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Schiff bases attached L-glutamine and L-asparagine: First investigation on antimutagenic and antimicrobial analyses

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Abstract

This study was conducted to evaluate the antimutagenic and antimicrobial activities of Schiff bases attached L-glutamine and L-asparagine. Antibacterial activities of the compounds against *S. aureus*, *Sh. dys. typ 7*, *L. monocytogenes 4b*, *E. coli*, *S. typhi H*, *S. epidermis*, *Br. abortus*, *M. luteus*, *B. cereus*, *P. putida*, and antifungal activity against *Candida albicans* were studied. These compounds were investigated for antimutagenic properties against Aflatoxin Bı (AFBı) using micronuclei (MN) assay in human lymphocyte cell culture *in vitro*. The protective role of these compounds against AFBı-induced MN is probably related to its doses.

Keywords: antimicrobial properties, Aflatoxin Bı, L-Asparagine, L-Glutamine, Mn(III) complexes, Mutagenicity

Introduction

The chemistry of molecule-attached amino acid has been receiving significant current attention, because of their contribution to developments in medicinal chemistry (Sarı et al. 2013, Kuhl et al. 2005). Amino acids have promise as ideal targets for tumor imaging. They are required for sustenance of continuous uncontrolled growth of tumor cells. Numerous studies have demonstrated that malignant tumors can be detected with high sensitivity and specificity by imaging their increased metabolic rates of amino acids. Therefore, many natural and artificial amino acids have been radiolabeled for positron emission tomography (PET) imaging of tumor (McConathy et al. 2002).

Schiff bases attached amino acid is remarkable due to the imine group. Schiff bases are involved in many different biological processes: decarboxylation, transamination, electron transfer, etc. Abram and Alberto investigated on amino acid–Schiff as novel inhibitors (2006). They proposed that they may be used as lung scintigraphic agent of amino acid–Schiff bases. Complexes of attached amino acid Schiff base are used as non-enzymatic models for the metal-pyridoxal (vitamin B_6) amino acid Schiff base systems, which are the key intermediates in many metabolic reactions of amino acids catalyzed by enzymes which require pyridoxal as a cofactor. So, the chemistry of transition metal complexes of amino acid-Schiff bases has received special attention due to their importance in variety of pharmaceutical and biological process. Liping Lu et al. studied the inhibitory activity against human tyrosine phosphatase 1B in vitro of oxovanadium (IV) complexes with amino acid–Schiff base (Lu et al. 2011). Zasukhina et al. have studied the antimutagenetic activity of compounds including nitrogen (2003). Many researches demonstrated that the genotoxicity of some metal salts (e.g., Cd(II), Ni(II), and Pt(II)) might depend on the phase of the cell cycle in human lymphocytes (Hartman and Hartwig 1998, Snow 1992, Coluccia et al. 1984).

Recently, several studies have demonstrated that certain amino acids (such as cysteine, glycine, tryptophan, lysine, arginine, glutamine and alanine) provide antimutagenic effect by different test systems (Roy et al. 2002, Tavares et al. 1998, Handique and Aprem 1997). However, so far, no report has shown a protective effect of these compounds against AFBı genotoxicty. AFBı is the most potent of the naturally occurring mycotoxins. We know that AFBı causes various health effects on chickens in a dose–response pattern (Zhou et al. 2006, Pokharel et al. 2006). Therefore, it represents a serious risk to health in human populations (International Agency for Research on Cancer 1993). One of the major challenges in medical and drug delivery is to develop new antimutagens due to good prospects of their practical use for the prevention of delayed negative effects of induced mutagens in human, the main of which are high prevalence to hereditary diseases and cancer (Zasukhina et al. 2003). Therefore, this study was carried out to evaluate the antimicrobial and antimutagenic effects of Schiff bases attached L-glutamine and L-asparagine and their Mn (III) complexes on human peripheral blood in vitro, using micronucleus

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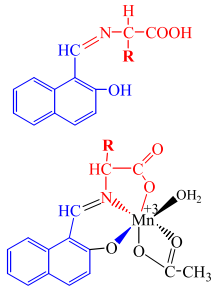

R	Abbreviation Schiff bases	Mn(III) Complexes
H_2NCOCH_2-	(Asn-Sch)	[Mn(Asn-Sch)]•1.5 H_2O
$H_2NCOCH_2CH_2CH$-	(Gln-Sch)	[Mn(Gln-Sch)]• H_2O

Figure 1. Structures and abbreviations of studied molecules.

assay. First of all, amino acid–Schiff bases were synthesized using the condensation methods. Then, theirs Mn (III) complexes were synthesized by means of template method (Figure 1).

