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A REVIEW: AN APPROACH TOWARDS THE ANALYTICAL METHOD DEVELOPMENT FOR DETERMINATION OF NEWER DRUGS

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ABSTRACT

In this present scenario for treating various diseases several new drugs were invented. Before launching to the market these drugs must undergo analytical validation process. In this review some of analytical techniques such as ultraviolet/ visible spectrophotometry, fluorimetry, capillary electrophoresis, and chromatographic methods (gas chromatography and high-performance liquid chromatography), LC-MS, GC-MS, SOLID PHASE EXTRACTION, NMR, MASS Spectrophotometry LC/MS/MS LC/UV X-ray crystallography were discussed.

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INTRODUCTION

Modern drug discovery involves the identification of screening hits, medicinal chemistry and optimization of those hits to increase the affinity, selectivity and oral bioavailability. Once a compound that fulfills all of these requirements has been identified, it will begin the process of drug development and in-vitro analytical studies prior to clinical trials.[1] The marine environment is a rich source of both biological and chemical diversity. This diversity has been the source of unique chemical compounds with the potential for industrial development as pharmaceuticals, cosmetics, nutritional supplements, molecular probes, fine chemicals and agrochemicals. [2] About five lakh species of marine organisms have been reported from the oceans and seas from various parts of the world. Some of the organisms are antimicrobial, antiviral, antibiotic, anticancer, anti-inflammatory and prostaglandins. Many of the species contains toxic compounds. [3]

UV-Visible spectrophotometry is one of the most frequently employed technique in pharmaceutical analysis in which ultraviolet or visible radiation absorbed by a substance in solution. [4] Capillary electrophoresis (CE) offers several advantages over high-pressure or high-performance liquid chromatography (HPLC). These include simplicity, rapid analysis, automation, ruggedness, different mechanisms for selectivity, and low cost. [5]

High-performance liquid chromatography (HPLC) is a type of liquid chromatography used to separate and quantify compounds that have been dissolved in solution. HPLC is used to determine the amount of a specific compound in a solution. [6] Gas chromatography technique is a sensitive, accurate, reproducible, quantitative and versatile tool well adapted for the analysis of complex mixtures. [7] Liquid chromatography-mass spectrometry (LC-MS, or alternatively HPLC-MS) is an analytical chemistry technique that combines the physical separation capabilities of liquid chromatography (or HPLC) with the mass analysis capabilities of mass spectrometry.[8] Gas Chromatography–Mass Spectrometry (GC-MS) is a method that combines the features of gas-liquid chromatography and mass spectrometry to identify different substances within a test sample.[9] Solid phase extraction (SPE) is an extraction method that uses a solid phase and a liquid phase to isolate one, or one type, of analyte from a solution. [10]

Pharmaceutical Potentials

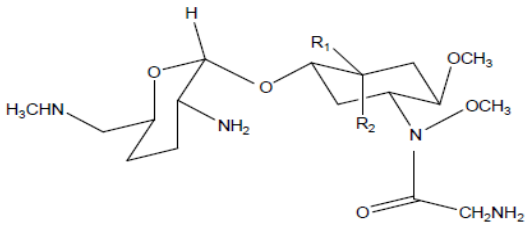
Despite the much compounds isolated from marine organisms and the biological activities attributed to many of them, those that have either been marketed or are under development are very few. The potential for marine natural products as pharmaceutical was first developed in the 1950, which led to two marine-derived pharmaceuticals that are still in use today. Ara-C is an anti-cancer drug (used against acute myelocytic leukemia and non-Hodgkin's lymphoma) and Ara-A used as an antiviral drug for treating herpes. [11]

Potential therapeutic compounds from marine sources. [11]

