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Interaction of some new 2-(substituted-thio)-quinazolin-4-ones with molybdenum hydroxylases: A pharmacophore prediction

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ABSTRACT

Background: Molybdenum hydroxylases have been implicated as key oxidative enzymes in some diseases.
Methods: Twenty 2-(substituted-thio)-quinazolin-4-one derivatives recently synthesized in our laboratory were examined for their inhibitory activity toward molybdenum hydroxylases.
Results and conclusion: The tested quinazolines inhibited both xanthine oxidase and aldehyde oxidase enzymes in a competitive pattern with *Ki* values range of 66–753 μM. Pharmacophore prediction methodology was used to study the structure requirements of those inhibitors.

1. Introduction

Molybdenum hydroxylases are group of enzymes that share the transition metal molybdenum (MoVI) [1]. The principal mammalian molybdenum-containing enzymes are aldehyde oxidase (EC 1.2.3.1), xanthine oxidase (EC 1.1.3.22), xanthine dehydrogenase (EC 1.1.1.204) and sulphite oxidase (EC 1.8.3.1). Xanthine oxidase/dehydrogenase is the key enzyme in the sequential metabolism of hypoxanthine to xanthine and uric acid [2,3], while aldehyde oxidase is an important enzyme in the detoxification of foreign xenobiotics [4]. Molybdenum hydroxylases have been implicated as key oxidative enzymes in some diseases [5,6]. Aldehyde oxidase catalyses nucleophilic attack at an electron-deficient carbon adjacent to a ring nitrogen atom in *N*-heterocyclic compounds, oxidizing the compounds into a cyclic lactams, beside the conversion of aldehydes into carboxylic acids [7]. Aldehyde oxidase inhibitors include chemicals that are structurally similar to its substrates, which thought to act at the molybdenum centre. Consequently, chlorpromazine, amsacrine, hydralazine and isovanillin are potent aldehyde oxidase inhibitors that resemble *N*-methylphenothiazine, *N*-[(2′-dimethylamino)-ethyl]acridine-4-carboxamide (DACA), phthalazine and vanillin, respectively [3,8–11].

Quinazolines have similarity with a number of aldehyde oxidase substrates including nitrogen-containing heterocycles such as methotrexate, famciclovir, acyclovir, and phthalazine (Km = 40–200 μM) [8,12]. Quinazolines display a broad spectrum of biological and pharmacological activities [13], including dihydrofolate reductase [14,15], farnesyl protein transferase [16], cyclin-dependent kinases [17] and molybdenum hydroxylases [18,19]. Several modifications of the quinazoline nucleus were implemented to pursue a study of the structural requirements of quinazolines to inhibit molybdenum hydroxylase enzymes.

2. Results and discussion

In the present study, the potency of twenty quinazoline derivatives, synthesized in our laboratory (Fig. 1) [20], as inhibitors for aldehyde oxidase and xanthine oxidase was investigated. The quinazolines perused in this study were able to inhibit the initial rates of phthalazine or indole-3-aldehyde oxidation by guinea pig liver aldehyde oxidase in a competitive pattern. Similar mode has been shown with the oxidation of xanthines by xanthine oxidase. In

