# Chemistry and Biology of Synthetic and Naturally Occurring Antiamoebic Agents†

Shailendra Singh,*,‡,§ Neelam Bharti,‡ and Prabhu P. Mohapatra§

*Department of Medicinal Chemistry, College of Pharmacy, University of Florida, Gainesville, Florida 32610, and Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida 32611*

*Received May 3, 2007*

## Contents



## 1. Introduction and Background

Parasitic infections constitute one of the most widespread human health problems, and most of them occur through contaminated food or water. The human intestine is a major target of these ingested pathogenic microorganisms, resulting in severe infections, of which amoebiasis (potential life-threatening dysentery) is one. Amoebiasis is the second leading cause of death from a protozoan parasite, *Entamoeba histolytica* (*E. histolytica*), and remains as a major health problem in third world countries.[1] It affects more than 10% of the world's population, and untreated infection may lead to severe complications including hepatic amoebiasis and intestinal tissue destruction.[2] Globally, amoebiasis accounts for 50 million clinical cases and is responsible for approximately 110,000 deaths annually.[3,4] Only malaria surpasses amoebiasis in mortality of infectious diseases.[5]

*Entamoeba* protozoa represents two species, pathogenic *E. histolytica* and nonpathogenic *E. dispar*. Pathogenic form *E. histolytica* has a simple life cycle, existing as either the infectious cyst form or the pathogenic amoeboid trophozoite stage. Infections usually begin with the ingestion of the cysts in the food or water that has been contaminated. *E. histolytica* cysts are round, quadrinucleated, and surrounded by a refractile wall that may include chitin. They survive the acid of the stomach, reach the small intestine, and, within the colon, excyst to form the trophozoite stage. Unlike the inert cysts, *E. histolytica* trophozoites are highly motile with a pleomorphic shape. Trophozoites ingest bacteria and food particles, reproduce by binary fission, encyst within the colon, and excrete into the environment in stool. Trophozoites may exit in the stool as well, but they cannot survive outside the human host.[1,3]

There are numerous antiamoebic drugs used in medical practice (Figure 1) and mainly divided into two classes: tissue and luminal amoebicides. Tissue amoebicides such as metronidazole, tinidazole, and emetine kill amoeba in host tissue and organ, whereas the poorly absorbed luminal amoebicides, iodoquinol, diloxanide furoate, and paromomycin, are active only in the intestinal lumen. Metronidazole [1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole] ($IC_{50} = 0.33$ $\mu$g/mL) is currently the most effective antiamoebic medication, but in severe infection it needs to be administered with promomycin or other antimicrobial drugs.[6−11] However, it is mutagenic in bacteria and carcinogenic in rodents. In addition, this drug has several other side effects including gastrointestinal disturbance, especially nausea, vomiting, and diarrhea.[12−14] Infrequent adverse effects include headache and stomatitis, and long-term systemic treatment with metronidazole is associated with the development of leucopenia, neutropenia, and/or central nervous system (CNS) toxicity.[15] Resistance to metronidazole in many pathogenic bacteria and protozoa is also known.[16,17] Owing to these undesired side effects and also taking into account the possibility of the development of resistant strains of the amoeba against metronidazole, there is a clear need for new, effective, and safer amoebicidal agents.

Many active pharmaceutical ingredients possess one heterocyclic ring or another. Diverse functionalized organic compounds like thiosemicarbazones, Schiff bases, acetamides, carbamates, bisphosphonates, triazines, pyrazolines, benzimidazoles, oxime ethers, and others were synthesized

* To whom correspondence should be addressed. Phone: 001-352-273-7730. Fax: 001-352-392-9455. E-mail: singhss@ufl.edu.
† Dedicated to Prof. Fehmida Naqvi, Department of Chemistry, Jamia Millia Islamia, New Delhi, India, on her 65th birthday.
‡ College of Pharmacy, University of Florida.
§ Department of Chemistry, University of Florida.

10.1021/cr068217k CCC: $71.50 
Published on Web 04/17/2009

Dr. Shailendra Singh was born in Shamli (district, Muzaffarnagar), India, in 1976. He received his B.Sc. (1995) and M.Sc. (1997) degrees from the Chaudhary Charan Singh University, Meerut, India. After completing his M.Phil. (1998) from Indian Institute of Technology, Roorkee, India, he worked as a project fellow in the same department from 1998− 2000 under a Ministry of Environment and Forest Scheme. He was awarded his Ph.D. degree (2003) in organic chemistry under Professor Fehmida Naqvi from Jamia Millia Islamia, New Delhi, India. His doctoral work was focused on synthesis, characterization of heterocyclic compounds, and evaluation of their antiprotozoal activity. During his Ph.D., he also received a junior research fellowship (2000−2001) and a senior research fellowship (2002−2003) from Council of Scientific and Industrial Research, New Delhi, India. Then he joined Professor Alan R. Katritzky (Director), Center of Heterocyclic Compounds, University of Florida, Gainesville, FL, U.S.A., as a Research Associate, where he worked on the development and utilization of ionic liquids in green chemistry along with the benzotriazole methodology in heterocyclic chemistry from 2003−2005. Currently, he is working as a postdoctoral fellow with Professor Raymond J. Bergeron at Department of Medicinal Chemistry, University of Florida, Gainesville, FL, U.S.A., where his research is focused on total synthesis of natural products and drug development for iron overload treatment. He has published over 25 peer-reviewed articles in international journals.

Dr. Neealm Bharti acquired her Ph.D. degree in organic chemistry from Jamia Millia Islamia, New Delhi, India, in 2002. In 2002, she joined Professor Raymond J. Bergeron's group at Department of Medicinal Chemistry, University of Florida, Gainesville, FL, U.S.A., as a postdoctoral fellow, where she is engaged in a drug development program for iron overload that involves total synthesis of marine bacterial siderophores and polyamine vectors. She received her Bachelor of Science (1994) and Master of Science (1997) degrees from the Chaudhary Charan Singh University, Meerut, India. She completed her Master of Philosophy in instrumental methods of chemical analysis from Indian Institute of Technology, Roorkee, India, in 1998. Then she joined Department of Chemistry, Jamia Millia Islamia, as a Junior Research Fellow and later on was awarded a Senior Research Fellowship by Council of Scientific and Industrial Research, New Delhi, India, in 2000 for three years. Her field of interest concerns natural bioactive compounds from marine bacteria and higher plants. She has authored more than twenty articles in medicinal journals.

Prabhu P. Mohapatra was born in Khairagarh, Orissa, India, in 1969. He obtained his Ph.D. degree in synthetic organic chemistry in 1999 under the direction of Prof. Shive M. S. Chauhan at Delhi University, Delhi, India. His doctoral work focused on the biomimetic oxidation reactions using metalloporphyrins as chemical models of cytochrome P450. Then he joined Ranbaxy Research Laboratories, Gurgaon, India (1999−2001), as a Research Associate and worked on the development of several active pharmaceutical ingredients. He started his postdoctoral research with Prof. George R. Newkome at The University of Akron, OH, U.S.A. (2001−2003), where he studied nanoassembly of fractal polymers. His second postdoctoral appointment with Prof. Alan R. Katritzky at the University of Florida, Gainesville, FL, U.S.A. (2003−2007), involved research on benzotriazole assisted synthetic methodology development. Currently he is working at Reviva Pharmaceuticals Inc., San Jose, CA, U.S.A., as a Scientist, Medicinal Chemistry.

and screened for their antiamoebic activity. Metal chelates play an important role in the biological systems because they are an essential part of metalloproteins and enzymes.[18] Lately, there has been an increased interest in the use of metal complexes as chemotherapeutic agents, for example, cisplatin and its analogues in cancer treatment.[19] A number of transition metal complexes have been prepared and tested against amoebiasis both in vivo and in vitro, and some of them showed very exciting results. Medicinal plants are considered as an important source of potentially useful compounds for the development of new chemotherapeutic agents. According to WHO (World Health Organization), about 80% of the people in less developed countries rely almost exclusively on traditional medicine for their primary health care needs.[20] Extracts from numerous plants are used in the indigenous system of medicine for the treatment of dysentery, and a number of natural products have been isolated and explored for their antiamoebic activity. This review will cover the synthesis and antiamoebic activity of different classes of organic compounds and metal complexes as well as a brief description of isolated natural products screened against *E. histolytica*.

## 2. Synthetic Antiamoebic Compounds

### 2.1. Thiosemicarbazones and Their Metal Complexes

The chemistry of thiosemicarbazones and thiosemicarbazides has received considerable attention because of their biological activity and industrial applications.[21−24] Thiosemicarbazone analogues substituted with sulfur and nitrogen are more versatile intermediates with respect to the oxygenated ones.[25,26] Thiosemicarbazone derivatives were synthesized from thioglycolic acid intermediate **2.001** as shown in Scheme 1.[27−35] Reaction of carbon disulfide with a primary/secondary amine in aqueous ethanolic solution of potassium

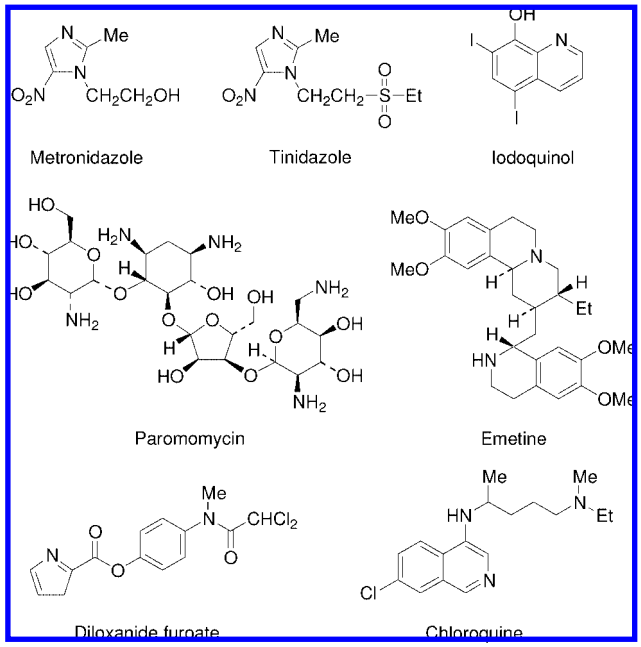
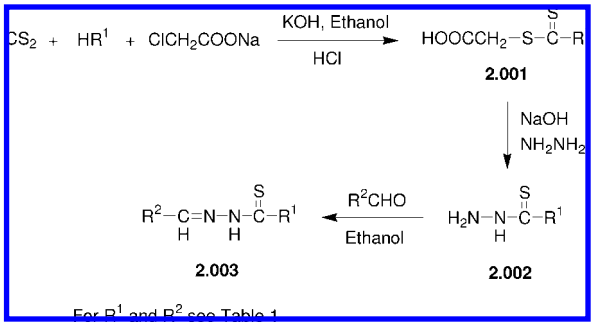



**Figure 1.** Antiamoebic drugs used in medical practice.

**Scheme 1. Synthesis of Thiosemicarbazones 2.003**




hydroxide and sodium chloroacetate followed by acidification gave thioglycolic acid **2.001**, which was then refluxed with aqueous sodium hydroxide and hydrazine hydrate to give substituted thiosemicarbazide **2.002**. Treatment of **2.002** with heterocyclic aldehyde gave the corresponding thiosemicarbazone **2.003**. A large number of thiosemicarbazones were prepared using a variety of aliphatic, aromatic, and cyclic amines along with different heterocyclic aldehydes.

The in vitro antiamoebic activities of thiosemicarbazone analogues against *E. histolytica* are summarized in Table 1.[27−35] Compounds substituted with aliphatic amines did not show any activity, while results were encouraging for the thiosemicarbazone derivatives with cyclic and aromatic amines. Thiosemicarbazones bearing aliphatic, cyclic, and aromatic amines at the $N^4$ position showed $IC_{50}$ values in the ranges 1.88−15.38, 1.09−9.84, and 2.56−6.18 $\mu$M, respectively. In the cases of thiophene/5-nitrothiophene-2-carboxaldehyde thiosemicarbazones, the compounds substituted with cyclic amines were more active than the aryl analogues. It was also observed that antiparasitic activity was limited to those compounds in which the alkylidene group was attached to the 2-position, rather than 3- or 4-position, of the heterocyclic ring and also to those in which a thiocarbonyl, rather than a carbonyl, group was present.[36]

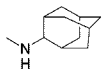
Thiosemicarbazones usually react as bidentate ligands with metal cations by bonding through the thionic sulfur and the azomethine nitrogen atom, although in some cases they behave as tridentate ligands bonded through the sulfur, nitrogen, and another heteroatom present in a ring.[37] The biological properties of thiosemicarbazones are often related to metal ion coordination in different ways since some of them increase the biological activity by forming chelates with specific metal ions. Lipophilicity, which controls the rate of entry of molecules into the cell, is modified by coordination, so the metal complex can become more active than the free ligand.[38] Complexation with the metal also protects the drug against enzymatic degradation because of the inertness of certain metal−ligand linkages. Therefore, the activity can be reinforced by the combined effect of the ligand and metal residue.[39−41] Since cisplatin emerged as the most important antitumor drug, numerous complexes of general formula $ML_2X_2$ have been synthesized, characterized, and tested against different diseases in order to study the effects of the metal M, the inert group L, and the leaving group X on the structural and kinetic properties involved in biological activity. The mechanism of action can involve binding to the metal in vivo, or the metal complex may be a vehicle for activation of the ligand as the cytotoxic agent. Moreover, coordination may lead to a significant reduction of drug-resistance.[42]

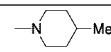
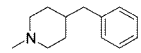
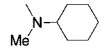
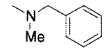
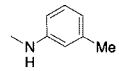
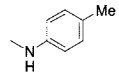
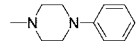
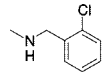
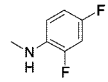
With the intention to find new drugs against *E. histolytica* safer than the reference drug metronidazole, Pd(II), Ru(II), and Cu(II) thiosemicarbazones complexes were widely explored. The palladium complexes derived from thiosemicarbazones were reported as potential antitumor agents.[43−45] The electron-rich Ru complexes of 4-nitroimidazole are less toxic then their corresponding ligands.[46] This phenomenon was observed in another class of nitroimidazoles[47] and may be attributed to the redox potential of the Ru metal. Additional advantages of ruthenium are the availability of both the Ru(II) and Ru(III) oxidation states under physiological conditions and the general substitution inertness of their ions when coordinated to nitrogen ligands.[48] Copper(II) ion plays a special role in the catalytic processes of living organisms, being involved in the active center of a number of metalloproteins and enzymes,[49−51] since its chelating ability and positive redox potential allow participation in biological transport reactions.[52] Therefore, Cu(II) complexes possess a wide spectrum of biological activity against various diseases.[53−55]

Pd(II) **2.004**[30,32,33,56] and Ru(II) **2.005**[28,29,33,34] complexes of thiophene/5-nitrothiophene-2-carboxaldehyde were synthesized by mixing equimolar amounts of the appropriate thiosemicarbazone with $[Pd(DMSO)_2Cl_2]$ or $[Ru(\eta^4\text{-}C_8H_{12})(CH_3CN)_2Cl_2]$ in refluxing methanol (Figure 2). Copper(II) complexes **2.006**[27,35] of thiophene/5-nitrofuran-2-carboxaldehyde thiosemicarbazones were prepared by the reaction of thiosemicarbazone with cupric chloride (2:1 ratio) in refluxing methanol (Figure 2). The spectral data showed that all the thiosemicarbazones behaved as bidentate ligands and bonded with the central metal ion (Pd, Ru, and Cu) by coordination through the thionic sulfur and the azomethine nitrogen atom.

Palladium(II) and ruthenium(II) complexes of thiophene/5-nitrothiophene-2-carboxaldehyde thiosemicarbazones showed moderate inhibition while their Cu(II) complexes showed $IC_{50} = 0.21-2.85$ $\mu$M (Table 1). The better activities of thiosemicarbazone metal complexes compared to their respective ligands may be due to chelation, which reduces the polarity of the central metal atom because of partial sharing of its positive charge with the ligand. This, in turn, favors permeation of the complexes through the lipid layer

**Table 1. In vitro Antiamoebic Activity [$IC_{50}$ in $\mu$M] of Thiosemicarbazones (L) 2.003 and their Pd(II) 2.004, Ru(II) 2.005, and Cu(II) 2.006 Complexes**

| $R^1$ \ $R^2$ |  |  |  |
|---|---|---|---|
| -$NHCH_2CH_2CH_3$ | 4.97 (L)[27]<br>0.97 (Cu)[27] | 15.38 (L)[31]<br>4.76 (Pd)[56] | - |
| -$NHCH(CH_3)_2$ | - | 9.60 (L)[31]<br>4.07 (Pd)[56] | 11.45 (L)[35]<br>2.85 (Cu)[35] |
| -$NHCH_2CH_2CH_2CH_3$ | 10.17 (L)[27]<br>1.81 (Cu)[27] | 12.17 (L)[31]<br>4.70 (Pd)[56] | 6.59 (L)[35]<br>1.57 (Cu)[35] |
| -$N(CH_2CH_3)_2$ | - | 10.10 (L)[31]<br>2.56 (Pd)[33]<br>4.19 (Ru)[33] | - |
| -$NHCH(CH_3)CH_2CH_3$ | 2.61 (L)[27]<br>0.26 (Cu)[27] | 13.50 (L)[31]<br>4.25 (Pd)[56] | 8.70 (L)[35]<br>1.54 (Cu)[35] |
| -$N(CH_2CH_2CH_3)_2$ | - | 6.40 (L)[31]<br>3.03 (Pd)[56] | 6.11 (L)[35]<br>0.38 (Cu)[35] |
| -$N[CH(CH_3)CH_2CH_3]_2$ | - | 11.63 (L)[31]<br>1.61 (Pd)[56] | - |
| -$N(CH_3)CH_2CH_2CH_2CH_3$ | - | 7.70 (L)[32]<br>4.06 (Pd)[32] | 2.39 (L)[35]<br>1.02 (Cu)[35] |
| -$NHCH_2CH(CH_3)_2$ | 1.88 (L)[27]<br>0.36 (Cu)[27] | - | 8.11 (L)[35]<br>1.39 (Cu)[35] |
|  | 2.53 (L)[28]<br>0.73 (Ru)[28] | 2.86 (L)[31]<br>1.45 (Pd)[56] | 5.00 (L)[35]<br>0.93 (Cu)[35] |
|  | 2.09 (L)[28]<br>0.60 (Ru)[28] | 2.41 (L)[31]<br>0.87 (Pd)[56] | - |
|  | 1.69 (L)[28]<br>0.78 (Ru)[28] | 1.73 (L)[32]<br>0.81 (Pd)[32] | - |
|  | 2.49 (L)[28]<br>1.02 (Ru)[28] | 1.71 (L)[31]<br>0.79 (Pd)[56] | - |
|  | 1.09 (L)[29]<br>0.30 (Ru)[29] | 1.71 (L)[32]<br>0.73 (Pd)[32] | |
|  | 1.67 (L)[29]<br>0.52 (Ru)[29] | 3.05 (L)[33]<br>0.96 (Pd)[33]<br>1.81 (Ru)[33] | 2.68 (L)[35]<br>0.34 (Cu)[35] |

| $R^1$ \ $R^2$ |  |  |  |
|---|---|---|---|
|  | 2.58 (L)[29]<br>0.75 (Ru)[29] | 3.72 (L)[33]<br>1.56 (Pd)[33]<br>2.40 (Ru)[33] | - |
|  | 1.11 (L)[29]<br>0.31 (Ru)[29] | 2.56 (L)[33]<br>0.84 (Pd)[33]<br>1.56 (Ru)[33] | - |
|  | 4.41 (L)[29]<br>1.23 (Ru)[29]<br>0.21 (Cu)[27] | 8.30 (L)[31]<br>0.79 (Pd)[56] | 9.84 (L)[35]<br>2.60 (Cu)[35] |
|  | 2.56 (L)[29]<br>0.76 (Ru)[29] | 3.71 (L)[32]<br>1.70 (Pd)[32] | 4.90 (L)[35]<br>1.15 (Cu)[35] |
|  | 2.87 (L)[29]<br>0.81 (Ru)[29] | 4.59 (L)[32]<br>1.95 (Pd)[32] | - |
|  | 3.13 (L)[29]<br>0.67 (Ru)[29] | 4.78 (L)[32]<br>2.05 (Pd)[32] | |
|  | 3.02 (L)[29]<br>0.74 (Ru)[29] | 4.65 (L)[32]<br>1.99 (Pd)[32] | - |
|  | 3.29 (L)[30]<br>1.65 (Pd)[30] | 2.91 (L)[33]<br>1.23 (Pd)[33]<br>2.04 (Ru)[33] | - |
|  | 5.42 (L)[29]<br>1.39 (Ru)[29] | 4.40 (L)[34]<br>1.16 (Ru)[34] | - |
|  | 2.78 (L)[30]<br>1.15 (Pd)[30] | 2.05 (L)[34]<br>0.61 (Ru)[34] | - |
|  | 5.74 (L)[30]<br>3.06 (Pd)[30] | 4.48 (L)[34]<br>1.43 (Ru)[34] | - |
|  | 6.18 (L)[30]<br>2.65 (Pd)[51] | 5.29 (L)[34]<br>1.40 (Ru)[34] | - |
|  | 5.73 (L)[30]<br>2.41 (Pd)[30] | 4.59 (L)[34]<br>1.19 (Ru)[34] | - |

of the cell membrane.[57] The copper(II) complex of thiophene-2-carboxaldehyde thiosemicarbazone substituted with *N*-methylcyclohexyl amine displayed higher activity, although Ru(II) complex of adamantamine thiophene-2-carboxaldehyde and Pd(II) complexes of 5-nitrothiophene-2-carboxaldehyde thiosemicarbazones substituted with the same amine were also found active. Some other Cu, Pd, and Ru complexes exhibited $IC_{50} < 1$ $\mu$M. In all the thiosemicarbazones and their metal complexes, it was concluded that cyclic amines at the $N^4$ position exhibited better antiamoebic activity than the aryl analogues.

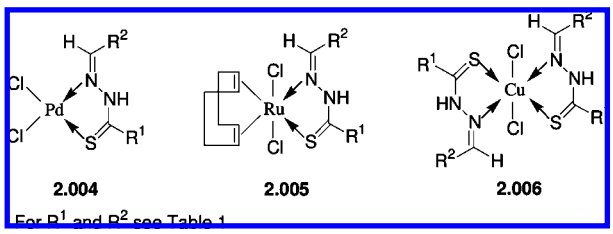



**Figure 2.** Pd(II), Ru(II), and Cu(II) complexes of thiosemicarbazones.

Another series of thiosemicarbazones along with their vanadium complexes was reported by Maurya and coworkers.[58] Reaction of thiosemicarbazide with pyridoxal chloride in methanol gave the respective thiosemicarbazones in 48−53% yield. Dioxovanadium(V) complexes **2.007** of ONS donor pyridoxalthiosemicarbazones with different amines were generated in 14−22% yield (Figure 3), and these complexes were also converted to their $\mu$-oxo binuclear analogues **2.008** in 43−70% yield. All these thiosemicarbazones did not show any activity, whereas their vanadium complexes possess remarkable potencies against *E. histolytica*. Furthermore, $\mu$-oxobis{oxovanadium(V)} complexes ($IC_{50}$ = 0.5−1.9 $\mu$M) showed better activity than the

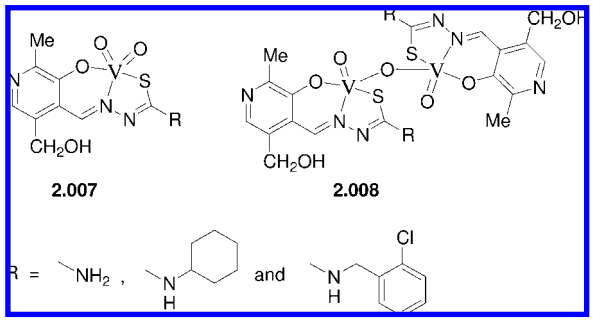
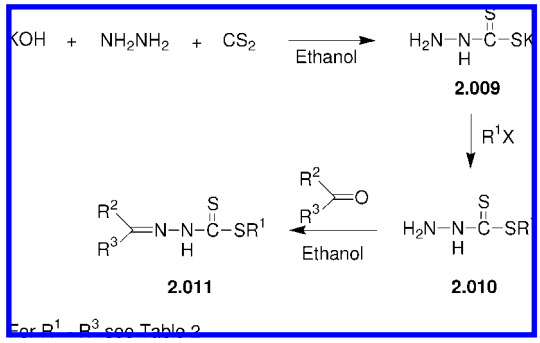



**Figure 3.** Dioxovanadium(V) and $\mu$-oxobis{oxovanadium(V)} complexes of ONS donor pyridoxalthiosemicarbazones.

**Scheme 2. Synthesis of Schiff Bases of *S*-Alkyldithiocarbazates 2.011**



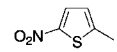
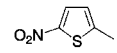
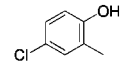
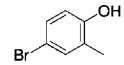
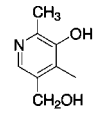
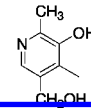

dioxovanadium(V) complexes ($IC_{50} = 0.8-4.1$ $\mu$M). Within this series, some vanadium complexes were found to be remarkably active, and the $\mu$-oxo*bis*{oxovanadium(V)} complex of pyridoxal thiosemicarbazone with cyclohexylamine showed the most promising amoebicidal activity.

## 2.2. Schiff Bases and Their Metal Complexes

Schiff bases derived from *S*-alkyldithiocarbazate with various aromatic aldehydes and ketones display a broad spectrum of potential chemotherapeutic properties including antitumor activity.[59,60] Schiff bases and their metal complexes have experienced long-standing applications in biology and medicine[60−62] as well as in chemical and petrochemical industries.[63,64] Recently, an in vitro insulin mimetic potential of these compounds was reported.[65] A series of Schiff bases **2.011** was prepared by refluxing *S*-alkyldithiocarbazates with heterocyclic aldehydes/ketones in ethanol (Scheme 2).[66−70] Intermediate *S*-alkyldithiocarbazates **2.010** were generated by the reaction of potassium hydroxide, hydrazine hydrate, and carbon disulfide in ethanol followed by the addition of alkyl halide. Dithiocarbazates exhibit thione−thiol tautomerism. However, the existence of a strong band in the region of 1045−1064 $cm^{-1}$ in the IR spectra of **2.011** due to C═S stretching suggested that the thione form is most stable.

Schiff bases of *S*-alkyldithiocarbazates were screened in vitro against *E. histolytica* by using the microdilution method (Table 2).[66−70] Most of the Schiff bases displayed 50% inhibitory concentration at <10 $\mu$M except the pyridoxal Schiff base of *S*-methyldithiocarbazate. Dithiocarbazates containing a sulfur atom showed better biological activity compared to the nonsulfur ON ligands.[71] This is reminiscent of the natural product allicin, a sulfinothioic acid [−S(O)−S−] derivative isolated from garlic (*allium sativum*) and an antimicrobial agent.[72] 2-Acetylpyridine dithiocarbazates were better growth inhibitors as compared to other heterocyclic

**Table 2. In vitro Antimaoebic Activity of Schiff Bases of *S*-alkyldithiocarbazates 2.011**

| $R^1$ | $R^2$ | $R^3$ | $IC_{50}$ (μM) | ref |
|---|---|---|---|---|
| $-CH_3$ |  | $CH_3$- | 1.73 | 66,67 |
| $-CH_2C_6H_5$ |  | $CH_3$- | 1.26 | 66,67 |
| $-CH_3$ |  | H- | 2.26 | 68 |
| $-CH_2C_6H_5$ |  | H- | 1.69 | 68 |
| $-CH_2C_6H_5$ |  | H- | 5.19 | 69 |
| $-CH_2C_6H_5$ |  | H- | 3.57 | 69 |
| $-CH_2C_6H_5$ |  | H- | 4.19 | 69 |
| $-CH_2C_6H_5$ |  | H- | 9.45 | 70 |
| $-CH_3$ |  | H- | 11.05 | 70 |

dithiocarbazates, and the *S*-benzyl analogue exhibited the most promising antiamoebic activity within this series.

Maurya et al. synthesized various dioxovanadium(V) complexes containing an ONS Schiff base, where O is a phenolate, N is an amine, and S is a thiolate function from a ligand system obtained by condensation of *S*-benzyl/*S*-methyldithiocarbazate and pyridoxal/salicylaldehyde.[69,70] Vanadium complexes are of specific physiological interest because of their redox activity ($V^{IV}/V^{V}$); their redox potential can be tuned by the choice of the ligand and set so as to provide redox interaction with oxygen species such as peroxide and superoxide. The superoxide radical anion generated in the process can trigger further physiological changes.[73,74] It was observed that the ligands themselves were inactive whereas the vanadium complexes have some activity. The oxo-bridged binuclear vanadium complex $[\{VO(L)\}_2\mu-O]$ **2.012** (L = pyridoxal *S*-benzyldithiocarbazate) showed better inhibition than metronidazole (Figure 4).

Bharti et al.[66,67] reported a series of Ru(II) and Pd(II) complexes of Schiff bases from 2-acetylpyridine and *S*-alkyldithiocarbazates in 47−69% yield. All the Schiff bases exhibited 50% inhibition concentration in the range of 0.33−0.39 $\mu$g/mL. Two Schiff base metal complexes {Ru(II) and Pd(II) complex of 2-acetylpyridine *S*-benzyldithiocarbazate} **2.013** and **2.014** showed good inhibition against *E. histolytica* (Figure 5). The use of ligands containing a sulfur functionality apparently improves the activity. A similar observation was made for the Pd(II), Pt(II), and Ru(II) complexes of SN donor Schiff bases derived from *S*-alkyldithiocarbazate by Shailendra et al.,[68] compared with the corresponding complexes with ON ligands, suggesting that sulfur plays a general role in activity enhancement.

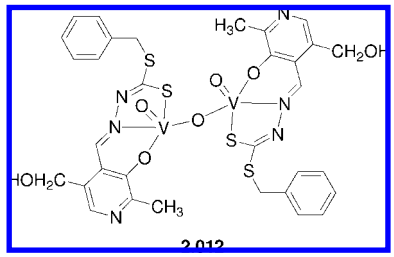


**Figure 4.** Oxo-bridged binuclear vanadium complex [{VO(pydx-sbdt)}$_2\mu$−O].

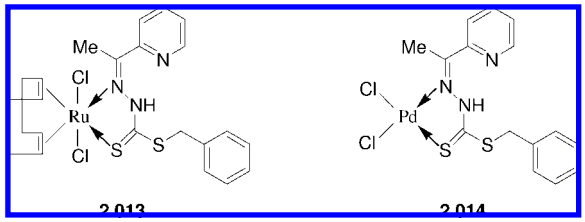
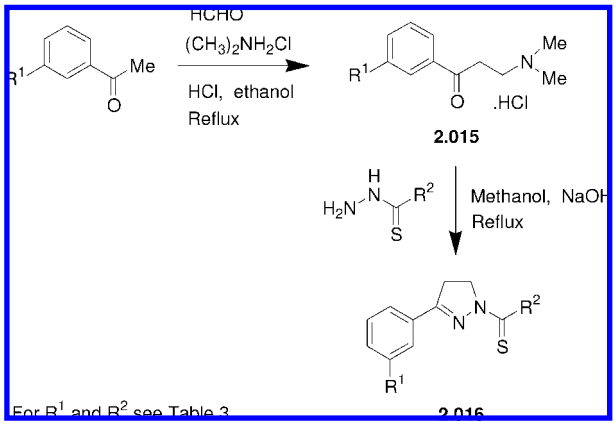


**Figure 5.** Ru(II) and Pd(II) complexes of *S*-benzyldithiocarbazate Schiff bases.

**Scheme 3. Synthesis of 1-Substituted Pyrazoline Analogues 2.016**

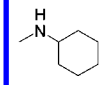
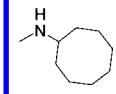
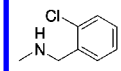
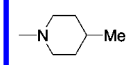
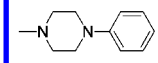
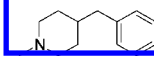


## 2.3. Pyrazolines and Their Metal Complexes

Pyrazoles and their reduced form pyrazolines are well-known nitrogen containing heterocyclic compounds.[75,76] They display a broad spectrum of biological activities.[77−81] Pyrazolines and quinoxalines have been developed as non-steroidal anti-inflammatory drugs and block the formation of prostaglandins.[82,83] Pyrazole metal complexes show extensive coordination chemistry as well as catalytic and biological properties.[84,85] A set of 1-*N*-substituted pyrazoline analogues **2.016** was synthesized by the cyclization of Mannich bases **2.015** with substituted thiosemicarbazides in 9−28% yield (Scheme 3).[86,87] The Mannich bases **2.015** were generated by the reaction of various ketones with formaldehyde and dimethylamine hydrochloride in 42−87% yield.

