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Metal-Free *trans*-Aziridination of Zerumbone: Synthesis and Biological Evaluation of Aziridine Derivatives of Zerumbone

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Herein, we describe a metal-free, iodosobenzenediacetate mediated *trans*-aziridination of zerumbone by the direct use of sulphonamides. The preliminary *in vitro*-screening showed better anti-proliferative and anti-diabetic activity compared to parent compound zerumbone.

Natural products, especially plant-derived compounds occupy a proficient position in the development of numerous useful drugs. Diversity oriented synthesis has been used in success for the generation of biologically relevant/drug-like molecules *via* simple chemical transformation of readily available natural products. [1] For the past few decades, there has been surge in the development of new plant-derived medicines[2] and in this line, *Zingiber zerumbet* Smith (L.), has attained much attention from the scientific community because of its interesting biological properties.[3] As a continuation of our ongoing work on the synthesis of bio-actives from affordable and easily available natural sources, we were interested in the structural modification of zerumbone, the marker compound present in *Zingiber zerumbet*.[4]

Aziridines are one of the important synthetic targets due to its biological profile (Figure 1) as well as its ring strain, which makes it an active and versatile intermediate for further functionalization.[5] Though zerumbone-epoxide is naturally occurring, there are no report on its nitrogen counterpart. Hence, taking new challenges in the functionalization of zerumbone may result in the formation of valuable bio-active agents. In 2006, Minakata *et al*. reported the first metal-free aziridination reaction of olefins with sulphonamides as the nitrogen source using *tert*-butyl hypoiodite.[6] While numerous methods are known, the metal-free hypervalent iodine mediated aziridination reactions have achieved much attention during last decade due to its practically favourable reaction conditions. The hypervalent iodine-iminoiodinane mediated amination, aziridination and halocyclisation reactions of olefins attained considerable attention during the last few years.[7] In the present work, we describe our efforts in the *trans*-aziridination of zerumbone by employing iodosobenzenediacetate (PIDA) under metal-free conditions. Also, the preliminary anti-proliferative as well as anti-diabetic screenings of the synthesized derivatives were carried out.

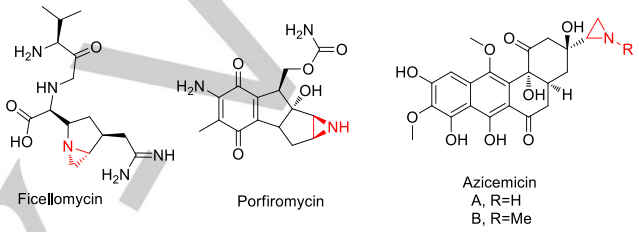
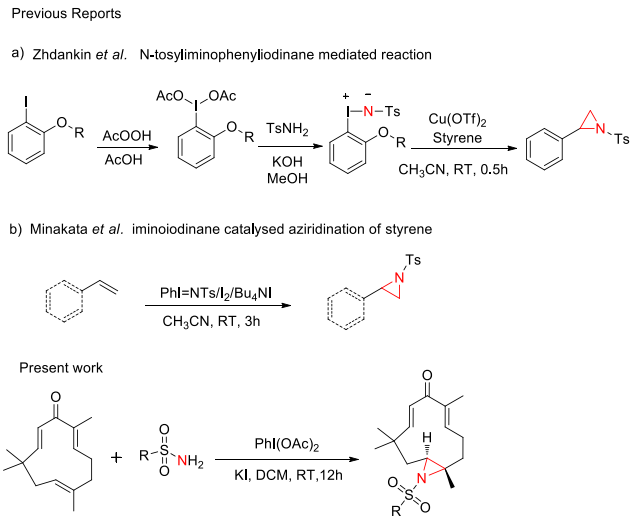


Figure 1. Biologically relevant aziridine bearing molecules

We set off our investigation with zerumbone (**1**) and benzenesulphonamide (**2a**) in the presence of iodosobenzenediacetate as the oxidising agent and KI as the promoter in dichloromethane at room temperature for 12 hours. To our delight, we obtained the desired product in 42 % yield. The structure of the product was well characterized using various spectroscopic analyses and unambiguously confirmed by single crystal X-ray analysis of compound **3l**.



