Antiinfective Proanthocyanidin Compounds and Methods of Use Thereof

Abstract: One aspect of the invention relates to novel proanthocyanidin compounds that are useful as antiinfective agents. In one embodiment, the invention relates to a pure and isolated compound of formula I or II. For example, compounds of the invention are useful antiviral agents against another aspect of the invention relates to methods of treating and infection, such as a viral infection, in a subject comprising administering to the subject in need thereof the aforementioned compound.
1. A pure and isolated compound represented by formula I or II:

\[ \text{I} \quad \text{II} \]

wherein independently for each occurrence:

- \( R_1 \) and \( R_7 \) represent alkoxy, alkenyloxy, alkynyloxy, aryloxy, aralkyloxy, hydroxy, -OC(O)-R, alkyl, alkenyl, alkynyl, acetyl, formyl, halide, cyano, nitro, SH, amino, amido, sulfonyl, or sulfonamido;

- \( R_3 \) and \( R_4 \) represent H, hydroxy, alkoxy, alkenyloxy, alkynyloxy, or aryloxy;

- \( R_5, R_6, R_8, \text{ and } R_9 \) represent H, hydroxy, alkyl, alkenyl, alkynyl, aryloxy, aralkyloxy, -OC(O)-Rn, alkyl, alkenyl, alkynyl, aralkyl, acetyl, formyl, halide, cyano, nitro, SH, amino, amido, sulfonyl, or sulfonamido;

- \( R_{10} \) represents H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, or a carbohydrate;

- A represents an aryl group;

- L represents O, S, or NR;

- \( R \) represents H, hydroxy, alkyl, alkenyl, alkynyl, aralkyl, acetyl, formyl, or sulfonyl; and \( n \) and \( m \) represent an integer from 1 to 5, inclusive;

wherein any of the aforementioned alkoxy, alkenyloxy, alkynyloxy, aryloxy, aralkyloxy, alkyl, alkenyl, alkynyl, cycloalkyl, aryl and aralkyl groups may be optionally substituted with one or more groups selected from the group consisting of hydroxy, alkoxy, alkenyloxy, alkynyloxy, aryloxy, aralkyloxy, halide, formyl, acetyl, cyano, nitro, SH, amino, amido, sulfonyl, or sulfonamido.
2. The compound of claim 1, wherein

- \( R_1 \) represents H, alkoxy, aryloxy, aralkyloxy, hydroxy, \(-OC(O)-R_7\), alkyl, acetyl, formyl, or halide;
- \( R_2 \) represents H, hydroxy, alkoxy, or aryloxy;
- \( R_3, R_4, R_5, \) and \( R_6 \) represent H, alkoxy, aryloxy, aralkyloxy; \(-OC(O)-R_7\), alkyl, aralkyl, acetyl, formyl, or halide;
- \( R_7 \) represents H, alkyl, aryl, or aralkyl;
- \( A \) represents an aryl group;
- \( L \) represents O; and
- \( n \) represents an integer from 1 to 5, inclusive;

wherein any of the aforementioned alkoxy, alkenyloxy, alkynyloxy, aryloxy, aralkyloxy, alkyl, alkenyl, alkynyl, aryl and aralkyl groups may be optionally substituted with one or more groups selected from the group consisting of hydroxy, alkoxy, alkenyloxy, alkynyloxy, aryloxy, aralkyloxy; halide, formyl, acetyl, cyano, nitro, SH, amino, amido, sulfonylethyl, or sulfonylamido.

3. The compound of claim 1, wherein: \( L \) is O.

4. The compound of claim 1, wherein: \( R_3, R_4, R_5, R_6, R_7, \) and \( R_8 \) are H or hydroxy, and wherein at least 3 of \( R_3, R_4, R_5, R_6, R_7, \) and \( R_8 \) are hydroxy.

5. The compound of claim 1, wherein: \( R_1 \) and \( R_7 \) are each independently hydroxy; and \( n \) and \( m \) are each equal to 2 or 3.

