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Stereoselective Synthesis and Antiallodynic Activity of 3-Hydroxylated Paroxetines

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Dedication ((optional))

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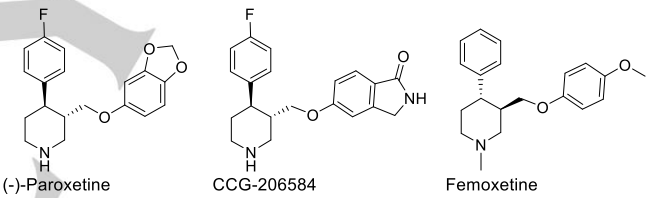
Abstract: The design, stereoselective synthesis and in vivo antiallodynic activity of four novel paroxetine analogs, named 3-hydroxy paroxetines (3HPXs), is reported. Among the novel synthesized compounds, three of them showed antiallodynic effect, while the (*R*,*R*)-3HPX resulted to be 2.5 times more bioactive than (-)-paroxetine itself in neuropathic rats. Consequently, the current investigation not only discloses a novel promising analgesic drug, but also reveals that functionalization at the C-3 position of paroxetine could be as effective as the common functionalization at either C-4 or within the sesamol group.

Neuropathic pain is caused by a lesion or disease of the somatosensory nervous system,[1] and affects around 6.5 to 10 % of the general population.[2] Although this type of pain can be either spontaneous or evoked, it is possible to differentiate various types of alterations as a pain response to a normally nonpainful stimulus (allodynia) or as an increased response to a painful stimulus (hyperalgesia).[3] It is known that neuropathic pain is associated with a negative impact on the quality of life and there is a modest efficacy response to existing analgesics like non-steroidal anti-inflammatory drugs or opioids.[4] In contrast, antidepressants such as amitriptyline, duloxetine, fluoxetine or paroxetine, and antiepileptics like gabapentin and pregabalin, have shown efficacy under various neuropathic pain conditions.[5,6]

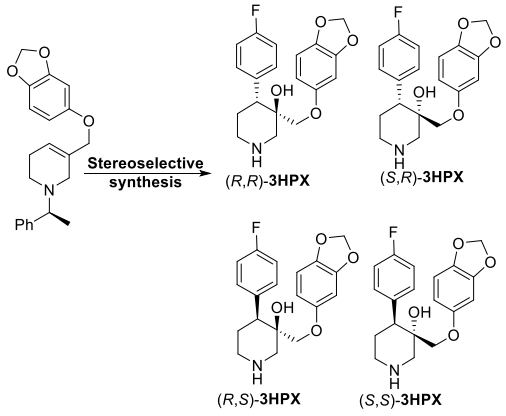
In this regard, (-)-paroxetine is a potent selective serotonin reuptake inhibitor (SSRI), which was initially prescribed for the treatment of depression and anxiety disorders,[7] and later, has proved to be effective for further clinical disorders.[8,9] Since SSRIs is a family of antidepressants that inhibits the reuptake of 5-HT into the presynaptic neuron once the 5-HT has been released affecting the duration and intensity of the 5-HT communication,[10-13] paroxetine significantly attenuates mechanical allodynia and thermal hyperalgesia in different model of neuropathic pain.[6,14-17]

Although various paroxetine analogs have been synthesized, such as CCG-2065846[18] and femoxetine[19] (inhibitor of G-protein-coupled receptor kinase 2 and antidepressant, respectively, Figure 1), to the best of our knowledge, the synthesis of paroxetine analogs as potential analgesic drugs has not been reported yet.

Figure 1. (-)-Paroxetine and two representative bioactive analogues

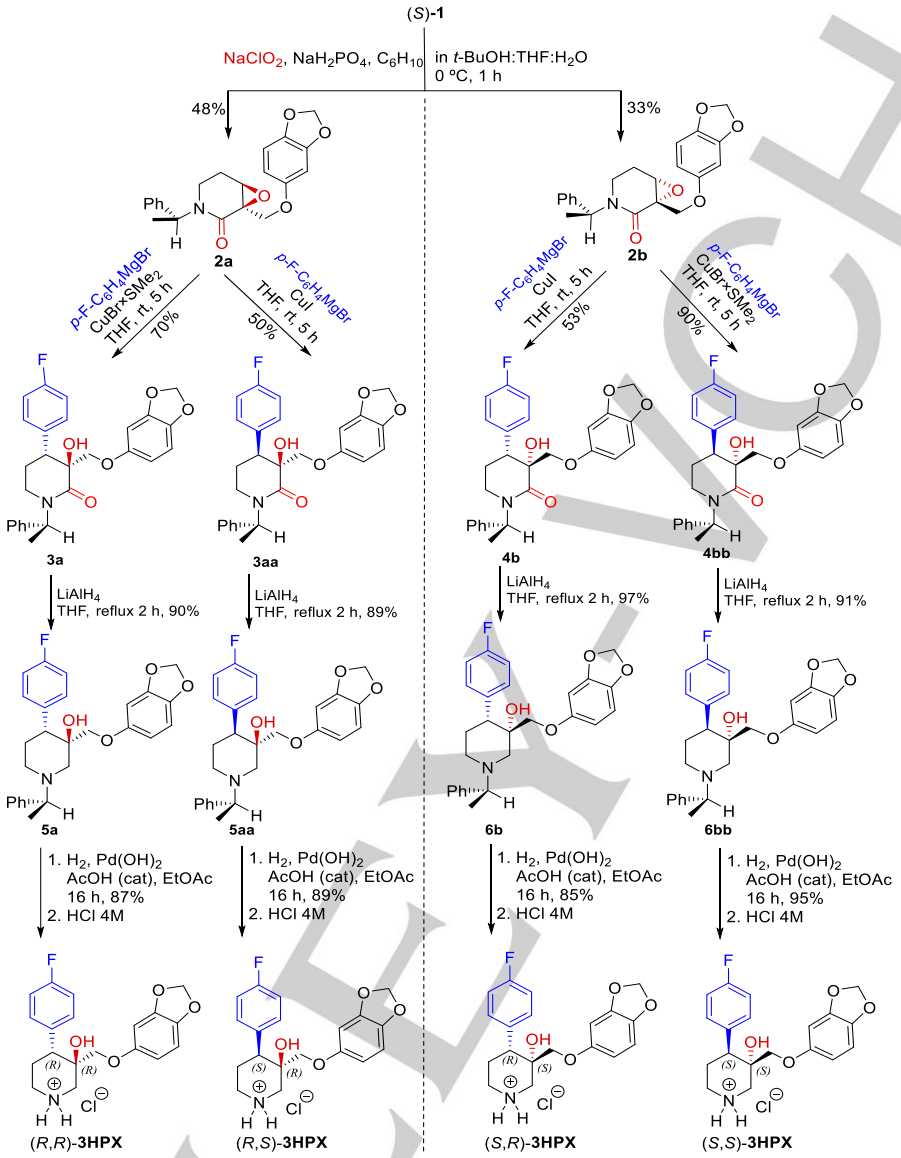


Scheme 1. Proposed synthesis of four 3-hydroxyparoxetines (3HPXs) from (*S*)-**1**



Consequently, we envisioned the synthesis and the antiallodynic study of four novel analogs of paroxetine from which they feature a hydroxyl group at C-3 position. With this structural modification, we anticipated effective biological activity either by increasing the solubility of the analogues in aqueous media or by means of an effective hydrogen bond interaction with the receptor.[20,21] To this end, we designed the synthesis of four 3-hydroxylated paroxetines (3HPX) from chiral dehydropiperidine (*S*)-**1**[22] (Scheme 1).

Scheme 2. Synthesis route of 3-hydroxylated paroxetine in the hydrochloride form [3HPX]·HCl



Scheme 3. Regio- and stereoselective epoxide-ring-opening with retention of the configuration

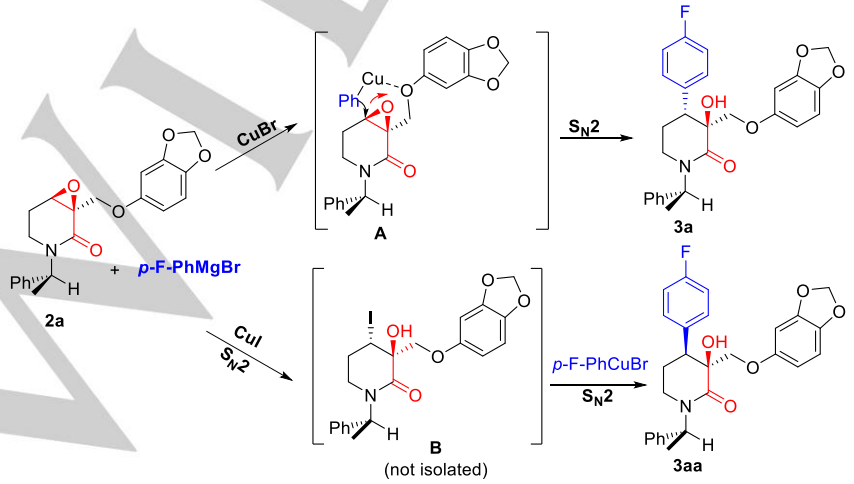


Figure 2. Time course of the antiallodynic effect of intraperitoneal (i.p.) when paroxetine (PPX) is administrated in neuropathic rats (A). Bars show the maximum possible effect (%MPE, B). Data are expressed as mean ± S. E. M. of six animals. *P < 0.05 versus SNL group and #P < 0.05 versus sham group was determinated by one-way ANOVA followed by Tukey test

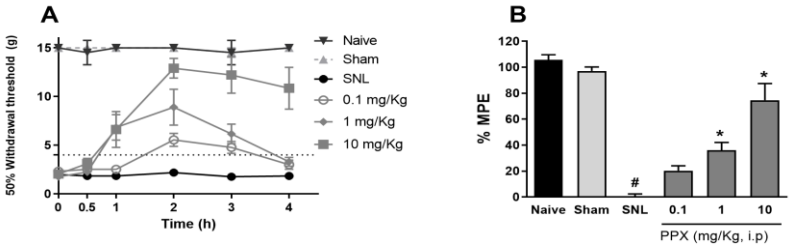
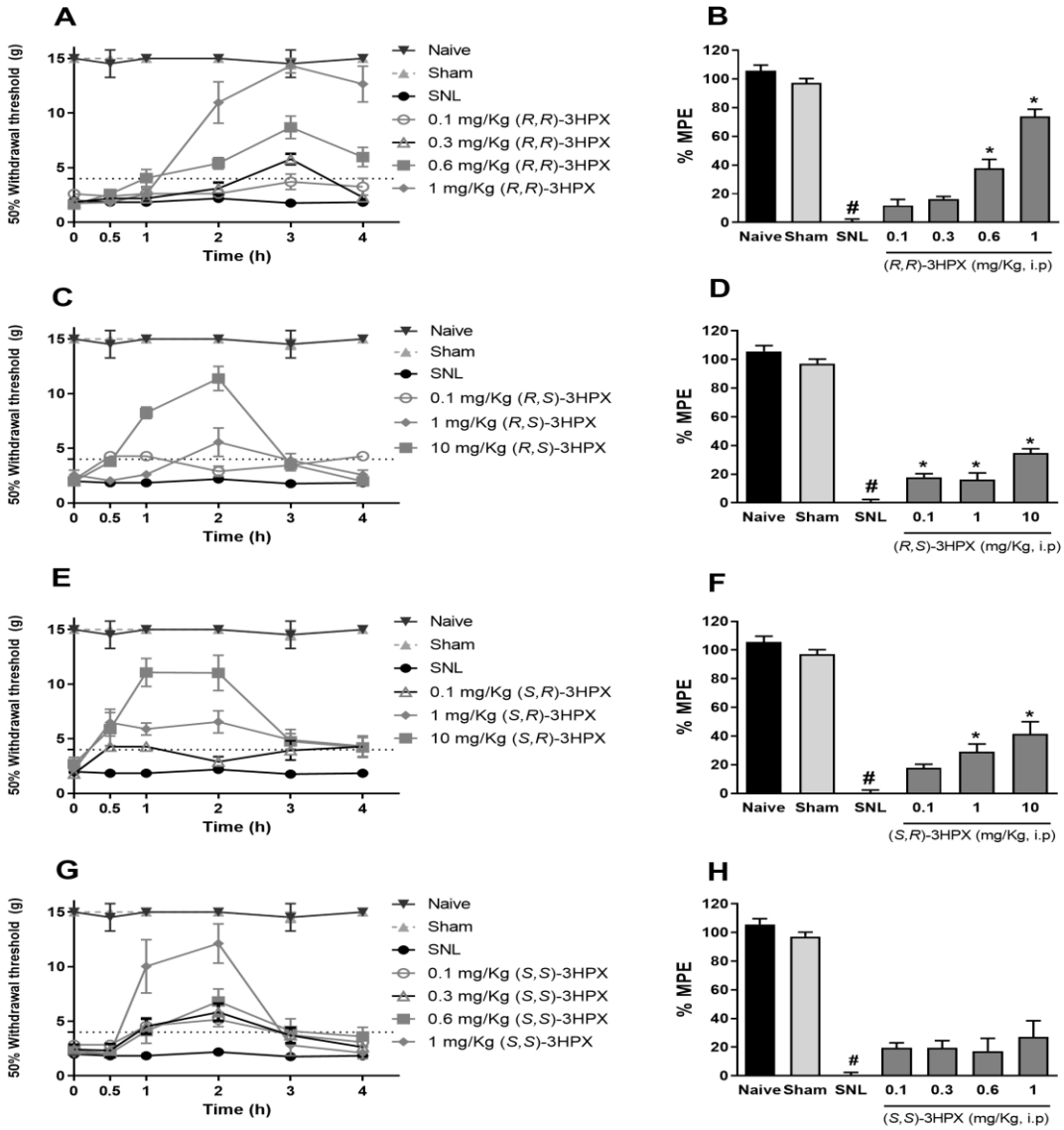


Figure 3. Time course of the antiallodynic effect of (*R*,*R*)-**3HPX** (**A**), (*R*,*S*)-**3HPX** (**C**), (*S*,*R*)-**3HPX** (**E**) and (*S*,*S*)-**3HPX** (**G**). Data are presented as 50% withdrawal threshold (**A**, **C**, **E**, **G**) or as % of maximum possible effect (%MPE, **B**, **D**, **F**, **H**). Data are the mean ± S.E.M., n = 6 per group. *P < 0.001 vs SNL, #P <0.001 vs sham as determinate by one-way ANOVA followed by Tukey test



Synthesis

The synthesis of 3HPXs is depicted in Scheme 2. Diastereomeric glycidic amides **2a** and **2b** were obtained in high yield, but moderate diastereomeric ratio from (*S*)-**1** by applying a modified tandem oxidation of allyl amines to glycidic amides protocol.[23] The modification consists in the use of cyclohexene (C_6H_{10}) as electrophilic scavenger instead of 2-methyl-2-butene. Regio- and stereoselective ring-opening of glycidic amides **2a** and **2b** with the corresponding Grignard reagent (*p*-F-C_6H_4MgBr) via a S_N2 displacement to tertiary alcohols **3a** and **4bb**, respectively, was achieved by employing CuBr•SMe_2 as catalyst (e. g., **2a** to **3a** via **A**; see Scheme 3).[22] On the other hand, ring-opening of epoxyamides **2a** and **2b** with retention of the configuration to **3aa** and **4b**, respectively, was achieved by using the same Grignard reagent but different cupper catalyst (CuI). The retention of the configuration at C-4 can be explained in terms of an initial S_N2 epoxide-ring-opening reaction mediated by CuI to give a transient *trans*-halohydrin followed by a subsequent S_N2 subtitution with the aryl cuprate to give the corresponding alcohols **3aa** from **2a** and **4b** from **2b** (e. g., **2a** to **3aa** via **B**; see Scheme 3).[22] The four tertiary alcohols **3a**, **3aa**, **4b** and **4bb** were subjected to carbonyl reduction with $LiAlH_4$ to give **5a**, **5aa**, **6b** and **6bb**, respectively, in high chemical yields. Finally, removal of benzyl group of each 3-hydoxy piperidines **5a**, **5aa**, **6b** and **6bb** with H_2 and $Pd(OH)_2$ under acidic media (4M, HCl), provided the target products (*R*,*R*)-**3HPX**, (*R*,*S*)-**3HPX**, (*S*,*R*)-**3HPX**, and (*S*,*S*)-**3HPX**, respectively, in their hydrochloride forms (Scheme 2).

Pharmacology: antiallodynic effect of paroxetine and paroxetine analogues in neuropathic rats.

In order to evaluate the antiallodynic effect to paroxetine and the paroxetine analogues in their hydrochloride form [(*R*,*R*)-3HPX, (*R*,*S*)-3HPX, (*S*,*R*)-3HPX and (*S*,*S*)-3HPX], the animals were subjected to the L5/L6 spinal nerve ligation (SNL) to produce tactile allodynia in rats. Fourteen days after SNL surgery, we observed a decrease of the 50% withdrawal threshold in the right hind paw in the SNL-vehicle compared to the sham animals. Intraperitoneal administration of paroxetine (0.1-10 mg/Kg) showed dose-dependently increased of the withdrawal threshold (Figure 2A). The antiallodynic effect of paroxetine was observed 2 h after administration, and the dose of 10 mg/kg reached a maximal percentage of the effect of 75% (Figure 2B) over 6 h, aproximately (Figure 2).

Intraperitoneal administration of (*R*,*R*)-**3HPX** (Figure 3A and 3B) and (*S*,*R*)-**3HPX** (Figure 3E and 3F) showed a dose-dependently enhanced of the withdrawal threshold. However, (*R*,*R*)-**3HPX** exhibited the best antiallodynic effect with a dose of 1 mg/Kg at 2 h (Figure 3A) and reached maximal effect (73.9 ± 4.8 %) at 4 h (Figure 3B). Remarkably, the DE_{50} of this paroxetine analog is 0.7014 mg/Kg, i.p. while the DE_{50} of paroxetine is 1.70 mg/Kg, i.p.; therefore it is clear that (*R*,*R*)-**3HPX** is more potent that paroxetine *in vivo*. On the other hand, (*R*,*S*)-**3HPX** and (*S*,*R*)-**3HPX** showed a modest antiallodynic effect 34.6 ± 3.1 % (Figure 3C and 3D) and 41.5 ± 8.5 % (Figure 3E and 3F), respectively. Unfortunately, the paroxetine analog (*S*,*S*)-**3HPX** (Figure 3G and 3H) did not show antiallodynic effect at any tested doses.

Our results are in agreement with previous studies, where in acute or sub-acute (7 days) intraperitoneal administration of paroxetine, attenuated the mechanical allodynia,[11] and thermal or mechanical hyperalgesia[12] in neuropathic-pain models. Furthermore, paroxetine produced antiallodynic and antihyperalgesic effect in diabetic rats.[13,24] Consequently, given the promising results obtained with (*R*,*R*)-**3HPX**, we anticipate this novel synthetic alkaloid can be seen as a potential drug for the treatment of neuropathic pain.

In summary, we have achieved a concise asymmetric synthesis and studied the antiallodynic effect of four novel synthetic alkaloids from which one of them resulted to be 2.5 time more bioactive than (-)-paroxetine in neuropathic rats. Although it is clear that the position and orientation of the hydroxyl group placed at the C-3 position plays a crucial role in the biological activity, we have not had further evidence to prove it yet, albeit further experimental and computational studies are underway to investigate the action mechanism of this novel highly bioactive synthetic alkaloid.

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Keywords: allodynia • neuropathic pain • paroxetine • stereoselective synthesis • alkaloids

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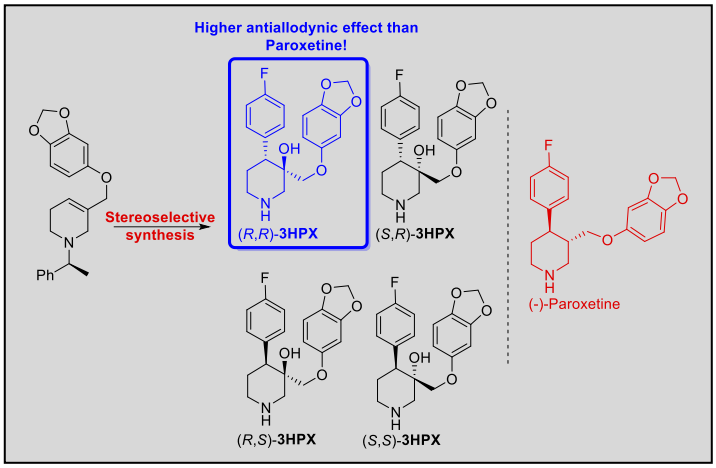

A novel synthetic alkaloid named as *R*,*R*-3HPX is introduced as a promising analgesic drug.

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