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Natural Products, Synthetic and Non-Nucleoside Compounds as Inhibitors of Enzymes Related to DNA: Update 2013

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Abstract: This review article tries to be an update of 2008 Pungitore's review. Again, this paper tries to summarize the investigation about natural products, synthetic and non-nucleoside compounds with the ability to inhibit enzymes that play a crucial role in DNA metabolism such as replication, transcription, retro-transcription, recombination, and chromosome segregation during mitosis. The focus is placed on DNA polymerases, topoisomerases and reverse transcriptase inhibitors because most of the literature emphasized on their inhibitory activity. A great diversity of chemical compounds encompassing triterpenes, flavonoids, chromones, lipids, iridoids, phytosterols, coumarins, anthracyclines, quinones, protoberberines, tannins, lignans, acetogenins, benzimidazoles and other natural products, produced by different species of organisms, have inhibitory activities against enzymes related to DNA metabolism allowing these enzymes to arise as important molecular targets for cancer and AIDS research.

Keywords: DNA polymerases, inhibitors, natural products, non-nucleoside, reverse transcriptase, topoisomerases.

INTRODUCTION

It is well known that natural products play a significant role in drug discovery and development processes. This is particularly evident for cancer, where over 60% of the drugs currently used in chemotherapy are from natural origin. The finding and development of new lead compounds are a consequence of the rapid growth in the discovery of molecular targets that may be applied to the discovery of novel tools for diagnosis, prevention and treatment of human diseases. DNA polymerases (DNA pols), topoisomerases (Topos) and reverse transcriptase (RT) enzymes have recently emerged as important molecular targets for the development of anticancer and anti-viral agents [1-2].

DNA pol and topoisomerases are enzymes that play a crucial role in DNA metabolism such as replication, transcription, recombination, and chromosome segregation during mitosis. For this motive, it has long been accepted that these enzymes are important molecular targets for the development of cancer chemotherapeutic agents. Several of their inhibitors have been introduced into clinical trials including dideoxy-nucleotides, phospholipids, fatty acids, flavonoids, iridoids, triterpenoids, camptothecines, anthacyclines, aminoacridines and ellipticines [3-6]. However, more effective agents are still needed. Therefore, information concerning with structural characteristics of inhibitors could offer valuable insight for the design of anticancer agents and could generate a tool to better understand the roles of specific enzymes for DNA replication and repair.

Due to the essential role that RT plays in viral replication, it has become a major target for antiretroviral drugs [7]. There are two classes of RT inhibitors, the nucleoside (NRTIs) and non-nucleoside (NNRTIs) reverse transcriptase inhibitors, each disturbing the RT enzyme at a different location. NRTIs are the analogs of deoxyribonucleosides which lack the hydroxyl group on the 3' carbon of the deoxyribose sugar. NNRTIs are chemically different molecules that do not depend on host cell metabolism to be converted into its active form. Furthermore, these hydrophobic molecules inhibit the HIV-1 RT catalytic activity through the interaction with an allosteric site of the enzyme [7-8]. This interaction leads to a substantial reduction of the nucleotides incorporation rate resulting in halting the DNA synthesis [9]. Five NNRTIs have been approved by the FDA for clinical use including nevirapine (Viramunes), delavirdine (Rescriptors), efavirenz (Sustivas, Stocrins), etravirine (Intelences), and rilpivirine (Edurants), and several more compounds have entered into clinical trials and development [9]. Nevirapine and delavirdine are considered ''first-generation'' NNRTIs and viruses can easily develop drug resistance, even with single amino acid mutations in the RT [10]. The most recently approved NNRTIs, etravirine and rilpivirine, are believed to require at least three amino acid mutations in the NNRTI region before significant resistance was observed [11-12]. This higher barrier to the development of resistance is considered possible because of the large number of conformations that these molecules can adopt; this phenomenon allows different binding modes within the allosteric site of RT [9].

Information about structures and functions of DNA polymerases, topoisomerases and transcriptase reverse can be found in the previous review [1]. In the following paragraphs natural products, synthetic compounds and derivatives with DNA polymerase, topoisomerase and reverse transcriptase inhibitory activity are categorized according to their chemical structures.

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DNA POLYMERASES

The human genome encodes at least 15 DNA polymerases (pols) that contribute in cellular DNA synthesis [13-14]. Polymerases have a highly conserved structure demonstrating their important cellular function in every living organism. Eukaryotic cells contain 3 replicative pols (α, δ, and ε), 1 mitochondrial pol (γ), and at least 10 non replicative pols (β, ζ, η, θ, ι, κ, λ, μ, ν, and terminal deoxynucleotidyl transferase: TdT) [15-16]. Furthermore, on the basis of their homology sequence, eukaryotic pols can be divided into 4 main families, termed A, B, X, and Y [16]. Family A includes mitochondrial pol γ, as well as pols θ and ν. Family B includes 3 replicative pols (α, δ, and ε) and pol ζ. Family X comprises pols β, λ, and μ, as well as TdT, and family Y includes pols η, ι, and κ [17].

Natural products and synthetic compounds have played an important role in the development of anticancer drugs acting on DNA replication. Table **1** shows an update of the diversity of compounds discovered after the previous review [1]. The chemical group of these compounds and IC_{50} values are also included in this Table.

Table 1. Compounds with inhibitory activity of DNA polymerase.

N°	Compound	Origen	Chemical Characteristic	Inhibitory Activity, DNA polymerases	Ref.
1	Betulinic acid	*Couepia polyandra Edgeworthia gardneri*	Triterpenoid	*β* lyase and polymerase, IC_{50} = 33.70 and 46.25 *μ*M	[18]
2	Penta-1,2,3,4,6-O-galloyl-β-D-glucose	*Punica granatum Rhus typhina*	Phenols derivatives	α, δ, ε, η, ι, κ and β , IC_{50} = 13.00-160.00 *μ*M	[19]
3	Epicatechin-(4β-8)-epicatechin-(4β-8)-epicatechin-(4β-8)-epicatechin	*Vitis vinifera* and many plants	Proanthocyanidins	*α, β*, IC_{50} = 0.18, 31.20 *μ*M	[20]
4	Epicatechin-(4β-8)-epicatechin-(4β-8)-epicatechin-(4β-8)-epicatechin-(4β-8)-epicatechin	*Vitis vinifera* and many plants	Proanthocyanidins	*α, β*, IC_{50} = 0.07, 26.00 *μ*M	[20]
5	Epicatechin-(4β-8)-epicatechin-(4β-8)-epicatechin, 3,3'',3''''-O-trigallate	*Vitis vinifera* and many plants	Proanthocyanidins	*α, β*, IC_{50} = 0.23, 38.50 *μ*M	[20]
6	Epicatechin-(4β-8)-epicatechin-(4β-8)-catechin 3,3'',3''''-O-trigallate	*Vitis vinifera* and many plants	Proanthocyanidins	*α, β*, IC_{50} = 0.24, 40.70 *μ*M	[20]
7	Épicatechin-(4β-8)-epicatechin-(4β-8)-epicatechin	*Vitis vinifera* and many plants	Proanthocyanidins	*α, β*, IC_{50} = 0.57, 57.90 *μ*M	[20]
8	Glucosyl ceramide, AS-1-4	*Glycine max L.*	Lipids	*λ*, IC_{50}= 12.20 *μ*M	[21]
9	Sulfobacin B	*Chryseobacteorium sp*	Lipids	Pol I, IC_{50} = 1.60 *μ*M	[22]
10	Iridoid aglycone	Synthetic derivatives	Iridoid	*Taq*, IC_{50} = 13.47 *μ*M	[23]
11	Iridoid aglycone	Synthetic derivatives	Iridoid	*Taq*, IC_{50} = 17.65 *μ*M	[23]
12	Iridoid aglycone	Synthetic derivatives	Iridoid	*Taq*, IC_{50} = 18.31 *μ*M	[23]
13	Edgeworin	*Edgeworthia gardneri*	Coumarins	*β* lyase and polymerase, IC_{50} = 38.88 and 31.43 *μ*M	[18]
14	5-acyl-juglones	*Juglans nigra*	Quinones	Mamalian DNA pol, IC_{50} = 6.30 - 8.40 *μ*M	[24]
15	5-acyl-juglones	*Juglans nigra*	Quinones	Mamalian DNA pol, IC_{50} = 0.68 - 11.90 *μ*M	[24]
16	1,3-dihydroxy-2-methoxymethylanthraquinone	*Morinda citrifolia*	Anthraquinones	Mamalian DNA pol.	[25]
17	3-hydroxy-1-methoxy-2-methoxymethylanthraquinone	*Morinda citrifolia*	Anthraquinones	Mamalian DNA pol.	[25]
18	Nordamnacanthal	*Morinda citrifolia*	Anthraquinones	Mamalian DNA pol.	[25]
19	Damnacanthal	*Morinda citrifolia*	Anthraquinones	Mamalian DNA pol.	[25]

(Table 1) contd…..

N°	Compound	Origen	Chemical Characteristic	Inhibitory Activity, DNA polymerases	Ref.
20	Sorandidiol	*Morinda citrifolia*	Anthraquinones	Mamalian DNA pol, IC_{50} = 29.70 - 35.90 μM	[25]
21	Kohamaic acid A	Marine sponge, *Ircinia sp.*	Sesterterpenic acid	α, β, IC_{50} = 7.60, 8.40μM	[26]
22	(1*S**,4a*S**,8a*S**)-9-(1,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethylnaphthalen-1-yl)nonanoic acid	Synthetic derivatives	Fatty acid conjugates	Mamalian DNA pol.	[26]
23	(1*S**,4a*S**,8a*S**)-13-(1,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethylnaphthalen-1-yl)tridecanoic acid	Synthetic derivatives	Fatty acid conjugates	Mamalian DNA pol.	[26]
24	(1*S**,4a*S**,8a*S**)-17-(1,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethylnaphthalen-1-yl)heptadecanoic acid	Synthetic derivatives	Fatty acid conjugates	Mamalian DNA pol, IC_{50} = 3.22 - 8.76 μM	[26]
25	(1*S**,4a*S**,8a*S**)-21-(1,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethylnaphthalen-1-yl)henicosanoic acid	Synthetic derivatives	Fatty acid conjugates	Mamalian DNA pol.	[26]
26	5-arylidene-2,4-thiazolidinediones	Synthetic derivatives	Rhodanine derivatives	λ, β, IC_{50} = 5.90, 64.40 μM	[27]
27	5-arylidene-2,4-thiazolidinediones	Synthetic derivatives	Rhodanine derivatives	λ , β, IC_{50} = 10.00, 45.50 μM	[27]
28	5-arylidene-2,4-thiazolidinediones	Synthetic derivatives	Rhodanine derivatives	λ , β, IC_{50} = 8.10, 42.90 μM	[27]
29	5-arylidene-2,4-thiazolidinediones	Synthetic derivatives	Rhodanine derivatives	λ , IC_{50} = 11.00 μM	[27]
30	5-arylidene-2,4-thiazolidinediones	Synthetic derivatives	Rhodanine derivatives	λ , β, IC_{50} = 8.30, 80.00 μM	[27]
31	5-arylidene-2,4-thiazolidinediones	Synthetic derivatives	Rhodanine derivatives	λ , β, IC_{50} = 12.40, 88.80 μM	[27]
32	5-arylidene-2,4-thiazolidinediones	Synthetic derivatives	Rhodanine derivatives	λ , IC_{50} = 9.30 μM	[27]
33	Desmethyldehydroaltenusin	*Talaromyces flavus*	Dehydroaltenusin	α, IC_{50} = 0.89 μM	[28]
34	Dehydroaltenusin derivates	Synthetic derivatives	Dehydroaltenusin derivates	α, β, IC_{50} = 0.18, 35.00μM	[28]
35	Dehydroaltenusin derivates	Synthetic derivatives	Dehydroaltenusin derivates	α, β, IC_{50} = 0.09, 24.00μM	[28]
36	Dehydroaltenusin derivates	Synthetic derivatives	Dehydroaltenusin derivates	α, β, IC_{50} = 0.06, 11.00μM	[28]
37	Demethoxydehydroaltenusin	Synthetic derivatives	Dehydroaltenusin derivates	α, β, IC_{50} = 0.24, 89.00μM	[28]
38	Octadecyl *trans*-p-Coumarate	*Artemisia annua*	Alkyl p-coumarates	α, β, IC_{50} = 68.00, 23.10 μM	[29]
39	Octadecyl *cis*-p-Coumarate	*Artemisia annua*	Alkyl p-coumarates	α, β, IC_{50} = 45.50, 32.10 μM	[29]
40	Octadecyl p-Hydroxyphenylpropiolate	Synthetic derivatives	Alkyl p-coumarates	α, β, IC_{50} = 53.00, 16.30 μM	[29]
41	Mucocin	Synthetic derivatives	Acetogenins	Mamalian, fish and insect DNA pol.	[30]
42	Jimenezin	Synthetic derivatives	Acetogenins	Mamalian, fish and insect DNA pol.	[30]

(Table 1) contd…..

N°	Compound	Origen	Chemical Characteristic	Inhibitory Activity, DNA polymerases	Ref.
43	Muconin	Synthetic derivatives	Acetogenins	Mamalian, fish and insect DNA pol.	[30]
44	Pyranicin	Synthetic derivatives	Acetogenins	Mamalian, fish and insect DNA pol. IC_{50} = 2.30-15.80 μM	[30]
45	Pyragonicin	Synthetic derivatives	Acetogenins	Mamalian, fish and insect DNA pol.	[30]
46	19-epi- jimenezin	Synthetic derivatives	Acetogenins	Mamalian, fish and insect DNA pol.	[30]
47	10-epi- pyragonicin	Synthetic derivatives	Acetogenins	Mamalian, fish and insect DNA pol.	[30]
48	γ-Lactone derivatives	Synthetic derivatives	Acetogenins	Mamalian, fish and insect DNA pol.	[30]
49	Penicilliols A	*Penicillium daleae*	5-methoxy-3(2H)-furanones	ι, IC_{50} = 19.80 μM	[31]
50	Penicilliols B	*Penicillium daleae*	5-methoxy-3(2H)-furanones	ι, IC_{50} = 32.50 μM	[31]

Notes: IC_{50}: Inhibitory Concentration 50 %, MIC: Minimum Inhibitory Concentration and Ki: Inhibition Constant.

Triterpenes. Bioassay-guided fractionation of extracts prepared from *Couepia polyandra* and *Edgeworthia gardneri* resulted in the isolation of the DNA pol β (pol β) inhibitor betulinic acid (**1**) (Fig. **1**). A study of this pol β inhibitor revealed that it inhibits both the lyase and polymerase activities of the enzyme with IC_{50} values equal to 33.7 ± 4.9 and 46.25 ± 3.1 μM, respectively [18].

Phenols derivatives. Penta-1,2,3,4,6-O-galloyl-*β*-D-glucose (PGG, **2**) (Fig. **1**) has shown "*in vivo"* inhibitory activity on the growth of human prostate cancer (PCa) xenografts in athymic nude mice and mouse lung cancer allograft in syngeneic mice without evident adverse effect on their body weight. A fast inhibition of DNA synthesis was observed in S-phase cells in PGG-exposed cancer cells and in PGG-treated isolated nuclei. Moreover, it was tested whether and how PGG directly inhibits pols and other DNA metabolic enzymes. The data showed that PGG selectively inhibits replicative pols (α, δ and ε) with IC_{50} ranging from 13 to 66 nM. Compound **2** also inhibits bypass synthesis pols (e.g., η, ι, κ) with IC_{50} between 30-45 nM and base excision repair pol β with IC_{50} 108-160 nM. The inhibitory mechanism of pols α and κ by PGG is non-competitive with respect to dNTP and DNA template-primer, opposite to pol β, which is competitive with respect to dNTP and DNA template–primer [19].

Proanthocyanidins, known as condensed tannins or oligomeric flavonoids, exist in many edible plants and have shown various interesting biological activities. A group of procyanidin oligomers (compounds **3**-**7**) (Fig. **1**) consisting of (-)-epicatechin and (+)-catechin were assayed against several DNA pols showing important activity against calf DNA pol α and rat DNA pol β with IC_{50} ranging from 0.178±0.009 to 0.575±0.028 μM and 31.2±1.6 to 57.9±3.0; respectively [20].

Lipids. During a DNA pol inhibitors screening from soybean (Glycine max L.) it was isolated with a steroidal glycoside (glucosyl ceramide, AS-1-4, compound **8**) (Fig. **1**) with selective activity against eukaryotic pol λ showing an IC_{50} value of 12.2 μM. This selectivity makes it a prime candidate for use as chemotherapeutic agent [21]. The sulfonolipid, sulfobacin B (**9**) (Fig. **1**), was isolated from *Chryseobacterium* sp. and functions as a von Willebrand factor receptor antagonist and as a DNA pol–inhibitor. Although, the most important inhibitory effect was against pol I with IC_{50} values of 1.6 μM, sulfobacin B did not influence the activity of plant, prokaryotic pols and other DNA metabolic enzymes such as pol α (primase activity), RNA polymerase, polynucleotide kinase or deoxyribonuclease I [22].

Iridoids. With the object to find out some molecular targets implicated in the biological activity of iridoids, Pungitore *et al*. (2012) reported three synthetic simplified bicyclic aglycones of iridoids (compounds **10 - 12**) (Fig. **1**) with biological activity against *Taq* DNA pol; IC_{50} values were 13.47, 17.65 and 18.31 μM, respectively [23].

Coumarins. Bioassay-guided fractionation of extracts prepared from *Edgeworthia gardneri* resulted in the isolation of a DNA pol β inhibitor, the coumarin called edgeworin (**13**) (Fig. **2**). Further studies revealed the inhibition of both the lyase and polymerase activities of DNA pol β with IC_{50} values of 38.88 ± 5.1 and 31.43 ± 2.9 μM, respectively. Also, it was found that edgeworin potentiated the inhibitory action of the anticancer drug bleomycin in cultured A549 cells, without any influence on the expression of pol β in cells. The results of the unscheduled DNA synthesis assay support the thesis that the potentiation of bleomycin cytotoxicity by DNA pol β inhibitors is the result of an inhibition of DNA repair process [18].

Quinones. Quinones are a class of organic compounds derived from aromatic compounds via the exchange of a number of –CH= groups for –C(=O)– groups, and any necessary rearrangement of double bonds, resulting in a fully conjugated cyclic dione structure. Juglone occurs naturally in the leaves, roots, husks, and bark of plants in the *Juglandaceae* family, particularly the black walnut (*Juglans nigra*), and is toxic or growth stunting for many types of plants. It is sometimes used as a herbicide, as a dye for

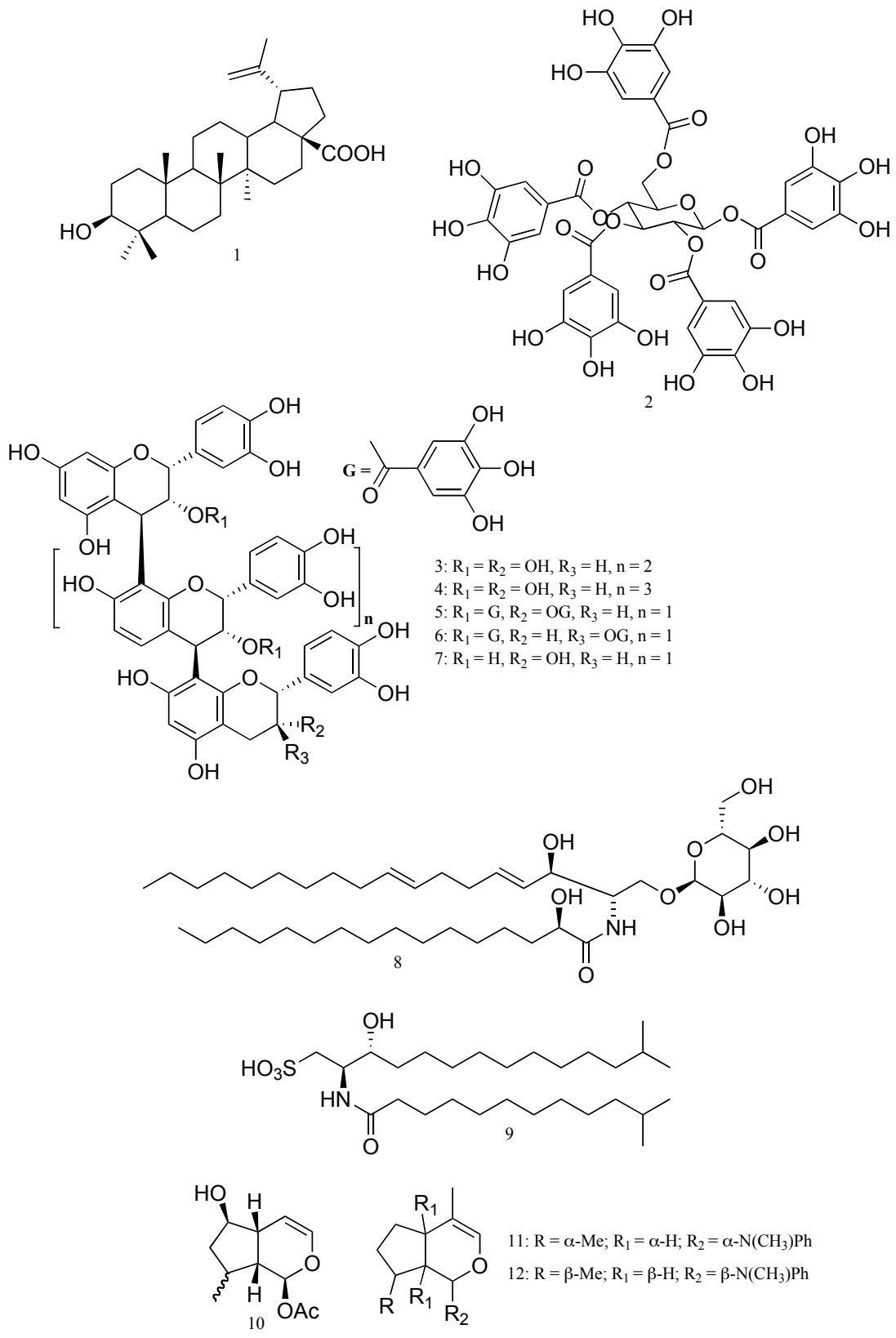


Fig. (1). Structures of compounds with DNA polymerases inhibitory activity.

cloth and inks, and as a coloring agent for food and cosmetics. Juglone is known for its wide range of biological activities, such as induction of oxidative stress in many animal cell systems, inhibition of germination of various plant species and inhibition of the peptidyl-prolyl isomerase activity. Also, the 5-acyl-juglones, compound **14** and **15** (Fig. **2**), have shown important activity against mammalian DNA pol [24].

During the development of new uses for the Noni (*Morinda citrifolia*) root, anthraquinones, rubiadin, rubiadin 1-methyl ether, lucidin, damnacanthol, 1,3-dihydroxy-2-methoxymethylanthraquinone (**16**), 3-hydroxy-1-methoxy-2-methoxymethylanthraquinone (**17**), nordamnacanthal (**18**), damnacanthal (**19**), sorandidiol (**20**) and morindone were isolated (Fig. **2**). Compounds **16**, **17**, **18**, **19** and **20** exhibited remarkable inhibitory activities against animal pols, being the anthraquinone **20,** the strongest one. Among mammalian pols, compound **20** inhibited the polymerase activities of A (pol γ), B (pols α, δ and ε) and Y (pols η, ι and κ) families, but did not influence the activities of X family (pols β, λ and TdT); this tendency correlates with the suppression of human colon cancer cell HCT116 growth. These results suggested that the Noni root containing anthraquinones may be used as an anticancer functional food [25].

Sesterterpenic acid. The kohamaic acid A (KA-A, compound **21**) (Fig. **2**), a new natural product which acted as inhibitory agent of the first cleavage of fertilized sea urchin eggs, was also found to selectively inhibit the activities of mammalian DNA pols. Furthermore, KA-A conjugated fatty acids (compound **22-25**) (Fig. **2**) have been evaluated against DNA pols. Compound **24** [(1S*,4aS*,8aS*)-17-(1,4,4a,5,6,7,8,8a-octahydro-2,5,5,8a-tetramethyl-naphthalen-1-yl)heptadecanoic acid] showed to be the strongest one showing a range of IC_{50} values for mammalian pols between 3.22 to 8.76 μM; therefore, the length of the fatty acid side chain of KA-A is important for pols inhibition. KA-A derivatives prevented human cancer cell (promyelocytic leukemia cell line, HL-60) growth with the same tendency as the inhibition of mammalian pols [26].

Rhodanines. Rhodanine derivatives have been proven to be attractive chemotherapeutic compounds due to their outstanding biological activities and have undergone a rapid development as anticonvulsant, antibacterial, antiviral, and anti-diabetic agents. At the same time, these compounds have also been reported as hepatitis C virus (HCV) protease inhibitors and used as inhibitors of uridine diphospho-N-acetylmuramate/l-alanine ligase. Rhodanines are classified as nonmutagenic and a long-term anti-diabetic study of the rhodanine-based compound, demonstrated that it is clinically well tolerated. Additionally, rhodanines have been designed as inhibitors of various enzymes such as bacterial β-lactamase and Mur ligases, and were found to have a remarkable mildew-proofing activity. Also, the activity of other rhodanines (compounds **26-32**) (Fig. **3**) against DNA pol λ and β has been reported; being compound **26** the most active against DNA pol λ with IC_{50} values of 5.9 μM [27].

Dehydroaltenusin derivatives. Dehydroaltenusin [1] was first isolated from mycelium extracts of *Alternaria tennuis* and *Alternaria kikuchiana* by Rosett *et al*. in 1957 and its structure was subsequently determined by X-ray crystallography. Desmethyldehydroaltenusin (**33**) (Fig. **3**), a related natural product, was isolated from the organic soluble metabolites of *Talaromyces flavus*. Kuramochi *et al.* 2009, re-

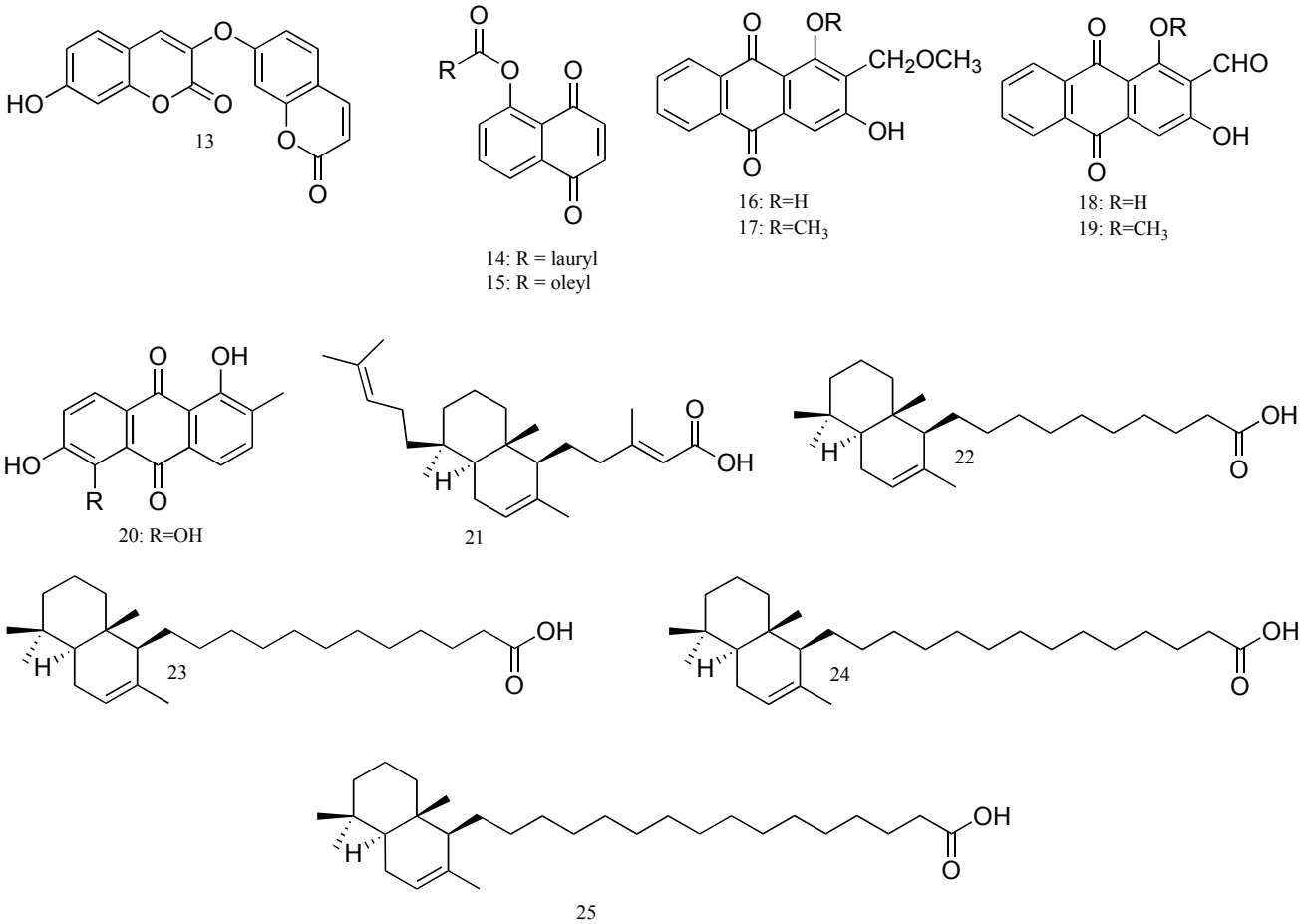


Fig. (2). Structures of compounds with DNA polymerases inhibitory activity.

ported a group of dehydroaltenusin derivatives (compounds **34**-**37**) (Fig. **3**) with activity against DNA pols α and β, the inhibitory activities were more important against DNA pol α, with IC_{50} ranges between 0.06 to 0.89 μM [28].

Alkyl p-coumarates. A composite plant *Artemisia annua* L. is an annual herbaceous plant, which is known in China as a traditional antimalarial medicine, and in Southeast Asia as an antipyretic and hemostatic. A previous biological study on the active constituents of *A. annua* disclosed artemisinin, arteannuin B, and many sesquiterpenes as anti-malarial or anti-tumor components. This plant has recently been reinvestigated and esters of *p*-coumaric acid with long-chain alcohols as a mixture of six compounds of different chain length of C_{20}, C_{22}, C_{24}, and *cis* and *trans* isomers were isolated. These alkyl *p*-coumarates (**38**-**39**) together with other similar synthetic derivates (**40**) (Fig. **3**) showed inhibitory activity against DNA pols α and β [29].

Acetogenins. Acetogenins from the *Annonaceous* plant are a fatty acid-derived natural product, their chemically synthesized counterpart such as mucocin (compound **41**), jimenezin (compound **42**), muconin (compound **43**), pyranicin (compound **44**) and pyragonicin (compound **45**), 19-epi-jimenezin (compound **46**), 10-epi-pyragonicin (compound **47**), and a γ-lactone (compound **48**, which is estimated to be a biosynthetic precursor of acetogenins) (Fig. **4**), were investigated for their activity against polymerases. Compounds **44** and **45** strongly inhibited and compound **47** moderately inhibited the activities of mammalian DNA pols, such as replicative pol α and repair/recombination-related pol β and λ, and also inhibited human DNA topoisomerase (topos) I and II activities. On the other hand, compounds **41**-**43** and **48** did not influence the activities of any pols or topos. Compound **44** was the strongest inhibitor of the pols and topos tested, and the IC_{50} values were 2.3 and 15.8 μM, respectively. These compounds also suppressed human cancer cell growth with almost the same tendency than the inhibition of pols and topos. Compound **44** was also the strongest suppressor of the proliferation of the HL-60 promyelocytic leukemia cell line with an LD_{50} value of 9.4 μM, and arrested the cells at G1 phases, indicating that it blocks DNA replication by inhibiting the activity of pols rather than topos [30].

Furanones. Penicilliols A (**49**) and B (**50**) (Fig. **4**) are novel 5-methoxy-3(2H)-furanones isolated from cultures of a fungus (*Penicillium daleae* K.M. Zalessky) derived from a sea moss. These compounds selectively inhibited the activi-

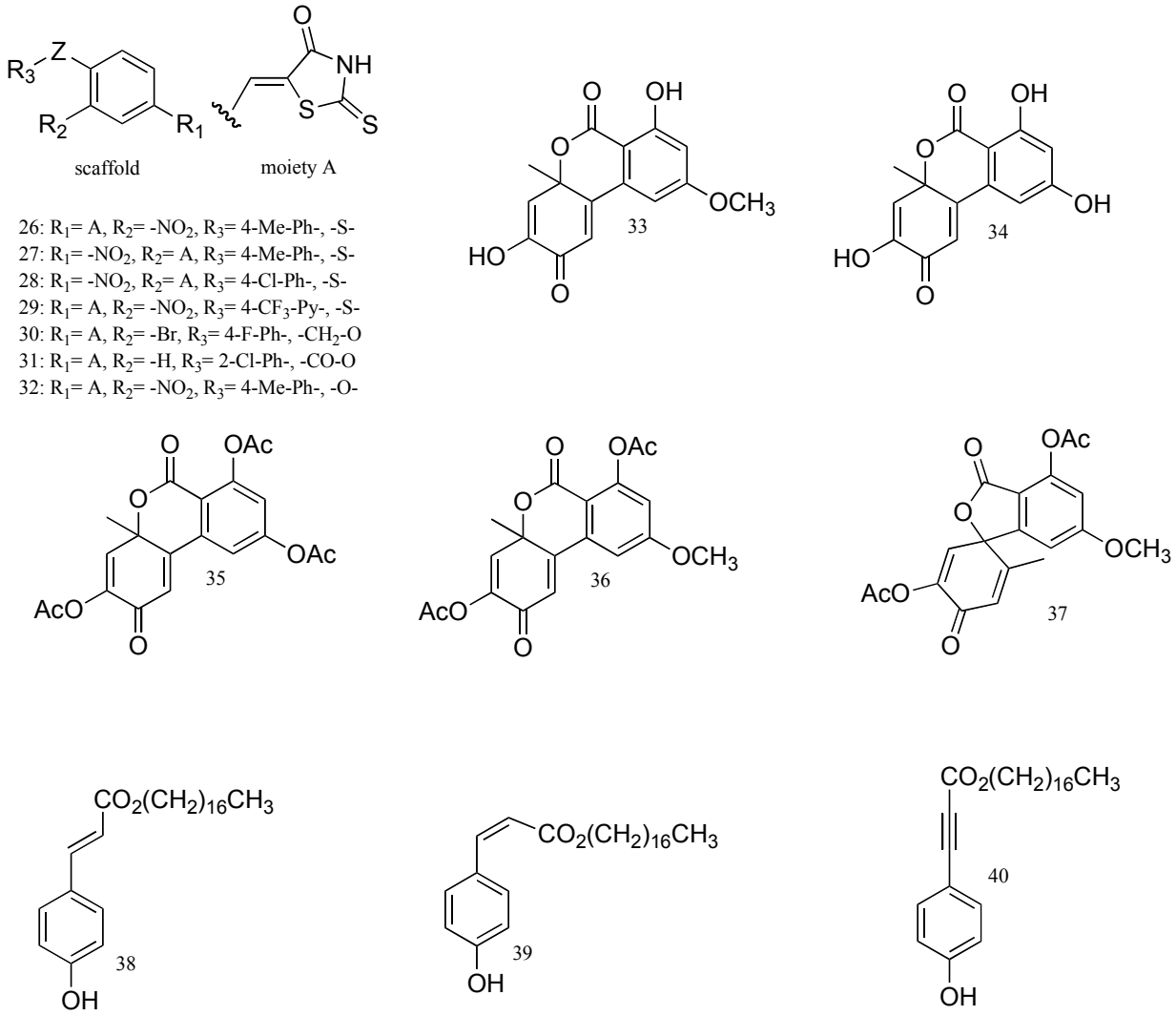


Fig. (3). Structures of compounds with DNA polymerases inhibitory activity.

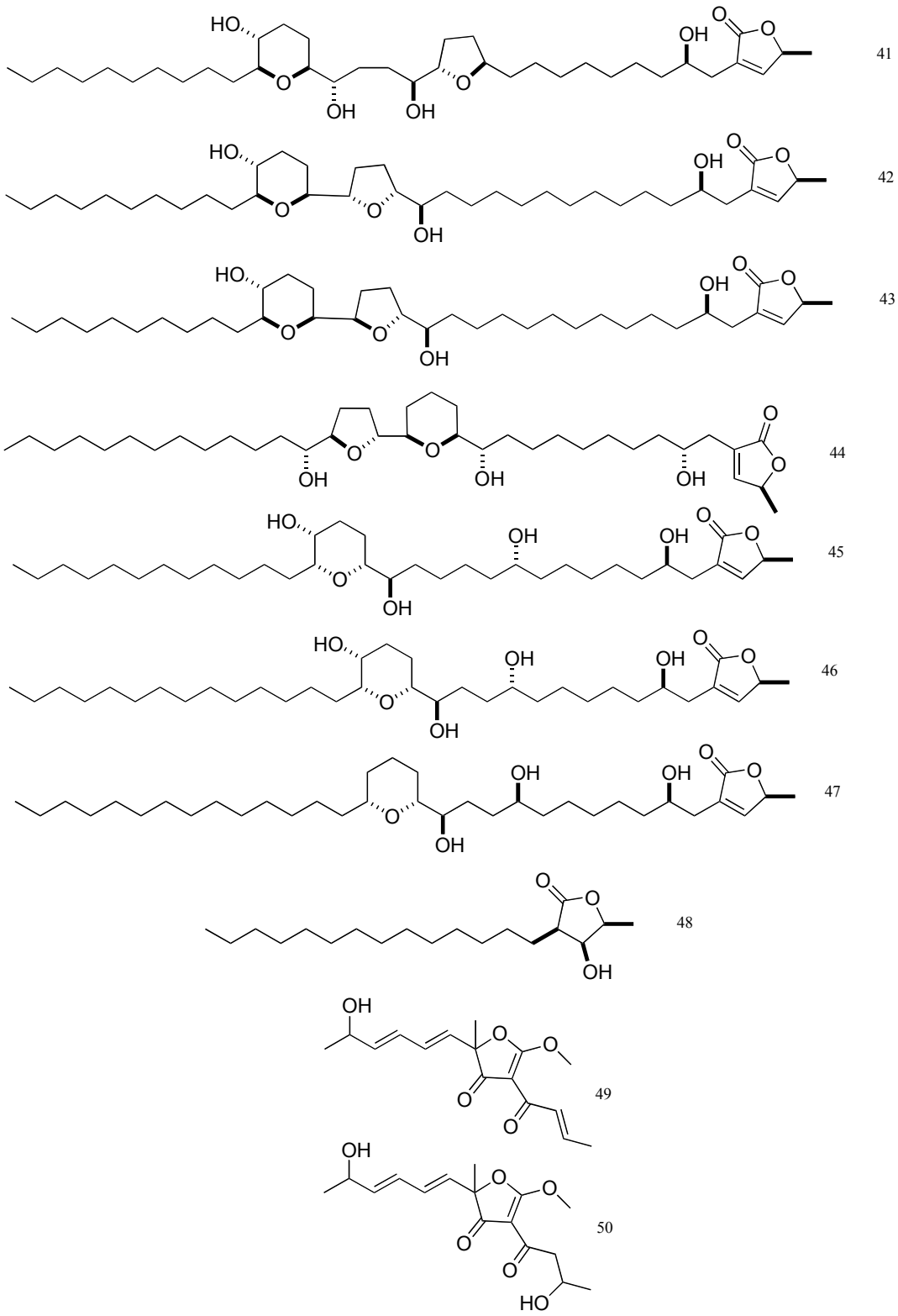


Fig. (4). Structures of compounds with DNA polymerases inhibitory activity.

ties of eukaryotic DNA pols Y family being compound **49** stronger than compound **50**. Among mammalian Y family pols, the most strongly inhibited by compounds **49** and **50** was mouse pol ι activity, with IC_{50} values of 19.8 and 32.5 μM, respectively [31].

DNA TOPOISOMERASES

DNA topoisomerases (topos) are ubiquitous enzymes that catalyze essential enzymes to solve the topological problems accompanying key nuclear processes such as DNA

replication, transcription, repair and chromatin assembly by introducing temporary single or double strand breaks in the DNA [32-34]. In addition, these enzymes fine-tune the steady-state level of DNA supercoiling to facilitate protein interactions with DNA and to prevent excessive supercoiling. There are two fundamental types of topoisomerases, which differ in both mechanism and cellular function [32].

Type I DNA topo are classified into two subfamilies: type IA and type IB. The enzymes of type IA subfamily, including bacterial DNA topo I and II, eukaryotic DNA topo III and reverse gyrase [35-36] form a tyrosyl linkage with a 5´-phosphate group of the DNA strands produced due to the enzyme action [33]. Whereas the enzymes of type IB subfamily, including eukaryotic and vaccine virus DNA topos I [37] and V; establish the tyrosyl bond with the 3´-phosphate group [33]. Type IA topos relax only negative supercoiled DNA with Mg^{2+} requirement, whereas type IB topos relax both negative and positive supercoiled DNA even in the absence of metallic cofactors, although Mg^{2+} and Ca^{2+} stimulate the relaxation activity [38-39].

Type II topo enzymes, such as the α and β forms of human topoisomerase II, alter the linking number in steps of two by breaking both DNA strands, passing another segment of duplex DNA through the break, and then resealing the broken strands. The importance of topoisomerases is underscored by the fact that they are the cellular targets of clinically important anticancer and antibacterial drugs. During the reaction, the enzyme forms a non-covalent closed clamp around the DNA, where both DNA strands remain intact. ATP binding is required to form a closed clamp with topoisomerase II, and ATP hydrolysis induces a conformational change that leads to reopening of the clamp [40].

The discovery of the DNA topos also solved a problem concerning the activity of a number of natural products with anticancer activity and DNA damage but without covalent reaction with DNA.

Table **2** shows an update of the diversity of compounds discovered after the previous review [1]. The chemical groups of these compounds and IC_{50} values are also included.

Table 2. Compounds with DNA topoisomerase inhibitory activity.

N°	Compound	Origen	Chemical Characteristic	Inhibitory Activity, Topoisomerase	Ref.
51	9-aminoacridines	Synthetic derivatives	Acridines	II, IC_{50} = no data	[41]
52	9-aminoacridines	Synthetic derivatives	Acridines	II, IC_{50} = no data	[41]
53	9-aminoacridines	Synthetic derivatives	Acridines	II, IC_{50} = no data	[41]
54	9-aminoacridines	Synthetic derivatives	Acridines	II, IC_{50} = no data	[41]
55	Seconeolitsine	Synthetic derivatives	Alkaloids	I (Topo A) IC_{50} = 17.00 μM	[42]
56	N-methyl-seconeolitsine	Synthetic derivatives	Alkaloids	I (Topo A) IC_{50} = 17.00 μM	[42]
57	Alternariol	*Alternaria alternata*	Phenol	I and II, IC_{50} = no data	[43]
58	Erybraedin C	*Bituminaria bituminosa*	Phenol	I, IC_{50} = 7.00 μM	[44]
59	Bis(2,3-dibromo-4,5-dihydroxybenzyl) ether	*Rhodomela confervoides*	Bromophenols	I, IC_{50} = no data	[45]
60	Ochratoxin A	*Aspergillus* and *Penicillium moulds*	Phenolic mycotoxin	II, IC_{50} = no data	[46]
61	Conjugates of camptothecin	Synthetic derivatives	Camptothecin derivatives	I, IC_{50} = no data	[47]
62	Conjugates of camptothecin	Synthetic derivatives	Camptothecin derivatives	I, IC_{50} = no data	[47]
63	Conjugates of camptothecin	Synthetic derivatives	Camptothecin derivatives	I and II, IC_{50} = no data	[47]
64	Conjugates of camptothecin	Synthetic derivatives	Camptothecin derivatives	I and II, IC_{50} = no data	[47]
65	2-(2,4-Difluorophenyl)-5-[5-(4-methylpiperazin-1-yl)-1Hbenzimidazol-2-yl]-1H-benzimidazole	Synthetic derivatives	Benzimidazoles	I, IC_{50} = no data	[48]
66	2-(2,4-Dichlorophenyl)-5-[5-(4-methylpiperazin-1-yl)-1Hbenzimidazol-2-yl]-1H-benzimidazole	Synthetic derivatives	Benzimidazoles	I, IC_{50} = no data	[48]
67	2-(3,4-Dimethoxyphenyl)-5-[5-(4-methylpiperazin-1-yl)-1Hbenzimidazol-2-yl]-1H-benzimidazole	Synthetic derivatives	Benzimidazoles	I, IC_{50} = no data	[48]

(Table 2) contd…...

N°	Compound	Origen	Chemical Characteristic	Inhibitory Activity, Topoisomerase	Ref.
68	2-(3,4,5-Trimethoxyphenyl)-5-[5-(4-methylpiperazin-1-yl)-1H-benzimidazol-2-yl]-1H-benzimidazole	Synthetic derivatives	Benzimidazoles	I, IC_{50} = no data	[48]
69	Disuccinyl betulin	Synthetic derivatives	Betulin derivatives	IB, IC_{50} = no data	[49]
70	Diglutaryl dihydrobetulin	Synthetic derivatives	Betulin derivatives	IB, IC_{50} = no data	[49]
71	Disuccinyl dihydrobetulin	Synthetic derivatives	Betulin derivatives	IB, IC_{50} = no data	[49]
72	11-keto-β-boswellic acid	Synthetic derivatives	Boswellic acid derivatives	I and II, IC_{50} = no data	[50]
73	Aesculioside IV-23C1	*Aesculus pavia*	Triterpenoid glycosides	I, IC_{50} = 53.00 μM	[51]
74	Aesculioside IV-23E	*Aesculus pavia*	Triterpenoid glycosides	I, IC_{50} = 32.70 μM	[51]
75	Aesculioside IV-23D1	*Aesculus pavia*	Triterpenoid glycosides	I, IC_{50} = 27.10 μM	[51]
76	Aesculioside IVa	*Aesculus pavia*	Triterpenoid glycosides	I, IC_{50} = 51.80 μM	[51]
77	Aesculioside IVc	*Aesculus pavia*	Triterpenoid glycosides	I, IC_{50} = 49.70 μM	[51]
78	Aesculioside IVb	*Aesculus pavia*	Triterpenoid glycosides	I, IC_{50} = 36.00 μM	[51]
79	Aesculioside IId	*Aesculus pavia*	Triterpenoid glycosides	I, IC_{50} = 23.80 μM	[51]
80	Aesculioside IIId	*Aesculus pavia*	Triterpenoid glycosides	I, IC_{50} = 48.60 μM	[51]
81	Aesculioside IIIf	*Aesculus pavia*	Triterpenoid glycosides	I, IC_{50} = 53.70 μM	[51]
82	Aesculioside IIIe	*Aesculus pavia*	Triterpenoid glycosides	I, IC_{50} = 45.10 μM	[51]
83	N,N´-Bis[2-(5-nitro-1,3-dioxo-2,3-dihydro-1Hbenz[de]-isoquinolin-2-yl)]butylaminoethyl]-2-propanediamine	Synthetic derivatives	Bisnaphthalimides	II, IC_{50} = no data	[52]
84	1,5-Dihydro-4-(substituted phenyl)-3H-furo[3,4-*b*]carbazol-3-ones	Synthetic derivatives	Carbazoles	II, IC_{50} = no data	[53]
85	Bischalcones	Synthetic derivatives	Chalcones	II, IC_{50} = no data	[54]
86	Chalcones	Synthetic derivatives	Chalcones	II, IC_{50} = no data	[54]
87	Delphinidin	Many fruits and vegetables of the daily diet	Anthocyanidins	I and II, IC_{50} = no data	[55]
88	Fisetin	Many fruits and vegetables of the daily diet	Flavonoids	I and II, IC_{50} = 17.40 μM	[56]
89	Myricetin	Many fruits and vegetables of the daily diet	Flavonoids	I and II, IC_{50} = 11.10 μM	[56]
90	3,7-diacylquercetin analogue	Synthetic derivatives	Flavonoids	Gyrase and IV, IC_{50} = 9.16 and 0.22 μM	[57]
91	Kaempherol glycoside	*Vicia faba* and *Lotus edulis*	Flavonol	I and II, IC_{50} = 110.00 and 240.00 μM	[58]
92	Icosyl *cis-p*-coumarate	Synthetic derivatives	Esters of p-coumaric acid	I and II, IC_{50} = no data	[59]
93	Docosyl *cis-p*-coumarate	Synthetic derivatives	Esters of p-coumaric acid	I and II, IC_{50} = no data	[59]
94	Tetracosyl *cis-p*-coumarate	Synthetic derivatives	Esters of p-coumaric acid	I and II, IC_{50} = no data	[59]
95	Icosyl *p*-coumarate	Synthetic derivatives	Esters of p-coumaric acid	I and II, IC_{50} = no data	[59]
96	Docosyl *p*-coumarate	Synthetic derivatives	Esters of p-coumaric acid	I and II, IC_{50} = 30.00 and 5.00 μM	[59]

(Table 2) contd…...

N°	Compound	Origen	Chemical Characteristic	Inhibitory Activity, Topoi-somerase	Ref.
97	Tetracosyl *p*-coumarate	Synthetic derivatives	Esters of p-coumaric acid	I and II, IC_{50} = no data	[59]
98	Eleutherin	*Eleutherine bulbosa*	Pyranonaphthoquinone	II, IC_{50} = no data	[60]
99	Indolizinoquinoline-5,12-dione derivatives	Synthetic derivatives	Indolizinoquinoline-5,12-dione	I, IC_{50} = no data	[61]
100	Mansonone F derivative	Synthetic derivatives	Sesquiterpene o-quinone	I and II, IC_{50} = no data	[62]
101	Mansonone F derivative	Synthetic derivatives	Sesquiterpene o-quinone	I and II, IC_{50} = no data	[62]
102	Mansonone F derivative	Synthetic derivatives	Sesquiterpene o-quinone	I and II, IC_{50} = no data	[62]
103	12,13-dihydro-N-methyl-6,11,13-trioxo-5H-benzo[4,5]cyclohepta[1,2-b]naphthalen-5,12-imine	Synthetic derivatives	Naphthoquinone adduct	I, IC_{50} = 21.41 μM	[63]
104	Synthesized pyranonaphthoquinones	Synthetic derivatives	Pyranonaphthoquinones	II, IC_{50} = no data	[64]
105	Synthesized pyranonaphthoquinones	Synthetic derivatives	Pyranonaphthoquinones	II, IC_{50} = no data	[64]
106	Synthesized pyranonaphthoquinones	Synthetic derivatives	Pyranonaphthoquinones	II, IC_{50} = no data	[64]
107	Synthesized pyranonaphthoquinones	Synthetic derivatives	Pyranonaphthoquinones	II, IC_{50} = no data	[64]
108	Synthesized pyranonaphthoquinones	Synthetic derivatives	Pyranonaphthoquinones	II, IC_{50} = no data	[64]
109	Synthesized pyranonaphthoquinones	Synthetic derivatives	Pyranonaphthoquinones	II, IC_{50} = no data	[64]
110	1,3,6-trihydroxy-2-hydroxymethyl-9,10-anthraquinone-3-O-α-L-rhamnopyranosyl-(1→2)-β-D-(6′-O-acetyl)-glucopyranoside	*Rubia cordifolia*	Anthraquinone	I and II, IC_{50} = no data	[65]
111	Evodiamine	*Tetradium family*	Amine	I, IC_{50} = no data	[66]
112	Glycosylated 2-phenyl-indoles	Synthetic derivatives	Indol	I and II, IC_{50} = no data	[67]
113	Glycosylated 2-phenyl-indoles	Synthetic derivatives	Indol	I and II, IC_{50} = no data	[67]
114	Glycosylated 2-phenyl-indoles	Synthetic derivatives	Indol	I and II, IC_{50} = no data	[67]
115	Psoralen	*Ruta graveolens*	Furanocoumarin	I, IC_{50} = no data	[68]
116	Bergapten	*Ruta graveolens*	Furanocoumarin	I, IC_{50} = no data	[68]
117	Xanthotoxin	*Ruta graveolens*	Furanocoumarin	I, IC_{50} = no data	[68]
118	Genz-644282	Synthetic derivatives	Camptothecin derivatives	I, IC_{50} = no data	[69]
119	ARC-111	Synthetic derivatives	Phenanthridine derivative	I, IC_{50} = no data	[70]
120	Saucerneol D	*Saururus chinensis*	Lignan	I and II, IC_{50} = no data	[71]
121	Cationic porphyrins analogs	Synthetic derivatives	Cationic porphyrins	I and II, IC_{50} = no data	[72]
122	Cationic phthalocyanines analogs	Synthetic derivatives	Cationic phthalocyanines	I and II, IC_{50} = no data	[72]
123	Cationic corroles analogs	Synthetic derivatives	Cationic corroles	I and II, IC_{50} = no data	[72]
124	Indenoisoquinolines derivatives	Synthetic derivatives	Indenoisoquinolines	I, IC_{50} = no data	[70]
125	Indenoisoquinolines derivatives	Synthetic derivatives	Indenoisoquinolines	I, IC_{50} = no data	[70]
126	Indenoisoquinolines derivatives	Synthetic derivatives	Indenoisoquinolines	I, IC_{50} = no data	[70]
127	Indenoisoquinolines derivatives	Synthetic derivatives	Indenoisoquinolines	I, IC_{50} = no data	[70]
128	1,4-dihydroxy-2-carbomethoxy-3-prenylnaphthalene-1-O-β-D-glucopyranoside	*Rubia cordifolia*	Dihydronaphtoquinones	I and II, IC_{50} = no data	[65]
129	Mollugin-1-O-β-D-glucopyranoside	*Rubia cordifolia*	Dihydronaphtoquinones	I and II, IC_{50} = no data	[65]

(Table 2) contd…..

N°	Compound	Origen	Chemical Characteristic	Inhibitory Activity, Topoisomerase	Ref.
130	3*R*,3a*S*,4*R*,6a*R*-3,4,6-tris(hydroxymethyl)-3,3a,4,6a-tetrahydro-2H-cyclopenta[*b*]furan-2-one	*Rubia cordifolia*	Monoterpenoid	I and II, IC_{50} = no data	[65]
131	Wedelolactone	*Wedelia calandulaceae* and *Eclipta prostrata*	Coumestan	II, IC_{50} = no data	[73]
132	Simocyclinone D-8	Synthetic derivatives	Amide	Gyrase, IC_{50} = no data	[74]
133	Thimerosal	Synthetic derivatives	Thiomercury compound	IIR, IC_{50} = 9.00 μM	[75]
134	4-Benzoyl-1-(4-methyl-imidazol-5-yl)-carbonylthiosemicarbazide	Synthetic derivatives	Thiosemicarbazides	IV, IC_{50} = 90.00 μM	[76]
135	4-benzoyl-1-(indol-2-yl)-carbonylthiosemicarbazide	Synthetic derivatives	Thiosemicarbazides	IV, IC_{50} = 14.00 μM	[76]
136	Aroylthiourea derivatives of 4-β-amino-40-O-demethyl-4-desoxy- podophyllotoxin	Synthetic derivatives	Aroylthiourea derivatives	II, IC_{50} = no data	[77]
137	Aroylthiourea derivatives of 4-β-amino-40-O-demethyl-4-desoxy- podophyllotoxin	Synthetic derivatives	Aroylthiourea derivatives	II, IC_{50} = no data	[77]
138	Aroylthiourea derivatives of 4-β-amino-40-O-demethyl-4-desoxy- podophyllotoxin	Synthetic derivatives	Aroylthiourea derivatives	II, IC_{50} = no data	[77]
139	Aroylthiourea derivatives of 4-β-amino-40-O-demethyl-4-desoxy- podophyllotoxin	Synthetic derivatives	Aroylthiourea derivatives	II, IC_{50} = no data	[77]
140	Xanthone analogue	Synthetic derivatives	Xanthone	II, IC_{50} = no data	[78]
141	Xanthone analogue	Synthetic derivatives	Xanthone	II, IC_{50} = no data	[78]
142	Yuanhuacine	*Daphne genkwa*	Diterpene	I, IC_{50} = no data	[79]

Notes: IC_{50}: Inhibitory Concentration 50 %.

Acridines. Hiasa *et al.* 2009 reported that four novel substituted 9-aminoacridine derivatives (**51-54**) (Fig. **5**) inhibited the "*in vitro"* proliferation of pancreatic cancer cell lines. In addition, in xenograft tumor model, these compounds also inhibit the "*in vivo"* proliferation of pancreatic cancer. Unlike amsacrine, these compounds do not poison topoisomerase II. Similar to amsacrine, however, these compounds intercalate into DNA in a way that they would alter the apparent topology of the DNA substrate. Thus, inhibition of the relaxation activity of topo II by these compounds has been reexamined using a DNA strand passage assay. It was found that these compounds, indeed inhibit the catalytic activity of topo II. Therefore, these novel acridine-based compounds with anti-pancreatic cancer activity are catalytic inhibitors, not poisons, of human topo II [41].

Alcaloids. Two phenanthrenes, seconeolitsine (**55**) and N-methyl-seconeolitsine (**56**), (Fig. **5**) effectively inhibited both Topo A activity and cell growth at equivalent concentrations (~17 μM). Evidence for "*in vivo"* Topo A targeting by seconeolitsine was provided by the protection of growth inhibition in a *Streptococcus pneumoniae* culture in which the enzyme was overproduced [42].

Phenol compounds. Alternariol (**57**) (Fig. **5**), a mycotoxin synthetized by *Alternaria alternata*, has been reported to possess genotoxic properties. Additionally, it has been reported that this compound binds to the minor groove of the DNA and acts as a topoisomerase I and II poison, which is likely to cause or at least contribute to the impairment of DNA integrity in mammalian cells [43].

The interaction of human topoisomerase I and erybraedin C (**58**) (Fig. **5**), a pterocarpan purified from the plant *Bituminaria bituminosa,* demonstrated an antitumour activity due to this compound is able to inhibit both the cleavage and the religation steps of the topo I reaction. In both cases, preincubation of the drug with the enzyme is required to produce a complete inhibition [44].

Bis(2,3-dibromo-4,5-dihydroxybenzyl) ether (**59**) (Fig. **5**) is a marine bromophenol compound derived from marine algae. Some reports have shown that it possesses cytotoxic activity. However, the mechanisms of its apoptotic activity as well as its potential cellular targets remain unclear. Studies have demonstrated that compound **59** displays "*in vitro*" broad-spectrum anticancer capabilities and exhibits potent apoptotic activity in K562 cells via mitochondrial pathway. Further studies revealed that this compound inhibits the activity of topoisomerase I but it neither stimulates the formation of topoisomerase I DNA complex nor intercalates into DNA. Ethidium bromide displacement fluorescence assay

and molecular modeling results showed that compound **59** mainly targets DNA binding its minor groove, and thereafter inhibiting the activity of topoisomerase I [45].

The mycotoxin ochratoxin A (**60**) (Fig. **5**) a widespread natural contaminant of feed and food, is produced by some strains of *Aspergillus* and *Penicillium* moulds. In the last years, this compound has received growing attention because this carcinogenic, teratogenic, hepatotoxic, and mainly nephrotoxic activity against human and animal cells. Additionally, it has been reported that it inhibits DNA topo II and induces polyploidy in cultured CHO cells [46].

Camptothecin derivatives. Two conjugates (**61**-**62**) (Fig. **5**) of camptothecin (CPT) and 4β-anilino-4′-O-demethylepipodophyllotoxin have shown to exert antitumor activity through inhibition of topo I. Also, there are two new synthetic conjugates (**63**-**64**) (Fig. **5**) with activity against topo I and II [47].

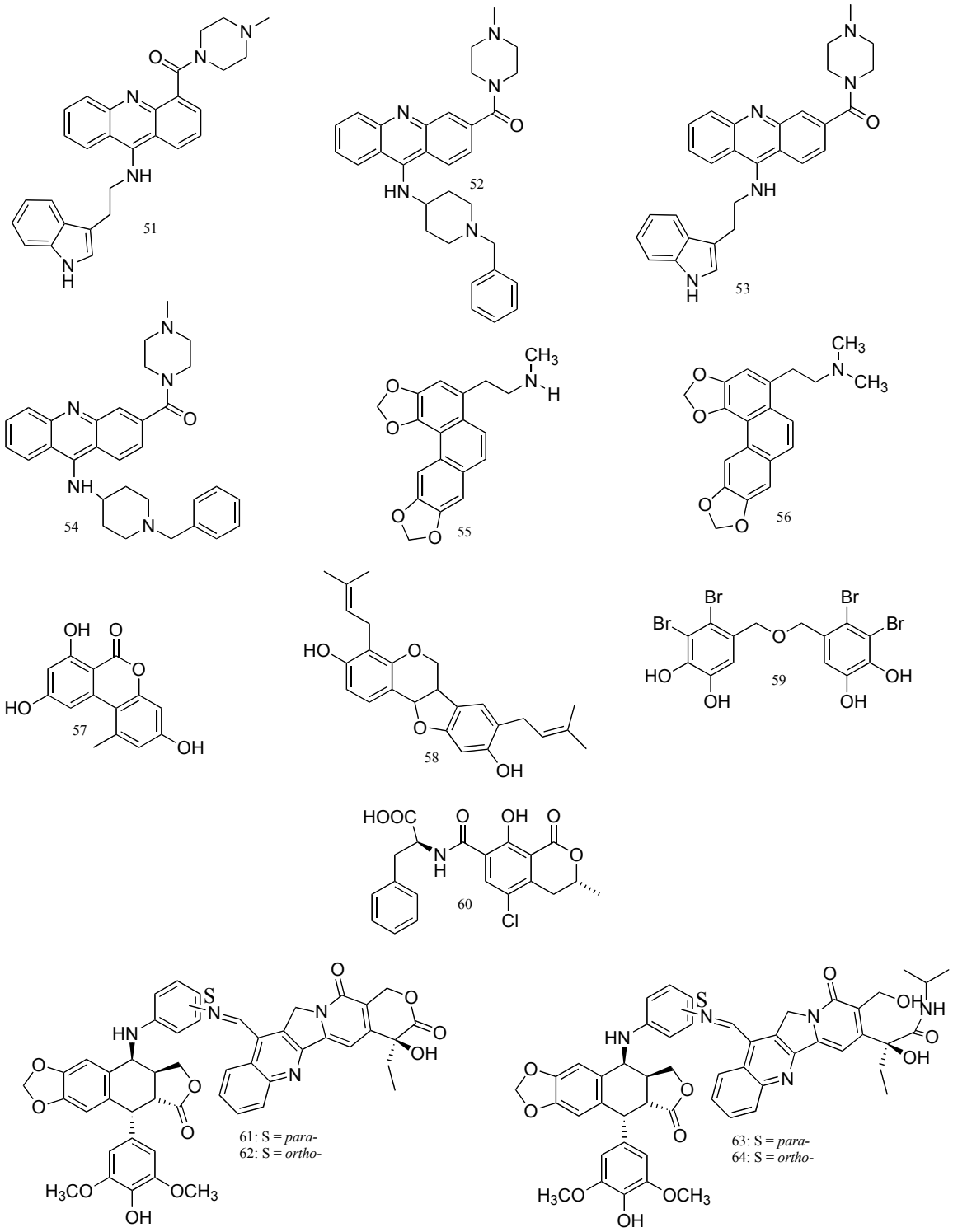


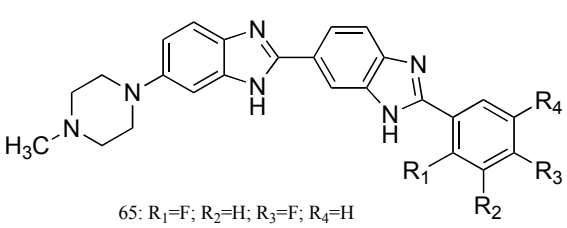
Fig. (5). Structures of compounds with DNA polymerases inhibitory activity.

Benzimidazoles. Several synthetic 2-aryl-5-substituted-2,5-bisbenzimidazole (compounds **65-68**) (Fig. **6**) showed inhibitory activity against topo I with IC_{50} in the micro molar range [48].

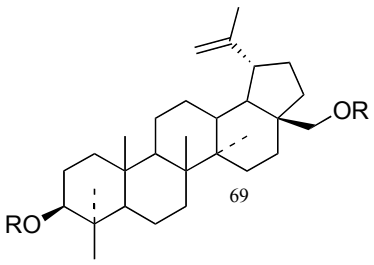
Triterpenes. Betulin (lup-20(29)-ene-3β,28-diol) is an abundant naturally occurring triterpene, constituent of the cork layer of the outer bark of *Betula alba*, *Betula pendula*, *Betula pubescent*, and *Betula platyphylla*. Betulin and the more active form betulinic acid exhibit antimalarial, anti-HIV, and anti-inflammatory as well as cytotoxic activities on cancer cell lines. Disuccinyl botulin (**69)**, diglutaryl dihydrobetulin (**70**) and disuccinyl dihydrobetulin (**71**) (Fig. **6**) inhibit the parasite growth as well as the relaxation activity of type IB *Leishmania donovani* topoisomerase [49].

Boswellic acids have invariably been reported for their antiproliferative potential in various cell systems. Moreover, the growth inhibitory effect of propionyloxy derivative of 11-keto-β-boswellic acid (PKBA; a semisynthetic analog of 11-keto-β-boswellic acid, **72**) (Fig. **6**) on HL-60 promyelocytic leukemia cells was reported. DNA relaxation assay of PKBA revealed inhibition of both topoisomerases I and II at a concentration of 20 μg/ml [50].

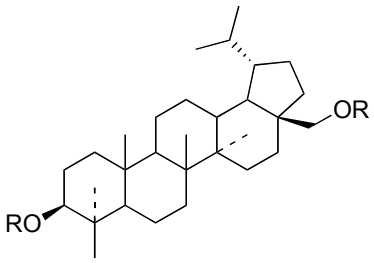
Triterpenoid or steroidal glycosides, known as saponins, are widely distributed in nature, particularly in plants. Research interests on saponins arose rapidly in the last two decades, so there are several reviews reporting their occurrence in nature, classification, elucidation, and bioactivities [1]. The existing studies have been primarily focused on isolation, elucidation, and initial bioactivity screening of saponins particularly from Asian plants. Saponins have shown hemolytic, molluscicidal, anti-inflammatory, antibacterial, antifungal, and antiviral activities. Anti-tumor potential of saponins has been reported in both chemoprevention and chemotherapy. Ten cytotoxic aesculiosides (**73-82**) (Fig. **6**)

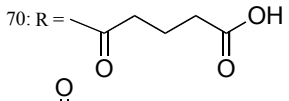


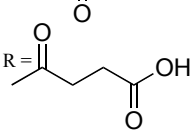
65: R_1=F; R_2=H; R_3=F; R_4=H
66: R_1=Cl; R_2=H; R_3=Cl; R_4=H
67: R_1=H; R_2=OCH_3; R_3=OCH_3; R_4=H
68: R_1=H; R_2=OCH_3; R_3=OCH_3; R_4=OCH_3

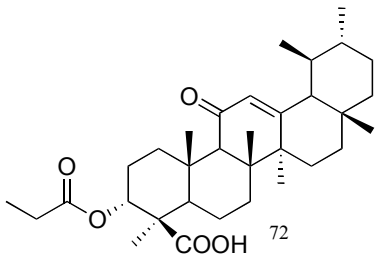


69

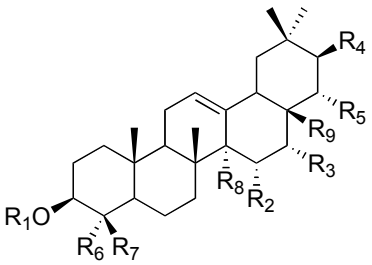


70: R = 

71: R = 



72



73: R_1 = AFU, R_2 = H, R_3 = OH, R_4 =O-Ang, R_5 = O-Ang, R_6 = CH_3, R_7 = CH_2OH, R_8 = CH_3, R_9 = CH_2OH
74: R_1 = AFA, R_2 = OH, R_3 = OH, R_4 =O-Ang, R_5 = O-Ang, R_6 = CH_3, R_7 = CH_3, R_8 = CH_3, R_9 = CH_2OH
75: R_1 = AFA, R_2 = H, R_3 = OH, R_4 = O-Ang, R_5 = O-Ang, R_6 = CH_3, R_7 = CH_3, R_8 = CH_3, R_9 = CH_2OH
76: R_1 = AFA, R_2 = OH, R_3 = OH, R_4 = O-Ang, R_5 = O-MB, R_6 = CH_3, R_7 = CH_3, R_8 = CH_3, R_9 = CH_2OH
77: R_1 = AFA, R_2 = H, R_3 = OH, R_4 = O-Ang, R_5 = O-MB, R_6 = CH_3, R_7 = CH_3, R_8 = CH_3, R_9 = CH_2OH
78: R_1 = AFU, R_2 = H, R_3 = OH, R_4 = O-Ang, R_5 = O-MB, R_6 = CH_3, R_7 = CH_2OH, R_8 = CH_3, R_9 = CH_2OH
79: R_1 = AF, R_2 = H, R_3 = OH, R_4 = O-Ang, R_5 = OH, R_6 = CH_3, R_7 = CH_2OH, R_8 = CH_3, R_9 = CH_2OH
80: R_1 = AFU, R_2 = OH, R_3 = OH, R_4 = O-Tig, R_5 = O-Tig, R_6 = CH_3, R_7 = CH_2OH, R_8 = CH_3, R_9 = CH_2OH
81: R_1 = AFU, R_2 = OH, R_3 = OH, R_4 = O-Tig, R_5 = O-Tig, R_6 = CH_3, R_7 = CH_3, R_8 = CH_3, R_9 = CH_2OH
82: R_1 = AFU, R_2 = OH, R_3 = OH, R_4 = O-Tig, R_5 = O-Ang, R_6 = CH_3, R_7 = CH_2OH, R_8 = CH_3, R_9 = CH_2OH

AFU: $Araf^1$-$^3GlcA^2$-^1Glc; AFA: $Araf^1$-$^3GlcA^2$-^1Gal; AF: $Araf^1$-^3GlcA.
Ang: angeloyl; Tig: tigeloyl; MB: 2-methylbutanoyl; Araf: α–L-arabinofuranosyl; GlcA: β-D- glucuronopyranosyl acid; Glc: β-D-glucopyranosyl; Gal: β-D- galactopyranosyl.

Fig. (6). Structures of compounds with topoisomerases inhibitory activity.

isolated from *Aesculus pavia* inhibited topo 1 catalytic activity by the directly interaction with the free enzyme preventing the formation of the DNA–topo 1 complex with IC_{50} in the micro molar range [51].

Naphthalimides. Anticancer naphthalimides constitute an important class of drugs characterized by a high cytotoxic activity upon a variety of murine and human tumor cells. These drugs perform their biological activity both by forming a DNA-intercalator-topoisomerase II ternary complex and by inhibiting other enzymes and/or transcription factors that act on DNA. The strong interactions with DNA play a crucial role for their pharmacological properties. The compound N,N´-Bis[2-(5-nitro-1,3-dioxo-2,3-dihydro-1Hbenz [de]-isoquinolin-2-yl)]butylaminoethyl]-2-propanediamine (**83**) (Fig. **7**) showed growth-inhibitory properties against HT-29 human colon carcinoma cell line and biochemical studies showed its effect on human DNA topo II [52].

Carbazoles. New 1,5-Dihydro-4-(substituted phenyl)-3H-furo[3,4-*b*]carbazol-3-ones were synthesized via a key step Diels-Alder reaction under microwave irradiation. 3-formylindole was successfully used in a 6-step synthesis to obtain those heterocycle complexes. These carbazoles do not present a strong interaction with the DNA, and do not modify the relaxation of the DNA in the presence of topo I or II except for one promising compound, the structure **84** (Fig. **7**) which is a potent topoisomerase II inhibitor, and its cellular activity is interested compared to etoposide [53].

Chalcones and Bischalcones. The DNA topo II of chloroquine-sensitive and chloroquine-resistant strains of the rodent malaria parasite *Plasmodium berghei* were utilized as a target for testing antimalarial compounds. Compounds belonging to the bischalcone (**85**) and chalcone (**86**) (Fig. **7**) series significantly inhibited the enzyme activity and the parasitaemia percentage of chloroquine-sensitive and chloroquine-resistant strains. The "*in vitro"* topo II inhibition by chalcone and bischalcone analogs can be correlated with their "*in vivo*" antimalarial activity [54].

Anthocyanins. Anthocyanins represent a class of plant dye which occur in many fruits and vegetables of the daily diet. They are glycosides of the anthocyanidins, which differ with respect to the substitution pattern at the phenyl ring. The most abundant anthocyanidins in food are delphinidin, cyanidin, malvidin, peonidin, and pelargonidin. Anthocyanins have been suggested to possess antioxidative, vasoprotective, anti-inflammatory and chemopreventive properties as well as antiobesity effects. The anthocyanidin delphinidin (**87**) (Fig. **7**) has recently been shown to inhibit human topo I and II, without stabilizing the covalent DNA/topo intermediate. Anthocyanidins modulate the activity of human DNA topo I and II, and affect cellular DNA integrity [55].

Flavonoids. Flavonoids comprise a large group of secondary metabolites in plants. They are characterized by a diphenylpropane structure (C6–C3–C6), widely distributed in the plant kingdom and common constituents of fruits, vegetables and certain beverages. Flavonoids have shown "*in vitro"* anticancer and "*in vivo"* anti-carcinogenesis effects, with some of them entering into clinical trials for prevention or treatment of specific cancers. Several studies have shown, however, that flavonoids may also possess toxic and carcinogenic properties. Fisetin (**88**) (Fig. **7**) induced both topo I and topo II-DNA complexes, but it behaved as a catalytic inhibitor of both enzymes. Myricetin (**89**) (Fig. **7**) induced high levels of topo-DNA complexes with both enzymes. Particularly, this activity in leukemia cells may be therapeutically useful and deserves further study [56].

Quercetin and quercetin-3-O-glycosides are the most abundant flavonoids in the human diet; they are associated with a myriad of biological activities and may contribute to the prevention of human diseases. As they are widely sold as food supplements and also inhibit the growth of Gram-positive and Gram-negative organisms at high concentrations, it is interesting to diffuse their antibacterial activities. Novel 3,7-diacylquercetin (**90**) analog was prepared (Fig. **7**) to assess their target specificities and preferences in bacteria. The significant enzymatic inhibition of both *Escherichia coli* DNA gyrase and *Staphylococcus aureus* topo IV suggests that these compounds are dual inhibitors [57].

Flavonols. Legumes are a rich source of phenolic compounds such as flavonoids, phenolic acids, and lignans. These phytochemical compounds exhibit antioxidant activities and have been proposed to exert chemopreventive actions through various mechanisms. The effect of nine polyphenolic compounds derived from parts of two unique varieties of the Leguminosae, *Vicia faba* and *Lotus edulis*, on the activity of eukaryotic topoisomerases was examined. Polyphenolic compounds that act as catalytic inhibitors of wheat germ topo I (IC_{50}: 120-350 μM), human topo I (IC_{50}: 110-260 μM) and topo II (IC_{50}: 240-600 μM) activities were identified. Some compounds inhibited all enzymatic activities to a similar extent, while others exhibited specificity toward individual enzymes. The strongest catalytic inhibitor was a kaempherol glycoside (**91**) with an acetyl group linked to a sugar moiety (Fig. **7**) [58].

Docosyl p-coumarate. *Artemisia annua* L. is an annual herbaceous plant, which is known in China as a traditional antimalarial medicine, and in Southeast Asia as an antipyretic and hemostatic drug. The chemical constituents of this plant and novel sesquiterpenes and esters of p-coumaric acid with long-chain alcohols of different chain length of C_{20}, C_{22}, C_{24}, and *cis*- and *trans*-isomers (compounds **92-97**) were isolated and synthesized (Fig. **7**). Compounds **95**, **97** and **93** and **96** were potent inhibitors of human topos I and II, respectively. They also suppressed HCT116 human colon carcinoma cell line growth, with or without p53 inhibition, suggesting that cell growth inhibition had the same tendency as the topos inhibition [59].

Quinones. The pyranonaphthoquinone family of antibiotics is isolated from plants, fungi and aphid pigments and has been shown to exhibit activity against various Gram-positive bacteria, pathogenic fungi and yeasts, as well as several viruses. This class of compounds has been postulated to act as bioreductive alkylating agents and hence it is important to postulate them as structural leads for cancer therapy. Eleutherin (**98**) (Fig. **8**) was isolated from the tubers of *Eleutherine bulbosa* and was identified as a catalytic inhibitor of topo II [60].

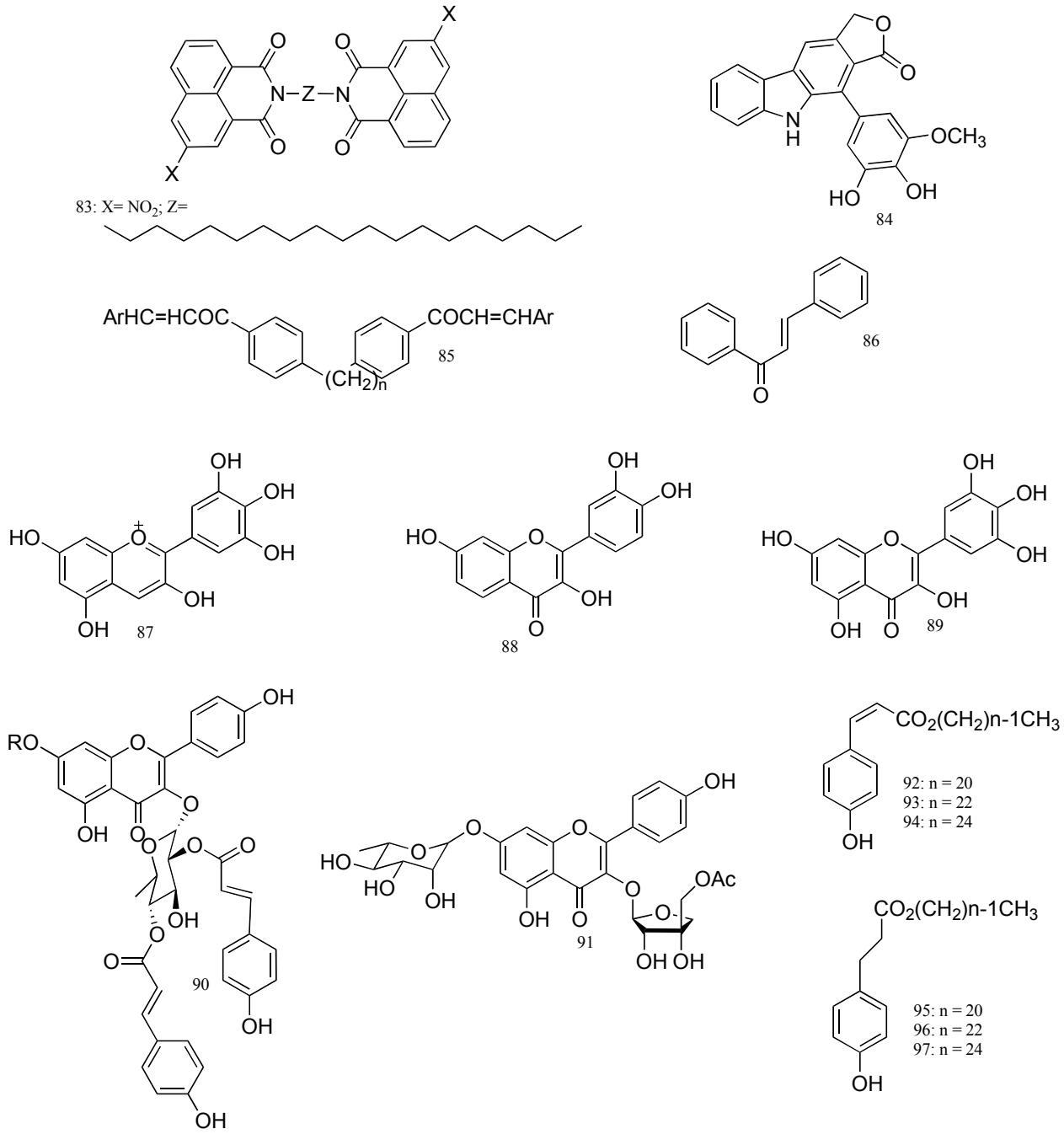


Fig. (7). Structures of compounds with topoisomerases inhibitory activity.

A series of novel synthetic derivatives indolizinoquinoline-5,12-dione was designed and synthesized; some of them exhibited a significant antiproliferative activity toward four human cancer cell lines and great topo I inhibitory activity. Among them, compound **99** (Fig. **8**) exhibited well consistent antiproliferative and topo I inhibitory activites. This study indicated that the indolizinoquinoline-5,12-dione structure might serve as a potential pharmacophore for the design of anticancer chemical entities, and topo I might be a biological target [61].

Mansonone F is a naturally occurring sesquiterpene o-quinone that exists at low level in natural plants such as *Mansonia altissima* and *Ulmus pumila*. This compound shows a wide variety of biological activities, such as antibacterial and anti-proliferative effects. A series of mansonone F derivatives was designed and synthesized (**100**-**102**) (Fig. **8**). These compounds were found to be strong inhibitors for topoisomerases, with much more significant inhibition for topo II rather than topo I [62].

The naphthoquinone adduct 12,13-dihydro-N-methyl-6,11,13-trioxo-5H-benzo[4,5]cyclohepta[1,2-b]naphthalen-5,12-imine (**103**) (Fig. **8**) contains structural features of both the anthracycline and isoquinone chemotherapeutics. An initial characterization showed that this compound is cytotoxic to mammalian cells and can inhibit topos I and II [63].

The synthesized pyranonaphthoquinones were evaluated against the R isoform of human topo II. Among the 11 derivatives studied, it was found that six of them (**104**-**109**)

(Fig. **8**) act "*in vitro"* as catalytic inhibitors of the enzyme. These six derivatives strongly preclude the enzyme from decatenating or relaxing suitable substrates [64].

Activity-directed isolation of the ethyl acetate fraction from the roots of *Rubia cordifolia* resulted in the identification of a new anthraquinone, 1,3,6-trihydroxy-2-hydroxymethyl- 9,10-anthraquinone-3-O-α-L-rhamnopyranosyl-(1→2)-β-D-(6′-O-acetyl)-glucopyranoside (**110**) (Fig. **8**). This new compound showed an inhibition of 30 and 84% for topos I and II at 100 μM [65].

Evodiamine (**111**). It is a compound (Fig. **9**) that was extracted from the *Tetradium* family of plants, which has shown to reduce fat uptake in mouse studies. It is suspected that its mechanism of action is similar to capsaicin and it is also a new topo I inhibitor [66].

Indoles. The glycosylated 2-phenyl-indoles (**112 -114**) (Fig. **9**) which possess a tosylated indole core, generally showed more potent inhibitory ability against both topo I and topo II at 100 μM than the other analogs. Inhibition mode assays demonstrated that there were no topo I or topo II poisoning effects for active analogs, and that the compounds therefore act as topos I/II suppressors [67].

Furanocoumarins. Potent topo I inhibitory activity from extracts of *Ruta graveolens* was observed; moreover, all extracts were able to stabilize the DNA-Topo covalent complex. The irreversible topo I mediated relaxation of plasmid in an enzyme–substrate preincubation study, indicated that the observed inhibitory activity of extract constituents was not mediated through conformational changes in the DNA. Furthermore, this study showed an increased inhibition of

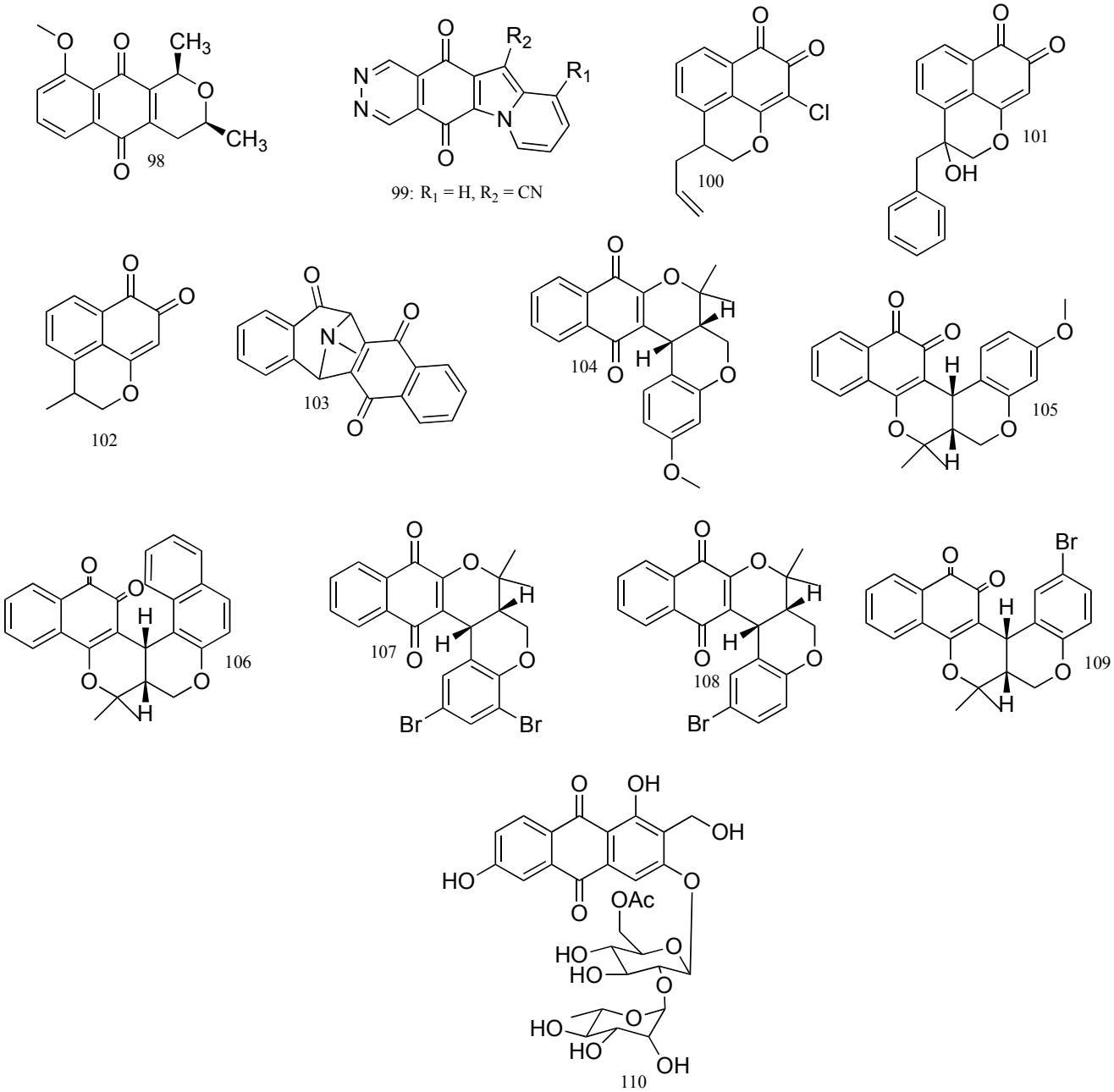


Fig. (8). Structures of compounds with topoisomerases inhibitory activity.

topo activity and promotion of DNA–enzyme complex. The activity could be assigned to furanocoumarins-psoralen (**115**), bergapten (**116**) and xanthotoxin (**117**) (Fig. **9**), identifying them as novel, potent topo I inhibitors [68].

