Kinetics of Adsorption of Heavy Metal Cu (II) from Aqueous Phase on Modified Agricultural Waste

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ABSTRACT

Tyrosinase is a multifunctional, glycosylated and copper-containing oxidase which catalyzes the first two steps in mammalian melanogenesis and is responsible for enzymatic browning reactions in damaged fruits during post-harvest handling and processing. Neither hyperpigmentation in human skin nor enzymatic browning in fruits are desirable. These phenomena have encouraged researchers to seek new potent tyrosinase inhibitors for use in foods and cosmetics. This article surveys tyrosinase inhibitors, newly discovered from natural and synthetic sources. The inhibitory strength is comparable to that of the standard inhibitor kojic acid. Also, their inhibitory mechanisms are discussed. The new obtained compounds were also tested as PDE5 inhibitors and did not show significant inhibitory effect.

Keywords: Biological Activity, Enzyme Inhibitors, Organic Synthesis, Pyrazolo[4,3-E][1,2,4]Triazines, Sulfonamides.

INTRODUCTION

Azoloazines are biological interesting molecules, and their chemistry is receiving considerable attention.[1-3] Furthermore, the multiple biological activities of pyrazole and its annelated derivatives are of increasing interest as antimycotics[4], antidepressants[5], fungicidal[6] or herbicidal agents[7]. Compounds containing the pyrazolo[4,3-*e*][1,2,4]triazine moiety have attracted considerable attention due to their anticancer and antibacterial activity[8-10]. The most important members in this family of naturally occurring purine analogues are pseudoiodinine[8], nostocine A[9] and fluviols A-E[10] produced by *Pseudomona fluorescens* var. *pseudoiodinine* and *Nostoc spongiaeforme*, respectively. Despite the fact that pyrazolo[4,3-*e*][1,2,4]triazines have been less studied in the group of condensed pyrazolotriazines, some of them show moderate inhibition of purine nucleoside phosphorylase[11] and cytotoxic activity in A549 lung carcinoma cell line at submicromolar range[12], induction of caspase-dependent cell death, and inhibition of cyclin-dependent kinase 2 (CDK2)[13].

It should be noted that so far no analogues of sildenafil containing the skeleton of 1*H*-pyrazolo[4,3-*e*][1,2,4]triazine ring system have been described in the literature. With regard to

the above discussed facts, we envisage a high potential of the pyrazolo[4,3-*e*][1,2,4]triazine system regarding the discovery of new biological activities.

In this context and in continuation of our program aimed at the discovery and development of new bioactive molecules, we represent here the preparation of novel analogues of Sildenafil and *iso*Vigra[16] (termed *aza*-analogues of Sildenafil **8a-j** and *aza-iso*Viagra **9**) in which the carbonyl group, present in the structures of Sildenafil and *iso*Viagra, is replaced with the nitrogen atom N7, present on the triazine ring (Fig. 1), to test their PDE5 and tyrosinase inhibitory activity.

