

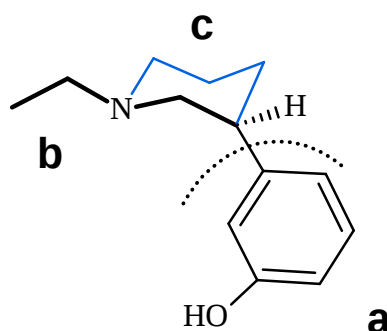
# Supplementary Information-2

## Calculation of relative chirality indices for the 3-(3-hydroxyphenyl)piperidines *R* and *S* isomers and the chiral CCR2 antagonists

The steps followed in calculating the relative chirality indices (RCI) for the *R* and the *S* isomers denoted as  $^RRCI$  and  $^SRCI$ , respectively are given below:

1. The four groups are attached to the chiral carbon assigned priority following the Cahn, Ingold and Prelog (CIP) system as a, b, and d, where a is the highest priority and d is the lowest priority group.
2. SMILES notation is written for each group of the four groups and in order to maintain the connectivity of the atom (vertex) connected to the chiral carbon the chiral carbon is also included to the groups. This is illustrated in the following examples:

### Example 1 from 3HPP data set



**Figure 3.** Application of sequence rule to 3HPP

The four groups the priorities according to CIP rules and SMILES notation after including the chiral carbon (shown in **red bold face**) are:

a = -C<sub>6</sub>H<sub>5</sub>OH; SMILES including the chiral carbon is **C**c1cc(O)ccc

b = -CHCH<sub>2</sub>N(CH<sub>2</sub>)CH<sub>2</sub>CH<sub>3</sub>, similarly SMILES is **C**CCN(C)CC

c = -CH<sub>2</sub>CH<sub>3</sub>, SMILES is **C**CCCN(C)C

d = - H; d = H, when *d* is hydrogen the weight ( $\delta$ ) is zero

Various molecular descriptors are calculated for each of the four substituents (*a*, *b*, *c*, and *d*) using the SMILES notations as the input. Computer program POLLY (Copy right of U of M), TRIPLET (Copy right of U of M) and *INDCAL* developed by Natarajan *et al.* are used to compute the molecular descriptors for each of the substituents attached to the chiral center. A list of molecular descriptors calculated, and their short definitions are given in Table 2.

3. The descriptors thus calculated for each substituent  $a$ ,  $b$ ,  $c$  and  $d$  are taken as the weight of that substituent namely  $\delta_a$ ,  $\delta_b$ ,  $\delta_c$ , and  $\delta_d$ .
4. Relative Chirality Indices (RCI) for are then calculated for the  $R$  and  $S$  isomers using the following formulae:

$${}^R RCI = \delta_a + \{\delta_a + (\delta_a \times \delta_b)\} + \{\delta_a + (\delta_a \times \delta_b) + (\delta_a \times \delta_b \times \delta_c)\} + (\delta_a \times \delta_b \times \delta_c \times \delta_d)$$

$${}^S RCI = \delta_a + \{\delta_a + (\delta_a \times \delta_c)\} + \{\delta_a + (\delta_a \times \delta_c) + (\delta_a \times \delta_b \times \delta_c)\} + (\delta_a \times \delta_b \times \delta_c \times \delta_d)$$

5. Based on the type of molecular descriptor assigned to the substituents the RCI are denoted as  ${}^R RCI_{V0}$ ,  ${}^R RCI_{BI}$ ,  ${}^S RCI_{SUM-R}$ ,  ${}^R RCI_{OPM}$  etc. the subscript indicates the type of molecular descriptor used in assigning the weights ( $\delta$ ) to the four substituents attached to the chiral carbon.

Table 2. Illustration for the calculation RCI for the molecule shown in Example 1.

|   |                           | Zero order valence connectivity index |       |
|---|---------------------------|---------------------------------------|-------|
|   | SMILES                    |                                       | $V_0$ |
| A | <chem>Cc1cc(O)ccc1</chem> |                                       | 4.757 |
| B | <chem>CCN(C)CC</chem>     |                                       | 4.861 |
| C | <chem>CCCCN(C)(C)</chem>  |                                       | 5.568 |
| D | <chem>H</chem>            |                                       | 0     |

$${}^R RCI_{V0} = 4.757 + \{4.757 + (4.757 \times 4.861)\} + \{4.757 + (4.757 \times 4.861) + ((4.757 \times 4.861 \times 5.568))\} + 0$$

$$= 189.284$$

$${}^S RCI_{V0} = 4.757 + \{4.757 + (4.757 \times 5.568)\} + \{4.757 + (4.757 \times 5.568) + ((4.757 \times 4.861 \times 5.568))\} + 0$$

$$= 196.011$$