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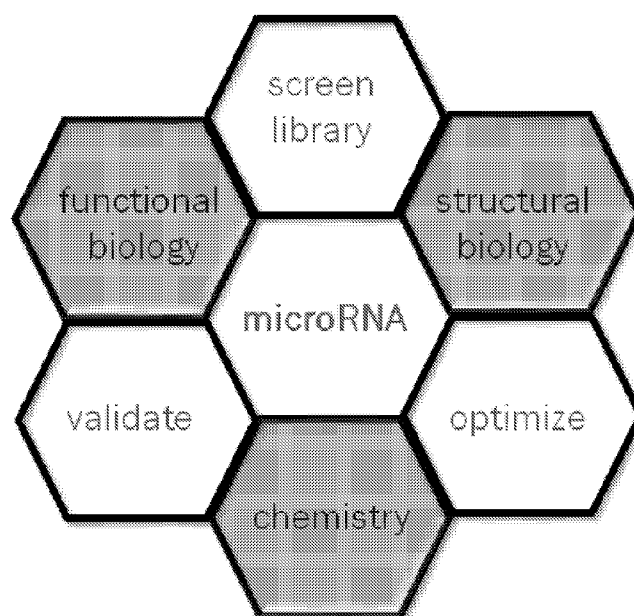
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(54) Title: OLIGONUCLEOTIDE BINDING AGENTS

Figure 1



(57) **Abstract:** The present disclosure relates to development and performance of screening methods capable of efficiently identifying candidate lead compounds that bind regulatory RNA oligonucleotides in a sequence-specific manner and exert a biological effect upon such regulatory molecules. Candidate lead compounds possessing RNA binding sequence specificity and targeted biological activity are described, as are approaches for merging structural, NMR-derived data with biological reporter assay results. Compound validation approaches capable of identifying the site(s) of action of such compounds within targeted RNA oligonucleotides are also provided.



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OLIGONUCLEOTIDE BINDING AGENTS

Cross-Reference to Related Application

The present application is related to and claims priority under 35 U.S.C. § 119(e) to U.S. provisional patent application No. 62/490,362, entitled “Oligonucleotide Binding Agents,” filed April 26, 2017. The entire content of the aforementioned patent application is incorporated herein by this reference.

Background of the Invention

RNAs, especially non-coding RNAs, have been identified as critical to regulation of gene expression, with particular relevance to various disease states (*e.g.*, various microRNAs in particular have been identified as associated with a number of diseases, including cancer). While oligonucleotide-based agents (*e.g.*, “antagomiRs”) that possess sequences complementary to regulatory RNAs (*e.g.*, microRNAs) can be used to target/inhibit such regulatory RNAs in a sequence-specific manner, oligonucleotide therapeutics confront significant developmental and therapeutic hurdles related to delivery to a subject, as contrasted with small molecule inhibitors of regulatory RNAs. Small molecules that bind to and modulate regulatory RNAs can more efficiently be developed into therapeutic agents. There is therefore an unmet need for developing compound screening assays and identifying compounds by performance of such screening assays that can modulate the activity of regulatory RNAs with sequence specificity comparable to oligonucleotide therapeutics, while concurrently providing a significant delivery advantage over oligonucleotide therapeutics.

Summary of the Invention

The present disclosure is based, at least in part, upon the development and performance of screening methods capable of efficiently identifying candidate lead compounds that bind regulatory RNA oligonucleotides and exert a biological effect through such regulatory molecules. Certain aspects of the disclosure also provide the identity of such candidate lead compounds, their biological activity, and even identify the site of action for such candidate lead compounds within a targeted regulatory RNA oligonucleotide. Candidate lead compound

identification and validation methods useful for merging structural, NMR-derived data with results obtained in biological reporter assays are also provided.

In one aspect, the disclosure provides a method for identifying a candidate lead compound involving: (a) contacting an oligonucleotide with a test compound in a biological functional assay, where oligonucleotide-test compound binding results in a biological result that is not observed in the biological functional assay without the test compound; and (b) contacting the oligonucleotide with the test compound, thereby forming an oligonucleotide-test compound solution; performing NMR upon the oligonucleotide-test compound solution, where oligonucleotide-test compound binding produces an NMR result not observed in a solution lacking the test compound; and detecting the NMR result in the oligonucleotide-test compound solution, where detecting selective biological function in the presence of the test compound in (a) and detecting the NMR result in (b) identifies the test compound as a candidate lead compound.

In one embodiment, the biological functional assay is a cell-based reporter system, a proliferation assay, an immunoassay or a polymerase chain reaction-based assay.

In another aspect, the disclosure provides a method for identifying a candidate lead compound involving (a) contacting an oligonucleotide with a test compound in the presence of a cell-based reporter system; and detecting selective activation of the cell-based reporter system in the presence of the test compound; and (b) contacting the oligonucleotide with the test compound, thereby forming an oligonucleotide-test compound solution; performing NMR upon the oligonucleotide-test compound solution, where oligonucleotide-test compound binding produces an NMR result not observed in a solution lacking the test compound; and detecting the NMR result in the oligonucleotide-test compound solution, where detecting selective activation of the cell-based reporter system in the presence of the test compound in (a) and detecting the NMR result in (b) identifies the test compound as a candidate lead compound.

In one embodiment, the oligonucleotide includes RNA. Optionally, the oligonucleotide is a coding or a non-coding RNA, optionally the oligonucleotide is a microRNA, a tRNA, a rRNA, a tiRNA, a lincRNA, a NAT, a lncRNA, a, eRNA, a T-UCR, a circRNA, a piRNA, an esiRNA, an siRNA, an antisense oligonucleotide, a tasiRNA, a snoRNA, a scaRNA or a snRNA.

In certain embodiments, the oligonucleotide is a microRNA. Optionally, the site of microRNA processing pathway activity of the candidate lead compound is assessed. In certain

embodiments, assessing the site of microRNA processing pathway activity of the candidate lead compound involves measuring levels of pri-microRNA, pre-microRNA and mature microRNA, as compared to an appropriate control. In some embodiments, the candidate lead compound exhibits selective elevation or selective decrease of mature microRNA levels in cells administered the candidate lead compound, as compared to DMSO-treated control cells, optionally thereby indicating that the candidate lead compound interacts with the microRNA maturation pathway at the mature microRNA level. In related embodiments, the candidate lead compound exhibits selective elevation or selective decrease of pri-microRNA levels in cells administered the candidate lead compound, as compared to DMSO-treated control cells, optionally thereby indicating that the candidate lead compound interacts with the microRNA maturation pathway at the pri-microRNA level.

In another embodiment, the method further involves assessing the site at which the candidate lead compound binds the oligonucleotide, optionally involving assessing candidate lead compound binding following introduction of one or more mutant residues into the oligonucleotide. In certain embodiments, the candidate lead compound stabilizes a structural conformation of the oligonucleotide, optionally thereby inhibiting an activity of the oligonucleotide.

In one embodiment, the NMR result not observed in a solution lacking the test compound is the presence of an NMR peak observed for the oligonucleotide-test compound solution that is not observed in a control solution lacking the test compound.

In another embodiment, the oligonucleotide is a microRNA-21 transcript or a fragment thereof including at least 15 consecutive nucleotides of microRNA-21. In a related embodiment, the microRNA-21 transcript sequence fragment includes the Drosha cleavage site of a microRNA-21 transcript. In certain embodiments, the microRNA-21 transcript sequence fragment includes the Dicer cleavage site of a microRNA-21 transcript.

In one embodiment, the cell-based reporter system is a fluorescent protein reporter system (optionally a GFP, CFP, BFP, RFP and/or YFP reporter system) or is a luciferase reporter system. Optionally, the cell-based reporter system is a luciferase reporter system involving a vector encoding for both firefly luciferase and renilla luciferase, optionally where firefly luciferase is operably linked to a microRNA-complementary sequence, optionally where the

microRNA-complementary sequence is positioned at the 3'-terminus of the firefly luciferase open reading frame, optionally where the microRNA-complementary sequence is fused to the 3'-terminus of the firefly luciferase transcript, optionally where the microRNA-complementary sequence is a microRNA-21 complementary sequence.

In certain embodiments, the test compound is a small molecule.

In another embodiment, detecting selective activation of the cell-based reporter system in the presence of the test compound in step (a) includes assigning a numeric score to the test compound-oligonucleotide reporter system results.

In one embodiment, detecting selective activation of the cell-based reporter system in the presence of the test compound in step (a) involves identifying at least a 1.5-fold elevation of the level of a signal in the presence of the test compound, relative to the level of the signal in the absence of the test compound, optionally detecting selective activation of the cell-based reporter system in the presence of the test compound in step (a) involves identifying at least a 1.75-fold elevation of the level of a signal in the presence of the test compound, relative to the level of the signal in the absence of the test compound, optionally detecting selective activation of the cell-based reporter system in the presence of the test compound in step (a) involves identifying at least a two-fold elevation of the level of a signal in the presence of the test compound, relative to the level of the signal in the absence of the test compound.

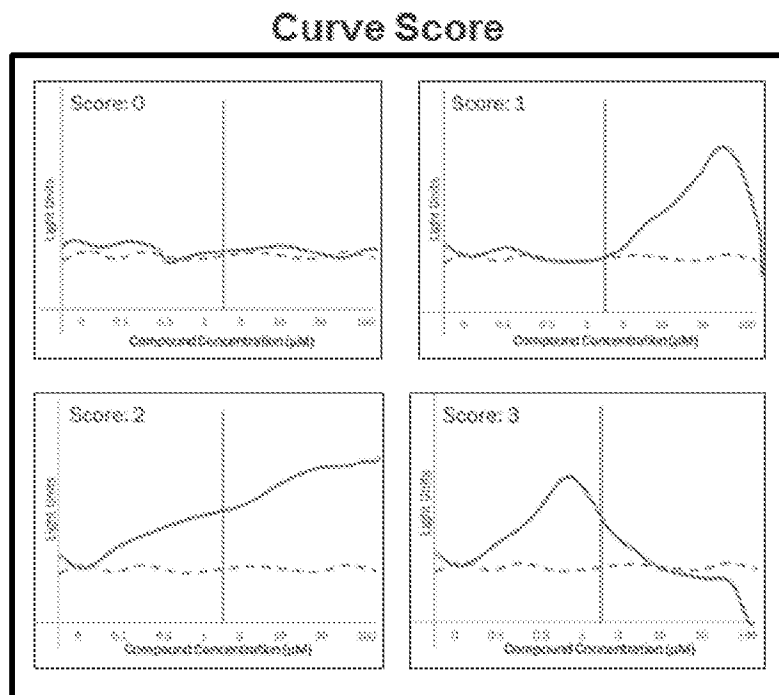
In some embodiments, the test compound inhibits microRNA-21 activity by at least 1.5-fold more than the level of microRNA-21 activity in control cells in the absence of the test compound, optionally the test compound inhibits microRNA-21 activity by at least 1.75-fold more than the level of microRNA-21 activity in control cells in the absence of the test compound, optionally the test compound inhibits microRNA-21 activity by at least two-fold more than the level of microRNA-21 activity in control cells in the absence of the test compound, optionally where the control cells are DMSO-treated. In a related embodiment, the numeric score assigned to the test compound-oligonucleotide reporter system results is on a 10 point scale.

In one embodiment, the test compound is assigned (i) an integer score based upon the shape of a dose-response curve for the biological functional assay in the presence of the test compound and (ii) an integer score based upon the dose-responsiveness of the biological

functional assay to the test compound. Optionally, the test compound is assigned (i) an integer score between 0 and 3 based upon the shape of a dose-response curve for the cell-based reporter system in the presence of the test compound (optionally, where 0 is given to test compounds that show no signal; 1 indicates a signal only at higher concentrations; 2 indicates a signal proportional to its concentration; and 3 indicates a signal at low concentrations) and (ii) an integer score between 0 and 7 based upon the dose-responsiveness of the cell-based reporter system to the test compound (optionally, where the higher value is assigned when a signal is shown at lower concentrations).

In certain embodiments, oligonucleotide-test compound binding is identified by detecting shifting of peaks in NMR spectra in the presence of a test compound, as compared to a control NMR spectra in the absence of the test compound.

In another embodiment, the test compound is assigned an integer score between 0 and 3 based upon the shape of a dose-response curve for the cell-based reporter system in the presence of the test compound, as represented below:



Raw Firefly Luminescence data

--- Control

— Treated sample

Scoring threshold (red line): set between 1 and 3 μM compound

and the test compound is assigned an integer score between 0 and 7 based upon the following dose-response criteria in the cell-based reporter system in the presence of the test compound:

<u>Activity</u>	<u>Score</u>
≥2-fold activity change at 0.1 μM or less	7
≥2-fold activity change at 0.3 μM to 0.1 μM	6
≥2-fold activity change at 1 μM to 0.3 μM	5
≥2-fold activity change at 3 μM to 1 μM	4
≥2-fold activity change at 10 μM to 3 μM	3
≥2-fold activity change at 30 μM to 10 μM	2
≥2-fold activity change at 100 μM to 30 μM	1
≥2-fold activity change at >100 μM or not observed	0.

In some embodiments, detecting the NMR peak in the oligonucleotide-test compound solution in (b) involves assigning a numeric score to the oligonucleotide-test compound NMR results. Optionally, a score of 0, 1, 2, 3 or 4 is assigned to the oligonucleotide-test compound NMR results, where a score of 4 indicates high-quality NMR-detected binding, optionally where scoring is assigned as follows:

- +1 for signal demonstrating binding;
- +1 for signal-to-noise ratio >3;
- +1 for sharp ligand peaks in the mixture;
- +1 for pattern of ligand peaks consistent with the pattern expected from the chemical structure.

In certain embodiments, the method further involves assigning a numeric score of 0, 1, 2, 3 or 4 to the oligonucleotide-test compound NMR results, where a score of 4 indicates high-quality NMR-detected binding. In a related embodiment, a combined score of the biological functional assay and the NMR assay of 10 or greater identifies the test compound as a compound that binds the oligonucleotide and/or is bioactive.

In some embodiments, a method of the disclosure involves (a) contacting an oligonucleotide with a test compound in the presence of a cell-based reporter system; and detecting selective activation of the cell-based reporter system in the presence of the test compound; and (b) contacting the oligonucleotide with the test compound, thereby forming an oligonucleotide-test compound solution; performing NMR upon the oligonucleotide-test

compound solution, where oligonucleotide-test compound binding produces an NMR result not observed in a solution lacking the test compound; and detecting the NMR result in the oligonucleotide-test compound solution, where detecting selective activation of the cell-based reporter system in the presence of the test compound in (a) and detecting the NMR result in (b) identifies the test compound as a candidate lead compound

Certain embodiments further involve performing a cellular proliferation assay upon the test compound.

In some microRNA embodiments, the method further involves identifying whether the test compound binds to a double stranded fragment including one or more of the Drosha cleavage site of a microRNA transcript, a fragment including the Dicer cleavage site of a microRNA transcript, or both, optionally where NMR is performed upon a Dicer cleavage site-containing structure.

In certain embodiments, the method further involves validating binding of the test compound to the oligonucleotide by performance of NMR upon oligonucleotide-test compound solutions titrated across multiple test compound concentrations. Optionally, the NMR results performed upon oligonucleotide-test compound solutions titrated across multiple test compound concentrations show dose-responsiveness.

In one embodiment, the test compound is selected from a library of test compounds. Optionally, the test compound library is assembled using chemoinformatics and/or crystallography.

Another aspect of the disclosure provides a test compound library of less than 1000 compounds, where the library includes at least 10 or more test compounds selected by a chemoinformatics and/or crystallography process to be likely oligonucleotide-binding compounds.

An additional aspect of the disclosure provides a method for validating a candidate lead compound and identifying the site of candidate lead compound-microRNA interaction involving: identifying binding of a candidate lead compound to a microRNA or a microRNA fragment; altering the sequence of the microRNA or microRNA fragment *via* introduction of one or more point mutations, thereby generating a mutated microRNA or a mutated microRNA fragment; and identifying absence of binding of the candidate lead compound to the mutated microRNA or

mutated microRNA fragment, thereby validating the candidate lead compound and identifying the site of candidate lead compound-microRNA interaction.

A further aspect of the invention provides a method for validating a candidate lead compound and identifying the site of activity of the candidate lead compound within the microRNA pathway involving: identifying binding of a candidate lead compound to a microRNA or a microRNA fragment; assaying levels of pri-microRNA, pre-microRNA and mature microRNA in the presence of the candidate lead compound, as compared to in the absence of the candidate lead compound; and identifying the site of activity of the candidate lead compound within the microRNA pathway based upon the relative levels of pri-microRNA, pre-microRNA and mature microRNA assayed in the presence of the candidate lead compound, as compared to in the absence of the candidate lead compound, thereby validating the candidate lead compound and identifying the site of activity of the candidate lead compound within the microRNA pathway.

Definitions

By “agent” is meant any small compound, antibody, nucleic acid molecule, or polypeptide, or fragments thereof.

By “alteration” is meant a change (increase or decrease) in the expression levels or activity of a gene or polypeptide as detected by standard art known methods such as those described herein. As used herein, an alteration includes a 10% change in expression levels, preferably a 25% change, more preferably a 40% change, and most preferably a 50% or greater change in expression levels.

By “ameliorate” is meant decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease.

In this disclosure, “comprises,” “comprising,” “containing” and “having” and the like can have the meaning ascribed to them in U.S. Patent law and can mean “includes,” “including,” and the like; “consisting essentially of” or “consists essentially” likewise has the meaning ascribed in U.S. Patent law and the term is open-ended, allowing for the presence of more than that which is recited so long as basic or novel characteristics of that which is recited is not changed by the presence of more than that which is recited, but excludes prior art embodiments.

The disclosure also provides the use of derivatives of the disclosed compositions, such as salts with physiologic organic and inorganic acids like HCl, H₂SO₄, H₃PO₄, malic acid, fumaric acid, citronic acid, tartaric acid, and acetic acid.

“Detect” refers to identifying the presence, absence, or amount of the polypeptide, nucleic acid (e.g., DNA, RNA, microRNA, rRNA, etc.) and/or other composition/substance/moiety to be detected.

By “effective amount” is meant the amount of an agent required to ameliorate the symptoms of a disease relative to an untreated patient. The effective amount of active agent(s) used to practice the present disclosure for therapeutic treatment of a disease varies depending upon the manner of administration, the age, body weight, and general health of the subject. Ultimately, the attending physician or veterinarian will decide the appropriate amount and dosage regimen. Such amount is referred to as an “effective” amount.

By “fragment” is meant a portion of a nucleic acid or polypeptide molecule. This portion contains, preferably, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of the entire length of the reference nucleic acid molecule or polypeptide. A fragment may contain 5, 7, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1000 or more nucleotides or amino acids.

By “gene” is meant a locus (or region) of DNA that encodes a functional RNA or protein product, and is the molecular unit of heredity.

As used herein, the term “isolated” means separated from constituents, cellular and otherwise, in which the polynucleotide, peptide, polypeptide, protein, antibody, or fragments thereof, are normally associated with in nature. As is apparent to those of skill in the art, a non-naturally occurring polynucleotide, peptide, polypeptide, protein, antibody, or fragments thereof, does not require “isolation” to distinguish it from its naturally occurring counterpart. In addition, a “concentrated”, “separated” or “diluted” polynucleotide, peptide, polypeptide, protein, antibody, or fragments thereof, is distinguishable from its naturally occurring counterpart in that the concentration or number of molecules per volume is greater than (“concentrated”) or less than (“separated” or “diluted”) than that of its naturally occurring counterpart.

By “marker” is meant any protein or polynucleotide having an alteration in expression level or activity that is associated with a disease or disorder.

By “modulate” is meant alter (increase or decrease). Such alterations are detected by standard art known methods such as those described herein.

“Non-naturally occurring” as applied to an oligonucleotide means that the oligonucleotide contains at least one moiety that is different from the corresponding wildtype or native oligonucleotide sequence. Non-natural sequences (e.g., sequences comprising nucleotides that do not occur in corresponding native sequence(s)) can be determined by performing BLAST search using, e.g., the lowest smallest sum probability where the comparison window is the length of the sequence of interest (the queried) and when compared to the non-redundant (“nr”) database of Genbank using BLAST 2.0. The BLAST 2.0 algorithm is described in Altschul et al. (1990) *J. Mol. Biol.* 215:403-410. Software for performing BLAST analyses is publicly available through the National Center for Biotechnology Information.

By “nucleic acid” is meant biopolymers, or large biomolecules, essential for all known forms of life. Nucleic acids, which include DNA (deoxyribonucleic acid) and RNA (ribonucleic acid), are made from monomers known as nucleotides. Each nucleotide has three components: a 5-carbon sugar, a phosphate group, and a nitrogenous base. If the sugar is deoxyribose, the polymer is DNA. If the sugar is ribose, the polymer is RNA. Together with proteins, nucleic acids are the most important biological macromolecules; each are found in abundance in all living things, where they function in encoding, transmitting and expressing genetic information—in other words, information is conveyed through the nucleic acid sequence, or the order of nucleotides within a DNA or RNA molecule. Strings of nucleotides strung together in a specific sequence are the mechanism for storing and transmitting hereditary, or genetic information via protein synthesis. Nucleic acids include but are not limited to: deoxyribonucleic acid (DNA), ribonucleic acid (RNA), double-stranded DNA (dsDNA), single-stranded DNA (ssDNA), messenger RNA (mRNA), ribosomal RNA (rRNA), transfer RNA (tRNA), micro RNA (microRNA), and small interfering RNA (siRNA).

By “nucleic acid sequence” is meant a succession of letters that indicate the order of nucleotides within a DNA (using GACT) or RNA (GACU) molecule. By convention, sequences are usually presented from the 5' end to the 3' end. For DNA, the sense strand is used. Because nucleic acids are normally linear (unbranched) polymers, specifying the sequence is equivalent to defining the covalent structure of the entire molecule. For this reason, the nucleic acid

sequence is also termed the primary structure. The sequence has capacity to represent information. Biological DNA represents the information which directs the functions of a living thing. In that context, the term genetic sequence is often used. Sequences can be read from the biological raw material through DNA sequencing methods. Nucleic acids also have a secondary structure and tertiary structure. Primary structure is sometimes mistakenly referred to as primary sequence.

Ranges provided herein are understood to be shorthand for all of the values within the range. For example, a range of 1 to 50 is understood to include any number, combination of numbers, or sub-range from the group consisting 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50, as well as all intervening decimal values between the aforementioned integers such as, for example, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, and 1.9. With respect to sub-ranges, “nested sub-ranges” that extend from either end point of the range are specifically contemplated. For example, a nested sub-range of an exemplary range of 1 to 50 may comprise 1 to 10, 1 to 20, 1 to 30, and 1 to 40 in one direction, or 50 to 40, 50 to 30, 50 to 20, and 50 to 10 in the other direction.

By “reduces” is meant a negative alteration of at least 10%, 25%, 50%, 75%, or 100%.

By “reference” is meant a standard or control condition.

As used herein, “obtaining” as in “obtaining an agent” includes synthesizing, purchasing, or otherwise acquiring the agent.

By “small molecule” is meant a compound typically characterized in that it contains several carbon-carbon bonds, and has a molecular weight of less than 5000 Daltons (5 kD), optionally less than 3 kD, optionally less than 2 kD, and in certain embodiments, less than 1 kD. In some cases, a small molecule has a molecular weight equal to or less than 700 Daltons, optionally equal to or less than 500 Daltons.

By “subject” is meant a mammal, including, but not limited to, a human or non-human mammal, such as a bovine, equine, canine, ovine, murine, rattus or feline.

As used herein, the terms “treat,” “treating,” “treatment,” and the like refer to reducing or ameliorating a disorder and/or symptoms associated therewith. It will be appreciated that,

although not precluded, treating a disorder or condition does not require that the disorder, condition or symptoms associated therewith be eliminated.

As used herein, the terms “prevent,” “preventing,” “prevention,” “prophylactic treatment” and the like refer to reducing the probability of developing a disorder or condition in a subject, who does not have, but is at risk of or susceptible to developing a disorder or condition.

Unless specifically stated or obvious from context, as used herein, the term “or” is understood to be inclusive. Unless specifically stated or obvious from context, as used herein, the terms “a”, “an”, and “the” are understood to be singular or plural.

Unless specifically stated or obvious from context, as used herein, the term “about” is understood as within a range of normal tolerance in the art, for example within 2 standard deviations of the mean. About can be understood as within 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.1%, 0.05%, or 0.01% of the stated value. Unless otherwise clear from context, all numerical values provided herein are modified by the term about.

The recitation of a listing of chemical groups in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable or aspect herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

A “therapeutically effective amount” is an amount sufficient to effect beneficial or desired results, including clinical results. An effective amount can be administered in one or more administrations.

Any compositions or methods provided herein can be combined with one or more of any of the other compositions and methods provided herein.

Other features and advantages of the disclosure will be apparent to those skilled in the art from the following detailed description and claims.

Brief Description of the Drawings

Figure 1 depicts a schematic overview of the approach to the present disclosure. Figure 1 shows the relationship of applying functional biology, structural biology and chemistry to screening, validating and optimizing microRNA (microRNA) molecules as an exemplary target oligonucleotide. The approach of the present disclosure combines NMR and biological

functional assays in a platform to identify compounds that bind oligonucleotides, including, e.g., RNAs, microRNAs and/or non-coding RNAs in a rapid manner. In some embodiments, the present disclosure describes targeting of oncomirs (oncogenes) that drive tumor development and/or may be involved in other diseases.

Figure 2 depicts a schematic overview of the microRNA pathway and also shows (at right) Antagomir-21 inhibitory/degradative activity upon mature microRNA-21. As described herein, microRNA is a small non-coding RNA molecule (containing about 19-22 nucleotides in its mature form) which functions in RNA silencing and post-transcriptional regulation of gene expression. The human genome may encode over 2500 microRNAs, which are abundant in many mammalian cell types and appear to target at least 60% of the genes of humans and other mammals.

Figures 3A and 3B depict expression of microRNA-21 in cancer and that anti-microRNA-21 agents exhibit anti-tumor therapeutic benefit. Figure 3A is a graph demonstrating microRNA-21 profiles for all stages of breast cancer, as compared to levels in normal solid tissue. The dark line in each box represents the median. Figure 3B is a series of photographs demonstrating expression of microRNA-21 in microRNA-21 induced B-cell lymphoma. Tumor bearing mice were examined with and without microRNA-21 overexpression (at day 0, microRNA-21 was overexpressed, but reduction of microRNA-21 was then achieved *via* use of Cre and Tet-off technologies (Medina *et al. Nature* 467: 86-90), and the time course was monitored). A loss of microRNA-21 was witnessed over time to result in shrinkage of B-cell lymphoma tumors at days 2-6, as shown. As demonstrated in Figures 3A and 3B, microRNA-21 has been found to be overexpressed in different cancers. The anti-tumor benefit observed for reduction of microRNA-21 levels demonstrates that microRNA-21 represents not just a biomarker for disease but also a target for treatment.

Figure 4 depicts an illustration showing that microRNA-21 has been identified as overexpressed in many cancers, including glioblastoma, breast cancer, lung cancer, prostate cancer, stomach cancer, colon cancer, cervical cancer, and head and neck cancer.

Figure 5 depicts a schematic of the role in microRNA-21 in tumor suppression. microRNA-21 plays a role in inhibition of RECK, Maspin, MARKs, TPM1, PTEN, and PDCD4 (Programmed Cell Death 4, a neoplastic transformation inhibitor).

Figures 6A and 6B depict diagrams demonstrating constructs for parallel compound screening. Figure 6A depicts a diagram of a reporter gene cell based assay used in an MCF-7 breast cancer cell line, for identification of agents capable of suppressing microRNA-21 activity. The construct includes a microRNA-21 complementary sequence as well as reporter sequences for firefly luciferase and renilla luciferase (with renilla luciferase acting as a transfection control). Expression of antagomiR-21 acts as a positive control, turning on firefly luciferase expression in the reporter assay *via* release of microRNA-21 inhibition of firefly luciferase expression. The expression cassette may include sequences complementary to other microRNAs, as an alternative or even in addition to microRNA-21. Figure 6B depicts microRNA stem loop structures and the location of sequences within the RNA structure that are targeted by Dicer and Drosha. These structures were employed for NMR detection assays, in compound screening methods described herein. The red sequences represent the mature/functional microRNA-21.

Figures 7A and 7B depict histograms, a 96-well plate layout and diagrams of primary compound screening. Figure 7A presents a histogram and diagram of a 96 well plate, with the histogram demonstrating that inhibition of microRNA-21 by an antagomiR-21 construct increased reporter gene detection by approximately 50-fold. A scrambled antagomiR-21 sequence did not lead to expression of the reporter gene (microRNA-21 inhibition of firefly luciferase expression was maintained at baseline levels). Figure 7B is a diagram of the screening scheme used to detect compounds that bind RNA molecules. As described herein, cells that represent a disease model (*e.g.*, MCF-7 breast cancer cells) were plated on Day 1. On Day 2, reporter constructs containing a complementary sequence to miR-21 or a scrambled sequence in the 3' UTR of Firefly microRNAs (*e.g.*, microRNA-21; pmicroRNA-GLO) were transiently transfected into the disease model cell line. Transfected cells were treated with compounds to be screened at different concentrations (*e.g.*, 10 μ M, 1 μ M, etc.). On Day 5, the reporter assay (*e.g.*, Dual-GLO assay) was performed and data was analyzed. The reporter enzymes (renilla and firefly luciferase) were evaluated at 48 hours after compound treatment (the Day 5 mark).

Figure 8 depicts a series of diagrams that define the criteria for primary compound screening selection. As described herein, hits are identified as any compound that inhibits microRNA activity (e.g., microRNA-21 activity) in cell culture by at least 1.5-fold or greater, as compared to cells treated with DMSO alone. The fold change is determined by comparing total average normalized luciferase activity of compound treated cells to normalized luciferase activity of DMSO treated cells. As described herein, 93 compounds (13%) of a 696 compound library exhibited readings above this threshold.

Figures 9A and 9B depict the NMR approach employed for primary screening of compounds targeting RNA molecules. Figure 9A is a diagram depicting an exemplary NMR spectrum obtained during the small molecule library screen and a Venn diagram showing classification of the corresponding hits identified by the NMR screen. Using NMR, peaks that corresponded to compounds binding Dicer or Drosha constructs indicated a positive hit. As described herein, subsets of tested compounds were classified according to whether they bind Dicer, Drosha, or to both constructs. Figure 9B depicts a diagram showing the overlap of hits that were identified according to their performance in cell-based assays and in NMR profiling. Subsets of compounds regarded as positive hits under both NMR and cell-based assays were selected for immediate further examination.

Figures 10A, 10B and 10C depict a series of chromatograms and graphs that demonstrate the scoring methods as described herein. Figure 10A is a sample NMR spectrum depicting peaks and how they would be scored. Figure 10B depicts a series of curves for the reporter gene assay. As described herein, compounds are assigned a score based on graphs of curves of the intensity of light units at different compound concentrations, as compared to a control curve. Light units are measured based on raw firefly luminescence data. Figure 10C depicts a graph demonstrating the potency score used in the reporter assay screen. Luciferase is normalized to Renilla and the fold change is determined by comparing normalized compound samples relative to DMSO control samples. As described herein, compounds are assigned a potency score based on the lowest concentration that achieves a 2-fold or higher change in activity. More potent compounds receive a higher score, while less potent compounds have a lower score. As demonstrated in Figures 10B and 10C, there is a bias towards selecting compounds with higher activity at lower concentrations. For scoring, a maximum 14 point scale scoring system is based on 4 possible

points from NMR screens and 10 possible points from the reporter gene assay based on the dose response observed (including 0-3 points for curve shape, as in Figure 10B, and 0-7 points assessed for concentration level at which two-fold increase in light units is first achieved).

Figure 11 depicts a series of screened compounds identified as hits (potential leads), along with their molecular weight, NMR score, functional score, total score, IC₅₀ and IC₂₅. Compounds with total scores from 9 to 13 are depicted.

Figures 12A and 12B depict a series of schematics that demonstrate the microRNA pathway and possible points of agent-mediated microRNA-21 modulation. Figure 12A depicts a schematic of the entry points for small molecules modulating microRNA (*e.g.*, microRNA-21) maturation and/or activity of mature microRNAs (schematic adapted from the Sharp lab website at web.mit.edu/sharplab/researchsummary.html). Figure 12B depicts the microRNA pathway and points at which a test compound may act on microRNAs. Graphs depict the results of the reporter assay of test microRNA antagonists (*i.e.*, antagomiR, *e.g.*, antagomiR-21), as compared to untreated and scrambled control for pri-microRNA, pre-microRNA, and mature-microRNA (*e.g.*, pri-microRNA-21, pre-microRNA-21, and mature-microRNA-21). As demonstrated in Figure 12B, the antagomiR-21 inhibits the activity of microRNA-21 at the mature-microRNA-21 stage, likely by promoting degradation of mature microRNA-21.

Figures 13A and 13B depict graphs demonstrating the results of reporter and proliferation assays performed on a positive anti-microRNA-21 compound. Figure 13A depicts the reporter assay results including graphs of raw luciferase activity and the fold change relative to DMSO for the compound (BSI101023) at different concentrations used for scoring. Figure 13B depicts the proliferation assay results measuring the percent cell count confluency of compound BSI101023 at different concentrations compared to DMSO. As demonstrated herein, cell growth declines in a dose dependent manner with increasing concentration of the test compound BSI101023.

Figures 14A to 14C depict additional biological assays for testing the functionality of a microRNA-binding compound. Figure 14A depicts a scratch assay used to test the compound BSI101023. The compound was analyzed for the ability to block re-population of cells at different compound concentrations, as compared to a DMSO-treated control. Figure 14B depicts

the downstream effects of microRNA-21 antagonism with test compounds BSI101023, BSI101534, and BSI101484. Introduction of BSI101023 has similar effects on microRNA-21 as those observed for a positive control antagomiR-21 oligonucleotide agent. Figure 14B demonstrates that compounds BSI101023 and BSI101484 increased the expression of Programmed Cell Death 4 (PDCD4), a downstream effector of microRNA-21, consistent with the anti-microRNA-21 activity observed. Figure 14C shows a proliferation and apoptosis analysis of MCF-7 cells treated with an antagomiR-21 oligonucleotide.

Figures 15A and 15B depict quantitative analysis of microRNA processing species at IC₂₅. Figure 15A depicts a schematic of the microRNA-21 pathway and the point at which the antagomiR-21 compound BSI101023 was identified to act. Figure 15B is a graph depicting the percent expression of pri-microRNA-21, pre-microRNA-21, and mature-microRNA-21 relative to DMSO control after cell exposure to BSI101023, or to antagomiR. *P<0.05. ***P<0.0005. NS is “not significant”. While antagomiR-21 was observed to cause a significant reduction in mature microRNA-21 (consistent with sequestering and degradation of mature microRNA-21 by the antagomiR), mature microRNA-21 was observed to accumulate when BSI101023 was administered (suggesting that RISC-loading of mature microRNA-21 was blocked by BSI101023).

Figures 16A, 16B and 16C depict graphs demonstrating the results of reporter, proliferation, and downstream effector assays performed on a positive anti-microRNA-21 compound. Figure 16A depicts the reporter assay results including graphs of raw luciferase activity and the fold change relative to DMSO for the compound (BSI101484) at different concentrations, which were used for scoring of test compounds. Figure 16B depicts the proliferation assay results measuring the percent confluency of compound BSI101484 at different concentrations, as compared to DMSO-treated cells. As demonstrated herein, cell growth declined in a dose dependent manner with increasing concentration of potential compound behaving as an anti-microRNA BSI101023. Figure 16C depicts the downstream effects of microRNA-21 antagonism when test compounds BSI101023, BSI101484, and BSI101534 were administered. Introduction of BSI101484 had similar effects upon microRNA-21, as compared to BSI101023 and a positive control (antagomiR-21). Figure 16C demonstrates

that compounds BSI101023 and BSI101484 also increased the expression of Programmed Cell Death 4 (PDCD4), a downstream effector of microRNA-21.

Figures 17A and 17B depict schematics and results of apoptosis assays in MCF-7 cells. Figure 17A shows that treatment with BSI101484 or 101023 caused dose dependent apoptosis in MCF-7 in 120 hrs. Figure 17B shows a real time apoptosis assay, performed using IncuCyte Zoom and caspase-3/7 reagent.

Figures 18A and 18B depict a schematic of the microRNA processing pathway and quantitative analysis of microRNA processing species for various anti-microRNA-21 agents, relative to DMSO-treated control cells, at IC₂₅. Figure 18A depicts a schematic of the microRNA-21 pathway and the point at which the anti-microRNA-21 compound BSI101484 likely acts. Figure 18B is a graph depicting the percent expression of pri-microRNA-21, pre-microRNA-21, and mature-microRNA-21 relative to DMSO-treated control cells, after exposure to antagomiR-21 as a positive control, anti-microRNA-21 compound BSI101484, or to no antagomiR. ***P<0.0005. NS is “not significant”.

Figures 19A to 19E depict a series of schematics and spectra that demonstrate the confirmation of NMR titration from screening to initial SAR. Figure 19A depicts the scheme for performing NMR analysis of positive hits in the top panel. In the bottom panel, the structure of double stranded RNA targeted by anti-microRNA agents is shown. In some embodiments, the mechanism of how a test compound inhibits microRNA involves an agent acting as and/or mimicking a wobble base and through binding to microRNA, creating a stable form of microRNA that is not cleaved by Dicer or Drosha. Figure 19B depicts a microRNA-21 stem loop structure and NMR spectra obtained for a microRNA-21-interacting test compound, BSI101534. As demonstrated in the NMR spectra, there was a shift of in peaks corresponding to bases U24 and G27 observed in the presence of BSI101534, the effect of which was dose-dependent, consistent with BSI101534 binding microRNA-21. BSI101534 binds only to the Dicer target sequence-containing construct, in the A26 bulge region, as demonstrated by mapping the positions of U24 and G27 onto the stem-loop diagram. Figure 19C depicts the microRNA stem loop diagrams and NMR spectra obtained for test compounds BSI101484 and BSI101023. Compounds BSI101484 and BSI101023 also bind to the A26 bulge region. Figure 19D depicts the microRNA stem loop diagram and NMR spectra for a fragment of test compound BSI101484

– called BSI104171. Figure 19E depicts a NMR spectra and stem loop diagram using naturally occurring nucleobases (D58) as a control. No peaks shift when the nucleobases are added. Thus, no binding was observed between the U, T, A, and G nucleobases and/or nucleosides tested with a naturally-occurring nucleobase (D58).

Figures 20A and 20B depict stem loop diagrams and NMR spectra obtained in examining the role of the effects of the sequence context of the A26 bulge on binding of certain anti-microRNA-21 test compounds. Figure 20A shows NMR spectra for test compounds BSI101534, BSI101484, and BSI 104171 mixed with an RNA construct lacking the A-bulge (D57). The RNA peaks do not shift in the presence of any of the three compounds; there is no binding. Therefore, it was concluded that the A26 bulge region was necessary for binding. Figure 20B depicts additional structures and NMR spectra for the test compound BSI101534. By changing the length of the microRNA but retaining the A26 bulge region, it was demonstrated that the A26 region is sufficient for microRNA-21 binding by the anti-microRNA-21 test compounds.

Figures 21A to 21H depict stem loop diagrams and NMR spectra that demonstrate whether the binding of test compounds to Dicer-containing microRNAs is sequence-context dependent. Figure 21A depicts a scheme for mutational mapping of local sequence context, to identify context relevant to microRNA-binding test compounds. In altered microRNA-21-derived constructs, sequences in the bulge region were substituted to mimic bulge regions from non-microRNA-21s (in Figure 21A, hsa-mir-103a-1 and a mutant form thereof, as shown). Additionally, sequences outside the bulge region were altered to mimic the non-bulge regions of other non-microRNA-21s. Figure 21B depicts alternate stem loop schemes and NMR spectra for microRNA-21-derived constructs where 1) the neighboring base pairs remain but the bulge is altered (“hsa-mir-16-1”) and 2) neighboring base pairs are altered while the bulge region is altered, yet the bulge nucleotide is retained (“hsa-mir-155”). NMR spectra the different altered microRNA-21-derived constructs are depicted as BSI101534 and BSI104171 are added. Peaks that shift when both BSI101534 and BSI104171 are added to the hsa-mir-16-1 construct (retaining neighboring base pairs) are shaded. The compounds bind to the construct with the U bulge in the same sequence context as miR21 but not to the A bulge in the miR155 sequence context. Figure 21C depicts further changes to the sequence context based on the has-mir-155

construct from Figure 21B. When the upper base pair flanking the A-bulge is restored to GC (“hsa-mir-155-mut”), binding by BSI101534 and BSI104171 is restored somewhat. Figure 21D depicts stem loop diagrams and NMR spectra for microRNA-21-derived constructs where both the bulge region and sequences outside the bulge region are altered to those of hsa-mir-103a-1. NMR spectra of the RNA in the presence of BSI101534 and BSI104171 are shown.

Unexpectedly, the compounds bind to hsa-mir-103a-1, even though the bulge and flanking base pairs are different from mir-21. Figure 21E shows that hsa-mir-103a-1 can adopt an alternative base-pairing scheme compared to that predicted by mfold. The alternative scheme preserves the CG base pairs flanking the bulge, similar to the mir21 context. This account for the binding in the mir-103 context. Figure 21F depicts stem loop diagrams and NMR spectra for the microRNA-21-derived hsa-mir-103a-1 construct of Figure 21D, with a mutation to lock the hairpin into the structure predicted by mfold. With the hairpin locked into the predicted miR103 secondary structure, BSI101534 and BSI104171 no longer bind (no shift observed).. Figure 21G depicts stem loop structures and NMR spectra for a microRNA-21-derived structure having the hsa-mir-200c bulge region sequence, which possesses a mismatch instead of the A bulge. NMR spectra for this construct in the presence of BSI101534 and are shown. No binding was observed for either compound. Figure 21H presents a summary of exploration of the sequence context for compound binding.

Figure 22 shows the NOESY (Nuclear Overhauser effect spectroscopy) spectrum for the miR21 D29 hairpin. NOE crosspeaks are observed for sequential bases G27 and A28, and G66 and A67, demonstrating that these bases are close together in space (within 5 Å), as expected from the sequence and the predicted helical structure. Strikingly, crosspeaks are observed for the bulge base, A26, to both G27 and G66, suggesting that the base stacks into the helix. A model, based for the structure, based on pdb entry 5A17, is shown.

Figures 23A and 23B depict schematics for the likely binding mode for compounds to the microRNA-21 bulge region. The flanking GC/CG base pairs stabilize the helix. The bulge nucleotide flips in and interacts with the compound. The compound makes favorable stacking interaction with the neighboring base pairs. If the compound is extended, there is the potential to make additional favorable interactions with the rest of the RNA. Figure 23B shows crosspeaks identified in 2D NOESY spectrum.

Figure 24 depicts a schematic showing the hit finding and lead generation process employed.

Figures 25A and 25B show two hits identified by the parallel screening process. Figure 25A shows the diiminoisoindoline hit, BSI101484. A search of the in-house library identified the analog, BSI104171. A summary of the results for both compounds in the reporter assay and NMR is presented in the table. Figure 25B shows the 4-Hydroxyquinoline hit, BSI101534. Again, searching the in-house library turned up analogs BSI101536 and BSI101473, which were also tested. The results are presented in the table..

Figure 26 depicts stem loop diagrams of microRNA-21 constructs prepared for crystallization. Based upon a 103-mer microRNA-21 full length construct, three microRNA-21 constructs were set up for crystallization. These include a microRNA-21 58-mer “Dicer construct”, a microRNA-21 45-mer Dicer tetraloop, and a microRNA-21 two strand stem of 21 and 22-mers (a duplex comprising a 21mer and a 22mer, with bulge nucleotide as shown).

Figures 27A and 27B depict graphs demonstrating differentially expressed microRNAs in Stage 2b breast cancer patients. Figure 27A depicts the median microRNA counts per million microRNA reads found in stage 2b primary breast tumor samples. Figure 27B depicts the fold changes observed in stage 2b primary tumor compared to normal tissue for various microRNAs. Differential expression of the microRNAs shown are statistically significant with adjusted p-values < 0.001. All fold changes shown are greater than 2.5 or less than -2.5.

Figure 28 depicts a graph demonstrating microRNA-21 expression levels observed in breast cancer, by stage (TCGA). Elevated microRNA-21 expression was identified across all stages examined.

Figure 29 depicts the downstream effects of microRNA-21 antagonism with test compounds BSI101023, BSI101534, BSI100945, and BSI101484. Administration of BSI101023 exhibited similar effects on microRNA-21 levels as a positive control, antagomiR-21. Compounds BSI101023 and BSI101484 specifically increased the expression of Programmed Cell Death 4 (PDCD4), a downstream effector of microRNA-21.

Figure 30 presents a list of suitable miRNA targets expressly contemplated for application of the methods and compositions of the instant disclosure, together with disease targets expressly contemplated for each such suitable miRNA target.

DETAILED DESCRIPTION OF THE INVENTION

The present disclosure is based, at least in part, upon the development and successful performance of screening methods that efficiently identify candidate lead compounds that bind regulatory RNA oligonucleotides (*e.g.*, microRNAs) and exert a biological effect upon such regulatory molecules. Certain aspects of the disclosure provide specific candidate lead compounds that were discovered to bind and inhibit microRNA-21 in a sequence-specific manner, thereby identifying compounds likely to exert therapeutic effects upon microRNA-21 overexpressing cancers (*e.g.*, glioblastoma, breast cancer, lung cancer, prostate cancer, stomach cancer, colon cancer, cervical cancer, and head and neck cancer). Certain aspects of the disclosure also provide validation methods capable of identifying the specific site(s) of action for such candidate lead compounds within a targeted regulatory RNA oligonucleotide. Test compound screening methods capable of merging structural, NMR-derived data with results obtained in biological reporter assays in an efficient and effective manner to identify candidate lead compounds that bind and modulate activity of regulatory RNA oligonucleotides (*e.g.*, microRNAs and other non-coding RNAs) are also provided. The parameters of the disclosure are set forth in additional detail below.

Methods of the present invention

The present disclosure describes a parallel integrative approach to identifying novel compounds – particularly small molecules – which bind and/or inhibit oligonucleotides, *e.g.*, microRNA function. Fields of genetics/bioinformatics, functional biology, structural biology (NMR and/or crystallography), medicinal chemistry, and cheminformatics may be combined to identify and validate compounds which bind oligonucleotides, *e.g.*, compounds that bind and disrupt microRNAs relevant to different diseases states. Figure 1 shows the relationship of applying functional biology, structural biology and chemistry to screening, validating and optimizing compounds that bind microRNA (microRNA) molecules. The approach of the present disclosure combines NMR and biological functional assays in a harmonized platform to identify

rapidly highly effective compounds that bind RNAs, microRNAs and non-coding RNAs. In certain embodiments, the present disclosure describes methods of inhibiting oncomirs (oncogenes) that drive tumor development and/or may be involved in other diseases.

Conveniently, the compounds of the present invention may be numerically scored using the present methods to identify compounds that bind and modulate the activity of, for example inhibit, oligonucleotides such as RNA, specifically microRNA. For each assay used herein, a numeric value is assigned based on the likelihood that the result indicates a positive binding and/or inhibition of the compound to the oligonucleotide and preferably at lower concentrations of the compound. The values may then be combined to generate a score for each compound such that a high score indicates a high likelihood of favorable binding characteristics such as specificity, for example as detected by NMR, and ability to inhibit the activity of the oligonucleotide at useful concentrations, for example using a biological functional assay. Figure 10 in particular provides examples of such scoring techniques, and Figures 11 and 13 provides additional examples of scoring.

In one embodiment, NMR is used to identify compounds that bind an oligonucleotide, such as microRNA, based on peaks in the spectrum generated when the compound is in the presence of the oligonucleotide. A peak appearing at greater than 1% of the reference spectrum indicates that binding between compound and oligonucleotide is detected. Such a peak is assigned a score of +1. A signal to noise ratio of greater than 3.0 indicates signal above noise is significant. This is assigned an additional score of +1. Sharp peaks indicate nonspecific binding is excluded; this is also assigned a score of +1. The spectrum is compared to that predicted from the compound's chemical structure and concentration. Agreement indicates that the good compound integrity and solubility. This is assigned a score of +1. Based on these parameters, a screened compound has a possible NMR score of 0-4, with a score of 4 indicating high quality binding.

In another embodiment or in addition to the NMR assay described above, a biological functional assay is used to identify compounds that modulate the function of the oligonucleotide, such as inhibit the activity of microRNA. Compounds can inhibit microRNAs at various stages of the microRNA pathway including: at the level of transcription and/or the initial transcript (pri-microRNA), pre-microRNA, microRNA duplex, and mature RNA. Inhibition may take place

inside the nucleus and/or in the cytoplasm. Inhibition can be detected by cell based assays, for example using cell lines transfected with a reporter construct that includes an oligonucleotide sequence complementary to the microRNA of interest, for example miR-21, which is linked to a reporter gene such as luciferase or a fluorescent protein such as GFP and similar. In this type of assay, the reporter gene expression is silenced in the presence of the active microRNA of interest, or target microRNA, and activated when the microRNA of interest is inhibited by binding of a suitable compound. Inhibition is measured by comparing the signal generated by cells treated with the test compound against that generated in suitable positive (known microRNA antagonists) and negative controls. Inhibition can be described as a statistically significant increase of the signal compared to the negative control, for example the signal is at least 1.25-fold, at least 1.5-fold, at least 1.75-fold, at least 2-fold, at least 2.5-fold, at least 3-fold, etc, greater than the negative control. Figure 10C provides an example of such a comparison. The greater the inhibition, the more potent the compound is, and compounds can be assigned a potency score. In one example, a potency score of 0 to 7 is assigned to the compound, with 7 being the most potent. Alternative assays may be used, for example proliferation assays, scratch assays, non-cell based assays such as immunoassays such as Western blots, ELISAs, and bead based assays such as AlphaLISA™ (Perkin Elmer), as well as PCR assays such as RT-PCR, qPCR and the like.

Furthermore, compounds can be assigned a score based on the shape of curves of the signal generated in the biological functional assay at different compound concentrations as compared to the negative control. This curve-based score biases the overall score towards compounds that have a higher activity at lower concentration. As exemplified in Figure 10B, compounds are given low scores for showing no inhibition or inhibition only at higher concentrations. A higher score is given to compounds that show increased activity at higher concentrations, while the highest score is given to compounds that show strong inhibition at low concentrations, for example below a set threshold of desirable concentration. In this example, a dose response score is given between 0 (no inhibition) and 3 (high inhibition at low concentration).