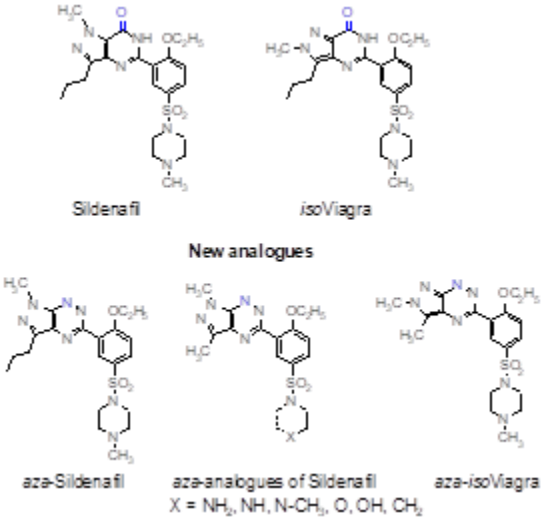
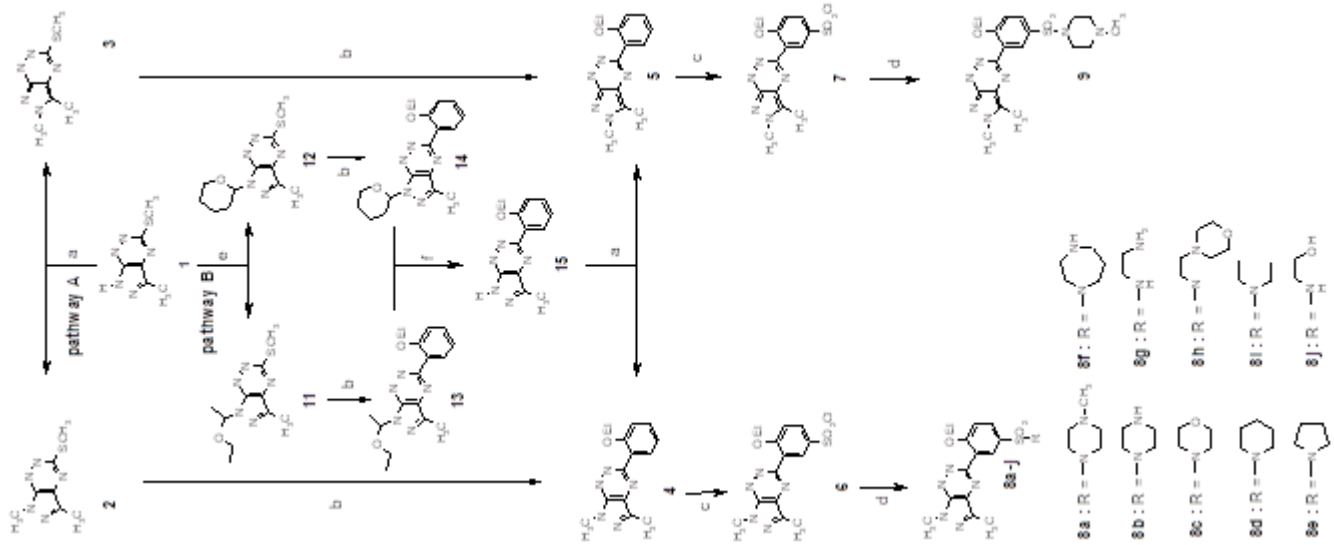


Figure 1. Structures of Sildenafil, iso Viagra and new analogues: aza-isoViagra, aza-Sildenafil, and its aza-analogues.

RESULTS AND DISCUSSION

Synthesis

The synthesis of *aza*-analogues of Sildenafil 8**a-j** and *aza*-isoViagra **9** are outlined in Scheme 1, and the preparation could be achieved in two pathways (Scheme 1).



Scheme 1. Synthetic path to the *aza*-analogues of Sildenafil **8a-j**. Reagents and conditions: (a) CH_3I, $EtOH/H_2O/K_2CO_3$; (b) ethoxyphenyl-boronic acid, $Pd(PPh_3)_4$, CuMeSal, THF, under argon atmosphere, reflux, overnight; (c) $ClSO_3H$, 0°C to rt, 2h; (d) appropriate amine, anhydrous MeCN, rt, overnight; (e) ether (ethyl vinyl ether or 2*H*-pyran, benzene, conc. HCl, 40°C, 8hs; (f) conc. HCl, MeOH, r.t., 12h.

SUMMARY

A practical, high yielding, and scalable method for the preparation of new pyrazolo[4,3-*e*][1,2,4]triazine derivatives as new *aza*-analogues of Sildenafil from inexpensive commercially available starting materials is described. The new Sildenafil analogues were designed by replacing the carbonyl group of the scaffold by a triazine nitrogen atom. Biotesting experiments for Sildenafil and lodenafil carbonate analogues showed good

tyrosinase inhibitory activity, but very low PDE5A inhibitory potency, and further modification of the structure are under way to increase the potency against tyrosinase.

ACKNOWLEDGMENT

The authors would like to express appreciation to prof. JingShan Shen from Shanghai Institute of Materia Medica, Chinese Academy of Science for PDE5 assay and to prof. *Wolfgang Voelter from* Interfacultary Institute for Biochemistry, Hoppe-Seyler-Str.4, 72076 Tubingen, Germany for tyrosinase inhibitory activity research.

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