Materials and methods

Chemicals and physical measurements

All chemicals investigated in the study were of reagent grade, and were purified when it was necessary. All organic solvents used in this study were purified according to the standard methods. The amino acids (L-Glutamine and L-Asparagine), 2-hydroxy-1-naphthaldehyde, methanol, and n-heptane were purchased from Sigma-Aldrich. Manganese (III) acetate was prepared using the method of Gunduz *et al.* (Gunduz et al. 1994). Elemental analyses were performed with a LECO-CHNS-9320 instrument. Metal contents were determined using a Philips PU 9285 atomic absorption instrument. ^{1}H NMR spectra were recorded with a Bruker DPX-300 MHz and 100 MHz using TMS as an internal standard and $CDCl_3$ as a solvent. Electronic spectra were recorded on a UV-1800 ENG240V spectrophotometer in ethanol. IR spectra were recorded on a Mattson-5000 FTIR instrument in KBr pellets. Melting points were determined with a Barnstead-Electrothermal-9200 melting point apparatus. Magnetic measurements were performed with a Sherwood Scientific magnetic susceptibility balance (Model No: MK 1) at 21°C with $Hg[Co(NCS)_4]$ as a calibration.

Test microorganisms and medium

The bacterial subcultures chosen were as follows: *Listeria monocytogenes 4b* ATCC19115, *Staphylococcus aureus* ATCC25923, *Escherichia coli* ATCC1280, *Salmonella typhi H* NCTC901.8394, *Brucella abortus* RSKK03026, *Staphylococcus epidermis sp., Micrococcus luteus*ATCC9341, *Shigella dysenteria* type 7 NCTC 9363, *Pseudomonas putida sp., Bacillus cereus* RSKK863. An antifungal susceptibility test was carried out using *Candida albicans* Y-1200-NIH, Tokyo.

Synthesis

Schiff bases: A solution of 2-hydroxy-1-naphthaldehyde (5 mmol, 0.61 g) in methanol (50 ml) was added to amino acid (L-glutamine and L-asparagine, 5 mmol) MeOH solution (50 ml), and the synthesis method was performed according to an our previous article (Sakıyan et al. 2004).

Mn(III) complexes (template method): Mn(III) complexes were prepared using the template method (Sakiyan 2007). First, $Mn(CH_3COO)_3.2H_2O$ was synthesized according to our previous article (Gunduz et al. 1994). Then, the amino acid (L-glutamine and L-aspartic acid), 2-hydroxy-1-naphthaldehyde, and $Mn(CH_3COO)_3$ were dissolved in methanol and was synthesized according to the procedure (Sakiyan 2007).

Detection of antimicrobial activity

The ligands and complexes were tested for their antimicrobial activity using well-diffusion method. Each ligand and complex was kept dry at room temperature and dissolved (10^{-3} M) in DMF. DMF was used as a solvent and also as a control. It was found to have no antimicrobial activity against any of the tested organisms. A volume of 1% (v/v) of 24-h broth culture containing 10^6 CFU/ml was placed in sterile Petri dishes. Mueller-Hinton agar (MHA) (15 ml) kept at 45°C was then poured into the Petri dishes and allowed to solidify. Then, 6-mm-diameter wells were punched carefully using a sterile cork borer and were entirely filled with the test solutions. The plates were incubated for 24 h at 37°C. On completion of the incubation period, the mean value obtained for the two holes was used to calculate the zone of growth inhibition of each sample. Bacterial subcultures and yeast were tested for resistance to five antibiotics (produced by Oxoid Lt., Basingstoke, UK): ampicillin (preventing the growth of gram-negative bacteria), nystatin (binding to sterols in the fungal cellular membrane, altering the permeability and allowing leakage of the cellular contents), kanamycin (used in molecular biology as an agent to isolate bacteria), sulfamethoxazol (bacteriostatic antibacterial agent that interferes with folic acid synthesis in susceptible bacteria), amoxycillin (b-lactam antibiotic used to treat bacterial infections caused by susceptible microorganisms).

