Contribució a l'Estudi dels Receptors de Serotonina. Molècules Basades en Indens i Indans

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1. A series of novel indene derivatives designed by a scaffold selection from (*Z*)-stilbenes gave access to several examples of (*Z*)-arylmethylideneindenes **I** and simple indenylsulfonamides **II** that acted as 5-HT_6 serotonin receptor ligands. Different synthetic multistep routes could be applied to these targeted compounds, each with their own complexity and limitations. The indenylsulfonamides **II** were prepared by a convenient synthetic pathway using (sulfonylamino)indenylacetic acids as the key intermediates and several routes were then examined. The best option to prepare the advanced intermediates was based on an aldol-type reaction between indan-1-one sulfonamides and the lithium salt of ethyl acetate, followed immediately by dehydration with acid and hydrolysis/isomerization under basic catalysis. The (3-indenyl)acetic acids were then transformed to the corresponding acetamides, which were effectively reduced to indenylsulfonamides using an optimized procedure with an alane complex (AlH_3-NMe_2Et).

   The binding at the 5-HT_6 receptor was with moderate affinity (K_i = 216.5 nM) for an example of **I**-type ligands and enhanced affinities for several **II**-type indenylsulfonamides ($K_i \geq$ 20.2 nM). Notably, the indenylsulfonamides functioned as 5-HT_6 agonists. The structural changes responsible for enhancing the 5-HT_6 receptor binding profile are governed by the chemical tractability of the indene-based systems and additional studies are needed for general synthetic approaches to the designed indene-based compounds. Summing up, **II**-type indenylsulfonamides appeared interesting for further development due to the utility of 5-HT_6 receptor agonists in the investigation of the functional role of 5-HT_6 receptors.

2. By developing an indole-to-indene core change, efforts were directed towards the design and synthesis of structural analogues both closely and distantly related to the already prepared examples of indenylsulfonamides. The variety of the targeted **II**-type ligands and their synthetic complexity required multistep synthetic approaches. After analyzing different alternatives, a four-step sequence was applied using the inden-5-amines with a disubstituted *N*,*N*-aminoethyl group at the indene 3-position as the key intermediates, which enabled the preparation of different **II**-type ligands to be diversified at the 5-position. This route required the preparation of the advanced inden-5-amines following a sequential conversion from suitable 6-nitroindan-1-ones. On the other hand, the 'reverse sulfonamide' analogue was prepared using a five-step synthesis starting from the corresponding 6-aminoindan-1-one. A limiting factor of this protocol was that, although a variety of aryl(heteroaryl)sulfonyl chlorides are either commercially available or easily accessible, their amine counterparts are difficult to obtain, as was the case for the imidazothiazolylamine, so the commercial 1-naphthylamine was used instead.

   The novel indenylsulfonamides **II** exhibited variable binding affinities for the 5-HT_6 receptor and the *in vitro* profiles of the preferred compounds revealed them to be selective 5-HT_6 receptor agonists. Hence, the scaffold was modified by satisfactorily replacing a π-excessive heteroaromatic indole ring with a non-aromatic carbocyclic indene system, and the structural changes responsible for enhancing the binding affinities were modulated by: (i) the nature of the indene scaffold; (ii) the substitution at the aminoethyl side chain; and (iii) the nature of the aryl(heteroaryl)sulfonyl portion of the sulfonamide moiety. The affinity was driven by the 6-chloroimidazo[2,1-*b*][1,3]thiazole structural motif, leading to the most promising compounds and the of **II**-type indenylsulfonamides functioned as potent agonists at 5-HT_6 receptors with EC_{50} values in the low-nanomolar or even subnanomolar range. A representative compound of the family, *N*-(indenyl)imidazothiazolesulfonamide, proved to be a highly potent and selective 5-HT_6 receptor agonist (K_i = 4.5 nM, EC_{50} = 0.95 nM).

