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Marine Sesquiterpene/Quinones

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1. Introduction

Over the last two decades discoveries in the field of marine natural products chemistry have yielded a remarkable array of novel secondary metabolites. These have included structure classes arising from a variety of biosynthetic pathways, some of which are unique to the marine environment. One class of marine metabolite that has received a considerable amount of attention, both through the abundance of structural variants and the biological properties ascribed to specific examples, is that involving the mixed biogenesis of a sesquiterpene unit with a quinol or a quinone. This review sets out to present a comprehensive survey of the known examples of this structure class, **1** to **108** (1-52).

2. A Survey of Marine Sesquiterpene/Quinones

Although marine sesquiterpene/quinones have predominantly been isolated from sponges, some of the earliest examples were reported from brown algae, and at least one example has been described from a gorgonian. The following survey of marine sesquiterpene/quinones and quinols (along with related natural analogues), comprises a listing of structure diagrams along with a Table. The structure diagrams are presented in an order reflecting the structural complexity of their respective sesquiterpene subunits. Thus, the order of presentation progresses through acyclic, monocyclic, bicyclic and tricyclic sesquiterpene carbon skeletons. An effort has also been made, wherever possible, to present the aromatic subunits in increasing order of substitution and/or oxidation state. Where appropriate, trivial names are indicated, along with references to literature associated with the issue of isolation and structure elucidation (1-52). These references are listed in the bibliography in chronological order. Additional references that address biological (54-99) and/or synthetic investigations (100-109), but do not contribute to the structure elucidation, are acknowledged later in this review. Although a number of synthetic analogues and derivatives have

been prepared and reported, this survey is restricted exclusively to naturally occurring examples. The Table represents a consolidated listing highlighting source organism, along with physical and optical properties, plus a comment on the current status of absolute stereochemistry.

In compiling this survey it became apparent that many marine sesquiterpene/quinones were poorly documented with respect to their stereochemistry. Indeed, in several instances the failure to characterise marine natural products with respect to their chiroptical properties (measurement of an $[\alpha]_D$) has made it impossible for future workers to properly address the issue of absolute stereochemistry. Furthermore, many early assignments of absolute stereochemistry to marine sesquiterpene/quinones were either incorrect, or at best ambiguous. In a number of cases the absolute stereochemistry issue was not even addressed in the primary literature, a point that several subsequent reviews have overlooked. This has the effect of perpetuating a "stereochemical bias" with no experimental foundation. The proper stereochemical characterisation of natural products is all the more important given the not infrequent reports of enantiomeric pairs of metabolites being reported from separate collections of the same, or related, source organisms. In order to appreciate the biosynthetic stereochemical versatility of marine organisms it is essential that the absolute stereostructures of new marine metabolites be considered, or at the very least their chiroptical properties suitably documented. This is all the more significant given the influence that stereochemistry is known to play with regards to biological activity. A brief account of some of the "problems" that have evolved with regards to stereochemical assignment among marine sesquiterpene/quinones, together with some strategies that we have pursued in chemical correlation, are outlined later in this review.

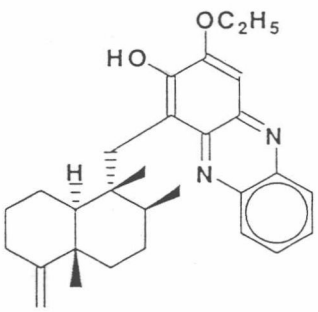
Every effort has been made to include all known naturally occurring marine sesquiterpene/quinones as of September 1992. While compounds **90** to **93** appear not to satisfy the criteria of the survey, they are in fact aromatic ring contracted analogues. Likewise, although compounds **97** to **108** have received recognition in the literature as polyketides, in the absence of any definitive biosynthetic evidence to the contrary it is the contention of this author that they be considered as norsesquiterpene/quinones. Some anomalies highlighted during the compiling of this survey are presented below;

8-epichromazonarol [37]