Screening of pyrazoline derivatives **2.016** against *E. histolytica* revealed that all the 3-bromo- and 3-chlorophenyl substituted cyclized pyrazolines were more active than their respective unsubstituted analogues (Table 3). The cyclized pyrazolines with unsubstituted phenyl rings showed moderate activity. Among all the bromo- and chloro-derivatives, the most active compounds in this class were pyrazolines substituted with *N*-methylbutyl amine, *N*,*N*-diethyl amine, *N*,*N*-dipropyl amine, cyclooctyl amine, *N*-phenylpiperizine, and *N*-benzylpiperizine. The presence of these bulky groups

**Table 3. In vitro Antiamoebic Activity (IC50 in $\mu$M) of Pyrazoline Derivatives 2.016**

| $R^2$ \ $R^1$ | H | Br | Cl | ref |
|---|---|---|---|---|
| -$NHCH_2CH_2CH_3$ | 14.0 | 8.5 | 8.0 | 86 |
| -$NHCH(CH_3)_2$ | 23.0 | 15.2 | 12.2 | 86 |
| -$NHCH_2CH_2CH_2CH_3$ | 23.3 | 14.2 | 12.3 | 86 |
| -$NHCH_2CH(CH_3)_2$ | 11.2 | 6.1 | 5.0 | 86 |
| -$N(CH_3)CH_2CH_2CH_2CH_3$ | 5.7 | 2.4 | 0.7 | 86 |
| -$N(CH_2CH_3)_2$ | 4.2 | 1.2 | 1.0 | 86 |
| -$N(CH_2CH_2CH_3)_2$ | 2.0 | 0.8 | 0.6 | 86 |
|  | 6.5 | 4.2 | 3.7 | 87 |
|  | 5.2 | 3.1 | 2.4 | 87 |
|  | 2.5 | 2.0 | 1.5 | 87 |
|  | 7.6 | 2.6 | 2.2 | 87 |
|  | 4.8 | 3.6 | 2.8 | 87 |
|  | 3.1 | 1.6 | 1.2 | 87 |
|  | 2.3 | 1.4 | 1.0 | 87 |

at position N-1 of thiocarbamoyl group and the substitution of halogen on the phenyl ring at position 3 of the pyrazoline ring greatly enhanced their activity. It is also important to note that substitution of chlorine at the 1-*N*-thiocarbamoyl group does not affect the antiamoebic activity.

Abid and co-workers synthesized a series of 1-*N*-thiocarboxamide-3-phenyl-2-pyrazolines **2.018** by cyclization of Mannich bases **2.017** with unsubstituted thiosemicarbazides in 35−51% yield (Scheme 4).[88] Reaction of **2.018** with 2,3-dichloroquinoxaline afforded 1-(thiazolo[4,5-*b*]quinoxaline-2-yl)-3-phenyl-2-pyrazoline derivatives **2.019** in 41−70% yield.

In this series, 3-bromo- and 3-chlorophenyl substituted pyrazolines **2.018** with 4-methyl substitution on the pyrazoline ring demonstrated good activity (Table 4). The conversion of pyrazoline derivatives **2.018** to quinoxaline derivatives **2.019** enhanced their activity. Among all the quinoxaline derivatives, the compounds having 3-chloro-, 3-bromo-4-methyl, and 3-chloro-4-methyl substitution on the pyrazoline ring were specifically more active. It was concluded once again that the presence of a halogen substituent on the phenyl ring and a 4-methyl group on the pyrazoline ring greatly affects the in vitro antiamoebic activity.

Recently, a series of 1-*N*-substituted thiocarbamoyl-3,5-diphenyl-2-pyrazoline derivatives **2.021** were reported by Budakoti et al. (Scheme 5).[89,90] First, a base-catalyzed Claisen−Schmidt condensation of benzaldehyde with acetophenone produced the chalcone **2.020** (93% yield). Cyclization of **2.020** with various N-4 substituted thiosemi-

**Scheme 4. Synthesis of 1-Thiocarboxamide-3-phenyl-2-pyrazolines 2.019**

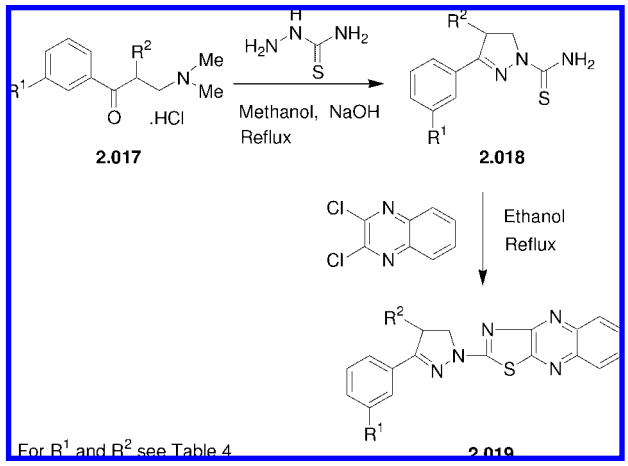
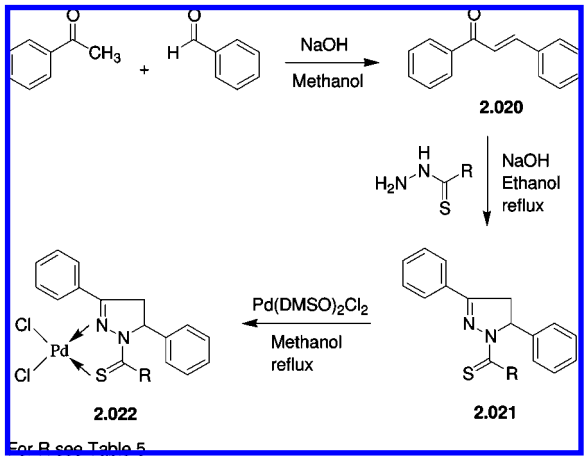



**Table 4. In vitro Antiamoebic Activity of Pyrazoline 2.018 and Quinoxaline 2.019 Derivatives[a]**

| | $IC_{50}$ ($\mu$M) of 2.018 | | $IC_{50}$ ($\mu$M) of 2.019 | |
|---|---|---|---|---|
| $R_1$ | $R^2 = H$ | $R^2 = CH_3$ | $R^2 = H$ | $R^2 = CH_3$ |
| H | 17.2 | 10.2 | 6.76 | 2.34 |
| Cl | 13.2 | 5.9 | 4.98 | 1.45 |
| Br | 8.7 | 4.4 | 1.09 | 0.72 |

[a] Data is taken from ref 88.

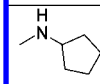
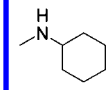
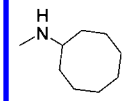
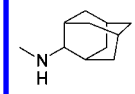
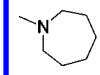
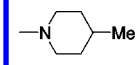
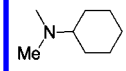
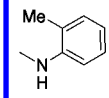
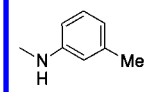
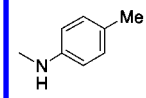
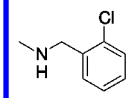
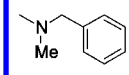
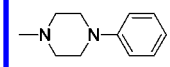
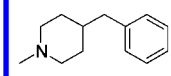
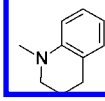
**Scheme 5. Synthesis of 1-Substituted Thiocarbamoyl-3,5-diphenyl-2-pyrazoline Derivatives 2.021 and Their Pd(II) Complexes 2.022**




carbazides gave the desired pyrazoline derivatives **2.021** in 8−24% yield with a wide variety of aliphatic and aromatic amines. The palladium(II) complexes **2.022** were also prepared by mixing an equimolar ratio of pyrazoline **2.021** with $[Pd(DMSO)_2Cl_2]$ in 76−92% yield.

The $IC_{50}$ values of the pyrazolines **2.021** were found to be in the range of 0.38−11.02 $\mu$M (Table 5). The compounds containing a methyl group at the *para*-position were more active compared to the *ortho*- and *meta*-substituted compounds. 4-Methylpiperidine as the 1-*N*-substitution also showed good activity within this series, and some of the Pd(II) complexes **2.022** have better $IC_{50}$ as compared to the reference drug. The presence of bulky groups at position 1-N of the thiocarbamoyl group enhanced activity, and compounds having a methyl group at the *para*-position showed the most promising antiamoebic activity.

**Table 5. In vitro Antiamoebic Activity of Pyrazolines 2.021 and their Pd(II) 2.022 Complexes**

| R | $IC_{50}$ (μM) of 2.021 | $IC_{50}$ (μM) of 2.022 | ref |
|---|---|---|---|
|  | 3.90 | 2.24 | 89 |
|  | 2.23 | 1.44 | 89 |
|  | 2.03 | 0.70 | 89 |
|  | 1.39 | 0.42 | 89 |
|  | 5.34 | 2.08 | 89 |
|  | 2.23 | 0.77 | 89 |
|  | 1.10 | 0.83 | 89 |
|  | 2.70 | 0.90 | 89 |
|  | 4.79 | 4.58 | 90 |
|  | 10.7 | 1.82 | 90 |
|  | 0.38 | 0.05 | 90 |
|  | 11.02 | 1.24 | 90 |
|  | 2.80 | 0.70 | 90 |
|  | 1.80 | 0.76 | 90 |
|  | 1.60 | 0.40 | 90 |
|  | 0.45 | 1.10 | 90 |

## 2.4. Benzimidazoles and Their Metal Complexes

Discovery of 5,6-dimethyl-1-(α-D-ribofuranosyl)benzimidazole, an integral part of the chemical structure of vitamin $B_{12}$, has generated considerable interest in the area of benzimidazole nucleosides and nucleotides.[91,92] Benzimidazole and its derivatives are widely used in searches for new

**Scheme 6. Synthesis of Pyrimidobenzimidazole Derivatives 2.025**

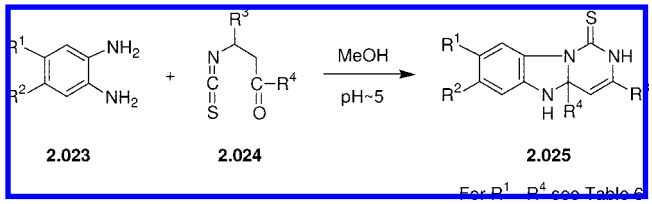



**Table 6. In vitro Antiamoebic Activity of Pyrimidobenzimidazole Derivatives 2.025**

| $R^1$ | $R^2$ | $R^3$ | $R^4$ | $IC_{50}$ ($\mu$M) | ref |
|---|---|---|---|---|---|
| H | H | $CH_3$ | H | 3.56 | 109 |
| H | $CH_3$ | $CH_3$ | H | 2.96 | 109 |
| $NO_2$ | H | $CH_3$ | H | 9.69 | 109 |
| COOH | H | $CH_3$ | H | 2.62 | 109 |
| H | Cl | $CH_3$ | H | 15.61 | 109 |
| $C_6H_5CO$ | H | $CH_3$ | H | 3.99 | 109 |
| $CH_3$ | $CH_3$ | $CH_3$ | H | 1.82 | 109 |
| H | H | H | $CH_3$ | 3.06 | 110 |
| $NO_2$ | H | H | $CH_3$ | 1.21 | 110 |
| $C_6H_5CO$ | H | H | $CH_3$ | 1.39 | 110 |
| H | $CH_3$ | H | $CH_3$ | 2.70 | 110 |
| $CH_3$ | $CH_3$ | H | $CH_3$ | 2.55 | 110 |
| COOH | H | H | $CH_3$ | 1.52 | 110 |

drugs.[93−98] Recently, interest in the synthesis and characterization of transition metal complexes of the benzimidazole ligands has been stimulated as a result of their biological and pharmacological activity.[99−104] Benzimidazoles are commonly synthesized by coupling *o*-phenylenediamine with carboxylic acids.[105] Alternatively *o*-phenylenediamine can be treated with benzaldehydes, followed by cyclization of the intermediate Schiff base in the presence of various oxidants such as nitrobenzene,[105,106] 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,[107] benzofuroxan,[108] and $MnO_2$.[106] Sondhi et al. described one-step synthesis of pyrimidobenzimidazoles (Scheme 6), in which isothiocyanatobutanal **2.024** was condensed with *o*-phenylenediamine **2.023** in refluxing methanol at pH ≈ 5 to give pyrimidobenzimidazole derivatives **2.025** in 18−46% yield.[109,110]

In this series, most of the compounds showed biological activity, and some of them had $IC_{50}$ value comparable to metronidazole (Table 6). Introduction of a benzyl group or a carboxylic acid group at the pyrimidobenzimidazole ring system enhanced their activity considerably. The presence of one methyl group in the pyrimidobenzimidazole ring system had only a slight affect, whereas pyrimidobenzimidazole derivatives with three methyl groups exhibited better activity.

Another series of benzimidazoles was reported by Bharti et al. (Figure 6) along with their vanadium, molybdenum, and tungsten metal complexes.[71,111] 2-(Salicylideneimine)benzimidazole **2.026** was synthesized by mixing equimolar amounts of salicylaldehyde and 2-aminobenzimidazole in refluxing methanol, whereas 2-(α-hydroxyalkyl/aryl)benzimidazoles **2.027**−**2.029** were prepared by refluxing *o*-phenylenediamine and substituted carboxylic acids in 4N HCl followed by neutralization with ammonium hydroxide. Dioxovanadium and dioxomolybdenum complexes were prepared by the reaction of aqueous $KVO_3$/$MoO_3$ solution with the potassium salt of 2-(salicylideneimine)benzimidazole in refluxing methanol, respectively. Reaction of 2-(α-hydroxyalkyl/aryl)benzimidazole with peroxovanadium(V) generated peroxovanadium complexes, whereas similar per-

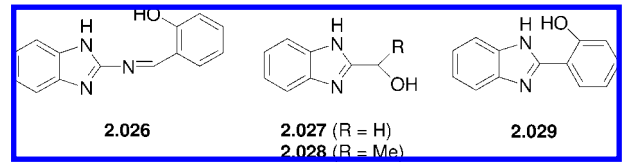



**Figure 6.** Series of benzimidazoles.

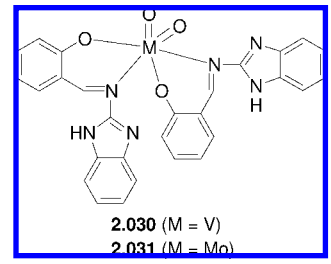
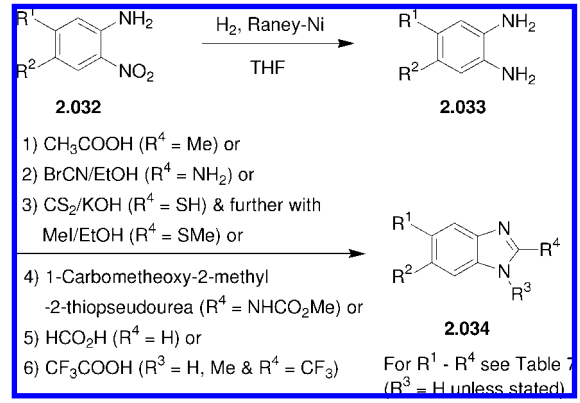



**Figure 7.** Dioxovanadium and dioxomolybdenum complexes of 2-(salicylideneimine) benzimidazole.

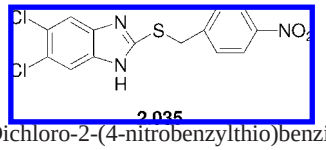
**Scheme 7. Synthesis of Benzimidazole Derivatives 2.034**




oxo complexes of molybdenum and tungsten were prepared by stirring $MoO_3$ or $WO_3 \cdot H_2O$ in aqueous 30% $H_2O_2$ solution with 2-(α-hydroxyalkyl/aryl)benzimidazole in aqueous ethanol. The dioxomolybdenum and dioxotungsten complexes were also isolated by the reaction of $[MoO_2(acac)_2]$ or $[WO_2(acac)_2]$ (acacH = acetylacetone) with 2-(α-hydroxyalkyl/aryl)benzimidazole.

When these compounds were screened for in vitro antiamoebic activity, 10 compounds showed $IC_{50}$ values < 10 $\mu$M and two of them showed values < 3 $\mu$M.[71] All four benzimidazole derivatives **2.026**−**2.029** did not show considerable activity. On the other hand, the biological activity of the dioxovanadium **2.030** and dioxomolybdenum **2.031** complexes of 2-(salicylideneimine)benzimidazole (Figure 7) proved that introduction of a metal to the organic moiety enhanced the activity of the compound, and 50% inhibition was shown at 2.35 and 2.99 $\mu$M, respectively.

Castillo et al. synthesized a series of 25 benzimidazole derivatives from substituted 1,2-phenylamine intermediates **2.033**, prepared by reduction of the corresponding 2-nitroanilines **2.032** with Raney-Ni and $H_2$ in tetrahydrofuran (THF) (Scheme 7).[112,113] The appropriate 1,2-phenylamines **2.033** were converted into their respective benzimidazole derivatives **2.034** by using different reaction conditions: (i) refluxing in acetic acid, (ii) reaction with cyanogen bromide in ethanol, (iii) reaction with potassium hydroxide and carbon disulfide in ethanol followed by the addition of methyl iodide, (iv) reaction with 2-methylthiopseudourea sulfate and methyl chloroformate in aqueous NaOH, (v) refluxing in formic acid, and (vi) reaction with 50% aqueous trifluoroacetic acid.




2.035

**Figure 8.** 5,6-Dichloro-2-(4-nitrobenzylthio)benzimidazole **2.035**.

**Table 7. Antiamoebic Activity of Benzimidazole Derivatives 2.034 ($R^3$ = H Unless Stated)**

| $R^1$ | $R^2$ | $R^4$ | $IC_{50}$ ($\mu$M) | ref |
|---|---|---|---|---|
| H | H | Me | 0.007 | 112 |
| H | H | $NH_2$ | 0.114 | 112 |
| H | H | $NHCO_2Me$ | 0.204 | 112 |
| H | H | SH | 0.133 | 112 |
| H | H | SMe | 0.393 | 112 |
| H | H | H | 0.042 | 112 |
| Cl | H | Me | 0.084 | 112 |
| Cl | H | $NH_2$ | 0.125 | 112 |
| Cl | H | $NHCO_2Me$ | 0.350 | 112 |
| Cl | H | SH | 0.005 | 112 |
| Cl | H | SMe | 0.192 | 112 |
| Cl | H | H | 0.039 | 112 |
| Cl | Cl | Me | 0.025 | 112 |
| Cl | Cl | $NH_2$ | 0.059 | 112 |
| Cl | Cl | $NHCO_2Me$ | 0.046 | 112 |
| Cl | Cl | SH | 0.055 | 112 |
| Cl | Cl | SMe | 0.356 | 112 |
| Cl | Cl | H | 0.096 | 112 |
| H | H | $CF_3$ | 0.069 | 113 |
| Cl | H | $CF_3$ | 0.022 | 113 |
| Cl | Cl | $CF_3$ | 0.011 | 113 |
| H | H | $CF_3$ | 0.0040 ($R^3$ = Me) | 113 |
| Cl | H | $CF_3$ | 0.046 ($R^3$ = Me) | 113 |
| H | Cl | $CF_3$ | 0.008 ($R^3$ = Me) | 113 |
| Cl | Cl | $CF_3$ | 0.033 ($R^3$ = Me) | 113 |

Biological assay results against *E. histolytica* (Table 7) indicate that, with very few exceptions, most of the benzimidazole derivatives **2.034** demonstrated higher activity than metronidazole. Three compounds, 2-methyl-1*H*-benzimidazole, 5-chloro-1*H*-benzimidazole-2-thiol, and 6-chloro-1-methyl-2-trifluoromethyl-1*H*-benzimidazole were found to be 50, 70, and 43 times more potent than metronidazole. The biological activity of the compounds with the 2-methoxycarbonylamino group indicated that large groups at the 5(6)-position drastically decrease the activity against the parasite. It was also noted that benzimidazole derivatives containing a methyl group at the 1-position were found to be as active as with an H atom at that position, suggesting that H at the 1-position is not necessary for antiprotozoal activity.

Recently, Kazimierczuk et al. prepared two series of nitro- and halogen-substituted benzimidazole derivatives by reaction of various substituted benzimidazoles with appropriate halogenoalkylamines in acetonitrile using 1,8-diazobicyclo[5,4,0]undec-7-en as a base.[114] Antibacterial and antiprotozoal activity of the newly obtained compounds were studied, and out of 10 compounds, only 5,6-dichloro-2-(4-nitrobenzylthio)benzimidazole **2.035** (Figure 8) was found to be active against *E. histolytica*.6q

## 2.5. Metronidazole Metal Complexes

Metronidazole (mnz) is a therapeutic agent of choice for amoebiasis[115] and is also used in combination with other antimicrobial drugs against yeast infections.[116] Under anaerobic conditions inside the cell, it is reduced to a cytotoxic nitro radical and binds nonspecifically to the organism's DNA and enzymes, which are thus inactivated.[117−121] High doses or long-term administration of mnz can cause a peripheral neuropathy with sensory disturbances, and the emergence of resistance to this drug is known in many pathogenic bacteria and protozoa.[17] Other available drugs have their own limitations, and today, parasite resistance is also a global problem. Metal based drugs such as Au(I) complexes (e.g., auranofin) have been used successfully for the treatment of various diseases[122−125] including P388 leukemia.[126,127] Many neutral palladium(II) and palladium(IV) complexes were found to exhibit potential antitumor activity.[128,129] Moreover, Ru complexes of chloroquine act as potential antimalarial agents against *P. falciparum*.[130] So it is well-known that coordination of metal ion has a positive effect on drug efficacy.

A series of Pd, Pt, Cu, Au, and Ru complexes of metronidazole was prepared by Bharti and others[131,132] by the reaction of *trans*-$[PdCl_2(DMSO)_2]$, *cis*-$[PtCl_2(DMSO)_2]$, $[Cu(OAc)_2]\cdot H_2O$, $CuCl_2\cdot 2H_2O$, $[Au(PPh_3)Cl]$, and $RuCl_3\cdot 3H_2O$ with metronidazole, which led to the formation of *trans*-$[PdCl_2(mnz)_2]$ **2.036**, *trans*-$[PtCl_2(mnz)_2]$ **2.037**, *trans*-$[Cu_2(OAc)_4(mnz)_2]$ **2.038**, $[Cu(mnz)_2(\mu\text{-}Cl)(H_2O)]_2Cl_2$ **2.039**, $[Au(PPh_3)(mnz)]PF_6$ **2.040**, and $[Ru(mnz)_2(Cl)_2(H_2O)_2]$ **2.041**, respectively, in 52−80% yield. X-ray crystallographic studies showed that the first two complexes, *trans*-$[PdCl_2(mnz)_2]$ **2.036** (Figure 9) and *trans*-$[PtCl_2(mnz)_2]$ **2.037** (Figure 10), were isostructural and exhibited similar unit-cell volumes. Both of these complexes were centrosymmetric, and the metal ions have *trans* geometries. The central atoms Pd and Pt have ideal square-planar coordination geometry with M−N and M−Cl distances, and the imidazole rings form dihedral angles with the Cl−M−Cl plane for Pd and Pt metronidazole complexes.

The copper complex $[Cu_2(OAc)_4(mnz)_2]$ **2.038** (Figure 11) in the presence of acetate forms a dimer through Cu−Cu interaction and four bridging $\mu_2$-acetato ligands. The structure was centrosymmetric with the Cu-centers forming distorted octahedral coordination geometry. This distortion occurs in the equatorial positions occupied by the bridging acetate ligands whose donor groups were not sufficiently separated to span the Cu−Cu bond and form ideal octahedral geometry. The second Cu complex $[Cu(mnz)_2(\mu\text{-}Cl)(H_2O)]_2Cl_2$ **2.039** (Figure 12) consists of a dimer, where two monomeric, centered Cu-atoms were connected by two $\mu$-bridged Cl ligands. The asymmetric unit was composed of one-half of a molecule with a center of symmetry, about which the whole molecule was generated, being at the midpoint between the two Cu atoms. Each Cu center is five-coordinated and bonded, in addition to the two Cl atoms, to two metronidazole ligands, as well as to one $H_2O$ molecule.

The in vitro activity of complexes **2.036**−**2.041** displayed that the ratio of $IC_{50}$ of all complexes to mnz were 4- to 18-fold, which indicated that the complexes were far more active than metronidazole (Table 8). The percent inhibitions for the Pd, Pt, Cu, Au, and Ru complex precursors were also determined to establish that these metal complex precursors have no activity against *E. histolytica*. The studies showed that inhibition was mostly due to the presence of metal complexed metronidazole. The copper and palladium mnz complexes were considerably superior to others and demonstrated higher activity, which proved the fact that metal incorporation enhances the drug activity.

Bharti et al.[131] reported the in vivo antiamoebic activity of metronidazole metal complexes *trans*-$[PdCl_2(mnz)_2]$ **2.036**, *trans*-$[PtCl_2(mnz)_2]$ **2.037**, and *trans*-

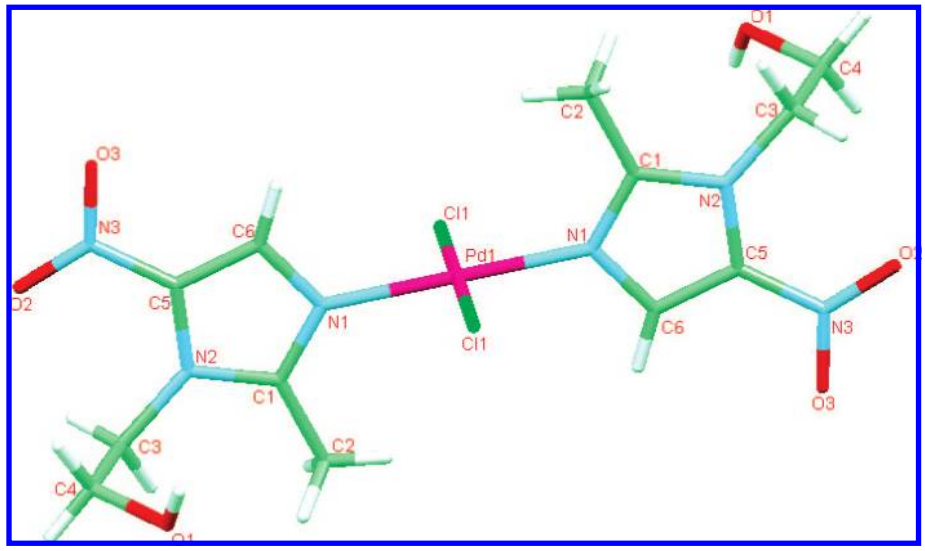



**Figure 9.** Molecular structure of $[PdCl_2(mnz)_2]$ **2.036**. This figure was generated from data downloaded from the Cambridge Crystallographic Database as originally published in ref 131.

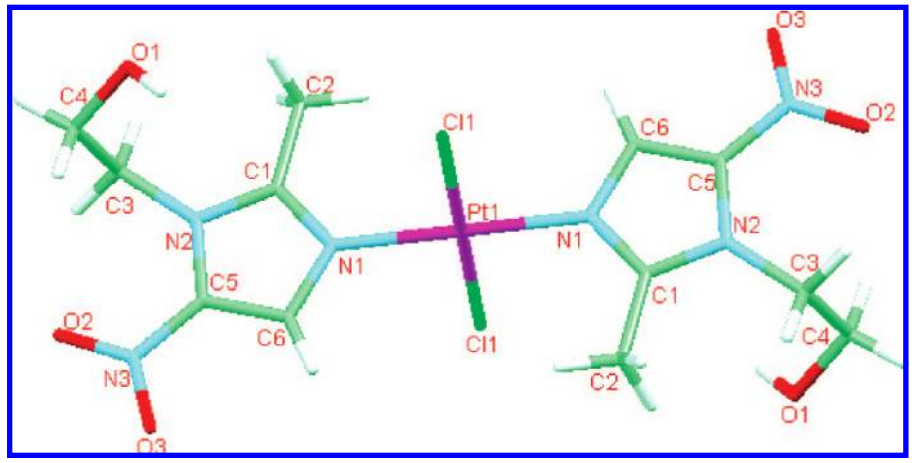



**Figure 10.** Molecular structure of *trans*-$[PtCl_2(mnz)_2]$ **2.037**. This figure was generated from data downloaded from the Cambridge Crystallographic Database as originally published in ref 131.

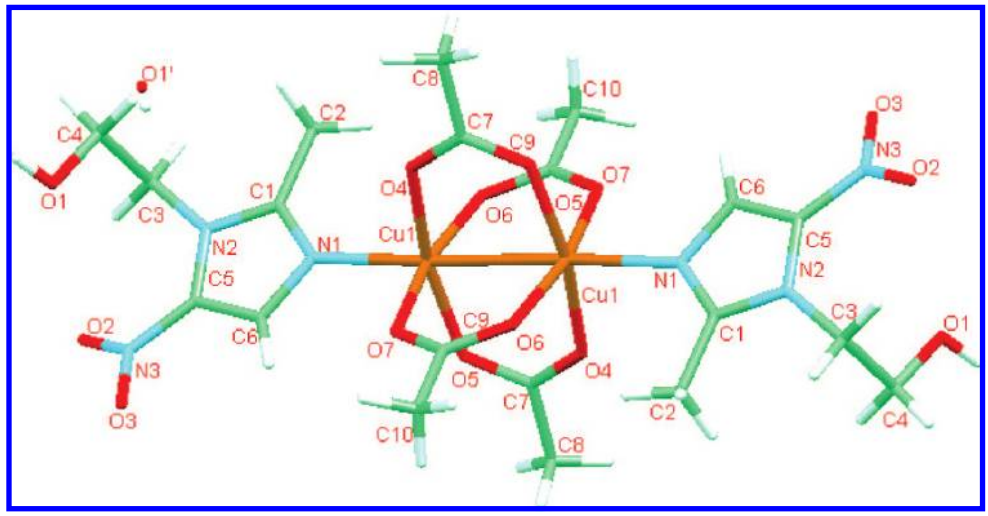



**Figure 11.** Molecular structure of $[Cu_2(OAc)_4(mnz)_2]$ **2.038**. This figure was generated from data downloaded from the Cambridge Crystallographic Database as originally published in ref 131.

$[Cu_2(OAc)_4(mnz)_2]$ **2.038** in male golden hamsters infected by amoeba to produce a systematic experimental amoebic hepatic abscess (EAHA). All compounds were administered orally, and their effectiveness was determined as the proportion of score reduction relative to untreated controls. Treatment with 0−30 mg/kg of complexes **2.036**−**2.038** and mnz for 5 days of administration did not show a clear dose-dependent effect, while the same treatment for 10 days produced a reduction of 71−92% (**2.036**), 49−71% (**2.037**), 58−86% (**2.038**), and 40−58% (mnz) in the EAHA score.

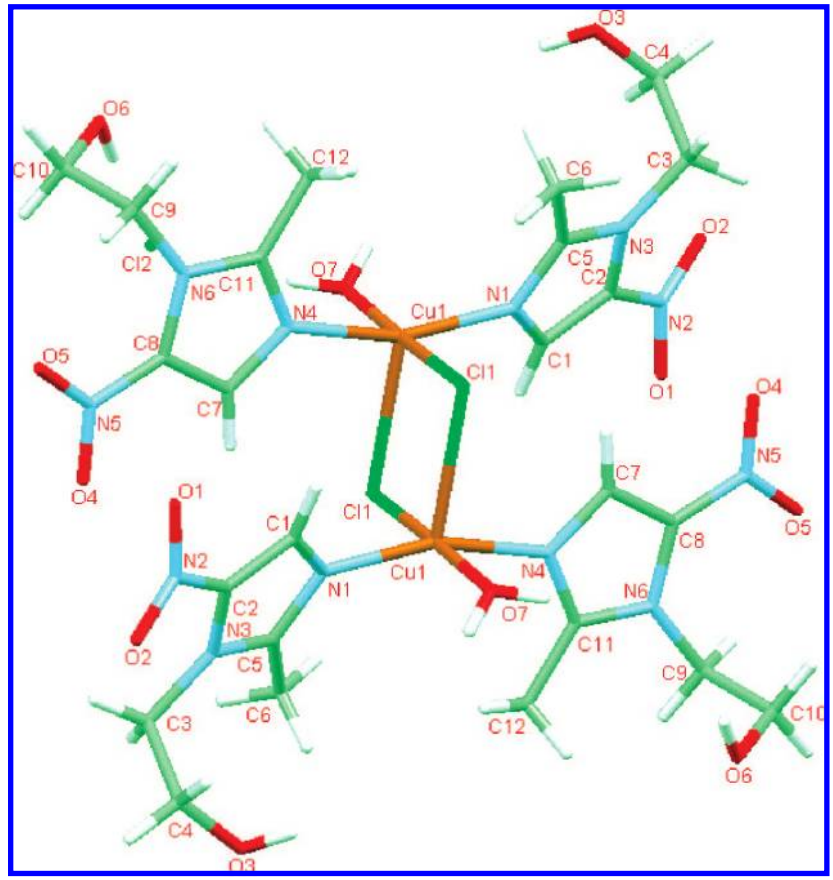



**Figure 12.** Molecular structure of $[Cu(mnz)_2(\mu\text{-}Cl)(H_2O)]_2Cl_2$ **2.039**. This figure was generated from data downloaded from the Cambridge Crystallographic Database as originally published in ref 132.

