STRUCTURE-ACTIVITY STUDIES

OF NOVEL NONCAMPTOTHECIN

TOPOISOMERASE I-TARGETING AGENTS

by

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A Dissertation submitted to the

Graduate School-New Brunswick

Rutgers, The State University of New Jersey

in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

Graduate Program in Medicinal Chemistry

written under the direction of

Professor Edmond J. LaVoie, Ph.D.

and approved by

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New Brunswick, New Jersey

May, 2008

ABSTRACT OF THE DISSERTATION

STRUCTURE-ACTIVITY STUDIES OF NONCAMPTOTHECIN TOPOISOMERASE I-TARGETING AGENTS

By WEI FENG

Dissertation Director: Professor Edmond J. LaVoie, Ph.D.

Topoisomerases are ubiquitous enzymes that participate in processes such as DNA replication, transcription and repair. Two camptothecin derivatives, topotecan (Hycamtin®) and irinotican (CPT-11/ Camptosar®), are currently used in the clinic as topoisomerse I targeting anticancer agents. Camptothecins can stabilize the enzyme-DNA cleavage complex, leading to DNA damage and ultimately cell death. Despite their unique tumor suppression mechanism, topotecan and irinotican can undergo hydrolysis and inactivation *in vivo* due to an unstable lactone moiety. In addition, both topotecan and irinotican are substrates for efflux transporters, BCRP and MDR1, which are associated with drug resistance. 8,9-Dimethoxy-5-(2-dimethylaminoethyl)-2,3-methylenedioxy-5H-dibenzo[*c,h*][1,6]naphthyridine-6- one (ARC-111) has been identified as exceptionally active TOP1-targeting agent with potent antitumor activity both *in vitro* and *in vivo*. Unlike camptothecins, ARC-111 is not a substrate for major efflux transporters, and does not bind to human serum albumin. ARC-111 structurally related analogs, 12-carboxamides

of benzo[*i*]phenathridine and the "reversed lactams" have also exhibited excellent cytotoxicity and potent TOP1 targeting activity. In this dissertation, further insights into structure-activity relationship of ARC-111 and related compounds have been carefully examined. Alteration of both D-ring and side chain of ARC-111 have afforded potent TOP1-targeting agents. Inspired by the success of ARC-111, the design, synthesis and biological activities of other B-ring modified benzo[*i*]phenathridines have been systematically investigated. In review of possible metabolites of ARC-111, together with the known structure-activity relationships associated with the "reversed lactams", 11-carboxamides and 12-carboxamides of benzo[*i*]phenathridine, have prompted the examination of α,α-dimethyl substitution on the amino side chain on pharmacologic activity. Efficient synthetic methods associated with these novel non-camptothecin anticancer agents have also been developed. Several agents identified in this study have demonstrated excellent cancer cell cytotoxicity, TOP1 targeting specificity, as well as *in vivo* antitumor efficacy, comparable as the lead compound, ARC-111.

ACKNOWLEDGEMENT

First, my most earnest acknowledgement must go to my mentor, Prof. Edmond J. LaVoie. My graduate study would not have been possible without his exceptionally valuable guidance and support. He always encouraged me when I made some progress in my research, even a tiny step.

My sincere gratitude goes to Prof. Joseph E. Rice for his insightful advice, both with my academic courses and experimental design. I am also indebted to my committee members, Drs. S. David Kimball and Roger A. Jones for their time and constructive suggestions about my research proposal.

I give special thanks to Dr. Longqin Hu for his knowledge and insight when I took his course. I am thankful to Ms. Mary Devlin, our principal secretary, who is always patient and ready to help me no matter how many times I disturb her each day. I appreciate the work of Ms. Angela Liu and Mr. Yuan-chin Tsai from UMDNJ for biological assays.

I will always miss the happy time I spent in our laboratory. I am deeply grateful to Dr. Mavurapu Satyanarayana for numerous discussions, sharing reaction experiences, and allowing me to use his clean NMR tubes, sometimes. I would like to thank Ms. Suzanne Rzuczek for tolerating my grammar and spelling mistakes when proof-reading my dissertation. My thanks also go to Mss. Liang Cheng, Lisa Sharma, Shejin Zhu, and Mr. Diandian Shen for their friendship.

DEDICATION

To my parents, Guizhang Feng and Junlan Ma

Who made all of this possible

And also to

My beloved wife, Lihua Du,

For her understanding and support

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF SCHEMES

INTRODUCTION

Every year, the lives of more than 10 million people are claimed by cancer and this number could increase by 50% to 15 million by 2020.[1] Cancer is a leading cause of mortality, accounting for about 13% of all deaths worldwide each year. However, with the advances in molecular biology and medicinal chemistry, cancer is becoming less threatening. A decline in certain cancers death rates and an increased life expectancy is due to earlier detection of tumors, use of efficacious radiotherapy, and most importantly, the discovery of more specific and selective chemotherapy.[2]

Cancer cells are recognized as abnormal and rapidly proliferating cells with an aberrantly high level of DNA related activities, such as DNA replication, transcription or recombination. Therefore, drugs targeting tumor DNA are regarded as powerful weapons against cancer. Currently, there are several classes of DNA targeting cancer chemotherapies in clinical use, which mainly include alkylating agents, antimetabolites, antitumor antibiotics and topoisomerase targeting agents.[3] Among these agents, drugs targeting topoisomerases, are widely used and have proven to be efficacious. Camptothecin derivatives topotecan and irinotican are clinically successful topoisomerase I targeting agents.[4-6] The unique antitumor activity of these drugs have inspired

tremendous research in this area and topoisomerase I targeting agents have been intensily investigated over past twenty years.

Topotecan and irinotecan, like many other anticancer drugs, suffer from drug resistance due to their recognition by efflux transporters present in certain cancer cells. Unfavorable physicochemical and pharmacokinetic properties of camptothecin derivatives present other obstacles limiting their clinical utility. For example, topotecan and irinotecan possess a labile lactone moiety which quickly opens and inactivates the drug in a physiological environment.[7] These short-comings provide significant opportunities for the development of novel topoisomerse I targeting agents with improved therapeutic properties.

Our group has been contributing to the design of novel TOP I inhibitors since the early 1990s. Some excellent TOP1 targeting agents have been discovered by our group, including ARC-111 and related analogs, which have undergone pre-clinical toxicological studies and are in preparation for future clinical studies. Our research in recent years has remained focusing on the design and synthesis of novel non-camptothecin TOP I targeting agents with the potential to overcome multidrug resistance as well as to possess greater potency and selectivity than the currently available TOP1-targeting drugs.

1.1 DNA Topology and Topoisomerases

Deoxyribonucleic acid (DNA), as the prime genetic molecule carries all the hereditary information responsible for cell development and functioning. DNA is a long polymer with a remarkably complex topology.[8-10] The DNA molecule is topologically constrained because of its extreme size, its containment in chromatin and interaction with other

components (Figure 1A).[11-13] The two twisted strands of double helix DNA can adopt various topologies such as supercoiling, knotting or catenation (Figure 1B).[13-16]

A. B.

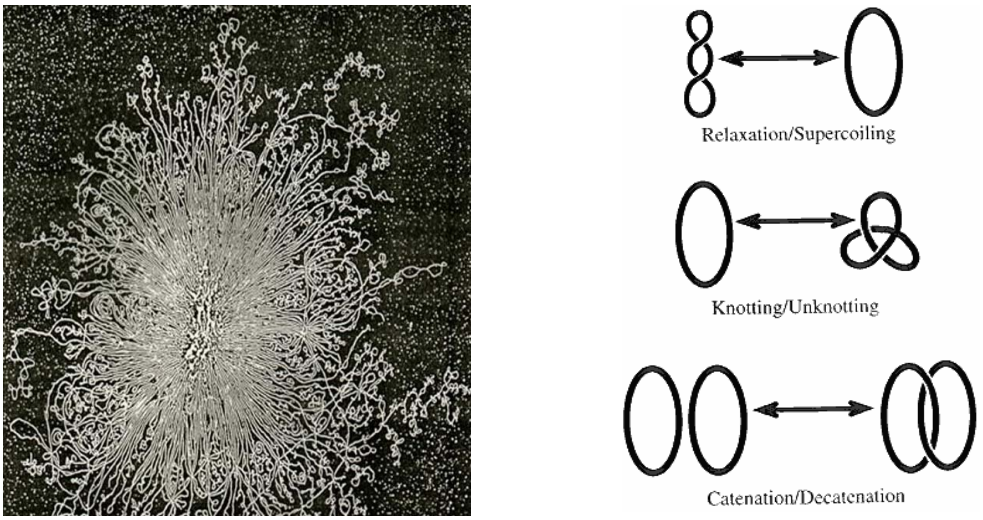


Figure 1. A) Bacterial double-strand DNA. (adopted from Ref. 11) B) DNA topology: supercoiling, knotting and catenation (adopted from Ref. 15)

The two strands of duplex DNA must be separated in the course of cellular activities such as replication, transcription, recombination or repair. A remarkable class of enzymes, known as topoisomerases, is found to be able to change the topology of DNA. Topoisomerases were first discovered by Wang's group from *Eschericia coli (E. coli)* in 1971.[17,18]

Topoisomerases are divided into two types based upon the number of DNA strands cut in order to modify DNA topology. Type I topoisomerases make transient single-stranded breaks in DNA while type II topoisomerases make transient double-stranded breaks.[19] Type I topoisomerases do not require ATP in the process; type II topoisomerases require ATP as a cofactor.[19,20] Type I topoisoerases are further categorized into type IA and IB,

depending on the enzyme attacking the 5' end or the 3' end of DNA (Figure 2).[19-21] Eukaryotic DNA topoisomerases I (TOP1) is the pharmacologic target of camptothecin derivatives.

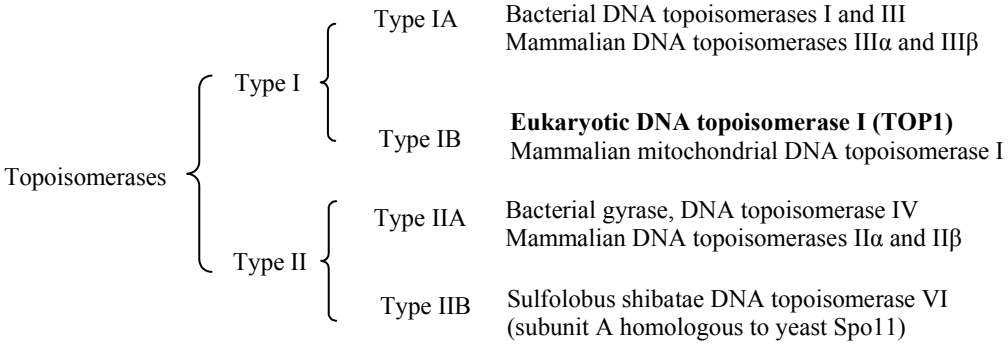


Figure 2. Categories of topoisomerases [19-21]

1.2 Structure and Function of Topoisomerase I (TOP1)

Human TOP1 is a 91-kDa monomeric protein. It has been subdivided into four domains: N-terminal domain, core domain, linker domain and C-terminal domain according to their different functions.[23,24] The N-terminal domain is a highly charged, unstructured region and it is not directly related to DNA relaxation activity.[23-26] The core domain includes all catalytic residues except tyrosine 723. It can be further subdivided into three core sub domains. The linker domain is protease sensitive and dispensable for relaxation activity *in vitro*. The C-terminal domain contains the active site tyrosine 723.[23-26] A crystal structure of TOP1 complexed with DNA is shown in Figure 3.[21,27] The "cap" lobe refers to core subdomain I and II. The other lobe is the base part of the enzyme, which contains subdomain III and the C-terminal fragment. Between these two lobes is a long helix named "connector". Another connection between these two lobes is through a pair of loops. This pair of loops, called "lips", are located opposite to the connector and interact with each other by a salt bridge and possible van der Waals contacts. The "lips" of

TOP1 can open or close depending on whether the enzyme is releasing or binding DNA. There is a "putative hinge" located on the top of the connector.[21,28]

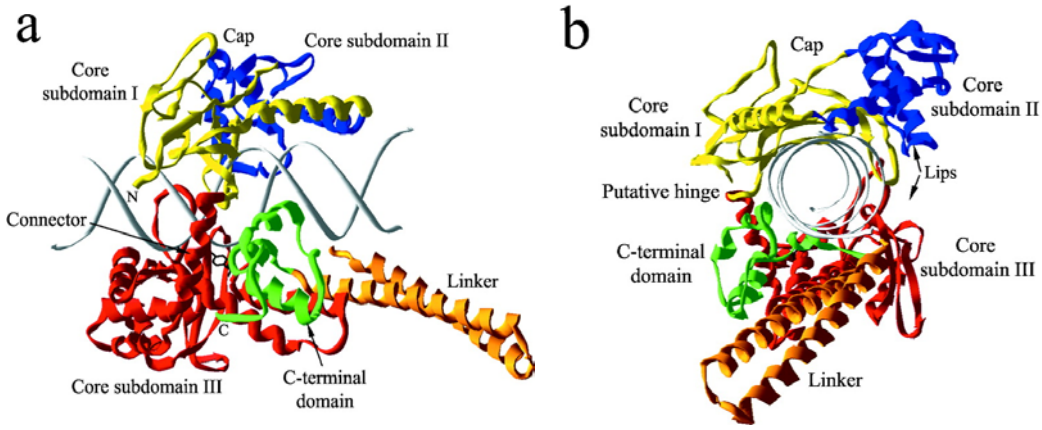


Figure 3. Two views of the structure of human topoisomerase I noncovalently complexed with a 22 base pair DNA a) DNA parallel to the paper plane b) DNA vertical to the paper plane (Adopted from Ref. 21).

In a highly negatively supercoiled DNA, the cleavage of the DNA strand by TOP1 is favored and does not need ATP because of strain. The key step of this catalytic process is the nucleophilic attack of O-4 oxygen of Tyr723 on the scissile phosphate of DNA.[22,29] The new phosphoester link generated (Figure 4) between the tyrosine and the 3' end of DNA covalently connects the enzyme and DNA.[22,29,31,32]

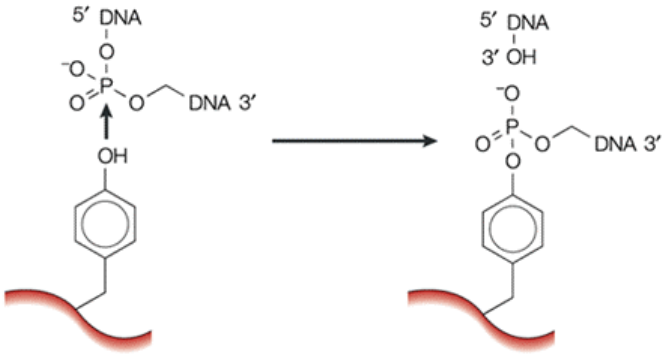


Figure 4. The key covalent intermediate formed by topoisomerase I attacking on DNA 3' end (Adopted from Ref. 22)

A possible model of the TOP1 action mechanism has been proposed. [21,33,34,35] Before cleavage, DNA strands bind to the base lobe of TOP1 which is followed by closing of the "lips" (Figure 5b and 5c). The closed conformation of TOP1 directs the strand near to the tyrosine active site. Then the tyrosine phenoxy group attacks this strand on its phosphate via an ester-exchange (Figure 5d). After cleavage, the enzyme probably opens

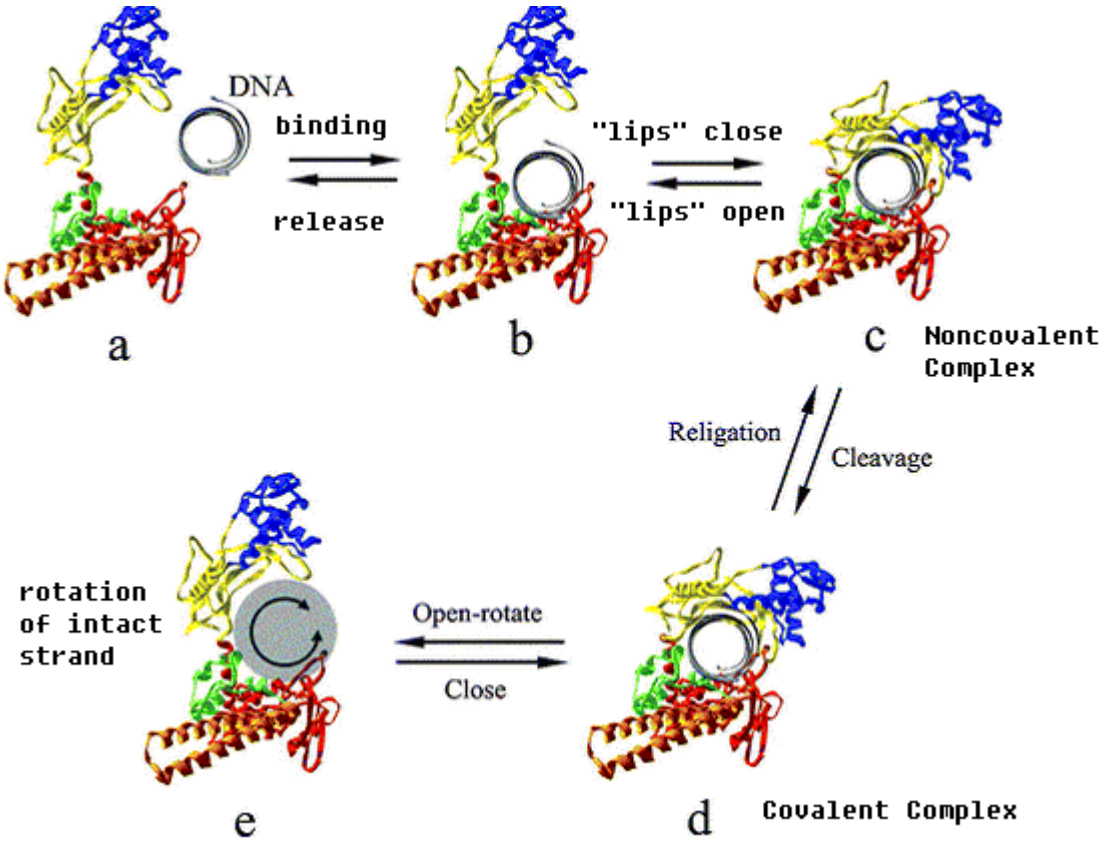


Figure 5. Type I topoisomerases changes topology of DNA. All processes are reversible. a) The enzyme opens up to accommodate DNA binding. b) DNA strands bind to the base lope of the enzyme. c) The "lips" of enzyme close and conformation of enzyme changs to bring the active tyrosine group near to the scissile DNA strand phosphate backbone. d) Transesterification occurs and covalent bond is formed between enzyme and DNA. e) The intact strand of DNA rotates in the enzyme. Enzyme adopts an opened conformation to facilitate rotation. (Adopted from Ref. 21)

up to allow the helical duplex downstream to rotate to release torsion. Then the enzyme closes again to direct the free 5' end of DNA back to the active site of enzyme. Finally, another ester-exchange rejoins the cleaved strand ends with release of free tyrosine of TOP1. A graphic illustration is shown in Figure 5. [21]

Topoismerases usually collaborate with other enzymes to regulate DNA replication and transcription. Inhibition of topoisomerase fuction may lead to failure of the entire DNA replication or transcription process. Drugs may either target topoisomerase itself or bind to the DNA/TOP complex to inhibit the proper function of topoisomerase.[36,37] The drugs only inhibiting topoismerases include the coumermycin family of antibiotics[36], suramin[38], fostriecin[39], merbarone[40], bis(2,6-dioxopiperazines),[41,42] β-Lapachone,[43] and some other natural products.[44] Camptothecin derivatives, as representatives for the other class, stabilize the DNA/TOP1 complex and slow down the religation step, which is normally very fast. The reversible ternary DNA/TOP1/DRUG complex is the key intermediate which is ultimately responsible for the cell killing activity of camptothecin TOP1 targeting agents.[45]

1.3 Camptothecins as TOP1 Targeting Agents

Camptothecin(CPT) was first isolated from the bark of the Chinese tree, *Camptotheca acuminate* in 1966 by M. E. Wall and M. C. Wani.[45,46] CPT was reported to possess potent antitumor activity against a wide spectrum of cancer cell lines.[47-49] However, due to poor solubility and unpredictable side effects (such as myleosuppression, diarrhea and hemorrhagic cystitis), the early study on CPT was discontinued.[50] In 1985, an important study on CPT brought new life to this antitumor agent.[51] This study revealed that TOP1 is

the sole target of CPT that is associated with its cell killing activity.[51] This unique TOP1 targeting activity[51-53] encouraged medicinal chemists to develop more CPTs with increased water solubility and less toxicity. This research directly led to the discovery of two clinical drugs: topotecan (Hycamtin®) and irinotican (CPT-11/ Camptosar®), a prodrug of its ultimate active derivative, SN-38.[54-56]

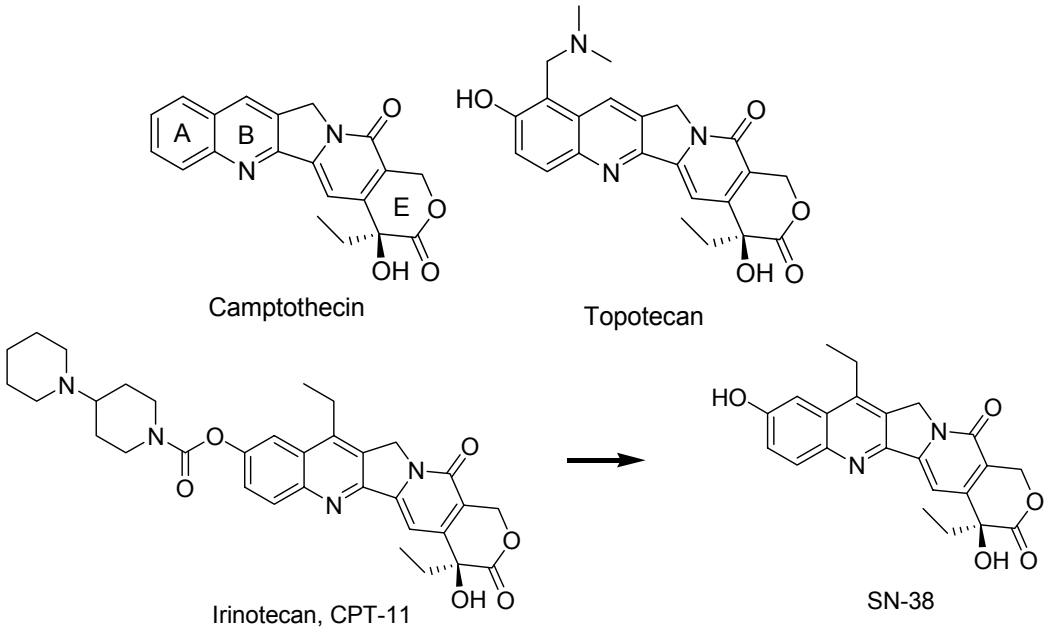


Figure 6. Camptothecin, topotecan, irinotecan and SN-38

CPT does not bind to TOP1, nor does it bind strongly to DNA. It targets TOP1 by stabilizing the complex between TOP1 and DNA. This TOP1/DNA/CPT ternary covalent complex accounts for the DNA damage. These damages trigger apoptosis and eventually cause cell death. Additional evidence of this targeting mechanism is cancer cells outside of S-phase are resistant to CPT, which indicates CPT inhibition is related to DNA replication events.[57]

The reversible TOP1/DNA/CPT complex can slow down the DNA religation but by itself is not sufficient to cause cell death. However, when this complex is formed on

replicating DNA, DNA polymerase slides up to the last nucleotide at the 5' end of a nicked DNA strand and leads to irreversible DNA double-strand breaks.[58-62] Similarly, RNA polymerase can also collide with the cleavage ternary complex on the transcribed strand. The arrested elongation of RNA leads to irreversible TOP1-linked single strand breaks.[63,64]

To explain the anticancer activity of camptothecins, a replication fork collision model (Figure 7) has been proposed.[60-62] Similarly, another RNA polymerase collision model also has been used to provide mechanistic insights into CPT inducing the DNA damage in the RNA transcription process.[63,64]

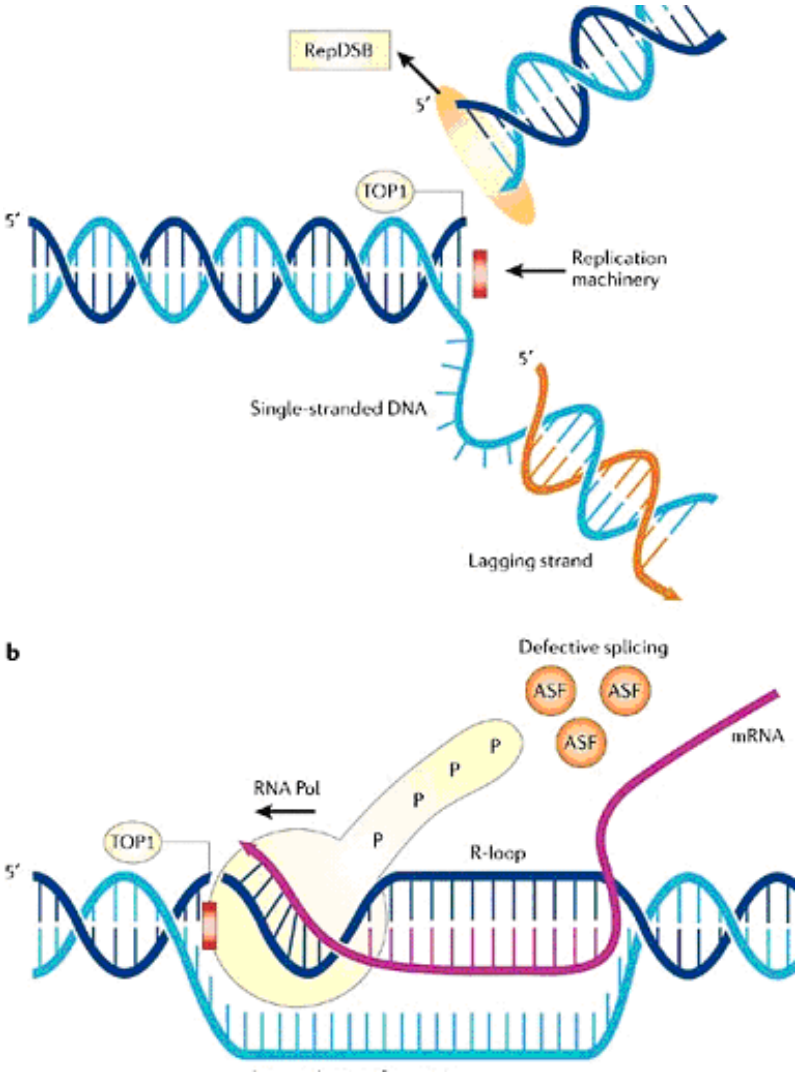


Figure 7. DNA replication and transcription collision models

Besides CPT's specific inhibition of TOP1 enzymes, another attractive advantage of CPT is its high selectivity for cancer cells over normal cells.[62] This phenomenon can be attributed to two factors. First, proliferating cancer cell lines need a higher level of TOP1 to conduct their abnormally active replication and transcription processes. With overexpressed TOP1, cancer cell should be more sensitive to CPT. Second, certain genes which are responsible for repairing DNA damage are usually mutated in tumor cells.[66,67, 68] These altered genes failed to trigger a downstream response to repair DNA damage.[68] Without repairing damaged DNA, tumor cells are more likely to choose the apoptosis pathway resulting in programmed cell death. Convincing evidence is provided by Liu showing that the degradation of TOP1, an effective protection in response to CPT in normal cells, malfunctions in many cancer cell lines.[68]

Topotecan and irinotecan are successful cancer therapies currently used in the clinic. However, there are several drawbacks associated with these antitumor agents, which potentially limit their efficacy. The E ring of CPT contains a lactone moiety which is not stable under physiological pH of 7.4. As much as 50% of CPT is hydrolyzed to its ring-opened form under these conditions.[69] The hydrolyzed forms of all of the camptothecin analogs are inactive as a TOP1 targeting agents. The hydrolysis product of lactone, also has a very high affinity for human serum albumin (HSA).[70] The plasma binding of the ring-opened form further drives equilibrium associated with the hydrolysis of CPT towards formation of more inactive carboxylate. The ratio of the active form of CPT to its hydrolyzed form has been determined to be 1:9 in the presence of human serum.[70,71] Topotecan and irinotecan have less affinity to HSA, but are still hydrolyzed rapidly under physiologic conditions.[72]

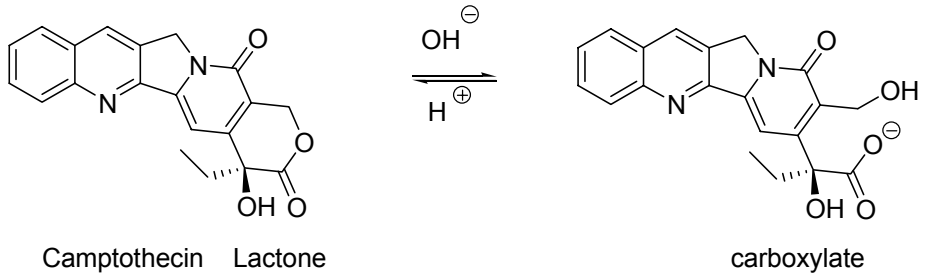


Figure 8. Hydrolysis results in formation of a ring-opened, inactive form of camptothecin

Multiple drug resistance (MDR) has been a factor which adversely affects the efficacy of many anticancer agents.[73] The most common cause of MDR is energy dependent efflux of cytotoxic drugs.[74,75] ATP-binding cassette (ABC) transporters mediate this efflux mechanism, pumping drugs out of cellular membranes. There are 48 genes found in the human genome which encode ATP-binding cassette transporters.[73] Many of them are overexpressed in cancer cell lines and result in antitumor drug resistance. P-glycoprotein (also known as MDR1), is one member of the ABC transporter family. When over expressed in tumor cells it confers resistance to the widest variety of compounds. BCRP (also known as ABCG2, or breast cancer resistance protein) is another high-capacity transporter of the ABC transporter family.[76-80] Both topotecan and irinotecan are substrates for both the MDR1 and the BCRP efflux transsporters.[75]

Many other CPT derivatives have also been designed and synthesized.[20,81,82] These excellent SAR studies provide insights into the mechanism of drug action. However, these derivatives have still frequently been identified as substrates for one or more of the efflux transporters associated with multidrug resistance. The problems associated with the vulnerability of the lactone moiety also persist for most CPT derivatives. These

observations appear to be, at least in part, associated with a camptothecin core structure. Thus, the inherent core structure of camptothecin can limit the distribution and cellular accumulation of these antitumor agents into tumor tissue.

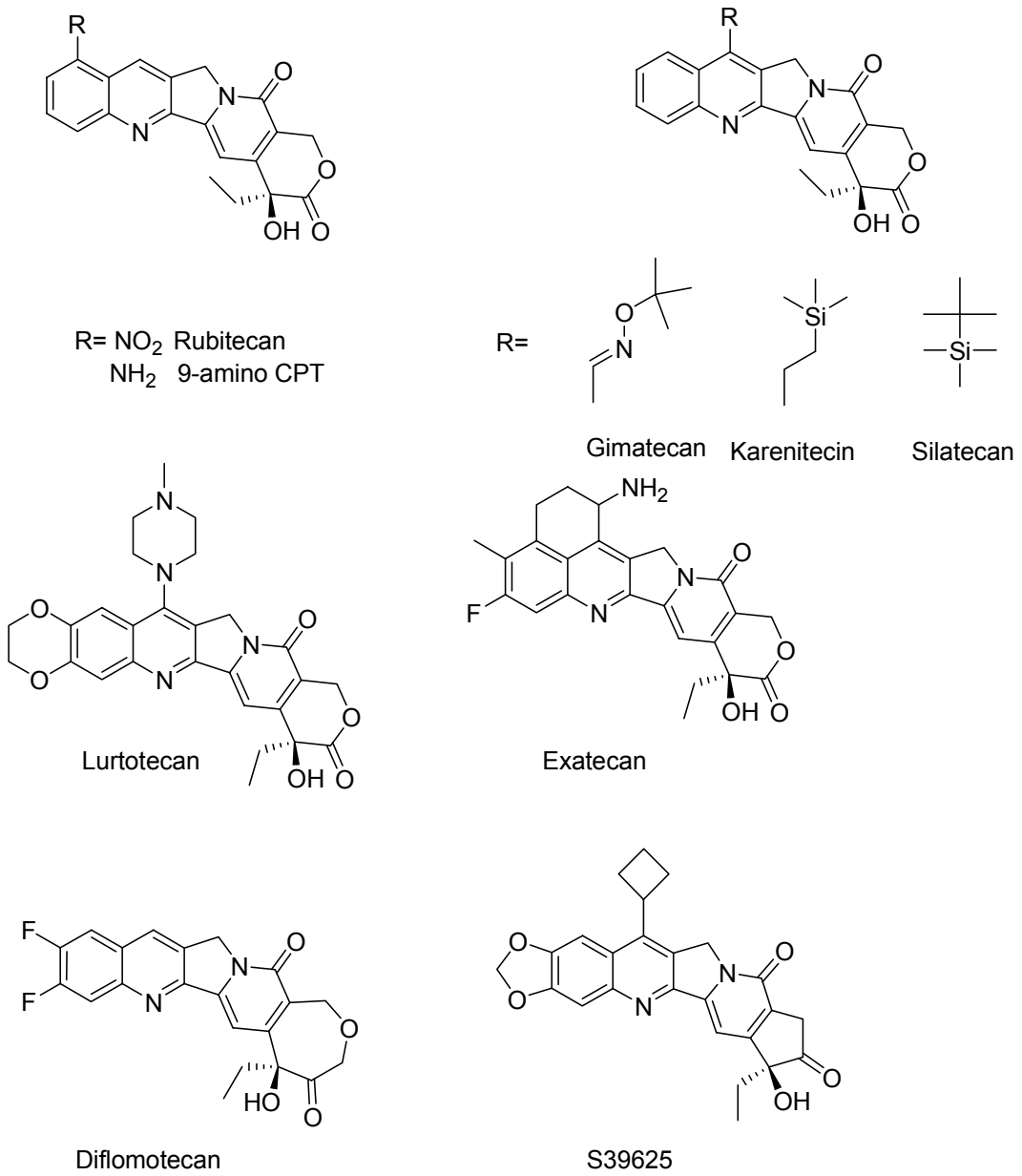


Figure 9. Camptothecin derivatives

1.4 From Natural Products to ARC-111

Clinical success of CPTs has validated TOP1 as an excellent therapeutic target. However, limitations of CPT, such as low bioavailability and widely developed multiple drug resistance, appear rooted within its structural features. Therefore, it is important and necessary to develop a structurally novel non-camptothecin TOP1 targeting agent. Additionally, drugs with the same target may demonstrate different spectrum of biological activities, as has been shown with the TOP2-targeting agents, amsacrine and etoposide.[83]

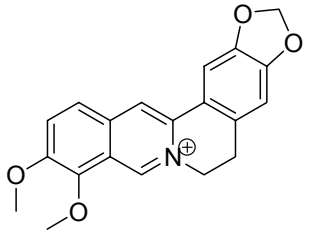
Natural products are an attractive source of new therapeutic candidate compounds as many clinical drugs, including anticancer drugs, have been found or derived from extracts of plants, animals, marine organisms and microorganisms.[84-87] Our earlier group research into the development of selective non-camptothecin TOP1-targeting agents also started with the plant alkaloids, namely protoberberines[88,89] and benzo[*c*]phenanthridine alkaloids[90,91,92]. Recently, ARC-111 has been identified as a potent and highly selective TOP1 inhibitor.[93] ARC-111 and its structurally-related derivatives are currently in clinical development. Indolocarbazoles[94,95] and indinoisoqiunolines[96] are among other non-camptothecin TOP1 targeting agents that have been identified.

1.4.1 Identification of MDD-carolyne

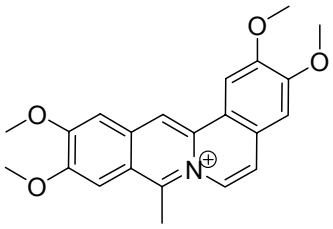
Our earlier research was encouraged by the antitumor activities of two families of natural products, protoberberine alkaloids and benzo[*c*]phenanthridine alkaloids. Natural protoberberine alkaloids, such as berberine and berberubine, have been found to exhibit weak anti-tumor activity.[88,89] With minor modifications on the protoberberine skeleton, a synthetic protoberberine alkaloid, coralyne, has demonstrated exceptional TOP1 targeting

activity and good cytotoxicity.[97,98] Benzo[*c*]phenanthridine alkaloids, such as nitidine and fagaronine, also possess potent antitumor activity. [90,91,92] The similarities between these two families prompted SAR studies on these natural products and their derivatives. Research within our group focused on designing molecules and examined the needed structural features to provide for selective TOP1-targeting activity while retaining cytotoxicity as an antitumor agent.

Protoberberine derivatives

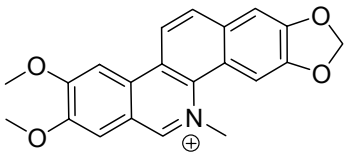


Berberine

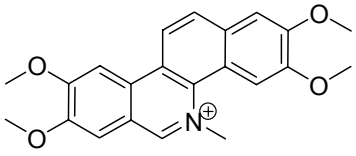


Coralyne

Benzo[c]phenanthridine derivatives



Nitidine



Fagaronine

Figure 10. Protoberberine alkaloids and benzo[*c*]phenanthridine alkaloids

The common structure of both families is a 3-phenylisoquinolinium core structure. Further SAR studies have shown the compound must be rigid to maintain good TOP1 targeting activity. Also, R_1 is located at a forbidden zone and prefers to be a hydrogen. R_4 can be removed without negative impact on activity. Methoxy or methylenedioxy groups

were identified as the most favorable substituents on the ring-A and ring-D (Figure 11).[99,101,102,103]

MDD-coralyne was developed by our group as a cytotoxic TOP1 targeting agent.[99,100] Although MDD-coralyne is much less active than CPT, it did serve as a good lead compound for the development of novel non-camptothecin TOP1 targeting agents (Figure 11).[104,105,106]

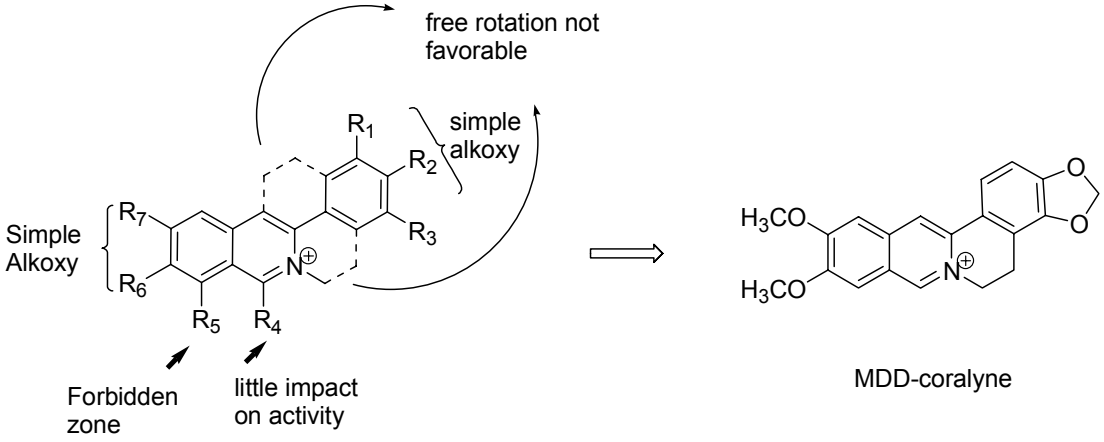


Figure 11. Identification of MDD-coralyne

1.4.2 Benzo[*i*]phenanthridines and Dibenzo[*c,h*]cinnolines

The permanent charge on MDD-coralyne and related compounds limit cell penetration and uptake. It also dramatically increases molecule polarity and makes synthetic development extremely difficult. To remove this iminium charge while maintaining the molecule's rigidity, we proposed a translocation of the nitrogen atom. This relocation of nitrogen afforded a structurally new scaffold. The biological data did confirm that the new compounds retained TOP1-targeting activity and cytotoxicity, and of course, possess improved solubility and synthetic accessibility (Figure 12).[100,107,113]

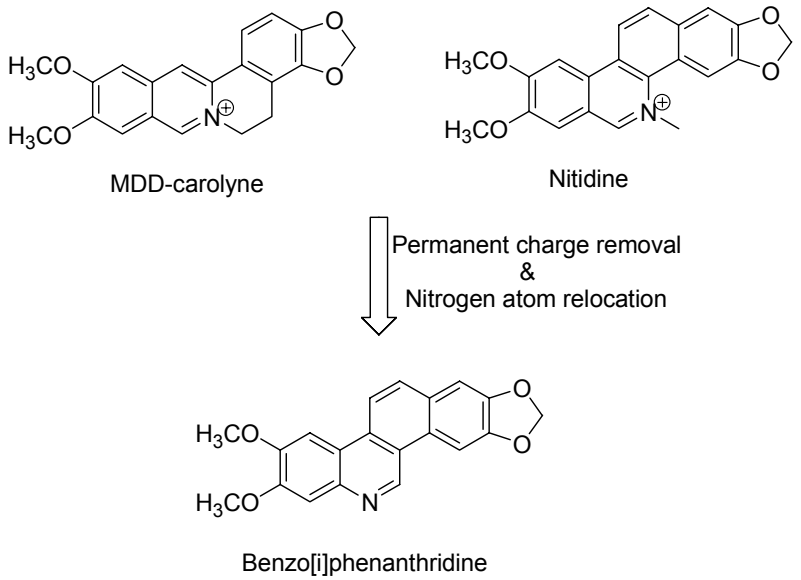


Figure 12. Removal of iminium charge and relocation of the nitrogen atom

An exchange of methylenedioxy and dimethoxy substituents yielded a compoumd with 10 fold increase in activity (Figure 13). However, replacement of the methylenedioxy groups with dimethoxyl substituents resulted in a complete loss of TOP1-targeting activity.[108,109] These data demonstrate that subtle changes on this pattern can lead to severe activity change.

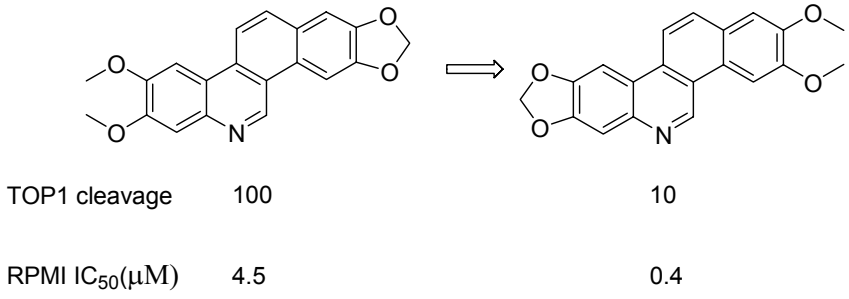


Figure 13. Functional group exchange afforded ten-fold activity increase

Discovery of cinnolines was another breakthrough in our research (Figure 14). A proposed heteroatom combination yields a class of novel potent TOP1 targeting agents, dibenzo[*c,h*]cinnolines.[110,111]

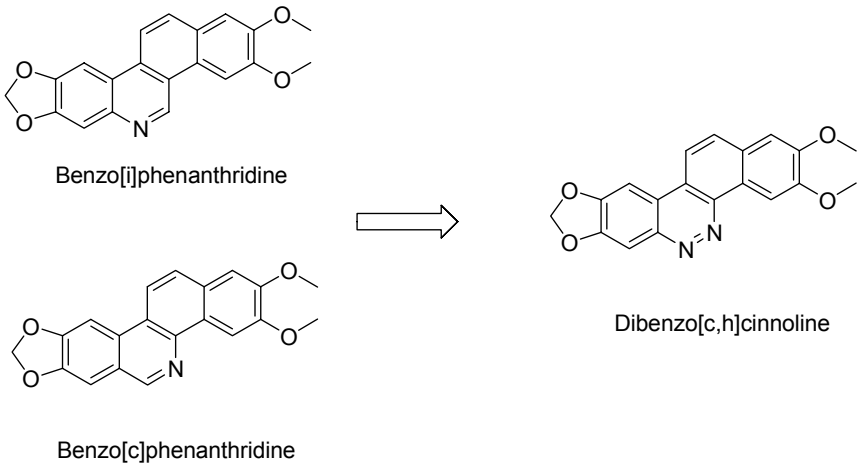


Figure 14. Combining heteroatom yields the dibenzo[*c,h*]cinnoline pharmacophore

1.4.3 Characterization of ARC-111 as a Novel TOP1 Targeting Anticancer Drug

The elevated activities of these lead compounds encouraged us to conduct further optimization. Our research focused on preparation of analogs with improved solubility while maintaining selective TOP1-targeting activity. SAR studies have shown the B-ring of lead compounds can tolerate more versatile functionalities (Figure 15). Therefore, a lactam group seemed to be a good moiety because of synthetic accessibility of the amide proton. Two novel classes of lactam derivatives were synthesized and evaluated.[112] The representatives of both classes have demonstrated excellent TOP1 targeting activity and nanomolar cytotoxicity, which are superior than their parent leads, even more potent than CPT-11 in DNA cleavage assays.[93,112,114,115]

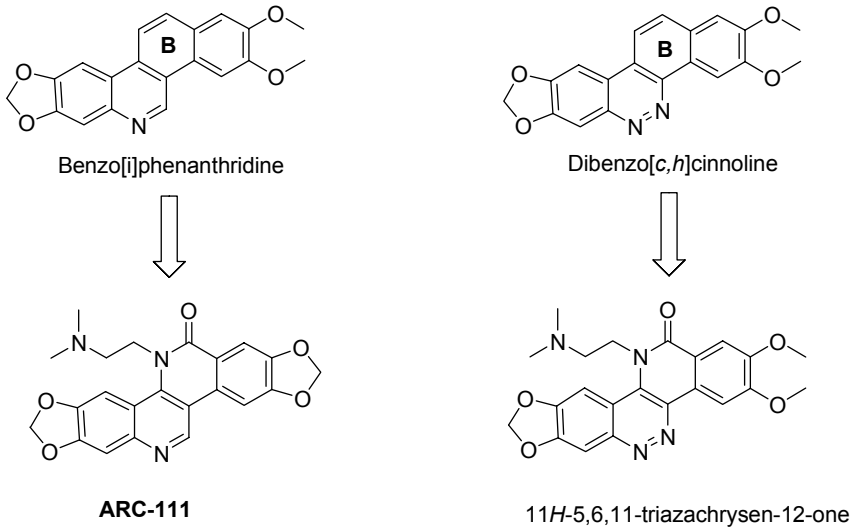


Figure 15. Design of more soluble TOP1 targeting agents

The *in vivo* activity of ARC-111 and its 12-aza analog have been evaluated. Tumor regression has been observed *in vivo* with human tumor xenografts in athymic nude mice. The cinnoline derivative has demonstrated good antitumor activity.[93,112] ARC-111, however, is more efficacious *in vivo* than its 12-aza analog. It has shown comparable tumor suppression as CPT-11 at only 5% of dose.[116] The weaker in vivo activity of cinnolines may be due to unusual rapid metabolic clearance of these diaza-containing compounds or an increased sensitivity of the lactam to hydrolysis relative to the lactam in ARC-111. The mechanistic and metabolic studies on these cinnolines are still under investigation.

The identification of ARC-111 (Topovale), 8,9-dimethoxy-5-(2-*N*,*N*-dimethyl-aminoethyl)-2,3-methylenedioxy-5H-dibenzo[*c,h*][1,6]naphthyridine-6-one, was a major leap forward in the development of non-camptothecin TOP1 targeting agents. ARC-111 has been characterized as a novel, and extraordinarily potent, TOP1 targeting anticancer drug.[93] It has shown extraordinary antitumor activities both *in vitro* and *in vivo*, and also

exhibited broad spectrum antitumor activities against a panel of solid tumors. ARC-111 has exhibited to be as active as irinotecan in the HCT-8 colon tumor model and even better activity than irinotecan and topotecan in SKNEP anaplastic Wilm's tumor model.[93,116]

The TOP1-targeting specificity of ARC-111 has also been proven by depletion of the TOP1 immunoreactive band, elevation of the small ubiquitin modifier-TOP1 conjugate and activation of TOP1 degradation. ARC-111 has also demonstrated similarly a TOP1 targeting mechanism to CPTs by exhibiting reduced cytotoxicity against TOP1-deficient P388/CPT45, TOP1 mutant CPT-K5 and u937/CR cells.[93,116]

A more recent study has shown that ARC-111 also inhibits accumulation of hypoxia-inducible factor-1α, an essential regulator of tumorigenesis. This unique mechanism of ARC-111 reinforces itself as a potent antitumor agent on hypoxic tumors.[117]

Moreover, ARC-111 has significant advantages over topotecan and irinotecan. Unlike these CPT-related clinical drugs, ARC-111 is neither a substrate for BCRP, nor a substrate for MDR1.[93] In addition, ARC-111 is chemically stable and its cytotoxicity is not affected by the presence of human serum album.[93]

In studies performed in athymic nude mice with human tumor xenografts, the effective dose of ARC-111 is only 2 mg/kg while the dose for CPT-11 is 50 mg/kg.[116] ARC-111 can be easily synthesized from commercially available starting materials within five steps in excellent yields.[112,116]

A docking study has proposed the binding mode for ARC-111 is similar to topotecan in crystal structure of topotecan/DNA/TOP1 (Figure 16).[118]

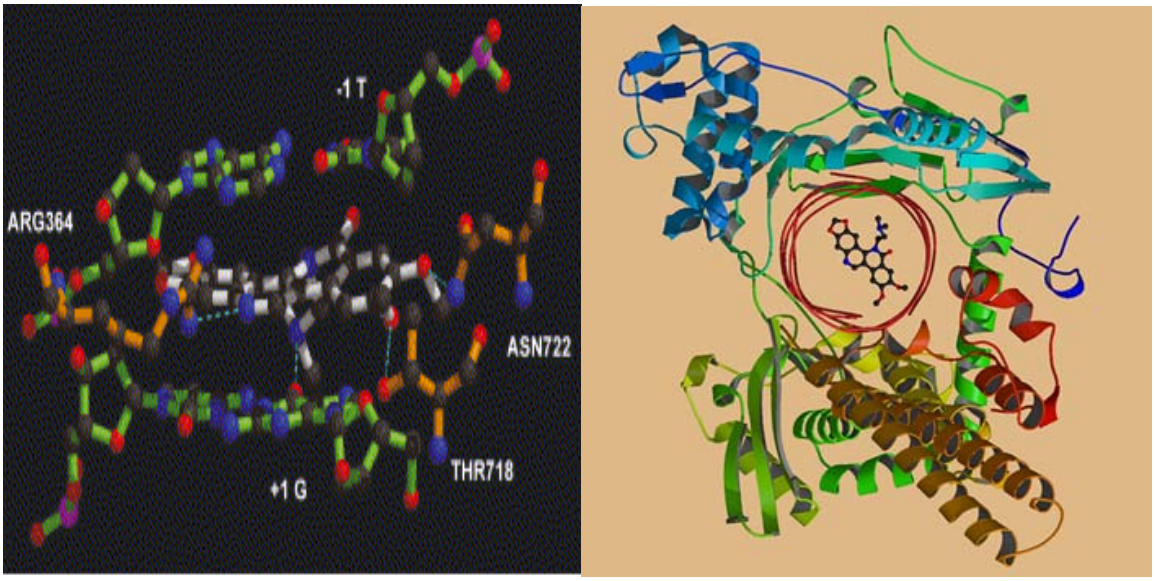
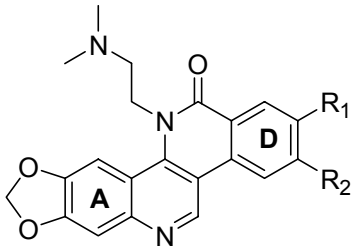


Figure 16. A presentation of ARC-111/DNA/TOP1 complex (graph on left adopted from Ref. 118; graph on right adopted from http://medchem.rutgers.edu/lavoie.shtml)

Inspired by the success of ARC-111 our group has conducted SAR studies on its substituents. Studies on nitro and amino substitution in the A-ring and D-ring have identified several equally active compounds as ARC-111. Generally, nitro-substituted compounds are more active than amino-substituted compounds. The most successful compounds are 8-nitro and 9-nitro derivatives, which exhibit comparable potency to ARC-111. Substitution of a nitro group on ring-A is less favorable than a methylenedioxy group, but better than the unsubstituted compound (Figure 17). [119,120]



R_1=NO_2 R_2=H
R_1=H R_2=NO_2

Figure 17. Potent nitro- substituted compounds

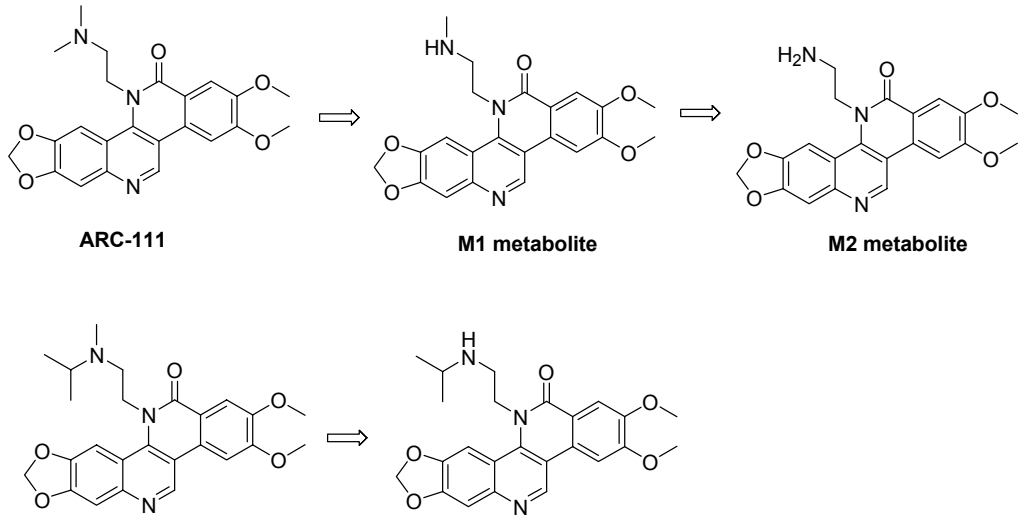


Figure 18. Metabolites of ARC-111 and related isopropyl derivative

Investigations on anticipated metabolites of ARC-111 have found that N-dealkylation metabolites M1 and M2 are substrates for MDR1 and BCRP. A series of ARC-111 derivatives have been designed and synthesized in order to retard *N*-dealkylation or provide novel metabolites, which are not substrates for MDR1 and BCRP. Isopropylmethyl-aminosubstituted compound was prepared as it could offer an advantage on the basis of anticipated metabolites. The bulkier isopropyl group could slow down the metabolism, and the M1 metabolite of this compound is not a substrate for either MDR1 or BCRP (Figure 18).[121]

More recently, ester and amide derivatives of benzo[*i*]phenathridine carboxylic acid were synthesized and evaluated (Figure 19).[122,124,125] While ester derivatives are less potent and not very specific on targeting TOP1, several amide derivatives have exhibited excellent cytotoxicity and potent TOP1 targeting activity.[122,124] However, all amides are

substrates for MDR1 and BCRP. [123] The "reversed lactam" analogs of ARC-111 were also prepared.[122,125] These compounds have demonstrated superior activities to ARC-111.[125] It is also important to note the reversed lactam derivatives are not substrates for MDR1 and BCRP.[122,125,126]

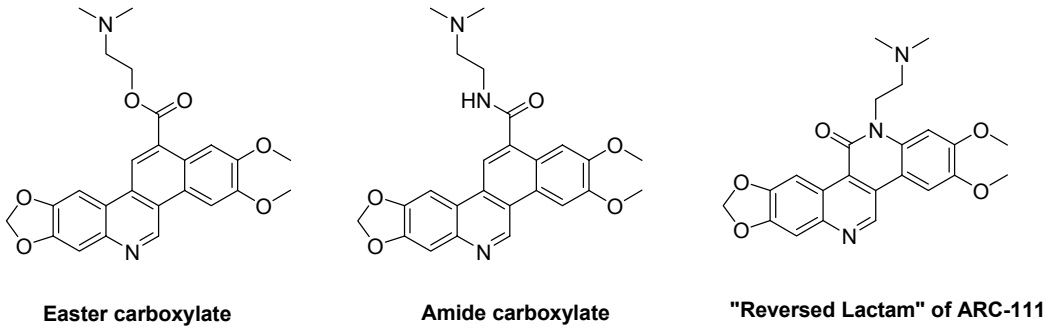
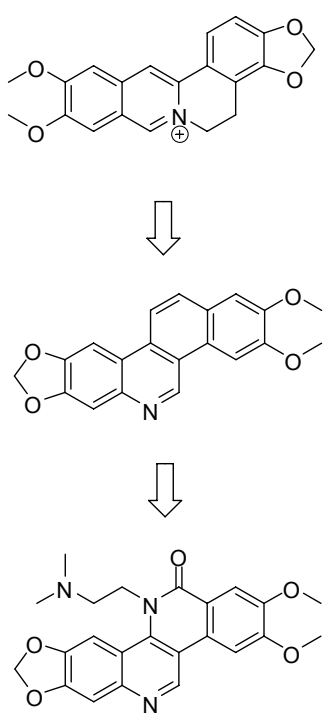


Figure 19. ARC-111 structurally related compounds

Starting from carolyne and nitidine, our research group has successfully developed several generations of TOP1 targeting agents, representing different research stages. MDD-carolyne has good TOP1-targeting activity but possesses an iminium functionality which is detrimental to cell penetration.[99,100,104] Benzo[*c*]phenanthridines demonstrated much improved cytotoxicity and TOP1 targeting activity than MDD-carolynes, but still lacked sufficient solubility properties that allowed these agents to be formulated for good distribution in vivo.[108,109] ARC-111, as the most successful lead compound so far, has comparable cytotoxicity to CPT and could be easily formulated for evaluation in *in vivo* bioassays (Figure 20). [93,123]



Name	Year	TOP1-mediated DNA cleavage	Cytotoxicity IC_{50} (μM)
MDD-Carolyne	1995	40	5.9
BZ-III-26	1997	1	0.4
ARC-111	2002	0.3	0.002

Figure 20. A historical review of lead compounds developed in our research group

1.5 Rationale

The success of ARC-111 encourages us to further investigate the compatibility of the substituents on ring B of benzo[*i*]phenanthridines. As our previous studies on TOP1 inhibitors have shown, a subtle modification may dramatically change the profile of the compounds activity. Although ARC-111 and its derivatives are suitable enough to enter clinical development, we may still optimize our lead compound to achieve even better cytotoxicity and TOP1 targeting activity. Considering the complexity and unpredictability of clinical trials, it is also necessary to develop back-up candidates which have different pharmacokinetic characteristics (Figure 21). In this research project, we focused on achieving the following goals:

1. Modify the side chain of ARC-111, specifically on the amino group, in order to identity other suitable functionalities on the ARC-111 side chain to obtain better anti-tumor activities both *in vitro* and *in vivo*.
2. Develop an efficient synthetic scheme synthesizing various side chains on ARC-111, focusing on side chain compatibility on the TOP1/drug/DNA ternary complex.
3. Investigate the synthetic route to make versatile 11- and 12-position benzo[*i*]phenanthridines.

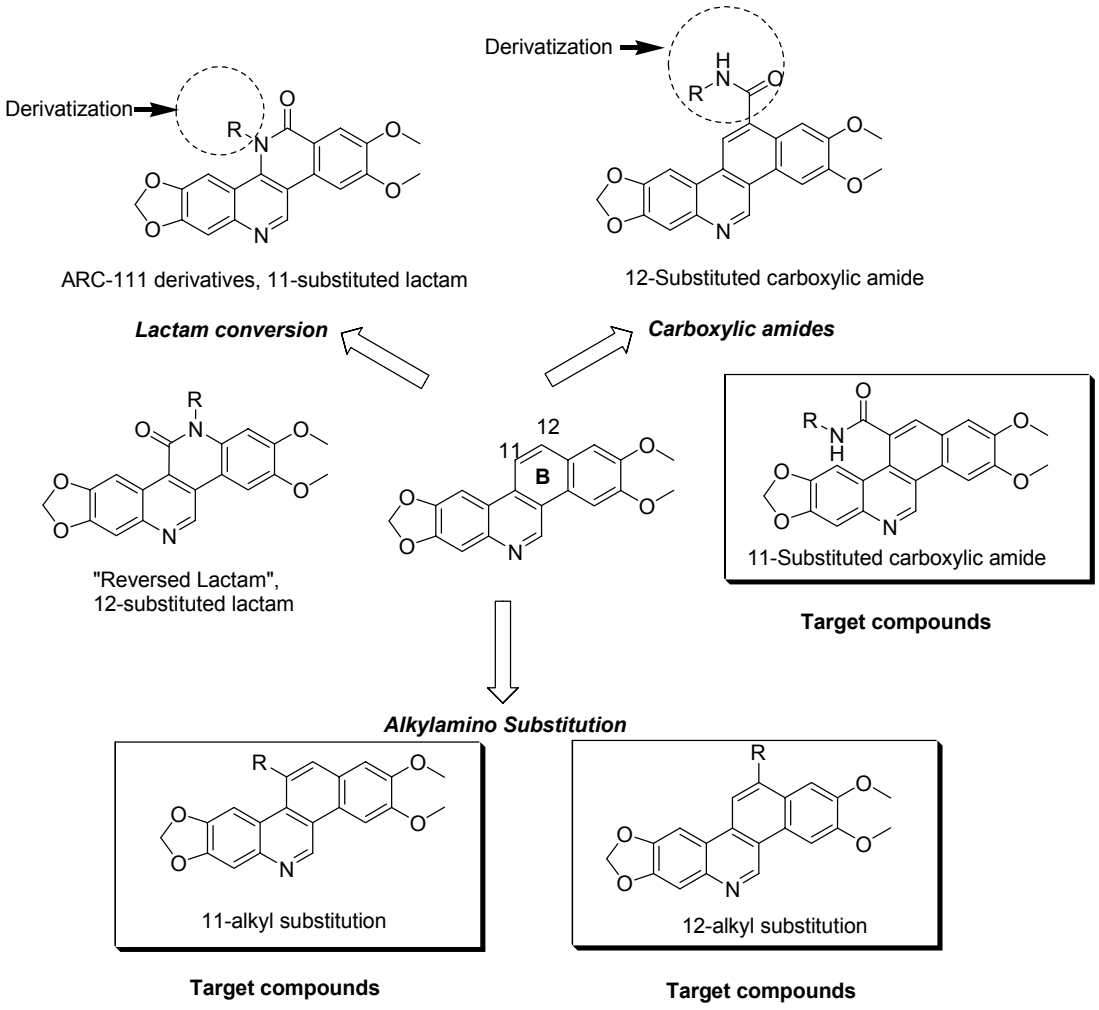
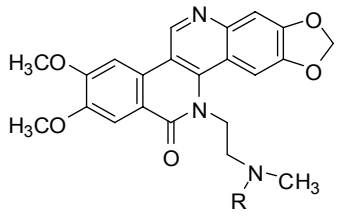


Figure 21. Target Compounds Focused on B-ring modifications

RESULTS AND DISCUSSION

2.1 Design and Synthesis of Amino Group Modified 5-(2-Aminoethyl)dibenzo [*c*,*h*][1,6]naphthyridin-6-ones

5*H*-8,9-dimethoxy-5-(2-N,N-dimethylaminoethyl)-2,3-methylenedioxydibenzo[*c*, *h*][1,6]-naphthyridin-6-one (ARC-111), **1** (Figure 21) has been identified as a lead compound for clinical development by our group.[93,116] Analogs of ARC-111 with various alkyl amino groups, i. e. 5-[2-(N,N-dialkylaminoethyl)] substituents, have also exhibited potent activity.[121] Compounds **2** and **3** (Figure 22) are among the tertiary alkylamine analogs that exhibited similar TOP1-targeting activity and cytotoxic activity to **1** (IC_{50} values ranging from 2-6 nM in RPMI8402 cells).



1, R = CH_3, **ARC-111**
2, R = CH_2CH_3
3, R = $CH(CH_3)_2$

Figure 22. ARC-111 and related alkylamino derivatives

The success of simple modifications encouraged further exploration of the dimethylamino group of ARC-111.The effect on biological activity of the addition of a trifluoromethyl, cyano, or ethynyl substituent on the *N*-methyl group of compounds related to ARC-111 was of interest at the beginning stage of our research.

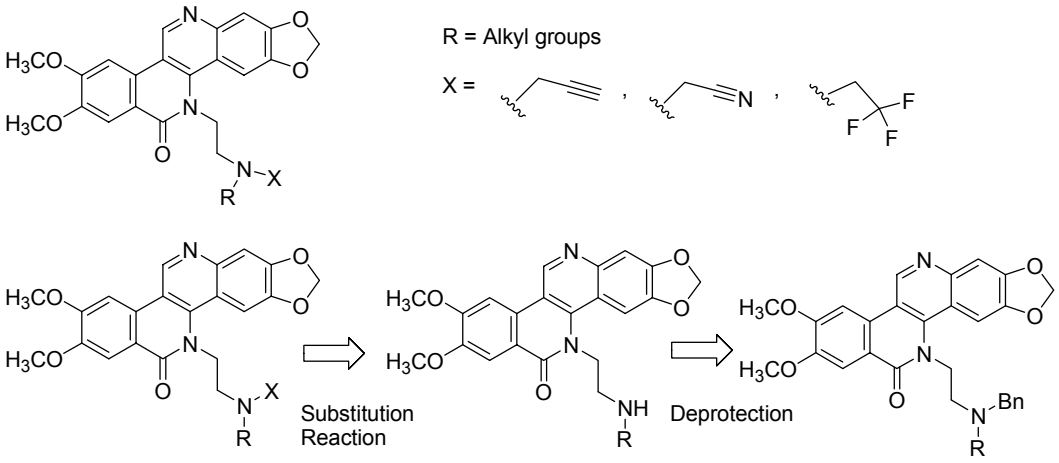
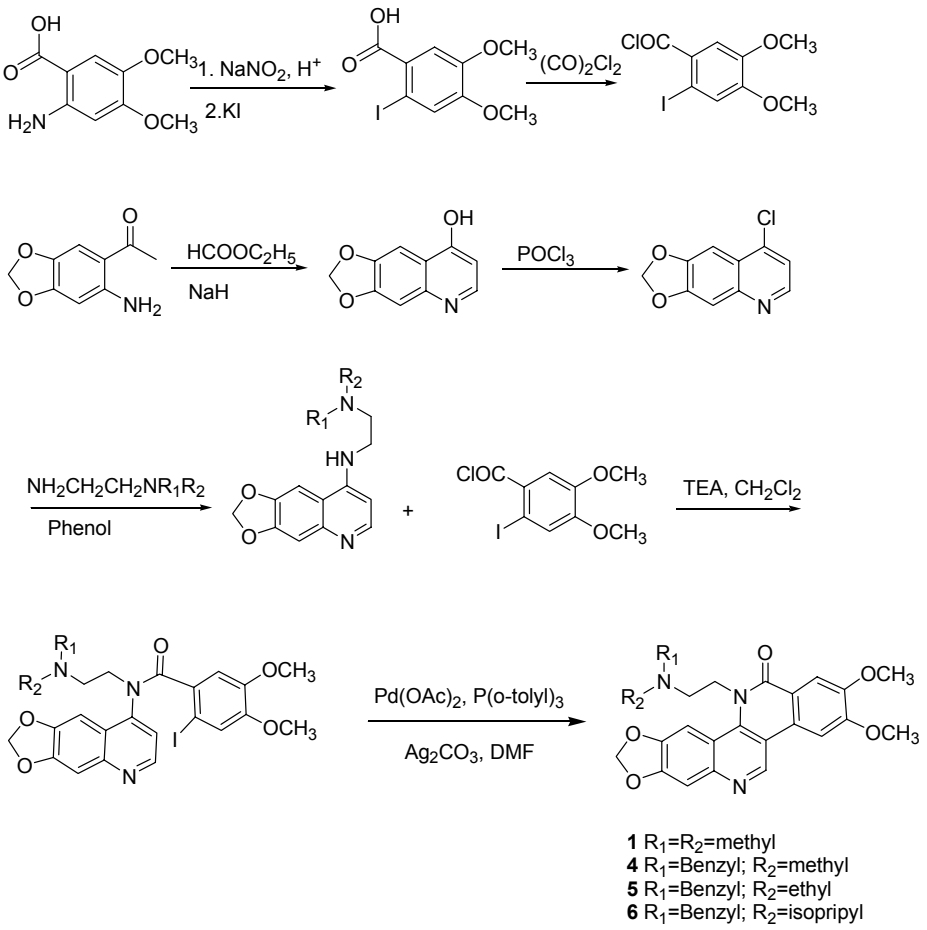


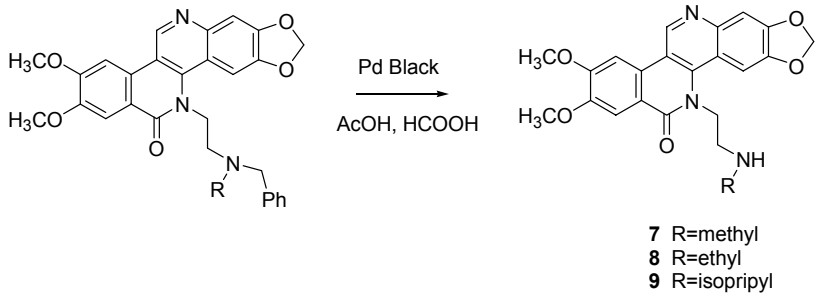
Figure 23. Retro synthetic analysis for argeting compounds of amino group modifications

The target molecules could be synthesized from the secondary amine by varied nucleophilic substitution reaction. The secondary amines can be prepared by deprotecting the corresponding benzyl amines, which have been synthesized previously by our group utilizing the synthetic scheme for ARC-111.[121] Scheme 1 shows the synthesis of ARC-111, which is very straightforward and high-yielding.[116] By treating the *o*-aminoacetophenone with sodium hydride in ethyl formate, 4-hydroxyquinoline was obtained in excellent yield. The chloroquinoline was then prepared by refluxing 4-hydroxyquinoline in phosphorus oxychloride. 4-chloroquinoline was subjected to a S_NAR nucleophilic displacement to form the corresponding 4-aminoquinolines. These intermediates, upon reaction with 2-iodo-4,5-dimethoxybenzoyl chloride, yielded *o*-iodobenzamides. The Heck reaction was employed for the cyclyzation of the *o*-iodobenzamides to provide the benzo[*c*,*h*][1,6]-naphthyridin-6-ones in refluxing DMF. Compounds **4**, **5**, and **6** were synthesized before in good yields.[121,126]



Scheme 1. Synthetic scheme of ARC-111 and related derivatives

Debenzylation reactions of compounds **4-6** were carried out in acetic acid using palladium black with formic acid acting as a hydrogen source (Scheme 2).[121] Other reduction conditions were found to be less effective.



Scheme 2. Reduction of benzyl protected amines to provide secondary amines

To prepare the trifluoromethyl substituted derivative, 1,1,1-trifluoro-2-iodo-ethane[127] was reacted with **7**. The desired compound was isolated after stirring 3 days in a very low yield (< 10%). Heating did not improve the yield. The electrophile, 1,1,1-trifluoro-2-iodo-ethane may not be active enough to be attacked by the secondary amine. Another attempt using TFA and $NaBH_4$[128] afforded a complex mixture without any product detected. Under such acidic conditions, $NaBH_4$ appeared to reduce the heterocyclic pharmacophore. Finally, compound **7** was treated with trifluoromethanesulfonic acid 2,2,2-trifluoroethyl ester and diisopropylethylamine (DIEA)[129] to afford **10** in good yield (Figure 24). DMF was found to be a better solvent than acetonitrile. Surprisingly, when potassium carbonate was used as a base, more by-products were observed, which were inseparable, tending to elute from column chromatography together with the desired product.

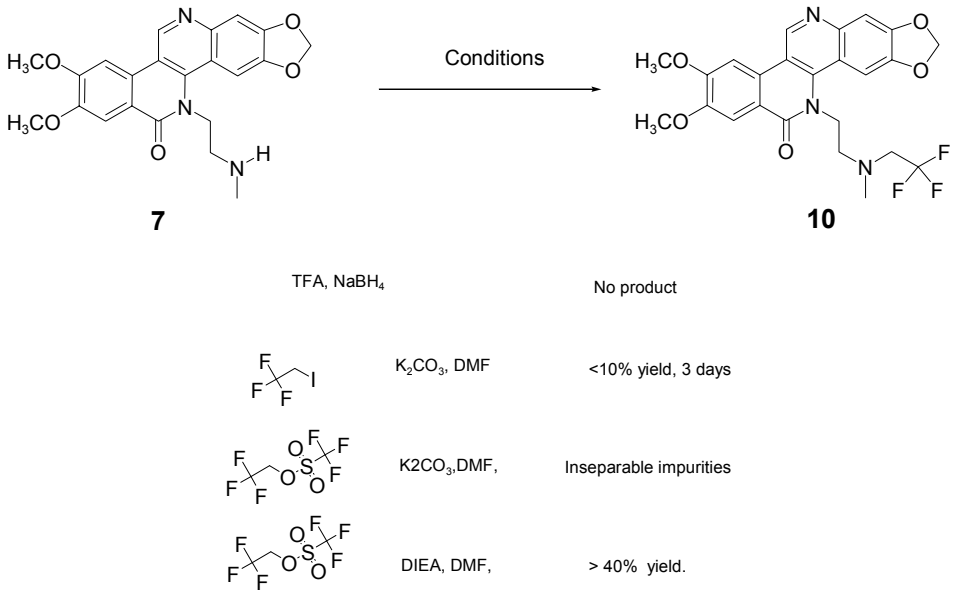
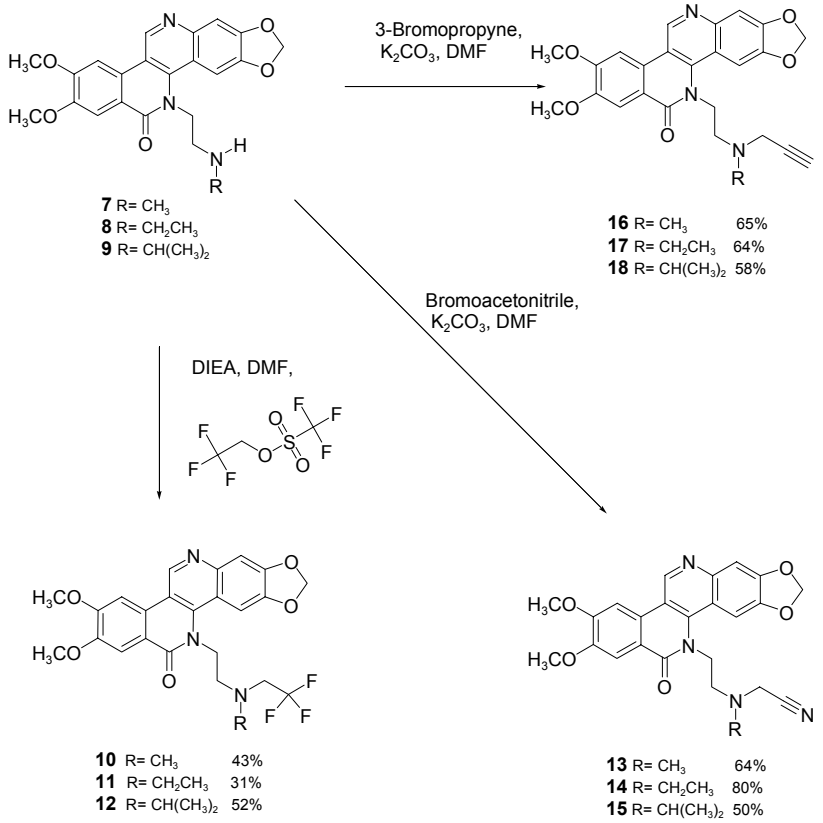


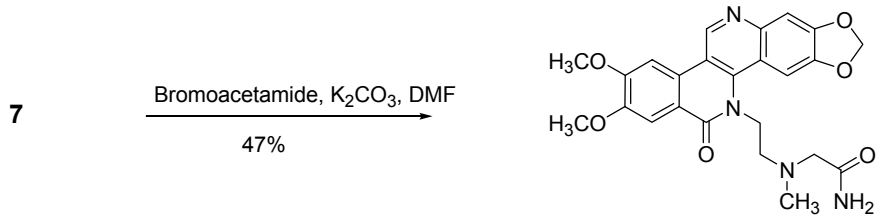
Figure 24. Attempts on synthesis of trifluoromethyl substituted compound

Similarly, alkylation of **8** and **9** using trifluoromethanesulfonic acid 2,2,2-trifluoroethyl ester worked smoothly to provide **11** and **12**. Substitution of **7**, **8** and **9** using bromoacetonitrile and potassium carbonate[130] provided compounds **13**, **14** and **15,** respectively (Scheme 3). Conversion of **7**, **8** and **9** to compounds **16**, **17** and **18** were carried out in DMF at 80 ºC using 3-bromopropyne and anhydrous potassium carbonate[131] (Scheme 3). Generally, all reactions were carried out in DMF smoothly to provide desired products in good yields. When acetonitrile or chloroform was used as a solvent, reactions were sluggish even under reflux and prolonged reaction time due to poor solubility of the starting amines. A summary of reaction schemes is shown in Scheme 3.



Scheme 3. Preparation of amino group modified compounds **10-18.**

These studies were extended to examine the effect of an aminocarbonyl substituent on the N-methyl substituent of ARC-111. Compound **19** was synthesized from **7** by reaction with bromoacetamide and potassium carbonate[132]. The reaction scheme is outlined in Scheme 4. Compound **19**, together with **13-15** were synthesized by Dr. M. Satyanarayana in our group.[133]



19

Scheme 4. Preparation of **19** from **7**

The relative TOP1-targeting activities and cytotoxicities of the various *N*-substituted 5-[2-(*N*-alkylamino)ethyl]dibenzo[*c*,*h*][1,6]naphthyridines are listed in Table 1. The TOP1-targeting activity of compounds can be indicated by TOP1-cleavage data.[112,113] Topoisomerase I mediated cleavage values are reported as REC, relative effective concentration, i.e., concentration relative to topotecan whose value is arbitrarily assumed as 1, that are able to produce the same cleavage on the plasmid DNA in the presence of human topoisomerase I.[134-136] The *N*-(2,2,2-trifluoroethyl) derivatives, **10-12**, did not exhibit appreciable TOP1-targeting activity. The basis for this loss in activity cannot be explained on the basis of steric factors in light of the potent TOP1-targeting activity observed for **1-3.** In contrast to these data, the cyano derivatives, **13-15**, were highly active TOP1-targeting agents with similar potency to ARC-111 and camptothecin. These three compounds have demonstrated more than 5 fold potency on DNA cleavage than the clinic drug topotecan. The N-methyl-N-propargyl derivative, **16**, and the

N-methyl-N-acetamide derivative, **19,** also retained potent TOP1-targeting activity relative to that observed for **1-3**. The N-ethyl-N-propargyl derivatrive, **17**, and the N-isopropyl-N-propargyl derivative, **18,** were much less active as TOP1-targeting agents.

Table 1. Biological activity of amino group modified ARC-111 derivatives

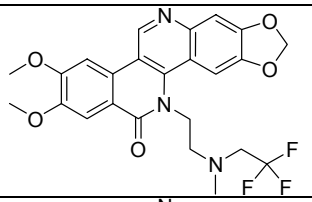
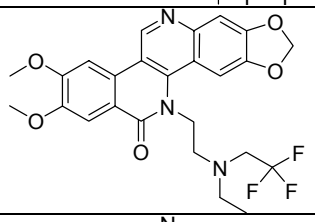
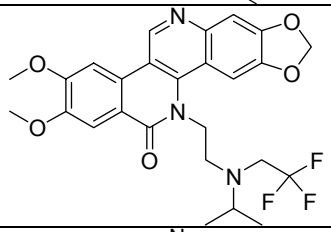
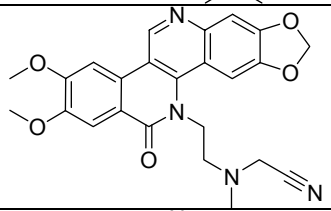
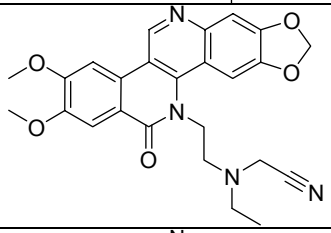
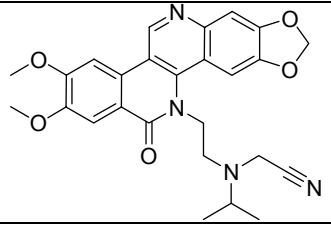
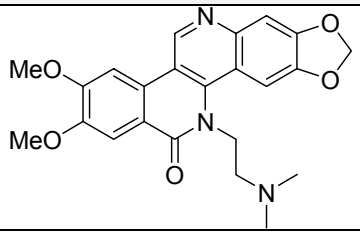
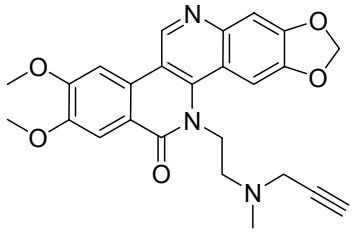
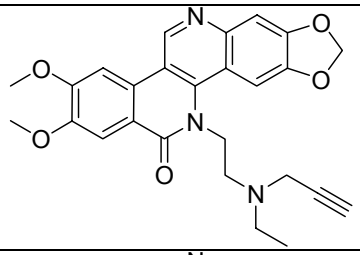
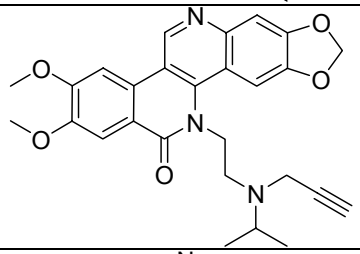
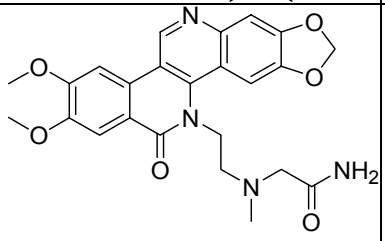
	Structure	TOP1-mediated cleavage	Cytotoxicity IC_{50} (μM)			
			RPMI8402	CPT-K5	P388	P388/CPT45
1	**ARC-111**	0.3	0.002	0.90	0.001	0.23
10		>10	0.25	>10	0.25	>10
11		>10	0.7	>10	0.61	>10
12		>10	1.9	>10	1.1	>10
13		< 0.2	0.004	0.98	0.003	0.22
14		< 0.2	0.001	0.67	0.001	0.13
15		< 0.2	0.002	1.3	0.002	0.06

Table 1. Biological activity of amino group modified ARC-111 derivatives (continued).

	Structure	TOP1-mediated cleavage	Cytotoxicity IC_{50} (μM)			
			RPMI 8402	CPT-K5	P388	P388/ CPT45
1		0.3	0.002	0.90	0.001	0.23
16		0.1	0.008	4.5	0.02	0.4
17		>10	0.017	>10	0.035	2.3
18		>10	0.065	>10	0.08	3.7
19		0.3	0.003	3.5	0.009	0.39

Cytotoxicity of compounds was tested against four different cancer cells and determined using the MTT-microtiter plate tetrazolinium cytotoxicity assay.[137-141] CPT-K5 is a variant of RPMI8402 that possess a mutant form of TOP1 that is camptothecin resistant.[142] CPT45 is a variant of P388 that has limited expression of TOP1 that is also camptothecin resistant.[143]

Those derivatives with potent TOP1-targeting activity also exhibited more pronounced cytotoxicity. The cytotoxicity of compounds **13-15** did not vary dramatically from one another having IC_{50} values that ranged from 3 to 7 nM and 2 to 4 nM in RPMI8402 and P388, respectively. Compound **16** was less cytotoxic with IC_{50} values that ranged 2 to 20 fold higher than **13-15** in these cell lines. Compounds **17** and **18** had similar cytotoxicity in RPMI8402 to each other, but were 2 to 6 fold less cytotoxic than **16.** The aminocarbonyl derivative, **169**, exhibited similar cytotoxicity to **13-15**.

The variant of RPMI8402 cells, CPT-K5 cell line, and variant of P388, P388/CPT-45 have been used to investigate the role of TOP1 in the mechanism of cytotoxicity of suspect TOP1-targeting agents. Resistance to CPT-K5 cells, which possesses a mutant form of TOP1 as well as expresses the efflux transporter BCRP, and to P388/CPT45, which has minimal expression of TOP1, is consistent with TOP1-targeting as the primary mechanism associated with cytotoxic activity. These results suggest that TOP1-targeting is associated with cytotoxicity, even in the case of those derivatives with comparatively weak TOP1-targeting activity. The *in vitro* data confirmed that compounds **13-15**, **16**, and **19** are novel potent TOP1-targeting agents.

Multiple drug resistance is a major disadvantage for many anticancer drugs including topotecan and irinotecan. Experiments were designed to investigate whether the

compounds we have synthesized are substrates for MDR1 and BCRP. Data are provided in Table 2 on the relative cytotoxicity in the parent cell line, KB3-1, KBV-1, a variant that overespresses the efflux transporter MDR1[144,145], and KBH5.0, a variant that overexpresses BCRP[93]. Differences in relative cytotoxicity between these variant cell lines and the parent cell line, KB3-1, may be indicative of a compound that is a substrate for an efflux transporter. In light of their 7-fold difference in IC_{50} values, these data suggest that **13-15** and **19** are substrates for MDR1. While not among the more potent cytotoxic agents, **16** does not appear to be a substrate for either MDR1 or BCRP. It is of interest to note that of the compounds evaluated only **19** appears to be a substrate for BCRP.

Table 2. Test data for determination of efflux transporter substrates

Compd	KB3-1	KBV-1	KBH5.0
1	0.005	0.005	0.006
10	0.41	1.0	0.63
11	0.65	2.9	0.75
12	1.0	4.4	1.1
13	0.005	0.043	0.027
14	0.004	0.034	0.007
15	0.006	0.043	0.009
16	0.02	0.07	0.034
17	0.07	0.1	0.11
18	0.10	0.43	0.07
19	0.01	0.38	0.32
Topotecan	0.04	0.44	0.44

Compounds **11** and **13-19** were evaluated for antitumor activity *in vivo* in athymic nude mice with MDA-MB-435 human tumor xenografts.[146] The results of this bioassay are outlined in Table 3. Tumor regression curves of some compounds are illustrated in Figures 25, 26 and 27.

Table 3. *In vivo* test of amino group modified ARC-111 derivatives

Compd. Code	Route	Average tumor volume (mm^3) Day 7	Day 14	Day 21	Day 28	Day 35	Day 42	Day 49	Total dose (mg/kg)/mouse
11	I.P.[a]	127	176	268	310	435	543	718	111 mg/kg
13	I.P.[a]	149	222	370	392	528	669	919	111 mg/kg
14	I.P.[a]	100	156	178	202	293	361	435	117 mg/kg
15	I.P.[b]	142	175	213	220	250	286	314	168 mg/kg
16	I.P.[c]	144	167	218	284	317	358	433	223 mg/kg
17	I.P.[a]	115	106	170	204	331	349	488	117 mg/kg
18	I.P.[a]	99	112	165	170	234	310	357	117 mg/kg
19	I.P.[d]	147	178	230	319	344	434	527	301 mg/kg
Vehicle	I.P.[e]	126	181	332	408	573	747	966	
1	I.P.[f]	120	123	145	158	175	189	242	37.5 mg/kg

[a]Initial dose was 2.0 mg/kg qd x 5/week for 2 weeks and was gradually increased to 6.0 mg/kg x 5/ week; [b]Initial dose was 5.0 mg/kg qd x 5/week and was increased to 6.0 mg/kg qd x 5/week for 2 weeks, then adjusted to 6.0 mg/kg qd x 3/week for one week. This dose was then again modified to the initial dose of 5.0 mg/kg qd x 5/week.; [c]Initial dose was 5.0 mg/kg qd x 5/week for 1 week and was gradually increased to 7.0 mg/kg x 5/week.;[d] Initial dose was 5.0 mg/kg qd x 5/week for one and a half weeks and was increased to 6.0 mg/kg qd x 5/week for two and a half weeks. Administration was increased to 14.0 mg/kg qd x 5/week for one and a half weeks then adjusted back to 10.0 mg/kg qd x 5/week for 1 week and finally adjusted to 12.0 mg/kg qd x 5/week.[e]Vehicle consisted of 0.1% citrate in H_2O and was administered qd x 5/week. [f]Initial dose was 1.5 mg/kg, which was administered qd x 3/5 days.

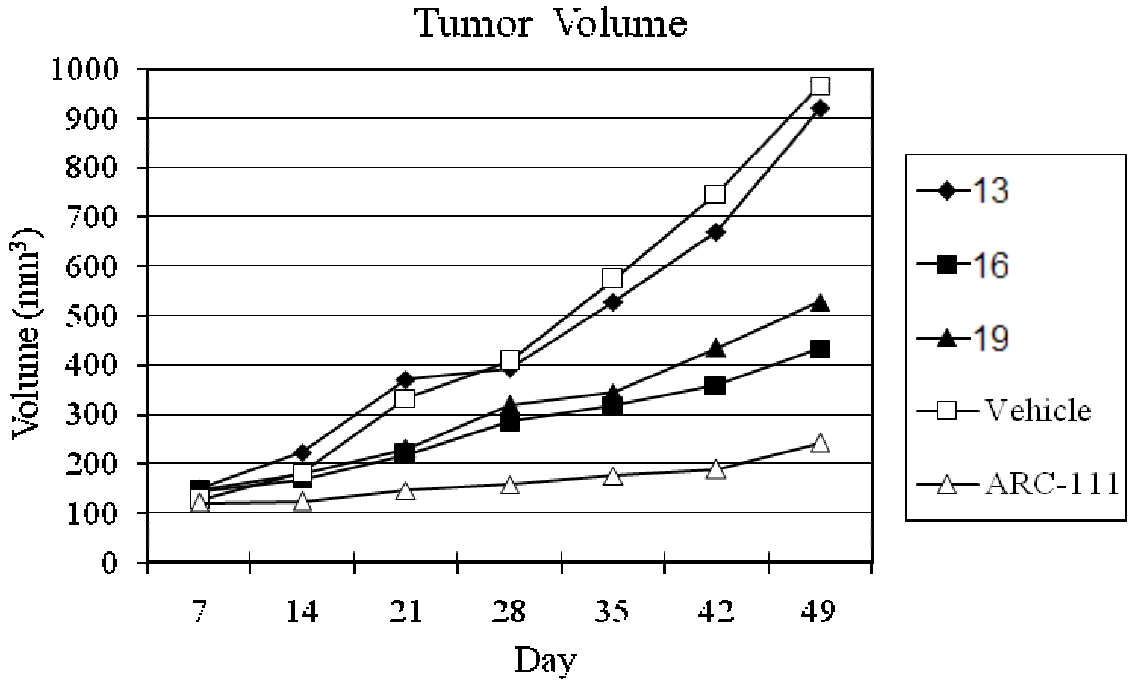


Figure 25. Compounds **13**, **16**, **19**, Vehicle and ARC-111

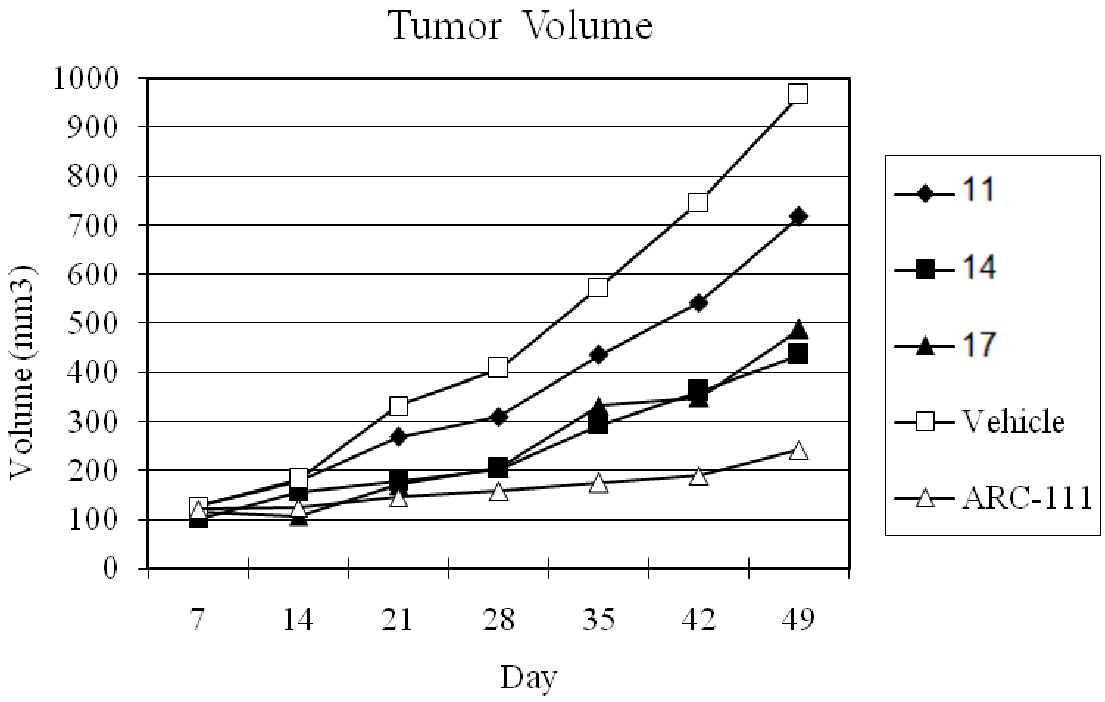


Figure 26. Compounds **11**, **14**, **17,** Vehicle and ARC-111

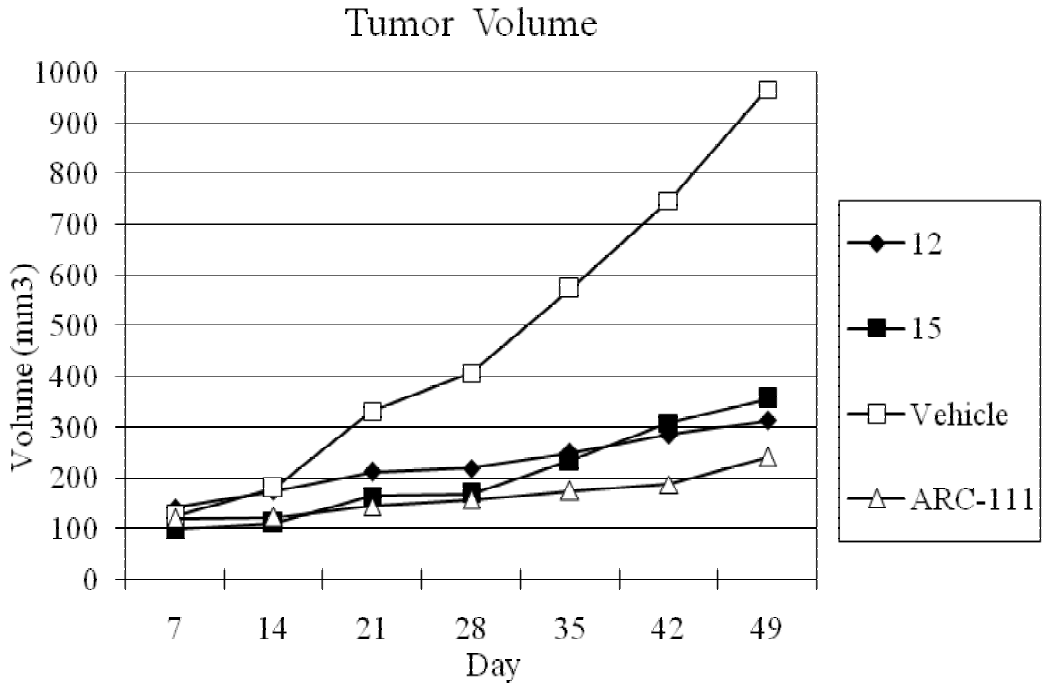


Figure 27. Compounds **15**, **18**, Vehicle and ARC-111.

Figure 25 clearly illustrates that the *N*-methyl-*N*-cyanomethyl analog **13** is less active than the N-methyl-N-propargyl **16** or *N*-methyl-*N*-acetamide **19** at their maximally-tolerated doses. The *N*-methyl-*N*-2,2,2-trifluoroethyl analog **11** was also less efficacious than the *N*-ethyl-*N*-cyanomethyl analog **14** and the *N*-ethyl-*N*-propargyl derivative **17**. Both **14** and **17** were less potent and effective than ARC-111 in this bioassay. The *N*-isopropyl-*N*-cyanomethyl and the *N*-isopropyl-*N*-propargyl derivatives, **15** and **18** respectively, had similar antitumor activity. Both of these derivatives, however, appear from these preliminary *in vivo* studies to be less potent and less efficacious than ARC-111.

These comparative studies did not result in the identification of an analog of ARC-111 with comparable *in vivo* potency and efficacy. The presence of electron-withdrawing substituents on the N-methyl substitunets of these various analogs of compounds **1-3** negatively affected the relative ease with which they could be formulated for injection. The decreased basicity of these derivatives lessened the solubility of their citrate salts and may have also impacted their absorption and distribution. Further studies are planned to assess the influence of more polar substituents on the amino group of the 5-(2-aminoethyl) substituent of ARC-111 and realted compounds.

2.2 Facile Synthesis of Side Chain Derivatives of Dibenzo[*c*,*h*][1,6]naphthyridin-6-ones with Varied Polar substituents

The excellent biological activities ARC-111 has demonstrated are partially attributed to its good solubility. The citrate salt of ARC-111 is soluble in water and can be easily administered *in vivo.*[93] We propose other hydrophilic groups, such as hydroxyl, polyamino, or some heterocyclic groups, can also be utilized as solublizing groups to

achieve good activities. Interestingly, many publications have also reported similar modifications on CPT.[147-151] Improved pharmacologic properties have been reported for camptothecin derivatives, which have incorporated within their structure polyhydroxylated alkylamino substituents.[150] Of special note was the 7-tri(hydroxymethyl)aminomethyl analog of 10,11-methylenedioxycamptothecin (Figure 28). Recent studies on the synthesis and cytotoxicity of polyamine analogs of camptothecin have also identified potent TOP1 targeting agents.[151] These data prompted our efforts to develop a convenient synthetic approach for preparing derivatives of ARC-111 that would incorporate such functionalities.

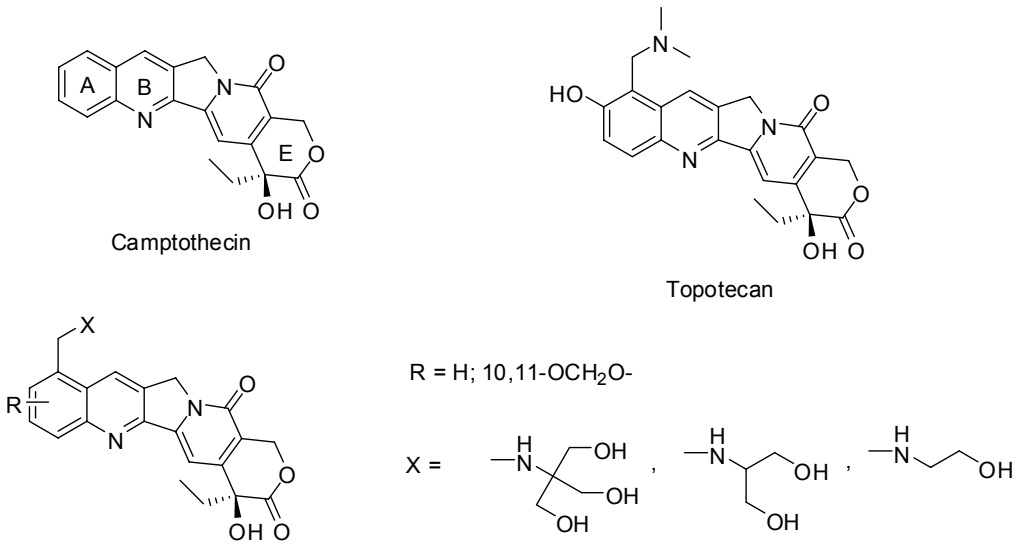


Figure 28. Camptothecin and related hydrophilic derivatives

To prepare these compounds, we could adapt the original ARC-111 approach, installing these groups early in the synthesis. Because some steps of the scheme require high temperature and acidic conditions, protecting groups will be needed (Figure 29). Another synthetic method is to prepare a common intermediate, which bears a leaving group at the end of the side chain (Figure 29).

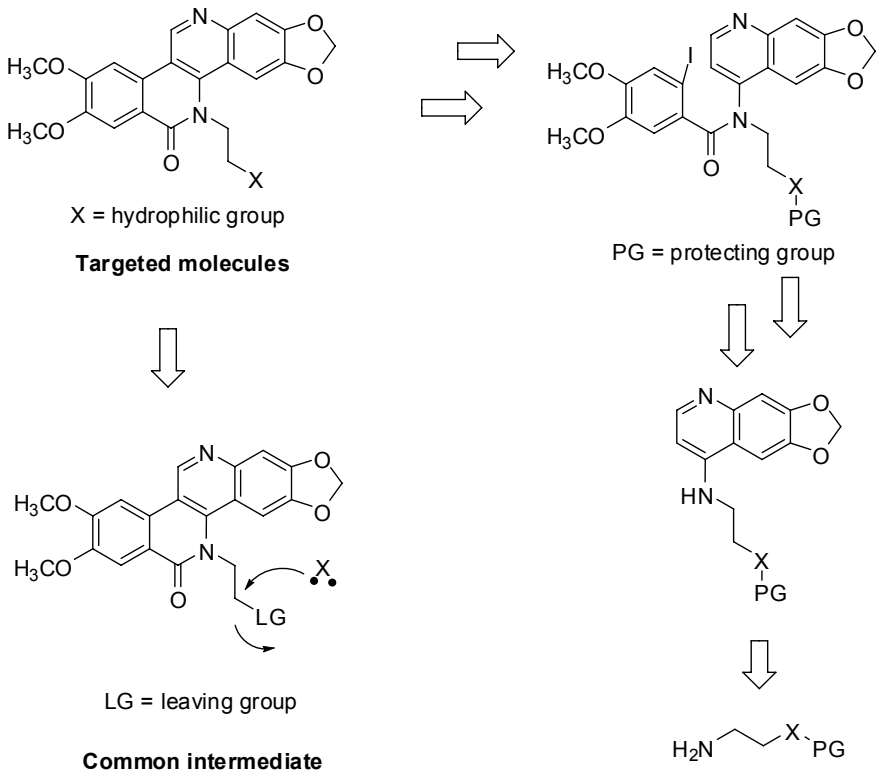


Figure 29. Retrosynthetic analysis of hydrophilic derivatives of ARC-111

To make a common intermediate with a good leaving group, we tried to synthesize a hydroxyl derivative of ARC-111, **20**. However, conversion of the hydroxyl group to other leaving groups was much harder than we expected. Reaction of the hydroxyl compound **20** with TsCl, MsCl or Tf_2O gave a complex mixture. Addition of Tris to the activated hydroxyl group utilizing Mitsunobu conditions[152,153] also failed to give the desired compound. There was no desired brominated compound detected under bromination conditions using PBr_3. The reactions attempted were listed in Figure 30. These studies were carried out by Dr. M. Satyanarayana in our group.[133]

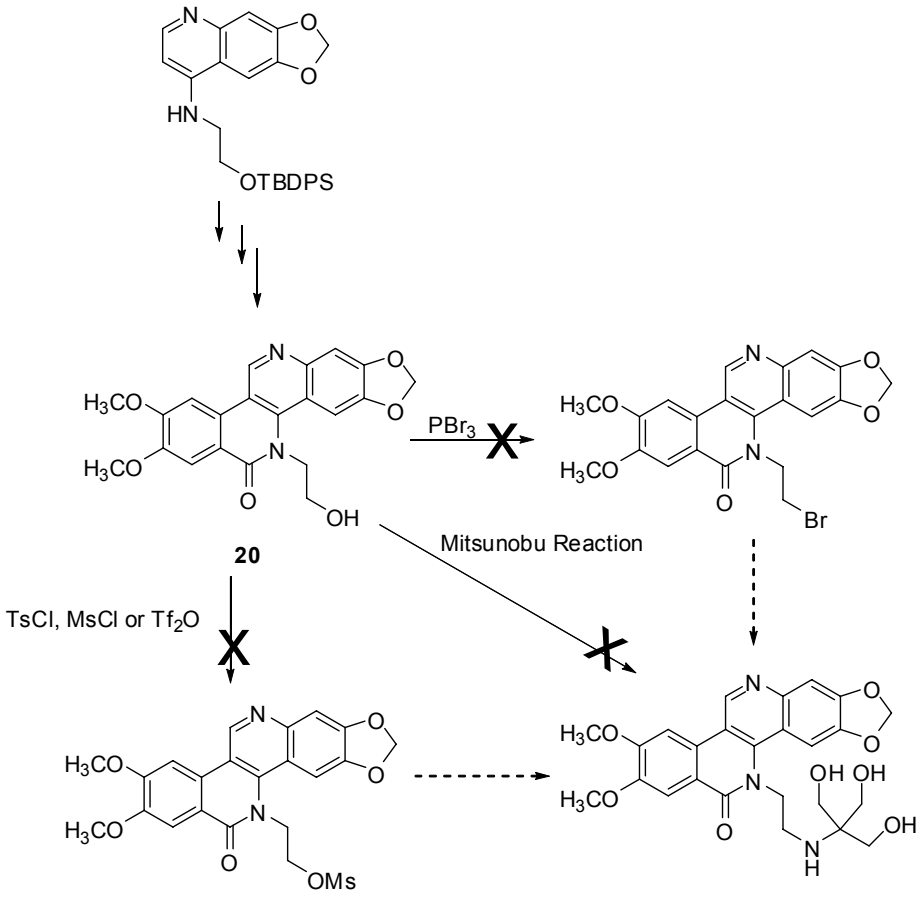


Figure 30. Attempts on hydroxyl derivative of ARC-111

The disappointing results we obtained early from hydroxyl compound **20** prompted us to examine different approaches. In the case of the imidazole derivative, the required side chain was synthesized in two steps. Reaction of amino compound **21** with 4-chloroquinoline afforded 4-aminoquinoline, compound **22,** in moderate yield. The 4-aminoquinoline compound **22**, however, had very poor solubility in most organic solvents. Acylation of 4-aminoquinoline in DMF was very sluggish even after more than 5 equivalents of acyl chloride was added. Most starting 4-aminoquinoline was recovered eventually (Figure 31). Considering this synthetic scheme is lengthy and low yielding, we decided to look for other more efficient and convenient approaches.

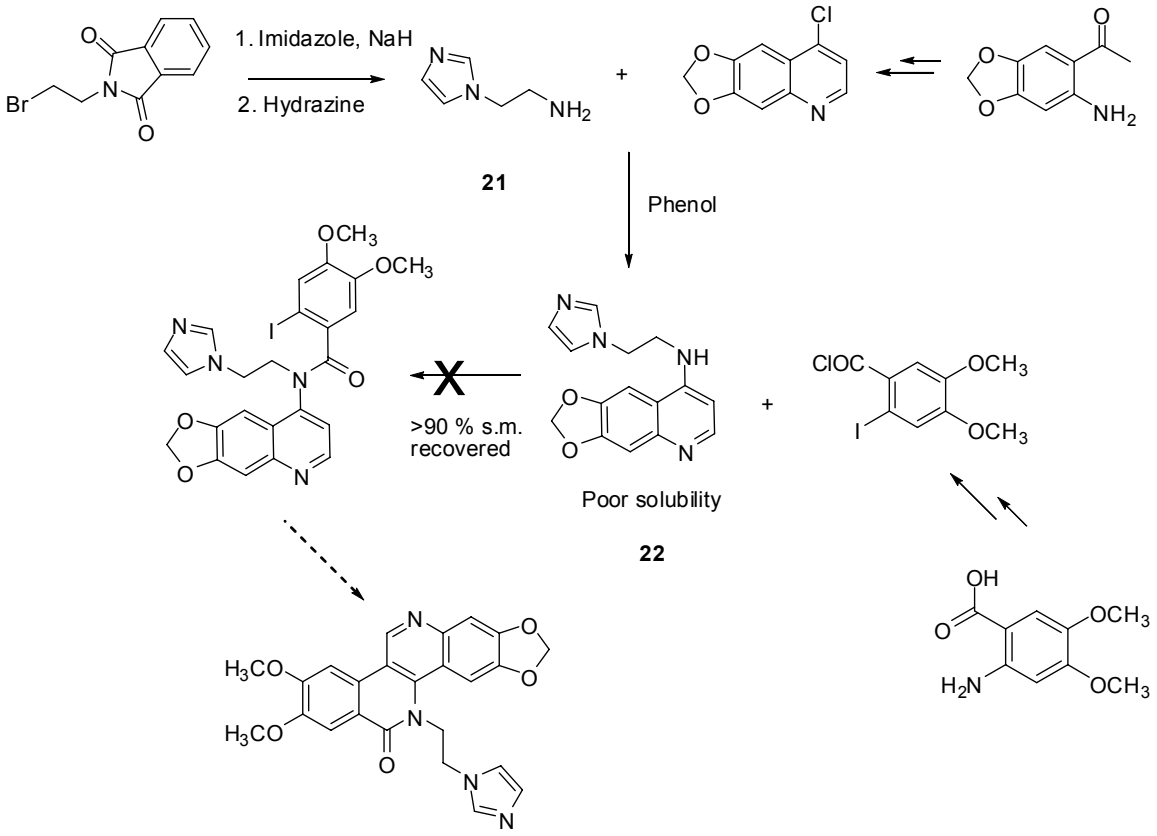


Figure 31. Tedious and low yielding synthetic approach adapting from ARC-111 synthesis

There were several reported cases using *N,N,N*-trimethylammonium group as a leaving group.[154,155] In comparison with other common leaving groups, such as TsO-, MsO-, or TfO etc., *N, N ,N*-trimethylammonium is scarcely investigated as a leaving group for nucleophilic displacement. Since ARC-111 can be synthesized with ease in 58% overall yield, we decided to investigate the reactivity of *N,N,N*-trimethylammonium derivative of ARC-111. The synthesis of the *N,N,N*-trimethylammonium derivative was readily accomplished by addition of methyl iodide to a solution of ARC-111 in 20% methanol in methylene chloride. The trimethylammonium salt **23** was used without further purification. Generally, the displacement reaction worked successfully to provide the

targeted compound. Together with the desired product, two by-products, in all cases, were also isolated. Reaction was carried out in a sealed tube heated to 150 ºC for 2-5 hours.

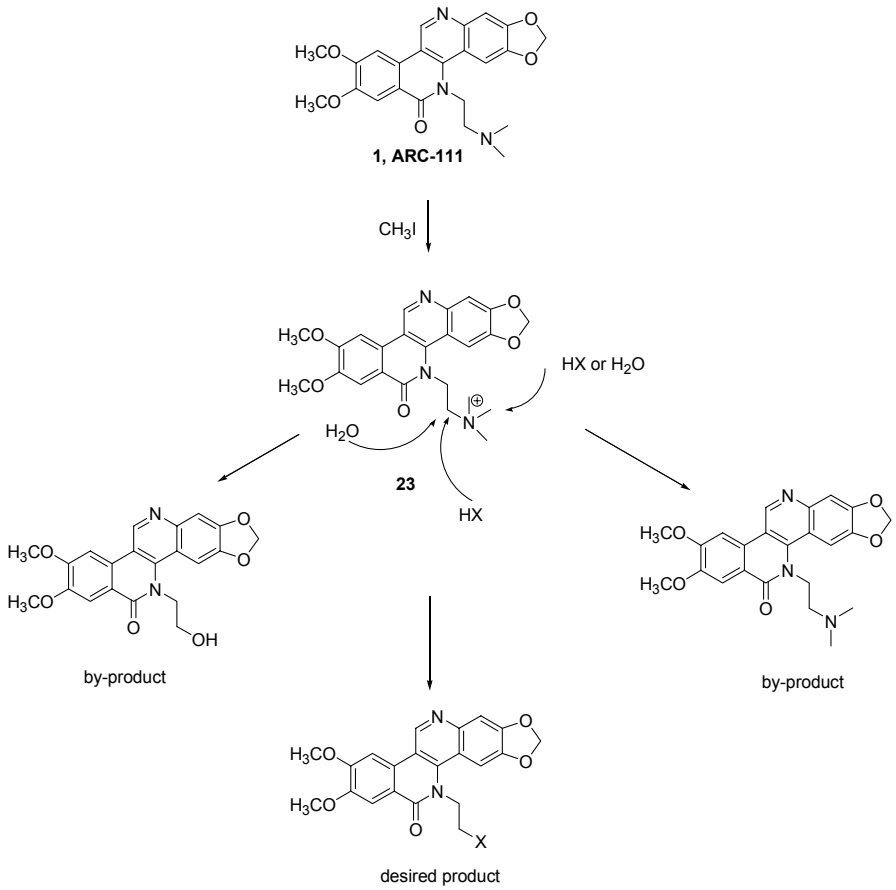
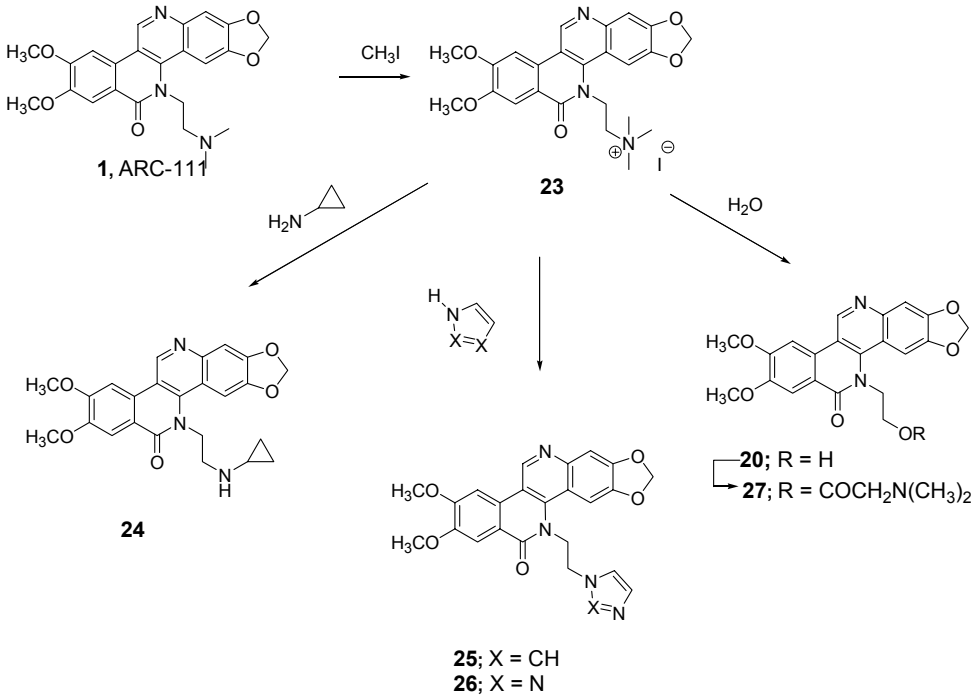


Figure 32. Nucleophilic Displacement of trimethylammonium group

Both by-products can be explained from the reaction mechanism. The trace water existed in reaction system may attack the methylene group to form hydroxyl compound **20**. The ARC-111 can be formed by nucleophiles attacking (water or nitrogen containing compounds) on any of the three methyl groups (Figure 32).

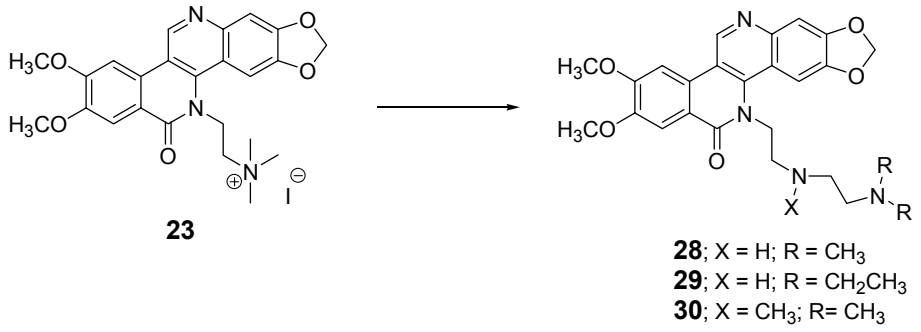
Direct displacement of this quaternary ammonium with hydroxide, cyclopropylamine, imidazole, 1*H*-1,2,3-triazole, alkylethylenediames, ethanolamine, or polyhydroxylated alkylamines was explored and the yields of both products and by-products were also determined.

Treatment of this quaternary ammonium compound, as illustrated in Scheme 5, in anhydrous DMSO with cyclopropylamine, imidazole, or 1*H*-1,2,3-triazole provided **24**, **25** and **26**, respectively in yields that ranged from 19-25%. Previous methods for the preparation of the 2-hydroxyethyl derivative, **20**, involved a lengthy consecutive synthetic route and the need for protection and deprotection of the hydroxyl functionality. As an alternative method for generating small quantities of **20**, heating of **23** in DMSO containing 5.6% water provided a convenient method. While **20** had only limited water-solubility, the hydroxyl moiety can serve as a handle for the development of pro-drug derivatives. As was performed with the camptothecin,[156] **20** was condensed with glycine to form the more water soluble glycinate ester **27** using DCC in the presence of DMAP. DMSO proved to be the most favorable solvent. Compound **23** was not sufficiently soluble in other solvents, such as methanol, chloroform or toluene.



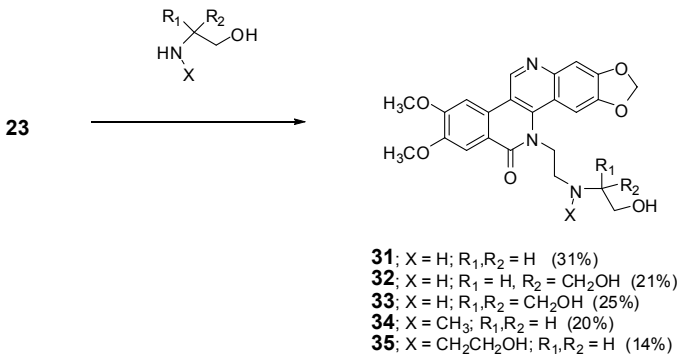
Scheme 5. Synthesis of compounds **20**, **24-27**

The preparation of 2-[*N, N*-dialkylaminoalkylamino] on the ethyl linkage extending from the 5-position of dibenzo[*c*,*h*][1,6]naphthyridin-6-ones could be problematic under the current methodology used for the preparation of ARC-111 and related compounds. As illustrated in Scheme 6, treatment of **23** with *N, N*-dimethylethylenediamine, *N ,N*-diethylethylenediamine, and *N, N, N'*-trimethylethylene- diamine did prove to be an effective method for preparing **28**, **29**, and **30**, respectively. Yields ranged from 25-26% using ethylenediamine that retained a primary amine. In the case of **30** where *N, N, N'*-trimethylethylenediame was employed, the yield from reaction of the secondary amine was only 10%. These yields are considered pratical for preparation of 100 mg quantities of targeted compounds, and therefore the use of **23** did provide for a convenient method for the preparation and biological assessment of several new polyamino analogs related to ARC-111.



Scheme 6. Synthesis of polyamino derivatives of ARC-111

We were especially interested in assessing the biological activity of several new analogs of ARC-111 wherein there were hydroxyalkyl groups attached to the 5-(2-aminoethyl) moiety. Treatment of **23** with the appropriate ethanolamine derivative as shown in Scheme 7 did provide **31-35** in modest yield.



Scheme 7. Synthesis of hydroxyalkylamino derivatives of ARC-111

The trimethylammonium iodide salt of ARC-31 (the cinnoline analog of ARC-111) could also be readily prepared. Treatment of various nucleophiles successfully resulted in the formation of several new derivatives. Similar to what we have observed for ARC-111 derivatives, the hydroxyl compound and ARC-31 were also isolated as by-products (Figure 33). The reactions related to cinnolines were mainly completed by Dr. M. Satyanarayana in our group.[133]

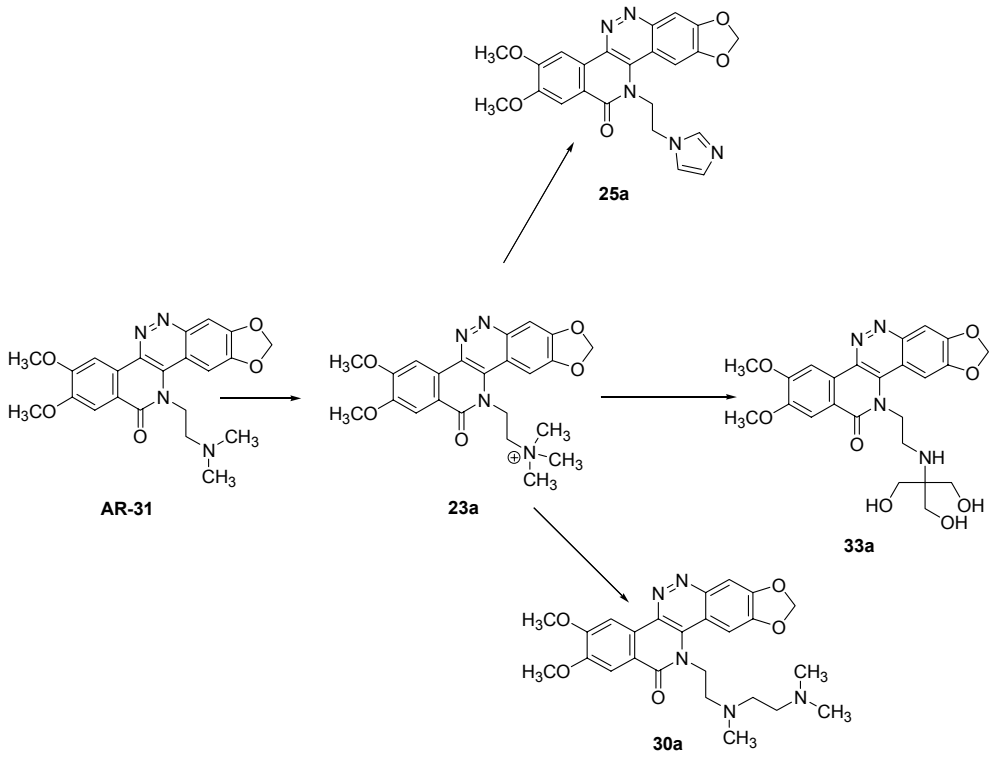
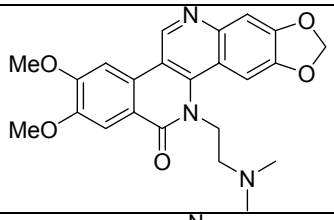
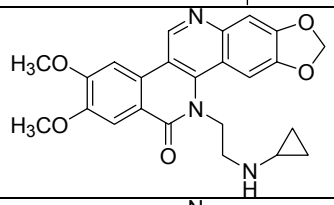
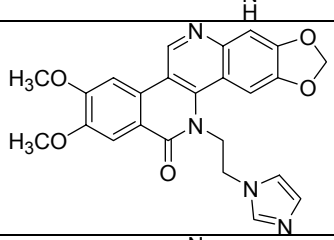
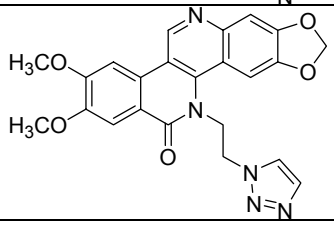


Figure 33. ARC-31 derivatives formed via its trimethylammonium iodide salt.

Table 4 lists the comparative TOP-1 targeting activities and cytotoxic activities of the cyclopropylamino derivative **24** and two heterocyclic derivatives **25** and **26**. Compound **20** was compared with its prodrug form **27** in Table 5. The results observed with polyamino derivatives were summarized in Table 6, while data on hydroxy derivatives **32-35** are provided in Table 7.

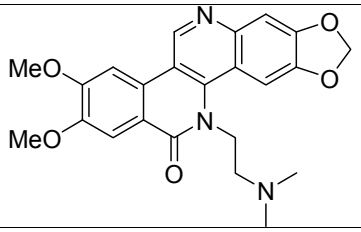
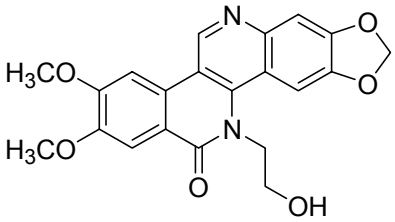
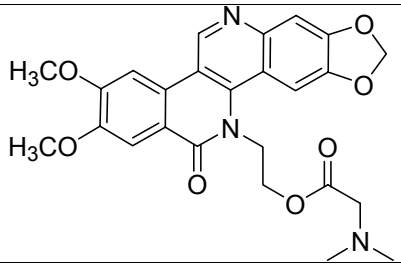
Table 4. Comparison of **24**, **25** and **26**

	Structure	TOP1-mediated cleavage	Cytotoxicity IC_{50} (μM)			
			RPMI 8402	CPT-K5	P388	P388/ CPT45
CPT		0.2	0.004	>10	0.004	>10
1		0.3	0.002	0.90	0.001	0.23
24		0.33	0.01	0.3	0.009	0.11
25		2.3	0.21	>10	0.2	>10
26		> 10	3.5	>10	4.4	>10

Compound **24** is a potent TOP1-targeting agent with DNA cleavage data similar to ARC-111. In contrast, **25** and **26** are much less potent compounds. Heterocyclic structures do not improve activity of these compounds. However, **24** is still slightly less cytotoxic

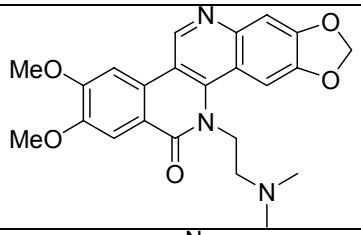
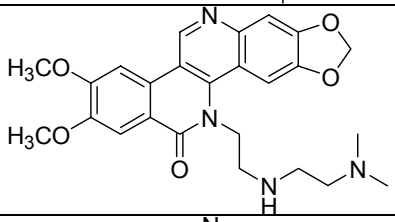
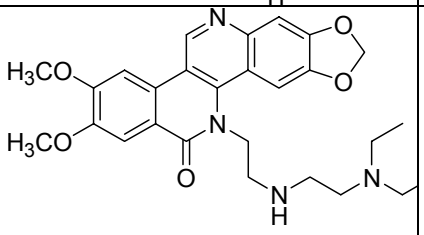
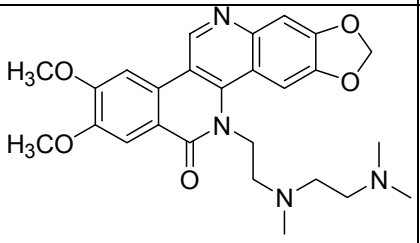
than ARC-111. The cross-resistance **24** has demonstrated in CPT-K5 and P388/CPT45 cells confirms its TOP1 targeting mechanism. The least active TOP1-targeting agent, the 5-[2-(1*H*-imidazoyl-1-yl)]ethyl derivative **26**, is also the least cytotoxic when evaluated in both of these cell lines.

Table 5. Comparison of **1**, **20** and **27**

	Structure	TOP1-mediated cleavage	Cytotoxicity IC_{50} (μM)			
			RPMI 8402	CPT-K5	P388	P388/ CPT45
CPT		0.2	0.004	>10	0.004	>10
1		0.3	0.002	0.90	0.001	0.23
20		4.71	0.03	>10	0.03	0.9
27		0.26	0.031	4.6	0.027	0.39

Compound **27** has shown much more potent Top1 targeting activity than compound **20**, which despite having relatively poor TOP1-targeting activity, exhibits significant cytotoxicity. Similar results have been observed earlier for compound **20**. Compound **27** possesses excellent solubility. The poor solubility of compound **20** may account for its lower potency in the cleavage assay (Table 5).

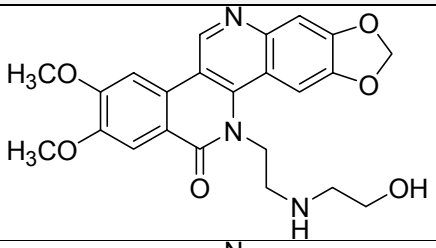
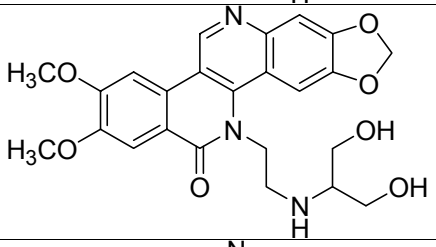
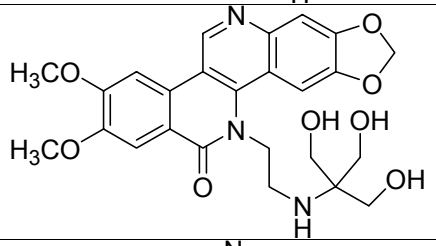
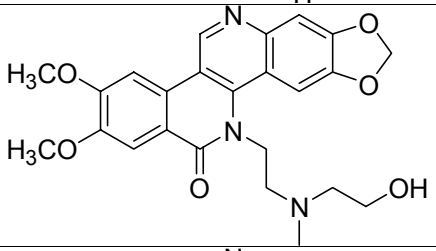
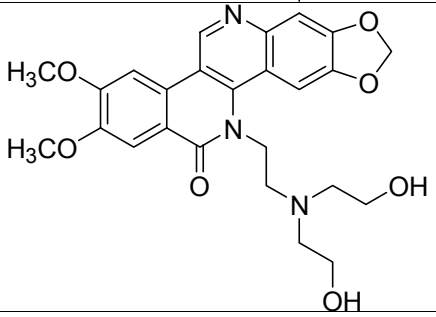
Table 6. A comparison of polyamino derivatives of ARC-111

	Structure	TOP1-mediated cleavage	Cytotoxicity IC_{50} (μ M)			
			RPMI 8402	CPT-K5	P388	P388/ CPT45
CPT		0.2	0.004	>10	0.004	>10
1		0.3	0.002	0.90	0.001	0.23
28		6.4	0.14	2.6	0.075	0.34
29		5.2	0.15	9	0.23	0.35
30		0.72	0.045	2.2	0.035	0.07

Compounds **28-30** are polyamino derivatives of ARC-111. Unfortunately, these three compounds have less Top1 targeting potency than ARC-111 or CPT. The best among these three compounds is **30**, which has an IC_{50} of 45 nM cytotoxicity against RPMI8402 cancer cell lines. Compound **28** and **29** are 50 fold less cytotoxic than CPT.

Compounds **31**, and **34,** as shown in Table 7, are among the more cytotoxic analogs, which is consistent with these analogs being the more potent TOP1-targeting agents. The 5-[2-(2-hydroxyethyl)amino]ethyl derivatives **31** and **34** did exhibit exceptional potency as TOP1-targeting agents with greater intrinsic activity than either CPT or ARC-111. Similar cytotoxicity was observed for **31** relative to CPT, while **34** was slightly less active. The IC_{50} values observed for **32**, and **35** ranged from 20 to 48 nM. Compound **32** has similar TOP1-targeting activity to CPT. The relative TOP1-targeting activities of **35** are somewhat lower. With the exception of **35**, comparative data between RPMI8402 and CPT-K5 suggest that TOP1-targeting activity of hydroxyl derivatives of ARC-111 is significantly linked to the observed cytotoxic activity. Comparative data between P388 and CPT/45 in Table 7 also suggest that for most of the compounds evaluated, TOP1-targeting activity is significantly linked to the observed cytotoxic activity. Less than one order of magnitude difference in cytotoxicity activity between this pair of tumor cells was observed for **35.** These data suggest that mechanisms other than TOP1-targeting activity likely contribute to the observed cytotoxic activity of **35**. As the MTT assay cannot distinguish between cytotoxic and cytostatic activity, it is possible that **35** may bind to cellular DNA and thereby exert a significant cytostatic effect.

Table 7. Comparison of hydroxyl derivatives of ARC-111

	Structure	TOP1-mediated cleavage	Cytotoxicity IC_{50} (μM)			
			RPMI 8402	CPT-K5	P388	P388/ CPT45
31		0.04	0.008	0.4	0.004	0.13
32		0.2	0.054	>10	0.08	2
33		2.0	0.33	7	0.33	3.5
34		0.04	0.015	0.58	0.012	0.33
35		0.48	0.04	0.32	0.03	0.25

The cytotoxicity data for KB3-1 cells and for the variants KBV-1 and KBH5.0 are listed in Table 8. KBV-1 cells overexpress the efflux transporter MDR1, and KBH5.0 cells

overexpress the efflux transporter BCRP. CPT-11 and topotecan are substrates for the efflux transporters MDR1 and BCRP. Decreased cytotoxicity against KBV-1 cells relative to the parent cell line KB3-1 is indicative of substances that are substrates for the efflux transporter MDR1. Similarly, resistance to the cytotoxic effects of a substance observed in KBH5.0 cells relative to its parent cell line KB3-1 is indicative of it being a substrate for BCRP efflux transporters. These data suggest that with the exception of **20**, **27**, and **33**, ten of the thirteen new compounds synthesized and evaluated in this study are substrates for MDR1. Fewer compounds, however, were shown to be substrates for BCRP.

Comparative data on the cytotoxic activity in KBH5.0 cells relative to KB3-1 cells suggest that **28**, **31**, **32** and **35** are substrates for the BCRP efflux transporter.

Table 8. The cytotoxicity data for KB3-1, KBV-1 and KBH5.0 cells

Compound	Cytotoxicity (μM)		
	KB3-1	**KBV-1**	**KBH5.0**
1	0.005	0.005	0.006
24	0.004	0.04	.008
25	0.15	1.8	0.58
26	0.7	10	6
20	0.027	0.04	0.04
27	0.032	0.035	0.05
28	0.06	3.4	0.75
29	0.04	1.2	0.3
30	0.05	0.6	0.21
31	0.003	0.3	0.12
32	0.026	2.0	0.75
33	.25	1.8	1.8
34	.006	.06	.05
35	.023	.35	.28

In summary, compounds **24**, **27, 31**, and **34** were identified from these *in vitro* studies as of particular interest. These compounds have solubility properties that allow them to be readily formulated, each exhibits good TOP1-targeting activity and

cytotoxicity, and none of these analogs are substrates for the BCRP efflux transporter. Further studies in tumor-bearing mice are needed to assess their *in vivo* efficacy.

The synthetic methodology employed for the preparation of these analogs permits a broad array of varied analogs to be conveniently prepared from a single derivative of ARC-111. Many of the these analogs could not be prepared without significant modifications to the synthetic approach typically used in our laboratory for the preparation of 5*H*-2,3-dimethoxy-8,9-methylenedioxy-5-ethyldibenzo[*c*,*h*][1,6]-naphthyridin-5-ones. While this methodology does not represent an optimal synthetic approach to any one of these compounds, it does provide a facile synthetic route that permits one to assess a broad array of analogs and to select those of interest for further evaluation.

2.3 Further Exploration on ARC-111 Analogs: D-ring Modification and Metabolite Synthesis

Previous SAR studies on benzo[*i*]phenanthridines have confirmed the importance of alkoxy substituents on the heterocyclic system.[108,109] The position and the size of these alkoxy groups have significant impact on compound activity. The D-ring of ARC-111 contains two methoxy groups on the 8 and 9 positions, a substitution pattern similar to our second generation lead. Studies have identified 8- or 9-nitro 5*H*-dibenzo[*c,h*]naphthyridin-6-ones as potent TOP1-targeting agents.[120] Amino or hydrophilic 2-(*N,N*-dimethylamino)-ethyl or a N,N-dimethylacetamide derivatives, in contrast, have negative effects on TOP1-targeting activity. [120,157]

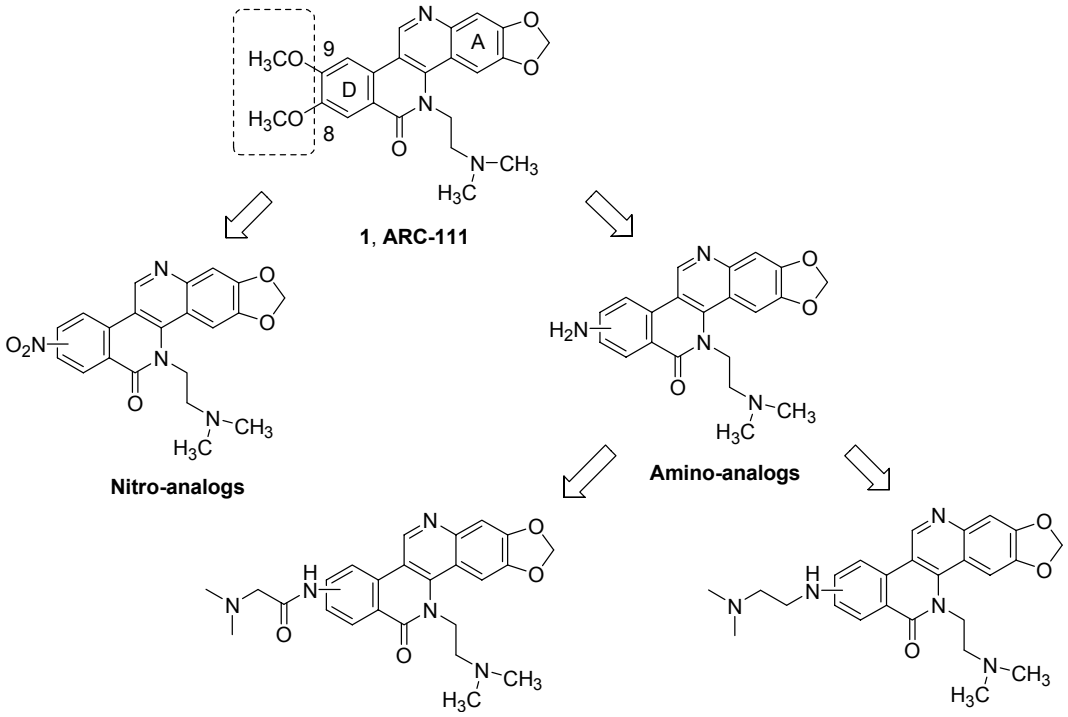


Figure 34. D-ring derivations of ARC-111

These studies were extended to examine the effect of the replacement of its 8,9-dimethoxy groups with 8,9-diethoxy substituents, as shown on compound **36** in Figure 35. In a later metabolite study, another two D-ring modified derivatives, **37** and **38** were also proposed as possible metabolites (Figure 35).The slight change of the size on D-ring substituents is of special interest. The biological data of these compounds could provide further insight into the structure-activity associated with this family of potent non-camptothecin TOP1-targeting agents.

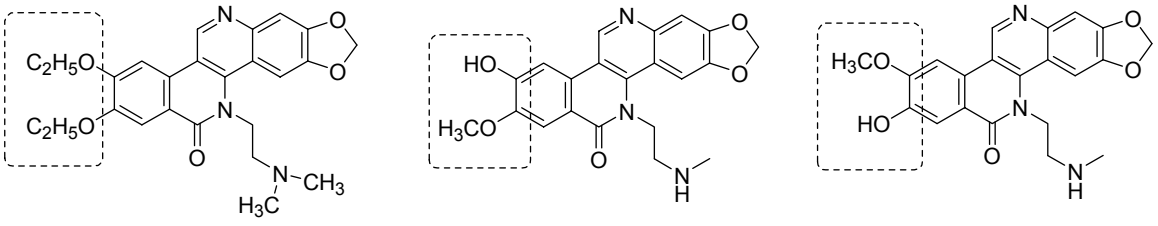
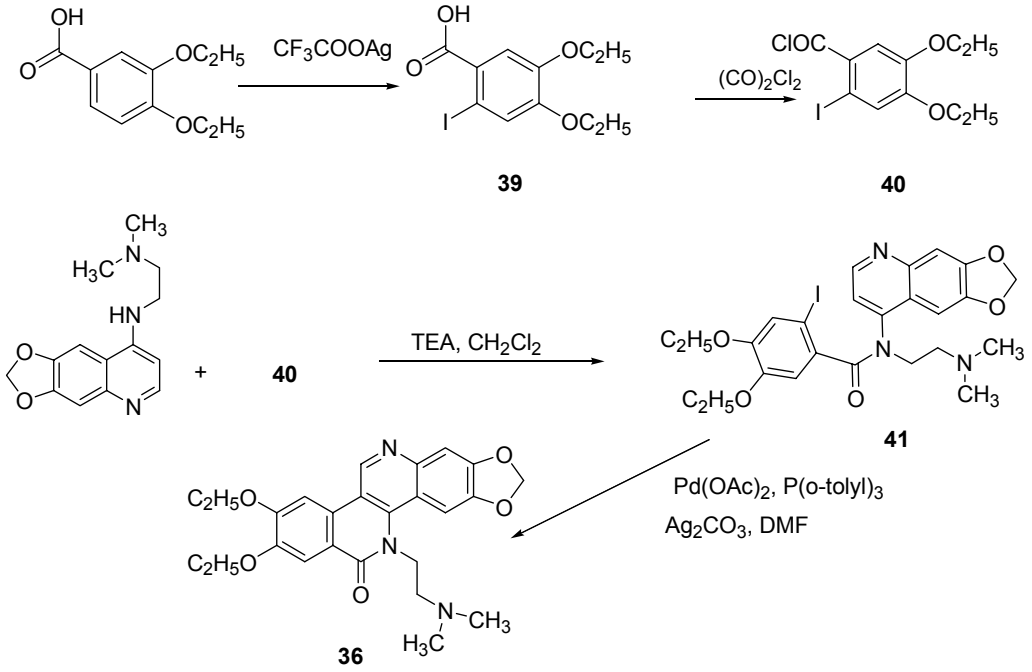


Figure 35. D-ring alkoxy groups modified derivatives

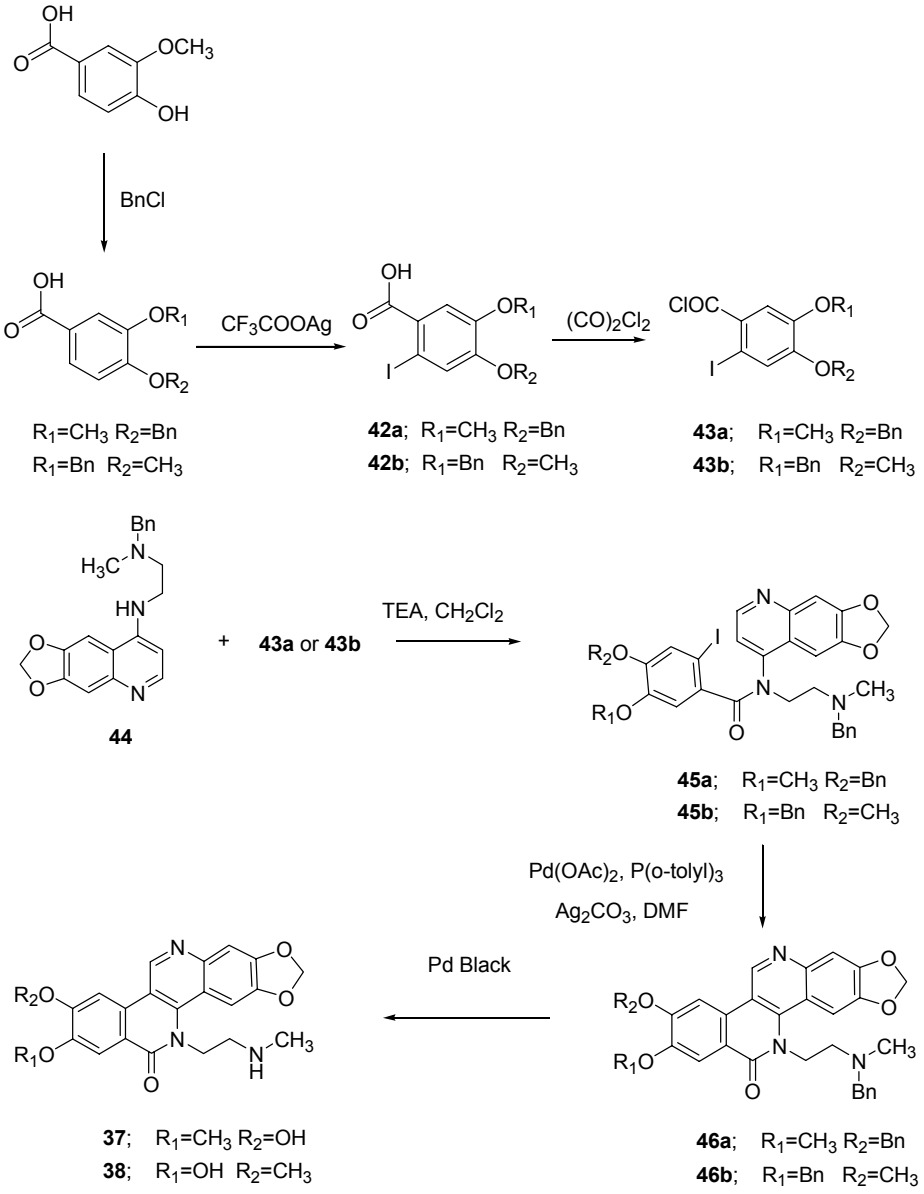
The preparation of the diethoxy analog **36** was performed as outlined in Scheme 8. Using similar methodology as previously described,[116] 3,4-diethoxybenzoic acid was treated with iodine and silver trifluroacetate in $CHCl_3$ to yield 4,5-diethoxy-2-iodobenzoic acid **39** in 60% yield, with 10-20% starting material recovered. Conversion of **39** to its acid chloride **40** was carried out in anhydrous CH_2Cl_2 with oxalyl chloride. Without further purification **40** was added directly to the solution of appropriate 4-amino-6,7-methylenedioxyquinoline and TEA in CH_2Cl_2. Intramolecular Heck cyclization of iodobenzamide **41** was performed in refluxing DMF for 2 hours to afford **36** in 34% yield, using $Pd(OAc)_2$, P(*o*-tolyl)$_3$, and Ag_2CO_3.



Scheme 8. Preparation of **36.**

Syntheses of the other two D-ring modified 5*H*-dibenzo[*c,h*]naphthyridin-6-ones, **37** and **38**, were completed utilizing the original ARC-111 synthesis with minor adaptations as outlined in Scheme 9. Iodination of benzoic acid was carried out in $CHCl_3$ with iodine and silver trifluroacetate to afford **42**.[158] Treatment of **42** with oxalyl chloride

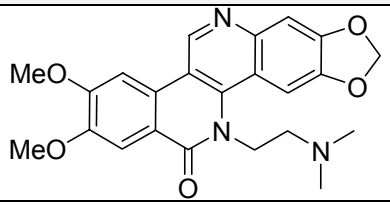
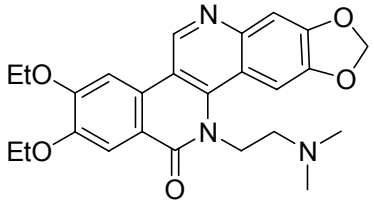
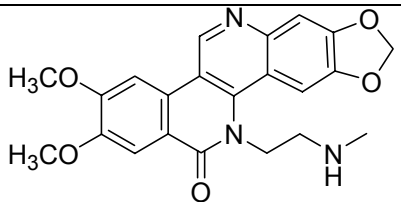
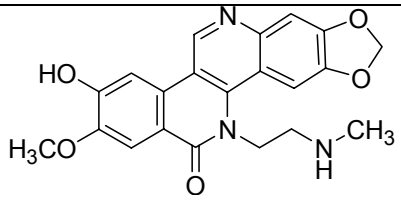
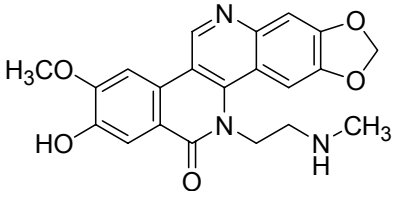
in dichloromethane provided **43**, which was sequentially reacted with 4-aminoquinoline **44** to yield amide compound **45** in good yield. Cyclization of **45** using Heck conditions gave **46** successfully, using $Pd(OAc)_2$, P(*o*-tolyl)$_3$, and Ag_2CO_3.[159,160] The removal of two benzyl groups was accomplished in one step in the presence of palladium black to afford final compound **37** in excellent yield.[161] The other metabolite **38** was similarly prepared by Dr. Mavurapu Satyanarayana in our group.[133]



Scheme 9. Synthesis of compound **37** and **38**

A comparison of D-ring modified compounds is listed in Table 9. A dramatic loss of activity was observed for diethoxy compound **36**. A more than 30 fold TOP1-mediated cleavage activity drop clearly indicates that compound **36** is much weaker than ARC-111 as a TOP1-targeting agent. Consistent with its cleavage data, cytotoxicity of **36** against

Table 9. A comparison of D-ring modified compounds **36-38**

	Structure	TOP1-mediated cleavage	Cytotoxicity IC_{50} (μM)			
			RPMI 8402	CPT -K5	P388	P388/ CPT45
1		0.3	0.002	0.90	0.001	0.23
36		>10	0.15	0.14	0.015	0.013
7		0.1	0.0003	0.25	0.0003	0.07
37		N.D.	0.003	0.25	0.002	0.03
38		N.D.	0.0025	0.25	0.002	0.03

RPMI8402 and P388 is at least 15 fold less active than the lead compound, ARC-111. However, the other two compounds, **37** and **38,** did exhibit potent TOP-1 targeting activities.

As shown in Table 9, modification to the D-ring of ARC-111 is not favored if a group bigger than methoxyl group was substituted. A smaller group, like simple hydroxyl group, is able to maintain the initial activity. Since all alkoxy groups are considered similar in terms of electronic contribution to the ring system, it can be concluded that substituent size has a crucial effect on the TOP1 targeting activity.

Compounds **37** and **38** are suspect metabolites of ARC-111 derivatives. There are still several other suspect metabolites to be investigated. The proposed drug metabolism pathway of ARC-111 is outlined in Figure 36. Demethylation on the side chain amino group gave compound **7**, which is another promising drug candidate in preclinical studies. The secondary amine compound **7** can be further metabolized to primary amine **47** after another demethylation on the amino group. Another possible fate of **7** is conversion to phenol derivative **37** or **38,** after demethylation on 9- or 8-methoxy group respectively. Biological data have demonstrated compounds **7**, **37**, **38** and **47** are all potent TOP1 targeting agents. The activity of these metabolites may help explain the continuous animal tumor suppression even after discontinuing administration of ARC-111. The primary amine **47**, most probably will be oxidized to an aldehyde via a deamination process. The aldehyde **48** can be reduced to an alcohol or oxidized to a carboxylic acid. The alcohol metabolite **20**, however, is 10 fold less active than ARC-111.

Most metabolites in Figure 36 have already been synthesized except **48** and **49**. Since **48** is expected to be less stable, preparation of stable metabolite carboxylic acid **49** became the focus of our research.

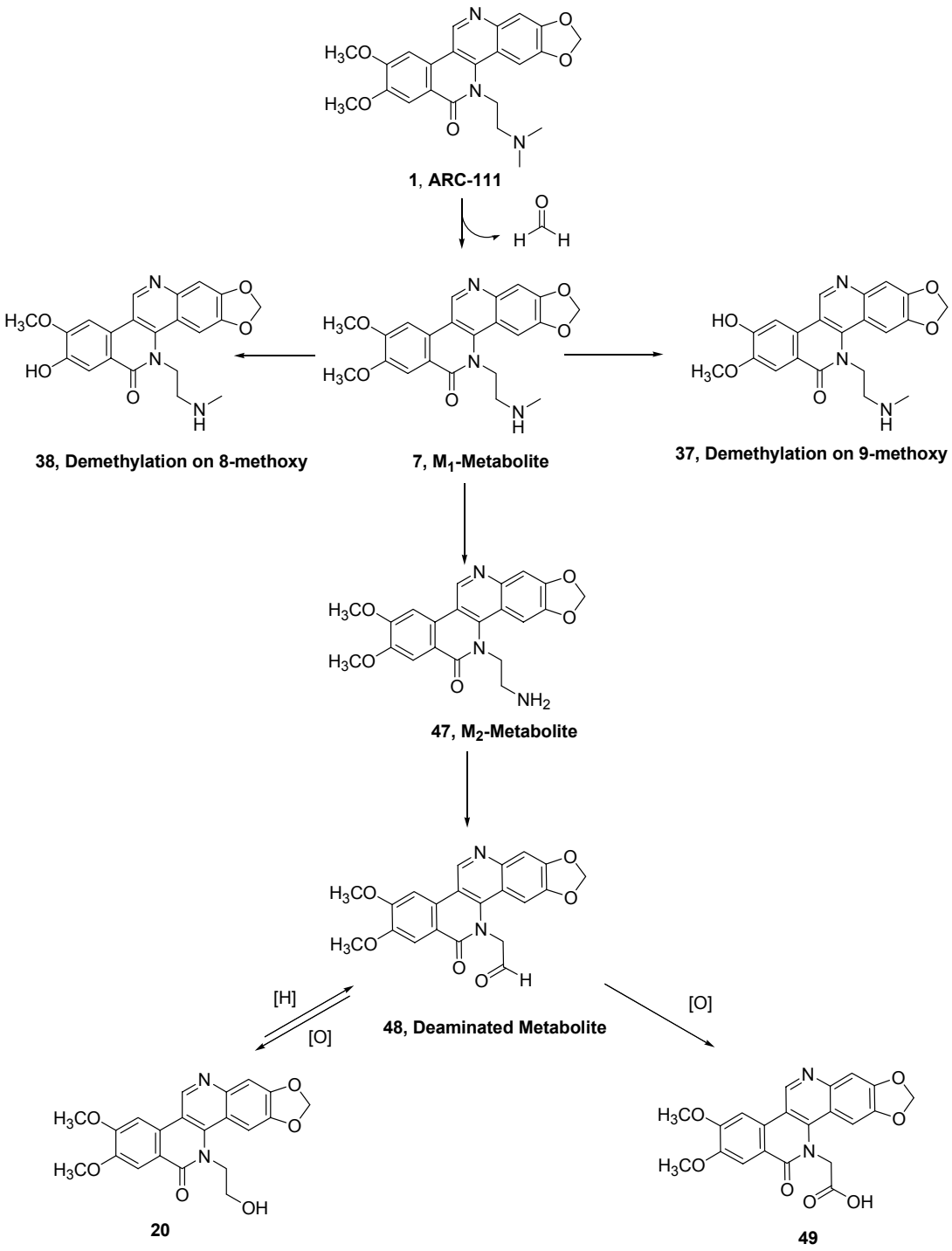
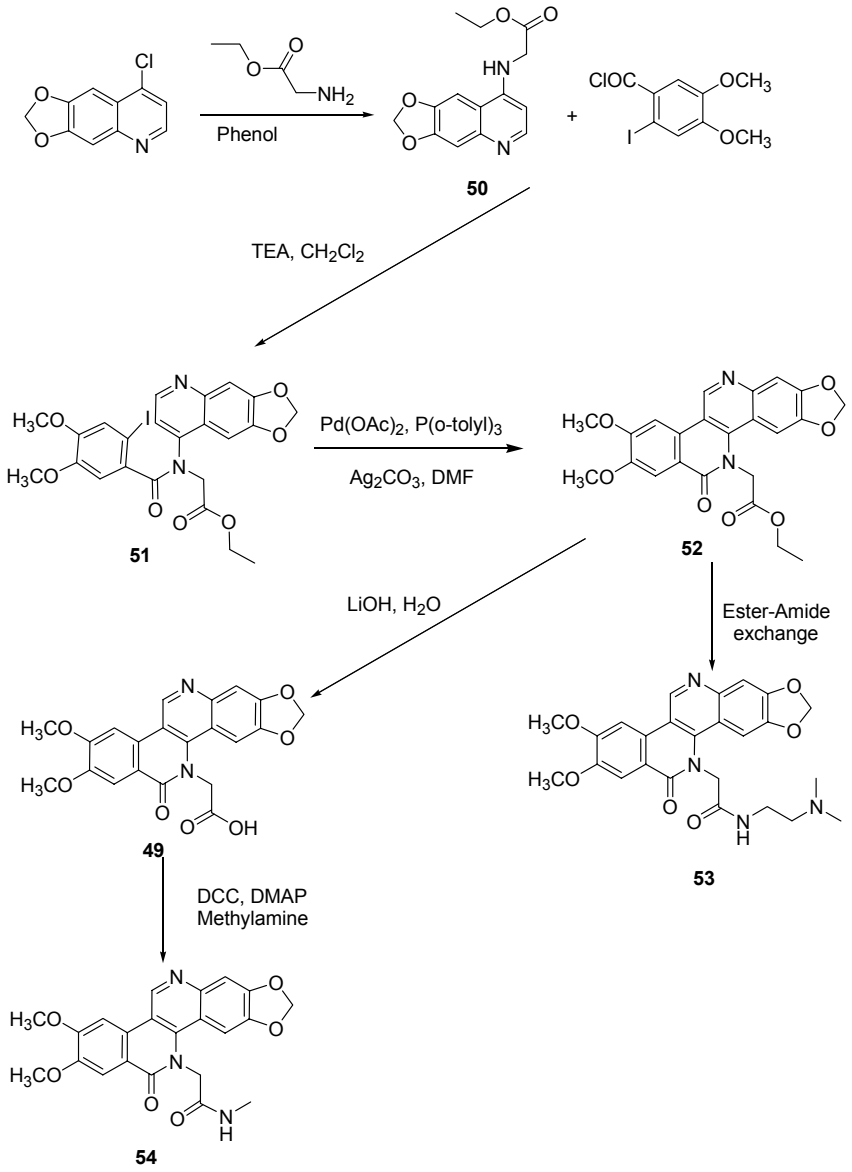


Figure 36. Proposed metabolism of ARC-111

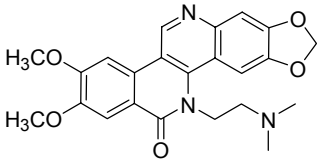
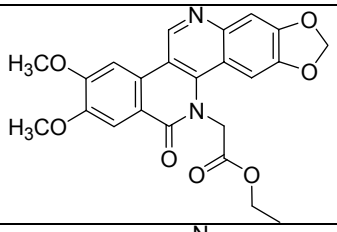
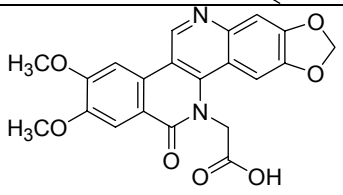
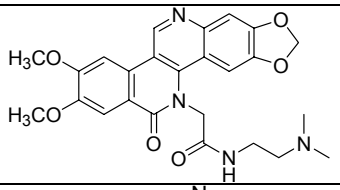
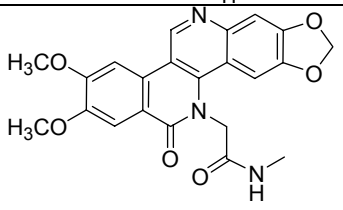
Synthesis of metabolite **49** as outlined in Scheme 10 used ARC-111 synthetic strategy. The ester functionality was well tolerated in the S_NAr and amidation conditions. Compound **52** was synthesized in good yield after Heck reaction. Hydrolysis provides the target compound finally in nearly quantitative yield. Two derivatives of acid metabolite, **53** and **54** were also synthesized (Scheme 10).



Scheme 10. Syntheses of metabolite 49 and related derivatives

The cytotoxicity data of metabolite **49** have shown a significant loss compared to ARC-111 (Table 10). However, the synthetic precursor compound **52** has demonstrated decent anticancer activity. It also showed excellent selectivity on RPMI8402 and P388 over CPT-K5 and CPT45. The decreased activity of **49** is probably due to its problematic

Table 10. Comparison of metabolite 49 and related derivatives with ARC-111

	Structure	TOP1-mediated cleavage	Cytotoxicity IC_{50} (μM)			
			RPMI 8402	CPT-K5	P388	P388/ CPT45
1		0.3	0.002	0.90	0.001	0.23
52		7.5	0.08	>10	0.04	>10
49		>10	>10	>10	3.3	6
53		10	0.15	0.3	0.03	0.04
54		>10	0.023	0.29	0.014	0.04

anionic charge. Interestingly, the hydrolysis product of CPT is an inactive form of the drug, which also possesses a carboxylic acid functionality. The amide derivatives **53** and **54** gained some cytotoxicity compared with **49**, although they are weaker TOP1 targeting agents than ARC-111.

The data in Table 11 has suggested that all D-ring modified products and metabolite derivatives, except compounds **36** and **49**, are substrates for BCRP. Compounds **37**, **38,** and **53** are substrates for MDR1.

Table 11. Relative cytotoxicity in cancer cell lines, KB3-1, KBV-1, and KBH5.0

Compound	Cytotoxicity (μM)		
	KB3-1	**KBV-1**	**KBH5.0**
1	0.005	0.005	0.006
36	0.07	0.19	0.1
37	0.004	0.028	0.04
38	0.001	0.07	0.048
52	0.05	0.07	0.1
49	3	4.5	6
53	0.035	5	1
54	0.02	0.065	0.25

2.4 Design and Synthesis of 12-Substituted Benzo[*i*]phenanthridines

Starting from a lead compound which has incorporated within its structure either a benzo[*i*]phenanthridine or dienzo[*c,h*]cinnoline, several 5-(2-aminoethyl)dibenzo[*c*,*h*]-[1,6]naphthyridin-6-ones and 11-2-(2-aminoethyl) isoquinolin[4,3-c]cinnolin-12-ones have been identified as exceptionally active topoisomerase I- (TOP1) targeting agents with potent antitumor activity.[115,116] ARC-111 and AR-31 are excellent representatives of these two classes of compounds (Figure 37). Analogs within these series of compounds have proved to be active as antitumor agents *in vivo* when administered by gavage or parenterally to tumor-bearing mice. An important feature of these compounds is the good

water solubility associated with their citrate salts. On the other hand, only limited studies were performed on benzo[*i*]phenathridines or dienzo[*c,h*]cinnolines in light of their limited solubility and difficulties associated with formulation for *in vivo* assessment of biological activity.

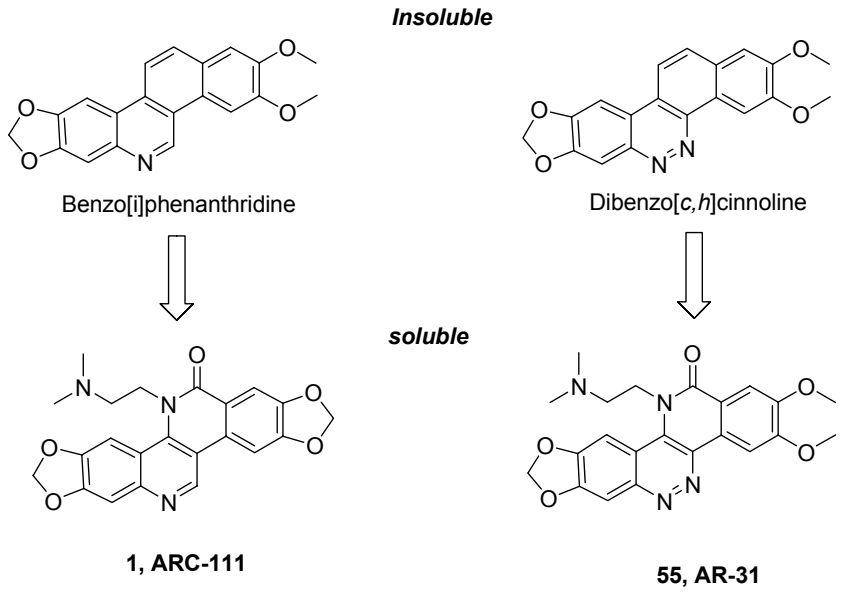


Figure 37. Design of more soluble TOP1 targeting agents by introducing a lactam moiety on B-ring of lead compounds

The reversed lactam of ARC-111, **56,** represents a new series of non-camptothecin TOP1-targeting agents consisting of various 6-substituted dibenzo[*c*,*h*][2,6]-naphthyridin -5-ones.[122,125] Analogs within this series of compounds have also been shown to have exceptional TOP1-targeting activity and potent cytotoxic activity. Recently, it has been demonstrated that 12-carboxamide derivatives of benzo[i]phenathridine also have the potential for further developement as an additional series of non-camptothecin TOP1-targeting agents.[122,125] The potential of these compounds as TOP1-targeting agents was made apparent by the biological activity associated with **57** (Figure 38). Different

from ARC-111 and the reversed lactam, 12-carboxamides retain the B-ring aromaticity and are more structurally similar to the lead compound, benzo[*i*]phenathridine.

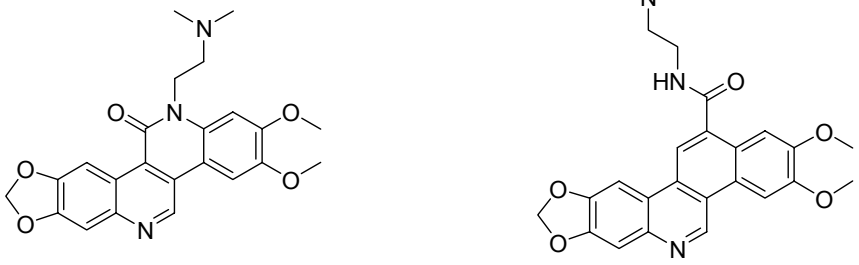


Figure 38. Reversed lactam of ARC-111 and 12-carboxamide derivative of benzo[*i*]phenathridine

There were several unknowns regarding their structure-activity relationships within this series. In addition, there were certain limitations associated with synthetic methodology that was employed in the preparation of the 12-carboxamide derivatives of benzo[*i*]phenathridine: The synthesis of 12-carboxamide derivatives of benzo[*i*]phenanthridine involves photolysis, which is viewed unfavorably for industrial or scale-up production for clinical studies. To maintain this series of compounds as candidates for clinical development, it was critical to develop an alternative to the phtotocyclization step. Regarding the structure-activity relationships within this series, it was uncertain as to whether or not simpler amides, such as primary amide, would retain activity. While it is evident that the presence of the aminoalkyl group attached to the 12-carboxamide significantly improved the hydrophilic property of this compound, it was not known whether similarly substituted benzo[*i*]phenanthridines, particularly those with polar substituents at the 12-position, would exhibit similar biological activity (Figure 39). With a

simple amino alkyl side chain installed on the B-ring of benzo[*i*]phenathridine, we could determine whether such benzo[i]phenanthridines would have similar biological activity.

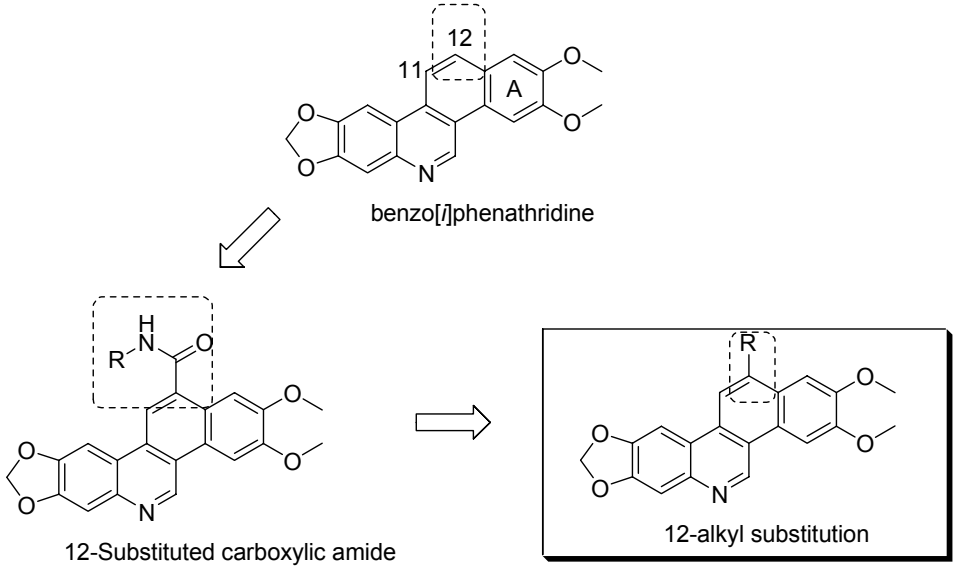
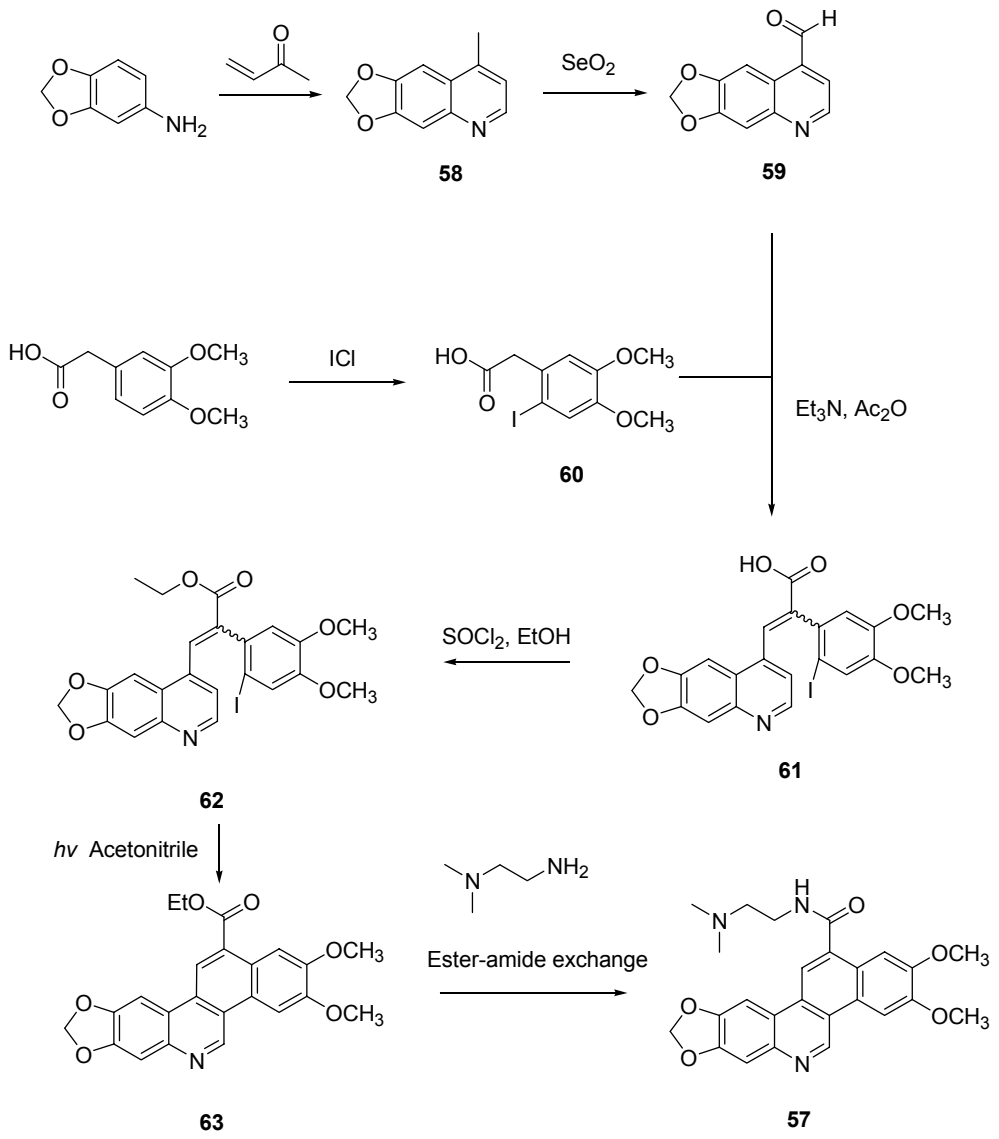


Figure 39. Design of simple polar substitution on the 12-position of benzo[*i*]phenathridine

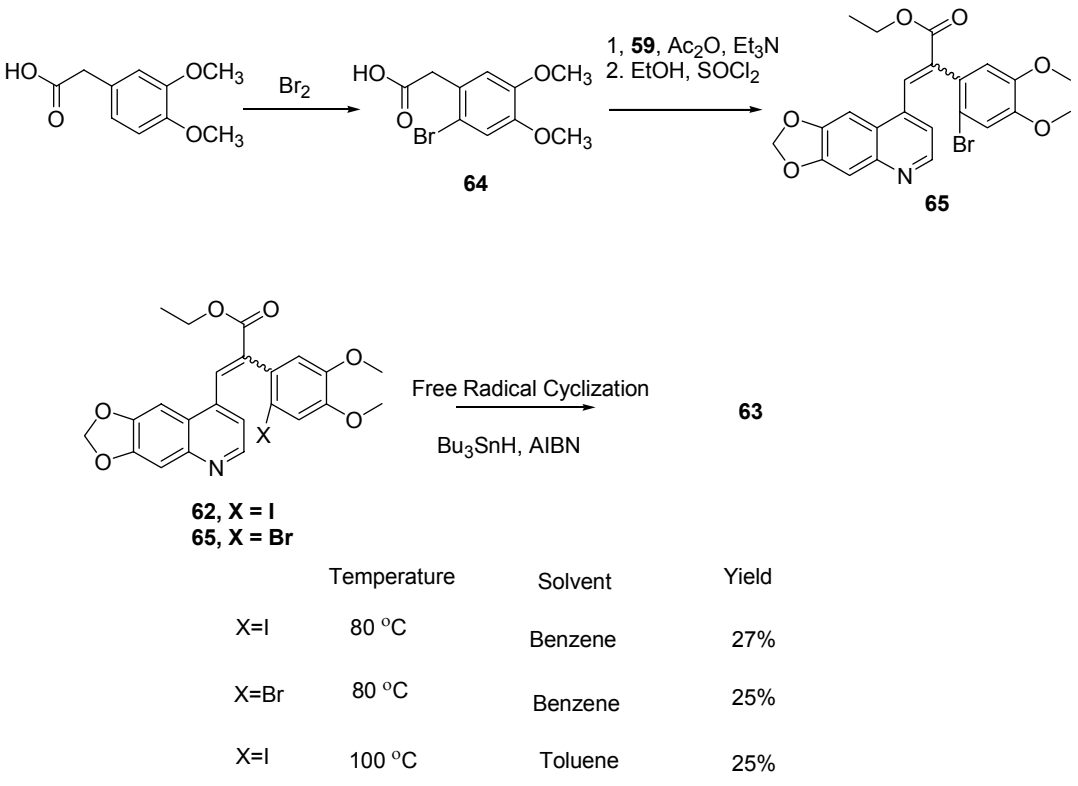
Synthecic scheme used for the prepration of compound **57** is illustrated in Figure 49. 6,7-Methylenedioxy-4-methylquinoline **58** was prepared from commercially available 3,4-methylenedioxyaniline.[163] Oxidation of **58** with SeO_2[164] provided 4-formyl-6,7-dimethoxy quinoline, **59**. Condensation[165] of **59** with 2-iodo-4,5-dimethoxyphenylacetic acid **60** in acetic anhydride in the presence of triethylamine provided **61** in good yield. The esterification of compound was then carried out in EtOH in the presence of thionyl chloride. The resulting ester was then photocyclized in acetonitrile[166] to provide benzo[*i*]phenanthridines. The 12-carboxyethyl ester benzo[*i*]phenanthridine derivative **63** was heated in the presence of *N,N*-dimethylethylenediamine to form the benzo[*i*]phenanthridine 12-carboxamides **57**.



Scheme 11. Synthesis of compound **57**

The key cyclization reaction associated with the synthesis of compound **63** was preformed under UV activation. To minimize side reactions, our reaction was carried out in a very dilute acetonitrile solution. To synthesize a 100 mg of product nearly one liter of solvent was needed. Besides, the photoreactor apparatus can not be conveniently used in process chemistry. To find more efficient synthetic alternatives, other cyclization methods, such as radical-mediated cyclization, were investigated in our lab.[167-170] Fortunately, radical cyclization reaction initiated by tributyltin and AIBN smoothly gives the desired

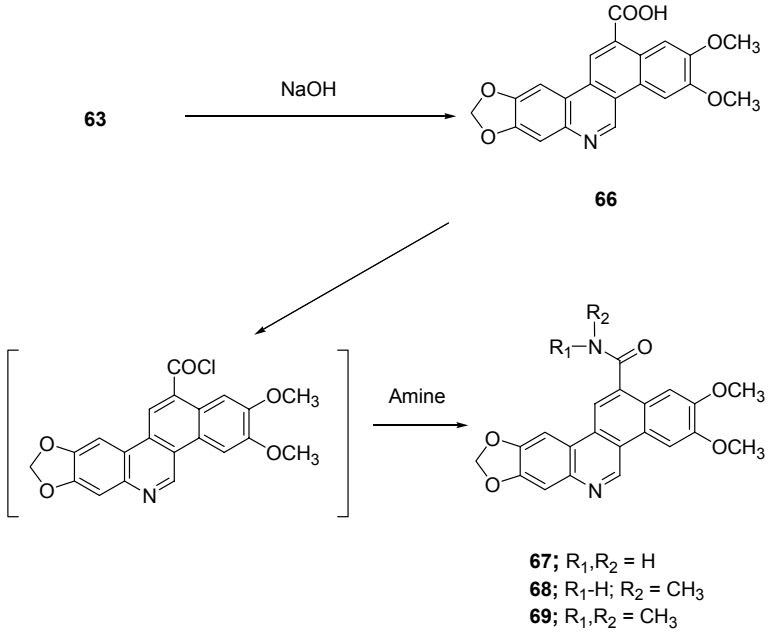
compound in moderate yield.[168-170] Although this alternative cyclization method did not improve reaction yield, it did provide an industrially feasible solution to bypass the problematic photolysis.



	Temperature	Solvent	Yield
X=I	80 °C	Benzene	27%
X=Br	80 °C	Benzene	25%
X=I	100 °C	Toluene	25%

Figure 40. Investigations of photolysis alternatives

Three simpler amides were designed and synthesized following previously reported method.[122,124,126] The ethyl ester **63** could be readily converted to the carboxylic acid **66** in almost quantitative yield. While the poor solubility of this acid limited its versatility as an intermediate in these syntheses, it could be converted in neat $SOCl_2$ to form the acid chloride. As outlined in Figure 51, the acid **66** was converted to its acid chloride, which was used without further purification and treated with either ammonia or the appropriate alkylamine to provide **67-69** (Scheme 12). This work was mainly completed by Dr. Mavarapu, S. in our group.[133]



Scheme 12. Syntheses of simple amide derivatives

Our research focused heavily on syntheses of simple 12-aminoalkyl substituted benzo[*i*]phenanthridines. The first synthetic scheme we tried was mainly based on a Wittig reaction.[171-173] The resulting stilbene product from the Wittig reaction could be presumably cyclized using photocyclic conditions. The retrosynthetic analysis for this synthesis is shown in Figure 41.

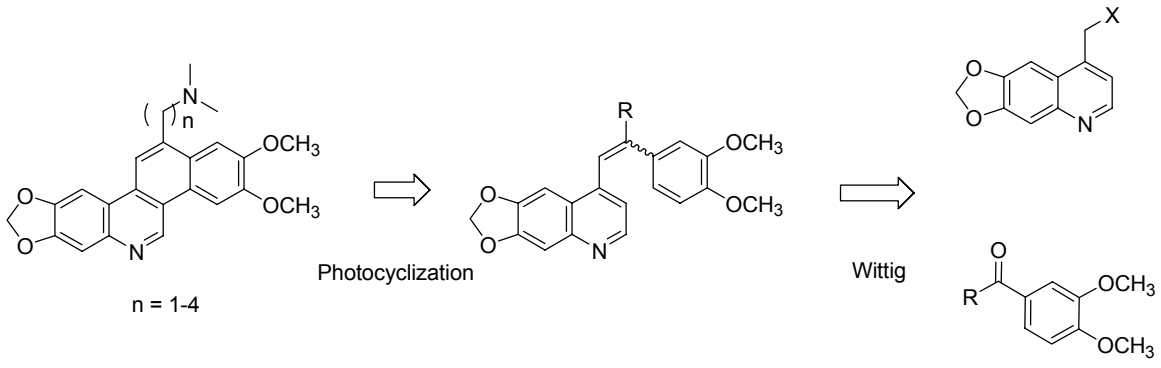
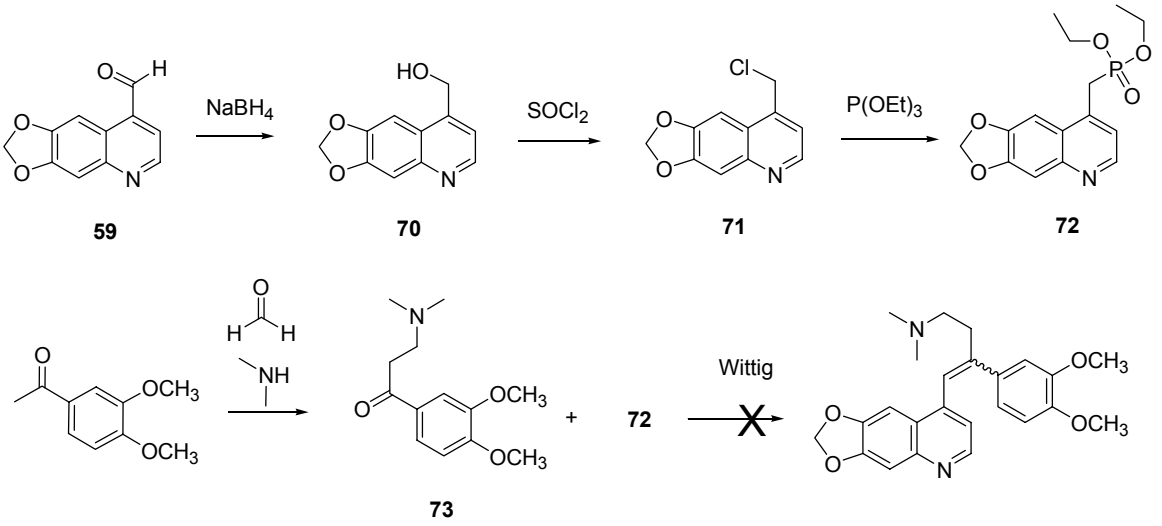


Figure 41. Retrosynthetic analysis of 12-aminoalkyl substituted benzo[*i*]phenanthridines.

Aldehyde **59** was reduced to alcohol **70** in good yield. The resulting alcohol was then displaced by chlorine using thionyl chloride. The substitution reaction of chloride **71** afforded Wittig precursor **72**. The corresponding ketone precursor **73** was prepared by a Mannich reaction from acetophenone in satisfactory yield.[174,175] Unfortunately, the Wittig reaction gave a complex mixture and no desired product was detected. Changing of the base or the phosphine precursor did not improve the results (Scheme 13).[172]



Scheme 13. Attempted synthesis of 12-aminoalkyl substituted benzo[*i*]phenanthridines

Another approach was dependent upon the function group interconversion of the ester **63**. The benzyl alcohol **74** can be achieved from ester via LAH reduction.[176] However, early attempts to develop suitable leaving groups turned out to be unsuccessful (Figure 42). It is noteworthy that similar results have been observed in attempts to convert hydroxyl groups at the 5-(2-hydroxyethyl) substituent of naphthyridin-6-ones related to ARC-111 to a suitable leaving group in an effort to form various 5-ethyl with varied substituents at its 2-position (see Section 2.2).

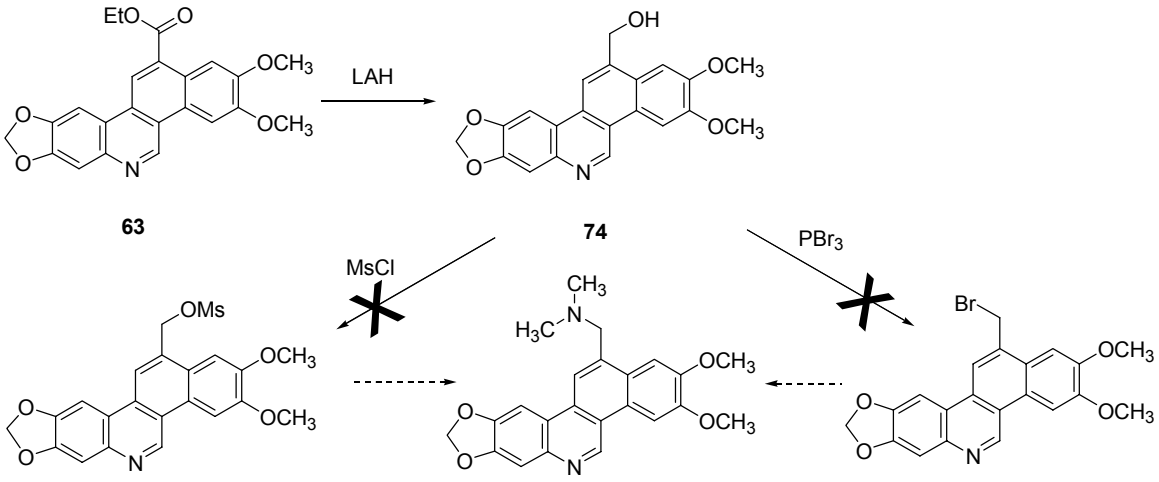
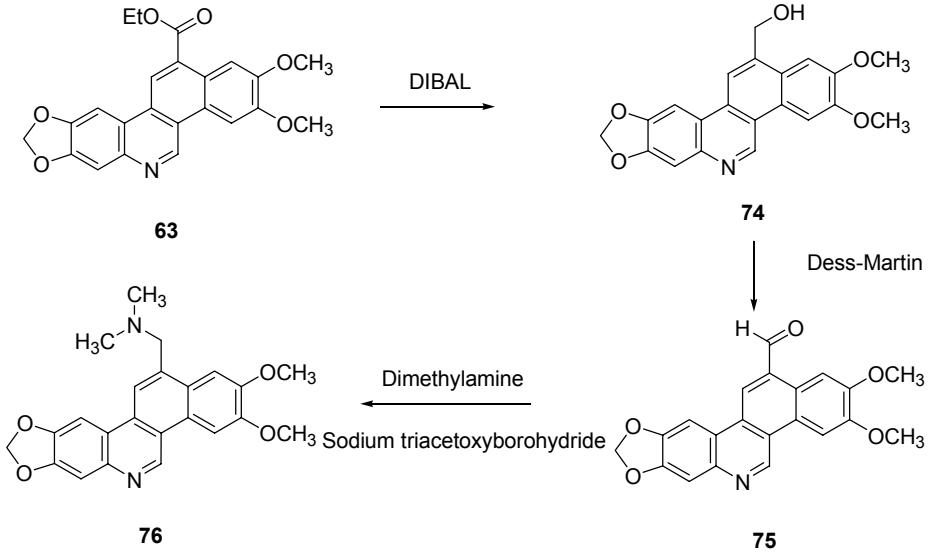


Figure 42. Attempts to prepare 12-dimethylaminomethyl benzo[*i*]phenanthridine

The synthetic approach that was ultimately successful for the preparation of 12-(N,N-dimethylamino)methyl benzo[*i*]phenanthridine, compound **76**, is outlined in Scheme 12. Dr. M. Satyanarayana improved upon the reduction of **63** by using DIBAL as

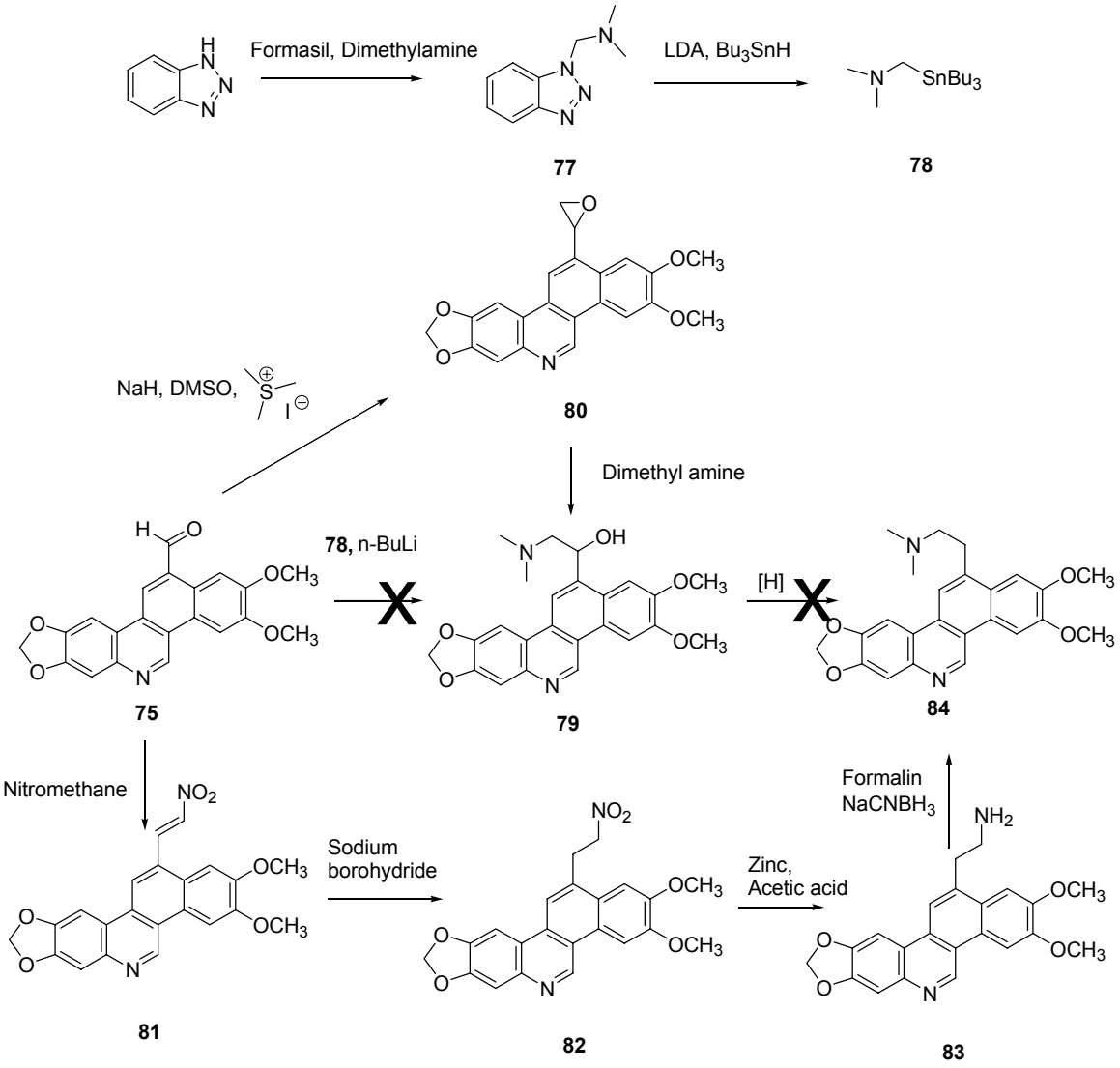


Scheme 14. Synthesis of 12-dimethylaminomethyl benzo[*i*]phenanthridine

reducing reagent.[177] Oxidation of **74** with MnO_2 afforded aldehyde compound **75** smoothly in 50-60% yield.[178] Later, it was found oxidation with a Dess-Martin reagent can improve the yield by 20%.[179] Treatment of **75** with dimethylamine followed by *in situ* reduction

with triacetyloxyborohydride at 0 °C provided the target compound **76** in good yield.[180] Aldehyde **75** is a very stable compound and turns out to be a pivotal synthetic intermediate for other 12-substituted benzo[*i*]phenanthridines targeted for synthesis and biological evaluation.

The synthesis of the 12-(2-aminoethyl)- and 12- (2-N,N-dimethylaminoethyl) benzo[*i*]phenathridine derivatives were prepared as outlined in Scheme 15.

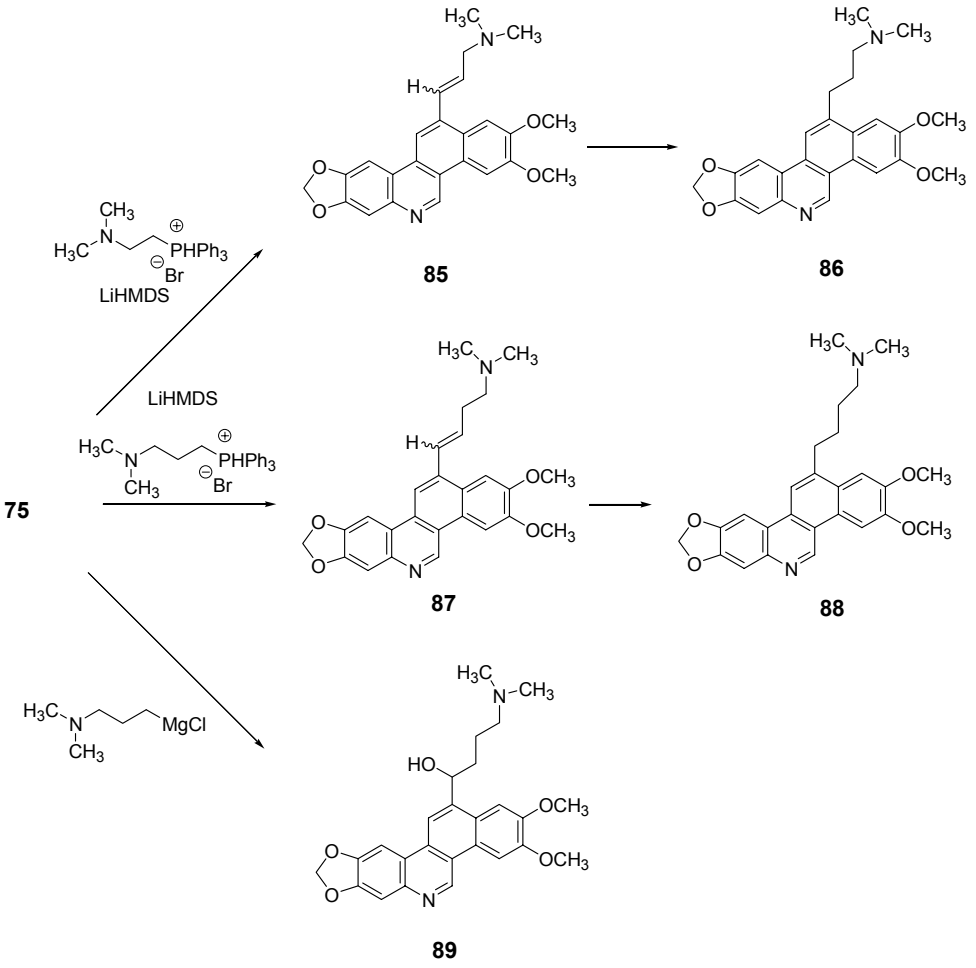


Scheme 15. Synthesis of 12-dimethylaminoethyl benzo[*i*]phenanthridine

A tributyltin derivative of N,N-dimethylmethane was prepared from 1-(N,N-dimethyl- aminomethyl)benzotriazole, which was prepared by a Mannich reaction.[181] Transmetallation of this organotin derivative with lithium diisopropylamide[182] at -78 °C followed by treatment with aldehyde **75** afforded an inseparable mixture and no detectable formation of **79** detected. Corey's epoxide synthesis using trimethylsulfide ylide and NaH in DMSO did successfully convert the aldehyde **75** to compound **80**.[183] Epoxide opening reaction by dimethyl amine gave compound **79** in good yield.[184] Unfortunately, **79** when subjected to catalytic hydogenolysis did not yield the target compound **84**. Eventually, condensation of **75** with nitromethane gave **81** in 75% yield.[185] Compound **81** was first reduced to **82** using $NaBH_4$,[186] which was then further reduced to the primary amine **83** using Zn/AcOH.[187] *N,N*-Dimethylation of **83** was accomplished using formalin in the presence of $NaCNBH_3$ to provide **84** in 61% yield.[180] Although this synthetic approach for **84** is longer than we expected, it did provide several interesting intermediates, like **82** and **83**, that allowed for a complete study of structure-activity relationships.

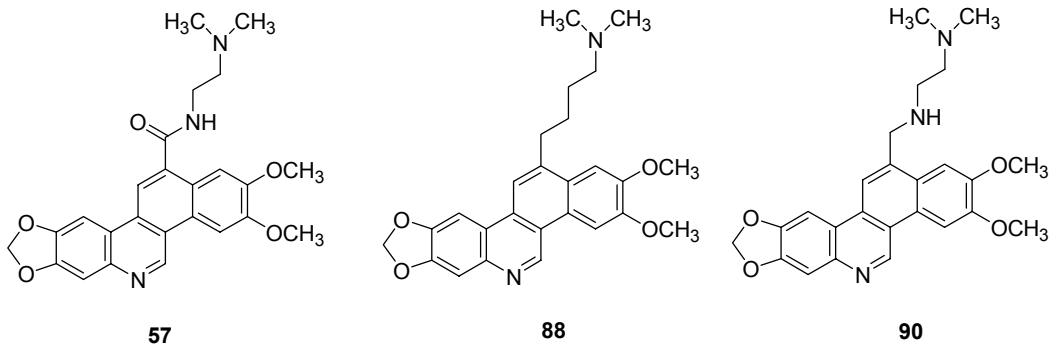
The synthetic methods used for the preparation of the 12-[3-(N,N-dimethylamino)-propyl and 12-[4-(N,N-dimethylamino)butyl benzo[*i*]phenanthridine derivatives are outlined in Scheme 16. A Wittig reaction with **75** and 2-(dimethylaminoethyltriphenyl-phosphonium bromide in THF in the presence of LiHMDS provided the 12-(3-dimethylamino)prop-1-enyl derivative **85**,[188] which was converted to **86** in the presence of 10% Pd/C and hydrogen. In a similar manner **75** was treated with 3-(dimethylamino)propyltriphenylphosponium bromide in the presence of LiHMDS to give the 12-(4-dimethylamino)but-1-enyl derivative **87**, which was hydrogenated to give

88. Treatment of **75** with freshly prepared dimethylaminopropyl magnesium chloride provided the 12-(4-dimethylamino-1-hydroxy)butyl derivative **89**.[189]



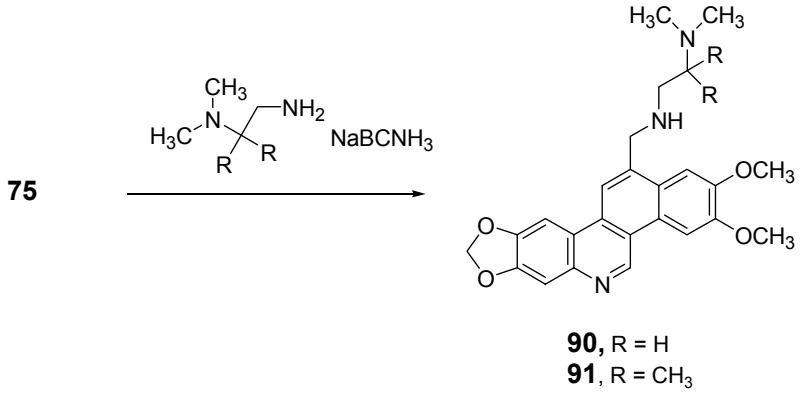
Scheme 16. Synthesis of 12-dimethylamino-propyl and butyl benzo[*i*]phenanthridine

Another alkylamino derivative **90** was of great interest to us. The only difference between **90** and **57** is the carbonyl group, as shown in Figure 43. The difference between **90** and **88** is merely an amino functionality. Biological data comparison of these three compounds should be very informative for SAR study. The synthesis of compounds **90** and **91** were prepared as illustrated in Scheme 17 by treatment of **75** with the appropriate ethylenediame followed by reduction with sodium cyano-borohydride, $NaCNBH_3$. These two compounds were prepared by Dr. M. Satyanarayana in our group.



57 **88** **90**

Figure 43. Structural comparison of compounds **57**, **88** and **90**



75

90, R = H
91, R = CH_3

Scheme 17. Synthesis of compounds **90** and **91**

The relative TOP1-targeting activities and the results of cellular assays of these benzo[*i*]phenanthridines in both RPMI8402 and P388, as well as their respective campothecin resistant variants, CPT-K5 and P388/CPT-45 are provided in Table 12-15. Five benzo[*i*]phenanthridine derivatives evaluated in this study, **74**, **83**, **84**, **88**, and **91**, had TOP1-targeting activity comparable to CPT. All of these compounds, however, were at least an order of magnitude less potent when evaluated for cytotoxic avtivity in RPMI8402 or P388 cells. Camptothecin resistant variants have been established for both of these cell lines. CPT-K5 is the variant of RPMI8402 cells, wherein a mutant form of TOP1 has been attributed to its camptothecin resistance. P388/CPT45 is the variant of P388. The lack of expression of TOP1 has been associated with the resistance to camptothecin relative to its parent cell. Cross-resistance to these cell lines by a cytotoxic agent is indicative of TOP1 as

Table 12. A comparison of 12-substituted compounds with one carbon side chain

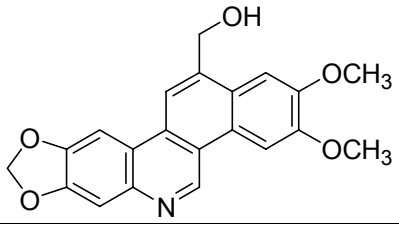
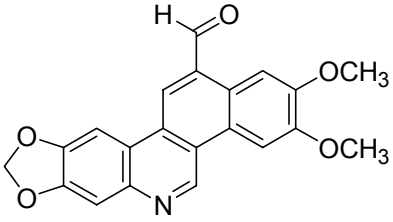
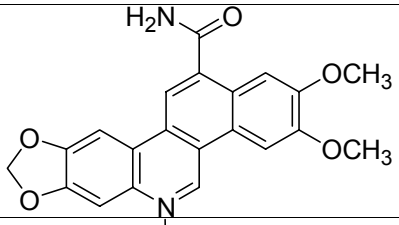
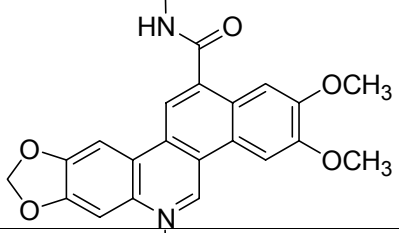
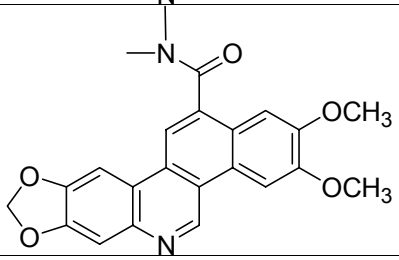
	Structure	TOP1-mediated cleavage	Cytotoxicity IC_{50} (μM)			
			RPMI 8402	CPT-K5	P388	P388/ CPT45
CPT		0.2	0.004	>10	0.004	>10
1		0.3	0.002	0.90	0.001	0.23
74		0.25	0.03	0.03	0.03	0.03
75		4.67	0.003	0.003	0.002	0.002
67		6.0	>10	1.2	>10	6.0
68		1.18	0.04	>10	0.03	0.3
69		1.13	0.6	>10	0.48	>10

Table 13. A comparison of 12-substituted compounds **76**, **81-84**

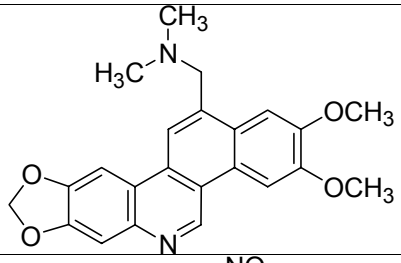
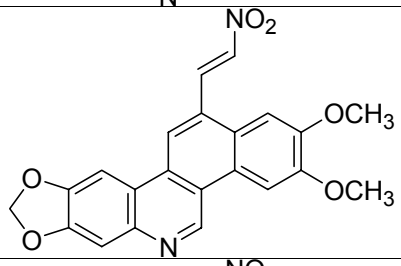
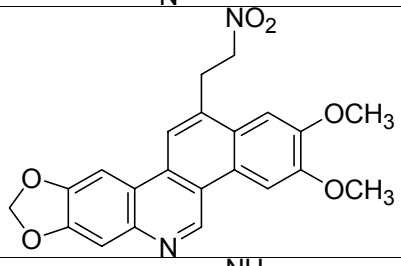
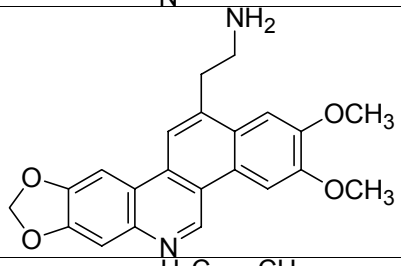
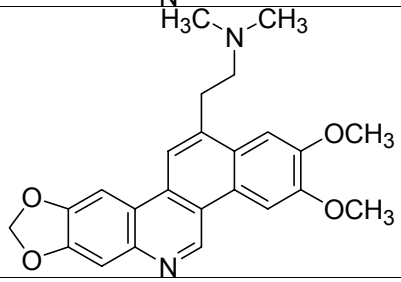
	Structure	TOP1-mediated cleavage	Cytotoxicity IC_{50} (μM)			
			RPMI 8402	CPT-K5	P388	P388/ CPT45
CPT		0.2	0.004	>10	0.004	>10
1		0.3	0.002	0.90	0.001	0.23
76		1.13	0.033	0.033	0.005	0.015
81		9.2	0.033	0.035	0.025	0.025
82		7.7	0.38	0.3	0.28	0.29
83		0.3	0.025	0.25	0.016	0.3
84		0.5	0.03	0.45	0.03	0.3

Table 14. A comparison of 12-substituted compounds with three or four carbon side chain

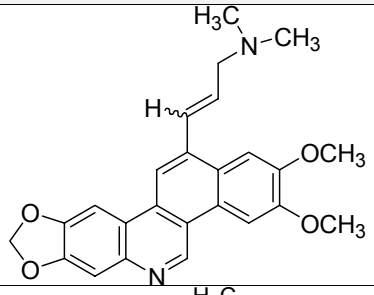
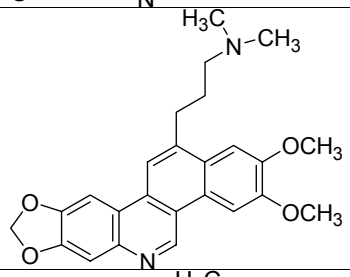
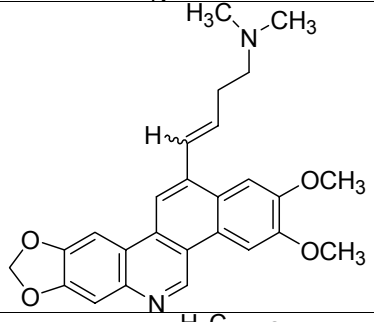
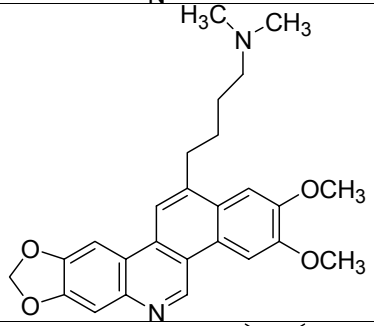
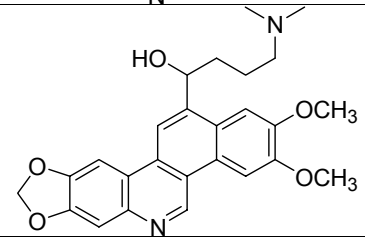
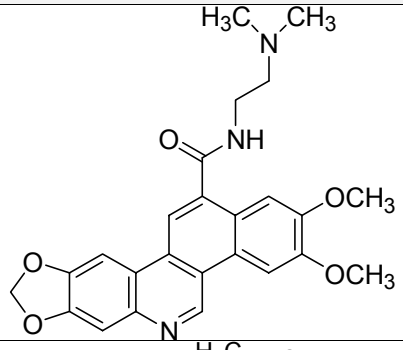
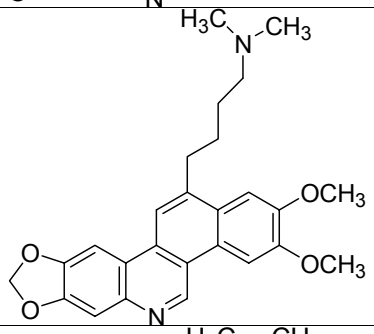
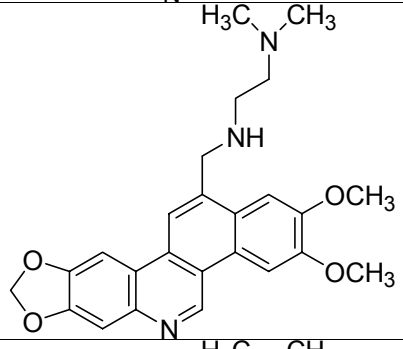
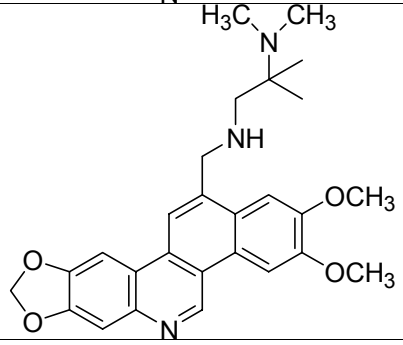
	Structure	TOP1-mediated cleavage	Cytotoxicity IC_{50} (μM)			
			RPMI 8402	CPT-K5	P388	P388/ CPT45
85		7.7	0.045	0.083	0.03	0.037
86		10	0.18	0.14	0.038	0.1
87		15.3	0.3	0.22	0.03	0.06
88		0.20	1	2.25	1.35	2.1
89		9.2	0.3	2.1	0.41	0.51

Table 15. A comparison of 12-substituted compounds **57**, **88**, **90** and **91**

	Structure	TOP1-mediated cleavage	Cytotoxicity IC_{50} (μM)			
			RPMI 8402	CPT-K5	P388	P388/ CPT45
57		0.1	0.003	1.0	0.003	0.32
88		0.20	1	2.25	1.35	2.1
90		1.87	0.024	0.03	0.02	0.024
91		0.44	0.02	0.03	0.012	0.016

a principal target associated with its cytotoxicity in the MTT assay. In marked contrast to **1** (ARC-111) as well as **57**, several of the benzo[*i*]phenanthridines in this study did not exhibit cross-resistance to these camptothecin-resistant cell lines. Only the 12-(2-aminoethyl) and the 12-[2-(*N,N*-dimethylamino)ethyl] derivatives, **82** and **84**, together with the 12-carboxamides **67-69** exhibited significant cross-resistance to both CPT-K5, as well as P388/CPT45 cells. It is of interest to note that all three 12-carboxamides clearly demonstrated significant cross-resistance to that previously observed with other 12-carboxamide derivatives. While **67-69** are not among the more potent TOP1-targeting agents, the comparative assay data clearly indicate that TOP1-targeting activity is associated with their activity in the MTT assay. Based upon the extent of DNA cleavage with a purified enzyme in the presence of these test compounds, several compounds, such as **74** and **88**, had similar potency to camptothecin as TOP1-targeting agents. The absence of significant cross-resistance with these cell lines, however, suggests that mechanisms other than TOP1-targeting activity are primarily responsible for MTT assay data for compounds **74-76, 81-82** and **85-91**. The MTT assay cannot distinguish between a cytotoxic response and a growth inhibitory response. As these substituted benzo[*i*]phenanthridines, unlike dibenzo[*c*,*h*][1,6]-naphthyridin-6-one derivatives, would tend to be planar molecules with an enhanced potential for intercalation into DNA, it is possible that their dominant effect could be to inhibit cell growth. Cytotoxic activity mediated by stabilization of the TOP1-DNA cleavable complex, therefore, could be masked by their ability to inhibit cell growth through DNA intercalation. The most potent of the benzo[*i*]phenahtridines evaluated in this study using the MTT assay is **75**, which had comparable weak TOP1-targeting activity.

Table 16. Relative cytotoxicity in cancer cell lines, KB3-1, KBV-1, and KBH5.0

Compd	Cytotoxicity IC_{50} (μM)		
	KB3-1	**KBV-1**	**KBH5.0**
CPT	**0.015**	**0.025**	**0.026**
1	0.005	0.005	0.006
57	0.005	0.22	0.06
74	0.045	0.075	0.08
75	0.004	0.016	0.019
76	0.03	0.17	0.06
81	0.03	1.78	0.04
82	0.3	0.44	0.49
83	0.05	0.5	0.2
84	0.025	0.08	0.07
67	1.2	>10	>10
68	0.031	0.1	0.08
69	0.6	0.7	0.38
85	0.16	0.37	0.29
86	0.04	0.5	0.18
87	0.32	0.4	0.32
88	0.4	4	0.95
89	0.17	1.9	0.55
90	0.025	0.027	0.038
91	0.02	0.03	0.04

The cytotoxicity data for KB3-1 cells along withn the variants KBV-1 and KBH5.0 are listed in Table 16. KBV-1 cells overexpress the efflux transporter MDR1, and KBH5.0 cells overexpress the efflux transporter BCRP. As was observed for **57**, several of these benzo[*i*]phenanthridine derivatives including **81**, **83**, **86**, **88** and **89** are substrates for MDR1. Unlike **57**, none of the compounds appear to be substrates for the BCRP efflux transporter.These data indicate that select 12-substituted 2,3-dimethyoxy-8,9-methylenedioxy-benzo[*i*]phenanthridine derivatives can have potent TOP1-targeting activity. Based upon TOP1-targeting activity and the results of our cellular assays, the 12-carboxamide and the 12-(2-aminoethyl) derivatives are among the more promising derivatives. Further studies are required to evaluate the efficacy of these various 12-substituted benzo[*i*]phenathridines as antitumor agents in laboratory animals.

2.5 11-Substituted Benzo[*i*]phenanthridines

ARC-111 and its reversed lactam analog, **56**, are potent TOP1 targeting agents. Compared with the lead compound benzo[*i*]phenanthridine, these two compounds not only add water soluble side chains, but had altered B-ring subsitutents and aromatic properties relative to similar A- and D-ring substituted benzo[*i*]phenanthridines. Studies on 12-position derivation of benzo[*i*]phenanthridines have identified 12-carboxamides as excellent drug candidates. The previous chapter in this paper also described synthesis and evaluation of 12-position simple aminoalkyl substituted compounds. Several potent TOP1 targeting agents in this series were dentified (see Chapter 2.4). It became apparent that 11-position substituted compounds could potentially possess similar pharmacologic activity.

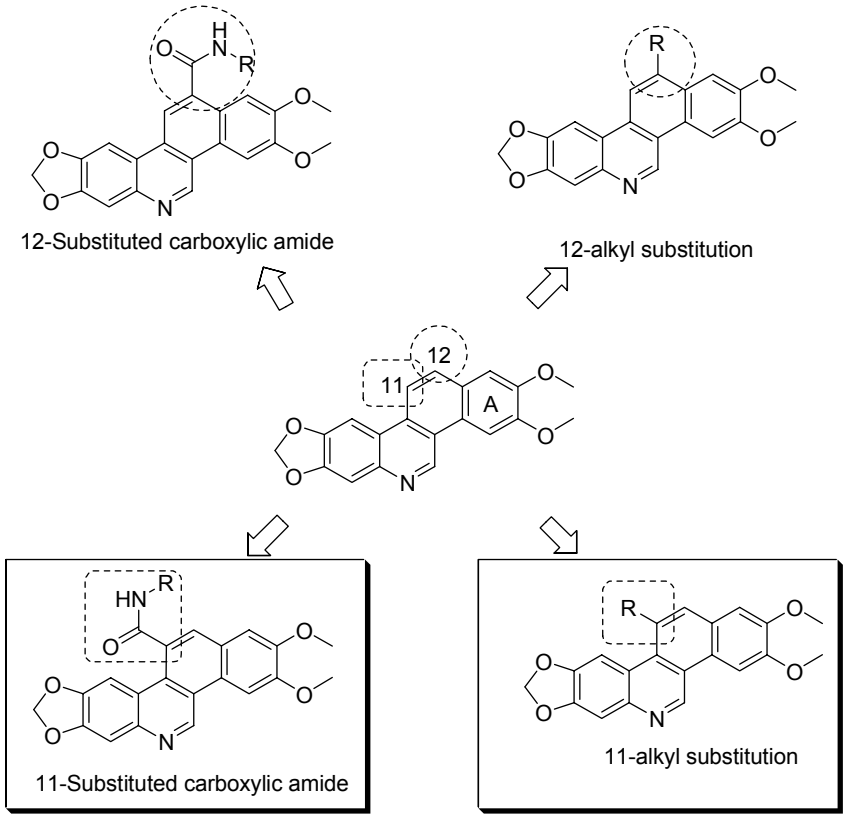


Figure 44. Target molecules from B-ring 11-position derivatives.

Like the relationship between reversed lactam **56** and ARC-111, the 11-position derivatives can be regarded as being sterically similar to ARC-111 with its 12-carboxamides and 12-aminoalkyl derivatives being sterically more similar to **56** (Figure 44). Since reversed lactam retained activity compared with ARC-111, 11-substituted compounds were expected to exhibit similar activity to 12-carboxamides and 12-aminoalkyl derivatives of benzo[*i*]phenathridine evaluated in previous studies.

The most obvious synthetic approach for 11-carboxamides was to simulate the synthetic route for 12-carboxamides, utilizing strategies such as condensation and photocyclization (Route A in Figure 45). Another promising approach depends on a Wittig reaction and subsequent oxidation of 11-methyl group. (Route B in Figure 45).

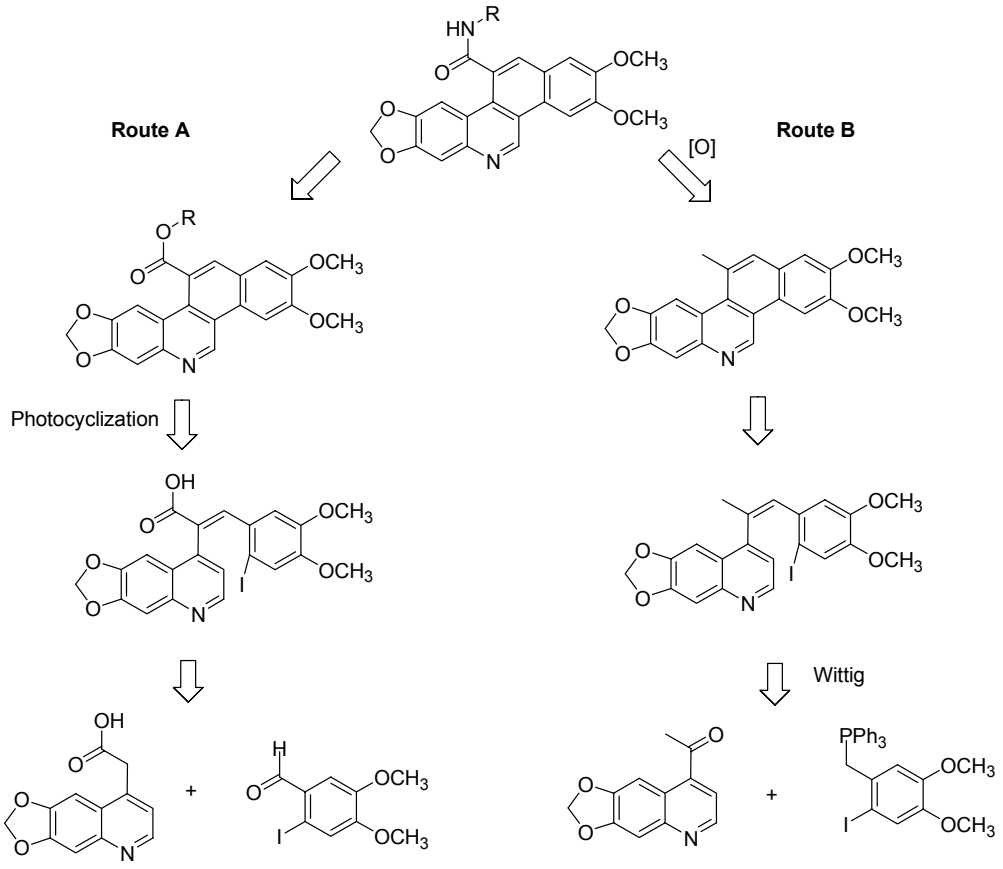


Figure 45. Retrosynthetic analysis of 11-substituted amides

For Route A, two condensation precursors were synthesized successfully. However, under condensation conditions, treatment of the carboxylic acid compound with the aldehyde resulted in a black mixture. The desired stilbene compound was not detected after work-up. Extensive studies associated changing condensation conditions turned out to be fruitless. This work was mainly preformed by Dr. Mohamod Hossen in our group.[190] Considering possible decarboxylation of compound **92**, an alternative condensation precursor **94** was synthesized.[191] Unfortunately, condensation reaction of **93** and **94** lead to a complex mixture (Figure 46).

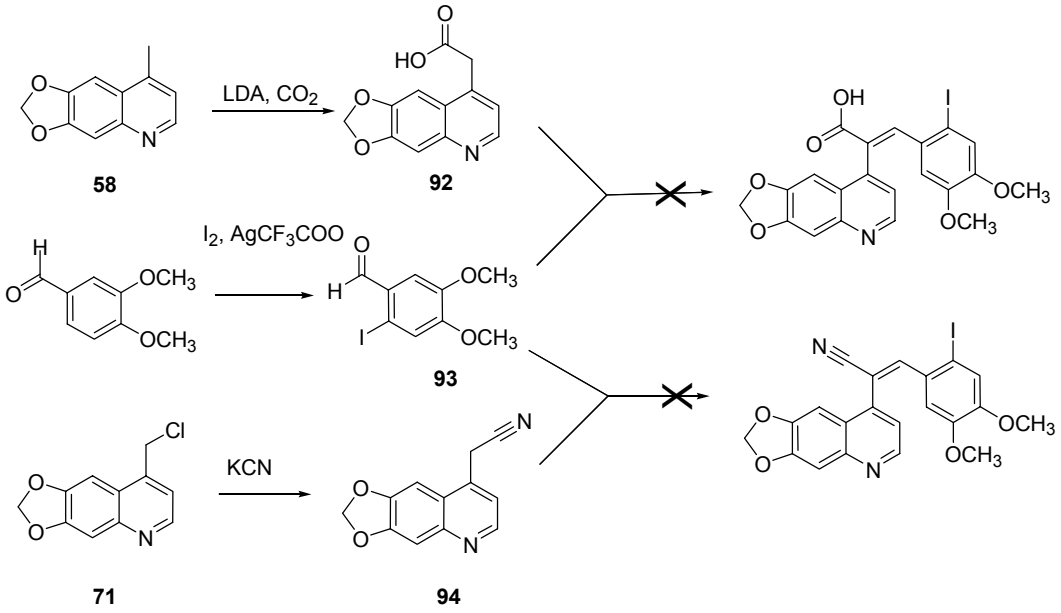
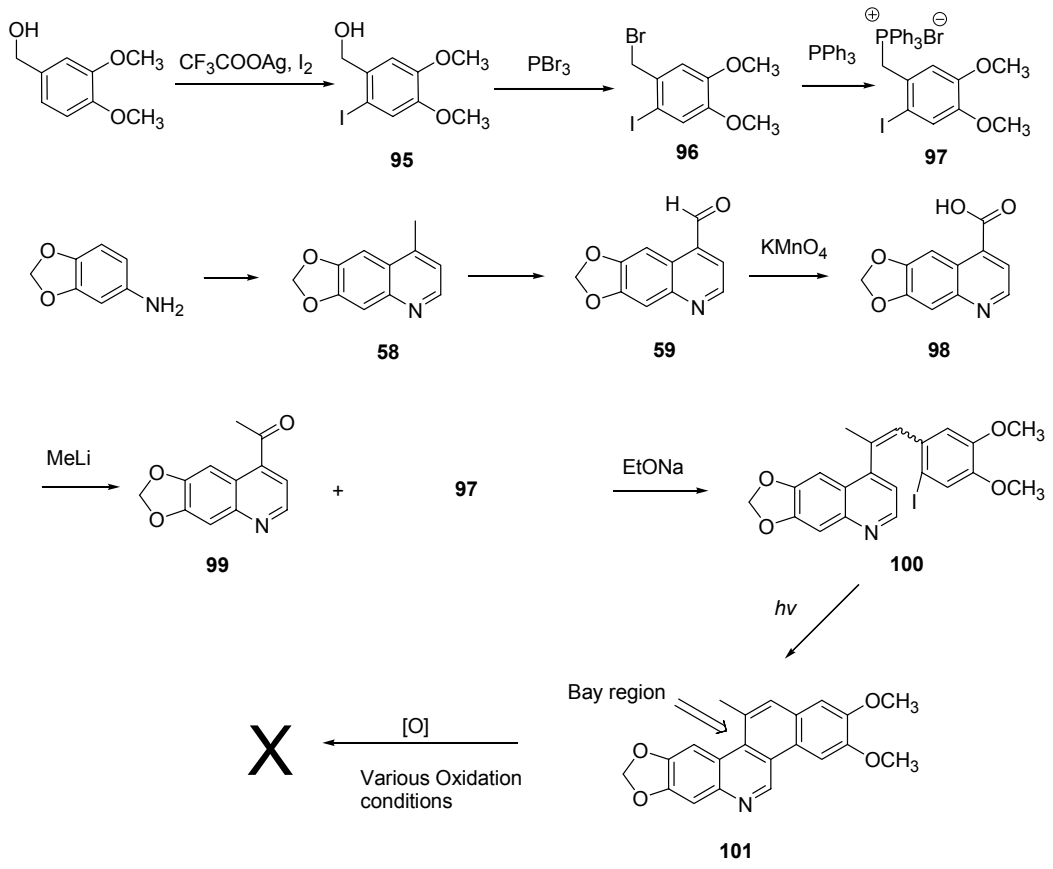


Figure 46. Attempts on synthesis of 11-carboxamide using condensation reaction

Another approach using the Wittig reaction gave stilbene compound **100** in excellent yield by condensation of **97** and **99**.[157] The photocyclization reaction was successfully carried out in photoreactor to give a methyl substituted product **101**.[157] Regretfully, the compound **101** was resistant to various oxidation conditions and starting material was recovered in most cases.[157] The location of the methyl group actually is within

the "bay" region,[192,193] which is hindered by surrounding atoms and tends to impede the reaction of ordinary oxidizing reagents. The synthetic scheme of compound **101** was first developed in our lab by Ms. Lisa Sharma.[157]



Scheme 18. Attempts on synthesis of 11-carboxamides via a Wittig reaction

The failure of 11-methyl group oxidation was assigned to steric hindrance. However, the success of the Wittig reaction and photocyclization encouraged us to further expand the reaction scope. We tried to synthesize appropriate ketone precursor with the desired side chain already installed. The synthesis of intermediate **102** became the new focus of our research (Figure 47).

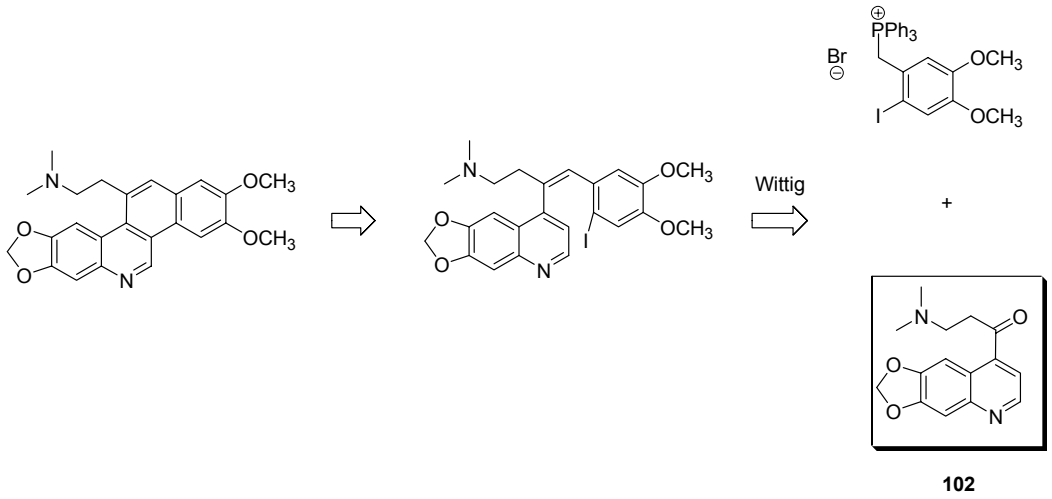


Figure 47. Retrosynthetic analysis of 12-aminoethyl benzo[*i*]phenanthridine

The preparation of compound **102** turned out challenging. A Mannich reaction involving three components, compound **99**, paraformaldehyde, and dimethylamine, did not yield the desired compound (Figure 48). Most of starting material **99** was recovered intact.

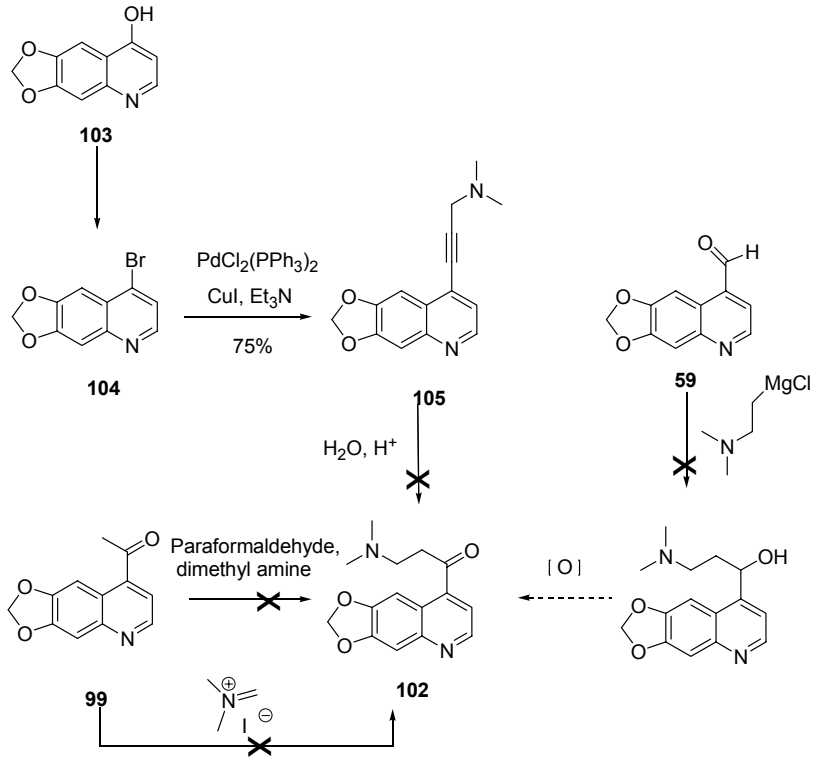
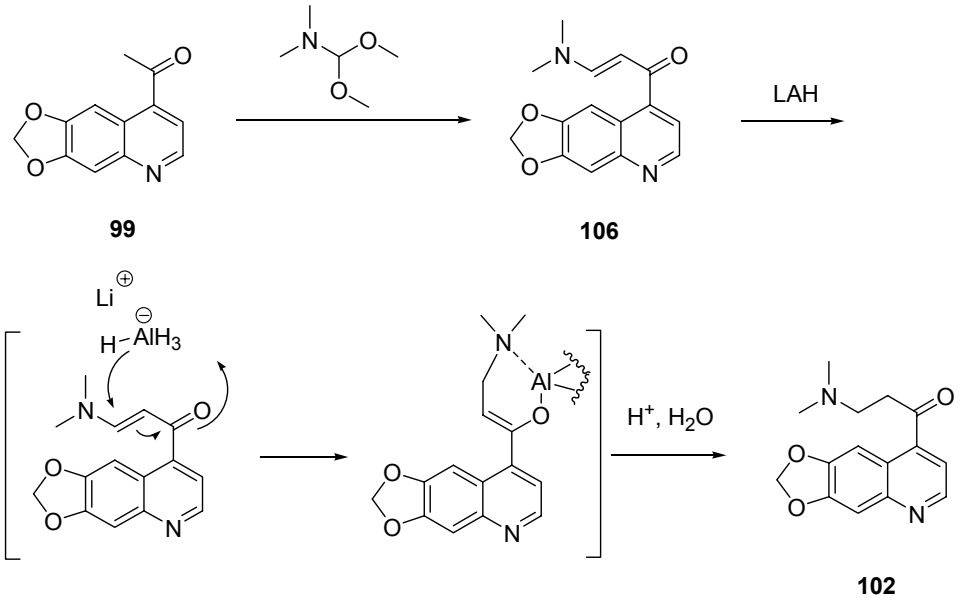


Figure 48. Attempts on preparation of compound **102**

Treatment of **99** with Eshermoser's salt[194], however, resulted in decomposition of the starting material, either with acid or without acid participated. Reaction of aldehyde with freshly prepared Gringard reagent failed to generate the alcohol. The failure of the addition reaction may be due to instability of the Gringnard reagent.[195] [195] Sonogashira reaction smoothly coupled dimethyl-prop-2-ynyl-amine with bromoquinoline to give **105** (Figure 48).[196] Attempts to subsequently oxidize **105** as a means of forming **102** were unsuccessful.[197]

The successful preparation of compound **102** was finally achieved by a two step synthesis from ketone **99** as outlined in Scheme 19. A condensation reaction of ketone **99**

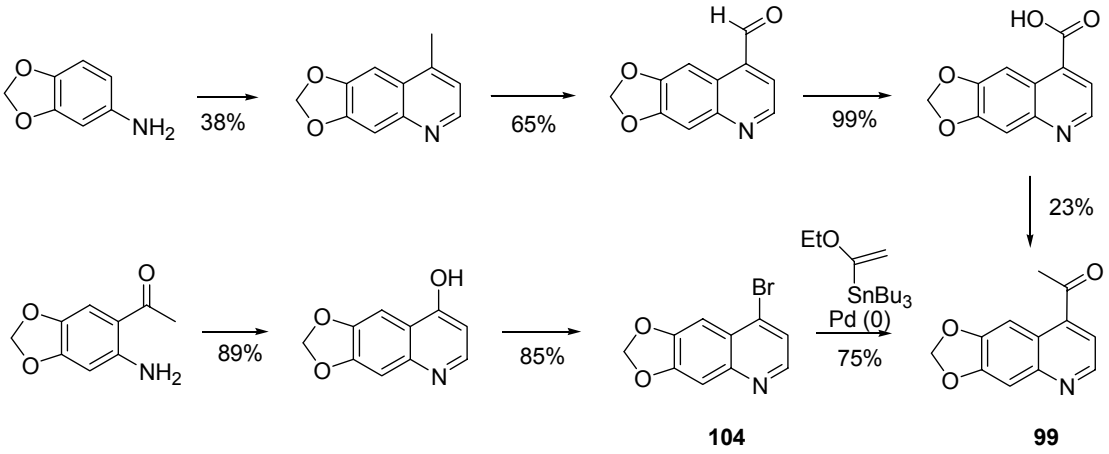


Scheme 19. Preparation of compound **102** by a two step synthesis

and dimethoxymethyl dimethylamine cleanly afforded unsaturated ketone **106**.[198] Reduction of **106** was carried out in THF using LAH as reducing reagent.[199] Interestingly, LAH usually reduces unsaturated ketone to alcohol as final product. But in this case, an intra-molecular chelating complex of Aluminum can be formed due to stabilization by

amino group. This complex was stable enough until reaction was quenched. The enol form of the compound **102** then hydrolyzed to ketone (Scheme 19).[199,200]

An improved synthesis of compound **99** was also discovered. The bromide compound **104** can be conveniently synthesized from 4-hydroxyquinoline in good yield.[201] The Stille[202] coupling of commercially available tributyl(1-ethoxyvinyl)stannane with bromoquinoline efficiently furnished the synthesis of **99** with a total yield of 54%.[203] In contrast, initial synthesis of the ketone has an overall yield of 5.6%.



Scheme 20. An improved synthesis of 4-acetylquinoline **99**

From benzyl bromide **96**, the triphenyl-phosphonium bromide **97** was synthesized as reported (Figure 49). To a solution of **97**, NaOEt was added and an orange solution was observed. A solution of compound **102** was then added to above solution. To our disappointment, compound **102** quickly discomposed once treated with ylide. The other starting material **97** remained as the only separable compound. It was later found that **102** is thermally instable and decomposes to release dimethylamine under such conditions. Use of *t*-BuOK did not improve the reaction. A modified Wittig precursor compound **107** was prepared via Arbuzov reaction.[204,205] Treatment of compound **107** with *n*-BuLi at -78 ºC yielded a yellow yilide solution. However, reaction of this solution with **102** again leaded

to a complex mixture. The unexpected instability of compound **102** under basic reaction condition blocked our attempts on preparation of 11-substituted benzo[*i*]phenanthridines using Wittig reaction (Figure 49).

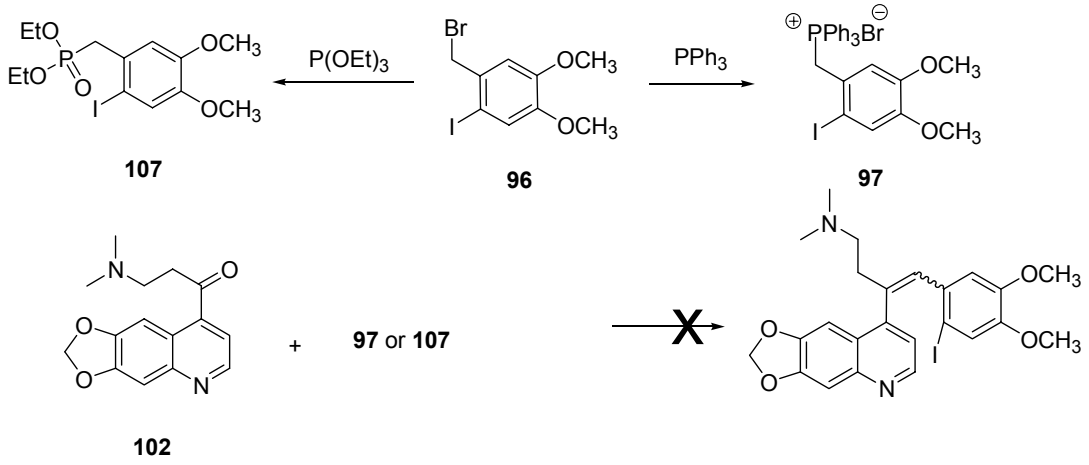


Figure 49. Failed attempts on Wittig reactions with **102** and ylide

The instability of compound **102** may due to its β-amino group. Therefore, compound **111** was designed as a more stable precursor for the Wittig reaction (Figure 50). Mono hydroxyl protection of propanediol gave **108** in good yield.[206] Oxidation of alcohol to aldehyde **109** using Swern condition worked smoothly.[207,208] Lithiation of bromoquinoline followed by addition to **109** yielded **110** cleanly. Oxidation of alcohol to the ketone successfully afforded compound **111**. However, the Wittig reaction again failed to form the desired compound. The reaction mixture color quickly changed to brown-black from orange and there was no product that could be isolated.

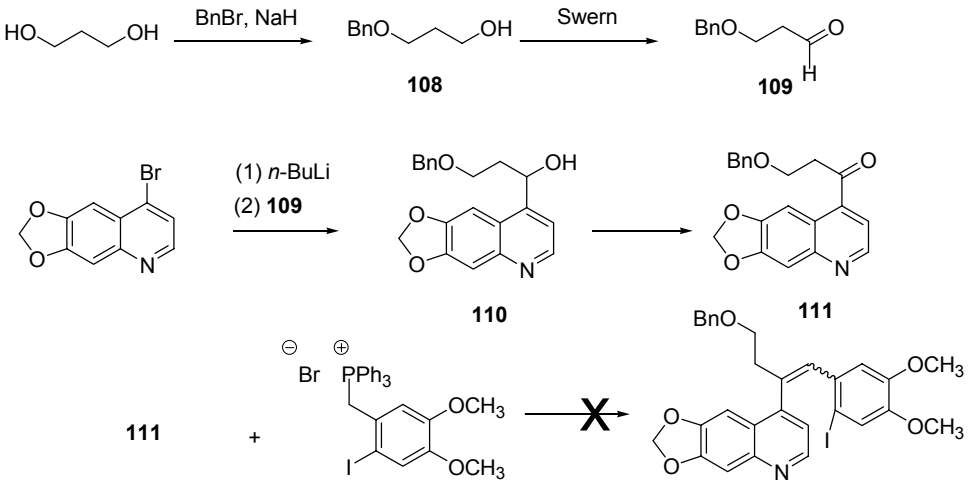


Figure 50. Failed attempts on Wittig reactions with **111** and yilide

Neither of the previously proposed synthetic routes was successful method for the preparation of the desired 11-substituted benzo[*i*]phenanthridines. We started to look for other synthetic approaches. Several successful coupling reactions encouraged us to revisit the palladium-mediated reactions. The improved synthesis of **102** benefited from an efficient Stille coupling reaction. Another successful palladium coupling, Sonogashira reaction, was applied in the synthesis of **105**. It was also reported that 4-bromoquinoline is a good substrate for the Buchwald reaction.[209,210] Although oxidative insertion[211,212] of palladium is usually favored in electron rich systems, 4-bromoquinoline did undergo oxidative insertion facilely. A synthetic approach to the desired 11-substituted benzo[*i*]phenanthridines utilizing Stille coupling reaction was explored.

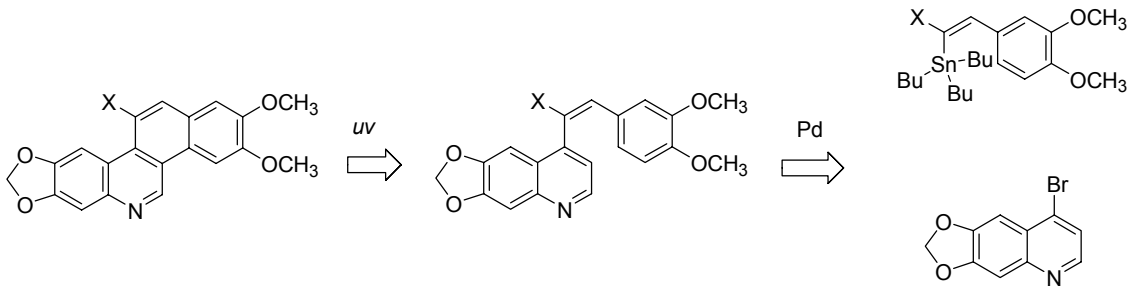
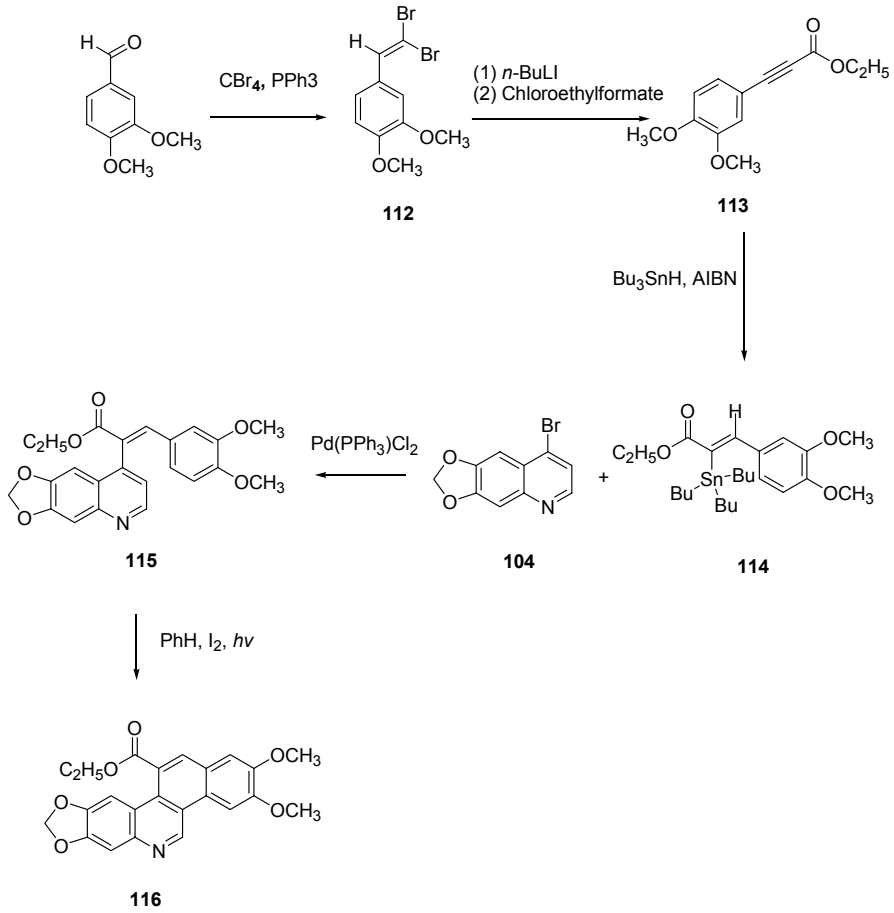


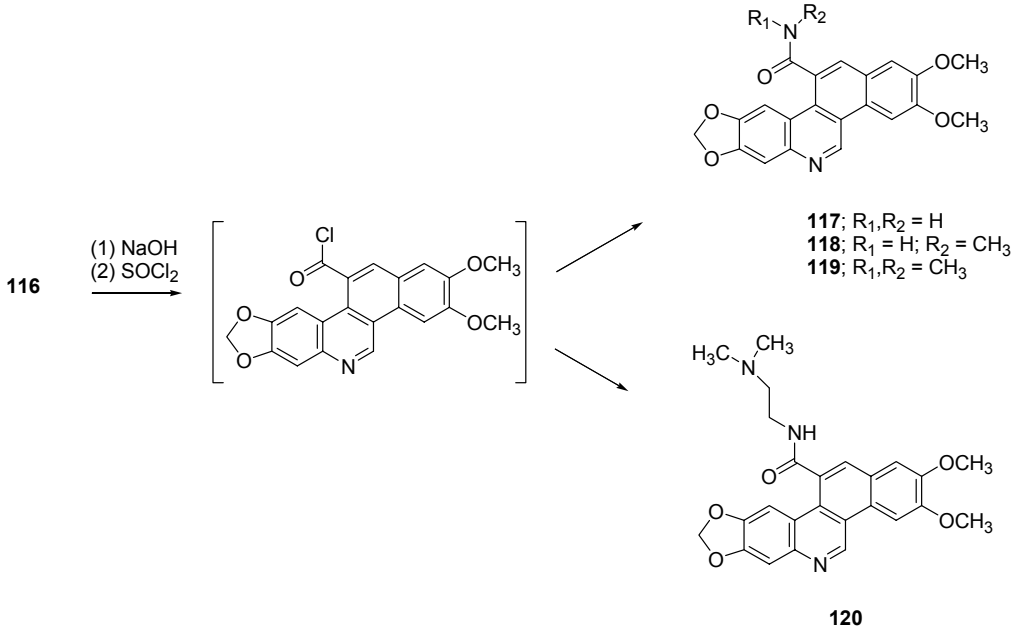
Figure 51. Proposed synthesis utilizing Stille coupling

The key intermediate used for the preparation of 11-substituted 2,3-dimethoxy-8,9-methylenedioxybenzo[*i*]phenanthridines was the 11-ethoxycarbonyl derivative, **114**. The methodology employed for the synthesis of this intermediate is outlined in Scheme 21. Ethyl 3-(3,4-dimethoxyphenyl)propynoate **113** was synthesized from 3,4-dimethoxybenzaldehyde via dibromolefin **112** using Corey's procedure. [213,214] Hydrostannation of **113** was accomplished by Bu_3SnH in the presence of AIBN to give (*Z*)-vinylstannane **114** stereoselectively.[215] The Stille cross-coupling reaction of the resulting vinylstannane **114** with bromoquinoline **104** proceeded smoothly to afford compound **115** in good yield.[216] Photocyclization of **115** in the presence of a catalytic amount of iodide resulted in the formation of **116** in 35% yield.[217]



Scheme 21. Synthesis of compound **116**

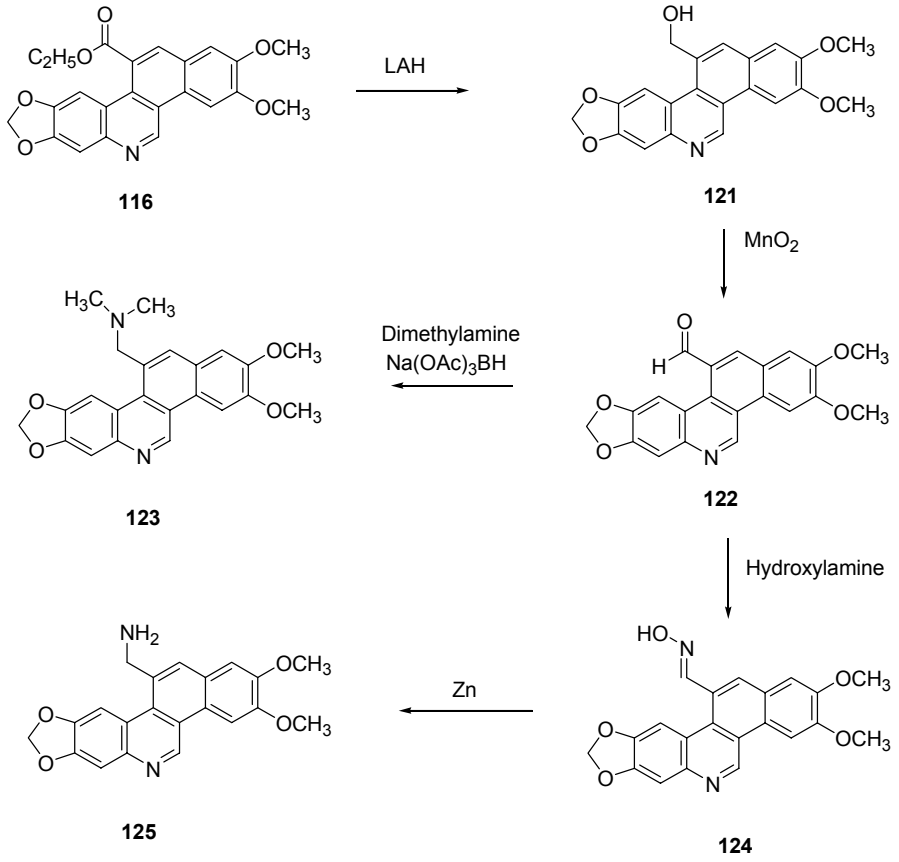
The 11-ethoxycarbonyl derivative **116** was subject to basic hydrolysis conditions in aqueous ethanol and the product carboxylic acid was converted to its acid chloride using thionyl chloride. This acid chloride was then used without further purification for the formation of a series of 11-carboxamides. These included the primary carboxamide, the *N*-methylcarboxamide, and the *N, N*-dimethylcarboxamide, **117-119**. Treatment of the acid chloride with *N, N*-dimethylaminoethylenediamine resulted in the formation of *N*-[(2-*N,N*-dimethylamino)ethyl]carboxamide **120** (Scheme 22).



Scheme 22. Synthesis of benzo[*i*]phenanthridine 11-carboxamides

The preparation of 11-aminomethyl- and 11-N,N-dimethylaminomethyl-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*]phenanthridine, **125** and **123** was accomplished as outlined in Scheme 23. Reduction of ethyl ester **116** to its hydroxymethyl derivative **121** was accomplished using lithium aluminiumhydride in THF. Oxidation of the hydroxymethyl group with MnO_2 resulted in the formation of the 11-formyl derivative **122**. Reductive amination using dimethylamine followed by treatment with sodium triacetoxyborohydride gave **123** cleanly. Reductive amination with ammonium acetate,

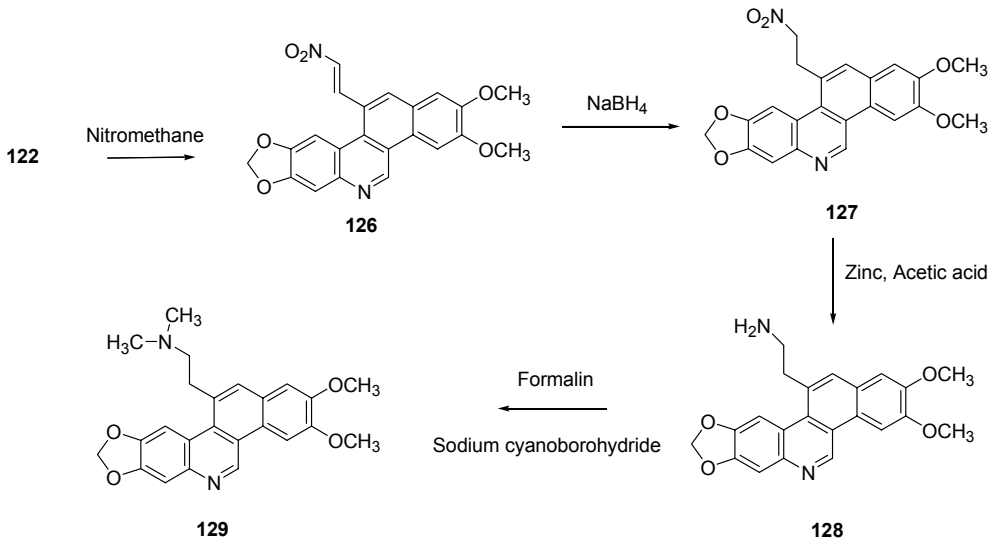
however, affored a very low yield of compound **125**. Condensation of hydroxylamine and aldehyde **122** give compound **124** smoothly.[218] Without further purification compound **124** was treated with zinc powder in the presence of ammonium formate.[219] The synthesis of **125** from reduction of compound **124** was much cleaner than direct reductive amination from compound **122**.



Scheme 23. Synthesis of **123** and **125**

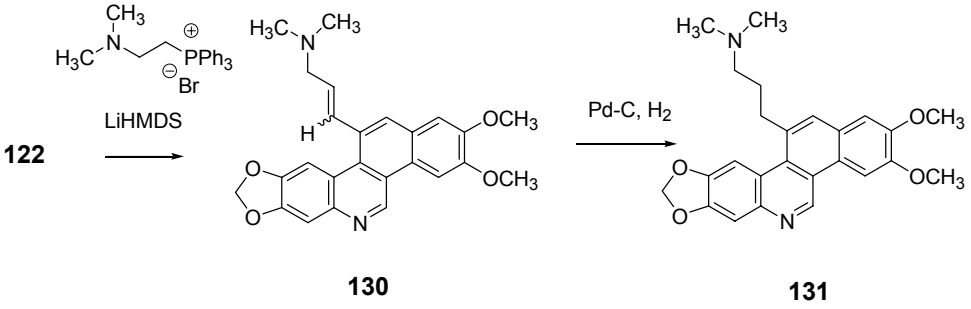
The preparation of the 11-(2-aminoethyl)- and 11-[(2-*N,N*-dimethylamino)ethyl]-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*]phenanthridine **128** and **129** are outlined in Scheme 24. Condensation of 11-formyl derivative **122** with nitromethane provided 2-nitroethylene derivative **126**, which could be reduced to the 11-(2-nitroethyl)-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*]phenanthridine **127**. In presence of zinc in acetic

acid, the nitro group was reduced to give **128**. Reductive methylation using formalin in the presence of sodium cyanoborohydride provided the N,N-dimethyl derivative, **129**.



Scheme 24. Synthesis of **128** and **129**

The synthetic approach used in the preparation of 11-[3-(*N,N*-dimethylamino)propyl)]2,3-dimethoxy-8,9-methylenedioxybenzo[*i*]phenanthridine **19** is outlined in Scheme 25. A solution of formyl intermediate **122** in THF was added to a mixture of 2-(dimethylamino)ethyltriphenylphosphonium bromide and LiHMDS in THF. The resulting product **130** was reduced to the propyl derivative **131** using hydrogen and 10% Pd-C.



Scheme 25. Synthesis of **130** and **131**

The intrinsic TOP1-targeting activities of the various 11-substituted 2,3-dimethoxy-8,9-methyeledioxybenzo[*i*]phenanthridines that were synthesized are summarized in Table 17-19.

With the exception of the 11-(2-hydroxymethyl), the 11-[2-(N,N-dimethylamino)ethyl], and the 11-[2-N,N-dimethylethyl)aminocarboxy] derivatives, **121**, **129**, and **120**, none of the other compounds evaluated had comparable TOP1-targeting activity to CPT or ARC-111.

As had been previously observed with 12-carboxyester derivatives of 2,3-dimethoxy-8,9-methyeledioxybenzo[*i*]phenanthridines, **116** did not exhibit significant TOP1-targeting activity. This is in contrast to the 11-hydroxymethyl and formyl derivatives, **121** and **122**. Similar TOP1-targeting activity to that of **122** was observed for both the 11-aminomethyl and 11-(*N,N*-dimethylamino)methyl derivatives, **125** and **123**.

The nitro precursor compounds **126** and **127** proved to be much less active as TOP1-targeting agents than the primary or tertiary amino derivatives, **128** and **129**, respectively. The 11-[3-(N,N-dimethylaminopropyl)] derivative **131** was also much more potent as a TOP1-targeting agent than its 1-propenyl precursor, **130**.

A slight decrease in TOP1-activity was observed among the 11-carboxamide derivatives with the addition of N-methyl substituents to the primary carboxamide **117**. A significant increase in TOP1-targeting activity was observed among these carboxamides in the case of the 11-[(2-N,N-dimethylamino)ethylamino]carboxy derivative **120**.

Table 17. A comparison of 11-substituted carboxylic derivatives

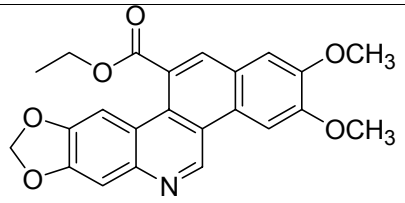
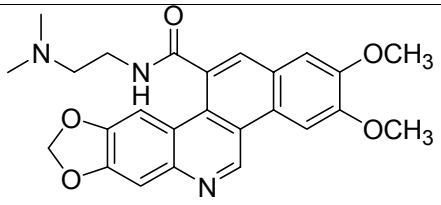
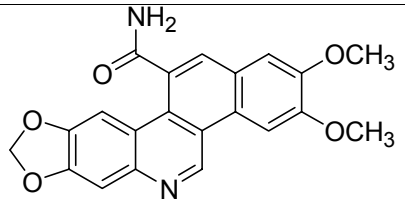
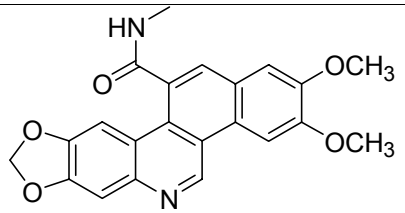
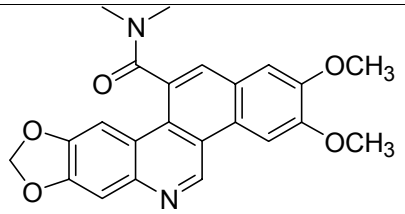
	Structure	TOP1-mediated cleavage	Cytotoxicity IC_{50} (μM)			
			RPMI 8402	CPT-K5	P388	P388/ CPT45
CPT		0.2	0.004	>10	0.004	>10
1		0.3	0.002	0.90	0.001	0.23
57		0.1	.003	1.0	0.003	0.32
116		>10	10	>10	4	>10
120		0.2	0.035	0.63	0.015	0.26
117		1.1	0.14	>10	0.035	>10
118		0.84	0.28	>10	0.025	>10
119		>10	1.6	>10	0.98	>10

Table 18. A comparison of 11-substituted compounds

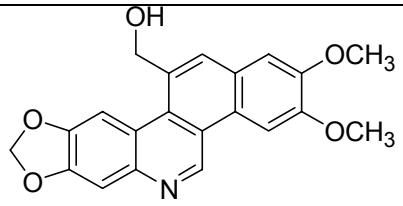
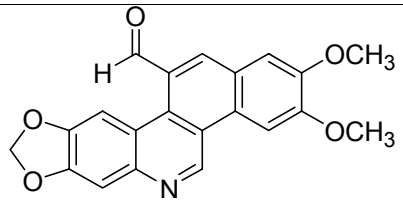
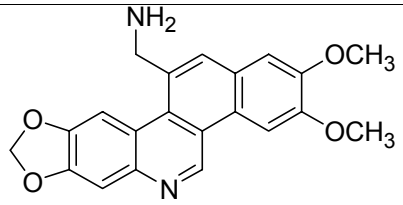
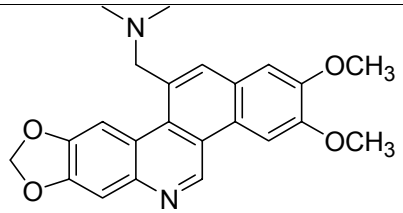
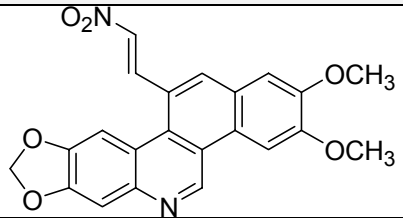
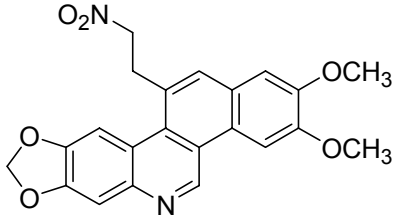
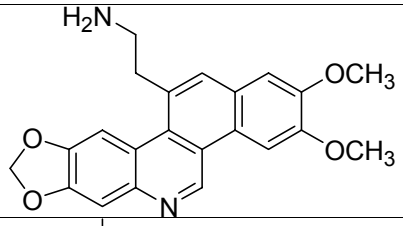
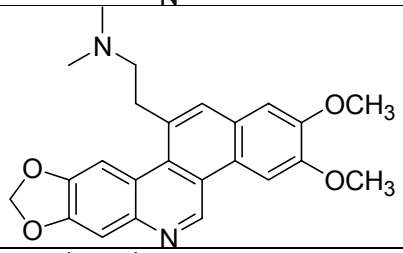
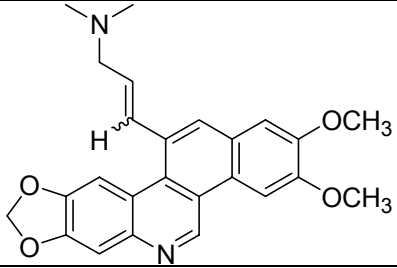
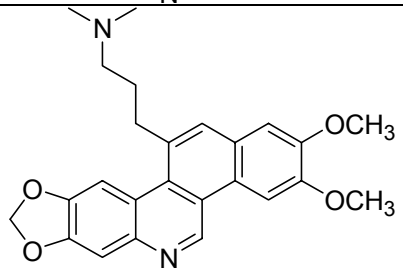
	Structure	TOP1-mediated cleavage	Cytotoxicity IC_{50} (μM)			
			RPMI 8402	CPT-K5	P388	P388/ CPT45
CPT		0.2	0.004	>10	0.004	>10
1		0.3	0.002	0.90	0.001	0.23
121		0.2	0.12	>10	0.06	>10
122		0.8	0.1	>10	0.12	10
125		0.2	0.08	1.6	0.022	0.3
123		0.2	0.1*	2.3*	0.1*	2.1*

Table 19. A comparison of 12-alkyl substituted compounds

	Structure	TOP1-mediated cleavage	Cytotoxicity IC_{50} (μM)			
			RPMI 8402	CPT-K5	P388	P388/ CPT45
126		>10	0.55	>10	0.18	10
127		>10	0.06	>10	0.07	>10
128		1.0	0.032	0.2	0.014	0.18
129		0.42	0.02	0.33	0.015	0.18
130		>10	0.035	0.35	0.04	0.35
131		0.77	0.06	0.29	0.04	0.2

The relative cytotoxic activities of these 11-substituted 2,3-dimethoxy-8,9-methyeledioxybenzo[*i*]phenanthridines in RPMI8402 and P388 cells, as well as their camptothecin-resistant variants, CPT-K5 and P388/CPT-45 are also provided in Table 17-19. The very weak cytotoxic activity observed with **116** is likely associated with its limited aqueous solubility and its potential for hydrolysis to the carboxylic acid. The relative cytotoxicity of **121** and **122** in RPMI8402 and P388 was lower than would be anticipated on the basis of their TOP1-targeting activity. Their limited aqueous solubility could also have influenced their activity in these assays. The cross-resistance observed in both CPT-K5 and P388/CPT-45 clearly indicates that TOP1-targeting is the major mechanism associated with their cytotoxic activity.

The methylamino derivatives **125** and **123** had improved cytotoxicity relative to **121** and **122**. While both **125** and **123** did exhibit cross-resistance to the CPT-resistance cell lines, it is of interest to note that these differences were less distinct than for **121** and **122**. The unsaturated nitro derivative **126** was less cytotoxic than saturated analog **127**. It is possible that the more rigid conformation associated with the *cis* and *trans* isomers of **126** may be less favorable. Both **126** and **127** did exhibit significant cross-resistance in the CPT-resistant cell lines despite comparatively weak intrinsic TOP1-targeting activity. The primary and tertiary 11-[2-aminoethyl] derivatives **128** and **129** were among the more cytotoxic 11-substituted benzo[i]phenanthridine derivatives that were evaluated. While both **128** and **129** did exhibit cross-resistance to the CPT-resistance cell lines, it is of interest to note, like the aminomethyl derivatives **125** and **123**, the differences were less distinct that those observed with other derivatives. While the 11-[3-dimethylaminoprop-1-enyl] derivative **130** was much less potent than

11-[3-(dimethylamino)propyl] derivative **131** as a TOP1-targeting agent, these compounds did exhibit similar cytotoxic activity with IC_{50} values ranging from 35-60 nM.

The conversion of the primary carboxamide **117** to its secondary carboxamide **118** by the addition of a *N*-methyl substituent did not adversely affect cytotoxic activity. A consistent decrease in cytotoxicity was noted when **118** was converted into its tertiary amide **119**.

A significant increase in cytotoxic activity was observed with the 11-[(2-dimethylamino)ethylamino]carboxy derivative **120**, which is consistent with it having the most potent TOP1-targeting activity among these carboxamides.

The cytotoxity of these 11-substituted benzo[*i*]phenanthridines in KB3-1 cells and for the variants KBV-1 and KBH5.0 are listed in Table 20. The data provided in Table 20 indicate that **128**, **130**, and **131** are substrates for the MDR1 efflux transporter.

The primary carboxamide **117** is the only compound that proved to be a good substrate for the BCRP efflux transporter. In addition, this compound also appears to be a weak substrate for the MDR1 transporter. The 11-[(2-dimethylamino)ethylamino]carboxy derivative **120** does appear to be a weak substrate for the BCRP efflux transporter.

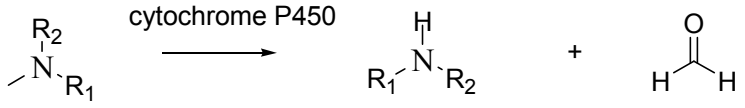
These data suggest, in the case of 11-aminoalkyl benzo[*i*]phenanthridine derivatives, that the length of the alkyl linker, as well as the degree to which the amino group is substituted, can influence their potential to serve as substrates for the MDR1-efflux transporter. In addition, subtle changes to carboxamide of 11-aminocarboxy benzo[*i*]phenanthridine derivatives did influence their potential to serve as substrates for the BCRP efflux transporter.

Table 20. Relative cytotoxicity in cancer cell lines, KB3-1, KBV-1, and KBH5.0

	Cytotoxicity IC_{50} (μM)		
	KB3-1	**KBV-1**	**KBH5.0**
1	0.005	0.005	0.006
57	0.005	0.22	0.06
116	>10	>10	>10
121	0.15	0.4	0.4
122	0.13	0.3	0.29
125	0.03*	0.1*	0.2*
123	0.06*	0.25*	0.28*
126	0.18	0.45	0.42
127	0.15	0.36	0.32
128	0.02	0.5	0.11
129	0.021	0.06	0.04
130	0.03	0.33	0.07
131	0.035	0.4	0.13
117	0.055	0.4	2.7
118	0.23	0.42	0.48
119	1.2	4.0	3.6
120	0.027	1.4	0.2

2.6 Synthesis, Evaluation and Comparison of α,α-Dimethyl ARC-111 Analogs

Biotransformation reactions during drug metabolism often convert drugs into more readily excreted polar compounds.[220-222] These metabolites may or may not retain the initial activity of the drug, although in most cases the metabolism pathway leads to inactivation or more rapid elimination of the drug. The metabolic rate of drug, therefore, directly influences their duration and intensity of action.[220] The functionality transformations catalyzed by metabolic enzyme systems can be categorized into two phases of reactions; phase I reactions (also known as nonsynthetic reactions) and phase II reactions (also termed conjugation reactions).[220,221] Phase I reactions usually convert the parent drug into a more polar metabolite by introducing or unmasking a functional group (-OH, -NH_2, -SH). Phase II reactions, following phase I reaction, combine glucuronic acid, sulfuric acid, acetic acid, or other polar molecules with the newly established functional group to form a highly polar conjugate.[220,221] Figure 53 shows two common metabolic reactions, *N*-dealkylation by cytochrome P450[223] and deamination by amine oxidase.[224] The anticipated metabolic pathway of ARC-111 can be envisioned to result in several suspect metabolites (Figure 54; see section **2.3** for syntheses for ARC-111metabolites).



$$RCH_2NH_2 + O_2 + H_2O \xrightarrow{\text{amine oxidase}} RCHO + H_2O_2 + NH_3$$

Figure 53. Demethylation and deamination mechanism in metabolism

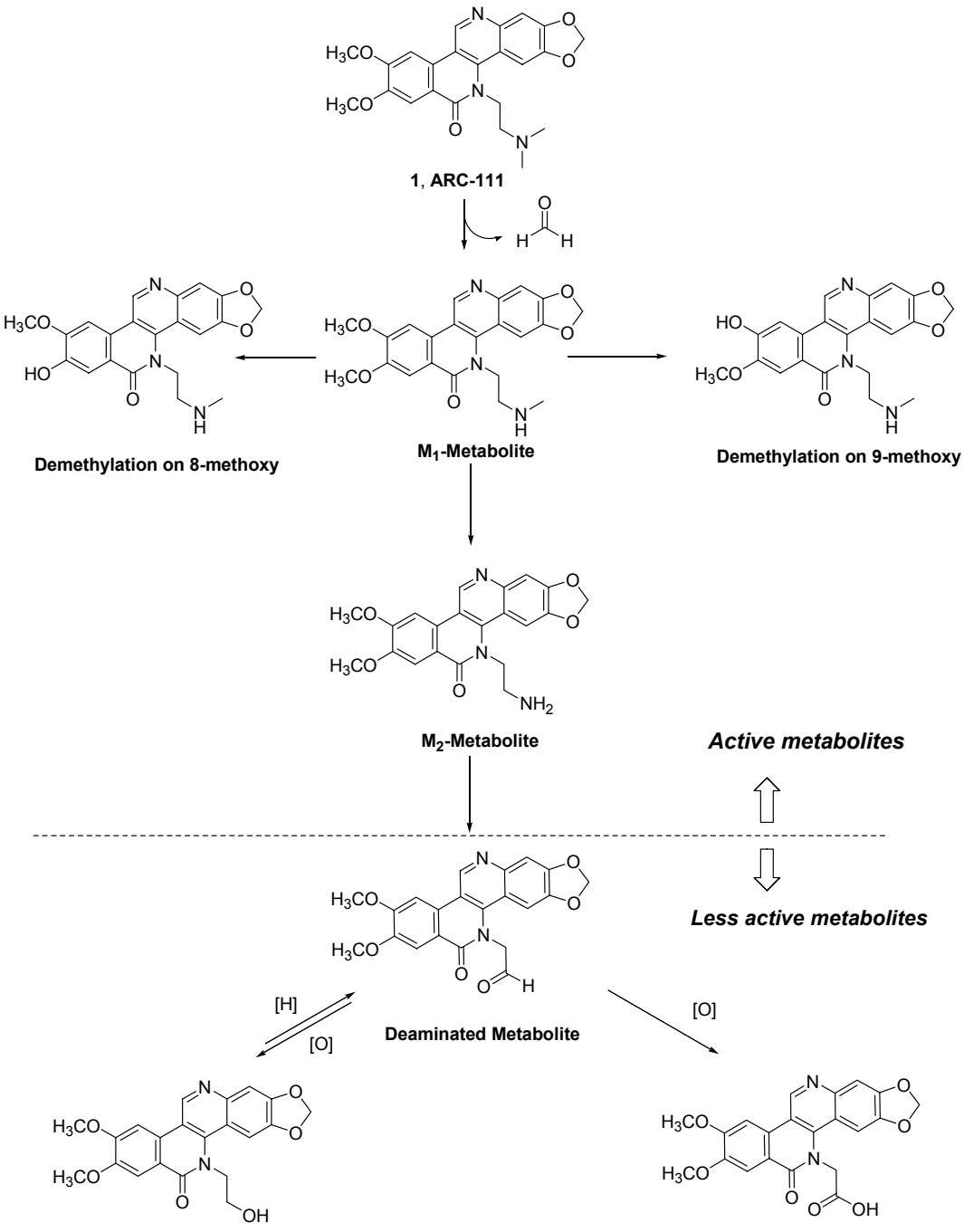


Figure 54. Suspect metabolites in the metabolism pathway of ARC-111

A common structural feature of ARC-111, its reversed lactam, as well as 11- and 12-carboxamides of benzo[i]phenathridine is a (2-*N,N*,-dimethylamino)ethyl substituent as shown in Figure 55. By addition of two methyl groups to the α-position of the terminal amine, the amino group becomes more hindered and less susceptible to metabolic enzymes.

Moreover, even after the tertiary amine is dealkylated to a primary amine, the deamination would be blocked as there are no available protons on the α-carbon. In other words, these α,α-dimethyl derivatives are likely to be relatively resistant to deamination *in vivo*.

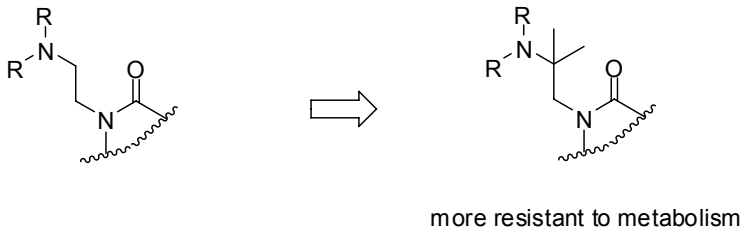
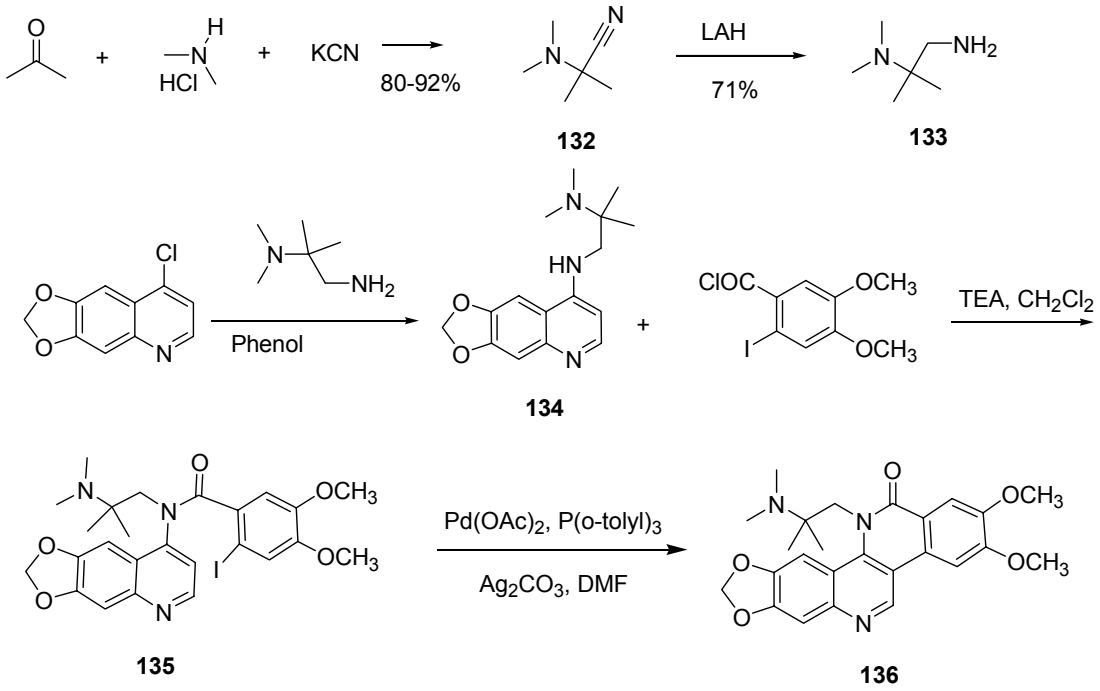


Figure 55. α,α-Dimethyls of amino group inhibit deamination metabolism

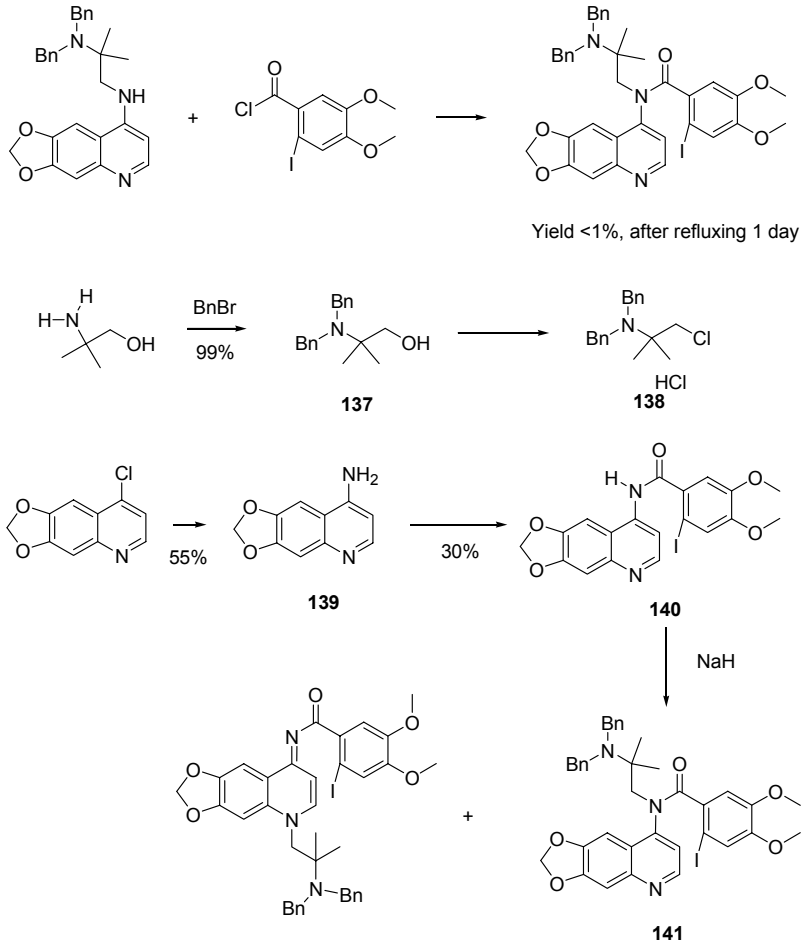
The preparation of **136** was performed as outlined in Scheme 26, using similar methodology as for ARC-111. A three component synthesis afforded nitrile derivative **132** in good yield.[224] Reduction of **132** using LAH produced required ethlyenediamine **133**.[225]



Scheme 26. Synthesis of compound **136**

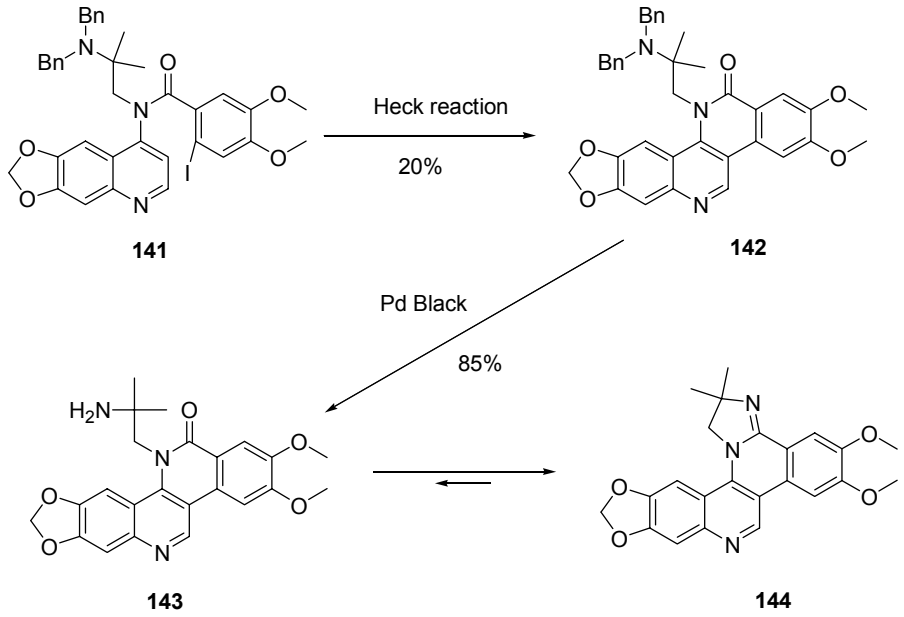
Acyl chloride was added directly to the solution of **134** and TEA in CH_2Cl_2. Intramolecular Heck cyclization of iodobenzamide **135** was performed in refluxing DMF for 2 hours to afford **136** in good yield.

The traditional synthetic approach failed to prepare **141**, the intermediate for making a primary amine analog of **136.** As shown in Scheme 27, the amidation reaction did not work well for the synthesis of **141**, probably due to steric effect. An alternative procedure afforded amide **140** in moderate yield from 4-aminoquinoline. The alkylation of



Scheme 27. An alternative synthetic scheme for **141**

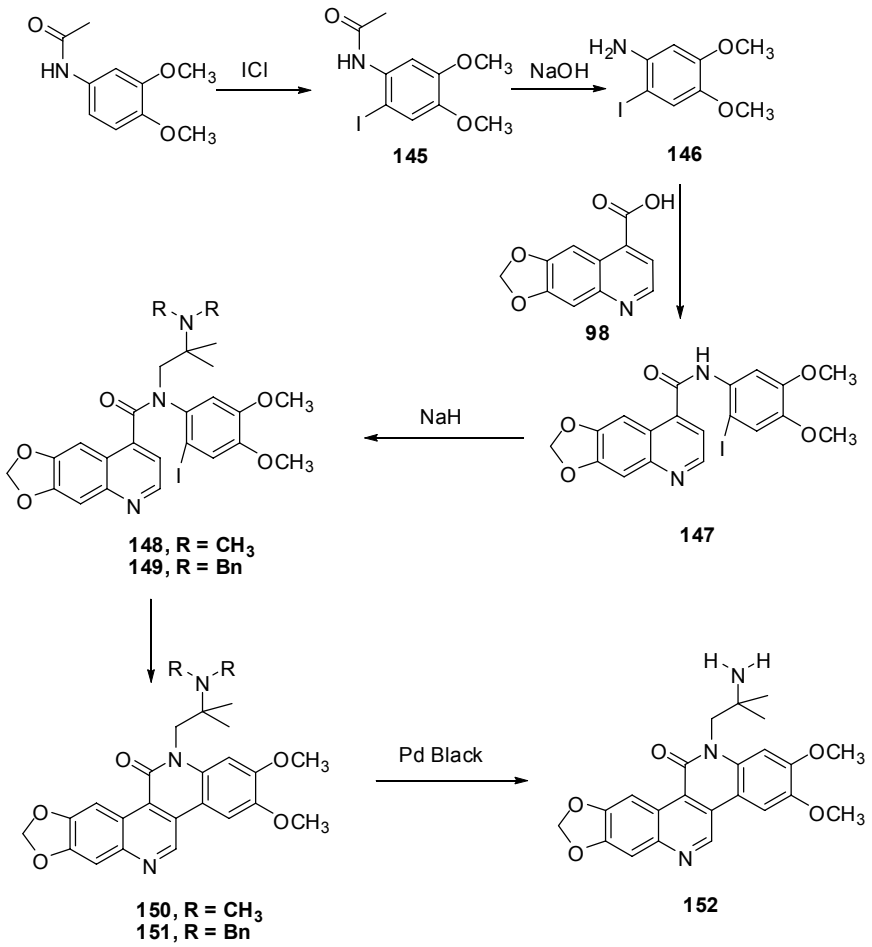
the amide nitrogen was carried out in DMF using NaH as a base to eventually give **141**. The by-product isolated was a 1-quinolyl substitution product. Similar by-pruducts were observed previously by other researchers.[123] Heck cyclization of compound **141** provided compound **142**, which was reduced to remove the protecting group. Interestingly, the major product isolated after column purification was compound **144**, an intra-molecular cyclization product of **143** (Scheme 28).



Scheme 28. Synthesis of compound **143** and **144**

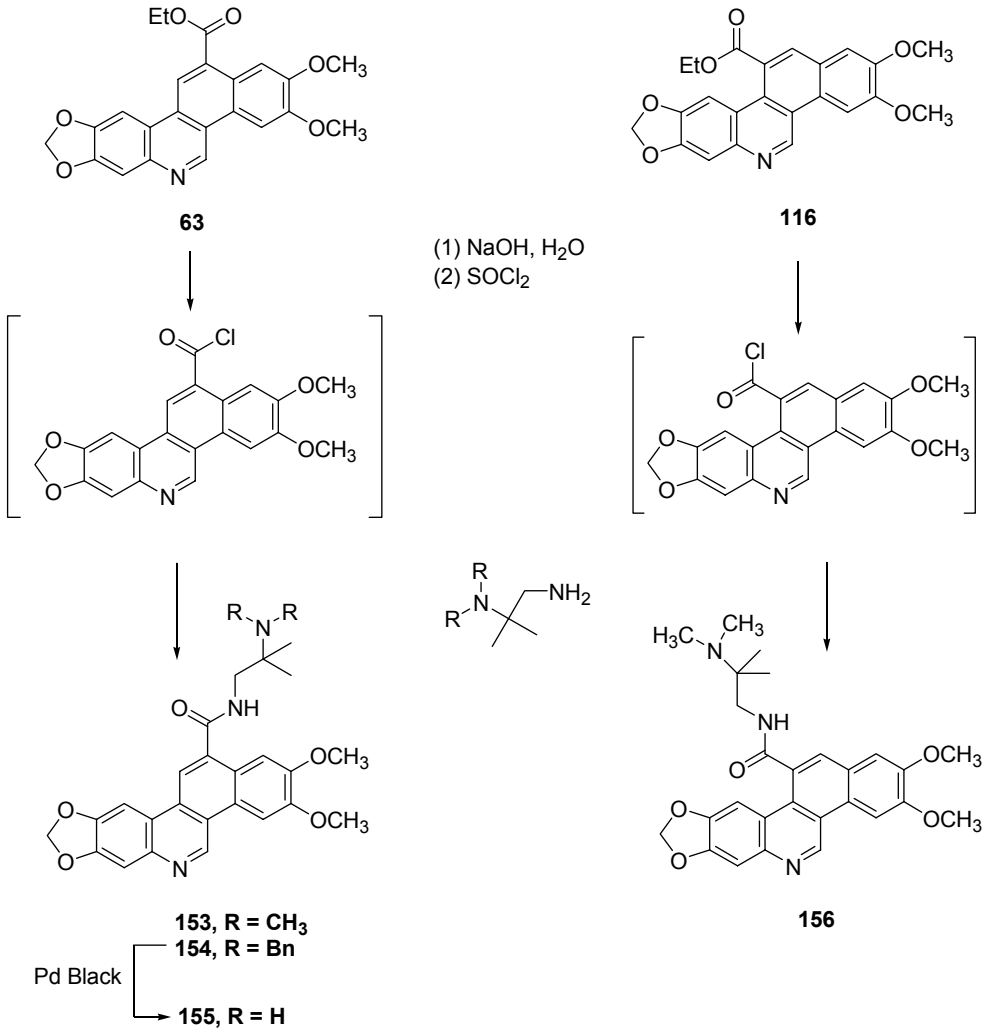
α,α-Dimethyl derivatives of reversed lactam were synthesized according to a reported procedure from our lab.[122,125] The starting aniline was protected by an acetyl group to give compound **145**. Iodination of **145** afforded compound **146** in good yield. Amide **147** was synthesized via coupling of carboxylic acid with **146**. Alkylation of **147** in DMF gave **148** or **149,** using the corresponding chloride. Cyclization of compound **148** or

149 was completed under UV irradiation. Removal of benzyl groups on **151** was carried out in acetic acid with palladium black and formic acid to give compound **152** in excellent yield (Scheme 29).



Scheme 29. Synthesis of compound **152** and **150**

Preparation of compounds **153** and **154** was preformed smoothly using the same method as previously reported. The primary amine analog of **155** was synthesized from **154** via palladium black reduction (Scheme 30). Compounds **153-155** were mainly synthesized by Dr. M. Satyanarayana in our group. Compound **156** was synthesized using a similar method described earlier in this paper (see section 2.5).



Scheme 30. Synthesis of α,α-dimethyl derivatives of carboxamides

The relative TOP1-targeting activities and the results of cellular assays of these α,α-dimethyl derivatives in both RPMI8402 and P388, as well as their respective campothecin resistant variants, CPT-K5 and P388/CPT-45 are provided in Table 21-22. *N,N*-dimethyl, *α, α*-dimethyl derivative **136** is shown to be at least an order of magnitude less potent than ARC-111 when evaluated for cytotoxic activity in RPMI8402 or P388 cells. Similarly, *N,N*,α,α-tetramethyl derivative **150** was much less active than its lead, reversed lactam **56**. In contrast to **136** and **150**, carboxamide derivative compounds

153 and **156** demonstrated exceptional cytotoxic activity in RPMI8402 or P388 cells, even slightly better than lead compounds **57** and **120**. The poor solubility of α,α-dimethyl primary amine derivative of the 12-carboxamide analog, compound **155**, may have contributed to its decreased cytotoxicity compared with **153**. The primary amine analog **152** also exhibited a significant activity decrease in cytotoxicity relative to its tertiary amine counterpart, compound **150**. Compound **143** demonstrated comparable activity as ARC-111. Among the newly developed α,α-dimethyl derivatives, compounds with pronounced cytotoxicity also exhibited potent TOP1-targeting activity. **143**, **153** and **156** had similar potency to camptothecin as TOP1-targeting agents.

Data provided in Table 23 are the relative cytotoxicity in the parent cell line, KB3-1, KBV-1, a variant that overexpresses the efflux transporter MDR1, and KBH5.0, a variant that overexpresses BCRP. Differences in relative cytotoxicity between these variant cell lines and the parent cell line, KB3-1, may be indicative of a compound that is a substrate for an efflux transporter. In light of their difference in IC_{50} values, these data suggest that all derivatives developed are substrates for MDR1. Two potent TOP-1 targeting agents, amides **153** and **156** are not substrates for BCRP.

Table 21. A comparison of α,α-dimethyl analogs: lactams and reversed lactams

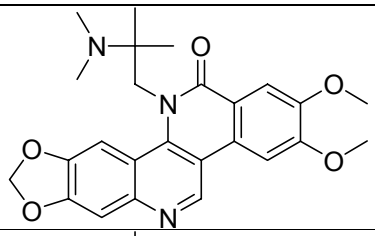
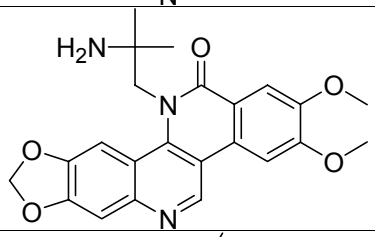
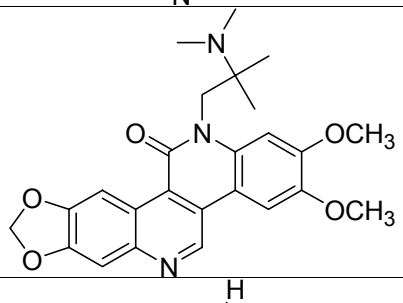
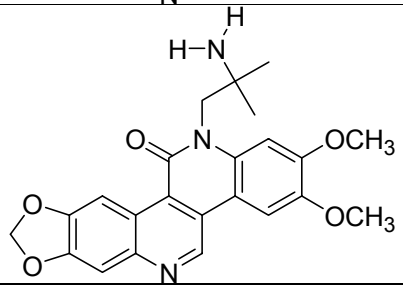
	Structure	TOP1-mediated cleavage	Cytotoxicity IC_{50} (μM)			
			RPMI 8402	CPT-K5	P388	P388/ CPT45
1		0.3	0.002	0.90	0.001	0.23
136		2.2	0.025	0.45	0.05	0.27
143		0.11	0.007	1.63	0.014	0.038
150		0.4	0.07	0.3	0.15	0.03
152		4.3	0.3	2.3	0.29	0.34

Table 22. A comparison of α,α-dimethyl analogs: 11- and 12-carboxamides

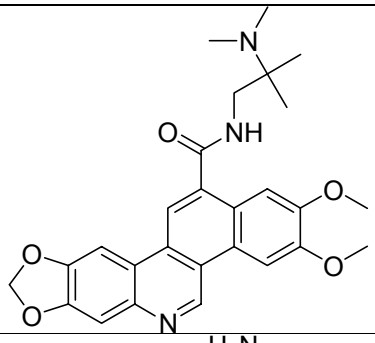
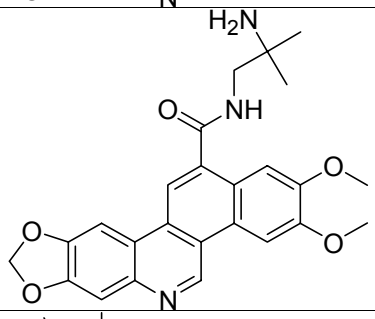
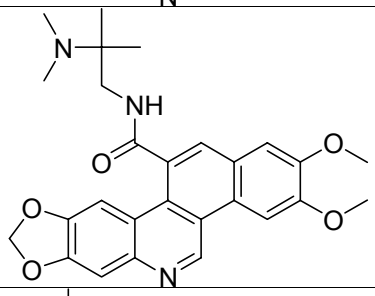
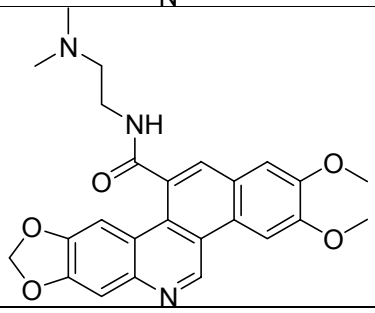
	Structure	TOP1-mediated cleavage	Cytotoxicity IC_{50} (μM)			
			RPMI 8402	CPT-K5	P388	P388/ CPT45
1		0.3	0.002	0.90	0.001	0.23
153		0.1	0.002	0.79	0.002	0.25
155		1.1	0.01	2.2	0.02	0.76
156		0.09	0.003	0.5	0.002	0.23
120		0.2	0.035	0.63	0.015	0.26

Table 23. Relative cytotoxicity in cancer cell lines, KB3-1, KBV-1, and KBH5.0

Compound	Cytotoxicity		
	KB3-1	**KBV-1**	**KBH5.0**
1	0.005	0.005	0.006
136	0.08	0.4	0.25
143	0.005	0.03	0.02
150	0.035	0.28	0.054
152	0.1	0.43	0.28
153	0.001	0.03	0.004
155	0.004	0.48	0.19
156	0.003	0.065	0.01
120	0.027	1.4	0.2

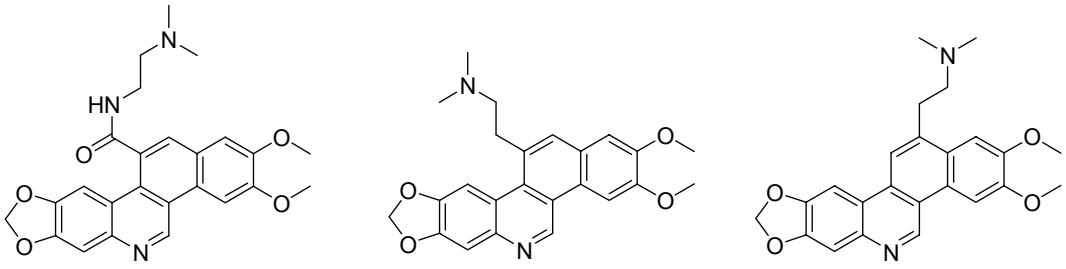
Compounds outlined in this section are currently under investigation for antitumor activity *in vivo* in athymic nude mice with MDA-MB-435 human tumor xenografts.

SUMMARY

Topoisomerase I is a validated therapeutic target for development of anticancer agents. Topotecan (Hycamtin®) and irinotican (CPT-11/ Camptosar®), are linical drugs, which stabilize the transient TOP1/DNA complex. Stabilization by means of this ternary complex of enzyme, DNA, and drug ultimately results in cancer cell death. The lactone moieties of both drugs are susceptible to hydrolysis and the hydrolyzed product has high affinity for human serum albumin. In addition, both drugs are substrates for efflux transporters associated with multiple drug resistance. These limitations have prompted the present studies on non-camptothecin TOP1-targeting agents.

8,9-Dimethoxy-5-(2-dimethylaminoethyl)-2,3-methylenedioxy-5H-dibenzo[*c,h*][1,6]naphthyridine-6-one (ARC-111) has been identified as an exceptionally active TOP1-targeting agent with potent antitumor activity both *in vitro* and *in vivo*. ARC-111 analogs, 12-carboxamides of benzo[*i*]phenathridine and the "reversed lactams" have also exhibited excellent cytotoxicity and potent TOP1 targeting activity. These three classes of compounds can be regarded as B-ring modified benzo[*i*]phenathridines. Our current studies have emphasized the synthesis and evaluation of other B-ring modified 3,4-dimethoxy-8,9-methylenedioxy-benzo[*i*]phenathridines, which include 11-carboxamides, 12-aminoalkyl derivatives, and 11- aminoalkyl derivatives of benzo[*i*]phenathridine. Improvements on top1-targeting activity and cytotoxicity have been observed within every class of compounds compared to the innitrial lead compound. These novel non-camptothecin TOP-1 targeting agents can be easily formulated and administered in laboratory animals due to the introduction of a soluble side chain. The side chain moiety is also speculated to to significantly improve the bioavailability of these

agents. Although simple aminoalkyl substituted derivatives have demonstrated much more pronounced activity than the lead compound, they are slightly less active than the other five classes of compounds. Considering DNA is highly hydrated, absence of amide functionality may diminish compound interactions with surrounding water molecules.



Representatives for newly developed benzo[*i*]phenathridines

SAR studies focused on ARC-111 have identified several equally potent derivatives. Earlier D-ring modifications have lead to the 8- or 9-nitro substituted ARC-111 derivatives. Suspect metabolites, 8 or 9-hydroxy compounds, have also exhibited excellent activity. Groups bigger than methoxy, such as diethoxy within the D-ring, are severely detrimental to TOP1-targeting activity. Derivations on the amino group of the side chain have also successfully developed hydroxyethylamino, aminoethylamino, cyanomethyl and cyclopropylamino derivatives, together with earlier found secondary amino metabolites, as potent TOP1-targeting agents.

Investigations on metabolites of ARC-111 and other related analogs inspired the design of α,α-dimethyl substitution on the amino side chain. The introduction of such moieties on 12- or 11-carboxamides slightly improved TOP1-targeting activity *in vitro*. More importantly, recent studies show α,α-dimethyl-12-carboxamide derivative has demonstrated antitumor potency, with a significant improvement with regards to its *in*

vivo activity. In general, the presence of α,α-dimethyl substituents on lactams were proved to be detrimental to the anticancer activity.

Several efficient synthetic methodologies have also been developed associated with our efforts to advance the the structure-activity relationship of these unique TOP-1 targeting agents.These include: 1) A facile *N,N,N*-trimethylammonium displacement conveniently introduces various functionalities, whose syntheses otherwise could be problematic or tedious utilizing traditional synthetic schemes; 2) Several synthetic methods have been applied to successfully prepare various lengths of aminoalkyl chains on the 11- or 12-position of benzo[*i*]phenathridine. This method could be expanded on general synthesis of aminoalkyl chains; 3) An alternative cyclization method for the synthesis of benzo[*i*]phenathridines was developed. This radical-mediated, non-photolytic cyclization provides an industrially feasible solution to overcome shortcomings of traditional photocyclization. 4) An efficient preparation of 11-substituted benzo[*i*]phenathridine has been developed in our group. A pratical route to the syntheis of 11-substituted benzo[*i*]phenathridine has not been previously reported.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover Unimelt capillary melting point apparatus. Column chromatography refers to flash chromatography conducted on SiliTech 32-63 μM, (ICN Biomedicals, Eschwegge, Ger.) using the solvent systems indicated. Infrared spectral data were obtained using a Thermo-Nicolet Avatar 360 Fourier transform spectrophotometer and are reported in cm^{-1}. Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on a Varian Gemini-2000 Fourier transform spectrophotometer. NMR spectra (200 MHz ^{1}H and 50 MHz ^{13}C) were recorded in the deuterated chloroform, methanol, or DMSO, as indicated. Deuterated solvents were purchased from Cambridge Isotopes Laboratory (Cambridge, Ma.). Chemical shifts are reported in δ units downfield from tetramethylsilane (TMS). Coupling constants are reported in hertz (Hz). Mass spectra were obtained from the Washington University Resource for Biomedical and Bio-organic Mass Spectrometry within the Department of Chemistry at Washington University, St. Louis, Mo. If a mass spectrum was run in FAB or ESI mode, the molecular ion is indicated by including an additional "Li" or "H" at the end of the molecular formula. Tetrahydrofuran was freshly distilled from sodium and benzophenone prior to use, and methylene chloride was freshly distilled from calcium hydride. All other solvents were distilled or purified by standard methods. Unless otherwise noted, all starting materials were obtained from Aldrich Chemical Company (Milwaukee, WI) or Acros Organics (Fisher Scientific, Pittsburgh, PA). Low temperature baths (-78 °C) were obtained using a dry ice-acetone mixture.

2,3-Methylenedioxy-8,9-dimethoxy-5-[*N*-methyl-*N*-(2,2,2-trifluoro-ethyl)aminoethyl] dibenzo[*c*,*h*][1,6] naphthyridin-6-one (10).

To a mixture of 2,3-Methylenedioxy-8,9-dimethoxy-5-(2-methylaminoethyl)dibenzo [*c*,*h*][1,6]naphthyridin-6-one (**7**) (75 mg, 0.184 mmol) in DMF 8 mL was added DIEA (0.32 mL, 1.84 mmol) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (0.92 mmol, 213 mg) at room temperature. The resulting reaction mixture was heated up to 80°C with stirring for 4 h. The reaction mixture was allowed to cool to room temperature, and then diluted with $CHCl_3$. The $CHCl_3$ solution was washed with water, then brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel using dichloromethane:methanol to afford a white solid (39 mg) in 43% yield; mp 237-239 °C; IR (neat): 1647; ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H), 3.04 (q, 2H, J = 9.4), 3.22 (t, 2H, J = 6.8), 4.04 (s, 3H), 4.11 (s, 3H), 4.62 (t, 2H, J = 6.8), 6.16 (s, 2H), 7.44 (s, 1H), 7.64 (s, 1H), 7.70 (s, 1H), 7.84 (s, 1H), 9.33 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 42.2, 47.9, 55.2, 55.4, 55.4, 57.3 (q, J = 30.8), 99.8, 101.0, 101.3, 106.2, 107.7, 110.9, 113.8, 118.3, 124.6 (q, J = 279.6), 126.7, 140.0, 142.5, 146.2, 146.8, 149.0, 149.3, 153.2, 163.3; HRMS *m/z* calcd for $C_{25}H_{27}N_3O_5H$: 490.1590; found: 490.1567.

2,3-Methylenedioxy-8,9-dimethoxy-5-[*N*-ethyl-*N*-(2,2,2-trifluoro-ethyl)aminoethyl] dibenzo[*c*,*h*][1,6] naphthyridin-6-one (11)

To a mixture of 2,3-Methylenedioxy-8,9-dimethoxy-5-(2-ethylaminoethyl)dibenzo [*c*,*h*][1,6]naphthyridin-6-one (**8**) (77 mg, 0.184 mmol) in DMF 8 mL was added DIEA (0.32 mL, 1.84 mmol) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (0.92 mmol, 213 mg) at room temperature. The resulting reaction mixture was heated up to 80°C with

stirring for 7 h. The reaction mixture was allowed to cool to room temperature, and then diluted with $CHCl_3$. The $CHCl_3$ solution was washed with water, then brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel using dichloromethane:methanol to afford a white solid (29 mg) in 31% yield; mp 246-248 °C; IR (neat): 1644; ^{1}H NMR ($CDCl_3$) δ 0.98 (t, 3H, J = 7.0), 2.72 (q, 2H, J = 7.0), 3.11 (q, 2H, J = 9.6), 3.26 (t, 2H, J = 7.4), 4.05 (s, 3H), 4.12 (s, 3H), 4.60 (t, 2H, J = 7.4), 6.17 (s, 2H), 7.44 (s, 1H), 7.64 (s, 1H), 7.70 (s, 1H), 7.85 (s, 1H), 9.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 11.1, 48.1, 48.2, 52.1, 53.8 (q, J = 30.4), 55.4, 55.4, 99.8, 100.9, 101.4, 106.2, 107.7, 110.8, 113.7, 118.3, 124.7 (q, J = 279.4), 126.7, 139.8, 142.5, 146.3, 146.8, 149.0, 149.3, 153.2, 163.3; HRMS *m/z* calcd for $C_{25}H_{24}F_3N_3O_5H$: 504.1746; found: 504.1748.

2,3-Methylenedioxy-8,9-dimethoxy-5-[*N*-isopropyl-*N*-(2,2,2-trifluoroethyl)amino ethyl]dibenzo[*c*,*h*][1,6] naphthyridin-6-one (12)

To a mixture of 2,3-Methylenedioxy-8,9-dimethoxy-5-(2-isopropylaminoethyl)dibenzo [*c*,*h*][1,6]naphthyridin-6-one (**8**) (80 mg, 0.184 mmol) in DMF 8 mL was added DIEA (0.32 mL, 1.84 mmol) and 2,2,2-trifluoroethyl trifluoromethanesulfonate (0.92 mmol, 213 mg) at room temperature. The resulting reaction mixture was heated up to 80°C with stirring for 7 h. The reaction mixture was allowed to cool to room temperature, and then diluted with $CHCl_3$. The $CHCl_3$ solution was washed with water, then brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel using dichloromethane:methanol to afford a white solid (50 mg) in 52% yield; mp 258-261 °C; IR (neat): 1650; ^{1}H NMR ($CDCl_3$) δ 1.01 (d, 6H, J =6.6), 3.0 (m, 1H), 3.07 (q, 2H, J = 9.6), 3.24 (t, 2H, J = 7.6), 4.05 (s, 3H), 4.12 (s, 3H), 4.58 (t, 2H, J = 7.6), 6.17 (s, 2H), 7.46 (s,

1H), 7.67 (s, 1H), 7.73 (s, 1H), 7.87 (s, 1H), 9.37 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 17.4, 48.9, 49.2, 51.3 (q, J = 31.9), 51.8, 55.4, 55.4, 99.8, 100.9, 101.3, 106.2, 107.7, 110.8, 113.8, 118.3, 124.6 (q, J = 279.6), 126.8, 139.9, 142.5, 146.2, 146.8, 149.0, 149.3, 153.2, 163.3; HRMS *m/z* calcd for $C_{26}H_{26}F_3N_3O_5H$: 518.1903; found: 518.1903.

2,3-Methylenedioxy-8,9-dimethoxy-5-[*N*-cyanomethyl-*N*-methyl-aminoethyl]dibenzo [*c*,*h*][1,6] naphthyridin-6-one (13)

To a solution of 2,3-methylenedioxy-8,9-dimethoxy-5-[2-methylaminoethyl]dibenzo[*c*,*h*] [1,6]naph-thyridin-6-one (50 mg, 0.123 mmol) (**7**) in DMF (10 mL) was added potassium carbonate (170 mg, 1.23 mmol) and bromoacetonitrile (26 μl, 0.370 mmol) at room temperature. The resulting reaction mixture was heated at 75 °C with stirring for 35 min. The reaction mixture was allowed to cool to room temperature, and then diluted with $CHCl_3$. The $CHCl_3$ solution was washed with water, and then brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel using dichloromethane:methanol to afford a white solid (35 mg) in 64% yield; mp 235-236 °C; IR (neat): 2239, 1639; ^{1}H NMR ($CDCl_3$): δ 2.32 (s, 3H), 3.07 (t, 2H, J = 6.6 Hz), 3.43 (s, 2H), 4.08 (s, 3H), 4.14 (s, 3H), 4.70 (t, 2H, J = 6.6 Hz), 6.20 (s, 2H), 7.50 (s, 1H), 7.66 (s, 1H), 7.69 (s, 1H), 7.89 (s, 1H), 9.39 (s, 1H); ^{13}C NMR ($CDCl_3$+CD_3OD): δ 35.9, 40.8, 44.7, 53.0, 55.4, 99.4, 101.1, 105.3, 107.7, 111.1, 113.7, 116.1, 118.1, 126.3, 140.0, 142.2, 145.5, 147.0, 149.2, 149.4, 153.2, 163.5; HRMS *m/z* Calcd for $C_{24}H_{22}N_4O_5H$ 447.1668; found 447.1660.

2,3-Methylenedioxy-8,9-dimethoxy-5-[*N*-cyanomethyl-*N*-ethyl-aminoethyl]dibenzo [*c*,*h*][1,6] naphthyridin-6-one (14)

To a solution of 2,3-methylenedioxy-8,9-dimethoxy-5-[2-ethylaminoethyl]dibenzo[*c*,*h*] [1,6]naph-thyridin-6-one (100 mg, 0.237 mmol) (**8**) in DMF (10 mL) was added potassium carbonate (130 mg, 0.948 mmol) and bromoacetonitrile (33 μl, 0.475 mmol) at room temperature. The resulting reaction mixture was heated at 75 °C with stirring for 40 min. The reaction mixture was allowed to cool to room temperature, and then diluted with $CHCl_3$. The $CHCl_3$ solution was washed with water, and then brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel using dichloromethane:methanol to afford a white solid (87 mg) in 80%; mp 226.5-227.5 °C; IR (neat): 2285, 1634; ^{1}H NMR ($CDCl_3$): δ 0.83 (t, 3H, J = 7.2 Hz), 2.49 (q, 2H, J = 7.2 Hz), 3.05 (t, 2H, J = 6.6 Hz), 3.42 (s, 2H), 4.08 (s, 3H), 4.14 (s, 3H), 4.72 (t, 2H, J = 6.6 Hz), 6.20 (s, 2H), 7.51 (s, 1H), 7.67 (s, 1H), 7.68 (s, 1H), 7.89 (s, 1H), 9.38 (s, 1H); ^{13}C NMR ($CDCl_3$+CD_3OD): δ 11.43, 40.84, 47.27, 47.37, 50.93, 55.26, 55.44, 99.47, 100.09, 101.60, 104.90, 107.69, 111.25, 113.75, 114.07, 118.04, 126.23, 140.102, 141.75, 144.83, 147.06, 149.46, 153.38, 163.35; HRMS *m/z* Calcd for $C_{25}H_{24}N_4O_5H$ 461.1825; found 461.1826.

2,3-Methylenedioxy-8,9-dimethoxy-5-[*N*-cyanomethyl-*N*-isopropyl-aminoethyl] dibenzo[*c*,*h*][1,6] naphthyridin-6-one (15)

To a solution of 2,3-methylenedioxy-8,9-dimethoxy-5-[2-isopropylaminoethyl]dibenzo [*c*,*h*][1,6]naphthyridin-6-one (100 mg, 0.23 mmol) (**9**) in DMF (15 mL) was added potassium carbonate (127 mg, 0.92 mmol) and bromoacetonitrile (32 μl, 0.46 mmol) at

room temperature. The resulting reaction mixture was heated at 75 °C with stirring for 90 min. The reaction mixture was allowed to cool to room temperature, and then diluted with $CHCl_3$. The $CHCl_3$ solution was washed with water, and then brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel using dichloromethane:methanol to afford a white solid (54 mg) in 49% yield; mp 219.5-220.5°C; IR (neat): 2287, 1644; ^{1}H NMR ($CDCl_3$): δ 0.90 (d, 6H, J = 6.6 Hz), 2.78 (m, 1H), 3.12 (t, 2H, J = 6.6 Hz), 3.41 (s, 2H), 4.07 (s, 3H), 4.14 (s, 3H), 4.68 (t, 2H, J = 6.6 Hz), 6.19 (s, 2H), 7.48 (s, 1H), 7.66 (s, 2H), 7.88 (s, 1H), 9.36 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 18.33, 37.79, 47.38, 47.69, 52.44, 55.47, 99.49, 100.99, 101.49, 105.76, 107.90, 111.12, 113.74, 116.11, 118.32, 126.34, 140.02, 142.03, 145.54, 146.91, 149.23, 149.42, 153.29, 163.30; HRMS *m/z* Calcd for $C_{26}H_{26}N_4O_5H$ 475.1981; found 475.1982.

2,3-Methylenedioxy-8,9-dimethoxy-5-[*N*-methyl-*N*-(prop-2-ynyl)aminoethyl] dibenzo[*c*,*h*][1,6] naphthyridin-6-one (16)

To a mixture of 2,3-methylenedioxy-8,9-dimethoxy-5-[2-methylaminoethyl]dibenzo [*c*,*h*][1,6]naphthyridin-6-one (100 mg, 0.246 mmol) in DMF (15 mL) was added potassium carbonate (190 mg, 1.38 mmol) and 3-bromo-propyne (103mg, 0.69mmol) at room temperature. The resulting reaction mixture was heated up to 80°C with stirring for 30 min. The reaction mixture was allowed to cool to room temperature, and then diluted with $CHCl_3$. The $CHCl_3$ solution was washed with water, then brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel using dichloromethane:methanol to give an off-white solid 67 mg in 65% yield; mp 239-241 °C; IR (neat): 1648; ^{1}H NMR ($CDCl_3$) δ 2.22 (t, 1H, J=2.2), 2.34 (s, 1H), 3.09 (t, 2H, J=6.6),

3.30 (d, 2H, J = 2.2), 4.04 (s, 3H), 4.11 (s, 3H), 4.61 (t, 2H, J = 6.6), 6.16 (s, 2H), 7.42 (s, 1H), 7.65 (s, 1H), 7.77 (s, 1H), 7.85 (s, 1H), 9.31 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 42.0, 46.4, 48.9, 54.0, 56.3, 56.3, 73.4, 78.6, 101.0, 102.0, 102.2, 107.1, 108.8, 111.7, 114.8, 119.3, 127.6, 140.9, 143.4, 147.2, 147.7, 149.9, 150.2, 154.1, 164.1; HRMS (M^+ + H) calcd for $C_{25}H_{24}N_3O_5$: 446.1716; found: 446.1716.

2,3-Methylenedioxy-8,9-dimethoxy-5-[*N*-ethyl-*N*-(prop-2-ynyl)aminoethyl]dibenzo [*c*,*h*][1,6] naphthyridin-6-one (17)

To a mixture of 2,3-methylenedioxy-8,9-dimethoxy-5-[2-ethylaminoethyl]dibenzo [*c*,*h*][1,6]naphthyridin-6-one (100 mg, 0.24 mmol) in DMF (15 mL) was added potassium carbonate (190 mg, 1.38 mmol) and 3-bromo-propyne (103mg, 0.69mmol) at room temperature. The resulting reaction mixture was heated up to 80°C with stirring for 60 min. The reaction mixture was allowed to cool to room temperature, and then diluted with $CHCl_3$. The $CHCl_3$ solution was washed with water, then brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel using dichloromethane:methanol to give an off-white solid 70 mg in 64% yield; mp 227-229 °C; IR (neat): 1648; ^{1}H NMR ($CDCl_3$) δ 0.95 (t, 3H, J=7.4), 2.18 (t, 1H, J=2.2), 2.56 (q, 2H, J=7.4), 3.12 (t, 2H, J=7.0), 3.33 (d, 2H, J = 2.2), 4.04 (s, 3H), 4.10 (s, 3H), 4.56 (t, 2H, J = 7.0), 6.15 (s, 2H), 7.41 (s, 1H), 7.59 (s, 1H), 7.78 (s, 1H), 7.84 (s, 1H), 9.28 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.7, 42.1, 47.9, 49.1, 51.6, 56.3, 56.3, 73.0,78.7, 101.1, 101.9, 102.2, 107.0, 108.8, 111.6, 114.7, 119.3, 127.4, 140.8, 143.3, 147.1, 147.6, 149.8, 150.2, 154.0, 164.0; HRMS (M^+ + H) calcd for $C_{26}H_{26}N_3O_5$: 460.1872; found: 460.1890.

2,3-Methylenedioxy-8,9-dimethoxy-5-[*N*-isopropyl-*N*-(prop-2-ynyl)aminoethyl] dibenzo-[*c*,*h*][1,6] naphthyridin-6-one (18)

To a mixture of 2,3-methylenedioxy-8,9-dimethoxy-5-[2-ethylaminoethyl]dibenzo [*c*,*h*][1,6]naphthyridin-6-one (100 mg, 0.23 mmol) in DMF (15 mL) was added potassium carbonate (190 mg, 1.38 mmol) and 3-bromo-propyne (103mg, 0.69mmol) at room temperature. The resulting reaction mixture was heated up to 80°C with stirring for 60 min. The reaction mixture was allowed to cool to room temperature, and then diluted with $CHCl_3$. The $CHCl_3$ solution was washed with water, then brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on silica gel using dichloromethane:methanol to give an off-white solid 63 mg in 58% yield; mp 217-219 °C; IR (neat): 1649; ^{1}H NMR ($CDCl_3$) δ 0.98 (t, 6H, *J*=6.6), 2.13 (t, 1H, *J*=1.8), 2.93 (m, 1H,), 3.16 (t, 2H, *J*=7.0), 3.33 (d, 2H, *J* = 1.8), 4.04 (s, 3H), 4.11 (s, 3H), 4.58 (t, 2H, *J* = 7.0), 6.15 (s, 2H), 7.41 (s, 1H), 7.60 (s, 1H), 7.80 (s, 1H), 7.85 (s, 1H), 9.29 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.5, 39.6, 48.1, 49.7, 52.4, 56.3, 56.3, 72.4, 80.8, 101.2, 101.9, 102.2, 107.0, 108.8, 111.7, 114.8, 119.4, 127.6, 141.0, 143.4, 147.1, 147.6, 149.8, 150.2, 154.1, 164.1; HRMS *m/z* calcd for $C_{27}H_{28}N_3O_5H$: 474.2029; found: 474.2031.

2,3-Methylenedioxy-8,9-dimethoxy-5-[*N*-(2-amino-2-oxoethyl)-*N*-methylaminoethyl] -dibenzo[*c*,*h*][1,6]naphthyridin-6-ones (19)

To a solution of 2,3-methylenedioxy-8,9-dimethoxy-5-[2-methylaminoethyl]dibenzo[*c*,*h*] [1,6]naphthyridin-6-one (150 mg, 0.368 mmol) (**7**) in DMF (10 mL) was added potassium carbonate (170 mg, 1.23 mmol) and bromoacetamide (56 mg, 0.405 mmol) at room temperature. The resulting reaction mixture was heated at 75 °C with stirring for 40 min. The reaction mixture was allowed to cool to room temperature, and then diluted with

$CHCl_3$. The $CHCl_3$ solution was washed with water, and then brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel using dichloromethane:methanol to afford a white solid (80 mg) in 47% yield; mp 228-229 °C; IR (neat): 3423, 1671, 1647; ^{1}H NMR ($CDCl_3$+CD_3OD): δ 2.17 (s, 3H), 2.93 (s, 2H), 3.00 (t, 2H, *J* = 6.6 Hz), 4.00 (s, 3H), 4.08 (s, 3H), 4.14 (s, 3H), 4.63 (t, 2H, *J* = 6.6 Hz), 6.14 (s, 2H), 7.39 (s, 1H), 7.63 (s, 1H), 7.65 (s, 1H), 7.80 (s, 1H), 9.30 (s, 1H); ^{13}C NMR ($CDCl_3$+CD_3OD): δ 41.9, 47.2, 47.6, 55.2, 60.2, 99.4, 101.1, 101.5, 105.2, 107.6, 111.5, 113.7, 116.0, 118.0, 126.3, 141.0, 142.0, 144.8, 147.0, 149.5, 153.4, 163.3, 171.4; HRMS *m/z* Calcd for $C_{24}H_{24}N_4O_6H$ 465.1774; found 465.1791.

2,3-methylenedioxy-8,9-dimethoxy-5-(2-hydroxyethyl)dibenzo[*c*,*h*][1,6]naphthyridin-6-one (20)

To a solution of **23** (100 mg, 0.246 mmol) in anhydrous DMSO (8 mL) was added water (0.45 mL, 2.46 mmol). The reaction mixture was heated to 150 ^{o}C for 5 h in a sealed tube, and then cooled to ambient temperature. The resulting mixture was concentrated by Kugelrohr, dissolved in $CHCl_3$ (20 mL) and then washed with water and brine. The organic layer was dried over Na_2SO_4, concentrated and chromatographed in 10:1 CH_2Cl_2/MeOH to afford a white solid 23 mg (in 24% yield); Compound characterization was identical to the literature.[116]

2-Imidazol-1-yl-ethylamine (21)[229]

To a solution of imidazole (3.5 g, 50 mmol) in DMF (15 mL) was added NaH (2 g, 50 mmol) and the resulting mixture was stirred at rt for 2h. To the above solution was added 2-bromoethylphthalimide (12 g, 47.5 mmol) and the reaction mixture was heated to 100 ^{o}C for 8 h. The reaction mixture was concentrated to remove DMF. The residue was extracted with hot toluene, and the toluene layer was concentrated to remove the solvent. The residue was triturated with ethyl ether to yield a beige solid 1.5 g. The product was used for next step without further purification. A mixture of crude product, 5.56 mmol of hydrazine hydrate, and 20 mL of EtOH was heated at reflux temperature for 8 h, cooled, treated with 17 mL of 4 N HCl, and refluxed for 6 h. The white precipitate (phthalhydrazide) was removed by filtration, and the mother liquor was concentrated to low volume and filtered again. The filtrate was concentrated, treated with 20 mL of H_2O and 1.1 g NaOH, and extracted with 400 mL of CH_2C1_2 in four portions. The organic layer was dried over $MgSO_4$, and concentrated to give a semi-solid 142 mg (3% overall yield). ^{1}H NMR ($CDCl_3$) δ 1.85 (s, 2H), 3.04 (t, 2H, *J*=6.2), 4.00 (t, 2H, *J*=6.2), 6.98 (s, 1H), 7.06 (s, 1H), 7.53 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 41.7, 49.1, 118.0, 128.4, 136.4.

4-[2-(imidazol-1-yl)ethylamino]-6,7-methylenedioxyquinoine (22)

4-Chloroquinoline (261 mg, 1.3 mmol) was stirred in refluxing phenol for 2.5 hours, then the bath temp was lowered to 125 °C, and 2-1midazol-1-yl-ethylamine (140 mg, 1.3 mmol) was added. The mixture was stirred at this temperature for 20 h, and then phenol was removed on the Kugelrohr, and the resulting crude residue was partitioned between chloroform (100 mL) and 3% HCl (300 mL), and the aqueous phase was washed with

chloroform (3 x 100 mL), made basic with 20% NaOH, and extracted with chloroform (4 x 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated, to give 1.2 g as a light gray solid, in 17% yield; mp 170-175 °C; ^{1}H NMR ($CDCl_3$) δ 3.71 (t, 2H, J=6.0), 4.30 (t, 2H, J=6.0), 6.05 (s, 2H), 6.39 (d, 1H, J=5.4) 6.94 (s, 1H), 7.08 (s, 1H), 7.12 (s, 1H), 7.31 (s, 1H), 7.58 (s, 1H), 8.15 (d, 1H, J=5.4); ^{13}C NMR ($CDCl_3$) δ 43.1, 45.2, 46.4, 96.8, 97.6, 101.9, 103.9, 114.3, 119.7, 127.8, 137.4, 145.6, 147.0, 147.7, 150.1, 150.6.

***N, N, N*-Trimethyl ammonium salt (23).**

To a solution of **1** (1 mmol) in 100 mL CH_2Cl_2-MeOH (4:1) was added methyl iodine (10 mmol) dropwise at room temperature. The resulting reaction suspension was stirred at the same temperature overnight, and then concentrated *in vacuo*. The resulting white powder was pure enough and could be used for the next step without further purification.

2,3-Dimethoxy-8,9-methylenedioxy-11H-isoquino-[4,3-c]cinnolin-12-one-11-[2-*N*,*N*, *N*,-trimethyethanaminium]iodide (23a)

To a solution of **ARC-31** (100 mg, 0.237 mmol) in a mixture of DCM and methanol (20 mL, 4:1) was added methyl iodide (0.145 mL, 2.3 mmol) drop wise at room temperature and stirred for overnight. Reaction mixture was concentrated under vaccum and dried under high vaccum to give **8** in quantitative yield; mp 255 ^{o}C (decom.); IR ($CHCl_3$) 1461; ^{1}H NMR (DMSO-d_6): 8.38 (s, 1H), 7.82 (s, 1H), 7.69 (s, 1H), 7. 67 (s, 1H), 6.40 (s, 2H), 4.96 (t, 2H, J = 6.2), 4.04 (s, 3H), 3.95 (s, 3H), 3.79 (t, 2H, J = 6.2), 3.19 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 54.7, 55.6, 55.8, 61.0, 98.1, 103.2, 105.0, 107.5, 112.6, 118.4, 127.9, 129.6,

133.6, 148.6, 150.4, 150.8, 151.1, 153.9, 161.7; HRMS (M^+ + H) Calcd for $C_{23}H_{24}IN_4O_5H$: 437.1825; found: 437.1805.

2,3-methylenedioxy-8,9-dimethoxy-5-(*N*-cyclopropylaminoethyl)dibenzo[*c*,*h*] [1,6]naphthyridin-6-one (24).

To a solution of **23** (100 mg, 0.246 mmol) in anhydrous DMSO (8 mL) was added cyclopropylamine (140 mg, 2.46 mmol). The reaction mixture was heated to 150 ^oC for 4 h in a sealed tube, and then cooled to ambient temperature. The resulting mixture was concentrated by Kugelrohr, dissolved in $CHCl_3$ (20 mL) and then washed with water and brine. The organic layer was dried over Na_2SO_4, concentrated and chromatographed in 10:1 CH_2Cl_2/MeOH to afford a white solid 27 mg (in 25% yield); mp 237-239 ºC; IR (KBr) 1644; ^1H NMR ($CDCl_3$) δ 0.40 (m, 6H), 2.19 (m, 1H), 3.43 (t, 2H, J = 7.0), 4.05 (s, 3H), 4.12 (s, 3H), 4.56 (t, 2H, J = 7.0), 6.16 (s, 2H), 7.45 (s, 1H), 7.67 (s, 1H), 7.75 (s, 1H), 7.88 (s, 1H), 9.36 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 5.7, 29.4, 47.7, 49.8, 55.4, 55.4, 100.1, 101.0, 101.3, 106.2, 107.8, 110.7, 113.9, 126.7, 140.1, 142.6, 146.4, 146.7, 149.4, 153.3, 163.3; HRMS calcd for $C_{24}H_{23}N_3O_5H$: 434.1716; found 434.1708.

2,3-methylenedioxy-8,9-dimethoxy-5-(*N*-imidazolylaminoethyl)dibenzo[*c*,*h*] [1,6]naphthyridin-6-one (25)

To a solution of **23** (100 mg, 0.246 mmol) in anhydrous DMSO (8 mL) was added imidazole (167 mg, 2.46 mmol). The reaction mixture was heated to 150 ^oC for 3 h in a sealed tube, and then cooled to ambient temperature. The resulting mixture was

concentrated by Kugelrohr, dissolved in $CHCl_3$ (20 mL) and then washed with water and brine. The organic layer was dried over Na_2SO_4, concentrated and chromatographed in 10:1 CH_2Cl_2/MeOH to afford a white solid 25 mg (in 23% yield); mp 275-279 ºC; IR (KBr) 1647; ^{1}H NMR ($CDCl_3$+CD_3OD) δ 4.04 (s, 3H), 4.10 (s, 3H), 4.49 (t, 2H, J = 6.6), 4.87 (t, 2H, J = 6.6), 6.17 (s, 2H), 6.67 (m, 1H), 6.79 (m, 1H), 7.28 (m, 1H), 7.30 (s, 1H), 7.41 (s, 1H), 7.64 (s, 1H), 7.83 (s, 1H), 9.26 (s, 1H); HRMS calcd for $C_{24}H_{20}N_4O_5H$: 445.1512; found 445.1519.

2,3-Dimethoxy-8,9-methylenedioxy-11-[(*1H*-imidazol-1-yl)ethyl]-*11H*-isoquino-[4,3-*c*]cinnolin-12-one (25a)

Prepared from **23a** in 29% yield using similar procedure for **25**; mp 280-282 ^{o}C(decom); IR ($CHCl_3$) 1646; ^{1}H NMR (CD_3COOD): δ 8.69 (s, 1H), 8.20 (s, 1H), 7.72 (s, 1H), 7.60 (s, 1H), 7. 36 (s, 1H), 7.15 (s, 1H), 7.13 (s, 1H), 6.12 (s, 2H), 5.01 (bs, 2H), 4.66 (bs, 2H), 3.89 (s, 3H), 3.81 (s, 3H); HRMS (M^+ + H) Calcd for $C_{23}H_{19}N_5O_5H$: 446.1464; found: 446.1455

2,3-methylenedioxy-8,9-dimethoxy-5-(*N*-triazolylaminoethyl)dibenzo[*c*,*h*][1,6]naphthyridin-6-one (26)

To a solution of **23** (100 mg, 0.246 mmol) in anhydrous DMSO (8 mL) was added 1*H*-1, 2, 3-triazole (170 mg, 2.46 mmol). The reaction mixture was heated to 150 ^{o}C for 4 h in a sealed tube, and then cooled to ambient temperature. The resulting mixture was concentrated by Kugelrohr, dissolved in $CHCl_3$ (20 mL) and then washed with water and brine. The organic layer was dried over Na_2SO_4, concentrated and chromatographed in 10:1 CH_2Cl_2/MeOH to afford a white solid 21 mg (in 19% yield); mp 273-277 ºC; IR

(KBr) 1651; ^{1}H NMR ($CDCl_3$+CD_3OD) δ 4.06 (s, 3H), 4.12 (s, 3H), 4.97 (t, 2H, J = 6.0), 5.12 (t, 2H, J = 6.0), 6.16 (s, 2H), 7.26 (m, 2H), 7.40 (s, 1H), 7.43 (s, 1H), 7.61 (s, 1H), 7.90 (s, 1H), 9.25 (s, 1H); HRMS calcd for $C_{23}H_{19}N_5O_5H$: 446.1464; found 446.1454.

Glycinate ester of 2,3-methylenedioxy-8,9-dimethoxy-5-[(2-hydroxyethyl)amino-ethyl]dibenzo[*c*,*h*][1,6]naphthyridin-6-one (27)

To a solution of **20** (40 mg, 0.10 mmol) in 6 mL DMF was added DCC (21 mg. 0.10 mmol) and DMAP (5 mg, 0.04 mmol) at room temperature. The resulting mixture was stirred at the same temperature for 30 min and dimethylamino-acetic acid (103 mg, 1 mmol) was added. The reaction mixture was stirred at room temperature for 12 h and diluted with 100 mL dichloromethane, then washed with water and brine. The organic layer was concentrated and chromatographed in 10:1 CH_2Cl_2/MeOH. The product was obtained as a white solid. Yield: 34%; mp 241-245 ºC; IR (KBr) 1635, 1751; ^{1}H NMR ($CDCl_3$+CD_3OD) δ 2.18 (s, 6H), 2.89 (s, 2H), 4.05 (s, 3H), 4.12 (s, 3H), 4.64 (t, 2H, J = 5.4), 4.85 (t, 2H, J = 5.4), 6.17 (s, 2H), 7.45 (s, 1H), 7.55 (s, 1H), 7.66 (s, 1H), 7.87 (s, 1H), 9.35 (s, 1H); HRMS calcd for $C_{25}H_{25}N_3O_7H$: 480.1771; found 480.1764.

2,3-methylenedioxy-8,9-dimethoxy-5-[*N*-(*N*,*N*-dimethylaminoethyl)aminoethyl] dibenzo[*c*,*h*][1,6]naphthyridin-6-one (28)

To a solution of **23** (100 mg, 0.246 mmol) in anhydrous DMSO (8 mL) was added *N, N*-dimethylethylenediamine (217 mg, 2.46 mmol). The reaction mixture was heated to 150 ^{o}C for 4 h in a sealed tube, and then cooled to ambient temperature. The resulting mixture was concentrated by Kugelrohr, dissolved in $CHCl_3$ (20 mL) and then washed with water and brine. The organic layer was dried over Na_2SO_4, concentrated and chromatographed in 10:1 CH_2Cl_2/MeOH to afford a white solid 28 mg (in 25% yield); mp 223-226ºC; IR (KBr) 1649; ^{1}H NMR ($CDCl_3$) δ 2.62 (s, 6H), 3.02 (t, 2H, J = 6.6), 3.14 (t, 2H, J = 6.6), 3.51 (t, 2H, J = 5.4), 4.04 (s, 3H), 4.12 (s, 3H), 4.66 (t, 2H, J = 5.4), 6.18 (s, 2H), 7.33 (s, 1H), 7.45 (s, 1H), 7.69 (s, 1H), 7.82 (s, 1H), 9.36 (s, 1H); HRMS calcd for $C_{25}H_{28}N_4O_5H$: 465.2138; found 465.2131.

2,3-methylenedioxy-8,9-dimethoxy-5-[*N*-(*N,N*-diethylaminoethyl)aminoethyl] dibenzo[*c,h*][1,6]naphthyridin-6-one (29)

To a solution of **23** (50 mg, 0.123 mmol) in anhydrous DMSO (8 mL) was added *N, N*-diethylethylenediamine (286 mg, 2.46 mmol). The reaction mixture was heated to 150 ^{o}C for 4 h in a sealed tube, and then cooled to ambient temperature. The resulting mixture was concentrated by Kugelrohr, dissolved in $CHCl_3$ (20 mL) and then washed with water and brine. The organic layer was dried over Na_2SO_4, concentrated and chromatographed in 10:1 CH_2Cl_2/MeOH to afford a white solid 16 mg (in 26% yield); mp 222-227 ºC; IR (KBr) 1655; ^{1}H NMR ($CDCl_3$) δ 1.30 (t, 6H, J = 7.4), 3.03 (q, 4H, J=7.4), 3.10 (m, 4H), 3.43 (t, 2H, J = 5.2), 4.03 (s, 3H), 4.12 (s, 3H), 4.65 (t, 2H, J = 5.2), 6.17 (s, 2H), 7.37 (s, 1H), 7.44 (s, 1H), 7.67 (s, 1H), 7.82 (s, 1H), 9.35 (s, 1H); HRMS calcd for $C_{23}H_{19}N_5O_5H$: 493.2451; found 493.2455.

2,3-methylenedioxy-8,9-dimethoxy-5-[*N*-(*N,N*-dimethylaminoethyl)methylamino-ethyl] dibenzo[*c,h*][1,6]naphthyridin-6-one (30)

To a solution of **23** (50 mg, 0.123 mmol) in anhydrous DMSO (8 mL) was added *N, N, N'*-trimethylethylenediamine (251 mg, 2.46 mmol). The reaction mixture was heated to 150 ^{o}C for 5 h in a sealed tube, and then cooled to ambient temperature. The resulting mixture was concentrated by Kugelrohr, dissolved in $CHCl_3$ (20 mL) and then washed with water and brine. The organic layer was dried over Na_2SO_4, concentrated and chromatographed in 10:1 CH_2Cl_2/MeOH to afford a white solid 6 mg (in 10% yield); mp 217-220 ºC; IR (KBr) 1641; ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 3H), 2.79 (s, 6H), 2.86 (t, 2H, J = 5.8), 3.07 (t, 2H, J = 5.8), 3.12 (t, 2H, J = 7.2), 4.02 (s, 3H), 4.11 (s, 3H), 4.62 (t, 2H, J = 7.2), 6.17 (s, 2H), 7.42 (s, 1H), 7.60 (s, 1H), 7.67 (s, 1H), 7.79 (s, 1H), 9.33 (s, 1H); HRMS calcd for $C_{26}H_{30}N_4O_5H$: 479.2294; found 479.2285.

2,3-Dimethoxy-8,9-methylenedioxy-11-[2((2-dimethylamino)ethyl(methyl)amino)ethyl]-11H-isoquino-[4,3-c]cinnolin-12-one (30a)

Prepared from **23a** in 8% yield using similar procedure for **30**; mp 218-220^{o}C; IR ($CHCl_3$) 1652; ^{1}H NMR ($CDCl_3$): δ 8.63 (s, 1H), 8.04 (s, 1H), 7.83 (s, 1H), 7.81 (s, 1H), 6.23 (s, 2H), 4.66(t, 2H, J = 5.4), 4.15(s, 3H), 4.06(s, 3H), 3.09 (t, 2H, J = 5.4); 2.58 (m, 2H), 2.37 (m, 5H), 2.20 (s, 6H); HRMS (M^+ + H) Calcd for $C_{25}H_{28}N_5O_5H$: 480.2241; found: 480.2240.

2,3-methylenedioxy-8,9-dimethoxy-5-[*N*-(2-hydroxyethyl)aminoethyl]dibenzo[*c*,*h*] [1,6]naphthyridin-6-one (31)

To a solution of **23** (407 mg, 1.0 mmol) in anhydrous DMSO (8 mL) was added ethanolamine (305 mg, 5.0 mmol). The reaction mixture was heated to 150 ^{o}C for 5 h in a sealed tube, and then cooled to ambient temperature. The resulting mixture was concentrated by Kugelrohr, dissolved in $CHCl_3$ (20 mL) and then washed with water and brine. The organic layer was dried over Na_2SO_4, concentrated and chromatographed in 10:1 CH_2Cl_2/MeOH to afford a white solid 135 mg (in 31% yield); mp 247-250 ºC; IR (KBr) 1641, 3422; ^{1}H NMR ($CDCl_3$) δ 2.81 (t, 2H, J = 5.2), 3.32 (t, 2H, J = 6.6), 3.61 (t, 2H, J = 5.2), 4.05 (s, 3H), 4.12 (s, 3H), 4.59 (t, 2H, J = 6.6), 6.16 (s, 2H), 7.45 (s, 1H), 7.67 (s, 1H), 7.69 (s, 1H), 7.86 (s, 1H), 9.36 (s, 1H); HRMS calcd for $C_{23}H_{23}N_3O_6H$: 438.1660; found 438.1665.

2,3-methylenedioxy-8,9-dimethoxy-5-[(2-hydroxy-1-hydroxymethyl-ethyl)amino-ethyl]dibenzo[*c*,*h*] [1,6]naphthyridin-6-one (32)

To a solution of **23** (100 mg, 0.246 mmol) in anhydrous DMSO (8 mL) was added serinol (224 mg, 2.46 mmol). The reaction mixture was heated to 150 ^{o}C for 16 h in a sealed tube, and then cooled to ambient temperature. The resulting mixture was concentrated by Kugelrohr, dissolved in $CHCl_3$ (20 mL) and then washed with water and brine. The organic layer was dried over Na_2SO_4, concentrated and chromatographed in 10:1 CH_2Cl_2/MeOH to afford a white solid 14 mg (in 21% yield); mp 237-242 ºC; IR (KBr) 1647, 3422; ^{1}H NMR ($CDCl_3$+CD_3OD) δ 2.64 (m, 1H), 3.29 (t, 2H, J = 6.6), 3.49 (m, 4H), 4.04 (s, 3H),

4.12 (s, 3H), 4.47 (t, 2H, *J* = 6.6), 6.06 (s, 2H), 7.30 (s, 1H), 7.48 (s, 1H), 7.61 (s, 1H), 7.71 (s, 1H), 9.24 (s, 1H); HRMS calcd for $C_{23}H_{23}N_3O_6H$: 468.1771; found 468.1761.

2,3-methylenedioxy-8,9-dimethoxy-5-[*N*-(tris(hydroxymethyl)methyl)aminoethyl] dibenzo[*c*,*h*][1,6]naphthyridin-6-one (33)

To a solution of **23** (50 mg, 0.123 mmol) in anhydrous DMSO (8 mL) was added tris(hydroxymethyl)aminomethane (300 mg, 2.46 mmol). The reaction mixture was heated to 150 ^{o}C for 2 h in a sealed tube, and then cooled to ambient temperature. The resulting mixture was concentrated by Kugelrohr, dissolved in $CHCl_3$ (20 mL) and then washed with water and brine. The organic layer was dried over Na_2SO_4, concentrated and chromatographed in 10:1 CH_2Cl_2/MeOH to afford a white solid 15 mg (in 25% yield); mp 239-240 ºC; IR (KBr) 1637, 3431; ^{1}H NMR (DMSO-d_6) δ 3.11 (t, 2H, *J* = 5.8), 3.28 (s, 6H), 3.89 (s, 3H), 4.01 (s, 3H), 4.37 (t, 2H, *J* = 5.8), 6.21 (s, 2H), 7.36 (s, 1H), 7.65 (s, 1H), 7.77 (s, 1H), 7.90 (s, 1H), 9.52 (s, 1H); HRMS calcd for $C_{25}H_{27}N_3O_8H$: 498.1876; found 498.1876.

2,3-Dimethoxy-8,9-methylenedioxy-11-[2-(1,3-dihydroxy-2-(hydroxymethyl)propan-2-ylamino)ethyl]-1H-isoquino-[4,3-c]cinnolin-12-one (33a)

To a solution of **8** in anhy. DMSO (5 mL) in a sealed tube was added tris (hydroxymethyl) aminomethane and stirred at 150 ^{o}C for 4 h. DMSO was removed by Kugelrohr distillation and the crude was purified by flash chromatography eluting with chloroform:methanol to give compound **33a**. Yield: 11%; mp 245-247 ^{o}C; IR ($CHCl_3$) 3366, 1654; ^{1}H NMR ($CDCl_3$+CD_3OD): δ 8.56 (s, 1H), 8.09 (s, 1H, -NH), 7.77 (s, 1H), 7.76 (s, 1H), 7. 75 (s,

1H), 6.25 (s, 2H), 4.53 (t, 2H, J = 5.4), 4.19 (s, 3H, -OH), 4.16 (s, 3H), 4.07 (s, 3H), 3.62 (s, 6H), 3.53 (t, 2H, J = 5.4); ^{13}C NMR (DMSO-d_6) δ 59.9, 60.1, 64.5, 65.3, 67.3, 72.2, 103.8, 107.4, 109.2, 111.6, 116.7, 122.8, 132.1, 134.5, 137.2, 152.8, 154.3, 155.0, 155.0, 157.8, 165.9; HRMS (M^+ + H) Calcd for $C_{24}H_{26}N_4O_8H$: 499.1829; found: 499.1818.

2,3-methylenedioxy-8,9-dimethoxy-5-[*N*-(2-hydroxyethyl)methylaminoethyl] dibenzo[*c*,*h*][1,6]naphthyridin-6-one (34)

To a solution of **23** (100 mg, 0.246 mmol) in anhydrous DMSO (8 mL) was added 2-methylaminoethanol (185 mg, 2.46 mmol). The reaction mixture was heated to 150 ^{o}C for 16 h in a sealed tube, and then cooled to ambient temperature. The resulting mixture was concentrated by Kugelrohr, dissolved in $CHCl_3$ (20 mL) and then washed with water and brine. The organic layer was dried over Na_2SO_4, concentrated and chromatographed in 10:1 CH_2Cl_2/MeOH to afford a white solid 22 mg (in 20% yield); mp 263-264 ºC; IR (KBr) 1638, 3423; ^{1}H NMR ($CDCl_3$+CD_3OD) δ 2.24 (s, 3H), 2.56 (t, 2H, J = 5.4), 3.11 (t, 2H, J = 6.6), 3.54 (t, 2H, J = 5.4), 4.05 (s, 3H), 4.12 (s, 3H), 4.65 (t, 2H, J = 6.6), 6.17 (s, 2H), 7.47 (s, 1H), 7.68 (s, 1H), 7.85 (s, 1H), 7.88 (s, 1H), 9.38 (s, 1H); HRMS calcd for $C_{25}H_{25}N_3O_6H$: 452.1821; found 452.1819.

2,3-methylenedioxy-8,9-dimethoxy-5-[*N*-bis(2-hydroxyethyl)aminoethyl]dibenzo [*c*,*h*][1,6]naphthyridin-6-one (35)

To a solution of **23** (100 mg, 0.246 mmol) in anhydrous DMSO (8 mL) was added diethanolamine (224 mg, 2.46 mmol). The reaction mixture was heated to 150 ^{o}C for 4 h in a sealed tube, and then cooled to ambient temperature. The resulting mixture was concentrated by Kugelrohr, dissolved in $CHCl_3$ (20 mL) and then washed with water and brine. The organic layer was dried over Na_2SO_4, concentrated and chromatographed in 10:1 CH_2Cl_2/MeOH to afford a white solid 16 mg (in 14% yield); mp 216-220 ºC; IR (KBr) 1647, 3384; ^{1}H NMR ($CDCl_3$+CD_3OD) δ 2.62 (t, 4H, J = 5.2), 3.01 (t, 2H, J = 6.2), 3.46 (t, 4H, J = 5.2), 3.98 (s, 3H), 4.07 (s, 3H), 4.58 (t, 2H, J = 6.2), 6.12 (s, 2H), 7.36 (s, 1H), 7.63 (s, 1H), 7.65 (s, 1H), 7.77 (s, 1H), 9.27 (s, 1H); HRMS calcd for $C_{25}H_{27}N_3O_7H$: 482.1927; found 482.1916.

2,3-Methylenedioxy-8,9-diethoxy-5-(2-*N*,*N*-dimethylaminoethyl)dibenzo[*c*,*h*]-[1,6]naphthyridin-6-one (36)

A mixture of **41** (1.5 g, 2.6 mmol), $Pd(OAc)_2$ (117 mg, 0.52 mmol), P(*o*-tolyl)$_3$ (390 mg, 1.3 mmol), and Ag_2CO_3 (1.43 g, 5.2 mmol) in dimethylformamide (DMF) (35 mL) was heated to reflux with stirring for 30 min. The reaction mixture was cooled, diluted with chloroform, and filtered through Celite, and the solvent was removed under vacuum. The crude residue was chromatographed in 99:1 chloroform/methanol to provide 500 mg (34%) of the cyclized product as a white solid; mp 229-232 °C; IR (neat): 1649; ^{1}H NMR ($CDCl_3$) δ 1.58 (m, 6H), 2.38 (s, 6H), 2.99 (t, 2H, J = 6.6), 4.30 (m, 4H), 4.58 (t, 2H, J = 6.6), 6.16 (s, 2H), 7.43 (s, 1H), 7.63 (s, 1H), 7.85 (s, 1H), 9.31 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.7, 14.7, 45.8, 49.1, 57.9, 64.7, 64.9, 101.2, 102.2, 103.2, 107.0, 109.8, 111.7, 114.8,

119.1, 127.3, 140.8, 143.5, 147.2, 147.6, 149.8, 149.9, 153.8, 164.1; HRMS *m/z* Calcd for $C_{29}H_{27}O_5N_3H$: 450.2029. Found: 450.2030.

2,3-Methylenedioxy-8-methoxy-9-hydroxy-5-(2-*N*-methylaminoethyl)dibenzo[*c*,*h*] [1,6]naphthyridin-6-one (37)

Compound **46** (120 mg, 0.209 mmol) was dissolved in acetic acid (10 mL). Formic acid (5 mL) was added, and then palladium black (100 mg) was added. The mixture was stirred at rt for 8h. The resulting mixture was filtered through a cotton plug and filtrate was concentrated. The residue was chromatographed in 99:1 chloroform/methanol to provide 75 mg (91%) product as a white solid; mp 269-273 °C; ^{1}H NMR (CD_3COOD) δ 2.71 (s, 3H), 3.74 (m, 2H), 3.94 (s, 3H), 4.83 (m, 2H), 6.20 (s, 2H), 7.30 (s, 1H), 7.54 (s, 1H), 7.70 (s, 1H), 7.45 (s, 1H), 9.44 (s, 1H); ^{13}C NMR (CD_3COOD) δ 33.0, 47.5, 48.8, 55.6, 100.6, 101.5, 103.5, 106.6, 108.6, 112.5, 114.7, 117.4, 127.2, 139.6, 140.8, 142.9, 149.0, 149.6, 152.0, 152.9, 164.6; HRMS *m/z* Calcd for $C_{29}H_{27}O_5N_3H$: 394.1397. Found: 394.1397.

2,3-Methylenedioxy-8-hydroxy-9-methoxy-5-(2-*N*-methylaminoethyl)dibenzo[*c*,*h*] [1,6]naphthyridin-6-one (38)

Compound **46b** (250 mg, 0.436 mmol) was dissolved in a mixture of acetic acid (10 mL) and formic acid (2.5 mL) and palladium black (200 mg) was added. The mixture was stirred at room temperature for 0.5 h. The resulting mixture was filtered through a cotton plug and filtrate was concentrated. The residue was washed with small amounts of chloroform, methanol and ethyl acetate to provide 145 mg (84%) of product as an off white solid; mp 195-197 °C; IR ($CHCl_3$) 3382, 1644; ^{1}H NMR (CD_3COOD) δ 2.29 (s, 3H), 3.73

(bs, 2H), 4.05 (s, 3H), 4.83 (s, 2H), 6.20 (s, 2H), 7.32 (s, 1H), 7.70 (s, 2H), 7.83 (s, 1H), 7.95 (s, 1H), 9.71 (s, 1H); ^{13}C NMR (CD_3COOD) δ 33.0, 47.5, 48.8, 55.9, 100.5, 101.2, 102.8, 103.6, 111.9, 112.6, 114.6, 118.1, 125.8, 139.0, 140.2, 142.7, 148.2, 149.0, 152.0, 153.6, 164.3; HRMS calcd for $C_{21}H_{19}N_3O_5H$: 394.1397; found 394.1393

4,5-Diethoxy-2-iodobenzoic acid (39)

To a suspension of 3,4-diethoxybenzoic acid (1.8 g, 8.59 mmol) and siver trifluroacetate (2.0 g, 9.02 mmol) in 15 mL $CHCl_3$ was added I_2 (2.29 g, 9.02 mmol) portionwise at 0 °C. The resulting reaction mixture was warmed up to room temperature with stirring overnight. The reaction mixture was quenched with 10 mL water. The organic layer was washed with sat. $Na_2S_2O_3$ solution (2 × 10 mL), brine (1 × 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel using ethyl acetate: hexanes (1:1), yielding 1.4 g in 50% yield as a light brown solid; mp 195-197 °C; IR (neat): 1694; ^{1}H NMR ($CDCl_3$) δ 1.49 (m, 6H), 4.14 (m, 4H), 7.44 (s, 1H), 7.63 (s, 1H), 9.2 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 13.7, 63.8, 64.0, 84.7, 115.4, 124.4, 124.4, 147.2, 151.6, 170.5; HRMS *m/z* Calcd for $C_{11}H_{13}IO_4H$: 334.9775; Found: 334.9784.

***N*-([1,3]dioxolo[4,5-g]quinolin-8-yl)-N-(2-(dimethylamino)ethyl)-4,5-diethoxy-2-iodo benzamide (41)**

Oxalyl chloride (1.3 mL, 11.3 mmol) was added to a mixture of 2-iodo-4,5-diethoxybenzoic acid (1.95 g, 5.65 mmol) in methylene chloride (40 mL), and the mixture was heated to reflux under nitrogen with stirring for 4 h. The mixture was concentrated to dryness under vacuum to provide crude **40**. The acid chloride was used

without purification and redissolved in 40 mL of methylene chloride, and a solution of 4-aminoquinoline (1.24 g, 4.78 mmol) added, then triethylamine (2.0 mL, 27 mmol) was added. The mixture was heated to reflux with stirring for 16 h and was then cooled to room temperature. The mixture was washed with saturated $NaHCO_3$ (3 × 100 mL) and extracted into dilute aqueous HCl (3 × 100 mL). The combined aqueous phases were washed with chloroform (2 × 100 mL), basified (30% NaOH), and extracted with chloroform (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried (Mg_2SO_4), and evaporated, yielding 2.6 g in 94% yield as a light brown sticky glue; IR (neat): 1654. ^{1}H NMR ($CDCl_3$) δ 1.00 (t, 3H, J = 7.0), 1.28 (t, 3H, J = 7.0), 2.19 (s, 6H), 2.55 (m, 2H), 3.25 (m, 1H), 3.52 (q, 2H, J = 7.0), 3.85 (q, 2H, J = 7.0), 4.44 (m, 1H), 6.09 (m, 2H), 6.31 (s, 1H), 6.97 (s, 1H), 7.25 (d, 1H, J = 4.6), 7.29 (s, 1H), 7.35 (s, 1H), 7.25 (d, 1H, J = 4.6); ^{13}C NMR ($CDCl_3$) δ 14.3, 14.6, 45.6, 46.9, 56.6, 64.3, 64.6, 82.8, 98.5, 102.2, 106.7, 112.3, 120.2, 123.0, 123.2, 133.6, 146.0, 147.5, 148.3, 148.4, 149.0, 149.6, 151.0, 170.0; HRMS *m/z* Calcd for $C_{25}H_{28}IO_5N_3H$: 578.1146 Found: 578.1149.

4-Benzyloxy-2-iodo-5-methoxybenzoic acid (42a)

To a suspension of 4-benzyloxy-3-methoxy-benzoic acid (2 g, 7.75 mmol) and siver trifluroacetate (3.42 g, 15.5 mmol) in 15 mL $CHCl_3$ was added I_2 (3.93 g, 15.5 mmol) portionwise at 0 °C. The resulting reaction mixture was warmed up to reflux with stirring overnight. The reaction mixture was filtered to remove insoluble solid. The organic layer was washed with sat. $Na_2S_2O_3$ solution (2 × 10 mL), brine (1 × 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel using ethyl acetate: hexanes (1:1), yielding 1.7 g in 57% yield as an off-white solid; mp

187-190 °C; IR (neat): 1674; ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H), 5.17 (s, 2H), 7.36-7.42 (m, 5H), 7.50 (s, 1H), 7.63 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.24, 70.33, 84.4, 114.4, 123.9, 125.4, 126.6, 127.5, 127.9, 134.8, 148.4, 151.1, 168.8; HRMS *m/z* Calcd for $C_{11}H_{13}IO_4H$: 382.9775; Found: 382.9784.

5-Benzyloxy-2-iodo-4-methoxybenzoic acid (42b)

To a suspension of 3-benzyloxy-4-methoxy-benzoic acid (1 g, 3.87 mmol) and silver trifluroacetate (1.71 g, 7.74 mmol) in 15 mL $CHCl_3$ was added I_2 (1.96 g, 7.74 mmol) portion wise at 0 °C. The resulting reaction mixture was heated up to reflux with stirring overnight. The reaction mixture was filtered and then washed with sat. $Na_2S_2O_3$ (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield MS-I-99 in 51% yield as a white solid; mp 195-197 °C; IR ($CHCl_3$) 3584, 1684; ^{1}H NMR ($CDCl_3$) δ 3.76 (s, 3H), 4.56 (s, 1H), 4.99 (s, 2H), 7.27 (m, 6H), 7.45 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.2, 70.1, 83.7, 115.3, 122.8, 126.7, 127.1, 127.5, 128.7, 135.4, 146.9, 150.8, 169.7; HRMS calcd for $C_{15}H_{13}IO_4H$: 384.9931; found 384.9929

Compound **44** were synthesized following the procedure reported in Ref. 121. Compound characterization was identical to the literature.

N-([1,3]dioxolo[4,5-g]quinolin-8-yl)-N-(2-(dimethylamino)ethyl)-4-benzyloxy -5-methoxy-2-iodobenzamide (45a)

Oxalyl chloride (1.0 mL, 11.7 mmol) was added to a mixture of **42a** (1.5 g, 3.9 mmol) in methylene chloride (40 mL), and the mixture was heated to reflux under nitrogen with stirring for 4 h. The mixture was concentrated to dryness under vacuum to provide crude **43a**. The acid chloride was used without purification and redissolved in 40 mL of methylene chloride, and a solution of **44** (1.3 g, 3.8 mmol) added, then triethylamine (0.5 mL, 3.9 mmol) was added. The mixture was heated to reflux with stirring for 16 h and was then cooled to room temperature. The reaction was quenched with saturated $NaHCO_3$ (3 × 100 mL) and extracted with chloroform (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried (Mg_2SO_4), and evaporated under reduced pressure. The residue was chromatographed on silica gel using dichloromethane: methanol (50:1), yielding 560 mg in 21% yield as a light brown sticky glue, with about 1 g **44** recovered; IR (neat): 1650. ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3H), 2.95 (m, 2H), 3.50 (s, 2H), 3.72 (s, 2H), 3.25 (m, 1H), 3.80 (m, 1H), 4.79 (m, 1H), 5.12 (s, 12H), 6.31 (m, 2H), 6.60 (s, 1H), 7.41-7.59 (m, 14H), 8.68 (d, 1H, J = 4.6); ^{13}C NMR ($CDCl_3$) δ 41.3, 45.9, 54.2, 54.6, 61.6, 70.3, 81.6, 97.5, 101.3, 105.8, 110.1, 119.3, 121.9, 123.2, 126.1, 126.6, 127.3, 127.5, 128.0, 128.1, 128.2, 133.3, 135.0, 137.7, 145.0, 147.4, 147.8, 148.0, 148.1, 150.1, 168.9.

N-[2-(Benzyl(methyl)amino)ethyl]-N-(6,7-methylenedioxyquinolin-4-yl)-5-benzyloxy-2-iodo-4-methoxybenzamide (45b)

Oxalyl chloride (8.0 mL, 11.7 mmol) was added to a suspension of **42b** (1.4 g, 3.6 mmol) in methylene chloride (40 mL), and the mixture was heated to reflux under nitrogen with stirring for 4 h. The mixture was concentrated to dryness under vacuum to provide crude

acid chloride. The crude acid chloride **43b** was redissolved in 40 mL of methylene chloride and a solution of **44** (600 mg, 1.8 mmol) in DCM (30 mL) followed by triethylamine (0.5 mL, 3.9 mmol) was added. The mixture was heated to reflux with stirring for 16 h and evaporated under reduced pressure. The crude residue was chromatographed on silica gel using dichloromethane: methanol (50:1), yielding 1.03 g in 82% yield as a light brown solid; mp 65-67 °C; IR ($CHCl_3$) 1651; ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 3H), 2.73 (m, 2H), 3.48 (s, 2H), 3.57 (m, 1H), 3.66 (s, 3H), 4.42 (s, 2H), 4.56 (m, 1H), 5.99 (s, 1H), 6.03 (s, 1H), 6.43 (s, 1H), 7.27 (m, 14H), 8.42 (d, 1H, J = 4.8); ^{13}C NMR ($CDCl_3$) δ 41.3, 45.8, 54.1, 55.1, 61.5, 70.0, 82.4, 97.6, 101.3, 105.7, 112.0, 119.4, 121.4, 121.8, 126.0, 126.1, 127.2, 127.7, 128.2, 132.7, 135.2, 137.7, 144.9, 146.5, 147.3, 147.4, 148.0, 149.4, 150.0, 168.8; HRMS calcd for $C_{35}H_{32}IN_3O_5H$: 702.1460; found 702.1466

2,3-Methylenedioxy-8-methoxy-9-benzyloxy-5-[2-(*N*-benzyl-*N*-methylaminoethyl)] dibenzo[*c*,*h*][1,6]naphthyridin-6-one (46a)

A mixture of **45a** (500 mg, 0.713 mmol), $Pd(OAc)_2$ (32 mg, 0.143 mmol), P(*o*-tolyl)$_3$ (87 mg, 0.285 mmol), and Ag_2CO_3 (413 mg, 1.07 mmol) in dimethylformamide (DMF) (35 mL) was heated to reflux with stirring for 1 h. The reaction mixture was cooled, diluted with chloroform, and filtered through Celite, and the solvent was removed under vacuum. The crude residue was chromatographed in 99:1 chloroform/methanol to provide 140 mg (34%) of the cyclized product as a white solid; mp 239-242 °C; IR (neat): 1650; ^{1}H NMR ($CDCl_3$) δ 2.26 (s, 3H), 3.12 (t, 2H, J = 6.6), 3.58 (s, 2H), 4.15 (s, 3H), 4.75 (t, 2H, J = 6.6), 5.51 (s, 2H), 6.28 (s, 2H), 7.36-7.97 (m, 14H), 9.28 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 41.4, 48.2, 55.0, 55.4, 62.1, 70.4, 100.3, 101.2, 103.5, 106.1, 108.3, 110.8, 113.9, 118.6, 126.0, 126.4,

127.2, 127.5, 127.6, 128.0, 128.0, 135.2, 137.8, 140.0, 142.5, 146.3, 146.7, 148.9, 149.8, 152.2, 163.1; HRMS *m/z* Calcd for $C_{29}H_{27}O_5N_3H$: 574.2336. Found: 574.2336.

5-[2-(Benzyl(methyl)amino)ethyl]-8-benzyloxy-9-methoxy-2,3-methylenedioxy dibenzo[*c*,*h*][1,6]naphthyridin-6-one (46b)

A mixture of **45b** (1.03 g, 1.47 mmol), $Pd(OAc)_2$ (66 mg, 0.294 mmol), P(*o*-tolyl)$_3$ (179 mg, 0.588 mmol), and Ag_2CO_3 (608 mg, 2.20 mmol) in dimethylformamide (10 mL) was heated to reflux with stirring for 1 h. The reaction mixture was cooled, diluted with chloroform, and filtered through Celite, and the solvent was removed under vacuum. The crude residue was chromatographed in 99:1 chloroform/methanol to provide 580 mg (69%) of the cyclized product as a white solid; mp 159-161 °C; IR ($CHCl_3$) 1650; ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H), 3.01 (t, 2H, J = 6.4), 3.48 (s, 2H), 4.06 (s, 3H), 4.56 (t, 2H, J = 6.4), 5.24 (s, 2H), 6.12 (s, 2H), 7.17 (s, 5H), 7.35 (m, 7H), 7.79 (s, 1H), 7.86 (s, 1H), 9.23 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 41.3, 48.1, 55.1, 55.3, 62.0, 69.9, 100.3, 101.2, 101.3, 106.0, 109.6, 110.5, 113.7, 118.2, 126.0, 126.7, 127.2, 127.7, 128.0, 135.4, 137.8, 139.8, 142.4, 146.2, 146.6, 148.4, 148.8, 153.5, 162.9; HRMS calcd for $C_{35}H_{31}N_3O_5H$: 574.2336; found 574.2342

2-[2,3-Methylenedioxy-6-oxy-8,9-dimethoxydibenzo[*c*,*h*][1,6]naphthyridin-5-yl] acetic acid (49)

A mixture of carboxylic ethyl ester **52** (95 mg, 0.22 mmol) and LiOH (10 mg, 0.43 mmol) in water and THF (1: 2) 10 mL was heated to reflux with stirring for 1h. The reaction mixture was acidified with 2N HCl to pH = 4, and then evaporated to dryness. The residue

was dissolved in 10 mL water, filtered, and then washed with excess water to afford a white solid 87 mg in 98% yield. ^{1}H NMR (DMSO-d_6) δ 3.90 (s, 3H), 4.05 (s, 3H), 4.98 (s, 2H), 6.21 (s, 2H), 7.39 (s, 1H), 7.53 (s, 1H), 7.66 (s, 1H), 8.01 (s, 1H), 9.61 (s, 1H); ^{13}C NMR (DMSO-d^6) δ 52.3, 55.6, 56.4, 100.3, 102.1, 103.1, 103.9, 108.0, 111.4, 114.1, 117.7, 126.3, 126.4, 140.9, 141.0, 148.0, 150.3, 151.0, 154.2, 162.3, 170.1; HRMS *m/z* Calcd for $C_{29}H_{27}O_5N_3$-H: 407.0861. Found: 407.0862.

Ethyl 2-(6,7-methylenedioxy-quinolin-4-ylamino)acetate (50)

4-Chloroquinoline (1.0 g, 4.8 mmol) was stirred in refluxing phenol for 2.5 hours, then the bath temp was lowered to 128 °C, and amino-acetic acid ethyl ester (1.03g, 10.0 mmol) was added. The mixture was stirred at this temperature for 3 hours, and then phenol was removed on the Kugelrohr, and the resulting crude residue was partitioned between chloroform (100 mL) and 20% NaOH (100 mL), and extracted with chloroform (4 x 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated, to give 910 mg as an off-white solid, in 70% yield; mp 188-191 °C; IR (neat): 1732; ^{1}H NMR ($CDCl_3$) δ 1.34 (t, 3H, J = 6.8), 4.03 (d, 2H, J = 4.4), 4.32 (q, 2H, J = 6.8), 5.35 (s, 1H), 6.08 (s, 2H), 6.25 (d, 2H, J = 5.0), 7.10 (s, 1H), 7.31 (s, 1H), 8.41 (d, 2H, J = 5.0); ^{13}C NMR ($CDCl_3$) δ 13.3, 44.0, 61.0, 95.0, 98.1, 100.8, 105.6, 145.4, 145.5, 146.3, 147.3, 147.8, 149.4, 169.2; HRMS *m/z* Calcd for $C_{29}H_{27}O_5N_3H$: 275.1026. Found: 275.1026.

2-[N-([1,3]dioxolo[4,5-g]quinolin-8-yl)-2-iodo-4,5-dimethoxybenzamido)]acetate, ethyl ester (51)

Oxalyl chloride (1.3 mL, 15.0 mmol) was added to a mixture of 2-iodo-4,5-dimethoxy-benzoic acid (1.54 g, 5.0 mmol) in methylene chloride (40 mL), and the mixture was heated to reflux under nitrogen with stirring for 4 h. The mixture was concentrated to dryness under vacuum to provide crude acyl chloride. The acid chloride was used without purification and redissolved in 40 mL of methylene chloride, and a solution of **50** (900 mg, 3.32 mmol) added, then triethylamine (2.1 mL, 15.0 mmol) was added. The mixture was heated to reflux with stirring for overnight and was then cooled to room temperature. The mixture was washed with saturated $NaHCO_3$ (3 × 100 mL) and extracted with chloroform (3 × 100 mL). The combined organic layers were washed with brine (100 mL), dried (Mg_2SO_4), and evaporated under reduced pressure. The residue was chromatographed on silica gel using dichloromethane: methanol (50:1), yielding 1.5 g in 80% yield as yellow solid; IR (neat): 1746; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H, J = 7.2), 3.34 (s, 3H), 3.74 (s, 3H), 4.22 (d, 1H, J = 17.2), 4.27 (q, 2H, J = 7.2), 4.88 (d, 1H, J = 17.2), 6.14 (m, 2H), 6.51 (s, 1H), 7.06 (s, 1H), 7.36 (s, 1H), 7.38 (d, 1H, J = 5.6), 7.52 (s, 1H), 8.54 (d, 1H, J = 5.6); ^{13}C NMR ($CDCl_3$) δ 13.3, 49.9, 54.6, 55.1, 60.8, 81.8, 97.3, 101.3, 105.9, 110.2, 119.3, 121.2, 121.3, 131.4, 145.1, 147.2, 147.5, 147.6, 148.3, 149.2, 150.1, 167.4, 169.5; HRMS *m/z* Calcd for $C_{29}H_{27}O_5N_3H$: 565.0466. Found: 565.0465.

2-[2,3-Methylenedioxy-6-oxy-8,9-dimethoxydibenzo[*c*,*h*][1,6]naphthyridin-5-yl] acetate, ethyl ester (52)

A mixture of **51** (1.31 g, 2.32 mmol), $Pd(OAc)_2$ (103.3 mg, 0.46 mmol), P(*o*-tolyl)$_3$ (283 mg, 0.93 mmol), and Ag_2CO_3 (960 mg, 3.48 mmol) in dimethylformamide (DMF) (15 mL) was heated to reflux with stirring for 1 h. The reaction mixture was cooled, diluted with

chloroform, and filtered through Celite, and the solvent was removed under vacuum. The crude residue was chromatographed in 99:1 chloroform/methanol to provide 100 mg (10%) of the cyclized product as a white solid; IR (neat): 1726; ^{1}H NMR ($CDCl_3$) δ 1.37 (t, 3H, J = 7.0), 4.00 (s, 3H), 4.10 (s, 3H), 4.39 (q, 2H, J = 7.0), 5.01 (s, 2H), 6.13 (s, 2H), 7.38-7.80 (m, 4H), 9.32 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 52.6, 56.3, 56.4, 62.1, 100.1, 102.3, 107.2, 109.0, 111.9, 114.5, 118.9, 127.8, 140.3, 143.5, 143.5, 147.3, 147.9, 150.1, 150.5, 154.5, 163.9, 169.2; HRMS *m/z* Calcd for $C_{29}H_{27}O_5N_3H$: 437.1343. Found: 437.1343.

