

interferon therapy, as only a small subset of patients are likely to have a sustained clinical response to a course of interferon therapy. As a result, interferon based therapies are used in only a small percentage of all diagnosed patients who elect for treatment.

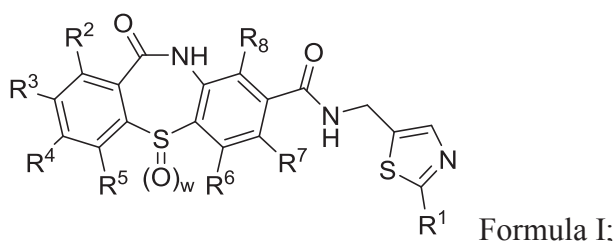
Thus, current HBV treatments can range from palliative to watchful waiting.

Nucleos(t)ide analogs suppress virus production, treating the symptom, but leave the infection intact. Interferon α has severe side effects and less tolerability among patients and is successful as a finite treatment strategy in only a small minority of patients. Accordingly, there is a clear on-going need for more effective processes for making compounds capable of treating viral infections, for example, hepatitis B.

SUMMARY

The present disclosure provides, for example, a process for preparing hepatitis B core protein modulators, e.g., a process for preparing compounds which may have allosteric effector properties against Hepatitis B virus Cp, a protein found as a dimer, a multimer, and as the protein shell of the HBV core. For example, provided herein is a process for preparing compounds which may be useful for treating viral infections, such as hepatitis B.

In one aspect, the present disclosure refers to a process for preparing a compound represented by Formula I:



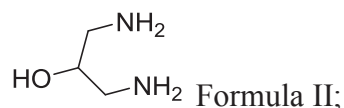
wherein w is 0, 1, or 2;

R^1 is selected from the group consisting of C_{1-6} alkyl (optionally substituted with one, two or three halogens), phenyl, and 4-6 membered monocyclic heteroaryl; wherein phenyl and 4-6 membered monocyclic heteroaryl may optionally be substituted with one or more substituents each independently selected from R^{11} ;

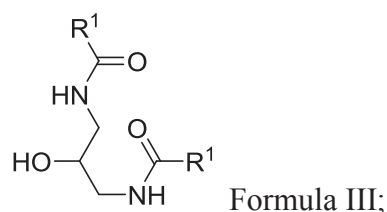
R^{11} is selected from the group consisting of hydrogen, halogen, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, and $-S(O)_w-C_{1-6}$ alkyl (wherein w is 0, 1 or 2);

R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^8 are each independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, and C_{1-6} alkoxy; wherein C_{1-6} alkyl and C_{1-6} alkoxy may be optionally substituted with one, two, three or more substituents each independently selected from the group consisting of halogen, hydroxyl, and C_{1-6} alkoxy; comprising:

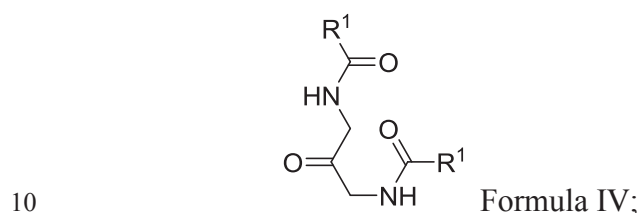
- 5 amidating a compound of Formula II:



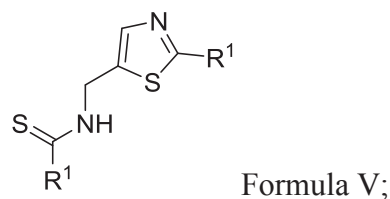
to provide a compound of Formula III:



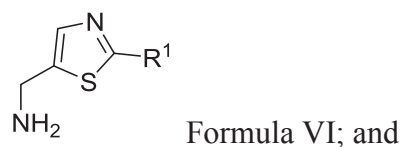
oxidizing the compound of Formula III to provide a compound of Formula IV:



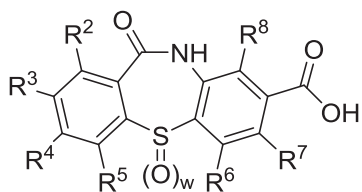
cyclizing the compound of Formula IV to provide a thiazole compound of Formula V:



hydrolyzing the compound of Formula V to provide a compound of Formula VI:



- 15 coupling the compound of Formula VI with a tricyclic compound of Formula VII:

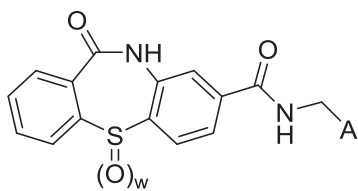


Formula VII;

wherein w is 0, 1 or 2;

R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^8 are each independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, and C_{1-6} alkoxy; wherein C_{1-6} alkyl and C_{1-6} alkoxy may be optionally substituted with one, two, three or more substituents each independently selected from the group consisting of halogen, hydroxyl, and C_{1-6} alkoxy; to provide the compound of Formula I.