Thus, by combining the scores from the NMR and biological functional assays, test compounds can be evaluated for their ability to bind oligonucleotides, for example microRNA,

as well as the quality of that binding in a simple, consistent and easy to compare manner. Test compounds that have a good composite score may be then be designated candidate lead compounds.

It can be appreciated that using the methods of the present invention, not only gross binding of the compound to oligonucleotides, for example microRNA, can be detected, but also the specific binding site can be identified by providing one or more specific target sequences corresponding to different regions of the oligonucleotide. For example, binding pri-microRNA, pre-microRNA, microRNA duplex, and mature microRNA can be detected, as well as binding to certain key sequences within the oligonucleotide, such as the Dicer and/or Drosha cleavage sites of microRNA. Inhibition of the microRNA can also be measured by measuring transcription, translation and degradation to determine at which step the inhibition occurs. Such methods can be used to validate and characterize test compounds and candidate lead compounds.

Regulatory RNA Oligonucleotides (e.g., microRNAs) as Therapeutic Targets

As described herein, microRNA is a small non-coding RNA molecule (containing about 19-22 nucleotides) which functions in RNA silencing and post-transcriptional regulation of gene expression. The human genome may encode over 2500 microRNAs, which are abundant in many mammalian cell types and appear to target at least 60% of the genes of humans and other mammals, as depicted in Figure 2 (which also shows a histogram in which degradation of mature microRNA-21 provoked by an antisense agent specifically targeting microRNA-21 (“Antagomir-21”) is documented). As such, microRNAs represent a substantial class of targets for treating disease *via* modulation of gene expression. In particular, a role exists for microRNAs in fibrosis, where microRNA-21 is upregulated and microRNA-29 is downregulated in kidney, liver, and lung fibrosis. Additionally, a complex regulatory network of microRNAs is also involved in Parkinson’s Disease. Suitable microRNA targets include microRNA-21 and the miRNAs recited in Figure 30.

Exemplary disease targets for candidate lead compounds that bind to RNA oligonucleotides include fibrosis, cancer (*e.g.*, *via* regulation of microRNAs and other non-coding RNAs) and other associated diseases and disorders. For example, such disease targets may include retinoblastoma, renal cell carcinoma, prostate cancer, papillary thyroid carcinoma,

pancreatic ductal adenocarcinoma, pancreatic cancer, pancreatic adenocarcinoma, ovarian cancer, osteosarcoma, oropharyngeal cancer, oral squamous cell carcinoma, oral carcinoma, oral cancer, non-small cell lung cancer, neuroblastoma, nasopharyngeal carcinoma, multiple myeloma, mucinous cystadenocarcinoma, malignant melanoma, lung cancer, liver cancer, laryngeal squamous cell carcinoma, laryngeal carcinoma, laryngeal cancer, kidney cancer, hypopharyngeal squamous cell carcinoma, hepatocellular carcinoma, hepatoblastoma, head and neck squamous cell carcinoma, head and neck cancer, glioma, glioblastoma, gastrointestinal stromal tumor, gastric cancer, esophageal squamous cell carcinoma, esophageal cancer, endometrial cancer, diffuse large b-cell lymphoma, colorectal carcinoma, colorectal cancer, colon cancer, stomach cancer, chronic myelogenous leukemia, cholangiocarcinoma, cervical carcinoma, cervical cancer, breast cancer, b-cell lymphoma, adrenal cortical carcinoma and squamous carcinoma, all of which are associated with microRNA-21. Other disease targets contemplated for suitable miRNAs of the instant disclosure are recited for each miRNA in Figure 30.

Test Compound Library

Test compound libraries may be conveniently assembled from commercial sources and/or custom generated. For example, the libraries exemplified herein were curated by mining and identifying compounds from the literature and from internal fragment libraries. The compounds fell within the RO3 or RO5 (Lipinski definition), and the libraries were organized for high throughput screening.

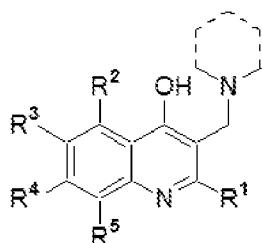
Cancer Cell Lines

In addition to the MCF-7 cell line exemplified herein, screening as described in the instant disclosure can be performed upon any one or many of known cancer cell lines, including, *e.g.*, 600MPE, AU565, BT-20, BT-474, BT-483, BT-549, Evsa-T, Hs578T, MDA-MB-231, SkBr3, T-47D, CCF-STTG1, SW 1088, SW 1783, CHLA-02-ATRT, A172, U-138 MG, LN-18, LN-229, U-87 MG, U-118 MG, T98G, Hs 683, CHLA-01-MED, CHP-212, H4, D341 Med, Daoy, PFSK-1, DBTRG-05MG, M059K, M059J, IMR-32, BC3H1, bEnd.3, Neuro-2a, NB41A3, N1E-115, C6, C6/LacZ, 9L/lacZ, C6/lacZ7, F98EGFR, F98npEGFRvIII, F98, RG2, NCI-H1373, NCI-H1395, SK-LU-1, HCC2935, HCC4006, HCC827, NCI-H1581, NCI-H23, NCI-H522,

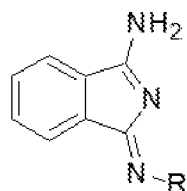
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Candidate Lead Compounds

Certain aspects of the disclosure relate to identification of the following candidate lead compounds as capable of binding microRNA-21 in an inhibitory manner.



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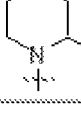


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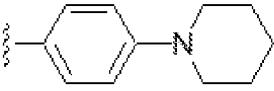
Formula (II)

Formula (I) selected from the following:

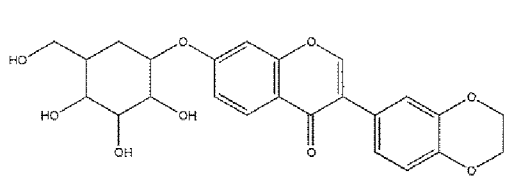
Compound	R ¹	R ²	R ³	R ⁴	R ⁵	
BSI101534	Ph	H	-OMe	H	H	
BSI101536	Ph	H	-OMe	H	H	
BSI101473	-CH ₃	-OMe	H	H	-OMe	

, and/or

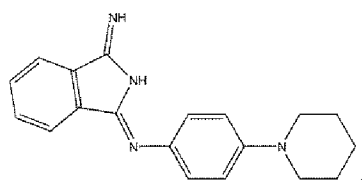
Formula (II) selected from the following:

Compound	R
BSI101484	
BSI104171*	H

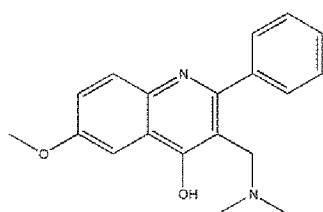
, or a salt thereof.



Formula (III)

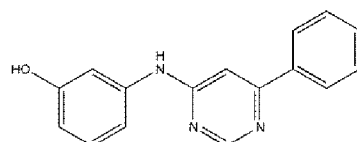


Formula (IV)



Formula (V)

and



Formula (VI)

or a salt thereof.

Derivatization of the above compounds is also specifically contemplated.

Pharmaceutical Compositions

In certain embodiments, the present disclosure provides for a pharmaceutical composition comprising a candidate compound of the present disclosure. A candidate compound can be suitably formulated and introduced into a subject and/or the environment of a cell by any means that allows for a sufficient portion of the compound to exert an effect in the subject or cell, if it is to occur. Many formulations for small molecules are known in the art and can be used.

For administration to a subject, the candidate lead compounds of the disclosure can be provided in pharmaceutically acceptable compositions. These pharmaceutically acceptable compositions comprise a therapeutically-effective amount of one or more of the candidate lead compounds, formulated together with one or more pharmaceutically acceptable carriers (additives) and/or diluents. As described in detail herein, the pharmaceutical compositions of the present disclosure can be specially formulated for administration in solid or liquid form, including those adapted for the following: (1) oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), gavages, lozenges, dragees, capsules, pills, tablets (e.g., those targeted for buccal, sublingual, and systemic absorption), boluses, powders, granules, pastes for application to the tongue; (2) parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; (3) topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin; (4) intravaginally or intrarectally, for example, as a pessary, cream or foam; (5) sublingually; (6) ocularly; (7) transdermally; (8) transmucosally; or (9) nasally. Additionally, compounds can be implanted into a patient or injected using a drug delivery system. See, for example, Urquhart, et al., Ann. Rev. Pharmacol. Toxicol. 24: 199-236 (1984); Lewis, ed. "Controlled Release of Pesticides and Pharmaceuticals" (Plenum Press, New York, 1981); U.S. Pat. No. 3,773,919; and U.S. Pat. No. 3,270,960, content of all of which is herein incorporated by reference.

As used here, the term "pharmaceutically acceptable" refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without

excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used here, the term "pharmaceutically-acceptable carrier" means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, manufacturing aid (e.g., lubricant, talc magnesium, calcium or zinc stearate, or steric acid), or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: (1) sugars, such as lactose, glucose and sucrose; (2) starches, such as corn starch and potato starch; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, methylcellulose, ethyl cellulose, microcrystalline cellulose and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) lubricating agents, such as magnesium stearate, sodium lauryl sulfate and talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol (PEG); (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) pH buffered solutions; (21) polyesters, polycarbonates and/or polyanhydrides; (22) bulking agents, such as polypeptides and amino acids (23) serum component, such as serum albumin, HDL and LDL; (22) C.sub.2-C.sub.12 alcohols, such as ethanol; and (23) other non-toxic compatible substances employed in pharmaceutical formulations. Wetting agents, coloring agents, release agents, coating agents, sweetening agents, flavoring agents, perfuming agents, preservative and antioxidants can also be present in the formulation. The terms such as "excipient", "carrier", "pharmaceutically acceptable carrier" or the like are used interchangeably herein.

The phrase "therapeutically-effective amount" as used herein means that amount of a compound, material, or composition comprising a compound described herein which is effective for producing some desired therapeutic effect in at least a sub-population of cells in an animal at a reasonable benefit/risk ratio applicable to any medical treatment. For example, an amount of a

compound administered to a subject that is sufficient to produce a statistically significant, measurable decrease in the size of a tumor.

Determination of a therapeutically effective amount is well within the capability of those skilled in the art. Generally, a therapeutically effective amount can vary with the subject's history, age, condition, sex, as well as the severity and type of the medical condition in the subject, and administration of other pharmaceutically active agents.

As used herein, the term "administer" refers to the placement of a composition into a subject by a method or route which results in at least partial localization of the composition at a desired site such that desired effect is produced. Routes of administration suitable for the methods of the disclosure include both local and systemic administration. Generally, local administration results in more of the administered candidate lead compound being delivered to a specific location as compared to the entire body of the subject, whereas, systemic administration results in delivery of the candidate lead compound to essentially the entire body of the subject. One method of local administration is by intramuscular injection.

In the context of administering a compound treated cell, the term "administering" also include transplantation of such a cell in a subject. As used herein, the term "transplantation" refers to the process of implanting or transferring at least one cell to a subject. The term "transplantation" includes, e.g., autotransplantation (removal and transfer of cell(s) from one location on a patient to the same or another location on the same patient), allotransplantation (transplantation between members of the same species), and xenotransplantation (transplantations between members of different species).

Furthermore, the candidate lead compounds can be formulated in the form of ointments, creams powders, or other formulations suitable for topical formulations. Such formulations can comprise one or more agents that enhance penetration of active ingredient through skin. For topical applications, the candidate lead compound can be included in wound dressings and/or skin coating compositions.

A candidate lead compound or composition comprising same can be administered by any appropriate route known in the art including, but not limited to, oral or parenteral routes, including intravenous, intramuscular, subcutaneous, transdermal, airway (aerosol), pulmonary,

nasal, rectal, and topical (including buccal and sublingual) administration.

Exemplary modes of administration include, but are not limited to, injection, infusion, instillation, inhalation, or ingestion. "Injection" includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intraventricular, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, intracerebrospinal, and intrasternal injection and infusion. In preferred embodiments of the aspects described herein, the compositions are administered by intravenous infusion or injection.

A compound described herein can be co-administrated to a subject in combination with a pharmaceutically active agent. Exemplary pharmaceutically active compound include, but are not limited to, those found in Harrison's Principles of Internal Medicine, 13^{sup}.th Edition, Eds. T. R. Harrison et al. McGraw-Hill N.Y., NY; Physicians' Desk Reference, 50^{sup}.th Edition, 1997, Oradell New Jersey, Medical Economics Co.; Pharmacological Basis of Therapeutics, 8^{sup}.th Edition, Goodman and Gilman, 1990; United States Pharmacopeia, The National Formulary, USP XII NF XVII, 1990; current edition of Goodman and Oilman's The Pharmacological Basis of Therapeutics; and current edition of The Merck Index, the complete content of all of which are herein incorporated in its entirety.

The candidate lead compound and the pharmaceutically active agent can be administrated to the subject in the same pharmaceutical composition or in different pharmaceutical compositions (at the same time or at different times). When administrated at different times, the candidate lead compound and the pharmaceutically active agent can be administered within 5 minutes, 10 minutes, 20 minutes, 60 minutes, 2 hours, 3 hours, 4, hours, 8 hours, 12 hours, 24 hours of administration of the other. When the candidate lead compound and the pharmaceutically active agent are administered in different pharmaceutical compositions, routes of administration can be different.

The amount of the candidate lead compound that can be combined with a carrier material to produce a single dosage form will generally be that amount of the candidate lead compound that produces a therapeutic effect. Generally, out of one hundred percent, this amount will range from about 0.01% to 99% of the compound, preferably from about 5% to about 70%, most

preferably from 10% to about 30%.

Toxicity and therapeutic efficacy can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, e.g., for determining the LD₅₀ (the dose lethal to 50% of the population) and the ED₅₀ (the dose therapeutically effective in 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index and it can be expressed as the ratio LD₅₀/ED₅₀. Compositions that exhibit large therapeutic indices are preferred.

As used herein, the term ED denotes effective dose and is used in connection with animal models. The term EC denotes effective concentration and is used in connection with in vitro models.

The data obtained from the cell culture assays and animal studies can be used in formulating a range of dosage for use in humans. The dosage of such compounds lies preferably within a range of circulating concentrations that include the ED₅₀ with little or no toxicity. The dosage may vary within this range depending upon the dosage form employed and the route of administration utilized.

The therapeutically effective dose can be estimated initially from cell culture assays. A dose may be formulated in animal models to achieve a circulating plasma concentration range that includes the IC₅₀ (i.e., the concentration of the therapeutic which achieves a half-maximal inhibition of symptoms) as determined in cell culture. Levels in plasma may be measured, for example, by high performance liquid chromatography. The effects of any particular dosage can be monitored by a suitable bioassay.

The dosage may be determined by a physician and adjusted, as necessary, to suit observed effects of the treatment. Generally, the compositions are administered so that the candidate lead compound is given at a dose from 1 µg/kg to 150 mg/kg, 1 µg/kg to 100 mg/kg, 1 µg/kg to 50 mg/kg, 1 µg/kg to 20 mg/kg, 1 µg/kg to 10 mg/kg, 1 µg/kg to 1 mg/kg, 100 µg/kg to 100 mg/kg, 100 µg/kg to 50 mg/kg, 100 µg/kg to 20 mg/kg, 100 µg/kg to 10 mg/kg, 100 µg/kg to 1 mg/kg, 1 mg/kg to 100 mg/kg, 1 mg/kg to 50 mg/kg, 1 mg/kg to 20 mg/kg, 1 mg/kg to 10 mg/kg, 10 mg/kg to 100 mg/kg, 10 mg/kg to 50 mg/kg, or 10 mg/kg to 20 mg/kg. It is to be understood that ranges given here include all intermediate ranges, for example, the range 1 mg/kg to 10 mg/kg includes 1 mg/kg to 2 mg/kg, 1 mg/kg to 3 mg/kg, 1 mg/kg to 4 mg/kg, 1

mg/kg to 5 mg/kg, 1 mg/kg to 6 mg/kg, 1 mg/kg to 7 mg/kg, 1 mg/kg to 8 mg/kg, 1 mg/kg to 9 mg/kg, 2 mg/kg to 10 mg/kg, 3 mg/kg to 10 mg/kg, 4 mg/kg to 10 mg/kg, 5 mg/kg to 10 mg/kg, 6 mg/kg to 10 mg/kg, 7 mg/kg to 10 mg/kg, 8 mg/kg to 10 mg/kg, 9 mg/kg to 10 mg/kg, and the like. It is to be further understood that the ranges intermediate to the given above are also within the scope of this disclosure, for example, in the range 1 mg/kg to 10 mg/kg, dose ranges such as 2 mg/kg to 8 mg/kg, 3 mg/kg to 7 mg/kg, 4 mg/kg to 6 mg/kg, and the like.

In some embodiments, the compositions are administered at a dosage so that the candidate lead compound or a metabolite thereof has an in vivo concentration of less than 500 nM, less than 400 nM, less than 300 nM, less than 250 nM, less than 200 nM, less than 150 nM, less than 100 nM, less than 50 nM, less than 25 nM, less than 20 nM, less than 10 nM, less than 5 nM, less than 1 nM, less than 0.5 nM, less than 0.1 nM, less than 0.05 nM, less than 0.01 nM, less than 0.005 nM, less than 0.001 nM after 15 mins, 30 mins, 1 hr, 1.5 hrs, 2 hrs, 2.5 hrs, 3 hrs, 4 hrs, 5 hrs, 6 hrs, 7 hrs, 8 hrs, 9 hrs, 10 hrs, 11 hrs, 12 hrs or more of time of administration.

With respect to duration and frequency of treatment, it is typical for skilled clinicians to monitor subjects in order to determine when the treatment is providing therapeutic benefit, and to determine whether to increase or decrease dosage, increase or decrease administration frequency, discontinue treatment, resume treatment or make other alteration to treatment regimen. The dosing schedule can vary from once a week to daily depending on a number of clinical factors, such as the subject's sensitivity to the polypeptides. The desired dose can be administered every day or every third, fourth, fifth, or sixth day. The desired dose can be administered at one time or divided into subdoses, e.g., 2-4 subdoses and administered over a period of time, e.g., at appropriate intervals through the day or other appropriate schedule. Such sub-doses can be administered as unit dosage forms. In some embodiments of the aspects described herein, administration is chronic, e.g., one or more doses daily over a period of weeks or months. Examples of dosing schedules are administration daily, twice daily, three times daily or four or more times daily over a period of 1 week, 2 weeks, 3 weeks, 4 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, or 6 months or more.

The pharmaceutical compositions can be included in a kit, container, pack, or dispenser together with instructions for administration.

Methods of Treatment

The present disclosure provides for both prophylactic and therapeutic methods of treating a subject at risk of (or susceptible to) a disease or disorder.

In certain aspects, the disclosure provides a method for preventing in a subject, a disease or disorder as described herein, by administering to the subject a therapeutic agent (*e.g.*, a candidate compound as described herein). Subjects at risk for the disease can be identified by, for example, one or a combination of diagnostic or prognostic assays known in the art. Administration of a prophylactic agent can occur prior to the detection of, *e.g.*, a disease or disorder in a subject, or the manifestation of symptoms characteristic of the disease or disorder, such that the disease or disorder is prevented or, alternatively, delayed in its progression.

Another aspect of the disclosure pertains to methods of treating subjects therapeutically, *i.e.*, altering the onset of symptoms of the disease or disorder. These methods can be performed *in vitro* (*e.g.*, by culturing the cell with a candidate compound) or, alternatively, *in vivo* (*e.g.*, by administering a candidate compound to a subject).

The practice of the present disclosure employs, unless otherwise indicated, conventional techniques of chemistry, molecular biology, microbiology, recombinant DNA, genetics, immunology, cell biology, cell culture and transgenic biology, which are within the skill of the art. See, *e.g.*, Maniatis et al., 1982, Molecular Cloning (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.); Sambrook et al., 1989, Molecular Cloning, 2nd Ed. (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.); Sambrook and Russell, 2001, Molecular Cloning, 3rd Ed. (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.); Ausubel et al., 1992), Current Protocols in Molecular Biology (John Wiley & Sons, including periodic updates); Glover, 1985, DNA Cloning (IRL Press, Oxford); Anand, 1992; Guthrie and Fink, 1991; Harlow and Lane, 1988, Antibodies, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.); Jakoby and Pastan, 1979; Nucleic Acid Hybridization (B. D. Hames & S. J. Higgins eds. 1984); Transcription And Translation (B. D. Hames & S. J. Higgins eds. 1984); Culture Of Animal Cells (R. I. Freshney, Alan R. Liss, Inc., 1987); Immobilized Cells And Enzymes (IRL Press, 1986); B. Perbal, A Practical Guide To Molecular Cloning (1984); the treatise, Methods In Enzymology (Academic Press, Inc., N.Y.); Gene Transfer Vectors For

Mammalian Cells (J. H. Miller and M. P. Calos eds., 1987, Cold Spring Harbor Laboratory); Methods In Enzymology, Vols. 154 and 155 (Wu et al. eds.), Immunochemical Methods In Cell And Molecular Biology (Mayer and Walker, eds., Academic Press, London, 1987); Handbook Of Experimental Immunology, Volumes I-IV (D. M. Weir and C. C. Blackwell, eds., 1986); Riott, Essential Immunology, 6th Edition, Blackwell Scientific Publications, Oxford, 1988; Hogan et al., Manipulating the Mouse Embryo, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986); Westerfield, M., The zebrafish book. A guide for the laboratory use of zebrafish (*Danio rerio*), (4th Ed., Univ. of Oregon Press, Eugene, 2000).

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present disclosure, suitable methods and materials are described below. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

This disclosure is further illustrated by the following examples which should not be construed as limiting.

EXAMPLES

Example 1: Role of aberrant microRNA expression in disease

Aberrant expression of a number of microRNAs has been shown to be involved in the development of a number of cancers. In particular, as shown in Figure 4, microRNA (*e.g.*, microRNA-21) overexpression has been detected in cancers including: glioblastoma, breast cancer, lung cancer, prostate cancer, stomach cancer, colon cancer, cervical cancer, and head and neck cancer. As Figure 5 demonstrates, microRNA-21 plays a role in tumor suppression *via* inhibition of RECK, Maspin, MARKs, TPM1, PTEN, and PDCD4 (Programmed Cell Death 4, a neoplastic transformation inhibitor). microRNA-21 profiles for all stages of breast cancer compared to normal solid tissue are shown in Figure 3A. microRNA-21 counts per 1 million

microRNA reads were plotted against primary tumor and solid normal tissue. The dark line in each box represents the median. Figure 3B demonstrates expression of microRNA-21 in B-cell lymphoma, with microRNA-21 initially overexpressed at day 0, yet then inactivated *via* Cre and Tet-off technologies (Medina *et al. Nature* 467: 86-90), resulting in reduced microRNA-21 expression, which in turn produced shrinkage of B-cell lymphoma tumors at days 2-6, as shown.

Various microRNAs have been identified as overexpressed in breast cancer. Figures 27A and 27B depict graphs demonstrating differentially expressed microRNAs in Stage 2b breast cancer patients. Figure 27A depicts the median microRNA counts per million microRNA reads in stage 2b primary breast tumors. Figure 27B depicts the fold changes in stage 2b primary tumor compared to normal tissue for various microRNAs. Differential expression of the microRNAs shown were statistically significant with adjusted p-values < 0.001. All fold changes shown were greater than 2.5 or less than -2.5. Figure 28 depicts a graph demonstrating microRNA-21 expression profile in breast cancer by stage (TCGA). MCF-7 breast cancer cells were grown in the presence of insulin. The expression of 871 microRNAs was examined via microarrays. microRNA-21, let-7f, and let-7a were especially overexpressed in breast cancer cells, exhibiting a microarray intensity signal of over 20,000. These results further underscored the role of microRNA-21 overexpression in breast cancer.

Thus, microRNA-21 has been observed to be overexpressed in different cancers (*e.g.*, breast and blood cancer). In addition, microRNAs (*e.g.*, microRNA-21) represent not just a biomarker for disease but also a target for treatment.

Example 2: Primary screening of compounds using NMR and biological assays

NMR was used to screen a library of compounds for microRNA binding, as a form of testing performed in parallel with the biological reporter assay screening methods described herein. Figures 9A and 9B depict the NMR approach to primary screening of compounds targeting RNA molecules. Figure 9A shows a diagram depicting an NMR spectrum from a small molecule library screen and a classification of the corresponding hits. A small molecule library of 696 compounds was assembled and screened to identify agents possessing the ability to bind Dicer cleavage site sequence-containing and/or Drosha cleavage site sequence-containing microRNA constructs. Figure 6B depicts microRNA stem loop structures and the location of sequences within the RNA structure that are targeted by Dicer and Drosha, respectively.

Compounds bound to these structures were detected by NMR. Using NMR, peaks indicative of compounds binding to Dicer and/or Drosha constructs were recorded as positive NMR assay hits. Figure 10A shows a sample NMR spectrum depicting peaks and how such chromatograms were translated into an NMR assay score. A peak selectively appearing in compound-treated assays (as compared to DMSO or other control assays) at greater than 1% of the reference spectrum indicated that binding between compound and RNA was detected. Such a peak was assigned a score of +1. A signal to noise ratio of greater than 3.0 indicated signal above noise was significant. Such a result was also assigned a score of +1 in the NMR assay. Sharp peaks indicated nonspecific binding was excluded; this also was assigned a score of +1 in the NMR assay. Finally, the spectrum was compared against the spectrum predicted for the chemical structure and concentration. Agreement suggests good chemical integrity and solubility and earned an additional score of +1. Based on these parameters, a screened compound has a possible NMR score of 0-4.

Dicer processing of the RNA structure comprising a Dicer cleavage site used in NMR experiments was also confirmed. RNA was transcribed and end-labelled in preparation for gel purification. RNA was *in vitro* transcribed and subjected to treatment with Dicer. hrDicer (human recombinant Dicer) was confirmed to process such RNAs (data not shown). hrDicer was specifically confirmed to generate products having the expected size of mature microRNA-21.

As described herein, subsets of tested compounds were classified according whether they bind a Dicer cleavage site-containing construct, a Drosha cleavage site-containing construct, or both constructs. Of the positive hits identified in this assay, 66 compounds bound Dicer cleavage site-containing microRNA constructs, 5 compounds bound Drosha cleavage site-containing microRNA constructs, and 14 compounds were shown to bind to both Dicer cleavage site containing- and Drosha cleavage site-containing microRNA constructs.

In parallel with the above-described NMR binding assays, cell-based reporter assays were also performed upon the 696-compound library. In particular, reporter constructs were transfected into MCF-7 breast cancer cell lines, which were then used to screen compounds for microRNA inhibition. Figure 6A depicts a diagram of the reporter gene construct, pmirGLO vector, that was used in the cell based assay. The construct included a microRNA-21 complementary sequence as well as reporter sequences for firefly luciferase and renilla

luciferase. Optionally, the expression cassette could be designed to include sequences complementary to microRNAs other than microRNA-21 (the one exemplified herein). Administration of antagomiR-21 acted a positive control in such assays, turning on firefly luciferase expression in the reporter assay as a result of its sequestration/degradation of mature microRNA-21, which would otherwise exert a silencing effect upon the microRNA-21 complementary sequence of the reporter construct. An IncuCyte ZOOM System was used to perform the cell-based assays described herein.

As described herein and summarized in Figure 7B, MCF-7 breast cancer cells were plated on Day 1. On Day 2, reporter constructs containing a complementary sequence to microRNA-21 (pmicroRNA-GLO) were transiently transfected into the MCF-7 cell line. Transfected cells were treated with compounds at concentrations of 1 μ M and 10 μ M. On Day 5, the Dual-GLO reporter assay was performed and data was analyzed. The reporter enzymes (renilla and firefly luciferase) were expressed and assessed by 48 hours post-transfection (the Day 5 mark). Fold change in luciferase units were plotted against antagomiR-21 (positive control) and a scrambled version of antagomiR-21 (negative control). As shown in Figure 7A, this example demonstrated that inhibition of microRNA-21 by an antagomiR-21 construct increased expression of the reporter gene (firefly luciferase, normalized to renilla luciferase as a transfection efficiency control) by approximately 50 times. A scrambled antagomiR-21 sequence did not produce expression of the reporter gene.

Candidate compound hits in the reporter assay were identified as any compound that inhibited microRNA activity (*e.g.*, microRNA-21 activity) in cell culture by at least 1.5-fold above cells treated with DMSO alone, as depicted in Figure 8. (Optionally, the threshold at which candidate compound hits are identified in the reporter assay can be established as at least 1.25-fold, at least 1.75-fold, at least 2-fold, at least 2.5-fold, at least 3-fold, etc.) Fold change values were determined by comparing total average normalized luciferase activity of compound treated cells to normalized luciferase activity of DMSO treated cells. As described herein, 93 compounds (13%) of the 696 compound library produced readings above threshold in the reporter assay and were selected as positive hits.

In the reporter assay, compounds were assigned a score based upon the shape of curves of light unit intensity observed at different compound concentrations, as compared to a control

curve, as shown in Figure 10B. Light units were measured based on raw firefly luminescence data. Figure 10C depicts a graph demonstrating the potency score also used in the reporter assay screen. Luciferase was normalized to Renilla and the fold-change was determined by comparing normalized compound samples relative to DMSO control samples. As described herein, compounds were assigned a score based upon identifying the lowest concentration at which a 2 fold or higher change in activity was achieved. More potent compounds receive a higher score in this phase of the reporter assay, while less potent compounds were scored lower, on a potency scale of 0 to 7. As demonstrated in Figures 10B and 10C, there was a bias towards selecting compounds that possessed higher activity at lower concentrations. For scoring, a maximum 14 point scale scoring system was employed, based upon 4 possible points awarded from NMR screens and 10 possible points awarded from the reporter gene assay, based on the dose response of such compounds (with curve shape producing a score of between 0 and 3, and potency score ranging from 0 to 7). Hits were classified according to their performance in both the cell-based assays and in NMR profiling. As depicted in Figure 9B, 15 hits were identified for further analysis by aggregating the cell-based assays and NMR profiling screens. Figure 11 depicts a list of screened compounds identified as positive hits under the parallel screening methods described herein. The molecular weight, NMR score, functional score, total score, IC₅₀ and IC₂₅ values obtained are listed for compounds BSI101023, BSI101484, BSI101534, and BSI100945. BSI101023, BSI101484, BSI101534, and BSI100945 have total combined NMR and cell-based scores of 13, 10, 10, and 9 respectively.

qPCR methods were also employed in screening for test compounds that bind small RNAs. A TaqMan strategy was employed for identifying compounds that bind mature microRNA-21. snU6 was used as a loading control in such assays. A SyberGreen detection strategy was employed for identifying compounds that bind pre-microRNA-21. snU6 was also used as a loading control in these assays. As described herein, qPCR strategies have also been performed upon long RNAs, to examine the pri-microRNA-21 form.

Example 3: Additional screening of compounds using NMR and biological assays

Subsets of the compounds regarded as positive hits under both NMR and cell-based assays were further examined for their interactions with microRNAs. Figure 13A depicts the reporter assay results for hit compound BSI101023, including graphs of raw luciferase activity

and the fold change relative to DMSO at different concentrations. BSI101023 was analyzed in a proliferation assay where the percent cell confluency of MCF-7 was measured in the presence of BSI101023 (at 3 μ M, 10 μ M, 30 μ M, and 100 μ M), as compared to a DMSO (at 0.5%) control. As demonstrated in Figure 13B, cell growth declines in a dose-dependent manner with increasing concentration of the test compound BSI101023.

Scratch assays were used to analyze the functionality of certain test compounds identified as microRNA-binding. BSI101023 was analyzed for the ability to block re-population of cells at different compound concentrations, as compared to a DMSO-treated control, as depicted in Figure 14A. Relative wound density was measured for DMSO (at 0.5%) and BSI101023 (at 12.5 μ M, 25 μ M, 50 μ M, and 100 μ M). It was thereby demonstrated that BSI101023 inhibited cell migration, consistent with its abrogation of microRNA-21 activity. Figure 14B depicts the downstream effects of microRNA-21 antagonism when hit compounds BSI101023, BSI101534, and BSI101484 were administered. The fold change in Programmed Cell Death 4 (PDCD4) levels – a downstream molecule in the microRNA-21 pathway – was examined (using GAPDH as an internal control) relative to DMSO treatment in scrambled antagomiR-21 samples, samples treated with the antagomiR-21 oligonucleotide agent, and in samples treated with BSI101023 (20 μ M), BSI101484 (20 μ M), and BSI101534 (4 μ M), with results plotted in histogram format. BSI101023 and BSI101484 both significantly increased expression of PDCD 4, a downstream effector of microRNA-21, and also induced expression of accumulation of the mature species. For statistical analyses, * is $P < 0.05$ and ** is $P < 0.005$. Both results paralleled those observed for the positive control antagomiR-21 oligonucleotide agent. As described elsewhere herein, BSI101023 appears to inhibit loading of mature microRNA-21 into the RISC complex, while BSI101484 has been projected to bind to the loop present in the pri-microRNA-21, apparently leading to an early stage degradation of pri-microRNA-21.

Thus, it was demonstrated that compounds BSI101023 and BSI101484 caused a decline in cell growth in a manner that was dose-dependent as concentrations increased. Furthermore, compounds BSI101023 and BSI101484 increased the expression of Programmed Cell Death 4 (PDCD4), a downstream effector of microRNA-21, as shown in Figures 14A, 14B, 16A, 16B, and 37.

Example 4: Analysis of the microRNA pathway

Small molecules can interface with the microRNA maturation pathway at a number of pathway locations. Figure 12A depicts a schematic of the entry points for small molecules modulating microRNA (*e.g.*, microRNA-21) activity. Compounds can inhibit microRNAs at various stages of the microRNA pathway including: pri-microRNA, pre-microRNA, microRNA duplex, and mature RNA. Inhibition may take place inside the nucleus, in the cytoplasm, or both. Figure 12B depicts the microRNA pathway and points at which test compounds can act on microRNAs. Histograms depict the results of reporter assays performed upon a test microRNA antagonist (antagomiR, *i.e.*, the antagomiR-21 oligonucleotide agent) known to act upon mature microRNA-21, as compared to untreated and scrambled controls, showing observed levels of pri-microRNA, pre-microRNA, and mature-microRNA (*e.g.*, pri-microRNA-21, pre-microRNA-21, and mature-microRNA-21). Luciferase activity for a random scrambled antagomiR sequence (scrambled) was compared to activity observed for the antagomiR-21 oligonucleotide agent. Such results demonstrated the ability of the antagomiR-21 oligonucleotide agent, as expected, to bind to microRNA-21 and trigger reporter gene expression in the biological functional screening methods described herein. These results also demonstrated that the antagomiR-21 oligonucleotide agent blocked expression of microRNA-21 at the mature-microRNA-21 stage, *via* triggering of mature-microRNA-21 degradation.

To determine at what stage in the microRNA pathway hit compounds of the above-described assay(s) were acting, quantitative analyses of microRNA processing species was performed upon various hit compounds. Quantitative analysis was performed at IC₂₅ to observe levels of microRNA processing species in the presence versus absence of hit compounds. Figure 15A depicts a schematic of the microRNA-21 pathway, which shows the point at which the compound BSI101023 appears to act. Figure 15B depicts the percent expression levels of pri-microRNA-21, pre-microRNA-21, and mature-microRNA-21 observed relative to a DMSO control for respective exposures to no treatment, the antagomiR-21 oligonucleotide agent or to BSI101023 (20μM). For statistical analyses, * is P<0.05, *** is P<0.0005, and NS is “not significant”. As demonstrated by Figure 15B, BSI101023 appeared to act at the mature microRNA-21 stage by inhibiting loading of mature microRNA-21 into the RISC complex,

thereby creating the significant accumulation of mature microRNA-21 observed for BSI101023 treatment.

The site of action of BSI101484 was also examined. Figure 18A depicts a schematic of the microRNA-21 pathway and the point at which the antagomiR-21 compound BSI101484 appears to act. Figure 18B shows the percent expression levels of pri-microRNA-21, pre-microRNA-21, and mature-microRNA-21 observed relative to a DMSO control for respective exposures to no treatment, the antagomiR-21 oligonucleotide agent or to test compound BSI101484 (20 μ M). For statistical analyses, *** is $P < 0.0005$ and NS is “not significant”. As demonstrated in Figure 18B, BSI101484 appeared to act at the pri-microRNA-21 stage by binding to the loop present in the pri-microRNA-21, to produce an early stage degradation.

Predicted site of microRNA pathway interaction results were obtained for four test compound hits (BSI101023, BSI101484, BSI100945, BSI101534), and quantitative analysis of levels of microRNA processing species were observed at IC₂₅ (data not shown). The percent expression of pri-microRNA-21, pre-microRNA-21, and mature-microRNA-21 relative to DMSO control was assessed following no treatment (negative control) or after treatment with antagomiR-21, BSI101023, BSI101484, BSI100945 or BSI101534, respectively. Compounds BSI101023, BSI101484, BSI101534, and BSI100945 were analyzed at 20 μ M, 20 μ M, 5 μ M, and 20 μ M respectively.

Example 5: Identification of candidate compound binding sites within targeted microRNAs

NMR was also used to validate the site of binding of test compounds within targeted microRNA sequences. To prepare RNA for the NMR studies, *in vitro* transcription was performed and gel purified microRNA was used. The RNA was desalted with a Sep-pak C18 column. After de-salting, the RNA was dried in a genevac evaporator. Figure 19A in the top panel depicts the scheme employed for performing NMR analysis upon positive screening assay hits (candidate lead compounds). In the bottom panel, the method for mapping the compound binding site is shown. The imino protons (left) are well-resolved in the NMR spectra and assigned to specific bases. Upon binding of a small molecule (center reaction), the local electronic environment is perturbed, both by the presence of the compound and possible structural rearrangements. This causes the local chemical shift environment to change (red in

hairpin on the right), causing peaks shifts in the NMR spectrum of the RNA. Figure 19B depicts a microRNA-21 stem loop structure and associated NMR spectra obtained when candidate lead compound BSI101534 was administered and assayed. BSI101534 was tested for microRNA binding at concentrations of 100 μ M, 200 μ M, 400 μ M, and 800 μ M. As demonstrated in the stem loop diagram and the NMR spectra obtained, there was a shift of NMR spectra, consistent with BSI101534 binding microRNA-21. Furthermore, dose-responsiveness was observed, as shown. These results demonstrated that BSI101534 bound only to the Dicer-containing construct, at the A26 bulge region. Figure 19C depicts the microRNA stem loop structure and NMR spectra obtained for test compounds BSI101484 and BSI101023. BSI101023 was tested at concentrations of 100 μ M, 200 μ M, 400 μ M, and 800 μ M. BSI101484 was tested at concentrations of 12.5 μ M, 25 μ M, and 50 μ M. As depicted in Figure 19C, compounds BSI101484 and BSI101023 also bound in the A26 bulge region. A fragment of candidate lead compound BSI101484, called BSI104171, was also generated and tested for microRNA binding. BSI104171 was analyzed at concentrations of 7.5 μ M, 15 μ M, 30 μ M, 60 μ M, 120 μ M, and 240 μ M. Figure 19E shows a stem loop structure and associated NMR spectra obtained when free, naturally occurring nucleobases were administered to the D58 construct as a control. No binding was observed between the U, T, A, and G nucleobases and/or nucleosides tested in the presence of the D58 structure. Thus, candidate lead compounds BSI10148, BSI104171, BSI101023, etc. were not simply acting as free nucleobases in their respective interactions with the D58 structure.

Because the candidate lead compounds assayed by NMR were identified to bind microRNAs in the bulge region, NMR was used to further examine the role of the A26 bulge region in microRNA stability, thereby further refining understanding of the precise site and mechanism of interaction of such candidate lead compounds with the bulge region sequence. Structural features of the bulge region sequence are depicted in Figure 22. Figure 20A depicts the effect of removing the A26 bulge from a stem loop structure that was exposed to test compounds BSI101534, BSI101484, and BSI104171. "D57"-associated NMR spectra, which showed no chemical shift perturbation in the NMR spectra and therefore no binding, demonstrated that no specific binding of such test compounds occurred when the A26 bulge region was altered to remove the bulge nucleotide. Criticality of the bulge nucleotide to BSI101534, BSI101484, and

BSI 104171 binding was therefore confirmed. Meanwhile, Figure 20B depicts NMR spectral shifts observed upon administration of candidate lead compound BSI101534 to indicated “D58” and “D29” structures, where the “D29” structure eliminates the loop region of microRNA-21, replacing it with only a tetraloop, yet binding of BSI101534 to the bulge region sequence of this “D29” structure was unaltered. BSI101534 at 200 μ M was reacted with RNA at 15 μ M. Thus, changing the length of the microRNA yet retaining the A26 bulge region demonstrated that A26 bulge sequence was sufficient for BSI101534 (and likely other candidate lead compounds) to bind microRNA (here, microRNA-21).

NMR titration was also used to examine whether the binding of candidate lead compounds to Dicer cleavage site-containing microRNAs was sequence-context dependent. Figure 21A depicts the scheme employed for mutational mapping of the candidate lead compound binding site(s). Alteration of the bulge sequence region of microRNA-21 was performed *via* introduction of corresponding sequence regions derived from other microRNAs, as well as introduction of point mutations into such constructs. In altered microRNA-21-derived constructs, sequences in the bulge region were substituted to mimic bulge regions from non-microRNA-21s (in Figure 21A, hsa-mir-103a-1 and a mutant form thereof, as shown). Additionally, sequences outside the bulge region were altered to mimic the non-bulge regions of other microRNAs (microRNAs other than microRNA-21). Figure 21B shows alternate stem loop schemes and NMR spectra for microRNA-21-derived constructs where 1) the neighboring base pairs remain but the bulge is altered (“hsa-mir-16-1”) and 2) neighboring base pairs are altered while the bulge region is altered, yet the bulge nucleotide is retained (“hsa-mir-155”). NMR spectra for the different altered microRNA-21-derived constructs (15 μ M) mixed with BSI101534 (100 μ M) and BSI104171 (120 μ M) are depicted – peaks that shift for hsa-mir-16-1 (retaining neighboring base pairs) upon addition of BSI101534 and BSI104171 but not in controls is shaded. Figure 21C depicts alternate stem loop schemes and NMR spectra for microRNA-21-derived constructs where the construct from Figure 21B possessing hsa-mir-155 bulge region with un-altered bulge nucleotide was compared to the same construct possessing an altered bulge region sequence (“hsa-mir-155-mut”). NMR spectra for the altered construct (15 μ M) and its variant with BSI101534 (100 μ M) and BSI104171 (120 μ M) are depicted. Figure 21D depicts stem loop structures and NMR spectra for microRNA-21-derived constructs where

both the bulge region and sequences outside the bulge region are altered to those of hsa-mir-103a-1. NMR spectra for the altered construct (15 μ M) with BSI101534 (100 μ M) and BSI104171 (120 μ M) are depicted. Figure 21E depicts stem loop structures and NMR spectra for the microRNA-21-derived hsa-mir-103a-1 construct of Figure 21A, where both the bulge region and sequences outside the bulge region are altered with nucleotides of hsa-mir-103a-1. NMR spectra for the hsa-mir-103a-1 construct (15 μ M) with BSI101534 (100 μ M) and BSI104171 (120 μ M) revealed wobble at the bulge residue of this construct, which effectively shifted the location of the bulge within this construct between two states as shown. Figure 21F depicts confirmation of the effect of the wobble observed in stem loop structures of Figure 21E, where blocking of such wobble via mutation (in the “hsa-mir-103a-1-mut” construct) was revealed to block binding of microRNA-binding test compounds. The bottom NMR traces of Figure 21F show constructs of hsa-mir-103a-1 (15 μ M) that allowed both wobble and binding of BSI101534 (100 μ M) and BSI104171 (120 μ M), whereas the top NMR traces of Figure 21F show that BSI101534 and BSI104171 no longer bound the “hsa-mir-103a-1-mut” construct (altered such that relative position of a C-G base pair within the duplex was swapped across the duplex). Figure 21G depicts stem loop structures and NMR spectra for a microRNA-21-derived structure having the hsa-mir-200c bulge region sequence, which possesses a mismatch. NMR spectra for the altered microRNA-21 construct (15 μ M) with BSI101534 (100 μ M) and BSI104171 (120 μ M) are depicted. No binding was witnessed for either compound. These results demonstrated that the candidate lead compounds identified in the parallel screen described above all bound microRNA-21 in a sequence-dependent manner, and specifically appeared to do so by stabilizing a specific wobble position within the microRNA-21 bulge region sequence (effectively intercalating into the dsRNA structure and interacting with bulge nucleotides in a structurally stabilizing manner).

Illustrations of predicted interactions between a compound and the RNA bulge motif are depicted in Figure 27. Such illustrations demonstrate that screened compounds likely interacted with the RNA bulge motif through mechanisms including: association with neighboring GC/CG base pairs; interactions with the bulge nucleotide; stacking with neighboring bases; and additional interactions between the RNA and the substituent group.

Screening results for BSI101484 and related compound BSI104171 were also compiled and compared, as depicted in Figure 25A. Figure 25B depicts the structure and fold changes

observed relative to DMSO for compound BSI101534, as well as for other related compounds. Screening assay results for BSI101534, BSI101536, and BSI101473 are also presented in Figure 25B. Figures 25A and 25B therefore demonstrate that BSI101484, BSI104171, BSI101534, BSI101536, and BSI101473 compounds all exhibited microRNA binding in the NMR titration studies, as well as biological activities associated with such binding. Notably, BSI101484 exhibited a higher fold change relative to DMSO at a lower concentration, as compared to BSI101534. Such results demonstrate that additional optimization of binding and/or efficacies can be performed upon candidate lead compounds initially identified *via* the above-described screening approaches.

Example 6: SAR expansion and validation

Structure activity relationships (SARs) between identified positive hits (candidate lead compounds) and microRNA molecules can also be further analyzed and validated. In the present Example, test compounds BSI101484 and BSI101534 are evaluated to determine the contribution of each substituent to the interaction of these compounds with microRNA molecules. Structural features of the test compound are altered and the effect exerted upon test compound binding of microRNAs is examined in preliminary *in vitro* and toxicity assays.

Crystallographic analysis of lead compound binding to microRNAs are employed to further complement the chemical and biological screening methods described above. Crystallography sheds light upon the relevant specific atoms responsible for the binding interaction between microRNAs and candidate lead compounds identified in the screens described herein. Figure 26 depicts stem loop structures of microRNA-21 constructs that have been prepared for crystallization assays. Such structures are ultimately derived from the indicated 103-mer microRNA-21 full length construct, and the three microRNA-21-derived constructs shown were set up for crystallization. These included a microRNA-21 58-mer Dicer construct, a microRNA-21 45-mer Dicer tetraloop, and a microRNA-21 two strand stem of 21 and 22-mers. Crystals, once formed, are assessed using crystallography approaches known in the art, thereby further refining identification of the specific site(s) of interaction of the candidate lead compounds with targeted RNA sequences.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the disclosure described herein. Such equivalents are intended to be encompassed by the following claims.

What is claimed is:

1. A method for identifying a candidate lead compound comprising:
 - (a) contacting an oligonucleotide with a test compound in a biological functional assay, wherein oligonucleotide-test compound binding results in a biological result not observed in the biological functional assay without the test compound; and
 - (b) contacting the oligonucleotide with the test compound, thereby forming an oligonucleotide-test compound solution; performing NMR upon the oligonucleotide-test compound solution, wherein oligonucleotide-test compound binding produces an NMR result not observed in a solution lacking said test compound; and detecting said NMR result in the oligonucleotide-test compound solution,
wherein detecting selective biological function in the presence of the test compound in (a) and detecting said NMR result in (b) identifies the test compound as a candidate lead compound.
2. The method of claim 1, wherein the biological functional assay is selected from the group consisting of a cell-based reporter system, a proliferation assay, an immunoassay or a polymerase chain reaction-based assay.
3. The method of claim 1 or 2, wherein the oligonucleotide is selected from the group consisting of coding and non-coding RNAs, optionally wherein the oligonucleotide is selected from the group consisting of a microRNA, a tRNA, a rRNA, a tiRNA, a lincRNA, a NAT, a lncRNA, a, eRNA, a T-UCR, a circRNA, a piRNA, an esiRNA, an siRNA, an antisense oligonucleotide, a tasiRNA, a snoRNA, a scaRNA and a snRNA.
4. The method of claim 3, further comprising assessing the site of microRNA processing pathway activity of the candidate lead compound by measuring levels of pri-microRNA, pre-microRNA and mature microRNA, as compared to an appropriate control.

5. The method of any of the preceding claims, wherein the oligonucleotide is a microRNA-21 transcript or a fragment thereof comprising at least 15 consecutive nucleotides of microRNA-21 and optionally comprises the Drosha and/or Dicer cleavage site.
6. The method of claim 1, wherein detecting the biological result of the biological functional assay in the presence of the test compound in step (a) comprises identifying at least a 1.5-fold elevation of the level of a signal in the presence of the test compound, relative to the level of the signal in the absence of the test compound, optionally wherein detecting the biological result of the biological functional assay in the presence of the test compound in step (a) comprises identifying at least a 1.75-fold elevation of the level of a signal in the presence of the test compound, relative to the level of the signal in the absence of the test compound, optionally wherein detecting the biological result of the biological functional assay in the presence of the test compound in step (a) comprises identifying at least a two-fold elevation of the level of a signal in the presence of the test compound, relative to the level of the signal in the absence of the test compound.
7. The method of any of the preceding claims, wherein the test compound is assigned (i) an integer score based upon the shape of a dose-response curve for the biological functional assay in the presence of the test compound and (ii) an integer score based upon the dose-responsiveness of the biological functional assay to the test compound.
8. The method of claim 7, wherein the integer score of (i) is between 0 and 3, wherein 0 is given to test compounds that show no signal; 1 indicates a signal only at higher concentrations; 2 indicates a signal proportional to its concentration; and 3 indicates a signal at low concentrations; and the integer score of (ii) is between 0 and 7, with the higher value assigned when a signal is shown at lower concentrations.
9. The method of any of the preceding claims, wherein detecting said NMR result in the oligonucleotide-test compound solution in (b) comprises assigning a numeric score to the oligonucleotide-test compound NMR results.

10. The method of claim 9, wherein a score of 0, 1, 2, 3 or 4 is assigned to the oligonucleotide-test compound NMR results, wherein a score of 4 indicates high-quality NMR-detected binding, optionally wherein scoring is assigned as follows:

+1 for signal demonstrating binding;

+1 for signal-to-noise ratio >3;

+1 for sharp ligand peaks in the mixture;

+1 for pattern of ligand peaks consistent with the pattern expected from the chemical structure.

11. The method of claim 8 or claim 10, wherein the combined scores of the biological functional assay and the NMR assay of 10 or greater identifies the test compound as a compound that binds the oligonucleotide and/or is bioactive.