6. The compound of claim 1, wherein \( A \) is a benzene ring.

7. A pure and isolated compound represented by formula Ia or Ua:
wherein independently for each occurrence:

\[ R_{1\text{o}} \text{ and } R_{7\text{a-e}} \text{ represent alkoxy, alkenyloxy, alkynyloxy, aryloxy, arylalkyloxy, hydroxy, } -OC(O)-R_{i}, \text{ alkyl, alkenyl, alkynyl, acetyl, formyl, halide, cyano, nitro, SH, amino, amido, sulfonyl, or sulfonamido; } \]

\[ R_{2\text{a-b}} R_{8} \text{ represent H, hydroxy; alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, or aryloxy; } \]

\[ R_{9}, R_{4}, R_{5}, R_{6}, \text{ and } R_{10} \text{ represent H, hydroxy, alkoxy, alkenyloxy, alkynyloxy, aralkyloxy, aralkyloxy; } -OC(O)-R_{i}, \text{ alkyl, alkenyl, alkynyl, aralkyl, acetyl, formyl, halide, cyano, nitro, SH, amino, amido, sulfonyl, or sulfonamido; } \]

\[ Ru \text{ represents H, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, arylalkyl or a carbohydrate; and } \]

\[ n \text{ and } m \text{ represent an integer from 1 to 8, inclusive; } \]

wherein any of the aforementioned alkoxy, alkenyloxy, alkynyloxy, aryloxy, aralkyloxy, alkyl, alkenyl, alkynyl, cycloalkyl, aryl and aralkyl groups may be optionally substituted with one or more groups selected from the group consisting of hydroxy, alkoxy, alkenyloxy, alkynyloxy, aryloxy, aralkyloxy, halide, formyl, acetyl, cyano, nitro, SH, amino, amido, sulfonyl, or sulfonamido.

8. The compound of claim 7, wherein independently for each occurrence:

\[ R_{i\text{o}} \text{ and } R_{i\text{a-f}} \text{ represent hydroxy, and } R_{i\text{a-f}} \text{ are hydroxy and } n \text{ is equal to 2 or 3, and at } R_{10}, \text{ are hydroxy, and } m \text{ is equal to 2 or 3; } \]

9. The compound of claim 7, wherein \( R_{2\text{a-b}} R_{8} \) are each hydroxy.

10. The compound of claim 7, wherein \( R_{9}, R_{4}, R_{5}, R_{6}, R_{7}, \) and \( R_{10} \) are H or hydroxy.

11. A pure and isolated compound selected from the group consisting of:
12. A pharmaceutical composition comprising a compound of any of claims 1 to 11 and a pharmaceutically acceptable carrier.

13. A method of treating a subject for an infection comprising administering to the subject in need thereof and effective amount of a compound of any of claims 1 to 11.

14. The method of claim 13, wherein the infection is a viral, bacterial, fungal, protozoan or prion infection.

15. The method of claim 13, wherein the infection is a viral infection caused by an envelope virus.
16. The method of claim 13, wherein the infection is viral infection caused by a non-envelope virus.

17. The method of claim 13, wherein the infection is a viral infection caused by an envelope virus selected from the group consisting of human influenza, avian influenza, HIV, SARS, HPV, herpes simplex virus (HSV), dengue, yellow fever, West Nile, and encephalitis viruses.

18. The method of claim 13, wherein the infection is a viral infection caused by a non-envelope virus selected from the group consisting of Norwalk virus, hepatitis A, polio, and rhinoviruses.

19. The method of claim 13, wherein the infection is a bacterial infection selected from the group consisting of: Streptococcus, Staphylococcus, Bordetella, Corynebacterium, Mycobacterium, Neisseria, Haemophilus, Actinomycetes, Streptomyces, Nocardia, Enterobacter, Yersinia, Fuscella, Pasteurella, Moraxella, Acinetobacter, Erysipelothrix, Brannhamella, Actinobacillus, Streptobacillus, Listeria, Calymmatobacterium, Brucella, Bacillus, Bordetella/Clostridium, Treponema, Escherichia, Salmonella, Klebsiella, Vibrio, Proteus, Erwinia, Borrelia, Leptospira, Spirillum, Campylobacter, Shigella, Legionella, Pseudomonas, Aeromonas, Rickettsia, Chlamydia, Borrelia and Mycoplasma.

20. The method of claim 13, wherein the bacterial infection is selected from the group consisting of Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus faecalis, Streptococcus faecium, Streptococcus dwars, Neisseria gonorrhoeae, Neisseria meningitidis, Staphylococcus aureus, Staphylococcus epidermidis, Corynebacterium diphtheriae, Gardnerella vaginalis, Mycobacterium tuberculosis, Mycobacterium bovis, Mycobacterium ulcerans, Mycobacterium lepra, Actinomyces israelii, Listeria monocytogenes, Bordetella spp., Bordetella pertussis, Bordetella parapertussis, Bordetella bronchiseptica, Escherichia coli, Shigella dysenteriae, Haemophilus influenzae, Haemophilus aegyptius, Haemophilus parainfluenzae, Haemophilus ducreyi, Bordetella, B. pertussis, B. parapertussis, B. bronchiseptica.