Cytogenetic analysis

Peripheral blood lymphocytes were taken from four (two men and two women) non-smoking healthy individuals. Lymphocyte cultures were set up by adding 0.5 mL of heparinized whole blood to RPMI-1640 chromosome medium supplemented with 15% heat-inactivated fetal calf serum, 100 IU/mL streptomycine, 100 IU/mL penicillin, and 1% L-glutamine. Lymphocytes were stimulated to divide by 1% phytohaemaglutinin.

The experiments were performed in 18 groups as follows:

Group 1:Control;
Group 2: 5 µM AFB1;

Group 3: (Asn-Sch) 40 µM;
Group 4: 5 µM AFB1 + (Asn-Sch) (5 µg/ml);
Group 5: 5 µM AFB1 + (Asn-Sch) (10 µg/ml);
Group 6: 5 µM AFB1 + (Asn-Sch) (20 µg/ml);
Group 7: [Mn(Asn-Sch)(OAc 40 µM;
Group 8: 5 µM AFB1 + [Mn(Asn-Sch)(OAc)(H_2O)] (5 µg/ml)
Group 9: 5 µM AFB1 + [Mn(Asn-Sch)(OAc)(H_2O)] (10 µg/ml);
Group 10: 5 µM AFB1 + [Mn(Asn-Sch)(OAc)(H_2O)] (20 µg/ml)
Group 11: Gln-Sch 40 µM;
Group 12: 5 µM AFB1 + Gln-Sch (5 µg/ml);
Group 13: 5 µM AFB1 + Gln-Sch (10 µg/ml);
Group 14: 5 µM AFB1 + Gln-Sch (20 µg/ml);
Group 15: [Mn(Gln-Sch)OAc] 40 µM;
Group 16: 5 µM AFB1 + [Mn(Gln-Sch)OAc)(H_2O)] (5 µg/ml);
Group 17: 5 µM AFB1 + [Mn(Gln-Sch)OAc)(H_2O)] (10 µg/ml);
Group 18: 5 µM AFB1 + [Mn(Gln-Sch)OAc)(H_2O)] (20 µg/ml)

On micronuclei (MN) analysis, Cytochalasin B was added 44 h after phytohemagglutinin (PHA) stimulation to a final concentration of 3 g/ml. Twenty-eight hours later (after 72-h cultivation), the cells were harvested by centrifugation (1000 g × 10 min). The supernatant was removed, the cells were mixed thoroughly, and 5 ml of cold hypotonic solution (0.05 M KCl) was added. The cells were subsequently incubated at 37°C for 20 min and centrifuged again (1000 g × 10 min). The pellet was mixed thoroughly, and 5-ml fresh fixative (1:3, aceticacid/methanol) was added dropwise. This fix ation procedure was repeated three times, and the tube was centrifuged again. The cell pellet was then resuspended in 1 ml of fresh fixative, dropped onto a clean microscopic slide, incubated at 37°C or at room temperature overnight, and stained with Giemsadye. Coded slides were scored blind by two independent individuals. Only binucleated cells were scored for MN analysis. For each subject, at least 2000 binucleated cells were analyzed for the presence of MN. For the MN scoring, the micronucleus criteria described by Countryman and Heddle were used: a diameter less than 1/3 of the main nucleus, non-refractility, not touching, and with the same color as the nucleus or lighter (for MN analysis, SPSS 15.0 program was used).

Results and discussion

Analytical data and some of the physical properties of the Schiff bases and their complexes are summarized in Table I. The complexes are only soluble in DMF and DMSO, but insoluble in organic solvents like C_2H_5OH, CCl_4 and benzene.

