SEMISYNTHESIS AND BIOACTIVITIES OF LICHEN SUBSTANCES

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ABSTRACT

Lichens constitute a class of small perennial plants, which are a combination of two organisms a fungal partner (mycobiont) and one or more photosynthetic partners (photobiont) growing together in symbiotic association.

In an attempt to isolate compounds from natural sources, three lichens, namely *Parmotrema grayana*, *Cladonia sp.* and *Heterodermia obscurata* were chemically investigated. Isolated compounds were subjected to various bioassays.

Chemical investigation of these lichens led to the isolation of atranorin (**1**), + usnic acid (**2**), divericatic acid (**3**), methyl haematommate (**4**), methyl orsellinate (**5**), orcinol (**6**), orsellinic acid (**7**), lecanoric acid (**8**), zeorin (**9**), methyl-β-orcinolcarboxylate (**10**), lobaric acid (**11**), and sekikaic acid (**12**).

The depsides divericatic acid (**3**), lecanoric acid (**8**), sekikaic acid (**12**), and the depsidone lobaric acid (**11**) showed very significant antioxidant activity in SOI, the IC_{50} values being lower than the standards (propyl gallate). Simple aromatic compounds namely orciniol (**6**) and orsellenic acid (**7**), showed high urease inhibition, even higher than the standard thiourea. Methyl- β-orcinolcarboxylate (**10**), methyl orsellinate (**5**), and the triterpenoid zeorin (**9**), showed significant inhibition against α-glucosidase, with IC_{50} values several folds less than the respective standard.

The second part of thesis deals with the conversion of major lichen metabolites into minor ones and testing their bioactivities

The depiside, erythrin (**13**) isolated in 7.6% yield from *Roccella montagnei* was successfully converted into its isomeric diphenyl ether **15** *via* a Smiles rearrangement. Oxidative coupling of these diphenyl ether using palladium (II) acetate, lead to an efficient

and unambiguous approach to substituted dibenzofurans. To the best of our knowledge this is the first report on the formation of diphenyl ethers and dibenzofurans using naturally occurring depsides, *via* Smiles rearrangement

The oxidative coupling of fully protected diphenyl ether **17** led to dibenzofuran **18** and **19**. Dibenzofuran **19**, earlier synthesized by completely synthetic route, has been converted to pannaric acid (**24**) and schizopeltic acid (**25**) derivatives by previous workers. Thus, our synthesis of the dibenzofuran **19** constitutes a formal synthesis of the above natural products, in a resourceful manner.

Although fully protected diphenyl ethers such as compound **17** had been used previously in the preparation of dibenzofurans, unprotected diphenyl ethers had not been subjected to oxidative coupling in the presence of palladium acetate. Oxidative coupling of free carboxylic acid containing diphenyl ethers **15** and **16** led to the dibenzofurans **21** and **20**, respectively.

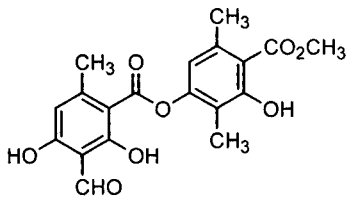
The dibenzofuran **20** and **21** are structural analogue of naturally occurring dibenzofuran hypostrepsilic acid (**27**). Thus this study opens way to form these new analogues in a versatile manner using oxidative coupling of carboxylic acid containing diphenyl ethers such as **15** and **16**.

Even though the bioactivities of hypostrepsilic acid (**27**) and its related class of dibenzofurans are not known, very interestingly, their structural analogues **20** and **21**, showed very promising activities. Both dibenzofurans showed very good activity in DPPH radical scavenging assay, and dibenzofuran **21** also was active in SOI radical scavenging assay. Dibenzofuran **20** showed antibacterial activity against *Pseudomonas aeruginosa*, whereas dibenzofuran **21** showed very high β-glucuronidase enzyme inhibitory activity at level higher than the standard.