Assignment of the trivial name 8-epichromazonarol to the metabolite **37** isolated from *Smenospongia aurea* is misleading since it implies a stereochemical relationship with chromazonarol (an algal metabolite) that has not be established. The arbitrary absolute stereochemistry depicted in this review is more closely related to that of the known sponge metabolite ent-chromazonarol, rather than the algal metabolite chromazonarol. In fact the absolute stereochemistry of **37** remains unknown.

smenorthoquinone [77]

Although smenorthoquinone was initially assigned an *ortho* quinone structure, both the spectroscopic data and results from chemical transformations are more consistent with the *para* quinone structure shown in this review. The principal evidence cited for an *ortho* rather than *para* quinone structure was the ability of smenorthoquinone to form an adduct **109** with *ortho*-phenylenediamine. Ilimaquinone [75], which has been clearly established to be a *para*-quinone, undergoes a similar reaction with *ortho*-phenylenediamine to yield the adduct **110**. In both cases this is possible due to the tautomerization between *ortho* and *para* forms (see Figure 1). Most telling however is the spectroscopic data for smenorthoquinone, which is very similar indeed to that of ilimaquinone. Such a correlation would not be likely if smenorthoquinone was an *ortho* rather than *para* quinone as originally proposed.



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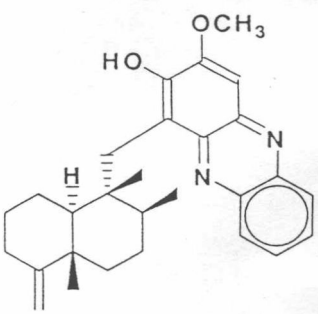

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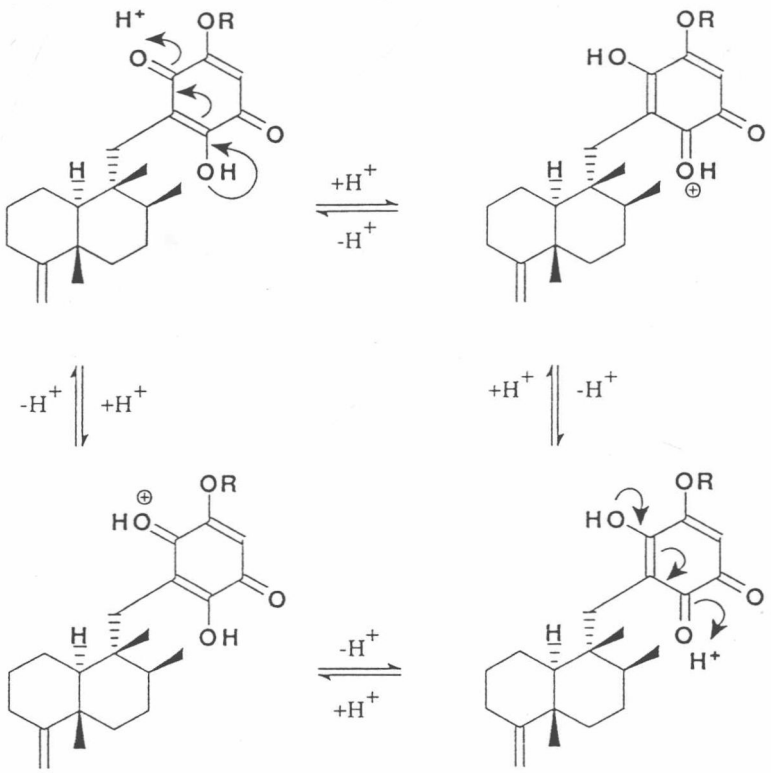


Figure 1 : Tautomerization between *ortho* and *para* forms of ilimaquinone (75)

dictyoceratin-A and/or smenospondiol [86]

Although the literature suggests that these two compounds are enantiomers, this interpretation is doubtful given that both compounds possess $[\alpha]_D$ measurements that are +ve and of comparable magnitude. Indeed, the absolute stereochemistry initially assigned to dictyoceratin-A on the basis of c.d. measurements on a degradation product (25) is very likely incorrect. The magnitude of this c.d. measurement was exceptionally small, and earlier studies (29) on the absolute stereochemistry of ilimaquinone have shown that c.d. measurements on 4-keto-5-methyl-*trans*-decalins are unreliable with respect to assigning