IR, UV–visible, and NMR spectra of Schiff bases and their Mn(III) complexes

Table I summarizes the main IR and UV–visible bands of the azomethine (Schiff bases) and their Mn(III) complexes. In the IR spectra of the Schiff bases, the most characteristic bands appear at 1656–1644 cm^{-1} as an overlap which is attributable to ν(C = O) and ν(C = N) stretching of the keto and imine forms (Sakiyan 2007). These bands are shifted to 1627–1617 cm^{-1} in the complexes, which means that the imino nitrogen and phenolic oxygen of the ligands are coordinated to the Mn(III) ion (Sakiyan 2007). The IR spectra of the complexes show medium-to-intense broad bands at 586–575 cm^{-1} assigned to ν(M–N) stretching, and bands at 510–459 assigned to ν(M-O) vibration (Sakıyan et al. 2004, Sarı et al. 2006). The ^{1}H NMR spectrum of amino acid–Schiff bases, recorded in DMSO-d_6, showed the following signals: phenolic -OH proton at 14.33–13.96 ppm (1H), -COOH protons at 10.74–10.92 ppm (1H), aromatic-H proton at 6.59–8.05 ppm (2H) phenyl as a multiplet and -CH = N- at 9.10–8.93 ppm (1H). The three signals are at 4.50 ppm and 2.00–2.90 ppm -CH and -CH_2 protons. In the spectra of Schiff bases, two medium-intensity bands exhibit at ~ 300 nm and ~ 400–420 nm. It follows from the literature that these bands can be assigned to the phenol-imine and keto-amine forms (Sakiyan 2007). They may be attributed to n→ π*, and π→π* type transitions, respectively. Although in the spectra of all

Table I. Analytical data, important IR vibration frequencies (cm^{-1}), UV-Visible spectra values (nm) of all synthesized molecules, and ^{1}H-NMR spectral data of Schiff bases attached L-Glutamine, L-Asparagine.

Abbreviation of compounds	Elementel Analysis found (calcd.) %			Important FTIR vibration (cm^{-1}) and V-GB spectra (nm; cm^2mol^{-1})			
(F. Weight; Mp°C)	C	H	N	υ(N-H) υ(OH)	υ(C = O) υ(C = N)	υ(M-N) υ(M-O)	λmax; ε x10^2
(Asn-Sch)	60.8	4.5	9.9	3379	1685,	–	308 (5.9)
295.30; 185	(61.0)	(5.1)	(9.5)	3192	1631	–	400 (4.8)
							418 (4.8)
[Mn(Asn-Sch)(OAc)	47.5	3.3	6.1	–	1708,1774	586	308 (10.5)
X]•1.5n	(48.0)	(4.3)	(6.6)	3396	1616	510	368 (4.4)
425.29; 210–240							490 (0.7)
(Gln-Sch)	65.6	4.4	8.1	–	–	–	304 (7.6)
330.32; 178	(63.4)	(5.4)	(9.3)	3458,3327	1714,1656	–	402 (7.8)
				3196	1616		420 (7.9)
[Mn(Gln-Sch)(OAc)	51.1	3.9	5.4	–	–	586	318 (2.4)
X]•n	(50.2)	(4.5)	(6.5)	3419	1731	459	402 (1.1)
430.30; 200							510 (0.2)

^{1}H-NMR Spectra for Schiff bases

–OH	–COOH	–CH = N		ArC-H	C-H	CH_2
(Asn-Sch)	14.09	10.75	9.10	6.71–8.01	4.65	2.98–2.87
(Gln- Sch)	13.96	10.74	8.99	6.62–8.01	4.61	2.38–2.69

X, n: –H_2O.

Table II. Antimicrobial activity of studied compounds (0.25 µg/ml) and standard reagents (diameter of zone inhibition (mm)).

Microorganisms		(Asn-Sch) [Mn(Asn-Sch)(OAc)(H_2O)]	(Gln-Sch) [Mn(Gln-Sch) (OAc)(H_2O)]	Control
	Sh.dys. typ 7	17/15	15/12	–
Gram (+)	*P.putida*	11/22	21/11	–
	S.typhi H	11/14	11/12	–
	Br. abortus	15	15/14	–
	L.monocytogenes 4b	−/11	−/11	–
	B.cereus	15/14	20/20	–
Gram (−)	*S.aureus*	13/−	12/12	–
	S.epidermis	−/13	11/14	–
	M.luteus	15/17	25/21	–
	E.coli	14/13	12/13	–
Yeast	*C. albicans*	*12/20*	*25/16*	-