12. The method of any of the preceding claims comprising:

(a) contacting an oligonucleotide with a test compound in the presence of a cell-based reporter system; and detecting selective activation of the cell-based reporter system in the presence of the test compound; and

(b) contacting the oligonucleotide with the test compound, thereby forming an oligonucleotide-test compound solution; performing NMR upon the oligonucleotide-test compound solution, wherein oligonucleotide-test compound binding produces an NMR result not observed in a solution lacking said test compound; and detecting said NMR result in the oligonucleotide-test compound solution,

wherein detecting selective activation of the cell-based reporter system in the presence of the test compound in (a) and detecting said NMR result in (b) identifies the test compound as a candidate lead compound.

13. A method for validating a candidate lead compound and identifying the site of candidate lead compound-microRNA interaction comprising:

identifying binding of a candidate lead compound to a microRNA or a microRNA fragment;

altering the sequence of the microRNA or microRNA fragment via introduction of one or more point mutations, thereby generating a mutated microRNA or a mutated microRNA fragment; and

identifying absence of binding of the candidate lead compound to the mutated microRNA or mutated microRNA fragment according to the method of any of the preceding claims,

thereby validating the candidate lead compound and identifying the site of candidate lead compound-microRNA interaction.

14. A method for validating a candidate lead compound and identifying the site of activity of the candidate lead compound within the microRNA pathway comprising:

identifying binding of a candidate lead compound to a microRNA or a microRNA fragment according to any of the methods of the preceding claims;

assaying levels of pri-microRNA, pre-microRNA and mature microRNA in the presence of the candidate lead compound, as compared to in the absence of the candidate lead compound; and

identifying the site of activity of the candidate lead compound within the microRNA pathway based upon the relative levels of pri-microRNA, pre-microRNA and mature microRNA assayed in the presence of the candidate lead compound, as compared to in the absence of the candidate lead compound,

thereby validating the candidate lead compound and identifying the site of activity of the candidate lead compound within the microRNA pathway.

15. The method of any of the preceding claims, wherein the test compound is a small molecule.

Figure 1

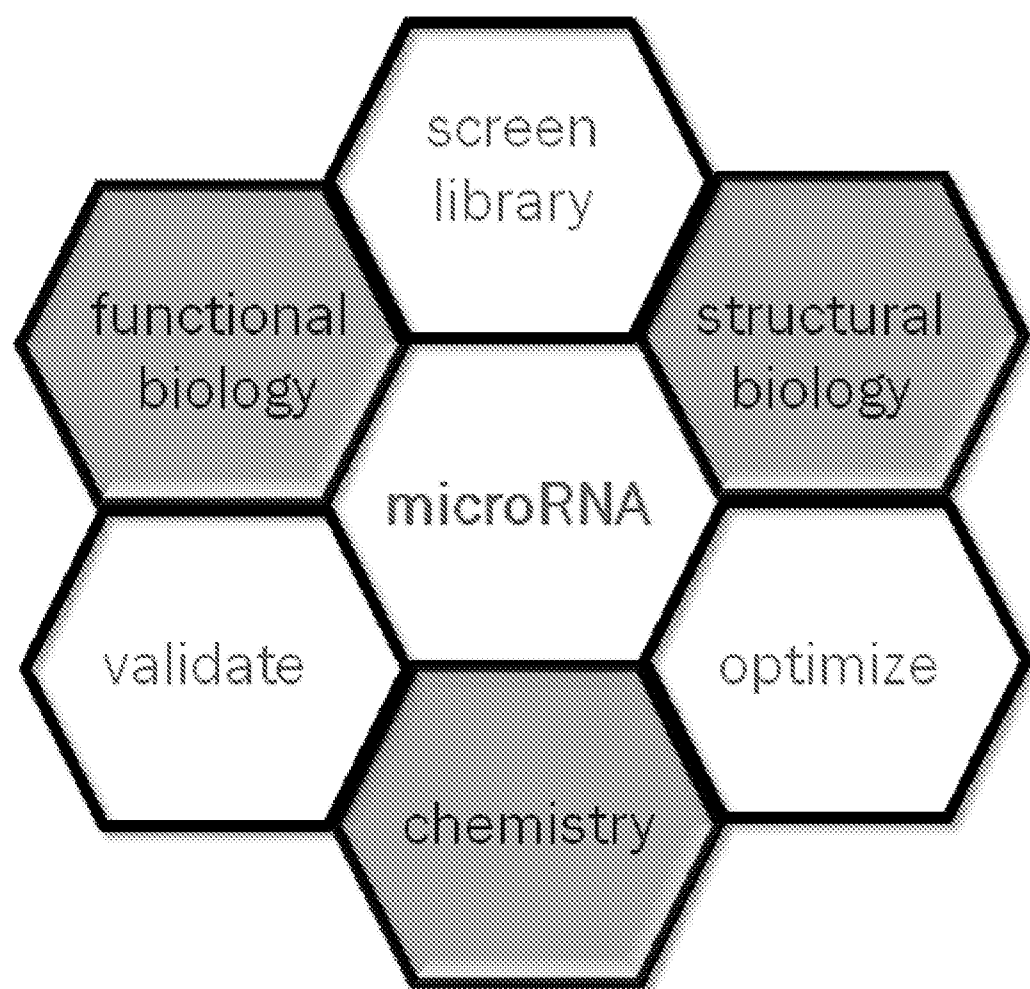


Figure 2

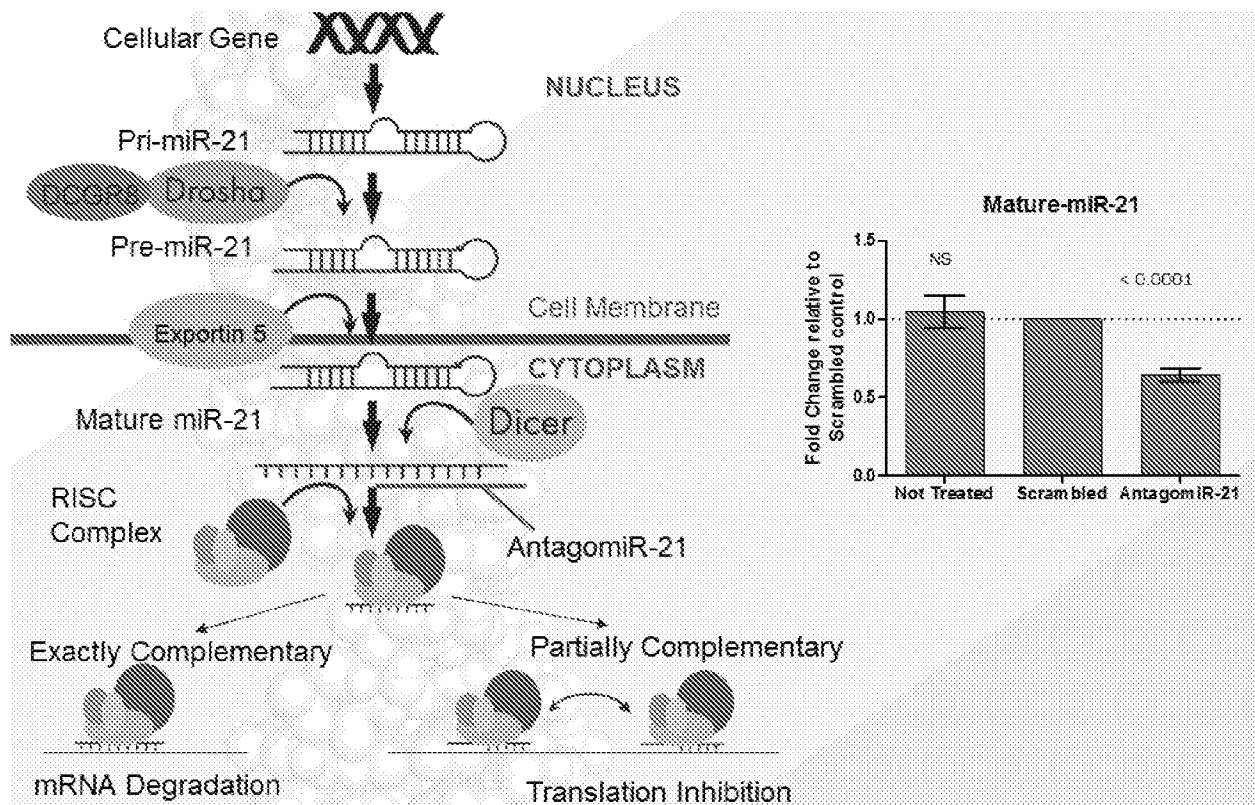


Figure 3A

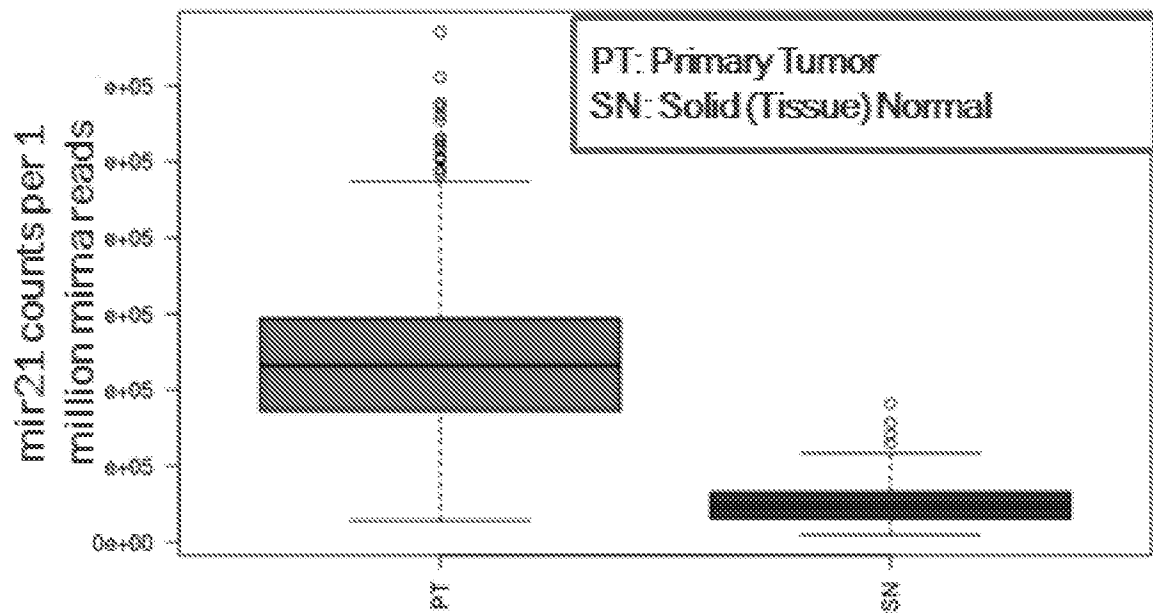


Figure 3B

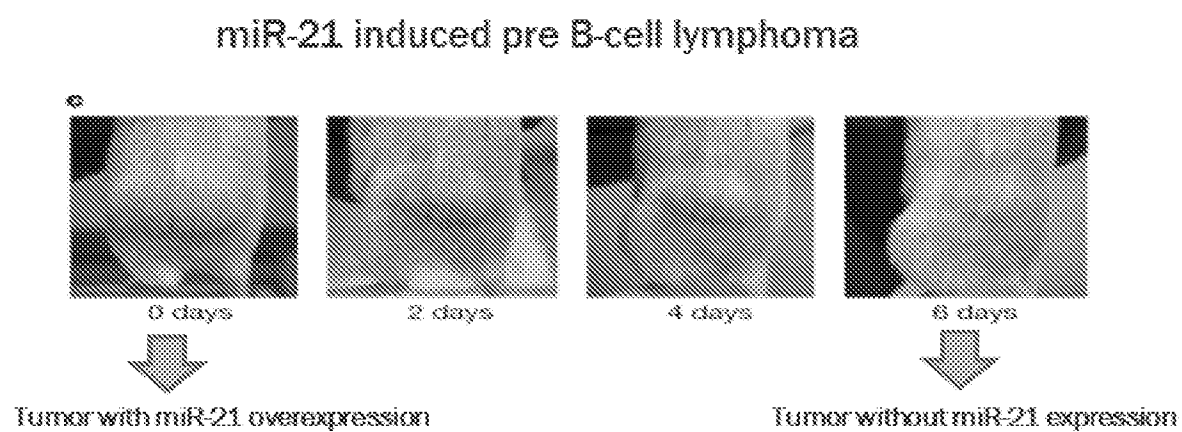


Figure 4

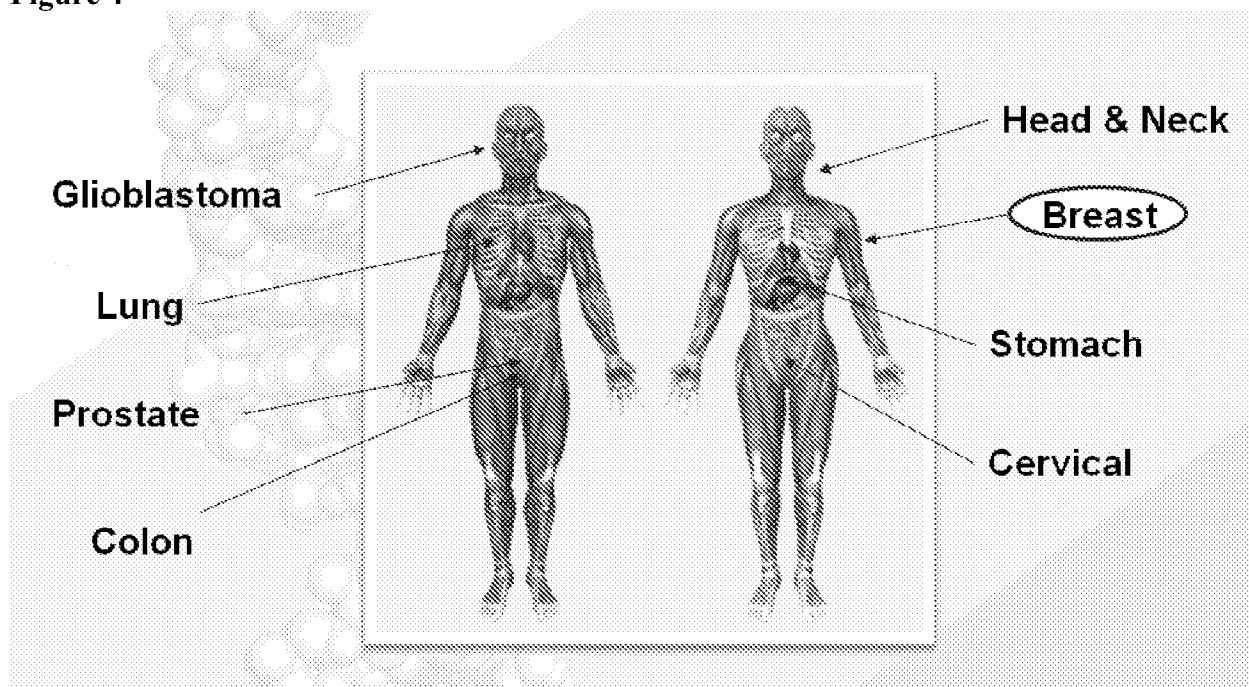
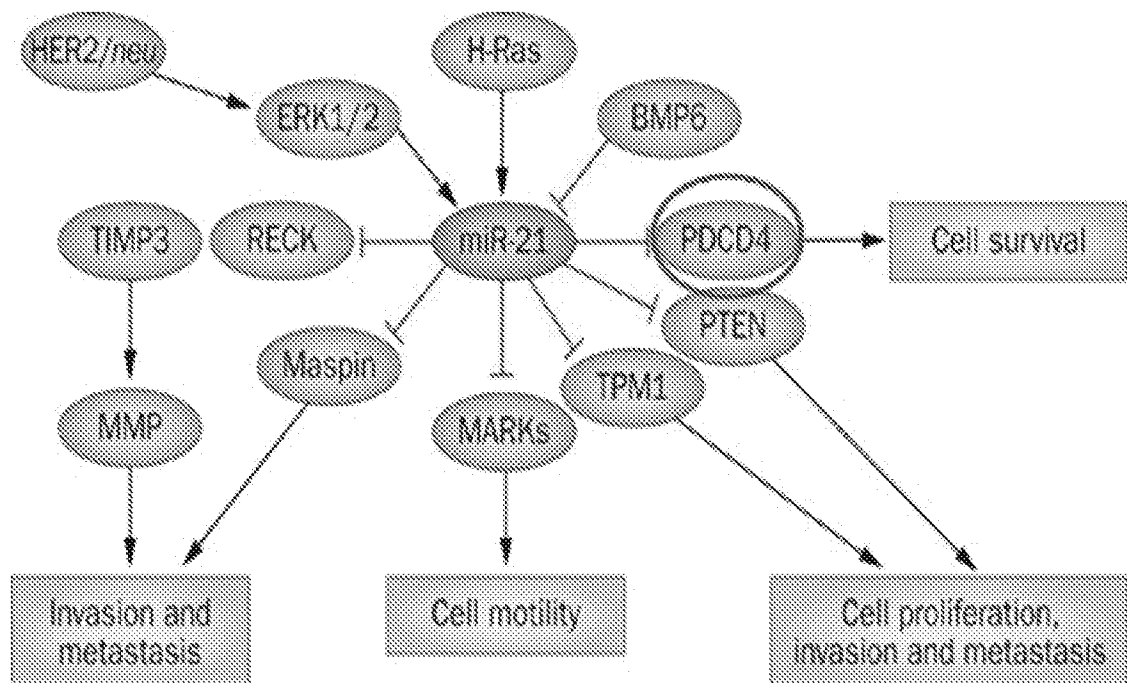


Figure 5



PDCD4 - Programmed Cell Death 4
(Neoplastic Transformation Inhibitor)

Figure 6A

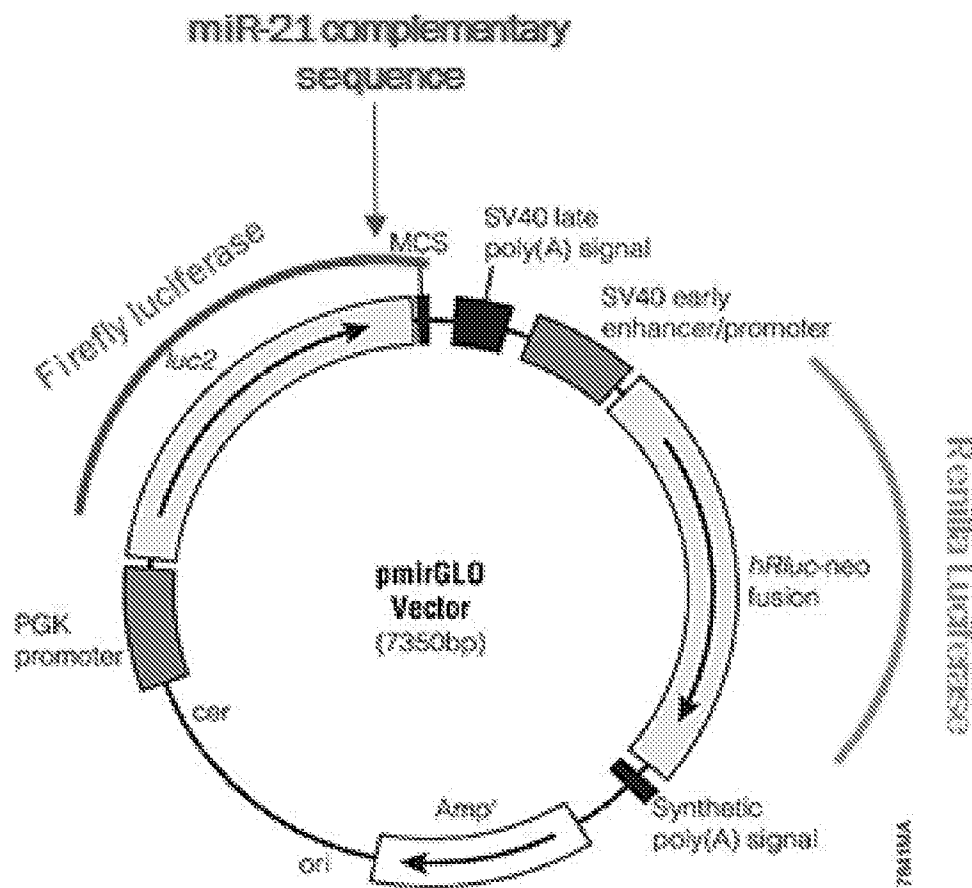


Figure 6B

NMR Screening & Assignment

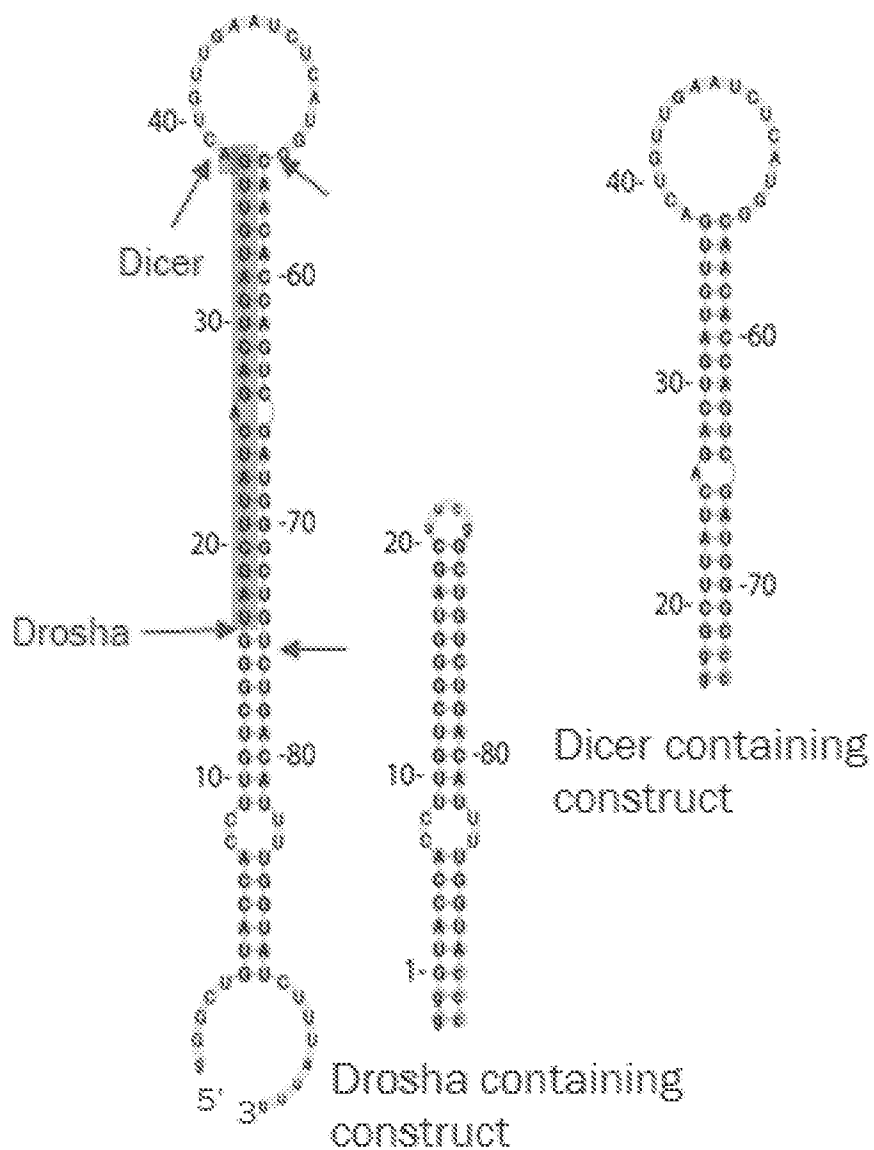


Figure 7A

Inhibition of miR-21 by an antagomiR-21 increases the reporter gene detection window by approximately 50 times.

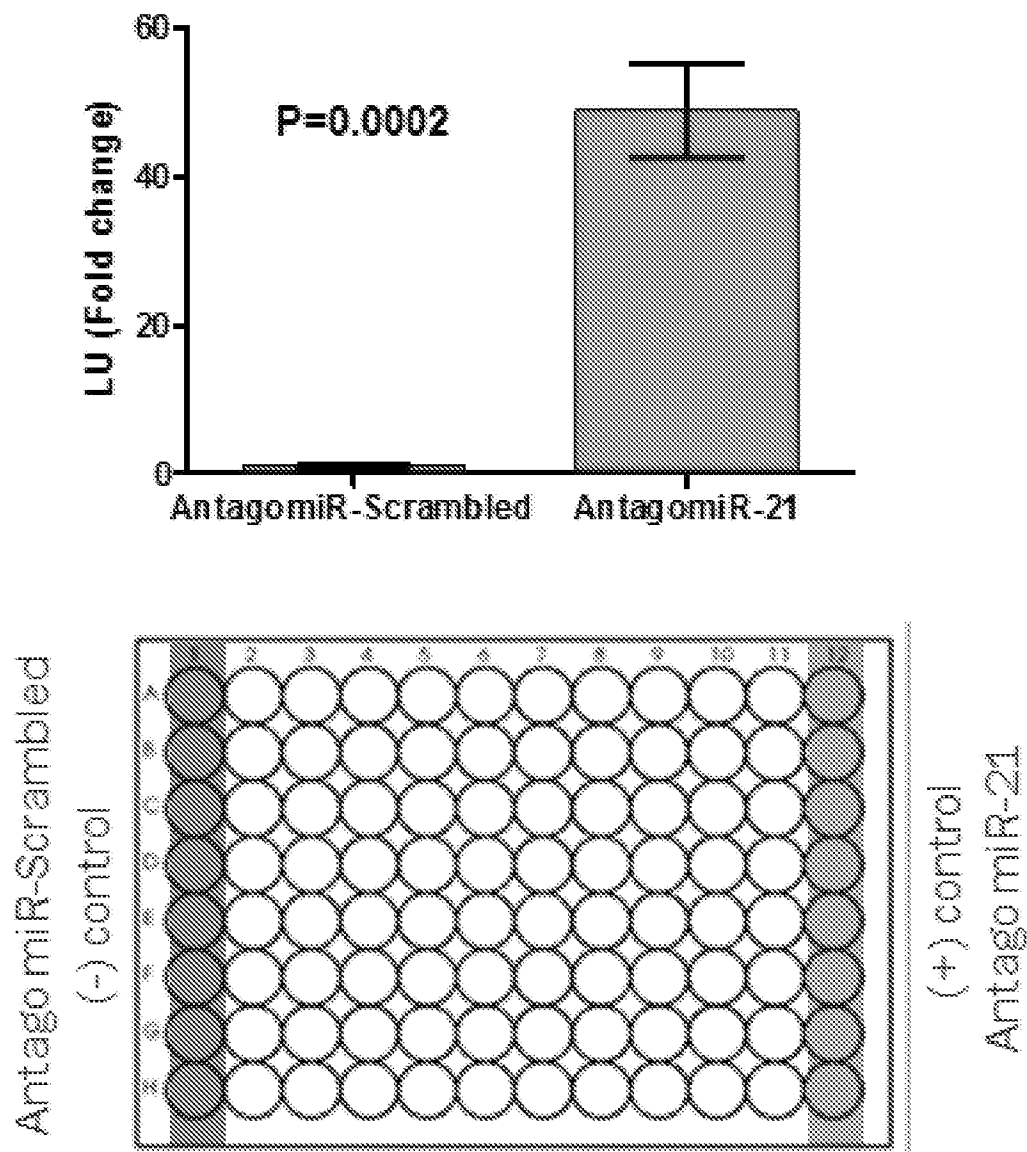


Figure 7B

Screening Scheme

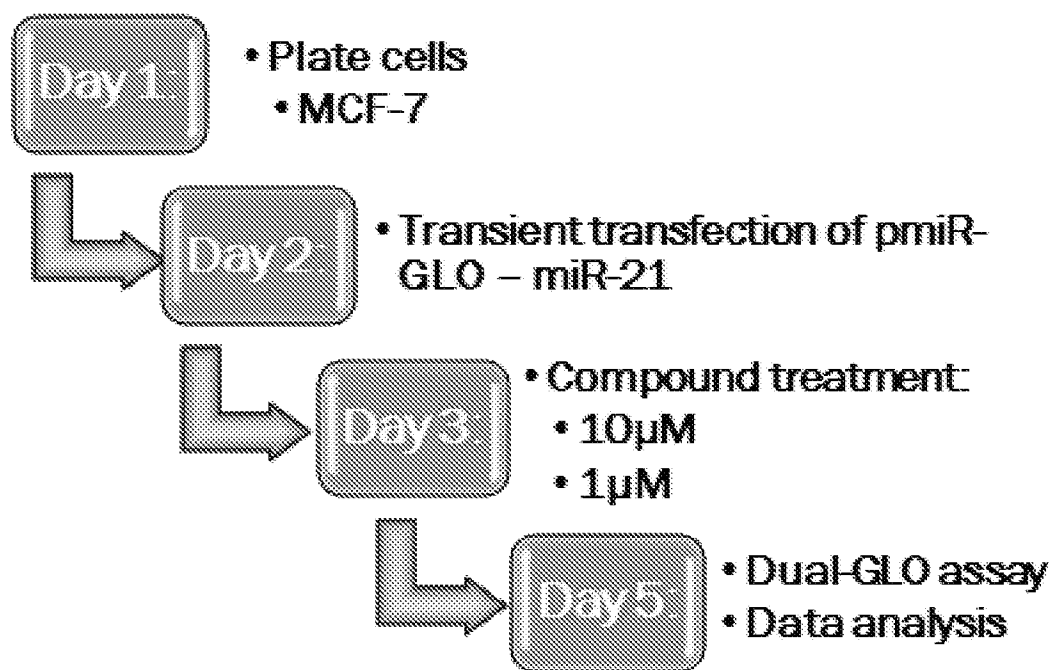


Figure 8

Parameters for Hit Definition

Fold increase calculation

Luciferase activity = Average Luciferase activity reads of non normalized samples (raw data) - background

Normalized Luciferase activity =
$$\frac{\text{Firefly Luciferase}}{\text{Renilla Luciferase}} \rightarrow \text{Average}$$

Fold Change =
$$\frac{\text{Normalized Luciferase Compound treated}}{\text{Normalized Luciferase DMSO treated}} \rightarrow \text{Average}$$

Hit Definition

Any compound that would inhibit miR-21 activity by at least 1.5 fold above the DMSO treated cells (threshold)

Screening outcome

93 compounds (13%) out of a 696 compound library had readings above the selected threshold and therefore were chosen as positive hits.

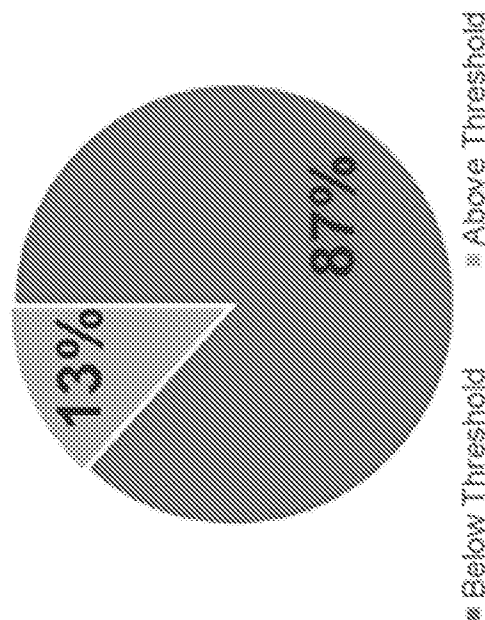


Figure 9A

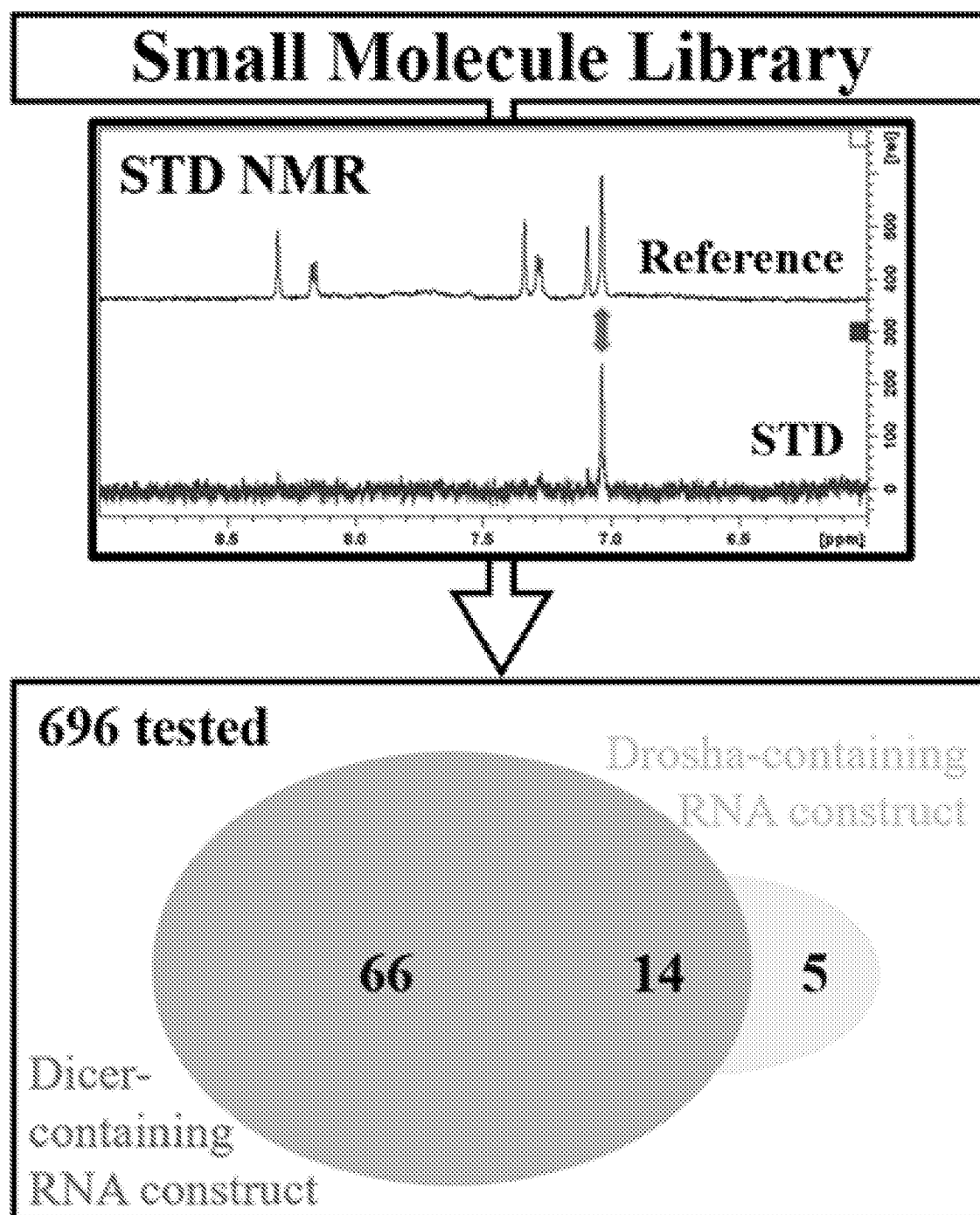


Figure 9B

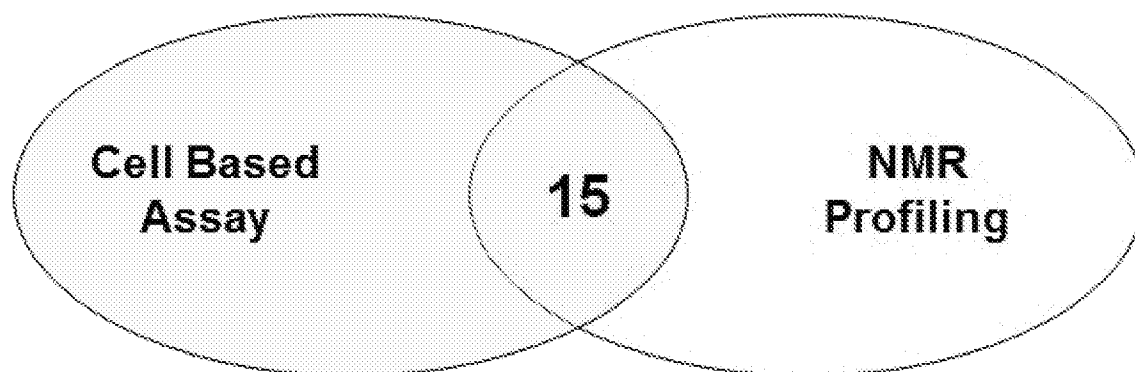
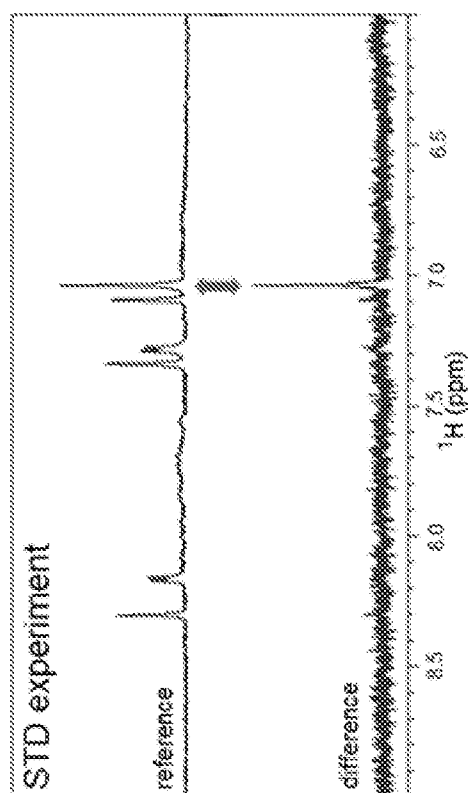


Figure 10A



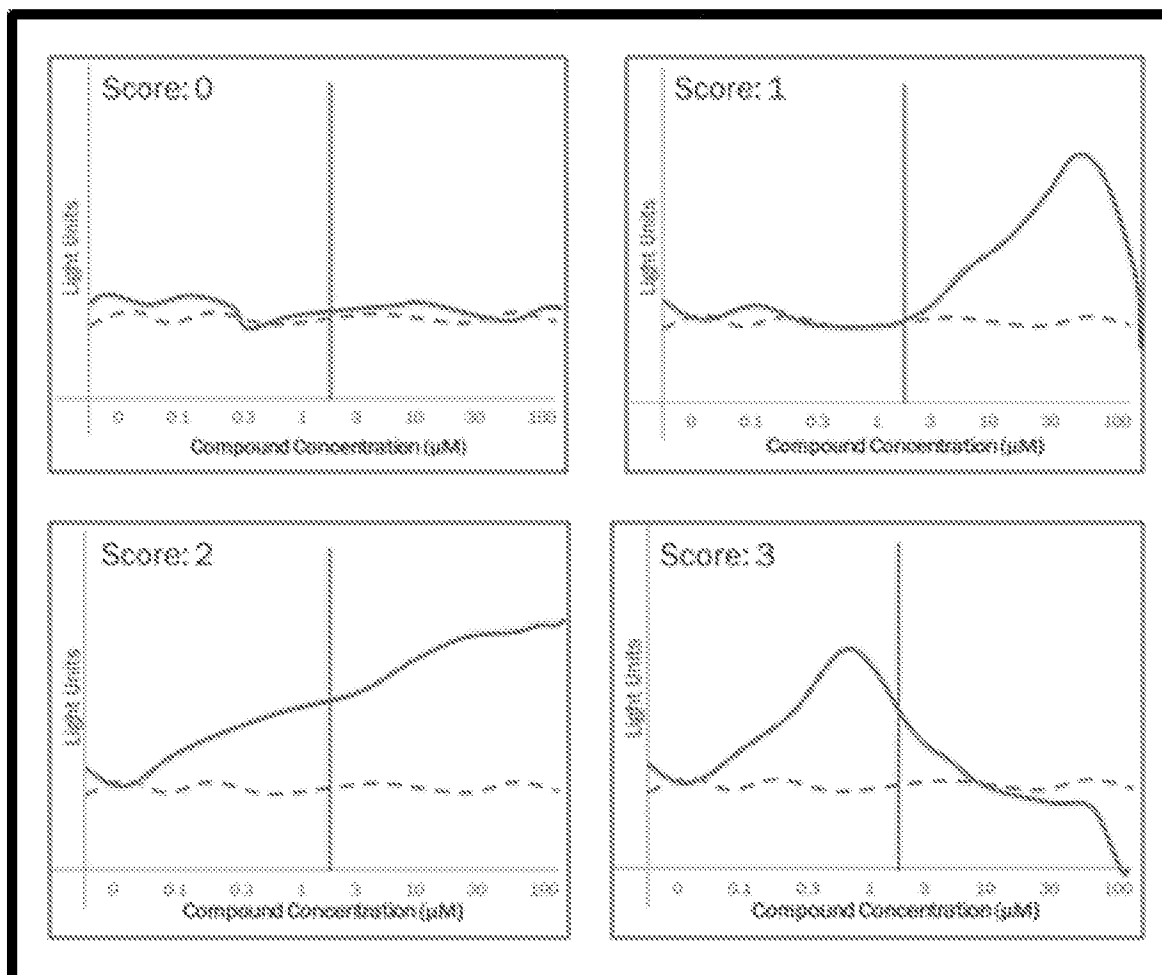
NMR Scoring

- STD > 1% +1 **Binding between compound and RNA detected**
- S/N > 3.0 +1 **Signals significant above noise**
- Sharp peaks +1 **Nonspecific binding excluded**
- Spectrum OK +1 **QC for compound integrity and concentration**

Total possible NMR score: +4

Figure 10B

Curve Score



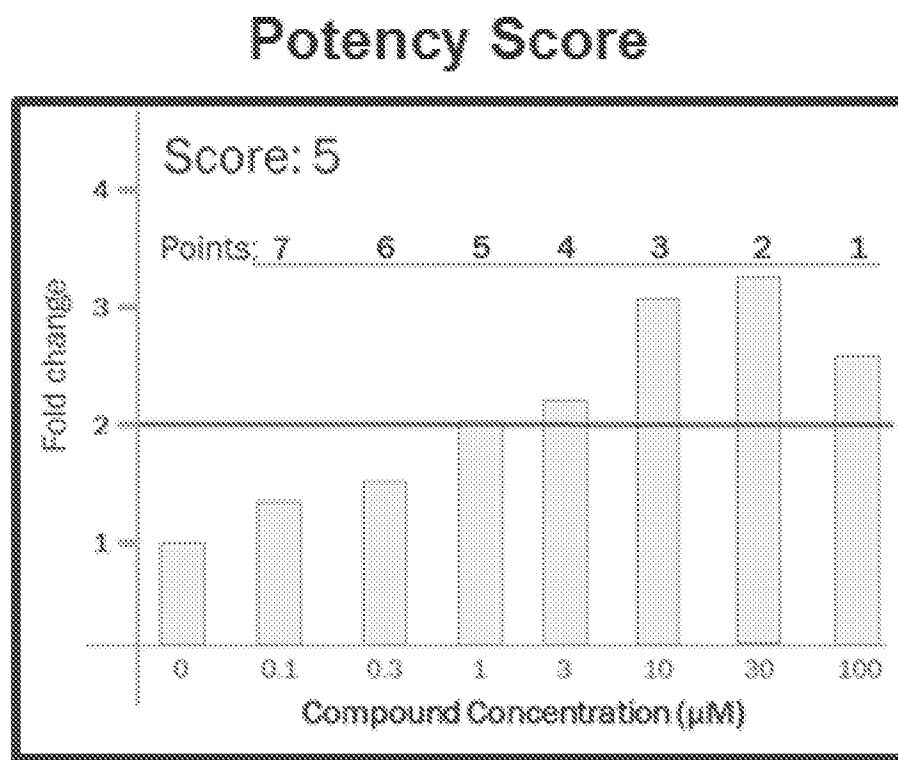
Raw Firefly Luminescence data

— — Control

———— Treated sample

Scoring threshold (red line): set between 1 and 3µM compound

Figure 10C

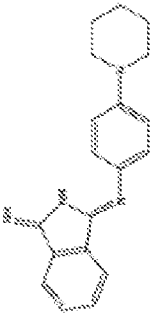
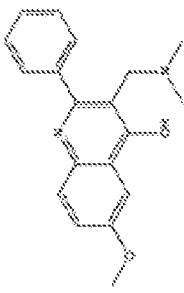


Fold change over negative control:

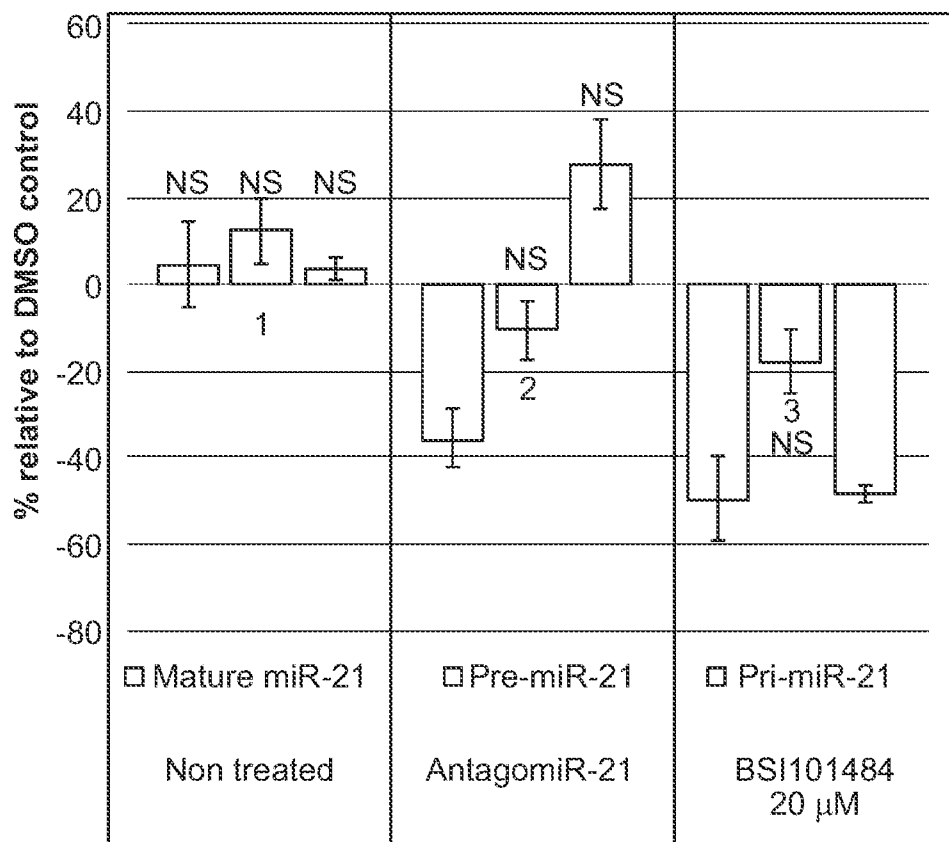
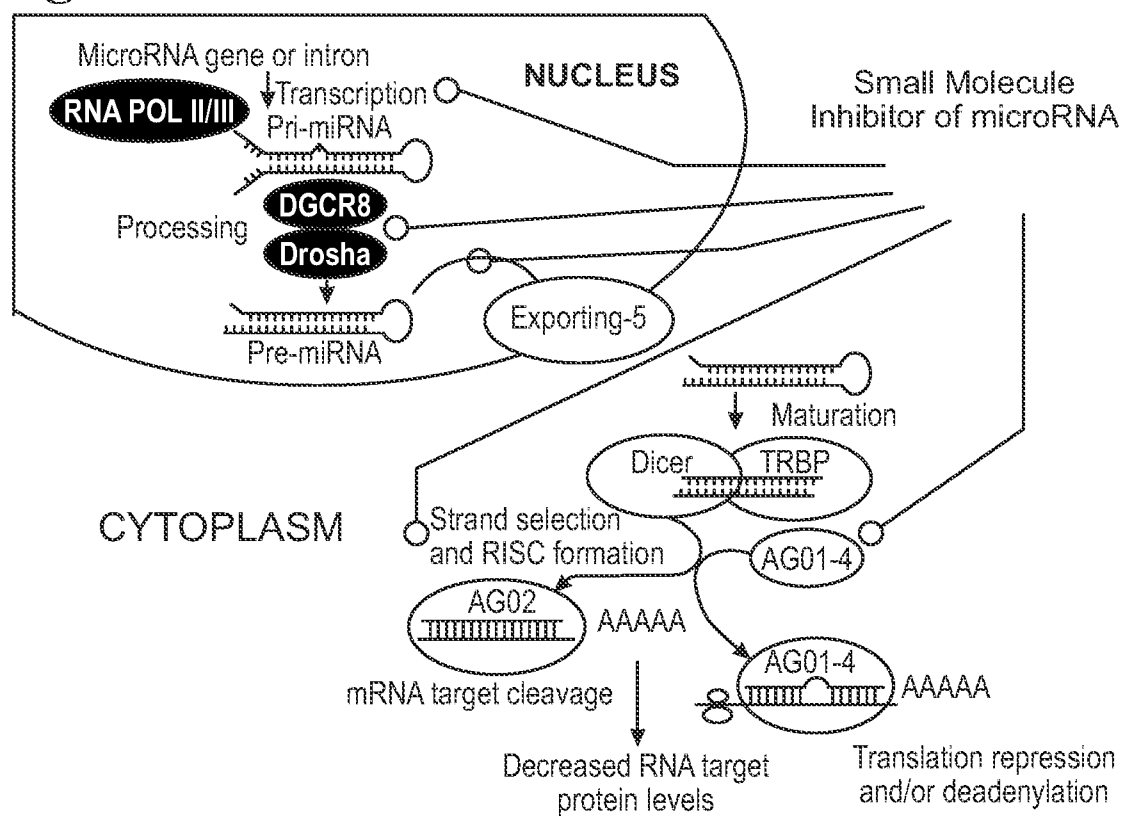
- Luciferase was normalized to *Renilla*
- Fold change: normalized samples relative to normalized DMSO control