**Table 8. In vitro Antiamoebic Activity of Metronidazole Metal Complexes 2.036−2.041**

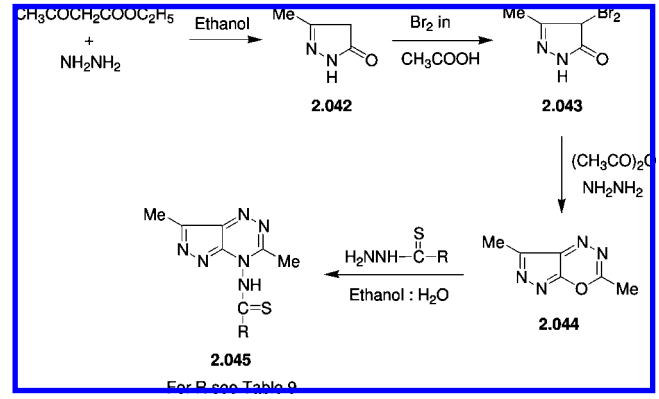
| compound no. | $IC_{50}$ ($\mu$M) | ref |
|---|---|---|
| **2.036** | 0.10 | 131 |
| **2.037** | 0.20 | 131 |
| **2.038** | 0.11 | 131 |
| **2.039** | 0.10 | 132 |
| **2.040** | 0.32 | 132 |
| **2.041** | 0.51 | 132 |
| metronidazole | 1.81 | 131, 132 |

At 10 mg/kg dose, all the compounds produced an effect quantitatively comparable with that produced by 30 mg/kg of mnz. Compound **2.036** at 5 mg/kg produced a reduction in EAHA that was slightly higher (4%) than the effect of 30 mg/kg of mnz. These results clearly demonstrated that the metronidazole−metal complexes were potent inhibitors of *E. histolytica* both in vitro and in vivo.

## 2.6. Triazines

1,2,4-Triazines are a well-known class of heterocyclic compounds and display significant biological activity especially with condensed heterocyclic systems.[133−136] Pyrimidine nucleic bases containing triazines show interesting properties;[137−139] for example, azacytidine, a synthetic triazine analogue of cytidine, shows strong antileukemic activity.[140,141] PS-15, a prodrug of diaminotriazine, is active against resistant malarial strains.[142] Moreover, triazine derivatives are cytotoxic to parasites since they offer excellent selectivity between parasites and host cells.[143−145] A series of triazine derivatives was reported by Singh et al. by the synthetic route shown in Scheme 8.[146] Treatment of ethyl

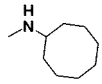
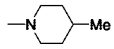
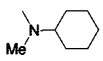
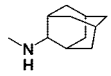
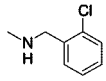
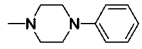
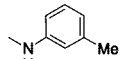
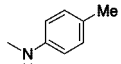
**Scheme 8. Synthesis of Triazine Derivatives 2.045**




acetoacetate with hydrazine hydrate gave 3-methyl pyrazol-5-one **2.042**; further bromination and subsequent cyclization with acetic anhydride and hydrazine hydrate generated 3,7-dimethylpyrazolo[4,3]oxadiazine **2.044**, which on reaction with substituted thiosemicarbazides afforded the target 3,7-dimethylpyrazolo[3,4-*e*][1,2,4]triazin-4-yl thiosemicarbazide derivatives **2.045** in 35−65% yield.

3,7-Dimethylpyrazolo[3,4-*e*][1,2,4]triazin-4-yl thiosemicarbazide derivatives **2.045** were synthesized with a wide range of aliphatic and aromatic amines and screened against *E. histolytica* (Table 9). Compounds substituted with aliphatic amines did not show any biological activity, while good activities were observed for the triazine derivatives bearing cyclic and aromatic amines. Out of 20 triazine derivatives, the two compounds having cyclooctyl and adamantamine amines at $N^4$ position demonstrated potent antiamoebic activity compared to metronidazole.

**Table 9. In vitro Antiamoebic Activity of Triazine Derivatives 2.045**[a]

| R | $IC_{50}$ (μM) | R | $IC_{50}$ (μM) |
|---|---|---|---|
| -NHCH(CH$_3$)$_2$ | 5.62 | -N(CH$_2$CH$_3$)$_2$ | 7.31 |
| -NHCH$_2$CH$_2$CH$_2$CH$_3$ | 6.20 | -NHCH$_2$CH(CH$_3$)CH$_3$ | 4.84 |
| -N(CH$_3$)CH$_2$CH$_2$CH$_2$CH$_3$ | 5.02 | -N(CH$_2$CH$_2$CH$_3$)$_2$ | 5.44 |
|  | 1.96 |  | 1.28 |
|  | 0.81 |  | 2.09 |
|  | 2.36 |  | 2.04 |
|  | 4.19 |  | 3.92 |
|  | 0.84 |  | 1.41 |
|  | 4.18 |  | 2.27 |
|  | 1.85 |  | 2.04 |

[a] Reprinted with permission from ref 146. Copyright 2005 Elsevier Science Ltd.

## 2.7. Oxime Ethers

Oxime ether derivatives exhibit interesting biological activity.[147−151] For example, indene-substituted oxime ethers have been used as germicides and insecticides,[152] and *o*-(phenyl/heterocyclyl)methyl oxime ethers function as insecticides and nematocides.[153] Oxime ethers also inhibit both EGFR and HER2 tyrosine kinases.[154] Erythromycin A oxime ether displayed higher antibacterial activity than erythromycin A.[155] Oxime ethers can be prepared by (i) intermolecular electrophilic O-amination of aliphatic alcohols,[156] (ii) radical alkylation of nitro compounds,[157] and (iii) Pd catalyzed O-allylic substitution of oximes[158] and may be utilized to synthesize tricyclic heterocycles,[159] dihydrobenzofurans, and benzofurans.[160] Abid and co-workers synthesized a series of oxime ethers as shown in Scheme 9 in 68−73% yield by condensing 2-acetylpyridine/2-acetylfuran with hydroxylamine hydrochloride in refluxing ethanol and pyridine (2:1) mixture.[161] O-Alkylation of oximes **2.046** with hydrochloride salts of 2-chloroethylamine, 2-(dimethylamino)ethyl chloride, 2-(diisopropylamino)ethyl chloride, 1-(2-chloroethyl)pyrrolidine, 1-(2-chloroethyl)piperidine, and 4-(2-chloroethyl)morpholine with sodium methoxide in refluxing methanol generated the corresponding oxime ether derivatives **2.047**. Treatment of oxime ethers with hydrogen chloride gas in methanol produced the hydrochloride salt of oxime ether derivatives **2.048** in 39−73% yield.

These oxime ethers with different alkyl groups were screened against *E. histolytica* in order to establish the contribution of the type and size of the substituted groups on antiamoebic activity (Table 10). Biological activity of oxime ethers with unsubstituted and *N,N*-disubstituted amino groups showed that compounds containing piperidine and morpholine only were active. Oxime ether derivatives having a bulkier group demonstrated better activity, while with aliphatic amines they were inactive.

**Scheme 9. Synthesis of Oxime Ethers 2.048**

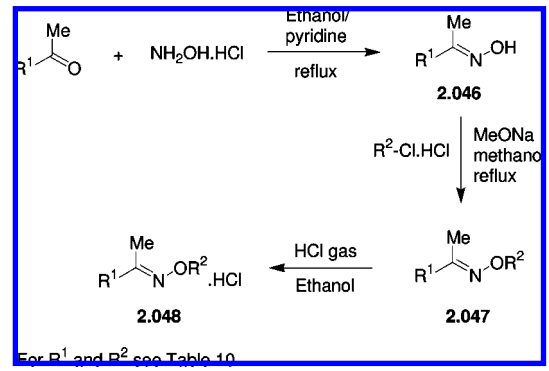
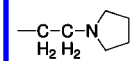
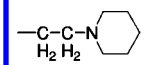
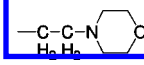



**Table 10. In vitro Antiamoebic Activity ($IC_{50}$ in μM) of Oxime Ether Derivatives 2.048**[a]

| R$^2$ \ R$^1$ |  |  |
|---|---|---|
| -CH$_2$CH$_2$NH$_2$ | 14.7 | 17.2 |
| -CH$_2$CH$_2$N(CH$_3$)$_2$ | 10.3 | 13.4 |
| -CH$_2$CH$_2$N(iPr)$_2$ | 7.4 | 8.1 |
|  | 2.2 | 2.5 |
|  | 1.4 | 1.7 |
|  | 0.5 | 0.6 |

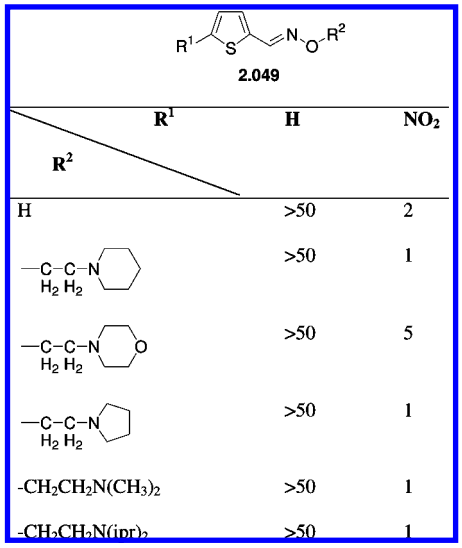
[a] Data is taken from ref 161.

Delmas et al. also reported various oxime ether derivatives from thiophene-2-carboxaldehyde or 5-nitrothiophene-2-carboxaldehyde in 52−90% yield.[162] The oximes were obtained by refluxing 2-formylthiophene/5-nitrothiophene with hydroxylamine hydrochloride in ethanol/pyridine mixture. Oxime ether derivatives **2.049** were generated by the condensation of aldoximes with the corresponding chloroethylamine in the presence of sodium methoxide. These oxime ether derivatives **2.049** were tested in vitro against different protozoa parasites, but only nitro derivatives exhibited antiamoebic activity against *E. histolytica* (Table 11). Concerning the nature of the amine in the 2-aminoethoxyiminomethyl-5-nitrothiophene series, the presence of an aliphatic chain was superior to a cyclic amine. The oxime ether derivative substituted with an *N*-diisopropylamino group was found to be most potent against the protozoa parasites.

## 2.8. Acetamides

Acetamides act as positron emission tomography ligands to image the peripheral-type benzodiazepine receptor[163] and are potent antagonists of different receptors.[164−166] Acetamides are also used in the treatment of obesity[167] and inflammation-mediated diseases.[168] Cozzi and co-workers[169] synthesized a series of *N*-(2-ethoxyethyl)-*N*-(4-phenoxybenzyl)dichloroacetamide derivatives in which the diphenylether

**Table 11. Antiamoebic Activity (MIC in μg/mL) of Oxime Ethers 2.049[a]**




[a] Data is taken from ref 162.

moiety was replaced by diphenylthioether, diphenylmethane, benzophenone, biphenyl, and 4-pyridylphenylether moieties (Scheme 10). Acylation of secondary amines **2.050** with dichloroacetylchloride in dichloroethane with 1N NaOH produced **2.051**, while reduction with aqueous $TiCl_3$ or with $Fe/NH_4Cl$ gave **2.052**. Compounds **2.053** ($R^1$ = H and Cl) were prepared from corresponding **2.052** via intermediate diazo derivatives by a Sandmeyer reaction. The remaining compounds **2.053** were generated using different procedures depending on the group $R^1$.[169]

In vitro biological activity against *E. histolytica* was expressed as the minimal inhibitory concentration (MIC) in μg/mL (Table 12). In dichloroacetamides **2.053**, more than 25 derivatives were prepared with different substituents, and simple observations were made regarding structure−activity relationship. A nitro group on the diphenylether moiety is not essential to achieve high activity, unlike with oxime ethers. Acylamino radicals could replace the nitro group and gave activity equivalent to or even better than the reference drug etofamide. Unsubstituted ($R^1$ = H) or presence of a lipophilic chloro group reduced the activity of dichloroacetamide derivatives. Replacement of the 4-$NO_2$-phenoxy with a 4-pyridyloxy group also caused a significant reduction in the activity. In this series, it appears that the presence of the dichloroacetamide residue is essential for antiamoebic activity since the hydroxyacetamido analogue is inactive. For the role of group $R^2$ in general dichloroacetamides, no clear conclusion was drawn, but diphenylthioether and diphenyl derivatives displayed less activity compared to the compounds having diphenylether, diphenylmethane, and benzophenone moieties. Slight variations in the *N*-(2-alkoxyethyl) chain did not influence the activity, since the minimal inhibition concentration of *N*-(2-methoxyethyl)-*N*-[4-(aminophenoxy-)benzyl]dichloroacetamide was practically the same as that of the corresponding *N*-(2-ethoxyethyl) derivatives.

Kalyanam et al.[170] prepared a series of dichloroacetamides of 1,5-benzodiazepinones and tetrahydroquinoxalinones. 5-(2,2-Dichloroacetyl)-1,3,4,5-tetrahydro-benzo[*b*][1,4]diazepin-2-one **2.054** (Figure 13) displayed notable activity in this series against luminal amoebiasis. Compound **2.054** showed 100% curative activity at a minimum dose of 10 mg/kg compared to the reference drug quinfamide (0.8 mg/kg),[171] and therefore, **2.054** was less active than quinfamide against luminal infections of *E. histolytica*. In this series, none of the compounds were found to be active against invasive amoebiasis.

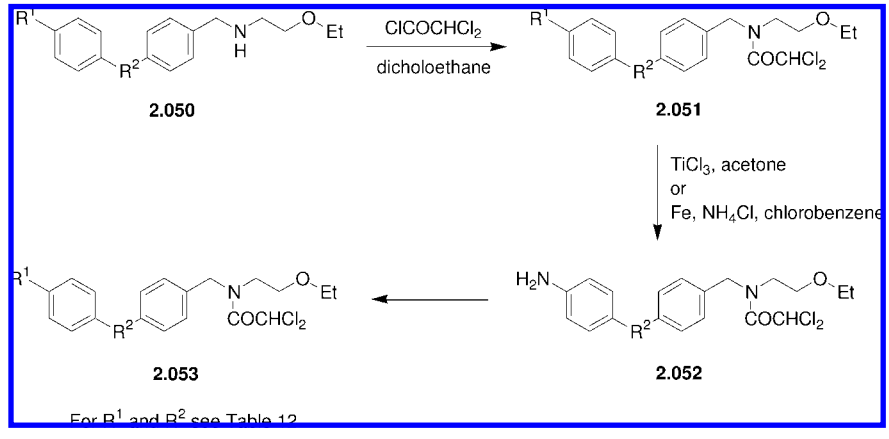
A series of 56 furylhaloacetamides was synthesized by chloroacetylation of the respective furfurylamines by Shridhar et al.[172] and tested in vitro for their antiamoebic activity. 2-Chloro-*N*-(5-chloro-furan-2-ylmethyl)-*N*-ethylacetamide **2.055** (Figure 14) had in vitro activity comparable to metronidazole but was found to be inactive when tested in vivo.6q

## 2.9. Carbamates

Carbamates received special attention because of their reactivity and synthetic methodologies, applications over the years, and new contributions that are available.[173,174] The carbamate group has reasonable chemical and biological stability and multiple applications as a protective group for the amine function of amino acids in peptide chemistry.[174−182] They are also valuable intermediates in the synthesis of polyurethanes.[183,184] Some important synthetic methods include the reaction of carbamoyl chloride with an alcohol or metal alkoxide, the reaction of cyanogen chloride or cyanic acid with an alcohol, the reaction of a chloroformate with ammonia, the reaction of amide with lead tetraacetate, the reductive carbonylation of aromatic nitro compounds, and the reaction of carbon dioxide with amines, etc.[173,185]

Ordaz-Pichardo and co-workers prepared a set of carbamates **2.056** in 46−95% yield by the reaction of aryl- and

**Scheme 10. Synthesis of Dichloroacetamides 2.053**



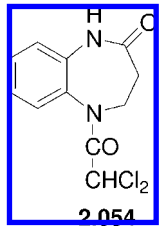
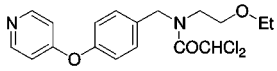
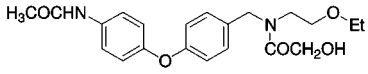
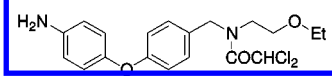



**Figure 13.** 5-(2,2-Dichloroacetyl)-1,3,4,5-tetrahydro-benzo[*b*][1,4]diazepin-2-one **2.054**.

**Table 12. Antiamoebic Activity of Dichloroacetamides 2.053**[a]

| $R^1$ | $R^2$ | MIC (μg/mL) |
|---|---|---|
| H | O | 0.096 |
| Cl | O | 0.269 |
| $OCH_3$ | O | 0.059 |
| $CH_3SO_2$ | O | 0.037 |
| $NH_2$ | O | 0.059 |
| HCONH | O | 0.037 |
| $CH_3CONH$ | O | 0.013 |
| $CH_3CH_2CONH$ | O | 0.020 |
| t-Bu-CONH | O | 0.022 |
| $CF_3CONH$ | O | 0.051 |
| PhCONH | O | 0.029 |
| Z-Gly-NH | O | 0.081 |
| Gly-NH | O | 0.024 |
| (L) Norv-NH | O | 0.027 |
| (L) Met-NH | O | 0.027 |
| $CH_3CH_2OCONH$ | O | 0.046 |
| $H_2NCONH$ | O | 0.020 |
| $CH_3CH_2OCONH$ | O | 0.038 |
| $NH_2$ | S | 0.240 |
| $NH_2$ | Direct linkage | 0.240 |
| $NH_2$ | CO | 0.037 |
| $NH_2$ | $CH_2$ | 0.027 |
| $CH_3CONH$ | $CH_2$ | 0.220 |
| $H_2NCONH$ | $CH_2$ | 0.220 |
|  | | 0.090 |
|  | | 20.0 |
|  | | 0.065 |

[a] Reprinted with permission from ref 169. Copyright 1983 Elsevier Science Ltd.

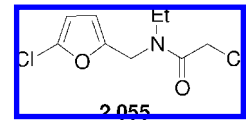



**Figure 14.** 2-Chloro-*N*-(5-chloro-furan-2-ylmethyl)-*N*-ethylacetamide **2.055**.

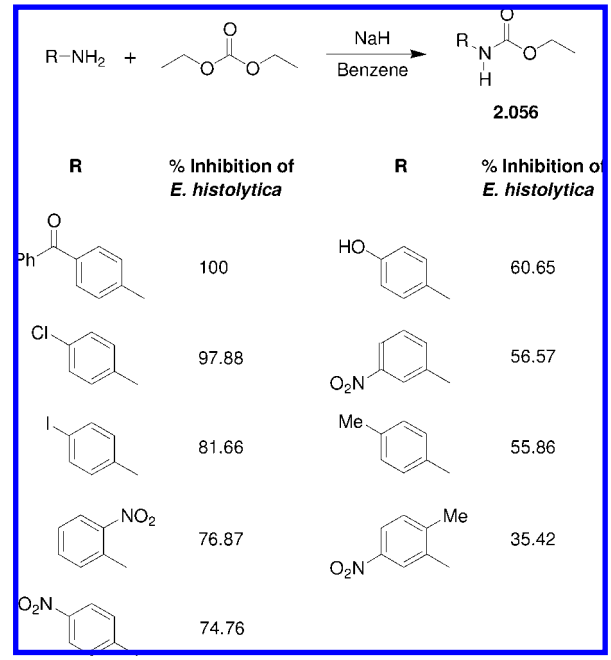



**Figure 15.** Set of carbamates **2.056** in 46−95% yield prepared by the reaction of aryl- and alkylamines with diethylcarbonate.

alkylamines with diethylcarbonate[186] and reported their antiamoebic activity on trophozoites of *E. histolytica* (Figure 15).[187] Trophozoites were treated with 100 $\mu$g/mL of the compound and compared with the control without drug in vitro. Two compounds demonstrated considerable activity, whereas the remainders have no significant effect after 48 h. In vivo studies were done using amoebic liver abscess in hamster model and doses of 75 and 100 mg/100 g of body weight for ethyl 4-chlorophenyl carbamate, which reduced the extent of the amoebic liver abscess by 84 and 94%, respectively. This compound was selected for further studies and was found to be nontoxic for cultured rat hepatic cells.

## 2.10. Amidines

Amidines display a large variety of biological properties[188−191] and are utilized as precursors in many heterocyclic syntheses.[192−195] Metal complexes of amidines with a 1,2,4-triazole ring display low-temperature molecular ferromagnetics.[196] Further bicyclic amidines have been identified as highly active acylation catalysts.[197] Venugopalan et al. synthesized various substituted diphenyl bisamidines **2.059** by the reaction of substituted benzidines **2.057** with pyrrolidines **2.058** at 100 °C in the presence of $POCl_3$ with 10−52% yields (Scheme 11).[198] The substituted pyrrolidones **2.058** were prepared earlier by other research groups.[199−201] Michael addition of the carbanions, generated from nitro alkanes with acrylate in the presence of Triton B, gave the adducts that underwent catalytic reduction in the presence of Raney Ni in ethanol followed by heating at 50 °C, to yield the substituted pyrrolidones **2.058**.

When the diphenyl bisamidines were initially tested for their in vitro activity against *E. histolytica* using a polyxenic

**Scheme 11. Synthesis of Diphenyl Bisamidines 2.059**

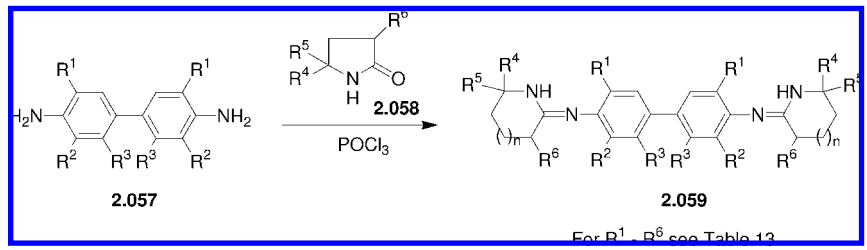



**Table 13. in Vitro and In Vivo Antiamoebic Activity of Diphenyl Bisamidines 2.059 ($R^{2-6}$ = H unless stated)**

| | | | in vitro | in vivo | |
|---|---|---|---|---|---|
| $R^1$ | $R^{2-6}$ | *n* | MIC ($\mu$g/mL) | extra intestinal (hepatic) (mg/kg × 4 per os) | intestinal (caecal) (mg/kg × 4 per os) |
| Cl | H | 0 | 75 | 82[b] | 200[c] |
| Cl | H | 1 | 200 | 100[b] | 100[c] |
| OMe | H | 0 | 200 | 150[a] | NT |
| OMe | H | 1 | 200 | 150[a] | NT |
| Me | H | 1 | 200 | 150[a] | NT |
| Br | H | 0 | 100 | 150[a] | 300 |
| Br | H | 1 | 200 | 150[a] | 300[a] |
| Br | H | 2 | 200 | 150[a] | NT |
| F | H | 0 | 100 | 28[b] | 125[b] |
| F | $R^4$ = Me | 0 | 200 | 31[b] | 150[b] |
| F | $R^{4-6}$ = Me | 0 | 100 | 150[a] | NT |
| F | $R^4$ = Et | 0 | 100 | 39[b] | 200[c] |
| $NO_2$ | H | 0 | 100 | 37[b] | 150[c] |
| Cl | $R^4$=Me | 0 | 100 | 100[a] | NT |
| H | $R^3$=F | 0 | 200 | 100[a] | NT |
| Cl | $R^2$ = Cl | 0 | 200 | 100[a] | NT |
| Me | $R^2$ = Me | 1 | 200 | 100[a] | NT |

[a] Highest dose tested and was inactive. [b] Approximate $ED_{50}$. [c] 100% effective dose. (Reprinted with permission from ref 198. Copyright 1996 Elsevier Science Ltd.)

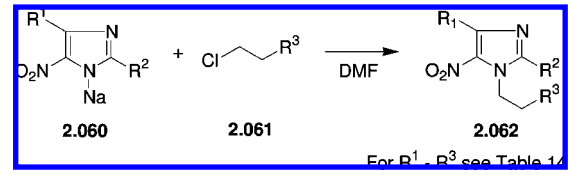
culture, they displayed inhibition in the range of 75−200 $\mu$g/mL, which was less pronounced than that of the reference drugs (Table 13). Out of the compounds tested in this series using golden hamsters and Wistar rats, only six diphenyl bisamidines displayed activity, and one compound, 3,3′-difluoro-*N*$^4$,*N*$^{4'}$-dipyrrolidin-2-ylidene-biphenyl-4,4′-diamine ($R^1$ = F, $R^{2-6}$ = H, and *n* = 0), was the most effective. This compound showed in vitro activity at 100 $\mu$g/mL and displayed excellent in vivo activity against hepatic infection in the hamster. The $ED_{50}$ value of this amidine derivative was comparable to metronidazole and diloxanide furoate with respect to both hepatic and cecal amoebiasis.

A series of amidines and sulfonamides of 5- and 6-amino-2,3-*bis*(4-alkyl-1-piperazinyl)quinoxalines were synthesized by Fabio et al.[202] and tested against ceacal and hepatic forms of *E. histolytica* infections in rats and hamsters, respectively. Some compounds were found to have acceptable activity against infections but were too toxic to be considered for further biological studies.

## 2.11. Imidazoles

The imidazole ring can be found in important biological components such as histidine and histamine as well as in many drugs including antifungal agents and nitroimidazoles.[203−206] Giraldi et al.[207,208] synthesized a series of *N*-alkylaminonitroimidazoles **2.062** by refluxing the sodium salt of nitroimidazoles **2.060** with N-substituted aminoethyl chlorides **2.061** in 35−89% yields (Scheme 12). Two possible isomeric

**Scheme 12. Synthesis of *N*-Alkylaminonitroimidazoles 2.062**




products 1-aminoalkyl-5(4)-nitroimidazoles were obtained and examined for their antiamoebic activity.

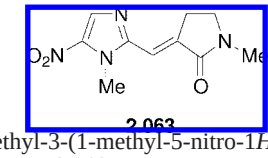
From the biological data summarized in Table 14, it was noted that, with the same group $R^3$ present in the nitroimidazole ring, the compounds with an unsubstituted position 2 displayed higher activity than the compounds with a methyl group at the same position. 5-Nitroimidazoles show a much higher activity than 4-nitroimidazoles with the same aminoalkyl group at position 1, but in the case of styrylimidazoles, higher activity was observed with the nitro group at position 4. Under the influence of different groups at position 1 for both pairs of isomers, the biological activity was generally observed to be in the following order: pyrrolidine > piperidine > diethylamine > morpholine. Some *N*-alkylaminonitroimidazoles showed very interesting biological activity, and the introduction of a styryl group in the imidazole ring showed enhancement of the antiamoebic activity of these nitroimidazoles.

Upcroft et al. prepared a set of 13 5-nitroimidazoles by using the literature procedures and tested them against 3 protozoan parasites including *E. histolytica*.[209] One of the compounds, 1-methyl-3-(1-methyl-5-nitro-1*H*-imidazol-2-ylmethylene)pyrrolidin-2-one **2.063**, was found to be active (minimum lethal concentration > 5 $\mu$M) against *E. histolytica* (Figure 16).

## 2.12. Bisphosphonates

Recently, Ghosh et al. studied a series of 102 bisphosphonates and their effect on the growth inhibition of *E. histolytica* and *P. falciparum*.[210] Eubank and Reeves discovered that hydrolytically stable analogues of pyrophosphonates and bisphosphonates had activity against *E. histolytica* and proposed that these compounds inhibited the parasite pyrophosphate dependent phosphofructokinase (PFK).[211] More recently, several nitrogen containing bisphosphonates were found to be potent, nanomolar inhibitors of the enzyme farnesypyrophosphate synthase (FPPS).[212−218] Various types of bisphosphonates like 1-hydroxy-1,1-bisphosphonates, 1,2-bisphosphonates, aminomethylene bisphosphonates, alkyl or arylaminoethylene bisphosphonates, and bisphosphonate ethyl esters have been synthesized by different reported methods as shown in Scheme 13.[210]

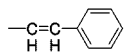
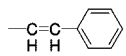
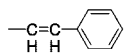
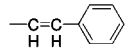
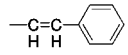
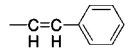
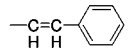
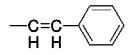
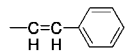
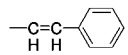
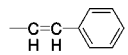
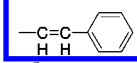
Among 102 compounds of this series, 47 were reported to be active against *E. histolytica* in vitro, as shown in Figure 17. Pyridyl aminomethylene bisphosphonates exhibited interesting growth-inhibition results. Nitrogen containing




2.063

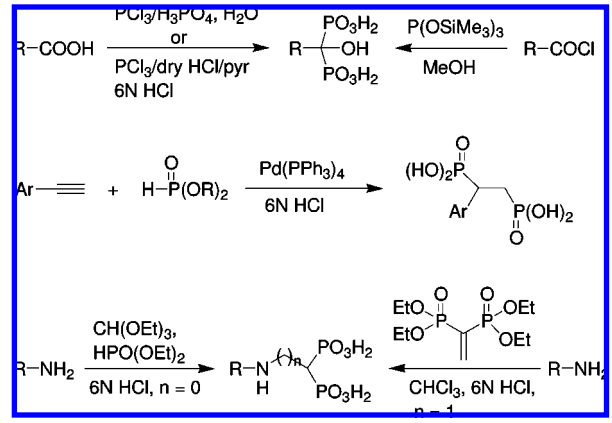
**Figure 16.** 1-Methyl-3-(1-methyl-5-nitro-1*H*-imidazol-2-ylmethylene)pyrrolidin-2-one **2.063**.

**Table 14. Antiamoebic Activity of *N*-Alkylaminonitroimidazoles 2.062[a]**

| $R^1$ | $R^2$ | $R^3$ | $LD_{50}$ (μg/mL) | ref |
|---|---|---|---|---|
| H | Me |  | 27.0 | 207 |
| H | Me |  | 6.0 | 207 |
| H | Me |  | 27.0 | 207 |
| H | Me |  | 74.0 | 207 |
| H | H |  | 16.0 (4)[a]<br>8.0 (5)[a] | 207 |
| H | H |  | 16.0 (4)[a]<br>12.0 (5)[a] | 207 |
| H | H |  | 16.0 (4)[a]<br>12.0 (5)[a] | 207 |
| H | H |  | 58.0 (4)[a]<br>7.0 (5)[a] | 207 |
| H | H |  | >100.0 (4)[a]<br>62.0 (5)[a] | 207 |
|  | H |  | 8.2 | 208 |
|  | H |  | 8.2 | 208 |
|  | H |  | 6.0 | 208 |
|  | H |  | 24.6–37.0 | 208 |
|  | Me |  | 6.0 | 208 |
|  | Me |  | 4.0 | 208 |
|  | Me |  | 8.2 | 208 |
|  | Me |  | 8.2–13.0 | 208 |
|  | H |  | 4.0 (4)[a]<br>12.0 (5)[a] | 208 |
|  | H |  | 4.0 (4)[a]<br>12.0 (5)[a] | 208 |
|  | H |  | 5.0 (4)[a]<br>10.0 (5)[a] | 208 |
|  | H |  | 18.0 (4)[a]<br>30.0 (5)[a] | 208 |

[a] Position of nitro group in imidazole ring.

**Scheme 13. Synthesis of Bisphosphonates.**




bisphosphonates with relatively large aromatic side chains were found to be the most active. Activity of pyridine based bisphosphonates was correlated with the basicity of the aromatic group (activity decreasing with increasing p$K_a$ values). In particular, most active compounds have p$K_a \approx 2$. A known inhibitor of the enzyme farnesylpyrophosphonate (FPP) synthase, alkyl-1-hydroxy-1,1-bisphosphonate, was also found to be active, but interestingly, many other potent FPP synthase inhibitors such as risedronate or pamidronate were found to be inactive.

The activity of the alkyl bisphosphonates was strongly dependent on overall side chain length and lipophilicity, i.e., compounds with more lipophilic chains generally appeared to have relatively good activity against *E. histolytica*. Activity rapidly increased from three carbon chain to six carbon chain, and optimal activity was reported with the C9 and C10 alkyl chains (13.3 and 11.0 $\mu$M, respectively) and then began to fall off; the $IC_{50}$ increases to ~200 $\mu$M for the very long chain (C17). It was suggested that alkyl phosphonates were good inhibitors of *E. histolytica* growth due, at least in part, to the lipophilic nature of their alkyl side chains in enhancing membrane transport and targeting FPPS. Five bisphosphonates were screened for their ability to delay the development of amoebic liver abscess formation in an *E. histolytica* infected hamster model (Table 15). Two compounds were found to decrease liver abscess formation at 10 mg/kg ip (intraperitoneal) with little or no effect on normal liver mass. It was also reported that activity of bisphosphonates was relatively specific against protozoa.