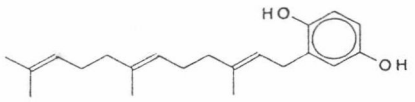
absolute stereochemistry. It would appear that dictyoceratin-A and smenospondiol are one in the same.

siphonodictyoic acid [87]

The aromatic subunit in siphonodictyoic acid is closely related to that in dictyoceratin-A [86] and smenodiol [27] (along with a number of terrestrial and synthetic compounds) and yet there exist significant discrepancies in the ^{13}C n.m.r. shifts for several aromatic carbons. Our investigations on synthetic model compounds confirm that this is not due to unexpected solvent shifts, nor abnormal substituent effects. It is distinctly possible that either the aromatic substitution pattern in siphonodictyoic acid is incorrect, or the 13C n.m.r. data is in error. The substitution pattern was initially assigned by predicting the expected aromatic ^{13}C n.m.r. chemical shifts for alternative substitution patterns, based on the additivity rules derived from monosubstituted benzenes. Extrapolation of these rules to highly substituted aromatic systems is fraught with difficulties, an observation acknowledged by the original authors in re-assigning the substitution pattern to the co-occurring metabolite siphonodictyal-B [30] (26).

siphonodictyol-G [88]

Although there is no specific spectroscopic or chemical evidence to dispute the assigned substitution pattern about the aromatic subunit in siphonodictyol-G, it is worth noting that the same method was used to determine this pattern as in siphonodictyoic acid [87] and siphonodictyal-B [30]. That some doubt exists about this assignment in the latter two compounds must raise questions about the validity of the assignment in siphonodictyol-G.



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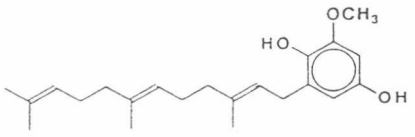
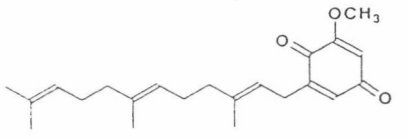


6-(3,7,11-trimethyl-2,6,10-dodecatrienyl)-2-methoxy-p-hydroquinone[53] (2)



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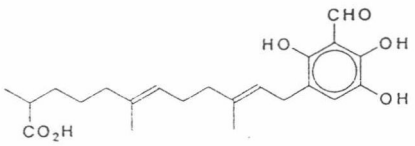
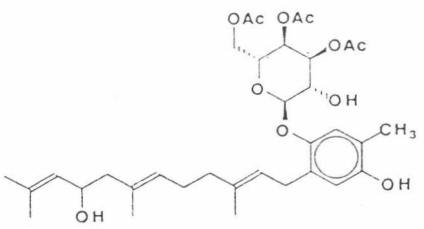
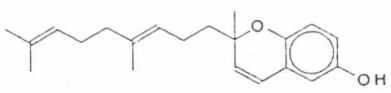


siphonodictyal-E[26] (4)



moritoside[23] (5)



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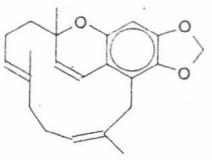
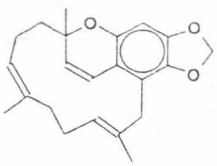


smenochromene-A[48] (7)



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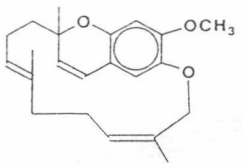

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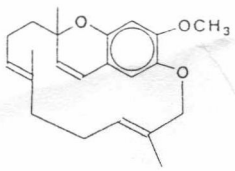

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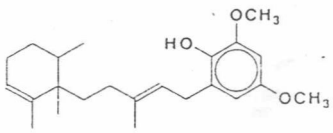
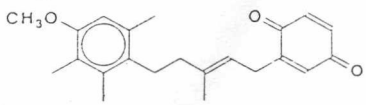
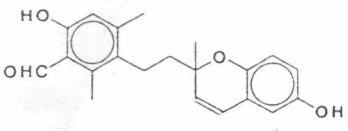