2-[2,3-Methylenedioxy-6-oxy-8,9-dimethoxydibenzo[*c*,*h*][1,6]naphthyridin-5-yl] acetate, dimethylaminoethyl amide (53)

A suspension of **52** (50 mg, 0.115 mmol) in *N,N*-dimethylethylenediamine 10 mL was refluxed under nitrogen overnight The reaction mixture was then cooled to room temperature and evaporated to dryness. The crude residue was chromatographed in 90:10 chloroform/methanol to provide 17 mg (31%) of the desired product as a white solid; IR (neat): 1651; ^{1}H NMR ($CDCl_3$+CD_3OD) δ 2.25 (s, 6H), 2.52 (t, 2H, J = 6.0), 3.51 (t, 2H, J = 6.0), 3.98 (s, 3H), 4.09 (s, 3H), 4.89 (s, 2H), 6.10 (s, 2H), 7.36 (s, 1H), 7.63 (s, 1H), 7.70 (s, 1H), 7.79 (s, 1H), 9.28 (s, 1H); ^{13}C NMR ($CDCl_3$+CD_3OD) δ 36.22, 44.2, 53.4, 55.3, 55.4, 57.2, 99.8, 101.2, 105.6, 107.9, 110.8, 113.8, 117.8, 126.8, 137.5, 140.0, 142.3, 146.0, 146.9, 149.3, 149.5, 153.6, 163.4, 167.8; HRMS *m/z* Calcd for $C_{29}H_{27}O_5N_3$-H: 479.1925. Found: 479.1924.

2-[2,3-Methylenedioxy-6-oxy-8,9-dimethoxydibenzo[*c*,*h*][1,6]naphthyridin-5-yl] acetate, methyl amide (54)

To a solution of **49** (40 mg, 0.081 mmol) in 7 mL DMF was added DCC (20 mg. 0.10 mmol) and DMAP (10 mg, 0.08 mmol) at room temperature. The resulting mixture was stirred at the same temperature for 30 min and methylamine (0.4 mL, 2 M solution in THF) was added. The reaction mixture heated to 80 °C in a sealed tube for 3 h and diluted with 100 mL dichloromethane, then washed with water and brine. The organic layer was concentrated and chromatographed in 10:1 CH_2Cl_2/MeOH. The product was obtained as a white solid, 11 mg in 32% yield; ^{1}H NMR (DMSO-d^6) δ 2.71 (d, 3H, J = 4.2), 3.92 (s, 3H), 4.06 (s, 3H), 4.85 (s, 2H), 6.24 (s, 2H), 7.45 (s, 1H), 7.65 (s, 1H), 7.70 (s, 1H), 8.09 (s, 1H), 8.37 (s, 1H), 9.69 (s, 1H); HRMS *m/z* Calcd for $C_{29}H_{27}O_5N_3$-H: 422.1347. Found: 422.1347.

2,3-Dimethoxy-8,9-methylenedioxybenzo[*i*]phenanthridine-12-carboxylic acid 2-(*N*,*N*-dimethylamino)ethyl amide (57)

A solution of **63** (100 mg, 0.25mmol) in *N*,*N*-dimethylethylenediamine (30 ml) was heated to 110 °C for 5 days. After the reaction was completed, the residual amine was removed under vacuum. The residue was dissolved in CH_2Cl_2 (30 ml) and washed with water (3 × 10 ml) and brine (10 ml). The organic layers were dried over sodium sulfate, evaporated, and the residue was chromatographed eluting with 3–5% methanol–dichloromethane to provide 60 mg of **57** in 60% yield as a yellow solid; mp: 226.4–227.1 °C; IR (KBr) 1654; ^{1}H NMR ($CDCl_3$ + 1 drop CD_3OD) δ 2.34 (s, 6H), 2.69 (t, 2H, J = 6.2), 3.70 (t, 2H, J = 6.2), 4.01 (s, 3H), 4.10 (s, 3H), 6.11 (s, 2H), 7.35 (s, 1H), 7.75

(s, 1H), 7.79 (s, 1H), 7.93 (s, 1H), 8.29 (s, 1H), 9.59 (s, 1H); ^{13}C NMR ($CDCl_3$ + 1 drop CD_3OD) δ 37.5, 45.2, 55.9, 56.0, 58.3, 99.3, 102.0, 102.1, 106.2, 106.3, 117.7, 120.8, 120.9, 123.9, 125.7, 129.6, 136.1, 141.6, 144.7, 148.7, 149.6, 149.9, 150.6, 170.0; HRMS calcd for $C_{25}H_{25}N_3O_5H$, 448.1872; found: 448.1865.

4-Methyl-6,7-methylenedioxyquinoline (58)[124]

Iron (III) chloride (54.2 g, 0.2 mol) was dissolved in glacial acetic acid (600 ml) with warming to 60 °C. 3,4-Methylenedioxyaniline (27.4 g, 0.2 mol) was added and the mixture was stirred for 5 min. Methyl vinyl ketone (17.4 ml, 0.21 mol) was added dropwise over 5 min. Following the completion of addition, the mixture was heated to reflux with stirring for 1.5 h. The mixture was cooled and the precipitate was filtered and washed with additional acetic acid. This material was then basified by addition to cold 30% NaOH, and the resulting mixture was filtered and air-dried. The crude material was then extracted with chloroform (7 × 200 ml), and the combined extracts were washed with 10% K_2CO_3 (3 × 300 ml), dried ($MgSO_4$), and concentrated under vacuum. The resulting material was recrystallized from ethyl ether, yielding 16.6 g as a fluffy light beige solid, in 44% yield; mp: 100.5–101.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 3H), 6.04 (s, 2H), 7.04 (d, 1H, J = 4.4), 7.13 (s, 1H), 7.32 (s, 1H), 8.55 (d, 1H, J = 4.4); ^{13}C NMR ($CDCl_3$) δ 19.2, 99.3, 101.8, 106.3, 120.6, 125.1, 142.9, 146.5, 147.9, 147.9, 150.3.

4-Formyl-6,7-methylenedioxyquinoline (59)[124]

A mixture of **58** (5.01 g, 27 mmol) in 30 ml dioxane was heated to 75 °C and then a solution of SeO_2 in 5:1 dioxane–H_2O (36 ml) was added dropwise. The mixture was heated

to reflux with stirring for 4.5 h, filtered, and the filtrate was evaporated. The residue was dissolved in chloroform (50 ml), washed with water (3 × 50 ml), dried ($MgSO_4$), and evaporated. The residue was chromatographed, eluted with $CHCl_3$, yielding 3.48 g as a beige solid in 65% yield; mp: 146.0–147.5 °C; IR ($CHCl_3$) 1702; ^{1}H NMR ($CDCl_3$) δ 6.18 (s, 2H), 7.45 (s, 1H), 7.63 (d, 1H, J = 4.4), 8.41 (s, 1H), 8.96 (d, 1H, J = 4.4), 10.35 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 100.4, 102.3, 106.3, 121.4, 124.7, 135.7, 148.0, 148.3, 150.8, 151.0, 193.4.

Compound **60** were synthesized following the procedure reported in Ref. 121. Compound characterization was identical to the literature.[124]

3-(6,7-Methylenedioxyquinolin-4-yl)-2-(2-iodo-4,5-dimethoxyphenyl)acrylic acid (61)[124]

A mixture of **59** (400 mg, 2.0 mmol) and 2-iodo-4,5-dimethoxyphenylacetic acid (966 mg, 3.0 mmol) in acetic acid (3.5 ml) and TEA (0.31 ml) was heated to reflux with stirring for 90 min. The mixture was cooled to about 70 °C, poured into water, and the resulting mixture was stirred for 30 min with no additional heating. The entire mixture was then evaporated under vacuum and the residue was chromatographed eluting with 97:3 chloroform–methanol, to provide 725 mg as a yellow solid, in 73% yield; mp: 270.5–271.5 °C; IR (KBr) 1704; ^{1}H NMR (DMSO-d_6) δ 3.47 (s, 3H), 3.72 (s, 3H), 6.24 (s, 2H), 6.67 (s, 1H), 6.83 (d, 1H, J = 4.7), 7.23 (s, 1H), 7.33 (s, 1H), 7.41 (s, 1H), 8.15 (s, 1H), 8.44 (d, 1H, J = 4.7); HRMS calcd for $C_{21}H_{16}INO_6H$, 506.0101; found: 506.0110.

3-(6,7-Methylenedioxyquinolin-4-yl)-2-(2-iodo-4,5-dimethoxyphenyl)acrylic acid ethyl ester (62)[124]

Thionyl chloride (5 ml) was added dropwise to a mixture of **61** (1.51 g, 3.0 mmol) in absolute ethanol (125 ml), and the mixture was refluxed for 5 h with stirring. The mixture was cooled and evaporated under vacuum. The residue was dissolved in chloroform (250 ml) and washed with satd $NaHCO_3$ (3 × 250 ml), dried ($MgSO_4$), evaporated, and chromatographed eluting with chloroform, to provide 1.59 g in 99% yield, as an orange oil; IR ($CHCl_3$) 1713; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H, J = 7.0), 3.47 (s, 3H), 3.80 (s, 3H), 4.31 (q, 2H, J = 7.0), 6.07 (d, 2H), 6.39 (s, 1H), 6.71 (d, 1H, J = 4.6), 7.18 (s, 1H), 7.29 (s, 2H), 8.20 (s, 1H), 8.38 (d, 1H, J = 4.6); ^{13}C NMR ($CDCl_3$) δ 14.3, 55.9, 56.1, 61.8, 88.2, 99.6, 102.0, 106.4, 113.5, 119.1, 121.4, 123.6, 132.4, 136.4, 139.2, 140.2, 146.8, 147.5, 148.5, 149.3, 150.6, 166.0; HRMS calcd for $C_{23}H_{20}INO_6H$, 534.0419; found: 534.0412.

2,3-Dimethoxy-8,9-methylenedioxybenzo[*i*]phenanthridine-12-carboxylic acid ethyl ester (63)

Method A[124]: A solution of **62** (450 mg, 0.85 mmol) in acetonitrile (800 ml) was transferred to the photoreactor apparatus and was degassed by nitrogen purge for 30 min. The solution was then irradiated through a Vycor filter for 45 min. The mixture was removed from the photoreactor, and an equal portion of **6a** (450 mg, 0.85 mmol) in acetonitrile (800 ml) was reacted according to the same procedure. The cyclized product, which had precipitated out during the course of the reaction, was isolated by filtration and

washed with additional acetonitrile. Thorough drying provided **63** in 51% yield (348 mg) as a yellow solid;

Method B (non-photocyclization): The starting material ester **62** or **65** (533 mg, about 1mmol) was dissolved in anhydrous benzene (15ml) and the solution was heated to reflux under nitrogen. A solution of AIBN (82 mg, 0.5 mmol) and tributyltin hydride (437 mg, 1.5 mmol) in 5 ml benzene was added to the refluxing starting material solution over 10 min under nitrogen. The resulting reaction mixture was stirred at same temperature for 6 hours. (Additional solution of AIBN and tributyl hydride may be needed if starting material is still present.) The reaction mixture was cooled to rt and concentrated under vacuum. The residue was purified by column using ethyl acetate/hexanes (Hexanes from 100% to 50%). The product **2** was obtained as a yellow powder in 27% yield; mp: 250–251 °C (dec.); IR (KBr) 1716; ^{1}H NMR ($CDCl_3$ + 1 drop CD_3OD) δ 1.48 (t, 3H, J = 7.1), 3.98 (s, 3H), 4.13 (s, 3H), 4.53 (q, 2H, J = 7.1), 6.26 (s, 2H), 7.73 (s, 1H), 7.93 (s, 1H), 8.11 (s, 1H), 8.18 (s, 1H), 8.70 (s, 1H), 10.24 (s, 1H); ^{13}C NMR ($CDCl_3$ + 1 drop CD_3OD) δ 14.2, 55.9, 56.6, 62.5, 99.5, 100.0, 102.9, 103.8, 106.6, 120.4, 121.2, 123.2, 124.7, 126.8, 131.8, 132.7, 135.0, 139.8, 151.4, 151.5, 152.3, 152.4, 166.7; HRMS calcd for $C_{23}H_{19}NO_6H$, 406.1290; found: 406.1270.

2-(2-bromo-4,5-dimethoxyphenyl)acetic acid (64)

To a solution of 4,5-dimethoxyphenylacetic acid(10 g, 51 mmmol) in NaOH aqueous solution was added bromine (8.56 g, 48 mmol) slowly. After stirring for min the reaction mixture was cooled to rt. The precipate was filtered off was washed with water (10 ml x 2). The precipate was recrystallized from aqueous MeOH to yield beige crystal 11.5 g in 82%

yield.^{1}H NMR ($CDCl_3$) δ 3.75 (s, 2H), 3.85 (s, 6H), 6.78 (s, 1H), 7.03 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 40.0, 55.2, 55.3, 113.2, 114.2, 114.8, 124.5, 147.6, 148.2, 175.5.

N-([1,3]dioxolo[4,5-g]quinolin-8-yl)-N-(2-(dimethylamino)ethyl)-4-benzyloxy -5-methoxy-2-bromobenzamide (65)

A mixture of **59** (1.1g, 5.47 mmol) and 2-bromo-4,5-dimethoxyphenylacetic acid (1.5 g, 5.47 mmol) in acetic acid (10 ml) and TEA (1 ml) was heated to reflux with stirring for 90 min. The mixture was cooled to about 70 °C, poured into water, and the resulting mixture was stirred for 30 min with no additional heating. The entire mixture was then evaporated under vacuum and the residue was chromatographed eluting with 97:3 chloroform–methanol, to provide 1.1 g as a yellow solid, in 50% yield; Thionyl chloride (5 ml) was added dropwise to a mixture of above motioned solid (1.51 g, 3.3 mmol) in absolute ethanol (125 ml), and the mixture was refluxed for 5 h with stirring. The mixture was cooled and evaporated under vacuum. The residue was dissolved in chloroform (250 ml) and washed with satd $NaHCO_3$ (3 × 250 ml), dried ($MgSO_4$), evaporated, and chromatographed eluting with chloroform, to provide 1.59 g in 99% yield, as a light yellow semi-solid; IR (neat) 1715; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, *J*=7.0), 3.46 (s, 3H), 3.79 (s, 3H), 4.28 (q, 2H, *J*=7.0), 6.06 (s, 2H), 6.34 (s, 1H), 6.70 (d, 1H, *J*=4.6), 6.95 (s, 1H), 7.26 (s, 1H), 7.29 (s, 1H), 8.18 (s, 1H), 8.39 (d, 1H, *J*=4.6); ^{13}C NMR ($CDCl_3$) δ 13.3, 55.1, 55.2, 60.9, 98.6, 101.0 105.6, 112.9, 113.7, 114.5, 118.1, 112.6, 127.1, 135.9, 136.5, 138.5, 145.9, 146.6, 147.4, 147.5, 148.7, 149.7, 165.3.

2,3-Dimethoxy-8,9-methylenedioxybenzo[*i*]phenanthridine-12-carboxylic acid (66)[124]

A mixture of **63** (40 mg, 0.1 mmol) in 10% NaOH (45 ml) and ethanol (10 ml) was heated to reflux with stirring overnight. The mixture was concentrated to dryness and water (30 ml) was added. The resulting mixture was acidified by the addition of acetic acid and the free acid was then isolated by filtration. After complete drying, 32 mg (87%) was obtained as a yellow solid; mp: 277.7–278.6 °C (dec.); IR (KBr) 1706; HRMS calcd for $C_{21}H_{15}NO_6Li$, 384.1059; found: 384.1061.

12-(*N*-Aminocarbonyl)-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*]phenanthridine (67) [133]

A mixture of carboxylic ethyl ester **63** (0.1 mmol) in 10% NaOH (5 ml) and ethanol (10 ml) was heated to reflux with stirring for 1h. The reaction mixture was acidified with 2N HCl to pH = 4, and then evaporated to dryness. The residue was suspended in 10 ml dichloromethane and 0.5 ml thionyl chloride was added. The resulting reaction mixture was refluxed for 2h and then concentrated. The reaction residue was again suspended in dichloromethane and 0.5 ml triethylamine was added. After 15 min, 0.5 ml ammonia solution (2.0 M in tetrahydrofuran) was added and the resulting reaction mixture was refluxed for 1h. The organic solvent and excess amine were removed under reduced pressure and the residue was chromatographed in 20:1 CH_2Cl_2/MeOH to provide a off-white powder in 15% yield; mp 291-295 ºC; IR (KBr) 1649; ^{1}H NMR (DMSO-d_6) δ 3.91 (s, 3H), 4.09 (s, 3H), 6.27 (s, 2H), 7.56 (s, 1H), 7.79 (br, 1H), 7.90 (s, 1H), 8.25 (br, 1H), 8.33 (s, 1H), 8.46 (s, 1H), 8.64 (s, 1H), 10.16 (s, 1H); HRMS calcd for $C_{21}H_{16}N_2O_5H$: 377.1159; found 377.1149.

12-(*N*-Methylaminocarbonyl)-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*] phenanthridine (68)[133]

To a suspension of the acid, **66** (50 mg, 0.132 mmol) in chloroform (30 mL) was added thionyl chloride (3 mL, 41 mmol) and refluxed for 5h and stirred at room temperature overnight. Reaction mixture was concentrated to dryness on rotavap and dried under high vaccum. To this brown solid was added anhy. DCM (30 mL), TEA (3 mL, 21 mmol) and the mixture stirred for 15 min at room temperature. Then solid anhy. $MeNH_2$.HCl (200 mg, 29 mmol) was added and stirred for 2h. The reaction mixture was concentrated under vaccum and the crude residue was purified by flash chromatography eluting with 2% methanol in chloroform to give a yellow solid in 23% yield; mp 341–343 ^oC (dec.); IR ($CHCl_3$) 3438, 1638; ^1H NMR ($CDCl_3$): δ 3.24 (d, 3H, J = 5.2), 4.06 (s, 3H), 4.13 (s, 3H), 6.14 (s, 2H); 7.26 (s, 1H), 7.41 (bs, 1H), 7.61 (s, 1H), 7.73 (s, 1H), 7.95 (s, 1H), 8.07 (s, 1H), 9.67 (s, 1H), HRMS (M^+ + H) Calcd for $C_{22}H_{18}N_2O_5H$: 391.1294; found: 391.1309.

12-(*N,N*-Dimethylaminocarbonyl)-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*] phenanthridine (69)[133]

To a suspension of the acid, **66** (85 mg, 0.225 mmol) in chloroform (30 mL) was added thionyl chloride (3 mL, 41 mmol) and refluxed for 5h and stirred at room temperature overnight. Reaction mixture was concentrated to dryness on rotavap and dried under high vaccum. To this brown solid was added anhy. DCM (30 mL), TEA (3 mL, 21 mmol) and the mixture stirred for 15 min at room temperature. Then Me_2NH (1.1 mL, 2.25 mmol, 2M in THF) was added and stirred for 2h. The reaction mixture was concentrated under vaccum and the crude residue was purified by flash chromatography eluting with 2%

methanol in chloroform to give a yellow solid in 76% yield; mp 233–234^{o}C; IR ($CHCl_3$) 2969, 2932, 1620; ^{1}H NMR ($CDCl_3$): δ 2.88 (s, 3H), 3.33 (s, 3H), 4.02 (s, 3H), 4.16 (s, 3H), 6.17 (s, 2H); 7.20 (s, 1H), 7.62 (s, 1H), 7.82 (s, 1H), 8.11 (s, 1H), 8.17 (s, 1H), 9.86 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 34.1, 38.0, 55.1, 55.3, 98.4, 101.3, 101.5, 104.3, 105.2, 115.3, 119.3, 119.9, 122.5, 124.8, 129.5, 136.6, 140.0, 143.1, 148.0, 149.0, 149.5, 150.2, 169.4; HRMS (M^{+} + H) Calcd for $C_{23}H_{20}N_2O_5H$: 405.1432; found: 404.1439.

[1,3]dioxolo[4,5-g]quinolin-8-ylmethanol (70)

To a solution of 59 in MeOH 20 mL was added sodium boronhydride portionwise at rt. The resulting mixture was heated to 65°C for 2 h. The reaction mixture was evaporated to dryness and then dissolved in sat. ammonium chloride solution. The suspension was extracted with dichloromethane (20 mL x 3) and the organic extracts were concentrated. The residue was chromatographed, eluted with hexanes: ethyl acetate, yielding 1.5 g as a off-white solid in 90% yield; ^{1}H NMR ($CDCl_3$) δ 5.28 (s, 2H), 6.32 (s, 2H), 7.44 (s, 1H), 7.57 (d, 1H, J=4.4), 7.61 (s, 1H), 8.56 (d, 1H, J=4.6); ^{13}C NMR ($CDCl_3$) δ 60.5, 97.8, 101.0, 104.6, 106.1, 121.9, 143.1, 145.2, 146.6, 147.2, 149.6.

8-(chloromethyl)-[1,3]dioxolo[4,5-g]quinoline (71)

To a solution of 70 (1.5 g, 7.39 mmol) in dichloromethane was added thionyl chloride (2.7 mL, 36.9 mmol) slowly at -5 °C, and the solution was warmed up to rt with stirring overnight. 50 mL Potassium carbonate solution (10%) was added to the cooled reaction mixture and the organic layer was dried over sodium sulfate and evaporated to dryness. The white solid obtained (1.4 g, 86% yield) was used for next step without further

purification. ^{1}H NMR ($CDCl_3$) δ 5.06 (s, 2H), 6.33 (s, 2H), 7.47 (d, 1H, *J*=4.6), 7.53 (s, 1H), 7.62 (s, 1H), 8.87 (d, 1H, *J*=4.6); ^{13}C NMR ($CDCl_3$) δ 41.9, 98.0, 101.1, 105.7, 118.9, 122.3, 139.8, 146.2, 147.0, 147.7, 149.8.

Diethyl[([1,3]dioxolo[4,5-g]quinolin-8-yl)methyl]phosphonate (72)

A suspension of **71** (288 mg, 1.3 mmol) in triethyl phosphate (1 mL) was heated to 150 °C for 2 h under nitrogen. The reaction mixture was then cooled to rt and evaporated using Kugelror. The residue was chromatographed eluting with 97:3 dichloromethane–methanol, to provide 220 mg as a yellow oil, in 53% yield; ^{1}H NMR ($CDCl_3$) δ 1.36 (t, 6H, *J*=7.4), 3.63 (d, 2H, *J*=22.2), 4.16 (m, 4H), 6.25 (s, 2H), 7.37 (d, 1H, *J*=4.4), 7.52 (s, 1H), 7.52 (s, 1H), 8.76 (d, 1H, *J*=4.4); ^{13}C NMR ($CDCl_3$) δ 15.3 (d, *J*=6.1), 30.0 (d, *J*=137.4), 61.5 (d, *J*=6.8), 98.9 (d, *J*=1.6), 100.9, 105.3, 120.6 (d, *J*=6.5), 123.7, 136.1(d, *J*=9.1), 146.0 (d, *J*=2.6), 146.6 (d, *J*=3.4), 147.3, 149.6.

1-(3,4-dimethoxyphenyl)-3-(dimethylamino)propan-1-one (73)

To a solution of 1-(3,4-dimethoxyphenyl)ethanone (5 g, 27.7 mmol) in 30 mL ethanol was added paraformaldehyde (1.16 g, 38.8 mmol) and dimethylamine hydochloride (2.9 g, 36 mmol). The resulting mixture was heated to reflux for overnight. The reaction mixture was evaporated and dissolved in dichloromethane and washed with 1N HCl solution (15 mL x 2). The aqeous solution was basified with 30% NaOH solution and extracted with dichloromethane. The organic layer was dried over sodium sulfate and evaporated to afford a yellow oil 2.63 g in 40% yield. ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 6H), 2.95 (t, 2H, *J*=7.8), 3.32

(t, 2H, *J*=7.8), 4.13 (s, 3H), 4.15 (s, 3H), 7.09 (d, 1H, *J*=8.4), 7.73-7.83 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 35.6, 44.6, 53.8, 55.1, 55.2, 109.2, 109.3, 121.9, 129.3, 148.2, 152.4, 196.9.

12-Hydroxymethyl-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*]phenanthridine (74)

A solution of **63** (0.55 mmol) in THF dropwise was added at 0 ^{o}C to a stirred solution of LAH (1.1 mmol) in 20 mL. The resulting reaction suspension was stirred for 2 hours at 0 ^{o}C, and then carefully quenched by addition of 0.05 mL water, 0.05 mL 15% NaOH and 0.15 mL water sequentially. The resulting reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was chromatographed in 10:1 $CHCl_3$/MeOH to provide a yellow powder in 55% yield; mp 267-269 ºC; IR (KBr) 3448; ^{1}H NMR ($CDCl_3$+CD_3OD) δ 4.05 (s, 3H), 4.12 (s, 3H), 5.19 (s, 2H), 6.12 (s, 2H), 7.53 (s, 1H), 7.45 (s, 1H), 7.84 (s, 1H), 8.01 (s, 1H), 8.25 (s, 1H), 9.64 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.3, 55.7, 61.9, 99.2, 101.8, 103.0, 104.4, 106.3, 116.0, 119.6, 119.8, 124.7, 124.7, 129.4, 140.2, 141.7, 145.7, 147.8, 148.8, 148.9, 149.8; HRMS calcd for $C_{21}H_{17}NO_5H$: 364.1185; found 364.1179.

12-Formyl-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*]phenanthridine (75)

A solution of **74** (1 mmol), MnO_2 (10 mmol) in 30 mL DMF was stirred for 2 hours at room temperature. The resulting reaction mixture was filtered through a celite bed and filtrate was concentrated *in vacuo*. The residue was chromatographed in 20:1 CH_2Cl_2/MeOH to provide a brown powder in 74% yield; mp 260-263 ºC; IR (KBr) 1685; ^{1}H NMR ($CDCl_3$+CD_3OD) δ 4.12 (s, 3H), 4.17 (s, 3H), 6.20 (s, 2H), 7.58 (s, 1H), 7.97 (s, 1H), 8.17 (s, 1H), 8.74 (s, 1H), 8.92 (s, 1H), 9.93 (s, 1H), 10.50 (s, 1H); HRMS calcd for $C_{21}H_{15}NO_5H$: 362.1028; found 362.1023.

12-Dimethylaminomethyl-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*]phenanthridine (76)

To a solution of **75** (0.03 mmol) in 30 mL anhydrous CH_2Cl_2 and DMF (5:1) was added dimethylamine (2M in THF, 0.15 mmol) at room temperature. The resulting reaction solution was cooled to 0 ^oC and sodium triacetoxyborohydride (0.15 mmol) was added. After stirring at 0 ^oC for 5 minutes, 10 μL AcOH was added. The reaction mixture was warmed up to room temperature overnight, and then quenched with 0.1 mL water. The resulting mixture was partitioned between sat. $NaHCO_3$ and CH_2Cl_2. The organic layer was concentrated and the residue was chromatographed in 10:1 CH_2Cl_2/MeOH to provide a yellow powder in 60% yield; mp 210-216 ºC; ^1H NMR ($CDCl_3$+CD_3OD) δ 2.39 (s, 6H), 3.94 (s, 2H), 4.09 (s, 3H), 4.15 (s, 3H), 6.16 (s, 2H), 7.56 (s, 1H), 7.83 (s, 1H), 7.95 (s, 1H), 8.16 (s, 1H), 8.20 (s, 1H), 9.86 (s, 1H); HRMS calcd for $C_{23}H_{22}N_2O_4H$: 391.1658; found 391.1653.

1-(Dimethylaminomethyl)benzotriazole (77)[181]

To a cooled solution of benzotriazole (4.34 g, 36.4 mmol) and dimethylamine (20 mL, 2 M solution in MeOH, 40 mmol), in MeOH was added formasil (3.4 mL, 43.6 mmol) dropwise. After an hour the cooling bath was removed and the reaction mixture was stirred at rt overnight. The reaction was concentrated and dissolved in ether. The insoluble material was filtered and the filtrate was concentrated. The residue was chromatographed in 5:1 hexanes/ethylacetate to provide a white solid 5.8 g in 90% yield. Two isomers were obtained. The main isomer: ^1H NMR ($CDCl_3$) δ 2.60 (s, 6H), 5.61 (s, 2H), 7.58-8.30 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 41.7, 69.2, 109.1, 117.4, 119.0, 123.0, 125.5, 126.6

***N,N*-Dimethyl-1-(tributylstannyl)methanamine (78)**[182]

To a solution of LDA (1.5 M solution, 9.13 mL) in 20 mL THF was added tributyltin hydride (3.98 g, 13.7 mmol) at 0 °C dropwise over 10 min. Then a solution of **77** in 10 mL THF was added dropwise. After 2 h, the reaction was quenched with wet ether and diluted with ether (100 mL). The organic solution was extracted with sat. ammonium chloride, 10% NaOH, water and brine. The organic layer was concentrated and the crude product was purified by distillation to afford a colorless oil 1.2 g in 50% yield. bp: 120-125 ^{o}C (10 mm Hg); ^{1}H NMR ($CDCl_3$) δ 1.15-1.51 (m, 21H), 1.68 (m, 6H), 2.41 (s, 6H), 2.73 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 9.1, 12.8, 26.6, 28.4, 47.6, 48.7.

12-(4-Dimethylamino-1-hydroxy)ethyl-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*] phenanthridine (79)

To a solution of 80 (10 mg, 0.027 mmol) in THF 5 mL was added a solution of dimethyl amine (40% in water solution, 1 mL). The resulting reaction mixture was stirred at rt for 4 h. The reaction mixture was evaporated to remove solvents and the residue was chromatographed in 20:1 CH_2Cl_2/MeOH to provide a yellow solid 5 mg in 45% yield ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 6H), 2.75 (m, 2H), 4.05 (s, 3H), 4.08 (s, 3H), 5.58 (m, 1H), 6.18 (s, 2H), 7.43 (s, 1H), 7.55 (s, 1H), 8.01 (s, 1H), 8.17 (s, 1H), 8.60 (s, 1H), 9.84 (s, 1H).

2,3-dimethoxy-8,9-methylenedioxy-13-(oxiran-2-yl)benzo[*i*]phenanthridine (80)

To a heaxanes prewashed NaH (4.4 mg, 0.11 mmol) was added DMSO 0.24 mL. The resulting reaction mixture was heated to 75 ºC for 30 min. The yellow-green solution was

then cooled down to 0 ºC and THF 0.24 mL was added. Then a solution of Me_3SI (24.5 mg, 0.11 mmol) in 0.2 mL DMSO was added over 3 min. To the resulting solution was added **75** (in THF solution, 0.028 mmol) dropwise over 2 min, and reaction mixture was warmed up to rt with stirring for 1 h. The reaction was quenched by addition of 0.1 mL water and evaporated to remove solvents. The residue was partitioned into water and dichloromethane. The organic layer was concentrated and the residue was directly used for next step without further purification. Product was obtained as a yellow powder, 10 mg in 96% yield. ^{1}H NMR ($CDCl_3$) δ 2.90 (dd, 1H, J = 6.0, 3.0), 3.43 (dd, 1H, , J = 6.0, 4.2), 4.10 (s, 3H), 4.17 (s, 3H), 4.54 (dd, 1H, J = 4.2, 3.0), 6.17 (s, 2H), 7.55 (s, 1H), 7.56 (s, 1H), 7.96 (s, 1H), 8.21 (s, 1H), 8.30 (s, 1H), 9.89 (s, 1H).

2,3-Dimethoxy-8,9-methylenedioxy-12-(2-nitrovinyl)benzo[*i*]phenanthridine (81)

A suspension of **75** (0.1 mmol), ammonium acetate (0.5 mmol) in 2 mL nitromethane was stirred overnight at 80 ^{o}C. The resulting reaction mixture was triturated with a small amount of CH_2Cl_2 and the residue was pure enough and used for the next reaction without further purification; yield: 75%; mp 250-253 ºC; IR (KBr) 1509; ^{1}H NMR ($CDCl_3$+CD_3OD) δ 4.10 (s, 3H), 4.16 (s, 3H), 6.18 (s, 2H), 7.39 (s, 1H), 7.53 (s, 1H), 7.80 (d, 1H, J = 13.2), 7.90 (s, 1H), 8.18 (s, 1H), 8.43 (s, 1H), 8.80 (d, 1H, J = 13.2), 9.86 (s, 1H); HRMS calcd for $C_{22}H_{16}N_2O_6H$: 405.1086; found 405.1079.

2,3-Dimethoxy-8,9-methylenedioxy-12-(2-nitroethyl)benzo[*i*]phenanthridine (82)

To a stirred suspension of $NaBH_4$ (0.5 mmol) in 5mL 1,4-dioxane/EtOH (2:1) was added a solution of **81** (0.1 mmol) in 1,4-dioxane (5 mL) dropwise at 0 ^{o}C. After this addition, the

reaction mixture was stirred for an additional 30 minutes. The resulting reaction mixture was diluted with ice-water and quenched with 50% aqueous AcOH. The resulting suspension was concentrated and then partitioned between sat. $NaHCO_3$ and CH_2Cl_2. The organic layer was again concentrated and the residue was chromatographed in 10:1 CH_2Cl_2/MeOH to provide a yellow powder in 61% yield; mp 260-264 ºC; IR (KBr) 1554;^{1}H NMR ($CDCl_3$+CD_3OD) δ 3.95 (t, 2H, J = 6.6), 4.09 (s, 3H), 4.11 (s, 3H), 4.18 (t, 2H, J = 6.6), 6.18 (s, 2H), 7.42 (s, 1H), 7.59 (s, 1H), 7.89 (s, 1H), 8.16 (s, 1H), 8.22 (s, 1H), 9.91 (s, 1H); HRMS calcd for $C_{22}H_{18}N_2O_6H$: 407.1243; found 407.1233.

12-(2-Aminoethyl)-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*]phenanthridine (83)

To a stirred suspension of **82** (0.012 mmol) in 1mL acetic acid was added Zn power (0.24 mmol) portionwise over 5 minutes at room temperature. The reaction mixture was stirred for an additional 3 hours, and then filtered. The filtrate was diluted with saturated sodium bicarbonate, concentrated, and partitioned between sat $NaHCO_3$ and CH_2Cl_2. The organic layer was again concentrated and the residue was chromatographed in 10:1:0.1 CH_2Cl_2/MeOH/TEA to provide a yellow-green powder in 41% yield; mp 196-201 ºC; ^{1}H NMR ($CDCl_3$+CD_3OD) δ 3.21 (t, 2H, J = 5.8), 3.40 (t, 2H, J = 5.8), 4.07 (s, 3H), 4.14 (s, 3H), 6.14 (s, 2H), 7.45 (s, 1H), 7.49 (s, 1H), 7.87 (s, 1H), 8.08 (s, 1H), 8.13 (s, 1H), 9.79 (s, 1H); HRMS calcd for $C_{22}H_{20}N_2O_4H$: 377.1501; found 377.1494.

12-(2-Dimethylamino)ethyl-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*] phenanthridine (84)

To a solution of **83** (0.02 mmol) and formalin (0.1 mmol) in 3 mL MeOH was added a solution of $NaBH_3CN$ (in 0.1 mL MeOH, 0.15 mmol) at 0 ^oC. The resulting reaction solution was stirred for an additional 30 minutes at 0 ^oC, and then 2 drops of AcOH was added. The reaction mixture was warmed up to room temperature with stirring for another 2 hours. The resulting mixture was quenched by 0.1 mL 1N NaOH solution, concentrated, and extracted by $CHCl_3$ (2 x 15 mL). The organic layer was concentrated and the residue was chromatographed in 15:1 CH_2Cl_2/MeOH to provide a yellow powder in 58% yield; mp 195-198 ºC; ^1H NMR ($CDCl_3$+CD_3OD) δ 2.45 (s, 6H), 2.79 (t, 2H, J = 8.0), 3.40 (t, 2H, J = 8.0), 4.09 (s, 3H), 4.16 (s, 3H), 6.17 (s, 2H), 7.52 (s, 1H), 7.56 (s, 1H), 7.93 (s, 1H), 8.15 (s, 1H), 8.20 (s, 1H), 9.89 (s, 1H); HRMS calcd for $C_{24}H_{24}N_2O_4H$: 405.1814; found 405.1805.

12-(3-Dimethylamino)prop-1-enyl-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*] phenanthridine (85)

To a suspension of 2-(dimethylamino)ethyltriphenylphosphonium bromide (0.063 mmol) in 5 ml THF was added LiHMDS (1.0 M in THF, 0.07 mmol) dropwise at room temperature. A solution of **75** (0.051 mmol) in THF was added to the reaction mixture dropwise and the resulting solution was stirred for 1.5 h, quenched by 0.1 mL water, concentrated and partitioned into CH_2Cl_2/water. The organic layer was concentrated under reduce pressure and the residue was chromatographed in 20:1 CH_2Cl_2/MeOH to provide a yellow powder in 60% yield; as a mixture 1:3 of *cis*/*trans* isomers mp 212-217 ºC; ^1H NMR ($CDCl_3$+CD_3OD) of the major isomers (*trans*) δ 2.44 (s, 6H), 3.33 (d, 2H, J =6.2), 4.08 (s, 3H), 4.16 (s, 3H), 6.16 (s, 2H), 6.49 (dt, 1H, J =15.8, 6.2), 7.29 (d, 1H, J = 15.8),

7.48 (s, 1H), 7.54 (s, 1H), 7.90 (s, 1H), 8.15 (s, 1H), 8.28 (s, 1H), 9.85 (s, 1H); HRMS calcd for $C_{25}H_{24}N_2O_4H$: 417.1810; found 417.1801.

12-(3-Dimethylamino)propyl-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*]-phenanthridine (86)

A suspension of **85** (0.035 mmol) and Pd-C (5 mg) in 10 mL ethanol was shaken under hydrogen (40 psi) for 24 h. The mixture was filtered through celite and concentrated *in vacuo*. The residue was chromatographed in 20:1 CH_2Cl_2/MeOH to provide a yellow powder in 50% yield; mp 195-200 ºC; ^{1}H NMR ($CDCl_3$) δ 2.12 (m, 2H), 2.39 (s, 6H), 2.60 (t, 2H, J = 7.4), 3.27 (t, 2H, J = 8.0), 4.09 (s, 3H), 4.16 (s, 3H), 6.17 (s, 2H), 7.49 (s, 1H), 7.55 (s, 1H), 7.93 (s, 1H), 8.13 (s, 1H), 8.19 (s, 1H), 9.88 (s, 1H); HRMS calcd for $C_{25}H_{26}N_2O_4H$: 419.1971; found 419.1964.

12-(4-Dimethylamino)but-1-enyl-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*] phenanthridine (87)

To a suspension of 3-(dimethylamino)propyltriphenylphosphonium bromide (0.095 mmol) in 5 mL THF was added LiHMDS (1.0 M in THF, 0.1 mmol) dropwise at room temperature. A solution of **75** (0.075 mmol) in THF was added to the reaction mixture dropwise and the resulting solution was stirred for 1.5 h, quenched by 0.1 mL water, concentrated and partitioned into CH_2Cl_2/water. The organic layer was concentrated under reduced pressure and the residue was chromatographed in 20:1 CH_2Cl_2/MeOH to provide a yellow powder in 62% yield of a 1:3 mixture of the *cis*/*trans* isomers: mp 215-219 ºC; ^{1}H NMR ($CDCl_3$+CD_3OD) the major isomer (*trans*) had: δ 2.45 (s, 6H), 2.72 (m, 4H), 4.01 (s, 3H), 4.09 (s, 3H), 6.10 (s, 2H), 6.38 (dt, 1H, J =15.4, 6.2), 7.17 (d, 1H, J = 15.4), 7.26 (s,

1H), 7.41 (s, 1H), 7.94 (s, 1H), 8.07 (s, 1H), 8.25 (s, 1H), 9.70 (s, 1H); HRMS calcd for $C_{26}H_{26}N_2O_4H$: 431.1971; found 431.1967.

12-(4-Dimethylamino)butyl-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*] phenanthridine, (88)

A suspension of **87** (0.035 mmol) and Pd-C (5 mg) in 10 mL ethanol was shaken under hydrogen (40 psi) for 24 h. The mixture was filtered through celite and concentrated under under reduced pressure. The residue was chromatographed in 20:1 CH_2Cl_2/MeOH to provide a yellow powder in 50% yield; mp 213-217 ºC; ^{1}H NMR (DMSO-d_6) δ 1.85 (m, 4H), 2.75 (s, 6H), 3.38 (m, 4H), 3.99 (s, 3H), 4.07 (s, 3H), 6.29 (m, 2H), 7.44 (s, 1H), 7.63 (s, 1H), 8.31 (s, 1H), 8.32 (s, 1H), 8.37 (s, 1H), 10.13 (s, 1H); HRMS calcd for $C_{26}H_{28}N_2O_4H$: 433.2123; found 433.2130.

12-(4-Dimethylamino-1-hydroxy)butyl-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*] phenanthridine (89)

To a solution of **75** (0.2 mmol) in THF (8 mL) was added dropwise freshly prepared dimethylaminopropyl magnesium chloride THF solution (0.8 M, 0.3 mL) at 0 ^{o}C. The resulting reaction mixture was stirred at the same temperature for 15 min and then warmed up to room temperature with stirring overnight. The reaction was quenched with 0.1 mL water, concentrated and the residue was chromatographed in 15:1 CH_2Cl_2/MeOH to provide a yellow powder in 32% yield; mp 213-217 ºC; IR (KBr) 3440; ^{1}H NMR ($CDCl_3$+CD_3OD) δ 2.11 (m, 4H), 2.84 (s, 6H), 3.17 (t, 2H, J = 6.0), 4.11(s, 3H), 4.15 (s, 3H), 5.57 (t, 2H, J = 6.0), 6.15 (m, 2H), 7.36 (s, 1H), 7.46 (s, 1H), 7.88 (s, 1H), 7.96 (s, 1H), 8.37 (s, 1H), 9.88 (s, 1H); HRMS calcd for $C_{26}H_{28}N_2O_5H$: 449.2076; found 449.2069.

12-[(2-N,N-Dimethylaminoethyl)]aminomethyl-2,3-dimethoxy-8,9-methylenedioxy-benzo[*i*]phenanthridine (90)[133]

To a solution of aldehyde, **75** (12 mg, 0.033 mmol) in DCM (30 mL) was added N,N-dimethylethylenediamine (18 μL, 0.166 mmol) and stirred for 10 min at RT. To this $NaCNBH_3$ (6 mg, 0.099 mmol) was added and stirred for 2h. Reaction mixture was diluted with 10% NaOH solution (0.5 mL) and extracted with DCM. Organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude was purified by flash chromatography eluting with 1% methanol in chloroform to get a pale yellow solid in 28% yield; mp 255–256^oC; IR ($CHCl_3$) 3448; ^1H NMR ($CDCl_3$): δ 2.27 (s, 6H), 2.59 (t, 2H, J = 6.0), 2.90 (t, 2H, J = 6.0) 4.06 (s, 3H), 4.14 (s, 3H), 4.35 (s, 2H), 6.14 (s, 2H); 7.50 (s, 1H), 7.54 (s, 1H), 7.99 (s, 1H), 8.15 (s, 1H), 8.31 (s, 1H), 9.81 (s, 1H); HRMS (M^+ + H) Calcd for $C_{25}H_{27}N_3O_4H$: 434.2091; found: 434.2093.

12-[(2-N,N-Dimethylamino-2,2-dimethylethyl)aminomethyl-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*]phenanthridine (91)[133]

To a solution of aldehyde, **75** (10 mg, 0.027 mmol) in DCM (30 mL) was added 2-N,N-dimethyl-2,2-dimethylethylenediamine (100 μL, 0.862 mmol) and stirred for 10 min at RT. To this $NaCNBH_3$ (6 mg, 0.099 mmol) was added and stirred for 2h. Reaction mixture was diluted with 10% NaOH solution (0.5 mL) and extracted with DCM. Organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography eluting with 1% methanol in chloroform to get a pale yellow solid in 96% yield; mp 191–192 ^oC; IR ($CHCl_3$) 3423, 2915; ^1H NMR

($CDCl_3$): δ 1.07 (s, 6H), 2.20 (s, 6H), 2.65 (s, 2H), 4.07 (s, 3H), 4.15 (s, 3H), 4.36 (s, 2H), 6.16 (s, 2H); 7.56 (s, 1H), 7.78 (s, 1H), 7.96 (s, 1H), 8.17 (s, 1H), 8.31 (s, 1H), 9.89 (s, 1H); HRMS (M^+ + H) Calcd for $C_{27}H_{31}N_3O_4H$: 462.2393; found: 463.2421.

Compound **92** and **93** were synthesized by Dr. Hussan Mohammad.[190]

6,7-methylenedioxyquinolin-8-yl-acetonitrile (94)

To a solution of 71 (221 mg, 1 mmol) in DMSO 20 mL was added KCN (520 mg, 8 mmol) and 18-crown-6 (52 mg, 0.02 mmol). The reaction mixture was stirred overnight. The reaction mixture was then diluted with chloroform and washed with NaOH (1N, 20 mL). The organic layer was washed with brine and then concentrated. The crude product was purified by flash chromatography eluting with 1% methanol in chloroform to get a white solid 120 mg in 57% yield; ^{1}H NMR ($CDCl_3$) δ 4.04 (s, 2H), 6.16 (s, 2H), 7.09 (s, 1H), 7.39 (d, 1H, *J*=4.4), 7.44(s, 1H), 8.72 (d, 1H, *J*=4.4); ^{13}C NMR ($CDCl_3$) δ 20.7, 96.8, 101.3, 106.0, 115.4, 118.4, 122.1, 133.2, 145.9, 147.2, 148.1, 150.0.

4,5-Dimethoxy-2-iodo-benzyl alcohol (95)

A solution of iodine (1.47 g, 5.9 mmol) in dry $CHCl_3$ (100 ml) was added over a suspension of CF_3COOAg (1.29 g, 5.9 mmol) and 3,4-dimethoxybezyl alcohol (1.0 g, 5.9 mmol) in $CHCl_3$ (20 ml). The reaction mixture was stirred at room temperature for 30 min. The resulting yellow precipitate was filtered, and the filterate was washed with saturated sodium thiosulphate (2 x 100 ml). The organic layer was concentrated under vacuum to provide **95** in 58% yield (1.02 g). mp 83-84.5 ^{o}C (lit. mp 83-85 ^{o}C); ^{1}H NMR δ 3.89 (s,

6H), 4.63 (s, 2H), 6.96 (s, 1H), 7.22 (s, 1H); ^{13}C NMR δ 55.8, 56.1, 68.9, 85.2, 111.4, 121.3, 135.1, 148.7, 149.3.

4,5-Dimethoxy-2-iodo-benzyl bromide (96)[157]

PBr_3 (1.82 ml, 18.3 mmol) was added to a solution of 49 (2.6 g, 8.8 mmol) in dry CH_2Cl_2 (88 ml) and reaction mixture was stirred at room temperature for overnight. Solvent was evaporated under vacuum and resulting oil was treated with saturated $NaHCO_3$. The resulting aqueous phase was extracted with CH_2Cl_2 (2 x 50 ml) and the combined organic extracts were dried (anhyd. Na_2SO_4) and concentrated under vacuum to yield 2.82 g (90%) **95** as light yellow oil; ^{1}H NMR δ 3.86 (s, 3H), 3.87 (s, 3H), 4.58 (s, 2H), 6.96 (s, 1H), 7.22 (s, 1H); ^{13}C NMR δ 39.4, 56.0, 56.2, 88.5, 112.7, 121.8, 132.5, 149.6.

(4,5-Dimethoxy-2-iodo-benzyl)triphenylphosphonium bromide (97)[157]

Compound **96** (700 mg, 1.95 mmol) and PPh_3 (511 mg, 1.95 mmol) were taken in toluene (14 ml) under nitrogen and refluxed for overnight. It was then cooled and filtered. The solid was washed with hexane and dried on high vaccum to yield 550 mg (46%) of 51 as a white solid; mp 198-199 ^{o}C;;HRMS (M-Br) calcd for $C_{27}H_{25}IO_2PH$: 539.0637; found 539.0629.

6,7-Methylenedioxyquinoline-4-carboxylic acid (98) [125]

A solution of **59**(4.8 g, 23.8 mmol) in pyridine (150 mL) was cooled to −5 °C. The mixture was maintained at this temperature as a solution of potassium permanganate (10.0 g, 63.3 mmol in 150 mL of water) was added dropwise over the course of 1 h. The mixture was stirred at −5 °C for an additional hour and then left to stir overnight. The mixture was

filtered and the filtrate was evaporated under vacuum. The solid on the filter was extracted with 100 mL of water with heating to 80 °C, and the aqueous extract was added to the residue resulting from evaporation of the acetone solution. This mixture was acidified to pH 5 using HCl. The precipitated free acid was filtered and washed well with water, ethanol, ethyl acetate, and ethyl ether sequentially, and then dried under vacuum for 2 days to provide 4.6 g of **98** in 90% yield; mp >300 °C; IR (KBr) 3446, 1689; ^{1}H NMR (DMSO-d_6) δ 6.27 (s, 2H), 7.45 (s, 1H), 7.79 (d, 1H, J = 4.8), 8.08 (s, 1H), 8.79 (d, 1H, J = 4.8); ^{13}C NMR ($CDCl_3$ + 1 drop TFA-d) δ 98.1, 102.0, 104.9, 122.2, 128.6, 139.2, 139.7, 140.1, 153.6, 156.5, 166.6.

4-Acetyl-6,7-methylenedioxyquinoline (99)

Method A[157]: Compound **98** (500 mg, 2.3 mmol) was dissolved in THF (35 ml) and kept at 10 ^{o}C under nitrogen. Then MeLi (8.3 ml 11.5 mmol) was added all at once to this solution and the reaction mixture was allowed stirr for 4 hours, and then gradually allowed to warm to room temperature. The reaction mixture was slowly added to 25 ml water and this mixture was extracted with CH_2Cl_2 (2 x 50 ml) and the organic layer was washed with brine (2 x 50 ml) and dried (anhyd. Na_2SO_4) and concentrated under vacuum. The residue was subjected to column chromatography using chloroform to provide 114 mg (23%) of **99** as a yellow solid;

Method B: To a solution of 4-bromoquinoline **104** (1 g, 3.97 mmol) in toluene (20 mL) were successively added tributyl-(1-ethoxy-vinyl)-stannane (1.91 mL, 4.96 mmol), and $PdCl_2(PPh_3)_2$ (458 mg, 0.4 mmol). The reaction mixture was heated up to reflux for 3 h

under nitrogen. The reaction mixture was cooled to rt, diluted with chloroform and then filtered. To the filtrate was added dilute HCl solution and the resulting mixture was stirred for 1 h. The mixture was basified with 30% NaOH solution and extracted with chloroform (20 mL x 2). Organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography eluting with ethyl acetate in hexanes to get a yellow solid 640 mg in 75% yield; mp 79-80.5 ^oC IR (CH_2Cl_2) 1679 cm^{-1}; ^1H NMR δ 2.71 (s, 3H), 6.12 (s, 2H), 7.40 (s, 1H), 7.51 (d, 1H, *J*=3.2), 7.91 (s, 1H), 8.79 (d, 1H, *J*=3); ^{13}C NMR δ 29.5, 100.9, 101.8, 105.8, 118.6, 120.7, 140.1, 147.2, 147.9, 149.5, 150.4, 201.0.

(4-(1-(2-Iodo-4,5-dimethoxyphenyl)prop-1-en-2-yl)quinoline-6,7-methylenedioxy (100) [157]

A solution of 1.5 ml freshly prepared 0.2 M sodium ethoxide (0.3 mmol) in ethanol was added over 5 min to a stirred solution of 51 (172 mg, 0.27 mmol) in 1.5 ml dry ethanol at room temperature. The resulting ylide was stirred for 10 min and a solution was added consisting of 0.23 mmol of 56 (50 mg, 0.23 ml) in 1 ml dry ethanol. It was refluxed overnight. The milky white solution had turned in yellowish-brown. The solvent was removed under vacuum and the residue dissoleve in CH_2Cl_2 (10 ml). The CH_2Cl_2 solution was washed with water (10 ml), brine (20 ml) and concentrated under vacuum. The residue was chromatographed with chloroform to provide 100 mg (100%) of 57 as yellow-colored sticky glue; ^1H NMR δ 2.33 (s, 3H), 4.09 (s, 3H), 4.13 (s, 3H), 6.30 (s, 2H), 6.64 (s, 1H), 7.12 (s, 1H), 7.40 (d, 1H, *J*=6.6), 7.52 (s, 1H), 7.62 (s, 1H), 7.72 (s, 1H), 8.88 (d, 1H,

J=4.2); ^{13}C NMR δ 26.3, 54.9, 55.9, 100.4, 101.3, 105.5, 101.8, 111.5, 118.7, 120.8, 133.0, 136.9, 148.4; HRMS calcd for $C_{21}H_{19}INO_4H$: 476.0359; found 476.0342.

2,3-Dimethoxy-11-methylbenzo[*i*]phenanthridine-8,9-methylenedioxy (101)[157]

A solution of **100** (100 mg, 0.29 mmol) in acetonitrile (700 ml) was transferred to the photoreactor apparatus and was degassed by nitrogen purge for 30 min. The solution was then irradiated by UV lamp through a Vycor filter for 30 min. The mixture was removed from the photo reactor and the solvent was concentrated until solid precipitated out. It was filtered and washed with ether and hexane and dried to get a light brown solid in 20% yield; mp 188-189 ^{o}C; ^{1}H NMR (CD_2Cl_2) δ 2.83 (s, 3H), 4.04 (s, 6H), 6.20 (s, 2H), 7.28 (s, 1H), 7.63 (s, 1H), 7.74 (s, 1H), 8.33 (s, 1H), 8.40 (s, 1H), 9.33 (s, 1H); HRMS calcd for $C_{21}H_{18}NO_4H$: 348.1236; found: 348.1228.

3-Dimethylamino-1-[1,3]dioxolo[4,5-g]quinolin-8-yl-propan-1-one (102)

To a solution of LAH (23.6 mg, 0.62 mmol) in THF was added **106** (240 mg, 0.89 mmol) at -5 ^{o}C under nitrogen. After addition, the reaction mixture was dumped into 10 mL ethyl acetate and water was added. The mixture was filtered and the filtrate was concentrated to give a yellow solid 100 mg in 41% yield. The product was found to be instable on silica gel column. ^{1}H NMR ($CDCl_3$) *δ* 2.48 (s, 6H), 2.99 (t, 3H, *J*=7.0), 3.39 (t, 3H, *J*=7.0), 6.33 (s, 2H), 7.61 (s, 1H), 7.66 (d, 1H, *J*=4.8), 7.94 (s, 1H), 8.99 (d, 1H, *J*=4.6); ^{13}C NMR ($CDCl_3$) *δ* 39.5, 44.5, 53.4, 100.2, 101.2, 105.2, 116.8, 120.2, 140.7, 146.5, 147.2, 148.7, 149.9, 202.1.

Compound **103** was synthesized following the procedure reported in Ref. 123. Characterization of the compound was identical to the reported data.

Compound **104** was synthesized following the procedure reported in Ref. 201. Characterization of the compound was identical to the reported data. ^{1}H NMR ($CDCl_3$) δ 6.12 (s, 2H), 7.33 (s, 2H), 7.43 (s, 1H), 7.50 (d, 1H, *J*=4.8), 8.43 (d, 1H, *J*=4.6); ^{13}C NMR ($CDCl_3$) δ 101.3, 101.5, 105.1, 122.6, 124.3, 131.5, 146.4, 146.7, 148.3, 150.4.

Dimethyl-[3-(6,7-dimethoxyquinolin-4-yl)-prop-2-ynyl]-amine (105)

To a solution of dimethyl-prop-2-ynyl-amine in acetonitrile (20 mL) were successively added triethylamine (0.84 mL, 6 mmol), CuI (15.2 mg, 0.08 mmol), **104** (504 mg, 2 mmol) and $Pd(PPh_3)_4$ (28.1 mg, 0.04 mmol). The reaction mixture was stirred at rt for I h and heated up to 60 ^{o}C for 5 h. The reaction mixture was cooled to rt, diluted with chloroform and then filtered. The filtrate was washed by $NaHCO_3$ solution (5%, 20 mL) and extracted by HCl (1N, 20 mL x 2). The aqueous solution was then basified by 30% NaOH 20 mL and extracted with chloroform (20 mL x 2). Organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography eluting with 1% methanol in chloroform to get a beige solid 381 mg in 75% yield; ^{1}H NMR ($CDCl_3$) δ 2.64 (s, 6H), 3.84 (s, 2H), 6.33 (s, 2H), 7.55 (d, 1H, *J*=4.6), 7.57 (s, 1H), 7.75 (s, 1H), 8.83 (d, 1H, *J*=4.6); ^{13}C NMR ($CDCl_3$) δ 43.6, 47.9, 80.7, 92.9, 100.6, 101.0, 105.3, 121.4, 124.5, 127.5, 145.7, 146.6, 147.7, 150.0.

3-Dimethylamino-1-[1,3]dioxolo[4,5-g]quinolin-8-yl-propenone (106)

To a solution of **99** (83 mg, 0.39 mmol) was added dimethoxymethyl-dimethyl-amine 2 mL and the resulting reaction mixture was heated to 110 ^{o}C for 3 h. The reaction mixture was then cooled to rt and evaporated to dryness. The residue was purified by flash chromatography eluting with 1% methanol in chloroform to get a pale yellow solid 73 mg in 70% yield; IR ($CHCl_3$) 1642; ^{1}H NMR ($CDCl_3$) δ 3.04 (s, 3H), 3.25 (s, 3H), 5.58 (d, 2H, *J*=12.8), 6.24 (s, 2H), 7.41 (d, 1H, *J*=4.4), 7.52 (s, 1H), 7.64 (m, 2H), 8.85 (d, 1H, *J*=4.4); ^{13}C NMR ($CDCl_3$) δ 36.4, 44.3, 100.5, 100.9, 105.0, 116.2, 121.0, 127.7, 131.1, 146.4, 146.6, 147.4, 149.7, 154.8, 190.0.

(2-Iodo-4,5-dimethoxy-benzyl)-phosphonic acid diethyl ester (107)

A suspension of **96** (485 mg, 1.37 mmol) in triethyl phosphate (3 mL) was heated to 150 °C for 3 h under nitrogen. The reaction mixture was then cooled to rt and evaporated using Kugelror. The residue was chromatographed eluting with 97:3 dichloromethane–methanol, to provide 550 mg as a yellow oil, in 97% yield; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 6H, *J*=6.8), 3.32 (d, 2H, *J*=21.6), 3.85 (s, 3H), 3.86 (s, 3H), 4.05 (m, 4H), 7.03 (d, 1H, *J*=2.6), 7.21 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 15.6 (d, *J*=6.0), 36.9 (d, *J*=133.5), 55.1, 55.3, 61.4 (d, *J*=6.9), 88.1 (d, *J*=10.7), 112.3 (d, *J*=4.2), 120.7 (d, *J*=6.0), 126.7 (d, *J*=8.8), 147.7, 148.4.

Compound **108** was synthesized following the procedure reported in Ref. 206. Characterization of the compound was identical to the reported data in Ref. 228.

3-Benzyloxy-propionaldehyde (109) [227]

To a solution of oxalyl chloride (1.57 mL, 18 mmol) in anhydrous DCM (20 ml), at -78 °C and under nitrogen atmosphere, methyl sulfoxide (2.2 ml, 31 mmol) was added. After 15 minutes 3-benzyloxy-1-propanol **108** (5.74 g, 38.3 mmol) was added and the reaction mixture was stirred at -78 °C for 45 minutes. After the addition of triethylamine (11.4 ml, 82 mmol), the solution was stirred for 20 minutes at -78 °C and for further 20 minutes at r.t.. The mixture was treated with sat. aq. NaHCO3 and the aqueous layer was extracted three times with DCM. The combined organic phases were dried over Na_2SO_4, filtered and evaporated to dryness. The crude residue was flash chromatographed (25 - 35% ethyl acetate in hexanes) to give pure **109** (1.5 g, 91 %) as a viscous oil; ^{1}H NMR ($CDCl_3$) δ 2.70 (dt, 2H, *J*=5.8, 1.8), 3.82 (t, 2H, *J*=5.8), 4.53 (s, 2H), 7.31-7.35 (m, 5H), 9.80 (t, 1H, *J*=1.8); ^{13}C NMR ($CDCl_3$) δ 43.0, 63.0, 72.4, 126.8, 126.9, 127.6, 137.0, 200.3.

3-Benzyloxy-1-[1,3]dioxolo[4,5-g]quinolin-8-yl-propan-1-ol (110)

To a solution of **104** (930 mg, 3.7 mmol) in THF was added *n*-BuLi (2.42 mL, 3.89 mmol) at -78 ^{o}C dropwise. The resulting reaction mixture was stirred at the same temperature for 15 min, and then a solution of **109** (605 mg, 3.7 mmol) in THF was added dropwise over 3 min. The reaction mixture was then slowly warmed up to rt and quenched with water. The reaction solvent was evaporated and partitioned into chloroform and water. The organic layer was dried (anhyd. Na_2SO_4) and concentrated under vacuum. The residue was chromatographed with hexanes and ethyl acetate to provide 400 mg (32%) of **110** as a yellow oil; ^{1}H NMR ($CDCl_3$) δ 2.04-2.15 (m, 2H,), 3.67-3.75 (m, 2H), 4.22 (s, 1H), 4.55 (s, 2H), 5.46 (m, 1H), 6.07 (m, 2H), 7.22-7.35 (m, 7H), 7.41 (d, 1H, *J*=4.6), 8.58 (d, 1H,

J=4.6); ^{13}C NMR ($CDCl_3$) δ 37.4, 68.3, 69.3, 73.4, 98.6, 101.7, 106.3, 116.1, 122.0, 127.7, 127.8, 128.5, 137.7, 146.4, 147.8, 147.9, 148.7, 149.9.