## 2.13. Miscellaneous

Parthasarathy et al.[219] synthesized a variety of dichloromethane sulfonamides, including a close structural analogue of the well-known antiamoebic drug, diloxanide furoate, which has been used in combined therapy for amoebiasis because it is particularly effective against lumen-dwelling amoeba. Its cyclized analogue, quinfamide, is twice as effective as diloxanide furoate and also primarily a luminally active agent.[220,221] Both compounds contain a dichloroacetyl group ($-CO-CHCl_2$), which closely resembles a dichloromethanesulfonyl group ($-SO_2-CHCl_2$). Furoyl, cyclohexanoyl esters, and Mannich bases of dichloromethanesulfonamide have also been prepared and tested for their efficacy in eradicating natural *E. muris* infection in rats.[219] Among all the compounds tested in this series, only the furoyl ester of *N*-methyl-*N*-dichloromethanesulfonyl-*p*-hydroxybenzene exhibited 100% curative activity at a dose of 10 mg/kg, for 3 days. This was comparable to diloxanide

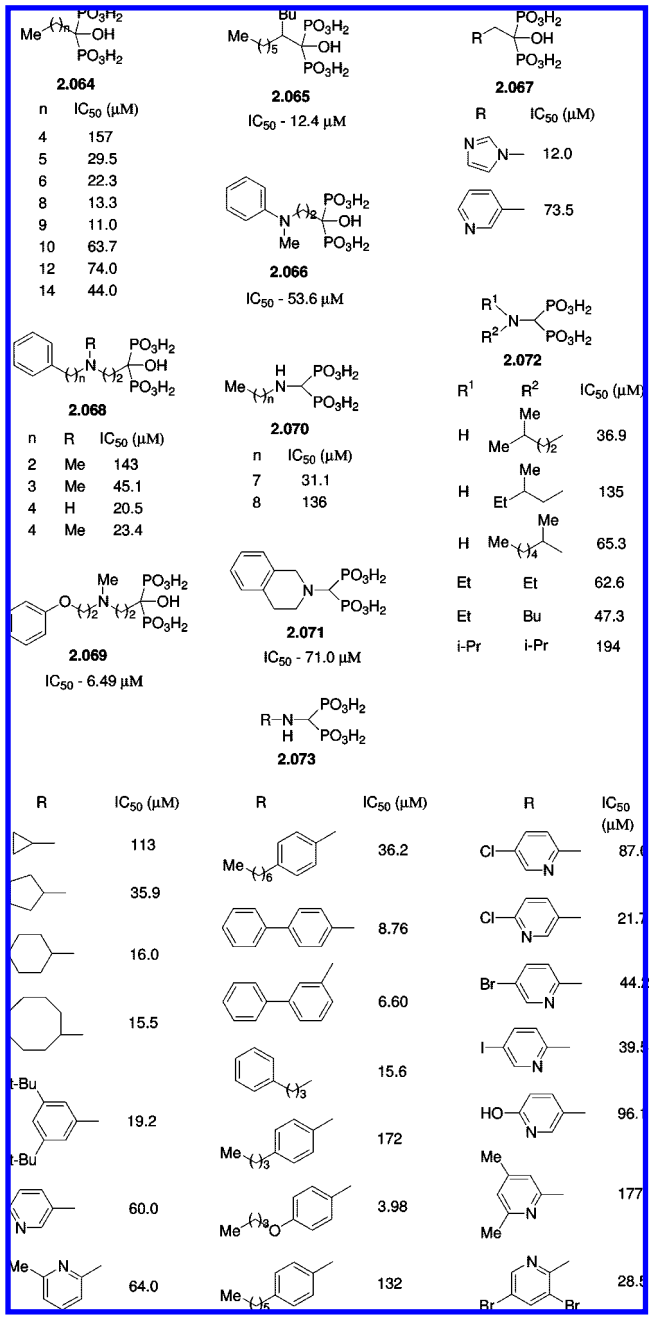



**Figure 17.** In vitro antiamoebic activity of bisphosphonates against *E. histolytica*.

furoate activity with the minimum curative dose of 1.6 mg/kg, for 3 days.

Hydrazone moieties are important pharmacophores of several anti-inflammatory and antiplatelet drugs.[222−224] Maurya et al. prepared some hydrazones from 2-acetylpyridine and nicotinic acid or 2-furoic acid hydrazide as well as their oxovanadium complexes.[225] The in vitro antiamoebic activity against *E. histolytica* of hydrazones and their vanadium complexes showed that the ligands did not have any activity; however, their binuclear, *μ-bis*(oxo)*bis*{oxovanadium(V)} complexes displayed better activity than metronidazole.

A series of 2,3-*bis*(4-bromomethylphenyl)dimethoxyquinoxaline and 2,3-*bis*(4-aminophenyl)dimethoxyquinoxaline derivatives have been synthesized by Venugopalan et al.[226] Under in vitro antiamoebic evaluation, most of the compounds displayed MIC ≈ 50−200 μg/mL, which is poor compared to those for nitroimidazole and diloxanide furoate.

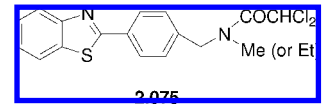
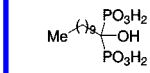
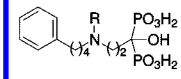
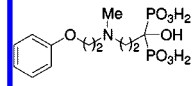
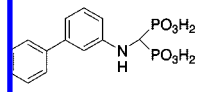
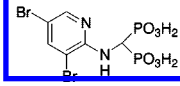


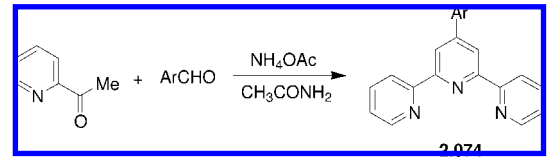

**Figure 18.** *N*-(4-Benzothiazol-2-yl-benzyl)-2,2-dichloro-*N*-alkylacetamide **2.075**.

**Table 15. Effects of Bisphosphonates on Liver Abscess Formation in *E. histolytic*[a] Infected Hamsters**

| Drug | Liver abscess (mg) | | Normal liver weight (mg) | |
|---|---|---|---|---|
| | mean | % decrease | mean | % decrease |
| control | 888 | 0 | 2365 | 0 |
|  | 285 | 68 | 2163 | 9 |
|  | 94 | 89 | 1756 | 26 |
|  | 1058 | −19 | 2295 | 3 |
|  | 570 | 36 | 2459 | −4 |
|  | 767 | 14 | 2883 | −22 |

[a] Reprinted with permission from ref 210. Copyright 2004 Americal Chemical Society.

**Scheme 14. Synthesis of Terpyridines 2.074**




In vivo activity of these quinoxalines against hepatic amoebiasis in golden hamsters was also low compared to those for the standard antiamoebic drugs. Sarkar et al. synthesized different 4,4′-bithiazoles and 4-(2-thiazolyl)aminoquinolines and tested them in vitro.[227] Two compounds, 2,2′-diacetylamino-(4,4′)bithiazole and 4-(5-nitro-2-thiazolyl)amino-2-methyl-3-*n*-propyl-8-methoxyquinoline, showed one-half of MIC whereas 4-(5-nitro-2-thiazolyl)amino-2-methyl-8-methoxyquinoline showed one-fourth of MIC compared to metronidazole.

Sharma and co-workers prepared some nitrovinylindole analogues.[228] 3-(2-Nitrovinylindole) and its *N*-methyl derivatives showed some activity (MIC = 31.25 μg/mL). Terpyridines **2.074** were synthesized by the reaction of arylaldehyde, 2-acetylpyridine with ammonium acetate, and acetamide at 180 °C in 10−78% yield (Scheme 14).[229] Although one of the terpyridines (Ar = 5-methylthiophene) exhibited some activity, it also proved to be toxic.

Singh et al.[230] and later Agarwal et al.[231] synthesized various substituted indoles, but none of the compounds showed antiamoebic activity in axenic culture below the concentration of 62 μg/mL; at lower doses, all the compounds were found to be inactive. 2,6-Disubstituted-1(3)*H*-imidazo[4,5-*c*]carbazoles have been prepared,[232] and all the compounds showed in vitro antiamoebic activity only above

31 μg/mL. Sastry et al. synthesized some heterocycles including 2*H*,7*H*-[1,4]-thiazino[2,3-*g*]-1,4-benzoxazine-3,8(4*H*,9*H*)-diones and 2*H*-7,8-dihydro-[1,5]thiazepino[2,3-*g*]-1.4-benzoxazine-3,9(4*H*,10*H*)-diones.[233] In vitro evaluation of these compounds showed no activity at concentrations < 100 μg/mL. 1-(3-Substituted-2-hydroxypropyloximino)benzocycloalkanes and substituted pyrazoles synthesized by Sinha et al. did not show any significant in vitro activity.[234,235] In vivo screening of these compounds at 100 mg/kg/day × 5 doses showed no curative activity at this dose level. Asthana et al. prepared a series of 9-substituted acridines,[236] and none of them were active below 125 μg/mL concentration.

Gradnik et al. prepared some N-derivatives of *l*-emetine by the reaction of *l*-emetine with 1-alkoxy-, 1-alkylthio-, and 1-dialkylamino-2,3-epoxypropanes.[237] These derivatives were found to be less active although less toxic than *l*-emetine. Some quinolines and other heterocyclic compounds were synthesized by De and co-workers and none of them was found to be active in vitro against *E. histolytica*.[238,239] A series of benzothiazolylbenzylamines along with their dichloroacetyl amides were prepared from 4-(2-benzothiazolyl-)benzyl bromide and from their respective benzylamines by Palmer et al. and tested for antimicrobial activity against *S. pyogenes*, *E. histolytica*, and *M. tuberculosis*.[240] Out of 35 compounds, only *N*-(4-benzothiazol-2-yl-benzyl)-2,2-dichloro-*N*-alkylacetamide **2.075** (Figure 18) showed some activity (MIC = 2.5 μM) against *E. histolytica*.

## 3. Naturally Occurring Antiamoebic Compounds

Millions of people in the third world encourage revival of the practice of herbal medicines because they have believed in them for centuries and regard them as "their" system of medicine due to low cost, easy access, and ancestral experience.[241] In developed countries, high-throughput screening tests are used for bioassay-guided fractionation, leading to the isolation of active principles that may be developed into clinical agents either as the natural product or as a synthesized analogue with enhanced clinical action or reduced adverse side effects. Therefore, there is a great need to harness scientific and clinical research to investigate the quality, safety, and efficacy of these herbal therapies. The prevalence of amoebiasis is more closely associated with sanitation and poor lifestyle rather than the location and climate of the region.[242] Because of nonavailability of guaranteed conventional medical facilities, people have commonly looked for natural remedies from traditional plants as found in folklore. Development of a potential natural product into a drug candidate requires the screening of large numbers of plant extracts, the isolation and identification of the active compounds, the uncovering of their mechanism of action, and toxicity tests to demonstrate selectivity toward the host and parasite.

In the past few decades, studies in the search for antiamoebic agents from natural products were mainly based on the traditional uses of these plants. These studies encouraged the world scientific community to isolate and characterize biologically active natural products. Different plant extracts were tested and the most active fractions were selected for extensive biological and phytochemical studies, which further lead to the isolation and characterization of its active principles. Herein, authors present a compilation of such studies, as shown in Table 16with a list of isolated natural products in alphabetical order evaluated for their antiamoebic activity. A number of alkaloids, terpenoids, quassinoids, flavonoids, iridoids, and other phenolic compounds from higher plants displayed activity against *E. histolytica* and other protozoa. The majority of these compounds have been tested in vitro and some have been tested in vivo; very few have been accessed clinically. This part of the review covers a literature survey of naturally occurring compounds tested against *E. histolytica*.

### 3.1. Alkaloids

Many of the earliest isolated compounds with biological activity were alkaloids, and over the past few decades they have been investigated for their pharmacological applications.[243] Emetine **3.073**, one of the first drugs reported for the treatment of amoebiasis, was isolated in 1817 from the root and rhizome of *Cephaelis ipecacuanha*.[244] The mode of action of emetine was suggested by inhibition of protein and DNA synthesis; however, clinical use of emetine was limited by its severe side effects. One of emetine's synthetic analogues, 2,3-dehydroemetine, was less toxic than emetine because of faster rates of metabolism and excretion.[245,246] In vitro antiamoebic and cytotoxic activities of a series of 18 alkaloids, structurally similar to emetine, was investigated by Keene et al.[247] Emetine was highly active against *E. histolytica*, but removal of the 9,10-dimethoxy moiety from the emetine molecule resulted in a 52-fold loss of activity, which proved the significance of the 9,10-dimethoxy group in antiamoebic activity of emetine. It was observed that tubulosine **3.196** and pseudotubulosine have overall the same stereochemistry as emetine but are not nearly as active. Another naturally occurring alkaloid cryptopleurine, **3.058**,[248,249] and benzylisoquinoline alkaloid, berberine **3.023**,[250] exhibited in vitro activity against *E. histolytica*, but the latter showed better in vivo activity in mice. Several quinolizidine alkaloids isolated from a species of *Sophora* have been shown to possess amoebicidal activity, including matrine **3.131**, its *N*-oxide, and cytisine **3.059**.[251] Initially isolated from *Cinchona succiruba*, quinine **3.169** has been used as an antimalarial compound for more than a century.[252] It was the principal compound among 31 alkaloids tested with related structures and, interestingly, was one of the few agents used for the treatment of amoebic dysentery.[253] Quinine **3.169** and quinidine **3.167** were marginally inferior to quinidinone **3.168,** whereas aricine **3.018** and 10-methoxy-cinchonamine **3.134** were found to be superior to quinidinone **3.168**.

A number of species of *Alstonia* (Apocynaceae) are used in traditional medicine in India and Philippines to treat dysentery, and it is believed that indole alkaloids such as alstonine **3.012** are responsible for their activity.[251,254] Wright et al. isolated nine alkaloids from the roots of *Alstonia angustifolia* and assessed them for their antiprotozoal activities.[255] Two dimeric alkaloids, macrocarpamine **3.127** and villastonine **3.205**, possessed significant activity but were 4−8 times less potent than emetine against *E. histolytica*, whereas a third dimeric alkaloid, macralstonine **3.126**, was virtually ineffective. Macralstonine is composed of two alstonerine molecules, while macrocarpamine and villastonine have one alstonerine unit and one pleiocarpamine molecule combined. Monomeric alkaloids, alstonerine **3.011**, alstophylline **3.013**, 11-methoxyakuammicine **3.133**, norfluorocurarine **3.147**, pleiocarpamine **3.159**, and vincamajine **3.206**, were all considerably less potent than the dimers. Their activity profile suggested that the ring systems present in the dimers are necessary for activity. It was well-established

**Table 16. Antiamoebic Activity of Isolated Natural Products**

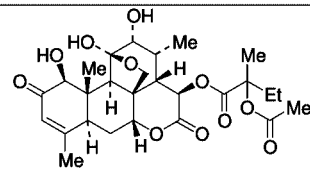
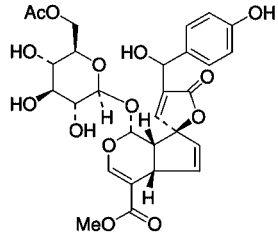
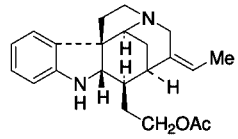
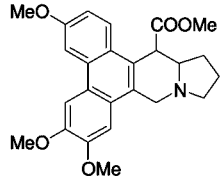
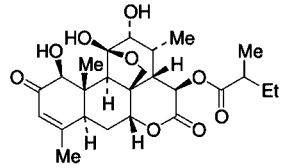
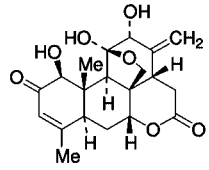
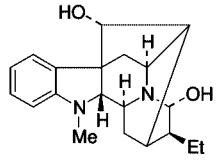
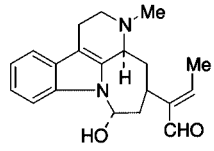
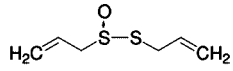
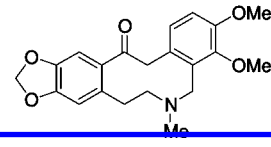
| Entry | Name of the Compound | Structure | Isolated from the Plant | Antiamoebic Activity | ref |
|---|---|---|---|---|---|
| **3.001** | 2'-Acetoxy-glaucarubinone |  | *Simarouba amara* | $IC_{50}$ (0.155 μg/mL) | 300 |
| **3.002** | Acetylgaertneroside |  | *Morinda morindoides* | $IC_{50}$ (5.4 μg/mL) | 283 |
| **3.003** | *O*-Acetylisoretuline |  | *Strychnos variabilis* | $IC_{50}$ (Inactive at 66 μM) | 301 |
| **3.004** | Acetyltylophorine |  | *Tylophora indica* | MIC (50 μg/mL) | 302 |
| **3.005** | Ailanthinone |  | *Simarouba amara* | $IC_{50}$ (0.063 μg/mL) | 265 |
| **3.006** | Ailanthone |  | *Brucea antidysenterica* | $IC_{50}$ (0.14 μg/mL) | 278 |
| **3.007** | Ajmaline |  | *Rauwolfia schueli* | $IC_{50}$ (>100 μg/mL) | 303 |
| **3.008** | Akagerine |  | *Strychnos usambarensis* | $IC_{50}$ (17.1 μg/mL) | 256 |
| **3.009** | Allicine |  | *Allium sativum* | MIC (30 μg/mL) | 304 |
| **3.010** | Allocrytopine |  | *Argemone subfusiformis* | $IC_{50}$ (135 μM) | 305 |

**Table 16. Continued**

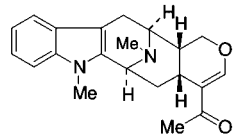
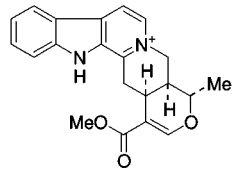
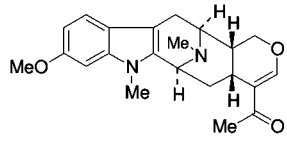
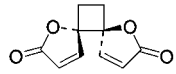
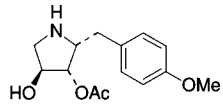
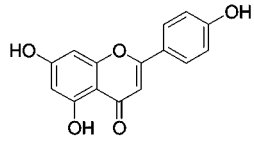
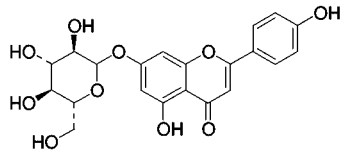
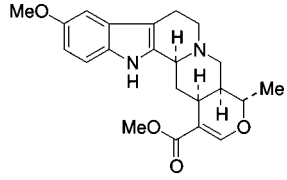
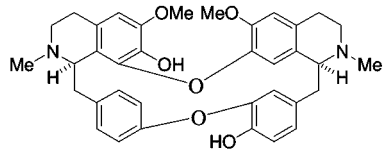
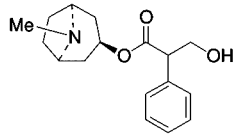
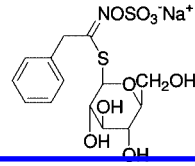
| Entry | Name of the Compound | Structure | Isolated from the Plant | Antiamoebic Activity | ref |
|---|---|---|---|---|---|
| **3.011** | Alstonerine |  | *Alstonia macrophylla* | $ED_{50}$ (75.3 μM) | 255 |
| **3.012** | Alstonine |  | *Alstonia constricta* | Not found | 251 |
| **3.013** | Alstophylline |  | *Alstonia angustifolia* | $ED_{50}$ (67.7 μM) | 255 |
| **3.014** | Anemonin |  | *Anemone pulsatilla* | Not found | 251 |
| **3.015** | Anisomycin |  | *Streptomyces griseolus* | $ED_{50}$ (2.0 μM) | 306 |
| **3.016** | Apigenin |  | *Morinda morindoides* | $IC_{50}$ (12.7 μg/mL) | 284 |
| **3.017** | Apigenin-7-*O*-glucoside |  | *Cuphea pinetorum* | $IC_{50}$ (59.8 μg/mL) | 307 |
| **3.018** | Aricine |  | *Rauwolfia ligustrina* | $IC_{50}$ (3.6 μg/mL) | 303 |
| **3.019** | Aromoline |  | *Triclisia patens* | $IC_{50}$ (5.05 μM) | 308 |
| **3.020** | Atropine |  | *Datura stramonium* | $IC_{50}$ (>100 μg/mL) | 303 |
| **3.021** | Benzyl glucosinolate |  | *Lipidium virginicum* | $IC_{50}$ (20.4 μg/mL) | 309 |

**Table 16. Continued**

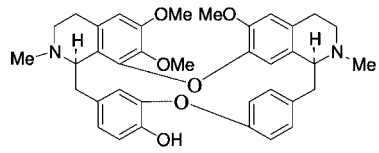
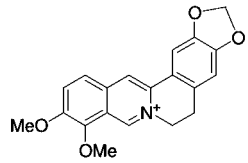
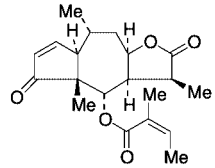
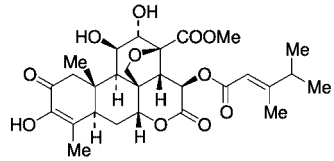
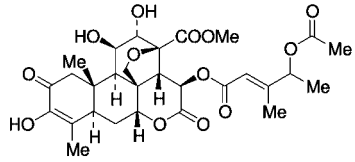
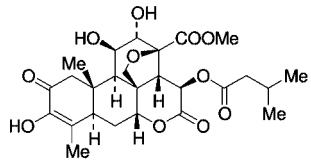
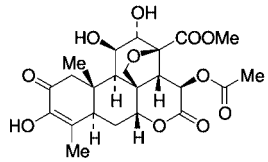
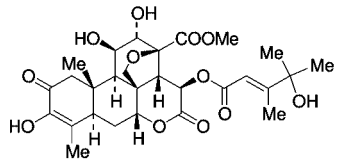
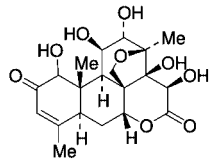
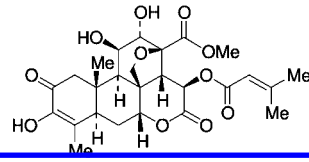
| Entry | Name of the Compound | Structure | Isolated from the Plant | Antiamoebic Activity | ref |
|---|---|---|---|---|---|
| **3.022** | Berbamine |  | *Triclisia patens* | $IC_{50}$ (36.8 μM) | 308 |
| **3.023** | Berberine |  | *Berberis aristata* | $IC_{50}$ (0.5-1 μg/mL) | 249 |
| **3.024** | Brevilin A |  | *Centipeda minima* | $IC_{50}$ (4.5-9 μM) | 310 |
| **3.025** | Bruceantin |  | *Brucea javanica* | $IC_{50}$ (0.019 μg/mL) | 265 |
| **3.026** | Bruceantinol |  | *Brucea antidysenterica* | Inactive | 278 |
| **3.027** | Bruceine A |  | *Brucea javanica* | $IC_{50}$ (0.097 μg/mL) | 265 |
| **3.028** | Bruceine B |  | *Brucea javanica* | $IC_{50}$ (0.306 μg/mL) | 265 |
| **3.029** | Bruceine C |  | *Brucea javanica* | $IC_{50}$ (0.279 μg/mL) | 265 |
| **3.030** | Bruceine D |  | *Brucea javanica* | $IC_{50}$ (0.386 μg/mL) | 265 |
| **3.031** | Brusatol |  | *Brucea javanica* | $IC_{50}$ (0.062 μg/mL) | 267 |

**Table 16. Continued**

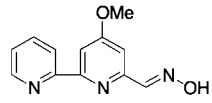
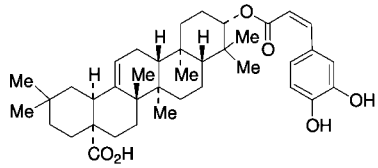
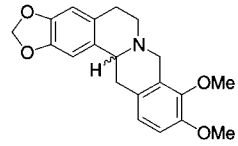
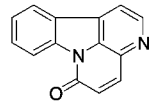
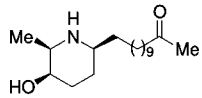
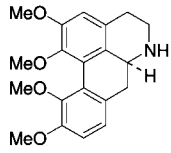
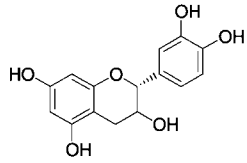
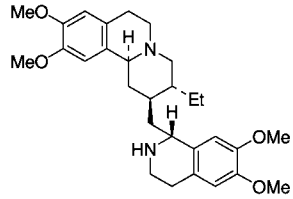
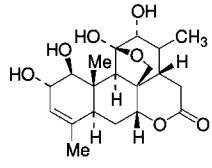
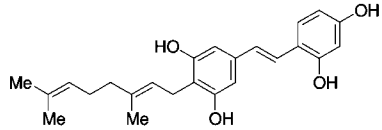
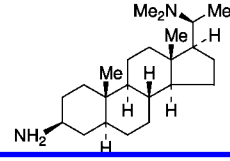
| Entry | Name of the Compound | Structure | Isolated from the Plant | Antiamoebic Activity | ref |
|---|---|---|---|---|---|
| **3.032** | Caerulomycin |  | *Streptomyces caeruleus* | MIC (15.6 μg/mL) | 311 |
| **3.033** | 3-β-Caffeoyl-12-oleanen-28-oic acid |  | *Geranium niveum* | $IC_{50}$ (19.25 μg/mL) | 288 |
| **3.034** | Canadine |  | *Hydrastis canadensis* | $IC_{50}$ (126 μM) | 305 |
| **3.035** | Canthin-6-one |  | *Brucea javanica* | $IC_{50}$ (23 μg/mL) | 303 |
| **3.036** | Cassine |  | *Senna racemosa* | $IC_{50}$ (11.96 μg/mL) | 296 |
| **3.037** | Catalpifoline |  | *Croton hemiargyreus* | $IC_{50}$ (147 μM) | 305 |
| **3.038** | (+)-Catechin |  | *Uncaria gambier* | $IC_{50}$ (65.55 μg/mL) | 287 |
| **3.039** | Cephaeline |  | *Cephaelis ipecacuanha* | $IC_{50}$ (3.26 μg/mL) | 300 |
| **3.040** | Chaparrin |  | *Castela nicholsoni* | Inactive | 278 |
| **3.041** | Chlorophorin |  | *Chlorophora excelsa* | MIC (0.25 μg/mL) | 295 |
| **3.042** | Chonemorphine |  | *Chonemorpha fragnans* | MIC (100 μg/mL) | 312 |

**Table 16. Continued**

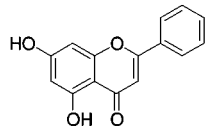
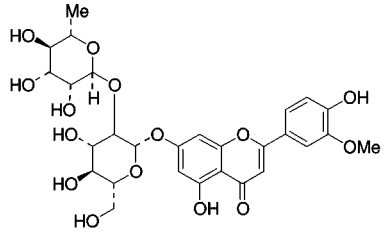
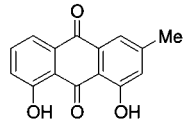
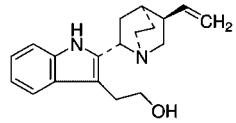
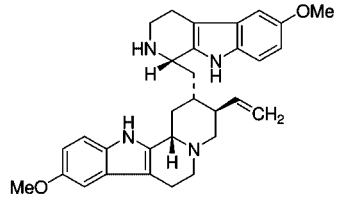
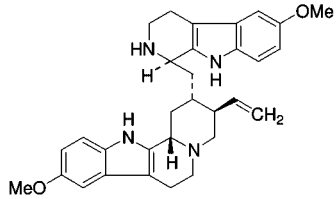
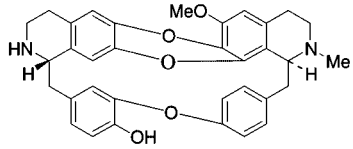
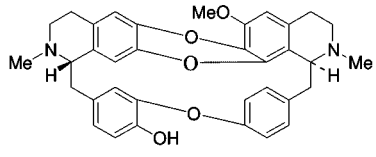
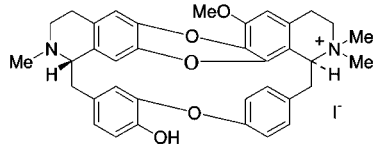
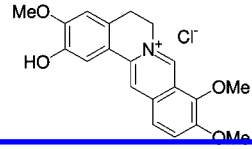
| Entry | Name of the Compound | Structure | Isolated from the Plant | Antiamoebic Activity | ref |
|---|---|---|---|---|---|
| **3.043** | Chrysin |  | *Teloxys graveolens* | $IC_{50}$ (81.0 µg/mL) | 290 |
| **3.044** | Chrysoeriol-7-*O*-neohesperidoside |  | *Morinda morindoides* | $IC_{50}$ (>125 µg/mL) | 284 |
| **3.045** | Chrysophanol |  | *Senna racemosa* | $IC_{50}$ (6.21 µg/mL) | 296 |
| **3.046** | Cinchonamine |  | *Cinchona ledgeriana* | $IC_{50}$ (14.8 µg/mL) | 303 |
| **3.047** | 3α, 17α-Cinchophylline |  | *Cinchona ledgeriana* | $IC_{50}$ (2.2 µg/mL) | 247 |
| **3.048** | 3α, 17β-Cinchophylline |  | *Cinchona ledgeriana* | $IC_{50}$ (0.96 µg/mL) | 247 |
| **3.049** | Cocsoline |  | *Triclisia patens* | $IC_{50}$ (18.0 µM) | 308 |
| **3.050** | Cocsuline |  | *Triclisia patens* | $IC_{50}$ (23.5 µM) | 308 |
| **3.051** | Cocsuline methiodide |  | *Triclisia patens* | $IC_{50}$ (36.2 µM) | 308 |
| **3.052** | Columbamine chloride |  | *Thalictrum uchiyamai* | $IC_{50}$ (156 µM) | 305 |

**Table 16. Continued**

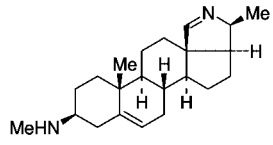
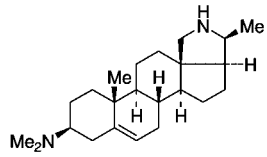
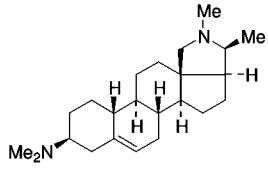
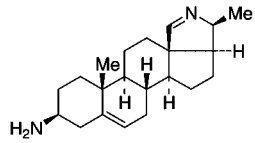
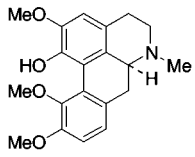
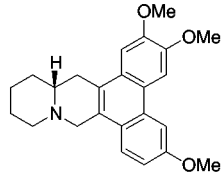
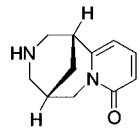
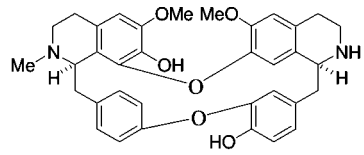
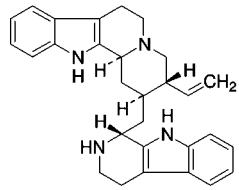
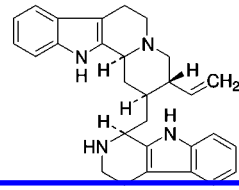
| Entry | Name of the Compound | Structure | Isolated from the Plant | Antiamoebic Activity | ref |
|---|---|---|---|---|---|
| **3.053** | Conessidine |  | *Holarrhena pubescens* | $IC_{50}$ (2.29 μg/mL) | 300 |
| **3.054** | Conessimine |  | *Holarrhena pubescens* | $IC_{50}$ (1.87 μg/mL) | 300 |
| **3.055** | Conessine |  | *Holarrhena pubescens* | $IC_{50}$ (8.97 μg/mL) | 300 |
| **3.056** | Conkurchine |  | *Holarrhena pubescens* | $IC_{50}$ (12.0 μg/mL) | 300 |
| **3.057** | Corydine |  | *Stephania dinklagei* | $IC_{50}$ (90.6 μM) | 305 |
| **3.058** | Cryptopleurine |  | *Cryptolepis sanguinolenta* | $IC_{50}$ (0.031 μg/mL) | 313 |
| **3.059** | Cytisine |  | *Sophora viciifolia* | Not found | 251 |
| **3.060** | Daphnoline |  | *Triclisia patens* | $IC_{50}$ (>86.2 μM) | 308 |
| **3.061** | 3β,17α-18,19-Dehydroochrolifuanine |  | *Cinchona ledgeriana* | $IC_{50}$ (2 μg/mL) | 247 |
| **3.062** | 3β,17β-18,19-Dehydroochrolifuanine |  | *Cinchona ledgeriana* | $IC_{50}$ (1.7 μg/mL) | 247 |