In another aspect, the present disclosure refers to a process for preparing a compound represented by Formula VIII:



Formula VIII;

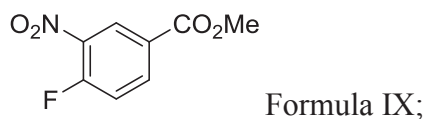
wherein w is 0, 1 or 2;

A is a 5-6 membered monocyclic heteroaryl having 1, 2 or 3 heteroatoms each independently selected from the group consisting of S, N, and O; wherein said heteroaryl may optionally be substituted with one or more substituents selected from R^f ;

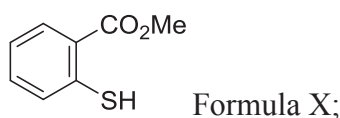
R^f is independently selected, for each occurrence, from the group consisting of hydrogen, halogen, hydroxyl, cyano, $R^a R^b N$ -, $R^a R^b N$ -carbonyl-, $R^a R^b N$ -SO₂-, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkyl-S(O)_w-, (wherein w is 0, 1 or 2), C_{1-6} alkylcarbonyl-N(R^a)- and C_{1-6} alkoxycarbonyl-N(R^a)-; wherein C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-6} alkoxy, C_{1-6} alkyl-S(O)_w-, C_{1-6} alkylcarbonyl-N(R^a)-, C_{1-6} alkoxycarbonyl-N(R^a)- may be optionally substituted by one or more substituents selected from the group consisting of halogen, hydroxyl, and C_{1-6} alkoxy;

R^a and R^b are independently selected, for each occurrence, from the group consisting of hydrogen and C_{1-3} alkyl; wherein C_{1-3} alkyl may optionally be substituted by one or more

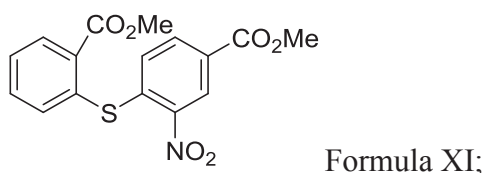
substituents selected from fluorine, hydroxyl, C₁₋₃alkoxy; or R^a and R^b, together with the nitrogen to which they are attached, may form a 4-6 membered heterocyclic ring; comprising:
coupling a compound of Formula IX:



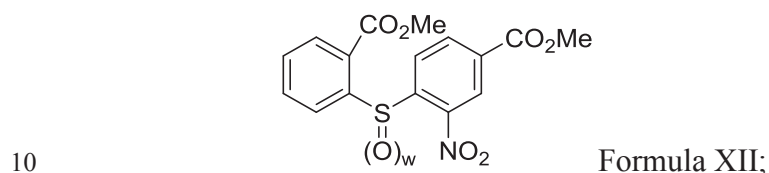
5 with a compound of Formula X:



to provide a compound of Formula XI:

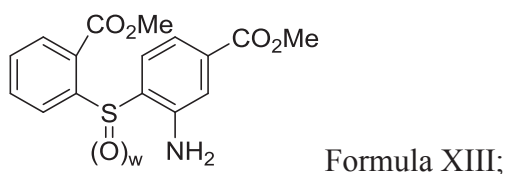


optionally oxidizing the compound of Formula XI to provide a compound of Formula XII:



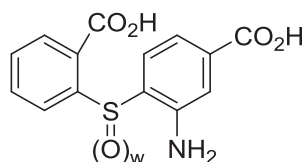
wherein w is 1 or 2;

reducing the compound of Formula XII to provide a compound of Formula XIII:



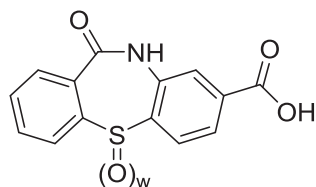
wherein w is 1 or 2;

15 hydrolyzing the compound of Formula XIII to provide a compound of Formula XIV:



Formula XIV;

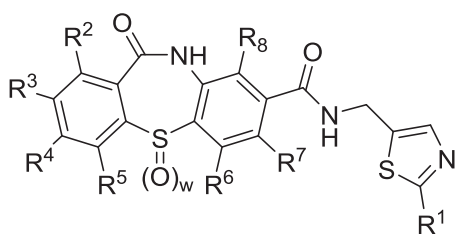
cyclizing the compound of Formula XIV to provide a tricyclic compound of Formula VII:



Formula VII; and

amidating the compound of Formula VII to provide the compound of Formula VIII.

