[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.

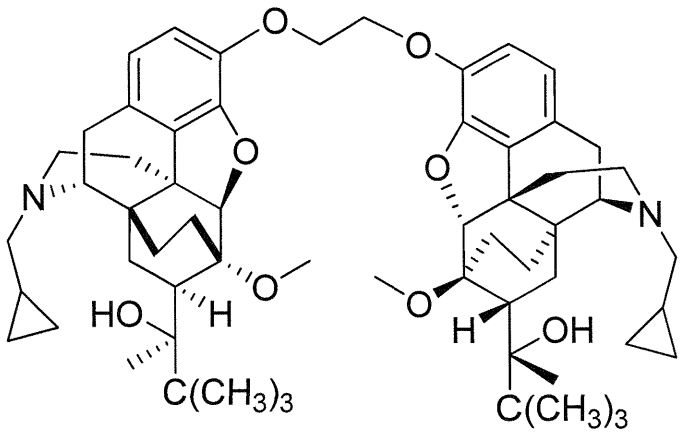
[0013] There has accordingly been a long-standing need for a chronic treatment of IBS-D that decreases intestinal motility, thereby decreasing the incidence of diarrhea, is an analgesic, is not associated with pancreatitis, and more than merely treating symptoms, addresses underlying hypersensitivity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

BRIEF SUMMARY

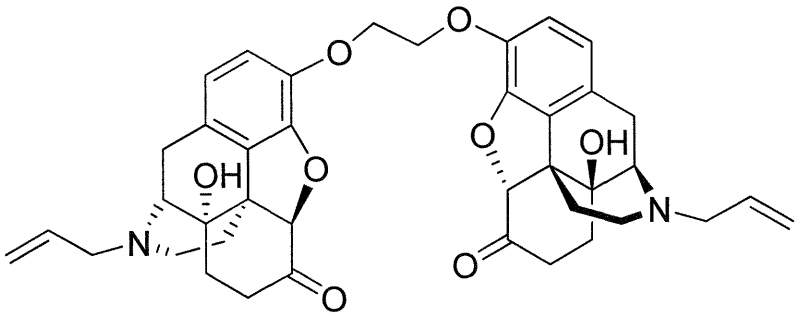
[0013a] In one aspect of the present disclosure, there is provided a homo-dimer compound of a pharmaceutically active agent selected from the group consisting of buprenorphine, naloxone, naltrexone, des-venlafaxine, albuterol and acetaminophen wherein two such agents are covalently ether-linked through 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.

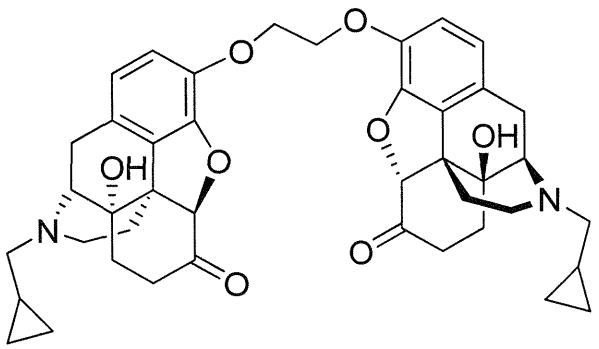
[0013c] In a further aspect of the present disclosure, there is provided a buprenorphine dimer compound having the Formula:



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

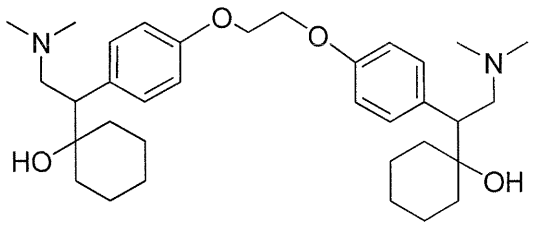


[0013e] In a further aspect of the present disclosure, there is provided a naltrexone dimer compound having the Formula:



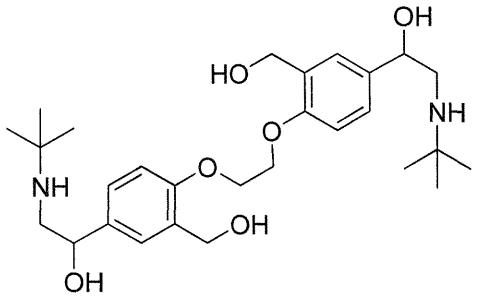
or a pharmaceutically acceptable salt or solvate thereof.

[0013f] In another aspect of the present disclosure, there is provided a des-venlafaxine dimer compound having the Formula:



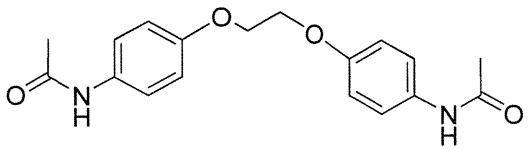
or a pharmaceutically acceptable salt or solvate thereof.

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



or a pharmaceutically acceptable salt or solvate thereof.

[0013h] In another aspect of the present disclosure, there is provided an acetaminophen 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.

[0017] The dimerization of des-venlafaxine prevents passage of the active agent across the blood brain barrier, and although the dimer is no longer effective in the treatment of depression, that requires CNS penetration, its functional ligands remain active and act locally in the intestinal tract, thus avoiding all centrally mediated adverse events, including sexual dysfunction. The dimerization, therefore, permits the agent to be safely utilized in the treatment of gastroparesis and chronic idiopathic constipation. The des-venlafaxine dimer is expected to function as a peripheral serotonin norepinephrine reuptake inhibitor. Unlike des-venlafaxine, the dimer is expected to act only peripherally in the gastrointestinal tract. Serotonin inherently has propulsive effect on the gastrointestinal tract and the dimer, therefore, could be used for treatment of intestinal conditions such as gastroparesis, chronic idiopathic constipation and pseudointestinal obstruction (ileus).

[0018] The effect of dimerizing acetaminophen, according to the present disclosure, is to prevent formation of the quinone metabolite of the parent compound, which is hepatotoxic in acute and chronic use. In addition, blocking the phenolic hydroxyl of the monomer, dimerization reduces the ionic nature of the active agent, potentially enhancing transport through the blood-brain barrier and hence, analgesia.

[0019] Dimerization of albuterol enhances resistance to gastrointestinal and hepatic metabolism, increasing bioavailability of the drug when taken orally for the treatment of bronchospasm, which occurs in various pulmonary conditions, including asthma and chronic obstructive pulmonary disease.

[0020] In at least the case of morphinan compounds and until the present time, conventional thought seems to have been, when derivatizing active agents in search of, e.g., prodrug activity, phenolic hydroxyl groups were to be avoided lest receptor binding be affected adversely. Surprisingly, the compounds of the present disclosureare believed to retain their characteristic activities despite derivatization involving the phenolic hydroxyl groups of the corresponding monomers.

BRIEF DESCRIPTION OF THE DRAWINGS

[0021] **Figure 1** provides a synthetic route to buprenorphine dimer HCl salt.

[0022] **Figure 2** provides a synthetic route to naloxone dimer HCl salt.