**Table 16. Continued**

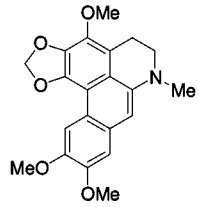
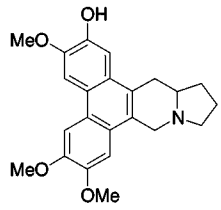
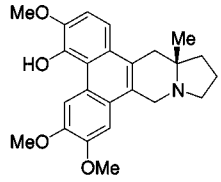
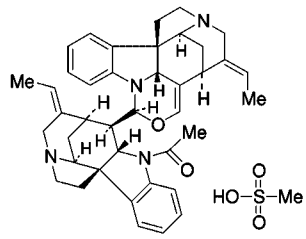
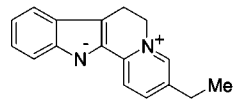
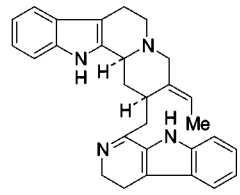
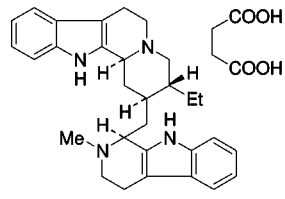
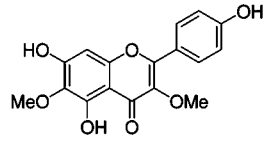
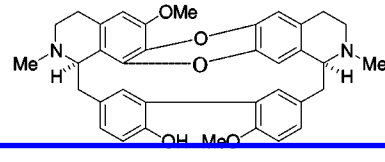
| Entry | Name of the Compound | Structure | Isolated from the Plant | Antiamoebic Activity | ref |
|---|---|---|---|---|---|
| **3.063** | Dehydroocoteine |  | *Ocotea puberula* | $IC_{50}$ (136 μM) | 305 |
| **3.064** | Demethyltylophorine |  | *Tylophora indica* | MIC (25 μg/mL) | 302 |
| **3.065** | 14-Deoxy-13a-methyl tylohirsutinidine |  | *Tylophora hirsuta* | MIC (12.5 μg/mL) | 302 |
| **3.066** | Didehydroisostrychnobiline methanesulphonate |  | *Strychnos variabilis* | $IC_{50}$ (Inactive at 35 μM) | 301 |
| **3.067** | 5,6-Dihydroflavopereirine |  | *Strychnos usambarensis* | $IC_{50}$ (24.31 μM) | 311 |
| **3.068** | 3',4'-Dihydro usambarensine |  | *Strychnos usambarensis* | $IC_{50}$ (2.18 μg/mL) | 256 |
| **3.069** | 18,19-Dihydro usambarine oxalate |  | *Strychnos usambarensis* | $IC_{50}$ (0.65 μg/mL) | 256 |
| **3.070** | 3,6-Dimethoxy kaempferol |  | *Conyza filaginoides* | $IC_{50}$ (105.3 μg/mL) | 287 |
| **3.071** | Dinklacorine |  | *Triclisia patens* | $IC_{50}$ (34.4 μM) | 308 |

**Table 16. Continued**

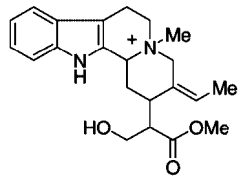
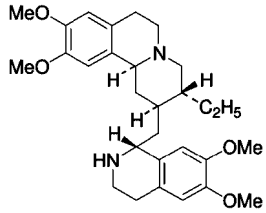
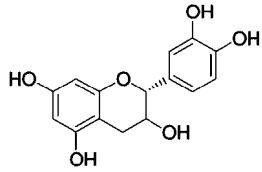
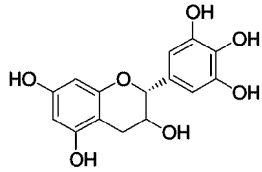
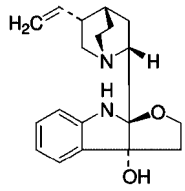
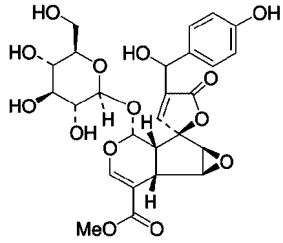
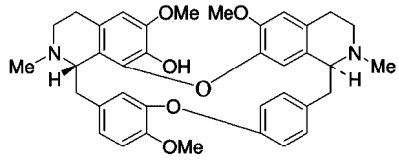
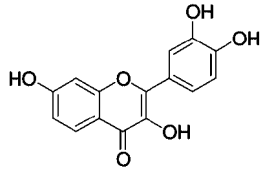
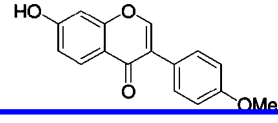
| Entry | Name of the Compound | Structure | Isolated from the Plant | Antiamoebic Activity | ref |
|---|---|---|---|---|---|
| **3.072** | Diploceline |  | *Strychnos gossweileri* | $IC_{50}$ (50 µg/mL) | 314 |
| **3.073** | Emetine |  | *Cephaelis ipecacuanha* | $IC_{50}$ (0.07 µg/mL) | 303 |
| **3.074** | (−)-Epicatechin |  | *Celastrus angulatus* | $IC_{50}$ (1.92 µg/mL) | 287 |
| **3.075** | (−)-Epigallocatechin |  | *Elaeaguus glabra* | $IC_{50}$ (6.89 µg/mL) | 287 |
| **3.076** | 3-Epiquinamine |  | *Brucea javanica* | $IC_{50}$ (12.9 µg/mL) | 303 |
| **3.077** | Epoxygaertneroside |  | *Morinda morindoides* | $IC_{50}$ (1.3 µg/mL) | 283 |
| **3.078** | Fangchinoline |  | *Triclisia patens* | $IC_{50}$ (24.2 µM) | 308 |
| **3.079** | Fisetin |  | *Continus coggygria* | $IC_{50}$ (189.01 µg/mL) | 287 |
| **3.080** | Formononetin |  | *Virgilia oroboides* | MIC (>1.0 µg/mL) | 295 |

**Table 16. Continued**

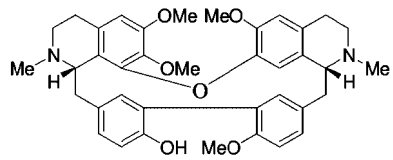
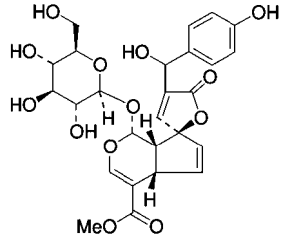
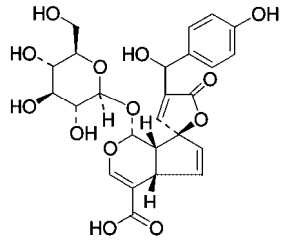
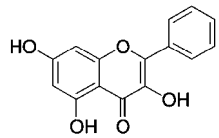
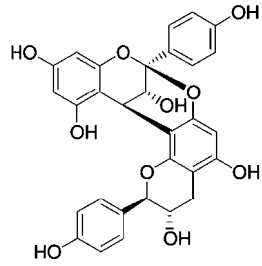
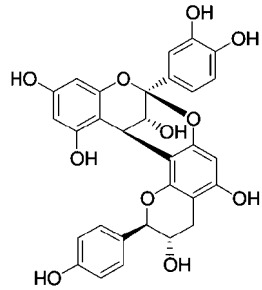
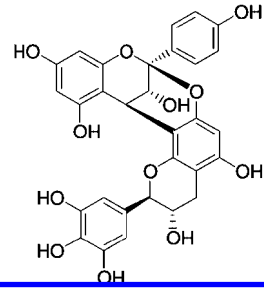
| Entry | Name of the Compound | Structure | Isolated from the Plant | Antiamoebic Activity | ref |
|---|---|---|---|---|---|
| **3.081** | Funiferine |  | *Triclisia patens* | $IC_{50}$ (45.5 μM) | 308 |
| **3.082** | Gaertneroside |  | *Morinda morindoides* | $IC_{50}$ (4.3 μg/mL) | 283 |
| **3.083** | Gaetneric acid |  | *Morinda morindoides* | $IC_{50}$ (7.1 μg/mL) | 283 |
| **3.084** | Galangin |  | *Alpinia officinarum* | $IC_{50}$ (158.67 μg/mL) | 287 |
| **3.085** | Geranin A |  | *Geranium niveum* | $IC_{50}$ (184.7 μg/mL) | 288 |
| **3.086** | Geranin B |  | *Geranium niveum* | $IC_{50}$ (13.6 μg/mL) | 288 |
| **3.087** | Geranin C |  | *Geranium niveum* | $IC_{50}$ (52.0 μg/mL) | 289 |

**Table 16. Continued**

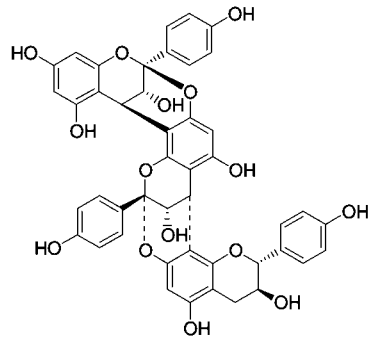
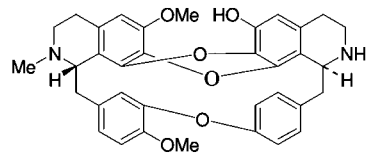
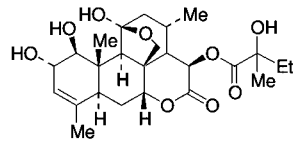
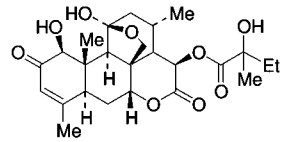
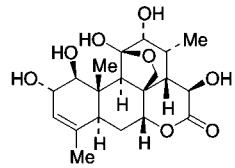
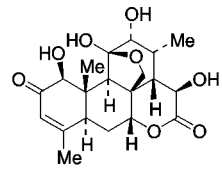
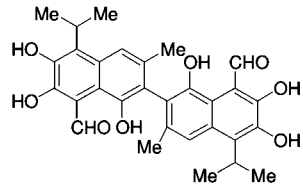
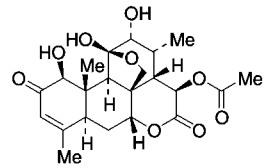
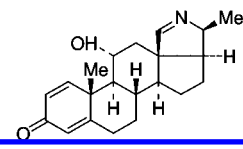
| Entry | Name of the Compound | Structure | Isolated from the Plant | Antiamoebic Activity | ref |
|---|---|---|---|---|---|
| **3.088** | Geranin D |  | *Geranium niveum* | $IC_{50}$ (28.6 µg/mL) | 289 |
| **3.089** | Gilletine |  | *Triclisia patens* | $IC_{50}$ (20.9 µM) | 308 |
| **3.090** | Glaucarubin |  | *Simarouba glauca* | $IC_{50}$ (1.57 µg/mL) | 278 |
| **3.091** | Glaucarubinone |  | *Simarouba amara* | $IC_{50}$ (0.168 µg/mL) | 265 |
| **3.092** | Glaucarubol |  | *Brucea antidysenterica* | $IC_{50}$ (Inactive at 2 µg/mL) | 278 |
| **3.093** | Glaucarubolone |  | *Brucea antidysenterica* | $IC_{50}$ (0.12 µg/mL) | 278 |
| **3.094** | Gossypol |  | *Gossypium herbacium* | $IC_{50}$ (0.015 µM) | 291 |
| **3.095** | Holacanthone |  | *Simarouba amara* | $IC_{50}$ (0.162 µg/mL) | 300 |
| **3.096** | Holonamine |  | *Holarrhena pubescens* | $IC_{50}$ (3.96 µg/mL) | 300 |

**Table 16. Continued**

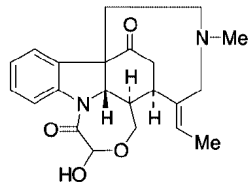
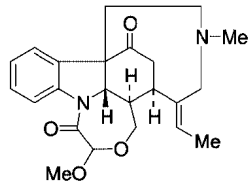
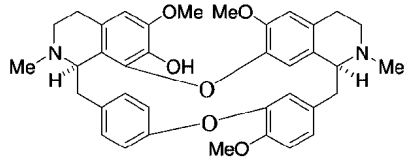
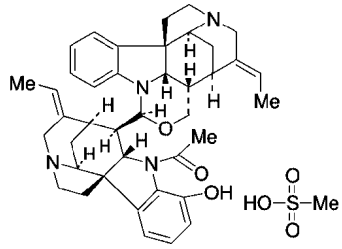
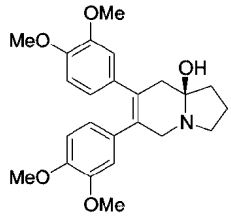
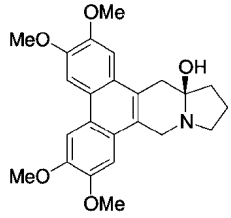
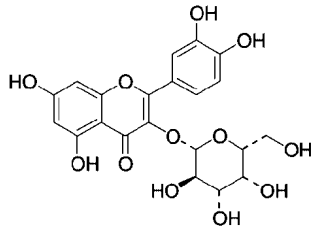
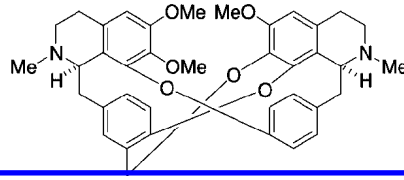
| Entry | Name of the Compound | Structure | Isolated from the Plant | Antiamoebic Activity | ref |
|---|---|---|---|---|---|
| **3.097** | Holstiine |  | *Strychnos henningsii* | $IC_{50}$ (Inactive at 65 μM) | 301 |
| **3.098** | Holstiline |  | *Strychnos henningsii* | $IC_{50}$ (Inactive at 63 μM) | 301 |
| **3.099** | Homoaromoline |  | *Triclisia patens* | $IC_{50}$ (17.3 μM) | 308 |
| **3.100** | 12'-Hydroisostrychnobiline methanesulphonate |  | *Strychnos variabilis* | $IC_{50}$ (Inactive at 34 μM) | 301 |
| **3.101** | 13a-Hydroxy septicine |  | *Tylophora hirsute* | MIC (800 μg/mL) | 302 |
| **3.102** | 13a-Hydroxy tylophorine |  | *Tylophora hirsute* | MIC (50 μg/mL) | 302 |
| **3.103** | Hyperin |  | *Geranium niveum* | $IC_{50}$ (143.61 μg/mL) | 287 |
| **3.104** | Insularine |  | *Triclisia patens* | $IC_{50}$ (11.1 μM) | 308 |

**Table 16. Continued**

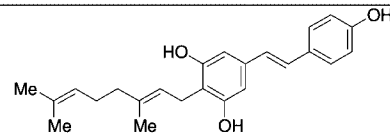
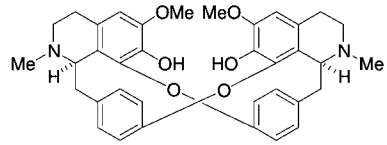
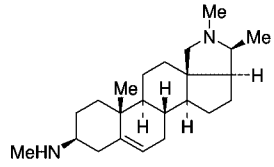
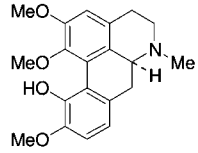
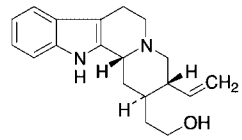
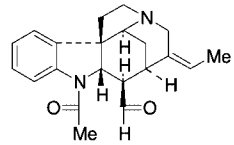
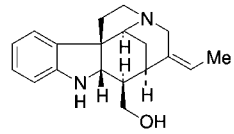
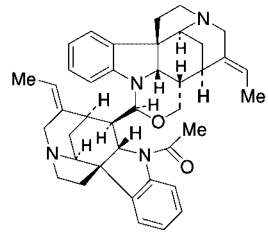
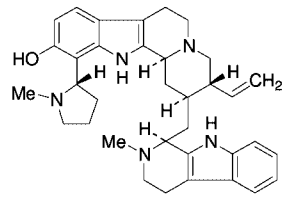
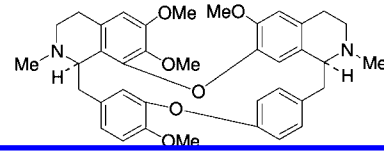
| Entry | Name of the Compound | Structure | Isolated from the Plant | Antiamoebic Activity | ref |
|---|---|---|---|---|---|
| **3.105** | Iroko |  | *Chlorophora excelsa* | MIC (1.0 μg/mL) | 295 |
| **3.106** | Isochondodendrine |  | *Triclisia patens* | $IC_{50}$ (17.7 μM) | 308 |
| **3.107** | Isoconessimine |  | *Holarrhena pubescens* | $IC_{50}$ (20.9 μg/mL) | 300 |
| **3.108** | Isocorydine |  | *Stephania dinklagei* | $IC_{50}$ (>147 μM) | 305 |
| **3.109** | 3-Isocorynantheol |  | *Cinchona ledgeriana* | $IC_{50}$ (4.1 μg/mL) | 247 |
| **3.110** | Isoretulinal |  | *Strychnos variabilis* | $IC_{50}$ (Inactive at 75 μM) | 301 |
| **3.111** | Isoretuline |  | *Strychnos variabilis* | $IC_{50}$ (Inactive at 74 μM) | 301 |
| **3.112** | Isostrychnobiline |  | *Strychnos variabilis* | $IC_{50}$ (Inactive at 41 μM) | 301 |
| **3.113** | Isostrychnopentamine |  | *Strychnos usambarensis* | $IC_{50}$ (19.5 μM) | 301 |
| **3.114** | Isotetrandrine |  | *Triclisia patens* | $IC_{50}$ (22.2 μM) | 308 |

**Table 16. Continued**

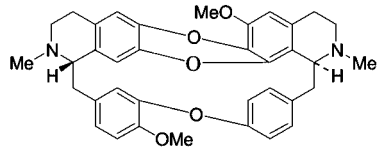
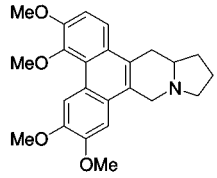
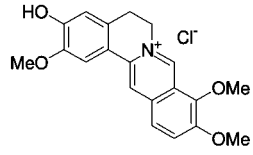
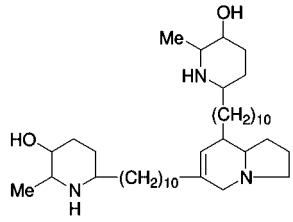
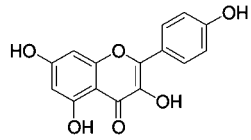
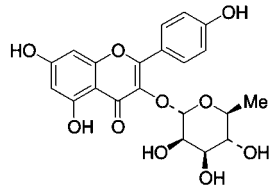
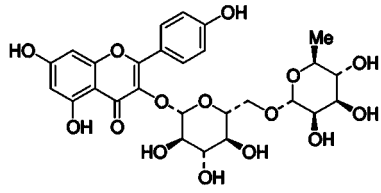
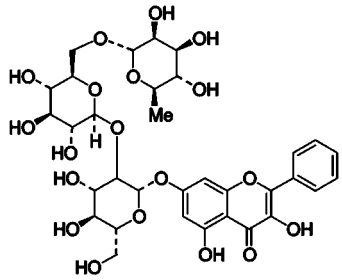
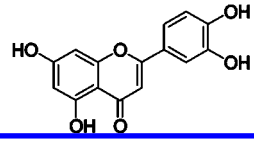
| Entry | Name of the Compound | Structure | Isolated from the Plant | Antiamoebic Activity | ref |
|---|---|---|---|---|---|
| **3.115** | Isotrilobine |  | *Triclisia patens* | $IC_{50}$ (10.8 μM) | 308 |
| **3.116** | Isotylocrebrine |  | *Tylophora hirsuta* | MIC (25 μg/mL) | 302 |
| **3.117** | Jatrorrhizine chloride |  | *Enantia chlorantha* | $IC_{50}$ (82.7 μM) | 305 |
| **3.118** | Juliflorine |  | *Prosopis juliflora* | $IC_{50}$ (10.0 μg/mL) | 315 |
| **3.119** | Kaempferol |  | *Cuphea pinetorum* | $IC_{50}$ (7.93 μg/mL) | 316 |
| **3.120** | Kaempferol-3-*O*-rhamnoside |  | *Morinda morindoides* | $IC_{50}$ (64.7 μg/mL) | 284 |
| **3.121** | **Kaempferol-3-*O*-rutinoside** |  | ***Morinda morindoides*** | **$IC_{50}$ (72.5 μg/mL)** | **284** |
| **3.122** | **Kaempferol-7-*O*-rhamnosyl-sophoroside** |  | ***Morinda morindoides*** | **$IC_{50}$ (>125 μg/mL)** | **284** |
| **3.123** | **Luteolin** |  | ***Morinda morindoides*** | **$IC_{50}$ (17.8 μg/mL)** | **284** |

**Table 16. Continued**

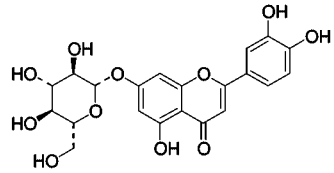
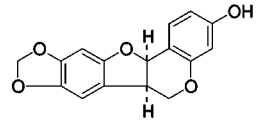
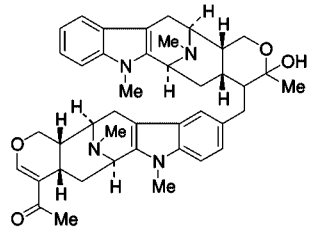
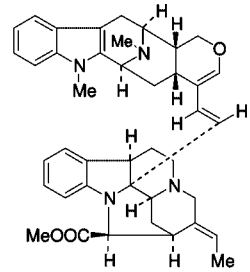
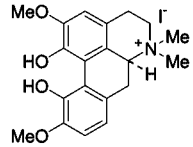
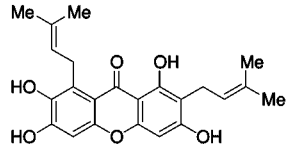
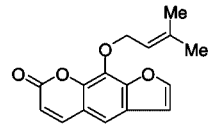
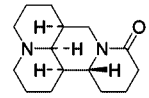
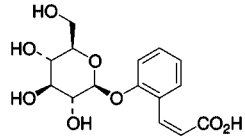
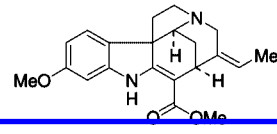
| Entry | Name of the Compound | Structure | Isolated from the Plant | Antiamoebic Activity | ref |
|---|---|---|---|---|---|
| **3.124** | Luteolin-7-*O*-glucoside |  | *Cuphea pinetorum* | $IC_{50}$ (44.7 μg/mL) | 307 |
| **3.125** | Maackiain |  | *Virgilia oroboides* | MIC (1.0 μg/mL) | 295 |
| **3.126** | Macralstonine |  | *Alstonia angustifolia* | $ED_{50}$ (Inactive at 70 μM) | 255 |
| **3.127** | Macrocarpamine |  | *Alstonia angustifolia* | $ED_{50}$ (8.12 μM) | 255 |
| **3.128** | Magnoflorine iodide |  | *Thalictrum thalictroides* | $IC_{50}$ (111 μM) | 305 |
| **3.129** | Mangostin |  | *Garcinia mangostina* | Not found | 280 |
| **3.130** | Marmelosin |  | *Aegle marmelos* | Not found | 251 |
| **3.131** | Matrine |  | *Sophora subprostrata* | Not found | 251 |
| **3.132** | Melilotoside |  | *Teloxys graveolens* | $IC_{50}$ (12.5 μg/mL) | 290 |
| **3.133** | 11-Methoxy akuammicine |  | *Alstonia angustifolia* | $ED_{50}$ (70.5 μM) | 255 |

**Table 16. Continued**

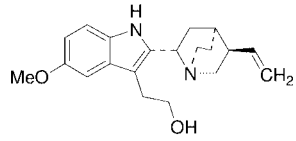
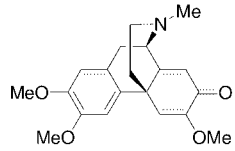
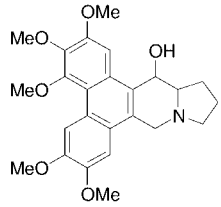
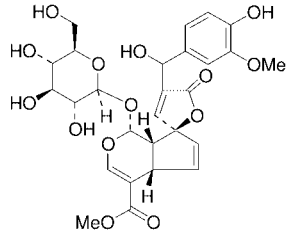
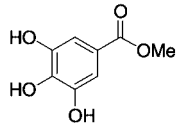
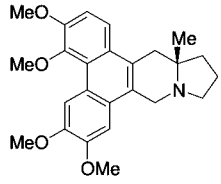
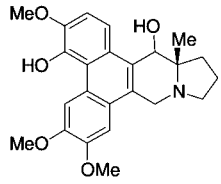
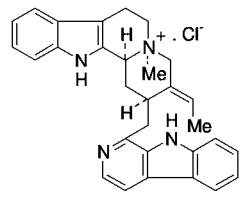
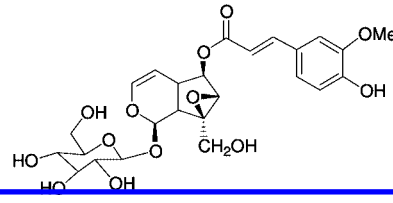
| Entry | Name of the Compound | Structure | Isolated from the Plant | Antiamoebic Activity | ref |
|---|---|---|---|---|---|
| **3.134** | 10-Methoxy cinchonamine |  | *Cinchona ledgeriana* | $IC_{50}$ (4.5 μg/mL) | 303 |
| **3.135** | *O*-methylflavinantine |  | *Rhigiocarya racemifera* | $IC_{50}$ (73.4-147 μM) | 305 |
| **3.136** | 4-Methoxy-14-hydroxytylophorine |  | *Tylophora indica* | MIC (3.12 μg/mL) | 302 |
| **3.137** | Methoxy-gaertneroside |  | *Morinda morindoides* | $IC_{50}$ (2.3 μg/mL) | 283 |
| **3.138** | Methyl gallate |  | *Geranium niveum* | $IC_{50}$ (22.6 μg/mL) | 288 |
| **3.139** | 13a-Methyl tylohirsutine |  | *Tylophora hirsute* | MIC (25 μg/mL) | 302 |
| **3.140** | 13a-Methyl tylohirsutinidine |  | *Tylophora hirsute* | MIC (400 μg/mL) | 302 |
| **3.141** | $N_b$-methyl usambarensine chloride |  | *Strychnos usambarensis* | $IC_{50}$ (4.12 μg/mL) | 256 |
| **3.142** | Minecoside |  | *Kigelia pinnata* | $IC_{50}$ (0.74 μM) | 286 |

**Table 16. Continued**

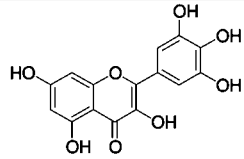
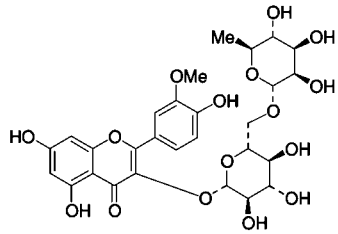
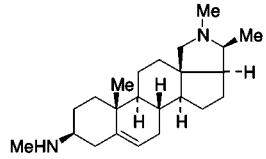
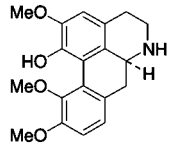
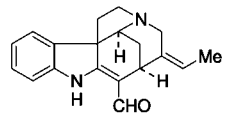
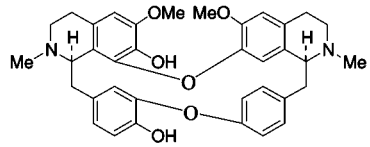
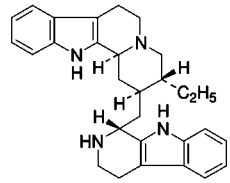
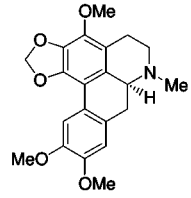
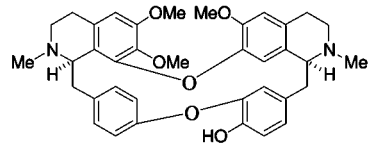
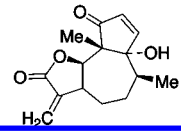
| Entry | Name of the Compound | Structure | Isolated from the Plant | Antiamoebic Activity | ref |
|---|---|---|---|---|---|
| **3.143** | Myricetin |  | *Ampelopsis cantoniensis* | $IC_{50}$ (115.21 μg/mL) | 287 |
| **3.144** | Narcissin |  | *Teloxys graveolens* | $IC_{50}$ (17.2 μg/mL) | 290 |
| **3.145** | Norconessine |  | *Holarrhena antidysenterica* | Active at 1:5000 dilution | 317 |
| **3.146** | Norcorydine |  | *Litsea wightiana* | $IC_{50}$ (76.4-153 μM) | 305 |
| **3.147** | Norfluorocurarine |  | *Alstonia angustifolia* | $ED_{50}$ (84.1 μM) | 255 |
| **3.148** | Obamegine |  | *Triclisia patens* | $IC_{50}$ (30.8 μM) | 308 |
| **3.149** | Ochrolifuanine A |  | *Ochrosia miana* | $IC_{50}$ (1.3 μg/mL) | 247 |
| **3.150** | Ocoteine |  | *Thalictrum isopyroides* | $IC_{50}$ (51.2 μM) | 305 |
| **3.151** | Oxyacanthine |  | *Triclisia patens* | $IC_{50}$ (32.3 μM) | 308 |
| **3.152** | Parthenin |  | *Parthenium hysterophorus* | MIC (10-12.5 μg/mL) | 318 |

**Table 16. Continued**

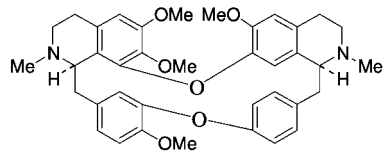
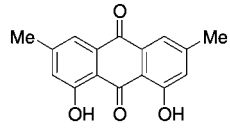
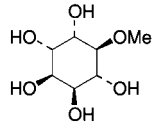
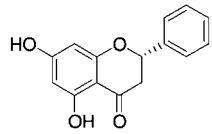
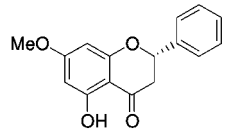
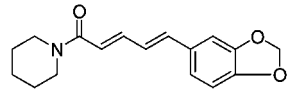
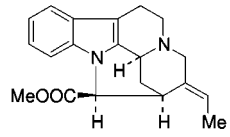
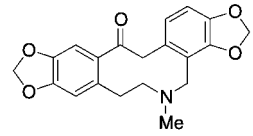
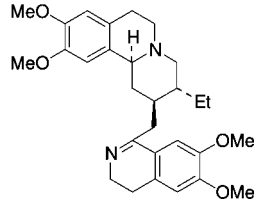
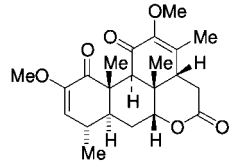
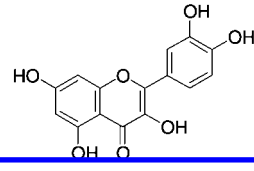
| Entry | Name of the Compound | Structure | Isolated from the Plant | Antiamoebic Activity | ref |
|---|---|---|---|---|---|
| **3.153** | Phaeanthine |  | *Triclisia patens* | $IC_{50}$ (17.4 μM) | 308 |
| **3.154** | Physcion |  | *Senna racemosa* | $IC_{50}$ (12.70 μg/mL) | 296 |
| **3.155** | Pinitol |  | *Senna racemosa* | $IC_{50}$ (16.59 μg/mL) | 296 |
| **3.156** | Pinocembrin |  | *Teloxys graveolens* | $IC_{50}$ (80.76 μg/mL) | 287 |
| **3.157** | Pinostrobin |  | *Teloxys graveolens* | $IC_{50}$ (184.45 μg/mL) | 287 |
| **3.158** | Piperine |  | *Piper longum* | Not active | 319 |
| **3.159** | Pleiocarpamine |  | *Alstonia angustifolia* | $ED_{50}$ (47.4 μM) | 255 |
| **3.160** | Protopine |  | *Corydalis speciosa* | $IC_{50}$ (70.7-142 μM) | 305 |
| **3.161** | Psychotrine |  | *Cephaelis ipecacuanha* | $IC_{50}$ (8.19 μg/mL) | 300 |
| **3.162** | Quassin |  | *Quassia amara* | $IC_{50}$ (0.5 μg/mL) | 303 |
| **3.163** | Quercetin |  | *Cuphea pinetorum* | $IC_{50}$ (114.3 μg/mL) | 316 |