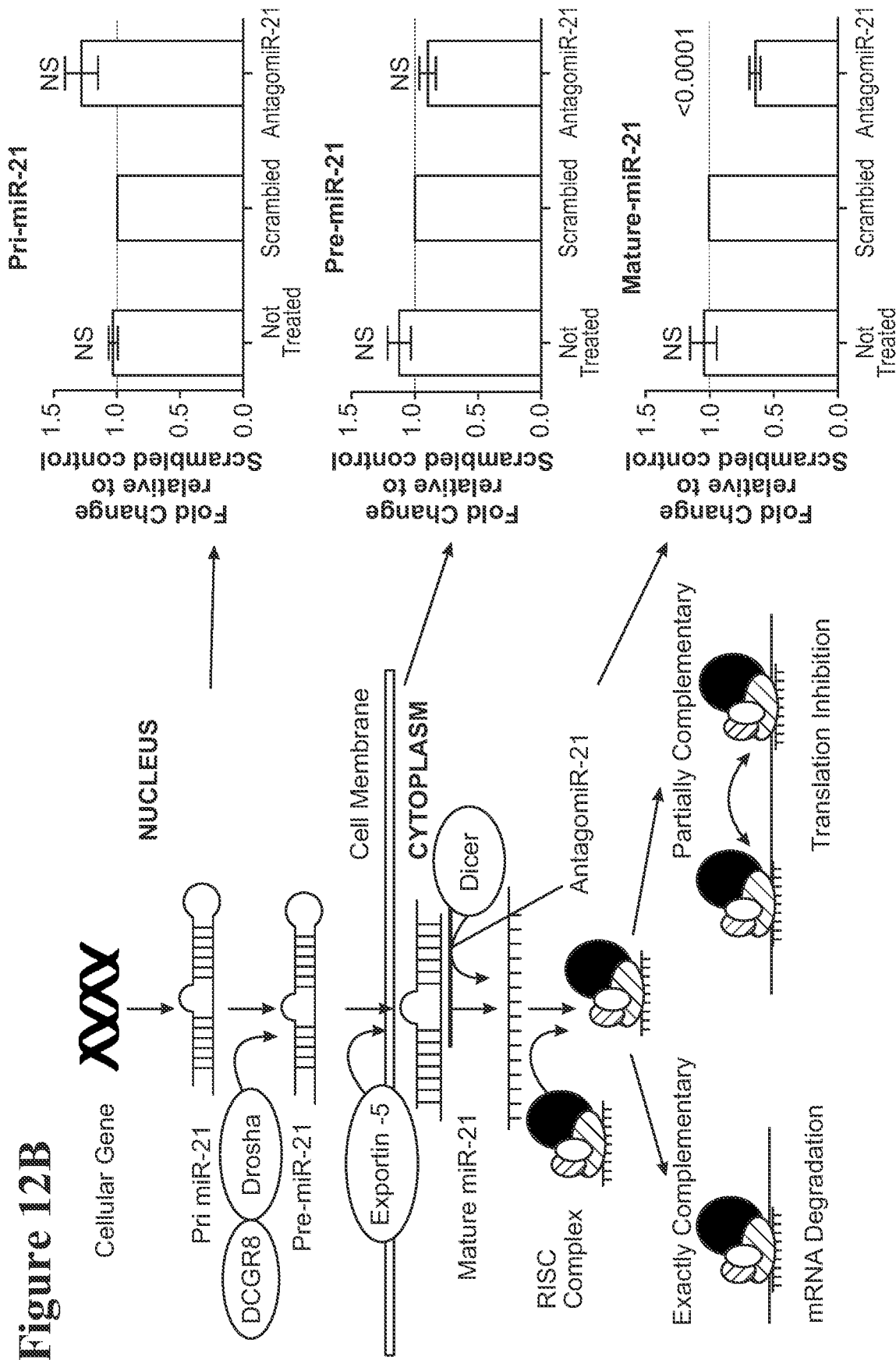
Threshold: set at 2 fold relative the DMSO control (red line)

Figure 11

Compound	Structure	MW	NMR Score	Functional Biology Score	Total Score	IC ₅₀ (MCF-7 cells)	IC ₂₅ (MCF-7 cells)
BSI101023		456.4	4	9	13	81μM	48μM
BSI101484		304.4	4	6	10	30μM	20μM
BSI101534		308.4	4	6	10	25 μM	5 μM
BSI100945		263.3	2	7	9	35μM	10μM

18/100

Figure 12A



20/100

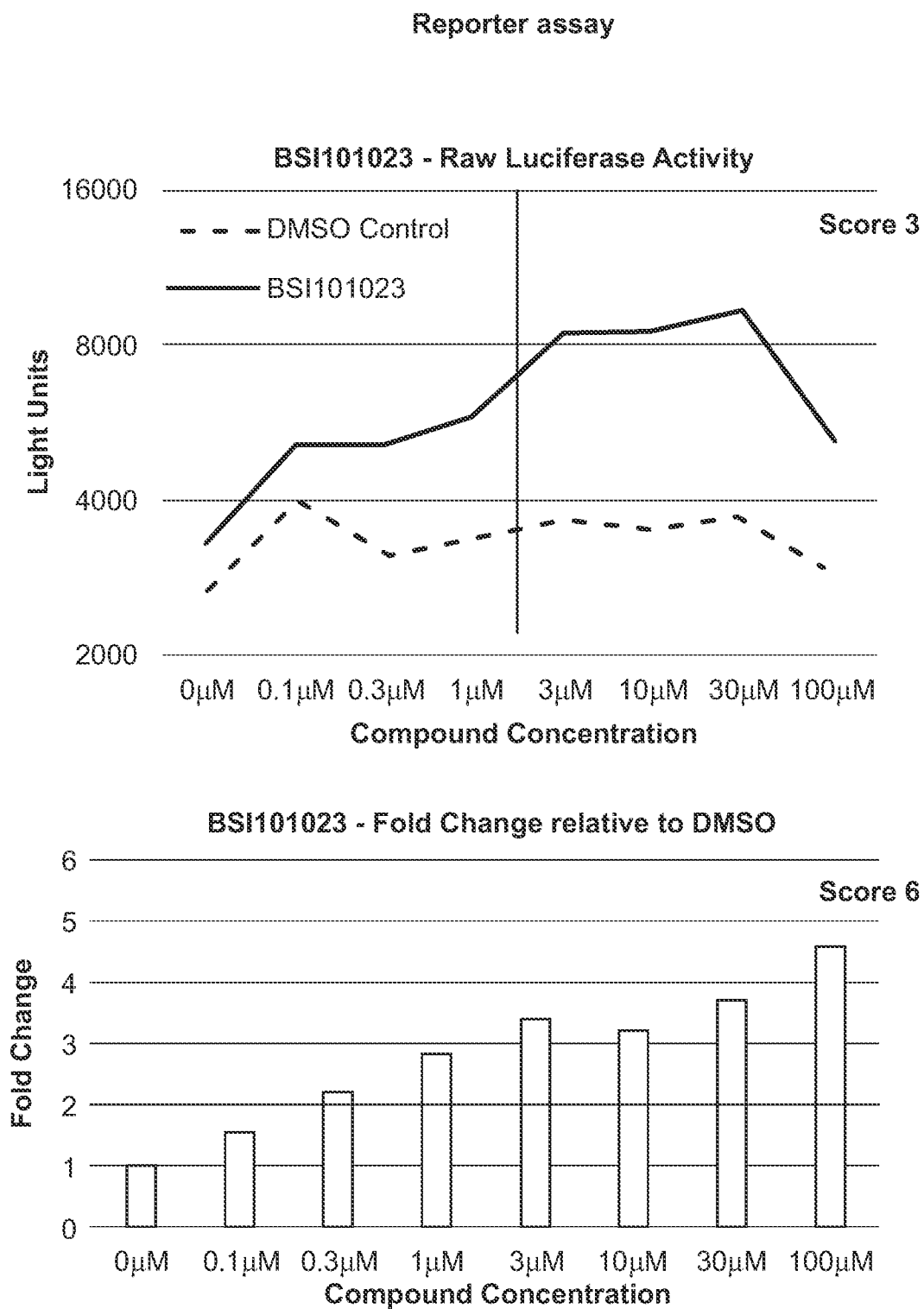
Figure 13A

Figure 13B

Proliferation assay

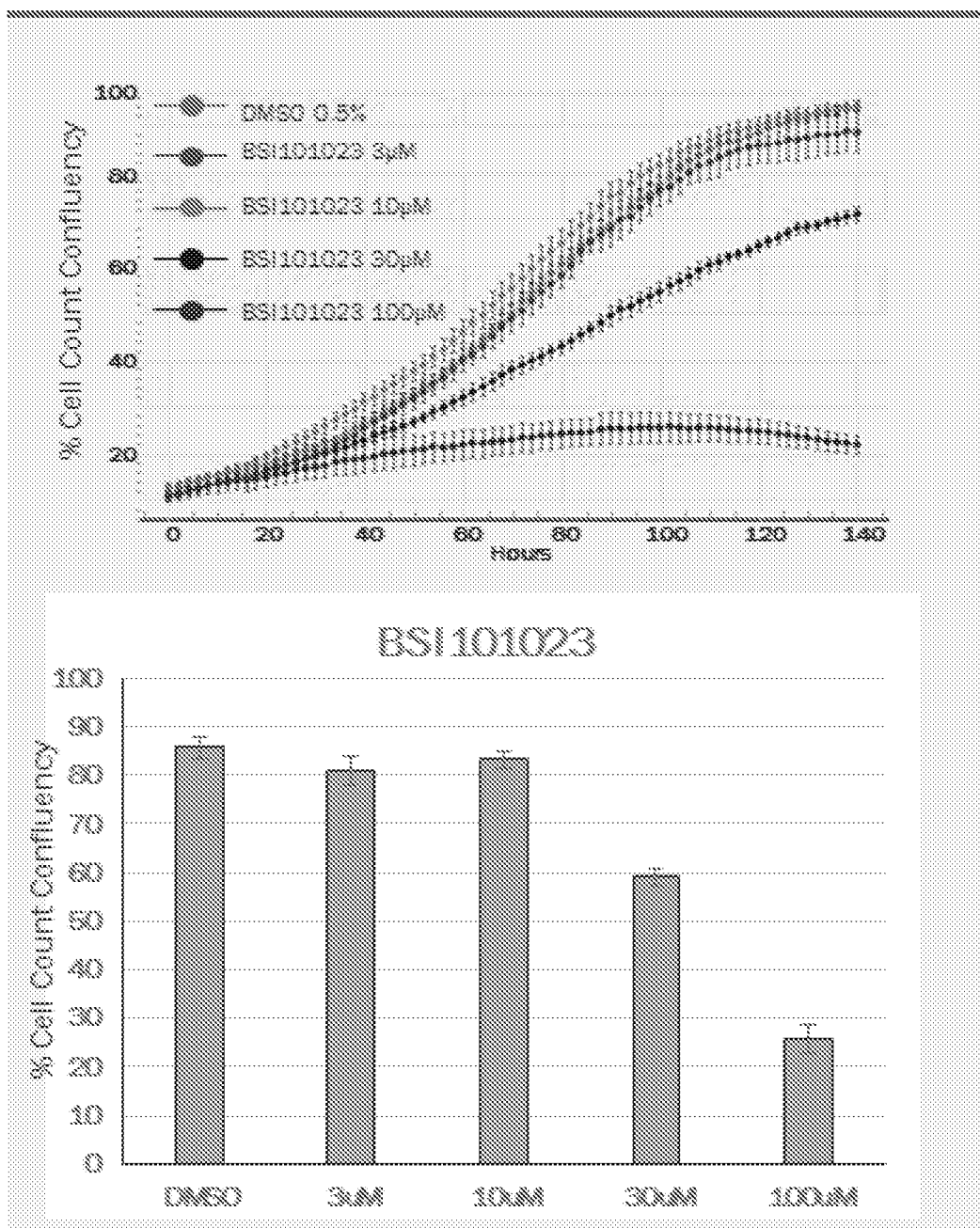


Figure 14A

Scratch Assay

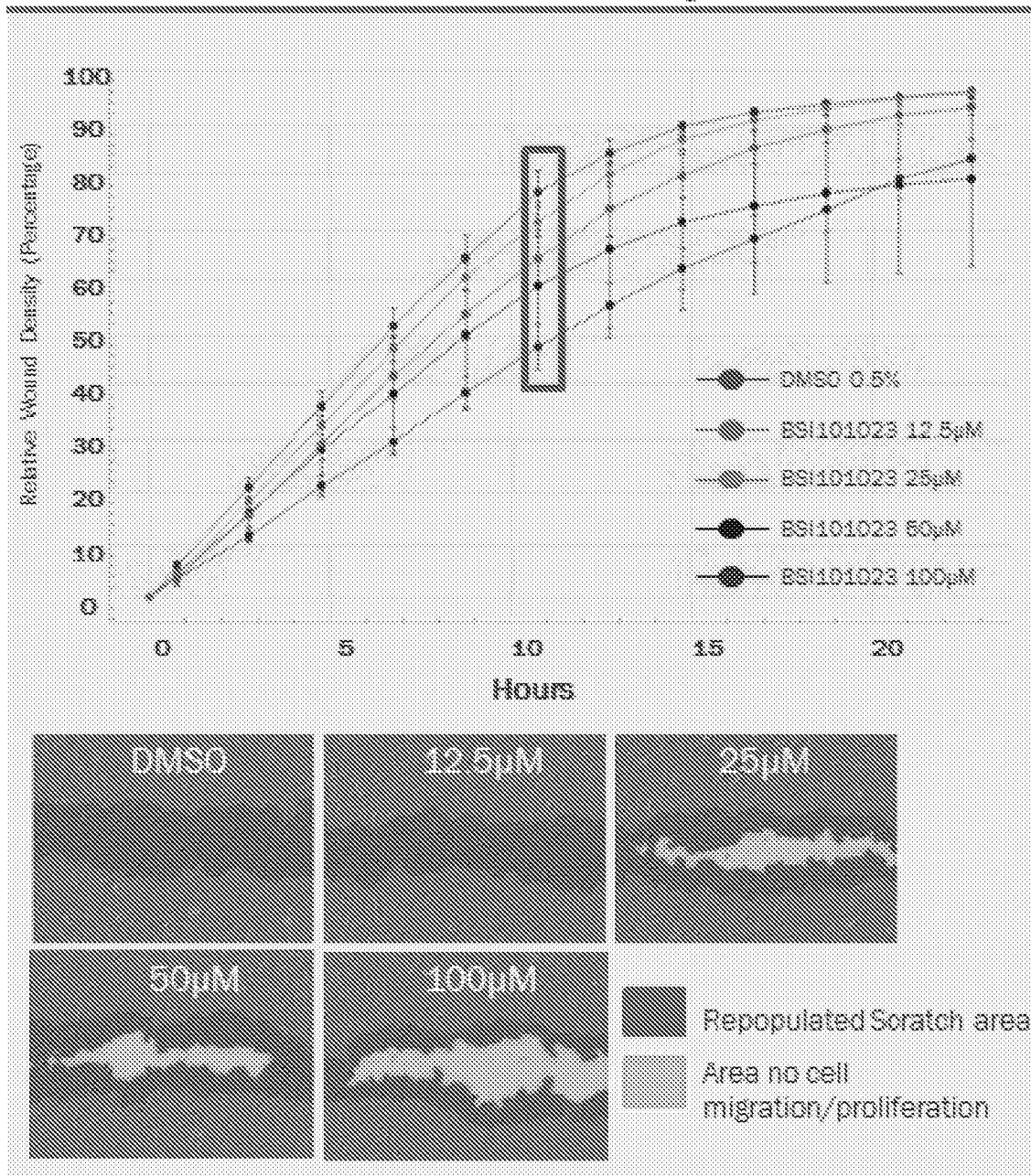
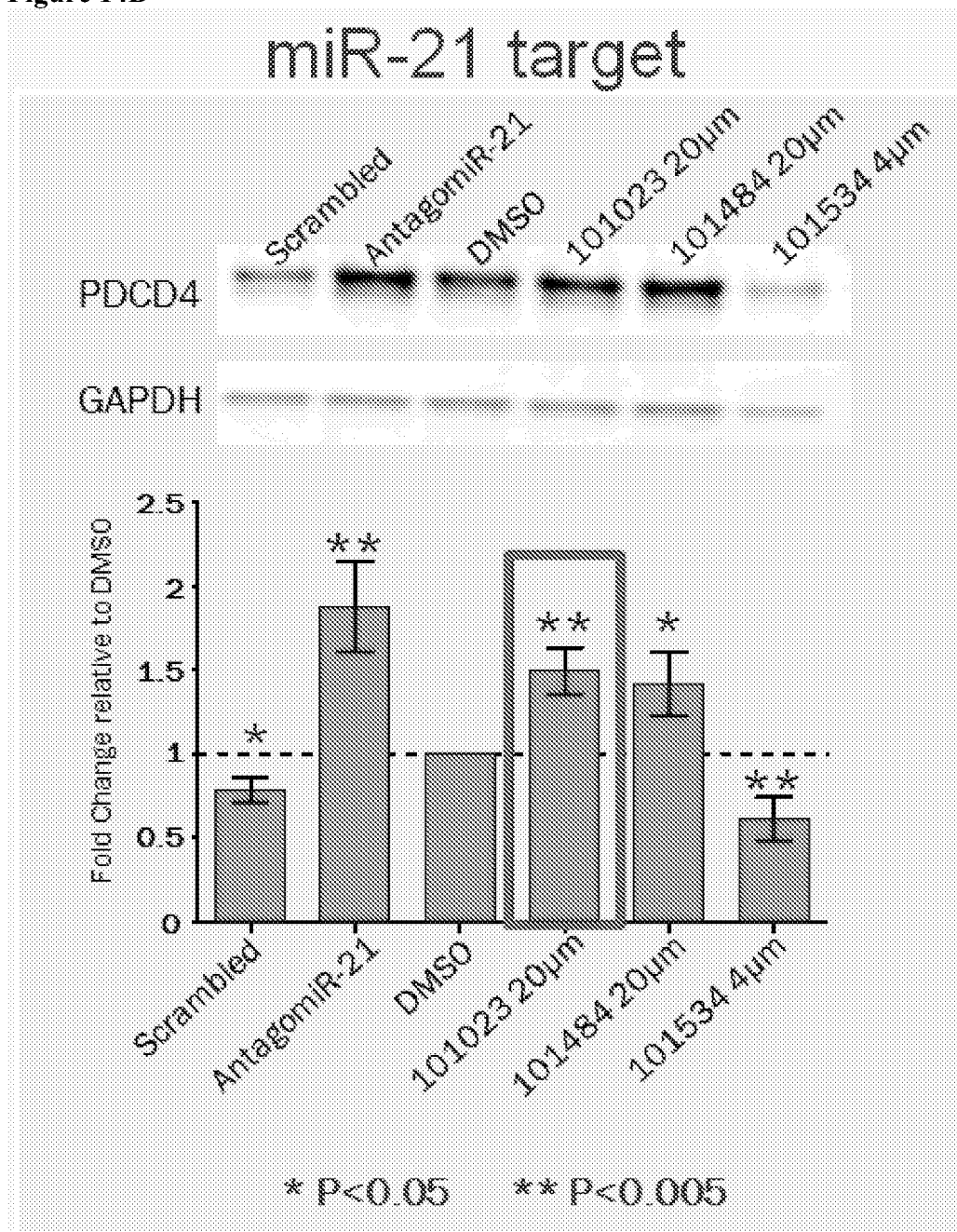
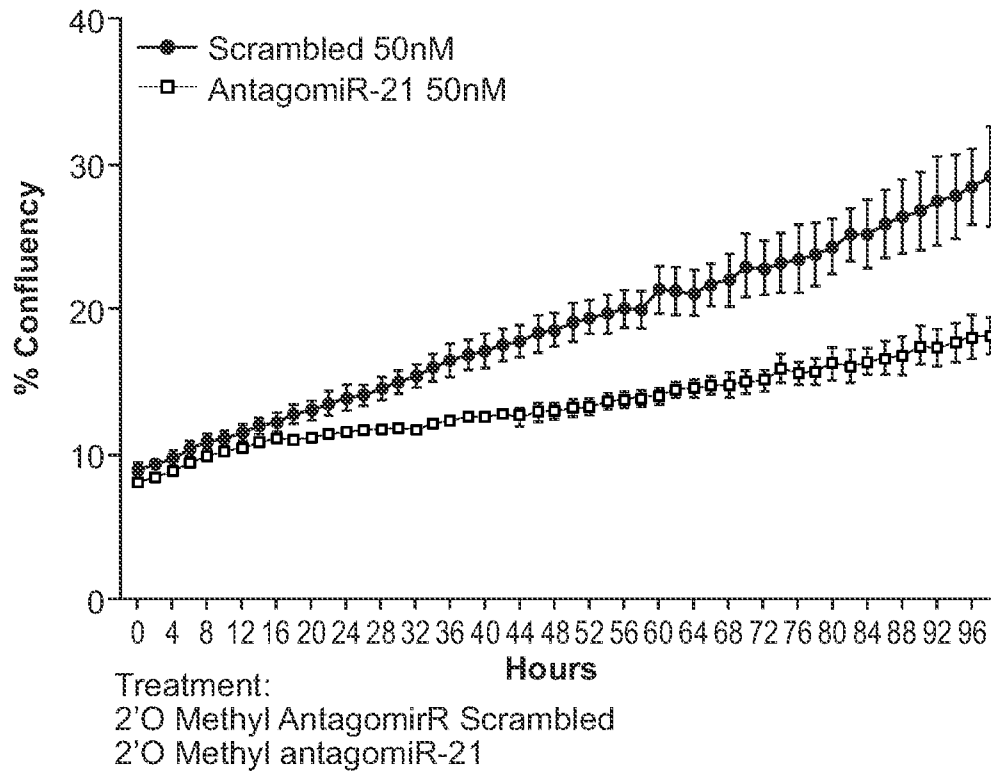
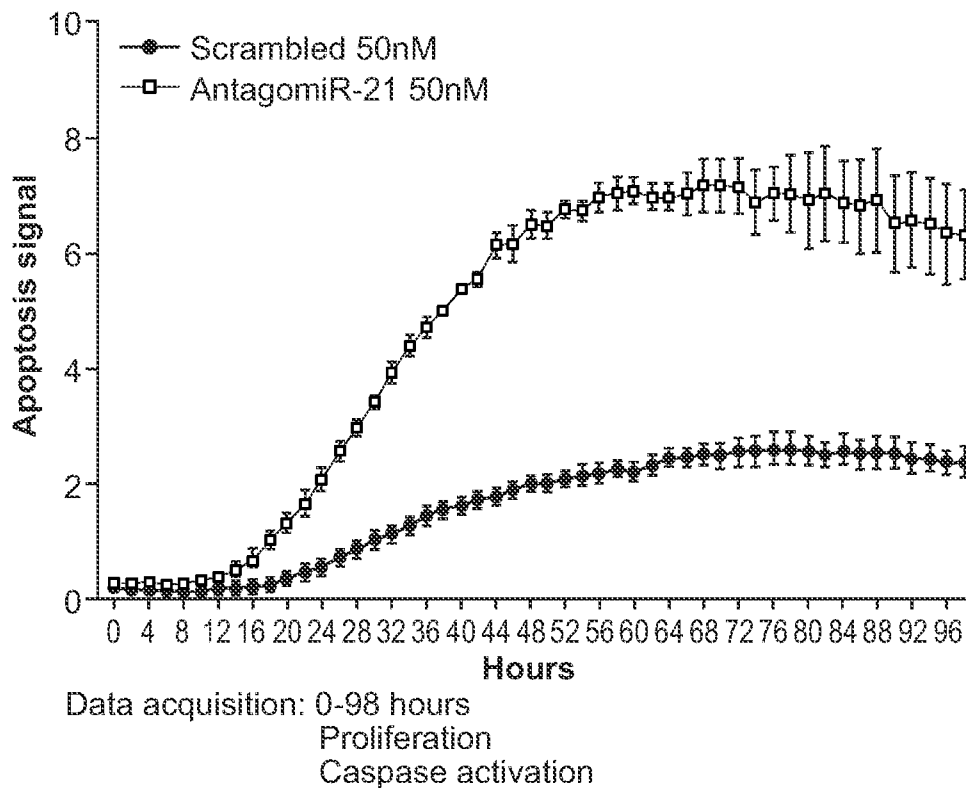


Figure 14B



24/100

Figure 14C**Live cell imaging****MCF-7 PROLIFERATION****MCF-7 APOPTOSIS**

SUBSTITUTE SHEET (RULE 26)

Figure 15A

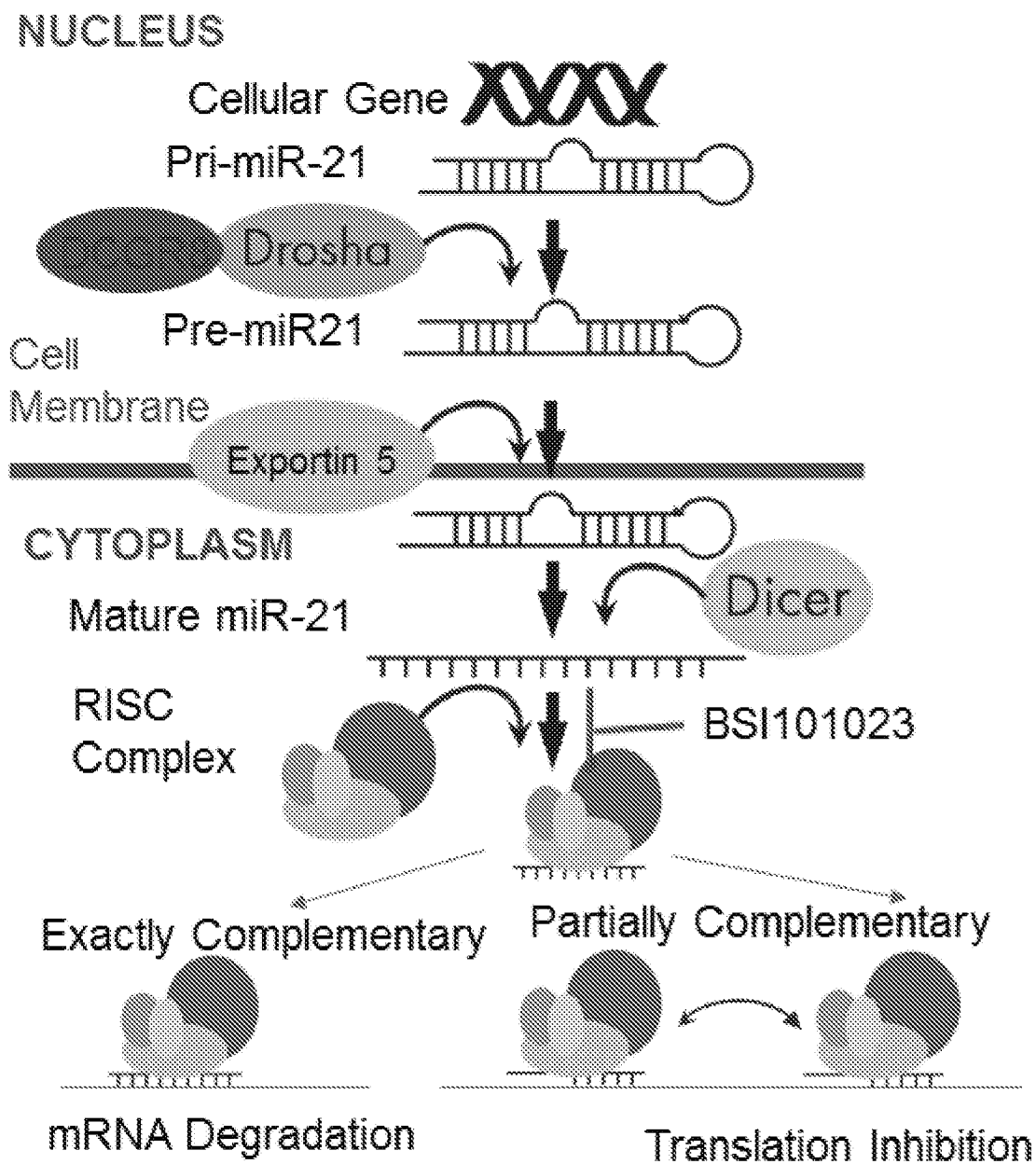


Figure 15B

Quantitative Analysis of miR-21 Processing Species by qPCR

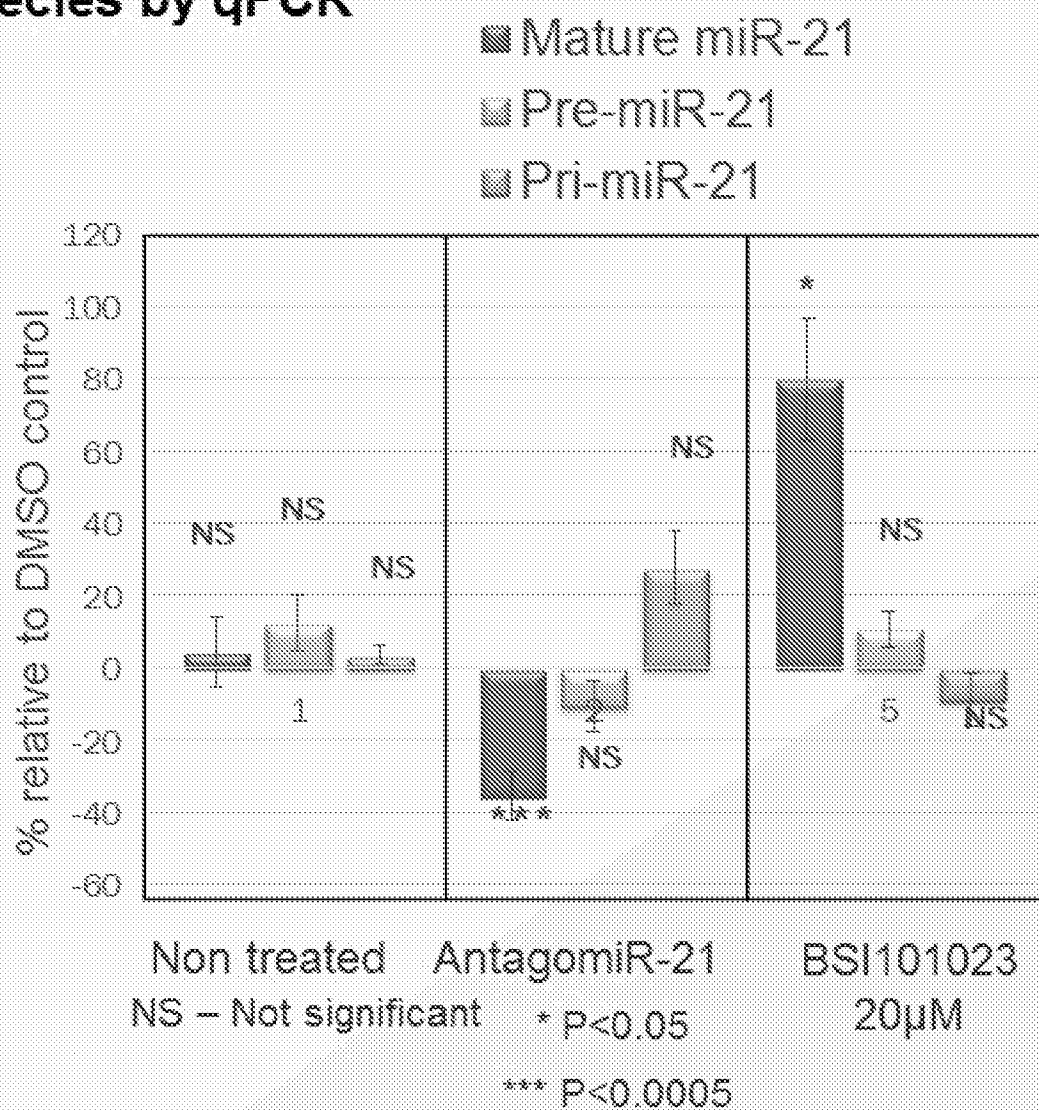


Figure 16A

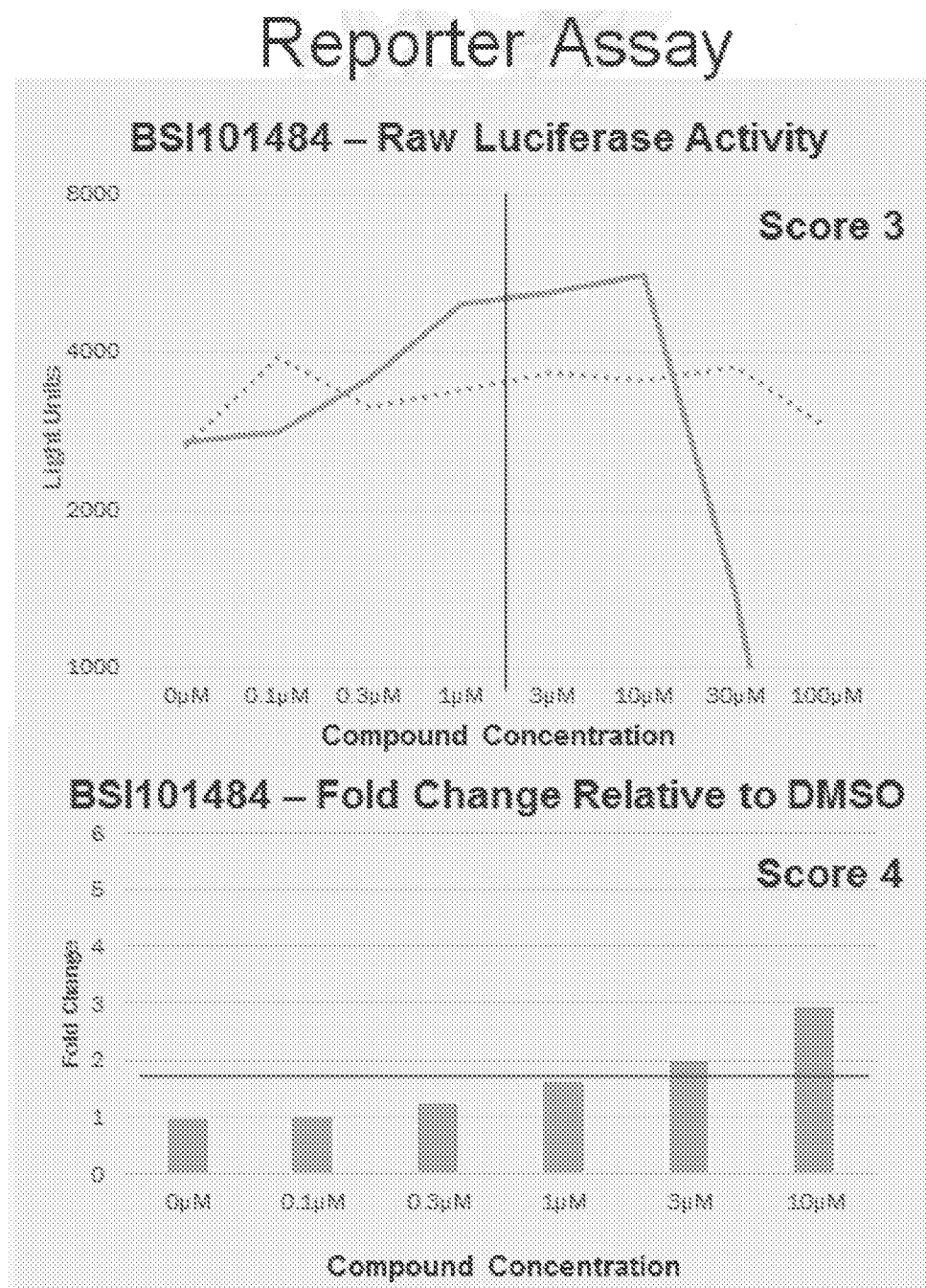


Figure 16B

Proliferation Assay

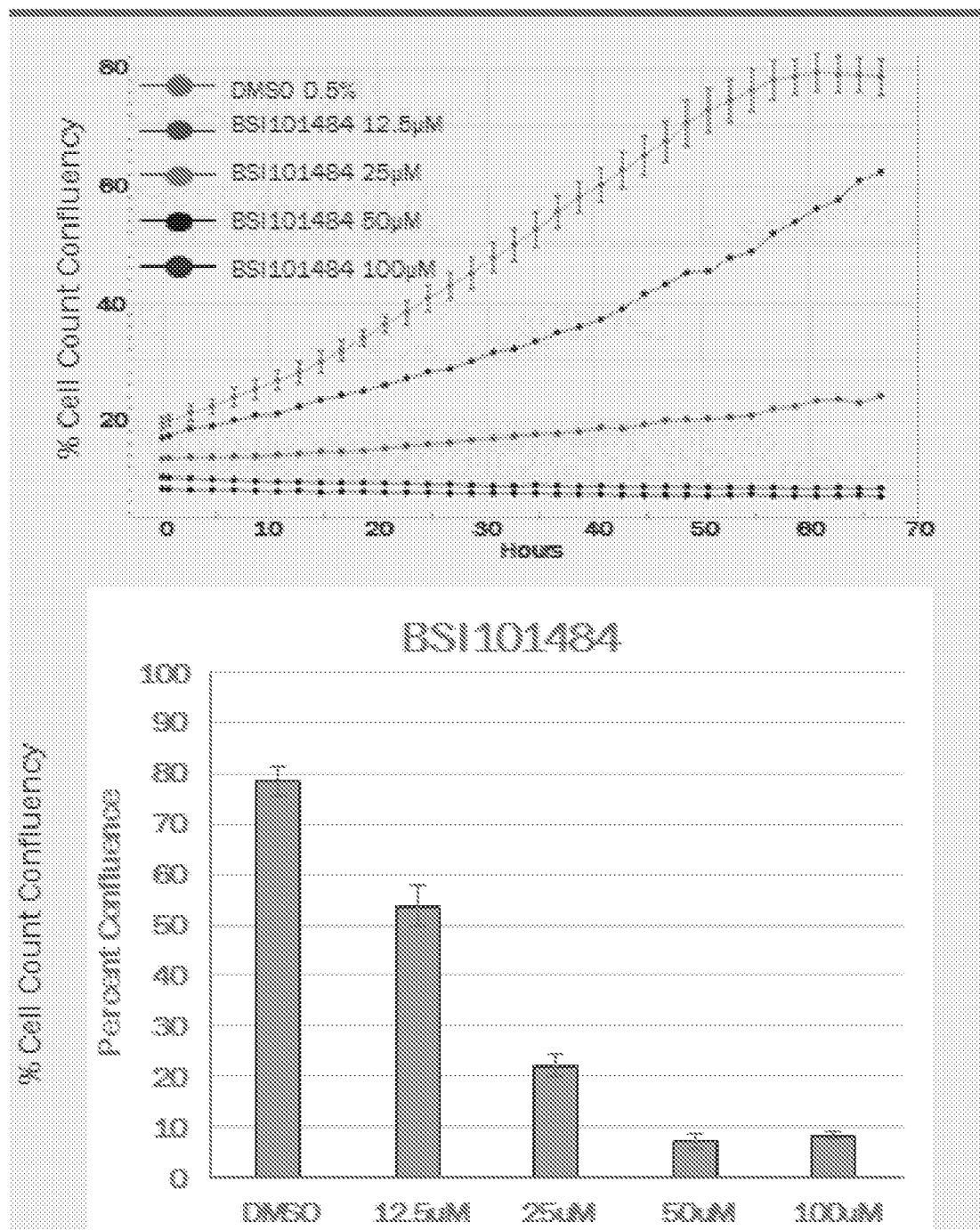


Figure 16C

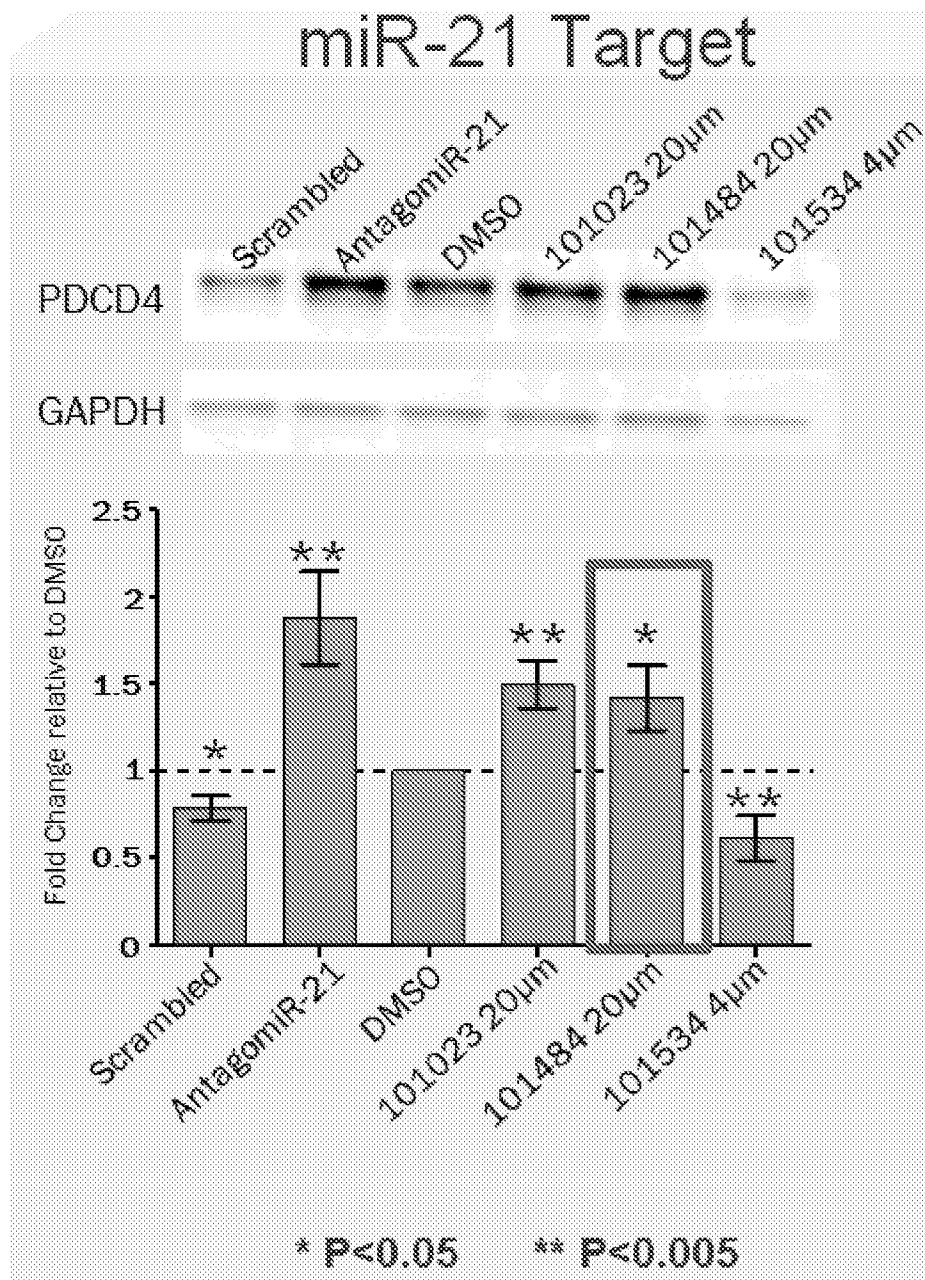
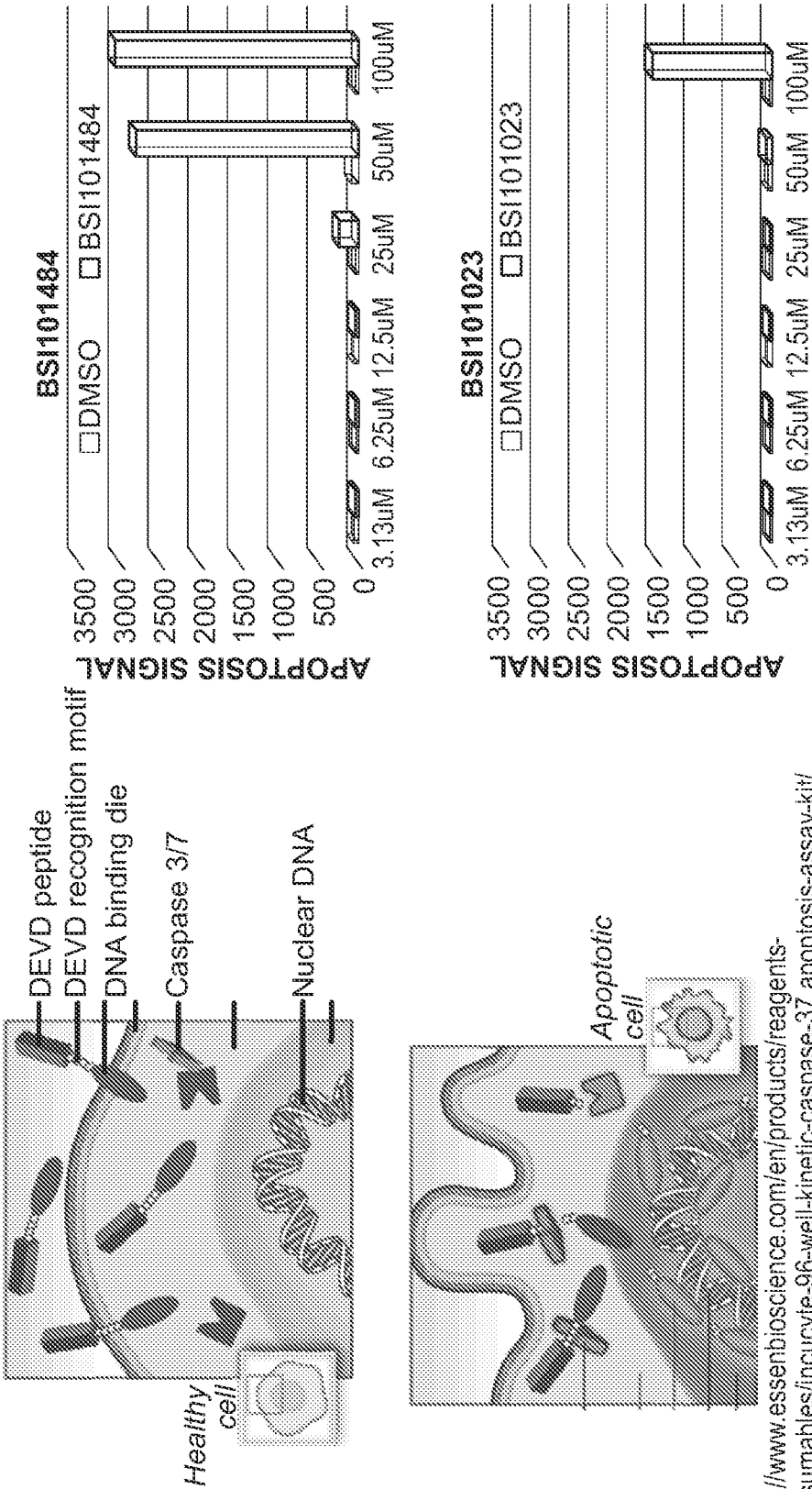


Figure 17A

Treatment with BSI101484 or 101023 causes dose dependent apoptosis in MCF-7 in 120 hrs



<http://www.essenbioscience.com/en/products/reagents-consumables/incubate-96-well-kinetic-caspase-37-apoptosis-assay-kit/>

