H]⁻, 81 (20); HRMS (EI): m/z [M+H]⁺: 454.1006, found: 454.1007; Anal. calcld for C₈H₇F₃N₂O₅·0.25acetone: C 59.55, H 3.62, N 6.10, F 14.53, found: C 59.15, H 3.67, N 5.88, F 12.15.

Compounds 8k and 8s was prepared in a similar manner to 8a; full experimental data for these compounds are given in the Supporting Information.

Synthesis of 9a: A mixture of benzamide 7a (142 mg, 0.34 mmol) and Pd/C (5 %, 8 mg) in EtOH (20 mL) was hydrogenated at 1 atm for 18 h. The suspension was filtered and the filtrate was concentrated to dryness in vacuo to give compound 9a (137 mg, 96% yield). An analytical sample of 9a was obtained by crystallization from MeOH; mp: 254–255°C; ¹H NMR (500 MHz, D₂DMSO): δ = 1.40–1.44 (m, 2 H, 13(14)-Hendal), 1.59–1.67 (complex signal, 6 H, 7(8)-Hendal and 13(14)-Hendal), 2.60 (br s, 2 H, 10-H and 11-H), 2.72 (brs, 4 H, 6(9)-H and 12(15)-H), 7.94 (d, J = 8.0 Hz, 2 H, Ar-3(5)-H), 8.13 (d, J = 8.0 Hz, 2 H, Ar-2(6)-H), 11.47 ppm (brs, 1 H, NH); ¹³C NMR
Like compound 12a, derivatives 12-k-m, o-p were prepared in a similar manner to 3j; full experimental data for these compounds are given in the Supporting Information.

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