**Table 16. Continued**

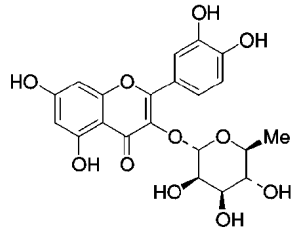
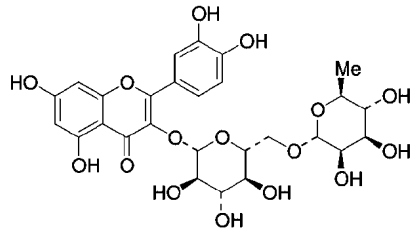
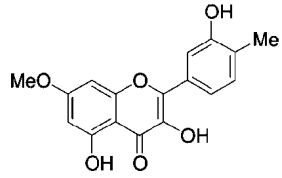
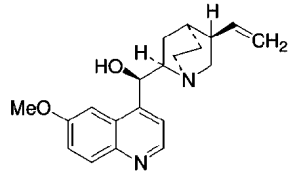
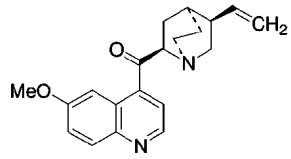
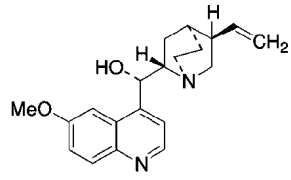
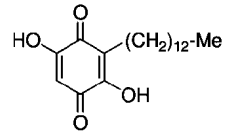
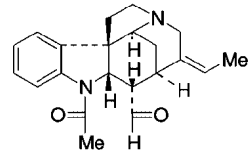
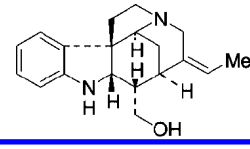
| Entry | Name of the Compound | Structure | Isolated from the Plant | Antiamoebic Activity | ref |
|---|---|---|---|---|---|
| **3.164** | Quercetin-3-*O*-rhamnoside |  | *Cuphea pinetorum* | $IC_{50}$ (84.7 μg/mL) | 307 |
| **3.165** | Quercetin-3-*O*-rutinoside |  | *Morinda morindoides* | $IC_{50}$ (120.7 μg/mL) | 284 |
| **3.166** | Quercetin-7,4'-dimethylether |  | *Morinda morindoides* | $IC_{50}$ (70.3 μg/mL) | 284 |
| **3.167** | Quinidine |  | *Cinchona ledgeriana* | $IC_{50}$ (16.6 μg/mL) | 303 |
| **3.168** | Quinidinone |  | *Cinchona ledgeriana* | $IC_{50}$ (7.4 μg/mL) | 303 |
| **3.169** | Quinine |  | *Cinchona ledgeriana* | $IC_{50}$ (14.8 μg/mL) | 303 |
| **3.170** | Rapanone |  | *Ardisia oxyphylla* | $EC_{100}$ (200 μg/mL) | 320 |
| **3.171** | Retulinal |  | *Strychnos variabilis* | $IC_{50}$ (Inactive at 75 μM) | 301 |
| **3.172** | Retuline |  | *Strychnos variabilis* | $IC_{50}$ (Inactive at 74 μM) | 301 |

**Table 16. Continued**

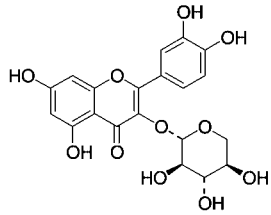
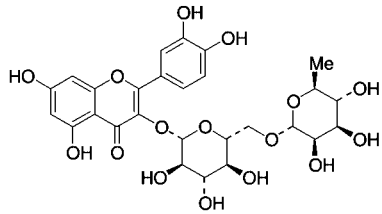
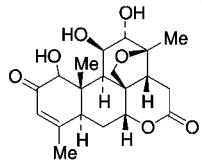
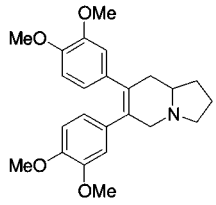
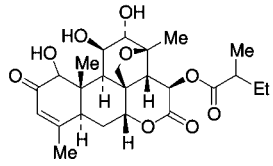
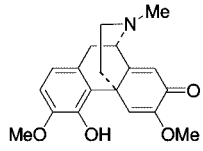
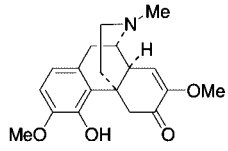
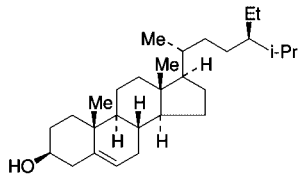
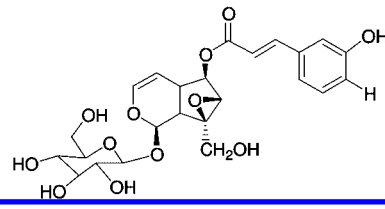
| Entry | Name of the Compound | Structure | Isolated from the Plant | Antiamoebic Activity | ref |
|---|---|---|---|---|---|
| **3.173** | Reynoutrin |  | *Geranium niveum* | $IC_{50}$ (108.92 μg/mL) | 287 |
| **3.174** | Rutin |  | *Forsythia suspense* | $IC_{50}$ (119.67 μg/mL) | 287 |
| **3.175** | Samaderine E |  | *Samadera indica* | Inactive | 278 |
| **3.176** | *d*-Septicine |  | *Tylophora indica* | MIC (400 μg/mL) | 302 |
| **3.177** | Simalikalactone D |  | *Brucea antidysenterica* | $IC_{50}$ (0.047 μg/mL) | 278 |
| **3.178** | Sinoacutine |  | *Croton lechleri* | $IC_{50}$ (76.4-153 μM) | 305 |
| **3.179** | Sinomenine |  | *Sinomenium acutum* | $IC_{50}$ (56.2 μM) | 305 |
| **3.180** | *β*-Sitosterol |  | *Cuphea pinetorum* | $IC_{50}$ (52.3 μg/mL) | 307 |
| **3.181** | Specioside |  | *Kigelia pinnata* | $IC_{50}$ (0.39 μM) | 286 |

**Table 16. Continued**

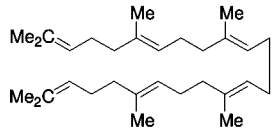
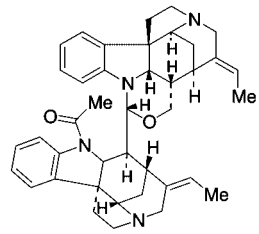
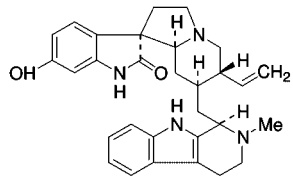
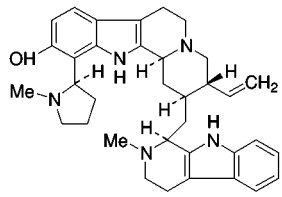
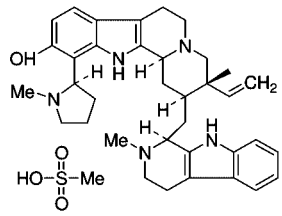
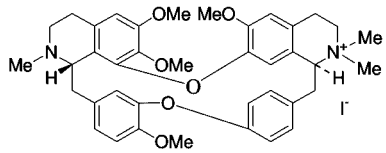
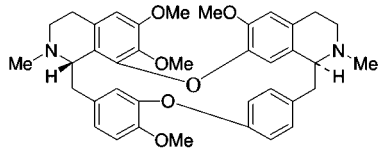
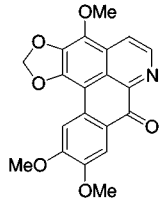
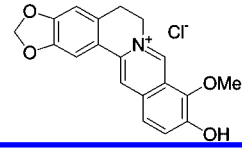
| Entry | Name of the Compound | Structure | Isolated from the Plant | Antiamoebic Activity | ref |
|---|---|---|---|---|---|
| **3.182** | Squalene |  | *Cuphea pinetorum* | $IC_{50}$ (270.1 μg/mL) | 307 |
| **3.183** | Strychnobiline |  | *Strychnos variabilis* | $IC_{50}$ (Inactive at 35 μM) | 301 |
| **3.184** | Strychnofoline |  | *Strychnos usambarensis* | $IC_{50}$ (Inactive at 52 μM) | 301 |
| **3.185** | Strychnopentamine |  | *Strychnos usambarensis* | $IC_{50}$ (7.7 μg/mL) | 256 |
| **3.186** | Strychnopentamine methanesulphonate |  | *Strychnos usambarensis* | $IC_{50}$ (10.1 μg/mL) | 256 |
| **3.187** | Tetrandine methiodide |  | *Triclisia patens* | $IC_{50}$ (39.5 μM) | 308 |
| **3.188** | Tetrandrine |  | *Triclisia patens* | $IC_{50}$ (16.9 μM) | 308 |
| **3.189** | Thalicminine |  | *Thalictrum isopyroides* | $IC_{50}$ (75.1 μM) | 305 |
| **3.190** | Thalifendine chloride |  | *Fibraurea chloroleuca* | $IC_{50}$ (116 μM) | 305 |

**Table 16. Continued**

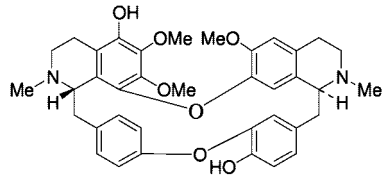
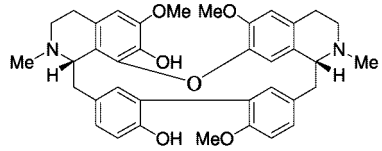
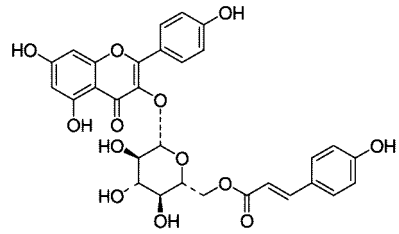
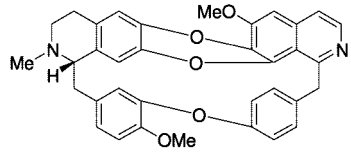
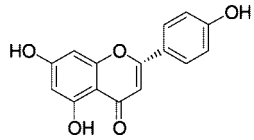
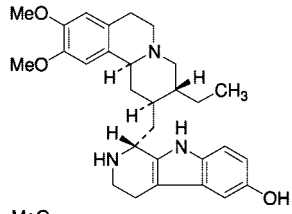
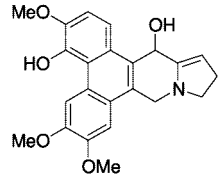
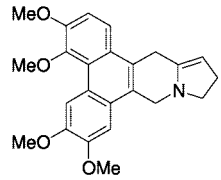
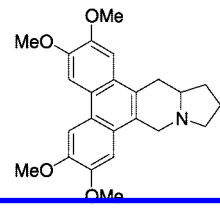
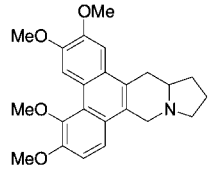
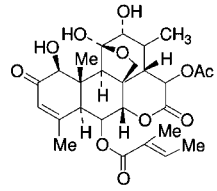
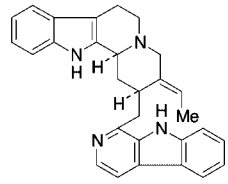
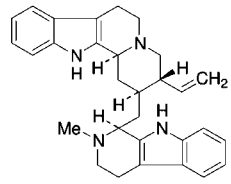
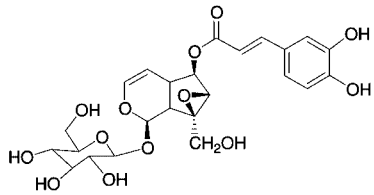
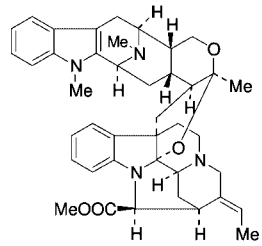
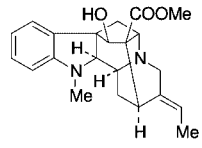
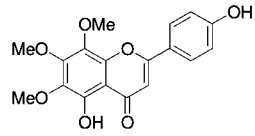
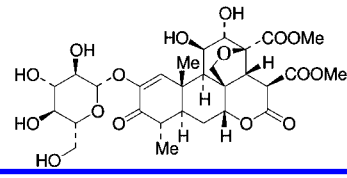
| Entry | Name of the Compound | Structure | Isolated from the Plant | Antiamoebic Activity | ref |
|---|---|---|---|---|---|
| **3.191** | Thalisopidine |  | *Triclisia patens* | $IC_{50}$ (80.1 μM) | 308 |
| **3.192** | Tiliagene |  | *Triclisia patens* | $IC_{50}$ (31.6 μM) | 308 |
| **3.193** | Tiliroside |  | *Helianthemum glomeratum* | $IC_{50}$ (17.45 μg/mL) | 287 |
| **3.194** | Trigilletimine |  | *Triclisia patens* | $IC_{50}$ (41.7 μM) | 308 |
| **3.195** | 4,5,7-Trihydroxy flavanone |  | *Salvia Mexicana* | $IC_{50}$ (98.24 μg/mL) | 287 |
| **3.196** | Tubulosine |  | *Strychnos usambarensis* | $IC_{50}$ (1.6 μg/mL) | 247 |
| **3.197** | Tylohirsutinidine |  | *Tylophora hirsute* | MIC (200 μg/mL) | 302 |
| **3.198** | Tylohirsutinine |  | *Tylophora hirsuta* | MIC (50 μg/mL) | 302 |
| **3.199** | Tylophorine |  | *Tylophora indica* | MIC (6.25 μg/mL) | 302 |

**Table 16. Continued**

| Entry | Name of the Compound | Structure | Isolated from the Plant | Antiamoebic Activity | ref |
|---|---|---|---|---|---|
| **3.200** | Tylophorinine |  | *Tylophora indica* | MIC (400.0 μg/mL) | 302 |
| **3.201** | Undulatone |  | *Hannoa undulate* | Inactive | 278 |
| **3.202** | Usambarensine |  | *Strychnos usambarensis* | $IC_{50}$ (0.49 μg/mL) | 256 |
| **3.203** | Usambarine |  | *Strychnos usambarensis* | $IC_{50}$ (0.46 μg/mL) | 256 |
| **3.204** | Verminoside |  | *Kigelia pinnata* | $IC_{50}$ (0.19 μM) | 286 |
| **3.205** | Villastonine |  | *Alstonia angustifolia* | $ED_{50}$ (11.8 μM) | 255 |
| **3.206** | Vincamajine |  | *Alstonia angustifolia* | $ED_{50}$ (Inactive at 70 μM) | 255 |
| **3.207** | Xanthomicrol |  | *Brickellia paniculata* | $IC_{50}$ (274.85 μg/mL) | 287 |
| **3.208** | Yadanzioside F |  | *Brucea javanica* | $IC_{50}$ (2.33 μg/mL) | 265 |

that lipophilicity plays an important part in drug pharmacokinetics. The activity of macralstonine **3.126** against *E. histolytica* and *P. falcipaum* was increased by esterification, possibly by facilitating its transport across lipid barriers and cell membranes as a result of its increased lipophilicity. The most potent alkaloid found in this study, villastonine **3.205**, was also explored for its cytotoxic effect against KB cells, which was parallel to its antiamoebic activity, suggesting that there is no selective toxicity toward amoebae. However, emetine was highly toxic to KB cells, but it was three times less toxic to amoebae. When compared to emetine, villastonine **3.205** was shown to have a more favorable antiamoebic/cytotoxic ratio.

Wright and co-workers studied seven alkaloids from *Strychnos usambarensis* and assessed them for their in vitro antiprotozoal activity.[256] Of these, usambarensine **3.202**, 3′,4′-dihydro usambarensine **3.068**, usambarine **3.203**, and 18′,19′-dihydro usambarine **3.069** have marked in vitro activities against *E. histolytica.* Interestingly, the activities of these alkaloids against *E. histolytica* and *P. falciparum* were quite different, suggesting that minor changes in structure may possibly have a positive impact on activity against one of the organisms and reduce it against the other. Usambarine **3.203** is highly active against *E. histolytica* in comparison to *P. falciparum* in vitro, but an usambarine analogue (strychnopentamine **3.185**), which has C-11 hydroxy and *N*-methylpyrrolidine group at C-12, demonstrated low antiamoebic but high antiplasmodial activity. These substituents at C-11 and C-12 clearly affect the antiprotozoal activity profiles of the compounds. In contrast to usambarensine, 3′,4′-dihydrousambarensine **3.068** has slightly weaker antiamoebic activity, which again suggests even minor structural differences have an effect on antiamoebic activity. The different profiles of activity seen with individual alkaloids suggest that there may be subtle differences in the active site of action of these compounds. Usambarensine **3.202** possesses activities similar to those of emitine and can be explained by molecular conformation studies that have shown that usambarensine may adopt a conformation similar to that of emetine, and it is also possible that these compounds are protein synthesis inhibitors, like emetine. The mode of action of usambarine and related alkaloids is still unknown, but it was suggested that they inhibit the protein synthesis and act as DNA intercalators.[257] Strychnopentamine **3.185** and isostrychnopentamine **3.113** possess potent antiplasmodial activities and are less active against *E. histolytica*, while usambarine was found to be a potent antiamoebic compound. It was concluded that emetine and usambaresine type alkaloids require the presence of two aromatic systems in a definite arrangement in their least energy conformation state. Cytotoxic activities of usambarine **3.203** and usambarensine **3.202** against KB cells were found to be the most selective among the tested alkaloids against *E. histolytica.* Cytotoxicity to antiamoebic ratio for usambarine was 20.4, while for usambarensine this ratio was 18.8, which was about 50 times more selective when compared with emetine. Emetine was more toxic to KB cells than to amoebae (cytotoxic/antiamoebic ratio = 0.14). An oxindole alkaloid, strychnofoline **3.184**, was the only compound isolated from *S. usambarensis* without any antiprotozoal activity. Compounds containing only one indole ring system did not show any antiprotozoal properties, which suggested that the presence of two indole moieties is essential for activity in these compounds.

Conessine **3.055** is the major steroidal alkaloid isolated from *Halarrhena antidysenterica*, which was introduced in Europe as a cure for amoebic dysentery in the 19th century.[258] It was observed that the crude extracts from *Tabernaemontana* species have in vitro amoebicidal activity.[259] A number of species from the Simaroubaceae family have been used in indigenous medicine for the treatment of amoebic dysentery[251,258,260−262] including *Ailanthus*, *Brucea*, *Castela*, *Picrasma*, *Quassia*, and *Simarouba*. Ailanthone **3.006** from *Ailanthus altissima* has been reported to be active in vitro and in vivo,[263] but its use was precluded because of severe toxicity. Bisbenzylisoquinoline alkaloids contain two isoquinoline moieties linked to two benzyl molecules and classified into 26 structural classes on the basis of the number, position, and type of connecting bridges between two monomers. Marshall et al. studied 24 bisbenzylisoquinoline alkaloids for their antiplasmodial, antiamoebic, and cytotoxic activity and found that they have some selectivity in their antiprotozoal action.[308] The most active bisbenzylisoquinoline alkaloids against *E. histolytica* were aromoline **3.019**, isotrilobine **3.115**, and insularine **3.104** with the $IC_{50}$ in the range of 5−11 $\mu$M, while 19 alkaloids were found to be active against *P. falciparum* and displayed $IC_{50}$ values < 10 $\mu$M. Tested alkaloids did not show significant cytotoxic activity against KB cells. The in vitro activity of the tested alkaloids was markedly different against *E. histolytica* than against *P. falciparum.*

## 3.2. Quassinoids

The research and application of quassinoids continued to extend through the 1990s with the isolation, structure elucidation, and pharmaceutical evaluation of many new compounds. Quassinoids, a group of degraded triterpenes found in various species of the Simaroubaceae, have been shown to be potent antiprotozoal agents.[264,265] *Brucea javanica* fruits have been used clinically for the treatment of amoebic dysentery but found to be less effective than emetine.[251,266] *B. javanica* fruit extracts were explored by Wright et al., and major constituents bruceines A **3.027**, B **3.028**, and C **3.029** were found to be active against *E. histolytica*.[265] Bruceine A was more active when compared to bruceines B and C. Bruceine B possesses simple acetate, and bruceine C has 3′,4′-dimethyl-4'hydroxy-pent-2′-eneoic functionality at C-15, although the nature of these ester groups do not have any impact on antiamoebic activity as bruceines B and C both were highly active. On the other hand, bruceantin **3.025** was 10−15 times more active then bruceines B and C even though bruceantin lacks a 4′-hydroxy group on the C-15, which is a part of bruceine C. Despite the structural difference from bruceines B and C, bruceine D **3.030** possesses similar antiamoebic activity. Wright et al. compared in vitro activities of a number of quassinoids against four species of protozoa with their cytotoxicity against human KB cells in vitro.[267] Although bruceantin **3.025** was ∼50 fold more active than metronidazole against *E. histolytica*, it was highly toxic to KB cells. It was found that four compounds, ailanthinone **3.005**, bruceine D **3.030**, brusatol **3.031**, and glaucarubinone **3.091**, were slightly less toxic to KB cells than to *E. histolytica*.

*Quassia amara* and *Picrasma excelsa* contain quassin **3.162**, which was found to be active against *E. histolytica* in vivo and in vitro but was slightly cytotoxic.[268,269] Glaucarubin **3.090** from *Simarouba glauca* has been used medicinally in France and Germany[251,270] and also showed

more selectivity with ailanthinone **3.005** toward *E. histolytica* than the other quassinoids.[271−277] Similarly, $IC_{50}$ values for in vitro amoebicidal activities have been reported for a series of bruceolides.[278,279] Structure−activity comparison showed that minor differences in side chains lead to difference in activity between bruceantin **3.025**, bruceantinol **3.026**, and brusatol **3.031**. Glaucarubolone **3.093** and glaucarubinone **3.091** had similar activities but different side chain structures; the former had a free hydroxyl group at C-15, while the latter had a five-carbon ester. Bruceantin **3.025** was almost 100 times more active then the glaucarubin **3.090** ($IC_{50}$ = 1.57 $\mu$g/mL). Quassinoids have been shown to be potential protein synthesis inhibitors in parasite as well as mammalian cells; the selectivity seen could be due to the difference in protein sysnthesis mechanism between different protozoal parasites. A comparative study on the antiprotozoal activities of quassinoids has suggested that there are interspecies differences in protozoan protein synthesis that result in a difference in selectivity toward one species or other. Other nonalkaloid natural products having amoebicidal activity include mangostin **3.129** from *Garcinia mangostina*,[280] marmelosin **3.130** from *Aegle marmelos*, and anemonin **3.014** from *Anemone pulsatilla*.[251]

## 3.3. Flavonoids and Iridoids

Natural flavonoids are plants' secondary metabolites and have been referred to as nature's biological response modifiers. A recent study done at Children's Hospital & Research Center Oakland has shown that epicatechin, quercetin, and luteolin can inhibit the development of fluids that result in diarrhea by targeting the intestinal cystic fibrosis transmembrane conductance regulator Cl-transport, inhibiting cAMP-stimulated Cl-secretion in the intestine.[281] Flavonoids have been considered as the active principles of many antidiarrheic plants, and it has been speculated that these propeties are consequences of their inhibitory effects against protozoa.

An aqueous decoction from fresh leaves of *Morinda morindoides*, one of the most popular medicinal plants used in Zairese traditional medicine, was employed for the treatment of malaria, intestinal worms, and amoebiasis.[282] A number of flavonoids and iridoids have been isolated from *Morinda morindoides* leaves.[283−285] Plant extracts were found to be highly active against *E. histolytica*, which was explained as the synergistic effect of the iridoids, flavonoids, or other constituents present in the tested fractions. Tested iridoids and flavonoids showed promising biological activity, and the most active were epoxygaertneroside **3.077** and methoxygaertneroside **3.137** followed by gaertneroside **3.082** and gaertneric acid **3.083**. The results indicated that the presence of an epoxy group between C-6 and C-7 or a methoxy group at C-3′ was important for prominent antiamoebic activity. The carboxyl group present at C-14 has a negative impact on the activity. Since the isolated compounds and the crude extract had the same order of magnitude of $IC_{50}$, the combined effects of these iridoids only account for partial antiamoebic activity observed. All extracts and isolated compounds were evaluated for possible cytotoxicity against MT-4 cells during an anti-HIV screening in which they were found to be inactive. All test samples did not show any cytotoxic effect at the highest test concentration of 100 $\mu$g/mL; therefore, the observed antiamoebic activity was not related to a nonspecific cytotoxicity. Recently, three iridoids, specioside **3.181**, verminoside **3.204**, and minecoside **3.142**, were isolated from an African tree *Kigelia pinnata*, which showed in vitro antiamoebic activity comparable to metronidazole.[286]

Calzada et al. studied 18 natural flavonoids against *E. histolytica*; among them, (−)-epicatechin **3.074**, (−)-epigallocatechin **3.075**, and kaempferol **3.119** were found to be the most active.[287] The flavonoids kaempferol **3.119**, apigenin **3.016**, and luteolin **3.123** exhibited significantly higher activities than their corresponding glycosides. Kaempferol **3.119** and quercetin **3.163** have a free hydroxyl at C-3 in ring C, and the presence of a glucosyl moiety or a coumaroyl glucosyl group at C-3C position substantially decreased the antiprotozoal activity of kaempferol; on the other hand, the activity of quercetin was increased by the presence of a sugar moiety at the C-3C position, but its antigiardial activity was decreased, suggesting selective activity toward one protozoa. Kaempferol **3.119** exhibited the highest activity against *E. histolytica* and *G. lamblia*, suggesting the prerequisite kaempferol residue in these flavanol glycosides. It was observed from different studies that kaempferol meight be an important constituent of *C. pinetorum*, a plant used as an antidiarrheic to treat dysentery. The structure−activity relationship showed that antiamoebic activity of a flavonoid required a 7-hydroxyl group in ring A, which accounts for the significant activity of apigenin **3.016** and luteolin **3.123**. It was also discovered that the 4-keto group and the 2,3-double bond of ring C were not necessary for high antiprotozoal activity, whereas it seems to be associated with the nonplanarity of the A and C ring components of the flavan-3-ol. Since *trans*-isomers were less active against protozoal than *cis*-(−)-epicatechin and (+)-catechin, it was suggested that the 2,3-*cis*(α) stereochemistry might be an important prerequisite for the observed activity. It was also noted that a 5,7-dihydroxy substituent at ring A and the presence of a 3-hydroxy group were the common structural features of the most active compounds, for example, kaempferol **3.119**, (−)-epicatechin **3.074**, and (−)-epigallocatechin **3.075**. Quercetin **3.163** and myricetin **3.143** were less active in comparison with (−)-epicatechin and (−)-epigallocatechin, and the antiprotozoal activity further decreased significantly when the degree of oxygenation was increased in the B ring.

Four new A-type proanthocyanidins, geranin A {*epi*-afzelechin-(4$\beta$→8,2$\beta$→*O*→7)-afzelechin} **3.085**, geranin B {*epi*-catechin-(4$\beta$→8,2$\beta$→*O*→7)-afzelechin} **3.086**, geranin C {*epi*-afzelechin-(4$\beta$→8,2$\beta$→*O*→7)-gallocatechin} **3.087**, and geranin D {*epi*-afzelechin-(4$\beta$→8, 2$\beta$→*O*→7)-afzelechin-(4$\beta$→8,2$\beta$→*O*→7)-afzelechin} **3.088**, were isolated from the root of *Geranium niveum* with reynoutrin **3.173**, hyperin **3.103**, methyl gallate **3.138**, and 3-$\beta$-caffeoyl-12-olanen-28-oic acid **3.033**.[288,289] These compounds did not display any cytotoxic activity. Geranin B **3.086** was the most active, whereas geranin D **3.088** showed moderate activity against *E. histolytica*. Two new flavonoids, chrysin **3.043** and narcissin **3.144**, were isolated from *Teloxys graveolens* and tested in vitro; results showed that only narcissin showed some activity.[290]

## 3.4. Miscellaneous

Gossypol **3.094**, a polyphenolic compound, is a constituent of cottonseed oil, which has attracted great interest because of its antiprotozoal activity against *P. falciparum*, *T. curzi*, and *E. histolytica*.[291] The in vitro activity of gossypol against *E. histolytica* was 11 and 39 times greater than those of metronidazole and emetine, respectively. It also showed potent in vivo activity on golden hamster model. The in vitro

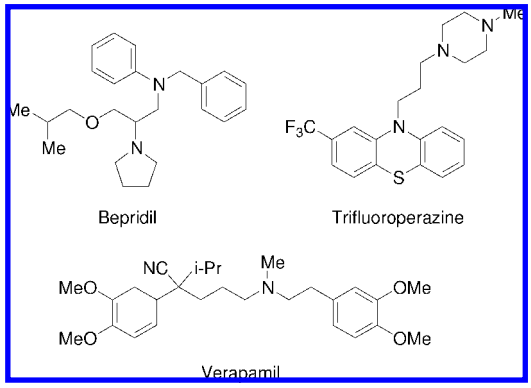



**Figure 19.** Bepridil, verapamil, and trifluoroperazine (TFP).

activity of (±)-, (+)-, and (−)-gossypol against axenic trophozoites showed that the (−)-isomer was more active than the recemate and the (+)-isomer.[292] Studies have shown that (+)-gossypol and its isomer, (−)-gossypol, both bind to serum albumin and other proteins, and this gossypol−protein complex was found to be inactive. It was concluded that, because of the high binding affinity for the protein molecule, (+)-gossypol was relatively less active. The mode of action of gossypol includes the inhibition of NADH- dependent enzymes, which explains its effect on mammalian cells and parasite. These results indicate that the antiamoebic activity of gossypol is mainly due to its content of (−)-isomer in all the strains tested. Since (−)-gossypol was more active, it could be speculated that it has more affinity for NADP-dependent enzyme, which can show a major inhibitory effect.

Another natural product with interesting activity against *E. histolytica* was allicine (diallylsulphine) **3.009**, isolated from a crushed clove of garlic (*Allium sativum*).[293] Allicine has been reported to inhibit the growth of *E. histolytica*. As *E. histolytica* is known to contain a number of essential thioproteins and enzymes, it has been suggested that allicine may act on the parasite by inhibiting processes essential for the maintenance of redox balance. Only fresh garlic extract was active against the microorganism in vitro, as was expected owing to the unstable nature of allicine. Garlic may be a useful, cheap, and safe treatment for amoebiasis,[294] but further studies will be needed to confirm this.

Aromatic phenols chlorophorin **3.041** and iroko **3.105** were isolated from *Virgilia oroboides* and tested along with maackiain **3.125** (pterocarpan) and formomometin **3.080** (isoflavone) from *Chlorophora excelsa*.[295] Chlorophorin **3.041** showed the highest antiamoebic activity followed by maackiain **3.125** and iroko **3.105**. Recently, four compounds (chrysophanol **3.045**, physcion **3.154**, pinitol **3.155**, and cassine **3.036**) were isolated from *Senna racemosa* and screened.[296] Only chrysophanol **3.045** showed moderate activity, while the structurally similar anthraquinone physcion **3.154** was inactive, which again proved that small structural differences could lead to a difference in activity.

An α-methylene-γ-lactone sesquiterpene, parthenin **3.152**, was isolated from *Parthenium hysterophorus* and tested in vitro and in vivo against *E. histolytica*, as well as for cytotoxicity in mice.[318] It showed significant in vitro activity but was less active then metronidazole when assessed in vivo in golden hamster model with induced liver abscesses. Hamsters were treated with four different doses; unfortunately, none of them attained the inhibition of liver necroses in comparison to reference drug. It was reported that parthenin was toxic to animals within the therapeutic range. Many natural products from plant species have been shown to have activity against one or more species of protozoa, but few have been shown to be highly selective antiprotozoal agents.[297] Some of these compounds have been shown to be highly active against *E. histolytica*[265] and *P. falciparum* in vitro and *P. berghei* in mice.[298,299] A prerequisite for potential antiprotozoal agents is that they should display a high degree of selectivity toward the parasite, i.e., have low toxicity to the host.