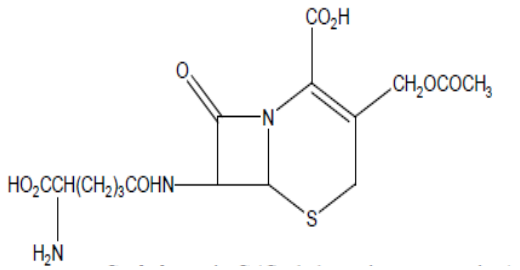
Drugs	Therapeutic Category	Source
2S-acetamido-3sacetoxy-5E	Antimicrobial	Pseudodistoma sp
5α-pregna-1,20-dien-3-one	Anti-inflammatory	Capenella thyrsoidea
Amphidinolides G and H	Anticancer	Amphidinium sp
Aplidine	Anticancer	Aplidium albicans
Apratoxin	Anticancer	Lyngbya sp.
Ara A	Antiviral	Tethya crypta
Auripyrone A and B	Anticancer	Dolabella auricularia
Avarol and Avarone	Antiviral	Disidea avara
Axisonitrile 3	Antimalarial	Acanthella klethra
Bryostatins 1 And 2	Anticancer	Bugula neritina
Cephalosporins	Antimicrobial	Cephalosporium acremonium
Cephalostatin 1	Anticancer	Cephalodiscus gilchristi
Clavepictine A and B	Anticancer	Clavelina picta
Dictyostatin 1	Anticancer	Spongia genus
Didemnin B	Antiviral	Tridemnum sp
Discodermolide	Anticancer	Discodermia dissolute
Dolastatin H	Anticancer	Dolabella auricularia
E7389	Anticancer	Halicondria okadai
Ecteinascidin 743	Anticancer	Ecteinascidia turbinate
Eleutherobin	Anticancer	Eleutherobia sp
Isodolastatin H	Anticancer	Dolabella auricularia
Istamycin	Antimicrobial	Streptomyces tenjimariensi
Kalihinol A	Antimalarial	Acanthella sp
KRN 7000	Anticancer	Agelas mauritianus
Lejimalides A-D	Anticancer	Eudistoma cf. rigida
Manzamine A	Antimalarial	Haliclona sp
Modiolides A and B	Antimicrobial	Paraphaeosphaeria sp
Niphatesine D	Anticancer	Niphates species
Okadaic acid	Molecular probe	Prorocentrum belizeanum

Orthopedic implants	Bone grafting	Coral (Family Isididae)
Polyketide synthase	Enzyme	Pseudoceratina clavata
PrialtTM	Analgesic	Conus magus
Rietone	Antiviral	Alcyonium fauri
Salinosporamide A	Anticancer	Salinospora
Seragakinone A	Antimicrobial	Cocodinium sp
Sesquiterpene furan	Anti-inflammatory	Sinularia sp
Sesterterpene, palaulol	Anti-inflammatory	Fascaplysinopsis sp
Sorbicillactone A and B	Anticancer	Ircinia fasciculote
Speradine A	Antimicrobial	Aspergillus tamari
Speradine A	Ca2+-ATPase and histone deacetylase inhibitor	Aspergillus tamari
Spongiostatin 4	Anticancer	Spirasrella spinispirulifer
Sporiolides A and B	Anticancer	Cladosporium sp
Squalimine	Anticancer	Shark
Topsentin	Anti-inflammatory	Spongosporites ruetzleri
Tsitsixenicin A	Anti-inflammatory	Capenella thyrsoidea
Tsitsixenicin B	Anti-inflammatory	Alcyonium valdivae
α-Kainic acid	Antiparasitic	Digenia simplex

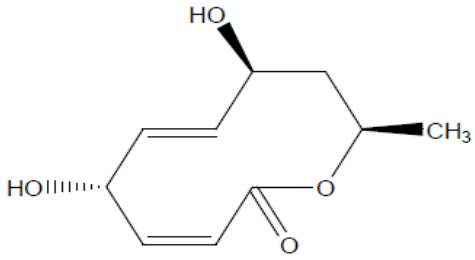
Chemical structure of few marine drugs [11, 12]