(11)[13]



panicein-A[1] (12)



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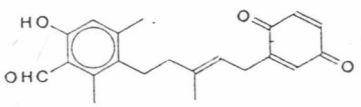

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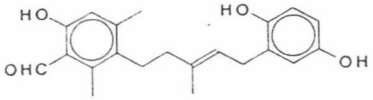

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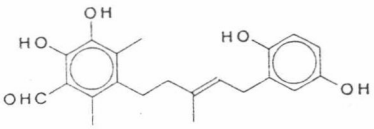

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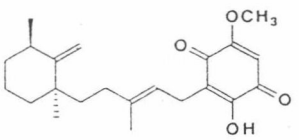
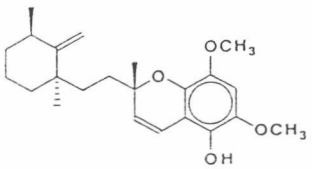


metachromin-A[31] (17)



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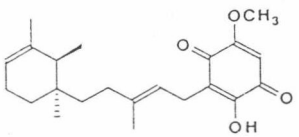

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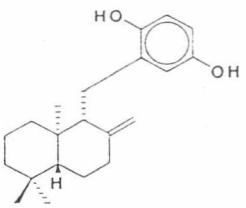
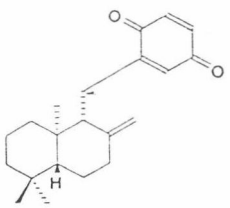
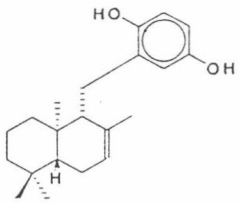


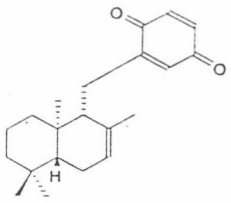
zonarol[2,6,53] (20)



zonarone[2,19] (21)



isozonarol[2,53] (22)



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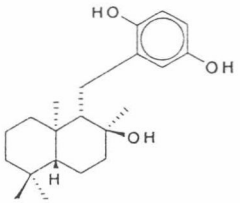

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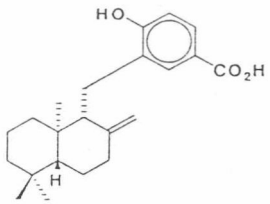

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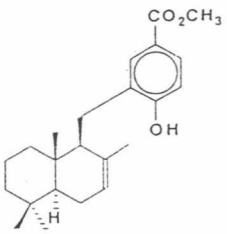
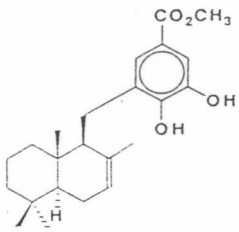
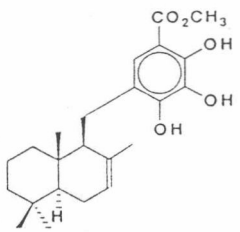


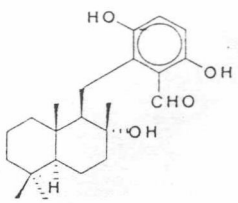
(-) dactylosponol[51] (26)



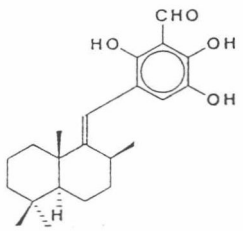
smenodiol[48] (27)



(-) dactylospontriol[51] (28)



siphonodictyal-A[14] (29)



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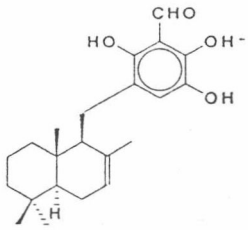

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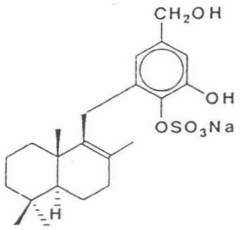