Phenanthridines. Camptothecin derivatives are powerful anticancer drugs because of their ability to trap topo I DNA cleavage complexes. However, they exhibit clinical limitations due to the instability of their α-hydroxylactone six-membered E-ring structure. In addition, they exhibit bone marrow and intestinal toxicity, especially in adults. It has been reported a novel topo I inhibitor, Genz-644282 (**118)** (Fig. **9**) that induces, together with its metabolites, topo I cleavage by a similar way to camptothecin [69]. Also, the ARC-111 (**119**) (Fig. **9**) is a phenanthridine derivative licensed to Genzyme Company [70].

Lignans. *Saururus chinensis* is a perennial herbaceous plant that has been used in the treatment of various diseases such as edema, jaundice, gonorrhea, fever and inflammation in Korean folk medicine. Previous chemical studies of the genus *Saururus* have shown the presence of more than 20 lignans. Thirteen lignans, erythro-austrobailignan-6, meso-dihydroguaiaretic acid, sauchinone, 1'-epi-sauchinone, saucerneol D (**120**) (Fig. **9**), manassantin B, manassantin A, nectandrin B, machilin D, saucerneol F, saucerneol G, saucerneol H and saucerneol I, were specifically isolated with the ethyl acetate extract of *S. chinensis* roots. Compound **120** showed potent inhibitory activities against DNA topos I and II [71].

Porphyrins. A series of cationic porphyrins and analogs such as cationic corroles and phthalocyanines (**121**-**123**) (Fig. **9**) was found to have "*in vitro"* biological activities

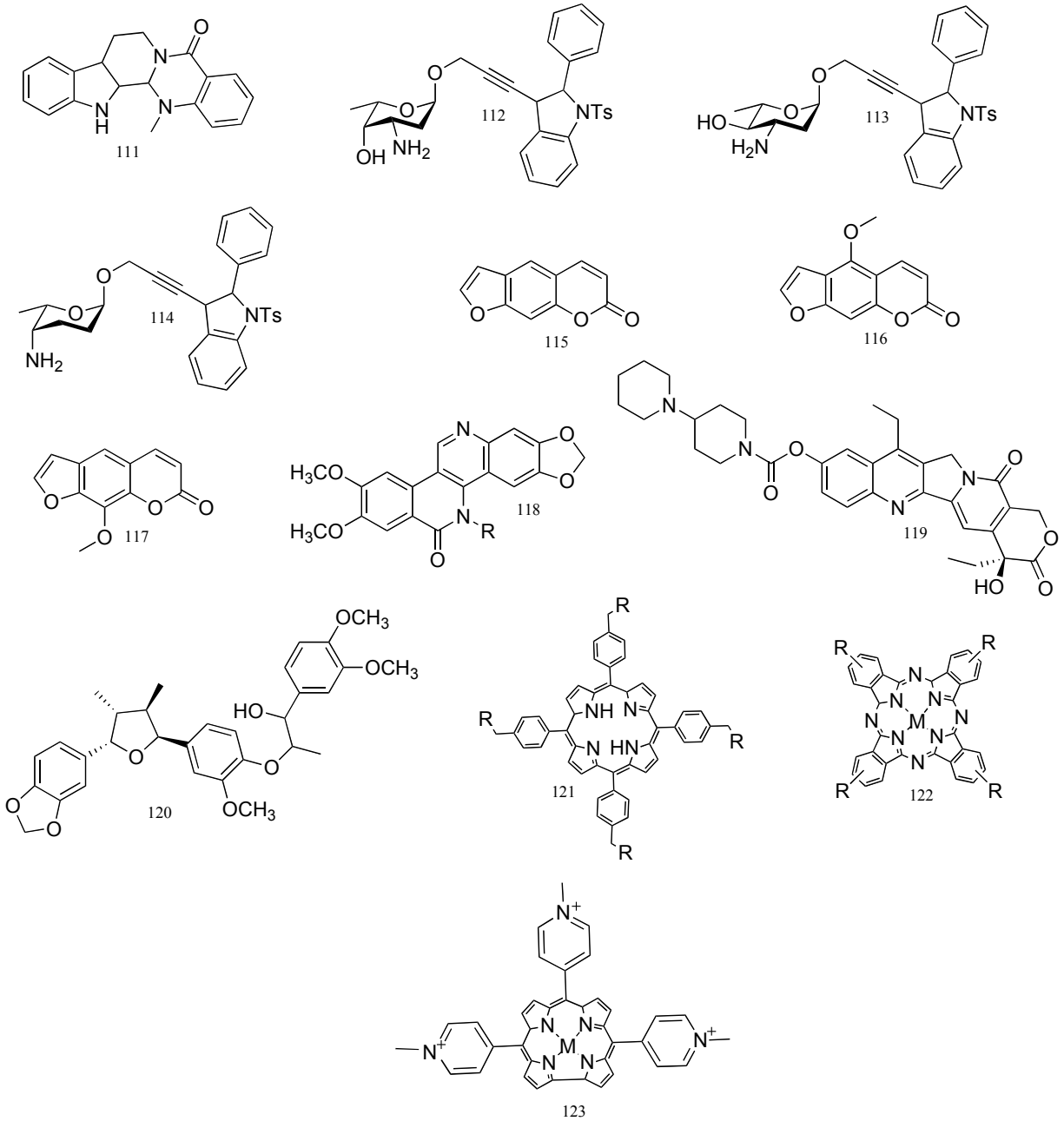


Fig. (9). Structures of compounds with topoisomerases inhibitory activity.

towards topos I and II. These compounds do not induce topo I-DNA covalent complexes but inhibit it by directly binding to DNA, which limits the enzyme access to the DNA substrate. The lowest concentration where the inhibition effect is clearly visible was between 0.1 and 0.6 μM. Furthermore, some complexes were found to inhibit the activity of topo II [72].

Indenoisoquinolines. The indenoisoquinolines (IND) (**124-127**) (Fig. **10**) are among the three classes of noncamptothecin topo I inhibitors in clinical development. Two IND have been selected for clinical development, and an IND has been filed [70].

Dihydronaphtoquinones. Two new dihydronaphtoquinones, 1,4-dihydroxy-2-carbomethoxy-3-prenylnaphthalene-1-O-β-D-glucopyranoside (**128**) and mollugin-1-O-β-D-glucopyranoside (**129**) (Fig. **10**) were isolated from *Rubia cordifolia* roots and showed activity against Topos I and II [65].

Lactones. A new monoterpenoid, 3*R*,3a*S*,4*R*,6a*R*-3,4,6-tris(hydroxymethyl)-3,3a,4,6a-tetrahydro-2H-cyclopenta[*b*] furan-2-one (**130**) (Fig. **10**) was isolated from *R. cordifolia* roots and showed inhibitory activity against Topos I and II [65].

A coumestan isolated in 1956 named Wedelolactone (**131**) (Fig. **10**), is one of the active polyphenolic compounds obtained from extracts of *Wedelia calandulaceae* and *Eclipta prostrata*. These plants are used in traditional Asian and South American medicine for the treatment of septic shock, liver diseases, viral infections, and snake bites. Compound **131** has been demonstrated to possess a wide range of biological effects, including inhibition of phospholipase A2, IKK kinase, hepatitis virus C RNA-pol, and Na^+, K^+-ATPase activities. Recently, it has been observed that this compound interacted with dsDNA and inhibited the activity of DNA Topo IIα [73].

Simocyclinone. Simocyclinone D-8 (**132**) (Fig. **10**), a semi-synthetic compound derived from yeast, has been shown to decrease the proliferation of MCF-7 breast cancer cells and to be a potent bacterial DNA gyrase inhibitor, a homologue of human topo II [74].

Thiocompounds. Thimerosal (**133**) (Fig. **10**), a compound chemically synthesized, is an organic mercury compound that is widely used as a preservative in vaccines and other solution formulations. The use of this compound has shown concern about its ability to cause neurological abnormalities due to mercury accumulation during a normal schedule of childhood vaccinations. Thimerosal also potently inhibited the decatenation activity of DNA Topo IIR, likely through the reaction with critical free cysteine thiol groups [75].

Thiosemicarbazides. 4-Benzoyl-1-(4-methyl-imidazol-5-yl)-carbonylthiosemicarbazide (**134**) (Fig. **10**) was synthesized, and its antibacterial and type IIA topo (DNA gyrase and Topo IV) activity was evaluated. Compound **134** was found to have high therapeutic potential against opportunistic Gram-positive bacteria and inhibitory activity against topo IV (IC_{50}=90 μM) but not against DNA gyrase. An increase in activity against topo IV (IC_{50}=14 μM) was observed when the imidazole moiety of **134** was replaced with the indole group in 4-benzoyl-1-(indol-2-yl)-carbonylthiosemicarbazide (**135**) (Fig. **10**) [76].

A novel series of aroylthiourea synthetic derivatives of 4-β-amino-40-O-demethyl-4-desoxy- podophyllotoxin (**136 – 139)** (Fig. **10**) was synthesized. Their cytotoxicity against three cancer cell lines was investigated by MTT assay. The kDNA decatenation assay indicated that these compounds inhibited Topo II-mediated kDNA decatenation [77].

Xanthone. Xanthones, which are mainly found as secondary metabolites from higher plants and microorganisms, have diverse pharmacological usages such as antihypertensive, anti-thrombotic, and anticancer activity, based on their diverse structures. Simple and interesting structural scaffolds and diverse biological spectra of xanthones have led many scientists to isolate or synthesize xanthone analogs for the development of prospective drug candidates. Compound **140** (Fig. **10**) efficiently blocked topo II function at 20 μM and compound **141** (Fig. **10**) needs a concentration of 100 μM for this inhibitory activity [78].

Diterpene. Yuanhuacine (**142**) is one kind of daphne diterpene *ortho*-ester (fig. **10**) extracted from *Daphne genkwa*, which has been shown to possess potent "*in vitro"* activities against P-388, L-1210, KB, human promyelocytic HL-60 and A-549 cell lines. Its anti-neoplastic activity in an "*in vivo"* P-388 lymphocytic leukemia screen with BDF1 male mice and suppressive effects against solid tumor growth in Lewis lung carcinoma-inoculated mice, have been reported. Also, it has been reported that yuanhuacine shows potent inhibitory activities against DNA topo I, which is probably one of its anticancer mechanisms [79].

REVERSE TRANSCRIPTASE

The viral enzyme reverse transcriptase (RT) catalyzes the synthesis of a complementary DNA strand to the genomic RNA to give a DNA/RNA hybrid. This enzyme is both an RNA- and DNA-dependent DNA polymerase, which means that it can synthesize a complementary DNA strand from an RNA template, as well as from a DNA template. After the hybrid strand formation, the RNA strand is destroyed by another domain of RT, known as RNase H. RT catalyzes the synthesis of double-stranded (ds) DNA from the complementary single-stranded (ss) DNA. This dsDNA migrates to the host cell's nucleus under the direction of the viral enzyme integrase, which then catalyzes integration of the viral DNA into the host's chromosome. Once it is incorporated into the chromosomal DNA of the host cell, the viral DNA, now known as provirus, can use host enzymes to transcribe viral genomic RNA and mRNA [80-83].

Table **3** shows an update of the diversity of compounds discovered after the previous review. The chemical groups of these compounds and IC_{50} values are also included.

Essential Oil. The essential oils of *Ridolfia segetum* (L.) Moris and *Oenanthe crocata* L., collected in Sardinia, Italy, have been assayed for analyzing the inhibitory effect against two enzyme-associated activities of the HIV-1 RT, RNA-dependent DNA polymerase (RDDP) activity and ribonuclease H (RNase H) activity. In biochemical assays, the essential oils inhibited HIV-1 RT RDDP activity in a dose-dependent manner, while they were inactive towards RNase H activity [84].

