[0012] Eluxadoline® (Forest Laboratories, Inc.) is a μ opioid receptor agonist and δ opioid receptor antagonist that has met primary endpoints of improvement in stool consistency and reduction of abdominal pain in Phase III testing, albeit without a demonstrable effect on reducing colonic hypersensitivity that results in hyperalgesia. Moreover, several cases of pancreatitis, a potentially life threatening disease, were reported in Phase II trials. Cases of pancreatitis were reported even after patients with a known history of biliary disease were excluded from clinical study enrollment. In general, μ agonists have a constricting effect on the Sphincter of Oddi, a muscular valve that regulates the flow of bile and pancreatic juice from the bile duct into the duodenum. It is very important that a drug with μ-receptor agonist activity and that is prescribed for long-term use, not lead to constriction of the Sphincter of Oddi.

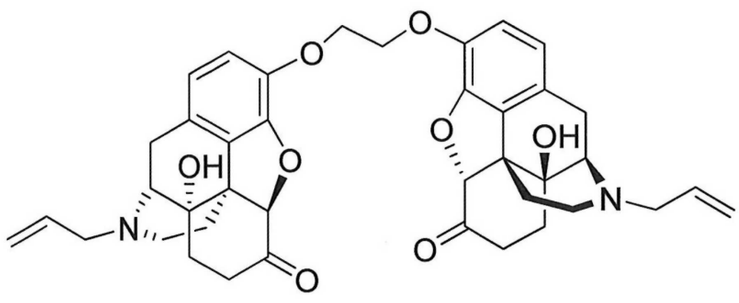
[0013] There has accordingly been a long-standing need for a chronic treatment of IBS-D that decreases intestinal motility, thereby decreasing the incidence of diarrhea, is an analgesic, is not associated with pancreatitis, and more than merely treating symptoms, addresses underlying hypersensitivity and resulting hyperalgesia associated with IBS-D.

BRIEF SUMMARY

[0013a] In one aspect of the present disclosure, there is provided a homo-dimer compound of a pharmaceutically active agent selected from the group consisting of naloxone and naltrexone, wherein two such agents are covalently ether-linked through phenolic hydroxyl groups of the agents by an ethylene residue, or a pharmaceutically acceptable salt or solvate thereof.

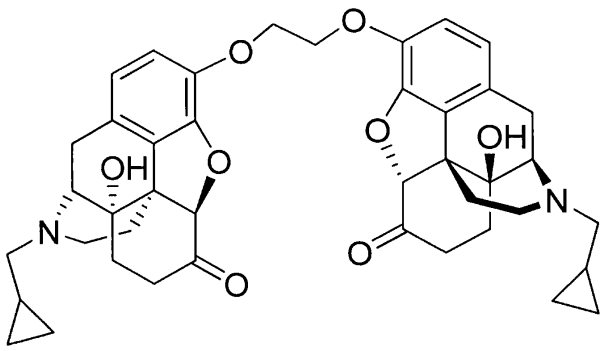
[0013b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and a dimer compound disclosed herein.

[0013c] In another aspect of the present disclosure, there is provided a naloxone dimer compound having the Formula:



or a pharmaceutically acceptable salt or solvate thereof.

[0013d] In a further aspect of the present disclosure, there is provided a naltrexone dimer compound having the Formula:



or a pharmaceutically acceptable salt or solvate thereof.

[0014] We have discovered that dimerization of a defined group of pharmaceutically agents by *O*-alkylation through their phenolic hydroxyl groups, such that the active agent residues are bridged by an ethylene linker, yields distinct advantages relative to the active monomers, while preserving their receptor pharmacology.

[0015] In opioids and other pharmaceutical agents characterized by a single phenolic hydroxyl group, the covalent linkage of two such agents via such groups by the ethylene linker yields homo-dimers which are essentially more resistant to presystemic metabolism than their parent molecules. The ethylene linkage is highly stable and in particular cases yields other distinct advantages as well.

[0016] In the case of the opioid compounds buprenorphine, naloxone, and naltrexone the corresponding dimers are resistant to tampering, e.g., kitchen chemistry conversion to drugs of abuse; and are substantially non-absorbed in the GI tract, permitting their peripheral use without entering the central nervous system with consequent adverse effects such as addiction or opioid withdrawal.

WHAT IS CLAIMED IS:

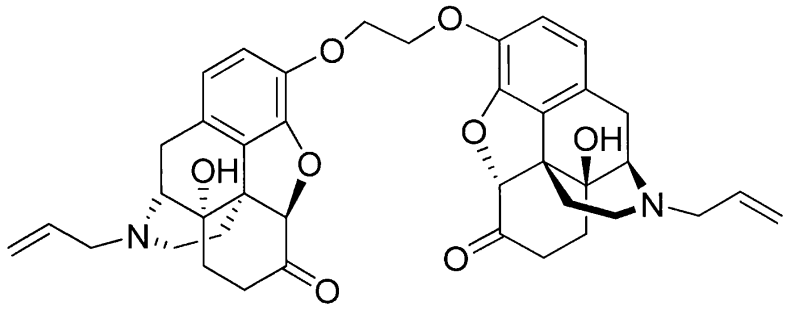
1. A homo-dimer compound of a pharmaceutically active agent selected from the group consisting of naloxone and naltrexone, wherein two such agents are covalently ether-linked through phenolic hydroxyl groups of the agents by an ethylene residue, or a pharmaceutically acceptable salt or solvate thereof.

2. A homo-dimer compound according to claim **1,** wherein the compound is in the form of a pharmaceutically acceptable salt.

3. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or excipient and a dimer compound according to claim **1** or **2**.

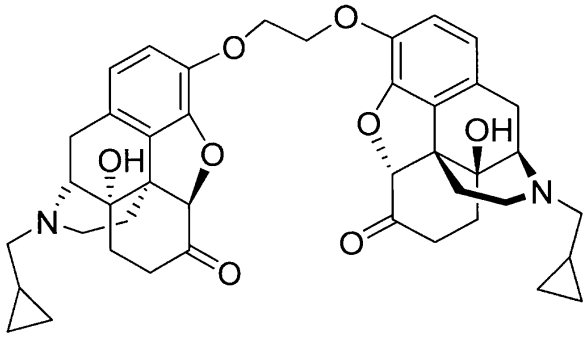
4. The pharmaceutical composition of claim **3**, wherein said composition is formulated as an oral tablet or capsule or extended release oral tablet or capsule.

5. A naloxone dimer compound having the Formula:



or a pharmaceutically acceptable salt or solvate thereof.

6. A naltrexone dimer compound having the Formula:



or a pharmaceutically acceptable salt or solvate thereof.

7. A dimer compound of any one or claims 2, 5, or 6, in a citric acid salt form.