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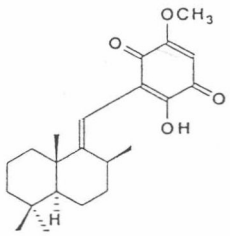
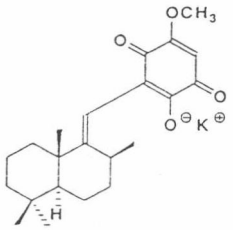
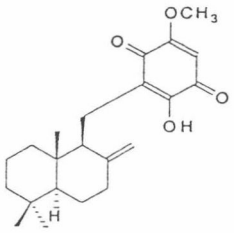


spongiaquinone[8,53] (33)



spongiaquinone potassium salt[53] (34)



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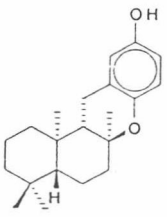
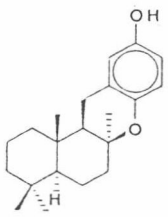
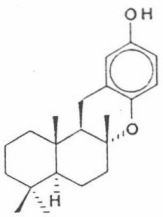


chromazonarol[4,6,13,19] (36)



8-epichromazonarol[13] (37)



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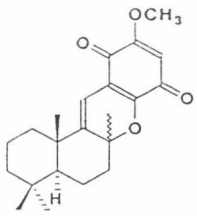

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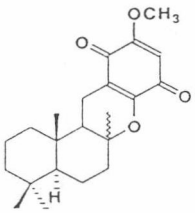
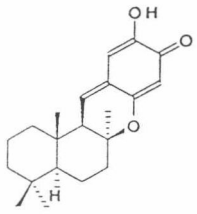
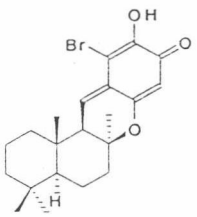


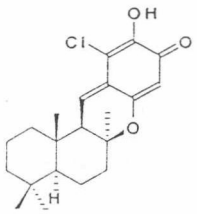
cyclospongiaquinone-1[8] (40)



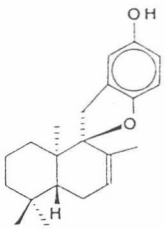
puupehenone[9,16,28] (41)



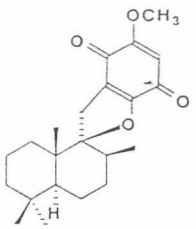
bromopuupehenone[9] (42)



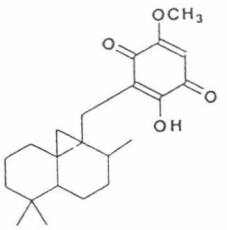
chloropuupehenone[9] (43)



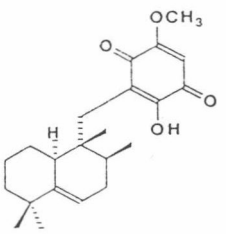
isochromazonarol[4,19] (44)



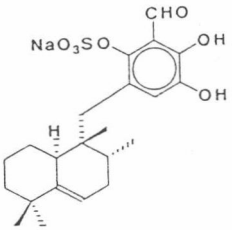
cyclospongiaquinone-2[8] (45)



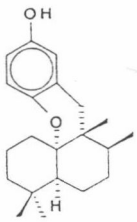
dictyoceratidaquinone[44] (46)



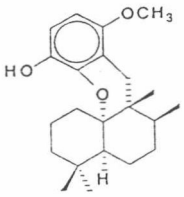
mamanuthaquinone[47] (47)



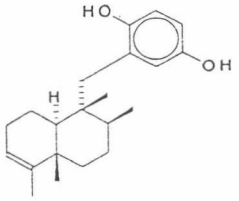
siphonodictyal-D[26] (48)



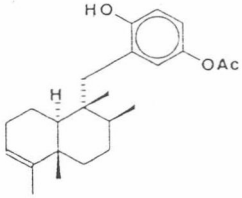
aureol[13] (49)



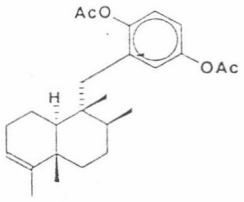
strongylin-A[46] (50)



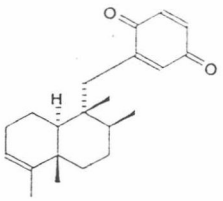
avarol[3,7] (51)



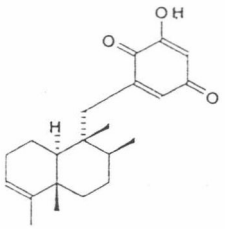
avarol monoacetate[37] (52)



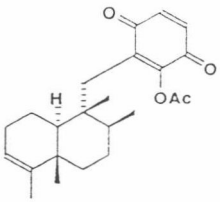
diacetoxyavarol[42] (53)



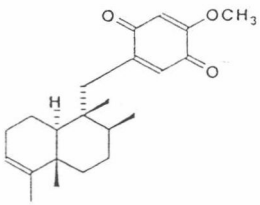
avarone[3] (54)



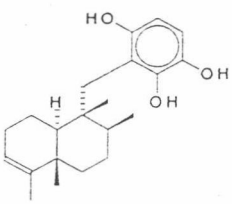
3'-hydroxyavarone[45] (55)



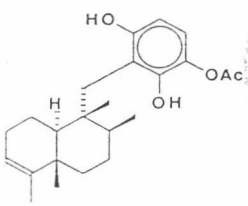
6'-acetoxyavarone[45] (56)



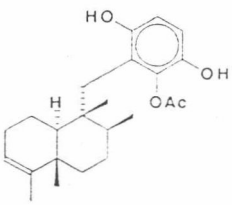
4'-methoxyavarone[40] (57)



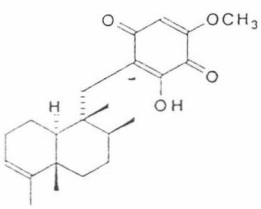
6'-hydroxyavarol[45] (58)



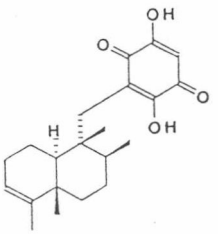
6'-hydroxy-5'-acetyl-avarol[42] (59)



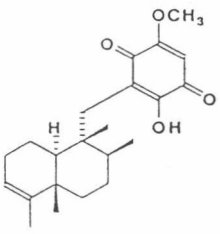
6'-acetoxyavarol[45] (60)



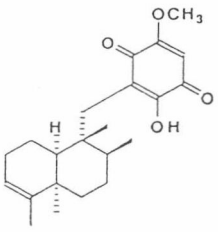
6'-hydroxy-4'-methoxyavarone[45] (61)



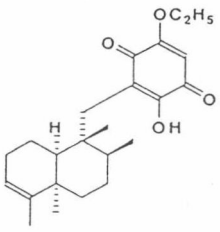
3',6'-dihydroxyavarone[45] (62)



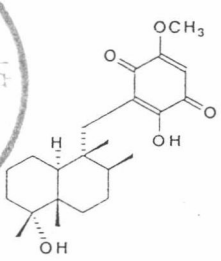
isospongiaquinone[8,39] (63)



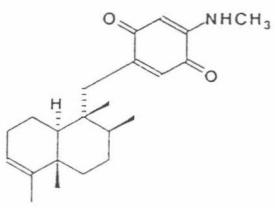
5-epi-isospongiaquinone[52] (64)



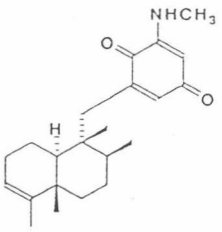
5-epi-homoisospongiaquinone[52] (65)



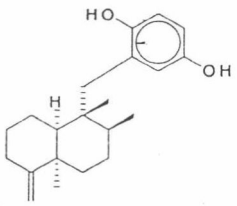
hyatoquinone[30,49] (66)



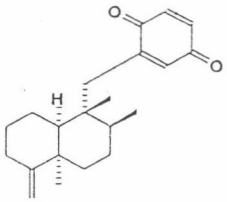
(67)[15]