Figure 17B

Real Time Apoptosis Assay - IncuCyte Zoom
Caspase-3/7 reagent

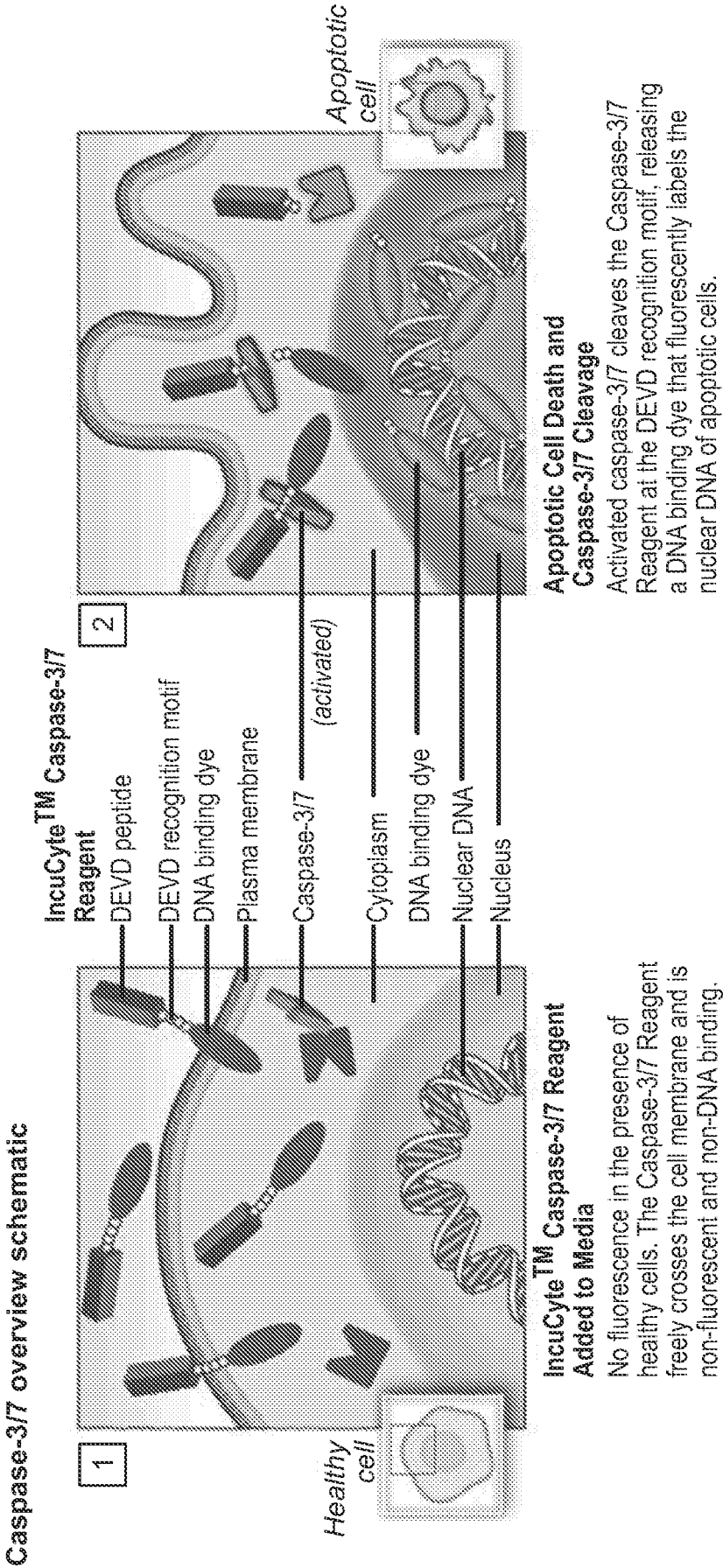


Figure 18A

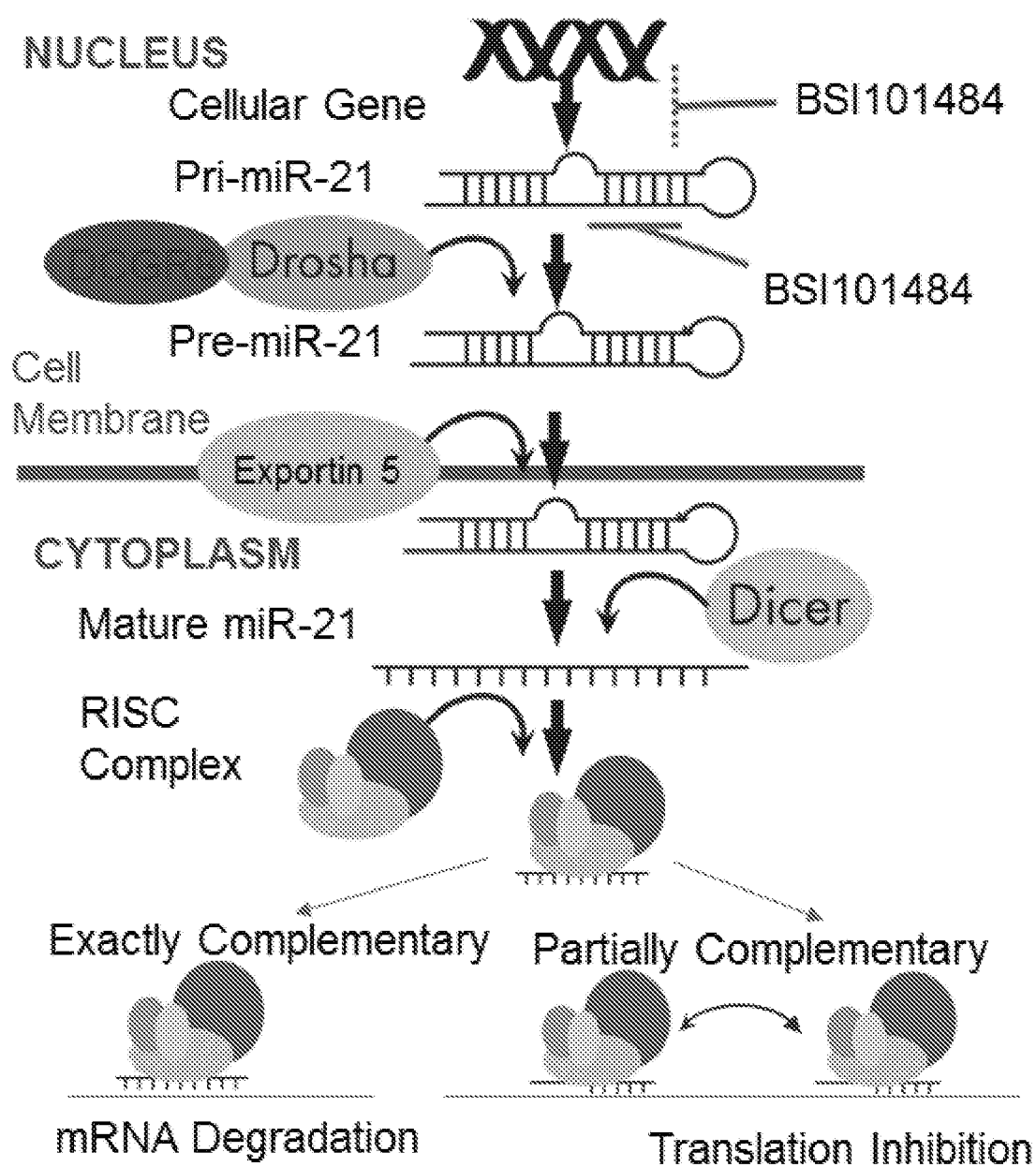
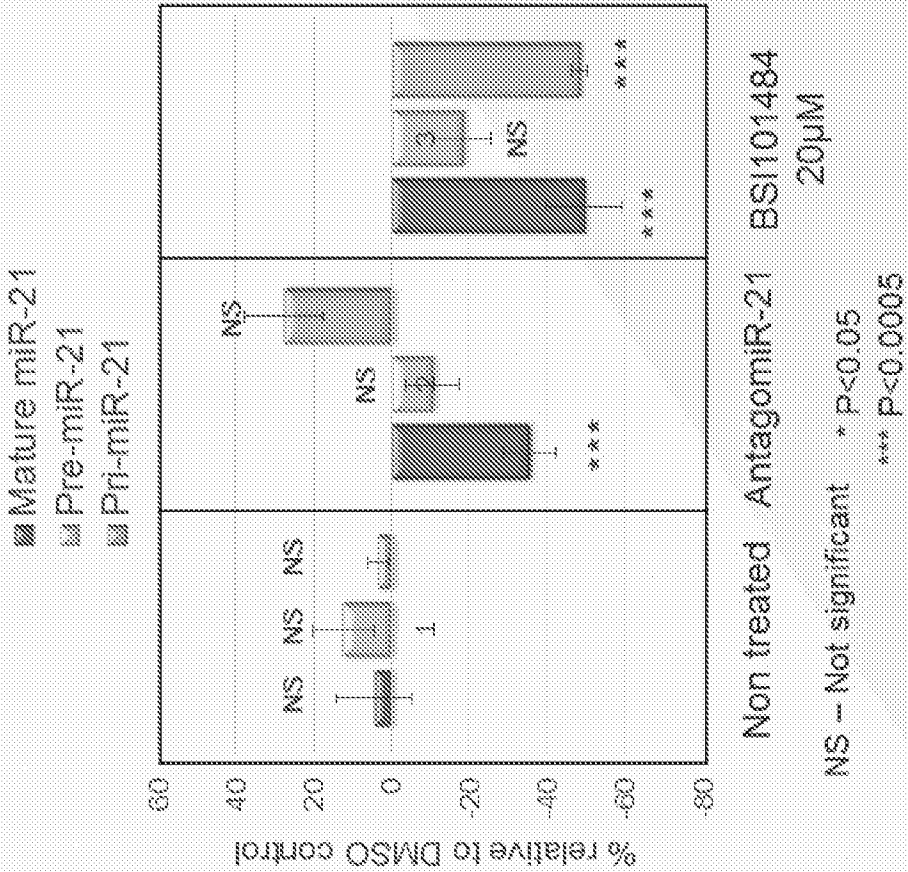
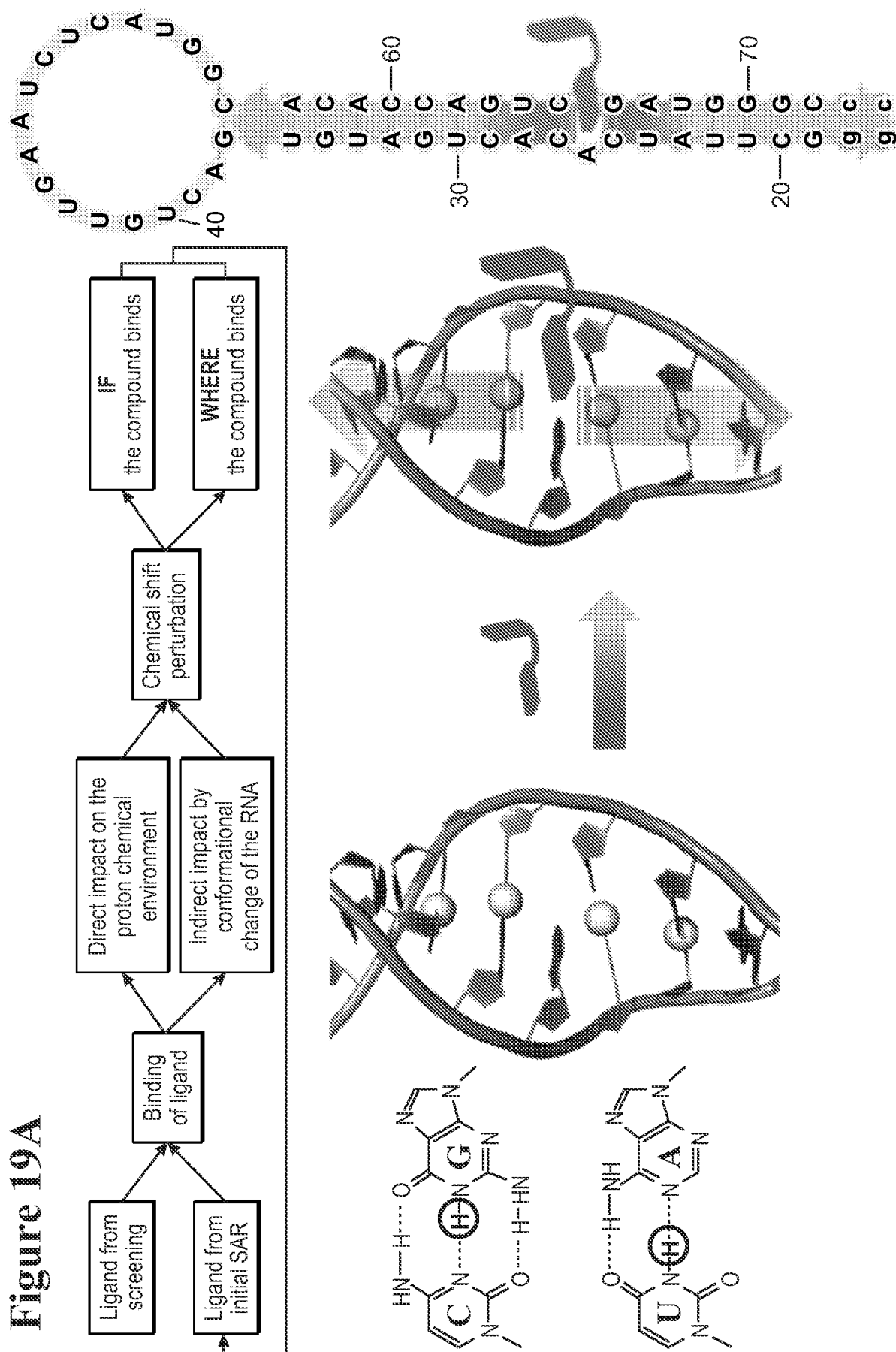


Figure 18B

Quantitative Analysis of microRNA Processing Species by qPCR



34/100



35/100

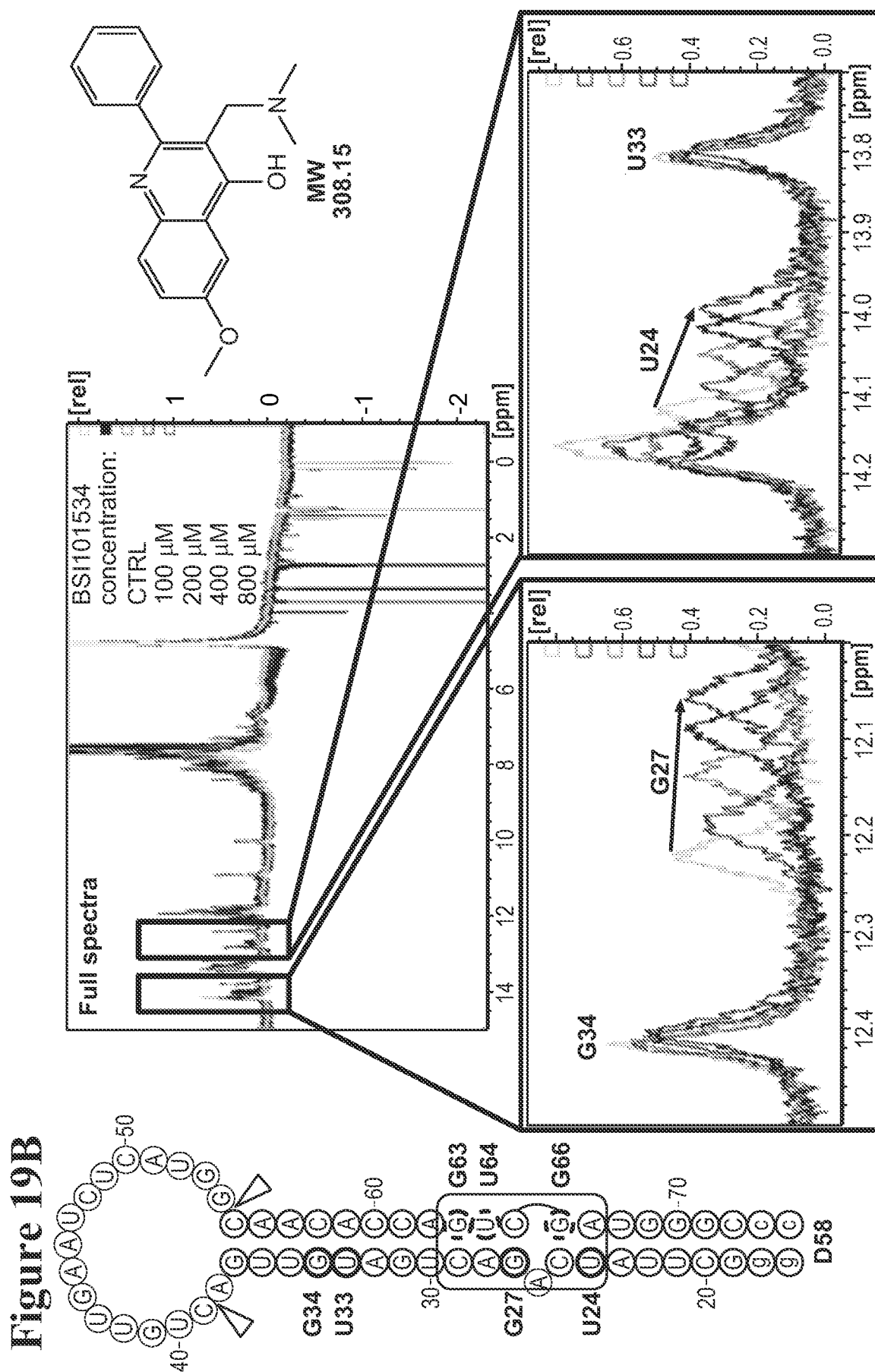
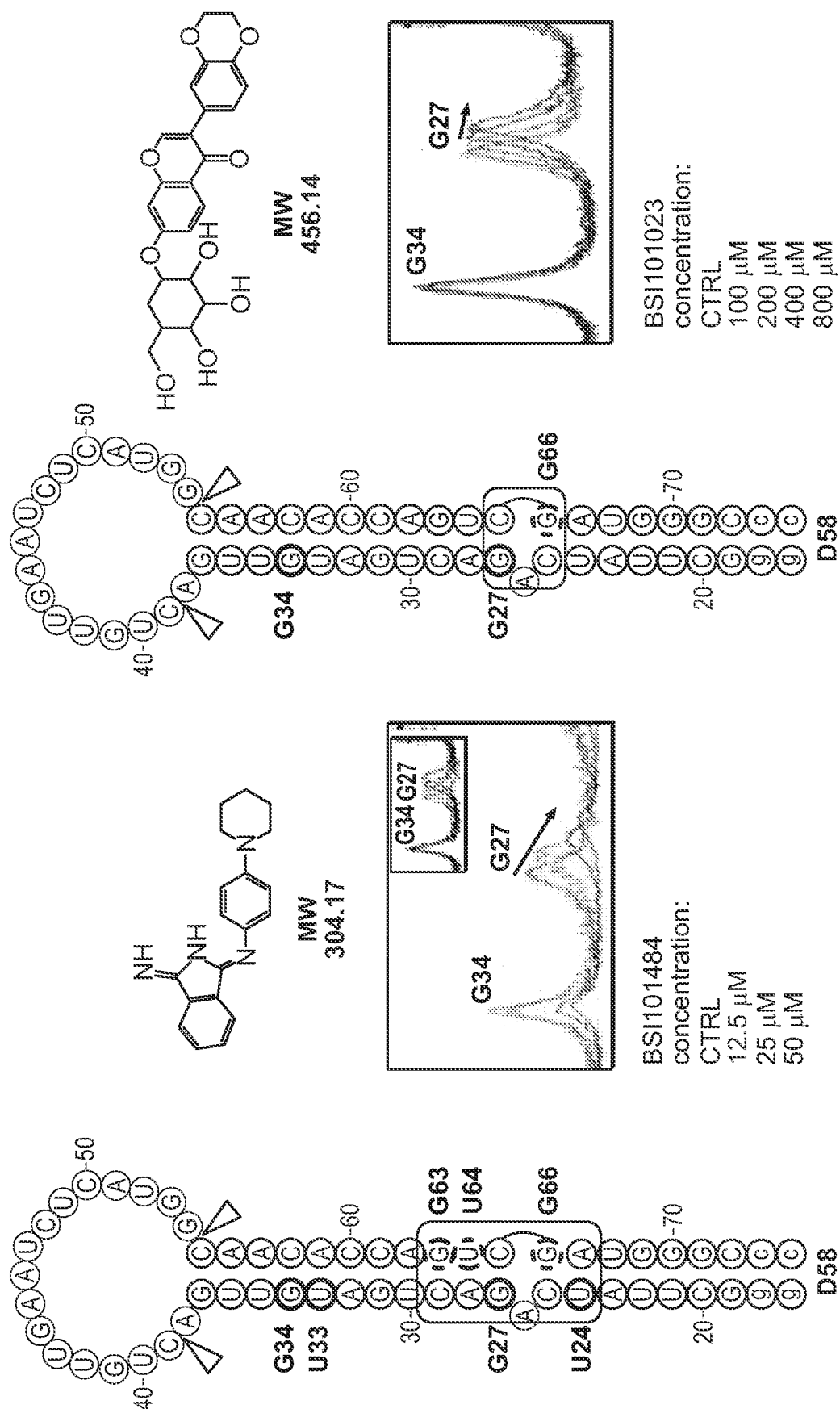
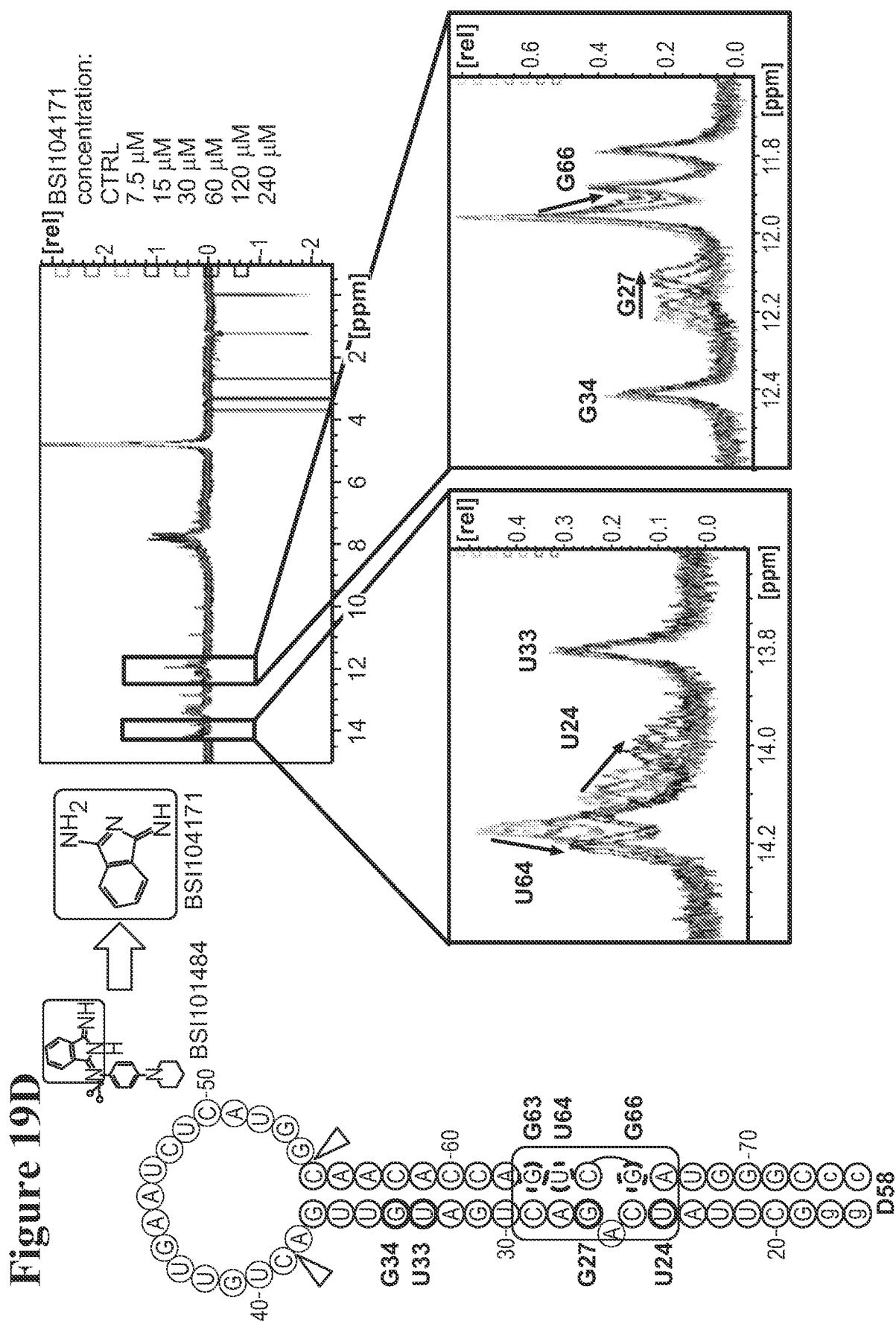


Figure 19C

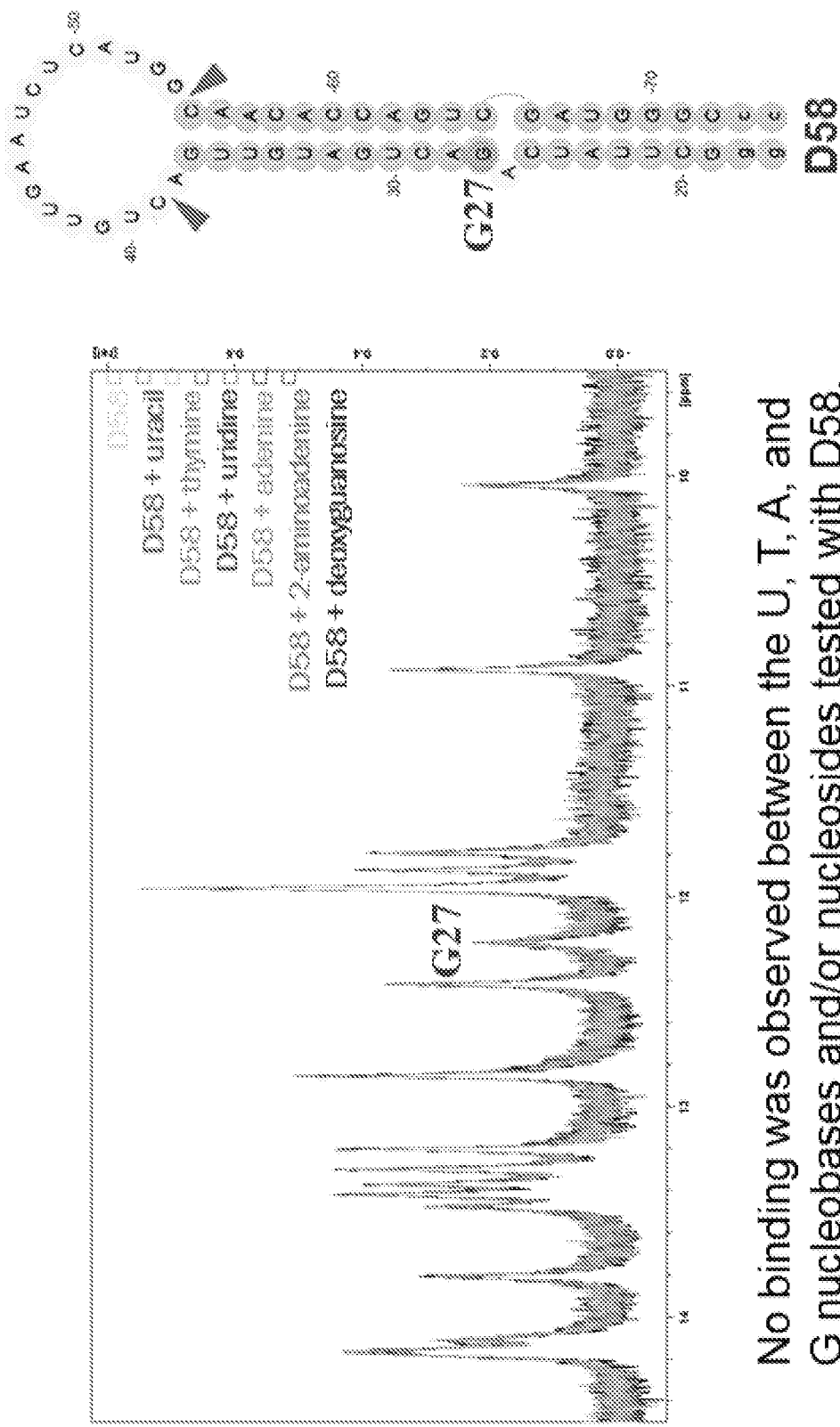


37/100



SUBSTITUTE SHEET (RULE 26)

Figure 19E



No binding was observed between the U, T, A, and G nucleobases and/or nucleosides tested with D58.

40/100

Figure 20B

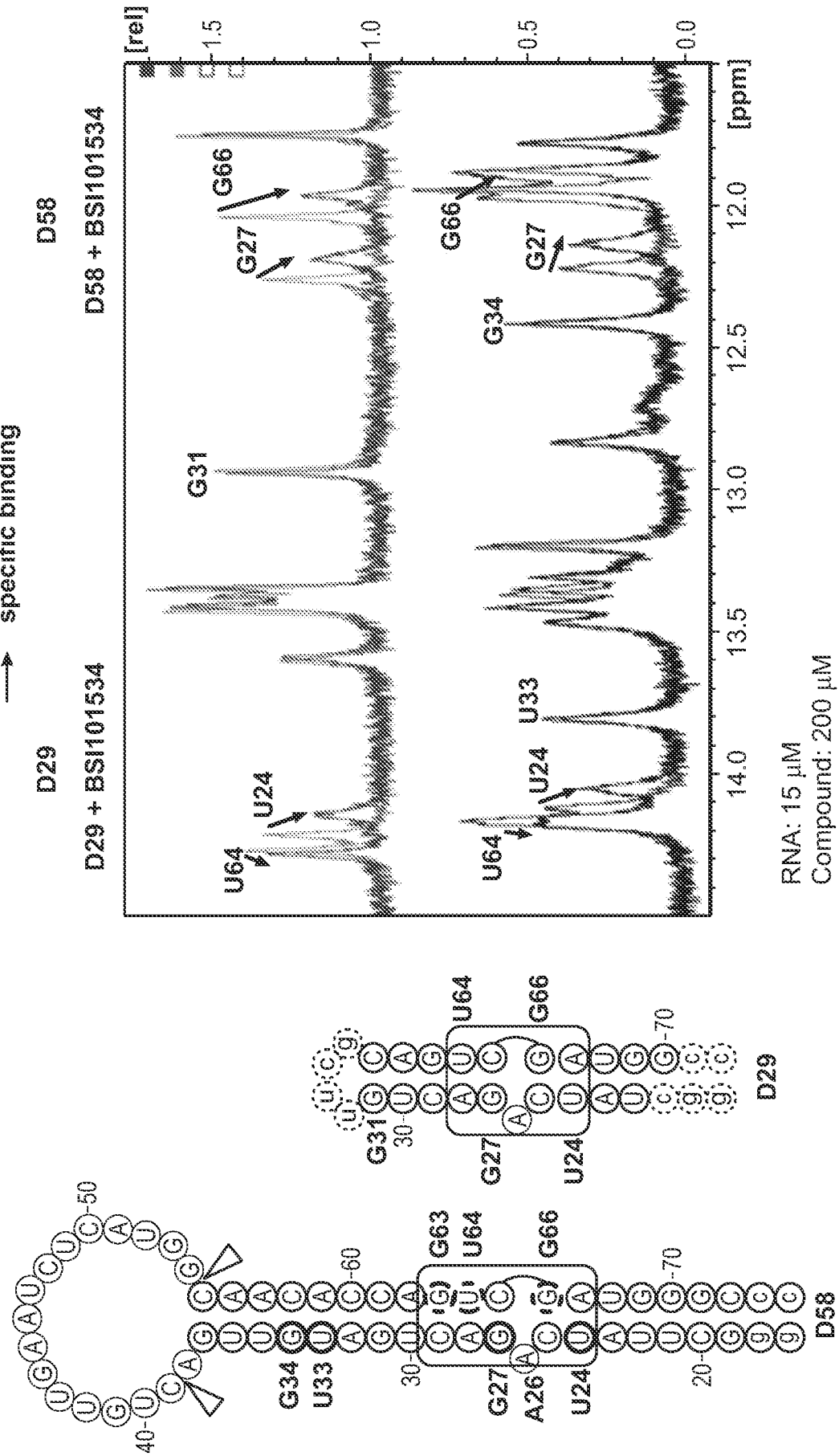
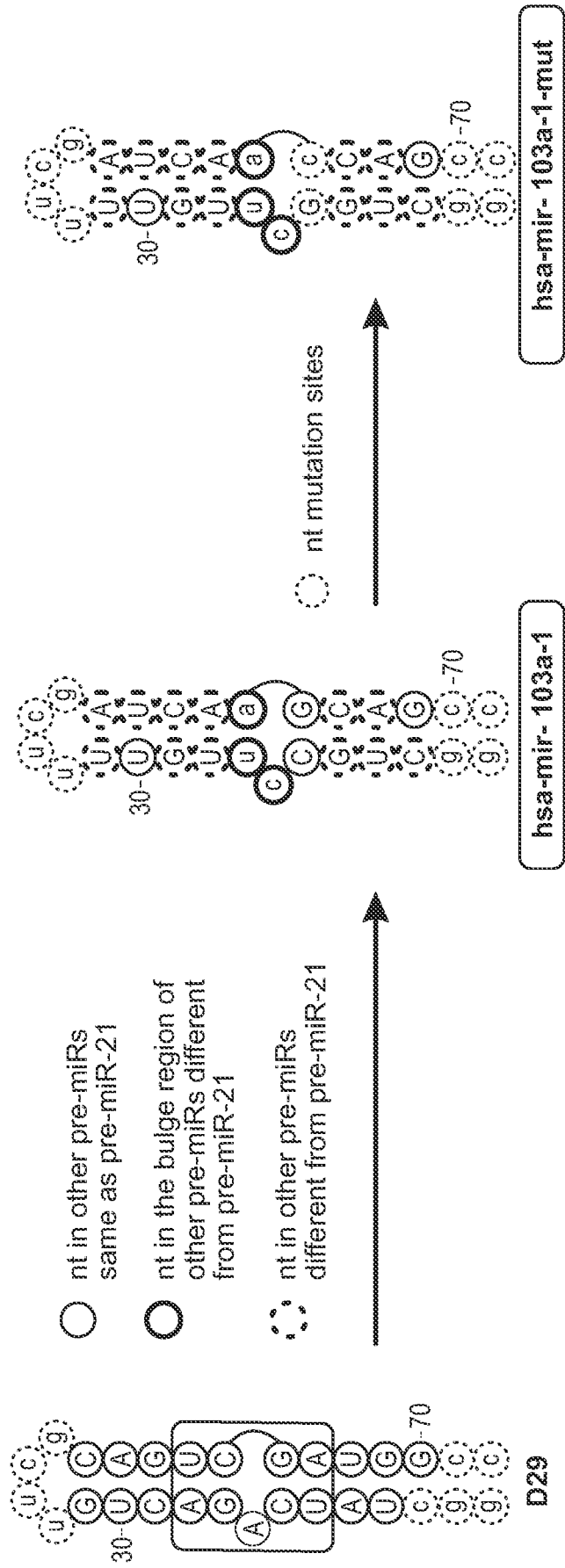


Figure 21A

Mutational mapping of local sequence context

- Pre-miRs containing similar sequence contexts
- Sequence variety for both the bulge and neighboring base pairs



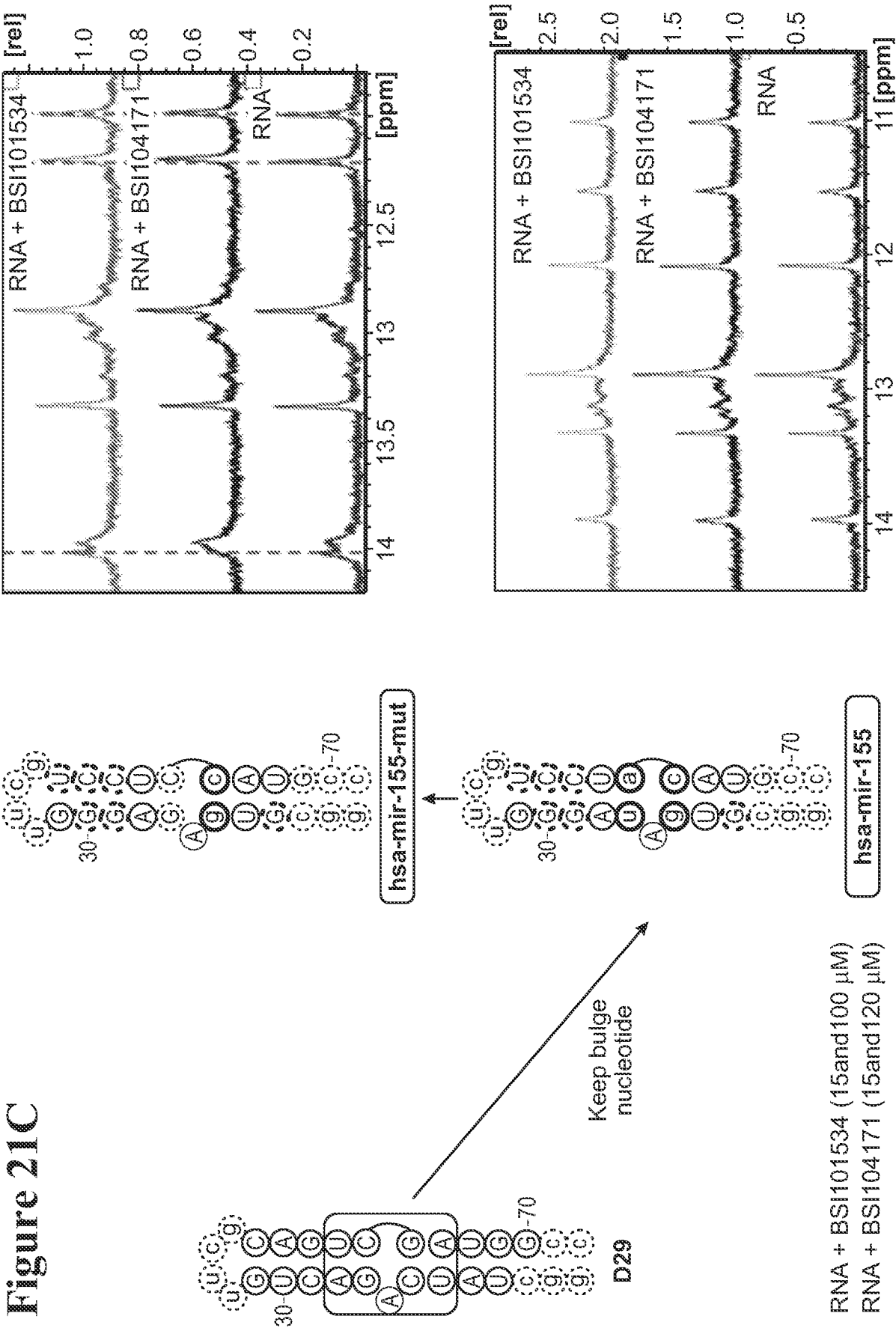


Figure 21D

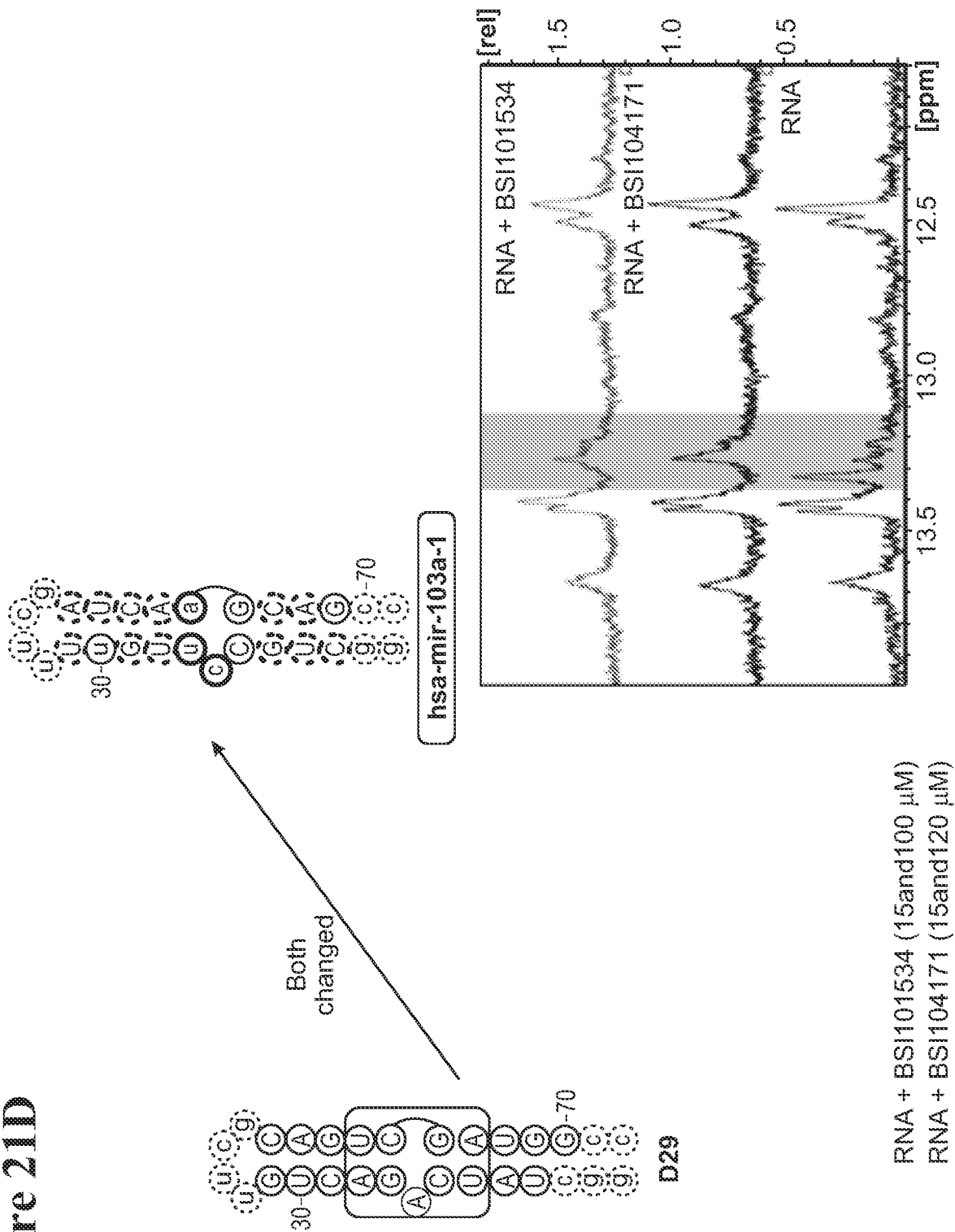
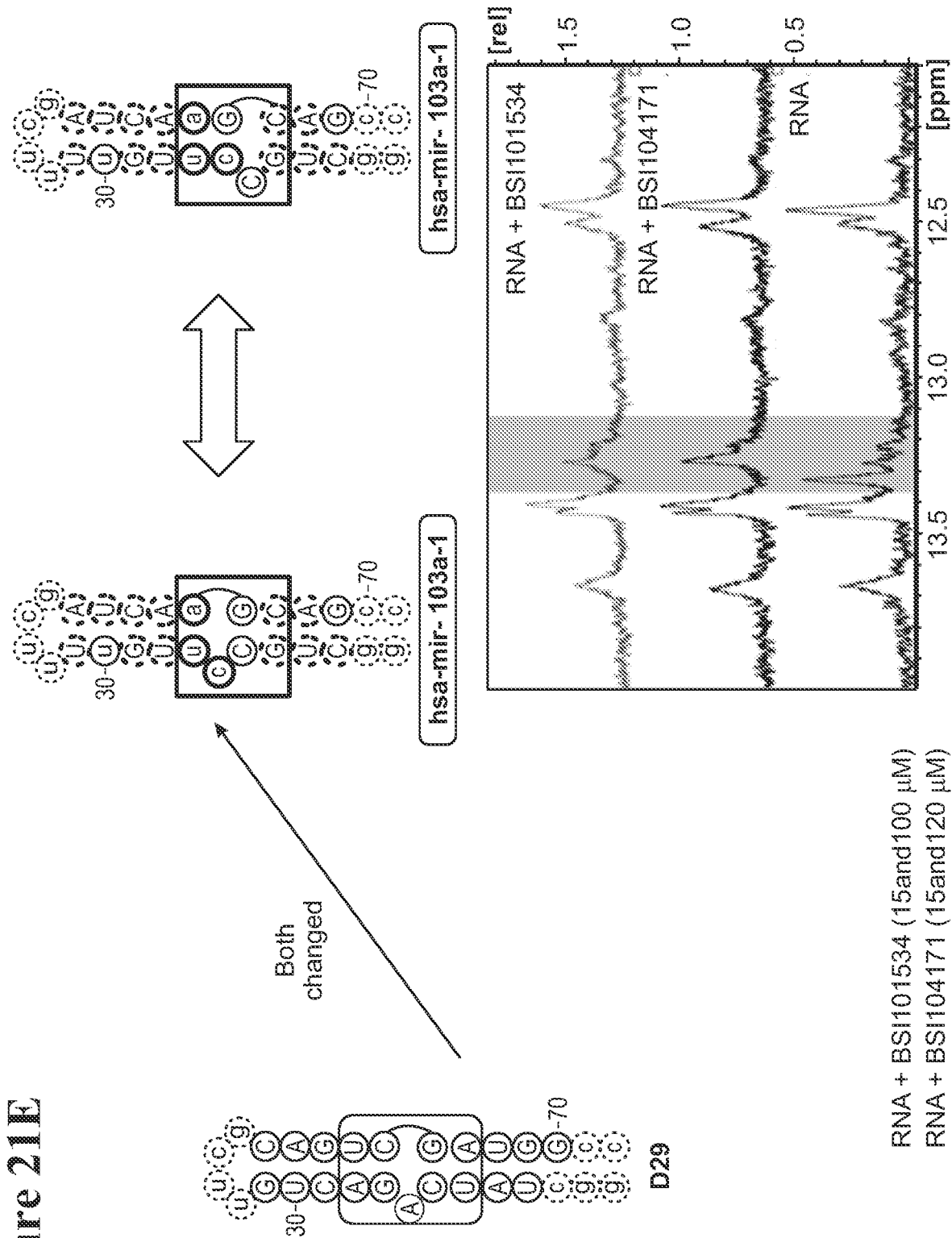


Figure 21E



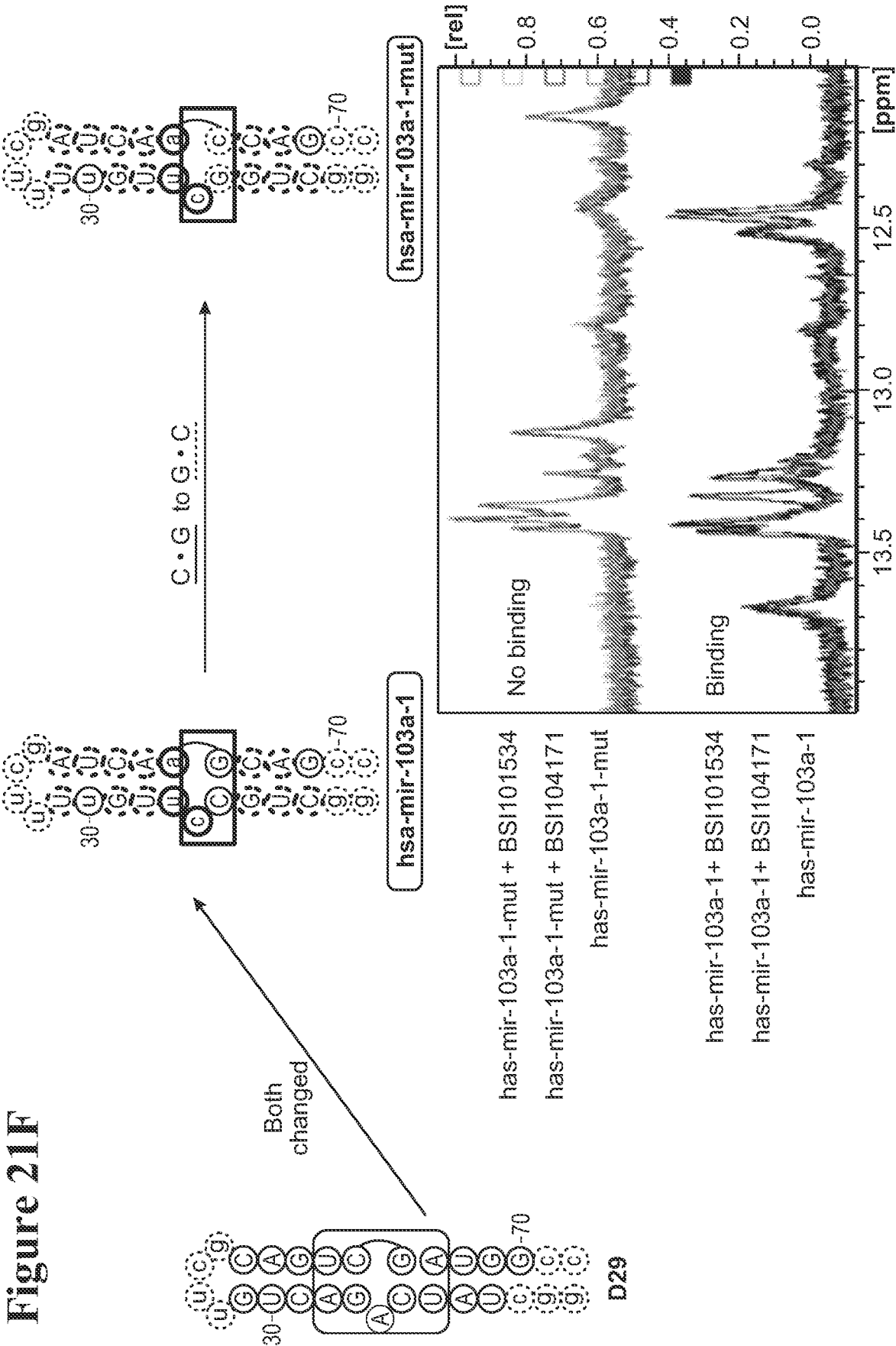


Figure 21G

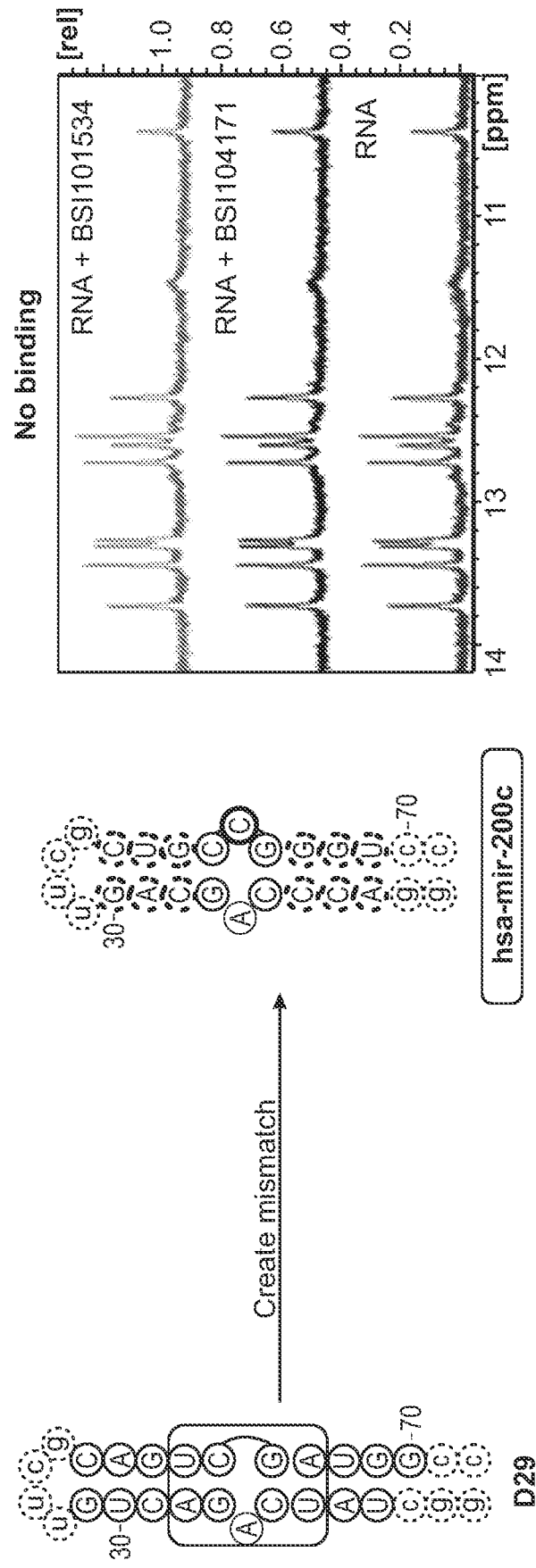
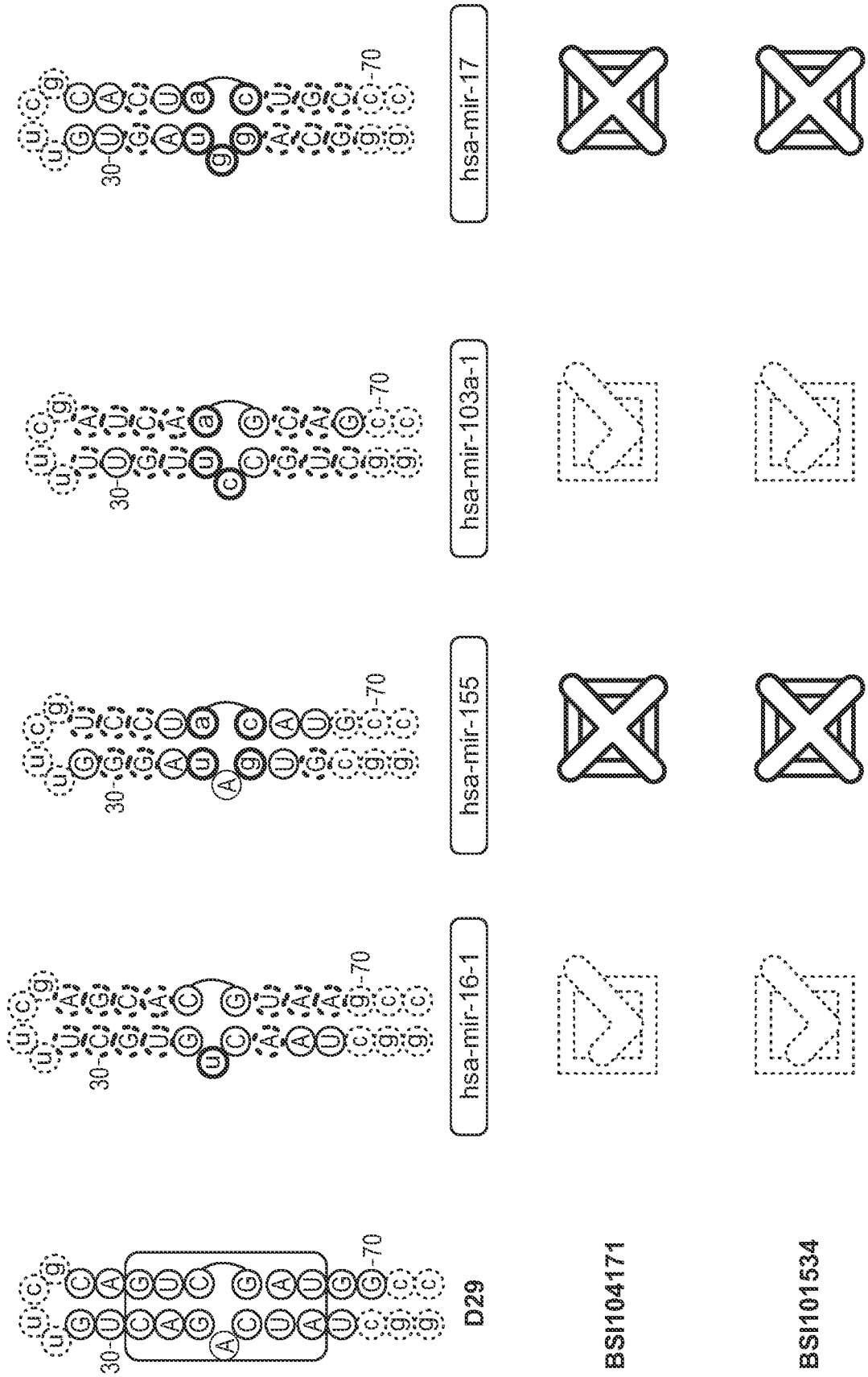