Scheme 1. Metal-free aziridation of alkenes using sulphonamide.

The reaction conditions were optimised with various additives, solvents and temperature. From the optimization studies, a

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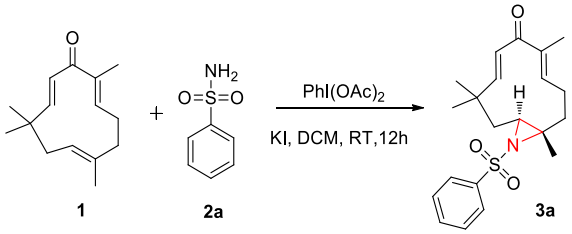
combination of zerumbone 1 equiv., sulphonamide 2 equiv., PIDA 1.5 equiv., potassium iodide 2 equiv., in 2 mL of dichloromethane at room temperature for 12 h was found to be the best condition, with 62 % yield (Table 1). Also, to improve the yield of the reactions, we synthesized an ylide between iodosobenzenediacetate and benenesulphonamide which on reaction with zerumbone yielded the corresponding product in 60 % yield. Aziridination through ylide formation from PIDA, followed by reaction with zerumbone was unsuccessful with sulphonamides except **2a** and **2j. T**he reaction worked well with zerumbone and sulphonamides in presence of PIDA as the oxidizing agent.

Table 1. Optimisation studies for aziridine synthesis



1 2a 3a

Entry[a]	Additives	Solvent	Temperature(°C)	Yield(%)[c]
1	KI	DMF	RT	NR
2	KI	DMF	100	NR
3	KI	DCM	RT	42
4	KI + I_2	DCM	40	33
5[b]	**KI**	**DCM**	**RT**	**62**
6	$Bu_4N^+Cl^-$	DCM	RT	15
7	NaI	DCM	RT	11
8	NaI	DCM	RT	NR
9	NaI	DCE	RT	20
10	KI	DCE	RT	14
11	KI	CH_3CN	RT	8
12	KI	TFE	RT	NR

[a] Reaction conditions: zerumbone (1 equiv.), sulphonamide (1 equiv.), PIDA (1.5 equiv.), KI (1 equiv.), [b]zerumbone (1 equiv.), sulphonamide (2 equiv.), PIDA (1.5 equiv.), KI (2 equiv.), [c]isolated yield.

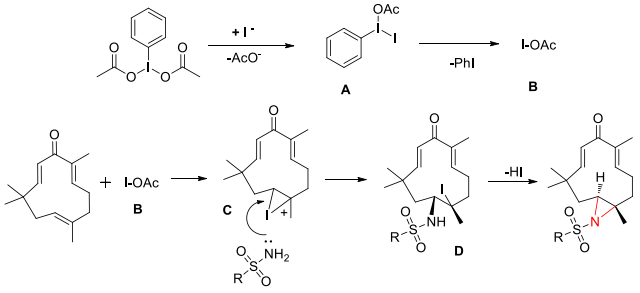
With the optimal conditions in hand, we further investigated the scope of the reaction with functionally different sulphonamides (Table 2). Sulphonamides bearing various functional groups at *para* position were found to be the suitable substrate for this transformation. Moreover, steric hindrance plays an important role in the yield of the reaction. In comparison with *ortho* substituted sulphonamides, *para* functionalized substrates afforded good yield except in the case of 2,3-dichlorobenzenesulphonamide (entry 7). Also, in the case of sulphanilamide **2y** (entry 25), due to its poor solubility in dichloromethane, we obtained only a trace amount of product.

A plausible mechanism for the *trans*-aziridination of zerumbone is shown in Scheme 2. Initially iodosobenzenediacetate reacts with iodide ion to give a ligand exchanged halonium species **A** which simultaneously converts into an active hypohalite intermediate **B**. The intermediate **B** on reaction with zerumbone at its unactivated double bond forms an intermediate **C** and the subsequent intermolecular addition of sulphonamide followed by the S_N2 replacement reaction gives **D**. The elimination of hydroiodide from **D** led to *trans*-product with complete selectivity.