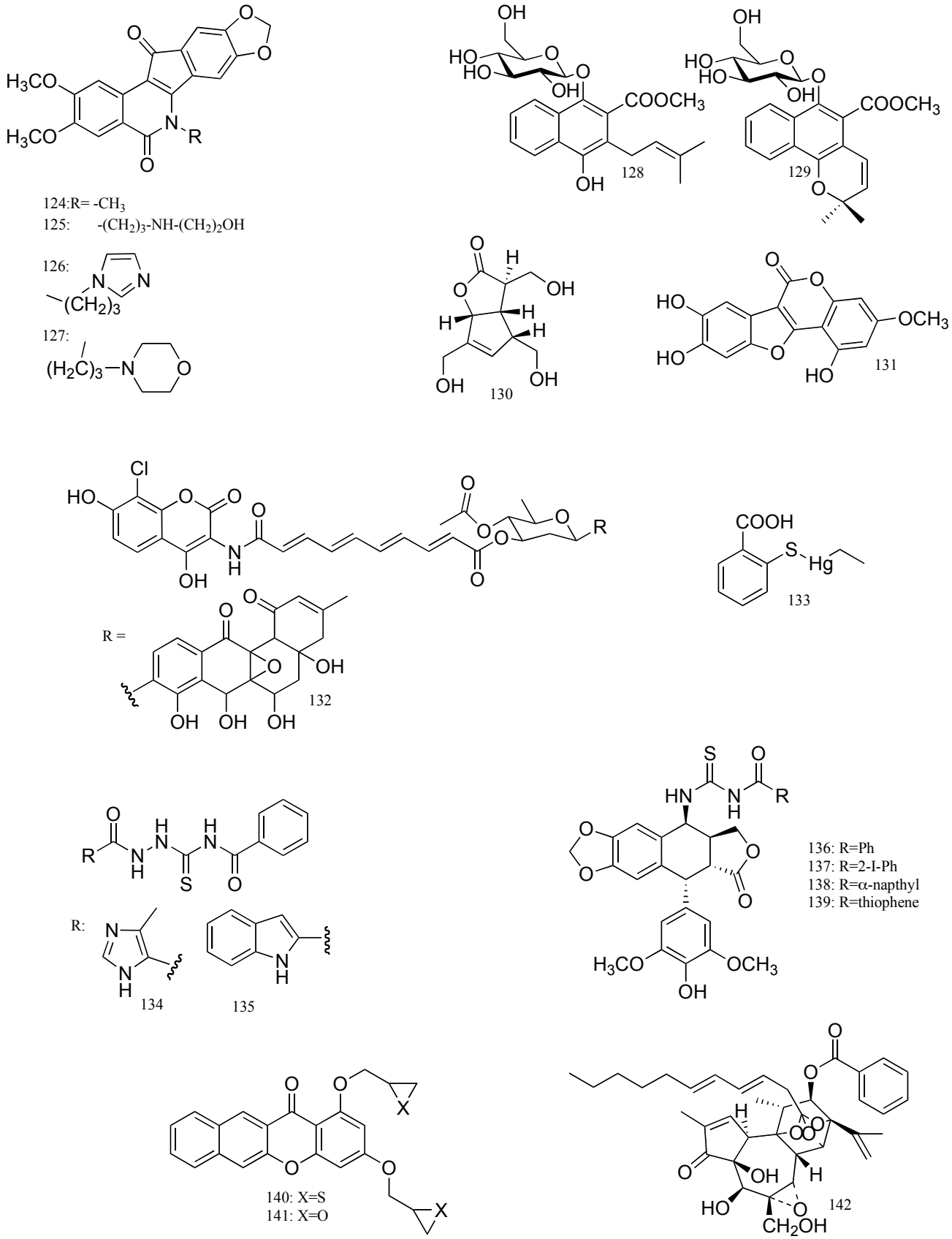


Fig. (10). Structures of compounds with topoisomerases inhibitory activity.

Table 3. Compounds with Reverse Transcriptase Inhibitory Activity.

N°	Compound	Origen	Chemical Characteristic	Activity (RT and HIV)	Ref.
143	2,4-diarylaniline analog	Synthetic derivatives	Diarylaniline	EC_{50}= 0.53 nM	[85]
144	*N*-{2-[4-(aminosulfonyl)phenyl]ethyl}-2-(2-thienyl)acetamide	Synthetic derivatives	Thiocompounds	RNA and DNA- pol. act., IC_{50} = 1.20 and 2.10 μM	[86]
145	6-(Arylmethyl)-1-alkyl-5-halouracils	Synthetic derivatives	Aryluracils	EC_{50}= 0.006- 0.637 μM	[87]
146	6-(Arylmethyl)-1-alkyl-5-halouracils	Synthetic derivatives	Aryluracils	EC_{50}= 0.002- 0.091 μM	[87]
147	6-(Arylmethyl)-1-alkyl-5-halouracils	Synthetic derivatives	Aryluracils	EC_{50}= 0.009- 0.601 μM	[87]
148	6-(Arylmethyl)-1-alkyl-5-dimethylaminouracils	Synthetic derivatives	Aryluracils	EC_{50}= 0.014- 2.198 μM	[87]
149	6-(Arylmethyl)-1-alkyl-5-halouracils	Synthetic derivatives	Aryluracils	EC_{50}= 0.006- 2.543 μM	[87]
150	dihydroalkylthiobenzyloxopyrimidine	Synthetic derivatives	Pyrimidines	IC_{50} = 3.640 μM	[88]
151	Difluoromethylbenzoxazole pyrimidine thioether derivative	Synthetic derivatives	Pyrimidine thioether	EC_{50}= 6.400 nM	[89]
152	Thiourea derivative	Synthetic derivatives	Pyridines	EC_{50}= 0.026 μM	[90]
153	Thiourea derivative	Synthetic derivatives	Pyridines	EC_{50}= 0.012 μM	[90]
154	Imidazol-5-ones	Synthetic derivatives	Imidazole	IC_{50} = 3.900 μM	[91]
155	Imidazol-5-ones	Synthetic derivatives	Imidazole	IC_{50} = 3.500 μM	[91]
156	Imidazol-5-ones	Synthetic derivatives	Imidazole	IC_{50} = 2.500 μM	[91]
157	Imidazol-5-ones	Synthetic derivatives	Imidazole	IC_{50} = 3.800 μM	[91]
158	Pyridone analog	Synthetic derivatives	Pyridone	IC_{50} = 35.000 nM	[92]
159	Piperidine-linked amino-triazine derivative	Synthetic derivatives	Piperidine	EC_{50}= 4.601 nM	[93]
160	1-benzyl-1H-1,2,3-triazoles	Synthetic derivatives	Triazoles	IC_{50} = no data	[94]
161	1-benzyl-1H-1,2,3-triazoles	Synthetic derivatives	Triazoles	IC_{50} = no data	[94]
162	1-benzyl-1H-1,2,3-triazoles	Synthetic derivatives	Triazoles	IC_{50} = no data	[94]

Notes: IC_{50}: Inhibitory Concentration 50 %, EC_{50}: Median Effective Concentration.

Diarylaniline. The current optimization of 2,4-diarylaniline analogs (DAANs) on the central phenyl ring provided a series of new active DAAN derivatives. A new compound (**143**) (Fig. **11**) exhibited extremely high potency against wild-type HIV virus (EC_{50} = 0.53 nM) [85].

Thiocompounds. The compound, *N*-{2-[4-(aminosulfonyl)phenyl]ethyl}-2-(2-thienyl)acetamide (**144**) (Fig. **11**), inhibited both RNA-dependent and DNA-dependent DNA pol activities, with apparent IC_{50} values of 1.2 and 2.1 μM, respectively. This inhibition was specific against RT-associated polymerase activity and did not affect the RNase H activity [86].

Aryluracils. The aryluracils compounds (**145-149**) (Fig. **11**) exhibited highly potent anti-HIV-1 activity against both wild-type and non-nucleoside reverse transcriptase inhibitors (NNRTI)-resistant HIV-1 strains [87].

Pyrimidines. A series of novel dihydroalkylthiobenzyloxopyrimidines has been designed and synthesized. Biological evaluation of their HIV-1 RT inhibitory activities was performed using Nevirapine as a reference compound. Among the series, compound **150** (Fig. **11**) shows the highest RT inhibitory activity, which was better than Nevirapine [88].

Thioether derivatives. The synthesis and antiviral properties of new difluoromethylbenzoxazole pyrimidine thioether derivatives as non-nucleoside HIV-1 RT inhibitors were reported. The compound **151** (Fig. **11**) showed a significant EC_{50} value close to 6.4 nM against HIV-1 IIIB [89].

Pyridines compounds. Several novel thiourea derivatives of the NNRTI HI-236 substituted at the C-2 oxygen of the phenyl ring have been synthesized and evaluated for their inhibitory activity against HIV-1 replication in MT-2 cell line cultures. Two of the thiourea derivatives (**152-153**) (Fig. **11**) showed excellent activities [90].

Imidazoles compounds. A novel series of substituted imidazol-5-ones was designed, synthesized (**154-157**) (Fig. **11**) and evaluated for "*in vitro"* RT inhibition activity using RT assay kit (Roche, Colorimetric) showing an important inhibitory activity [91].

Pyridone. New pyridone NNRTIs were prepared and compound **158** (Fig. **11**) was an active inhibitor of the replication of wild-type and NNRTI-resistant HIV [92].

Piperidines. A novel series of piperidine-linked amino-triazine derivatives was designed, synthesized and evaluated for "*in vitro"* anti-HIV activity as non-nucleoside RT inhibitors. Screening results indicated that most compounds showed excellent activity against wild-type HIV-1 with EC_{50} values in low nanomolar concentration range, especially compound **159** (Fig. **11**) with EC_{50} of 4.61 nM [93].

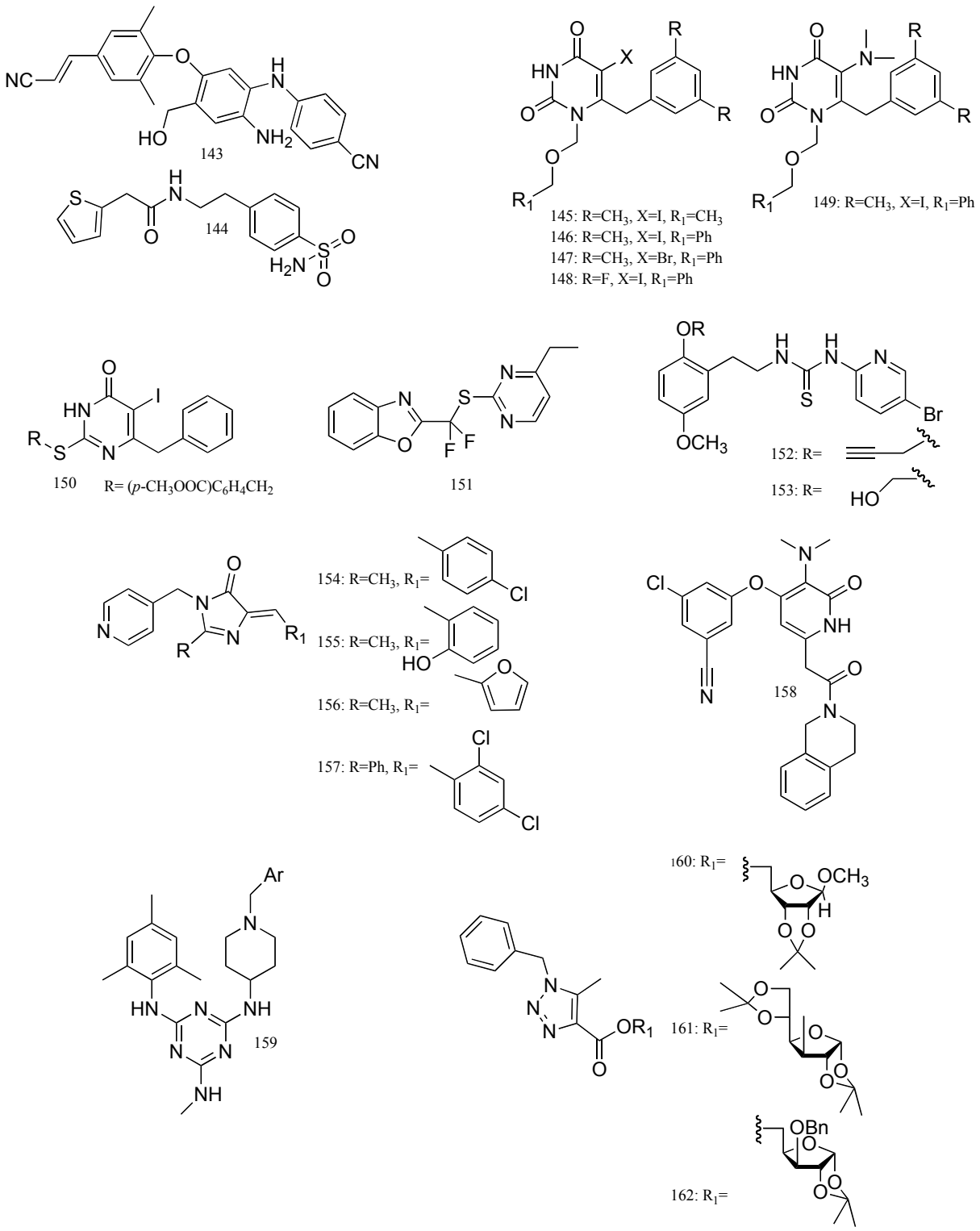


Fig. (11). Structures of compounds with reverse transcriptase inhibitory activity.

Triazole derivatives. The synthesis of several 1-benzyl-1H-1,2,3-triazoles attached to different carbohydrate templates and their "*in vitro"* inhibitory profile against HIV-1 RT was described. The results showed that compounds **160-162** (Fig. **11**) were the most active against HIV-1 RT [94].

CONCLUSION

This review article demonstrated that natural products and synthetic compounds, in minor level, play a central role in the discovery of leads compounds for the development of drugs for human diseases treatments. Although, an immense diversity of chemical structures with inhibitory activity

against DNA pols, topos and RT have been discovered and developed, much of nature remain to be explored; particularly, marine environments and microbial niches could be important sources for novel bioactive compounds remaining to be discovered. A multidisciplinary approach, involving the generation of truly novel molecular diversity from natural products, and chemical transformation and bioactivity assays to molecular level, provides an excellent method for the discovery and development of new drugs against cancer and AIDS.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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ABBREVIATIONS

A-549	=	Human lung adenocarcinoma epithelial cell line
ATP	=	Adenosine Triphosphate
BDF1	=	Bromodomain Factor 1
DAANs	=	2,4-diarylaniline analogs
DNA	=	Deoxyribonucleic Acid
dNTP	=	deoxynucleotide
ds	=	double-stranded
EC_{50}	=	Effective Concentration 50
FDA	=	Food and Drug Administration
HIV	=	Human Immunodeficiency Virus
IC_{50}	=	Inhibitory Concentration 50
IKK kinase	=	IκB kinase
IND	=	Indenoisoquinolines
KA-A	=	kohamaic acid A
KB	=	Human carcinoma cell
L-1210	=	Mouse lymphocytic leukemia cells
LD_{50}	=	Lethal Dose 50
mRNA	=	Messenger RNA
MT-2	=	Cell line transformed by human T-cell leukemia virus type 1
MTT	=	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NNRTIs	=	Non-Nucleoside (NNRTIs) Reverse Transcriptase Inhibitors
NRTIs	=	Nucleoside Reverse Transcriptase Inhibitors
P-388	=	Mouse leukaemia cells
PCa	=	Prostate Cancer
PGG	=	Penta-1,2,3,4,6-O-galloyl-β-D-glucose
PKBA	=	Propionyloxy derivative of 11-Keto-β-Boswellic Acid
Pol	=	polymerase
Pols	=	polymerases
RDDP	=	RNA-dependent DNA polymerase
RNA	=	Ribonucleic acid
RNase H	=	Ribonuclease H
RNase	=	Ribonuclease
RT	=	Reverse Transcriptase
ss	=	single-stranded
Taq	=	*Thermus aquaticus*
TdT	=	Terminal deoxynucleotidyl Transferase
Topo	=	Topoisomerase
Topos	=	Topoisomerases

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