Figure 21H



BSI104171

BSI101534

Figure 22

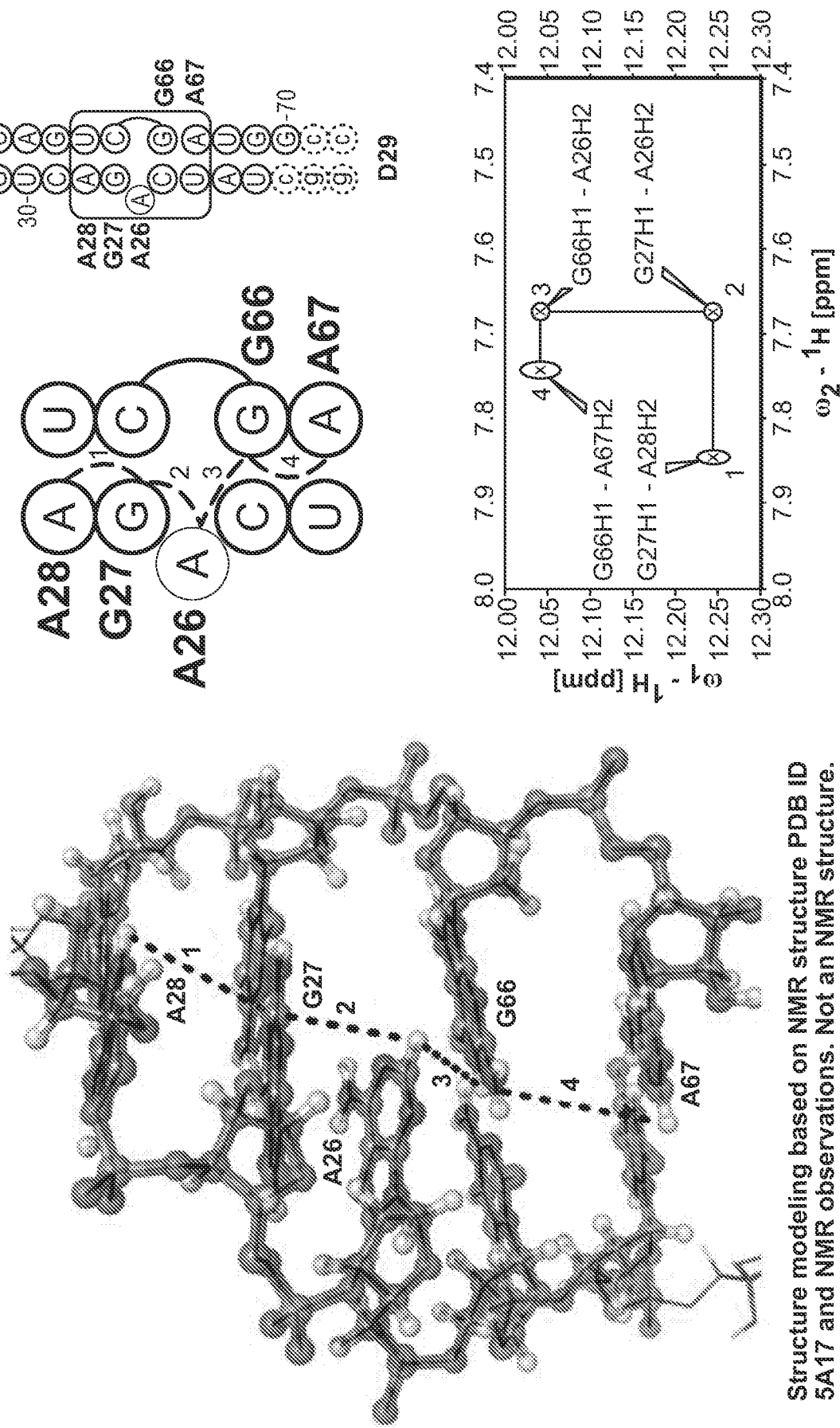


Figure 23B

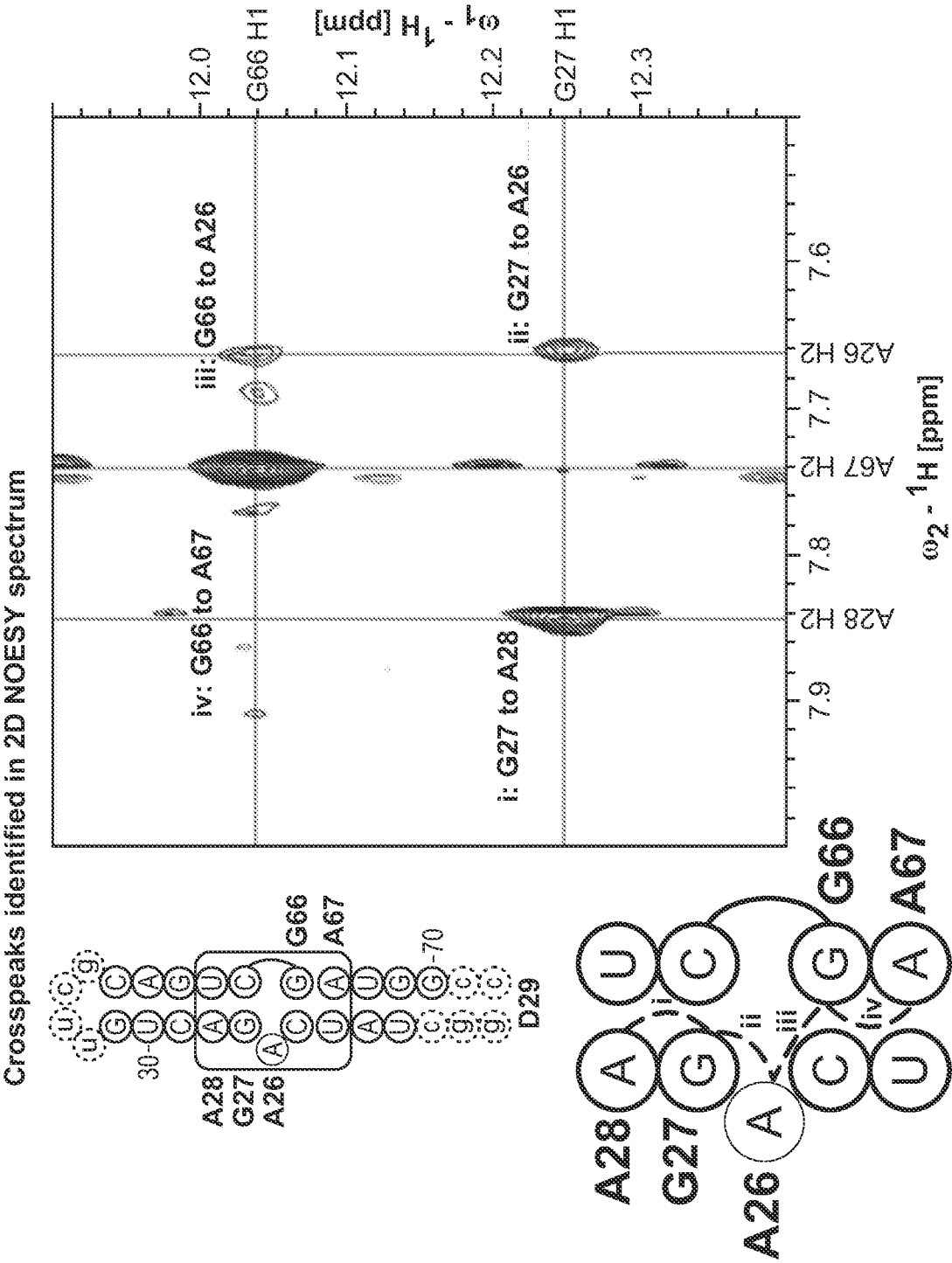


Figure 24

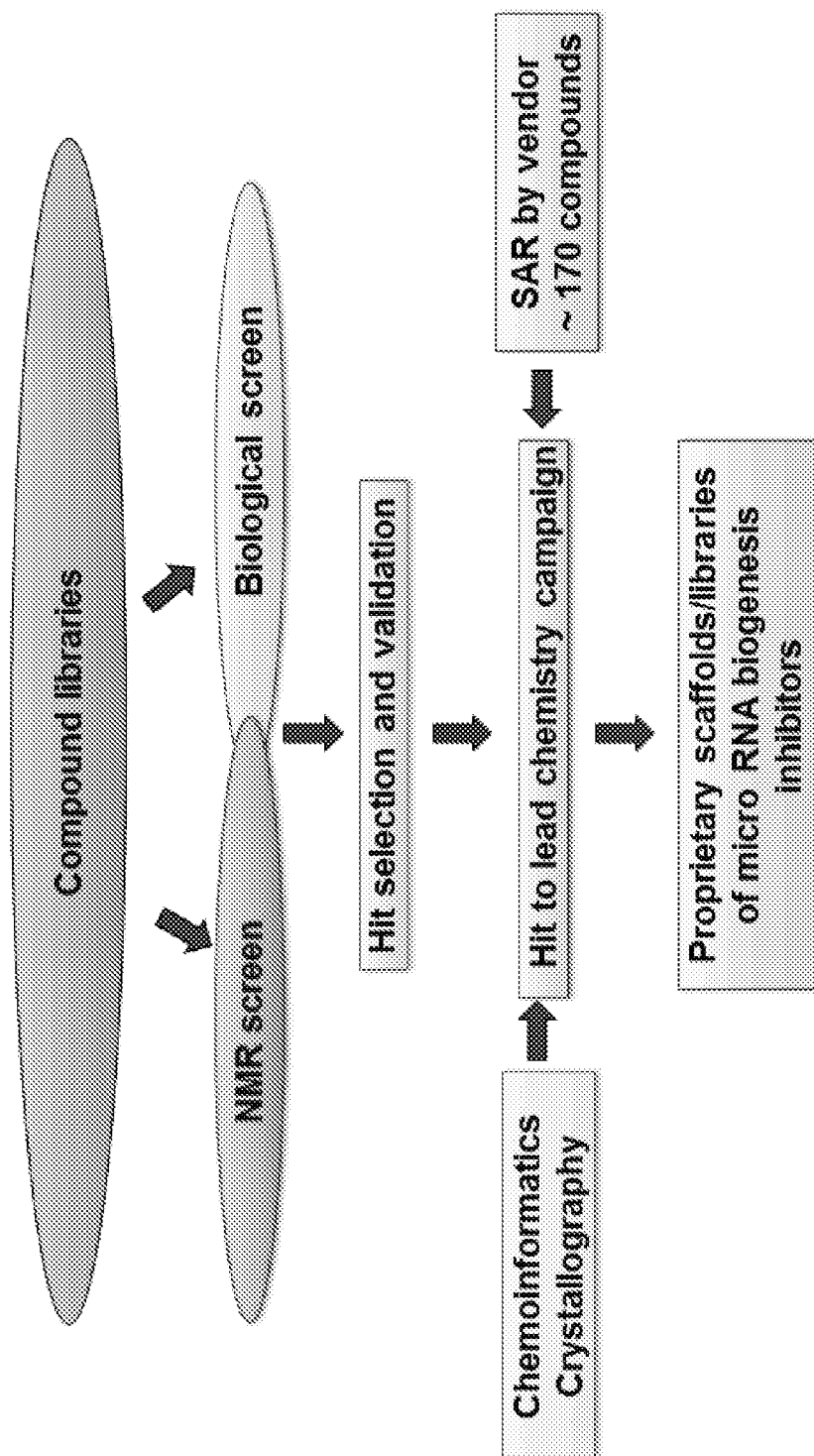
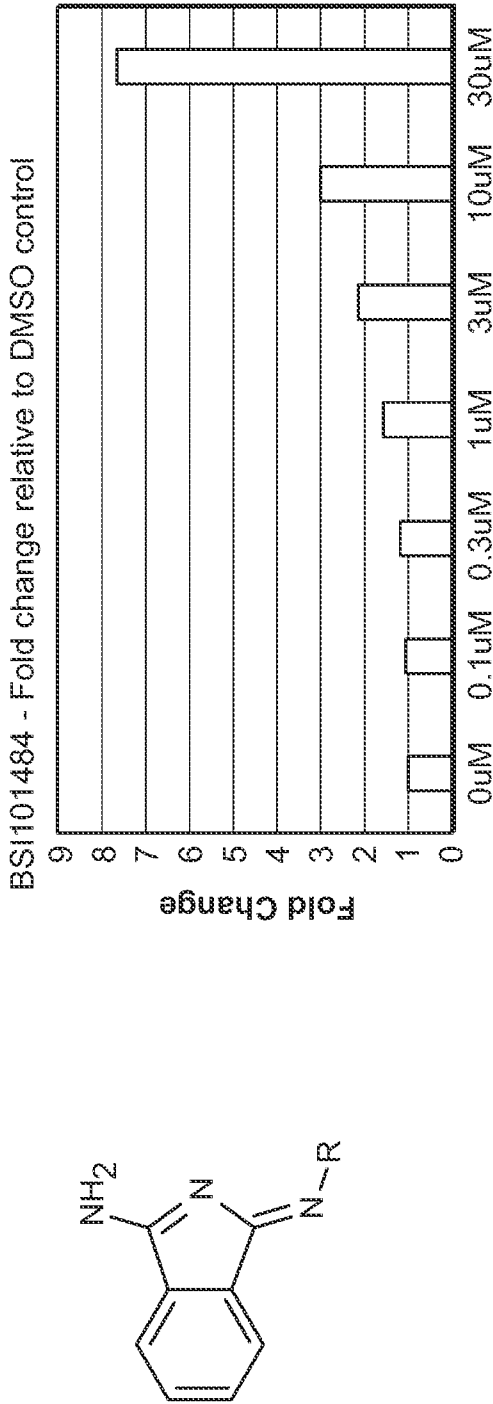


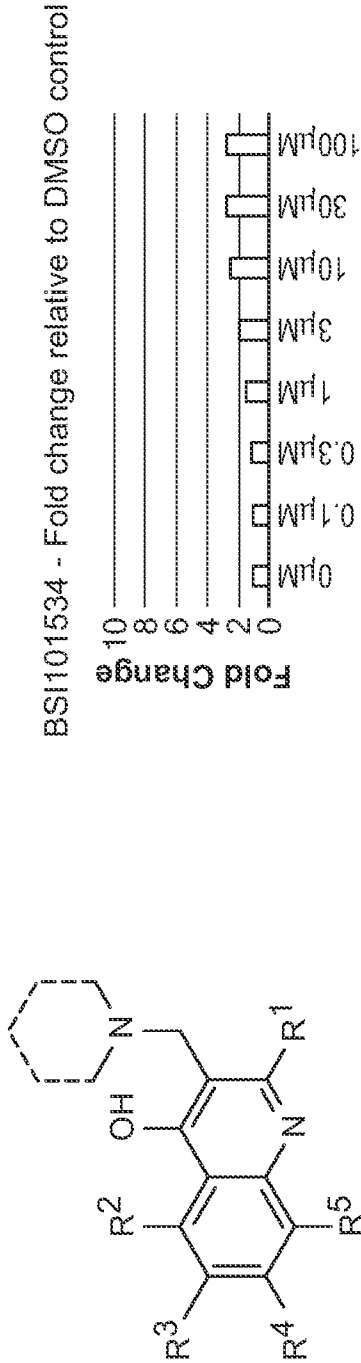
Figure 25A

BSI101484, a singleton identified by screen of 600+ focused library



Compound	R	IC ₅₀ MTT (μM)	IC ₅₀ CTG (μM)	NMR Binding
BSI101484		31.6	29.2	YES
BSI104171*	H	77.33	99.7	YES

Figure 25B



Compound	R ¹	R ²	R ³	R ⁴	R ⁵		IC ₅₀ MTT (μ M)	NMR Binding
BSI101534	Ph	H	-OMe	H	H		5.3	YES
BSI101536	Ph	H	-OMe	H	H		25.04	YES
BSI101473	-CH ₃	-OMe	H	H	-OMe		>200	YES

Figure 26

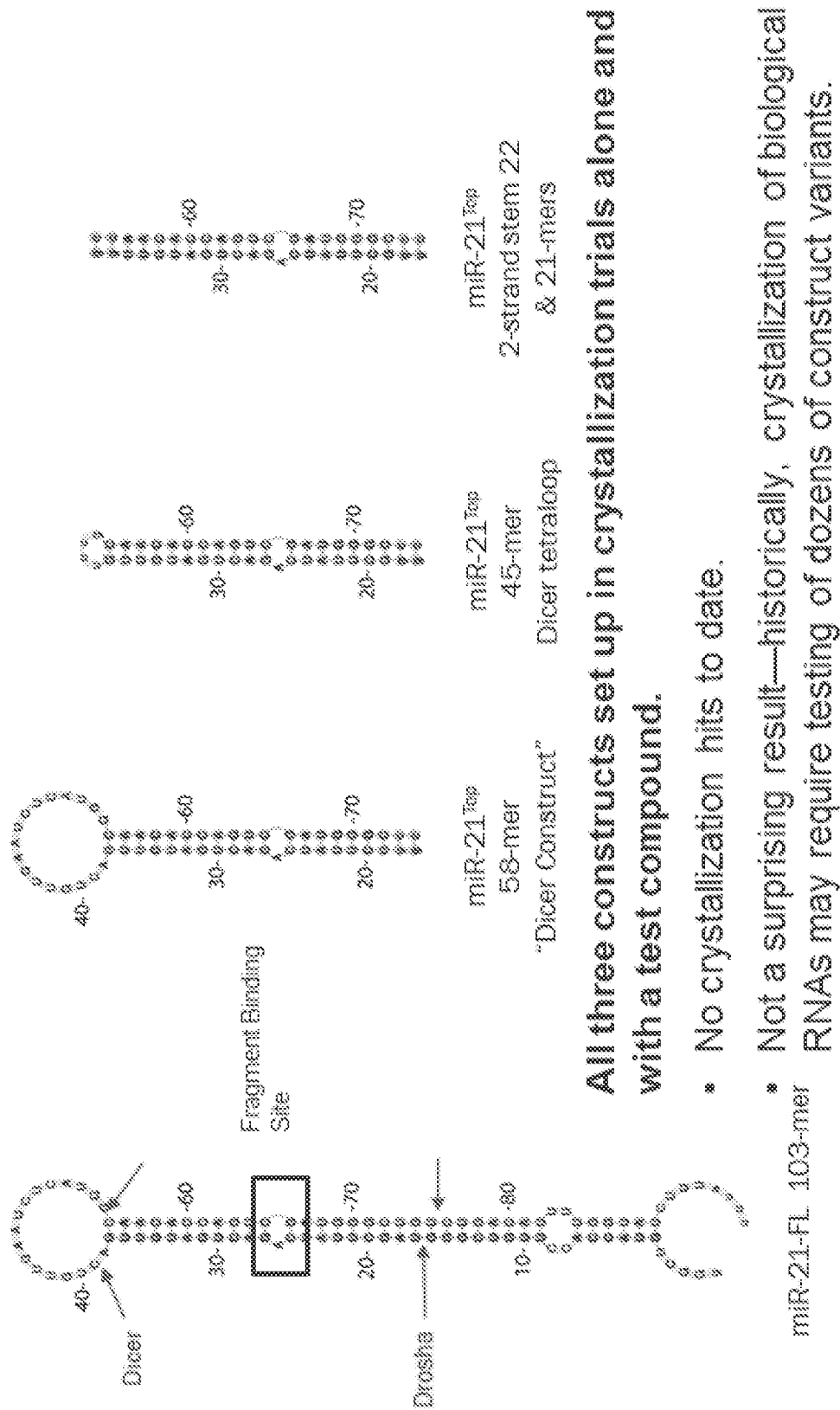


Figure 27A

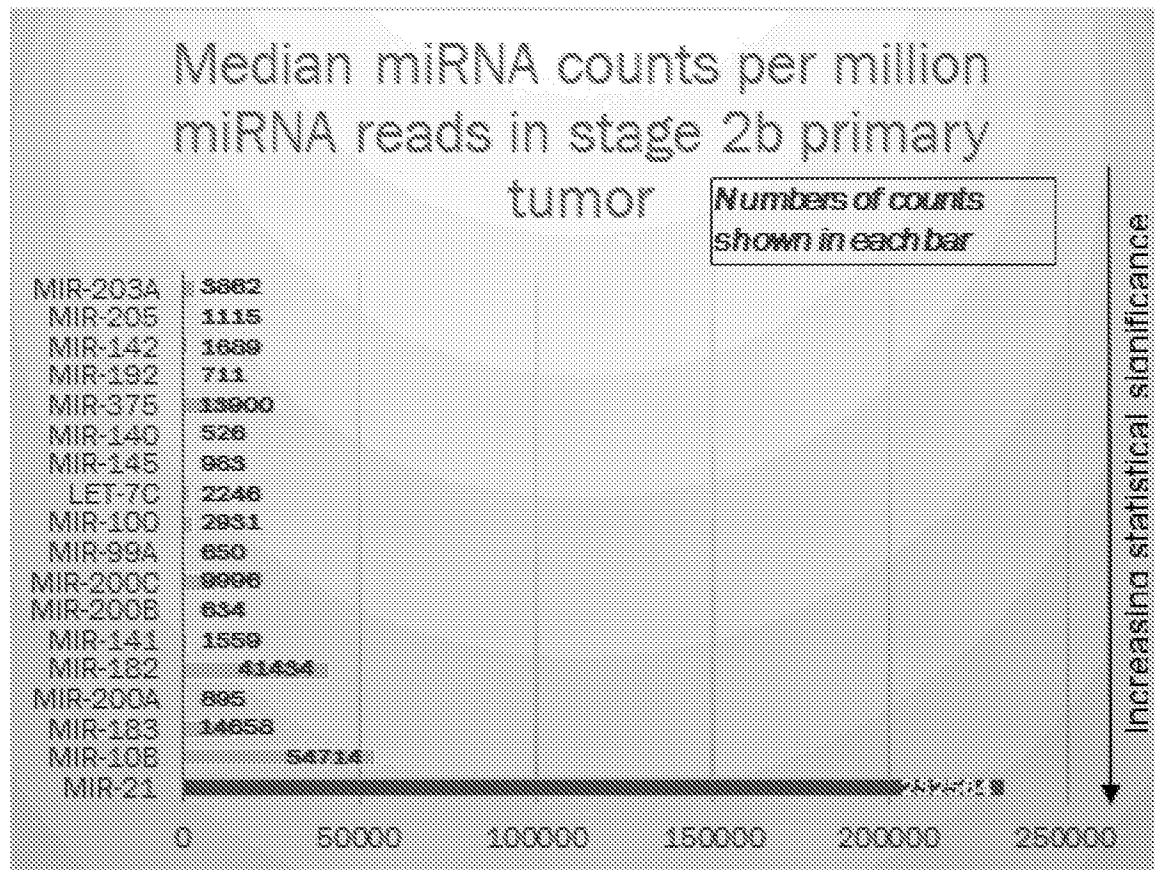


Figure 27B

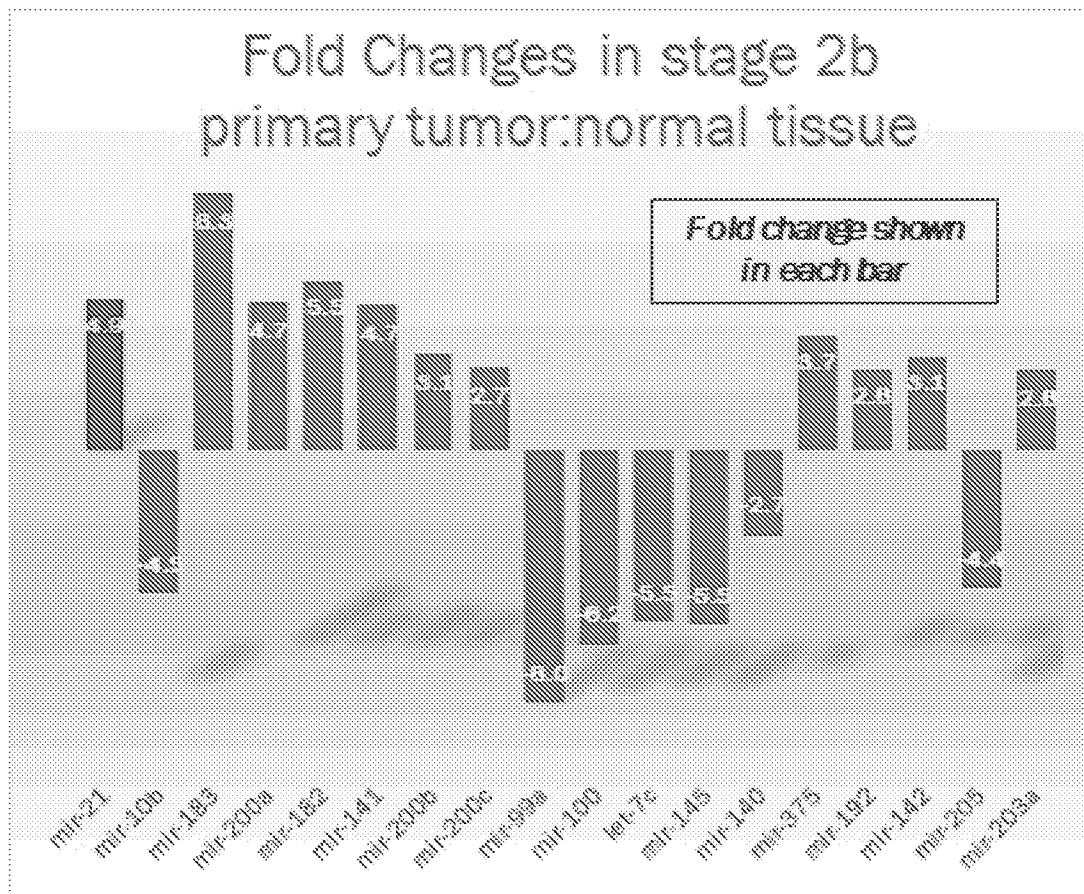


Figure 28

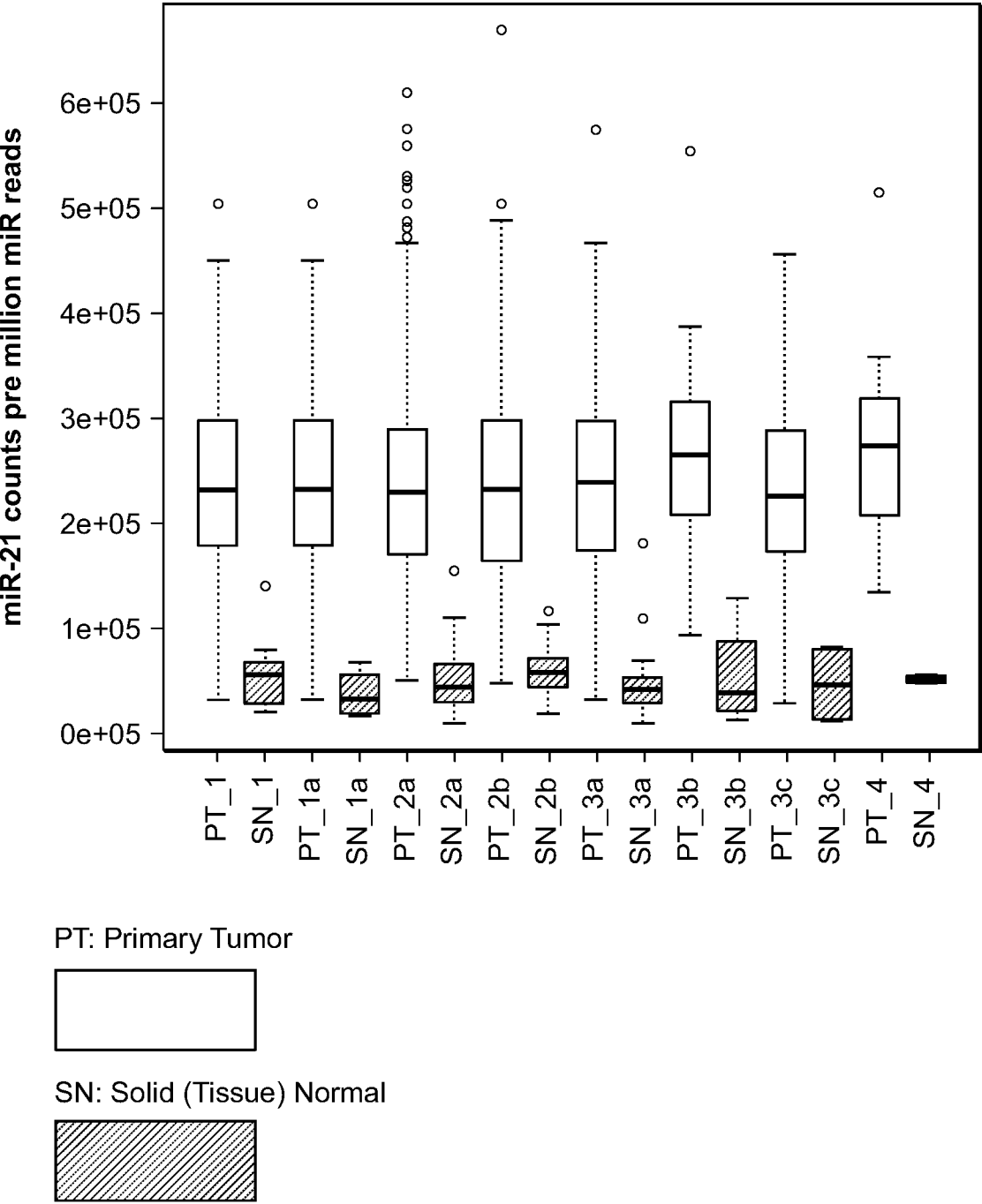


Figure 29

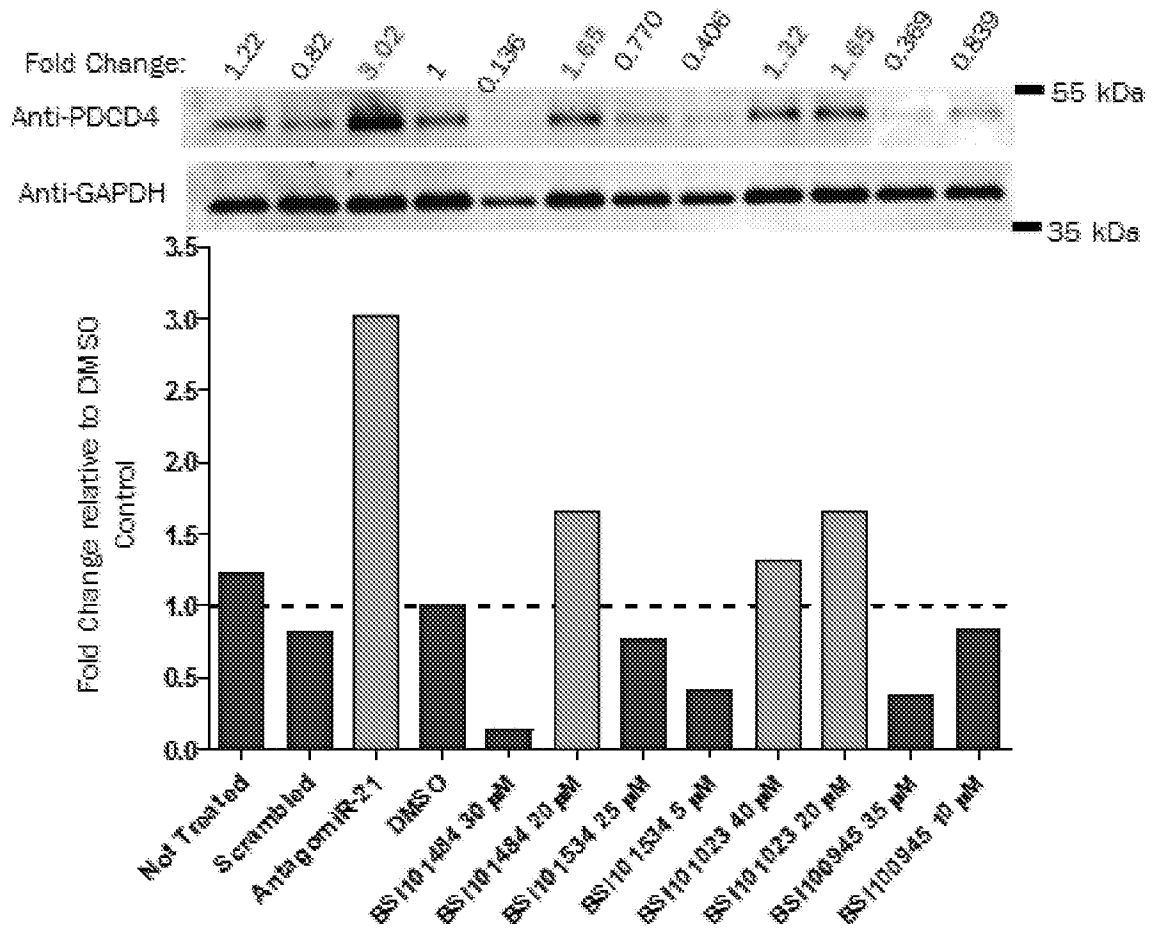


Figure 30

miR-ID	Cancer
hsa-let-7a	Acute Myeloid Leukemia, Breast Cancer, Chondrosarcoma, Colon Cancer, Colorectal Cancer, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Glioma, Nasopharyngeal Carcinoma, Non-Small Cell Lung Cancer, Oral Squamous Cell Carcinoma, Osteosarcoma, Pancreatic Ductal Adenocarcinoma, Renal Cell Carcinoma
hsa-let-7a-3p	Prostate Cancer
hsa-let-7b	Acute Lymphoblastic Leukemia, Breast Cancer, Bronchioloalveolar Carcinoma, Colon Cancer, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Lung Cancer, Malignant Melanoma, Nasopharyngeal Carcinoma, Neuroblastoma, Pancreatic Ductal Adenocarcinoma, Renal Clear Cell Carcinoma
hsa-let-7c	Acute Promyelocytic Leukemia, Acute Myeloid Leukemia, Breast Cancer, Bronchioloalveolar Carcinoma, Nasopharyngeal Carcinoma, Colon Cancer, Esophageal Squamous Cell Carcinoma, Hepatocellular Carcinoma, Lung Cancer, Neuroblastoma, Non-Small Cell Lung Cancer, Pancreatic Ductal Adenocarcinoma, Prostate Cancer, Renal Clear Cell Carcinoma
hsa-let-7d	Breast Cancer, Nasopharyngeal Carcinoma, Bronchioloalveolar Carcinoma, Chronic Myelogenous Leukemia, Colon Cancer, Esophageal Squamous Cell Carcinoma, Head And Neck Squamous Cell Carcinoma, Lung Cancer, Neuroblastoma, Oral Cancer, Oral Squamous Cell Carcinoma, Pancreatic Ductal Adenocarcinoma, Renal Cell Carcinoma
hsa-let-7e	Breast Cancer, Esophageal Squamous Cell Carcinoma, , Bronchioloalveolar Carcinoma, Colon Cancer, Glioblastoma, Lung Cancer, Nasopharyngeal Carcinoma, Neuroblastoma, Pancreatic Ductal Adenocarcinoma, Papillary Thyroid Carcinoma
hsa-let-7f	Glioma, Hepatocellular Carcinoma, Oral Squamous Cell Carcinoma
hsa-let-7g	Breast Cancer, Bronchioloalveolar Carcinoma, Colon Cancer, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Hepatocellular Carcinoma, Lung Cancer, Nasopharyngeal Carcinoma, Neuroblastoma, Pancreatic Ductal Adenocarcinoma
hsa-let-7g-5p	Glioblastoma

Figure 30 – (continued)

hsa-let-7i	Breast Cancer, Bronchioloalveolar Carcinoma, Colon Cancer, Esophageal Squamous Cell Carcinoma, Hepatocellular Carcinoma, Lung Cancer, Nasopharyngeal Carcinoma, Neuroblastoma, Ovarian Cancer, Pancreatic Ductal Adenocarcinoma
hsa-mir-1	Acute Myeloid Leukemia, Bladder Cancer, Breast Cancer, Cervical Cancer, Chordoma, Colorectal Cancer, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Head And Neck Squamous Cell Carcinoma, Hepatocellular Carcinoma, Kidney Cancer, Lung Cancer, Mucinous Cystadenocarcinoma, Nasopharyngeal Carcinoma, Non-Small Cell Lung Cancer, Oral Squamous Cell Carcinoma, Osteosarcoma, Renal Cell Carcinoma
hsa-mir-100	Bladder Cancer, Breast Cancer, Cervical Carcinoma, Chondrosarcoma, Colon Cancer, Colorectal Cancer, Esophageal Cancer, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Glioblastoma, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer, Oral Squamous Cell Carcinoma, Osteosarcoma, Ovarian Cancer, Ovarian Carcinoma, Prostate Cancer, Renal Cell Carcinoma
hsa-mir-100-5p	Esophageal Adenocarcinoma, Gastric Cancer
hsa-mir-101	Bladder Cancer, Breast Cancer, Cervical Cancer, Cervical Carcinoma, Cholangiocarcinoma, Colon Cancer, Colorectal Cancer, Endometrial Cancer, Esophageal Cancer, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Glioblastoma, Glioma, Hepatocellular Carcinoma, Laryngeal Squamous Cell Carcinoma, Liver Cancer, Lung Cancer, Malignant Melanoma, Nasopharyngeal Carcinoma, Non-Small Cell Lung Cancer, Osteosarcoma, Ovarian Cancer, Ovarian Carcinoma, Pancreatic Cancer, Papillary Thyroid Carcinoma, Prostate Cancer, Renal Cell Carcinoma, Renal Clear Cell Carcinoma, Retinoblastoma
hsa-mir-101-3p	Esophageal Squamous Cell Carcinoma, Gastric Cancer
hsa-mir-103	Colorectal Cancer, Gastric Cancer, Hepatocellular Carcinoma, Prostate Cancer
hsa-mir-105	Glioma, Hepatocellular Carcinoma, Prostate Cancer
hsa-mir-106a	Cervical Squamous Cell Carcinoma, Colorectal Cancer, Endometrial Cancer, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Glioblastoma, Glioma, Non-Small Cell Lung Cancer, Ovarian Cancer, Renal Cell Carcinoma
hsa-mir-106a*	Follicular Lymphoma, Renal Cell Carcinoma
hsa-mir-106a-5p	Clear Cell Renal Cell Cancer

Figure 30 – (continued)

hsa-mir-106b	Breast Cancer, Cervical Carcinoma, Colorectal Cancer, Endometrial Cancer, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Glioma, Head And Neck Squamous Cell Carcinoma, Hepatocellular Carcinoma, Laryngeal Carcinoma, Medulloblastoma, Osteosarcoma, Pituitary Carcinoma, Renal Cell Carcinoma, Thyroid Cancer
hsa-mir-106b-5p	Glioma, Renal Cell Carcinoma
hsa-mir-107	Acute Promyelocytic Leukemia, Breast Cancer, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Glioma, Head And Neck Squamous Cell Carcinoma, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer, Prostate Carcinoma
hsa-mir-10a	Breast Cancer, Cervical Cancer, Chronic Myelogenous Leukemia, Colorectal Cancer, Diffuse Large B-Cell Lymphoma, Gastric Cancer, Non-Small Cell Lung Cancer, Pancreatic Cancer
hsa-mir-10a-5p	Renal Cell Carcinoma
hsa-mir-10b	Pancreatic Cancer, Osteosarcoma, Oral Cancer, Non-Small Cell Lung Cancer, Nasopharyngeal Carcinoma, Medulloblastoma, Malignant Melanoma, Lung Cancer, Hepatocellular Carcinoma, Glioma, Glioblastoma, Gastric Cancer, Esophageal Cancer, Endometrial Cancer, Colorectal Cancer, Bladder Cancer, Breast Cancer, Pancreatic Ductal Adenocarcinoma
hsa-mir-10b-5p	Gastric Cancer
hsa-mir-1178	Pancreatic Cancer
hsa-mir-1179	Colorectal Cancer, Esophageal Squamous Cell Carcinoma
hsa-mir-1180	Bladder Cancer, Hepatocellular Carcinoma
hsa-mir-1181	Ovarian Cancer, Pancreatic Cancer
hsa-mir-1202	Glioma
hsa-mir-1207-5p	Breast Cancer, Gastric Cancer, Hepatocellular Carcinoma, Lung Cancer
hsa-mir-122	Bladder Cancer, Breast Cancer, Gallbladder Carcinoma, Gastric Cancer, Glioma, Hepatocellular Carcinoma, Liver Cancer, Osteosarcoma, Pituitary Carcinoma, Renal Cell Carcinoma, Renal Clear Cell Carcinoma
hsa-mir-122*	Hepatocellular Carcinoma
hsa-mir-1225-5p	Gastric Cancer
hsa-mir-1228	Breast Cancer, Gastric Cancer, Hepatocellular Carcinoma
hsa-mir-1228*	Gastric Cancer
hsa-mir-1229	Breast Cancer, Colorectal Cancer
hsa-mir-122a	Gastrointestinal Cancer, Hepatocellular Carcinoma
hsa-mir-1233	Renal Cell Carcinoma
hsa-mir-1236	Bladder Cancer, Hepatocellular Carcinoma, Renal Cell Carcinoma

Figure 30 – (continued)

hsa-mir-1236-3p	Lung Adenocarcinoma
hsa-mir-1238	Non-Small Cell Lung Cancer
hsa-mir-124	Anaplastic Astrocytoma, Bladder Cancer, Breast Cancer, Cervical Cancer, Cervical Squamous Cell Carcinoma, Colorectal Cancer, Esophageal Cancer, Gastric Cancer, Glioblastoma, Glioma, Hepatocellular Carcinoma, Lung Adenocarcinoma, Malignant Melanoma, Medulloblastoma, Nasopharyngeal Carcinoma, Neuroblastoma, Non-Small Cell Lung Cancer, Oral Squamous Cell Carcinoma, Osteosarcoma, Ovarian Cancer, Pancreatic Cancer, Pancreatic Ductal Adenocarcinoma, Prostate Cancer, Retinoblastoma
hsa-mir-124-3p	Astrocytoma, Bladder Cancer, Breast Cancer, Gastric Cancer, Papillary Thyroid Carcinoma
hsa-mir-1244	Lung Carcinoma
hsa-mir-124-5p	Glioma
hsa-mir-1246	Breast Cancer, Cervical Cancer, Colorectal Cancer, Lung Cancer, Non-Small Cell Lung Cancer
hsa-mir-1247	Pancreatic Cancer, Non-Small Cell Lung Cancer, Renal Cell Carcinoma
hsa-mir-1247-5p	Hepatocellular Carcinoma
hsa-mir-124a	Acute Lymphoblastic Leukemia, Epithelial Ovarian Cancer, Glioblastoma, Glioma, Mantle Cell Lymphoma
hsa-mir-1250	Oral Squamous Cell Carcinoma
hsa-mir-1254	Colorectal Cancer
hsa-mir-1258	Breast Cancer, Hepatocellular Carcinoma
hsa-mir-125a	Acute Myeloid Leukemia, Breast Cancer, Cervical Cancer, Colorectal Cancer, Esophageal Squamous Cell Carcinoma, Glioblastoma, Laryngeal Carcinoma, Ovarian Cancer
hsa-mir-125a-3p	Gastric Cancer, Non-Small Cell Lung Cancer
hsa-mir-125a-5p	Breast Cancer, Colon Cancer, Malignant Melanoma, Glioblastoma, Non-Small Cell Lung Cancer, Pancreatic Ductal Adenocarcinoma, Prostate Carcinoma, Retinoblastoma
hsa-mir-125b	Acute Myeloid Leukemia, Anaplastic Thyroid Carcinoma, Bladder Cancer, Breast Cancer, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Colorectal Cancer, Follicular Cancer, Gastric Cancer, Glioblastoma, Glioma, Hepatocellular Carcinoma, Lung Cancer, Malignant Melanoma, Neuroblastoma, Non-Small Cell Lung Cancer, Oral Squamous Cell Carcinoma, Osteosarcoma, Prostate Cancer, Ovarian Cancer, Retinoblastoma
hsa-mir-125b-1-3p	Mesenchymal Cancer
hsa-mir-125b-2*	Colorectal Cancer

Figure 30 – (continued)

hsa-mir-125b-5p	Esophageal Squamous Cell Carcinoma
hsa-mir-126	Bladder Cancer, Breast Cancer, Colon Cancer, Colorectal Cancer, Esophageal Cancer, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Glioblastoma, Glioma, Hepatocellular Carcinoma, Malignant Melanoma, Malignant Mesothelioma, Non-Small Cell Lung Cancer, Oral Squamous Cell Carcinoma, Osteosarcoma, Ovarian Cancer, Pancreatic Ductal Adenocarcinoma, Papillary Thyroid Carcinoma, Renal Cell Carcinoma, Small Cell Lung Cancer, Thyroid Cancer
hsa-mir-126*	Non-Small Cell Lung Cancer
hsa-mir-1260b	Non-Small Cell Lung Cancer, Renal Cell Carcinoma
hsa-mir-126-3p	Thyroid Cancer
hsa-mir-126-5p	Acute Myeloid Leukemia, Cervical Cancer
hsa-mir-1266	Gastric Cancer
hsa-mir-1269	Hepatocellular Carcinoma
hsa-mir-1269a	Colorectal Cancer, Hepatocellular Carcinoma
hsa-mir-1269b	Hepatocellular Carcinoma
hsa-mir-127	Breast Cancer, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Hepatocellular Carcinoma, Lung Cancer, Pancreatic Carcinoma
hsa-mir-1271	Gastric Cancer, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer, Oral Squamous Cell Carcinoma, Ovarian Cancer, Pancreatic Cancer, Prostate Cancer
hsa-mir-127-3p	Glioblastoma, Osteosarcoma
hsa-mir-1274a	Gastric Cancer
hsa-mir-1275	Nasopharyngeal Carcinoma
hsa-mir-127-5p	Hepatocellular Carcinoma
hsa-mir-128	Acute Lymphoblastic Leukemia, Acute Myeloid Leukemia, Colorectal Cancer, Gastric Cancer, Glioblastoma, Glioma, Head And Neck Squamous Cell Carcinoma, Hepatocellular Carcinoma, Lung Cancer, Meningioma, Osteosarcoma, Prostate Cancer
hsa-mir-1280	Bladder Cancer, Colorectal Cancer, Malignant Melanoma, Non-Small Cell Lung Cancer
hsa-mir-128-3p	Hepatocellular Carcinoma
hsa-mir-1284	Gastric Cancer
hsa-mir-1285	Renal Cell Carcinoma
hsa-mir-1288	Esophageal Squamous Cell Carcinoma
hsa-mir-128a	Hepatocellular Carcinoma, Medulloblastoma
hsa-mir-128b	Gastric Cancer
hsa-mir-129	Breast Cancer, Colorectal Cancer, Glioblastoma, Glioma, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer, Prostate Cancer