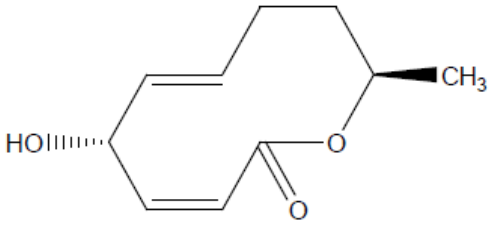
Istamycin A R_1 = H, R_2 = NH_2
Istamycin B R_1 = NH_2, = H
(Streptmyces tenjimariensis)



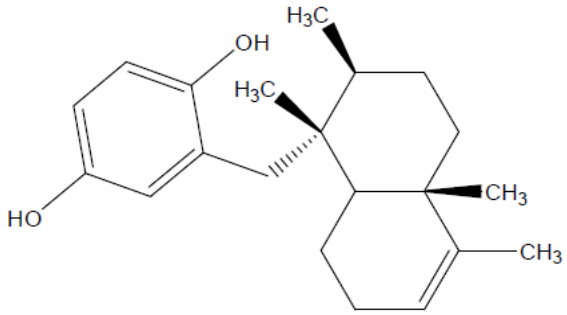
Cephaloaporin C *(Cephalsprium acreminium)*



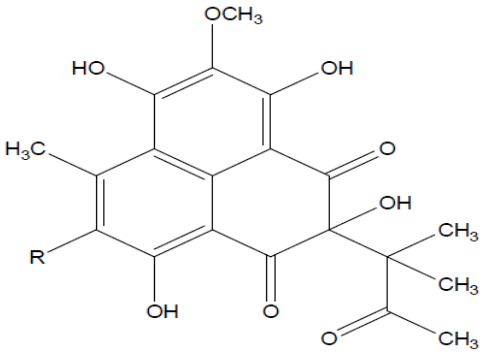
Mpdiolide A *(Paraphaeosphaeria sp.)*



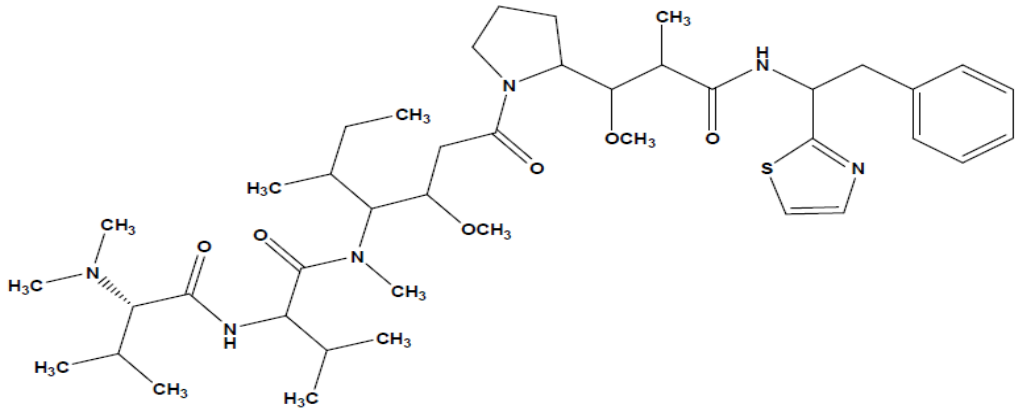
Mpdiolide B *(Paraphaeosphaeria sp.)*



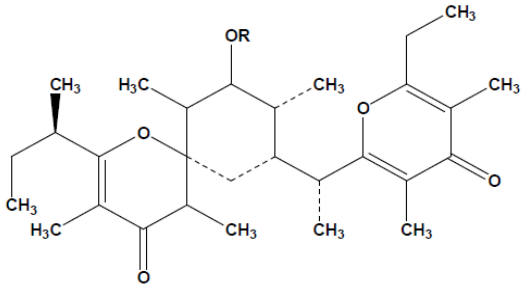
Avarol *(Disidea avara)*



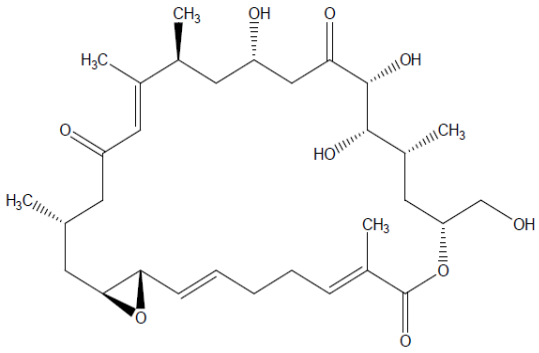
R=H, Sculezonnes A (Mytilus coruscus)
R=OH, Sculezonnes B (Mytilus coruscus)



Dolastatin- 10 *(Dolabella auricularia)*

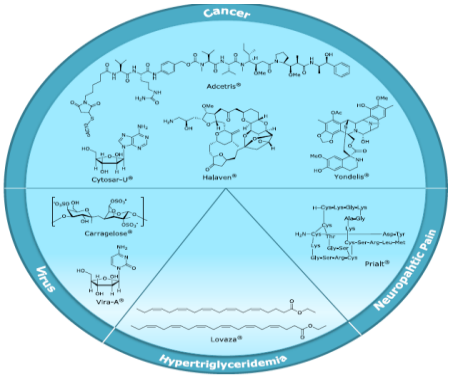


R = $COCH_2CH(CH_3)_2$ = Auripyrone A *(Dolabella auricularia)*
R = $COCHCH_3(C_2H_5)$ = Auripyrone B *(Dolabella auricularia)*



Amphidinolide H *(Amphidinium sp.)*

Chemical structures of marine drugs on the market divided by therapeutic area [13, 14]



Marketed marine natural products in the pharmaceutical sector [13]

Compound Name (Trademark)	NP or Derivative	Original NP/ Source Organism	Treatment	Status 2013
Æ-941 (Neovastat®)	NP mixture	Shark cartilage	Cancer	No data
ASG-5ME	NP derivative	Dolastatin 10/ sea hare Dolabella auricularia	Cancer	Phase I
Brentuximab vedotin (SGN-35) (Adcetris®)	NP derivative	Dolastatin 10/ sea hare Dolabella auricularia	Cancer	FDA/EMEA approved
Bryostatin I	NP	Bryozoan Bugula neritina	Cancer Alzhemier‘s	Phase I Phase II
CDX-011	NP derivative	Dolastatin 10/ sea hare Dolabella auricularia	Cancer	Phase II
Conotoxin G (CGX-1160)	NP	Marine snail Conus geographus	pain	No data