Pozitif control	*S.aureus*	*P.putida*	*E.coli*	*S.typhi H*	*Br. abortus*	*C.albicans*
K30	25	14	25	20	–	–
SXT25	24	18	18	17	–	–
AMP10	30	8	10	11	–	–
AMC30	30	15	14	19	–	–
NYS100	–	–	–	–	–	20

SXT25, Sulphamethoxazol 25µg; AMP10, Ampicillin 10µg; NYS100, Nystatin 100µg ; K30, Kanamycin 30µg; AMC30, Amoxycillin 30µg.

complexes the band at ~300 nm exists, the other bands at ~ 400 and 420 nm are shifted to shoulder bands. This means that in the complex Schiff bases the bands exist only in the phenol-imine form and coordinated Mn(III) ion with phenolic oxygen and imine nitrogen (Sakiyan 2007). For manganese (III) complexes a rather broad band appears at 475–510 nm in the visible region, and this may be attributed to the $^5Eg \rightarrow {}^5T_{2g}$ transition in the octahedral complexes (Sakiyan 2007).

Biological activity and antimutagenic activity of amino acid–Schiff bases and their Mn(III) complexes

Amino acid–Schiff bases and their Mn(III) complexes were screened for antimicrobial activity in DMF solvent as a control substance. The compounds were tested with the same concentrations in DMF solution (0.25 µg/ml). All the synthesized compounds and antibiotic exhibited varying degree of inhibitory effects on the growth of different tested strains (Table II, Figure 2.). Synthesized amino acid–Schiff bases were inactive against *L.monocytogenes*, whereas their complexes were active. In general, [Mn(Asn-Sch)(OAc)(H_2O)] complexes are more potent bactericides than the (Asn-Sch). This enhancement in activity may be explained on the basis of chelation theory (Sari et al. 2013, Sakiyan and Yilmaz 2003). Chelation reduces the polarity of the metal ion. Hence, a complex has lipophilic character, and increases the interaction between metal ion and the lipid. This lead to the breakdown of the permeability barrier of the cell wall, resulting in interference with the normal cellular processes (Sarı et al. 2006; Lemonnier et al. 2012). (Gln-Sch) was observed to be the most active against *M. luteus*. Furthermore, (Gln-Sch) was shown to be the most active against studied bacteria. This result may be due to differences in the structure. Electron-donating effect of glutamine group is higher than that of asparagine group. So, -NH_2 molecule of glutamine group has a stronger electron-donating effect than asparagine group. This amine (-NH_2) group has a strong interaction with protein or DNA chain of bacteria. In additon, the antibacterial activity of these compounds was also compared with five commercial antibiotics, namely Kanamycin, Sulfamethoxazol, Ampicillin, Amoxycillin and Nystatin. It was seen that the synthesized compounds were effective as the antibiotics mentioned.

Antimutagene activity

AFB1 caused significant MN formations on peripheral lymphocytes, as seen in Table III. This increase was found to be statistically significant ($P < 0.001$ and $P < 0.05$). On the other hand, these effects of AFB1 on MN were reduced after treatment with [Mn(Asn-Sch)(OAc)(H_2O)], (Asn-Sch),

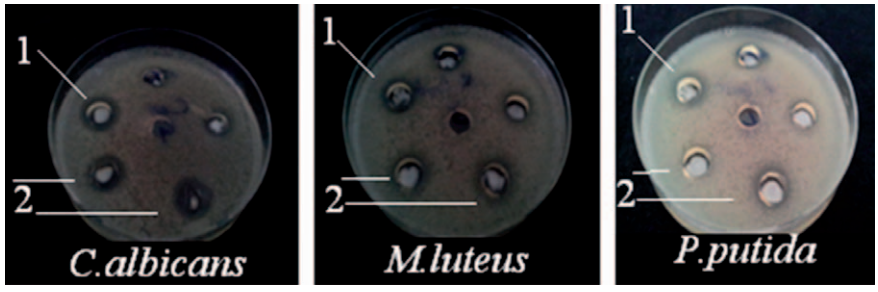

Figure 2. Imaging of antimicrobial affectivities of [Mn(Gln-Sch) (OAc)(H_2O)] and (Gln-Sch) against *C. albicans, M. luteus* and *P. putida* (2: [Mn (Gln-Sch) (OAc)(H_2O)], 1: (Gln-Sch)).