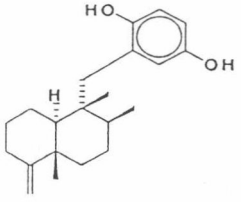
(68)[15]



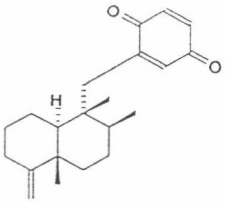
arenarol[18] (69)



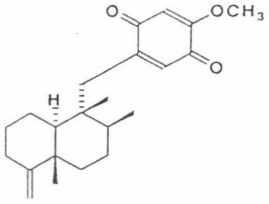
arenarone[18] (70)



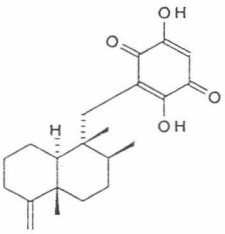
neoavarol[40] (isoavarol)[41] (71)



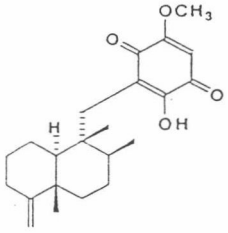
neoavarone[40] (72)



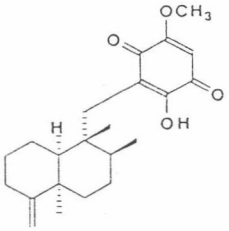
4'-methoxyneoavarone[40] (73)



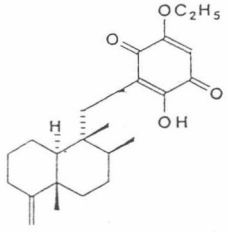
smenoquinone[35] (74)



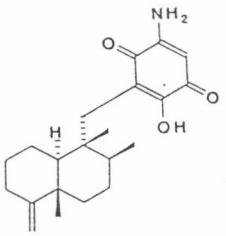
ilimaquinone[12,29] (75)



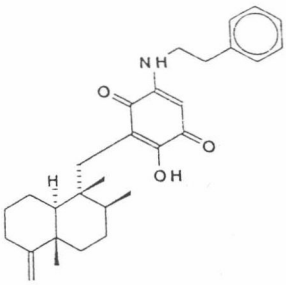
5-epi-ilimaquinone[20,53] (76)



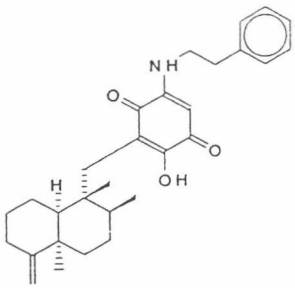
smenorthoquinone[35,52] (77)



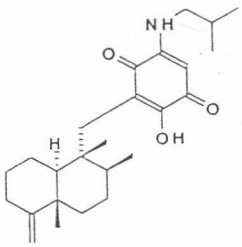
smenospongine[27,35] (78)



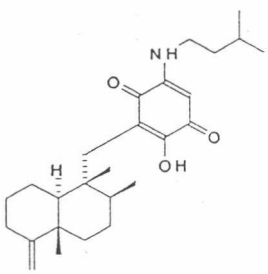
smenospongidine[35] (79)



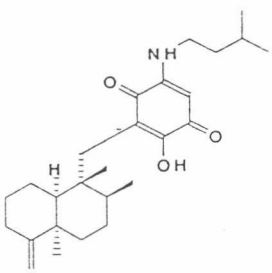
(+) epi-smenospongidine[51] (80)



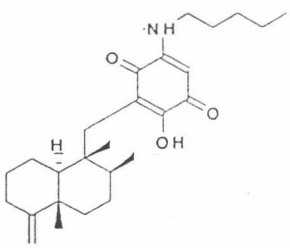
smenospongorine[35] (81)



smenospongiarine[35] (82)



(+) epi-smenospongiarine[51] (83)



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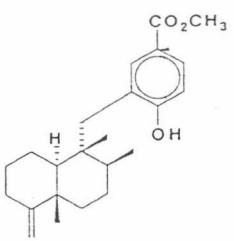

dictyoceratin-C[36] (85)