Cytarabine (Cytosar-U®; Depocyt®)	NP derivative	Spongothymidine/ sponge Cryptotethya crypta	Cancer	Approved
Discodermolide	NP	Sponge Discodermia dissouta	Cancer	No data
DMXBA (GTS-21)	NP derivative	Anabeseine/ worm Paranemertes peregrina	Alzhemier‘s	Phase II
E7389	NP derivative	Halichondria B/ sponge Halichondria okadai	Cancer	No data
Elisidepsin (Irvalec®)	NP derivative	Kahalides/ Sea slug Elysia rufescens	Cancer	Discontinued
Eribulin mesylate (Halaven®)	NP derivative	Halichondrin B/ sponge Halichodria okadai	Cancer	FDA/EMEA approved
Hemiasterlin	NP	Sponge Hemiastrella minor	Cancer	Discontinued
HTI-286	NP derivative	Hemiasterlin/ sponge Hemiastrella minor	Cancer	No data
Iota-carrageenan (Carragelose®)	NP	Iota-carrageenan/ redAlgee Eucheuma/Cnondus	Antiviral Viral	Over-the-counter drug (OTC)
IPL-576092 and derivatives	NP derivatives	Contignasterol/ Sponge Petrosia contignata	Anti-asthmatic	No data
Kahalalide F	NP	Sea slug Elysia rufescens	Cancer	No data
KRN-7000	NP derivative	Agelasphins/ sponge Agelas mauritianus	Cancer	No data
Lurbinectedin (PM01183)	NP derivative	Ecteinascidins/ tunicate Ecteinascidia turbinata	Cancer	Phase II
Marizomib	NP	Salinosporamide A/ Marine actinomycete Salinispora tropica	Cancer	Phase I
NVP-LAQ824	NP derivative	Psammaplin A/ sponge Aplysinella rhax	Cancer	No data
Omega-3-acid ethyl esters (Lovaza®)	NP derivative	Omega-3-fatty acids/ fish	Hypertriglyceridemia	Approved
Pliditepsin (Aplidin®)	NP	Ascidian Aplidium albicans	Cancer	Phase II/III
Plinabulin (NPI-2358)	NP derivative	Halimide (NPI-2350)/ marine fungus Aspergillus sp.	Cancer	Discontinued

PM00104 (Zalypsis®)	NP derivative	Jorumycin/ sea slug Joruna funebris	Cancer	Phase II
PM060184	NP	Sponge Lithoplocamia lithistoides	Cancer	Phase I
Pseudopterosins	NP derivative	Pseudopterosins/ Soft coral Pseudoptergorgia elisabethae	Wound healing	Discontinued
SGN-75	NP derivative	Dolastatin 10/ sea hare Dolabella auricularia	Cancer	Phase I
Soblidotin	NP derivative	Dolastatin 10/ Sea hare Dolabella auricularia	Cancer	Discontinued
Spisulosine (ES-285)	NP	Marine clam Spisula polynyma	Cancer	No data
Squalamine	NP	Dogphish shark Squalus acanthias	Cancer	No data
Synthadotin	NP derivative	Dolastatin 15/ Sea hare Dolabella auricularia	Cancer	Discontinued
Tasidotin (ILX-651)	NP derivative	Dolastatin 15/ sea hare Dolabella auricularia	Cancer	Discontinued
Trabectedin (Yondelis®)	NP	Ecteinascidin 743/ tunicate Ecteinascidia turbinata	Cancer	EMEA approved
Vidarabine (Vira-A®)	NP derivative	Spongouridine/ sponge Cryptotethya crypta	Anti-viral	US discontinued
Ziconotide (Prial®)	NP derivative	ω-Conotoxin/ marine snail Conus magus	Neuropahtic Pain	Approved

Analysis of Cephalosporin and Anti-cancer drugs from marine source by different analytical methods [15-23]

Drug	Method	Description
Cefuroxime axetil	Ultraviolet spectroscopy	Wavelengths: 281 nm Solvent: 0.1N HCl Linearity Range: 0.4 – 2 mg/ml Correlation Coefficient: 0.998
Ceftriaxone sodium	A simple spectrophotometric estimation	Wavelength: 490.4 nm Linearity Range: 5-25 µg/ml Correlation Co-Efficient: 0.998
Cefixime trihydrate	Ultraviolet spectroscopy	Wavelength: 287 nm. Linearity Range: 2-20 µg/ml Correlation Coefficient: 0.999
Cefuroxime axetil	HPTLC	Stationary Phase: Precoated Silica Gel 60F 254 Mobile Phase: Chloroform: Methanol: Toluene (4:2:2V/V) Wavelength: 290 nm
Cephalexin	HPTLC	Stationary Phase: Aluminum Backed Layer Of Silica Gel 60 F254 Mobile Phase: Toluene: Methanol: Tri ethyl amine (6:4:0.1 V/V/V) Wavelength: 254 nm
Cefotaxime sodium	RP-HPLC	Stationary Phase: SS Wakosil II- C8 Column (250 mm ×4.6 mm I.D., 5 mm) Mobile Phase: Ammonium : Acetate Buffer (Ph 6.8) : Acetonitrile (85:15 V/V) Wavelength: 252 nm Flow Rate: 0.8 ml/min
Ceftriaxone sodium in pharmaceutical formulations	HPLC	Stationary Phase:18 Inert sil Column (150 mm × 4.6 mm, 3 mm) Mobile Phase: Degassed Mixture Of Buffer: Methanol (74:26 v/v) Wavelength: 241.5 nm
Cefpirome sulfate	RP-HPLC	Stationary Phase: Lichrocart Lichrospere 100 C18, (250 mm X 4 mm, 5µ) Mobile Phase: Methanol : Water (50:50 V/V) Wavelength: 270 nm
Cepodoxime proxetil and dicloxacillin sodium in tablets	RP- HPLC	Stationary Phase: Kromasil C 18 Analytical Column (250×4.6 mm, 5 mm) Mobile Phase: Acetonitrile: Methanol: Tri floro acetic acid (0.001%) With PH 6.5 (30:50:20V/V/V) Wavelength: 235 nm
Cefoperazone and sulbactam in parenteral preparation	RP-HPLC	Stationary Phase: Kromasil C8 (15 Cm × 4.6 mm , 5µ) Mobile Phase: Phosphate Buffer Ph 3.5 Adjusted With Ortho Phosphoric Acid and Acetonitrile(35:65) Wavelength: 215 nm

Cefuroxime axetil and potassium clavulanate in pharmaceutical dosage form	RP-HPLC	Stationary Phase : Micros orb MV 100-5 C-18 Column (250mm×4.6mm,5µm) Mobile Phase : Methanol: Water (90 :10 V/V) Wavelength: 230 nm
Cefuroxime axetil and its impurities	RP-HPLC	Stationary phase : Lunn c-18 column Mobile phase : water and methanol Wavelength: 278 nm
Cefoperazone and Tazobactam in marketed formulation	RP-HPLC	Stationary Phase : 0.02 Mm Potassium Di hydrogen Phosphate Buffer, PH 4.0 and Methanol (80:20, V/V) Mobile Phase :Thermo BDS Hypersil C18 Column (250 × 4.6 Mm I.D.5 mm) Wavelength: 250 nm.
Aplidine	HPLC	Stationary Phase : octadecyl modified silica Mobile phase : water–acetonitrile mixture at pH 4. Wavelength: fluorescence detection at 410 and 560 nm for excitation
Bryostatin	HPLC	n-hexane/EtOAc/MeOH/H2O (26:5:1:0.01) as mobile phase for normal phase HPLC and acetonitrile (CH3CN)/H2O system for reverse phase HPLC
Ecteinascidin- 743	RP-HPLC	Stationary Phase : Zorbax SB-C18 column (75×4.6 mm I.D., particle size 3.5 µm) Mobile phase : acetonitrile–25 mM phosphate buffer, pH 5.0 (70:30, v/v) Wavelength: 210 nm
Dolastatin-10	HPLC	Stationary Phase : C8 reversed-phase Mobile phase : acetonitrile-2-propanol-water
Cytarabine	RP-HPLC	Stationary Phase : HC-C18(2) column Mobile phase : Acetonitrile and purified water with previously adjusted pH 2.8 with orthophosphoric acid (2: 98 v/v) Wavelength: 280 nm

CONCLUSION

The efficient development and validation of analytical methods are critical elements in the development of pharmaceuticals. This review represents that few drugs are approved for the use in market obtained from marine source. According to the literature review it can be concluded that for marketed marine formulations in single component and its combination with other drug spectroscopy and chromatography methods available. Comparing various validation parameters of already reported methods, it can be concluded that different analytical methods like spectrophotometric, HPTLC, HPLC, GC-MS and LC-MS can be developed for these formulations. There is a great scope for development of newer analytical methods for latest drugs because there is no reported method for some newly approved drugs and their combination with other drugs.

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