DPhG | Deutsche Pharmazeutische Gesellschaft e.V.

GDCh
Gesellschaft Deutscher Chemiker

EFMC
European Federation for Medicinal Chemistry

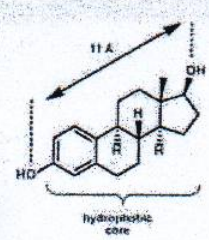
EFMC-ISMC 2012 is organised by the German Chemical Society (GDCh) Division of Medicinal Chemistry and the German Pharmaceutical Society (DPHG) Section of Pharmaceutical/Medicinal Chemistry

P573

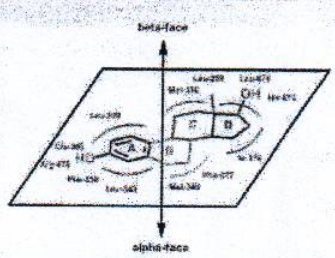
Design of a Selective Estrogen Receptor Beta Agonist as a Possible Neuroprotective Intervention of Multiple Sclerosis

Lars Hagberg, Konrad Koehler, Theresa Appelquist, Henrik Jernstedt, Elisabeth Kallin, Lars Krüger, Daniel Nöteberg, Patrik Rhönnstad

Karo Bio AB, Novum, 141 57 Huddinge, Sweden



Structure of the natural hormone 17-β-estradiol indicating key pharmacophoric features required for high affinity binding



Schematic diagram of the binding cavity of ERβ

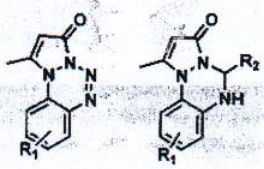
The estrogen receptor (ER) is a member of the nuclear receptor superfamily, which functions as hormone-regulated modulators of intracellular signalling and gene expression. ER exists as two subtypes (ERα and ERβ), and studies have showed intriguing differences in the tissue distribution and genes regulated by the two subtypes. Emerging data suggest that the development of subtype-selective ligands that specifically target ERβ may be a superior approach for the treatment of multiple sclerosis (MS). Current therapies for MS are primarily targeting the immune system exerting anti-inflammatory actions and show effect in the relapse remitting phase when the degree of inflammation is high, but have limited effect in the progressive phase when the degree of neurodegeneration is high. Recently published studies have revealed positive effects of estrogens in experimental autoimmune encephalomyelitis (EAE) that are mediated by both ERα and ERβ. By using an ERβ agonist for neuroprotective treatment in MS, ERα-mediated side effects, such as increased cancer risks and thrombosis, would be avoided. The high sequence similarity and structural conservation between the ligand binding domains of the two ER subtypes has made it a challenging undertaking to develop subtype-selective ligands for the ERs. The first ERβ-selective ligands to be discovered were phyto-estrogens (such as the heteroaromatic genistein) of largely planar topology. The explanation for their modest selectivity is that the binding cavity of ERβ is slightly narrower than that of ERα. This allows better packing of flat aromatic ligands such as genistein in the ERβ binding cavity compared with ERα. Ligands that enforce strong repulsive interactions with ERα while avoiding corresponding unfavourable interactions with ERβ tend to display much greater and more robust selectivity compared with ligands that achieve selectivity through differences in attractive interactions. The current focus of our ER programme is the treatment of multiple sclerosis through the neuroprotective properties of ERβ. We will present structural data for a series of highly selective ERβ ligands whose selectivity is a result of substituents that are orthogonal to the core producing an overall ligand topology that is non-planar. In addition, we will present data where a proprietary selective ERβ agonist reduces neurological scorings in a relapsing–remitting EAE rat model and shows neuroprotective effects after glutamate excitotoxicity in vitro, suggesting ERβ agonists as a possible novel neuroprotective therapy of multiple sclerosis.

P574

1,2-Dihydropyrazole[1,2-*a*]benzo[1,2,4]-triazine-3-one: Deaza Analogue Tricyclic Scaffold with Valuable Antiproliferative Activity

Francesco Mingoia,[a] Riccardo Delisi,[b] Anna Martorana,[b] Anna Maria Almerico,[b] Antonino Lauria[b]

[a] Istituto per lo Studio dei Materiali Nanostrutturati - CNR, Via U. La Malfa 153, 90146 Palermo, Italy; mingoia@pa.ismn.cnr.it
[b] Università degli Studi di Palermo, Dip. di Scienze e Tecnologie Molecolari e Biomolecolari (STEMBIO): Sez. di Chim. Farmaceutica e Biologica, via Archirafi 32, 90123 Palermo Italy



1 2

1-[1,2-*a*]Benzo[1,2,3,4]tetrazin-3-one derivatives (**1**) have been previously designed as new alkylating agent because of their peculiar chemical behavior. Most of the synthesized derivatives showed antiproliferative activity against more than 50 types of human tumor cell lines reaching in some cases micromolar values.[1] Here, with the aim of modulating the biological profile, we planned to switch our interest to the deaza tricycle 1,2-dihydropyrazole[1,2-*a*]benzo[1,2,4]triazine-3-one (**2**) exploiting the advantage of introducing new moieties in R2 useful for SAR studies. Variously fused pyrazolo-triazine derivatives showed antiproliferative activity as novel potent inhibitors of kinase CK2[3] and of CYP1A1, the enzyme involved in the metabolism of chemical carcinogens.[2] Even more, hydrazide derivatives have exhibited remarkable inhibitory activity against SiHa and LS180 human tumor cell lines, with absence of toxicity towards the HSF control cell line.[4,5] In the present study, we designed and synthesized a set of new derivatives of type **2** containing selected functional groups in order to evaluate their potential anticancer properties.

References

[1] A. M. Almerico, F. Mingoia, P. Diana, P. Barraja, A. Lauria, A. Montalbano, G. Cirrincione, G. Dattolo, *J. Med. Chem.* **2005**, *48*, 2859–2866.
[2] A. M. El Massry, A. M. Asal, S. N. Khattab, N. S. Haiba, H. A. Hawney, M. Helmy, V. Langer, A. Amer, *Bioorg. Med. Chem.* **2012**, *20*, 2624–2637.
[3] Z. Nie, C. Peretta, P. Erikson, S. Margosiak, J. Lu, A. Averill, R. Almassy, S. Chu, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 619–623.
[4] K. Sztanke, K. Pasternak, J. Rzymowska, M. Sztanke, M. Kandefer-Szerzen, *Eur. J. Med. Chem.* **2008**, *43*, 1085–1094.
[5] G. Ciciani, M. Coronnello, G. Guerrini, S. Selleri, M. Cantore, P. Failli, E. Mini, A. Costanzo, *Bioorg. Med. Chem.* **2008**, *16*, 9409–9419.