21. The method of claim 13, wherein the infection is a fungal infection caused by B. cinerea, Penicillium sp., P. expansum, P. italicum, P. digitalum, Rhizopus sp., R. solaniffr, R. nigricans, Alternaria sp., A. alternata, A. solani, Diplodia sp., Diplodia natalenses, Monilia sp., M. fructicola, Pseudomonas sp., P. cepacia, Xanthomonas sp., Erwinia sp. and Corynebacterium.

22. The method of claim 13, wherein the infection is prion infection selected from the group consisting of scrapie in sheep, bovine spongiform encephalopathy (BSE), transmissible mink encephalopathy (TME), chronic wasting disease (CWD) in elk and mule deer, feline spongiform encephalopathy in cats, exotic ungulate encephalopathy (EUE) in nyala, oryx, and greater kudu, Creutzfeldt-Jakob Disease (CJD), Iatrogenic Creutzfeldt-Jakob disease, Variant Creutzfeldt-Jakob disease, Familial Creutzfeldt-Jakob disease, Sporadic Creutzfeldt-Jakob diseases; Gerstmann-Straussler-Scheinker syndrome (GSS), Fatal Familial Insomnia (FFI), Kuru, and Alpers syndrome.

23. The method of claim 13, wherein the infection is protozoan infection selected from the group consisting of Entamoeba histolytica, Giardia lambila, Trichomonas vaginalis, Trypanosoma brucei T. cruzi, Leishmania donovani, Balantidium coli, Toxoplasma gondii, Plasmodium spp., Babesia microti, sleeping sickness (Trypanosomeniasis), Amoebiasis, Giardiasis, Trichomoniasis, African Sleeping Sickness, American Sleeping Sickness, Leishmaniasis, Balantidiasis, Toxoplasmosis, Malaria, and Babesiosis.

24. A method of preparing a compound of any one of claims 1-11, comprising extracting a botanical with water to obtain an eluate, loading the eluate onto a filtering agent, washing the eluate with a buffer to provide a filtering agent-bound fraction, and releasing the filtering agent bound fraction with a high ionic strength buffer.

25. A method of making a compound of any one of claims 1-11, comprising:
   a) reacting an acetylphenone with a benzaldehyde to form a chalcone;
   b) epoxidizing the chalcone to form an epoxide; and
   c) cyclizing the epoxide to form a dihydroflavanol.

26. A method of making a compound of any one of claims 1-11, comprising:
   a) reacting an acetylphenone with a benzaldehyde to form a chalcone;
   b) cyclizing the chalcone to form a flavanone; and
   c) oxidizing the flavanone to to yield a dihydroflavanol.
27. The method of claims 25 or 26, further comprising dehydrogenating the dihydroflavonol to form a flavonol.

28. The method of claim 27, further comprising reducing the C-2 carbonyl to form a leucoanthacyanin.

29. The method of any one of claims 25 or 26, further comprising condensation of the dihydroflavonol to yield an A type proanthocyanidin.

30. The method of making a vaccine base on the binding site of a compound of claims 1-11 comprising:
   a. the binding site amino acid sequence that numbers 3-7 amino acids
   b. the binding site amino acid sequence the encompasses the 10 A binding site of the compounds.
   c. utilizing the binding site sequence as an antigen for antibody and vaccine production
   d. utilizing a biomimic form of the adhcsin sequence as an antigen for antibody and vaccine production

31. A diagnostic comprising a compound of any one of claims 1-11, tethered to a plate.

32. The diagnostic of claim 31, wherein the compound is tethered via an ester or amide linkage to the A ring of the compound.

33. A diagnostic comprising a compound of any one of claims 1-11 in a solution.

34. A method of identifying a pathogen, comprising:
   a) incubation of a sample suspected of containing the pathogen or amyloid with a compound of any one of claims 1 to 11 in a solvent to form a mixture;
   b) filtering the mixture with a membrane filter to remove unbound compounds;
   c) detecting the compound using DART TOF-MS analysis.

35. A biodefense filter comprising a compound of any one of claims 1-11.

36. The biodefense filter of claim 35, wherein the filter is incorporated into a facial mask.

37. The biodefense filter of claim 35, wherein the filter is incorporated into an article of clothing.

38. The biodefense filter of claim 35, wherein the filter is incorporated into an HVAC system.

39. The biodefense filter of claim 35, wherein the filter is incorporated into a water treatment system.