Table 2. Scope with various sulphonamides

Entry		Sulphonamide	Product	Yield(%)[a]
1	2a	R^1= H, R^2=H, R^3= H	3a	62
2	2b	R^1= CH_3, R^2=H, R^3= H	3b	40
3	2c	R^1= Cl, R^2=H, R^3= H	3c	24
4	2d	R^1= Br, R^2=H, R^3= H	3d	42
5	2e	R^1= NO_2, R^2=H, R^3= H	3e	26
6	2f	R^1= CF_3, R^2=H, R^3= H	3f	46
7	2g	R^1= Cl, R^2=Cl, R^3= H	3g	78
8	2h	R^1= H, R^2=CF_3, R^3= H	3h	54
9	2i	R^1= H, R^2=H, R^3= CH_3	3i	53
10	2j	R^1= H, R^2=H, R^3= Cl	3j	53
11	2k	R^1= H, R^2=H, R^3= Br	3k	52
12	2l	R^1= H, R^2=H, R^3= NO_2	3l	50
13	2m	R^1= H, R^2=H, R^3=CF_3	3m	51
14	2n	R^1= H, R^2=H, R^3=$COCH_3$	3n	33
15	2o	R^1= H, R^2=H, R^3=OCH_3	3o	51
16	2p	R^1= H, R^2=H, R^3=COOH	3p	35
17	2q		3q	26
18	2r		3r	87
19	2s		3s	37
20	2t		3t	40
21	2u		3u	51
22	2v	X^1= Br, X^2= H	3v	43
23	2w	X^1= Cl, X^2= H	3w	34
24	2x	X^1= Cl, X^2= Cl	3x	40
25	2y		3y	Trace
26	2z	$CH_3SO_2NH_2$	3z	28

Reaction conditions: zerumbone (1 equiv.), sulphonamide (2 equiv.), PIDA (1.5 equiv.), KI (2 equiv.), [a]isolated yield.



Scheme 2. Proposed reaction mechanism for aziridination of zerumbone

The modern drug discovery is mainly focusing on the target oriented synthesis of novel pharmacophores which amplifies the synthesis of active drugs. Natural products are evolutionarily optimised as drug-like molecules and profoundly impacted

advances in biology and therapy. Many of the natural products and their derivatives have recognised for many years as a source of therapeutic agents. Having in hand a set of zerumbone-aziridine derivatives (**3a-3z**), we undertook a study of their anti-proliferative and anti-diabetic properties.

In the present work we carried out *in vitro* cytotoxic studies of zerumbone-aziridine derivatives against five human cancer cell lines viz., A549 (Human lung adenocarcinoma), HCT116 (Human colon carcinoma), HeLa (Human cervix carcinoma), HT1080 (Human Fibrosarcoma) and MDAMB231 (Human breast adenocarcinoma) using MTT assay and the results were tabulated in terms of IC_{50} values (Table 3). The treatment of zerumbone and its synthetic derivatives on normal cell line (H9c2 - rat heart myoblast cells) showed nontoxicity when compared to other cell lines.[8]

