immune response to HCV; and ribavirin, which is taken orally, is believed to work by preventing HCV replication. Taken alone, ribavirin does not effectively suppress HCV levels, but an interferon/ribavirin combination is more effective than interferon alone. Typically, hepatitis C is treated with a combination of pegylated interferon alpha and ribavirin for a period of 24 or 48 weeks, depending on the HCV genotype.

[0006] The goal of treatment is sustained viral response -- meaning that HCV is not measurable in the blood after therapy is completed. Following treatment with a combination of pegylated interferon alpha and ribavirin, sustained cure rates (sustained viral response) of about 75% or better occur in people with HCV genotypes 2 and 3 in 24 weeks of treatment, about 50% in those with HCV genotype 1 with 48 weeks of treatment, and about 65% in those with HCV genotype 4 in 48 weeks of treatment.

[0007] Treatment may be physically demanding, particularly for those with prior history of drug or alcohol abuse, because both interferon and ribavirin have numerous side effects. Common interferon-associated side effects include flu-like symptoms, extreme fatigue, nausea, loss of appetite, thyroid problems, high blood sugar, hair loss, and skin reactions at the injection site. Possible serious interferon-associated side effects include psychoses (*e.g.*, suicidal behavior), heart problems (*e.g.*, heart attack, low blood pressure), other internal organ damage, blood problems (*e.g.*, blood counts falling dangerously low), and new or worsening autoimmune disease (*e.g.*, rheumatoid arthritis). Ribavirin-associated side effects include anemia, fatigue, irritability, skin rash, nasal stuffiness, sinusitis, and cough. Ribavirin can also cause birth defects, so pregnancy in female patients and female partners of male patients must be avoided during treatment and for six months afterward.

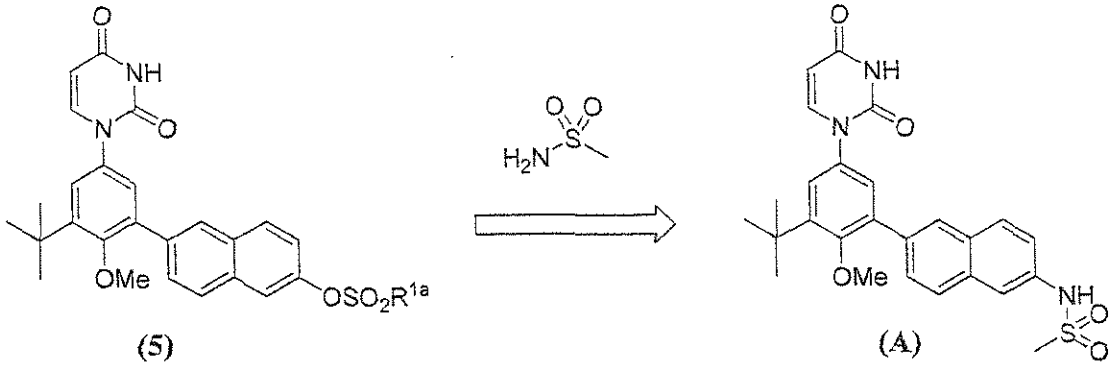
[0008] Some patients do not complete treatment because of the serious side effects discussed above; other patients (non-responders) continue to have measurable HCV levels despite treatment; and yet other patients (relapsers) appear to clear the virus during therapy, but the virus returns sometime after completion of the treatment regimen. Thus, there continues to be a need for alternative compositions and methods of treatment (used either in combination with, or in lieu of, an interferon agent and/or ribavirin) to prevent the progression of liver damage from hepatitis C. This disclosure provides processes for preparing one such compound—*N*-(6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (compound **(A)**)—and salts thereof.

SUMMARY

[0009] This disclosure is directed to a process for preparing *N*-(6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (compound **(A)**) or a salt thereof, wherein the process comprises sulfonamidation of a sulfonate (compound **(5)**).

[0009a] In one aspect, there is provided a process for preparing *N*-(6-(3-*tert*-buytl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(*2H*)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (compound (**A**)) or a salt thereof, wherein the process comprises:

sulfonamidating compound (**5**):



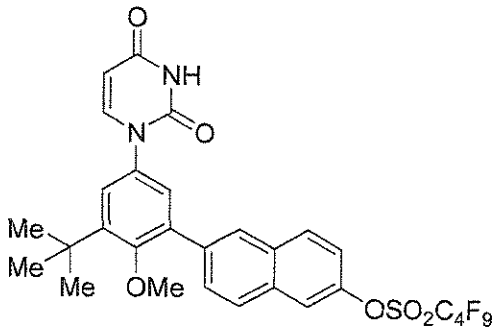
wherein R^{1a} is selected from the group consisting of *p*-tolyl, phenyl, methyl, ethyl, trifluoromethyl, perfluorobutyl, perfluoropentyl, perfluorohexyl, perfluorooctyl and isomers and homologs thereof.

[0010] This disclosure also is directed to compound (**A**) and salt thereof prepared by the above process.

[0011] This disclosure also is directed to compound (A) and potassium or sodium salt thereof prepared by the above process.

[0012] This disclosure also is directed to a process for preparing compound (5).

[0012a] In one aspect, there is provided a compound or salt thereof, wherein the compound corresponds in structure to formula (5a):



(5a)

[0013] This disclosure also is directed to compound (4).

[0014] This disclosure also is directed to various intermediates useful for preparing compound (4) as well as to processes for preparing those intermediates.

[0015] This disclosure also is directed to compositions (including pharmaceutical compositions) that comprise compound (A) or salt thereof that are prepared by the above processes. Optionally, the compositions can comprise one or more additional therapeutic agents.

[0016] This disclosure also is directed to methods of use of the above compounds and compositions to, for example, inhibit replication of a ribonucleic acid (RNA) virus (including HCV) or treat a disease treatable by inhibiting HCV RNA polymerase (including hepatitis C).

[0017] Further benefits of this disclosure will be apparent to one skilled in the art.

DETAILED DESCRIPTION

[0018] This detailed description is intended only to acquaint others skilled in the art with this disclosure, its principles, and its practical application so that others skilled in the art may adapt and apply the disclosure in its numerous forms, as they may be best suited to the requirements of a particular use. This description and its specific examples are intended for purposes of illustration only. This disclosure, therefore, is not limited to the embodiments described in this patent application, and may be variously modified.

A. Process for Preparing N-(6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide *(compound I)* and the corresponding salt.

[0019] As discussed above, this disclosure is directed, in part, to a process for preparing *N*-(6-(3-*tert*-butyl-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2-methoxyphenyl)naphthalen-2-yl)methanesulfonamide (compound (A)) or a salt thereof. The salt of compound (A) may be the potassium salt, the sodium salt or any other suitable salt. In embodiments, the salt of compound (A) is the potassium salt. In embodiments, the salt of compound (A) is the sodium salt. The process comprises sulfonamidation of compound (5), wherein R^{1a} is, aryl, such as *p*-tolyl or phenyl, methyl, ethyl, trifluoromethyl, perfluorobutyl, or isomers of perfluorobutyl and other higher and lower homologs such as, but not limited to, perfluoropentyl, perfluorohexyl, and perfluorooctyl: