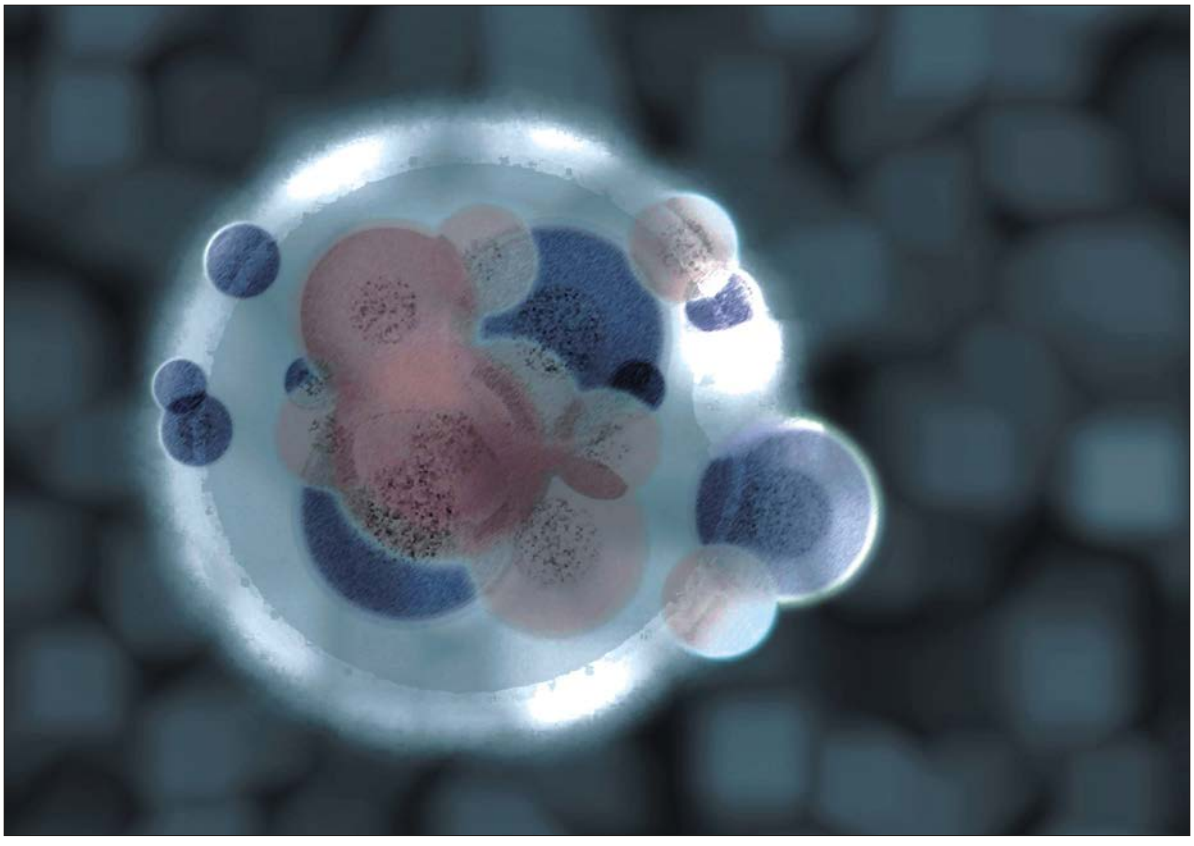

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Interaction of 2-thio-4-oxo-quinazoline Derivatives with Guinea Pig Liver Molybdenum Hydroxylases, Xanthine Oxidase and Aldehyde Oxidase

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Abstract: Aldehyde oxidase and xanthine oxidase are molybdenum-containing enzymes distributed throughout animal kingdom. Aldehyde oxidase has a wide range of substrates including aldehydes and *N*-heterocycles while xanthine oxidase involves in oxidation of purine analogues to corresponding uric acid. In addition to cytochrome P450 isoenzymes, molybdenum hydroxylases are major defense mechanism for the removal of drugs/xenobiotics from the body. Fifty quinazoline derivatives have been synthesized and characterized by NMR infrared, mass spectrum and elementary analyses. These substituted quinazolines have been examined for their interaction with mol ybdenum hydroxylases and found to be weak inhibitor. They inhibit both enzymes in a competitive pattern with inhibitor constants (K_i) values ranging from 90-1200 μM. The relationship between K_i and relative lipophilicity of quinazolines, as inhibitors of molybdenum hydroxylase enzymes, has been compared. The specific-site of interaction and inhibitory potency of quinazolines on molybdenum hydroxylase have been discussed in this study.

Key words: Quinazolines derivatives, aldehyde oxidase, xanthine oxidase, molybdenum hydroxylases

INTRODUCTION

Molybdenum hydroxylases are group of enzymes that share the same transition metal molybdenum (Mo^{VI})[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]. Calzi *et al.*[4] suggested that aldehyde oxidase is an important enzyme in detoxification of foreign xenobiotics. This hypothesis has been supported by studies on the distribution of this enzyme in liver and lung[4]. However, molybdenum hydroxylases have been implicated as key oxidative enzymes in some diseases[5,6]. Aldehyde oxidase catalyses nucleophilic attack at an electron-deficient carbon atom adjacent to a ring nitrogen atom in N-heterocyclic compounds which are oxidised to cyclic lactams[7]. In addition, aldehydes are converted to carboxylic acids in the presence of aldehyde oxidase[7].

Aldehyde oxidase inhibitors include chemicals that are structurally similar to its substrates, which thought to act at the molybdenum centre. Consequently, chlorpromazine[8], amsacrine[9], hydralazine[10] and isovanillin[11] are potent aldehyde oxidase inhibitors that resemble *N*-methylphenothiazine, *N*-[(2'-dimethylamino)-ethyl]acridine-4-carboxamide (DACA), phthalazine and vanillin, respectively[8-11]. Noteworthy, that allopurinol, a potent xanthine oxidase inhibitor is in very close resemblance to xanthine, an excellent xanthine oxidase substrate.

Interestingly, quinazolines have some similarity with a number of aldehyde oxidase substrates including nitrogen-containing heterocycles such as methotrexate, famciclovir, acyclovir, 2-pyrimidinone and phthalazine (K_m = 40-200 μM)[8-12].

Due to the structural similarity between quinazolines and the above substrates the former compounds were tested for their ability to inhibit oxidation of specific aldehyde oxidase and xanthine oxidase substrates. In this study, we compared the potency of 50 quinazoline derivatives, as inhibitors, for molybdenum hydroxylases, aldehyde oxidase and xanthine oxidase of initial rates of substrate oxidation.

MATERIALS AND METHODS

Instrumentation: Enzyme activity was determined spectrophotometrically using a Cary 50 UV/VIS

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spectrophotometer (Varian Australia Ptv. Ltd., Mulgrave/Victoria, Australia), which was linked to a cell temperature control unit. With the exception of enzyme, which was kept in ice until mixing with other components, all solutions were pre-warmed to 37°C. The spectrophotometer was computer-controlled by Carry WinUV® spectroscopy software package with additional kinetics software (2002).

Reagents and chemicals: All reagents and solvents are of analytical grade. All chemicals and reagents, were purchased from Sigma-Aldrich Chemical Company Ltd (Louis, MO 633178, USA). Substituted quinazoline has been prepared in our laboratory[13], all of which have been characterized by NMR infrared, mass spectroscopy and elementary analyses (the methods of synthesis and physicochemical properties will be published). Quinazolines were dissolved in dimethyl sulfoxide (DMSO).

Sorenson's phosphate buffer (67 mM), pH 7.0: Sorenson's phosphate buffer (67 mM) was made from two separate solutions containing either 9.511 g L^{-1} Na_2HPO_4 or 9.118 g L^{-1} KH_2PO_4 in distilled water. The buffer was made by adding 611 mL of Na_2HPO_4 solution to 389 mL of KH_2PO_4 solution and the pH was adjusted to pH 7.0 with 0.3 M phosphoric acid, using a pH-meter. EDTA (0.0372 g) was added to one liter of above mixture to give a final concentration of 100 μM EDTA. The buffer was stable for at least one month at 4°C.

Animals care: Male/Female Dunkin-Hartley guinea pigs (500-600 g) were inbred and housed in pairs in plastic cages under a cycle of 07:00-21:00 h light and 21:00-07:00 h dark daily. They were given free access to a diet of FD1 guinea pig pellets and hay, twice weekly and water *ad libitum*. They were maintained at a temperature of 18-19°C and humidity at 50%. The animals were killed by cervical dislocation between 09:00 am and 10:00 am daily.

Preparation of partially purified molybdenum hydroxylases from guinea pig liver: Aldehyde oxidase and xanthine were partially purified from liver homogenate of mature male/female Dunkin-Hartley guinea pigs following a published methodology[14]. Partially purified enzyme was stored in liquid N_2 and throw up at room temperature when needed.

Determination of initial oxidation rates: Aldehyde oxidase activity in partially purified molybdenum hydroxylase fractions was monitored, at 37°C, using 100 μM phthalazine (enzyme fraction was diluted, 1:10) and 100 μM indole-3-aldehyde (1:40 dilution) as substrates in 67 mM Sorenson's phosphate buffer, pH 7.0, containing 100 μM EDTA. Enzyme activity of guinea pig liver molybdenum hydroxylase fractions was also measured in the presence of two appropriate quinazoline-derivatives as inhibitors. The initial velocity for substrate oxidation (5-different concentrations, phthalazine (10-500 μM) and indole-3-aldehyde (2.5-50 μM)) was determined by measuring the change in absorbance/minute and calculating enzyme activities in μmol/min/mg protein in the presence and absence of inhibitor. Potassium ferricyanide (1 mM) has been used as an electron acceptor following the change in spectrum at 420 nm. The molar absorptivity of potassium ferricyanide is 1,040 $M^{-1}cm^{-1}$, but it should be noted that for each molecule of substrate oxidised two molecules of potassium ferricyanide are reduced and therefore, double the molar absorptivity must be used when calculating enzyme activity (2×1040 $M^{-1}cm^{-1}$). The following equation was used to calculate the enzyme activity[15]:

$$\text{Initial rate of substrate oxidation } (\mu\text{mol/min/mg protein}) = \frac{[\text{Absorbance change / minute}] \times 1000}{[\text{Molar absorptivity}] \times [\text{Protein concentration in cuvette (mg/mL)}]}$$

Initial rates of xanthine oxidase has been measured using xanthine (2.5-50 μM) and oxygen as substrate and electron acceptor, respectively, following the increase in absorbance at 295 nm due to the formation of uric acid. A molar absorptivity of 11,000 $M^{-1}cm^{-1}$ was used to determine enzyme activity.

Calculation of inhibitor kinetic constants: Lineweaver-Burk double reciprocal plot of 1/V versus 1/[S] was used to determine the inhibitor constants and the type of inhibition. While, the results indicate that the inhibitor is a competitive inhibitor of aldehyde oxidase and xanthine oxidase the following equation was used in calculating the inhibition constant (K_i):

$$K_i = \frac{[I]}{\frac{K_{mi}}{K_m} - 1}$$

where, [I] is the inhibitor concentration, K_m and K_{mi} are the Michaelis-Menten constants in the absence and presence of inhibitor, respectively. The relative lipophilicity of quinazoline derivatives was calculated using ChemDraw® Software Package.

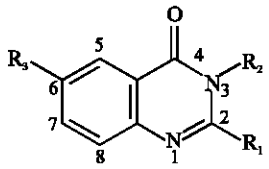
RESULTS AND DISCUSSION

Quinazolines are versatile nitrogen heterocyclic compounds displaying a broad spectrum of biological and pharmacological activities[16]. The quinazoline analogues of methotrexate have been demonstrated to be potent inhibitors, *in vitro*, for several enzymes including dihydrofolate reductase[17], farnesyl protein transferase[18], cyclin-dependent kinases[19] and molybdenum hydroxylases[20,21]. Thus, we implement several modification into the quinazoline nucleus to pursue a study of the structural requirements of quinazolines to be inhibitors for molybdenum hydroxylase enzymes. Table 1 shows the quinazoline derivatives covered in this study.

The quinazolines perused in this study were to be, in general, weak inhibitors of guinea pig liver molybdenum hydroxylases. Quinazolines 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 xanthine by xanthine oxidase. In general, aldehyde oxidase was more sensitive to this quinazoline series than xanthine oxidase.

Aldehyde oxidase and xanthine oxidase are metalloflavoproteins. These enzymes are homodimers of around 300 kDa, depending on species. Each subunit contains an active site, but it is thought that the monomers are not independently active[7]. Molybdenum

Table 1: Quinazoline derivatives screened in this study



Compound No.	R_1	R_2	R_3
Q1	-SH	$-C_2H_5$	$-NO_2$
Q2	-SH	$-C_6H_5$	$-NO_2$
Q3	-SH	$-CH_2-C_6H_5$	$-NO_2$
Q4	$-SCH_3$	$-C_2H_5$	$-NO_2$
Q5	$-SCH_3$	$-C_6H_5$	$-NO_2$
Q6	$-SCH_3$	$-CH_2-C_6H_5$	$-NO_2$
Q7	$-SCH_3$	$-C_6H_5$	$-NH_2$
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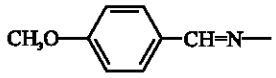
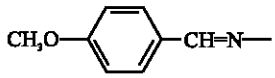
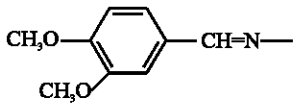
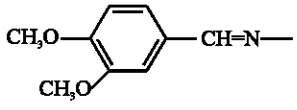
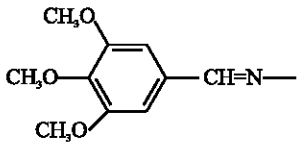
Q9	$-SCH_3$	$-C_6H_5$	
Q10	$-SCH_3$	$-CH_2-C_6H_5$	
Q11	$-SCH_3$	$-C_6H_5$	
Q12	$-SCH_3$	$-CH_2-C_6H_5$	
Q13	$-SCH_3$	$-C_6H_5$	

Table 1: Continued

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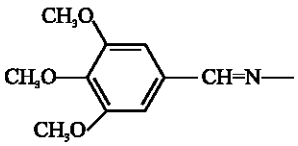
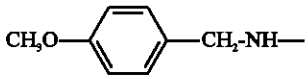
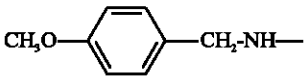
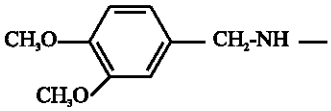
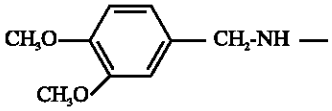
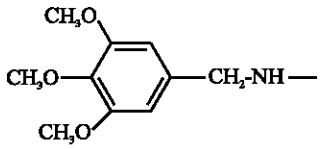
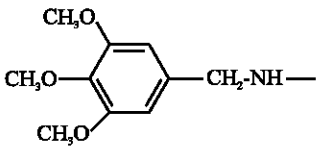
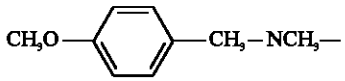
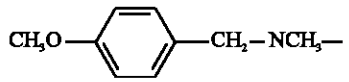
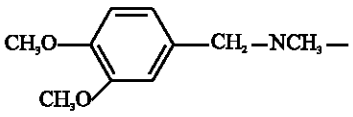
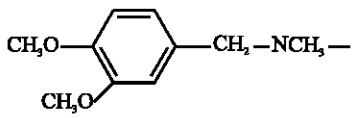
Q14	$-SCH_3$	$-CH_2-C_6H_5$	
Q15	$-SCH_3$	$-C_6H_5$	
Q16	$-SCH_3$	$-CH_2-C_6H_5$	
Q17	$-SCH_3$	$-C_6H_5$	
Q18	$-SCH_3$	$-CH_2-C_6H_5$	
Q19	$-SCH_3$	$-C_6H_5$	
Q20	$-SCH_3$	$-CH_2-C_6H_5$	
Q21	$-SCH_3$	$-C_6H_5$	
Q22	$-SCH_3$	$-CH_2-C_6H_5$	
Q23	$-SCH_3$	$-C_6H_5$	
Q24	$-SCH_3$	$-CH_2-C_6H_5$	

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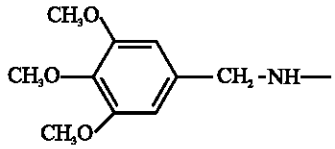
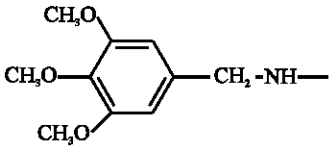
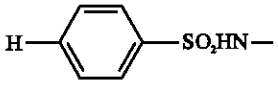
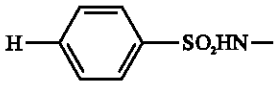
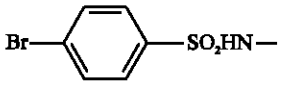
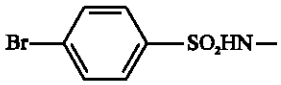
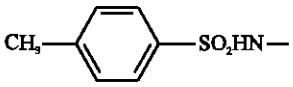
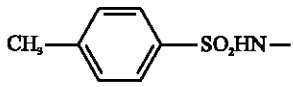
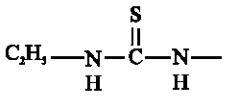
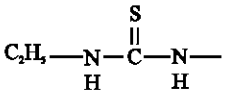
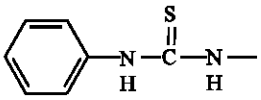
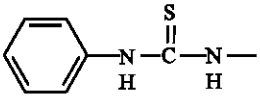
Q25	$-SCH_3$	$-C_6H_5$	
Q26	$-SCH_3$	$-CH_2-C_6H_5$	
Q27	$-SCH_3$	$-C_6H_5$	
Q28	$-SCH_3$	$-CH_2-C_6H_5$	
Q29	$-SCH_3$	$-C_6H_5$	
Q30	$-SCH_3$	$-CH_2-C_6H_5$	
Q31	$-SCH_3$	$-C_6H_5$	
Q32	$-SCH_3$	$-CH_2-C_6H_5$	
Q33	$-SCH_3$	$-C_6H_5$	
Q34	$-SCH_3$	$-CH_2-C_6H_5$	
Q35	$-SCH_3$	$-C_6H_5$	
Q36	$-SCH_3$	$-CH_2-C_6H_5$	