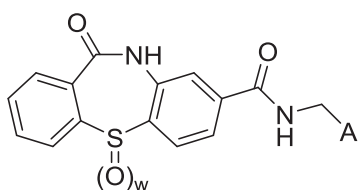
- 5 In certain examples, provided herein is a process for preparing a compound of Formula I:



Formula I; wherein w, R¹, R², R³, R⁴, R⁵, R⁶,

R⁷, and R⁸ are as defined below.

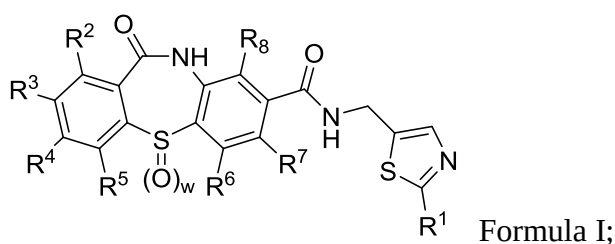
- 10 In certain other examples, provided herein is a process for preparing a compound of Formula VIII:



Formula VIII; wherein w and A are as defined below.

Claims

1. A process for preparing a compound represented by Formula I:



wherein w is 0, 1, or 2;

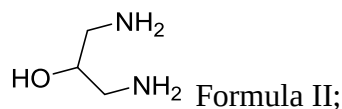
5 R^1 is selected from the group consisting of C_{1-6} alkyl (optionally substituted with one, two or three halogens), phenyl, and 4-6 membered monocyclic heteroaryl; wherein phenyl and 4-6 membered monocyclic heteroaryl may optionally be substituted with one or more substituents each independently selected from R^{11} ;

10 R^{11} is selected from the group consisting of hydrogen, halogen, cyano, C_{1-6} alkyl, C_{1-6} alkoxy, and $-S(O)_w-C_{1-6}$ alkyl (wherein w is 0, 1 or 2);

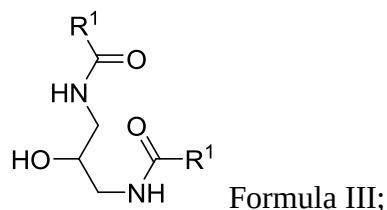
R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^8 are each independently selected from the group consisting of hydrogen, halogen, C_{1-6} alkyl, and C_{1-6} alkoxy; wherein C_{1-6} alkyl and C_{1-6} alkoxy may be optionally substituted with one, two, three or more substituents each independently selected from the group consisting of halogen, hydroxyl, and C_{1-6} alkoxy;

15 comprising:

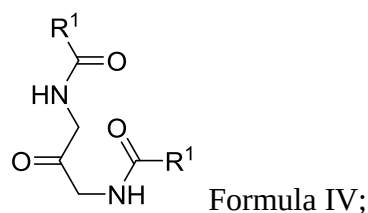
amidating a compound of Formula II:



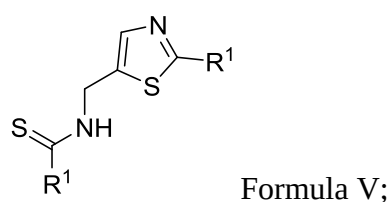
to provide a compound of Formula III:



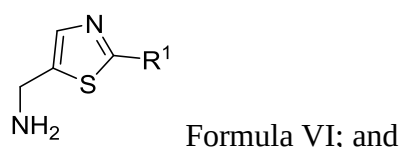
oxidizing the compound of Formula III to provide a compound of Formula IV:



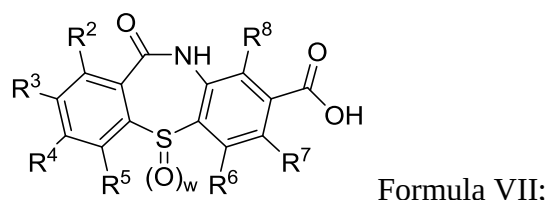
cyclizing the compound of Formula IV to provide a thiazole compound of Formula V:



- 5 hydrolyzing the compound of Formula V to provide a compound of Formula VI:



coupling the compound of Formula VI with a tricyclic compound of Formula VII:

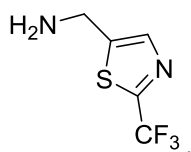


wherein w is 0, 1 or 2;