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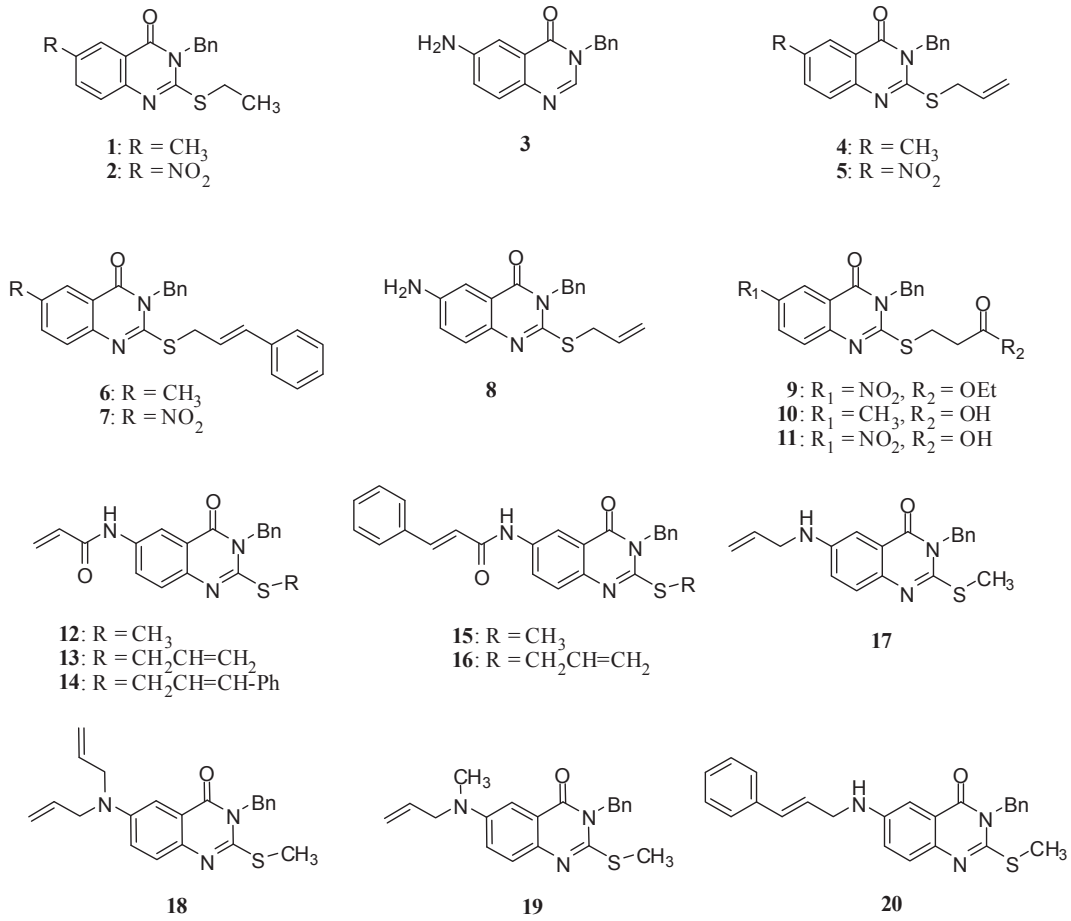

Fig. 1. Structures of the tested quinazolines.

general, aldehyde oxidase was more sensitive to this quinazoline series than xanthine oxidase. Inhibitor constants values, which ranged from 66 to 753 μM are presented in Table 1. It should be noted that the extent of aldehyde oxidase inhibition by some of the aforementioned inhibitors depends on the species under test. However, guinea pig liver aldehyde oxidase has been shown to be an excellent model for the human liver enzyme, therefore it has been used throughout this study [21,22]. Compound 3 proved to be the most active inhibitor toward aldehyde oxidase (K_i = 66 μM) with selectivity index 8.58.

Table 1
Inhibitory constants of the tested quinazolines (1–20) for xanthine oxidase (XO) and aldehyde oxidase (AO).

Compound	K_i (μM) with XO[a]	K_i (μM) with AO[a]	Selectivity index (SI)[b]
1	447	134	3.4
2	416	145	2.9
3	566	66	8.6
4	437	159	2.8
5	375	111	3.4
6	368	204	1.8
7	422	264	1.6
8	351	190	1.9
9	753	185	4.1
10	676	208	3.3
11	664	123	5.4
12	563	168	3.4
13	684	154	4.4
14	690	156	4.4
15	528	276	1.9
16	254	188	1.4
17	552	210	2.6
18	632	220	2.9
19	694	225	3.1
20	716	229	3.1

[a] Mean of K_i, inhibitory constant (n = 3–4 determinations, $r^2 > 0.991$).
[b] *In vitro* AO selectivity index (XO *Ki*/AO *Ki*).

The compliance of the test compounds to the Lipinski's rule of five [23] was calculated. Briefly, this simple rule is based on the observation that most of the biological active drugs have a molecular weight of 500 or less, a logP no higher than 5, up to five hydrogen bond donor sites and up to ten hydrogen bond acceptor sites (N and O atoms). The results disclosed in Table 2 show that all of the test compounds comply with these rules. Theoretically, these compounds should present good passive oral absorption and differences in their bioactivity can not be attributed to this property. The introduction of substituent at positions 2- and 6- of the quinazoline core, and the variation of the functions on these sites have allowed the evaluation of the influence of lipophilicity and steric parameters on the pharmacophoric residue of the molecule. Table 2 gathers xanthine oxidase/aldehyde oxidase inhibitory activity, values of ClogP (lipophilic factors) as well as molar refractometry (steric factors). These data were determined by the use of HyperChem program [24] for each compound. Within the tested series of compounds (1–20), it was observed that sharp increase of the xanthine oxidase inhibitory activity occurs when molar refractometry increases from 109.3 cm^3/mol (9) to 135.0 cm^3/mol (16).