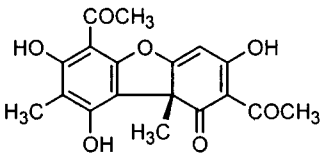
The final part of thesis deals with the structure-reactivity relationship of lichen compounds (both natural and synthetic) in various bioassays. Comparison studies revealed that depsides, and depsidones showed good antioxidant activity in SOI due to the extended conjugation of such compounds. *Thus lichens have natural mechanisms or components to combat oxidative stress, which is probably why they we have shown very promising antioxidant activities in SOI assay.* On the other hand, the synthetic dibenzofurans showed good activity in DPPH assays.

Interestingly, all the simple aromatic compounds, namely orsellinic acid (**7**), orcinol (**6**), methyl-β-orcinolcarboxylate (**10**), methyl haematommate (**4**), and methyl orsellinate (**5**) showed very good inhibition against the enzyme urease.

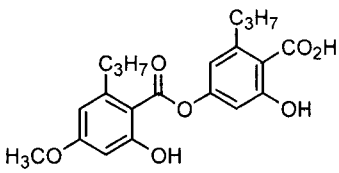
Comparison studies also revealed that by simple conversion such as hydrolysis of the depside brings about drastic change to the respective bioactivity. For example, erythrin (**13**) was inactive against all the fungi tested whereas methyl orsellinate (**5**), showed significant antifungal activity against all the tested fungi.



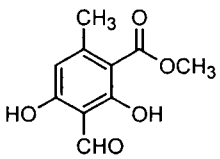
Atranorin (**1**)



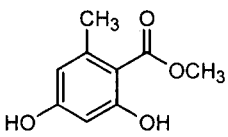
(+) Usnic acid (**2**)



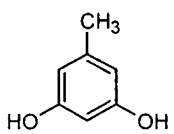
Divaricartic acid (**3**)



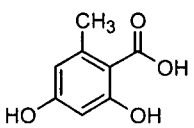
Methylhaematomate (**4**)



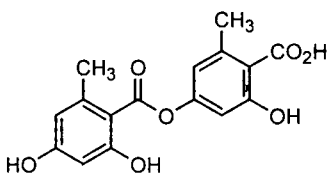
Methylorsellinate (**5**)



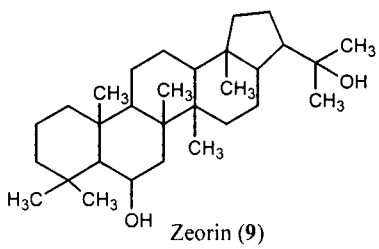
Orcinol (**6**)



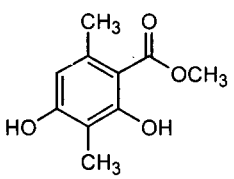
Orsellenic acid (**7**)



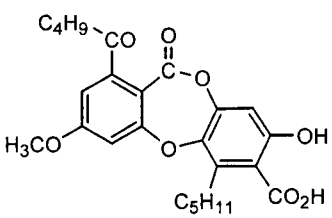
Lecanoric acid (**8**)



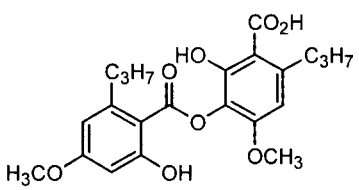
Zeorin (**9**)



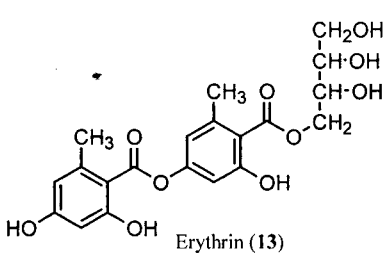
Methyl β-orcinolcarboxylate (**10**)



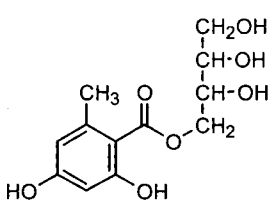
Lobaric acid (**11**)