## 4. Drug Targets

Developing drugs for protozoal infections presents undeniable challenges; the most recent approach to successful drug design is to identify druggable targets. A drug target is a key molecule involved in a particular metabolic pathway that is specific to the infectivity or survival of a microbial pathogen. In recent years, by comparing biochemical pathways of parasite and host, many new targets are being uncovered that are generally proteins, enzymes, and nucleic acids. Complete gene sequencing of *E. histolytica*, published recently,[321] provided a remarkable view as it assisted in reconstruction of its metabolism and made it relatively easy to understand the relationship between the host and the parasite. Although the prospect of the drug targets are beyond the scope of this review, we are including the summarized information available on this aspect of amoebiasis

*E. histolytica*, an amitochondrial protist, lacks both mitochondria and hydrogenosomes.[322] It is proved in different studies that this parasite uses carbohydrate as its main source of energy.[323] In *E. histolytica*, a pathway involved in the fermentation of glucose uses PPi-dependent phosphofructokinase, which is the main rate-limiting glycolytic enzyme. The parasite uses PPi-dependent phosphofructokinase as a phosphate donor in carbohydrate metabolism, which is significantly different from the ATP-dependent phosphofructikinase found in the host.[324] Other glycolytic pathway enzymes like triosephosphate isomerase (TPI), enolase, and pyruvate phosphate kinase play key roles in glucose metabolism and can be potential therapeutic targets for drug design against *Entamoeba*. Triosephosphate isomerase is a specific enzyme with cystein residue that regulates glyceraldehyde-3-phosphate.[325] Methylmethane thiosulfonate, a thiole specific reagent, inactivates the EhTIM and dissociates it into more stable compounds. Enolase catalyzes the conversion of 2-phosphoglycerate to phosphoenol pyruvate. The sequencial difference of *E. histolytica* enolase from host enolase in a specific region makes it quite an attractive target for antiparasitic drugs.[326] Pyruvate phosphate dikinase (PPDK) is again another inorganic pyrophosphate dependent enzyme in the glycolytic pathway that substitutes pyruvate kinase present in humans and could serve as a target.

Calcium, a divalent cation, functions as an important signaling molecule to control many signal transduction pathways and plays an important role in the parasite-induced death of the target cell and pathogenesis.[327,328] The effect of calcium chelators, and calcium channel blockers, on growth and encystation in *E. histolytica* was explored by Makioka and established that extracellular calcium was essential for these processes.[329] Recently, different studies have demonstrated the involvement of calmodulin (CaM) and protein kinase C in secretory activity and encystation of *E. histolytica*.[330,331] A number of different calcium binding proteins have been identified, and two of them, EhCaBP1 and EhCaBP2, were characterized and studied for their role.[332,333] Amoebic cytolysis was effected significantly when

treated with calcium binding compounds like ethylene diaminetetraacetate (EDTA) and ethyleneglycol bis(β-aminoethylether)-*N*,*N*′-tetraacetate (EGTA). Na, Ca channel blockers bepridil and verapamil (Figure 19), antagonist of intracellular calcium flux 8-(*N*,*N*-diethylamino)octyl-3,4,5-trimethoxybenzoate (TMB-8), and calmodulin inhibitors *N*-(6-aminohexyl)-chloro-1-naphtalene sulfonamide (W-7) and trifluoroperazine (TFP) (Figure 19) also inhibited the growth and encystation.[329] *E. histolytica* is a cyst-forming parasite, and the cyst wall contains chitin and other unique molecules (polysaccharide and protein). Cyst wall assembly and encystment pathways could be new targets for chemotherapy based on the fact that calcium channel blockers and antagonist inhibit the encystation and cytoskeleton process.

Cysteine proteinases play an important role in infection and invasion and can be considered potential targets for *Entamoeba* because of their role in pathogenesis.[334] It was proposed that cystein proteinases degraded intestinal mucus, aided penetration of host tissue, degraded host proteins, activated host cell proteolytic cascade, and produced metastatic lesions. Developing inhibitors for cystein proteases make it an obvious choice to control intestinal and hepatic amoebiasis.[335] Natural polyamines, putrescine, spermidine, and spermine are positively charged key molecules that interact with DNA and are involved in the cell cycle and proliferation and regulation of apoptosis. Ornithine decarboxylate, a key enzyme in polyamine biosynthesis, produces putrescine from ornithine. Putrescine gets converted to spermidine by the addition of an amino propyl group from decarboxylated adensyl methionine and then spermine as well. Spermidine synthase catalyzes spermidine biosynthsis, which is an essential molecule for the synthesis of trypanothione in *E. histolytica*. Trypanothione synthetase, a spermidine dependent enzyme, could be a suitable drug target.[336] The knowledge of cellular mechanism and its cellular components interaction is instrumental to the development of new effective drugs and vaccines.

## 5. Conclusion and Future Prospects

*E. histolytica* infects an estimated 50 million people and is a significant cause of morbidity and mortality. It is clear from the impressive number of scientific publications that the search for a better amoebicidal agent than the currently used medications triggered the synthesis of numerous heterocyclic compounds and their biological studies as amoebicidal agents. The present review encompasses a survey of synthetic heterocyclic compounds and their metal complexes as well as numerous natural products as antiamoebic agents. In the future, rational design of more efficient drugs can be realized when the potential protein targets for amoebic diseases are clearly identified. In view of the urgent need for more efficacious and safer drugs to treat amoebiasis, this important area of research needs to be encouraged to produce faster results. Numerous plants used in the indigenous system of medicine for the treatment of dysentery require more thorough investigation in order to validate their activity and other toxicological effects. Yet there is no drug that can be considered to be ideal for the treatment of amoebiasis, particularly for the treatment of severe infections. The stratagem of using herbs and herbal products in antiamoebic therapy is indeed archaic, and intensive investigation of plants in indigenous medicine may uncover new leads for amoebicidal drugs.

Amoebiasis could be eradicated by practicing adequate sanitation worldwide, but it is unlikely that public health interventions will be available to all the world population in the near future; therefore, other approaches need to be considered. The role of amoebiasis in diarrheal illness could be far greater than even suspected because of the high prevalence of *E. histolytica* in developing countries. Recently, effective recombinant antigen-based vaccines have been developed and tested in animals, but there are unanswered questions regarding the effectiveness of these vaccines in preventing disease in man since testing of these vaccines in humans has yet to be performed.[337] Currently, development of vaccines is still in its infancy, and *E. histolytica* infections do not seem to result in long-term immunity to reinfection in man.[338,339] It is definitely a challenging task in the current scenario to completely eradicate amoebiasis; therefore, we hope that this review will encourage further research in finding new avenues for the control and treatment of this disease.

## 6. Abbreviations

| | |
|---|---|
| *E. histolytica* | *Entamoeba histolytica* |
| mnz | metronidazole |
| $IC_{50}$ | 50% inhibition concentration |
| $ED_{50}$ | 50% effective dose |
| $LD_{50}$ | 50% lethal dose |
| MIC | minimum inhibitory concentration |

## 7. Acknowledgments

We are thankful to Dr. Aditi Singh, Indian Institute of Technology; Dr. Ram Singh, University of Delhi, India; and Dr. R. N. Ondarza, National Autonomous University of Mexico, Mexico, for providing us with several literature references. Our special thanks to Dr. Dennis Hall from University of Florida for his creative suggestions, and Dr. Amir Azam from Jamia Millia Islamia, India for motivation.

## 8. References

(1) Stanley, S. L. *Lancet* **2003**, *361*, 1025.
(2) Marion, S.; Guillen, N. *Int. J. Parasitol.* **2006**, *36*, 131.
(3) Ackers, J. P.; Mirelman, D. *Curr. Opin. Microbiol.* **2006**, *9*, 367.
(4) Stanley, S. L. *Trends Parasitol.* **2001**, *17*, 280.
(5) Haque, R.; Ali, I. K.; Akther, S.; Petri, W. A., Jr *J. Clin. Microbiol.* **1998**, *36*, 449.
(6) Castelli, M.; Malagoli, M.; Lupo, L.; Bofia, S.; Paolucci, F.; Cermelli, C.; Zanca, A.; Baggio, G. *J. Antimicrob. Chemother.* **2000**, *46*, 541.
(7) Silvestri, R.; Artico, M.; Marceddu, S. T.; DeMontis, F.; LaColla, P. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 253.
(8) Demirayak, S.; Karaburun, A. C.; Kiraz, N. *Eur. J. Med. Chem.* **1999**, *34*, 275.
(9) Lamp, K. C.; Freeman, C. D.; Klutman, N. E.; Lacy, M. K. *Clin. Pharmacol.* **1999**, *36*, 353.
(10) Simms, J. S. *Primary Care Update Ob. Gyn.* **1996**, *3*, 153.
(11) Jokipii, L.; Jokipii, A. M. M. *Antimicrob. Agents Chemother.* **1985**, *28*, 561.
(12) Kapoor, K.; Chandra, M.; Nag, D.; Paliwal, J. K.; Gupta, R. C.; Saxena, R. C. *Int. J. Clin. Pharmacol. Res* **1999**, *19*, 83.
(13) Khaw, M.; Panosian, C. B *Clin. Microbiol. Rev.* **1995**, *8*, 427..
(14) Calzada, F.; Cervantes-Martinez, J. A.; Yepez-Mulia, L. *J. Ethnopharmacol.* **2005**, *98*, 191.
(15) Rossi, S. *Australian Medicines Handbook*; Adelaide: South Australia, 2006.
(16) Orozco, E.; Lopez, C.; Gomez, C.; Perez, D. G.; Marchat, L.; Banuelos, C.; Delgadillo, D. M. *Parasitol. Int.* **2002**, *51*, 353.
(17) Adagu, I. S.; Nolder, D.; Warhurst, D. C.; Rossignol, J. F. *J. Antimicrob. Chemother.* **2002**, *49*, 103.
(18) Sigel, H. *Angew. Chem., Int. Ed.* **1975**, *14*, 394.
(19) Hacker, M. P.; Douple, E. B.; Krakoff, I. H. *Platinum Coordination Complexes in Cancer Chemotherapy*; Martinus Nijhoff: Boston, 1984.
(20) *Ciba foundation Symposium 185, Ethnobotany and The Search for New Drugs*; John Wiley & Sons: New York, 1994.
(21) Beraldo, H.; Gambino, D. *Mini-Rev. Med. Chem.* **2004**, *4*, 31.
(22) Tenorio, R. P.; Goes, A. J. S.; de Lima, J. G.; de Faria, A. R.; Alves, A. J.; Aquino, T. M. *Quim. Nova* **2005**, *28*, 1030.
(23) Agarwal, K. C.; Sartorelli, A. C. *J. Med. Chem.* **1969**, *12*, 771.

(24) Liu, M. C.; Lin, T. S.; Cory, J. G.; Cory, A. H.; Sartorelli, A. C. *J. Med. Chem.* **1996**, *39*, 2586.
(25) Bellesia, F.; Boni, M.; Ghelfi, F. *Tetrahedron* **1993**, *49*, 199.
(26) Bernardi, F.; Csizmadia, I. G.; Mangini, A. *Organic Sulphur Chemistry*; Elsevier: Amsterdam, The Netherlands, 1985.
(27) Sharma, S.; Athar, F.; Maurya, M. R.; Azam, A. *Eur. J. Med. Chem.* **2005**, *40*, 1414.
(28) Shailendra; Bharti, N.; Gonzalez Garza, M. T.; Cruz-Vega, D. E.; Castro-Garza, J.; Saleem, K.; Naqvi, F.; Azam, A. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2675.
(29) Singh, S.; Athar, F.; Maurya, M. R.; Azam, A. *Eur. J. Med. Chem.* **2006**, *41*, 592.
(30) Shailendra; Bharti, N.; Naqvi, F.; Azam, A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 689.
(31) Bharti, N.; Husain, K.; Gonzalez Garza, M. T.; Cruz-Vega, D. E.; Castro-Garza, J.; Mata-Cardenas, B. D.; Naqvi, F.; Azam, A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3475.
(32) Bharti, N.; Shailendra; Sharma, S.; Naqvi, F.; Azam, A. *Bioorg. Med. Chem.* **2003**, *11*, 2923.
(33) Singh, S.; Bharti, N.; Naqvi, F.; Azam, A. *Eur. J. Med. Chem.* **2004**, *39*, 459.
(34) Singh, S.; Athar, F.; Azam, A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5424.
(35) Sharma, S.; Athar, F.; Maurya, M. R.; Naqvi, F.; Azam, A. *Eur. J. Med. Chem.* **2005**, *40*, 557.
(36) Dobek, A. S.; Klayman, D. L.; Dickson, E. T., Jr.; Scovill, J. P.; Tramont, E. C. *Antimicrob. Agents Chemother.* **1980**, *18*, 27.
(37) Petering, D. H.; Petering, H. G.; Sartoreli, A. C.; Johns, D. G. *Handbook of Experimental Pharmacology*; Springer: Berlin, 1975; p 841.
(38) Farrell, N. *Coord. Chem. Rev.* **2002**, *232*, 1.
(39) Weder, J. E.; Hambley, T. W.; Kennedy, B. J.; Lay, P. A.; Foran, G. J.; Rich, A. M. *Inorg. Chem.* **2001**, *40*, 1295.
(40) Zhou, Q.; Hambley, T. W.; Kennedy, B. J.; Lay, P. A.; Turner, P.; Warwick, B.; Biffin, J. R.; Regtop, H. L. *Inorg. Chem.* **2000**, *39*, 3742.
(41) Weder, J. E.; Hambley, T. W.; Kennedy, B. J.; Lay, P. A.; MacLachlan, D.; Bramley, R.; Delfs, C. D.; Murray, K. S.; Moubaraki, B.; Warwick, B.; Biffin, J. R.; Regtop, H. L. *Inorg. Chem.* **1999**, *38*, 1736.
(42) West, D. X.; Padhye, S. B.; Sonawane, P. B. Structure and Bonding; Springer Verlag: New York, 1991; Vol. 76, p 1.
(43) Quiroga, A. G.; Ranninger, C. N. *Coord. Chem. Rev.* **2004**, *248*, 119.
(44) Matesanz, A. I.; Souza, P. *J. Inorg. Biochem.* **2007**, *101*, 245.
(45) Otero, L.; Vieites, M.; Boiani, L.; Denicola, A.; Rigol, C.; Opazo, L.; Olea-Azar, C.; Maya, J. D.; Morello, A.; Krauth-Siegel, R. L.; Piro, O. E.; Castellano, E.; Gonzalez, M.; Gambino, D; Cerecetto, H *J. Med. Chem.* **2006**, *49*, 3322.
(46) Chan, P. K. L.; Skov, K. A.; James, B. R.; Farrell, N. P. *Int. J. Radiat. Oncol. Biol. Phys.* **1986**, *12*, 1059.
(47) Stratford, I. J.; Hoe, S.; Adams, G. E.; Hardy, C.; Williamson, C. *Int. J. Radiat. Biol. Phys. Chem. Med.* **1983**, *43*, 31.
(48) Clarke, M. J. Chemistry and Biochemistry of Platinum. In *Gold and Other Chemotherapeutic Agents*; ACS Symposium Series; American Chemical Society: Washington, DC, 1983; Vol. 209, p 335.
(49) Rodriguez-Argueelles, M. C.; Lopez-Silva, E. C.; Sanmarlin, J.; Pelagatti, P.; Zani, F. *J. Inorg. Biochem.* **2005**, *99*, 2231.
(50) Spiro, T. G. *Copper Proteins*; Wiley International: New York, 1981.
(51) Brill, A. S. *Transition Metals in Biochemistry*; Springer Verlag: Berlin, 1977.
(52) Peisach, J.; Aisen, P.; Blumberg, W. *The Biochemistry of Copper*; Academic Press: New York, 1966.
(53) West, D. X.; Liberta, A. E.; Padhye, S. B.; Chikate, R. C.; Sonawane, P. B.; Kumbhar, A. S.; Yerande, R. G. *Coord. Chem. Rev.* **1993**, *123*, 49.
(54) Viossat, B.; Daran, J. C.; Savouret, G.; Morgant, G.; Greenaway, F. T.; Dung, N. H.; Pham-Tram, V. A.; Sorenson, J. R. J. *J. Inorg. Biochem.* **2003**, *96*, 375.
(55) Navarro, M.; Cisneros-Fajardo, E. J.; Lehmann, T.; Sanchez-Delgado, R. A.; Atencio, R.; Silva, P.; Lira, R.; Urbina, J. A. *Inorg. Chem.* **2001**, *40*, 6879.
(56) Bharti, N.; Athar, F.; Maurya, M. R.; Azam, A. *Bioorg. Med. Chem.* **2004**, *12*, 4679.
(57) Ramadan, A. M. *J. Inorg. Biochem.* **1997**, *65*, 183.
(58) Maurya, M. R.; Kumar, A.; Abid, M.; Azam, A. *Inorg. Chim. Acta* **2006**, *359*, 2439.
(59) Tofazzal, M.; Tarafder, H.; Saravanan, N.; Crouse, K. A.; Ali, M. A. *Transition Met. Chem.* **2001**, *26*, 613.
(60) Ali, M. A.; Livingstone, S. E. *Coord. Chem. Rev.* **1974**, *13*, 101.
(61) Johnson, D. K.; Murphy, T. B.; Rose, N. J.; Goodwin, W. H.; Pickart, L. *Inorg. Chim. Acta* **1982**, *67*, 159.
(62) Saxena, A.; Koacher, J. K.; Tandon, J. P. *J. Antibact. Antifungal Agents* **1981**, *9*, 435.
(63) Srinivasan, K.; Perrier, S.; Korchi, J. K. *J. Mol. Catal.* **1986**, *36*, 297.
(64) Bhattacharya, P. K. *Proc. Indian Acad. Sci.* **1990**, *102*, 247.
(65) Rehder, D.; Pessoa, J. C.; Geraldes, C. F.; Castro, M. M.; Kabanos, T.; Kiss, T.; Meier, B.; Micera, G.; Pettersson, L.; Rangel, M.; Salifoglou, A.; Turel, I.; Wang, D. J. *Biol. Inorg. Chem.* **2002**, *7*, 384.
(66) Bharti, N.; Maurya, M. R.; Naqvi, F.; Azam, A. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2243.
(67) Bharti, N.; Maurya, M. R.; Naqvi, F.; Bhattacharya, A.; Bhattacharya, S.; Azam, A. *Eur. J. Med. Chem.* **2000**, *35*, 481.
(68) Shailendra; Bharti, N.; Naqvi, F.; Azam, A. *Helv. Chim. Acta* **2002**, *85*, 2713.
(69) Maurya, M, R.; Khurana, S.; Shailendra; Azam, A.; Zhang, W.; Rehder, D. *Eur. J. Inorg. Chem.* **2003**, *10*, 1966.
(70) Maurya, M. R.; Kumar, A.; Bhat, A. R.; Azam, A.; Bader, C.; Rehder, D. *Inorg. Chem.* **2006**, *45*, 1260.
(71) Bharti, N.; Shailendra; Gonzalez Garza, M. T.; Cruz-Vega, D. E.; Castro-Garza, J.; Saleem, K.; Naqvi, F.; Maurya, M. R.; Azam, A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 869.
(72) Ankri, S.; Miron, T.; Raboinkov, A.; Wilchek, M.; Mirelman, D. *Antimicrob. Agents Chemother.* **1997**, *41*, 2286.
(73) McCord, J. M.; Fridovich, I. *Superoxide and Superoxide Dismutases*; Academic Press: New York, 1977.
(74) Sawyer, D. T.; Valentine, J. S. *Acc. Chem. Res.* **1981**, *14*, 393.
(75) Katritzky, A. R.; Rees, C. W.; Elguero, J. *Comprehensive Heterocyclic Chemistry II, Volume 5*; Pergamon Press: Oxford, U.K., 1984; p 167.
(76) Katritzky, A. R.; Rees, C. W.; Scriven, E. F.; Elguero, J. *Comprehensive Heterocyclic Chemistry II, Volume 3*; Pergamon Press: Oxford, U.K., 1996; p 1.
(77) Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. *Pyrazoles as Drugs, Facts and Fantasies, Targets in Heterocyclic Systems*; Italian Society of Chemistry: Rome, Italy, 2002; Vol. 6, p 52.
(78) Gokhan, N.; Yesilada, A.; Ucar, G.; Erol, K.; Bilgin, A. A. *Arch. Pharm. Pharm. Med. Chem.* **2003**, *336*, 362.
(79) Holla, B. S.; Akbarali, P. M.; Shivanada, M. K. *IL Farmaco* **2000**, *55*, 256.
(80) Plaska, E.; Aytemir, M.; Uzbay, T.; Erol, D. *Eur. J. Med. Chem.* **2001**, *36*, 539.
(81) Turan-Zitouni, G.; Chevallet, P.; Killic, F. S.; Erol, K. *Eur. J. Med. Chem.* **2000**, *35*, 635.
(82) Lombardino, G. *Nonsteroidal Anti-inflammatory Drugs*; John Wiley & Sons: New York, 1985.
(83) Address, K. J.; Feigon, J. *Biochemistry* **1994**, *33*, 12397.
(84) La Monica, G.; Ardizzoia, G. A. *Prog. Inorg. Chem.* **1997**, *46*, 151.
(85) Onoa, G. B.; Moreno, V.; Font-Bardia, M.; Solans, X.; Pe'rez, J. M.; Alonso, C. *J. Inorg. Chem.* **1999**, *75*, 205.
(86) Abid, M.; Azam, A. *Bioorg. Med. Chem.* **2005**, *13*, 2213.
(87) Abid, M.; Azam, A. *Eur. J. Med. Chem.* **2005**, *40*, 935.
(88) Abid, M.; Azam, A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2812.
(89) Budakoti, A.; Abid, M.; Azam, A. *Eur. J. Med. Chem.* **2006**, *41*, 63.
(90) Budakoti, A.; Abid, M.; Azam, A. *Eur. J. Med. Chem.* **2007**, *42*, 544.
(91) Bonnett, R. *Chem. Rev.* **1963**, *63*, 573.
(92) Hill, H. A.; Pratt, J. M.; Williams, R. J. P. *Chem. Br.* **1969**, *5*, 156.
(93) Craigo, W. A.; LeSueur, B. W.; Skibo, E. B. *J. Med. Chem.* **1999**, *42*, 3324.
(94) Gudmundsson, K. S.; Tidwell, J.; Lippa, N.; Koszalka, G. W.; van Draanen, N.; Ptak, R. G.; Drach, J. C.; Townsend, L. B. *J. Med. Chem.* **2000**, *43*, 2464.
(95) Trivedi, R.; De, S. K.; Gibbs, R. A. *J. Mol. Catal.* **2006**, *245*, 8.
(96) Townsend, L. B.; Revankav, G. R. *Chem. Rev.* **1970**, *70*, 389.
(97) Kim, J. S.; Gatto, B.; Yu, C.; Liu, A.; Liu, L. F.; LaVoie, E. J. *J. Med. Chem.* **1996**, *39*, 992.
(98) Khalafi-Nezhad, A.; Rad, M. N. S.; Mohabatkar, H.; Asrari, Z.; Hemmateenejad, B. *Bioorg. Med. Chem.* **2005**, *13*, 1931.
(99) Rajan, R.; Rajaram, R.; Nair, B. U.; Ramasami, T.; Mandal, S. K. *J. Chem. Soc., Dalton Trans.* **1996**, *9*, 2019.
(100) Garcia-Lozano, J.; Server-Carrio, J.; Coret, E.; Folgado, J. V.; Escriva, E.; Ballesteros, R. *Inorg. Chim. Acta* **1996**, *245*, 75.
(101) Cardwell, T. J.; Edwards, A. J.; Hartshorn, R. M.; Holmes, R. J.; McFadyan, W. D. *Aust. J. Chem.* **1997**, *50*, 1009.
(102) Gable, R. W.; Hartshorn, R. M.; McFadyen, W. D.; Nunno, L. *Aust. J. Chem.* **1996**, *49*, 625.
(103) Piguet, C.; Bocquet, B.; Mueller, E.; Williams, A. F. *Helv. Chim. Acta* **1989**, *72*, 323.
(104) Aminabhavi, T. M.; Biradar, N. S.; Patil, S. B.; Hoffman, D. E. *Inorg. Chim. Acta* **1986**, *125*, 125.
(105) Sluka, J.; Danek, J.; Bedrnik, P.; Budesinsky, Z. *Collect. Czech. Chem. Commun.* **1981**, *46*, 2703.
(106) Khairy, El-B.; Hammad, M. *Egypt. J. Chem.* **1978**, *21*, 171.

(107) Eynde, J. J. V.; Delfosse, F.; Lor, P.; Haverbeke, Y. V. *Tetrahedron* **1995**, *51*, 5813.
(108) Patzold, F.; Zeuner, F.; Heyen, T.; Niclas, H. J. *Synth. Commun.* **1992**, *22*, 281.
(109) Sondhi, S. M.; Rajvanshi, S.; Johar, M.; Bharti, N.; Azam, A.; Singh, A. K. *Eur. J. Med. Chem.* **2002**, *37*, 835.
(110) Sondhi, S. M.; Johar, M.; Shukla, R.; Raghubir, R.; Bharti, N.; Azam, A. *Aust. J. Chem.* **2001**, *54*, 461.
(111) Maurya, M. R.; Bharti, N. *Transition Met. Chem.* **1999**, *24*, 389.
(112) Valdez, J.; Cedillo, R.; Hernandez-Campos, A.; Yepez, L.; Hernandez-Luis, F.; Navarrete-Vazquez, G.; Tapia, A.; Cortes, R.; Hernandez, M.; Castillo, R. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2221.
(113) Navarrete-Vazquez, G.; Cedillo, R.; Hernandez-Campos, A.; Yepez, L.; Hernandez-Luis, F.; Valdez, J.; Morales, R.; Cortes, R.; Hernandez, M.; Castillo, R. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 187.
(114) Kazimierczuk, Z.; Upcroft, J. A.; Upcroft, P.; Gorska, A.; Starosciak, B.; Laudy, A. *Acta Biochim. Pol.* **2002**, *49*, 185.
(115) Freeman, C. D.; Klutman, N. E.; Lamp, K. C. *Drugs* **1997**, *54*, 679.
(116) Barnhost, D. A, Jr.; Foster, J. A.; Chern, K. C.; Meisler, D. M. *Ophthalmology* **1996**, *103*, 1880.
(117) Rasmussen, B. A.; Bush, K.; Tally, F. P. *Clin. Infect. Dis.* **1997**, *24*, 5110.
(118) Edwards, D. I. *J. Antimicrob. Chemother.* **1993**, *31*, 9.
(119) Castelli, M.; Malagoli, M.; Ruberto, A. I.; Baggio, A.; Casolari, C.; Carmelli, C.; Bossa, M. R.; Rossi, T.; Paolucci, F.; Roffia, S. *J. Antimicrob. Chemother.* **1997**, *40*, 19.
(120) Sigeti, J. S.; Guiney, D. G., Jr.; Davis, C. E. *J. Infect. Dis.* **1983**, *148*, 1083.
(121) Muller, M. *Surgery* **1983**, *93*, 165.
(122) Shaw, C. F., III *Chem. Rev.* **1999**, *99*, 2589.
(123) Rhodes, M. D.; Sadler, P. J.; Scawen, M. D.; Silyer, S. *J. Inorg. Biochem.* **1992**, *46*, 129.
(124) Best, S. L.; Sadler, P. J. *Gold Bull.* **1996**, *29*, 87.
(125) Farrell, N. Transition Metal Complexes as Drugs and Chemotherapeutic Agents. In *Catalysis by Metal Complexes*; James, B. R., Ugo, R., Eds.; Kluwer: Dordrecht, The Netherlands, 1989.
(126) Mirabelli, C. K.; Johnson, R. K.; Song, C. M.; Fancette, L.; Muirhead, K.; Crooke, S. T. *Cancer Res.* **1985**, *45*, 32.
(127) Sadler, P. J.; Sue, R. E. *Met.-Based Drugs* **1994**, *1*, 107.
(128) Matesanz, A. I.; Perez, J. M.; Navarro, P.; Moreno, J. M.; Colocio, E.; Sauza, P. *J. Inorg. Biochem.* **1999**, *76*, 29.
(129) Quiroga, A. G.; Perez, J. M.; Montero, E. I.; Masaguer, J. R.; Alonso, C.; Navarro-Ranninger, C. *J. Inorg. Biochem.* **1998**, *70*, 117.
(130) Sanchez-Delgado, R. A.; Navarro, M.; Perez, H.; Urbina, J. *J. Med. Chem.* **1996**, *39*, 1095.
(131) Bharti, N.; Shailendra; Coles, S. J.; Hursthouse, M. B.; Mayer, T. A.; Gonzalez Garza, M. T.; Cruz-Vega, D. E.; Mata-Cardenas, B. D.; Naqvi, F.; Maurya, M. R.; Azam, A. *Helv. Chim. Acta* **2002**, *85*, 2704.
(132) Athar, F.; Husain, K.; Abid, M.; Agarwal, S. M.; Coles, S. J.; Hursthouse, M. B.; Maurya, M. R.; Azam, A. *Chem. Biodivers.* **2005**, *2*, 1320.
(133) Jezierska, A.; Maczynski, M.; Koll, A.; Ryng, S. *Arch. Pharm.* **2004**, *337*, 81.
(134) Mansour, A. K.; Eid, M. M.; Khalil, N. S. A. M. *Nucleosides Nucleotides Nucleic Acids* **2003**, *22*, 1825.
(135) Haning, H.; Niewohner, U.; Schenke, T.; Es-Sayed, M.; Schmidt, G.; Lampe, T.; Bischoff, E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 865.
(136) Makhlouf, A. A.; Maklad, Y. A. *Arzneim.-Forsch.* **2004**, *54*, 42.
(137) Yamazaki, T.; Muramoto, M.; Nishimura, S.; Kita, Y *Eur. J. Pharmacol.* **2004**, *484*, 147.
(138) Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society*; Wiley: Chichester, U.K., 1997.
(139) Sihver, W.; Bier, D.; Holschbach, M. H.; Schulze, A.; Wutz, W.; Olsson, R. A.; Coenen, H. H. *Nucl. Med. Biol.* **2004**, *31*, 173.
(140) Martin, D.; Teijeiro, C.; Pina, J. J. *J. Electroanal. Chem.* **1996**, *407*, 189.
(141) Smith, R. D.; Li, J.; Noguchi, C. T.; Schechter, A. N. *Blood* **2000**, *95*, 863.
(142) Jensen, N. P.; Ager, A. L.; Bliss, R. A.; Canfield, C. J.; Kotecka, B. M.; Rieckmann, K. H.; Terpinski, J.; Jacobus, D. P. *J. Med. Chem.* **2001**, *44*, 3925.
(143) Barrett, M. P.; Fairlamb, A. H. *Parasit. Today* **1999**, *15*, 136.
(144) De Koning, H. P.; Jarvis, S. M. *Mol. Pharmacol.* **1999**, *56*, 1162.
(145) Klenke, B.; Stewart, M.; Barrett, M. P.; Brun, R.; Gilbert, I. H. *J. Med. Chem.* **2001**, *44*, 3440.
(146) Singh, S.; Husain, K.; Athar, F.; Azam, A. *Eur. J. Pharm. Sci.* **2005**, *25*, 255.
(147) Ramalingan, C.; Park, Y. T.; Kabilan, S. *Eur. J. Med. Chem.* **2006**, *41*, 683.
(148) Emami, S.; Falahati, M.; Banifatemi, A.; Amanlou, M.; Shafiee, A. *Bioorg. Med. Chem.* **2004**, *12*, 3971.
(149) Park, H.-J.; Lee, K.; Park, S.-J.; Ahn, B.; Lee, J.-C.; Cho, H. Y.; Lee, K.-I. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3307.
(150) Karakurt, A.; Aytemir, M. D.; Stables, J. P.; Ozalp, M.; Kaynak, F. B.; Ozbey, S.; Dalkara, S. *Arch. Pharm.* **2006**, *339*, 513.
(151) Karakurt, A.; Dalkara, S.; Ozalp, M.; Ozbey, S.; Kendi, E.; Stables, J. P. *Eur. J. Med. Chem.* **2001**, *36*, 421.
(152) Tu, S.; Xu, L.; Zhang, H.; Li, Z.; Yu, C.; Cui, D. Preparation of indene-substituted oxime ethers as germicides and insecticides. CN Patent 1824648, 2006.
(153) Hofmann, M.; Langewald, J.; Kuhn, D. G.; Oloumi-Sadeghi, H.; Braun, F.-J.; Culbertson, D. L. Preparation of *O*-(phenyl/heterocyclyl)methyl oxime ether compounds as insecticides, acaricides and nematocides. WO Patent 2006125637, 2006.
(154) Kume, M.; Matsuo, K.; Omori, N.; Takayama, M.; Omori, A.; Endo, T. Preparation of (arylamino)quinazolinecarboxaldehyde and (arylamino)quinazolinyl ketone oximes, oxime ethers, and hydrazones as inhibitors of tyrosine kinases such as EGFR and HER2 tyrosine kinases. WO Patent 2006090717, 2006.
(155) Brain, E. G.; Forrest, A. K.; Hunt, E.; Shillingford, C.; Wilson, J. M. *J. Antibiot.* **1989**, *42*, 1817.
(156) Hassner, A.; Patchornik, G.; Pradhan, T. K.; Kumareswaran, R. *J. Org. Chem.* **2007**, *72*, 658.
(157) Lee, J. Y.; Hong, Y.-T.; Kim, S. *Angew. Chem.* **2006**, *45*, 6182.
(158) Miyabe, H.; Yoshida, K.; Reddy, V. K.; Matsumura, A.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 5630.
(159) Jaramillo-Gomez, L. M.; Loaiza, A. E.; Martin, J.; Rios, L. A.; Wang, P. G. *Tetrahedron Lett.* **2006**, *47*, 3909.
(160) Miyata, O.; Takeda, N.; Naito, T. *Yuki Gosei Kagaku Kyokaishi* **2006**, *64*, 1282.
(161) Abid, M.; Husain, K.; Azam, A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4375.
(162) Delmas, F.; Gasquet, M.; Timon-David, P.; Madadi, N.; Vanelle, P.; Vaille, A.; Maldonado, J. *Eur. J. Med. Chem.* **1993**, *28*, 23.
(163) Zhang, M. R.; Kumata, K.; Maeda, J.; Haradahira, T.; Noguchi, J.; Suhara, T.; Halldin, C.; Suzuki, K. *J. Med. Chem.* **2007**, *50*, 848.
(164) Nanda, K. K.; Nolt, M. B.; Cato, M. J.; Kane, S. A.; Kiss, L.; Spencer, R. H.; Wang, J.; Lynch, J. J.; Regan, C. P.; Stump, G. L.; Li, B.; White, R.; Yeh, S.; Bogusky, M. J.; Bilodeau, M. T.; Dinsmore, C. J.; Lindsley, C. W.; Hartman, G. D.; Wolkenberg, S. E.; Wesley, T. B. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5897.
(165) Letourneau, J.; Riviello, C.; Ho, K. K.; Chan, J. H.; Ohlmeyer, M.; Jokiel, P.; Neagu, I.; Morphy, J. R.; Napier, S. E. Preparation of 2-(4-oxo-4H-quinazolin-3-yl)acetamides as vasopressin V3 receptor antagonists. WO Patent 2006095014, 2006.
(166) Keseru, G.; Vago, I.; Farkas, S.; Horvath, C.; Bielik, A.; Borza, I.; Weber, C.; Kolok, S.; Nagy, J. Preparation of new aryloxy acetamides as NMDA receptor antagonists. WO Patent 2006010968, 2006.
(167) Jaroskova, L.; Linders, J. T. M.; Van der Veken, L. J. E.; Willemsens, G. H. M.; Bischoff, F. P. Preparation of *N*-(adamantan-2-yl)acetamides as 11-beta hydroxysteroid dehydrogenase inhibitors for treatment of obesity. WO Patent 2006024627, 2006.
(168) Askew, B. C.; Aya, T.; Biswas, K.; Cai, G.; Chen, J. J.; Han, N.; Liu, Q.; Nguyen, T.; Nishimura, N. ; Nomak, R.; Peterkin, T.; Qian, W.; Yang, K.; Yuan, C. C.; Zhu, J.; D'Amico, D. C.; Human, J. B.; Huang, Q. Preparation of 1,2,3,4-tetrahydropyrazin-2-yl acetamides as bradykinin B1 receptor antagonists for treating pain and diseases such as inflammation-mediated diseases. U.S. Patent 2006025400, 2006.
(169) Cozzi, P.; Menchetti, P.; Fusar, D.; de Carneri, I.; Trane, F.; Bianchi, A *Eur. J. Med. Chem.* **1983**, *18*, 203.
(170) Kalyanam, N.; Manjunatha, S. G. *Indian J. Chem., Sect. B* **1991**, *30B*, 1077.
(171) Aravujo, R. F.; Benevides, L. M.; Vega, M. C.; Gomez, G. R. *Clin. Ther.* **1983**, *6*, 47.
(172) Shridhar, D. R.; Reddy, P. G.; Moorty, S. R.; Madan, O. P. M.; Janakiram, C.; Bhopale, K. K.; Tripathi, K.; Datta, G. P.; Das, S. R *Indian J. Chem., Sect B* **1979**, *17B*, 483.
(173) Chaturvedi, D.; Ray, S. *Monatsh. Chem.* **2006**, *137*, 127.
(174) Adams, P.; Baron, F. A. *Chem. Rev.* **1965**, *65*, 567.
(175) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley and Sons: New York, 1991; p 315.
(176) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*; John Wiley and Sons: New York, 1999; p 503.
(177) Goodman, L.; Gilman, A.; Rall, T. W.; Nies, A. S.; Taylor, P. *The Pharmacological Basis of Therapeutics*; Pergamon Press: New York, 1990.
(178) Mateen, A.; Chapalamadugu, S.; Kaskar, B.; Batti, A. R.; Chaudry, G. R. *Biol. Degrad. Biorem. Toxic Chem.* **1994**, *198*, 198.
(179) Tomlin, C. D. S. *The Pesticide Manual*; Crop Protection Publication: Farnham, U.K., 1994.
(180) Wigfield, Y. Y. *Food Sci. Technol.* **1996**, *77*, 1501.
(181) Alexander, J.; Bindra, D. S.; Glass, J. D.; Holahan, M. A.; Renyer, M. L.; Rork, G. S.; Sitko, G. R.; Stranieri, M. T.; Stupienski, R. F.; Veerapanane, H.; Cook, J. J. *J. Med. Chem.* **1996**, *39*, 480.

