norepinephrine transporters (SERT and NET, respectively). However, both duloxetine and venlafaxine have higher affinity for SERT relative to NET (Vaishnavi et al. (2004) *Biol. Psychiatry* 55(3):320-322).

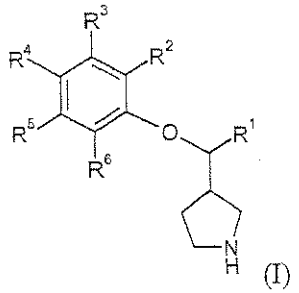
Preclinical studies suggest that inhibition of both SERT and NET may be necessary for maximally effective treatment of neuropathic and other chronic pain states (Jones et al. (2006) *Neuropharmacology* 51(7-8):1172-1180; Vickers et al. (2008) *Bioorg. Med. Chem. Lett.* 18:3230-3235; Fishbain et al. (2000) *Pain Med.* 1(4):310-316; and Mochizucki (2004) *Human Psychopharmacology* 19:S15-S19). However, in clinical studies, the inhibition of SERT has been reported to be related to nausea and other side effects (Greist et al. (2004) *Clin. Ther.* 26(9):1446-1455). Thus, therapeutic agents having more balanced SERT and NET affinity or slightly higher NET affinity are expected to be particularly useful for treating chronic pain while producing fewer side effects, such as nausea.

Thus, a need exists for novel compounds that are useful for treating chronic pain, such as neuropathic pain. In particular, a need exists for novel compounds that are useful for treating chronic pain and that have reduced side effects, such as nausea. A need also exists for novel dual-acting compounds that inhibit both SERT and NET with high affinity (e.g., $pIC_{50} \geq 8.0$ or $K_i \leq 10$ nM) and balanced inhibition (e.g., a SERT/NET binding K_i ratio of 0.1 to 100).

SUMMARY ~~OF THE INVENTION~~

The present disclosure~~invention~~ provides novel compounds that have been found to possess serotonin reuptake inhibitory activity and norepinephrine reuptake inhibitory activity. Accordingly, compounds of the present disclosure~~invention~~ are expected to be useful and advantageous as therapeutic agents for those diseases and disorders that can be treated by inhibition of the serotonin and/or norepinephrine transporter, such as neuropathic pain.

One aspect of the present disclosure~~invention~~ relates to a compound of formula I:



(I)

where:

R^1 is selected from $-C_{2-6}$alkyl, $-C_{3-8}$cycloalkyl optionally substituted with 1 or 2

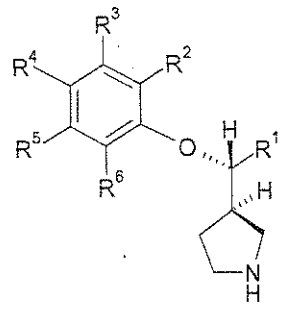
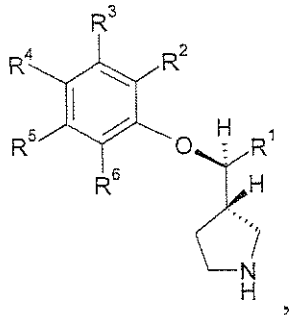
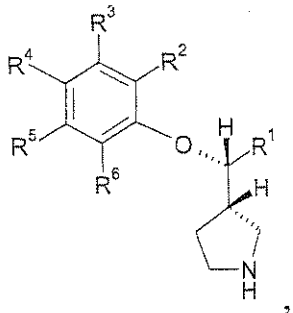
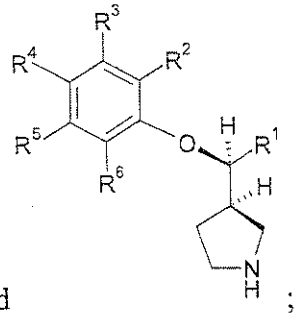
fluoro atoms, -C_{2-6}alkenyl, and -C_{2-6}alkynyl;

R^2 through R^6 are independently selected from hydrogen, halo, -C_{1-6}alkyl, -CF_3, -O-C_{1-6}alkyl, -CN, -C(O)-C_{1-6}alkyl, -S-C_{1-6}alkyl, -C_{3-8}cycloalkyl, and -NO_2; or R^4 and R^5 are taken together to form -CH=CH-CH=CH-; or R^5 and R^6 are taken together to form -CH-CH=CH-CH-;

with the proviso that when R^1 is ethyl, R^2 is fluoro, R^4 is chloro, R^5 is hydrogen, and R^6 is hydrogen, then R^3 is not fluoro or chloro;

or a pharmaceutically acceptable salt thereof.

Another embodiment~~aspect~~ of the present disclosure~~invention~~ relates to compounds of formula I having a configuration selected from:


,

,

, and

;

or enriched in a stereoisomeric form having such configuration.

Yet another aspect of the present disclosure~~invention~~ relates to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a compound of the present disclosure~~invention~~. Such compositions may optionally contain other active agents such as anti-Alzheimer's agents, anticonvulsants, antidepressants, anti-Parkinson's agents, dual serotonin-norepinephrine reuptake inhibitors, non-steroidal anti-inflammatory agents, norepinephrine reuptake inhibitors, opioid agonists, selective serotonin reuptake inhibitors, sodium channel blockers, sympatholytics, and combinations thereof. Accordingly, in yet another embodiment~~aspect~~ of the present disclosure~~invention~~, a pharmaceutical composition comprises a compound of the present disclosure~~invention~~, a second active agent, and a pharmaceutically acceptable carrier. Another embodiment~~aspect~~ of the present disclosure~~invention~~ relates to a combination of active agents, comprising a compound of the

present disclosure~~invention~~ and a second active agent. The compound of the present disclosure~~invention~~ can be formulated together or separately from the additional agent(s). When formulated separately, a pharmaceutically acceptable carrier may be included with the additional agent(s). Thus, yet another embodiment~~aspect~~ of the present disclosure~~invention~~ relates to a combination of pharmaceutical compositions, the combination comprising: a first pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof and a first pharmaceutically acceptable carrier; and a second pharmaceutical composition comprising a second active agent and a second pharmaceutically acceptable carrier. The present disclsoure~~invention~~ also relates to a kit containing such pharmaceutical compositions, for example where the first and second pharmaceutical compositions are separate pharmaceutical compositions.