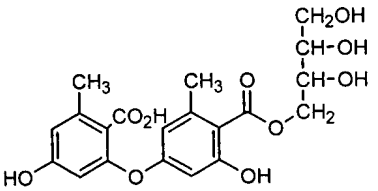
Sekikiac acid (**12**)



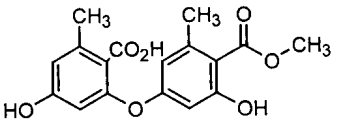
Erythrin (**13**)



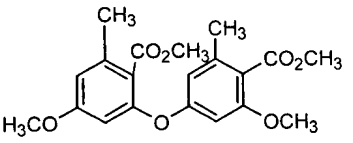
Monotangeol (**14**)



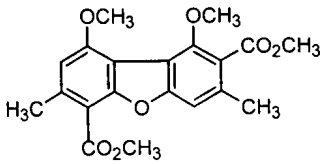
Diphenyl ether **15**



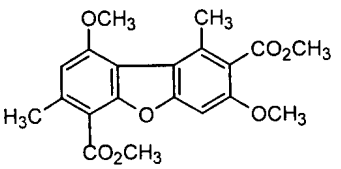
Diphenyl ether **16**



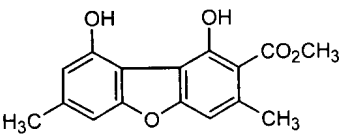
Diphenyl ether **17**



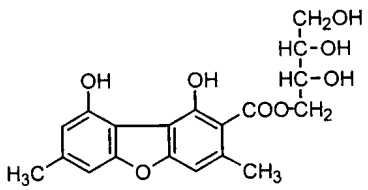
Dibenzofuran **18**



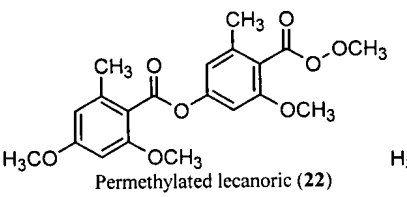
Dibenzofuran **19**



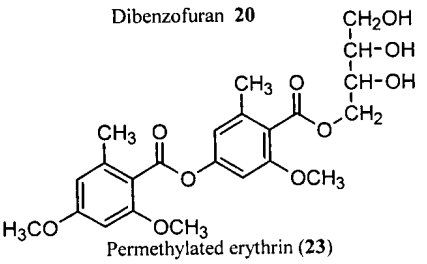
Dibenzofuran **20**



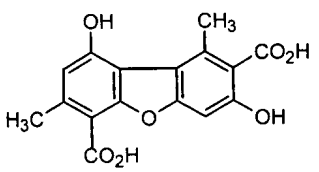
Dibenzofuran **21**



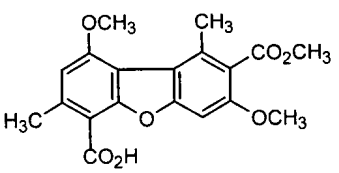
Permethylated lecanoric (**22**)



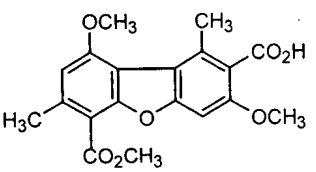
Permethylated erythrin (**23**)



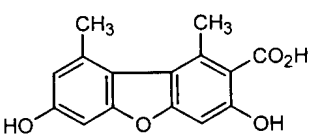
Pannaric acid (**24**)



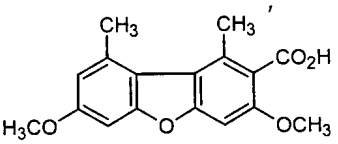
Schizopeltic acid (**25**)



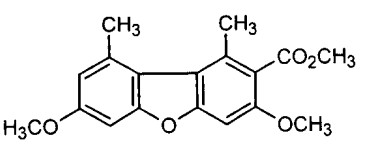
Isoschizopeltic acid (**26**)



Hypostrepsilic acid (**27**)



Ascomatic acid (**28**)



Methylascomate (**29**)