(182) Barbachyn, M. R.; Hutchinson, D. K.; Brickner, S. J.; Cynamon, M. H.; Kilburn, J. O.; Klemens, S. P.; Glickman, S. E.; Grega, K. C.; Hendges, S. K.; Toops, D. S.; Ford, C. W.; Zurenko, G. E. *J. Med. Chem.* **1996**, *39*, 680.
(183) Turker, J. G. *Anti-Corros. Methods Mater.* **1986**, *33*, 10.
(184) Fiala, V.; Sctova, O.; Trabascku, M.; Vosku, A. *Biomaterials* **1987**, *8*, 259.
(185) Feroci, M.; Casadei, M. A.; Orsini, M.; Palombi, L.; Inesi, A. *J. Org. Chem.* **2003**, *68*, 1548.
(186) Angeles, E.; Santillan, A.; Martinez, I.; Ramirez, A.; Moreno, E. *Synth. Commun.* **1994**, *24*, 2441.
(187) Ordaz-Ichardo, C.; Shibayama, M.; Villa-Trevino, S.; Arriaga-Alba, M.; Angeles, E.; de la Garza, M. *Antimicrob. Agents Chemother.* **2005**, *49*, 1160.
(188) Hodson, H. F.; Randall, A. W. Biologically active amidines. U.S. Patent 3728389, 1973.
(189) Marchenko, N. B.; Granik, V. G.; Glushkov, R. G.; Budanova, L. I.; Kuzovkin, V. A.; Parshin, V. A.; Al'tshuler, R. A. *Khim. Farm. Zh.* **1976**, *10*, 46.
(190) Kitamura, S.; Fukushi, I.; Miyawaki, T.; Kawamura, M.; Terashita, E.; Naka, T. *Chem. Pharm. Bull.* **2001**, *49*, 268.
(191) Racane, L.; Tralic-Kulenovic, V.; Kitson, R. P.; Karminski-Zamola, G. *Monatsh. Chem.* **2006**, *137*, 1571.
(192) Gautier, J. A.; Miocque, M.; Farnoux, C. C. The Chemistry of Amidines and Imidates; John Wiley & Sons: London, 1975; p 283.
(193) Granik, V. G. *Usp. Khim.* **1983**, *52*, 669.
(194) Liu, C.; Lin, J.; Leftheris, K. *Tetrahedron Lett.* **2006**, *48*, 435.
(195) Ito, K.; Kizuka, Y.; Ihara, S. *J. Heterocycl. Chem.* **2006**, *43*, 1217.
(196) Guetlich, P.; Hauser, A.; Spiering, H. *Angew. Chem., Int. Ed.* **1994**, *33*, 2024.
(197) Birman, V. B.; Li, X.; Han, Z. *Org. Lett.* **2007**, *9*, 37.
(198) Venugopalan, B.; Patel, B.; Karnik, P. J.; De Souza, N. J.; Chatterjee, D. K.; Iyer, N. *Eur. J. Med. Chem.* **1996**, *31*, 485.
(199) Moffett, R. B.; White, J. L. *J. Org. Chem.* **1952**, *17*, 407.
(200) Cologne, J.; Pouchol, J. M. *Bull. Soc. Chim. Fr.* **1962**, 598.
(201) Langlois, M.; Guillonnean, C.; Van, T. V.; Maillard, J. *Eur. J. Med. Chem.* **1978**, *13*, 161.
(202) Fabio, P. F.; Lang, S. A.; Lin, Y.; Tomcufcik, A. S. *J. Med. Chem.* **1980**, *23*, 201.
(203) Katritzky, A. R.; Rees. C. W. *Comprehensive Heterocyclic Chemistry*; Pergamon Press: Oxford, U.K., 1984; Vol. 5, p 469.
(204) Grimmett, M. R. *Imidazole and Benzimidazole Synthesis*; Academic Press: San Diego, CA, 1997.
(205) Brown, E. G. *Ring Nitrogen and Key Biomolecule*; Kluwer Academic Press: The Netherlands, 1998.
(206) Bellina, F.; Cauteruccio, S.; Rossi, R. *Tetrahedron* **2007**, *63*, 4571.
(207) Giraldi, P. N.; Mariotti, V.; Nannini, G.; Tosolini, G. P.; Dradi, E.; Logemann, W.; de Carneri, I.; Monti, G. *Arzneim.-Forsch.* **1970**, *20*, 52.
(208) Giraldi, P. N.; Mariotti, V.; de Carneri, I. *J. Med. Chem.* **1968**, *11*, 66.
(209) Upcroft, J. A.; Campbell, R. W.; Benakli, K.; Upcroft, P.; Vanelle, P. *Antimicrob. Agents Chemother.* **1999**, *43*, 73.
(210) Ghosh, S.; Chan, J. M. W.; Lea, C. R.; Meints, G. A.; Lewis, J. C.; Tovian, Z. S.; Flessner, R. M.; Loftus, T. C.; Bruchhaus, I.; Kendrick, H.; Croft, S. L.; Kemp, R. G.; Kobayashi, S.; Nozaki, T.; Oldfield, E. *J. Med. Chem.* **2004**, *47*, 175.
(211) Eubank, W. B.; Reeves, R. E. *J. Parasitol.* **1982**, *68*, 599.
(212) Cromartie, T. H.; Fisher, K. J.; Grossman, J. N. *Pestic. Biochem. Physiol.* **1999**, *63*, 114.
(213) Martin, M. B.; Arnold, W.; Heath, H. T. I.; Urbina, J. A.; Oldfield, E. *Biochem. Biophys. Res. Commun.* **1999**, *263*, 754.
(214) van Beek, E.; Pieterman, E.; Cohen, L.; Lowik, C.; Papapoulos, S. *Biochem. Biophys. Res. Commun.* **1999**, *264*, 108.
(215) Keller, R. K.; Fliesler, S. J. *Biochem. Biophys. Res. Commun.* **1999**, *266*, 560.
(216) Grove, J. E.; Brown, R. J.; Watts, D. J. *J. Bone Miner. Res.* **2000**, *15*, 971.
(217) Bergstrom, J. D.; Bostedor, R. G.; Masarachia, P. J.; Reszka, A.; Rodan, G. *Arch. Biochem. Biophys.* **2000**, *373*, 231.
(218) Dunford, J. E.; Thompson, K.; Coxon, F. P.; Luckman, S. P.; Hahn, F. M.; Poulter, C. D.; Ebetino, F. H.; Rogers, M. J. *J. Pharmacol. Exp. Ther.* **2001**, *296*, 235.
(219) Parthasarathy, P. C.; Ananthan, L.; Likhate, M. A.; Manjunatha, S. G.; Kalyanam, N. *Eur. J. Med. Chem.* **1993**, *28*, 195.
(220) Slighter, R. G.; Yarinsky, A.; Drobeck, H. P.; Bailey, D. M. *Parasitology* **1980**, *81*, 157.
(221) Bailey, D. M.; Mount, E. M; Siggins, J.; Carlson, J. A. *J. Med. Chem.* **1979**, *22*, 599.
(222) Todeschini, A. R.; Miranda, A. L. P.; Silva, K.C. M.; Parrini, S. C.; Barreiro, E. J. *Eur. J. Med. Chem.* **1998**, *33*, 189.
(223) Barreiro, E. J.; Fraga, C. A. M.; Miranda, A. L. P.; Rodrigues, C. R. *Quim. Nova* **2002**, *25*, 129.
(224) Cunha, A. C.; Figueiredo, J. M.; Tributino, J. L. M.; Miranda, A. L. P.; Castro, H. C.; Zingali, R. B.; Fraga, C. A. M.; Souza, M. C. B. V.; Ferreira, V. F.; Barreiro, E. J. *Bioorg. Med. Chem.* **2003**, *11*, 2051.
(225) Maurya, M. R.; Agarwal, S.; Abid, M.; Azam, A.; Bader, C.; Ebel, M.; Rehder, D. *Dalton Trans.* **2006**, *7*, 937.
(226) Venugopalan, B.; Sureshi, S.; Karnik, P. J.; De Souza, N. J.; Chatterjee, D. K.; Iyer, S. N. *Indian J. Chem., Sect. B* **1991**, *30B*, 777.
(227) Sarkar, B. R.; Pathak, B.; Dutta, S.; Lahiri, S. C. *J. Indian Chem. Soc.* **1984**, *61*, 151.
(228) Sharma, G. L.; Mukhopadhyay, S.; Kaur, R.; Banerjee, S. K. *Indian J. Med. Res.* **1987**, *86*, 783.
(229) Kalyanam, N.; Likhate, M. A.; Manjunatha, S. G. *Indian J. Chem., Sect. B* **1992**, *31B*, 555.
(230) Singh, R.; Bhagavateeswaran, H.; Jain, P. C.; Anand, N. *Indian J. Chem., Sect. B* **1982**, *21B*, 853.
(231) Agarwal, A.; Agarwal, S. K. *Indian J. Chem., Sect B* **1995**, *34B*, 323.
(232) Agarwal, A.; Agarwal, S. K.; Bhakuni, D. S. *Indian J. Chem., Sect. B* **1992**, *31B*, 44.
(233) Sastry, C. V. R.; Rao, K. S.; Krishnan, V. S. H.; Rastogi, K.; Jain, M. L.; Narayan, G. K. A. S. S. *Indian J. Chem., Sect. B* **1989**, *28B*, 48.
(234) Sinha, A. K.; Rastogi, S. N.; Das, S. R. *Indian J. Chem., Sect. B* **1991**, *30B*, 1041.
(235) Sinha, A. K.; Rastogi, S. N. *Indian J. Chem., Sect. B* **1991**, *30B*, 684.
(236) Asthana, P.; Rastogi, S. N. *Indian J. Chem., Sect. B* **1991**, *30B*, 853.
(237) Gradnik, B.; Dall'Asta, L.; Pedrazzoli, A. *J. Med. Chem.* **1971**, *14*, 255.
(238) De, A. U.; Pathak, B. *J. Med. Chem.* **1970**, *13*, 152.
(239) De, A. U.; Pathak, B. *J. Med. Chem.* **1969**, *12*, 1110.
(240) Palmer, P. J.; Hall, G.; Trigg, R. B.; Warrington, J. V. *J. Med. Chem.* **1971**, *14*, 1223.
(241) Chaudhury, R. R. *Herbal Medicine for Human Health*; WHO Regional Publication, SEARO, No. 20; World Health Organization: New Delhi, India, 1992.
(242) Stanley, S. L. *Parasitol. Today* **1996**, *12*, 7.
(243) Chan-Bacab, M. J.; Pena-Rodriguez, L. M. *Nat. Prod. Rep.* **2001**, *18*, 674.
(244) Janot, M. M. *The Alkaloids, Chemistry and Physiology*; Academic Press: New York, 1953; Vol. 3, p 363.
(245) *Anon Martindale: The Extra Pharmacopoeia*; Wade, A., Ed.; The Pharmaceutical Press: London, 1983; p 77.
(246) Goodman, L. S.; Gilman, A.; Gilman, A. G. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*; Macmillan Publication Company: New York, 1980; p 1061.
(247) Keene, A. T.; Phillipson, J. D.; Warhurst, D. C.; Koch, M.; Seguin, E. *Planta Med.* **1987**, *53*, 201.
(248) Gupta, R. S.; Krepinsky, J. J.; Siminovitch, L. *Mol. Pharmacol.* **1980**, *18*, 136.
(249) Subbaiah, T. V.; Amin, A. H. *Nature* **1967**, *215*, 527.
(250) Wright, C. W. Antiamoebic and Antimalarial Natural Products, Ph.D. Thesis, University of London, London, 1989.
(251) Steck, E. A. *The Chemotherapy of Protozoan Disease, Volume 1*; Walter Reed Army Research Institute, U. S. Government Printing Office: Silver Spring, MD, 1972.
(252) Hobhouse, H. *Seeds of Change: Five Plants That Transformed Mankind*; Sidwick and Jackson: London, 1985.
(253) Martinez-Baez, M. Historical Introduction. In *Amoebiasis, Human Parasitic Disease*; Martinez-Palomo, A., Eds.; Elsevier: Amesterdam, The Netherlands, 1986; Vol. 2, p 1.
(254) Perry, L. M.; Metzger, J. *Medicinal Plants of East and Southeast Asia*; MIT Press: Cambridge, U.K., 1980; p 22.
(255) Wright, C. W.; Allen, D.; Cai, Y.; Phillipson, J. D.; Said, I. M.; Kirby, G. C.; Warhurst, D. C. *Phytother. Res.* **1992**, *6*, 121.
(256) Wright, C. W; Bray, D. H.; O'Neill, M. J.; Warhurst, D. C.; Phillipson, J. D.; Quetin-Leclercq, J.; Augenot, L. *Planta Med.* **1991**, *57*, 337.
(257) Dassonneville, L.; Wattez, N.; Mahieu, C.; Colson, P.; Houssier, C.; Frederich, M.; Tits, M.; Angenot, L.; Bailly, C. *Anticancer Res.* **1999**, *19*, 5245.
(258) Druey, J. *Angew. Chem.* **1960**, *72*, 677.
(259) Beek, Van T. V. Pharmacognostical Studies of Some Tabernaemontana Species, Ph.D. Thesis, University of Leiden, Netherlands, 1984.
(260) Geissman, T. A. *Annu. Rev. Pharmacol.* **1964**, *4*, 305.
(261) Hegnauer, R. *Chemotaxonomie der Pflanzer*; Birkhauser Verlag: Basel, Switzerland, 1973; Vol. 6, p 387.
(262) Morton, J. F. *Medicinal Plants of Middle America*; C. C. Thomas: Springfield, IL, 1952; p 386.
(263) Casinovi, C. G.; Fardella, G.; Grandolini, G.; Burinato, C. *IL Farmaco* **1981**, *36*, 116.

(264) O'Neill, M. J.; Bray, D. H.; Boardman, P.; Phillipson, J. D.; Warhurst, D. C.; Peters, W.; Suffness, M. *Antimicrob. Agents Chemother.* **1986**, *30*, 101.
(265) Wright, C. W.; O'Neill, M. J.; Phillipson, J. D.; Warhurst, D. C. *Antimicrob. Agents Chemother.* **1988**, *32*, 1725.
(266) Chang, Y. T. *Chin. Med. J.* **1951**, *69*, 87.
(267) Wright, C. W.; Anderson, M. M.; Allen, D.; Phillipson, J. D.; Kirby, G. C.; Warhurst, D. C.; Chang, H. R. *J. Eukaryotic Microbiol.* **1993**, *40*, 244.
(268) Amin, N.; Mahfouz, M.; Sherif, M. A. F. *Q. J. Pharm* **1945**, *18*, 116.
(269) Rao, S. S.; Grollman, A. P. *Biochem. Biophys. Res. Commun.* **1967**, *29*, 696.
(270) Polonsky, J. *Fortschr. Chem. Org. Naturst.* **1973**, *30*, 101.
(271) Cuckler, A. C.; Kuna, S.; Mushett, C. W.; Silber, R. H.; Stebbins, R. B.; Stoerk, H. C.; Arison, R. N.; Cuchie, F.; Malanga, C. M. *Arch. Int. Pharmacodyn.* **1958**, *114*, 307.
(272) Phillips, B. P. *Am. J. Trop. Med.* **1951**, *31*, 561.
(273) Woodruff, A. W.; Bell, S.; Schofield, F. D. *Trans. R. Soc. Trop. Med. Hyg.* **1956**, *50*, 114.
(274) Van, A. F.; Miller, J. W.; Mintz, D. T.; Schack, J. A.; Ottolenghi, P.; Most, H. *Am. J. Trop. Med. Hyg.* **1956**, *5*, 501.
(275) Del-Pozo, E. C.; Alcaraz, M. *Am. J. Med.* **1956**, *20*, 412.
(276) Taylor, D. J.; Bond, H. W.; Sherman, J. F. *Antibiot. Ann.* **1954**, *2*, 745.
(277) Pfaffman, M. A.; Klein, R. L. *Proc. Soc. Exp. Biol. Med.* **1966**, *121*, 539.
(278) Gillin, F. D.; Reiner, D. S.; Suffness, M. *Antimicrob. Agents Chemother.* **1982**, *22*, 342.
(279) Harris, A. Biological and Chemical Studies on Several Species of the *Simoubaceae*. Ph.D. Thesis, University of London, England, 1983.
(280) Yates, P.; Stout, G. H. *J. Am. Chem. Soc.* **1958**, *80*, 1691.
(281) Schuier, M.; Helmut, S.; Beate, I.; Horst, F. *J. Nutr.* **2005**, *135*, 2320.
(282) Kambu, K. *Elements de Phytotherapie Comparee*; Plantes Medicinales Africaines, CRP: Kinshasa, Congo, 1990; p 61.
(283) Cimanga, K.; Kambu, K.; Tona, L.; Hermans, N.; Apers, S.; Totte, J.; Pieters, L.; Vlietinck, A. J. *Planta Med.* **2006**, *72*, 751.
(284) Cimanga, R. K.; Kambu, K.; Tona, L.; Hermans, N.; Apers, S.; Totte, J.; Pieters, L.; Vlietinck, A. J. *J. Ethnopharmacol.* **2006**, *107*, 83.
(285) Cimanga, K.; Hermans, N.; Apers, S.; Miert, S. V.; den Heuvel, H. V.; Claeys, M.; Pieters, L.; Vlietinck, A. *J. Nat. Prod.* **2003**, *66*, 97.
(286) Bharti, N.; Singh, S.; Naqvi, F; Azam, A. *Arkivoc* **2006**, *10*, 69.
(287) (a) Calzada, F.; Meckes, M.; Cedillo-Rivera, R. *Planta Med.* **1999**, *65*, 78. (b) Calzada, F.; Alanis, A. D. *Phytother. Res.* **2007**, *21*, 78.
(288) Calzada, F.; Cerda-Garcia-Rojas, C. M.; Meckes, M.; Cedillo-Rivera, R.; Bye, R.; Mata, R. *J. Nat. Prod.* **1999**, *62*, 705.
(289) Calzada, F.; Cedillo-Rivera, R.; Bye, R.; Mata, R. *Planta Med.* **2001**, *67*, 677.
(290) Calzada, F.; Velazquez, C.; Cedillo-Rivera, R.; Esquivel, B. *Phytother. Res.* **2003**, *17*, 731.
(291) Gonzalez-Garza, M. T.; Said-Fernandez, S. *Exp. Parasitol.* **1988**, *66*, 253.
(292) Gonzalez-Garza, M. T.; Matlin, S. A.; Mata-Cardenas, B. D.; Said-Fernandez, S. *J. Pharm. Pharmacol.* **1993**, *45*, 144.
(293) Block, E. *Sci. Am.* **1985**, *252*, 114.
(294) Mirelman, D.; Monheit, D.; Varon, S. *J. Infect. Dis.* **1987**, *156*, 243.
(295) Padayachee, T.; Odhav, B. *J. Ethnopharmacol.* **2001**, *78*, 59.
(296) Moo-Puc, R. E.; Mena-Rejon, G. J.; Quijano, L.; Cedillo-Rivera, R. *J. Ethnopharmacol.* **2007**, *112*, 415.
(297) Wright, C. W.; Phillipson, J. D. *Phytother. Res.* **1990**, *4*, 127.
(298) O'Neill, M. J.; Bray, D. H.; Boardman, P.; Chan, K. L.; Phillipson, J. D. *J. Nat. Prod.* **1987**, *50*, 41.
(299) O'Neill, M. J.; Bray, D. H.; Boardman, P.; Wright, C. W.; Phillipson, J. D.; Warhurst, D. C.; Gupta, M. P.; Correya, M.; Solis, P. *J. Ethnopharmacol.* **1988**, *22*, 183.
(300) Wright, C. W.; Kane, S. R.; O'Neill, M. J.; Phillipson, J. D.; Warhurst, D. C. In vitro antiamoebic activity of some plants used in traditional medicine. In *Biochemistry and Molecular Biology of "Anaerobic" Protozoa*; Lloyd, D., Coombs, G. H., Paget, T. A. P., Eds.; Harwood: London, 1989; p 242.
(301) Wright, C. W.; Allen, D.; Cai, Y.; Chen, Z.; Phillipson, J. D.; Kirby, G. C.; Warhurst, D. C.; Tits, M.; Angenot, L. *Phytother. Res.* **1994**, *8*, 149.
(302) Bhutani, K. K.; Sharma, G. L.; Ali, M. *Planta Med.* **1987**, *53*, 532.
(303) Keene, A. T.; Harris, A.; Phillipson, J. D.; Warhurst, D. C. *Planta Med.* **1986**, *52*, 278.
(304) Mirelman, D.; Monheit, D.; Varon, S. *J. Infect. Dis.* **1987**, *156*, 493.
(305) Wright, C. W.; Marshall, S. J.; Russell, P. F.; Anderson, M. M.; Phillipson, J. D.; Kirby, G. C.; Warhurst, D. C.; Schiff, P. L. *J. Nat. Prod.* **2000**, *63*, 1638.
(306) Enther, N.; Grollman, A. P. *J. Protozoal.* **1973**, *20*, 160.
(307) Calzada, F. *Phytother. Res.* **2005**, *19*, 725.
(308) Marshall, S. J.; Russell, P. F.; Wright, C. W.; Anderson, M. M.; Phillipson, J. D.; Kirby, G. C.; Warhurst, D. C.; Schiff, P. L. *Antimicrob. Agents Chemother.* **1994**, *38*, 96.
(309) Calzada, F.; Barbosa, E.; Cedillo-Rivera, R. *Phytother. Res.* **2003**, *17*, 618.
(310) Yu, H. W.; Wright, C. W.; Cai, Y.; Yang, S. L.; Phillipson, J. D.; Kirby, G. C.; Warhurst, D. C. *Phytother. Res.* **1994**, *8*, 436.
(311) Chatterjee, D. K.; Raether, W.; Iyer, N.; Ganguli, B. N. *Z. Parasitenkd.* **1984**, *70*, 569.
(312) Cedeno, J. R.; Chatterjee, D. K.; Iyer, N.; Krogstad, D. J.; Ganguli, B. N. *Parasitol. Res.* **1987**, *74*, 30.
(313) Tona, L.; Kambu, K.; Ngimbi, N.; Cimanga, K.; Vlietinck, A. J. *J. Ethnopharmacol.* **1998**, *61*, 57.
(314) Gasquet, M.; Quetin-Leclercq, J.; Timon-David, P.; Balansard, G.; Angenot, L. *Planta Med.* **1992**, *58*, 276.
(315) Ahmed, A.; Khan, K. A.; Ahmed, V. *Pak. J. Zool.* **1966**, *28*, 365.
(316) Calzada, F.; Alanis, A. D.; Meckers, M.; Tapia-Contretas, A.; Cedillo-Rivera, R. *Phytother. Res.* **1998**, *12*, 70.
(317) White, A. C. *J. Pharm. Exp. Ther.* **1933**, *48*, 79.
(318) Sharma, G. L.; Bhutani, K. K. *Planta Med.* **1988**, *54*, 120.
(319) Ghoshal, S.; Prasad, B. N. K.; Lakshmi, V. *J. Ethnopharmacol.* **1996**, *50*, 167.
(320) Shah, V.; Sunder, R.; De Souza, N. J. *J. Nat. Prod.* **1987**, *50*, 730.
(321) Loftus, B.; Anderson, I.; Davies, R.; Alsmark, U. C. M.; Samuelson, J.; Amedeo, P.; Roncaglia, P.; Berriman, M.; Hirt, R. P.; Mann, B. J.; Nozaki, T.; Suh, B.; Pop, M.; Duchene, M.; Ackers, J.; Tannich, E.; Leippe, M.; Hofer, M.; Bruchhaus, I.; Willhoeft, U.; Bhattacharya, A.; Chillingworth, T.; Churcher, C.; Hance, Z.; Harris, B.; Harris, D.; Jagels, K.; Moule, S.; Mungall, K.; Ormond, D.; Squares, R.; Whitehead, S.; Quail, M. A.; Rabbinowitsch, E.; Norbertczak, H.; Price, C.; Wang, Z.; Guillen, N.; Gilchrist, C.; Stroup, S. E.; Bhattacharya, S.; Lohia, A.; Foster, P. G.; Sicheritz-Ponten, T.; Weber, C.; Singh, U.; Mukherjee, C.; El-Sayed, N. M.; Petri, W. A.; Clark, C. G.; Embley, T. M.; Barrell, B.; Fraser, C. M.; Hall, N. *Nature* **2005**, *433*, 865.
(322) Singh, S.; Malik, B. K.; Sharma, D. K. *Bioinformation* **2007**, *2*, 68.
(323) Muller, M. *Annu. Rev. Microbiol.* **1988**, *42*, 465.
(324) Ondarza, R. N. *Infect. Disord. Drug Targets* **2007**, *7*, 266.
(325) Rodriguez-Romero, A.; Hernandez-Santoyo, A.; del Pozo Yauner, L.; Kornhauser, A.; Fernandez-Velasco, D. A. *J. Mol. Biol.* **2002**, *322*, 669.
(326) Hidalgo, M. E.; Sanchez, R.; Perez, D. G.; Rodriguez, M. A.; Garcia, J.; Orozco, E. *FEMS Microbiol. Lett.* **1997**, *148*, 123.
(327) Ravdin, J. I.; Murphy, C. F.; Guerrant, R. L.; Long-Krug, S. A. *J. Infect. Dis.* **1985**, *152*, 542.
(328) Ravdin, J. I.; Sperelakis, N.; Guerrant, R. L. *J. Infect. Dis.* **1982**, *146*, 335.
(329) Makioka, A.; Kumagai, M.; Ohtomo, H.; Kobayashi, S.; Takeuchi, T. *Parasitol. Res.* **2001**, *87*, 833.
(330) Munoz, M. L.; Moreno, M. A.; Perez-Garcia, J. N.; Tovar, G. R.; Hernandez, V. I. *Mol. Microbiol.* **1991**, *5*, 1707.
(331) Weikel, C. S.; Murphy, C. F.; Orozco, E.; Ravdin, J. I. *Infect. Immunol.* **1998**, *56*, 1485.
(332) Prasad, J.; Bhattacharya, S.; Bhattacharya, A. *Cell. Mol. Biol. Res.* **1993**, *39*, 167.
(333) Chakrabarty, P.; Sethi, D. K.; Padhan, N.; Kaur, K. J.; Salunke, D. M.; Bhattacharya, S.; Bhattacharya, A. *J. Biol. Chem.* **2004**, *279*, 12898.
(334) Chaudhary, K.; Roos, D. S. *Nat. Biotechnol.* **2001**, *32*, 1089.
(335) Que, X.; Reed, S. L. *Clin. Microbiol. Rev.* **2000**, *2*, 196.
(336) Ondarza, R. N.; Hernandez, E.; Iturbe, A.; Hurtado, G.; Tamayo, E. M. *Biotechnol. Appl. Biochem.* **1999**, *30*, 41.
(337) Stanley, S. L., Jr. Prevention and Potential of New Interventions. In *Amoebiasis*; Ravdin, J. I., Eds.; Imperial College Press: London, 2000; p 137.
(338) Haque, R.; Ali, I. M.; Sack, R. B.; Farr, B. M.; Ramakrishna, G.; Petri, W. A., Jr *J. Infect. Dis.* **2001**, *183*, 1787.
(339) Blessman, J.; Linh, P. V.; Nu, P. A.; Thi, H. D.; Muller-Myhsok, B.; Buss, H.; Tannich, E. *Am. J. Trop. Med. Hyg.* **2002**, *66*, 578.

CR068217K