3-Benzyloxy-1-[1,3]dioxolo[4,5-g]quinolin-8-yl-propan-1-one (111)

To a solution of **110** (350 mg, 1.04 mmol) in 20 mL dichloromethane was added MnO2 (2 g) and the resulting reaction mixture was stirred for 2 days. The reaction mixture was filtered through a celite pad and the filtrated was concentrated under vacuum. The residue was chromatographed with chloroform to provide 210 mg (60%) of **111** as yellow oil; ^{1}H NMR ($CDCl_3$) δ 3.25 (t, 2H, *J*=6.2), 3.90 (t, 2H, *J*=6.2), 4.51 (s, 2H), 6.08 (s, 2H), 7.26-7.27 (m, 5H), 7.30 (s, 1H), 7.44 (d, 1H, *J*=4.8), 7.75 (s, 1H), 8.78 (d, 1H, *J*=4.8); ^{13}C NMR ($CDCl_3$) δ 41.5, 64.7, 72.5, 100.2, 101.2, 105.2, 108.8, 117.0, 120.0, 120.1, 126.8, 127.5, 137.0, 140.5, 146.5, 147.1, 148.7, 149.9, 201.5.

1,1-Dibromo-2-(3,4-dimethoxyphenyl)ethylene (112) [214]

A mixture of CBr_4 (29.8 g, 0.09 mol) and PPh_3 (47.2 g, 0.18 mol) in dichloromethane (200 mL) was stirred under nitrogen at room temperature for 1 h. To this mixture was added 3,4-dimethoxybenzaldehyde (10.0 g, 0.06 mol)at 0 ºC and the mixture was stirred for 16 h at room temperature. The resulting precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was chromatographed in 10:1 Hexanes/EtOAc to provide a colorless oil in 55% yield; IR (KBr) 1600, 2834; ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3H), 3.90 (s, 3H), 6.85 (d, 1H, *J* = 8.0), 7.10 (dd, 1H, *J* = 8.0, 2.2), 7.18 (d, 1H, *J* = 2.2), 7.41 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.0, 55.1, 86.5, 110.0, 110.4, 121.1, 127.1, 135.6, 147.8, 148.5.

Ethyl 3-(3,4-dimethoxyphenyl)propynoate (113) [214]

To a solution of **112** (4.0 g, 12.5 mmol) in dry THF was added BuLi (1.6 M in hexane) (17.2 mL, 27.5 mmol) at -78 ºC under nitrogen and the mixture was warmed up to room temperature with stirring for 1 h. Then the reaction mixture was cooled down to -78 ºC and ethyl chloroformate (1.62 g, 15.0 mmol) was added. The resulting reaction mixture was stirred at room temperature for 30 min. The reaction was quenched by addition of sat. NH_4Cl and then extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed in 20:1 Hexanes/EtOAc to provide a colorless oil in 96% yield; IR (KBr) 1704, 2211; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, 3H, J = 7.2), 3.88 (s, 3H), 3.91 (s, 3H), 4.29 (q, 2H, J = 7.2), 6.84 (d, 1H, J = 8.4), 7.06 (d, 1H, J = 2.0), 7.23 (dd, 1H, J = 8.4, 2.0); ^{13}C NMR ($CDCl_3$) δ 13.2, 55.2, 55.1, 61.0, 79.1, 86.1, 110.3, 110.6, 114.5, 126.3, 148.0, 150.7, 153.3.

Ethyl (*Z*)-3-(3,4-dimethoxyphenyl)-2-(tributylstannyl)propenoate (114)

To a solution of **113** (510 mg, 2.18 mmol) and Bu_3SnH (666 mg, 2.29 mmol) in benzene was added AIBN (9 mg, 0.0545 mmol) under nitrogen and the mixture was stirred at room temperature for 19 h. Solvent was removed and the residue was chromatographed in 5:1 Hexanes/EtOAc to provide a colorless oil in 66% yield; ^{1}H NMR ($CDCl_3$) δ 0.70-1.00 (m, 15H), 1.00-1.40 (m, 15H), 3.75 (s, 6H), 4.11 (q, 2H, J = 7.0), 6.69-6.75 (m, 3H), 8.21 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 10.9, 12.6, 13.4, 26.2, 28.0, 54.9, 54.9, 59.6, 110.0, 110.6, 119.9, 130.7, 136.5, 147.8, 148.8, 152.7, 170.8.

2-(6,7-Methylenedioxyquinolin-4-yl)-3-(4,5-dimethoxyphenyl)acrylic acid ethyl ester (115)

A mixture of **114** (500 mg, 0.952 mmol), 4-bromo-6,7-methylenedioxyquinoline, **7**, (240 mg, 0.952 mmol) and $PdCl_2(PPh_3)_2$ (33.4 mg, 0.0476 mmol) in DMF (15 mL) was stirred under nitrogen at 60 ºC for 5 h aq. KF (276.1 mg, 4.76 mmol) was added and the reaction mixture was stirred for 1 h. The insoluble material was filtered off and the filtrate was extracted with dichloromethane. The organic layer was washed with brine, dried and concentrated under reduced pressure. The residue was chromatographed in 1:1 Hexanes/EtOAc to provide a light yellow foam in 57% yield; IR (KBr) 1705; ^{1}H NMR ($CDCl_3$) δ 1.23 (t, 3H, J = 7.0), 3.18 (s, 3H), 3.80 (s, 3H), 4.26 (q, 2H, J = 7.0), 6.06 (m, 2H), 6.22 (d, 1H, J = 2.2), 6.68 (d, 1H, J = 8.4), 6.82 (dd, 1H, J = 8.4, 2.2), 7.06 (s, 1H), 7.19 (d, 1H, J = 4.8), 7.44 (s, 1H), 8.05 (s, 1H), 8.76 (d, 1H, J = 4.8); ^{13}C NMR ($CDCl_3$) δ 13.3, 54.0, 54.9, 60.4, 99.4, 100.9, 105.3, 109.8, 111.1, 119.7, 123.3, 124.86 125.1, 125.6, 141.2, 141.8, 146.2, 147.3, 147.5, 147.6, 149.7, 150.0, 166.0; HRMS calcd for $C_{23}H_{21}NO_6H$: 408.1447; found 408.1437.

2,3-Dimethoxy-8,9-methylenedioxybenzo[*i*]phenanthridine-11-carboxylic acid ethyl ester (116)

A solution of **115** (100 mg, 0.245 mmol) and iodine (2 mg) in benzene (250 mL) was irradiated by a Hanovia 450W medium-pressure lamp through a Pyrex filter for 6h, with air bubbling through the reaction mixture. The solvent was removed under reduced pressure and the residue was chromatographed in 10:1 $CHCl_3$/MeOH to provide a light yellow powder in 35% yield; mp 240-243 ºC; IR (KBr) 1712; ^{1}H NMR ($CDCl_3$) δ 1.44 (t, 3H, J =

7.0), 4.06 (s, 3H), 4.16 (s, 3H), 4.54 (q, 2H, J = 7.0), 6.15 (s, 2H), 7.29 (s, 1H), 7.47 (s, 1H), 7.55 (s, 1H), 8.09 (s, 1H), 8.18 (s, 1H), 9.89 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.2, 55.2, 55.3, 61.1, 101.0, 101.2, 101.8, 106.3, 107.6, 118.6, 120.6, 124.9, 125.1, 125.5, 127.0, 131.6, 142.7, 144.3, 146.7, 148.3, 149.4, 151.0, 170.0; HRMS calcd for $C_{23}H_{19}NO_6H$: 406.1273; found 406.1273.

11-Aminocarbonylmethyl-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*] phenanthridine (117)

A mixture of **116** (41 mg, 0.1 mmol) in 10% NaOH (5 mL) and ethanol (10 mL) was heated to reflux with stirring for 1h. The reaction mixture was acidified with 2N HCl to pH = 4, and then evaporated to dryness. The residue was suspended in 10 mL dichloromethane and 0.5 mL thionyl chloride was added. The resulting reaction mixture was refluxed for 2h and then concentrated. The reaction residue was again suspended in dichloromethane and 0.5 mL triethylamine was added. After 15 min, 0.5 mL ammonia solution (2.0 M in tetrahydrofuran) was added and the resulting reaction mixture was refluxed for 1h. The organic solvent and excess amine was removed under reduced pressure and the residue was chromatographed in 20:1 CH_2Cl_2/MeOH to provide a off-white powder in 65% yield; mp 265-269 ºC; IR (KBr) 1647; ^{1}H NMR (CD_3COOD) δ 3.95 (s, 3H), 4.09 (s, 3H), 6.25 (s, 2H), 7.56 (s, 1H), 7.64 (s, 1H), 7.94 (br, 1H), 8.08 (s, 2H), 8.36 (br, 1H), 8.42 (s, 1H), 10.18 (s, 1H); ^{13}C NMR (CD_3COOD) δ 55.5, 55.9, 101.9, 102.0, 102.7, 106.4, 108.2, 118.8, 120.9, 124.7, 125.6, 130.6, 142.7, 146.1, 147.2, 148.5, 149.8, 150.9, 173.0; HRMS calcd for $C_{21}H_{16}N_2O_5H$: 377.1132; found 377.1134.

11-(N-Methylamino)carbonylmethyl-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*] phenanthridine (118)

A mixture of **116** (41 mg, 0.1 mmol) in 10% NaOH (5 mL) and ethanol (10 mL) was heated to reflux with stirring for 1h. The reaction mixture was acidified with 2N HCl to pH = 4, and then evaporated to dryness. The residue was suspended in 10 mL dichloromethane and 0.5 mL thionyl chloride was added. The resulting reaction mixture was refluxed for 2h and then concentrated. The reaction residue was again suspended in dichloromethane and 0.5 mL triethylamine was added. After 15 min, 0.5 mL methylamine (2.0 M in tetrahydrofuran) was added and the resulting reaction mixture was refluxed for 1h. The organic solvent and excess amine was removed under reduced pressure and the residue was chromatographed in 20:1 CH_2Cl_2/MeOH to provide a off-white powder in 67% yield; mp 271-273 ºC; IR (KBr) 1653; ^{1}H NMR (DMSO-d_6) δ 2.91 (d, 3H, J = 4.4), 4.08 (s, 3H), 4.08 (s, 3H), 6.24 (m, 2H), 7.55 (s, 1H), 7.63 (s, 1H), 7.73 (s, 1H), 8.06 (s, 1H), 8.42 (s, 1H), 9.00 (br, 1H), 10.19 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 26.2, 55.5, 55.9, 101.6, 101.9, 102.7, 106.5, 108.1, 118.7, 120.8, 124.8, 125.6, 130.1, 130.3, 142.8, 146.1, 146.1, 147.2, 148.5, 149.8, 151.0, 171.3; HRMS calcd for $C_{22}H_{18}N_2O_5H$: 391.1288; found 391.1290.

11-(N,N-Dimethylamino)carbonylmethyl-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*] phenanthridine (119)

A mixture of **116** (41 mg, 0.1 mmol) in 10% NaOH (5 mL) and ethanol (10 mL) was heated to reflux with stirring for 1h. The reaction mixture was acidified with 2N HCl to pH = 4, and then evaporated to dryness. The residue was suspended in 10 mL dichloromethane and 0.5 mL thionyl chloride was added. The resulting reaction mixture was refluxed for 2h and

then concentrated. The reaction residue was again suspended in dichloromethane and 0.5 mL triethylamine was added. After 15 min, 0.5 mL dimethylamine (2.0 M in tetrahydrofuran) was added and the resulting reaction mixture was refluxed for 1h. The organic solvent and excess amine were removed under reduced pressure and the residue was chromatographed in 20:1 CH_2Cl_2/MeOH to provide a off-white powder in 75% yield; mp 271-275 ºC; IR (KBr) 1621; ^{1}H NMR ($CDCl_3$) δ 2.68 (s, 3H), 3.31 (s, 3H), 4.06 (s, 3H), 4.17 (s, 3H), 6.15 (m, 2H), 7.27 (s, 1H), 7.58 (s, 1H), 7.72 (s, 1H), 7.89 (s, 1H), 8.15 (s, 1H), 9.97 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 34.4, 37.5, 55.2, 55.3, 100.2, 101.0, 101.3, 106.7, 107.1, 118.9, 120.3, 124.7, 125.6, 126.5, 128.5, 128.8, 142.7, 144.8, 147.8, 148.3, 149.5, 150.5, 171.8; HRMS calcd for $C_{23}H_{20}N_2O_5H$: 405.1445; found 405.1447.

2,3-Dimethoxy-8,9-methylenedioxybenzo[*i*]phenanthridine-11-carboxylic acid 2-(dimethylamino)ethylamide (120)

A mixture of **116** (41 mg, 0.1 mmol) in 10% NaOH (5 mL) and ethanol (10 mL) was heated to reflux with stirring for 1h. The reaction mixture was acidified with 2N HCl to pH = 4, and then evaporated to dryness. The residue was suspended in 10 mL dichloromethane and 0.5 mL thionyl chloride was added. The resulting reaction mixture was refluxed for 2h and then concentrated. The reaction residue was again suspended in dichloromethane and 0.5 mL triethylamine was added. After 15 min, 0.5 mL dimethylaminoethylenediamine was added and the resulting reaction mixture was refluxed for 1h. The organic solvent and excess amine were removed under reduced pressure and the residue was chromatographed in 20:1 CH_2Cl_2/MeOH to provide a off-white powder in 63% yield; mp 221-225 ºC; IR

(KBr) 1635; ^{1}H NMR ($CDCl_3$) δ 2.26 (s, 6H), 2.64 (t, 2H, J = 6.0), 3.71 (m, 2H), 4.03 (s, 3H), 4.11 (s, 3H), 6.09 (s, 2H), 7.15 (br, 1H), 7.18 (s, 1H), 7.38 (s, 1H), 7.66 (s, 1H), 7.85 (s, 1H), 7.94 (s, 1H), 9.61 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 36.9, 44.2, 55.1, 55.2, 56.7, 100.9, 101.1, 101.7, 106.1, 107.1, 118.4, 120.4, 124.8, 125.1, 126.5, 129.3, 129.9, 142.4, 144.3, 146.8, 148.0, 149.3, 150.4, 171.0; HRMS calcd for $C_{25}H_{25}N_3O_5H$: 448.1872; found 448.1870.

11-Hydroxymethyl-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*]phenanthridine (121)

To a stirred solution of LAH (41.8 mg, 1.1 mmol) in 20 mL THF was added a THF solution of **116** (223.3 mg, 0.55 mmol) dropwise at 0 ^{o}C. The resulting reaction suspension was stirred for 2 h at 0 ^{o}C, and then carefully quenched by addition of 0.05 mL water, 0.05 mL 15% NaOH and 0.15 mL water sequentially. The resulting reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was chromatographed in 10:1 $CHCl_3$/MeOH to provide a yellow powder in 57% yield; mp 270-272 ºC; IR (KBr) 3448; ^{1}H NMR (DMSO-d_6) δ 3.95 (s, 3H), 4.07 (s, 3H), 5.08 (s, 2H), 5.88 (s, 1H), 6.25 (s, 2H), 7.54 (s, 1H), 7.56 (s, 1H), 8.19 (s, 1H), 8.37 (s, 1H), 8.57 (s, 1H), 10.13 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 55.5, 55.8, 64.2, 101.7, 102.7, 104.2, 106.3, 107.7, 119.7, 121.5, 124.4, 126.3, 130.3, 132.4, 133.1, 143.1, 146.3, 147.4, 148.1, 149.6, 150.4; HRMS calcd for $C_{21}H_{17}NO_5H$: 364.1185; found 364.1196.

11-Formyl-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*]phenanthridine (122)

A solution of **121** (363 mg, 1 mmol), MnO_2 (870 mg, 10 mmol) in 30 mL DMF was stirred for 2 h at room temperature. The resulting reaction mixture was filtered through a celite

bed and filtrate was concentrated under reduced pressure. The residue was chromatographed in 20:1 CH_2Cl_2/MeOH to provide a brown powder in 62% yield; mp 250-255 ºC; IR (KBr) 1685; ^{1}H NMR ($CDCl_3$+CD_3OD) δ 3.99 (s, 3H), 4.11 (s, 3H), 6.11 (s, 1H), 7.36 (s, 1H), 7.39 (s, 1H), 7.49 (s, 1H), 8.05 (s, 1H), 8.43 (s, 1H), 9.79 (s, 1H), 10.51 (s, 1H); HRMS calcd for $C_{21}H_{15}NO_5H$: 362.1028; found 362.1039.

11-Dimethylaminomethyl-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*]phenanthridine (123)

To a solution of **122** (7.2 mg, 0.02 mmol) and dimethylamine (0.2 mmol, 2 M in THF) in 3 mL MeOH was added a solution of $NaBH_3CN$ (9.4 mg, in 0.1 mL MeOH, 0.15 mmol) at 0 ^{o}C. The resulting reaction solution was stirred for an additional 30 min at 0 ^{o}C, and then 2 drops of AcOH was added. The reaction mixture was warmed up to 40 ^{o}C with stirring for another 2 h. The resulting mixture was quenched by 0.1 mL 1N NaOH solution, concentrated, and extracted using $CHCl_3$ (2 x 15 mL). The organic layer was concentrated and the residue was chromatographed in 15:1 CH_2Cl_2/MeOH to provide a yellow powder in 55% yield; mp 220-222 ºC; ^{1}H NMR ($CDCl_3$) δ 2.48 (s, 6H), 3.93 (s, 2H), 4.08 (s, 3H), 4.15 (s, 3H), 6.16 (s, 2H), 7.28 (s, 1H), 7.58 (s, 1H), 7.92 (s, 1H), 8.14 (s, 1H), 8.93 (s, 1H), 9.93 (s, 1H); HRMS calcd for $C_{23}H_{22}N_2O_4H$: 391.1652; found 391.1654.

11-Aminomethyl-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*]phenanthridine (125)

Method A: To a solution of **122** (7.2 mg, 0.02 mmol) and ammonium acetate (15.4 mg, 0.2 mmol) in 3 mL MeOH was added a solution of $NaBH_3CN$ (9.4 mg, in 0.1 mL MeOH, 0.15 mmol) at 0 ^{o}C. The resulting reaction solution was stirred for an additional 30 min at 0 ^{o}C,

and then 2 drops of AcOH was added. The reaction mixture was warmed up to 40 ^{o}C with stirring for another 2 h. The resulting mixture was quenched by 0.1 mL 1N NaOH solution, concentrated, and extracted using $CHCl_3$ (2 x 15 mL). The organic layer was concentrated and the residue was chromatographed in 15:1 CH_2Cl_2/MeOH to provide a yellow powder in 47% yield; Method B: A solution of **122**, hydroxylamine hydrochloride, pyridine in 5 mL EtOH was heated to reflux for 3 h. The reaction mixture was concentrated and partitioned in water and chloroform. The organic layer was dried over sodium sulfate and then concentrated. The crude product **124** was used directly for reduction without further purification. To a suspension of **124** and ammonium formate in MeOH was added Zn powder 10 mg, and the resulting reaction mixture was heated to reflux for 2 h. The reaction mixture was filtered concentrated, and then partitioned into water/chloroform. The organic layer was dried over sodium sulfate and evaporated. The crude product was purified by flash chromatography eluting with 1% methanol in chloroform to get a yellow powder 7 mg in 70% yield;

mp 189-194 ºC; ^{1}H NMR ($CDCl_3$) δ 4.07 (s, 3H), 4.15 (s, 3H), 4.61 (s, 2H), 6.17 (s, 2H), 7.26 (s, 1H), 7.60 (s, 1H), 8.05 (s, 1H), 8.12 (s, 1H), 8.56 (s, 1H), 9.94 (s, 1H); HRMS calcd for $C_{21}H_{18}N_2O_4H$: 363.1339; found 363.1342.

2,3-Dimethoxy-8,9-methylenedioxy-11-(2-nitrovinyl)-benzo[*i*]phenanthridine (126)

A suspension of **122** (36 mg, 0.1 mmol), ammonium acetate (38.6 mg, 0.5 mmol) in 2 mL nitromethane was stirred overnight at 80 ^{o}C. The resulting reaction mixture was triturated with a small amount of CH_2Cl_2 and the residue was pure enough and used for the next reaction without further purification; yield: 89%; mp 241-245 ºC; IR (KBr) 1509; ^{1}H NMR

($CDCl_3$+CD_3OD) δ 4.08 (s, 3H), 4.18 (s, 3H), 6.19 (s, 2H), 7.33 (s, 1H), 7.63 (s, 1H), 7.67 (s, 1H), 7.76 (d, 1H, J = 13.2), 8.06 (s, 1H), 8.12 (s, 1H), 8.80 (d, 1H, J = 13.2), 9.91 (s, 1H); HRMS calcd for $C_{22}H_{16}N_2O_6H$: 405.1087; found 405.1089.

2,3-Dimethoxy-8,9-methylenedioxy-11-(2-nitroethyl)-benzo[*i*]phenanthridine (127)

To a stirred suspension of $NaBH_4$ (38 mg, 1 mmol) in 10 mL 1,4-dioxane/EtOH (2:1) was added a solution of **126** (80.8 mg, 0.2 mmol) in 1,4-dioxane (5 mL) dropwise at 0 ^oC. After this addition, the reaction mixture was stirred for an additional 30 min. The resulting reaction mixture was diluted with ice-water and quenched with 50% aqueous AcOH. The resulting suspension was concentrated and then partitioned between sat $NaHCO_3$ and CH_2Cl_2. The organic layer was again concentrated and the residue was chromatographed in 10:1 CH_2Cl_2/MeOH to provide a yellow powder in 69% yield; mp 277-280 ºC; IR (KBr) 1554;

^{1}H NMR ($CDCl_3$+CD_3OD) δ 3.99 (s, 3H), 4.08 (s, 3H), 4.16 (t, 2H, J = 7.6), 4.79 (t, 2H, J = 7.6), 6.13 (s, 2H), 7.19 (s, 1H), 7.52 (s, 1H), 7.82 (s, 1H), 7.94 (s, 1H), 8.04 (s, 1H), 9.82 (s, 1H); HRMS calcd for $C_{22}H_{18}N_2O_6H$: 407.1243; found 407.1231.

11-(2-Aminoethyl)-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*]phenanthridine (128)

To a stirred suspension of **127** (50 mg, 0.12 mmol) in 1.0 mL acetic acid was added Zn power (15.7 mg, 0.24 mmol) portionwise at room temperature. The reaction mixture was stirred for an additional 3 h, diluted with saturated sodium bicarbonate, and then filtered. The filtrate was concentrated, and partitioned between sat. $NaHCO_3$ solution and CH_2Cl_2. The organic layer was again concentrated and the residue was chromatographed in 10:1:0.1

CH_2Cl_2/MeOH/TEA to provide a yellow-green powder in 41% yield; mp 192-198 ºC; ^{1}H NMR ($CDCl_3$+CD_3OD) δ 3.27 (t, 2H, J = 6.6), 3.62 (t, 2H, J = 6.6), 4.07 (s, 3H), 4.14 (s, 3H), 6.17 (s, 2H), 7.24 (s, 1H), 7.60 (s, 1H), 7.87 (s, 1H), 8.11 (s, 1H), 8.13 (s, 1H), 9.94 (s, 1H); HRMS calcd for $C_{22}H_{20}N_2O_4H$: 377.1501; found 377.1497.

12-(2-Dimethylamino)ethyl-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*] phenanthridine (129)

To a solution of **128** (8 mg, 0.02 mmol) and formalin (0.1 mmol) in 3 mL MeOH was added a solution of $NaBH_3CN$ (9.4 mg, in 0.1 mL MeOH, 0.15 mmol) at 0 ^{o}C. The resulting reaction solution was stirred for an additional 30 min at 0 ^{o}C, and then 2 drops of AcOH were added. The reaction mixture was warmed up to room temperature with stirring for another 2 h. The resulting mixture was quenched by 0.1 mL 1N NaOH solution, concentrated, and extracted by $CHCl_3$ (2 x 15 mL). The organic layer was concentrated and the residue was chromatographed in 15:1 CH_2Cl_2/MeOH to provide a yellow powder in 53% yield; mp 199-201 ºC; ^{1}H NMR ($CDCl_3$+CD_3OD) δ 2.46 (s, 6H), 2.85 (t, 2H, J = 7.8), 3.65 (t, 2H, J = 7.8), 4.07 (s, 3H), 4.14 (s, 3H), 6.17 (s, 2H), 7.28 (s, 1H), 7.60 (s, 1H), 7.89 (s, 1H), 8.10 (s, 1H), 8.18 (s, 1H), 9.94 (s, 1H); HRMS calcd for $C_{24}H_{24}N_2O_4H$: 405.1814; found 405.1809.

11-[(3-Dimethylamino)prop-1-enyl]-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*] phenanthridine (130)

To a suspension of 2-(dimethylamino)ethyltriphenylphosphonium bromide (40 mg, 0.095 mmol) in 5 mL THF was added LiHMDS (1.0 M in THF, 0.1 mmol) dropwise at room

temperature. A solution of **122** (28 mg, 0.077 mmol) in THF was added to the reaction mixture dropwise and the resulting solution was stirred for 1.5 h, quenched by 0.1 mL water, concentrated and partitioned into CH_2Cl_2/water. The organic layer was again concentrated under reduced pressure and the residue was chromatographed in 20:1 CH_2Cl_2/MeOH to provide a yellow powder in 47% yield; two inseparable isomers were obtained. The major isomer: mp 220-225 ºC; ^{1}H NMR ($CDCl_3$+CD_3OD) δ 2.47 (s, 6H), 3.29 (d, 2H, J=6.6), 4.08 (s, 3H), 4.16 (s, 3H), 6.18 (s, 2H), 6.35 (dt, 1H, J=15.8, 6.6), 7.27 (s, 1H), 7.29 (d, 1H, J = 15.8), 7.58 (s, 1H), 7.71 (s, 1H), 8.13 (s, 1H), 8.62 (s, 1H), 9.94 (s, 1H); HRMS calcd for $C_{25}H_{24}N_2O_4H$: 417.1814; found 407.1801.

11-[(3-Dimethylamino)propyl]-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*] phenanthridine (131)

A suspension of **130** (15 mg, 0.037 mmol) and Pd-C (10 mg) in 10 mL ethanol was shaken under hydrogen (40 psi) for 24 h. The mixture was filtered through celite and concentrated under reduced pressure. The residue was chromatographed in 20:1 CH_2Cl_2/MeOH to provide a yellow powder in 44% yield; mp 204-209 ºC; ^{1}H NMR ($CDCl_3$) δ 2.10 (m, 2H), 2.34 (s, 6H), 2.54 (t, 2H, J = 7.8), 3.49 (t, 2H, J = 7.8), 4.07 (s, 3H), 4.14 (s, 3H), 6.17 (s, 2H), 7.26 (s, 1H), 7.60 (s, 1H), 7.89 (s, 1H), 8.12 (s, 1H), 8.14 (s, 1H), 9.95 (s, 1H); HRMS calcd for $C_{25}H_{26}N_2O_4H$: 419.1971; found 419.1978.

2-Dimethylamino-2-methyl-propionitrile (132)[224]

A solution of KCN (13g, 200 mmol) in 100 mL water was added to a stirred, cooled suspension of dimthylamine hydrochloride (16.3g, 200 mmol) and acetone (6.96 g, 120 mmol). The mixture was stirred overnight at rt and then extracted with ether (50 mL x 3). The organic layer was dried over Na_2SO_4 and then concentrated under vacuum to provide product 9.32 g in 92% yield as a colorless, water-like liquid. ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 6H), 2.36 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 26.8, 40.8, 57.2, 119.7.

2-Dimethylamino-2-methyl-propylamine (133)[225]

To a suspension of LAH (3.8 g, 100 mmol) in 150 mL ether was added a solution of **132** (5.6g, 50 mmol) in ether (12 mL) dropwise at -5°C. The reaction was stirred at rt for 5 h and then cooled down to -5°C. 4 mL water, 4 mL 15% NaOH and 12 mL water were added sequentially. The resulting mixture was filtered and filtrate was extracted with water, brine and dried over Na_2SO_4. The organic extract was concentrated under vacuum and then distilled to afford a colorless water-like liquid 5.3 g in 91% yield. bp 145-147 °C; ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 6H), 1.38 (s, 2H), 2.20 (s, 6H), 2.56 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 19.2, 37.5, 49.9, 55.8.

4-(2-dimethyamino-2-methyl)propylamino-6,7-methylenedioxyquinoline (134)

4-Chloroquinoline (1.0 g, 4.8 mmol) was stirred in refluxing phenol for 2.5 hours, then the bath temp was lowered to 125 °C, and 2-dimethylamino-2-methyl-propylamine (1.0 g, 8.7 mmol) was added. The mixture was stirred at this temperature for 20 h, and then phenol was removed on the Kugelrohr, and the resulting crude residue was partitioned between

chloroform (100 mL) and 3% HCl (300 mL), and the aqueous phase was washed with chloroform (3 x 100 mL), made basic with 20% NaOH, and extracted with chloroform (4 x 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated, to give 1.2 g as a beige solid, in 96% yield; mp 158-160 °C; ^{1}H NMR ($CDCl_3$) δ 1.17 (s, 6H), 2.27 (s, 6H), 3.08 (d, 2H, J = 3.6), 5.93 (s, 1H), 6.09 (s, 2H), 6.29 (d, 1H, J = 5.6), 7.28 (s, 1H), 7.36 (s, 1H), 8.36 (d, 1H, J = 5.6); ^{13}C NMR ($CDCl_3$) δ 21.1, 38.3, 51.7, 55.7, 96.3, 98.6, 101.5, 106.7, 114.4, 146.5, 146.6, 149.1, 149.7,149.9.

N-(6,7-Methylenedioxyquinolin-4-yl)-N-[(2-(dimethylamino)-2-methyl-propyl]-2-iodo-4,5-dimethoxybenzamide (135)

Oxalyl chloride (800 mg, 5.0 mmol) was added to a solution of **10** (310 mg, 1.0 mmol) in anhydrous methylene chloride (40 mL) and the stirred mixture was refluxed for 4 hours. The mixture was then concentrated to dryness under reduced pressure. The acid chloride was dissolved in 40 mL of methylene chloride and added to a solution of **134** (240 mg, 8.84 mmol), and triethylamine (1.1 g, 11 mmol) in methylene chloride (50 mL) and the resulting mixture was stirred at reflux under nitrogen for 2 hours. The reaction mix was cooled and washed with a saturated solution of sodium bicarbonate (3 x 75 mL), and extracted into dilute HCl (4 x 100 mL). The aqueous extract was then neutralized with 30% NaOH and extracted with $CHCl_3$ (4 x 100 mL), washed with brine (100mL), dried ($MgSO_4$) and evaporated, yielding 315 mg as a light yellow sticky semisolid glue, in 65% yield; IR (neat): 1655; ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 3H), 1.18 (s, 3H), 1.91 (s, 6H), 3.21 (s, 3H), 3.60 (d, 1H, J = 14.0), 3.66 (s, 3H), 4.47 (d, 1H, J = 14.0), 6.07 (s, 2H), 6.25 (s, 1H), 6.96 (s, 1H), 7.27 (s, 1H), 7.29 (s, 1H), 7.38 (d, 1H, J = 4.8), 8.45 (d, 1H, J = 4.8); ^{13}C NMR

($CDCl_3$) δ 19.6, 24.4, 38.2, 54.5, 55.4, 56.0, 58.8, 82.5, 98.6, 102.1, 106.7, 110.3, 121.1, 121.6, 122.5, 134.2, 147.3, 147.9, 147.9, 148.0, 148.7, 149.4, 150.6, 170.4.

8,9-Dimethoxy-2,3-methylenedioxy-5-[2-(*N*,*N*-dimethylamino)-2-methyl-propyl]-5*H*-dibenzo[*c*,*h*][1,6]naphthyridin-6-one (136)

A mixture of **11** (315 mg, 0.546 mmol), $Pd(OAc)_2$ (25 mg, 0.110 mmol), P(*o*-tolyl)$_3$ (68 mg, 0.220 mmol), and Ag_2CO_3 (302.5 mg, 1.1 mmol) in dimethylformamide (DMF) (35 mL) was heated to reflux with stirring for 30 min. The reaction mixture was cooled, diluted with chloroform, and filtered through Celite, and the solvent was removed under vacuum. The crude residue was chromatographed in 99:1 chloroform/methanol to provide 260 mg (52%) of the cyclized product as a white solid; mp 241-243 °C; IR (neat): 1649; ^{1}H NMR ($CDCl_3$) δ 0.67 (s, 6H), 1.18 (s, 3H), 2.04 (s, 6H), 40.5 (s, 3H), 4.12 (s, 3H), 4.90 (m, 2H), 6.14 (s, 2H), 7.28 (s, 1H), 7.39 (s, 1H), 7.60 (s, 1H), 7.64 (s, 1H), 7.85 (s, 1H), 9.30 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.9, 22.4, 38.5, 53.9, 56.3, 56.3, 60.2, 101.0, 102.1, 107.0, 109.5, 112.7, 115.9, 120.0, 127.1, 128.4, 141.7, 143.1, 146.8, 147.4, 149.9, 150.1, 154.0, 165.3. HRMS *m/z* Calcd for $C_{25}H_{27}O_5N_3Li$: 456.2111; Found: 456.2093.

2-Dibenzylamino-2-methyl-propan-1-ol (137) [227]

To a solution of 2-amino-2-methyl-propan-1-ol (5.1 mL, 53.3 mmol) in acetone and water (4:1, 100 mL) were added benzyl bromide and potassium carbonate (14.74 g, 106.6 mmol). The resulting reaction mixture was heated to reflux for 40 h. The reaction mixture was evaporated and partitioned in dichloromethane and water. The organic layer was then washed with brine (100 mL), dried (Mg_2SO_4), and evaporated, yielding 15 g in 98% yield

as a light yellow solid; ^{1}H NMR ($CDCl_3$) δ 1.13 (s, 6H), 3.02 (s, 1H), 3.47 (s, 2H), 3.76 (s, 4H), 7.17-7.28 (m, 10H).

(2-Chloro-1,1-dimethyl-ethyl)dibenzylamine, hydrochloride (138)

To a solution of **137** (1 g, 3.72 mmol) in chloroform was added thionyl chloride (1.35 mL, 18.5 mmol) dropwise under nitrogen. The resulting reaction mixture was heated to reflux for 3 h. The reaction solvent and excess thionyl chloride were removed under vacuum. The residue was triturated with ether to afford a white plate 1.2 g in 99% yield. ^{1}H NMR ($CDCl_3$) δ 1.54 (s, 6H), 3.23 (s, 2H), 4.25-4.73 (m, 4H), 7.44 -7.47(m, 6H), 7.68-7.70 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 31.2, 58.8, 60.2, 64.9, 128.3, 129.5, 130.6, 132.7.

4-Amino-6,7-methylenedioxyquinoline (139)

A mixture of 4-chloro-6,7-methylenedioxy-quinoline (2.6 g, 12.5 mmol) and phenol (12.0 g, 128 mmol) was heated to 150 °C for 90 minutes. During the final 30 minutes ammonium acetate (10.0 g, 125 mmol) was heated to 150 °C in a separate flask, and then the molten ammonium acetate was added to the reaction flask in one batch. The mixture was allowed to react at this temperature for 90 minutes, then the solvent was removed under vacuum and the solid product was diluted by 30 mL isopropyl alcohol. The precipitate was filtered, washed with additional water, and dried, yielding 1 g as a white solid, in 43%; ^{1}H NMR (DMSO-d^6) δ 6.15 (s, 2H), 6.47 (d, 1H, J=5.2), 6.80 (s, 2H), 7.13

(s, 1H), 7.59 (s, 1H), 8.13 (d, 1H, *J*=5.2); ^{13}C NMR (DMSO-d^6) δ 99.1, 102.5, 102.7, 104.7, 114.1, 145.9, 146.6, 147.4, 150.9, 152.5.

_N_-([1,3]Dioxolo[4,5-g]quinolin-8-yl)-4,5-dimethoxy-2-iodobenzamide (140)

Oxalyl chloride (1.37 mL, 15.9 mmol) was added to a mixture of 2-iodo-4,5-dimethoxybenzoic acid (1.8 g, 5.85 mmol) in DMF (40 mL), and the mixture was heated to reflux under nitrogen with stirring for 4 h. The reaction mixture was concentrated to dryness under vacuum to provide crude acylchloride. The acid chloride was used without purification and redissolved in 40 mL of methylene chloride, and a solution of 4-aminoquinoline **139** (1 g, 5.3 mmol) was added, then triethylamine (2.0 mL, 27 mmol) was added. The mixture was heated to 80 °C with stirring for 16 h and was then cooled to room temperature. The white precipitate was filtered and the solid was chromatographed on silica gel using dichloromethane: methanol (10:1), yielding 760 mg in 30% yield as an off-white solid; ^{1}H NMR (DMSO-d^6) δ 3.82 (s, 6H), 6.22 (s, 2H), 7.24 (s, 1H), 7.35 (s, 1H), 7.39 (s, 1H), 7.74 (s, 1H), 7.88 (d, 1H, *J*=5.0), 8.63 (d, 1H, *J*=5.0; ^{13}C NMR (DMSO-d^6) δ 56.7, 56.9, 83.2, 99.5, 102.9, 106.1, 113.1, 113.4, 118.9, 122.3, 135.7, 141.6, 148.0, 148.2, 148.8, 149.5, 151.0, 169.1.

N-([1,3]Dioxolo[4,5-g]quinolin-8-yl)-N-(2-(dibenzylamino)-2-methylpropyl)-4,5-dimethoxy-2-iodobenzamide (141)

A mixture of **140** (200 mg, 0.418 mmol), 2-(dibenzylamino)-2-methyl-propyl chloride HCl (164 mg, 0.502 mmol) and sodium iodide (94.1 mg, 0.627 mmol) in DMF (20 mL) was cooled to 0 °C and sodium hydride (50 mg of a 60% mineral oil suspension, 1.3 mmol) was

added in small portions over 5 min. Cooling bath was removed. The mixture was allowed to warm to room temperature with stirring for 45 min. The reaction flask was then transferred to an oil bath that had been preheated to 70 °C, and the mixture was stirred at this temperature for 4 h. TLC was used to monitor the reaction. The mixture was cooled to room temperature and quenched by addition of a few drops of water. The solvent was removed under vacuum. The crude product was dissolved in 1 N HCl (50 mL). The aqueous solution was washed with chloroform (150 mL), then made basic by the addition of 30% NaOH, and extracted with chloroform (150 mL). The organic layers were combined, dried (MgSO4) and evaporated under vacuum. The residue was chromatographed using 98:2 chloroform/methanol to provide a semi-solid 171 mg in 56% yield. ^{1}H NMR ($CDCl_3$) δ 1.97 (s, 6H), 3.24 (s, 2H), 3.46 (s, 3H), 3.94 (s, 3H), 3.97 (s, 4H), 6.30 (s, 2H), 6.46 (s, 1H), 6.63 (d, 1H, *J*=5.0), 7.21(s, 1H), 7.39-7.62 (m, 12H), 8.52 (d, 1H, *J*=5.0); ^{13}C NMR ($CDCl_3$) δ 23.5, 54.6, 55.2, 59.3, 59.3, 61.4, 82.0, 86.1, 98.8, 100.7, 104.9, 109.8, 110.7, 120.5, 126.1, 127.3, 128.3, 130.2, 138.9, 146.1, 146.3, 147.6, 147.7, 148.8, 149.5, 150.9, 159.4.

2,3-Methylenedioxy-8,9-dimethoxy-5-[2-(*N*,*N*-dibenzylamino)-2-methyl-propyl) dibenzo[*c*,*h*][1,6]naphthyridin-6-one (142)

A mixture of **141** (105 mg, 0.14 mmol), $Pd(OAc)_2$ (6.5 mg, 0.03 mmol), P(*o*-tolyl)$_3$ (17 mg, 0.06 mmol), and Ag_2CO_3 (80 mg, 0.28 mmol) in dimethylformamide (DMF) (10 mL) was heated to reflux with stirring for 45 min. The reaction mixture was cooled, diluted with chloroform, and filtered through Celite, and the solvent was removed under vacuum. The crude residue was chromatographed in 99:1 chloroform/methanol to provide 15 mg (18%)

of the cyclized product as a white solid; ^{1}H NMR ($CDCl_3$) δ 0.56 (s, 3H), 0.68 (s, 3H), 3.66 (s, 4H), 4.06 (s, 3H), 4.14 (s, 3H), 6.16 (s, 2H), 7.07-7.14 (m, 10H), 7.47 (s, 1H), 7.49(s, 1H), 7.67(s, 1H), 7.88(s, 1H), 9.34(s, 1H) ; ^{13}C NMR ($CDCl_3$) δ 23.9, 52.9, 55.5, 55.6, 60.5, 61.9, 99.8, 101.1, 101.4, 105.3, 108.8, 112.2, 119.0, 125.4, 125.6, 126.0, 127.0, 127.1, 127.5, 140.7, 141.0, 141.2, 144.3, 146.8, 149.4, 153.3, 164.0.

2,3-Methylenedioxy-8,9-dimethoxy-5-(2-methyl-2-amino-propyl) dibenzo[*c*,*h*][1,6] naphthyridin-6-one (143) and its cyclized form (144)

Compound **142** (120 mg, 0.209 mmol) was dissolved in acetic acid (10 mL). Formic acid (5 mL) was added, and then palladium black (100 mg) was added. The mixture was stirred at rt for 8h. The resulting mixture was filtered through a cotton plug and the filtrate was concentrated. The residue was chromatographed in 99:1 chloroform/methanol to provide 7 mg (70%) product **144** as a white solid. During column purification, compound **143** was believed to be converted to **144**; ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 6H), 3.77 (s, 3H), 3.48 (s, 3H), 4.34 (s, 2H), 5.91 (s, 2H), 7.05 (s, 1H), 7.37 (s, 1H), 7.49 (s, 1H), 7.66 (s, 1H), 8.86 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.3, 55.5, 55.6, 64.2, 64.6, 99.9, 102.0, 102.4, 105.2, 107.3, 110.1, 113.3, 115.2, 121.5, 125.9, 142.5, 146.4, 147.1, 149.8, 149.8, 152.8, 154.7.

4,5-Dimethoxy-2-iodoacetanilide (145)[125]

A 1.0 M solution of iodine monochloride in methylene chloride (41.7 mL) was added dropwise to a solution of *N*-(3,4-dimethyoxyphenyl)acetamide (7.4 g, 37.9 mmol) in

methylene chloride (45 mL) and acetic acid (7.5 mL). The mixture was stirred under nitrogen overnight and then washed with saturated sodium thiosulfate (2× 150 mL) and brine (150 mL). The methylene chloride solution was dried ($MgSO_4$) and evaporated, and the crude residue was chromatographed using 19:1 chloroform/hexanes, to provide 6.2 g of **145** as a white solid, in 52% yield; mp 140–141.5 °C; IR ($CHCl_3$) 3397, 1687; ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 3H), 3.86 (s, 3H), 3.90 (s, 3H), 7.17 (s, 1H), 7.26 (br, 1H), 7.86 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 24.8, 56.1, 56.4, 77.6, 106.4, 120.4, 132.4, 146.6, 149.7, 168.4.

4,5-Dimethoxy-2-iodoaniline (146)[125]

A mixture of **145** (1.0 g, 3.12 mmol) and NaOH (6.25 g, 156 mmol) in ethanol (125 mL) and water (30 mL) was heated to reflux with stirring for 4 h. The mixture was cooled and the solvent was removed under vacuum. The residue was partitioned between chloroform (100 mL) and water (100 mL). The organic phase was washed with water (2× 100 mL), dried ($MgSO_4$), and evaporated under vacuum to give 810 mg of **146** in 93% yield, as a light pink oil; ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H), 3.83 (s, 3H), 6.39 (s, 1H), 7.08 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.9, 56.8, 71.2, 99.7, 121.7, 141.3, 142.8, 150.7.

6,7-Methylenedioxyquinoline-4-carboxylic acid-(2-iodo-4,5-dimethoxyphenyl)amide (147)

A suspension of **98** (500 mg, 2.3 mmol) in thionyl chloride (30 mL) was heated at reflux for 2 h, during which time the starting material completely dissolved. The mixture was cooled and then evaporated to dryness under vacuum. The acid chloride was dissolved in

anhydrous methylene chloride (30 mL) and triethylamine (3.0 g, 30 mmol) was added. A solution of **146** (535 mg, 1.9 mmol) in methylene chloride (15 mL) was added, and the resulting mixture was refluxed under nitrogen overnight. The mixture was cooled and additional methylene chloride was added, bringing the total volume up to 100 mL. This solution was washed with saturated sodium bicarbonate (2× 100 mL) and brine (100 mL), dried ($MgSO_4$) and evaporated under vacuum. The crude residue was chromatographed in chloroform to provide 512 mg of **8** as a very pale yellow solid, in 56% yield; mp 210–211 °C; IR ($CHCl_3$) 3375, 1680; ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H), 4.00 (s, 3H), 6.17 (s, 2H), 7.25 (s, 1H), 7.47 (s, 1H), 7.55 (d, 1H, J = 4.4), 7.77 (s, 1H), 7.90 (br, 1H), 8.11 (s, 1H), 8.84 (d, 1H, J = 4.4); ^{13}C NMR ($CDCl_3$) δ 56.3, 56.5, 78.3, 100.9, 102.2, 106.4, 111.9, 116.9, 120.5, 121.9, 131.9, 139.9, 147.7, 147.9, 149.3, 149.8, 151.3, 165.6; HRMS calcd for $C_{19}H_{15}IN_2O_5H$: 479.0104; found: 479.0081.

6,7-Methylenedioxyquinoline-4-carboxylic acid, *N*-[2-(*N*,*N*-dimethylamino)-2-methylpropyl]-*N*-(2-iodo-4,5-dimethoxyphenyl) amide (148)

A mixture of **147** (400 mg, 0.84 mmol), 2-(dimethylamino)-2-methyl-propyl chloride HCl (340 mg, 2 mmol) and sodium iodide (188 mg, 1.26 mmol) in DMF (15 mL) was cooled to 0 °C and sodium hydride (160 mg of a 60% mineral oil suspension, 4.0 mmol) was added in small portions over 5 min. Cooling bath was removed. The mixture was allowed to warm to room temperature with stirring for 45 min. The reaction flask was then transferred to an oil bath that had been preheated to 50 °C, and the mixture was stirred at this temperature for 3 h. TLC was used to monitor the reaction. The mixture was cooled to room temperature and quenched by addition of a few drops of water. The solvent was

removed under vacuum. The crude product was dissolved in 1 N HCl (50 mL). The aqueous solution was washed with chloroform (350 mL), then made basic by the addition of 30% NaOH, and extracted with chloroform (375 mL). The organic layers were combined, dried ($MgSO_4$) and evaporated under vacuum. The residue was chromatographed using 98:2 chloroform/methanol to provide 310 mg of **148** as a semi-solid in 61% yield; ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 3H), 1.29 (s, 3H), 2.09 (s, 6H), 3.32 (s, 3H), 3.38 (d, 1H, *J*=14.6), 3.70 (s, 3H), 4.66 (d, 1H, *J*=14.6), 6.08 (s, 2H), 6.83 (s, 1H), 6.95(s, 1H), 7.16 (d, 1H, *J*=4.8), 7.50 (s, 1H), 8.43 (d, 1H, *J*=4.8); ^{13}C NMR ($CDCl_3$) δ 18.6, 23.1, 37.6, 53.0, 54.6, 55.1, 57.7, 86.2, 100.2, 101.0, 105.4, 114.9, 115.4, 119.3, 120.8, 136.5, 141.1, 145.8, 146.3, 146.9, 147.4, 147.8, 149.6, 168.3.

6,7-Methylenedioxyquinoline-4-carboxylic acid, *N*-[2-(*N*,*N*-dibenzylamino)-2-methylpropyl]-*N*-(2-iodo-4,5-dimethoxyphenyl) amide (149)

A mixture of **147** (367 mg, 0.767 mmol), 2-(dibenzylamino)-2-methyl-propyl chloride HCl (600 mg, 1.84 mmol) and sodium iodide (173 mg, 1.15 mmol) in DMF (15 mL) was cooled to 0 °C and sodium hydride (160 mg of a 60% mineral oil suspension, 4.0 mmol) was added in small portions over 5 min. Cooling bath was removed. The mixture was allowed to warm to room temperature with stirring for 45 min. The reaction flask was then transferred to an oil bath that had been preheated to 70 °C, and the mixture was stirred at this temperature for 1 h. TLC was used to monitor the reaction. The mixture was cooled to room temperature and quenched by addition of a few drops of water. The solvent was

removed under vacuum. The crude product was dissolved in 1 N HCl (50 mL). The aqueous solution was washed with chloroform (350 mL), then made basic by the addition of 30% NaOH, and extracted with chloroform (375 mL). The organic layers were combined, dried (MgSO4) and evaporated under vacuum. The residue was chromatographed using 98:2 chloroform/methanol to provide a semi-solid. An inseparable 1:1 mixture of deiodinated compound and product was obtained. The product yield was estimated from NMR as approximately 280 mg in 50% yield. ^{1}H NMR ($CDCl_3$) δ 1.57 (s, 3H), 1.59 (s, 3H), 3.05 (s, 2H), 3.11 (s, 2H), 4.05 (s, 3H), 4.07 (s, 3H), 6.25 (s, 2H), 7.09 (s, 1H), 6.95-7.60 (m, 11H), 8.71 (d, 1H, *J*=4.8), 7.91(s, 1H), 8.15 (s, 1H), ,8.93 (d, 1H, *J*=4.8).

6-(2-Dimethylamino-2-methyl-propyl)-8,9-dimethoxy-2,3-methylenedioxy-6*H*-dibenzo[*c*,*h*] [2,6]naphthyridin-5-one (150)

A solution of **148** (310 mg, 0.54 mmol) in 950 mL of 2% HCl was transferred to the photoreactor apparatus and degassed by nitrogen purge for 30 min. The solution was irradiated through a Vycor filter for 90 min. The mixture was basified (30% NaOH) and extracted with ethyl acetate (450 mL). The combined organic extracts were evaporated and the residue was chromatographed on silica eluting with 98:2 chloroform/methanol to provide 60 mg of **150** as a yellow solid in 25% yield; ^{1}H NMR ($CDCl_3$) δ 1.08 (s, 6H), 2.46 (s, 6H), 3.99 (s, 2H), 4.00 (s, 6H), 6.10 (s, 2H), 7.34 (s, 1H), 7.61 (s, 1H), 7.64 (s, 1H), 9.33(s, 1H), 9.41(s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.5, 37.8, 49.2, 55.3, 55.4, 59.0, 100.2,

101.3, 102.7, 103.0, 105.0, 109.1, 121.0, 121.3, 124.8, 133.2, 142.4, 143.5, 144.6, 148.7, 149.0, 150.3, 161.1; HRMS calcd for $C_{25}H_{27}N_3O_5Li$: 456.2111; found 456.2115.

6-(2-Dibenzylamino-2-methyl-propyl)-8,9-dimethoxy-2,3-methylenedioxy-6*H*-dibenzo[*c*,*h*] [2,6]naphthyridin-5-one (151)

A mixture of **149** (140 mg, 0.192 mmol), $Pd(OAc)_2$ (8.6 mg, 0.038 mmol), P(*o*-tolyl)$_3$ (23.1 mg, 0.076 mmol), and Ag_2CO_3 (105 mg, 0.28 mmol) in dimethylformamide (DMF) (10 mL) was heated to reflux with stirring for 1 h. The reaction mixture was cooled, diluted with chloroform, and filtered through Celite, and the solvent was removed under vacuum. The crude residue was chromatographed in 99:1 chloroform/methanol to provide 17 mg (15%) of the cyclized product as a yellow solid; ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 6H), 4.14 (s, 4H), 4.24 (s, 6H), 6.37 (s, 2H), 7.25-7.57 (m, 11H), 7.70 (s, 1H), 8.00 (s, 1H), 9.75 (s, 1H), 9.79(s, 1H; ^{13}C NMR ($CDCl_3$) δ 22.3, 49.4, 53.7, 55.3, 55.5, 60.6, 99.3, 101.2, 103.0, 103.6, 105.7, 109.7, 121.5, 125.7, 127.2, 127.5, 133.1, 141.2, 142.7, 144.3, 144.6, 148.8, 149.0, 150.0, 161.3; HRMS calcd for $C_{37}H_{35}N_3O_5H$: 602.2655; found 602.2628.

6-(2-amino-2-methyl-propyl)-8,9-dimethoxy-2,3-methylenedioxy-6*H*-dibenzo[*c*,*h*] [2,6]naphthyridin-5-one (152)

Compound **151** (10 mg, 0.017 mmol) was dissolved in acetic acid (3 mL). Formic acid (0.5 mL) was added, and then palladium black (20 mg) was added. The mixture was stirred at rt for 24 h. The resulting mixture was filtered through a cotton plug and the filtrate was concentrated. The residue was chromatographed in 99:1 chloroform/methanol to provide 5 mg (70%) product **152** as a pale yellow solid. ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 6H), 4.05 (s, 3H),

4.07 (s, 3H), 4.55 (s, 2H), 6.17 (s, 2H), 7.33 (s, 1H), 7.48 (s, 1H), 7.82 (s, 1H), 9.32(s, 1H), 9.40(s, 1H); HRMS calcd for $C_{23}H_{24}N_3O_5H$: 422.1707; found 422.1716.

2,3-Dimethoxy-N-(2-(dimethylamino)-2-methylpropyl)-8,9-methylenedioxybenzo[*i*] phenanthridine-12-carboxamide (153)[133]

To a suspension of **63** (450 mg, 1.2 mmol) in anhy $CHCl_3$ (250 mL) was added $SOCl_2$ (18 mL, 247 mmol) and refluxed for 5h. Reaction mixture was concentrated on rotavap and dried under high vaccum for 1h. The solid residue was suspended in a mixture of anhy DCM (150 mL) and TEA (10 mL, 72 mmol) and stirred for 2h. Then it was charged with **133** (2.5 g, 21 mmol) and stirred for 1h, diluted with sat. $NaHCO_3$ solution and extracted. Organic layer was dried, filtered, concentrated and the residue was purified by flash chromatography to yield **153** in 84%; mp 274-276 °C; IR ($CHCl_3$) 3384, 1663; ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 6H), 2.31 (s, 6H), 3.62 (d, 2H, J = 5), 4.04 (s, 3H), 4.15 (s, 3H), 6.13 (s, 2H), 7.28 (bs, 1H), 7.56 (s, 1H), 7.67 (s, 1H), 7.73 (s, 1H), 8.02 (s, 1H), 8.17 (s, 1H), 9.72 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.6, 37.4, 46.8, 55.0, 55.1, 98.2, 101.1, 105.1, 105.6, 116.4, 119.7, 119.9, 124.7, 128.5, 135.5, 140.8, 143.8, 147.6, 148.5, 148.9, 149.6, 169.2; HRMS calcd for $C_{27}H_{29}N_3O_5Li$: 482.2267; found 482.2278

N-(2-(Dibenzylamino)-2-methylpropyl)-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*] phenanthridine-12-carboxamide (154)[133]

To a suspension of **66** (97 mg, 0.26 mmol) in DCM (15 mL) was added excess of $SOCl_2$ (5 mL, 69 mmol) and refluxed for 3 h. Reaction mixture was concentrated under vaccum to complete dryness. The residue was suspended in DCM (10 mL) and refluxed with

2-dibenzylamino-2-methyl- propylenediamine (400 mg, 1.5 mmol) for 2 h. Reaction mixture was washed with water (20 mL), brine (20 mL), dried (Na_2SO_4) and filtered. Solvent was evaporated on rotavap and the crude was purified by flash chromatography get a light yellow solid **154** in 60% yield; mp 257-259 °C; IR ($CHCl_3$) 1651; ^{1}H NMR ($CDCl_3$) δ 1.54 (s, 6H), 3.84 (d, 2H, J = 5), 3.99 (s, 4H), 4.14 (s, 3H), 4.39 (s, 3H), 6.43 (s, 2H), 7.22 (m, 7H), 7.34 (m, 4H), 7.86 (s, 1H), 7.94 (s, 1H), 7.98 (s, 1H), 8.28 (s, 1H), 8.34 (s, 1H), 10.1 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.8, 48.2, 53.7, 56.0, 56.3, 99.5, 102.1, 102.3, 106.4, 116.7, 121.0, 124.1, 126.0, 127.1, 128.5, 137.5, 141.1, 144.3, 149.0, 150.2, 151.0, 169.3; HRMS calcd for $C_{39}H_{37}N_3O_5Li$: 634.2893; found 634.2879.

N-(2-amino-2-methylpropyl)-2,3-dimethoxy-8,9-methylenedioxybenzo[*i*] phenanthridine-12-carboxamide (155)[133]

To a solution of **154** (22 mg, 0.03 mmol) in acetic acid (5 mL) and formic acid (1 mL) was added Pd black (20 mg) and stirred at room temperature for 2 h. Reaction mixture was filtered through celite, concentrated under reduced pressure, basified with 10% NaOH (4 mL) and extracted with 2% methanol in chloroform (60 mL). Organic layer was dried over Na_2SO_4, filtered and concentrated. Crude was purified by a short column to yield a light yellow solid **155** in 58% yield; mp 269-271 °C (dec); IR ($CHCl_3$) 3373, 1635; ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 6H), 3.83 (bs, 2H), 4.02 (s, 3H), 4.16 (s, 3H), 6.12 (s, 2H), 7.35 (s, 1H), 7.75 (s, 1H), 8.09 (s, 1H), 8.51 (s, 1H), 9.80 (s, 1H); HRMS calcd for $C_{25}H_{25}N_3O_5Li$: 454.1954; found 454.1943

2,3-Dimethoxy-8,9-methylenedioxybenzo[*i*]phenanthridine-11-carboxylic acid 2-(dimethylamino)-2-methylpropylamide (156)

A mixture of **116** (15 mg, 0.037 mmol) in 10% NaOH (5 mL) and ethanol (10 mL) was heated to reflux with stirring for 1h. The reaction mixture was acidified with 2N HCl to pH = 4, and then evaporated to dryness. The residue was suspended in 10 mL dichloromethane and 0.5 mL thionyl chloride was added. The resulting reaction mixture was refluxed for 2h and then concentrated. The reaction residue was again suspended in dichloromethane and 0.5 mL triethylamine was added. After 15 min, 0.5 mL 2-dimethylamino-2-methyl-propylenediamine was added and the resulting reaction mixture was refluxed for 1h. The organic solvent and excess amine were removed under reduced pressure and the residue was chromatographed in 20:1 CH_2Cl_2/MeOH to provide a off-white powder 11 mg in 62% yield; mp 222-225 ºC; IR (KBr) 1642; ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 6H), 2.15 (s, 6H), 3.55 (d, 2H, *J*=4.8), 4.05 (s, 3H), 4.15 (s, 3H), 6.10 (s, 2H), 6.93 (br, 1H), 7.25 (s, 1H), 7.50 (s, 1H), 7.83 (s, 1H), 7.97 (s, 1H), 8.05 (s, 1H), 9.85 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.8, 37.2, 47.8, 54.7, 55.2, 55.3, 100.9, 101.2, 101.8, 106.3, 107.2, 118.6, 120.6, 124.9, 125.2, 126.7, 129.6, 129.7, 142.6, 144.5, 147.0, 148.1, 149.3, 150.5, 171.0; HRMS calcd for $C_{27}H_{29}N_3O_5H$: 476.2185; found 476.2180.

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PUBLICATIONS AND PRESENTATIONS

(1) Feng, W.; Mavurapu, S.; Cheng, L.; Tsai, Y.; Liu, A.; Liu, L. F.; LaVoie, E. J. Synthesis and evaluation of *N*-substituted 5-[2-(*N*-alkylamino)ethyl]dibenzo[*c*,*h*][1,6] naphthyridines as novel topoisomerase I-targeting antitumor agents. *Submitted*
(2) Feng, W.; Mavurapu, S.; Tsai, Y.; Liu, A.; Liu, L. F.; LaVoie, E. J. Novel topoisomerase I-targeting antitumor agents synthesized from the *N,N,N*-trimethylammonium derivative of ARC-111, 5*H*-2,3-dimethoxy-8,9-methylenedioxy-5-[(2-*N,N,N*-trimethylammonium)ethyl]dibenzo[*c*,*h*][1,6]naphthyridin-5-one.*Submitted*
(3) Feng, W.; Mavurapu, S.; Tsai, Y.; Liu, A.; Liu, L. F.; LaVoie, E. J. Facile formation of hydrophilic derivatives of 5*H*-8,9-dimethoxy-5-(2-N,N-dimethylamino-ethyl)-2,3-methylenedioxydibenzo[*c*,*h*][1,6]naphthyridin-6-one (ARC-111) and its 12-aza analog via quaternary ammonium intermediates. *Submitted*
(4) Feng, W.; Mavurapu, S.; Tsai, Y.; Liu, A.; Liu, L. F.; LaVoie, E. J. Synthesis and evaluation of *N*-substituted 5-[2-(*N*-alkylamino)ethyl]dibenzo[*c,h*][1,6] naphthyridines as novel topoisomerase I-targeting antitumor agents. *Abstracts of Papers, 231st ACS National Meeting*, Atlanta, GA, United States, March 26-30, **2006**.
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