Table 3. Anti-proliferative studies of zerumbone and its aziridine derivatives

Entry	Compounds	IC_{50} (μM)				
		HT 1080	A549	HeLa	HCT116	MDAMB231
1	3a	>30	24.66 ± 0.653	>30	4.62 ± 0.153	>30
2	3b	26.34 ± 0.554	24.11 ± 0.474	16.66 ± 1.205	4.50 ± 0.733	>30
3	**3e**	**15.33 ± 0.615**	**17.21 ± 1.169**	**>30**	**4.5 ± 0.208**	**12.5 ± 1.299**
4	3f	25.72 ± 0.325	23.88 ± 1.329	>30	4.6 ± 0.242	>30
5	3h	22.59 ± 0.70	22.20 ± 1.209	>30	5.3 ± 0.090	16.8 ± 0.894
6	3i	>30	28.33 ± 0.130	17.64 ± 1.216	4.85 ± 0.3955	>30
7	3j	25.95 ± 1.410	25.28 ± 1.140	>30	4.48 ± 0.219	>30
8	3k	>30	>30	>30	4.5 ± 0251	>30
9	3l	>30	>30	>30	5.56 ± 0.283	>30
10	3m	22.36 ± 1.22	22.16 ± 1.350	>30	4.3 ± 0.150	>30
11	3n	24.17 ± 0.024	24.78 ± 1.410	>30	4.71 ± 0.327	>30
12	3o	>30	20.19 ± 0.020	>30	4.47 ± 0.183	>30
13	**3r**	**17.52 ± 0.745**	**16.18 ± 0.480**	**18.29 ± 1.136**	**5.23 ± 0.115**	**17.8 ± 1.347**
14	3t	22.12 ± .091	23.53 ± 1.410	>30	4.65 ± 0.791	20.2 ± 1.165
15	3u	>30	26.34 ± 0.912	>30	4.41 ± 0.600	>30
16	3v	>30	24.87 ± 0.207	>30	5.23 ± 0.277	>30
18	Zerumbone	>30	>30	16.62 ± 0.063	4.97 ± 0.459	24.4 ± 0.644
19	Paclitaxel	8.64 ± 0.205 nM	7.31 ± 0.102 nM	7.75 ± 077 nM	5.5 ± 0.208 nM	9.12 ± 1.109 nM

IC_{50} values of the zerumbone derivatives which showed maximum activity are highlighted using bold letters; values represented are an average of three independent experiments ± SD

Among the sixteen derivatives screened, compounds **3e** and **3r** showed significant growth inhibition against HT1080, A549 and MDAMB231cell lines after 24 hours of incubation compared to zerumbone and other compounds.

Inhibition of digestive enzymes (*α*-glucosidase, *α*-amylase *etc.*) is one of the targets for the control and management of postprandial glycaemia in diabetic treatment. During prolonged hyperglycaemia, advanced glycation end products (AGEs) are formed in the body due to the modifications of proteins or lipids that become non-enzymatically glycated and oxidized after contact with sugars. AGEs formed under hyperglycemic conditions are reported to lead to various diabetic complications. Compounds which reduce glycation products As a search for new hyperglycaemic lead compounds from biologically relevant zerumbone molecule, we also evaluated the *in vitro* *α*-glucosidase, *α*-amylase and anti-glycation activity of some of the derivatives. From the screening studies, **3j** turned out to be more potent *α*-glucosidase inhibitor with an IC_{50} value of 45.845 ± 1.075 μM than the standard drug, acarbose (82.635 ± 0.075 μM). In the *α*- amylase inhibition studies, **3g** showed better activity with an IC_{50} value, 30.49±0.36 μM and derivative **3k** exhibited most potent anti-glycation property with an IC_{50} value 47.865 ± 0.405 μM (standard ascorbic acid 149.605±0.375 μM). From the results we demonstrate that **3g** bearing two halogen atoms showed promising anti-diabetic activity compared to other derivatives. The results of our studies areshown in Table 4.[9]