Figure 30 – (continued)

hsa-mir-1290	Colon Cancer, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Non-Small Cell Lung Cancer, Renal Clear Cell Carcinoma
hsa-mir-1291	Renal Cell Carcinoma
hsa-mir-129-1-3p	Gastric Cancer
hsa-mir-129-2-3p	Gastric Cancer
hsa-mir-129-3p	Gastric Cancer, Renal Cell Carcinoma
hsa-mir-1294	Esophageal Squamous Cell Carcinoma
hsa-mir-1295b-3p	Colorectal Cancer
hsa-mir-129-5p	Chondrosarcoma, Breast Cancer, Gastric Cancer, Glioblastoma, Hepatocellular Carcinoma, Laryngeal Squamous Cell Carcinoma, Lung Cancer, Medullary Thyroid Carcinoma, Ovarian Cancer
hsa-mir-1296	Prostate Cancer
hsa-mir-1296-5p	Gastric Cancer
hsa-mir-1297	Glioma, Liver Cancer, Lung Adenocarcinoma, Prostate Cancer
hsa-mir-1299	Hepatocellular Carcinoma
hsa-mir-1301	Liver Cancer, Prostate Cancer
hsa-mir-1303	Gastric Cancer, Neuroblastoma
hsa-mir-1307	Colorectal Cancer, Prostate Cancer
hsa-mir-130a	Breast Cancer, Chronic Myelogenous Leukemia, Endometrial Cancer, Esophageal Cancer, Gastric Cancer, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer, Osteosarcoma, Prostate Cancer
hsa-mir-130a-3p	Nasopharyngeal Carcinoma
hsa-mir-130b	Colorectal Cancer, Endometrial Cancer, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Glioblastoma, Glioma, Hepatocellular Carcinoma, Lung Cancer, Non-Small Cell Lung Cancer, Neuroblastoma, Osteosarcoma, Ovarian Cancer, Papillary Thyroid Carcinoma, Prostate Cancer
hsa-mir-130b-3p	Bladder Cancer, Breast Carcinoma
hsa-mir-132	Breast Cancer, Colorectal Cancer, Gastric Cancer, Glioma, Hepatocellular Carcinoma, Liver Cancer, Lung Cancer, Non-Small Cell Lung Cancer, Osteosarcoma, Ovarian Cancer, Pancreatic Cancer, Pancreatic Carcinoma
hsa-mir-132-3p	Gastric Cancer
hsa-mir-133a	Pancreatic Cancer, Ovarian Cancer, Osteosarcoma, Non-Small Cell Lung Cancer, Lung Squamous Cell Carcinoma, Hepatocellular Carcinoma, Head And Neck Squamous Cell Carcinoma, Glioma, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Colorectal Cancer, Bladder Cancer, Breast Cancer, Cervical Cancer, Renal Cell Carcinoma
hsa-mir-133a-3p	Esophageal Adenocarcinoma

Figure 30 – (continued)

hsa-mir-133b	Bladder Cancer, Cervical Carcinoma, Colorectal Cancer, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Glioblastoma, Glioma, Hepatocellular Carcinoma, Lung Adenocarcinoma, Lung Cancer, Nasopharyngeal Carcinoma, Non-Small Cell Lung Cancer, Osteosarcoma, Prostate Cancer, Renal Cell Carcinoma
hsa-mir-134	Breast Cancer, Colorectal Cancer, Endometrial Cancer, Gastric Cancer, Glioma, Head And Neck Squamous Cell Carcinoma, Glioma, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer, Osteosarcoma, Renal Cell Carcinoma
hsa-mir-134-5p	Nasopharyngeal Carcinoma
hsa-mir-135a	Bladder Cancer, Breast Cancer, Colorectal Cancer, Gastric Cancer, Hepatocellular Carcinoma, Lung Cancer, Malignant Melanoma, Non-Small Cell Lung Cancer, Pancreatic Ductal Adenocarcinoma, Prostate Cancer, Renal Cell Carcinoma
hsa-mir-135a-3p	Ovarian Cancer
hsa-mir-135a-5p	Clear Cell Renal Cell Cancer, Gastric Cancer
hsa-mir-135b	Cervical Cancer, Colonic Adenocarcinoma, Colorectal Cancer, Gastric Cancer, Glioblastoma, Lung Cancer, Non-Small Cell Lung Cancer, Prostate Cancer
hsa-mir-135b-5p	Gastric Cancer
hsa-mir-136	Chondrosarcoma, Glioblastoma, Glioma, Non-Small Cell Lung Cancer, Oral Squamous Cell Carcinoma
hsa-mir-137	Thyroid Cancer, Squamous Carcinoma, Renal Cell Carcinoma, Papillary Thyroid Carcinoma, Ovarian Cancer, Non-Small Cell Lung Cancer, Osteosarcoma, Neuroblastoma, Multiple Myeloma, Malignant Melanoma, Lung Cancer, Hepatocellular Carcinoma, Glioma, Glioblastoma, Anaplastic Astrocytoma, Astrocytoma, Bladder Cancer, Colorectal Cancer, Gastric Cancer, Uveal Melanoma
hsa-mir-138	Anaplastic Thyroid Carcinoma, Cervical Cancer, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Colorectal Cancer, Esophageal Squamous Cell Carcinoma, Glioblastoma, Head And Neck Squamous Cell Carcinoma, Hepatocellular Carcinoma, Lung Cancer, Malignant Melanoma, Nasopharyngeal Carcinoma, Non-Small Cell Lung Cancer, Oral Squamous Cell Carcinoma, Ovarian Cancer, Osteosarcoma, Papillary Thyroid Carcinoma, Prostate Cancer, Renal Cell Carcinoma, Renal Clear Cell Carcinoma, Small Cell Lung Cancer
hsa-mir-138-5p	Bladder Cancer, Colorectal Cancer, Nasopharyngeal Carcinoma, Oral Squamous Cell Carcinoma, Pancreatic Cancer

Figure 30 – (continued)

hsa-mir-139	Breast Cancer, Colorectal Cancer, Colorectal Carcinoma, Glioma, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer
hsa-mir-139-3p	Colorectal Cancer, Head And Neck Cancer, Laryngeal Cancer
hsa-mir-139-5p	Breast Cancer, Colorectal Cancer, Glioblastoma, Glioma, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer
hsa-mir-140	Non-Small Cell Lung Cancer, Gastric Cancer, Esophageal Cancer, Colorectal Cancer, Breast Cancer, Uveal Melanoma
hsa-mir-140-3p	Chordoma, Lung Cancer, Non-Small Cell Lung Cancer
hsa-mir-140-5p	Colorectal Cancer, Glioma, Hepatocellular Carcinoma, Hypopharyngeal Carcinoma, Hypopharyngeal Squamous Cell Carcinoma, Liver Cancer, Ovarian Cancer
hsa-mir-141	Renal Clear Cell Carcinoma, Renal Cell Carcinoma, Prostate Cancer, Pancreatic Cancer, Ovarian Cancer, Osteosarcoma, Oral Cancer, Non-Small Cell Lung Cancer, Malignant Melanoma, Lung Cancer, Lung Adenocarcinoma, Hepatocellular Carcinoma, Glioma, Gastric Cancer, Esophageal Cancer, Colorectal Cancer, Colon Cancer, Breast Cancer, Bladder Cancer, Thyroid Cancer
hsa-mir-141-3p	Esophageal Squamous Cell Carcinoma, Hepatocellular Carcinoma, Prostate Cancer
hsa-mir-142-3p	Osteosarcoma, Oral Squamous Cell Carcinoma, Non-Small Cell Lung Cancer, Nasopharyngeal Carcinoma, Mantle Cell Lymphoma, Hepatocellular Carcinoma, Glioblastoma, Colorectal Cancer, Colon Cancer, Breast Cancer, Acute Myeloid Leukemia, Acute Lymphoblastic Leukemia, Renal Cell Carcinoma
hsa-mir-142-5p	Mantle Cell Lymphoma, Malt Lymphoma, Lung Cancer, Hepatocellular Carcinoma, Colorectal Cancer, Clear Cell Renal Cell Cancer, Osteosarcoma
hsa-mir-143	Renal Cell Carcinoma, Prostate Cancer, Pancreatic Ductal Adenocarcinoma, Osteosarcoma, Oral Squamous Cell Carcinoma, Oral Cancer, Non-Small Cell Lung Cancer, Nasopharyngeal Carcinoma, Malignant Melanoma, Lung Cancer, Hepatocellular Carcinoma, Glioma, Glioblastoma, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Esophageal Cancer, Endometrial Cancer, Colorectal Carcinoma, Colorectal Cancer, Colon Cancer, Cervical Cancer, Breast Cancer, Bladder Cancer, Retinoblastoma
hsa-mir-143-3p	Esophageal Squamous Cell Carcinoma, Gastric Cancer

Figure 30 – (continued)

hsa-mir-144	Bladder Cancer, Breast Cancer, Cholangiocarcinoma, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Hepatocellular Carcinoma, Laryngeal Squamous Cell Carcinoma, Lung Cancer, Nasopharyngeal Carcinoma, Oral Squamous Cell Carcinoma, Osteosarcoma, Ovarian Cancer, Pancreatic Ductal Adenocarcinoma, Renal Cell Carcinoma, Thyroid Cancer, Uveal Melanoma
hsa-mir-144-3p	Glioma, Gastric Cancer, Renal Cell Carcinoma
hsa-mir-145	Retinoblastoma, Renal Cell Carcinoma, Prostate Cancer, Primary Cns Lymphomas, Pancreatic Ductal Adenocarcinoma, Pancreatic Cancer, Pancreatic Adenocarcinoma, Ovarian Cancer, Osteosarcoma, Oral Squamous Cell Carcinoma, Non-Small Cell Lung Cancer, Neuroblastoma, Nasopharyngeal Carcinoma, Lung Cancer, Lung Adenocarcinoma, Liver Cancer, Kidney Cancer, Intrahepatic Cholangiocarcinoma, Hepatocellular Carcinoma, Glioma, Glioblastoma, Gastric Cancer, Gallbladder Carcinoma, Esophageal Squamous Cell Carcinoma, Esophageal Cancer, Endometrial Cancer, Colorectal Carcinoma, Colorectal Cancer, Colon Cancer, Chondrosarcoma, Cervical Cancer, Breast Cancer, Bladder Cancer, Uveal Melanoma
hsa-mir-145-3p	Non-Small Cell Lung Cancer
hsa-mir-145-5p	Gastric Cancer, Colorectal Cancer, Hepatocellular Carcinoma
hsa-mir-1468-5p	Glioma
hsa-mir-1469	Lung Cancer
hsa-mir-146a	Prostate Cancer, Papillary Thyroid Carcinoma, Pancreatic Cancer, Oral Squamous Cell Carcinoma, Non-Small Cell Lung Cancer, Malignant Melanoma, Lung Cancer, Hepatocellular Carcinoma, Glioma, Gastric Cancer, Follicular Thyroid Carcinoma, Esophageal Squamous Cell Carcinoma, Colorectal Cancer, Colon Cancer, Chronic Myelogenous Leukemia, Breast Cancer, Renal Cell Carcinoma
hsa-mir-146a-5p	Bladder Cancer, Gastric Cancer, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer
hsa-mir-146b	Anaplastic Thyroid Carcinoma, Breast Cancer, Esophageal Cancer, Follicular Thyroid Carcinoma, Glioma, Non-Small Cell Lung Cancer, Malignant Melanoma, Oral Squamous Cell Carcinoma, Papillary Thyroid Carcinoma, Primary Thyroid Lymphoma, Prostate Cancer, Renal Cell Carcinoma
hsa-mir-146b-5p	Gallbladder Carcinoma, Glioblastoma, Glioma, Hepatocellular Carcinoma, Osteosarcoma, Papillary Thyroid Carcinoma

Figure 30 – (continued)

hsa-mir-147	Breast Cancer, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer, Oral Squamous Cell Carcinoma
hsa-mir-148a	Anaplastic Thyroid Carcinoma, Bladder Cancer, Breast Cancer, Cervical Squamous Cell Carcinoma, Chordoma, Colorectal Cancer, Gastric Cancer, Glioblastoma, Gastrointestinal Cancer, Glioma, Hepatocellular Carcinoma, Kidney Cancer, Laryngeal Squamous Cell Carcinoma, Nasopharyngeal Carcinoma, Non-Small Cell Lung Cancer, Oral Squamous Cell Carcinoma, Osteosarcoma, Ovarian Cancer, Pancreatic Cancer, Pancreatic Ductal Adenocarcinoma, Renal Cell Carcinoma
hsa-mir-148a-3p	Bladder Cancer
hsa-mir-148b	Colorectal Cancer, Gastric Cancer, Hepatocellular Carcinoma, Liver Cancer, Lung Cancer, Non-Small Cell Lung Cancer, Ovarian Cancer, Ovarian Carcinoma, Pancreatic Cancer
hsa-mir-148b-3p	Breast Cancer
hsa-mir-149	Breast Cancer, Colorectal Cancer, Gastric Cancer, Glioblastoma, Head And Neck Squamous Cell Carcinoma, Hepatocellular Carcinoma, Nasopharyngeal Carcinoma, Neuroblastoma, Non-Small Cell Lung Cancer
hsa-mir-149-3p	Gastric Cancer
hsa-mir-149-5p	Renal Cell Carcinoma
hsa-mir-150	Adult T-Cell Leukemia, Breast Cancer, Cervical Cancer, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Colorectal Cancer, Cutaneous T-Cell Lymphoma, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Hepatocellular Carcinoma, Intrahepatic Cholangiocarcinoma, Lung Adenocarcinoma, Lung Cancer, Mantle Cell Lymphoma, Non-Small Cell Lung Cancer, Osteosarcoma, Pancreatic Cancer, Pancreatic Ductal Adenocarcinoma, Prostate Cancer
hsa-mir-150*	Colorectal Cancer, Pancreatic Cancer
hsa-mir-150-3p	Esophageal Squamous Cell Carcinoma
hsa-mir-150-5p	Colorectal Cancer, Glioma, Hepatocellular Carcinoma, Pancreatic Cancer
hsa-mir-151	Chronic Myelogenous Leukemia
hsa-mir-151-3p	Osteosarcoma
hsa-mir-151-5p	Gastric Cancer, Papillary Thyroid Carcinoma
hsa-mir-151a-3p	Esophageal Adenocarcinoma
hsa-mir-152	Breast Cancer, Colorectal Cancer, Endometrial Cancer, Gastric Cancer, Gastrointestinal Cancer, Glioblastoma, Glioma, Hepatocellular Carcinoma, Multiple Myeloma, Non-Small Cell Lung Cancer, Osteosarcoma, Ovarian Cancer, Pancreatic Cancer

Figure 30 – (continued)

hsa-mir-152-3p	Hepatocellular Carcinoma
hsa-mir-153	Breast Cancer, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Glioblastoma, Hepatocellular Carcinoma, Laryngeal Squamous Cell Carcinoma, Lung Cancer, Non-Small Cell Lung Cancer, Osteosarcoma, Ovarian Cancer, Prostate Cancer
hsa-mir-153-3p	Malignant Melanoma
hsa-mir-154	Breast Cancer, Colorectal Cancer, Glioma, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer, Osteosarcoma, Prostate Cancer
hsa-mir-154-5p	Prostate Cancer
hsa-mir-155	Acute Myeloid Leukemia, Anaplastic Large-Cell Lymphoma, Bladder Cancer, Breast Cancer, Cervical Cancer, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Clear Cell Renal Cell Cancer, Colon Cancer, Colorectal Cancer, Cutaneous T-Cell Lymphoma, Diffuse Large B-Cell Lymphoma, Endometrial Cancer, Gallbladder Carcinoma, Gastric Cancer, Glioma, Hepatocellular Carcinoma, Laryngeal Squamous Cell Carcinoma, Liver Cancer, Lung Adenocarcinoma, Lung Cancer, Malignant Melanoma, Malt Lymphoma, Mantle Cell Lymphoma, Nasopharyngeal Carcinoma, Non-Small Cell Lung Cancer, Oral Squamous Cell Carcinoma, Ovarian Cancer, Papillary Thyroid Carcinoma, Prostate Cancer, Rectal Cancer, Rectal Carcinoma, Renal Clear Cell Carcinoma, Squamous Carcinoma, Waldenstrom'S Macroglobulinemia
hsa-mir-155-3p	Hepatocellular Carcinoma
hsa-mir-155-5p	Colorectal Carcinoma, Gastric Cancer, Hepatocellular Carcinoma
hsa-mir-15a	Breast Cancer, Cervical Carcinoma, Chronic Lymphocytic Leukemia, Colorectal Cancer, Esophageal Cancer, Gastric Cancer, Glioma, Hepatocellular Carcinoma, Lung Cancer, Neuroblastoma, Non-Small Cell Lung Cancer, Osteosarcoma, Pancreatic Cancer, Pancreatic Ductal Adenocarcinoma, Prostate Cancer, Squamous Carcinoma
hsa-mir-15a-3p	Colorectal Cancer, Gastric Cancer
hsa-mir-15a-5p	Hepatocellular Carcinoma
hsa-mir-15b	Cervical Carcinoma, Chronic Lymphocytic Leukemia, Colorectal Cancer, Glioblastoma, Glioma, Hepatocellular Carcinoma, Lung Cancer, Malignant Melanoma, Neuroblastoma, Non-Small Cell Lung Cancer, Pancreatic Cancer, Tongue Cancer
hsa-mir-15b-5p	Hepatocellular Carcinoma, Non-Small Cell Lung Cancer

Figure 30 – (continued)

hsa-mir-16	Bladder Cancer, Breast Cancer, Cervical Carcinoma, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Colorectal Adenocarcinoma, Colorectal Cancer, Esophageal Squamous Cell Carcinoma, Glioblastoma, Glioma, Head And Neck Squamous Cell Carcinoma, Hepatocellular Carcinoma, Laryngeal Carcinoma, Lung Adenocarcinoma, Nasopharyngeal Carcinoma, Non-Small Cell Lung Cancer, Oral Squamous Cell Carcinoma, Osteosarcoma, Pancreatic Ductal Adenocarcinoma, Papillary Thyroid Carcinoma, Renal Cell Carcinoma, Squamous Carcinoma Chronic Lymphocytic Leukemia, Gastric Cancer
hsa-mir-16-1-3p	Non-Small Cell Lung Cancer
hsa-mir-16-5p	Acute Myeloid Leukemia, B-Cell Lymphoma, Breast Cancer, Breast Carcinoma, Cholangiocarcinoma, Chronic Myelogenous Leukemia, Colorectal Cancer, Colorectal Carcinoma, Esophageal Adenocarcinoma, Gastric Cancer, Glioma, Lung Cancer, Malignant Melanoma, Mantle Cell Lymphoma, Nasopharyngeal Cancer, Medulloblastoma, Osteosarcoma, Ovarian Cancer, T-Cell Lymphoblastic Lymphoma
hsa-mir-17	Breast Cancer, Cervical Cancer, Colorectal Cancer, Gastric Cancer, Hepatocellular Carcinoma, Malignant Melanoma, Nasopharyngeal Carcinoma, Non-Small Cell Lung Cancer, Ovarian Cancer, Pancreatic Cancer, Pituitary Carcinoma
hsa-mir-17-5p	Acute Myeloid Leukemia, Acute Promyelocytic Leukemia, Breast Cancer, Cervical Cancer, Chondrosarcoma, Chronic Lymphocytic Leukemia, Colon Cancer, Colorectal Cancer, Gastric Cancer, Glioblastoma, Glioma, Hepatocellular Carcinoma, Oral Squamous Cell Carcinoma, Osteosarcoma, Pancreatic Cancer
hsa-mir-181a	Gastric Cancer, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer
hsa-mir-181a-5p	Acute Promyelocytic Leukemia, Breast Cancer, Cervical Cancer, Chronic Lymphocytic Leukemia, Gastric Adenocarcinoma, Gastric Cancer, Glioblastoma, Glioma, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer, Oral Squamous Cell Carcinoma, Osteosarcoma, Ovarian Cancer, Prostate Cancer, Retinoblastoma
hsa-mir-181b	Breast Cancer
hsa-mir-181b-3p	Astrocytoma, Squamous Carcinoma
hsa-mir-181b-5p	Gastric Cancer, Glioblastoma, Glioma, Hepatocellular Carcinoma, Neuroblastoma, Non-Small Cell Lung Cancer, Osteosarcoma, Ovarian Cancer, Papillary Thyroid Carcinoma, Pancreatic Cancer, Prostate Cancer
hsa-mir-181c	

Figure 30 – (continued)

hsa-mir-181d	Esophageal Squamous Cell Carcinoma, Glioma, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer, Papillary Thyroid Carcinoma, Prostate Cancer
hsa-mir-182	Bladder Cancer, Breast Cancer, Colorectal Adenocarcinoma, Colorectal Cancer, Colorectal Carcinoma, Endometrial Cancer, Gallbladder Carcinoma, Gastric Adenocarcinoma, Gastric Cancer, Glioma, Head And Neck Squamous Cell Carcinoma, Hepatocellular Carcinoma, Lung Cancer, Malignant Melanoma, Mesenchymal Cancer, Medullary Thyroid Carcinoma, Non-Small Cell Lung Cancer, Osteosarcoma, Ovarian Cancer, Ovarian Carcinoma, Pancreatic Cancer, Papillary Thyroid Carcinoma, Prostate Cancer, Renal Clear Cell Carcinoma, Uveal Melanoma
hsa-mir-182-5p	Bladder Cancer, Breast Cancer, Prostate Cancer, Renal Cell Carcinoma
hsa-mir-1826	Breast Cancer, Colorectal Cancer, Kidney Cancer
hsa-mir-1827	Colorectal Cancer
hsa-mir-183	Astrocytoma, Bladder Cancer, Breast Cancer, Cervical Cancer, Colon Cancer, Colorectal Cancer, Endometrial Cancer, Esophageal Squamous Cell Carcinoma, Esophageal Cancer, Follicular Thyroid Carcinoma, Gastric Cancer, Glioblastoma, Glioma, Hepatocellular Carcinoma, Kidney Cancer, Medullary Thyroid Carcinoma, Nasopharyngeal Carcinoma, Non-Small Cell Lung Cancer, Osteosarcoma, Papillary Thyroid Carcinoma, Prostate Cancer, Renal Cell Carcinoma, Retinoblastoma
hsa-mir-183-3p	Lung Cancer
hsa-mir-183-5p	Breast Cancer, Colorectal Cancer
hsa-mir-184	Glioma, Head And Neck Squamous Cell Carcinoma, Hepatocellular Carcinoma, Malignant Melanoma, Neuroblastoma, Non-Small Cell Lung Cancer, Squamous Carcinoma
hsa-mir-185	Breast Cancer, Chondrosarcoma, Colorectal Cancer, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Glioma, Hepatocellular Carcinoma, Malignant Melanoma, Non-Small Cell Lung Cancer
hsa-mir-185-5p	Cutaneous T-Cell Lymphoma, Gastric Cancer
hsa-mir-186	Bladder Cancer, Cervical Cancer, Colon Carcinoma, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Lung Cancer, Malignant Melanoma, Multiple Myeloma, Non-Small Cell Lung Cancer, Pancreatic Ductal Adenocarcinoma, Prostate Cancer
hsa-mir-186-5p	Colon Cancer
hsa-mir-187	Gastric Cancer, Non-Small Cell Lung Cancer, Oral Squamous Cell Carcinoma, Colorectal Cancer, Prostate Cancer

Figure 30 – (continued)

hsa-mir-187*	Oral Squamous Cell Carcinoma
hsa-mir-187-3p	Hepatocellular Carcinoma
hsa-mir-187-5p	Non-Small Cell Lung Cancer
hsa-mir-188	Nasopharyngeal Carcinoma, Oral Squamous Cell Carcinoma
hsa-mir-188-5p	Hepatocellular Carcinoma, Prostate Cancer
hsa-mir-18a	B-Cell Lymphoma, Bladder Cancer, Breast Cancer, Breast Carcinoma, Cholangiocarcinoma, Chronic Myelogenous Leukemia, Colon Cancer, Esophageal Squamous Cell Carcinoma, Colorectal Cancer, Gastric Cancer, Glioblastoma, Hepatocellular Carcinoma, Lung Cancer, Malignant Melanoma, Mantle Cell Lymphoma, Medulloblastoma, Nasopharyngeal Carcinoma, Neuroblastoma, Non-Small Cell Lung Cancer, Osteosarcoma, Pancreatic Cancer, Pancreatic Ductal Adenocarcinoma, Prostate Cancer Lung Cancer, Non-Small Cell Lung Cancer
hsa-mir-18a-5p	Breast Cancer, Malignant Melanoma
hsa-mir-18b	Gastric Cancer
hsa-mir-190	Non-Small Cell Lung Cancer, Glioblastoma, Osteosarcoma
hsa-mir-1908	Hepatocellular Carcinoma
hsa-mir-190b	Osteosarcoma, Intrahepatic Cholangiocarcinoma, Hepatocellular Carcinoma, Gastric Cancer, Colorectal Carcinoma, Colorectal Cancer, Breast Cancer, Pancreatic Cancer
hsa-mir-191	Lung Cancer, Hepatocellular Carcinoma, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Epithelial Ovarian Cancer, Colorectal Cancer, Colon Cancer, Chronic Lymphocytic Leukemia, Bladder Cancer, Acute Myeloid Leukemia, Acute Lymphoblastic Leukemia, Pancreatic Ductal Adenocarcinoma
hsa-mir-192	Esophageal Squamous Cell Carcinoma
hsa-mir-192-5p	Epithelial Ovarian Cancer, Colon Cancer, Non-Small Cell Lung Cancer
hsa-mir-193a	Non-Small Cell Lung Cancer, Lung Cancer, Esophageal Squamous Cell Carcinoma, Breast Cancer, Renal Cell Carcinoma
hsa-mir-193a-3p	Colorectal Cancer
hsa-mir-193a-5p	Ovarian Cancer, Non-Small Cell Lung Cancer, Malignant Melanoma, Hepatocellular Carcinoma, Glioma, Gastric Cancer, Colorectal Cancer, Cervical Cancer, Breast Cancer, Primary Cns Lymphomas
hsa-mir-193b	Pancreatic Ductal Adenocarcinoma, Ovarian Cancer, Osteosarcoma, Non-Small Cell Lung Cancer, Lung Cancer, Laryngeal Squamous Cell Carcinoma, Hepatocellular Carcinoma, Glioma, Gastric Cancer, Esophageal Squamous Cell
hsa-mir-194	

Figure 30 – (continued)

	Carcinoma, Colorectal Cancer, Bladder Cancer, Prostate Cancer
hsa-mir-194-5p	Bladder Cancer
hsa-mir-195	Prostate Carcinoma, Prostate Cancer, Papillary Thyroid Carcinoma, Osteosarcoma, Non-Small Cell Lung Cancer, Neuroblastoma, Lung Cancer, Hepatocellular Carcinoma, Glioma, Glioblastoma, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Esophageal Cancer, Colorectal Cancer, Chronic Lymphocytic Leukemia, Cervical Cancer, Breast Cancer, Bladder Cancer, Adrenal Cortical Carcinoma, Renal Clear Cell Carcinoma
hsa-mir-195-5p	Hepatocellular Carcinoma, Gastric Cancer, Osteosarcoma
hsa-mir-196a	Pancreatic Ductal Adenocarcinoma, Pancreatic Cancer, Ovarian Carcinoma, Non-Small Cell Lung Cancer, Lung Cancer, Laryngeal Cancer, Hepatocellular Carcinoma, Head And Neck Squamous Cell Carcinoma, Glioblastoma, Gastrointestinal Stromal Tumor, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Esophageal Adenocarcinoma, Colorectal Cancer, Cervical Cancer, Breast Cancer, Squamous Carcinoma
hsa-mir-196a-5p	Gastric Cancer
hsa-mir-196b	Oral Squamous Cell Carcinoma, Oral Cancer, Glioblastoma, Gastric Cancer, Esophageal Cancer, Colorectal Cancer, Pancreatic Cancer
hsa-mir-196b-5p	Papillary Thyroid Carcinoma
hsa-mir-197	Multiple Myeloma, Lung Cancer, Hepatocellular Carcinoma, Glioblastoma, Gastric Cancer, Follicular Thyroid Carcinoma, Esophageal Cancer, Breast Cancer, Uterine Leiomyoma
hsa-mir-1974	Adrenal Cortical Carcinoma
hsa-mir-1976	Non-Small Cell Lung Cancer
hsa-mir-198	Pancreatic Cancer, Osteosarcoma, Lung Cancer, Hepatocellular Carcinoma, Glioma, Colorectal Cancer, Glioblastoma, Breast Cancer, Pancreatic Ductal Adenocarcinoma
hsa-mir-199a	Ovarian Cancer, Non-Small Cell Lung Cancer, Hepatocellular Carcinoma, Kidney Cancer, Gastric Cancer, Colon Cancer, Chondrosarcoma, Primary Cns Lymphomas
hsa-mir-199a-3p	Papillary Thyroid Carcinoma, Osteosarcoma, Kidney Cancer, Hepatocellular Carcinoma, Glioma, Gastric Cancer, Esophageal Adenocarcinoma, Renal Cell Carcinoma

Figure 30 – (continued)

hsa-mir-199a-5p	Non-Small Cell Lung Cancer, Malignant Melanoma, Hepatocellular Carcinoma, Gastric Cancer, Esophageal Cancer, Esophageal Adenocarcinoma, Colorectal Cancer, Bladder Cancer, Osteosarcoma
hsa-mir-199b	Follicular Thyroid Carcinoma, Colorectal Cancer, Choriocarcinoma, Acute Myeloid Leukemia, Hepatocellular Carcinoma, Prostate Cancer
hsa-mir-199b-3p	Esophageal Adenocarcinoma
hsa-mir-199b-5p	Osteosarcoma, Medulloblastoma, Hepatocellular Carcinoma, Colon Cancer, Breast Cancer, Papillary Thyroid Carcinoma
hsa-mir-19a	Osteosarcoma, Non-Small Cell Lung Cancer, Neuroblastoma, Multiple Myeloma, Medulloblastoma, Mantle Cell Lymphoma, Lung Cancer, Laryngeal Squamous Cell Carcinoma, Glioma, Gastric Cancer, Colorectal Cancer, Chronic Myelogenous Leukemia, Cholangiocarcinoma, Cervical Cancer, Breast Carcinoma, Breast Cancer, Bladder Cancer, B-Cell Lymphoma, T-Cell Lymphoblastic Lymphoma
hsa-mir-19a-3p	Colorectal Cancer, Breast Cancer, Multiple Myeloma
hsa-mir-19b	Medulloblastoma, Mantle Cell Lymphoma, Lung Cancer, Hepatocellular Carcinoma, Gastric Cancer, Colorectal Cancer, Chronic Myelogenous Leukemia, Cholangiocarcinoma, Cervical Cancer, Breast Carcinoma, Breast Cancer, B-Cell Lymphoma, Osteosarcoma
hsa-mir-19b-3p	Nasopharyngeal Carcinoma
hsa-mir-200a	Pancreatic Ductal Adenocarcinoma, Pancreatic Cancer, Ovarian Cancer, Oral Cancer, Non-Small Cell Lung Cancer, Neuroblastoma, Nasopharyngeal Carcinoma, Meningioma, Malignant Melanoma, Lung Cancer, Lung Adenocarcinoma, Hepatocellular Carcinoma, Glioma, Gastric Adenocarcinoma, Esophageal Cancer, Esophageal Adenocarcinoma, Colorectal Cancer, Breast Cancer, Bladder Cancer, Renal Cell Carcinoma
hsa-mir-200a-3p	Gastric Cancer, Renal Cell Carcinoma
hsa-mir-200b	Prostate Cancer, Pancreatic Ductal Adenocarcinoma, Ovarian Cancer, Osteosarcoma, Oral Cancer, Non-Small Cell Lung Cancer, Nasopharyngeal Carcinoma, Mucinous Cystadenocarcinoma, Malignant Melanoma, Lung Cancer, Lung Adenocarcinoma, Hepatocellular Carcinoma, Glioma, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Endometrial Cancer, Colorectal Cancer, Colon Cancer, Cholangiocarcinoma, Cervical Carcinoma, Breast Cancer, Bladder Cancer, Astrocytoma, Tongue Cancer

Figure 30 – (continued)

hsa-mir-200b-3p	Oral Squamous Cell Carcinoma, Glioma, Ovarian Cancer
hsa-mir-200c	Rectal Cancer, Pancreatic Ductal Adenocarcinoma, Ovarian Cancer, Oropharyngeal Cancer, Oral Cancer, Non-Small Cell Lung Cancer, Nasopharyngeal Carcinoma, Mucinous Cystadenocarcinoma, Malignant Melanoma, Lung Cancer, Lung Adenocarcinoma, Laryngeal Cancer, Kidney Cancer, Hepatocellular Carcinoma, Head And Neck Squamous Cell Carcinoma, Glioma, Gastric Cancer, Endometrial Cancer, Colorectal Cancer, Colon Cancer, Cholangiocarcinoma, Breast Cancer, Bladder Cancer, Renal Clear Cell Carcinoma
hsa-mir-200c-3p	Gastric Cancer
hsa-mir-202	Lung Cancer, Hepatocellular Carcinoma, Follicular Lymphoma, Esophageal Squamous Cell Carcinoma, Osteosarcoma
hsa-mir-202-3p	Colorectal Carcinoma, Gastric Cancer
hsa-mir-203	Rhabdomyosarcoma, Prostate Cancer, Pancreatic Ductal Adenocarcinoma, Pancreatic Cancer, Pancreatic Adenocarcinoma, Ovarian Cancer, Osteosarcoma, Oral Squamous Cell Carcinoma, Non-Small Cell Lung Cancer, Multiple Myeloma, Malignant Melanoma, Lung Carcinoma, Lung Cancer, Lung Adenocarcinoma, Laryngeal Squamous Cell Carcinoma, Kidney Cancer, Hypopharyngeal Cancer, Hepatocellular Carcinoma, Head And Neck Squamous Cell Carcinoma, Glioma, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Esophageal Cancer, Esophageal Adenocarcinoma, Colorectal Cancer, Cervical Cancer, Breast Cancer, Bladder Cancer, Basal Cell Carcinoma, Squamous Carcinoma
hsa-mir-203a	Hepatocellular Carcinoma, Esophageal Cancer, Renal Cell Carcinoma
hsa-mir-203a-3p	Nasopharyngeal Carcinoma
hsa-mir-204	Retinoblastoma, Renal Clear Cell Carcinoma, Renal Cell Carcinoma, Prostate Cancer, Osteosarcoma, Non-Small Cell Lung Cancer, Nasopharyngeal Carcinoma, Malignant Melanoma, Lung Carcinoma, Intrahepatic Cholangiocarcinoma, Glioma, Gastric Cancer, Esophageal Cancer, Colon Cancer, Breast Cancer, Thyroid Cancer
hsa-mir-204-3p	Glioma, Hepatocellular Carcinoma
hsa-mir-204-5p	Papillary Thyroid Carcinoma, Malignant Melanoma, Hepatocellular Carcinoma, Gastric Cancer, Colorectal Cancer, Breast Cancer, Prostate Cancer

Figure 30 – (continued)

hsa-mir-205	Renal Cell Carcinoma, Prostate Cancer, Pancreatic Cancer, Ovarian Cancer, Osteosarcoma, Non-Small Cell Lung Cancer, Malignant Melanoma, Lung Cancer, Laryngeal Squamous Cell Carcinoma, Laryngeal Carcinoma, Kidney Cancer, Hepatocellular Carcinoma, Head And Neck Squamous Cell Carcinoma, Glioma, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Esophageal Cancer, Endometrial Cancer, Colorectal Cancer, Chronic Myelogenous Leukemia, Cervical Squamous Cell Carcinoma, Cervical Cancer, Breast Cancer, Bladder Cancer, Adrenal Cortical Carcinoma, Thyroid Cancer
hsa-mir-205-3p	Non-Small Cell Lung Cancer
hsa-mir-205-5p	Non-Small Cell Lung Cancer
hsa-mir-206	Ovarian Cancer, Oral Squamous Cell Carcinoma, Non-Small Cell Lung Cancer, Medulloblastoma, Malignant Melanoma, Lung Cancer, Lung Adenocarcinoma, Laryngeal Squamous Cell Carcinoma, Hepatocellular Carcinoma, Head And Neck Squamous Cell Carcinoma, Glioblastoma, Gastric Cancer, Colorectal Cancer, Clear Cell Renal Cell Cancer, Cervical Cancer, Breast Cancer, Bladder Cancer, Rhabdomyosarcoma
hsa-mir-208	Esophageal Squamous Cell Carcinoma
hsa-mir-208a	Lung Cancer
hsa-mir-208a-3p	Gastric Cancer
hsa-mir-208b	Osteosarcoma
hsa-mir-20a	Pituitary Carcinoma, Ovarian Cancer, Osteosarcoma, Oral Squamous Cell Carcinoma, Nasopharyngeal Cancer, Medulloblastoma, Mantle Cell Lymphoma, Malignant Melanoma, Lung Cancer, Hepatocellular Carcinoma, Glioma, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Colorectal Cancer, Chronic Myelogenous Leukemia, Cholangiocarcinoma, Cervical Cancer, Breast Carcinoma, Breast Cancer, B-Cell Lymphoma, Acute Myeloid Leukemia, Prostate Cancer
hsa-mir-20a-3p	Gastric Cancer
hsa-mir-20a-5p	Colorectal Cancer, Non-Small Cell Lung Cancer
hsa-mir-20b	Gastric Cancer, Esophageal Cancer, Breast Cancer, Bladder Cancer, Hepatocellular Carcinoma
hsa-mir-20b-5p	Esophageal Squamous Cell Carcinoma, Renal Cell Carcinoma

Figure 30 – (continued)

hsa-mir-21	Retinoblastoma, Renal Cell Carcinoma, Prostate Cancer, Papillary Thyroid Carcinoma, Pancreatic Ductal Adenocarcinoma, Pancreatic Cancer, Pancreatic Adenocarcinoma, Ovarian Cancer, Osteosarcoma, Oropharyngeal Cancer, Oral Squamous Cell Carcinoma, Oral Carcinoma, Oral Cancer, Non-Small Cell Lung Cancer, Neuroblastoma, Nasopharyngeal Carcinoma, Multiple Myeloma, Mucinous Cystadenocarcinoma, Malignant Melanoma, Lung Cancer, Liver Cancer, Laryngeal Squamous Cell Carcinoma, Laryngeal Carcinoma, Laryngeal Cancer, Kidney Cancer, Hypopharyngeal Squamous Cell Carcinoma, Hepatocellular Carcinoma, Hepatoblastoma, Head And Neck Squamous Cell Carcinoma, Head And Neck Cancer, Glioma, Glioblastoma, Gastrointestinal Stromal Tumor, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Esophageal Cancer, Endometrial Cancer, Diffuse Large B-Cell Lymphoma, Colorectal Carcinoma, Colorectal Cancer, Colon Cancer, Chronic Myelogenous Leukemia, Cholangiocarcinoma, Cervical Carcinoma, Cervical Cancer, Breast Cancer, B-Cell Lymphoma, Adrenal Cortical Carcinoma, Squamous Carcinoma
hsa-mir-210	Renal Cell Carcinoma, Ovarian Cancer, Osteosarcoma, Non-Small Cell Lung Cancer, Medulloblastoma, Malignant Melanoma, Lung Cancer, Kidney Cancer, Hepatocellular Carcinoma, Glioma, Glioblastoma, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Esophageal Cancer, Colorectal Cancer, Breast Cancer, Bladder Cancer, Adrenal Cortical Carcinoma, Renal Clear Cell Carcinoma
hsa-mir-210-3p	Glioblastoma, Renal Clear Cell Carcinoma
hsa-mir-211	Malignant Melanoma, Hepatocellular Carcinoma, Glioma, Glioblastoma, Gastric Cancer, Colorectal Cancer, Colon Cancer, Breast Cancer, Non-Small Cell Lung Cancer
hsa-mir-211-5p	Hepatocellular Carcinoma, Kidney Cancer
hsa-mir-212	Pancreatic Ductal Adenocarcinoma, Pancreatic Cancer, Ovarian Cancer, Osteosarcoma, Non-Small Cell Lung Cancer, Nasopharyngeal Carcinoma, Hepatocellular Carcinoma, Gastric Cancer, Colorectal Cancer, Cervical Cancer, Breast Cancer, Prostate Cancer
hsa-mir-212-3p	Glioblastoma
hsa-mir-21-3p	Oral Cancer, Laryngeal Cancer, Hepatocellular Carcinoma, Oral Squamous Cell Carcinoma

Figure 30 – (continued)

hsa-mir-214	Primary Cns Lymphomas, Pancreatic Cancer, Ovarian Cancer, Osteosarcoma, Oral Cancer, Nasopharyngeal Carcinoma, Multiple Myeloma, Malignant Melanoma, Lung Cancer, Lung Adenocarcinoma, Hepatocellular Carcinoma, Glioma, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Esophageal Cancer, Colorectal Cancer, Colon Cancer, Cervical Squamous Cell Carcinoma, Cervical Cancer, Breast Cancer, Bladder Cancer, Renal Cell Carcinoma
hsa-mir-214-3p	Esophageal Cancer, Breast Cancer, Hepatocellular Carcinoma
hsa-mir-215	Non-Small Cell Lung Cancer, Hepatocellular Carcinoma, Glioma, Gastric Cancer, Colorectal Cancer, Colon Cancer, Cervical Cancer, Pancreatic Cancer
hsa-mir-21-5p	Rectal Cancer, Hepatocellular Carcinoma, Colorectal Cancer, Clear Cell Renal Cell Cancer, Squamous Carcinoma
hsa-mir-216a	Oral Squamous Cell Carcinoma, Hepatocellular Carcinoma, Glioma, Esophageal Squamous Cell Carcinoma, Colorectal Cancer, Pancreatic Cancer
hsa-mir-216a-3p	Colorectal Cancer
hsa-mir-216b	Nasopharyngeal Carcinoma, Malignant Melanoma, Hepatocellular Carcinoma, Gastric Cancer, Gastric Adenocarcinoma, Esophageal Squamous Cell Carcinoma, Breast Cancer, Ovarian Cancer
hsa-mir-216b-5p	Pancreatic Cancer
hsa-mir-217	Pancreatic Ductal Adenocarcinoma, Osteosarcoma, Lung Cancer, Hepatocellular Carcinoma, Glioma, Glioblastoma, Gastric Cancer, Colorectal Cancer, Breast Cancer, Renal Cell Carcinoma
hsa-mir-218	Renal Cell Carcinoma, Prostate Cancer, Pancreatic Ductal Adenocarcinoma, Osteosarcoma, Oral Cancer, Nasopharyngeal Cancer, Malignant Melanoma, Lung Squamous Cell Carcinoma, Lung Cancer, Hepatocellular Carcinoma, Head And Neck Squamous Cell Carcinoma, Glioma, Gastrointestinal Stromal Tumor, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Esophageal Cancer, Colorectal Cancer, Choriocarcinoma, Chondrosarcoma, Cervical Squamous Cell Carcinoma, Cervical Cancer, Breast Cancer, Bladder Cancer, Renal Clear Cell Carcinoma
hsa-mir-218-5p	Glioma, Gallbladder Carcinoma, Non-Small Cell Lung Cancer
hsa-mir-219	Non-Small Cell Lung Cancer
hsa-mir-219-5p	Hepatocellular Carcinoma, Glioma, Glioblastoma, Colorectal Cancer, Chordoma, Papillary Thyroid Carcinoma

Figure 30 – (continued)

hsa-mir-22	Renal Clear Cell Carcinoma, Prostate Cancer, Osteosarcoma, Non-Small Cell Lung Cancer, Medulloblastoma, Malignant Melanoma, Lung Cancer, Liver Cancer, Kidney Cancer, Hepatocellular Carcinoma, Glioblastoma, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Colorectal Cancer, Colon Cancer, Cervical Cancer, Breast Cancer, T-Cell Lymphoma
hsa-mir-220a	Oral Squamous Cell Carcinoma
hsa-mir-221	Squamous Carcinoma, Renal Cell Carcinoma, Prostate Cancer, Papillary Thyroid Carcinoma, Pancreatic Cancer, Pancreatic Adenocarcinoma, Ovarian Cancer, Osteosarcoma, Oral Squamous Cell Carcinoma, Non-Small Cell Lung Cancer, Neuroblastoma, Malignant Melanoma, Liver Cancer, Laryngeal Squamous Cell Carcinoma, Hepatocellular Carcinoma, Glioma, Glioblastoma, Gastrointestinal Stromal Tumor, Gastric Cancer, Follicular Thyroid Carcinoma, Extrahepatic Cholangiocarcinoma, Esophageal Cancer, Colorectal Cancer, Colon Carcinoma, Cervical Cancer, Breast Cancer, Bladder Cancer, Anaplastic Thyroid Carcinoma, Thyroid Carcinoma
hsa-mir-221-3p	Hepatocellular Carcinoma, Pancreatic Cancer
hsa-mir-222	Prostate Cancer, Papillary Thyroid Carcinoma, Pancreatic Cancer, Oral Squamous Cell Carcinoma, Non-Small Cell Lung Cancer, Malignant Melanoma, Hepatocellular Carcinoma, Glioma, Glioblastoma, Gastrointestinal Stromal Tumor, Gastric Cancer, Chordoma, Chondrosarcoma, Breast Cancer, Bladder Cancer, Anaplastic Thyroid Carcinoma, Adenoid Cystic Carcinoma, Thyroid Carcinoma
hsa-mir-222-3p	Endometrial Cancer
hsa-mir-223	Prostate Cancer, Pancreatic Ductal Adenocarcinoma, Osteosarcoma, Oral Squamous Cell Carcinoma, Oral Cancer, Nasopharyngeal Carcinoma, Nasopharyngeal Cancer, Mucinous Cystadenocarcinoma, Mantle Cell Lymphoma, Lung Cancer, Kidney Cancer, Hepatocellular Carcinoma, Glioblastoma, Gastric Cancer, Gallbladder Carcinoma, Esophageal Squamous Cell Carcinoma, Esophageal Cancer, Esophageal Adenocarcinoma, Endometrial Cancer, Colorectal Cancer, Chronic Myelogenous Leukemia, Chronic Lymphocytic Leukemia, Cervical Cancer, Breast Cancer, Acute Myeloid Leukemia, Splenic Marginal Zone Lymphoma
hsa-mir-223-3p	Esophageal Squamous Cell Carcinoma, Bladder Cancer, Prostate Cancer
hsa-mir-22-3p	Hepatocellular Carcinoma

Figure 30 – (continued)

hsa-mir-224	Prostate Cancer, Ovarian Cancer, Osteosarcoma, Non-Small Cell Lung Cancer, Meningioma, Hepatocellular Carcinoma, Glioma, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Colorectal Cancer, Cervical Cancer, Breast Cancer, Renal Clear Cell Carcinoma
hsa-mir-224-3p	Cervical Cancer
hsa-mir-224-5p	Hepatocellular Carcinoma, Ovarian Cancer
hsa-mir-2278	Chronic Myelogenous Leukemia
hsa-mir-2392	Gastric Cancer
hsa-mir-23a	Osteosarcoma, Non-Small Cell Lung Cancer, Neuroblastoma, Laryngeal Carcinoma, Laryngeal Cancer, Hepatocellular Carcinoma, Glioma, Gastric Cancer, Gastric Adenocarcinoma, Colorectal Cancer, Colon Carcinoma, Breast Cancer, Prostate Cancer
hsa-mir-23b	Prostate Cancer, Ovarian Cancer, Oral Squamous Cell Carcinoma, Nasopharyngeal Carcinoma, Hepatocellular Carcinoma, Glioma, Gastric Cancer, Colorectal Cancer, Chondrosarcoma, Cervical Cancer, Bladder Cancer, Renal Cell Carcinoma
hsa-mir-23b-5p	Acute Myeloid Leukemia
hsa-mir-24	Osteosarcoma, Oral Squamous Cell Carcinoma, Non-Small Cell Lung Cancer, Nasopharyngeal Carcinoma, Lung Cancer, Laryngeal Squamous Cell Carcinoma, Hepatocellular Carcinoma, Glioma, Gastric Cancer, Colorectal Cancer, Breast Carcinoma, Breast Cancer, Bladder Cancer, Prostate Cancer
hsa-mir-24-2-5p	Breast Cancer
hsa-mir-24-3p	Hepatocellular Carcinoma, Glioma, Colorectal Cancer, Breast Cancer, Bladder Cancer, Hodgkin'S Lymphoma
hsa-mir-25	Prostate Cancer, Ovarian Cancer, Non-Small Cell Lung Cancer, Malignant Melanoma, Hepatocellular Carcinoma, Head And Neck Squamous Cell Carcinoma, Glioma, Glioblastoma, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Endometrial Cancer, Colorectal Cancer, Colon Cancer, Cervical Carcinoma, Astrocytoma, Small Cell Lung Cancer
hsa-mir-25-3p	Osteosarcoma
hsa-mir-26a	Prostate Cancer, Primary Thyroid Lymphoma, Papillary Thyroid Carcinoma, Ovarian Cancer, Osteosarcoma, Oral Squamous Cell Carcinoma, Malignant Melanoma, Lung Cancer, Hepatocellular Carcinoma, Glioma, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Colon Cancer, Chronic Myelogenous Leukemia, Cholangiocarcinoma, Breast Cancer, Bladder

Figure 30 – (continued)

	Cancer, Acute Myeloid Leukemia, Renal Cell Carcinoma
hsa-mir-26a-5p	Hepatocellular Carcinoma, Colorectal Cancer, Bladder Cancer, Prostate Cancer
hsa-mir-26b	Renal Cell Carcinoma, prostate Cancer, Osteosarcoma, Oral Squamous Cell Carcinoma, Non-Small Cell Lung Cancer, Nasopharyngeal Carcinoma, Malignant Melanoma, Lung Cancer, Hepatocellular Carcinoma, Glioma, Glioblastoma, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Colorectal Cancer, Breast Cancer, B-Cell Lymphoma, Gastric Cancer, Bladder Cancer, Hepatocellular Carcinoma
hsa-mir-26b-5p	
hsa-mir-27a	Squamous Carcinoma, small Cell Lung Cancer, Renal Cell Carcinoma, Prostate Cancer, Pancreatic Cancer, Ovarian Cancer, Osteosarcoma, Non-Small Cell Lung Cancer, Lung Cancer, Liver Cancer, Laryngeal Carcinoma, Hepatocellular Carcinoma, Glioma, Gastric Cancer, Gastric Adenocarcinoma, Esophageal Squamous Cell Carcinoma, Esophageal Cancer, Colorectal Cancer, Chronic Myelogenous Leukemia, Cervical Cancer, Breast Cancer, Acute Myeloid Leukemia, Acute Leukemia, Head And Neck Squamous Cell Carcinoma
hsa-mir-27a*	
hsa-mir-27a-3p	Oral Squamous Cell Carcinoma, nasopharyngeal Carcinoma, Hepatocellular Carcinoma, Glioma, Gastric Cancer, Esophageal Squamous Cell Carcinoma,
hsa-mir-27b	Ovarian Cancer, oral Squamous Cell Carcinoma, Non-Small Cell Lung Cancer, Hepatocellular Carcinoma, Glioma, Gastric Cancer, Cervical Carcinoma, Cervical Cancer, Acute Myeloid Leukemia,
hsa-mir-27b-3p	Breast Cancer, Gastric Cancer
hsa-mir-28-3p	Esophageal Squamous Cell Carcinoma, esophageal Cancer, Colorectal Cancer,
hsa-mir-28-5p	Renal Cell Carcinoma, ovarian Cancer, Hepatocellular Carcinoma, Colorectal Cancer,
hsa-mir-2861	Cervical Cancer
hsa-mir-296	Hepatocellular Carcinoma, colorectal Cancer,
hsa-mir-296-5p	Glioblastoma, gastric Cancer, Esophageal Squamous Cell Carcinoma,
hsa-mir-297	Lung Adenocarcinoma
hsa-mir-299-3p	Colon Carcinoma