3. Further studies in quest of 5-HT_6 receptor indene-based ligands were focused on the influence of the *N*,*N*-dimethylaminoethyl side chain on the indene 3-position. A few examples of ring-constrained **III**-type *N*-(inden-5-yl)sulfonamides and the structurally simplified indenylsulfonamide counterparts have been designed and synthesized on the basis of previously established structural requirements for enhancing the affinity of indene-based ligands towards the 5-HT_6 receptor, especially the aryl(heteroaryl)sulfonyl portion of the sulfonamide functionality, e.g. the imidazothiazole motif. The syntheses of the ring-constrained indenylsulfonamides were carried out following three-step procedures, starting from substituted indanones leading to the corresponding key indenamines, which permitted the preparation of **III**-type ligands to be diversified. The first synthetic step to the appropriate key inden-5-amines took advantage of an aldol-type reaction between different indan-1-ones and the lithium salt of ethyl acetate previously employed, the protocol being adapted to lactams such as *N*-methyl-2-pyrrolidinone or *N*-methyl-2-piperidinone.

   Some ring-constrained indenylsulfonamides **III** exhibited a high binding affinity for the 5-HT_6 receptor and functioned as antagonists, although with moderate potency at the micromolar level. When the basic amine side chain on the indene 3-position was constrained in a five-membered ring, e.g. the pyrrolidine analog (K_i = 3 nM), or a six-membered ring, e.g. the piperidine analog (K_i = 18 nM), the compounds appeared able to adopt a conformation that permits these high binding affinities for the 5-HT_6 receptor. Despite lacking the basic amine side arm, the structurally simplified *N*-(inden-5-yl)sulfonamide counterparts maintained a binding affinity of $K_i \geq 43$ nM, which indicates that neither the *N*,*N*-aminoethyl nor the conformationally restricted aminoethyl side arm on the indene 3-position are required for binding.

4. Changing the *N*,*N*-(dimethylamino)ethyl side chain in the *N*-[3-(aminoethyl)inden-5-yl]sulfonamide 5-HT_6 serotonin receptor agonists **II** for a conformationally rigid guanylhydrazone moiety on the indene 3-position led to the identification of novel indanylguanylhydrazone sulfonamides **IV** as highly potent and selective 5-HT_6 receptor antagonists. Several examples of **IV**-type compounds were designed on the basis of established structural requirements for the binding at 5-HT_6 receptors and prepared following two-step procedures. Thus, suitable 6-aminoindan-1-ones were transformed into the corresponding indan-1-one sulfonamides by sulfonylation with the appropriate sulfonyl chlorides, and subsequent condensation with hydrazine derivatives under acidic conditions gave the targeted indanylguanylhydrazones **IV**. The structure of the new compounds was confirmed by spectroscopic methods and on the basis of a NOESY experiment it was inferred that the C=N– bond belonged to an *E*-isomer structure. The replacement of the conformationally flexible *N*,*N*-aminoethyl side chain by a rigid guanylhydrazone moiety at the indene 3-position gave access to novel indanylsulfonamide guanylhydrazones **IV**, which exhibited excellent binding affinities and an antagonistic response at the 5-HT_6 receptor, with K_i and IC_{50} values in the nanomolar range ($K_i \geq 1.2$ nM, $IC_{50} \geq 47$ nM).

5 The ensemble of indene-based frameworks constituted by the *N*-[3-(aminoethyl)inden-5-yl]sulfonamide agonists **II**, the conformationally rigid antagonists **III** and the structurally simplified *N*-(inden-5-yl)sulfonamide counterparts, as well as the indanylsulfonamide guanylhydrazone antagonists **IV** may be useful biological tools for the fundamental understanding of the 5-HT_6 receptor. A representative compound of novel indenylsulfonamide 5-HT_6 agonists **II**, *N*-(inden-5-yl)imidazothiazole-5-sulfonamide (K_i = 4.5 nM, EC_{50} = 0.95 nM), appeared to be a suitable candidate for further studies since potent and selective 5-HT_6 agonists are needed to remodel the current knowledge of the functional role and therapeutic importance of 5-HT_6 receptors, leading to the development of 5-HT_6 agents for the treatment of CNS-mediated diseases such as anxiety, depression and other mental disorders. Moreover, 5-HT_6 receptor agonists are of interest for the treatment of disorders or diseases associated with food intake, including obesity, bulimia and anorexia.