Table 4. Anti-diabetic screening studies

Entry	Product	IC_{50} μM		
		α-glucosidase	α-amylase	anti-glycation
1	3f	283.215 ± 1.215	226.805 ± 0.41	149.005 ± 0.145
2	**3g**	124.03 ± 0.94	**30.49 ± 0.36**	179.78 ± 0.26
3	3h	>1000	297.59 ± 0.41	1406.26 ± 0.13
4	**3j**	**45.845 ± 1.075**	395.14 ± 0.03	430.45 ± 0.365
5	**3k**	>1000	382.49 ± 0.32	**47.865 ± 0.45**
6	3l	147.77 ± 1.51	409.27 ± 0.16	229.685 ± 0.485
7	3m	>1000	266.3 ± 0.21	238.69 ± 0.41
8	3n	195.94 ± 0.775	355.05 ± 0.115	148.29 ± 0.08
9	3r	>1000	551.895 ± 0.195	109.765 ± 0.505
10	3u	144.355 ± 0.535	738.085 ± 0.875	128.496 ± 0.493
11	3v	587.7 ± 1.51	520.55 ± 0.46	145.695 ± 0.405
12	Zerumbone	271.053 ± 1.028	51.070 ± 1.028	104.86 ± 1.028
13	Acarbose	82.635 ± 0.075	8.255 ± 0.055	---
14	Ascorbic acid	---	---	149.605 ± 0.375

IC_{50} values of the zerumbone derivatives which showed maximum activity are highlighted using bold letters; values represented are an average of three independent experiments ± SD

In summary, we have employed a metal-free one pot strategy for the *trans*- aziridination of zerumbone using sulphonamides as the reaction partners for the first time and the derivatives were screened for anti-proliferative as well as anti-diabetic activities. Among the zerumbone-aziridine derivatives screened, **3e** and **3r** displayed superior anti-proliferative activity than the parent compound towards Human colon carcinoma and Human breast adenocarcinoma cell lines. Also, in the anti-diabetic screening studies, most of the derivatives exhibited promising *α*-glucosidase inhibition properties than the parent zerumbone molecule. Further investigations on the synthetic utility of zerumbone-aziridine derivatives are in progress.

Experimental Section

General Procedure for aziridination of zerumbone with sulphonamide : A mixture of Zerumbone(1.0 equiv.), Sulphonamide (2.0 equiv.), iodosobenzenediacetate (1.5 equiv.), and KI (2 equiv.) were weighed in a reaction tube, Dichloromethane (2 mL) was added and allowed to stir at room temperature for 12 hours. The reaction mixture was then quenched with aqueous sodium thiosulphate solution and extracted with dichloromethane, dried over anhydrous sodium sulfate. The solvent was evaporated in vacuo and the residue on silica gel (100-200 mesh) column chromatography with mixtures of hexane-ethyl acetate yielded the products.

Synthesis of sulphonamides 2r, 2s and 2t : To a solution of **2q** (1equiv.l) in water (10 mL), sulfonylchloride(1.2 equiv.) was added and stirred at room temperature until the reaction was complete. The reaction mixture was then extracted with ethylacetate, dried over anhydrous sodium sulfate, then concentrated under reduced pressure and the residue on silica gel (100-200 mesh) column chromatography with mixtures of hexane-ethyl acetate yielded the products.[10]

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Keywords: Zerumbone • aziridination • hypervalent compounds • Sulphonamides • anti-proliferative • anti-diabetic

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[11] CCDC number for compound **3l** is **1530684**.

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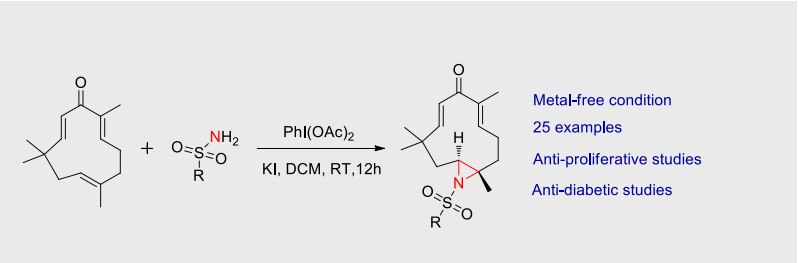

Metal-free Aziridination *

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Metal-Free trans-Aziridination of Zerumbone: Synthesis and Biological Evaluation of Aziridine Derivatives of Zerumbone

* The reaction of zerumbone with sulphonamides, *via* a one-pot metal free synthetic strategy using iodosobenzenediacetate as the oxidising agent furnished the zerumbone-aziridine derivatives. We also carried out the anti-proliferative as well as anti-diabetics screening of the synthesised compounds.

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