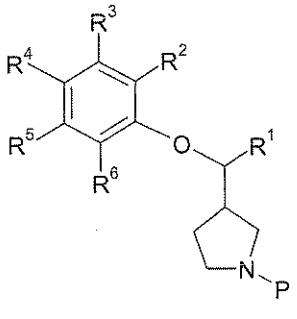
Compounds of the present disclosure~~invention~~ possess serotonin reuptake inhibitory activity and norepinephrine reuptake inhibitory activity, and are therefore expected to be useful as therapeutic agents for treating patients suffering from a disease or disorder that is treated by the inhibition of the serotonin and/or the norepinephrine transporter. Thus, one embodiment~~aspect~~ of the present disclosure~~invention~~ relates to a method of treating: a pain disorder such as neuropathic pain; a depressive disorder such as major depression; an affective disorder such as an anxiety disorder; attention deficit hyperactivity disorder; a cognitive disorder such as dementia; stress urinary incontinence; obesity; or vasomotor symptoms associated with menopause, comprising administering to a patient a therapeutically effective amount of a compound of the present disclosure~~invention~~.

Still another embodiment~~aspect~~ of the present disclosure~~invention~~ relates to a method for inhibiting serotonin reuptake in a mammal comprising administering to the mammal, a serotonin transporter-inhibiting amount of a compound of the present disclosure~~invention~~. Yet another embodiment~~aspect~~ of the present disclosure~~invention~~ relates to a method for inhibiting norepinephrine reuptake in a mammal comprising administering to the mammal, a norepinephrine transporter-inhibiting amount of a compound of the present disclosure~~invention~~. And another embodiment~~aspect~~ of the present disclosure~~invention~~ relates to a method for inhibiting serotonin reuptake and norepinephrine reuptake in a mammal comprising administering to the mammal, a serotonin transporter- and norepinephrine transporter-inhibiting amount of a compound of the present disclosure~~invention~~.

Since compounds of the present disclosure~~invention~~ possess serotonin reuptake inhibitory activity and norepinephrine reuptake inhibitory activity, such compounds are also useful as research tools. Accordingly, one embodiment~~aspect~~ of the present disclosure~~invention~~ relates to a method of using a compound of the present disclosure~~invention~~ as a research tool, comprising conducting a biological assay

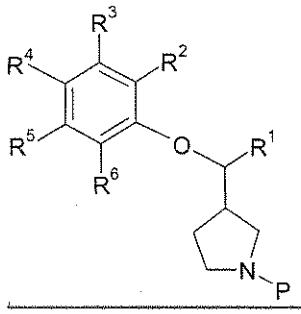
using a compound of the present disclosure~~invention~~. Compounds of the present disclosure~~invention~~ can also be used to evaluate new chemical compounds. Thus another embodiment~~aspect~~ of the present disclosure~~invention~~ relates to a method of evaluating a test compound in a biological assay, comprising: (a) conducting a biological assay with a test compound to provide a first assay value; (b) conducting the biological assay with a compound of the present disclosure~~invention~~ to provide a second assay value; wherein step (a) is conducted either before, after or concurrently with step (b); and (c) comparing the first assay value from step (a) with the second assay value from step (b). Exemplary biological assays include a serotonin reuptake assay and a norepinephrine reuptake assay. Still another embodiment~~aspect~~ of the present disclosure~~invention~~ relates to a method of studying a biological system or sample comprising serotonin transporters, norepinephrine transporters, or both, the method comprising: (a) contacting the biological system or sample with a compound of the present disclosure~~invention~~; and (b) determining the effects caused by the compound on the biological system or sample.

The present disclosure~~invention~~ also relates to processes and intermediates useful for preparing compounds of the present disclosure~~invention~~. Accordingly, one aspect of the present disclosure~~invention~~ relates to a process for preparing compounds of formula I, the process comprising deprotecting a compound of formula XI:



(XI)

or a salt thereof, where P is an amino-protecting group to provide compounds of formula I, where R^1 and R^{2-6} are as defined for formula I. In other embodiment~~aspect~~s, the present disclosure~~invention~~ relates to novel intermediates used in such processes. In an aspect, the present disclosure relates to an intermediate useful in the synthesis of a compound as defined above, having the formula:



where P represents an amino-protecting group.

Yet another embodimentaspect of the present disclosureinvention relates to the use of a compound of the present disclosureinvention for the manufacture of a medicament, especially for the manufacture of a medicament useful for treating pain disorders, depressive disorders, affective disorders, attention deficit hyperactivity disorder, cognitive disorders, stress urinary incontinence, for inhibiting serotonin reuptake in a mammal, or for inhibiting norepinephrine reuptake in a mammal. Another aspect of the present disclosure relates to a compound as defined above, for use in therapy. Still another embodimentaspect of the present disclosureinvention relates to the use of a compound of the invention as a research tool. Other aspects and embodiments of the present disclosureinvention are disclosed