SYNTHESIS OF *N*-ALKYL-1-PHENYL-5-METHYLSULFONYLINDOL-2-CARBOXAMIDE AS NEW COX-2 SELECTIVE INHIBITORS

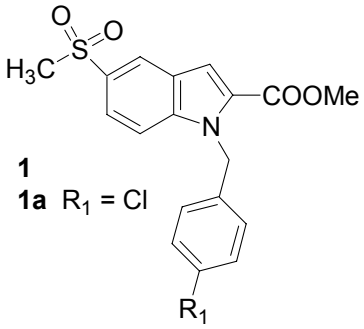
Olga Cruz-López, Juan José Díaz-Mochón, Joaquín M. Campos, Miguel Á. Gallo, Antonio Espinosa

Departamento de Química Farmacéutica y Orgánica, Facultad de Farmacia, c/ Campus de Cartuja s/n, 18071 Granada (Spain)

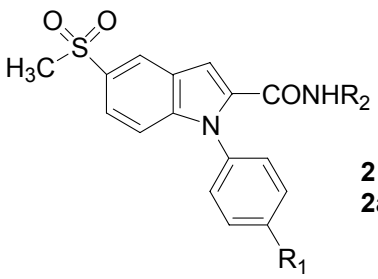
We have identified novel COX-2 selective inhibitors using pharmacophore models. This approach was used to design indomethacin analogues **1** that exhibited consistent structure-activity relationships leading to the potent and selective COX-2 inhibitor **1a** [1]. In this communication, a series of molecules with an *N*-alkyl-1-phenyl-5-methylsulfonyl indol-2-carboxamide structure is presented as new ciclooxygenase-2 selective inhibitors.

This study was undertaken according to the following steps:

1. A butyl group as an *N*-alkyl group was introduced. Five compounds with this group were synthesized, in which the *para* substituent of the phenyl group was modified. Of all the studied substituents the compound with the methylthio group showed a better potency and an inhibitory selectivity**.**
2. We studied how the length of the *N*-alkyl moiety affects the biological activity while maintaining the methylthio substituent.
3. With the most active compound so far obtained (**2a**) a series of modifications that affect the CO-NH fragment were carried out.



1
1a R_1 = Cl



2
2a R_1 = SMe; R_2 = *n*-Bu

From the analysis of the biological results obtained for these compounds it can be stated that the presence of an electron-releasing group at the *para* position of the phenyl group, specifically the methylthio group, and the lengthening of the *N*-alkyl chain with a butyl or a pentyl group, leads to an increase in both potency and selectivity in the COX-2 inhibition.

[1] Palomer, A.; Cabré, F.; Pascual, J.; Campos, J.; Trujillo, M. A.; Entrena, A.; Gallo, M. A.; García, L.; Mauleón, D.; Espinosa. A. Identification of novel cyclooxygenase-2 selective inhibitors using pharmacophore models. *J. Med. Chem.*, **2002**, *45*, 1402-1411.