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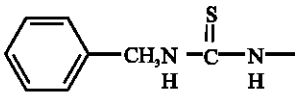
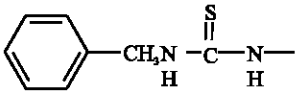
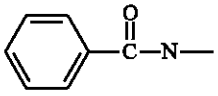
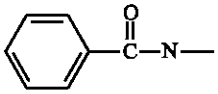
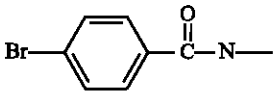
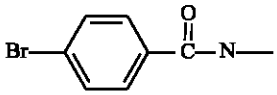
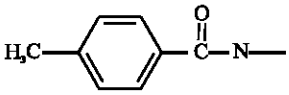
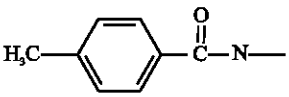
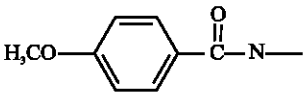
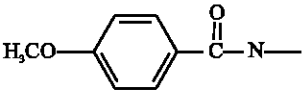
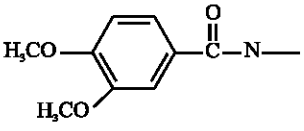
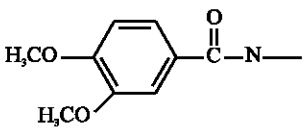
Q37	$-SCH_3$	$-C_6H_5$	
Q38	$-SCH_3$	$-CH_2-C_6H_5$	
Q39	$-SCH_3$	$-C_6H_5$	
Q40	$-SCH_3$	$-CH_2-C_6H_5$	
Q41	$-SCH_3$	$-C_6H_5$	
Q42	$-SCH_3$	$-CH_2-C_6H_5$	
Q43	$-SCH_3$	$-C_6H_5$	
Q44	$-SCH_3$	$-CH_2-C_6H_5$	
Q45	$-SCH_3$	$-C_6H_5$	
Q46	$-SCH_3$	$-CH_2-C_6H_5$	
Q47	$-SCH_3$	$-C_6H_5$	
Q48	$-SCH_3$	$-CH_2-C_6H_5$	

Table 1: Continued

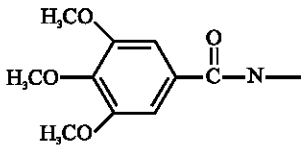
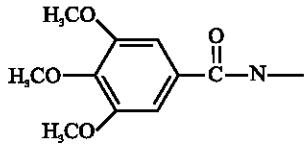
Compound No.	R_1	R_2	R_3
Q49	$-SCH_3$	$-C_6H_5$	
Q50	$-SCH_3$	$-CH_2-C_6H_5$	

Table 2: Inhibitor constants for xanthine oxidase (XO) and aldehyde oxidase (AO) and relative lipophilicities with quinazoline series

Compound No.	K_i (μM) XO/AO	Log K_o	Compound No.	K_i (μM) XO/AO	Log K_o
Q1	625/105	2.25	Q26	885/590	5.73
Q2	540/103	2.68	Q27	92/610	6.02
Q3	445/184	2.26	Q28	87/585	6.21
Q4	490/142	2.59	Q29	89/520	4.79
Q5	335/113	3.02	Q30	121/640	4.55
Q6	470/109	3.61	Q31	117/880	5.80
Q7	700/148	3.22	Q32	109/730	5.65
Q8	850/136	3.29	Q33	925/770	3.36
Q9	1100/310	5.77	Q34	1035/755	3.35
Q10	905/310	5.84	Q35	910/700	4.67
Q11	700/295	5.64	Q36	865/645	5.26
Q12	625/370	5.71	Q37	620/530	5.55
Q13	810/435	5.51	Q38	715/590	5.93
Q14	555/400	5.58	Q39	510/505	5.49
Q15	950/740	5.13	Q40	500/610	5.56
Q16	1200/665	5.20	Q41	590/585	6.31
Q17	910/735	5.00	Q42	485/570	6.38
Q18	965/645	5.07	Q43	455/505	5.97
Q19	1000/700	4.88	Q44	480/460	6.04
Q20	1150/760	4.95	Q45	305/450	5.36
Q21	1085/640	5.92	Q46	460/445	5.43
Q22	990/635	5.99	Q47	415/550	5.23
Q24	980/580	5.79	Q48	380/510	5.30
Q24	1035/615	5.86	Q49	400/430	5.11
Q25	990/600	5.66	Q50	395/425	5.18

* Mean of at least three determinations for K_i ($n = 3$-4, $r^2 > 0.995$)

hydroxylases have in common a folding pattern that gives, from the N-terminus, two discrete iron-sulphur centers, [2Fe-2S] domains, followed by a flavin domain and finally the molybdenum-binding portion of the protein[1,4]. From the type of inhibition and the similarity between molybdenum hydroxylases-substrates and quinazoline, the site of interaction is thought to be molybdenum center.