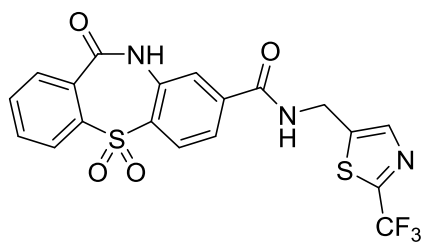
- 10 R², R³, R⁴, R⁵, R⁶, R⁷, and R⁸ are each independently selected from the group consisting of hydrogen, halogen, C₁-₆alkyl, and C₁-₆alkoxy; wherein C₁-₆alkyl and C₁-₆alkoxy may be optionally substituted with one, two, three or more substituents each independently selected from the group consisting of halogen, hydroxyl, and C₁-₆alkoxy;
- to provide the compound of Formula I.

- 15 2. The process of claim 1, wherein amidating the compound of Formula II comprises contacting the compound of Formula II with an amine base and an acylating agent.

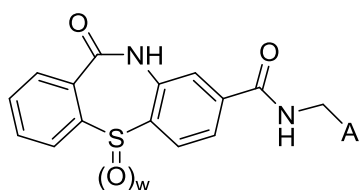
3. The process of claim 1 or 2, wherein the acylating agent is an acid anhydride or an acid chloride.
4. The process of any one of claims 1-3, wherein the acylating agent is trifluoroacetic anhydride.
- 5 5. The process of any one of claims 1-4, wherein the amine base is triethylamine.
6. The process of any one of claims 1-5, wherein oxidizing the compound of Formula III comprises contacting the compound of Formula III with a chromium-based oxidizing reagent.
7. The process of claim 6, wherein the chromium-based oxidizing reagent is Jones reagent.
8. The process of any one of claims 1-7, wherein cyclizing the compound of Formula IV
10 comprises contacting the compound of Formula IV with a thionating reagent.
9. The process of claim 8, wherein the thionating reagent is phosphorus pentasulfide.
10. The process of any one of claims 1-9, wherein hydrolyzing the compound of Formula V comprises contacting the compound of Formula V with an aqueous amine base.
11. The process of claim 10, wherein the aqueous amine base is aqueous methylamine.
- 15 12. The process of any one of claims 1-11, wherein coupling the compound of Formula VI with the compound of Formula VII is conducted in the presence of a coupling agent.
13. The process of claim 12, wherein the coupling agent is hydroxybenzotriazole/ ethyl-(*N,N'*-dimethylamino)propylcarbodiimide hydrochloride.
14. The process of any one of claims 1-13, wherein R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , and R^8 are each
20 independently selected from the group consisting of hydrogen, fluoride, chloride, methyl, and methoxy.
15. The process of any one of claims 1-14, wherein R^1 is trifluoromethyl.
16. The process of any one of claims 1-15, wherein the compound of Formula VI is:



17. The process of any one of claims 1-16, wherein the compound of Formula I is:



18. A process for preparing a compound represented by Formula VIII:



Formula VIII;

wherein w is 0, 1 or 2;

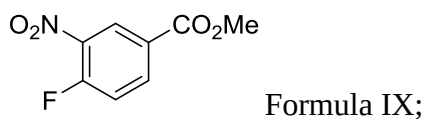
A is a 5-6 membered monocyclic heteroaryl having 1, 2 or 3 heteroatoms each independently selected from the group consisting of S, N, and O; wherein said heteroaryl may optionally be substituted with one or more substituents selected from R^f;

R^f is independently selected, for each occurrence, from the group consisting of hydrogen, halogen, hydroxyl, cyano, R^aR^bN-, R^aR^bN-carbonyl-, R^aR^bN-SO₂-, C₁₋₆alkyl, C₃₋₆cycloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, C₁₋₆alkyl-S(O)_w-, (wherein w is 0, 1 or 2), C₁₋₆alkylcarbonyl-N(R^a)- and C₁₋₆alkoxycarbonyl-N(R^a)-; wherein C₁₋₆alkyl, C₃₋₆cycloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkoxy, C₁₋₆alkyl-S(O)_w-, C₁₋₆alkylcarbonyl-N(R^a)-, C₁₋₆alkoxycarbonyl-N(R^a)- may be optionally substituted by one or more substituents selected from the group consisting of halogen, hydroxyl, and C₁₋₆alkoxy;

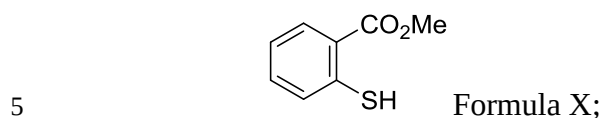
R^a and R^b are independently selected, for each occurrence, from the group consisting of hydrogen and C₁₋₃alkyl; wherein C₁₋₃alkyl may optionally be substituted by one or more substituents selected from fluorine, hydroxyl, C₁₋₃alkoxy; or R^a and R^b, together with the nitrogen to which they are attached, may form a 4-6 membered heterocyclic ring;

comprising:

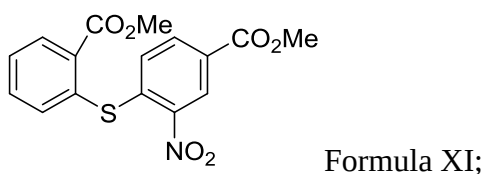
coupling a compound of Formula IX:



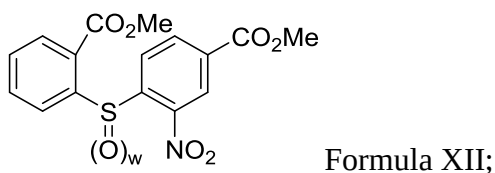
with a compound of Formula X:



to provide a compound of Formula XI:

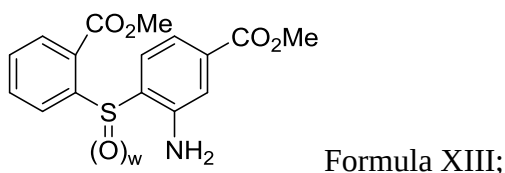


optionally oxidizing the compound of Formula XI to provide a compound of Formula XII:



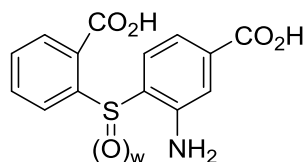
10 wherein w is 1 or 2;

reducing the compound of Formula XII to provide a compound of Formula XIII:



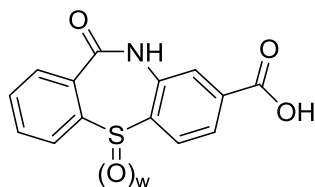
wherein w is 1 or 2;

hydrolyzing the compound of Formula XIII to provide a compound of Formula XIV:



Formula XIV;

cyclizing the compound of Formula XIV to provide a tricyclic compound of Formula VII:



Formula VII; and

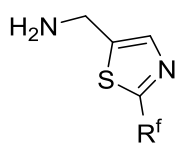
amidating the compound of Formula VII to provide the compound of Formula VIII.

- 5 19. The process of claim 18, wherein coupling the compound of Formula IX with the compound of Formula X is conducted in the presence of a base.
20. The process of claim 18 or 19, wherein the base is cesium carbonate.
21. The process of any one of claims 18-20, wherein oxidizing the compound of Formula XI comprises contacting the compound of Formula XI with aqueous hydrogen peroxide.
- 10 22. The process of any one of claims 18-20, wherein oxidizing the compound of Formula XI comprises contacting the compound of Formula XI with sodium metaperiodate and catalytic ruthenium (III) chloride.
23. The process of any one of claims 18-22, wherein reducing the compound of Formula XII comprises contacting the compound of Formula XII with Pd/C under hydrogen gas.
- 15 24. The process of any one of claims 18-23, wherein hydrolyzing the compound of Formula XIII comprises contacting the compound of Formula XIII with an aqueous base.
25. The process of claim 24, wherein the aqueous base is aqueous lithium hydroxide.
26. The process of any one of claims 18-25, wherein cyclizing the compound of Formula XIV comprises contacting the compound of Formula XIV with carbodiimidazole.

27. The process of any one of claims 18-26, wherein amidating the compound of Formula VII comprises contacting the compound of Formula VII with a primary amine represented by A-CH₂-NH₂ in the presence of a coupling agent.

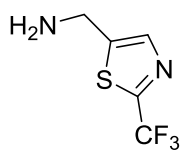
28. The process of claim 27, wherein the coupling agent is hydroxybenzotriazole/ ethyl-
5 (N',N'-dimethylamino)propylcarbodiimide hydrochloride.

29. The process of claim 27 or 28, wherein the primary amine is represented by:

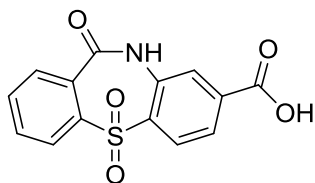


; wherein R^f is C₁₋₆alkyl optionally substituted by one or more fluorine atoms.

30. The process of any one of claims 27-29, wherein the primary amine is:



31. The process of any one of claims 18-30, wherein the compound of Formula VII is:



32. The process of any one of claims 18-31, wherein the compound of Formula VIII is:

