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Research paper

Drifting of heme-coordinating group in imidazolylmethylxanthones leading to improved selective inhibition of CYP11B1

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ABSTRACT

An abnormal increase in glucocorticoid levels is responsible for pathological disorders affecting different organs and systems, and the selective inhibition of appropriate steroidogenic enzymes represents a validated strategy to restore their physiological levels. In continuing our studies on CYP11B inhibitors, in this paper a small series of 6-substituted 3-imidazolylmethylxanthones was designed and synthesized, according to the data acquired from previously reported series of derivatives and from a purposely-performed docking study. The new compounds proved to be potent inhibitors of CYP11B isoforms, being effective on CYP11B1 in the low nanomolar range and improving selectivity with respect to CYP11B2, compared to previously reported related compounds. These data further confirmed that a suitable mutual arrangement of the imidazolylmethyl pharmacophore and a properly selected substituent on the xanthone core allows a fine tuning of the activity towards the different CYPs and further corroborate the role of the xanthone scaffold as a privileged structure in this field.

1. Introduction

Cortisol is a glucocorticoid steroidal hormone produced in the adrenal gland and mainly released in response to stress. It is also involved in many different metabolic processes, in suppression of immune system and in neurogenesis. A dysregulation of its biosynthesis, leading to an abnormal increase of its physiologic levels, is related to life-threatening diseases, including Cushing's syndrome and chronic wound healing [1,2]. These hormone-related pathologies could be managed by reducing the excessive glucocorticoid production, acting on properly selected steroidogenic enzymes. In this context 11β-hydroxylase (CYP11B1), one of the two isoforms of steroid 11-hydroxylases, catalysing the conversion of 11-deoxycortisol in cortisol in the last step of its biosynthetic pathway, can be considered a validated drug target [3]. This cytochrome is also involved in the hydroxylation of 11-deoxycorticosterone in corticosterone, which is then converted in aldosterone by the other isoform of 11-hydroxylases, aldosterone synthase (CYP11B2). The overproduction of aldosterone proved to be involved in steroid-related diseases as well, such as hypertension, congestive heart failure and myocardial fibrosis [4].

These enzyme isoforms are mainly expressed in the adrenal cortex, CYP11B1 in the zona fasciculata and CYP11B2 in the zona glomerulosa, and share a degree of sequence homology up to 93%, making the design of specific and selective inhibitors particularly challenging. In recent years, highly selective CYP11B2 inhibitors have been reported [5–8], characterized by a significant structural scaffold variance, still bearing the key features for an efficient cytochrome inhibition, such as nitrogen-containing heterocyclic functions (pyridine or imidazole), able to interact with the heme-iron of the active site.

Despite some exciting progresses in the development of selective compounds have been recently reported [9–11], no specific CYP11B1 inhibitor has been approved to treat hypercortisolism. Metyrapone (Fig. 1) is the only CYP11B inhibitor used in some countries for adrenal insufficiency diagnosis and occasionally in

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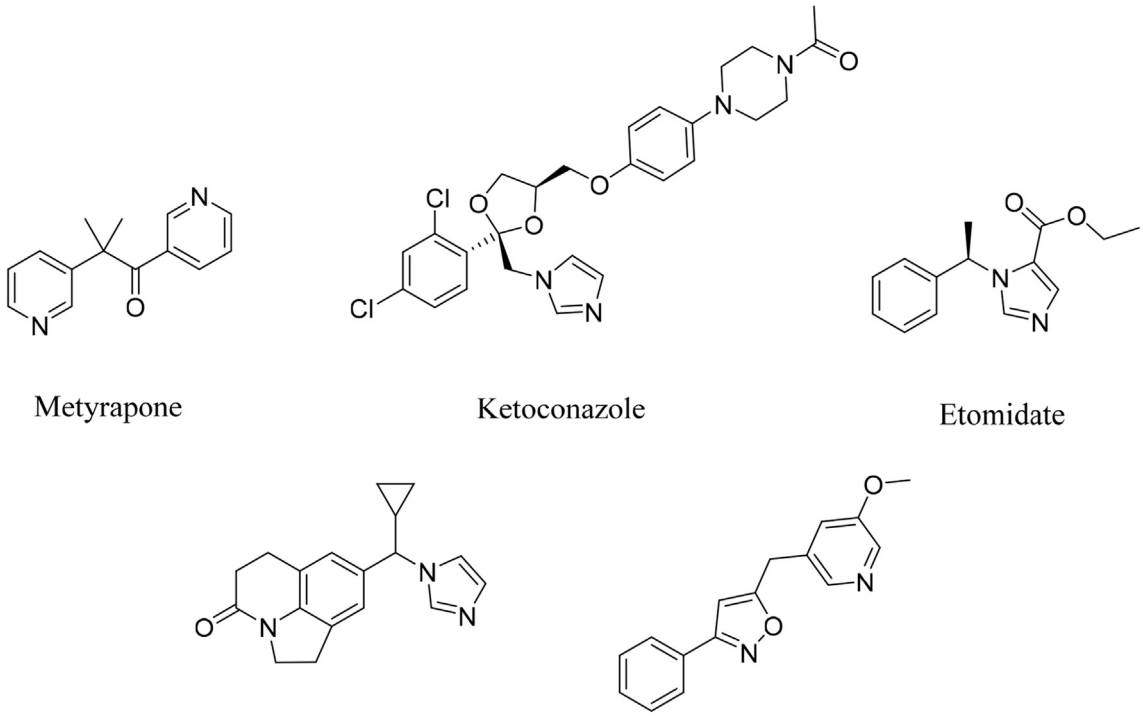

Fig. 1. Representative CYP11B1 inhibitors.

Cushing's syndrome, but its poor selectivity accounts for the onset of several side effects. It is also worth noting that the antifungal drug ketoconazole and the anesthetic etomidate (Fig. 1) could be used as multiple enzyme inhibitors in the management of Cushing syndrome, although the emergence of toxicity issues should be carefully monitored [12]. Taking these drawbacks into account, several studies are in progress in order to obtain more active and selective potential drugs. In particular, starting from the structure of etomidate, a series of more rigid pyrrolo quinolin-one derivatives (Fig. 1) were designed as CYP11B1 inhibitors and further optimized, leading to more selective compounds with respect to CYP11B2 [13]. Moreover, a series of pyridylmethyl isoxazole derivatives (Fig. 1) endowed with nanomolar inhibition potency on CYP11B1 and a better selectivity factor over aldosterone synthase with respect to metyrapone were very recently described [14].

In recent papers we reported the design and synthesis of two different series of 1-imidazolylmethylxanthones (1-ImiXs), carrying different substituents either in position 4 [15] or in position 6 [16] of the central core, as potent inhibitors of CYP11B enzymes (Fig. 2). These compounds were designed on the basis of the hits retrieved from a virtual screening of our aromatase (CYP19) inhibitors library of compounds on CYP11B2, used as starting point for subsequent optimisation, taking into account the different features emerged from the pharmacophore search. When comparing the results of the biological evaluation of these two sets of molecules, it could be seen that the shift of substituents from position 4 to position 6 led to a general decrease in the inhibitory potency toward both enzymes, although for a couple of compounds (fluorine and nitro derivatives) low-nanomolar range activities were observed. This could be the result of different effects, i.e. a less appropriate fitting of 6-substituted compounds in the binding site and/or the modification of the relative location of the substituents and the imidazolylmethyl side chain, the crucial moiety for the primary interaction of the molecule with the heme iron of the enzyme, leading to its positioning into the binding site.

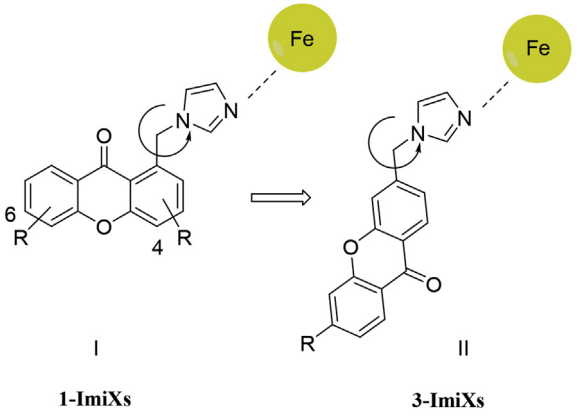

Fig. 2. Design of the studied compounds.

On the other hand, from the initial virtual screening, the compound carrying a 3-imidazolylmethyl moiety and no further substitution on the central core [17] emerged among unsubstituted ImiXs as the most promising potential selective inhibitor of CYP11B1 (see Table 1).

Taken together, all these data proved the role of the xanthone core as a valuable scaffold for the development of different cytochromes inhibitors. This planar oxygenated heterocycle could be considered as a "privileged structure" for the inhibition of CYP11B1 and CYP11B2 as its large conjugated π system could conveniently form π-π interactions with the many aromatic amino acid residues in the active sites. Since the competitive inhibition is a consequence of the coordination of the sp^2 hybridized imidazole N to the heme iron, which normally shows a perpendicular setting, and thus acts as an anchor to binding [18], alteration of the substitution pattern could change the orientation of the whole molecule and therefore lead to different inhibitory activity against these two homologue enzymes.