Figure 30 – (continued)

hsa-mir-29a	Papillary Thyroid Carcinomapancreatic Cancer, Oral Squamous Cell Carcinoma, Non-Small Cell Lung Cancer, Neuroblastoma, Monocytic Leukemia, Mesenchymal Cancer, Mantle Cell Lymphoma, Lung Cancer, Hepatocellular Carcinoma, Head And Neck Squamous Cell Carcinoma, Gastric Cancer, Colorectal Cancer, Cholangiocarcinoma, Cervical Squamous Cell Carcinoma, Breast Cancer, Acute Myeloid Leukemia,
hsa-mir-29a-3p	Gastric Cancer
hsa-mir-29b	Prostate Cancerovarian Cancer, Osteosarcoma, Oral Squamous Cell Carcinoma, Non-Small Cell Lung Cancer, Monocytic Leukemia, Mantle Cell Lymphoma, Lung Adenocarcinoma, Glioma, Glioblastoma, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Endometrial Cancer, Colorectal Cancer, Chronic Lymphocytic Leukemia, Acute Myeloid Leukemia, Mesenchymal Cancer
hsa-mir-29b-1-5p	
hsa-mir-29c	Pancreatic Cancernon-Small Cell Lung Cancer, Nasopharyngeal Carcinoma, Nasopharyngeal Cancer, Mesenchymal Cancer, Mantle Cell Lymphoma, Lung Cancer, Lung Adenocarcinoma, Hepatocellular Carcinoma, Head And Neck Squamous Cell Carcinoma, Glioma, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Breast Cancer, Bladder Cancer, Colon Cancer
hsa-mir-29c-3p	
hsa-mir-29c-5p	Gallbladder Carcinoma
hsa-mir-300	Osteosarcomanon-Small Cell Lung Cancer, Laryngeal Squamous Cell Carcinoma, Head And Neck Squamous Cell Carcinoma, Glioblastoma, Breast Cancer,
hsa-mir-301a	Prostate Cancerepancreatic Cancer, Pancreatic Adenocarcinoma, Non-Small Cell Lung Cancer, Multiple Myeloma, Hepatocellular Carcinoma, Gastric Cancer, Endometrial Cancer, Colorectal Cancer,
hsa-mir-301a-3p	Pancreatic Cancerylaryngeal Squamous Cell Carcinoma,
hsa-mir-301b	Prostate Cancerepancreatic Carcinoma, Non-Small Cell Lung Cancer, Lung Cancer, Gastric Cancer, Endometrial Cancer,
hsa-mir-302a	Prostate Cancerecolon Cancer,
hsa-mir-302b	Lung Cancerehepatocellular Carcinoma, Glioblastoma, Gastric Cancer, Gastric Adenocarcinoma, Esophageal Squamous Cell Carcinoma, Esophageal Cancer,
hsa-mir-302b-3p	Gastric Cancer
hsa-mir-302c	Hepatocellular Carcinoma
hsa-mir-302c-3p	Renal Cell Carcinoma
hsa-mir-302d	Glioblastoma

Figure 30 – (continued)

hsa-mir-30a	Renal Cell Carcinomaprostate Cancer, Ovarian Carcinoma, Non-Small Cell Lung Cancer, Lung Adenocarcinoma, Hepatocellular Carcinoma, Gastric Cancer, Colorectal Carcinoma, Colorectal Cancer, Chondrosarcoma, Breast Cancer, Hepatocellular Carcinomacolorectal Cancer,
hsa-mir-30a-3p	Non-Small Cell Lung Cancerliver Cancer, Hepatocellular Carcinoma, Head And Neck Squamous Cell Carcinoma, Glioma, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Colorectal Cancer, Colon Carcinoma, Colon Cancer, Breast Cancer,
hsa-mir-30a-5p	Prostate Cancernon-Small Cell Lung Cancer, Medulloblastoma, Hepatocellular Carcinoma, Glioblastoma, Gastric Cancer, Esophageal Cancer, Colorectal Cancer,
hsa-mir-30b	Pancreatic Ductal Adenocarcinoma
hsa-mir-30b-5p	Renal Cell Carcinomanon-Small Cell Lung Cancer, Endometrial Cancer, Acute Myeloid Leukemia,
hsa-mir-30c	Renal Cell Carcinomaprostate Cancer, Non-Small Cell Lung Cancer, Medulloblastoma, Hepatocellular Carcinoma, Lung Cancer, Gastric Cancer,
hsa-mir-30d	Non-Small Cell Lung Cancer
hsa-mir-30d-5p	Prostate Cancernon-Small Cell Lung Cancer, Hepatocellular Carcinoma, Liver Cancer, Glioma, Gastric Cancer, Chronic Myelogenous Leukemia, Breast Cancer,
hsa-mir-30e	Glioma
hsa-mir-30e*	Renal Clear Cell Carcinoma
hsa-mir-30e-3p	Non-Small Cell Lung Cancer
hsa-mir-30e-5p	Prostate Cancerpapillary Thyroid Carcinoma, Pancreatic Ductal Adenocarcinoma, Oral Squamous Cell Carcinoma, Oral Carcinoma, Non-Small Cell Lung Cancer, Medulloblastoma, Malignant Melanoma, Lung Carcinoma, Lung Cancer, Lung Adenocarcinoma, Liver Cancer, Intrahepatic Cholangiocarcinoma, Hepatocellular Carcinoma, Head And Neck Squamous Cell Carcinoma, Glioblastoma, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Esophageal Cancer, Colorectal Cancer, Colon Cancer, Chronic Myelogenous Leukemia, Chordoma, Cervical Cancer, Breast Cancer, Hepatocellular Carcinoma
hsa-mir-31	Hepatocellular Carcinoma
hsa-mir-3117	Hepatocellular Carcinoma
hsa-mir-3127	Hepatocellular Carcinoma
hsa-mir-3131	Hepatocellular Carcinoma
hsa-mir-31-5p	Retinoblastoma
hsa-mir-3163	Glioma
hsa-mir-3175	

Figure 30 – (continued)

hsa-mir-3188	Breast Cancer
hsa-mir-3189-3p	Astrocytoma, Glioblastoma
hsa-mir-32	Acute Myeloid Leukemia, Breast Cancer, Gastric Cancer, Colorectal Cancer, Hepatocellular Carcinoma, Liver Cancer, Non-Small Cell Lung Cancer, Oral Squamous Cell Carcinoma, Osteosarcoma, Uveal Melanoma
hsa-mir-320	Osteosarcomacervical Cancer, Chronic Myelogenous Leukemia, Colon Cancer, Colorectal Cancer, Gastric Cancer, Glioblastoma, Glioma, Non-Small Cell Lung Cancer, Breast Cancer, Colon Cancer, Gastric Cancer, Colorectal Cancer, Glioblastoma, Glioma, Hepatocellular Carcinoma, Nasopharyngeal Carcinoma, Non-Small Cell Lung Cancer, Osteosarcoma, Pancreatic Cancer
hsa-mir-320a	Colorectal Cancer
hsa-mir-320b	Bladder Cancer
hsa-mir-320c	Glioma
hsa-mir-320d	Prostate Cancer
hsa-mir-323	Pancreatic Ductal Adenocarcinoma
hsa-mir-323-3p	Pancreatic Ductal Adenocarcinoma
hsa-mir-323-5p	Glioblastoma
hsa-mir-323a-3p	Nasopharyngeal Carcinoma
hsa-mir-324-3p	Hepatocellular Carcinoma
hsa-mir-324-5p	Hepatocellular Carcinoma
hsa-mir-325	Chronic Myelogenous Leukemia, Colorectal Cancer, Gastric Cancer, Glioblastoma, Glioma, Lung Cancer, Osteosarcoma
hsa-mir-326	Glioma, Non-Small Cell Lung Cancer
hsa-mir-328	Breast Cancer, Gastric Cancer, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer, Oral Squamous Cell Carcinoma, Osteosarcoma, Pancreatic Cancer
hsa-mir-329	Prostate Cancer, Glioblastoma, Colorectal Cancer, Glioma, Non-Small Cell Lung Cancer
hsa-mir-330	Breast Cancer, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Non-Small Cell Lung Cancer
hsa-mir-330-3p	Glioblastoma
hsa-mir-330-5p	Acute Myeloid Leukemia
hsa-mir-331	Cervical Cancer, Colorectal Cancer, Gastric Cancer, Glioblastoma, Hepatocellular Carcinoma, Prostate Cancer
hsa-mir-331-3p	Adrenal Cortical Carcinoma, Astrocytoma, Bladder Cancer, Breast Cancer, Cervical Cancer, Chondrosarcoma, Colorectal Cancer, Esophageal Squamous Cell Carcinoma, Glioma, Hepatocellular Carcinoma, Meningioma, Neuroblastoma, Non-Small Cell Lung Cancer, Osteosarcoma, Pancreatic Cancer, Ovarian
hsa-mir-335	

Figure 30 – (continued)

	Cancer, Primary Gallbladder Carcinoma, Prostate Cancer, Renal Clear Cell Carcinoma
hsa-mir-335-5p	Gastric Cancer
hsa-mir-337	Pancreatic Ductal Adenocarcinoma
hsa-mir-337-3p	Gastric Cancer, Neuroblastoma
hsa-mir-338	Oral Squamous Cell Carcinoma, nasopharyngeal Carcinoma, Gastric Cancer,
hsa-mir-338-3p	Non-Small Cell Lung Cancer, neuroblastoma, Liver Cancer, Hepatocellular Carcinoma, Glioma, Gastric Cancer, Colorectal Carcinoma, Colorectal Cancer,
hsa-mir-338-5p	Glioblastoma
hsa-mir-339	Gastric Cancer, Non-Small Cell Lung Cancer
hsa-mir-339-3p	Colorectal Cancer
hsa-mir-339-5p	Breast Cancer, Hepatocellular Carcinoma, Ovarian Cancer, Papillary Thyroid Carcinoma
hsa-mir-33a	Pancreatic Cancer, malignant Melanoma, Lung Cancer, Hepatocellular Carcinoma, Glioma, Cervical Cancer, Breast Cancer,
hsa-mir-33a-3p	Hepatocellular Carcinoma
hsa-mir-33a-5p	Hepatocellular Carcinoma, Osteosarcoma
hsa-mir-33b	Lung Adenocarcinoma, Hepatocellular Carcinoma, Gastric Cancer, Colorectal Cancer, Breast Cancer, Esophageal Squamous Cell Carcinoma, Osteosarcoma
hsa-mir-340	Osteosarcoma, Oral Cancer, Non-Small Cell Lung Cancer, Hepatocellular Carcinoma, Glioblastoma, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Endometrial Cancer, Breast Cancer, Prostate Cancer
hsa-mir-342	Acute Promyelocytic Leukemia, Colorectal Cancer, Glioblastoma
hsa-mir-342-3p	Non-Small Cell Lung Cancer, Hepatocellular Carcinoma, Cervical Cancer, Osteosarcoma
hsa-mir-342-5p	Colon Cancer
hsa-mir-345	Colorectal Cancer, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer, Oral Squamous Cell Carcinoma, Prostate Cancer
hsa-mir-346	Breast Cancer, Follicular Thyroid Carcinoma, Nasopharyngeal Carcinoma, Ovarian Cancer

Figure 30 – (continued)

hsa-mir-34a	Squamous Carcinoma, Retinoblastoma, Renal Cell Carcinoma, Rectal Cancer, Prostate Cancer, Papillary Thyroid Carcinoma, Pancreatic Ductal Adenocarcinoma, Pancreatic Cancer, Ovarian Cancer, Osteosarcoma, Oropharyngeal Cancer, Oral Squamous Cell Carcinoma, Oral Cancer, Non-Small Cell Lung Cancer, Neuroblastoma, Malignant Melanoma, Lung Cancer, Laryngeal Carcinoma, Laryngeal Cancer, Hepatocellular Carcinoma, Hepatoblastoma, Head And Neck Squamous Cell Carcinoma, Glioma, Glioblastoma, Gastric Cancer, Extrahepatic Cholangiocarcinoma, Esophageal Squamous Cell Carcinoma, Esophageal Cancer, Endometrial Cancer, Colorectal Cancer, Colon Cancer, Clear Cell Renal Cell Cancer, Choriocarcinoma, Chordoma, Cholangiocarcinoma, Cervical Carcinoma, Cervical Cancer, Breast Cancer, Bladder Cancer, B-Cell Lymphoma, Acute Myeloid Leukemia, Uveal Melanoma
hsa-mir-34a-5p	Colorectal Cancer, Hepatocellular Carcinoma
hsa-mir-34b	Prostate Cancer, Papillary Thyroid Carcinoma, Pancreatic Cancer, Ovarian Carcinoma, Ovarian Cancer, Osteosarcoma, Non-Small Cell Lung Cancer, Nasopharyngeal Carcinoma, Lung Cancer, Hepatocellular Carcinoma, Hepatoblastoma, Gastric Cancer, Endometrial Serous Adenocarcinoma, Chronic Lymphocytic Leukemia, Breast Cancer, Uveal Melanoma
hsa-mir-34b-3p	Prostate Cancer
hsa-mir-34b-5p	Malignant Melanoma
hsa-mir-34c	Breast Cancer, Chronic Lymphocytic Leukemia, Colon Cancer, Colorectal Cancer, Endometrial Cancer, Gastric Cancer, Hepatoblastoma, Lung Cancer, Malignant Melanoma, Nasopharyngeal Carcinoma, Osteosarcoma, Ovarian Cancer, Ovarian Carcinoma, Prostate Cancer, Pancreatic Cancer, Uveal Melanoma
hsa-mir-34c-3p	Hepatocellular Carcinoma, Non-Small Cell Lung Cancer
hsa-mir-34c-5p	Glioma
hsa-mir-361-3p	Non-Small Cell Lung Cancer
hsa-mir-361-5p	Hepatocellular Carcinoma, Lung Cancer, Glioma, Gastric Cancer, Colorectal Cancer, Non-Small Cell Lung Cancer
hsa-mir-3619-5p	Prostate Cancer
hsa-mir-362	Cervical Cancer, Renal Cell Carcinoma
hsa-mir-362-3p	Hepatocellular Carcinoma, Gastric Cancer, Breast Cancer, Renal Cell Carcinoma
hsa-mir-362-5p	Hepatocellular Carcinoma, Neuroblastoma
hsa-mir-363	Hepatocellular Carcinoma, Head And Neck Squamous Cell Carcinoma, Head And Neck Cancer, Gastric Cancer, Osteosarcoma

Figure 30 – (continued)

hsa-mir-363-3p	Colorectal Cancer, Gastric Cancer, Lung Adenocarcinoma, Papillary Thyroid Carcinoma
hsa-mir-3646	Breast Cancer
hsa-mir-365	Malignant Melanoma, Lung Cancer, Hepatocellular Carcinoma, Colon Cancer, Breast Cancer, Non-Small Cell Lung Cancer, Bladder Cancer
hsa-mir-3658	Laryngeal Squamous Cell Carcinoma
hsa-mir-365a-3p	Retinoblastoma
hsa-mir-365b-3p	Lung Cancer
hsa-mir-3662	Gastric Cancer, Hepatocellular Carcinoma, Medulloblastoma, Osteosarcoma, Pancreatic Cancer
hsa-mir-367	Glioblastoma
hsa-mir-369-3p	Pancreatic Ductal Adenocarcinoma
hsa-mir-369-5p	Acute Myeloid Leukemia, Bladder Cancer, Breast Cancer, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Glioma, Hepatocellular Carcinoma, Laryngeal Squamous Cell Carcinoma, Liver Cancer, Malignant Melanoma, Oral Squamous Cell Carcinoma, Non-Small Cell Lung Cancer, Osteosarcoma
hsa-mir-370	Glioma
hsa-mir-370-3p	Hepatocellular Carcinoma
hsa-mir-371-5p	Cervical Cancer, Colorectal Cancer, Endometrial Cancer, Epithelial Ovarian Cancer, Glioma, Head And Neck Squamous Cell Carcinoma, Hepatocellular Carcinoma, Oral Squamous Cell Carcinoma, Ovarian Carcinoma, Prostate Cancer, Renal Cell Carcinoma
hsa-mir-372	Lung Squamous Cell Carcinoma
hsa-mir-372-3p	Cervical Carcinoma, Breast Cancer, Colon Cancer, Epithelial Ovarian Cancer, Esophageal Squamous Cell Carcinoma, Gastric Adenocarcinoma, Glioma, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer, Oral Squamous Cell Carcinoma, Osteosarcoma, Pancreatic Cancer
hsa-mir-373	Breast Cancer, Colon Cancer, Esophageal Cancer, Gastric Cancer, Lung Adenocarcinoma
hsa-mir-374a	Osteosarcoma
hsa-mir-374a-5p	Prostate Cancer, T-Cell Lymphoblastic Lymphoma
hsa-mir-374b	Cervical Cancer
hsa-mir-374c-5p	

Figure 30 – (continued)

hsa-mir-375	Papillary Thyroid Carcinoma, Pancreatic Ductal Adenocarcinoma, Pancreatic Carcinoma, Pancreatic Cancer, Oropharyngeal Cancer, Osteosarcoma, Oral Carcinoma, Oral Cancer, Non-Small Cell Lung Cancer, Nasopharyngeal Carcinoma, Multiple Myeloma, Laryngeal Squamous Cell Carcinoma, Laryngeal Hepatocellular Carcinoma, Head And Neck Squamous Cell Carcinoma, Glioma, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Esophageal Cancer, Esophageal Adenocarcinoma, Colorectal Cancer, Colon Cancer, Cervical Squamous Cell Carcinoma, Breast Cancer, Squamous Carcinoma
hsa-mir-376a	Ovarian Cancer, Malignant Melanoma, Hepatocellular Carcinoma, Glioblastoma, Chondrosarcoma, Pancreatic Ductal Adenocarcinoma
hsa-mir-376b	Breast Cancer
hsa-mir-376c	Cervical Cancer, Gastric Cancer, Malignant Melanoma, Non-Small Cell Lung Cancer, Osteosarcoma
hsa-mir-376c-3p	Gastric Adenocarcinoma
hsa-mir-377	Non-Small Cell Lung Cancer, Gastric Cancer, Hepatocellular Carcinoma, Oral Squamous Cell Carcinoma, Pancreatic Ductal Adenocarcinoma, Renal Clear Cell Carcinoma
hsa-mir-377-3p	Colorectal Cancer
hsa-mir-378	Acute Myeloid Leukemia, Breast Cancer, Colorectal Cancer, Gastric Cancer, Glioma, Nasopharyngeal Carcinoma, Ovarian Cancer, Prostate Cancer, Renal Cell Carcinoma
hsa-mir-378a-3p	Colorectal Cancer
hsa-mir-378a-5p	Colorectal Cancer
hsa-mir-379	Breast Cancer, Osteosarcoma
hsa-mir-379-5p	Hepatocellular Carcinoma
hsa-mir-381	Breast Cancer, Colon Cancer, Colorectal Cancer, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Hepatocellular Carcinoma, Lung Adenocarcinoma
hsa-mir-382	Non-Small Cell Lung Cancer, Colorectal Cancer, Osteosarcoma, Ovarian Cancer, Prostate Cancer
hsa-mir-383	Non-Small Cell Lung Cancer, Medulloblastoma, Lung Cancer, Hepatocellular Carcinoma, Glioma, Breast Cancer, Ovarian Cancer
hsa-mir-384	Glioma, Colorectal Cancer, Hepatocellular Carcinoma
hsa-mir-3908	Glioblastoma
hsa-mir-3910	Hepatocellular Carcinoma
hsa-mir-3928	Osteosarcoma
hsa-mir-3940-5p	Non-Small Cell Lung Cancer

Figure 30 – (continued)

hsa-mir-409-3p	Bladder Cancer, Breast Cancer, Colon Cancer, Colorectal Cancer, Gastric Cancer, Glioma, Lung Adenocarcinoma, Osteosarcoma, Ovarian Cancer
hsa-mir-410	Gastric Cancer, Non-Small Cell Lung Cancer, Oral Squamous Cell Carcinoma, Pancreatic Cancer
hsa-mir-410-3p	Breast Cancer
hsa-mir-411	Lung Cancer, Ovarian Cancer
hsa-mir-411-5p	Breast Cancer
hsa-mir-421	Gastric Cancer, Breast Cancer, Glioma, Nasopharyngeal Carcinoma, Neuroblastoma, Osteosarcoma, Prostate Cancer
hsa-mir-422a	Colorectal Cancer, Glioma, Glioblastoma, Head And Neck Squamous Cell Carcinoma, Hepatocellular Carcinoma, Osteosarcoma
hsa-mir-423	Breast Cancer, Hepatocellular Carcinoma
hsa-mir-423-3p	Laryngeal Carcinoma
hsa-mir-423-5p	Colorectal Cancer, Glioma
hsa-mir-424	Acute Myeloid Leukemia, Bladder Cancer, Chronic Lymphocytic Leukemia, Cervical Cancer, Chronic Myelogenous Leukemia, Colon Cancer, Colorectal Cancer, Endometrial Cancer, Glioma, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer, Osteosarcoma, Ovarian Cancer
hsa-mir-424-3p	Non-Small Cell Lung Cancer
hsa-mir-424-5p	Esophageal Squamous Cell Carcinoma, Gastric Cancer, Hepatocellular Carcinoma, Pancreatic Cancer
hsa-mir-425	Breast Cancer, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Malignant Melanoma
hsa-mir-425-5p	Cervical Cancer, Colorectal Cancer, Gastric Cancer
hsa-mir-4260	Colorectal Cancer
hsa-mir-4261	Colorectal Cancer
hsa-mir-4262	Hepatocellular Carcinoma
hsa-mir-4282	Colorectal Carcinoma
hsa-mir-429	Astrocytoma, Bladder Cancer, Breast Cancer, Colon Cancer, Cervical Cancer, Colorectal Cancer, Colorectal Carcinoma, Gastric Cancer, Glioblastoma, Glioma, Hepatocellular Carcinoma, Lung Adenocarcinoma, Lung Cancer, Non-Small Cell Lung Cancer, Malignant Melanoma, Oral Cancer, Oral Squamous Cell Carcinoma, Osteosarcoma, Ovarian Cancer, Prostate Cancer, Renal Cell Carcinoma
hsa-mir-4295	Bladder Cancer, Glioma
hsa-mir-4317	Gastric Cancer
hsa-mir-432	Lung Adenocarcinoma, Ovarian Cancer
hsa-mir-432-3p	Esophageal Squamous Cell Carcinoma
hsa-mir-4328	Mucinous Cystadenocarcinoma

Figure 30 – (continued)

hsa-mir-433	Gastric Cancer, Hepatocellular Carcinoma, Colorectal Cancer, Liver Cancer, Oral Squamous Cell Carcinoma, Ovarian Cancer, Retinoblastoma Glioma
hsa-mir-433-3p	
hsa-mir-4417	Hepatocellular Carcinoma
hsa-mir-4458	Colon Cancer, Hepatocellular Carcinoma
hsa-mir-448	Colorectal Cancer, Gastric Cancer, Hepatocellular Carcinoma, Lung Squamous Cell Carcinoma, Ovarian Cancer
hsa-mir-4484	Glioblastoma
hsa-mir-4487	Colorectal Cancer
hsa-mir-449	Gastric Cancer
hsa-mir-449a	Breast Cancer, Colorectal Cancer, Endometrial Cancer, Gastric Adenocarcinoma, Gastric Cancer, Glioblastoma, Hepatocellular Carcinoma, Liver Cancer, Lung Cancer, Nasopharyngeal Carcinoma, Neuroblastoma, Non-Small Cell Lung Cancer, Osteosarcoma, Ovarian Cancer, Prostate Cancer
hsa-mir-449b	Lung Cancer
hsa-mir-4500	Non-Small Cell Lung Cancer
hsa-mir-450a	Hepatocellular Carcinoma
hsa-mir-450b-3p	Breast Cancer
hsa-mir-450b-5p	Colorectal Cancer
hsa-mir-451	Acute Myeloid Leukemia, Bladder Cancer, Breast Cancer, Chronic Myelogenous Leukemia, Colon Cancer, Colorectal Carcinoma, Esophageal Carcinoma, Glioma, Head And Neck Squamous Cell Carcinoma, Hepatocellular Carcinoma, Lung Adenocarcinoma, Mucinous Cystadenocarcinoma, Nasopharyngeal Carcinoma, Non-Small Cell Lung Cancer, Osteosarcoma, Pancreatic Cancer, Renal Cell Carcinoma
hsa-mir-451a	Breast Cancer, Hypopharyngeal Squamous Cell Carcinoma, Papillary Thyroid Carcinoma
hsa-mir-452	Colorectal Cancer, Esophageal Cancer, Glioma, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer, Osteosarcoma, Prostate Cancer
hsa-mir-4530	Breast Carcinoma
hsa-mir-454	Esophageal Cancer, Glioblastoma, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer, Osteosarcoma, Uveal Melanoma
hsa-mir-455	Breast Cancer, Colon Cancer, Gastric Cancer, Colorectal Cancer, Non-Small Cell Lung Cancer
hsa-mir-455-3p	Esophageal Squamous Cell Carcinoma
hsa-mir-455-3p	Esophageal Squamous Cell Carcinoma
hsa-mir-455-5p	Colon Cancer, Gastric Cancer, Malignant Melanoma
hsa-mir-4649-3p	Nasopharyngeal Carcinoma

Figure 30 – (continued)

hsa-mir-466	Prostate Cancer
hsa-mir-4723-5p	Prostate Cancer
hsa-mir-4775	Colorectal Cancer
hsa-mir-4782-3p	Non-Small Cell Lung Cancer
hsa-mir-4787-5p	Pancreatic Ductal Adenocarcinoma
hsa-mir-4792	Nasopharyngeal Carcinoma
hsa-mir-483	Colorectal Cancer
hsa-mir-483-3p	Adrenal Cortical Carcinoma, Esophageal Squamous Cell Carcinoma, Hepatocellular Carcinoma
hsa-mir-483-5p	Adrenal Cortical Carcinoma, Glioblastoma, Glioma, Hepatocellular Carcinoma, Oral Squamous Cell Carcinoma
hsa-mir-484	Cervical Cancer, Colon Cancer
hsa-mir-485-3p	Breast Cancer, Hepatocellular Carcinoma
hsa-mir-485-5p	Breast Cancer, Gastric Cancer, Hepatocellular Carcinoma, Malignant Melanoma
hsa-mir-486	Acute Myeloid Leukemia, Esophageal Cancer, Colorectal Cancer, Glioma
hsa-mir-486-3p	Retinoblastoma
hsa-mir-486-5p	Esophageal Squamous Cell Carcinoma, Lung Cancer, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer, Papillary Thyroid Carcinoma, Prostate Cancer
hsa-mir-487a	Glioma
hsa-mir-487b-3p	Colonic Adenocarcinoma
hsa-mir-488	Gastric Cancer, Osteosarcoma
hsa-mir-489	Hepatocellular Carcinoma
hsa-mir-489-3p	Breast Cancer
hsa-mir-489-5p	Breast Cancer, Gastric Cancer
hsa-mir-490	Colorectal Cancer, Gastric Cancer, Hepatocellular Carcinoma, Lung Cancer, Osteosarcoma
hsa-mir-490-3p	
hsa-mir-490-5p	Bladder Cancer, Renal Cell Carcinoma
hsa-mir-491	Hepatocellular Carcinoma
hsa-mir-491-5p	Esophageal Cancer, Cervical Cancer, Nasopharyngeal Carcinoma, Non-Small Cell Lung Cancer
hsa-mir-492	Hepatoblastoma
hsa-mir-493	Bladder Cancer, Gastric Cancer, Malignant Melanoma, Pituitary Carcinoma
hsa-mir-493-5p	Hepatocellular Carcinoma
hsa-mir-494	Acute Myeloid Leukemia, Breast Cancer, Cervical Cancer, Colorectal Cancer, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Glioma, Hepatocellular Carcinoma, Nasopharyngeal Carcinoma, Non-Small Cell Lung Cancer, Oral Cancer, Ovarian Cancer,

Figure 30 – (continued)

	Pancreatic Cancer, Pancreatic Ductal Adenocarcinoma
hsa-mir-495	Bladder Cancer, Breast Cancer, Endometrial Cancer, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Glioma, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer, Medulloblastoma, Renal Cell Carcinoma
hsa-mir-495-3p	Gastric Cancer
hsa-mir-497	Renal Cell Carcinoma, Prostate Cancer, Thyroid Cancer, pancreatic Cancer, Ovarian Cancer, Osteosarcoma, Oral Squamous Cell Carcinoma, Non-Small Cell Lung Cancer, Nasopharyngeal Carcinoma, Multiple Myeloma, Kidney Cancer, Hepatocellular Carcinoma, Glioma, Gastric Cancer, Colorectal Cancer, Cervical Cancer, Breast Carcinoma, Breast Cancer, Adrenal Cortical Carcinoma,
hsa-mir-498	Breast Cancer, Colorectal Cancer, Esophageal Squamous Cell Carcinoma, Non-Small Cell Lung Cancer, Ovarian Cancer
hsa-mir-499-5p	Colorectal Cancer, Non-Small Cell Lung Cancer
hsa-mir-499a-5p	Oral Squamous Cell Carcinoma
hsa-mir-500	Gastric Cancer, Hepatocellular Carcinoma
hsa-mir-5003-3p	Breast Cancer
hsa-mir-500a	Hepatocellular Carcinoma
hsa-mir-500a-3p	Hepatocellular Carcinoma
hsa-mir-501	Hepatocellular Carcinoma
hsa-mir-501-3p	Prostate Cancer
hsa-mir-501-5p	Gastric Cancer, Hepatocellular Carcinoma, Lung Adenocarcinoma
hsa-mir-502	Colon Cancer, Hepatocellular Carcinoma
hsa-mir-502-3p	Hepatocellular Carcinoma
hsa-mir-502-5p	Breast Cancer, Gastric Cancer
hsa-mir-503	Breast Cancer, Colon Cancer, Colorectal Cancer, Esophageal Cancer, Gastric Cancer, Glioblastoma, Glioma, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer, Oral Squamous Cell Carcinoma, Osteosarcoma, Ovarian Cancer, Prostate Cancer
hsa-mir-503-3p	Breast Cancer
hsa-mir-504	Glioblastoma, Hypopharyngeal Squamous Cell Carcinoma
hsa-mir-505	Endometrial Cancer, Hepatocellular Carcinoma

Figure 30 – (continued)

hsa-mir-506	Pancreatic Ductal Adenocarcinoma, Renal Clear Cell Carcinoma, pancreatic Cancer, Osteosarcoma, Oral Squamous Cell Carcinoma, Neuroblastoma, Nasopharyngeal Carcinoma, Liver Cancer, Hepatocellular Carcinoma, Glioma, Gastric Cancer, Glioblastoma, Esophageal Cancer, Colorectal Cancer, Colon Cancer, Cervical Cancer, Breast Cancer,
hsa-mir-508-3p	Gastric Cancer, Kidney Cancer
hsa-mir-508-5p	Glioma, Hepatocellular Carcinoma
hsa-mir-509-3p	Gastric Cancer, Kidney Cancer, Ovarian Cancer, Renal Cell Carcinoma
hsa-mir-509-5p	Non-Small Cell Lung Cancer, Prostate Cancer, Renal Cell Carcinoma
hsa-mir-510	Breast Cancer
hsa-mir-5100	Lung Cancer
hsa-mir-510-5p	Renal Cell Carcinoma
hsa-mir-511	Lung Adenocarcinoma
hsa-mir-512-3p	Non-Small Cell Lung Cancer
hsa-mir-512-5p	Non-Small Cell Lung Cancer
hsa-mir-513a-5p	Osteosarcoma
hsa-mir-513b	Gastric Cancer
hsa-mir-513c	Neuroblastoma
hsa-mir-516b	Non-Small Cell Lung Cancer
hsa-mir-517a	Breast Cancer, Colorectal Cancer
hsa-mir-517c	Glioblastoma
hsa-mir-518a-3p	Colorectal Cancer
hsa-mir-518b	Esophageal Squamous Cell Carcinoma
hsa-mir-519a	Glioblastoma, Glioma, Hepatocellular Carcinoma
hsa-mir-519d	Hepatocellular Carcinoma, Breast Cancer, Lung Adenocarcinoma, Osteosarcoma, Ovarian Cancer
hsa-mir-520a-3p	Non-Small Cell Lung Cancer, Small Cell Lung Cancer
hsa-mir-520b	Colorectal Cancer, Hepatocellular Carcinoma
hsa-mir-520c	Breast Cancer, Glioma
hsa-mir-520c-3p	Hepatocellular Carcinoma
hsa-mir-520d-3p	Gastric Cancer
hsa-mir-520d-5p	Colorectal Cancer
hsa-mir-520e	Breast Cancer
hsa-mir-520f	Gastric Cancer
hsa-mir-520g	Breast Cancer, Hepatocellular Carcinoma
hsa-mir-522	Hepatocellular Carcinoma
hsa-mir-524-5p	Gastric Cancer
hsa-mir-525-3p	Liver Cancer
hsa-mir-525-5p	Laryngeal Cancer
hsa-mir-526b	Breast Cancer, Non-Small Cell Lung Cancer

Figure 30 – (continued)

hsa-mir-526b-3p	Colon Cancer
hsa-mir-532	Gastric Cancer, Ovarian Cancer
hsa-mir-532-5p	Malignant Melanoma, Ovarian Carcinoma, Retinoblastoma
hsa-mir-539	Hepatocellular Carcinoma, Nasopharyngeal Carcinoma, Osteosarcoma, Prostate Cancer, Thyroid Cancer
hsa-mir-541	Pancreatic Ductal Adenocarcinoma
hsa-mir-541-3p	Non-Small Cell Lung Cancer
hsa-mir-542-3p	Astrocytoma, Bladder Cancer, Colorectal Cancer, Gastric Cancer, Glioblastoma, Hepatocellular Carcinoma, Malignant Melanoma, Oral Squamous Cell Carcinoma
hsa-mir-542-5p	Osteosarcoma
hsa-mir-543	Colorectal Cancer, Endometrial Cancer, Gastric Cancer, Osteosarcoma, Prostate Cancer
hsa-mir-544	Breast Cancer, Cervical Cancer, Gastric Cancer, Glioma
hsa-mir-544a	Breast Cancer
hsa-mir-545	Hepatocellular Carcinoma, Lung Cancer
hsa-mir-548a-5p	Hepatocellular Carcinoma
hsa-mir-548b	Glioma
hsa-mir-548c	Ovarian Cancer
hsa-mir-548c-3p	Glioma
hsa-mir-548p	Hepatocellular Carcinoma
hsa-mir-551a	Colorectal Cancer, Ovarian Cancer
hsa-mir-551b	Gastric Cancer
hsa-mir-551b-3p	Gastric Cancer, Ovarian Cancer
hsa-mir-552	Colorectal Cancer
hsa-mir-556-3p	Bladder Cancer
hsa-mir-558	Gastric Cancer, Neuroblastoma
hsa-mir-561	Gastric Cancer
hsa-mir-564	Chronic Myelogenous Leukemia, Glioblastoma, Lung Cancer
hsa-mir-566	Glioma
hsa-mir-567	Breast Cancer
hsa-mir-5691	Papillary Thyroid Carcinoma
hsa-mir-570	Hepatocellular Carcinoma, Lung Cancer
hsa-mir-572	Ovarian Cancer, Renal Cell Carcinoma
hsa-mir-573	Hepatocellular Carcinoma, Malignant Melanoma, Prostate Cancer
hsa-mir-574	Chronic Myelogenous Leukemia
hsa-mir-574-3p	Breast Cancer, Esophageal Cancer, Hepatocellular Carcinoma, Osteosarcoma
hsa-mir-574-5p	Colorectal Cancer
hsa-mir-576-3p	Bladder Cancer

Figure 30 – (continued)

hsa-mir-576-5p	Glioblastoma
hsa-mir-577	Colorectal Cancer, Gastric Cancer, Glioblastoma, Hepatocellular Carcinoma
hsa-mir-582	Colorectal Cancer
hsa-mir-582-5p	Colorectal Cancer, Hepatocellular Carcinoma
hsa-mir-584	Anaplastic Thyroid Carcinoma, Esophageal Squamous Cell Carcinoma, Glioma
hsa-mir-584-3p	Gastric Cancer
hsa-mir-585	Non-Small Cell Lung Cancer
hsa-mir-586	Osteosarcoma
hsa-mir-588	Lung Squamous Cell Carcinoma
hsa-mir-589	Non-Small Cell Lung Cancer
hsa-mir-589-5p	Hepatocellular Carcinoma
hsa-mir-590	Non-Small Cell Lung Cancer
hsa-mir-590-3p	Colon Cancer, Glioblastoma, Hepatocellular Carcinoma, Prostate Cancer
hsa-mir-590-5p	Breast Cancer, Cervical Cancer, Colorectal Cancer, Gastric Cancer, Hepatocellular Carcinoma, Malignant Melanoma
hsa-mir-592	Colorectal Cancer, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer
hsa-mir-595	Glioblastoma, Ovarian Cancer
hsa-mir-597	Breast Cancer
hsa-mir-598	Colorectal Cancer
hsa-mir-599	Hepatocellular Carcinoma, Non-Small Cell Lung Cancer
hsa-mir-601	Breast Cancer
hsa-mir-603	Glioma, Osteosarcoma
hsa-mir-605	Malignant Melanoma
hsa-mir-605	Non-Small Cell Lung Cancer
hsa-mir-608	Colon Cancer, Glioblastomachordoma,
hsa-mir-610	Colorectal Cancer, Glioma, Hepatocellular Carcinoma, Lung Cancer
hsa-mir-612	Hepatocellular Carcinoma
hsa-mir-613	Bladder Cancer, Breast Cancer, Colorectal Cancer, Esophageal Squamous Cell Carcinoma, Hepatocellular Carcinoma, Ovarian Cancer, Pancreatic Cancer, Papillary Thyroid Carcinoma, Prostate Cancer, Retinoblastoma
hsa-mir-614	Lung Cancer
hsa-mir-615-3p	Non-Small Cell Lung Cancer
hsa-mir-615-5p	Pancreatic Cancer, Hepatocellular Carcinoma, Pancreatic Ductal Adenocarcinoma
hsa-mir-616	Non-Small Cell Lung Cancer
hsa-mir-618	Prostate Cancer
hsa-mir-622	Colorectal Cancer, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Glioblastoma, Glioma, Hepatocellular Carcinoma

Figure 30 – (continued)

hsa-mir-623	Lung Adenocarcinoma
hsa-mir-625	Malignant Melanomahepatocellular Carcinoma, Gastric Cancer, Colorectal Cancer, Breast Cancer,
hsa-mir-625*	Non-Small Cell Lung Cancer
hsa-mir-625-3p	Colorectal Carcinoma
hsa-mir-626	Glioblastoma
hsa-mir-627	Gastric Cancercolonic Adenocarcinoma,
hsa-mir-628-5p	Prostate Cancer,
hsa-mir-629	Gastric Cancer,
hsa-mir-630	Breast Cancer, Esophageal Squamous Cell Carcinoma, Colorectal Cancer, Glioma, Hepatocellular Carcinoma, Kidney Cancer, Lung Cancer, Non-Small Cell Lung Cancer, Ovarian Cancer, Pancreatic Cancer, Renal Clear Cell Carcinoma
hsa-mir-632	Oral Squamous Cell Carcinoma,
hsa-mir-634	Hepatocellular Carcinomacervical Cancer,
hsa-mir-635	Non-Small Cell Lung Cancer,
hsa-mir-637	Hepatocellular Carcinoma,
hsa-mir-638	Osteosarcomamalignant Melanoma, Hepatocellular Carcinoma, Gastric Cancer, Esophageal Squamous Cell Carcinoma, Colorectal Cancer, Breast Cancer, Bladder Cancer, Thyroid Cancer
hsa-mir-639	Lung Cancer
hsa-mir-641	Prostate Cancer
hsa-mir-642a-5p	Gastric Canceresophageal Squamous Cell Carcinoma,
hsa-mir-644a	Colorectal Cancer
hsa-mir-645	Osteosarcoma, Renal Cell Carcinoma
hsa-mir-646	Gastric Cancer
hsa-mir-647	Hepatocellular Carcinomagastric Cancer, Glioma,
hsa-mir-650	Gastric Cancer
hsa-mir-652	Breast Cancer, Non-Small Cell Lung Cancer
hsa-mir-652-3p	Esophageal Squamous Cell Carcinoma, Ovarian Cancer
hsa-mir-655	Hepatocellular Carcinoma
hsa-mir-655-3p	Glioma
hsa-mir-656	Hepatocellular Carcinoma
hsa-mir-657	Lung Cancer
hsa-mir-660	Breast Cancer
hsa-mir-660-5p	Glioma, Ovarian Cancer
hsa-mir-661	Nasopharyngeal Carcinoma, Lung Cancer, Hepatocellular Carcinoma, Glioblastoma, Papillary Thyroid Carcinomagastric Cancer,
hsa-mir-663	

Figure 30 – (continued)

hsa-mir-663a	Hepatocellular Carcinoma, Non-Small Cell Lung Cancer, Pancreatic Ductal Adenocarcinoma
hsa-mir-663b	Pancreatic Cancer
hsa-mir-664	Hepatocellular Carcinoma, Osteosarcoma, cervical Cancer,
hsa-mir-665	Osteosarcoma
hsa-mir-668	Oral Squamous Cell Carcinoma
hsa-mir-671-5p	Breast Cancer, Invasive Ductal Carcinoma
hsa-mir-675	Breast Cancer, Colon Cancer, Glioma, Head And Neck Squamous Cell Carcinoma, Hepatocellular Carcinoma
hsa-mir-675-5p	Colon Cancer, Non-Small Cell Lung Cancer
hsa-mir-7	Prostate Cancer, Renal Cell Carcinoma, pancreatic Carcinoma, Pancreatic Cancer, Non-Small Cell Lung Cancer, Lung Cancer, Hepatocellular Carcinoma, Glioma, Glioblastoma, Gastric Cancer, Epithelial Ovarian Cancer, Colorectal Cancer, Cervical Cancer, Breast Cancer, Hepatocellular Carcinoma, Renal Cell Carcinoma
hsa-mir-708	Non-Small Cell Lung Cancer
hsa-mir-708-5p	Esophageal Squamous Cell Carcinoma
hsa-mir-718	Acute Myeloid Leukemia, Breast Cancer, Cervical Cancer, Colorectal Cancer
hsa-mir-720	Pancreatic Cancer, Nasopharyngeal Carcinoma, Prostate Cancer
hsa-mir-744	Lung Cancer
hsa-mir-7515	Cervical Cancer
hsa-mir-758	Glioblastoma, Malignant Melanoma
hsa-mir-7-5p	Ovarian Cancer
hsa-mir-760	Breast Cancer, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer, Ovarian Carcinoma
hsa-mir-761	Hepatocellular Carcinoma, Prostate Cancer
hsa-mir-765	Colorectal Cancer
hsa-mir-766	Renal Cell Carcinoma
hsa-mir-766-3p	Breast Cancer, Osteosarcoma, Prostate Cancer
hsa-mir-802	Breast Cancer, Glioblastoma
hsa-mir-873	Breast Cancer, Colorectal Cancer, Gastric Cancer, Head And Neck Squamous Cell Carcinoma, Osteosarcoma
hsa-mir-874	Hepatocellular Carcinoma
hsa-mir-874-3p	Hepatocellular Carcinoma, Oral Squamous Cell Carcinoma
hsa-mir-877	Hepatocellular Carcinoma, Neuroblastoma, Laryngeal Cancer, Renal Clear Cell Carcinoma
hsa-mir-885-5p	Thyroid Cancer
hsa-mir-886-3p	Cervical Carcinoma
hsa-mir-886-5p	Endometrial Cancer
hsa-mir-887-5p	

Figure 30 – (continued)

hsa-mir-888-5p	Hepatocellular Carcinoma
hsa-mir-892a	Colorectal Cancer, Hepatocellular Carcinoma
hsa-mir-892b	Breast Cancer
hsa-mir-9	Bladder Cancer, Breast Cancer, Cervical Adenocarcinoma, Cervical Cancer, Colorectal Cancer, Esophageal Squamous Cell Carcinoma, Gastric Adenocarcinoma, Gastric Cancer, Glioma, Hepatocellular Carcinoma, Laryngeal Squamous Cell Carcinoma, Malignant Melanoma, Nasopharyngeal Carcinoma, Non-Small Cell Lung Cancer, Oral Squamous Cell Carcinoma, Osteosarcoma, Ovarian Cancer, Uveal Melanoma
hsa-mir-92	Bladder Cancer, Colorectal Cancer, Gastric Cancer, Medulloblastoma, Neuroblastoma, Pancreatic Cancer
hsa-mir-922	Hepatocellular Carcinoma
hsa-mir-92a	Acute Myeloid Leukemia, Acute Promyelocytic Leukemia, B-Cell Lymphoma, Breast Cancer, Breast Carcinoma, Cervical Cancer, Cholangiocarcinoma, Chronic Myelogenous Leukemia, Colorectal Cancer, Endometrial Cancer, Esophageal Squamous Cell Carcinoma, Hepatocellular Carcinoma, Lung Cancer, Malignant Melanoma, Mantle Cell Lymphoma, Nasopharyngeal Carcinoma, Non-Small Cell Lung Cancer, Osteosarcoma, Ovarian Cancer
hsa-mir-92a-3p	Glioma
hsa-mir-92b	Glioblastoma, Glioma, Hepatocellular Carcinoma, Non-Small Cell Lung Cancer, Oral Squamous Cell Carcinoma, Osteosarcoma
hsa-mir-93	Colon Cancer, Colorectal Cancer, Colorectal Carcinoma, Endometrial Cancer, Esophageal Squamous Cell Carcinoma, Glioma, Head And Neck Squamous Cell Carcinoma, Hepatocellular Carcinoma, Laryngeal Squamous Cell Carcinoma, Lung Cancer, Nasopharyngeal Carcinoma, Non-Small Cell Lung Cancer, Osteosarcoma, Ovarian Carcinoma
hsa-mir-935	Gastric Cancer, Liver Cancer
hsa-mir-93-5p	Breast Cancer, Hepatocellular Carcinoma
hsa-mir-937	Lung Cancer
hsa-mir-938	Colorectal Cancer
hsa-mir-9-3p	Medullary Thyroid Carcinoma, Gastric Cancer, Papillary Thyroid Carcinoma
hsa-mir-940	Bladder Cancer, Gastric Cancer, Hepatocellular Carcinoma, Pancreatic Carcinoma, Prostate Cancer
hsa-mir-941	Hepatocellular Carcinoma
hsa-mir-942	Esophageal Squamous Cell Carcinoma
hsa-mir-944	Breast Cancer, Cervical Cancer, Colon Cancer, Endometrial Cancer, Lung Cancer, Non-Small Cell Lung Cancer

100/100

Figure 30 – (continued)

hsa-mir-95	Colorectal Cancer, Colorectal Carcinoma, Non-Small Cell Lung Cancer
hsa-mir-9500	Lung Cancer
hsa-mir-95-3p	Hepatocellular Carcinoma
hsa-mir-96	Bladder Cancer, Breast Cancer, Chronic Myelogenous Leukemia, Colorectal Cancer, Esophageal Cancer, Glioma, Hepatocellular Carcinoma, Lung Cancer, Nasopharyngeal Carcinoma, Non-Small Cell Lung Cancer, Ovarian Cancer, Pancreatic Cancer, Prostate Cancer, Renal Cell Carcinoma
hsa-mir-96-5p	Colorectal Cancer
hsa-mir-98	Breast Cancer, Bronchioloalveolar Carcinoma, Colon Cancer, Esophageal Squamous Cell Carcinoma, Glioma, Hepatocellular Carcinoma, Lung Cancer, Malignant Melanoma, Nasopharyngeal Carcinoma, Neuroblastoma, Non-Small Cell Lung Cancer, Oral Squamous Cell Carcinoma, Ovarian Cancer, Pancreatic Ductal Adenocarcinoma, Papillary Thyroid Carcinoma
hsa-mir-98-5p	Hepatocellular Carcinoma
hsa-mir-99a	Bladder Cancer, Breast Cancer, Cervical Cancer, Cervical Carcinoma, Endometrial Cancer, Esophageal Squamous Cell Carcinoma, Gastric Cancer, Hepatocellular Carcinoma, Lung Adenocarcinoma, Nasopharyngeal Carcinoma, Non-Small Cell Lung Cancer, Osteosarcoma, Pancreatic Cancer, Renal Cell Carcinoma
hsa-mir-99b	Cervical Cancer, Cervical Carcinoma, Esophageal Cancer, Esophageal Squamous Cell Carcinoma, Hepatocellular Carcinoma, Lung Cancer
hsa-mir-99b-3p	Oral Squamous Cell Carcinoma
mmu-mir-290-3p	Breast Cancer
mmu-mir-290-5p	Breast Cancer

4819-9850-3523.1

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US18/29533

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 5, 7-12, 15
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US18/29533

A. CLASSIFICATION OF SUBJECT MATTER

IPC - C12Q 1/68; G01N 33/15; A61B 5/055 (2018.01)

CPC - C12Q 1/68, 1/6804, 1/6806, 1/682; G01N 33/15; A61B 5/055

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X -- Y	WO 2005/023986 A2 (ISIS PHARMACEUTICALS, INC.) 17 March 2005; abstract; page 20, lines 33-34; page 64, lines 5-6; page 65, lines 7-8; page 176, lines 33-34; page 177, line 1; page 228, lines 19-20	1-2, 3/1-2 ----- 4/3/1-2, 6
X -- Y	(DISNEY, MD et al.) Rational Design of Small Molecules Targeting Oncogenic Noncoding RNAs from Sequence. Accounts of Chemical Research. 20 December 2016, Epub 22 November 2016, Vol. 49, No. 12; pages 2698-2704; page 6, 4th paragraph; page 7, 4th and 5th paragraphs; DOI: 10.1021/acs.accounts.6b00326	13-14 ----- 4/3/1-2
Y	(PETERSON, KR et al.) A Cell-Based High-Throughput Screen for Novel Chemical Inducers of Fetal Hemoglobin for Treatment of Hemoglobinopathies. PLoS One. 16 September 2014, Vol. 9, No. 9; pages 1-12; abstract; page 5, 1st column, 1st paragraph; DOI: 10.1371/journal.pone.0107006	6



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

27 June 2018 (27.06.2018)

Date of mailing of the international search report

09 JUL 2018

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