Table III. Comparison the effects on the number of MN different concentrations of (Asn-Sch), [Mn(Asn-Sch)(OAc], (Gln-Sch), [Mn(Gln-Sch)OAc] together with AFB_1 in human peripheral lymphocytes.

	Counted of MN	Sight of MN	MN/Cell		Counted of MN	Sight of MN	MN/Cell
Control	1029	35	3.40 ± 0.81^{a}	Control	1019	32	3.10 ± 076^{a}
AFB_1 5 μM	1015	58	5.7 ± 0.81^{f}	AFB_1 5 μM	1005	56	5.6 ± 076^{f}
Mn(Asn-Sch)(OAc) (40μM)	1036	44	4.2 ± 0.81^{c}	Asn-Sch (40μM)	1026	41	4.0 ± 076^{d}
AFB_1(5μM)+ Mn(Asn-Sch)(OAc)(5μM)	1035	39	4.6 ± 0.81^{b}	AFB_1(5μM)+ Asn-Sch (5μM)	1015	45	4.4 ± 076^{e}
AFB_1(5μM)+ Mn(Asn-Sch)(OAc)(10μM)	1011	40	4.3 ± 0.81^{d}	AFB_1(5μM)+ Asn-Sch (10μM)	1010	39	3.9 ± 076^{c}
AFB_1(5μM)+ Mn(Asn-Sch)(OAc)(20μM)	1021	47	3.8 ± 0.81^{e}	AFB_1(5μM)+ Asn-Sch (20μM)	1019	37	3.6 ± 076^{b}
Control	1019	34	3.3 ± 0.81^{ab}	Control	1010	38	3.8 ± 0.81^{a}
AFB_1 5 μM	1010	49	4.9 ± 0.81^{d}	AFB_1 5 μM	1019	55	5.4 ± 0.81^{e}
Mn(Gln-Sch)(OAc)(40μM)	1006	42	4.2 ± 0.81^{c}	Gln-Sch (40μM)	1002	49	4.9 ± 0.81^{d}
AFB_1(5μM)+ Mn(Gln-Sch)(OAc)(5μM)	1009	36	3.6 ± 0.81^{b}	AFB_1(5μM)+ Gln-Sch (5μM)	1020	44	4.3 ± 0.81^{c}
AFB_1(5μM)+ Mn(Gln-Sch)(OAc)(10μM)	1011	34	3.4 ± 0.81^{ab}	AFB_1(5μM)+ Gln-Sch (10μM)	1015	41	4.0 ± 0.81^{b}
AFB_1(5μM)+ Mn(Gln-Sch)(OAc)(20μM)	1018	32	3.1 ± 0.81^{a}	AFB_1(5μM)+ Gln-Sch (20μM)	1012	37	3.7 ± 0.81^{a}

$^{a}P < 0.05$ compared with control, $^{b}P < 0.05$ compared with Asn-Sch (40 μM) group, $^{c}P < 0.05$ compared with Asn-Sch (5 μM) group, $^{d}P < 0.05$ compared with Asn-Sch (10 μM) group, $^{e}P < 0.05$ compared with Asn-Sch (20 μM) group, $^{f}P < 0.05$ compared with AFB1 (5 μM) group.

(Gln-Sch), and [Mn(Gln-Sch)(OAc)(H_2O)] ($P < 0.001$ and < 0.05). Especially the treatment with glutamines groups was more effective than the treatment with asparagine groups. Mutagenic results of MN assay showed that any concentration of these compounds did not show mutagenic activity. Previous researches have reported antimutagenic activity of some free amino acids (Roy et al. 2002, Tavares et al. 1998, Handique and Aprem 1997). Consequently, in the present study, it has been revealed that these compounds are the active inhibitors of mutagenic activity of AFB1. Antimutagenic effects of these compounds are probably related to their action on the enzymatic activation system. This effect of studied compounds can be attributed primarily to their antioxidant action or cofactor for enzymes system, which is known to protect DNA and other cellular components from damage by oxygen radicals.

Conclusion

In summary, compounds attached to amino acid have been prepared for preliminary screening as antimicrobial and antimutagenic agents. They exhibited a very good antimicrobial activity against a wide range of microorganisms. Results from this study showed that antimutagenic activity and antimicrobial affectivity are compatible with each other.

Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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