Inhibitor constants (K_i) values, which ranged from 90-1200 μM are presented in Table 2. From this Table 2, it is perceivable that xanthine oxidase sensitive to inhibition by quinazoline-derivatives containing sulfamide moiety whereas aldehyde oxidase more liable to unsubstituted amino-or nitro-groups. Beedham *et al.*[22] have studied 15 quinazoline derivatives as a substrate for hepatic aldehyde oxidase from different sources including human and guinea pigs. They concluded that quinazolines oxidised at either 2- or 4-positions, which are occupied in our compounds, (K_m =15-400 μM, V_{max} = 0.004-0.151 μmol/min/mg)[22]. Furthermore, Beedham and her colleagues have investigated the effect of quinazolines as inhibitors for aldehyde oxidase and showed that quinazolines containing an oxo-group adjacent to a ring nitrogen are weak competitive inhibitors of all species studied[22]. This study coves more possible metabolites of quinazolines, which differ in chemical structure from those reported by Beedham group. From the K_i values, it is unlikely that these concentrations of quinazolines could be reached *in vivo* and hence inhibits molybdenum hydroxylase enzymes. As a result, we may conclude that no interaction between quinazoline-metabolites and molybdenum hydroxylases substrates, such as methotrexate and famciclovir.

Heterocycles containing an amino[23] or nitro[10] substituent, adjacent to a ring nitrogen, are potent aldehyde oxidase inhibitors. Although oxo-quinazolines

are weak inhibitors it has been found that substitution of a phenyl- (Q27, 29 and 31) or benzyl- (Q28, Q30 and Q32) group into 3-position of quinazolines in the presence of sulfamide at 6-position increase the inhibitory properties of quinazolines for xanthine oxidase. In different to xanthine oxidase, aldehyde oxidase was more sensitive to inhibition by unsubstituted nitro and amino-quinazolines (Q1-Q8)[24]. This discrepancy between these enzymes is not unusual phenomenon. With this respect, allopurinol is traditionally used as a specific xanthine oxidase inhibitor both *in vivo* and *in vitro*, whereas menadione is often employed *in vitro* as a specific aldehyde oxidase inhibitor[25,26]. Furthermore, allopurinol has been found to be a moderate substrate for aldehyde oxidase while menadione is an electron acceptor for xanthine oxidase[25,26]. In contrast to previous study[22], the less lipophilic quinazoline is the most potent inhibitor of aldehyde oxidase activity. The values of log K_o presented in this study and the previous one are in very close agreement if compared independently to other compounds. Aldehyde oxidase substrates have almost similar log K_o values to that found with compounds (Q1-Q8)[22,27]. However, there was no clear relationship between lipophilicty of substituted quinazoline and affinity to xanthine oxidase (Table 2).

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[22,28].

Studies indicate that quinazoline undergoes an extensive metabolism by various enzyme such as molybdenum hydroxylases[17-21]. In fact, aldehyde oxidase is widely distributed throughout human body with significant activity towards N-heterocycles such as quinine and quinidine (K_m<1 μM). In an attempt to prevent some *in vitro* metabolism of quinazolines, herein, we report the inhibitory profile of a series of quinazolines that resistant to the oxidation by molybdenum hydroxylases and with minimal drug-drug interaction (K_i>90 μM). Further studies on the anti-tumour efficacy of these derivatives are in progress in our laboratories with promising results.

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